Doctor of Philosophy

Stent Length and Long-Term Outcomes after Percutaneous Coronary Intervention with New-Generation Drug-Eluting Stents

The Graduate School

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Stent Length and Long-Term Outcomes after Percutaneous Coronary Intervention with New-Generation Drug-Eluting Stents

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Abstract

Background: Percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) ≥20 mm in length is increasingly being used in the treatment of significant coronary artery disease (CAD). We evaluated the long-term effectiveness and safety of long DESs in patients with diffuse CAD.

Methods and Results: A total of 4,722 patients with CAD undergoing PCI with new-generation DESs were analyzed. The patients were classified into the short (stented length <20 mm, n=1,050), intermediate (stented length ≥20 mm, <40 mm, n=2,672), and long (stented length ≥40 mm, n=1,000) stent groups. The primary outcome was target lesion failure (TLF), defined as a composite of cardiac death, target-vessel myocardial infarction, or target lesion revascularization. During the follow-up period (median 49.1 months), the 4-year rate of TLF significantly increased according to the stented length (5.1% in the short stent group, 9.1% in the intermediate stent group, and 18.1% in the long stent group, p<0.001). Similarly, the rate of death from any cause or target vessel myocardial infarction was significantly higher in the long stent group than the short or intermediate stent group. Long stent, but not intermediate stent, was an independent predictor of all-cause death or cardiac death compared to short stent.

Conclusions: Patients with long stent implantation showed a higher risk for TLF and death after PCI with new-generation DESs than those with short or intermediate stent implantation. In the current DESs era, it may be appropriate to redefine long lesions as those requiring a stented length ≥40 mm.

Contents

Lists of tables

Lists of figures

INTRODUCTION

Long coronary lesions, traditionally defined as those with a length greater than 20 mm, pose a profound challenge to interventionists. Balloon angioplasty of long lesions is associated with a higher risk of acute vessel closure and late restenosis[1-4]. Although coronary stenting results in improved outcomes, long lesions remain vulnerable to restenosis in the bare-metal stent era[5-7]. Longer stent lengths are significantly related to a higher risk of target lesion failure (TLF) after percutaneous coronary intervention (PCI) with bare-metal stents[6,7].

Drug-eluting stents (DESs) dramatically reduce restenosis rates and are now the first-line devices for contemporary PCI. New-generation DESs further improve patients' safety profiles and are increasingly being used in the treatment of high-risk complex lesions[8,9]. In real-world practice, therefore, patients with diffuse long lesions represent a significant portion of those undergoing PCI. These patients seem to be at greater risk for TLF than those without a long lesion[10-13]. However, data on the effectiveness of long DESs in real-world practice are limited, and there is a lack of clarity on the acceptable stent length. In the present study, we investigated the long-term safety and efficacy of new-generation DES depending on the stented length in real-world patient populations

METHODS

Study population

The study population comprised patients who underwent PCI procedures with new-generation DESs for significant coronary artery disease (CAD) at two academic hospitals in Korea from August 1, 2008 to December 31, 2015. For the present analysis, patients with a history of prior coronary artery bypass graft (CABG) surgery, prior PCI, bifurcation lesions requiring side branch intervention, a mixture of different DES types, concomitant valvular or aortic surgery, cardiogenic shock and other comorbid conditions with a life expectancy shorter than 12 months, and those with planned surgery necessitating the interruption of antiplatelet drug therapy within 6 months after the procedure were excluded.

The current analysis included patients treated with six different types of DESs; cobalt–chromium everolimus-eluting stents (CoCr-EES, Xience V; Abbott Vascular, Santa Clara, California, USA), cobalt–chromium sirolimus-eluting stents (CoCr-SES, Orsiro; Biotronik, Berlin, Germany), platinum–chromium EES (PtCr-EES, Promus Element; Boston Scientific, Natik, Massachusetts, USA), Resolute zotarolimus-eluting stent (Re-ZES, Resolute Integrity; Medtronic, Meerbusch, Germany), Biomatrix biodegradable-polymer biolimus-eluting stents (Bi-BES, BioMatrix; Biosensors International, Singapore), and Nobori biodegradable-polymer biolimus-eluting stents (No-BES, Nobori; Terumo Clinical Supply, Kakamigahara, Japan). Patients were divided into three groups according to the stented length: the 1) short stent (stented length <20 mm), 2) intermediate stent (stented length ≥20 mm, <40 mm), and 3) long stent (stented length ≥40 mm) groups. In patients who received PCI for multivessel CAD, classification was performed according to the longest stent length. The study protocol was approved by the ethics committee at both hospitals.

Procedures and Follow-up

PCI was performed according to standard techniques at the discretion of the treating physician. The study did not specify the type of PCI treatment; therefore, the application of predilatation,

use of intravascular ultrasound, and selection of a specific DES type were at the discretion of the interventional cardiologists. Periprocedural anticoagulation was administered according to standard regimens[14]. All patients undergoing PCI received a loading dose of aspirin and adenosine diphosphate receptor antagonists before or during the intervention. After the procedure, aspirin was continued indefinitely and adenosine diphosphate receptor antagonists was prescribed for at least 6–12 months[15]. Treatment beyond this duration was provided at the discretion of the physician. Data on all the baseline characteristics and outcomes were collected using a dedicated case report form by specialized personnel at each participating center. Clinical follow-up of the patients was performed based on the patients' follow-up visits and medical records.

Clinical Outcomes and Definitions

The primary outcome of the current analysis was TLF, defined as a composite of cardiac death, target vessel myocardial infarction (MI), and target lesion revascularization (TLR). Secondary clinical outcomes included death (cardiac or non-cardiac), MI (periprocedural or spontaneous), repeat revascularization (TLR or non-TLR), and stent thrombosis. In addition, an analysis of TLF except periprocedural MI was performed to investigate the effect of stented length on long term outcome.

Death was considered as resulting from a cardiac cause, unless an unequivocal non-cardiac cause could be established. The diagnosis of MI was based on the universal definition of MI[16], and was categorized as procedural or spontaneous MI. Repeat revascularization included any type of percutaneous or surgical revascularization procedure, regardless of whether the procedure was clinically or angiographically driven and categorized as TLR or non-TLR. Definite stent thrombosis was defined according to Academic Research Consortium criteria[17]. Hyperlipidemia was defined as a total cholesterol level >200 mg/dl or the use of antihyperlipidemic treatment. All the outcomes of interest were confirmed by the source documentation collected at each hospital and were centrally adjudicated by an independent

researcher who was blinded to the study devices**.**

Statistical Analysis

Continuous and categorical covariates were summarized as mean ± standard deviation or count (percentage, %). Differences in the baseline variables of the patients between the groups were compared using analysis of variance (continuous variables) and chi-square statistics (categorical variables). Survival curves were constructed using Kaplan-Meier estimates and tested by the log-rank statistic. Cumulative events of the clinical outcomes were assessed using Kaplan–Meier estimates and compared with the log-rank test. All analyses were truncated at 4 years of follow-up, owing to differences in the follow-up duration according to the DES type. Multivariable Cox proportional hazards regression modeling was used to examine the independent effect of stent length on clinical outcomes. After unadjusted analyses were initially performed, multivariable Cox regression analyses were performed to adjust for the potential confounders identified by the investigators using a literature search and a priori based on clinical knowledge. These covariates included age, sex, presence of diabetes, presence of hypertension, presence of chronic renal failure, clinical presentation (stable angina, unstable angina, or MI), ejection fraction <50%, extent of CAD, and use of intravascular ultrasound. In the Cox model, the proportionality assumptions were assessed by the Schoenfeld residual test and no relevant violations were detected. All reported p-values are two-sided, and p-values <0.05 were considered statistically significant. Analysis was performed with SPSS software, version 21.0 (SPSS, Inc, Chicago, IL, USA).

RESULTS

Baseline Characteristics

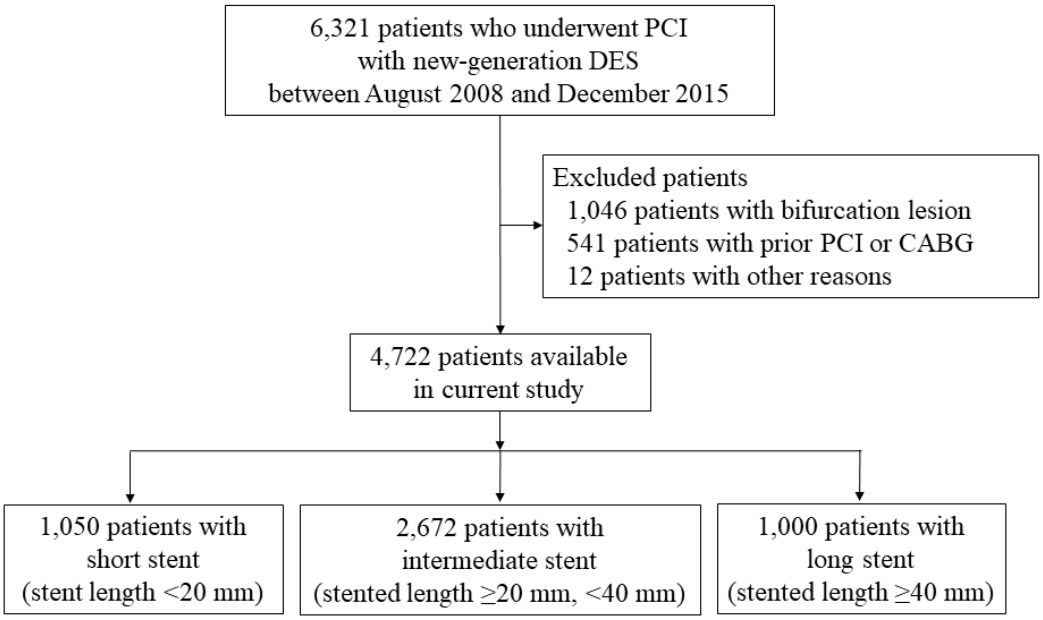
Of 6,321 patients who underwent PCI with new-generation DESs, 4,722 met the eligibility criteria for the present study (**Figure 1**). The clinical characteristics of the patients are shown in **Table 1**. The mean age of the patients was 62.3 years, 3,366 (71.3%) of the patients were men, and 1,418 (30.0%) had diabetes mellitus. Patients with longer stents tended to be older; had a higher prevalence of risk factors such as hypertension, diabetes mellitus, current smoking and hyperlipidemia; had a higher incidence of stroke; and had a lower left ventricular ejection fraction. Angiographically, patients with longer stents had a higher extent of CAD, a higher rate of use of intravascular ultrasound, and a lower rate of complete revascularization (**Table 2**).

Clinical Outcomes

The median follow-up duration was 49.1 months (interquartile range, 33.7 ± 67.3 months). The 4-year rate of TLF significantly increased according to the stented length (5.1% in the short stent group, 9.1% in the intermediate group, and 18.1% in the long stent group, $p<0.001$, **Figure 2**, **Table 3** and **Figure 3**). Likewise, the rate of death from any cause was significantly higher in the long stent group than the short or intermediate stent groups. A similar finding was observed regarding the rate of target vessel MI. However, the rate of TLR did not significantly differ across the three groups.

Multivariate Analysis

After multivariable adjustment for traditional risk factors and potential confounders, longer stents were found to be associated with a significantly higher risk for TLF (adjusted hazard ratio [HR], 1.929; 95% confidence interval [CI], 1.641 – 2.268; $p <0.001$). They were also associated with a significantly higher risk of death from cardiac causes (adjusted HR, 1.722; 95% CI, 1.221 – 2.427, $p=0.002$) and periprocedural MI (adjusted HR, 2.460; 95% CI, 1.980 – 3.056; $p <0.001$, **Table 4**).



CABG = coronary artery bypass graft; DES = drug-eluting stent; PCI = percutaneous coronary intervention

Figure 1. Flow Chart of Patient Inclusion and Exclusion.

Table 1. Baseline Characteristics according to Stent Length

Variables	Short stent group (N=1,050)	Intermediate stent group (N=2,672)	Long stent group (N=1,000)	P-value
Age, years	62.0 ± 11.2	62.8 ± 11.0	63.5 ± 10.7	0.002
Male sex	717 (68.3%)	1903 (71.2%)	746 (74.6%)	0.007
Body mass index, kg/m^2	24.9 ± 3.0	24.8 ± 3.1	24.8 ± 3.1	0.508
Hypertension	603 (57.4%)	1544 (57.8%)	628 (62.8%)	0.014
Diabetes mellitus	254 (24.2%)	777 (29.1%)	387 (38.7%)	<0.001
Requiring insulin	20 (1.9%)	59 (2.2%)	46 (4.6%)	<0.001
Current smoking	250 (23.8%)	726 (27.2%)	257 (25.7%)	<0.001
Hyperlipidemia	327 (31.1%)	901 (33.7%)	459 (45.9%)	<0.001
Previous myocardial infarction	6 (0.6%)	14 (0.5%)	15 (1.5%)	0.007
Previous stroke	61 (5.8%)	143 (5.4%)	95 (9.5%)	<0.001
Previous heart failure	21 (2.0%)	55 (2.1%)	20 (2.0%)	0.990
Atrial fibrillation	26 (2.5%)	76 (2.8%)	24 (2.4%)	0.689
Family history of CAD	36 (3.4%)	131 (4.9%)	56 (5.6%)	0.055
Chronic lung disease	15 (1.4%)	54 (2.0%)	17 (1.7%)	0.453
Chronic renal failure	33 (3.1%)	113 (4.2%)	51 (5.1%)	0.084
Peripheral vascular disease	12 (1.1%)	56 (2.1%)	22 (2.2%)	0.120
Clinical presentation				<0.001
Stable angina	356 (33.9%)	960 (35.9%)	502 (50.2%)	
Unstable angina	434 (41.3%)	904 (33.8%)	269 (26.9%)	
Myocardial infarction	260 (24.8%)	808 (30.2%)	229 (22.9%)	
Ejection fraction, %	59.5 ± 10.6	57.7 ± 11.2	57.1 ± 10.5	<0.001

In-hospital or discharge medications				
Aspirin	1048 (99.8%)	2647 (99.1%)	994 (99.4%)	0.045
ADP receptor antagonist	1038 (98.9%)	2649 (99.1%)	989 (98.8%)	0.563
β-blocker	539 (51.4%)	1470 (55.1%)	611 (61.2%)	<0.001
Calcium channel blocker	506 (48.2%)	1240 (46.4%)	590 (59.2%)	<0.001
ACE inhibitor or ARB	452 (43.0%)	1278 (47.8%)	468 (46.8%)	0.031
Statin	959 (91.3%)	2464 (92.2%)	917 (91.7%)	0.649

ACE = angiotensin converting enzyme; ADP = adenosine diphosphate; ARB = angiotensin receptor blocker; CAD = coronary artery disease

Table 2. Baseline Angiographic and Procedural Characteristics according to the Stent Length

Variables	Short stent group (N=1,050)	Intermediate stent group (N=2,672)	Long stent group (N=1,000)	P-value
Disease extent				<0.001
1-vessel disease	713 (67.9%)	1451 (54.3%)	395 (39.5%)	
2-vessel disease	245 (23.3%)	767 (28.7%)	359 (35.9%)	
3-vessel disease	92 (8.8%)	454 (17.0%)	246 (24.6%)	
Disease vessel				
Left main	70 (6.7%)	129 (4.8%)	141 (14.1%)	<0.001
LAD	563 (53.6%)	1705 (63.8%)	760 (76.0%)	<0.001
LCX	240 (22.9%)	457 (17.1%)	184 (18.4%)	0.001
RCA	259 (24.7%)	812 (30.4%)	398 (39.8%)	<0.001
Number of treated lesions	1.1 ± 0.3	1.3 ± 0.5	1.8 ± 0.8	<0.001
Number of stents	1.1 ± 0.4	1.3 ± 0.6	2.7 ± 1.1	<0.001
Length of stents, mm	16.2 ± 3.8	28.6 ± 5.6	58.1 ± 13.6	< 0.001
Diameter of stents, mm	3.2 ± 0.8	3.3 ± 0.5	3.3 ± 0.4	0.030
DES type				<0.001
CoCr-SES	33 (3.1%)	44 (1.6%)	6 (0.6%)	
CoCr-EES	472 (45.0%)	1231 (46.1%)	507 (50.7%)	
PtCr-EES	39 (3.7%)	308 (11.5%)	136 (13.6%)	
Re-ZES	332 (31.6%)	740 (27.7%)	222 (22.2%)	
Bi-BES	129 (12.3%)	220 (8.2%)	51 (5.1%)	
No-BES	45 (4.3%)	129 (4.8%)	78 (7.8%)	
Use of IVUS	782 (74.5%)	2080 (77.8%)	873 (87.3%)	<0.001
Moderate-to-severe calcification	9 (0.9%)	50 (1.9%)	62 (6.2%)	<0.001
Thrombus	29 (2.8%)	92 (3.4%)	39 (3.9%)	0.353
Complete revascularization	701 (66.8%)	1508 (56.4%)	541 (54.1%)	<0.001

BES = biolimus-eluting stent; CoCr-EES = cobalt-chromium everolimus-eluting stent; CoCr-SES = cobalt-chromium sirolimus-eluting stent; DES = drug-eluting stent; IVUS =

intravascular ultrasound; LAD = left anterior descending artery; LCX = left circumflex artery; PtCr-EES = platinum-chromium everolimus-eluting stents; RCA = right coronary artery; Re-ZES = resolute zotarolimus-eluting stents.

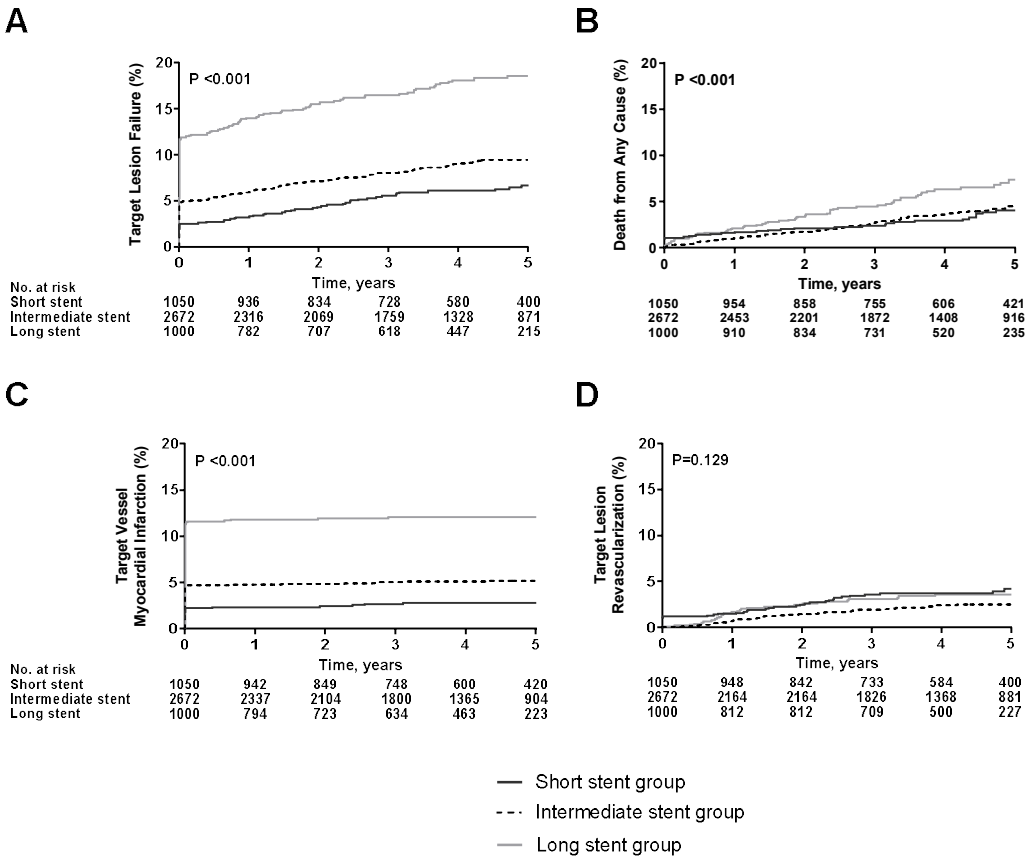


Figure 2. Kaplan-Meier Curves for the Cumulative Incidence of (A) Target Lesion Failure, (B) Death from Any Cause, (C) Target Vessel Myocardial Infarction, and (D) Target Lesion Revascularization according to the Stent Length Group: Short (solid line), Intermediate (dashed line), and Long (gray line) Stent Groups.

Table 3. Four-Year Event Rates of Primary and Secondary Clinical Outcomes according to the Stent Length Group*

	Short stent group (N=1,050)	Intermediate stent group (N=2,672)	Long stent group (N=1,000)	P-value
Primary outcome*				
Target lesion failure†	5.1 (3.7 - 6.5)	9.1 (7.9 - 10.2)	18.1 (15.6 - 20.6)	<0.001
Secondary outcomes*				
Death from any cause	1.9 (1.0 - 2.8)	3.6 (2.8 - 4.4)	6.3 (4.7 - 7.9)	<0.001
Death from cardiac causes	1.1 (0.4 - 1.8)	2.3 (1.7 - 3.0)	4.5 (3.0 - 5.9)	<0.001
Death from non-cardiac causes	0.8 (0.2 - 1.4)	1.3 (0.8 - 1.8)	1.9 (1.0 - 2.8)	0.215
Myocardial infarction	1.9 (1.1 - 2.8)	5.5 (4.6 - 6.4)	12.2 (10.1 - 14.2)	<0.001
Periprocedural	1.2 (0.6 - 1.9)	4.7 (3.9 - 5.5)	11.6 (9.6 - 13.6)	<0.001
Spontaneous	0.7 (0.1 - 1.2)	1.0 (0.5 - 1.4)	0.8 (0.2 - 1.4)	0.455
Any revascularization	10.2 (8.1 - 12.2)	11.2 (9.9 - 12.5)	10.3 (8.3 - 12.3)	0.449
TLR	2.7 (1.6 - 3.8)	2.4 (1.8 - 3.1)	3.6 (2.3 - 4.8)	0.129
Non-TLR	1.4 (0.6 - 2.2)	1.9 (1.3 - 2.5)	1.8 (0.8 - 2.7)	0.158
Definite stent thrombosis	0.2 (-0.1 - 0.5)	0.2 (0.0 - 0.4)	0.1 (-0.1 - 0.3)	0.829

*Cumulative rates (95% confidence interval) of events are based on Kaplan–Meier estimates.

†Target lesion failure was defined as death from cardiac causes, target-vessel myocardial infarction, or TLR.

TLR = target lesion revascularization.

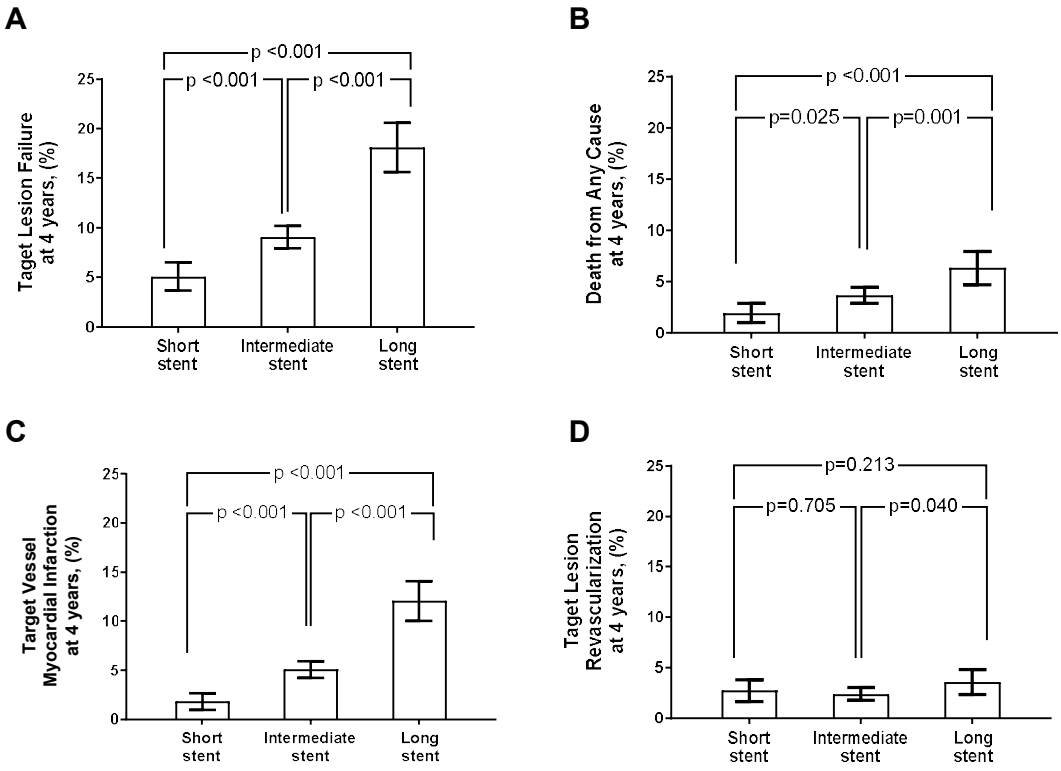


Figure 3. Four-Year Event Rates of (A) Target Lesion Failure, (B) Death from Any Cause, (C) Target Vessel Myocardial Infarction, and (D) Target Lesion Revascularization, according to the Stent Length.

Table 4. Adjusted Hazard Ratios for Primary and Secondary Clinical Outcomes according to each Stent Length Group

	Intermediate stent compared to short stent		Long stent compared to short stent		Long stent compared to intermediate stent	
	Adjusted HR* (95% CI)	P-value	Adjusted HR* (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Primary outcome*						
Target lesion failure†	1.891 (1.334 - 2.680)	<0.001	3.682 (2.560 - 5.295)	<0.001	1.947 (1.571 - 2.413)	<0.001
Secondary outcomes*						
Death from any cause	1.567 (0.878 - 2.797)	0.128	2.615 (1.420 - 4.815)	0.002	1.668 (1.138 - 2.445)	0.009
Death from cardiac causes	1.634 (0.795 - 3.359)	0.182	2.885 (1.358 - 6.129)	0.006	1.766 (1.113 - 2.802)	0.016
Death from non-cardiac causes	1.437 (0.543 - 3.806)	0.466	2.133 (0.748 - 6.083)	0.157	1.484 (0.747 - 2.949)	0.260
Myocardial infarction	2.961 (1.760 - 4.982)	<0.001	5.781 (3.394 - 9.848)	<0.001	1.953 (1.510 - 2.525)	<0.001
Periprocedural	4.138 (2.165 - 7.907)	<0.001	9.201 (4.782 - 17.702)	<0.001	2.224 (1.704 - 2.902)	<0.001
Spontaneous	1.018 (0.404 - 2.564)	0.969	0.827 (0.268 - 2.550)	0.741	0.812 (0.337 - 1.958)	0.812
Any revascularization	0.933 (0.714 - 1.220)	0.613	0.817 (0.589 - 1.135)	0.229	0.876 (0.674 - 1.139)	0.323
TLR	0.891 (0.519 - 1.530)	0.676	1.410 (0.767 - 2.593)	0.269	1.582 (0.977 - 2.563)	0.062
Non-TLR	1.238 (0.586 - 2.617)	0.576	1.140 (0.472 - 2.573)	0.771	0.921 (0.474 - 1.790)	0.808
Definite stent thrombosis	0.943 (0.179 - 4.974)	0.945	0.510 (0.043 - 6.041)	0.594	0.541 (0.062 - 4.748)	0.580

*Models were adjusted for age, sex, presence of diabetes mellitus, presence of hypertension, presence chronic renal failure, clinical presentation, ejection fraction <50%, disease extent of coronary artery disease, and use or nonuse of intravascular ultrasound.

†Target lesion failure was defined as death from cardiac causes, target vessel myocardial infarction, or TLR.

CI = confidence interval; TLR = target lesion revascularization; HR = hazard ratio.

The independent predictors of TLF, death from cardiac causes, and death from any causes after adjustment for clinical characteristics are presented in **Table 5**. Intermediate and long stents were independent predictors of TLF compared to short stents. Among patients with a stented length ≥20 mm, long stents were also independent predictors of TLF compared to intermediate stents. As for deaths from cardiac causes and those from any cause, long stents were independent predictors compared to short and intermediate stents. However, intermediate stents were not independent predictors of death from cardiac causes or death from any cause compared to short stents.

To determine whether the effect of stent length in the overall population was consistent, subgroup analysis was performed. A significantly higher risk of the primary outcome was consistent in major clinical subgroups, such as old age, hypertension, diabetes mellitus, acute coronary syndrome, and chronic renal failure (**Figure 4**).

TLF except Periprocedural MI

The 4-year rate of TLF except periprocedural MI significantly increased according to the stented length (4.2% in the short stent group, 5.3% in the intermediate group, and 7.7% in the long stent group, p=0.001, **Figure 5**).

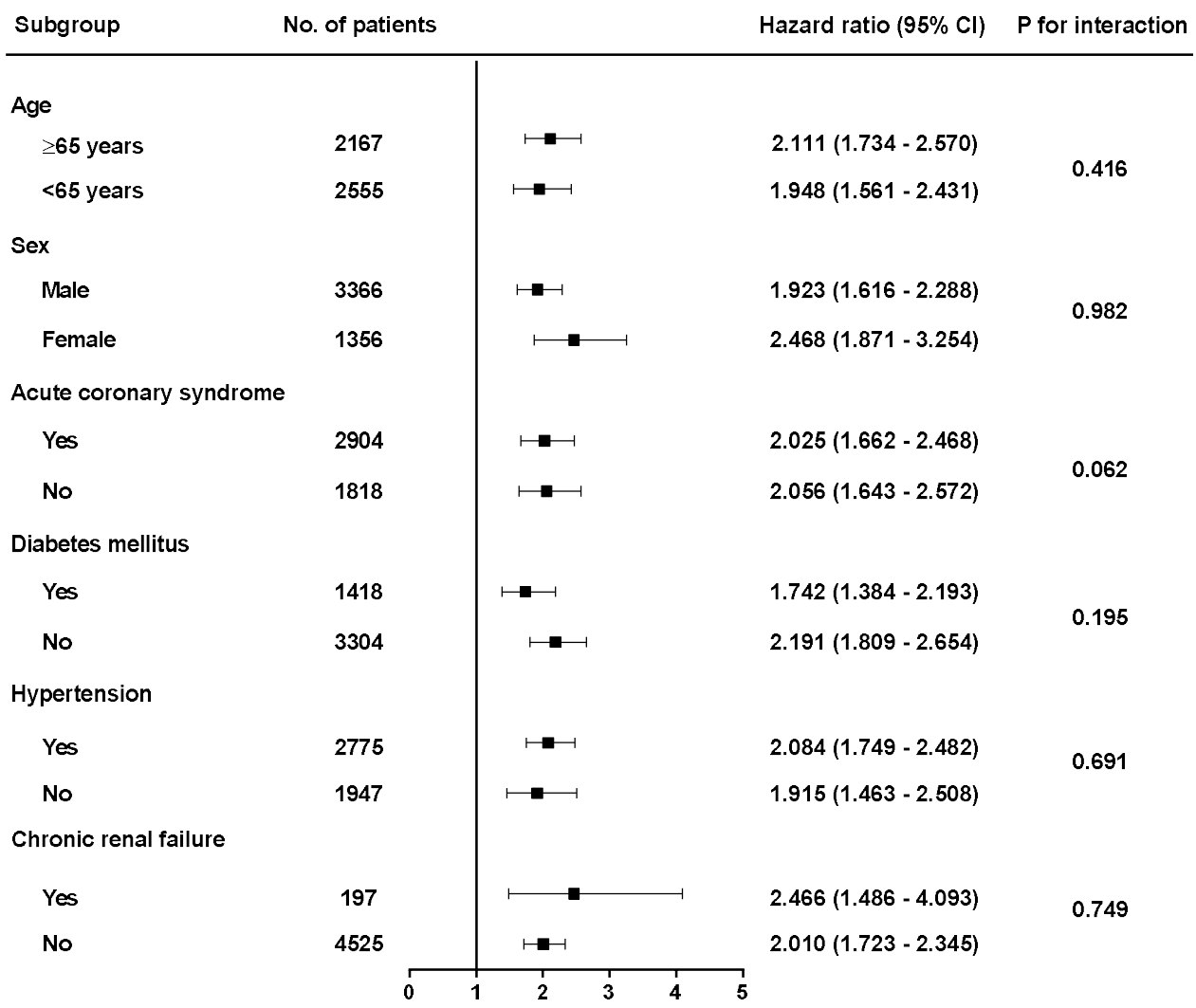
The independent predictors of TLF except periprocedural MI, death from cardiac causes, and death from any causes after adjustment for clinical characteristics including periprocedural MI are presented in **Table 6**. After adjustment, periprocedural MI was, but stented length was not an independent predictor of TLF except periprocedural MI. However, long stents, compared to short and intermediate stents were associated with a significantly higher risk of death from cardiac causes and those from any causes, even after adjustment for periprocedural MI. However, intermediate stents were not independent predictors of death from cardiac causes or death from any cause compared to short stents.

Table 5. Independent Predictors of Target Lesion Failure, Death from Cardiac Causes, and Death from Any Cause

Variables	Target lesion failure		Death from cardiac causes		Death from any cause	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Short stent	Reference	-	Reference	-	Reference	-
Intermediate stent	1.876 (1.325 - 2.656)	0.001	1.662 (0.809 - 3.412)	0.166	1.592 (0.893 - 2.839)	0.115
Long stent	3.651 (2.555 - 5.216)	<0.001	3.018 (1.438 - 6.331)	0.003	2.652 (1.451 - 4.844)	0.002
Long stent, compared to intermediate stent	1.946 (1.577 - 2.401)	<0.001	1.816 (1.159 - 2.846)	0.009	1.666 (1.146 - 2.421)	0.008
Age, years	1.018 (1.008 - 1.028)	<0.001	1.051 (1.029 - 1.074)	<0.001	1.059 (1.040 - 1.078)	<0.001
Sex, male	*	*	*	*	1.394 (0.937 - 2.075)	0.102
Diabetes mellitus	1.225 (0.992 - 1.512)	0.059	2.242 (1.421 - 3.536)	0.001	1.889 (1.306 - 2.731)	0.001
Hypertension	1.306 (1.049 - 1.626)	0.017	1.596 (0.953 - 2.674)	0.076	1.537 (1.017 - 2.322)	0.041
Chronic renal failure	2.166 (1.535 - 3.056)	<0.001	4.390 (2.604 - 7.400)	<0.001	3.831 (2.448 – 5.997)	<0.001
Clinical presentation	*	*	*	*	*	*
Left ventricular ejection fraction <50%	*	*	2.354 (1.508 - 3.675)	<0.001	2.418 (1.677 - 3.486)	<0.001
Extent of coronary artery disease	*	*	0.729 (0.548 - 0.969)	0.030	0.784 (0.621 - 0.990)	0.041
Use of intravascular ultrasound	1.780 (1.322 - 2.397)	0.001	*	*	*	*

CI = confidence interval; HR = hazard ratio

*Not in the final multivariate model



CI = confidence interval

Figure 4. Risk of Target Lesion Failure according to Subgroup and Increase in Stent Length

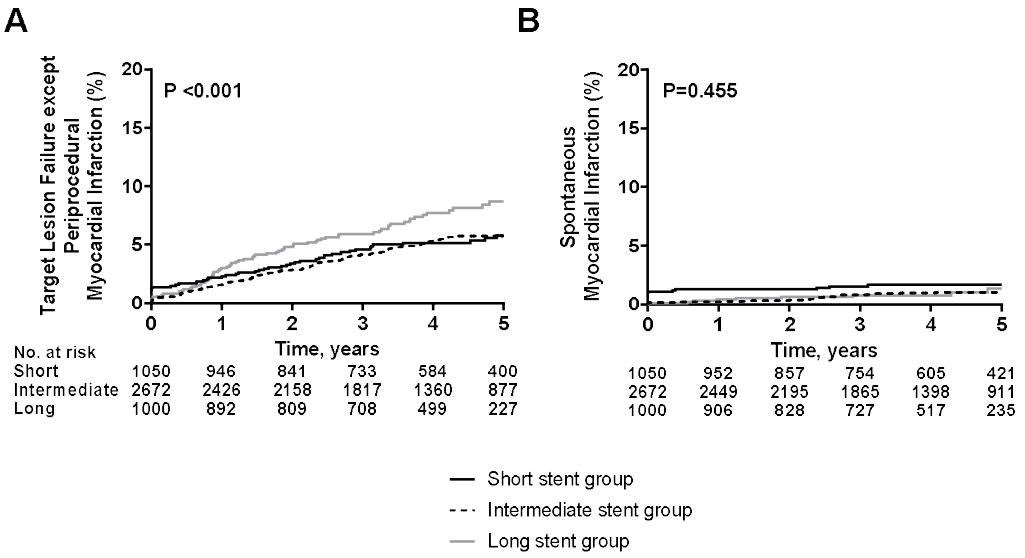


Figure 5. Kaplan-Meier Curves for the Cumulative Incidence of (A) Target Lesion Failure except Periprocedural Myocardial Infarction and (B) Spontaneous Myocardial Infarction according to the Stent Length Group: Short (solid line), Intermediate (dashed line), and Long (gray line) Stent Groups.

Table 6. Independent Predictors of Target Lesion Failure except Periprocedural Myocardial Infarction, Death from Cardiac Causes, and Death from Any Cause

Variables	Target lesion failure except periprocedural myocardial infarction		Death from cardiac causes		Death from any cause	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Short stent	Reference	-	Reference	-	Reference	-
Intermediate stent	*	*	1.562 (0.759-3.213)	0.226	1.562 (0.875-2.788)	0.132
Long stent	*	*	2.578 (1.213-5.479)	0.014	2.544 (1.383-4.681)	0.003
Long stent, compared to intermediate stent	*	*	1.651 (1.045-2.608)	0.032	1.629 (1.117-2.378)	0.011
Age, years	1.014 (1.001-1.028)	0.038	1.049 (1.027-1.072)	<0.001	1.053 (1.035-1.072)	<0.001
Sex, male	*	*	*	*	*	*
Diabetes mellitus	1.658 (1.232-2.231)	0.001	2.244 (1.425-3.536)	<0.001	1.886 (1.305-2.727)	0.001
Hypertension	1.513 (1.090-2.100)	0.013	1.546 (0.921-2.594)	0.099	1.483 (0.981-2.241)	0.062
Chronic renal failure	3.704 (2.476-5.540)	<0.001	4.510 (2.682-7.586)	<0.001	4.027 (2.582-6.281)	<0.001

Clinical presentation	*	*	*	*	*	*
Left ventricular ejection fraction <50%	1.445 (1.043-2.002)	0.027	2.526 (1.615-3.952)	<0.001	2.519 (1.745-3.635)	<0.001
Extent of coronary artery disease	*	*	0.734 (0.551-0.978)	0.035	0.782 (0.620-0.986)	0.038
Use of intravascular ultrasound	*	*	*	*	*	*
Periprocedural myocardial infarction	1.904 (1.205-3.008)	0.006	2.456 (1.352-4.461)	0.003	1.678 (0.963-2.926)	0.068

CI = confidence interval; HR = hazard ratio

*Not in the final multivariate model

DISCUSSION

Stent length and TLF

Among patients with significant CAD undergoing PCI with new-generation DESs, longer stents progressively increased the risk of TLF according to the stented length, even after adjustment for other relevant variables. Longer stents were also associated with a significantly higher risk of death from any cause, death from cardiac causes, and target vessel MI. These results are consistent with those of previous studies[12,18,19]. In our study, 3,672 (77.8%) patients belonged to the intermediate or long stent groups and, according to current guidelines, would be deemed as having long lesions (≥20 mm) [4,20,21]. The use of contemporary PCI with DES lengths ≥20 mm is very common and yields acceptable outcomes. Although the risk of TLF was significantly higher in the intermediate stent group than the short stent group, the risk of all-cause death or cardiac death did not differ between the groups. These findings suggest defining coronary lesions requiring a stented length ≥40 mm may be more appropriate as long lesions, rather than those with a lesion length of 20 mm, in the current DES era.

Stent length and risks of clinical outcomes

Patients with long stent implantation are known to have an increased risk of procedural complications and poor clinical outcomes. In the bare-metal stent era, long stents are defined as those with a stented length of 20 mm or 35 mm, and long stent implantation is associated with poor clinical outcomes[7,22,23]. In the DES era, stents longer than 41 mm or 60 mm were reported to be associated with poor clinical outcomes[11,24]. As PCI with DESs has become a mainstream procedure in the treatment of significant CAD, the number of patients with long stents has increased in routine clinical practice. In our study, 77.8% of the patients had a stent length ≥20 mm, indicating that a significant portion of patients undergoing PCI are treated with long stents, per the current definition of long lesions. The risk of TLF significantly increased in accordance with the stented length, mainly driven by higher risks of death from

cardiac causes and periprocedural MI. In addition, compared to short and intermediate stents, long stents (length ≥40 mm) were independent predictors of death from cardiac causes and death from any cause. However, intermediate stents were not independent predictors of death from cardiac causes and death from any cause compared to short stents.

Stent length and TLF except periprocedural MI

Approximately, 3 to 6% of patients have periprocedural MI following PCI and several studies have reported that periprocedural MI is associated with in increased risk of morbidity and mortality[25-27]. In our study, periprocedural MI occurred in 254 (5.4%) patients and 4-year rate of TLF except periprocedural MI was significantly higher in longer stent group. After PCI, a number of factors have been associated with periprocedural MI, related to the patients, lesion, and the procedure itself. In order to minimize the effect of various factors on periprocedural MI and to investigate the effect of stented length on long term outcome, an analysis of target lesion failure except periprocedural MI was also performed. After adjustment, stented length was non an independent predictor of TLF except periprocedural MI. However, long stents, not intermediate stents were associated with significantly higher risk of death from cardiac causes and those from any causes, even after adjustment for periprocedural MI. Commercially available new-generation DESs predominantly measure 38 mm in length, and PCI for long lesions length ≥40 mm may require the implantation of two or more stents. These findings suggest that a long coronary lesion may be defined as that requiring a stented length ≥40 mm in the current DES era.

In our study, patients with longer stents had a higher rate of concomitant medical illnesses and greater extent of CAD, which may increase the risk of poor outcomes. In addition, patients with longer stents showed significantly lower rates of complete revascularization, suggesting that they were being treated with a more conservative strategy. Considering that incomplete revascularization is associated with poor clinical outcomes, patients requiring long stents may have an additional risk of poor outcomes[28]. CABG, compared to PCI with DESs,

is more likely to result in the achievement of complete revascularization in patients with complex CAD, leading to better clinical outcomes. Therefore, further study may be needed to compare the efficacy of CABG versus PCI with DESs in patients with long lesions requiring a stented length greater than 40 mm[29].

Limitations

First, owing to the observational design of the study, the overall findings should be considered as being of a hypothetical and hypotheses-generating nature only. Second, as the choice of treatment was left to the physician, our findings are subject to selection bias. Third, as most of the patients in our study were Asians, it remains uncertain whether the findings can be applied to other ethnic or social groups with different patient and procedural characteristics. Fourth, owing to the limited number of hard clinical endpoints, our study was underpowered for the detection of significant differences in serious safety outcomes such as stent thrombosis. Finally, longer follow-up durations are required to examine whether additional differences may emerge in the rate of late-occurring events among new-generation DESs.

CONCLUSION

Among patients with significant CAD undergoing PCI with new-generation DESs, long stent implantation (length $\geq$40 mm) was associated with a higher risk for TLF and death than short or intermediate stent implantation. In the current DES era, it may be appropriate to redefine long lesions as those requiring a stented length $\geq$40 mm.

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국문요약

배경: 관상동맥중재술에 약물 용출 스텐트의 사용이 증가함에 따라 20mm 이상의 스텐트의 사용이 증가하고 있으나 이러한 스텐트 사용에 따른 장기적 효과와 안정성에 대한 근거는 부족하다. 본 연구에서는 새로운 약물 용출성 스텐트를 이용하여 관상동맥중재술을 받은 환자를 대상으로 스텐트의 길이가 예후에 미치는 영향을 분석하고자 한다.

방법 및 결과: 새로운 약물 용출성 스텐트를 이용하여 관상동맥중재술을 시행 받은 4,722 명의 환자를 후향적으로 모집하였다. 환자들은 짧은 길이 스텐트 (스텐트 길이 <20 mm, n=1,050), 중간 길이 스텐트 (스텐트 길이 ≥20 mm, <40 mm, n=2,672), 긴 길이 스텐트 (스텐트 길이 ≥40 mm, n=1,000) 그룹으로 나누어 분석하였다. 본 연구의 일차 연구종료점은 심장질환으로 인한 사망, 목표혈관 심근경색, 목표혈관 재개통술의 복합사건으로 정의되는 목표병변 실패로 정의하였다. 중앙값 49.1 개월의 추적관찰 기간동안, 4 년 시점에서의 목표병변의 실패는 스텐트 길이가 증가함에 따라서 유의하게 증가하였다. (짧은 길이 스텐트 그룹; 5.1%, 중간 길이 스텐트 그룹; 9.1%, 길 길이 스텐트 그룹; 18.1%, p<0.001). 심혈관계 원인을 인한 사망 및 목표혈관 심근경색의 발생도 짧은 길이 및 중간 길이 스텐트에 비교하여 긴 길이 스텐트 그룹에서 더 많이 발생하였다. 긴 길이 스텐트는 짧은 길이 스텐트와 비교하여 모든 원인의 사망 및 심혈관계 사망의 예후 인자였으나 중간 길이 스텐트는 유의하지 않았다.

결론: 새로운 약물 용출성 스텐트를 이용하여 관상동맥중재술을 받은 환자에서 40 mm 이상의 긴 길이의 스텐트는 짧은 길이 및 중간길이 스텐트와 비교하여 목표병변 실패 및 사망의 위험도가 증가하였다. 현재의 새로운 약물 용출성 스텐트 시대에는 40 mm 이상의 스텐트를 삽입하는 경우를 긴 스텐트로 정의하는 것이 적절하다고 판단된다.