

Lesion Length Impacts Long Term Outcomes of Drug-Eluting Stents and Bare Metal Stents Differently

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Abstract

Background: Long lesions have been associated with adverse outcomes in percutaneous coronary interventions with bare metal stents (BMS). However, the exact impact of lesion length on the short- and long-term outcomes of drug-eluting stent (DES) implantations is not as clear.

Methods and Results: This study compared the impact of lesion length on angiographic and clinical outcomes of BMS and DES in a single-center prospective registry. Lesion length was divided into tertiles. The primary endpoints were angiographically defined binary in-stent restenosis (ISR) rate and major adverse cardiac event (MACE). Of the 4,312 de novo lesions in 3,447 consecutive patients in the CAPTAIN registry, 2,791 lesions (of 2,246 patients) received BMS, and the remaining 1,521 lesions (of 1,201 patients) received DES. The mean follow-up duration was 4.5 years. The longer the lesion, the higher the ISR rate (14%, 18%, and 29%, $p < 0.001$) and the lower the MACE-free survivals ($p = 0.007$) in the BMS group. However, lesion length showed no such correlation with ISR rates (4.7%, 3.3%, and 7.8%, $p = 0.67$) or MACE-free survivals ($p = 0.19$) in the DES group.

Conclusions: In our single-center prospective registry, lesion length defined in tertiles has no impact on the short-term (ISR) or long-term (MACE) outcomes of patients implanted with DES. In contrast, longer lesion correlates with higher ISR and MACE rates in BMS group.

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Introduction

The management of long coronary lesions has become increasingly important in clinical practice because of the rising incidence of long or complex lesions in aging populations and their increasing comorbidity [1]. In-stent restenosis (ISR) is one of the main challenges in treating long lesions with stents while major adverse cardiac events (MACE) free survival is the gold standard for stents comparisons. Generally speaking, drug-eluting stents (DES) have been shown to be more efficacious than bare metal stents (BMS) in reducing ISR and MACE [2–5]. Stent length and lesion length have both been reported as very important predictors of ISR in the BMS era [6–9]. These two factors are thought to be less important in the DES era because DES reduce ISR dramatically in almost every type of lesion [10–11]. On the other hand, the effect of lesion length on the long term outcomes in the DES era has been ignored. A very recent study suggested that longer stents are associated with increased MACE rates at 1 year [12]. The exact difference in impact of lesion length on the long term outcomes for BMS and DES, however, is not clear. To bridge this gap, this study was conducted with the aim of comparing the real impact of lesion length on BMS and DES in terms of ISR and MACE-free survival. Data were collected from a

prospectively created database, and angiographic follow-up was decided upon prior to data interpretation.

Methods

Subjects

The CAPTAIN (Cardiovascular Atherosclerosis and Percutaneous TrAnsluminal INterventions) registry is a physician-initiated prospective single-center observational study in a tertiary medical center, which enrolls consecutive patients undergoing stent implantation.

Both short and long term outcomes of stent implantations are examined in this paper. For short-term outcomes, a total of 4,745 consecutive patients with de novo native coronary artery lesions who had undergone successful emergency or elective percutaneous coronary intervention (PCI) at this hospital between November 1996 and December 2010 were registered. Patients were referred for coronary angiography based on angina, an abnormal stress test, or elevated markers of myocardial damage. Because of different timelines of restenosis between BMS and DES, follow-up angiographies were performed for 4,312 target lesions in 3,447 patients at either 6 months (in the BMS group) or 9 months (in the DES group) after the index procedure [13–18]. For long term

outcomes, patients were scheduled to undergo clinical follow-up at 30 days, 6, 9, 12 months, and thereafter annually. The stents used in this study were either BMS (Palmaz-Schatz, Crown, Bx, Multi-link, Duet, Tristar, Penta, Pixel, Express, Liberte, S7, Driver, and Vision), or DES (Cypher, Taxus, Endeavor, Xience V). The BMS used in this study measured between 2.5 mm and 5 mm in diameter and between 7 mm and 38 mm in length. The DES used were between 2.25 and 4 mm in diameter and between 12 and 38 mm in length. After stent implantation, dual antiplatelet treatment of aspirin and a thienopyridine derivative (ticlopidine, 200 mg/day or clopidogrel, 75 mg/day) was to be maintained for 3–12 months. Thereafter, the decision regarding the duration of dual antiplatelet therapy was left to the discretion of each attending physician. Lifelong use of aspirin was suggested after the procedure except when a contraindication existed.

Lesions were classified into tertiles, and cut points were 14 and 21 mm for the BMS group and 16 and 24 mm for the DES group. If a patient had multiple stent implantations, the longest lesion was used in analysis.

Definition of endpoints

The primary endpoints are binary ISR and MACE. Binary ISR at follow-up was defined as a stenosis occupying $\geq 50\%$ of vessel diameter and occurring in the segment inside the stent or within a 5 mm segment proximal or distal to the stent. MACE was defined as a composite of cardiac death, ST-elevation and non-ST-elevation myocardial infarction (MI), coronary artery bypass grafting (CABG), or target lesion revascularization (TLR). An independent researcher unaware of the patient's treatment reviewed all clinical end points during follow-up. Lesion length was measured as the length of contiguous coronary narrowing (defined as percent diameter stenosis $>50\%$) [19]. Angiographic variables derived from the index procedure and restudy, including absolute lesion length, stent length, reference vessel diameter, minimal luminal diameter, percent diameter stenosis, and late loss, were measured by automated edge detection or a digital caliper before and after stent deployment at baseline and follow-up coronary angiography, using the contrast-filled guiding catheter as a calibration reference [20]. A small vessel was defined as one having a pre-procedural reference diameter of less than 2.5 mm. Baseline clinical characteristics were collected during the index procedure. Lesions were qualitatively classified using the modified American College of Cardiology/American Heart Association grading system.

Statistics

Categorical data were shown as percentages and compared between groups using chi-square. Continuous variables are presented as the mean \pm standard deviation, and comparisons were made by analysis of variance (ANOVA). Spearman rank correlation was applied for association between ordinal variables. Cumulative curves for MACE were obtained using the Kaplan-Meier method and the groups were compared in terms of survival on log-rank tests. Data analysis was performed using STATA version 10 (StataCorp LP, College Station, TX, USA). A p value <0.05 was considered significant.

Results

In a 14-year period, 3,447 patients were entered into a prospectively collated database. Angiographic follow-ups were 80% and 79% in the BMS and DES groups, respectively. ISR and late loss were assessed angiographically in 4,312 lesions (2,791 implanted with BMS and 1,521 with DES). MACE was followed

in 3,447 patients (2,246 patients with BMS and 1,201 with DES). In both the BMS and DES groups, the patients had generally similar demographic and baseline clinical characteristics irrespective of lesion length, with the following exceptions: In the DES group, the middle subgroup had the lowest incidence of hypertension (Table 1). Lesion characteristics distribute similarly in the BMS and DES groups. The reference diameter of the target lesions in all subgroups for either BMS or DES was about 3.2 mm. In both BMS and DES groups, longer lesions were more calcified, more complex, and had been treated by multiple stents. The incidence of small vessels was generally very low in all subgroups (Table 2).

The overall angiographic ISR rate was much higher for the BMS group than for the DES group (20.3% vs. 5.3%, $p < 0.001$). In the BMS group, the ISR rate correlated perfectly with lesion length (14%, 18%, and 29%, Spearman's $\rho = 1$, $p < 0.001$) (Figure 1). However, ISR rates showed no such correlation with lesion length in the DES group (4.7%, 3.3%, and 7.8%, Spearman's $\rho = 0.5$, $p = 0.67$).

On chronic results, BMS and DES patients were both divided into tertiles based on lesion length. The BMS patients were followed up for ten years, and the DES patients were followed up for eight years. The survival curve for the BMS group shows that lesion length affected survival rates ($p = 0.007$). On the other hand, the survival rates of DES patients did not differ among the lesion length tertiles ($p = 0.19$) (Figure 2).

Discussion

This study presents three major findings. First, the DES group had much lower ISR and better MACE-free survival than the BMS group at any lesion length. Second, ISR rates correlated perfectly and positively with lesion lengths in the BMS group. However, lesion length had no such correlation to ISR in the DES group. Finally, longest lesions had the worst long-term MACE-free survival in the BMS group while such results were not as pronounced in the DES group.

Lesion length and stent length have been reported as important predictors of ISR for various types of BMS and DES [19]. From a very early stage of coronary intervention, studies have shown that shorter BMSs were associated with fewer clinical events and lower ISR rates [21]. Stented segment length was also found to be an important and independent predictor of restenosis when using various types of BMS in more than 1000 lesions [6]. Kereiakes et al, in their meta-analysis of 4 multi-link stent trials, described a fairly linear correlation between stent lengths and IRS rates for stents in 6 length groups [22]. That assertion is supported by the present study, in which we also observed that in the BMS group, the longer the lesion length, the higher the ISR rates. Similarly, stent length and lesion length have been reported as independent predictors of IRS in various DES such as sirolimus-eluting stents [23–25]. However, in the present study we did not see the same result. According to our data, lesion length has no significant effect on ISR rate for DES until lesions are longer than 24 mm.

Several studies have suggested that longer lesions were associated with higher MACE rates in the BMS and DES eras [12,26,27]. Our results showed similar results in the BMS group, but not in the DES group. Although different populations, follow-up protocols, and definitions of endpoints prevented direct comparisons between this and these observational studies, our study is distinctive in its very long follow-up time frame. In both BMS and DES groups, most of the MACEs were contributed mainly by TLR performed in scheduled angiography. The impact of lesion length on MACE in BMS would have been much smaller

Table 1. Clinical characteristics.

Tertile (mm)	BMS (n = 2,246)			DES (n = 1,201)			BMS vs. DES (p)	
	Shortest (<14) (n = 812)	Middle (14–21) (n = 825)	Longest (>21) (n = 609)	Shortest (<16) (n = 401)	Middle (16–24) (n = 411)	Longest (>24) (n = 389)	P	P
Age (years)	61 ± 10	61 ± 11	60 ± 11	62 ± 12	61 ± 12	60 ± 11	NS	60.8 ± 0.2 vs. 60.9 ± 0.3 (NS)
Male (%)	82	83	83	81	84	81	NS	82.3 vs. 82 (NS)
Hypertension (%)	51	48	49	60	52	59	0.04	50.7 vs. 57 (<0.001)
Diabetes (%)	23	22	22	26	26	28	NS	23 vs. 27.3 (0.003)
Smoking (%)	50	49	50	38	42	41	NS	49.6 vs. 40.7 (<0.001)
Dyslipidemia (%)	58	60	62	53	55	54	NS	59.5 vs. 53.8 (0.001)
% of diseased coronary arteries							0.02	(NS)
1-vessel	37	43	43	40	46	39		40.7 vs. 41.6
2-vessel	34	33	32	33	31	35		33.1 vs. 33
3-vessel	26	23	24	24	22	25		24.5 vs. 23.77
Left main	3	1	1	3	1	1		1.6 vs. 1.6

Values are mean ± SD where appropriate. BMS, bare metal stent; DES, drug-eluting stent NS, not significant. doi:10.1371/journal.pone.0053207.t001

Table 2. Lesions and Procedural Characteristics.

Tertile (mm)	BMS (n = 2,791)			DES (n = 1,521)			BMS vs. DES (p)	
	Shortest (<14) (n = 906)	Middle (14–21) (n = 1,012)	Longest (>21) (n = 873)	Shortest (<16) (n = 447)	Middle (16–24) (n = 519)	Longest (>24) (n = 555)	P	P
Lesion length (mm)	12.1±2.2	16.9±2.2	29.4±8.8	12.6±2.2	19.1±1.9	33.8±13	<0.0001	18.3±0.2 vs. 22.6±0.3 (<0.0001)
Reference (mm)	3.2±0.5	3.2±0.5	3.1±0.5	3.2±0.5	3.2±0.4	3.2±0.4	NS	3.18±0.01 vs. 3.19±0.01 (NS)
Multiple stents (%)	0	2	23	0	1	34	<0.0001	8 vs. 12.9 (<0.0001)
AHA type B2+C (%)	60	74	97	71	82	98	<0.0001	76.9 vs. 84.6 (<0.0001)
Lesion site (%)							<0.0001	NS
Left Main	4	1	1	4	1	2		2.2 vs. 2.2
LAD	44	45	51	44	50	51		47.7 vs. 50.8
LCX	18	19	12	22	19	12		17.1 vs. 17.8
RCA	29	33	34	23	26	34		33 vs. 29.3
Calcification (%)	13	13	25	12	11	16	0.04	16.7 vs. 12.9 (0.0001)
Angulated >45° (%)	7	6	7	3	2	2	NS	6.7 vs. 2.1 (<0.0001)
Eccentric (%)	58	49	36	46	43	31	<0.0001	48 vs. 39.6 (<0.0001)
Small vessel (%)	8	4	5	3	4	1	0.003	5.8 vs. 2.7 (0.0001)
Bifurcation lesion (%)	11	10	10	11	11	10	NS	10 vs. 10.1 (NS)
Ostial lesion (%)	9	4	6	14	7	8	<0.0001	6.1 vs. 9.6 (<0.0001)
Chronic total occlusion (%)	5	12	22	10	24	24	<0.0001	13 vs. 20 (<0.0001)
Angiographic follow up								
Late loss (mm)	0.9±0.6	1±0.66	1.2±0.7	0.38±0.58	0.35±0.56	0.51±0.7	<0.0001	1.05±0.01 vs. 0.42±0.02 (<0.0001)
Restenosis (%)	14	18	29	4.7	3.3	7.8	0.004	20.3 vs. 5.3 (<0.0001)

BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery. doi:10.1371/journal.pone.0053207.t002

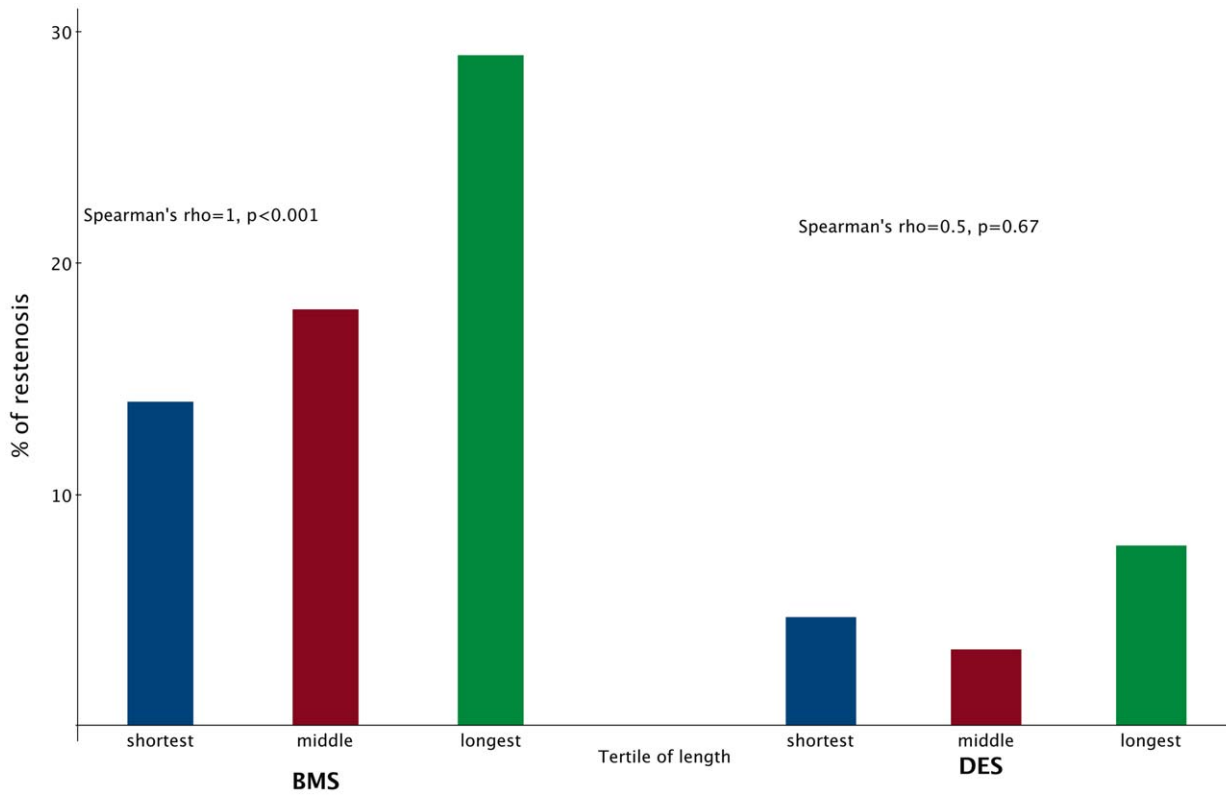


Figure 1. Intra-stent restenosis rate defined by scheduled angiographic follow-up of various lesion length. BMS: bare metal stent. DES: drug-eluting stents.

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if only “hard” endpoints such as cardiac deaths and myocardial infarctions had been considered as endpoints.

To our knowledge, this report is the first one that has directly compared IRS or very long term MACE-free survival between BMS and DES for every lesion length subgroups of a single registry. DES decreases IRS more dramatically than does BMS [23,28]. For example, Dawkins reported 12% vs. 36% ISR rates of DES vs. BMS in a TAXUS VI trial [29]. The present study supports these findings. Most data from numerous trials regarding lesion length and ISR in the DES era showed that DES resolved the issue of restenosis in lesions of various lengths [30,31]. Again, this paper supports that conclusion, but only for lesions that are shorter than 24 mm. DES is still superior to BMS in lesions longer than 24 mm, but the advantage is not as great as in shorter lesions.

The results of this study may have some clinical implications for the daily practice of interventional cardiologists. DES has lessened the impact of lesion length on ISR rate and MACE-free survival to some degree; therefore operators might feel comfortable in deploying DES for long lesions. One should be aware that some long lesions in this study (23% in BMS and 34% in DES) were covered by multiple overlapping stents, implying that DES were more effective in treating long lesions even when multiple stenting was involved. For example, Råber et al. reported a relatively high (18%) target lesion revascularization rate in 333 patients who had received multiple and overlapping DES [32]. However, before further evidence becomes available, one may argue that lesion length per se—instead of being a true underlying reason for higher ISR rate in the DES group—might merely be a surrogate for many other factors such as severity of disease, flow reserve, local inflammation, or lesion complexity. For example, the extent of intimal hyperplasia is significantly greater in lesions treated with

longer stents [33]. Therefore, more studies regarding the pathological effects of lesion length are needed. Nevertheless, lesion length is still a convenient parameter for making clinical decisions and predicting outcomes.

The present study has several limitations that should be mentioned. First, this is a registry observation from a single center, so the choice of stents and follow-up angiography might be biased considerably by operators, patients, or the availability of devices. Second, optimal medication choices, especially antiplatelet therapy, the technique and concept of percutaneous coronary intervention, and the design of devices, were evolving greatly during the long period of this study, the effect of which this analysis did not take into account. The difference of ticlopidine and clopidogrel, however, were examined, and it showed no effects on MACE. (Figure S1 of supplement data) Third, a major consideration that should be emphasized is the heterogeneity of DES. Recent randomized trials have shown that second-generation DES are superior to first-generation DES (especially palitaxel-eluting stents) in their ability to lower incidence of restenosis [34]. However, the very long term follow-up frame might have partially compensated for these limitations. The ‘all comers’ design of this study, which included a variety of stents, lesions, and patients, should be able to reflect the true impact of lesion length in the real world.

In conclusion, lesion length has different effects on ISR rates and MACE-free survival in BMS and DES in the real world. Lesion length positively associates with ISR rate for BMS, and longest lesions have the worst MACE-free survival. DES considerably lowers the effects of lesion length on ISR rates and MACE-free survival.

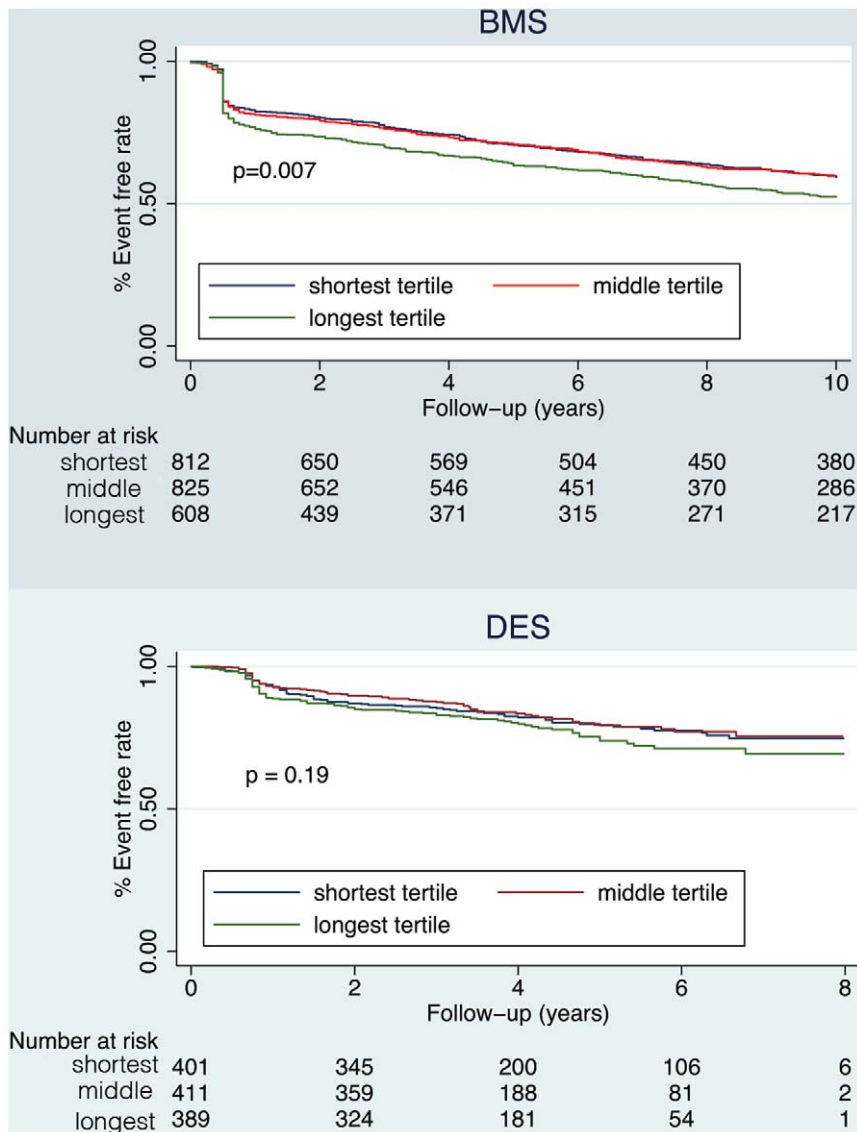


Figure 2. Kaplan-Meier estimates: major adverse cardiac events (MACE) free survival of patients with various lesion length. BMS: bare metal stent. DES: drug-eluting stents.
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Supporting Information

Figure S1 MACE free survival of BMS group before and after clopidogrel era were similar. (Logrank $p = 0.5$). Blue line indicates the survival curve of patients treated with ticlopidine while red line indicates the curve of patients treated with clopidogrel. (DOC)

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Author Contributions

Conceived and designed the experiments: SHC ICH. Performed the experiments: CCC MJH CYW CHL. Analyzed the data: SHC. Contributed reagents/materials/analysis tools: CCC MJH CYW CHL. Wrote the paper: SHC ICH.

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