Clinical Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2017, Vol. 45(4) 1406–1416

DOI: 10.1177/0300060517708515
journals.sagepub.com/home/imr
SAGE

Over-expansion of drug-eluting stents in patients with left main coronary artery disease: An *in vivo* study

Yicong Ye, Hao Qian, Ming Yang, Xueqing Zhu, Tianpeng Gan, Shuyang Zhang and Yong Zeng

Abstract

Objective: We aimed to determine the capacity of drug-eluting stent (DES) over-expansion in left main coronary artery disease.

Methods: Left main interventions with the largest available DES platforms (4.0 mm) and post-dilation performed with large non-compliant balloons ($\geq$ 4.5 mm) were included. Maximal stent diameter (mm) and area (mm^2) were measured using post-intervention intravascular ultrasound (IVUS). Stent diameter and area were calculated with the balloon diameter and inflation pressure. The diameter and area expansion indices were defined as follows: maximal/calculated stent diameter and maximal/calculated stent area, respectively.

Results: Twenty-three consecutive patients were included. The maximal stent diameter was 4.40 mm (4.30–4.80 mm), and 22 of 23 patients showed a diameter expansion index greater than 0.90. The area expansion index was 0.862. The expansion index $<$ 0.85 group had a significantly higher percentage of calcification $\geq 90^{\circ}$ on IVUS than did the expansion index $\geq$ 0.85 group (72.7% versus 16.7%, $P = 0.007$). One stent fracture occurred during over-expansion and one ischemic event occurred during follow-up.

Conclusions: DESs with a nominal diameter of 4.0 mm can be effectively over-expanded in left main coronary artery disease. Achievement of predicted stent area can be affected by calcification.

Keywords

Coronary stent, over-expansion, left main coronary artery

Date received: 1 January 2017; accepted: 13 April 2017

Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College, China

Corresponding authors:
Yong Zeng and Shuyang Zhang, Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100730, China.
Emails: pumchzy@163.com; pumchzhangsy@163.com

Introduction

The left main coronary artery (LMCA) is the initial portion of the left coronary artery circulation, which supplies the majority of the left ventricle. Significant LMCA disease, which is commonly defined as narrowing of the luminal diameter of greater than 50%, is considered the highest risk coronary artery disease subtype and is associated with a poorer prognosis than non-LMCA disease.[1] Before the era of drug-eluting stents (DESs), percutaneous interventions involving the LMCA were associated with considerable risks of acute complications and early mortality,[2,3] as well as long-term restenosis.[4] Therefore, for the last several decades, coronary artery bypass grafting (CABG) has been the standard revascularization treatment for LMCA lesions.

The results of recent, randomized, controlled, trials have shown that the performance of PCI with DESs has comparable cardiac adverse event rates with those of CABG in patients with LMCA disease, especially in patients with less anatomically complex lesions.[5–9] On the basis of these favourable findings, the current guidelines recommend performing PCI as an alternative revascularization strategy for treatment of LMCA lesions with low or intermediate anatomic complexity (Class II).[10,11]

One of the major issues associated with LMCA PCI procedures is the large reference diameter of the left main stem. Several intravascular ultrasound (IVUS) studies have shown that the maximal LMCA diameter can be up to 4.8–5.5 mm,[12,13] while the maximal diameter of most commercially available DESs is 4.0 mm. Stent over-expansion with larger post-dilation balloons may be the only method of reducing the risk of incomplete stent apposition. The over-expansion capacity of contemporary DES platforms has been thoroughly investigated in several *in vitro* studies,[14–16] while *in vivo* data regarding this phenomenon are still limited. Therefore, we aimed to determine the efficacy and safety of over-expansion of the current commercially available DESs (4.0 mm) in patients with LMCA disease.

Materials and methods

This was a single-centre, retrospective study. All PCIs performed between January 2013 and June 2016 were retrospectively reviewed to identify the LM interventions that met the following inclusion criteria: (1) interventions performed on *de novo* LMCA lesions, (2) interventions performed using DESs with a nominal diameter of 4.0 mm, (3) interventions involving post-dilation using non-compliant balloons with a nominal diameter of no less than 4.5 mm, (4) and interventions in which IVUS measurements were performed before stent deployment and after the final post-dilation. The following interventions were excluded from the study: (1) interventions involving use of the two-stent technique for LM bifurcations and (2) interventions in which post-dilation was performed with the kissing balloon technique. The appropriate institutional review board approved the study and informed consent was obtained from each patient.

IVUS measurement protocol

All IVUS images were independently reviewed and analysed by a skilled interventional cardiologist who was blinded to the nominal diameters and inflation pressure of the post-dilation balloons. An Eagle Eye® catheter (Volcano Europe BVBA, Brussels, Belgium) was used for pre- and post-interventional IVUS measurements. A total of 100 μg of intracoronary nitroglycerin was injected before each measurement. The ultrasound images were recorded from the left anterior descending or left circumflex artery to the left main ostium. A validated computer-based contour detection program allowed semi-automatic detection of the lumen, stent, and vessel boundaries in

longitudinally reconstructed views of the region of interest.

IVUS data analysis

Quantitative analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies.[17] For the pre-interventional IVUS measurements, the left main lesion segment with the smallest luminal cross-sectional area was selected, and the following parameters were measured: (1) minimal lumen diameter (mm), (2) minimal lumen area (mm^2), and (3) plaque burden. For the post-interventional IVUS measurements, the left main in-stent segment with the largest in-stent area was selected, and the following parameters were measured: (1) maximal stent diameter (mm) and (2) maximal stent area (mm^2). Additionally, the left main in-stent segment with the smallest in-stent area was selected for measuring the minimum stent area (mm^2). We used the maximal stent diameter/area mainly because it is more likely to be affected by the plaque burden and plaque components than by stent over-expansion capability. Calcification was measured in degrees using the semi-quantitative grading method in the location of maximal stent area measurement.[17] Calcification was divided into two categories: (1) $< 90^\circ$, less than one quadrant; and (2) $\geq 90^\circ$, no less than one quadrant.

The predicted stent diameter (mm) was calculated using the balloon diameter and inflation pressure of the final post-dilation based on the data provided by the manufacturers. The predicted stent area (mm^2) was defined as follows: $\pi \times (\text{predicted stent diameter}/2)^2$. The diameter expansion index was defined as the ratio of the maximal stent diameter to the predicted stent diameter after post-dilation. The area expansion index was defined as the ratio of the maximal stent area to the predicted stent area after post-dilation.

Statistical analyses

Categorical variables are shown as numbers (percentages). Continuous data are shown as medians (interquartile ranges). Spearman correlation analysis was used to determine the correlation between the maximal stent diameter and predicted stent diameter, as well as the correlation between the maximal/minimal stent area and predicted stent area. The Mann–Whitney U test and chi-square test were used for intergroup comparison of continuous and categorical variables, respectively. The multiple regression model was used to further determine the potential factors associated with stent expansion. Statistical analyses were performed with the SPSS statistical software package (version 20.0, IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 5.0, GraphPad Software Inc., San Diego, CA, USA).

Results

A total of 23 consecutive patients were eligible for inclusion in this study. Most of the patients were men and the median age of the study population was 66 years. Acute coronary syndrome was the major indication for PCI (87.0%) and most of the lesions featured bifurcations (78.3%). The baseline and angiographic characteristics of the study population are summarized in Table 1. Four commercially available DESs with the largest stent platform were analysed, including the PROMUS Element™ (N = 5), XIENCE Xpedition™ (N = 8), Resolute Endeavor™ (N = 7), and Partner™ (N = 3) stents. The designs of these four DESs are shown in Table 2.

All of the included patients' IVUS images were suitable for analysis. The maximal stent diameter was 4.40 mm (interquartile range: 4.30–4.80 mm) (Figure 1(a)) and the

Table 1. Baseline and angiographic characteristics of the study population.

Variables	N = 23
Male, n (%)	20 (87.0%)
Age, years*	66 (56-68)
Hypertension, n (%)	13 (56.5%)
Diabetes, n (%)	6 (26.1%)
Current smoker, n (%)	15 (65.2%)
Family history of coronary artery disease, n (%)	4 (17.4%)
Dyslipidemia, n (%)	16 (36.6%)
Previous revascularization	
PCI, n (%)	3 (13.0%)
CABG, n (%)	0 (0%)
Indication for PCI	
Acute coronary syndrome, n (%)	20 (87.0%)
Stable angina, n (%)	3 (13.0%)
Left main lesions	
Bifurcation, n (%)	18 (78.3%)
Ostium/shaft, n (%)	5 (21.7%)
Left ventricular ejection fraction	
>50%, n (%)	20 (87.0%)
30-50%, n (%)	2 (8.7%)
<30%, n (%)	1 (4.3%)
Rotablation, n (%)	1 (4.3%)

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.
*Data are presented as median (interquartile range).

maximal stent area was 14.0 mm (interquartile range: 13.1–15.6 mm) (Figure 1(b)). The diameter expansion index was 0.968 (interquartile range: 0.940–1.004), and 22 of 23 patients had diameter expansion indices greater than 0.90 (Figure 1(c)). The maximal stent diameter was linearly correlated with the calculated stent diameter, with a correlation coefficient of 0.718 ($P < 0.001$) (Figure 2). However, the area expansion index was only 0.862 (0.806–0.917). There was also a linear correlation between the maximal stent area and calculated stent area (correlation coefficient: 0.562, $P < 0.001$) (Figure 2). There was no significant association between the minimal stent area and calculated stent area (correlation coefficient: 0.38, $P = 0.073$) (Appendix Figure 4)

According to the area expansion indices of the patients, the patients were further divided into the following two groups: the expansion index ≥ 0.85 group (N = 12) and the expansion index < 0.85 group (N = 11). There were no significant differences in LMCA lesion characteristics, minimal lumen diameter/area before PCI, stent length, stent deployment pressure, post-dilation balloon diameter, and post-dilation

Table 2. Design of four different drug-eluting stents.

DES	Largest platform	Metal material	Drug coating	Crown	Connectors	Manufacturers	Maximal diameter recommended by manufacturers
PROMUS Element™	4.0 mm	PtCr	Everolimus	10	2	Boston Scientific, Natick, MA, USA	4.75 mm
XIENCE Xpedition™	4.0 mm	CoCr	Everolimus	9	3	Abbott Vascular, Santa Clara, CA, USA	4.5 mm
Resolute Endeavor™	4.0 mm	CoCr	Zotarolimus	10	2-3	Medtronic, Minneapolis, MN, USA	4.5 mm
Partner™	4.0 mm	Stainless steel	Sirolimus	9	3	Lepu Medical, Beijing,China	4.25 mm

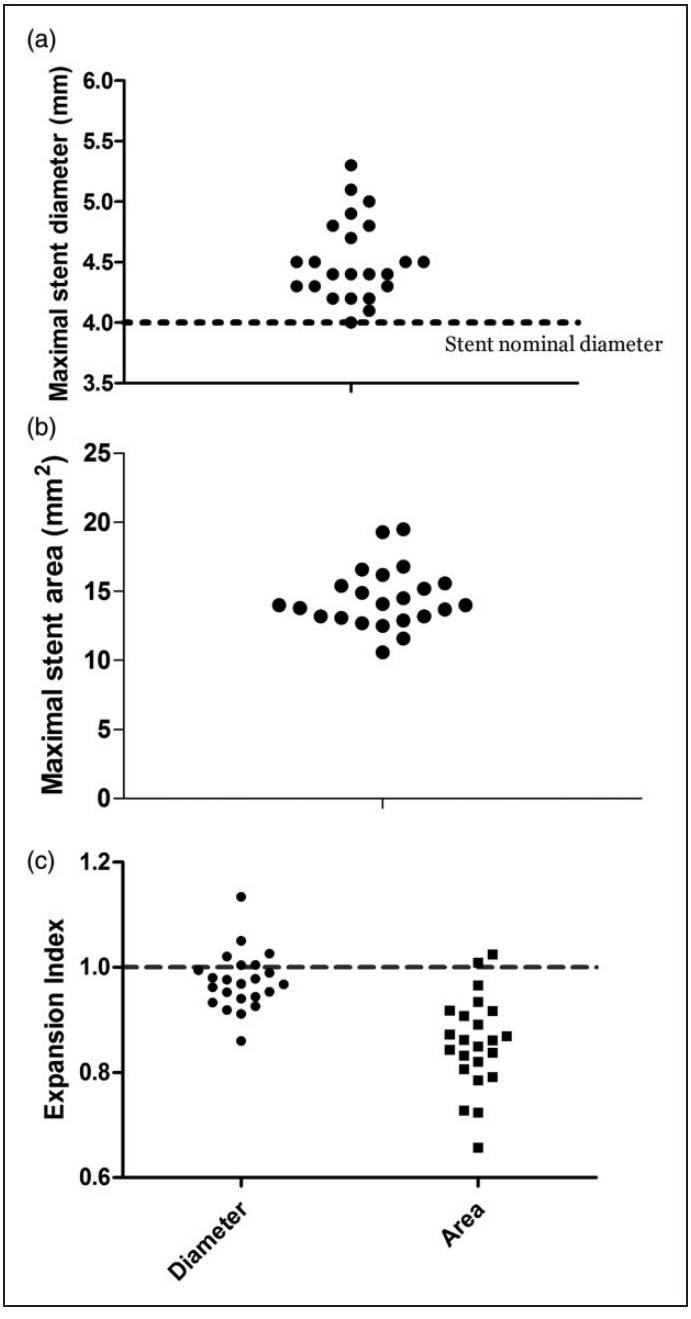

Figure 1. Maximal stent diameter (a) and area (b) measured by post-intervention IVUS; diameter and area expansion indices of the included stents (c).

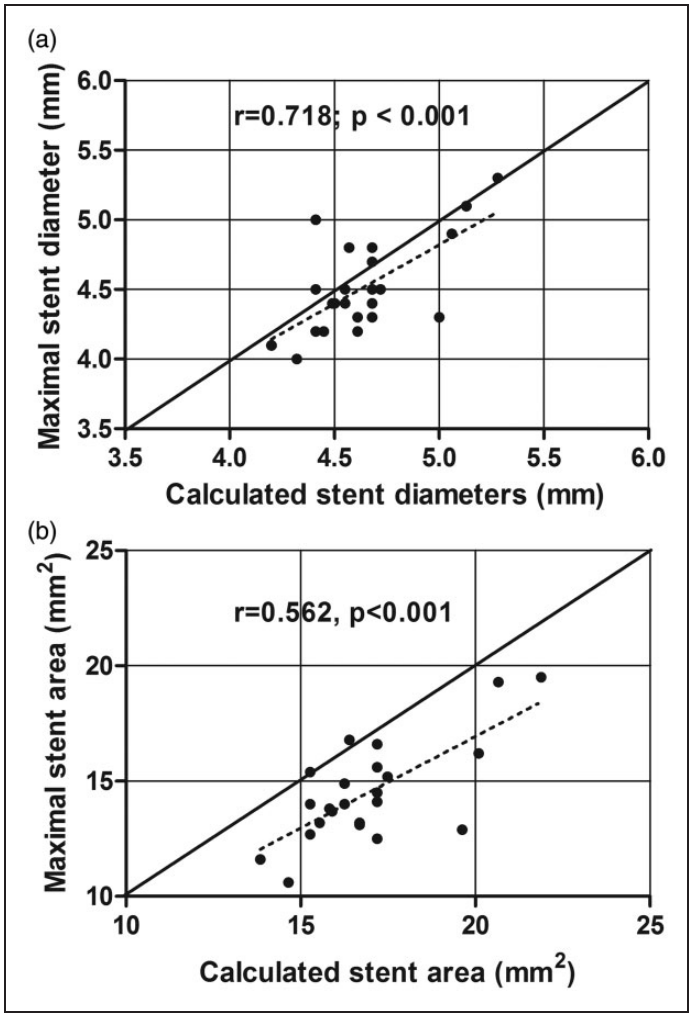

Figure 2. Relationship between the maximal stent diameter and calculated stent diameter (a); relationship between the maximal stent area and calculated stent area (b).

pressure between the two groups. However, there was a significant difference in IVUS calcification between the two groups. Patients with an expansion index < 0.85 had a significantly higher calcification percentage $\geq 90^\circ$ on IVUS than did patients with an expansion index ≥ 0.85 (72.7% versus 16.7%, $P = 0.007$) (Table 3). In the multiple regression model, calcification ($\geq 90^\circ$) was still significantly associated with a lower expansion index (< 0.85), even after adjustment for bifurcation lesions, pre-intervention minimal lumen area, plaque burden, post-dilation balloon size, and pressure ($B = 4.056$, $P = 0.046$).

Only one adverse event occurred during the over-expansion process. This event occurred in a 50-year-old patient with isolated stenosis of the LMCA ostium. A PROMUS Element stent (4.0 mm $\times$ 16 mm) was deployed at 16 atm after pre-dilation of the lesion (Figure 3(a)). After post-dilation with a Quantum 5.0-mm $\times$ 8-mm stent at 16 atm (Figure 3(b)), the distal portion of

Table 3. Comparison of lesion characteristics, stents, and post-dilation balloon diameters between the expansion index (area) ≥ 0.85 and expansion index (area) < 0.85 groups.

	expansion index $\geq$0.85 (N = 12)	expansion index $<$0.85 (N = 11)	P value
Left main bifurcation lesion, n	8 (66.7%)	10 (91.7%)	0.159
Minimal lumen diameter before PCI, mm	2.20 (2.00 - 2.40)	2.20 (2.05-2.53)	0.749
Minimal lumen area before PCI, mm^2	6.30 (4.00-7.30)	4.65 (4.35-6.18)	0.378
Maximal plaque burden, %	69.5 (62.9-81.6)	74.1 (71.5-80.5)	0.181
IVUS calcification $\geq 90^{\circ}$, n	2 (16.7%)	8 (72.7%)	0.007
Stent length, mm	18 (15-20)	18 (15-20)	1.000
Stent deployment pressure, atm	14 (10-16)	12 (12-16)	0.950
Post-dilation balloon diameter	/	/	/
4.5 mm	10 (83.3%)	9 (81.8%)	0.924
5.0 mm	2 (16.7%)	2 (18.2%)	/
Post-dilation balloon pressure, atm	15 (12-20)	14 (12-18)	0.385

PCI: percutaneous coronary intervention; IVUS: intravascular ultrasound.

the stent fractured and the struts fell into the lumen (Figure 3(c)), as confirmed by IVUS (Figure 3(d), supplementary video). Another PROMUS 4.0-mm × 12-mm stent was immediately implanted to cover the fractured segment of the previous stent.

The medium follow-up duration was 16 months (6–27 months). One patient was admitted for revascularization because of in-stent restenosis of the target lesion.

Discussion

In this study, we attempted to determine the over-expansion capacity of DESs with a nominal diameter of 4.0 mm, as determined by IVUS. Our major finding was that over-expansion of DESs with post-dilation (4.5–5.0-mm post-dilation balloon) could effectively achieve the predicted stent diameter. However, the predicted stent area achievement varied, which could have been due to the presence of calcification.

An *in vitro* study showed that most of the current DES platforms could be over-expanded above their nominal diameters.[14] For DESs with the largest design (4.0 mm), a maximal stent diameter > 5.5 mm could be achieved using a 6.0-mm semi-compliant balloon at 14 atm.[14] However, the *in vivo* behaviour of these stents during the over-expansion process may vary considerably. Interactions between stents and plaques/arteries may cause recoil, deformation, and fracture of stents. Previous studies have shown that the magnitude of stent recoil reported *in vivo* is significantly greater than that reported in bench testing. In an *in vivo* animal study (Yorkshire pigs), Carrozza *et al.*[18] found that stent recoil can reach up to 30%, even after oversized post-dilation, in normal and compliant coronary arteries. Bermejo *et al.*[19] found that elastic recoil was one of the major mechanisms responsible for residual luminal stenosis in patients with coronary artery disease. Additionally, in their study, the luminal dimensions after stenting were only 57% of the maximal achievable luminal dimensions after high-pressure stent deployment, which was confirmed by subsequent studies.[20,21] Therefore, unlike previous *in vitro* studies,[14,16] our study provided direct *in vivo* evidence regarding over-expansion in patients with LMCA disease.

Notably, one adverse event involving an acute severe stent fracture, which is a rare complication of stent deployment, occurred

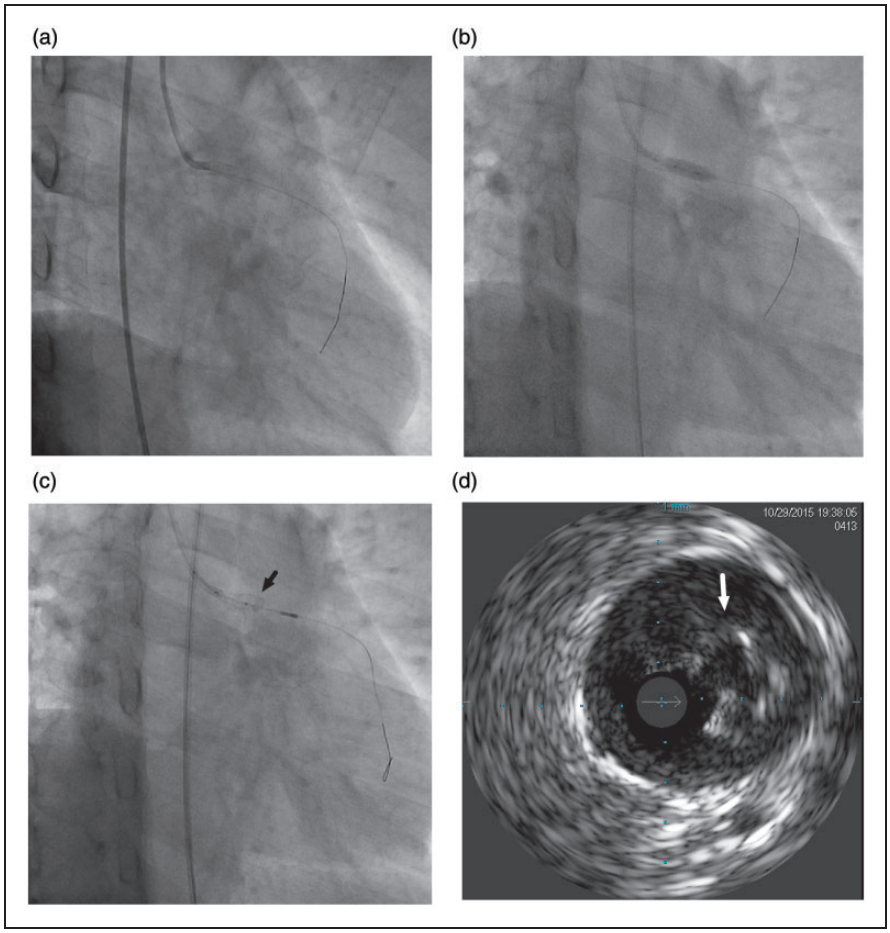

Figure 3. A case of acute stent fracture during the process of over-expansion.
(a) Image acquired immediately after stent deployment (PROMUS Element 4.0 mm × 16 mm); (b) post-dilation with a Quantum 5.0-mm × 8-mm stent at 16 atm; (c) distal portion of a fractured stent; (d) IVUS shows that the stent had fractured and that the struts had fallen into the lumen.

during over-expansion in our study. PROMOUS Element stents use a helical two-connector design to achieve maximal flexibility. However, this design may jeopardize the stability of the platform while the stent is over-expanded. Therefore, the number of connectors in PROMOUS Premier™ stents has been increased to five (4.0 mm platform) in the proximal stent segment to enhance radial strength. Although the findings of the current *in vitro* study showed that current DES platforms could be over-expanded to achieve a maximal stent diameter > 5.5 mm,[14] the following two points must be taken into consideration. The first point is regarding sample size. Only one stent for each platform is usually tested. The second point is regarding stent-plaque interactions. Plaque distribution and components can lead to variations in radial force in different parts of the stent during over-expansion. Moreover, significant crown deformation has been observed in most of the platforms when a maximal stent diameter >5.5 mm was achieved *in vitro*.[14]

Therefore, DES over-expansion *in vivo* should be applied with caution, especially when using stents with a predicted diameter > 5.0 mm.

The long-term outcome of DES over-expansion in this population is still unknown. Kuriyama et al.[22] reported that bare metal stent over-dilation resulted in a larger intimal-luminal dimension and provided a larger follow-up lumen. Unfortunately, follow-up IVUS data were not available in our study. Therefore, we were unable to assess the effect of over-expansion on intimal hyperplasia.

Our study has several limitations. First, because of the small sample size of the study, it may have been underpowered for detecting other potential differences between two groups. Second, as we mentioned above, follow-up IVUS results were not available for the patients who were included in this study. Third, we could not assess the effect of over-expansion on other DES parameters, such as drug coating and delivery. Finally, different stent types, and differences in lesion location and preparation may also have affected the final results of stent expansion.

Conclusion

The findings of our *in vivo* study indicate that DESs with a nominal diameter of 4.0 mm can be over-expanded in patients with LMCA disease. Achievement of the predicted stent area can be affected by the percentage of calcification. Stent fracture is a potential complication of over-expansion of stents *in vivo*.

Acknowledgements

None

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Lee PH, Ahn JM, Chang M, et al. Left main coronary artery disease: Secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol* 2016; 68: 1233–1246.
2. Tan WA, Tamai H, Park SJ, et al. Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. *Circulation* 2001; 104: 1609–1614.
3. Black A, Cortina R, Bossi I, et al. Unprotected left main coronary artery stenting: Correlates of midterm survival and impact of patient selection. *J Am Coll Cardiol* 2001; 37: 832–838.
4. Park SJ, Hong MK, Lee CW, et al. Elective stenting of unprotected left main coronary artery stenosis: Effect of debulking before stenting and intravascular ultrasound guidance. *J Am Coll Cardiol* 2001; 38: 1054–1060.
5. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 2008; 51: 538–545.
6. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (syntax) trial. *Circulation* 2010; 121: 2645–2653.
7. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 2011; 364: 1718–1727.
8. Fernández-Ruiz I. Coronary artery disease: CABG surgery or PCI for left main CAD? *Nat Rev Cardiol* 2016 Nov 17. [Epub ahead of print].
9. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease.

N Engl J Med 2017; 376: 1089. [Epub ahead of print].
10. Windecker S, Kolh P, et al.; Authors/Task Force members. 2014 ESC/EACTS guidelines on myocardial revascularization: The task force on myocardial revascularization of the European society of cardiology (ESC) and the European association for cardiothoracic surgery (EACTS) developed with the special contribution of the European association of percutaneous cardiovascular interventions (EAPCI). *Eur Heart J* 2014; 35: 2541–2619.
11. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines, and the American association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons. *Circulation* 2014; 130: 1749–1767.
12. Ge J, Erbel R, Gerber T, et al. Intravascular ultrasound imaging of angiographically normal coronary arteries: A prospective study in vivo. *Br Heart J* 1994; 71: 572–578.
13. Maehara A, Mintz GS, Castagna MT, et al. Intravascular ultrasound assessment of the stenoses location and morphology in the left main coronary artery in relation to anatomic left main length. *Am J Cardiol* 2001; 88: 1–4.
14. Foin N, Sen S, Allegria E, et al. Maximal expansion capacity with current des platforms: a critical factor for stent selection in the treatment of left main bifurcations? *EuroIntervention* 2013; 8: 1315–1325.
15. Ng J, Foin N, Ang HY, et al. Overexpansion capacity and stent design model: an update with contemporary des platforms. *Int J Cardiol* 2016; 221: 171–179.
16. Foin N, Alegria E, Sen S, et al. Importance of knowing stent design threshold diameters and post-dilatation capacities to optimize stent selection and prevent stent overexpansion/incomplete apposition during PCI. *Int J Cardiol* 2013; 166: 755–758.
17. Mintz GS, Nissen SE, Anderson WD, et al. American college of cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American college of cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol* 2001; 37: 1478–1492.
18. Carrozza JP. Jr, Hosley SE, Cohen DJ, et al. In vivo assessment of stent expansion and recoil in normal porcine coronary arteries: Differential outcome by stent design. *Circulation* 1999; 100: 756–760.
19. Bermejo J, Botas J, Garcia E, et al. Mechanisms of residual lumen stenosis after high-pressure stent implantation: A quantitative coronary angiography and intravascular ultrasound study. *Circulation* 1998; 98: 112–118.
20. Aziz S, Morris JL, Perry RA, et al. Stent expansion: A combination of delivery balloon underexpansion and acute stent recoil reduces predicted stent diameter irrespective of reference vessel size. *Heart* 2007; 93: 1562–1566.
21. Takano Y, Yeatman LA, Higgins JR, et al. Optimizing stent expansion with new stent delivery systems. *J Am Coll Cardiol* 2001; 38: 1622–1627.
22. Kuriyama N, Kobayashi Y, Kuroda N, et al. Effect of coronary stent overexpansion on lumen size and intimal hyperplasia at follow-up. *Am J Cardiol* 2002; 89: 1297–1299.

Appendix

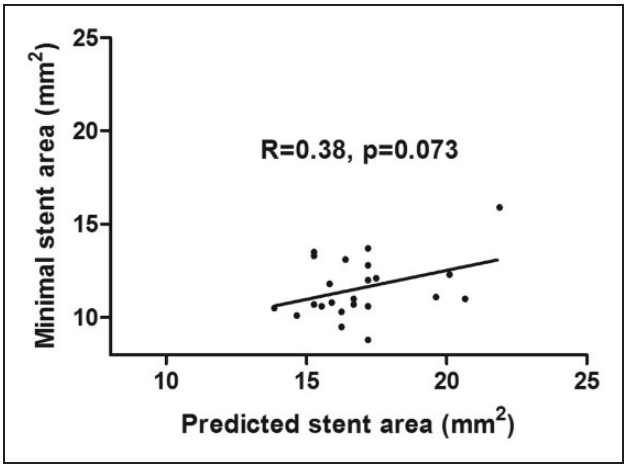

Figure 4. Relationship between minimal stent area and calculated stent area.