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Impact of Postoperative Lumen Gain on the Reduction of Restenosis Risk after Endovascular Treatment using Drug-coated Balloon for Femoropopliteal Lesions Assessed by Intravascular Ultrasound

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Aim: This study aimed to reveal whether a larger postprocedural minimum lumen area (MLA) would reduce restenosis risk after endovascular therapy (EVT) using drug-coated balloons (DCBs) in femoropopliteal (FP) lesions.

Methods: This retrospective, nonrandomized, single-arm, and multicenter registry analyzed patients with FP lesions undergoing intravascular ultrasound (IVUS)-guided EVT with DCB between 2017 and 2021. The primary outcome was restenosis 1 year after EVT. The association between IVUS-based MLA and restenosis risk was investigated using a generalized propensity score (GPS) method to address imbalance of baseline covariates. The dose–response function of IVUS-measured MLA for restenosis risk was developed using the GPS-adjusted Cox proportional hazards regression model.

Results: This study enrolled consecutive 489 patients with 595 lesions undergoing DCB treatment. The median MLA (interquartile range) was 13.20 (9.90–16.91) mm^2. Kaplan–Meier estimates showed that freedom from restenosis was 84.4% at 1 year. The GPS-adjusted dose–response function showed that MLA was inversely associated with restenosis risk. The upper limit of 95% confidence interval (CI) of the slope was lower than 0 between 10.6 and 17.0 mm^2 of MLAs. The 1-year cumulative incidence of restenosis was estimated to be 9.8% (95% CI, 5.8%–13.7%) for the 3rd quartile of MLA (16.91 mm^2) versus 18.5% (12.3%–24.1%) for the 1st quartile (9.90 mm^2), with a hazard ratio of 0.51 (95% CI, 0.39–0.67; $p<0.001$).

Conclusions: The present GPS analysis suggested that larger IVUS-measured MLA might be associated with lower risk of 1-year restenosis after DCB treatment for FP lesions.

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Key words: Infrainguinal endovascular, Angioplasty, Drug-coated balloon, Intravascular ultrasound

Introduction

The recent development in endovascular therapy (EVT) devices has reduced reintervention rates in femoropopliteal (FP) lesions[1-3], and the latest guideline of the European Society of Cardiology recommends EVT for FP lesions shorter than 25 cm (class I indication)[4]. Moreover, that of the Society of

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Cardiovascular Angiography and Interventions recommends drug-coated balloons (DCBs) as the first-choice EVT device for the treatment of FP lesions[5]. Randomized controlled trials (RCTs) have reported the superiority of DCB in primary patency (69.5%–79.8%) and freedom from target lesion revascularization (TLR) at 2 or 3 years (84.8%–90.9%) to standard balloon angioplasty[6, 7]. By contrast, real-world registries reported lower rates of freedom from TLR after DCB treatment (68.6%–83.3%) probably due to higher proportions of complex lesions, including chronic total occlusion (CTO) and severe calcification[8, 9]. Unlike self-expandable stent implantation, balloon angioplasty leaves residual stenosis after dilatation as it is, which is likely to adversely influence the patency rate after DCB treatment. The performance of the DCB treatment in daily practice still has room for improvement.

Intravascular ultrasound (IVUS), displaying high-resolution, cross-sectional images of the vessel walls, can provide useful information on plaque morphology, vessel diameter, calcification angle, and postprocedural lumen area. Therefore, IVUS-guided intervention has become a standard strategy in percutaneous revascularization of peripheral arteries as well as coronary intervention, especially in Japan[10-13]. A previous single-center registry showed that a larger IVUS-measured minimum lumen area (MLA) after DCB treatment was associated with a lower restenosis rate[14]. This association implies the effectiveness of larger lumen gain on primary patency after DCB treatment. However, the MLA can be dependent on several lesion characteristics such as vessel sizes and calcification, which are classical risk factors for restenosis after DCB treatment[13, 14]. The MLA might be a marker of less severe lesion characteristics. Thus, this multicenter study was conducted to investigate the association of larger MLA and the restenosis risk after DCB treatment.

Aim

This study aimed to reveal whether a larger postprocedural lumen gain would reduce the restenosis risk after EVT using DCB in FP lesions.

Materials and Methods

Study Design, Criteria, and Participants

This Drug-cOated baLloon treatment for periPHeral artery disease assessed by INtravascular ultrasound (DOLPHIN) study was a retrospective, nonrandomized, single-arm, and multicenter study of patients with symptomatic peripheral artery disease (Rutherford categories 2–6) who underwent IVUS-guided EVT using DCB for FP lesions between December 2017 and February 2021. Patients with (1) nonatherosclerotic disease, (2) life expectancy <1 year, (3) acute limb ischemia, (4) in-stent restenosis, (5) aneurysmal lesions, and (6) indication of primary major amputation were excluded **(Fig. 1)**. Patients with FP lesions shorter than 25 cm were recommended primary EVT[4]. By contrast, those with diffuse FP lesions were recommended bypass surgery at first, and EVT was conducted when the surgery could not be performed[4]. We reviewed a total of 489 patients with 595 FP lesions who underwent EVT using both DCB and IVUS from a retrospective database of 7 cardiovascular centers. Dual antiplatelet therapy (100 mg/day aspirin with 75 mg/day clopidogrel or 3.75 mg/day prasugrel) was prescribed for at least 1 week prior to EVT and continued for at least 1 month after EVT[15]. Subsequent therapies were at the discretion of the treating physicians. Oral anticoagulation was prescribed in patients with atrial fibrillation, deep vein thrombosis, or previous implantation of a mechanical heart valve.

The study protocol was approved by the local ethics committee of all participating centers, and the study was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design, where existing medical records were used. Alternatively, patients could opt out of the study. Relevant information regarding the study is available to the public in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Procedures

Following local anesthesia, a 4.5–7.0 French guiding sheath was inserted into the ipsi- or contralateral common femoral artery. In CTO lesions, the wire-crossing technique was dependent on the discretion of each operator. The bidirectional approach was performed as needed. After successful balloon dilatation, two DCBs, IN.PACT Admiral (Medtronic Invatec, Frauenfeld, Switzerland) with 3.5 μg/mm^2 of paclitaxel or Lutonix (BD/Bard, Tempe, AZ, USA) with 2.0 μg/mm^2 of paclitaxel, were utilized at the operator's discretion at each institution. Successful balloon dilatation was defined as a residual stenosis less than 50% without major (≥ Grade D) flow-limiting dissection[6, 7]. When necessary, bailout stenting was performed to treat vessel dissection and/or recoil also according to the discretion of the operators. Since atherectomy devices and the

intravascular lithotripsy were not commercially available in Japan during the study period, they were not used in the course of treatment.

IVUS Analysis and Measurement

Baseline and postprocedural IVUS examinations were performed with Vision/Eagle Eye Platinum catheter (Philips Volcano, Rancho Cordova, CA, USA), AnteOwl WR/Navifocus WR/AltaView (TERUMO, Tokyo, Japan), or OptiCross/Atlantis (Boston Scientific, Marlborough, MA, USA), which was pulled back through the lesion for image capture. The size of the DCB was adapted to the distal vessel diameter with a balloon-to-vessel ratio of 1:1. Reference segments were defined as the most normal-looking cross-sections within the same arterial segment (typically less than 20 mm distal to the target lesion) but proximal to any large side branch[10]. An external elastic membrane (EEM) cross-sectional area was measured at the distal reference segment[10, 11]. After DCB treatment, the image slices were analyzed to evaluate the MLA. All parameters were analyzed by participating specialists at each hospital certified by the academic society in Japan according to the current clinical expert consensus document of the EVT imaging[16].

Definitions

Primary patency was defined as the absence of both restenosis and revascularization in the treated lesion. Restenosis was defined as a peak systolic velocity ratio of >2.4 on duplex ultrasonography, $>50\%$ diameter stenosis, or occlusion on follow-up angiography[7]. In each hospital, color Doppler ultrasonography was performed routinely at 6 and 12 months after EVT during the study period to evaluate vascular patency according to the recommendation from the Society for Vascular Surgery[17]. Severe calcification was defined as Peripheral Arterial Calcium Scoring System grade 4 [18].

Data Analysis and Statistical Methods

Data on baseline characteristics are presented as means ± standard deviations for continuous variables and frequencies (percentages) for categorical variables, if not otherwise mentioned. A p value of <0.05 was considered significant, and 95% confidence intervals (CIs) were reported where appropriate. The association between the MLA and the restenosis risk was analyzed using the generalized propensity score (GPS) method, an extension of propensity score methods for continuous exposures[19]. To calculate the GPS, we first developed the ordinary least square (OLS) regression of the continuous-exposure MLA on baseline covariates. The baseline covariates that were entered as explanatory variables in the OLS regression model were sex, age, smoking, diabetes mellitus, dialysis, chronic limb-threatening ischemia (CLTI), EVT history, popliteal involvement, reference vessel diameter (RVD), lesion length, CTO, severe calcification, IVUS-evaluated distal reference EEM area, poor below-the-knee runoff, low-dose DCB use, and bailout stenting. Using the OLS regression model, we subsequently calculated the GPS as the conditional probability density function of the continuous-exposure MLA given the observed baseline covariates.

The balancing property of the GPS was checked by the blocking method[19]. Briefly, we divided the study population into four subgroups according to the quartiles of the continuous-exposure MLA. We thereafter compared baseline covariates between one arbitrary subgroup and the others using t statistics with GPS stratification evaluated at the average of the exposure stratum.

We finally estimated the dose–response function of the continuous-exposure MLA to the restenosis risk. For the estimation, we regressed the restenosis risk on the continuous-exposure MLA and the estimated GPS (evaluated at the observed MLA value) using a Cox proportional hazards regression model. During model development, we adopted a quadratic approximation, including the interaction term between the MLA and the GPS[19]. Based on the developed regression model, we estimated the restenosis risk corresponding to an arbitrary value of the continuous-exposure MLA and the GPS that was evaluated at the MLA value in each individual. The dose–response function was then obtained by averaging the estimates in the overall study sample. Since the dose–response function was expected to be nonlinear, we graphically demonstrated the function along with the derivative of the function. We also demonstrated the difference in the restenosis risk between the quartiles of MLA. All statistical analyses were performed with R version 4.1.1 (R Development Core Team, Vienna, Austria).

Results

The study flowchart is shown in **Fig. 1**. Baseline characteristics are summarized in **Table 1**. The mean patient age was 74 ± 9 years, and 69.7% (n=489) of the study participants were male. The prevalence values of diabetes mellitus and chronic kidney disease on dialysis were 62.6% and 32.9%, respectively. Approximately 1/4 (27.1%, n=595) of the patients presented with CLTI. The mean RVD and diameter stenosis were 5.2 ± 0.8 mm and 87.1% ± 11.3%,

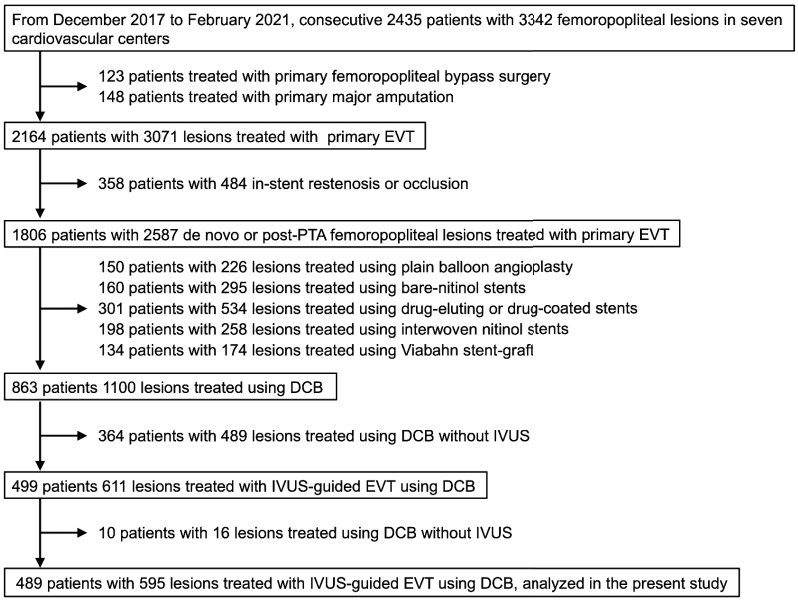

Fig. 1. Study flowchart. PTA, percutaneous transluminal angioplasty.

Table 1. Baseline characteristics

Patient characteristics	(*n*=489)
Male sex	341 (69.7%)
Age (years)	74±9
Smoking	112 (22.9%)
Diabetes mellitus	306 (62.6%)
Dialysis	161 (32.9%)
Hemodialysis / peritoneal dialysis	157 (32.1%) / 4 (0.8%)
Ankle-brachial index at baseline	0.63±0.24
Oral antithrombotic therapy	
Aspirin	388 (79.3%)
Thienopyridine	433 (88.5%)
Cilostazol	148 (30.3%)
Anticoagulation	76 (15.5%)
Limb characteristics	(*n*=595)
Chronic limb-threatening ischemia	161 (27.1%)
Rutherford classification	
2/3	434 (72.9%)
4	55 (9.2%)
5	90 (15.2%)
6	16 (2.7%)
History of revascularization	70 (11.8%)
Popliteal involvement	300 (50.4%)
Reference vessel diameter (mm)	5.2±0.8
Diameter stenosis (%)	87.1±11.3
Lesion length (cm)	14.2±9.7
Chronic total occlusion	155 (26.1%)
Severe calcification	167 (28.1%)
Poor below-the-knee runoff	269 (45.2%)
Low-dose DCB use	201 (33.8%)
Bailout stenting	20 (3.4%)
Findings of intravascular ultrasound	(*n*=595)
Distal reference EEM area (mm^2)	33.1±11.8
MLA (mm^2)	13.9±5.3

Categorical variables are expressed as number and percentage. Continuous variables are indicated as mean±standard deviation. DCB=drug coated balloon, EEM=external elastic membrane, MLA=minimum lumen area.

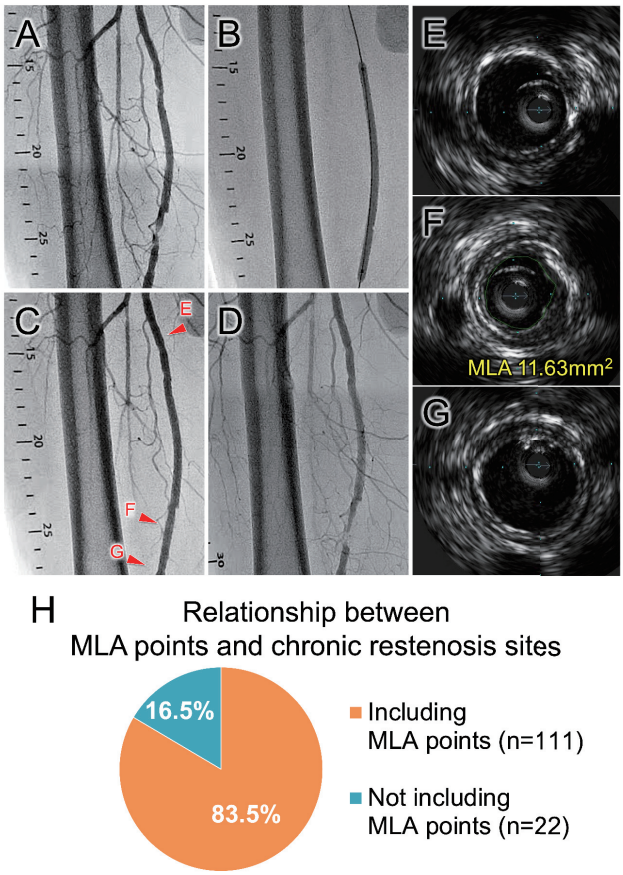

Fig. 2. A representative case in which chronic restenosis occurred in the MLA point at the index EVT and the relationship between MLA points and chronic restenosis sites

(A) An 81-year-old man with end-stage renal disease receiving hemodialysis complained of Rutherford class III claudication. Baseline angiography showed stenosis in his distal SFA. (B) A 5.0-mm DCB was dilated in his SFA. (C) Final angiography revealed that residual stenosis was less than 50% after dilatation. (D) Angiography showed the restenosis 10 months later in the same location as the MLA point at the index EVT. (E–G) At the index EVT, postprocedural IVUS showed that the MLA was 11.63 mm^2 (F), whereas lumen areas at the proximal (E) and distal (G) reference sites were 20.67 and 20.54 mm^2, respectively. (H) Chronic restenosis was observed in 133 patients. The 83.5% of chronic restenosis included the MLA points that were detected with IVUS at the index EVT. SFA, superficial femoral artery.

respectively. The mean lesion length was 14.2 ± 9.7 cm. EVT was performed for 78 patients with 88 lesions longer than 25 cm due to frailty (39.8%), advanced age (20.3%), low cardiac function (17.7%), uncontrolled diabetes merits (8.9%), patients' disagreement of surgical bypass (6.9%), small saphenous veins (6.4%), and leg infection (3.8%). The proportions of CTO and severe calcification were 26.1% and 28.1%, respectively. The mean MLA was 13.9 ± 5.3 mm^2, with a median (interquartile range) of 13.20 (9.90–16.91) mm^2. The mean ankle-brachial index was significantly increased from 0.63 ± 0.24 at baseline to 0.87 ± 0.17 after EVT ($p < 0.001$). During a median follow-up period (interquartile range) of 12 (6–21) months, restenosis was detected in 133 cases. The Kaplan–Meier estimate of 1-year primary patency, that is, freedom from restenosis, was 84.4% (95% CI, 81.1%–87.7%). **Fig. 2(A–G)** shows the representative case in which chronic restenosis occurred in the MLA point detected with IVUS at the index EVT. **Fig. 2H** demonstrates that the 88.1% of the chronic restenosis included the MLA points at the index EVT.

The OLS regression analysis demonstrated that the baseline characteristics independently associated with the MLA were RVD (adjusted regression coefficient $\beta = 2.08$ per 1 mm increase, $p < 0.001$), IVUS-measured distal EEM area ($\beta = 2.17$ per 10 mm^2 increase, $p < 0.001$), and CTO ($\beta = -0.83$, $p = 0.034$) **(Table 2)**. The adjusted R^2 of the multivariate OLS regression was 0.50 **(Fig. 3)**. Based on the multivariate OLS regression, we developed the

Table 2. Ordinary least square regression analysis of minimum lumen area on baseline covariates

	Unadjusted β	Adjusted β
Male sex	1.98 (0.46), $P<0.001$	-0.05 (0.36), $P=0.89$
Age (per 10 years)	0.34 (0.25), $P=0.16$	-0.04 (0.20), $P=0.84$
Smoking	-0.94 (0.51), $P=0.066$	-0.59 (0.39), $P=0.12$
Diabetes mellitus	-0.29 (0.45), $P=0.52$	0.08 (0.34), $P=0.81$
Dialysis	0.26 (0.46), $P=0.57$	0.24 (0.38), $P=0.53$
Chronic limb-threatening ischemia	-0.81 (0.49), $P=0.094$	-0.02 (0.38), $P=0.96$
History of revascularization	-1.56 (0.67), $P=0.020$	-0.29 (0.49), $P=0.54$
Popliteal involvement	-1.44 (0.43), $P=0.001$	-0.46 (0.33), $P=0.17$
Reference vessel diameter (per 1 mm)	3.85 (0.24), $P<0.001$	2.08 (0.25), $P<0.001$
Lesion length (per 100 mm)	-0.56 (0.22), $P=0.011$	-0.00 (0.19), $P=1.00$
Chronic total occlusion	-2.19 (0.48), $P<0.001$	-0.83 (0.39), $P=0.034$
Severe calcification	-0.72 (0.48), $P=0.14$	-0.55 (0.38), $P=0.15$
Reference EEM area (per 10 mm^2)	2.90 (0.14), $P<0.001$	2.17 (0.16), $P<0.001$
Poor below-the-knee runoff	-0.30 (0.43), $P=0.49$	-0.52 (0.33), $P=0.11$
Low-dose DCB use	-0.56 (0.46), $P=0.22$	0.30 (0.34), $P=0.39$
Bailout stenting	1.02 (1.20), $P=0.40$	1.68 (0.91), $P=0.064$

Data are regression coefficients β (standard errors) and p values. Unadjusted β were from the univariate ordinary least square (OLS) regression of minimum lumen area (MLA), and adjusted β were from the multivariate OLS regression of MLA in which all the variables listed in the Table were entered as the explanatory variables. DCB = drug-coated balloon, EEM = external elastic membrane.

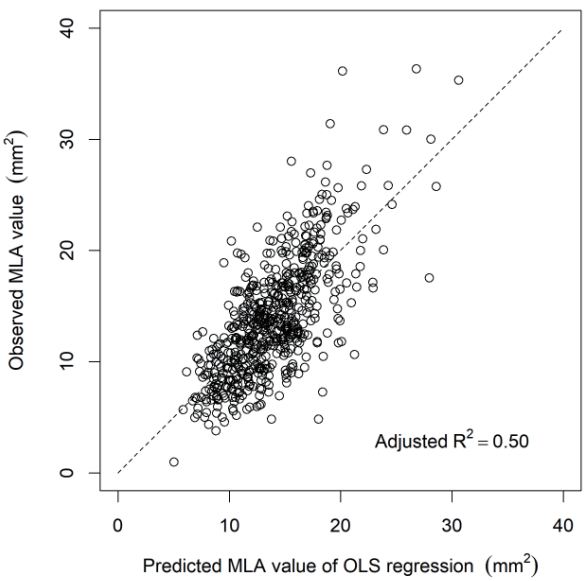

Fig. 3. Scatter plot between the predicted MLA values of OLS regression and the observed MLA values

The predicted MLA values are derived from the multivariate OLS regression in Table 2.

GPS. After the GPS adjustment, all baseline covariates had t statistics of lower than 1.96 (i.e., not significant) **(Table 3)**, suggesting that they were well balanced by the GPS adjustment. The GPS-adjusted dose–response function is illustrated in **Fig. 4**. The MLA was in general inversely associated with the restenosis risk. The upper limit of 95% CI of the slope was lower than 0 between 10.6 and 17.0 mm^2 of the MLAs. The estimated 1-year cumulative incidence rate of restenosis was 9.8% (95% CI, 5.8%–13.7%) for the 3rd quartile of the MLA (16.91 mm^2) versus 18.5% (12.3%–24.1%) for the 1st quartile (9.90 mm^2), with a hazard ratio of 0.51 (95% CI, 0.39–0.67; $p<0.001$) **(Table 4)**.

Table 3. Balance of baseline covariates before and after generalized propensity score adjustment

	Unadjusted				Adjusted for the GPS			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Male sex	2.80	2.09	-2.33	-3.11	0.09	-0.63	0.80	-0.65
Age	2.14	-1.36	0.34	-1.14	-0.82	0.65	-0.41	0.37
Smoking	-1.80	0.23	0.36	1.35	0.33	-0.23	-0.03	0.10
Diabetes mellitus	-1.91	-0.24	2.21	-0.16	1.27	0.12	-1.15	0.53
Dialysis	-0.94	1.00	-0.15	0.12	0.84	-0.38	0.14	-0.50
Chronic limb-threatening ischemia	-2.03	1.22	-0.83	1.86	0.89	-0.64	0.52	-0.53
History of revascularization	-2.48	0.81	0.74	1.44	0.66	-0.60	-0.13	0.05
Popliteal involvement	-1.98	0.12	-1.59	3.50	-0.21	-0.47	0.76	-0.35
Reference vessel diameter	11.55	3.18	-3.71	-12.04	-1.90	-0.28	0.66	0.75
Lesion length	-3.31	0.79	1.09	1.48	0.92	-0.57	-0.23	0.35
Chronic total occlusion	-3.71	0.45	1.01	2.77	0.30	-0.56	0.08	0.11
Severe calcification	-1.52	0.44	-1.12	2.43	0.64	-0.38	0.49	-0.80
Reference EEM area	12.62	4.18	-0.40	-12.30	-0.31	-0.04	-0.48	1.22
Poor below-the-knee runoff	-1.53	1.49	0.36	-0.31	0.80	-0.57	0.14	0.03
Low-dose DCB use	-1.37	0.33	0.00	1.09	0.03	-0.29	-0.02	0.42
Bailout stenting	-1.35	1.24	1.21	-0.49	0.85	-0.56	-0.72	0.27

Data are *t* statistics between one subgroup and the others. The study population was divided according to the quartiles of minimum lumen area: Q1 (from 1.00 to 9.87 mm^2), Q2 (from 9.90 to 13.20 mm^2), Q3 (from 13.23 to 16.90 mm^2), and Q4 (from 16.91 to 36.33 mm^2).
Categorical variables are expressed as number and percentage. Continuous variables are indicated as mean ± standard deviation or median (interquartile range). DCB = drug-coated balloon, EEM = external elastic membrane, GPS = generalized propensity score.

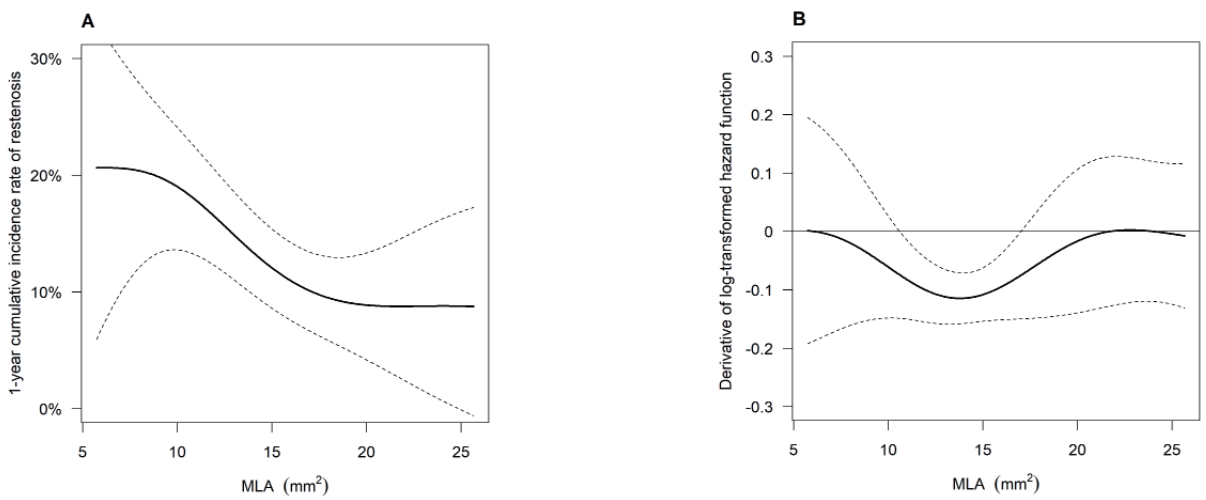

Fig. 4. Dose–response function of the MLA for the restenosis risk

(A) The 1-year cumulative incidence rate of restenosis corresponding to an arbitrary MLA value (bold line) and its 95% CI (dotted lines). (B) The derivative (i.e., slope) of the log-transformed hazard function (bold line) and its 95% CI (dotted lines). A value higher and lower than 0 indicates an increased and decreased restenosis risk, respectively, whereas the value equal to 0 indicates an unchanged restenosis risk. The upper limit of the 95% CI was lower than 0 between 10.6 and 17.0 mm^2 of the MLA. The natural exponentiation of the value was equivalent to the hazard ratio for a one-unit increase in the MLA.

Table 4. Restenosis risk corresponding to quartiles of minimum lumen area

MLA	1st quartile (9.90 mm^2)	2nd quartile (13.23 mm^2)	3rd quartile (16.91 mm^2)
1-year restenosis rate	18.5% [12.3% to 24.1%]	14.3% [9.8% to 18.5%]	9.8% [5.8% to 13.7%]
Hazard ratio			
vs. the 1st quartile	1.00 (reference)	0.75 [0.63 to 0.90] (P=0.001)	0.51 [0.39 to 0.67] (P<0.001)
vs. the 2nd quartile	1.33 [1.12 to 1.58] (P=0.001)	1.00 (reference)	0.67 [0.57 to 0.80] (P<0.001)
vs. the 3rd quartile	1.97 [1.50 to 2.59] (P<0.001)	1.49 [1.25 to 1.76] (P<0.001)	1.00 (reference)

Data are estimated by generalized propensity score adjustment [95% confidence intervals]. MLA = minimum lumen area.

Discussion

Few large-scale studies have investigated whether postprocedural findings could be associated with restenosis risk after DCB treatment. The restenosis after DCB treatment has been reportedly affected by various factors, including vessel diameter, CTO, and severe calcification[13-15]. The MLA was expected to be highly dependent on baseline characteristics, and the present study successfully addressed those confounding influences by using the GPS method. The primary finding of the current GPS analysis was an inverse association between the postprocedural MLA and the 1-year restenosis risk after DCB treatment. The 1-year restenosis rate was 9.8% for the 3rd quartile of the MLA versus 18.5% for the 1st quartile ($p<0.001$). The current findings indicate that the incidence of restenosis after DCB treatment could be reduced by restoring a larger postprocedural MLA, independently of baseline characteristics. Moreover, MLA points at the index EVT were included in 83.5% of restenosis sites. If MLA might be insufficient at the index EVT, enlargement of the MLA points with additional dilatation might improve the patency rate after DCB treatment.

DCBs are primarily drug delivery devices, and adequate transfer of paclitaxel to the media of the vessel wall relies on complete wall apposition of the devices. Inadequate sizes of pre-balloons and DCBs might therefore result in the poor apposition of the balloon to the wall with suboptimal drug delivery and poor suppression of neointimal hyperplasia. Allan et al. conducted an RCT and showed that the use of IVUS results in larger vessel diameter and significant reduction in the restenosis rate 1 year after DCB treatment (9.1% vs. 37.5%, $p=0.001$)[20]. Furthermore, in a retrospective study, Kurata et al. suggested that larger DCB sizes are selected based on EEM diameter than based on lumen diameter (5.2 vs. 4.8 mm), with a 2-year restenosis rate of 19.7% for the EEM-based strategy compared with 33.1% for the lumen-based strategy[15]. These two investigations indicate that selecting sufficiently large balloon sizes might be beneficial to the reduction of restenosis after IVUS-guided EVT treatment.

Indeed, too large device sizes for the vessel would do more harm than good because of extensive medial stress and vessel perforation[21]. Our main finding was a generally inverse association of the MLA with restenosis risk, but balloon sizes should be selected carefully to manage both restoring the sufficient lumen enlargement and minimizing vessel injury. Therefore, our balloon angioplasties were based on vessel diameters at distal reference sites measured by IVUS to avoid overdilation in this study. The association of more aggressive dilatation with restenosis risk remained to be investigated.

As the dose–response function shows **(Fig. 4)**, the slope of restenosis risk to the MLA was significantly smaller than 0 between the MLAs of 10.6 and 17.0 mm^2, suggesting that the beneficial effects of MLA enlargement on restenosis reduction might be gained between this range. On the contrary, in cases with a very small MLA (e.g., much smaller than 10.6 mm^2), the beneficial effects might not be gained unless an enlarged MLA exceeded 10.6 mm^2, whereas in those with a sufficiently large MLA (e.g., much larger than 17.0 mm^2), further MLA enlargement might not bring about additional risk reduction. Future studies are warranted to determine the lower and upper limits of the MLA for the best performance of DCB.

Study Limitations

This study has several limitations. First, this study had a retrospective, nonrandomized and single-arm design, causing a potential bias. However, we believe that adopting the GPS method could minimize the bias as much as possible. Second, the EVT procedure such as wiring in CTO lesions and selection of types of balloons were dependent on each operator's decision without following any pre-established protocol, which might cause a bias. Third, angiographic and IVUS findings, baseline characteristics, and clinical events were not evaluated by an external core laboratory. However, to reduce the bias of measuring the parameters, the observers assessed the findings according to the current consensus document[16]. Fourth, the current guideline recommends bypass surgery for patients with FP lesion longer than 25 cm[4]; however, 16.0% of patients with long FP lesions underwent EVT in this study because of poor general condition and comorbidities. Fifth, patients were followed up in each hospital; however, there was no established follow-up protocol during the study period. Sixth, this study included 32.9% of patients on dialysis, and this patient characteristic was not common to other countries[22].

Conclusions

The present multicenter registry suggested that 1-year restenosis after DCB treatment might be inversely associated with the postprocedural MLA measured by IVUS after the GPS adjustment.

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