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CLINICAL RESEARCH
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Angiographic late lumen loss revisited: impact on long-term target lesion revascularization

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Aim In current device trials, the values of angiographic late lumen loss (LLL) have become extremely low and the relationship between LLL and clinical endpoints has not been recently re-evaluated. The impact of LLL on target lesion revascularization (TLR) in a patient- and study-level analysis of contemporary coronary devices was investigated.

Methods and results We performed a patient-level meta-analysis of seven randomized controlled trials including 2426 patients treated with first- and second-generation drug-eluting stents (DES) and a study-level meta-analysis of 40 studies including 19 199 patients treated with CE-marked DES. In the patient-level analysis, the probability regression curve showed an exponential relationship between in-stent LLL and 2-year incidence of TLR. The optimal cut-off value of LLL based on Youden's index for 2-year TLR event was 0.50 mm. In the Cox proportional hazard model, LLL >0.50 mm was independently associated with an increased incidence of TLR up to 4 years after angiographic follow-up {adjusted hazard ratio (HR) 6.62 [95% confidence interval (95% CI) 4.67–9.39], $P < 0.001$}. In the meta-regression analysis of the DES studies, pooled mean value of LLL was as low as 0.23 mm (95% CI 0.20–0.26), and there was a moderate correlation between the 1- and 5-year incidence of TLR and the percentage of the lesions with LLL >0.50 mm ($R^2 = 0.44$, $P < 0.001$ at 1 year, $R^2 = 0.40$, $P < 0.001$ at 5 years).

Conclusion An angiographic LLL ≤0.50 mm was not predictive of the incidence of TLR whereas a LLL >0.50 mm was. Low LLL in contemporary device trials may not be a sufficiently discriminating parameter for the comparative evaluation of devices.

Keywords Late lumen loss • Quantitative coronary angiography • Target lesion revascularization • Drug-eluting stent

Introduction

Angiographic late lumen loss (LLL), which is calculated as the difference in lumen diameter between post-procedure and follow-up, was first reported in the early 1990s.[1] Since then LLL, especially between 6 and 13 months after the index treatment, has been widely used to assess the efficacy of various angioplasty techniques such as balloon angioplasty, bare metal stents (BMS), drug-eluting stents (DES), and bioresorbable scaffolds (BRS). Furthermore, LLL has been considered the gold standard for device approval by regulatory bodies, because the investigation of a continuous parameter, such as LLL, requires a smaller sample size than binary restenosis rate or clinical outcomes, such as target lesion revascularization (TLR).[2,3] The sufficient discriminating capability and predictive ability for clinical

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outcomes of LLL have been reported with the population including the patients treated with BMS.[4,5] In the BMS era, values of LLL were relatively high, ranging from 0.6 to 0.9 mm,[6,7] whilst with current DES, values range between 0.1 and 0.3 mm.[8,9] In the current DES era, statistical significant differences in LLL between devices does not always translate into meaningful differences in the incidence of clinical endpoints, such as TLR.[10–14] In their pooled data analysis of BMS and first-generation DES, Pocock *et al.*[5] demonstrated an exponential relationship between LLL and 1-year TLR, suggesting that low values for LLL were not associated with an increased incidence of TLR at 1 year. The relationship between long-term clinical outcomes and the LLL observed with second- or newer-generation DES, with their improved efficacy and safety, has not been fully investigated. To detect the so-called late 'catch-up' phenomenon, long-term investigations of clinical outcomes after follow-up angiography are warranted.[15] The clinical significance of differences in LLL, particularly within low range, has still to be investigated.

The aim of the current analysis was to investigate the impact of angiographic LLL on the incidence of long-term TLR and to identify an exact threshold affecting the events by using pooled patient-level and study-level analysis.

Methods

Patient-level analysis

Study population

The current analysis included seven randomized controlled trials with the following criteria: trials conducted by the same clinical research organization (Cardialysis, Rotterdam, the Netherlands) between 2000 and 2017 which (i) enrolled patients treated with first- and second-generation DES, (ii) had protocol-mandated angiographic follow-up for which quantitative coronary angiography (QCA) analyses were performed by the same angiographic core laboratory (Cardialysis BV), and (iii) had clinical endpoints which were obtained after 2 years of follow-up (1 trial: 2 years, 1 trial: 3 years, 5 trials: 5 years). These seven trials enrolled a total of 6387 patients, and had 12 treatment arms (6174 patients) which used seven different DES—sirolimus-eluting stent (SES) (Cypher; Cordis Corp., Miami, FL, USA), paclitaxel-eluting stent (PES) (Taxus; Boston Scientific, Natick, MA, USA), Endeavour zotarolimus-eluting stent (E-ZES) (Endeavor; Medtronic, Santa Rosa, CA, USA), Resolute zotarolimus-eluting stent (R-ZES) (Resolute; Medtronic, Santa Rosa, CA, USA), biolimus-eluting stent (BES) (BioMatrix Flex; Biosensors Inc., Newport Beach, CA, USA and Nobori; Terumo Corp., Tokyo), cobalt chromium everolimus-eluting stent (EES) (Xience; Abbott Vascular, Santa Clara, CA, USA), novolimus-eluting stent (NES) (DESyne; Elixir Medical, Sunnyvale, CA, USA), whereas one treatment arm received BMS (the RAVEL trial; Bx Velocity) and one treatment arm received BRS (the TROFI II trial; ABSORB BVS). These latter two arms (BMS and BRS) were excluded from the current patient-level analysis (Supplementary material online, *Table S1*). Among the included trials, four enrolled patients with simple lesions upon restrictive inclusion criteria (RAVEL, REALITY, Nobori I, and Excella II trial); one only enrolled patients with ST-segment elevation myocardial infarction (TROFI II trial) and two were so-called 'all comers trials' including patients with minimal exclusion criteria (LEADERS and Resolute all comers trial). In the 12 DES arms, 3024 patients were allocated to angiographic follow-up, with 2651 patients actually returning for this follow-up study procedure. Details of the study protocols have been reported previously.[8,10–12,16–19]

Angiographic follow-up and quantitative coronary angiography analysis

In each trial protocol mandated follow-up angiography was performed 6 to 13 months after the index procedure (Supplementary material online, *Table S1*).[8,10–12,16–19] In all the trials, if a target lesion was revascularized at any time between baseline and protocol mandated follow-up angiography, the pre-revascularization angiogram was analysed and QCA results were, for statistical purposes, carried forward to the time of the protocol mandated follow-up angiography. In the Resolute all comers trial, as per the protocol, the QCA of the angiograms of those patients experiencing a stent thrombosis within 14 days of the index procedure were not included in the QCA analysis. These 10 patients were therefore not included in the current analysis.[17]

In all the trials, off-line QCA analyses were performed by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) with the CAAS system (Pie Medical Imaging, Maastricht, the Netherlands) according to standard operational protocols.[2] In each trial, the following QCA parameters were calculated both in-stent and in-segment (including the 5-mm proximal and distal stent margins): minimum lumen diameter (MLD), interpolated reference vessel diameter (RVD), percent diameter stenosis (DS) [%DS: (1 - MLD/RVD) × 100], and LLL (difference in MLD between the post-procedure and follow-up).

Clinical follow-up and definition of clinical endpoints

The duration of clinical follow-up after the index procedure ranged from 2 to 5 years (Supplementary material online, *Table S1*). Clinical follow-up was performed by an outpatient visit or by telephone.

Out of the seven trials, six used the Academic Research Consortium (ARC) definition of clinically indicated (clinically driven, ischaemic-driven) TLR.[20] In the remaining one study (RAVEL study), a protocol specific definition was used for TLR as described in Supplementary material online.

In all trials, the clinical events of TLR were adjudicated by independent clinical event committees (CEC).

Study-level analysis

Systematic review for a meta-analysis of contemporary device trials

For a study-level meta-analysis of contemporary device trials, two independent reviewers (T.A. and Y.M.) systematically searched (April 2018) MEDLINE/Pub Med, EMBASE, and available presentations of clinical trials at major international meetings (ESC, AHA, ACC, Euro PCR, TCT, and CRT). Clinical studies were included with the following criteria: (i) studies including patients who underwent PCI for *de novo* lesions in coronary arteries; (ii) with angiographic in-device LLL between 6 and 13 months after index procedure analysed by an independent core laboratory; (iii) with clinically indicated TLR at least 9 months after index procedure, which was adjudicated according to ARC or the relevant definition (before the publication of ARC definition) by an independent CEC; and (iv) including patients treated with drug-eluting/coated stent (non-dedicated bifurcation stent) approved by CE mark. Search terms for the review are described in Supplementary material online. Studies with inadequate data for abstraction, duplication of data, case reports, and case series were excluded. Data were abstracted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[21] Quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[22]

Statistical methods

Categorical variables were reported as counts and percentage. Continuous variables were presented as mean ± standard deviation (SD).

A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) or R version 3.4 (R Foundation, Vienna, Austria), and the meta-regression model was fitted using the metafor package.

Patient-level analysis

In the current analysis, when a patient had multiple lesions treated, the highest LLL among the lesions was used for the patient-level analysis. The frequency distribution of LLL of the entire population is graphically represented with histograms.

Prediction model for the probability of target lesion revascularization based on in-stent late lumen loss

Univariate logistic regression analysis was applied in order to develop a prediction model for the probability of TLR at 2 years based on in-stent LLL by using the pooled patient-level database in which 2-year clinical outcomes were available.[5] The model was evaluated for goodness-of-fit with the Hosmer–Lemeshow test. Predictive accuracy was assessed by means of the area under the receiver operating characteristic curve (AUC). Optimal cut-off value of LLL for predicting 2-year TLR was determined by Youden's index with reasonable sensitivity and specificity.

Assessment of the impact of late lumen loss *on long-term target lesion revascularization*

The incidence of TLR for 48 months after follow-up angiography was investigated by the Kaplan–Meier estimates. The population was stratified in two groups according to the optimal cut-off value of LLL derived from Youden's index. For the Kaplan–Meier estimates, days were counted from the date of the angiographic follow-up to interrogate the impact of LLL on subsequent TLR.

To investigate the impact of LLL on the incidence of TLR 48 months after follow-up angiography (5 years after the index procedure), multivariable Cox proportional hazard modelling was performed while adjusting for other previously known determinants of long-term TLR (diabetes, bypass graft, small vessel, calcification, bifurcation, aorto-ostial lesion, in-stent restenosis, and first-generation DES).[23,24]

Additionally, to assess detailed value range of LLL impacting on TLR, the patients in the upper median group were restratified into quintiles (five categories) and investigated with the Kaplan–Meier analysis and Cox regression analysis.

Study-level analysis

The study-level meta-analysis was performed to identify the pooled mean value of LLL of the CE-marked DES and to demonstrate the validity of the cut-off value of LLL determined in the patient-level analysis by a comprehensive overview of all available data published in the literature.

A random-effects model was applied to calculate the pooled mean in-stent LLL of the included studies with a 95% confidence interval (95% CI). The correlation between in-stent LLL and incidence rates of TLR was assessed with a random-effects meta-regression model. Mean LLL was entered into respective models to assess its correlations with the incidence rates of TLR.[25] The correlation between TLR the rate and percentage of the lesions with LLL more than the cut-off value, which was calculated by mean and SD of LLL assuming the normality of the LLL distribution, was investigated (Supplementary material online, *Figure S1*).[26] The assumption of homogeneity between the treatment effects in different studies was tested using Q statistic and further quantified by I^2 statistic. For the main outcomes of the meta-regression analysis, sensitivity analyses were performed by limiting to the studies with the device arms including more than 100 patients. The methodological details of the meta-regression analysis are described in Supplementary material online.

Results

In the patient-level analysis, out of the 2651 patients who underwent follow-up angiography, 2426 patients with available LLL were included in the current analysis. The details of the included patients and angiographic follow-up data are shown in Supplementary material online, *Table S1*. The median clinical follow-up time was 838.5 days (interquartile range 731–1827 days).

The patient-level analysis assessing the relationship between late lumen loss and incidence of target lesion revascularization

In *Figure 1*, both curves of probability and actual incidence show a steep increase in TLR when in-stent LLL reaches high value (0.5 mm), whereas in-stent LLL in lower value does not correlate with the probability of TLR. This trend is more evident with second-generation DES, which generally have lower probabilities of TLR. The details of the function are described in Supplementary material online. The model fitted the data (Hosmer–Lemeshow test $P = 0.160$; $\chi^2 = 11.81$) and had a good predictive accuracy (AUC 0.80).

The optimal cut-off value of late lumen loss and its association with long-term target lesion revascularization - patient-level analysis

Using Youden's index, the optimal cut-off value of in-stent LLL was indicated as 0.50 mm. Based on this cut-off value, sensitivity, specificity, positive predictive value, and negative predictive value were 0.67, 0.84, 0.21, and 0.97, respectively.

When the population was stratified according to this cut-off value (0.50 mm), the incidence rate of TLR in the high LLL group (LLL >0.50 mm) was 24.6% at 4 years after follow-up angiography whereas the rate in the low LLL group (LLL ≤0.50 mm) was 4.6% in the Kaplan–Meier estimates (log-rank $P < 0.001$) (*Figure 2A*). The incidence of TLR was mainly driven by revascularization performed at the time of the follow-up angiography or in the following days. The landmark analysis (0–1 month and 1–48 months after angiography) shows that the patients with LLL >0.50 mm were still associated with an increased incidence of TLR over time, especially 12 months after follow-up angiography (*Figure 2B*).

In the Cox regression analysis, the adjusted hazard ratio (HR) of LLL >0.50 mm was 6.62 with a 95% CI of 4.67–9.39. Compared with first-generation DES, use of a second-generation DES was an independent predictor of TLR with an adjusted HR 0.54 (95% CI 0.34–0.84, $P = 0.006$) (*Table 1*).

The results of the Kaplan–Meier analysis and Cox regression analysis with the patients stratified according to quintile are presented in Supplementary material online, *Figure S2* and *Table S2*. The adjusted HR of the third quintile (between 0.375 and 0.505 mm) was 2.13 (95% CI 1.11–4.07, $P < 0.001$) while the lower quartiles were not significantly associated with the incidence of TLR.

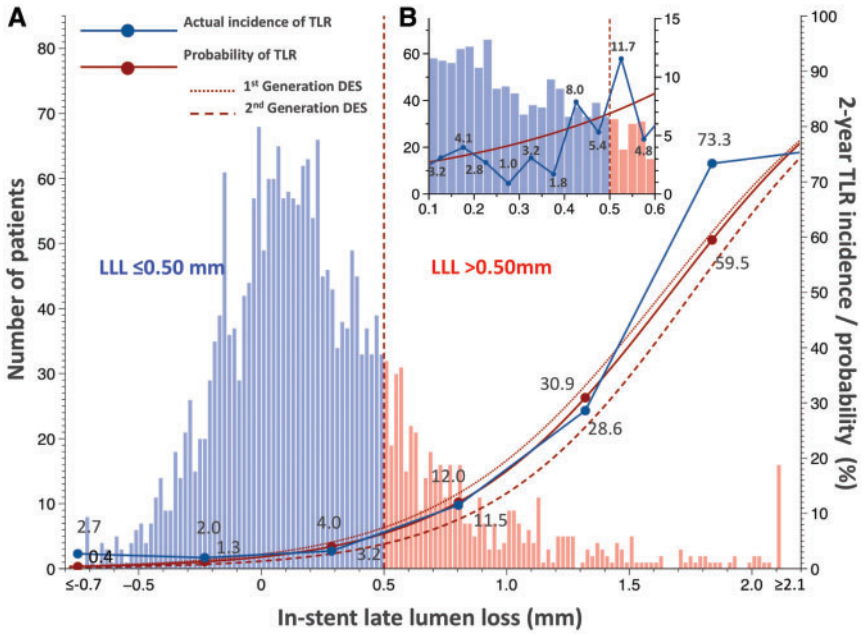


Figure 1 Logistic regression curve to predict probability of target lesion revascularization and actual incidence of target lesion revascularization. (*A*) The probability curves generated by logistic regression analysis to estimate the probability of target lesion revascularization at 2 years are presented with the actual incidence of target lesion revascularization in the current cohort ($n = 2426$). Histogram shows the distribution of in-stent LLL in the current cohort. (*B*) Magnified diagram of (*A*) to focus on LLL between 0.1 and 0.6 mm. DES, drug-eluting stent; LLL, late lumen loss; TLR, target lesion revascularization.

The study-level meta-regression analysis assessing the correlation between in-stent late lumen loss and incidence of target lesion revascularization

After the electronic databases search, 3130 citations were identified. Using the inclusion/exclusion criteria, we reviewed 231 abstracts, of which we assessed 114 as full-text publications (Supplementary material online, *Figure S2*). Sixty-eight CE-marked-device arms in 40 randomized controlled DES trials with an independent core laboratory and clinical event committee adjudicating clinically indicated TLR according to the ARC or the relevant definition (before the publication of ARC definition) (19 199 patients with available LLL). A summary of the included studies and results of risk of bias assessment are tabulated in Supplementary material online, *Tables S1* and *S2*. A pooled mean in-device LLL of included studies was 0.23 mm (95% CI 0.20–0.26) [first-generation DES: 0.26 mm (0.21–0.31), second- and next-generation DES: 0.22 mm (0.17–0.26)] (*Figure 3*).

In the meta-regression analysis, the significant but poor correlation between mean in-device LLL and the 1-year incidence of TLR was observed ($R^2 = 0.27$, $P < 0.001$) (*Figure 4A*). The percentage of the lesions with LLL >0.50 mm was moderately correlated with the 1-year incidence of TLR ($R^2 = 0.44$, $P < 0.001$) (*Figure 4B*). At 5 years, the percentage of the lesions with LLL >0.50 mm with TLR rate remained correlated with TLR rate ($R^2 = 0.40$, $P < 0.001$) whereas the correlation between mean LLL and TLR rate was still weak ($R^2 = 0.18$, $P = 0.01$) (Supplementary material online, *Figure S3*). The sensitivity analyses limiting to 56 device arms with more than 100 patients yielded similar results in the correlation between mean LLL/percentage of the lesions with LLL >0.50 mm and 1-year TLR rate ($R^2 = 0.42$, $P < 0.001$ for mean LLL, $R^2 = 0.26$, $P < 0.001$ for percentage of the lesions with LLL >0.50 mm).

Discussion

Major findings of the current analysis are: (i) there was an exponential relationship between in-stent LLL and the incidence of TLR; (ii) the optimal cut-off value of LLL for TLR event was 0.50 mm; (iii) in the Kaplan–Meier analysis, the incidence rate of TLR in the patients with LLL >0.50 mm was 24.6% at 4 years after follow-up angiography whereas the rate in the patients with LLL ≤0.50 mm was 4.6%; (iv) the pooled mean in-stent LLL of the DES trials was as low as 0.23 mm and (v) the percentage of the lesions with LLL >0.50 mm was significantly correlated with 1- and 5-year incidence of TLR in the study trials (*Take home figure*).

The impact of late lumen loss on long-term target lesion revascularization

As shown in *Figure 1*, the incidence of TLR is exponentially related to in-stent LLL. In that relationship, LLL in low value was not associated with the increased incidence of TLR, suggesting that modest lumen loss would not impair maximal hyperaemic coronary blood flow.[27]

In the Kaplan–Meier estimates, patients with LLL >0.50 mm had the greater incidence of TLR than those with LLL ≤0.50 mm [adjusted HR 6.62 (95% CI 4.67–9.39); $P < 0.001$] (*Table 1*, *Figure 2*).

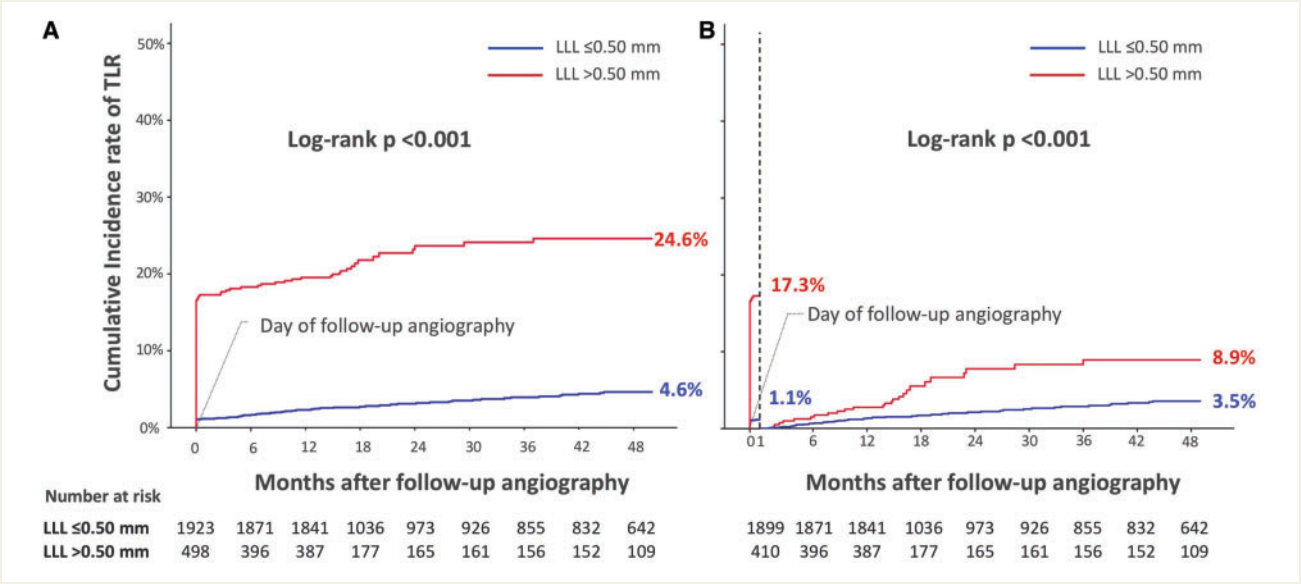


Figure 2 Kaplan–Meier (*A*) and landmark (*B*) estimates of target lesion revascularization after follow-up angiography. LLL, late lumen loss.

The validity of this cut-off value was demonstrated in the meta-regression analysis with CE-marked DES studies (*Figure 4B*). In the landmark analysis, the incidence of TLR in the patients with LLL >0.50 mm kept increasing even 12 months after follow-up angiography. This suggests that those patients with an in-stent LLL >0.50 mm are likely to undergo a TLR during longer-term follow-up, even if repeat revascularization was deferred at the time of the follow-up angiography (*Figure 2B*).

The correlation between mean in-stent late lumen loss and incidence rate of target lesion revascularization in the drug-eluting stents studies

In the meta-regression analysis of DES trials, mean values of LLL had a poor correlation with the incidence of 1- and 5-year TLR ($R^2 = 0.27$ at 1 year, $R^2 = 0.18$ at 5 years) (*Figure 4*). Mauri *et al.*[28] previously demonstrated a strong correlation between mean LLL and incidence of binary angiographic restenosis at 6- to 8-month follow-up with curvilinear regression in their study-level analysis ($R^2 = 0.73$). That analysis included BMS arms (27/40 treatment arms) and the range of mean LLL was between -0.01 and 1.21 mm. The correlation between mean LLL and TLR rate might diminish in the current DES era.

The limitation of late lumen loss in the contemporary device trials

In the current DES era, LLL may not be the best efficacy parameter to discriminate between devices. Although LLL is sensitive enough to differentiate between devices at low values, this discrimination has limited clinical significance.[4] Furthermore, the concept of 'lower is better' that has been extrapolated from BMS trials may not be applicable for contemporary DES. Very low or negative values of LLL on angiography could reflect the absence of neointimal coverage or even the presence of late acquired stent malapposition, which can be associated with safety issues such as stent thrombosis. Within this low range, a 'sweet spot' for optimal LLL should exist allowing for a large flow patency but sufficient stent coverage nevertheless.

Table 1 Multivariable Cox regression analysis investigating the independent predictors for target lesion revascularization after follow-up angiography

Variables	Adjusted hazard ratio (95% CI)	*P*-value
LLL >0.50 mm	6.62 (4.67, 9.39)	<0.001
Diabetes	1.33 (0.93, 1.91)	0.117
Small vessel[a]	1.20 (0.84, 1.71)	0.320
Calcification	1.40 (0.99, 1.98)	0.060
Bifurcation	1.43 (1.00, 2.04)	0.052
Aorto-ostium	0.50 (0.07, 3.64)	0.495
Restenotic lesion	4.22 (1.71, 10.42)	0.002
Bypass graft	2.47 (0.33, 18.41)	0.376
Second-generation DES (vs. first-generation DES)	0.54 (0.34, 0.84)	0.006

[a]Reference vessel diameter ≤2.25 mm.
CI, confidence interval; DES, drug-eluting stent; LLL, late lumen loss.

Perspective on late lumen loss in the current drug-eluting stents era: potential clinical application

When LLL is applied to the efficacy comparison of DES in the current era, the limited discriminant capability of LLL with low value should

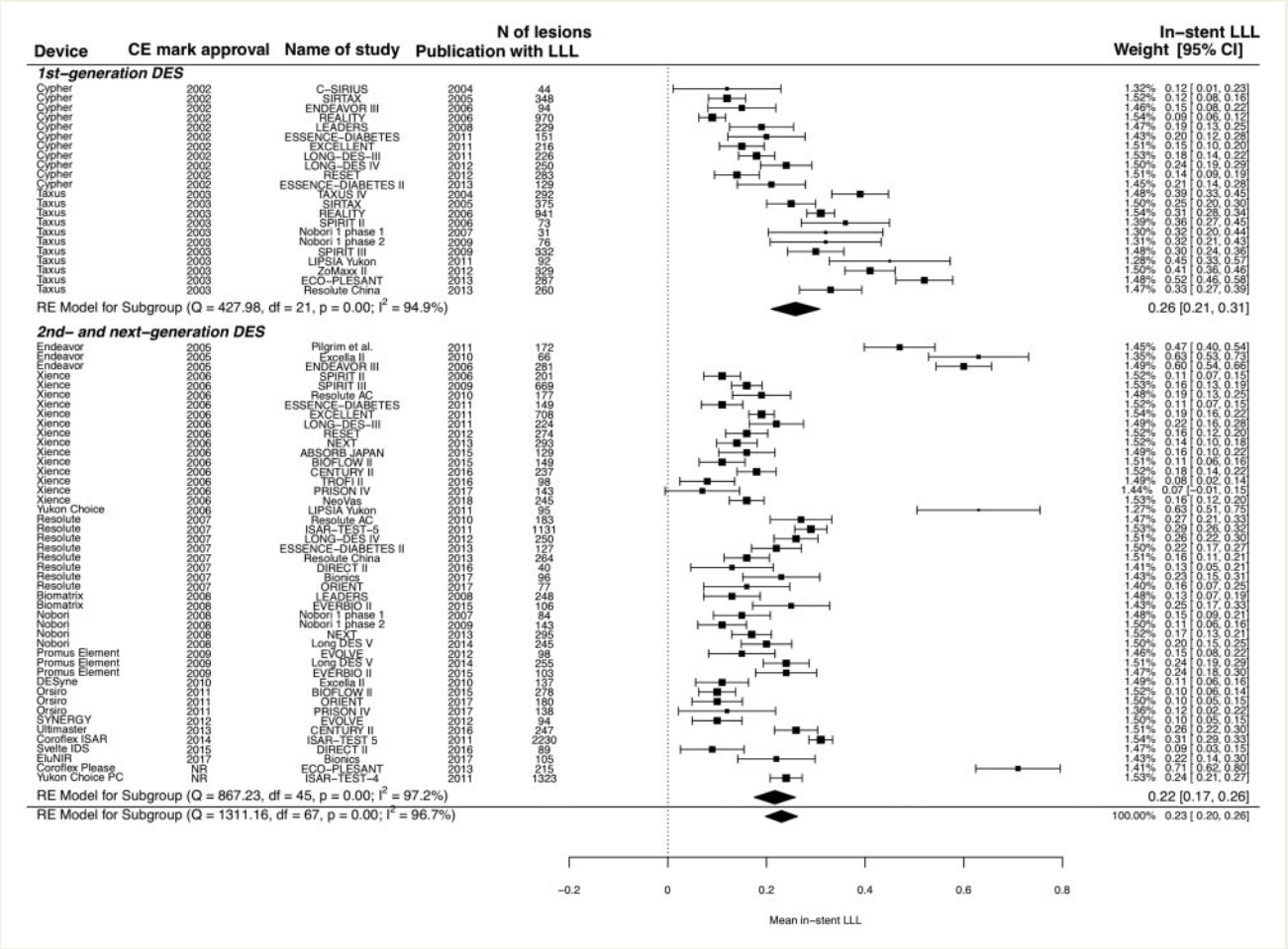


Figure 3 Forest plots of angiographic in-device late lumen loss in the CE-marked drug-eluting stent trials. CI, confidence interval; LLL, late lumen loss; N, number.

be acknowledged. However, the results of the current study offer insight into the potential applicability of LLL in both clinical practice and device efficacy assessment in trials.

In clinical practice, the cut-off value of 0.50 mm can be used as the information for making a treatment decision. A low LLL (≤0.50 mm) observed in the cathlab is clinically negligible. In other word, if the clinician observed a moderate restenosis with a reduction of the MLD of the device <0.50 mm, such a lesion would likely not be treated. The TLR rate of the patients with LLL ≤0.50 mm was 4.6% at 4 years after follow-up angiography whereas the adjusted HR of LLL ≤0.50 mm for 4-year TLR was 0.15 (95% CI 0.11–0.22). The negative predictive value of this cut-off was 0.97. The TLR rate of the patients with LLL >0.50 mm was 24.6% at 4 years after follow-up angiography whereas the adjusted HR of LLL >0.50 mm for 4-year TLR was 6.6 (95% CI 4.7–9.4). These results are in line with the recent analysis of the relationship between angiographic-derived FFR (QFR) and LLL, indicating an exponential correlation.[29] In the range of LLL ≤0.50 mm, delta QFR across the devices remained minimal. The current analysis demonstrated that even taking into consideration the long-term progression/regression of neointima, LLL ≤0.50 mm should be a deterrent factor for future revascularization.

Moreover, in the interpretation or design of the device study, this cut-off of LLL (0.50 mm) might be used as a non-inferiority boundary of LLL when objective performance criteria/goal (OPC/OPG) are used for the device efficacy assessment. OPC/OPG have been used to establish a comparator in single-arm studies such as pre-approval studies of heart valves including transcatheter heart valves for the Food and Drug Administration (FDA).[30–32] Given the result of the current study, the cut-off value of LLL (0.50 mm) might be applicable for the maximum allowable value on the efficacy assessment of the pre-market coronary stent study. The OPC for the coronary stent have been proposed by the ESC/EAPCI task force on the evaluation of coronary stents.[33] In that document, the upper bound of 95% CI (i.e. 0.34 mm) of the LLL derived from the pooled LLL data was suggested as a maximum allowance value but not explicitly stated. However, according to our result, the value of 0.34 mm might be too stringent as a maximum allowance value.

Angiographic endpoint (QCA) is more easily acquired and assessed when compared to intravascular imagings such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) in evaluating the device efficacy, since QCA always captures the luminal loss irrespective of the (urgent) clinical setting. At the moment of

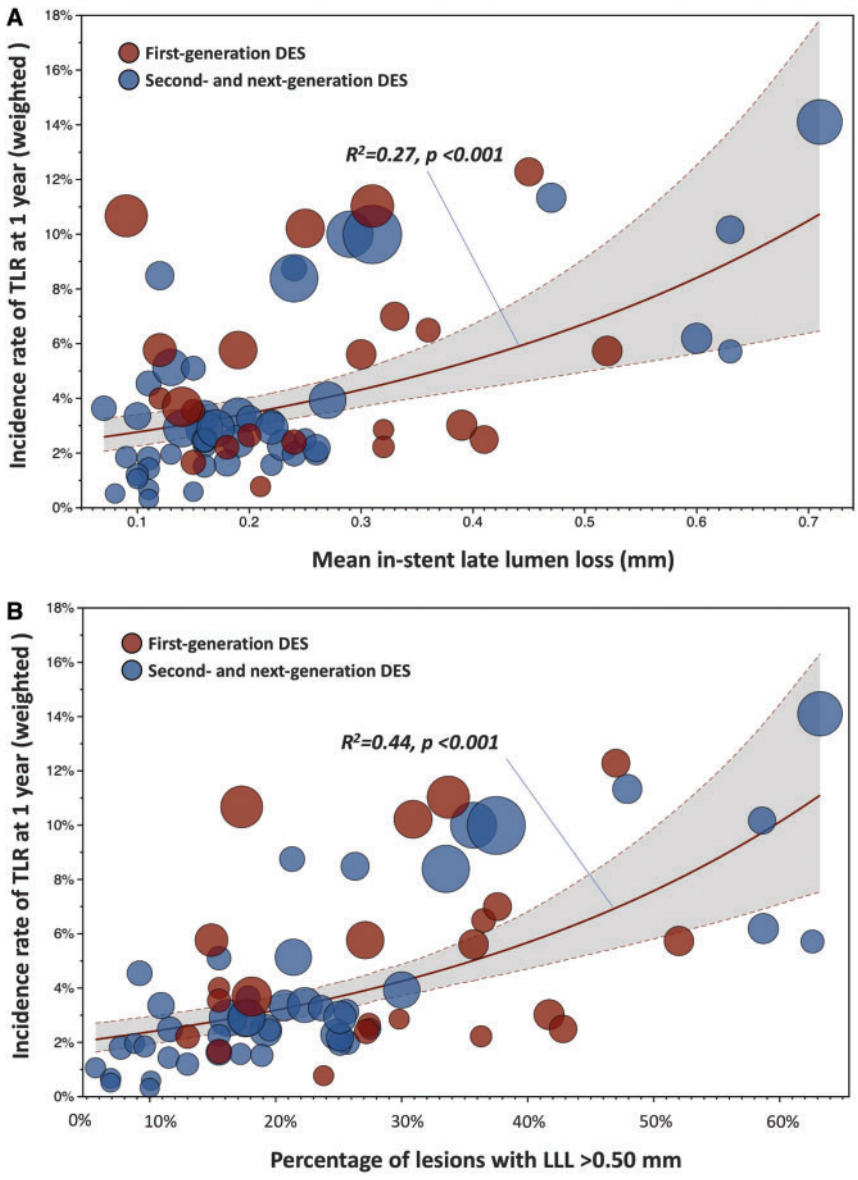
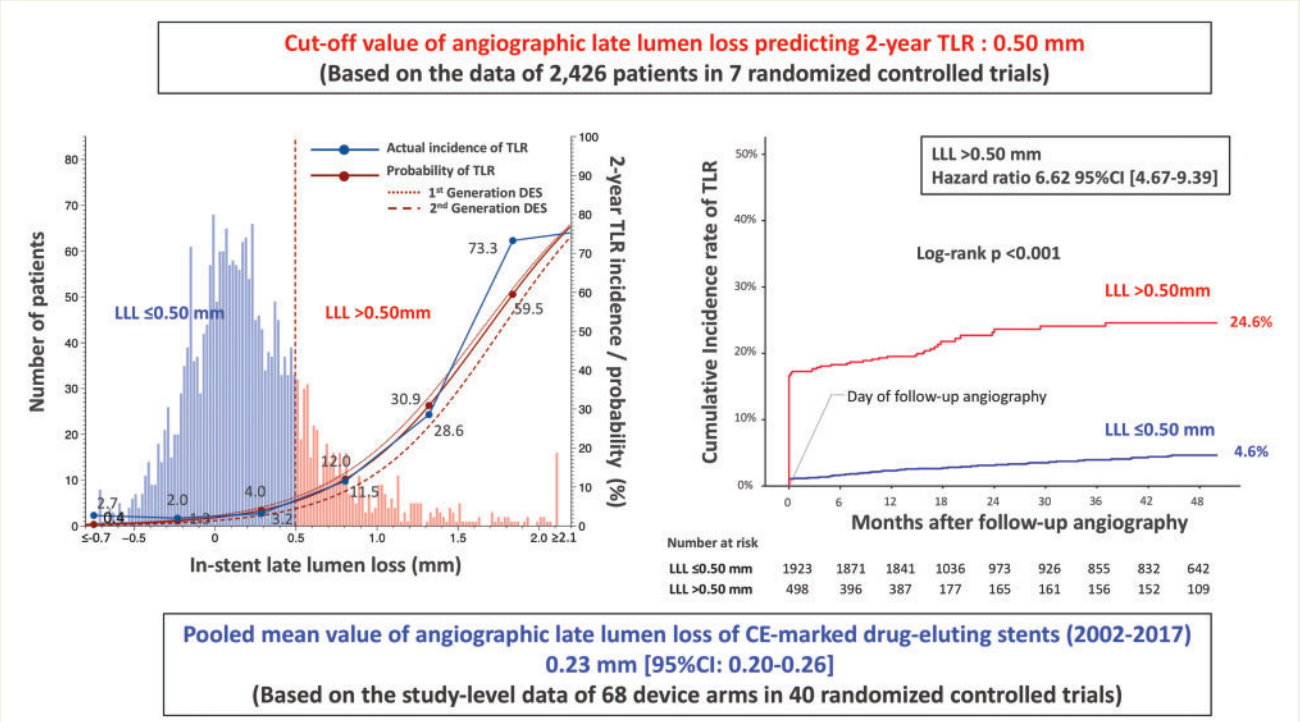


Figure 4 Meta-regression analysis between mean in-stent late lumen loss (*A*), percentage of lesions with late lumen loss >0.50 mm (*B*) and the incidence of 1-year target lesion revascularization in the drug-eluting stent trials. Grey areas between dotted lines indicate 95% confidence intervals of regression curves. Bubble size for each study is proportional to the inverse of the variance. DES, drug-eluting stent; LLL, late lumen loss; TLR, target lesion revascularization.

repeat revascularization, the value of QCA before the repeat revascularization is used and carried forward as the follow-up QCA parameter (e.g. LLL) whereas, in most of the cases, pre-repeat revascularization performed in urgent clinical setting and outside the investigating centre, IVUS or OCT is not available.[34]

Limitations

There are several limitations to the current analysis. First, in the patient-level analysis, we selected seven randomized controlled trials analysed by the same angiographic core laboratory with exact criteria described in the Methods section. However, the current analysis might have involved selected population with undetected biases. Second, in the patient-level analysis, there were disparities in the definitions of clinical events among the trials even though all the trials were conducted by the same clinical research organization. Third, in the patient-level analysis, the timings of the follow-up angiography were different across the trials. However, time to event counted from the moment of follow-up angiography for the survival analysis so that subsequent clinical events were landmarked from that moment. Fourth, inherent to these angiographic follow-up studies, there might be operator bias with regard to the performance of a repeat intervention driven even by the oculostenotic reflex even though TLRs reported in the studies were adjudicated as clinically indicated TLR according to the ARC definition. Fifth, there were relatively small



Take home figure In 2426 patients from seven randomized controlled trials treated with first- and second-generation drug-eluting stents, the probability regression curve showed an exponential relationship between in-stent late lumen loss and 2-year incidence of target lesion revascularization. Late lumen loss <0.5 mm was not associated with increased incidence of target lesion revascularization. Pooled mean value of angiographic late lumen loss of CE-marked drug-eluting stents (2002-2017) in 40 randomized controlled trial was as low as 0.23 mm. CI, confidence interval; DES, drug-eluting stent; TLR, target lesion revascularization.

number of the patients with LLL >1.0 mm in the study population. Sixth, the meta-regression analysis with the percentage of the lesion with LLL >0.50 mm was conducted under the assumption of normality of LLL distribution.[35–37]

Conclusions

In the current study, a limited prediction ability of LLL was observed in low value range, suggesting that low values of LLL may not serve as predictor of TLR. The optimal cut-off value of LLL for predicting TLR with a reasonable sensitivity and specificity was identified as 0.50 mm. This cut-off value has a potential to be applied to the clinical treatment decision making and the establishment of non-inferiority boundary of efficacy endpoint in device studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: P.W.S., M.S., B.C., and Y.O. have served as consultants to and/or as members of the advisory board of Abbott Vascular. C.C. has received research grants from Heart Flow and Biosensor. S.W. has received research contracts to the institution from Amgen, Abbott, Biotronik, Boston Scientific, and St Jude. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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