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Inter- and intra-core laboratory variability in the quantitative coronary angiography analysis for drug-eluting stent treatment and follow up

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Abstract

Aim: To evaluate inter-core laboratory variability of quantitative coronary angiography (QCA) parameters in comparison with intra-core laboratory variability in a randomized controlled trial evaluating drug-eluting stents.

Methods: A total of 50 patients with 62 coronary lesions were analyzed by four analysis experts belonging to an Angiographic Core Laboratory (ACL: 1 expert) and a Cardiovascular Imaging Core Laboratory (CICL: 3 experts). QCA was based on the same standard operating procedure, but selections of projection and cine frames were at the discretion of each analyst. Inter- and intra-core laboratory variabilities were evaluated by accuracy, precision, Bland Altman analysis, and coefficient of variation.

Results: Pre-MLD (minimal lumen diameter) was significantly smaller in results from ACL than those from all CICL experts. Number of analyzed projections did not affect pre-MLD results. Acute gain was larger in ACL than in CICL2. No significant difference was observed in late loss and loss index between inter-core laboratories. Agreement between core labs in the Bland-Altman analysis for each QCA parameter was as follows (mean difference, 95% limits of agreement): pre-MLD (–0.32, –0.74 to 0.10), stent MLD (0.08, –0.28 to 0.44), acute gain (0.22, –0.44 to 0.88), and late loss (–0.07, –0.69 to 0.55). Agreement between analysts in CICL (mean difference, 95% limits of agreement) was: pre MLD (–0.03, –0.37 to 0.31), stent MLD (0.15, –0.15 to 0.45), acute gain (0.05, –0.45 to 0.55), and late loss (0.04, –0.52 to 0.60). The widest limits of agreement among three analyses were shown in both analyses. Width of limited agreement in the intra-core laboratory analysis tended to be smaller than the inter-core laboratory analysis with these parameters. Coefficient of variation tended to be larger in lesion length (LL), acute gain, late loss, and loss index in inter- and in intra- core laboratory comparisons.

Conclusion: Inter-core laboratory QCA variability in late loss and loss index analysis could be similar to intra-core laboratory variability, but more strict alignment between core laboratories would be necessary for initial procedural data analysis.

Keywords: clinical trial, core laboratory, coronary angiography, drug-eluting stent, late loss, long-term, minimal lumen diameter, quantitative coronary angiography, validation

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Introduction

Quantitative coronary angiography (QCA) has played a crucial role in evaluating interventional techniques and assessing the results of new technologies.[1] Beyond angiographic metrics, recently developed angiography-derived fractional flow reserve (FFR) may be a useful tool for diagnosing ischemia-producing lesions in patients with non-complex coronary artery disease.[1,2] Meanwhile, although QCA metrics such as acute gain and late lumen loss proved to be instrumental in assessing new technologies, it is true that there

are still multiple factors that affect QCA results, including guide catheter size,[3] contrast injection into the vessel, cine projection selection, number of cine projections, cine frame selection,[4] and decision of reference vessel segment. During the QCA process, manual processes cannot be completely eliminated. Therefore, sources of variability could exist during the process of preparation of cine films and QCA; it would be still preferable to evaluate inter- and intra-observer reliability of QCA analysis in multicenter controlled trials despite the development of well-accepted and widely distributed QCA systems. Previous studies that evaluated inter- and intra- core laboratory (lab) variability of QCA results have been published mainly over the last 20 years.[5–7] In the era of drug-eluting stent (DES), complex lesions such as diffuse, bifurcated, or chronic total lesions have been indicated for percutaneous coronary intervention (PCI) more frequently than balloon angioplasty or bare-metal stent owing to new devices and improved long-term results. For complex lesions, QCA analysis may be less accurate compared with simple analysis under the use of current QCA algorithms.[8,9] Recently, an inter-core lab variability in analyzing QCA for bifurcation lesions was reported using dedicated software for bifurcations.[10] Although these studies reported acceptable variability between core labs, the corresponding core labs used the same cine frame in exactly the same cine projections.[7,10] That is, a comparison was performed under conditions favorable for QCA. However, manually selected cine series and frame selection might influence the results from the standpoint of practical analysis even in core labs in which experienced analysts analyze angiographic data using the same protocol. To date, no core lab validation study has been conducted for lesions, including complex ones, in which cine film series and cine frame were selected at the discretion of the analysis experts.

Methods

Subjects

The Japan-Drug Eluting Stents Evaluation: A Randomized Trial [J-DESsERT (J-D)] study is a prospective, multicenter, randomized, non-inferiority trial in terms of target vessel failure at 8 months after the index PCI procedure comparing Cypher™ sirolimus-eluting stent (SES) (Cordis/Johnson & Johnson, Miami Lakes, FL, USA) with Taxus™ paclitaxel-eluting stent (PES) (Boston Scientific Corp, Natick, MA, USA) in Japan.[11] Patients eligible for implantation of DES were enrolled in J-D and randomly assigned to undergo PCI with either SES or PES. Of the 3533 patients enrolled in J-D between May 2008 and August 2010, follow-up angiography at 8 months after stent implantation was performed in 600 patients as a QCA sub-study. Among the QCA sub-group subjects, the initially registered consecutive 50 patients were used for this study.

Study background: validation of Japan Cardiovascular Imaging Core Lab as a core lab

The Angiographic Core Lab (ACL) at Brigham and Women's Hospital was an independent core lab in the J-D study. When the J-D study started, CICL was organized by the sponsor of J-D (Association for Establishment of Evidence in Interventions) to promote randomized controlled trials in the field of interventional cardiology in Japan. CICL intended to validate QCA analysis quality by comparing QCA results with those from ACL using the same cine films registered in the J-D. This validation study was included in the J-D QCA sub-study. Three QCA analysis experts working in CICL participated in this study. The two core labs were aligned by the standard operating procedure (SOP) of QCA (Appendix).

The J-D study was approved by the institutional review board or medical ethics committee at each participating center, and written informed consent was obtained from all patients. The trial was registered on the http://www.clinicaltrials.gov website, with a unique identifier [ClinicalTrials.gov identifier: NCT00708669].

QCA methods

(1) The QCA protocol was based fundamentally on the SOP of ACL.[7] QCA data analyzed at ACL was used as a control. CICL attempted to decrease the absolute differences as much as possible by strengthening the consensus on the SOPs. Three CICL experts (CICL1, 2, 3) subsequently analyzed the same cine films blindly to analyze data from ACL and other CICL experts.

(2) Cine angiographic acquisition protocol (guidelines to angiography) in the J-D study At least a 6-Fr (diagnostic and/or guiding catheter) size was required as the reference

source.[3] Quality evaluation of cine angiograms taken at research sites and feedback to each site using feedback sheets were performed to improve and unify cine angiograms among research sites at the beginning of the J-D study.

(3) Cine projections and cine frames were selected independently by experts in ACL and CICL.
Inter- and intra- core lab variability in QCA analysis was evaluated using analysis data by four experts.

(4) QAngioXA version 6.0 (Medis, the Netherlands) was used in both core labs[12] as an unified QCA system.

(5) Image calibration was performed using the contrast-filled diagnostic or guiding catheter (at least
6-Fr size).[3]

(6) Selection of cine projections and cine frames to analyze

During qualitative review of the cine angiograms the experts had selected, two (orthogonal if available) projections, demonstrating the normal reference segment and stenosis in an unforeshortened projections without overlap, were selected for analysis. However, in some cases, the number of views applicable for QCA was limited (the second view does not fulfill the criteria), and selection of projections was at the discretion of experts. The values of two projections were averaged. If one view was selected, the single number was adopted. Normal reference and minimal lesion diameters were averaged from two projections. Cine frame for each view was also selected by each expert in each core lab.

(7) Once image calibration had been performed, normal and diseased arterial segments were selected for analysis, and the computer-assisted edge detection algorithm was applied to obtain quantitative coronary dimensions.

(8) A 10-mm segment of normal reference vessel was calculated proximal and distal to the stenosis and was averaged for the determination of user-defined reference diameters.

(9) For the options of the QCA package, such as Gradient Field Transform (GFT),[9] flagging was used at the discretion of experts.

(10) Manual collection
On the judgment of the operator, manual adjustments were permitted if necessary.

(11) QCA variables
QCA variables included minimal lumen diameter (MLD), mean reference diameter (mean R) (mean of proximal and distal reference diameters), % diameter stenosis (%DS) (calculated from MLD and mean of proximal and distal reference diameters), lesion length (LL), acute gain (post MLD–pre MLD), stent MLD, late loss (post stent MLD–follow-up stent MLD), and loss index (late loss/acute gain).

(12) When comparing QCA data between two core labs, ACL data was used as a control.

Statistical analysis

All continuous variables are expressed as mean ± standard deviation (SD). The ratio of selected projection numbers (single or two), and restenosis rate are expressed as categorical variables. The two studied comparison levels are expressed in terms of systematic and random errors, whereby the systematic error (accuracy) is defined by the average value of the signed differences between the individual analyses at ACL and CICL (inter-core lab) or measurements by CICL 1, 2, and 3 (intra-core lab). The random error (precision) is defined by the SD of the signed difference of the individual analyses at ACL and CICL1, 2, and 3 or measurements by CICL 1, 2, and 3. Coefficient of variation is defined as precision/mean value of the corresponding parameter to show the relative variation among different parameters. Inter- and intra-core lab analyses of agreement (relationship) between pairs of observations of the same lesion were analyzed using Bland–Altman plots and linear regression correlation. The following pairwise comparisons were made: (1) inter-core lab comparison (ACL *versus* CICL1, ACL *versus* CICL2, and ACL *versus* CICL3) and (2) intra-core lab comparison (CICL1 *versus* CICL2, CICL1 *versus* CICL3, and CICL2 *versus* CICL3).

For all continuous variables (MLD, mean R, LL, stent MLD, %DS, acute gain, late loss, loss index), normal distribution was evaluated using Shapiro–Wilk W test. For normally distributed variable, inter-core lab comparison of QCA variables was made using one-way analysis of variance (ANOVA) with Dunnett *post hoc* analysis among four experts analysis using data at ACL as control. Intra-core lab comparison was performed using one-way ANOVA with Tukey–Kramer HSD test among

Table 1. Baseline patient and lesion characteristics.

Patient number	50
Sex female	13
Age (years)	68.8 ± 8.4
Diagnosis (AP/UAP/SMI)	40/4/6
Number of diseased vessels (1/2/3)	35/14/1
Prior myocardial infarction	9
Prior CABG	1
Lesion characteristics	
Lesion number	62
Target vessel (LAD/LCx/LMT/RCA)	28/17/0/17
Lesion type (A/B1/B2/C)	4/22/21/15
Lesion length (mm)	15.25 ± 6.05
Ratio of lesion length >20 mm	15
Implanted drug-eluting stents	
Cypher (patients/lesions/stent number)	24/30/31
Taxus (patients/lesions/stent number)	26/32/35

CABG, coronary artery bypass grafting.

three experts. When skewed variables are detected in at least one group, multiple comparison was evaluated by nonparametric analysis using Kruskal–Wallis test with Steel test in inter-core lab analysis and with Steel–Dwass test in intra-observer analysis. For all continuous variables, comparative test for homogeneity of variance (equality of variances) between groups in precision was compared between groups using F-test. Proportional variables were compared using chi-squared test and test or Fisher's exact test when applicable. Results are considered significant at $p < 0.05$. Statistical analysis was performed with JMP®10 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient and lesion characteristics

This study consisted of 50 patients with 62 lesions (Table 1). The mean age of study subjects was 68.8 years; 15 patients had multiple vessel disease. Of the lesions, 36 (58.1%) were complex (types B2 and C), and 15 (24.2%) were type C lesions (lesion length: >20 mm) according to the American Heart Association/American College of Cardiology classification.[13] Cypher stent or paclitaxel stents were implanted randomly according to the study protocol.[11]

Comparison of QCA variables between inter-core lab experts

Pre-MLD was significantly smaller in ACL expert than that for all CICL experts (Table 2). Pre-LL was smaller in ACL expert than that in CICL2 expert. ACL expert showed smaller post-MLD than CLCL3 expert and showed smaller post-mean R than CICL1 expert. Acute gain was larger in ACL expert than that in CICL2 expert, which was due mainly to the difference in pre-MLD. In the follow-up data, no significant difference was observed in all variables between inter-core lab experts. A significant difference was observed in pre-LL between CICL1 and CICL2, in post-mean R between CICL1 and CICL 3, and in post %DS between CICL1 and CICL3.

Accuracy, precision, coefficient of variation, agreement in Bland–Altman analysis, and correlation coefficient in all variables between inter- and intra- core lab experts

In accuracy, differences in values were very small in almost all groups except pre-MLD (–0.26 ± 0.20 to −0.32 ± 0.21) and %DS (9.94 ± 7.67 to 11.1 ± 7.63) in inter-core lab analysis (Table 3). In precision, the value was a little smaller in intra-core lab than in inter-core lab analysis in pre-MLD (0.14–0.17 *versus* 0.20–0.21), pre-mean R (0.16–0.18 *versus* 0.20–0.24), %DS (6.03–6.63 *versus* 7.67–8.88), stent MLD (0.11–0.15 *versus* 0.15–0.18), and acute gain (0.23–0.25 *versus* 0.25–0.33). Values were similar in LL (3.89–6.03 *versus* 4.48–4.88), late loss (0.20–0.32 *versus* 0.23–0.31), and loss index (0.15–0.22 *versus* 0.17–0.23). The agreement between core labs in the Bland-Altman analysis for each QCA metric was as follows (mean difference, 95% limits of agreement): pre-MLD (–0.32, –0.74 to 0.10), stent MLD (0.08, –0.28 to 0.44), acute gain (0.22, –0.44 to 0.88), and late loss (–0.07, –0.69 to 0.55). The agreement between analysts in CICL was as follows (mean difference, 95% limits of agreement): pre MLD (–0.03, –0.37 to 0.31), stent MLD (0.15, –0.15 to 0.45), acute gain (0.05, –0.45 to 0.55), and late loss (0.04, –0.52 to 0.60). The widest limits of

Table 2. Baseline QCA data.

		Pre ($n=62$)	*p* value (*versus* ACL)	Post ($n=62$)	*p* value (*versus* ACL)	Follow up ($n=53$)	*p* value (*versus* ACL)
MLD (mm)	ACL	0.75 ± 0.38	NA	2.51 ± 0.41	NA	2.31 ± 0.65	NA
	CICL1	1.04 ± 0.42	0.0001	2.62 ± 0.43	0.312	2.33 ± 0.64	0.998
	CICL2	1.01 ± 0.38	0.0006	2.55 ± 0.45	0.914	2.28 ± 0.67	0.994
	CICL3	1.07 ± 0.35	<0.0001	2.69 ± 0.40	0.046	2.46 ± 0.65	0.518
mean R (mm)	ACL	2.63 ± 0.46	NA	2.62 ± 0.47	NA	2.75 ± 0.44	NA
	CICL1	2.72 ± 0.53	0.641	2.84 ± 0.51	0.038	2.87 ± 0.50	0.434
	CICL2	2.65 ± 0.50	0.986	2.69 ± 0.49	0.757	2.76 ± 0.47	0.998
	CICL3	2.71 ± 0.45	0.706	2.60 ± 0.47	0.993	2.82 ± 0.43	0.791
%DS (%)	ACL	72.0 ± 11.9	NA	4.3 ± 9.8	NA	16.5 ± 18.6	NA
	CICL1	62.0 ± 13.0	<0.0001	7.1 ± 7.3	0.216	18.9 ± 16.8	0.833
	CICL2	62.1 ± 12.2	<0.0001	4.8 ± 9.6	0.986	17.6 ± 20.1	0.979
	CICL3	60.9 ± 10.3	<0.0001	1.1 ± 8.9	0.124	13.2 ± 18.2	0.693
lesion length (mm)	ACL	15.25 ± 6.05	NA	NA	NA	NA	NA
	CICL1	15.22 ± 6.28	1.0	NA	NA	NA	NA
	CICL2	18.53 ± 6.93	0.014	NA	NA	NA	NA
	CICL3	16.05 ± 6.32	0.829	NA	NA	NA	NA
stent (mm)	ACL	NA	NA	2.89 ± 0.40	NA	2.80 ± 0.55	NA
	CICL1	NA	NA	2.96 ± 0.45	0.673	2.82 ± 0.59	0.996
	CICL2	NA	NA	2.82 ± 0.43	0.629	2.70 ± 0.55	0.702
	CICL3	NA	NA	2.92 ± 0.42	0.952	2.81 ± 0.55	0.999
acute gain (mm)	ACL	NA	NA	1.76 ± 0.42	NA	NA	NA
	CICL1	NA	NA	1.59 ± 0.45	0.066	NA	NA
	CICL2	NA	NA	1.54 ± 0.45	0.014	NA	NA
	CICL3	NA	NA	1.63 ± 0.39	0.215	NA	NA
late loss (mm)	ACL	NA	NA	NA	NA	0.24 ± 0.43	NA
	CICL1	NA	NA	NA	NA	0.34 ± 0.41	0.573

(Continued)

Table 2. (Continued)

		Pre ($n=62$)	*p* value (*versus* ACL)	Post ($n=62$)	*p* value (*versus* ACL)	Follow up ($n=53$)	*p* value (*versus* ACL)
	CICL2	NA	NA	NA	NA	0.31 ± 0.53	0.806
	CICL3	NA	NA	NA	NA	0.30 ± 0.50	0.875
loss index	ACL	NA	NA	NA	NA	0.14 ± 0.28	NA
	CICL1	NA	NA	NA	NA	0.23 ± 0.31	0.377
	CICL2	NA	NA	NA	NA	0.19 ± 0.38	0.831
	CICL3	NA	NA	NA	NA	0.18 ± 0.33	0.908

ACL, Brigham and Women's Hospital angiographic core laboratory; CICL, cardiovascular imaging core laboratory; %DS, % diameter stenosis; MLD, minimal lumen diameter; NA, not available; QCA, quantitative coronary angiography.

Table 3. Accuracy, precision, CV, correlation coefficient.

	Inter-core lab					Intra-core lab				
		Accuracy	Precision	CV	*R* *p value*		Accuracy	Precision	CV	*R* *p value*
pre MLD (mm)	ACL –CICL1	–0.29	0.20	0.22	0.884 <0.0001	CICL1 –CICL2	0.03	0.16	0.16	0.927 <0.0001
	ACL –CICL2	–0.26	0.20	0.22	0.854 <0.0001	CICL1 –CICL3	–0.03	0.17	0.16	0.921 <0.0001
	ACL –CICL3	–0.32	0.21	0.25	0.836 <0.0001	CICL2 –CICL3	–0.06	0.14	0.13	0.925 <0.0001
pre mean R (mm)	ACL –CICL1	–0.09	0.21	0.08	0.918 <0.0001	CICL1 –CICL2	0.06	0.17	0.06	0.950 <0.0001
	ACL –CICL2	–0.02	0.24	0.09	0.876 <0.0001	CICL1 –CICL3	0.01	0.16	0.06	0.955 <0.0001
	ACL –CICL3	–0.08	0.20	0.07	0.903 <0.0001	CICL2 –CICL3	–0.05	0.18	0.07	0.937 <0.0001
pre % DS (%)	ACL –CICL1	9.94	7.67	0.11	0.814 <0.0001	CICL1 –CICL2	–0.06	6.28	0.10	0.877 <0.0001
	ACL –CICL2	9.89	8.88	0.13	0.729 <0.0001	CICL1 –CICL3	1.17	6.63	0.11	0.863 <0.0001
	ACL –CICL3	11.11	7.63	0.11	0.774 <0.0001	CICL2 –CICL3	1.22	6.19	0.10	0.862 <0.0001
lesion length (mm)	ACL –CICL1	0.01	4.86	0.32	0.691 <0.0001	CICL1 –CICL2	–3.32	6.03	0.36	0.586 <0.0001

(Continued)

Table 3. (Continued)

	Inter-core lab					Intra-core lab				
		Accuracy	Precision	CV	*R* *p value*		Accuracy	Precision	CV	*R* *p value*
	ACL –CICL2	–3.31	4.88	0.29	0.726 <0.0001	CICL1 –CICL3	–0.83	3.89	0.25	0.811 <0.0001
	ACL –CICL3	–0.80	4.48	0.29	0.738 <0.0001	CICL2 –CICL3	2.48	5.33	0.31	0.681 <0.0001
stent MLD (mm)	ACL –CICL1	–0.07	0.16	0.05	0.932 <0.0001	CICL1 –CICL2	0.15	0.15	0.05	0.941 <0.0001
	ACL –CICL2	0.08	0.18	0.06	0.913 <0.0001	CICL1 –CICL3	0.04	0.11	0.04	0.971 <0.0001
	ACL –CICL3	–0.03	0.15	0.05	0.933 <0.0001	CICL2 –CICL3	–0.11	0.14	0.05	0.947 <0.0001
acute gain (mm)	ACL CICL1	0.17	0.25	0.15	0.835 <0.0001	CICL1 –CICL2	0.05	0.25	0.16	0.843 <0.0001
	ACL –CICL2	0.22	0.33	0.20	0.717 <0.0001	CICL1 –CICL3	–0.04	0.24	0.15	0.852 <0.0001
	ACL –CICL3	0.13	0.28	0.17	0.760 <0.0001	CICL2 –CICL3	–0.09	0.23	0.15	0.864 <0.0001
late loss (mm)	ACL –CICL1	–0.10	0.23	0.79	0.847 <0.0001	CICL1 –CICL2	0.03	0.32	0.98	0.801 <0.0001
	ACL –CICL2	–0.07	0.31	1.13	0.814 <0.0001	CICL1 –CICL3	0.04	0.28	0.88	0.828 <0.0001
	ACL –CICL3	–0.06	0.29	1.07	0.815 <0.0001	CICL2 –CICL3	0.01	0.20	0.66	0.924 <0.0001
loss index	ACL –CICL1	–0.09	0.17	0.92	0.848 <0.0001	CICL1 –CICL2	0.04	0.22	1.05	0.812 <0.0001
	ACL –CICL2	–0.04	0.23	1.39	0.801 <0.0001	CICL1 –CICL3	0.05	0.16	0.78	0.874 <0.0001
	ACL –CICL3	–0.03	0.18	1.13	0.842 <0.0001	CICL2 –CICL3	0.01	0.15	0.81	0.918 <0.0001

ACL, Brigham and Women's Hospital angiographic core laboratory; CICL, cardiovascular imaging core laboratory; CV, coefficient of variation ; %DS, % diameter stenosis; MLD, minimal lumen diameter.

agreement among three analyses was shown in both inter-core lab and intra-core lab analyses. Overall, the value of coefficient of variation (CV) had similar tendencies between intra-core lab and inter-core lab variations (a little smaller in intra-core lab variation than inter-core lab variation) for all parameters. CV was as small as 0.10 in pre-mean R, pre-%DS, and stent MLD. CV of pre-MLD, LL, and acute gain was between 0.15 and 0.36. CV of late loss and loss index was largest (0.66–1.39). In correlation coefficient, each value was >0.80 except for pre-%DS (0.729–0.814) and

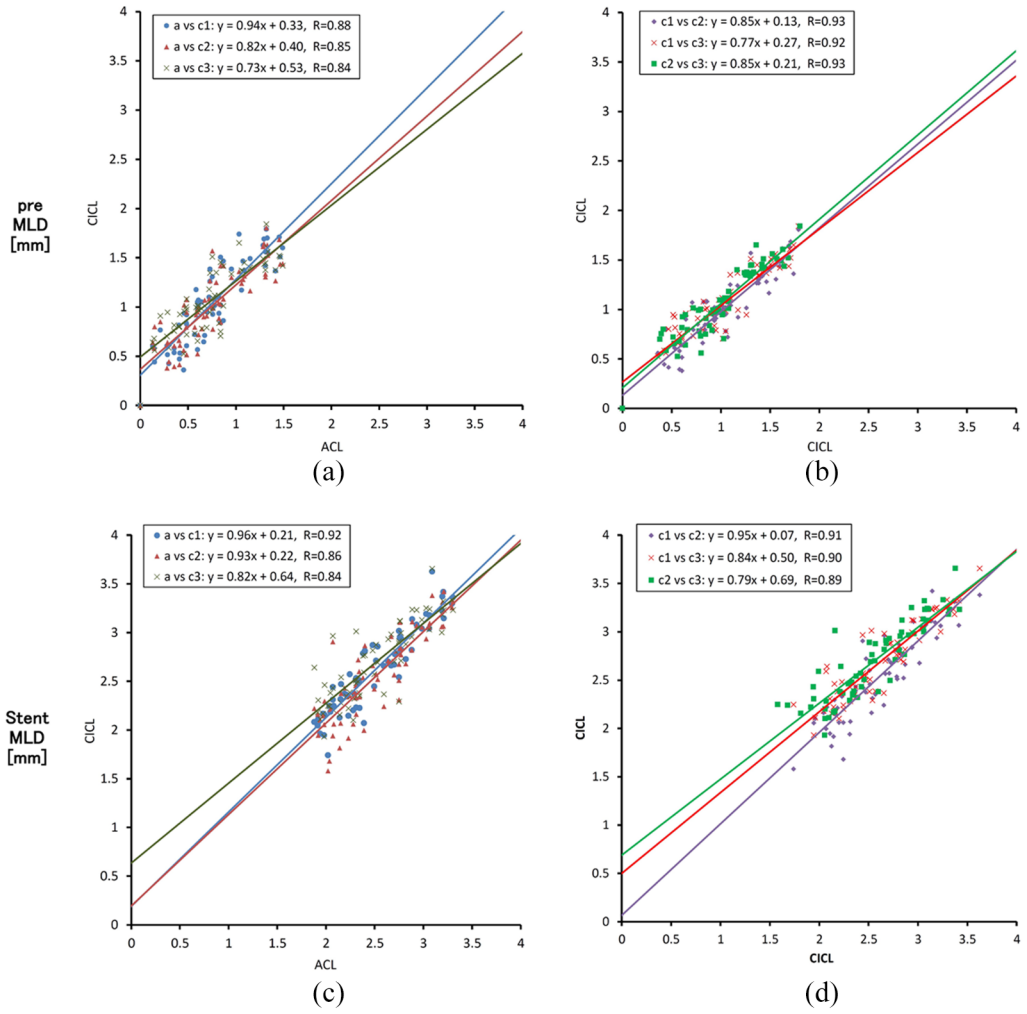

Figure 1. Correlation of pre-MLD (a, b) and stent MLD (c, d) between two analysis experts in inter- and intra-core lab analyses. Inter-core lab (a, c) and intra-core lab (b, d) correlations are shown side by side for visual comparison. In intra-core lab correlation curves, the horizontal axis shows CICL 1, 2 and vertical axis CICL 2,3, respectively. A good correlation is present between the two groups at follow up in both inter- and intra- core lab comparisons, with an *R* value of >0.90. MLD pre- and post- stent shows a slightly lower *R* value of <0.90 but >0.80 in inter-core lab comparison.
a, ACL; c1, CICL1; c2, CICL2; c3, CICL3;
MLD, minimal lumen diameter.

LL (0.691–0.738) in inter-core lab and only LL (0.586–0.811) in intra-core lab. In pre-MLD, pre-mean R, stent MLD, late loss, and loss index values were high ($R>0.80$) in both inter- and intra- core lab analyses. The correlation curves are shown in Figure 1 (A, B) (pre-MLD and stent MLD) and in Figure 2 (A, B) (acute gain and late loss) side by side. The Bland–Altman plots between the two groups are shown in Figure 3 (A, B) (pre-MLD and stent MLD) arranging inter-core lab and intra-core lab data side-by-side (pre-MLD, stent MLD, and follow-up MLD) and in Figure 4 (A, B) (acute gain and late loss). CV was smallest in pre-mean R and stent MLD and largest in late loss and loss index for both inter-core lab and intra-core lab analyses.

Coincident rate of the projection numbers between inter- and intra-core lab experts

The coincident rate of the projection number tended to be higher in intra-core lab than in inter-core lab pre-and post-PCI (Table 4). Projection number increased post-PCI and at

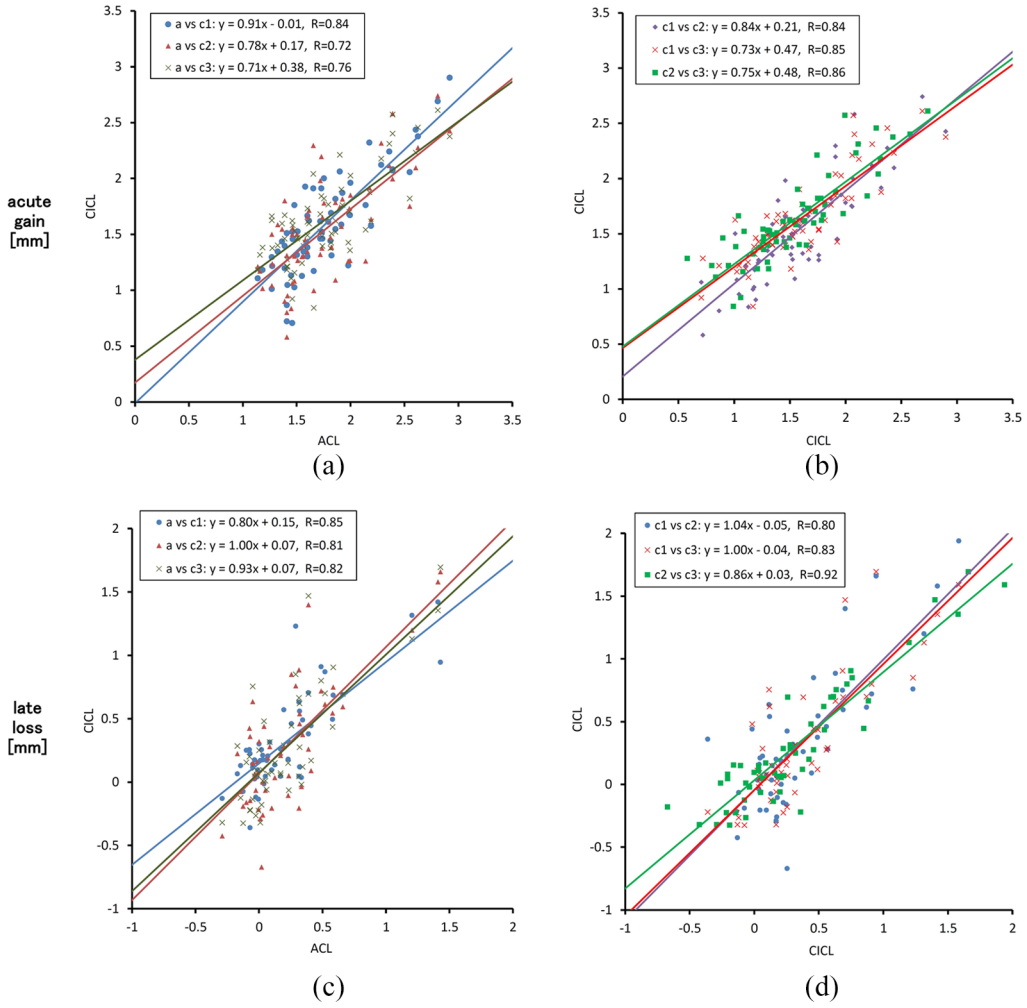

Figure 2. Correlation of acute gain (a, b) and late loss (c, d) between analysis experts in inter- and intra-core lab analyses. Inter-core lab (a, c) and intra-core lab (b, d) correlations are shown side by side for visual comparison. In intra-core lab correlation curves, horizontal axis shows CICL 1, 2 and vertical axis CICL 2,3, respectively. A good correlation is present between the two groups at follow up in both inter- and intra- core lab comparison, with an *R* value of >0.80, except for acute gain with a lower *R* value of 0.72.
a, ACL; c1, CICL1; c2, CICL2; c3, CICL3.

follow up in intra- and inter-core lab analysis. The ratio of projection number (single or two) was significantly higher in CICL1 than ACL and CICL2 in pre-PCI. It was significantly higher in CICL1 than in ACL in post-PCI and at follow up. Thus, it depended on each expert but not on each core lab. Significant difference in pre-MLD existed between ACL and CICL experts whether or not projection number was coincident in both laboratories (Table 5). This means projection number (single or two) did not affect the difference in pre-MLD between inter- and intra-core lab experts.

Comparison of restenosis rate between two core lab individuals

The restenosis rates at follow up were 4.8% (three cases) in ACL and CICL3, 8.1% (five cases) in CICL1, and 6.5% (four cases) in CICL2. No significant difference was observed among experts ($p=0.854$). The same three cases showed >50% in % DS in all experts. Three cases revealed >50% only in CICL 1 (50.6%, 50.9%) and 2 (69.2%), respectively.

Discussion

Inter-core lab variability of late lumen loss was comparable with intra-core lab variability in 62

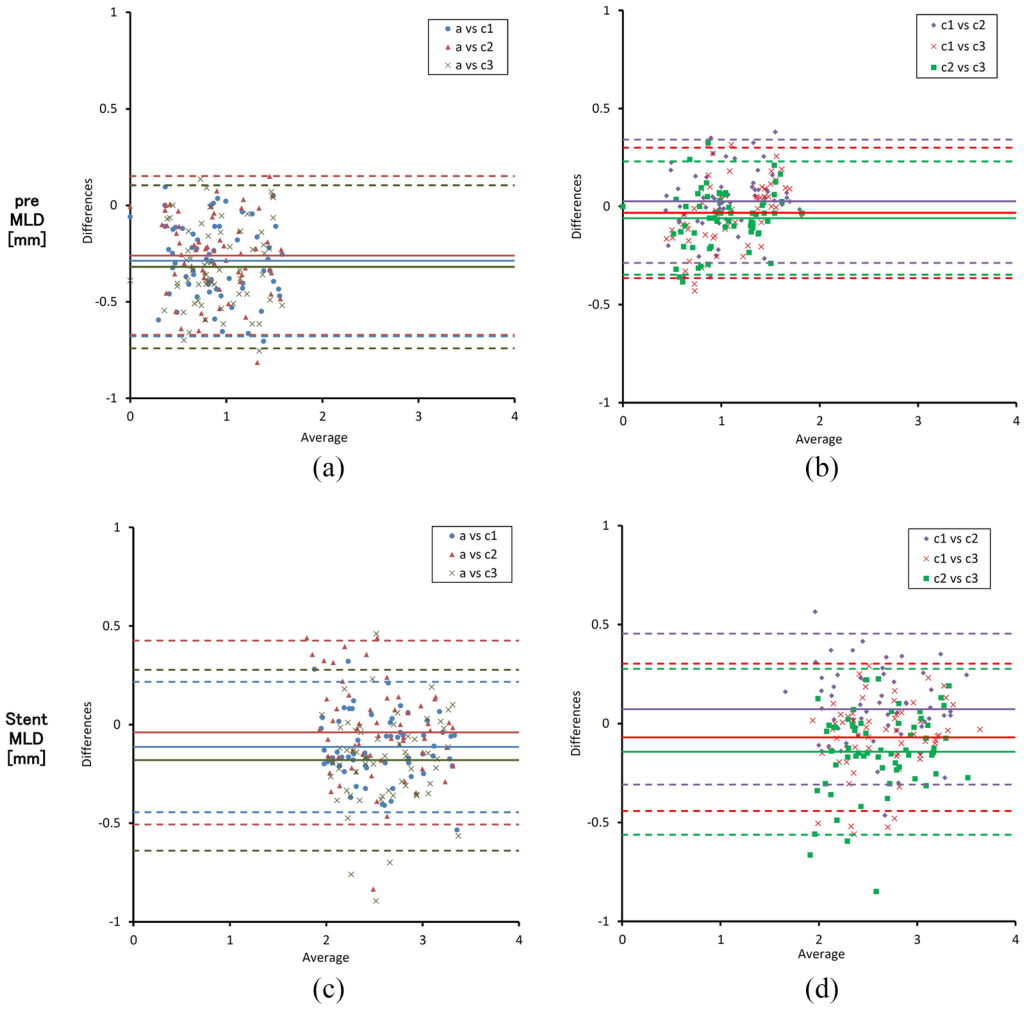

Figure 3. Bland–Altman plots of pre-MLD (a, b) and stent MLD (c, d) by inter- and intra-core lab analyses. The differences between the two core labs (panels on the left) and between the two analysis experts in CICL (panels on the right) are plotted against the mean values for each data set. Three data sets are superimposed in this graph with different colored marks. The mean value is on the horizontal axis plotted against the indicated differences on the vertical axis. The solid lines represent the mean difference, whereas the dashed lines indicate the 95% limits of agreement (2×SD of the mean difference). Note that the comparison of the mean difference (accuracy) and precision between inter-core lab (c) and intra-core lab (d) analysis was similar in stent MLD, with less wide limits of agreement in intra-core lab (b) in pre-MLD.
a, ACL; c1, CICL1; c2, CICL2; c3, CICL3; MLD, minimal lumen diameter.

lesions treated with DES in the J-D study under the conditions of same SOP and QCA system but free projection and cine frame selection. No significant difference was observed in restenosis rate between two core labs. In contrast, pre-MLD showed a significant difference between two core labs. These results suggest that QCA results of follow-up data (late loss, loss index, and restenosis rate) from different core labs using the same SOP in the era of DES could be rendered as not significantly different even if performed under free cine projection and cine frame selection. However, QCA results of initial procedural data need more strict alignment in QCA analysis between core labs.

Strength of this QCA variability study

The strengths of this study are as follows. (1) The basic QCA protocol was in alignment with SOP

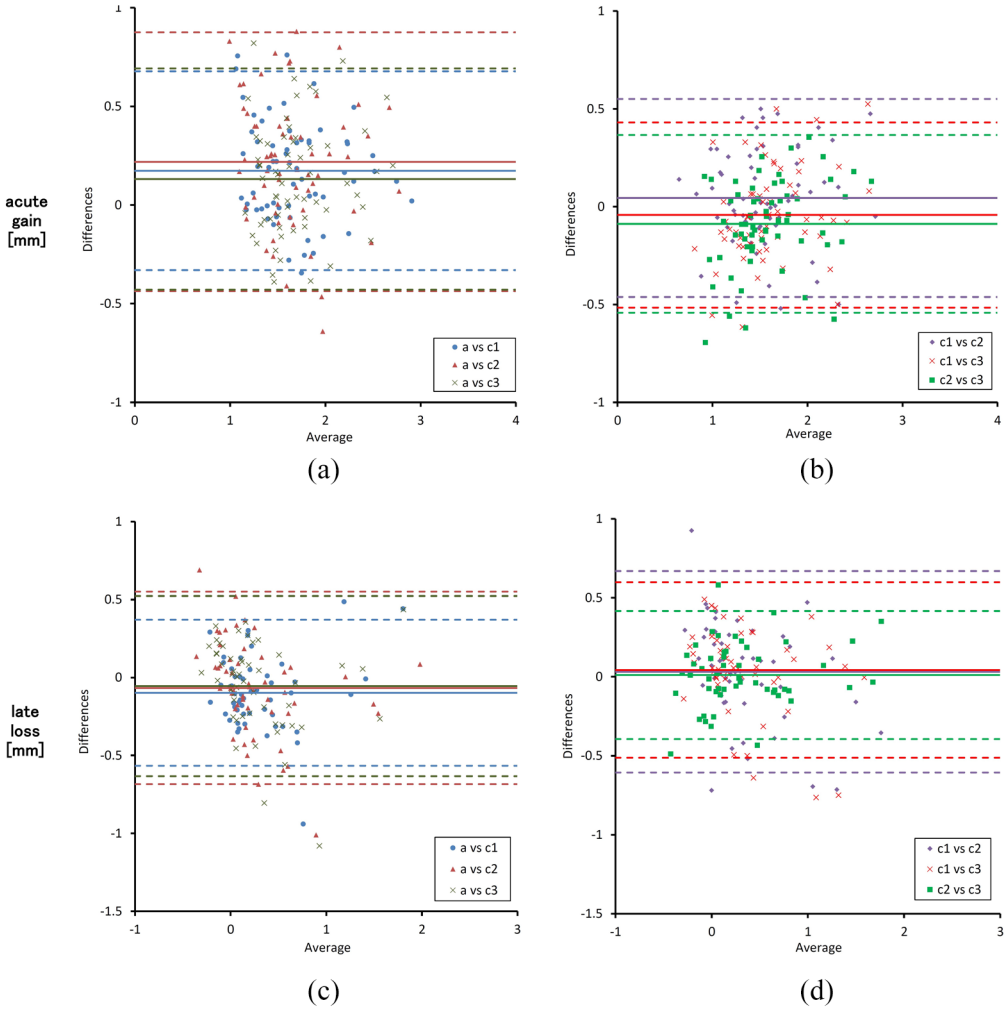

Figure 4. Bland–Altman plots of acute gain (a, b) and late loss (c, d) in inter- and intra-core lab analyses. The differences between the two core labs (panels on the left) and between two analysis experts in CICL (panels on the right) are plotted against the mean values for each data set. Three data sets are superimposed in this graph with different colored marks. The mean value is on the horizontal axis plotted against the signed differences on the vertical axis. The solid lines represent the mean difference, whereas the dashed lines indicate the 95% limits of agreement (2×SD of the mean difference). Note that the comparison of the mean difference (accuracy) and precision in inter-core lab (c) and intra-core lab (d) analysis was similar in late loss with less wide limits of agreement in acute gain in the intra-core lab (b) analysis.
a, ACL; c1, CICL1; c2, CICL2; c3, CICL3; MLD, minimal lumen diameter.

in the two core labs but cine projections and frame number of each projection were at the discretion of each expert. Thus, this study could evaluate the influence of these on QCA. Difference in selection of the angiographic view itself is a major determinant of variability in QCA.[14] Although it has been shown that differences in frame selection from the same angiographic view do not influence the accuracy and variability to a large extent,[15] selection was limited to the end-diastolic phase. Our recent study showed the influence of cine frame selection on the QCA results under blind cine frame selection.[4] The target lesions included complex type B2 and type C lesions (58.2%), which could be the potential source of variance between experts. These features might have yielded differences between our study and previous studies that also evaluated inter- core lab variability.[5,6] (3) Follow-up data, including late loss, loss index, and restenosis rate,

Table 4. Coincident rate of the projection number between two core laboratories and between analysis experts.

Inter core laboratories			
	Pre	**Post**	**Follow-up**
ACL *versus* CICL1	49 (79.0%)	53 (85.5%)	43 (81.1%)
ACL *versus* CICL2	44 (71.0%)	47 (75.8%)	44 (83.0%)
ACL *versus* CICL3	45 (72.6%)	53 (85.5%)	43 (81.1%)
Intra core laboratory			
	Pre	Post	Follow-up
CICL1 *versus* CICL2	51 (82.3%)	52 (83.9%)	44 (83.0%)
CICL1 *versus* CICL3	56 (90.3%)	58 (93.5%)	49 (92.5%)
CICL2 *versus* CICL3	53 (85.5%)	56 (90.3%)	46 (86.8%)
Percent of projection number			
(Pre)	2	1	mean
ACL	50 (80.6%)	12 (19.4%)	1.81
CICL1	61 (98.4%)	1 (1.6%)	1.98
CICL2	50 (80.6%)	12 (19.4%)	1.81
CICL3	55 (88.7%)	7 (11.3%)	1.89
(Post)	2	1	mean
ACL	51 (82.3%)	11 (17.7%)	1.82
CICL1	60 (96.8%)	2 (3.2%)	1.97
CICL2	50 (80.6%)	12 (19.4%)	1.81
CICL3	56 (90.3%)	6 (9.7%)	1.90
(Follow up)	2	1	mean
ACL	41 (77.4%)	12 (22.6%)	1.77
CICL1	51 (96.2%)	2 (3.8%)	1.96
CICL2	42 (79.2%)	11 (20.8%)	1.79
CICL3	49 (92.5%)	4 (7.5%)	1.92

ACL, Brigham and Women's Hospital angiographic core laboratory; CICL, cardiovascular imaging core laboratory.

which are representative and important parameters in the interventional cardiology and obtained from pre, post, and follow-up parameters, were also evaluated. (4) The same QCA system and algorithm were used in both labs to eliminate the variability due to different systems.[5,8,10,12]

Variability of follow-up data between the two core labs

Late luminal loss has been proposed as a robust marker for evaluating DES in the overall population (either randomized or observational),[16,17] which is more reliable than restenosis rates at discriminating the effectiveness of different DES. In this study, although there were small differences in %DS and restenosis rate between two core labs, we think that these differences did not significantly affect clinical prognosis, because the two core labs showed similar late loss and restenosis rates at 8 month follow up. Inter core-lab variability (systemic and random errors) was similar to intra- core lab variability and remained within a level equivalent to that of previous studies. Thus, this study suggests that the two independent core labs might give the same QCA results of follow-up data for DES treatments if the same SOP and QCA system were used at the DES treatment stage.

Variability in initial data between the two core labs

In contrast, a significant difference was observed between the two core labs in pre-MLD and LL. The difference in LL could be due to projection selection and cine frame selections.[4,18] Because the difference in LL was detected also between intra-core lab analysis, these results might be due to each expert, rather than to the core lab. Cardiac construction may cause vessel flexion, which leads to change in LL. Determined reference sites might affect lesion length in very diffuse lesions with tapering. Because most non- foreshortening views, in which LL was measured, usually could be selected easily, the key projection should not be different among experts so frequently. Thus, selection of projection may not explain much LL variance. The use of three-dimensional QCA could be a potential alternative to lessen inter- and intra-core lab variability in LL, because accurate and robust reconstruction of the vessel centerline is achieved and the reproducibility of its applications, for example, the assessments of obstruction length and optimal viewing angle, is guaranteed.[2,19]

Difference in projection number and its effects on QCA outcome

We assumed that the number of projection(s) might have affected the MLD measurements

Table 5. Comparison of pre MLD between ACL and CICL.

	Overall	Coincident projection no.	Non coincident projection no.
ACL	0.75 ± 0.38 (*n* = 62)	0.75 ± 0.38 (*n* = 49)	0.76 ± 0.40 (*n* = 13)
CICL1	1.04 ± 0.42 (*n* = 62)	1.03 ± 0.42 (*n* = 49)	1.06 ± 0.41 (*n* = 13)
p value	<0.0001	<0.0001	0.0003
ACL	0.75 ± 0.38 (*n* = 62)	0.72 ± 0.40 (*n* = 44)	0.83 ± 0.33 (*n* = 18)
CICL2	1.01 ± 0.38 (*n* = 62)	0.98 ± 0.40 (*n* = 44)	1.07 ± 0.35 (*n* = 18)
p value	<0.0001	<0.0001	0.0005
ACL	0.75 ± 0.38 (*n* = 62)	0.77 ± 0.37 (*n* = 45)	0.70 ± 0.40 (*n* = 17)
CICL3	1.07 ± 0.35 (*n* = 62)	1.09 ± 0.32 (*n* = 45)	1.00 ± 0.43 (*n* = 17)
p value	<0.0001	<0.0001	0.0001

ACL, Brigham and Women's Hospital angiographic core laboratory; CICL, cardiovascular imaging core laboratory; MLD, minimal lumen diameter.

because a single view could show larger %DS than mean of two orthogonal views in eccentric lesions. However, this was not the case in our study. Each technician selected two suitable projections (ideally orthogonal) and the frame for each projection blinded from each other. Perfect single projection, or another projection with some compromise, was at the discretion of experts in both core labs. There was a little difference in ratio of projection number (single or two) among four experts. It seemed to depend on the experts rather than on the core labs. The coincident rate of projection number did not affect QCA results in MLD in our study. The results of our study confirm a recent report that showed that the worst view *versus* the average views provided similar results regarding percent diameter stenosis.[20]

Limitations

This study has several limitations. First, consistency in measuring complex and/or tight lesions might have been inadequate despite the consistency of algorithm and basic protocol of QCA SOP. More rigorous alliance in performing QCA analysis such as GFT and flagging might have decreased the difference of pre-MLD values between inter-core labs.[9] Although the dose and frequency of manual contour corrections, GFT, and flagging would be important for inter-core lab variability, they were not recorded in this study. Second, the sample size of the study was small, and we did not perform a power calculation to evaluate the difference in QCA parameters between inter- and intra-core labs. The justification of angiographic core laboratory as a reference might have been inadequate. We cannot completely exclude the possibility of significant difference in other parameters besides those that already showed significant difference by adopting a larger number of lesions.

Conclusion

There has been a continuing need for a central core lab in multicenter trials to optimize consistency. In some large studies, multiple central core labs could be required. Our study showed that inter-core lab QCA variability, including follow-up data from different core labs, could be similar to intra-core lab variability using same SOP and system, despite free projection and frame selection, but results of initial procedural data need more strict alignment between core labs.

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Conflict of interest statement

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Supplemental material

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