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Validation of a simplified intravascular ultrasound core lab analysis method in stented coronary arteries

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Abstract

Objectives: To validate a simplified core laboratory intravascular ultrasound (IVUS) analysis method based on frames with visually determined minimal lumen areas (MLAs) as compared with a comprehensive (per frame) analysis method.

Background: IVUS-guided percutaneous coronary intervention has proven to be superior to angiography-guided stenting. In clinical practice, cross-sections with visually determined MLA are measured to determine lesion severity or minimal stent area (MSA), however, its accuracy has not been compared with a comprehensive per frame analysis method.

Methods: A total of 50 stented coronary segments of anonymized core lab datasets were analyzed using a comprehensive analysis method and reanalyzed by two core lab analysts using the simplified method including a maximum of seven frames to be analyzed (the visually determined MSA, the first and last frame, and the MLA of each reference segment). The main parameters of interest were MSA, MLA in the reference segments, and plaque burden.

Results: The simplified method showed moderate agreement for measurement of the proximal MLA (7.51 ± 2.52 vs. 6.32 ± 1.88 mm^2, intraclass correlation coefficient [ICC] = 0.73), good agreement for the distal MLA (5.41 ± 1.85 vs. 5.11 ± 1.38 mm^2, ICC = 0.84) and plaque burden proximal (0.49 ± 0.12 vs. 0.50 ± 0.11, ICC = 0.88), and excellent agreement for the MSA (5.35 ± 1.05 vs. 5.32 ± 0.99 mm^2, ICC = 0.94) and plaque burden distal (0.47 ± 0.14 vs. 0.47 ± 0.12, ICC = 0.92), when compared with the comprehensive analysis method. Inter- and intraobserver analysis revealed good-to-excellent agreement for all parameters.

Conclusions: Measuring poststenting IVUS cross-sections with visually determined MLAs by experienced core lab analysts is an accurate and reproducible method to identify MLAs.

KEYWORDS
intravascular ultrasound, percutaneous coronary intervention, stent

1 | INTRODUCTION

Intravascular ultrasound (IVUS) allows a better appreciation of vessel and lumen dimensions, detailed morphological lesion classification guiding tailored lesion preparation, accurate stent sizing, and assessment of poststenting results.[1]

A consistent body of evidence has been accumulated over the past 30 years demonstrating superior outcomes of IVUS-guided stenting as compared to angiography-guided percutaneous coronary intervention (PCI).[2–6] Although the use of IVUS proved to result in significantly lower rates of death, myocardial infarction, and repeat revascularization in a wide variety of patients and lesions, this benefit appeared to be restricted to those patients in whom IVUS criteria for optimal PCI were met.[2,4]

As such, several stent optimization algorithms have been proposed by both clinical trials and expert panel documents, such as the MUSIC and ULTIMATE criteria and the optimization criteria as suggested by the European Association of Percutaneous Cardiovascular Interventions.[4,7,8] Irrespective of the different cut-offs per algorithm, minimal stent area (MSA) and relative stent expansion appeared to be the most consistent predictors for outcomes after PCI, with MSA being the more important.[2,9–16]

Clinical trials evaluating IVUS-guided procedures often relied on extensive per-frame analyses performed by experienced core laboratories.[17] Such analyses are time consuming, especially in light of larger trials with long stented lengths and multiple pullbacks per patient. The analysis of visually selected frames would avoid costs and time associated with these extensive analyses, but this approach has never been validated in a core lab setting.

In this article, we propose a standardized simplified core laboratory method for IVUS analyses based on visually determined minimal dimensions. The aim of the present study is to evaluate the performance of the simplified core laboratory method versus the gold standard (per-frame core laboratory method) and to assess the inter- and intraobserver reproducibility of the simplified core laboratory method.

2 | MATERIALS AND METHODS

2.1 | Patient population

The present data set included IVUS pullbacks of patients enrolled in the FANTOM II trial that underwent IVUS-guided PCI at the index procedure.[18] In brief, this trial evaluated the long-term safety and the efficacy of the Fantom bioresorbable scaffold (REVA Medical), a desaminotyrosine-derived polycarbonate sirolimus-eluting bioresorbable scaffold with a strut thickness of around 125 μm. Inclusion criteria included the presence of stable or unstable coronary artery disease with evidence of myocardial ischemia or a positive functional study, single de novo coronary artery lesions with an average reference diameter ranging between 2.5 and 3.5 mm, and an estimated lesion length <20 mm. The study was approved by the local ethics committee and all patients provided written informed consent.

2.2 | IVUS datasets

Postprocedural motorized IVUS pullbacks were performed after an intracoronary bolus of 200 μg nitroglycerine at 40 MHz (Boston Scientific or Infraredx) with a pullback speed of 0.5 mm/s. The catheter was positioned distal to the stented segment, at least 10 mm from the distal stent edge. The automated pullback acquired imaging data from the distal reference segment to at least 10 mm proximal to the proximal stent edge. Out of 61 available datasets, 50 were selected based on image quality for the present analysis.

2.3 | Standard core laboratory method versus a simplified method

The standard core laboratory method for the assessment of a poststenting segment of interest consisted of a per frame (1 frame/mm) analysis of motorized IVUS pullbacks including the stent implant and 5 mm proximal and distal to the stent (the proximal and distal reference segment). Three contours were delineated on IVUS: the endoluminal contour (lumen area), the leading edge of the struts (stent area), and the external elastic membrane area (vessel area). Minimal, maximal and mean lumen, stent, and vessel areas were calculated per segment. Relative stent expansion was defined as MSA/mean reference lumen area.[7] Plaque burden was calculated as plaque area (vessel area − lumen area)/vessel area and reported as mean value per segment. The standard method uses the average of all cross-sections analyzed.

The simplified core laboratory method started with the identification of the 5 mm reference segments (distal and proximal) and the contouring of four landmark frames: the first and the last frame of both the distal and proximal 5 mm reference segment (Figure 1). Additionally, at both the proximal and distal reference segments, the cross-sections with the visually determined minimal lumen area (MLA) were identified and measured. If the visually determined MLA coincided with one of the landmark frames, an additional distal or proximal frame adjacent to the landmark frame was used. The MSA frame was selected as the frame with the visually identified smallest stent area. Lumen, vessel, and stent areas (if applicable), were delineated at the site of the identified frames. MLA measurements were derived from the three frames measured at each of the proximal and distal reference segments. Two different stent expansion indices (ratio of MSA to mean reference lumen area) were evaluated: the first being based on six frames for the reference (MLA, first and last frame of each reference segment) and the second being based on four frames for the reference segment (first and last frame of each reference segment). For the assessment of plaque burden, we proposed three indices: plaque burden based on the same three

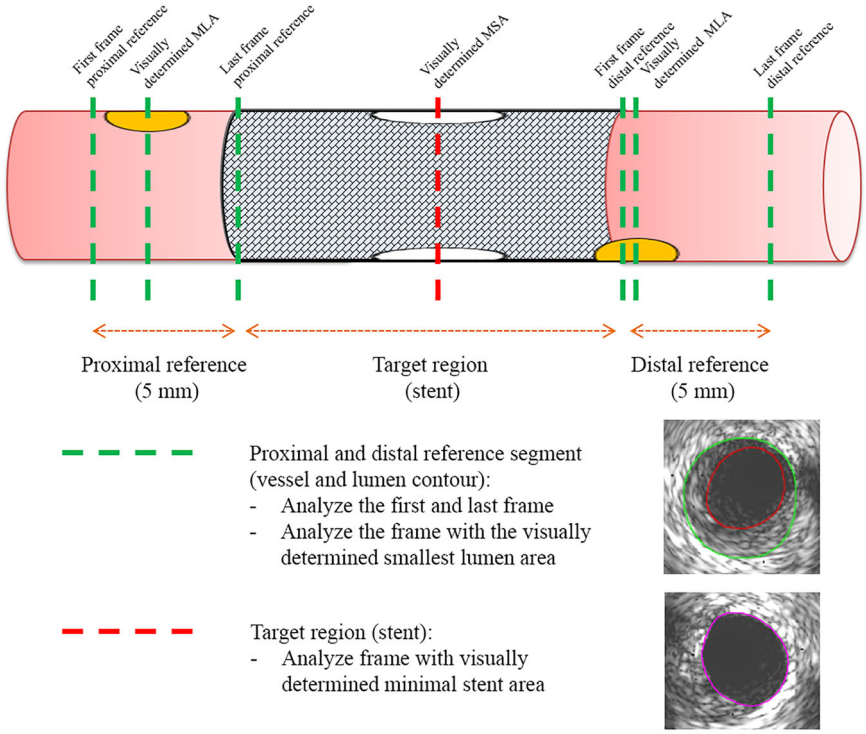

FIGURE 1 Depiction of the simplified core laboratory method for assessment of poststenting minimal lumen areas (MLAs). The simplified core laboratory method requires a maximum of seven frames to be identified analyzed: the four landmark frames (beginning and ending frames of the distal and proximal reference segment, green dotted lines), the visually identified MLA at both reference segments (green dotted lines), and the visually identified minimal stent area (red dotted line). [Color figure can be viewed at wileyonlinelibrary.com]

and two frames as described above, and plaque burden based on the MLA frame only.

Both the original as the new proposed simplified analyses were performed on motorized IVUS pullbacks at an independent core laboratory (Cardialysis) using QIvus® version 3.1 (Medis).

2.4 | Endpoints

Main outcome measures included the MSA, the MLA at the proximal and distal reference, and the plaque burden (MLA frame) at both distal and proximal reference segment. A complete list of parameters derived from the simplified method is provided in Supporting Information: Table S1.

2.5 | Accuracy and reproducibility assessment

All 50 stented segments (coronary wall covered by a stent plus 5 mm proximal and distal to the stent) were analyzed using the standard core laboratory method, including review by a second reader. Datasets were reanonymized and randomly renumbered three times, creating datasets A1, A2, and B. To assess accuracy, one experienced core laboratory analyst (Observer A) analyzed Dataset A1 using the simplified method, and we compared the output with the standard core laboratory method (reference). To assess interobserver reproducibility, a second experienced core laboratory analyst (Observer B) analyzed Dataset B. Finally, to assess intraobserver reproducibility, Analyst A analyzed Dataset A2 at least 2 weeks separated from each other.

2.6 | Statistical analysis

Variables are presented as means ± standard deviations, and compared using the paired *t*-test. Absolute and relative differences (RDs) of mean measurements were calculated as well as limits of agreements per the Bland–Altman method (mean difference ± 2 standard deviations). Intraclass correlation coefficients (ICCs) were calculated for all comparisons. ICC was classified as excellent (0.90–1.00), good (0.75–0.89), and moderate (0.50–0.74). Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc.) and a $p < 0.05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Accuracy

Table 1 summarizes the accuracy findings when comparing the simplified analysis of Observer A versus the reference (standard core lab method). The proximal MLA (7.51 ± 2.52 vs. 6.32 ± 1.88 mm^2, $p < 0.001$, RD = 18.8%, ICC = 0.73) showed moderate agreement, while the distal MLA (5.41 ± 1.85 vs. 5.11 ± 1.38 mm^2, $p = 0.029$, RD = 6.0%, ICC = 0.84), and the MSA (5.35 ± 1.05 vs. 5.32 ± 0.99 mm^2, $p = 0.61$, RD = 0.5%, ICC = 0.94), showed good and excellent agreement, respectively (see Figure 2 for correlation and Bland–Altman plots). Plaque burden measurements exhibited good (all plaque burden metrics in the proximal reference segment, and plaque burden distal based on two and three frames) to excellent (distal plaque burden based on MLA frame) agreement. Both stent expansion indices (based on four or six frames) showed good

TABLE 1 Accuracy of a simplified method compared with the standard core lab method

All mean areas are expressed in mm^2	Observer A (first analysis)	Reference	*p*-Value	Difference (absolute)	Difference (relative, %)	LOA	ICC
Proximal reference segment							
MLA	7.51 ± 2.52	6.32 ± 1.88	<0.001	1.19	18.8	[−1.37, 3.74]	0.73
Mean lumen area (three frames)	8.44 ± 2.61	8.14 ± 2.48	0.039	0.30	3.7	[−1.43, 2.04]	0.94
Mean lumen area (two frames)	8.89 ± 2.71	8.14 ± 2.48	<0.001	0.75	9.2	[−1.01, 2.51]	0.90
Mean vessel area (three frames)	15.5 ± 4.31	16.3 ± 4.15	<0.001	−0.77	−4.7	[−2.96, 1.43]	0.95
Mean vessel area (two frames)	15.9 ± 4.38	16.3 ± 4.15	0.023	−0.39	−2.4	[−2.42, 1.63]	0.97
Plaque burden (MLA frame)	0.49 ± 0.12	0.50 ± 0.11	0.39	−0.01	−1.6	[−0.12, 0.11]	0.88
Plaque burden (two frames)	0.44 ± 0.12	0.50 ± 0.11	<0.001	−0.006	−12.1	[−0.15, 0.03]	0.80
Plaque burden (three frames)	0.46 ± 0.12	0.50 ± 0.11	0.003	−0.03	−6.5	[−0.16, 0.09]	0.82
Distal reference segment							
MLA	5.41 ± 1.85	5.11 ± 1.38	0.029	0.31	6.0	[−1.47, 2.08]	0.84
Mean lumen area (three frames)	6.22 ± 1.79	6.13 ± 1.70	0.24	0.09	1.5	[−0.94, 1.13]	0.95
Mean lumen area (two frames)	6.62 ± 1.81	6.13 ± 1.70	<0.001	0.49	8.0	[−0.59, 1.57]	0.92
Mean vessel area (three frames)	11.2 ± 3.33	11.9 ± 3.35	<0.001	−0.61	−5.1	[−1.64, 0.42]	0.97
Mean vessel area (two frames)	11.6 ± 3.28	11.9 ± 3.35	<0.001	−0.30	−2.5	[−1.36, 0.77]	0.98
Plaque burden (MLA frame)	0.47 ± 0.14	0.47 ± 0.12	0.63	0.004	0.8	[−0.10, 0.11]	0.92
Plaque burden (two frames)	0.41 ± 0.12	0.47 ± 0.12	<0.001	−0.06	−11.9	[−0.12, 0.01]	0.87
Plaque burden (three frames)	0.44 ± 0.15	0.47 ± 0.12	0.021	−0.02	−5.0	[−0.15, 0.10]	0.88
Stented segment							
Minimal stent area	5.35 ± 1.05	5.32 ± 0.99	0.61	0.03	0.5	[−0.65, 0.70]	0.94
Stent expansion index (six frames)	0.76 ± 0.16	0.77 ± 0.14	0.22	−0.01	−1.8	[−0.17, 0.15]	0.85
Stent expansion index (four frames)	0.72 ± 0.14	0.77 ± 0.14	<0.001	−0.06	−7.5	[−0.20, 0.09]	0.80

Abbreviations: ICC, intraclass correlation coefficient; LOA, limits of agreement; MLA, minimal lumen area.

accuracy. Supporting Information: Tables S2 and S3 present similar accuracy results comparing the second analysis of Observer A and the analysis of Observer B with the reference.

3.2 | Interobserver reproducibility

Table 2 summarizes the interobserver reproducibility findings when comparing the simplified analysis of Observer B versus Observer A. The assessment of interobserver reproducibility for the minimal lumen and stent areas showed no differences (proximal MLA: 7.45 ± 2.52 vs. 7.51 ± 2.52 mm^2, $p = 0.46$, RD = −0.8%, ICC = 0.98; distal MLA: 5.35 ± 1.82 vs. 5.41 ± 1.85 mm^2, $p = 0.56$, RD = −1.2%, ICC = 0.93; and MSA: 5.42 ± 1.04 vs. 5.35 ± 1.05 mm^2, $p = 0.15$, RD = 1.4%, ICC = 0.94) (see Figure 3 for correlation and Bland–Altman plots). Plaque burden measurements both distal and proximal demonstrated good-to-excellent agreement. For most parameters, the ICC yielded an excellent agreement, but the stent expansion indices showed good agreement. Supporting Information: Table S4 presents similar reproducibility results comparing the second analysis of Observer A and the analysis of Observer B.

3.3 | Intraobserver reproducibility

Table 3 summarizes the intraobserver reproducibility findings when comparing the second and first analyses of Observer A. The assessment of intraobserver reproducibility for the five key parameters of interest showed no differences (see Figure 4 for correlation and Bland–Altman plots). For all parameters reported the ICC showed excellent agreement.

4 | DISCUSSION

The main findings of this study can be summarized as follows: (1) a simplified method for the assessment of lumen areas poststenting with visually guided selection of frames where lumen area is minimal,

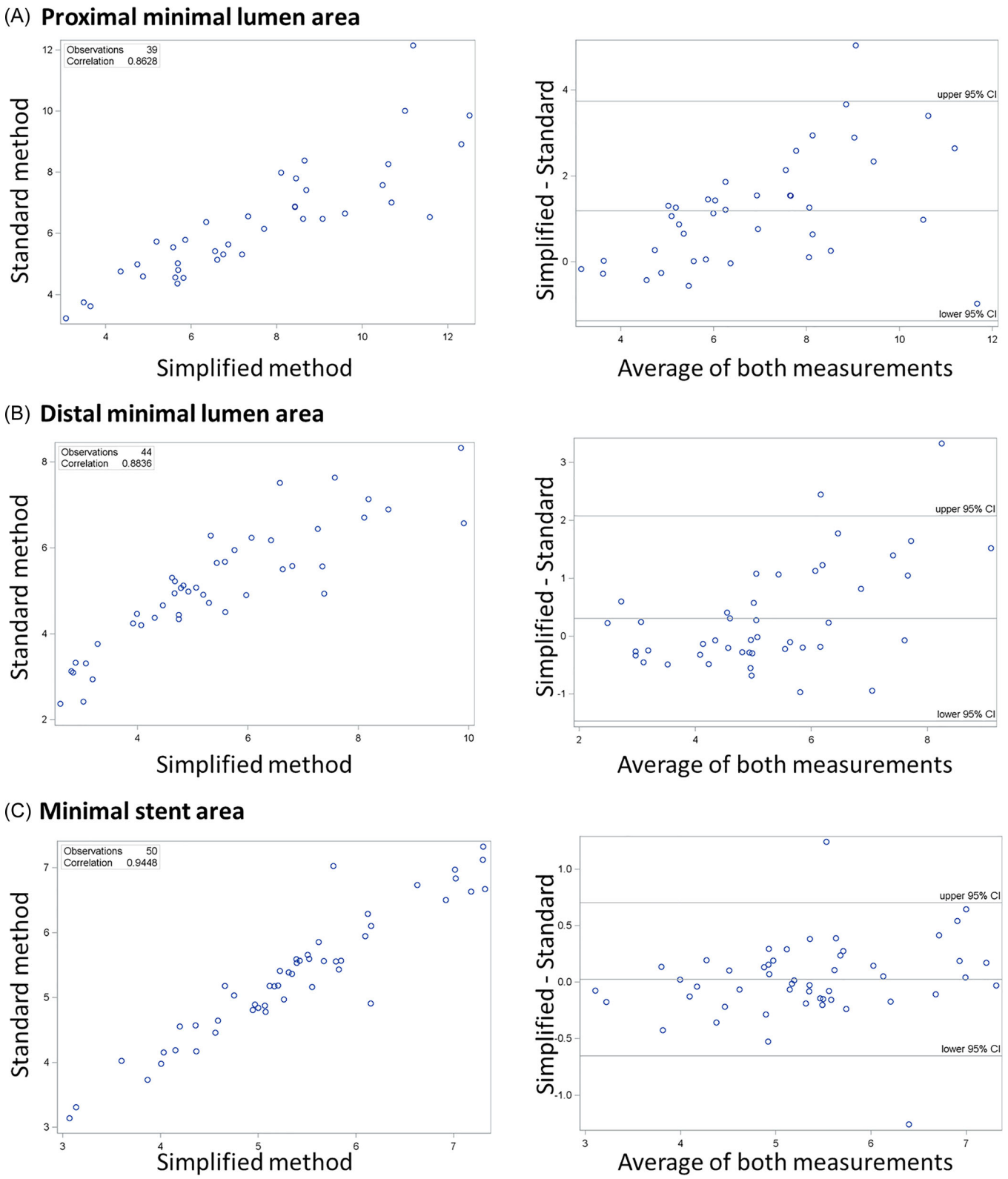

FIGURE 2 Scatter and Bland–Altman plots depicting the accuracy of a simplified method to measure minimal lumen areas. Panel 1A shows the accuracy of the simplified method versus the standard method for the proximal minimal lumen area, Panel 1B displays the accuracy for the distal minimal lumen area, and Panel 1C shows the accuracy for the minimal stent area. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Interobserver reproducibility with the simplified method

All mean areas are expressed in mm^2	Observer B (first analysis)	Observer A (first analysis)	*p*-Value	Difference (absolute)	Difference (relative, %)	LOA	ICC
Proximal reference segment							
MLA	7.45 ± 2.52	7.51 ± 2.52	0.46	−0.06	−0.8	[−1.10, 0.98]	0.98
Mean lumen area (three frames)	8.18 ± 2.66	8.44 ± 2.61	<0.001	−0.27	−3.2	[−1.16, 0.62]	0.98
Mean lumen area (two frames)	8.54 ± 2.75	8.89 ± 2.71	<0.001	−0.35	−4.0	[−1.45, 0.74]	0.97
Mean vessel area (three frames)	15.9 ± 4.26	15.5 ± 4.31	<0.001	0.41	2.6	[−0.91, 1.72]	0.98
Mean vessel area (two frames)	16.2 ± 4.34	15.9 ± 4.38	0.014	0.24	1.5	[−0.92, 1.41]	0.99
Plaque burden (MLA frame)	0.52 ± 0.12	0.49 ± 0.12	<0.001	0.03	6.0	[−0.06, 0.12]	0.90
Plaque burden (two frames)	0.47 ± 0.11	0.44 ± 0.12	<0.001	0.03	7.5	[−0.04, 0.10]	0.92
Plaque burden (three frames)	0.51 ± 0.12	0.46 ± 0.12	<0.001	0.04	8.9	[−0.07, 0.16]	0.83
Distal reference segment							
MLA	5.35 ± 1.82	5.41 ± 1.85	0.56	−0.06	−1.2	[−1.44, 1.31]	0.93
Mean lumen area (three frames)	6.02 ± 1.77	6.22 ± 1.79	0.011	−0.20	−3.2	[−1.16, 0.77]	0.96
Mean lumen area (two frames)	6.36 ± 1.79	6.62 ± 1.81	0.001	−0.26	−3.9	[−1.23, 0.70]	0.95
Mean vessel area (three frames)	11.4 ± 3.34	11.2 ± 3.33	0.008	0.19	1.7	[−0.69, 1.07]	0.99
Mean vessel area (two frames)	11.7 ± 3.27	11.6 ± 3.28	0.014	0.17	1.4	[−0.68, 1.02]	0.99
Plaque burden (MLA frame)	0.49 ± 0.14	0.47 ± 0.14	0.046	0.02	3.5	[−0.09, 0.12]	0.92
Plaque burden (two frames)	0.44 ± 0.13	0.41 ± 0.12	<0.001	0.03	7.5	[−0.05, 0.11]	0.92
Plaque burden (three frames)	0.46 ± 0.14	0.44 ± 0.15	0.072	0.02	3.8	[−0.10, 0.14]	0.91
Stented segment							
Minimal stent area	5.42 ± 1.04	5.35 ± 1.05	0.15	0.07	1.4	[−0.61, 0.76]	0.94
Stent expansion index (six frames)	0.80 ± 0.17	0.76 ± 0.16	<0.001	0.04	5.0	[−0.09, 0.17]	0.89
Stent expansion index (four frames)	0.76 ± 0.15	0.72 ± 0.14	<0.001	0.04	5.7	[−0.09, 0.17]	0.87

Abbreviations: ICC, intraclass correlation coefficient; LOA, limits of agreement; MLA, minimal lumen area.

mimicking clinical practice, proved to be an accurate alternative for a more extensive all-inclusive per-frame analysis when performed by a dedicated core laboratory; (2) the simplified method showed adequate inter- and excellent intraobserver reproducibility.

The recent ULTIMATE trial proved that stent underexpansion, residual edge disease, and large edge dissections are among the most important predictors of stent failure at 1 and 3-year follow-up.[4,19] Improved long-term outcome in the IVUS arm was only achieved in those patients who met these predefined optimization criteria, indicating that the benefit of IVUS relies on the accurate interpretation of the results and the feasibility of measuring the MSA, stent expansion, and plaque burden online, directly post-PCI.[4,19]

Historically, evaluation of the most important IVUS predictors of target vessel failure has been based on core lab assessments of large randomized controlled trial data. Extensive per frame analyses including the analyses of 1–2 frames/mm allow to accurately derive luminal, vessel, stent, and plaque areas, as well as volumes. Whereas these analyses provide data with a high granularity, they proved to be time-consuming and not feasible in routine practice. At present little is known on how these offline core lab analyses correlate to a simplified method that could mimic practically feasible online IVUS assessment to guide PCI.

In our study, we proposed a novel, simplified IVUS analysis method that has the potential (1) to standardize quantitative IVUS assessment during clinical practice and (2) to eliminate the need for extensive offline pullback analysis in clinical trials.

We showed that MSA as determined by the simplified analysis has excellent agreement when compared with the comprehensive per-frame core lab analysis. The MSA, which is thought to be the most clinically relevant parameter, was statistically identical between the two analysis methods. Although we found that the simplified IVUS analysis significantly overestimated (proximal MLA, distal MLA) or underestimated (stent expansion and plaque burden indices) some metrics, the magnitude of the RDs were in most cases negligible (ranging from 0% to 10%). An exception was the proximal MLA, in which we found a more strikingly present overestimation by the simplified IVUS analysis (RD = 18.8%). In fact, previous reports already demonstrated larger mean differences when comparing

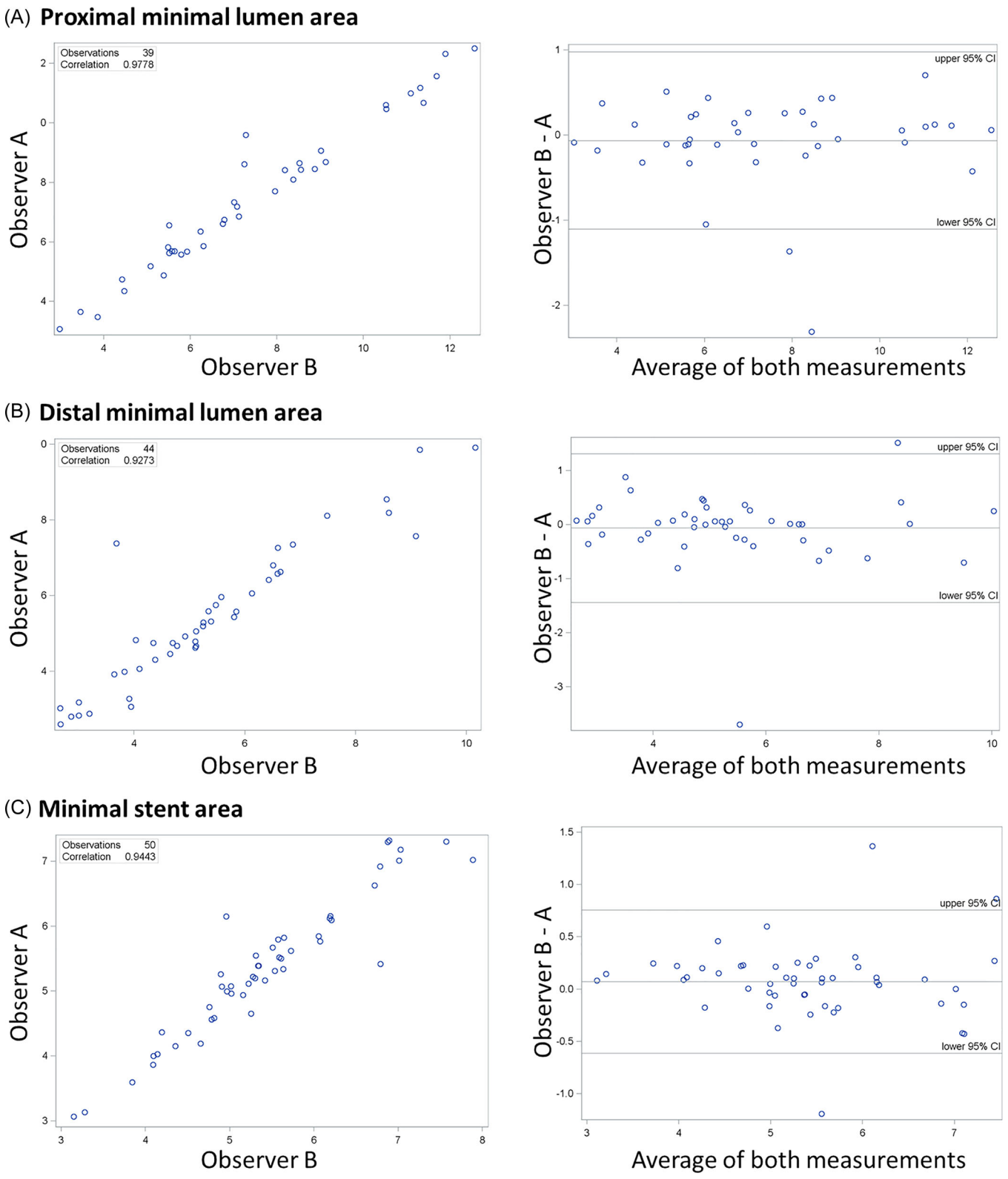

FIGURE 3 Scatter and Bland–Altman plots depicting the interobserver reproducibility of a simplified method to measure minimal lumen areas. Panel 2A shows the interobserver reproducibility of Observer A versus Observer B for the proximal minimal lumen area, Panel 2B displays the interobserver reproducibility for the distal minimal lumen area, and Panel 2C shows the interobserver reproducibility for the minimal stent area. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Intraobserver reproducibility with the simplified method

All mean areas are expressed in mm^2	Observer A (second analysis)	Observer A (first analysis)	*p*-Value	Difference (absolute)	Difference (relative, %)	LOA	ICC
Proximal reference segment							
MLA	7.45 ± 2.47	7.51 ± 2.52	0.34	−0.06	−0.8	[−0.85, 0.73]	0.99
Mean lumen area (three frames)	8.46 ± 2.65	8.44 ± 2.61	0.69	0.02	0.2	[−0.58, 0.62]	0.99
Mean lumen area (two frames)	8.95 ± 2.77	8.89 ± 2.71	0.37	0.06	0.7	[−0.74, 0.86]	0.99
Mean vessel area (three frames)	15.5 ± 4.18	15.5 ± 4.31	0.87	−0.01	−0.1	[−0.75, 0.73]	1.00
Mean vessel area (two frames)	16.0 ± 4.33	15.9 ± 4.38	0.53	0.04	0.3	[−0.74, 0.82]	1.00
Plaque burden (MLA frame)	0.49 ± 0.12	0.49 ± 0.12	0.72	0.002	0.4	[−0.07, 0.07]	0.96
Plaque burden (two frames)	0.43 ± 0.12	0.44 ± 0.12	0.61	−0.003	−0.7	[−0.07, 0.07]	0.96
Plaque burden (three frames)	0.47 ± 0.12	0.46 ± 0.12	0.84	0.002	0.3	[−0.09, 0.10]	0.92
Distal reference segment							
MLA	5.28 ± 1.88	5.41 ± 1.85	0.22	−0.13	−2.4	[−1.50, 1.23]	0.93
Mean lumen area (three frames)	6.21 ± 1.83	6.22 ± 1.79	0.84	−0.01	−0.2	[−0.71, 0.68]	0.98
Mean lumen area (two frames)	6.66 ± 1.86	6.62 ± 1.81	0.49	0.04	0.6	[−0.68, 0.75]	0.98
Mean vessel area (three frames)	11.2 ± 3.26	11.2 ± 3.33	0.98	0.001	0.01	[−0.68, 0.69]	1.00
Mean vessel area (two frames)	11.6 ± 3.27	11.6 ± 3.28	0.070	0.09	0.7	[−0.51, 0.68]	1.00
Plaque burden (MLA frame)	0.47 ± 0.15	0.47 ± 0.14	0.68	0.003	0.7	[−0.10, 0.10]	0.94
Plaque burden (two frames)	0.41 ± 0.12	0.41 ± 0.12	0.67	0.002	0.5	[−0.06, 0.06]	0.97
Plaque burden (three frames)	0.44 ± 0.15	0.44 ± 0.15	0.46	−0.01	−1.2	[−0.10, 0.09]	0.95
Stented segment							
Minimal stent area	5.42 ± 1.01	5.35 ± 1.05	0.19	0.07	1.3	[−0.68, 0.82]	0.93
Stent expansion index (six frames)	0.78 ± 0.17	0.76 ± 0.16	0.10	0.01	2.0	[−0.11, 0.14]	0.92
Stent expansion index (four frames)	0.72 ± 0.15	0.72 ± 0.14	0.36	0.01	1.0	[−0.11, 0.12]	0.92

Abbreviations: ICC, intraclass correlation coefficient; LOA, limits of agreement; MLA, minimal lumen area.

segments with larger luminal areas, which are prone to higher volumetric variability.[20,21] However, it is important to note that this overestimation in the proximal MLA led to marginal differences in indices that were derived from this proximal MLA, like plaque burden proximally based on the MLA (RD = −1.6%) and based on three frames (RD = −6.5%), and stent expansion based on six frames (RD = −1.8%).

Both stent expansion indices derived from the simplified analysis method (six or four frames used for the calculation of the mean reference) correlated well with the reference method and yielded good accuracy (both ≥0.80). In the past decades, several definitions for relative stent expansion have been adopted in clinical trials and consensus documents. Some propose to evaluate the relative stent expansion based on the distal reference segment only,[2–4,22] whereas others incorporate both the distal and proximal reference area in the calculation of the relative stent expansion.[7,8,23] Moreover, a number of more complex stent expansion models taking into account vessel tapering as well have been proposed in other clinical trials.[24,25] Until recently, absolute stent expansion (i.e., MSA) was seen as the most important predictor of patient outcome. However, absolute stent expansion should be used with caution, as maximal MSA is limited to vessel and stent size (and thus to stent location, and study population). A recent analysis of the IVUS substudy from ADAPT-DES evaluated the performance of absolute stent expansion, eight different relative stent expansion metrics, stent asymmetry, and stent eccentricity to predict lesion-specific outcomes (target lesion revascularization or stent thrombosis).[24] Interestingly, only stent expansion at MSA location (MSA/vessel area at MSA frame) was associated with clinical outcomes, whereas standard metrics such as MSA and conventional stent expansion were not. Irrespective of the final definition used, the present study supports the validity of a simplified method to compute stent expansion metrics based on the visually identified MSA frame.

With respect to inter- and intraobserver variability of the simplified analysis method we were able to mimic previously documented inter- and intraobserver variability of extensive per frame core lab analysis methods.[20,26,27] Overall, the inter- and

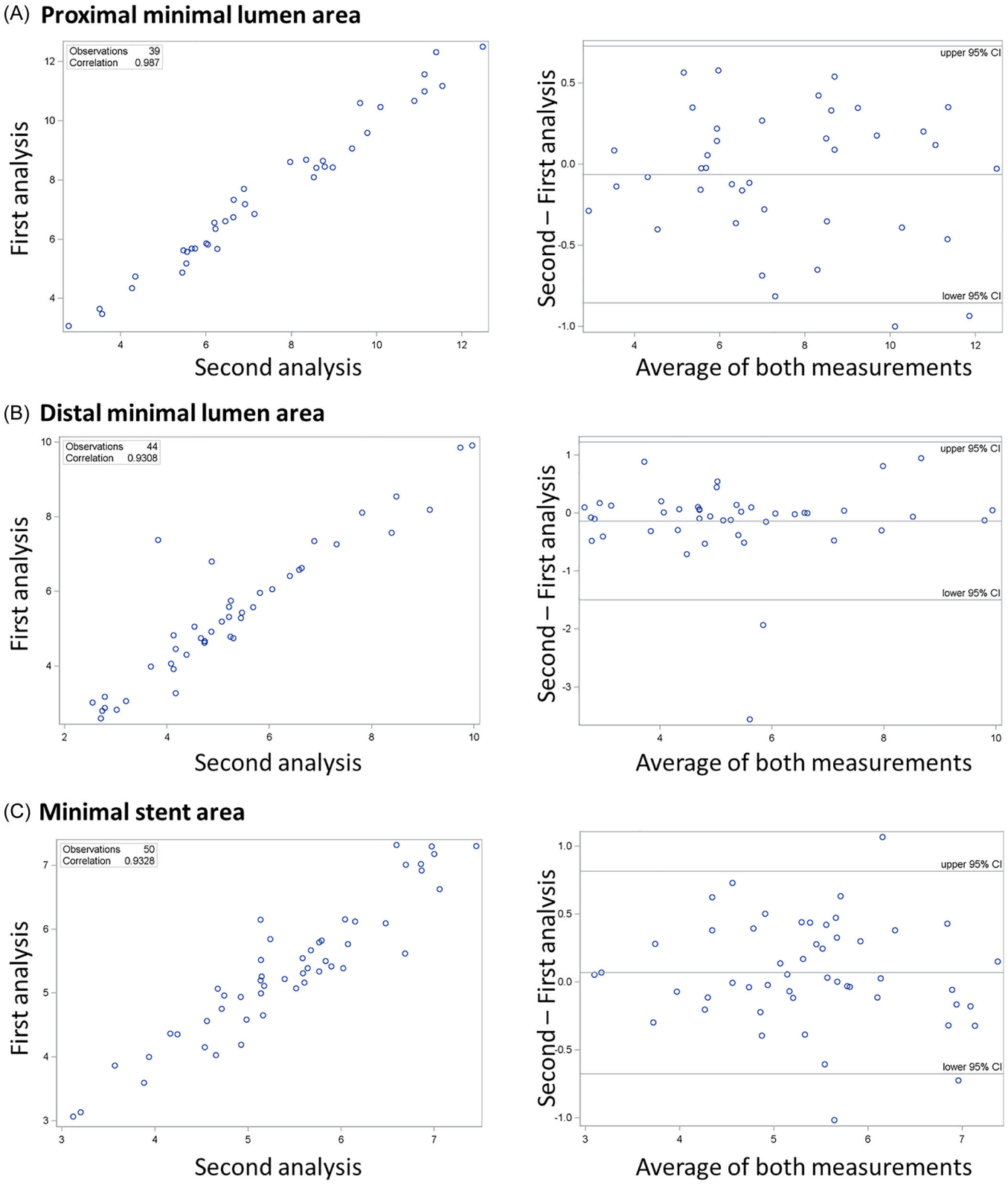

FIGURE 4 Scatter and Bland–Altman plots depicting the intraobserver reproducibility of a simplified method to measure minimal lumen areas. Panel 3A shows the intraobserver reproducibility of the first analysis versus the second analysis of Observer A for the proximal minimal lumen area, Panel 3B displays the intraobserver reproducibility for the distal minimal lumen area, and Panel 3C shows the intraobserver reproducibility for the minimal stent area. [Color figure can be viewed at wileyonlinelibrary.com]

intraobserver analysis yielded very high agreement for all parameters of interest.

The simplified analysis method has the potential to facilitate the improvement of long-term cardiovascular outcomes by providing a standardized way to accurately assess quantitative IVUS parameters during routine practice. At present, extensive online per frame pullback analysis is not feasible and validated artificial intelligence (AI) algorithms allowing automated lumen border detection of IVUS imaging are not yet available. With the proposed simplified IVUS analysis method we aimed to propose a validated and standardized framework for IVUS analysis feasible in routine practice with minimal inter- and intraobserver variability. Until validated AI algorithms are available, implementation of this standardized approach could help to better identify those cases at risk for target lesion failure.

Moreover, the simplified IVUS analysis method might also be of particular relevance for clinical research. By eliminating any redundant information derived from full pullback analysis, valuable resources such as time and cost can be saved. Small randomized controlled trials, without the financial budget, or even large randomized controlled trials, without the intention of deriving complete pullback information, could use this newly validated analysis method as an alternative to the extensive per frame core lab method.

4.1 | Limitations

A strength of this study is the involvement of a dedicated core lab equipped with experienced core lab analysts. The use of 40 MHz IVUS catheters might be a limitation with the now widespread availability of 60 MHz IVUS catheters, but we hypothesize that this does not affect the generalizability of our results. Secondly, the analyses were performed on pullbacks that met the required quality for core lab analysis, by highly trained core lab analysts including second review by an experienced interventional cardiologist. Our findings should therefore be interpreted with caution in a less controlled and maybe less experienced environment.

5 | CONCLUSION

Measuring poststenting IVUS cross-sections with visually determined MLAs by experienced core lab analysts is an accurate and reproducible method to identify MLAs when compared to a comprehensive per frame analysis. These findings may have implications for the design of clinical trials where posstenting IVUS optimization is considered.

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CONFLICT OF INTEREST

Dr. Daemen received institutional grant/research support from Astra Zeneca, Abbott Vascular, Boston Scientific, ACIST Medical Systems, Medtronic, Pie Medical, and ReCor Medical. Dr. Spitzer is a board member at Cardialysis. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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