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Coronary intravascular lithotripsy and rotational atherectomy for severely calcified stenosis: Results from the ROTA.shock trial

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Abstract

Background: Severely calcified coronary lesions present a particular challenge for percutaneous coronary intervention.

Aims: The aim of this randomized study was to determine whether coronary intravascular lithotripsy (IVL) is non-inferior to rotational atherectomy (RA) regarding minimal stent area (MSA).

Methods: The randomized, prospective non-inferiority ROTA.shock trial enrolled 70 patients between July 2019 and November 2021. Patients were randomly (1:1) assigned to undergo either IVL or RA before percutaneous coronary intervention of severely calcified coronary lesions. Optical coherence tomography was performed at the end of the procedure for primary endpoint analysis.

Results: The primary endpoint MSA was lower but non-inferior after IVL (mean: 6.10 mm^2, 95% confidence interval [95% CI]: 5.32–6.87 mm^2) versus RA (6.60 mm^2, 95% CI: 5.66–7.54 mm^2; difference in MSA: −0.50 mm^2, 95% CI: −1.52–0.52 mm^2; non-inferiority margin: −1.60 mm^2). Stent expansion was similar (RA: 0.83 ± 0.10 vs. IVL: 0.82 ± 0.11; $p = 0.79$). There were no significant differences regarding contrast media consumption (RA: 183.1 ± 68.8 vs. IVL: 163.3 ± 55.0 mL; $p = 0.47$), radiation dose (RA: 7269 ± 11288 vs. IVL: 5010 ± 4140 cGy cm^2; $p = 0.68$), and procedure time (RA: 79.5 ± 34.5 vs. IVL: 66.0 ± 19.4 min; $p = 0.18$).

Abbreviations: IVL, intravascular lithotripsy; MI, myocardial infarction; MSA, minimal stent area; NC balloon, noncompliant balloon; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RA, rotational atherectomy; TLF, target lesion failure; TLR, target lesion revascularization.

Conclusion: IVL is non-inferior regarding MSA and results in a similar stent expansion in a random comparison with RA. Procedure time, contrast volume, and dose-area product do not differ significantly.

KEYWORDS
calcified stenosis, drug-eluting stent, optical coherence tomography, rotational atherectomy

1 | INTRODUCTION

Coronary stenosis with severe calcification poses a particular challenge for percutaneous coronary intervention (PCI) and occurs more frequently as patient age increases.[1,2] A high plaque burden, calcified nodules, and coronary microcalcifications, concur to the complexity of these lesions and complicate interventional treatment.[3–5] For successful PCI of severely calcified lesions, it is imperative to achieve a sufficient plaque modification before stent implantation, thereby avoiding underexpansion that is associated with a significantly poorer clinical outcome.[6,7]

Balloon dilatation with dedicated balloons such as cutting-, scoring-, or ultrahigh-pressure devices often fails to prepare the calcified lesion adequately, as they are unable to apply the force required for calcium fractures and sufficient vessel expansion. Rotational atherectomy (RA) and orbital atherectomy, the current standard therapies for interventional treatment of severely calcified coronary lesions, have the problem of guidewire bias, possibly resulting in ineffective ablation, and may have limited effects on deep calcifications that result in incomplete stent expansion.[8–10] Additionally, periprocedural complications including periprocedural myocardial infarction (MI), perforation, atrioventricular block, or slow/no-flow are significantly more frequent with atherectomy than with balloon-based devices.[11–13]

Intravascular lithotripsy (IVL) has been recently introduced to modify calcified coronary lesions and is able to overcome some limitations of balloon angioplasty. IVL catheters are equipped with emitters that deliver pulsatile shockwaves. An electrical discharge vaporizes the fluid within the balloon to generate a rapidly expanding and collapsing bubble, with the mechanical energy being transduced to the vessel wall that modifies calcifications even in deeper vessel layers. In contrast to atherectomy techniques, IVL is less often associated with complications such as guidewire bias and possibly leads to a more homogeneous lesion preparation with fewer periprocedural complications.

To date, no randomized data are available for a comparison of RA and IVL for the interventional treatment of calcified coronary lesions. Therefore, the aim of this study was to compare IVL with RA in a randomized manner for the interventional treatment of severely calcified coronary vessel with respect to plaque modification and lumen and stent areas as determined by optical coherence tomography (OCT). As it is a rapid exchange, balloon-based technique, IVL has a lower procedural complexity than RA and might be suitable to provide an effective treatment option for calcified coronary lesions to a broader collective of patients.

2 | METHODS

2.1 | Study design

The ROTA.shock study is a randomized, prospective, non-blinded, double-arm, multicenter non-inferiority trial designed to compare the performance of the Shockwave™ coronary IVL system (Shockwave Medical Inc.) with rotational atherectomy regarding stent areas, lumen areas, and plaque modification as determined by OCT, as well as procedural success. The primary endpoint was the minimal stent area (MSA) at the end of the procedure, which is one of the most important predictors of stent failure or adverse clinical events after implantation of drug-eluting stents.[14–16] Secondary endpoints were mean stent diameter, minimal lumen diameter, mean lumen diameter, minimal lumen area, mean lumen area, mean stent area, minimal stent diameter, stent expansion, stent eccentricity, strut fractures, stent malapposition, troponin levels 24 h postprocedure, procedure time, contrast media consumption, radiation dose, target lesion failure (TLF) and target lesion revascularization (TLR) during in-hospital follow-up after 1 and 6 months.

From July 2019 until November 2021, 70 patients with clinically significant and severely calcified coronary lesions were included in 6 centers in Germany to be randomly assigned to RA or IVL. Randomization was performed in a 1:1 manner using envelopes. The main inclusion criteria were clinically relevant coronary stenosis with proven myocardial ischemia and severe calcification defined by coronary angiography as radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen as assessed by the operator.[17,18] Additional inclusion criteria were an angiographic reference vessel diameter between 2.5 and 4.0 mm, and a patient age > 18 years. The main exclusion criteria were cardiogenic shock and bifurcation lesions requiring two-stent strategies. Additional exclusion criteria were chronic total occlusions and in-stent restenoses. Detailed inclusion and exclusion criteria are shown in Supporting Information: Table 1.

All patients gave written informed consent before enrolment. The study was conducted in accordance in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the ethics

committee of the Medical Faculty, Justus Liebig University Giessen, Germany (Number: 231/18). The study was registered at https://www.clinicaltrials.gov with the identifier NCT04047368.

2.2 | Study procedure

After randomization of patients to either IVL or RA, PCI was performed via radial or femoral access with 6 or 7Fr. Before intervention, intraarterial or intravenous heparin was given to maintain an activated clotting time ≥250 s. At the beginning of the procedure, a native OCT scan of the lesion to be treated was acquired using a 2.7Fr Dragonfly™ imaging catheter (Optis™, Abbott Vascular). The mechanical retraction speed was 18 mm/s over a length of 54 mm with automated OCT acquisition. Flushing of the vessel was carried out with 20 mL of standard contrast media (e.g., Ultravist™ 370, Bayer AG) at an injection rate of 4 mL/s. Predilatation with a noncompliant (NC) balloon up to a diameter of 2.0 mm was undertaken if the imaging catheter could not be advanced due to the stenosis. If the imaging catheter could not be passed distal to the stenosis despite NC predilatation, native OCT was dispensed with.

If the patient was randomized to RA, a dedicated wire was advanced through the lesion. The burr size was selected according to a burr-to-angiographic reference vessel diameter ratio of 0.5. The rotational speed ranged between 140,000–180,000 rpm. NC balloon dilatation after RA and before stent implantation was recommended.

If the patient was randomized to IVL, the IVL balloon catheter (Shockwave C2™, Shockwave Medical) was inserted using a standard coronary guidewire and positioned in the lesion. The balloon diameter was selected 1:1 in relation to the angiographic reference vessel diameter. After positioning the IVL catheter in the target lesion, the balloon was inflated to 4 atm. After each treatment cycle of ten pulses the balloon was inflated to 6 atm (Shockwave C2™, Shockwave Medical). Treatment cycles were repeated as necessary to cover the whole target lesion and at least two to three cycles were administered to every segment of the calcified lesion, according to the study protocol.

Immediately after RA or IVL a second OCT scan (post-IVL/RA OCT) was acquired to assess the plaque modification by the two techniques.

PCI was continued by NC balloon dilatation and stent implantation of second-generation drug-eluting stents (e.g., Xience™, Abbott Vascular) according to current clinical guidelines. Stent diameter was selected according to angiographically determined reference lumen diameter. After stent implantation postdilatation with an NC balloon was obligatory. The NC balloon diameter was either equivalent to the stent diameter or up to 0.5 mm larger.

Upon completion of the procedure, intracoronary nitroglycerine was administered and a final OCT, covering the complete stent length, was acquired. Dual antiplatelet therapy was prescribed according to current clinical guidelines.

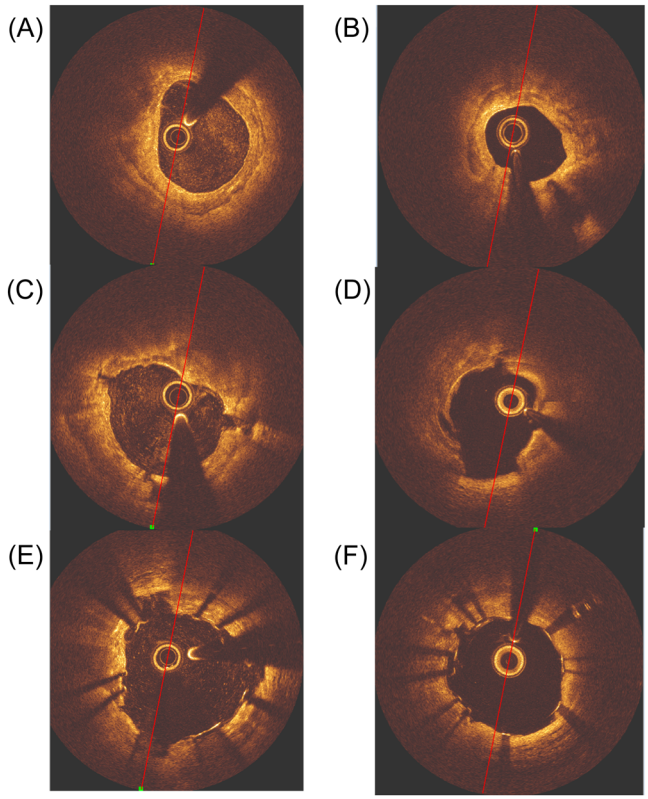

FIGURE 1 Representative optical coherence tomography (OCT) scans comparing intravascular lithotripsy (IVL) (A, C, E) and rotational atherectomy (RA) (B, D, F). OCT cross-sections of severely calcified coronary stenoses are shown in A and B. (C) The same vessel segment as A after IVL with characteristic fractures of the calcified plaque at 3, 6, and 10 o'clock. (D) The same segment as B after RA, with intima dissection at 8–9 o'clock and a fracture of the calcified plaque at 12 o'clock. (E) The final result after IVL and stent implantation of the same vessel segment shown in A and C. (F) The final result after RA and stent implantation of the same vessel segment shown in B and D. [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | OCT analysis

OCT image analysis was performed offline at the core lab (Medical Clinic 1, University Hospital Giessen) using dedicated software (QIVUS™ OCT Software, Medis). Representative OCT results after IVL and RA are shown in Figure 1. OCT cross-sectional images were analyzed at 1 mm intervals using the methods recommended in the expert consensus report for OCT and previous publications.[19–24] Detailed OCT analytical methods are provided in Supporting Information: Table 2. Final OCT pullbacks were analyzed in the first step to match the corresponding vessel segments in baseline and post-IVL/RA OCT using anatomical landmarks (e.g., side branches, characteristic plaque structures). Figure 2 shows an analysis of representative OCT scans.

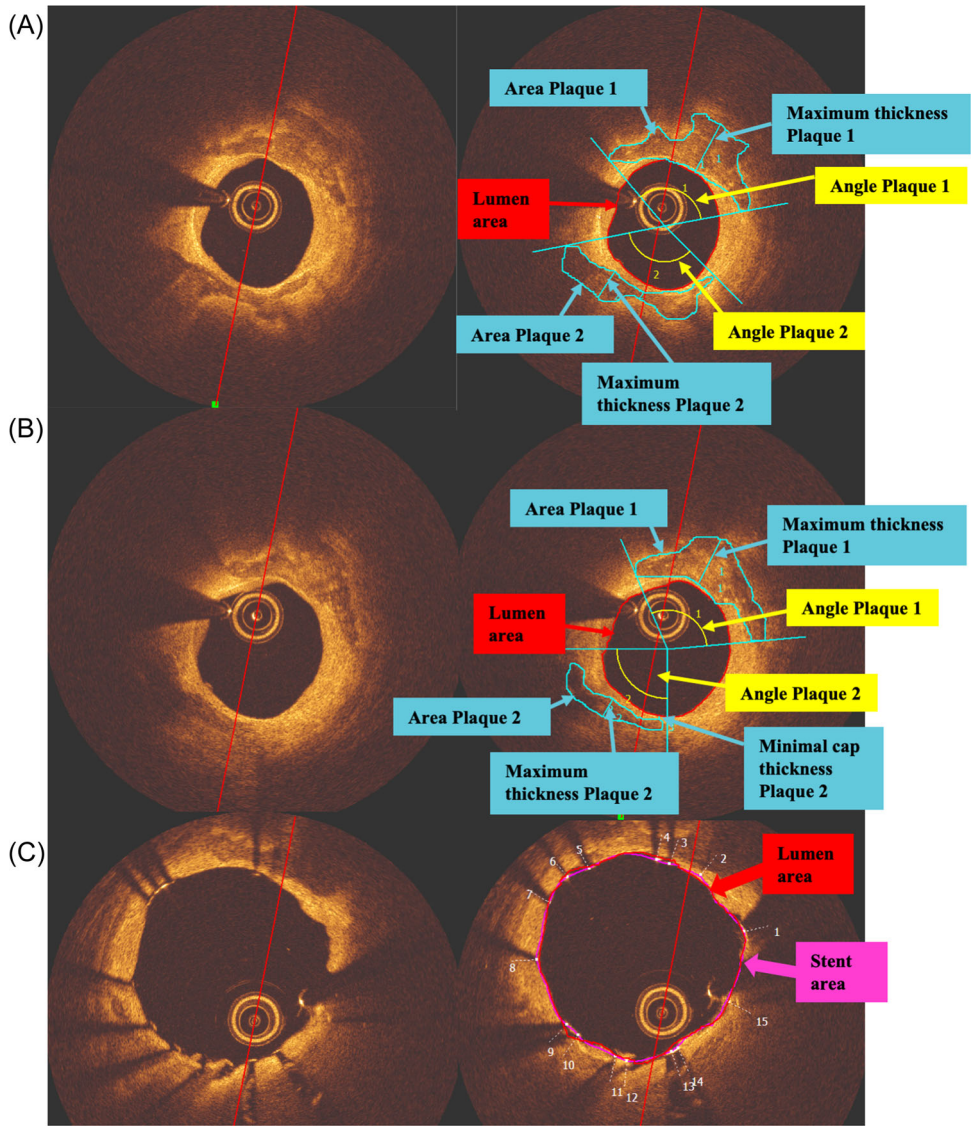

FIGURE 2 Representative optical coherence tomography (OCT) analysis of the same vessel segment at three different stages. Analysis of the preprocedural OCT (A), analysis of the OCT after intravascular lithotripsy (B), and analysis of the final OCT after stent implantation (C). The left OCT cross-section shows the native scan. Lengths, areas, and angles are marked on the OCT cross-sections on the right side. [Color figure can be viewed at wileyonlinelibrary.com]

2.4 | Follow-up

In-hospital follow-up data were collected until the patients' discharge. Blood sampling to measure high-sensitive troponin was performed before and 24 h after the index procedure. Postdischarge follow-up assessments were conducted 1 and 6 months after the index procedure by standardized telephone interview (see Supporting Information: Table 3).

2.5 | Statistical analysis

The study hypothesis was non-inferiority of IVL against the standard therapy RA regarding the primary endpoint MSA. In the preliminary case series for this project including four patients, an MSA of $6.1 \pm 1.7\,mm^2$ was determined after IVL. In comparison, Li et al.[25] showed in 2016 an MSA of $5.0 \pm 1.4\,mm^2$ after performing RA in 36 patients. Based on these data, sample size calculations were performed using the statistical program R with the TrialSize package (function: TwoSampleMean.NIS; Two Sample Mean Test for Non-Inferiority/Superiority).[26] An α error of 0.05, a power of 0.8, and a pooled SD of 1.5 were specified. The basic assumption was made that the MSA after IVL should not be smaller than $5.0\,mm^2$. This resulted in a sample size of 28 patients per group (IVL and RA).[26] Due to the possibility of exclusions of individual patients or lost-to-follow-up, a sample size of 35 patients per group was defined.

Statistical analysis of the per-protocol patient collective (final OCT available) regarding the primary endpoint was performed by calculating 95% confidence intervals (95% CIs) for the difference of the primary endpoint between IVL and RA. If the lower bound of the

CI does not exceed the non-inferiority margin, non-inferiority can be accepted. The non-inferiority margin used for the non-inferiority test was the difference between the prespecified margin of MSA after IVL (should not be smaller than 5.0 mm^2) and the observed MSA after RA (6.60 mm^2). In addition, a one-sided *t* test with a type 1 error of 0.025 was applied.

For all additional endpoints, metrically scaled variables are presented as means (±SD). Frequencies are presented as absolute values and percentages. Statistical analysis of additional endpoints for the protocol-defined patient collective was performed using Wilcoxon rank test. For dichotomous variables Fisher's exact test was utilized. Statistical analysis was performed using the statistical program R (R: A language and environment for statistical computing. R Foundation for Statistical Computing; Version 3.5.3).

3 | RESULTS

3.1 | Patient data

Seventy patients were included in the trial. The mean patient age was 73.3 ± 7.2 years and the majority were male (75.4%). There were no significant differences regarding baseline characteristics when comparing the RA and IVL group (Table 1). IVL was performed successfully in 33 out of 35 patients (94%) randomized to IVL treatment. In two of the 35 patients randomized to IVL, a cross-over to RA was necessary, because neither the IVL balloon nor an NC balloon for predilatation could be advanced into the lesion. Therefore, RA was performed in 37 patients, as there were two additional cross-over patients who were originally randomized to IVL. RA was performed successfully in all of these 37 patients. Final OCT scans for primary endpoint analysis were available from 28 patients (85%) out of the IVL group and from 33 patients out of the RA group (89%) (Figure 3). In two patients, one from the IVL group and one from the RA group, the OCT catheter could not be advanced over the stented segment to acquire the final run. The final OCT scans of the other seven patients were lost to analysis due to a software error and could not be reconstructed. This error occurred in the line of a software update of the OCT console that irretrievably deleted these seven runs.

TABLE 1 Baseline characteristics.

	Overall (*n* = 61)	RA (*n* = 33)	IVL (*n* = 28)	*p*
Age (years)	73.3 ± 7.2	74.4 ± 7.1	72.0 ± 7.3	0.18
Male	46 (75.4)	25 (75.8)	21 (75.0)	>0.99
BMI (kg/m^2)	27.8 ± 4.9	28.3 ± 4.9	27.1 ± 5.0	0.27
Previous MI	23 (37.7)	12 (36.4)	11 (39.3)	0.79
Previous PCI	41 (67.2)	23 (69.7)	18 (64.3)	0.83
Previous CABG	9 (14.8)	4 (12.1)	5 (17.9)	0.72
Hypertension	58 (95.1)	30 (90.9)	28 (100)	0.89
Diabetes mellitus	22 (36.1)	11 (33.3)	11 (39.3)	0.79
Hyperlipidemia	46 (75.4)	23 (69.7)	23 (82.1)	0.37
Active smoking	5 (8.2)	1 (3.0)	4 (14.3)	0.22
LVEF (%)	55.5 ± 6.9	54.9 ± 7.0	56.3 ± 6.9	0.86
Clinical presentation				
STEMI	1 (1.5)	0 (0.0)	1 (3.6)	0.46
NSTEMI	6 (9.8)	3 (9.1)	3 (10.7)	>0.99
Unstable angina	2 (3.3)	0 (0.0)	2 (7.1)	0.21
Stable CAD	50 (82.0)	29 (87.9)	21 (75.0)	0.32

Note: $x \pm s$ represents $X \pm 1$ SD; *a* (*b*) represents *n* (%).

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; IVL, intravascular lithotripsy; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; RA, rotational atherectomy.

3.2 | Procedural data

Predilatation before IVL or RA was performed more often in the IVL group than in the RA group and was necessary in 60.4% ($p = 0.04$) to position the IVL balloon within the target lesion. Predilatation before RA was performed in 30.3% of the patients in the RA group, which was mainly triggered by the intent to acquire a preprocedural OCT scan as allowed by the study protocol. Due to the severe calcification, a preprocedural OCT scan could only be acquired in 32 (52.5%) of the patients. NC balloon dilatation after IVL or RA and before stent implantation was performed in all patients as predetermined by the study protocol using a 1:1 ratio of balloon diameter to angiographic reference vessel size. There were no significant differences regarding contrast media consumption, radiation dose, and procedure time comparing both the techniques. No flow-limiting dissections, vessel occlusions, or incidents of cardiogenic shock were reported. Detailed procedural results are given in Table 2.

3.3 | Native OCT analysis

Preprocedural OCT analysis showed similar lumen dimensions in the RA and IVL groups with severe lesion calcification. The maximum angle of calcified plaque was 207.2 ± 80.0° with a mean thickness of 0.61 ± 0.10 mm over a total length of 16.72 ± 4.00 mm with no significant differences regarding lesion calcification in RA and IVL group (Table 3).

3.4 | Primary endpoint analysis

The final MSA after the procedure was smaller but non-inferior in the IVL (mean: 6.10 mm^2, 95% CI: 5.32–6.87 mm^2) compared with the RA group (mean: 6.60 mm^2, 95% CI: 5.66–7.54 mm^2) (Table 4 and Figure 4). The non-inferiority margin (−1.60 mm^2) used for the non-inferiority test is the difference between the prespecified margin of

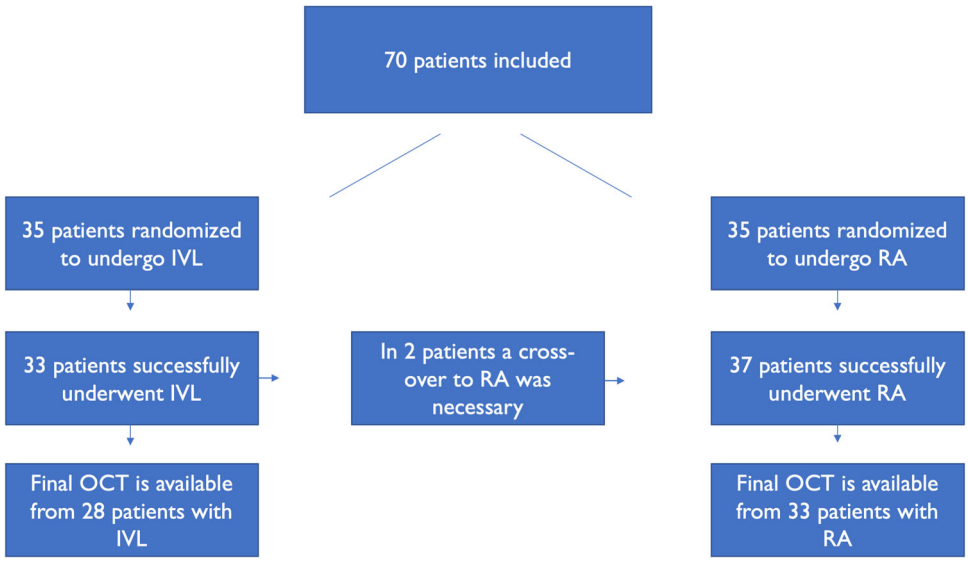

FIGURE 3 Study flow-chart. IVL, intravascular lithotripsy; OCT, optical coherence tomography; RA, rotational atherectomy. [Color figure can be viewed at wileyonlinelibrary.com]

MSA after IVL (should not be smaller than 5.0 mm^2; Figure 5A) and the observed MSA after RA (6.59 mm^2). Non-inferiority analysis showed that the 95% CI of the difference between MSA after IVL and RA (−0.50 mm^2, 95% CI: −1.52–0.52 mm^2) does not violate the non-inferiority margin of −1.60 mm^2 (Figure 5B). Therefore, IVL is non-inferior to RA regarding MSA.

3.5 | Final OCT analysis

There were no significant differences regarding stent and lumen dimensions when comparing the results after IVL with those after RA. There was, however, a tendency for a higher mean stent area with RA than with IVL (9.52 ± 3.01 mm^2 vs. 8.55 ± 2.31 mm^2; $p = 0.13$). Nevertheless, the resulting stent expansion was almost identical between the two groups (RA: 0.83 ± 0.10 vs. IVL: 0.82 ± 0.11; $p = 0.79$), as reference lumen area was slightly larger in the RA group than in the IVL group (11.41 ± 3.61 vs. 10.39 ± 2.94 mm^2; $p = 0.38$). There were no significant differences regarding stent malapposition, tissue prolapse, and stent strut fractures between the two groups. Detailed results are provided in Table 5.

3.6 | Outcome

The increase in high-sensitive troponin levels 24 h postprocedure did not differ when comparing RA and IVL. There were no cases of TLF, TLR, major adverse cardiac events, or repeat coronary angiography during in-hospital and 1-month follow-up in either group. During the 6-month follow-up, there was one case of TLF and TLR in the IVL group due to angiographical in-stent restenosis (RA: 0/33 vs. IVL 1/28) being treated by balloon angioplasty and drug-eluting balloon application. Repeat PCI for nontarget vessel revascularization was performed in four patients of the RA group and in two patients of the IVL group. Two patients of the RA group and two patients of the IVL group died during the 6-month follow-up, and there were no cases of suspected cardiovascular death reported.

4 | DISCUSSION

The main findings of this first randomized trial comparing IVL with RA in the interventional treatment of severely calcified coronary lesions are as follows: (1) IVL is non-inferior to RA regarding MSA; (2) IVL and RA result in a similar degree of stent expansion; (3) there are no significant differences in periprocedural myocardial damage when comparing RA and IVL; (4) procedure time, radiation dose, and contrast media consumption do not differ significantly when comparing both the techniques; (5) successful treatment with IVL might be limited by positioning failure of the IVL balloon.

4.1 | Previous trials of IVL

All previous large-scale studies of IVL (DISRUPT CAD I–IV) were designed for regulatory approval of coronary IVL and were therefore single-arm studies designed to assess safety and effectiveness.[27–30] This trial is the first to randomly compare IVL with RA, a well-established technique for plaque debulking or modifying.[27–30] Primary endpoint analysis confirmed non-inferiority of IVL in comparison with RA regarding postprocedural MSA, despite slightly smaller MSA after IVL than after RA (Table 4 and Figures 4 and 5). This seems to be mainly attributable to the fact that the reference vessel area was slightly larger in the RA group than in the IVL group (Table 5) and the analysis of native

TABLE 2 Procedural characteristics.

	Overall (n = 61)	RA (n = 33)	IVL (n = 28)	p
Target vessel				0.34
LM	6 (9.8)	3 (9.1)	3 (10.7)	
LAD	24 (39.3)	14 (42.4)	10 (35.7)	
Cx	4 (6.6)	0 (0.0)	3 (10.7)	
RCA	28 (45.8)	16 (48.5)	12 (42.9)	
Femoral access	23 (37.7)	15 (45.5)	8 (28.6)	0.20
Radial access	40 (65.6)	19 (57.6)	21 (75.0)	0.18
Max. sheath size (French)	6.4 ± 0.7	6.5 ± 0.6	6.3 ± 0.7	0.39
Lesion length (mm)	18.0 ± 9.0	18 ± 7.0	17 ± 8.0	0.73
Predilatation before IVL or RA	27 (44.3)	10 (30.3)	17 (60.7)	0.04
Max. pressure (atm)	17.4 ± 5.8	16.7 ± 5.7	17.7 ± 5.9	0.42
Max. balloon diameter (mm)	2.76 ± 0.63	2.90 ± 0.70	2.68 ± 0.59	0.40
RA max. burr size (mm)		1.56 ± 0.15		
RA number of runs		2.7 ± 1.6		
IVL balloon diameter (mm)			3.13 ± 0.48	
IVL number of treatment cycles			5.2 ± 2.8	
NC balloon dilatation after IVL or RA	61 (100)	33 (100)	28 (100)	>0.99
Max. pressure (atm)	18.2 ± 6.0	18.0 ± 5.7	18.7 ± 5.9	0.50
Max. balloon diameter (mm)	3.30 ± 0.63	3.32 ± 0.64	3.27 ± 0.55	0.64
Stent diameter (mm)	3.31 ± 0.58	3.35 ± 0.54	3.24 ± 0.45	0.41
Stent length (mm)	23.3 ± 6.8	24.1 ± 7.5	22.5 ± 5.9	0.56
Stent max. implantation pressure (atm)	15.5 ± 2.5	15.7 ± 2.7	15.3 ± 2.3	0.71
Postdilatation	61 (100)	33 (100)	28 (100)	>0.99
Max. pressure (atm)	17.8 ± 4.7	17.7 ± 4.0	17.9 ± 5.6	0.75
Max. balloon diameter (mm)	3.75 ± 0.65	3.84 ± 0.70	3.64 ± 0.58	0.29
OCT native scan available	32 (52.5)	17 (51.5)	15 (53.6)	>0.99
OCT scan post-RA/IVL available	38 (62.3)	19 (57.6)	19 (67.9)	0.44
OCT final scan available	61 (100)	33 (100)	28 (100)	>0.99
Contrast media (mL)	174.0 ± 63.1	183.1 ± 68.8	163.3 ± 55.0	0.47
Dose area product (cGy cm^2)	6232 ± 8773	7269 ± 11288	5010 ± 4140	0.68
Procedure time (min)	73.1 ± 28.9	79.5 ± 34.5	66.0 ± 19.4	0.18
Periprocedural increase in troponin level (level 24 h postprocedure/level before procedure)	52.9 ± 119.6	38.3 ± 56.1	68.0 ± 161.2	0.53

Note: $x \pm s$ represents $X \pm 1$ SD; a (b) represents n (%).

Abbreviations: Cx, circumflex artery; IVL, intravascular lithotripsy; LAD, left anterior descending artery; LM, left main; NC, noncompliant; OCT, optical coherence tomography; RA, rotational atherectomy; RCA, right coronary artery.

OCT scans showed modestly larger lumen dimensions in the RA group than in the IVL group (Table 3). The MSA for IVL reported in the present study (6.10 ± 1.99 mm^2) is similar to the value reported in the OCT substudy of the CAD III trial (6.47 ± 2.07 mm^2).[29] Stent expansion, a parameter that is not influenced by differences in baseline lumen dimensions, was nearly identical between the two techniques and was equivalent to that reported in the OCT substudy of the CAD III trial after IVL.[29] Hence, RA and IVL both seem to achieve a sufficient stent expansion in severely calcified lesions.

In the current trial, it appeared that there is no significant difference in periprocedural myocardial damage as determined by the periprocedural increase in troponin levels.

TABLE 3 Native OCT analysis.

	Overall (*n* = 32)	RA (*n* = 17)	IVL (*n* = 15)	*p*
Mean lumen diameter (mm)	2.72 ± 0.55	2.75 ± 0.60	2.70 ± 0.51	0.75
Mean lumen area (mm^2)	6.31 ± 2.47	6.43 ± 2.67	6.18 ± 2.31	0.77
Minimum lumen diameter (mm)	1.74 ± 0.45	1.72 ± 0.43	1.76 ± 0.50	0.84
Minimum lumen area (mm^2)	2.54 ± 1.27	2.47 ± 1.15	2.62 ± 1.42	0.84
Maximum lumen diameter (mm)	3.71 ± 0.79	3.68 ± 0.77	3.75 ± 0.83	0.93
Maximum lumen area (mm^2)	10.80 ± 4.39	11.05 ± 4.48	11.56 ± 5.41	0.94
Calcified plaque				
Maximum angle (°)	207.2 ± 80.0	191.4 ± 63.5	225.1 ± 94.5	0.43
Mean angle (°)	86.5 ± 23.0	81.3 ± 18.5	92.4 ± 26.7	0.29
Total length (mm)	16.72 ± 4.00	17.00 ± 2.81	16.40 ± 5.12	0.26
Indexed area per frame (mm^2)	0.38 ± 0.26	0.37 ± 0.24	0.39 ± 0.30	0.96
Mean thickness (mm)	0.61 ± 0.10	0.63 ± 0.12	0.62 ± 0.10	0.40
Calcified nodules present	16 (50%)	8 (47.1)	8 (53.3)	0.73

Note: $x \pm s$ represents $X \pm 1$ SD; *a* (*b*) represents *n* (%).

Abbreviations: IVL, intravascular lithotripsy; OCT, optical coherence tomography; RA, rotational atherectomy.

TABLE 4 Primary endpoint analysis.

	Overall (*n* = 61)	RA (*n* = 33)	IVL (*n* = 28)	*p*
MSA (mm^2)	6.37 ± 2.36	6.60 ± 2.65	6.10 ± 1.99	0.41

Note: $x \pm s$ represents $X \pm 1$ SD.

Abbreviations: IVL, intravascular lithotripsy; MSA, minimal stent area; RA, rotational atherectomy.

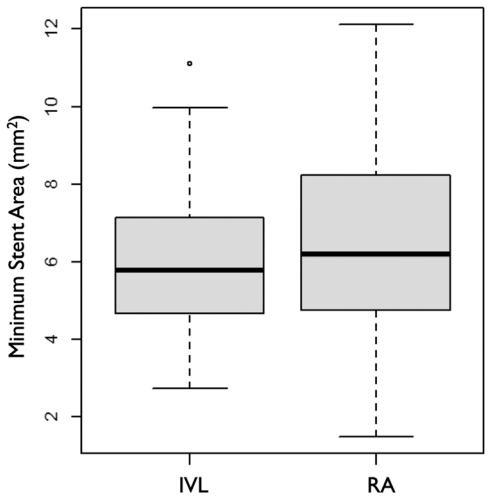

FIGURE 4 Box plot of the primary endpoint comparing MSA after IVL and RA. IVL, intravascular lithotripsy; MSA, minimal stent area; RA, rotational atherectomy. Error bars: IVL: 2.74–9.98 mm^2; RA: 1.58–12.12 mm^2.

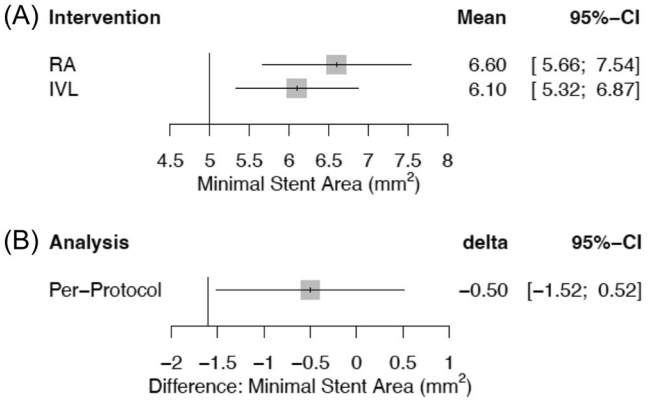

FIGURE 5 Forest plots of primary endpoint analysis. (A) The Forest plot demonstrates that the 95% confidence interval (95% CI) of IVL and RA do not reach the margin at 5 mm^2 (black line). (B) The Forest plot shows that the 95% CI of the difference in MSA between IVL and RA does not violate the non-inferiority margin (black line). The non-inferiority margin used for the non-inferiority test is the difference between the MSA after IVL (should not be smaller than 5.0 mm^2) and the observed MSA after RA (6.60 mm^2). IVL, intravascular lithotripsy; MSA, minimum stent area; RA, rotational atherectomy.

4.2 | Lesion preparation before IVL or RA

Predilatation was performed significantly more often before IVL (60.7%) than before RA (30.3%; $p = 0.04$), reflecting the necessity for lesion preparation to successfully place the IVL balloon in the

TABLE 5 Final OCT analysis.

	Overall (*n* = 61)	RA (*n* = 33)	IVL (*n* = 28)	*p*
Mean lumen diameter (mm)	3.42 ± 0.52	3.48 ± 0.58	3.35 ± 0.44	0.25
Mean lumen area (mm^2)	9.49 ± 2.80	9.52 ± 3.01	8.55 ± 2.31	0.13
Minimum lumen diameter (mm)	2.84 ± 0.56	2.88 ± 0.65	2.79 ± 0.44	0.33
Minimum lumen area (mm2)	6.50 ± 2.40	6.70 ± 2.71	6.27 ± 1.99	0.48
Maximum lumen diameter (mm)	4.05 ± 0.69	4.07 ± 0.70	4.03 ± 0.69	0.58
Maximum lumen area (mm^2)	13.24 ± 4.42	13.36 ± 4.35	13.11 ± 4.58	0.57
Mean stent diameter (mm)	3.35 ± 0.52	3.42 ± 0.57	3.26 ± 0.44	0.13
Mean stent area (mm^2)	9.08 ± 2.73	9.52 ± 3.01	8.55 ± 2.31	0.13
Minimum stent diameter (mm)	2.81 ± 0.55	2.86 ± 0.63	2.75 ± 0.45	0.29
Maximum stent diameter (mm)	3.84 ± 0.63	3.92 ± 0.68	3.75 ± 0.56	0.32
Maximum stent area (mm^2)	11.89 ± 3.78	12.42 ± 4.13	11.27 ± 3.30	0.32
Mean reference lumen area (mm^2)	10.92 ± 3.00	11.41 ± 3.61	10.39 ± 2.94	0.38
Mean luminal gain (mm^2)	3.18 ± 1.92	3.44 ± 1.83	2.86 ± 1.70	0.30
Stent expansion	0.83 ± 0.11	0.83 ± 0.10	0.82 ± 0.11	0.79
Maximum stent eccentricity	0.65 ± 0.09	0.65 ± 0.09	0.65 ± 0.08	0.97
Stent strut fractures present	8 (13.1)	4 (12.1)	4 (14.3)	>0.99
Tissue prolapse present	25 (41.0)	13 (39.4)	12 (42.9)	0.80
Stent malapposition present	53 (86.9)	27 (81.8)	26 (92.9)	0.27
Stent malapposition: maximum distance (mm)	0.71 ± 0.34	0.64 ± 0.28	0.79 ± 0.39	0.29
Stent malapposition: mean area of malapposition (mm^2)	0.66 ± 0.41	0.60 ± 0.40	0.72 ± 0.42	0.23
Number of cracks per frame	0.74 ± 1.25	0.82 ± 1.26	0.64 ± 1.25	0.67

Note: $x \pm s$ represents $X \pm 1$ SD; *a* (*b*) represents *n* (%).

Abbreviations: OCT, optical coherence tomography; RA, rotational atherectomy.

target lesion in some cases. The rate of predilatation before IVL reported in our study (60.7%) is higher than the rates reported in previous trials (CAD IV: 20.3%, CAD III: 55.2%, CAD II: 41.7%, CAD I: 37%).[27–30] This is presumably due to the study protocol that allowed NC balloon predilatation to acquire a native OCT scan, if it was impossible to advance the OCT imaging catheter through the target lesion without prior balloon dilatation. This is also the reason for the unusually high rate of pre-dilatation in the RA group (30.3%), as predilatation is usually not indicated before RA. However, this bias affects both groups and should therefore not influence the results overall. A preprocedural OCT scan could only be performed in 32 (52.5%) patients. This highlights the limitations of intravascular imaging by OCT for planning of the PCI strategy in the setting of severely calcified coronary stenoses.

A clear drawback of the IVL technique in comparison to RA is the fact that it is sometimes not possible to advance the IVL balloon into the target lesion due to its crossing profile. While RA was performed successfully in all cases (37/37), in two patients cross-over from IVL to RA was documented.

4.3 | Future perspectives

In general, IVL is a promising option for interventional treatment of severely calcified lesions that is non-inferior to RA regarding MSA and leads to a similar stent expansion. Despite some limitations in lesion crossing, this rapid-exchange balloon system may provide an effective method of plaque modification to a broader collective of patients for preventing stent underexpansion in severely calcified lesions and the associated poorer clinical outcome. To date, it remains unclear which technique, IVL or RA, leads to a better clinical outcome or if the clinical outcome is the same. This analysis was not powered for outcome analysis. Future large-scale clinical trials will be required to meaningfully compare clinical outcomes of the two techniques.

4.4 | Limitations

This study has some inherent limitations. First, the biometrical study planning was based on an estimated MSA after RA of 5.0 ± 1.4 mm^2

previously reported by Li et al.[25] In fact, the MSA after RA we observed in our study was higher (6.60 ± 2.65 mm^2) and MSA after IVL was lower than after RA (6.10 ± 1.99 mm^2). Therefore, the threshold for non-inferiority was lower than originally intended with the pre-assumed MSA of 5.0 ± 1.4 mm^2 for RA and the MSA of 6.1 ± 1.7 mm^2 calculated from a preliminary case series for IVL. Nevertheless, the difference for MSA between RA and IVL is very small, and it is unlikely that the slightly lower MSA after IVL would translate into a poorer clinical outcome than after RA, especially since stent expansion is nearly identical between the two techniques. Furthermore, it has to be kept in mind that, despite randomization, baseline vessel dimensions and reference vessel area in final OCT scans were larger in the RA than in the IVL group, leading to a bias for the comparison of MSA between these two groups. However, the equivalent stent expansion confirms the comparable effectiveness of the two techniques and is usually not influenced by differences in baseline vessel dimensions, assuming that stent diameter is selected according to reference vessel diameter.

Bias is present in the reported rate of pre-dilatation due to the fact that the study protocol allowed predilatation to acquire a native OCT scan, and this was therefore sometimes performed just to follow the protocol. However, this bias affects both groups in the same way and should not influence the basic result that pre-dilatation needs to be performed significantly more often with IVL than with RA.

Another potential limitation is the patient exclusion rate: only 61 of 70 patients were finally analyzed, as for nine patients there were no final OCT scans available for primary endpoint analysis. Nevertheless, an exclusion rate in this range was assumed in the power calculation and is therefore unlikely to have influenced the results.

Additionally, the rate of male patients was higher than expectable due the prevalence of coronary artery disease in general population which poses another potential bias.

5 | CONCLUSIONS

IVL is non-inferior regarding MSA and results in a similar stent expansion in a random comparison with RA. Additionally, there is no significant difference regarding the periprocedural myocardial damage induced by both techniques. Despite the observation that it is sometimes difficult to cross the target lesion with an IVL balloon, which is not a factor with RA, this balloon-based technique appears to be suitable to provide an effective treatment option to a broader collective of patients with severely calcified coronary lesions.

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CONFLICT OF INTEREST STATEMENT

T. Gori received grant support and speaker's honoraria from Abbott vascular and speaker's honoraria from Boston Scientific and Shockwave Medical. L. Gaede received speaker's honoraria from Abbott vascular, Boston Scientific, and Shockwave Medical. M. Weferling has received speaker's honoraria from Boston Scientific and Shockwave Medical. H. Möllmann received speaker's honoraria from Boston Scientific and Shockwave Medical. H. Nef received grant support and speaker's honoraria from Abbott vascular and Shockwave Medical. All other authors report no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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