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Procedural and clinical impact of intravascular lithotripsy for the treatment of peri-stent calcification

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ABSTRACT

Background: Use of intravascular lithotripsy (IVL) for treating peri-stent calcification is increasing. However, this indication remains 'off-label'. We aimed to investigate the efficacy and clinical outcomes of in-stent IVL.
Methods: Patients from five European centers who underwent in-stent IVL were included between 2019 and 2023. Demographic, clinical, procedural and follow-up data were collected from electronic hospital records. Angiographic and intracoronary imaging (ICI) data were analyzed in a centralized core-laboratory.
Results: Of 101 patients (71.2 ± 9.2 years), 56(55 %) received in-stent IVL for late stent failure (median 109 days post-PCI) due to calcific neoatherosclerosis or extra-stent calcification(late-IVL), while 45(45 %) underwent bail-out IVL due to stent infraexpasion (immediate-IVL). Both late-IVL and immediate-IVL significantly improved angiographic %diameter stenosis (73.7[59.6–89.8]% to 16.4 [10.4–26.9]%;$p < 0.0001$ and 28.6[22.5–43.3]% to 14.1 [10.3–29.4]%;$p < 0.0001$, and minimum lumen area (MLA) (3.4 ± 1.2 to 8.6 ± 2.5 mm2;$p < 0.002$ and 5.4 ± 1.9 to 7.3 ± 1.9;$p < 0.0001$).Device(98 %) and procedural success(80 %) were high. MACE rates in-hospital (2 %), 30-days (3 %),6-months(5 %) and 1-year(7 %) were low and comparable in both groups. Acute diameter gain was lower in immediate-IVL (2.1 ± 0.7 mm vs. 0.5 ± 0.4 mm;$p < 0.0001$). This, however, was explained by significant differences in pre-IVL angiographic and ICI parameters (%diameter stenosis 73.7[59.6–89.8] vs. 28.6[22.5–43.3]%; $p < 0.0001$ and MLA (3.4 ± 1.2 vs 5.4 ± 1.9 mm^2; $p < 0.0001$), whereas post-IVL percentage diameter stenosis (16.4(10.4–26.9) vs. 14.1(10.3–29.4);$p = 0.914$) and MLA (8.6 ± 2.5vs. 7.4 ± 1.9 mm^2;$p = 0.064$) in late- and immediate-IVL were comparable.
Conclusions: IVL in-stent due to peri-stent calcification is an effective strategy, both late and immediately after stent implantation. Overall, MACE rates at short- and mid-term were low and comparable in both groups, although clinical findings should be taken with caution.

1. Introduction

Severe coronary calcification is found in up to 25 % or more of patients requiring invasive coronary treatment [1,2] and is associated with stent underexpansion, leading to higher periprocedural complication rates and long-term rates of in-stent restenosis (ISR), stent thrombosis [3], myocardial infarction (MI), and death [4–7]. Occurrence of calcification in previously stented lesions requiring reintervention is associated with even higher rates of stent failure due to stent underexpansion and ISR [8,9]. Peri-stent calcification presents mainly in two well-differentiated forms: in-stent calcified neoatherosclerosis and extra-stent calcification (Fig. 1). Differentiation between the two mechanisms is necessary as both

Abbreviations: DES, drug eluting stent; ICI, intracoronary imaging; ISR, in-stent restenosis; ISU, immediate stent underexpansion; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; QCA, quantitative coronary analysis; TIMI, Thrombolysis In Myocardial Infarction; TVR, target vessel revascularization.

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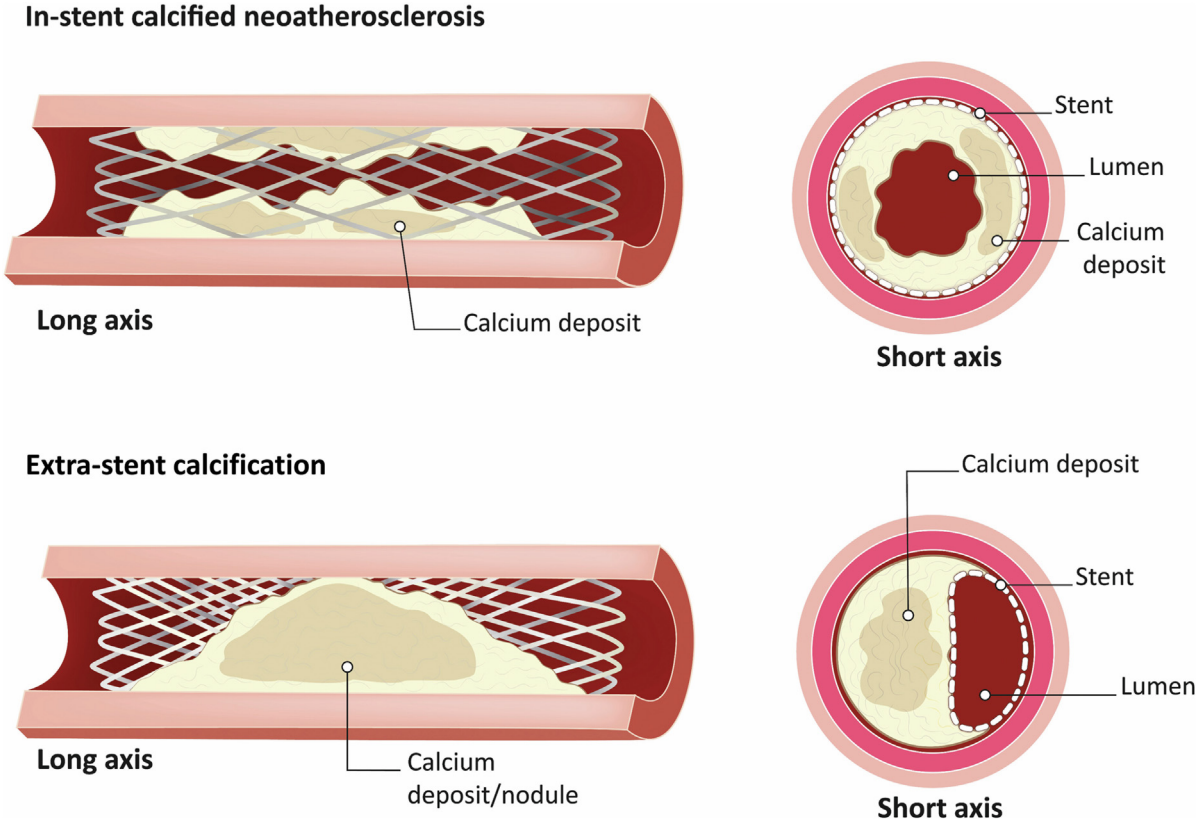

Fig. 1. Mechanisms of stent failure due to peri-stent calcification.

may require tailored plaque modification strategies to achieve an effective lesion preparation and procedural success [9–13]. Intravascular lithotripsy (IVL) is an emerging technology, consisting of the emission of acoustic shock waves in a balloon-based system, which selectively induces fractures in the calcium deposits within the vessel wall, modifying vessel compliance and thereby improving vessel luminal gain and stent expansion [14–17]. This distinctive nature sets IVL apart from both the other modified balloons and atheroablative techniques, making it potentially suitable for in-stent treatment of both peri-stent calcification subtypes. However, the in-stent application of IVL is still 'off -label' as the electrohydraulic discharge might damage the drug polymer coating in drug eluting stents (DES) or the stent frame itself, potentially worsening mid- and long-term outcomes, especially in recently implanted stents. Still, there is a significant increase in the use of IVL for both severe calcific neoatherosclerosis and as a bail-out strategy for immediate stent underexpansion (ISU) caused by extra-stent calcification (Figs. 2 and 3). This has been shown in small series [18–24], primarily focusing on delayed ISR and procedural success or early outcome. Hence, the potential clinical effect of electrohydraulic damage of the stent caused by IVL has not been elucidated.

The aim of this study was to examine the efficacy, and clinical impact at mid-term in-stent IVL, both immediately and late after stent implantation.

2. Methods

2.1. Population and data collection

In this international multicenter registry, patients (>18 years) who underwent IVL in-stent because of peri-stent calcification (Fig. 1) were retrospectively enrolled from five European centers between 2019 and 2023. IVL was performed in all cases by using the Shockwave Intravascular Lithotripsy Coronary System (Shockwave Medical, Santa Clara, California). Decisions regarding technical aspects of IVL (timing, balloon size, number of pulses delivered, maximal pressure), utilization of high-pressure pre- and post-dilatation, supplementary stent placement, and use of intracoronary imaging (ICI) for procedural optimization were left to the operator's discretion, with documentation of these decisions in the procedural report. Demographic, clinical, procedural and follow-up data were collected from the hospital electronic records. Angiographic and ICI data were analyzed in a centralized core-laboratory at the Leiden University Medical Center. Patients who were unable to provide informed consent were excluded from the study ($N = 1$). The local ethical committee at each institution approved the retrospective analysis of clinically collected data.

2.2. Definitions and imaging analysis

Stent underexpansion was determined by the operator during the procedure both angiographically (fluoroscopic stent examination, stent enhancement software when available, incomplete balloon-expansion) and by ICI when available. The presence of calcific neoatherosclerosis was determined with ICI, either by OCT (well-delineated, signal-poor areas with sharp borders within the neointima) or by IVUS (in-stent hyperechoic signal with acoustic shadowing and/or reverberation, Fig. 3) [8,25–28].

Quantitative coronary analysis (QCA) and ICI were retrospectively analyzed offline to evaluate luminal gain following IVL. QCA in-stent was performed pre- and post-IVL, using Medis Suite QCA (2D/3D) software (Medis Suite 4.0.24.4; Medis Medical Imaging System BV, Leiden, The Netherlands). Measurements included minimum lumen diameter (minimum LD), percentage diameter stenosis (percentage DS) and percentage area stenosis (percentage AS). Additionally, the minimum diameter of the non-compliant balloon inflated directly before and after IVL was measured. Analysis of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) was performed using QCU-CMS 4.69 (Leiden University Medical Center, Leiden, The Netherlands). Performance and timing of ICI for procedural optimization, was left to operators discretion. When available, ICI measurements were performed, including reference vessel diameter (RVD) and reference vessel area (RVA), minimum lumen area (MLA) and

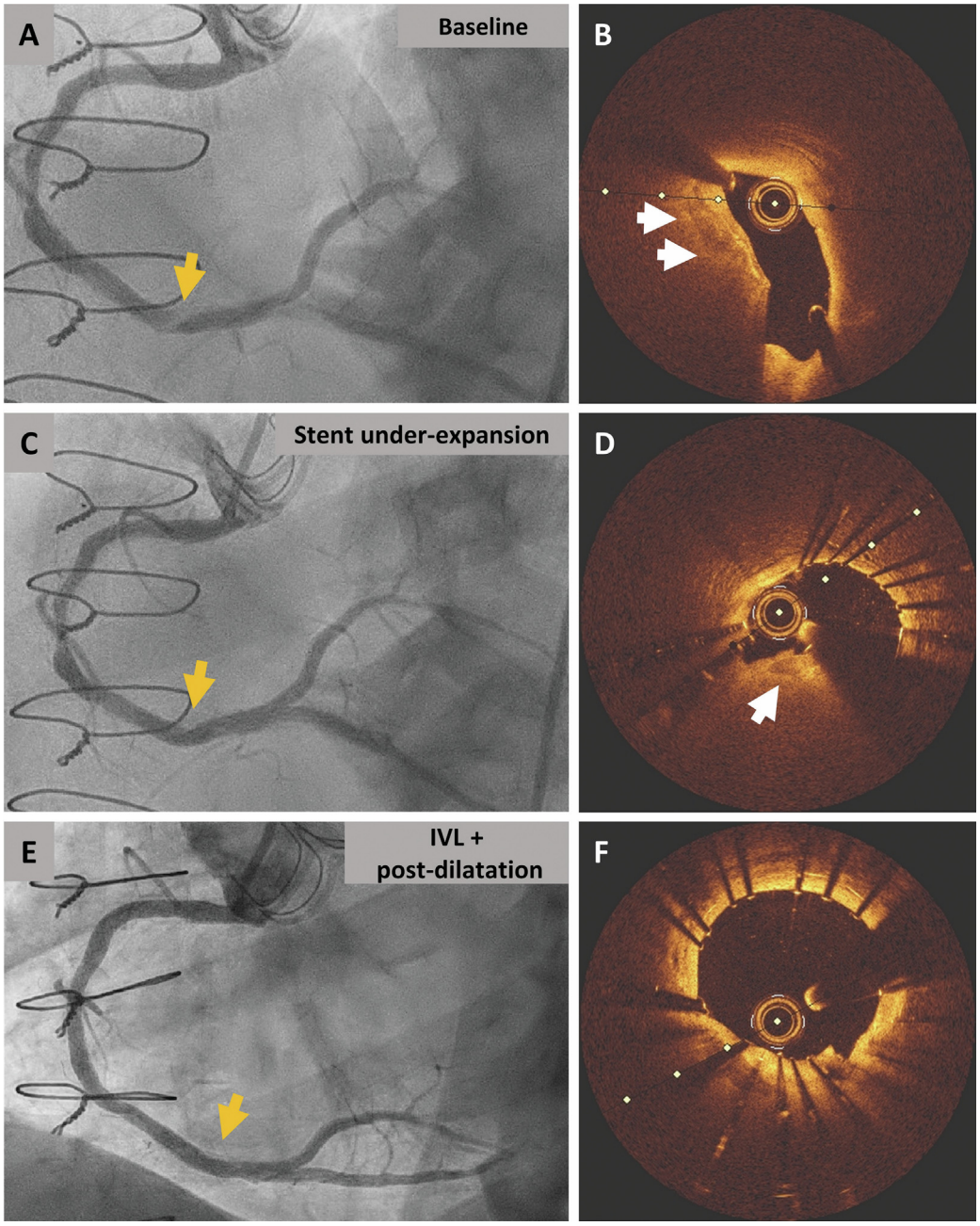

Fig. 2. Use of in-stent intravascular lithotripsy in immediate stent underexpansion. A: Baseline coronary angiogram with target lesion at distal right coronary artery (RCA, arrow). B: Optimal computed tomography (OCT), showing eccentric focal calcification (arrows). C: Post-stenting angiogram, pointing out the presence of focal stent infraexpansion (arrow), confirmed with OCT (D, arrow). E: Angiogram after IVL (80 pulses) and post-dilatation, showing improvement of stent expansion. F: Final OCT showing satisfactory expansion of the stent.

minimum stent area (MSA). Percentage DS and percentage AS were calculated using the formulas ([RVD-MLD]/RVD)*100 and ([RVA-MLA]/RVA) *100, respectively. Stent expansion was determined with the formula (MSA/RVA)*100, and the eccentricity index was computed by subtracting the minimum LD from the maximum LD and dividing it by the latter. Lastly, we documented the maximum calcification angle and thickness pre-IVL as well as the presence of calcification fractures and dissection post-IVL.

2.3. Study endpoints

The primary endpoint was procedural success, defined as a composite of residual stenosis <30 % (assessed by QCA), final Thrombolysis In Myocardial Infarction (TIMI) 3 coronary flow and absence of in-hospital major adverse cardiovascular events (MACE: cardiac death, non-fatal target vessel myocardial infarction (MI) or clinically driven target lesion revascularization). Secondary endpoints included device success (defined as the ability to deliver the IVL catheter across the target lesion, and delivery of IVL pulses without angiographic complications), technical success (defined as the presence of TIMI 3 flow and a residual stenosis <30 %) and the occurrence of MACE and all-cause mortality at 30 days, 6 months and one year follow-up after in-stent IVL.

2.4. Statistical analysis

Continuous variables are presented as either the mean ± standard deviation or median with interquartile range (25th–75th percentile), as appropriate. Differences between paired continuous variables were assessed with the paired *t*-test if normally distributed, otherwise the Wilcoxon

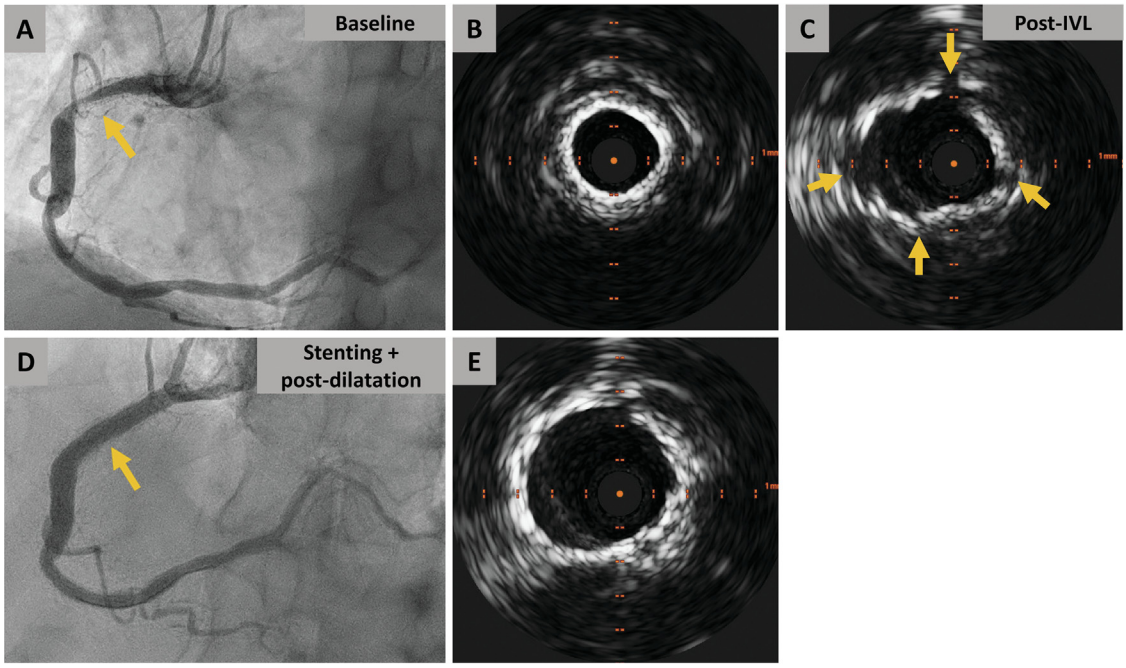

Fig. 3. In-stent intravascular lithotripsy in severe in-stent restenosis because of calcified neoatherosclerosis. A: Baseline coronary angiogram showing severe in-stent restenosis at the proximal right coronary artery (RCA, arrow). B: Intravascular ultrasound (IVUS) demonstrating the presence of extensive (360 degrees) calcified neoatherosclerosis. C: IVUS post-IVL showing several fractures of the calcification (arrows). D: Angiogram after stenting and post-dilatation, showing excellent stent expansion (arrow) and confirmed by IVUS (E).

signed-rank test was used. Differences between unpaired continuous variables were assessed with the unpaired t-test if normally distributed, and with the Mann-Whitney *U* test if not normally distributed. Categorical variables were reported as frequencies and percentages and were analyzed using the $\chi 2$ or Fischer exact test. Kaplan-Meier analysis was performed to estimate cumulative survival free of MACE at one-month and one-year follow-up. Statistical analysis was performed with SPSS for Windows version 25.0 (IBM, Armonk, New York). All tests were two-sided, and a $P < 0.05$ was considered statistically significant.

3. Results

A total of 101 patients (male 74 %, age 71 ± 9.2 years) meeting the inclusion criteria were enrolled in the study. Fifty-six (55 %) IVL procedures were conducted on previously placed stents (late-IVL group), while 45 (45 %) patients underwent IVL as a bail-out strategy for ISU (immediate-IVL) due to extra-stent calcification. In the late-IVL group, the predominant mechanism of stent failure was extra-stent calcification ($n = 21$, 38 %), followed by in-stent calcified neoatherosclerosis ($n = 17$, 30 %) and a combination of the two mechanisms in ($n = 11$, 20 %), whereas the mechanism could not be determined due to lack of ICI in 7 patients (13 %). Baseline patient characteristics are summarized in Table 1. A significantly higher proportion of patients in the late-IVL group had dyslipidemia ($p = 0.021$) and previous myocardial infarction (MI) ($p < 0.0001$) at baseline. The primary indication for percutaneous coronary intervention (PCI) was stable angina (44 %), and the majority of the IVL procedures (45 %) were performed in the right coronary artery (RCA). Target lesions consisting of multiple layered stents were more frequent in the late-IVL group (34 % vs. 11 %;$p = 0.010$), whereas the immediate-IVL group showed a longer median target stent length (38 vs. 24 mm;$p = 0.012$) and a higher prevalence of long (>20 mm) lesions (76 % vs. 54 %;$p = 0.023$).

Most procedural parameters were comparable between the two groups (Table 2). Median procedural time (80 vs. 70 min;$p = 0.044$), median fluoroscopy time (29 vs. 20 min;$p = 0.015$) and median contrast volume (230 vs. 150 ml;$p < 0.0001$) were significantly higher in the immediate-IVL

Table 1
Baseline demographics and medical history

	Overall ($n = 101$)	Late-IVL ($n = 56$)	Immediate-IVL ($n = 45$)	*P*-value
Age, years	71.2 ± 9.2	69.6 ± 9.5	73.2 ± 8.5	
Male, n(%)	75(74)	41(73)	34(76)	0.789
Hypertension, n(%)	69(68)	39(70)	30(67)	0.749
Dyslipidemia, n(%)	62(61)	40(71)	22(49)	0.021
Family history of CAD, n(%)	20(20)	12(21)	8(18)	0.647
Diabetes, n(%)	46(46)	27(48)	19(42)	0.548
Smoking history, n %)	38(38)	25(45)	13(29)	0.104
Previous MI, n(%)	48(48)	38(68)	10(22)	<0.0001
Previous PCI, n(%)	70(69)	56(100)	14(31)	<0.0001
Previous CABG, n(%)	25(25)	15(27)	10(22)	0.597
Previous stroke, n(%)	7(7)	2(4)	5(11)	0.237
Clinical presentation				0.209
Stable angina, n(%)	44(44)	25(45)	19(42)	
Unstable angina, n(%)	20(20)	12(21)	8(18)	
NSTEMI, n(%)	28(28)	17(30)	11(24)	
STEMI, n(%)	9(9)	2(4)	7(16)	
Target stent type				0.153
BMS, n(%)	3(3)	3(5)	0	
DES, n(%)	92(91)	49(88)	43(96)	
BMS + DES, n(%)	1(1)	0(0)	1(2)	
Target vessel				0.281
LM, n(%)	4(4)	4(7)	0	
LAD, n(%)	34(34)	17 (30)	17(38)	
LCx, n(%)	15(15)	7(13)	8(18)	
RCA, n(%)	45(45)	27(48)	18(40)	
Bypass, n(%)	3(3)	1(2)	2(4)	
Target stent				
Diameter, mm	3.5(3.0–3.5)	3.5(3.0–3.5)	3.5.(3.0–3.5)	0.058
Length, mm	30(20–48)	24(18–38)	38(22–59)	0.012
Multiple stent layers, n(%)	24(24)	19(34)	5(11)	0.010

CABG = coronary artery bypass graft surgery; CTO = chronic total occlusion; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

Table 2
Procedural characteristics.

	Overall (*n* = 101)	Late-IVL (*n* = 56)	Immediate-IVL (*n* = 45)	P-value
Lesion characteristics				
Bifurcation, n(%)	20(20)	11(20)	9(20)	0.964
Ostial, n(%)	16(16)	12(21)	4(9)	0.105
Tortuous, n(%)	11(11)	5(9)	6(13)	0.533
In-stent CTO, n(%)	11(11)	6(11)	5(11)	0.918
Long-segment, n(%)	64(63)	30(54)	34(76)	0.023
IVL				
Balloon diameter, mm	3.5 (3.0–4.0)	3.5(3.5–4.0)	3.5(3.0–4.0)	0.586
Number of pulses	80(60–80)	80(60–80)	70(60–80)	0.233
High pressure pre-dilatation, n(%)	93(92)	51(91)	42(93)	0.729
High pressure post-dilatation, n(%)	92(91)	49(88)	43(96)	0.292
Pre-dilatation balloon diameter, mm	3.5 (3.0–3.5)	3.5(3.0–3.5)	3.5(3.0–4.0)	0.344
Pre-dilatation balloon maximum pressure (atm)	22(20–24)	20(18.5–24)	23(20–24)	0.274
Post-dilatation balloon diameter, mm	3.5 (3.5–4.0)	3.5(3.5–4.0)	3.5(3.5–4.0)	0.364
Plaque modification, n(%)	17(17)	9(16)	8(18)	1
Timing plaque modification				
Pre-IVL	14(14)	6(11)	8(18)	0.228
Rotablation, n(%)	9(9)	3(5)	6(13)	
Cutting balloon, n(%)	5(5)	4(7.1)	1(2)	
OPN balloon, n(%)	1(1)	0	1(2)	
Post-IVL				0.441
Cutting balloon, n(%)	1(1)	1(2)	0	
OPN balloon, n(%)	1(1)	1(2)	0	
Treatment after IVL				<0.0001
Stent implantation, n(%)	54(54)	43(77)	11(24)	
Balloon angioplasty, n(%)	37(37)	7(13)	30(67)	
Drug-coated balloon, n(%)	6(6)	5(9)	1(2)	
Complications	6(6)	2 (4)	4(9)	0.403
Dissection, n(%)	1(1)	0	1(2)	
Perforation, n(%)	3(3)	1(2)	2(4)	
Other, n(%)	2(2)	1(2)	1(2)	
Procedural time, min	77 (65–109.5)	70 (62.7–104.5)	80(70–138)	0.044
Fluoroscopy time, min	22 (17–37.5)	20(16–28.5)	29(18–45)	0.015
Contrast volume, ml	165 (135–250)	150 (115–180)	230(160–290)	<0.0001

IVL = intravascular lithotripsy;; CTO = chronic total occlusion; OPN = ultra-high pressure balloon.

group. Median IVL balloon diameter was 3.5 (3.0–4.0) mm and delivered a median of 80 (60–80) pulses to the target lesion. In the majority of patients, high-pressure pre- and post-dilatation was performed (92 % and 91 % respectively). Additional plaque modification techniques were employed in 17 (17 %) cases, most of them (82 %) prior to IVL, being rotablation the most frequently used (53 %). The post-IVL treatment differed significantly between the two groups, with more additional stents implanted in the late-IVL group (77 % vs. 24 %;$p < 0.0001$), whereas more patients in the immediate-IVL group received only balloon angioplasty (67 % vs. 13 %; $p < 0.0001$). Drug-coated balloon were employed only in 6 (6 %) patients.

QCA analysis (Supplementary Table 1) showed significantly improved minimum LD (0.8 ± 0.6 to 2.9 ± 0.5 mm;$p < 0.0001$) and (2.2 ± 0.6 to 2.7 ± 0.6 mm;$p < 0.0001$), and percentage diameter stenosis (73.7 [59.6–89.8]% to 16.4 [10.4–26.9]%; $p < 0.0001$) and (28.6[22.5–43.3]% to 14.1[10.3–29.4]%;$p < 0.0001$), in late- and immediate-IVL respectively. The mean luminal gain after IVL was 1.4 ± 1.0 mm, which was significantly higher in the late-IVL group (2.1 ± 0.7 vs. 0.5 ± 0.4 mm; $p < 0.0001$) (Table 3). Group comparison revealed higher pre-IVL minimum LD (0.8 ± 0.7 vs. 2.3 ± 0.7 mm;$p < 0.0001$) and percentage diameter stenosis (73.7[59.6–89.8] vs. 28.6[22.5–43.3]%;$p < 0.0001$) in the late-IVL

Table 4
Intracoronary imaging analysis.

	Overall (n = 101)	Late-IVL (n = 56)	Immediate-IVL (n = 45)	P-value
Pre IVL				
RVD, mm	3.8(3.4–4.3)	4(3.5–4.48)	3.6(3.2–4.1)	0.084
RVA, mm^2	11.5(9–14.6)	12.6 (9.8–15.2)	9.8(8.4–12.7)	0.139
Minimum LD, mm	2 ± 0.6	1.9 ± 0.6	2.3 ± 0.5	0.068
MLA, mm^2	4.08 ± 1.75	3.4 ± 1.2	5.4 ± 1.9	<0.0001
Percentage DS	49.2 ± 17.9	53.4 ± 18.5	39.2 ± 11.6	0.011
Percentage AS	63.1 ± 19.	69.4 ± 16.7	48.2 ± 15.1	<0.0001
MSA, mm^2	5.5 ± 2.1	5.4 ± 2.2	5.8 ± 2.1	0.521
Stent expansion (%)	49 ± 19.8	45.5 ± 22.4	55 ± 11.7	0.036
Eccentricity index MLA	0.1 (0.06–0.2)	0.1 (0.05–0.2)	0.2(0.1–0.3)	0.083
Calcium angle, degrees	268.3 ± 95.5	305.4 ± 82.1	201.4 ± 82.0	<0.0001
Post IVL				
RVD, mm	4(3.5–4.4)	4.2(3.7–4.5)	3.7(3.3–4.1)	0.031
RVA, mm^2	12.6 (10.2–14.5)	13.7 (11.1–15.4)	10.3 (9.9–12.5)	0.011
Minimum LD, mm	3.0 ± 0.6	3.2 ± 0.5	2.6 ± 0.4	0.001
MLA, mm^2	8.2 ± 2.4	8.6 ± 2.5	7.4 ± 1.9	0.064
Percentage DS	25.8 ± 9.1	24.7 ± 7.9	28.4 ± 11.5	0.210
Percentage AS	34 ± 13.9	35.0 ± 13.7	31.4 ± 14.8	0.417
MSA, mm^2	8.4 ± 2.3	8.8 ± 2.3	7.5 ± 1.9	0.078
Stent expansion (%)	66.6 ± 13.2	65.7 ± 12.6	68.6 ± 14.8	0.491
Eccentricity index MLA	0.1 (0.03–0.2)	0.08 (0.03–0.2)	0.2(0.08–0.3)	0.011
Calcium fractures present, n(%)	16(40)	14(54)	2(14)	0.020
Vessel dissection present, n(%)	4(9)	2(7)	2(14)	0.581

IVL = intravascular lithotripsy; minimum LA; minimum lumen area; minimum LD = minimum lumen diameter; MLA = minimum lumen area; MSA = minimum stent area; percentage DS = percentage diameter stenosis; percentage AS = percentage area stenosis; RVA = reference vessel area; RVD = reference vessel diameter.

Table 3
Quantitative coronary analysis.

	Overall (n = 101)	Late-IVL (n = 56)	Immediate-IVL (n = 45)	P-value
Pre IVL				
Minimum LD, mm	1.5 ± 1	0.8 ± 0.7	2.3 ± 0.7	<0.0001
Percentage DS	50.6(30.2–77.3)	73.7(59.6–89.8)	28.6(22.5–43.3)	<0.0001
Percentage AS	75.2(50.9–94.5)	93.1(83.5–99.1)	48.7(39.9–67.8)	<0.0001
Minimum balloon diameter, mm	2.5 ± 0.6	2.3 ± 0.6	2.7 ± 0.7	0.039
Post IVL				
Minimum LD, mm	2.9 ± 0.6	2.9 ± 0.5	2.7 ± 0.6	0.184
Percentage DS	14.5(10.5–29)	16.4(10.4–26.9)	14.1(10.3–29.4)	0.914
Percentage AS	27.7(20.4–49.7)	30.3(21.2–45.9)	26.3(19.4–50.1)	0.990
Minimum balloon diameter, mm	3.3 ± 0.2	3.4 ± 0.5	3.2 ± 0.6	0.139
Acute diameter gain, mm	1.4 ± 1.0	2.1 ± 0.7	0.5 ± 0.4	<0.0001

IVL = intravascular lithotripsy; minimum LD = minimum lumen diameter; percentage DS = percentage diameter stenosis; percentage AS = percentage area stenosis; RVD = reference vessel diameter.

Table 5
Procedural outcomes.

	Overall (n = 101)	Late-IVL (n = 56)	Immediate-IVL (n = 45)	P-value
Device success, n(%)	99(98)	56(100)	43(96)	0.196
Technical success <50 %, n(%)	101(100)	56(100)	45(100)	1
Procedural success <50 %, n(%)	99(98)	56(100)	43(96)	0.196
Technical success <30 %, n(%)	82(81)	47(84)	35(78)	0.432
Procedural success <30 %, n(%)	81(80)	47(84)	34(76)	0.294

Table 6
Major adverse cardiovascular events and all-cause mortality.

	Overall (n = 101)	Late-IVL (n = 56)	Immediate-IVL (n = 45)	P-value
MACE				
In-hospital, n(%)	2 (2)	0	2(4)	0.196
30-days, n(%)	3(3)	0	3(7)	0.090
6-months, n(%)	5(5)	2(4)	3(7)	0.671
1-year, n(%)	7(7)	4(7)	3(7)	1
All-cause mortality				
In-hospital, n(%)	2(2)	0	2(4)	0.196
30-days, n(%)	2(2)	0	2(4)	0.204
6-months, n(%)	3(3)	1(2)	2(4)	0.610
1-year, n(%)	6(6)	2(4)	4(9)	0.409

MACE = major adverse cardiovascular events.

group, whereas post-IVL minimum LD (2.9 ± 0.5 vs. 2.7 ± 0.6 mm;p = 0.184) and percentage diameter stenosis (16.4(10.4–26.9) vs. 14.1 (10.3–29.4);p = 0.914) were comparable.

Intracoronary imaging was conducted in 58 (57 %) patients for procedural guidance of which IVUS was performed in 50 (86 %) and OCT in 8 (14 %) patients. The ICI catheter was not able to pass initially the target lesion in 9 (9 %) patients. Therefore, no pre-IVL images were available for analysis in these patients. Matching pre- and post-IVL ICI images of 42 (42 %) patients were captured. In both patients from the late-IVL and immediate-IVL group the percentage diameter stenosis (53.4 ± 18.5 % to 28.4 ± 11.5 %;p < 0.0001) and (39.2 ± 11.6 to 28.4 ± 11.5 %; p < 0.0001), and MLA (3.4 ± 1.2 to 8.6 ± 2.5 mm2;p < 0.002) and (5.4 ± 1.9 to 7.3 ± 1.9;p < 0.0001), respectively, significantly improved following IVL-therapy (Supplementary Table 2). Comparisons between immediate-IVL vs. late-IVL (Table 4) revealed that immediate-IVL patients exhibited better pre-IVL values (higher MLA and stent expansion and lower percentage DS and AS and calcification angle), whereas most post-IVL values were comparable. Only the post-IVL minimum LD, RVD and RVA were smaller in the immediate-IVL group.

In 24 patients, IVL was performed in a multilayered-stent lesion: 19 (80 %) in the late-IVL and 5 (20 %) in the immediate-IVL group. Group comparisons are presented in Supplementary Table 3. When focusing in the late-IVL group, multilayered-stent lesions treated with IVL showed a significant larger luminal gain assessed by QCA vs. single-stent lesions (2.4 ± 0.6 vs. 2.0 ± 0.8, p = 0.043). This trend was also observed by ICI, although available pre- and post-stenting ICI was available only in 42 % and 49 % respectively.

Device success was reached in 99 (98 %) patients. In the remaining two patients, the IVL balloon was found to be slightly proximal to the target lesion. Technical and procedural success with a residual stenosis <30 % was reached in 82 (81 %) and 81 (80 %) patients, respectively. Device success, technical success (<30 % and < 50 %) and procedural success (<30 % and < 50 %) were comparable for both groups (Table 5).

During one-year follow-up, MACE occurred in 7 (7 %) individuals, involving 2 cardiac deaths, one MI followed by TVR and 5 elective TVRs. All-cause mortality occurred in six (6 %) patients. Group comparison showed no significant differences in the occurrence of events (Table 6) and MACE-free 30-day (p = 0.115) and one-year survival (p = 0.529) (Fig. 4). Among the documented events, two patients (2 %) experienced in-hospital MACE, none of them directly related with IVL procedure. One was caused by a iatrogenic type A aortic dissection following high pressure balloon post-dilatation after IVL in a patient with severe stent recoil attributable to a calcific nodule; the second patient died because of cardiogenic shock and multiorgan failure. It should be noted that although in-hospital and 30-days follow-up was available in all cases, 1-year follow-up was complete in 59/101 patients (58.4 %).

4. Discussion

This is the largest-to-date study that has examined the efficacy and clinical impact of in-stent IVL, and that compared the procedural and clinical outcomes of IVL in stent because of peri-stent calcification, both immediate and late after stent implantation. The main findings of the present study are: 1) IVL is an effective option for in-stent application, with comparable procedural results for both immediate and late application; 2) the high efficacy of in-stent IVL is accompanied by low rate of adverse clinical events at 1-year follow-up; 3) the potential IVL-induced damage of the stent drug-polymer in patients undergoing IVL due to ISU was not associated to a higher rate of MACE at 1-year follow-up, although this findings must should be drawn with caution due to the intrinsic limitations of the study.

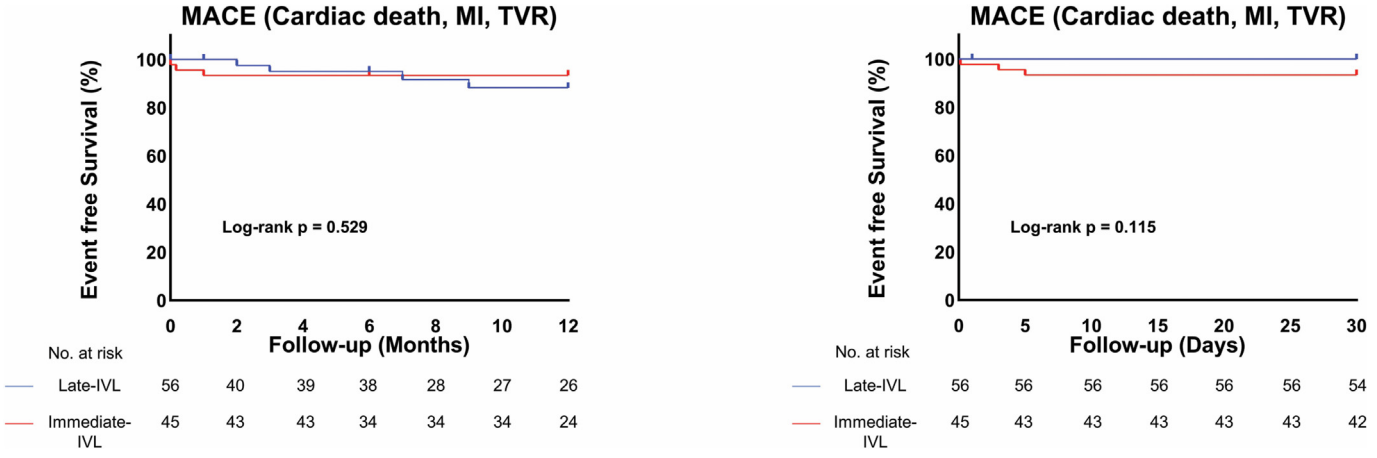

Fig. 4. Major cardiovascular events-free survival curves in patients treated with intravascular lithotripsy for peri-stent calcification. 30-days and 1-year MACE-free survival of patients treated for immediate stent underexpansion (immediate-IVL; red line) vs. patients treated for delayed stent failure due to peri-stent calcification (late-IVL; blue line). MACE = major adverse cardiovascular events; MI = myocardial infarction;TVR = target vessel revascularization. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Both groups were comparable on most baseline demographics and procedural characteristics. The observed disparity in the prevalence of previous PCI, MI and procedures performed in multiple-layered stents was to be expected, as all individuals with ISR underwent prior PCI. It should be expected a more variable effect of IVL on extra-stent calcification in patients with multiple-layered stents, due to the absorption of sonic energy by the increased metal thickness [23,24,29]. The majority of multiple-layered stents lesions treated with IVL were included in the "late-IVL" group. In this specific subset, a significantly larger luminal gain assessed by QCA was observed, suggesting the benefit of IVL in this scenario. These findings should be interpretated with caution and need further confirmation in larger prospective studies.

The post-IVL treatment also differed significantly; more stents were implanted in the late-IVL group, whereas more patients in the immediate-IVL group underwent balloon angioplasty (Table 2), in order to avoid the implantation of a new stent layer [8]. The low rate of drug-coated balloon use, a potentially useful tool in an ISR setting, may be explained by limited availability for most participating centers at the time of the study.

Imaging analysis within each group (QCA and ICI) showed a significant improvement of MLD, MLA, percentage DS, MSA and stent expansion following IVL therapy. In addition, good procedural results (device, technical and procedural success) and low rates of MACE (in any case related to the IVL procedure) were observed (Table 6), and were comparable in both groups, exemplifying IVLs efficacy even in ISU. These results are in line with the DISRUPT-CAD studies [16], examining the effectiveness of IVL in de novo lesions, and the more recent SMILE and CRUNCH registries, examining the effectiveness of in-stent IVL. Group comparison of imaging analysis has shown significantly higher minimum LD and lower percentage DS for patients with immediate vs late-IVL, whereas post-IVL minimum LD, and percentage DS were comparable between the two groups (Tables 3 and 4). The observed lower luminal gain in immediate-IVL patients, as also reported in the CRUNCH registry, may be explained by the presence of larger baseline values in this group. ISU may result from insufficient lesion preparation, and may increase the complexity of the procedure as reflected by the longer procedural and fluoroscopic time and larger amount of contrast volume.

IVL is still considered as an off-label in-stent therapy, as it is unknown if the potential damage of IVL on DES leads to increased mid- to long-term event rates (stent thrombosis and target lesion revascularization). A recent study performed by Achimal et al., examining the effect of IVL on the antiproliferative nature of DES, concluded that IVL causes microdamage in the drug polymer, but that this microdamage does not elevate risk of ISR [29]. The results of our study are consistent with the SMILE and CRUNCH registries [23,24], examining the short-term safety and effectiveness of in-stent IVL, although with limited number of immediate-IVL cases included. Additionally, it shows that IVL has similar procedural results and MACE rates after a longer follow-up in both immediate and late application, which suggests that the microdamage of DES caused by IVL in an acutely underexpanded stent might not be clinically relevant. However, these findings have to be examined in larger prospective studies, where patients with ISU treated with IVL are followed-up with OCT assessment of the stent to check for neointimal coverage. Nevertheless, it should be emphasized that adequate lesion preparation in calcific lesions, preferably guided by ICI, is critical in order to allow a successful stent implantation.

4.1. Limitations

Several limitations should be acknowledged, most of them arising from the retrospective observational nature of the study and its limited sample size. For the purpose of this project, the participating centers were not required to submit data regarding similar lesions subsets treated with different treatment strategies options. Lack of control group hampers the added value of IVL in this scenario and is particularly relevant when interpretating the clinical outcomes observed. In addition, the decisions regarding the timing of IVL, the utilization of high-pressure pre- and post-dilatation, the placement of supplementary stents, and the use and timing of ICI for procedural optimization were left to the operator's discretion. Therefore, it was not possible to measure the effect of IVL therapy on its own. We did not analyzed potential differences among the different mechanisms of stent failure in the late-IVL group due to small sample size. Furthermore, paired analysis of ICI data was not available for all patients.

5. Conclusions

IVL is effective treatment strategy for stent failure resulting from peristent calcification, both immediately and late after stent implantation. Overall, MACE rates both at short- and mid-term were low and comparable in both group, although findings regarding clinical outcomes should be taken with caution.

Disclosures

The Department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Abbott Vascular, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare and Medtronic. F. van der Kley received consultancy fees from Edwards Lifesciences and Abbott Vascular. Alfonso Jurado is proctor for Boston Scientific, Philips/Biomenco and Medtronic and received speaker fees from Shockwave, Boston, Abbott, World Medica. JM. Montero received a research grant from Shockwave Medical and speaker fees from Abiomed, Boston Scientific and Penumbra Inc. The remaining authors have no conflicts of interest to declare.

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B.O. Bingen: Conceptualization; Formal analysis; Project administration; Supervision; Validation; and Writing - review & editing.

J.G. Cordoba-Soriano: Data curation and Writing - review & editing.

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F. van der Kley: Resources; Writing - review & editing,

JW Jukema: Funding acquisition; Project administration; Resources; Writing - review & editing.

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Declaration of competing interest

The Department of Cardiology of the Leiden University Medical Center received unrestricted research grants from Abbott Vascular, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, GE Healthcare and Medtronic.

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Appendix A. Supplementary data

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