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Clinical

Efficacy and Safety of Intravascular Lithotripsy Versus Rotational Atherectomy in Balloon-Crossable Heavily Calcified Coronary Lesions

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ABSTRACT

Background: Severe coronary artery calcification is associated with poor procedural and clinical outcomes in patients undergoing percutaneous coronary intervention. Rotational atherectomy (RA) and intravascular lithotripsy (IVL) are techniques used to optimize lesion preparation and facilitate stent implantation in this anatomical scenario. However, their comparative efficacy and safety remain unknown.

Methods: We retrospectively analyzed 101 patients who underwent PCI utilizing RA or IVL for lesion preparation in heavily calcified balloon-crossable coronary stenosis. The primary endpoint was procedural success. In addition, the occurrence of major adverse cardiovascular events (MACE, defined as the composite of all-cause mortality, target lesion revascularization (TLR), stroke and stent thrombosis (ST)) at 6-months was analyzed.

Results: High rates of procedural success were achieved in both RA and IVL (82 % vs. 92 %; $p = 0.25$), with a low in hospital complication rate (8 % vs. 4 %; $p = 0.678$). No significant differences were found in overall MACE at 6-months (12 % vs 6 %; $P = 0.487$), death (8 % vs. 2 %; $p = 0.362$), TLR (2 % vs. 2 %; $p = 1.000$), stroke (2 % vs. 2 %; $P = 1.000$) or ST (2 % vs. 0 %; $P = 1.000$). Moreover, IVL is associated with a significantly shorter fluoroscopy time (32 [22–45] vs 26 [16–37]; $P = 0.041$).

Conclusions: Both IVL and RA are safe and effective methods for treatment of heavily calcified coronary lesions with similar outcomes at short term follow up.

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1. Introduction

Severe coronary artery calcification (CAC) is present in approximately 20 % of patients undergoing percutaneous coronary intervention (PCI) and represents a major challenge for the success of the procedure [1–3]. Vessel injury during lesion preparation, failure of stent delivery and suboptimal stent expansion are frequently encountered during PCI in severely calcified lesions, which negatively impacts the patients' prognosis [1–3]. Heavily calcified coronary lesions may be prepared for stent implantation with high-pressure or cutting/scoring balloons, however lesion preparation without altering the intravascular calcium may lead to complications such as dissections and perforations or prove ineffective altogether [4]. In contrast, rotational atherectomy

(RA), includes alteration of coronary calcium by intraluminal abrasion. This method has been used for lesion preparation in the presence of CAC since the late 80's and is associated with more favorable outcomes in this context in recent studies [5,6]. More recently, intravascular lithotripsy (IVL) has been introduced as a novel modality for attacking CAC, by utilizing a specialized balloon capable of delivering pressure waves in order to achieve calcium fractures and subsequent proper lesion preparation [7,8]. As such, in balloon-crossable severely calcified coronary lesions, both RA and IVL are regarded as reasonable options in contemporary PCI. However, their comparative safety and efficacy in this context has not been studied previously. We therefore performed this retrospective analysis to compare the performance of RA vs IVL in patients with balloon-crossable heavily calcified coronary lesions.

2. Methods

2.1. Study population

The study population consisted of patients with balloon-crossable heavily calcified coronary lesions, defined as a coronary lesion that can

Abbreviations: CAC, coronary artery calcification; IVL, intravascular lithotripsy; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RA, rotational atherectomy; ST, stent thrombosis; TLR, target lesion revascularization.

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be crossed with a balloon after successful guidewire crossing [9], either with RA (between January 2006 and January 2019, before the introduction of IVL) or IVL (between June 2019 and June 2021) at the Leiden University Medical Center. Severe CAC was defined by qualitative angiography radiopacities seen without cardiac motion before contrast injection, usually affecting both sides of the arterial lumen radiopacities noted before contrast injection [10]. Exclusion criteria included balloon-uncrossable lesions, combined used of RA and IVL for the same target lesion or cardiogenic shock. This retrospective study of clinically acquired data was approved by the Institutional Review Board and the need for patient written informed consent was waived.

2.2. Procedural characteristics

All procedures were performed by experienced operators and according to current guidelines [11]. Vascular access and the use of intracoronary imaging were at the operators' discretion. Dual antiplatelet therapy was prescribed and was administered according to general recommendations [11]. Both RA and IVL were indicated after crossing the target coronary lesion with a guidewire and performing high pressure balloon predilatation, showing evident suboptimal balloon expansion (Fig. 1). RA was performed with the Rotablator system (Boston Scientific, Natick, Massachusetts). Ratio of burr to vessel size was kept at 0.5–0.7 and rotational speed was set at 150,000 to 170,000 rpm. Each run of RA was for 20 s. at maximum with at least 2–3 runs per lesion. Continuous intracoronary infusion of verapamil, nitroglycerin, and unfractionated heparin was administered. IVL was performed by using the Shockwave Intravascular Lithotripsy Coronary System (Shockwave

Medical, Santa Clara, California). IVL balloon size was selected at 1:1 ratio to reference vessel diameter. The IVL was inflated at a maximum of 6 atm. and IVL pulses were delivered, with balloon deflation after each 10 pulses to minimize ischemia. IVL treatment was repeated until full balloon expansion was achieved or the maximum of 80 pulses was reached. Postdilatation with non-compliant balloon at high pressures after lesion preparation and/or after stent placement was performed at operator's discretion. Final angiographic results were assessed by quantitative coronary angiography using validated software (Medis Suite 4.0.24.4, Medis Medical Imaging System BV, Leiden, the Netherlands). Angiographic success was defined as in-stent residual stenosis $\leq 30\%$ without significant angiographic complications (severe coronary dissection impairing flow [type D-F], perforation, abrupt closure or no-reflow). Procedural success was defined as angiographic success without in-hospital complications. Major adverse cardiovascular events (MACE) were defined as the composite of all-cause mortality, target lesion revascularization (TLR), stroke and stent thrombosis (ST).

2.3. Follow-up and data collection

Guideline-based medical treatment was prescribed in all patients at discharge [11]. Dual antiplatelet and/or anticoagulation therapy (when indicated) was administered according to current guidelines [11]. Clinical data were retrospectively collected from the departmental information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands). Missing data from referral hospitals were requested by phone contact or by contacting the general practitioner of the patient.

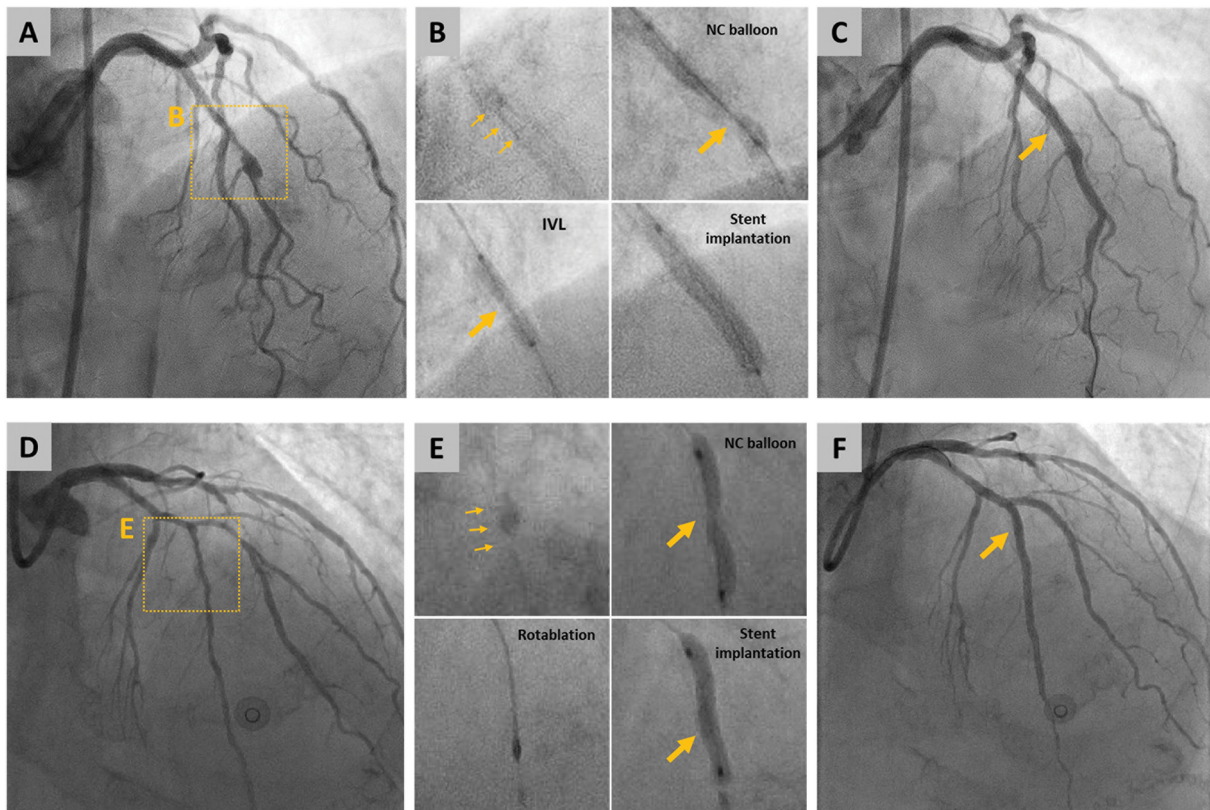


Fig. 1. Examples of balloon-crossable heavily calcified coronary lesions treated either with intravascular lithotripsy (IVL, panels A–C) or rotational atherectomy (RA, panels D–F). Patient 1, Panel A: target lesion located at the mid left anterior descending (LAD) artery. Panel B: zoom corresponding to the dotted yellow square in Panel A showing severe calcification on fluoroscopy (upper left, arrows); “dog bone” effect during balloon inflation (upper right, arrow), which resolves during IVL (lower left, arrow) allowing optimal stent expansion (lower right). Panel C shows the final result (arrow). Patient 2, Panel D: target lesion located at the mid LAD. Panel E: zoom corresponding to the dotted yellow square in Panel C showing severe calcification on fluoroscopy (upper left, arrows); “dog bone” effect during balloon inflation (upper right, arrow), treated with RA (lower left, arrow) facilitating optimal stent expansion (lower right). Panel F shows the final result (arrow).

2.4. Study endpoints

The primary endpoint was procedural success assessed by quantitative coronary angiography. The secondary endpoint was the occurrence of MACE at 6 months follow-up.

2.5. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation or median and interquartile range as appropriate. Differences between groups were analyzed using the unpaired Student's *t*-test for normally distributed continuous variables and the Mann-Whitney *U* test for non-normally distributed variables. Categorical data are presented as frequencies and percentages and were analyzed using the χ^2 or Fisher's exact test. The cumulative events were stratified using the Kaplan–Meier curve and comparison between groups was performed using the log-rank test. Uni- and multivariable binary logistic regression analyses were performed to evaluate predictor of MACE. Variables with a *P*-value <0.25 on univariable analysis were included in the multivariate analysis. All statistical tests were two-sided, and a *P*-value <0.05 was considered statistically significant. Data analyses were performed using SPSS version 25.0 software (IBM SPSS Statistics for Windows, Armonk, NY, USA).

3. Results

A total of 101 patients (73.28 ± 8.81 years-old, 63.4 % of patients were males) were included in the study, of whom 51 (50.5 %) were treated with RA and 50 (49.5 %) with IVL. Baseline clinical characteristics are shown in Table 1. Previous PCI was more frequently observed in patients treated with IVL (46 % vs. 23 %; *P* = 0.030). Angiographic and procedural characteristics are presented in Table 2. Patients treated with RA had higher rates of femoral access (67 % vs. 32 %; *P* = 0.001), longer fluoroscopy time (32 [22–45] vs. 26 [16–37] min; *P* = 0.041) and longer calcific lesion length (29.4 ± 11.4 mm. vs. 25.0 ± 10.0 mm; *P* = 0.044). When compared with patients treated with RA, patients treated with IVL had larger reference vessel diameters (3.3 ± 0.5 mm vs. 3.1 ± 0.4 mm; *P* = 0.002), had more frequently in-stent restenosis (38 % vs. 4 %; *P* = 0.000); underwent postdilatation more often (74 % vs. 39 %; *P* = 0.001) and with larger balloons (3.7 ± 0.5 mm vs. 3.4 ± 0.5 mm vs. 3.1 ± 0.3 mm; *P* ≤ 0.0001) and showed larger final minimal luminal diameter after stenting (2.9 ± 0.4 mm vs. 2.6 ± 0.5 mm; *P* = 0.002). In addition, intracoronary imaging was used more frequently in the IVL group (50 % vs. 6 %; *P* < 0.0001).

In-hospital outcomes are presented in Table 3. There were no significant differences neither in angiographic success rates (94 % IVL vs. 86 %

RA; *P* = 0.318), nor in procedural success rates (92 % IVL vs. 82 % RA; *P* = 0.250). In-hospital complications were low in both groups without statistically significant differences (4 % IVL vs 8 % RA; *P* = 0.678).

Follow-up outcomes at 6-months are presented in Table 4. There were no significant differences regarding overall MACE (12 % RA vs. 6 % IVL; *P* = 0.487). In addition, there were no significant differences between groups regarding death, TLR, stroke or ST. Survival analysis revealed no significant differences between groups for the occurrence of MACE at 6-months (Fig. 2).

To evaluate impact of the selected debulking technique and other variables potentially related with the occurrence of MACE, univariable and multivariable analysis were performed (Table 5). On multivariable analysis, only procedural success was independently associated with the occurrence of MACE.

4. Discussion

The main findings of our study are: 1) both IVL and RA are effective and safe techniques for preparation of balloon-crossable heavily calcified coronary lesions, showing high rates of procedural success (92 % and 82 % respectively) and low periprocedural complication rates (4 % and 8 % respectively); 2) there were no significant differences between IVL and RA in the occurrence of MACE at 6-months follow-up 3) IVL was more often applied than RA to treat in-stent restenosis, lesions with larger reference diameter and shorter calcified lesion length.

There are no previous reports comparing the efficacy and safety of IVL and RA. The rates of procedural success, angiographic success and MACE in the present study are in line with previous studies analyzing IVL [7,12–14] and bail-out RA [15,16] separately.

When comparing IVL and RA, several mechanistic and procedural differences have to be taken into account. The IVL system emits pulsatile mechanical energy, known to penetrate up to 7 mm of tissue, inducing microfractures in both deep and superficial calcium [17]. RA makes use of a high-speed rotating diamond-coated burr acting as an abrasive surface against superficial calcific plaque. These particular features determine the potential advantages of each technique in particular anatomical scenarios, such as deep calcium deposits for IVL or extensive superficial calcific plaque in RA, and therefore several treatment algorithms have been proposed to facilitate device selection [18]. The abrasive nature of RA may explain a reluctance to apply this technique in in-stent restenosis, as found in the present study, in order to circumvent distal embolization of stent fragments. However, past studies have demonstrated that RA can be safely applied to treat undilatable underexpanded stents [19]. The safety and efficacy of IVL in this particular setting has been recently reported [20–22]. In addition, IVL is applied using a rapid exchange monorail balloon, connected to an IVL generator and inflator, which can be advanced over a standard workhorse wire.

Table 1
Baseline clinical characteristics.

	Total (n = 101)	Rotational atherectomy (n = 51)	Intravascular lithotripsy (n = 50)	<i>P</i> value
Age (years)	73.3 $\pm$ 8.8	72.8 $\pm$ 8.7	73.7 $\pm$ 8.9	0.652
Male, n (%)	64 (63.4)	30 (59)	34 (68)	0.453
Diabetes mellitus, n (%)	34 (33.4)	14 (27)	20 (40)	0.261
Hypertension, n (%)	66 (65.3)	28 (55)	38 (76)	0.044
Dyslipidemia, n (%)	64 (63.4)	34 (67)	30 (60)	0.625
Current smoking, n (%)	17 (16.8)	8 (16)	9 (18)	0.964
Family history CAD, n (%)	23 (22.8)	10 (20)	13 (26)	0.597
Previous MI, n (%)	29 (28.7)	16 (31)	13 (26)	0.706
Previous PCI, n (%)	35 (34.7)	12 (23)	23 (46)	0.030
Previous CABG, n (%)	24 (23.8)	12 (23)	12 (24)	1.000
Previous CVA, n (%)	11 (10.9)	6 (12)	5 (10)	1.000
LVEF <50 %, n (%)	34 (33.7)	22 (43)	12 (24)	0.068
ACS at presentation, n (%)	38 (37.6)	20 (39)	18 (36)	0.898
eGFR <60 ml/min/1.73 m ² , n (%)	24 (23.8)	11 (22)	13 (26)	0.772

ACS: acute coronary syndrome, CABG: coronary artery bypass grafting, CAD: coronary artery disease, CVA: cerebrovascular accident, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, MI: myocardial infarction, PCI: percutaneous coronary intervention. Bold values statistically significant with *p* values <0.05 .

Table 2
Angiographic and procedural characteristics.

	Total (n = 101)	Rotational atherectomy (n = 51)	Intravascular lithotripsy (n = 50)	P value
Target vessel, n (%)				0.397
LAD, n (%)	43 (42.6)	22 (43)	21 (42)	
LCx, n (%)	12 (11.9)	8 (15)	4 (8)	
RCA, n (%)	41 (40.6)	20 (39)	21 (42)	
LM, n (%)	5 (5)	1 (2)	4 (8)	
Three vessel coronary disease, n (%)	19 (18.8)	9 (17)	10 (20)	0.962
In-stent restenosis, n (%)	21 (20.8)	2 (4)	19 (38)	<0.001
Chronic total occlusion, n (%)	7 (6.9)	1 (2)	6 (12)	0.060
Bifurcation lesion, n (%)	25 (24.8)	10 (20)	15 (30)	0.327
Femoral access, n (%)	50 (49.5)	34 (67)	16 (32)	0.001
Radial access, n (%)	51 (50.5)	17 (33)	34 (68)	
Fluoroscopy time, min	29 (17–40)	32 (22–45)	26 (16–37)	0.041
Contrast volume, ml	221 ± 75.0	221 ± 73.5	221 ± 77.1	0.957
Intra coronary imaging, n (%)	28 (27.7)	3 (6)	25 (50)	<0.001
IVL balloon diameter, mm	N/A	N/A	3.5 (3.0–4.0)	N/A
IVL pulses, n	N/A	N/A	80 (60–80)	N/A
Burr size, mm	N/A	1.5(1.5–1.7)	N/A	N/A
Stent postdilatation, n (%)	57 (56.4)	20 (39)	37 (74)	0.001
Postdilatation balloon diameter, mm	3.6 ± 0.5	3.5 ± 0.5	3.7 ± 0.5	0.012
Postdilatation pressure, atm	21.2 ± 3.4	20.6 ± 2.9	21.5 ± 3.6	0.337
Number of stents, n	2.1 ± 1.0	2.2 ± 1.2	2.1 ± 0.8	0.594
Stent diameter, mm	3.3 ± 0.5	3.1 ± 0.3	3.5 ± 0.5	<0.001
Total stent length, mm	41 (28–59)	37 (24–55)	48 (30–60)	0.124
Calcific lesion length, mm	27.2 ± 10.9	29.4 ± 11.4	25.0 ± 10.0	0.044
Reference vessel diameter, mm	3.2 ± 0.5	3.1 ± 0.4	3.3 ± 0.5	0.002
Final minimal lumen diameter, mm	2.7 ± 0.5	2.6 ± 0.5	2.9 ± 0.4	0.002
Final in stent residual stenosis, %	20 (15–23)	20 (18–23)	19 (15–24)	0.466

LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, IVL: intravascular lithotripsy, RCA: right coronary artery. Bold values statistically significant with p values <0.05

Table 3
Primary endpoints and in-hospital outcomes:

	Total (n = 101)	Rotational atherectomy (n = 51)	Intravascular lithotripsy (n = 50)	P value
Angiographic success, n (%)	91 (90)	44 (86)	47 (94)	0.318
Procedural success, n (%)	88 (87)	42 (82)	46 (92)	0.250
In-hospital complications total, n (%)	6 (6)	4 (8)	2 (4)	0.678
Cardiac death, n (%)	2 (2)	1 (2)	1 (2)	
Procedure-related MI, n (%)	1 (1)	1 (2)	0 (0)	
Stroke, n (%)	1 (1)	1 (2)	0 (0)	
Coronary perforation, n (%)	3 (3)	2 (4)	1 (2)	
Severe coronary dissection type D-F, N (%)	0 (0)	0 (0)	0 (0)	
No reflow, n (%)	0 (0)	0 (0)	0 (0)	
Vascular access complications, n (%)	2 (2)	1 (2)	1 (2)	
Emergency CABG, n (%)	0 (0)	0 (0)	0 (0)	

CABG: coronary artery bypass grafting, MI: myocardial infarction.

RA, on the other hand, utilizes an over-the-wire system that employs a 0.009-in. diameter, 330 cm length Rotawire, over which a burr can be advanced. The burr is connected to a drive shaft, which has to be connected to a flush solution and the rotablation console. The Rotawire is generally considered not to be suitable enough to advance balloons

Table 4
Clinical outcomes at 6-months follow-up.

	Total (n = 101)	Rotational atherectomy (n = 51)	Intravascular lithotripsy (n = 50)	P value
Total MACE, n (%)	9 (9)	6 (12)	3 (6)	0.487
All-cause death, n (%)	5 (5)	4 (8)	1 (2)	
TLR, n (%)	2 (2)	1 (2)	1 (2)	
Stroke, n (%)	2 (2)	1 (2)	1 (2)	
Stent thrombosis, n (%)	1 (1)	1 (2)	0 (0)	

MACE: major adverse cardiovascular events, TLR: target lesion revascularization.

and stents. Hence, the Rotawire is frequently exchanged for a work-horse wire in order to finish the procedure after calcium modification, implying. The more straightforward setup of IVL and the potentially lower resource consumption (i.e. cath-lab time, material, etc.) may significantly reduce procedural complexity when using IVL compared to RA. Indeed, in our study fluoroscopy time (as a derivative of procedural time) was significantly lower in IVL. Similar differences in fluoroscopy times were found in previous studies comparing other (i.e. cutting and scoring) balloon-based methods of lesion preparation with RA [6,23].

IVL, specifically the Shockwave C2 system, utilizes balloons from 2.5 to 4.0 mm diameter, that are used in a 1:1 balloon:vessel ratio. Every balloon up to 4.0 mm can fit through a standard 6Fr coronary guide catheter. RA, on the other hand, makes use of burrs that range from 1.25 to 2.0 mm in diameter and are typically used in a 0.5–0.7:1 burr:vessel ratio. If the remaining lumen of the targeted lesion is larger than 2.0 mm, rotablation will have limited plaque modification effect. Moreover, burrs beyond 1.5 mm diameter require larger guiding catheters (≥7Fr). The above mentioned disparities may account for the significant differences in reference vessel diameter, stent diameter,

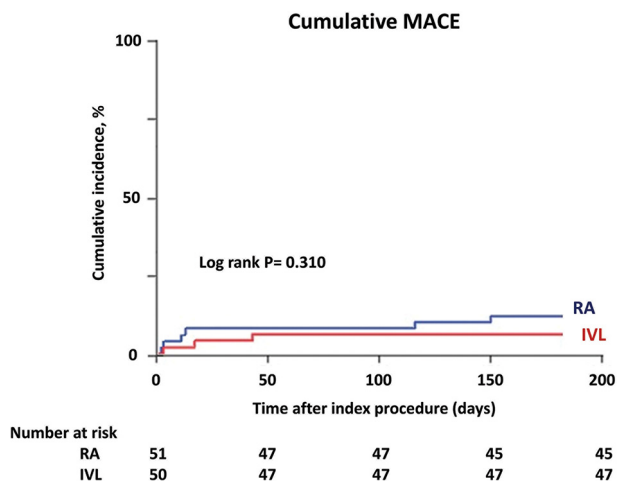


Fig. 2. Kaplan-Meier survival curves of cumulative MACE incidence in patients treated with rotational atherectomy versus those treated with intravascular lithotripsy. IVL: intravascular lithotripsy. MACE: Major adverse cardiovascular events. RA: Rotational atherectomy.

postdilatation balloon diameter and final minimal luminal diameter between IVL and RA found in the present study.

Finally, selection of IVL or RA comes with its respective economic implications. As recently demonstrated, IVL has a higher initial device cost, which in turn might be compensated by a lower overall resource use during PCI [24]. The timing of device selection is still an ongoing debate. Despite of the demonstrated clinical benefit of a “planned” strategy in patients requiring RA [25], in a significant proportion of cases RA is performed as bailout after failure to expand a predilating balloon [15]. Hence, the costs associated to these techniques might force some operators to use them as second line after failure of conventional techniques during PCI.

Despite of the important differences observed between groups regarding the use of intravascular imaging or vascular access, only procedural success was found to be associated with the occurrence of MACE on multivariate analysis. This illustrates the importance of optimal lesion preparation aiming to optimize the results of the PCI.

Several limitations should be considered. This is a single-center, observational retrospective analysis of prospectively clinically acquired

data, with all the inherent limitations associated to the nature of the study. The use of intracoronary imaging was low, especially in the RA group. These might be explained by a lower awareness of the role of intravascular imaging in the historical RA cohort (whereas the use of intracoronary imaging for lesion characterization and PCI optimization has become standard in current practice), inability of delivering intracoronary imaging equipment through the target lesion and procedural associated costs. This difference in the use of intracoronary imaging in the RA group might indicate as well the presence of more severe calcification/stenosis, which may have influenced the observed results. There was a higher rate of femoral access observed in the RA group. This difference might be explained by previous standards of care in the historical institutional RA cohort, potential need of larger burrs by pre-procedural evaluation, etc. Although no data regarding bleeding was collected, this might have an important clinical impact. Due to the relatively small sample size and limited follow-up, no definitive conclusion can be derived from our study. Prospective studies with larger patient cohorts and longer follow-up are warranted in order to confirm our results.

5. Conclusion

Both IVL and RA are effective and safe techniques for preparation of balloon-crossable heavily calcified coronary lesions with high procedural success rates. No significant differences in the occurrence of MACE at 6-months follow-up were observed.

CRediT authorship contribution statement

Mohamed A.A. Mousa: Conceptualization, Methodology, data analysis, original draft preparation.

Brian O. Bingen: Conceptualization, Methodology, data analysis, manuscript edition.

Ibtihal Al Amri: Conceptualization, Methodology, data analysis, manuscript edition.

B.J.A Mertens: data analysis and statistical analysis.

Salma Tahab: manuscript revision.

Aly Tohamy: data collection, manuscript revision.

Amr Youssef: manuscript revision.

J. Wouter Jukema: manuscript revision and edition.

Jose M. Montero-Cabezas: Conceptualization, Methodology, data analysis, manuscript revision and edition.

Table 5

Uni- and multivariate logistic regression analyses of the variables associated with the occurrence of MACE.

Variable	Univariable analysis			Multivariable analysis		
	Odds ratio	95 % confidence interval	P-value	Odds ratio	95 % confidence interval	P-value
Age (years)	1.014	0.936–1.098	0.735			
Sex	2.344	0.588–9.344	0.227	2.073	0.449–9.573	0.350
Hypertension	0.938	0.220–4.000	0.931			
Diabetes	0.904	0.486–1.681	0.749			
Dyslipidemia	1.430	0.359–5.697	0.612			
Smoking	1.684	0.634–1.684	0.634			
Previous myocardial infarction	1.454	0.284–7.452	0.654			
Previous CABG	2.667	0.316–22.479	0.367			
Previous PCI	1.958	0.385–0.973	0.419			
ACS at presentation	0.814	0.191–3.466	0.781			
Femoral access	1.250	0.315–4.953	0.751			
eGFR <60 ml/min/1.73 m ²	0.375	0.044–3.161	0.367			
Three-vessels disease	0.421	0.95–1.863	0.250	0.253	0.047–1.363	0.110
Use of IVL	0.479	0.113–2.031	0.318			
Use of intracoronary imaging	3.323	0.396–27.872	0.268			
In-stent restenosis	2.222	0.262–18.832	0.464			
Calcific lesion length	0.416	0.080–2.175	0.299			
Stent diameter	0.346	0.066–1.824	0.211	0.356	0.074–1.718	0.198
Final minimal lumen diameter	0.482	0.117–1.986	0.312			
Procedural success	7.378	1.673–32.535	0.008	10.173	1.997–51.820	0.005

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; eGFR = estimated glomerular filtration rate; IVL = intravascular lithotripsy; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention.

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Declaration of competing interest

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