A Systematic Review and Meta-Analysis Including 354 Patients from 13 Studies of Intravascular Lithotripsy for the Treatment of Underexpanded Coronary Stents

Rodolfo Caminiti, MD[a,1], Giampaolo Vetta, MD[a,1], Antonio Parlavecchio, MD[a], Alfonso Ielasi, MD[b], Michele Magnocavallo, MD[c], Domenico Giovanni Della Rocca, MD, PhD[d,e], Enrico Cerrato, MD, PhD[f], Scipione Carerj, MD[a], Gianluca Di Bella, MD, PhD[a], Antonio Micari, MD, PhD[a], and Giampiero Vizzari, MD, PhD[a,*]

Calcified coronary plaque (CCP) represents a challenging scenario for interventional cardiologists. Stent underexpansion (SU), often associated with CCP, can predispose to stent thrombosis and in-stent restenosis. To date, SU with heavily CCP can be addressed using very high−/high-pressure noncompliant balloons, off-label rotational atherectomy/orbital atherectomy, excimer laser atherectomy, and intravascular lithotripsy (IVL). In this meta-analysis, we investigated the success rate of IVL for the treatment of SU because of CCP. Studies and case-based experiences reporting on the use of IVL strategy for treatment of SU were included. The primary end point was IVL strategy success, defined as the adequate expansion of the underexpanded stent. A metanalysis was performed for the main focuses to calculate the proportions of procedural success rates with corresponding 95% confidence intervals (CIs). Random-effects models weighted by inverse variance were used because of clinical heterogeneity. This meta-analysis included 13 studies with 354 patients. The mean age was 71.3 years (95% CI 64.9 to 73.1), and 77% (95% CI 71.2% to 82.4%) were male. The mean follow-up time was 2.6 months (95% CI 1 to 15.3). Strategy success was seen in 88.7% (95% CI 82.3 to 95.1) of patients. The mean minimal stent area was reported in 6 studies, the pre-IVL value was 3.4 mm^2 (95% CI 3 to 3.8), and the post-IVL value was 6.9 mm^2 (95% CI 6.5 to 7.4). The mean diameter stenosis (percentage) was reported in 7 studies, the pre-IVL value was 69.4% (95% CI 60.7 to 78.2), and the post-IVL value was 14.6% (95% CI 11.1 to 18). The rate of intraprocedural complications was 1.6% (95% CI 0.3 to 2.9). In conclusion, the "stent-through" IVL plaque modification technique is a safe tool to treat SU caused by CCP, with a high success rate and a very low incidence of complications. **(Am J Cardiol 2023;205:223−230)**

Keywords: percutaneous coronary interventions, calcified lesions, intravascular lithotripsy, stent underexpansion

Calcified coronary plaque (CCP) can complicate lesion preparation and optimal stent delivery or expansion, with consequent suboptimal results.[1] Moreover, in most cases, CCP treatment leads to an increased risk of complications such as vessel perforation.[1] Stent underexpansion (SU), secondary to inadequate lesion preparation, represents a common risk factor for stent thrombosis and in-stent restenosis (ISR).[2,3] The management of SU related to CCP remains one of the most challenging settings for interventional cardiologists, and no expert consensus is currently available. Traditionally, the treatment of SU can be performed with noncompliant, high-/very high−pressure balloons, leading to a high risk of procedural failure and a high complication rate.[4] The off-label use of common "debulking" techniques, such as rotational atherectomy (RA)/orbital atherectomy (OA) and excimer laser atherectomy (ELCA), in this setting has been found to be effective with variable success rates and a high risk of procedural complications.[5−9]

The Shockwave System (Shockwave Medical Inc., Santa Clara, California) is a coronary lithotripsy tool composed of a semicompliant balloon, requiring inflation at a low

[a]Cardiology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [b]Cardiology Division, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Galeazzi Sant'Ambrogio, Milan, Italy; [c]Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, "Sapienza" University of Rome, Policlinico Umberto I, Rome, Italy; [d]Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas; [e]Heart Rhythm Management Centre, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, European Reference Networks Guard-Heart, Brussels, Belgium; and [f]Interventional Cardiology Unit, San Luigi Gonzaga University Hospital of Orbassano and Rivoli Infermi Hospital of Rivoli, Turin, Italy. Manuscript received January 20, 2023; revised manuscript received and accepted July 30, 2023.

Funding: none.

[1]Drs. Caminiti and Vetta contributed equally to this work.

See page 229 for Declaration of Competing Interest.

*Corresponding author: Tel: +39 349 421 9688.

E-mail address: giampierovizzari@hotmail.it (G. Vizzari).

https://doi.org/10.1016/j.amjcard.2023.07.144

pressure (around 4 atmospheres), and some emitters located inside the balloon (2 for coronary and 4 to 5 for peripheral); once activated, the emitters generate bubbles in the contrast-saline solution, causing the expansion and collapse of the fluid and releasing a circumferential sonic pressure wave (around 50 atmospheres) inside the vessel, resulting in deep and superficial calcium cracking.[10] Coronary "lithoplasty" proved to be safe in the treatment of de novo lesions, with a low complication rate, a high procedural success, and wide availability.[11−13] IVL was only approved for use in de novo setting; however, recent data from large registries and case series confirmed its potential role as an attractive approach for SU caused by CCP, with encouraging results.[14] This meta-analysis aimed to evaluate the procedural success, complication rate, and major adverse cardiovascular events (MACEs) of the IVL treatment of SU because of CCP.

Methods

A systematic search in Excerpta Medica Database (EMBASE), PubMed/MEDLINE, Cochrane, Ovid, and Scopus was performed from inception until November 30, 2022. The reference lists of bibliographies of identified articles were also reviewed. This search was conducted using the terms (coronary stent underexpansion) AND (lithotripsy) OR (lithoplasty). Our search was limited to English studies published in peer reviewed journals.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses was used to define the methods for this study.[15] The studies had to fulfill the following criteria to be included in the meta-analysis: (1) including patients with SU treated with IVL and (2) reporting the procedural success rate and/or procedural complications rate and/or MACE rate.

A total of 2 authors (R.C. and G.V.) selected the studies and extracted the data independently. Data were extracted using standardized protocol and reporting forms. A total of 2 reviewers (R.C. and G.V.) independently evaluated the quality items, and disagreements were resolved by consensus. The quality assessment of all included studies was done using the Newcastle−Ottawa quality assessment scale for cohort studies, which was accommodated to the studies included in this metanalysis for assessing the risk for bias.[16]

The primary end point was IVL procedural success, defined as a residual angiographic stenosis <30% or <20%, according to the included study assessed by quantitative coronary analysis and/or intravascular imaging (intravascular ultrasound and/or optical coherence tomography).

The safety study end points were (1) procedural complications (device failure, vessel perforation, dissection D-F, slow/no-reflow phenomenon, and periprocedural myocardial infarction [MI]) and (2) MACEs, defined as the composite of cardiac death, MI, and target vessel revascularization during follow-up.

Descriptive statistics are presented as means and SDs for continuous variables or several cases (n) and percentages (%) for dichotomous and categorical variables.

A metanalysis was performed for the main focuses to calculate the proportions of procedural success, procedural complications, and MACE rates, with corresponding 95% confidence intervals (CIs). Random-effects models weighted by inverse variance were used because of clinical heterogeneity. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate of the primary end point. Meta-regression analyses were performed for baseline and periprocedural features to assess the effect on procedural success using the Meta-regress command of STATA. Publication bias was assessed by graphical inspection of the funnel plots and the Egger test. Statistical significance was defined as a 2-tailed $p < 0.05$. Statistical analysis was performed using the metadata function of STATA version 16 (StataCorp LLC, College Station, Texas).

Results

We screened 273 articles, of which 75 full-text articles were retrieved and reviewed for possible inclusion. Ultimately, 13 studies fulfilled the inclusion criteria and were included in the meta-analysis (Figure 1).

Our meta-analysis included 13 studies[14,17−27] with 354 patients; the study by Mastrangelo et al[25] was divided in 2 separate subanalyses because of different groups. Table 1 lists the included studies characteristics. The definitions of procedural success and safety for each of the included studies are shown in Table 2. The mean age was 71.3 years (95% CI 64.9 to 73.1), and 77% (95% CI 71.2 to 82.4%) were male, as listed in Table 3. A large proportion of patients had hypertension (90.1%, 95% CI 83.6% to 95.3%) and dyslipidemia (80.3%, 95% CI 73.6% to 86.4%), previous MI was found in over half of the population (56.4%, 95% CI 43.6% to 68.9%), and diabetes mellitus was found in 45.9% (95% CI 39.4% to 52.6%). The indication for coronary angiography was acute coronary syndrome in 45% (unstable angina 13.9% [95% CI 7.8% to 17.6%], non−ST-segment elevation MI 25.8% [95% CI 18.6% to 30.4%], ST-segment elevation MI 5.3% [95% CI 1.2% to 7.7%]), and chronic coronary syndrome in 55% (95% CI 46.1% to 63.7%).

The lesions treated were 360: the most involved vessel was the left anterior descending (45.9%, 95% CI 36.6% to 55.3%), followed by the right coronary artery (31.8%, 95% CI 24.5% to 39.5%), left circumflex artery (10%, 95% CI 6% to 14.6%), and left main artery (7.9%, 95% CI 4.3% to 12.2%).

Lesion preparation before IVL therapy with a noncompliant balloon predilatation was performed in 82.6% (95% CI 69.6% to 93%) of patients, whereas a very high−pressure balloon (OPN NC, Sis Medical, Frauenfeld, Switzerland) was used in 29.8% (95% CI 12.2% to 50.5%). Postdilatation (after IVL) was performed in 83.8% (95% CI 75% to 91.2%) of the patients. The mean IVL balloon diameter was 3.4 mm (95% CI 3.2 to 3.5), the mean lithotripsy pulses were 70.9 (95% CI 62.2 to 79.6), and the mean IVL balloon maximum pressure was 5.2 atmospheres (95% CI 4.3 to 6.2). Intravascular ultrasound imaging was performed in 33.1% (95% CI 20.1% to 47.4%) of patients, and optical coherence tomography was performed in 23.7% (95% CI 10.9% to 39%). The mean follow-up time was 2.6 months (95% CI 1 to 15.3).

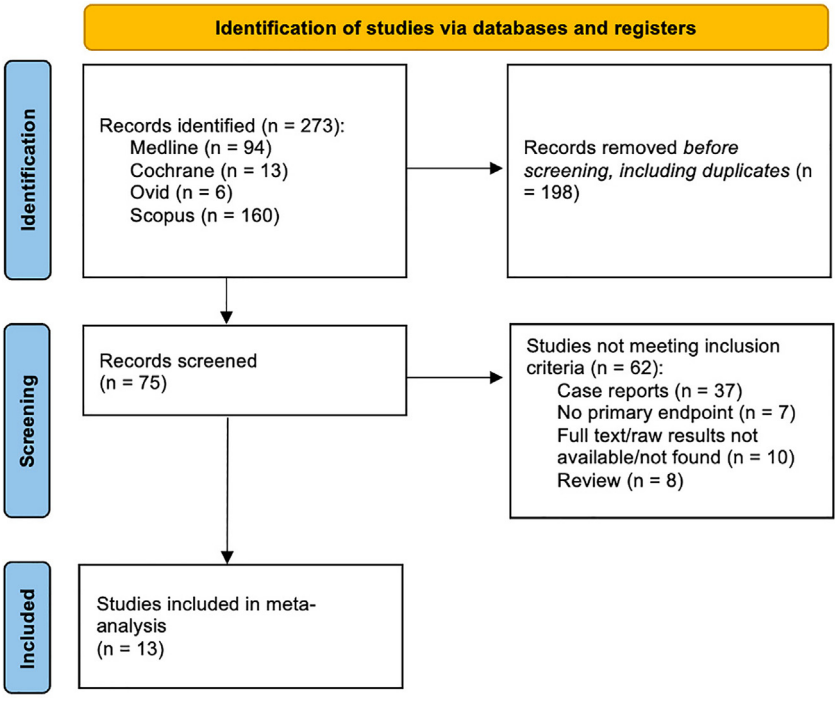

Figure 1. Evidence search and selection of PRISMA.

The average minimal stent area was reported in 6 studies, the baseline value was 3.4 mm^2 (95% CI 3 to 3.8), and post-IVL treatment increased to 6.9 mm^2 (95% CI 6.5 to 7.4).

SU, expressed as percent diameter stenosis assessed by quantitative coronary analysis, was reported in 7 studies, 69.4% at baseline (95% CI 60.7 to 78.2), and significantly decreased post-IVL therapy to 14.6% (95% CI 11.1 to 18).

The mean minimum luminal diameter was reported in 5 studies, the pre-IVL value was 1.1 mm (95% CI 0.8 to 1.4), and the post-IVL value was 2.9 mm (95% CI 2.6 to 3.2).

The primary efficacy end point was reported in 12 studies. The total lesions that underwent IVL were 342 and procedural success was achieved in 289 lesions, according to the study definition, with a pooled procedural success rate of 88.7% (95% CI 82.3 to 95.1) (Figure 2). The heterogeneity was high (I^2 = 75.7%). The meta-regression analysis suggested a negative influence of left main lesions on procedural success (β −0.91 [−1.46 to −0.37] p = 0.001) (Supplementary Table 1, Supplementary Figure 1). Conversely, the meta-regression analysis suggested a positive influence of predilatation with OPN on procedural success (β 0.27 [0.02 to 0.53] p = 0.035). No other cofactors influenced the outcomes (Supplementary Table 1, Supplementary Figure 2). The sensitivity analysis, according to the definition of procedural success, demonstrated no significant inter-relations (Supplementary Figure 3).

Procedural complications and MACEs were reported in 13 studies. The pooled procedural complications rate was 1.6% (95% CI 0.3 to 2.9) (Figure 3): 2 cases of dissection (types D and F), 1 perforation (Ellis type III), and 1 periprocedural MI because of IVL balloon rupture. The heterogeneity was low (I^2 = 0%).

The pooled MACE rate was 1.7% (95% CI 0.1 to 3.2) (Figure 4); 11 MACEs occurred at follow-up: 1 cardiac death and 10 spontaneous MI, 8 because of target vessel revascularization. The heterogeneity was high (I^2 = 22%). The leave-one-out analysis revealed no meaningful differences between studies in the primary end point (Supplementary Figure 4).

A graph and summary of the Newcastle−Ottawa quality assessment scale for cohort studies for each individual study is reported in Supplementary Figure 5. The funnel plot for the end points showed asymmetry, which was confirmed by the Egger test (p <0.01) (Supplementary Figure 6). Considering the random-effects model analysis and the paucity of data in previous research, the authors deemed it appropriate to continue the meta-analysis.

Discussion

SU can predispose to stent thrombosis and ISR, and it is often associated with CCP, representing a major challenge for interventional cardiologists. Many tools have been investigated for off-label use in SU treatment, with different complications rate, safety, and availability and variable procedural success rate.

The Element registry showed very encouraging results with the contrast-enhanced ELCA in the treatment of SU, but it has a significant dissection and perforation rate (7.2%) and limited availability in catheter laboratories and requires proper training and accurate in-stent application, and its use in underexpanded stent edges is not recommended.[9] RA/OA is effective for the ablation of the stent struts and fragmentation of the underlying calcium and fibrotic tissue, which is known as stentablation.[5–7] In contrast, these techniques are affected by a high complication

Table 1
Baseline characteristics of included studies

		A. Ielasi et al.	M. A.A. Mousa et al.	J. Yeoh et al.	A. Aksoy et al.	M. N. Tovar Forero et al.	F. J. Brunner et al.	A. Mastrangelo et al.*	A. Mastrangelo et al.†	W. Wanha et al.	K. Yaginuma et al.	H. El Jattari et al.	A. Aziz et al.	H. Sinclair et al.	E. J. Tassone et al.
Year		2020	2021	2019	2019	2022	2021	2022	2022	2022	2020	2022	2020	2020	2020
Patient		34	5	13	16	70	6	22	11	62	7	40	46	12	10
Lesions		39	5	13	16	64	6	23	11	62	7	40	46	12	10
Follow-up time		1	12.8±6.5	1	1	1	4.5±1.5	8.9±3.1	13.4±8.4	1	N/A	N/A	N/A	N/A	1
Age		69.6±1	69.2±9.6	70.2±8.1	75.9±8.6	73.1±9.2	75.3±8.3	72.5±7.2	73.6±8.7	69±7.1	69.9±8.1	N/A	N/A	N/A	65.8±7.2
Sex n (%) male		26 (76.4)	4 (80)	10 (76)	11 (68.8)	53 (75.7)	6 (100%)	18 (81.8)	9 (81.8)	41 (66.1)	6 (85)	N/A	N/A	N/A	9 (90)
Hypertension n (%)		29 (85.2)	4 (80)	8 (61)	16 (100)	62 (88.6)	6 (100%)	18 (81.8)	7 (63.6)	58 (93.5)	N/A	N/A	N/A	N/A	10 (100)
Diabetes Mellitus n (%)		18 (52.9)	3 (60)	6 (46)	5 (31.3)	37 (52.9)	2 (33.3%)	7 (31.8)	2 (18.2)	28 (45.2)	N/A	N/A	N/A	N/A	7 (70)
Dyslipidemia n (%)		28 (82.3)	2 (40)	9 (69)	10 (62.5)	50 (71.4)	4 (66.7%)	17 (77.3)	8 (72.7)	58 (93.5)	N/A	N/A	N/A	N/A	10 (100)
Prior MI n (%)		14 (41.1)	1 (20)	0	14 (87.5)	38 (54.3)	3 (50.0%)	21 (95.5)	5 (54.5)	43 (69.4)	N/A	N/A	N/A	N/A	8 (80)
Clinical	**Stable Angina**	19 (55.9)	0	7 (53)	8 (40)	33 (47.1)	4 (67)	15 (68.2)	11 (100)	30 (48.4)	N/A	N/A	N/A	N/A	N/A
Presentation	**Unstable Angina**	5 (14.7)	0		3 (18.8)	12 (17.1)	2 (33)	1 (31.8)	0	10 (16.1)	N/A	N/A	N/A	N/A	N/A
	NSTEMI	09 (26.5)	3 (70%)	6 (46)	3 (18.8)	18 (25.7)	0	4 (18.2)	0	20 (32.3)	N/A	N/A	N/A	N/A	N/A
	STEMI	1 (2.9)	1 (30%)		1 (6.3)	7 (10)	0	2 (9.1)	0	2 (3.2)	N/A	N/A	N/A	N/A	N/A
Vessel n (%)	**LM**	4 (10.1)	0	0	4 (23.6)	11 (15.7)	0	1 (4.4)	1 (9.1)	6 (9.7)	0	N/A	N/A	N/A	0
	LAD	19 (48.6%)	3 (60%)	9 (69)	6 (35.3)	36 (51.4)	2 (33)	12 (52.2)	6 (54.6)	16 (25.8)	0	N/A	N/A	N/A	8 (80)
	RCA	6 (15.3)	1 (20%)	4 (30)	5 (29.4)	19 (27.1)	4 (67)	8 (34.8)	2 (18.2)	31 (50.0)	5 (71)	N/A	N/A	N/A	1 (10)
	LCX	3 (7.6)	1 (20%)	0	2 (11.8)	9 (12.9)	0	2 (8.7)	2 (18.2)	9 (14.5)	2 (29)	N/A	N/A	N/A	1 (10)
IVUS n (%)		19 (48.7)	0	0	6 (35.3)	N/A	1 (16)	6 (26.1)	3 (27.3)	14 (22.6)	6 (85)	N/A	N/A	0	10 (100)
OCT n (%)		9 (23.1)	0	13 (100)	5 (29.4)	N/A	2 (33)	5 (21.7)	0	15 (24.2)	0	N/A	N/A	5 (62.5)	N/A

* In-stent restenosis subgroup of A. Mastrangelo et al, study.

† Bailout subgroup of A. Mastrangelo et al, study.

IVUS = intravascular ultrasound; LAD = left anterior descending; LCX = left circumflex; LM = left main; MI = myocardial infarction; OCT = optical coherence tomography; RCA = right coronary artery.

Table 2
Primary endpoints, safety endpoints, and MACE definition of included studies

	Primary endpoint (procedural success)	Safety endpoint and/or MACE definition
A. Ielasi et al.	The primary endpoint of the study was successful IVL dilatation defined as IVL balloon delivery and application at the target site followed by an increase (after NC balloon expansion failure) of at least 1 mm2 in minimal stent cross-sectional area (MSA) on intracoronary imaging or an increase of at least 20% in minimal stent diameter (MSD) by quantitative coronary analysis (QCA)	Periprocedural cardiac death, target-vessel myocardial infarction (MI), target lesion revascularization (TLR) and stent thrombosis (ST) occurring during the hospitalization.
M. A.A. Mousa et al. (CS)	Angiographic success was defined as a final residual stenosis <30%.	N/A
J. Yeoh et al. (CS)	N/A	Safety parameters including coronary perforation, no reflow and ventricular arrhythmias, and in-hospital and 30-day major adverse cardiac and cerebrovascular events (MACCE) were recorded. MACCE was defined as a composite of acute coronary syndrome, cerebrovascular events, need for repeat revascularization, and death.
A. Aksoy et al.	Primary end point was strategy success (stent expansion with <20% in-stent residual stenosis).	Safety outcome was procedural complication, defined as coronary dissection, slow or no reflow, new coronary thrombus formation during PCI, abrupt vessel closure and device failure (inability to place the balloon, malfunction, or burst). In-hospital major adverse cardiovascular event (MACE) defined as proposed by American Heart Association and the Academic Research Consortium-2 in fourth universal definition for myocardial infarction associated with PCI.
M. N. Tovar Forero et al.	The primary efficacy endpoint was device success, a composite of technical success (successful lesion crossing + successful delivery of intended number of IVL pulses + successful retrieval of the device) and residual %DS <50% as assessed by offline QCA analysis. Secondary endpoints included procedural success (defined as device success in the absence of MACE until discharge) and technical success.	The primary safety endpoint was in-hospital major adverse cardiac events (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction and any repeat revascularization.
F. J. Brunner et al.	Angiographic success was defined as residual lumen stenosis <20% and Thrombolysis in Myocardial Infarction 3 flow.	N/A
A. Mastrangelo et al.*	The primary effectiveness endpoint was angiographic success, defined as the composite of successful IVL balloon delivery to the target lesions, adequate stent expansion, residual stenosis <20%, and final thrombolysis in myocardial infarction (TIMI) 3 flow.	The primary safety endpoint was the occurrence of MACEs, defined as the composite of cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR) during follow-up. The secondary safety endpoint was freedom from IVL-related serious complications [flow-limiting coronary dissection (types D to F), persistent slow flow/no-reflow phenomena, acute ST, coronary perforation, malignant arrhythmias (ventricular tachycardia or ventricular fibrillation), and IVL device failure (malfunction or burst of the balloon)].
W. Wanha et al.	The primary efficacy endpoint was the procedural success, defined as a relative stent expansion >80.	The secondary endpoint was freedom from device-oriented composite endpoint (DOCE) (defined as a composite of cardiac death, target lesion revascularization (TLR), target lesion revascularization, (TLR), and target vessel myocardial infarction (MI)) at 30 days.
K. Yaginuma et al. (CS)	N/A	N/A
H. El Jattari et al.	The primary endpoint was final procedural success. Optimal final procedural success was defined as angiographic ≤30% residual stenosis, no coronary artery dissection or perforation, and Thrombolysis in Myocardial Infarction (TIMI) 3 flow.	Secondary endpoints included IVL therapy effect, angiographic result post stenting, and MACE. Optimal IVL therapy effect was defined as no IVL balloon waist visual on fluoroscopy, no coronary artery dissection or perforation, and TIMI 3 flow.
A. Aziz et al.	Angiographic success was defined as the ability to complete the procedure with complete expansion of balloon and/or stent (with residual stenosis <30%) with TIMI 3 flow.	The measured endpoints during this follow-up were: death from any cause, cardiac death; target vessel myocardial infarction (TVMI); target lesion revascularisation (TLR); TVR; stent thrombosis (definite and probable); and major adverse cardiac event (MACE). The MACE rate was defined as combination of cardiac death, TVMI and TLR.
H. Sinclair et al.	Technical success was defined as successful delivery and deployment of the IVL balloon catheter. Procedural success was defined as residual angiographic stenosis <30%.	Angiographic complications were defined as dissection, slow flow, perforation, abrupt closure, or no reflow in the treated artery. The outcomes collected were death, myocardial infarction, or repeat target vessel revascularization.
E. J. Tassone et al. (CS)	N/A	N/A

CS = case series; MACCEs = major adverse cardiac and cerebrovascular events; MSA = minimal stent area; MSD = minimal stent diameter; QCA = quantitative coronary analysis; ST = stent thrombosis; TIMI = thrombolysis in myocardial infarction; TLR = target lesion revascularization.

rate (12.5% to 27.2%),[5,28] such as no-reflow phenomenon, because of distal embolization of the ablated fragments, burr related complications, vessels perforation, and stent disruption requiring additional stenting (71% to 95%).[7,8]

The IVL appears to be safer than RA/OA and ELCA, considering the smooth learning curve of this tool (comparable with a common rapid exchange balloon system) and the least traumatic effect on the vessel wall.[24]

The Disrupt CAD I, II, and III studies demonstrated the efficacy of coronary lithoplasty in a de novo setting, achieving a 98.2% success rate,[12,13] and pooled data from these studies confirmed the low complication rate (up to

Table 3
Baseline characteristics pooled analysis of included studies

		Pooled Analysis (95% C.I.)*
Age. years		71.3 (64.9-73.1)
Sex Male		77% (71.2-82.4)
Hypertension		90.1% (83.6-95.3)
Diabetes Mellitus		45.9% (39.4-52.5)
Dyslipidemia		80.3% (73.6-86.4)
Prior MI		56.4% (43.6-68.9)
Clinical Presentation	**Stable Angina**	55% (46.1-63.7)
	Unstable Angina	12.4% (7.8-17.6)
	STEMI	4% (1.2-7.7)
	NSTEMI	24.3% (18.6-30.4)
Vessel	**LM**	7.9% (4.3-12.2)
	LAD	45.9% (36.6 – 55.3)
	RCA	31.8% (24.5 – 39.5)
	LCX	10% (6- 14.6)
IVUS		33.1% (20.1-47.4)
OCT		23.7% (10.9 – 39)
IVL Balloon Diameter, mm		3.4 (3.2-3.5)
OPN Balloon Predilatation		29.8% (12.2-50.5)
NC Ballon Predilatation		82.6% (69.6-93)
Follow-up time, months		2.6 (1–15.3)

* Values are percentage or median.

IVUS = intravascular ultrasound; LAD = left anterior descending; LCX = left circumflex; LM = left main; NC = noncompliant; OCT = optical coherence tomography; RCA = right coronary artery.

6.8%).[29,30] To date, IVL therapy can only be used for lesion preparation of CCP before stent implantation.

Although the use of IVL for the treatment of SU is actually considered off-label, recent case series and registries provided interesting results confirmed by this meta-analysis.

IVL therapy in SU treatment can be achieved by modifying the CCP underlying the stent by converting acoustic waves into mechanical energy propagating around the vessel circumference. In this way, the luminal and the stent area are gained, despite the presence of neointimal hyperplasia and/or multiple stent layers in some cases.[10,24]

The Dragon and CRUNCH registries, which are included in this meta-analysis, have identified the predictors for unsuccessful stent expansion with IVL, including CKD, additional stent layers, ostial position of the target segment, or poststenting bailout therapy.[24,26]

It is important to note that in the setting of acute SU, immediately after stent implantation, IVL as a bailout therapy could theoretically increase the risk of degradation of the drug-eluting stent polymer and alteration of the stent structure.[26] This concern poses indications for testing IVL efficacy in the long term.

Nevertheless, the data collected in our analysis, with an average follow-up of 2.56 months, showed no critical stent failure issues in either chronic or acute settings.

The results from the meta-regression highlighted 2 essential findings: first, there is a lower procedural success rate associated with left main lesions. This is because of the increased risk of complications during predilatation and the prolonged inflation period required for lithotripsy balloons. Nevertheless, this should not discourage the use of IVL in such cases. Second, the study found that lesions predilated with OPN balloons demonstrated a better efficacy with IVL therapy. This highlights the importance of lesion preparation before lithotripsy and suggests that an incremental strategy from NC balloon to OPN balloon before litoplasty balloon may improve the overall efficacy of IVL therapy.

Thus, this meta-analysis found IVL therapy to be very promising for the treatment of SU, suggesting that this tool may represent the preferred choice for this complex interventional setting.

This meta-analysis has some limitations. Meta-regression is questionable for studies with small samples, but the high heterogeneity not explained by the sensitivity analysis can be explained by the meta-regression. The quality of the studies included in the meta-analysis is not very high, as evidenced by the assessment of risk of bias, but they are all published studies. The funnel plot and Egger test showed asymmetry for the end points; however, considering the random-effects model analysis and the paucity of data in previous studies, the results of our meta-analysis are

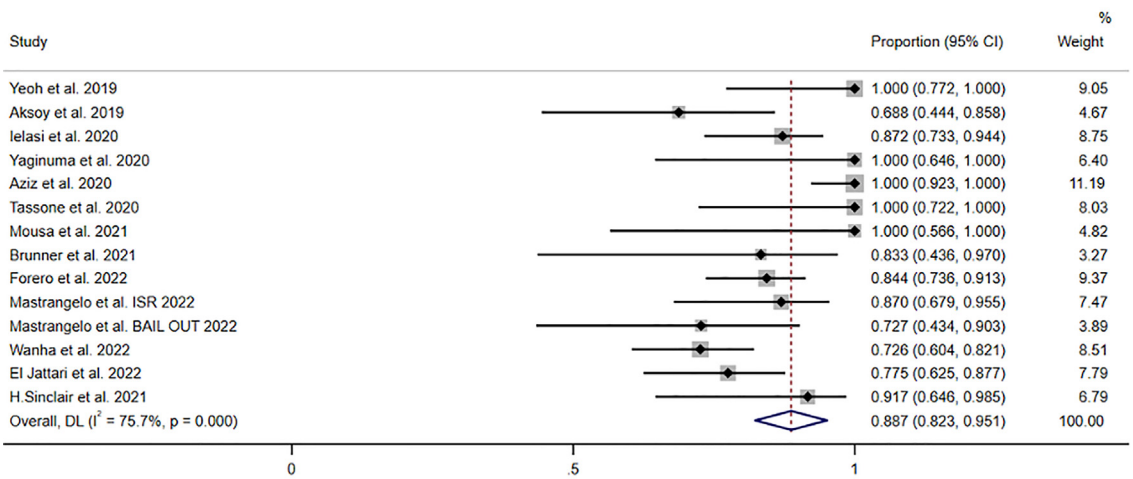

Figure 2. Pooled procedural success rate of intravascular lithotripsy in-stent underexpansion treatment.

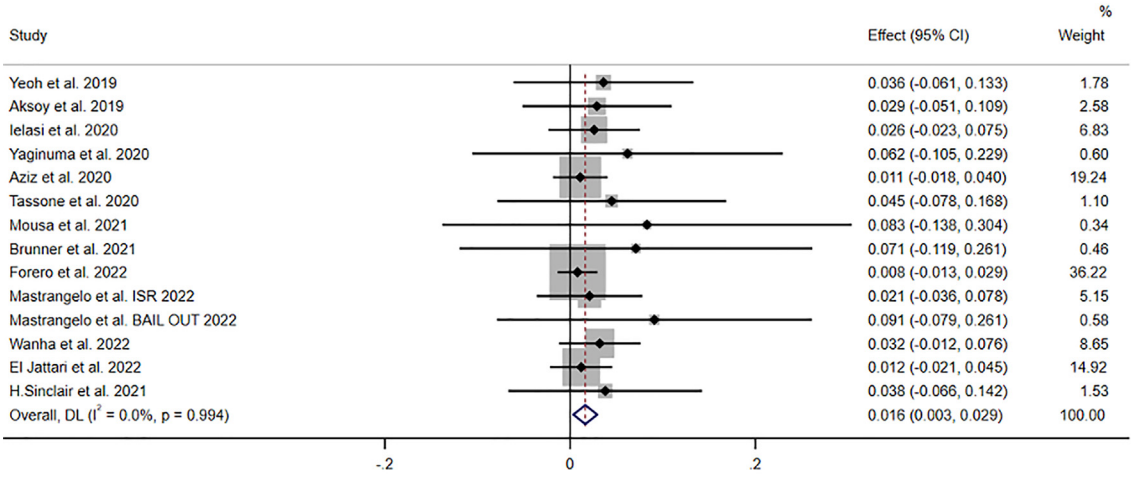

Figure 3. Pooled procedural complications rate of intravascular lithotripsy in-stent underexpansion treatment.

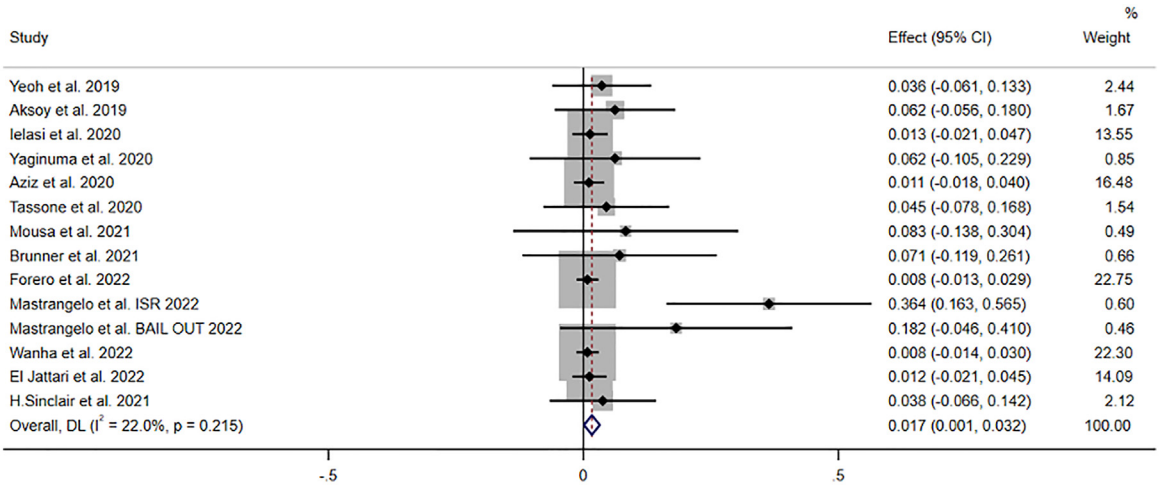

Figure 4. Pooled major cardiovascular events at follow-up of treated patients.

important. Furthermore, there is a wide heterogeneity in the length of follow-ups between the studies.

In conclusion, the stent-through IVL coronary plaque modification technique is a safe tool to treat SU caused by calcified lesions, with a high success rate and a very low incidence of complications.

Declaration of Competing Interest

The authors have no competing interests to declare.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.07.144.

1. Kawaguchi R, Tsurugaya H, Hoshizaki H, Toyama T, Oshima S, Taniguchi K. Impact of lesion calcification on clinical and angiographic outcome after sirolimus-eluting stent implantation in real-world patients. *Cardiovasc Revasc Med* 2008;9:2–8.
2. Choi SY, Witzenbichler B, Maehara A, Lansky AJ, Guagliumi G, Brodie B, Kellett MA Jr, Dressler O, Parise H, Mehran R, Dangas GD, Mintz GS, Stone GW. Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with revascularization and Stents in acute myocardial infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv* 2011;4:239–247.
3. Yin D, Mintz G, Song L, Chen Z, Lee T, Kirtane A, Parikh M, Moses J, Fall K, Jeremias A, Ali Z, Shlofmitz R, Maehara A, Collaborators. In-stent restenosis characteristics and repeat stenting underexpansion: insights from optical coherence tomography. *EuroIntervention* 2020;16:e335–e343.
4. Wańha W, Januszek R, Kołodziejczak M, Kuźma Ł, Tajstra M, Figatowski T, Smolarek-Nicpoń M, Gruz-Kwapisz M, Tomasiewicz B, Bartuś J, Łoś A, Jagielak D, Roleder T, Włodarczak A, Kulczycki J, Kowalewski M, Hudziak D, Stachowiak P, Gorący J, Sierakowska K, Reczuch K, Jaguszewski M, Dobrzycki S, Smolka G, Bartuś S, Ochała A, Gąsior M, Wojakowski W. Procedural and 1-year outcomes following large vessel coronary artery perforation treated by covered stents implantation: multicentre CRACK registry. *PLoS One* 2021;16:e0249698.

5. Ferri LA, Jabbour RJ, Giannini F, Benincasa S, Ancona M, Regazzoli D, Mangieri A, Montorfano M, Colombo A, Latib A. Safety and efficacy of rotational atherectomy for the treatment of undilatable underexpanded stents implanted in calcific lesions. *Catheter Cardiovasc Interv* 2017;90:E19–E24.
6. Édes IF, Ruzsa Z, Szabó G, Lux Á, Gellér L, Molnár L, Nowotta F, Hajas Á, Szilveszter B, Becker D, Merkely B. Rotational atherectomy of undilatable coronary stents: stentablation, a clinical perspective and recommendation. *EuroIntervention* 2016;12:e632–e635.
7. Neupane S, Basir M, Tan C, Sultan A, Tabaku M, Alqarqaz M, Khandelwal A, Gupta A, Don C, Alaswad K. Feasibility and safety of orbital atherectomy for the treatment of in-stent restenosis secondary to stent under-expansion. *Catheter Cardiovasc Interv* 2021;97:2–7.
8. Whiteside HL, Nagabandi A, Kapoor D. Safety and efficacy of stentablation with rotational atherectomy for the management of underexpanded and undilatable coronary stents. *Cardiovasc Revasc Med* 2019;20:985–989.
9. Latib A, Takagi K, Chizzola G, Tobis J, Ambrosini V, Niccoli G, Sardella G, DiSalvo ME, Armigliato P, Valgimigli M, Tarsia G, Gabrielli G, Lazar L, Maffeo D, Colombo A. Excimer laser LEsion modification to expand non-dilatable sTents: the ELLEMENT registry. *Cardiovasc Revasc Med* 2014;15:8–12.
10. Forero MNT, Daemen J. The coronary intravascular lithotripsy system. *Interv Cardiol* 2019;14:174–181.
11. Brinton TJ, Ali ZA, Hill JM, Meredith IT, Maehara A, Illindala U, Lansky A, Götberg M, Van Mieghem NM, Whitbourn R, Fajadet J, Di Mario C. Feasibility of shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses. *Circulation* 2019;139:834–836.
12. Ali ZA, Nef H, Escaned J, Werner N, Banning AP, Hill JM, De Bruyne B, Montorfano M, Lefevre T, Stone GW, Crowley A, Matsumura M, Maehara A, Lansky AJ, Fajadet J, Di Mario C. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: the disrupt CAD II study. *Circ Cardiovasc Interv* 2019;12:e008434.
13. Hill JM, Kereiakes DJ, Shlofmitz RA, Klein AJ, Riley RF, Price MJ, Herrmann HC, Bachinsky W, Waksman R, Stone GW, Disrupt CAD III Investigators. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. *J Am Coll Cardiol* 2020;76:2635–2646.
14. Ielasi A, Moscarella E, Testa L, Gioffrè G, Morabito G, Cortese B, Colangelo S, Tomai F, Arioli F, Maioli M, Leoncini M, Tumminello G, Benedetto S, Lucchina PG, Pennesi M, Ugo F, Viganò E, Bollati M, Missiroli B, Gaspardone A, Calabrò P, Bedogni F, Tespili M. IntravaScular lithotripsy for the management of UndILatable coronary StEnt: the SMILE registry. *Cardiovasc Revasc Med* 2020;21:1555–1559.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.
17. Yeoh J, Cottens D, Cosgrove C, Mallek K, Strange J, Anderson R, Wilson S, Hanratty C, Walsh S, McEntegart M, Hill J, Spratt JC. Management of stent underexpansion using intravascular lithotripsy-Defining the utility of a novel device. *Catheter Cardiovasc Interv* 2021;97:22–29.
18. Aksoy A, Salazar C, Becher MU, Tiyerili V, Weber M, Jansen F, Sedaghat A, Zimmer S, Leick J, Grube E, Gonzalo N, Sinning JM, Escaned J, Nickenig G, Werner N. Intravascular lithotripsy in calcified coronary lesions: a prospective, observational, multicenter registry. *Circ Cardiovasc Interv* 2019;12:e008154.
19. Yaginuma K, Werner GS. Resolving chronic stent under-expansion in calcified lesions by intravascular lithoplasty. *J Cardiol Cases* 2020;23:136–139.
20. Aziz A, Bhatia G, Pitt M, Choudhury A, Hailan A, Upadhyaya S, Lee L, Testa L, Casenghi M, Ielasi A, Cortese B, Rides H, Basavarajaiah S. Intravascular lithotripsy in calcified-coronary lesions: a real-world observational, European multicenter study. *Catheter Cardiovasc Interv* 2021;98:225–235.
21. Tassone EJ, Tripolino C, Morabito G, Grillo P, Missiroli B. Shockwave coronary lithoplasty for the treatment of under-expanded stent. *J Cardiol Cardiovasc Sci* 2020;4:1–5.
22. Mousa MAA, Bingen BO, Amri IA, Digiacomo S, Karalis I, Jukema JW, Montero-Cabezas JM. Bail-out intravascular lithotripsy for the treatment of acutely underexpanded stents in heavily calcified coronary lesions: a case series. *Cardiovasc Revasc Med* 2022;40:189–194.
23. Brunner FJ, Becher PM, Waldeyer C, Zengin-Sahm E, Schnabel RB, Clemmensen P, Westermann D, Blankenberg S, Seiffert M. Intravascular lithotripsy for the treatment of calcium-mediated coronary in-stent restenoses. *J Invasive Cardiol* 2021;33:E25–E31.
24. Tovar Forero MT, Sardella G, Salvi N, Cortese B, di Palma G, Werner N, Aksoy A, Escaned J, Salazar C, Gonzalo N, Ugo F, Cavallino C, Sheth T, Kardys I, Van Mieghem NM, Daemen J. Coronary lithotripsy for the treatment of underexpanded stents; the international multicentre CRUNCH registry. *EuroIntervention* 2022;18:574–581.
25. Mastrangelo A, Monizzi G, Galli S, Grancini L, Ferrari C, Olivares P, Chiesa M, Calligaris G, Fabbiocchi F, Montorsi P, Bartorelli AL. Intravascular lithotripsy in calcified coronary lesions: A single-center experience in "real-world" patients. *Front Cardiovasc Med* 2022;9:829117.
26. Wańha W, Tomaniak M, Wańczura P, Bil J, Januszek R, Wolny R, Opolski MP, Kuźma Ł, Janas A, Figatowski T, Gąsior P, Milewski M, Roleder-Dylewska M, Lewicki Ł, Kulczycki J, Włodarczak A, Tomasiewicz B, Iwańczyk S, Sacha J, Koltowski Ł, Dziarmaga M, Jaguszewski M, Kralisz P, Olajossy B, Sobieszek G, Dyrbuś K, Łebek M, Smolka G, Reczuch K, Gil RJ, Dobrzycki S, Kwiatkowski P, Rogala M, Gąsior M, Ochała A, Kochman J, Witkowski A, Lesiak M, D'Ascenzo F, Bartuś S, Wojakowski W. Intravascular lithotripsy for the treatment of stent underexpansion: the multicenter IVL-DRAGON registry. *J Clin Med* 2022;11:1779.
27. El Jattari H, Holvoet W, De Roeck F, Cottens D, Ungureanu C, Bennett J, McCutcheon K, Ghafari C, Carlier S, Zivelonghi C, Segers VFM, Dens J. Intracoronary lithotripsy in calcified coronary lesions: A multicenter observational study. *J Invasive Cardiol* 2022;34:E24–E31.
28. Hernández-Enríquez M, Campelo-Parada F, Lhermusier T, Bouisset F, Roncalli J, Elbaz M, Carrié D, Boudou N. Long-term outcomes of rotational atherectomy of underexpanded stents. A single center experience. *J Interv Cardiol* 2018;31:465–470.
29. Kereiakes DJ, Virmani R, Hokama JY, Illindala U, Mena-Hurtado C, Holden A, Hill JM, Lyden SP, Ali ZA. Principles of intravascular lithotripsy for calcific plaque modification. *JACC Cardiovasc Interv* 2021;14:1275–1292.
30. Kereiakes DJ, Di Mario C, Riley RF, Fajadet J, Shlofmitz RA, Saito S, Ali ZA, Klein AJ, Price MJ, Hill JM, Stone GW. Intravascular lithotripsy for treatment of calcified coronary lesions: patient-level pooled analysis of the disrupt CAD studies. *JACC Cardiovasc Interv* 2021;14:1337–1348.