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FOCUS ON TRANSCATHETER AORTIC VALVE REPLACEMENT AND CORONARY CANNULATION

ORIGINAL RESEARCH: CORONARY

A Prospective, Multicenter, Real-World Registry of Coronary Lithotripsy in Calcified Coronary Arteries

The REPLICA-EPIC18 Study

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ABSTRACT

BACKGROUND Intravascular lithotripsy (IVL) has demonstrated effectiveness in the treatment of calcified lesions in selected patients with stable coronary disease.

OBJECTIVES The authors sought to assess the performance of coronary IVL in calcified coronary lesions in a real-life, all comers, setting.

METHODS The REPLICA-EPIC18 study prospectively enrolled consecutive patients treated with IVL in 26 centers in Spain. An independent core laboratory performed the angiographic analysis and event adjudication. The primary effectiveness endpoint assessed procedural success (successful IVL delivery, final diameter stenosis <20%, and absence of in-hospital major adverse cardiovascular events [MACE]). The primary safety endpoint measured freedom from MACE at 30 days. A predefined substudy compared outcomes between acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) patients.

RESULTS A total of 426 patients (456 lesions) were included, 63% of the patients presenting with ACS. IVL delivery was successful in 99% of cases. Before IVL, 49% of lesions were considered undilatable. The primary effectiveness endpoint was achieved in 66% of patients, with similar rates among CCS patients (68%) and ACS patients (65%). Likewise, there were no significant differences in angiographic success after IVL between CCS and ACS patients. The rate of MACE at 30 days (primary safety endpoint) was 3% (1% in CCS and 5% in ACS patients [$P = 0.073$]).

CONCLUSIONS Coronary IVL proved to be a feasible and safe procedure in a "real-life" setting, effectively facilitating stent implantation in severely calcified lesions. Patients with ACS on admission showed similar angiographic success rates but showed a trend toward higher 30-day MACE compared with patients with CCS. (REPLICA-EPIC18 study [Registry of Coronary Lithotripsy in Spain]; NCT04298307) (J Am Coll Cardiol Intv 2024;17:756-767) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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The presence of coronary artery calcification (CAC) remains one of the main challenges in the percutaneous treatment of coronary stenosis. Several factors, such as age, diabetes, dyslipidemia, hypertension, smoking, and impaired renal function, have been linked to CAC development. Its presence is associated with unfavorable outcomes in both the general population and patients undergoing revascularization.[1] CAC hinders percutaneous coronary interventions (PCI) by impeding device crossing, leading to procedural failure and increased complications.[2] Calcification can cause substantial surface damage to the stent polymer or drug coating by scratching and scraping against the arterial wall.[3,4] Additionally, CAC can alter the drug release kinetics of drug-eluting stents and preclude adequate stent expansion and apposition.[5-7]

Intravascular lithotripsy (IVL) is an innovative balloon-based technology that employs sound waves to generate local intravascular calcification fractures.[8,9] This approach has been evaluated in single-arm, nonrandomized studies as an adjunct to coronary stenting, showing high rates of device success and favorable early angiographic and clinical outcomes.[10-13] However, these reports are limited by their focus on a highly selected population, excluding patients with acute coronary syndrome (ACS).

To address these limitations, the REPLICA-EPIC18 (Registro Prospectivo de LItotricia CoronariA [Registry of Coronary Lithotripsy in Spain]) study was designed as a prospective, multicenter, single-arm, open-label trial that aimed to evaluate the effectiveness and safety of IVL in treating calcified coronary lesions within a real-life cohort of consecutive patients, including those with ACS.

METHODS

STUDY DESIGN AND OVERSIGHT. REPLICA-EPIC-18 is a prospective, multicenter, single-arm, open-label, all-comers study, conducted at 26 hospitals in Spain, designed to assess the effectiveness and safety of the coronary IVL system to treat calcified coronary lesions in a real-life unselected cohort of patients. The protocol pre-established a comparative analysis of subgroups between patients with chronic coronary syndrome (CCS) and ACS. The study was registered at ClinicalTrials.gov (NCT04298307) and was approved by the central ethics committee and notified to the local ethics committee of all participant centers; all patients signed written informed consent. The principal investigators and study chair had unrestricted access to the data, prepared the manuscript, and vouch for the accuracy and completeness of the reported data and for the fidelity of this report to the study protocol. Only devices with CE marking were used.

STUDY POPULATION. Patients were eligible for enrollment if they had calcified coronary artery disease requiring PCI and coronary IVL was deemed necessary, the procedure performed at the operator's discretion. The only exclusion criteria were express refusal of the patient to participate in the study, life expectancy <1 year, or hemodynamic instability with

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAC = coronary artery calcification

CCS = chronic coronary syndrome

IVL = intravascular lithotripsy

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TVR = target vessel revascularization

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Killip class III or IV. The study observed the principles established by the Declaration of Helsinki and Good Clinical Practice guidelines.

STUDY DEVICE. The Shockwave Medical IVL catheter and its technique for use have been previously described.[8,9] The catheter consists of a 0.014-inch guidewire-compatible, fluid-filled balloon angioplasty catheter with 2 lithotripsy emitters incorporated into the shaft of the 12-mm-long balloon segment. Each catheter can provide up to 80 total IVL pulses and is intended for single use. The IVL balloon catheter is connected via a cable to a portable, battery-powered generator. Following delivery to the target lesion, the balloon is inflated to low pressure (4 atm), and the lithotripsy emitters are energized. Electrical energy delivered to the emitters initiates the formation of steam bubbles within the balloon that expand and collapse, creating transient (~1 ms) circumferential acoustic pressure pulses/sonic pressure waves that deliver ~50 atm of instantaneous pressure to selectively fracture superficial and deep calcium within the arterial wall. These sonic pressure waves are delivered circumferentially and transmurally through the vessel wall, resulting in calcium microfractures due to transient shear mechanisms.

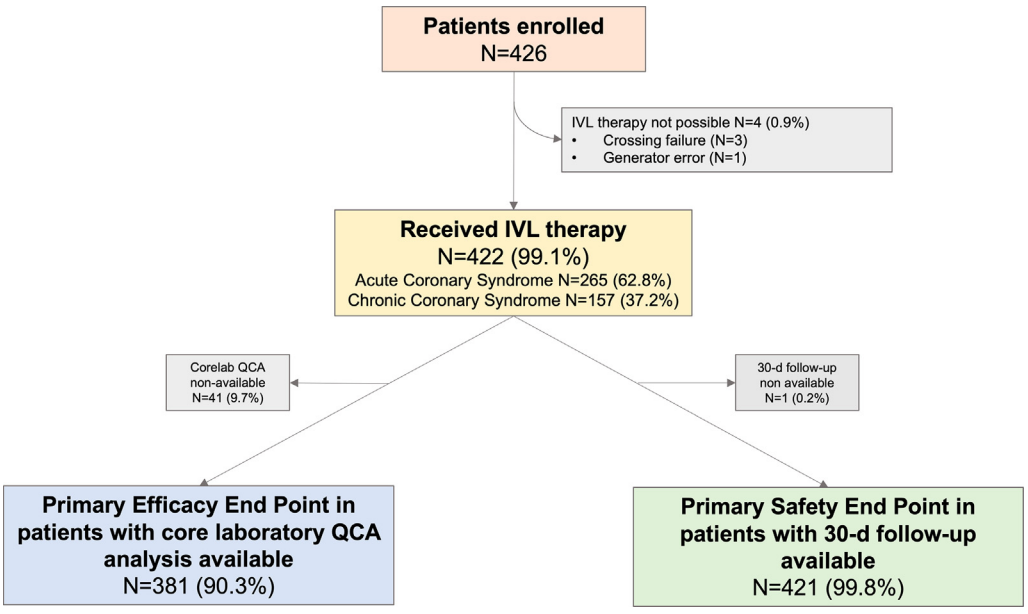
STUDY PROCEDURES. Patients that signed informed consent and met study eligibility criteria were enrolled before IVL catheter insertion. Preparation of the lesion with semicompliant balloon, noncompliant balloon, high-pressure balloon, cutting balloon, scoring balloon, rotational atherectomy, orbital atherectomy, or excimer laser coronary angioplasty before IVL was left at operator's discretion. There was no obligation to perform intracoronary imaging techniques per protocol, but their use was highly recommended. Stent optimization techniques were also left to the operator's discretion. Lesions were considered undilatable when it was not possible to cross with a conventional balloon and required plaque debulking techniques such as rotational atherectomy, orbital atherectomy, or excimer laser atherectomy and/or when adequate expansion was not achieved with a noncompliant balloon at ≥18 atm.

CORONARY ANGIOGRAPHY ANALYSIS. Coronary angiography analysis was performed by an independent central imaging Core Laboratory (BARCICORE-Lab) with a dedicated software (QAngio 7.0, Medis). Coronary calcification on angiography was classified as no/mild, moderate, or severe by 2 experienced analysts according to a previous definition.[14] All study lesions were serially analyzed at pre-intervention, post-IVL, and postintervention. Quantitative coronary angiographic analysis was performed in matched segments according to the postintervention stent segment. Interpolated reference vessel diameter was automatically estimated by the software at the site of the minimal lumen diameter, but analysts were allowed to manually modify it in case of long lesions with different locations of the reference vessel diameter between the 3 serial analyses as appropriate.[15]

STUDY ENDPOINTS. The primary efficacy criteria was procedural success defined as successful PCI with a residual stenosis <20% by core laboratory assessment, without in-hospital complications (cardiac death, myocardial infarction [MI], or need for target vessel revascularization [TVR]). The primary safety criteria was occurrence of 30-day major adverse clinical events (MACE) defined as death, MI or TVR. An independent clinical events committee reviewed and adjudicated all MACE. Detailed endpoint definitions are listed in the Supplemental Appendix.

STATISTICAL ANALYSIS. Demographic, clinical, and procedural data are presented for the entire group and according to clinical presentation as ACS or CCS. Continuous variables are expressed as mean ± SD (or if the values do not follow a normal distribution, as median [IQR]). Categorical variables are expressed as frequencies and percentages. The data obtained were analyzed using the unilateral analysis of variance for continuous variables, and the Fisher exact test or the chi-square test for categorical variables, when appropriate. Nonparametric tests were used with variables without a normal distribution or when normalization was not possible. The Kaplan-Meier survival curves are presented for the previously specified criteria. A multivariate logistic regression analysis was performed to identify clinical, angiographic, and procedural variables that predicted a final stent stenosis ≥20%; the model includes variables that are related to final stent stenosis ≥20% in the univariate analysis ($P < 0.20$), age, and sex. Multicollinearity among the variables incorporated into the regression model has been dismissed. To address intercenter variability, we used random intercepts for each center in a mixed effects model framework. A P value of 0.05 was considered to set statistical significance. All analyses were performed with the use Stata 15.0 (Stata Corp).

FIGURE 1 Patients Flow Chart



Primary efficacy endpoint was analyzed in 381 patients with adequate core laboratory coronary angiography analysis. One patient was lost at 30 day follow up. IVL intravascular lithotripsy; QCA quantitative coronary analysis.

RESULTS

PATIENTS AND PROCEDURES. From February 9, 2020, to April 19, 2022, 426 consecutive patients with calcified coronary artery disease requiring PCI in whom coronary IVL was deemed necessary were enrolled (Figure 1). Baseline clinical characteristics are presented in Table 1. On admission, 265 patients (62.8%) had ACS, whereas 157 patients (37.2%) had CCS. Patients with CCS had more frequently concomitant valvular heart disease, whereas patients with ACS had more frequently heart failure on admission. IVL therapy was not possible in 4 patients (0.9%): in 3 cases due to balloon crossing failure and in 1 case due to generator error. Adequate quantitative coronary angiography core laboratory analysis was obtained in 376 patients (89.1%). Clinical follow-up at 30 days was available in 421 patients (99.8%).

Table 2 shows lesion characteristics and procedural details. A total of 224 lesions (49.1%) were considered undilatable before IVL, and only 44 lesions (9.4%) were directly treated with IVL without plaque preparation (direct IVL was more frequent in patients with ACS); lesion preparation included semicompliant, noncompliant, and high-pressure balloons, cutting balloon or scoring balloons, as well as rotational atherectomy, orbital atherectomy, or excimer laser atherectomy. IVL balloon rupture was infrequent (5.8%). Treatment of 197 lesions (43.2%) was guided by intracoronary imaging (intravascular ultrasound or optical coherence tomography). In 102 lesions, IVL was conducted on previously implanted stents: 77 cases were due to in-stent restenosis and 25 were due to acute stent underexpansion; treatment of in-stent restenosis was more frequent in patients with ACS.

ANGIOGRAPHIC OUTCOMES. Supplemental Table 1 documents core laboratory coronary angiography analysis. Final in-stent stenosis was 15% ± 13% without differences between CCS and ACS patients. A total of 123 lesions (30.8%) had a final in-stent stenosis ≥20%. Figure 2 shows final in-stent stenosis distribution (Figure 2A), and luminal gain and changes in segment diameter stenosis following IVL treatment and final result (Figure 2B).

PRIMARY SAFETY AND EFFECTIVENESS ENDPOINTS. Primary efficacy criteria (successful PCI with a residual stenosis <20% by quantitative coronary analysis core laboratory assessment without in-hospital complications defined as cardiac death, MI, or need for TVR) was achieved in a 66% of patients: a total of 123 patients had residual stenosis ≥20% in at least 1 treated lesion and 8 patients presented in-hospital

TABLE 1 Baseline Clinical Characteristics According to ACS or CCS at Admission

	All Patients (N 422)	Patients With CCS (n 157)	Patients With ACS (n 265)	*P* Value
Age, y	73 ± 10	72 ± 8	73 ± 10	0.13
Male	339 (80.3)	133 (84.7)	206 (77.7)	0.081
Hypertension	355 (84.1)	127 (80.9)	228 (86.0)	0.16
Diabetes	223 (52.1)	85 (54.1)	138 (52.1)	0.68
Dyslipidemia	317 (75.1)	116 (73.9)	201 (75.9)	0.65
Current smoker	51 (12.1)	14 (8.9)	37 (14.0)	0.12
Peripheral artery disease	73 (17.3)	26 (16.6)	47 (17.7)	0.76
Prior valvular disease	58 (13.8)	35 (22.4)	23 (8.7)	<0.001
Prior heart failure	79 (18.7)	36 (22.9)	43 (16.2)	0.088
Prior MI	158 (37.4)	52 (33.1)	106 (40.0)	0.16
Prior PCI	173 (41.0)	66 (42.0)	107 (40.4)	0.74
Prior CABG	41 (9.7)	14 (8.9)	27 (10.2)	0.67
Prior stroke	39 (9.3)	16 (10.2)	23 (8.7)	0.61
eGFR <60 mL/min	91 (21.6)	36 (22.9)	55 (20.8)	0.60
Clinical status on admission				<0.001
STEMI	32 (7.6)	0 (0)	32 (12.1)	
NSTEMI	169 (40.1)	0 (0)	169 (63.8)	
UA	64 (15.2)	0 (0)	64 (24.2)	
Stable angina	103 (24.4)	103 (65.6)	0 (0)	
Silent ischemia	54 (12.8)	54 (34.3)	0 (0)	
Heart failure on admission	84 (19.9)	22 (14.0)	62 (19.9)	0.020
LVEF				0.32
>50%	297 (70.4)	109 (69.4)	188 (70.9)	
41% 50%	62 (14.7)	24 (15.3)	38 (14.3)	
31% 40%	38 (9.0)	11 (7.0)	27 (10.2)	
≤30%	25 (5.9)	13 (8.3)	12 (4.5)	
Arterial access				0.72
Radial	321 (76.3)	119 (75.8)	202 (76.5)	
Femoral	99 (23.5)	38 (24.2)	99 (23.5)	
Humeral	1 (0.2)	0 (0)	1 (0.4)	
Hemodynamic support				0.027
Intra aortic balloon pump	11 (2.6)	3 (1.9)	8 (3.0)	
Impella	4 (1.0)	4 (2.6)	0 (0)	

Values are mean ± SD or n (%). Information in Table 1 is related to patients treated with IVL. From 426 patients enrolled in REPLICA, there were 4 patients in whom IVL was not possible, for different reasons. These patients were not included in Table 1.

ACS acute coronary syndrome; CABG coronary artery bypass grafting; CCS chronic coronary syndrome; eGFR estimated glomerular filtration rate; LVEF left ventricular ejection fraction; MI myocardial infarction; NSTEMI non-ST-segment elevation myocardial infarction; PCI percutaneous coronary intervention; STEMI ST-segment elevation myocardial infarction; UA unstable angina.

death, MI, or TVR, without differences between patients with ACS or CCS (68.3% vs 64.7%; *P* 0.47).

The 30-day follow-up was completed in 421 patients (99.8%). Primary safety (freedom from 30-day MACE) was achieved in 406 patients (96.4%), with a trend to more MACE in patients with ACS when compared with CCS (4.5% vs 1.3%; *P* 0.073). Figure 3 shows freedom from MACE at 30-day follow-up in patients with CCS vs ACS.

Clinical outcomes did not significantly differ based on angiographic success (final stenosis <20%), including rates of MACE (2.7% if stenosis <20% vs 2.4% if stenosis ≥20%; *P* 0.87), cardiovascular death (0.8% vs 0.8%; *P* 0.97), nonfatal MI (1.6% vs 2.3%; *P* 0.65), target lesion revascularization (0.8% vs 1.6%; *P* 0.55), or stent thrombosis (0% vs 1.2%; *P* 0.23).

The Central Illustration depicts key clinical and lesion characteristics and distribution of angiographic success according to presence of ACS upon admission; additionally, it provides insights into MACE and other cardiovascular events during the 30-day follow-up period.

SECONDARY CLINICAL ENDPOINTS. MACE through 30 days occurred in 3.6% of patients and was primarily driven by MI (Table 3). There were 7 deaths (1.7%) within 30 days, of which 4 were cardiovascular

TABLE 2 Lesion Characteristics in All Patients Treated With IVL According to ACS or CCS at Admission

	All (N 456)	CCS (n 168)	ACS (n 288)	*P* Value
Target vessel				0.12
Left main coronary artery	50 (11.0)	12 (7.1)	38 (13.2)	
Left anterior descending coronary artery	203 (44.5)	78 (46.4)	125 (43.4)	
Left circumflex coronary artery	58 (12.7)	18 (10.7)	40 (13.9)	
Right coronary artery	145 (31.8)	60 (35.7)	85 (29.5)	
Severe CAC	371 (81.4)	138 (82.1)	233 (80.9)	0.74
Chronic total occlusion	23 (5.0)	10 (6.0)	13 (4.5)	0.50
Angiographic thrombus	15 (3.2)	1 (0.6)	14 (4.7)	0.014
Bifurcation involvement	123 (27.0)	44 (26.2)	79 (27.4)	0.77
In stent restenosis treatment	77 (16.9)	20 (11.9)	57 (19.8)	0.03
Undilatable lesion	224 (49.1)	80 (47.6)	144 (50.0)	0.62
Lesion preparation before IVL				
Direct IVL	44 (9.4)	24 (14.3)	19 (6.6)	0.007
Semicompliant balloon	215 (47.2)	73 (43.5)	142 (49.3)	0.23
Noncompliant balloon	230 (50.4)	86 (51.2)	144 (50.0)	0.81
High pressure balloon	72 (15.8)	17 (10.1)	55 (19.1)	0.011
Cutting balloon	91 (20.0)	36 (21.4)	55 (19.1)	0.55
Scoring balloon	48 (10.5)	14 (8.3)	34 (11.8)	0.24
Rotational atherectomy	53 (11.6)	12 (7.1)	41 (14.2)	0.023
Orbital atherectomy	8 (1.8)	3 (1.8)	5 (1.7)	0.97
Excimer laser atherectomy	10 (2.2)	4 (2.3)	6 (2.1)	0.83
Number of IVL balloons	1.06 ± 0.27	1.05 ± 0.21	1.06 ± 0.29	0.57
Number of pulses	61 ± 19	63 ± 20	60 ± 19	0.14
IVL balloon diameter	3.2 ± 0.5	3.2 ± 0.5	3.1 ± 0.5	0.29
Maximum inflation pression	6.2 ± 1.5	6.0 ± 1.0	6.3 ± 1.8	0.10
IVL balloon rupture	27 (5.8)	8 (4.6)	19 (6.4)	0.59
Number of stents	1.3 ± 0.6	1.4 ± 0.7	1.3 ± 0.6	0.41
Stent postdilation				
No stent postdilation	97 (21.3)	32 (19.1)	65 (22.6)	0.37
Semicompliant balloon	24 (5.3)	9 (5.4)	15 (5.2)	0.95
Noncompliant balloon	280 (61.4)	113 (67.3)	167 (58.0)	0.050
High pressure balloon	15 (3.3)	5 (3.0)	10 (3.5)	0.77
IVL	102 (22.4)	30 (17.9)	72 (25.0)	0.08
Other	10 (2.2)	2 (1.2)	8 (2.8)	0.26
Intracoronary diagnostic study				0.04
Not performed	252 (55.3)	87 (51.8)	165 (57.3)	
IVUS	94 (20.6)	29 (17.3)	65 (22.6)	
OCT	103 (22.6)	50 (29.8)	53 (18.4)	
Pressure wire	7 (1.5)	2 (1.2)	5 (1.7)	

Values are n (%) or mean ± SD.
CAC coronary artery calcification; IVUS intravascular ultrasound; OCT optical coherence tomography; other abbreviations as in Table 1.

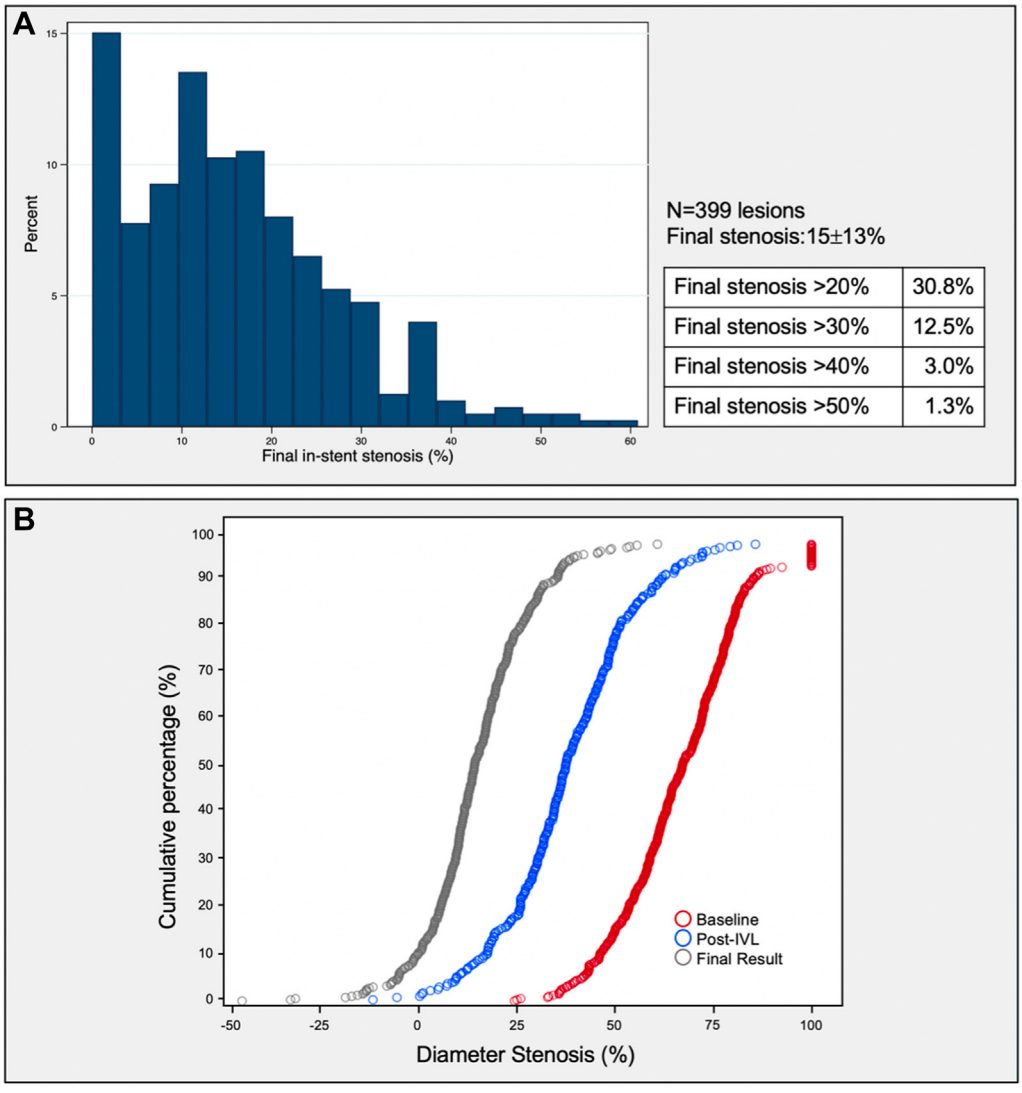
deaths (1.0%). Protocol-defined periprocedural MI occurred in 4 patients (1.0%). MI through 30 days occurred in 10 patients (2.4%), all of them with ACS on admission; stent thrombosis (Academic Research Consortium definite or probable) occurred in 3 patients (1.1%), all with ACS as baseline clinical status. There were 5 patients (1.2%) with TVR, all with ACS as baseline clinical status.

PREDICTORS OF STENT UNDEREXPANSION. As mentioned earlier, the core laboratory analysis identified stent underexpansion (final in-stent stenosis ≥20%) in 123 lesions, constituting 30.8% of cases. The causes for stent underexpansion are detailed in the univariate analysis found in Supplemental Table 2. Additionally, **Table 4** highlights the variables that served as independent predictors of stent underexpansion in the multivariate logistic regression analysis.

DISCUSSION

The REPLICA-EPIC18 study was conducted to assess the efficacy and safety of IVL for the treatment of

FIGURE 2 **Central Core Laboratory Coronary Angiography Analysis**

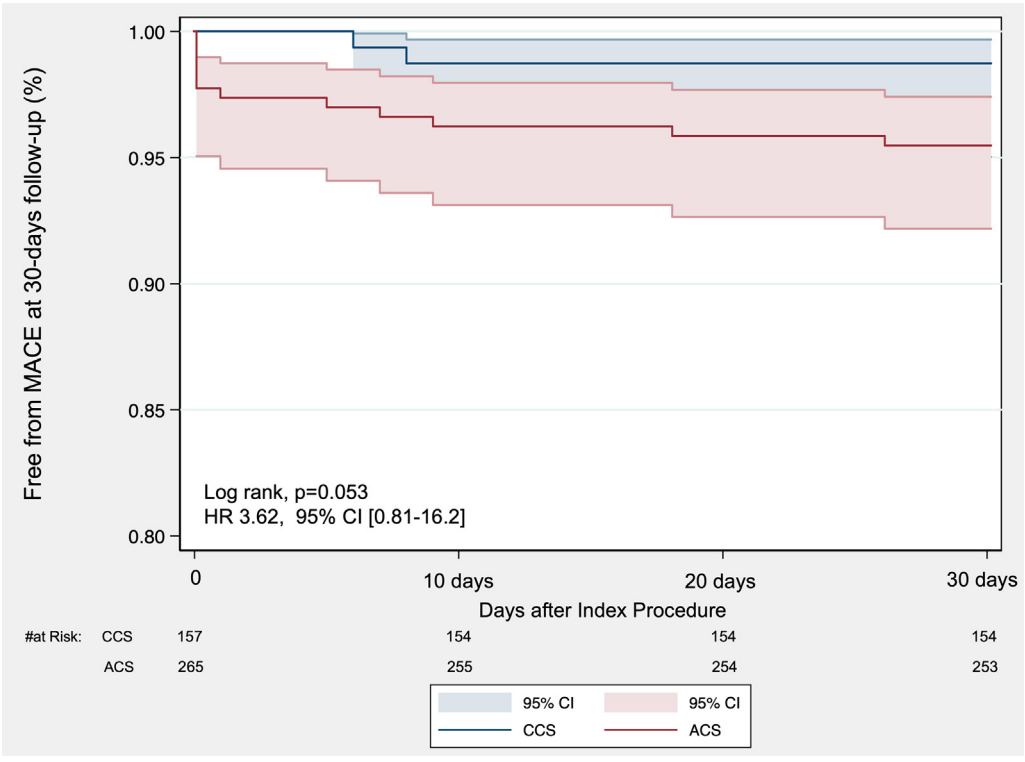


(A) Final in stent stenosis distribution (analysis per lesion). (B) Diameter stenosis distribution; baseline (red circles), after intravascular lithotripsy (IVL) (blue circles), and final result (grey circles).

severely calcified coronary lesions in an unselected "real-life" setting that included patients with ACS, lesions in tortuous vessels, true bifurcation lesions, lesions with acute thrombus, chronic total occlusions, underexpanded stents, and unprotected left main coronary artery or ostial target lesions. Plaque modification devices such as rotational atherectomy, orbital atherectomy, or excimer laser atherectomy were used when appropriate. The key findings of the study are as follows: 1) treatment with coronary IVL was feasible in the vast majority of lesions; 2) less than one-third of lesions had a final stenosis ≥20% despite 49% of lesions being considered undilatable before IVL; 3) complications directly related to the IVL device were very low; and 4) immediate and 30-day outcomes were excellent, with a very low rate of MACE despite the high-risk nature of the patient population.

Treating coronary lesions with severe calcification poses challenges and carries the risk of early complications such as perforation or dissection, as well as inadequate lesion preparation leading to stent underexpansion,[6] which are predictors of adverse long-term clinical outcomes, including stent thrombosis and restenosis.[6,15] Over the years, various

FIGURE 3 Kaplan-Meier Curves Comparing MACE at 30-Day Follow-Up Between CCS and ACS Patients



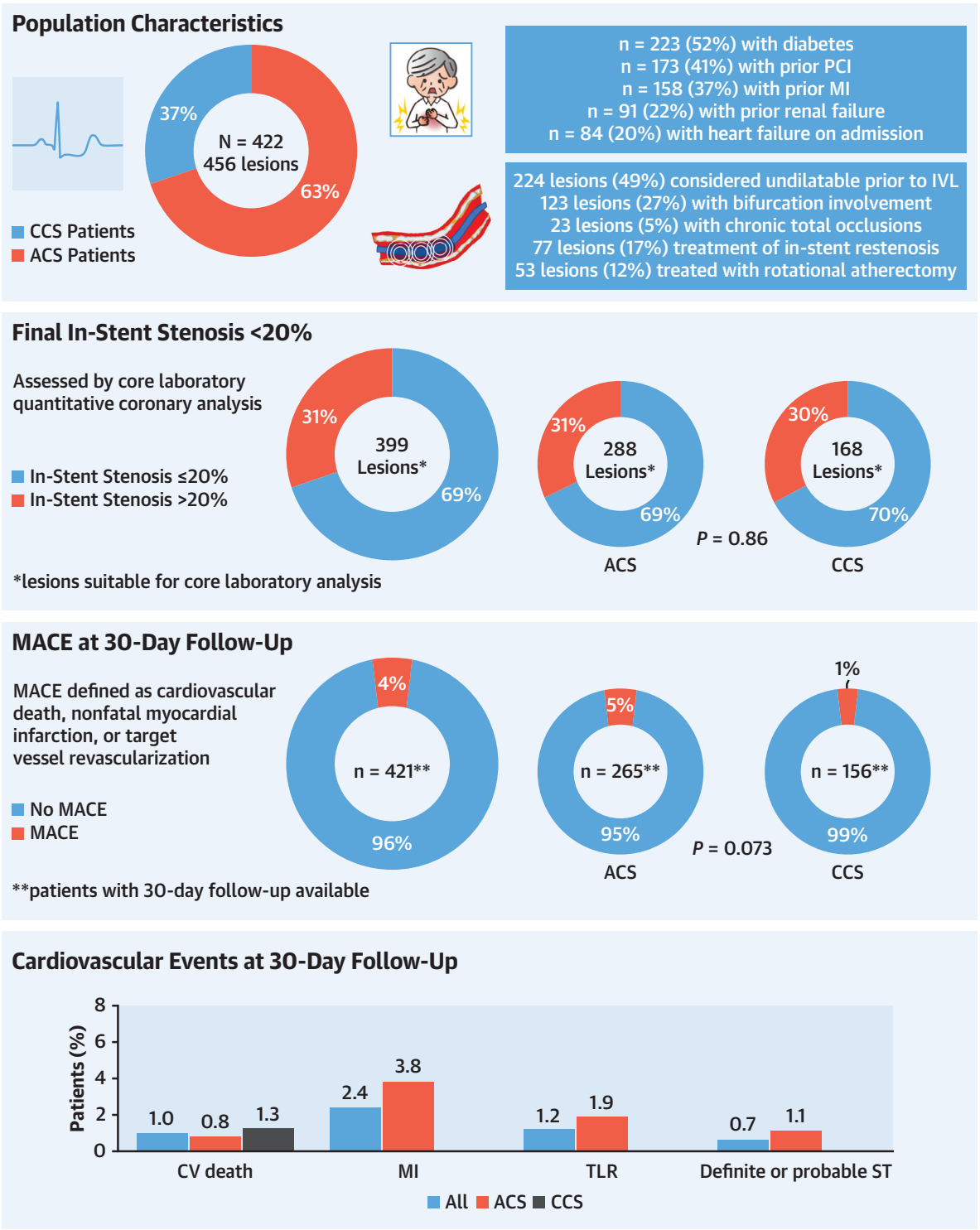
ACS acute coronary syndrome; CCS chronic coronary syndrome; MACE major adverse cardiac event(s).

plaque modification techniques, including rotational atherectomy, orbital atherectomy, excimer laser atherectomy, as well as specialty balloon catheters such as the cutting balloon or high-pressure balloon, have been developed to improve stent expansion and clinical outcomes.[16] However, a patient-level meta-analysis found that severe calcification was associated with a 44% increase in cardiac death, a 23% increase in target vessel MI, and a 21% increase in target lesion failure compared with noncalcified lesions.[17]

The use of coronary IVL has been evaluated in several prospective and retrospective registries.[8,10-12,14] The largest study to date, Disrupt CAD III (Disrupt CAD III With the Shockwave Coronary IVL System), enrolled 431 patients and supported U.S. regulatory approval for coronary IVL. However, patients with recent acute MI, lesions in tortuous vessels, true bifurcation lesions, lesions with acute thrombus, chronic total occlusions, unprotected left main or ostial target lesions, and planned use of atherectomy, scoring, or cutting balloon were excluded.[12] The findings of the REPLICA-EPIC18 study suggest that early outcomes in unselected patients treated with coronary IVL are similar to those observed in the selected patients included in the Disrupt CAD III trial, with very low device-related complications. These results support the safety and effectiveness of coronary IVL in an all-comers, complex anatomic scenario.

Despite the increased complexity of target lesions compared with previous studies, the crossing rate of IVL balloons in our study was exceptionally high, with only 3 cases where the IVL balloon failed to cross the lesion. This high success rate may be attributed to the frequent use of debulking devices before IVL balloon crossing. The combination of various plaque modification techniques, as recommended in previous studies,[18] played a vital role in achieving the favorable outcomes observed in REPLICA-EPIC18, where <10% of lesions were directly treated with IVL. The utilization of rotational atherectomy in patients with ACS was higher than expected, accounting for nearly 15% of lesions. This elevated usage was primarily attributed to the challenges faced in crossing the lesion with conventional devices. Remarkably, there was no significant increase in

CENTRAL ILLUSTRATION **Patient and Lesion Characteristics, Angiographic Success, and Cardiovascular Events at 30-Day Follow-Up**



Rodriguez-Leor O, et al. J Am Coll Cardiol Intv. 2024;17(6):756–767.

ACS acute coronary syndrome; CCS chronic coronary syndrome; CV cardiovascular; IVL intravascular lithotripsy; MACE major adverse cardiac event(s); MI myocardial infarction; PCI percutaneous coronary intervention; ST stent thrombosis; TLR target lesion revascularization.

TABLE 3 In-Hospital and 30 Day Follow-Up Clinical Outcomes

	All Patients (N 422)	Patients With CCS (n 157)	Patients With ACS (n 265)	*P* Value
Procedure related complications				
Acute coronary occlusion	1 (0.2)	0 (0)	1 (0.4)	
Coronary perforation	3 (0.7)	1 (0.6)	2 (0.8)	0.89
Coronary dissection	10 (2.4)	6 (3.8)	4 (1.6)	0.13
Side branch occlusion	3 (0.7)	1 (0.6)	1 (0.4)	0.71
Slow flow	0 (0)	0 (0)	0 (0)	
Cardiac tamponade	0 (0)	0 (0)	0 (0)	
Stroke	0 (0)	0 (0)	0 (0)	
Death	0 (0)	0 (0)	0 (0)	
In hospital clinical outcomes				
MACE	8 (1.9)	0 (0)	8 (3.0)	
Death	3 (0.7)	0 (0)	3 (1.1)	
Cardiovascular death	1 (0.2)	0 (0)	1 (0.4)	
MI	6 (1.4)	0 (0)	6 (2.3)	
Procedure related MI	4 (1.0)	0 (0)	4 (1.5)	
Non procedure related MI	2 (0.5)	0 (0)	2 (0.8)	
TLR	1 (0.2)	0 (0)	1 (0.4)	
TVR	1 (0.2)	0 (0)	1 (0.4)	
Stent thrombosis	0 (0)	0 (0)	0 (0)	
Unplanned revascularization	2 (0.5)	0 (0)	2 (0.8)	
30 d follow up clinical outcomes[a]				
MACE	15 (3.6)	2 (1.3)	12 (4.5)	0.073
Death	7 (1.7)	2 (1.3)	5 (1.9)	0.64
Cardiovascular death	4 (1.0)	2 (1.3)	2 (0.8)	0.59
MI	10 (2.4)	0 (0)	10 (3.8)	
TLR	5 (1.2)	0 (0)	5 (1.9)	
TVR	5 (1.2)	0 (0)	5 (1.9)	
Definite or probable stent thrombosis	3 (1.1)	0 (0)	3 (1.1)	

Values are n (%). [a]At 30 days, clinical evaluation was available in 156 patients with CCS, thus the total number of patients was 421.
MACE major adverse cardiovascular event(s); TLR target lesion revascularization; TVR target vessel revascularization; other abbreviations as in Table 1.

complication rates associated with the preceding use of rotational atherectomy.

Successful stent expansion, defined as residual in-stent stenosis <20%, was achieved in 69.2% of lesions. In the core laboratory analysis of Disrupt CAD III, residual in-stent stenosis <50% was observed in 100% of cases and <30% in 99.5% of cases. In our study, we achieved residual in-stent stenosis <50% in 98.7% of cases and <30% in 86.9% of cases. Notably, in our study, 49% of lesions were initially deemed undilatable using conventional devices before IVL, which usually present an additional hurdle in achieving optimal stent expansion, and in up to 102 lesions, IVL was used to treat an underexpanded stent. Angiographic obstruction length, obstruction stenosis, and vessel reference diameter, as well as need for final post-dilatation, were found to be independent predictors of final in-stent stenosis ≥20%. The impact of these angiographic results on long-term clinical outcomes is yet to be determined. However, the 1-year follow-up of Disrupt CAD III demonstrated a low incidence of MACE, with 4.3% ischemia-driven target lesion revascularization and 1.1% stent thrombosis.[19]

STUDY LIMITATIONS. First, this nonrandomized study design lacks a concurrent control group, which is a limitation. Despite this limitation, the study demonstrated a high procedural success rate and a remarkably low periprocedural MACE rate, even

TABLE 4 Independent Predictors of Stent Underexpansion in the Logistic Multivariate Regression Analysis

	OR (95% CI)	*P* Value
Age	1.01 (0.97 1.03)	0.93
Male	1.45 (0.73 2.88)	0.29
Hypertension	2.02 (0.94 4.32)	0.07
Severe calcification, core laboratory analysis	1.41 (0.78 2.56)	0.26
Baseline CL QCA segment obstruction length	1.06 (1.03 1.05)	<0.001
Baseline CL QCA obstruction stenosis	1.03 (1.01 1.05)	0.022
Baseline CL QCA segment reference diameter	1.70 (1.09 2.62)	0.018
Chronic total occlusion treatment	1.19 (0.15 9.47)	0.87
Undilatable lesion	1.33 (0.77 2.29)	0.31
Use of cutting balloon	1.53 (0.80 2.92)	0.20
Number of IVL pulses	1.01 (0.99 1.02)	0.19
Final post dilation performed	2.11 (1.05 4.23)	0.036

CL-QCA core laboratory quantitative coronary analysis; IVL intravascular lithotripsy.

considering the severity of lesion calcification and patient complexity in the study population. These positive outcomes, combined with the ease-of-use and rapid learning curve associated with IVL, strongly suggest that the technology may have a crucial role to play in the treatment of complex and high-risk calcified lesions. Second, there were certain lesions that were not appropriate for core laboratory analysis for various reasons. In 22 cases, the complexity of the lesions, such as overlapping branches or bifurcation treatment with 2 stents, made them unsuitable for analysis. In 18 cases, the poor quality of the recordings, including the absence of a final result angiographic study or only fluoroscopy recording, prevented proper assessment. Additionally, in 14 cases, the recordings were not sent to the core laboratory for analysis. Third, only 43% of lesions were treated guided by intracoronary imaging. Although the use of intracoronary imaging is especially useful in the treatment of calcified lesions, these data represent real-life use outside the controlled context of clinical trials, and in fact, in the Disrupt CAD III trial, only 100 patients out of 431 had intracoronary optical coherence tomography imaging.[12]

CONCLUSIONS

In a group of consecutive unselected patients with calcified lesions, including those presenting with ACS, the feasibility of IVL treatment was successfully demonstrated. Despite up to 49% of lesions being considered undilatable before IVL, the procedure yielded satisfactory immediate angiographic results. Additionally, the incidence of immediate and short-term complications remained remarkably low, even in this high-risk population. It is important to note that the durability of the clinical benefits associated with IVL-optimized stent implantation should be determined in a longer-term clinical follow-up.

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PERSPECTIVES

WHAT IS KNOWN? Intravascular lithotripsy represents an innovative option for percutaneous treatment of calcified coronary lesions. Previous reports were limited by their focus on highly selected lesions and population, excluding patients with acute coronary syndrome.

WHAT IS NEW? In a real-world scenario, including patients with acute coronary syndrome and complex lesions, intravascular lithotripsy was feasible with good immediate angiographic results, a very low rate of complications related to the device, and excellent immediate and 30-day outcomes despite the high-risk nature of the patient population.

WHAT IS NEXT? The impact of these good initial results on long-term clinical outcomes is yet to be determined.

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KEY WORDS acute coronary syndrome, coronary artery calcification, intravascular lithotripsy

APPENDIX For an expanded Methods section, supplemental tables, and a list of the investigators, institutions, and organizations participating in the REPLICA-EPIC18 study, please see the online version of this paper.