



Intravascular Lithotripsy for Vessel Preparation in Calcified Coronary Arteries Prior to Stent Placement

— Japanese Disrupt CAD IV Study 1-Year Results —

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Background: Intravascular lithotripsy (IVL) delivers acoustic pressure waves to modify calcium, enhance vessel compliance, and optimize stent deployment. The Disrupt CAD IV study enrolled patients with severe coronary artery calcification and demonstrated low 30-day major adverse cardiovascular events (MACE) and high procedural success following IVL with no final serious angiographic complications. To date, long-term outcomes have not been reported. This analysis evaluates 1-year outcomes of Disrupt CAD IV.

Methods and Results: Disrupt CAD IV was a prospective single-arm multicenter study of IVL performed in a Japanese population with severe coronary artery calcification. Main outcomes included MACE (a composite of cardiac death, myocardial infarction [MI], or target vessel revascularization [TVR]), and target lesion failure (TLF; a composite of cardiac death, target vessel MI, and target lesion revascularization [TLR]) at 1 year. Compliance with patient follow-up at 1 year was 100%. MACE occurred in 9.4% of patients (cardiac death 0.0%, MI 6.3%, TVR 4.7%) and TLF occurred in 6.3% of patients, with both rates driven by non-Q wave MIs (6.3%). The TLR rate at 1 year was 1.6% and no stent thrombosis events were reported.

Conclusions: Treatment of severely calcified coronary lesions with IVL was associated with low rates of 1-year MACE and TLR, suggesting durable safety and effectiveness of IVL-facilitated coronary stent implantation in severely calcified lesions in a Japanese population.

Key Words: Calcification; Intravascular lithotripsy; Japan; Percutaneous coronary intervention

Percutaneous coronary intervention (PCI) with placement of a drug-eluting stent is the most common type of coronary artery revascularization. Encountering heavily calcified plaque during PCI may interfere with catheter crossing, balloon dilatation, and/or stent expansion, resulting in a higher risk of procedural failure, stent underexpansion, stent malapposition, and an increased risk of major adverse cardiovascular events (MACE).^{1,2} Currently available devices that are intended for lesion preparation to facilitate PCI in calcified coronary arteries include high-pressure non-compliant balloons, scoring or cutting balloons, and atherectomy. Each of these treatments may be associated with risks that limit their clinical utility. Modified balloons exert high luminal pressure to achieve adequate vessel dilatation in severely calcified lesions, which increases the risk of barotrauma-

related angiographic complications.³ Although atherectomy devices are able to modify superficial calcium, they have limited ability to modify deep calcium that may restrict vessel expansion during PCI,^{4,5} with higher rates of procedural complications and MACE.^{2,3,6-9} An optimal vessel preparation strategy for severe calcium would result in both high procedural success and low complication rates.

Intravascular lithotripsy (IVL) is a method of vessel preparation that generates acoustic pressure waves to disrupt calcification in the vessel wall to facilitate PCI. Clinical trials of vessel preparation using coronary IVL prior to PCI in the US and Europe have reported high procedural success rates with a low risk of complications in both the short term¹⁰⁻¹² and through 1 year of follow-up.¹³ In addition, studies conducted in Singapore^{14,15} and Japan¹⁶ have evaluated short-term outcomes of coronary IVL in Asian

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patients with calcified coronary arteries prior to PCI. However, to the authors' knowledge, no study has reported longer-term follow-up with coronary IVL in an Asian population. The purpose of this study was to evaluate the safety and effectiveness of coronary IVL over 1 year of follow-up in a Japanese population.

Methods

Study Design

Disrupt CAD IV With the Shockwave Coronary IVL System (Disrupt CAD IV) was a prospective multicenter single-arm study performed in Japan to assess the safety and effectiveness of coronary IVL prior to PCI in patients with severely calcified coronary arteries. Study participants provided written informed consent, and study procedures were performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, ISO 14155, applicable national requirements in Japan, and local institutional review boards and ethics committees. The study was prospectively registered at ClinicalTrials.gov (NCT04151628) with notification to the Pharmaceuticals and Medical Devices Agency (PMDA) to conduct the study in Japan. Independent groups were used to ensure data integrity by providing study monitoring (IQVIA Services Japan, Tokyo, Japan), core laboratory analysis of angiography and optical coherence tomography (OCT) images (Cardiovascular Research Foundation, New York, NY, USA), data management (MedPace, Cincinnati, OH, USA), data analysis (Cardiovascular Research Foundation), and clinical events committee adjudication of adverse events (Cardiovascular Research Foundation). A data safety monitoring board provided trial oversight. The study investigators had full access to data, controlled the decision to publish, and agreed to be accountable for the accuracy and completeness of the reported data. This paper reports 1-year outcomes from Disrupt CAD IV. Patients remain in follow-up for 2 years after treatment in this study.

Patients

A complete list of study entry criteria has been published elsewhere.¹⁶ Briefly, study participants were those scheduled for PCI who presented with stable, unstable, or silent ischemia, and severely calcified de novo coronary artery lesions, with target lesion length ≤ 40 mm and target vessel reference diameter between 2.5 and 4.0 mm. Patients with New York Heart Association Class III or IV heart failure, renal failure, active systemic infection, uncontrolled diabetes, uncontrolled severe hypertension, or recent myocardial infarction (MI), stroke, or transient ischemic attack were excluded.

Study Device and Procedure

Severely calcified coronary vessels were prepared prior to PCI with a single-use coronary IVL catheter (Shockwave Medical, Santa Clara, CA, USA), as described previously.¹⁶ The IVL catheter contains multiple lithotripsy emitters along the shaft of an integrated, fluid-filled balloon that create acoustic pressure waves to selectively disrupt and fracture superficial and deep calcium in situ. The IVL catheter was introduced into the target vessel over a 0.014-inch guidewire and positioned across the target lesion using balloon markers as visual guides. The IVL balloon, sized in a 1:1 ratio to the reference vessel diameter, was inflated to 4 atm to provide apposition to the ves-

sel wall and 10 IVL pulses were delivered by the connected generator; the balloon was then temporarily inflated to 6 atm and then deflated to re-establish blood flow, and the process was repeated until complete balloon inflation was achieved. Angiography was used to determine the appropriate number of pulses to achieve optimal vessel preparation. Subsequent stent placement was performed, followed by high-pressure post-dilatation with a non-compliant balloon. OCT imaging was performed before and after IVL, as well as after stent placement, to characterize the extent of pre-existing calcification and the magnitude of calcium fracture and stent expansion after treatment. Anticoagulation and antiplatelet regimens were administered according to established guidelines.^{17,18} Patient follow-up in this study was scheduled at hospital discharge and then 30 days, 6 months, 1 year, and 2 years after the procedure.

Outcomes

The primary safety endpoint was freedom from MACE (a composite of cardiac death, MI, or target vessel revascularization [TVR]) within 30 days of treatment. Periprocedural MI was defined as a peak post-PCI CK-MB concentration >3 -fold the upper limit of normal (ULN) with or without new pathologic Q waves at discharge (in-hospital MI). The Fourth Universal Definition of Myocardial Infarction was used to define MI beyond discharge.¹⁹

The primary effectiveness endpoint was procedural success, which was a composite of freedom from in-hospital MACE and stent delivery with residual stenosis $<50\%$ as determined by the imaging core laboratory. The primary safety and effectiveness endpoints, as well as complete 30-day outcomes, have been previously reported¹⁶ and are presented here for context.

All 1-year outcome measures were secondary endpoints. Target lesion failure (TLF) was a composite of cardiac death, target vessel MI, or ischemia-driven (ID-) TVR. We defined a serious angiographic complication as Type D–F dissection per the National Heart, Lung, and Blood Institute (NHLBI) classification system,²⁰ perforation using the Ellis classification,²¹ abrupt closure, or persistent slow/no flow. Angina severity was assessed using the Canadian Cardiovascular Society (CCS) angina classification system, which is a physician-reported scale that grades the relationship of angina symptoms with physical activity level.²²

Statistical Analysis

The primary safety (30-day MACE) and effectiveness (procedural success) endpoints of the trial were tested by evaluating a hypothesis of non-inferiority to outcomes from patients in the US and Europe treated with coronary IVL in the Disrupt CAD III study.¹² The present descriptive analysis reports 1-year outcomes from the Disrupt CAD IV study. Analyses were performed on an intent-to-treat population, which excluded the first enrolled patient at each site to promote investigator proficiency with the coronary IVL system. Baseline patient characteristics are reported as the mean \pm SD for continuous variables and as counts and percentages for categorical variables. The change in CCS class over 1 year of follow-up was analyzed with the McNemar test. Data analysis was performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Between November 2019 and April 2020, 72 patients were

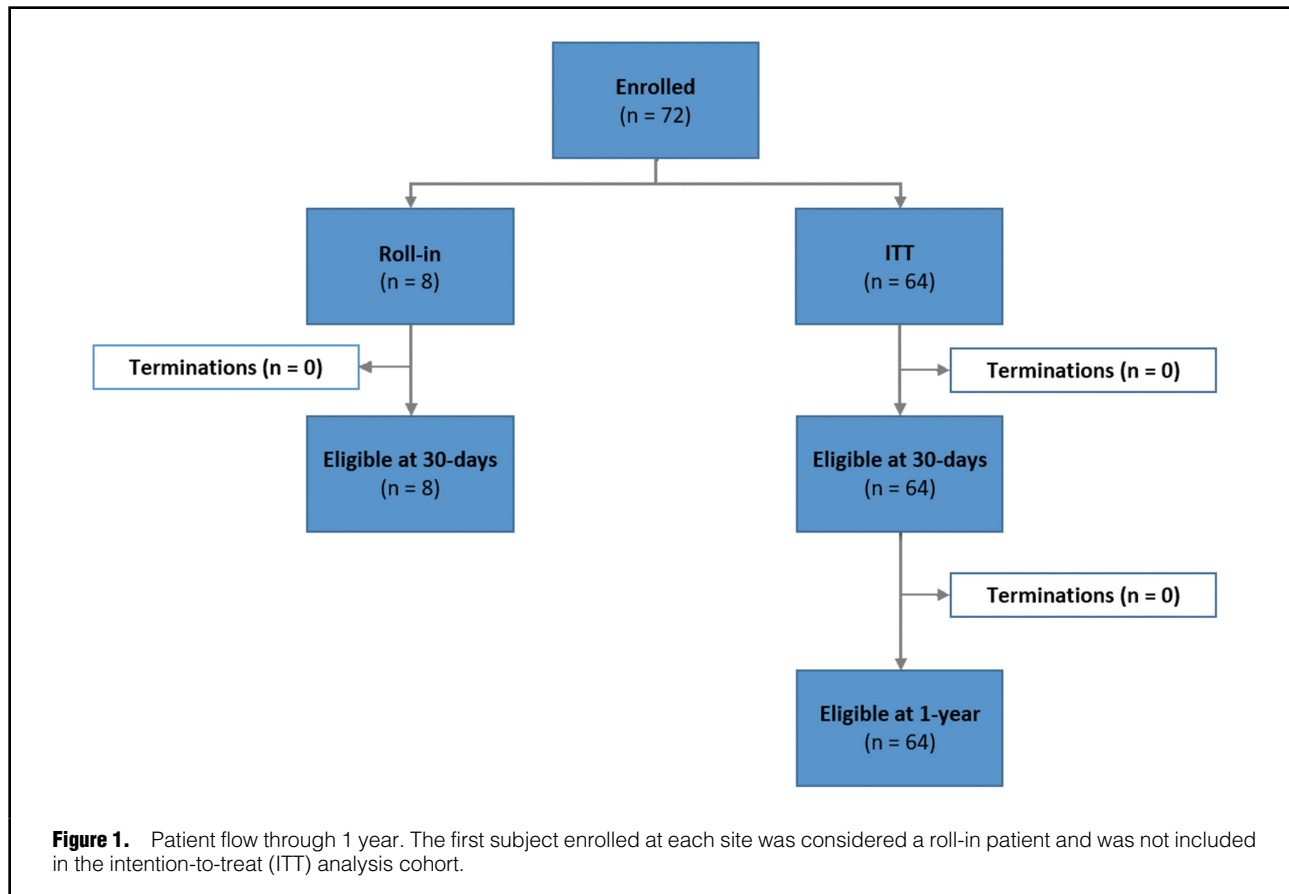
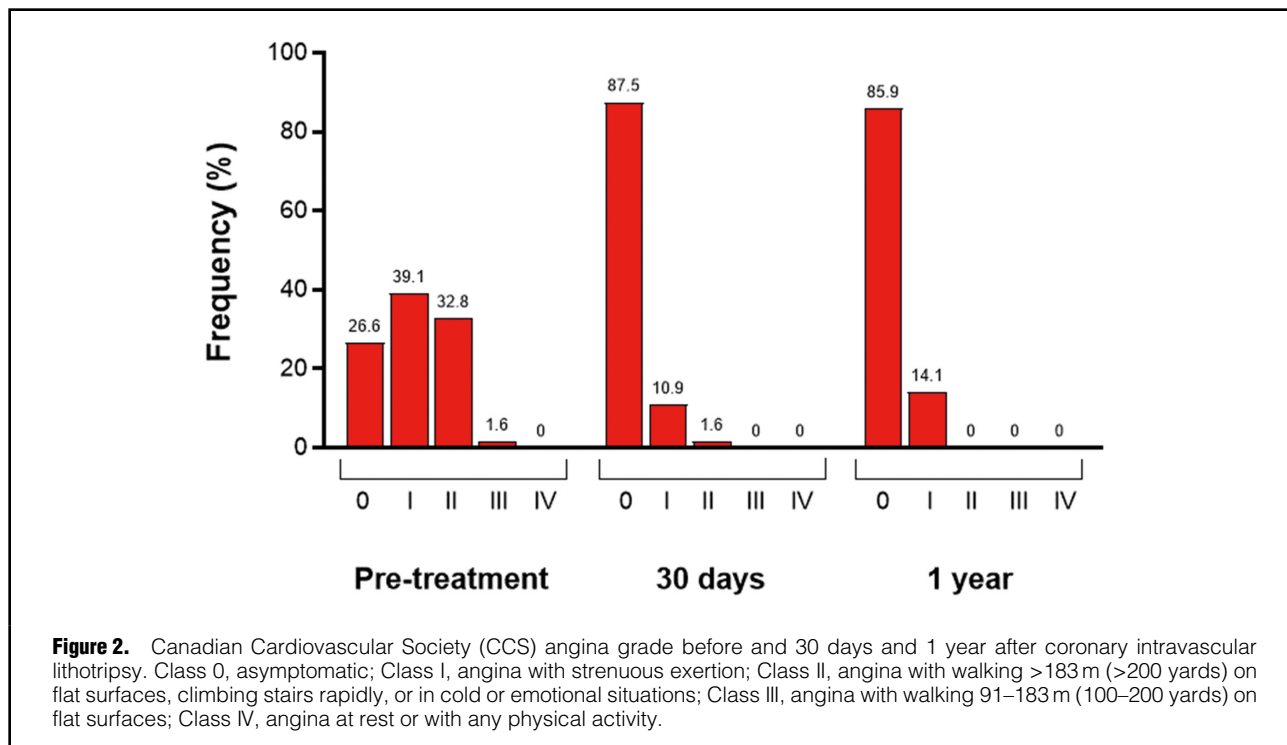


Table. Clinical Outcomes With Coronary Intravascular Lithotripsy Through 1 Year of Follow-up			
	In-hospital	30 days	1 year
All-cause mortality	0.0 (0/64)	0.0 (0/64)	0.0 (0/64)
MACE	6.3 (4/64)	6.3 (4/64)	9.4 (6/64)
Cardiac death	0.0 (0/64)	0.0 (0/64)	0.0 (0/64)
Q wave MI	0.0 (0/64)	0.0 (0/64)	0.0 (0/64)
Non-Q wave MI	6.3 (4/64)	6.3 (4/64)	6.3 (4/64)
TVR	0.0 (0/64)	0.0 (0/64)	4.7 (3/64)
Target lesion failure	6.3 (4/64)	6.3 (4/64)	6.3 (4/64)
Cardiac death	0.0 (0/64)	0.0 (0/64)	0.0 (0/64)
Target vessel MI	6.3 (4/64)	6.3 (4/64)	6.3 (4/64)
Q wave	0.0 (0/64)	0.0 (0/64)	0.0 (0/64)
Non-Q wave	6.3 (4/64)	6.3 (4/64)	6.3 (4/64)
Ischemia-driven TLR	0.0 (0/64)	0.0 (0/64)	1.6 (1/64)
Revascularization	0.0 (0/64)	0.0 (0/64)	15.6 (10/64)
TVR	0.0 (0/64)	0.0 (0/64)	4.7 (3/64)
Non-TVR	0.0 (0/64)	0.0 (0/64)	12.5 (8/64)
Stent thrombosis	0.0 (0/64)	0.0 (0/64)	0.0 (0/64)

Data show percentages with n/N in parentheses. MACE, major adverse cardiovascular events; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

enrolled at 8 centers in Japan, with 64 patients comprising the intention-to-treat population. All patients returned for each follow-up visit through 1 year, with no patient death or withdrawal from the study (100% follow-up compliance; **Figure 1**). Baseline patient characteristics and 30-day

outcomes from this trial have been reported previously.¹⁶ Briefly, 75% of patients were male, the mean age was 75±8 years, and the most common comorbidities were hyperlipidemia (86%), hypertension (83%), history of tobacco use (63%), and diabetes (48%). Nearly half (47%) the patients



had previously undergone coronary intervention and 73% presented with CCS class I–III angina. The target lesion was most commonly located in the left anterior descending artery (75%), mean lesion length was 28 ± 10 mm, mean diameter stenosis was $66 \pm 11\%$, and 100% of patients presented with severe coronary calcification over a mean length of 50 ± 16 mm.

In all cases, coronary IVL was successfully delivered and stent placement was successful, with mean stent expansion of 99.5% at the site of maximum calcification and a minimum stent area of 5.7 ± 1.5 mm² by OCT. Comparing pretreatment to final in-stent angiographic results, mean diameter stenosis decreased from 66% to 10% and the minimum lumen diameter increased from 1.0 ± 0.4 to 2.7 ± 0.4 mm. OCT imaging following coronary IVL confirmed circumferential and longitudinal calcium fracture in most patients.¹⁶ During the 30-day follow-up period, 4 (6.3%) patients experienced MACE. All 30-day MACE events were in-hospital non-Q wave MI events; no deaths, Q wave MIs, or TVRs were reported. Comparing patients treated in the current trial with those in the Disrupt CAD III trial, both primary endpoints were achieved with non-inferiority demonstrated for freedom from 30-day MACE (93.8% vs. 91.2%; $P=0.008$) and procedural success (93.8% vs. 91.6%; $P=0.007$).

The cumulative incidence of events through 1 year of follow-up was 9.4% for MACE, 6.3% for TLF, 4.7% for TVR, and 1.6% for ID-TLR, all of which occurred in 6 patients (Table). No death or stent thrombosis events occurred at 1 year and no MI events occurred after discharge because all 4 MI events were in-hospital non-Q wave MI events. The single ID-TLR event occurred in a patient readmitted for chest pain on Day 119 following the index procedure. Angiography revealed 99% stent edge stenosis at the left main coronary artery and patent proximal left anterior descending artery stent bifurcation. PCI

was performed with deployment of a single 3.5-mm \times 12-mm drug-eluting stent to the left main coronary artery and post-dilatation with a 4.0-mm balloon. Final angiography revealed 0% residual stenosis and Thrombolysis in Myocardial Infarction (TIMI) 3 flow. The patient was discharged to home the next day in a stable condition. Coronary IVL-facilitated PCI was highly effective in relieving angina, with 27% of patients graded as asymptomatic (CCS Class 0) at pretreatment, compared with 86% at 1 year ($P<0.001$; Figure 2).

Discussion

Early results from the Disrupt CAD IV study demonstrated successful delivery of coronary IVL with low rates of procedural complications and MACE.¹⁶ The present report expands those findings by providing outcome data through 1 year of follow-up. The key finding from the present study is that the favorable safety and effectiveness observed with coronary IVL through 30 days are durably maintained over 1 year. This was evident by an absence of post-discharge MI, death, or stent thrombosis through 1 year, only 3 (4.7%) TVR procedures through 1 year, and complete resolution of angina in approximately 90% of patients.

Vascular calcification is especially prevalent among older patients and those with diabetes and chronic kidney disease. Severe calcification is encountered in approximately 8% of patients undergoing PCI,²³ and may interfere with catheter delivery, balloon expansion, and stent expansion. Coronary IVL was developed to facilitate PCI in severely calcified lesions by fracturing superficial and deep calcium, subsequently improving vessel compliance, and allowing maximum stent expansion. There have been several reports demonstrating excellent short-term outcomes of coronary

IVL in Asian patients with calcified coronary arteries prior to PCI.¹⁴⁻¹⁶ The results presented here are novel because they represent the first long-term data with coronary IVL in Asian patients. Wong et al²⁴ were the first group to report 1-year outcomes with coronary IVL. Among 44 patients treated at a single center in Australia, there were no procedural complications, no reports of Q wave MI or cardiovascular death through 1 year, and a TLR rate of 6.8%. Aksoy et al²⁵ reported 1-year outcomes of 57 patients treated with coronary IVL at a single center in Germany. Angiographic complications were rare (0.2%), MACE occurred in 10.5% of cases over 1 year, the TVR rate was 1.8%, and there were no cases of stent thrombosis. The Disrupt CAD III study of 384 patients treated with coronary IVL in the US and Europe also reported favorable 1-year outcomes, including 13.8% MACE, 1.1% cardiac death, and 1.1% stent thrombosis.¹³ Although approximately 25% of patients in CAD III were enrolled in the CAD III OCT substudy and all patients in CAD IV underwent OCT-guided PCI, both studies demonstrated favorable clinical outcomes at 1 year. The results of the present trial corroborate those from previous studies and support the long-term safety and effectiveness of coronary IVL-facilitated PCI regardless of geography.

Although cross-trial comparisons are difficult, understanding longer-term results reported using atherectomy and non-compliant balloons for coronary vessel preparation are warranted. The J2T Registry is a multicenter registry of rotational atherectomy for calcified coronary lesions that enrolled 1,090 Japanese patients with similar characteristics as those in the present study (i.e., mean age of 70 years, male predominance [75%], and heavily calcified de novo lesions).²⁶ The 1-year outcomes for MACE (23%), all-cause mortality (8%), TVR (14%), and TLR (17%) following treatment with rotational atherectomy in the J2T Registry were markedly greater relative to the 1-year outcomes reported in the present study with IVL. Similar findings were reported in the Coronary Orbital Atherectomy System Study (COAST), which enrolled patients in the US and Japan under the Medical Device Harmonization by Doing program.²⁷ COAST evaluated the safety and effectiveness of the Micro Crown orbital atherectomy system for the treatment of calcified de novo coronary artery lesions and reported 1 year rates of MACE, TVR, and TLR of 22.2%, 9.4%, and 6.3%, respectively.²⁷ Although an explanation for these differences in adverse clinical outcome rates remains speculative, it has been suggested that atherectomy may cause thermal injury and induce platelet activation, which, in turn, may contribute to a higher risk of neointimal hyperplasia and restenosis.^{28,29} In contrast, coronary IVL acoustic shockwaves are delivered through a low-pressure balloon (4 atm) to selectively modify superficial and deep wall calcium that remains in situ with demonstrated low risk of vascular injury and low reported angiographic complication rates.³⁰⁻³² The results of the propensity-score matched study of Aksoy et al²⁵ are also helpful in making relevant comparisons of coronary IVL to non-compliant balloon percutaneous coronary angioplasty. Coronary IVL resulted in higher procedural success (82.5% vs. 61.4%; $P=0.004$) and with comparable MACE at 1 year (10.5% vs. 11.1%). Ultimately, coronary IVL appears to offer a combination of high procedural success and low long-term MACE rates relative to other methods of coronary vessel preparation in this patient population.

Study Limitations

This is the first known study to report long-term outcomes with coronary IVL in a series of Japanese patients receiving PCI. However, this study has some limitations. First, coronary IVL has not been directly compared to other modalities for vessel preparation, such as atherectomy, in prospective trials, which may complicate the interpretation of comparative results. Furthermore, the adjunctive use of atherectomy in conjunction with coronary IVL was not evaluated in the present study. Complementary use of IVL with atherectomy to treat specific complex coronary lesions warrants further investigation. Second, the number of adverse events identified in this trial was insufficient to identify risk factors using statistical techniques. A larger study is necessary to determine whether specific demographic, medical history, or angiographic characteristics influence procedural success or MACE rates with coronary IVL. Finally, although PCI with a drug-coated balloon without stenting of de novo coronary lesions has been explored as an alternative “leave nothing behind” strategy, Disrupt CAD IV did not evaluate coronary IVL treatment prior to the use of a drug-coated balloon. However, several case reports and “real-world” registries have reported excellent procedural safety and mid-term effectiveness outcomes with coronary IVL followed by drug-coated balloon treatment in severely calcified coronary lesions that are consistent with the findings of Disrupt CAD IV.³³⁻³⁵ Additional studies are needed to further evaluate the use of drug-coated balloons as definitive treatment following PCI with coronary IVL.

Conclusions

Treatment of severely calcified coronary lesions with IVL was associated with low rates of 1-year MACE and TLR, suggesting durable safety and effectiveness of IVL-facilitated coronary stent implantation in severely calcified lesions in a Japanese population.

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Disclosures

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IRB Information

This study was approved by the Tokushukai Group Institutional Review Board (Reference no. 024-19-08).

Data Availability

The deidentified participant data will not be shared.

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