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Intravascular Lithotripsy for Treatment of Calcified Coronary Lesions

Patient-Level Pooled Analysis of the Disrupt CAD Studies

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ABSTRACT

OBJECTIVES The aim of this pooled analysis was to assess the cumulative safety and effectiveness of coronary intravascular lithotripsy (IVL).

BACKGROUND The clinical outcomes of IVL to optimize target lesion preparation in severely calcified de novo coronary stenoses have been examined in 4 prospective studies (Disrupt CAD I [NCT02650128], Disrupt CAD II [NCT03328949], Disrupt CAD III [NCT03595176], and Disrupt CAD IV [NCT04151628]).

METHODS Patient data were pooled from the Disrupt CAD studies, which shared uniform study criteria, endpoint definitions and adjudication, and procedural follow-up. The primary safety endpoint was freedom from major adverse cardiovascular events (composite of cardiac death, all myocardial infarction, or target vessel revascularization) at 30 days. The primary effectiveness endpoint was procedural success, defined as stent delivery with a residual stenosis ≤30% by quantitative coronary angiography without in-hospital major adverse cardiovascular events. Secondary outcomes included serious angiographic complications, target lesion failure, cardiac death, and stent thrombosis at 30 days.

RESULTS Between December 2015 and April 2020, 628 patients were enrolled at 72 sites from 12 countries. Presence of severe calcification was confirmed in 97.0% of target lesions with an average calcified segment length of 41.5 ± 20.0 mm. The primary safety and effectiveness endpoints were achieved in 92.7% and 92.4% of patients, respectively. At 30 days, the rates of target lesion failure, cardiac death, and stent thrombosis were 7.2%, 0.5%, and 0.8%. Rates of post-IVL and final serious angiographic complications were 2.1% and 0.3%, with no IVL-associated perforations, abrupt closure, or episodes of no reflow.

CONCLUSIONS In the largest cohort of patients treated with coronary IVL assessed to date, coronary IVL safely facilitated successful stent implantation in severely calcified coronary lesions with a high rate of procedural success. (J Am Coll Cardiol Intv 2021;14:1337–48) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ARC = Academic Research Consortium

CI = confidence interval

IVL = intravascular lithotripsy

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

MLD = minimal luminal diameter

OR = odds ratio

PCI = percutaneous coronary intervention

TLF = target lesion failure

TRA = transradial access

Percutaneous coronary intervention (PCI) with drug-eluting stent implantation is the most frequent mode of coronary artery revascularization. Advanced age and an increasing frequency of diabetes mellitus, hypertension, and renal insufficiency contribute to an increasing prevalence and severity of coronary calcification (1–3). Despite the use of high-pressure noncompliant balloon catheters, cutting and scoring balloons, and atheroablative technologies (i.e., laser, orbital, and rotational atherectomy) to modify calcium (3–7), PCI of heavily calcified lesions may be associated with early complications (coronary dissection, vessel perforation, myocardial infarction [MI]) and/or late adverse events (stent restenosis, thrombosis, and repeat revascularization). Coronary calcification may limit stent delivery and deployment and results in stent underexpansion, strut malapposition, and direct damage to the stent surface (including polymer), with potential impairment of drug delivery (8–11). Stent underexpansion is the most powerful predictor of subsequent stent thrombosis and/or restenosis (11–16). Atheroablation by atherectomy is limited by guidewire bias (6,7) and may be associated with periprocedural complications including slow flow, no reflow, coronary dissection, perforation, and MI (4,5,17–19).

SEE PAGE 1349

Intravascular lithotripsy (IVL) incorporates principles used to transmit acoustic energy for the treatment of nephrolithiasis (i.e., extracorporeal lithotripsy) (20,21). IVL has been evaluated as an adjunct to coronary stenting in severely calcified lesions in the Disrupt CAD I (Shockwave Coronary Rx Lithoplasty® Study), Disrupt CAD II (Shockwave Coronary Lithoplasty® Study), Disrupt CAD III (Disrupt CAD III With the Shockwave Coronary IVL System), and Disrupt CAD IV (Disrupt CAD IV With the Shockwave Coronary IVL System) studies. These individual single-arm, prospective, multicenter, nonrandomized studies demonstrated high rates of device and procedural success as well as excellent early angiographic and clinical outcomes (22–25), providing evidence for device effectiveness and safety as well as insights into the mechanism(s) of calcium modification. In the present study, we performed an individual patient-level pooled analysis of the Disrupt CAD studies to assess the cumulative safety and effectiveness of IVL to optimize target lesion preparation in patients with severely calcified de novo coronary stenoses and to identify the predictors of success following IVL treatment.

METHODS

STUDIES AND STUDY OBJECTIVES. Patients treated with the Shockwave Medical (Santa Clara, California) IVL system and coronary IVL catheter for the treatment of de novo calcified coronary artery disease were pooled from the Disrupt CAD studies. The study designs, detailed inclusion criteria, and outcomes of the 4 Disrupt CAD studies have been described previously (22–25). The major features of each study are shown in Supplemental Table 1. Briefly, all were prospective, multicenter, single-arm studies that evaluated the safety and effectiveness of coronary IVL prior to stenting in patients who presented with stable or unstable angina or silent ischemia due to severely calcified de novo coronary lesions. Subject inclusion criteria were similar across all studies. The definition of severe calcification by operator assessment required the presence of fluoroscopic radiopacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least one location, and total length of calcium of at least 15 mm and extending partially into the target lesion, or an intravascular imaging-demonstrated calcium angle of ≥270° in at least one cross section. Each study was approved by the Institutional Review Board or ethics committee at participating centers, and all patients provided written informed consent. The coronary IVL procedure was performed consistently across studies, according to each study protocol and the instructions for use. All Disrupt CAD studies used similar endpoint definitions, an independent adjudication processes for the angiographic core laboratory and clinical events committee, and 30-day follow-up procedures. Post-procedure, dual-antiplatelet therapy was prescribed per applicable guidelines for a minimum of 6 months. Complete 30-day follow-up is available for all studies (Supplemental Table 1).

STUDY ENDPOINTS. The primary safety endpoint was 30-day major adverse cardiovascular events (MACE), defined as clinical events committee-adjudicated composite occurrence of cardiac death, MI or target vessel revascularization. To provide consistency with prior studies (4,5), peri-procedural MI was defined as peak post-PCI creatine kinase-MB level >3 times the upper limit of normal with or without new pathological Q waves. Post-discharge MI was also defined using creatine kinase-MB level >3

times the upper limit of normal for Disrupt CAD I and Disrupt CAD II. The fourth universal definition of MI (26) was incorporated in Disrupt CAD III and Disrupt CAD IV for post-discharge MI given the rapid adoption of troponin as a biomarker. This minor change in definition had little impact on overall 30-day MI rates given that 97% of MI events occurred within the in-hospital phase. The primary effectiveness endpoint was procedural success, defined as stent delivery with residual in-stent stenosis ≤30% as assessed by the angiographic core laboratory and without in-hospital MACE. Note that the more contemporary procedural success angiographic definition of ≤30% was chosen for this analysis rather than the threshold of <50% that was used in prior regulatory approval CAD studies (4,24). Secondary endpoints included procedural success with a residual stenosis threshold of <50%, final post-procedural percentage diameter stenosis, post-IVL and final serious angiographic complications (defined as grade D or greater dissection, perforation, abrupt closure, and slow flow or no reflow), as well as target lesion failure (TLF) and Academic Research Consortium-defined definite or probable stent thrombosis at 30 days. Subgroup and multivariate analyses for the primary safety and effectiveness endpoints have been included.

STATISTICAL ANALYSIS. All analyses were performed on the intent-to-treat population consisting of all patients in each of the 4 studies, with the exception of roll-in patients from Disrupt CAD III and Disrupt CAD IV. Primary endpoints were analyzed for heterogeneity using a logistic regression model including an intercept and fixed effect for study. Point estimates and Clopper-Pearson 95% confidence intervals (CIs) were constructed for primary endpoints. Adjudicated patient-level data were pooled, and consistent definitions were applied across studies. Continuous data are expressed as mean ± SD, and categorical variables are expressed as percentages and frequencies. No imputations for missing data were performed. Covariates were selected a priori from historical relatedness to adverse events after calcified lesion PCI. The following subgroups were evaluated for consistency of the primary safety and effectiveness endpoints: study, age, sex, diabetes mellitus, renal insufficiency, prior coronary artery bypass graft surgery, reference vessel diameter, lesion length, and bifurcation lesions. The independent predictors of MACE at 30 days and procedural success with a threshold residual stenosis ≤30% were determined by multivariate logistic regression using stepwise selection with a 2-sided level of significance of 0.05, adjusted by study. Covariates entered into each model appear in the footnote of the corresponding results table. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

TABLE 1 Baseline Characteristics (N = 628)

Baseline characteristics	
Age, yrs	71.8 ± 8.9
Male	484 (77.1)
Country/region	
United States	335 (53.3)
Europe	213 (33.9)
Japan	64 (10.2)
Australia	16 (2.6)
Diabetes	241 (38.4)
Hypertension	539 (85.8)
Hyperlipidemia	531 (84.6)
Prior myocardial infarction	137 (21.8)
Prior coronary artery bypass grafting	60 (9.6)
Prior stroke or TIA	54 (8.6)
Current or former smoker	357 (56.8)
Renal insufficiency (eGFR <60 ml/min/1.73 m^2)	157/625 (25.1)
Pacemaker or ICD/CRT-D	39 (6.2)
Angina classification	
Class 0	89 (14.5)
Class I	142 (23.1)
Class II	228 (37.1)
Class III	143 (23.2)
Class IV	13 (2.1)
Angiographic characteristic (core laboratory)	
Target vessel	
Protected left main coronary artery	9 (1.4)
Left anterior descending coronary artery	368 (58.6)
Circumflex coronary artery	75 (11.9)
Right coronary artery	176 (28.0)
Reference vessel diameter, mm	2.95 ± 0.51 (N = 625)
Minimum luminal diameter, mm	1.07 ± 0.38 (N = 625)
Diameter stenosis, %	63.7 ± 11.8 (N = 625)
Lesion length, mm	24.4 ± 11.5 (N = 624)
Calcified length, mm	41.5 ± 20.0 (N = 623)
Severe calcification*	609 (97.0)
Bifurcation lesion with side branch involvement	190 (30.3)

Values are mean ± SD or n (%). *Defined as radiopaque densities noted without cardiac motion generally involving both sides of the arterial wall.

eGFR = estimated glomerular filtration rate (using the MDRD [Modification of Diet in Renal Disease] formula); ICD/CRT-D = implantable cardioverter-defibrillator with or without biventricular pacing capability; TIA = transient ischemic attack.

RESULTS

PATIENTS AND PROCEDURES. Between December 21, 2015, and April 6, 2020, a total of 628 patients were enrolled at 72 sites in 12 countries, including the United States, the United Kingdom, Japan, France, Germany, Italy, Australia, Spain, Belgium, the Netherlands, Sweden, and Denmark (Supplemental Table 1). Patient follow-up at 30 days was completed in 626 patients (99.7%), with 2 patients lost to follow-up. Pooled baseline clinical and angiographic

characteristics are presented in Table 1. The mean patient age was 71.8 ± 8.9 years, 77.1% were men, 38.4% had diabetes, 25.1% had renal insufficiency, and 53.3% were enrolled in the United States. The mean reference vessel diameter of the target lesion was 2.95 ± 0.51 mm, mean lesion length was 24.4 ± 11.5 mm, and side-branch involvement was present in 30.3% of lesions. Severe calcification by core laboratory assessment was present in 97.0% of all lesions, and the total calcified segment length was 41.5 ± 20.0 mm. Procedural data are shown in Table 2. Radial access was used in 62.7% (281 of 448) of the procedures in which access route was recorded. Target lesion pre-dilatation was performed in 47.6% of procedures, and IVL was successfully delivered in 98.7% of procedures, with a mean of 74.7 ± 42.7 pulses delivered per lesion. Balloon post-dilatation was performed immediately after IVL in 16.8% of cases and following subsequent stent implantation in 94.1% of procedures. Stent delivery was successful in 99.5% of patients. The median length of hospital stay was 1 day.

PRIMARY ENDPOINTS. Primary endpoint outcomes are shown in Table 3. The rate of the primary safety endpoint of 30-day MACE was 7.3% (95% CI: 5.4% to 9.7%), driven by non-Q-wave MI (5.9%; 95% CI: 4.2% to 8.1%). MACE status was known for 99.7% of patients (626 of 628). The primary effectiveness endpoint, procedural success with ≤30% residual stenosis, was achieved in 92.4% of patients (95% CI: 90.0% to 94.3%). These findings were consistent across all 4 Disrupt CAD studies (Figure 1).

SECONDARY ENDPOINTS. Procedural success with <50% residual stenosis was achieved in 93.2% of patients (95% CI: 90.9% to 95.0%) (Supplemental Figure 1). The rate of in-hospital MACE was 6.5% (95% CI: 4.7% to 8.8%), driven by non-Q-wave MI (5.7%; 95% CI: 4.1% to 7.9%) (Table 3). Post-IVL and post-stent quantitative coronary angiographic measurements are shown in Table 4. Angiographic outcomes are shown in Figure 2. Diameter stenosis was significantly reduced immediately following IVL treatment (63.7 ± 11.8% vs. 35.4 ± 13.0%; p < 0.0001), and final in-stent residual stenosis (following post-dilatation) was 12.1 ± 6.8%. Serious angiographic complications immediately following IVL treatment were observed in 2.1% of patients, due to flow-limiting dissection (1.8%) and slow flow (0.4%), with no occurrences of perforation, abrupt closure, or no reflow (Central Illustration). Final post-stent serious angiographic complications occurred in 0.3% of patients, with no occurrences of slow flow or no reflow (Figure 2). As shown in Table 3, TLF, cardiac death, and definite or probable stent thrombosis events through 30 days occurred in 7.2% (95% CI: 5.3% to 9.5%), 0.5% (95% CI: 0.1% to 1.4%), and 0.8% (95% CI: 0.3% to 1.9%) of patients. Case summaries for cardiac death

TABLE 2 Procedural Details (N = 628)

Total procedure time, min	57.0 (41.5–83.0)
Contrast volume, ml	179.8 ± 77.3
Access*	
Radial	281/448 (62.7)
Femoral	163/448 (36.4)
Brachial	3/448 (0.7)
Ulnar	1/448 (0.2)
Pre-dilatation	299 (47.6)
Patients undergoing IVL	620 (98.7)
Maximum IVL inflation pressure, atm	6.0 ± 0.5
Number of lithotripsy catheters	1.3 ± 0.6
IVL balloon/RVD ratio	1.2 ± 0.2
Number of pulses	74.7 ± 42.7
Post-IVL dilatation	84/500 (16.8)
Stent delivery	625 (99.5)
Number of stents implanted	1.3 ± 0.5
Post-stent dilatation	588 (94.1)
Total stent length, mm	33.2 ± 14.4
Duration of hospitalization	1.0 (1.0–1.0)

Values are median (interquartile range), mean ± SD, or n/N (%). *Access data collected in Disrupt CAD III and Disrupt CAD IV only.

Disrupt CAD III = Disrupt CAD III With the Shockwave Coronary IVL System; Disrupt CAD IV = Disrupt CAD IV With the Shockwave Coronary IVL System; IVL = intravascular lithotripsy; RVD = reference vessel diameter.

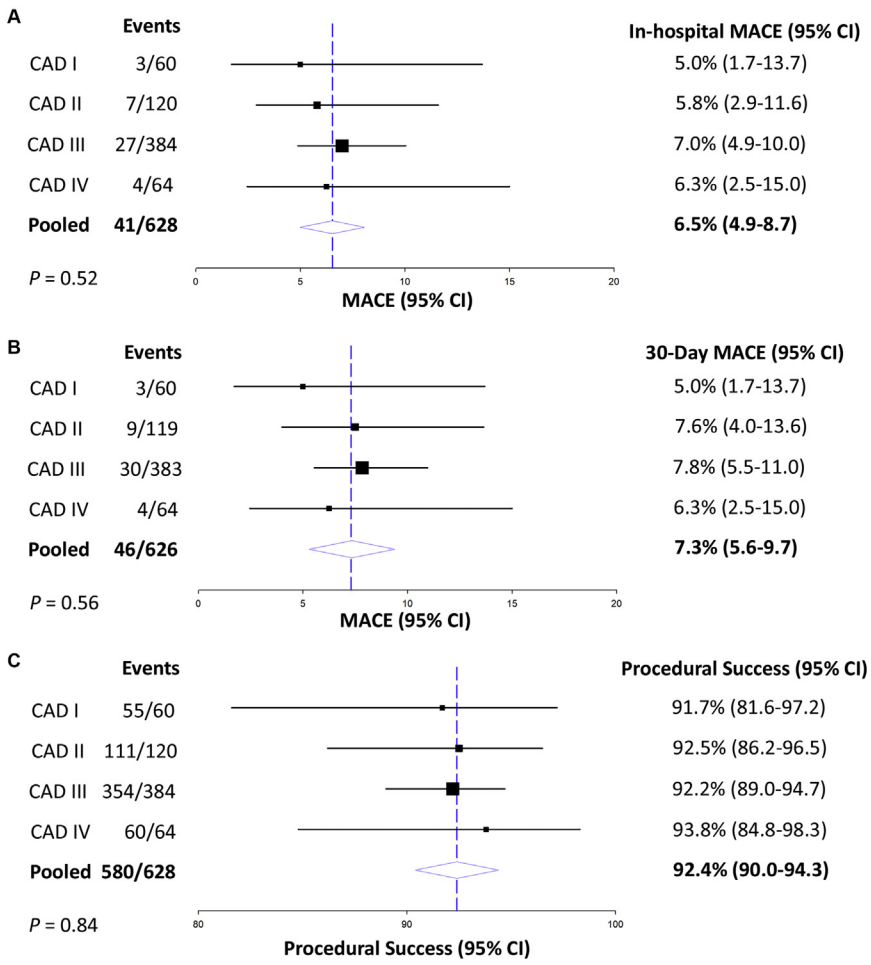
TABLE 3 Primary and Secondary Endpoints (N = 628)

In-hospital MACE	6.5 (4.7–8.8)
Cardiac death	0.2 (0.0–0.9)
All myocardial infarction	6.4 (4.6–8.6)
Non-Q-wave	5.7 (4.1–7.9)
Q-wave	0.6 (0.2–1.6)
Target vessel revascularization	0.3 (0.0–1.2)
30-day MACE*	7.3 (5.4–9.7)
Cardiac death	0.5 (0.1–1.4)
All myocardial infarction	6.9 (5.0–9.1)
Non-Q-wave	5.9 (4.2–8.1)
Q-wave	1.1 (0.5–2.3)
Target vessel revascularization	1.1 (0.5–2.3)
Procedural success	
Residual stenosis <50%	93.2 (90.9–95.0)
Residual stenosis ≤30%	92.4 (90.0–94.3)
Secondary endpoints at 30 days*	
Target lesion failure at 30 days	7.2 (5.3–9.5)
Cardiac death	0.5 (0.1–1.4)
TV MI	6.9 (5.0–9.1)
ID TLR	1.0 (0.4–2.1)
Stent thrombosis (definite or probable)	0.8 (0.3–1.9)
Definite	0.6 (0.2–1.6)
Probable	0.3 (0.0–1.2)

Values are % (95% confidence interval). *N = 626 for 30-day follow-up endpoints.

ID = ischemia-driven; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization.

FIGURE 1 **MACE and Procedural Success for Patients Enrolled in the Disrupt CAD Studies**



In-hospital **(A)** and 30-day **(B)** major adverse cardiovascular event (MACE) rates demonstrate consistent outcomes across the individual Disrupt CAD studies. Procedural success defined using the residual stenosis ≤30% threshold **(C)** demonstrates consistent results among the Disrupt CAD studies. Heterogeneity among studies was evaluated using logistic regression with study as a fixed effect. All p values were not statistically significant, indicating consistency across the 4 studies for in-hospital and 30-day MACE and procedural success. **Blue dashed line** represents the overall weighted estimate for each parameter. CAD I = Shockwave Coronary Rx Lithoplasty® Study; CAD II = Shockwave Coronary Lithoplasty® Study; CAD III = Disrupt CAD III With the Shockwave Coronary IVL System; CAD IV = Disrupt CAD IV With the Shockwave Coronary IVL System; CI = confidence interval.

and stent thrombosis events have been described previously (23,24).

SUBGROUP ANALYSIS. Freedom from 30-day MACE and procedural success with ≤30% residual stenosis were lower in patients with lesion lengths ≥25 mm versus <25 mm (freedom from 30-day MACE, 90.0% vs. 94.6% [p = 0.03]) and bifurcation lesions (freedom from 30-day MACE, 88.9% vs. 94.3% [p = 0.03]; procedural success, 88.9% vs. 93.8% [p = 0.05]). No differences in 30-day MACE (Figure 3) or procedural success were observed among any other subgroup analyzed (Figure 4).

PREDICTORS OF 30-DAY MACE AND PROCEDURAL SUCCESS. Predictors of 30-day MACE and procedural success are shown in Table 5. By multivariate logistic regression, prior MI (odds ratio [OR]: 2.06; 95% CI: 1.01 to 4.06; p = 0.04) and treatment of bifurcation

TABLE 4 Angiographic Outcomes, Core Laboratory Assessed (N = 628)

Post-IVL angiographic outcomes*	
Acute gain, mm	0.82 ± 0.48
Minimum luminal diameter, mm	1.89 ± 0.48
Residual diameter stenosis, %	35.4 ± 13.0
Final in-segment angiographic outcomes	
Acute gain, mm	1.48 ± 0.48
Minimum luminal diameter, mm	2.54 ± 0.47
Residual diameter stenosis, %	16.4 ± 8.3
<50%	99.4 (98.6-99.9)
≤30%	95.7 (94.0-97.3)
Final in-stent angiographic outcomes†	
Acute gain, mm	1.68 ± 0.47
Minimum luminal diameter, mm	2.75 ± 0.44
Residual diameter stenosis, %	12.1 ± 6.8
<50%	100.0 (99.4-100.0)
≤30%	98.9 (97.7-99.6)

Values are mean ± SD or % (95% confidence interval). *N = 555; post-IVL angiographic data capture was not required per protocol in the Disrupt CAD studies. †N = 625 for final in-stent angiographic outcomes.

IVL = intravascular lithotripsy.

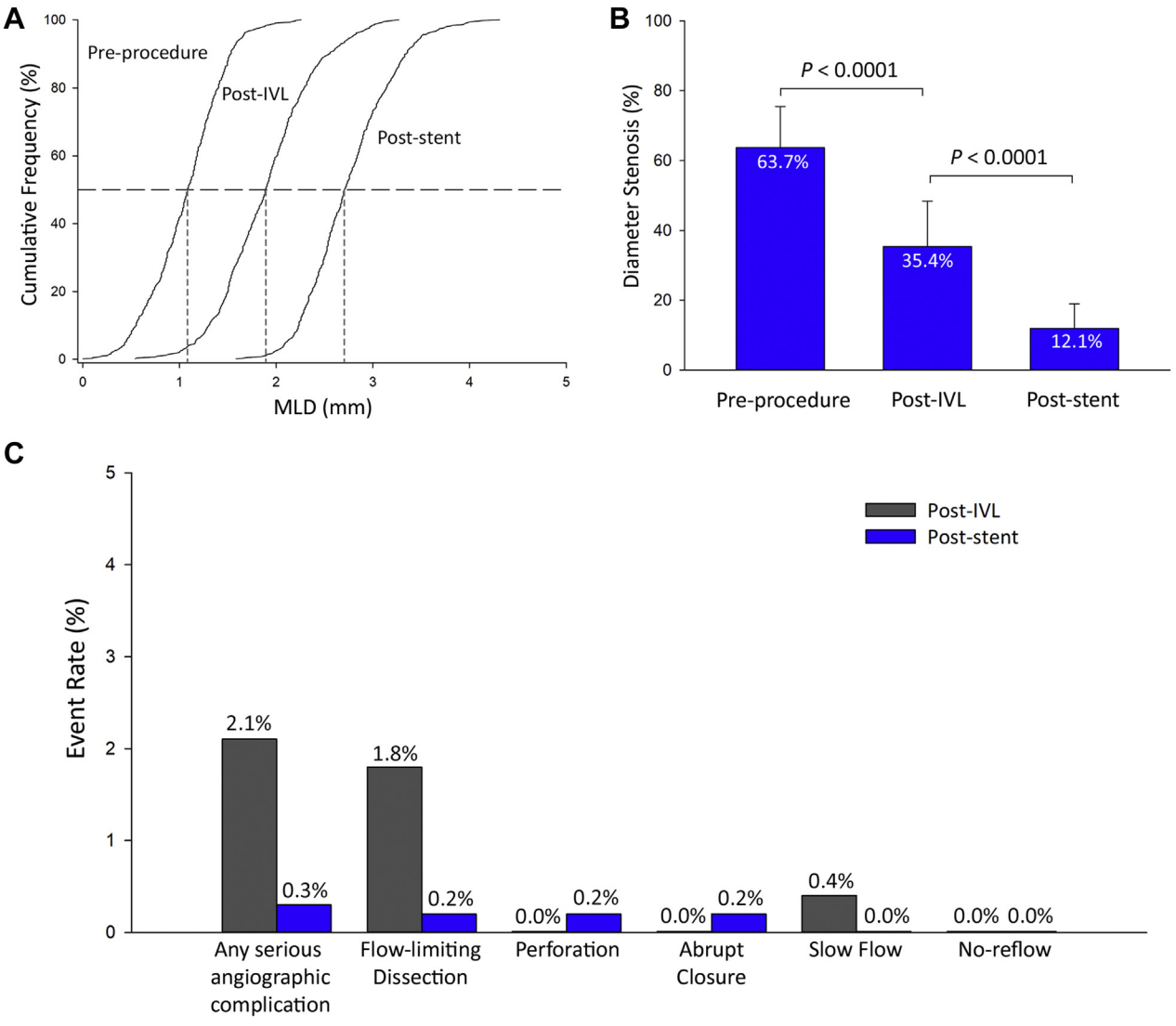
lesions (OR: 2.41; 95% CI: 1.27 to 4.54; p = 0.006) and longer lesions (OR per 10 mm: 1.31; 95% CI: 1.00 to 1.69; p = 0.049) were independent predictors of 30-day MACE, while prior MI (OR: 0.45; 95% CI: 0.24 to 0.88; p = 0.016) and treatment of bifurcation lesion (OR: 0.47; 95% CI: 0.25 to 0.87; p = 0.015) were predictors of lack of procedural success.

DISCUSSION

The present pooled individual patient data analysis from the 4 Disrupt CAD studies represents the largest systematic assessment to date of IVL treatment in de novo, severely calcified coronary arteries to facilitate and optimize target lesion preparation prior to stent implantation. The major findings of this analysis are as follows: 1) IVL prior to coronary stent implantation was safe, with relatively low rates of in-hospital and 30-day MACE given the complexity of the target lesions undergoing PCI; 2) IVL was effective in achieving high procedural success rates with consistency of treatment effect across most subgroups analyzed; and 3) prior MI, bifurcation target lesions, and longer lesion length were associated with increased MACE rates and lower rates of procedural success. Importantly, despite the early learning curve of IVL use in the multiple operators, centers, and countries participating in these studies, as well as the complexity of the lesions and vessels treated, IVL device safety was consistently demonstrated. Indeed, rates of MACE in-hospital and to 30 days in this complex lesion cohort were low compared with prior studies (3–7) and were driven largely by the incidence of peri-procedural non-Q-wave MI as defined by a low but similar threshold (>3 times the upper reference limit for creatine kinase-MB) across trials. Both independent adjudication of patient-level data and size of the present analysis lend credibility to the low event rates observed. Furthermore, these low in-hospital and 30-day event rates were achieved despite the fact that 97% of all target lesions treated were classified as severely calcified by an independent angiographic core laboratory. Indeed, the average target lesion and calcified vessel segment lengths (24.4 ± 11.5 mm and 41.5 ± 20.0 mm, respectively) for the pooled analysis population are among the longest reported for any PCI trial to date (4,18,27,28). Given the known procedural complications of atheroablative technologies in heavily calcified coronary arteries (4,18,28), the absence of vessel perforation, abrupt coronary closure, and no-reflow events following calcium modification by IVL is particularly noteworthy.

The very low rates of serious angiographic complications are consistent with IVL's mechanism of action, which involves circumferential and longitudinal multiplane calcium fracture in situ without the generation of atheroembolic debris and/or significant heat energy. The acoustic energy delivery of IVL is circumferential and is not affected by wire bias or device size, in contrast to other atheroablative technologies. In severely calcified lesions, IVL improves vessel compliance, mitigating the need for aggressive high-pressure balloon dilatation prior to stent delivery, with its associated potential for barotrauma and severe dissection. This unique mechanism of action is reflected by the significant improvements observed by quantitative coronary angiography in minimal luminal diameter (MLD) and percentage diameter stenosis after IVL alone despite an average peak IVL balloon pressure of only 6 atm. Moreover, post-IVL dilatation prior to stent delivery was performed at the operator's discretion and was not used in the vast majority of patients (83.2%). Nonetheless, stent delivery was successful in 99.5% of patients. In addition, the safety and effectiveness of IVL were not appreciably affected by use proficiency, despite a limited number of "roll-in" cases (1 per center) and the limited prior operator experience with IVL (24). This is in sharp contrast with the training required and the "learning curve" evident during early operator experience with atheroablative technologies. This observation likely reflects the fact

FIGURE 2 Procedural Angiographic Outcomes Following IVL Treatment

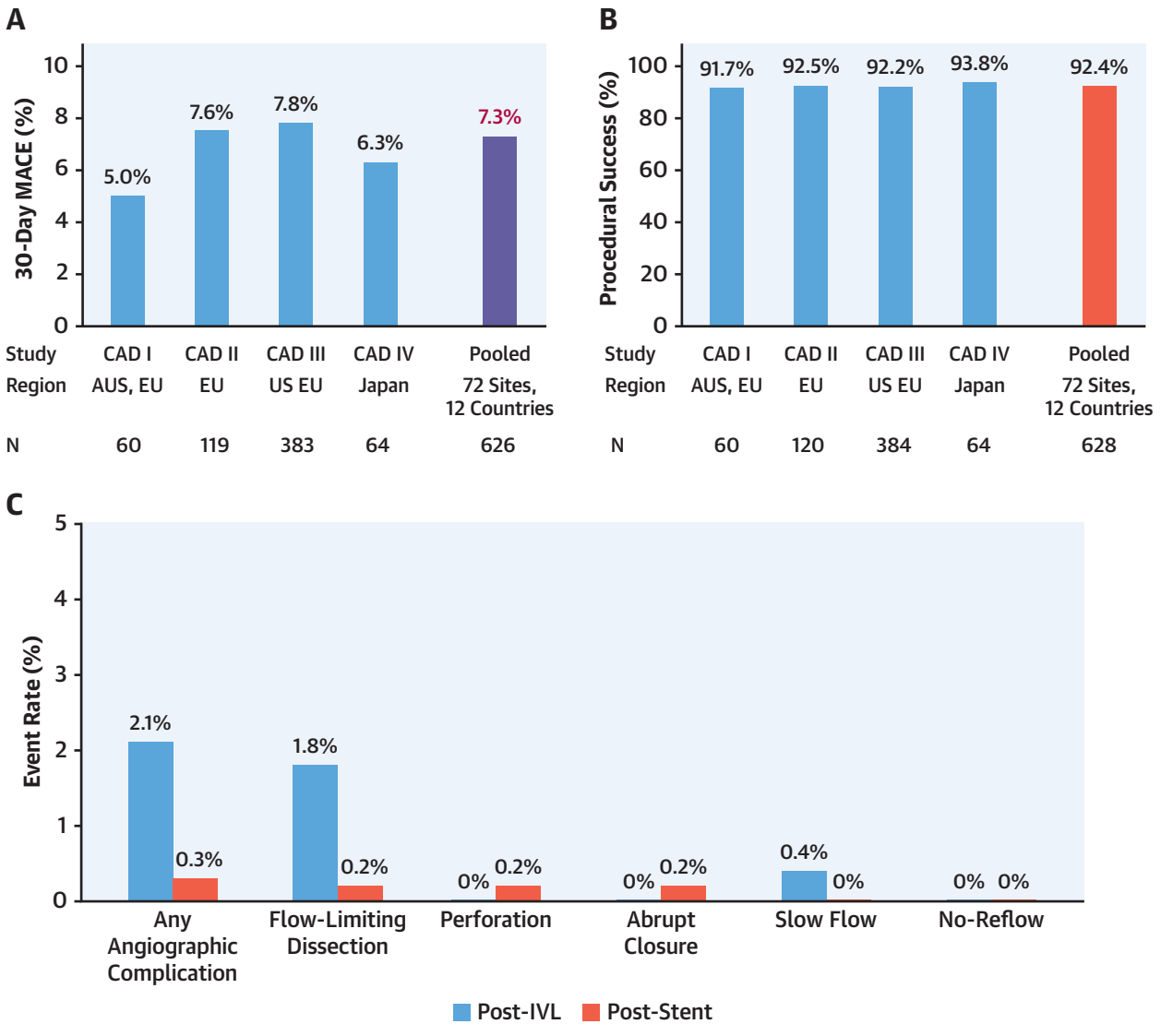


Core laboratory–assessed minimum luminal diameter cumulative frequency curves **(A)** demonstrate an increase in minimal luminal diameter (MLD) immediately following intravascular lithotripsy (IVL) treatment with further increase post-stent. Core laboratory–assessed diameter stenosis **(B)** demonstrates a significant decrease in diameter stenosis immediately following IVL treatment ($p < 0.0001$) and post-stent ($p < 0.0001$). For MLD and diameter stenosis measurements, pre-procedure n = 625, post-IVL n = 555, and post-stent n = 625. Post-stent assessments of MLD and diameter stenosis include post-dilatation in 94.1% of patients. Note that post-IVL angiographic imaging was not required in the Disrupt CAD studies. Core laboratory assessment of serious angiographic complications **(C)** immediately following IVL treatment (n = 561) and post-stent (n = 628) demonstrated a low rate of flow-limiting dissections (grade D or greater) with no perforation, abrupt closure, or no-reflow events following IVL treatment. Diameter stenosis values are mean and SD **(error bars)**.

that IVL involves the most basic of interventional technologies (i.e., a balloon catheter) for a delivery system, which minimizes the impact of learned technical proficiency.

The present large, patient-level data analysis expands and extends prior clinical experience with IVL, enables credible subgroup analysis, and facilitates multivariate assessment of predictors of success. In this regard, IVL's treatment effect benefit, relative to atheroablation, was evident regardless of age and the presence of diabetes mellitus or chronic kidney disease (29–31). The present analysis confirms the previously established relationship between target lesion length, bifurcation involvement, and history of

CENTRAL ILLUSTRATION **Safety and Effectiveness of Intravascular Lithotripsy Across the Disrupt CAD Studies**



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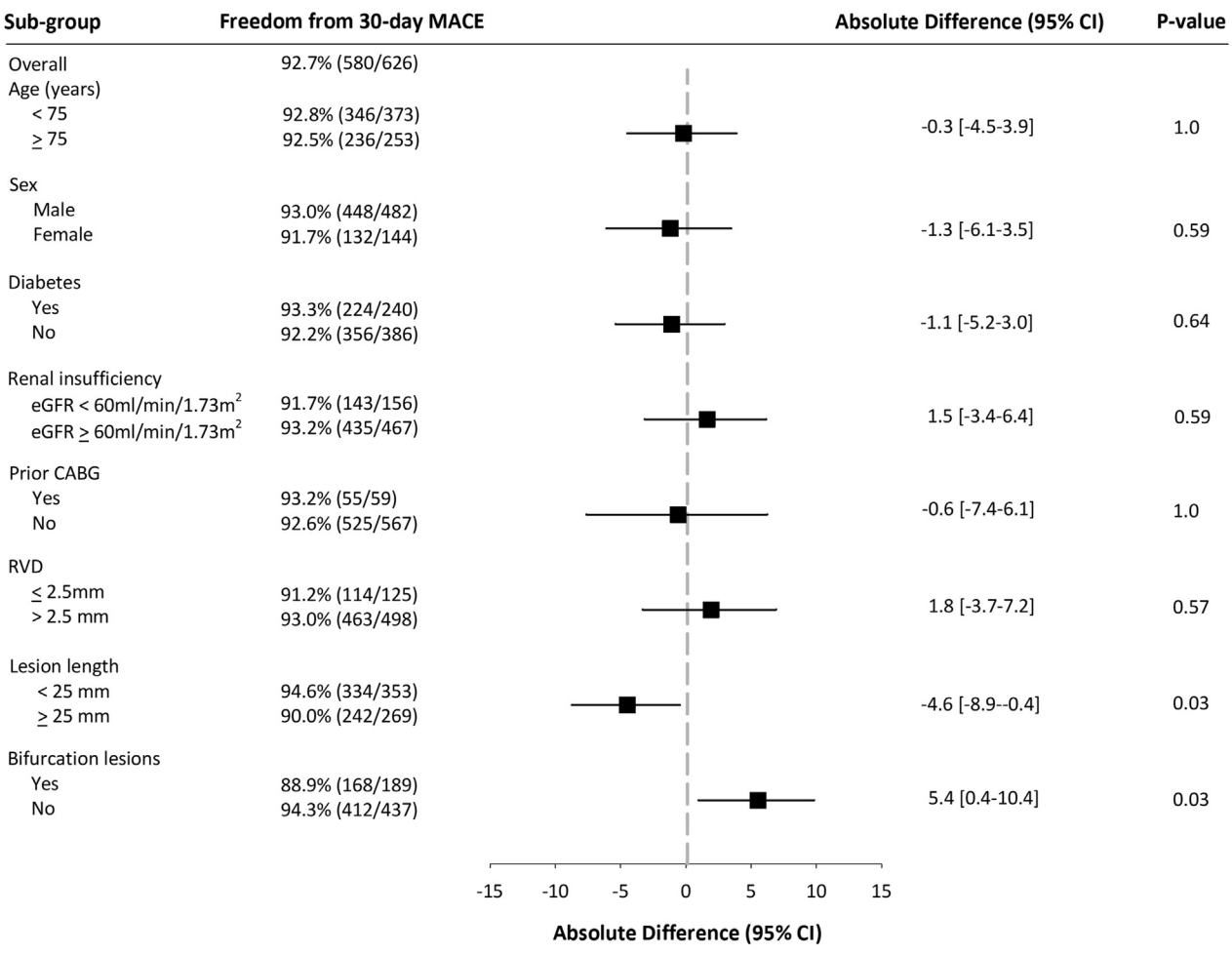
Disrupt CAD major adverse cardiovascular event (MACE) rates at 30 days **(A)** and procedural success **(B)**, defined as successful stent delivery with in-stent residual stenosis ≤30% (core laboratory assessed) without in-hospital MACE, demonstrated consistent outcomes among the individual Disrupt CAD studies. Heterogeneity among studies was evaluated using logistic regression with study as a fixed effect. All p values were not statistically significant, indicating consistency across the 4 studies for 30-day MACE ($p = 0.56$) and procedural success ($p = 0.84$). Pooled core laboratory assessment of serious angiographic complications **(C)** immediately following intravascular lithotripsy (IVL) treatment ($n = 561$) and post-stent ($n = 628$) demonstrated a low rate of flow-limiting dissections (grade D or greater) with no perforation, abrupt closure, or no-reflow events following IVL treatment. AUS = Australia; EU = Europe; IVL = intravascular lithotripsy; U.S. = United States.

prior MI with higher MACE rates following PCI (including atheroablative procedures) and thus may provide guidance regarding patient selection and procedural planning. These readily available clinical and angiographic variables were also independent predictors of IVL effectiveness (procedural success) and should be considered in shared decision-making discussions with patients. Not surprisingly, these

FIGURE 3 **Subgroup Analyses for the Primary Safety Endpoint of Freedom From 30-Day MACE**



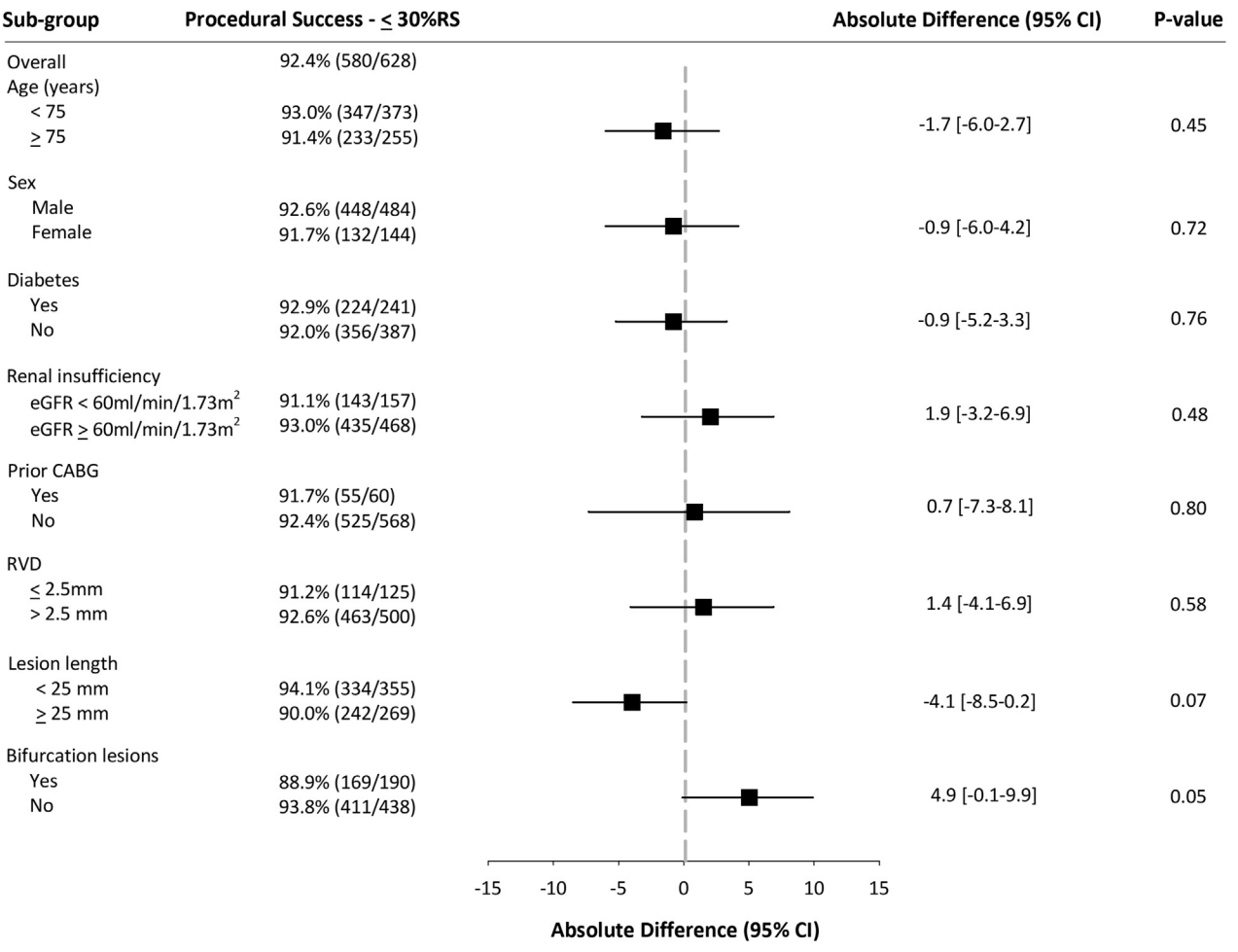
Significant differences in 30-day MACE were observed in the longer lesion length and bifurcation lesion subgroups. No differences in 30-day MACE were observed in all other subgroups. Dichotomization for age, renal insufficiency, reference vessel diameter (RVD), and lesion length were selected on the basis of clinically relevant thresholds. CABG = coronary artery bypass graft surgery; eGFR = estimated glomerular filtration rate; other abbreviations as in Figure 1.

same variables have demonstrated prognostic importance for safety and effectiveness of PCI with stent implantation, with or without adjunctive atheroablation (32–34).

The present analysis provides additional important observations that are pertinent to PCI of severely calcified vessels. Both the frequency of transradial access (TRA) and the high procedural safety may favorably affect the short (median, 1 day; interquartile range, 0.0 days) length of hospital stay observed in this pooled experience. The apparent relative ease of IVL using TRA (~63% of all procedures recorded) despite the initial and early experience is noteworthy, as prior clinical observations have suggested that TRA is associated with fewer bleeding complication events following PCI (compared with transfemoral access) (35,36). In context of the few severe angiographic complications and low in-hospital MACE rates following IVL observed in this pooled experience, TRA plus IVL may be a particularly synergistic combination.

STUDY LIMITATIONS. First, although all 4 Disrupt CAD studies were carefully conducted with independent core laboratory and clinical events committee adjudication, they were all single-arm studies lacking a concurrent control population. The lack of a randomized comparator precludes definitive comparisons with balloon-based (scoring, cutting, noncompliant) or atheroablative (rotational or orbital

FIGURE 4 Subgroup Analyses for Procedural Success With ≤ 30% RS



Significant difference in procedural success was observed in the bifurcation lesion subgroup. No differences in procedural success were observed in all other subgroups. Dichotomization for age, renal insufficiency, RVD, and lesion length were selected on the basis of clinically relevant thresholds. RS = residual stenosis; other abbreviations as in Figures 1 and 3.

atherectomy, laser) techniques for PCI of severely calcified vessels.

Second, substudy data from intravascular imaging by optical coherence tomography that provides insights to the proposed IVL mechanism of action are not provided in the present clinical report. Pooled analysis of this experience is ongoing and will be the focus of a future report. Nevertheless, adequate intravascular imaging data have been reported from the individual trials to support the premise of in situ circumferential and longitudinal multiplane calcium fracture with fracture expansion following stent implantation as the dominant mechanism of vascular calcium modification by IVL (24,25,37). These reports have documented high values for post-procedure percentage stent expansion and minimal stent area measured by optical coherence tomography, which may favorably affect long-term TLF rates.

Third, the safety and effectiveness of IVL demonstrated in the present analysis are applicable to the patient cohort studied and may not be generalizable to "all comers" with severe coronary calcification and do not apply to the routine treatment of moderately calcified lesions. Indeed, specific clinical (acute coronary syndromes) and angiographic target lesion subsets (ostial, left main, nondilatable lesions, bypass graft, in-stent restenosis, lesion length >40 mm, etc.) were not included in this analysis. In addition, as the

combined use of IVL with atheroablative technologies was excluded from the Disrupt CAD studies, further investigation is needed to understand the potential complementary utility of these technologies. Data from the "real world" experience will be acquired with the forthcoming U.S. post-market study to address these study limitations.

Finally, ongoing follow-up will determine whether the favorable short-term results of IVL in severely calcified lesions confer long-term event-free survival.

CONCLUSIONS

The present Disrupt CAD pooled individual patient data analysis represents the largest cohort of patients treated with IVL as an adjunct to stent implantation in severely calcified coronary arteries. This analysis demonstrates both safety (low rates of in-hospital and 30-day MACE, low rates of severe angiographic complications) and effectiveness (high rates of procedural success) of IVL when applied for this indication. Multivariate analysis identified clinical (history of MI) and target lesion-specific (lesion length ≥25 mm, bifurcation lesion) variables to be significant independent predictors of MACE and lack of procedural success in this patient group.

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Dr. Kereiakes is a consultant for SINO Medical Sciences Technologies, Boston Scientific, Elixir Medical, Svelte Medical Systems, Caliber Therapeutics/Orchestra BioMed, and Shockwave Medical; and is a stockholder in Ablative Solutions. Dr. Riley has received honoraria from Boston Scientific, Asahi Intecc, and Medtronic. Dr. Di Mario has received research grants from Amgen, Behring, Chiesi, Daiichi-Sanyo, Edwards Lifesciences, Medtronic, Shockwave, and Volcano Philips. Dr. Shlofmitz is a speaker for Shockwave Medical. Dr. Saito is a consultant for Terumo and Japan Lifeline. Dr. Ali has received grants from the National Heart, Lung, and Blood Institute, Abbott Vascular, and Cardiovascular Systems; has received personal fees from Amgen, AstraZeneca, and Boston Scientific; and holds equity in Shockwave Medical. Dr. Price has received consulting and speaker honoraria from Abbott Vascular, Boston Scientific, Biosense Webster, Medtronic, Shockwave Medical, and W.L. Gore. Dr. Hill has received fees and grant support from Abbott Vascular, Boston Scientific, Abiomed, and Shockwave Medical; and is a stockholder in Shockwave Medical. Dr. Stone has received speaker honoraria from Cook Medical and Terumo; is a consultant for Valfix Medical, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, and CardioMech; and has equity and options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, the BioStar family of funds, SpectraWave, Orchestra BioMed, Aria, Cardiac Success, and Valfix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

TABLE 5 Independent Predictors of 30-Day MACE and Procedural Success

	OR (95% CI)	p Value
30-day MACE		
Bifurcation lesion	2.41 (1.27–4.54)	0.006
Prior MI	2.06 (1.01–4.06)	0.040
Lesion length per 10 mm	1.31 (1.00–1.69)	0.049
Procedural success*		
Bifurcation lesion	0.47 (0.25–0.87)	0.015
Prior MI	0.45 (0.24–0.88)	0.016

The independent predictors of MACE at 30 days and procedural success were determined by multivariate logistic regression using stepwise selection with a univariate threshold for entry of $p < 0.10$ and a level of significance for the final multivariate model of $p < 0.05$, adjusted by study. The following variables were entered into the models: age (75 years), sex, prior MI, lesion length per 10 mm, left ventricular ejection fraction (≥50%), diabetes, estimated glomerular filtration rate (<60 ml/min/1.73 m^2), hyperlipidemia, hypertension, prior stroke or transient ischemic attack, body mass index per 5 kg/m^2, current or former smoker, right ventricular dysfunction (>2.5 mm), bifurcation, and lesion location (LAD vs. non-LAD). *Procedural success defined as stent delivery with residual stenosis ≤30% without in-hospital MACE.

CI = confidence interval; LAD = left anterior descending coronary artery; MACE = major adverse cardiovascular event(s); MI = myocardial infarction; OR = odds ratio.

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PERSPECTIVES

WHAT IS KNOWN? Severe coronary calcification impedes stent delivery and expansion and increases adverse clinical events after PCI.

WHAT IS NEW? This Disrupt CAD pooled individual patient data analysis represents the largest cohort of patients treated with IVL as an adjunct to stent implantation in severely calcified coronary arteries. This analysis demonstrates both safety (low rates of in-hospital and 30-day MACE, low rates of severe angiographic complications) and effectiveness (high rates of procedural success) of IVL when applied for this indication across multiple geographies and operator experience. Multivariate analysis identified clinical (history of MI) and target lesion-specific (lesion length ≥25 mm, bifurcation lesion) variables to be significant independent predictors of MACE and lack of procedural success in this patient group.

WHAT IS NEXT? Ongoing clinical follow-up in the Disrupt CAD studies will determine whether the early results of IVL to facilitate stent implantation in severely calcified lesions translate into high rates of long-term event-free survival.

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KEY WORDS calcification, coronary artery disease, patient-level pooled analysis

APPENDIX For a supplemental figure, table, and references, please see the online version of this paper.