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Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease

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ABSTRACT

BACKGROUND Coronary calcification hinders stent delivery and expansion and is associated with adverse outcomes. Intravascular lithotripsy (IVL) delivers acoustic pressure waves to modify calcium, enhancing vessel compliance and optimizing stent deployment.

OBJECTIVES The purpose of this study was to assess the safety and effectiveness of IVL in severely calcified de novo coronary lesions.

METHODS Disrupt CAD III (NCT03595176) was a prospective, single-arm multicenter study designed for regulatory approval of coronary IVL. The primary safety endpoint was freedom from major adverse cardiovascular events (cardiac death, myocardial infarction, or target vessel revascularization) at 30 days. The primary effectiveness endpoint was procedural success. Both endpoints were compared with a pre-specified performance goal (PG). The mechanism of calcium modification was assessed in an optical coherence tomography (OCT) substudy.

RESULTS Patients (n = 431) were enrolled at 47 sites in 4 countries. The primary safety endpoint of the 30-day freedom from major adverse cardiovascular events was 92.2%; the lower bound of the 95% confidence interval was 89.9%, which exceeded the PG of 84.4% ($p < 0.0001$). The primary effectiveness endpoint of procedural success was 92.4%; the lower bound of the 95% confidence interval was 90.2%, which exceeded the PG of 83.4% ($p < 0.0001$). Mean calcified segment length was 47.9 ± 18.8 mm, calcium angle was 292.5 ± 76.5°, and calcium thickness was 0.96 ± 0.25 mm at the site of maximum calcification. OCT demonstrated multiplane and longitudinal calcium fractures after IVL in 67.4% of lesions. Minimum stent area was 6.5 ± 2.1 mm^2 and was similar regardless of demonstrable fractures on OCT.

CONCLUSIONS Coronary IVL safely and effectively facilitated stent implantation in severely calcified lesions. (J Am Coll Cardiol 2020;76:2635–46) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent

FDA = U.S. Food and Drug Administration

IDE = investigational device exemption

IVL = intravascular lithotripsy

MACE = major adverse cardiovascular events

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

PG = performance goal

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

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 relatively small single-arm, nonrandomized studies, which have demonstrated high rates of device success with excellent early angiographic as well as late clinical outcomes (22–24). Although these reports provide preliminary evidence for effectiveness and safety as well as insights into the mechanism of calcium modification, they are limited by a small sample size. Disrupt CAD III is a statistically powered, multicenter, single-arm study designed for U.S. regulatory approval to assess the safety and effectiveness of IVL to optimize stent deployment in patients with severely calcified de novo coronary stenoses.

SEE PAGE 2647

METHODS

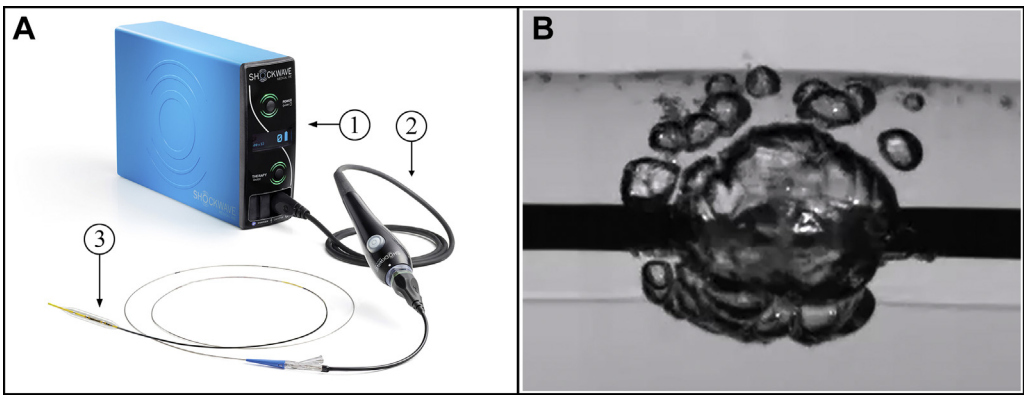
STUDY DESIGN AND OVERSIGHT. The Disrupt CAD III study design has been described previously (25). The study was performed under a U.S. Food and Drug Administration (FDA) Investigational Device Exemption (IDE), and its design was similar to the predicate approval study, ORBIT II (Orbital Atherectomy System in Treating De Novo, Severely Calcified Coronary Lesions), for orbital atherectomy (4). Study organization and participating centers are listed in Supplemental Table 1. The study protocol was approved by the Institutional Review Board at each participating center, and all patients signed written, informed consent. The sponsor funded the study and participated in site selection and management as well as data collection and analysis. 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.

STUDY POPULATION. Patients presenting with stable, unstable, or silent ischemia and severely calcified de novo coronary artery lesions undergoing PCI were eligible for enrollment. Target lesions were ≤40 mm in length with reference vessel diameters of 2.5 to 4.0 mm. Patients with acute MI and specific complex lesion features were excluded. Complete inclusion and exclusion criteria for the study are listed in Supplemental Table 2. One roll-in patient was allowed at each site to promote investigator proficiency with the IVL system and were not included in the primary analysis.

STUDY DEVICE. The Shockwave Medical (Santa Clara, California) IVL system and coronary IVL catheter and their technique for use have been described (25,26). The device 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 (**Figure 1**) (22). The coronary IVL system is delivered on a rapid exchange catheter and is available in 2.5-, 3.0-, 3.5-, and 4.0-mm diameters. Each catheter can provide up to 80 total IVL pulses and is intended for single use. IVL balloon position is adjusted with overlap to provide complete coverage of longer lesions.

STUDY PROCEDURES. Patients that signed informed consent and met study eligibility criteria were enrolled once the IVL catheter was inserted. The IVL catheter was delivered over the physicians' choice of 0.014-inch guidewire. If the catheter was unable to cross the lesion, adjunctive approaches (e.g., buddy wire, pre-dilatation with a small diameter balloon [1.5 to 2.0 mm], or guide catheter extension) were used at operator's discretion before reinsertion of the IVL catheter. Atherectomy devices and cutting/scoring balloons were not permitted per protocol.

FIGURE 1 **Shockwave IVL System**



(A) Intravascular lithotripsy (IVL) generator **(1)**, IVL connector cable **(2)**, and IVL catheter **(3)**. **(B)** IVL emitters produce an electric spark that generates a rapidly expanding vapor bubble contained within the integrated balloon while the acoustic pressure wave radiates spherically outwards, selectively modifying vascular calcium.

An appropriately sized (1:1 to reference vessel diameter) IVL balloon was inflated to 4 atm in the target lesion, and 10 IVL pulses were delivered followed by temporary balloon inflation to 6 atm. This IVL treatment was repeated until full balloon expansion was achieved with interval deflation to allow for distal perfusion. If the maximum number of 80 pulses was delivered, but lesion preparation remained incomplete (i.e., residual stenosis >50%), an additional IVL catheter could be used. IVL catheters with different diameters could also be used if significant vessel tapering occurred in the target lesion. Noncompliant balloon dilatation was performed prior to stenting in lesions with residual stenosis ≥50% following IVL. Following stent implantation, high-pressure (>16 atm) post-dilatation with a noncompliant balloon was required. Dual antiplatelet therapy (DAPT) was prescribed per current guidelines for a minimum of 6 months (27). Patients on chronic oral anticoagulation for atrial fibrillation could have abbreviated DAPT with aspirin discontinued within 30 days of PCI (oral anticoagulant and $P2Y_{12}$ receptor inhibitor maintained) (28). Post-procedure assessments were required within 12 to 24 h of the procedure or prior to discharge (if same day). Follow-up was done by clinic or telephone visit at 30 days and at 6, 12, and 24 months.

HEART RHYTHM ASSESSMENT. Reports of transient ventricular capture during IVL therapy from commercial use prompted further evaluation to assess the frequency and clinical correlates of this phenomenon (29). In consultation with the FDA, ECG and blood pressure data were collected pre-IVL, during IVL delivery, and immediately following IVL treatment to evaluate the effect of IVL treatment on heart rhythm and hemodynamics.

OCT IMAGING SUBSTUDY. Optical coherence tomography (OCT) imaging was planned in 100 patients at 3 time points (pre-IVL, post-IVL, and following stent deployment at the end of procedure) to more accurately characterize the extent of calcification and provide insights into the mechanism of IVL in facilitating stent expansion.

DATA MANAGEMENT. An independent clinical events committee adjudicated all major adverse cardiac events (MACE). Independent angiographic and OCT core laboratories (Cardiovascular Research Foundation, New York, New York) analyzed all images in accordance with the core laboratory recommended protocol. An independent data safety monitoring board reviewed data related to safety, data integrity, and overall conduct of the study on a periodic basis, and each time recommended to continue the study without modification.

STUDY ENDPOINTS. The primary safety endpoint was freedom from MACE (composite occurrence of cardiac death, MI, or target vessel revascularization [TVR]) at 30 days following the index procedure. Periprocedural MI was defined according to the predicate ORBIT II study (4) as peak post-PCI CK-MB level >3× the upper limit of normal (ULN). The primary effectiveness endpoint was procedural success defined as successful stent delivery with a residual stenosis <50% by core laboratory assessment without in-hospital MACE (25). Sensitivity analyses included

TABLE 1 Baseline Clinical Characteristics (N = 384)

Age, yrs	71.2 ± 8.6
Male	294 (76.6)
Diabetes	154 (40.1)
Hypertension	342 (89.1)
Hyperlipidemia	342 (89.1)
Prior myocardial infarction	69 (18.0)
Prior coronary artery bypass grafting	36 (9.4)
Prior stroke or TIA	29 (7.6)
Current smoker	47 (12.2)
Renal insufficiency (eGFR <60 ml/min/1.73 m^2)	101 (26.4)
Pacemaker	18 (4.7)
ICD/CRT-D	6 (1.6)
Angina classification	
Class 0	48/381 (12.6)
Class I	56/381 (14.7)
Class II	142/381 (37.3)
Class III	126/381 (33.1)
Class IV	9/381 (2.4)
Angiographic characteristic (core laboratory)	
Target vessel	
Protected left main artery	6 (1.6)
Ostial	1/6 (16.7)
Proximal	0/6 (0.0)
Mid	1/6 (16.7)
Distal	4/6 (66.7)
Left anterior descending artery	217 (56.5)
Ostial	1/215 (0.5)
Proximal	114/215 (53.0)
Mid	56/215 (26.0)
Distal	44/215 (20.5)
Circumflex artery	49 (12.8)
Ostial	11/49 (22.5)
Proximal	22/49 (44.9)
Mid	11/49 (22.5)
Distal	5/49 (10.2)
Right coronary artery	112 (29.2)
Ostial	0/111 (0.0)
Proximal	31/111 (27.9)
Mid	53/111 (47.7)
Distal	27/111 (24.3)
Reference vessel diameter, mm	3.03 ± 0.47 [381]
Minimum lumen diameter, mm	1.06 ± 0.36 [381]
Diameter stenosis, %	65.1 ± 10.8 [381]
Lesion length, mm	26.1 ± 11.7 [381]
Calcified length, mm	47.9 ± 18.8
Severe calcification*	384 (100.0)
Bifurcation lesion with side branch involvement	115 (29.9)

Values are mean ± SD, n (%), n/N (%), or mean ± SD [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 formula; ICD/CRT-D = implantable cardiac-defibrillator with or without biventricular pacing capability; TIA = transient cerebral ischemic event.

procedural success using a residual stenosis threshold of ≤30% and 30-day MACE using contemporary MI definitions (30,31). Detailed endpoint definitions and pre-specified secondary endpoints are listed in Supplemental Table 3.

STATISTICAL ANALYSIS. The statistical methodology has been described (25). Both primary safety and effectiveness endpoints were based on the ORBIT II study that enrolled a similar patient population with similar primary endpoints and definitions and used an objective performance goal (PG) (4,5). A relative risk (RR) of 1.5 was required consistent with predicate device studies (32). The primary safety PG was thus set at 84.4% (100% less 1.5× the observed MACE rate of 10.4% in ORBIT II), and the primary effectiveness PG was set at 83.4% (100% less 1.5× the observed procedural failure rate of 11.1% in ORBIT II).

The overall sample size for Disrupt CAD III was based on the primary safety endpoint. The endpoint was met if the 1-sided lower 95% confidence limit was greater than the PG (25). Assuming that actual freedom from MACE at 30 days was 89.6% (as observed in ORBIT II) with 5% attrition, a sample size of 392 patients would provide 90% power to meet the PG with a 1-sided type 1 error of 5% (i.e., accounting for attrition, a minimum sample size of 372 patients with 30-day follow-up was required) (4). For the primary effectiveness endpoint, assuming the actual procedure success rate was 88.9% (as observed in ORBIT II) (4) and 5% attrition, a sample size of 360 patients would provide 90% power to meet the PG with a 1-sided type 1 error of 5% (33). Thus, the study had at least 81% power to meet both coprimary endpoints and would be deemed successful only if both primary safety and effectiveness endpoints were met.

Primary analysis was performed on the intent-to-treat population consisting of all enrolled patients regardless of treatment, excluding roll-in patients. Patients who experienced MACE within 30 days or were event-free with adequate 30-day follow-up were included in the primary safety endpoint analysis. For the primary effectiveness endpoint, patients with missing data required to define procedural success were excluded from the primary analysis. The safety analysis dataset consisted of all enrolled patients including roll-in patients. Missing endpoint data were not imputed for the primary safety and effectiveness analyses. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND PROCEDURES. From January 9, 2019, to March 27, 2020, 431 patients were enrolled at 47 sites in 4 countries (United States, United Kingdom, France, and Germany). Among these were 47 roll-in patients, leaving 384 patients in the intention-to-treat dataset for the primary and secondary endpoint analyses (Supplemental Figure 1).

TABLE 2 Procedural Details (N = 384)

Total procedure time, min	53.0 (38.0, 74.0)
Fluoroscopy time, min	15.0 (11.0, 24.0)
Contrast volume, ml	167.9 ± 71.9
Access	
Radial	227 (59.1)
Femoral	154 (40.1)
Brachial	2 (0.5)
Ulnar	1 (0.3)
Pre-dilatation	212 (55.2)
Patients undergoing IVL	377/384 (98.2)
Maximum pre-dilatation balloon size, mm	2.1 ± 0.3
Maximum IVL inflation pressure,* atm	6.0 ± 0.3
Number of lithotripsy catheters	1.2 ± 0.5
Number of pulses	68.8 ± 31.9
Post-IVL dilatation	78/377 (20.7)
Stent delivery	381 (99.2)
Number of stents implanted	1.0 (1.0, 2.0)
0	3 (0.8)
1	289 (75.3)
2	85 (22.1)
3	7 (1.8)
Post-stent dilatation	377/381 (99.0)
Total stent length, mm	31.0 ± 12.0
Duration of hospitalization, days	1.0 (0.0, 1.0)

Values are median (Q1, Q3), mean ± SD, or n (%). *Intravascular lithotripsy (IVL) pulses were delivered at a balloon pressure of 4 atm; maximum IVL inflation pressure occurred post-IVL pulse delivery.

Baseline clinical and angiographic characteristics are presented in **Table 1**. Most patients were men with a high prevalence of cardiovascular risk factors. Mean baseline reference vessel diameter was 3.0 ± 0.5 mm, with lesion length of 26.1 ± 11.7 mm and total calcified length (which could extend beyond the margins of the lesion) of 47.9 ± 18.8 mm. Severe calcification by core lab assessment was present in all lesions and 29.9% had side branch involvement. Procedural data are shown in **Table 2**. Target lesion pre-dilatation was performed in 55.2% of procedures, while extension catheters and buddy wires were used in 16.7% and 2.9% of cases, respectively. IVL delivery occurred in 98.2% of procedures with a mean of 68.8 ± 31.9 IVL pulses delivered. Balloon post-dilatation was performed after IVL in 20.7% of cases and following stent implantation in 99.0% of procedures.

PRIMARY SAFETY AND EFFECTIVENESS ENDPOINTS. The primary safety endpoint (freedom from 30-day MACE) was achieved in 92.2% of patients. The 1-sided lower bound of the 95% confidence interval (CI) exceeded the PG (89.9% vs. 84.4%; $p < 0.0001$), thus meeting the primary safety endpoint (**Figure 2A**).

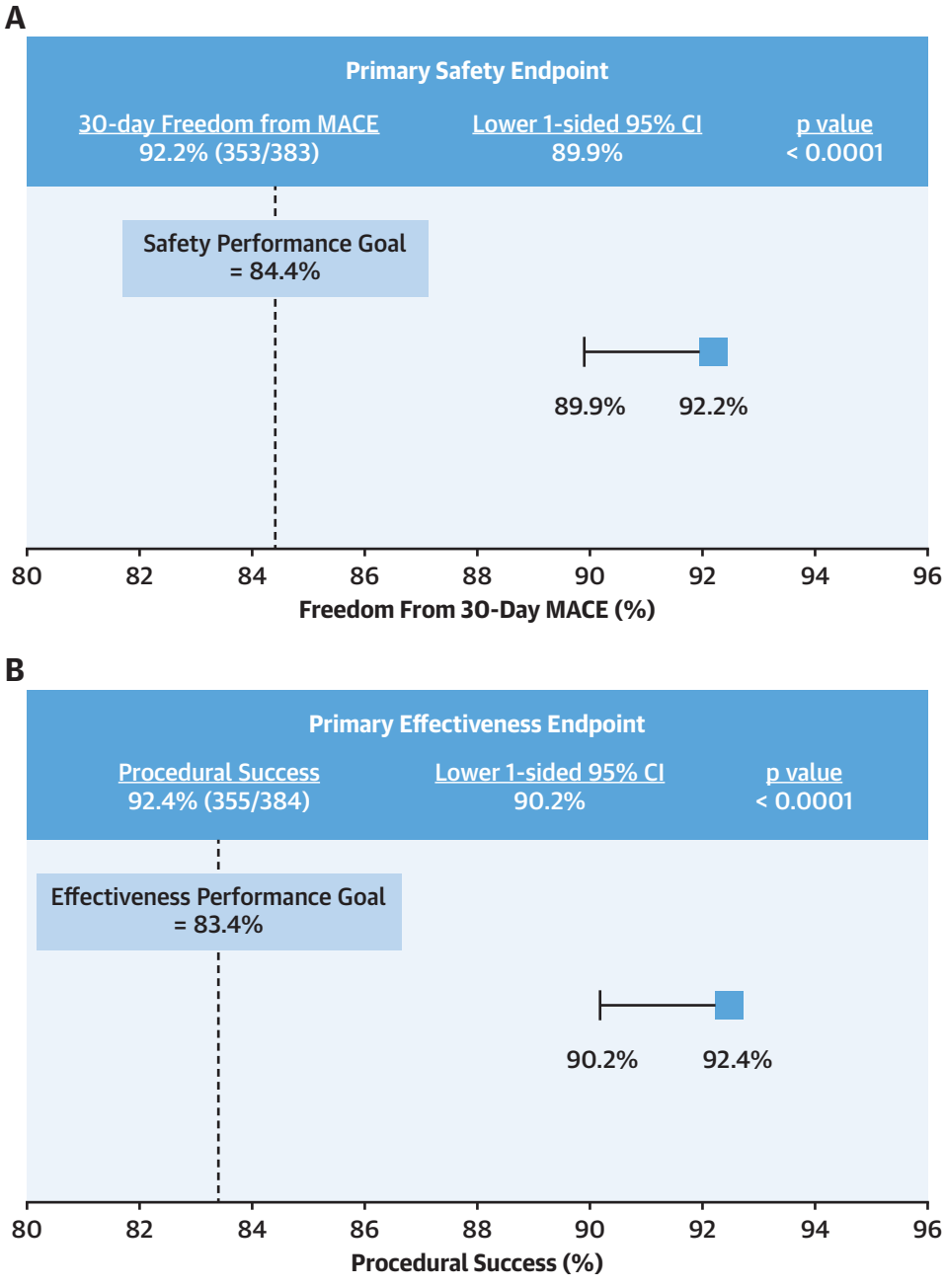
The primary effectiveness endpoint (stent delivery with a residual stenosis <50% without in-hospital MACE) was achieved in 92.4% of patients. The 1-sided lower bound of the 95% CI exceeded the PG (90.2% vs. 83.4%; $p < 0.0001$), thus meeting the primary effectiveness endpoint (**Figure 2B**). Successful stent delivery, <50% in-stent residual stenosis, and freedom from in-hospital MACE occurred in 99.2%, 100%, and 93.0% of patients, respectively. Individual components of in-hospital MACE are presented in **Table 3**.

Subgroup analyses for the primary safety and effectiveness endpoints appear in Supplemental Figures 2 and 3. Both outcome measures were consistent across 8 clinical and angiographic subgroups.

SECONDARY CLINICAL ENDPOINTS. MACE and target lesion failure (TLF) through 30 days occurred in 7.8% and 7.6% of patients, respectively, and was primarily driven by target vessel MI (**Table 3**). There were 2 deaths (0.5%) within 30 days. One death occurred prior to hospital discharge (post-operative day [POD] 9) following emergency CABG required for abrupt coronary closure associated with a complicated and unsuccessful DES delivery. A second death occurred after discharge on POD 6 due to ST-segment elevation MI complicated by cardiogenic shock due to target vessel, nontarget lesion thrombosis distal to the stent. Further details of the cardiac deaths are included in Supplemental Table 4. Protocol-defined peri-procedural MI occurred in 26 patients (6.8%). Sensitivity analyses using alternative peri-procedural MI definitions resulted in a similar rate using the Fourth Universal Definition (7.3%) (30), and a lower rate using the Society for Cardiac Angiography and Interventions definition of a clinically relevant MI (2.6%) (31). Stent thrombosis (Academic Research Consortium definite or probable) occurred in 3 (0.8%) patients within 30 days, on PODs 6, 7, and 21; all were associated with known predictors of stent thrombosis including stent underexpansion and midstent filling defect (Supplemental Table 5). Angina class was significantly improved with the percentage of patients reporting Class 0 angina (asymptomatic) increasing from 12.6% at baseline to 72.9% at 30 days (Supplemental Table 6).

ANGIOGRAPHIC OUTCOMES. Post-procedural quantitative coronary angiography (QCA) measures and procedural angiographic complications are shown in **Table 4**, and cumulative frequency distribution curves are shown in Supplemental Figure 4. Post-procedural in-stent residual stenosis <50% was achieved in 100%, and ≤30% was achieved in 99.5% of lesions. Final in-stent residual stenosis was 11.9 ± 7.1% and acute gain was 1.7 ± 0.5 mm. Serious angiographic complications were observed in 2 patients (0.5%) at the end of the procedure (**Table 4**). Freedom from any serious angiographic complication

FIGURE 2 Primary Safety and Effectiveness Endpoints Compared With Their Performance Goals



(A) The primary safety endpoint was freedom from 30-day major adverse cardiovascular events (MACE), defined as cardiac death, myocardial infarction, or target vessel revascularization. The rate of the primary safety endpoint was 92.2% with a 1-sided lower 95% confidence interval (CI) of 89.9%, which was greater than the pre-defined performance goal of 84.4% ($p < 0.0001$). **(B)** The primary effectiveness endpoint was procedural success, defined as successful stent delivery with a residual stenosis <50% by angiographic core laboratory analysis without in-hospital MACE. The rate of the primary effectiveness endpoint was 92.4% with a 1-sided lower 95% CI of 90.2%, which was greater than the pre-defined performance goal of 83.4% ($p < 0.0001$). Thus, both the primary safety and effectiveness endpoints were met.

immediately following IVL delivery and at any time point during the procedure were 97.4% and 96.9%, respectively (Supplemental Table 7).

HEART RHYTHM ASSESSMENT. Heart rhythm assessment was performed using the safety analysis dataset (n = 416 evaluable assessments). IVL-induced capture was noted during IVL in 41.1% of cases (Supplemental Table 8). Decreased systolic blood pressure during the IVL procedure was more frequent in patients with IVL-induced capture compared to those without (40.5% vs. 24.5%; p = 0.0007). However, the magnitude of the drop in systolic blood pressure was similar between the 2 groups (p = 0.07). IVL-induced capture did not result in sustained ventricular arrhythmias during or immediately after the IVL procedure in any patient and was not associated with adverse events. Sustained ventricular tachycardia occurred in 1 patient after pre-dilatation, prior to IVL treatment, and was not associated with IVL-induced capture. Multivariable Cox regression analysis identified heart rate ≤60 beats/min, male sex, and total number of IVL pulses delivered as independent predictors of IVL-induced capture (Supplemental Table 9).

OCT SUBSTUDY. A total of 100 patients were enrolled in the OCT substudy. The pre-procedure minimal lumen area (MLA) was 2.2 ± 0.8 mm^2 with percent area stenosis of 72.4 ± 11.6%. Severe lesion calcification was confirmed: the calcium angle was 292.5 ± 76.5° and calcium thickness was 0.96 ± 0.25 mm at the site of maximum calcification (**Table 5**). The minimum calcium angle that resulted in calcium fracture after IVL treatment was 192.3° ± 67.0°. After IVL treatment and stent implantation, the minimum stent area (MSA) was 6.5 ± 2.1 mm^2, area stenosis decreased to 21.9 ± 18.9% (p < 0.001), and final stent expansion was 78.4 ± 25.8% at the site of MSA (101.7 ± 28.9% at the site of maximum calcification). Calcium fractures were identified after IVL in 67.4% of lesions with multiple fractures observed in 67.7% of these cases. Calcium fractures were circumferentially distributed and were observed in multiple longitudinal planes. Minimum stent area, area stenosis, and stent expansion were similar regardless of calcium fracture identification by OCT (MSA: fracture [6.3 ± 2.1 mm^2], no fracture [6.8 ± 2.1 mm^2]; p = 0.26; area stenosis: fracture [22.4 ± 19.1%], no fracture [20.9 ± 18.7%]; p = 0.72; and stent expansion: fracture [100.3 ± 29.8%], no fracture [104.9 ± 26.9%]; p = 0.49). The percentage of lesions with calcium fractures and the maximum calcium fracture depth were similar between post-IVL and post-stent images; however, the maximum fracture width increased following stent expansion (from 0.55 ± 0.45 mm after IVL to 1.32 ± 1.04 mm after stent implantation; p < 0.001). An example of calcium fracture and stent expansion after IVL is shown in the **Central Illustration**.

TABLE 3 Primary and Secondary Endpoints (N = 384)

In-hospital MACE	27 (7.0)
Cardiac death	1 (0.3)
All myocardial infarction	26 (6.8)
Non-Q-wave myocardial infarction	22 (5.7)
Q-wave myocardial infarction	4 (1.0)
Target vessel revascularization	2 (0.5)
30-day MACE	30/383 (7.8)
Cardiac death	2/383 (0.5)
All myocardial infarction	28/383 (7.3)
Non-Q-wave*	23/383 (6.0)
Q-wave*	6/383 (1.6)
Target vessel revascularization	6/383 (1.6)
Secondary endpoints	
Device crossing success†	368 (95.8)
Angiographic success (with residual stenosis <50%)‡	370 (96.4)
Angiographic success (with residual stenosis ≤30%)‡	369 (96.1)
Procedural success (with residual stenosis ≤30%)§	354 (92.2)
All-cause death at 30 days	2 (0.5)
Cardiac	2 (0.5)
Noncardiac	0 (0.0)
Vascular	0 (0.0)
Target lesion failure at 30 days	29 (7.6)
Cardiac death	2 (0.5)
TV-MI	28 (7.3)
ID-TLR	5 (1.3)
Myocardial infarction (protocol-defined)	28 (7.3)
TV-MI	28 (7.3)
Peri-procedural MI (protocol-defined)	26 (6.8)
Nonprocedural MI	4 (1.0)
Peri-procedural MI (Fourth Universal Definition type 4a)	28 (7.3)
Peri-procedural MI (Society for Cardiac Angiography and Interventions definition)	10 (2.6)
All revascularization at 30 days	10 (2.6)
Target vessel	6 (1.6)
ID-TVR	6 (1.6)
ID-TLR	5 (1.3)
Non-ID-TVR	0 (0.0)
Non-ID-TLR	0 (0.0)
Nontarget vessel	6 (1.6)
Stent thrombosis (definite or probable)	3 (0.8)
Definite	3 (0.8)
Probable	0 (0.0)

Values are n (%) or n/N (%). *1 patient had 2 events; 1 Q-wave and 1 non-Q-wave MI. †Device crossing success defined as delivery of the IVL catheter across the target lesion and delivery of lithotripsy without serous angiographic complications immediately after IVL. ‡Angiographic success defined as stent delivery with <50% or ≤30% residual stenosis and without serious angiographic complications. §Procedural success defined as successful stent delivery with ≤30% residual stenosis and without in-hospital MACE.

ID = ischemia-driven; MACE = major adverse cardiovascular events; MI = myocardial infarction; TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization.

DISCUSSION

The Disrupt CAD III study evaluated the utility of IVL for lesion preparation of severely calcified coronary

TABLE 4 Core Laboratory-Assessed Angiographic Outcomes (N = 384)

Final in-segment angiographic outcomes	
Acute gain, mm	1.41 ± 0.48
Minimum lumen diameter, mm	2.47 ± 0.45
Residual diameter stenosis, %	17.8 ± 8.8
<50%	381/383 (99.5)
≤30%	363/383 (94.8)
Final in-stent angiographic outcomes	
Acute gain, mm	1.68 ± 0.46
Minimum lumen diameter, mm	2.74 ± 0.43
Residual diameter stenosis, %	11.9 ± 7.1
<50%	381/381 (100.0)
≤30%	379/381 (99.5)
Final serious angiographic complications*	2 (0.5)
Severe dissection (Type D-F)†	1 (0.3)
Perforation‡	1 (0.3)
Abrupt closure†	1 (0.3)
Slow flow	0 (0.0)
No-reflow	0 (0.0)

Values are mean ± SD, n/N (%), or n/(%). *Serious angiographic complications include severe dissection (Type D-F), perforation, abrupt closure, slow flow, and no-reflow. †Patient had a Type F dissection and resulting abrupt closure after guidewire and PTCA which ultimately led to failed stent delivery. The patient experienced a MACE and expired on POD 9. ‡Core laboratory assessed class II perforation post-stent that was treated with post-dilatation at the proximal stent location; the patient remained stable with no ECG changes and no evidence of pericardial effusion via serial follow-up echocardiograms. The patient was discharged the following day and was MACE-free at 30 days.

ECG = electrocardiogram; POD = post-operative day; PTCA = percutaneous balloon angioplasty.

stenoses prior to stent implantation. The major findings of this investigation are as follows: 1) treatment with coronary IVL met the primary safety and effectiveness endpoints of the study; 2) coronary IVL prior to DES implantation was well tolerated with a low rate of major peri-procedural clinical and angiographic complications; 3) transient IVL-induced left ventricular capture occurred frequently, but was benign with no lasting sequelae in any patient; and 4) OCT demonstrated multiplane and longitudinal calcium fractures after IVL in 67.4% of lesions, with excellent stent expansion in those with and without calcium fractures identified by OCT despite the marked severity of the calcified lesions treated.

Disrupt CAD III was designed to assess the relative safety and effectiveness of coronary IVL prior to coronary DES implantation for U.S. regulatory approval. The study had nearly identical enrollment criteria and endpoints as the predicate ORBIT II study of orbital atherectomy (4). Although Disrupt CAD III was not randomized, the PGs for the safety and effectiveness endpoints were based on those observed in ORBIT II, which were superior to most prior studies in severely calcified lesions (thus minimizing the risk of noninferiority creep). Both primary effectiveness and safety endpoints were met despite greater target lesion complexity in Disrupt CAD III compared with ORBIT II (e.g., mean lesion length 26.1 ± 11.7 mm vs. 18.9 ± 0.4 mm, mean calcified length 47.9 ± 18.8 mm vs. 28.6 ± 0.8 mm). In this regard, the mean calcified segment length (47.9 ± 18.8 mm) by QCA, calcium angle (292.5 ± 76.5°) and thickness (0.96 ± 0.25 mm) at the site of maximum calcification by OCT represent the most severe target lesion calcification treated in any IDE study of calcium modification technology to date. Disrupt CAD III also confirms and extends prior observations from smaller studies (Disrupt CAD I, Disrupt CAD II) regarding the safety and effectiveness of IVL as an adjunct to coronary stent implantation despite a progressive increase in lesion complexity across studies (Supplemental Table 10).

The MACE rate within 30 days was primarily driven by peri-procedural MIs in 6.8% of patients. To afford comparison to the ORBIT II study, a sensitive definition of peri-procedural MI (post-PCI peak CK-MB >3× ULN) of debatable clinical relevance was used. In a sensitivity analysis using the Society for Cardiac Angiography and Interventions "clinically relevant" definition of peri-procedural MI that has been associated with subsequent death after its occurrence (31), such large MIs occurred in only 2.6% of patients. Although most U.S. operators had no prior experience with the novel IVL technology, overall procedural success rates were high and major angiographic complications were infrequent. Freedom from 30-day MACE, procedural success, and device crossing success were similar between roll-in procedures (first case for each site) and procedures included in the pivotal analysis (Supplemental Table 11) despite severe calcification of all target lesions reflecting the relative ease of IVL device use. Slow-flow was observed in only 2 patients after IVL and 0.8% of patients at any time during the procedure, and no patient developed no-reflow. No perforations were observed after IVL treatment, prior to stent implantation, despite the complexity of vessels treated. The 3 subacute stent thrombosis events can be explained by known clinical, angiographic, or OCT predictors of stent thrombosis, and none were definitely related to the IVL device. Similarly, neither of the 2 cardiac deaths were definitely related to the study device. Finally, although IVL-induced ventricular capture with transient mild hypotension was relatively frequent (41.1% of cases), its occurrence was benign and without clinical consequence. Thus, Disrupt CAD III confirms the safety of coronary IVL as an adjunct to stent implantation in severely calcified lesions.

The primary effectiveness endpoint of procedural success was achieved in 92.4% of patients and was limited mainly by in-hospital MACE (7.0%). Although longer-term clinical follow-up is required to assess

TABLE 5 Serial OCT Measurements and Calcium Fracture Characteristics

	Pre-IVL (n = 97)	Post-IVL (n = 92)	Post-Stent (n = 98)	p Value: Pre-IVL vs. Post-IVL	p Value: Pre-IVL vs. Post-Stent	p Value: Post-IVL vs. Post-Stent
At MLA site						
Lumen area, mm^2	2.16 ± 0.80 [96]	3.57 ± 1.35 [92]	6.51 ± 2.03 [98]	<0.001	<0.001	<0.001
Area stenosis	72.4 ± 11.6 [91]	56.1 ± 16.4 [84]	21.9 ± 18.9 [94]	<0.001	<0.001	<0.001
Calcium angle, °	189.2 ± 96.0 [83]	151.2 ± 80.7 [67]	121.1 ± 71.1 [72]	0.01	<0.0001	0.02
Max calcium thickness, mm	0.87 ± 0.30 [83]	0.83 ± 0.28 [67]	0.83 ± 0.26 [72]	0.40	0.38	1.0
Stent area, mm^2			6.53 ± 2.12 [98]	–	–	–
Stent expansion, %			78.2 ± 19.7 [94]	–	–	–
At pre-IVL max calcium site*						
Lumen area, mm^2	4.08 ± 2.32 [97]	5.86 ± 2.13 [91]	8.85 ± 2.23 [95]	<0.001	<0.001	<0.001
Area stenosis, %	49.1 ± 28.0 [91]	26.6 ± 26.5 [83]	-8.2 ± 30.7 [91]	<0.001	<0.001	<0.001
Calcium angle, °	292.5 ± 76.5 [95]	257.5 ± 80.0 [91]	224.6 ± 75.0 [95]	0.003	<0.001	0.003
Max calcium thickness, mm	0.96 ± 0.25 [95]	0.93 ± 0.21 [91]	0.89 ± 0.20 [95]	0.38	0.06	0.25
Stent area, mm^2			8.30 ± 2.15 [94]	–	–	–
Stent expansion, %			101.7 ± 28.9 [90]	–	–	–
At final MSA site						
Lumen area, mm^2	4.15 ± 2.06 [89]	4.94 ± 1.94 [88]	6.66 ± 2.12 [98]	0.009	<0.001	<0.001
Area stenosis	47.8 ± 25.2 [84]	40.7 ± 22.9 [80]	20.0 ± 19.9 [94]	0.06	<0.001	<0.001
Calcium angle, °	157.0 ± 78.1 [66]	146.1 ± 76.8 [65]	128.9 ± 66.0 [71]	0.43	0.03	0.16
Max calcium thickness, mm	0.91 ± 0.24 [66]	0.88 ± 0.24 [65]	0.87 ± 0.24 [71]	0.48	0.33	0.81
Stent area, mm^2			6.47 ± 2.07 [98]	–	–	–
Stent expansion, %			78.4 ± 25.8 [94]	–	–	–
Calcified nodule	18 (18.6)					
Calcium fracture analysis						
Calcium fracture, %	–	62 (67.4)	69 (70.4)	–	–	0.75
1 fracture	–	20 (21.7)	19 (19.4)			
2 fractures	–	15 (16.3)	16 (16.3)			
≥3 fractures	–	27 (29.3)	34 (34.7)			
Maximum fracture depth, mm	–	0.48 ± 0.25 [62]	0.49 ± 0.20 [69]	–	–	0.80
Maximum fracture width, mm	–	0.55 ± 0.45 [62]	1.32 ± 1.04 [69]	–	–	<0.001
Minimum calcium angle at fracture site, °	–	192.3 ± 67.0 [64]	173.5 ± 60.4 [69]	–	–	0.09
Maximum calcium angle at fracture site, °	–	263.7 ± 72.6 [64]	240.4 ± 73.1 [69]	–	–	0.07

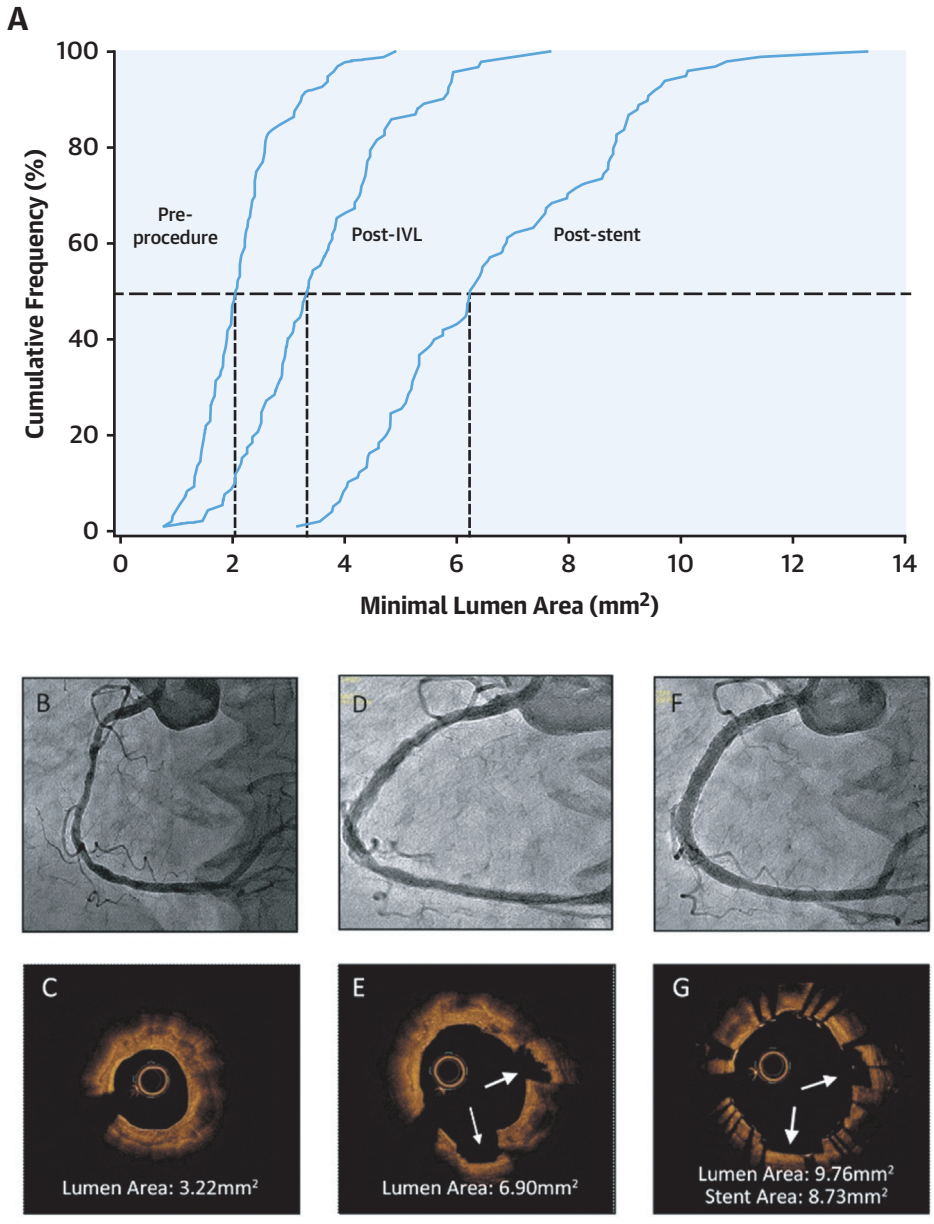
Values are mean ± SD [n] or n (%). *Max calcium site was defined as the site with maximum calcium arc: if multiple sites had the same arc, the site with both maximum arc and thickness was selected.
MLA = minimal luminal area; MSA = minimal stent area.

the late outcomes of IVL-facilitated DES treatment of severely calcified lesions, OCT imaging demonstrated large mean post-procedural MSA (6.5 ± 2.1 mm^2) and excellent stent expansion (101.7 ± 28.9% at the site of maximal calcification) compared to historical PCI in calcified lesions (34), which would be expected to be associated with favorable late rates of clinically driven target lesion revascularization and stent thrombosis (15,16).

Cross-trial comparisons between Disrupt CAD III and ORBIT II were facilitated by similar trial inclusion and exclusion criteria, endpoints, and definitions. In contrast, meaningful cross-trial comparisons between Disrupt CAD III and the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) and PREPARE-CALC (Comparison of Strategies to Prepare Severely Calcified Coronary Lesions) trials are not possible given differences in each of these trial parameters as well as stent type (18,35). Randomized trials comparing rotational atherectomy and IVL are required to define the relative safety and effectiveness of these devices, and whether there are certain lesion types that respond better to one device than another.

Disrupt CAD III provides new data that confirm and extend prior observations regarding the unique mechanism of action of IVL. By emitting acoustic pressure waves in a circumferential, transmural fashion, IVL frequently produces circumferential calcium fractures in multiple planes and in this regard rarely results in uniplanar “troughs” that can occur due to guidewire bias with atherectomy technologies. Calcium fracture is the likely mechanism through which IVL enhances vessel compliance to facilitate optimal stent expansion, as evidenced by increased fracture width following stent expansion.

CENTRAL ILLUSTRATION **Luminal Area Gain Following IVL Treatment and Stent Deployment**



Hill, J.M. et al. J Am Coll Cardiol. 2020;76(22):2635–46.

(A) Cumulative frequency distribution curves demonstrating increased lumen area gain post-intravascular lithotripsy (IVL) and post-stent implantation by optical coherence tomography (OCT). **(B)** Angiography demonstrates a long stenotic lesion in the mid-right coronary artery. **(C)** OCT cross-sectional image acquired before IVL demonstrates 360° circumferential calcium in the area of stenosis. **(D)** Angiography demonstrates improvement in the area of stenosis after IVL. **(E)** OCT cross-sectional image acquired post-IVL demonstrates 2 deep calcium fractures **(arrows)** and large luminal gain. **(F)** Angiography post-stent implantation demonstrates no significant residual stenosis. **(G)** OCT cross-sectional image acquired post-stenting demonstrates further fracture displacement and widening **(arrows)**, with full stent expansion and additional increase in the acute area gain.

STUDY LIMITATIONS. First, the nonrandomized study design lacks a concurrent control group. The comparison to an objective PG is an established pathway for IDE approval and was derived in conjunction with the FDA. Orbital atherectomy was similarly approved in the United States based on a single-arm study that used an objective PG design. The high absolute procedural success rate and low absolute peri-procedural MACE rate (despite the severity of lesion calcification in the study population) coupled with its ease-of-use and rapid learning curve suggests that IVL may play an important role in the treatment of complex, high-risk calcified lesions. Second, the endpoint definitions for both peri-procedural MI and procedural success were chosen to match those used in the ORBIT II study for regulatory purposes and do not reflect current standards. Nevertheless, pre-specified sensitivity analyses using more contemporary definitions support and confirm the conclusions derived from the primary endpoint analyses. Third, OCT identified calcium fractures in 67.4% of lesions after IVL; however, excellent MSA, area stenosis, and stent expansion outcomes were observed regardless of calcium fracture visualization. This may represent a limitation of OCT to detect subtle morphological changes in calcified plaque that are beyond the resolution limits of current OCT technology (36). Fourth, protocol exclusion of adjunctive tools for plaque modification (atherectomy or cutting/scoring balloons) to facilitate IVL balloon crossing avoided confounding of the efficacy and the known complications associated with these devices and afforded an objective assessment of the mechanism of IVL plaque modification. Finally, although protocol exclusion of extremely tortuous vessels, true bifurcation lesions, and unprotected left main or ostial target lesions precludes generalizability of study findings to these subgroups, affording a cross-study comparison with the ORBIT II trial required enrollment of a similar study population. Future studies are required to determine whether there are any specific clinical or anatomic circumstances that are particularly suited to and are more safely or effectively treated with one or the other of these alternative lesion preparation strategies. Preliminary clinical experience suggests that atheroablative technologies may be required in specific situations to facilitate IVL-balloon placement and that these techniques may be complimentary (37).

CONCLUSIONS

Intravascular lithotripsy safely and effectively facilitates stent delivery and optimizes stent expansion in patients with severely calcified coronary lesions. Longer-term clinical follow-up (ongoing in this study through 2 years) is required to determine the durability of clinical benefit associated with IVL-optimized stent implantation.

AUTHOR DISCLOSURES

This study was supported by Shockwave Medical, Inc. 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. Kereiakes has served as a consultant for SINO Medical Sciences Technologies, Inc., Boston Scientific, Elixir Medical, Svelte Medical Systems, Inc., Caliber Therapeutics/Orchestra Biomed, and Shockwave Medical; and is a stockholder in Ablative Solutions, Inc. Dr. Shlofmitz has served as a speaker for Shockwave Medical, Inc. Dr. Riley has received honoraria from Boston Scientific, Asahi Intecc, and Medtronic. Dr. Price has received personal fees from ACIST Medical, AstraZeneca, Abbott Vascular, Boston Scientific, Chiesi USA, Medtronic, and W.L. Gore. Dr. Herrmann has received research funding from Abbott, Boston Scientific, Medtronic, and Shockwave Medical; and is a consultant for Abbott, Medtronic, and Shockwave. Dr. Bachinsky has served as a consultant, served on the Speakers Bureau, and received research grant support from Abbott Vascular, Boston Scientific, BD Bard Vascular, Medtronic, and Shockwave Medical. Dr. Waksman has served on the Advisory Board of Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, and Pi-Cardia Ltd; has served as a consultant for Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, and Pi-Cardia Ltd.; has received grant support from AstraZeneca, Biotronik, Boston Scientific, Chiesi; has served as a speaker for AstraZeneca and Chiesi; and is a stockholder in MedAlliance. Dr. Stone has served as a speaker for Cook Medical; has served as 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/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, and Valfix.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: IVL causes multiplanar and longitudinal calcium fracture, increases vessel compliance, and facilitates stent expansion in patients with heavily calcific coronary atherosclerosis.

TRANSITIONAL OUTLOOK: Future studies should include more complex patient and angiographic lesion subsets to assess the generalizability of these observations, and clarify the relationships between measures of calcium fracture, stent expansion and long-term clinical outcomes.

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KEY WORDS calcification, coronary artery disease, optical coherence tomography

APPENDIX For supplemental figures and tables, please see the online version of this paper.