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Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease: The Disrupt CAD III Study

Brief Title: Disrupt CAD III Study

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Twitter summary: Disrupt CAD III demonstrates safety and efficacy of intravascular lithotripsy to optimize stent expansion in severely calcified coronary artery disease

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.
Objective: 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 (MACE: cardiac death, myocardial infarction or target vessel revascularization) at 30 days. The primary effectiveness endpoint was procedural success. Both endpoints were compared to a pre-specified performance goal (PG). The mechanism of calcium modification was assessed in an optical coherence tomography (OCT) sub-study.
Results: Patients (n=431) were enrolled at 47 sites in four countries. The primary safety endpoint of the 30-day freedom from MACE was 92.2%; the lower bound of the 95% confidence interval (CI) was 89.5% 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% CI 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 multi-plane and longitudinal calcium fractures after IVL in 67.4% of lesions. Minimum stent area was 6.5 ± 2.1mm^2 and was similar regardless of demonstrable fractures on OCT.
Conclusions: Coronary IVL safely and effectively facilitated stent implantation in severely calcified lesions.

Condensed Abstract

The Disrupt CAD III multicenter, single-arm study demonstrated safety and effectiveness of coronary intravascular lithotripsy (IVL) as an adjunct to stent implantation in severely calcified coronary artery lesions. Multi-plane and longitudinal calcium fractures were observed in 67.4% of lesions, resulting in a minimum stent area was 6.5 ± 2.1mm^2 by optical coherence tomography.

Keywords: coronary artery disease, calcification, optical coherence tomography

Abbreviations list

ARC= Academic Research Consortium
DES= drug-eluting stent
FDA= 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
SCAI= Society for Cardiac Angiography and Interventions

Introduction

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 non-compliant 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 under expansion, 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, non-randomized 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 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.

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, for orbital atherectomy (4). Study organization and participating centers are listed in Online 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, 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 (RVD) of 2.5 to 4.0 mm. Patients with acute myocardial infarction and specific complex lesion features were excluded. Complete inclusion and exclusion criteria for the study are listed in Online 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, CA, USA) 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 two 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" guidewire. If the catheter was unable to cross the lesion, adjunctive approaches (e.g., buddy wire, pre-dilatation with a small diameter balloon [1.5-2.0 mm], or guide catheter extension) were used at operator discretion before reinsertion of the IVL catheter. Atherectomy devices and cutting/scoring balloons were not permitted per protocol.

An appropriately sized (1:1 to RVD) 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. Non-compliant 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 non-compliant balloon was required. Dual antiplatelet therapy (DAPT) was prescribed per current guidelines for a minimum of six months (27). Patients on chronic oral anti-coagulation for atrial fibrillation could have abbreviated DAPT with aspirin discontinued within 30 days of PCI (oral anticoagulant and P2Y12 receptor inhibitor maintained)

(28). Post-procedure assessments were required within 12-24 hours 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 sub-study. Optical coherence tomography (OCT) imaging was planned in 100 patients at three 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, NY) 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. Peri-procedural MI was defined according to the predicate ORBIT II study (4) as peak post-PCI CK-MB level >3x 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 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 Online 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 utilized 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 times the observed MACE rate of 10.4% in ORBIT II) and the primary effectiveness PG was set at 83.4% (100% less 1.5 times 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 one-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 one-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 one-sided type 1 error of 5% (33). Thus, the study had at least 81% power to meet both co-primary 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 (ITT) 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).

Results

Patients and procedures. From January 9, 2019 to March 27, 2020, 431 patients were enrolled at 47 sites in four countries (U.S., U.K., 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 (Online Figure 1).

Baseline clinical and angiographic characteristics are presented in Table 1. Most patients were male with a high prevalence of cardiovascular risk factors. Mean baseline reference vessel diameter was 3.0 ± 0.5 mm with lesion length of 26.0 ± 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 99.2% of procedures.

Primary safety and effectiveness endpoints. The primary safety endpoint (freedom from 30-day MACE) was achieved in 92.2% of patients. The one-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 one-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 Online 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, non-target lesion thrombosis distal to the stent. Further details of the cardiac deaths are included in Online 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 4th Universal Definition (7.3%)(30), and a lower rate using the SCAI

definition of a clinically relevant MI (2.6%)(31). Stent thrombosis (ARC 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 under-expansion and mid-stent filling defect (Online 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 (Online 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 Online 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 ± 0.5mm. Serious angiographic complications were observed in two patients (0.5%) at the end of the procedure (Table 4). Freedom from any serious angiographic complication immediately following IVL delivery and at any time point during the procedure were 97.4% and 96.9%, respectively (Online 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 (Online 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 two 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 one 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 per minute, male sex, and total number of IVL pulses delivered as independent predictors of IVL-induced capture (Online Table 9).

OCT sub-study. A total of 100 patients were enrolled in the OCT sub-study. 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; 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.

Discussion

The Disrupt CAD III study evaluated the utility of IVL for lesion preparation of severely calcified coronary 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; (4) OCT demonstrated multi-plane 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 non-inferiority 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 versus 18.9 ± 0.4 mm, mean calcified length 47.9 ± 18.8 mm versus 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 (Online 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 >3X ULN) of debatable clinical relevance was used. In a sensitivity analysis using the SCAI "clinically relevant" definition of peri-procedural MI that has been associated with subsequent death after its occurrence (31), such large MIs occurred in only 2.4% 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 (Online Table 11) despite severe calcification of all target lesions reflecting the relative ease of IVL device use. Slow-flow was observed in only two 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 three sub-acute 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 two 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 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 ($101.7 \pm 28.9\%$ 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 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.

Limitations. First, the non-randomized 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 FDA. Orbital atherectomy was similarly approved in the U.S. 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 morphologic 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.

Perspectives

Competency in patient care and procedural skills

Coronary IVL achieves multi-planar and longitudinal calcium fracture with increased vessel compliance and optimized stent expansion. The single arm, multi-national Disrupt CAD III trial assessing coronary IVL as an adjunct to coronary stent implementation achieved the co-primary endpoints for safety and effectiveness in patients with severely calcified coronary arteries.

Transitional Outlook

Future studies should include more complex patient and angiographic lesion subsets to assess generalizability of Disrupt CAD III trial findings, and to further evaluate the relationship between objective measures of calcium fracture, optimized stent expansion and long-term clinical benefit.

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Figures and figure legends

Figure 1. Shockwave IVL system. (A) 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.

Figure 2. Primary safety and effectiveness endpoints compared with their performance goals. (A) The primary safety endpoint was freedom from 30-day MACE, defined as cardiac death, myocardial infarction, or target vessel revascularization. The rate of the primary safety endpoint was 92.2% with a one-sided lower 95% confidence interval 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 lab analysis without in-hospital MACE. The rate of the primary effectiveness endpoint was 92.4% with a one-sided lower 95% confidence interval 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.

Central Illustration. Luminal area gain following IVL treatment and stent deployment. A.) Cumulative frequency distribution curves demonstrating increased lumen area gain post-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 two deep calcium fractures (white 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.

H.) OCT longitudinal image acquired post-stenting demonstrates longitudinal fracture displacement (arrows).

Table 1. Baseline clinical characteristics

Patient characteristic	**N = 384**
Age, years	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/1.73m^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	26.0 ± 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 n (%) or mean ± standard deviation [n]. *Defined as radiopaque densities noted without cardiac motion generally involving both sides of the arterial wall. TIA= transient cerebral ischemic event; eGFR=estimated glomerular filtration rate using the MDRD formula; ICD/CRT-D= implantable cardiac defibrillator with or without bi-ventricular pacing capability.

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	2.0 (1.0, 2.0)

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

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)
- Non-cardiac	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)

	N = 384
Myocardial infarction (protocol-defined)	28 (7.3)
- TV-MI	28 (7.3)
- Periprocedural MI (protocol-defined)	26 (6.8)
- Non-procedural MI	4 (1.0)
- Periprocedural MI (4th Universal Definition type 4a)	28 (7.3)
- Periprocedural MI (SCAI 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)
Non-target vessel	6 (1.6)
Stent thrombosis (definite or probable)	3 (0.8)
- Definite	3 (0.8)
- Probable	0 (0.0)

Values are n (%). *One patient had two events; one Q-wave and one 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; TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization.

Table 4. Angiographic outcomes

Core laboratory-assessed	**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)

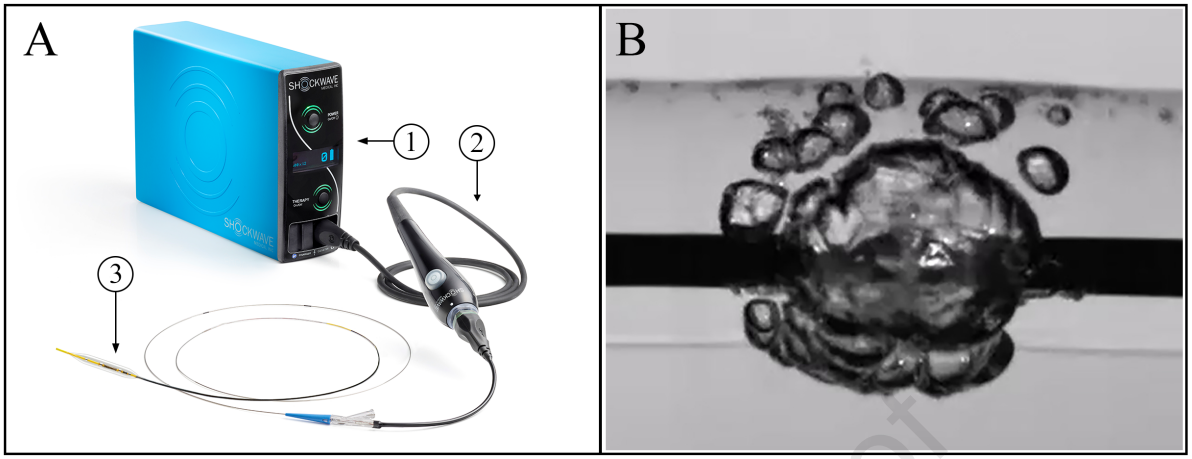
Values are n (%) or mean ± standard deviation. *Serious angiographic complications include severe dissection (Type D-F), perforation, abrupt closure, slow flow and no-reflow. [†]Patient had a worsening post-IVL dissection to a Type F dissection and resulting abrupt closure after PTCA which ultimately led to failed stent delivery. The patient experienced a MACE and expired on POD 9. [‡]Core lab assessed class II perforation post-stent that was treated with post-dilatation at the proximal stent location; 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.

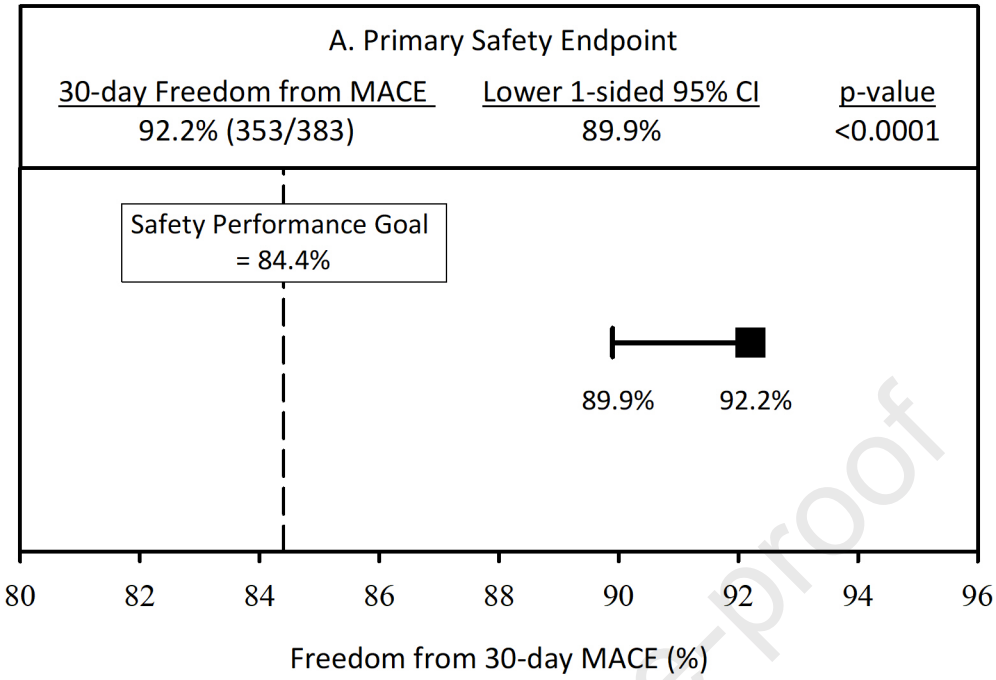
Table 5. Serial OCT measurements and calcium fracture characteristics

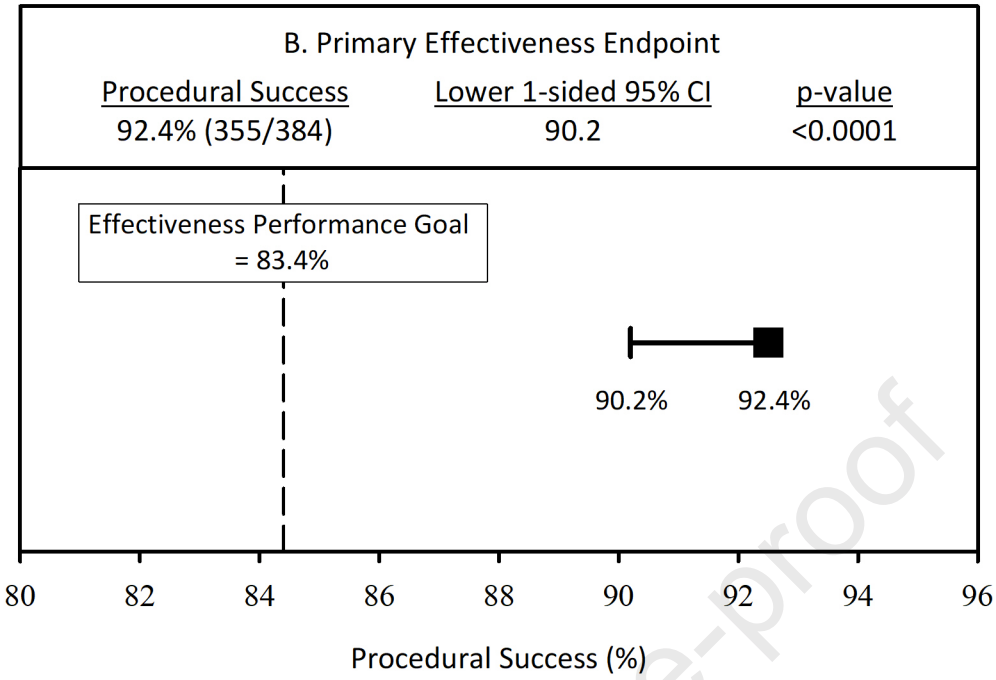
	Pre-IVL (n = 97)	Post-IVL (n = 92)	Post-stent (n = 98)	P-value (Pre-IVL vs Post-IVL)	P-value (Pre-IVL vs Post-stent)	P-value (Post-IVL vs Post-stent)
At MLA site						
Lumen area, mm^2	2.16 ± 0.80 [96]	3.57 ± 1.35 [92]	6.51 ± 2.03 [98]	<0.001	<0.001	<0.001
Area stenosis	72.4 ± 11.6 [91]	56.1 ± 16.4 [84]	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]	-	-	-

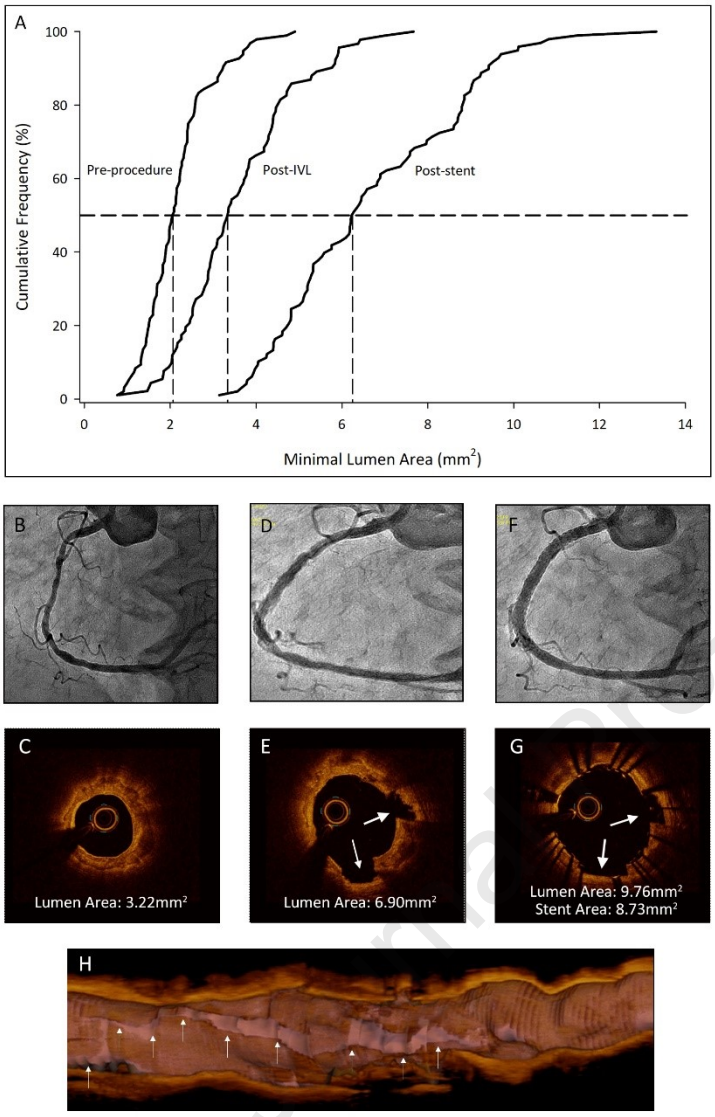
Stent expansion, %			78.4 ± 25.8 [94]	-	-	-
Calcified nodule	18 (18.6)					
Calcium fracture analysis						
Calcium fracture, %	_	62 (67.4)	69 (70.4)	-	-	0.75
1 fracture	_	20 (21.7)	19 (19.4)			
2 fractures	_	15 (16.3)	16 (16.3)			
≥3 fractures	_	27 (29.3)	34 (34.7)			
Maximum fracture depth, mm	_	0.48 ± 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

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







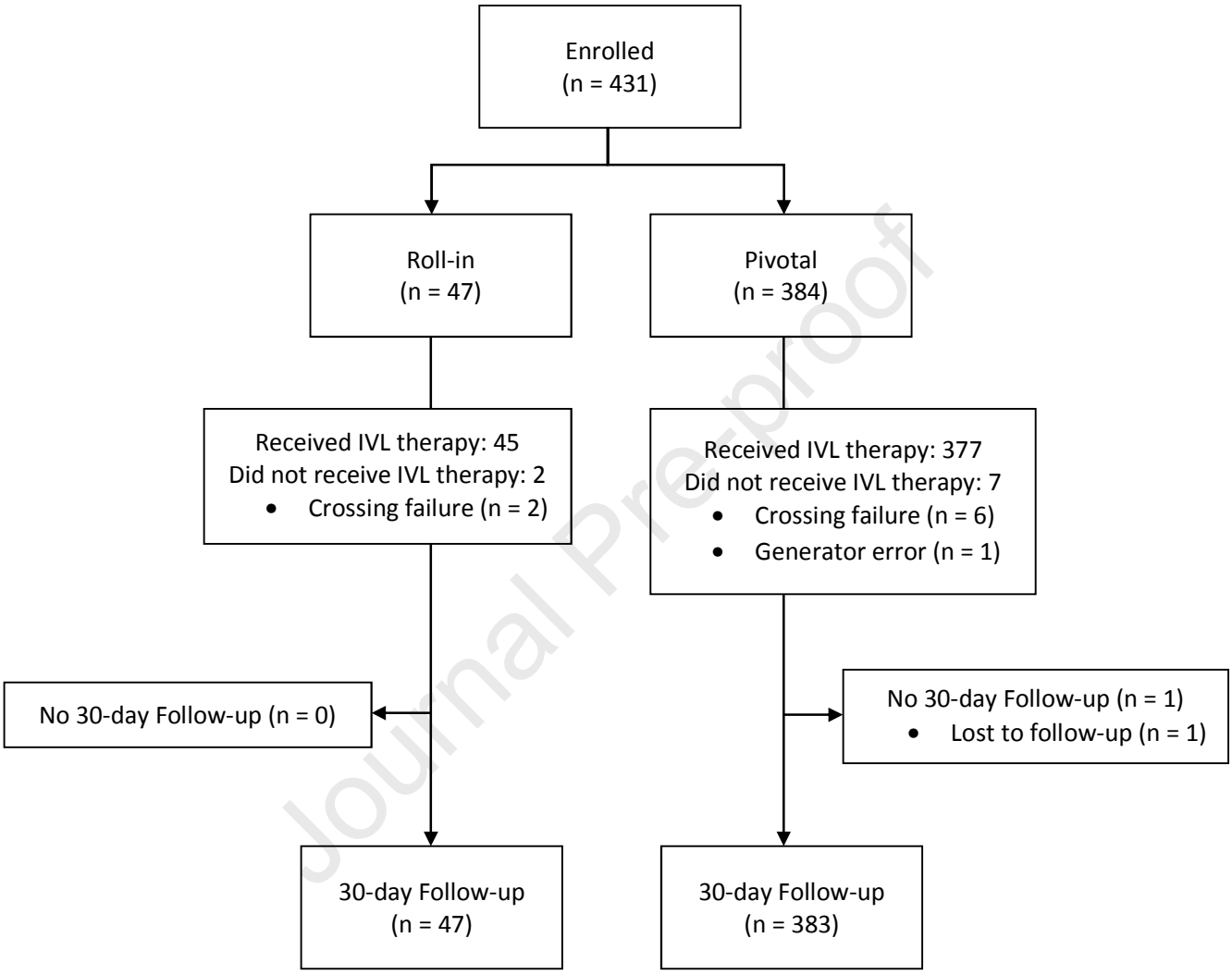


Supplemental appendix

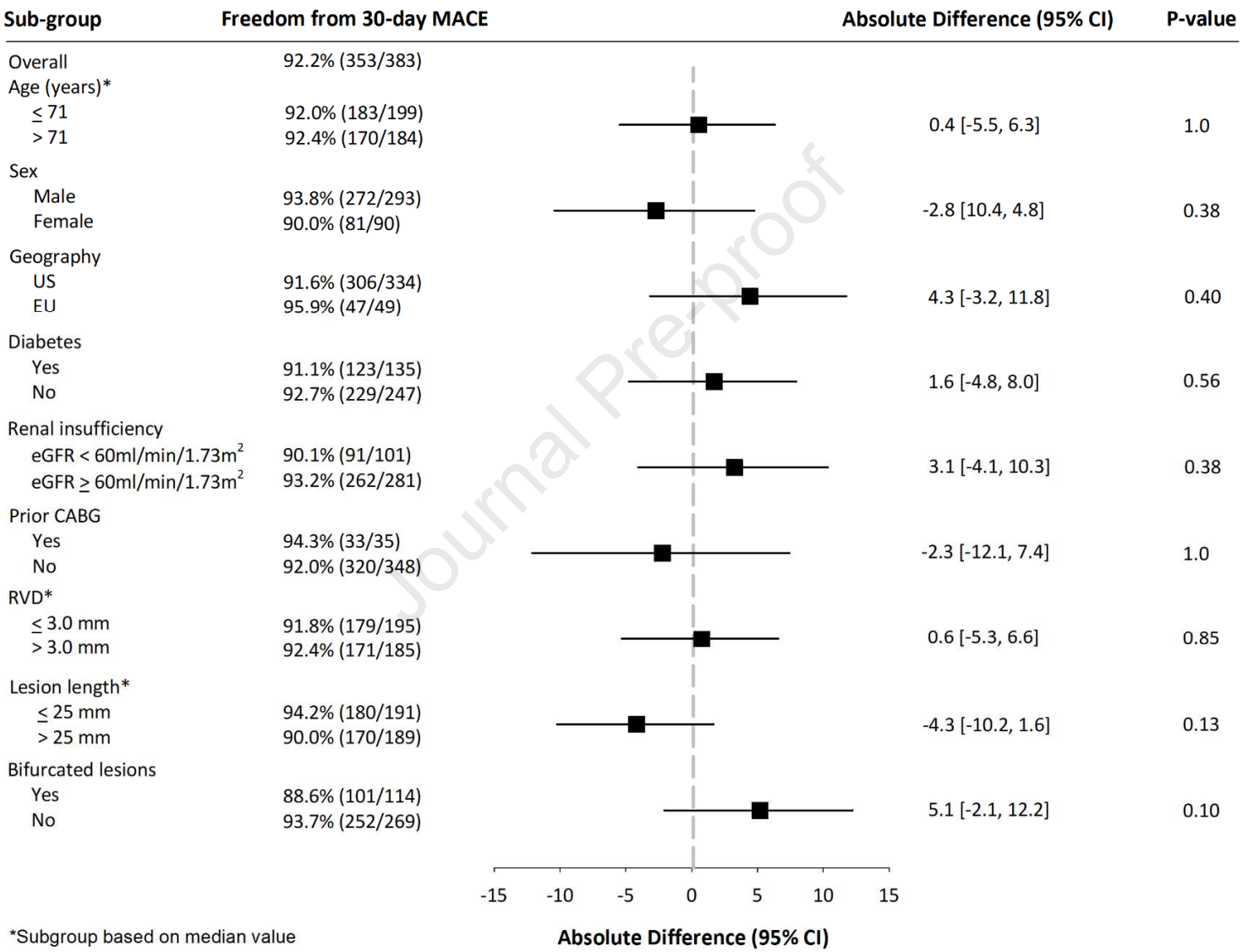
Safety and Effectiveness of Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Artery Disease: the Disrupt CAD III Study

Jonathan M. Hill, MD, Dean J. Kereiakes, MD, Richard A. Shlofmitz, MD, Andrew J. Klein, MD, Robert F. Riley, MD, Matthew J. Price, MD, Howard C. Herrmann, MD, William Bachinsky, MD, Ron Waksman, MD, Gregg W. Stone, MD

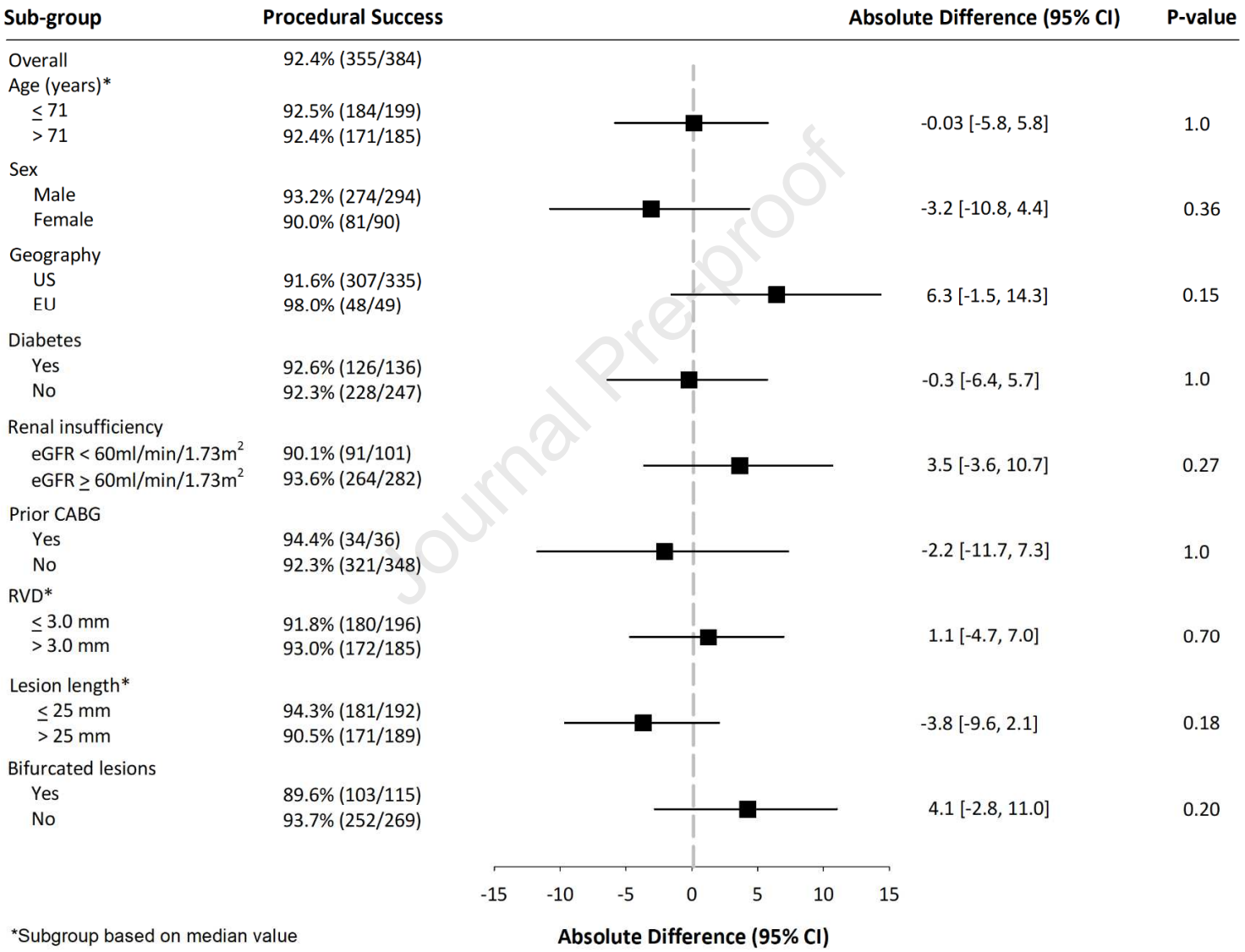
Online Figure 1. Patient flow through 30-days



Online Figure 2. Subgroup analyses for the primary safety endpoint of freedom from 30-day MACE.



Online Figure 3. Subgroup analyses for the primary effectiveness endpoint of procedural success (stent delivery with a residual stenosis <50% without in-hospital MACE).



Online Figure 4. Cumulative frequency distribution curve at baseline, post-IVL and post final stent implantation by quantitative coronary angiography. A) Minimal luminal diameter; B) Diameter stenosis.

Figure 4A:

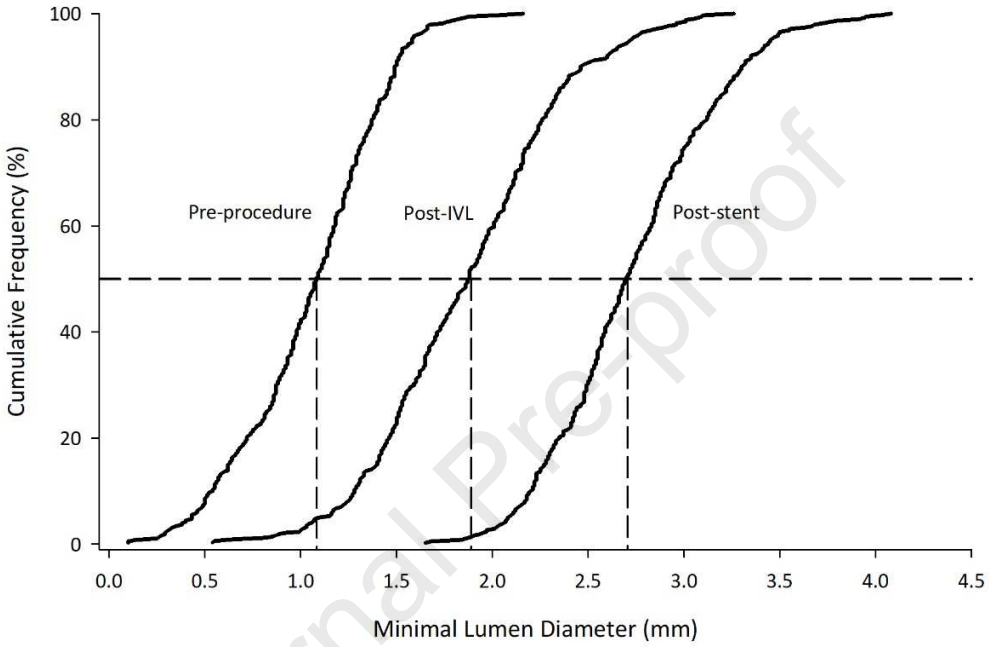
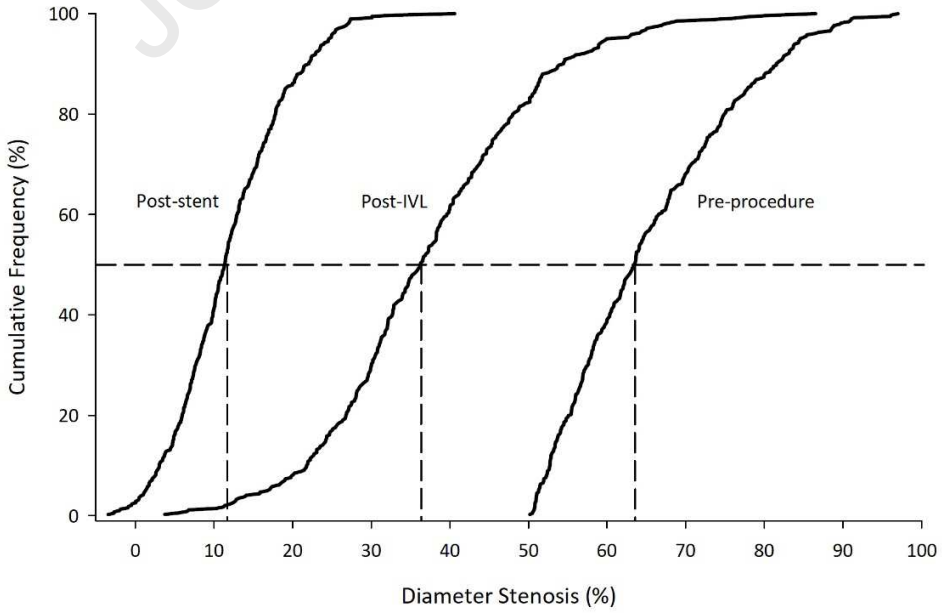


Figure 4B:



Online Table 1. Disrupt CAD III study organization and participating centers

Steering committee: Gregg W. Stone, Mount Sinai Heart, New York, NY (Chair); Dean J. Kereiakes, The Christ Hospital, Cincinnati, OH (Co-Principal Investigator); Jonathan Hill, Royal Brompton Hospital, London, UK (Co-Principal Investigator); David Kandzari, Piedmont Healthcare, Atlanta, GA; Jeff Moses, Columbia University, New York, NY; Keith Oldroyd, Golden Jubilee National Hospital, Glasgow, UK; Matthew Price, Scripps Memorial Hospital, La Jolla, CA; Sunil Rao, Duke University Hospital, Durham, NC;

Site monitoring: Medpace, Cincinnati, OH

Data analysis and biostatistics: Cardiovascular Research Foundation, New York, NY

Clinical Events Committee: Cardiovascular Research Foundation, New York, NY

Angiographic and OCT core laboratory: Cardiovascular Research Foundation, New York, NY

Biomarker central laboratory: Medpace Reference Laboratory, Cincinnati, OH

Data Safety Monitoring Board: Cardiovascular Research Foundation, New York, NY

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Online Table 2. Inclusion and exclusion criteria

General Inclusion Criteria:

1. ≥18 years of age;
2. Native coronary artery disease (including stable or unstable angina and silent ischemia) suitable for PCI;
3. For patients with unstable ischemic heart disease, biomarkers (troponin or CK-MB) must be less than or equal to the upper limit of lab normal within 12 hours prior to the procedure (note: if both labs are drawn, both must be normal);
4. For patients with stable ischemic heart disease, biomarkers may be drawn prior to the index procedure or at the time of the procedure from the side port of the sheath;
   a. If drawn prior to the procedure, biomarkers (troponin or CK-MB) must be less than or equal to the upper limit of lab normal within 12 hours of the procedure (note: if both labs are drawn, both must be normal);
   b. If biomarkers are drawn at the time of the procedure from the side port of the sheath prior to any intervention, results do not need to be analyzed prior to enrollment (note: CK-MB is required if drawn from the sheath);
5. Left ventricular ejection fraction > 25% within 6 months (note: in the case of multiple assessments of LVEF, the measurement closest to enrollment will be used for this criteria; may be assessed at time of index procedure);
6. Patient or legally authorized representative, signs a written Informed Consent form to participate in the study, prior to any study-mandated procedures;
7. Lesions in non-target vessels requiring PCI may be treated either:

a. >30 days prior to the study procedure if the procedure was unsuccessful or complicated; or

b. >24 hours prior to the study procedure if the procedure was successful and uncomplicated (defined as a final lesion angiographic diameter stenosis <30% and TIMI 3 flow (visually assessed) for all non-

target lesions and vessels without perforation, cardiac arrest or need for defibrillation or cardioversion or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, and with no post-procedure biomarker elevation >normal; or

c. >30 days after the study procedure.

Angiographic Inclusion Criteria:

1. The target lesion must be a *de novo* coronary lesion that has not been previously treated with any interventional procedure;
2. Single *de novo* target lesion stenosis of protected LMCA, or LAD, RCA or LCX (or of their branches) with:
   a. Stenosis of ≥70% and <100%; or
   b. Stenosis ≥50% and <70% (visually assessed) with evidence of ischemia via positive stress test, or fractional flow reserve value ≤0.80, or iFR <0.90 or IVUS or OCT minimum lumen area ≤4.0 mm^2;
3. The target vessel reference diameter must be ≥2.5 mm and ≤4.0 mm;
4. The lesion length must not exceed 40 mm;
5. The target vessel must have TIMI flow 3 at baseline (visually assessed; may be assessed after pre-dilatation);
6. Evidence of calcification at the lesion site by, a) angiography, with fluoroscopic radio-opacities 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 by b) IVUS or OCT, with presence of ≥270 degrees of calcium on at least 1 cross section
7. Ability to pass a 0.014" guide wire across the lesion.

General Exclusion Criteria:

1. Any comorbidity or condition which may reduce compliance with this protocol, including follow-up

visits;

2. Patient is a member of a vulnerable population as defined in 21 CFR 56.111, including individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces, and persons kept in detention;
3. Patient is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint;
4. Patient is pregnant or nursing (a negative pregnancy test is required for women of child-bearing potential within 7 days prior to enrollment);
5. Unable to tolerate dual antiplatelet therapy (i.e., aspirin, and either clopidogrel, prasugrel, or ticagrelor) for at least 6 months (for patients not on oral anticoagulation);
6. Patient has an allergy to imaging contrast media which cannot be adequately pre-medicated;
7. Patient experienced an acute MI (STEMI or non-STEMI) within 30 days prior to index procedure, defined as a clinical syndrome consistent with an acute coronary syndrome with troponin or CK-MB greater than 1 times the local laboratory's upper limit of normal;
8. New York Heart Association (NYHA) class III or IV heart failure;
9. Renal failure with serum creatinine >2.5 mg/dL or chronic dialysis;
10. History of a stroke or transient ischemic attack (TIA) within 6 months, or any prior intracranial hemorrhage or permanent neurologic deficit;
11. Active peptic ulcer or upper gastrointestinal (GI) bleeding within 6 months;
12. Untreated pre-procedural hemoglobin <10 g/dL or intention to refuse blood transfusions if one should become necessary;
13. Coagulopathy, including but not limited to platelet count <100,000 or International Normalized ratio

(INR) >1.7 (INR is only required in patients who have taken warfarin within 2 weeks of enrollment);

14. Patient has a hypercoagulable disorder such as polycythemia vera, platelet count >750,000 or other disorders;
15. Uncontrolled diabetes defined as a HbA1c ≥10%;
16. Patient has an active systemic infection on the day of the index procedure with either fever, leukocytosis or requiring intravenous antibiotics;
17. Patients in cardiogenic shock or with clinical evidence of left-sided heart failure (S3 gallop, pulmonary rales, oliguria, or hypoxemia);
18. Uncontrolled severe hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg);
19. Patients with a life expectancy of less than 1 year;
20. Non-coronary interventional or surgical structural heart procedures (e.g., TAVR, MitraClip, LAA or PFO occlusion, etc.) within 30 days prior to the index procedure;
21. Planned non-coronary interventional or surgical structural heart procedures (e.g., TAVR, MitraClip, LAA or PFO occlusion, etc.) within 30 days after the index procedure;
22. Patient refusing or not a candidate for emergency coronary artery bypass grafting (CABG) surgery;
23. Planned use of atherectomy, scoring or cutting balloon, or any investigational device other than lithotripsy;
24. High SYNTAX Score (≥33) if assessed as standard of care, unless the local heart team has met and recommends PCI is the most appropriate treatment for the patient;
25. Unprotected left main diameter stenosis >30%;
26. Target vessel is excessively tortuous defined as the presence of two or more bends >90º or three or more bends >75º;
27. Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel;
28. Evidence of aneurysm in target vessel within 10 mm of the target lesion;

29. Target lesion is an ostial location (LAD, LCX, or RCA, within 5 mm of ostium) or an unprotected left main lesion;
30. Target lesion is a bifurcation with ostial diameter stenosis ≥30%;
31. Second lesion with >50% stenosis in the same target vessel as the target lesion including its side branches;
32. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft;
33. Previous stent within the target vessel implanted within the last year;
34. Previous stent within 10 mm of the target lesion regardless of the timing of its implantation;
35. Angiographic evidence of a dissection in the target vessel at baseline or after guidewire passage.

CK-MB, creatine kinase myocardial band; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; LAA, left atrial appendage; LAD, left anterior descending; LCX, left circumflex; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack; TAVR, transcatheter aortic valve replacement; TIMI, thrombolysis in myocardial infarction.

Online Table 3. Pre-specified endpoints and definitions

Primary Endpoints	Definition
Primary safety endpoint	Freedom from major adverse cardiac events (MACE) within 30 days of the index procedure.
Primary effectiveness endpoint	Procedural Success defined as stent delivery with a residual stenosis <50% (angiographic core laboratory-assessed) and without in-hospital MACE.
MACE	Composite occurrence of cardiac death, myocardial infarction (MI), or target vessel revascularization.
Myocardial infarction (protocol definition)	CK-MB level >3 times the upper limit of lab normal (ULN) value with or without new pathologic Q waves at discharge (periprocedural MI) and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI)
Target vessel revascularization	Revascularization at the target vessel (inclusive of the target lesion) after the completion of the index procedure.
Secondary Endpoints	**Definition**
Device crossing success	Ability to deliver the IVL catheter across the target lesion, and delivery of lithotripsy without serious angiographic complications immediately after IVL
Angiographic success (<50% residual stenosis)	Stent delivery with <50% residual stenosis and without serious angiographic complications.
Angiographic success (≤30% residual stenosis)	Stent delivery with ≤30% residual stenosis and without serious angiographic complications.
Procedural success	Stent delivery with a residual stenosis ≤ 30% (core laboratory-assessed) and without in-hospital MACE.
Serious angiographic complications	Severe dissection (Type D to F), perforation, abrupt closure, and persistent slow flow or persistent no reflow.
MACE at 6, 12, and 24 months	Cardiac death, myocardial infarction (MI), or target vessel revascularization (TVR).
Target lesion failure (TLF)	Cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or ischemia-driven target lesion revascularization (ID-TLR) by

	percutaneous or surgical methods at 30 days, 6, 12 and 24 months.
At each time period	All death, cardiac death, MI, TV-MI, procedural and nonprocedural MI, ID-TVR, ID-TLR, ID-non-TLR, ID-non-TVR, all revascularizations (ID and non-ID), and stent thrombosis (ARC definite, probable, definite or probable)
Sensitivity analysis	Reported for MI using the Fourth Universal Definition of MI and the Society for Cardiovascular Angiography and Interventions (SCAI) definition of a clinically relevant MI at 30 days, 6, 12 and 24 months

ARC, Academic Research Consortium; MACE, major adverse cardiac events; TV-MI, target vessel myocardial infarction.

Online Table 4. Cardiac death patient narratives

Patient #1 (109-002): The patient was a 69-year-old male smoker with a past medical history of hypertension, hyperlipidemia, and prior RCA PCI due to STEMI (28-Oct-2019).
Index Procedure Baseline Assessments: CCS III, LVEF 45%, normal CK-MB. Vascular access was obtained via the right radial artery. Coronary angiography revealed (visual estimate) 90% diameter stenosis of proximal LAD, 75% diameter stenosis of OM1, patent RCA stents and moderate disease in the distal RCA. PCI of the LAD was performed with pre-dilatation using a 2.5 mm NC balloon, followed by 6 cycles (60 pulses) of IVL using a 3.5 mm IVL balloon to the proximal LAD. Following IVL there was reduced TIMI flow and spasm that resolved with intracoronary nitroglycerine. Following two unsuccessful attempts to deliver a DES, guidewire position was lost. PCI was reattempted via the left common femoral artery with difficult guidewire passage. Contrast staining and abrupt closure of the LAD was observed by angiography. Despite PTCA with a 2.5 mm NC balloon, abrupt closure persisted and the patient experienced severe chest pain and hypotension. An IABP was inserted and vasopressors were started. Patient developed ventricular fibrillation and cardiac arrest with resuscitation performed. Final angiography revealed 100% occlusion with dissection of the proximal LAD and TIMI 0 flow. Emergency CABG with LIMA to LAD was performed.
Follow-up Post-procedurally the patient experienced respiratory failure and cardiogenic shock with marked elevation in biomarkers (peak CK-MB 95x ULN, peak cTn >2400x ULN) with anterior Q-wave MI on ECG. Post-operative echocardiogram revealed LVEF 20-25%. IABP was successfully removed on POD 4. Hospital course was complicated by bilateral pleural effusions requiring thoracentesis, worsening hypotension requiring vasopressors, and hepatic failure. Patient was deemed unstable for LVAD. Following family conference regarding poor clinical status, patient was transitioned to comfort care, extubated and subsequently expired on POD 9. CEC considered elevated biomarkers, TVR and cardiac death to be probably related to the study device and definitely related to the study procedure.

Patient #2 (121-008): The patient was a 90-year-old female non-smoker with a past medical history of hypertension, hyperlipidemia, and prior PCI (30-Jul-2019).
Index Procedure Baseline Assessments: CCS III, LVEF 35%, normal cTn. Vascular access was obtained via the radial artery. Coronary angiography revealed (visual estimate) 90% diameter stenosis of mid LAD, diffusely diseased small D2, and 60% diameter stenosis of distal LAD. PCI was performed with 2 cycles of IVL using a 3 mm balloon resulting in 22% residual stenosis post-IVL, and implantation of a Xience DES 3 x 30 mm stent. Repeat angiography revealed second diagonal (D2) vessel closure, likely due to plaque shift after stent deployment. The physician was unable to wire the D2 to perform PTCA. Final angiography revealed 0% LAD stenosis and TIMI 3 flow. Patient remained hemodynamically stable but reported persistent chest pain post-procedure. Biomarkers were elevated post-procedure (peak CK-MB 13.1x ULN; cTn >9.7x ULN); peri-procedural MI secondary to D2 occlusion (In-hospital, non-Q-wave MI) was diagnosed.

Follow-up
Patient was discharged on POD 2 in stable condition on DAPT.

Patient returned for evaluation of abdominal pain, vomiting and irritability on POD 6. ECG showed wide complex tachycardia and anterior STEMI subsequently progressing to PEA arrest. CPR was initiated with return of circulation and vasopressor support was initiated. Coronary angiography revealed a patent mid LAD stent and thrombotic occlusion of the LAD distal to the stent. Medical management with vasopressor support and IABP was placed. Patient's status was made do not resuscitate and she expired on POD 6.

CEC considered peri-procedural non-Q-wave MI to be possibly related to study device and definitely related to study procedure. CEC considered the Q-wave MI as probably related to study device and definitely related to study procedure. CEC considered the cardiac death to be possibly related to study device and definitely related to study procedure.

Online Table 5. Stent thrombosis patient narratives

Patient #1 (104-007): The patient was a 76-year-old male, former smoker, with past medical history of chronic kidney disease, hypertension, hyperlipidemia, diabetes mellitus, and 2-vessel CAD (with prior PCI in 2015).
Index Procedure Baseline Assessments: CCS 0, LVEF 45%, normal CK-MB and cTn. Coronary angiography revealed (visual estimate) 80% diameter stenosis of mid LAD, 50% diameter stenosis of proximal LAD with abnormal iFR, RCA CTO with extensive collaterals, and patent LCx stent. PCI was performed to the LAD with 80 pulses of IVL delivered using 2 separate IVL catheters in sequence. The first 3.0 mm IVL catheter delivered 3 cycles and the second catheter (also 3.0 mm) delivered 5 cycles. Post-IVL a 30% residual stenosis was treated with a 3.0 x 28 mm Synergy stent and post-dilated with a 3.5 mm balloon. Post stent, a localized dissection of the proximal LAD likely related to the guide extension catheter was observed. The dissected area was treated with balloon angioplasty and additional stents were placed (Synergy 3.0 x 20 mm, Synergy 3.5 x 12 mm). Final angiographic assessment noted TIMI III flow, occlusion of the diagonal and septal side-branches with collateral flow to RCA. The patient was experiencing chest pain and IABP was placed with improvement of symptoms. Final angiography revealed (site visual estimate) 0% residual stenosis of proximal and mid LAD.
Follow-up Short runs of NSVT occurred on POD 3 and patient was stabilized on beta blocker. Ticagrelor was discontinued due to shortness of breath and a loading dose and daily dose of Plavix was administered. Patient was discharged in stable condition on POD 5 with medication regimen including aspirin and clopidogrel. Patient was re-admitted on POD 6 with anterior STEMI, chest pain and dyspnea. Retrospective review of the index procedure angiogram revealed an under expanded stent of the third DES due to calcification not treated with IVL. TTE showed mildly dilated LV cavity, LVEF 25-30%, anterior-apical and anteroseptal akinesis, mild MR, and mild AR. Coronary angiography revealed 100% proximal LAD occlusion with stent thrombosis involving the previously under-expanded proximal LAD stent. Balloon angioplasty of the proximal LAD was performed and IABP was placed. A post-PCI 80% residual stenosis with TIMI 3 flow was obtained and CABG was performed on POD 8. Serial cardiac biomarkers were elevated (peak cTn 374 x ULN) and Q-wave MI was noted on ECG. The post-CABG course was complicated by cardiac and respiratory arrest, small bowel resection, and chest tube insertion for bilateral pleural effusions and pneumonia. The patient was discharged on POD 35 in stable condition. CEC considered Q-wave MI, TVR, and stent thrombosis to be not related to study device and definitely related to study procedure. Root cause of the stent thrombosis was stent under expansion due to coronary calcification not treated with IVL during the index procedure.

Patient #2 (123-008): The patient was a 72-year-old male non-smoker with a past medical history of hypertension, type II diabetes mellitus, and prior PCI (mid RCA and OM in 2016).

Index Procedure Baseline Assessments: CCS III, LVEF 60%, normal CK-MB and cTn. Vascular access was obtained via the radial artery. Coronary angiography revealed (visual estimate) 80% diameter stenosis of proximal LAD and 90% diameter ostial stenosis of small diagonal. PCI was performed with 4 cycles of IVL using a 3.5 mm IVL balloon. Balloon angioplasty of the diagonal branch was performed post IVL with 20% residual stenosis and a 3.5 x 30 mm DES was deployed to the proximal LAD and post-dilated with 3.5 mm NC balloon. Final angiography revealed 0% residual stenosis of the proximal LAD, 20% stenosis of the diagonal, and TIMI 3 flow.
Follow-up Clopidogrel 75 mg daily was continued at discharge with no additional loading dose given during hospital stay. Patient was re-admitted on POD 7 for STEMI. ECG revealed anterolateral ST elevations with reciprocal ST changes in the inferior and low lateral leads. Subsequent VF arrest was successfully resuscitated, vasopressor therapy was initiated and patient was intubated. Coronary angiography revealed proximal LAD stent occlusion with TIMI 0 flow, 60% diameter stenosis of LCx, and patent OM stent. PCI with aspiration thrombectomy was performed and an additional DES was placed in the proximal LAD. Impella mechanical cardiac support was instituted for hypotension and shock. Echo revealed LVEF of 10%. During hospitalization, patient subsequently developed pneumonia, AKI, and dysphonia/dysphagia. Retrospective review of the index procedure angiogram conducted after the TVR identified a mid-LAD filling defect in-stent at the end of the procedure which is predictive for a stent thrombosis. The patient was eventually discharged on medication regimen including DAPT. CEC considered Q-wave MI, TVR and stent thrombosis to be possibly related to study device and definitely related to study procedure.

Patient #3 (402-008): The patient was a 63-year-old male non-smoker with a past medical history of type 1 diabetes mellitus, hypertension, and prior NSTEMI (01-Jan-2020).
Index Procedure Baseline Assessments: CCS II, LVEF 63%, normal CK-MB and cTn. Vascular access was obtained via the radial artery. Coronary angiography revealed (visual estimate) 90% diameter stenosis of RCA. PCI was performed with 8 cycles of IVL using a 4.0 mm IVL balloon. Post IVL, a 43% residual stenosis was treated with a 4.0 x 38 mm DES deployed to mid RCA, and post-dilated with a 4.5 mm NC balloon. Final angiography revealed 0% residual stenosis with TIMI 3 flow. OCT imaging revealed evidence of stent under expansion with a minimum stent area of 7.9mm^2.
Follow-up Patient was discharged in stable condition on POD 1 with a medication regimen including aspirin and ticagrelor. Patient was admitted on POD 14 with NSTEMI and reported severe chest pain. Cardiac biomarkers were elevated on evaluation (cTn 3.8x ULN, Non Q-wave MI). ECG revealed no acute changes. Echo

revealed no regional wall motion abnormality.

Coronary angiography was performed on POD 21 via radial access and revealed (visual estimate) 50-74% diameter stenosis of proximal LAD, mid LAD, and mid RCA (sub-acute stent thrombosis). PCI was performed with balloon angioplasty to mid RCA. Final angiography revealed 0% residual stenosis of mid RCA and TIMI 3 flow.

Patient was discharged on POD 22 in stable condition on prasugrel and aspirin. The CEC considered the events of Non Q-wave MI, TVR and stent thrombosis to be possibly related to the study device and definitely related to the study procedure.

Online Table 6. Change in CCS angina class from baseline to 30 days

	Baseline (n=381)	**30 day (n = 377)**	**P-value**
Angina classification			<0.001
Class 0	48 (12.6)	275 (72.9)	
Class I	56 (14.7)	66 (17.5)	
Class II	142 (37.3)	28 (7.4)	
Class III	126 (33.1)	7 (1.9)	
Class IV	9 (2.4)	1 (0.3)	

Values are n (%)

Online Table 7. Serious angiographic complications anytime during the procedure

	Pre-IVL (n=384)	Post-IVL (n=341)	Post-dilatation before stent (n=64)	Post-stent (n=357)	Post OCT or IVUS (n=122)	Final (n=384)	Any time point (n=384)
Any serious angiographic complication*	0 (0.0)	9 (2.6)	1 (1.6)	3 (0.8)	0 (0.0)	2 (0.5)	12 (3.1)
Severe dissection (Type D-F)	0 (0.0)	7 (2.1)	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.3)	8 (2.1)
Perforation	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	2 (0.5)
Abrupt closure	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Slow flow	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.8)
No-reflow	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Serious angiographic complications include severe dissection (Type D-F), perforation, abrupt closure, slow flow and no-reflow; Values are n (%).

Online Table 8. IVL-induced capture

	No IVL-induced capture (n=245)	IVL-induced capture (n = 171)	P-value
Pre-procedure heart rate	69.0 ± 11.9	65.9 ± 11.4	0.009
Drop in systolic BP during IVL procedure	58/237 (24.5)	66/163 (40.5)	0.0007
- Magnitude of systolic BP decrease, mmHg	23.5 ± 15.0	18.9 ± 14.2	0.07
Sustained ventricular arrhythmia during or immediately after IVL procedure	1 (0.4)	0 (0.0)	1.0

Values are mean ± standard deviation, n/N (%)

Online Table 9. Independent predictors of IVL-induced capture by multivariable analysis

	Coefficient	SE	Odd Ratio (95% CI)	P-value
HR ≤60 beats per minute	0.4418	0.1155	2.42 (1.54-3.81)	<0.001
Male sex	-0.2711	0.1229	0.58 (0.36-0.94)	0.027
Number of IVL pulses	0.0064	0.0031	1.01 (1.00-1.01)	0.037
LAD vessel	0.2062	0.1062	1.51 (1.00-2.29)	0.052
Prior ICD/Pacemaker	0.4028	0.2099	2.24 (0.98-5.10)	0.055
Prior PCI	-0.2023	0.1051	0.67 (0.44-1.01)	0.054
Intercept	-0.1811	-	-	

Online Table 10. Comparison of Disrupt CAD clinical studies

	Disrupt CAD I	Disrupt CAD II	Disrupt CAD III	Disrupt CAD IV*
Status	Completed	Completed	Completed	Completed
Target lesions	Severely calcified, coronary artery lesions	Severely calcified, coronary artery lesions	Severely calcified, coronary artery lesions	Severely calcified, coronary artery lesions
Study design	Single arm, safety and feasibility	Single arm, safety and effectiveness	Single arm, safety and effectiveness	Single arm, safety and effectiveness
# Patients	60	120	384	64
# Sites	7	15	49	8
Regions	AU, EU	EU	U.S., EU	Japan
Study conduct	Independent angiographic core lab and CEC	Independent angiographic core lab and CEC	Independent angiographic core lab and CEC	Independent angiographic core lab and CEC
Key characteristics and outcomes				
Lesion length, mm	20.3 ± 10.5	19.5 ± 9.8	26.0 ± 11.7	---
Calcified length, mm	22.3 ± 12.5	25.7 ± 12.4	47.9 ± 18.8	---
Severe calcification	100.0%	94.2%	100%	---
Pre % diameter stenosis	68.1 ± 13.1	60.0 ± 12.0	65.1 ± 10.8	
Final % diameter stenosis	13.3 ± 11.6	7.8 ± 7.1	11.9 ± 7.1	---
Final acute gain, mm	1.7 ± 0.6	1.7 ± 0.5	1.7 ± 0.5	---
Final flow-limiting dissections (Type D-F)	0.0%	0.0%	0.3%	---
Final serious angiographic complications	0.0%	0.0%	0.5%	---
30-day MACE	5.0%	7.6%	7.8%	---

*Disrupt CAD IV data not yet available. Values are mean ± standard deviation.

Online Table 11. Outcomes for roll-in and pivotal patients

Patient characteristic	Roll-in (n=47)	Pivotal (n=384)	P-value
Age, years	70.3 ± 7.6	71.2 ± 8.6	0.69
Male	35 (74.5)	294 (76.6)	0.72
Diabetes	17 (36.2)	154 (40.1)	0.64
Hypertension	42 (89.4)	342 (89.1)	1.0
Hyperlipidemia	38 (80.9)	342 (89.1)	0.15
Prior myocardial infarction	11 (23.4)	69 (18.0)	0.43
Prior coronary artery bypass grafting	2 (4.3)	36 (9.4)	0.41
Prior stroke or TIA	5 (10.6)	29 (7.6)	0.40
Current smoker	6 (12.8)	47 (12.2)	0.82
Renal insufficiency (eGFR <60 ml/min/1.73m^2)	14 (29.8)	101 (26.4)	0.60
Pacemaker	2 (4.3)	18 (4.7)	1.0
ICD/CRT-D	1 (2.1)	6 (1.6)	0.56
Angina Classification			0.08
Class 0	13 (27.7)	48/381 (12.6)	
Class I	5 (10.6)	56/381 (14.7)	
Class II	17 (36.2)	142/381 (37.3)	
Class III	11 (23.4)	126/381 (33.1)	
Class IV	1 (2.1)	9/381 (2.4)	
Angiographic characteristic (core laboratory)			
Target vessel			0.33

Protected left main artery	0 (0.0)	6 (1.6)	
Left anterior descending artery	28 (59.6)	217 (56.5)	
Circumflex artery	9 (19.1)	49 (12.8)	
Right coronary artery	10 (21.3)	112 (29.2)	
Reference vessel diameter, mm	3.06 ± 0.43	3.03 ± 0.47 [381]	0.42
Minimum lumen diameter, mm	1.03 ± 0.41	1.06 ± 0.36 [381]	0.53
Diameter stenosis, %	66.5 ± 12.1	65.1 ± 10.8 [381]	0.83
Lesion length, mm	27.0 ± 12.0	26.0 ± 11.7 [381]	0.50
Calcified length, mm	45.8 ± 16.2	47.9 ± 18.8	0.73
Severe calcification*	47 (100)	384 (100.0)	---
Bifurcation lesion with side branch involvement	19 (40.4)	115 (29.9)	0.18
Outcomes			
Freedom from 30-day MACE	42 (89.4)	353/383 (92.2)	0.57
Procedure success†	41 (87.2)	355 (92.4)	0.25
Device crossing success‡	44 (93.6)	368 (95.8)	0.45

Values are n (%) or mean ± standard deviation. *Defined as radiopaque densities noted without cardiac motion generally involving both sides of the arterial wall. †Procedural success defined as successful stent delivery with 50% residual stenosis and without in-hospital MACE. ‡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. TIA= transient cerebral ischemic event; eGFR=estimated glomerular filtration rate using the MDRD formula; ICD/CRT-D= implantable cardiac defibrillator with or without bi-ventricular pacing capability.