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Running Title: Coronary IVL Disrupt CAD Patient-Level Pooled Analysis

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Tweet/handle: Disrupt CAD IPD pooled analysis demonstrates consistent safety and effectiveness of intravascular lithotripsy to optimize lesion preparation in severely calcified coronary artery disease; @djkereiakes, @DrJMHill, @GreggWStone, @matthewjpricemd, @drdrewkleinphi, @perc_surgeon, @ron_waksman, @ziadalinyc

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ABSTRACT

Aims. The clinical outcomes of intravascular lithotripsy (IVL) to optimize target lesion preparation in severely calcified *de novo* coronary stenoses have been examined in four prospective studies (Disrupt CAD I, II, III, and IV). The aim of this pooled analysis was to assess the cumulative safety and effectiveness of coronary IVL.

Methods. Patient data were pooled from the Disrupt CAD studies which shared uniform study criteria, endpoint definitions and adjudication, and procedural follow-up. The primary safety endpoint was freedom from MACE (composite of cardiac death, all MI, or TVR) at 30 days. The primary effectiveness endpoint was procedural success, defined as stent delivery with a residual stenosis ≤30% by QCA without in-hospital MACE. Secondary outcomes included serious angiographic complications, target lesion failure (TLF), cardiac death (CD) and stent thrombosis (ST) at 30 days.

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

Conclusions. In the largest cohort of patients treated with coronary IVL assessed to date, coronary IVL safely facilitated successful stent implantation in severely calcified coronary lesions with a high rate of procedural success.

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

CONDENSED ABSTRACT

The Disrupt CAD individual patient data pooled analysis demonstrated safety and effectiveness of coronary intravascular lithotripsy (IVL) as an adjunct to stent implantation in severely calcified coronary artery lesions. Procedural success rates were high and angiographic and 30-day clinical outcomes were favorable despite the severity of disease treated.

ABBREVIATIONS AND ACRONYMS

ARC= Academic Research Consortium
DES= drug-eluting stent
IVL= intravascular lithotripsy
MACE= major adverse cardiovascular events
PCI= percutaneous coronary intervention

INTRODUCTION

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is the most frequent mode of coronary artery revascularization. Advanced age and an increasing frequency of diabetes mellitus, hypertension and renal insufficiency contribute to an increasing prevalence and severity of coronary calcification (1-3). Despite the use of high pressure non-compliant balloon catheters, cutting/scoring balloons and atheroablative technologies (i.e., laser, orbital and rotational atherectomy) to modify calcium (3-7), PCI of heavily calcified lesions may be associated with early complications (coronary dissection, vessel perforation, myocardial infarction [MI]) and/or late adverse events (stent restenosis, thrombosis and repeat revascularization). Coronary calcification may limit stent delivery and deployment, and results in stent under-expansion, strut malapposition and direct damage to the stent surface (including polymer), with potential impairment of drug delivery (8-11). Stent under-expansion is the most powerful predictor of subsequent stent thrombosis and/or restenosis (11-16). Although atheroablation facilitates stent expansion, calcium modification by atherectomy 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 severely calcified lesions in the Disrupt CAD I, II, III, and IV studies. These individual single-arm, prospective, multicenter non-randomized studies demonstrated high rates of device and procedural success as well as excellent early angiographic and clinical outcomes (22-25), providing evidence for device effectiveness and safety as well as insights into the mechanism(s) of calcium modification. In the present study, we performed an

individual patient-level pooled analysis of the Disrupt CAD studies to assess the cumulative safety and effectiveness of IVL to optimize target lesion preparation in patients with severely calcified *de novo* coronary stenoses and to identify the predictors of success following IVL treatment.

METHODS

Studies and Study Objectives. Patients treated with the Shockwave Medical (Santa Clara, CA, USA) IVL system and coronary IVL catheter for the treatment of *de novo* calcified coronary artery disease were pooled from the Disrupt CAD studies. The study designs, detailed inclusion criteria, and outcomes of the four Disrupt CAD studies have been described previously (22-25). The major features of each study are shown in Online Table 1. Briefly, all were prospective, multicenter, single-arm studies which evaluated the safety and effectiveness of coronary intravascular lithotripsy (IVL) prior to stenting in patients who presented with stable or unstable angina or silent ischemia due to severely calcified *de novo* coronary lesions. Subject inclusion criteria were similar across all studies. The definition of severe calcification by operator assessment required the presence of fluoroscopic radiopacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least 1 location, and total length of calcium of at least 15 mm and extending partially into the target lesion, or an intravascular imaging-demonstrated calcium angle of ≥270° in at least 1 cross section. Each study was approved by the institutional review board or ethics committee at participating centers and all patients provided written, informed consent. The coronary IVL procedure was performed consistently across studies, according to each study protocol and the Instructions for Use (IFU). All Disrupt CAD studies used similar endpoint definitions, an independent adjudication processes for the angiographic core lab and Clinical Events Committee (CEC), and 30-day

follow-up procedures. Post procedure, dual antiplatelet therapy (DAPT) was prescribed as per applicable guidelines for a minimum of 6 months. Complete 30-day follow-up is available for all studies (Online Table 1).

Study Endpoints. The primary safety endpoint was 30-day major adverse cardiovascular events (MACE), defined as CEC-adjudicated composite occurrence of cardiac death (CD), myocardial infarction (MI) or target vessel revascularization (TVR). To provide consistency with prior studies (4,5), peri-procedural MI was defined as peak post-PCI CK-MB level >3x the upper limit of normal (ULN) with or without new pathologic Q-waves. Post-discharge MI was also defined using CK-MB level >3x ULN for CAD I and II. The 4th Universal Definition of MI (26) was incorporated in CAD III and IV for post-discharge MI given the rapid adoption of troponin as a biomarker. This minor change in definition had little impact on overall 30-day MI rates given that 97% of MI events occurred within the in-hospital phase. The primary effectiveness endpoint was procedural success, defined as stent delivery with a residual in-stent stenosis ≤30% as assessed by the angiographic core laboratory and without in-hospital MACE. Note that the more contemporary procedural success angiographic definition of ≤30% was chosen for this analysis rather than the threshold of <50% which was utilized in prior regulatory approval CAD studies (4,24). Secondary endpoints included procedural success with a residual stenosis threshold of <50%, final post-procedural percent diameter stenosis, post-IVL and final serious angiographic complications (defined as ≥ Grade D dissection, perforation, abrupt closure, slow flow/no-reflow), as well as target lesion failure (TLF) and Academic Research Consortium-defined definite or probable stent thrombosis at 30 days. Sub-group and multivariable analyses for the primary safety and effectiveness endpoints have been included.

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

RESULTS

Patients and Procedures. Between December 21, 2015 and April 6, 2020, a total of 628 patients were enrolled at 72 sites in 12 countries, including the United States, UK, Japan, France, Germany, Italy, Australia, Spain, Belgium, Netherlands, Sweden, and Denmark (Online Table 1). Patient follow-up at 30 days was completed in 626 patients (99.7%) with two patients lost to follow-up. Pooled baseline clinical and angiographic characteristics are presented in Table 1. The

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

Primary endpoints. Primary endpoint outcomes are shown in Table 3. The primary safety endpoint of 30-day MACE was 7.3% (95% CI: 5.4%-9.7%), driven by non-Q wave MI (6.9%, 95% CI: 5.0%-9.1%). MACE status was known for 99.7% (626/628) of patients. The primary effectiveness endpoint, procedural success with ≤30% residual stenosis, was achieved in 92.4% (95% CI: 90.0%-94.3%) of patients. These findings were consistent across all four Disrupt CAD studies (Figure 1).

Secondary endpoints. Procedural success with <50% residual stenosis was achieved in 93.2% (95% CI: 90.9%-95.0%) of patients. In-hospital MACE was 6.5% (95% CI: 4.7%-8.8%), driven by non-Q wave MI (5.7%, 95% CI: 4.1%-7.9%) (Table 3). Post-IVL and post-stent quantitative coronary angiography (QCA) measurements are shown in Table 4. Angiographic outcomes are shown in Figure 2. Diameter stenosis was significantly reduced immediately following IVL treatment (63.7% ± 11.8% vs 35.4% ± 13.0%, p<0.0001), and final in-stent

residual stenosis (following post-dilatation) was 12.1 ± 6.8% Serious angiographic complications immediately following IVL treatment were observed in 2.1% of patients due to flow-limiting dissection (1.8%) and slow flow (0.4%), with no occurrences of perforation, abrupt closure, or no-reflow. Final post-stent serious angiographic complications occurred in 0.3% of cases, with no occurrences of slow flow or no-reflow (Figure 2). As shown in Table 3, target lesion failure (TLF), cardiac death and definite or probable stent thrombosis events through 30 days occurred in 7.2% (95% CI: 5.3%-9.5%), 0.5% (95% CI: 0.1%-1.4%) and 0.8% (95% CI: 0.3%-1.9%) of patients. Case summaries for cardiac death and stent thrombosis events have been described previously (23,24).

Sub-group Analysis. Freedom from 30-day MACE and procedural success with ≤30% residual stenosis were lower in patients with lesion lengths ≥25 mm vs. <25mm (freedom from 30-day MACE: 90.0% vs. 94.6%, p=0.03; procedural success: 90.7% vs. 94.9%, p=0.05) and bifurcation lesions (freedom from 30-day MACE: 88.9% vs. 94.3%, p=0.03; procedural success: 89.5% vs. 94.8%, p=0.02). No differences in 30-day MACE (Figure 3) or procedural success were observed among any other sub-group analyzed (Figure 4).

Predictors of 30-day MACE and Procedural Success. Predictors of 30-day MACE and procedural success are shown in Table 5. By multivariable logistic regression, prior MI (OR: 2.06; 95% CI: 1.01-4.06, p=0.04) and treatment of bifurcation lesions (OR: 2.41; 95% CI: 1.27-4.54, p=0.006) and longer lesions (OR per 10mm: 1.31; 95% CI: 1.00-1.69, p=0.049) were independent predictors of 30-day MACE, while prior MI (OR: 0.53; 95% CI: 0.27-1.09, p=0.02) and treatment of bifurcation lesion (OR: 0.41; 95% CI: 0.22-0.78, p=0.018) were predictors of lack of procedural success.

DISCUSSION

The present pooled individual patient data analysis from the four Disrupt CAD studies represents the largest systematic assessment to-date of IVL treatment in *de novo*, severely calcified coronary arteries to facilitate and optimize target lesion preparation prior to stent implantation. The major findings of this analysis include: (1) IVL prior to coronary stent implantation was safe, with relatively low rates of in-hospital and 30-day MACE given the complexity of the target lesions undergoing PCI; (2) IVL was effective in achieving high procedural success rates with consistency of treatment effect across most subgroups analyzed; and (3) prior MI, bifurcation target lesions, and longer lesion length were associated with increased MACE rates and lower rates of procedural success. Importantly, despite the early learning curve of IVL use in the multiple operators, centers and countries participating in these studies, as well as the complexity of the lesions and vessels treated, IVL device safety was consistently demonstrated. Indeed, rates of MACE in-hospital and to 30 days in this complex lesion cohort were low compared to prior studies (3-7) and were driven largely by the incidence of periprocedural non-Q wave myocardial infarction as defined by a low but similar threshold (>3X URL for CKMB) across trials. Both independent adjudication of patient level data and size of the present analysis lend credibility to the low event rates observed. Further, these low in-hospital and 30-day event rates were achieved despite the fact that 97% of all target lesions treated were classified as severely calcified by an independent angiographic core laboratory. Indeed, the average target lesion and calcified vessel segment lengths (24.4 ± 11.5 mm and 41.5 ± 20.0 mm, respectively) for the pooled analysis population are among the longest reported for any PCI trial to date (4,18,27,28). Given the known procedural complications of atheroablative technologies in heavily calcified coronary arteries (4,18,28), the absence of vessel perforation,

abrupt coronary closure or no-reflow events following calcium modification by IVL is particularly noteworthy.

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

The present large, patient-level data analysis expands and extends prior clinical experience with IVL, enables credible subgroup analysis and facilitates multivariable assessment of predictors of success. In this regard, IVL treatment effect benefit, relative to atheroablation,

was evident regardless of age, presence of diabetes mellitus or chronic kidney disease (29-31). The present analysis confirms the previously established relationship between target lesion length, bifurcation involvement and history of prior MI with higher MACE rates following PCI (including atheroablative procedures), and thus may provide guidance regarding patient selection and procedural planning. These readily available clinical and angiographic variables were also independent predictors of IVL effectiveness (procedural success) and should be considered in shared decision-making discussions with patients. Not surprisingly, these same variables have demonstrated prognostic importance for safety and effectiveness of PCI with stent implantation, with or without adjunctive atheroablation (32-34).

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

Limitations

Several limitations of the current analysis should be acknowledged. First, although all four Disrupt CAD studies were carefully conducted with independent core laboratory and Clinical Events Committee adjudication, they were all single arm studies lacking a concurrent control population. The lack of a randomized comparator precludes definitive comparisons with

balloon-based (scoring, cutting, non-compliant) or atheroablative techniques (rotational or orbital atherectomy, laser) for PCI of severely calcified vessels. Second, substudy data from intravascular imaging by optical coherence tomography (OCT) that provides insights to the proposed IVL mechanism of action is not provided in the present clinical report. Pooled analysis of this experience is ongoing and will be the focus of a future manuscript. Nevertheless, adequate intravascular imaging data have been reported from the individual trials to support the premise of *in situ* circumferential and longitudinal multi-plane calcium fracture with fracture expansion following stent implantation as the dominant mechanism of vascular calcium modification by IVL (24,25,37). These reports have documented high values for post procedure percent stent expansion and minimum stent area measured by OCT, which may favorably impact long-term TLF rates. Third, the safety and effectiveness of IVL demonstrated in the current report is applicable to the patient cohort studied and may not be generalizable to "all-comers" with severe coronary calcification and does not apply to the routine treatment of moderately calcified lesions. Indeed, specific clinical (acute coronary syndromes) and angiographic target lesion subsets (ostial, left main, non-dilatable lesions, bypass graft, in-stent restenosis, lesion length >40 mm, etc.) were not included in this analysis. In addition, since the combined use of IVL with atheroablative technologies was excluded from the DISRUPT CAD studies, further investigation is needed to understand the potential complementary utility of these technologies. Data from the 'real world' experience will be acquired with the forthcoming U.S. post-market study to address these study limitations. Finally, ongoing follow-up will determine whether the favorable short-term results of IVL in severely calcified lesions confers long-term event-free survival.

CONCLUSIONS

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

PERSPECTIVES

WHAT IS KNOWN?

Severe coronary calcification impedes stent delivery and expansion and increases adverse clinical events after PCI.

WHAT IS NEW?

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

WHAT IS NEXT?

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

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FIGURE LEGENDS

Figure 1. MACE and procedural success for patients enrolled in the Disrupt CAD studies.

In-hospital (A) and 30-day (B) MACE rates demonstrate consistent outcomes across the individual Disrupt CAD studies. Procedural success defined using the residual stenosis ≤30% threshold (C) demonstrates consistent results among the Disrupt CAD studies. Heterogeneity among studies was evaluated using logistic regression with study as a fixed effect. All p-values were not statistically significant indicating consistency across the four studies for in-hospital and 30-day MACE and procedural success. Blue dashed line represents the overall weighted estimate for each parameter.

Figure 2. Procedural angiographic outcomes following IVL treatment.

Core-lab assessed minimum lumen diameter cumulative frequency curves (A) demonstrate an increase in MLD immediately following IVL treatment with further increase post-stent. Core-lab assessed diameter stenosis (B) demonstrates a significant decrease in diameter stenosis immediately following IVL treatment ($p<0.0001$) and post-stent ($p<0.0001$). For MLD and diameter stenosis measurements: pre-procedure n=625; post-IVL n=555; post-stent n=625. Post-stent assessments of MLD and diameter stenosis include post-dilatation in 94.1% of patients. Note that post-IVL angiographic imaging was not required in the Disrupt CAD studies. Core-lab assessment of serious angiographic complications (C) immediately following IVL treatment (n=561) and post-stent (n=628) demonstrated a low rates of flow-limiting dissections (≥ grade D) with no perforation, abrupt closure, or no-reflow events following IVL treatment.

MLD = minimum lumen diameter. Diameter stenosis values are mean and standard deviaion (error bars).

Figure 3. Sub-group analyses for the primary safety endpoint of freedom from 30-day MACE.

Significant differences in 30-day MACE were observed in the longer lesion length and bifurcation lesion subgroups. No differences in 30-day MACE were observed in all other subgroups. Dichotomization for age, renal insufficiency, RVD, and lesion length were selected based on clinically relevant thresholds.

eGFR = estimated glomerular filtration rate; RVD = reference vessel diameter

Figure 4. Subgroup analyses for the Procedural Success with ≤ 30% residual stenosis.

Significant difference in procedural success was observed in the bifurcation lesion subgroup. No differences in procedural success were observed in all other subgroups. Dichotomization for age, renal insufficiency, RVD, and lesion length were selected based on clinically relevant thresholds.

eGFR = estimated glomerular filtration rate; RVD = reference vessel diameter

Central Illustration. Safety and effectiveness of IVL across the Disrupt CAD studies.

Disrupt CAD I-IV MACE rates at 30 days (A) and procedural success (B), defined as successful stent delivery with in-stent residual stenosis ≤30% (core-lab assessed) without in-hospital MACE, demonstrated consistent outcomes among the individual Disrupt CAD studies. Heterogeneity among studies was evaluated using logistic regression with study as a fixed effect. All p-values were not statistically significant indicating consistency across the four studies for 30-day MACE (p=0.56) and procedural success (p=0.84). Pooled core-lab assessment of serious angiographic complications (C) immediately following IVL treatment (n=561) and post-stent (n

=628) demonstrated a low rates of flow-limiting dissections (≥ grade D) with no perforation, abrupt closure, or no-reflow events following IVL treatment.

Table 1. Baseline characteristics

Baseline characteristics	**N = 628**
Age, years	71.8 ± 8.9
Male	484 (77.1)
Country/Region	
United States	335 (53.3)
Europe	213 (33.9)
Japan	64 (10.2)
Australia	16 (2.6)
Diabetes	241 (38.4)
Hypertension	539 (85.8)
Hyperlipidemia	531 (84.6)
Prior myocardial infarction	137 (21.8)
Prior coronary artery bypass grafting	60 (9.6)
Prior stroke or TIA	54 (8.6)
Current or former smoker	357 (56.8)
Renal insufficiency (eGFR <60 ml/min/1.73m^2)	157/625 (25.1)
Pacemaker or ICD/CRT-D	39 (6.2)
Angina Classification	
Class 0	89 (14.5)
Class I	142 (23.1)
Class II	228 (37.1)
Class III	143 (23.2)
Class IV	13 (2.1)
Angiographic characteristic (core laboratory)	
Target vessel	
Protected left main artery	9 (1.4)
Left anterior descending artery	368 (58.6)
Circumflex artery	75 (11.9)
Right coronary artery	176 (28.0)

Reference vessel diameter, mm	2.95 ± 0.51 [N=625]
Minimum lumen diameter, mm	1.07 ± 0.38 [N=625]
Diameter stenosis, %	63.7 ± 11.8 [N=625]
Lesion length, mm	24.4 ± 11.5 [N=624]
Calcified length, mm	41.5 ± 20.0 [N=623]
Severe calcification*	609 (97.0)
Bifurcation lesion with side branch involvement	190 (30.3)

Values are 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 = 628
Total procedure time, min	57.0 (41.5, 83)
Contrast volume, mL	179.8 ± 77.3
Access*	
Radial	281/448 (62.7)
Femoral	163/448 (36.4)
Brachial	3/448 (0.7)
Ulnar	1/448 (0.2)
Pre-dilatation	299 (47.6)
Patients undergoing IVL	620 (98.7)
Maximum IVL inflation pressure, atm	6.0 ± 0.5
Number of lithotripsy catheters	1.3 ± 0.6
IVL Balloon to RVD ratio	1.2 ± 0.2
Number of pulses	74.7 ± 42.7
Post-IVL dilatation	84/500 (16.8)
Stent delivery	625 (99.5)
Number of stents implanted	1.3 ± 0.5
Post-stent dilatation	588 (94.1)
Total stent length, mm	33.2 ± 14.4
Duration of hospitalization	1.0 (1.0, 1.0)

Values are n (%), median (Q1, Q3) or mean ± standard deviation. *Access data collected in CAD III and CAD IV only.

Table 3. Primary and Secondary Endpoints

	N = 628
In-hospital MACE	6.5 [4.7-8.8]
Cardiac death	0.2 [0.0-0.9]
All myocardial infarction	6.4 [4.6-8.6]
Non–Q-wave	5.7 [4.1-7.9]
Q-wave	0.6 [0.2-1.6]
Target vessel revascularization	0.3 [0.0-1.2]
30-day MACE*	7.3 [5.4-9.7]
Cardiac death	0.5 [0.1-1.4]
All myocardial infarction	6.9 [5.0-9.1]
Non–Q-wave	5.9 [4.2-8.1]
Q-wave	1.1 [0.5-2.3]
Target vessel revascularization	1.1 [0.5-2.3]
Procedural Success	
Residual stenosis <50%	93.2 [90.9-95.0]
Residual stenosis ≤30%	92.4 [90.0-94.3]
Secondary endpoints at 30 days*	
Target lesion failure at 30 days	7.2 [5.3-9.5]
Cardiac death	0.5[0.1-1.4]
TV-MI	6.9 [5.0-9.1]
ID-TLR	1.0 [0.4-2.1]
Stent thrombosis (definite or probable)	0.8 [0.3-1.9]
Definite	0.6 [0.2-1.6]
Probable	0.3 [0.0-1.2]

Values are % [95% CI]. *N = 626 for 30-day follow-up endpoints.

Table 4. Angiographic outcomes

Core laboratory-assessed	**N = 628**
Post-IVL angiographic outcomes*	
Acute gain, mm	0.82 ± 0.48
Minimum lumen diameter, mm	1.89 ± 0.48
Residual diameter stenosis, %	35.4 ± 13.0
Final in-segment angiographic outcomes	
Acute gain, mm	1.48 ± 0.48
Minimum lumen diameter, mm	2.54 ± 0.47
Residual diameter stenosis, %	16.4 ± 8.3
<50%	99.4 [98.6-99.9]
≤30%	95.7 [94.0-97.3]
Final in-stent angiographic outcomes†	
Acute gain, mm	1.68 ± 0.47
Minimum lumen diameter, mm	2.75 ± 0.44
Residual diameter stenosis, %	12.1 ± 6.8
<50%	100.0 [99.4-100.0]
≤30%	98.9 [97.7-99.6]

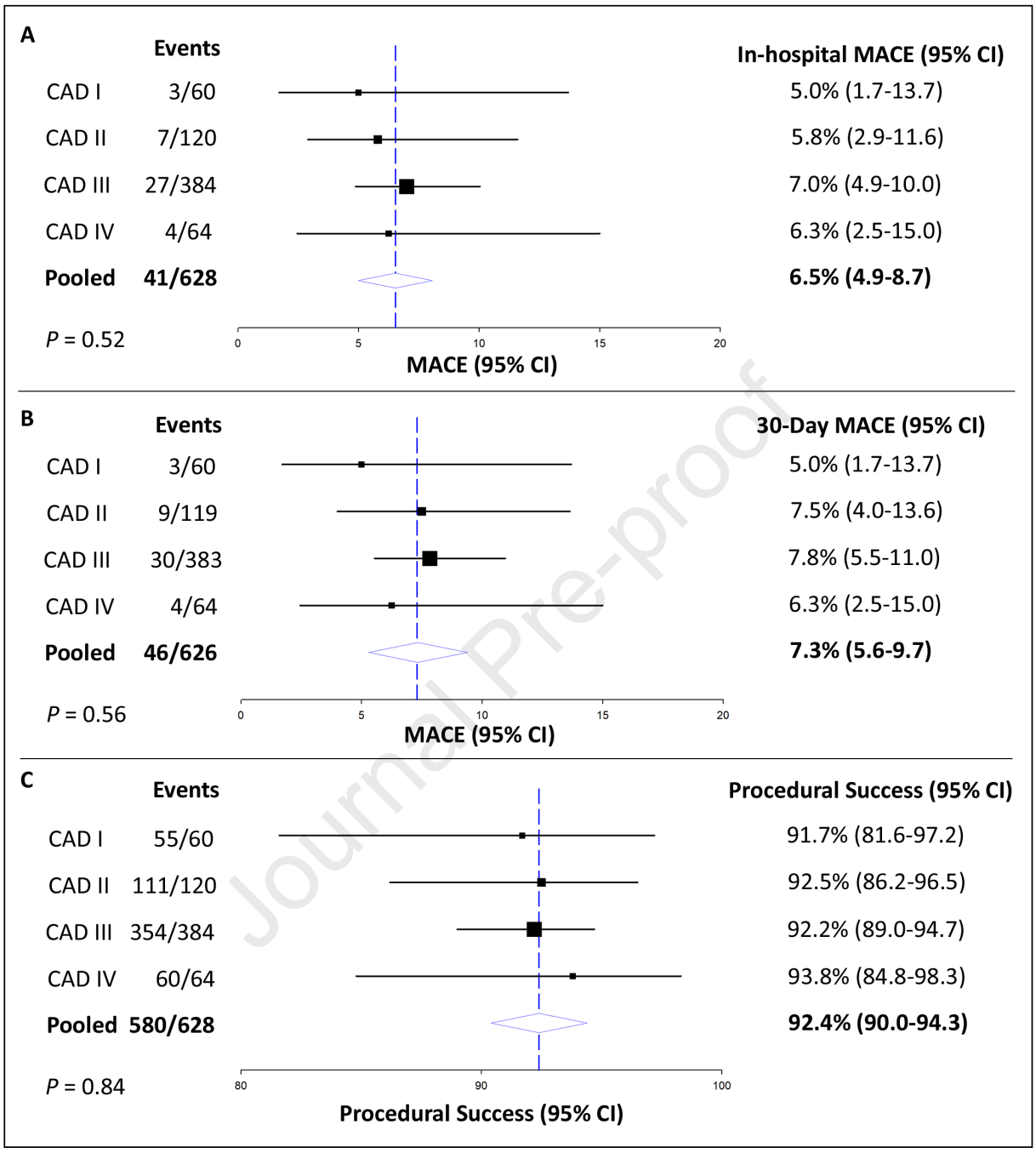
Values are % [95% CI] or mean ± standard deviation. *N = 555; post-IVL angiographic data capture was not required per protocol in the Disrupt CAD studies. †N = 625 for final in-stent angiographic outcomes.

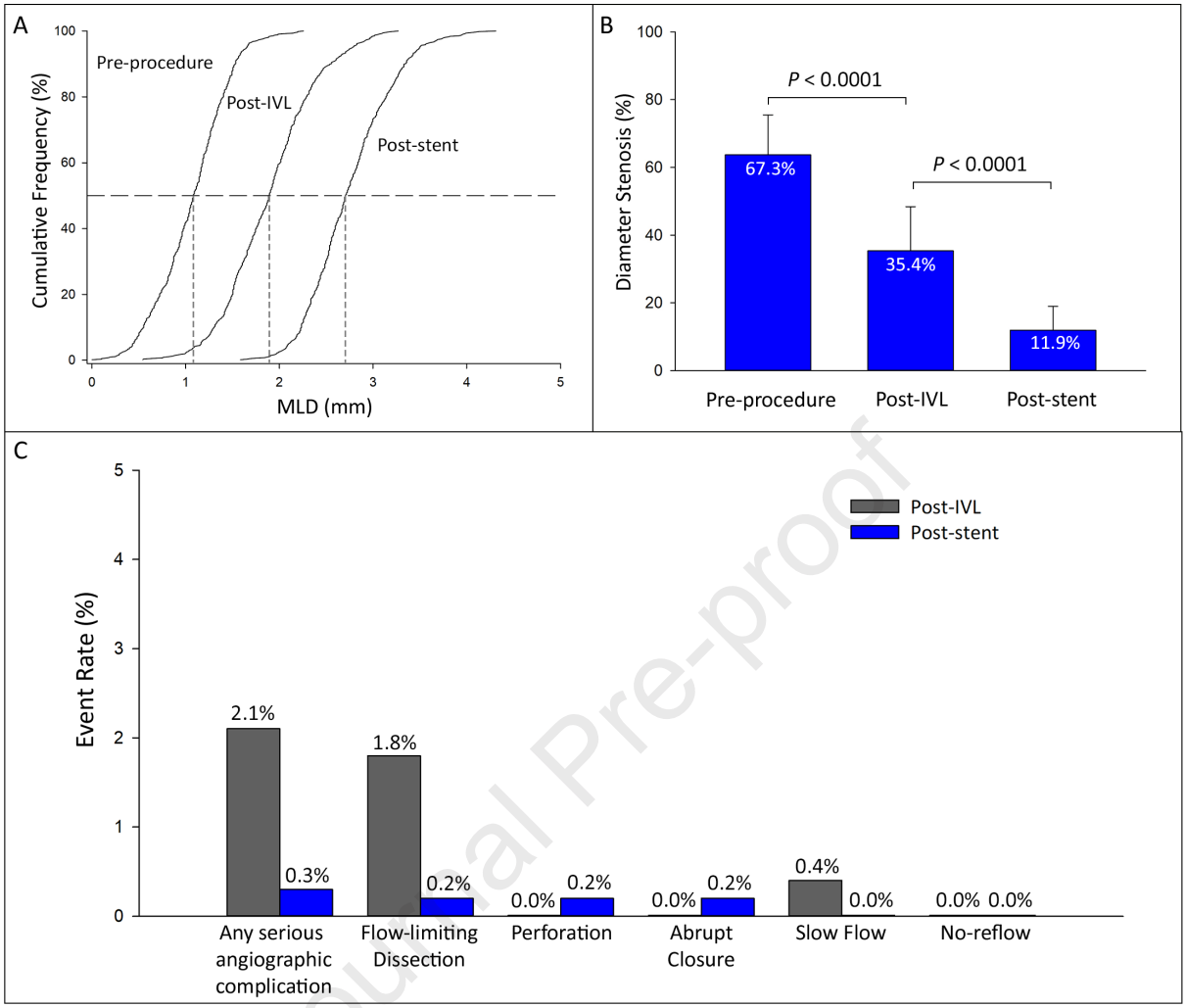
Table 5. Independent Predictors of 30-day MACE and Procedural Success

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

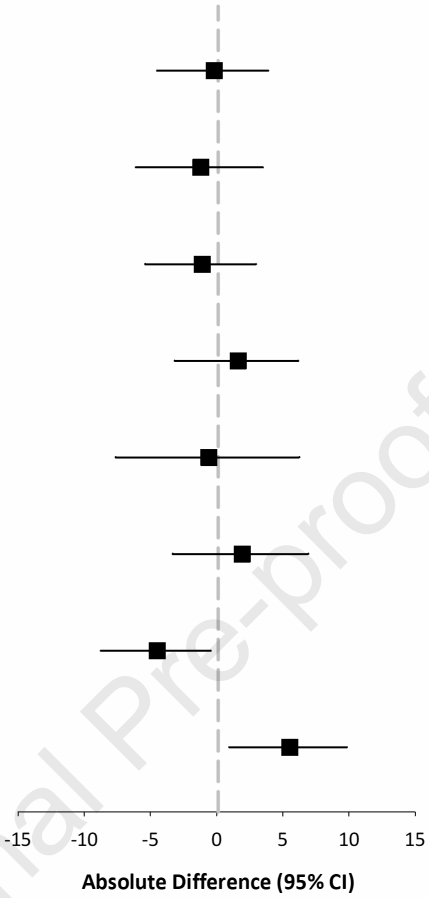
The independent predictors of MACE at 30 days and procedural success were determined by multivariate logistic regression using stepwise selection with a $p<0.1$ univariate threshold for entry and a $p<0.05$ level of significance for the final multivariate model, adjusted by study. The following variables were entered into the models: Age (75 years), sex, prior MI, lesion length per 10mm, LVEF (≥50%), diabetes, eGFR (<60ml/min/1.73m2), hyperlipidemia, hypertension, prior stroke or TIA, BMI per 5, current or former smoker, RVD (>2.5mm), bifurcation, lesion location (LAD vs non-LAD). *Procedural success defined as stent delivery with residual stenosis ≤30% without in-hospital MACE.

MACE = major adverse cardiovascular events; MI = myocardial infarction

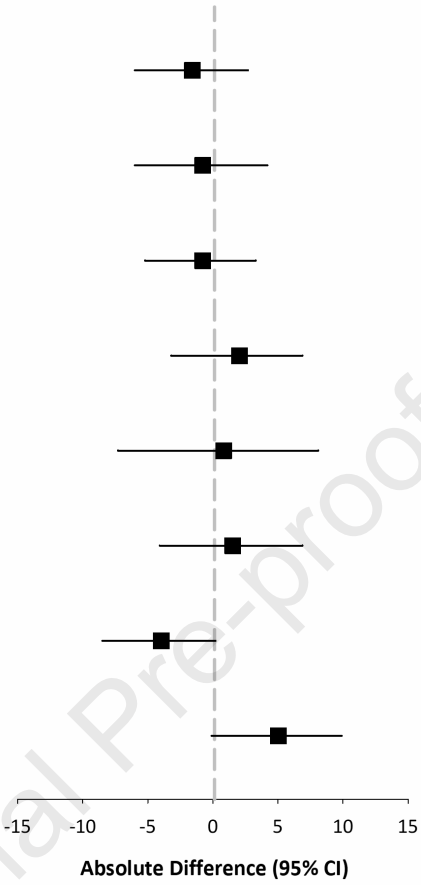


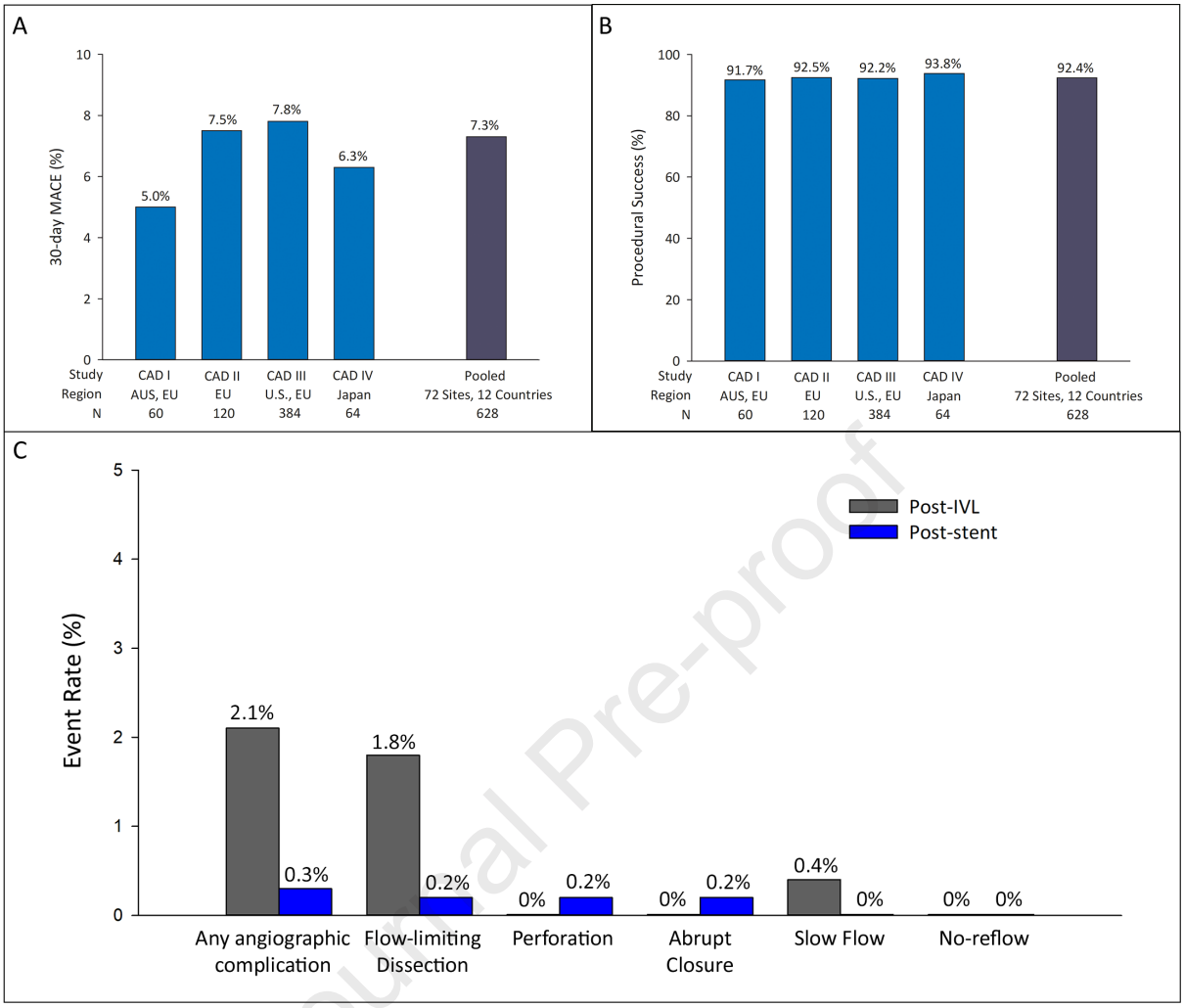


Sub-group	Freedom from 30-day MACE	Absolute Difference (95% CI)	P-value
Overall	92.7% (581/627)		
Age (years)			
< 75	92.8% (346/373)	-0.3 [-4.5-3.9]	1.0
≥ 75	92.5% (236/255)		
Sex			
Male	93.0% (450/484)	-1.3 [-6.1-3.5]	0.59
Female	91.7% (132/144)		
Diabetes			
Yes	93.4% (225/241)	-1.2 [-5.4-3.0]	0.64
No	92.2% (357/387)		
Renal insufficiency			
eGFR < 60ml/min/1.73m^2	91.7% (144/157)	1.5 [-3.2-6.2]	0.59
eGFR ≥ 60ml/min/1.73m^2	93.2% (436/468)		
Prior CABG			
Yes	93.3% (56/60)	-0.7 [-7.6-6.2]	1.0
No	92.6% (526/568)		
RVD			
≤ 2.5mm	91.2% (114/125)	1.8 [-3.3-6.9]	0.45
> 2.5 mm	93.0% (465/500)		
Lesion length			
< 25 mm	94.6% (336/355)	-4.6 [-8.7--0.5]	0.03
≥ 25 mm	90.0% (242/269)		
Bifurcation lesions			
Yes	88.9% (169/190)	5.4 [1.0-9.8]	0.03
No	94.3% (413/438)		

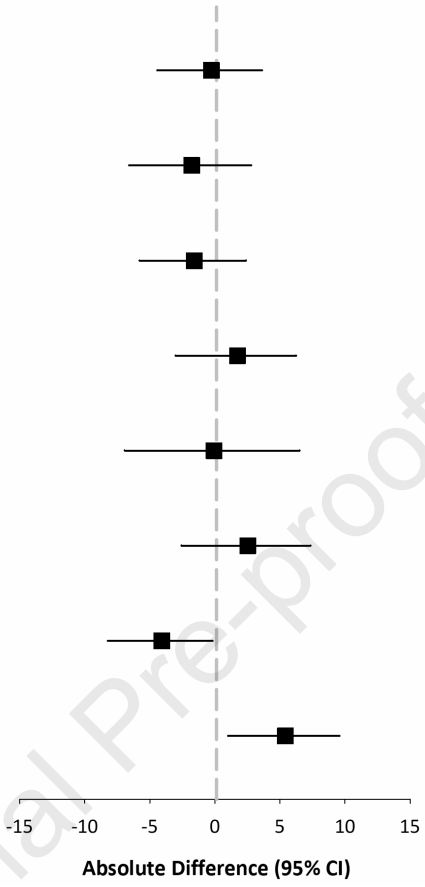


Sub-group	Procedural Success - ≤ 30%RS	Absolute Difference (95% CI)	P-value
Overall	92.4% (580/628)		
Age (years)			
< 75	93.0% (347/373)	-1.7 [-6.0-2.7]	0.45
≥ 75	91.4% (233/255)		
Sex			
Male	92.6% (448/484)	-0.9 [-6.0-4.2]	0.72
Female	91.7% (132/144)		
Diabetes			
Yes	92.9% (224/241)	-0.9 [-5.2-3.3]	0.76
No	92.0% (356/387)		
Renal insufficiency			
eGFR < 60ml/min/1.73m^2	91.1% (143/157)	1.9 [-3.2-6.9]	0.48
eGFR ≥ 60ml/min/1.73m^2	93.0% (435/468)		
Prior CABG			
Yes	91.7% (55/60)	0.7 [-7.3-8.1]	0.80
No	92.4% (525/568)		
RVD			
≤ 2.5mm	91.2% (114/125)	1.4 [-4.1-6.9]	0.58
> 2.5 mm	92.6% (463/500)		
Lesion length			
< 25 mm	94.1% (334/355)	-4.1 [-8.5-0.2]	0.07
≥ 25 mm	90.0% (242/269)		
Bifurcation lesions			
Yes	88.9% (169/190)	4.9 [-0.1-9.9]	0.05
No	93.8% (411/438)		





Sub-group	Procedural Success - < 50% RS	Absolute Difference (95% CI)	P-value
Overall	93.2% (585/628)		
Age (years)			
< 75	93.3% (348/373)	-0.4 [-4.4-3.6]	0.87
≥ 75	92.9% (237/255)		
Sex			
Male	93.6% (453/484)	-1.9 [-6.6-2.8]	0.45
Female	91.7% (132/144)		
Diabetes			
Yes	94.2% (227/241)	-1.7 [-5.8-2.4]	0.52
No	92.5% (358/387)		
Renal insufficiency			
eGFR < 60ml/min/1.73m^2	91.7% (144/157)	1.6 [-3.0-6.2]	0.36
eGFR ≥ 60ml/min/1.73m^2	93.3% (439/468)		
Prior CABG			
Yes	93.3% (56/60)	-0.2 [-6.9-6.5]	1.0
No	93.1% (529/568)		
RVD			
≤ 2.5mm	91.2% (114/125)	2.4 [-2.6-7.4]	0.33
> 2.5 mm	93.6% (468/500)		
Lesion length			
< 25 mm	94.9% (337/355)	-4.7 [-8.2--0.2]	0.05
≥ 25 mm	90.7% (244/269)		
Bifurcation lesions			
Yes	89.5% (170/190)	5.3 [1.0-9.6]	0.02
No	94.8% (415/438)		



SUPPLEMENTAL APPENDIX

INTRAVASCULAR LITHOTRIPSY FOR THE TREATMENT OF SEVERELY CALCIFIED CORONARY LESIONS: A PATIENT-LEVEL POOLED ANALYSIS OF THE DISRUPT CAD I, II, III AND IV STUDIES

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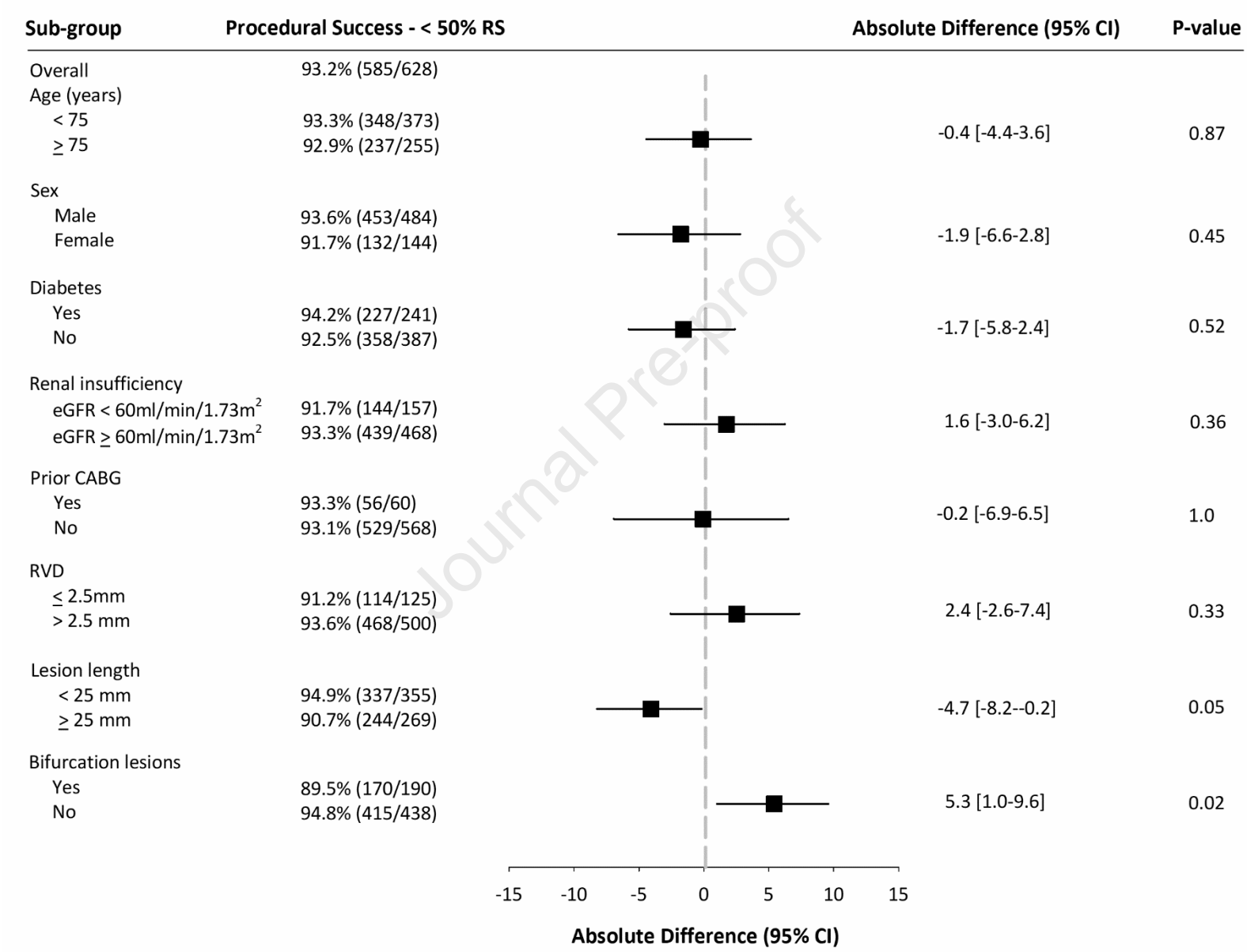

Online Figure 1. Sub-group analyses for the Procedural Success with < 50% residual stenosis

Online Table 1. Major characteristics of the four Disrupt CAD studies.

	Disrupt CAD I[1]	Disrupt CAD II[2]	Disrupt CAD III[3]	Disrupt CAD IV[4]
ClinicalTrials.gov identifier	NCT02650128	NCT03328949	NCT03595176	NCT04151628
Study design	Prospective, multi-center, single-arm	Prospective, multi-center, single-arm	Prospective, multi-center, single-arm	Prospective, multi-center, single-arm
Enrollment period	Dec 2015 – Sep 2016	May 2018 – Mar 2019	Jan 2019 – Mar 2020	Nov 2019 – Apr 2020
Number of patients	60	120	384	64
Number of centers	7	15	47	8
Participating regions	AU, EU	EU	U.S., EU	Japan
Independent angiographic core lab assessment	Yes	Yes	Yes	Yes
Independent Clinical Events Committee adjudication	Yes	Yes	Yes	Yes
Peri-procedural MI definition	CK-MB >3x ULN with or without new pathologic Q-wave	CK-MB >3x ULN with or without new pathologic Q-wave	CK-MB >3x ULN with or without new pathologic Q-wave	CK-MB >3x ULN with or without new pathologic Q-wave
Target lesions	Severely calcified, *de novo* coronary artery lesions	Severely calcified, *de novo* coronary artery lesions	Severely calcified, *de novo* coronary artery lesions	Severely calcified, *de novo* coronary artery lesions
Lesion locations	LM, LAD, RCA, LCx	LM, LAD, RCA, LCx	LM, LAD, RCA, LCx	LM, LAD, RCA, LCx
Target lesion length	≤ 32 mm	≤ 32 mm	≤ 40 mm	≤ 40 mm
Target lesion reference vessel diameter	2.5mm – 4.0mm	2.5mm – 4.0mm	2.5mm – 4.0mm	2.5mm – 4.0mm
Target lesion stenosis	≥50% and <100%	≥50% and <100%	≥70% and <100%	≥70% and <100%
30-day follow-up complete	60/60 (100%)	119/120 (99.2%)	383/384 (99.7%)	64/64 (100%)

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