Journal of the Society for Cardiovascular Angiography & Interventions 1 (2022) 100011

Contents lists available at ScienceDirect

Journal of the Society for Cardiovascular Angiography & Interventions

journal homepage: www.jscai.org

Original Research

Sex-Specific Outcomes After Coronary Intravascular Lithotripsy: A Patient-Level Analysis of the Disrupt CAD Studies

Yasin Hussain, MD [a], Kathleen E. Kearney, MD [b], J. Dawn Abbott, MD [c], Dean J. Kereiakes, MD [d], Carlo Di Mario, MD, PhD [e], Shigeru Saito, MD [f], Ecaterina Cristea, MD [a], Robert F. Riley, MD [d], Jean Fajadet, MD [g], Richard A. Shlofmitz, MD [h], Ziad A. Ali, MD, DPhil [h,i], Andrew J. Klein, MD [j], Matthew J. Price, MD [k], Jonathan M. Hill, MD [l], Gregg W. Stone, MD [m], Alexandra J. Lansky, MD [a,n,*]

[a] *Division of Cardiology, Yale School of Medicine, New Haven, Connecticut*
[b] *University of Washington, Seattle, Washington*
[c] *Brown University, Providence, Rhode Island*
[d] *The Christ Hospital and the Lindner Research Center, Cincinnati, Ohio*
[e] *Careggi University Hospital, Florence, Italy*
[f] *Shonan-Kamakura General Hospital, Kamakura, Kanagawa, Japan*
[g] *Clinique Pasteur, Toulouse, France*
[h] *St. Francis Hospital, Roslyn, New York*
[i] *Cardiovascular Research Foundation, New York, New York*
[j] *Piedmont Heart Interventional Cardiology, Atlanta, Georgia*
[k] *Scripps Clinic, La Jolla, California*
[l] *Royal Brompton Hospital, London, United Kingdom*
[m] *The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York*
[n] *Barts Heart Centre, London, United Kingdom*

A B S T R A C T

Background: Coronary artery calcification increases the procedural complexity of percutaneous coronary intervention and is associated with worse outcomes, especially in women. Intravascular lithotripsy (IVL) has been demonstrated to be safe and effective for vessel preparation in severely calcified stenotic lesions before stent implantation. Sex-based outcomes of IVL-facilitated stenting have not been defined.

Methods: We performed a patient-level pooled analysis of the 4 prospective, single-arm Disrupt CAD studies that evaluated the safety and efficacy of IVL-facilitated stenting. Patient baseline and procedural characteristics and clinical outcomes were examined based on sex. The primary safety end point was 30-day major adverse cardiovascular events, defined as the composite of cardiac death, myocardial infarction, or target vessel revascularization. The primary efficacy end point was procedural success, defined as stent delivery with residual in-stent stenosis ≤30% without in-hospital major adverse cardiovascular events.

Results: A total of 628 patients were included, of which 144 (22.9%) were women. Women were older ($P < .001$) and more likely to have hyperlipidemia ($P = .03$), renal insufficiency ($P = .05$), and prior myocardial infarction ($P = .05$). Women had smaller mean reference vessel diameter (2.7 ± 0.4 mm vs 3.0 ± 0.5 mm, $P < .001$), shorter lesion length (22.4 ± 10.3 mm vs 25.0 ± 11.7 mm, $P = .01$), and less side branch involvement (22.9% vs 32.4%, $P = .03$). Severe coronary calcification defined by angiography, stent delivery success, lesion predilatation, post-IVL dilatation, and poststent dilatation was similar between groups. There were no significant differences between women and men in the primary safety end point (8.3% vs 7.1%, $P = .61$; adjusted odds ratio 1.66; 95% confidence interval 0.78, 3.34; $P = .17$) or the primary efficacy end point (91.7% vs 92.6%, $P = .72$; adjusted odds ratio 0.58; 95% confidence interval 0.29, 1.24; $P = .15$). Post-IVL serious angiographic complications (flow-limiting dissection, perforation, abrupt closure, slow flow, no reflow) were similar for women and men (1.6% vs 2.3%, $P = .75$).

Conclusions: Despite more comorbidities and smaller vessel size, IVL-facilitated stenting of severely calcified lesions achieves similar safety and efficacy in women and men.

Abbreviations: DES, drug-eluting stents; IVL, intravascular lithotripsy; MACE, major adverse cardiovascular events; MI, myocardial infarction; OA, orbital atherectomy; PCI, percutaneous coronary intervention; RA, rotational atherectomy; RVD, reference vessel diameter; TVR, target vessel revascularization.

Keywords: Sex; Coronary artery disease; Intravascular lithotripsy; Calcium; Percutaneous coronary intervention.

* Corresponding author.
E-mail address: alexandra.lansky@yale.edu (A.J. Lansky).

https://doi.org/10.1016/j.jscai.2021.100011
Received 27 November 2021; Received in revised form 16 December 2021; Accepted 21 December 2021

Percutaneous coronary intervention (PCI) with second-generation drug-eluting stents (DES) is the standard of care for selected patients with coronary artery disease.[1,2] Despite DES, treatment of calcified lesions remains challenging and is associated with significantly worse acute and long-term outcomes compared with noncalcified lesions.[3-5] Calcified lesions now account for approximately a third of lesions treated in contemporary interventional practice as we face an aging population with a higher prevalence of diabetes, hypertension, and renal insufficiency.[6] Women with moderate-to-severe lesion calcium are particularly vulnerable to poor outcomes. In a dedicated DES registry of 6371 female patients, of which 1622 (25.5%) had moderate/severe calcium, outcomes at 3 years were significantly worse with a reported 38% higher mortality, a 48% higher rate of death or myocardial infarction (MI), and a 56% higher rate of death, MI, or target lesion revascularization (TLR) compared with treatment of mildly or noncalcified lesions.[7] Plaque modification with atherectomy improves lesion compliance, allowing optimal stent expansion, but is associated with increased periprocedural complications including coronary dissections, perforation, and higher rates of periprocedural MI.[8-10] The procedural risks of atherectomy are accentuated in women who have rates of serious flow-limiting coronary dissections and cardiac tamponade that are 4- to 5-fold higher than men treated with rotational atherectomy, leading to 2-fold higher rates of in-hospital major adverse cardiac events (MACE).[11] Similar results have been reported with orbital atherctomy.[12] Acute procedural complications in women may limit the use of atherectomy to optimize DES expansion (one of the strongest predictors of subsequent stent thrombosis and restenosis[13,14]) and likely contribute to the poor outcomes reported in the longer term.

Intravascular lithotripsy (IVL) (Shockwave Medical Inc) is a novel approach that uses acoustic pressure waves to fracture both superficial and deep calcium deposits *in situ*.[15] The safety and efficacy of lesion preparation with coronary IVL before DES implantation for patients undergoing PCI of severely calcified coronary lesions were evaluated in the observational Disrupt CAD I through IV studies.[16-19] We aimed to evaluate 30-day safety and procedural efficacy of IVL-facilitated stent implantation in women compared with men.

Methods

Study population and objectives

This is a sex-based comparison of a patient-level pooled analysis of the Disrupt CAD I-IV studies evaluating coronary IVL-facilitated stenting for *de novo* severely calcified coronary artery lesions in patients with stable or unstable angina or silent ischemia. Study designs, detailed inclusion criteria, and outcomes of the Disrupt CAD I-IV studies have been described previously.[16,17,19-21] The Disrupt CAD I-IV studies had similar eligibility criteria (Supplemental Table S1). Severe calcification was defined by the angiographic appearance (before contrast injection) of radiopacities involving both sides of the arterial wall of at least 15 mm in length or based on intravascular imaging demonstrating a calcium angle $\geq 270^{\circ}$ in at least 1 cross section. Lesion predilation was permitted, and IVL followed by DES implantation was consistently performed in each trial.[16-20] The studies had similar end point definitions adjudicated by an independent clinical events committee, and angiograms were reviewed by the same independent core laboratory (Supplemental Table S2). Clinical follow-up was performed in all studies at 30 days. The Disrupt CAD studies were performed in accordance with the Declaration of Helsinki, institutional review board or ethics committee approval was obtained for each study at the participating centers (Supplemental Table S3), and all patients provided written informed consent.

Study end points

The primary safety end point was 30-day MACE, defined as the composite of cardiac death, MI, or target vessel revascularization (TVR).

Table 1
Baseline clinical and angiographic characteristics.

Characteristic	Women, $n = 144$	Men, $n = 484$	*P* value
Age, y	74.2 ± 9.0	71.1 ± 8.8	<.001
Diabetes mellitus	59 (41.0)	182 (37.6)	.47
Hypertension	124 (86.1)	415 (85.7)	.91
Hyperlipidemia	130 (90.3)	401 (83.0)	.03
Prior myocardial infarction	23 (16.0)	114 (23.6)	.053
Prior coronary artery bypass grafting	9 (6.3)	51 (10.5)	.12
Prior stroke or transient ischemic attack	13 (9.0)	41 (8.5)	.83
Current or former smoker	62/143 (43.4)	295/480 (61.5)	<.001
Renal insufficiency[a]	45/143 (31.5)	112/482 (23.2)	.046
Pacemaker or ICD/CRT-D	7 (4.9)	32/483 (6.6)	.44
Canadian Cardiovascular Society angina classification			.03
Class 0	17/139 (12.2)	72/476 (15.1)	
Class I	21/139 (15.1)	121/476 (25.4)	
Class II	57/139 (41.0)	171/476 (35.9)	
Class III	42/139 (30.2)	101/476 (21.2)	
Class IV	2/139 (1.4)	11/476 (2.3)	
Angiographic characteristic (core laboratory)			
Target vessel			.43
Protected left main	0 (0.0)	9 (1.9)	
Left anterior descending	87 (60.4)	281 (58.1)	
Left circumflex	17 (11.8)	58 (12.0)	
Right	40 (27.8)	136 (28.1)	
Reference vessel diameter, mm	2.74 ± 0.43	3.02 ± 0.51 (481)	<.001
Minimum lumen diameter, mm	1.00 ± 0.43	1.08 ± 0.38 (481)	.04
Diameter stenosis, %	63.2 ± 12.2	63.9 ± 11.7 (481)	.52
Lesion length, mm	22.4 ± 10.3	25.0 ± 11.7 (480)	.01
Calcium length, mm	38.7 ± 18.1	42.4 ± 20.4 (479)	.052
Severe calcification[b]	138 (95.8)	471 (97.3)	.08
Bifurcation lesion with side branch involvement	33 (22.9)	157 (32.4)	.03

Values are *n* (%), *n/N* (%), mean ± standard deviation, or mean ± standard deviation (*n*).
ICD/CRT-D, implantable cardiac defibrillator with or without bi-ventricular pacing capability
[a] Estimated glomerular filtration rate (using the Modification of Diet in Renal Disease [MDRD] formula) < 60 mL/min/1.73 m^2.
[b] Defined as radiopaque densities noted without cardiac motion generally involving both sides of the arterial wall.

Periprocedural MI was defined in all studies as the peak post-PCI creatine kinase–myocardial band level >3× the upper limit of normal with or without new pathologic Q-waves, consistent with prior atherectomy studies.[10,17,22] Spontaneous MI after discharge was defined using a creatine kinase–myocardial band threshold of >3× upper limit of normal for Disrupt CAD I and II and the Fourth Universal Definition of MI[23] in Disrupt CAD III and IV. The primary efficacy end point was procedure success, defined as a residual in-stent stenosis ≤30% (angiographic core laboratory assessment) without in-hospital MACE. The secondary efficacy end points included procedural success with a residual diameter stenosis threshold of <50%, final postprocedural percent diameter stenosis, post-IVL and final serious angiographic complications (defined as dissection grade ≥D, perforation, abrupt closure, slow flow/no reflow), as well as target lesion failure, defined as the composite of cardiac death, target vessel MI, or ischemia-driven TLR at 30 days, and definite or probable stent thrombosis at 30 days as defined by the Academic Research Consortium.[24]

Statistical analysis

The primary analysis population was by intention-to-treat, consisting of all enrolled patients. Adjudicated patient-level data were pooled and compared based on sex. Continuous data are presented as mean ± standard deviation, and categorical variables are presented as percentages and frequencies. Multivariable logistic regression was performed to determine the independent relationship of sex to the primary 30-day safety and efficacy

Table 2
Procedural characteristics.

Characteristic	Women, $n = 144$	Men, $n = 484$	P value
Total procedure time, min	58.3 ± 26.5	66.2 ± 33.6	.004
Contrast volume, mL	170.3 ± 77.8	182.6 ± 77.0	.09
Vascular access[a]			.10
Radial	59/106 (55.7)	222/342 (64.9)	
Femoral	45/106 (42.5)	118/342 (34.5)	
Brachial	1/106 (0.9)	2/342 (0.6)	
Ulnar	1/106 (0.9)	0/342 (0.0)	
Predilatation	65 (45.1)	234 (48.3)	.50
Patients undergoing IVL	140 (97.2)	480 (99.2)	.09
Maximum IVL inflation pressure, atm	5.9 ± 0.4	6.0 ± 0.5	.26
Number of lithotripsy catheters	1.2 ± 0.4	1.4 ± 0.7	<.001
IVL balloon-to-RVD ratio	1.3 ± 0.2	1.2 ± 0.2	.049
Number of pulses	63.0 ± 35.2	78.1 ± 44.1	<.001
Post-IVL dilatation	15/114 (13.2)	69/386 (17.9)	.24
Stent delivery	143 (99.3)	482 (99.6)	1.00
Number of stents implanted	1.2 ± 0.5	1.3 ± 0.5	.24
Poststent dilatation	134 (93.1)	454 (93.8)	.75
Total stent length, mm	31.3 ± 13.6	33.8 ± 14.6	.07
Duration of hospitalization, days	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	.95

Values are mean ± standard deviation, n/N (%), n (%), or median (first quartile, third quartile).
IVL, intravascular lithotripsy; RVD, reference vessel diameter.
[a] Vascular access data collected in Disrupt CAD III and Disrupt CAD IV only.

outcomes. The following variables were entered into each model: sex, age, diabetes, smoking, chronic kidney disease, reference vessel diameter, minimal luminal diameter, and lesion length. Primary end point heterogeneity was analyzed using a logistic regression model including an intercept and fixed effect for study. Point estimates and Clopper–Pearson 95% confidence intervals (CIs) were constructed for primary end points. All statistical analyses were performed with SAS, version 9.4 (SAS Institute).

Results

From December 21, 2015, to April 6, 2020, a total of 628 patients including 144 (22.9%) women and 484 (77.1%) men were enrolled at 72 centers from 12 countries in the United States and Europe. Follow-up at 30 days was available in 626 of 628 (99.7%) patients. Women were older and more frequently had hyperlipidemia and renal insufficiency than men (Table 1). Women had a smaller reference vessel diameter and less side branch involvement, but severe calcification and calcium length were not different compared with men (Table 1).

Femoral access tended to be more common in women than in men, but the rate of successful IVL delivery, target lesion predilatation, and post-IVL and poststent dilatation was similar in women and men. Procedure duration was shorter in women, and fewer IVL catheters (1.2 ± 0.4 vs 1.4 ± 0.7, $P < .001$) and IVL pulses (63.0 ± 35.2 vs 78.1 ± 44.1, $P < .001$) were used than in men. Women had a significantly shorter lesion length (22.4 ± 10.3 vs 25.0 ± 11.7, $P = .01$). Stent implantation was similar in both sexes (99.3% vs 99.6%, $P = 1.00$), as was the median length of stay of 1 day (Table 2).

Primary end points

The primary safety end point of 30-day MACE was similar in women and men (8.3% vs 7.1%, $P = .61$; adjusted odds ratio [OR] 1.66; 95% CI 0.78, 3.34; $P = .17$). The primary efficacy end point of procedural success with ≤30% residual stenosis was achieved at high rates in both women and men with no significant difference (91.7% vs 92.6%, $P = .72$; adjusted OR 0.58; 95% CI 0.29, 1.24; $P = .15$) (Table 3).

Secondary end points

In-hospital outcomes including the MACE (7.6% vs 6.2%, $P = .54$) and its components (cardiac death, MI, and TVR) occurred with similar frequency in women and men (Table 3). At 30 days, the rates of cardiac death, MI, and TVR were also similar between groups. Ischemia-driven TLR and stent thrombosis were similar and infrequent between groups (Table 3).

Table 3
Primary and secondary endpoints.

Endpoint	Women, $n = 144$	Men, $n = 484$	P value
In-hospital MACE	11 (7.6)	30 (6.2)	.54
Cardiac death	0 (0.0)	1 (0.2)	1.00
All myocardial infarction	11 (7.6)	29 (6.0)	.48
Non–Q-wave	11 (7.6)	25 (5.2)	.26
Q-wave	0 (0.0)	4 (0.8)	.58
Target vessel revascularization	0 (0.0)	2 (0.4)	1.00
30-Day MACE	12/144 (8.3)	34/482 (7.1)	.61
Cardiac death	1/144 (0.7)	2/482 (0.4)	1.00
All myocardial infarction	11/144 (7.6)	32/482 (6.6)	.67
Non–Q-wave	11/144 (7.6)	26/482 (5.4)	.32
Q-wave	1/144 (0.7)	6/482 (1.2)	.70
Target vessel revascularization	1/144 (0.7)	6/482 (1.2)	.70
Procedural success			
Residual stenosis <50%	132 (91.7)	453 (93.6)	.42
Residual stenosis ≤30%	132 (91.7)	448 (92.6)	.72
Secondary end points at 30 d			
Target lesion failure	12/144 (8.3)	33/482 (6.8)	.54
Ischemia-driven target lesion revascularization	1/144 (0.7)	5/482 (1.0)	1.00
Stent thrombosis (definite or probable)	0/144 (0.0)	5/482 (1.0)	.35

Values are n (%) or n/N (%).
MACE, major adverse cardiovascular event.

Table 4
Core laboratory-assessed angiographic outcomes.

Outcome	Women, $n = 144$	Men, $n = 484$	P value
Post-IVL angiographic outcomes[a]	$n = 126$	$n = 429$	
Acute gain, mm	0.78 ± 0.40	0.84 ± 0.50	.21
Minimum lumen diameter, mm	1.80 ± 0.39	1.92 ± 0.50	.004
Residual diameter stenosis, %	34.1 ± 11.6	35.8 ± 13.4	.18
Post-IVL serious angiographic complications	2/128 (1.6)	10/435 (2.3)	.75
Severe dissection (type D-F)	2/126 (1.6)	8/434 (1.8)	.53
Perforation	0/126 (0.0)	0/435 (0.0)	—
Abrupt closure	0/126 (0.0)	0/435 (0.0)	—
Slow flow	0/126 (0.0)	2/435 (0.5)	1.00
No reflow	0/126 (0.0)	0/435 (0.0)	—
Final in-segment angiographic outcomes			
Acute gain, mm	1.37 ± 0.45	1.51 ± 0.49	.004
Minimum lumen diameter, mm	2.39 ± 0.40	2.59 ± 0.48	<.001
Residual diameter stenosis, %	16.3 ± 8.0	16.5 ± 8.4	.85
<50%	143 (100.0)	481 (99.4)	.59
≤30%	136 (95.1)	465 (96.1)	.61
Final in-stent angiographic outcomes			
Acute gain, mm	1.59 ± 0.40	1.71 ± 0.48	.002
Minimum lumen diameter, mm	2.60 ± 0.37	2.79 ± 0.45	<.001
Residual diameter stenosis, %	11.4 ± 6.6	12.3 ± 6.9	.18
<50%	143/143 (100.0)	482/482 (100.0)	1.00
≤30%	143/143 (100.0)	475/482 (98.5)	.21
Final serious angiographic complications	0 (0.0)	2 (0.4)	1.00
Severe dissection (type D-F)	0 (0.0)	1 (0.2)	.51
Perforation	0 (0.0)	1 (0.2)	1.00
Abrupt closure	0 (0.0)	1 (0.2)	1.00
Slow flow	0 (0.0)	0 (0.0)	—
No reflow	0 (0.0)	0 (0.0)	—

Values are mean ± standard deviation or n/N (%).
IVL, intravascular lithotripsy.
[a] Post-IVL angiographic data capture was not required per protocol in the Disrupt CAD studies.

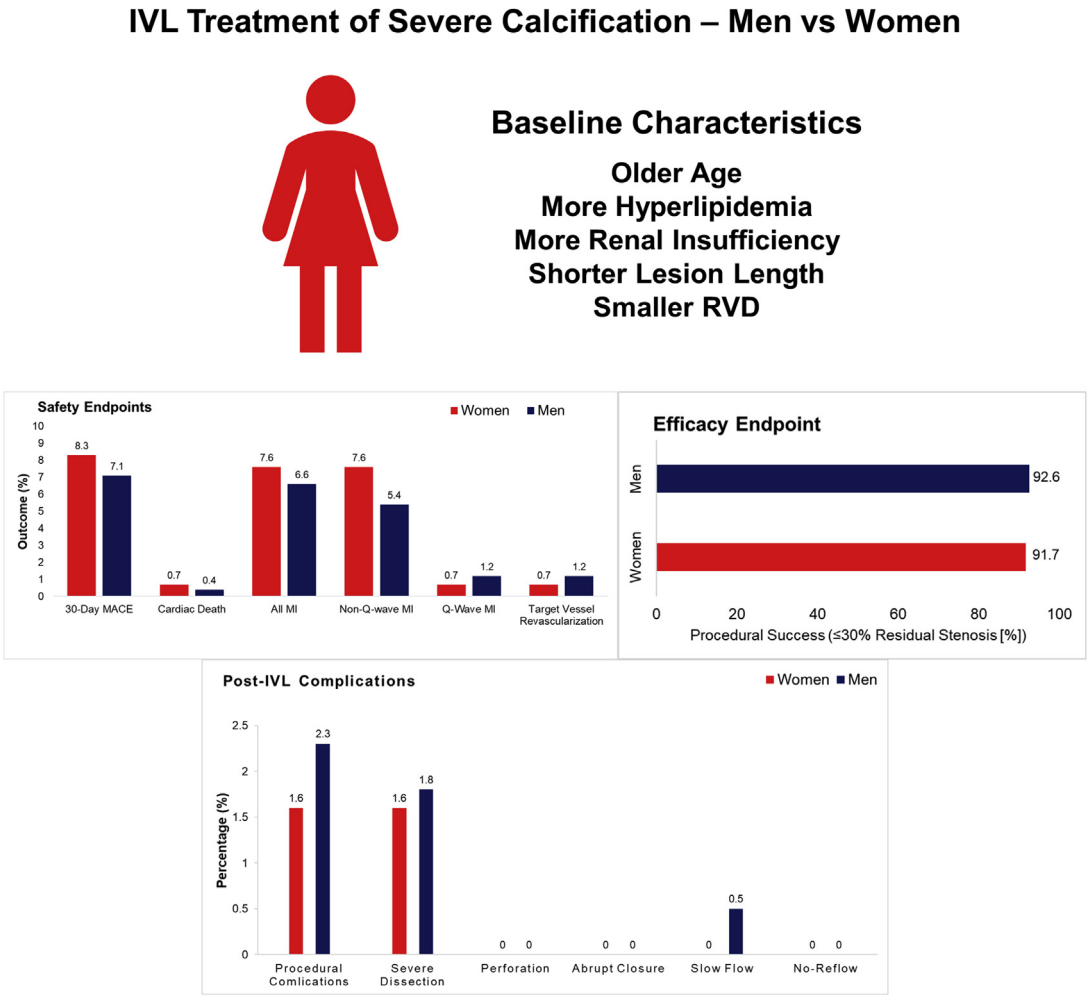
Immediately after IVL, acute gain (0.78 ± 0.40 mm vs 0.84 ± 0.50 mm, $P = .21$) and residual diameter stenosis (34.1% ± 11.6% vs 35.8% ± 13.4%, $P = .18$) were similar in women and men (Table 4). The final residual stenosis after stenting and final balloon after dilatation were similar in women and men (11.4% ± 6.6% vs 12.3% ± 6.9%, $P = .18$). Severe angiographic complications immediately after IVL treatment were infrequent in women and in men (1.6% vs 2.3%, $P = .75$) and included low rates of flow-limiting dissection (1.6% vs 1.8%, $P = .53$) and slow flow (0.0% vs 0.5%, $P = 1.00$), with no perforations, abrupt closure, or no reflow after IVL. Final poststent serious angiographic complications occurred in 0.0% of women and 0.4% of men.

Discussion

This patient-level pooled analysis from the Disrupt CAD I-IV studies is the largest series to evaluate sex-based outcomes of severely calcified coronary lesions treated with IVL lesion preparation before stent implantation. IVL-facilitated DES implantation was safe and effective independent of patient sex and was associated with infrequent angiographic complications, without evidence of excess acute angiographic or clinical complications in women (Central Illustration).

PCI of calcified lesions remains a significant predictor of procedural failure in the DES era.[25] Lesions with severe calcification have higher rates of no reflow and abrupt closure after stent implantation,[5] and coronary calcification is associated with stent under-expansion, deformation, and fracture and is a powerful independent predictor of restenosis and thrombosis.[26-28] A recent patient-level meta-analysis of 18 randomized DES trials (19,833 patients) with 5-year follow-up reported that moderate and severe target lesion calcification, present in 31.3% of patients, was associated with higher rates of target lesion failure (hazard ratio [HR] 1.21; 95% CI 1.09-1.34, $P < .001$), cardiac death (HR 1.44; 95% CI 1.20-1.72, $P < .001$), MI (HR 1.15; 95% CI 1.00-1.33, $P = .05$), and repeat revascularization (HR 1.11; 95% CI 1.02-1.20, $P = .02$).[29] In women, treatment of moderate/severe lesion calcium is particularly challenging. The Women in Innovation and Drug-Eluting Stents Collaboration showed that DES implantation of moderate and severely calcified lesions was associated with increased cardiac death (HR 1.44; 95% CI 1.00-2.07, $P = .046$), MI (HR 1.67; 95% CI 1.28-2.18, $P = .0001$), and TLR (HR 1.63; 95% CI 1.27-2.10, $P = .0001$) compared with lesions with no or mild calcification.[7]

Lesion preparation improves compliance of calcified lesions, allowing better stent expansion and improved long-term outcomes.[22,30] Although atheroablative strategies have been the standard approach for calcified lesion preparation, they are not universally available and are associated particularly in women with an increased risk of procedural complications, including vessel perforation, abrupt vessel closure, and no reflow due to platelet activation and particulate embolization.[9,10,31] In a retrospective analysis of 765 patients who underwent rotational atherectomy at a large referral center, periprocedural complications were significantly higher in women than those in men, including higher rates of coronary dissection (OR 3.78; 95% CI 1.42-10.05, $P = .004$), cardiac tamponade (OR 5.14; 95% CI 1.03-25.64, $P = .026$), and BARC 2 or greater bleeding (OR 2.37; 95% CI 1.07-5.23, $P = .028$) and a higher incidence of MACE at a median of 4.7 years of follow-up (HR 1.92; 95% CI 1.34-2.77, $P < .001$).[11] Similarly, in the prospective, multicenter ORBIT



II study, women undergoing orbital atherectomy had a higher risk of coronary dissection than men (OR 4.2; 95% CI 1.5-11.4, $P = .005$).[12]

Mechanisms of vascular injury in women may be due to direct mechanical injury related to smaller coronary arteries and higher burr:artery and balloon:artery ratios, increasing the risk of procedural complications.[32,33] Inherent vascular fragility has been reported in postmenopausal women, who represent most women undergoing PCI of calcied lesions. Postmenopausal status has been associated with increased arterial stiffness and lack of vessel compliance and may increase the risk of vessel damage during atheroablation.[34]

In the current patient-level analysis of IVL-facilitated stenting, serious angiographic and procedural complications were infrequent in both women and men with no excess complication in women. This favorable safety profile is likely related to the mechanism of action of IVL which delivers acoustic energy circumferentially, resulting in multiplane calcium fracture without atheroembolic debris or platelet activation from frictional heat generation.[35] In contrast to atheroablative technologies, IVL is not affected by wire bias or device size and has a rapid learning curve given its low-pressure balloon catheter delivery.[18] By improving transmural vessel compliance, IVL removes the need for high-pressure balloon dilatation before stent delivery, thus reducing vessel trauma and arterial dissection.[36] Significant improvements are observed in minimal lumen diameter and percent diameter stenosis after IVL alone despite a low IVL balloon pressure of 6 atm and the reduced need for post-IVL dilatation before stent delivery in both men and women. Despite smaller vessel size, IVL delivery was equally successful in women and men, and IVL allowed for >99% success in stent delivery in both sexes. Although women had fewer IVL catheters (1.2 ± 0.4 vs 1.4 ± 0.7, $P < .001$) and IVL pulses (63.0 ± 35.2 vs 78.1 ± 44.1, $P < .001$) used than men possibly due to less extensive lesion length (22.4 ± 10.3 vs 25.0 ± 11.7, $P = .01$), the rates of successful stent delivery after IVL were high for both women and men and appear similar from that reported with orbital atherectomy (99.4%) and rotational atherectomy (98.0%).[12,31] With IVL, immediate procedural complications were rare (1.6% women and 2.3% men), with no perforations or abrupt closures, and final post-stent complications were infrequent (0% women and 0.4% men); these rates appear to be significantly lower than have been reported with rotational or orbital atherectomy in women.[11,12] These findings thus support the use of IVL for plaque modification before stenting of severely calcified lesions in women.

Limitations

Although all 4 Disrupt CAD studies were carefully conducted with independent core laboratory and clinical event committee adjudication, they were all single-arm studies lacking a concurrent control population. Women represented only 23% (n = 144) of the cohort, and although this is the largest series evaluating sex-based outcomes with IVL, it may be underpowered to detect differences in outcomes. Lack of randomization precludes comparisons with balloon-based or alternative atheroablative techniques for treatment of severely calcified lesions. The studies excluded patients with acute coronary syndromes and lesions that were ostial, unprotected left main, in-stent restenosis, length >40 mm, non-dilatable, and bypass grafts, and the results are not generalizable to all comers. In addition, all target lesions were severely calcified; the outcomes of different approaches to moderately calcified target lesions deserve further study. While we report ORs for the primary end points, ORs are inherently limited when the assessed outcome is common, as is the case for the primary efficacy end point.[37] Finally, the present report focused on 30-day outcomes only; ongoing follow-up will assess the long-term safety and efficacy of IVL use in women.

Conclusions

This patient-level pooled analysis demonstrates that IVL for lesion preparation of severely calcified lesions is safe and effective in both women and men. Women had more comorbidities and smaller vessel size but shorter target lesions than men. After adjustment for these and other baseline differences, women had similarly high rates of procedural success and low rates of 30-day MACE after IVL-facilitated DES implantation as men in severely calcified target lesions.

Declaration of competing interest

J. Dawn Abbott reported serving as a consultant for Philips, Medtronic, Abbott, and Recor and research grants from Boston Scientific and Microport. Dean J. Kereiakes reported serving as a consultant for SINO Medical Sciences Technologies, Elixir Medical, Svelte Medical Systems, Caliber Therapeutics/Orchestra BioMed, and Shockwave Medical and is a stockholder in Ablative Solutions. Carlo Di Mario reported research grants from Amgen, Behring, Chiesi, Daiichi-Sanyo, Edwards Lifesciences, Medtronic, Shockwave, and Volcano Philips. Shigeru Saito reported serving as a consultant for Terumo and Japan Lifeline. Robert F. Riley reported honoraria from Boston Scientific, Asahi Intecc, and Medtronic. Richard A. Shlofmitz reported serving as a speaker for Shockwave Medical. Ziad A. Ali reported grants from the National Heart, Lung, and Blood Institute, Abbott Vascular, Philips, Boston Scientific, Acist Medical, Opsens Medical, Medtronic, Abiomed and Cardiovascular Systems, has received personal fees from Amgen, AstraZeneca, and Boston Scientific, and holds equity in Shockwave Medical. Matthew J. Price reported consulting and speaker honoraria from Abbott Vascular, Boston Scientific, Biosense Webster, Medtronic, Shockwave Medical, and W.L. Gore. Jonathan M. Hill reported fees and grant support from Abbott Vascular, Boston Scientific, Abiomed, and Shockwave Medical and is a stockholder in Shockwave Medical. Gregg W. Stone has received speaker honoraria from Cook and Infraredx, has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Reva, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, Gore, and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, MedFocus family of funds. The other authors have nothing to report.

Funding sources

Shockwave Medical funded the CAD I-IV studies and analysis.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at https://doi.org/10.1016/j.jscai.2021.100011.

Peer review statement

Given their roles as Deputy Editor and Editor in Chief, Dean J. Kereiakes and Alexandra Lansky had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Andrew M. Goldsweig.

References

1. Lawton JS, Tamis-Holland JE, Bangalore S, et al. ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;79:197–215.
2. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619.
3. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: pathogenesis and prognostic implications. *J Am Coll Cardiol*. 2014;63:1703–1714.

4. Huisman J, van der Heijden LC, Kok MM, et al. Impact of severe lesion calcification on clinical outcome of patients with stable angina, treated with newer generation permanent polymer-coated drug-eluting stents: a patient-level pooled analysis from TWENTE and Dutch PEERS (TWENTE II). *Am Heart J*. 2016; 175:121–129.
5. Généreux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials. *J Am Coll Cardiol*. 2014;63:1845–1854.
6. Allison MA, Criqui MH, Wright CM. Patterns and risk factors for systemic calcified atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2004;24:331–336.
7. Giustino G, Mastoris I, Baber U, et al. Correlates and Impact of coronary artery calcifications in women undergoing percutaneous coronary intervention with drug-eluting stents: from the Women in Innovation and Drug-Eluting Stents (WIN-DES) Collaboration. *JACC Cardiovasc Interv*. 2016;9:1890–1901.
8. Kini AS, Vengrenyuk Y, Pena J, et al. Optical coherence tomography assessment of the mechanistic effects of rotational and orbital atherectomy in severely calcified coronary lesions. *Catheter Cardiovasc Interv*. 2015;86:1024–1032.
9. Abdel-Wahab M, Richardt G, Joachim Büttner H, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv*. 2013;6:10–19.
10. Chambers JW, Feldman RL, Himmelstein SI, et al. Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). *JACC Cardiovasc Interv*. 2014;7:510–518.
11. Ford TJ, Khan A, Docherty KF, et al. Sex differences in procedural and clinical outcomes following rotational atherectomy. *Catheter Cardiovasc Interv*. 2020;95: 232–241.
12. Kim CY, Lee AC, Wiedenbeck TL, Lee MS, Chambers JW. Gender differences in acute and 30-day outcomes after orbital atherectomy treatment of de novo, severely calcified coronary lesions. *Catheter Cardiovasc Interv*. 2016;87:671–677.
13. Kobayashi Y, Okura H, Kume T, et al. Impact of target lesion coronary calcification on stent expansion. *Circ J*. 2014;78:2209–2214.
14. Choi KH, Song YB, Lee JM, et al. Impact of intravascular ultrasound-Guided percutaneous coronary intervention on long-term clinical outcomes in patients undergoing complex procedures. *JACC Cardiovasc Interv*. 2019;12:607–620.
15. Yeoh J, Hill J. Intracoronary lithotripsy for the treatment of calcified plaque. *Interv Cardiol Clin*. 2019;8:411–424.
16. Brinton TJ, Ali ZA, Hill JM, et al. Feasibility of Shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses. *Circulation*. 2019;139: 834–836.
17. Ali ZA, Nef H, Escaned J, et al. Safety and Effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: the disrupt CAD II study. *Circ Cardiovasc Interv*. 2019;12:e008434.
18. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease: the disrupt CAD III study. *J Am Coll Cardiol*. 2020;76:2635–2646.
19. Saito S, Yamazaki S, Takahashi A, et al, Disrupt CAD IV Investigators. Intravascular lithotripsy for vessel preparation in severely calcified coronary arteries prior to stent placement- primary outcomes from the Japanese disrupt CAD IV study. *Circ J*. 2021; 85:826–833.
20. Kereiakes DJ, Hill JM, Ben-Yehuda O, Maehara A, Alexander B, Stone GW. Evaluation of safety and efficacy of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: design and rationale for the disrupt CAD III trial. *Am Heart J*. 2020;225:10–18.
21. Kereiakes DJ, Di Mario C, Riley RF, et al. Intravascular lithotripsy for treatment of calcified coronary lesions: patient-level pooled analysis of the disrupt CAD studies. *JACC Cardiovasc Interv*. 2021;14:1337–1348.
22. Généreux P, Lee AC, Kim CY, et al. Orbital atherectomy for treating de novo severely calcified coronary narrowing (1-year results from the pivotal ORBIT II trial). *Am J Cardiol*. 2015;115:1685–1690.
23. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.
24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351.
25. Levi A, Kornowski R, Vaduganathan M, et al. Incidence, predictors, and outcomes of failed primary percutaneous coronary intervention: a 10-year contemporary experience. *Coron Artery Dis*. 2014;25:145–151.
26. Mori S, Yasuda S, Kataoka Y, Morii I, Kawamura A, Miyazaki S. Significant association of coronary artery calcification in stent delivery route with restenosis after sirolimus-eluting stent implantation. *Circ J*. 2009;73:1856–1863.
27. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995–998.
28. Sonoda S, Morino Y, Ako J, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J Am Coll Cardiol*. 2004;43:1959–1963.
29. Guedeney P, Claessen BE, Mehran R, et al. Coronary calcification and long-term outcomes according to drug-eluting stent generation. *JACC Cardiovasc Interv*. 2020; 13:1417–1428.
30. Yamamoto MH, Maehara A, Kim SS, et al. Effect of orbital atherectomy in calcified coronary artery lesions as assessed by optical coherence tomography. *Catheter Cardiovasc Interv*. 2019;93:1211–1218.
31. Abdel-Wahab M, Toelg R, Byrne RA, et al. High-speed rotational atherectomy versus modified balloons prior to drug-eluting stent implantation in severely calcified coronary lesions. *Circ Cardiovasc Interv*. 2018;11:e007415.
32. Mikhail GW. Coronary revascularisation in women. *Heart*. 2006;92(suppl 3): iii19–iii23.
33. Sharma SK, Tomey MI, Teirstein PS, et al. North American expert review of rotational atherectomy. *Circ Cardiovasc Interv*. 2019;12:e007448.
34. Samargandy S, Matthews KA, Brooks MM, et al. Arterial stiffness accelerates within 1 year of the final menstrual period: the SWAN Heart Study. *Arterioscler Thromb Vasc Biol*. 2020;40:1001–1008.
35. Kereiakes DJ, Virmani R, Hokama JY, et al. Principles of intravascular lithotripsy for calcific plaque modification. *JACC Cardiovasc Interv*. 2021;14:1275–1292.
36. Biondi-Zoccai GG, Agostoni P, Sangiorgi GM, et al. Incidence, predictors, and outcomes of coronary dissections left untreated after drug-eluting stent implantation. *Eur Heart J*. 2006;27:540–546.
37. Cummings P. The relative merits of risk ratios and odds ratios. *Arch Pediatr Adolesc Med*. 2009;163:438–445.