NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

Coronary arteries (the main blood vessels supplying blood to the heart) can become narrowed or blocked with fatty deposits. At times, the fatty deposits contain calcium and the arteries become stiff (calcified). Usually, a thin wire is passed down the affected artery (percutaneously, that is, via an artery in the groin or arm), and a small balloon is inflated to widen the narrowed artery, squashing the fatty deposits against the arterial wall so that blood can flow freely. Sometimes a small wire mesh tube (stent) is also inserted and left in place to keep the artery open. In this procedure, the balloon used to stretch the artery contains a device that delivers ultrasound shock waves. These break up the hard deposits (lithotripsy) to make it easier to insert the stent and to avoid damaging the artery.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2019 (01-07-2019).

Procedure name

- Intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

Specialist societies

- British Cardiovascular Intervention Society (BCIS)
- British Cardiovascular Society (BCS)
- Royal College of Physicians (Edinburgh)
- Royal College of Surgeons (Edinburgh)
- Royal College of Physicians London
- The Royal College of Physicians and Surgeons of Glasgow

Description of the procedure

Indications and current treatment

Coronary artery calcification (intimal and medial calcifications) increases the complexity of percutaneous treatment strategies in coronary interventions. It contributes to arterial wall stiffness, suboptimal stent delivery and expansion, in-stent restenosis, high rates of stent thrombosis and the need for subsequent target lesion revascularisation after endovascular interventions.

Standard endovascular treatment options for modifying calcification or plaques during percutaneous coronary intervention (PCI) include: balloon angioplasty using standard or super high-pressure non-compliant balloons; cutting or scoring

balloons; and stenting with or without coronary atherectomy (such as excisional, rotational, orbital or laser atherectomy). These treatments aim to allow optimal stent expansion and achieve maximal luminal gain. However, they may sometimes lead to localised wall injury, balloon rupture or the risk of coronary vessel dissections or perforation.

More recently intravascular shockwave lithotripsy has become another endovascular therapeutic option for PCI.

What the procedure involves

In this procedure, shockwave intravascular lithotripsy is administered to the calcified coronary artery before stent deployment during PCI.

A percutaneous guidewire is passed from the radial or femoral artery into a coronary artery. Then, an intravascular lithotripsy catheter with embedded emitters enclosed in an integrated angioplasty balloon is passed and connected to an external generator with a connector cable. The catheter is advanced to the target lesion guided by radiopaque markers on the catheter. The balloon is then inflated with a saline and contrast solution to ensure contact with vessel wall. The lithotripsy cycle is then activated. For every cycle, the catheter emits localised, high-energy, pulsatile, unfocused, circumferential, acoustic, sonic, pressure waves (lasting microseconds). These waves pass through the inflated balloon into the wall of the coronary artery. As the waves travel along the wall and the connective tissue, they disrupt calcium deposits (both intimal and medial calcium) by microfracturing the calcified lesions.

The cycle can be repeated until the lesion has been expanded sufficiently to allow optimal stent placement and optimisation. Intravascular lithotripsy during PCI may improve stent delivery and expansion and modify focal intravascular calcium while limiting localised injury to the endovascular surface.

Efficacy summary

Device or procedural success

In a case series of 60 patients (DISRUPT CAD I study) with severely calcified coronary arteries treated with intravascular lithotripsy (IVL) before stenting and PCI, the IVL balloon was delivered successfully in 98% (59/60) of patients and the stent in 100%.[1]

In a case series of 120 patients (DISRUPT CAD II study) with severely stenotic, calcified de novo coronary artery lesions treated with intravascular lithotripsy (IVL) for vessel preparation before stenting and PCI, the IVL balloon and stent were delivered successfully in all patients.[3]

In a case series of 71 patients with moderate to severely calcified coronary lesions (78 lesions) treated with IVL, there was successful device delivery and complete lithotripsy treatment to the target lesion in all patients.[4]

Clinical success

In the case series of 60 patients (DISRUPT CAD I study), clinical success was reported in 95% (57/60) of patients. Clinical success was defined as residual diameter stenosis of less than 50% after stenting without in-hospital major adverse cardiac event (MACE, defined as cardiac death, myocardial infarction or target vessel revascularisation).[1]

In the case series of 120 patients (DISRUPT CAD II study), clinical success was reported in 94% (113/120) of patients. Clinical success was defined as the ability of IVL to produce a diameter stenosis of less than 50% after stenting with no evidence of MACE.[3]

In the case series of 71 patients, success strategy (defined as successful delivery and expansion with less than 20% residual stenosis of target lesion, TIMI 3, no stent failure) was reported in 78% (61/78) of patients. Success strategy was reached in 85% (33/39) patients with primary IVL in native, severely calcified de novo lesions (39 lesions), in 77% (17/22) of patients with secondary IVL in lesions where non-compliant balloon dilation failed (22 lesions), and in 65% (11/17) of patients with tertiary IVL in lesions with stent under expansion after previous stenting (17 lesions).[4]

Angiographic outcomes

In the case series of 60 patients (DISRUPT CAD I study), median diameter stenosis (on angiography) was reduced from 73% (range 59% to 77%) at baseline to 12% (range 7% to 21%) at 6-month follow up. Also, minimum lumen diameter increased from 0.9 mm^2 (range 0.6 to 1.1 mm^2) to 2.6 mm^2 (range 2.3 to 2.9 mm^2), with an acute area gain of 1.7 mm^2 (range 1.3 to 2.1 mm^2) after coronary IVL and stenting.[1]

In the case series of 120 patients (DISRUPT CAD II study), angiographic success (defined as success in facilitating stent delivery, with less than 50% residual stenosis and freedom from perforation, slow flow, no flow or type D,E,F dissection at any point during the procedure) was reported in all patients. The residual stenosis after IVL was 9.4%, which further decreased to 7.8% after stent implantation. Also, minimum lumen diameter increased from 1.21 mm to 2.88 mm with an acute area gain of 1.67 mm after coronary IVL and stenting.[3]

A subgroup analysis of the DISRUPT CAD I study, which included 31 patients and assessed the performance of IVL on heavily calcified coronary lesions and stent placement using optical coherence tomography, showed a reduction in area

stenosis (from 67% to 40%), an increase in minimum lumen area (from 2.23 mm^2 to 4.16 mm^2) and an acute area gain of 2.08 mm^2 after IVL. The mean stent area was 8.37 mm^2 and mean stent expansion was 112% after stent deployment. Calcium modification was achieved after IVL in 43% (12/28) of lesions and after stenting in 55% (17/31) of lesions, with a high frequency of fractures per lesion in the heavily calcified lesions compared with the least calcified lesions (highest tertile versus lowest tertile; p=0.0009). There was also a greater incidence of calcium fracture in the highest calcification tertile (78% compared with 22%; p=0.057). Stent expansion was similar among all tertiles of calcification severity.[2]

A subgroup analysis of the DISRUPT CAD II study, which included 48 patients before IVL and 47 patients after stenting, reported that IVL statistically significantly increased minimal lumen area from 2.33 mm^2 to 6.10 mm^2 ($p<0.001$) after stent implantation and decreased calcium angle (from 175 to 127 degrees, p=0.05). Calcium fracture was identified in 79% (37/47) of lesions post IVL with multiple fractures in 55% (26/47) of lesions. Mean fracture length was 5.5 mm with 3.4 fractures per lesion and 1.6 fractures per frame. Maximum calcium thickness was 0.8 mm and angle at the calcium fracture site was 224 degrees. At pre-IVL maximum calcium site, mean calcium thickness decreased from 0.93 to 0.89 mm (p=0.004) and calcium angle decreased from 266 to 215 degrees ($p<0.0001$) after stent implantation. The acute area gain was 4.79 mm^2 and final stent expansion was 102%.[3]

In the case series of 71 patients, the mean diameter stenosis of calcified lesions at baseline was 71.8%, which decreased to 45% immediately after IVL and to 17.5% after stenting. Mean minimal lumen diameter was 1.01 mm at baseline, which increased to 1.90 mm after IVL and to 2.88 mm after stenting.[4]

In a case series of 26 patients with heavily calcified coronary arteries treated with IVL during PCI before stent deployment, there was angiographic success (less than 20% residual stenosis) in all patients.[6]

Safety summary

Cardiac death

In the case series of 60 patients, cardiac death (not related to the device) was reported in 3% (2/60) of patients.[3]

In the case series of 120 patients, cardiac death (14 days after treating a 95% lesion in the distal right coronary artery because of probable stent thrombosis) was reported in 1 patient.[3]

In the case series of 54 patients, cardiac death as a result of ST-elevation myocardial infarction complicated by cardiogenic shock in catheter lab was reported in 1 patient.[5]

Freedom from MACE at 30 days

In the case series of 60 patients, 95% (57/60) of patients did not have MACE at 30 days. However, 5% (3/60) of patients had asymptomatic non-Q-wave periprocedural myocardial infarctions.[1]

In the case series of 120 patients, 94% (113/120) of patients reported no MACE in-hospital. However, 6% (7/120) of patients had asymptomatic non-Q-wave periprocedural myocardial infarctions. All these were not related to the device but involved elevated cardiac biomarkers. At 30 days, 8% (9/119) of patients reported non-Q wave myocardial infarctions, 1 patient reported Q wave myocardial infarction and 1 patient needed target vessel revascularisation. Stent thrombosis (definite or probable) was reported in 2% (2/120) of patients.[3]

In the case series of 71 patients, 1 patient reported MACE at 30 days and unstable angina was reported in 1 patient after 7 days.[4]

Freedom from MACE at 6 months

In the case series of 60 patients, 92% (55/60) of patients did not have MACE at 6 months. However, 8% (5/60) of patients had complications, which included 3 asymptomatic non-Q-wave myocardial infarctions and 2 cardiac deaths (neither of which were related to the procedure).[1]

Dissections postintravascular lithotripsy

Deep arterial dissection due to angioplasty (type B according to the National Heart Lung and Blood Institute) occurred in 13% (4/31) of patients in the subgroup analysis of the DISRUPT CAD study of 31 patients. This was successfully treated with stent implantation.[2]

Deep arterial dissection after IVL and stenting (type B and C) was reported in 1 patient each in the case series of 120 patients (DISRUPT CAD II study). Both patients were managed conservatively.[3]

Coronary type B dissections without further sequelae were reported in 5% (4/78) of lesions in the case series of 71 patients.[4]

Device failure

Device failure (balloon rupture or bursting in complex lesions with no sequelae during treatment) was reported in 9% (7/78) of lesions in the case series of

71 patients. 4 of these were in patients with secondary IVL in lesions where a non-compliant balloon dilation failed (22 lesions), and 3 were in patients with primary IVL in native calcified de novo lesions (n=39).[4]

Ventricular capture

Ventricular capture (identified as a change in QRS morphology with the onset precisely coinciding with the electromagnetic 'spike' of the shockwave pulse-'shocktopics' and asynchronous cardiac pacing) was reported in 78% (42/54) of patients in the case series of 54 patients. Multivariable logistic regression analysis identified heart rate as the only independent predictor of an increased risk of IVL-induced ventricular capture. Patients with a heart rate of less than 65 beats per minute before IVL were 16 times more likely (OR 16.3, 95% confidence interval 2.4 to 110.8], p=0.004) to experience induced 'shocktopics' compared with patients who had a heart rate of 65 beats per minute or more.[5]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: IVL balloon rupture creating dissections, and IVL leading to PVC or transient V pacing. They considered that there were no theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intravascular lithotripsy for calcified coronary arteries during PCI. The following databases were searched, covering the period from their start to 01-07-2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded in which no clinical outcomes were reported, or in which the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with calcified coronary arteries
Intervention/test	Intravascular lithotripsy during percutaneous coronary intervention
Outcome	Articles were retrieved if the abstract contained information relevant to the safety, efficacy or both.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 362 patients from 6 case series[1,2,3]. There is an overlap of patients between study 1 and 2.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in appendix A.

Table 2 Summary of key efficacy and safety findings on intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention

Study 1 Briton TJ 2019

Details

Study type	Case series (cohort study -DISRUPT CAD I study -NCT02650128)
Country	Europe and Australia -5 countries (multicentre)
Recruitment period	2015-16
Study population and number	n=**60 patients with severely calcified coronary artery lesions needing revascularisation** Target vessel: left anterior descending artery (n=28), right coronary artery (n=23), circumflex artery (n=8), protected left main artery (n=2). Diameter stenosis 72.5% (range 58.5 to 77%); lesion length 18.2mm (range 14.1 to 25.4mm); calcified length 21mm; reference vessel diameter 3mm; lumen diameter 0.9 mm (range 0.6 to 1.1 mm^2); initial stenosis 68%.
Age and sex	Mean 72 years; 80% (48/60) male
Patient selection criteria	Patients with a clinical indication for coronary intervention needed to have more than 1 lesion needing PCI with a diameter stenosis more than 50%, a native coronary lesion less than 32 mm and heavy calcification defined as calcification within the lesion on both sides of the vessel assessed during angiography by the operator.
Technique	Coronary IVL followed by subsequent stent implantation and PCI at the discretion of the operator.
Follow up	**30 days and 6 months**
Conflict of interest/source of funding	Study sponsored by Shockwave medical. All authors received fees, grants from different companies. One author is a cofounder of the device and one author had equity in the company, and another author is a full-time employee of the company.

Analysis

Follow-up issues: short term follow up. Loss to follow up not reported.

Study design issues: prospective single-arm study in 7 hospitals. Primary efficacy end point was clinical success, defined as the ability of IVL to produce a diameter stenosis of less than 50% after stenting with no evidence of in-hospital MACE (cardiac death, myocardial infarction, or target vessel revascularisation). The primary safety end point was freedom from MACE through 30 days defined as cardiac death, myocardial infarction, or target vessel revascularisation.

Study population issues: severe calcification was present in all patients. Patients also had multiple comorbidities.

Other issues: there is an overlap of patients between study 1 and 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **60**

Efficacy outcomes

Clinical success %	95 (57/60)
Device success %	98 (59/60)
Stent delivery %	100 (60/60)
Final in-stent angiographic outcomes	
Mean minimum lumen diameter, mm	2.6 (range 2.3 to 2.9)
In-stent acute gain, mm	1.7 (range 1.3 to 2.1)
In-stent diameter stenosis reduced %	12 (range 7 to 21)
Patients with residual diameter stenosis <50% after stenting	100 (60/60)
Patients with residual diameter stenosis< 30% after stenting	92 (55/60)
Patients with residual diameter stenosis <20% after stenting	73 (44/60)

Safety

Adverse events

	%(n)
Grade D dissections (post IVL needed stenting, resolved at final angiography)	3.3 (2/60)
MACE at 30 days	**5 (3/60)**
Cardiac death	0
Non-Q-wave MI (involved elevated cardiac biomarkers, not related to the device)	5 (3/60)
Q-wave MI	0
TVR	0
MACE at 6 months	**8.5 (5)**
Cardiac death (not related to the device)	3 (2/60)
Non-Q-wave MI	5 (3/60)
Q-wave MI	0
TVR	0

No perforations, residual dissections, abrupt closure, slow flow or no reflow reported at follow up.

Abbreviations used: IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularisation.

Study 2 Ali ZA 2017

Details

Study type	Case series (sub-study of DISRUPT CAD I study NCT02471586)
Country	Europe and Australia in 5 countries, multicentre (7 hospitals)
Recruitment period	2015-2016
Study population and number	n=**31 patients having planned PCI for angina with severely calcified stenotic coronary de novo lesions** Target vessels: left anterior descending 14, circumflex 5, right coronary artery 12 severe calcification in 87% (27/31); lesion length: 21.7±11.6mm; calcification length: 21.3±10.3mm.
Age and sex	Mean 71 years; 80% (25/31) male
Patient selection criteria	Inclusion criteria: patients having planned PCI for stable or unstable angina or silent ischemia with severe calcification (assessed by angiography), single target lesions located in a native coronary artery with visually estimated reference vessel diameter of 2.5 to 4.0mm and length <32mm. Exclusion criteria: unprotected left main, planned concomitant use of atherectomy or speciality balloon, chronic total occlusions, and stent within 5mm of the lesion.
Technique	Intravascular lithotripsy (IVL using Shockwave coronary lithoplasty system) done (with mean 2 lithoplasty balloons per lesion) for vessel preparation and subsequent metallic or drug-eluting stent placement done using OCT in all. A minimum of 20 pulses per target lesion were done, delivering mean 4 lithoplasty treatments (range 2 to 7). If lesion exceeded 12 mm balloon length, it was repositioned and lithoplasty repeated. PCI was done via femoral or radial access; anticoagulation, anti-platelet therapy and other medications given as per local standard of care.
Follow up	**Post procedure**
Conflict of interest/source of funding	Study designed and sponsored by the company as part of the DISRUPT CAD trial. All authors received fees, grants from different companies. One author is a cofounder of the device and one author had equity in the company, and another author is a full-time employee of the company.

Analysis

Follow-up issues: short follow-up period, loss to follow up not reported.

Study design issues: small multicentre prospective single-arm observational study, OCT done only in selected patients in the DISRUPT CAD I study, and findings were analysed; an independent clinical events committee judged all MACE and an independent laboratory analysed all imaging.

Study population issues: Patients had multiple comorbidities. Predilation was needed only in 6 patients.

Other issues: this is a sub-study of the DISRUPT CAD I study above (Brinton 219).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **31**

Angiographic outcomes (Mean±SD)

	Baseline	Post PCI
Reference vessel diameter, mm	2.87±0.99	2.96±0.47
Minimum lumen diameter, mm	0.99±0.41	2.51±0.35
Diameter stenosis %	65.1±14.4	13.9±12.5
Acute gain, mm		1.54±0.54
Stent length, mm		30.7±11.9

OCT imaging analysis

	Pre IVL (N=26)	Post IVL (N=28)	Post stent (N=31)	Final MSA site
Lesion length, mm	31.50±9.74	-	-	
Minimal lumen area, mm^2	2.23±1.11	4.16±1.86	5.99±1.97	
Mean lumen area mm^2	4.85±1.86	-	8.49±3.04	
Area stenosis %	66.50±11.30	39.80±24.20	20.50±20.30	
Acute area gain mm^2		2.08±1.65	3.69±1.52	2.36±1.88
Minimal stent area mm^2			8.37±3.17	5.94±1.98
Mean stent expansion mm^2			112.0±37.2	79.4±2.70

OCT features of calcium fracture

	Post IVL (n=28)	Post stent implantation (n=31)	P value
Calcium fracture %	43 (12/28)	55 (17/31)	0.08
Fracture depth mm	0.42±0.21	0.43±0.25	0.72
Fracture length mm	2.79±4.49	3.36±4.99	0.02
Fracture angle	20.50±19.50	29.50±33.70	0.06

Safety

No major intraprocedural complications or postoperative PCI sequalae.

Complications post lithotripsy	% (n)
Deep dissection >type B (NHLBI) because of angioplasty (treated with stent implantation)	13% (4/31)
Slow flow or no reflow	0
Abrupt closure	0
Perforation	0
Final complications post PCI	**0**

Calcium fractures per lesion	0.00	1.00	0.03
Multiple calcium fracture/frame	26 (7/28)	29 (9/31)	0.34

Effect of IVL according to tertiles of calcium severity

The frequency of calcium fractures per lesion increased in the most severely calcified plaques (highest tertile versus lowest tertile, p=0.009) with a trend towards a greater incidence of calcium fracture (77.8% versus 22.2%, p=0.057).

Abbreviations used: IVL, intravascular lithotripsy; MSA, minimal stent area; NHLBI, National Heart Lung Blood Institute; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SD, standard deviation.

Study 3 Ali ZA 2019

Details

Study type	Case series (DISRUPT CAD II study -NCT03328949)
Country	US and Europe -9 countries
Recruitment period	2018-19
Study population and number	n=**120 patients with severely stenotic, calcified de novo coronary artery lesions needing revascularisation had vessel preparation for stent implantation with intravascular lithotripsy (IVL)** Target vessel: left anterior descending artery 62.5% (n=75), right coronary artery 25% (n=30), circumflex artery 11.7% (n=14) and protected left main artery 0.8% (n=1). Lesion characteristics: diameter stenosis 60±12.0%; lesion length 19.5±9.8 mm; calcified length 25.7±12.4mm; reference vessel diameter 3.04±0.53 mm; minimum lumen diameter 1.21±0.42 mm; severe calcification in 94.2% (113/120). 71% lesions were concentric and 30% had side branch involvement.
Age and sex	Mean 72 years; 78% (94/120) male
Patient selection criteria	Inclusion criteria: patients with silent ischemia, unstable or stable angina with evidence of myocardial ischemia, or stabilised acute coronary syndrome without elevation in cardiac biomarkers. Those with a single target lesion needing PCI with a diameter stenosis more than 50%, a native coronary lesion length less than 32 mm and severe calcification defined as calcification within the lesion on both sides of the vessel assessed during angiography as determined by the operators. Exclusion criteria: planned use of atherectomy, speciality balloons, or investigational coronary devices.
Technique	Coronary IVL followed by subsequent stent implantation and PCI was done at the discretion of the operator. PCI was performed via femoral or radial access. IVL catheter insertion done as described in procedure description section. Sometimes an adjunctive tool (a buddy wire, small balloon or guide catheter extension) is used in case of difficulty while passing the catheter over the lesion. Atherectomy was not permitted as per protocol. If lesion preparation is not complete after maximal number of pulses, then further IVL catheters (with similar or different diameters) were used. The mean number of IVL catheters used per lesion were 1.2. Pre-dilatation to deliver the IVL catheter was needed in 42% patients. Mean balloon size was 2.2 mm. Subsequent stent implantation and medications were administered as per standard protocol. A mean number of 1.3 drug eluting stents were implanted per patient and post dilation was needed in 79% patients.
Follow up	**30 days**
Conflict of interest/source of funding	Study was designed by principal investigators and sponsor (Shockwave medical Inc). The majority of authors received fees, grants, research support and honoraria from different companies. One author is a cofounder of the device and one author had equity in the company, and another author is a full-time employee of the company.

Analysis

Follow-up issues: short term follow up. Loss to follow up not reported.

Study design issues: small prospective, multicentre post-approval study done in 15 hospitals. Primary efficacy end point was in-hospital MACE (cardiac death, myocardial infarction, or target vessel revascularisation). Secondary end point was clinical success, defined as the ability of IVL to produce a diameter stenosis of less than 50% after stenting with no evidence of MACE. An optical coherence tomography (OCT) sub-study was done to evaluate the mechanism action of IVL, quantifying calcium characteristics and calcium fracture. Independent lab assessed angiography and OCT and an independent clinical events committee assessed MACE.

Study population issues: severe calcification was present in all patients. Patients also had multiple comorbidities.

Other issues: there is an overlap of patients between 3 studies (Brinton 2019 [disrupt CAD I study], Ali ZA 2017 [sub-study of CAD I study], Ali ZA 2019 [CAD II study]).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **120**

Procedure outcomes

Total procedure time, minutes	68.3±34.2
IVL treatment time, minutes	7.9±5.2

Efficacy outcomes

	n=120
Clinical success %	94.2 (113/120)
Angiographic success* %	100 (120/120)
Stent delivery %	100 (120/120)
Final in-segment angiographic outcomes	
Mean minimum lumen diameter, mm	2.83 ±0.48
In-stent acute gain, mm	1.63 ±0.49
Residual diameter stenosis %	9.4±7.5
Patients with residual diameter stenosis <50% after stenting	100 (120/120)
Patients with residual diameter stenosis < 30% after stenting	99.2 (119/120)
Final in-stent angiographic outcomes	
Mean minimum lumen diameter, mm	2.88 ±0.47
In-stent acute gain, mm	1.67 ±0.49
Residual diameter stenosis %	7.8±7.1
Patients with residual diameter stenosis <50% after stenting	100 (120/120)
Patients with residual diameter stenosis< 30% after stenting	100 (120/120)

**defined as success in facilitating stent delivery with<50% residual stenosis and freedom from perforation, slow flow, no reflow or type D,E,F dissection at any point during the procedure.*

OCT sub study analysis

	Pre IVL (n=48)	**Post Stent (n=47)**	**P value**
At pre-IVL minimal lumen area site			
Lesion length, mm	29.±9.8	-	-
Minimal lumen area, mm^2	2.33±1.35	6.10±2.17	<0.001
Calcium angle, degrees	175.8±96.9	127.1±97.6	0.055
Maximum calcium thickness	0.9±0.3	0.8±0.3	0.45
Calcium fracture %		1.9% (5/28)	
Acute area gain mm^2		3.99±1.72	

Safety

Adverse events

	% (n=120)
Dissections, type	
Grade B (post stent IVL managed conservatively)	0.8 (1/120)
Grade C (post stent IVL managed conservatively)	0.8 (1/120)
MACE in hospital	**5.8 (7/120)**
Non-Q-wave MI (involved elevated cardiac biomarkers, not related to the device)	5.8 (7/120)
MACE at 30 days	**7.6 (9/120)**
Cardiac death (14 days after treating a 95% lesion in the distal right coronary artery due to probable stent thrombosis)	0.8 (1/120)
Non-Q-wave MI (in hospital)	5.9 (7/120)
Q-wave MI	0.8 (1/120)
TVR	0.8 (1/120)
Stent thrombosis (definite or probable)	1.7 (2/120)

No perforations, abrupt closure, slow flow or no reflow reported at follow up.

stent area mm^2		6.06±2.20	
stent expansion %		79.1±2.1	
At pre IVL maximum calcium site	**n=48**	**n=38**	
Minimal lumen area, mm^2	3.64±1.78	8.47±3.04	<0.0001
Calcium angle, degrees	266.3±77.1	215.1±69.4	<0.0001
Maximum calcium thickness	0.93±0.2	0.89±0.2	0.004
Calcium fracture %		50% (19/38)	
Acute area gain mm^2		4.79±2.45	
stent area mm^2		7.77±2.65	
stent expansion %		102.8±30.6 (n=35)	
At final minimal stent area	**n=48**	**n=47**	
Minimal lumen area, mm^2	4.26±2.86	6.25±2.25	<0.0001
Calcium angle, degrees	176.6±100.4 (n=23)	149.4±94.8 (n=30)	0.0004
Maximum calcium thickness	1.0±0.3 (n=23)	0.9±0.3 (n=30)	0.055
Calcium fracture %		23.3% (7/30)	
Acute area gain mm^2		2.52±2.03 (n=35)	
stent area mm^2		5.92±2.14	
stent expansion %		77.6±20.5 (n=44)	

OCT features of calcium fracture by IVL

	Post IVL (n=47)
Calcium fracture %	78.7 (37/47)
Multiple fractures (> 2)	55.3 (26/47)
Fracture depth, mm	0.6±0.3 (n=37)
Fracture length, mm	5.5±5.0 (n=37)
Calcium fracture angle at the site, degrees	224.5±70.9
Maximum calcium thickness, mm	0.8±0.3
Calcium fractures per lesion, n	3.4±2.6
Multiple calcium fracture/frame, n	1.6±0.8 (7/28)

Abbreviations used: IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TVR, target vessel revascularisation.

Study 4 Aksoy A 2019

Details

Study type	Case series
Country	Germany (multicentre)
Recruitment period	2018
Study population and number	n=**71 patients with moderate to severely calcified coronary lesions (n=78) treated with IVL** Calcification %: (82 % (64/78) lesions were severely calcified, 18% (14/71) lesions were moderately calcified). Targeted vessels: left anterior descending artery (43.6%, n=34), right coronary artery (33%, n=26), ramus circumflexus (6.4%, n=5), left main artery (16.7%, n=13) Group A: primary IVL in native, severley calcified de novo lesions (n=39 lesions) Group B: secondary IVL in lesions where noncompliant balloon dilatation failed (n=22 lesions, 20 patients) Group C: tertiary IVL in lesions with stent under expansion after previous stenting (n=17 lesions)
Age and sex	Mean 76 years; 72% (51/71) male
Patient selection criteria	Patients with significant calcified coronary lesions and in-stent stenosis due to severe calcification were screened (based on the angiographic degree of calcification) for eligibility for IVL.
Technique	Intravascular lithotripsy (IVL using Shockwave coronary^2 balloon) done for vessel preparation and subsequent metallic or drug-eluting stent placement done. Coronary angiography was done as per conventional standards. Intracoronary nitroglycerin was administered before baseline. PCI was done during the same procedure or as a staged procedure. Post interventional antiplatelet therapy was given to all patients.
Follow up	**30 days**
Conflict of interest/source of funding	Study funded by clinical study research program at the University Hospital Bonn. 4 authors are principal or sub-investigators of the Disrupt CAD II study.

Analysis

Follow-up issues: very short follow-up period.

Study design issues: prospective observational registry data from 3 centres was assessed for the overall cohort and for each type of treatment (primary IVL therapy, secondary IVL and tertiary IVL). Primary end points were strategy success (defined as stent expansion with less than 20% in stent residual stenosis of target lesion in the presence of TIMI 3 flow without stent failure) and safety outcomes (procedural complications and in hospital MACE as proposed by American Heart Association and Academic Research Consortium 2). Data were collected by review of medical records and followed-up by telephone interview. Intravascular imaging was done in 50% (35/71) cases, 23 by ultrasound and 12 by OCT.

Study population issues: 46.5% patients had stable angina, 15.5% had unstable angina, 14% had non ST segment elevation acute coronary syndromes and 14% had acute heart failure. Patients had cardiac risk factors such as hypertension, hypercholesterolemia and diabetes. There was no difference in baseline, procedural characteristics between the groups.

Other issues: in 6 patients mechanical circulatory support was used.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **71 (78 lesions)**

Efficacy outcomes

	Overall % (n=78)	Group A % (n=39)	Group B % (n=22)	Group C % (n=17)
Success strategy (successful delivery and expansion with <20% residual stenosis of target lesion, TIMI 3, no stent failure)	78.2 (61/78)	84.6 (33/39)	77.3 (17/22)	64.7 (11/17)
Successful device delivery and complete lithotripsy treatment of the target lesion	100 (78/78)	100 (39/39)	100 (22/22)	100 (17/17)

Angiography outcomes (OCT analysis)

	Baseline (mean±SD)	Post IVL (mean±SD)	Post PCI (mean±SD)
Overall cohort			
Reference vessel diameter, mm		3.51±0.46	
Minimal lumen diameter, mm	1.01±0.49	1.90±0.61	2.88±0.56 (p<0.001)
Acute gain, mm	-	0.89±0.76	1.87±0.60
Diameter stenosis %	71.8±13.1	45.1±17.4	17.5±15.2
Group A			
Reference vessel diameter, mm		3.58±0.46	
Minimal lumen diameter, mm	1.1±0.46	1.85±0.63 (p=0.01)	2.94±0.56 (p<0.0001)
Acute gain, mm	-	0.75±0.60	1.84±0.57
Diameter stenosis %	69.45±13.25	46.34±18.28	16.98±14.23
Group B			
Reference vessel diameter, mm		3.49±0.50	
Minimal lumen diameter, mm	1.05±0.56	2.17±0.56	2.81±0.51 (p<0.01)

Safety

Safety outcomes

	Overall % (n=78)	Group A % (n=39)	Group B % (n=22)	Group C % (n=17)
Device failure (balloons burst in complex lesions/ ruptured with no sequelae)	9 (7/78)	7.7 (3/39)	18.2 (4/22)	0
In hospital MACE	0	0	0	0
Unstable angina (after 7 days)	1.3 (1/78)			
30 days MACE (MI, TVF, or cardiac death)	1.3 (1/78)	0	0	11.1 (1/17)
Coronary dissection, type B, without further sequelae	5.1 (4/78)	7.7 (3/39)	5.9 (1/22)	0

Perforations, slow flow, reflow, or abrupt vessel closure did not occur in any treated lesions.

Acute gain, mm	-	1.12±0.92	1.81±0.65
Diameter stenosis %	71.0±13.29	41.69±17.47	19.0±13.09
Group C			
Reference vessel diameter, mm		3.5±0.46	
Minimal lumen diameter, mm	0.77±0.39	1.88±0.53	2.78±0.57 (P<0.001)
Acute gain, mm	-	1.11±0.56	2.01±0.68
Diameter stenosis %	77.3±10.47	45.04±15.53	20.33±16.93

Abbreviations used: IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction; TVF, target vessel failure.

Study 5 Wilson SJ 2019

Details

Study type	Case series (retrospective study)
Country	UK
Recruitment period	September 2018 to March 2019
Study population and number	n=**54 patients with severely calcified coronary artery lesions treated with IVL during PCI** Indications for PCI non-ST elevation acute coronary syndrome (NSTEACS) in 33.3% (n=18) and ST-elevation myocardial infarction (STEMI) in 18.5% (n=10) of patients, chronic stable angina 46% (n=26), PCI before TAVI (n-1)
Age and sex	Age 71-77 years; 78% (42/54) male
Patient selection criteria	All patients with a clinical indication for revascularisation and had coronary IVL because of non-dilatable coronary artery disease with concentric calcification identified on angiography and or intravascular imaging.
Technique	Patients having PCI (conventional manner) had coronary IVL with the Shockwave Medical system before stent implantation at operator discretion. Pulsatile sonic waves are delivered locally at a rate 1 pulse per second for up to 10 seconds. The process is repeated (up to a maximum of 80 pulses) until the lesion is adequately prepared for stent deployment. At 3 mm from source the energy density is $9.6 \pm 1.6 \times 10^{-3}$ mJ/mm^2.
Follow up	**Post procedure**
Conflict of interest/source of funding	2 authors received consulting research support and honoraria from Shockwave medical. The cofounder and an employee of the company assisted the authors.

Analysis

Study design issues: retrospective review of all cases done in a single centre; electrophysiological assessment was done, ECG recordings from each patient were reviewed for evidence of induced 'shocktopics' and asynchronous cardiac pacing by 2 cardiologists. ECH recordings were also assessed for evidence of 'shocktopics' triggering atrial or ventricular tachyarrhythmia including non-sustained and sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Events were recorded by 7 different operators.

Study population issues: the majority of patients were in sinus rhythm (n=44), 7 were in atrial fibrillation, 1 was in atrial flutter and 2 patients had a pacemaker.

Key efficacy and safety findings

Safety

Number of patients analysed: **54**

Adverse events

	% (n)
Death (STEMI complicated by cardiogenic shock in catheter lab)	1
Incidence of ventricular capture (shocktopics and asynchronous cardiac pacing)*	77.8 (42/54)
Atrial pacing	n=3
Shockwave pulses not associated with ventricular capture (sensed but miscounted as an R wave by ECG monitoring)	n=3
Atrial or ventricular tachyarrhythmia due to IVL induced capture	0

*identified as a change in QRS morphology with the onset precisely coinciding with the electromagnetic 'spike' of the shockwave pulse. A shocktopic was defined as an isolated ventricular capture beat. Asynchronous cardiac pacing was defined as more than 2 consecutive ventricular capture beats.

- Compared to patients who did not have ventricular capture, patients in whom this occurred had a lower intrinsic heart rate (61 versus 82 bpm, p<0.001), were more likely to have IVL balloon to the left anterior descending artery (45.2% versus 33.3%), or right coronary artery (42.9% versus 16.7%, p=0.03) and had a shorter QTc interval (424 versus 450 msec, p=0.03).
- Ventricular capture was associated with a fall in systolic blood pressure of between 10 and 35 mmHg that resolved immediately on return of intrinsic rhythm.
- 2 patients who had a pacemaker experienced ventricular capture (but device check revealed no evidence of pacemaker malfunction)

Predictors of ventricular capture

Multivariable logistic regression analysis identified heart rate as the only independent predictor of an increased risk of IVL induced ventricular capture. Patients with a heart rate < 65 bpm prior to IVL were 16 times more likely (OR 16.3 [2.4-110.8], p=0.004) to experience induced 'shocktopics' compared to patients with a heart ≥ 65.

'Shocktopic' beat morphology was largely uniform in each patient and appeared dependent on the target lesion location.

Abbreviations used: ACS, acute coronary syndrome; ECG, electrocardiogram; IVL, intravascular lithotripsy; OR, odds ratio; STEMI, ST-elevation myocardial infarction;

Study 6 Wong B 2019

Details

Study type	Case series (retrospective study)
Country	New Zealand
Recruitment period	2018-19
Study population and number	n=**26 patients with severely calcified coronary artery lesions treated with IVL during PCI** Indications for PCI ACS (n=14), stable angina (n=11), PCI before TAVI (n-1)
Age and sex	Mean 72 years; 69% (18/26) male
Patient selection criteria	All patients who had IVL during PCI were sequentially included (including those with acute coronary syndrome and unprotected left main stem intervention).
Technique	Patients having PCI (conventional manner) had coronary IVL before stent implantation at operator discretion. Among patients with ACS, 71% had IVL to the infarct related artery during the index procedure.29% were staged PCIs to severe non-culprit lesions. Upfront IVL was used in 58% of patients, and rest were used after inadequate predilation with balloon angioplasty as a bailout procedure. Different shockwave IVL balloons sizes were used. In 46% patients, after IVL further predilation was done with non-compliant balloons before stent deployment. Lithotripsy done for a maximum of 8, 10 second cycles per device. Each area had minimum 2 cycles of IVL. Mean number of stents used was 1.3. 2 patients needed 6 Fr guide catheter for IVL balloon delivery, and 3 patients needed a buddy wire support technique. 1 patient had an IVL therapy within an old under expanded stent. IVL commonly used in the left anterior descending coronary artery (50%), right coronary artery (35%) and left circumflex artery (12%). In 1 patient, it was used in an unprotected left main stem ostium, in another patient it was used in a patient with inferior ST-elevation myocardial infarction. In 1 patient it was used in multiple vessels (left anterior descending and right coronary artery).
Follow up	**Hospital discharge**
Conflict of interest/source of funding	Study sponsored by Shockwave medical. All authors received fees, grants from different companies. One author is a cofounder of shockwave and one had equity in the company, and another is a full-time employee of the company.

Analysis

Follow-up issues: follow up was limited to hospital discharge and no long-term data available.

Study design issues: retrospective study, procedure was not standardised, predilation was used invariably in the study; no intravascular imaging was used systematically in the study; Angiographic success was defined as achieving less than 20% residual stenosis, no edge dissection and thrombolysis in myocardial infarction 3 flow. All complications were recorded. The primary outcome was the ability to deliver the IVL balloon and successful deployment of the stent. Successful clinical outcome was defined as stent delivery without procedural or in-hospital complications (death, MI and target vessel failure).

Study population issues: all target lesions had moderate calcification angiographically. IVL was used in various calcified coronary lesions. There were no angiographic exclusions including length, tortuosity, bifurcation lesions and prior stent placements. Patients had multiple comorbidities.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **26** **Efficacy outcomes** Procedural and clinical success was achieved in all patients. Angiographic success was achieved in all.	**Adverse events** No procedural or in-hospital complications reported.
Abbreviations used: ACS, acute coronary syndrome; IVL, intravascular lithotripsy; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; TVR, target vessel revascularisation.	

Validity and generalisability of the studies

- IVL as an adjunct to PCI and stent implantation was evaluated in very few small case series with small sample size and short follow-up period (30 days to 6 months) between 2017 to 2019. The mean age of these patients was 72 years old and 70% of the patients were male. Patients who had treatment had multiple comorbidities.
- Short term clinical data from these studies are promising.
- There are no studies comparing with standard of care.
- There are several case reports that report the experience of IVL as an adjunct to PCI and these have been added to the appendix.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Bioresorbable stent implantation for treating coronary artery disease NICE interventional procedures guidance 492 (2014) Available from http://www.nice.org.uk/guidance IPG492
- Optical coherence tomography to guide percutaneous coronary intervention NICE interventional procedures guidance 481 (2014) Available from http://www.nice.org.uk/guidance IPG481
- Percutaneous laser coronary angioplasty NICE interventional procedures guidance 378 (2011) Available from http://www.nice.org.uk/guidance IPG378
- Intraoperative fluorescence angiography for the evaluation of coronary artery bypass graft patency. NICE interventional procedure guidance 98 (2004) Available from http://www.nice.org.uk/guidance IPG98

Technology appraisals

- Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease (ID1397) NICE technology appraisal guidance Publication expected August 2019
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisal guidance 152 (2008) Available from http://www.nice.org.uk/guidance/TA152
- Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003) replaces TA4 'Ischaemic heart disease coronary artery stents') NICE technology appraisal guidance October 2001 (last modified: July 2008). Available from http://www.nice.org.uk/guidance/TA71

NICE guidelines

- Chest pain of recent onset: assessment and diagnosis NICE guideline 95 (2010, updated 2016) Available from http://www.nice.org.uk/guidance/NG95
- Stable angina. NICE clinical guideline 126 (2011) Available from http://www.nice.org.uk/guidance/NG126
- Unstable angina and NSTEMI. The early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94 (2010) Available from http://www.nice.org.uk/guidance/NG94
- MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007) Available from http://www.nice.org.uk/guidance/NG48
- **Medtech guidance**
- HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (2017) NICE medical technologies guidance 32
- The VeriQ system for assessing graft flow during coronary artery bypass graft surgery. NICE medical technology guidance 8 (2011)
- SeQuent Please balloon catheter for in-stent coronary restenosis. NICE medical technologies guidance 1 (2010)

- **Medtech briefing**
- MIB174: CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease (2019) NICE medtech innovation briefing 174
- QAngio XA 3D/QFR imaging software for assessing coronary obstructions (2018) NICE medtech innovation briefing 146
- The PressureWire fractional flow reserve measurement system for coronary artery disease (2014) NICE medtech innovation briefing 2
- **Diagnostics guidance**
- New generation cardiac CT scanners (Aquilion ONE, Brilliance iCT, Discovery CT750 HD and Somatom Definition Flash) for cardiac imaging in people with suspected or known coronary artery disease in whom imaging is difficult with earlier generation CT scanners (2012, updated 2017) NICE diagnostics guidance 3

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. 1 specialist adviser questionnaires for intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure but 1 patient organisation representing patients who have had

this procedure provided submissions and these were discussed by the committee.

Company engagement

A structured information request was sent to one company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- NCT03595176 Disrupt CAD III with the Shockwave Coronary IVL System. Prospective single-arm study in de novo calcified, stenotic coronary arteries before stenting, n=392, estimated completion date July 2022, status: recruiting. Three sub-studies are included in this protocol; OCT sub-study (n=100), permanent pacemaker and implantable cardioverter defibrillator sub-study (n=20) and hemodynamic sub-study (n=20).
- NCT04151628 Prospective, multicentre, single-arm study of the SWM-1234 in calcified coronary arteries (Disrupt CAD IV Study - Japan) with the Shockwave Coronary C2 IVL system. n=72 patients with de novo, calcified coronary artery lesions presenting with stable or unstable angina and silent ischemia that are suitable for percutaneous coronary intervention assessed for safety and effectiveness of IVL to treat lesions prior to stenting. status: recruiting, study completion date June 2022.
- Investigator sponsored ongoing research
  - The IVL left main study; a prospective multicentre, non-randomised open pilot study in 50 patients with obstructive calcific distal left main disease (>270 degree calcium in at least one stenotic segment) and a clinical indication for revascularisation. Study period: 24 months followed up to 12 months, primary end point: efficacy-minimum stent area and residual area stenosis (<50%) index immediately post procedure; safety-composite of

major adverse events (all cause mortality, non-fatal MI or target revascularisation) at 30 days. Location: UK.

- Lithotripsy to aid DCB only PCI, a prospective single arm, single centre study of IVL treatment for DCB only PCI according to criteria on German consensus recommendation on DCB treatment of coronary artery disease. 50 patients with calcific coronary artery lesions of significant severity to warrant interventional therapy and a clinical need for PCI will be included. Study duration 12 months followed up to 4 months. Primary end point - procedural success (defined as DCB or stent delivery with a residual stenosis <30% and without in-hospital MACE). Location: Germany.
- The REPLICA clinical trial: Spanish real-world registry of coronary intravascular lithotripsy for the treatment of calcified coronary arteries. Nationwide multicentre prospective observational registry. 400 patients across 30 sites with calcified coronary artery disease requiring PCI with stent implantation will be included. Study duration 24 months followed up to 12 months; primary end point procedural success (defined as the performance of IVL without in-hospital complications, with good angiographic results [TIMI grade 3 and residual stenosis <20%]). Location: Spain.
- Balloon angioplasty versus shockwave IVL for calcified coronary stenoses (BASIL study). A prospective single centre randomised (1:1) study. 60 patients with severe coronary calcification as assessed by intravascular ultrasound with presence of >270 degrees arc of calcification will be included. Study duration 18 months followed up to 30 days. Primary end point angiographic success (defined as the ability to pre-dilate the target lesion to facilitate stent delivery without bailout techniques or cross over, no intra procedural complications, residual stenosis <20% after stent deployment) and clinical success (defined as no procedural related major adverse events and death prior to discharge). Location: New Zealand.

References

1. Brinton TJ, Ali ZA, Hill J et al. (2019) Feasibility of shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses: first description. Circulation 139(6): 834-36
2. Ali ZA, Brinton TJ, Hill JM et al. (2017) Optical coherence tomography characterisation of coronary lithoplasty for treatment of calcified lesions: first description. JACC: Cardiovascular Imaging 10(8): 897-906
3. Ali ZA, Nef H, Escaned J. Safety and Effectiveness of Coronary Intravascular Lithotripsy for Treatment of Severely Calcified Coronary Stenoses: The Disrupt CAD II Study. Circulation Cardiovascular Interventions. 2019 Oct;12(10):e008434. doi: 10.1161/CIRCINT
4. Aksoy A, Salazar C, Becher MU (2019). Intravascular Lithotripsy in Calcified Coronary Lesions: A Prospective, Observational, Multicenter Registry. Circulation Cardiovascular Interventions. 2019 Nov;12(11): e008154. doi: 10.1161/CIRCINTERVENTIONS.119.008154. Epub 2019 Nov 11.
5. Wilson SJ, Spratt JC, Hill J et al. (2019) Coronary intravascular lithotripsy is associated with a high incidence of "shocktopics" and asynchronous cardiac pacing. EuroIntervention. 2019 May 21. pii: EIJ-D-19-00484. doi: 10.4244/EIJ-D-19-00484. [Epub ahead of print]
6. Wong B, El-Jack S, Newcombe R et al. (2019) Shockwave intravascular lithotripsy for calcified coronary lesions: first real-world experience. Journal of Invasive Cardiology 31(3): 46-8

Additional relevant papers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Ali, Z, McEntegart, M, Hill, J and Spratt,J. (2018) Intravascular lithotripsy for treatment of stent underexpansion secondary to severe coronary calcification *European Heart Journal*, 41 (3), 14, 485–486,	Case report	A 73-year old man with recurrent angina, a high-grade proximal LAD lesion and severe in-stent stenosis (ISS) secondary to stent under expansion had IVL. The outcome was successful.	Larger studies added to table 2.
Costoya IR, Marcos HT, Montilla BV et al. (2019) Coronary lithoplasty: initial experience in coronary calcified lesions. Rev Est Cardio (article in press)	Case report N=3 patients with multivessel coronary artery disease had IVL.	The lithoplasty balloon was successfully used to treat 6 severely calcified lesions. There were no intraprocedural complications such as dissections or perforations.	Larger studies added to table 2.
Curtis, E, Khan, A, El-Jack, A and Glenie, T. Precipitation of de novo Atrial Fibrillation during Shockwave Intravascular Lithotripsy After Pacing Capture During the Treatment of Proximal Right Coronary Artery Disease: A Case Report. Euro Heart Journal. 2019; doi:10.1093/ehjcr/ytz147	Case report	72-year-old man undergoing planned percutaneous intervention to a heavily calcified proximal right coronary artery (RCA) lesion using S-IVL developed pacing capture from the device and subsequently new atrial fibrillation (AF) during the procedure. The technique resulted in successful treatment of the coronary lesion and he spontaneously reverted within an hour of the procedure before discharge.	Larger studies added to table 2.
Cicovic, A, Cicovic, S. Wong, B, Stotrup, N, Ghattas, A and Glenie T. A Quicker Pace: Shockwave Lithotripsy Pacing with Electromechanical Capture. JACC CI. 2019: **https://doi.org/10.1016/j.jcin.2019.04.024**	Case report 73 year old woman with calcified lesions in the left anterior ascending artery and right coronary artery had IVL for lesion preparation during PCI.	3 cycles of shockwave therapy given, clear capture of the shockwave spike was captured on ECG, this gave rise to aortic wave forms. The procedure was uneventful with deployment of stents. Patient reported no symptoms and was discharged the next day.	Larger studies included in table.
Dini, Carlotta Sorini; Tomberli, Benedetta; Mattesini, Alessio; Intravascular lithotripsy for calcific coronary and peripheral artery	Review	With coronary and peripheral balloons approved in Europe, peripheral balloons approved in the USA and multiple new trials beginning, we review the indications for these recently	Review

stenoses. European Society of Cardiology; 2019; vol. 15 (no. 8); 714-721		introduced devices (rotational and orbital atherectomy, IVL), summarise the clinical outcomes of the available trials and describe the design of ongoing studies.	
Gonzalez IC, Ferreiro RG, Moreiras JV et al. (2019) Facilitated transfemoral access by shockwave lithoplasty for transcatheter aortic valve replacement. JACC: Cardiovascular Interventions 12(5): e35-8	Case report N=1 patient with severe aortic stenosis, coronary artery disease (CAD) and severe peripheral artery disease had IVL to help transfemoral transcatheter aortic valve replacement.	Results showed a significant reduction in stenosis severity with high acute gain, no major adverse events.	Larger studies added to table 2.
De Silva K, Roy J, Webb I et al. (2019) A calcific, undilatable stenosis; Lithoplasty – a new tool in the box? JACC: Cardiovascular Interventions 10(3): 304-6	Case report A 69-year-old man with severe calcific disease in the right coronary artery had PCI after balloon dilation. He had PCI with adjunctive lithotripsy for calcium debulking.	OCT done pre and post lithoplasty showed the calcium 'cracking' effect of the technique. The segment of disease was then treated with a stent with good angiographic result.	Larger studies added to table 2.
Kassimis G, Raina T, Kontogiannis N et al. (2019) How should we treat heavily calcified coronary artery disease in contemporary practice? From atherectomy to intravascular lithotripsy. Cardiovascular Revascularization Medicine. Available January 2019	Review	With the introduction of several adjunctive PCI tools, like cutting and scoring balloons, atherectomy devices, and intravascular lithotripsy technology, the treatment of calcified coronary lesions has become feasible, predictable and safe. This review highlights the techniques in the clinical setting and gives examples of how best to apply them through better patient and lesion selection, with the main objective being optimising drug eluting stent delivery and implantation, and subsequent improved outcomes.	Review
Khan S, Li B, Salata K, et al. (2019) The current status of lithoplasty in vascular calcifications: A systematic review. Surgical Innovation: 1-11	Systematic review N=9 studies 211 patients with vascular calcification lesions had lithoplasty. Follow up: 5.5 months.	Most lesions (72%, 152/212) were in peripheral artery beds, with the remainder occurring in coronary vessels. Lesioned vessels typically had severe calcium burden 62.6% (131/210), with an average initial stenosis of 76.6% (range, 68.1% to 77.8%). After treatment, the average residual stenosis was 21.0% (range, 13.3% to 26.2%), with a mean acute gain of vessel diameter of 2.5 mm. A limited number of type D dissections	The review included both peripheral and coronary circulation studies. Evidence is from limited quality case series, case reports, and conference abstracts.

		occurred, with a total of 2.4% (5/211) of patients needing stent implantation. Recent studies suggest that lithoplasty is a promising intervention to decrease vessel stenosis in both peripheral artery disease and coronary artery disease, with minimal occurrence of major adverse events. Further research studies, with more rigorous study designs, are needed to determine the effectiveness of lithoplasty in vascular calcifications.	Peripheral artery disease is out of the remit of this guidance.
Kwok, O.-H.; Tse, H.-F. Ventricular Capture During Shockwave Intravascular Lithotripsy JACC: Cardiovascular Interventions; 2019; vol. 12 (no. 20); e175-e179	Case report	71-year-old with heavily calcified proximal left anterior descending coronary artery (LAD). Shockwave intravascular lithotripsy (IVL) balloon used for cracking of the calcified lesion. During the 10 s of IVL treatment, there was ventricular capture, mimicking the paced ventricular rhythm. The asynchronous ventricular capture resulted in a transient drop of blood pressure. The patient was asymptomatic. A drug-eluting stent was implanted, which was further expanded by noncompliant balloons under OCT guidance. Final angiogram and OCT run showed an excellent result.	Larger studies included in table 2.
Legutko J, Niewiera L, Tomala M et al. (2019) Successful shockwave intravascular lithotripsy for severely calcified undilatable lesion of the left anterior descending coronary artery in patient with recurrent myocardial infarction. Kardiologia Poloska (published online June 6)	Case report N=1 patient with severely calcified, critical narrowing of left anterior descending coronary artery associated with a history of recurrent myocardial infarction had IVL	Angiography, intravascular ultrasound and OCT confirmed optimal PCI result with perfect stent expansion and apposition. No complications occurred during hospitalisation and patient was discharged home 48 hours after the procedure free of angina and ventricular arrhythmia.	Larger studies included in table 2.
Luigi De Maria G, Scarsini R, and Banning A (2019) Management of Calcific Coronary Artery Lesions: Is it Time to Change Our Interventional Therapeutic Approach? JACC: Cardiovascular Interventions 12 (15), 1465-1478	Review	This review provides an overview about coronary lesions with a high calcium content with special focus on existing and emergent technologies. We also provide a proposed procedural algorithm to facilitate optimal use of technology according to specific features of LHCC and coronary anatomy.	Review

Mathias B, Federico M, Stefan T et al. (2019) The effect of lithoplasty on coronary arteries. Cardiovascular medicine 22:02013	Case report 79-year-old man with non-ST-elevation myocardial infarction and a heavily calcified bifurcation stenosis of the left anterior descending artery (LAD) had IVL	The subsequent OCT showed calcium containing cracks in the intima and the media of the LAD. The bifurcation lesion was treated with 2 stents. The final OCT showed good stent expansion and apposition.	Larger studies included in table 2.
Morabito G, Tripolino Cesare, Tassone EJ (2018). A Case of Stent Under-Expansion due to Calcified Plaque Treated with Shockwave Lithoplasty. Cardiology; 2018; vol. 141 (no. 2); 75-77	Case report Stent under-expansion due to heavily calcified plaque treated with the shockwave lithoplasty system.	A 77-year-old woman underwent coronary angiography, and intravascular ultrasound revealed stent under-expansion due to calcified plaque. Shockwave lithoplasty balloon was used to disrupt calcium deposits around the stent, thereby allowing a correct stent expansion with an excellent angiographic and intravascular ultrasound result.	Larger studies included in table 2.
Sgueglia GA, Gioffre G, Piccioni F et al. (2019) Slender distal radial five French coronary shockwave lithotripsy. Catheter cardiovascular Interventions 1-4	Case report 72-year-old man with calcific atherosclerosis of the left anterior descending artery with stenosis had IVL PCI using a 5 French guiding catheter.	Procedure was successful with optimal stenting results and reported no complications at 6 months follow up.	Larger studies added to table 2.
Shavadia JS, Minh NV, Kevi B. 2018 Challenges with severe coronary artery calcification in percutaneous coronary intervention: A Narrative Review of Therapeutic Options. Canadian Journal of Cardiology, 3 (12): 156-72	Review	Summary of the principles, technique, and contemporary evidence for the currently approved devices designed to treat severe coronary calcific lesions.	Review
Salazar C, Escaned J, Tirado G et al. (2019) Undilatable calcific coronary stenosis causing stent under expansion and late stent thrombosis. A complex scenario successfully managed with intravascular lithotripsy. JACC: Cardiovascular Interventions. 12(15): 1510-3	Case report N=71-year-old man with repeat STEMI had PCI. A suboptimal under expansion was achieved by coronary calcification. A new PCI using IVL was done to modify calcific plaques.	A good final angiography result was achieved. The case showed effectiveness of IVL to modify calcific plaques and act through a previously implanted stent.	Larger studies added to table 2.
Soriano, F, Veas, N. Piccinelli, E, and Oreglia, J. Coronary Dissection due to Intravascular lithoplasty balloon rupture. EuroIntervention.	Case report of a 47 year old man with heavily calcified left anterior descending stenosis in a tortuous anatomy. Patient had	IVL was done with a balloon at 4atm. At the second delivery phase, the IVL balloon broke with subsequent dissection of the LAD. Finally 2 stents were	Larger studies added to table 2.

2019; DOI: 10.4244/EIJ-D 19-00383	PCI using OCT and IVL.	delivered and post dilation was done.	
Tomasiewicz, B.; Kosowski, M.; Zimoch, W.; Heavily calcified coronary lesion treated by shockwave intravascular lithotripsy. Kardiologia Polska; 2019; vol. 77 (no. 9); 890-891	Case report -heavily calcified coronary lesion in the proximal left anterior descending artery treated with shockwave lithotripsy	This case shows that complex, heavily calcified coronary lesions always require a thoughtful approach, and often more than 1 plaque modification technique should be considered. Intra-vascular lithotripsy using the Shockwave device proved efficient and safe.	Larger studies included in table 2.
Tassone EJ, Tripolino C, Morabito G et al. (2018) When calcium gets tough, the tough cardiologist starts to play. Cardiology, 141: 167-71	Case report N=60-year-old man with calcific restenosis of a previously stented or treated lesion (left coronary artery) had coronary shockwave lithotripsy.	IVUS after 3 cycles showed a significant area gain more than 6 mm^2. There was an excellent postprocedure angiographic result and a minimal lumen area on final IVUS. The patient was discharged after 48 hours in good condition and without symptoms.	Larger studies added to table 2.
Tovar Forero, MN, Wilschut J, Van Mieghem NM et al. (2019) Coronary lithoplasty: a novel treatment for stent under expansion. European Heart Journal. 40, 2: 221	Case report N= 74-year-old man with a heavily calcified stenotic lesion in the proximal left anterior descending coronary artery and under expanded stent resistant to conventional non-compliant balloons had coronary shockwave lithotripsy.	Full expansion was achieved after 2 lithoplasty therapies. OCT imaging showed multiple calcium fractures. The procedure completed without any complications.	Larger studies added to table 2.
Tripolino, C.; Tassone, E.J.; Morabito, G. (2019) ST-Elevation Myocardial Infarction due to Stent Underexpansion Managed with Coronary Lithoplasty. Reviews on recent clinical trials; 2019 Volume 14, Issue 4, DOI : 10.2174/1574887114666190927164253	Case report	An 80-year-old Caucasian man with ST elevation myocardial infarction underwent emergent coronary angiography showing complete intrastent thrombosis at the proximal trait of LAD. After thrombus removal, it was evident stent under-expansion at its proximal edge caused by vascular calcification. Coronary shockwave lithoplasty was chosen to treat this lesion. After calcium deposits disruption we were able to obtain complete stent expansion. This demonstrates the usefulness and safety of the lithoplasty system in the context of ST elevation myocardial infarction.	Larger studies included in table 2
Tripolino, C.; Tassone, E.J.; Morabito, G. (2019) Intravascular ultrasound-	Case report	A 65-year-old man with angina, underwent coronary angiography and intravascular ultrasound	Larger studies included in table 2

guided shockwave treatment of stents overlapping under expansion of calcified left anterior descending artery. Journal of Cardiology Cases; vol. 20 (no. 4); 135-137		showing restenosis, in a site of overlapping stents, due to calcified tissue. Shockwave lithoplasty balloon was able to break calcified tissue in a site of overlapping stents, allowing subsequent vessel dilation and repeat stent implantation with optimal final stent expansion.	
Vainer J, Lux A, Ilhan M et al. (2019) Smart solution for hard times: successful lithoplasty of an undilatable lesion. Neth Heart J 27:216-7	Case report N=70-year-old woman with unsuccessful PCI with high-pressure balloons and rotational atherectomy had lithoplasty-assisted PCI.	Lithoplasty effectively resulted in plaque modification and a significant increase in diameter. OCT showed typical calcium tears and a large dissection. To cover the lesion, a drug-eluting stent was implanted. Proper stent expansion and apposition were confirmed with OCT.	Larger studies added to table 2.
Venuti G, D'Agosta G, Tamburino C et al. (2019). Coronary lithotripsy for failed rotational atherectomy, cutting balloon, scoring balloon and ultra-high-pressure non-compliant balloon. Catheter Cardiovascular Interventions 1-5	Case report N= 67-year-old man having planned PCI of the right coronary artery targeting an undilatable lesion already resistant to multiple specialised balloons and rotational atherectomy had coronary lithotripsy and new PCI on the RCA.	Calcium modification at the target segment was seen and 3 stents were deployed with a good final result. No intra hospital complications reported. Patient was free from angina at 3 months follow up.	Larger studies added to table 2.
Watkins, S, Good, R, Hill J, Brinton, TJ, Oldroyd, KG. Intravascular lithotripsy to treat a severely under-expanded coronary stent. EuroIntervention. 2018; Jaa-457 2018, DOI: 10.4244/EIJ-D-18-00780.	Case report 67 year old with occluded left anterior descending artery, right coronary artery stenosis, and under expansion of proximal lesion following PCI had IVL to facilitate full stent expansion.	The outcome was successful and effects were immediate and near complete stent expansion during the first cycle of energy.	Larger studies included in table 2.
Warisawa, T, Goto, S, Salazar, C, Akashi, Y, Escaned, J. Safety and feasibility of coronary lithotripsy supported by guide extension catheter for the treatment of calcified lesion in angulated vessel. CRM. 2019; **https://doi.org/10.1016/j.carrev.2019.02.014**	Case report	A case of successful coronary intervention with coronary lithotripsy facilitated by guide extension catheter for the treatment of severely calcified and bent vessel. The guide extension catheter accommodated it with ease and helped smooth delivery of it. This shows the usefulness of this device combination for patients with complex coronary anatomies.	Larger studies added to table 2.

Wong B, El -Jack S et al. (2019) Shockwave intravascular lithotripsy of calcified coronary lesions in ST-elevation myocardial infarction: first in-man experience. Journal of invasive cardiology 31 (5), e73-5	Case series N=3 patients having PCI for ST-elevation myocardial infarction (STEMI) using IVL as an adjunct procedure.	The 3 presented cases include an upfront use of S-IVL in a right coronary artery, an in-stent restenosis, and a community cardiac arrest/ST-elevated myocardial infarction equivalent when S-IVL was used as a bailout technique to help stent delivery in a tortuous calcified vessel. Early experience has been favourable.	Larger studies added to table 2. (cases also reported in study 3 in table 2)
Wong B, El -Jack S, Khan S et al. (2019) Treatment of heavily calcified unprotected left main disease with lithotripsy-the first case series. The journal of invasive cardiology, 31 (6): E143-7	Case series N=3 the use of S-IVL in a patient with left main-coronary artery disease (LM-CAD) with multivessel disease who declined surgery, a patient with an isolated LM-CAD and severe cardiomyopathy, and a late nonagenarian patient when surgical revascularisation was not an option reported.	No patients had procedural complications or major adverse events (stroke, myocardial infraction, death) during the index admission or within the first 30 days post discharge.	Larger studies included in table 2
Yeoh J, Hill J, Spratt JC et al. (2019) Intravascular lithotripsy assisted chronic total occlusion revascularization with reverse controlled antegrade retrograde tracking. Catheter Cardiovasc Interv, 93:1295-7	Case report 81-year-old female with heavily calcified right coronary artery chronic total occlusion (CTO) had PCI via reverse controlled antegrade/retrograde tracking (R-CART).Standard balloon inflation failed to create communication by modifying plaque and guidewire failed. So IVL was used in controlled antegrade/retrograde tracking.	IVL was used to help connection in R-CART to complete the CTO PCI when heavy calcification was present at the site of chronic occlusion. Multiple fractures helped connection between intimal and subintimal tissue planes.	Larger studies added to table 2.
Yeoh, J.; Hill, J. Intracoronary Lithotripsy for the Treatment of Calcified Plaque. Interventional Cardiology Clinics; 2019; vol. 8 (no. 4); 411-424	Review	This article reviews intravascular lithotripsy technology, the evidence in the literature, and the advantages and disadvantages compared with other forms of calcium modification and discusses its role in specific subsets of coronary lesions. It concludes with a discussion about the future direction of	Review

		research involving this new technology as its role within percutaneous cardiac procedures becomes more defined.	

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	18/11/19	Issue 11 of 12, November 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/11/19	Issue 11 of 12, November 2019
HTA database (CRD website)	18/11/19	-
MEDLINE (Ovid)	13/11/19	1946 to November 12, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	13/11/19	1946 to November 12, 2019
EMBASE (Ovid)	13/11/19	1974 to 2019 November 12

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

1 Coronary Artery Disease/ (59160)
2 Acute Coronary Syndrome/ (14603)
3 Myocardial Infarction/ (162853)
4 exp Angina Pectoris/ (42991)
5 Myocardial Ischemia/ (37984)
6 Vascular Calcification/ (3839)
7 Plaque, Atherosclerotic/ (8358)

8 Coronary Stenosis/ (11324)
9 ((coronar* or isch?em*) adj4 (arter* or heart* or vasc*) adj4 (diseas* or disord* or lesion* or stenos* or calcium*)).tw. (159973)
10 (coronar* adj4 (arterioscleros* or atherosclerosis*)).tw. (11361)
11 ((Myocardial* or heart*) adj4 (infarct* or isch?emia* or stenos*)).tw. (203190)
12 (heart adj4 attack*).tw. (5058)
13 (acute* adj4 coronar* adj4 syndrome*).tw. (25324)
14 angina*.tw. (49873)
15 (calcif* adj4 (coronar* or heart* or vasc*) adj4 (lesion* or stenon* or arter* or plaque*)).tw. (3544)
16 (vascular* adj4 (calcific* or calcinos*)).tw. (4292)
17 atheroma*.tw. (9995)
18 fibroatheroma*.tw. (571)
19 (atheroscler* adj4 plaque*).tw. (15619)
20 (arterial adj4 fat* adj4 streak*).tw. (21)
21 (CHD or CAD or MI or ACS or PCI).tw. (119335
22 Percutaneous Coronary Intervention/ (15980)
23 (percutan* adj4 coronar* adj4 intervention*).tw. (26552)
24 PCI.tw. (20069)
25 or/1-24 (520441)
26 Lithotripsy/ (9643)
27 (lithotrip* or litholapax* or lithoplast*).tw. (9772)
28 shockwave*.tw. (2177)
29 (IVL or S-IVL).tw. (395)
30 (calcif* and (plaque* adj4 modif*)).tw. (73)
31 or/26-30 (13311)
32 25 and 31 (156)
33 animals/ not humans/ (4609130)
34 32 not 33 (148)
35 limit 34 to english language (136)
36 limit 35 to ed=20190601-20191130 (16)