Early Australian experience with intravascular lithotripsy treatment of severe calcific coronary stenosis

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Abstract

Aims: Calcified coronary stenoses are a serious impediment to optimal stent expansion and can lead to stent failure and catastrophic adverse outcomes. We hereby present early Australian experience with intravascular lithotripsy for the treatment of calcific lesions in acute and chronic coronary syndromes.

Methods and results: This was a single-centre retrospective study of all patients treated with intravascular lithotripsy (IVL) between October 2019 and June 2021. Patient demographics, procedural variables, and treatment safety/efficacy outcomes were evaluated. During this period, there were 40 patients and 41 coronary lesions with IVL-assisted percutaneous coronary intervention (PCI) (70% male; mean age 72.8±9.5 years). Indications for PCI were acute coronary syndromes in 25 patients (62.5%), and stable angina in 15 patients (37.5%). Upfront IVL usage occurred in 5% of cases with the rest being bailout procedures due to suboptimal initial balloon predilatation or stent underexpansion. Angiographic success (<20% residual stenosis) occurred in 37 cases (92.5%), with mean residual stenosis of 8.25%±8.5%. Two patients experienced procedural complications (5%).

Conclusions: IVL appears to be a safe and effective modality in modifying coronary calcium to achieve optimal stent expansion in real-world practice. This device obviates the need for more complex lesion preparation strategies such as rotational or orbital atherectomy.

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Abbreviations

ACS	acute coronary syndrome
atm	atmosphere
CAD	coronary artery disease
DES	drug-eluting stent
IVL	intravascular lithotripsy
MACE	major adverse cardiovascular events
MI	myocardial infarction
NC	non-compliant
NSTEACS	non-ST-segment acute coronary syndrome
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
SD	standard deviation
STEMI	ST-segment elevation myocardial infarction
SVG	saphenous vein graft
TTE	transthoracic echocardiography

Introduction

Percutaneous treatment of heavily calcified coronary lesions remains a common challenge which is present in one-third of patients suffering from stable and acute coronary syndromes, and portends worse procedure-related and patient-related outcomes[1,2]. Severity of coronary artery calcification increases with age, presence of cardiovascular risk factors and comorbid conditions[3,4]. Percutaneous coronary intervention (PCI) in calcified lesions has been associated with major adverse cardiac events (MACE), increased rates of stent thrombosis, restenosis, and target lesion revascularisation[1,2].

Coronary calcification also increases procedural time and complexity. Moreover, the extent of coronary calcification (depth, arc, length and thickness) influences procedural success, stent delivery and expansion, and also potentially impairs drug delivery as well as damaging stent polymer[5,6]. Several technologies have been developed over the last three decades to overcome this hurdle, including cutting/scoring balloons, high-pressure non-compliant balloons, rotational or orbital atherectomy, and excimer laser[7-9]. These modalities rely upon tissue debulking or tissue compression and are associated with increased procedural complications such as coronary intimal layer dissection, coronary perforation, and distal embolisation[7,10]. So far, atherectomy devices and speciality balloons have not been proven to be superior to non-compliant balloons in improving clinical outcomes[8,9,11].

Intravascular lithotripsy (IVL) is a new addition to the armamentarium for treatment of calcified coronary lesions[1,2]. The IVL system transforms electrical energy into sonic waves that selectively fracture superficial and deep calcium at low-pressure balloon dilatation thus minimising vessel wall barotrauma[12,13]. The safety and efficacy of IVL were demonstrated in a series of DISRUPT CAD clinical trials[12-14]. In this study we present early single-centre Australian experience with the use of IVL in the treatment of severe coronary calcification in real-world patients treated for chronic and acute coronary syndromes.

This manuscript was approved by the Fiona Stanley Hospital Ethics Committee.

Methods

STUDY SETTING

We performed a retrospective analysis of all patients who underwent PCI and IVL shockwave therapy at our quaternary hospital from October 2019 to June 2021. Patient demographics and procedural data were prospectively collected and analysed. Indication for PCI was either stable coronary artery disease (CAD) with evidence of ischaemia or acute coronary syndromes (ACS), or single- or multivessel CAD with a diameter stenosis ≥70%. IVL was used in severely calcified coronary lesions resistant to high-pressure non-compliant balloon inflation (>18 atm) or upfront as an alternative to, or in combination with, traditional calcium modifying devices such as rotational atherectomy or ultrahigh-pressure balloons. Another indication for IVL therapy was bailout treatment of significantly underexpanded stents (>30% stenosis). There were no exclusion criteria.

STUDY DEVICE

The intravascular lithotripsy catheter (IVL; Shockwave Medical Inc.) is a monorail rapid exchange catheter that delivers an integrated semi-compliant balloon containing two lithotripsy emitters. The IVL balloon is filled with diluted contrast, with the recommended therapy delivery inflation pressure of 4 atmospheres (atm), a nominal pressure of 6 atm and a rated burst pressure of 10 atm. Sonic waves delivered at 4 atm balloon inflation generate peak pressure of approximately 50 atm[15]. Available IVL catheters are from 2.5 mm to 4.0 mm in diameter and 12 mm in length[12,13]. The IVL catheter is connected to the generator via a cable and is preset to deliver 10 sonic wave pulses per cycle (one pulse/second) for a maximum of eight cycles. The IVL balloon is sized 1:1 to the reference artery and inflated at a minimum of 4 atm to deliver acoustic energy and maximum of 10 atm if required to assess symmetrical expansion and confirm calcium modification.

PROCEDURES

PCIs were performed by experienced operators, and national guidelines were followed for assessment and treatment of acute and chronic coronary syndromes. The decision to proceed with IVL therapy was based on the discretion of the individual interventional cardiologist once they had concluded that high-pressure (>18 atm) non-compliant balloon inflation was ineffective to dilate the lesion adequately. Operators proceeded with any adjunctive tool to perform optimal PCI; these could be scoring/cutting balloons, or rotational atherectomy (note: orbital atherectomy is currently not available in Australia). Intravascular imaging was used as required, but its use was not universal. Stent implantation with a drug-eluting stent (DES) and PCI optimisation were performed as per standard of care.

ENDPOINTS AND DEFINITIONS

The primary safety endpoint was defined as freedom from MACE within 30 days following the index procedure. MACE was defined as cardiac death, myocardial infarction (MI), target lesion revascularisation, or stroke. Angiographical success was defined as success in stent delivery and <20% residual diameter stenosis after stenting of the target lesion, assessed by quantitative coronary angiography (QCA). Clinical success was defined as success in stent delivery and <20% residual diameter stenosis after stenting of the target vessel with no MACE.

Stent thrombosis was defined as definite stent thrombosis by angiography, and procedural myocardial infarction (MI) was defined according to the universal definition of MI[16]. This includes a troponin rise >x5 upper level of normal as well as one of the following: ischaemic electrocardiogram changes, new Q-waves, angiographic complications such as severe dissection, side branch occlusion or slow flow. Severe angiographic calcification was defined as radio-opacities observed without cardiac motion, usually affecting both sides of the arterial lumen, mimicking a double track line or guided by intracoronary imaging. Serious coronary intervention complications were recorded and defined as severe coronary dissection, coronary perforation, slow-flow or no-reflow phenomenon, and abrupt vessel closure.

STATISTICAL ANALYSIS

Continuous variables are described as mean±standard deviation (SD). Categorical variables are described as proportions.

Results

PATIENTS AND PROCEDURES

Between October 2019 and June 2021, 40 patients and 41 coronary lesions were treated with the coronary IVL system in our institution. Patients' baseline and coronary lesion characteristics are provided in **Table 1** and **Table 2**, respectively. Fifteen patients (37.5%) underwent IVL-assisted PCI for treatment of stable CAD with evidence of ischaemia, and 25 patients (62.5%) had IVL therapy during invasive treatment of ACS (ST-segment elevation myocardial infarction [STEMI] 17.5%, non-ST-segment acute coronary syndrome [NSTEACS] 45%).

The left anterior descending artery was the most common target vessel (48.8%). The mean reference vessel diameter was 3.38±0.61 mm with a mean lesion length of 32.4±18.4 mm. Calcification was extensive with a mean calcified length by coronary angiography of 33.7±12.2 mm.

Procedural details are provided in **Table 3**. Mean overall procedure duration was 88.17±38.9 minutes. However, 11 patients (27.5%) underwent two-vessel PCI including one chronic total occlusion PCI. Excluding these cases, the mean procedural time would be reduced to 77.7 minutes. One IVL catheter was used per patient in all cases. Predilatation prior to IVL use was performed in 38 (95%) cases. Upfront atherectomy with a 1.5 mm burr was required in one case as the IVL catheter was unable to

Table 1. Baseline and clinical demographics.

Number of patients	40
Age (years)	72.8±9.5
Men	28 (70%)
Diabetes mellitus	19 (47.5%)
Hypertension	28 (70%)
Dyslipidaemia	29 (72.5%)
Prior MI	13 (32.5%)
Prior coronary artery bypass graft	3 (7.5%)
Stroke/transient ischaemic attack	7 (17.5%)
Peripheral vascular disease	8 (20%)
Current smoker	7 (17.5%)
Ex-smoker	24 (60%)
Renal insufficiency stage 4 or 5 (eGFR <30)	7 (17.5%)
Left ventricular ejection fraction (by TTE)	51.5%±11.2%
Stable coronary artery disease	15 (37.5%)
NSTEACS	18 (45%)
STEMI	7 (17.5%)

Values are percentages (n) or mean±standard deviation.
eGFR: estimated glomerular filtration rate; MI: myocardial infarction; NSTEACS: non-ST-elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; TTE: transthoracic echocardiography

Table 2. Lesion characteristics.

Total number of lesions		41
Target vessel	Left main	2 (4.88%)
	Left anterior descending artery	20 (48.8%)
	Left circumflex artery	4 (9.75%)
	Right coronary artery	13 (31.7%)
	Saphenous vein graft	2 (4.88%)
Reference vessel diameter (mm)		3.39±0.56
Pre-IVL vessel stenosis		87.35%±8.5%
Lesion length (mm)		31.75±13.96
Calcified length (mm)		30.6±13.23
Side branch involvement		14 (34.1%)

Values are percentages (n) or mean±standard deviation.
IVL: intravascular lithotripsy

cross the lesion, and successful predilatation with a 2.5 mm OPN ultrahigh-pressure balloon (SIS Medical) was used in one patient after IVL crossing failure. IVL treatment was provided in these two cases to maximise calcium modification.

An average number of 1.29±0.68 DES were implanted per subject in 39 patients. One patient had drug-coated balloon angioplasty (SeQuent; B. Braun) of severe calcific stenosis inside two layers of underexpanded stents. Post-dilatation following stent implantations was performed in 39 (97.5%) patients. In four cases, IVL was used after new stent implantation due to >30% residual diameter stenosis and suboptimal stent expansion. Three patients underwent IVL therapy for treatment of severe calcification and stenosis at the site of old underexpanded stents.

Table 3. Procedural details.

Patients	n=40
Total procedural time (min)	88.17±38.9
Fluoroscopy time (min)	26.1±15.5
Contrast volume (ml)	212.85±90
Two-vessel PCI	11 (27.5%)
Number of IVL catheters per case	1
Number of IVL pulses	45.8±17.9
Maximum IVL inflation pressures (atm)	6
Number of stents used	1.29±0.68
Predilatation	39 (97.5%)
Post-dilatation	39 (97.5%)
Rotational atherectomy	1 (2.5%)
Cutting/scoring balloon	1 (2.5%)
OPN ultra high-pressure NC balloon	2 (5%)

Values are percentage (n) or mean±SD; atm: atmospheres; IVL: intravascular lithotripsy; NC: non-compliant; PCI: percutaneous intervention

ENDPOINTS

The in-hospital primary safety endpoint occurred in two patients, consisting of two MIs, neither of which were directly related to IVL treatment delivery. One case developed MI as a result of coronary dissection in PCI of a non-calcified lesion where a semi-compliant balloon was used for predilatation. The second patient with MI was in a case of coronary perforation managed by a covered stent sacrificing a diagonal branch. Two patients passed away in the follow-up period because of non-cardiac causes.

Clinical and angiographic success with <20% residual stenosis was achieved in 90% and 92.5% of patients, respectively. IVL catheter delivery, treatment of the target lesion, and subsequent stent delivery were successful in all patients. In four cases, the IVL catheter failed to cross the coronary lesion. Initial IVL therapy was delivered with only the distal balloon marker engaging the proximal lesion edge, which probably partially modified the calcified lesion and facilitated subsequent IVL balloon advancement through the stenosis.

The mean final residual stenosis post-IVL and stent implantation was 8.25%±8.5% **(Table 4)**. One coronary perforation (the same individual with MI due to sacrificed diagonal branch) occurred after post-dilatation of the implanted stent with a non-compliant

Table 4. Performance outcomes.

Patients	40
Clinical success	36 (90%)
Angiographic success (residual stenosis <20%)	37 (92.5%)
Stent delivery*	40 (100%)
Residual diameter stenosis <50%	40 (100%)
Mean residual stenosis (%)	8.25%±8.5%

Values are percentage (n) or mean±SD; *1 patient underwent treatment with drug coated balloon for in-stent re-stenosis

balloon which was managed with a covered stent implantation (PK Papyrus; Biotronik)[17]. There was one case of IVL therapy-induced coronary dissection, limited to the treated coronary segment, which was successfully covered with a stent **(Table 5)**. Representative angiographic and intracoronary imaging examples of the effects of IVL are shown in **Figure 1-Figure 3**.

Table 5. Clinical and angiographic complications.

Lesions treated	41
IVL-induced coronary dissection	1 (2.4%)
Coronary perforation*	1 (2.4%)
Abrupt vessel closure	0
Slow flow	0
No reflow	0
MACE	2 (5%)
Cardiac death	0
AMI*	2 (5%)
Target vessel revascularisation	0
Stroke	0
Stent thrombosis	0
Stent restenosis	0
Non-cardiac death	2 (5%)

Values are percentage (n) or mean±SD. *One individual patient suffered coronary perforation and myocardial infarction. AMI: acute myocardial infarction; MACE: major adverse cardiac events
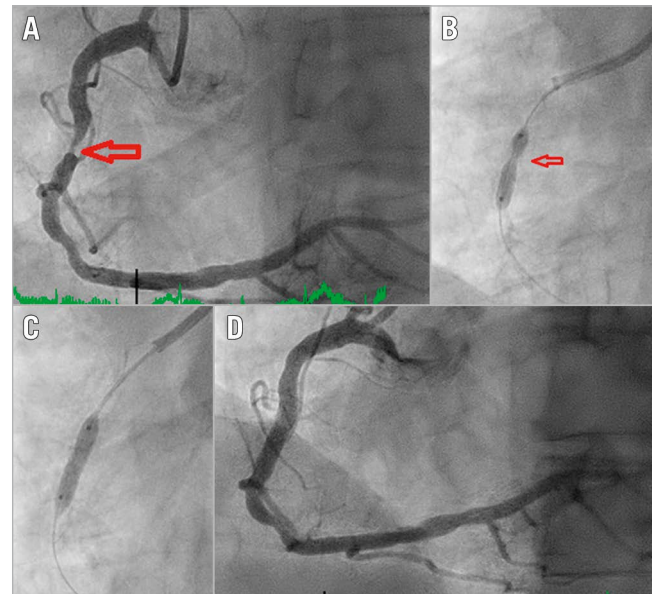

Figure 1. *Fluoroscopic demonstration of IVL-assisted angioplasty of a calcified right coronary artery stenosis. A) Diagnostic angiogram of right coronary artery with severe stenosis. B) NC balloon inflation (3.5/12 mm inflation at 20 atm) showing undilatable segment (arrow). C) Full expansion of IVL 3.5/12 mm balloon at 4 atm and one therapy cycle provided. D) Coronary angiography following stent implantation. IVL: intravascular lithotripsy; NC: non-compliant*
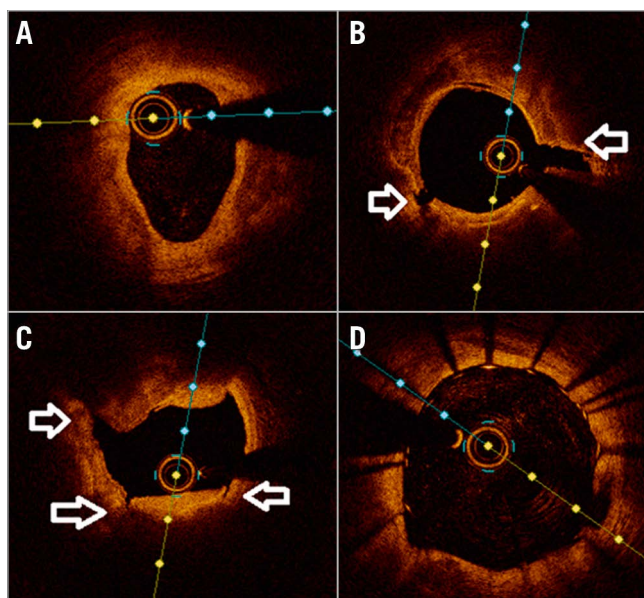
Figure 2. *Intracoronary imaging demonstration of IVL-assisted angioplasty of a severely calcified coronary stenosis. A) Pre-lithotripsy optical coherence tomography (OCT) scan showing severe calcification, B), C) Post-lithotripsy OCT showing fractured calcium (arrows), D) Final OCT image of stented vessel demonstrating well expanded/apposed stent.*

Discussion and limitations

Our retrospective study demonstrated the feasibility and safety of IVL therapy in preparation of severely calcified coronary stenoses prior to stent implantation in a real-world population. We also safely performed IVL therapy within three newly inserted stents with significant underexpansion of >30%, and in two patients with severe calcific stenoses at the sites of old stents. Major clinical and procedural findings of our study include: 1) coronary IVL therapy is safe and beneficial in treatment of severe coronary calcification; 2) the procedure was well tolerated with 100% success in stent delivery and a low risk of periprocedural complications; 3) IVL therapy can be combined with other adjunctive therapies for balloon non-dilatable/non-crossable calcific lesions in order to achieve optimal procedural outcomes; 4) the IVL device is easy to use with less technical complexity and preparation than rotational atherectomy.

Our findings are comparable to the recently published DISRUPT CAD III[14] study which was designed to assess the safety and effectiveness of IVL as an adjunct therapy in calcific coronary PCI. DISRUPT CAD III is a non-randomised single-arm multicentre prospective study which achieved the prespecified performance goals, prompting US regulatory approval in the utilisation of this technology for treatment of calcific coronary artery disease. However, there are some differences between our study and DISRUPT CAD III. First, in the DISRUPT CAD III, only *de novo* coronary lesions were included, whereas we also reported the performance of IVL in the treatment of calcified stenoses in coronary arteries stented years ago, and in newly implanted stents with >30% residual stenosis due to underexpansion in calcified
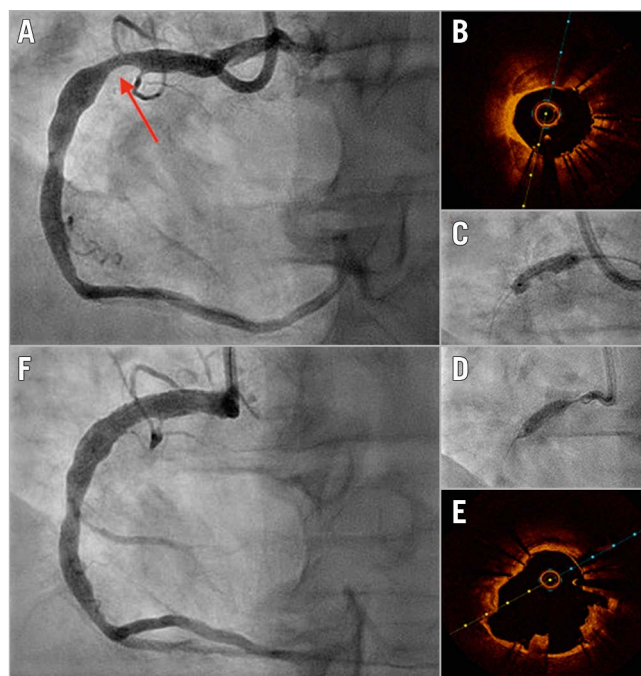

Figure 3. *Use of IVL in an underexpanded stent. A) Diagnostic angiogram of right coronary artery showing significant stent underexpansion. The stent (arrow) was inserted at another institution 48 hours prior to this admission. B) OCT image showing severe coronary calcification. C) NC balloon inflation (4.0/15 mm inflation at 20 atm) showing undilatable stent . D) Full expansion of IVL 4.0/12 mm balloon at 6 atm. E) OCT post-IVL Shockwave therapy showing calcium fractures and expanded stent. F) Post-IVL angiography showing well-expanded stent with residual 10% stenosis. IVL: intravascular lithotripsy; NC: non-compliant; OCT: optical coherence tomography*

lesions. While not currently supported by the product developer, off-label use of IVL to treat in-stent restenosis due to calcific neo-atherosclerosis[18] and to expand old underexpanded stents[19] has been reported. Currently, no evidence exists to support the safety of the immediate use of IVL in underexpanded stents, and concerns regarding possible disruption to the stent architecture and/or drug/polymer coating have been raised. However, we believe that rectifying in-stent restenosis or expanding an underexpanded stent holds a distinct clinical benefit to the patient, reducing the exceedingly high risk of stent thrombosis/restenosis[5,20-22] and subsequently MACE. The safety and efficacy of IVL therapy in newly inserted stents was similar to IVL in the treatment of *de novo* coronary lesions, although long-term follow-up data is lacking. We recommend appropriate lesion preparation and calcium modification before stent insertion, until further studies demonstrate the safety of this novel technology in newly inserted stents as a bailout option. The risks and benefits must be taken into account and this should only be considered on the rare occasions operators encounter suboptimal stent results.

Second, the majority of patients (95%) included in this study underwent IVL as a bailout following failed standard balloon

angioplasty, whereas predilatation prior to IVL was performed in 55% of DISRUPT CAD III lesions. Intracoronary imaging was used infrequently in both studies (25% in DISRUPT CAD III and 30% in this study). More routine use of intracoronary imaging would be beneficial to identify the lesions with moderate to severe calcification which would benefit from upfront calcium modification treatment.

Third, DISRUPT CAD III excluded patients with ACS, severe chronic kidney disease, saphenous vein grafts (SVG) and use of atherectomy or cutting/scoring balloons, which restricted the use of the IVL system to a subgroup of select patients. Our study included all patients who we believed would benefit from this novel technology including those with multivessel coronary disease, chronic total occlusions, in-stent restenosis, and under-expanded *de novo* stents, reflecting a real-world and diverse population. Our limited experience with the use of IVL in ACS patients or SVG PCI did not demonstrate any additional adverse outcomes, such as arrythmias due to "shocktopics" or slow-flow/no-reflow phenomena.

With regard to efficacy endpoints, DISRUPT CAD III defined procedural success as stent delivery with residual stenosis <50%, which is considered unsatisfactory and a suboptimal outcome in coronary intervention. The recommended stent expansion is at least 80% and ideally >90% with <20% residual stenosis[23]. Therefore, we defined angiographic success as <20% residual stenosis. Considering safety endpoints, we observed a similar serious angiographic complication rate with IVL therapy compared to the DISRUPT CAD III study (5% vs 7%, respectively). **Table 6** compares the findings between the DISRUPT CAD III and the current study.

Finally, one of the major setbacks in IVL is lesion crossing failure. Investigators in the DISRUPT CAD trial were not allowed to use other adjunctive coronary lesion preparation devices as part of the study protocol. This resulted in 8 IVL catheter crossing failures, however, we opted to combine IVL with other therapies in this group of patients. These technologies are complementary with different modes of action, and use of one does not preclude the use of another. Rotational and orbital atherectomy were both shown to improve procedural outcomes in ROTAXUS[8] and ORBIT II[9] trials, respectively. These modalities facilitate stent delivery and implantation by debulking calcified coronary stenoses, whereas IVL creates microfractures in coronary calcification, facilitating better stent expansion. As opposed to atherectomy debulking techniques, IVL therapy may possibly reduce the likelihood of atheromatous distal embolisation and associated risk of slow-flow/no-reflow phenomena[12]. Atherectomy devices primarily modify superficial coronary calcification, whereas IVL fractures both deep and superficial calcium layers[24,25]. Whether the combination of atherectomy and IVL improves outcome over either modality alone remains unclear and requires further study.

High-pressure non-compliant balloons and ultrahigh-pressure balloons (OPN; SIS Medical) are therapies that have been used over decades, however there is no compelling evidence to support

Table 6. Comparison between DISRUPT CAD III and current study.

	Current study	DISRUPT CAD III
Age (years)	72.8±9.5	71.2±8.6
Men	28 (70%)	294 (76.6%)
Diabetes mellitus	19 (47.5%)	154 (40.1%)
Hypertension	28 (70%)	342 (89.1%)
Dyslipidaemia	29 (72.5%)	342 (89.1%)
Prior MI	13 (32.5%)	69 (18.0%)
Prior coronary artery bypass graft	3 (7.5%)	36 (9.4%)
Stroke/transient ischaemic attack	7 (17.5%)	29 (7.6%)
Chronic renal insufficiency (eGFR 30-60 ml/min/1.73 m²)	8 (20%)	101 (26.4%)
Severe renal insufficiency (eGFR<30 ml/min/1.73 m²)	7 (17.5%)	Excluded
Reference vessel diameter (mm)	3.39±0.56	3.03±0.47
Lesion length (mm)	31.75±13.96	26.1±11.7
Calcified length (mm)	30.6±13.23	47.9±18.8
Side branch involvement	14 (34.1%)	115 (29.9%)
Pre % diameter stenosis	87.35±8.5	65.1±10.8
Final % diameter stenosis	8.5±9.1	11.9±7.1
MACE	2 (5%)	27 (7%)
Serious angiographic complications	2 (5%)	12 (3.1%)

eGFR: estimated glomerular filtration rate; MACE: major adverse cardiac events

improved procedural and/or clinical outcomes with their use. On the other hand, preclinical data suggest the resultant excessive coronary vessel wall stretch and deep injury are potent stimuli for neointimal hyperplasia[26,27]. Currently, little evidence is available on the impact of IVL therapy on neointimal hyperplasia. It is, however, postulated that due to a low balloon inflation pressure of 4 atm, there would be less barotrauma to the vessel wall and potentially less neointimal hyperplasia. Also, IVL differentially fractures hard calcium layers rather than affecting soft intimal and medial tissues, potentially reducing vessel wall injury[13].

These findings are representative of a single Australian centre and may not be generalisable to other institutions. This is an observational retrospective study lacking a concurrent control group, and not all variables are considered in the outcomes. Infrequent use of intracoronary imaging to ensure optimal lesion preparation and stent implantation is a disadvantage in our cohort. There is no long-term follow-up for our patients and future studies are required to investigate long-term procedural and clinical outcomes after IVL therapy.

Conclusions

In conclusion, our findings confirm the short-term safety and efficacy of IVL to manage severely calcified coronary lesions in broader clinical scenarios from stable CAD to ACS. Our outcomes are aligned with the current limited clinical trials, such as DISRUPT CAD III. Combination of the IVL Shockwave system

with other adjunctive therapies is a viable option in balloon non-dilatable/uncrossable calcific stenosis.

Impact on daily practice

Our results demonstrate real-world short-term safety and efficacy of IVL to manage severely calcified coronary lesions in acute and chronic coronary syndromes. Combination of the IVL Shockwave system with other adjunctive therapies is a viable option in calcific stenoses which are undilatable/uncrossable by balloon. The IVL Shockwave system is easy to use, with less technical complexity and preparation than rotational atherectomy.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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