# Intravascular Lithotripsy Catheter Balloon for Calcified Coronary Artery Pilot Study

## Investigators:

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## Study Site/s:

Cardiac Catheter Laboratory, Mackay Base Hospital: Mackay, Queensland, Australia

## Introduction and Background:

Acute coronary syndrome (ACS) is a manifestation of coronary artery disease which includes ST elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTEACS). Current Australian ACS guidelines recommend invasive management with diagnostic angiography and/or percutaneous coronary intervention (PCI) for all STEMI and high risk NSTEACS patients. PCI with implantation of a drug-eluting stent is a highly used method of restoration of perfusion to ischaemic coronary arteries (1). Calcified coronary lesions show increased prevalence and severity with advancing age, diabetes, hypertension and chronic kidney disease (2). This coronary calcification adversely impacts interventional outcomes by hindering stent delivery (3), damaging the drug-eluting polymer compound of stents (4) and impairing stent expansion and apposition (5).

Current PCI used to overcome the limitations imposed by coronary calcification include high-pressure balloon dilatation and atheroblative techniques such as laser, rotational and orbital atherectomy (3). However, current PCI methods in lesions that are heavily calcified are shown in literature to be either ineffective, fraught with procedural complications (i.e. artery perforation, dissection, or myocardial infarction), or subject to delayed adverse events (i.e. thrombosis, stent fracture, restenosis). Although current practice of atherectomy facilitates stent expansion, dilatation in eccentric calcium may be limited by guidewire bias towards the non-calcified segments of the artery, and in concentric calcium may be of insufficient pressure-generated force to lead to calcium fracture and vessel expansion.

Rotational and orbital atherectomy selectively ablate superficial calcium but have limited impact on deep calcium that limits vessel expansion during stent implantation (5,6). In addition, peri-procedural complications including perforation, slow flow and peri-procedural myocardial infarction (MI) are still significantly higher with atherectomy than balloon-based therapies (7-11).

Intravascular Lithotripsy (IVL) is a technique based on lithotripsy, an established treatment strategy for renal calcification, in which multiple lithotripsy emitters mounted on a traditional balloon catheter platform create diffusive pulsatile mechanical energy to disrupt calcium within the vessel wall at low inflation pressures. Previous studies have reported high rates of device success, safety and performance of coronary IVL in vessel preparation of calcified stenotic coronary lesions prior to stent implantation.

The Disrupt CAD II demonstrated successful delivery of the IVL balloon in 59 (98.5%) of subjects with reduction in residual stenosis to less than 50% in all 60 (100%) subjects. The angiographic luminal acute gain following stent implantation was 1.7mm and residual stenosis was 13.3%. Freedom from MACE was present in 57 (95%) subjects due to 3 (5%) non-Q wave MI at 30 days. At 6 months, freedom from MACE was present in 54 of 59 (91.5%) subjects due to 2 additional subjects suffering cardiac death. Results of the optical coherence tomography (OCT) sub-study identified modification with fracture as a major mechanism of action of IVL in vivo and demonstrated efficacy in the achievement of significant acute area gain and favourable stent expansion (13).

Building upon this success is the recent Disrupt CAD III study which involved 431 patients from 47 sites in four countries. The key findings were: (i) treatment with IVL met the primary safety and effectiveness outcomes of the study, (ii) IVL was well tolerated with low rate of major peri-procedural clinical and angiographic complications, (iii) there was excellent stent expansion identified by optical coherence tomography despite the calcification severity of the treated lesions. This study demonstrated the real-world safety and performance of the Coronary IVL System in severely calcified lesions, and FDA market approval was granted based on the results of this study.

Mackay Base Hospital Cardiac Catheterisation Laboratory has clinicians with the technical expertise to implement IVL. This Cath Lab was established in 2014 to address inaccessibility of interventional cardiac services in North Queensland, and PCI is routinely undertaken within the lab. A recent evaluation of the service demonstrated that as a result of the provided services, since implementation there has been a reduction of wait times to treatment by 3.2 days, reduction of median length of stay by four days, significantly improved patient satisfaction and reduction in proportional treatment costs by $ 14, 841 (51%) per patient (14).

## Objective

The primary aim of this study is to test the ability of IVL to intervene in difficult coronary lesions to produce acceptable residual stenosis (<50%) post stenting without in-hospital major adverse cardiac events.

## Method

### Participation and Population

Participants will be screened for participation in the study and will require informed consent. Recruitment will occur during the cardiac occasion of service in the outpatient clinic or in-patient episode of care. Patients must be > 18 years of age scheduled for a coronary stent procedure who have angiographic evidence of significant calcified stenosis of the left main coronary artery (LMCA), left anterior descending artery (LAD), right coronary artery (RCA), or left circumflex (LCX) and deemed suitable for revascularization by the treating cardiologist with the aid of suitable investigations (e.g. Cardiac Magnetic Resonance Imaging, Myocardial Perfusion Scan or Echocardiogram).

### Inclusion criteria

* Patient is > 18 years of age
* Troponin must be less than or equal to the upper limit of lab normal value within 24 hours prior to the procedure or if troponin is elevated, concomitant CK must be normal
* The target vessel must have a TIMI flow 3 at baseline
* Patients with significant (> 50% diameter stenosis) native coronary artery disease including stable or unstable angina and silent ischemia, suitable for PCI
* Ability to tolerate dual antiplatelet agent (i.e. aspirin, clopidogrel, prasugrel, or ticagrelor for 1 year and single antiplatelet therapy for life
* Single lesion stenosis of protected LMCA, or LAD, RCA or LCX artery > 50% in a reference vessel of 2.5mm – 4.0 mm diameter and < 32 mm length
* Presence of calcification within the lesion on both sides of the vessel as assessed by angiography
* Planned treatment of single lesion in one vessel
* Ability to pass a 0.014’’ guide wire across the lesion
* Patient, or authorized representative, signs a written Informed Consent form to participate in the study, prior to any study-mandated procedures
* Patient is able and willing to comply with all assessments in the study

### Exclusion criteria

* Concomitant use of other techniques to deal CAC such as atherectomy and special balloons
* Severe renal failure
* Severe anaemia
* Previous PCI within 30 days of planned procedure
* Patients not suitable for consenting such as severe memory impairment
* Acute coronary syndrome within 1 month from planned procedure
* Severe Heart Failure (NYHA III or IV)
* Unable to tolerate dual antiplatelet agents (Aspirin + clopidogrel or ticargrelor or prasugrel) for 1 year for any reason
* Contrast allergy
* Active infection

### Outcome measures

Primary Outcomes

* Safety outcome – freedom from major adverse cardiac events (MACE) within 30 days of procedure.
* Effectiveness outcome – Procedural success defined as stent delivery with a residual stenosis <50% and without in-hospital MACE.
* MACE – Composite occurrence of cardiac death, myocardial infarction, or target vessel revascularisation
* Myocardial infarction – CK-MB level > 3 times the upper limit of lab normal value with or without new pathologic Q waves at discharge (periprocedural MI) and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI).
* Target vessel revascularisation – Revascularisation at the target vessel (inclusive of the target lesion) after the completion of the index procedure.

Secondary Outcomes

* Device crossing success – ability to deliver the IVL catheter across the target lesion, and delivery of lithotripsy without angiographic complications immediately after IVL
* Angiographic success (<50% residual stenosis) – Stent delivery with <50% residual stenosis and without angiographic complications.
* Procedural success – Stent delivery with a residual stenosis (30% and without in-hospital MACE
* Angiographic complications – severe dissection, perforation, abrupt closure, and persistent slow flow or persistent lack of reflow.
* Target lesion failure (TLF) – Cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or ischemia-driven target lesion revascularisation (ID-TLR) by percutaneous or surgical methods at 30 days.

### Sample size calculation

No sample size calculation will be undertaken as this is a pilot/feasibly project and the study number is at capped at ten.

### Group allocation

This is a single arm trial and as such no group allocation will be undertaken.

**Device and procedure**

The Shockwave Medical (Santa Clara, CA, USA) IVL system and coronary IVL catheter consist of a fluid-filled balloon angioplasty catheter and guidewire. Lithotripsy emitters are housed in the 12mm balloon segment (Figure 1). Each catheter is single use and can deliver a total of 80 IVL pulses.



Figure 1. Image of IVL system and coronary IVL catheter

All participants will have the procedure completed by an investigator who is trained in using the Shockwave IVL. The IVL catheter will be inserted and delivered over guidewire. Atherectomy devices and cutting/scoring balloons will not be used. The IVL balloon will be inflated to 4 atm and 10 IVL pulses will be delivered followed by inflation of the balloon to 6 atm. This will be continued until the balloon has expanded to full capacity, whereby the stent can be implanted.

The investigator will record all results in a secure and confidential database. The values will be recorded on a collection tool designed specifically for this study (see Appendix). Table 1 includes a general overview of the categories of data to be collected.

Table 1: Assessment Items and Schedule

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Assessment | Screening/ Baseline (Day – 14 to Day 0) | Enrolment and Procedure (Day 0) | Post Treatment | Discharge | 30 Days (+/- 7D) |
| Informed Consent | X |  |  |  |  |
| Medical History | X |  |  |  |  |
| Physical Examination | X |  |  | X |  |
| NYHA Classification | X |  |  |  |  |
| Canadian Cardiovascular Society (CCS) Angina Classification | X |  |  |  |  |
| Laboratory Assessments | Ck, Platelets, Creatinine, Haemoglobin, BUN | Troponin |  | Troponin, CK, CK-MB, Creatinine, Haemoglobin |  |
| Urine pregnancy test, if female of childbearing potential within 7 days of procedure | X |  |  |  |  |
| LVEF | X |  |  |  |  |
| ECG | X |  |  | X |  |
| Coagulation Studies | X |  |  |  |  |
| Angiographic Lesion Assessment |  | X | X |  |  |
| Medication regime per protocol | X |  |  | X | X |
| Adverse Event Assessment |  | X | X | X | X |

### Data analysis

Statistical analysis will be performed using International Business Machines Statistical Package for the Social Sciences (IBM SPSS) Statistics 26.0 software. There will be no power assessment and only descriptive statistics will be reported. The continuous variables will be reported as mean +/- standard deviation or medial and interquartile range (IQR) as appropriate.

## Data Management

### Storage and Monitoring

All data for this trial will be entered into a secure and confidential electronic database. This database will only be assessable to those who are recording the data, the investigators, and statisticians. Health professionals who are providing care to the participants (medical officers, nursing staff, allied health, etc) will not have access to this database.

### Destruction and confidentiality.

Data will be stored for a minimum of five years after the end of the main analysis of the trial, in accordance with the NHMRC guidelines. Paper records will be stored in a locked storage room. Electronic records will be stored in password protected files on a password protected server within the Mackay HHS. After 5 years we will erase all the data and destroy the paper records.

## Ethical and Safety Considerations

### Research related risks

There are no additional foreseeable risks associated with this project. Participation in the study is voluntary. Participants will be able to withdraw from the study at any point without prejudice, by contacting the Primary Investigator. Coronary IVL has safely and effectively facilitated stent implantation in severely calcified lesions with no adverse events in similar study populations. The primary safety endpoint is the MACE rate (Major Adverse Cardiac Events) within 30 days or 6 months after surgery. DISRUPT CAD III was a prospective, multicentre study involving 47 sites in 4 countries, which found the incidence of MACE within 30 days was 7.8% (Hill et al, 2020). DISRUPT CAD III confirms and extends prior observations from smaller studies (DISRUPT CAD I and DISRUPT CAD II) regarding the safety of IVL, which showed similar MACE rates. This is despite most U.S operators in the DISRUPT CAD studies having no prior experience with the IVL technology. Participants in this study would otherwise be undertaking alternative percutaneous coronary interventions, which share share similar if not greater risks than are involved in coronary IVL. MACE rates in these coronary IVL studies can be compared with other percutaneous coronary interventions of similar inclusion/exclusion criteria, endpoints and definitions to further evaluate the risks of this research. In these comparisons, coronary IVL has lower 30 day MACE rate than orbital atherectomy, which was demonstrated in the ORBIT II trail to have 9.4% MACE rates (Chambers et al, 2014). No alterations in other aspects of clinical care will occur as a result of the study, and the cardiologist undertaking the procedure will have standard resources available at the time of operation to manage the usual risk of adverse events.

We will seek to employ safety monitoring processes that are commensurate with the details of our proposed research. We appreciate that this technology has not been used previously at MBH, and that is why our proposal is for a pilot with a small number of participants, where risk of adverse events can be closely monitored. An independent data and safety monitoring board (DSMB) will be established to review the study data and any adverse events.

The investigators will assess all safety events and will act on any event as clinical care dictates. The Principle Investigator will provide MHHS, the HREC, and the independent DSMB all relevant information relating to any serious adverse events and any significant safety issues potentially leading to a serious adverse event.

Adverse events

The following definitions will apply to this study, as per the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (Nov 2016).

**Adverse event (AE)** - Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.

**Adverse Reaction (AR)** - Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Comment: All adverse events judged by either the research team or the treating team as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression ‘reasonable causal relationship’ means to convey, in general, that there is evidence or argument to suggest a causal relationship.

**Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)** - Any adverse event/adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Note: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Note: Medical and scientific judgement should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations. Important medical events that are not immediately life threatening or do not result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

**Significant safety issue (SSI)** - A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability of the conduct of the trial.

**Suspected unexpected serious adverse reaction (SUSAR)** - An adverse reaction that is both serious and unexpected.

AEs are expected when their nature and severity are consistent with the current Product Information Brochure.

SAEs are to be reported for events that occur after enrollment and up to 3 months post-IVL, and are unexpected given the participant’s underlying condition, and in the opinion of the investigator the event is related to the IVL procedure/device.

SAEs and SUSARs are to be reported within 24 hours of the research team becoming aware of the event, using the ‘Reporting of Adverse Event’ form.

SAE and SUSAR reports will be reviewed by the DSMC, as stipulated under ICH-GCP guidelines and the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (Nov 2016). The DSMC are responsible for informing the relevant HRECs and the Administering Institution for the trial. The DSMC will act in an advisory capacity to the trial Steering Committee and will, in addition to the interim analysis, monitor withdrawals, review ethical conduct of the trial and SAEs.

### Researcher safety

All investigators involved in the project will conduct the project such that it complies with the respective professional Code of Conduct. There are no additional risks to clinicians beyond standard occupational requirements.

## Project feasibility

Appropriate support will be provided for this project to succeed. Training in device management will be provided by Shockwave Medical, Inc. The devices will be supplied by an in-kind contribution from Shockwave Medical, Inc.

Only ten patients will be required for the study, and in this way there will not be a considerable burden on clinical staff in patient monitoring and management. All measures that will be undertaken for evaluation of the outcomes are routinely taken as part of standard clinical care.

A period of nine months has been designated as an appropriate timeframe for the trial.

A Research Fellow is part of the research team to provide non-clinical academic support in data collection and synthesis.

**Translation of findings into practice**

If this research shows that the IVL technique meets the aforementioned outcome measures, we will work with Shockwave Medical, Inc to roll out a larger clinical trial at Mackay Base Hospital to assist in the accumulation of data to support Australian TGA approval. We will work with the sponsor so that benefits of this technology can be translated into ongoing practice for the benefit of care to MBH Cardiac Cath Lab patients.

## Dissemination of Results

We will disseminate the research findings through conference presentations and publication in peer-reviewed scientific journals. We aim to publish in a cardiology journal. We will produce a short summary of the results of the study which trial participants will have the option of receiving.

## Appendices

The following documents have been included as appendices:

* Data Collection tool
* Participant information and Consent forms
* Investigators CV’s.
* Adverse event reporting form

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