ModiFication of coRonAry*Calcium with laser based inTravascUlaR*lithotripsy for coronary artEry disease (FRACTURE)

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The objective of this clinical study is to assess the safety and effectiveness of the Bolt IVL System for the lithotripsy-enhanced percutaneous coronary intervention of de novo, calcified, stenotic coronary lesions prior to stenting. The data is...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON56316

Source
ToetsingOnline

Brief title
FRACTURE study

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Coronary artery stenose, shockwave and PTA

Research involving
Human

Sponsors and support

Primary sponsor: Bolt Medical, Inc.
Source(s) of monetary or material Support: Het bedrijf Bolt Medical;Inc (de sponsor van

de studie)

Intervention

Keyword: angioplasty, artery, coronary artery, Intravascular, Lithotripsy, PTA

Outcome measures

Primary outcome

Safety: The study*s primary safety endpoint is freedom from major adverse cardiac events (MACE) within 30 days following the index procedure. MACE is defined as the occurrence of cardiac death, Myocardial Infarction (MI), or Target Vessel Revascularization (TVR). • Myocardial Infarction (MI) is defined as CK-MB level >3 times the upper limit of lab normal (ULN) value with or without new pathologic Q wave >=6 to 24 hours post-procedure (periprocedural MI), and by the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI). • Target Vessel Revascularization (TVR) is defined as revascularization of the target vessel (including the target lesion) after completion of the index procedure. Effectiveness: The study*s primary effectiveness endpoint is procedural success defined as successful stent delivery with a final residual stenosis <50% (assessed by angiographic core laboratory) and freedom from in-hospital MACE. The study will be interpreted as a success if both the primary safety and primary effectiveness endpoints are met.

Secondary outcome

The secondary endpoints are: 1. Device success defined as the ability to deliver the Bolt IVL catheter across the target lesion, and delivery of lithotripsy without serious angiographic complications immediately after IVL.

2. Angiographic success defined as stent delivery with <50% final residual stenosis and without serious angiographic complications. 3. Procedural success defined as stent delivery with a final residual stenosis <=30% and without in-hospital MACE. 4. Angiographic success defined as stent delivery with <=30% final residual stenosis and without serious angiographic complications. 5. Serious angiographic complications defined as severe dissection (Type D to F), perforation, abrupt closure, and persistent slow flow or persistent no reflow. 6. MACE within 6, 12, and 24 months. 7. Target lesion failure (TLF) defined as cardiac death, target vessel myocardial infarction (TV-MI) (Q wave and non-Q wave), or ischemia-driven target lesion revascularization (ID-TLR) by percutaneous or surgical methods at 30 days, 6 months, 12 months, and 24 months. 8. At each time period: All deaths, cardiac deaths, MIs, TV-MIs, procedural and nonprocedural MIs, ID-TVRs, ID-TLRs, non-ID-TLRs, non-ID-TVRs, all revascularizations (ID and non-ID), and stent thrombosis (Academic Research Consortium (ARC) definite, probable, definite or probable). 9. Sensitivity analyses will be reported for MI using the Society for Cardiovascular Angiography and Interventions (SCAI) definition through discharge, and the Universal Definition of MI (Fourth) through discharge, 30 days, 6 months, 12 months, and 24 months.

Study description

Background summary

Coronary artery disease (CAD) is caused by atherosclerosis within the coronary arteries which results in arterial narrowing and restricted blood flow to the

heart. This can lead to symptoms of angina and decreased heart function. CAD is the most
common form of heart disease and the leading cause of death in the United States (Braun, 2018). Although the mortality for this condition has gradually declined in western countries, it still causes about one-third of all deaths in people older than 35
years (Nichols 2014).

Patients with symptomatic CAD typically fall into one of two subtypes, those with stable ischemic heart disease (SIHD) and those with acute coronary syndromes (ACS). SIHD results from slow growing plaques that over time narrow the coronary
artery until ischemia and symptoms develop. Non-invasive testing such as stress tests or cardiac CT scans are helpful in diagnosing this condition.
Anti-anginal medications are the initial treatment of choice for these patients, however those with
ongoing symptoms can derive significant benefit from revascularization (Bangalore, 2020). Patients with ACS have unstable atherosclerotic plaques that fissure or rupture and acutely or partially obstruct a coronary artery. These patient*s symptoms
usually do not resolve with medications alone and require urgent revascularization.

Current Treatments options are:
- Pharmacotherapy: Antiplatelets (e.g., aspirin, P2Y12 inhibitors), antianginals (e.g., beta-blockers, nitrates, calcium channel blockers), lipid control (e.g., statins, non-statin LDL lowering treatments, non-LDL therapies), glycemic control.
- Coronary Bypass grafting (CABG): Currently indicated for patients with complex 3-vessel coronary artery disease involving the proximal left anterior descending artery (LAD) and/or left main coronary artery (LM). Depending on the complexity of
disease, when compared to percutaneous coronary intervention in the SYNTAX trial, CABG is associated with a decrease need for repeat revascularization and similar to improved periprocedural morbidity and mortality, at the expense of a longer
initial hospitalization. For patients who are not surgical candidates due to multiple comorbid conditions, PCI and medical therapy remain the only therapeutic options.
- Transcatheter Coronary interventions:
• Percutaneous transluminal anioplasty (PTA): first performed in 1977, it was one of the first treatment options for CAD and is associated with low complication rates. Isolated balloon angioplasty is no longer the treatment of choice as it is plagued by
high rate of failure resulting from restenosis and vascular recoil.
• Cutting and scoring balloons special balloons that contain microsurgical blades bonded to its* surface with the intention of scoring/cutting into

atherosclerotic plaque.
• Drug-coated balloons (DCB) delivers antiproliferative drugs to local arterial tissue and reduces risk of restenosis (Picard, 2017).
• Atherectomy - a minimally invasive endovascular surgery technique to remove or debulk atherosclerotic plaque from diseased arteries.
• Lithotripsy (IVL): lithotripsy has been around since the early 1980s, and used to break down stones in the kidney, gallbladder, or ureter with sound waves. Since then, the procedure has been adapted for intravascular calcium modification using sonic
pressure waves to modify intimal and medial calcium.
• Cryoplasty: uses nitrous oxide to optimize the dilation effects of standard angioplasty by delivering cryothermal energy to the atherosclerotic plaque.
• Stents: routine implantation of stents has improved the clinical course after balloon angioplasty and is now standard in the treatment of stenosis of native coronary arteries and venous bypass vessels (Ruß, 2009).

The study involves the evaluation of a new medical device (BOLT IVL system) which uses a combination of Lithotripsy (IVL) with a low pressure balloon to break the plague and widen the affected artery.

Study objective

The objective of this clinical study is to assess the safety and effectiveness of the Bolt IVL System for the lithotripsy-enhanced percutaneous coronary intervention of de novo, calcified, stenotic coronary lesions prior to stenting.
The data is used for obtaining market access

Study design

The FRACTURE study is a Prospective, non-randomized, single-arm, multicenter, interventional study in US and international centers to obtain data for support of market access.

Each subject will participate for up to two (2) years. Total study duration will be approximately four (4) years.

The tests performed within the study are standard of care, limiting the risk of participating in the study for the patients.

Approximately 392 subjects and up to 50 roll-in subjects (range 392 - 442) will be enrolled at up to 50 global sites. At least 50% of the total enrollment will come from the United States. The primary analysis set for the endpoints will consist of an intent-to-treat (ITT) approach based on enrolled subjects for whom a lithotripsy procedure is attempted.
Study outcomes will also be analyzed using a per-protocol (PP) population. The

PP population includes all subjects who had no pre-specified inclusion and exclusion violations.

Intervention

The study procedure consists of standard percutaneous coronary interventional (PCI) techniques, including access site preparation, introduction of the catheter portion of the device, inflation and deflation of the balloon, withdrawal of the catheter, stent
implantation, and access site closure.

PCI is performed via either femoral or radial access with a minimum 6F guiding catheter. The IVL catheter is passed across the lesion over a standard 0.014* guidewire. If the IVL catheter will not cross the lesion, adjunctive tools (buddy wire, balloon
predilatation, or guide catheter extension) can be used at operator discretion before reinsertion of the IVL catheter. Atherectomy or cutting/scoring balloons is not permitted.

Once the balloon is placed in the target lesion area, the balloon is inflated to 4 atm and a treatment cycle is activated by pressing and holding the treatment activation button, leading to delivery of pulsatile acoustic (shockwaves) for up to the defined
number of pulses per treatment cycle.

A different diameter IVL balloon may be used if significant vessel tapering occurs in the target lesion.
The number of IVL catheters used is dependent on lesion length, vessel diameter of the treated segments, and total number of pulses required to effectively treat the target lesion.

Study burden and risks

Potential risks associated with the BOLT Intravascular Lithotripsy System can be associated with device use, general anesthesia, catheterization and diagnostic imaging for subjects with CAD.

The potential risks and discomforts associated specifically with treating CAD with the BOLT IVL System are expected to be similar to the risks associated with the use of other commercially available, standard of care devices.

Potential risks/adverse events associated with the BOLT IVL system, general anesthesia, catheterization and diagnostic imaging for subjects with CAD ,as reported in the published literature, are outlined below.

Risks/adverse events may be local or systemic in nature and vary from minor

reactions to major reactions that may be life-threatening or result in death.

Documented risks associated with standard catheter-based cardiac interventions/procedures are reported in the published literature and include, but are not limited to, the following:
• Abrupt vessel closure
• Allergic reaction to contrast medium, anticoagulant, and/or antithrombotic therapy
• Aneurysm
• Arrhythmia
• Arteriovenous fistula
• Bleeding complications
• Cardiac tamponade or pericardial effusion
• Cardiopulmonary arrest
• Cerebrovascular accident (CVA)
• Coronary artery/vessel occlusion, perforation, rupture, or dissection
• Coronary artery spasm
• Death
• Emboli (air, tissue, thrombus, or atherosclerotic emboli)
• Emergency or non-emergency coronary artery bypass surgery
• Emergency or non-emergency percutaneous coronary intervention
• Entry site complications
• Fracture of the guidewire or failure/malfunction of any component of the device that may or may not lead to device embolism, dissection, serious injury, or surgical intervention
• Hematoma at the vascular access site(s)
• Hemorrhage
• Hypertension/hypotension
• Infection/sepsis/fever
• Myocardial Infarction
• Myocardial Ischemia or unstable angina
• Pain
• Peripheral Ischemia
• Pseudoaneurysm
• Renal failure/insufficiency
• Restenosis of the treated coronary artery leading to revascularization
• Shock/pulmonary edema
• Slow flow, no reflow, or abrupt closure of coronary artery
• Stroke
• Thrombus
• Vessel injury requiring surgical repair
• Vessel dissection, perforation, rupture, or spasm

In addition, patients may be exposed to other risks associated with coronary interventional procedures, including risks from conscious sedation and local anesthetic, the radiographic contrast agents used during angiography, the drugs given to manage the subject during the procedure, and the radiation exposure

from fluoroscopy.

Risks identified as related to the device and its use:
• Allergic/immunologic reaction to the catheter material(s) or coating
• Device malfunction, failure, or balloon loss of pressure leading to device embolism, dissection, serious injury, or surgical intervention
• Atrial or ventricular extrasystole
• Atrial or ventricular capture
• Excess heat at target site due to malfunction of IVL Console

The intended clinical benefit of the Bolt IVL System is the relief of pain and ischemia associated with successful completion of revascularization of calcified, stenotic coronary arteries. The benefits of endovascular treatment of stenotic or occluded segments of coronary arteries as compared to surgical revascularization are also expected for the Bolt IVL System and may include:
• No surgical incision - faster recovery
• Shorter hospital stay
• No requirement for general anesthesia
• Less post-procedure pain
• Reduced complications

Expected clinical benefits of the Bolt IVL System as compared to the Shockwave Medical Intravascular Lithotripsy System may include:
• Reduced crossing profile and improved deliverability - The reduction of crossing profile reduces procedural time which in turn may reduce contrast usage, radiation dose, and anesthesia amounts. The reduction in procedural time occurs because of the reduction of the need for pre-dilatation balloons to facilitate Bolt IVL delivery.
• Potential for improved efficacy - Procedural efficacy is likely to increase as the result of a positive dose-response relationship associated with IVL therapy delivery. It has been elucidated in the CAD I/II/III Shockwave trials that increased IVL dose/pulses resulted in additional calcium fractures and luminal gain. Because the Bolt IVL therapy provides physicians with additional pulses per catheter, it is possible to deliver sufficient therapy during treatment more frequently.
• Emitter selectivity - providing the ability to deliver targeted therapy to a lesion.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is >=18 years of age; 2. Subjects with native coronary artery disease (including stable or unstable angina and silent ischemia) suitable for Percutaneous Coronary Intervention (PCI); 3. For patients with unstable ischemic heart disease, a local site-based biomarker (preferably troponin or hs-troponin) must be less than or equal to the upper limit of lab normal (ULN) within 12 hours prior to the study procedure; 4. For patients with stable ischemic heart disease, CK-MB will be drawn at the time of the study procedure from the side port of the sheath; results need not be analyzed prior to enrollment, but must be less than or equal to the upper limit of lab normal (ULN); 5. Left ventricular ejection fraction (LVEF) >25% within 6 months (note: in the case of multiple assessments of LVEF, the measurement obtained closest to enrollment will be used for this criterion; may be assessed at time of index procedure); 6. Subject or legally authorized representative signs a written Informed Consent form to participate in the study prior to any study-mandated procedures; 7. Lesions in non-target vessels requiring PCI may be treated either: o >30 days prior to the study procedure if the procedure was unsuccessful or complicated; or o >24 hours prior to the study procedure if the procedure was successful and without complications (defined as a final lesion angiographic diameter stenosis <30% and TIMI 3 flow (visually assessed) for all

nontarget lesions and vessels without perforation, cardiac arrest or need for defibrillation or cardioversion, or hypotension/heart failure requiring mechanical or intravenous hemodynamic support or intubation, and local site-based postprocedure biomarker (preferably troponin or hs-troponin) must be less than or equal to the upper limit of lab normal (ULN) within 12 hours prior to the study procedure); or o >30 days after the study procedure. 1. The target lesion must be a de novo coronary lesion that has not been previously treated with any interventional procedure; 2. Single de novo target lesion stenosis of protected LMCA, or LAD, RCA, or LCX (or of their branches) with: o Stenosis of >=70% and

Exclusion criteria

Exclusion Criteria: A potential study subject who meets any of the following exclusion criteria will be excluded:
1. Any comorbidity or condition which may reduce compliance with the protocol, including follow-up visits.
2. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.
3. Subject is pregnant or nursing (a negative pregnancy test is required for women of child-bearing potential within 7 days prior to enrollment).
4. Unable to tolerate dual antiplatelet therapy (i.e., aspirin, and either clopidogrel, prasugrel, or ticagrelor) for at least 3 months (for patients not on oral anticoagulation).
5. Subject has an allergy to imaging contrast media which cannot be adequately pre-medicated.
6. Subject experienced an acute MI (STEMI or non-STEMI) within 30 days prior to index procedure.
7. New York Heart Association (NYHA) class III or IV heart failure at time of index procedure.
8. Prospective need for hemodynamic support i.e., IABP or Impella
9. Chronic kidney disease with serum creatinine >2.5 mg/dL, eGFR <30 mL/min/1.73m2, or on chronic dialysis.
10. History of a stroke or transient ischemic attack (TIA) within 6 months, or any prior intracranial hemorrhage or permanent neurologic deficit.
11. Active peptic ulcer or upper gastrointestinal (GI) bleeding within 6 months.
12. Untreated pre-procedural hemoglobin <9 g/dL or intention to refuse blood transfusions if one should become necessary.
13. Coagulopathy, including but not limited to platelet count <100,000 or International Normalized Ratio (INR) >1.7 (INR is only required in subjects who have taken warfarin within 2 weeks of enrollment).
14. Subject has a hypercoagulable disorder such as polycythemia vera, platelet count >750,000, or other disorders.

15. Uncontrolled diabetes defined as a HbA1c >10%.
16. Subject has an active systemic infection on the day of the index procedure with either fever, leukocytosis, or requiring intravenous antibiotics.
17. Subjects in cardiogenic shock.
18. Uncontrolled severe hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg).
19. Subjects with a life expectancy of less than 1 year.
20. Non-coronary interventional or surgical structural heart procedures (e.g., TAVR, MitraClip, LAA closure, or PFO occlusion, etc.) within 30 days prior to the index procedure.
21. Planned non-coronary interventional or surgical structural heart procedures (e.g., TAVR, MitraClip, LAA closure, or PFO occlusion, etc.) within 30 days after the index procedure.
22. Subject refusing or not a candidate for emergency coronary artery bypass grafting (CABG) surgery.
23. Planned use of atherectomy, scoring or cutting balloon, Shockwave lithotripsy device, or any investigational device other than the study device.
24. High SYNTAX Score (>= 33) if assessed as standard of care, unless the local heart team has met and recommends PCI is the most appropriate treatment for the patient.

Angiographic Angiographic Exclusion Criteria
1. Unprotected left main diameter stenosis >50%.
2. Target vessel is excessively tortuous defined as the presence of two or more bends >90º or three or more bends >75º.
3. Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel.
4. Evidence of aneurysm in target vessel within 10 mm of the target lesion.
5. Target lesion is an ostial location (LAD, LCX, or RCA within, 5 mm of ostium) or an unprotected left main lesion.
6. Chronic Total Occlusion;
7. Target lesion is a bifurcation involving a side branch of 2.5 mm or more with ostial diameter stenosis >=50%, and intention to treat the side branch with balloon and/or stent.
8. Second lesion with >50% stenosis in the same target vessel as the target lesion including its side branches.
9. Target lesion is located in a native vessel that can only be reached by going through a saphenous vein or arterial bypass graft.
10. Previous stent within the target vessel implanted within the last year.
11. Previous stent within 10 mm of the target lesion regardless of the timing of its implantation.
12. Angiographic evidence of a dissection in the target vessel at baseline or after guidewire passage.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-01-2024
Enrollment:	65
Type:	Actual

Medical products/devices used

Generic name:	Bolt Intravascular Lithotripsy (IVL) System
Registration:	No

Ethics review

Approved WMO Date:	06-11-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL84599.000.23