Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction. The STEMI-DTU Pivotal trial.

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Demonstrate that primary Left Ventricular unloading and a thirty-minute delay-to-reperfusion, when compared to the control cohort, treated according to the current standard of care treatment of Anterior STEMI, has the following effects:1. Reduction...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON56212

Source
ToetsingOnline

Brief title
STEMI-DTU Trial

Condition

- Myocardial disorders

Synonym
heartinfarction, Myocardial Infarction

Research involving
Human

Sponsors and support

Primary sponsor: Abiomed, Inc.
Source(s) of monetary or material Support: Abiomed;Inc.

Intervention

Keyword: Delayed Reperfusion, Left Ventricular unloading, Myocardial Infarction

Outcome measures

Primary outcome

Primary Endpoint:

Infarct size normalized to the left ventricular mass (IS as % of LV mass), evaluated using Cardiac Magnetic Resonance (CMR) at 3-5 days following the index procedure.

Secondary outcome

Key Secondary Efficacy Endpoint:

Composite clinical secondary endpoint (compared between groups using the Finkelstein-Schoenfeld statistic):

I. Cardiovascular (CV) mortality [Time Frame: minimum follow-up of at least 12 months]

II. Cardiogenic Shock at >=24h from enrollment [Time Frame: minimum follow-up of at least 12 months]

III. LVAD or Heart Transplant [Time Frame: minimum follow-up of at least 12 months]

IV. Heart Failure [Time Frame: minimum follow-up of at least 12 months]

V. ICD or CRT placement [Time Frame: minimum follow-up of at least 12 months]

VI. Infarct Size, as percent of Left Ventricular Mass [Time Frame: 3-5 days]

Key Secondary Safety Endpoint:

Impella CP® related Major Bleeding or Major Vascular complications with pre-specified performance goals [Time Frame: 30 days]

Powered Secondary Endpoints:

1. Infarct size as a percentage of Area-at-Risk (AAR) [Time Frame: 3-5 days]
2. Percent Microvascular Obstruction (%MVO) [Time Frame: 3-5 days]
3. Left Ventricular End-Systolic Volume (LVESV) [Time Frame: 6 months]
4. Left Ventricular End-Diastolic Volume (LVEDV) [Time Frame: 6 months]
5. Left Ventricular End-Systolic Volume index (LVESVi) [Time Frame: 90 days]
6. Left Ventricular End-Diastolic Volume index (LVEDVi) [Time Frame: 90 days]
7. Ejection fraction (EF) [Time Frame: 6 months]

Additional Secondary Endpoints:

1. Cardiogenic Shock at >=24h from enrollment [Time Frame: minimum follow-up of at least 12 months]
2. Development of Cardiogenic Shock [Time Frame: minimum follow-up of at least 12 months]
3. Heart Failure [Time Frame: minimum follow-up of at least 12 months]
4. Death or Heart Failure [Time Frame: minimum follow-up of at least 12 months]
5. ICD or CRT placement [Time Frame: minimum follow-up of at least 12 months]
6. All-cause mortality [Time Frame: minimum follow-up of at least 12 months]
7. CV mortality [Time Frame: minimum follow-up of at least 12 months]

Exploratory Endpoints:

1. All-cause mortality [Time Frame: 30 days, 12, 24, 36, 48, 60 months]

2. CV mortality [Time Frame: 30-days, 12, 24, 36, 48, 60 months]

3. Cardiogenic Shock at >=24h from enrollment [Time Frame: minimum follow-up of at least 12 months]

4. Development of Cardiogenic Shock [Time Frame: minimum follow-up of at least 12 months]

5. Heart Failure [Time Frame: 30 days, 12, 24, 36, 48, 60 months]

6. Improvement in Quality of Life (QoL) over baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) [Time Frame: 30 days, 6, 12, 24, 36, 48, 60 months] and EuroQol (EQ-5D-5L) [Time Frame: discharge, 30 days, 6, 12, 24 months]

7. Death or Heart Failure [Time Frame: 30 days, 12, 24, 36, 48, 60 months]

8. AKI using the AKI network definitions [Time Frame: 30 days]

9. Post-PCI TIMI flow [Time Frame: Index procedure]

10. Cardiogenic Shock at >24h from Enrollment [Time Frame: 30 days]

11. Development of Cardiogenic Shock [Time Frame: 30 days]

12. Renal failure requiring for dialysis [Time Frame: 30 days, 12, 24, 36, 48, 60 months]

13. Myocardial infarction (MI) [Time Frame: 30 days, 12, 24, 36, 48, 60 months]

14. ICD or CRT placement [Time Frame: 30 days, 12, 24, 36, 48, 60 months]

Study description

Background summary

Heart Failure (HF) is a leading cause of mortality, morbidity and poses a heavy financial burden on healthcare systems and societies. In 2012, the total cost for HF in the US was estimated to exceed $30 billion, with over $20 billion in direct medical costs. It is projected that by 2030, the total cost for HF in the US will increase to nearly $70 billion1,2. Survival after the diagnosis of HF has improved over the past decade, yet mortality at 5-years remains over 50% and the absolute number of deaths attributed to HF has not changed over the past 20 years due to an overall increase in the incidence and prevalence of HF. The two most preventable causes of HF are hypertension and acute myocardial infarction (AMI).
Despite efforts to reduce cardiovascular risk factors, AMI remains a leading cause of morbidity and mortality, with an annual incidence of over 805,000 in the United States. Over the past 3 decades, early revascularization strategies and the introduction of effective systems of care for AMI management have reduced early mortality associated with AMI. However, despite timely reperfusion, 25% and 75% of patients experiencing their first AMI will develop HF within 1 and 5 years respectively. The inevitable loss of viable myocardium and subsequent scar among the survivors of AMI forces additional load on the remaining cardiac muscle to maintain an adequate cardiac output (CO). To achieve this, the heart must alter its structure and function (remodel) to increase the strength of contraction. While initially adaptive, ultimately this remodeling process becomes maladaptive and leads to worsening cardiac function, arrhythmias, and HF. One explanation for these poor outcomes is that reperfusion of ischemic myocardium can accelerate cardiomyocyte death and microvascular damage through a process referred to as myocardial Ischemia-Reperfusion Injury (IRI)9. These data suggest that despite improvements in the treatment of AMI, progression to HF remains an unsolved and major health problem. There is a need for new approaches aimed at IRI to promote myocardial salvage and limit myocardial damage in the setting of AMI.
Recent reports have highlighted the need for improved in-hospital treatment strategies in AMI by showing that reducing the time to reperfusion below 90 minutes, known as the Door to Balloon (DTB) time, does not further reduce mortality from AMI. Despite the success in reducing system delays, patients continue to sustain significant myocardial damage in AMI. Since myocardial infarct size directly correlates with the development of HF, reducing the size of an infarct is expected to translate into reduced incidence of HF and improved long-term survival.
Abiomed recently completed a multi-center, two-arm feasibility study, with 50 patients, to test the safety and feasibility of Primary Unloading and mechanical pre-conditioning in patients presenting with anterior ST-Segment Elevation Myocardial Infarction (STEMI). In this multicenter, prospective, randomized exploratory safety and feasibility trial, 50 patients with anterior

STEMI were assigned to either LV unloading followed by immediate PCI (U-IR) or LV Unloading and a 30 minutes delay - while maintaining LV Unloading - prior PCI (U-DR). All patients were treated using the Impella CP®. The primary safety outcome was a composite of major adverse cardiovascular and cerebrovascular events at 30 days. Efficacy parameters included the assessment of infarct size by using cardiac magnetic resonance imaging. The results have been published in Circulation. The DTU Safety and Feasibility Pilot study showed that all fifty patients completed the U-IR (n=25) or U-DR (n=25) protocols with respective mean door-to-balloon times of 72 versus 97 minutes. Major adverse cardiovascular and cerebrovascular event rates were not statistically different between the U-IR versus U-DR groups (8% versus 12%, respectively, P=0.99). In comparison with the U-IR group, delaying reperfusion in the U-DR group did not affect 30-day mean infarct size measured as a percentage of LV mass (15±12% versus 13±11%, U-IR versus U-DR, P=0.53). From these results, the authors concluded that LV unloading using the Impella CP device with a 30-minute delay before reperfusion is feasible within a relatively short time period in anterior STEMI. The DTU-STEMI pilot trial did not identify prohibitive safety signals that would preclude proceeding to a larger pivotal study of LV unloading before reperfusion. An appropriately powered pivotal trial comparing LV unloading before reperfusion to the current standard of care is required.
In the current submission we propose the second phase of our approach: Two-Arm, Multi-Center Randomized Controlled study to evaluate the impact of primary unloading and a thirty-minute delay-to-reperfusion using the IMPELLA CP® in patients presenting with Anterior STEMI on Infarct size and a composite of clinical end-points compared to the current standard of care using PPCI alone.

Study objective

Demonstrate that primary Left Ventricular unloading and a thirty-minute delay-to-reperfusion, when compared to the control cohort, treated according to the current standard of care treatment of Anterior STEMI, has the following effects:

1. Reduction in Infarct Size
2. Reduction in the Incidence of Heart Failure-related clinical events
3. An acceptable safety profile

Study design

A prospective, multicenter, randomized, controlled open-label two-arm trial with an adaptive design.

Intervention

Prior to randomization, all patients will undergo Iliac & femoral angiograms, LVEDP measurement and an LV gram - to rule out contraindication for Impella CP®

placement. (An alternate method, such as bedside Echo, may be used in lieu of LV Gram; however, LVEDP measurement will still be necessary.)
Subjects randomized to the treatment arm, will undergo Impella CP® placement through a femoral arterial sheath and the Impella device will be activated to unload the left ventricle. The femoral arterial sheath will be placed using large bore access best practices (Appendix C). Coronary angiography will be performed no earlier than 30 minutes from Impella CP® placement.
Subjects randomized to the treatment arm will be supported at a Performance Level of P-8 or highest level attainable, for 4-24 hours with the Impella CP® device. The P Level can be lowered in the events of suction or other AIC console alarms. Once an alarm has been resolved, the P-Level will be raised to the highest level possible without causing a suction alarm. Systolic hypertension and/or tachycardia will be treated with recommended targets for heart rate (HR) <=80 bpm and systolic blood pressure (SBP) <=130 mmHg. [Appendix D provides Recommended Pharmacologic Therapy to Achieve SBP and HR Targets]
Subjects randomized to both the treatment and control arms will be treated based on the contemporary AHA/ACC/SCAI and ESC practice guidelines for STEMI management using primary PCI, both during their index admission and over the duration of the follow-up period.
Weaning from Left Ventricular support and removal of the Impella CP®
The subject will return to the catheterization laboratory for device and sheath removal. The criteria for weaning from Impella CP® support will be the following:
1. A minimum of 4 hours of support is required (operators are encouraged to support at the highest P-level possible given subject*s condition and fluid status).
2. The device may be left in for up to 24 hours. If it is left in for greater than 24 hours due to hemodynamic instability, this meets the definition of Cardiogenic shock. If it is left in for greater than 24 hours for another reason, this is a protocol deviation.
3. The subject tolerates 30 minutes of support at P-3 prior to device removal without hemodynamic instability, defined as sustained systolic BP <90 mmHg for longer than 30 minutes or the need for inotropes/pressors to maintain a systolic BP >90mmHg for longer than 30 minutes.
4. ACT/PTT/Anti-Xa levels show normalization of anticoagulation prior to Impella removal
5. The facility/healthcare team is prepared for safe weaning and removal of the device in the catheterization laboratory
In the event these criteria are not met, the operator may decide to continue with a longer duration of Impella support. This will not be considered a protocol deviation, unless duration is >24 hours for any reason other than hemodynamic instability.
If clinically appropriate, any additional coronary intervention or revascularization planned for the index admission, should be performed after the 3-5-day CMR has been completed.

Study burden and risks

The risks and burden associated with participation essentially are the risks usually encountered with venapunction and blood collection, and potential risk associated with contrast dye. Other risks are associated with the heart catheterization that is part of Standard of care.

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

Inclusion Criteria:
1. Age 18-85 years
2. First myocardial infarction

3. Acute anterior STEMI with >=2 mm in 2 or more contiguous anterior leads or >=4 mm total ST segment deviation sum in the anterior leads V1-V4 AND anterior wall motion abnormality noted on a diagnostic quality left ventriculogram or echocardiogram
4. Patient presents to the hospital between 1 - 6 hours of ischemic pain onset
5. Patient indicated for PPCI
6. Patient or the patient*s LAR (where applicable) has signed Informed Consent

Exclusion criteria

Exclusion Criteria:
1. Patient transferred from an outside hospital (OSH) where invasive coronary procedure was attempted (including diagnostic catheterization)
2. Unwitnessed cardiac arrest OR >=30 minutes of CPR prior to enrollment OR any cardiac arrest with impairment in mental status, cognition or any global or focal neurological deficit
3. Administration of fibrinolytic therapy within 24 hours prior to enrollment
4. Cardiogenic shock defined as: systemic hypotension (systolic BP <90 mmHg or the need for inotropes/pressors to maintain a systolic BP >90mmHg), plus one of the following: any requirement for pressors/inotropes prior to arrival at the catheterization laboratory, clinical evidence of end organ hypoperfusion, or use of IABP or any other mechanical circulatory support device
5. Inferior STEMI or suspected right ventricular failure
6. Any contraindication or inability to Impella placement, including PVD, tortuous vascular anatomy, femoral bruits or absent pedal pulses
7. Severe aortic stenosis
8. Acute cardiac mechanical complication: LV free wall rupture OR Interventricular septum rupture OR Acute mitral regurgitation

Medical Conditions & History:
9. Suspected or known pregnancy*
10. Suspected systemic active infection
11. History or known hepatic insufficiency prior to catheterization
12. On renal replacement therapy
13. COPD with home oxygen therapy or on chronic steroid therapy
Cardiovascular History:
14. Known or evidence of prior myocardial infarction, including pathologic Q waves in non-anterior leads
15. Prior CABG or LAD PCI
16. History of heart failure (EF <40% or documented hospitalization for heart failure within one year prior to screening)
17. Prior aortic valve surgery or TAVR
18. Left bundle branch block (new or old)
19. History of stroke/TIA within the prior 3 months, any history of Intracranial Hemorrhage or any permanent neurological deficit

20. History of bleeding diathesis or known coagulopathy (including heparin-induced thrombocytopenia), any recent GU or GI bleed or will refuse blood transfusions
21. Patient on systemic anticoagulation pre-procedure (including factor Xa inhibitors, thrombin inhibitors, warfarin)
Known Contraindication to:
22. Undergoing MRI or use of gadolinium [creatinine clearance CrCl<30 ml/min, non-compatible implant, claustrophobia]
23. Heparin, pork, pork products or contrast media
24. Receiving a drug-eluting stent
General:
25. Participation in the active treatment or follow-up phase of another clinical study of an investigational drug or device which has not reached its primary endpoint.
26. Any organ condition, concomitant disease (e.g., psychiatric illness, severe alcoholism, or drug abuse, severe cancer, hepatic or kidney disease), with life expectancy of <=2 years or other abnormality that itself, or the treatment of which, could interfere with the conduct of the study or that, in the opinion of the Investigator and/or Sponsor*s medical monitor, would pose an unacceptable risk to the patient in the study.
27. Patient has other medical, social or psychological problems that, in the opinion of the Investigator, compromises the subject*s ability to give written informed consent and/or to comply with study procedures, including follow-up CMRs.
28. Patient belongs to a vulnerable population [Vulnerable patient populations are defined as individuals with mental disability, persons in nursing homes, children, impoverished persons, homeless persons, nomads, refugees and those permanently incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces and persons kept in detention].

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-09-2021
Enrollment:	60
Type:	Actual

Medical products/devices used

Generic name:	Impella CP® heart pump
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	15-09-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2023
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	NL74153.078.21