Impella®-Supported PCI in High-Risk Patients with Complex Coronary Artery Disease and Reduced Left Ventricular Function: The PROTECT IV Trial

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The primary objective of the PROTECT IV Trial is to demonstrate the superiority of percutaneous coronary intervention (PCI) performed with Impella® mechanical circulatory support (MCS; Impella CP®, Impella CP® with SmartAssist® or Impella 2.5®...

Ethical review	Approved WMO
Status	Recruitment started
Health condition type	Coronary artery disorders
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON53537

Source
ToetsingOnline

Brief title
The PROTECT IV Trial

Condition

- Coronary artery disorders

Synonym
Coronary Artery Disease - narrowing/hardening of arteries that supply the heart with blood

Research involving
Human

Sponsors and support

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

Intervention

- Medical device

Keyword: Coronary Artery Disease (CAD), Percutaneous Coronary Intervention (PCI), Right Heart Catheterization

Explanation

N.a.

Outcome measures

Primary outcome

The composite of all-cause death, stroke, MI, unplanned clinically driven
revascularization, durable LVAD implant or heart transplant, or
other hospitalization for cardiovascular (CV) causes.

Secondary outcome

The following secondary endpoints are powered for hypothesis testing and will
be evaluated in the following hierarchical order to control type I error rate:
1. Death or NYHA Class III or IV at 1 year
2. Improvement in KCCQ from baseline to 6 months
3. 6MWD at 6 months
4. All CV hospitalizations through 3 years
5. Composite of CV death, stroke, MI, unplanned clinically driven
revascularization, durable LVAD implant or heart transplant, or other
hospitalization for cardiovascular causes through 3 years
6. CV death or HF hospitalizations through 3 years
7. Improvement in LVEF from baseline to 6 months
8. Achievement of complete anatomic revascularization after the index and
planned staged procedures

Other Secondary Endpoints:
The following secondary endpoints for safety and effectiveness are pre-
specified and will be evaluated at 30 days, 6 months and 1, 2 and 3 years after
randomization unless otherwise listed in the secondary endpoint hierarchy, but
are not powered for hypothesis testing and thus will be considered exploratory:
• The primary composite endpoint
• All-cause, cardiovascular death and non-cardiovascular death

• MI (all, procedural and non-procedural, target vessel and non-target vessel)
• Hospitalizations (cardiovascular, heart failure-related, non-heart
failure-related, non-cardiovascular)
• Cardiac arrest requiring CPR or intubation
• Cerebrovascular events (all, stroke and TIA)
• Composite death or stroke
• Composite CV death or stroke
• Composite death or MI
• Composite CV death or MI
• Composite death, stroke or MI
• Composite CV death, stroke or MI
• Ability to complete the intended revascularization plan (Core Lab assessed)
• Achievement of complete angiographic and functional (ischemic)
revascularization and their relationship to outcomes (Core Lab assessed)
• In-hospital acute kidney injury and change in renal function and/or need for
dialysis at 30 days, 6 months, 1 year and 3 years
• New onset atrial fibrillation or atrial flutter
• Major bleeding (BARC 3 to 5)
• Any medically actionable bleeding (BARC 2 to 5)
• Vascular complications (VARC 3 definition)
• Unplanned clinically driven revascularization
• Stent thrombosis (ARC-2 definite or probable)
• New ICD or CRT implant
• Durable LVAD, OHT or OHT listing
• Mitral, tricuspid and/or aortic valve repair or replacement
• Failure to explant an Impella or IABP device placed during the index or
planned staged procedure(s), at the end of the procedure and within 48 hours
after its placement
• Escalation (bail-out use) of MCS device usage beyond Impella CP in the
Impella arm or beyond IABP in the control arm
• The rate of unplanned Impella 2.5® or Impella CP® use in the Impella arm
(e.g., if starting with an Impella 2.5 device or starting without support in a
staged procedure) or unplanned IABP use in the control arm (both of which are
not considered device escalations)
• Length of hospital stay post-randomization
• NYHA Class
• Absolute measures and improvement in QoL (KCCQ and EQ-5D) and 6MWD from
baseline to 30 days, 1 year and 3 years
• Percentage of patients with >=5 point change in KCCQ from baseline to 30 days,
1 year and 3 years
• BNP or NT-proBNP levels at 30 days, 6 months and 1 year
• Absolute measures and change in LV dimensions (LVEF, GLS), LV regional wall
motion), RV function (RVFAC, TAPSE, GLS), valvular function and RVSP from
baseline to 6 months, 1 year and 3 years (Echocardiographic Core Lab assessed)
• Costs and cost-effectiveness during follow-up

NOTE: All 2-year and 3-year outcome measures will be reported when all subjects

have reached 2-year and 3-year follow-up. Some of these outcomes (e.g., the
 components of the primary composite outcome) may also be selectively reported
 at the time of the principal reporting of the primary endpoint (i.e., when all
 subjects have reached 1-year follow-up but only a proportion have reached
 2-year or 3-year follow-up)</p>

Study description

Background summary

The anatomical and clinical complexity of patients with coronary artery disease undergoing percutaneous coronary intervention is increasing. Similarly, there has been a rise in the frequency of patients with cardiomyopathy and reduced left ventricular ejection fraction (LVEF) undergoing PCI. This combination of subject comorbidities, anatomical complexity and hemodynamic compromise has expanded the subject population that are ineligible for or are poor candidates for CABG and who may have better outcomes with high-risk PCI (HRPCI). However, patients with impaired left ventricular function have poor cardiac reserve and are at high risk for hemodynamic collapse deterioration during complex PCI due to the negative inotropy from contrast agents and the ischemia induced by the procedure etc. (e.g., from balloon inflations and atherectomy), which may lead to major procedural complications and suboptimal stent implantation and limit the completeness of revascularization achieved, all of which are major predictors of early and late prognosis. Thus, MCS devices are used by some operators in select HRPCI procedures to reduce hemodynamic instability and enable optimal and complete revascularization. The benefits of MCS devices include the ability to maintain organ perfusion and reduced intracardiac filling pressures, thus reducing left ventricular volumes, wall stress and myocardial oxygen consumption. However, these devices may also result in complications, the most frequent of which are vascular and hemorrhagic. Thus, present equipoise is present as to the risk: benefit ratio of the routine use of MCS in high-risk patients with left ventricular dysfunction undergoing complex PCI. The Impella MCS devices (Impella 2.5, Impella CP and Impella CP with SmartAssist) are currently FDA-indicated for providing temporary (<6 hours) left ventricular support during elective or urgent HRPCI performed in hemodynamically stable patients with severe coronary artery disease, when a heart team (including a cardiac surgeon) has determined HRPCI is the appropriate therapeutic option.

Study hypothesis: By providing effective hemodynamic support in high-risk patients with complex CAD and reduced left ventricular function, PCI with Impella will be safer and will facilitate higher rates of optimal and complete revascularization, which will lead to improved long-term event-free survival,

quality-of-life and functional outcomes.

Study objective

The primary objective of the PROTECT IV Trial is to demonstrate the superiority of percutaneous coronary intervention (PCI) performed with Impella® mechanical circulatory support (MCS; Impella CP®, Impella CP® with SmartAssist® or Impella 2.5® devices) compared with PCI without Impella
in high-risk patients with reduced left ventricular ejection fraction
undergoing percutaneous intervention of complex coronary artery disease (CAD).

Study design

Prospective, multicenter, randomized, parallel-controlled, open-label two-arm Trial with an adaptive design. Eligible subjects will be randomized in a 1:1 ratio to PCI with Impella CP (Intervention Group) versus standard of care PCI with or without IABP (Control Group).

Intervention

Eligible subjects will be randomized in a 1:1 ratio to the percutaneous coronary intervention (PCI) with Impella CP® (Intervention Group) versus standard of care PCI with or without intra-aortic balloon pump IABP (Control Group).

Study burden and risks

Potential benefits from the use of the Impella CP System during HRPCI relative to standard of care PCI (with IABP or no mechanical circulatory support) include:
• Higher hemodynamic stability during PCI facilitating higher rates of optimal PCI resulting in reduced rates of major procedural complications, stent thrombosis and restenosis and more complete revascularization resulting in reduced rates of unplanned clinically driven revascularization and MI
• Improved early and late event-free survival and quality-of-life
• Improved LVEF during follow-up resulting in less heart failure and major arrhythmias

Contacts

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Trial sites

Trial sites in the Netherlands

Catharina-ziekenhuis
Target size: 25

Listed location countries

Germany, Italy, Switzerland, United States, Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria:
Subjects must meet all of the following Inclusion Criteria to participate in the Trial
1. Age >=18 years and <=90 years

2. Clinical presentation and baseline left ventricular function are as follows:
Either 2A or 2B must be present
A. Subject has CCS or NSTEMI with an LVEF <=40%
NOTE: The LVEF must be quantitatively measured as <=40% by echo within 30 days assuming no change in clinical condition. If multiple echos have been performed within 30 days, the most recent test must be used to qualify the patient. NOTE: Subject qualifies if the quantitative site read LVEF is <=30%; if the

quantitative read is >30% - <=40% the Echo Core Lab must confirm the LVEF is <=40% before subject enrollment (Core Lab will provide <48-hour turnaround). Similarly, if the site read is qualitative only (i.e., only provides broad ranges without detailed LVEF quantification), the Echo Core Lab must confirm the LVEF is <=40% before subject enrollment.
OR
B. Subject has STEMI >=24 hours and <30 days after symptom onset with an LVEF <=30%
NOTE: In patients qualifying with recent STEMI, the LVEF must be demonstrated to be <=30%quantitative echocardiography after the primary PCI procedure (if performed) and within 72- hours prior to the planned randomization. If primary PCI was not performed, the qualifying echocardiogram will be the one taken during the index hospitalization closest to the index procedure. If the site read is qualitative only (i.e., only provides broad ranges without detailed LVEF quantification), the Echo Core Lab must confirm the LVEF is <=30% before subject enrollment.

3. Local heart team (interventional cardiologist and cardiac surgeon) has determined that PCI is indicated and is the most appropriate management for the patient

4. Complex PCI will be performed: Either 4A or 4B must be met
A. One of the following must be present:
i. Triple vessel disease is present (visually-assessed angiographic DS >=80% [or >=40% if non-invasive evidence of ischemia on a localizing stress test or invasive evidence of ischemia (FFR <=0.80 or iFR <=0.89)] is present in all 3 epicardial coronary artery distributions in a main vessel or branch with visually-assessed reference vessel diameter
>=2.5 mm) with PCI planned in >=2 of these vessels in the proximal or mid LAD, proximal or mid-LCX or proximal, mid- or distal RCA [i.e., not a branch vessel])
OR
ii. Left main distal bifurcation or trifurcation disease (visually- assessed DS >=50% [or DS >=30% if non-invasive evidence of ischemia in both the anterior and posterolateral distributions or left main IVUS MLA <=6.0 mm2 or FFR <=0.80 or iFR <=0.89] is present) with planned intervention of the left main plus at least 2 branch vessels (i.e., the ostial LAD, ostial LCX or ostial ramus)
OR
iii. Left main equivalent disease with both ostial LAD and ostial LCX having visually-assessed angiographic DS
>=80% [or >=40% if non-invasive evidence of ischemia on a localizing stress test or invasive evidence of ischemia (FFR <=0.80 or iFR <=0.89] and requiring intervention in both branches
OR
iv. Intervention of the last remaining vessel (native coronary artery or bypass graft)
OR
B. Multivessel disease is present (visually-assessed angiographic DS >=80% [or

>=40% if non-invasive or invasive evidence of ischemia is present] in >=2 of the 3 epicardial coronary artery distributions in a main vessel or branch with visually-assessed reference vessel diameter >=2.5 mm) and PCI is planned of at least 2 separate complex lesions in main vessels or branch vessels each having one or more of the following characteristics:
i. Long lesion (>=28 mm visually assessed) requiring >=30 mm stent length (single or multiple)
ii. Severe angiographic calcification (see Protocol definition) or requiring atheroablation
iii. Any left main morphology not in Criterion A requiring intervention (e.g., isolated ostial or mid-shaft left main lesion or distal left main bifurcation lesion with a planned single provisional stent technique)
iv. Non-left main bifurcation lesion requiring intervention in both the main branch and side branch
v. CTO (TIMI 0 Flow)
vi. Giant thrombus (length >=3x vessel diameter)
vii. SVG (other than focal (<5 mm) disease of the proximal or distal anastomosis or in-stent restenosis)

5. Subject or legal guardian (permitted at US sites only) agrees to randomization and to follow all study procedures and provides informed written consent

Exclusion criteria

Exclusion Criteria:
Subjects must NOT meet any of the following Exclusion Criteria to participate in the Trial
1. STEMI <=24 hours from the onset of ischemic symptoms or at any time if mechanical complications of transmural infarction are present (e.g., VSD, papillary muscle rupture, etc.)
2. Cardiogenic shock (SBP <80 mmHg for >=30 mins and not responsive to intravenous fluids or hemodynamic deterioration for any duration requiring pressors or mechanical circulatory support, including IABP)
3. Subject is presently or recently intubated for the current admission (NOTE: recently intubated patients must be extubated for >24 hours with full neurologic recovery)
4. Cardiorespiratory arrest related to the current admission unless subject is extubated for >24 hours with full neurologic recovery and hemodynamically stable
5. Any contraindication or inability to Impella placement in both the left and right common femoral artery based on clinical or imaging findings, including iliofemoral artery diameter <5 mm, tortuous vascular anatomy or severe bilateral peripheral vascular disease of the iliac or femoral arteries that can*t be adequately treated (e.g., with intravascular lithotripsy)
NOTES:

a. Computed tomography (CT), magnetic resonance angiography (MRA) or contrast angiography to assess the aorta and iliofemoral vasculature to ensure Impella compatibility must be performed within 90 days prior to randomization. It is recommended that this evaluation be performed prior to the index procedure. Absent a qualifying pre-procedure imaging study, contrast angiography of the potential Impella access vessel(s) must be performed in the Cath Lab before the planned enrollment after which the subject may be randomized if he/she still qualifies. Of note, if pre-procedure imaging was performed and after this test but before randomization there was a worsening in PVD symptoms, repeat imaging must be performed prior to randomization.
b. If iliofemoral peripheral vascular disease is present precluding Impella use that can be adequately treated with angioplasty, atherectomy or lithotripsy (without a stent), the subject can be enrolled if such treatment is undertaken and is successful and uncomplicated - randomization must not be performed until such successful and uncomplicated treatment.
6. Iliofemoral stents placed within 6 months of enrollment with planned vascular access through these vascular segments
7. Vascular access for Impella is required in any location other than the left or right common femoral artery (i.e., axillary access, transcaval access, etc., for Impella access are not permitted)
8. Known left ventricular thrombus
9. Incessant ventricular arrhythmias that would likely preclude stable Impella positioning
10. Severe aortic stenosis or severe aortic insufficiency
11. Prior mechanical valve or self-expanding TAVR (NOTE: prior bioprosthetic surgical valve or balloon expandable TAVR implanted >24 hours pre-procedure is acceptable)
12. Prior CABG within three (3) months or successful prior PCI of at least one (1) attempted lesion within 12 months (including during the index hospitalization prior to randomization), that has not experienced stent thrombosis or restenosis during that 12-month period; the one (1) exception is that patients may be enrolled if a
primary PCI for STEMI was performed during the index hospitalization without MCS and that was >=24 hours and <30 days prior to randomization
NOTE: Successful PCI for this exclusion criterion is defined as a visually-assessed angiographic DS <=50% in at least one (1) attempted lesion.
13. Prior placement of IABP, Impella or any other MCS device for any reason during the index admission, prior to randomization
14. Known severe pulmonary hypertension (right ventricular systolic pressure (RVSP) on echo or pulmonary artery systolic pressure (PASP) on right heart catheterization) >70 mmHg unless active vasodilator therapy in the Cath Lab is able to reduce the pulmonary vascular resistance (PVR) to <3 Wood Units or between 3 and 4.5 Wood Units with v-wave less than twice the mean of the pulmonary capillary wedge pressure
15. Symptoms or signs of severe RV dysfunction, such as anasarca (NOTE: leg edema alone does not necessarily indicate severe RV dysfunction if the investigator believes it is due to LV dysfunction.

16. Severe tricuspid insufficiency
17. Platelet count <75,000 cells/mm3, bleeding diathesis or active bleeding, coagulopathy or unwilling to receive blood transfusions
18. On dialysis
19. Prior stroke with any permanent neurologic deficit within the previous three (3) months, or any prior intracranial hemorrhage or any prior subdural hematoma or known intracranial pathology pre-disposing to intracranial bleeding, such as an arteriovenous malformation or mass
20. Medical contraindication to discontinue vitamin K anatonists (for at least 72 hours) or the NOACs (new oral anticoagulants) (for at least 48 hours).
21. Plan for any surgery within 6 months necessitating discontinuing antiplatelet agents
22. Pregnant or child-bearing potential unless negative pregnancy test within 1 week
23. Participation in the active treatment or follow-up phase of another clinical study of an investigational drug or device that has not reached its primary endpoint
24. Any medical or psychiatric condition such as dementia, alcoholism or substance abuse which may preclude informed consent or interfere with any of the study procedures, including follow-up visits
25. Any non-cardiac condition with life expectancy <3 years (e.g., cirrhosis, oxygen or oral steroid dependent COPD, cancer not in remission, etc.)
26. Subject is currently hospitalized for definite or suspected COVID-19
27. Subject has previously been symptomatic with or hospitalized for COVID-19 unless he/she has been discharged (if hospitalized) and asymptomatic for >=4 weeks and has returned to his/her prior baseline (pre-COVID) clinical condition
28. Subject is asymptomatic (never ill) and COVID-19 PCR/antigen test is positive within the prior 4 weeks unless a) subject remains asymptomatic for >=2 weeks after the last positive test or b) the positive test occurred within six (6) months after the subject received a COVID vaccine.
29.The subject is unable to give adequate consent.

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	No intervention
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment started
Start date (anticipated):	20-10-2023
Enrollment:	25
Duration:	36 months (per patient)
Type:	Actual

WORLD

Recruitment status:	Recruitment started
Start date (anticipated):	01-10-2022
Enrollment:	1252
Type:	Actual

Medical products/devices used

Product type:	Medical device
Generic name:	Impella CP
Registration:	Yes - CE intended use

IPD sharing statement

Plan to share IPD: No

Plan description
N.a.

Ethics review

Approved WMO

Date:	21-04-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	20-07-2023

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-02-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2025
Application type:	Amendment
Review commission:	MEC-U

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
ClinicalTrials.gov	NCT04763200
CCMO	NL82544.100.22
Research portal	NL-006979