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Mechanical circulatory support in high-risk elective PCI: rationale and design of the PROTECT IV trial

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of heart failure with reduced ejection fraction (HFrEF). Coronary artery bypass grafting (CABG) improves long-term mortality in HFrEF. Percutaneous coronary intervention (PCI) is often performed as an alternative to CABG in patients at high surgical risk. However, in patients with HFrEF and limited myocardial reserve, PCI may result in haemodynamic instability, increasing risk and precluding optimal revascularisation. Mechanical circulatory support (MCS) during high-risk PCI may enhance haemodynamic stability during the procedure and enable complete revascularisation. We thus performed the PROTECT IV trial to determine whether PCI with routine use of the Impella CP microaxial flow pump improves early and late outcomes in patients with HFrEF and complex CAD compared with PCI with or without use of an intra-aortic balloon pump (IABP). PROTECT IV is a prospective, multicentre, randomised, parallel-controlled, open-label, superiority trial with an adaptive design. Patients with complex CAD and left ventricular ejection fraction ≤40% (n=1,252) deemed at excessive surgical risk for bypass grafting by the Heart Team will be randomised in a 1:1 ratio to PCI with Impella CP versus PCI with or without an IABP. The primary endpoint is the composite of all-cause death, stroke, myocardial infarction, unplanned clinically driven revascularisation, durable left ventricular assist device implant or heart transplant, or other hospitalisation for cardiovascular causes at 3-year follow-up, with at least 1-year follow-up in all patients. Prespecified substudies will evaluate the impact of MCS on renal function, the procedural role of right heart catheterisation, and the utility of myocardial viability assessment. The PROTECT IV trial will determine whether routine MCS with Impella CP during high-risk PCI improves the prognosis of patients with complex CAD and HFrEF.

KEYWORDS: HFrEF; high-risk PCI; Impella; microaxial flow pump; prognosis; randomised controlled trial

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Coronary artery disease (CAD) is the leading cause of heart failure with reduced ejection fraction (HFrEF)[1,2]. Patients with reduced left ventricular ejection fraction (LVEF) have a poor quality of life, frequent hospitalisations and high mortality. The Surgical Treatment for Ischemic Heart Failure (STICH) extension study showed that at 10 years, the rates of death from any cause, death from cardiovascular causes, and death from any cause or hospitalisation for cardiovascular causes were significantly lower in patients who underwent coronary artery bypass grafting (CABG) in addition to guideline-directed medical therapy (GDMT) than in those who received GDMT alone[3]. The role of revascularisation with percutaneous coronary intervention (PCI) in HFrEF has been challenged by the recent Revascularisation for Ischemic Ventricular Dysfunction (REVIVED)-BCIS2 trial, which showed no clear benefit of PCI over GDMT alone[4]. However, this trial was smaller than STICH, its follow-up was shorter, and the enrolled patients had no or only mild ischaemic and heart failure (HF) symptoms, with rates of previous myocardial infarction (MI) and three-vessel disease indicating less complex and less active CAD than in STICH. Non-randomised studies comparing PCI with CABG in patients with left ventricular (LV) dysfunction have reported conflicting results[5,6]. A propensity-adjusted study of 2,126 patients from the New York State database reported similar rates of survival at a median 2.9-year follow-up with PCI compared with CABG in patients with multivessel disease and LV dysfunction[6], whereas an observational analysis of 4,794 propensity-matched patients with LVEF ≤35% undergoing PCI or CABG in Ontario, Canada reported increased mortality after PCI at a median follow-up of 5.2 years[5]. However, patients with complex CAD and HFrEF are often poor candidates for CABG. Real-world data demonstrate that PCI is performed rather than CABG in at least 50% of patients due to high surgical risk or comorbidities, including frailty[7-10]. Ineligibility for CABG is not accounted for in non-randomised comparisons of PCI versus CABG, limiting their utility.

In patients with HFrEF and limited myocardial reserve, PCI may result in haemodynamic decompensation, including the development of cardiogenic shock or the need for resuscitation, which can lead to adverse procedural events. Moreover, even lesser degrees of haemodynamic instability may lead to a hurried procedure, resulting in suboptimal lesion selection (e.g., less use of intracoronary physiology assessment), inadequate lesion preparation and stent implantation (e.g., less use of intracoronary imaging), and a higher incidence of incomplete revascularisation, all of which are important predictors of early and late prognosis[11]. Approximately half of patients undergoing high-risk PCI experience loss of pulse pressure during the procedure[12]. Use of a mechanical circulatory support (MCS) device during PCI may afford greater haemodynamic stability and thus potentially improve early and late outcomes by preventing procedural complications and enabling more appropriate lesion preparation, optimal stent implantation and achievement of complete revascularisation (CR).

Two randomised controlled trials of MCS have been conducted in this setting to date: the Balloon Pump-Assisted Coronary Intervention Study (BCIS-1)[13] and A Prospective, Multi-center, Randomized Controlled Trial of the IMPELLA RECOVER LP 2.5 System Versus Intra Aortic Balloon Pump (IABP) in Patients Undergoing Non Emergent High Risk PCI (PROTECT II)[14]. In the BCIS-1 trial (n=301), IABP support during elective complex PCI in patients with LVEF ≤30% did not significantly reduce major adverse cardiac or cerebrovascular events (MACCE) at discharge (15.2% vs 16.0% with no planned IABP; p=0.85)[13]. However, an exploratory long-term analysis showed a reduction in all-cause mortality at a median 51-month follow-up in the IABP group (hazard ratio 0.66, 95% confidence interval [CI]: 0.44-0.98; p=0.039)[15].

In the PROTECT II trial (n=448), patients with LVEF ≤35% and complex CAD randomised to Impella 2.5 (Abiomed, J&J MedTech Heart Recovery)-supported versus IABP-supported PCI had similar major adverse events (MAE) rates at 30 days (35.1% vs 40.1%; p=0.227)[14]. At 90 days, in a prespecified per-protocol analysis, the MAE rate was lower in the Impella cohort (40.0% vs 51.0%; p=0.023). In addition, when major adverse cardiac events (MACE) and periprocedural MI were readjudicated according to more contemporary definitions, Impella use resulted in a relative 29% reduction in MACE compared with IABP at 90-day follow-up (p=0.042)[16]. These results ultimately led to U.S. Food and Drug Authority (FDA) premarket approval of the Impella CP (Abiomed, J&J MedTech Heart Recovery) for high-risk PCI patients as defined in the PROTECT II trial. However, the clinical community has continued to debate the results given that PROTECT II was stopped for futility before enrolment of the 654 planned patients was completed and because the study missed its 30-day primary intention-to-treat endpoint.

Compared with the Impella 2.5 device tested in PROTECT II, the Impella CP device offers substantially greater haemodynamic support[17]. A recent analysis compared the patient characteristics and outcomes of 504 "PROTECT II-like" patients enrolled in the prospective, observational PROTECT III post-approval study with patients treated by Impella support and enrolled in the PROTECT II trial[17]. In PROTECT III, contemporary

Abbreviations

CABG	coronary artery bypass grafting	**IVUS**	intravascular ultrasound
CAD	coronary artery disease	**LVEF**	left ventricular ejection fraction
CCS	chronic coronary syndrome	**MI**	myocardial infarction
CR	complete revascularisation	**NSTEMI**	non-ST-segment elevation myocardial infarction
CTO	chronic total occlusion	**OCT**	optical coherence tomography
HFrEF	heart failure with reduced ejection fraction	**PCI**	percutaneous coronary intervention
IABP	intra-aortic balloon pump	**STEMI**	ST-segment elevation myocardial infarction

patients undergoing high-risk PCI were older and had more complex CAD than in PROTECT II. Impella CP and Impella 2.5 were used in 68% and 32% of the PROTECT II-like patients, respectively. After propensity score matching, the more contemporary cohort had important differences in revascularisation technique, including the treatment of more lesions, more frequent use of atherectomy, and a longer duration of Impella support. These differences were associated with a greater reduction in SYNTAX score (more CR). Propensity-matched patients in PROTECT III experienced less hypotension during support (2.2% vs 10.2%; p<0.001) and less frequently developed malignant ventricular arrhythmias or required cardiopulmonary resuscitation (1.6% vs 6.9%; p<0.001) compared with those in PROTECT II. Despite the use of the larger-bore Impella CP device, the PROTECT III group also had fewer major bleeding events requiring blood transfusion (1.2% vs 9.4%; p<0.001). Even after excluding procedural events within the first 72 hours, propensity-matched PROTECT III patients experienced fewer MACCE between 3 and 90 days compared with those in PROTECT II (10.4% vs 16.9%; p=0.048). This study illustrates the improving outcomes of high-risk PCI with Impella support over the past decade but does not prove that MCS-assisted high-risk PCI is superior to high-risk PCI without MCS.

Further data on MCS-assisted high-risk PCI have been reported from single-arm observational studies and claims database analyses **(Table 1)**[13-15,17-24]. The use of MCS devices in these studies has been associated with mixed outcomes. In several studies, haemodynamic support during high-risk PCI led to a safer procedure and showed a possible benefit compared with an IABP[18,20]. Conversely, other studies have raised concerns about greater costs and potential harm with MCS, including increased bleeding, vascular complications, and even higher mortality in certain patient cohorts[21,23].

On the basis of these studies (in particular the two randomised trials), the most recent 2021 ACC/AHA/SCAI guidelines for myocardial revascularisation provide a Class IIb, Level of Evidence B recommendation for elective MCS use during PCI in certain high-risk patients, without favouring one device over the other (albeit noting that Impella provides greater haemodynamic support than an IABP)[25]. The 2024 ESC Guidelines for the management of chronic coronary syndromes provide a Class IIb, Level of Evidence C recommendation that in selected patients with HFrEF undergoing high-risk PCI for complex CAD, the use of a microaxial flow pump may be considered in experienced centres (IABP use as an option is not mentioned)[26].

Thus, there is currently equipoise regarding the risk-benefit ratio of routine use of MCS in general, and Impella CP in particular, in high-risk patients with LV dysfunction undergoing elective complex PCI. This evidence gap prompted the PROTECT IV trial, a multicentre, randomised, parallel-controlled, open-label study to assess the utility of routine Impella CP use during elective high-risk PCI in patients with complex CAD and LVEF ≤40%.

Methods

TRIAL POPULATION AND DESIGN

The Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function (PROTECT IV) trial will enrol 1,252 patients aged 18-90 years with complex CAD, LV dysfunction (defined as LVEF ≤40% in those with chronic coronary syndrome [CCS] or non-ST-segment elevation MI [NSTEMI], or LVEF ≤30% in those with ST-segment elevation MI [STEMI] ≥24 hours and <30 days after symptom onset), for whom the local Heart Team (interventional cardiologist and heart surgeon) deem that PCI is the most appropriate revascularisation option due to excessive surgical risk. Full inclusion/exclusion criteria and the requirements defining complex CAD for PCI are presented in **Table 2** and **Table 3**, respectively. PROTECT IV is sponsored and funded by Abiomed, J&J MedTech Heart Recovery.

Briefly, complex PCI is defined as either (a) triple-vessel disease, with PCI planned in at least two of the three major epicardial vessels in the proximal or mid-segments (not branch vessels); or (b) left main (LM) disease involving the distal bifurcation or trifurcation, with planned LM intervention in the ostial left anterior descending artery (LAD) and ostial left circumflex artery (LCx; ramus); or (c) LM equivalent disease with similar planned ostial LAD and ostial LCx (ramus) treatment; or (d) intervention of the last remaining vessel (native coronary artery or bypass graft); or (e) multivessel disease with PCI planned in at least two separate, complex lesions (i.e., long lesions ≥28 mm, severe calcification, chronic total occlusion [CTO], giant thrombus, etc.) in different epicardial territories. Regarding the LVEF inclusion criterion, patients may qualify if the site-read quantified LVEF is ≤30%. If the site-read LVEF is >30% and ≤40% or not quantified, the LVEF must be confirmed to be ≤40% by the independent study echocardiographic laboratory (ECL).

Enrolment will take place at up to 120 centres in the USA, Canada, and Europe. The trial is being conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The trial is registered on ClinicalTrials.gov: NCT04763200.

Written informed consent is obtained in all patients prior to any study-related procedures. Patients will be randomised in a 1:1 ratio to either Impella CP-assisted high-risk PCI (treatment group) or high-risk PCI with or without pre-PCI IABP (control group). Randomisation takes place in the cardiac catheterisation laboratory, immediately prior to the planned PCI procedure, and is stratified by site, LVEF ≤25%, and intended IABP use if randomised to the control group. Allowing IABP in the control group is justified by the long-term analysis of BCIS-1, which showed a reduction in all-cause mortality at the 51-month median follow-up in the IABP group[15]. In addition, the design of an international trial should reflect common practice, and IABP use remains frequent during high-risk PCI in the USA. Stratifying randomisation by intended IABP use in the control group will enable us to examine the impact of this strategy compared with Impella MCS.

The study flow is detailed in **Figure 1** and the **Central illustration**. Follow-up visits are required for all patients at 30 days after discharge, and after randomisation at 60 days, 90 days, and 6 months, and at 1, 2, and 3 years.

The first patient was randomised in April 2021 and enrolment will conclude in 2025.

Table 1. Large-scale studies of haemodynamically supported high-risk percutaneous coronary intervention published between 2010 and 2022.

Study	Year published	Enrolment periods	Trial design	No. of sites	Patient population	No. of patients	Group I	Group II	Primary endpoint	Key findings (group I vs group II)
BCIS-I[13]	2010	2005-2009	RCT in the United Kingdom	17	Patients undergoing high-risk PCI with IABP or no support	301	IABP (n=151)	No planned IABP (n=150)	MACCE (death, MI, cerebrovascular event, or further revascularisation at hospital discharge [capped at 28 days])	No difference in in-hospital MACCE rate MACCE 15.2% vs 16.0%; p=0.85; OR 0.94 (95% CI: 0.51-1.76) Major complications* 1.3% vs 10.7%; p<0.001; OR 0.11 (95% CI: 0.01-0.49) All-cause mortality at 6 months (secondary endpoint) 4.6% vs 7.4%; p=0.32; OR 0.61 (95% CI: 0.24-1.62)
PROTECT II[14]	2012	2007-2010	RCT in the USA, Canada, and the EU	112	Patients undergoing high-risk PCI with Impella 2.5 or IABP support	448	Impella 2.5 (n=225)	IABP (n=223)	MAE at discharge or 30-day follow-up: all-cause death, Q-wave or non-Q-wave MI, stroke, or transient ischaemic attack, any repeat revascularisation procedure, need for a cardiac or a vascular operation, acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI	No difference in 30-day MAE rate (primary endpoint); however, 90-day MAE rate (secondary endpoint) was significantly lower in the Impella per-protocol arm MAE at 30 days (intention-to-treat) 35.1% vs 40.1%; p=0.277 MAE at 90 days (intention-to-treat, secondary endpoint) 40.6% vs 49.2%; p=0.066 Prespecified per-protocol analysis for 30-day and 90-day MAE 34.3% vs 42.2%; p=0.092 40.0% vs 51.0%; p=0.023
Zeitouni et al[24]	2022	2009-2018	Prospective CathPCI registry, retrospective analysis	514 (using MCS)	Patients with stable CAD undergoing elective PCI with Impella, ECMO, IABP, or no support (CS, CA, and NYHA IV excluded)	6,905	IABP (n=2,035)	Other MCS (presumably Impella in the majority of cases; n=4,870)	MACE (death, cardiogenic shock, or new heart failure) Safety (stroke, tamponade, major bleeding, or vascular complications)	Use of IABP was associated with lower effectiveness than other MCS devices to prevent the composite of death, cardiogenic shock, or heart failure MACE 9.6% vs 6.0%; p≤0.0001, aOR 1.59 (95% CI: 1.32-1.91) Safety 18.2% vs 19.1%; p=0.0557, aOR 0.88 (95% CI: 0.77-0.99)
Bjarnason et al[23]	2022	2013-2019	Medicare database analysis	306	Patients undergoing PCI with PVAD (Impella or TandemHeart) or IABP support (undifferentiated high-risk PCI/CS population)	79,176	n.a.	n.a.	30-day mortality	Use of PVADs for PCI was not associated with lower in-hospital mortality Risk-adjusted 30-day mortality This was assessed according to quartiles based on the proportion of all PCIs that were performed with a PVAD (<17%, 17-28%, 28-38%, >38%) 31.5% vs 31.2% vs 31.3% vs 31%; p=0.074
J-PCI[22]	2022	2018	Prospective Japanese registry, retrospective analysis	551	Patients undergoing non-emergent PCI with Impella, ECMO+IABP, or IABP alone	1,627	IABP (n=1,402)	Impella (n=69), ECMO (n=156)	Primary endpoint: in-hospital mortality Secondary outcome: procedural complications (periprocedural MI, cardiac tamponade, heart failure or shock, definite stent thrombosis according to the ARC definition, emergency surgery, and major bleeding requiring blood transfusion)	VA-ECMO was associated with a higher incidence of procedural complications, and major bleeding was more frequently observed in patients receiving VA-ECMO or Impella than IABP IABP vs Impella vs ECMO In-hospital mortality 5.3% vs 7.2% vs 34.6%; p<0.01 Procedural complications 22.0% vs 27.5% vs 55.8%; p<0.01

Table 1. Large-scale studies of haemodynamically supported high-risk percutaneous coronary intervention published between 2010 and 2022 (cont'd).

Study	Year published	Enrolment periods	Trial design	No. of sites	Patient population	No. of patients	Group I	Group II	Primary endpoint	Key findings (group I vs group II)
Amin et al[21]	2020	2004-2016	Premier database analysis	432	Patients undergoing PCI with Impella or IABP support (undifferentiated high-risk PCI/CS population)	48,306	Impella (type not differentiated; n=4,782)	IABP (n=43,524)	Death, bleeding requiring transfusion, AKI, and stroke	Impella use was associated with higher rates of in-hospital adverse events and costs than IABP Individual patient comparative effectiveness analyses Death OR 1.24 (95% CI: 1.13-1.36) Bleeding OR 1.10 (95% CI: 1.00-1.21) AKI OR 1.08 (95% CI: 1.00-1.17) Stroke OR 1.34 (95% CI: 1.18-1.53)
Al-Khadra et al[20]	2020	2005-2014	NIS database analysis	n.a.	Patients undergoing PCI with PVAD or IABP support (CS, ACS, and AMI excluded)	21,848	PVAD (n=4,578)	IABP (n=17,270)	In-hospital mortality Vascular complications Cardiac complications Respiratory complications	PVAD patients had lower in-hospital mortality and vascular, cardiac, and respiratory complications than IABP patients In-hospital mortality 6.1% vs 8.8%, aOR 0.62 (95% CI: 0.51-0.77) Vascular complications 4.3% vs 7.5%, aOR 0.78 (95% CI: 0.62-0.99) Cardiac complications 5.6% vs 14.5%, aOR 0.29 (95% CI: 0.24-0.36) Respiratory complications 3.8% vs 9.8%, aOR 0.37 (95% CI: 0.28-0.48)
Lansky et al[18]	2022	2016-2019	Premier database analysis	304	Patients undergoing non-emergent PCI with Impella or IABP support (CS and STEMI excluded)	2,156	Impella (n=1,447)	IABP (n=709)	In-hospital survival In-hospital MI In-hospital CS	Use of Impella was associated with improved in-hospital survival and reduced in-hospital MI and CS In-hospital survival 95.3% vs 91.0%; p=0.0002, aOR 1.55 (95% CI: 1.02-2.36) In-hospital MI 2.5% vs 11.9%; p<0.0001, aOR 0.29 (95% CI: 0.18-0.46) In-hospital CS 8.3% vs 18.9%; p<0.0001, aOR 0.54 (95% CI: 0.39-0.74)
PROTECT III[17]	2022	2017-2020	Prospective, single-arm, observational, FDA-audited PAS†	45	Patients undergoing high-risk PCI with Impella 2.5 or CP support (and deemed PROTECT II like)	504	PROTECT III (68.1% Impella CP, 31.9% Impella 2.5)	PROTECT II (100% Impella 2.5)	MACCE at 90 days (death, MI, stroke/TIA, and any repeat revascularisation)	PIII patients had significantly lower 90-day MACCE rates (in unmatched and propensity score-matched populations) compared to PII patients† MACCE (matched population) 14.2% vs 22.3%; p=0.045
RESTORE-EF[19]	2022	2019-2021	Retrospective analysis of prospectively collected, observational US dataset, single arm	22	Patients undergoing high-risk PCI with Impella 2.5 or CP support and 90-day FU available	406	n.a.	n.a.	Change in LVEF within 90 days	LVEF improved significantly (primary endpoint), with a significantly greater LVEF improvement in patients with a residual SYNTAX score of 0 LVEF change within 90 days 35±15% to 45±14% (n=251; p<0.0001)

The minimum study population size for inclusion in the above table was 250 patients. *Major procedural complications include prolonged hypotension, ventricular tachycardia/fibrillation requiring defibrillation, or cardiorespiratory arrest requiring assisted ventilation. †The analysis of the PROTECT III study compares a PROTECT III cohort to a PROTECT II cohort; however, the PROTECT III study itself was a single-arm, observational study. ACS: acute coronary syndrome; AKI: acute kidney injury; AMI: acute myocardial infarction; aOR: adjusted odds ratio; ARC: Academic Research Consortium; CA: cardiac arrest; CAD: coronary artery disease; CI: confidence interval; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; FDA: U.S. Food and Drug Administration; FU: follow-up; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; MACCE: major adverse cardiac and cerebrovascular events; MACE: major adverse cardiac events; MAE: major adverse events; MCS: mechanical circulatory support; MI: myocardial infarction; n.a.: not available; NIS: National Inpatient Sample; NYHA: New York Heart Association; OR: odds ratio; PAS: post-approval study; PCI: percutaneous coronary intervention; PII: PROTECT II; PIII: PROTECT III; PVAD: peripheral ventricular assist device; RCT: randomised controlled trial; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack; VA-ECMO: venoarterial extracorporeal membrane oxygenation

Table 2. Full 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%* or B. Subject has STEMI ≥24 hours and <30 days after symptom onset with an LVEF ≤30%†
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 (visually-assessed angiographic DS ≥80% [or ≥40% if there is non-invasive evidence of ischaemia on a localising stress test or invasive evidence of ischaemia {FFR ≤0.80 or iFR ≤0.89}] in all 3 epicardial coronary artery distributions in a main vessel or branch with a 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 there is non-invasive evidence of ischaemia in both the anterior and posterolateral distributions or left main IVUS MLA ≤6.0 mm^2 or FFR ≤0.80 or iFR ≤0.89]) 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 the ostial LAD and ostial LCx having visually angiographic DS ≥80% (or ≥40% if there is non-invasive evidence of ischaemia on a localising stress test or invasive evidence of ischaemia [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 grafting) or B. Multivessel disease is present (visually assessed angiographic DS ≥80% [or ≥40% if non-invasive or invasive evidence of ischaemia 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 for 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 randomisation and to follow all study procedures and provides informed written consent

*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. The subject qualifies if the quantitative site-read LVEF is ≤30%; if the quantitative site-read LVEF is >30% and ≤40%, the echo core lab must confirm the LVEF is ≤40% before subject enrolment (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 enrolment. †In patients qualifying with recent STEMI, the LVEF must be demonstrated to be ≤30% by quantitative echocardiography after the primary PCI procedure (if performed) and within 72 hours prior to the planned randomisation. If primary PCI was not performed, the qualifying echocardiogram will be the one taken during the index hospitalisation 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 enrolment. ‡a. Multiple lesions can be in the same vessel if separated by ≥10 mm; however, each separate lesion has to have one or more of the above characteristics. b. PCI may be performed on additional non-qualifying lesions (i.e., without 1 or more of the above high-risk characteristics) as long as there are at least 2 lesions also undergoing PCI with each having 1 or more of the above characteristics). c. There are 2 exceptions to the rule that each separate lesion must have 1 or more of the above characteristics (as in inclusion criterion 4B above): the subject may qualify if undergoing complex PCI of a single lesion that has 2 or more of the above complex characteristics (as in inclusion criterion 4B) if also (i) there is a CTO of a proximal or mid-LAD, proximal or mid-LCx or proximal, mid- or distal RCA (i.e., not a branch vessel) that will not be treated; or (ii) the subject qualifies with recent STEMI with an LVEF ≤30%, and the complex PCI is planned in a non-infarct vessel (i.e., a complex PCI in the infarct vessel does not qualify). CCS: chronic coronary syndrome; CTO: chronic total obstruction; DS: diameter stenosis; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IVUS: intravascular ultrasound; LAD: left anterior descending artery; LCx: left circumflex artery; LVEF: left ventricular ejection fraction; MLA: minimal lumen area; NSTEMI: non-ST-segment elevation myocardial infarction; RCA: right coronary artery; STEMI: ST-segment elevation myocardial infarction; SVG: saphenous vein graft; TIMI: Thrombolysis in Myocardial Infarction

TRIAL HYPOTHESIS AND ENDPOINTS

The primary objective of PROTECT IV is to assess the effectiveness of haemodynamic support with Impella CP in high-risk patients with LVEF ≤40% and complex CAD undergoing PCI. The study aims to demonstrate that PCI with Impella CP is superior to PCI without it in reducing the primary composite endpoint of all-cause death, stroke, MI, unplanned clinically driven revascularisation, durable LV assist device (LVAD) implant or heart transplant, or other hospitalisation for cardiovascular causes during 3-year follow-up. The primary endpoint will be assessed as a time-to-first event analysis.

Eight secondary endpoints are powered for statistical testing **(Table 4)**. Additional non-powered, secondary endpoints include numerous clinical and safety outcomes, and changes in quality of life (QoL), functional capacity, and LV function during follow-up **(Table 5)**. An independent clinical events committee will be responsible for adjudicating protocol-defined clinical events, including but not limited to the primary endpoint, using original source documents.

Prespecified subgroups for analysis are presented in **Supplementary Table 1**. Substudies and the accompanying PROTECT IV registry are described in **Supplementary Appendix 1** and **Supplementary Table 2**.

Table 3. Full 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 ischaemic 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 haemodynamic deterioration for any duration requiring pressors or mechanical circulatory support, including IABP)
3. Subject is presently or recently intubated for the current admission*
4. Cardiorespiratory arrest related to the current admission unless subject is extubated for >24 hours with full neurological recovery and haemodynamically stable
5. Any contraindication or inability to Impella placement in either the left or 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 cannot be adequately treated (e.g., with intravascular lithotripsy)†
6. Iliofemoral stents placed within 6 months of enrolment 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., are not permitted for Impella)
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 TAVI‡
12. Prior CABG within 3 months or successful prior PCI of at least one attempted lesion within 12 months (including during the index hospitalisation prior to randomisation) that has not experienced stent thrombosis or restenosis during that 12-month period; the one exception is that patients may be enrolled if a primary PCI for STEMI was performed during the index hospitalisation without MCS and that was ≥24 hours and <30 days prior to randomisation§
13. Prior placement of IABP, Impella, or any other MCS device for any reason during the index admission, prior to randomisation
14. Known severe pulmonary hypertension (right ventricular systolic pressure on echo or pulmonary artery systolic pressure on right heart catheterisation) >70 mmHg unless active vasodilator therapy in the cath lab is able to reduce the pulmonary vascular resistance to <3 Wood units or between 3 and 4.5 Wood units with a V wave less than twice the mean of the pulmonary capillary wedge pressure
15. Symptoms or signs of severe RV dysfunction, such as anasarca¶
16. Severe tricuspid insufficiency
17. Platelet count <75,000 cells/mm^3, bleeding diathesis or active bleeding, coagulopathy, or unwilling to receive blood transfusions
18. On dialysis
19. Prior stroke with any permanent neurological deficit within the previous 3 months or any prior intracranial haemorrhage or any prior subdural haematoma or known intracranial pathology predisposing to intracranial bleeding, such as an arteriovenous malformation or mass
20. Taking a chronic oral anticoagulant that cannot be safely discontinued for at least 72 hours before and 72 hours after the index procedure (if a vitamin K antagonist) or that cannot be safely discontinued for at least 48 hours before and 48 hours after the index procedure (for a direct acting oral anticoagulant)
21. Plan for any surgery within 6 months necessitating discontinuing antiplatelet agents
22. Pregnant or childbearing 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 hospitalised for definite or suspected COVID-19
27. The subject has previously been symptomatic with or hospitalised for COVID-19 unless they have been discharged (if hospitalised) and asymptomatic for ≥4 weeks and have returned to their prior baseline (pre-COVID) clinical condition
28. Subject is asymptomatic with a positive COVID-19 PCR/antigen test within the prior 4 weeks unless (a) the subject remains asymptomatic for ≥4 weeks after the last positive test; or (b) the positive test occurred within 6 months after the subject received a COVID vaccine
29. Subject belongs to a vulnerable population (defined as individuals with mental disability, impoverished persons, homeless persons, nomads, refugees, and those permanently incapable of giving informed consent; vulnerable populations may also 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 those kept in detention)

*Recently intubated patients must be extubated for >24 hours with full neurological recovery. †a. Computed tomography, magnetic resonance angiography, or contrast angiography to assess the aorta and iliofemoral vasculature to ensure Impella compatibility must be performed within 90 days prior to randomisation. It is recommended that this evaluation be performed prior to the index procedure. Without a qualifying preprocedural imaging study, contrast angiography of the potential Impella access vessel(s) must be performed in the cath lab before the planned enrolment, after which the subject may be randomised if he/she still qualifies. Of note, if preprocedural imaging was performed and, after this test but before randomisation, there was a worsening in PVD symptoms, repeat imaging must be performed prior to randomisation. 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 – randomisation must not be performed until such successful and uncomplicated treatment has taken place. ‡Prior bioprosthetic surgical valve or balloon-expandable TAVI implanted >24 hours preprocedure is acceptable. §Successful PCI is defined as a visually assessed angiographic DS ≤50% in at least one attempted lesion. ¶Leg oedema alone may not necessarily indicate severe RV dysfunction, particularly if the investigator believes it is due to LV dysfunction. CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; DS: diameter stenosis; IABP: intra-aortic balloon pump; LV: left ventricular; MCS: mechanical circulatory support; PCI: percutaneous coronary intervention; PCR: polymerase chain reaction; PVD: peripheral vascular disease; RV: right ventricular; SBP: systolic blood pressure; STEMI: ST-segment elevation myocardial infarction; TAVI: transcatheter aortic valve implantation; VSD: ventricular septal defect

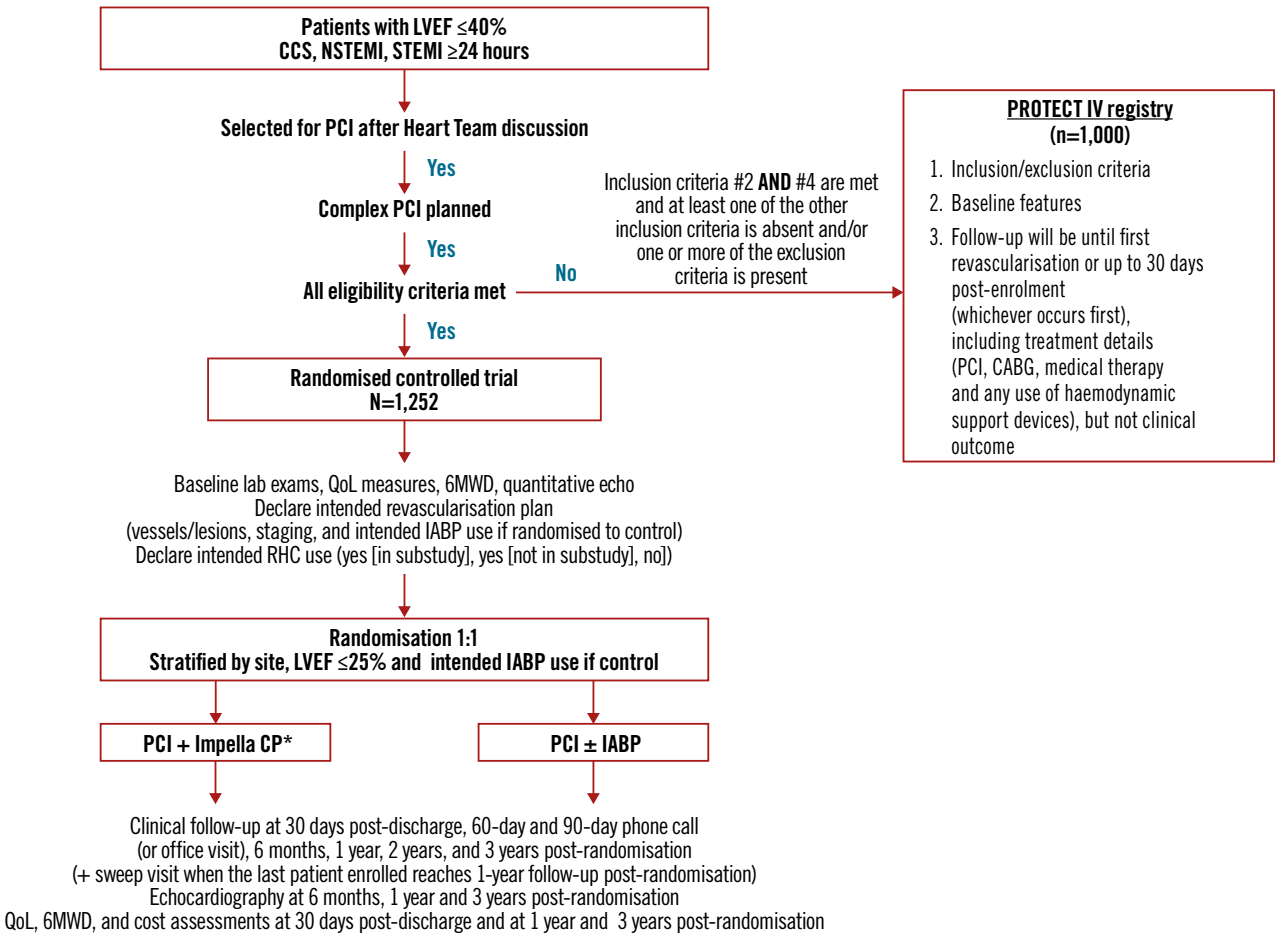


Figure 1. *Study flowchart. *Impella CP is the default device in the Impella arm, except in special circumstances, in which case the Impella 2.5 may be used. See* **Table 2** *for a description of inclusion criteria #2 and #4. 6MWD: six-minute walk distance; CABG: coronary artery bypass grafting; CCS: chronic coronary syndrome; GDMT: guideline-directed medical therapy; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; QoL: quality of life; RHC: right heart catheterisation; STEMI: ST-segment elevation myocardial infarction*

TREATMENT STRATEGY

Prior to randomisation, computed tomography (CT), magnetic resonance angiography (MRA), or contrast angiography must be performed to ensure that at least one iliofemoral system can safely accommodate the Impella CP.

In the cath lab, prior to randomisation, the investigator will declare their intended revascularisation plan, including the vessels and lesions to be treated, and whether staged revascularisation procedures are expected. They will also affirm whether they intend to use IABP support if the patient is randomised to the control arm, and any planned use of right heart catheterisation (RHC), either within or outside the formal RHC substudy.

Randomisation is performed in the cath lab immediately prior to the index procedure. Initiation of any PCI procedure or insertion of any MCS device is not permitted prior to randomisation.

After randomisation, MCS (whether Impella or IABP in the control arm if so declared) is initiated prior to the PCI procedure, with the Impella CP being the default device for all subjects in the Impella arm, unless special circumstances warrant use of the Impella 2.5 device (i.e., small vasculature or body weight). Ultrasound-guided arterial puncture with fluoroscopic guidance and angiographic confirmation of the puncture site location is mandated in all cases, in both trial arms. Micropuncture femoral artery access is strongly recommended for all operators familiar with the technique.

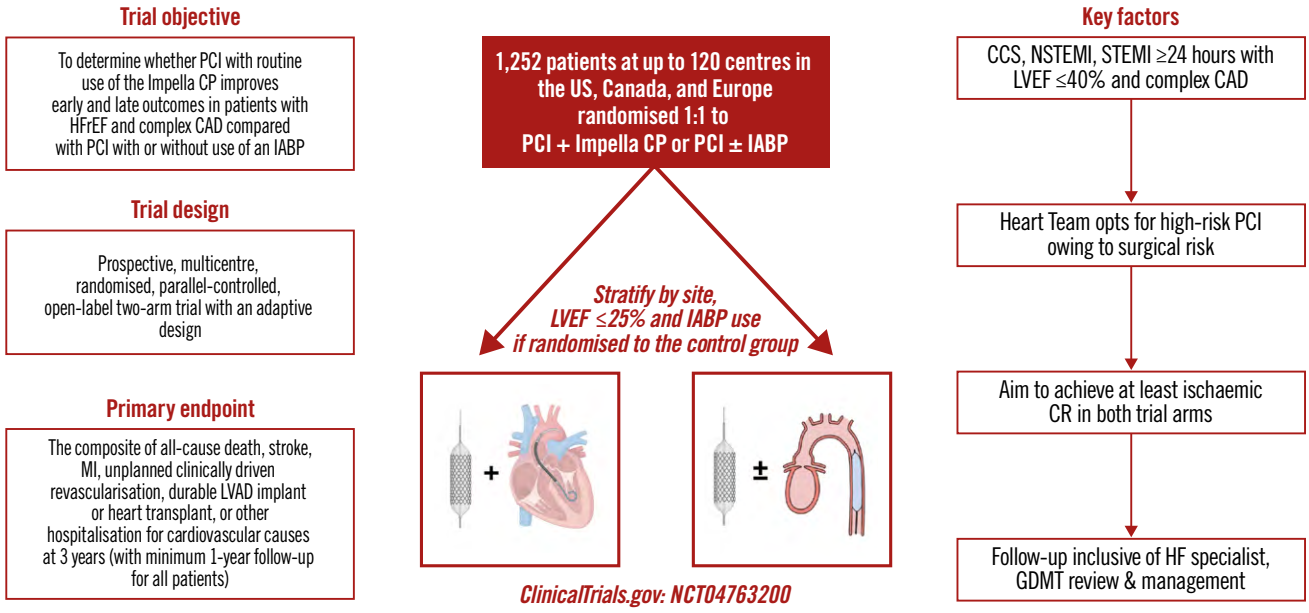
PCI is performed with a goal of achieving at least ischaemic CR in both trial arms. Post-PCI, if the original staging plan changes (i.e., planned staging is now necessary or is no longer needed), the new staging plan must be declared within 4 hours of the index PCI procedure. The planned staged PCI must then be performed within 6 weeks of the index procedure (or 12 weeks for a failed CTO procedure). In most cases, only one planned staged procedure should be performed.

COMPLEX PCI TECHNIQUES

The trial protocol recommends consideration of specific techniques and adjuncts as prescribed by the PROTECT IV Technique Committee, consisting of investigators with

EuroIntervention — Central Illustration

Design and rationale of the PROTECT IV trial.



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CAD: coronary artery disease; CCS: chronic coronary syndrome; CR: complete revascularisation; GDMT: guideline-directed medical therapy; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

proven expertise in the fields of complex PCI and MCS **(Supplementary Figure 1)**. Strategy recommendations include pressure wire-based physiological lesion assessment for lesion selection and the routine use of intravascular imaging for stent optimisation, which is mandatory to guide left main PCI. For CTO PCI, investigators are strongly encouraged to use microcatheters and distal vessel visualisation, applying all four lesion-crossing strategies (antegrade wire escalation, anterograde dissection re-entry, retrograde wire escalation, and retrograde dissection re-entry) as appropriate. The use of embolic protection devices is strongly recommended for saphenous vein graft interventions. To reduce the risk of acute kidney injury (AKI), intravascular volume administration of normal saline guided by invasively measured filling pressures is strongly recommended, minimising the contrast volume-to-estimated glomerular filtration rate ratio to ≤2.0-3.7.

The protocol also advises on mandatory or highly recommended aspects related to periprocedural anticoagulation, pretreatment with aspirin and $P2Y_{12}$ inhibitors, and choice and duration of dual antiplatelet therapy in patients with or without an indication for chronic oral anticoagulation.

BAILOUT DEVICE USAGE IN BOTH ARMS

In patients who become haemodynamically unstable during or after index PCI, the use of other MCS such as extracorporeal membrane oxygenation (ECMO), TandemHeart (LivaNova), or ProtekDuo (also LivaNova) is allowed in both arms during or after PCI and is considered "bailout MCS use". However, the use of Impella devices is not allowed in the control arm, and IABPs are not allowed in the Impella arm, unless their use is deemed lifesaving.

In the control arm, if PCI is initiated with no support and an IABP is subsequently required, this will be considered "unplanned IABP use". In the Impella arm, if PCI is initiated with an Impella 2.5 and then upgraded to an Impella CP, this will be considered "unplanned Impella use". Use of the Impella 5.0, 5.5, or RP (all Abiomed J&J MedTech Heart Recovery) in the Impella arm is considered bailout MCS use.

HEART FAILURE SPECIALIST AND GDMT-HF COMMITTEE

A key component of the PROTECT IV trial design is to ensure that all enrolled patients, regardless of treatment arm, are receiving optimal HF-related medical therapies according to societal guidelines[27-30]. Each site will assign an HF specialist to direct the appropriate utilisation of all HF therapies including GDMT, cardiac resynchronisation therapy (CRT) and implantable cardioverter-defibrillators (ICDs). The HF specialist must see the patient, either in person or via a tele-visit, during the index hospitalisation and any planned staged hospitalisations. At this time, they will assess the patient's New York Heart Association Class (independent

Table 4. Primary and powered secondary endpoints.

Endpoint	Definition	Timepoint
Primary endpoint	The composite of all-cause death, stroke, MI, unplanned clinically driven revascularisation, durable LVAD implant or heart transplant, or other hospitalisation for cardiovascular causes.	At 3 years, assessed when the last randomised patient has reached 1-year follow-up
Powered secondary endpoints (in hierarchical order of testing)	Death, or NYHA Class III or IV	1 year
	Improvement in KCCQ from baseline	6 months
	6MWD	6 months
	All CV hospitalisations	3 years
	Composite of CV death, stroke, MI, unplanned clinically driven revascularisation, durable LVAD implant or heart transplant, or other hospitalisation for a cardiovascular cause	3 years
	CV death or HF hospitalisations	3 years
	Improvement in LVEF from baseline	6 months
	Achievement of complete anatomical revascularisation after the index and planned staged procedures	Immediately post-procedure(s)

The individual power is >80% for each of the powered hierarchical secondary endpoints. 6MWD: 6-minute walk distance; CV: cardiovascular; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association

of the study investigator) in order to guide GDMT. The HF specialist will also see the patient in person or via a tele-visit at the 30-day, 60-day, and 90-day follow-up visits. After 90 days, continued visits with the HF specialist are strongly recommended throughout the 3-year follow-up period.

The HF specialist will ensure that maximally tolerated doses of all Class I-recommended GDMT are administered in all enrolled patients as soon as possible after randomisation, but in all cases within 90 days after randomisation. These and all subsequent adjustments must be made independently of randomisation assignment, dictated only by the patient's clinical status. Since all patients enrolled in this trial have an LVEF ≤40% (HFrEF), these recommendations apply to all study participants. The GDMT regimen should not be reduced during follow-up, even if serial LVEF measurements improve.

A GDMT-HF committee comprised of HF experts will provide oversight of these issues **(Supplementary Figure 1)**. This entails evaluating and approving all onsite HF specialists and reviewing HF medications and CRT/ICD device therapies for all enrolled subjects following randomisation, with site feedback as necessary.

STATISTICAL ANALYSIS AND SAMPLE SIZE DETERMINATION

Unless revised by the results of an interim adaptive design, approximately 1,252 subjects will be enrolled and randomised in a 1:1 ratio to intervention versus control. All subjects will undergo a minimum of 1 year and a maximum of 3 years of follow-up. The study will be unblinded for the primary data analysis once the last enrolled subject completes their 1-year follow-up. The null hypothesis that there is no difference in the risk of the composite primary endpoint after Impella-assisted high-risk PCI compared with high-risk PCI±IABP will be assessed using covariate-adjusted Cox proportional hazards regression at a two-sided 0.05 significance level. This analysis will be conducted in the intention-to-treat population, which includes all randomised patients regardless of MCS device use or crossover and whether the procedure was successful. Baseline covariates for adjustment are the intention to use versus not use an IABP if randomised to control (declared before randomisation); LVEF determined by the ECL, diabetes, age, sex, clinical syndrome presentation, chronic kidney disease, and angiographic core laboratory-determined SYNTAX score **(Supplementary Appendix 1)**. For the principal analysis of the primary endpoint, missing data, either at baseline or during follow-up, will not be replaced. As a sensitivity analysis, multiple imputation will be used to account for missing baseline and follow-up data.

Primary endpoint event rates in the control arm of 25%, 50%, and 75% are anticipated at 1 year, 2 years, and 3 years, respectively. A sample size of 1,252 randomised patients (approximately 626 in each arm) and 516 total primary endpoint events provides 90.4% power to detect a hazard rate reduction of 25% in the Impella group compared with the control group at a two-sided alpha level of 0.05. If the primary endpoint passes the test for statistical significance, the powered secondary endpoints will be tested sequentially at a two-sided alpha level of 0.05.

An unblinded Bayesian interim analysis will be conducted by an independent adaptive design committee after enrolment of ~85% of the planned 1,252 subjects **(Supplementary Appendix 1)**. Recommendations from this committee may include increasing the sample size to a maximum of 2,500 patients, prolonging the minimum follow-up in all patients (maximum follow-up remains 3 years), a combination of both, or no change.

Discussion

The PROTECT IV trial is, to our knowledge, the first adequately powered randomised comparison to test the hypothesis that haemodynamic support with Impella CP in patients with complex CAD and reduced LVEF undergoing elective high-risk PCI will facilitate a safer procedure with higher rates of optimal and complete revascularisation, leading to improved long-term event-free survival, QoL, and functional outcomes during 3-year follow-up.

Large-scale database analyses examining the results of Impella-supported elective PCI have reported conflicting findings[18,20,21,23]: some studies have reported higher costs and no

Table 5. Other secondary endpoints.

Prespecified, non-powered, exploratory endpoints assessed at 30 days, 6 months and 1, 2, and 3 years after randomisation unless otherwise listed in the primary or secondary powered endpoint hierarchy
Primary composite endpoint
All-cause mortality
CV death
Non-CV death
MI (all, procedural and non-procedural, target vessel and non-target vessel)
Hospitalisations (CV, HF-related, non-HF-related, non-CV)
Cardiac arrest requiring CPR or intubation
Cerebrovascular events (all stroke and TIA)
Composite death or stroke
Composite CV death or stroke
Composite of death or MI
Composite of CV death or MI
Composite of death, stroke, or MI
Composite of CV death, stroke, or MI
Ability to complete the intended revascularisation plan (angiographic core lab-assessed)
Achievement of complete angiographic and functional revascularisation and their relationship to outcomes (angiographic core lab-assessed according to a prespecified definition)
In-hospital acute kidney injury and change in renal function and/or the 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 revascularisation
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 (bailout 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-randomisation
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

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 selectively be 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. 6MWD: 6-minute walk distance; ARC: Academic Research Consortium; BARC: Bleeding Academic Research Consortium; BNP: brain natriuretic peptide; CPR: cardiopulmonary resuscitation; CRT: cardiac resynchronisation therapy; CV: cardiovascular; EQ-5D: EuroQol 5-Dimension; GLS: global longitudinal strain; HF: heart failure; IABP: intra-aortic balloon pump; ICD: implantable cardioverter-defibrillator; KCCQ: Kansas City Cardiomyopathy Questionnaire; LV: left ventricular; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; MI: myocardial infarction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; OHT: orthotopic heart transplant; QoL: quality of life; RV: right ventricular; RVFAC: right ventricular fractional area change; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; TIA: transient ischaemic attack; VARC: Valve Academic Research Consortium

improvement in clinical outcomes (or increased complications) with Impella[21,23], while others have noted improved outcomes with Impella support[18,20]. The randomised PROTECT II trial had a complex 10-component primary composite endpoint of efficacy and safety and was terminated early because of futility. However, in this study MAE were comparable at 30 days but diverged by 90 days in favour of patients who received an Impella 2.5[14]. In PROTECT II, Impella preserved patient

haemodynamics to a greater degree than an IABP, resulting in more CR[31], which was associated with improved clinical outcomes[32]. These findings were confirmed and extended by the prospective PROTECT III registry, which reported fewer procedural complications, higher rates of CR, and improved 90-day clinical outcomes after Impella-supported high-risk PCI compared with PROTECT II[17]. Collectively, these findings support the hypothesis that haemodynamic support may facilitate not only procedural safety but also enable CR, which has been associated with improvements in LV function[19] and prognosis[33]. In addition, the haemodynamic stability afforded by Impella may enable greater use of high-quality PCI techniques including physiological lesion assessment[34] and intravascular imaging[35], which have been associated with improved outcomes.

PROTECT IV is enrolling patients with complex CAD in need of revascularisation for progressive or unstable ischaemic and/or HF symptoms and reduced LVEF whom the local Heart Team has deemed to be at excessive risk or ineligible for cardiac surgery, necessitating PCI. The primary endpoint of PROTECT IV – the 3-year rate of all-cause death, stroke, MI, unplanned clinically driven revascularisation, durable LVAD implant or heart transplant, or other hospitalisation for cardiovascular causes – is of clinical importance in this high-risk population in whom both HF-related and ischaemic events are common.

Secondarily, PROTECT IV will determine whether Impella support during high-risk PCI improves long-term QoL, exercise and functional capacity, LV volumes and function, and renal function. Assessing the safety of Impella for this application in this study is also critical, with the protocol implementing best practices for vascular access, Impella weaning and closure to minimise complications. Finally, the critical importance of medical therapy in HFrEF patients is addressed by the involvement of HF specialists at each site to optimise the rapid titration of class I HF therapies and to provide long-term HF follow-up, as overseen by a GDMT-HF committee comprised of globally recognised HF experts.

Conclusions

The randomised PROTECT IV trial will provide high-quality evidence to conclude whether Impella CP-assisted PCI is superior to PCI±IABP in patients with complex CAD and reduced LVEF (≤40%) for the composite rate of all-cause death, stroke, MI, unplanned clinically driven revascularisation, permanent LVAD implantation or heart transplantation, or other hospitalisation for cardiovascular causes at 3-year follow-up.

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Conflict of interest statement

N. Mangner received a research and an educational grant from Abiomed, Johnson & Johnson MedTech Heart Recovery, to his institution, outside the submitted work; an educational grant from Boston Scientific to his institution, outside the submitted work; and received personal fees from Abbott, Abiomed, Johnson & Johnson MedTech Heart Recovery, Amgen, AstraZeneca, B. Braun, Biotronik, BMS/Pfizer, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Medtronic, Novartis, Sanofi Genzyme, and Shockwave Medical, outside the submitted work. C. O'Connor has received consulting fees from Abiomed, Johnson & Johnson MedTech Heart Recovery, and Merck. A. Kaki receives speaker honoraria from Abbott, Abiomed, Johnson & Johnson MedTech Heart Recovery, CathWorks, Medtronic, Recor Medical, and Terumo. E. Mahmud is a consultant for Abiomed, Johnson & Johnson MedTech Heart Recovery (PROTECT IV Steering Committee) and MicroPort (Co-PI Target IV); and receives DSMB fees from CRF and Baim Cardiovascular. S.J. Pocock is a consultant with Medtronic and Edwards Lifesciences. W.W. O'Neill has consulting and research funding from Abiomed, Johnson & Johnson MedTech Heart Recovery, Edwards Lifesciences,

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Supplementary data

Supplementary Appendix 1. Site selection; adaptive design interim analysis; angiographic core laboratory analysis; substudies in the PROTECT IV trial; the PROTECT IV registry.

Supplementary Table 1. Prespecified subgroups.

Supplementary Table 2. PROTECT IV substudies.

Supplementary Figure 1. Study governance.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00486

Supplementary data

Supplementary Appendix 1. Site selection; adaptive design interim analysis; angiographic core laboratory analysis; substudies in the PROTECT IV trial; the PROTECT IV registry.

Site Selection

Each PROTECT IV site must have a multidisciplinary team in place with representatives from interventional cardiology, cardiac surgery, and echocardiography, and a cardiologist specializing in HF. All sites are required to have the ability to perform Impella and ECMO procedures (the latter if needed for bail-out in the control arm). No single site may enroll more than 15% of the total randomized population. To ensure investigator knowledge of the protocol, the first patient enrolled at each site is reviewed by a central eligibility committee (comprised of members of the Steering and Technique committees) to ensure they meet inclusion/exclusion criteria, with randomization following committee approval. Full details on Study Governance are provided in **Supplementary Figure 1**.

Adaptive Design Interim Analysis

After enrollment of approximately 85% of the planned 1,252 subjects, an interim analysis will be conducted in which an independent Adaptive Design Committee will compute the Bayesian predictive power (PP) of the existing design, without the assumption of proportional hazards, and with access to unblinded data. If the predictive power is <50% or ≥90%, no changes will be made to the study design. If the PP is between 50% and 90%, a Bayesian analysis will be performed to determine the optimal increase to the sample size and/or minimum patient follow-up in order to increase the number of events and achieve a PP as close to 90% as possible (with maximum constraints of 2500 patients and 3-year follow-up). Since the adaptive changes are made only if PP ≥50% to <90%, no adjustments are needed to control the Type I error. The committee recommendations (without data unblinding) are sent to the (blinded) Steering Committee and (unblinded) DSMB. The trial sponsor and Steering Committee (both of whom remain blinded to the results) will make the final decision whether to change the study parameters based on the Committee recommendations.

Angiographic Core Laboratory Analysis

All diagnostic and procedural angiograms will be forwarded to a Central Angiographic Core Laboratory (Cardiovascular Research Foundation, New York) for independent review by observers who will be unaware of the clinical outcomes. Baseline lesion morphology assessment and documentation of intra-procedural complications will be recorded for all treated lesions[36].

Using the contrast-filled injection catheter as the calibration source, quantitative angiographic analysis will be performed using a validated automated edge-detection algorithm (Medis CMS, Leiden, The Netherlands)[37]. An interpolated normal diameter will be used to define the reference diameter at baseline, after stent implantation, and at follow-up, if performed. Minimal lumen diameter will be measured at these same time points within the stent (in-stent analysis), if placed, and within the segment between the proximal and distal reference vessel (in-segment analysis). Angiographic percent diameter stenosis will be defined as (1– [minimal lumen diameter/reference vessel diameter]) x 100. Lesion length will be defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen decrease by 20%.

The SYNTAX Score will be determined using a proprietary software within the Core Laboratory to identify baseline and residual lesion complexity before and after revascularization[38], accounting for prior coronary bypass surgery as needed[39]. The extent of baseline angiographic disease and residual completeness of anatomic revascularization will be assessed using prior published methodology[40]. All procedural angiograms will be reviewed by a senior interventional cardiologist (JJP).

SubStudies in the PROTECT IV Trial

There are four sub-studies in PROTECT IV: a renal sub-study in all patients to assess whether Impella use reduces AKI and chronic progressive renal dysfunction; a RHC sub-study to assess the role of hemodynamics at baseline and post PCI in informing prognosis and guiding MCS weaning; a cardiac magnetic resonance sub-study to assess the utility of myocardial viability assessments; and a proteomic signalling sub-study. More details are provided in the following sections and **Supplementary Table 2**.

Renal Sub-Study

The Renal sub-study will include all randomized trial subjects. It is hypothesized that in high-risk patients with complex CAD undergoing PCI, PCI with Impella will be superior to PCI without Impella in protecting the kidney from acute kidney injury (AKI) and will result in long-term preservation or improved kidney function in survivors.

In-hospital serum creatinine will be assessed at baseline (pre-PCI) and daily through five days post-PCI or discharge, whichever comes first. For subjects that are discharged on day 1 post-PCI, alternative options to assess serum creatinine after hospital discharge are as follows: a) an additional hospital visit for serum creatinine draw on day 2 and once between days 3 and 5 post-PCI; b) a local lab visit for serum creatinine draw on day 2 and once between days 3 and 5 post-PCI; or c) a phlebotomist visit to the subject's home on day 2 and once between days 3 and 5 post-PCI. If a subject is discharged on day 2 post-PCI and a serum creatinine was drawn that day in-hospital prior to discharge, one additional serum creatinine draw will still be required between days 3 and 5 via the alternative options. If a subject is discharged on day 3 and a serum

creatinine was drawn that day for hospital measurement, no additional serum creatinine is needed.

RHC Sub-Study

The RHC sub-study is an optional, exploratory sub-study without formal power calculation: sites electing to participate in this study agree to RHC insertion pre-PCI in all consented patients, regardless of treatment arm. If sites elect not to participate in this sub-study, they may still elect to perform RHC in select trial subjects at their discretion. Participating sites will collect numerous RHC hemodynamic measurements at various timepoints pre, during, and post PCI, and will use the RHC data to guide MCS weaning (mandatory for Impella, recommended for IABP). The aim of this sub-study is to evaluate the utility of RHC during high-risk PCI as a prognostic tool and to guide MCS weaning, as there currently is a lack of consensus on its use in this setting.

Viability Sub-Study

The Viability sub-study is optional. Participating sites will be asked to obtain informed consent of all eligible patients to undergo two CMR imaging studies to assess myocardial viability and left ventricular volumes and function (the first within one month prior to randomization with gadolinium injection, and the second at 6-month follow-up without gadolinium). The core laboratory results from these studies will be blinded to investigators and will not be used to make revascularization decisions, though site results of CMR studies (or other tests of viability) obtained per standard of care may be used to inform clinical decision-making.

Proteomic Signalling Sub-Study

High-throughput molecular biology techniques allow a deeper understanding of the pathophysiology of HF and more accurate phenotyping of HF patients. This may allow improved identification of those patients who would benefit from complete revascularization with hemodynamic support. This sub-study is designed to identify proteomic signatures for myocardial viability and recovery of LV function following Impella-supported and standard of care high-risk PCI. Blood samples will be taken from patients enrolled in the Viability sub-study at baseline and 6 months after PCI, at which point, high-density proteomic analysis will be performed using the SOMAScan® 7K assay. Bioinformatic analysis will identify protein signatures of interest in patients with and without myocardial viability, and with and without LV recovery. There is no prespecified sample size for this sub-study. Further details on all four sub-studies are provided in **Supplementary Table 2**.

PROTECT IV Registry

To assess the generalizability of the study results, the first 1,000 consecutive subjects with a qualifying clinical syndrome who meet the criteria for complex coronary artery disease and LV dysfunction, but who otherwise do not meet all of the other inclusion criteria or have at least one exclusion criterion, will be enrolled in the PROTECT IV Registry. The registry will collect data on these subjects' baseline features, reason(s) for randomization ineligibility, and type of first revascularization and MCS use through 30 days post enrollment. Outcomes, however, will not be assessed.

Supplementary Table 1. Prespecified subgroups.

The consistency of the primary endpoint will be examined in the following sub-groups by formal interaction testing:
Age (above vs. below median, by tertile and ≥75 years old vs. <75 years old)
Sex (male vs. female)
Race
Ethnicity
Diabetes (medication-treated vs. no diabetes or diabetes non-medication-treated; and diabetes insulin-treated vs. diabetes medication-treated but not insulin-treated vs. no diabetes or diabetes not medication-treated)
Clinical Presentation: CCS vs. MI and CCS vs. NSTEMI vs. STEMI
Baseline SYNTAX Score: above vs. below median and ≤32 vs. ≥33) – Angiographic Core Laboratory-determined
Baseline LVEF (above vs. below median; <30% vs. ≥30% to ≤40%; and <25% vs. ≥25%) – Echo Core Laboratory-determined
Baseline LVEDV (above vs. below median) – Echo Core Laboratory-determined
Baseline RVSP (above vs. below median) – Echo Core Laboratory-determined
Intended use of IABP in the control arm (stratified randomization)
Number of diseased vessels (Core Lab): 1 vs. 2 vs. 3 vs. left main
Number of vessels planned for PCI: 1 vs. 2 vs. 3 (left main = 2 or 3 depending on dominance)
PCI planned of left main vs. LAD (but not LM) vs. any other combination
Number of lesions with planned PCI (1 vs. 2 vs. 3 or more (left main = 2 or 3 depending on dominance)
Intended PCI of CTO
Right heart catheterization (inclusion in Sub-Study; RHC used)
Atherectomy performed
Intravascular imaging used
Baseline NYHA Class (0/I vs. II vs. III/IV)
Baseline KCCQ-OS (above vs. below median)
Baseline 6MWD (above vs. below median)
Baseline CKD (according to CKD KDIGO Criteria)
Procedural anticoagulation: Use of unfractionated heparin vs. bivalirudin
BNP/NT-proBNP (above vs. below median)
Oral antiplatelet agent preloading
IV antiplatelet agent preloading (cangrelor or GP IIb/IIIa inhibitor [upfront, non-bail-out use]; and each agent separately)
Oral or IV antiplatelet agent preloading
Pre- or post-PCI P2Y12 inhibitor use (prasugrel/ticagrelor vs. clopidogrel/ticlopidine)
Geography (US vs. non-US enrollment; EU vs. non-EU enrollment)

CCS, chronic coronary syndromes; CKD, chronic kidney disease; CTO, chronic total occlusion; IV, intravenous; KDIGO, Kidney Disease Improving Global Outcomes; LAD, left anterior descending artery; LM, left main; LVEDV, left ventricular end diastolic volume; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RHC, right heart catheterization; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 2. PROTECT IV substudies.

Sub-study	No. patients	Hypotheses Tested	Study Design	Outcome Measures
Renal	All patients (mandatory at all sites)	1. By providing effective periprocedural hemodynamic optimization in high-risk patients with complex CAD undergoing high-risk PCI, Impella MCS will protect the kidney from the development of new onset AKI* within 5 days. 2. The use of Impella MCS during HRPCI will result in preservation or improvement of kidney function (eGFR) from pre-procedure baseline to 1 year.	Serum creatinine will be assessed at baseline and daily through 5 days post PCI,* with lab creatinine measurements at each in-person follow-up visit (30 days, 6 months, 1 year, and 3 years).	Powered primary safety outcome assessed will be AKI. Non-powered secondary safety outcomes will be: 1. Change in mean serum creatinine from in-hospital baseline to peak within 5 days 2. Dialysis in-hospital and within 30 days, 6 months, 1 year and 3 years 3. Major adverse kidney events (MAKE): composite of death, dialysis or worsened kidney function (defined as ≥ 25% decline in eGFR) at 30 days, 6 months, 1 year, and 3 years Powered primary effectiveness outcome will be improvement or stabilization in eGFR at 12 months, with improvement defined as a ≥ 25% relative increase in eGFR from the outpatient reference creatinine-based eGFR to 12 months. Stabilization is defined as a < 25% relative increase in eGFR to a < 25% relative decrease in eGFR. Worsening is defined as a ≥ 25% relative decrease in eGFR. Non-powered secondary outcomes will be: 1. Improvement or stabilization in eGFR at 5 days, 30 days, 6 months, and 3 years 2. Slope of change in eGFR from baseline through 3 years using all available measurements

Sub-study	No. patients	Hypotheses Tested	Study Design	Outcome Measures
RHC	Voluntary for sites (participating sites to enroll all consecutive patients)	No formal hypotheses to be tested. Data from RHC may provide important guidance on LV filling pressures, PA pressures, and CO, to inform treatment decisions to optimize hemodynamics in patients with LV dysfunction. RHC data may also assist in safe weaning of MCS devices. However, RHC insertion requires an additional venipuncture, increasing risk of bleeding and vascular complications, and passage of the RHC catheter through the RH chambers and into the PA may rarely induce arrhythmias and other AEs. Equipoise is present as to the safety and effectiveness of routine RHC during HRPCI.	RHC performed prior to PCI and MCS insertion in all randomized patients in both arms, with use of RHC hemodynamic data to assist the safe performance of PCI and MCS use and removal. Sites not participating in the sub-study may still elect to use RHC before, during, or after PCI.	RHC measures (HR, BPs, CO, CI, LVEDP, SPAP/DPAP, PCWP, SvO2, CVP/RAP) will be recorded at: 1. Baseline (pre-MCS device insertion) 2. Five minutes after device insertion and activation pre-PCI† 3. At other times per clinical indications 4. Immediately post-PCI (time of last coronary angiogram)† 5. Immediately prior to device explant (5 minutes after Impella reduced to P3 and IABP reduced to 1:3), with consideration of device weaning per RHC measure criteria‡ 6. Immediately after device explant
Viability	Voluntary for sites (participating sites to enroll all consecutive patients)	In patients with left ventricular dysfunction (LVEF ≤40%) and severe coronary artery disease: 1. Revascularization of dysfunctional but viable segments is predictive of improving regional myocardial function as assessed by segmental percent wall thickening on CMR from baseline to 6 months. 2. Revascularization of dysfunctional but viable segments is predictive of improved global LVEF from baseline to 6 months.	Patients will undergo CMR (either 1.5T or 3T) within one month before revascularization and at 6-month follow-up.§ Baseline CMR evaluation includes: 1. Steady state free procession (SSFP) function; and 2. Phase contrast images which evaluate left and right ventricular function and valvular regurgitation; and 3. Late gadolinium enhancement (LGE) images with gadolinium injection, which evaluate myocardial viability. 6-month CMR evaluation includes: 1. SSFP function; and 2. Phase contrast images	Outcomes of interest to include: measurable improvement in regional systolic function, improvement in regional and global LV function (LVEF, LVESVi, LVEDVi, and LV GLS), RV volumes and functions, reduction in mitral regurgitation, and association of above viability measures with clinical endpoints (such as cardiac death, all-cause death, durable LVAD or heart transplant, and heart-failure rehospitalization).

Sub-study	No. patients	Hypotheses Tested	Study Design	Outcome Measures
Proteomic Signaling	Patients in the viability sub-study	1. CAD patients who have viability by MRI will have a unique proteomic signature that is distinct from CAD patients who do not have viability by MRI. 2. CAD patients who undergo supported PCI with Impella will have a proteomic signature at 6 months that is distinct from CAD patients who receive PCI with usual care. 3. CAD patients who have a change in LVEF >5% will have a proteomic signature at 6 months that is distinct from patients with a change in LVEF <5% at 6 months.	Blood samples will be taken at baseline and 6 months post PCI, with high-density proteomic analysis performed on patients with and without myocardial viability, and with and without recovery of LV function, at 6 months, in presence or absence of hemodynamic support.¶	Outcomes of interest will include the proteomic signatures of those with and without myocardial viability (per MRI), with and without LV function recovery (>5%), and with and without Impella support during PCI.

AKI, acute kidney injury; BP, blood pressure; CAD, coronary artery disease; CI, cardiac index; CMR, cardiovascular magnetic resonance imaging; CO, cardiac output; CV, cardiovascular; CVP, central venous pressure; DPAP, diastolic pulmonary artery pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEDP, left ventricular end diastolic pressure; LVEDVi, left ventricular end-diastolic volume; LVESVi, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; MAKE, major adverse kidney events; MRI, magnetic resonance imaging; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; SvO2, venous oxygen saturation.

***** AKI is defined as meeting at least one of the following criteria, modified from the KDIGO Criteria: 1) An absolute increase in serum creatinine ≥ 0.3 mg/dl from in-hospital baseline creatinine within 48 hours, or 2) A relative increase in serum creatinine ≥ 50% from in-hospital baseline creatinine within 5 days. At US sites, creatinine will be measured with the Nova Max eGFR Meter System (an investigational, in-vitro diagnostic device).

[†]With Impella at P8 and IABP at 1:1.

[‡] For patients with a baseline PA diastolic pressure ≤ 20 mmHg and SVO_2 ≥ 50%, MCS explantation may be performed if the PA diastolic pressure is still ≤ 20 mmHg and SVO_2 ≥ 50%, or, for patients in whom one or both of these parameters was worse than these limits at baseline, MCS explantation may be performed if there is no worsening of the PA diastolic pressure by ≥ 20% from baseline and no worsening of the SVO_2 by ≥ 10% from baseline. If one of these criteria is not met, the MCS device should not be explanted. If the device cannot be explanted after 48 hours, per these parameters, the MCS device may be kept in place for a longer duration or explanted with inotrope/vasopressor support.

[§]Patients eligible for randomization in the PROTECT IV trial, with local site capability to perform CMR imaging (1.5T or 3T) with and without gadolinium injection, and that agree (along with treating physician) to CMR imaging with gadolinium injection within 1 month prior to randomization and at 6 months without gadolinium, were included in the Viability sub-study. Patients with prior implantation of a non-MRI compatible cardiac pacemaker or implantable defibrillator, non-MRI compatible aneurysm clip, neural stimulator implant, any implanted or magnetically activated device, metal shavings in the orbits, any metallic foreign body, shrapnel or bullet in a location in which the physician feels would present a risk to the patient, any history indicating contraindication to MRI including claustrophobia, inability to follow breath hold instructions or to maintain a breath hold for > 15 seconds, or known hypersensitivity or contraindication to gadolinium contrast (including impaired renal function) were excluded.

[¶] The SOMAScan® 7K assay will be used to measure 5000 proteins simultaneously, with bioinformatics analysis to identify protein signatures of interest. An ELISA (enzyme linked immunosorbent assay) will be performed on 5-10 proteins of interest to confirm SOMAScan findings.

Supplementary Figure 1. Study governance.

Seth Bilazarian, MD, is a non-voting member of the Steering Committee and an employee of Abiomed, J&J MedTech Heart Recovery. Bobbi Bogaev, MD, is a member of the GDMT-HF committee and an employee of Abiomed, J&J MedTech Heart Recovery. Ralf Westenfeld, MD, is a non-voting member of the technique and renal committees and an employee of Abiomed, J&J MedTech Heart Recovery.