A Prospective, Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention: The PROTECT II Study

William W. O'Neill, Neal S. Kleiman, Jeffrey Moses, Jose P.S. Henriques, Simon Dixon, Joseph Massaro, Igor Palacios, Brijeshwar Maini, Suresh Mulukutla, Vladimír Dzavík, Jeffrey Popma, Pamela S. Douglas and Magnus Ohman

Circulation. 2012;126:1717-1727; originally published online August 30, 2012;
doi: 10.1161/CIRCULATIONAHA.112.098194
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

A Prospective, Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention

The PROTECT II Study

William W. O'Neill, MD; Neal S. Kleiman, MD; Jeffrey Moses, MD; Jose P.S. Henriques, MD, PhD; Simon Dixon, MBChB; Joseph Massaro, PhD; Igor Palacios, MD; Brijeshwar Maini, MD; Suresh Mulukutla, MD; Vladimír Džavík, MD; Jeffrey Popma, MD; Pamela S. Douglas, MD; Magnus Ohman, MD

Background—Although coronary artery bypass grafting is generally preferred in symptomatic patients with severe, complex multivessel, or left main disease, some patients present with clinical features that make coronary artery bypass grafting clinically unattractive. Percutaneous coronary intervention with hemodynamic support may be feasible for these patients. Currently, there is no systematic comparative evaluation of hemodynamic support devices for this indication.

Methods and Results—We randomly assigned 452 symptomatic patients with complex 3-vessel disease or unprotected left main coronary artery disease and severely depressed left ventricular function to intra-aortic balloon pump (IABP) (n=226) or Impella 2.5 (n=226) support during nonemergent high-risk percutaneous coronary intervention. The primary end point was the 30-day incidence of major adverse events. A 90-day follow-up was required, as well, by protocol. Impella 2.5 provided superior hemodynamic support in comparison with IABP, with maximal decrease in cardiac power output from baseline of -0.04 ± 0.24 W in comparison with -0.14 ± 0.27 W for IABP ($P=0.001$). The primary end point (30-day major adverse events) was not statistically different between groups: 35.1% for Impella 2.5 versus 40.1% for IABP, $P=0.227$ in the intent-to-treat population and 34.3% versus 42.2%, $P=0.092$ in the per protocol population. At 90 days, a strong trend toward decreased major adverse events was observed in Impella 2.5–supported patients in comparison with IABP: 40.6% versus 49.3%, $P=0.066$ in the intent-to-treat population and 40.0% versus 51.0%, $P=0.023$ in the per protocol population, respectively.

Conclusions—The 30-day incidence of major adverse events was not different for patients with IABP or Impella 2.5 hemodynamic support. However, trends for improved outcomes were observed for Impella 2.5–supported patients at 90 days.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00562016.

(*Circulation*. 2012;126:1717-1727.)

Key Words: heart-assist device ■ hemodynamics ■ Impella 2.5 ■ stents

Patients with multivessel or unprotected left main coronary artery disease and severely depressed left ventricular function have a markedly worse prognosis than the general population.[1,2] Historically, coronary artery bypass grafting has been the recommended revascularization strategy for these patients, especially in the presence of angina or heart failure symptoms.[3] These patients present an enormous technical challenge when features such as poor distal targets, severe comorbidities, reoperation, advanced age, or impaired renal function make surgical revascularization unattractive

Received March 7, 2012; accepted August 20, 2012.

From the University of Miami, Miami, FL (W.W.O.); Methodist DeBakey Heart and Vascular Center, Houston, TX (N.S.K.); Columbia University Medical Center New York Presbyterian Hospital, New York, NY (J.M.); Academic Medical Center, Amsterdam, The Netherlands (J.P.S.H.); Beaumont Hospital, Royal Oak, MI (S.D.); Harvard Clinical Research Institute, Boston, MA (J.M.); Massachusetts General Hospital, Boston, MA (I.P.); Pinnacle Health Medical Center, Wormleysburg, PA (B.M.); University of Pittsburgh Medical Center, Pittsburgh, PA (S.M.); Toronto General Hospital, Toronto, ON, Canada (V.D.); Beth Israel Deaconess Hospital, Boston, MA (J.P.); Duke Clinical Research Institute, Durham, NC (P.S.D.); and Duke University Medical Center, Durham, NC (M.O.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.112.098194/-/DC1.

Correspondence to William W. O'Neill, MD, Division of Cardiology, Department of Internal Medicine, Leonard M Miller School of Medicine, 1600 NW 10th Ave, Miami, FL 33156. E-mail WONEILL1@hfhs.org

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.112.098194**

because of the underlying expected risk for mortality and morbidity. Percutaneous coronary intervention (PCI) may then be a viable alternative for these patients.[4]

Clinical Perspective on p 1727

During PCI, repetitive contrast dye injections, balloon inflations, atherectomy passes, and stent manipulations transiently interrupt blood flow to the target coronary artery resulting in a negative inotropic effect.[3] Although this is generally well tolerated, there are circumstances in which even transient interruption of coronary blood flow causes hemodynamic compromise or collapse that may affect the conduct of PCI and the completeness of revascularization, and it may potentially lead to worse outcome, especially in patients with depressed left ventricular function. A number of devices have been used in an effort to provide hemodynamic support during these high-risk procedures.[5–7] However, no prospective comparative studies with respect to outcomes for these support devices have been conducted to date.

Accordingly, we conducted a prospective multicenter randomized trial to compare outcomes between the Impella 2.5 percutaneous left ventricular assist device versus the intra-aortic balloon pump (IABP) in patients deemed to require hemodynamic support during high-risk PCI.

Methods

Study Design and Patient Population

PROTECT II was a prospective, multicenter, randomized trial conducted in 112 sites in the United States, Canada, and Europe (sites and investigators are presented in the online-only Data Supplement). The study was designed to assess whether a high-risk percutaneous revascularization strategy with the support of the Impella 2.5 device would result in better outcome than a revascularization strategy with IABP support. Each site had to demonstrate previous experience with hemodynamic support for nonemergent PCI. Predetermined need for hemodynamic support, assessed by the treating physician, was required to qualify the patient for enrollment Patients were included who were aged ≥18 years and scheduled to undergo a nonemergent PCI on an unprotected left main or last patent coronary vessel with a left ventricular ejection fraction (LVEF) ≤35%. Patients with 3-vessel disease and LVEF ≤30% were also eligible. Major exclusion criteria included recent myocardial infarction (MI) with persistent elevation of cardiac enzymes, left ventricular thrombus, platelet count ≤75 000/mm^3, creatinine ≥4 mg/dL (patients already on dialysis were eligible), and severe peripheral vascular disease that precluded passage of the Impella 2.5 catheter or IABP. Complete inclusion and exclusion criteria are presented in the online-only Data Supplement.

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Review Committee of each participating center, and all patients provided written informed consent before enrollment. Food and Drug Administration Investigational Device Exemption (IDE G050017) was obtained by the study sponsor (Abiomed, Danvers, MA) in November 2007.

Device Description

The Impella 2.5 (Abiomed, Danvers, MA) is a 12F axial flow, rotary blood pump mounted on a 9F catheter deployed in a retrograde fashion across the aortic valve. The pump provides nonpulsatile forward blood flow of up to 2.5 L/min at its maximal rotation speed of 51 000 rpm. The device provides direct left ventricular unloading by aspirating blood from the left ventricle and expelling it into the aorta, thus increasing total cardiac output, reducing myocardial oxygen consumption, and decreasing the pulmonary capillary wedge pressure.[8–10] The device became commercially available in the United States during the course of the trial in June 2008 under 510(k) clearance.

Randomization and Study Procedures

After informed consent was obtained, right and left heart catheterization was generally performed by the use of femoral access. Following iliac angiography and vascular access assessment for suitability, operators declared their treatment plan based on the coronary anatomy and myocardium at jeopardy. Randomization to either the Impella 2.5 (n=225) or a commercially available IABP (n=223) was then executed in a 1:1 ratio through an automated interactive voice response system. Randomization was performed through 2 strata: geographical region (n=5) and angioplasty indication (unprotected left main/last remaining vessel versus 3-vessel disease). Crossover from one study arm to the other was not permitted. Operators were asked to aim for the most complete revascularization of the myocardium at jeopardy in a single procedure. The use of intracoronary drug-eluting or bare-metal stents, as well as adjunctive therapies such as rotational atherectomy, embolic protection devices, puncture site closure technique, anticoagulants, and glycoprotein IIb/IIIa receptor antagonists were left to the discretion of the operator. Therapeutic anticoagulation with activated clotting time >250 seconds was required. Revascularization was performed and hemodynamics, including right heart pressure, aortic pressure, and cardiac output, were measured every 15 minutes. Investigators were asked to discontinue hemodynamic support before discharge from the catheterization laboratory if the patient was deemed hemodynamically stable. Following PCI, if patients could be weaned from hemodynamic support, hemostasis was achieved by direct manual pressure when activated clotting time fell to <180 seconds or by direct surgical stitches that were deployed before the procedure. This technique, known as preclose, involves deployment of 2 Perclose devices sequentially (Abbott Vascular, IL). The stitches were deployed at 10 o'clock and 2 o'clock and isolated from the puncture site. At the end of the procedure, stitches were tied with the knot pusher, and, if necessary, manual pressure was applied to achieve complete hemostasis. Only sites experienced in this technique were allowed to use it. Patients were then admitted to the coronary care unit for observation and were discharged when appropriate. Follow-up was scheduled at 30 and 90 days postprocedure. The use of antiplatelet therapy was expected, but was left at the discretion of the investigator. Patients with intolerance to heparin, aspirin, and ADP receptor inhibitors were excluded from the study.

End Points

The primary end point was the composite rate of intra- and postprocedural major adverse events (MAEs) at discharge or 30-day follow-up, whichever was longer. A follow-up of the composite primary end point was performed at 90 days. The composite primary end point components included all-cause death, Q-wave or non–Q-wave MI, stroke, or transient ischemic attack, any repeat revascularization procedure (PCI or coronary artery bypass grafting), need for a cardiac or a vascular operation (including a vascular operation for limb ischemia), acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI. Non–Q-wave MI was defined as creatinine kinase-MB isoenzyme ≥3 times the upper limit of the normal range within 72 hours of the procedure or ≥2 times upper limit of the normal range beyond 72 hours postprocedure. Cardiac troponin values with the same thresholds were used if creatinine kinase-MB isoenzyme was not available. The development of new, pathological Q waves in ≥2 continuous leads was required to diagnose a Q-wave MI. Definitions of all primary end-point components are listed in the online-only Data Supplement.

Data Management

Data collection, management, and monitoring, events adjudication, and statistical analysis were conducted by an independent academic

clinical research organization (Harvard Clinical Research Institute, Boston, MA). Independent academic central core laboratories analyzed all angiographic (Beth Israel Deaconess, Boston, MA) and echocardiographic (Duke Clinical Research Institute, Durham, NC) data to determine angiographic success and device safety (including aortic insufficiency), respectively. An independent Clinical Events Committee adjudicated all MAEs and study end points blinded to treatment group assignment, and an independent data safety monitoring board (DSMB) monitored the safety trends on a monthly basis and provided oversight of data at 25% and 50% of planned study enrollment. In addition, the DSMB was provided with 1 formal preplanned interim analysis that included the first 50% of patients (n=327). The interim analysis aimed to evaluate the feasibility of the study with a futility guideline, and possible sample size adjustment, as well, based on the conditional power at the interim mark.[11] The conditional power is the probability of observing a statistically significant treatment effect at the end of a trial, conditional on the data observed at interim and under specific assumptions on the true treatment trends for the remaining 50% patients to be enrolled. A conditional power <40% at interim was the cutoff at which the DSMB could recommend stopping the study for futility. Coordination between the core laboratories, Clinical Events Committee, and DSMB was conducted by Harvard Clinical Research Institute. The study design and conduct were controlled by an executive committee chaired by the study Principal Investigator (W.W.O.).

Statistical Analyses

The study was powered assuming a 30-day MAE rate of 30% in the IABP arm and a relative Impella treatment effect of 33%, resulting in a 30-day MAE rate of 20% in the Impella 2.5 arm, based on the prevalence of events in previous observational IABP studies[4,5] and the PROTECT I feasibility trial.[12] Accounting for 10% missing data, a total of 654 patients (327 per arm) were necessary to detect this treatment effect difference between Impella 2.5 and IABP at 80% power and a 2-sided α-error of 5%.

The primary end point analysis is reported for all consented randomly assigned patients undergoing high-risk PCI in the study on the intent-to-treat (ITT) principle regardless of the protocol compliance and duration of follow-up. The prespecified per protocol (PP) population includes all consented randomly assigned patients who met the protocol eligibility criteria. The treatment comparison on the primary end point (30-day MAE) and on 90-day MAE were performed by using the χ^2 test. As an additional supportive analysis, Kaplan–Meier estimates of the cumulative incidence of MAE through 30 and 90 days were performed, and a log-rank test was used to compare the curves between the 2 study arms at these time points.

Secondary end points included in-hospital efficacy and safety end points consisting of efficacy of hemodynamic support assessed by maximal decrease of cardiac power output from baseline, creatinine clearance change from baseline 24 hours post-PCI, device failure assessed as Impella flow <1 L/min for >5 minutes at the performance level 5 or higher (out of 9) and rate of in-hospital MAEs.

In general, the remaining data are expressed as mean±SD, median (range), or proportion as appropriate. Univariate parametric analysis was performed by using a 2-tailed unpaired *t* test or a nonparametric Mann–Whitney test for continuous outcomes. χ^2 test or Fisher exact tests were used as appropriate for nominal data. A 2-way analysis of variance with repeated measures was performed to assess the difference in hemodynamics between the 2 study arms at different time points.

Treatment comparisons on the primary end point were also performed within prespecified subgroup by using the χ^2 test. Relative risks, calculated as the raw Impella 2.5 event rates divided by the raw IABP event rates, and their 2-sided 95% confidence intervals are presented within each subgroup. These prespecified analyses were planned to account for the randomization scheme used in the study, the potential learning curve effect, because no roll-in subject phase was included, and the unblinded access of the investigators to the study device. The prespecified subgroup analyses included (1) use of adjunctive atherectomy: patients treated with or without atherectomy; (2) coronary anatomy: unprotected left main /last patent conduit versus patients with 3-vessel disease; (3) morbidity risk: Society of Thoracic Surgery (STS) risk of <10 versus ≥10; and (4) learning curve effect: the first Impella 2.5 and IABP patient at each site versus all other treated patients.

All probability values were 2-tailed and considered significant when the probability was <0.05.

The statistical analyses for this report were performed by the Harvard Clinical Research Institute using a SAS version 9.2 (SAS Institute Inc, NC). The authors had full access to the data and take responsibility for its integrity. The corresponding author and study chair (W.W.O.) prepared the first and all subsequent drafts of this report, which were then shared with the coauthors for comments. All authors have read and agreed to the manuscript as written.

Results

Between November 27, 2007 and December 6, 2010, 452 patients were enrolled in the study (69% of the planned 654 patient enrollment). After review of the available interim data (n=327), the DSMB recommended the early discontinuation of the study for futility based on the observed conditional power of the 30-day results of the first 327 patients and the assumed similar trend for the remaining 327 patients to be included in the study. When the executive committee accepted the recommendation and study enrollment ceased (December 6, 2010), an additional 125 patients had been enrolled beyond the 327 patient halfway point which were not included in the interim analysis. Therefore, the total final cohort increased to 452 patients. Of these patients, 3 withdrew consent (IABP arm) and 1 died (Impella 2.5 arm) before undergoing PCI. Thus, the primary analysis of the full cohort included all 448 ITT patients randomly assigned to either Impella 2.5 (n=225) or IABP (n=223). The prespecified PP population included the 427 patients who met the protocol-mandated eligibility criteria (216 for Impella 2.5 and 211 for IABP). Study flow along with 30-day and 90-day completed follow-up are reported in Figure 1.

Baseline characteristics were similar between groups, with the exception of a higher incidence of heart failure and previous coronary artery bypass grafting in the Impella 2.5 arm (Table 1). Patients were on average 67±11 years of age, highly symptomatic (66% in New York Heart Association class III or IV), 87% had heart failure, and 51% had diabetes mellitus. They presented with an average LVEF of 24%±6%, a Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) score of 30±15, an STS mortality score of 6%±6%, and an STS combined mortality and morbidity score of 30%±15%. Two thirds of the patients were deemed inoperable by site surgical consultants, and only one third of this population received implantable defibrillators despite the low LVEF.

Procedural Characteristics

In both study arms, more lesions were attempted than originally anticipated. The number of attempted lesions and deployed stents were similar between the 2 groups, although the proportion of patients treated with ≥3 stents was slightly higher in the Impella 2.5 arm. There were significant differences between the 2 study arms with respect to the use of adjunctive therapies (Table 2). In the Impella 2.5 arm, glycoprotein IIb/IIIa receptor antagonists were used less frequently, whereas the use of rotational atherectomy tended

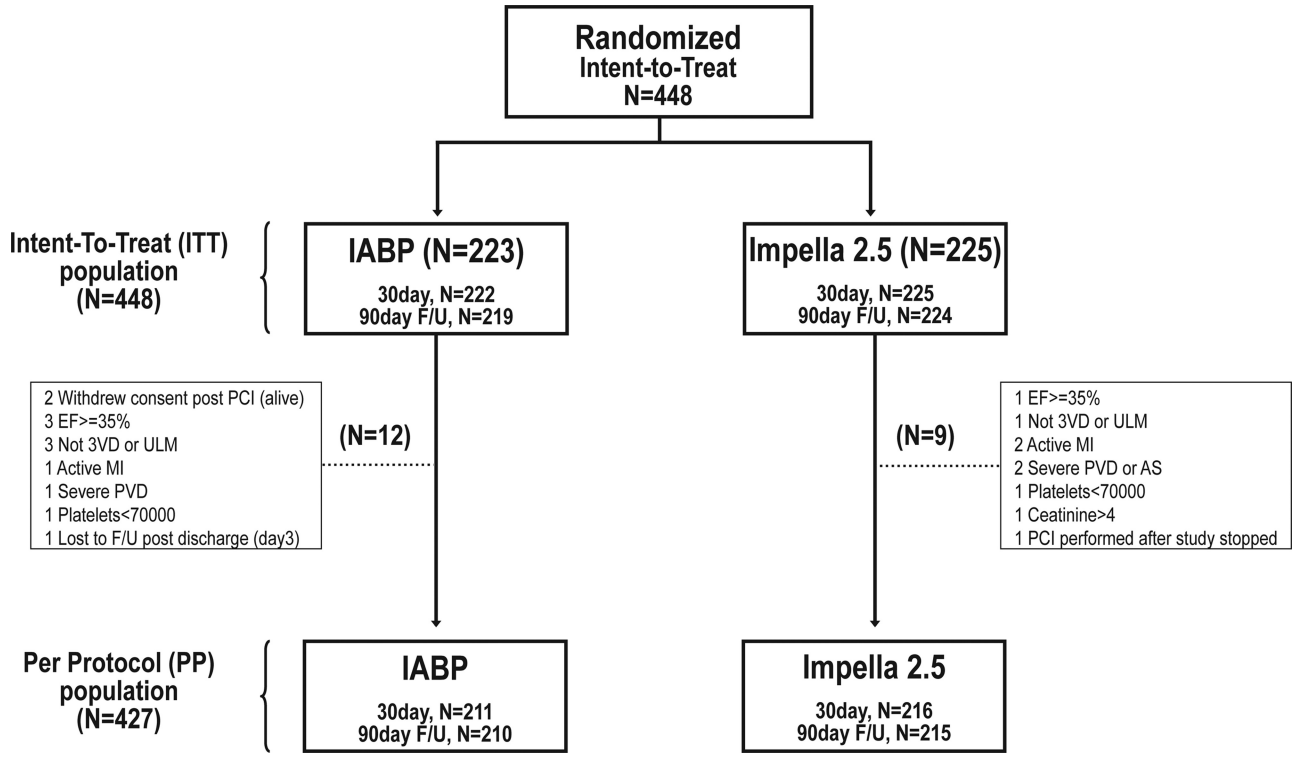

Figure 1. Study flow. IABP indicates intra-aortic balloon pump; F/U, follow up; 3VD, 3-vessel disease; EF, ejection fraction; ULM, unprotected left main disease; AS, aortic stenosis; MI, myocardial infarction; PVD, peripheral vascular disease; ITT, intent-to-treat population; and PP, per protocol population.

to be more frequent. The use of rotational atherectomy was also more vigorous in the Impella arm, with more runs and longer durations. Rotational atherectomy was also more frequently performed in unprotected left main lesions in the Impella 2.5 arm. Finally, the volume of contrast used was significantly greater in the Impella 2.5 arm. Patients randomly assigned to IABP had longer duration of support in comparison with those in the Impella 2.5 arm.

Table 1. Patient Baseline Characteristics

	IABP (n=223)	Impella 2.5 (n=225)	*P*
Age, y	67±11	68±11	0.488
Sex, male, %	81.2	80.0	0.668
History of CHF, %	83.4	91.1	0.014
Current NYHA (class III/IV), %	64.6	67.0	0.632
Diabetes mellitus, %	50.7	52.0	0.779
Renal insufficiency, %	30.2	23.1	0.091
Peripheral vascular disease, %	26.5	25.7	0.851
Implantable cardiac defibrillator, %	31.1	34.7	0.420
Previous CABG, %	28.7	38.2	0.033
LVEF, %	24.1±6.3	23.4±6.3	0.244
STS mortality score, %	6±7	6±6	0.809
SYNTAX score	29.3±13.5	30.3±13.1	0.514
Mayo PCI score, %	8.4±3.6	8.8±3.4	0.154
New York PCI score, %	10.8±3.4	11.2±3.3	0.207
Not surgical candidate, %	64.6	63.6	0.822

IABP indicates intra-aortic balloon pump; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS, Society of Thoracic Surgery; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

Clinical Outcomes for the ITT Population

At 69% of the planned enrollment, the primary end point of 30-day MAE occurred in 35.1% of patients in the Impella 2.5

Table 2. Procedural Characteristics

	IABP (n=223)	Impella 2.5 (n=225)	*P*
No. of lesions attempted	2.9±1.5	2.9±1.4	0.780
No. of stents placed	2.9±1.9	3.1±1.8	0.453
Use of heparin, %	83.3	93.3	<0.001
Glycoprotein IIb/IIIa inhibitors, %	26.0	13.8	0.001
Total contrast media, mL	241±114	267±142	0.036
Rotational atherectomy, %	9.0	14.2	0.083
Median No. of passes/lesion (IQR)	1 (1–2)	3 (2–5)	0.001
Median No. of passes/patient (IQR)	2.0 (2.0–4.0)	5.0 (3.5–9.5)	0.003
Median RA time/lesion (IQR), s	40 (20–47)	60 (40–118)	0.004
RA of left main artery, %	3.1	8.0	0.024
Saphenous vein graft treatment, %	9.0	12.1	0.288
Total support time, h	8.4±21.8	1.9±2.7	<0.001
Discharge from cath lab on device, %	36.7	5.9	<0.001

RA indicates rotational atherectomy; IQR, interquartile range; and IABP, intra-aortic balloon pump.

Table 3. Combined In- and Out-of-Hospital Hierarchical Outcomes for the Intent-to-Treat Population

	30 Days			90 Days		
	IABP (n=222)	Impella 2.5 (n=225)	*P*	IABP (n=219)	Impella 2.5 (n=224)	*P*
Composite of major adverse events	40.1	35.1	0.277	49.3	40.6	0.066
Death	5.9	7.6	0.473	8.7	12.1	0.244
Stroke/TIA	1.8	0.0	0.043	2.7	0.9	0.144
Myocardial Infarction	10.4	13.8	0.268	14.2	12.1	0.512
Repeat revascularization	4.1	1.3	0.075	7.8	3.6	0.056
Need for cardiac or vascular operation*	1.4	0.9	0.642	1.8	1.3	0.681
Acute renal dysfunction	4.5	4.0	0.792	4.6	4.0	0.776
Cardiopulmonary resuscitation/ventricular arrhythmia†	3.2	2.2	0.543	4.1	2.2	0.259
Aortic valve damage/increase in aortic insufficiency	0.0	0.0	. . .	0.0	0.0	. . .
Severe hypotension requiring treatment	8.6	4.9	0.121	5.5	4.0	0.469
Angiographic failure	0.5	0.4	0.992	0.0	0.4	0.322

The values shown are percentages. IABP indicates intra-aortic balloon pump; and TIA, transient ischemic attack.
*Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.
†Ventricular arrhythmia requiring cardioversion.

arm in comparison with to 40.1% in the IABP arm ($P=0.277$; Table 3). At 90 days, patients supported with Impella 2.5 showed a trend toward lower MAE rate in comparison with those supported with IABP (40.6% versus 49.3%, $P=0.066$; Table 3).

There was no significant difference in the occurrence of in-hospital death, stroke, MI, or the composite of death/stroke/MI between Impella 2.5 and IABP. After hospital discharge, fewer irreversible MAEs of death/stroke/MI (7.1% versus 12.8%, $P=0.047$) and of death/stroke/MI/repeat revascularization events (9.8% versus 18.3%, $P=0.01$) occurred in the Impella 2.5 arm in comparison with the IABP arm. At 90 days, there were also fewer repeat revascularization events with the Impella 2.5 in comparison with IABP in both hierarchical (3.6% versus 7.8%, $P=0.056$) and nonhierarchical (6.3% versus 11.9%, $P=0.039$) analyses.

Clinical Outcomes for the PP Population

At 69% of the planned enrollment, 30-day MAE occurred in 34.3% of Impella 2.5 patients in comparison with 42.2% of IABP patients ($P=0.092$). In comparison with the IABP arm, the 90-day MAE rate was significantly lower in the Impella 2.5 arm (40.0% versus 51.0%, $P=0.023$) yielding a relative risk reduction of 22% (Table 4). Although there was no difference in in-hospital death, stroke, MI, or the composite of death/stroke/MI between Impella 2.5 and IABP, fewer irreversible MAEs of death/stroke/MI (7.0% versus 12.9%, $P=0.042$) and of death/stroke/MI/repeat revascularization

Table 4. Combined In- and Out-of-Hospital Hierarchical Outcomes for the Per Protocol Population

	30 Days			90 Days		
	IABP (n=211)	Impella 2.5 (n=216)	*P*	IABP (n=210)	Impella 2.5 (n=215)	*P*
Composite of major adverse events	42.2	34.3	0.092	51.0	40.0	0.023
Death	6.2	6.9	0.744	9.0	11.6	0.383
Stroke/TIA	1.9	0.0	0.042	2.4	0.9	0.240
Myocardial infarction	10.9	13.4	0.425	14.8	11.6	0.340
Repeat revascularization	4.3	1.4	0.072	8.1	3.7	0.055
Need for cardiac or vascular operation*	1.4	0.9	0.634	1.9	1.4	0.680
Acute renal dysfunction	4.7	4.2	0.774	4.8	4.2	0.774
Cardiopulmonary resuscitation/ventricular arrhythmia†	3.3	2.3	0.531	4.3	2.3	0.258
Aortic valve damage/increase in aortic insufficiency	0.0	0.0	. . .	0.0	0.0	. . .
Severe hypotension requiring treatment	9.0	4.6	0.072	5.7	3.7	0.332
Angiographic Failure	0.5	0.5	0.987	0.0	0.5	0.322

The values shown are percentages. IABP indicates intra-aortic balloon pump; and TIA, transient ischemic attack.
*Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.
†Ventricular arrhythmia requiring cardioversion.

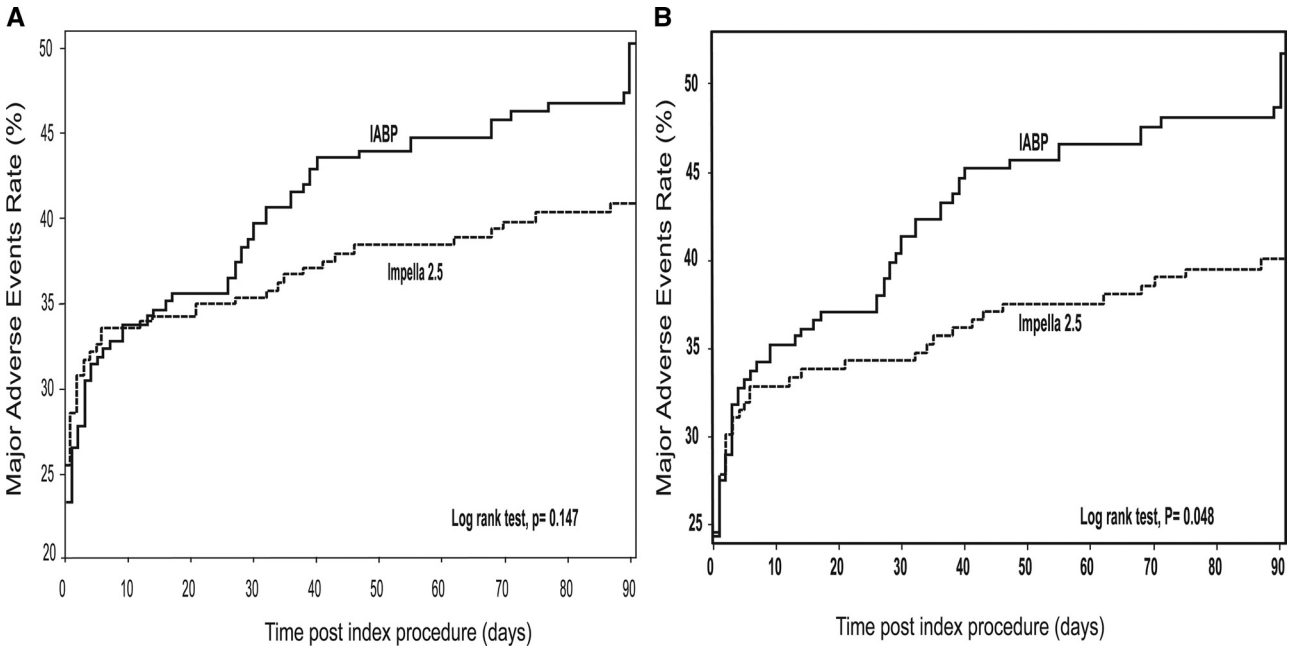

Figure 2. Kaplan–Meier curves of major adverse events to 90 days. **A**, intent-to-treat population. **B**, per protocol population. IABP indicates intra-aortic balloon pump.

(9.8% versus 18.6, $P=0.009$) occurred after hospital discharge in the Impella 2.5 arm in comparison with the IABP arm. At 90 days, there were also fewer repeat revascularization events in the Impella 2.5 arm in comparison with the IABP arm in both hierarchical (3.7% versus 8.1%, $P=0.055$) and nonhierarchical (6.0% versus 12.4%, $P=0.024$) analyses.

Clinical Benefit and Time to Major Adverse Events

In aggregate, patient cardiac function and functional status improved significantly after revascularization. At 90-day study exit follow-up, there was an average 22% relative increase in LVEF from baseline (27%±9 versus 33%±11, $P<0.001$) and a 58% improvement in New York Heart Association functional class III/IV (62% versus 26%, $P<0.001$). The improvement in LVEF and New York Heart Association was similar between the 2 study groups. However, and as depicted in the Kaplan–Meier curves for both ITT and PP populations (Figure 2A and 2B), patients treated with Impella 2.5 experienced fewer MAEs over the course of the study in comparison with those treated with IABP. Most of the differences in patient MAE outcomes occurred out of the hospital. These new events were overt and mainly driven by death or rehospitalizations for MI, stroke, and repeat revascularization in a patient population that was event free at discharge.

Secondary End Points and Prespecified Subgroup Analysis

Complete hemodynamic monitoring was obtained in 279 patients (138 for IABP and 141 for Impella 2.5). Cardiac power output,[13] defined as cardiac output×mean arterial pressure×0.0022, was calculated to account for systemic blood flow and maintenance of physiologically appropriate blood pressure during the procedural ischemic times. As determined by the maximal drop in cardiac power output from baseline, Impella 2.5 provided better hemodynamic support than IABP during these high-risk procedures (−0.04±0.24 versus −0.14±0.27 W, $P=0.001$). Change in creatinine clearance was similar between Impella and IABP patients 24 hours after PCI in comparison with baseline (4.64±15.06 versus 4.66±13.55, $P=0.988$), despite the higher volume of contrast media received by Impella patients. There were no Impella device failures, and no difference was observed in in-hospital composite MAE or any of its components between Impella and IABP arms for ITT (32.4% versus 30.9%, $P=0.733$) or PP populations (31.9% versus 32.7%, $P=0.867$).

Prespecified subgroup analyses on 30-day and 90-day MAE are depicted in Figure 3A and 3B (ITT) and Figure 4A and 4B (PP), respectively. Of particular interest, in the ITT population not treated with atherectomy (88% of the entire population, n=396), the Impella 2.5 patients had better outcomes in comparison with those who received an IABP, with a significant 25% relative risk reduction in the MAE incidence at 90 days (36.5% versus 48.7%, $P=0.014$). The 30-day MAE rate was also lower in the Impella 2.5 arm in comparison with the IABP arm (30.6% versus 39.6%, $P=0.060$). These findings were magnified for the PP nonatherectomy group with a 30% relative reduction in MAE at 30 days (29.3% versus 41.9%, $P=0.011$) and 90 days (35.5% versus 50.5%, $P=0.003$) in the Impella 2.5 arm in comparison with the IABP arm, respectively. Patients with STS scores <10 had better 90-day outcomes with Impella 2.5 than with IABP (37.4% versus 48.6%, $P=0.030$), whereas there was no difference between the 2 groups for patients with STS scores ≥10. Of note, 27% of the Impella patients with STS ≥10 had atherectomy, ≈3 times the rate of atherectomy use of the rest of the population, overlapping with the first subgroup analysis. Patients in the Impella 2.5 arm had strong

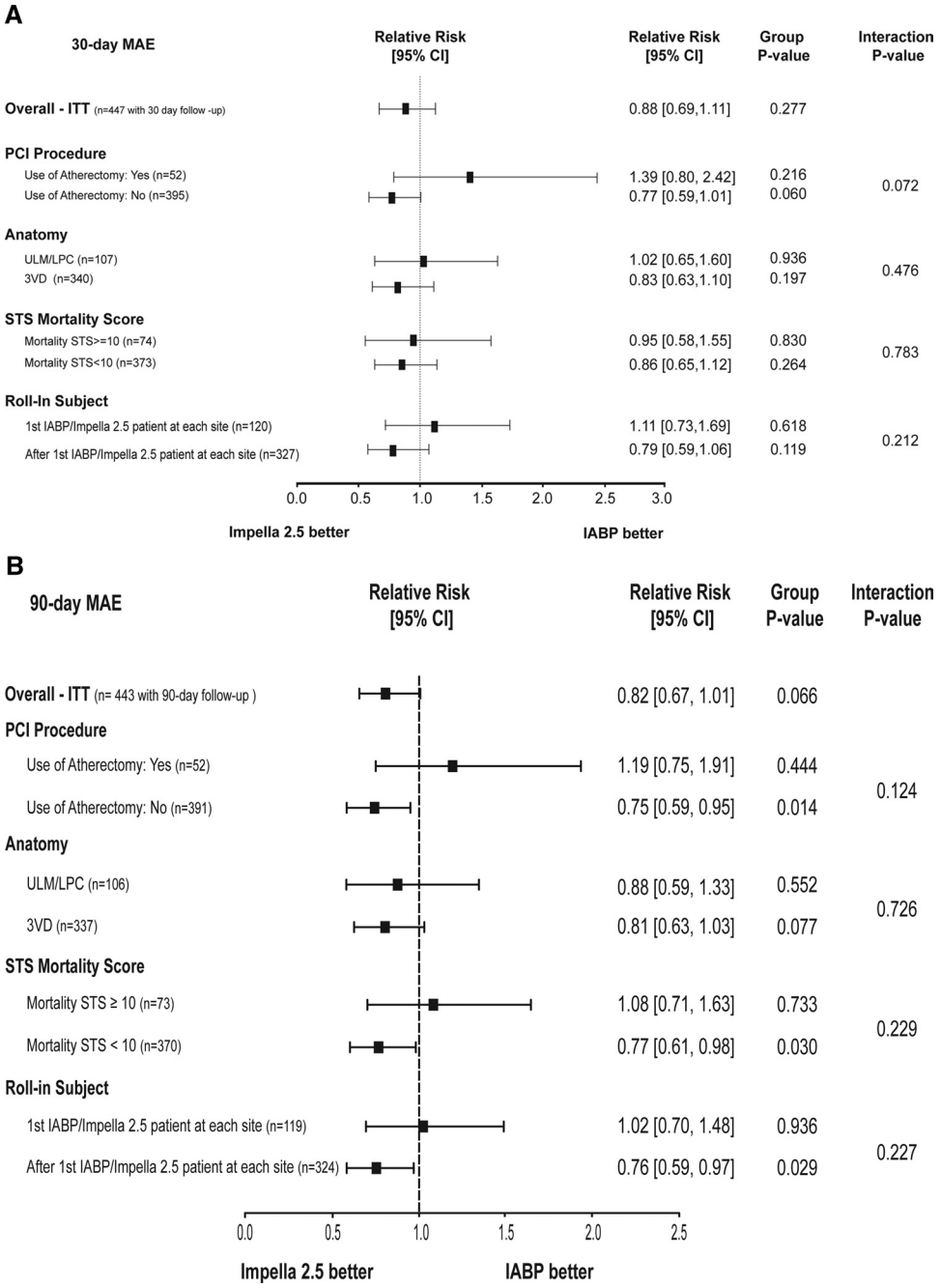

Figure 3. Prespecified prospectively defined subgroup analysis: intent-to-treat population. **A**, 30-day MAE. **B**, 90-day MAE. Roll-in subjects include only the first Impella 2.5 and IABP patient at each site versus the rest of the patients at each site excluding the first Impella 2.5 and IABP patients. MAE indicates major adverse event; STS, Society for Thoracic Surgery; IABP, intra-aortic balloon pump; ITT, intent-to-treat population; PCI, percutaneous coronary intervention; CI, confidence interval; ULM, unprotected left main disease; and LPC, last patent conduit; and 3VD, 3-vessel disease.

trends on 30-day MAE and significantly fewer MAEs at 90 days when the first IABP and Impella 2.5 patients enrolled at each site (roll-in subjects) were excluded from the analysis to account for the learning curve ($P=0.029$ in ITT and $P=0.016$ in PP populations, respectively).

Discussion

The PROTECT II trial included 448 prospectively treated patients who were deemed at high risk based on anatomic and clinical features. This is the largest high-risk PCI cohort studied in a randomized trial to date, and despite the fact that 63% of patients were deemed not suitable for surgical revascularization, the overall 30-day mortality rate was similar to the predicted outcomes from national surgical benchmarks.[14] The 90-day mortality rate is in line with the recent Surgical Treatment for Ischemic Heart Failure Study (STICH) trial.[15] Not only were the mortality rates acceptable, angiographic success was high and incidence of renal failure was low. These results demonstrate that high risk, symptomatic, coronary artery disease patients can be revascularized by

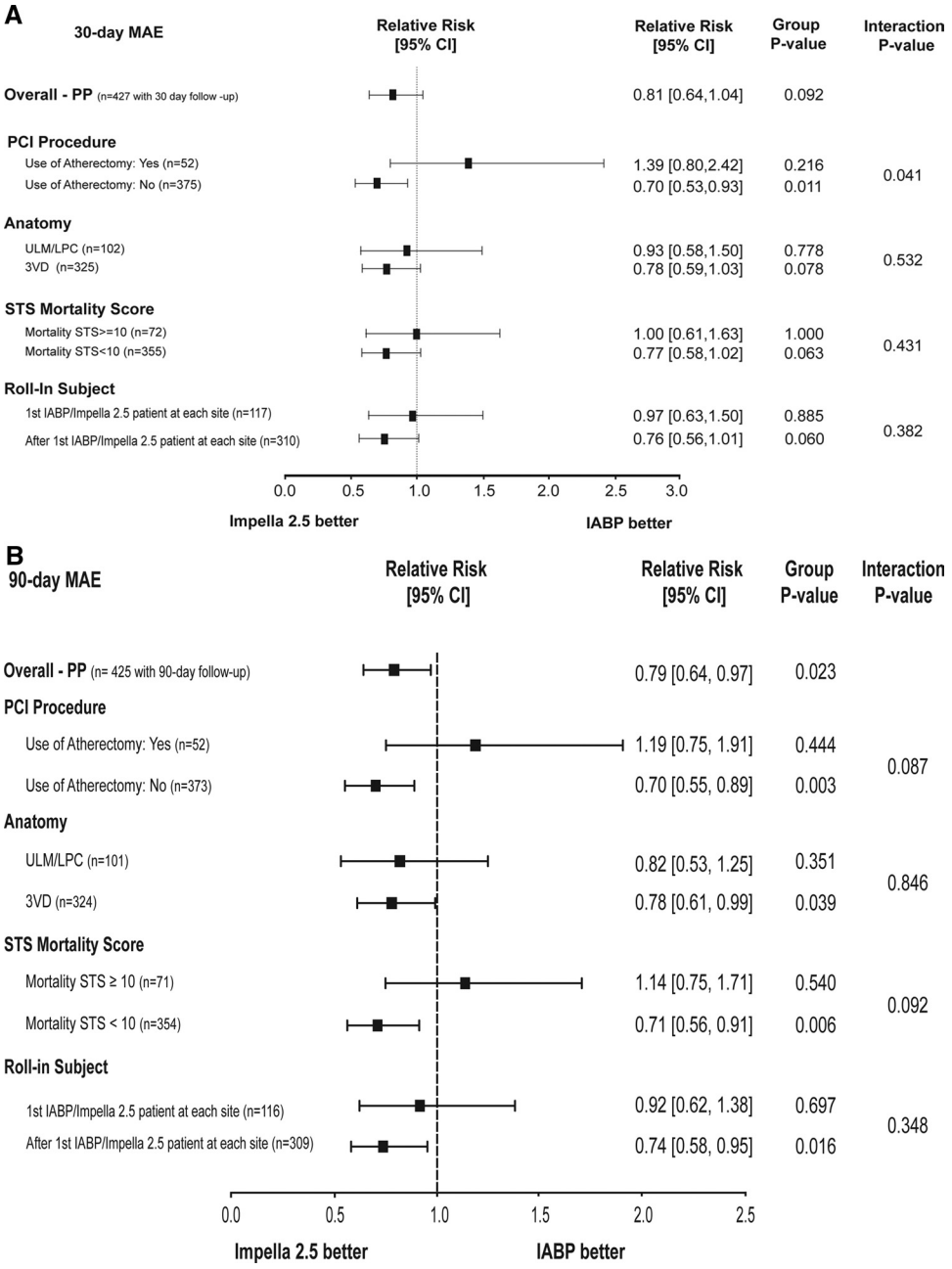

Figure 4. Prespecified prospectively defined subgroup analysis: per protocol population. **A**, 30-day MAE. **B**, 90-day MAE. Roll-in subjects include only the first Impella 2.5 and IABP patient at each site versus the rest of the patients at each site excluding the first Impella 2.5 and IABP patients. MAE indicates major adverse event; STS, Society for Thoracic Surgery; PP, per protocol; PCI, percutaneous coronary intervention; CI, confidence interval; ULM, unprotected left main disease; LPC, last patent conduit; and IABP, intra-aortic balloon pump.

using hemodynamic support and modern PCI technique with favorable safety and efficacy. The present report confirms that patients with severely depressed left ventricular function who undergo PCI for a stenotic left main lesion, last patent conduit, or lesions in the setting of 3-vessel disease have a markedly increased risk for mortality in comparison with general nonemergent PCI populations. Along with the recent British Balloon Pump–Assisted Coronary Intervention Study (BCIS-1),[16] this report can serve as a reference standard for future investigations of high-risk PCI. The major difference between this report and BCIS-1 is that patients enrolled in the PROTECT II study were deemed to require hemodynamic support to qualify for enrollment, whereas, in BCIS-1, equipoise existed as to whether or not hemodynamic support was required. In addition, our patient population presented with a higher rate of comorbidities, such as diabetes mellitus, stroke, previous PCI and coronary artery bypass grafting, in comparison with the BCIS-1 study. These differences may explain the higher event rates reported in PROTECT II. Despite this, there was a significant increase in LVEF and a significant improvement in the functional status post revascularization in both study arms. Our results suggest that PCI is a reasonable

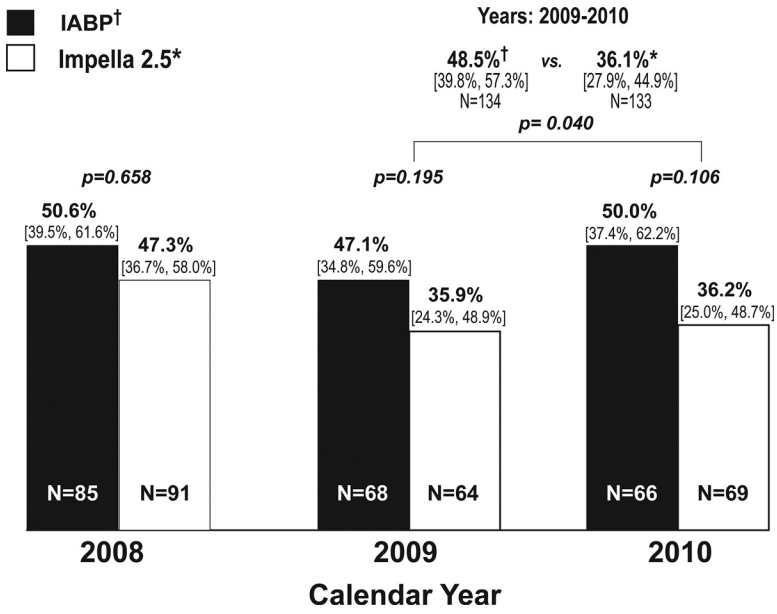

Figure 5. Ninety-day major adverse events rates over the course of the trial (intent-to-treat population). A comparison of 90-day outcome with 95% confidence interval for each treatment arm based on the calendar year of enrollment is depicted. IABP indicates intra-aortic balloon pump.

revascularization strategy for this high-risk population, because it improves heart failure symptoms and the quality of life of patients with limited therapeutic options.

The ITT analysis did not show a statistically significant difference in MAE at 30 days with 69% of the planned enrollment, whereas a trend toward better outcomes was observed at 90 days for the Impella 2.5–supported patients. For patients who truly qualified for treatment (PP), a trend toward improved outcome was observed at 30 days, with a significant 22% risk reduction at 90 days suggesting that the beneficial effect of Impella 2.5 during high-risk PCI resulted in a sustained positive impact up to 90 days.

There was no difference in mortality between groups in either the ITT or PP populations. Patients randomly assigned to the IABP arm had a significantly higher rate of repeat revascularization procedures. It is noteworthy that the rate of vascular operations in the Impella 2.5 arm was not different than that of the IABP arm, so there was no burden associated with the use of the larger sheath. Similarly, we did not observe any aortic or mitral valve dysfunction or left ventricular injury, which confirms the safety profile of the Impella 2.5 device with respect to ventricular and valve function and integrity, consistent with previous reports.[7,12,17,18]

Analysis of the Kaplan–Meier event curves suggests that the use of a 30-day end point is not sufficient in this population. Other investigations of PCI in severely compromised patients such as the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial[19] and the BCIS-1 study[16] found that event curves continue to diverge over time. Future investigations in this population should have a minimum of 90-day follow-up as an efficacy end point. The out-of-hospital events have important safety and cost implications, because only events that were overt and led to death or repeat hospitalization were captured during follow-up.

In our study, the more frequent and more vigorous use of rotational atherectomy in the Impella 2.5 arm was associated with a higher rate of periprocedural MI due to cardiac enzyme leaks ≥3 times the upper limit of the normal range (none of them were Q-wave MI), and likely confounded the overall results. The prespecified group of patients not treated with atherectomy (88% of the population) provides a more homogenous population for end-point analysis without the cofounding effect of atherectomy and creatinine kinase-MB isoenzyme postprocedural leak. In this subgroup, there was a 23% and 25% relative risk reduction at 30 and 90 days in the ITT population in favor of Impella 2.5. The benefit was magnified for the PP population, with a 30% MAE decrease in comparison with IABP at 30 and 90 days. A detailed analysis on the use of rotational atherectomy in our study will be reported separately.

Study Limitations

Because of the DSMB determination of futility, this trial was terminated on the assumption from the first 50% (327) of patients enrolled. Ultimately only 69% (452) of the planned enrollment occurred. Because the trial did not enroll the number of patients it was powered for, definitive statements concerning the primary end point are speculative. Unfortunately, unbeknownst to the DSMB, a significant learning curve occurred in this trial with marked improvement in safety for Impella-supported patients who were treated in the last half of the trial (Figure 5).

Because of the different radiographic appearance, operators could not be blind to treatment assignment. Knowledge of the presence of Impella support unfortunately led to a greater and more aggressive use of rotational atherectomy in this subgroup. These differences confounded the analysis because of the markedly higher rate of cardiac isoenzyme elevations.

Because the difference in 30-day MAE did not reach statistical significance for the entire study, the analysis of 90-day events remains exploratory. It must be emphasized, however, that 90-day follow-up with end-point analysis was prospectively planned and provides a picture of longer-term

safety. The increase in overt, clinical events between 30 and 90 days is an important clinical observation.

Conclusions

The PROTECT II trial identified and characterized a population of high-risk patients undergoing nonemergent PCI. In these patients, PCI resulted in a marked reduction of symptoms and increased left ventricular function. Hemodynamic support with Impella 2.5 did not result in a superior outcome of the primary end point at 30 days but showed a strong trend to superior outcome at 90 days in the total cohort and a significant improvement in the PP analysis at 90 days. Important adverse events continued to occur after 30-day follow-up, suggesting that intense medical observation is required for at least 90 days in these patients.

Acknowledgments

The authors thank Gelsys Sargenton for her assistance in preparation of the manuscript.

Sources of Funding

This study was funded by Abiomed (Danvers, MA).

Disclosures

Drs O'Neill and Kleiman report no conflicts. Dr Moses reported that his institution has received research grant from Abiomed as site principal investigator for the Mini-AMI trial. Dr Moses received a modest payment for participation at some Abiomed advisory board meetings. Dr Henriques reported that his institution has received research funding from Abiomed as investigator site for other Impella trials. Dr Henriques received modest speaker honoraria from Abiomed. Dr Dixon has no conflict of interest to report for this study. Dr Massaro reported that he has received funding for the study through Harvard Clinical Research Institute for biostatistics, trial design, and analyses. Dr Palacios reported that he has received modest speaker honoraria from Abiomed. Dr Maini reported that he or his institution have received research support/speaker honoraria from Abbott laboratories, InfraReDx, Abiomed, and Medtronic. Dr Mulukutla reported that he received modest compensation for participation in Abiomed advisory board meetings. Dr Džavík reported that he has received modest speaker honoraria from Abiomed. Dr Popma reported that his institution (angiographic core laboratory) has received a research grant from Abiomed for the angiographic analysis of the study. He has also received modest funding for participation in some advisory board meetings. Dr Douglas reported that her institution (Duke University/Duke Clinical Research Institute) has received funding from Abiomed for the echocardiography core laboratory analysis of the study. Dr Ohman reported that he has received grants from Daiichi Sankyo, Maquet (formerly Datascope), and Eli Lilly.

References

1. Anderson HV, Shaw RE, Brindis RG, Hewitt K, Krone RJ, Block PC, McKay CR, Weintraub WS. A contemporary overview of percutaneous coronary interventions. The American College of Cardiology – National Cardiovascular Data Registry (ACC – NCDR). *J Am Coll Cardiol*. 2002; 39:1096–1103.
2. Williams DO, Holubkov R, Yeh W, Bourassa MG, Al-Bassam M, Block PC, Coady P, Cohen H, Cowley M, Dorros G, Faxon D, Holmes DR, Jacobs A, Kelsey SF, King SB III, Myler R, Slater J, Stanek V, Vlachos HA, Detre KM. Percutaneous coronary intervention in the current era compared with 1985–1986: the National Heart, Lung, and Blood Institute Registries. *Circulation*. 2000;102:2945–2951.
3. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47;e1–e121.
4. Mishra S, Chu WW, Torguson R, Wolfram R, Deible R, Suddath WO, Pichard AD, Satler LF, Kent KM, Waksman R. Role of prophylactic intra-aortic balloon pump in high-risk patients undergoing percutaneous coronary intervention. *Am J Cardiol*. 2006;98:608–612.
5. Briguori C, Airoldi F, Chieffo A, Montorfano M, Carlino M, Sangiorgi GM, Morici N, Michev I, Iakovou I, Biondi-Zoccai G, Colombo A. Elective versus provisional intraaortic balloon pumping in unprotected left main stenting. *Am Heart J*. 2006;152:565–572.
6. Aragon J, Lee MS, Kar S, Makkar RR. Percutaneous left ventricular assist device: "TandemHeart" for high-risk coronary intervention. *Catheter Cardiovasc Interv*. 2005;65:346–352.
7. Henriques JP, Remmelink M, Baan J Jr, van der Schaaf RJ, Vis MM, Koch KT, Scholten EW, de Mol BA, Tijssen JG, Piek JJ, de Winter RJ. Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. *Am J Cardiol*. 2006;97:990–992.
8. Valgimigli M, Steendijk P, Sianos G, Onderwater E, Serruys PW. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. *Catheter Cardiovasc Interv*. 2005;65:263–267.
9. Remmelink M, Sjauw KD, Henriques JP, de Winter RJ, Koch KT, van der Schaaf RJ, Vis MM, Tijssen JG, Piek JJ, Baan J Jr. Effects of left ventricular unloading by Impella recover LP2.5 on coronary hemodynamics. *Catheter Cardiovasc Interv*. 2007;70:532–537.
10. Sjauw KD, Remmelink M, Baan J Jr, Lam K, Engström AE, van der Schaaf RJ, Vis MM, Koch KT, van Straalen JP, Tijssen JG, de Mol BA, de Winter RJ, Piek JJ, Henriques JP. Left ventricular unloading in acute ST-segment elevation myocardial infarction patients is safe and feasible and provides acute and sustained left ventricular recovery. *J Am Coll Cardiol*. 2008;51:1044–1046.
11. Denne JS. Sample size recalculation using conditional power. *Stat Med*. 2001;20:2645–2660.
12. Dixon SR, Henriques JPS, Mauri L, Sjauw K, Civitello A, Kar B, Loyalka P, Resnic FS, Teirstein P, Makkar R, Palacios IF, Collins M, Moses J, Benali K, O'Neill WW. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial). Initial U.S. experience. *J Am Coll Cardiol Cardiovasc Interv*. 2009;2:91–96.
13. Cotter G, Williams SG, Vered Z, Tan LB. Role of cardiac power in heart failure. *Curr Opin Cardiol*. 2003;18:215–222.
14. Jacobs JP, Edwards FH, Shahian DM, Prager RL, Wright CD, Puskas JD, Morales DL, Gammie JS, Sanchez JA, Haan CK, Badhwar V, George KM, O'Brien SM, Dokholyan RS, Sheng S, Peterson ED, Shewan CM, Feehan KM, Han JM, Jacobs ML, Williams WG, Mayer JE Jr, Chitwood WR Jr, Murray GF, Grover FL. Successful linking of the Society of Thoracic Surgeons database to social security data to examine survival after cardiac operations. *Ann Thorac Surg*. 2011;92:32–39.
15. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL; STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364:1607–1616.
16. Perera D, Stables R, Thomas M, Booth J, Pitt M, Blackman D, de Belder A, Redwood S; for the BCIS-1 Investigators. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2010;304:867–874.
17. Sjauw KD, Konorza T, Erbel R, Danna PL, Viecca M, Minden HH, Butter C, Engstrøm T, Hassager C, Machado FP, Pedrazzini G, Wagner DR, Schamberger R, Kerber S, Mathey DG, Schofer J, Engström AE, Henriques JP. Supported high-risk percutaneous coronary intervention with the Impella 2.5 device. The Europella Registry. *J Am Coll Cardiol*. 2009;54:2430–2434.

18. Maini B, Naidu SS, Mulukutla S, Kleiman N, Schreiber T, Wohns D, Dixon S, Rihal C, Dave R, O'Neill W. Real-world use of the Impella 2.5 circulatory support system in complex high-risk percutaneous coronary intervention: The USpella Registry. *Catheter Cardiovasc Interv*. November 22, 2011. doi: 10.1002/ccd. 23403. http://onlinelibrary.wiley.com. Accessed August 20, 2012.

19. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*. 1999;341:625–634.

CLINICAL PERSPECTIVE

Complex percutaneous coronary intervention with hemodynamic support may offer an effective therapy for high-risk patients with multivessel or unprotected left main lesions. In the PROTECT II trial we randomly assigned 452 high-risk patients undergoing percutaneous coronary intervention to hemodynamic support with intra-aortic balloon counterpulsation or a percutaneous (Impella 2.5) axial flow left ventricular assist device. Primary outcome was incidence of major adverse events at 30 days with prospectively planned follow-up to 90 days. The trial was able to enroll the most ill population of symptomatic ischemic heart disease patients ever enrolled in a percutaneous coronary intervention trial. These patients were highly symptomatic, 66% were in New York Heart Association class III or IV, 87% had a history of heart failure, 51% had diabetes mellitus, 26% had renal insufficiency, and ejection fraction was 24%. Despite these extreme risk features, the reported 30-day mortality of 6.7% is comparable to predicted surgical models. Angiography success was high, whereas stroke/transient ischemic attack and incidence of renal failure rates were low. At 90 days follow-up, 68% of patients had improvement in symptom status with 74% of patients either class I or class II. The trial was terminated prematurely because of the data safety monitoring board's determination of futility. At 30 days, no difference in incidence of major adverse events occurred for either intent-to-treat or per protocol analysis. Planned follow-up at 90 days reveals a strong trend of benefit for Impella-treated patients ($P=0.066$, intent-to-treat) and significant for patients who actually qualified ($P=0.023$, per protocol).

SUPPLEMENTAL MATERIAL

Supplemental Methods

1. List of Participating Sites

Site Name	First Name	Last Name
William Beaumont Hospital	Simon	Dixon
Brigham and Women's Hospital	Laura	Mauri
Columbia Presbyterian University Medical Center	Michael	Collins
	Jeffrey	Moses
Texas Heart Institute	Andrew	Civitello
Scripps Clinic	Paul	Teirstein
Academic Medical Center	Jose P.S.	Henriques
Mt. Sinai School of Medicine	Samin	Sharma
	Anapoorna	Kini
UPMC Presbyterian Hospital	Suresh	Mulukutla
University of Miami	Alan	Heldman
	William	O'Neill
York Hospital (PA)	William	Nicholson
University of Alabama	Gilbert	Zoghbi
	Raed	Aqel
	Vijay	Misra
TexSan Heart Hospital	Abram	Rabinowitz
Moffitt Heart & Vascular Group	Brijeshwar	Maini
The Lindner Clinical Trial Center	Dean	Kereiakes
Kings Daughters Medical Center	Richard	Paulus
Indiana University	Saihari	Sadanandan
California Pacific Medical Center	Peter	Hui
Lankenau Hospital / Main Line Health Heart Center	Amid	Khan
St. Elizabeth's Medical Center	Faisal	Khan
Forsyth Medical Center	John	Patterson
Providence Hospital and Medical Centers	Shukri	David
Northern Michigan Hospital	Louis	Cannon
Valley Hospital	Janet	Strain
UMDNJ - Robert Wood Johnson Medical School	Abel	Moreyra
Strong Memorial Hospital	Fred	Ling
St. Joseph's Research Institute	Larry	Crisco
Beth Israel Deaconess Medical Center	David	Leeman
Ohio State University Heart Center	Quinn	Capers
Johns Hopkins Hospital	Jon	Resar
Oakwood Hospital	Samir	Dabbous
St. Louis University Hospital	Michael	Lim
University of Chicago Medical Center	Neeraj	Jolly
Emory University Hospital Midtown	Henry	Liberman
Weill Cornell Medical Center	Shing Chiu	Wong
St. Francis Hospital & Health Centers	William	Berg
Liberty Hospital	Venkat	Pasnoori
	Paul	Kramer
Carolinas Medical Center	B. Hadley	Wilson
Clear Lake Regional Medical Center	Nadir	Ali
Intermountain Medical Center	James	Revenaugh

Lourdes Hospital	J. David	Talley
St. Mary's Medical Center	Mark	Studeny
University of Texas Memorial Hermann	Ali	Denktas
Owensboro Medical Health System	Roshan	Mathew
St. Vincent Heart Center of Indiana, LLC	Edward	Fry
North Memorial Heart and Vascular Institute	Steven	Roh
Hoag Memorial Hospital Presbyterian	Subbarao	Myla
Robert Packer Hospital	Kishore	Harjai
Methodist DeBakey Heart & Vascular Center	Neal	Kleiman
Southwest Methodist Hospital	Robert	Schnitzler
University of Kansas Hospital	Mark	Wiley
Central Minnesota Heart Center at St. Cloud Hospital	Bernard	Erickson
Hartford Hospital	Detlef	Wencker
Jefferson Regional Medical Center	Daniel	Rubin
Sutter Memorial Hospital	Michael	Fugit
Good Samaritan Hospital	Dogan	Temizer
Allegheny General Hospital	David	Lasorda
University of Oklahoma Health Sciences Center	Jorge	Saucedo
University of Virginia	Michael	Ragosta
Rush University Medical Center	Clifford	Kavinsky
Winthrop University Hospital	Srihari	Naidu
Morristown Memorial Hospital	Barry	Cohen
Alegent Health / Bergan Mercy Hospital	Himanshu	Agarwal
Massachusetts General Hospital	Igor	Palacios
Washington Adventist Hospital	Fayaz	Shawl
Centennial Heart Medical Center	Paul	Myers
Aurora St. Luke's Medical Center	Tanvir	Bajwa
Abbott Northwestern Hospital	Daniel	Lips
Integris Baptist Hospital	George	Chrysant
Community Hospital of Monterey Peninsula	Pir	Shah
Geisinger Clinic	Kimberly	Skelding
University of Michigan Health Systems	Stanley	Chetcuti
Ruby Memorial	Robert	Beto
Mercy Gilbert Medical Center	Nabil	Dib
Genesys Regional Medical Center	David	Dobies
Florida Hospital	Bruce	Stein
St. Luke's Hospital Mid America Heart Institute	J. Aaron	Grantham
Lahey Clinic Medical Center	Thomas	Piemonte
Research Physicians Network Alliance (RPNA) / Memorial Regional Hospital	Luis	Tami
Stony Brook University Medical Center	Luis	Gruberg
Henry Ford Hospital Heart & Vascular Institute	Akshay	Khandelwal
Maimonides Medical Center	Robert	Frankel
University of Washington	Steven	Goldberg
University of Maryland	Peter	Reyes
St. Joseph's Bellingham	William	Lombardi

Medical College of GA	Deepak	Kapoor
Gateway Cardiology	Bassam	Al-Joundi
University of Cincinnati Medical Center	Massoud	Leesar
University of Southern California	Ray	Matthews
Dartmouth-Hitchcock Medical Center	John	Robb
Miami Valley Hospital	James	Pacenta
Boston Medical Center	A. David	Litvak
Loyola University Medical Center	Ferdinand	Leya
Patel Research Institute at Pepin Heart Hospital	Charles	Lambert
Munroe Regional Medical Center	Gregory	vonMering
University Hospital, University of Cleveland	Michael J.	Cunningham
Minnesota Heart Clinic - Fairview Southdale Hospital	David	Laxson
Westchester Medical Center	Anthony	Pucillo
Harper University Hospital	Theodore	Schreiber
Veteran's Affairs Medical Center - Dallas	Subhash	Banerjee
Banner Good Samaritan Medical Center	Ashish	Pershad
	Timothy	Byrne
The Foundation for Cardiovascular Medicine	Maurice	Buchbinder
Bryan LGH Heart Institute	Timothy	Gardner
St. John Hospital & Medical Center	Thomas	Davis
Duke University Medical Center	Manesh	Patel
	Magnus	Ohman
California Cardiovascular Consultants/Washington Hospital	Ash	Jain
Toronto General Hospital	Vladimír	Dzavík
Ottawa Heart Institute	Derek	So
Royal Alexandra Hospital	William	Hui
Royal Victoria Hospital at McGill	Renzo	Cecere
Riverside Methodist	Barry	George
Yale New Haven	Michael	Cleman
University of Alberta Hospital	Robert	Welsh

Supplemental Methods

2. PROTECT II Inclusion and Exclusion Criteria

INCLUSION CRITERIA

Subjects must fulfill *all* of the following inclusion criteria:

1. Signed Informed Consent
2. Subject is indicated for a NON emergent percutaneous treatment of at least one *de novo* or restenotic lesion in a native coronary vessel or bypass graft
3. Subject age of 18 to 90
4. Patient presents with:

   a) Ejection Fraction ≤ 35% AND at least one of the following criteria:

   - Intervention on the last patent coronary conduit
   - Intervention on an unprotected left main coronary artery

   Or

   b) Ejection Fraction ≤ 30% AND intervention on patient presenting with triple vessel disease.
   Three-vessel or triple vessel disease is defined as at least one significant stenosis* in all three major epicardial territories: Left Anterior Descending Artery and/or side branch, left circumflex artery and/or side branch, Right Coronary Artery and or side branch.

   *Significant stenosis is defined as at least 50% diameter stenosis by visual estimate or any total occlusion. In the case of left coronary artery dominance, a lesion in the LAD and the proximal LCX qualifies as three-vessel disease.

EXCLUSION CRITERIA

Subjects must have *none* of the following exclusion criteria:

1. ST elevation myocardial infarction within 24 hours or CK-MB that have not normalized
2. Pre-procedure cardiac arrest within 24 hours of enrolment requiring CPR
3. Subject is in cardiogenic shock defined as:
   - CI < 2.2 l/min/m^2 and PCWP > 15mmHg
   - Hypotension (systolic BP < 90 mmHg for > 30 minutes or the need for supportive measures to maintain a systolic BP of greater than or equal to 90

mmHg) AND end organ hypoperfusion (cool extremities OR [a urine output of < 30 ml/hour AND a HR > 60 BPM])

4. Mural thrombus in the left ventricle
5. The presence of a mechanical aortic valve or heart constrictive device
6. Documented presence of aortic stenosis (aortic stenosis graded as ≥ +2 equivalent to an orifice area of 1.5cm^2 or less)
7. Documented presence of moderate to severe aortic insufficiency (echocardiographic assessment of aortic insufficiency graded as ≥ +2)
8. Severe peripheral arterial obstructive disease that would preclude IMPELLA® 2.5 System or IABP device placement
9. Abnormalities of the aorta that would preclude surgery, including aneurysms, and extreme tortuosity or calcifications
10. Subject with renal failure (creatinine ≥ 4mg/dL)
11. Subject has history of debilitating liver dysfunction with elevation of liver enzymes and bilirubin levels to ≥ 3x ULN or INR (Internationalized Normalized Ratio) ≥ 2
12. Subject has uncorrectable abnormal coagulation parameters (defined as platelet count ≤75,000/mm^3 or INR ≥2.0 or Fibrinogen ≤ 1.50 g/l.)
13. History of recent (within 1 month) stroke or TIA
14. Allergy or intolerance to heparin, aspirin, ADP receptor inhibitors (clopidogrel and ticlid) or contrast media
15. Subject with documented heparin induced thrombocytopenia
16. Participation in the active follow-up phase of another clinical study of an investigational drug or device

Supplemental Methods

3. PROTECT II Protocol/Study Specific Adverse Event Definitions

ACUTE RENAL DYSFUNCTION

Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 2 times baseline or greater than 2.5 mg/dL.

AORTIC INSUFFICIENCY

Aortic regurgitation graded by transthoracic echocardiographic measurement as ≥ 2 or an increase in aortic regurgitation by more than one (i.e, 2 grades and higher) assessment level on a 4-point scale as determined by echocardiographic measurement.

CARDIAC ARRHYTHMIAS

Sustained ventricular tachycardia or ventricular fibrillation requiring cardioversion (including ICD discharge) and/or IV amiodarone

CARDIOPULMONARY RESUSCITATION (CPR)

Cardiopulmonary resuscitation (CPR) involves a combination of mouth-to-mouth rescue breathing or assisted ventilation and chest compression.

CARDIAC OR VASCULAR OPERATION:

Need for: a) cardiac operation or thoracic or, b) abdominal vascular operation, or c) vascular operation for limb ischemia (limb ischemia =new incidences of hypoperfusion of the leg requiring treatment and marked by such symptoms as decreased skin temperature of the limb or decreased peripheral pulses).

DEATH - all cause mortality

All deaths occurring at any time during the course of the study.

Deaths will be divided into two categories: cardiac and non-cardiac.

Cardiac Death:

Defined as death due to any of the following:

- Acute myocardial infarction
- Heart failure/CHF/cardiogenic shock or pulmonary edema. All deaths from hypotension (systolic BP <90mmHg) and/or respiratory failure without other clear etiology will be considered as heart failure
- Cardiac perforation/Pericardial tamponade
- Arrhythmia or conduction abnormality
- Cerebrovascular accident within 30 days of procedure or suspected of being related to the procedure
- Death due to a complication of the procedure, including bleeding, vascular repair, transfusion reaction or bypass surgery.
- Any death in which a cardiac cause cannot be excluded

Non-cardiac Death

Defined as any death not attributable to a cardiac cause

MYOCARDIAL INFARCTION (MI)

The American College of Cardiology definition will be used for the diagnosis of MI. The diagnosis of MI will be made on the basis of clinical information available from hospitalization (laboratory data, ECG) and will require an appropriate clinical history consistent with acute MI.

A. Criteria for acute, evolving or recent MI

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   (a) ischemic symptoms;
   (b) development of pathologic Q waves on the ECG;
   (c) ECG changes indicative of ischemia (ST segment changes); or
   (d) coronary artery intervention (e.g., coronary angioplasty).

(2) Pathologic findings of an acute MI.

B. Criteria for established MI

Any one of the following criteria satisfies the diagnosis for established MI:

(1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.

(2) Pathologic findings of a healed or healing MI.

Cardiac Enzymes will be considered abnormal if:

1. *The enzyme profile must exhibit a typical rise and fall and result from an ischemic event.*
2. *For CK-MB or CK, the elevation must be > 2 times the upper limit of normal upper limit for the local laboratory. CK-MB result takes precedence over total CK result.*
3. *For cTn, the elevation must be > 2 ULN using local laboratory criteria established as diagnostic of MI. cTn takes precedence over CK-MB (i.e. when CK-MB is abnormal but cTn is normal, the enzyme profile will be considered normal)*
4. *When CK-MB is collected after a coronary revascularization procedure, the threshold for abnormality is increased to > 3 ULN for PCI procedures and >10ULN for CABG procedures. cTn post-procedure will not be used to diagnose post-procedure MI because of the lack of reliable long-term data at the current time, except in the situation where there are no available CK-MB data, in which case cTn will be used to establish a diagnosis. In this case cTn> 3ULN will be used to establish the diagnosis.*
5. *Isolated cardiac enzyme rise alone does not qualify as an MI event.*

NEUROLOGICAL DYSFUNCTION

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The NIH Stroke Scale must be re-administered at 30 days following the event to document the presence and severity of neurological deficits. Each neurological event must be subcategorized as:

1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction)
2) Ischemic or Hemorrhagic Cardiovascular Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study.

REPEAT REVASCULARIZATION

Any repeat revascularization that involves: i) the target lesion (the originally treated segment; for stented lesions this includes an area 5mm proximal or distal to the stented segment), or ii) target vessel (all coronary segments in the same epicardial artery as the treated lesion if that segment may have been involved during passage of the coronary guidewire or any treatment device), or iii) non-target vessels. This intervention could be either percutaneous or surgical bypass.

SEVERE HYPOTENSION:

Severe hypotension is defined as systolic blood pressure or augmented diastolic pressure (the higher of the two) <90 mmHg for ≥ 5 min requiring inotropic/pressor medications or IV fluid while on device support. Also considered as severe hypotension, are severe and life-threatening hypotensive events (i.e, sudden hydrodynamic collapse) with systolic blood pressure or augmented diastolic pressure (the higher of the two) <90 mmHg that requires immediate and aggressive treatment such as IV inotropic/pressor medications, resuscitative maneuvers, etc. to restore hemodynamics when patient is on device support (regardless of the duration of the hypotension). Only those severe hypotensive episodes which occur while the patient is on device support will be considered MAE and will be part of the primary and secondary endpoint analysis