

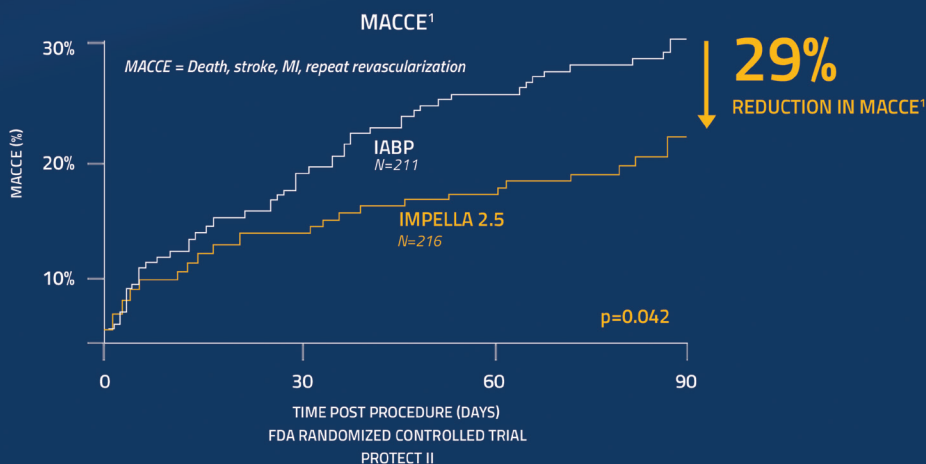
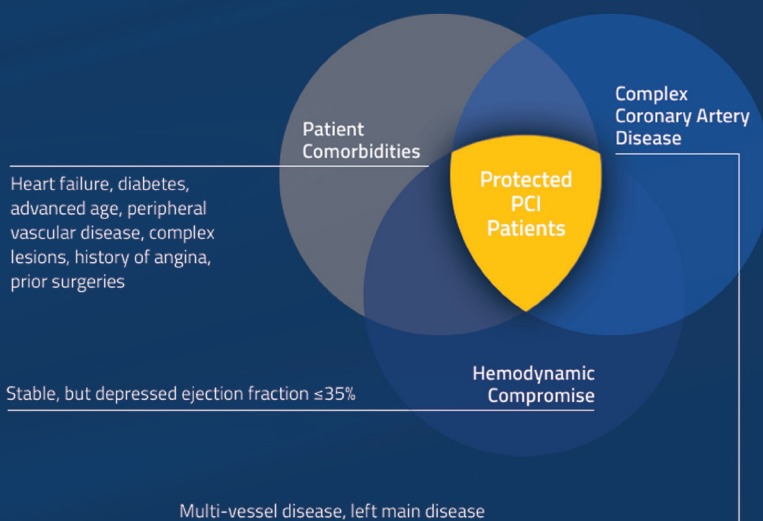
Cardiac Interventions

TODAY

January/February 2016

Expanding Your Patient Practice With a Protected PCI™ Program

Treating the most complex patients.



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Expanding Your Patient Practice With a Protected PCI™ Program: Treating the Most Complex Patients

Protected PCI™ provides a new treatment option for patients with complex coronary artery disease and gives physicians the opportunity to perform complete revascularization on high-risk patients.*

BY SETH BILAZARIAN, MD, FACC, FSCAI
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As the general patient population becomes more complex, there is a growing advanced heart failure population and subsequently, an increase of high-risk patients. Patients with severely depressed left ventricular (LV) function who undergo percutaneous coronary intervention (PCI) for a stenotic left

main coronary artery lesion, last patent conduit, or three-vessel disease have a markedly increased risk of mortality in comparison with the general nonemergent PCI population.¹

Historically, patients with complex coronary artery disease (CAD) have had few viable options. Frequently compromised with a variety of comorbidities, these patients were not candidates for coronary artery bypass grafting (CABG) and faced significant risk with PCI.¹⁻³ During PCI, contrast dye injections, balloon inflations, atherectomy passes, and stent manipulations temporarily interrupt blood flow in the target coronary artery,¹ which can reduce the force of the heart's contractions.⁴ This is generally well tolerated.¹ However, there are circumstances where temporary interruption of coronary blood flow can cause hemodynamic compromise or collapse that may affect the way the PCI procedure is conducted and the completeness of revascularization.¹

According to a recent report by The Advisory Board Company,⁵ the number of high-risk patients is expected to increase. "The prevalence of CAD is projected to grow 47% over the next 25 years, and the simultaneous growth of other chronic conditions and comorbidities will likely lead to expansion of the high-risk PCI patient population. As a result of the growing multimorbid patient population, the

case mix for PCI volumes is projected to shift." PCI volumes are projected to decline by 10%, but The Advisory Board Company projects that the proportion of more complex, comorbid patients will increase by 2019. Approximately 20% of inpatient PCI cases in 2014 involved major complications or comorbidities, but this is projected to grow to 24% of all inpatient PCIs by 2019 (Figure 1).

Recently, the clinical community has recognized the sea change in this complex and higher-risk patient population and the subsequent need for more complete revascularization and introduced an initiative called "Complex Higher Risk and Indicated Patients (CHIP)." The CHIP initiative is aimed at educating practitioners about how to identify the large, underserved complex patient population and appropriately revascularize them for optimal outcomes, an improved quality of life, and symptom relief for the patient.

For many complex PCI cases, hemodynamic support is necessary to protect the patient during a high-risk procedure.

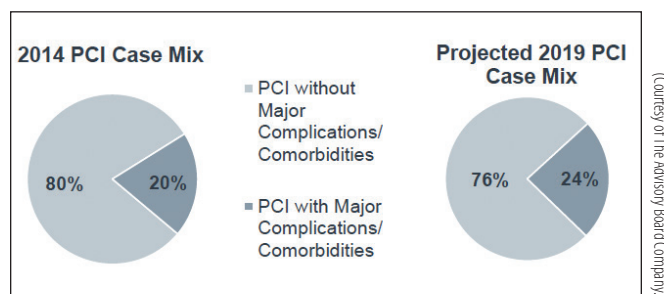


Figure 1. Approximately 20% of inpatient PCI cases in 2014 involved major complications or comorbidities, but this is projected to grow to 24% of all inpatient PCIs by 2019.⁵

*The Impella 2.5™ System is a temporary (< 6 hours) ventricular support device indicated for use during high-risk percutaneous coronary interventions (PCI) performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option. Use of the Impella 2.5™ in these patients may prevent hemodynamic instability, which can result from repeat episodes of reversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events.

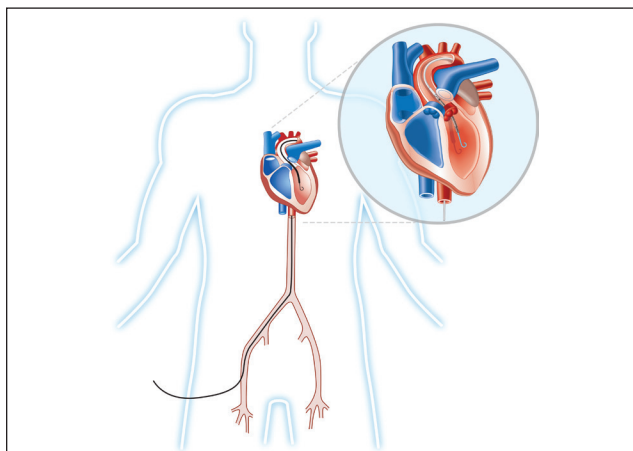


Figure 2. The Impella 2.5™ system in the body.

HISTORY OF HEMODYNAMIC SUPPORT

In 1968, a catheter-based device called the *intra-aortic balloon pump (IABP)* was developed to support the function of the heart.⁶ The IABP inflates and deflates in coordination with the beating of the heart to increase the amount of blood being pumped to the coronary arteries and the rest of the body. This method can provide modest hemodynamic benefit⁶ and has enabled some patients to undergo high-risk PCI who would not have previously been considered. However, IABP devices depend upon a reliable force at cardiac contraction and a stable electric rhythm to function optimally.⁶ These conditions may not be consistently present in the critically ill patient.⁶

The Impella 2.5™ circulatory support system (Abiomed, Inc.) was developed to provide continuous blood flow from the left ventricle to the aorta, whether the heart is beating or not.¹ This continuous blood flow protects the patient during the procedure, called *Protected PCI™*, a benefit discussed later in this article.

With the introduction of the Impella 2.5 circulatory support system in 2008 in the United States, more high-risk patients could safely undergo PCI and potentially benefit from improved cardiac function.¹ Also, because the Impella 2.5 technology delivers superior hemodynamic support compared to the IABP,⁷ it often allows the interventional cardiologist to perform a more complete revascularization in a single session, which can result in better outcomes.^{7,8}

In this article, we review the clinical experience of Protected PCI™ Procedure with the Impella 2.5 and explore the patient benefits.

WHAT IS THE IMPELLA 2.5™ HEART PUMP?

The Impella 2.5 is the smallest and least invasive percutaneous ventricular support blood pump available on the market. It directly unloads the left ventricle and propels blood forward, from the left ventricle into the aorta, in a manner consistent with normal physiology.

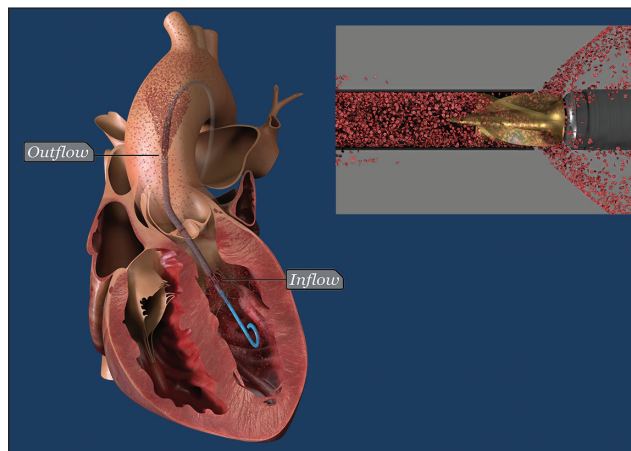


Figure 3. The Impella 2.5™ catheter in position inside the heart.

The Impella device provides both an active forward flow⁹⁻¹¹ and systemic aortic pressure contribution,^{9,12,13} leading to an effective increase in mean arterial pressure and overall cardiac power output and augments cardiac output with 2 to 2.5 L/min of pump flow.^{1,9,14} Combined with left ventricle unloading, Impella support reduces end-diastolic volume and pressure¹⁵⁻¹⁹ and augments peak coronary flow,^{9,12,15,16} leading to a favorable alteration of the balance of myocardial oxygen supply and demand.

This cascade of hemodynamic effects has been described in the literature^{6,9} and validated in computational modeling, as well as a variety of preclinical and clinical studies.^{1,6,9-20}

HOW IT WORKS

The Impella 2.5™ circulatory support system consists of a miniature heart pump enclosed inside a catheter and an outside control console connected to the pump by a thin wire that runs through the catheter.

The catheter is typically inserted into the femoral artery near the groin and advanced up the artery into the heart (Figure 2). When it is in position, the inlet port is inside the left ventricle, and the outlet port is above the aortic valve in the aorta (Figure 3).

The outflow portion of the catheter, positioned in the aorta, contains a tiny motor and a propeller-like blade

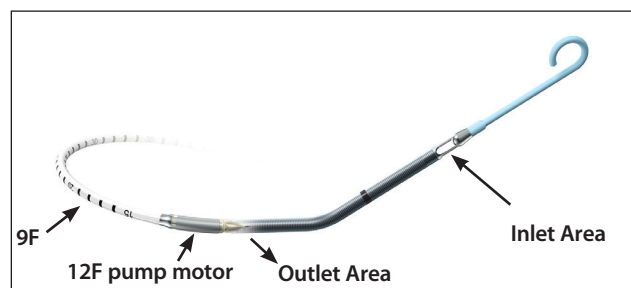


Figure 4. The Impella 2.5™ catheter.



Figure 5. The Automated Impella® Controller.

assembly that spins to pull blood out of the left ventricle and into the aorta (Figures 3 and 4).

The Automated Impella® Controller (Figure 5), provides continuous output and performance data on a display panel and allows the interventional cardiology team to control the operation of the Impella catheter.

PROTECTED PCI™ PROCEDURES USING THE IMPELLA 2.5™

The Impella 2.5 received premarket approval (PMA) on March 23, 2015, making it the only US Food and Drug Administration (FDA)-approved percutaneous hemodynamic support device proven safe and effective for elective and urgent high-risk PCI.

The PMA was based on clinical data involving more than 1,600 patients (Figure 6) from an FDA randomized, controlled trial and a US multicenter registry, plus more than 200 peer-reviewed publications in the high-risk PCI setting.

Greater Mean Arterial Pressure May Lead to Better Results

The clinical data showed that the Impella 2.5™ maintains patient hemodynamics during planned temporary coronary occlusions by maintaining mean arterial pressure (Figure 7). This may allow the interventional cardiologist to conduct a more thorough procedure and achieve a more complete revascularization in a single session.⁷

Fewer MACCE EVENTS

Major adverse cardiac and cerebrovascular events (MACCE) are an important indicator of device safety. During the PROTECT II clinical trial, Impella 2.5™ demonstrated a significant reduction in MACCE events at 90 days postprocedure than the IABP (Figure 8).²¹

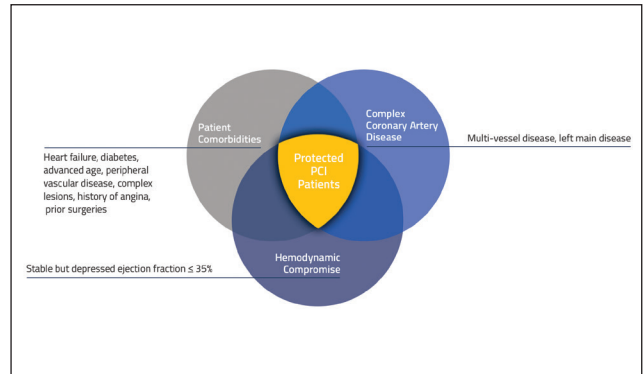


Figure 6. The profile of a patient appropriate for the Protected PCI™ procedure.

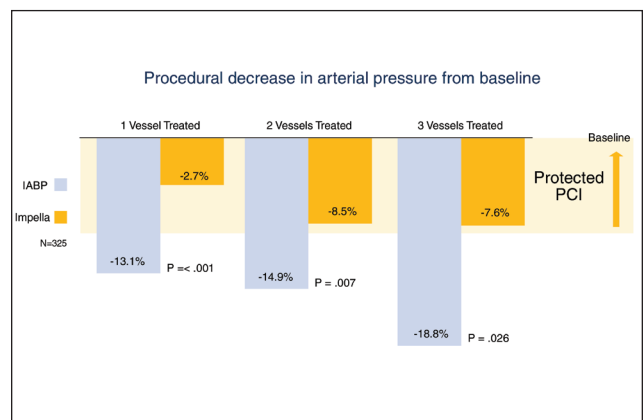


Figure 7. The decrease in arterial pressure during the procedure is significantly less on Impella 2.5™ than on IABP.⁷

Complete Revascularization Can Lead to Fewer Readmissions and Reduced Length of Stay

PROTECT II results showed that there were fewer readmissions (Figure 9) and fewer days in the hospital (Figure 10) with the Impella 2.5™ than with the IABP.²²

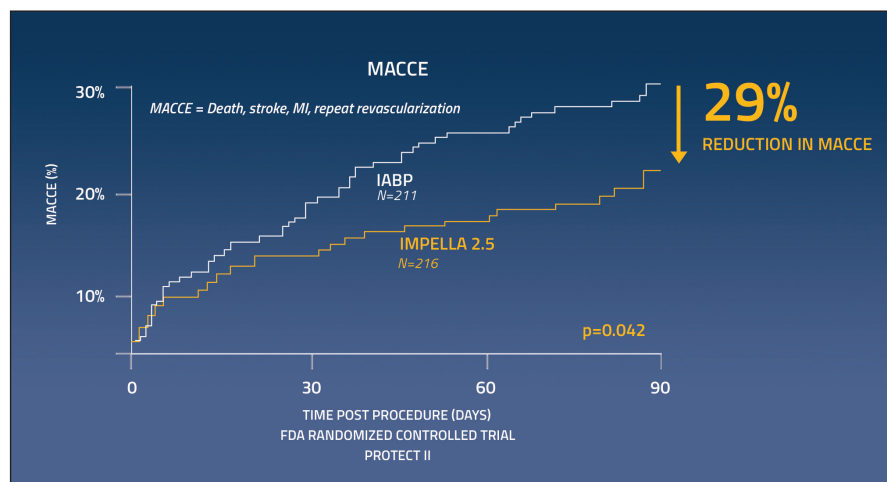


Figure 8. The Impella 2.5™ produced fewer MACCE events than IABP.²¹

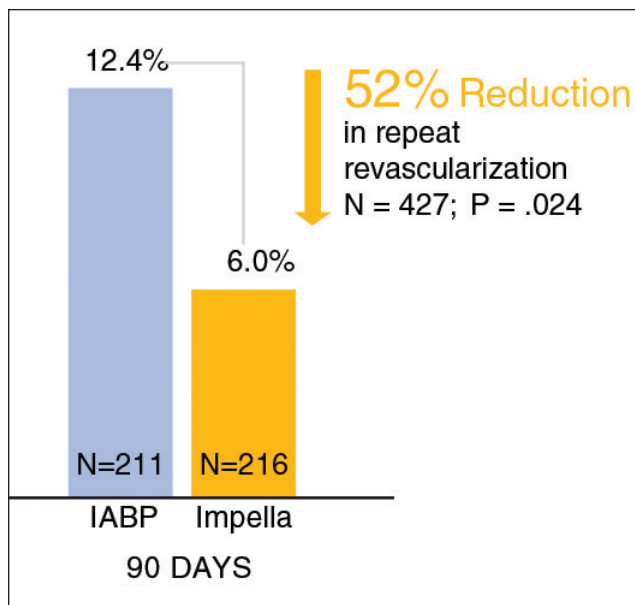


Figure 9. The patients treated with Impella 2.5™ had 52% fewer readmissions due to revascularization.²²

Reduction in Severity of Heart Failure Improves Quality of Life

The New York Heart Association (NYHA) functional classification of heart disease provides a simple way of describing the extent of heart failure. During the PROTECT II trial, there was a 58% reduction in class III and IV symptoms, the most serious classifications, in the cohort using the Impella 2.5™ device (Figure 11).¹

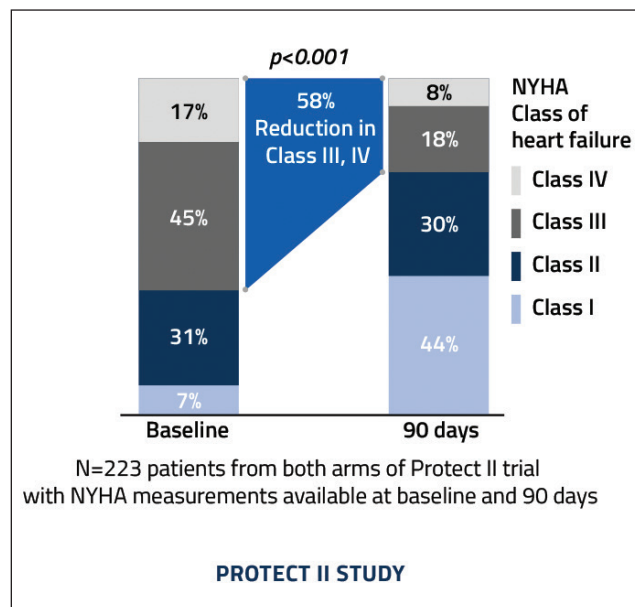


Figure 11. Patients treated with the Impella 2.5™ showed a significant improvement in NYHA classification after the PCI procedure.¹

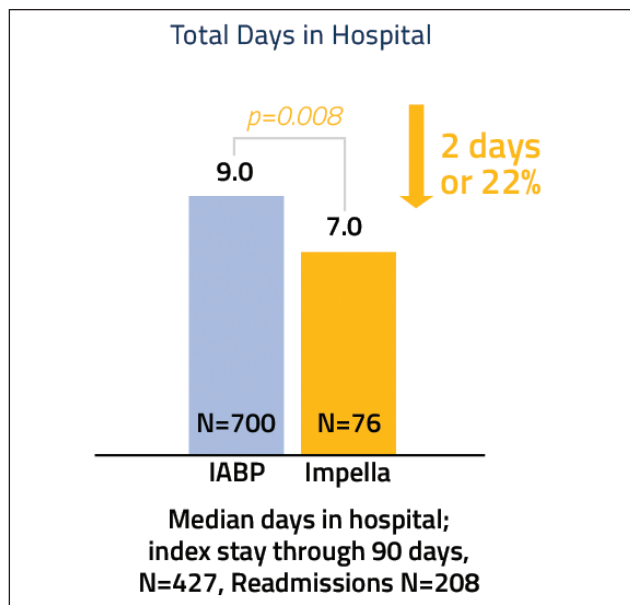


Figure 10. Patients treated with Impella 2.5™ stayed in the hospital 2 fewer days than IABP patients on average.²³

Clinical Evidence

As noted previously, the clinical evidence supporting the safety and effectiveness of the Impella 2.5™ heart pump in the Protected PCI™ procedure includes prospective, randomized, and nonrandomized clinical trial data, as well as unselected registry data and a literature review with a total of 1,638 patients. Table 1 provides a summary.

PROTECT I TRIAL

PROTECT I was a prospective, single-arm, multicenter feasibility study designed under FDA guidance to examine the safety and feasibility of the Impella 2.5™ in patients undergoing high-risk angioplasty procedures. Patients presenting with a left ventricular ejection fraction (LVEF) ≤ 35% and scheduled to undergo PCI on an unprotected left main lesion or last patent conduit were considered for enrollment.

The study showed an excellent safety profile of the device when used in this setting. The FDA reviewed these

TABLE 1. SUMMARY OF CLINICAL EVIDENCE		
Scientific Evidence	Patients in Cohort	Patients Treated With Impella 2.5™
PROTECT I	20	20
PROTECT II	452	225
cVAD Registry™	1,322	637
Literature review (N = 215)	2,537	756
TOTAL	4,331	1,638

data and approved the start of the PROTECT II trial after PROTECT I met its primary and secondary endpoints.

PROTECT II TRIAL

PROTECT II was a prospective, multicenter, randomized trial comparing outcomes between the Impella 2.5™ and the IABP in patients thought to require hemodynamic support during elective or urgent high-risk PCI. Beyond the goal of establishing a reasonable assurance for safety and effectiveness, the objective of the study was to demonstrate that prophylactic use of Impella 2.5 was superior to the IABP in preventing peri- and postprocedural major adverse events (MAEs) in this patient population. The study proposed to enroll 654 patients at up to 150 sites.

The primary endpoint for efficacy was a combination of 10 major adverse events:

- Death
- Stroke/transient ischemic attack
- Myocardial infarction (MI)
- Repeat revascularization
- Need for cardiac or vascular operation
- Acute renal dysfunction
- Cardiopulmonary resuscitation or ventricular arrhythmia requiring cardioversion
- Increase in aortic insufficiency by more than one grade
- Severe hypotension
- Failure to achieve angiographic success

This composite endpoint composed of multiple safety measures allowed for a comprehensive evaluation of the safety profile of the device. The endpoint was measured at 30 and 90 days.

The enrolled patient population consisted of either (1) patients undergoing elective or urgent hemodynamically supported high-risk PCI on an unprotected left main or last patent conduit with an LVEF $\leq 35\%$, or (2) patients with three-vessel disease and an LVEF $\leq 30\%$. Investigators were instructed to identify the target lesions prior to randomization and then aim for the most complete revascularization of the myocardium at jeopardy in a single procedure. The randomization was 1:1 between the Impella 2.5 and IABP study arms.

An Exceptionally High-Risk Cohort

The PROTECT II population comprised the sickest elective and urgent PCI population ever studied. Patients were symptomatic and presented with high-risk features, including complex coronary anatomy (mean SYNTAX score, 30 ± 13), depressed LVEF (mean LVEF, $24 \pm 6\%$), and other comorbidities, including previous procedures, with 64% of them ineligible as surgical candidates as determined by a surgical consult (see Figure 12 and Table 2). Comparing the SYNTAX study with the PROTECT II study patient, anatomic, surgical, and demographic characteristics are markedly different (Figure 12).

BENEFITS OF A PROTECTED PCI™ PROCEDURE WITH IMPELLA 2.5™

Hemodynamic Effects

During PROTECT II, patients had 53% fewer hypotensive events than IABP patients during the procedures (0.45 ± 1.37 vs 0.96 ± 2.05 event/patient; $P = .001$).¹ Impella also provided superior hemodynamic support for patients

TABLE 2. COMPARISON OF PCI ARM IN SYNTAX TRIAL AND SYNTAX REGISTRY TO PROTECT II

	SYNTAX Trial PCI Arm ²⁴ (N = 903)	SYNTAX PCI Registry ^{24,25} (n = 192) (Patients turned down for surgery)	PROTECT II ¹ (N = 427)
LVEF $\leq 35\%$ (%)	~2	~5.7	100
CHF (%)	4	9.7	87
Unstable angina (%)	29	38	40
Diabetes (%)	26	51	51
Prior MI (%)	32	40	68
Prior PCI	0	unk	40
Prior CABG*	0	0	34
Age (mean $\pm$ SD)	65 $\pm$ 10	71.2 $\pm$ 10.4	67 $\pm$ 11
EuroScore (mean $\pm$ SD)	4 $\pm$ 3	6 $\pm$ 3	8.7 $\pm$ 5
SYNTAX score	28 $\pm$ 11.5	32 $\pm$ 12.3	30 $\pm$ 13†
Not surgical candidates (%)	0	100	64‡

* SYNTAX does not incorporate prior CABG into risk stratification.

† 33% of patients in PROTECT II had prior CABG.

‡ 64% of patients determined inoperable by surgical consult. Additional 36% were determined not surgical candidates by treating physician.

		SURGICAL RISK		
		Low	Medium	High
ANATOMICAL RISK	Low	PCI	PCI	PCI
	Medium	CABG or PCI	CABG or PCI	Support & PCI
	High	CABG	CABG or PCI	Support & PCI
		SYNTAX STUDY		

Protected PCI
 FDA-indicated
 Safe & effective
 ACC/AHA PCI Guidelines

Figure 12. Revascularization strategy by risk category.

compared with the IABP (maximal decrease in cardiac power output, 0.04 ± 0.24 vs -0.14 ± 0.27 watts; $P = .001$, secondary endpoint).¹ Consistent with these differences in performance, longer support time after the procedure was used for the IABP patients (IABP support time, 8.4 ± 21.8 vs Impella support, 1.9 ± 2.7 ; $P < .001$),¹ and the proportion of patients discharged from the catheterization laboratory on device support was lower in the Impella group when compared with the IABP group (5.9% vs 36.7%; $P < .001$).¹

Clinical Outcomes

At 90 days, the number of patients experiencing major adverse events was lower with the Impella 2.5™ than IABP (Table 3 and Figure 13).

PRESPECIFIED SUBGROUP ANALYSIS OF THE PRIMARY PROTECT II ENDPOINT

Learning Curve

Researchers noted a short but significant learning curve in the PROTECT II trial. Patients in the Impella arm had fewer MAEs at 90 days compared with the IABP arm when the first subject enrolled at each site was excluded from the analysis (Table 4).²⁶ As a result of this learning curve effect, current Impella instructions for use contain information and cautions related to the need for proper training.

This learning curve was also observed over time. Figure 14 shows the outcomes of the trial by year of enroll-

TABLE 3. COMPOSITE PRIMARY ENDPOINT OF MAEs AT 90 DAYS FOR THE PER-PROTOCOL PATIENT POPULATION ¹		
Impella 2.5	IABP	P Value
40%	51%	.023

TABLE 4. COMPOSITE PRIMARY ENDPOINT OF MAEs AT 90 DAYS WITH FIRST SUBJECT ENROLLED AT EACH SITE EXCLUDED (N = 373) ²⁶		
Impella 2.5	IABP	P Value
38.5%	51%	.017

ment.^{1,26} This “over time” analysis was not prespecified for assessing the learning curve, but complements the prespecified analysis.

Atherectomy Versus Nonatherectomy

The superior hemodynamic support provided by the Impella device—and specifically better blood pressure stability—was associated with more frequent and more vigorous use of rotational atherectomy. This involved more passes per lesion ($P < .001$) and longer runs compared with IABP ($P < .004$).¹

For the atherectomy patients (12% of population), there was no significant difference in the composite MAE. There was also no difference in mortality, despite greater use of rotational atherectomy in this high-risk patient population (4% Impella vs 7.7% IABP; $P = .6$ at 30 days; and 12% vs 15.4%; $P = .8$ at 90 days, respectively).²⁷

There was a higher rate of periprocedural MI for Impella versus IABP (MI defined as serologic cardiac biomarker increased values of three times the upper limit of normal). All patients who experienced a postprocedural MI event were discharged after the procedure. There was no evidence of a functional impact on these patients.²⁷

Fewer repeat revascularization procedures were observed in the Impella arm than the IABP arm (at 90 days, 4/13 [30.8%] IABP vs 1/25 [4%] for Impella; $P = .021$).²⁷

The more favorable outcomes with Impella were even greater in the group of patients who did not undergo rotational atherectomy (88% of the patient population) (Figure 15, Table 5). At 90 days (N = 375), there was a statistically significant reduction in MAE rate for the Impella arm.²⁷

Coronary Anatomy Complexity

The differences in favor of Impella were also magnified in the subgroup of patients with three-vessel disease

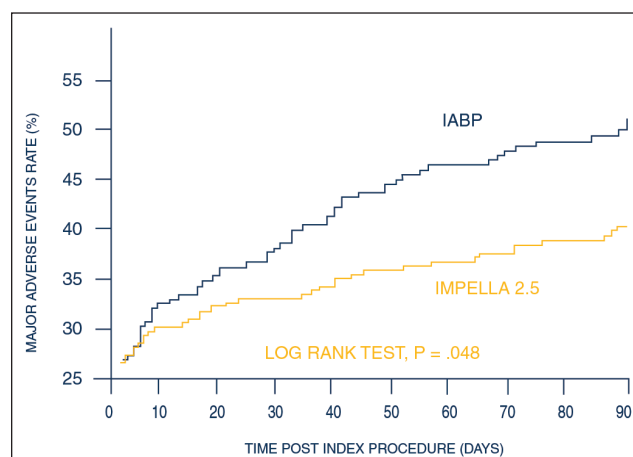


Figure 13. Kaplan-Meier curves for MAEs up to 90 days.

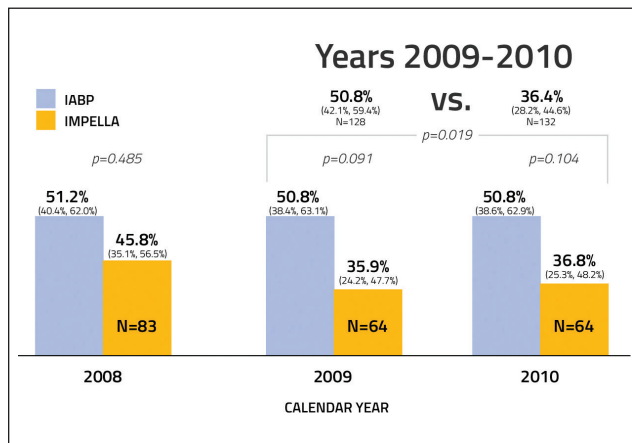


Figure 14. Ninety-day MAE rates over the course of the study.¹

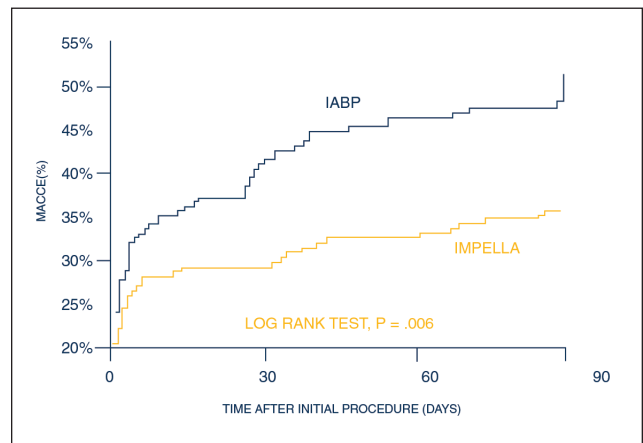


Figure 15. Prespecified analysis of primary endpoint for patients not undergoing rotational atherectomy.²⁷

(76% of population) compared with the IABP at 90 days (Table 6).⁷

POSTHOC ANALYSES CONDUCTED ON THE PRIMARY ENDPOINT

A Contemporary Definition of MI

The 2007 universal definition of MI used in the PROTECT II trial has since changed to reflect current knowledge. A post hoc analysis published in an article by Dangas et al in the *American Journal of Cardiology*²¹ incorporates the identical data from PROTECT II but was conducted using an updated model. The analysis uses an eight-times the upper limit of normal (ULN) threshold for periprocedural MI to reflect the contemporary and prognostically relevant definition (as described in an article authored by Stone et al in *Circulation*²⁸) instead of the three-times ULN used in the 2007 definition in the PROTECT II trial.

Significantly, the Society of Cardiovascular Angiography and Intervention (SCAI) consensus document by Moussa et al²⁹ recommends using a 10-times ULN threshold for the definition of periprocedural MI, and the more recent FDA-approved EXCEL PCI trial utilizes this 10-times ULN definition.

In this new analysis, significantly lower MACCE rates—defined as the composite of death, stroke, clinically significant MI ($\geq$ eight-times ULN) and repeat revascularization—were observed in the Impella 2.5™ group at 90 days compared with the IABP (Figure 16, Table 7).²¹

Importantly, in this analysis, the use of the Impella 2.5 device was identified as an independent predictor of protection against MACCE events (odds ratio, 0.77; $P = .02$).²¹

Extent of Revascularization Plays a Key Role

The benefit of hemodynamic support was evaluated as a function of the extent of revascularization. Overall, more

extensive revascularization was associated with improved 90-day outcomes in terms of MACCE events compared to a more limited revascularization ($P < .01$) (Table 8).⁸ The use of Impella 2.5™ was also associated with improved clinical outcomes compared with the IABP when extensive revascularization was performed.⁸

OTHER SIGNIFICANT ANALYSES

Out-of-Hospital Course and Rehospitalization

Significantly fewer out-of-hospital, irreversible MAEs (composite of death/stroke/MI, 7.0% vs 12.9%; $P = .042$; 46% relative reduction)¹ and fewer readmissions for repeat revascularization (6.0% vs 12.4%; $P = .024$)¹ were observed in the Impella® arm compared with IABP at 90 days. Also, the overall median length of stay for care during the study was shorter for Impella patients compared with IABP patients (7 days vs 9 days; $P = .026$; 22% relative reduction),²³ driven primarily by more readmission days for IABP.

Functional Status and Quality of Life

Overall, patient cardiac function and functional status in both arms improved significantly after revascularization,

TABLE 5. COMPOSITE PRIMARY ENDPOINT OF MAEs AT 90 DAYS FOR PATIENTS WHO DID NOT UNDERGO ROTATIONAL ATHERECTOMY (N = 375)²⁷

Impella 2.5	IABP	P Value
35.5%	50.5%	.003

TABLE 6. COMPOSITE PRIMARY ENDPOINT OF MAEs AT 90 DAYS FOR PATIENTS WITH THREE-VESSEL DISEASE

Impella 2.5	IABP	P Value
39.5%	51.0%	.039

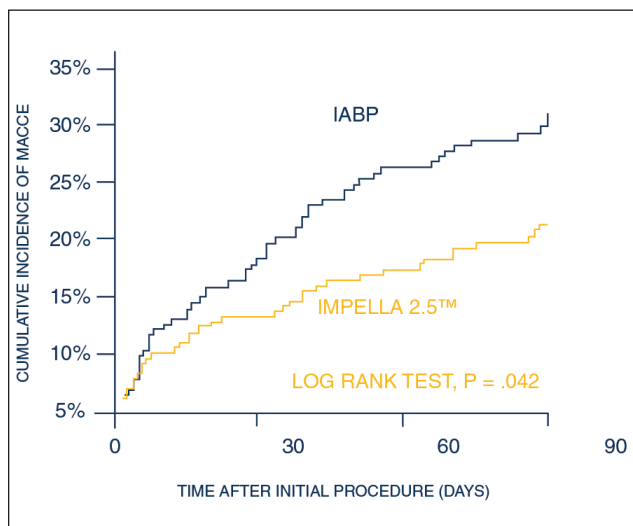


Figure 16. Post hoc analysis of the composite MACCE rates using a contemporary definition of periprocedural MI (eight-times ULN).²¹

confirming the benefit of PCI in this high-risk population. There was an average 22% increase in LVEF ($P < .001$) and a 58% reduction in the percent of patients remaining in NYHA functional class III/IV ($P < .001$) at 90 days.²³

CVAD REGISTRY™ SUPPORTS SAFETY AND EFFECTIVENESS

The cVAD/US Impella® registry* is a multicenter, retrospective registry with data from 49 sites in the United States and Canada. The data collected in the registry include institutional review board approval, complete data monitoring, adverse event definition per prior FDA-approved clinical trials, and clinical events committee adjudication.

As of January 2014, data have been collected in the registry for more than 1,300 patients implanted with the Impella family of devices over the previous 6 years. For this discussion, we have segregated the high-risk PCI population within the registry data. This unselected,

TABLE 7. COMPOSITE PRIMARY ENDPOINT OF MACCE AT 90 DAYS (N = 427)²¹

Impella 2.5	IABP	P Value
22%	31%	.033

TABLE 8. COMPOSITE PRIMARY ENDPOINT OF MACCE AT 90 DAYS WHEN EXTENSIVE REVASCULARIZATION WAS PERFORMED (N = 270)⁸

Impella 2.5	IABP	P Value
15.9%	28.5%	.013

nonrandomized HRPCL data from the registry (N = 637) support the safety and effectiveness determination. The registry data show:

- Patients undergoing high-risk PCI in routine practice are very sick and similar to PROTECT II patients with high-risk features, including a depressed LV function (mean LVEF, $30 \pm 16\%$) and a complex coronary anatomy likely excluding them as surgical candidates (mean STS, $6 \pm 6\%$)
- Impella during high-risk PCI provides adequate hemodynamic support with a significant increase in mean arterial pressure from baseline ($P < .001$)³⁰
- There is a consistent increase in the LVEF (LVEF, 31 ± 15 vs 36 ± 14 ; $P < .0001$) and a 52% reduction of NYHA class III/IV symptoms after discharge³⁰
- The use of Impella is safe in high-risk PCI—the risks for patients appear to be low and consistent with the PROTECT II results³⁰

IMPELLA® THERAPY IS COST-EFFECTIVE

According to the American Heart Association, cardiovascular disease is one of the most prevalent and costly disease categories, generating more than US \$300 billion in direct and indirect costs. Heart failure is also the leading reason for medical readmissions among the Medicare population, and approximately one of every four patients with acute heart failure is readmitted within 90 days of initial admission.

In multiple studies and economic models, Impella® therapy has demonstrated significant cost savings and cost effectiveness in reduced length of stay (Figures 17 and 18) and reduced readmissions from repeat procedures.^{22,23,31,32}

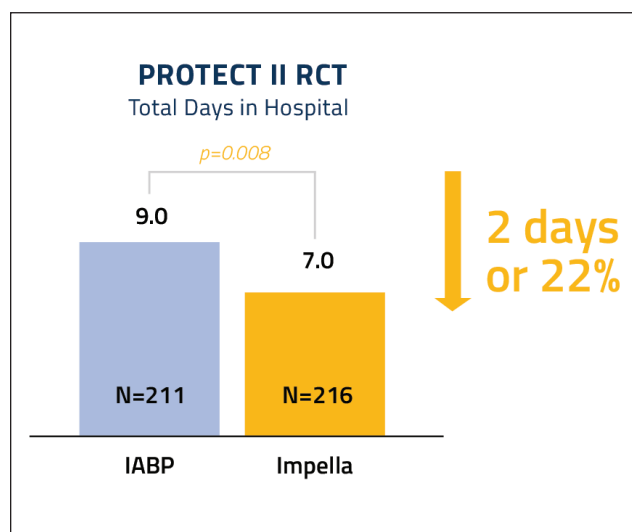


Figure 17. Reductions in hospital stay observed in the PROTECT II study.³²

*The US Impella® Registry has now grown into the global cVAD Registry™, which collects data from all Impella® products and indications.

CVAD REGISTRY™ DATA MIRROR REAL-WORLD RESULTS

New data published online in the *American Heart Journal* on August 15, 2015, authored by Mauricio Cohen, MD, and presented at Transcatheter Cardiovascular Therapeutics (TCT) 2015, reviewed the largest cohort of complex high-risk PCI patients supported by the Impella 2.5™ in real-world practice and in clinical trials. The data demonstrated that clinical trial results mirror real-world experience in the use of high-risk PCI with pVADs.

The objectives of the study were to describe the type of patients, procedural characteristics and outcomes of high-risk PCI supported with the Impella 2.5 in the United States and to compare these patients and procedures with the Impella arm of the PROTECT II trial. The researchers looked at retrospective data from the US Impella registry, analyzing 637 patients who met the criteria for the PROTECT II trial (LVEF ≤ 35% and intervention to the last patent conduit or UPLM, or LVEF ≤ 30% and three-vessel disease) who were treated at 47 US and two

Canadian sites between June 2007 and September 2013. All patients underwent PCI.

Among registry patients, 53.2% would have met the enrollment criteria for PROTECT II. Most had two-vessel disease, including 16% with left main disease. In routine practice, interventional cardiologists identified high-risk patients, with similar characteristics to the PROTECT II trial.

Results demonstrated that left ventricular function increased substantially from baseline to discharge in the registry group (21.4% to 28.4%; $P < .0001$). Assessment of NYHA class showed a 42.2% reduction from baseline to discharge in class III to IV symptoms in registry patients with available data ($P < .0001$) and a 27.8% reduction in PROTECT II trial participants ($P = .008$).

The article concluded that in this high-risk population, the use of Protected PCI™ with Impella 2.5 is associated with favorable outcomes with a relatively low incidence of adverse events.³³

Baseline Characteristics

	cVAD Registry All HRPCI Patients (n = 637)	PROTECT II "Like" Patients (n = 339)	PROTECT II Impella arm (n = 216)	P value*	P value†
Age (mean ± SD)	70.2 ± 11.5	69.6 ± 10.9	67.5 ± 11.0	.003	.03
Male gender	73.5%	79.1%	80.6%	.04	.67
Diabetes Mellitus	50.5%	49.4%	53.2%	.49	.38
PVD	30.2%	31.7%	25.4%	.18	.14
Previous stroke	9.7%	8.7%	12.0%	.356	.253
Chronic kidney disease	31.3%	30.0%	22.7%	.02	.06
NHYA Class III or IV	70.3%	77.6%	67.4%	.53	.04
Prior MI	51.6%	56.5%	69.3%	< .001	.003
Prior CABG	29.6%	30.2%	39.4%	.008	.03
Surgical consultation	48.8%	50.8%	45.4%	.38	.22
LV EF (mean ± SD)	30.1 ± 18.1	21.6 ± 7.7	23.4 ± 6.3	< .001	.004
STS PROM	5.9 ± 6.4	6.0 ± 6.0	5.8 ± 6.0	.86	.64

* P value comparing all cVAD Registry patients to the Impella 2.5 arm of the PROTECT II trial

† P value comparing the subset of cVAD Registry patients who met PROTECT II eligibility criteria to the patients in the Impella 2.5 arm of the PROTECT II trial.

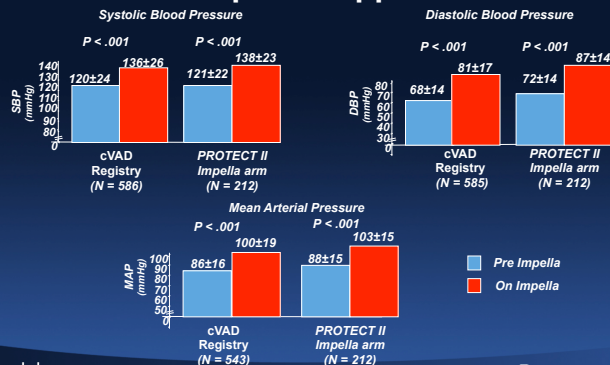
Procedural Characteristics

	cVAD Registry All HRPCI Patients (n = 637)	PROTECT II "Like" Patients (n = 339)	PROTECT II Impella arm (n = 216)	P value*	P value†
Diseased vessels (mean ± SD)	2.20 ± 0.91	2.22 ± 0.86	1.78 ± 0.72	< .001	< .001
Significant lesions (mean ± SD)	3.10 ± 1.65	3.07 ± 1.52	2.73 ± 1.42	.002	.009
Treated vessels (mean ± SD)	1.82 ± 0.59	1.82 ± 0.60	1.81 ± 0.67	.82	.75
Number of vessels treated					
1 vessel	28.4%	28.2%	33.8%	.14	.17
2 vessels	61.5%	61.3%	51.9%	.01	.03
3 vessels	10.1%	10.5%	14.4%	.09	.18
Lesions treated (mean ± SD)	2.47 ± 1.25	2.48 ± 1.23	2.88 ± 1.44	< .001	< .001
Stents placed (mean ± SD)	2.21 ± 1.14	2.24 ± 1.10	3.08 ± 1.78	< .001	< .001
SVG intervention	10.3%	11.3%	12.5%	.37	.66
Rotational atherectomy use	18.1%	16.4%	14.8%	.280	.630
Duration of support (mean ± SD)	2.24 ± 6.19	2.35 ± 6.91	1.86 ± 2.71	.384	.327

* P value comparing all cVAD Registry patients to the Impella 2.5 arm of the PROTECT II trial

† P value comparing the subset of cVAD Registry patients who met PROTECT II eligibility criteria to the patients in the Impella 2.5 arm of the PROTECT II trial.

Hemodynamic Improvement On Impella Support



Uspella → cVAD Registry

- Multicenter, observational registry designed to include **all Impella patients** at all participating sites
- Established initially as the **USpella Registry** in 2009 and uses electronic data collection (EDC) since August 2011
- Patient source documents and imaging films are collected and 100% of data are verified for accuracy
- 100% in-hospital outcomes collected
- Currently more than 2,655 patients enrolled, 47 participating sites, 19 new sites are being activated and Impella RP will be added



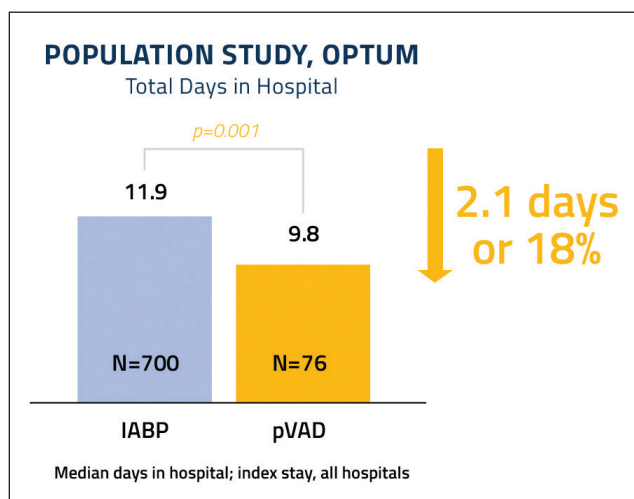


Figure 18. Reductions in hospital stay observed in OPTUM population-based study.²²

By providing support to the failing heart sooner with the minimally invasive Impella devices, clinicians are able to ensure that patients have better outcomes, and providers and payers avoid the longer-term cost outlays associated with alternative resource-intensive therapies and open heart procedures.²²

The PROTECT II economic study concluded that for patients with severe LV dysfunction and complex anatomy, Impella-assisted PCI significantly reduced major adverse events at an incremental cost per quality-adjusted life year (QALY) considered to be cost-effective for advanced cardiovascular technologies (\$39,000/QALY).²¹

In the 90 days following initial hospitalization, Impella patients experienced:

- Two fewer days in the hospital ($P = .001$)²¹
- A 52% reduction in hospitalizations due to repeat revascularization ($P = .024$)²¹
- 50% lower rehospitalization costs compared with the IABP ($P = .023$)²¹

A recent study of national trends in the utilization of pVADs and other short-term mechanical support by Stretch et al³⁰ observed a correlation between increased utilization of pVADs and decreased costs. A systematic review by Maini et al³¹ appraised the findings of six cost-effectiveness studies of pVADs. Length of stay reductions were observed in all studies, with a clinically relevant observation of fewer days in the intensive care unit, fewer days from readmissions, and 2 fewer days in the hospital over 90 days.

CURRENT CLINICAL EXPERIENCE

The Impella 2.5™ is routinely used in a variety of clinical settings to support patients at risk of hemodynamic instability in connection with elective or urgent PCIs.

GUIDELINES REFERENCING THE IMPELLA 2.5 DEVICE, INCLUDING:

- The American College of Cardiology
- The American Heart Association
- The Society for Cardiac Angiography and Interventions

More than 3,000 physicians worldwide have used the technology to support more than 40,000 patients. The device is approved in Europe (2004), Canada (2007), Latin and South Americas (2008-2012), and China (2013) for a variety of indications, including high-risk PCI.

In the United States, the device has been used since 2006, beginning with the PROTECT I FDA-approved trial for high-risk PCI. It has been used commercially since 2008 under a 510(k) clearance. As noted previously, Impella 2.5 was granted PMA in 2015 as safe and effective for use in certain patients. As the PMA states, the indicated use of the device includes the treatment of elective or urgent hemodynamically stable patients with severe CAD and depressed LVEF.

The FDA has determined that the use of the Impella 2.5 in connection with these patients may result in a reduction of peri- and postprocedural adverse events typically accompanying this kind of procedure.

Since the United States market introduction of Impella in 2008, more than 1,000 hospitals have supported more than 30,000 patients. In the past decade, a relatively large body of evidence has been generated through prospective clinical trials, unselected nonrandomized investigations and more than 215 peer-reviewed publications, making Impella one of the most studied circulatory support devices on the market. ■

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Impella 2.5™ Support During Left Main Coronary Artery Stenting and Transcatheter Occlusion of a Left Internal Mammary Artery Bypass Graft in a Patient With Severe Congestive Heart Failure

BY NEERAJ BADHEY, MD; SUBHASH BANERJEE, MD; AND EMMANOUIL S. BRILAKIS, MD, PhD

KEY CLINICAL ISSUES

- Successful use of hemodynamic support in a challenging case involving a patient with comorbidities of CHF, renal insufficiency, and critical stenoses of the LMCA and LAD
- PCI reinfusion where a LIMA graft had inadvertently been placed on the great cardiac vein in a previous surgery

A 64-year-old man was admitted with unstable angina and severe congestive heart failure (CHF) 3 months after an apparently uncomplicated coronary artery bypass graft (CABG) revascularization.

The CABG procedure was nonemergent after angiographic evaluation and identification of a 90% ostial stenosis of the left main coronary artery (LMCA) and significant stenotic disease (90%) proximal to the first diagonal branch of the left anterior descending coronary artery (LAD). The patient had a nondominant right coronary artery (RCA), with the posterior descending coronary artery (PDA) originating from the circumflex coronary artery (Cx). During the previous CABG procedure, the left internal mammary artery (LIMA) graft was believed to have been placed to the LAD, one reversed saphenous vein graft (SVG) was placed to the obtuse marginal (OM) branch of the Cx, and a second SVG was placed to the left PDA. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) at readmission revealed depressed left and right ventricular systolic function and right ventricular dilatation compared to the

results of TTE and TEE performed prior to CABG.

Coronary angiography (Figure 1) determined that the LIMA graft had inadvertently been placed on the great cardiac vein, resulting in a left-to-right shunt and biventricular high output failure/CHF. The LAD was devoid of coronary flow, the SVG to the left PDA was occluded, and the SVG to the OM was widely patent.

Renal insufficiency and CHF were considered high-risk factors for complications during a repeat CABG, therefore a percutaneous coronary intervention (PCI) was deemed most appropriate.

PROCEDURE DESCRIPTION

Temporary left ventricular support with the Impella 2.5™ cardiac assist system (Abiomed, Inc.) was

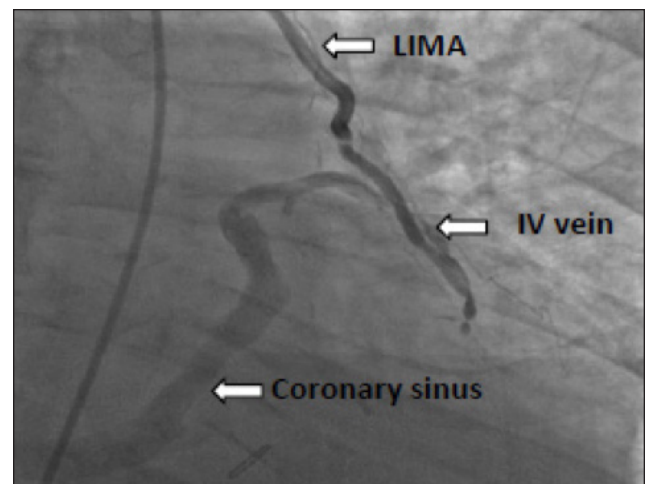


Figure 1. Angiogram of the LIMA graft to the great interventricular vein with drainage into the coronary sinus.

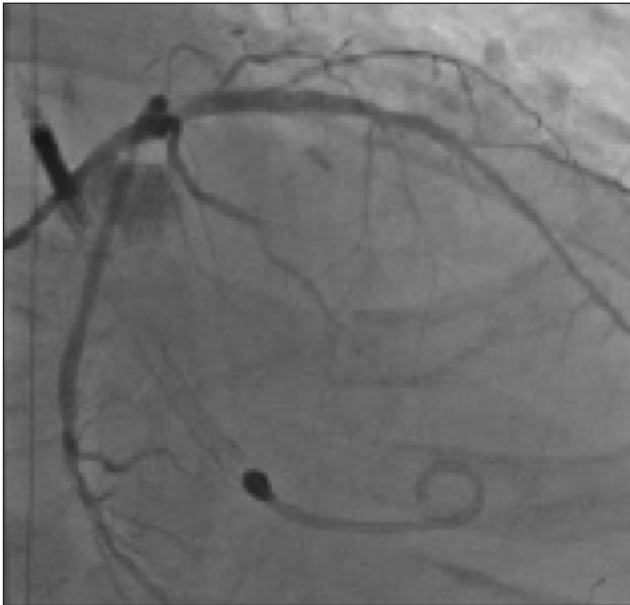


Figure 2. Excellent angiographic result after drug-eluting stent deployment.

indicated due to the CHF combined with the intention to perform unprotected LMCA stenting and transcatheter occlusion of the LIMA to the cardiac vein.

The Impella 2.5 catheter was positioned in the left ventricle and actuated to provide antegrade flow throughout the various phases of the PCI and transcatheter embolization procedure. The mid and proximal LAD and the LMCA were sequentially stented with drug-eluting stents, with an excellent angiographic result (Figure 2). A 6-mm Amplatzer™ Vascular Plug II (St. Jude Medical, Inc.) was deployed in the distal LIMA. Antegrade flow was significantly less, and the procedure was ended assuming thrombosis of the vascular plug would result in total occlusion of the LIMA (Figure 3).

PATIENT FOLLOW-UP

The Impella 2.5™ catheter was removed without complication, and the femoral access site was closed. The patient was discharged the next day.

Repeat angiography performed 1 week later showed persistent antegrade LIMA flow. Biventricular function had improved significantly with left ventricular EF estimated at 70%. A second embolization procedure was indicated, however, cardiac support for the second procedure was not warranted based on the satisfactory hemodynamic status of the patient. The Proxis™ embolic protection system catheter (St. Jude Medical, Inc.) was used to occlude the LIMA graft, while a second 4-mm Amplatzer Vascular Plug II was deployed proximal to the previously placed 6-mm plug. Antegrade flow into

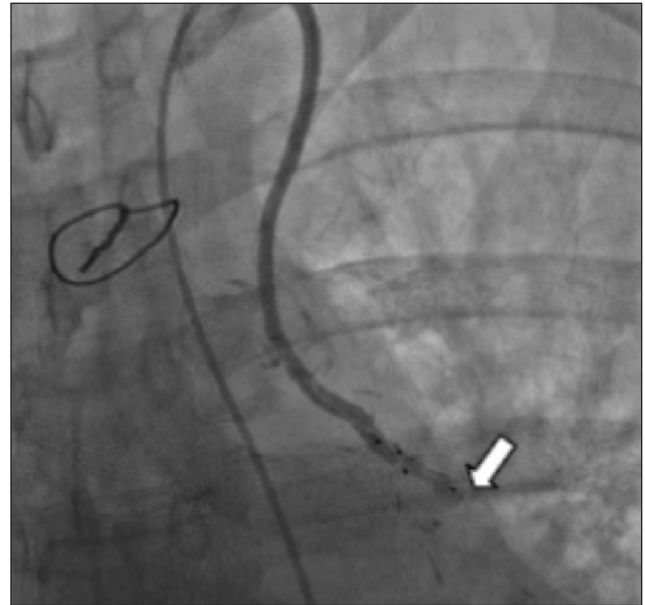


Figure 3. Final angiogram with no residual antegrade flow into the coronary sinus.

the coronary sinus was minimal. The patient had an uneventful recovery with subsequent complete resolution of CHF symptoms and return of normal renal function.

DISCUSSION

This unusual and exceptionally challenging case illustrates the use of the Impella 2.5™ cardiac assist system to provide critical left ventricular support during a high-risk PCI in a patient with comorbidities of CHF, renal insufficiency, and critical stenoses of the LMCA and LAD.

The Impella 2.5 device maintained a mean arterial blood pressure of 80 to 90 mm Hg throughout the 1-hour PCI procedure that included unprotected LMCA stenting, LAD stenting, and transcatheter occlusion of the LIMA graft. Cardiac output was augmented by 2 to 2.25 L/min during the interval of Impella support and the procedure was completed without complication.



Figure 4. The Impella 2.5™ catheter.

DEVICE DESCRIPTION

The Impella 2.5™ microaxial blood pump is percutaneously placed in the left ventricle to provide up to 2.5 liters per minute of nonpulsatile blood flow into the aorta. The pump is inserted through a 13-F sheath placed in the femoral artery, and the 9-F catheter body is passed across the aortic valve to position the inflow port in the left ventricle, with the outflow port and axial flow pump in the ascending aorta (Figure 4). ■

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Impella 2.5™ Support During Complex PCI in a Patient With Recent Acute Systolic Heart Failure and Residual Low Ejection Fraction

BY MARK A. GRISE, MD; TYRONE J. COLLINS, MD; AND SAMIR N. PATEL, MD

KEY CLINICAL ISSUES

- Successful high-risk coronary intervention of the LAD coronary artery and RCA in a patient with significant coronary artery disease and confounding cardiac dysfunction
- Effective use of hemodynamic support to protect the patient despite heart block and resulting asystole
- Maintenance of near-normal systemic blood pressure during three PCI procedures

A 77-year-old woman presented to the catheterization laboratory at Ochsner Heart and Vascular Institute with signs of acute systolic heart failure. Her history and diagnosis included current obesity, diabetes mellitus, hypertension, and dyslipidemia.

On coronary angiography (Figures 1 and 2), the left ventricular ejection fraction (EF) was 25%, down from 60% as measured 1 year previously. There was a high-grade lesion of 95% in the mid left anterior descending (LAD) artery. The right coronary artery (RCA) was severely diseased in both the proximal and mid portions. Cardiac enzymes were positive, including a peak troponin of 15. Four hours after angiography, the patient experienced asystolic arrest and was resuscitated by advanced cardiac life support.

A cardiac surgery consult determined that the patient's low EF, recent history of cardiac arrest, and other comorbidities made her an unacceptable candidate for surgical revascularization. She was subsequently maintained on mechanical ventilation, intravenous inotropic therapy, and intra-aortic balloon pump (IABP) support in the cardiac care unit for several days before being successfully extubated and weaned from IABP support. After the patient was stabilized, the decision was made to proceed with a percutaneous coronary

intervention (PCI) supported with the Impella 2.5™ circulatory support system (Abiomed, Inc.).

PROCEDURE DESCRIPTION

Thirteen days after her asystolic arrest, the stabilized patient returned to the catheterization laboratory for an Impella-supported, high-risk PCI. The Impella 2.5™ device was inserted percutaneously via the left femoral artery, and support was started on performance level 7 (P-7), with axial pump output flow of 2 to 2.1 L/min. The proximal LAD was predilated and subsequently stented with an excellent angiographic result (Figure 3).

After placement of a 0.014-inch guidewire in the RCA, the patient developed complete heart block. The heart block lasted for longer than 2 minutes, during which time Impella support was increased to P-9 with forward flows of 2.3 L/min. The patient remained conscious during the episode of complete heart block; although she had no pulsatile

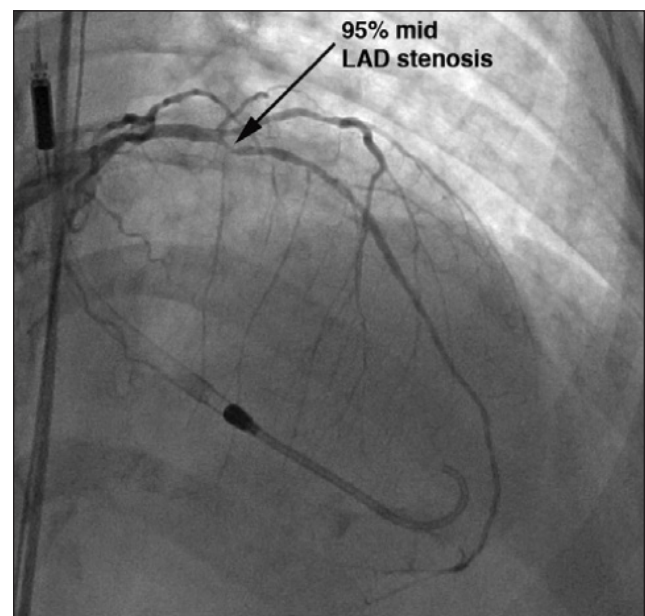


Figure 1. High-grade mid LAD stenosis.

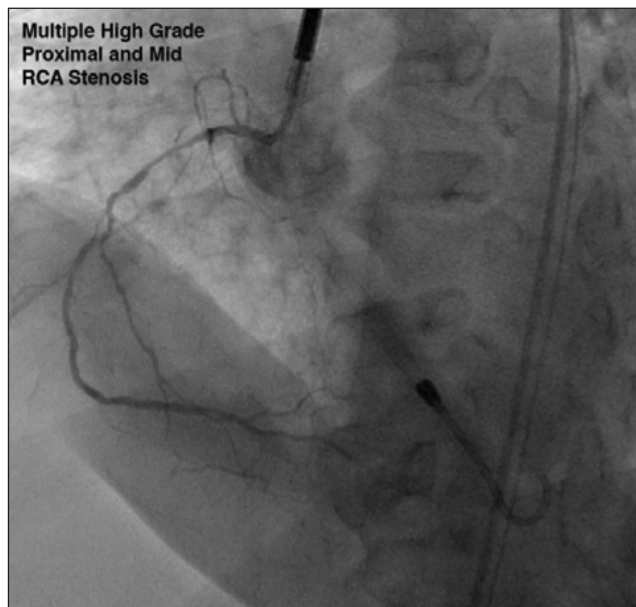


Figure 2. Multiple high-grade proximal and mid RCA stenoses.

flow, her mean arterial blood pressure was maintained at 50 mm Hg by the Impella 2.5 device. With the return of sinus rhythm, atropine was administered, and her heart rate and blood pressure quickly normalized. The proximal and mid RCA lesions were each subsequently stented with a drug-eluting stent (DES) without arrhythmia onset or sudden drop in blood pressure during the PCI (Figure 4).

PATIENT FOLLOW-UP

After completion of the PCI procedures, the patient was weaned from Impella circulatory support, the device

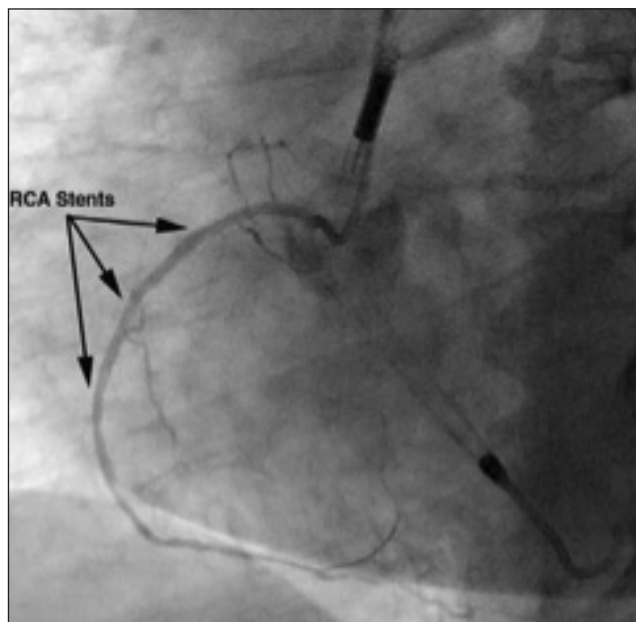


Figure 4. RCA after stent placement.

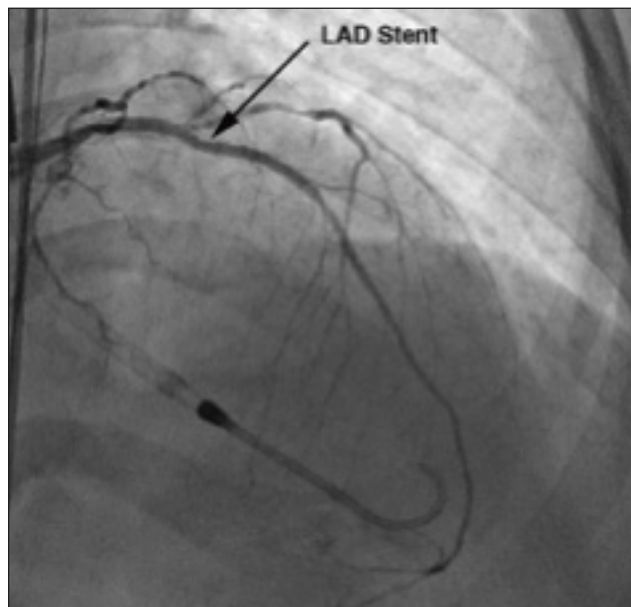


Figure 3. LAD after stent placement.

was removed, and the access site was closed with a suture-based closure device. The patient's clinical condition improved significantly over the next 24 hours, and she was subsequently discharged.

DISCUSSION

This patient with significant coronary artery disease and confounding cardiac dysfunction underwent a successful high-risk coronary intervention of the LAD coronary artery and RCA with placement of a DES at each lesion. The entire procedure was performed with the support of the Impella 2.5™ circulatory support system.

Maintenance of near-normal systemic blood pressure during three PCI procedures prevented hemodynamic compromise and was especially important during the 2-minute interval of cardiac arrest.

This case demonstrates the feasibility and ease of use of the Impella 2.5 device during high-risk, complex PCIs. The most striking aspect of this case was the support afforded the patient at the time of her heart block and resulting asystole. Despite the asystolic episode, she



Figure 5. The Impella 2.5™ catheter.

remained completely lucid and appeared to suffer no deleterious effects from this event.

While supported by the Impella 2.5, the patient remained stable and never exhibited any sign of distress. On restoration of cardiac rhythm, the revascularization procedures were completed with excellent angiographic and physiologic outcomes. Without the vital support provided by the Impella 2.5 device, the procedural outcome might have been appreciably worse.

DEVICE DESCRIPTION

The Impella 2.5™ microaxial blood pump is percutaneously placed in the left ventricle to provide up to 2.5 L/min

of nonpulsatile blood flow into the aorta. The pump is inserted through a 13-F sheath placed in the femoral artery, and the 9-F catheter body is passed across the aortic valve to position the inflow port in the left ventricle, with the outflow port and axial flow pump in the ascending aorta (Figure 5). ■

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Impella 2.5™ Supported Multivessel PCI With Left Main Stenting in the Setting of NSTEMI With Severe LV Dysfunction

BY C. DAVID JOFFE, MD, FACC, AND JACOB B. GIBSON, DO

KEY CLINICAL ISSUES

- Significant myocardial revascularization without complications in the setting of complex anatomic disease not amenable to CABG with angina and severe cardiac disease
- Effective use of hemodynamic support based on the following factors:
 - Patient status: advanced age
 - Complex multilesion, multivessel coronary artery disease with ongoing angina
 - Severe disease of distal left main and proximal Cx, totally occluded LAD, severe disease of the large OM branch of the Cx

A 74-year-old man presented to the emergency department with syncope preceded by chest pressure. He developed chest pressure and nausea, followed by a second syncopal episode. The discomfort continued after he regained consciousness, and he presented to the emergency room for evaluation. The patient had a history of severe coronary artery disease. He had undergone coronary artery bypass graft (CABG) procedures twice. The initial CABG in 1999 was for the left internal mammary artery (LIMA) to the left anterior descending (LAD) artery, saphenous vein graft (SVG) to the diagonal branches of the LAD artery, and SVG to the circumflex coronary artery (Cx). CABG was redone in 2007 involving an SVG jump graft to the posterior lateral branch and posterior descending artery (PDA) of the right coronary artery (RCA) for inferior wall myocardial infarction (MI) and cardiogenic shock. The redo procedure was complicated by right ventricular laceration during sternotomy.

The patient also had a history of ischemic cardiomyopathy, chronic systolic congestive heart failure without recent decompensation, long-standing type II diabetes mellitus, hypertension, and hyperlipidemia.

The initial cardiovascular workup revealed an elongated troponin I level at 0.678 ng/mL (< 0.034). The results of an EKG showed old inferior wall MI with minimal ST depression and no evidence of acute injury.

The patient was treated via non ST-segment elevation MI (NSTEMI) protocol and received clopidogrel, acetylsalicylic acid, metoprolol, atorvastatin, and insulin therapy. He was started on IV nitroglycerin, IV heparin, and IV eptifibatide. With medical therapy, the patient was completely pain free and feeling much better.

The next day, cardiac catheterization (Figures 1 and 2) showed severe disease of the distal left main and proximal Cx. The LAD was totally occluded. Right anterior oblique

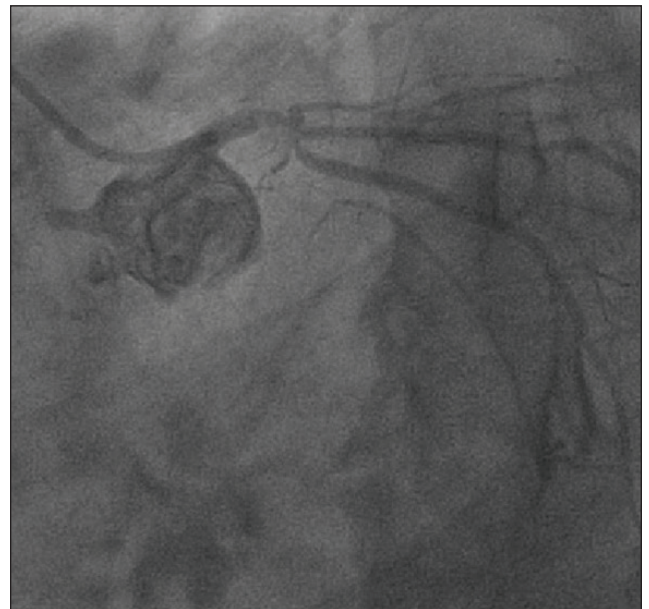


Figure 1. Severe disease of the distal left main and proximal Cx and totally occluded LAD.



Figure 2. Severe disease of large OM branch of Cx.

caudal projection showed severe disease of the large obtuse marginal (OM) branch of the Cx. There was severe distal disease of the RCA, patent SVG to the posterior lateral branch and PDA, dilated left ventricle (LV) with severe inferior wall hypokinesis, moderate hypokinesis of remaining segments, and severe LV systolic dysfunction with an ejection fraction of 30%.

The patient developed angina during the night after the diagnostic catheterization. In consultation, the cardiovascular surgery team believed that the patient was too high-risk for repeat surgery given the severe disease, severe LV dysfunction, ongoing angina, limited conduits, and history of right ventricular laceration. The findings were discussed with the patient, and the decision was



Figure 4. The Impella 2.5 circulatory support system catheter.

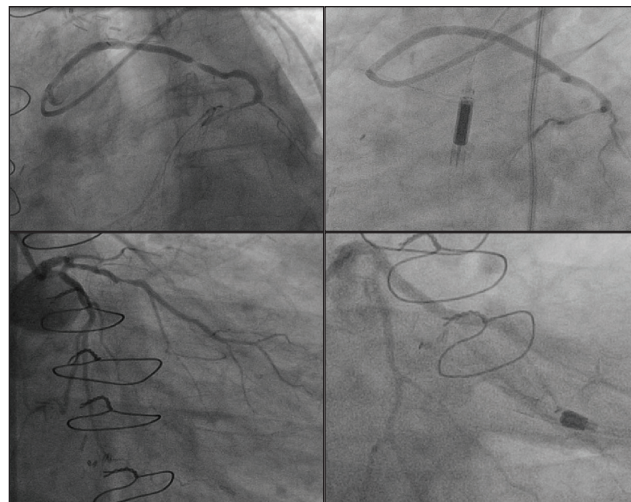


Figure 3. Final results were excellent.

made for high-risk, multivessel PCI with Impella 2.5™ system support (Abiomed, Inc.).

PROCEDURE DESCRIPTION

Circulatory support kept the patient hemodynamically stable during a complex, multivessel revascularization procedure. Imaging of the left iliac and common femoral arteries showed tortuosity but no significant peripheral vascular disease. The Impella 2.5™ catheter was placed without difficulty via the femoral artery. Coronary stents were placed in the proximal and distal SVG lesions. A coronary stent was placed in the mid OM, and balloon dilation was performed in the LM in the ostial Cx. A coronary stent to the LM was placed into the ostial OM. The Impella catheter was weaned and removed without difficulty prior to leaving the cath lab.

PATIENT FOLLOW-UP

The patient made a full recovery and is free of chest pain. He was discharged to home in stable condition.

DISCUSSION

This was a successful Impella-supported, high-risk, multivessel PCI in the setting of NSTEMI with severe LV dysfunction (Figure 3). Despite multiple runs of nonsustained ventricular tachycardia during the case, there were no hemodynamic consequences due to Impella support.

DEVICE DESCRIPTION

The Impella 2.5™ microaxial blood pump is percutaneously placed in the LV to provide up to 2.5 liters per minute of nonpulsatile blood flow into the aorta. The pump is inserted through a 13-F sheath placed in the femoral artery,

and the 9-F catheter body is passed across the aortic valve to position the inflow port in the left ventricle, with the outflow port and axial flow pump in the ascending aorta (Figure 4). ■

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INDICATION FOR USE

THE IMPELLA 2.5 SYSTEM IS A TEMPORARY (< 6 HOURS) VENTRICULAR SUPPORT DEVICE INDICATED FOR USE DURING HIGH RISK PERCUTANEOUS CORONARY INTERVENTIONS (PCI) PERFORMED IN ELECTIVE OR URGENT, HEMODYNAMICALLY STABLE PATIENTS WITH SEVERE CORONARY ARTERY DISEASE AND DEPRESSED LEFT VENTRICULAR EJECTION FRACTION, WHEN A HEART TEAM, INCLUDING A CARDIAC SURGEON, HAS DETERMINED HIGH RISK PCI IS THE APPROPRIATE THERAPEUTIC OPTION. USE OF THE IMPELLA 2.5 IN THESE PATIENTS MAY PREVENT HEMODYNAMIC INSTABILITY WHICH CAN RESULT FROM REPEAT EPISODES OF REVERSIBLE MYOCARDIAL ISCHEMIA THAT OCCUR DURING PLANNED TEMPORARY CORONARY OCCLUSIONS AND MAY REDUCE PERI- AND POST-PROCEDURAL ADVERSE EVENTS.

WARNINGS AND CONTRAINDICATIONS

THE IMPELLA 2.5 IS CONTRAINDICATED FOR USE WITH PATIENTS EXPERIENCING ANY OF THE FOLLOWING CONDITIONS: (1) MURAL THROMBUS IN THE LEFT VENTRICLE; (2) MECHANICAL AORTIC VALVE OR HEART CONSTRICTIVE DEVICE; (3) AORTIC VALVE STENOSIS/CALCIFICATION (EQUIVALENT TO AN ORIFICE OF 0.6 CM² OR LESS); (4) MODERATE TO SEVERE AORTIC INSUFFICIENCY (ECHOCARDIOGRAPHIC ASSESSMENT OF AORTIC INSUFFICIENCY GRADED AS $\geq$ +2); AND (5) SEVERE PERIPHERAL ARTERIAL DISEASE THAT PRECLUDES THE PLACEMENT OF THE IMPELLA® 2.5

ADDITIONALLY, POTENTIAL FOR THE FOLLOWING RISKS HAS BEEN FOUND TO EXIST WITH USE OF THE IMPELLA 2.5: ACUTE RENAL DYSFUNCTION; AORTIC INSUFFICIENCY; AORTIC VALVE INJURY; ATRIAL FIBRILLATION; BLEEDING; CARDIOGENIC SHOCK; CARDIAC TAMPONADE; CARDIOPULMONARY RESUSCITATION; CEREBRAL VASCULAR ACCIDENT/STROKE; DEATH; DEVICE MALFUNCTION; FAILURE TO ACHIEVE ANGIOGRAPHIC SUCCESS; HEMOLYSIS; HEPATIC FAILURE; INSERTION SITE INFECTION; LIMB ISCHEMIA; MYOCARDIAL INFARCTION; NEED FOR CARDIAC, THORACIC, OR ABDOMINAL OPERATION; PERFORATION; RENAL FAILURE; REPEAT REVASCULARIZATION; RESPIRATORY DYSFUNCTION; SEPSIS; SEVERE HYPOTENSION; THROMBOCYTOPENIA; THROMBOTIC VASCULAR (NON-CNS) COMPLICATION; TRANSIENT ISCHEMIC ATTACK; VASCULAR INJURY; VENTRICULAR ARRHYTHMIA, FIBRILLATION OR TACHYCARDIA

