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.

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. During PCI, contrast dye injections, balloon inflations, atherectomy passes, and stent manipulations temporarily interrupt blood flow in the target coronary artery, which can reduce the force of the heart’s contractions. This is generally well tolerated. 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.

According to a recent report by The Advisory Board Company, 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.

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
VICE PRESIDENT OF INTERVENTIONAL CARDIOLOGY PROGRAMS
ABIOMED, INC.

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*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 irreversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events.

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. (Courtesy of The Advisory Board Company.)
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. 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 benefit 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. These conditions may not be consistently present in the critically ill patient.

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. 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. Also, because the Impella 2.5 technology delivers superior hemodynamic support compared to the IABP, it often allows the interventional cardiologist to perform a more complete revascularization in a single session, which can result in better outcomes.

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.

The Impella device provides both an active forward flow and systemic aortic pressure contribution, 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. Combined with left ventricle unloading, Impella support reduces end-diastolic volume and pressure and augments peak coronary flow, 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 and validated in computational modeling, as well as a variety of preclinical and clinical studies.

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.
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.²⁷

**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
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).

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>
<thead>
<tr>
<th>Table 1. Summary of Clinical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Evidence</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>PROTECT I</td>
</tr>
<tr>
<td>PROTECT II</td>
</tr>
<tr>
<td>cVAD Registry™</td>
</tr>
<tr>
<td>Literature review (N = 215)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
</tr>
</tbody>
</table>
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.

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 ± 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™ PROEDURE 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; \( P = .001 \)). Impella also provided superior hemodynamic support for patients

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

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

* 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.
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; \( P < .001 \)), 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 enrollment.\(^{1,26} \) 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...
(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 Cardiology21 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 Circulation28) 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 (> 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,
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.

**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, nonrandomized HRPCI 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 ± 16%) and a complex coronary anatomy likely excluding them as surgical candidates (mean STS, 6 ± 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 discharge\(^{10}\)
- The use of Impella is safe in high-risk PCI—the risks for patients appear to be low and consistent with the PROTECT II results\(^{30}\)

**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.\(^{22,23,31,32}\)

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

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**Table 7. Composite Primary Endpoint of MACCE at 90 Days (N = 427)**\(^{21}\)

<table>
<thead>
<tr>
<th>Impella 2.5</th>
<th>IABP</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>22%</td>
<td>31%</td>
<td>.033</td>
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</tbody>
</table>

**Table 8. Composite Primary Endpoint of MACCE at 90 Days When Extensive Revascularization Was Performed (N = 270)**\(^{8}\)

<table>
<thead>
<tr>
<th>Impella 2.5</th>
<th>IABP</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.9%</td>
<td>28.5%</td>
<td>.013</td>
</tr>
</tbody>
</table>

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\(^{*}\) The US Impella® Registry has now grown into the global CVAD Registry™, which collects data from all Impella® products and indications.
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

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**CVAD REGISTRY™ DATA MIRROR REAL-WORLD RESULTS**

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**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>cVAD Registry</th>
<th>PROTECT II * arm</th>
<th>PROTECT II arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>70.2 ± 11.5</td>
<td>65.6 ± 10.9</td>
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</tr>
<tr>
<td>Male gender</td>
<td>73.5%</td>
<td>91.4%</td>
<td>80.6%</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>50.6%</td>
<td>45.4%</td>
<td>53.2%</td>
</tr>
<tr>
<td>PVD</td>
<td>30.2%</td>
<td>21.4%</td>
<td>25.4%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>20.7%</td>
<td>12.0%</td>
<td>35.6%</td>
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<tr>
<td>Chemical injury</td>
<td>31.5%</td>
<td>20.6%</td>
<td>29.7%</td>
</tr>
<tr>
<td>NYHA Class III on 2</td>
<td>72.5%</td>
<td>77.7%</td>
<td>67.4%</td>
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<tr>
<td>Prior MI</td>
<td>51.8%</td>
<td>66.6%</td>
<td>69.3%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>29.8%</td>
<td>35.9%</td>
<td>33.7%</td>
</tr>
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<td>Surgical consultation</td>
<td>48.8%</td>
<td>50.8%</td>
<td>45.4%</td>
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<tr>
<td>STEB PROM</td>
<td>5.9 ± 6.4</td>
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<td>5.8 ± 6.0</td>
</tr>
</tbody>
</table>

**Procedural Characteristics**

<table>
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<th>cVAD Registry</th>
<th>PROTECT II * arm</th>
<th>PROTECT II arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease vessels</td>
<td>2.20 ± 0.91</td>
<td>2.22 ± 0.66</td>
<td>1.78 ± 0.72</td>
</tr>
<tr>
<td>Significant lesions</td>
<td>3.19 ± 1.65</td>
<td>3.07 ± 1.52</td>
<td>2.73 ± 1.42</td>
</tr>
<tr>
<td>Total vessels</td>
<td>1.92 ± 0.59</td>
<td>1.82 ± 0.60</td>
<td>1.81 ± 0.67</td>
</tr>
<tr>
<td>Vessels treated</td>
<td>10.1%</td>
<td>10.1%</td>
<td>14.0%</td>
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<tr>
<td>Lesions treated</td>
<td>2.41 ± 1.25</td>
<td>2.46 ± 1.33</td>
<td>2.68 ± 1.34</td>
</tr>
<tr>
<td>Stents placed</td>
<td>2.21 ± 1.14</td>
<td>2.24 ± 1.10</td>
<td>3.03 ± 1.78</td>
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<td>SVS intervention</td>
<td>10.3%</td>
<td>11.1%</td>
<td>12.9%</td>
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<td>Rotational atherectomy use</td>
<td>18.1%</td>
<td>16.4%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Duration of support</td>
<td>2.24 ± 1.19</td>
<td>2.35 ± 0.91</td>
<td>1.86 ± 0.71</td>
</tr>
</tbody>
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**Uspsella → 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
POPULATION STUDY, OPTUM
Total Days in Hospital

<table>
<thead>
<tr>
<th></th>
<th>IABP</th>
<th>pVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>11.9</td>
<td>9.8</td>
</tr>
<tr>
<td>N</td>
<td>700</td>
<td>76</td>
</tr>
</tbody>
</table>

p=0.001

2.1 days or 18%

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 al.10 observed a correlation between increased utilization of pVADs and decreased costs. A systematic review by Maini et al.31 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 America (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 $10(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.

Seth Bilazarian, MD, FACC, FSCAI, is Vice President of Interventional Cardiology Programs for Abiomed, Inc. Dr. Bilazarian may be reached at sbilazarian@abiomed.com.

8. Abiomed. Data submitted for FDA pre-market approval (PMA) of Impella 2.5 high-risk PCI indication.


