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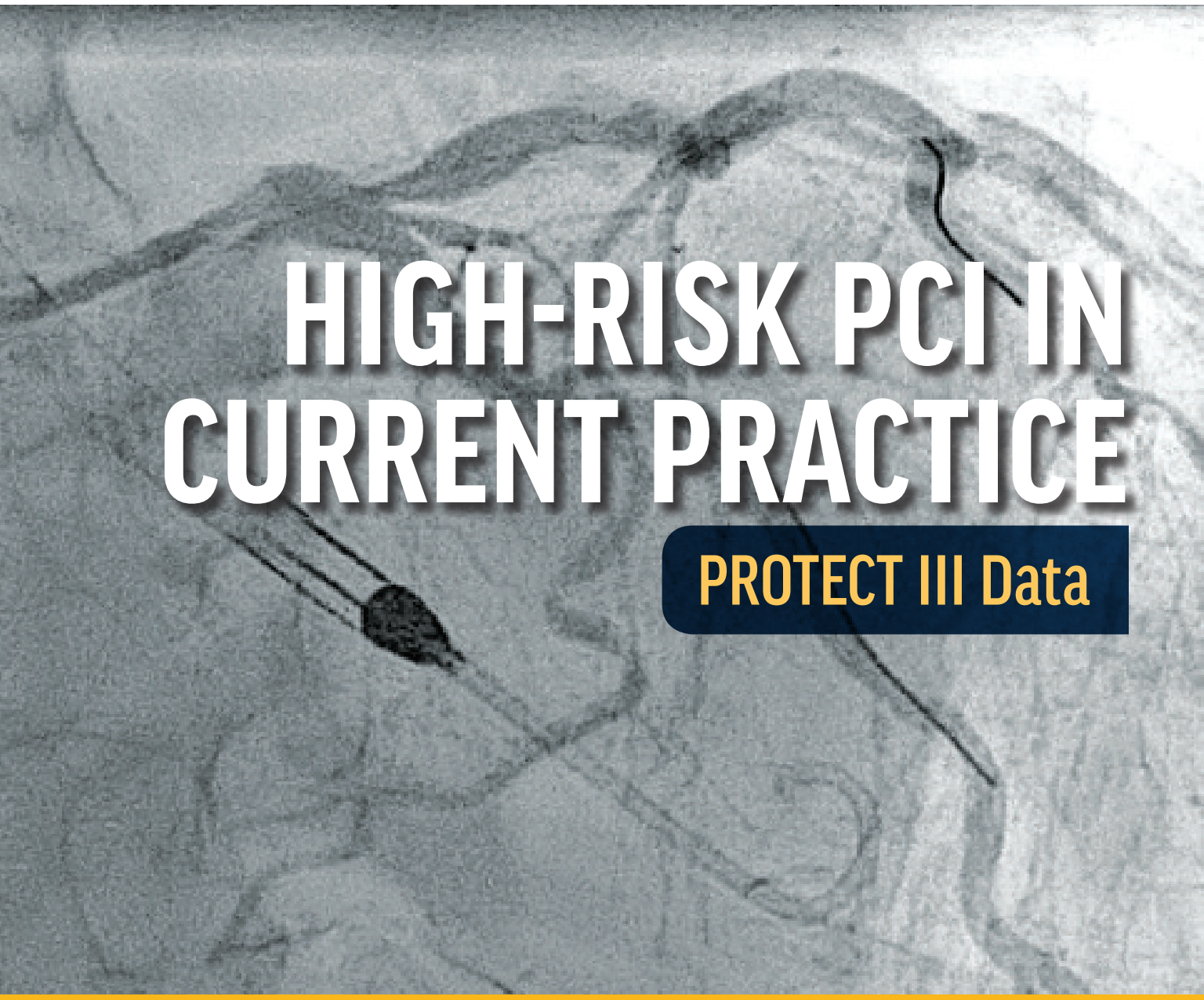
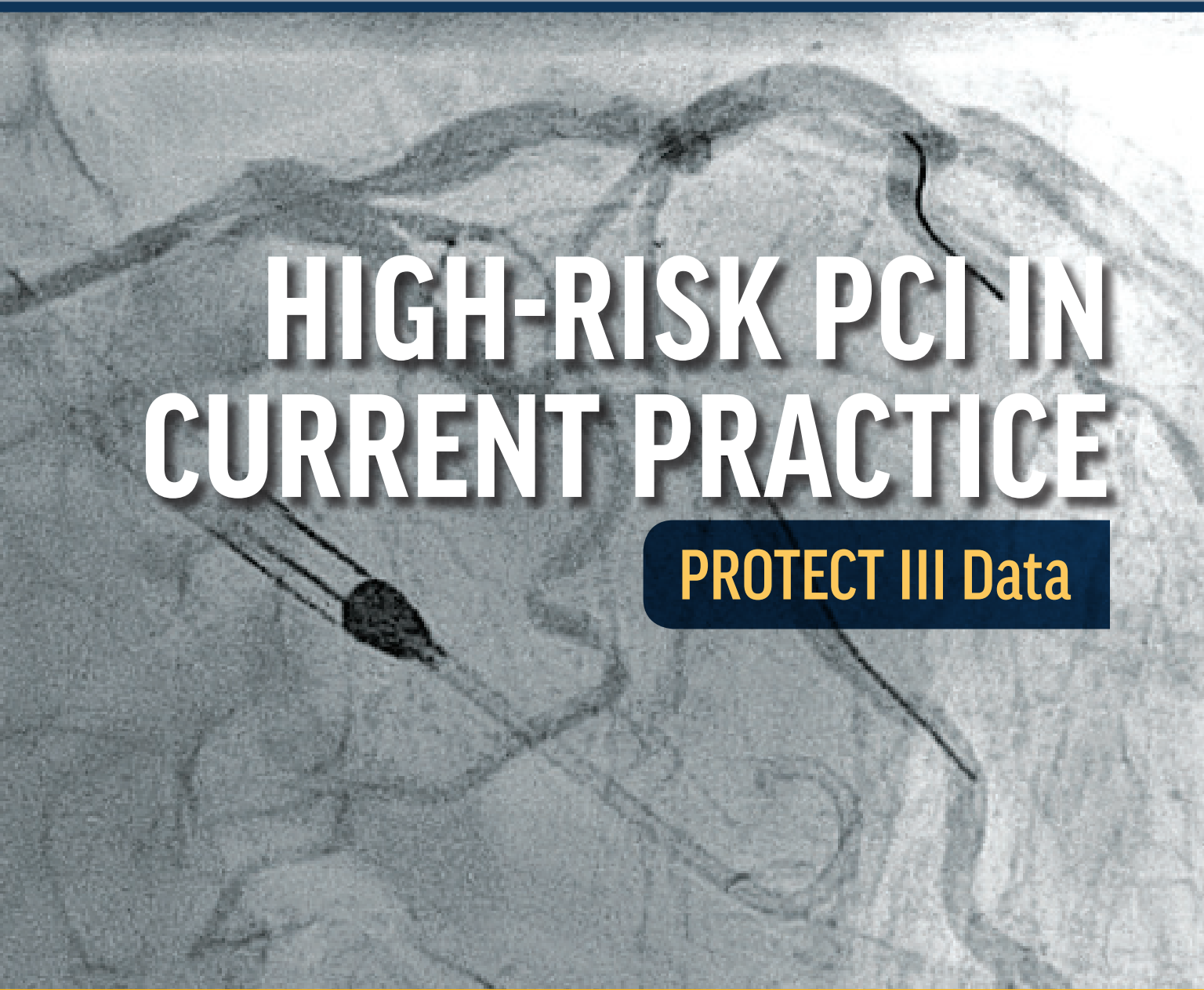


HIGH-RISK PCI IN CURRENT PRACTICE

PROTECT III Data

Impella®



HIGH-RISK PCI IN CURRENT PRACTICE

PROTECT III Data

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Current PCI Landscape and Opportunities for Improvement

An overview of the landscape, contemporary data, quality measures, and technologic trends that will guide complex CAD cases toward complete revascularization.

BY GEORGE W. VETROVEC, MD, MACC, MSCAI

Cardiovascular disease is a leading cause of death, claiming more lives each year than cancer and chronic lung disease combined, and accounts for approximately 15% of total United States health care expenditures.[1] Estimated direct costs of cardiovascular disease in the United States has increased from $103.5 billion in 1997 to $213.8 billion in 2015 and are projected to continue to increase between now and the year 2035.[1]

The rate of hospital readmission after percutaneous coronary intervention (PCI) is currently 8% to 17%.[2,3] Conservatively, this means 114,600 patients are readmitted to the hospital within 30 days of their procedure, with 25% of patients readmitted within 6 months after PCI.[2,3] An examination of recent data describing outcomes after PCI demonstrates an opportunity to achieve better quality outcomes and is discussed here.

PATIENTS ARE CURRENTLY UNDERTREATED

Although the National Inpatient Sample reports approximately 955,000 PCI procedures are performed on approximately 700,000 patients in the United States each year,[4] there is a large population of severe, symptomatic coronary artery disease (CAD) patients either not treated or "undertreated" due to increased risk of acute kidney injury (AKI), hemodynamic compromise, or comorbidities that prevent them from receiving treatment. The recently reported ISCHEMIA trial excluded high-risk populations, such as those with left main disease, significantly compromised left ventricular ejection fraction, and severely symptomatic patients. Despite similar survival in the lower-risk patients in this trial, questions remain about the impact of completeness of revascularization and potential late risk of myocardial infarction for medically treated patients.[5] Furthermore, PCI was associated with greater symptomatic benefits, particularly in the most symptomatic patients.[6] Two-thirds of heart failure (HF) patients have significant CAD. Despite this, Doshi et al[7] and O'Connor et al[8] reported that most patients admitted to the hospital for new-onset HF are not receiving testing for ischemic CAD either during their hospitalization or within 90 days before or after. Among 17,185 patients with new-onset HF, only 6,672 (39%) were tested, most with left ventricular ejection fraction ≤ 40%.[7,8] The low frequency of diagnosis leads to undertreatment of CAD patients, with or often without HF, and presents an opportunity to revisit our strategy and protocols for optimized patient care.

THE IMPORTANCE OF COMPLETE REVASCULARIZATION

Given that nearly 25% of all PCI procedures are for left main and multivessel disease, revascularization strategies are an important factor in achieving the best possible clinical outcomes. For many of these complex patients, complete revascularization in a single setting may pose patient safety issues due to renal dysfunction, contrast required, or operator fatigue.

Nearly 7% of all PCI patients have AKI,[9] with high-risk PCI patients being at an even greater risk. AKI is associated with a 10% in-hospital mortality, which increases to 34% when dialysis is required.[9] Due to concerns regarding renal insufficiency, staging has become an accepted approach and occurs in approximately 14% of patients,[10] typically those at high risk or with renal dysfunction.

While staging may limit total contrast administered, complete revascularization in a single setting often leads to a shorter hospital stay and eliminates the inertia to bring patients back for a second procedure, all supporting a more "surgery-like" result. Complete revascularization in a single setting is associated with a 30% to 50% reduction in major adverse cardiac and cerebrovascular events (MACCE) (Figure 1).[11-14] Incomplete revascularization, which occurs in as much as 45% of all high-risk PCI procedures, has been shown to have a detrimental impact on post-PCI survival.[11,12,15,16]

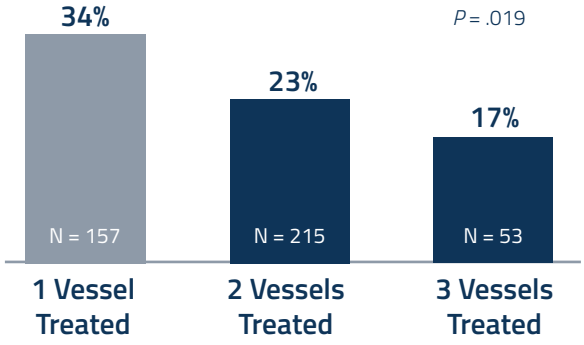

Figure 1. MACCE at 90 days. From PROTECT II clinical study (IABP and Impella arms, all patients).[13]

Improvements in PCI treatment strategies are needed to ensure complete and optimized revascularization with less renal risk. This presents an opportunity to achieve better long-term clinical outcomes with the benefits of a single procedure.

TOOLS TO IMPROVE PCI OUTCOMES

Despite broad availability, advanced techniques designed to improve PCI outcomes remain underutilized (Table 1). Drug-eluting stents have achieved broad adoption and, when combined with ancillary antiplatelet therapy, may provide better outcomes for unprotected left main disease, particularly in high-risk patients.[17] Other technologies, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), both designed to provide information about CAD plaque that aids in stent sizing and optimal stent expansion, are only used in approximately 15% of PCI procedures despite proven ancillary benefit.[18,19] Atherectomy is used in approximately 5% of PCI procedures nationwide but is more broadly adopted in high-risk cases (14%-30%)[15,20-22] and, in the PROTECT III study in which atherectomy was used in conjunction with the Impella® heart pump (Abiomed, Inc.), in 43% of the cases.[23] Given the low MACCE of 16.8% in PROTECT III (Figure 2), the clinical benefit of atherectomy plus Impella suggests PCI outcomes could be further optimized with this approach.

ADDRESSING ENHANCED COMPLETE REVASCULARIZATION

The Impella heart pump enhances cardiac flow by providing continuous-flow hemodynamic support to unload the left ventricle. Its mechanism of action may provide renal protection against AKI or drastically reduce the severity of renal injury, enabling complete revascularization in a single setting.

TABLE 1. CURRENT PCI OUTCOMES

Total US PCI Patients Per Year	Outcomes
~101,000	▪ **45% have IR (23.5% of 955,000 PCIs are left main or multivessel)** ▪ 30%–50% reduction in MACCE with complete revascularization vs IR
~133,700	▪ **14% of PCI are patients staged** ▪ Not all staged patients return for the second procedure
~66,850	▪ **7% of PCI patients have AKI** ▪ 50% of high-risk PCI patients are at significant risk of AKI ▪ AKI has a 10% in-hospital mortality rate that increases to 34% if dialysis is required
~114,600	▪ **8%–17% of patients are readmitted within 30 days for cardiovascular issues** ▪ 25% of patients are readmitted within 6 months after PCI
~165,100	▪ **17% AMI cardiogenic shock/other forms of shock** ▪ NCSI best practice protocol survival is 72%, with 98% native heart recovery ▪ INOVA SHOCK health system protocol survival is 77%
~52,400	▪ **5% of PCI procedures include coronary atherectomy** ▪ 14%–30% of all high-risk PCI procedures
~19,100	▪ **2% of all PCI procedures include Impella hemodynamic support** ▪ Impella-protected PCI procedures in 2018 (elective, urgent, emergent)

Abbreviations: AKI, acute kidney injury; AMI, acute myocardial infarction; IR, incomplete revascularization; MACCE, major adverse cardiac and cerebrovascular events; NCSI, National Cardiogenic Shock Initiative; PCI, percutaneous coronary intervention; US, United States.

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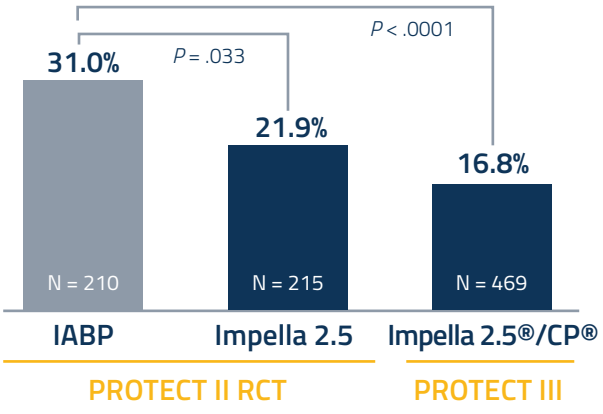

Figure 2. PROTECT III outcomes compared to PROTECT II. Composite MACCE at 90 days. RCT, randomized controlled trial.

The Global cVAD Renal Protection Study, the most comprehensive analysis to date assessing the impact of the Impella heart pump on renal function, reported an AKI incidence rate of 4.9% at 48 hours compared with the predicted AKI rate of 22% (Mehran risk scoring), a 77.6% risk reduction (Figure 3).[24] The renal protection from Impella was most effective in patients with the highest baseline risk score.[24]

Similarly, in a retrospective, single-center study in which 230 patients undergoing high-risk PCI received either Impella support or no hemodynamic support, the incidence of AKI was significantly lower in patients with Impella support (5.2% vs 27.8%; $P < .001$).[25] Furthermore, Impella patients were significantly more complex based on a higher frequency of nonsurgical candidates with a higher incidence of three-vessel disease (47% vs 31%), longer procedure times (148 min vs 121 min), and a higher median volume of contrast.[25]

Although current guidelines recommend AKI prevention protocols and use of the Impella heart pump has shown a sixfold reduction in AKI requiring dialysis in high-risk PCI, it is significantly underutilized, with only a small percentage of PCI patients in the United States receiving Impella support. It is suspected that even high-volume complex PCI hospitals using Impella in 10% to 20% of their high-risk cases may still be underutilizing hemodynamic support.

The use of hemodynamic support during PCI for high-risk patients, such as those with a low ejection fraction, renal insufficiency, and/or complex anatomy, helps maintain hemodynamic stability, which enables a more efficient and complete revascularization.[26]

THE IMPORTANCE OF IMPELLA SUPPORT IN IMPROVING SHOCK OUTCOMES

Over the past decade, advances in PCI and the initiation of treatment protocols have resulted in a dramatic decrease in deaths due to acute myocardial infarction (AMI). However, treatment of AMI complicated by cardiogenic shock has been slow to change and is considered by many to be the "last frontier" for ST-segment elevation myocardial infarction.

Approximately 165,000 patients present with cardiogenic shock each year, often with multivessel disease, and many are not yet treated based on accepted protocols. Of these cardiogenic shock patients, approximately 52,000 are treated with an intra-aortic balloon pump (IABP).[4] The significant use of IABP is surprising given it has a class III recommendation in both Europe and Japan, and its use in many countries is decreasing over recent years. However, use in the United States has remained relatively constant at approximately 52,000, despite a lack of clinical benefit in the IABP-SHOCK II trial.[27] However, the use of Impella for cardiogenic shock, as well as Protected PCI, amounts to only half the IABP cases at 23,500 per year,[28] and despite its proven clinical benefit(s), continues to be significantly underutilized.

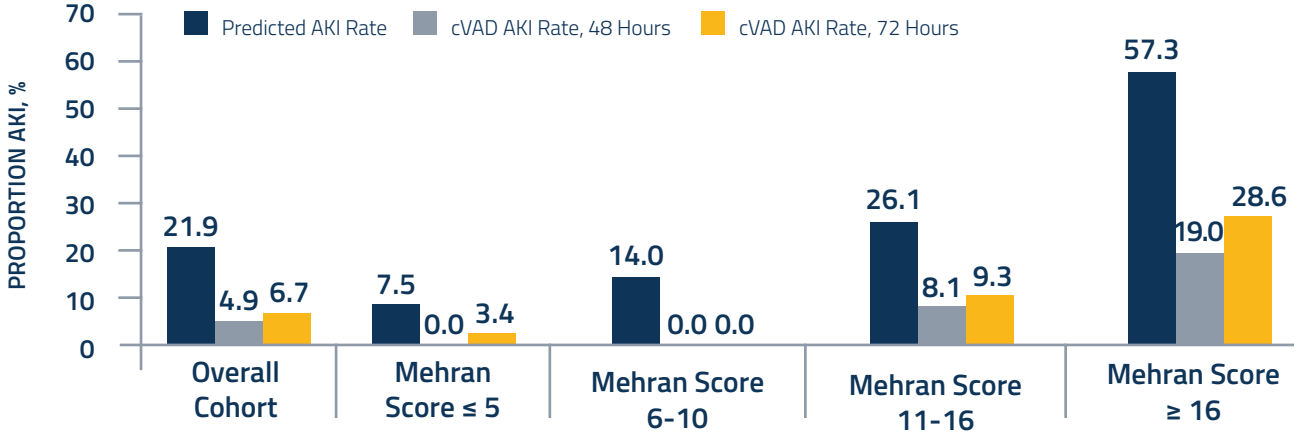

Figure 3. Incidence of AKI based on increasing Mehran risk score severity.

CONCLUSION

The current PCI landscape is often inconsistent with regard to the extent of screening for high-risk CAD, in which case revascularization (particularly complete revascularization) could significantly improve patient symptoms and quality of life, and could potentially increase survival. Technology has increased in terms of stents, coronary imaging, and hemodynamic support to allow safer high-risk PCI. Unfortunately, the application of these technologies is often incomplete, limiting the opportunity to provide high-quality nonsurgical revascularization to patients without other options. This incomplete adoption represents a major challenge to educate and encourage optimal CAD management. ■

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Evolving Evidence for Protected PCI With Impella® to Treat High-Risk Complex CAD Patients

PROTECT clinical studies consistently demonstrate MACCE reduction at 90 days.

BY SETH BILAZARIAN, MD, FACC, FSCAI

High-risk intervention is associated with increased morbidity and approximately twofold mortality as compared to patients receiving percutaneous coronary interventions (PCIs).[1,2] The criteria as to what defines high risk are still being debated; however, there is consensus that this category of patients includes candidates unsuitable for surgical revascularization due to high-risk clinical presentation, comorbidity, anatomic complexity, or a combination thereof.[3] Even though revascularization may be recommended for these patients per current guidelines and appropriate use documents,[4] PCI is less likely to be offered in the setting of high surgical risk.[5,6] High-risk PCI requires longer procedure time and is associated with an increased risk of hemodynamic instability and increased risk for intraprocedural and postdischarge adverse events, including cardiac arrest,[7,8] which also limits the patient's ability to tolerate interventions required to achieve durable and complete revascularization.

HEMODYNAMIC SUPPORT AND COMPLETE REVASCULARIZATION

Complete revascularization is associated with significantly lower rates of major adverse cardiovascular events (MACE; $P < .001$), myocardial infarction (MI) ($P = .0007$), and revascularization ($P < .001$) as compared with incomplete revascularization.[9,10] In addition, revascularization procedures conducted in a single session result in significantly fewer major adverse cerebral and cardiovascular events (MACCE; $P = .004$) and deaths ($P = .006$) compared to staged PCI procedures.[11] The use of hemodynamic support during PCI in patients with high-risk complex coronary artery disease (CAD) helps maintain hemodynamic stability, which enables complete revascularization.[12] Apart from providing hemodynamic stability, an ideal device should increase coronary perfusion, decrease myocardial oxygen consumption, increase cardiac microvascular perfusion, and bridge through myocardial stunning resulting from ischemia during PCI.[13-15]

The Impella heart pump (Abiomed, Inc.) assists the unloading of the left ventricle, increases coronary perfusion pressure, increases mean arterial pressure, and optimizes end-organ perfusion.[16] Impella provides a flow rate ranging from 2.5 L/min to 5.5 L/min, depending on the device and selected performance level, and can be placed either percutaneously or via surgical cutdown in the axillary or femoral artery. A Protected PCI is a PCI supported by the Impella Heart Pump and is indicated for high-risk, complicated CAD patients with or without depressed left ventricular (LV) systolic function. Impella is the most studied mechanical circulatory support device in the history of the FDA, with more than 1,350 patients in the PROTECT clinical studies (PROTECT I, II, and III).

PROTECT I was a prospective, single-arm, multicenter feasibility study of 20 patients that examined the safety and feasibility of the Impella 2.5® device. None of the patients developed hemodynamic compromise during PCI with Impella support. The study demonstrated that Impella 2.5 provides hemodynamic support during high-risk PCI and is safe and easy to implant.[17]

PROTECT II was a prospective, multicenter, randomized trial that compared Impella 2.5 with an intra-aortic balloon pump (IABP) in patients requiring hemodynamic support during elective or urgent high-risk PCI.[18] PROTECT II is the only FDA randomized controlled trial conducted for hemodynamically supported high-risk PCI. The study enrolled 452 patients at 112 sites in the United States and European Union. The primary efficacy endpoint was a composite of 10 major adverse events: death, stroke/transient ischemic attack, MI, repeat revascularization, need for cardiac or vascular operation, acute renal dysfunction, cardiopulmonary resuscitation or ventricular arrhythmia

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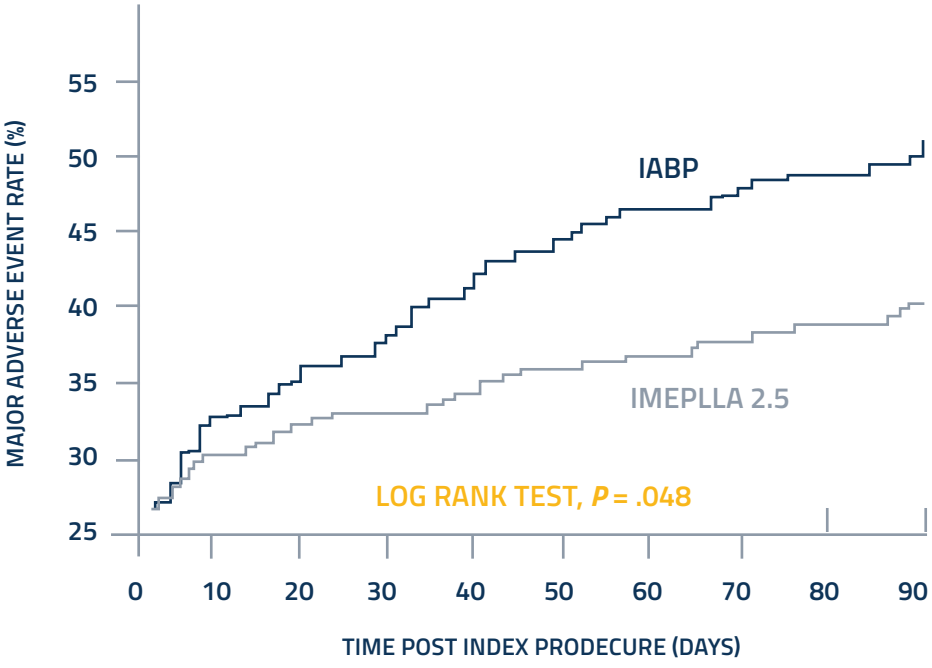

Figure 1. Kaplan-Meier curves for major adverse events. Composite of the primary endpoint up to 90 days.

requiring cardioversion, increase in aortic insufficiency by more than one grade, severe hypotension, and failure to achieve angiographic success. The multiple safety endpoints, including this primary endpoint, allowed for a comprehensive evaluation of Impella's safety profile at 30 days, with a follow-up analysis at 90 days (both prespecified). The primary endpoint analysis showed a significant reduction in major adverse events (MAE) at 90 days (40% vs 51%; *P* = .023) (Figure 1) as compared to the IABP.[18]

Other studies from the PROTECT II data set have shown that Impella 2.5 is associated with improved clinical outcomes as compared to IABP at 90-day follow-up:

- 44% lower MACCE (composite of death, stroke, MI, and repeat revascularization) (15.9% vs 28.5%; *P* = .013) (Figure 2)[19]
- 22% reduction in MAE (39.5% vs 51.0%; *P* = .039) for patients with three-vessel disease and impaired LV function[20]
- 90% reduction in repeat revascularization in patients undergoing rotational atherectomy (3.1% vs 30%; *P* = .006)[21]
- Impella support resulted in similar 30-day mortality in patients with and without previous coronary artery bypass grafting (CABG)[22]

Based on data from PROTECT I, II, and the ongoing cVAD study, FDA granted Impella a first-of-its-kind indication for high-risk PCI patients.[23] Further data collected as part of postmarket approval study, inside the cVAD study were presented as PROTECT III during the Transcatheter Cardiovascular Therapeutics (TCT) annual meeting in September 2019.[24]

PROTECT III

PROTECT III is an ongoing, prospective, single-arm FDA postapproval study of Impella (2.5 and CP®) in high-risk PCI.[24] The patient population is comparable to the PROTECT II study population. In the interim analysis presented at TCT 2019, 571 Impella CP and 327 Impella 2.5 patients from 45 sites in the United States were enrolled from March 2017 to July 2019. The endpoints were compared with the IABP and the Impella arms from PROTECT II.

In PROTECT III, an analysis of the echocardiography and angiography data was performed by independent core labs, and an independent clinical events committee adjudicated adverse events. The primary endpoint was MACCE at 90 days: death, stroke, MI, and repeat revascularization. PROTECT III included patients with significantly higher baseline and procedural risks. Patients in the PROTECT III study group were older (70.9 vs 67.5 years; *P* < .001), and

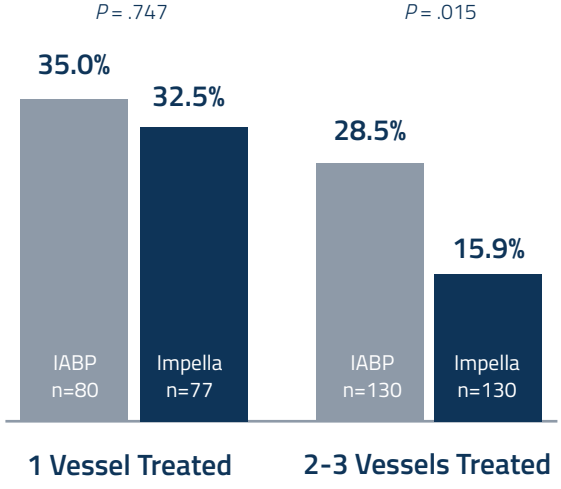

Figure 2. PROTECT II Study FDA premarket approval data of unprotected left main included in two or three vessels.

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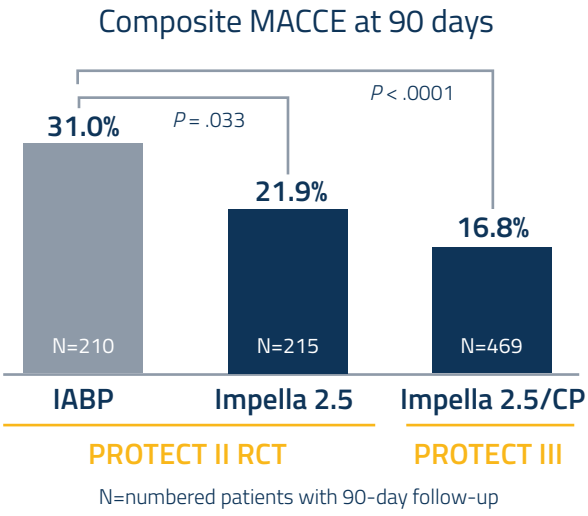

Figure 3. PROTECT III outcomes compared to PROTECT II.

more women were treated (26.3% vs 19.4%; *P* = .044) as compared to the PROTECT II group. However, LV ejection fraction (LVEF) was lower in the PROTECT II patients when compared to the PROTECT III cohort (23.4% vs 32.3%; *P* < .001). This was due to the expansion of the FDA indication to include patients without depressed ejection fraction. Patients in the PROTECT III group had worse angiographic characteristics with more left main disease (15.7% vs 11.5%; *P* = .011) and more pre-PCI TIMI 0/1 (14.7% vs. 7.0%; *P* < .001) as compared to the PROTECT II group. Impella support resulted in physicians treating a greater number of vessels (2.0 vs 1.81; *P* < .001), more triple-vessel revascularization (29.9% vs 14.4%; *P* < .001), more atherectomy use (43.3% vs 14.2%; *P* < .001), and a greater number of vessels treated with atherectomy (2.01 vs 1.44; *P* < .001) as compared to the PROTECT II group.

The results showed that Protected PCI with Impella decreased MACCE events by 54% in the PROTECT III cohort as compared to the IABP cohort in the PROTECT II trial (16.8% vs 31%; *P* < .001) (Figure 3).

The PROTECT III interim results validate the results of the PROTECT II randomized controlled trial in real-world clinical practice. A subgroup analysis of PROTECT III demonstrated that Impella support also reduced the incidence of acute kidney injury (5.7% vs 24.5%; *P* = .0002) as compared to a control group of patients who did not receive Impella support.[22,23] Other recent studies show similar renal protection benefits due to Impella support.[25-27]

COST-EFFECTIVENESS

In multiple studies and economic models, Protected PCI with Impella has demonstrated significant cost savings and cost-effectiveness with reduced length of stay and reduced readmissions from repeat procedures.[28-30] By providing support to the failing heart sooner, clinicians can improve patient outcomes and avoid the longer-term costs associated with alternative resource-intensive therapies and open heart procedures.[28]

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) and is considered to be cost-effective for advanced cardiovascular technologies ($39,000/QALY).[28] In the 90 days after initial hospitalization, Impella patients experienced:

- Two fewer days in the hospital (*P* = .001)[28]
- A 52% reduction in hospitalizations due to repeat revascularization (*P* = .024)[28]
- 50% lower rehospitalization costs compared to IABP (*P* = .023)[28]

The cost-effectiveness demonstrated with Impella is consistent with a study of national trends in the utilization of percutaneous ventricular assist devices (pVADs) (including Impella), and other short-term mechanical support, by Stretch et al who observed a correlation between increased utilization of pVADs and decreased costs.[30] A systematic review by Maini et al appraised the findings of six cost-effectiveness studies of pVADs.[29] 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 two fewer days in the hospital over 90 days (Figure 4).

INDICATIONS FOR PROTECTED PCI

The initial FDA approval for high-risk PCI using the Impella Heart Pump was based on several clinical studies, including PROTECT I and PROTECT II, which enrolled patients undergoing elective and urgent PCI who had advanced comorbidities and the most severe LV dysfunction. 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 patients deemed ineligible for CABG. Based on these studies, low EF was initially a requirement for indicated use of Impella with high-risk PCI. However, through the FDA-audited ongoing multicenter, prospective cVAD registry, data were evaluated, analyzed, and presented to the FDA demonstrating that depressed systolic function is only one of many factors that defines the high-risk patient. Patients with complex coronary anatomy or in whom complex procedures are planned (eg, use of ablative technologies such as directional, rotational, orbital, or laser atherectomy), extensive comorbidities including

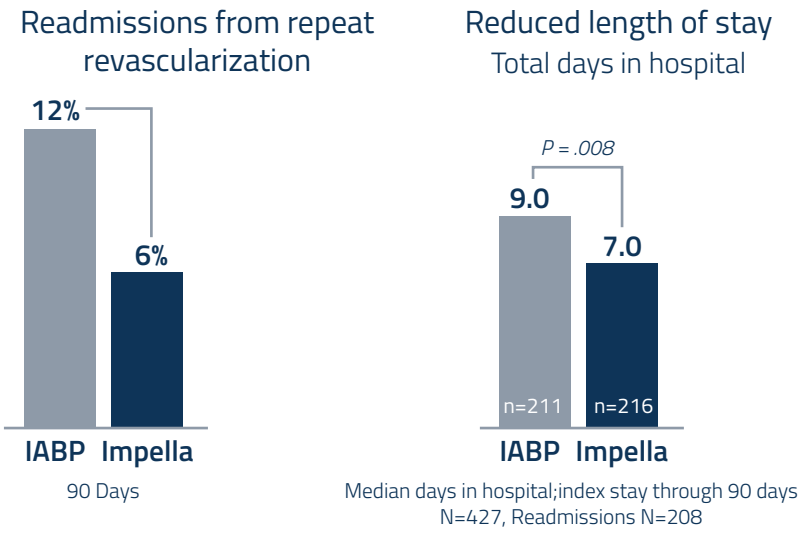

Figure 4. Length of stay reductions observed in PROTECT II randomized controlled trial[13] and Optum population-based study.

surgical ineligibility, or those at risk for hemodynamic collapse can also be considered high risk and may benefit from a Protected PCI procedure. Based on data from the cVAD Registry, the FDA granted approval to expand the indications for the Impella Heart Pump, eliminating depressed EF as a requirement for on-label use of Impella in Protected PCI. With this postmarket approval, patients with or without depressed LV systolic function in the presence of severe CAD or complex anatomy (eg, left main, multivessel, requiring atherectomy) may be appropriate when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option.

The data supporting this expanded indication included an analysis of 229 consecutive patients with mild to moderately reduced EF. In this cohort, most of the patients were ineligible for CABG due to surgical risk factors. On average, these patients were older, more often female, and had significantly more lesions treated and left main intervention than patients in the cVAD registry cohort with an EF < 35% (n = 464). This comparison demonstrated that high-risk PCI with Impella support was feasible, safe, and achieved favorable outcomes in patients with mild to moderately reduced EF.

SOCIETY GUIDELINES SUPPORT IMPELLA IN HIGH-RISK PCI

Intersocietal clinical guidelines (American College of Cardiology, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons) agree the Impella Heart Pump may be beneficial for technically challenging lesions or for prolonged PCI in patients.[3] The Interventional Scientific Council of the American College of Cardiology has also published a consensus document detailing the recommended approach to percutaneous mechanical circulatory support in patients undergoing high-risk PCI.[31]

CONCLUSION

High-risk PCI presentation is growing and despite the recommendation for percutaneous revascularization, these patients have less chance of receiving PCI due to suboptimal hemodynamic support. Impella allows the heart to rest, providing coronary and peripheral perfusion, enabling the physician to perform a more complete and optimized revascularization. The PROTECT II randomized control trial demonstrated that in high-risk patients, Impella support reduced MACCE at 90 days compared to patients on an IABP. PROTECT III utilizes prospectively collected data representing modern clinical practice for high-risk PCI. Despite a worse procedural and angiographic profile, as compared to the PROTECT II patient population, the clinical outcomes in PROTECT III show a reduction in MACCE compared to the IABP arm and validate the results seen in the PROTECT II study. Results from the PROTECT clinical studies consistently demonstrate a reduction in MACCE at 90 days after Protected PCI with the Impella Heart Pump. ■

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Renal Protection During Impella®-Supported PCI in Patients With High-Risk Complex Coronary Artery Disease

BY MICHAEL P. FLAHERTY, MD, PHD, FACC, FSCAI

Acute kidney injury (AKI) after percutaneous coronary intervention (PCI) is associated with a higher risk of acute myocardial infarction, increased bleeding, extended length of stay, increased cost, and up to a 12-fold increased risk of mortality.[1-3] AKI rates after PCI are a quality metric that may impact overall reimbursement. Patients with complex coronary artery disease are at increased risk of AKI due to coexisting risk factors (older age, gender, left ventricular [LV] ejection fraction [LVEF], chronic kidney disease, acute coronary syndrome, etc), longer procedure times with greater contrast volume, and associated hemodynamic instability. Furthermore, the risk of AKI surrounding high-risk PCI may limit procedural quality and/or complete revascularization, which results in staged future vessel interventions and increases adverse event rates at intermediate-term follow-up.[4-7] Although surgical revascularization is an option for some patients, it is associated with a higher AKI risk than PCI, reaching up to a 4.5-fold higher risk in patients with advanced baseline chronic kidney disease (CKD).[8-10]

Current AKI prevention strategies in high-risk patients focus on expanding intravascular volume via intravenous hydration while attempting to minimize contrast volume use. In addition, particularly in patients with low LVEF, AKI prevention focuses on pharmacologic hemodynamic support in hopes of optimizing renal perfusion by increasing cardiac output and maintaining a favorable mean arterial pressure (MAP). However, the use of inotropes and vasopressors for hemodynamic support does carry an increased mortality risk.[11-13] Furthermore, increasing MAP does not itself protect against AKI and may not translate into a mortality benefit and does not obviate the need for renal replacement therapy (RRT).[14] Methods to reduce AKI risk have demonstrated only a modest reduction in AKI incidence, without an observed mortality benefit.[15,16]

The Impella heart pump (Abiomed, Inc.) provides continuous-flow mechanical hemodynamic support while simultaneously unloading the left ventricle, thereby enhancing forward cardiac flow. Its unique mechanism of action may provide renal protection against AKI or drastically reduce the severity of renal injury. The impact of Impella support versus no support was studied in a sick cohort of 230 patients with LVEF ≤ 35% undergoing high-risk PCI.[17] One hundred fifteen patients who received Impella 2.5 support were compared to a matched cohort of 115 patients without Impella support. Patients in the Impella arm had a greater number of comorbidities, longer procedure times, and received a higher contrast volume. Despite these risks, Impella-supported patients experienced a fivefold reduction in AKI compared to unsupported patients (5.2 vs 27.8%; $P = .001$) (Figure 1) and fewer required hemodialysis (0.9% vs 6.1%; $P < .05$).[17] AKI reduction with Impella support was also observed when these authors' stratified analyses based on AKI Network (AKIN) stages and severity of baseline CKD. Moreover, Impella support was found to be an independent predictor of reduced AKI risk (odds ratio, 0.13; 95% CI, 0.09-0.31; $P < .001$) after adjusting for other risk factors, including LVEF, estimated glomerular filtration rate, procedure time, and contrast volume.[17]

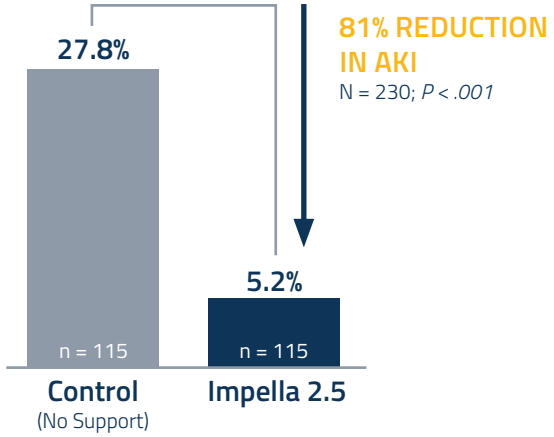

Figure 1. Incidence of AKI in high-risk PCI without hemodynamic support versus use of Impella 2.5®.

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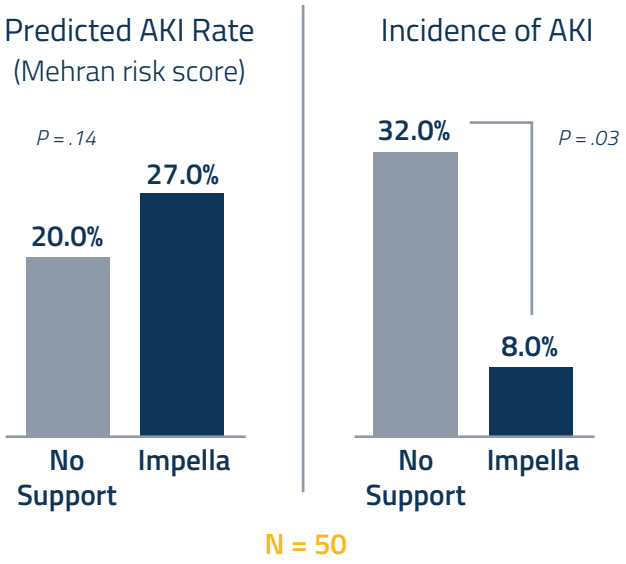

Figure 2. The patients on Impella support had a lower incidence of AKI.

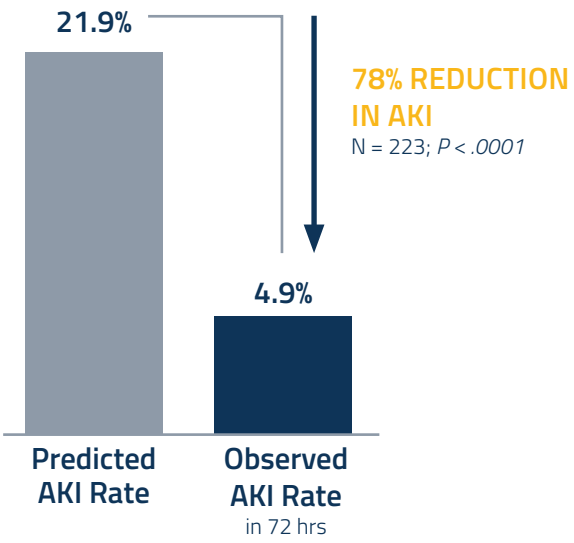

Figure 3. Impella support resulted in a 78% lower incidence of AKI compared to the predicted rate of AKI.

Current guidelines recommend AKI prevention protocols guided by Mehran risk score, which identifies patients at high risk for periprocedural AKI.[18] A recent report that utilized the Mehran risk score demonstrated that despite similar predicted AKI risk between Impella-supported high-risk PCI and nonsupported PCI (27% vs 20%; *P* = .14), Impella-supported patients experienced lower AKI risk (8% vs 32%; *P* = .03) (Figure 2).[19] Further evidence from the prospective, multicenter, global cVAD Renal Protection Study showed 78% lower observed AKI compared to the predicted risk from the Mehran AKI risk score (4.9% vs 21.9%) (Figure 3).[20]

The renoprotective effect of Impella was further validated in the PROTECT III substudy presented during Transcatheter Cardiovascular Therapeutics 2019. One hundred six Protected PCI patients were compared to 106 propensity-matched patients without Impella support. Patients with Impella support had a 77% lower incidence of AKI (5.7% vs 24.5%; *P* = .0002) along with a lower severity of AKI (Figure 4).[21]

Other mechanical circulatory support devices, such as intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO), have been used to provide hemodynamic support for high-risk procedures, although existing data have failed to demonstrate any benefit from either in protecting against AKI. In fact, IABP was identified as an independent predictor for AKI in a propensity-matched analysis of a ST-segment elevation myocardial infarction population.[22] A recent meta-analysis revealed a significantly increased risk of AKI when ECMO support was used. In this study, those who had AKI requiring RRT while on ECMO had a 3.7-fold higher risk of death.[23] In contrast, a significantly lower incidence of AKI was observed in a single-center experience when Impella-supported high-risk PCI was compared with ECMO support (12% vs 55%; *P* = .03) in patients with similar predicted Mehran risk scores (31% vs 35%; *P* = .55) (Figure 5).[24]

With regard to the renoprotective mechanisms accounting for AKI risk reduction with Impella support, these appear to be multifactorial. Putative mechanisms point to Impella-mediated maintenance of continuous renal perfusion during PCI, thereby reducing ischemic tubular necrosis and providing an estimated glomerular

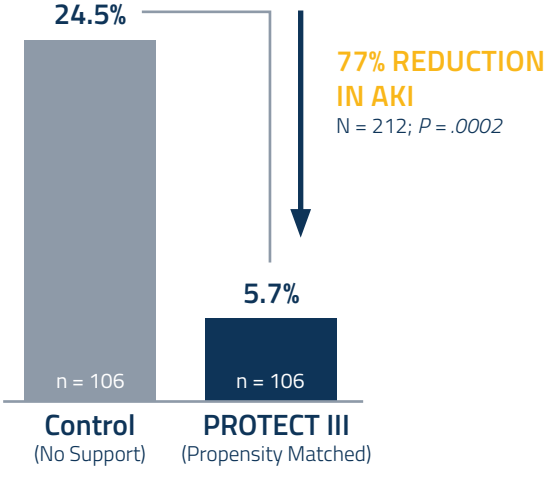

Figure 4. Impella support resulted in a 77% lower rate of AKI.

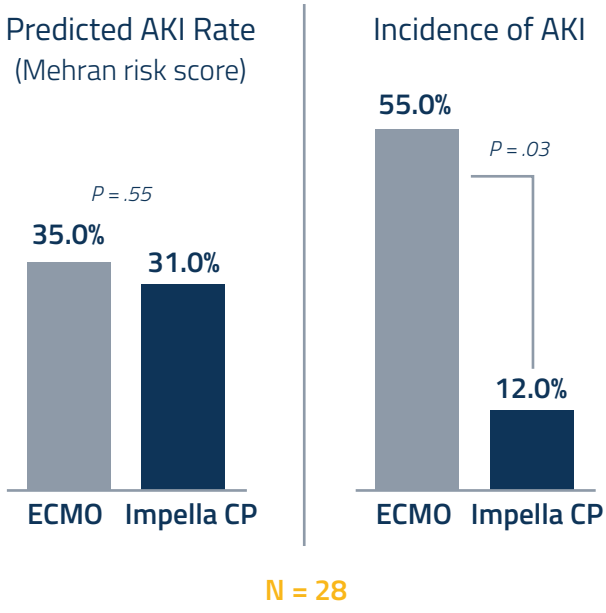

Figure 5. The patients supported with Impella CP® had a lower incidence of AKI.

filtration rate sufficient to prevent stagnation of nephrotoxic contrast in the renal tubules.[17] Other investigators suggest a novel finding that demonstrates a clear mechanistic link between Impella LV unloading and protective attenuation of the proinflammatory cardiorenal response to myocardial ischemia.[25]

CONCLUSION

In addition to increased mortality risk, AKI is associated with adverse outcomes after high-risk PCI. The incidence of AKI in Impella-supported patients relative to unsupported patients is significantly decreased during high-risk PCI. Relative to an individual's predicted AKI risk, Impella support mitigates that risk and protects against AKI. This decrease in AKI incidence with Protected PCI persists despite reduced LVEF or baseline renal dysfunction. Finally, Protected PCI with Impella lowers the incidence of AKI when compared to high-risk PCI in ECMO-supported patients and demonstrates a lower AKI rate than the overall predicted AKI risk in this population. Therefore, Impella-mediated hemodynamic support should be considered as an AKI risk reduction strategy during high-risk PCI in order to allow for more durable and complete revascularization and prevent staging of interventions. Perhaps most importantly, AKI incidence reduction achieved with Impella-supported high-risk PCI may potentially reduce in-hospital mortality, myocardial infarction, bleeding rates, and length of stay. ■

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Disclosures: None.

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The Benefit of Complete Revascularization and Efficacy of Complete Revascularization in a Single Setting

Comprehensive and well-documented data demonstrate that complete revascularization has distinct clinical advantages, especially in patients with complex multivessel disease.

BY RAJAN PATEL, MD, FACC, FAHA, FSCAI

Complicated multivessel disease (MVD) remains a clinical challenge for interventional cardiologists, posing two important questions: (1) what clinical evidence shows the benefit of complete revascularization (CR) over incomplete revascularization (IR), and (2) can complex multivessel coronary artery disease be adequately treated using percutaneous coronary intervention (PCI) in a single setting?

Available data suggest that CR, potentially in a single setting as opposed to a staged procedure, has advantages, especially for patients with MVD. These advantages include:

- Reduced incidence of all-cause mortality, myocardial infarction (MI), and major cardiac and cerebrovascular events (MACCE)
- Less early recurrent ischemia and need for subsequent procedures
- Preserved, and possibly improved, left ventricular function in select patients

COMPLETE REVASCULARIZATION LEADS TO BETTER OUTCOMES

Real-world data from the New York State PCI Reporting System,[1] along with three separate trials (ARTS-1, ARTS-II, and SYNTAX) comparing revascularization of MVD patients with PCI to coronary artery bypass grafting (CABG),[2-4] all showed that IR is very common, with rates approaching 70%. Yet, considerable evidence supports CR in high-risk coronary artery disease.

Improved Survival and Reduced MACCE

Using stress myocardial perfusion single-photon emission computed tomography (SPECT), Hachamovitch et al demonstrated that coronary revascularization, compared with medical therapy alone, leads to a greater survival benefit in patients with large zones of ischemia.[5] Figure 1 compares the cardiac death rate among patients with progressive percentages of myocardial ischemia. With increasing amounts of inducible ischemia, there was a mortality benefit among those treated with coronary revascularization compared to medical therapy alone.[5] Revascularization in patients with > 20% ischemic myocardium was associated with a markedly lower cardiac mortality (2% vs 6.7%) than the group treated with medical therapy alone ($P < .0001$).

The SYNTAX trial[4] randomized patients with coronary artery disease to revascularization with PCI or CABG. In the PCI group, cardiac death was lower when CR was achieved (6% with CR vs 9.1% with IR; $P = .049$), with a trend toward

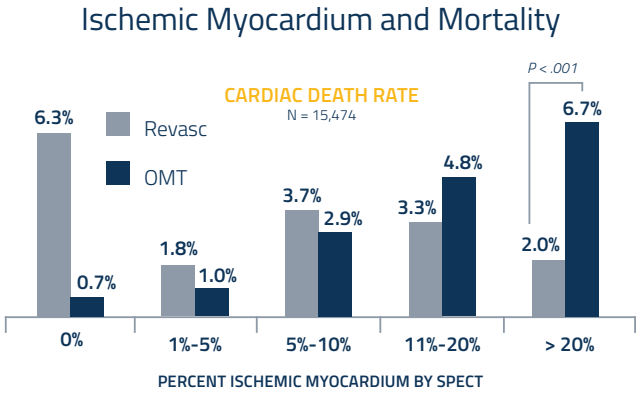

Figure 1. Mortality progressively increased in medically treated cases but not in those managed with revascularization. OMT, optimal medical therapy

all-cause mortality (11.9% vs 15.9%; *P* = .052). Cardiac death and all-cause mortality were also significantly lower among CABG group patients who received CR. In the Mayo Clinic PCI Registry, a cohort of 5,350 patients presenting with MVD who underwent PCI (either with bare-metal or drug-eluting stents), CR was associated with a survival benefit. In fact, the best survival was noted in patients without diabetes undergoing CR. The poorest survival was in diabetic patients who underwent IR.[6]

In a meta-analysis assessing three trials comparing PCI with CABG (SYNTAX, PRECOMBAT, and BEST), a reduction in MACCE was reported in the PCI cohort when CR was achieved (CR MACCE 15.3% vs IR MACCE 19.5%; *P* = .025). An even larger meta-analysis of 38 publications, including 156,240 patients with MVD undergoing PCI, showed an overall advantage with CR in terms of the death (odds ratio [OR], 0.69; 95% CI, 0.61-0.78), repeat revascularization (OR, 0.60; 95% CI, 0.45-0.80), myocardial infarction risk (OR, 0.64; 95% CI, 0.50-0.81), and postprocedural MACCE (OR, 0.63; 95% CI, 0.50-0.79).

Protected PCI With Impella® Linked to Increased Survival

The Roma-Verona Registry in Italy assessed patients with MVD and reduced left ventricular ejection fraction (LVEF) undergoing Protected PCI with Impella (Abiomed, Inc.).[7] The registry showed patients undergoing the most CR (based on the British Cardiovascular Intervention Society myocardial jeopardy score) had a survival advantage over those undergoing various degrees of incomplete revascularization (Figure 2).[8]

Although the primary endpoint in this study was mortality, an improvement in LVEF was also experienced by the majority of patients (Figure 3). The extent of coronary revascularization correlated with both LVEF recovery and survival.

IMPROVED OUTCOMES WITH SINGLE-STAGE REVASCULARIZATION

Reduced All-Cause Mortality

A prospective, observational, multicenter registry analysis (and the largest study of its kind) showed that single-stage CR improved long-term survival in patients with non–ST-segment elevation myocardial infarction (NSTEMI) and MVD. Outcomes from 19,980 patients, of which roughly half underwent single-stage acute CR during PCI, were compared with a propensity-matched group undergoing revascularization of only the implicated (culprit) vessel. Patients who underwent single-stage CR experienced a 5-year survival advantage for all-cause mortality (*P* = .0001) (Figure 4).[9]

Reduced MACCE and Target Lesion Revascularization Rates

Similarly, in a retrospective analysis of the SYNTAX study, staged cases were compared with patients undergoing single-setting PCI. Overall, a higher incidence

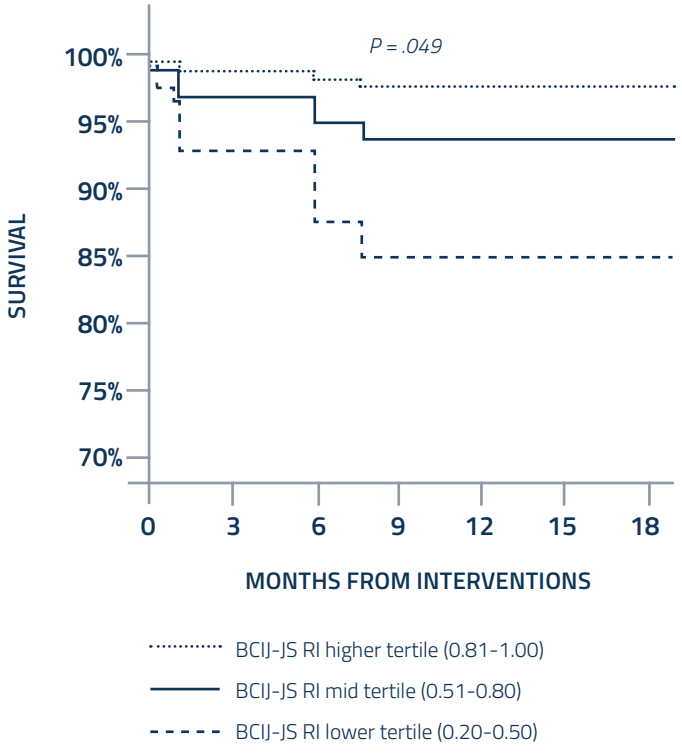

Figure 2. Survival curves according to extent of revascularization.

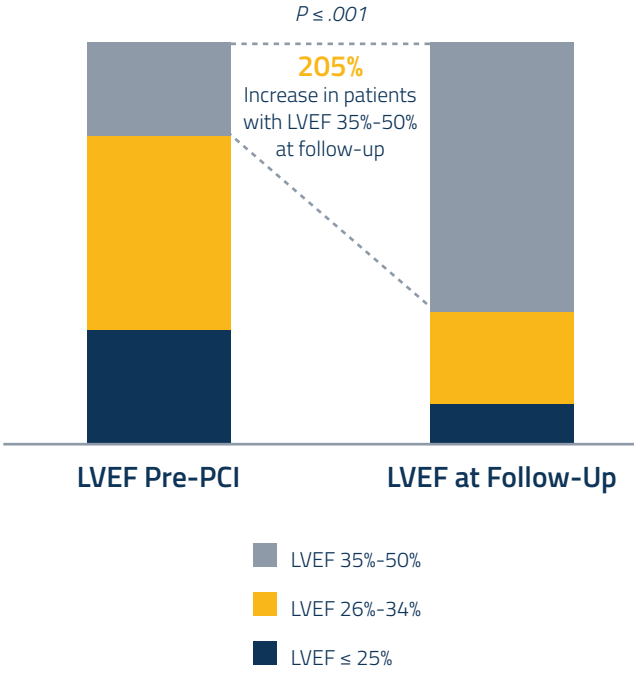

Figure 3. LVEF improvement during follow-up after Protected PCI.

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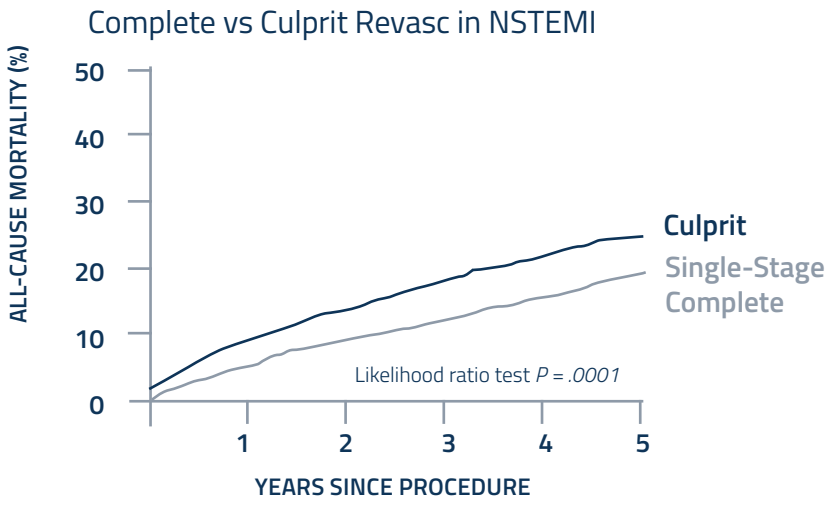

Figure 4. Kaplan-Meier curves show improved all-cause mortality after PCI with complete, single-stage CR in patients with MVD and NSTEMI.

of all-cause mortality was demonstrated in staged cases versus PCI in a single setting at 5 years (n = 778; 21.9% vs 12.6%; *P* = .006). Additionally, staging was associated with an increased incidence of urgent revascularization (32.8% vs 24.8%; *P* = .035), stroke (5.4% vs 1.9%; *P* = .031), and MACCE (48.1% vs 35.5%; *P* = .004) (Figure 5).[10] The SMILE randomized controlled trial was designed to examine the effects of staging coronary revascularization among NSTEMI patients with MVD. The primary endpoints (rates of MACCE, reinfarction, rehospitalization for unstable angina, and repeat coronary revascularization) were compared between a single-stage and multistage CR procedures. In SMILE, 584 patients were randomized during their index hospitalization either to one-stage PCI (n = 264) or to multistage PCI (n = 263). Results showed a significant reduction in both MACCE rates (hazard ratio [HR], 0.549; 95% CI, 0.363-0.828; *P* = .004) and target vessel revascularization rates (HR, 0.522; 95% CI, 0310-0.878; *P* = .013) in the subgroup that received CR in a single setting.[11]

Protected PCI With Impella Reduces Acute Kidney Injury During Single-Stage, Multivessel PCI

Because CR in a single setting often requires longer procedure times and larger amounts of contrast, acute kidney injury (AKI) is a concern. Studies have shown that patients with AKI after PCI have higher in-hospital mortality rates.[12] A retrospective single-center study of PCI with Impella support during high-risk PCI found that mechanical circulatory support reduced the overall AKI risk, even in those cases in which there was preexisting chronic kidney disease.[6]

Furthermore, treatment of MVD in a single setting may induce hemodynamic instability that can be mitigated with the Impella heart pump. Impella has demonstrated positive patient outcomes in several clinical studies and postmarket registries.[13-15]

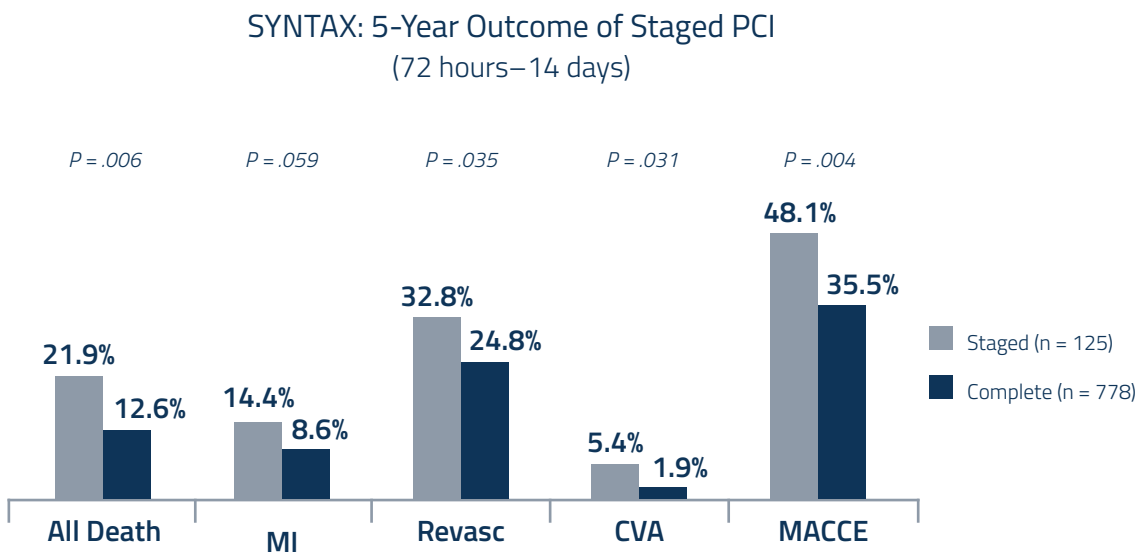

Figure 5. SYNTAX data shows improved 5-year outcomes with CR compared to staged procedures. CVA, cerebrovascular accident.

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CONCLUSION

CR leads to improved outcomes in terms of mortality, MI, repeat revascularization, and MACCE rates. Perhaps more controversial is the view that single-stage CR in patients with MVD is associated with better outcomes in MACCE and revascularization rates when compared with multistage PCI. Interventional cardiologists should consider achieving CR in a single setting based on a growing data set that CR has clinical advantages for patients with MVD. ■

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The Opportunity for Increased Quality of Care and Shared Savings With the Impella® Heart Pump

BY CHARLES SIMONTON, MD

Cardiovascular disease has been the number one cause of death in the United States since 1920.[1] In 2016, cardiovascular disease cost $555 billion and is expected to grow to $1.1 trillion by 2035, according to the American Heart Association.[1] Heart failure and recurrent cardiac symptoms are the leading causes of medical readmissions among the Medicare population,[2] with rates > 50% at 6 months.[3]

Over the last decade, there has been an increase in the use of percutaneous ventricular assist devices (pVADs), specifically the Impella 2.5® and Impella CP® (Abiomed, Inc.), which have demonstrated significant reductions in major adverse clinical events in patients undergoing high-risk percutaneous coronary intervention (PCI).[4] This has resulted in cost savings and cost-effectiveness for payers and providers in multiple studies and economic models, namely in reduced length of stay (LOS) and reduced readmissions from repeat procedures.[5-8]

> **"Sometimes trying to save costs by avoiding or delaying the use of innovative technologies sounds good, but you delay safe and effective therapy. Then the patients are sicker, and their outcomes are worse, which ends up being more costly for the patient and the health care system. Using a better therapy up front can give you a better long-term outcome while reducing cost."**
>
> –George Vetrovec, MD, professor emeritus, Virginia Commonwealth University

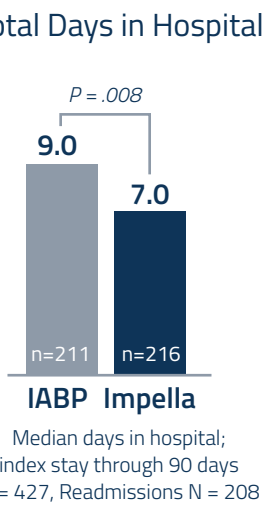

Figure 1. LOS reduction observed in PROTECT II randomized controlled trial.

The PROTECT II Economic Study concluded that for patients with severe left ventricular dysfunction and complex anatomy, Impella-assisted high-risk PCI significantly reduced major adverse events at an incremental cost per quality-adjusted life-year (QALY), referred to as ICER (incremental cost-effectiveness ratio), of $39,000/QALY, which is considered to be cost-effective for advanced cardiovascular technologies.[4]

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

- Two fewer days in the hospital (P = .008)[4] (Figure 1)
- A 52% reduction in hospitalizations due to repeat revascularization (P = .024)[4]
- 50% lower rehospitalization costs compared to the intra-aortic balloon pump (IABP) (P < .001)[4]

The national upward trend in the utilization of pVADs and other short-term mechanical support reported by Stretch et al[5] observed a correlation between increased utilization of pVADs and decreased costs.

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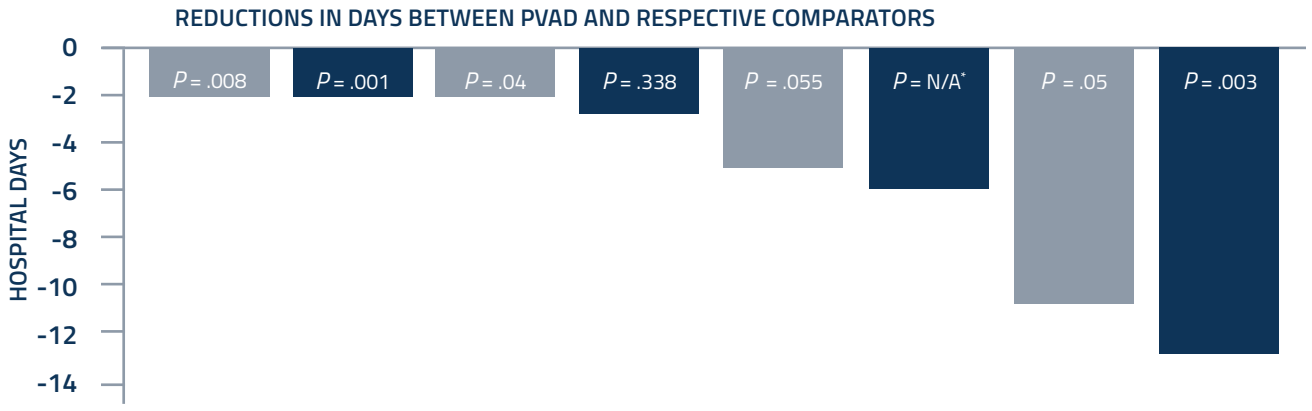

Figure 2. Hospital LOS findings associated with pVAD use.

REDUCTION IN LOS

A systematic review by Maini et al[8] reported the findings of several cost-effectiveness studies of pVADs. Reductions in LOS were observed in all studies (Figure 2), with a clinically relevant observation of fewer days in the intensive care unit and fewer readmissions. As such, they concluded pVAD use, specifically Impella 2.5, is a high-value technology in an era of accountable care.

A budget impact model supports these and other studies showing patients receiving Impella support had a 2-day reduction in LOS, or 18% in the nonemergent care model, compared to those in the IABP arm. In the emergent setting, patients in the pVAD arm demonstrated an average of 10.5 days' reduction in LOS, or 34% (Figure 3).[6]

COST SAVINGS

Research published by Maini and colleagues also evaluated the cost-effectiveness of pVADs in an emergent setting compared with traditional surgical hemodynamic support alternatives. For patients in cardiogenic shock requiring emergent hemodynamic support, Impella 2.5 resulted in better outcomes, shorter LOS, lower costs, and a survival benefit when compared with surgical hemodynamic support alternatives (Table 1).[9]

With a negative, or dominant, ICER of -$134,932/life-year gained, Impella therapy not only improved outcomes but resulted in a cost savings in acute myocardial infarction patients with cardiogenic shock in this study.[8]

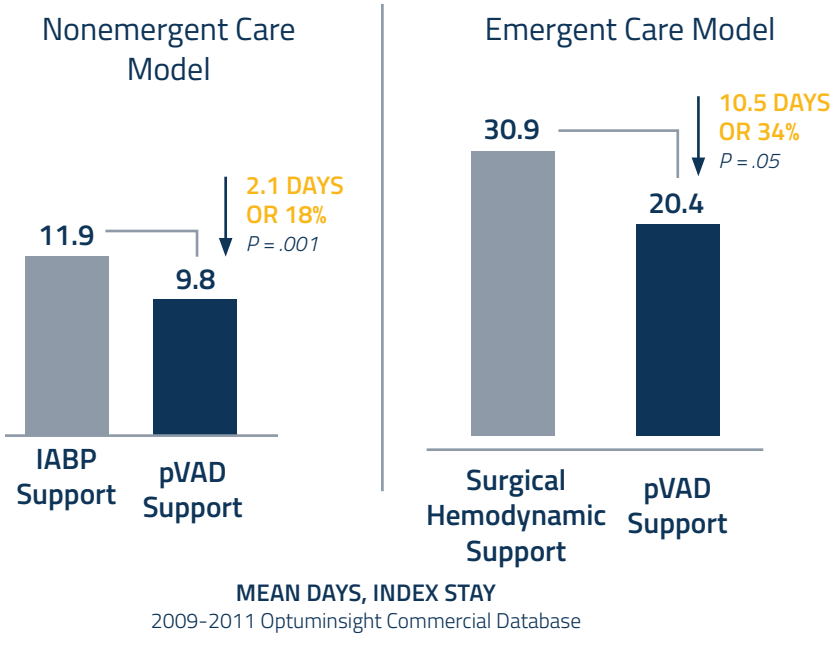

Figure 3. Impella demonstrates reduced LOS.

TABLE 1. SURVIVAL, COST, AND LENGTH OF STAY BENEFITS OF IMPELLA 2.5 VERSUS SURGICAL ALTERNATIVES

Outcome Measure	Impella 2.5	Surgical Alternative	*P* Value
Survival rate at discharge	56%	42%	*P* < .001
Cost	$112,340	$158,218	*P* < .001
Length of stay (d)	13.2	17.9	*P* = .055

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Most recently, Vetrovec and colleagues demonstrated that the use of the Impella pVAD is associated with reduced mortality rates, shorter LOS, and lower hospital costs compared to extracorporeal membrane oxygenation (ECMO) in patients with acute myocardial infarction and cardiogenic shock. pVAD use compared to ECMO resulted in total episode-of-care savings of $54,571.[10]

CONCLUSION

It is possible that new, minimally invasive technologies, such as the Impella pVAD, can provide the opportunity to concomitantly improve clinical outcomes, quality of care, and shared savings opportunities for patients and providers. As the heart failure population grows due to longer survival of patients with ischemic heart disease after revascularization procedures such as PCI, understanding the need to balance short-term costs of procedures versus the long-term savings associated with ongoing care and long-term improvement in outcomes will be key. ■

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Disclosures: None.

IMPELLA® LEFT-SIDE DEVICES INDICATION & SAFETY INFORMATION

INDICATIONS FOR USE

High-Risk PCI
The Impella 2.5®, Impella CP® and Impella CP® with SmartAssist® Systems are temporary (≤ 6 hours) ventricular support devices indicated for use during high-risk percutaneous coronary interventions (PCI) performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option. Use of the Impella 2.5, Impella CP, and Impella CP with SmartAssist Systems 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.

Cardiogenic Shock
The Impella 2.5®, Impella CP®, Impella CP® with SmartAssist®, Impella 5.0®, Impella 5.5® with SmartAssist® and Impella LD® Catheters, in conjunction with the Automated Impella Controller™ (collectively, "Impella® System Therapy"), are temporary ventricular support devices intended for short term use (≤ 4 days for the Impella 2.5, Impella CP, and the Impella CP with SmartAssist, and ≤ 14 days for the Impella 5.0, Impella 5.5 with SmartAssist and Impella LD) and indicated for the treatment of ongoing cardiogenic shock that occurs immediately (< 48 hours) following acute myocardial infarction or open heart surgery or in the setting of cardiomyopathy, including peripartum cardiomyopathy, or myocarditis as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures (including volume loading and use of pressors and inotropes, with or without IABP). The intent of Impella System Therapy is to reduce ventricular work and to provide the circulatory support necessary to allow heart recovery and early assessment of residual myocardial function.

IMPORTANT RISK INFORMATION FOR IMPELLA DEVICES

Contraindications
The Impella 2.5, Impella CP, Impella CP with SmartAssist, Impella 5.0, Impella 5.5 with SmartAssist and Impella LD are contraindicated for use with patients experiencing any of the following conditions: Mural thrombus in the left ventricle; Presence of a mechanical aortic valve or heart constrictive device; Aortic valve stenosis/calcification (equivalent to an orifice area of 0.6 cm2 or less); Moderate to severe aortic insufficiency (echocardiographic assessment graded as ≥ +2); Severe peripheral arterial disease precluding placement of the Impella System; Significant right heart failure*; Combined cardiorespiratory failure*; Presence of an Atrial or Ventricular Septal Defect (including post-infarct VSD)*; Left ventricular rupture*; Cardiac tamponade.*
*This condition is a contraindication for the cardiogenic shock indication only.

Potential Adverse Events
Acute renal dysfunction, Aortic valve injury, Bleeding, Cardiogenic shock, Cerebral vascular accident/Stroke, Death, Hemolysis, Limb ischemia, Myocardial infarction, Renal failure, Thrombocytopenia and Vascular injury

IMPELLA® RIGHT-SIDE DEVICES INDICATION & SAFETY INFORMATION

INDICATIONS FOR USE

The Impella RP® System is indicated for providing temporary right ventricular support for up to 14 days in patients with a body surface area ≥1.5 m2, who develop acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery.

CONTRAINDICATIONS
The Impella RP System is contraindicated for patients with the following conditions: Disorders of the pulmonary artery wall that would preclude placement or correct positioning of the Impella RP device. Mechanical valves, severe valvular stenosis or valvular regurgitation of the tricuspid or pulmonary valve. Mural thrombus of the right atrium or vena cava. Anatomic conditions precluding insertion of the pump. Presence of a vena cava filter or caval interruption device, unless there is clear access from the femoral vein to the right atrium that is large enough to accommodate a 22 Fr catheter.

POTENTIAL ADVERSE EVENTS
The potential adverse effects (e.g., complications) associated with the use of the Impella RP System: Arrhythmia, Atrial fibrillation, Bleeding, Cardiac tamponade, Cardiogenic shock, Death, Device malfunction, Hemolysis, Hepatic failure, Insertion site infection, Perforation, Phlegmasia cerulea dolens (a severe form of deep venous thrombosis), Pulmonary valve insufficiency, Respiratory dysfunction, Sepsis, Thrombocytopenia, Thrombotic vascular (non-central nervous system) complication, Tricuspid valve injury, Vascular injury, Venous thrombosis, Ventricular fibrillation and/or tachycardia.

In addition to the risks above, there are other WARNINGS and PRECAUTIONS associated with Impella devices. Visit www.abiomed.com/important-safety-infomation to learn more.

Visit protectedpci.com for more information.

Cardiac Interventions TODAY