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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.

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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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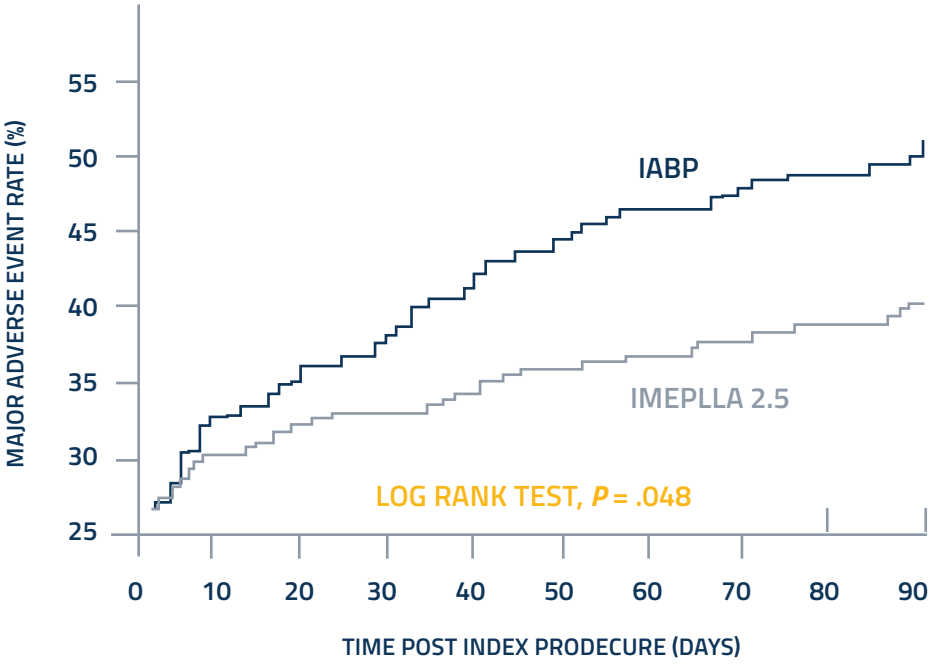

Figure 1. Kaplan-Meier curves for major adverse events. Composite of the primary endpoint up to 90 days.

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

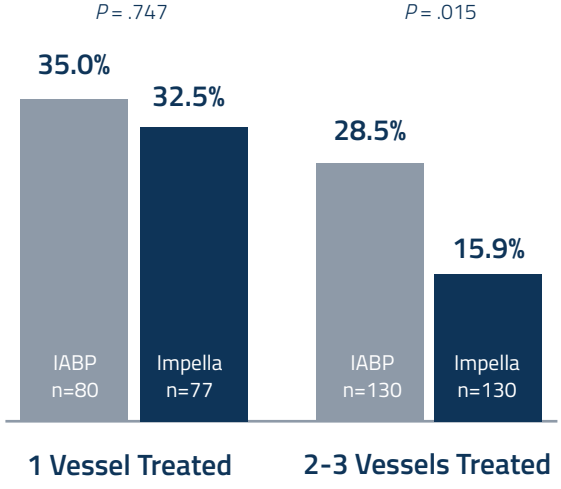

Figure 2. PROTECT II Study FDA premarket approval data of unprotected left main included in two or three vessels.

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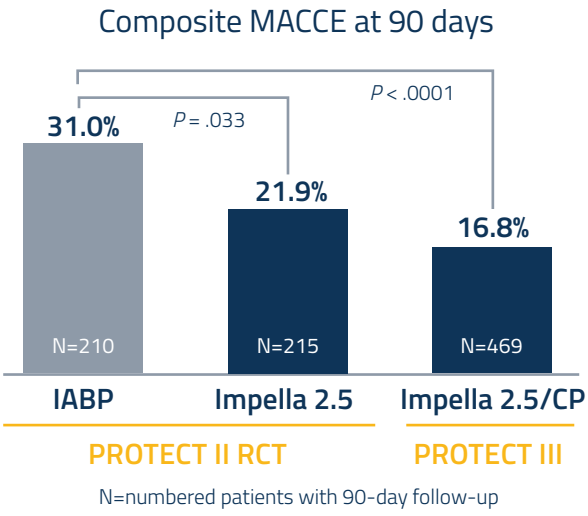

Figure 3. PROTECT III outcomes compared to PROTECT II.

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

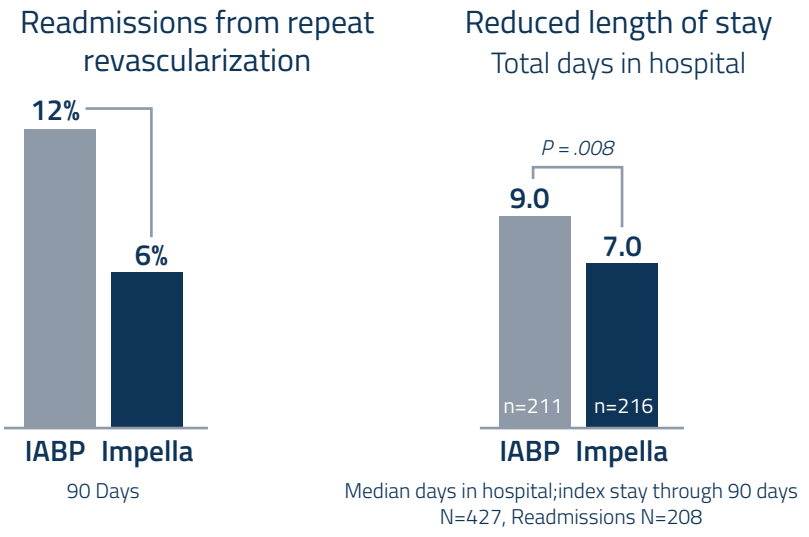

Figure 4. Length of stay reductions observed in PROTECT II randomized controlled trial[13] and Optum population-based study.

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. ■

1. Myat A, Patel N, Tehrani S, et al. Percutaneous circulatory assist devices for high-risk coronary intervention. J Am Coll Cardiol Interv, 2015;8:229–244.
2. Brennan JM, Curtis JP, Dai D, et al. Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention: results from 1,208,137 procedures in the NCDR (National Cardiovascular Data Registry). JACC Cardiovasc Interv. 2013;6:790–799.
3. Rihal CS, Naidu SS, Givertz MM, et al. 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care: endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. J Am Coll Cardiol. 2015 May 19;65:e7–e26.

4. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2016;133:1135-1147.
5. Bortnick AE, Epps KC, Selzer F, et al. Five-year follow-up of patients treated for coronary artery disease in the face of an increasing burden of co-morbidity and disease complexity (from the NHLBI Dynamic Registry). Am J Cardiol. 2014;113:573–579.
6. Pandey A, McGuire DK, de Lemos JA, et al. Revascularization trends in patients with diabetes mellitus and multivessel coronary artery disease presenting with non-ST elevation myocardial infarction: insights from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines (NCDR ACTION Registry-GWTG).Circ Cardiovasc Qual Outcomes. 2016;9:197–205.
7. Herrmann J. Peri-procedural myocardial injury: 2005 update. Eur Heart J. 2005;26:2493-2519.
8. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the american college of cardiology/american heart association task force on practice guidelines (ACC/AHA/SCAI writing committee to update the 2001 guidelines for percutaneous coronary intervention). J Am Coll Cardiol. 2006;47:e1-e121.
9. Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circulation. 2012;125:2613-2620.
10. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. J Am Coll Cardiol. 2013;62:1421-1431.
11. Watkins S, Oldroyd KG, Preda I, et al. Five-year outcomes of staged percutaneous coronary intervention in the SYNTAX study. EuroIntervention. 2015;10:1402-1408.
12. Kovacic JC, Kini A, Banerjee S, et al. Patients with 3-vessel coronary artery disease and impaired ventricular function undergoing PCI with Impella 2.5 hemodynamic support have improved 90-day outcomes compared to intra-aortic balloon pump: a sub-study of the PROTECT II trial. J Interv Cardiol. 2015;28:32-40.
13. de Souza CF, de Souza Brito F, De Lima VC, De Camargo Carvalho AC. Percutaneous mechanical assistance for the failing heart. J Interv Cardiol. 2010;23:195-202.
14. Burkhoff D, Naidu SS. The science behind percutaneous hemodynamic support: a review and comparison of support strategies. Catheter Cardiovasc Interv. 2012;80:816-829.
15. Naidu SS. Novel percutaneous cardiac assist devices: the science of and indications for hemodynamic support. Circulation. 2011;123:533-543.
16. Curran J, Burkhoff D, Kloner RA. Beyond reperfusion: acute ventricular unloading and cardioprotection during myocardial infarction. J Cardiovasc Transl Res. 2019;12:95-106.
17. Dixon SR, Henriques JP, Mauri L, et al. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (the PROTECT I Trial): initial U.S. experience. JACC Cardiovasc Interv. 2009;2:91-96.
18. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. Circulation. 2012;126:1717-1727.
19. Dangas GD, Kini AS, Sharma SK, et al. Impact of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump on prognostically important clinical outcomes in patients undergoing high-risk percutaneous coronary intervention (from the PROTECT II randomized trial). Am J Cardiol. 2014;113:222-228.
20. Kovacic JC, Kini A, Banerjee S, et al. Patients with 3-vessel coronary artery disease and impaired ventricular function undergoing PCI with Impella 2.5 hemodynamic support have improved 90-day outcomes compared to intra-aortic balloon pump: a sub-study of the PROTECT II trial. J Interv Cardiol. 2015;28:32-40.
21. Cohen MG, Ghatak A, Kleiman NS, et al. Optimizing rotational atherectomy in high-risk percutaneous coronary interventions: insights from the PROTECT II study. Catheter Cardiovasc Interv. 2014;83:1057-1064.
22. Shavelle DM, Banerjee S, Maini B, et al. Comparison of outcomes of percutaneous coronary intervention on native coronary arteries versus on saphenous venous aorta coronary conduits in patients with low left ventricular ejection fraction and Impella device implantation achieved or attempted (from the PROTECT II Randomized Trial and the cVAD Registry). Am J Cardiol. 2018;122:966-972.
23. US Food and Drug Administration; Center for Devices and Radiological Health. https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S018A.pdf. Accessed March 16, 2018.
24. Popma J. PROTECT III first look: high-risk PCI outcomes in 800 Impella-supported patients. Presented at the Transcatheter Cardiovascular Therapeutics (TCT) meeting; September 2019; San Francisco, California.
25. Flaherty MP, Pant S, Patel SV, et al. Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention. Circ Res. 2017;120:692-700.
26. Flaherty MP, Moses JW, Westenfeld R, et al. Impella support and acute kidney injury during high-risk percutaneous coronary intervention: the Global cVAD Renal Protection Study [published online July 29, 2019]. Catheter Cardiovasc Interv.
27. Chandrasekaran U, Burkhoff D, Ishikawa K, et al. Proceedings of the 3rd annual Acute Cardiac Unloading and REcovery (A-CURE) symposium. BMC Cardiovasc Disord. 2019;19(suppl 2):27.
28. Gregory D, Scotti DJ, de Lissovoy G, et al. A value-based analysis of hemodynamic support strategies for high-risk heart failure patients undergoing a percutaneous coronary intervention. Am Health Drug Benefits. 2013;6:88-99.
29. Maini B, Scotti DJ, Gregory D. Health economics of percutaneous hemodynamic support in the treatment of high-risk cardiac patients: a systematic appraisal of the literature. Expert Rev Pharmacoecon Outcomes Res. 2014;14:403-416.
30. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis. J Am Coll Cardiol. 2014;64:1407-1415.
31. Atkinson TM, Ohman EM, O'Neill WW, et al. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: an interventional perspective. JACC Cardiovasc Interv. 2016;9:871-883.

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