Editorial

Percutaneous left ventricular assist device in high risk percutaneous coronary intervention

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"*As to diseases, make a habit of two things-to help, or at least do no harm.*"—Hippocrates.

High-risk candidates for percutaneous coronary intervention (PCI) may include patients with severe multi-vessel coronary artery disease, unprotected left main coronary artery stenosis, or last patent conduit with a stenosis, especially in patients with a left ventricular (LV) ejection fraction of ≤35% (1-4). In addition, the condition and co-morbidities of the patient should be taken into consideration. Traditionally, revascularization in these patients could be better accomplished with coronary artery bypass graft (CABG) surgery; however, sometimes these patients are high-risk surgical candidates, have advanced age and/or have poor distal targets for bypass surgery (5). PCI in these patients is a viable option, however, episodic interruption of blood flow to the target coronary artery in these high-risk patients during contrast dye injections, balloon inflation and stent implantation may result in a decrease in LV performance raising procedural morbidity and/or mortality (3,4,6). Currently, it is thought that hemodynamic support devices like the Impella (Abiomed, Danvers, Massachusetts) percutaneous left ventricular assist device (PLVAD) or intra-aortic balloon pump (IABP) may provide support during high-risk PCI (2,3,7-9).

The largest high-risk PCI study using hemodynamic support available today is the PROTECT II trial that compared Impella 2.5 PLVAD to IABP (3). In this study, 452 symptomatic patients were randomized to Impella (n=226) or IABP (n=226) during high-risk PCI. Patients had a LV ejection fraction of ≤35% with a last patent conduit with a stenosis or unprotected left main coronary artery stenosis, or had a LV ejection fraction of ≤30% with severe three vessel coronary artery disease. The Impella 2.5 is a rotary pump that provides blood flow from the LV into the ascending aorta up to 2.5 L/min. This results in an increase in cardiac output, decrease in myocardial oxygen consumption, and decrease in LV diastolic and pulmonary capillary wedge pressures. The Impella is delivered percutaneously through a 12 French (F) sheath via the femoral artery and is placed in the LV in a retrograde fashion extending across the aortic valve. The Impella became available in the United States of America in 2008 (10,11). The PROTECT II trial demonstrated that in high-risk patients, PCI could be successfully performed using either Impella or IABP. The Impella compared to IABP provided better hemodynamic support with a greater cardiac power output and was associated with a reduction in adverse events driven mostly by a decrease in repeat revascularization at 90 days (3). To better define the effect of Impella in the "real-world", Cohen *et al.*, in a retrospective analysis using data from the USpella registry, compared the results of the Impella arm from the PROTECT II trial to those of the USpella registry patients; these findings were published in the November 2015 issue of the *American Heart Journal* (12).

USpella is an observational on-going multi-center voluntary registry of Impella use in which 47 sites in the United States and 2 sites in Canada are participating. From this registry, a total of 637 high-risk PCI patients were identified who were supported with the Impella 2.5 during PCI. Of the 637 patients, 339 were identified as having met eligibility criteria for enrollment in the

PROTECT II trial referred to as PROTECT II "like" patients. All patients from the USpella registry (n=637) and the sub-group of PROTECT II "like" patients (n=339) from the registry were compared with the patients randomized to the Impella arm from the PRTOETCT II trial (n=216). Baseline characteristics were mostly similar with some noticeable differences between the USpella registry and PROTECT II trial patients. Overall patients in the USpella registry were older, had higher incidence of chronic kidney disease, had less prior CABG or myocardial infarction, and greater LV ejection fraction compared to the PROTECT II trial patients. The PROTECT II "like" patients from the USpella registry were older, had less prior CABG or myocardial infarction, had more prior PCI, had more severe heart failure symptoms, and lower LV ejection fraction compared to the PROTECT II trial patients. All groups had a similar Society of Thoracic Surgery (STS) surgical risk score of approximately 6%. The total number of patients and the PROTECT II "like" patients from the USpella registry had a significantly higher number of diseased coronary arteries and total number of lesions compared to the PROTECT II trial patients; however, the number of treated lesions and number of stents were significantly higher in the PROTECT II trial likely due to the requirement by the trial to perform the most complete revascularization as possible in a single procedure (3,12).

Blood transfusions where not statistically different between the overall USpella registry patients (11%) and the PROTECT II "like" patients (9%) when compared to the PROTECT II trial patients (12.5%). Vascular complications requiring surgery were also not statistically different between the overall USpella registry patients (2.5%) and the PROTECT II "like" patients (2.3%) when compared to the PROTECT II trial patients (1.4%); however, vascular complications not requiring surgery where significantly lower in the overall USpella registry (5.1%), but not the PROTECT II "like" patients (5.6%), when compared to the PROTECT II trial patients (9.3%; P=0.03). Mortality in the USpella registry was numerically lower, but not statistically significant when compared to the PROTECT II trial (overall USpella registry 2.8%; PROTECT II "like" patients 2.7%; PROTECT II trial 4.6%). Myocardial infarction was also significantly lower in the USpella registry (overall USpella registry 1.3%; PROTECT II "like" patients 0.3%; PROTECT II trial 15.3%), as was repeat revascularizations (12). The lower rate of peri-procedural myocardial infarction likely was due to more stringent checking of cardiac biomarkers after PCI in the PROTECT II trial. In addition, one cannot exclude lack of documentation in the registry data, thus capturing less adverse events including repeat revascularization.

Data from the USpella registry demonstrated that "real-world" patients who underwent high-risk PCI using Impella support mostly had similar baseline characteristics and derived similar results to those patients enrolled in the Impella arm of the PROTECT II randomized trial (12). Interpretation of these results are important as utilization of PLVAD for prophylactic use in high-risk PCI has increased significantly over the last decade (13). Per the 2011 PCI Guidelines by the American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions, the elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients, however, this recommendation was based on expert opinion (4). Recommendations and increased popularity of PLVAD must be closely counterbalanced with their procedural morbidity, particularly bleeding and vascular complications due to larger vascular access needed for device insertion and due to the fact that two arterial access sites must be used, one for the Impella and one for PCI. Thus, the important question that arises is when is it necessary to use a PLVAD. There are certainly cases that Impella may be useful in high-risk PCI similar to those identified in the PROTECT II trial. It should be mentioned, however, that in similar high-risk patients PLVAD was not used also resulting in good outcomes. There is a lack of data in high-risk PCI comparing Impella with no Impella, and the decision currently solely falls on the interventional cardiologist clinic experience and judgment when to use a PLVAD.

The potential risk associated with larger vascular access for the Impella device and the need for a second arterial access site needs to be carefully deliberated when considering its use. A high rate of blood transfusions (11%) was noted in the USpella Registry (12). There was a learning curve effect, however, as transfusion rates decreased over the years from 12% in 2009 to 6% in 2011 as operators became more adept and proficient with vascular access and the utilization of percutaneous closure techniques for large vascular access sites; a similar trend was seen in the PROTECT II trial (3,12). In the original PROTECT I trial, the incidence of bleeding was greater compared to

PROTECT II with a hematoma incidence of 40%, however, this study included a small number of patients (2). In addition, several other studies have demonstrated bleeding complications associated with Impella use during PCI in high-risk patients ranging from 6% to 40% (2,14-17). Further, the incidence of bleeding is high with prolonged use of a hemodynamic support device (18). It should be emphasized that bleeding associated from PCI when evaluated in over 300,000 patients from the CathPCI National Cardiovascular Data Registry (NCDR) from January 2004 to March 2006 was only 2.4% (19).

Vascular complications were high with Impella use in the USpella registry and PROTECT II trial (12). In addition, other studies have also reported increase vascular complications as high as 15% likely associated from larger sheath size placement in the femoral artery in order to accommodate the 12F Impella device and need for a second arterial access site (14,17,20). In an observational study of over 100,000 patients undergoing PCI via femoral artery access using a 6F, 7F or 8F guiding catheter, vascular complication rates significantly increased with larger guiding catheter size. Post-procedural hemoglobin was more likely to fall by >3 g/dL in the 7F and 8F guiding catheter groups with a significantly higher rate of blood transfusions as compared to the 6F catheter group. Vascular access site complications were higher in the 8F group regardless of whether a vascular closure device was used (21). As a comparison, when analyzing over 3,000,000 patients from the CathPCI NCDR from January 2007 to September 2012, vascular complications were only 0.45% when femoral artery access was obtained for PCI (22).

Bleeding and vascular complications associated with PCI are much lower than reported in studies when using Impella, however, comparison may be misleading due to lack of knowledge of underlying patient co-morbidities, vascular access site information, type of pharmacotherapy used, and extent of coronary artery disease requiring PCI, but should be carefully noted.

The USpella registry and PROTECT II trial demonstrate favorable results with Impella use during high-risk PCI (3,12). The Impella can provide adequate hemodynamic support possibly preventing morbidity and mortally during high-risk PCI. The pioneering work by Dr. O'Neill and team on LV assist devices, particularly the Impella, have added considerable knowledge to the field. The Impella has provided interventional cardiologist with a tool to provide hemodynamic support during high-risk PCI to inoperable patients in which may have been treated medically in the past. However, it is important to not dismiss that given the larger sheath size and use of two arterial access sites the risk of sustaining higher rates of vascular and/or bleeding may occur. In addition, prolonged use of Impella may further increase complications. For obvious reasons, a control group was not used in these studies. It should be noted, however, that certain "gold standard" procedures in the past (e.g., IABP, leave-in pulmonary artery catheter, others) were eventually shown to have no benefit (23,24). Although unlikely, it would be of great clinical importance if a small pilot study were conducted to answer this important question; perhaps, Dr. O'Neill with his extensive experience and clinical wisdom can conduct such a study. It should also be noted that the Impella has enabled interventional cardiologist to perform complicated procedures and thus, has enhanced their experience; these interventional cardiologist are now often able to perform the same procedures without the Impella due to this experience. At present, it is prudent that careful selection of patients who would net a clinical benefit from undergoing prophylactic Impella insertion be determined on a per patient basis guided by clinical experience and judgment, and on cardiac catheterization laboratory experience. This dilemma will likely be encountered more frequently as patients with complex coronary artery disease are turned down for CABG due to their significant co-morbidities and more of these patients are treated with high-risk PCI; however, in our efforts to help, we should be careful and "*at least do no harm*" (25).

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Footnote

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