New LVAD May Benefit High-Risk PCI Patients

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NEW ORLEANS – Introduced to the U.S. market in 2008 as an upgraded alternative to the intra-arterial balloon pump, the Impella 2.5 showed clear signs of better performance in high-risk patients undergoing percutaneous coronary intervention in a multicenter, randomized trial with 447 patients.

But once Impella 2.5 entered the U.S. market, enrollment into the study slowed dramatically. Eventually, researchers stopped the trial substantially short of its enrollment target, and the pivotal study's primary end point did not show a statistically significant benefit for Impella 2.5.

The trial also ran into a second problem with a major confounding issue: Interventional cardiologists used rotational atherectomy more aggressively in Impella-treated patients. They seemingly were emboldened by the added cardiac support, and Impella-treated patients had an unbalanced rate of adverse effects.

Despite these problems, the trial results showed a role for the Impella device in high-risk, low-cardiac-output patients undergoing PCI, Dr. William O'Neill said at the meeting.

"This device produces superb hemodynamic support during high-risk interventions. It really allows a more complete procedure that leads to fewer late events," explained Dr. O'Neill, an interventional cardiologist and executive dean for clinical affairs at the University of Miami.

"With these [high-risk] patients, we skate rapidly over thin ice. This device allows us the luxury of taking more time and doing a more complete and safer procedure. I think [that capability] will translate into increased use [of the device] in these high-risk patients," he added.

Experts who heard the trial results were split on their interpretation of the findings.

"This was a negative study. What is driving the differences you see? I don't understand how to reconcile the results with your conclusion to go ahead [with using] this device," commented Dr. Ron Waksman, director of experimental angioplasty at Washington (D.C.) Hospital Center.

But Dr. Roxanna Mehran gave the findings a much more positive spin (see box, below right).

PROTECT II was a prospective, multicenter, randomized, controlled trial of the Impella Recover LP 2.5 system vs. IABP (intra-aortic balloon pump) in patients undergoing nonemergent, high-risk PCI. The trial began in November 2007 at 67 U.S. sites, 4 sites in Canada, and 1 site in the Netherlands. It enrolled patients with either unprotected left main coronary disease and a left ventricular ejection fraction of 35% or less, or patients with triple-vessel coronary disease and an ejection fraction of 30% or less.

The primary end point was the 30-day rate of death, MI, stroke, need for repeat revascularization, need for cardiovascular surgery or vascular surgery for limb ischemia, acute renal dysfunction, increased aortic insufficiency, severe hypotension, need for cardiopulmonary resuscitation, ventricular tachycardia, or failure to reopen the target coronaries by PCI.

The patients averaged 67 years old, 80% were men, and 56% had New York Heart Association class III or IV heart failure. Their average Society of Thoracic Surgeons (STS) mortality score was 6, their average SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score was 30, and 63% were considered ineligible for surgery. "The population was "extraordinarily high risk, the most complex patients ever enrolled in a multicenter, randomized, controlled trial," Dr. O'Neill said.

There were 447 patients enrolled in PROTECT II before the study's data and safety monitoring board stopped the trial last December citing "futility" on the primary end point. This number was 70% of the number of patients originally identified as needed to produce a statistically significant result for the primary end point. Enrollment into the study sharply slowed once the Impella device came onto the U.S. market in June 2008.

During PCI, the participating operators generally managed the Impella patients more aggressively. Heparin was given to 94% in the Impella arm and to 82% in the IABP control arm. Rotational atherectomy was performed in 15% of the Impella patients and in 10% of patients in the IABP arm, a statistically significant difference. Also, participating operators used atherectomy more aggressively in the Impella patients, with an average of five atherectomy passes per patient, compared with two passes in the IABP patients.

Although this shift in treatment approach may have ultimately benefited some of the Impella patients, it also "increased the major adverse event rate and confounded the analysis," Dr. O'Neill said. "About 70% of patients treated with atherectomy in the Impella group had an adverse event" – primarily rises in the level of creatine kinase–myoglobin – "compared with about 35% treated with atherectomy in the IABP group," he said in an interview. "It was a procedural imbalance that was hard to control for" in the safety and efficacy analysis.

There was no statistically significant difference for the study's primary outcome, the combined major adverse event rate in the intention-to-treat analysis at 30 days after treatment, as well as at 90 days after treatment. However, at both time points, patients in the Impella arm showed trends toward lower major adverse events rates. At 30 days, the Impella patients had a 36% rate, compared with a 40% rate in the IABP patients. At 90 days, the rates reached 41% and 50%, respectively.

In the per-protocol analysis, at 30 days the Impella patients had a major adverse event rate of 35%, compared with 43% in the IABP patients, which was not a statistically significant difference. At 90 days, the rates reached 41% and 51%, respectively, a difference that was statistically significant.

Dr. O'Neill addressed concerns that the major adverse event measure included many elements of sharply differing clinical importance. "What drove the difference [between the two study arms] was death, myocardial infarction, and need for urgent revascularization – not the small stuff. The real major adverse cardiac events were significantly better" when the Impella device was used, he said in an interview.

An analysis of several prespecified subgroups also highlighted certain types of patients who had significant benefit from the Impella device for the study's primary end point. Among the 88% of patients in the study who were not treated with rotational atherectomy, the 30-day major adverse event rate reached 30%, compared with 42% in the IABP patients, a statistically significant difference. A significant difference in the primary outcome in favor of the Impella patients also occurred in the subgroup that had an STS mortality score lower than 10.

The results also showed a strong trend toward a better primary outcome in the Impella-treated patients when the analysis excluded the first Impella-treated patient for each operator, a finding that highlighted an important learning curve in using the device, Dr. O'Neill said.

Analysis also showed that the 90-day rate of major adverse events in the Impella patients fell from 48% in 2008 to 39% in 2009 and to 37% in 2010. In contrast, the rate in the IABP patients stayed fairly constant (at 47%-52%) in all 3 years, again highlighting the role of experience with the Impella device in achieving better patient outcomes, he said.

"I think many clinicians will see [from these data] that Impella provides a lot of safety," Dr. O'Neill said. ■

VITALS

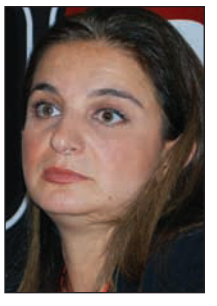
Major Finding: High-risk patients who were aided during PCI with an LVAD (Impella 2.5) had a 41% rate of major adverse events at 90 days, significantly better than the 51% rate in patients treated with a standard intra-aortic balloon pump. But in the intention-to-treat analysis, outcomes did not differ for the two groups at either 30 days or 90 days.

Data Source: PROTECT II, a randomized trial comparing LV support with the Impella 2.5 device and an intra-aortic balloon pump in 447 patients who were treated at 72 sites worldwide.

Disclosures: PROTECT II was funded by Abiomed, which markets the Impella device. Dr. O'Neill has been a consultant to Medtronic. Dr. Waksman has been a consultant to or received honoraria from Medtronic Vascular, Abbott Vascular, Biotronik, Merck, and Boston Scientific.

VIEW ON THE NEWS

Device Useful for Selected Patients



The results that Dr. O'Neill presented support the use of the Impella 2.5 device in certain clinical situations, specifically in extremely high-risk patients who have a low left ventricular ejection fraction and need protection when undergoing multivessel PCI. Having access to this type of adjunctive device is important, especially for high-risk patients. I can see myself using this device in patients similar to those enrolled in PROTECT II.

It's unfortunate that the trial did not give a definitive answer to the questions posed in the study. The trial was designed as a superiority trial and did not meet its primary end point. The results do not give us a scientific answer on when to use the device because the study stopped early. But studies like this can inform us tremendously on how to manage very high-risk patients. It's a tremendous effort to undertake the study and find the patients who would benefit from this device.

We saw in the results that physicians who used the Impella device had the confidence to more aggressively use atherectomy. That can't be proved, but it appears to be so. The higher use of rotational atherectomy resulted in more creatine kinase–myoglobin elevations in that arm, but the Impella group had fewer critically important MIs (defined as a CK-MB rise of more than eight times the upper limit of normal).

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