FDA panel endorses HDE for Berlin Heart's Excor Pediatric VAD

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Gaithersburg, MD – Because it is the only hope many children with severe heart failure have of surviving until they can get a transplant, Berlin Heart's **Excor Pediatric** ventricular assist device (VAD) should receive an humanitarian device exemption (HDE), the **FDA**'s Circulatory System Devices advisory committee concluded at its July 21, 2011 meeting [1].

Although about 85% of patients in the pivotal Excor trial suffered an adverse event—including strokes in almost 30%—the panel voted unanimously to recommend approval of an HDE for the device as a bridge-to-transplant in children with severe, isolated left-ventricular or biventricular dysfunction. The Excor system is available with pneumatically driven blood pumps in five different sizes, with stroke volumes of 10, 25, 30, 50, and 60 mL for different-sized children.

"This panel believes that the Excor provides considerable more time, by a full order of magnitude or greater, for children that are in need of transplantation," panel chair **Dr Clyde Yancy** (Northwestern University, Chicago, IL) summarized. "The application of this device will improve the opportunity for transplantation in children that are desperately ill and . . . will fulfill an unmet need and be a significant contribution to pediatric cardiology."

FDA grants HDEs for devices that treat or diagnose a disease or condition that affects fewer than 4000 individuals in the US per year. Because a company's revenue from such a device is limited, the standard of evidence required to obtain an HDE is lower than that of a regular premarket application. The HDE application must demonstrate the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefits outweigh the risk of injury or illness.

Despite high adverse event rates, survival is improved

The pivotal Excor trial was a single-arm study in children with severe heart failure waiting for a heart transplant. The study enrolled 48 patients aged 16 or younger into two treatment cohorts based on size: 24 patients with a body surface area <0.7 m^2 and 24 patients with a body surface area 0.7-1.5 m^2.

Because this is the only pediatric device of its kind, there was no randomized control group. Instead, the outcomes of patients supported by the Excor were compared with outcomes of patients who received extracorporeal membrane oxygenation (ECMO) enrolled in the Extracorporeal Life Support Organization (ELSO) registry. There are no FDA-approved ECMO circuits, but ECMO has been the standard of care for bridging pediatric patients to transplant. However, the ELSO registry did not include body surface area or data on transplantation or neurological status. Also, ECMO patients rarely survive on support for more than 30 days.

Several panelists said the comparison with the ELSO registry patients was not useful, but they were nevertheless impressed with the number of patients supported by the Excor who survived to transplant or weaning from the device. "Regardless of what group we compared it to, 90% survival to transplant or successful wean is remarkable, and in that regard, it's irrelevant what that the control was," **Dr Marc Moon** (Washington University, St Louis, MO) said.

Primary effectiveness summary

Group	Patients, n	Max days on device	Survived to transplant or weaning, %
Cohort 1, ITT	24	174.0	87.5

Cohort 1, per protocol	22	174.0	86.4
ECMO control 1	48	20.5	75.0
Cohort 2, ITT	24	42.5	91.7
Cohort 2, per protocol	22	144.0	90.9
ECMO control 2	48	27.5	66.7

Cohort 1 included patients with a body surface area <0.7 m^2. Cohort 2 included patients with a body surface area $\geq$0.7 m^2 and < 1.5 m^2.

ECMO = extracorporeal membrane oxygenation

ITT = intent to treat

"All the numbers I've heard [show] there is reduced mortality [with Excor]. So you're on this thing longer, you have a better chance of a rescue transplant, but at the same time, you seem to not pay for that with more mortality and that impressed me very much," **Dr John Somberg** (Rush University Medical Center, Lake Bluff, IL) said.

Pediatric cardiologist **Dr David Nykanen** (Arnold Palmer Medical Center, Orlando, FL) said that the average wait for a donor heart for pediatric transplant candidates is over four months, but patients can only be expected to survive on ECMO about two weeks. "That is the practical limitation of the existing devices for these kids. It's impossible. The Excor has demonstrated that it does provide these kids the opportunity to be transplanted and be well where the alternative is death."

Device is safe, but impact of adverse events needs more study

Because adverse events in the ELSO registry are not adjudicated, the FDA instructed Berlin Heart to evaluate the safety of Excor based on the number of adverse events/day and compare it with a prespecified target rate of 0.25 events/day—a goal that Excor met in both cohorts with rates of 0.068 and 0.078 events/day for cohorts 1 and 2, respectively.

Several panelists said that the rate of adverse events per day was not a useful measure, but instead were concerned about the number of patients who experienced an adverse event and total number of adverse events during follow-up.

Overall, about 92% of cohort 1 and 79% of cohort 2 had some kind of adverse event during the study. About 42% of cohort 1 and 50% of cohort 2 had a major bleeding incident. In addition, 62.5% of cohort 1 and 50% of cohort 2 had a major infection, and 29.2% of each group had a cerebrovascular accident.

"If you looked at this data de novo, one would be alarmed by the . . . stroke rate," **Dr Valluvan Jeevanandam** (University of Chicago, IL) said. "So if you compare this VAD to an adult VAD, it could compare unfavorably; however, there is nothing in the pediatric population you can compare it to." Jeevanandam also noted that pediatric patients are generally better able to recover from strokes than adults, and that it is probably impossible to avoid some clots from forming in pumps this small. "The [neurological event] rates are high, but I think they'd be expected to be high, and the overall results are still good."

The panelists agreed that given the severe illness of the patients and lack of better alternatives, the risk of adverse events does not outweigh the benefits of the device. However, they suggested that the company should carefully follow all patients treated with the Excor for at least five years to better understand the long-term neurological and quality-of-life impact of these adverse events in a study or registry.

"Stroke and infections do occur with the [Excor], but they didn't occur in the majority of patients and indeed most patients reached transplant . . . and most patients did well," **Dr Jeffrey Borer** (Downstate

Medical Center, New York, NY) said. "We don't yet have the follow-up data [to] comment on the clinical importance of these events."

Nykanen suggested that a registry of all patients treated with Excor would be better than either a smaller, focused study or just following patients from the pivotal trial. "We'd miss an opportunity with a postmarket study to follow every single one of these patients, which is what we should be doing. We don't know enough about them. We need the surveillance." He also suggested that the registry be indefinite rather than just five years.

Related links

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  [*Arrhythmia/EP* > *Arrhythmia/EP*, Jul 05, 2011]
- New recommendations for pediatric cardiac caths
  [*heartwire* > *Medscape Medical News*; May 09, 2011]
- ISHLT leaders preview new guidelines for managing heart-transplant recipients
  [*Heart failure* > *Heart failure*; Apr 23, 2010]
- British girl thriving three years after donor heart was removed following "piggyback" transplant
  [*Heart failure* > *Heart failure*; Jul 14, 2009]
- Miniaturized heart pumps: Difference between life and death in small children
  [*Interventional/Surgery* > *Interventional/Surgery*; Sep 30, 2008]
- Child's heterotopic donor heart removed, native heart revived after dormant decade
  [*heartwire* > *MediaPulse*; Apr 14, 2006]
- Ventricular assist device, hope for infants awaiting transplant, featured in NYT
  [*heartwire* > *MediaPulse*; Aug 23, 2004]