Percutaneous Closure of the Patent Ductus Arteriosus in Very Low Weight Infants: Considerations Following US Food and Drug Administration Approval of a Novel Device

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The Amplatzer Piccolo Occluder (or Amplatzer duct occluder II-additional sizes, ADO-II AS, Abbott, Chicago, Illinois) was approved by the US Food and Drug Administration on January 11, 2019.1 The class III device is indicated for percutaneous (catheter-based) closure of a patent ductus arteriosus (PDA) in an infant weighing >700 grams and a postnatal age of >3 days. After this regulatory approval, the healthcare community is tasked with answering fundamental questions on the appropriate use of the device in a subgroup of highly vulnerable patients. What is the strength of evidence for the device among very low weight (VLW) infants (<2.5 kg at time of closure)? Is Food and Drug Administration approval sufficient for widespread dissemination of the device or are additional safety and effectiveness data needed?

Traditionally, surgical ligation was used to provide definitive ductal closure for symptomatic infants when medical therapy fails or is contraindicated.2 Evidence of adverse outcomes associated with surgical ligation has led to increasing interest in the use of percutaneous techniques as a less invasive alternative for definitive ductal closure.3,7 Percutaneous PDA occlusion is considered the procedure of choice for adults, children, and infants ≥5 kg.8 Before the Amplatzer Piccolo Occluder, no Food and Drug Administration-approved devices were recommended for percutaneous PDA closure until infants weighed ≥5 kg.7 This weight threshold was based on concerns regarding the introduction of large introducer sheaths, stiff delivery systems, and protrusion of the occluder discs into the left pulmonary artery and descending aorta. Despite high rates of technical success with the off-label use of various devices,7 healthcare providers called for better devices to address the unique ductal morphology and profile of younger, more immature infants. Consequently, the Amplatzer Piccolo Occluder and its delivery system have a number of modifications (short length, low profile delivery system) that are more suitable for use in VLW infants (Figure).1,9

Healthcare professionals are left with an Food and Drug Administration-approved, nonsurgical alternative to achieve definitive ductal closure.1 However, the clinical benefits of closing a PDA among VLW infants remain unknown.10 Not surprisingly, treatment strategies vary markedly among institutions, with some centers aggressively pursuing PDA closure based on evidence that a persistent ductus is associated with greater rates of mortality and linked to harmful longer term outcomes, including chronic lung disease and heart failure.11-13 Alternatively, some centers, based on evidence that all forms of deliberate ductal closure have the potential for adverse side effects and that no studies have shown that treating all preterm infants with a PDA improves outcomes, have adopted a conservative (nonintervention) approach.14,15 These 2 approaches frame the ongoing debate and controversy regarding PDA treatment.

A summary of the published evidence on the use of Amplatzer Piccolo Occluder among VLW infants is provided, including a description of feasibility (technical success) and major adverse events (AEs; Table).16-24 According to federal regulations, the Food and Drug Administration is tasked with ensuring that “there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”25 Based on available evidence, the Food and Drug Administration concluded that the device met thresholds for approval. What outcomes are considered “clinically significant”? Would occluding the PDA and eliminating the left-to-right shunt, suffice? Or is evidence that, compared with alternative treatment strategies, percutaneous occlusion improves longer term outcomes, necessary? When healthcare providers offer treatments for the PDA, they do so in anticipation that the potential risks are justified by the potential benefits.27 Although the technical feasibility and short-term safety profile of the device are promising,24

AE Adverse event   
NEST National Evaluation System for health Technology   
PDA Patent ductus arteriosus   
VLW Very low weight

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the lack of comparative studies and longer term efficacy results have left healthcare providers with insufficient evidence to guide the practice of evidence-based medicine. In other words, “just because we can, does not mean we should.”

A number of strategies are available to accumulate evidence to better define optimal use of the device. Transparent, publicly reported, postmarketing surveillance is 1 strategy to inform healthcare providers, families, and regulators, particularly regarding device-related AEs.28 Traditionally, the Food and Drug Administration relied on healthcare providers to report AEs attributable to a medical device.29 However, healthcare providers may underreport such events, with some studies suggesting that only 1% of all device-related AEs are reported to the Food and Drug Administration, with more serious AEs less likely to be reported.29 In response, regulatory agencies and investigators are increasingly turning to active surveillance models.30

Active surveillance uses either formal registries with ongoing contact with providers to monitor outcomes and side effects over time or a more sophisticated use of electronic health records as a virtual registry. One noteworthy effort that will combine these methods, and is currently being promoted by the Food and Drug Administration, is the National Evaluation System for health Technology (NEST).31 NEST is a network of data partners, predominantly industry, across the medical device ecosystem. The primary goal of NEST is to generate informative clinical knowledge from diverse data sources (electronic health records, billing data, and clinical registries) in an effort to identify safety problems more quickly and to understand better the benefit–risk profiles of devices as used in clinical care.32 Moreover, NEST is seeking nontraditional partners like PEDSnet, a consortium of the nation’s largest children’s hospitals engaged in a unified electronic health record system for longitudinal studies, to combine the best methods from registries and records.23 Because the risk–benefit profiles of percutaneous occlusion are likely to change over time (refinements in clinical technique) and vary according to patient (degree of prematurity, birth weight, severity of respiratory disease, duration of PDA exposure from birth, and PDA size and illness severity), procedural (anesthesia, operator experience), and institutional (site volume) characteristics, the mechanisms for guiding active

### Table

<table>
<thead>
<tr>
<th>First authors (Publication year)</th>
<th>Year</th>
<th>Type of study</th>
<th>Single or multicenter</th>
<th>No. of successful implants/No. of attempted implants</th>
<th>Weight (kg) at time of procedure</th>
<th>No. of major AEs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sungur et al16</td>
<td>2013</td>
<td>Retrospective</td>
<td>Single center</td>
<td>6/7</td>
<td>1.8 ± 0.4</td>
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<tr>
<td>Agnoletti et al17</td>
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<td>Retrospective</td>
<td>Single center</td>
<td>1/1</td>
<td>2.01</td>
<td>0</td>
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<tr>
<td>Narin et al18</td>
<td>2016</td>
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<td>Single center</td>
<td>10/10</td>
<td>0.9 ± 0.1</td>
<td>0</td>
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<tr>
<td>Narin et al18</td>
<td>2017</td>
<td>Retrospective</td>
<td>Single center</td>
<td>12/12</td>
<td>1.4 ± 0.4</td>
<td>0</td>
</tr>
<tr>
<td>Morville et al25,†</td>
<td>2017</td>
<td>Prospective</td>
<td>Single center</td>
<td>31/32</td>
<td>1.4 ± 0.5</td>
<td>7†</td>
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<tr>
<td>Morville et al24,‡</td>
<td>2018</td>
<td>Prospective</td>
<td>Single center</td>
<td>17/18</td>
<td>1.0 ± 0.2</td>
<td>6§</td>
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<tr>
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<td>Retrospective</td>
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<td>27/27</td>
<td>1.26 (1.0-1.98)</td>
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<tr>
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<td>25/25</td>
<td>1.33 ± 0.20</td>
<td>2††</td>
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<tr>
<td>Berman et al24,¶</td>
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<td>Prospective</td>
<td>Multicenter</td>
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<td>1.6 ± 0.8</td>
<td>1**</td>
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</tbody>
</table>

Studies were included if the mean or median patient weight was <2.5 kg. Studies that enrolled mixed populations (infants and older children or adults) were included if individual outcomes among infants <2.5 kg could be ascertained. Studies that included various PDA closure devices were included if outcomes among infants <2.5 kg with Amplatzer Piccolo Occluder (or Amplatzer ductal occluder additional sizes, ADO-II AS) could be ascertained.

*As defined by Bergersen et al.25
†Potential overlap between studies.
‡Cardiac perforation by catheter wire, death (n = 1); blood loss, transfusion required (n = 1); hypotension, treatment required (n = 5).
*Cardiac preformation by catheter wire, death (n = 1); blood loss, transfusion required (n = 1); hypotension, treatment required (n = 4).
¶Embolization (n = 2); “surgical complications” noted in 3 other cases with no further elaboration.
**Embolization (n = 2); percutaneous retrieval.
††Embolization, percutaneous retrieval.
surveillance of these data as they accumulate are necessary to minimize risk and yield the greatest benefits from this novel device.

At present, the optimal use of the Amplatzer Piccolo Occluder is unknown because of the lack of comparative trials with alternative PDA treatments (conservative treatment, surgical ligation). Acknowledging the lack of data, the American Academy of Pediatrics has emphasized the need for equipoise among healthcare providers regarding enrollment of preterm infants into clinical trials designed to assess PDA treatment strategies.10 To inform the practice of evidence-based medicine, prospective clinical trials that compares percutaneous closure vs alternative treatment strategies using well-defined inclusion criteria, consistently applied treatment protocols, careful attention to potentially harmful exposures (anesthesia, sedation, radiation), mechanisms for AE surveillance, and longer term follow-up, are needed. This effort will require interdisciplinary (neonatology, pediatric cardiology, congenital cardiac catheterization, anesthesiology), and multi-institutional cooperation.

Before the accumulation of sufficient evidence, we suggest a number of potential strategies for the ongoing use of the device in the pediatric community. First, the device should be restricted to healthcare providers with requisite expertise and experience, and institutions with the infrastructure and interdisciplinary collaboration necessary for robust preprocedural and postprocedural evaluation and surveillance. Second, rather than an all-or-none approach, selective use of percutaneous PDA closure in the subgroup of infants beyond the window when drug therapy is most efficacious or spontaneous closure has yet to occur, and who continue to have adverse ductal sequelae, may optimize the risk–benefit profiles. Third, patient selection for device use should be based on clear evidence of a hemodynamically significant PDA that takes into account indicators (clinical, echocardiographic, biomarkers) of adverse ductal consequences. For example, rather than relying on ductal diameter alone as the primary marker of echocardiographic disease severity, additional measurements (eg, left ventricular output, shunt volume) may provide insights regarding the magnitude of the physiologic disturbance.33 Fourth, to inform the practice of fiscal stewardship, formal economic evaluations alongside clinical trials are necessary. Finally, the unique and complex ductal morphology of VLW infants warrants careful consideration of alternative devices (eg, Medtronic Micro Vascular Plug [Medtronic, Dublin, Ireland], Amplatzer Vascular Plug II) with high rates of technical feasibility and evidence of short-term benefits.34,35

Although the Amplatzer Piccolo Occluder provides the healthcare community with a nonsurgical alternative to achieve definitive ductal closure, fundamental questions on the optimal use of the device remain unanswered.36 Active surveillance and routine monitoring of percutaneous PDA closure devices may provide opportunities for earlier identification of adverse safety signals, which can inform healthcare providers, families, and regulators about potential problems or unexpected benefits. In the absence of comparative data, pragmatic, well-designed prospective trials with longer term, clinically meaningful outcomes, are needed.

References


