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# Percutaneous closure of patent ductus arteriosus in premature infants: A French national survey

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## Abstract

**Background:** Transcatheter closure of patent ductus arteriosus (PDA) in premature infants has been shown to be feasible in small series. Outcomes in larger series are currently lacking.

**Material:** All premature infants (< 36 weeks GA) who underwent transcatheter PDA closure were included in a multicenter French national survey. Demographic data (gestational age [GA], birth weight [BW]) and procedural data (weight [PW], age at procedure [AP], procedural success, fluoroscopy time, and type of device) were collected. Outcomes and procedural complications were reviewed.

**Results:** Between September 2013 and June 2017, 102 patients were included. In 71 cases, PDA pharmacological closure had been attempted. Mean GA was 27 ± 2.9 weeks. Mean BW and PW were 1,040 ± 715 g and 1,543 ± 698 g, respectively. Mean AP was 39 ± 26 days. Number of premature infants <1 kg, between 1 and 2 kg, and > 2 kg was 21, 59, and 22, respectively. Mean fluoroscopic time was 6.5 min. Success rate was 99%. Device- or procedure-related complications were reported in nine patients (8.9%) including three LPA stenoses (requiring surgery in two and balloon dilatation in one), two neo-coarctations (one requiring subsequent surgery), and three instances of tricuspid valve regurgitation at follow-up. Seven deaths were reported, none being related to the procedure. Mean follow-up was 39.75 ± 13.1 months.

**Conclusion:** In this large series of premature infants undergoing transcatheter PDA closure, it was demonstrated that this procedure can be performed successfully in the vast majority of patients with an acceptable complication rate. Future efforts should focus on minimizing complications, particularly device-related vascular stenoses.

KEYWORDS
low birth weight, patent ductus arteriosus, premature infants, transcatheter closure

**Abbreviations:** AP, age at procedure; BW, birth weight; GA, gestational age; LPA, left pulmonary artery; LV, left ventricle; PDA, patent ductus arteriosus; PW, procedural weight; TTE, transthoracic echocardiography.

  

## 1 | INTRODUCTION

Patent ductus arteriosus (PDA) is very common finding in premature infants, and prevalence of ductal patency is inversely related to gestational age and birth weight.[1] It is associated with adverse events such as necrotizing enterocolitis, chronic respiratory disease, pulmonary and cerebral hemorrhage, and death.[2] However, the causality of this relationship has never been established.[3] Practices regarding treatment of the PDA vary grately. In most centers, pharmacological treatment is first-line therapy,[4] however, medications fail in about 30% and can have important adverse effects (i.e., renal insufficiency and bleeding) and may be contraindicated in some patients.[5] Second-line treatment has traditionally been surgical ligation. In this fragile population, surgery has a low mortality but significant morbidity including phrenic or recurrent nerve palsy, pneumothorax, intraoperative bleeding, wound infection, and postligation cardiorespiratory syndrome.[6]

Transcatheter PDA closure is the gold standard in children weighing more than 5 kg.[7] Until recently, there was no dedicated device to treat premature infants. With new miniaturized devices and flexible delivery sheaths, transcatheter closure is now feasible in preterm infants with theoretically virtually no limit in regard to patient weight. Multiple reports have shown feasibility, success, and complication rates but the number of patients in these series was limited.[8–12] Herein, we report our national experience in a large multicenter study, aiming to describe the evolution of the technical aspects as well as outcomes of this procedure.

## 2 | MATERIALS AND METHODS

The French working group of Cardiac Catheterization in Congenital Heart Disease Patients (Club Français des Cardiologues Cathétériseurs des Cardiopathies Congénitales C4F) conducted a retrospective study on transcatheter PDA closure in preterm infants.

Four centers (out of 11 who perform pediatric cardiac catheterization) reported performing PDA closure in premature infants and agreed to participate in this study. All premature infants who had transcatheter PDA closure between September 2013 and June 2017 were included in this series. Informed consent was obtained for all patients.

Demographic data (i.e., date of birth, gender, gestational age, birth weight, medications for PDA closure [acetaminophen or Cox inhibitor] prior to intervention) and procedural data (i.e., vascular access, type of device, procedural success, contrast injection, radiation dose, and procedural duration) were recorded. Procedural complications, including but not limited to LPA obstruction and coarctation, were reviewed. Ductal patency, respiratory, and cardiac data at discharge were recorded.

### 2.1 | Procedural technique

The technique used varied between centers (Table 1), however, the following steps were used in all cases. All neonates were transferred to the cardiac catheterization laboratory and procedures were performed under general anesthesia. Patients were enveloped in a warm blanket, and their temperature was monitored throughout the procedure. In order to shorten the procedure as much as possible, only noninvasive hemodynamic data were collected during the catheterization. The femoral vein was cannulated using a 21-gauge needle through which a wire was introduced and advanced. A 4Fr sheath was then inserted. A catheter led by a soft 0.014-in. wire was advanced through the right heart and positioned across the PDA into the descending aorta.

Centers using 3 Fr catheters exchanged to a 4 Fr vertebral catheter (Cordis) and placed a 0.035-in. Teflon guide wire (St Jude Medical) in the descending aorta to enable advancement of the delivery system (4Fr TorqVue, St Jude Medical). In the center using a 4 Fr catheter, a stiff 0.014 wire (Spartacore) was advanced besides a Pilot wire through the catheter in the descending aorta and both wires helped to advance the delivery system to the correct position. All centers

**TABLE 1** Technical variations across four centers

| | Center 1 | Center 2 | Center 3 | Center 4 |
|---|---|---|---|---|
| Anesthesia | GA | GA | GA | GA |
| Vascular access | FV | FV | FV or FA | FV |
| Heparin | No | No | No/heparinization of fluid on the table only | No |
| Catheter | 3Fr Tempo Cordis | 3Fr MP Bard | 4 Fr JR1.5 special Cordis | 4 Fr cerebral Cordis |
| Guide wire | 0.018-in. Terumo<br>0.014-in. Biotronik<br>0.035-in. St Jude | 0.018-in. Terumo<br>0.014-in. Pilot 50<br>0.035-in. St Jude | 0.014-in. Pilot 50<br>0.014-in. Spartacore | 0.018-in. Terumo<br>0.014-in. Whisper extrasupport |
| Device | ADOIIAS | ADOIIAS | ADOIIAS, coils, MVP | ADOIIAS |
| Imaging modalities | TTE & fluoroscopy | TTE & fluoroscopy | TTE & fluoroscopy | TTE & fluoroscopy |
| Dye injection | No | No | Yes for PDA measurement | No |
| Cine angiogram | No | Yes-deployment of the device | Yes-one short for measurement purposes | Yes-deployment of the device |
| Fluoroscopy frame rate | 12 fps | 7 fps | 4-7fps | 10-15fps |

Abbreviations: FA, femoral artery; fluoro, fluoroscopy; fps, frame per second; FV, femoral vein; GA, general anesthesia; TTE, transthoracic echocardiography.

aimed to preserve the renal function by limiting the amount of contrast given to the patient. Three centers did not used angiography and relied exclusively on echocardiography to visualize the PDA (Figure 1 and Video S1). In one center, an average of 1.5 mL contrast was injected for PDA measurement. One center occasionally accessed the femoral artery to close the PDA. In that situation, a sheathless technique was used[13] to limit the size of vascular access in babies weighing less than 2 kg. Various devices were used to close PDA (i.e., Amplatzer ADO IIAS (St Jude Medical®, Minneapolis, Minnesota), coils and microvascular plug (MVP, Medtronic®, Minneapolis, Minnesota)).

Devices were selected to be 1 mm larger than the PDA diameter, and initially with a length smaller than or equal to the PDA. Positioning and deployment of the device was done using echocardiography and/or fluoroscopy. Before release, residual shunting and the presence of LPA or aortic obstruction were assessed. If present, the device was reloaded and repositioned. The device was then released. After the procedure, patients were transferred to the NICU for close monitoring.

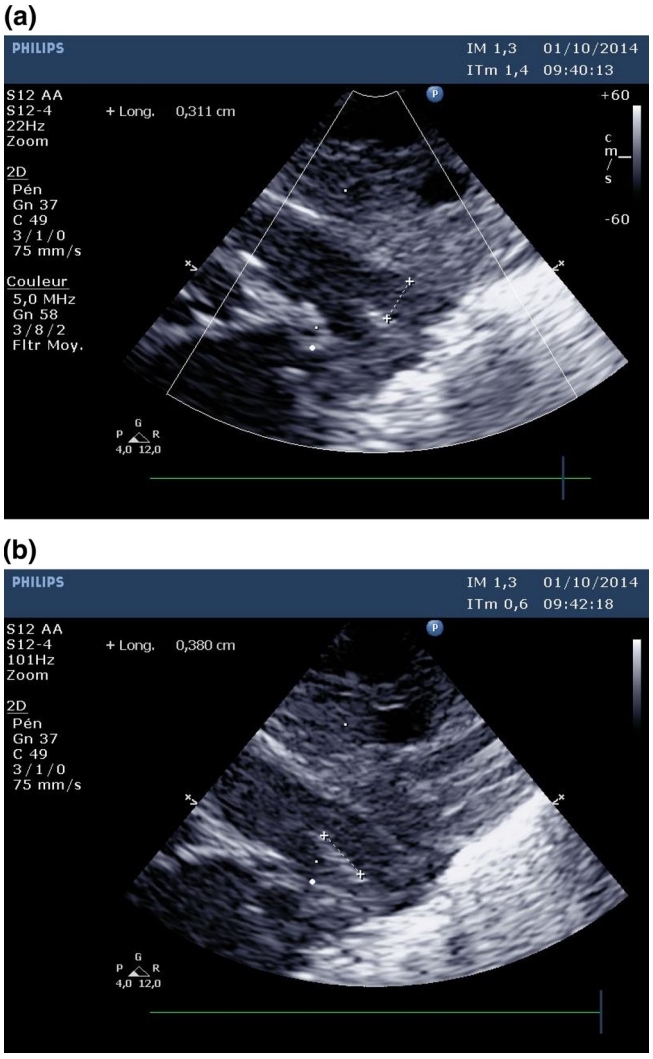


**FIGURE 1** 2D echocardiographic measurement of PDA (a) diameter and (b) length [Color figure can be viewed at wileyonlinelibrary.com]

## 2.2 | Statistical analysis

Categorical variables are given in the number of patients (percentage). Continuous variables are summarized by mean and SD, median and inter quartile range (IQR), and range (min, max). In case of missing values, the number of patients with missing values is reported. Groups were compared using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. All hypotheses were tested at the two-tailed 0.05 significance level. All statistical analyses were performed using SAS, version 9.4 (SAS Institute).

# 3 | RESULTS

Between September 2013 and June 2016, 102 patients from 4 centers were included in the study. Seventeen patients had already been included in prior publications.[14,15] Demographic details are shown in Table 2.

In 71 patients, pharmacological treatment (acetaminophen or Cox-inhibitor) had failed to close the PDA.

Patients were divided into three groups according to their procedural weight. Group 1 included infants weighing up to 1 kg ($n$ = 21), Group 2 between 1 and 2 kg ($n$ = 59), and Group 3 above 2 kg ($n$ = 22). Patients were statistically significantly different in the three groups in term of BW ($p$ = .0016) and AP ($p$ < .001). Figure 1 shows that patients were younger and smaller with increasing experience.

## 3.1 | Procedural data

Implant success rate was 99% (Table 3 and video S2). In one patient, the largest available device was placed, and then retrieved because of a large residual shunt and unstable device placement. Spontaneous closure was noted in follow-up.

Mean PDA diameter was 2.9 mm at the pulmonary end and 3.2 mm at the aortic end. Mean PDA diameter was similar among the

**TABLE 2** Demographic data

| | | GA (weeks) | BW (gr) | AP (days) | Procedural weight (gr) |
|---|---|---|---|---|---|
| Total | 102 | 27 ± 2.9 | 1,040 ± 715 | 39 ± 26 | 1,543 ± 698 |
| ≤ 1 kg | 21 | 25.8 ± 1.4 | 682 ± 110 | 22 ± 8 | 880 ± 105 |
| 1 to 2 kg | 59 | 26.5 ± 1.3 | 882 ± 195 | 32 ± 13 | 1,334 ± 234 |
| > 2 kg | 22 | 30.3 ± 4.5 | 1,458 ± 730 | 71 ± 32 | 2,707 ± 413 |

Abbreviations: AP, procedural age; BW, birth weight; GA, gestational age.

**TABLE 3** Procedural data

| | PDA diameter pulm side (mm) | PDA diameter Ao side (mm) | Fluoroscopy time (min) | Device | Dose (mGy) | Complications |
|---|---|---|---|---|---|---|
| Total | 2.9 | 3.2 | 6.5 | ADO II AS 91<br>MVP 10<br>Coil 1 | 30 ± 52 | TR 3<br>Late CoA 1<br>Mild aortic obstruction 1<br>LPAobstruction 3 |
| ≤ 1 kg | 3.2 | 3.2 | 6.1 | ADO II AS 19<br>MVP 2 | 11± 9 | Late Coa 1<br>TR 1 |
| 1 to 2 kg | 2.8 | 3.1 | 6.5 | ADO II AS 54<br>MVP 4<br>1 Sheathless | 29 ± 49 | LPA obstruction 3<br>TR 2 |
| > 2 kg | 2.8 | 3.6 | 6.9 | AOD II AS 17<br>MVP 4<br>1 sheathless<br>Coil 1 | 49 ± 74 | 1[%] failure |

Abbreviations: Ao side, aortic side; CoA, aortic coarctation; LPA, left pulmonary artery; pulm side: pulmonary side; sheathless access: use of arterial sheathless access with MVP to close PDA; TR, tricuspid regurgitation; % failure: too large for largest ADO II AS, spontaneous closure 72 hr postprocedure.

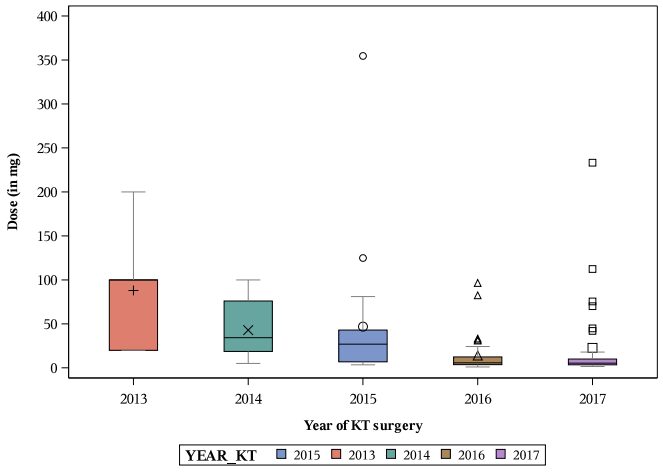


**FIGURE 2** Radiation exposure according to the years [Color figure can be viewed at wileyonlinelibrary.com]

three groups ($p$-value .2 for pulmonary end and $p$-value .43 for aortic end), but the shape of the PDA was more conical in older infants and tubular in the youngest infants.

Mean fluoroscopy time was 6.5 min and was similar among the three groups. Radiation exposure was significantly lower in smaller patients ($p$ = .09). Large variation in radiation exposure was noted among the different centers. Radiation significantly decreased with operator experience as shown in Figure 2.

## 3.2 | Devices used for PDA closure

Ninety one ADO II AS, 10 MVP, and 1 coil were used. There were no embolisations in this series, and no residual shunt was reported. ADO II devices were placed entirely within the PDA without any disk in the pulmonary artery or in the aorta.

MVP were deployed via the femoral vein in eight cases (4 Fr sheath) and via the femoral artery in two cases (sheathless, use of a microcatheter directly in the artery). The reason to choose arterial access was the presence of a thrombus in the right atrium secondary to umbilical central line with coexisiting ASD (technical details published in reference 12).

In Group 1, 4-mm devices were used in the majoritiy of cases. In Group 2, 4-mm and 5-mm devices were used; in Group 3, 5-mm devices were used in the majority of cases (Figure 3a). The length of the device tended to decrease over time and by the end of the study, only 2-mm length devices were used.

When looking at the weight/prosthesis diameter ratio in the three groups, PDA tended to be proportionally larger in smaller infants, which is consistent with what was already demonstrated by the similar diameter of the PDA in the three groups (Figure 3b). Given that the PDA diameter was similar in all three groups, the weight/prosthesis diameter was inversely correlated with patient weight. In addition, the weight/prosthesis diameter ratio decreased over time, indicating successful closure of PDA in smaller infants with growing experience.

## 3.3 | Complications

No local complications were reported. No secondary renal failure was noted in the center that used angiography to measure the PDA.

LPA stenosis was reported in three patients during the follow-up visit. Two patients had surgery to remove the device and one patient had LPA balloon dilation with a good long-term result. In one 890 g patient, an MVP7Q device was used to close a large PDA because the ADO II AS 5×2 was too small. Ten weeks after the procedure, the patient was noted to have aortic coarctation. Failure to treat the coarctation without stent implantation led to surgical treatment of the acquired coarctation. One patient with a mild Doppler gradient on the aortic isthmus is regularly followed-up; at the time of this publication, he is not hypertensive and has no left ventricular hypertrophy.

Three patients have tricuspid regurgitation secondary to tricuspid chordae rupture. This was related to a technical issue that were

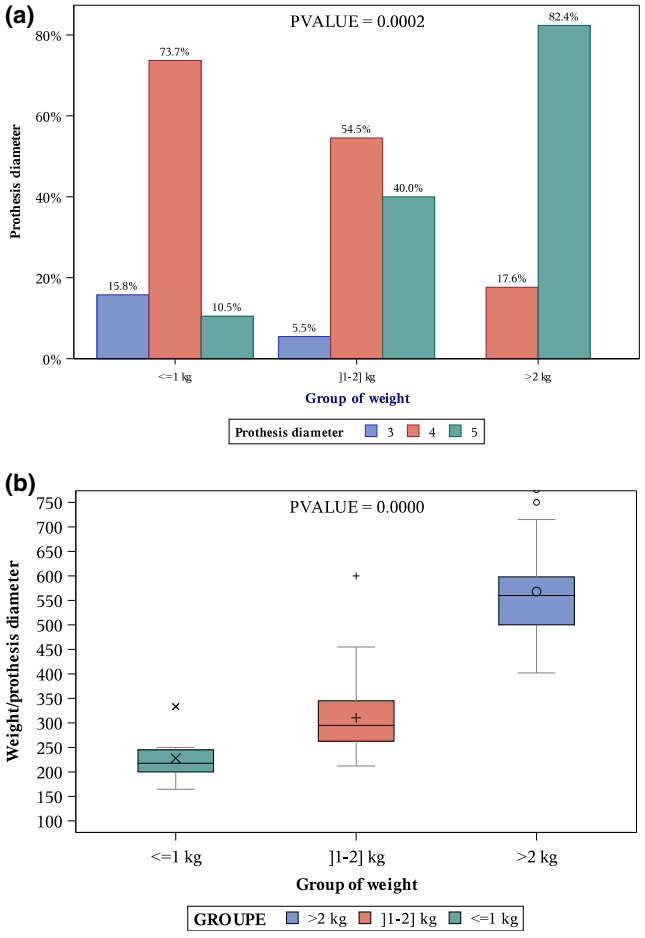


**FIGURE 3** ADO II AS device use (a) categorized prosthesis diameter according to the weight group; (b) weight/prosthesis diameter according to the weight group [Color figure can be viewed at wileyonlinelibrary.com]

subsequently modified. In these three infants, one 0.014-in. stiff guidewire had been used to advance the Torq Vue catheter with mismatch between the catheter lumen and guidewire diameter. After changing the technique by using 2–0.014-in. guidewires to advance the Torq Vue catheter, this complication was not subsequently encountered. No procedural complication were reported to have led to severe permanent cardiac lesions. The complication rate was similar between the three groups ($p$ = .44).

### 3.4 | Deaths

Seven deaths occurred during follow-up (mean follow-up 39.8 ± 13.1 months). None of the deaths were attributed directly to the procedure. Death rate was not different among the three groups ($p$ = .38).

Three patients died from persisting renal failure and anuria despite successful closure of the PDA. One patient died from necrotizing enterocolitis 6 days after the procedure. One patient died from hemochromatosis. One death was related to respiratory disease thought to be secondary to surfactant deficiency and one patient had an intracerebral bleed before PDA closure and eventually died secondary to neurologic sequelae.

## 4 | DISCUSSION

To our knowledge, we report the largest series to date of premature infants undergoing transcatheter PDA closure. Our study confirms the high rate of technical success and provides descriptive clinical and outcome data.

With regards to patient selection, this studies shows that with increasing center experience, patient weight, and age at the time of the procedure tend to decrease. We attribute this to a change in referral pattern with increasing experience and outcomes. Our neonatology colleagues began to refer preterm infants at younger ages for device closure as acceptable results were documented. This may have important future implications as successful treatment of PDA at an earlier age could potentially decrease common complications of prematurity that occur during a prolonged intensive care unit stay.

Procedural length, complications, and success rate were not different in the three groups, suggesting that the procedure was not technically more complex in smaller infants once experience had been acquired. Differences between centers existed in terms of techniques and devices used to achieve PDA closure, however, this study was unable to demonstrate any significant difference between devices or techniques used in terms of outcomes.

Similar to previous investigators,[13,14] our study demonstates that PDA closure in this population can be performed safely without contrast injection utilizing transthoracic echocardiographic guidance. This has numerous potential advantages including: lower radiation exposure, avoidance of potential negative effects of contrast, and the ability to one day move this procedure to the bedside.

ADO II AS was used in 91/102 patients. In general, 1 mm was added to the PDA size to choose the device diameter. Data have demonstrated that over time, all centers used the shortest length device available (2 mm) in the hopes of decreasing LPA or aortic obstruction, even if the PDA was long and tubular. In the latter 32 patients, in 2017, only 2-mm length devices were used, regardless of patient weight, ductal diameter, and device diameter. Angiographic measurements as well as echographic measurements showed that PDA size was relatively constant in the three groups making it proportionally much larger in the smaller infant group. MVP was used in 10 patients. This device was easily used without the need for a stiff catheter as it can be delivered via a simple 4 Fr catheter. However, in our experience, there are two major issues with this device: the unconstrained and constrained lengths (unconstrained length 12 mm for MVP-3Q and MVP-5Q and 16 mm for MVP-7Q) are rather long, and there is a general lack of radio-opacity making visualization difficult.

Complications were encountered in our series but none of them led to death or untreatable cardiac lesions. Patients with tricuspid regurgitation continue to be followed and the regurgitant volume remains constant without any adverse consequence on right cavity volume. It is remarkable that there was no difference in complication

rate among the three groups. This, along with minimal fluoroscopy time, highlights that the procedure is not more complex in small infants once experience has been acquired.

While mortality was high (7%), it is important to note that this was not directly related to the procedure in any case. This is a complex group of critically ill patients typically with multisystem organ involvement and not surprisingly mortality in this series was primarily related to persistant organ failure that was present before PDA closure or to other non-specific causes related to prematurity. In patients with renal insufficiency, cerebral hemorrhage and pulmonary dysplasia, prolonged exposure to a large hemodynamically significant PDA prior to closure may have had a detrimental effect on the ultimate outcome. We speculate in these cases that earlier PDA closure might have modified the clinical course of these patients.

### 4.1 | Limitations

This is a retrospective study. Data regarding incidence of post ligation cardiac syndrome as well as incidence of pulmonary dysplasia are lacking. Large prospective registries to evaluate mid-term evolution and incidence of prematurity-related omplications as well as medium-term occurrence of side effects of transcatheter PDA closure are needed to evaluate the global benefit of this new strategy to close PDA in premature infants.

## 5 | CONCLUSIONS

The present series demonstrates that transcatheter PDA closure is feasible in a large population of premature infants. The procedure can be performed with good results even in smaller infants. Different techniques exist, and this study was not powered to determine if one technique or device is superior to another. This study also demonstrates that closure can be performed safely without contrast injection using echocardiographic guidance. Complications did not lead to permanent cardiac damage. Mortality in this population remains high but appeared to be related primarily to patient status prior to the procedure rather than the procedure itself.

Transcatheter closure of PDA in premature infants appears to be a safe and effective alternative to surgical ligation after failure of pharmacological therapy or in cases where there is a contraindication to medical treatment. With increasing experience and knowledge gained from prospective, randomized trails, it is possible that one day this could become the first-line treatment of choice for closure of hemodynamically significant PDA in premature infants.

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### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

### FINANCIAL DISCLOSURE

Sophie Malekzadeh-Milani, Pierre Mauran, and Ahmad Akhavi received fundings from Saint-Jude Medical to travel to meetings.

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### REFERENCES

1. Semberova J, Sirc J, Miletin J, et al. Spontaneous closure of patent ductus arteriosus in infants ≤1500 g. Pediatrics. 2017;140(2): 20164258.
2. Schena F, Francescato G, Cappelleri A, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. J Pediatr. 2015;166(6):1488-1492.
3. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010;30 (4):241-252.
4. El-Mashad AE, El-Mahdy H, El Amrousy D, Elgendy M. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. Eur J Pediatr. 2017;176(2):233-240.
5. Ohlsson A1, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2015;18(2):CD003481.
6. Koehne PS, Bein G, Alexi-Meskhishvili V, Weng Y, Bührer C, Obladen M. Patent ductus arteriosus in very low birthweight infants: complications of pharmacological and surgical treatment. J Perinat Med. 2001;29(4):327-334.
7. Feltes TF, Bacha E, Beekman RH, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation. 2011; 123(22):2607-2652.
8. Backes CH, Cheatham SL, Deyo GM, et al. Percutaneous patent ductus arteriosus (PDA) closure in very preterm infants: feasibility and complications. J Am Heart Assoc. 2016;5(2):e002923.
9. Zahn E, Peck D, Phillips A, et al. Transcatheter closure of patent ductus arteriosus in extremely premature newborns. Early Results Midterm Follow-Up J Am Coll Cardiol Interv. 2016;9:2429-2437.
10. Wang-Giuffre EW, Breinholt JP. Novel use of the medtronic micro vascular plug for PDA closure in preterm infants. Catheter Cardiovasc Interv. 2017;89(6):1059-1065.
11. Sathanandam S, Justino H, Waller BR 3rd, Radtke W, Qureshi AM. Initial clinical experience with the medtronic micro vascular plug™ in transcatheter occlusion of PDAs in extremely premature infants. Catheter Cardiovasc Interv. 2017;89(6):1051-1058.
12. Sathanandam S, Balduf K, Chilakala S, et al. Role of transcatheter patent ductus arteriosus closure in extremely low birth weight infants. Catheter Cardiovasc Interv. 2019;93(1):89-96.
13. Boudjemline Y. Covidien micro vascular plug in congenital heart diseases and vascular anomalies: a new kid on the block for premature babies and older patients. Catheter Cardiovasc Interv. 2017;89(1):114-119.
14. Morville P, Akhavi A. Transcatheter closure of hemodynamic significant patent ductus arteriosus in 32 premature infants by amplatzer ductal occluder additional size-ADOIIAS. Catheter Cardiovasc Interv. 2017;90(4):612-617.

15. Morville P, Douchin S, Bouvaist H, Dauphin C. Transcatheter occlusion of the patent ductus arteriosus in premature infants weighing less than 1200 g. Arch Dis Child Fetal Neonatal Ed. 2018;103(3):F198-F201.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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