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PEDIATRIC AND CONGENITAL HEART DISEASE**Original Studies**

Results of the combined U.S. multicenter postapproval study of the Nit-Occlud PDA device for percutaneous closure of patent ductus arteriosus

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Abstract

Objectives: To report the results of the Nit-Occlud PDA prospective postapproval study (PAS) along with a comparison to the results of the pivotal and continued access trials.

Background: The Nit-Occlud PDA (PFM Medical, Cologne, Germany), a nitinol coil patent ductus arteriosus (PDA) occluder, was approved by the Food and Drug Administration in 2013.

Methods: The PAS enrolled a total of 184 subjects greater than 6 months of age, weighing at least 5 kg, with PDAs less than 4 mm by angiography at 11 centers. Patients were followed prospectively at 2 months, 12 months, and 24 months postprocedure. These outcomes were compared to the 357 subjects enrolled in the pivotal and continued access protocols. Efficacy and safety data were reported.

Results: Among 184 subjects enrolled for the PAS between 2014 and 2017, 180 (97.8%) had successful device implantation. After 12 months, 98.7% (150/152) had trivial or no residual shunt by echocardiography and two subjects had only small residual shunts. There were three

Institutions where the work was performed: Multi-center study.

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device embolizations that were all retrieved by snare without clinical consequence. Together with the pivotal and continued access study, 97.4% (449/461) had complete echocardiographic closure at 12 months in 541 enrolled subjects. The composite success was 94.4%. There were no mortalities and no serious device-related adverse events.

Conclusions: The Nit-Occlud PDA is a safe and effective device for closure of a small to moderate sized PDA. There were no serious device-related adverse events in a large cohort of three clinical trials.

KEYWORDS

coil, occluder device, patent ductus arteriosus

1 | INTRODUCTION

Patent ductus arteriosus (PDA) is one of the common congenital heart diseases. Transcatheter closure of PDA is indicated for medium- to large-sized PDA and small audible PDAs.¹ The Nit-Occlud PDA (PFM Medical, Cologne, Germany) is a nitinol coil designed with two cones of spirals specifically for use as a PDA occluder. Its premarket approval was approved by the Food and Drug Administration in 2013 based on the results of the pivotal trial. The Nit-Occlud is currently approved in the US for closure of PDAs smaller than 4 mm in infants greater than 5 kg and 6 months of age. The result of the combined United States multicenter pivotal and the continuing access study was reported in 2014, showing the excellent efficacy and safety of the Nit-Occlud PDA for closure of small- to medium-sized PDA.²

The Nit-Occlud PDA postapproval study (PAS) was designed to continue to evaluate the safety and efficacy of the Nit-Occlud PDA device in the postapproval phase. The objective of this study was to report the results of the Nit-Occlud PDA prospective PAS along with a comparison to the results of the pivotal and continued access trial.

2 | MATERIALS AND METHODS

2.1 | Device and procedure

The Nit-Occlud PDA device is a nitinol coil designed for PDA closure. The device specification has been previously described in detail.² The Nit-Occlud PDA device has a reverse-cone shape having proximal and distal coils that is made to fit into the ductal ampulla and anchor to the pulmonary side of the PDA (Figure 1A). There are six sizes available: 4 × 4 mm, 5 × 4 mm, 6 × 5 mm, 7 × 6 mm, 9 × 6 mm, 11 × 6 mm. Each device is named by diameter of distal coil diameter × proximal coil loop diameter. The smaller “Flexible” devices (4 × 4 mm, 5 × 4 mm, 6 × 5 mm) can be delivered through a 4-Fr delivery catheter, whereas the larger “Medium” devices (7 × 6 mm, 9 × 6 mm, 11 × 6 mm) require a 5-Fr delivery catheter. The size of device is selected according to the angiographic measurement of PDA on lateral aortography. The distal coil diameter should be no more than 2 mm larger than the aortic ampulla diameter and at least 3–4 mm larger than the pulmonary end and/or narrowest diameter of PDA. The length of device should not be longer than the ductal length.

The Nit-Occlud PDA device is usually deployed antegrade from the pulmonary side. Distal windings of the device are configured in the descending aorta (DAO) and pulled back to the ductal ampulla. Then, one of the “reverse cone” proximal windings are delivered at the pulmonary side. After confirming a satisfactory position of coil, the device is detached (Figure 1B). If embolized, the device can be retrieved by snaring any part of the coil and retracting it into a 6-Fr sheath.

2.2 | Study design

The Nit-Occlud PAS study was a prospective, nonrandomized multicenter trial conducted in 11 medical centers (Appendix 1) in the United States. The study evaluated the safety and effectiveness of the Nit-Occlud PDA device in the postapproval phase. The study's outcomes were defined to determine whether the Nit-Occlud PDA met or exceeded objective performance criteria (OPC) derived from historical results of device and surgical PDA closure.³ Local institutional review board approval was obtained in each participating center for this study. Informed consent was obtained for each study subject.

Inclusion criteria were: age between 6 months and 21 years, weight ≥ 5 kg, and an angiographically confirmed PDA with a minimum diameter of <4 mm. Exclusion criteria included presence of associated cardiac anomalies requiring surgery, bleeding or clotting disorders, pulmonary hypertension (with pulmonary vascular resistance ≥5 Woods unit), contrast or nickel allergy, pregnancy and acute illnesses.

Patients were evaluated before and during cardiac catheterization, at hospital discharge, and 2 months, 12 months, and 24 months after device implant. Subjects with documented residual PDA shunt, any significant left pulmonary artery (LPA) or DAO obstruction and/or on ongoing device-related issue at 12 months were followed yearly postimplant for an additional 4 years (24 months, 48 months, and 60 months). At follow-up, subjects were evaluated on history, physical examination and transthoracic echocardiography. Subject data were maintained in an electronic study database. The consistency of reports with source patient data were confirmed by the periodic site audits.

2.3 | Outcome measures

The primary outcome of the PAS was effectiveness and safety at 12-month after device implant. The effectiveness measure was

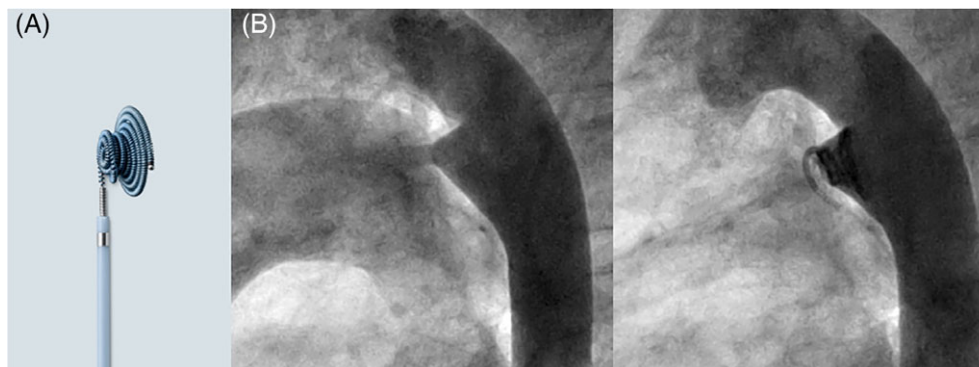


FIGURE 1 A, Nit-Occlud PDA coil. B, Descending aortography at the straight lateral projection. Baseline angiography (left) shows type A ductus arteriosus with moderate left to right shunt. After implantation of Nit-Occlud PDA coil, angiography (right) demonstrates a satisfactory position of Nit-Occlud PDA coil within the ductus arteriosus, resulting in no residual shunt [Color figure can be viewed at wileyonlinelibrary.com]

complete closure of PDA, defined as absence of residual PDA flow by color Doppler transthoracic echocardiography. The OPC for the effectiveness measure was 85%. The safety measure was serious device-related adverse event defined as life-threatening events that required surgery to correct, resulted in hospitalization or prolonged hospital stay, caused long-term disability, or resulted in genetic damage or birth defect. Other serious adverse events included cerebral or pulmonary embolism, bacterial endocarditis, device embolization requiring surgery, and persistent cardiac arrhythmia requiring a pacemaker. Total adverse events included serious adverse events and non-life threatening events, which were resolved either by nonsurgical intervention or with no intervention. The OPC for serious device-related adverse events was 1%. Composite success was defined as technical success of device implantation, clinical and echocardiographic closure of the PDA 1 year after device implantation, and absence of device- or procedure related death or serious device-related adverse events after 1 year follow-up. The OPC for the composite success was 80%.

In addition, these outcome measures were evaluated in the combined cohort of the pivotal, continued access and postapproval studies.

2.4 | Statistical analysis

Data were expressed as frequency (percentage) for binary outcomes. Standard errors and exact 95% confidence intervals were calculated. Statistical analysis was performed using the statistical softwares including SAS (SAS Institute Inc., Cary, North Carolina) and STATA (version 10, StataCorp, College Station, Texas) and StatXact software (Cytel Software, Cambridge, Massachusetts). Outcome measures were compared with OPC.

3 | RESULTS

A total of 184 subjects were enrolled from 11 sites in the PAS (Figure 2). The median age of patients was 3.4 years (range 4 months

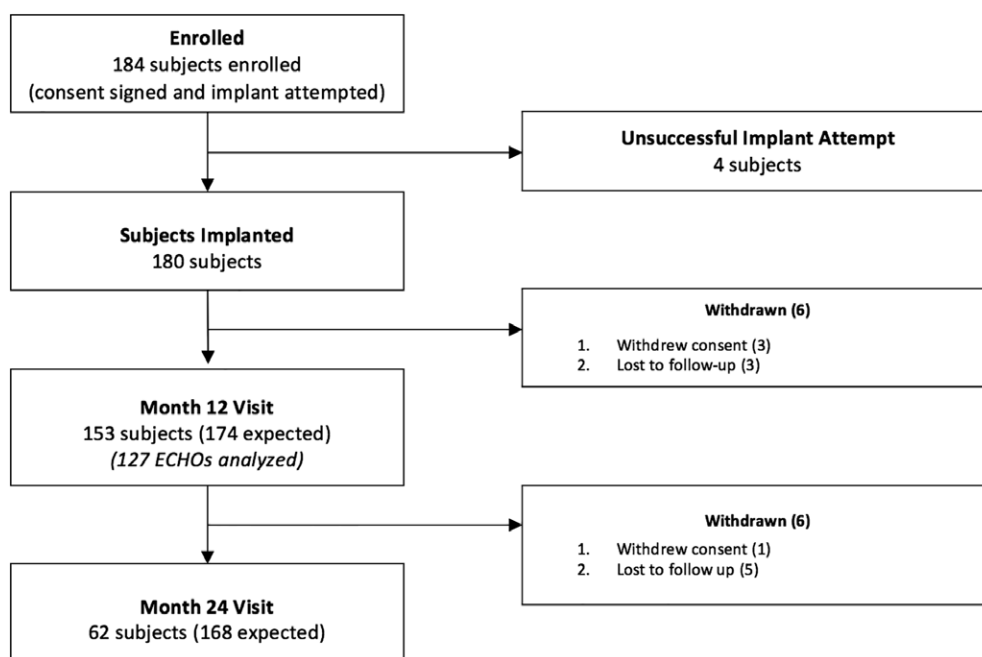


FIGURE 2 Study flow chart in the postapproval study

TABLE 1 General characteristics of subjects enrolled in the postapproval study

Characteristics	N = 184
Gender - n (%)	
Female	126 (68.5%)
Male	58 (31.5%)
Age (years) at enrollment	
Median [IQR]	3.4 [1.5, 5.4]
Range	0.3–21.1
Weight (kg) at enrollment	
Median [IQR]	14.1 [9.9, 20.8]
Range	5.5–86.9
History of congenital heart disease other than PDA - n (%)	44 (23.9%)
Atrial septal defect (ASD)	9 (4.9%)
ASD/PFO	1 (0.5%)
ASD/ventricular septal defect (VSD)	1 (0.5%)
ASD/PFO/coarctation of the aorta (CoA)	1 (0.5%)
ASD/PFO/valve stenosis	1 (0.5%)
ASD/VSD/valve stenosis	1 (0.5%)
Bicuspid aortic valve	2 (1.1%)
Cardiomyopathy	1 (0.5%)
Mitral regurgitation	1 (0.5%)
Patent foramen Ovale (PFO)	10 (5.4%)
Perimembranous (PM) vs. supracristal VSD	1 (0.5%)
PFO/aortic arch narrowing	1 (0.5%)
PFO/valve insufficiency	1 (0.5%)
Valve stenosis	2 (1.1%)
VSD	10 (5.4%)
VSD/CoA	1 (0.5%)
Previous cardiac intervention operations - n (%)	2 (1.1%)
Continuous murmur consistent with PDA Present on auscultation - n (%)	
Yes	171 (92.9%)
No	13 (7.1%)
PDA size ^a	N = 184
Minimum diameter (mm)	
Median [IQR]	1.7 [1.3, 2.1]
Range	0.6–3.6
Aortic diameter (mm)	
Mean ± SD	8.0 ± 2.5
Range	1.3–14.9
Length (mm)	
Median [IQR]	8.0 [6.3, 9.9]
Range	2.5–21.9
PDA type - n (%)	
Conical (type A)	154 (83.7%)
Short (type B)	2 (1.1%)
Tubular (type C)	4 (2.2%)
Complex (type D)	6 (3.3%)
Elongated (type E)	18 (9.8%)

^a Determined prior to device implant with aortogram.**TABLE 2** Procedure characteristics for the implant surgery of the postapproval study

Successful implant - n (%)	N = 184
Yes	180 (97.8%)
No	4 (2.2%)
Total fluoroscopy time (min)	N = 184
Median [IQR]	11.0 [8, 17]
Range	4–136
Duration of surgery in minutes	N = 174 ^a
Median [IQR]	52.5 [37, 76]
Range	4–190
Sedation or anesthesia type - n (%)	N = 184
General	120 (65.2%)
General with local	47 (25.5%)
Conscious sedation	16 (8.7%)
None noted	1 (0.5%)
Number of implant attempts ^b - n (%)	N = 184
1	166 (90.2%)
2	17 (9.2%)
3	1 (0.5%)
PDA approach ^c - n (%)	N = 180
Venous (antegrade)	172 (95.6%)
Arterial (retrograde)	8 (4.4%)
Device size implanted (mm) - n (%)	N = 180
4 × 4	11 (6.2%)
5 × 4	23 (12.9%)
6 × 5	39 (21.8%)
7 × 6	53 (29.4%)
9 × 6	39 (21.8%)
11 × 6	15 (8.4%)

^a N = 174 as two subjects did not have procedure start time collected, seven subjects did not have procedure stop time collected and one subject did not have start and stop time collected.^b Per protocol, it is possible the user may attempt to implant a Nit-Occlud PDA and realize the device is the incorrect size; this is an anticipated occurrence and is not considered a technical failure or a protocol deviation.^c For subjects with more than one implant attempt, data from the final implant are used for this summary table.

to 21.1 years) with median weight of 14.1 kg (range 5.5–86.9 kg). Female patients constituted 68.5% (126/184) of the subjects. Additional congenital heart diseases were present in 23.9% of the patients (44/184), most commonly interatrial communication. The majority (92.9%) of patients had an audible PDA murmur. Thirteen patients had PDAs without an audible murmur (Table 1).

The median minimum PDA diameter was 1.7 mm (range 0.6 mm–3.6 mm) with median PDA length of 8.0 mm (range 2.5 mm–21.9 mm). PDA was classified angiographically as Krichenko⁴ type A (conical) 83.7%, type B (short) 1.1%, type C (tubular) 2.2%, type D (complex) 3.3%, and type E (elongated) 9.8% (Table 1).

Successful implantation was achieved in 180 of 184 patients (97.8%). There were four technical failures (2.2%), which were attributed to a larger ductal size in three and premature release of device in

TABLE 3 Efficacy endpoint: echocardiographic closure of PDA at 12-month postdevice implant and additional timepoints

Month 2	N = 170 ^a
None	153 (90.0%)
Trivial	12 (7.1%)
Small	5 (2.9%)
Medium	0 (0.0%)
Severe	0 (0.0%)
Month 12	N = 152 ^b
None	142 (93.4%)
Trivial	8 (5.3%)
Small	2 (1.3%)
Medium	0 (0.0%)
Severe	0 (0.0%)
Month 24 ^c	N = 30
None	29 (96.7%)
Trivial	1 (3.3%)
Small	0 (0.0%)
Medium	0 (0.0%)
Severe	0 (0.0%)

^a N = 170 as two subjects did not have an echocardiogram at the month 2 visit.

^b N = 152 as one subject was missing residual leak data.

^c Month 24 echo not required per protocol and is noted here only if site reported the information.

one. For the three cases in which the PDA was deemed too large for NitOcclud closure, the device was deployed but not released. After successful retrieval of the NitOcclud devices, non-study devices were used to close these four PDAs. Median total fluoroscopy time was 11.0 min. The median procedure duration was 52.5 min. Of the 184 subjects enrolled, 133 were discharged the same day as the

TABLE 4 Safety endpoint: available data for serious device-related adverse events

	Number (%) of AEs	Number (%) of subjects with AE (N = 184) ^a
All AEs	122	77 (41.8%), [CI =34.3%, 49.3%]
Serious	16 (13.1%)	13 (7.1%)
Non-serious	106 (86.9%)	171 (92.9%)
AEs by relationship to device or procedure ^b		
Procedure-related	15 (12.3%)	14 (7.6%)
Occurred ≤12-months postprocedure	14 (11.5%)	13 (7.1%)
Device-related	6 (4.9%)	6 (3.2%)
Occurred ≤12-months postprocedure	6 (4.9%)	6 (3.2%)
Not device or procedure-related	102 (83.6%)	165 (89.7%)
Late onset device or procedure-related ^c	1 (0.8%)	1 (0.5%)

^a Subjects with failed implants were followed through month 1 and any reported AEs are included.

^b AEs classified as definitely or probably are considered *related*; AEs classified as possibly, unlikely or not related are *not related*.

^c Late onset includes AEs that occur after the initial hospitalization for the implant procedure.

implant procedure and the remaining 51 subjects were discharged the day after the procedure. All procedures were performed under general anesthesia (90.7%), or conscious sedation (8.7%). One subject's anesthesia type was unreported.

The device was delivered by the first attempt in 166/184 (90.2%), and via venous (antegrade) approach in 172/184 (95.6%). The device size implanted were 4 × 4 mm in 11 patients (6.2%), 5 × 4 mm in 23 (12.9%), 6 × 5 mm in 39 (21.8%), 7 × 6 mm in 53 (29.4%), 9 × 6 mm in 39 (21.8%) and 11 × 6 mm in 15 (8.4%) (Table 2).

3.1 | Efficacy and safety of postapproval study

Effectiveness endpoint was echocardiographic closure of PDA at 12-month postdevice implant (Table 3). This endpoint was also evaluated at hospital discharge, after 2 months, and after 12 months. At the 2-month follow-up, only 2.9% (5/170) of subjects had a small residual PDA shunt by echocardiography. No subjects had medium or severe residual shunt at the 2-month follow-up. At the 12-month follow-up, 98.7% (150/152) of subjects had trivial or no residual shunt assessed by echocardiography. Eight subjects had trivial shunt at the 12 month evaluation. The clinical closure rate (i.e., lack of a continuous murmur by auscultation) was 100% (152/152). At 24-month follow-up, 98.4% (60/61) had no detectable PDA murmur and all subjects with an echocardiography (n = 30) had no or trivial residual shunt on echocardiography.

The available data include AEs reported through the 12-month follow-up for the subjects with successful implantation. AE data were collected through 1-month postprocedure only for subjects that did not receive the study device. The safety endpoint was serious device-related adverse events at 24-months postdevice implant. However, subjects are continuing in follow-up and only 12-month follow-up data are currently available at this time. Despite having only 12-month data currently, the number of device related AEs by the 24-month may be minimal given there have been no late-reported related events to date across all studies.

There were no deaths and no cases of hemolysis. There were no subjects having significant obstruction in the LPA or DAO on echocardiography at 12-month follow-up, which was defined as a mean gradient >10 mmHg. Thirteen patients had 16 serious adverse events (Table 4). None of the serious adverse events were device-related, but three of the SAEs were probably or definitely procedure-related. There were 6 (4.9%) device-related and 14 (11.5%) procedure-related non-SAEs that occurred within the 12-month follow-up period. Device-related events included three device embolizations all of which occurred immediately following implantation (one embolized to the main pulmonary artery, one to the left femoral artery and a third to the abdominal aorta). In two cases, percutaneous retrieval was performed during the implantation procedure and another Nit-Occlud device was implanted successfully; the third subject was exited and a non-study device was implanted. Additional device-related AEs were device malposition (n = 1), and spontaneous detachment of coil from delivery cable without embolization (n = 3). Three procedure-related SAEs include the following: temporary loss of pulse requiring anticoagulation therapy (n = 2), left vocal cord paralysis (n = 1). Loss of pulse

TABLE 5 Study outcomes and OPC in the pivotal, continuing access and postapproval study (PAS)

	OPC rates ^a (%)	Pivotal and continuing access studies	PAS	Combined pivotal, continuing access and PAS		
				Study outcome	95% lower bound (%)	95% upper bound (%)
Technical success at implantation	95%	97.2% (347/357)	97.8% (180/184)	97.4% (527/541)	96.0%	NA
Clinical closure at 12 months	95%	98.1% (308/314)	100% (152/152)	98.5% (460/467)	97.2%	NA
Echocardiographic closure at 12 months	85%	96.8% (299/309)	93.4% (142/152)	95.9% (418/436)	93.9%	NA
Mortality at 12 months	0%	0% (0/314)	0% (0/153)	0% (0/467)	NA	6.4%
Total device- and procedure-related SAE at 12 months	1%	0% (0/314)	1.9% 3/153	0.6% 3/467	NA	1.7%
Total device- and procedure-related AE at 12 months	6%	4.7% (15/316)	13.1% 20/153	7.5% (35/468)	NA	9.8%
Composite success at 12 months	80%	95.1% (294/309)	92.8% (141/152)	94.4% (435/461)	92.3%	NA

^a OPC rate was defined previously in the pivotal study.²

resolved at follow-up, whereas left vocal cord paralysis required ongoing speech therapy.

The other non-serious procedure-related AEs reported through 12 months were the following: access site hematoma (n = 8), device malposition (n = 2), inability to re-deploy device (n = 1), transient mitral regurgitation (n = 1), and allergic skin reaction to tape (n = 1). Among 62 subjects completing 24-month follow-up, two subjects had late-onset procedure-related SAEs. These were both residual PDA shunts for which the operators chose to place additional non-study coils at 14 and 19 months post-NitOcclud implant. Composite success accounting for procedure technical success, clinical and echocardiographic closure of PDA, death, and device-related SAE at 1 year follow-up was 92.8% (141/152).

3.2 | Combined cohort of pivotal, continued access, and postapproval studies

Comparing with the Pivotal and Continuing Access Studies, the PAS had comparable technical success, clinical and echocardiographic closure at 12 months (Table 5). Although there were no device- and procedure-related SAEs in the pivotal and continued access studies, there were three procedure-related SAEs in the PAS. As mentioned above, two of these three SAEs were treated and resolved without clinical consequences.

Combining the subjects from the three clinical trials of pivotal, continued access and postapproval studies, technical success at implantation was 97.4% (527 of 541). There were 14 technical failures. At 12-month after device implant, 466 subjects completed clinical evaluation and 436 completed echocardiographic evaluation. Clinical and complete echocardiographic closure (defined as a complete absence of any shunt) at 12 months was 98.5% (460 of 467) and 95.9% (418 of 436). There was no death. Total device-related SAEs at 12 months was 0% (0/467) and procedure-related SAEs at 12 months was 0.6% (3/467). Composite success at 12 months was

94.4% (435/461). There were five device embolizations that were all retrieved by snare without clinical consequence.

4 | DISCUSSION

The NitOcclud PAS study prospectively enrolled 184 patients at 11 centers. When all three of the FDA mandated clinical trials of NitOcclud (pivotal, continuing access, and postmarket) were combined, a total of 541 prospectively enrolled patients were available for analysis. This large cohort with long-term follow-up allows for the performance of a well powered study of the technical success, safety and efficacy of this device. This publication reports both the PAS results as well as an overview of the combined results of all three trials.

The primary safety endpoint of the Nit-Occlud PAS study was assessed primarily by the rate of serious adverse events. In the PAS and in all three studies, there were no deaths, no device-related serious adverse events and no hemolysis in any of the patients. In a total of 461 patients, the rate of device related SAEs was 0.6%. The PAS had five procedure-related SAEs through 24-months postimplant, of which four were treated and resolved without clinical consequence. In the five episodes of Nit-Occlud embolizations, the device was easily snared and retrieved in all cases without the use of a 6–7 Fr sheath. Furthermore, obstruction of flow in the aorta or pulmonary artery was not seen.

The PAS also provided a third test of the Nit-Occlud PDA device's efficacy for closure of PDA's < 4 mm in diameter. At the 12-month follow-up, 98.7% (150/152) of subjects had trivial or no residual shunt assessed by echocardiography. When compared with the pivotal and continuing access studies, the PAS showed comparable outcome of technical success and efficacy. In the combined cohort of 541 patients, technical success at implantation was 97.4% with only 10 technical failures. The technical failures were primarily secondary to selection of PDAs too large to accommodate stable Nit-Occlud position. On these occasions, the device was uniformly and easily removed prior to deployment.

In the PAS study at the 12-month follow-up, 98.7% (150/152) of subjects had trivial or no residual shunt assessed by echocardiography. However, in all three studies, 95.9% of patients (n = 436) had no detectable PDA shunting by echocardiography at 12 months with the remainder having trivial or small shunts. Deployment of the Nit-Occlud coil into an ideal conformation is more operator dependent than deployment of self-expanding plug devices. For example, implanting the reversed windings on the aortic side of the narrowest PDA diameter with only one or one and a half loops deployed on the pulmonary side is typically ideal. Small residual shunts are more common when more than two of the reversed windings were on the PA side of the narrowest PDA diameter.

There are several alternative devices and coils for closure of PDA. Amplatzer Duct Occluder (ADO) I and II (St. Jude Medical, St. Paul, MN, USA) are FDA approved devices for the indication of PDA closure. Many other devices including the Amplatz Vascular Plug II (St. Jude Medical) and Flipper coils (Cook Medical, Bloomington, IN) have been used off-label for PDA closure. As such, no FDA pivotal trial data are available for these devices.

In the pivotal trial for the ADO I, there were 393 patients. The 12-month closure rate was 98.6% and there were five (2.7%) serious adverse events including one death.⁵ While direct comparisons of these devices are not perfect given subtle differences in the trials, clearly the closure rates are very similar. Both the ADO I and Nit-Occlud PDA have excellent overall device characteristics and outcomes for closure of small to moderate sized PDAs.^{5,6} As it is easily retrievable and repositionable using a low profile delivery catheter, the Nit-Occlud has very high technical success rate with minimal residual shunt at follow-up, and is unlikely to cause obstruction in the LPA and DAO.

4.1 | Study limitations

This study was a prospective observational study lacking a surgical or control group using an approved PDA device. Due to the absence of approved alternative coil-type PDA devices, the study was designed to compare the OPC benchmark designated by the FDA advisory panel. The PAS continues to follow-up the enrolled patients at 24 months postimplant and for 60 months for subjects with residual PDA shunt, any significant LPA or DAO obstruction, and/or an ongoing device-related issue at 12 months follow-up. Nevertheless, authors felt it reasonable to present the interim data of PAS.

5 | CONCLUSIONS

The Nit-Occlud PDA is a safe and effective device for closure of a small to moderate sized PDA in the PAS. At 12 months, echocardiographic closure was 95.9% with device- and procedure-related SAE of 0.6%. This efficacy and safety profile was well above or comparable to

the OPC benchmark designated by the FDA advisory panel and contemporary practice data.⁷ Most importantly, there were no serious adverse events including hemolysis, mortality or need of surgery in a large cohort of three clinical trials and all five device embolizations were percutaneously retrieved with a snare easily.

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CONFLICT OF INTEREST

No conflict of interest.

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SUPPORTING INFORMATION

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

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