JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 17, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.05.018

Transcatheter Occlusion of the Patent Ductus Arteriosus in 747 Infants <6 kg

Insights From the NCDR IMPACT Registry

Carl H. Backes, MD,[a,b,c,d] Kevin F. Kennedy, MS,[e] Megan Locke, BS,[a] Clifford L. Cua, MD,[b,c,d] Molly K. Ball, MD,[d] Tyler A. Fick, MD,[d] Brian K. Rivera, MS,[a] Charles V. Smith, PhD,[f] Ralf J. Holzer, MD,[g,h] Brian A. Boe, MD,[b,c,d] Darren P. Berman, MD,[b,c,d] Lisa Bergersen, MD, MPH,[i] Aimee K. Armstrong, MD[b,c,d]

ABSTRACT

OBJECTIVES The authors sought to identify risk factors associated with major adverse events (MAEs) in infants <6 kg undergoing transcatheter patent ductus arteriosus (PDA) occlusion.

BACKGROUND Transcatheter PDA occlusion is among the safest of interventional cardiac procedures in adults and older children, but use among infants <6 kg has not been characterized adequately.

METHODS Using the IMPACT (IMproving Pediatric and Adult Congenital Treatments) registry, we identified infants <6 kg undergoing transcatheter PDA occlusion (January 1, 2011, to March 1, 2015). Using mixed-effects multivariate regression, the authors assessed characteristics predictive of MAE or composite failure (procedural failure or MAE). Individual safety metrics (e.g., embolization, malposition) were also examined for differences across weight thresholds: extremely low weight (LW) (<2 kg), very LW (2 to <4 kg), and LW (4 to <6 kg).

RESULTS Transcatheter PDA occlusion was attempted in 747 infants <6 kg at 73 hospitals. Rate of procedural success was 94.3%. MAEs were observed in 12.6% of cases; the most common events were acute arterial injury and device embolization in 3.5% and 2.4% of cases, respectively. Younger age (<30 days) was associated with greater risk of a MAE (risk ratio: 3.3; 95% confidence interval: 1.5 to 7.6) and composite failure (risk ratio: 3.0; 95% confidence interval: 1.4 to 6.7). Risk of embolization was higher among extremely LW (10.5%) than very LW or LW infants (1.6% and 2.5%, respectively; $p = 0.050$).

CONCLUSIONS Among infants <6 kg, transcatheter PDA occlusion is technically feasible, but risks of MAE are noteworthy. These findings may help inform patient selection and procedural approach for transcatheter PDA occlusion and direct targeted research efforts to support the practice of evidence-based medicine. (J Am Coll Cardiol Intv 2017;10:1729–37)

Surgical patent ductus arteriosus (PDA) ligation provides definitive ductal closure for symptomatic infants when medical treatment fails or is contraindicated (1). However, risks associated with surgery are well described, including paresis of the vocal cords, phrenic nerve palsy, thoracic scoliosis, and inadvertent ligation of the left pulmonary artery and aorta (2,3). These observations have

From the [a]Center for Perinatal Research, Nationwide Children's Hospital, Columbus, Ohio; [b]Center for Cardiovascular and Pulmonary Research, Nationwide Children's Hospital, Columbus, Ohio; [c]The Heart Center, Nationwide Children's Hospital, Columbus, Ohio; [d]Department of Pediatrics at Nationwide Children's Hospital, Columbus, Ohio; [e]Mid-America Heart Institute, Kansas City, Missouri; [f]Seattle Children's Research Institute, Center for Developmental Therapeutics, Seattle, Washington; [g]Weill Cornell Medical College, Department of Pediatrics, New York, New York; [h]Cardiac Catheterization and Interventional Therapy, Sidra Cardiac Program, Sidra Medical and Research Center, Doha, Qatar; and the [i]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts. Dr. Bergersen is a consultant for 480 Biomedical. Dr. Armstrong has received a research grant from PFM Medical; has been a consultant for Abbott; and has been a proctor for Abbott and B. Braun Interventional Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Clinical Trial Registration: registered prospectively with the National Cardiovascular Data Registry (NCDR).

Manuscript received March 6, 2017; revised manuscript received April 17, 2017, accepted May 4, 2017.

ABBREVIATIONS AND ACRONYMS

AAI = acute arterial injury

ADO = Amplatzer Ductal Occluder

AVP = Amplatzer Vascular Plug

ELW = extremely low weight

IQR = interquartile range

LW = low weight

MAE = major adverse event(s)

NCDR = National Cardiovascular Data Registry

PA = pulmonary artery

PDA = patent ductus arteriosus

VLW = very low weight

led health care providers to consider alternative strategies of PDA closure during infancy (4,5).

Transcatheter PDA occlusion is among the safest of interventional cardiac procedures, and is considered the procedure of choice for adults, children, and infants ≥6 kg (6,7). Although an exact lower weight limit for the safe occlusion of a PDA has not been established (8), previous studies have excluded infants <6 kg or reported few or no cases of transcatheter PDA occlusion below this weight threshold (9,10). Some manufacturer recommendations for PDA devices specify use in patients weighing >6 kg (11). Although recent small, single-center experiences suggest that transcatheter PDA occlusion is feasible at <6 kg (12), other investigators have determined that, in light of data showing adverse events increase markedly below this weight threshold, surgical ligation should remain the first-line treatment for ductal closure (6). Optimal patient selection for transcatheter PDA closure in this subgroup of infants is obscured by the paucity of multicenter studies and lack of standardized definitions of adverse events. Recently, the American Heart Association called for an expanded knowledge base on the use of transcatheter PDA occlusion among lower weight infants (13).

The IMPACT (IMproving Pediatric and Adult Congenital Treatment) registry, part of the National Cardiovascular Data Registry (NCDR), is the largest database collecting data on pediatric and adult patients with congenital heart disease undergoing cardiac catheterization. Specifics on registry development and design have been published (14). The standardized set of data elements and definitions and the large procedural volumes provide a unique opportunity to evaluate the use of transcatheter PDA occlusion among infants <6 kg, which are the patients at the crux of the medical debate. In participation with the IMPACT registry, the goal of the present study was to identify risk factors associated with major adverse events (MAEs) in infants <6 kg undergoing transcatheter PDA occlusion.

METHODS

Data for the IMPACT registry are subject to rigorous quality assurance standards (15). Center enrollment in the registry is voluntary. As of March 2015, the IMPACT registry had 109 participating centers and enrolled >83,000 catheterization episodes of care. The nomenclature used in the IMPACT registry is the International Pediatric and Congenital Cardiac Code (16). All pertinent data related to PDA procedures were reviewed before formulation of the analytic plan. The present study used data from IMPACT version 1.0.1; data elements and definitions are available online at the NCDR website.

STUDY POPULATION. The study assessed cardiac catheterizations for PDA closure collected in the IMPACT registry from January 2011 to March 2015. Only infants <6 kg at the time of catheterization were included. Exclusion criteria included diagnosis of an additional congenital heart lesion (other than patent foramen ovale or atrial-level defect), prior history of cardiac catheterization or cardiac surgery, and infants undergoing additional procedures beyond PDA closure (e.g., atrial septal defect closure). These criteria were chosen to describe outcomes and complications likely attributable to transcatheter PDA occlusion.

STUDY VARIABLES. Baseline characteristics. Baseline characteristics screened as candidate predictors for the study included age at time of catheterization (<30 days, ≥30 days), weight at catheterization (extremely low weight [ELW], <2 kg; very low weight [VLW], 2 to <4 kg; and low weight [LW], 4 to <6 kg), sex, race, presence of known genetic or chromosomal syndrome (e.g., 22q11 deletion), presence of chronic lung disease, and presence of nonrespiratory comorbidity (e.g., necrotizing enterocolitis).

Pre-procedural characteristics. Pre-procedural characteristics included procedural indication (left ventricular volume overload, pulmonary hypertension, or bacterial endocarditis prevention), location before procedure (inpatient or outpatient), procedure status (elective vs. urgent or emergent or salvage), sedation (general anesthesia, intravenous sedation), and airway management (intubated before the procedure). Pre-procedural cardiac rhythm and use of diuretics and pulmonary vasodilators were also recorded.

Procedural characteristics. Procedure-specific data included PDA characteristics, including minimum diameter, diameter at aortic side, and length. Ductal lengths <4 mm were defined as "short" PDAs (17). Type of closure (coil or device) and device specifications (e.g., Amplatzer Ductal Occluder [ADO]; Amplatzer Vascular Plug [AVP], St. Jude Medical, Saint Paul, Minnesota) were recorded, when available. Because of previous reports of differences in procedural success and adverse events in neonates with long tubular ducts (Type C) than with other morphologies (17). Type C PDAs were compared with other PDA classifications, according to standard

angiographic criteria (18). Characteristics related to procedural access (access type, sheath size) were also recorded. Fluoroscopy time and dose, and length of time in cardiac catheterization suite were also evaluated. Per the IMPACT registry, a trivial residual shunt is defined by a diameter <3 mm compared to a significant shunt, which measures ≥3 mm in diameter, according to echocardiographic color Doppler or angiography.

Hemodynamic data, including systolic pulmonary artery (PA) pressure, were recorded, when available. Hemodynamic vulnerability was defined with previously published criteria (19). Patients missing relevant hemodynamic parameter data were placed in a third category of "missing," rather than excluding them entirely, to prevent model bias. For example, hemodynamic data might be missing for infants who were critically ill, wherein clinical status prevented a hemodynamic assessment before attempting transcatheter closure, or in infants who were so stable that a hemodynamic assessment was not deemed to be warranted clinically. Systolic PA pressure, Qp/Qs (ratio of pulmonary to systemic blood flow), and indexed pulmonary vascular resistance (in Wood Units/m^2) were recorded, when available.

Hospital characteristics. Variables related to hospital characteristics were assessed, including: 1) hospital-level annual catheterization volume, stratified by quartiles; and 2) hospital-level PDA catheterization volume, stratified by quartiles.

STUDY OUTCOMES. Procedural success. Procedural success (feasibility) was defined as placement of a coil or device in the PDA. Data on any case wherein a device (or coil) was introduced into the patient or the performance of any intervention in an attempt to correct the PDA defect were considered. Cases in which a device embolized but was later percutaneously retrieved, and the PDA was subsequently closed with a larger device or coil (during the same procedure) were considered procedural successes. These were, however, also listed as a MAE (described in the following text).

Major adverse events. MAEs were defined a priori (Table 1). Unless otherwise noted, adverse events were included up to 30 days following the catheterization procedure, aside from unplanned surgery and subsequent cardiac catheterization, which were coded until the time of hospital discharge. Because the IMPACT registry does not allow definitive attribution of all adverse events to the cardiac catheterization, the MAEs chosen for inclusion in this study: 1) could be definitively linked to the catheterization (e.g., device embolization); or 2) highly likely to be attributed to the cardiac catheterization (e.g., acute arterial injury [AAI]). Death was not included as a MAE because, in the version of the IMPACT registry in place at the time of data collection, death cannot be definitively linked to cardiac catheterization; therefore, events unrelated to the procedure may have contributed to the infant's demise (non-catheterization-related procedures, morbidities). However, recognizing the clinical importance of identifying cases where death occurred following catheterization, we originally intended to perform an additional analysis for MAE that included death within 24 h of the catheterization; however, no infants died within this timeframe. Length of hospital stay was also recorded to examine the potential association with MAEs.

TABLE 1 Adverse Events Considered "Major"

Cardiac arrest
Cardiac tamponade requiring pericardial drainage
Embolic stroke*
Device malposition or thrombus requiring surgery
Device embolization requiring device retrieval
Unplanned cardiac or vascular surgery†
Subsequent cardiac catheterization*
Arrhythmia requiring treatment‡
Acute arterial injury§
Major bleeding event‖

*Within 72 h. †Attributed to the catheterization. ‡Use of cardioversion, antiarrhythmic medication, or pacemaker. §Loss of distal pulse at the percutaneous entry site requiring intervention. ‖A bleeding event between start of procedure and 72 h post-procedure, bleeding at access site, or hematoma at access site *and* associated with one of the following: 1) hemoglobin drop of ≥3 g/dl; 2) transfusion of red blood cells; and 3) intervention at the bleeding site to reverse, stop, or correct the bleeding.

Composite outcome. Composite failure was defined as procedural failure of device (or coil) implantation *or* presence of MAE.

Secondary outcomes. Because composite outcomes are complicated by the magnitude of the risk of the intervention across component endpoints and by the relative importance of the different components, a number of individual safety metrics were also examined across weight thresholds. Potential differences in rates of device-related complications (embolization, malposition, obstruction in pulmonary artery, or obstruction in the aorta) based on device specifications were examined.

Covariates. Patient-, procedural-, and hospital-level factors that could affect the risk of MAE or composite failure were identified on the basis of clinical rationale and previous studies (20). Specific covariates pre-specified for inclusion in multivariate models were patient age, weight, presence of hemodynamic vulnerability, procedural indication, PDA

TABLE 2 Demographic-, Procedural-, and Hospital-Level Characteristics of Infants Experiencing and Not Experiencing a MAE

Major Adverse Event	Yes (n = 94)	No (n = 653)	p Value
Baseline			
Age at intervention			
<30 days	12 (12.8)	21 (3.2)	<0.001
≥30 days	82 (87.2)	632 (96.8)	
Weight at intervention			
Extremely low weight (<2 kg)	3 (3.2)	16 (2.5)	0.13
Very low weight (2 to <4 kg)	39 (41.5)	206 (31.5)	
Low weight (4 to <6 kg)	52 (55.3)	431 (66.0)	
Genetic/chromosomal syndrome*	17 (18.1)	102 (15.6)*	0.55
Chronic lung disease	28 (29.8)	179 (27.4)	0.64
Pre-procedural			
Procedural indication			
Left ventricular volume overload	61 (64.9)	425 (65.1)	0.40
Pulmonary hypertension	29 (30.9)	177 (27.1)	
Bacterial endocarditis prevention	4 (4.3)	51 (7.8)	
Procedural status			
Elective	66 (70.2)	519 (79.5)	0.04
Urgent or emergent†	28 (29.8)	132 (20.3)†	
Procedural			
Access type			
Venous only	6 (6.4)	54 (8.3)	0.53
Arterial and venous	88 (93.6)	599 (91.7)	
Closure type‡			
Coil	5 (6.1)	73 (11.5)	0.14
Device	77 (93.9)	561 (88.5)	
Hemodynamic vulnerability§			
Yes	58 (61.7)	328 (50.2)	0.021
No	20 (21.3)	211 (32.3)	
Missing	16 (17.0)	114 (17.5)	

Values are n (% of row total). All listed values are per procedure. *1 patient with missing data. †2 patients with missing data. ‡31 patients with missing data (12 and 19 from Yes and No columns, respectively). §As defined by Bergersen et al. (19); missing in 130 patients.

MAE = major adverse event(s).

classification, procedure status, and hospital volume (total catheterization volume, total PDA volume). Additional covariates were included in multivariate models to include any variables that reached a p value <0.10.

Statistical analysis. Characteristics of infants experiencing a MAE were compared with the characteristics of those not experiencing a MAE with unpaired Student *t* tests for continuous variables, and chi-square or Fisher exact tests for categorical variables. Given the nature of the database, procedures were used as the unit of analysis. Modified hierarchical Poisson regression was used to estimate the risk ratio of covariates predicting MAE or composite success endpoints. We used a random intercept model to account for the clustering of patients in hospitals, with no additional corrections for multiple procedures within patients or admissions. Values of $p < 0.05$ determined statistical significance. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for all analyses. The study was conducted on de-identified quality-improvement registry data and did not require informed consent. All authors have read and agreed to the manuscript as written. The IMPACT registry's Research and Publications Committee approved the final manuscript.

RESULTS

The IMPACT registry recorded 6,044 attempted percutaneous PDA closures between January 2011 and March 2015. Procedures among infants weighing ≥6 kg (n = 5,142), those with prior cardiac surgery or catheterization (n = 18), or undergoing additional procedures beyond PDA closure (n = 137) were excluded from analysis. The cohort for primary analysis included data from 73 hospitals on 747 infants <6 kg undergoing attempted transcatheter PDA occlusion.

BASELINE CHARACTERISTICS. Approximately one-third (258, 34.5%) of infants were born at <30 weeks of gestation. The median (interquartile range [IQR]) age and weight at catheterization were 4.3 (2.8 to 6.2) months and 4.6 (3.5 to 5.4) kg, respectively. Among 19 ELW infants, 2 (11%) were <30 days at the time of the procedure. Fifty-nine percent of transcatheter PDA occlusions were performed in infants who were female, and 60.1% were Caucasian. Incidence of a major nonrespiratory comorbidity at time of catheterization was <2% (10 of 474, 1.4%). Table 2 compares baseline, pre-procedural, and procedural characteristics of infants experiencing a MAE to characteristics of those not experiencing a MAE.

PRE-PROCEDURAL CHARACTERISTICS. Fewer than one-half of infants (341, 45.6%) were hospitalized before the procedure. More than one-half of infants were on diuretic treatment (402, 53.8%), and fewer than 10% were on pulmonary vasodilator therapy (61, 8.2%). The majority of cases were elective (585, 78.3%), were performed under general anesthesia (696, 93.2%), and were mechanically ventilated before the start of the procedure (706, 94.5%).

PROCEDURAL CHARACTERISTICS. The majority of infants (719, 96.3%) were in sinus rhythm at the time of the procedure. Among 19 ELW infants, 14 had venous-only access, and 5 had arterial and venous access. The median (IQR) minimum ductal diameter, diameter on the aortic side, and length were 2.95 (2.2 to 3.6), 5.96 (4.5 to 7.2), and 8.8 (6.8 to 11.2) mm, respectively. Among 638 infants with known device closure, 228 (35.7%) had AVP-II, 245 (38.4%) had ADO,

83 (13.0%) had AVP, and 70 (11.0%) had ADO-II. The remainder of the device-types occurred in <1% of cases.

Overall, 276 infants (36.9%) had Type A PDA, 16 (2.1%) Type B, 316 (42.3%) Type C, 35 (4.7%) Type D, 88 (11.8%) Type E, and 16 (2.1%) were not classified. The mean fluoroscopy time and dose were 19.7 ± 20.8 min and 84.7 ± 158.1 mGy, respectively. The median (IQR) of systolic PA pressures was 40 (30 to 48) mm Hg. Evidence of systemic arterial saturation below threshold (<95%), or mean PA pressure above threshold (≥45 mm Hg), were observed in 36.2% and 31.7% of cases, respectively. The median (IQR) of systolic PA pressures and Qp/Qs were 40 (30 to 48) mm Hg and 2.2 (1.5 to 3.0) mm Hg, respectively. Median (IQR) indexed pulmonary vascular resistance was 1.8 (1.2 to 3.0) Wood Units/m^2. Time in the catheterization suite was <2 h in 96% of cases. The majority (93.1%) had no or trivial residual ductal shunt following closure.

HOSPITAL CHARACTERISTICS. The medians (IQRs) of hospital-level annual catheterization and PDA catheterization case volumes were 265 (143 to 439) and 22 (13 to 33), respectively. Total hospital-level annual catheterization volume (number of hospitals) across each quartile is as follows: 1st quartile, 26 to 143 (n = 18); 2nd quartile, 144 to 265 (n = 18); 3rd quartile, 266 to 438 (n = 18); 4th quartile, >438 (n = 19). PDA catheterization volume among infants <6 kg (number of hospitals) across each quartile is as follows: 1st quartile, ≤1 (n = 18); 2nd quartile, 1 to 2 (n = 16); 3rd quartile, 3 to 4 (n = 20); and 4th quartile, >4 (n = 19).

PROCEDURAL SUCCESS/FAILURE. Among 747 attempted PDA closures, 705 (94.3%) had a device or coil successfully implanted. Among procedural failures (n = 42), the device was implanted but not released (n = 18), or implanted, released, retrieved, *and* not subsequently placed successfully during the same case (n = 24). Rates of procedural failure were similar across weight (<2 kg = 6.3%; 2 to <4 kg = 5.9%; 4 to <6 kg = 5.8%; p = 0.99) and age (<30 days = 7.1%; ≥30 days = 5.8%; p = 0.77) thresholds. PDA minimal lumen diameters were larger among cases designated to be procedural failures than successes (3.6 vs. 2.9 mm; p < 0.001). We observed no differences in diameter of the ductus on the aortic end (6.70 vs. 5.90 mm; p = 0.188) or PDA length (8.20 vs. 8.90 mm; p = 0.092) among procedural failures versus successes. We observed no evidence of greater rates of procedural failure among infants with a short ductus (<4 mm) than in cases with PDA lengths ≥4 mm (8.3% vs. 6.4%; p = 0.70).

TABLE 3 Multivariate Model of MAEs

	RR (95% CI)	p Value
Age at intervention <30 days vs. ≥30 days	3.34 (1.46–7.64)	<0.001
Weight at catheterization		
Extremely low weight (<2 kg)	1.22 (0.31–4.76)	0.77
Very low weight (2 to <4 kg)	1.53 (0.39–6.03)	0.54
Low weight (4 to <6 kg)	1.26 (0.75–2.1)	0.38
Procedural indication		
Bacterial endocarditis prevention vs. left-sided volume overload	0.64 (0.22–1.88)	0.42
Bacterial endocarditis prevention vs. pulmonary hypertension	0.65 (0.21–1.99)	0.44
Left-sided volume overload vs. pulmonary hypertension	1.01 (0.6–1.67)	0.98
PDA classification		
Type C vs. other PDA classifications	1.28 (0.8–2.04)	0.30
Procedure status		
Elective vs. urgent/emergent	0.82 (0.48–1.38)	0.44
Hemodynamic vulnerability*	1.67 (0.95–2.92)	0.07
Total catheterization volume		
1st quartile vs. 2nd quartile	1.83 (0.63–5.26)	0.26
1st quartile vs. 3rd quartile	2.03 (0.72–5.73)	0.17
1st quartile vs. 4th quartile	0.87 (0.31–2.4)	0.78
PDA specific catheterization volume†		
1st quartile vs. 2nd quartile	1.93 (0.58–6.43)	0.28
1st quartile vs. 3rd quartile	1.78 (0.58–5.44)	0.30
1st quartile vs. 4th quartile	2.01 (0.64–6.34)	0.23

All listed values are per procedure. *As defined by Bergersen et al. (19); missing in 130 patients. †Among infants <6 kg.

CI = confidence interval; MAE = major adverse event(s); PDA = patent ductus arteriosus; RR = risk ratio.

We observed no differences in rates of procedural failure between cases using coils (5 of 78, 6.4%) and those using devices (37 of 638, 5.7%; p = 0.79). We observed no difference in the likelihood of procedural success based on device specifications (AVP, ADO, etc.). Rates of procedural failure were higher in transcatheter PDA occlusion with primary indication of pulmonary hypertension (8.8%) than with left ventricular volume-overload or bacterial endocarditis prevention (5.3%, 0%; p = 0.04). Consistent with this observation, PA systolic pressures were higher among cases with procedural failure than procedural success (43 vs. 39 mm Hg; p = 0.01). No other hemodynamic parameter was associated with the likelihood of procedural success.

MAJOR ADVERSE EVENTS. A MAE occurred in 94 cases (12.6%). Covariates associated with the likelihood of MAEs are shown in Table 3. AAI was the most frequent MAE, occurring in 26 of 747 catheterization procedures (3.5%). Device embolization requiring retrieval occurred in 18 procedures (2.4%). An arrhythmia requiring intervention, unplanned cardiac surgery (as a result of cardiac catheterization),

TABLE 4 Multivariate Model of Composite Failure (MAE or Procedural Failure)

	RR (95% CI)	p Value
Age at intervention <30 days vs. ≥30 days	3.03 (1.36–6.74)	<0.001
Weight at catheterization		
Extremely low weight (<2 kg)	1.46 (0.43–4.98)	0.54
Very low weight (2 to <4 kg)	1.81 (0.53–6.22)	0.34
Low weight (4 to <6 kg)	1.24 (0.78–1.98)	0.36
Procedural indication		
Bacterial endocarditis prevention vs. left-sided volume overload	0.49 (0.17–1.41)	0.18
Bacterial endocarditis prevention vs. pulmonary hypertension	0.42 (0.14–1.25)	0.11
Left-sided volume overload vs. pulmonary hypertension	0.85 (0.54–1.34)	0.48
PDA classification		
Type C vs. other PDA classifications	1.28 (0.84–1.96)	0.24
Procedure status		
Elective vs. urgent/emergent	0.88 (0.54–1.44)	0.61
Hemodynamic vulnerability*	1.42 (0.87–2.33)	0.16
Total catheterization volume		
1st quartile vs. 2nd quartile	1.81 (0.71–4.61)	0.21
1st quartile vs. 3rd quartile	2.16 (0.87–5.33)	0.09
1st quartile vs. 4th quartile	0.82 (0.33–2.02)	0.66
PDA catheterization volume†		
1st quartile vs. 2nd quartile	1.31 (0.44–3.83)	0.62
1st quartile vs. 3rd quartile	1.59 (0.57–4.44)	0.37
1st quartile vs. 4th quartile	2.07 (0.72–5.96)	0.17

All listed values are per-procedure. *As defined by Bergersen et al. (19); missing in 130 patients. †Among infants <6 kg.
Abbreviations as in Table 3.

and major bleeding event, occurred in 13 (1.7%), 12 (1.6%), and 11 (1.5%) cases, respectively. The remainder of the individual MAEs occurred in <0.5% of procedures. Hospital stays were 7 days longer among infants who experienced a MAE than among those not experiencing a MAE (13 vs. 20 days; p = 0.01).

COMPOSITE OUTCOME. Covariates associated with the likelihood of composite failure, defined as procedural failure of device or coil implantation or presence of MAEs, are shown in Table 4. We observed that age <30 days at time of catheterization was the only patient-, procedural-, or hospital-level covariate that predicted the risk of composite failure.

SECONDARY OUTCOMES. Individual safety metrics across the various weight thresholds are shown in Table 5. The risk of embolization was higher among ELW infants (10.5%) than VLW or LW infants (1.6%, 2.5%, respectively; p = 0.050). Across the 3 weight categories, we observed no difference in the maximum sheath size among infants with and without an AAI.

We observed no differences in risk of device-related complications based on device specifications. Low sample sizes limit conclusions on individual safety metrics for several variables.

POST HOC ANALYSES. Some investigators have suggested that risks for cardiac catheterization are greater at weights <4 kg (21), but analysis restricted to infants <4 kg at the time of catheterization demonstrated no difference in the predictor (age <30 days) of MAEs. In the absence of a consensus definition on what constitutes an MAE, we iteratively removed AAI and major bleeding events from the outcome, with no significant change in the predictor (age <30 days) of MAEs. Recognizing the clinical importance of identifying instances where death occurred following cardiac catheterization, we compared rates of death among infants with and without a MAE. Among 26 deaths during initial hospitalization in the cohort (26 of 747, 3.5%), we observed a greater mortality among infants with a MAE (7 of 94, 7.4%) than those without a MAE (19 of 653, 2.9%; p = 0.024).

DISCUSSION

Across 73 hospitals, we observed 747 attempted percutaneous PDA closures in infants <6 kg, with a 94.3% procedural success rate and a 12.6% risk of a MAE. To our knowledge, the present study is the largest to date on the use of transcatheter PDA occlusion among infants <6 kg and provides an important first step in understanding the risk profile of transcatheter PDA occlusion in this subgroup of infants. However, in the absence of direct comparisons between transcatheter PDA occlusion and surgical ligation, conclusions on the optimal treatment among lower weight infants with a persistent ductus remain unanswered. Consequently, our results do not support the widespread dissemination of transcatheter PDA closure for infants <6 kg, but rather provide a foundation for selection of appropriate subjects for enrollment in comparative intervention trials necessary to inform the practice of evidence-based medicine.

In the present cohort of infants <6 kg, procedural success rates for transcatheter PDA closure are similar to those in more mature counterparts, but rates of MAE were 5- to 10-fold greater (10,22). Our study describes MAE rates among a unique subgroup of lower weight infants, including more than one-third (35.3%) who were <4 kg. Because risk of an adverse event is inversely related to patient weight at the time of catheterization (4), higher rates of

TABLE 5 Individual Safety Metrics Across Weight Thresholds

	Entire Cohort (<6 kg) (n = 747)	Extremely Low Weight (<2 kg) (n = 19)	Very Low Weight (2 to <4 kg) (n = 245)	Low Weight (4 to <6 kg) (n = 483)	p Value
Embolization*					
Embolization retrieved via catheterization	10 (1.3)	1 (5.3)	3 (1.2)	6 (1.2)	0.32
Embolization retrieved via surgery	8 (1.1)	1 (5.3)	1 (0.4)	6 (1.2)	0.12
Composite (any embolization)	18 (2.4)	2 (10.5)	4 (1.6)	12 (2.5)	0.050
Malposition or thrombus requiring surgery*	4 (0.5)	0 (0.0)	1 (0.4)	3 (0.6)	0.88
Acute arterial injury†	26 (3.5)	1 (5.3)	12 (4.9)	13 (2.7)	0.28
Obstruction‡					
Pulmonary artery	18 (2.4)	0 (0.0)	11 (4.7)	7 (1.5)	0.034
Aortic obstruction	15 (2.0)	0 (0.0)	7 (3.0)	8 (1.7)	0.470
Major bleeding event§					
Acute event (<72 h post-procedure)	11 (1.5)	1 (5.3)	1 (0.4)	9 (1.9)	0.11
Hematoma at access site	4 (0.5)	0 (0.0)	1 (0.4)	3 (0.6)	0.89
Composite (any major bleeding events)	15 (2.0)	1 (5.3)	2 (0.8)	12 (2.5)	0.10

Values are n (% column total). *2 cases with missing data. †Loss of distal pulse at the percutaneous entry site that required intervention. ‡Obstruction on the pulmonary artery or aorta by the PDA closure device. §Major bleeding event associated with one of the following: 1) hemoglobin drop of ≥3 g/dl; 2) transfusion red blood cells; or 3) intervention or surgery at the bleeding site to reverse, stop, or correct the bleeding.

MAEs were not unexpected. Differences in the definition of MAE across studies also likely contributed to observed differences. Although similar to previous studies using the IMPACT registry (23), we modified the definition of an MAE based on clinical rationale, to include elements (AAI, major bleeding events) relevant for lower weight infants (4). Importantly, iterative removal of these elements from our definition of an MAE did not change the observed findings.

Recent data suggest a marked change among clinicians toward conservative treatment approaches to PDA treatment, using positive pressure, diuretics, and fluid restriction to minimize the adverse consequences of ductal patency and provide time for spontaneous closure (24). Conservative treatment may reduce unnecessary interventions in many infants, but the question remains as to what to do if the PDA fails to close following a period of conservative treatment. Consistent with previous studies (25), postnatal age <30 days at the time of catheterization is an important predictor of morbidity during cardiac catheterization. Targeted use of transcatheter PDA occlusion in the subset of infants whose ductus fails to close after 30 days of conservative treatment and who continue to show evidence of adverse ductal sequelae may enable health care providers to minimize risk and yield the greatest benefits.

Despite using the largest available database, the relatively few ELW (<2 kg) (n = 19, 2.5%) infants limit detection of differences in MAE rates at lower weight thresholds. We await the results of an upcoming multicenter, device-sponsored (St. Jude Medical) trial to evaluate the safety and efficacy of the St. Jude Medical AMPLATZER Duct Occluder II AS (ADO II AS) exclusively in infants <2 kg (26).

STUDY LIMITATIONS. Data regarding clinical efficacy and the preventability of MAEs were not available. Efforts to develop strategies to link adverse events more definitively to cardiac catheterization are needed. Weight cutoffs are not evidence-based, and risks are likely to be continuous in nature. Because arterial access was obtained in >90% of patients in the present study, the need to identify approaches that minimize arterial access will likely reduce such complications (5). Definitions in the IMPACT registry were intended for pediatric and adult patients; thus, the criteria employed were not designed specifically for our subgroup of infants. Although the IMPACT registry uses standard PDA morphological classification, recent efforts to characterize a fetal type (Type F) PDA are ongoing (5). In the setting of a PDA, Qp/Qs calculations may be limited (7). Because the IMPACT registry provides data on in-hospital events only, the risk of underreporting adverse events (e.g., device malposition) that may have occurred following hospital discharge is recognized. Lack of longer-term experience and scrutiny with transcatheter PDA occlusion techniques in lower weight infants is acknowledged.

Although mortality was higher among infants with an MAE than in infants without an MAE,

death could not be definitively attributed to cardiac catheterization. Cases without a recorded attempt to close the PDA (e.g., unfavorable anatomy) were not captured; thus, procedural success (feasibility) rates may be overestimated. The risks of major bleeding events and vascular injury magnify the need to identify optimal anticoagulation protocols. Although we observed no association between PDA length and successful device placement, this likely remains an important factor in clinical practice. Recently, Zahn et al. (5) have shown that PDAs can be closed percutaneously outside of the catheterization laboratory (e.g., neonatal intensive care unit); however, data from the IMPACT registry are limited to the catheterization laboratory only. Finally, our analysis preceded a formal audit of the IMPACT registry; however, quality assurance standards are rigorously applied to the registry, and results of an audit are unlikely to affect the observed findings.

CONCLUSIONS

Data in the IMPACT registry indicated high rates of technical success among percutaneous PDA closure among infants <6 kg; however, risks of MAEs were noteworthy. Well-designed comparative trials (transcatheter occlusion, surgical ligation, conservative treatment) that use clearly defined inclusion criteria and treatment thresholds, standardized protocols for adverse events surveillance, and long-term follow-up are needed.

ADDRESS FOR CORRESPONDENCE: Dr. Carl H. Backes, Center for Perinatal Research and the Heart Center, Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205. E-mail: Carl.BackesJr@nationwidechildrens.org.

PERSPECTIVES

WHAT IS KNOWN? Transcatheter PDA occlusion is among the safest of interventional cardiac procedures in older children and adults, but use among lower weight infants (<6 kg) has not been characterized adequately.

WHAT IS NEW? Using the largest available U.S. database (IMPACT registry, part of the National Cardiovascular Data Registry), we describe risk factors for adverse events across 73 hospitals in 747 infants <6 kg undergoing attempted transcatheter PDA closure.

WHAT IS NEXT? The present findings are intended to inform patient selection and procedural approach for percutaneous PDA closure and direct targeted research efforts to support the practice of evidence-based medicine.

REFERENCES

1. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010;125:1020–30.

2. Mavroudis C, Backer CL, Gevitz M. Forty-six years of patient ductus arteriosus division at Children's Memorial Hospital of Chicago. Standards for comparison. Ann Surg 1994;220:402–9; discussion 409–10.

3. Ghani SA, Hashim R. Surgical management of patent ductus arteriosus. A review of 413 cases. J R Coll Surg Edinb 1989;34:33–6.

4. Backes CH, Rivera BK, Bridge JA, et al. Percutaneous patent ductus arteriosus (PDA) closure during infancy: a meta-analysis. Pediatrics 2017;139:e20162927.

5. Zahn EM, Peck D, Phillips A, et al. Transcatheter closure of patent ductus arteriosus in extremely premature newborns: early results and midterm follow-up. J Am Coll Cardiol Intv 2016;9:2429–37.

6. Abadir S, Boudjemline Y, Rey C, et al. Significant persistent ductus arteriosus in infants less or equal to 6 kg: percutaneous closure or surgery? Arch Cardiovasc Dis 2009;102:533–40.

7. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation 2006;114:1873–82.

8. Dimas VV, Takao C, Ing FF, et al. Outcomes of transcatheter occlusion of patent ductus arteriosus in infants weighing ≤ 6 kg. J Am Coll Cardiol Intv 2010;3:1295–9.

9. Abdelbasit MA, Alwi M, Kandavello G, Che Mood M, Samion H, Hijazi ZM. The new Occlutech® PDA occluder: initial human experience. Catheter Cardiovasc Interv 2015;86:94–9.

10. Moore JW, Greene J, Palomares S, et al. Results of the combined U.S. Multicenter Pivotal Study and the Continuing Access Study of the Nit-Occlud PDA device for percutaneous closure of patent ductus arteriosus. J Am Coll Cardiol Intv 2014;7:1430–6.

11. AGA Medical Corporation. Amplatzer Duct Occluder II: Instructions for Use. Plymouth, MN: AGA Medical Corporation, July 2014.

12. Baspinar O, Sahin DA, Sulu A, et al. Transcatheter closure of patent ductus arteriosus in under 6 kg and premature infants. J Interv Cardiol 2015;28:180–9.

13. Feltes TF, Bacha E, Beekman RH 3rd, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation 2011;123:2607–52.

14. Martin GR, Beekman RH, Ing FF, et al. The IMPACT registry: IMproving Pediatric and Adult Congenital Treatments. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2010;13:20–5.

15. Messenger JC, Ho KK, Young CH, et al. The National Cardiovascular Data Registry (NCDR) Data Quality Brief: the NCDR Data Quality Program in 2012. J Am Coll Cardiol 2012;60:1484–8.

16. Bergersen L, Everett AD, Giroud JM, et al. Report from The International Society for Nomenclature of Paediatric and Congenital Heart Disease: cardiovascular catheterisation for congenital and paediatric cardiac disease (part 1-procedural nomenclature). Cardiol Young 2011;21:252–9.

17. 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:e002923.

18. Krichenko A, Benson LN, Burrows P, Moes CA, McLaughlin P, Freedom RM. Angiographic classification of the isolated, persistently patent ductus arteriosus and implications for percutaneous catheter occlusion. Am J Cardiol 1989;63:877–80.

19. Bergersen L, Gauvreau K, Foerster SR, et al. Catheterization for Congenital Heart Disease Adjustment for Risk Method (CHARM). J Am Coll Cardiol Intv 2011;4:1037–46.

20. Bergersen L, Gauvreau K, Lock JE, Jenkins KJ. A risk adjusted method for comparing adverse outcomes among practitioners in pediatric and congenital cardiac catheterization. Congenit Heart Dis 2008;3:230–40.

21. Bergersen L, Gauvreau K, Jenkins KJ, Lock JE. Adverse event rates in congenital cardiac catheterization: a new understanding of risks. Congenit Heart Dis 2008;3:90–105.

22. El-Said HG, Bratincsak A, Foerster SR, et al. Safety of percutaneous patent ductus arteriosus closure: an unselected multicenter population experience. J Am Heart Assoc 2013;2:e000424.

23. Jayaram N, Beekman RH 3rd, Benson L, et al. Adjusting for risk associated with pediatric and congenital cardiac catheterization: a report from the NCDR IMPACT registry. Circulation 2015;132:1863–70.

24. Letshwiti JB, Semberova J, Pichova K, Dempsey EM, Franklin OM, Miletin J. A conservative treatment of patent ductus arteriosus in very low birth weight infants. Early Hum Dev 2017;104:45–9.

25. O'Byrne ML, Glatz AC, Shinohara RT, et al. Effect of center catheterization volume on risk of catastrophic adverse event after cardiac catheterization in children. Am Heart J 2015;169:823–32.e5.

26. U.S. National Institutes of Health. AMPLATZER Duct Occluder II Clinical Study (ADO II). ClinicalTrials.gov Identifier: NCT00713700. Available at: https://www.clinicaltrials.gov/ct2/show/NCT00713700. Accessed January 5, 2017.

KEY WORDS adverse event(s), IMPACT registry, patent ductus arteriosus, percutaneous, transcatheter