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Effects of Percutaneous Closure of Patent Ductus Arteriosus in Infants Less than One Year of Age: A Systematic Review

Megan K. Locke

megan.locke@otterbein.edu

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EFFECTS OF PERCUTANEOUS CLOSURE OF PATENT DUCTUS ARTERIOSUS IN
INFANTS LESS THAN ONE YEAR OF AGE: A SYSTEMATIC REVIEW

Otterbein University
Department of Biology and Earth Science
Westerville, Ohio 43081
Megan Locke

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Lisa Marr, M.D.
Project Advisor

__Signed in Person_____
Advisor's Signature

Jeff Vasiloff, M.D., MPH
Second Reader

__Signed in Person_____
Second Reader's Signature

Jennifer A. Bennett, Ph.D.
Honors Representative

__Signed in Person_____
Honors Rep's Signature

Abstract

Background: Patent ductus arteriosus (PDA) is the continuous opening of the ductus arteriosus in an infant's heart after birth. This, when left untreated, can lead to numerous complications, including pulmonary hypertension as a result of the increased flow of blood into the lungs or even death. Historically, the first treatment option to correct PDA was surgery, opening up the chest cavity to close the duct; however, it has been seen to cause later neurodevelopmental impairments leading to further problems for the infant [1]. Therefore, clinicians searched for an alternative, leading to the use of percutaneous closure. Catheter-based PDA closure is increasingly performed during infancy (<1 year of age); however, the safety and feasibility of this intervention is currently not completely characterized in infants. Thus, the purpose of this study is to assess the safety and feasibility of percutaneous PDA closure in infants as reported in the available medical literature.

Methods: We conducted a systematic review of all pertinent published data from January 1965 – December 2015. A total of 5 electronic databases were searched. Inclusion criteria were (1) peer review journal source; (2) patient age birth to 1 year; and (3) adequate assessment and reporting of adverse events (AEs) and other safety data.

Results: Of 1060 articles identified, 949 were reviewed, but only 19 articles met inclusion criteria satisfactorily. Eighteen articles were case-control studies and one was a cohort study. No randomized controlled studies were identified. A tally of patients from all 19 included articles revealed 505 patients underwent a percutaneous procedure to close PDA. Among these, 480 (95%) were amenable to placement of PDA device/coil. Of these, 471 (93%) were reported to have attained complete PDA closure. In addition,

a total of 154 AEs (30.5%) were identified. Of the total AEs, 76 (49%) were deemed clinically significant (CS), while 78 (51%) were felt to be not clinically significant (NCS).

Conclusions: Percutaneous PDA closures avoid the need for open thoracic surgery and its complications; however, percutaneous closure is attended by clinically significant AEs in about 15% of cases. Demonstrating that the procedure is feasible; nonetheless, there are risks worth noting. Supporting the need for randomized-controlled trials (RCTs) comparing percutaneous PDA closure with other treatment options (medications) or making a comparison to historical data of AE's associated with other treatment modalities like open thoracic surgery. Making this systematic review vital in order to better understand which treatment option offers the best outcomes for infants.

Introduction

In a normally functioning heart, deoxygenated blood enters the heart through the inferior and superior vena cavas into the right atrium. That deoxygenated blood from the body is sent from the right atrium to the right ventricle to be sent through the pulmonary artery. This blood is transferred into the lungs. The lungs oxygenate the blood and send it into the left atrium. From the left atrium, this oxygenated blood is pumped into the left ventricle. From the left ventricle the oxygenated blood is sent out to the systemic circulation (body) through the aorta in the heart of a healthy baby and in an adult heart [2]. As a fetus, all of the blood is oxygenated through the placenta connected to the mother, therefore negating the need for all the blood to be sent to the lungs, which are deflated in utero.

The ductus arteriosus is an essential component of the fetal blood circulation. The job of this duct is to shunt the already oxygenated blood (by the placenta) away from the high resistance pulmonary vascular bed (lungs) into the systemic circulation (body) [3]. At birth when the umbilical cord is cut, the placental circulation is removed and the pulmonary circulation becomes the only source of oxygenating the blood in the newborn's body. After the first breath, pulmonary vascular resistance falls. The shunting of blood through the ductus to avoid the lungs is no longer necessary, and will become detrimental to the neonates' health [4, 5].

A persistent patent ductus arteriosus (PDA) is the continued opening of the ductus arteriosus following birth. There are many risk factors that contribute to an infant having a PDA. Being born premature (before 40 weeks gestation) is the largest risk factor that contributes to the development of PDA; as premature infants might not have developed the appropriate signals required in the body to close the ductus arteriosus, therefore leaving it open [6]. The specific signal that could be potentially missed involved the steroid hormone Prostaglandin E₂. The chemical signal is missed by either immature receptors or a nonfunctional signal, leading to PDA [7]. Additional risk factors include a family/genetic history of PDA, a rubella infection while in utero, or even being born at a higher altitude [6].

Morbidity [8] and mortality [9] have been observed to be associated with PDA. PDAs are considered to be precursors to conditions such as heart failure, prolonged ventilator dependency, necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD) [1, 9, 10-15]. During infancy, a PDA is associated with a 6-fold higher mortality than age-matched controls with a closed ductus [16]. The pathological

explanation for a higher mortality risk is likely the elevated levels of blood flow to the lungs causing an abnormal response by the pulmonary arteries, damaging them. Pulmonary hypertension, leads to failure of the right side of the heart, resulting in a significant right to left shunt of blood through the PDA (Eisenmenger's syndrome), which can then be fatal due to lack of oxygen to the body [17]. Infants and premature infants are the most impacted by PDA and its effects. With being premature the incidence of PDA jumps from 2 in every 1,000 live term births to 8 in every 1,000 live births [6]. The prevalence of PDA in term-infants accounts for about 5-10% of all congenital heart problems within this group, with even more prevalence for preterm infants. In preterm infants that prevalence number jumps to about 20-60%, with the variation depending on demographics [18].

Surgical ligation, historically, has been considered the standard of care to close a PDA when medicinal treatment has failed or has been contraindicated (meaning medications were not indicated due to comorbidities). Surgical ligation of the PDA is a procedure in which the chest cavity is opened to gain access to the heart. The PDA is then clipped/sewn shut (ligated) manually [1]. Surgical PDA ligation results in definitive ductal closure, with evidence of improved respiratory status following the ligation procedure. Surgical ligation has also been shown to reduce overall mortality in infants with PDAs [1]. However, recent studies suggest surgical PDA ligation may, in fact, increase the risk of adverse outcomes, including moderate-to-severe functional disability, developmental delay, and motor impairment. These adverse events of surgical ligation lead to a longer and more painful treatment plan for the infant patient [19]. Why these outcomes are increased with surgical ligation is potentially related to

the trauma of open thoracic surgery on an infant whom is weak due to significant medical comorbidities. The negative effect of anesthesia is another reason surgical ligation leads to worse clinical outcomes. There are few randomize-controlled trials (RCTs) to support or disprove this theory.

These observations have led to an interest in replacement strategies, that are less invasive, to close the PDA during infancy, including catheter-based techniques. Evidence is growing on the benefits of catheter-based PDA closure, including reduced procedural times, less pain, shorter recovery time, and improved hemodynamic stability. Although percutaneous closure of PDA is considered among the safest of interventional cardiac procedures, the majority of evidence supporting catheter-based PDA closure comes from adults, children, and infants > 6 months of age. This leaves a gap in the literature for infants'; the group in which the prevalence and incidence for PDA is most common, as mentioned previously [18].

Concerns regarding adverse events (AEs) led the Federal Drug Administration (FDA) in 2003 to suggest that PDA closure using a device (Amplatzer Duct Occluder) be used only in patients >6 months of age [20]. Recently, the American Heart Association (AHA) stated their support for the practice of catheter-based PDA closure in children, but mentioned the need for a better understanding of the risks and benefits of percutaneous PDA closure among infants <6 months of age. Historically, clinical trials have either excluded infants all together or did not focus on that subgroup, based on concerns that percutaneous PDA closure may lead to vascular complications, among others, within this cohort. Most clinical trials were focused on children older than one year of age at the time of procedure [21, 22]. Despite the 2003 FDA recommendation,

numerous studies have been conducted since which demonstrate the feasibility of transcatheter PDA closure in infants <6 months of age. Current clinical trial studies have begun to show that catheter-based PDA closure can be safe and tolerated by infants, all of which are included within this systematic review [23-41]. This area of inquiry and controversy has provided clinicians with limited evidence-based guidelines on their clinical management of PDA in infants. In fact, a recent survey of pediatricians in the United States showed that while a majority of respondents believe that catheter-based PDA is a reasonable choice, most are unaware of the optimal timing of the intervention and are concerned that performing the intervention during infancy may worsen clinical outcomes and increase risk for harm as a result of the procedure [42].

While previous literature reviews on percutaneous PDA closure have broadly investigated outcomes among all pediatric patients (ages 0-18 years), the purpose of the present systematic review is to perform an efficient appraisal of the literature among those infants receiving percutaneous PDA closure when <1 year of age; the group at the crux of this medical debate. Procedures, in general, during infancy are more complex, due to an increase in comorbid conditions, smaller body/anatomy, and an increased state of frailty due to being young. Percutaneous PDA closure could potentially carry higher risks for the infants than those performed later in development, such as in children or adults. Hence, a separate consideration of the potential risks and benefits of percutaneous PDA closure in infants is necessary. This systematic review details the current literature on infant percutaneous PDA closure despite the lack of available comparative literature.

MATERIALS AND METHODS

Data Sources:

Comprehensive search strategies were developed with a clinical librarian and run in 5 databases: PubMed, Embase, Scopus, Web of Science, and the Cochrane Library. The search considered only articles published in peer-reviewed journals and written in English from January 1965 to December 2015. The references of related articles were likewise searched for any additional eligible citations, which were also considered for inclusion into the study. The article inclusion steps and keywords are seen in **Figure 1**. Both randomized and non-randomized-controlled trials were considered, as well as case series and cohort studies.

Study Selection:

Potentially applicable articles were assessed based on the following inclusion criteria: (1) the average age of the patient cohort was ≤ 1 year of age at the time of the procedure, (2) was peer-reviewed research, (3) involved percutaneous closure of PDA, and (4) assessment of adverse events (AEs) was reported within the text. After full-text assessments led to removal of irrelevant articles, duplicates, and those that did not satisfy all inclusion criteria; we identified 19 articles suitable for inclusion. Additional exclusion criteria included journal articles (1) not published in English, (2) average patient ages were not reported and could not be determined, and (3) a cohort of less than 3 infants.

Data Extraction:

Data were extracted by two reviewers, myself (the author) and Brian Rivera, a Research Associate at Nationwide Children's Hospital (for Dr. Backes), referred to as reviewers 1 and 2 respectively, using a standardized form, determined before data collection, and verified by a 3rd reviewer, Carl H. Backes, MD. Disagreements between the first two reviewers were resolved through discussion with the 3rd party, resulting in consensus.

The following information was collected from each included article:

- Author(s)
- Year of study
- Country
- Study design
- Number of patients
- Age of patients at time of procedure
- Primary indication for performing percutaneous PDA closure
- Comorbid conditions and concomitant treatment
- Procedural details
- Details of AEs
- Vascular complications
- Technical/procedural successes

The guidelines and definitions for specific data extraction are shown in **Table 1**. The articles were further analyzed for use of either a device (ex. Amplatzer™, Amplatzer II™) or a coil (ex. Gianturco, flipper, Nit-Occlud®) during the percutaneous procedure, examples of both a device and coil are seen in **Figure 2a and 2b** [5, 43]. When multiple device placements were attempted, only the final implant was recorded. Devices or coils requiring retrieval during the procedure were not counted if the PDA was closed by another method, such as surgical ligation. The condition of left pulmonary artery (LPA) stenosis and aortic stenosis was reported in the literature and recorded by reviewer 1. LPA and aortic stenoses were noted if they were reported in the literature as significant and only if they did not result in the patient undergoing surgical ligation of the PDA.

Each LPA or aortic stenosis was recorded at immediate follow-up and long-term follow up (average of > 6 months). If the median follow-up times were reported, the averages were calculated using a formula designed in a previous study [44].

Data Synthesis:

Adverse Event (AE) Severity

From the guidelines of a previous study's assessment of AEs, reviewers 1 and 2 assessed AE severity independently based on the criteria [45]. The scale from least clinically significant to most clinically significant increases levels 1 to 5. Levels 1-2 were defined as non-clinically significant (NCS) and levels 3-5 were considered to be clinically significant (CS) based on work previously done by C.H. Lin et al [46]. The reported AE severity scale used is shown in **Table 2**. Differences in classifications between the two reviewers were resolved by discussion with Dr. Backes. The final ratings were attained through consensus among the parties. If an AE occurred after the procedure or during the infant's recovery period, it was not included in the data analysis because the AE did not occur while undergoing the catheterization procedure or could not be attributed to the procedure. The adverse event had to happen while the procedure was being performed.

Adverse Event (AE) Attribution to PDA Closure

The attribution of AE to the percutaneous closure of the PDA was also assessed for each included clinical trial. Both reviewers assessed the degree of attribution of each AE to the percutaneous procedure and consensus was reached with Dr. Backes. When disagreements between reviewers occurred, the causality algorithm used by World

Health Organization Collaborating Centre for International Drug Monitoring (WHO) was used to determine the attribution of AE to the related procedure. The terminology was revised for the use of a device rather than for the use of medications. The guidelines for determining attribution of AE to percutaneous procedure can be seen in **Table 3**. Both reviewers also determined the quality of the studies analyzed in this systematic review using the Methodological Index for Non-Randomized Studies (MINORS) scale [47]. MINORS is a scale used to determine the quality of individual research studies based on what the article is including. A higher score 15-20 means it was conducted as a high quality research study. The guidelines were set by a previous study conducted seen in **Table 4**; our studies results can be seen in **Table 5** [47].

Data Analysis:

Bar graphs and pie charts were created using Microsoft Excel. Weighted meta-analysis of the results of adverse events in the included reports was performed using OpenMeta (analyst) software (http://www.cebm.brown.edu/open_meta/) and a random effects model (DerSimonian-Laird) with a 95% confidence level.

RESULTS

Searches:

Database searches resulted in a total of 1060 references, of which 111 were neither in English nor between the specified dates (January 1965 – December 2015). After screening titles and abstracts of the remaining 949 articles, 870 were excluded because of a lack of relevance to topic, lack of primary data, or lack of mention of

safety; the full texts of the remaining 79 articles were obtained. An additional 4 articles identified in the references warranted a full text assessment and were subsequently obtained as well. Of these 83 articles, after full-text assessments, 19 met all inclusion criteria.

Articles were excluded for the following reasons:

- Publication was not in English nor between specified dates (111)
- Not human subjects and/or lack of relevance (870)
- Average age of patients was >1 year at time of procedure (63)
- A cohort of less than 3 infants (1)

Of the 19 included studies, none were randomized-controlled trials, 1 was a cohort study and 18 were case reports or case series. The flow of articles through review is shown in **Figure 1**. Of the 19 articles there were 9 retrospective (second-hand) studies and 10 prospective (conducted first-hand) studies. There were only 2 comparative studies.

Reasons for Percutaneous PDA Closure:

As stated in **Table 1**, the infants were grouped by the primary reason(s) that the author(s) of the article cited as the reason for referral to percutaneous PDA closure instead of other methods of PDA closure, such as surgery or medications. The reasons stated by the author(s) included that of increased left ventricular dimensions (153), ventilator dependence (30), failure to thrive (2), pulmonary hypertension (49), multiple comorbidities (238), and unreported (33). This data is broken down for demonstration within **Figure 3**. The definition for how to categorize each comorbidity as the primary reason of referral for percutaneous closure that the authors of the research studies placed the infants in are described in **Table 6** [48]. Each definition was carried

throughout review of each article by each reviewer to maintain consistency in grouping the infants within each article to a specific group. If an infant was a part of the ventilator-dependent group, he/she was said to have required oxygen and/or was receiving respiratory support of any kind prior to the procedure, which was stated as the primary reason for referral. Although other infants may have been on a ventilator, they were only included if being on the ventilator was the primary reason for referral to percutaneous closure of the patent ductus arteriosus (PDA). If an infant was cited to have more than one of the purposed reasons for percutaneous closure as the primary reason then he/she was placed in the multiple comorbidities group. If the literature did not report any sort of primary reason for referral to percutaneous closure then those infants were categorized as unknown/unreported.

Procedural Success:

The procedural success definitions are shown within **Table 1**. The closure of the PDA with either a device or coil was determined based on what final equipment was used on the infant prior to leaving the catheterization lab. The use of device (377, 79%) greatly outweighed the use of a coil (98, 21%). Overall success was defined as complete closure of the duct by the end of the studies' follow-up. The overall success rate of each of the 19 included articles was determined on average to be 94%. A procedural success was defined as a device/coil being placed in the catheterization lab with no immediate residual shunt and subsequently leaving the lab with the implanted equipment. The procedural success rate was immediate closure without residual shunt 378 (74.8%, 505). Out of the remaining 127 cases with an immediate residual shunt, 93

more closed by the end of the study to give an overall success rate, complete PDA closure, of 93% (471/505).

Six of the included articles had a technical success rate of 100%. Technical success was the placement of a coil or device within the PDA and the infant leaving the catheterization lab with such coil or device. It was also considered a technical success if the device or coil embolized but was retrieved and another device or coil was used to replace the previous one. Of the articles that did not report a 100% success rate, none were lower than 80% success [23-41]. **Figure 4** displays each article's technical success rate, with the placement of either a device or coil, with a 95% average success based on the definition of technical success. Weighted analysis using a random-effects model showed the overall likelihood of technical success as being 0.96 (95% CI 0.94 – 0.98, $P < 0.01$; Heterogeneity: $\tau^2 = 0.0$, $Q (df=18) = 13.32$, $I^2 = 0\%$, $P = 0.77$). The corresponding forest plot is shown in **Figure 5**.

Procedural Failures:

The procedural failures definitions are seen within **Table 1**. A procedural failure was defined as a device or coil being deployed but subsequently being retrieved because of embolization or other health reasons and elective or emergent surgery performed to close the PDA. The average rate of procedural failure was about 5.5% (~28/505). Approximately 25% (127/505) of cases had a residual shunt on post-procedure echocardiography or angiography, as shown in **Figure 6**. Of the cases with a residual shunt immediately following the catheterization procedure, there were only 34 out of a total of 505 (6.7%) that reportedly did not fully close at the completion of the

study it was reported within. This led to the 93% overall success rate. There were 28 reported procedural failures (5.5% of all procedures) and 3 reported procedural abandonments (0.59% of all procedures). Failure was defined with the deployment of a device/coil resulting in removal of equipment and closure of the PDA by other methods; abandonment was defined as going into the catheterization lab with the intent to close the PDA through percutaneous methods, but the device/coil was not released and alternative closure methods were elected. Reasons cited for procedural failure or abandonment and incidence are given in **Table 7**.

Adverse Events (AEs)

Among 505 cases, 154 AEs (30.5%) were identified. Of these 154 AEs, 78 (50.6%) were non-clinically significant (NCS), 76 (49.4%) were clinically significant (CS), and 1 of the CS AEs (0.65%) was catastrophic (death). These AEs were categorized based on the definitions given in **Table 2**. There was about a 30% chance of any AE occurring within the cohort of 505 infants in accordance with the collected data [23-41], with no AE's occurring approximately 70% of the time. The occurrence of CS AEs was compared to that of the occurrence of NCS AEs. Prevalence AE calculation was done per the total number of AEs recorded (N=154). Within the 30% chance of an AE occurring, there were 78 (50.6%) AEs rated as NCS (levels 1-2) and CS AEs (levels 3-5) totaled 76 (49.4%) (**Figure 7**) [23-41]. Weighted analysis using a random-effects model showed the overall likelihood of a CS AE was 0.13 (95% CI 0.08 – 0.17, $P < 0.01$; Heterogeneity: $\tau^2 = 0.0$, $Q (df=18) = 37.93$, $I^2 = 53\%$, $P < 0.01$). The forest plot is shown in **Figure 8**. Weighted analysis, also using a random-effects model showed the

overall likelihood of a NCS AE was 0.20 (95% CI 0.13-0.27, $P < 0.01$; Heterogeneity: $\tau^2 = 0.02$, $Q (df=18) = 138.03$, $I^2 = 87\%$, $P < 0.01$). The corresponding forest plot is shown in **Figure 9**. The overall likelihood of an AE occurring was determined by taking the total number of AEs that were present dividing that number by the total number of infants within our cohort. This resulted in about a 30% chance of an AE occurring with about 70% of the chance no AE occurred.

Attribution of a reported AE and the percutaneous procedure were determined. The causality was assessed for all 154 reported AEs, as definite (106), probable (44), possible (4), unlikely (0), and unrelated (0). The course of action for determining attribution followed the guidelines set by WHO with modification for procedural complications instead of medicinal treatments, as seen in **Table 3**.

Vascular complications were noteworthy adverse events to occur. There were 12 noted reports, totaling 51 instances. These primarily consisted of thrombosis (33, 64.7%) requiring thrombolytic therapy and transient pulse loss (17, 33.3%). The remaining case was a report of “right femoral vein trauma” [28], which was the most serious vascular complication noted.

DISCUSSION

To our current knowledge, this is the first systematic review to specifically examine the safety and feasibility of percutaneous PDA closure in infants < 1 year of age based on the available literature and was conducted in order to focus on this specific infant sub-group that includes premature infants, whom are most at risk for developing PDA. Physicians and parents would gain the maximum benefit from a better

understanding of the risks associated with this treatment option [49-52]. The results of this study suggest a low incidence of complications, as is consistent with previous studies [23-41, 45, 53, 54]. The number of articles with a 100% success rate are suggestive that percutaneous closure of PDA in infants is very promising, despite the lack of experience with this treatment in this subgroup [23, 24, 27, 31, 33, 41]. The main finding of our systematic review is among infants < 1 year of age, referred for percutaneous PDA closure. The majority is successfully closed in the catheterization lab with low incidence of clinically-significant adverse events (CS AEs), only approximately a 13% risk in a cohort of 505 infants; however, the risk of minor complications is noteworthy.

Only one infant out of the total cohort of 505 was reported to have died as a direct result of percutaneous PDA closure, which was rated as a “catastrophic” CS AE by our severity level guidelines (**Table 2**) [25]. This particular premature infant weighed 1500 grams at time of catheterization and had a number of additional comorbidities including disseminated intravascular coagulation, stage IV intracranial hemorrhage, acute renal failure, and necrotizing enterocolitis [25]. This infant developed a pericardial tamponade during catheter manipulation and underwent emergency pericardiocentesis. However, the infant failed to respond to resuscitation and died. The infant was believed to have suffered cardiac perforation; however, as no autopsy was performed a perforation could not be officially confirmed [25].

In order to adequately address the central question of whether the benefits of catheter-based PDA closure outweigh the risks of the procedure, particularly for infants; randomized-controlled trials comparing percutaneous PDA closure, conservative (“non-

intervention”) management, or surgical ligation, are needed [55, 56]. These trials should have a uniform follow-up time in order to better define long-term effects and to have a baseline for comparison abilities from trial to trial. The length of follow-up was reported inconsistently in the included studies, thus preventing any determination of how time affects the outcomes of the infants within the studies. Researchers and clinicians must work together in order to help cement the definition of an aortic or LPA stenosis, which would greatly increase the likelihood of gaining meaningful results.

The results of this review are a compilation of many single-center studies that have conducted research cooperatively on infants and catheter-based closure of PDA. The use of mostly single-center studies is a result of the lack of multi-center studies conducted on this topic with < 1-year-old infants. Although, there are many multi-center studies conducted in order to determine risks of percutaneous PDA closure; they did not focus on this subset of patients. For example, El-Said et al conducted a multi-center study that demonstrated the high success rate and low complication rate of this procedure in subjects with an average age of greater than one year [45]. Many other studies, similar to El-Said’s article, have been conducted but were unable to be included in this review because of the age restraint [45, 53, 54]. The lack of multi-center studies hindered our ability to perform a meta-analysis of the literature due to the lack of comparative literature available within the age range of < 1 year at time of procedure.

For clinicians, the results of this systematic review demonstrates that treatment of PDA in infants <1 year of age using a percutaneous method is safe and feasible, and should be considered a treatment option when an infant is diagnosed with PDA. This systematic review also gives clinicians a starting point in which to assess the foreseen

risks of referring a patient for this procedure. However, this systematic review alone does not give the clinicians the ultimate thumbs up or thumbs down for recommending percutaneous PDA closure. Instead, this analysis provides researchers with results that lead to further questions about what treatment option is the best option for infants < 1 year of age. To answer those questions, there must be randomized-controlled trials (RCT) conducted comparing three different treatment options: percutaneous closure, surgical closure, and conservative treatment (“non-intervention”). These RCTs must be focused on infants since this patient population is most vulnerable to PDA and would benefit from the findings of which treatment option is best suited for this age group. This would lead to a better quality of life for infants’ with a corrected PDA.

Many limitations were found in the literature available at this time. As stated, the MINORS scale was used to determine the quality of the individual articles, guidelines seen in **Table 4** [47]. **Table 5** demonstrates the results of this rating by the same 3 reviewers, and the average score was taken as the quality rating. The MINORS scale was adapted to fit scoring of 18 studies that were non-comparative (8-item scale) and 1 study that was comparative (12-item scale) [47]. MINORS results showed overall low quality articles when applied to the 19 included research studies. A positive reporting bias is also commonly seen within case reports; therefore this limitation could skew the data one way. As more devices were used in the research studies, a bias may also be indicated for device over coil usage. There may also be bias towards more experienced surgeons performing percutaneous closure of the PDA. A selection bias may also exist, because the reports did not include randomized-control trials. A systematic review always runs the risk of not all relevant articles being included within it. Another limitation

is the lack of consistency in reporting LPA and Aortic Stenosis ranges and velocities because of the lack of a common definition for these stenoses. In addition, there was a limitation in regards to lack of reporting of follow-up lengths throughout all articles. In addition, not all articles reported the average follow-up length.

CONCLUSION

Percutaneous closure of patent ductus arteriosus (PDA) in infants < 1 year of age is safe and feasible according to a detailed review of the current literature. This systematic review provides an initial risk profile associated with percutaneous PDA closure in infants. However, there is a lack of comparative literature to determine the optimal treatment option among surgical ligation, medications, and percutaneous closure. The outcomes for each currently available treatment option have not been compared to one another and this leaves a gap in clinician treatment guidelines in infants with PDA. This calls for randomized-controlled trials to help determine the best treatment option for closing PDA within infants < 1 year of age.

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Figure Legends

Figure 1: Flow diagram of search criteria and resulting articles.

Figure 2a: Picture of a Device used in Percutaneous Closure of PDA

2b: Picture of a Coil used in Percutaneous Closure of PDA

Figure 3: Reasons given for percutaneous PDA closure.

Figure 4: Technical success versus technical failure of device deployment.

Figure 5: Technical Success Forest Plot

Figure 6: Incidence of residual shunt immediately following percutaneous closure.

Figure 7: Percentage of adverse events (N = 154) broken down by level, compared to no adverse events reported (N = 351).

Figure 8: Risk of Clinically Significant AEs Forest Plot

Figure 9: Risk of Non-Clinically Significant AEs Forest Plot

Table Legends

Table 1: Guideline Definitions for Data Collected

Table 2: Adverse Event (AE) Guideline for Rating Scale

Table 3: Guideline Definitions for Attribution Rating Scale

Table 4: MINORS Guidelines as Seen in Previous Study

Table 5: MINORS Rating with Averages

Table 6: Reasons for Percutaneous Closure Guideline Definitions

Table 7: Reasons for Procedural Failures and Abandonments

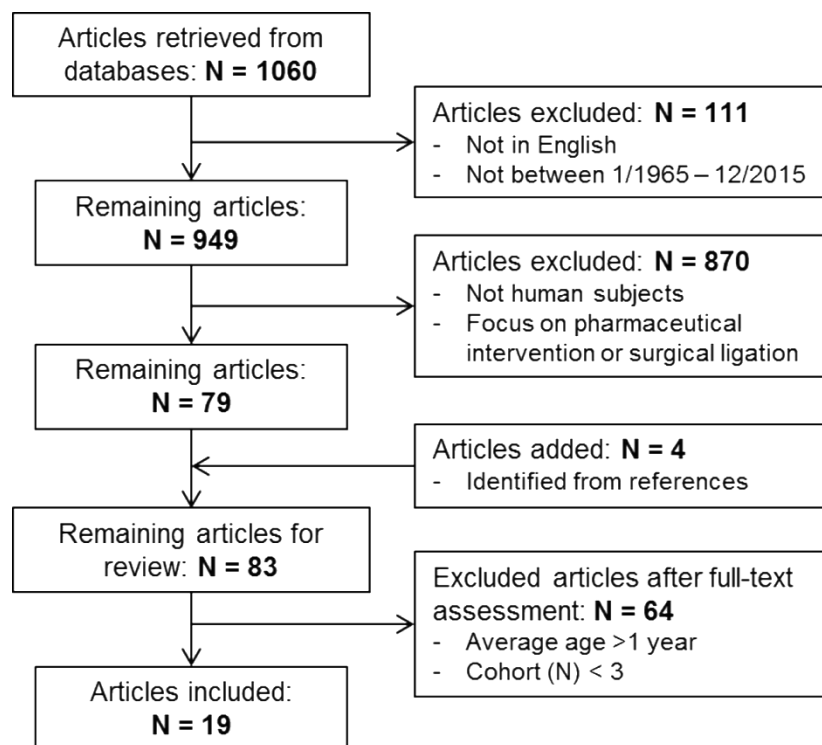
Figures and Tables (page # table or figure is found on)**Figure 1. Article Identification** (8, 12)

Table 1. Definition of Data Collected (9, 12, 13, 14)

Variable:	Defined As:
Reason(s) for percutaneous PDA closure	Primary reason or reasons for referral as cited by the author(s)
Overall success	Complete ductal occlusion (no residual shunts) by study completion, as reported by author(s)
Technical success	1. Infant leaves catheterization suite with device / coil in place, without embolization 2. Embolization of device / coil which is then retrieved, followed by closure using different device during same procedure
Procedural success	Lack of residual shunt following device / coil implantation as reported in post-procedural angiography
Procedural failure	Deployment, followed by retrieval of device / coil then subsequent elective or emergent surgery to close PDA by other means
Procedural abandonment	Device / Coil never released, PDA closure by other means
Vascular complications	Pulse loss, Need for thrombolytic therapy (heparin and/or streptokinase infusion, thrombectomy)

Table 2. Adverse Event Rating (10, 15, 17)

	Severity Level	Definition	Examples
Non-Clinically Significant	1. Mild	No harm comes to the patient; <u>no</u> intervention is required, but some monitoring to evaluate for potential change in condition	Equipment malfunction before deployment, easily retrievable
	2. Minor	Slight change in one's condition, not life threatening, resolves on own; <u>no additional</u> interventions necessary	Change in condition but does not require use of additional medical interventions; coil malposition or embolization retrieved in cath lab
Clinically Significant	3. Moderate	Slight to moderate change in one's condition that could become life threatening if not treated; requires medical interventions	Blood transfusions; any change in condition resulting in use of medical interventions; Device malposition or embolization retrieved in either cath lab or outside of cath lab
	4. Major	Any change in condition that could be life threatening if not treated; change in one's condition that could be permanent; requires interventions of either the invasive or transcatheter type	Any surgical retrieval of an embolized or malpositioned device; any elective surgical ligation of duct
	5. Catastrophic	Any death or any emergent surgery performed to prevent death	Death

Table 3. Attribution (11, 16)

Attribution of Adverse Event to Percutaneous Closure of PDA	
Rating	Definition (such as, but not limited to)
Definite	Clearly related to cath procedure (residual shunts, flow disturbances, device embolizations/migrations)
Probable	Likely related to cath procedure (transfusions, residual flow, pulse loss, death)
Possible	May be related to cath procedure (transfusions, hemolysis, infection)
Unlikely	Doubtfully related to cath procedure (secondary problems found prior to procedure)
Unrelated	Clearly not related to cath procedure (other abnormalities)

Table 4: MINORS Guidelines [47] (11, 19)

Methodological items for non-randomized studies	Score [†]
[†] The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.	
1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature	
2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)	
3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study	
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.	
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated	
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events	
7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint	
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes	
<i>Additional criteria in the case of comparative study</i>	
9. An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data	
10. Contemporary groups: control and studied group should be managed during the same time period (no historical comparison)	
11. Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results	
12. Adequate statistical analyses: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

Table 5. Minors Scaling (11, 19)

Article	N	MINORS Rating			Average Score
		reviewer 1	reviewer 2	reviewer 3	
Abu-Hazeem et al	8	12	13	13	12.7
Adelmann et al	5	10	8	10	9.3
Baspinar et al	69	5	5	5	5
Behjati-ardakani et al	48	7	10	9	8.7
Bentham et al	3	7	4	7	6
Dimas et al	62	7	9	9	8.3
Drighil et al	22	7	7	7	7
Fischer et al	12	10	8	10	9.3
Francis et al	8	7	9	9	8.3
Hijazi et al	24	14	14	14	14
Kusa et al	6	7	9	9	8.3
Lin et al	20	13	18	18	16.3
Parra-Bravo et al	29	10	10	10	10
Roberts et al	10	5	5	5	5
Sivakumar et al	28	7	7	7	7
Tomita et al	32	4	6	6	5.3
Ullah et al	52	9	9	9	9
Vijayalakshmi et al	61	12	7	12	10.3
Zahn et al	6	10	8	10	9.3

Figure 2. Pictures of both a Device and a Coil used in Percutaneous Closure (9)

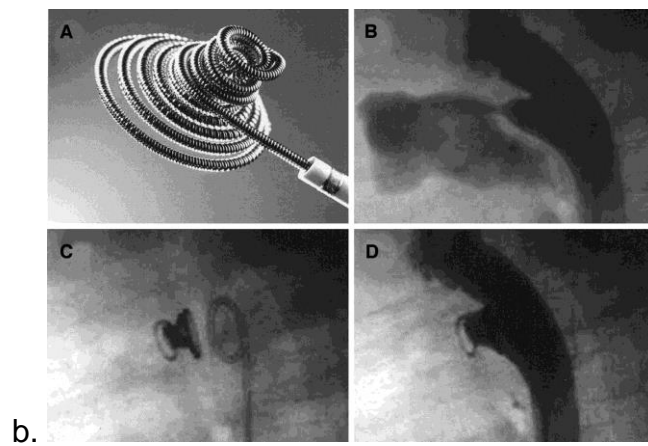
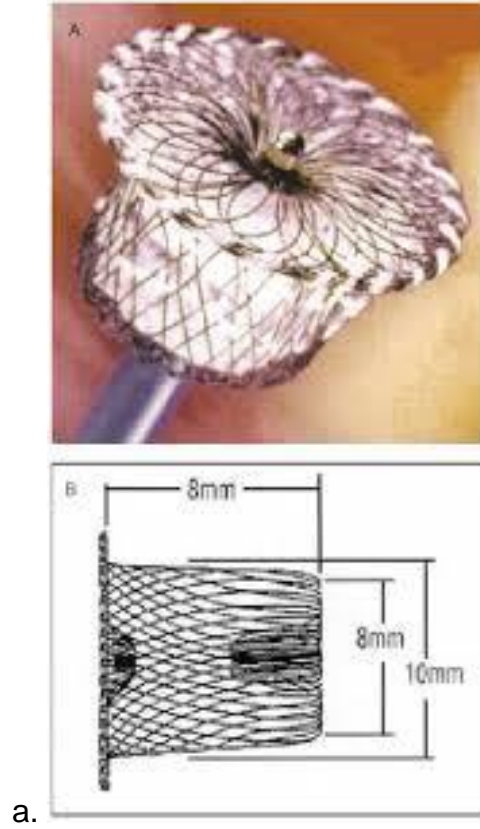


Figure 3. (12)

Reasons for Percutaneous PDA Closure

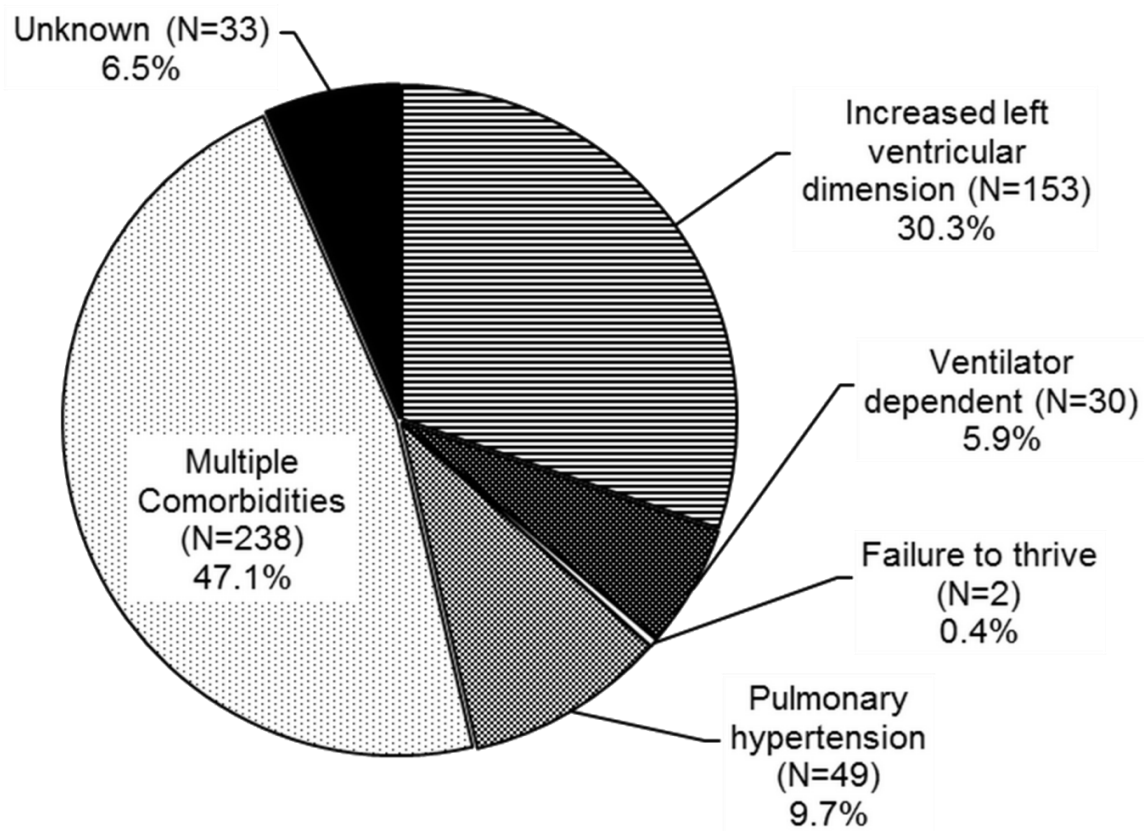


Table 6. Reasons for Percutaneous Closure Definitions (12)

Primary Reason Indicated by Author(s)	Definition: Primary Reason
Increased Left Ventricular Dimensions	Reported as having increased left ventricular dimensions or heart failure
Ventilator Dependence	Required oxygen and/or respiratory support prior to the procedure
Failure to Thrive	Reported as having inadequate weight gain, or alternatively, unusual weight loss
Pulmonary Hypertension (PH)	Reported as having PH within the literature, or having beginning signs such as accelerated flow within the pulmonary arteries to the lungs
Multiple Comorbidities	Reported as having more than one primary reason for percutaneous PDA closure
Unknown/Unreported	Primary reason was not cited within the literature by the author(s)

Figure 4. Technical Success (14)

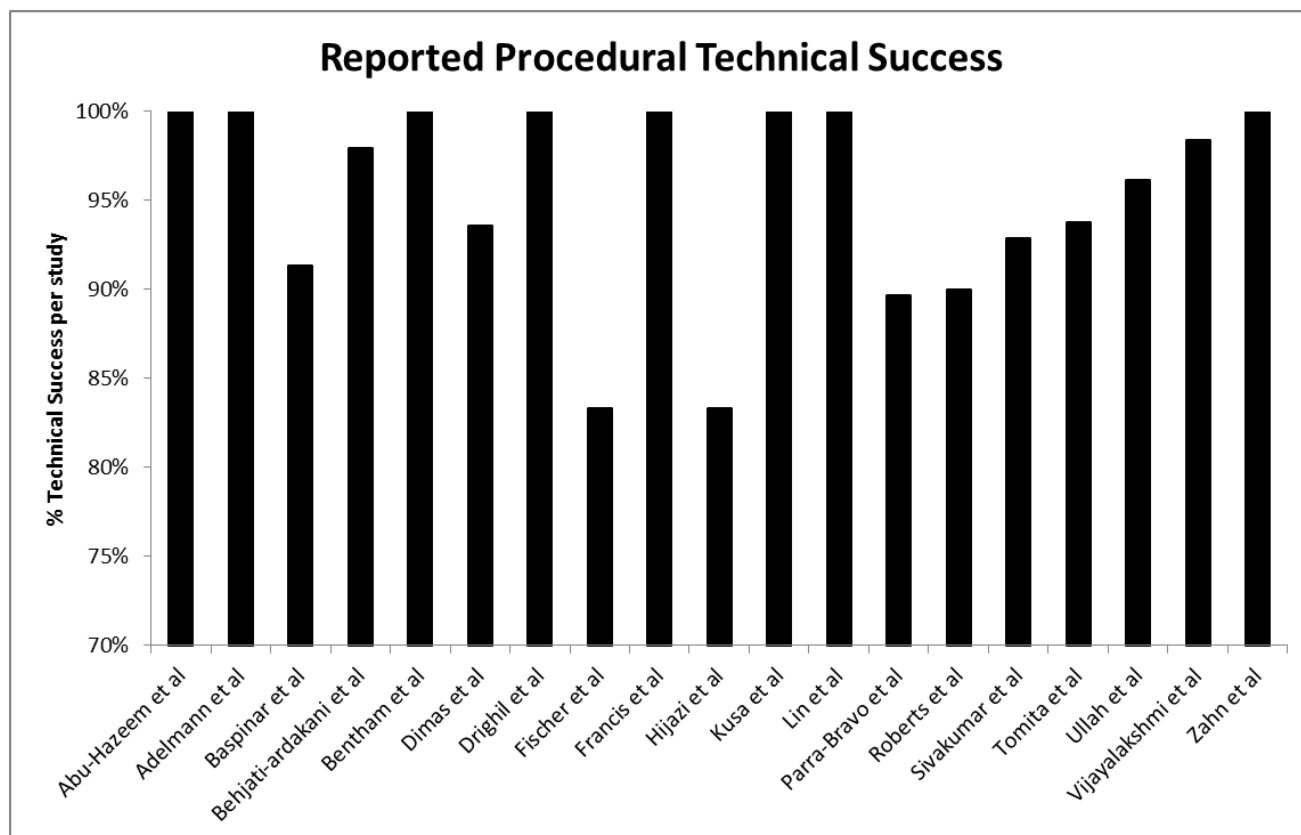


Figure 5. Technical Success Forest Plot (14)

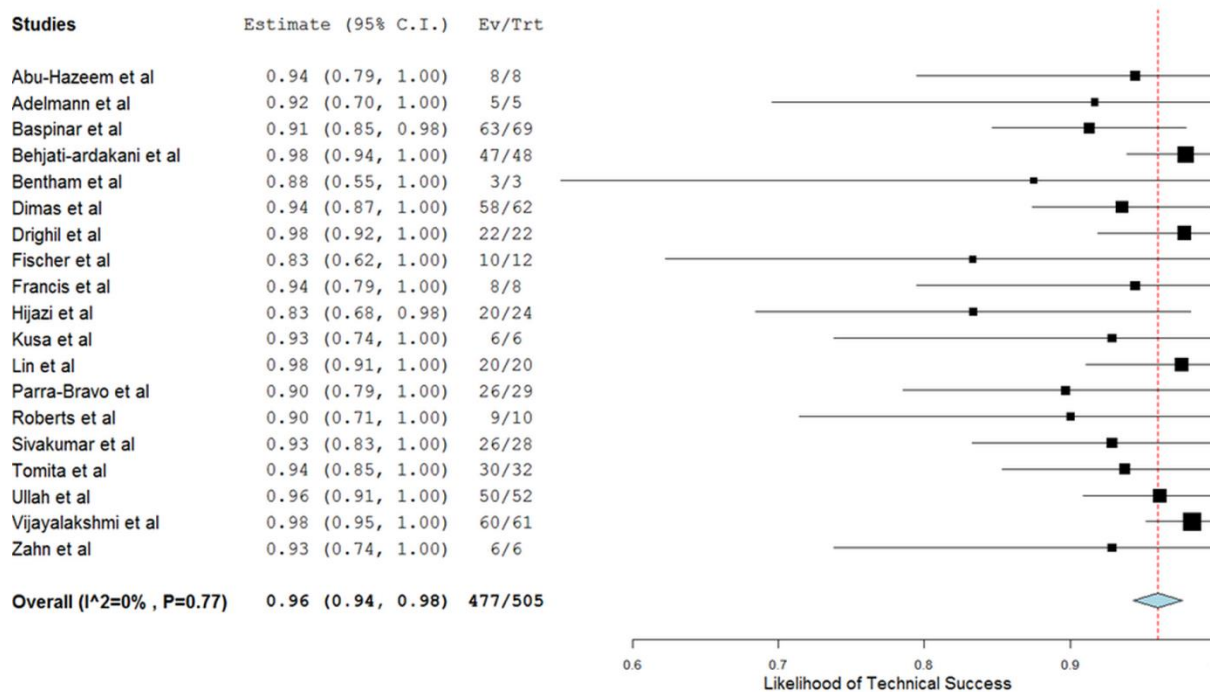


Figure 6. Percent No Residual Shunt Immediately following Procedure (14)

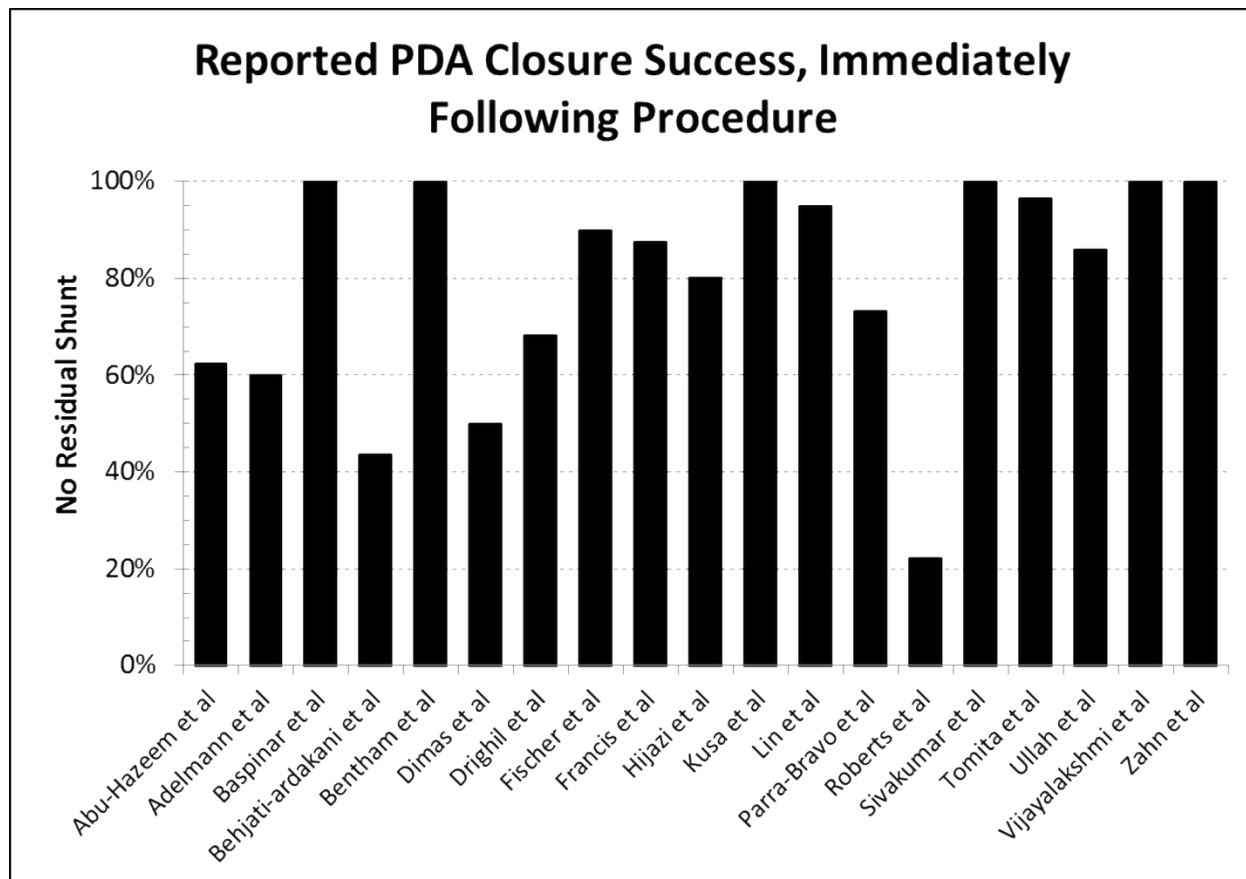


Table 7. Reasons for Procedural Failures and Abandonments (15)

Reason for Procedural Failure (N = 28)	N (% of failures)
Implant instability or misplacement	16 (57%)
Embolization of implant	5 (18%)
Malfunction of implant	5 (18%)
Patient went into cardiac arrest	1 (4%)
Death of patient	1 (4%)
Reason for Procedural Abandonment (N = 5)	N (% of abandonments)
“Performance Error” by physician or equipment	3 (60%)
Ductal morphology too intricate or complex	1 (20%)
Physiological coarctation of aorta noted	1 (20%)

Figure 7. Adverse Event Breakdown (15)

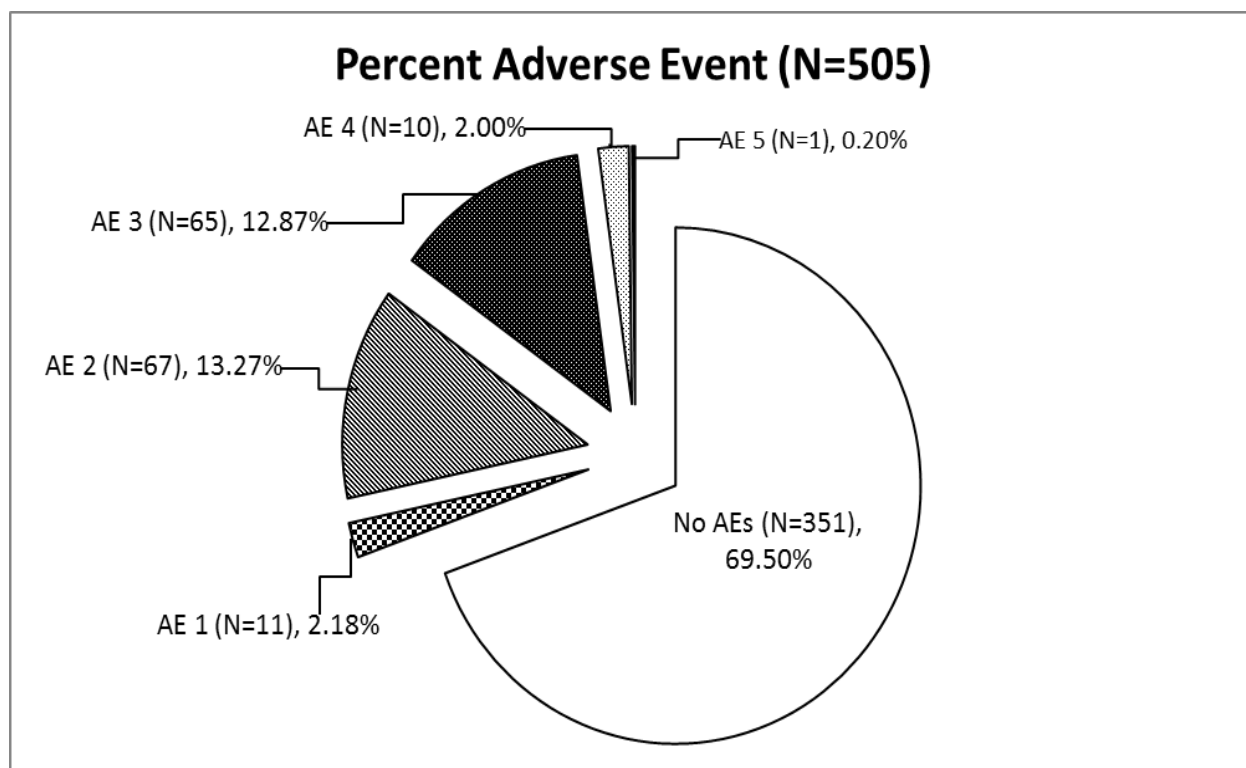


Figure 8. Risk of Clinically Significant AEs (15)

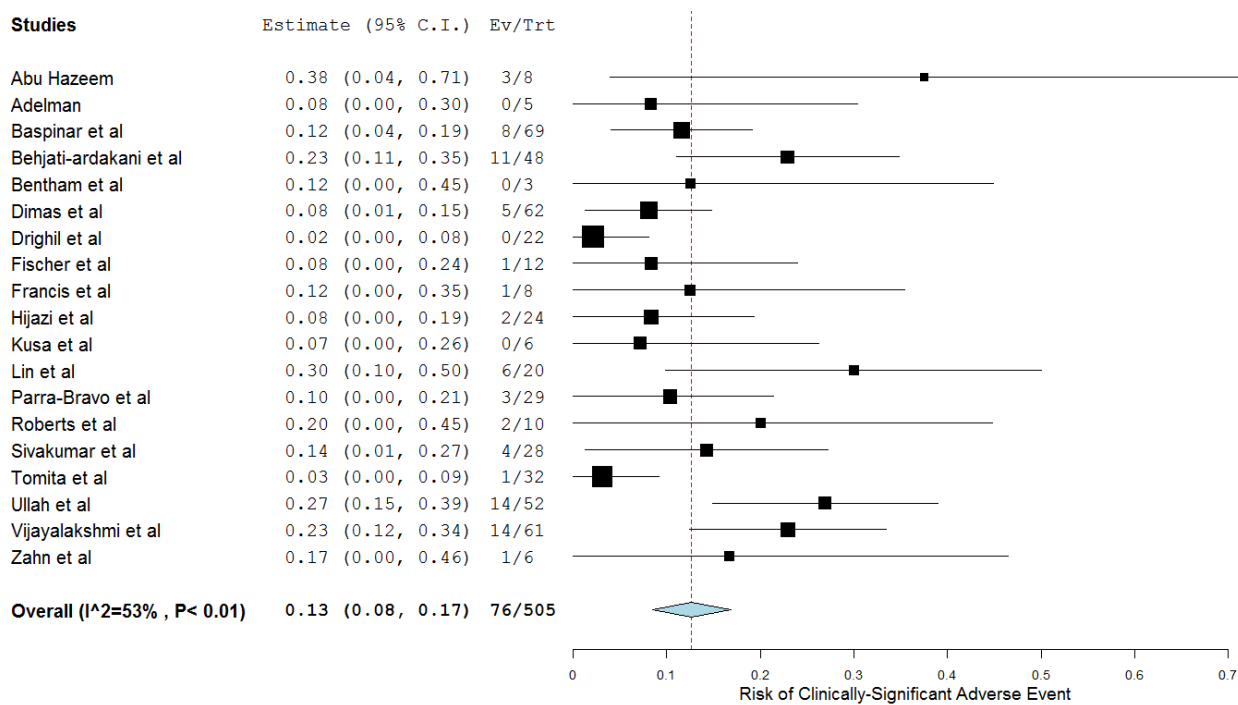


Figure 9. Risk of Non-Clinically Significant AEs (16)

