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Comprehensive Review

A Global Perspective on PDA Management in the Extremely Premature: Shifting Trend Toward Transcatheter Closure

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ABSTRACT

Patent ductus arteriosus (PDA) is a frequently encountered defect in infants born extremely premature (≤26 weeks' gestation). Historically, closure of the PDA was performed using cyclooxygenase inhibitor medications or by surgical ligations. However, the benefits of PDA closure using these therapies have never been demonstrated, albeit studies have previously not focused on the extremely premature infants. Therefore, there was a worldwide trend toward conservative management of the PDA. With improved survival of extremely premature infants, comorbidities associated with the PDA has increased, resulting in finding alternate treatments such as transcatheter patent ductus arteriosus closure (TCPC) for this population. Currently, there is a renewed interest toward selective treatment of the PDA in this high-risk cohort of small infants. This Comprehensive Review article inspects the globally changing trends in the management of the PDA in premature infants, with a special focus on the rising adoption of TCPC. Moreover, this article compiles data from several neonatal networks worldwide to help understand the problem at hand. Understanding the current management of premature infants and their outcomes is fundamentally essential if pediatric cardiologists are to offer TCPC as a viable therapeutic option for this population. This article aims to serve as a guide for pediatric cardiologists on this topic by compiling the results on landmark clinical trials on PDA management and the controversies that arise from these trials. Comparative outcomes from several countries are presented, including interpretations and opinions of the data from experts globally. This is a step toward coming to a global consensus in PDA management in premature infants.

Introduction

The prevalence of a patent ductus arteriosus (PDA) can be as high as 60% in preterm infants and 80% in infants weighing <1200 g at birth.[1] Spontaneous closure rates in extremely low birth weight (ELBW) infants are particularly low at 15%.[2,3] Significant complications of the PDA are well-described and are largely due to significant shunting of oxygenated blood from the aorta, through the PDA away from vital end organs to the

Abbreviations: BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; ELBW, extremely low birth weight; hsPDA, hemodynamically significant PDA; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; TCPC, transcatheter PDA closure; TTE, transthoracic echocardiogram.

Keywords: global perspective; patent ductus arteriosus; prematurity; transcatheter occlusion.

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pulmonary artery resulting in a combination of systemic hypoperfusion, pulmonary over circulation, and pulmonary hypertension throughout the neonatal period. This results directly or indirectly in end-organ damage manifested by a higher incidence of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), neonatal chronic lung disease (CLD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and risk of mortality.[4-6] There is neither consensus on managing ELBW infants with a PDA[7,8] nor do we know conclusively which infant population will benefit from treatment.[9-13] There is ongoing debate on how to manage PDA in preterm infants.[7-13] Approximately 15 years ago, based on evidence from a meta-analysis of several trials and observational studies that did not show any long-term benefits of medical closure or surgical ligation,[11,14-19] neonatologists became unsure of potential benefits of PDA closure in ELBW infants.[20]

This skepticism could be affected by the negative effects of medications used for PDA closure or surgical PDA ligation. Medical therapy is at best 50% effective in children born 23-26 weeks' gestation, and surgical ligation cause unwanted complications secondary to the thoracotomy.[21] This led many neonatologists to forego these therapies to close the PDA to an extent that the presence of PDA was no longer considered pathologic.[11] Most of these studies[22] were performed at a time when survival of ELBW infants and infants born <26 weeks was less than what it is today. Moreover, many of these trials were not optimal mostly because of a lack of equipoise.[22,23] In several trials, equal proportion of patients in the control arm received treatment.[22-27] Most trials neither used a transthoracic echocardiogram (TTE) to verify the significance of the PDA[22,23] nor enrolled high-risk patients such as those born 22-26 weeks' gestation or those ELBW.[22-27] Selection criteria did not consider the need for mechanical ventilation or oxygen needs at baseline. These pitfalls have confounded the reliability or applicability of these clinical trials to current needs, especially because survival of infants born 22 to 26 weeks' gestation have improved significantly[28-32] in many countries.

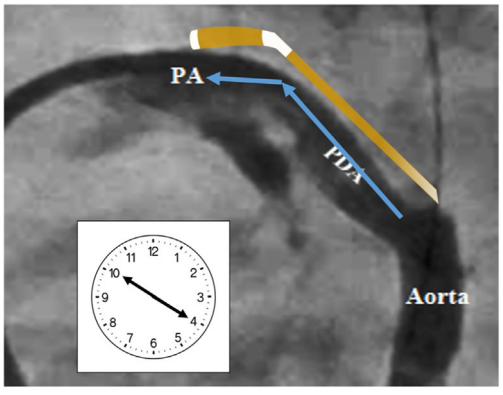
Coinciding with the US Food and Drug Administration approval of the Amplatzer Piccolo Occluder in the United States[33-35] for transcatheter patent ductus arteriosus closure (TCPC) and the availability of other off-label devices used safely and effectively for this purpose,[36-42] the pendulum seems to shift again, after 15 years, toward a more rational approach to selectively close hemodynamically significant patent ductus arteriosus (hsPDA) in the highest-risk premature infants.[43-49] One of the advantages of TCPC in this age group is the more consistent morphology of the duct. The PDA is typically long and tubular and resembles the fetal arterial duct.[42] It has been described to resemble a hockey stick (Figure 1). Among the many advantages of TCPC over medical therapy is that it guarantees definitive closure of the PDA[50-53] similar to surgical ligation, yet avoiding the risks associated with thoracotomy.[54,55] Recently, several centers worldwide have reported promising short-term results in ELBW infants after TCPC.[56-63] Enthusiasm seems to be growing among clinicians regarding this novel approach to rapid elimination of the PDA.

This article focuses primarily on reviewing the changing paradigm in the management of the PDA in premature infants throughout the world now with the availability of TCPC as an attractive option (Central Illustration). Based on personal communication and contributions from international experts on this topic, we present the current global perspective on PDA closure in premature infants, especially the highest-risk ones (gestational age [GA] at birth ≤26 weeks and birth weight <1000 g and who experience hsPDA requiring mechanical ventilation). Emphasis is particularly toward the growing experience of TCPC in this high-risk cohort of premature infants from countries that are leading the way with this new therapy.

Data presented in this review and tables are based on data presented by various national registries worldwide:

1. United States of America: Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD-NRN), data from 24 neonatal intensive care units (NICU) in the United States;
2. France: Epidemiological study on small gestational ages (EPIPAGE-2), a preterm birth cohort in France in 2011 from 1027 NICUs;
3. Japan: Neonatal Research Network (NRN Japan) report 2017 (includes 131 tertiary NICUs);
4. Australian and New Zealand Neonatal Network (all level II and III NICUs in Australia and New Zealand and 1 level III NICU from Singapore and Hong Kong);
5. Premature Baby Foundation of Taiwan that includes the top 5 medical centers;
6. Turkish Neonatal Society that includes all tertiary NICUs in Turkey;
7. German Health Interview and Examination Survey for Children and Adolescents (KiGGS);
8. Extremely Preterm Infants in Sweden Study (EXPRESS);
9. Israel Neonatal Network which includes all NICUs in Israel;
10. Swiss Society of Neonatology (SwissNeoNet) encompassing 9 level III, 10 level IIB, and 14 neurodevelopmental pediatric units.

Data from several leading centers worldwide were contributed by experts on this topic. Interpretation of the data and expert opinions on this topic are discussed in this exhaustive review article which aims to serve as a guide for pediatric cardiologists in expanding their understanding regarding the controversies and current trends in the management of PDA in extremely premature infants.



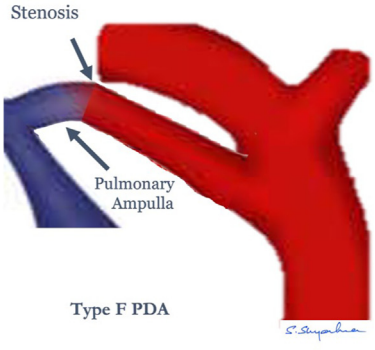
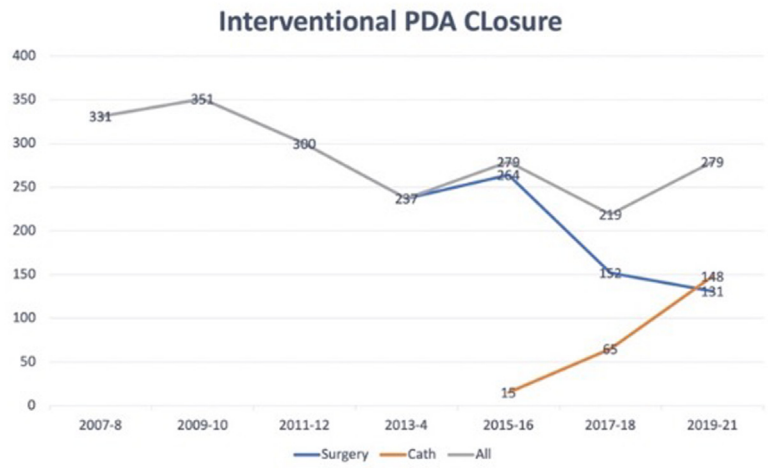


Figure 1.
Morphology of the PDA in premature infants. The PDA resembles a hockey stick with the long axis of the duct in a 10- to 4-o'clock orientation on a clock dial laterally. If the PDA has stenosis, it is typically at the junction of the handle and the blade of the hockey stick. The stenosis is always just posterior to the pulmonary ampulla that is slightly more dilated. During TCPC, implanting a device co-axial to the long axis of the duct and distal to the stenosis is recommended. PDA, patent ductus arteriosus; TCPC, transcatheter patent ductus arteriosus closure.



Central Illustration.
Trends in PDA closure. The graph below demonstrates the increasing trend toward transcatheter PDA closure compared with that of surgical ligation. Source: NRN generic database. PDA, patent ductus arteriosus.

North America

United States and Canada

Despite recent perinatal technological advances, at least 10.1% of births in the United States are preterm.[6] Survival for extremely preterm infants has increased dramatically over the past 20 years, although significant variance exists at 22 weeks' gestation,[28] with survival rates ranging from 0% in many centers ranging to rates approaching 60% in high-performance centers.[29,30] Data from 4987 infants born at 24 centers, in the NICHD-NRN, revealed active rates of resuscitation at 22.1%, 71.8%, 97.1%, 99.6%, and 99.8% for those born at 22, 23, 24, 25, and 26 weeks' gestation, respectively.[31] The overall rates of survival and survival "free of severe impairment" ranges from 5.1% and 3.4% at 22 weeks' to 81.4% and 75.6% at 26 weeks' gestation. Recent evidence suggests that PDA and right ventricular dysfunction as the most common cardiovascular phenotypes seen in premature infants between 22 and 23 weeks' gestation, with rates comparable with infants between 24 and 26 weeks' gestation.[32] This has prompted some centers to perform standardized echocardiography screening with early targeted PDA intervention.[29]

In the past 10 years, profound changes have been witnessed in the approach to care of infants with PDA in US centers with the emergence of conservative treatment. Although ~60 years have passed since the first reports by Powell[64] that PDA was a cause of respiratory morbidity in premature infants, never has such polarization of thinking existed. Observational studies showing increased rates of adverse neonatal outcomes among infants treated with PDA ligation compared with those with medical management alone[65] and randomized clinical trial (RCT) data demonstrating lack of beneficial effect on important neonatal outcomes are likely contributors to this paradigm shift[11] (Figure 2). Bixler et al[20] showed a significant decrease in diagnosis and medical/surgical treatment of PDA with no evidence of increased morbidities in a large cohort of >60,000 premature infants from 280 NICUs across the United States[20]; in particular, the rate of PDA ligation by surgery fell between 2006 and 2015 from 8.4% to 2.9% (Figure 3). However, the rate of PDA diagnosis also decreased from 51% to 38%, which is surprising with increasing numbers of surviving infants at the limits of viability. Possible explanations may include secular approaches to neonatal care (eg, postnatal steroids) or avoidance of echocardiography evaluation in centers with a noninterventional philosophy. These changes were mirrored in Canadian centers, with growth in conservative treatment rates from 14% to 38% and reduction in PDA surgery from 21% to 10%.[66] The discrepancy between the findings from epidemiologic studies and the results of RCTs may relate to the inconsistency in PDA enrollment criteria, variance in BPD diagnostic criteria, and heterogeneity in clinical trial design. In addition, there is increased recognition that mere presence of PDA may not be as important as the shunt volume and duration. For example, Liebowitz and Clyman[24] demonstrated that infants with prolonged exposure to a large PDA and >10 days of mechanical ventilation are at increased risk of moderate/severe BPD. The safety of conservative treatment has recently been evaluated in 2 North American centers. First, Altit et al[67] reported that policy change to a strict noninterventional approach to PDA resulted in a 31% increase in the incidence of death/BPD among infants younger than 26 weeks' gestation. Second, Relangi et al[68] demonstrated that a less-aggressive approach to PDA management led to greater odds of BPD, composite of BPD or death, and higher rates of treatment with postnatal steroids.[68] Furthermore, a large volume center recently reported a lowering in the incidence of BPD and improved survival for the highest-risk cohort of infants who underwent TCPC compared with historical data from the NICHD-NRN.[69]

A recent survey of neonatologists across sites in the Canada Neonatal Network, NRN (United States), and Children's Hospital Neonatal Consortium (United States) highlighted marked variability in the approach to PDA surgery. Most units performed <10 surgical ligations annually, with an average age at intervention of between 4 and 8 weeks old. In addition, more than two-thirds of the sites reported surgical ligations after 2 courses of nonsteroidal therapy, whereas sites with hemodynamics programs (centers where neonatologists perform targeted neonatal echocardiograms) were more likely to consider acetaminophen as rescue therapy before surgery.[70] Of note, data from a high-volume Canadian center over a 10-year timespan reported a secular trend toward later intervention (>4 weeks) in a recent 5-year epoch; however, the rate of BPD was higher in the second epoch.[71]

Increasing evidence of the feasibility and safety of percutaneous device closure in infants weighing <1.5 kg offers an alternative approach to PDA closure.[50,51] Of note, recent data from the NRN generic database demonstrate that rates of transcatheter device closure by pediatric interventional cardiologists have now surpassed rates of surgical ligation (Central Illustration). Currently in the United

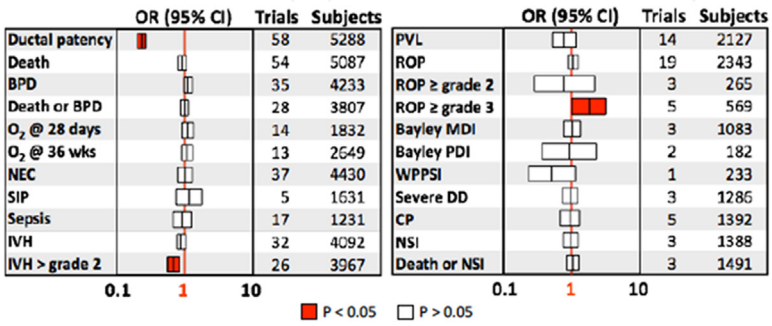


Figure 2.

Meta-analysis of 60 clinical trials on PDA closure in 5515 subjects.[11] Results suggest that the treatment groups showed no change in death or BPD rates and several other outcomes compared with no-treatment groups. Results were not different in trials categorized by type of medicines used, indications, timing of therapy, year of trial, or subject gestational age. BPD, bronchopulmonary dysplasia; CP, cerebral palsy; DD, developmental disorder; IVH, intraventricular hemorrhage; MDI, Mental Developmental Index; NEC, necrotizing enterocolitis; NSI, neurosensory impairment; PDA, patent ductus arteriosus; PDI, Psychomotor Developmental Index; PVL, paravalvular leak; ROP, retinopathy of prematurity; WPPSI, Wechsler Preschool & Primary Scale of Intelligence.

States, >100 hospitals have reported performing TCPC in infants weighing <2 kg. This trend is likely to continue with more centers opting away from surgical ligations and using TCPC as the definitive therapy. Although, currently, TCPC in the United States is primarily limited as a rescue therapy for PDA after failed medical therapy,[43,45,49,56] the trend has been to refer patients for TCPC at an earlier age currently compared with that observed 3 years before.[50,51] Currently, most centers that perform TCPC have patients referred between 3 and 4 weeks of age in high-risk cohorts.[43,49,50,51,56] Few high-volume centers (>50 TCPCs per year in babies weighing <2 kg) have seen the trend toward primary TCPC in the second week of life without attempt at pharmacologic closure.[49] There are at least 2 centers in the United States that currently performs TCPC routinely at the bedside[72,73] in the NICU. This takes away a major advantage that bedside surgical ligation had over TCPC. More centers in the United States are likely to adopt this strategy in the near future. Bedside TCPC avoids the risks of transport[60] of these extremely fragile newborns. In the future, there is a possibility that pediatric interventional cardiologists could travel from one NICU to another performing TCPC instead of premature infants being shuttled between hospitals. Bedside TCPC opens the possibility of definitive PDA closure at a much younger age of between 5 and 10 days of life.

In summary, in the United States, TCPC has almost replaced surgical PDA ligations as the definitive therapy of choice in most centers. There is a swing in the pendulum from conservative approach toward identifying high-risk patients for PDA management. Once most centers get past the learning curve associated with TCPC in ELBW infants, there is a possibility that TCPC could become the primary therapy for PDA in premature infants.

Mexico

A survey in Spanish was conducted for the purpose of this article among 25 leading neonatologists from 14 hospitals in Mexico (https://es.surveymonkey.com/r/FHDF9LF). There are a few single-center published studies that reported survival rates between 34% and 41% for preterm infants weighing <1000 g.[74-76] However, many of these survivors experience high incidences of morbidities: respiratory distress syndrome (84.6%), early-onset neonatal sepsis (78.8%), NEC (19.2%-46%), IVH (46%), pulmonary hemorrhage (46%), BPD (59.6%), acute kidney injury (36.5%), and retinopathy (25%). At least 30% of these morbidities are associated with PDA. Based on the survey, 75% of neonatologists in Mexico asserted that significant organ injury develops in >50% of preterm infants born <26 weeks' gestation secondary to the PDA. According to the survey, 73.4% of neonatologists preferred to start medical treatment for the PDA instead conservative management in <26 weeks' gestation immediately after diagnosis. Currently, there are only 3 public tertiary health care centers in Mexico that routinely perform TCPC. Eighty-three percent of neonatologists who responded to the survey consider TCPC as an alternative and at least as good as a surgical closure whereas 37.5% of the respondents consider the transcatheter option better than surgical closure.

Europe

France

Data were obtained from the EPIPAGE 2 study, a large, French national cohort of infants born between 22 and 34 weeks' gestation in

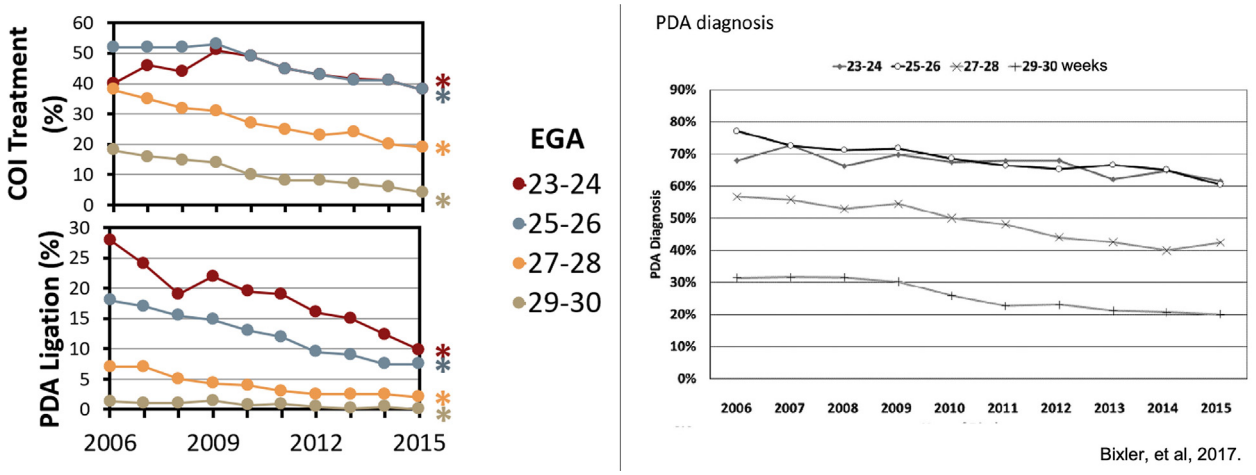


Figure 3.

Bixler et al[20] showed a significant decrease in diagnosis and cyclooxygenase inhibitor (COI)/surgical treatment of PDA in a large cohort of >60,000 premature infants from 280 neonatal intensive care units (NICUs) across the United States. In particular, the rate of PDA ligation by surgery decreased between 2006 and 2015 from 8.4% to 2.9%, and the rate of PDA diagnosis also decreased from 51% to 38%. PDA, patent ductus arteriosus.

France in 2011.[77-80] At 22 through 23 weeks' gestation, survival rates were 0.1% of all births and 0.7% of live births, but few of these infants were admitted to NICUs (6.1%).[77-79] At 24, 25, and 26 weeks' gestation, survival rates were 14.4%, 41.8%, 59.6% of all births and 31.2%, 59.1%, and 75.3% of live births, respectively.[77-79] Survival without severe morbidity was defined as survival without any of the following outcomes: IVH grade III or IV, cystic periventricular leukomalacia, stages I and II of NEC according to the Bells staging system, stage 3 or higher retinopathy and/or laser treatment, and severe BPD. Although these data were collected a decade ago, the management of premature infants has not changed dramatically over this period and should, therefore, reflect the standard of care in France during this period.[80]

A 2019 study from France reported 41.2%, 54.5%, and 65.3% survival rates for births at <24, 25, and 26 weeks' gestation, respectively.[80] The management of PDA remains highly variable among NICUs owing to a lack of consensus in France. A recent, observational study was performed in 28 level III NICUs (dedicated to very early preterm infants) in France among infants born at <32 weeks from January 2017 to December 2018 (n = 2641).[81] The proportion of medical and/or surgical treatment was ~20%.[81] Medical treatment to attempt to close PDA ranged from a minimum of 5% to a maximum of 53% among centers. The mean GA at birth was 26.4 ± 1.7 weeks. The mean postnatal age at the first treatment was 4.3 ± 6.6 days. The first-line treatment was ibuprofen in 89.5% of infants and paracetamol in 10.5%. In case of a paracetamol prescription, 34% of the treatments were initiated before 48 hours of life, whereas only 7% of those with ibuprofen treatements were initiated during the same period. No infant was treated with indomethacin. Infants who were refractory to pharmacologic closure were 7.4%, and 17% of those underwent surgical ligation. All infants undergoing surgical closure were operated after the first week of life.

In France, TCPC for extremely preterm infants has emerged recently as an alternative to surgery but only after the failure of medical therapy. The technique started in a limited number of centers in 2015, but most centers have started their programs in the past 2-3 years.[82] In France, a prospective, multicenter registry called the Premiclose registry is ongoing. More than 13 centers perform pediatric cardiac catheterizations in France, with 7 having an active TCPC program. All 7 programs routinely perform TCPC in babies weighing <1 kg, with 3 other centers ready to get the TCPC program available for ELBW infants. To date, the Premiclose registry has recorded >300 TCPC procedures performed in infants weighing <2 kg since 2019. Most patients are born before 26 weeks' gestation. TCPC is usually performed after 1 or 2 failed medical treatments or for contraindications of medical treatment. Data are not available regarding the proportion of infants treated with this procedure instead of surgical ligation.

Neonatologists and surgeons in France are supportive of this therapy, but this is highly variable and depends on center experience. Similar to that in the United States, as neonatologists get more familiar with the procedure, referral for surgical PDA ligation has declined significantly in France because the postprocedural care is shorter and easier with a faster recovery. More recently, referral for TCPC has evolved to include patients who would not have been referred for surgery in the past, with referrals coming earlier on sicker patients, broadening the indications for TCPC to eventually be the primary therapy of choice instead of following a failed medical therapy.

In summary, transcatheter PDA closure has replaced surgical ligation of the PDA in the past 2-3 years. The indications for referral for TCPC in France are evolving to earlier in life of extremely preterm infants, with the possibility of TCPC becoming the primary therapy of choice at least in the major centers in France.

Germany

In Germany, the last decade has seen an increase in survival of the extremely premature infants (survival rate for birth weight of 1000 g is 95%; 800 g, 85%; 700 g, 82%; and <500 g, 68%) as per the KiGGS database.[83] Therefore, the prevalence of PDA associated with various outcomes such as BPD and neurodevelopmental challenges have increased.[83] In Germany, most centers attempt pharmacologic closure first if the PDA is considered hemodynamically significant. However, as with the United States and France, the trend has been to not refer for surgical ligations as frequently as it had been 15 years ago, when >30% of infants born ≤28 weeks underwent surgical PDA ligations. Recent reports suggest that <10% of the 7000 premature infants born weighing <1500 g in 141 perinatal centers in Germany are referred for surgical ligation of the PDA.[82] In the 3 large centers in Berlin, Munich, and Frankfurt, TCPC is the choice of a definitive PDA closure. In 2019, the neonatologists of the German Heart Center in Munich started performing TCPC with TTE guidance at the bedside in the NICU.[84] This has allowed them to travel to 3 different NICUs in the city and, more recently, to 11 NICUs outside of Munich.

A retrospective 5-year analysis of 454 infants born weighing <1500 g (mortality rate 4%) at the University Clinic of Frankfurt (a medium-volume center in Germany) was performed for the purpose of this article. Patients who received some form of therapy for a PDA closure was 25%, of which 77% received pharmacotherapy, 13% received surgical ligation, and 10% received TCPC as the first-line treatment. Overall, TCPC was performed in 25%, including those who failed medical treatment. However, since 2018, there has been no surgical ligation of the PDA, with TCPC being preferred as the definitive closure technique. Referral for TCPC in the past 3 years in Germany has been trending toward younger and smaller babies, currently with most infants undergoing TCPC weighing <1000 g, the smallest weighing 680 g.

Asia

Taiwan

Taiwan has the lowest birth rate in the world, which hit a record low of 165,249 births in 2020. However, the rate of premature births in Taiwan has been rising yearly. The ratio of premature babies in Taiwan has increased from 9.3% in 2010 to 10% in 2020. Survival of babies born before 26 weeks, namely, periviable infants, has been a scope of interest in Taiwan. Chang et al[85] reported the outcomes of treatment in such infants from Taiwan's population database (2007-2011), based maintained by Premature Baby Foundation of Taiwan. Survival rates were 8% (4/50), 25% (27/108), 46.8% (117/250), 67.0% (211/315), and 76.8% (288/375) for infants born at 22, 23, 24, 25, and 26 weeks, respectively. Two-year follow-up evaluation was performed in 514 (79.4%) patients, and 204 (39.7%) of them showed neurodevelopmental impairment (NDI) with an incidence of 75%, 65.2%, 49.5%, 39.5%, and 32.8% for infants born at 22, 23, 24, 25, and 26 weeks, respectively. Su et al[86] compared the outcomes of this group among Taiwan and other countries. The overall outcomes of this group of Taiwanese infants are similar to the outcomes in the United States as reported by the NICHD-NRN.

Recently, 2 studies from Taiwan reported the 10-year experience (2010-2019) of caring for periviable infants in a single center[87] and 20 years of long-term, follow-up, multicenter data (1995-2016).[88] The overall survival rate of periviable infants recently was 65.8%.[87] In the follow-up,[88] the rates of survival without NDI in this group were 40%,

Table 1. Outcome—survival to discharge based on gestational age

Country	Gestational age			
	<24 wks (%)	24 wks (%)	25 wks (%)	26 wks (%)
United States	64.6	97.1	99.6	99.8
Japan	69.6	90.5	93.6	94.6
France	0.7	31.2	59.1	75.3
Taiwan	20.5	46.8	67	76.8
Israel	6.1	53.2	65.7	77.6
Sweden	64.1	78.9	88.2	93.3
Australia and New Zealand	54.5	69.5	82.6	91.5

55%, and 65% for survived infants of 23, 24, and 25 weeks' gestation, respectively. Survival without major neonatal morbidities were 10%, 18%, and 25% for survived infants of 23, 24, and 25 weeks' gestation, respectively.

In Taiwan, most centers have protocolized the management of PDA in the early life of extremely preterm infants and report that this approach decreases the use of indomethacin.[89-91] A TTE and Doppler assessment of the PDA shunt flow pattern is performed routinely for ELBW infants within 6-8 hours of life to decide whether to treat the PDA.[91,92] For hsPDA, 1 or 2 courses of medical therapy would be prescribed initially. Definitive closure, by either surgery or TCPC is considered for rescue therapy only if the PDA remains hemodynamically significant after attempts at medical closure.

There are 22 tertiary NICUs in Taiwan, with 7 of them selectively adapting TCPC in infants weighing <2 kg, but only 3 of these centers routinely perform the procedure in infants weighing <1 kg. There was an initial hesitancy among neonatologists and cardiac surgeons advocating for TCPC. At the National Cheng-Kung University in Taiwan, as per protocol, ELBW infants received prophylactic indomethacin therapy in the first 24 hours of life between 2000 and 2013. However, because the rate of spontaneous intestinal perforation was high, the protocol was modified.[89-91] Currently, 1 or 2 courses of medical therapy is attempted first for hsPDA before referral for TCPC or surgical ligation. Studies from this center revealed a trend toward early improvement in postinterventional respiratory trajectory in the transcatheter group,[93,94] compared with that in the surgical ligation group. However, there are still minor concerns regarding transport to the catheterization laboratory. Bedside echocardiographic-guided transcatheter closure is currently being considered, and processes are being put in place as alternatives to surgical PDA ligation in Taiwan.

Japan

Based on the Japanese national database for infants born between 22 and 24 weeks' gestation in 2017,[95] the survival rate was 80%.

Table 2. Outcome—bronchopulmonary dysplasia of any degree based on gestational age

Country	Gestational age			
	<24 wks (%)	24 wks (%)	25 wks (%)	26 wks (%)
United States	90	82	69	60
Japan	85	72	64	56
France	100	94	83	67
Taiwan	96	89	77	68
Israel	100	96	89	78
Sweden	84	81	75	61
Australia and New Zealand	92	81	72	60

Table 3. Outcome—grades III and IV intraventricular hemorrhage based on gestational age

Country	Gestational age			
	<24 wks (%)	24 wks (%)	25 wks (%)	26 wks (%)
United States	36	18	12	6
Japan	18	19	11	21
France	—	26	22.5	14.5
Taiwan	24	16	12	7
Israel	37	22	14	13
Sweden	36	18	16	15
Australia and New Zealand	32	18	14	8

However, in this cohort, the CLD rate was 75%, IVH 15%, and ROP 35%. The survival rate of infants between 25 and 26 weeks' gestation in Japan was 90%. Given more babies were born between 25 and 26 weeks compared to those between 22 and 24 weeks, the current survival rate of babies born <26 weeks in Japan (22-26 weeks) is 84% which is one of the highest in the world. However, morbidity rates such as the CLD rate was 70% to 75%, IVH was 10% to 15%, and ROP 30% to 35% (Available from: http://plaza.umin.ac.jp/nrndata/reports/nrn4_2018.pdf. Accessed on January 4, 2022), being high for this cohort.

In Japan, most neonatologists proactively perform an echocardiographic assessment for PDA by themselves.[96] If TTE suggests a significant PDA, many institutions actively pursue medical therapy irrespective of the existence of the symptoms if there are no contraindications. For babies with symptomatic PDAs who do not respond to medical therapy, or when medical therapy is contraindicated, with significant PDA on TTE, who experience feeding, renal, or respiratory impairments, surgical ligation is performed on a case-by-case basis.[97,98] In a Japanese multicenter study,[97,98] approximately 11% of 710 infants between 23 and 29 weeks' gestation underwent PDA surgery at 2 to 24 days old (median, 21 days). Currently, the Amplatzer Piccolo Occluder has not yet been approved by the Japanese Pharmceuticals and Medical Devices Agency for infants weighing <2 kg. Therefore, there are no reports of TCPC for preterm infants aged <26 weeks' gestation in Japan. TCPC is now being cautiously attempted in a stepwise fashion, starting with larger infants in Japan.

Thailand

In 2021, the national neonatal mortality rate of Thailand was 4.3 per 1000 live births.[99] During the last 2 years, the mortality rate of babies born before 26 weeks and 24 weeks were 27.4% and 52.6%, respectively.[100] Although accurate data are unavailable, neonatologists in Thailand currently prefer to treat hsPDAs in babies born <26 weeks' gestation by medical therapy. Before 24 hours after birth, prophylactic treatment with indomethacin is considered in selected high-risk infants. Before 6 days postnatally, early targeted therapy with

Table 4. Outcome—surgically treated necrotizing enterocolitis based on gestational age

Country	Gestational age			
	<24 wks (%)	24 wks (%)	25 wks (%)	26 wks (%)
United States	7.7	4.2	6	2.3
Japan	7.0	4.1	6.3	4.5
France	>20	7.0	7.5	6.5
Taiwan	12	5	5.6	3
Israel	37	22	14	13
Sweden	—	—	—	—
Australia and New Zealand	—	—	—	—

Table 5. Outcome—moderate to severe neurodevelopmental impairment (NDI) (18 m-6.5 y)

Country	Gestational age			
	<24 (%)	24 wks (%)	25 wks (%)	26 wks (%)
United States	20.8	15	8	6
Japan	32.0	24.9	17.6	14.3
France	—	47.8	28.5	22.4
Taiwan	69.6	49.5	39.5	32.8
Israel	—	—	—	—
Sweden	56.8	40.0	30.6	25.3
Australia and New Zealand	25.0	25.3	16.7	13.8

Definitions of NDI—USA: (NRN) NDI was defined as the composite outcome of a BSID III cognitive score of <70, a BSID III motor score of <70, a GMFCS level ≥2, bilateral blindness, and/or hearing impairment (HI).[106] Japan: NDIs were defined as any of the following: cerebral palsy (CP) with GMFCS of ≥2, VI, HI, or cognitive impairments with DQ of KSPD of <70.[107] France (EPIPAGE-2): severe neuromotor or sensory disabilities included any of GMFCS levels 3-5 CP or severe visual or auditory impairment; moderate disability included GMFCS level 2 CP with or without moderate visual or auditory impairment.[108] Sweden: severe NDI is an FSIQ score of less than mean FSIQ score −3 SDs or severe cognitive disability, CP (GMFCS level of ≥4), blindness (visual acuity of <20/400 in the better eye), or deafness (impairment not corrected with hearing aid). Moderate NDI is having an IQ score from −3 SDs to less than −2 SDs or moderate cognitive disability or CP (GMFCS levels of 2 to 3), visual impairment (visual acuity of <20/63 but ≥20/400 in the better eye) or HI (hearing loss corrected with hearing aid).[109] Australia and New Zealand (ANZNN): moderate NDI (GMFCS levels 2 to 3 CP, deafness requiring amplification, moderate language, and cognitive or motor delay). Severe NDI (GMFCS level 4 to 5 CP, blindness, or severe language, and cognitive or motor delay).[105]
DQ, developmental quotient; FSIQ, Full-Scale Intelligence Quotient; GMFCS, Gross Motor Function Classification System; KSPD, Kyoto Scale of Psychological Development.

ibuprofen or indomethacin is considered for babies requiring supplemental oxygen or ventilator dependent. Nonetheless, if the hsPDA cannot be closed medically, before progressing to surgical or transcatheter closure, the neonatologists may consider medical rescue treatment with paracetamol.

In Thailand, TCPC in preterm babies is an emerging procedure. Thammasat University Hospital was the first to establish this service in 2017. Since then, this is the only center in Thailand, which has been performing TCPC in infants weighing <2 kg but not for babies weighing <1 kg.

Israel

The Gestner Institute, the Israel Neonatal Society and Network, and the Israel Center for Disease Control published a report in 2021, which summarizes the data from 2015 to 2019.[101] Overall, there were 238 neonates born before 26 weeks' gestation. The mortality rate was 24% at 26 weeks, 35% at 25 weeks, 47% at 24 weeks, 94% at 23 weeks, and 100% before 23 weeks. The summed-up morbidity for neonates born before <26 weeks' gestation is high, with CLD in 95%, ROP in 66%, late-onset sepsis in 41%, IVH in 34%, and NEC in 22%.

Regarding ELBW infant, 366 of the 1500 (25%) showed hsPDA of which 156 were not treated, 182 were treated medically, and 28 treated surgically. The TCPC program in Israel was first started in Hadassah in May 2019. The first 10 procedures were performed successfully with no complications (weight, 810-1840 g; 5 <26 weeks' gestation, and 4 weighing <1000 g) with only 1 surgical ligation performed during this period. Currently, at least 3 centers in Israel perform TCPC routinely. In these hospitals, the neonatologists are highly supportive of this procedure and consider TCPC as the primary option without medical treatment. The plan is to extend this therapy and protocol to other hospitals in Israel.

Turkey

Multicenter neonatal outcomes including PDA management have been published regularly in Turkey since 2002 under the leadership of the Turkish Neonatology Association. Mortality rates in the database, which included 42,160 babies from 59 centers in 2019 was 68% in babies born at 22 to 24 weeks' gestation and 35% in babies born at 25 to 26 weeks' gestation.[102] In Turkey, currently, there are no survey studies for the preference of neonatologists to treat hsPDA in babies born at <26 weeks' gestation. According to the recommendation of the Turkish Neonatology Association guide, conservative approaches are preferred for PDA management. Pharmacologic treatment with oral ibuprofen is recommended as the first-line medical treatment, followed by intravenous paracetamol before surgical ligation if there is an inadequate response. Similarly, in infants with ongoing respiratory support with hsPDA detected on echocardiography, surgical ligation is recommended in cases of unresponsiveness to medical treatment (usually after the second trial) or if pharmacotherapy is contraindicated.[103] There are no multicenter study data readily available on TCPC in premature infants in Turkey.

In a survey conducted among 71 invasive pediatric cardiologists in Turkey,[104] ~75% of the centers preferred surgery for hsPDA unresponsive to medical treatment. Moreover, 22% of the 67 Turkish centers perform TCPC in premature infants, albeit not in those weighing <1 kg, with 77% of the survey participants stating that they had experience with <5 cases under 2 kg as of December 2021. Only 2 centers have performed >20 cases in preterm infants weighing <2 kg, with 2 other centers that have performed between 10 and 20 interventions as of December 2021. During the same period, the number of surgical ligations has reduced, and the trajectory suggests that TCPC is likely to supersede surgical PDA ligations in the next 1 to 2 years.

South America

Brazil

An increased survival of infants born at 22 to 26 weeks' gestation has been observed in Brazil in the last decade, with <50% mortality rate in the current era. The morbidity rates have also decreased: ROP, grade III-IV IVH, NEC, and BPD affect at 3.5%, 13.1%, 9.2%, and 35.5%, respectively, for those born at <26 weeks (data provided by Filomena Bernardes de Mello, neonatologist from a high-volume Maternity Hospital: Hospital e Maternidade Santa Joana, São Paulo, Brazil).

PDA affects 40% of these patients and contributes to mortality and morbidity. It is sought pre-emptively by echocardiography, and those with hemodynamically significant PDA are treated with indomethacin, ibuprofen, or acetaminophen. Echocardiography is used to define the hsPDA based more on functional criteria such as left atrial (compared to the aorta) and left ventricle enlargement, pulsatile and low velocity flow across the PDA, high flow velocity in the left pulmonary artery, and flow reversal in the descending aorta involving the splanchnic distribution. Although the size of the minimal diameter is also important, especially for transcatheter intervention, it has some intraobserver and

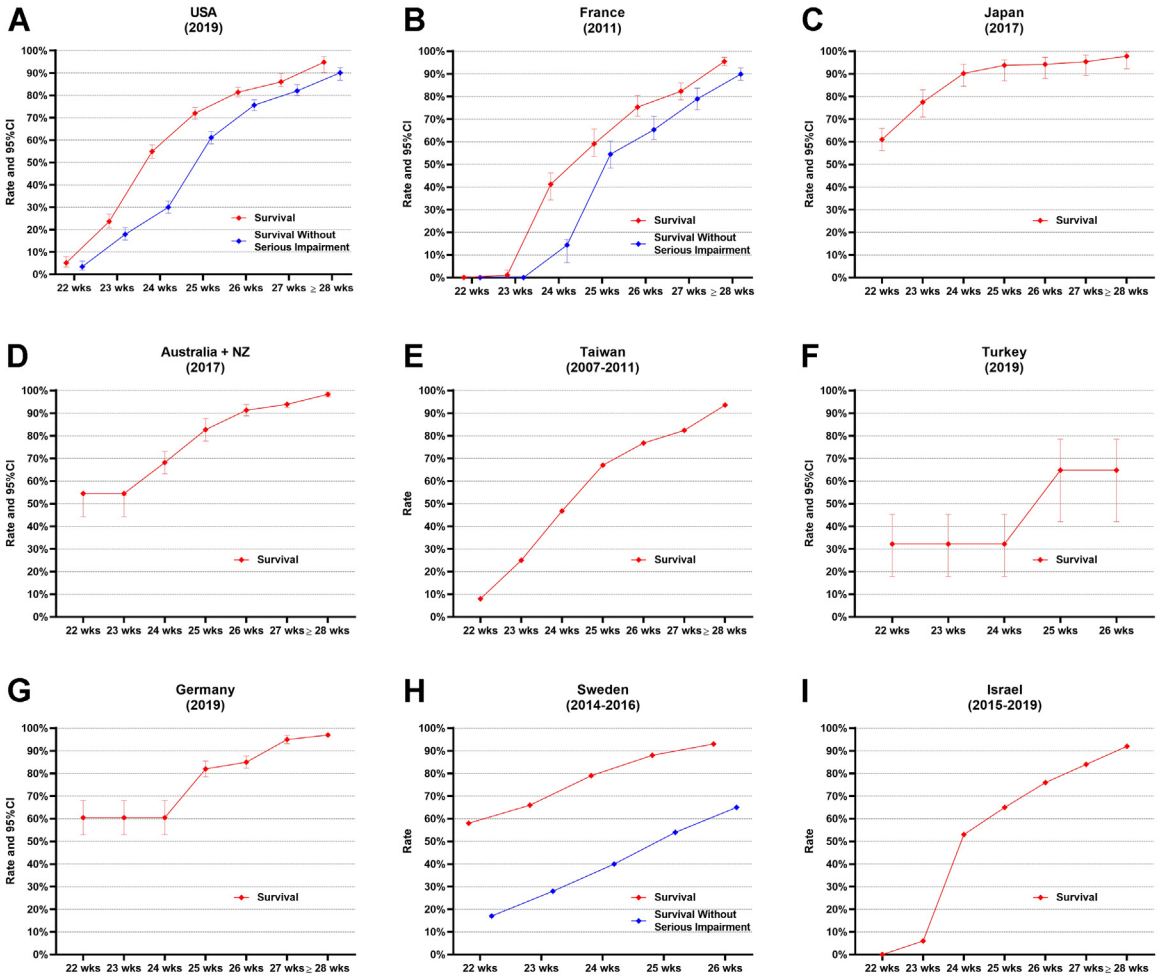


Figure 4.

Survival of extremely preterm infants, between 22 and 26 weeks' gestation, has improved tremendously over the past 2 decades as reported from various countries based on the following registries: (A) USA: NICHD-NRN 2019; (B) France: EPIPAGE-2 2011; (C) Japan: NRN, Japan 2017; (D) Australia and New Zealand: ANZNN report 2017; (E) Taiwan: PBFT 2007-2011; (F) Turkey: Turkish Neonatal Society 2019 report; (G) Germany: KiGGS 2019; (H) Sweden: EXPRESS (only live born and resuscitated) 2014-2016; (I) Israel: INN 2015-2019.

interobserver variation. Regardless of the GA, PDA of >2.0 mm usually results in hemodynamic deterioration. Conservative treatment and observation are applied to those with small PDAs with no left ventricle volume overload, increased pulmonary blood flow, and aortic steal. Surgical ligation with metal clips used to be the method of choice to manage those neonates in whom the medical treatment failed, sometimes after a second medical course. Timing for surgical intervention has varied significantly depending on the center, ranging between 30 and 60 days of life. In Brazil, it is speculated that this delayed closure might be responsible for higher rates of NEC.

Percutaneous closure of the PDA has gained a wider acceptance in Brazil since 2021 after the approval of the Amplatzer Piccolo Occluder for clinical use. As of January 2022, TCPC in premature infants has been performed by several operators in >10 centers in 4 states of the country. Initial experience with the first 20 neonates weighing <2 kg has been encouraging with a 100% success rate and no mortality or significant procedural morbidity. Similar results were observed in recently infants weighing <1 kg, as well. Support from the neonatologist and surgeon varies among different institutions. At Maternidade Santa Joana, although the surgeons are supportive, there is still reluctance among the neonatologist to refer for early transcatheter closure owing to the novel nature of the procedure. Despite that, TCPC was performed in 14 neonates, 1 of the 5 of whom weighed <1 kg at Santa Joana in 2021, compared with 15 surgical ligations performed between 2015 and 2020. This probably reflects an initial change of paradigm that usually occurs when a novel, less-invasive procedure is introduced in clinical practice. With evolving clinical experience, these numbers are likely to increase throughout Brazil with projections suggestive of a trend that is currently in the United States. In addition to Brazil, the county of Colombia in South America has at least 2 centers performing TCPC in premature infants routinely, with multiple other centers planning on adopting this trend.

Australia and New Zealand

As per the Australian and New Zealand Neonatal Network, the survival to discharge home rates for babies born at <24, 24, 25, and 26 weeks' gestation in 2019 were 62.5%, 69.5%, 82.6%, and 91.5%, respectively.[105] The incidence of other major morbidities such as CLD, pulmonary air leak, ROP, and IVH are as described in Tables 1-5.[106-109] The incidence of NEC was 6.7% for babies born <28 weeks' gestation in 2019.

There are no recent data or survey to reflect this. The approach to treatment is widely variable with no consensus on the decision to treat, timing, and agent. The last survey performed in 2009 by Hoellering and Cooke[110] revealed that expectant management was favored by 35% of the neonatologists that were surveyed, echocardiographic targeted prophylaxis by 32% of the neonatologists, presymptomatic treatment by 16%, and prophylaxis using medications by 17% of the surveyed

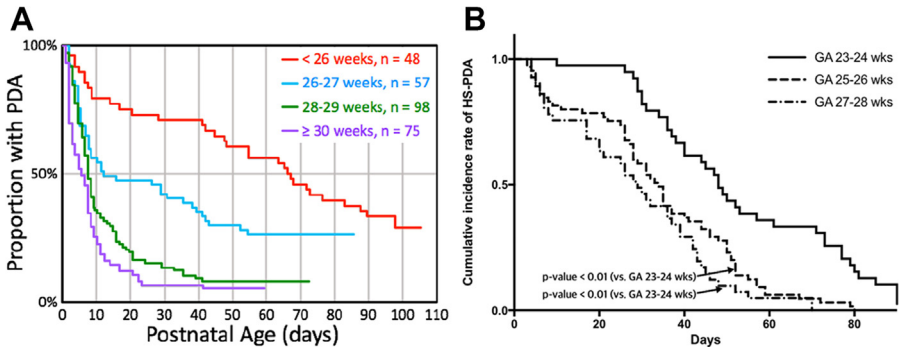


Figure 5.
Cumulative incidence rate of ductal patency during hospitalization in infants with initial hsPDA according to the gestational age group based on 2 studies. (A) Semberova et al[3] (B) Pierrat et al.[108] hsPDA, hemodynamically significant patent ductus arteriosus.

neonatologists. There were marked regional variations in practice. Within individual units, more than 1 approach is used in 14 of the 24 neonatal units. Multiple courses of indomethacin are used to treat PDA by 86% of the neonatologists. For 22% of consultants, management is not influenced by published literature. The reason for long courses of medical therapy was mostly secondary to neonatologists not preferring surgical ligation for these infants. TCPC is being offered at multiple tertiary hospitals in Australia as of 2020. Owing to its recent adoption, there has not been enough time to report multicenter data from Australia and New Zealand.

Discussion

Survival of extremely preterm infants, especially those born at <26 weeks' gestation, has improved tremendously over the past 2 decades, especially in highly industrialized countries[28-32,111] (Figure 4 and Table 1). This population of extremely premature infants is highly susceptible to a multitude of developmental abnormalities associated with hsPDA. Spontaneous ductal closure rates are the lowest for this group of patients as shown by multiple studies[3,112] (Figure 5). In infants born before <26 weeks' gestation, >50% of the PDAs remain large for almost 2 months after birth. These ducts are less responsive to medical closure using cyclooxygenase inhibitors and are poor candidates for invasive surgical ligations.[4,5,9] Owing to a lack of evidence, medical and surgical treatment rates of the PDA have decreased worldwide (Figure 6). However, conservative management of the PDA in infants born <26 weeks' gestation has resulted in decreased survival and are at increased risk for morbidities such as NEC, IVH and CLD.[4,5,9-13] Therefore, the pendulum has swung in the favor of early prophylactic medical therapy within the first 24 hours for those born at <26 weeks' gestation.[2,14,113] If the duct failed to close within 7 to 10 days and the patient still required mechanical ventilation or supplemental oxygen, the baby would be at very high risk to develop BPD,[114,115] pulmonary hypertension, and other sequelae.[46] Tables 1-5 list the incidence of various outcomes of prematurity in different countries based on gestational ages of between 22 and 26 weeks. It is important to understand the effect of hsPDA as related to current morbidities and its current management to improve outcomes.

TCPC presents a less-invasive alternative to surgical PDA ligation. It is definitive and carries a low-risk profile.[33,50,51] High-volume centers that have progressed beyond the learning curve can perform TCPC with very low complication rates in the smallest of patients.[33,50,51] In the United States, there are currently >100 centers that perform TCPC in infants weighing <2 kg, with >50 centers performing TCPC in infants weighing <1 kg. One center has experience of performing TCPC on >100 infants who were <1 kg at the time of the procedure.[50,51] Other European

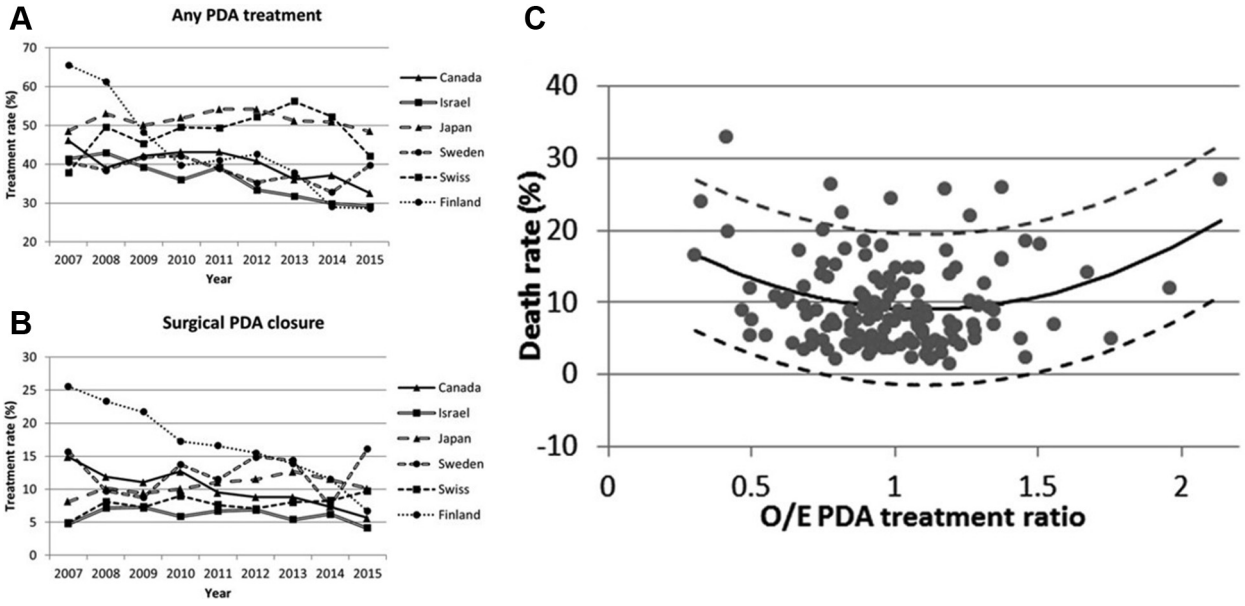


Figure 6.
Results from 139 NICUs around the world including 39,096 infants between 2007 and 2015 as part of the International Network for Evaluating Outcomes of Neonates (iNeo)[107] study suggests a worldwide decrease in both medical and surgical PDA treatment. Both low and high PDA treatment rates were associated with death or severe neurologic injury, whereas a moderate approach was associated with optimal outcomes. NICU, neonatanal intensive care unit; PDA, patent ductus arteriosus.

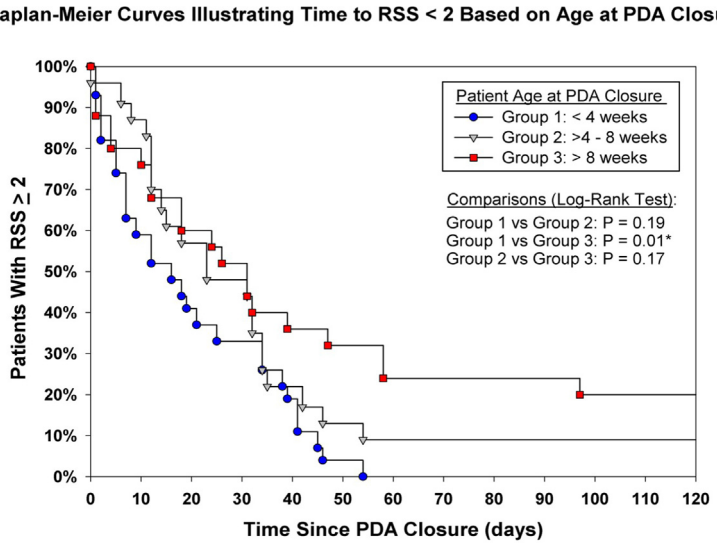


Figure 7.
Early TCPC could allow for faster weaning off ventilator and oxygen support. This Kaplan-Meier analysis suggests a lower proportion of patients with a respiratory severity score (RSS) of ≥2 after TCPC before 4 weeks than that of TCPC after 8 weeks of age in infants born at <27 weeks' gestation.[49] TCPC, transcatheter patent ductus arteriosus closure.

countries such as the United Kingdom, Ireland, Spain, France, and Germany are not far behind. Many centers in these countries are well past the learning curve and routinely perform TCPC in infants weighing <1 kg. Some countries in Asia, such as Turkey and Taiwan, are early adopters to TCPC and have well-established programs. However, countries such as Japan, albeit with extremely impressive survival for the infants of <26 weeks' gestation, are slow to establish TCPC programs, especially for infants weighing <2 kg. This delay is likely because the regulatory agency's long and conservative approval process for cardiovascular devices. Reports from China and India, 2 of the most populous countries, are sparse as far as TCPC in the infants weighing <1 kg, and, therefore, not included in this report. Similarly, reports are lacking from most African nations except for South Africa[116] and Egypt where TCPC is offered for ELBW infants in a few tertiary care centers.

However, TCPC in ELBW infants has gained acceptance in the United States before other nations. In the United States, TCPC seems to have replaced surgical ligation as the preferred method of definitive PDA closure in centers with a well-established pediatric interventional program. Other countries are likely to follow suit. Currently, infants are referred for TCPC as a late rescue therapy in the third to fourth week of

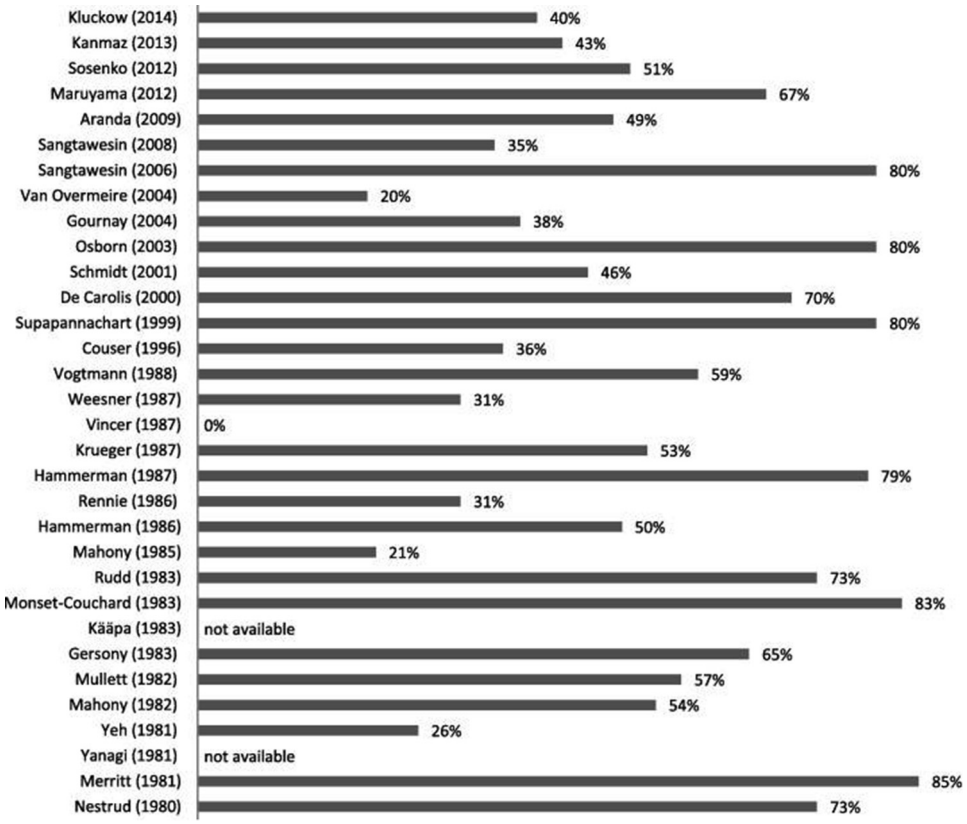


Figure 8.
List of RCTs with the percentage of patients in the control group who received PDA treatment.[22]

life,[2,49] rather than as the primary therapy in the first 2 weeks of life. There is evidence to suggest that intervention even 1 to 2 weeks earlier may be beneficial[14,22,23,45,49,113] (Figure 7). The reasons for the delayed decision by neonatologists are multifactorial. First, this is a relatively new therapy, neonatologists compare it with surgical ligation, and they are likely to be skeptical regarding its safety in the very small newborn, especially when they are of ELBW. Second, many neonatologists believe that TCPC requires femoral artery access, leading to vascular access complications.[43,117-119] It should be emphasized that TCPC is performed in this population through a femoral vein–only approach with an intraductal implantation of the device preventing arterial complications (as noted in previous reports), obstruction to the aorta, or the left pulmonary artery.[34] Third, most of these procedures are currently performed in the cardiac catheterization laboratory, which requires babies to be transferred to tertiary centers from birthing hospitals and transport from the NICU to the catheterization laboratory.[60] This adds to the anxiety for neonatologists to refer patients very early. Only 2 hospitals in the United States (Cedars–Sinai Hospital in Los Angeles, CA,[73] and LeBonheur Children's Hospital in Memphis, TN[72,120]) and 1 in Germany (German Heart Center, Munich[84]) are currently routinely performing TCPC at the bedside in the NICU, with a few other centers moving toward this approach. Finally, despite data showing low procedural complications, fear remains among neonatologists, especially for device embolization. However, experienced interventionists have recognized counterintuitively that device embolization risk is actually lower in the smaller-size infants.[34]

This is the first report to our knowledge that examines the outcomes of those born extremely prematurely in those countries that have active surveillance and registries. This report is also the first known review of the current global status of TCPC for ELBW infants. There is consistent observation globally that, coinciding with higher survival for infants between 22 and 26 weeks' gestation,[28-32,111] morbidity rates are also rising.[4-5,9-13] This could be attributed to a worldwide conservative management of the PDA in this population. Conservative approach was adopted for this population by extrapolating the evidence obtained from numerous clinical trials that were performed at an earlier and different era.[23-25] Many of these clinical trials did not include enough of those born between 22 and 26 weeks' gestation because, in the earlier era, these infants were considered periviable, rendering a flawed extrapolation of evidence. Equally important is the weak nature of the evidence. A critical analysis of the data from at least 32 RCTs shows that ~85% of the control group treated the PDA[22] (Figure 8). Hence, the conclusion from these earlier studies that PDA treatment did not result in improved outcomes is flawed. The only viable conclusion from these studies is that there was no significant outcome differences in early versus delayed treatment because there was a high number of PDAs that were ultimately treated in the control group. It should be noted that these studies were performed more than a decade ago (between 1980 and 2012) and simply do not apply to the current population at risk.[22] In many of these clinical trials, the investigators excluded certain infants from the trial either because of a perceived risk associated with randomization to a conservative approach or because they felt the infants were too sick to wait for randomization or to be enrolled in a clinical trial.[121] This lack of equipoise among investigators has also contributed to flaws in several clinical trials. Trials and observational studies to date that have not shown long-term benefits of medical closure or surgical ligation may have been affected by the negative effects of the medications or surgical intervention.[21]

Currently, with several devices being developed for newborn interventions,[33-35,122] such as the Amplatzer Piccolo Occluder, it has been proposed that future trials of PDA treatment need to focus on high-risk premature infants with objective evidence of hemodynamic significance, using more effective interventions such as transcatheter device closure, to better draw inference on the effect of PDA on clinical outcomes.[123] One such trial that commences in the United States in 2023 is the Percutaneous Intervention Versus Observational Trial of Arterial Ductus in Low weight Infants (PIVOTAL; ClinicalTrials.gov identifier: NCT03982342). Whether early TCPC (in the first 7-10 days of life) represents a paradigm shift in PDA management that will result in improved short-term and long-term outcomes, less BPD, improved neurodevelopment, or better long-term renal function remains to be seen. Long-term neurodevelopmental outcome data will be necessary to confirm genuine improvement in the management of prematurity[106-109] (Table 5). A careful rigorous study of the potential benefits of TCPC in this highly vulnerable population using well-designed and adequately powered trials is needed before the widespread adoption of this approach. Global collaboration and collaboration among societies such as SCAI, NICHD-NRN, and PDA Symposium, whose members belonging to different pediatric subspecialties,[62,124] will be the most effective way to arrive at a consensus in PDA management in premature infants.

Peer review statement

Associate Editor Frank F. Ing had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Guest Editor Dennis Kim.

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Ethics statement and patient consent

This manuscript has adhered to the relevant ethical guidelines. Patient consent was not required for the purpose of this manuscript.

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