Comparison of Various Pharmacologic Agents in the Management of Hemodynamically Significant Patent Ductus Arteriosus in Preterm: A Network Meta-Analysis and Risk-Benefit Analysis

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Keywords
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Abstract

Introduction: Various pharmacological treatments are available for preterm infants with patent ductus arteriosus (PDA), but their risks and benefits are controversial. This study aimed to identify the best treatment for PDA using network meta-analysis (NMA) and risk-benefit assessment (RBA).

Methods: Relevant randomized controlled trials (RCTs) were identified from MEDLINE, Scopus, and the Cochrane Library. RCTs were eligible if they were studied for preterm or low birth weight infants with presymptomatic PDA and hemodynamically significant PDA (hsPDA). The outcomes were PDA closure for a benefit and the composite risk outcome of adverse effects (AEs) for risk. An NMA was used to estimate the treatment effects of benefit and risk. The RBA helped to incorporate the risk and benefits of multiple treatments. Then, an incremental risk-benefit ratio was calculated by dividing the incremental risk by benefit using data from NMA, and they were jointly simulated using Monte Carlo methods. Finally, net clinical benefit (NCB) probability curves were constructed at varying acceptability thresholds.

Results: Seventy RCTs with hsPDA were eligible considering 13 different interventions, but data on presymptomatic PDA were not enough for pooling. The clustered ranking plot from NMA indicated that 3 interventions (i.e., high-dose oral ibuprofen, standard-dose oral acetaminophen, and standard-dose oral ibuprofen) yielded high PDA closure and low AE. These three treatments and additional commonly used indomethacin were considered in the RBA. Given an acceptable threshold of 25% or having one AE out of four PDA closures, high-dose oral ibuprofen had a 36% chance of having the highest NCB, followed by standard-dose oral acetaminophen (27%), and oral ibuprofen (23.7%). Subgroup analysis indicated that the chances of having the highest NCB of GA \geq 28 weeks were similar to that of all available studies. The best for GA <28...
weeks, no data for high-dose oral ibuprofen, was standard-dose oral acetaminophen, followed by standard-dose oral ibuprofen. **Conclusions:** Trade-off RBA indicated that high-dose oral ibuprofen might be the best treatment for preterm, GA ≥28 weeks, with hsPDA followed by the standard-dose oral acetaminophen and ibuprofen. Preferably, optimal high doses, postnatal age to start treatment, and long-term outcomes are needed to study in the future.

**Materials and Methods**

**Search Terms and Strategies**

We constructed search terms and strategies to identify relevant studies from the Cochrane Database, MEDLINE, and Scopus up to May 31, 2021. Additional reference lists of the selected studies were checked. The review protocol was registered with PROSPERO (CRD42016046261).

**Study Selection**

We included RCTs if they met the following criteria:

- Enrolled preterm neonates (GA <37 weeks) and/or LBW infants (<2,500 g) with either presymptomatic or hsPDA.
- Compared any pair with any dose/route of the following interventions: indomethacin, ibuprofen, acetaminophen, and placebo.
- Reported any of the following outcomes: PDA closure, death, CLD or bronchopulmonary dysplasia (BPD), IVH, NEC, retinopathy of prematurity (ROP), acute renal failure, and liver failure.

PDA was classified as hsPDA if preterm neonates had significant hemodynamic change, confirmed by echocardiography and/or clinical symptoms of congestive heart failure (i.e., active precordium and/or worsening respiratory status); otherwise, they were classified as presymptomatic PDA. For multiple reports, the one with the most complete data was used. We excluded studies that compared the same interventions, total mg/course, and route of administration, although subjects received the treatment at a different interval or duration. In addition, studies that diagnosed hsPDA based on only clinical data or defined hsPDA based on calculated scores from echocardiographic data were also excluded.

**Data Extraction**

Data were extracted independently by four authors (S.A.-O.V., C.O., and P.N.) using a standardized extraction form consisting of characteristics of studies/patients, interventions (i.e., dosages, interval, duration, route), and type of treatments and outcomes based on intention-to-treat analysis. Disagreements were resolved by consensus with the fourth author (A.T). Relevant missing data were sought by emailing the authors of the studies.

**Intervention and Outcomes**

Treatment regimens were categorized according to types, administration, and total dosages (milligrams/course) [13]. A total of 15 interventions with standard and high total doses/courses are defined in Table 1.

The benefit outcome was PDA closure, which was defined as ductal closure confirmed by echocardiography and/or clinical criteria after receiving the first course of treatments. The composite risk outcome was used instead of multiple risk outcomes to summarize data for NMA and the net clinical benefit (NCB). The composite outcome enables the incorporation of a flexible framework for assessing the risk-benefit analysis [14]. The composite risk outcomes were defined as the maximum number of adverse events among seven moderate to SAEs reported from individual studies, including mortality during the initial hospitalization, BPD (need-
**Table 1. Abbreviation of treatment groups**

| Treatment abbreviation | Types of treatment | Total doses* |
|------------------------|--------------------|--------------|
| Plac                   | Placebo or conservative treatment | –            |
| SOI                    | A standard dose of oral indomethacin | ≤0.6         |
| HOI                    | A high dose of oral indomethacin  | >0.6         |
| SII                    | A standard dose of intravenous indomethacin | ≤0.6         |
| HII                    | A high dose of intravenous indomethacin | >0.6         |
| SOB                    | A standard dose of oral ibuprofen  | ≤20          |
| HOB                    | A high dose of oral ibuprofen     | >20          |
| SIB                    | A standard dose of intravenous ibuprofen | ≤20         |
| HIB                    | A high dose of intravenous ibuprofen | >20          |
| SOA                    | A standard dose of oral acetaminophen | ≤180        |
| HOA                    | A high dose of oral acetaminophen | >180         |
| SIA                    | A standard dose of intravenous acetaminophen | ≤180        |
| HIA                    | A high dose of intravenous acetaminophen | >180        |
| SIIdrip                | A standard dose and continuous infusion of indomethacin | ≤0.6        |
| SIBdrip                | A standard dose and continuous infusion of ibuprofen | ≤20        |

* The unit of total doses = mg/kg.

ed to supplement oxygen at 36 weeks after conception), severe IVH grade ≥III [15, 16], severe ROP stage ≥III [17, 18], severe NEC stage ≥IIb [19], renal failure (serum creatinine >1.5 mg/dL, or >132 μmol/L, and/or urine output <0.5 mL/kg/h) [20], and liver failure (ALT and AST >2 times the upper boundary of the normal range) [21]. The clinical severity of these SAEs was equally weighted.

**Statistical Analysis**

An NMA was performed to compare relative treatment effects (i.e., risk ratios [RRs]) with placebo using a multivariate meta-analysis with a consistency model [22]. The inconsistency was checked based on a design-by-treatment interaction model using a global χ² test. A loop-specific method was also used to estimate the inconsistency factor (IF) and the ratio of two odds ratios (ROR). In addition, characteristics of patients, interventions, outcomes, and study designs were further explored if there was any evidence of inconsistency. The probability of being the best treatment was estimated using the surface under the cumulative ranking curve (SUCRA) from the frequentist approach. A cluster ranking plot was constructed considering both benefits and risks; the larger the SUCRA value, the higher the rate of PDA closure, and the lower the SAE rate. Interventions from NMA, which had high benefits and low composite risks (in the right upper quadrant of the clustered ranking plot), and commonly used intervention (indomethacin) were included in the RBA.

For the RBA, we estimated values of incremental risk (ΔR) and incremental benefit (ΔB) using “network setup” and specified the treatment effects using the risk difference compared with Plac (a base case). These ΔR and ΔB were further jointly simulated using Monte Carlo methods with 1,000 replications, assuming normal distributions for both ΔR and ΔB. The simulation randomly selected values from each specified distribution, allowing the joint uncertainty of the risks and benefits [23]. The IRBR is calculated by dividing ΔR by ΔB [24, 25]. A risk-benefit plane (RBP) was constructed, assigning ΔR and ΔB on Y-axis and X-axis, respectively, with varying risk-benefit acceptability thresholds (RBAT, μ) [24]. IRBRs falling in the right-lower quadrant indicate a dominant intervention or more benefit with less risk; IRBRs falling in the right upper quadrant provide higher benefit but with higher risk. Next, the risk-benefit acceptability curves (RBACs) were further constructed by estimating the percentages of the simulated IRBRs falling below and to the right of a threshold line [26]. These curves represent the probability that each intervention has the chance of being net-beneficial relative to placebo across a range of RBAT. However, the RBACs did not allow a comparison of all interventions at the same time. Thus, the NCB for each comparison with placebo of the 1,000 simulations was simultaneously calculated. Subsequently, the proportions in which each intervention had the highest NCB across a range of thresholds were estimated and plotted in net clinical benefit probability curves. This curve shows the treatment which is most likely to have the best risk-benefit profile at a given threshold value [9, 27]. A subgroup analysis was performed by GA <28 and ≥28 weeks. Additionally, sensitivity analysis was performed, including only a study reporting both PDA closure and risk outcomes. All analyses were performed using STATA version 16.0 (StataCorp LP, College Station, TX, USA), and the simulations were done using Microsoft Excel 2019 (Microsoft Corp., Seattle, WA, USA). A two-tailed p value <0.05 was considered statistically significant. The sequence of the complete analysis is shown in eTable 1.1 (for all online suppl. material, see www.karger.com/doi/10.1159/000526318).

**Quality of Evidence**

The risk of bias assessment was independently assessed by four authors (S.E., S.A.-O.V., C.O, and P.N.) using the Cochrane Collaboration tool [28]. Six domains were assessed: selection, performance, detection, attrition, reporting, and other biases. Each item was classified as low, high, or unclear risk of bias. Disagreements were resolved by consensus with a fifth author (A.T). The confidence in the results of NMA was graded using the CI Nema software. Six domains were assessed, including within-study-variation, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency [29].
Results

Study Characteristics

A total of 2,414 individual RCTs were identified from MEDLINE and Scopus additional 92 RCTs from systematic reviews and 6 studies from reference lists. After screening the titles and abstracts, 150/2,146 studies met our inclusion criteria. A total of 78 RCTs were eligible for pooling consisting of 8 [30–37] and 70 [38–107] for presymptomatic and hsPDA (shown in Fig. 1). The summary of searching was in online eTable 2.1-2.3; the reasons for exclusion after full-text screening were in online eTable 3.1. We analyzed only hsPDA because of a small number of presymptomatic studies (shown in online eTable 3.2). Data for a high dose of oral indomethacin (HOI) and a high dose of intravenous acetaminophen (HIA) were unavailable, leaving 13 out of 15 interventions for analysis. Among these, the common compara-
| Study and year of publication | Country | Intervention | n | Diagnosis of hsPDA | GA, weeks | BW, g | PDA size, mm | Age at treatment, h | Dose, mg/kg/dose | Duration, h | Total doses, mg/kg/course |
|-------------------------------|---------|--------------|---|-------------------|-----------|-------|--------------|-------------------|-------------------|-------------|-------------------------|
| Adamska et al. 2005 [38]      | Turkey  | SII          | 19 | Echo              | 27.6±2   | 1,003±192 | N/A          | 48                | 0.2-0.2-0.2      | 72          | 0.6                     |
|                               |         | SIB          | 16 |                   | 27.7±1.8 | 1,074±264 | N/A          | 10-5              | 72                | 20          |                         |
| Aksu et al. 2001 [40]         | Turkey  | SOI          | 11 | Echo              | 31.9±1.3 | 1,645±190 | N/A          | 3.5±0.6           | 0.2-0.2-0.2      | 36          | 0.6                     |
|                               |         | SOB          | 12 |                   | 32.1±1.2 | 1,706±187 | N/A          | 10-5              | 72                | 20          |                         |
| Al-lawama et al. 2018 [41]    | Jordan  | HOB          | 9  | Echo & clinical   | 28.0 (25.0–35.0) | 1,192±269 | N/A          | 72–120           | 10-10-10         | 72          | 30                      |
|                               |         | SOA          | 13 |                   | 28.0 (23.0–32.0) | 1,059±386 | N/A          | 10 every 6 h     | 72                | 120         |                         |
| Aly et al. 2007 [42]          | Egypt   | SII          | 9  | Echo              | 31.2±2.5 | 1,521±398 | 2.3          | 48–168            | 0.2-0.2-0.2      | 36          | 0.6                     |
|                               |         | SOB          | 12 |                   | 32.9±1.6 | 1,884±485 | 2.1          | 10-5              | 72                | 20          |                         |
| Bagheri et al. 2016 [43]      | Iran    | HOB          | 80 | Echo              | 31.7±2.2 | 1,643±58  | >1.5         | 82.1±51.0         | 20-10-10         | 72          | 40                      |
|                               |         | SOA          | 80 |                   | 31.5±2.3 | 1,646±59  | 15 every 6 h | 72                | 180         |                         |
| Bagnoli et al. 2013 [44]      | Italy   | Plac         | 67 | Echo              | 27.0±4.0 | 1,197±335 | >1.5         | 72–96             | –                | –           | –                       |
|                               |         | SIB          | 67 |                   | 27.0±2.5 | 989±326   |              | 10-5              | 72                | 20          |                         |
| Balachander et al. 2018 [45]  | India   | SOB          | 55 | Echo & clinical   | 31.5±2.9 | 1,513±415 | 2.4          | 79±2±38.4         | 10-5              | 72          | 20                      |
|                               |         | SOA          | 55 |                   | 31.5±2.9 | 1,535±408 | 2.4          | 79±2±38.4         | 15 every 6 h     | 48          | 120                     |
| Cheng et al. 2012 [46]        | Philippines | SII         | 10 | Echo              | 31.2±2.2 | 1,435±413 | 2.8          | 60–80             | 0.2-0.1-0.1      | 36          | 0.4                     |
|                               |         | SOB          | 10 |                   | 32.9±2.2 | 1,250±321 | 2.0          | 10-5              | 36                | 20          |                         |
|                               |         | HOB          | 10 |                   | 31.1±3.6 | 1,250±448 | 2.1          | 10-10-10          | 36                | 30          |                         |
| Cherif et al. 2008 [47]       | Tunisia | SOB          | 32 | Echo              | 29.3±1.2 | 1,227±188 | 2.6          | 48–96             | 10 for each dose, ECHO before next dose | 45.6       | 19                      |
|                               |         | SIB          | 32 |                   | 28.3±1.1 | 1,198±158 | 2.5          | 10 for each dose, ECHO before next dose | 45.6       | 19                      |
| Chotigeat et al. 2003 [48]    | Thailand | SII         | 15 | Echo & clinical   | 29.9±2.9 | 1,434±421 | 2.3          | 3.5±1.6           | 0.2-0.2-0.2      | 36          | 0.6                     |
|                               |         | SOB          | 15 |                   | 30.8±2.3 | 1,41±354  | 1.7          | 6.0±2.4           | 10-5              | 72          | 20                      |
| Christmann et al. 2002 [49]   | Netherlands | SII        | 14 | Echo & clinical   | 30.8±0.5 | 1,424±150 | N/A          | 120±33.6          | 0.2-0.1-0.1      | 36          | 0.4                     |
|                               |         | Sildrip      | 18 |                   | 29.4±0.5 | 1,150±77  | 96.0±16.8    | 0.011 mg/kg/h cont infusion | 36          | 0.4                     |
| Dang et al. 2013 [50]         | China   | SOB          | 80 | Echo              | 30.9±2.2 | 1,531±454 | 2.4          | 89.0±3.8          | 10-5              | 72          | 20                      |
|                               |         | SOA          | 80 |                   | 31.2±1.8 | 1,592±349 | 2.4          | 77.3±3.4          | 15 every 6 h     | 72          | 180                     |
| Dani et al. 2012 [52]         | Italy   | SIB          | 47 | Echo              | 26±1.7   | 835±215   | >1.5         | 12–24             | 10-5              | 72          | 20                      |
|                               |         | HIB          | 48 |                   | 25.6±1.8 | 781±225   |              | 20-10-10          | 72                | 40          |                         |
### Table 2 (continued)

| Study and year of publication | Country   | Intervention | n | Diagnosis of hspDA | GA, weeks | BW, g | PDA size, mm | Age at treatment, h | Dose, mg/kg/dose | Duration, h | Total doses, mg/kg/course |
|-------------------------------|-----------|--------------|---|--------------------|-----------|-------|--------------|------------------|----------------|-------------|--------------------------------|
| Dash et al. 2015 [53]         | India     | SII          | 39 | Echo               | 28.9±2.6 | 1,027±262 | 2.1          | 15.9±11.8        | 0.2-0.2-0.2    | 72           | 0.6                                           |
|                               |           | HOA          | 38 |                    | 28.5±2.7 | 989±299   | 2.0          | 14.7±8.4         | 15 every 6 h   | 168          | 420                                           |
| Ding et al. 2014 [55]         | China     | Plac         | 37 | Echo               | 30.2±1.5 | 1,469±448 | N/A           | >24              | –             | –           | –                                             |
|                               |           | SOB          | 35 |                    |           |          |              |                  |                | 10-5-5      | 72           | 20                                           |
| El Farrash et al. 2018 [56]   | Egypt     | SOB          | 30 | Echo               | 31.7±1.9 | 1,740±470 | 2.5          | 188±143.0        | 10-5-5         | 72           | 20                                           |
|                               |           | SOA          | 30 |                    | 30.5±1.6 | 1,530±560 | 2.2          | 145.2±126.2      | 15 every 6 h   | 72           | 180                                           |
| El-Mashad et al. 2017 [57]    | Egypt     | SII          | 100| Echo & clinical    | 26.0±2.1 | 1,100±140 | 2.7          | 74.4±122.4       | 0.2-0.2-0.2    | 36           | 0.6                                           |
|                               |           | SIB          | 100|                    | 25.0±2.1 | 1,000±120 | 2.8          | 768±100.8        | 10-5-5         | 72           | 20                                           |
|                               |           | SIA          | 100|                    | 26.0±1.9 | 1,100±130 | 2.7          | 64.8±105.6       | 15 every 6 h   | 72           | 180                                           |
| Erdeve et al. 2012 [58]       | Turkey    | SOB          | 40 | Echo               | 26.4±1.1 | 892±117   | >1.5          | 48-96            | 10-5-5         | 72           | 20                                           |
|                               |           | SIB          | 40 |                    | 26.3±1.3 | 872±123   |              |                  |               | 10-5-5      | 72           | 20                                           |
| Fakhraee et al. 2007 [59]     | Iran      | SOI          | 18 | Echo               | 30.9±2.0 | 1,522±358 | >1.5          | 74.4±14.4        | 0.2-0.2-0.2    | 72           | 0.6                                           |
|                               |           | SOB          | 18 |                    | 31.5±1.4 | 1,658±387 |              | 840±12.0         | 10-5-5         | 72           | 20                                           |
| Fesharaki et al. 2012 [60]    | Iran      | SOB          | 30 | Echo               | 30.9     | 1,324     | N/A           | 72-120           | 10-5-5         | 72           | 20                                           |
|                               |           | HOB          | 30 |                    | 29.8     | 1,300     |              |                  |               | 15-7.5–7.5  | 72           | 30                                           |
| Gersony et al. 1983 [61]      | USA       | Plac         | 281| Echo & clinical    | 29.32    | 1,109     | N/A           | 0–336            | –             | –           | –                                             |
|                               |           | SII          | 140|                    |          |          |              |                  | 0.2-0.1-0.1 for age 2–7 days 0.2-0.25-0.25 for age ≥8 d 72 | 0.4–0.7     |                                      |
| Ghanem et al. 2010 [63]       | Saudi Arabia | Plac     | 33 | Echo               | 28.9±2.7 | 1,047±403 | 2.2          | 57.6±21.6        | –             | –           | –                                             |
|                               |           | SOB          | 33 |                    | 28.8±2.8 | 1,035±353 | 2.3          | 60.0±14.4        | 10 for each dose, ECHO before next dose 34.8 | 12.25       |                                      |
| Gimeno et al. 2005 [64]       | Spain     | SII          | 24 | Echo               | 28.5 (27.0–30.0) | 1,206±513 | N/A           | 72               | 0.2-0.2-0.2    | 36           | 0.6                                           |
|                               |           | SIB          | 23 |                    | 28.0 (24.0–31.0) | 1,169±490 |              |                  |               | 10-5-5      | 72           | 20                                           |
| Golmen et al. 2011 [65]       | Turkey    | SOB          | 54 | Echo               | 28.5±1.9 | 1,170±297 | >1.5          | 48–96            | 10-5-5         | 72           | 20                                           |
|                               |           | SIB          | 54 |                    | 28.7±2.1 | 1,205±366 |              |                  |               | 10-5-5      | 72           | 20                                           |
| Hammerman and Aramburo 1990 [66] | USA | SII          | 19 | Echo & clinical    | 27.0±7.0 | 1,040±394 | N/A           | 240.0±120.0      | 0.2-0.2-0.2    | 72           | 0.6                                           |
|                               |           | HII          | 20 |                    | 28.0±3.0 | 1,099±435 |              | 2160±96.0        | 0.2-0.2-0.2-0.2 | 120          | 10                                           |
| Hammerman et al. 1995 [67]    | Israel    | SII          | 9  | Echo               | 29.0±2.0 | 1,200±300 | N/A           | N/A              | 0.2-0.1-0.1    | 36           | 0.4                                           |
|                               |           | Sildrip      | 9  |                    | 28.0±2.0 | 1,100±200 |              |                  | 0.011 mg/kg/h contin infusion 36 | 0.396       |                                      |
Table 2 (continued)

| Study and year of publication | Country | Intervention | n | Diagnosis of hPDA | GA, weeks | BW, g | PDA size, mm | Age at treatment, h | Dose, mg/kg/dose | Duration, h | Total doses, mg/kg/course |
|------------------------------|---------|--------------|---|-------------------|-----------|-------|-------------|-------------------|----------------|------------|------------------------|
| Hammerman et al. 2008 [68] | Israel  | SIB 31       | Echo 27.8±2.6 | 1,100 | 2.0 | 108.0 (55.2–184.0) | 10-5-5 | 72 | 20          |
|                              |         | Sildrip 33   | 27.8±2.8 | 1,060 | 2.0 | 88.8 (60.0–132.0) | 0.017 mg/kg/h | 36 | 0.612      |
| Härkin et al. 2016 [69]     | Finland | Plac 25      | Echo & clinical | 28.3±2.1 | 1,120±430 | 1.4 | 24 | –  | –  | – |
|                              |         | SIA 23       | 28.4±2.4 | 1,220±340 | 1.6 | 20 for 1st dose followed by 7.5 every 6 h | 120 | 140 |
| Hoxha et al. 2013 [70]      | Albania | SOB 44       | Echo 29.9 | 1,295 | 1.9 | 48–96 | 10 for each dose, ECHO before next dose | 24–48 | 11.7 |
|                              |         | SIB 36       | 29.3 | 1,289 | 2.1 | 10 for each dose, ECHO before next dose | 24–48 | 12.8 |
| Kappa et al. 1983 [71]      | Finland | Plac 14      | Echo & clinical | 32.5±3.1 | 2,119±625 | N/A | 18 (6.5–68) | –  | –  | – |
|                              |         | SOI 13       | 32.9±2.8 | 2,072±801 | –  | 0.2 for each dose, clinical evaluation before next dose | 24–48 | 0.28 |
| Khuwuthyakorn et al. 2018 [72] | Thailand | SOI 17      | Echo & clinical | 28.0 (25.0–30.0) | 930 (510–1,370) | 2.9 | 60.0 (23.0–504.0) | 0.2-0.1-0.1 for age>2 d 0.2-0.2 for age 2–7 days 0.2-0.25-0.25 for age>7 d | 36 | 0.6 |
|                              |         | SOB 15       | 29.0 (24.0–32.0) | 950 (520–1,360) | 2.8 | 64.0 (24.0–332.0) | 10-5-5 | 72 | 20          |
| Kluckow et al. 2014 [73]    | Australia | Plac 48     | Echo & clinical | 26.0±1.4 | 876±203 | >1.8 mm at age 3–5 h, >1.6 mm at age 6–8 h, >1.3 mm at age 9–12 h | 9.1±3.4 | –  | –  | – |
|                              |         | SII 44       | 26.0±1.4 | 892±205 | 8.3±2.9 | 0.2-0.1-0.1 | 72 | 0.4 |
| Krauss et al. 1989 [74]     | USA     | Plac 15      | Echo & clinical | N/A | 1,022±58 | N/A | 72–96 | –  | –  | – |
|                              |         | SII 12       | N/A | 1,183±77 | 0.2-0.2-0.2 | 72 | 0.6 |
| Lago et al. 2002 [76]       | Italy   | SII 81       | Echo 29.0±3.0 | 1,214±427 | N/A | 48–72 | 0.2-0.2-0.2 | 72 | 0.6 |
|                              |         | SIB 94       | 28.0±2.0 | 1,126±412 | 10-5-5 | 36 | 20          |
| Lago et al. 2014 [77]       | Italy   | SIB 56       | Echo 27.4±2.7 | 1,027±346 | 2.5 | 79.2±24.0 | 10-5-5 | 72 | 20          |
|                              |         | Sildrip 56   | 27.3±2.1 | 1,012±315 | 2.4 | 64.8±16.8 | 0.2±1.0–0.2 mg/kg/h | 72 | 20          |
| Lee et al. 2008 [78]        | Korea   | SII 18       | Echo & clinical | 29.4±2.6 | 1,290±360 | >1.5 | 93.6±43.2 | 0.2-0.2-0.2 | 36 | 0.6 |
|                              |         | SOB 16       | 30.2±3.0 | 1,480±560 | 93.6±33.6 | 10-5-5 | 72 | 20          |
| Lin et al. 2017 [80]        | Taiwan  | SII 75       | Echo & clinical | 26.3±1.6 | 812±160 | 1.9 | 79.2±33.6 | 0.2-0.1-0.1 | 72 | 0.4 |
|                              |         | SIB 75       | 26.2±1.7 | 801±153 | 1.8 | 76.8±48.0 | 10-5-5 | 72 | 20          |
| Study and year of publication | Country | Intervention | n | Diagnosis of hPDA | GA, weeks | BW, g | PDA size, mm | Age at treatment, h | Dose, mg/kg/dose | Duration, h | Total doses, mg/kg/course |
|-------------------------------|---------|--------------|---|-------------------|----------|-------|--------------|-------------------|-----------------|-------------|---------------------------|
| Lin et al. 2012 [79]          | China   | Plac         | 32| Echo & clinical  | 30.8±2.3 | 1,350±221 | >1.5          | 20.0±5.0          | –               | –           | 0                         |
|                               |         | SOB          | 32|                   | 31.2±2.4 | 1,301±260 | <1          | 23.0±4.0          | 10-5-5          | 72           | 20                        |
| Merritt et al. 1981 [82]      | USA     | Plac         | 13| Echo & clinical  | N/A      | ≤1,350    | >1.2          | 48.8              | –               | –           | –                         |
|                               |         | SII          | 12|                   |          |           |              | 167.4             | 0.2 for each dose, clinical & ECHO before next dose | 36           | 0.3                       |
| Mosca et al. 1997 [83]        | Italy   | SII          | 8 | Echo              | 28.0 (25.0–30.0) | 820 (600–1,390) | N/A          | 290 (50.0–120.0) | 0.2-1-0.1          | 72           | 0.6                       |
|                               |         | SIB          | 8 |                   | 29.0 (37.0–31.0) | 855 (620–1,620) |             | 240 (10.0–53.0)  | 10-5-5          | 72           | 20                        |
| Mullet et al. 1982 [84]       | USA     | Plac         | 23| Echo & clinical  | 29.5     | 1,212     |              | 1800             | –              | –           | –                         |
|                               |         | SOI          | 24|                   | 30.1     | 1,237     |              | 177.6            | 0.2-0.2          | 48           | 0.4                       |
| Nestrud et al. 1980 [85]      | Ark     | Plac         | 11| Echo & clinical  | 28.1±2.0 | 1,189±376 |              | 482.4±400.8      | –              | –           | –                         |
|                               |         | SOI          | 12|                   | 30.8±1.8 | 1,287±325 |              | 345.6±240.0      | 0.2 for each dose, clinical & ECHO before next dose | 648          | 0.54                      |
| Neu et al. 1981 [86]          | USA     | Plac         | 10| Echo & clinical  | 29.3±0.6 | 1,142±80  |              | 218.4            | –              | –           | –                         |
|                               |         | SOI          | 11|                   |          |           |              | 0.25–0.25        | 48             | 0.5                       |
| Oncel et al. 2014 [88]        | Turkey  | SOB         | 45| Echo & clinical  | 27.3±2.1 | 973±224   | 2.2           | 48–96            | 10-5-5          | 72           | 20                        |
|                               |         | SOA          | 45|                   | 27.3±1.7 | 931±217   | 2.4           | 15 every 6 h     | 2                | 180          | –                         |
| Osborn et al. 2003 [89]       | Australia| Plac        | 35| Echo              | 26.9±0.3 | 1,002±49  | >1.6          | 4.3 (2.0–12.0)   | –              | –           | –                         |
|                               |         | SII          | 35|                   | 26.7±0.3 | 958±43    |              | 0.2 for each dose, ECHO before next dose | 24–48         | 0.2–0.4                   |
| Patel et al. 2000 [90]        | UK      | SII         | 15| Echo & clinical  | 26.7 (23.2–30.0) | 838 (458–1,377) | N/A          | 2280±125.0       | 0.2-1-0.1          | 36           | 0.6                       |
|                               |         | SIB          | 18|                   | 26 (23.9–35.0) | 790 (620–2,780) |             | 2340±96.0        | 10-5-5          | 72           | 20                        |
| Pezzi et al. 1999 [91]        | Italy   | SII         | 8 | Echo              | 29.5±2.6 | 1,277±440 |              | 332.5±5.4        | 0.2-1-0.1          | 72           | 0.6                       |
|                               |         | SIB          | 9 |                   | 29.1±2.1 | 1,151±426 |              | 319±4.5          | 10-5-5          | 72           | 20                        |
| Pourarian et al. 2008 [92]    | Iran    | SOI         | 10| Echo & clinical  | 33.2±3.1 | 1,720±630 |              | 153.6 (120.0–192.0) | 0.2 for each dose, ECHO before next dose | 72           | 0.2–0.6                   |
|                               |         | SOB         | 10|                   | 31.3±4.4 | 1,860±402 |              | 132.0 (96.0–168.0) | 10-5-5, ECHO before next dose | 72           | 10–20                     |
| Pourarian et al. 2015 [93]    | Iran    | SOB         | 32| Echo              | 31.3±2.1 | 1,493±346 |              | 72–168           | 10-5-5          | 72           | 20                        |
|                               |         | HOB         | 33|                   | 30.0±2.6 | 1,339±524 |              | 20–10–10         | 72             | 40                        |
| Study and year of publication | Country | Intervention | n  | Diagnosis of hPDA | GA, weeks | BW, g | PDA size, mm | Age at treatment, h | Dose, mg/kg/dose | Duration, h | Total doses, mg/kg/course |
|-------------------------------|---------|--------------|----|-------------------|-----------|-------|--------------|-------------------|-----------------|-------------|--------------------------|
| Rudd et al. 1983 [95]         | UK      | Plac         | 15 | Echo & clinical   | 29.0±1.7  | 1,170±211 | N/A          | 264±194.4        | 0.7             | –           | –                        |
|                               |         | SOI          | 15 |                   | 28.9±1.2  | 1,105±251 | 244.8±127.2 | 0.2 for each dose, ECHO before next dose | 40.8            | 0.34        |                          |
| Salama et al. 2008 [96]       | Qatar   | SII          | 20 | Echo & clinical   | 27.8±2.8  | 1,050±440 | 2.6          | 170.4±45.6       | 0.2-0.2-0.2     | 72          | 0.6                      |
|                               |         | SOB          | 21 |                   | 27.7±2.5  | 1,094±480 | 2.5          | 194.4±36.0       | 10-5-5         | 72          | 20                       |
| Su et al. 2003 [98]           | Taiwan  | SII          | 31 | Echo              | 28.2±2.4  | 1,109±344 | >1.5         | 117.6 (48.0–168.0) | 0.2-0.2-0.2     | 36          | 0.6                      |
|                               |         | SIB          | 32 |                   | 28.7±2.2  | 1,134±200 | 98.4 (48.0–168.0) | 10-5-5       | 72          | 20                       |
| Su et al. 2008 [97]           | Taiwan  | SII          | 59 | Echo & clinical   | 25.0 (23.0–28.0) | 762 (540–980) | N/A   | 8.0 (3.0–24.0) | 0.2-0.1-0.1 for age<48 h 0.2-0.2-0.2 for age>48 h ECHO before next dose | 66          | 0.38        |                          |
|                               |         | SIB          | 60 |                   | 25.0 (23.0–28.0) | 825 (550–990) | 8.0 (4.0–21.0) | 10-5-5, ECHO before next doses | 54          | 16.25      |                          |
| Tammela et al. 1999 [100]     | Finland | SII          | 31 | Echo & clinical   | 27.9±2.3  | 1,154±388 | N/A          | 103.2 (28.8–480.0) | 0.2-0.1-0.1     | 72          | 0.6                      |
|                               |         | HII          | 30 |                   | 27.3±1.9  | 1,094±298 | 74.4 (24.0–168.0) | 0.1 × 7 doses | 168          | 0.7                      |
| VanOvermeire et al. 1997 [102]| Belgium | SII          | 20 | Echo & clinical   | 28.7±1.9  | 1,210±360 | 2.5          | 74.4±12.0        | 0.2-0.2-0.2     | 36          | 0.6                      |
|                               |         | SIB          | 20 |                   | 29.0±2.4  | 1,270±450 | 2.6          | 76.8±9.6         | 10-5-5         | 72          | 20                       |
| VanOvermeire et al. 2000 [103]| Belgium | SII          | 74 | Echo & clinical   | 29.0±2.1  | 1,230±380 | 2.5          | 74.4±12.0        | 0.2-0.2-0.2     | 36          | 0.6                      |
|                               |         | SIB          | 74 |                   | 29.0±2.3  | 1,230±390 | 2.5          | 74.4±14.4        | 10-5-5         | 72          | 20                       |
| Yadav et al. 2014 [104]       | India   | SOI          | 35 | Echo              | 30.3±3.1  | 1,380±450 | >1.5         | 240.0±146.15     | 0.2-0.2-0.2 for age<2–7 days 0.2-0.25-0.25 for age>7 d ECHO before next dose | 72          | 0.6        |                          |
|                               |         | SOB          | 48 |                   | 29.7±3.2  | 1,440±450 | 1,440±450    | 10-5-5           | 72          | 20                       |
| Yanagi et al. 1981 [105]      | USA     | Plac         | 9  | Echo              | 30.4±1.0  | 1,500±200 | N/A          | 223.2±36.0       | -              | -           | -                        |
|                               |         | SOI          | 8  |                   | 29.4±1.0  | 1,200±100 | 249.6±72.0   | 0.2-0.2-0.2 (only phase I) | 72          | 0.6        |                          |
| Yang et al. 2016 [106]        | China   | SOB          | 43 | Echo & clinical   | 33.4±2.1  | 2,091±657 | 1.8          | 139.2±48.0       | 10-5-5         | 72          | 20                       |
|                               |         | SOA          | 44 |                   | 33.6±2.1  | 2,219±406 | 2.1          | 153.6±43.2       | 15 every 6 h   | 72          | 180                      |
| Yeh et al. 1981 [107]         | USA     | Plac         | 27 | Echo & clinical   | 30.2±2.3  | 1,167±354 | N/A          | 261.6±146.4      | -              | -           | -                        |
|                               |         | SII          | 28 |                   | 31.5±2.3  | 1,233±408 | 213.1±127.2  | 0.3-0.3-0.3, clinical evaluation before next dose | 0.54        |                  |                          |
| Dani et al. 2020 [51]         | Italy   | SIB          | 52 | Echo              | 28.4±2.0  | 1,068±278 | N/A          | 46±16            | 10-5-5         | 72          | 20                       |
|                               |         | SIA          | 58 |                   | 28.2±1.4  | 1,022±266 | 46±15        | 15 every 6 h     | 72          | 180                      |
| Study and year of publication | Country | Intervention | n | Diagnosis of hsPDA | GA, weeks | BW, g | PDA size, mm | Age at treatment, h | Dose, mg/kg/dose | Duration, h | Total doses, mg/kg/course |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Davidson et al. 2020 [54] | USA | SII | 21 | Echo | 25.3±1.8 | 756±241 | 2.9±0.7 | 6.5 (4.9,3) | 0.2-0.2-0.2 for age 2–7 days 0.2-0.25-0.25 for age >7 days | 36 | 0.6 |
|  |  | SIA | 17 | | 25.7±1.4 | 785±203 | 2.7±0.7 | 8.0 (7,11) | 15 every 6 h | 72 | 180 |
| Ahranjani et al. 2020 [39] | Iran | SOB | 25 | Echo | GA <37 weeks | BW <2599 g | N/A | <15 days | 10-5-5 | 72 | 20 |
|  |  | SIA | 25 | | | | | 10 every 6 h | 72 | 120 |
| Ghaderian et al. 2019 [62] | Iran | SOB | 20 | Echo & clinical | 30.8±1.9 | 1,230±182 | ≥1.5 | <14 days | 10-5-5 | 72 | 20 |
|  |  | SOA | 20 | | 30.4±2.1 | 1,126±200 | | 15 every 6 h | 72 | 180 |
| Kumar et al. 2020 [75] | India | SOB | 80 | Echo & clinical | 28.7±1.7 | 1,129±268 | 2.1 (1.9–2.5) | 48–72 | 10-5-5 | 72 | 20 |
|  |  | SOA | 81 | | 28.7±1.6 | 1,167±249 | 2.3 (1.8–2.6) | 15 every 6 h | 72 | 180 |
| Meena et al. 2020 [81] | India | SOI | 35 | Echo & clinical | 31.8±2.3 | 1,410±320 | 1.8±0.3 | 260±102 | 0.2-0.1-0.1 for age <2 days 0.2-0.2-0.2 for age 2–7 days | 36 | 0.6 |
|  |  | SOB | 35 | | 31.4±1.7 | 1,340±220 | 1.9±0.7 | 258±135 | 10-5-5 | 72 | 20 |
|  |  | SIA | 35 | | 32.1±2.0 | 1,440±340 | 1.8±0.4 | 216±82 | 15 every 6 h | 72 | 180 |
| Oboodi et al. 2020 [87] | Iran | SOB | 70 | Echo & clinical | 31.1±2.4 | 1,354±333 | ≥1.5 | 130±57 | 10-5-5 | 72 | 20 |
|  |  | SIA | 70 | | 31.0±2.9 | 1,334±513 | | 128±96 | 15 every 6 h | 72 | 180 |
| Rahman et al. 2020 [94] | Indonesia | SOB | 11 | Echo & clinical | 34.9±1.4 | 1,904±315 | 3.1±1.1 | 192±146 | 10-5-5 | 72 | 20 |
|  |  | SOA | 11 | | 33.7±1.7 | 1,723±171 | 2.6±0.9 | 185±137 | 15 every 6 h | 72 | 180 |
| Sung et al. 2020 [99] | Korea | Plac | 72 | Echo | 26.7±2.0 | 915±243 | 2.5±0.6 | 202±60 | – | |
|  |  | SOB | 74 | | 26.8±2.1 | 893±256 | 2.5±0.5 | 199±55 | 10-5-5 | 72 | 20 |
| Tauber et al. 2020 [101] | USA | SIB | 5 | Echo | 26.3±2.3 | 916±300 | N/A | 192±120 | 10-5-5 | 72 | 20 |
|  |  | SIA | 5 | | 26.2±1.4 | 736±240 | | 168±72 | 15 every 6 h | 72 | 180 |

n, number of sample size; BW, birth weight; cont, continuous; d, day; DAO, descending aorta; g, gram; GA, gestational age; PDA, patent ductus arteriosus; mm, millimeters; h, hours; mg, milligram; Kg, kilogram; Plac, placebo; SOI, a standard dose of oral indomethacin; HOI, a standard dose of oral indomethacin; SII, a standard dose of intravenous indomethacin; HI, a high dose of intravenous indomethacin; SMA, superior mesenteric artery; SOB, a standard dose of oral ibuprofen; HOB, a high dose of oral ibuprofen; SIB, a standard dose of intravenous ibuprofen; HIB, a high dose of intravenous ibuprofen; SOA, a standard dose of oral acetaminophen; HOA, a high dose of oral acetaminophen; SIA, a standard dose of intravenous acetaminophen; HIA, a high dose of intravenous acetaminophen; MPA, main pulmonary artery; SIdrip, a standard dose and continuous infusion of indomethacin; SIdrip, a standard dose and continuous infusion of ibuprofen; wks, weeks.
tors were SII ($n = 2,294$) and SOB ($n = 2,180$); 3 studies [46, 81, 108] had three arms, one with SII-SOB-HOB and the others with SII-SIB-SIA and SOI-SOB-SIA. The mean GAs and BWs varied from 25 to 33.5 weeks and 736–2,455.74 g, respectively. All RCTs prescribed treatments at the postnatal age of ≤14 days (mean age range = 4–277 h), except in 1 study where the mean age was 411 h. PDA diameters ranged from 1.39 to 2.85 mm (shown in Table 2). All studies used echocardiographic criteria (e.g., PDA size, LA/AO, and/or reverse diastolic flow in the descending aorta) for the diagnosis of hsPDA, and 30/70 studies also had additional clinical criteria (e.g., tachycardia, bounding pulse, continuous murmur, or hepatomegaly).

**Inconsistency Assumption**

Sixty-nine and sixty-three studies provided data for PDA closure and composite risk outcomes. The global inconsistency was tested, which suggested no evidence of inconsistency for PDA closure and composite risk ($p$ values = 0.140 and 0.972); see online eTable 4.1. The loopspecific method indicated that comparisons of SOI-SIA, HOB-SOA, and SOB-SIB for PDA closure from Plac-SOI-SIA, SOB-HOB-SOA, and SII-SOB-SIB loops had significant IF; see online eTable 4.2 and online eFigure 4.1. Then, the characteristics of patients were compared among these three comparisons (see online eTable 4.3–4.5), indicating that most characteristics were not much different except age at treatment between SOI and SIA, i.e., about 8 versus 4 days. The loop-specific composite risk showed no statistically significant inconsistency; see online eTable 4.6 and online eFig. 4.2.

**Risk of Bias and GRADE**

Most studies were at low risk of bias for all items, except blinding participants and researchers (shown in online eTable 5.1; online eFig. 5.1). All studies were described as randomized, but 27 of 70 studies did not blind clinicians and patients. One of the main reasons was the different routes of administration. Adjusted funnel plots of PDA closure and composite risk were inspected visually to assess publication bias. They showed no substantial asymmetry (online eFig. 5.2). The majority of the confidence rating from GRADE was low-quality evidence for both PDA closure (47/78 comparisons) and composite risk outcomes (61/78 comparisons). The downgraded scores were mainly from imprecision and some from heterogeneity. For the comparisons included in RBA, i.e., HOB & Plac, SOA & Plac, SOB & Plac, and SII & Plac, the quality of evidence for PDA closure outcome was high while the evidence for composite risk outcome was moderate for SOB & Plac, SII & Plac, and low for the rest (online eTable 6.1–6.2).
Benefit Outcome
PDA closure data were extracted from 69 of 70 RCTs (n = 5,118), considering 13/15 interventions where their data were available. The direct meta-analysis and league table results are described in online eTable 7.1–7.2. NMA was performed, and a network map was shown in Figure 2a. The results from the league table indicated that all interventions showed a significantly higher PDA closure rate than placebo; the highest treatment effect was HOB; 2.26 (1.64, 3.10), followed by HIB; 2.26 (1.27, 4.01) and SOA; 2.03 (1.57, 2.63). From SUCRAs, the best treatment for PDA closure was HOB, followed closely by HIB, SOA, and SOB, with SUCRAs of 83.0, 75.7, 69.6, and 62.1, respectively.

Risk Outcome
Data on composite risk for the individual study were extracted from seven SAEs; see online eTable 8.1. Sixty-three studies with 13 interventions were analyzed in NMA compared with Plac (shown in Fig. 2b). Pairwise comparisons and league tables are shown in online eTable 8.2–8.3. SUCRAs for minimum SAE were estimated and showed that HOB had the highest probability of being the best or the lowest SAEs with SUCRA of 80.0, followed by SOA, SOB, and HII with SUCRAs of 76.5, 70.1, and 59.8, respectively.

Cluster Rank
Cluster rank was constructed by plotting the SUCRAs of PDA closure on the x-axis and the composite risk on the y-axis (shown in Fig. 3); higher SUCRA values reflect higher PDA closure and low SAEs. The cluster ranking plot can be divided into four quadrants; 3 interventions HOB, SOA, and SOB fell in the right upper dominant quadrant, meaning they had high PDA closure and low SAEs. These three treatments, plus the commonly used SII regimen, were further considered in RBA. HIB fell in the right lower quadrant indicating higher PDA closure but high SAEs.

Risk-Benefit Analysis
ΔR and ΔB of four treatments, compared with Placebo, were estimated and then pooled across RCTs. The point estimate of ΔR and ΔB were jointly simulated and fell in the SE quadrant, which yielded the point estimated IRBRs of −0.139 (−2.68, 2.40), −0.075 (−0.599, 0.449), −0.057 (−2.518, 2.404), and −0.009 (−0.217, 0.199) for HOB, SOA, SOB, and SII, respectively (shown in online eTable 9.1). These convey that the interventions have greater benefits and less risk than Plac. Next, Monte Carlo was run, allowing the joint uncertainty of the risks and benefits, and they were plotted on RBPs with varying thresholds from 0.25 to 2.0 (Fig. 4). The chance that IRBRs were less than μ was shown in online eTable 9.2. RBACs were plotted (Fig. 5a). However, these curves do not allow a comparison of all treatments simultaneously. Then, curves of the highest NCB of each treatment were constructed (Fig. 6a). HOB was the treatment with the highest probability of having the best NCB. Suppose decision-makers accept one additional SAE to obtain four PDA closures (threshold of 0.25); HOB was the treatment with the highest probability (36%), followed by SOA (27%) and SOB (23.7%) (see online eTable 9.3).

Subgroup Analysis
Subgroup analysis by GA <28 (n = 1,749) and ≥28 weeks (n = 3,398) were performed. Eighteen and 17 studies reported PDA closure and composite risk in GA <28 weeks, and 51 and 46 studies for those GA ≥28 weeks. The mean birth weights of these corresponding GA groups were 937.08 ± 118.80 and 1,332.78 ± 270.92. There was no evidence of inconsistency for all sub-pooling as for the global χ2 tests; see online eTable 4.1. Data for HOB was not available for GA <28 weeks. RBAC Results of subgroups were similar to overall results (shown in Fig. 5b, c; online eFig. 10.1–10.2; online eTable 10.1–10.2), in which HOB, SOA, and SOB were the three ranks for GA ≥28 weeks. For GA <28 weeks, SOA was the top, followed by SOB. Moreover, the results of the highest probabilities of NCB for GA <28 weeks (see Fig. 6b) and GA ≥28 weeks (see Fig. 6c) were similar to RBAC.

Discussion
We applied NMA and RBA for the treatment of hspPDA in preterm neonates to summarize the data and incorporate risks into benefits that facilitate decision-making.
Fig. 3. Clustered ranking plots for the relative ranking of treatment for the efficacy of PDA closure and composite risk outcomes in network meta-analysis. **a** For all studies, **b** For GA <28 weeks, **c** For GA ≥28 weeks. Clustered ranking plots for the medical treatments of PDA based on the SUCRA. The larger the SUCRA, the higher the rate of PDA closure, and the lower the rate of adverse effects.
An NMA indicated that HOB, SOA, and SOB seemed to be the 3 best treatments, which all had lower complications and higher benefits than placebo. Likewise, given the risk-benefit threshold from 0.25 to 3.5, HOB is the best choice to have the highest probability of NCB, followed by SOA and SOB. Treatment with HIB might gain high benefits but also increase the risk of SAEs. The probabilities of being the best treatment for GA ≥28 weeks were the same trends as the results from including all studies. However, HOB was not available for the smaller GA group.

Recently, there has been a considerable debate about whether or not to treat PDA in preterm. Although some studies have demonstrated the association between PDA in preterm with increased mortality and morbidities, e.g., CLD and NEC [3–6], a paucity of information shows short-term adverse effects after treatment. Individual variability may play an essential role in deciding the treatment, and the target population which responds and benefits from the treatment is paramount. Many are interested in treating symptomatic PDA, which widely uses echocardiography to demonstrate significant shunting via PDA. Although the long-term outcomes of treatment

**Fig. 4.** The risk-benefit acceptability planes of HOB, SOA, SOB, and SII compared with placebo. The horizontal bar represents the 95% CI for the difference in benefits of PDA closure, and the vertical bar is the 95% CI for the difference in the probability of the composite risk outcomes. The ● marks the point estimate of the risk-benefit ratio. Dashed lines are the risk-benefit acceptability threshold of 0.25, 0.5, 0.75, 1.0, and 2.0.
Fig. 5. Risk-benefit acceptability curves for the treatment of PDA in preterms compared with placebo at any risk-benefit acceptability threshold (µ). a For all studies. b For GA < 28 weeks. c For GA ≥ 28 weeks. The reference value is shown as the vertical dashed line with varying thresholds of 0.25, 0.5, 0.75, and 1.
Fig. 6. Net clinical benefit probability curves compared with placebo at any risk-benefit acceptability threshold (µ). a For all studies. b For GA <28 weeks. c For GA ≥28 weeks. The reference value is shown as the vertical dashed line with varying thresholds of 0.25, 0.5, 0.75, and 1.
have not been clearly identified, therapeutic closure of PDA seems to be accepted in current practice.

From our review, the mean BWs of most studies were classified as VLBW (less than 1,500 gm), and most treatments were started 3 days after birth. Similarly, in real-world clinical practice, the spontaneous closure rate is nearly 70% within 3 days after birth [109]. The infants were clinically observed and received treatment after that. Indomethacin and ibuprofen are widely used for PDA closure in preterm neonates. Their effectiveness is based on the role of prostaglandin in ductal constriction via the inhibition of COX enzymes. Our study found that both HOB and SOB had a higher rate of PDA closure than intravenous indomethacin, and incorporating risk into PDA closure also indicated a higher NCB of ibuprofen. Total doses of HOB ranged from 30 to 40 mg/kg/course; 10–20 mg/kg, followed by 7.5–10 mg/kg administered every 12–24 h for a total of 3 doses, compared with 20 mg/kg/course for SOB; 10 mg/kg, followed by 5 mg/kg administered every 12–24 h for a total of 3 doses. Although ibuprofen has been reported to associate with the risk of NEC and renal insufficiency [110], the RBA conveys that the benefit outweighed the risk. However, HOB for preterm with a smaller GA group was undetermined due to unavailable data.

Acetaminophen, which acts on the peroxidase site of prostaglandin H2 synthesis, has been increasingly used because of the contraindication from those two COX inhibitors. However, many are uncertain about its effectiveness and risks for first-line therapy compared with COX inhibitors. The standard dose of acetaminophen might be an alternative for hsPDA closure, with a dosage of 15 mg/kg every 6 h for 3 days or a total dose of 180 mg/kg/course. Enteral acetaminophen seems to have more treatment effects than the parenteral route. The reason to explain this may be from the steadier plasma levels of the drug administered orally, similar to the oral use of ibuprofen [111]. Liver toxicity from acetaminophen was considered for composite risk, but no data on long-term side effects, e.g., neurodevelopment, were reported. Therefore, more information is needed.

Nowadays, the continuous infusion has been an interesting issue of increasing effectiveness and reducing adverse effects. From our research, all included studies of SIIdrip and SIBdrip were compared with standard bolus doses [49, 67, 68, 77]. 36-h continuous infusion for SIIdrip, and 24-h continuous infusion of SIBdrip had more stable blood flow velocities in cerebral, renal, and mesenteric vessels. As a result, there might be the question of whether the continuous infusion of the standard dose is more favored in terms of risk and benefit assessment. However, results from the clustered ranking plot, SIIdrip and SIBdrip did not lie in the right upper dominant quadrant. Additionally, compared with standard bolus doses, SIIdrip and SIBdrip had no more benefits and fewer risks. However, summarized data of SIIdrip and SIBdrip were from only 3 studies (n = 114) and 1 study (n = 112), respectively. Further trial studies concerning continuous infusion are required.

Several NMAs were conducted to summarize the efficacy and safety of medical treatment for hsPDA. Two large NMAs [7, 8] were published. The first NMA included 67 RCTs covering 10 interventions [14]. They found that HOB (i.e., 15–20 mg/kg followed by 7.5–10 mg/kg administered every 12–24 h for 3 doses) was the best for hsPDA closure, followed by HIB and oral acetaminophen. However, there was no significant difference in the odds of adverse effects. The second NMA was recently published, combining data from 64 RCTs with 24 observational studies [8]. These two NMAs are different comparing from our NMA in some respects: we did not include studies comparing the same intervention and route with equal dosages/course [49, 77, 112–114], although the studies compared the different duration of administration (e.g., short vs. prolonged durations) or the same treatment with/without additional one medication (e.g., SII vs. SII and furosemide, or SII vs. SII and dopamine). This is because interventions from our study were grouped from the total dose/course. Additionally, we used data based on intention-to-treat instead of per-protocol approaches to maximize validity. A composite SAE was considered instead of individual adverse events [14], and RR and RD were used to estimate relative treatment effects instead of odds ratios. As a result, although the highest-ranked treatment for PDA closure was similar to Mitra’s study [7], the second and third-ranked therapies were different; SOA and SOB for our study but HIB and oral acetaminophen for Mitra’s study. Finally, we applied RBA to incorporate the composite risks and benefits, which have not been performed to date in the previous NMAs. Therefore, this should prove more helpful to clinicians in decision-making.

**Strengths and Limitations**

This is the first study of PDA treatment in preterm, which combined the estimations between NMA and RBA. Our summarization represents the treatment of hsPDA from various NICUs worldwide. Many of these studies had high methodologic quality. Besides, this approach allowed summarizing the joint distribution of
benefits and risks and provided a transparent benefit-risk outcome for treating hsPDA in preterm. However, there are some limitations: the uncertain appropriate starting time for treatment since there are various postnatal age treatments and some inconsistencies, the lack of data on HOB for small GA <28 weeks, and long-term SAEs.

**Conclusion**

Our study suggested that the best treatment, trading off risks and benefits with the various degrees of acceptability thresholds, in terms of PDA closure and SAEs was HOB, followed by SOA and SOB, particularly for the newborns GA ≥28 weeks. Whereas SOA, followed by SOB, might be the best for newborns GA <28 weeks. However, further well-designed studies are needed to define the optimal high doses, appropriate postnatal age for treatment, and long-term outcomes to ensure efficacy and safety in clinical practice.

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**Statement of Ethics**

The paper is exempt from Ethics Committee approval as this is a systematic review using data from published literature, and no additional patient data were collected.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

All the authors contributed to this study’s conception and design. S.E. searched for and selected studies, performed data extraction, statistical analyses and risk of bias assessment, and drafted the manuscript. A.T. designed the review methodology, assisted in statistical analyses and interpretation, critically revised the manuscript, and supervised all study parts. O.P. assisted in the risk-benefit analysis and critically revised the manuscript. S.A.-O.V. performed data extraction and risk of bias assessment, critically revised the manuscript, and supervised the clinical content. P.N. performed data extraction and risk of bias assessment. J.A. critically commented and revised the manuscript. C.O., the corresponding author, performed data extraction and risk of bias assessment, critically revised the manuscript, controlled the decision to publish, and attested that all listed authors met authorship criteria. All the authors approved the final manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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