Systematic review and network meta-analysis of intravenous ibuprofen vs. intravenous indomethacin vs. placebo in the management of clinically and/or echocardiographically important patent ductus arteriosus in preterm infants at greater than 24 hours of life.

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Statement of Originality

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Other acknowledgements

I wish to thank the following people for their support and contributions to this thesis:

Dedication

To my husband Stephen and son Matthew for their support and endless patience during the writing of this thesis.

To my nursing colleagues in the Neonatal Intensive Care Unit at John Hunter Children's Hospital.

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Abstract

Objectives

To evaluate the effects of indomethacin or ibuprofen compared with placebo on closure, morbidity and mortality in preterm infants <37 weeks' gestation with echocardiographically and/or clinically important patent ductus arteriosus (PDA) at >24 h of life.

Data sources

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, Cochrane Library, clinicaltrials.gov, controlled-trials.com, American Pediatric and European Paediatric Research Societies and Effective Care of the Newborn Infant.

Review methods

Systematic review with network meta-analysis of randomised studies comparing intravenous indomethacin, ibuprofen or placebo for PDA in preterm infants at >24 h of life.

Results

Ten trials compared intravenous indomethacin versus intravenous ibuprofen, nine compared intravenous indomethacin versus placebo and one intravenous ibuprofen versus placebo. Both intravenous indomethacin [pooled RR 2.39 (95% CI 2.05 to 2.78)] and intravenous ibuprofen [RR 2.40 (95% CI 2.03 to 2.84)] closed a PDA more effectively than placebo. Intravenous ibuprofen was associated with approximately 30% greater risk of chronic lung disease than intravenous indomethacin [RR 1.28 (95% CI 1.03 to 1.60)] or placebo [RR 1.29 (95% CI 0.99 to 1.70)]. Differences in risk or benefit were not significant between any combination of intravenous indomethacin, intravenous ibuprofen or placebo groups for intraventricular haemorrhage, necrotising enterocolitis and death. Reporting on neurological outcomes was insufficient for pooling. Sensitivity analyses indicate a gestational and post-natal age dependent effect on PDA closure and the risk of CLD. The majority of trials comparing intravenous indomethacin with placebo administered non-randomised rescue treatment to > 20% of the placebo group. Sample size estimations for intravenous indomethacin suggest large numbers are needed to provide adequate power to detect a difference in the risk of outcomes other than PDA closure. Smaller numbers are required for intravenous ibuprofen with a minimum of 131 per group for the outcome of CLD.

Conclusions

Intravenous indomethacin or ibuprofen administered to preterm infants for PDA at >24 h of life promoted ductal closure, but other short-term benefits were not seen. Data from randomized trials concerning the effect of treatment with indomethacin or ibuprofen for PDA closure on IVH, CLD, NEC, survival and longer-term neurodevelopmental outcomes is presently insufficient to guide current practice. There is a need for well-designed good quality modern randomized controlled trials comparing intravenous ibuprofen and intravenous indomethacin administered for echo-targeted PDA and PDA detected by clinical signs in preterm infants at greater than 24 hours of life. Such trials should be multi-centre and incorporate improved methods of handling the administration of rescue treatment in the placebo group in order to improve the chance of detecting a benefit or risk. Data on longer-term respiratory and neurological outcomes are also urgently needed. Suggested trial methods include comparing early targeted at <24 hours with placebo randomised to either echo-targeted or symptomatic PDA as rescue at > 24 hours of life. Comparisons can then be made between the risk of outcomes in preterm infants with PDA receiving rescue treatment based on echo alone compared to those randomised to symptomatic rescue treatment but remaining untreated.

Introduction

This thesis aims to examine the evidence for and against indomethacin and ibuprofen treatment for patent ductus arteriosus (PDA) in the preterm infant. Chapter 1 sets the background for the thesis within a comprehensive literature review followed by the research proposal and an overview of indirect comparisons. The literature review is divided into four sections: 1. Ductus arteriosus; 2. PDA encompassing PDA incidence, diagnosis and mechanisms potentially responsible for failure of spontaneous closure; 3. the theoretical consequences of PDA pathophysiology; and 4. an evaluation of PDA management with a focus on pharmacological treatment with prostaglandins inhibitors. The research proposal outlines the rationale, aim, objective and hypothesis for the proposed systematic review and network meta-analysis. Finally, an overview of indirect comparisons describing network meta-analysis methods and the reasoning behind the chosen approach will be presented.

Chapter 2 presents the published paper titled "Network meta-analysis of indomethacin vs. ibuprofen vs. placebo for PDA in preterm infants". Appendices containing an extended version of the paper, raw data tables, STATA output and supplementary tables referred to in the published paper are also included.

Chapter 3 is divided into 2 sections. Section 1 sets the scene by integrating new perspectives on the management of pathophysiology theoretically associated with PDA from recent studies, with findings from the literature review, systematic review and network meta-analysis. The degree to which current PDA guidelines reflect an evidence-based management approach to PDA management and the recommendations of recent surveys of neonatal practice is considered. New trials planning to compare indomethacin or ibuprofen directly with placebo are introduced along with evaluation of further progress in the methods and interpretation of indirect comparisons. Section 2 provides an interpretation of the projected sample sizes for current trials and whether these are likely to provide adequate power to demonstrate a treatment effect for indomethacin or ibuprofen in PDA management. Limitations of the methods used in the network meta-analysis, sample size recommendations for future trials are also discussed in addition to suggesting ways of improving precision of the effect estimate and other methods for improving the chance of detecting a treatment effect. Finally, an exploration of new trial directions designed to overcome the conventional trial design flaws and an evaluation of the existing trial network for areas of future enquiry in randomised trials will be presented.

Chapter 1– Literature Review

Section 1 The ductus arteriosus

Role in the maintenance of in-utero circulation

The existence of the ductus arteriosus in the human foetus was originally described in post-mortem examinations of human foetuses by16th century anatomist Guilio Cesare Aranzio. According to Peterffy (1) the ductus arteriosus is incorrectly referred to in the European literature as the duct of Botalli or Botalli's duct, after Italian surgeon Leonardo Botallo who only described the foramen ovale. In common with all other blood vessels, the ductus consists of 3 layers. Silver (2) described the tunica intima or inner lining of the ductus as a flattened endothelium surrounded by concentric rings of smooth muscle cells forming the tunica or ductal muscle media, covered by the outer elastic tunica adventitia. The ductus arteriosus forms an essential part of normal in-utero circulation, connecting the right and left sides of the foetal circulation in the absence of pulmonary function. Blood flow via the in-utero circulation occurs in response to varying pressure gradients established within the foetal circulation. Oxygenated blood returning from the placenta following diffusion of maternal oxygenation into the foetal placental circulation re-enters the foetus via the umbilical vein where the majority of blood is diverted through the ductus venosus into the inferior vena cava and the right side of the heart (3). The blood is ejected from the right ventricle into the pulmonary artery and meets with high pulmonary vascular resistance achieved by mechanical compression of pulmonary arterioles by the fluid filled, collapsed state of the alveoli and the lack of rhythmic distention (4) associated with spontaneous respiration (5). In addition to the high resting tone within the pulmonary vasculature, Lakshminrusimha (5) suggests that this high PVR is partly maintained by active vasoconstriction from mediators such as arachidonc acid metabolites, hypoxic vasoconstriction and endothelin . The blood flows across the ductus arteriosus from the right ventricle toward the comparatively low vascular resistance maintained within the placental circulation. In a similar manner, blood to flows across the foramen ovale from the greater pressure in the right atrium created by the diversion of blood away from the pulmonary circulation toward the lower pressure in the left atrium (6). Combined vascular shunting via the ductus and the foramen ovale, allows 90% of the oxygenated blood from the placenta to flow directly into left side of the foetal circulation, bypassing the lungs which are not involved in gas exchange, whilst 10% provides blood supply to lung tissue to maintain oxygenation and continued lung development (7). Maintenance of in-utero ductal patency, therefore, is vital for continued oxygenation and foetal survival.

Apart from the relationship between high pulmonary vascular resistance and low systemic resistance, the primary mechanism for regulation of in-utero ductal patency is mediated by prostaglandins synthesis from cells located within the placenta and the ductal intima (7). Prostaglandins are responsible for the regulation of multiple processes affecting a wide range of body systems and the entire mechanism of prostaglandins synthesis is highly complex. Put simply, arachidonic acid, a by-product of phospholipid metabolism, is converted by the enzymatic actions of the genetically expressed cyclooxygenase-1 and the stress-induced cyclooxygenase-2 into prostaglandin H2, the common precursor for the synthesis of all prostaglandins (8). At this stage prostaglandin production differentiates into individual cell types depending on the intended function. From experimental work using animal subjects, Coceani (9) described the relaxant action of prostaglandin E2 (PGE2) on ductal smooth muscle as essential to in-utero ductal patency. Bouayad (10) later described how PGE2 acts on E –type prostaglandin receptors; EP2, EP3 and EP4 as part of an enzymatic system located within the ductal vascular intima. These prostaglandin receptors act on the cell walls of the ductus to increase the intracellular concentration of cyclic AMP and reduce the sensitivity of the ductus to the contractile stimulus of calcium influx during membrane depolarization resulting in smooth muscle vasodilatation and ductal relaxation. In addition, Bouayad (10) identified the role of EP3 in opening potassium adenotriphosphate (K-ATP) channels leading to hyperpolarisation of ductal smooth muscle with inhibition of ductal tone and activation of the enzyme adenyl cyclase causing in-utero ductal vasodilatation and relaxation. PGE subtypes target multiple receptors within ductal tissue using various mechanisms to maintain in-utero ductal relaxation.

Localised nitric oxide (NO) and carbon monoxide (CO) production may also influence in-utero ductal tone and patency. Coceani (11) proposes that guanyl cyclase promotes ductal relaxation following activation by NO produced within the ductal endothelium. The precise triggers for NO release are not fully understood. Coceani (11, 12) hypothesises that NO may be released in response to the presence of inflammatory mediators or may form part of a compensatory mechanism acting to maintain in utero ductal patency in response to disruption prostaglandin E2 regulation by cyclooxygenase. Coceani (13) proposes that CO produced locally in ductal tissue may also relax the ductus arteriosus. Clyman (14) contends that the small amounts of CO produced in the ductus would not normally be sufficient to play a major role in ductal patency; but concedes there may be an up-regulation of CO in response to the presence of endotoxins. It is possible that both NO and CO act to maintain ductal patency in response to interference in the usual PGE2-mediated regulation.

Several mechanisms have been proposed to explain how ductal tone increases in preparation for transition to normal "neonatal" circulation as term gestation approaches. The original hypothesis of Nguyen (15) and Coceani (16), that a sharp decline in circulating blood levels of PGE2 are responsible for progressive increases in ductal wall muscle tone in the immediate antepartum period was challenged by Bouayad (17) who suggests instead that increased ductal tone near term gestation occurs from loss of ductal EP receptor sensitivity to the relaxant effect of PGE as a result of decreased ductal responsiveness to ductal relaxation by PGE2 rather than a drop in circulating PGE2 levels. Progressive reduction in ductal relaxation mediated by a decline in ductal responsiveness to PGE2 and circulating PGE2 levels occurring in utero as the foetus approaches term gestation contribute to the preparation for spontaneous ductal closure post-transition to normal circulation.

In utero and intrapartum transition to normal circulation

Normal birth mechanics greatly influence ductal closure and transition to normal "neonatal" circulation in the immediate postnatal period. Foetal breathing movements described by Bloom (18), occur from approximately 10 weeks gestation, with active reabsorption of alveolar fluid commencing several days prior to birth and continuing throughout labour and delivery. Mild hypoxia, hypercapnia and acidosis created by uterine contractions during labour stimulate the respiratory centre to increase respiratory efforts (19). Active compression of the thoracic cage as the baby pushes through the vaginal canal causes further displacement of alveolar fluid into the pulmonary circulation, which is partially reabsorbed via the lymphatic system (20). The negative pressure generated within the alveoli as a consequence of fluid displacement from the alveolar spaces causes atmospheric air to enter the lungs with expansion of the rib cage and downward movement of the diaphragm as the baby takes its first breath (21).

Lung expansion following the initiation of spontaneous respirations increases fluid reabsorption and stimulates surfactant release (22). Surfactant is a phospholipid substance produced by lamellar bodies in type II cells distributed among the epithelial cells lining the terminal airways of the lungs. It reduces the surface tension created by the presence of air and water within the alveoli, thereby opposing the tendency for alveolar constriction and collapse associated with lack of surfactant (23). Lower surface tension allows alveolar expansion to occur, which in turn lowers pulmonary vascular resistance (PVR) (24). Placental oxygenation of the foetal circulation ceases upon clamping of the umbilical cord precipitating a rapid fall in vena caval oxygen content whilst the initiation of spontaneous respiratory effort causes simultaneous rises in aortic oxygen content and oxygenation of left

ventricular output (25). PVR falls in response to increased arterial oxygen and the mechanical effect of lung expansion, further increasing the oxygen content of the blood returning to the left atrium (26, 27). The pre and post-ductal oxygen gradient established between the low oxygen content pulmonary, and high oxygen content aortic, ends of the ductus arteriosus creates a high level of oxygen tension within the ductus (14). This tension is thought to produce an intense hypoxia within the ductal muscle which becomes a powerful stimulus for ductal muscle contraction in the period immediately following birth (14).

Theories surrounding the mechanism of ex-utero spontaneous closure in the term newborn infant

Whilst there remains some controversy regarding the underlying mechanisms, it is generally agreed that there are two phases of ductal closure, functional and anatomical;

Functional Closure

This term describes the process of initial postnatal ductal constriction and cessation of blood flow across the duct. In healthy term infants this usually occurs in response to rising arterial oxygen levels within the first 12-15 hours following birth, accompanied by increased ductal tone in addition to a reduction in the relaxing effects of prostaglandins, which, as discussed in " role in maintenance of the in-utero circulation", commences before term gestation. In a series of experiments, Coceani (28) discovered that rising arterial oxygen levels oppose the effect of e- type prostaglandins (PGE) on ductal muscle relaxation further contributing to ductal closure. Loss of placental production of PGE following birth and increased PGE removal in the lung are also thought to influence ductal closure following successive experiments by Challis (29), Clyman (30), Nguyen (15) and Coceani (16). Postnatal reduction in the sensitivity of the ductus to PGE2 was indicated in 'in vivo' (live animal) and in vitro experiments by Clyman (31) and Abrams (32). Bouayad (17), recently proposed the theory that PGE levels drop in response to rising arterial oxygenation with a corresponding fall in the relaxant effect of PGE2, promoting ductal closure and causing blood flow through the ductus to cease. Progressive ductal constriction mediated by a decline in circulating PGE2 levels and ductal responsiveness to PGE2 may contribute to spontaneous closure in the well term infant in the postnatal period.

Investigators have offered different explanations for the promotion of functional ductal closure by various mechanisms other than reduced PGE2 in response to rising arterial oxygen levels at birth. Coceani (33, 34) proposes that cytochrome P_{450}, a hemoprotein located in the sub-cellular structure of the ductal muscle media, is also activated by the post birth rise in arterial oxygen levels and has a role in the synthesis of endothelin-1 (ET-1), a potent vasoconstrictor of the ductus. Fineman (35) questions the action of ET-1 in postnatal ductal closure as testing in live animal subjects did not replicate Coceani's (11, 33) experimental findings. Fineman's (35) study demonstrated a level of intrinsic ductal contraction in response to normal arterial oxygen levels at birth that did not seem to vary with changes in prostaglandins or ET-1 synthesis. Coceani (16, 36) places continued emphasis on the importance of ET-1 in mediating ductal constriction in response to increased arterial oxygen content following birth but concedes that its presence is not required for ductal closure.

An alternative theory originally posed by Nakanishi (37) from earlier in-vitro studies suggests that the change from low to high arterial oxygen content at birth closes the ATP sensitive potassium (K-ATP) channels leading to ductal smooth muscle cell depolarisation. The change in voltage is thought to allow voltage dependent calcium channels to operate causing an influx of calcium into the cells leading to ductal smooth muscle contraction at normal levels of oxygen. This theory is supported by the findings of a similar study by Michelakis (38). More recently, Hong (39) determined the existence of specialised channels in the cell membranes of ductal muscle cells allowing the influx of extracellular calcium to stimulate contraction of ductal muscle in response to normoxic conditions in animal subjects. The inference from the cumulative results of this research is that there is no single mechanism responsible for ductal closure and that functional ductal closure is reliant on a complex interaction of mechanisms apart from those involving prostaglandins.

Anatomical Closure

Anatomical closure describes complete and final closure of the ductus arteriosus over a period of days to weeks. This occurs following functional closure of the ductus. According to Clyman (40) permanent ductal closure relies upon endothelial proliferation and obliteration of the ductal opening. It is generally thought that for this to occur, the middle part of the ductus must remain hypoxic, a condition originally generated by the difference in oxygen content between the arterial and the venous ends of the ductus during transition to normal circulation, and that this must be sustained following functional closure. In support of this theory, Clyman (41), demonstrated that the most constricted areas of ductal tissue in live newborn baboons were more hypoxic, with greater endothelial proliferation and evidence of cellular disintegration. Additionally, vascular endothelial growth factor (VEGF), thought by Clyman (41) to be responsible for initiating ductal endothelial growth as part of anatomic closure, was mainly concentrated in hypoxic tissue indicating a role for ductal wall hypoxia in signalling VEGF to commence ductal obliteration. Further investigation by Kajino (42) suggests that initial ductal constriction compresses ductal wall intramural vascular supply or "vasa vasorum" reducing blood flow and increasing muscle wall hypoxia. Clyman (40, 43) proposes that ischaemic hypoxia inhibits locally produced ductal PGE2 and NO, stimulates the production of VEGF and causes ductal smooth muscle cell death, all of which combine to produce permanent, anatomical ductal closure.

Section 2 Patent ductus arteriosus (PDA)

Patent ductus arteriosus (PDA) generally describes the maintenance of a ductus arteriosus beyond normal transition to newborn circulation. PDA was originally reported in the context of infants with a spectrum of congenital abnormalities surviving into childhood and later life. For example, Bullock (44) associated the presence of PDA in infancy with cardiac enlargement and symptoms of pulmonary congestion, progressing to congestive cardiac failure (CCF), and death from bacterial complications". Although Kennedy (45) reported on the presentation of PDA as an isolated phenomenon potentially representing a response to poor blood oxygenation during or shortly after birth, it was not until a decade later that Record (46) revisited the concept. Early studies of PDA were generally limited to case reports. Lendrum (47) proposed that "the reopening of the channels of fetal circulation" occurred in response to failure of adjustment of the cardiovascular system to extra-uterine life. There are many factors which are thought to contribute to PDA.

Incidence of PDA

Overall PDA incidence has increased over the last 3 decades which may be at least partly attributable to the earlier diagnosis of PDA with the use of echocardiography. Between 27 and 64% of preterm infants of birthweight 1500-1900g were diagnosed with PDA according to clinical signs or confirmed via echocardiographic examination in studies by Neal (48) and Reller (49) respectively. In other studies, Dollberg (50), using a combination of echocardiography and clinical signs reported a PDA incidence of 25% in a large cohort study of preterm infants born at gestational ages of 24-32 weeks but Koch (51), demonstrated PDA in 66% of preterm infants of birthweight less than 1000g persisting longer than the first week of life using echocardiography alone. Partial reliance on clinical signs to detect PDA in the study by Dollberg in addition to a wide range of gestational ages and therefore birthweight may have led to a lower tendency to detect PDA than those seen in both Reller's and Koch's studies using echocardiography alone. A higher number of cases appear to be detected using echocardiography than clinical signs and in lower birthweight or gestational age subgroups. Another factor in the changing the incidence of PDA may be the improved survival of lower birthweight and lower gestational age preterm infants due to changes in respiratory management over time. This is supported by NICHD data (52, 53) which demonstrates an increasing incidence of PDA in conjunction with increased survival rates over the period between 1987 to 1998. Survival and PDA incidence both peaked following the introduction of surfactant in 1990 and again with increased use of antenatal steroids from the mid 1990's.

Predisposing factors associated with PDA incidence

Maintenance of a PDA in preterm infants beyond transition is multi-factorial. Predisposing factors associated with greater PDA incidence include; decreasing birthweight, lower gestational age, gender, genetics, environmental factors, no or incomplete antenatal steroid administration, preterm birth, the mechanics of preterm birth, hypoxia at birth, pulmonary disease, vascular immaturity and prostaglandin imbalance.

Birthweight

Greater PDA incidence has been associated with lower birthweight. Yearly PDA incidence in an entire admission cohort retrospectively studied by Zachman (54) varied from 2.5 to 15% for infants of all gestational ages. Examining the effect of birthweight subgroups < 1000g and > 2000g on PDA incidence demonstrated that PDA incidence rates were greater in preterm infants that were smaller at birth with 5.1 to 41% identified as having PDA compared to 0.6 - 5.4% of their larger counterparts. Similarly, Reller (49) detected PDA occurring within the first week of life in 64% of preterms weighing < 1500g compared with 77% of preterms weighing 500-1000g at birth. Mouzinho (55) also found a consistent relationship between birthweight and the incidence of symptomatic PDA (figure 1a) in preterm infants < 1500g. Recently Koch (51) demonstrated PDA in 66% of preterm infants of birthweight less than 1000g. The results of these studies imply that birthweight may be an important factor in PDA incidence.
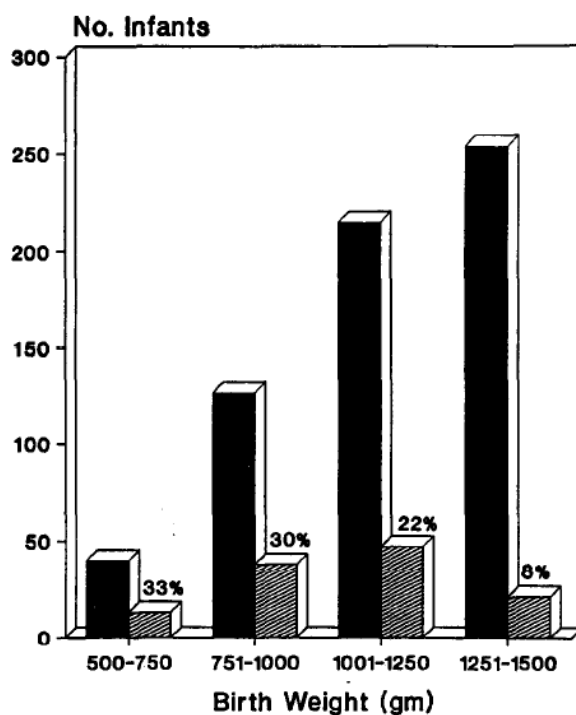
Fig. 1. Relationship between birth weight and the incidence of sPDA in infants surviving ≥ 72 h. Solid bars represent total number of infants studied and cross-hatched bars infants with sPDA.

Figure 1 a) Mouzinho (55) Reprinted with permission from Elsevier Ltd.

Gestational age

The importance of gestational age in the development of PDA has been well-established. Early illustrations of this include Burnard (56), who observed PDA occurring at greater than 2 days of life in 10% of preterm infants compared to spontaneous closure at an average of 10 hours of age in most full-term infants. Subsequently, Powell (57), Auld (58), and Danilowicz (59) reported on cases of persistent PDA in preterm infants. A similar association between decreasing gestational age and PDA was later confirmed by Mouzinho (55) (figure 1b) and this is supported by data from a recent NSW Mother's and Babies report (60) indicating 95% of infants with PDA requiring treatment were born at < 32 weeks gestation.
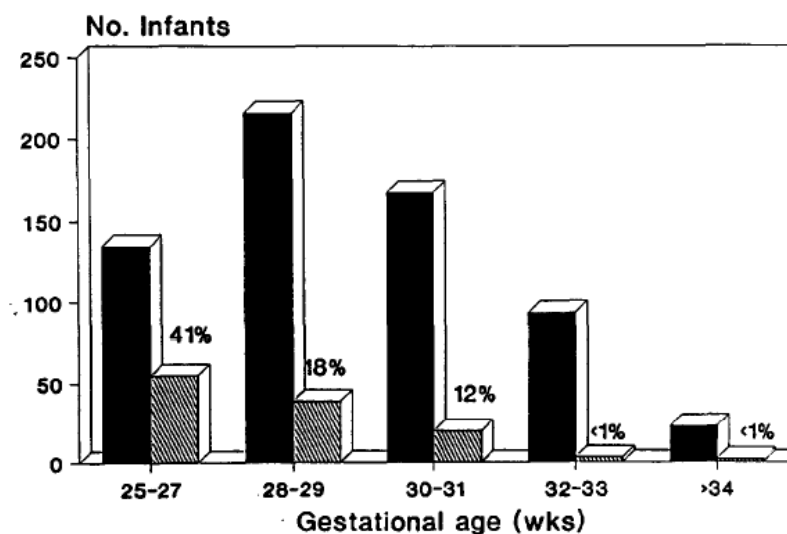
Fig. 2. Relationship between gestational age and the incidence of sPDA in infants surviving ≥ 72 h. Solid bars represent total number of infants studied and cross-hatched bars infants with sPDA.

Figure 1b). Mouzinho (55) Reprinted with permission from Elsevier Ltd.

Preterm infants have less exposure to normal physiological processes in preparation for birth than term infants. The usual fall in alveolar fluid production has not yet occurred and this in addition to surfactant deficiency may impair alveolar expansion and gas exchange resulting in ineffective respiration at delivery with increased need for resuscitation at birth (18). An association between low Apgar scores and PDA in ELBW infants in a study by Reller (49) implies a link between increased need for resuscitation and PDA development. Immaturity of mechanisms in preterm infants usually responsible for initiating respiration and transition to normal circulation at birth may increase the incidence of PDA in the postnatal period.

Gender, genetics and environment

Links between PDA and specific gender-related, genetic and environmental characteristics may offer alternative explanations for variations in PDA incidence among preterm infants.

Several studies have indicated an increased incidence of PDA in female preterm infants. Girling and Hallidie-Smith (61) found a higher incidence of PDA in female preterm infants among a case-cohort of preterm infants of similar gestational age and birthweight born at less than 35 weeks gestation with PDA or without PDA . Although Zachman (54) reported equal numbers of male and female infants with symptomatic PDA, females with PDA were 30% more likely to develop heart failure. In both studies it is possible that preterm males had a lower predisposition to symptomatic PDA and/or heart failure in association with PDA, however greater incidence of PDA in females may well have been influenced by lower numbers of male infants surviving to PDA diagnosis. Lack of reporting of differential data on mortality rates between males and females by Zachman (54) makes the effect of higher early mortality rates on gender-related PDA incidence in this study difficult to determine. In support of Zachman, Madiyono (62) found 4 times the incidence of PDA in female compared to male infants, however retrospective case selection means that exclusion of deaths prior to PDA identification potentially leading to distortion of this effect by survivor bias undermines the reliability of this finding. On the other hand, greater rates of spontaneous ductal closure associated with male compared to female gender in a prospective study by Nemerofsky (63) suggests the existence of mechanisms responsible for delayed ductal closure that are peculiar to female preterm infants. Evidence from observational studies implies that not only is PDA prevalence greater in female preterm infants, those females with PDA are more likely to develop cardiac failure than males. With the exception of the prospective study by Nemerofsky (63), PDA incidence rates may have been affected by methodological bias therefore the true incidence between males and females has not been reliably determined in these studies.

Contrary to this, other investigations suggest the existence of a genetic predisposition to PDA in male preterm infants. Lower PDA incidence was associated with presence of a specific DNA coding sequence, the "p" allele, in male preterm infants in logistic regression analyses conducted by Derzbach (64). More recently, Bhandari (65) found genetic or shared (familial) environment were the main contributors to the development of PDA following adjustment for multiple potential confounders including male gender, birthweight, RDS, gestational age, treating institution and duration of supplemental oxygen. Collectively these studies imply that individual genetic variation may independently affect PDA incidence by interfering with PGE2 and COX pathways between preterm infants sharing similar population characteristics, treatment and clinical course.

Antenatal maternal glucocorticoid therapy for threatened preterm labour

Administration of antenatal glucocorticoid therapy to women with threatened preterm labour with the aim of promoting lung maturation and surfactant production has been demonstrated in randomised trials to have efficacy in the reduction of respiratory distress, cerebrovascular haemorrhage and mortality in preterm infants. Glucocorticoid therapy may also have a role in preventing PDA by reducing the severity of respiratory distress in the immediate postnatal period as a common predisposing factor to the development of PDA. From early experimental studies, Momma (66) and Clyman (67) hypothesised that glucocorticoids mediate ductal closure by interfering with the PGE mechanism for maintaining ductal patency. In an observational cohort study by Waffarn (68), 6.5% of those preterm infants exposed to antenatal steroids developed a symptomatic PDA compared to 44% of preterm infants remaining unexposed. Similarly, an observational cohort of preterm infants with symptomatic PDA studied by Evans and Iyer (69) were less likely to have received antenatal steroids than their counterparts with an asymptomatic or closed duct. Improvements in oxygenation and lung mechanics as a result of increased lung maturation and surfactant production in response to antenatal maternal glucocorticoid administration may have a synergistic effect on ductal closure.

PDA incidence is included as an outcome in three of the randomised trials included in the systematic review of antenatal steroids vs. placebo for morbidity and mortality in preterm infants of women at risk of preterm birth by Roberts and Dalziel Stuart (70). The trial by Silver (71) demonstrated no change in incidence of PDA or RDS, whilst both Amorim (72) and Elimian (73) found a reduced incidence of PDA in those receiving antenatal steroids. Despite the existence of trials reporting on the outcome of PDA closure, successive Cochrane reviews and other systematic reviews evaluating the effect of antenatal steroids for lung maturation in preterm infants such as those by Crowley (74), Crowther (75) and Roberts (70), have not provided any recommendations arising from cumulative systematic review of the results of randomised trials on the effect of antenatal steroids on the incidence of PDA in preterm infants.

Hypoxaemia
Maintenance of the in-utero circulation during the postnatal period is also thought to be a neonatal circulatory response to ongoing hypoxaemia. In lower gestational age preterm infants, the usually rapid influx of oxygen into the alveoli at birth is limited due to poor alveolar expansion and impaired gas exchange resulting in lower oxygen content within the arterial circulation. The consequent reduction in the oxygen gradient between the arterial and venous ends of the ductus and smaller rise in arterial oxygen content is thought to lessen the stimulus for muscle contraction within the ductal intima. Hypoxemia and acidosis

stimulate pulmonary vasoconstriction decreasing pulmonary blood flow and left atrial blood oxygen return. The consequent fall in left atrial pressure allows blood to be shunted from the right to the left atrium across the foramen ovale. Blood is shunted from right to left from the pulmonary artery across the PDA and directly into the aorta (76).

Peripheral vascular resistance increases in response to hypoxia, resulting in the preferential perfusion of the head and heart. Blood pressure is maintained by increasing heart rate and therefore cardiac output; however such compensatory mechanisms are limited (23). In this way, blood continues to flow across the ductus arteriosus, initially from right to left as in foetal circulation, however a change in the direction of blood flow frequently occurs. Change in shunt direction from left to right is thought to occur due to the movement of blood from an area of high systemic resistance (SVR) in the aorta toward an area of low pulmonary vascular resistance (PVR) in the pulmonary artery with resolution of respiratory distress in the first few days of life (77). Contrary to this theory, Evans , Iyer (78) and Kluckow (79) propose that left to right shunting may occur despite the presence of increased PVR. High afterload secondary to increased SVR opposes the flow of oxygenated blood from the left ventricle into the descending aorta, resulting in the reversal of blood flow from left to right along the ascending the aorta, across the PDA, and into the pulmonary artery (78, 79). Movement of blood back up into the ascending aorta and across the PDA during diastole further reduces lower limb perfusion. The consequent increase in pulmonary artery blood flow is thought to contribute to pulmonary vascular engorgement, alveolar interstitial oedema and decreased gas exchange (80, 81). Ongoing hypoxaemia may reduce the difference in oxygen tension between the aortic and pulmonary arterial ends of the ductus arteriosus, removing what is usually a strong stimulus for ductal closure (refer to Section 1 the ductus arteriosus: In utero and intrapartum transition to normal circulation).

Respiratory Distress Syndrome
Hypoxaemia and acidosis resulting from respiratory distress syndrome (RDS) may predispose to PDA in preterm infants (82). Respiratory Distress Syndrome (RDS) is common in lower gestational age preterm infants and is characterised by surfactant deficiency and immature lung development (23, 83). Surfactant, a phospholipid substance responsible for reducing the alveolar surface tension in mammals, resists the collapsing forces exerted by the elastic recoil of the alveolar wall at end expiration (23). Surfactant production is reduced in lower gestational age preterm infants due to the presence of fewer and less functional type II cells lining the terminal bronchioles and alveoli. To initiate alveolar opening during respiration, the preterm infant has to generate higher transpulmonary opening pressures (23). The preterm infant addresses this by increasing both respiratory effort and rate,

however the ability to maintain gas exchange with respiratory compensation is limited by the compliant state of the chest wall acting to disperse the increased effort, a problem which is accentuated with decreasing gestational age (23). Lung immaturity impacts on the functional ability of the lungs of the preterm infant to participate in gas exchange (23). Alveoli and terminal bronchioles are also fewer in numbers and not yet fully formed in preterm infants and this reduces the surface area for gas exchange (23). The combination of surfactant deficiency and lung immaturity causes overdistention and collapse of normal alveoli compared to the slower filling, surfactant-deficient alveoli resulting in patchy atelectasis (23). Loss of alveolar elasticity from overdistention and collapse reduce compliance and produce uneven ventilation perfusion (V/Q) ratios due to alveolar capillary membrane (ACM) perfusion combined with insufficient alveolar gas exchange (23, 84) .This is referred to as "intrapulmonary shunting" (23, 84).

Progressive alveolar collapse, reducing compliance and worsening V/Q shunting with severe RDS contribute to failure of limited compensatory respiratory responses and hypoventilation. Partial to complete closure of alveoli during tidal respiration from alveolar collapse and hypoventilation increases V/Q shunting, exacerbating hypoxia and carbon dioxide retention (84). Alveolar atelectasis is responsible for the classic "ground-glass" or more severe "white-out" appearance on the CXR (84). Severe hypercarbia and hypoxaemia cause pulmonary vascular vasoconstriction which increases pulmonary vascular pressure (PVR) leading to right to left shunt of blood away from the pulmonary circulation across the foramen ovale and ductus arteriosus (84). Local ischaemia, worsened by the reduction in pulmonary blood supply from vasoconstriction and shunting, exacerbates alveolar and capillary epithelial damage. Pulmonary oedema is created by fluid movement into the alveolar space in response to high intra-pleural pressures generated by the respiratory effort and commonly occurring low serum protein of the preterm infant (23). Hyaline membranes form within the alveoli from the binding action of fibrin. The name "hyaline membrane disease" (HMD) originated from the pathological appearance of these hyaline membranes on X-Ray investigations; this condition is now more commonly known and referred to as respiratory distress syndrome (RDS) (23). Alveolar fluid and the hyaline membrane interfere with gaseous diffusion by increasing the diffusion distance and reducing the total lung surface area available for gaseous exchange (23). Oxygenation is progressively reduced leading to hypoxaemia and metabolic acidosis as a result of lactic acid produced by anaerobic cellular metabolism (84). Respiratory acidosis may develop secondary to the exhalation of lower amounts of carbon dioxide from ineffective gas exchange (84). Hypoxaemia may oppose ductal closure by reducing the difference in oxygen tension between the aortic and

pulmonary arterial ends of the ductus arteriosus, increasing pulmonary vascular resistance and maintaining ductal blood flow.

Observational studies support the tendency for PDA and RDS to co-exist in preterm infants. In separate studies, Girling and Hallidie-Smith (85) and Neal (48) noted increased PDA incidence in preterm infants with RDS which they theorise may contribute to delayed PDA closure in the preterm infant. Later studies by Reller (86) and van de Bor (87) demonstrate consistency with these findings. The majority of older gestational age preterm infants (87.5%) without RDS studied by Reller (88) underwent ductal closure by day 3 of life. Perhaps this represents the "normal" pattern of ductal closure in preterm infants without RDS as a potential contributing factor in delayed ductal closure. On the other hand, normal PDA closure in the absence of RDS does not adequately describe the temporal nature of the relationship between RDS and PDA.This renders the determination of the precise contribution of RDS to PDA and vice versa from observational studies difficult and subject to error. The potential contribution of PDA to RDS is discussed in further detail in Section 3 Pathophysiology attributed to PDA, PDA and pulmonary dysfunction, 1) Respiratory Distress Syndrome (RDS).

Alteration in prostaglandins mechanisms

Failure of functional closure
Altered prostaglandins secretion is thought to be an important mechanism in the failure of functional closure of the PDA in preterm infants. Coceani (89) initially suggested that ductal patency is a consequence of ductal muscle relaxation by prostaglandins and an apparent lack of responsiveness of the preterm ductus to oxygen. This finding was supported by Clyman (90) who further concluded that the preterm ductus was more sensitive than the term ductus to the relaxant effects of PGE2. Later, Coceani observed that preterm infants had higher levels of PGE2 produced locally in the ductus than term infants. Continued sensitivity of the preterm ductus to the relaxant effect of locally produced PGE2 may offer an explanation for postnatal failure of functional PDA closure.

Failure of anatomic closure
The inability of the ductus arteriosus in preterm infants to respond to the normal mechanisms of functional closure during transition to normal circulation is an important factor in the failure of anatomic closure and susceptibility to reopening following pharmacological treatment. Clyman (41) proposes that failure of anatomic closure stems from the resistance to the development of hypoxia during the transitional period with failure of initial constriction due to a smaller post-birth rise in arterial oxygen. The ductus arteriosus of preterm baboons

studied by Clyman (41) became only mildly hypoxic following birth compared to those of the full term baboons in which intense hypoxia developed in the ductus prior to closure. Signs of anatomic closure including endothelial proliferation, neo-intimal thickening and VEGF expression were absent in preterm baboons studied in the first week of life, even those in with evidence of ductal constriction. As VEGF regulation of endothelial deposition is dependent upon the generation of hypoxia within the ductal muscle media, Clyman (41) theorises that failure of the preterm infant to develop a sufficient level of hypoxia within the ductal tissue interferes with VEGF modulated narrowing of the ductal lumen. This results in failure of anatomic closure and increased likelihood of ductal reopening even in those lower gestational age preterm infants having achieved functional closure. Eventual anatomic closure of the PDA relies on multiple factors affecting the ability of the preterm infant to maintain sufficient arterial oxygenation including gestational age, need for resuscitation, and severity of RDS.

Other factors affecting spontaneous PDA closure
Other factors implicated in association with PDA in preterm infants include infection, fluid overload and phototherapy.

Fluid Overload
Fluid overload of preterm infants is theorized to increase the volume of left to right shunt resulting in increased incidence of PDA and exacerbation of PDA related heart failure. A Cochrane systematic review of the effect of high vs. low fluid intake on morbidity and mortality in preterm infants by Bell and Acarregui (91) indicated a statistically significant reduction in the incidence of PDA and NEC in association with restricted fluid intake. A recent observational study by Stephens (92) also indicated an increased incidence of PDA in association with fluid intake greater than 170mL/kg/day in the first few days of life. Fluid overload may increase PDA incidence by increasing cardiac congestion; however randomised trials have not so far demonstrated a difference in the risk of mortality, respiratory and neurological outcomes in association with preventative measures such as fluid restriction.

Phototherapy
Phototherapy has been associated with increased PDA incidence in low and extremely low birthweight infants and was initially thought to be a potential contributor to failure of spontaneous ductal closure. Ductal relaxation was greater in response to progressive light exposure in an experimental study comparing immature with mature lamb ductal rings by Clyman (93). He noted greater ductal relaxation in response to progressive light exposure

and PDA incidence was also greater in unprotected preterm infants exposed to phototherapy in a randomised trial of chest shielding to prevent PDA by Rosenfeld (94). The validity of the results of this study have since been questioned secondary to low diagnostic certainty associated with the accuracy of the methods used to detect PDA. An association between PDA and phototherapy was also found in a retrospective cohort study by Barefield (95). Fifty percent of preterm infants exposed to phototherapy had reopening of a PDA in a prospective study of 27 preterm infants by Benders (96) in the absence of a control group. Contrary to the results of earlier studies, a more recent randomised trial conducted by Travadi (97) found no difference in ductal diameter between treatment groups, leading to the conclusion that there is no difference in PDA incidence between preterm infants with or without chest shields and receiving phototherapy. Use of a proper randomisation sequence, blinding of those performing and reporting of echo assessments and the use of 2D echo to establish the size of PDA shunt by Travadi (97) may account for the marked difference between its findings and those of earlier studies, however there remains a possibility that the sample size in this study was insufficient to demonstrate a difference. There is little good quality recent evidence from these studies to suggest that phototherapy increases the incidence of PDA.

PDA diagnosis

Clinical signs
Hubbard (98) described the presence of a systolic murmur in association with a persistent PDA as a diagnostic sign of blood flow through the open ductus. Systolic murmur of "uneven intensity" heard at the upper left sternal border and bounding pulses were described in association with PDA by Prec (99), Neal (48), Thibeault (81) and Cotton (100).

At the same time, increased pulmonary venous congestion in association with a PDA may increase atrial filling pressures and left ventricular volume. Studies of LV function by Clyman (101) and Shimada (102) indicate that the immature heart of preterm infants is compliant and the atria dilate readily in response to the larger circulating blood volume, initially responding with a rise in cardiac output, however this compensatory mechanism only lasts for a few days. Clyman (101) suggests that the left ventricle is relatively less compliant, with small increases in left ventricular (LV) volume leading to large increases in pressure further contributing to pulmonary venous congestion (98). Left to right shunting of blood across the PDA with overloading of the pulmonary circulation theoretically contributes to increased LV volume. Falling systemic blood volume due to the presence of a large PDA is thought to result in inadequate tissue perfusion with metabolic acidosis frequently preceding signs of LV dysfunction. An increased LV "impulse" or "3rd heart sound described by Zahka and Erenberg (103)and commonly referred to as a "hyperactive praecordium" arises from the increased LV volume. Persistent Congestive Heart Failure (CHF) and RDS are important factors in the development of persistent PDA. Despite this, the association between clinical manifestations arising from these conditions and the presence of large ductal shunting in the first few days of life has since been questioned.

Clinically vs. echocardiographically detected PDA
Diagnostic criteria used for PDA have gradually shifted over the last 3 decades from reliance on the appearance of clinical manifestations to the incorporation of these with echocardiographic detection, to using echo detection alone. Several key findings were responsible for these changes.

Firstly, retrograde aortography examination of PDA by Thibeault (81) indicated that large left to right shunting can occur in the absence of the characteristic murmur meaning that it may remain undetected in some infants. On the basis of similar findings of PDA shunting in the absence of clinical signs commonly associated with a diagnosis of PDA including murmur, hyperactive precordium and bounding pulses. McGrath (104) named this phenomenon the "silent ductus'. In addition to using aortography to compare ductal shunting levels with

clinical signs, McGrath (104) used M-mode echocardiography to study the effect of the level of PDA shunting on heart function and the accuracy of left atrial to aortic root (La/Ao) size expressed as a ratio, to determine the degree of left atrial dilatation as a measure of the magnitude of left to right shunt across a PDA. Elevated La/Ao ratios consistent with shunting via a PDA on contrast aortography were established in 15% of preterm infants in the absence of clinical signs. The ability of the La/Ao ratio measurements to predict the magnitude of a PDA with respect to the level of ductal shunting was limited since only those infants with elevated La/Ao ratios on M-mode echocardiography were examined for the presence and level of ductal shunting using contrast aortography.

The findings of Thibeault (81) and McGrath (104) are supported by those of Valdes-Cruz (105) in which only 72% of prospectively studied infants shunting via a PDA were correctly identified using clinical signs. An entire study cohort was assessed using both clinical and echocardiographic criteria and presence of a PDA confirmed by contrast aortogram.This allowed comparison between the accuracy of clinical and echocardiographic criteria in detecting the existence of a large, small or closed duct. Echocardiographic parameters including determinants of cardiac output such as left ventricular pre-ejection/ejection time and La/Ao were even less specific than clinical signs, identifying the presence of left to right shunt in only 51% of cases. Sixty-six percent of ELBW to VLBW preterm infants in a cohort study by Reller (49) had early increases in La/Ao ratio reflecting left sided cardiac enlargement and impaired heart function occurring in the absence of murmur. Reller referred to PDA defined by these echocardiographic criteria and commonly occurring in the absence of clinical signs as "haemodynamically significant PDA" (HsPDA). Neither Valdes-Cruz nor Reller assessed the magnitude of shunt across the PDA or PDA size with aortography and Doppler angiography was not available at that time. The validity of Reller's comparison between echocardiographic criteria and clinical signs in relation to the level of ductal shunting and the size of the duct is questionable as ductal size or shunt were not confirmed. Separate use of echocardiographic parameters such as La/Ao ratio obtained using M-Mode echocardiography, and clinical signs such as continuous murmur may have low diagnostic accuracy in detecting ductal shunting. Combining echocardiographic evidence of cardiac enlargement and clinical criteria is likely to increase the specificity of these criteria in identifying the presence of ductal shunting.

Secondly, investigators such as Mellander (106), comparing the diagnostic accuracy of clinical and echocardiographic criteria found that clinical signs associated with symptomatic PDA may develop an average of 2 days after the commencement of left to right shunt. Similarly, Skelton (107) in a larger, blinded study, found that echocardiographically proven

HsPDA preceded the development of clinical signs by up to 4 days. Although the presence of a systolic murmur was greatly predictive in terms of sensitivity for ductal shunting from day 2 of life, a high number of false positives for the presence of murmur in preterm infants with a small or closed ductus demonstrated that this sign has poor specificity for the level of ductal shunting. In support of Reller's earlier investigations, Skelton again found the absence of murmur to be poorly predictive of the degree of ductal shunting. Evans and Archer (108), challenged traditional thinking regarding the direction of ductal shunting in the immediate postnatal period, using doppler echocardiography to demonstrate that left to right and bidirectional shunting across a PDA commonly occurs in preterm infants within the first 3 days of life, approximately 1 to 2 days earlier than originally conceived. Previous conceptions of the existence of high pulmonary artery pressures resulting from HMD (RDS) opposing left to right ductal shunt in preterm infants in the first days of life have also been contradicted by Evans and Archer's (108) findings. Wide variation in mean pulmonary artery pressures with a proportion of values falling within the normal range, led Evans and Archer (108) to conclude that although there were some sustained elevations in mean pulmonary artery pressures in preterm infants with HMD after 15 hours of life the presence of HMD does not necessarily imply an elevation in pulmonary artery pressure. These findings underscore the potential for early left to right ductal shunting in the presence of HMD in the absence of clinical signs. The implications of these studies are that early echocardiographic screening is required to detect ductal shunting in the absence of murmur; and although HsPDA was noted to be more prevalent in preterm infants with RDS, the importance of echocardiographically determined HsPDA to the clinical course of the preterm infant remains largely theoretical.

Finally, Kluckow (109) and Evans (110) correlated ductal diameters ≥ 2mm with subsequent development of symptomatic PDA, particularly in extreme preterm infants. The improved predictive ability of echocardiographic measurements compared to clinical signs in the determination of early ductal shunting and cardiac dysfunction associated with PDA raises questions regarding the effectiveness of PDA detection using a combination of echocardiographic criteria and/or clinical signs. More importantly, the question to be answered is whether treatment based on PDA detected using echocardiography, clinical signs or a combination of both, improve clinically important outcomes including mortality, respiratory, neurological, and gastrointestinal morbidity in preterm infants.

Spontaneous PDA closure in preterm infants

The natural history of PDA and spontaneous ductal closure in preterm infants has not been well described with early research focussed on describing the manifestations of PDA and possible links with respiratory distress syndrome (RDS). Although spontaneous closure was reported, for instance the majority of preterm infants examined in a case series by Powell (57) underwent spontaneous ductal closure between 1 to 16 weeks of life, early studies of spontaneous closure in preterm infants were generally lacking in detail and focussed on different PDA management approaches. One of the few original studies evaluating spontaneous PDA closure in preterm infants in the absence of any treatment to close the duct, by Girling and Hallidie-Smith (61), found that twelve out of sixteen preterm infants born at gestational ages 28 - 35 weeks with a systolic murmur attributed to symptomatic PDA underwent spontaneous closure of the ductus at 11 to 112 days of life. Considering PDA incidence is inversely proportional to gestational age, inclusion of preterm infants to 35 weeks gestation is likely to have increased the rate of spontaneous closure, an effect supported by the results of Neal's (111) investigations. Despite some reservations regarding the impact of increased RDS severity, Thibeault (81) concedes that spontaneous closure may occur in preterm infants born at gestational ages as low as 25 weeks. Later studies by Reller (112) also linked high rates of spontaneous closure with older gestational age, with 89% of preterm infants born at 30-37 weeks gestation undergoing spontaneous ductal closure by day 4 of life. Likelihood of spontaneous PDA closure has also been linked with RDS severity. Thibeault (113) found that preterm infants of gestational ages 24-34 weeks with mild or no RDS underwent spontaneous closure within 48 hours of birth. These studies indicate that spontaneous PDA closure rates are higher in preterm infants born at gestational ages greater than 30 weeks with mild or no RDS,

Another important factor in the analysis of the spontaneously closing duct includes the accuracy with which PDA is initially and subsequently detected. Clinical signs have low sensitivity and specificity to guide detection of large left to right PDA shunting, therefore studies such as those by Powell (57) and Girling and Hallidie-Smith (61) which used clinical signs to assess the presence of PDA are likely to have included a proportion of preterm infants without large diameter PDA or any PDA at all. Leatham (114) who studied phonographic recordings of systolic murmurs proposed that small ducts frequently produce the loudest audible murmurs. Inclusion of preterm infants in the symptomatic PDA group on the basis of a murmur alone may have led to misclassification of those preterm infants with small or closing ducts. This may have altered the rate of closure among those preterm infants diagnosed as having symptomatic PDA. Likewise, omission of preterm infants with large ductal shunting in the absence of murmur from the symptomatic PDA group in whom clinical signs were absent may have led to an apparent increase in the rate of spontaneous

PDA closure. The true rates of spontaneous closure in preterm infants with a symptomatic PDA are difficult to determine from earlier studies due to reliance on the presence of a murmur for PDA diagnosis, a clinical sign found to be poorly predictive of the level of PDA shunt.

Widespread use of surgical and pharmacological treatment to close the duct has limited the period in which modern studies may investigate spontaneous closure in preterm infants. For instance in an examination of spontaneous closure rates among preterm infants by Narayanan (115), the average age at treatment was no greater than 3 days of life for the most conservative randomised pharmacological treatment approach. Spontaneous PDA closure rates within this intervention group increased in direct proportion with gestational age. Thirty-one percent of preterm infants born at 26-27 weeks gestation underwent spontaneous closure compared to 21% of preterm infants born at 24-25 weeks gestation. In comparison, 44% percent of preterm infants born at a mean gestational age of 28-29 weeks had spontaneous PDA closure at 7 days of life in a randomised study of early vs. late indomethacin intervention to close a PDA by Van Overmeire (116). The inclusion of older gestational age preterm infants (29-31 weeks) in the Van Overmeire trial may partly explain the comparative increase in spontaneous closure rates between studies, however, the longer period allowed for PDA closure may also be a factor. Thirty-four percent of preterm infants born at less than 28 weeks gestation underwent spontaneous closure by 7 days of life in a similar study by Koch (51). In this study, regression analysis indicated that the variables levels of respiratory disease and receipt of antenatal steroids were highly predictive of higher rates of permanent spontaneous closure in ELBW neonates within the first week of life. Nemerofsky (63) found birthweight > 1000g and male gender was associated with spontaneous PDA closure in 49% of conservatively managed preterm infants by day 7 of life. These findings imply that even in lower birthweight and gestational age preterm infants, the likelihood of spontaneous PDA closure is increased by improved oxygenation as a result of less pre-existing respiratory disease combined with increased lung maturation mediated by antenatal steroids. These studies favour the allowing a period for the occurrence of spontaneous closure.

Section 3 Pathophysiology attributed to PDA

PDA and the cardiovascular system

Cardiac failure has been associated with higher levels of left to right ductal shunting in case studies examining the impact of PDA on left heart dimensions and function. Silverman (117) found a correlation between left atrial dilatation in preterm infants with PDA and left to right shunt and clinical signs of cardiac failure using (La/Ao) ratio, as an index of left atrial size to measure the effect of PDA shunt on the heart function. Increased left atrial and left ventricular dimensions were similarly found by Baylen (118) in a larger study of preterms with PDA and RDS in comparison to an untreated non-PDA control group. In addition, preterm infants with PDA had increased myocardial contractility indicated by greater percent shortening of the left ventricular myocardial fibres, which may reflect an increase in cardiac output compared to preterms without PDA. Baylen (118) proposes that this increase in contractility might reflect an attempt to compensate for a reduction in afterload arising from low blood flow due to the PDA shunting, or low systemic vascular resistance (SVR). Baylen's conclusions are supported by those of Halliday (119) who investigated the effects of PDA on myocardial contractility in a small cohort of preterm infants less than 27 weeks of age. Halliday (119) theorised that cardiac output increases in response to an elevation in LV preload as a consequence of left to right shunting via a large PDA , forming part of a compensatory mechanism to improve systemic blood flow. From this it was thought that PDA may have a compensatory role in the preservation of cardiac function in the preterm infant with immature cardiac function and low systemic vascular resistance during transition to normal circulation. Barlow (120) opposes this view, asserting that cardiac output remains unaltered in preterms with PDA despite enlarged left ventricular dimensions. Barlow (120) goes on to suggest that preterm infants have a higher resting myocardial contractility than term infants and that raised preload from HsPDA does not increase cardiac contractility. Limitations common to all these studies include; small groups of preterm infants that may not represent a wide spectrum of presentations, failure to adequately consider the impact of differences in respiratory severity and cardiac dynamics as a function of changing pulmonary vascular resistance (PVR) and inclusion of preterm infants of widely ranging postnatal ages and gestational ages. With the exception of Barlow (120), these studies were unable to demonstrate the magnitude of the ductal shunting via the PDA in relation to the degree of cardiac failure and attempted cardiac compensation. Study findings are contradictory and as discussed in Section 2 Clinically vs. echocardiographically detected PDA, the clinical relevance of cardiac indices such as La/Ao in relation to the importance of PDA-related pathophysiology have since been questioned. Ductal shunting may occur in response to high

SVR as a mechanism for increasing preload and myocardial contractility. Earlier studies suggest that PDA may have a role in adaptive responses to cardiac and vascular immaturity in the first few days of life however more recent findings incorporating assessment of ductal shunting oppose this theory.

Shunting via a large PDA has been associated with an effect on systemic blood flow and blood pressure in a number of echocardiographic studies incorporating the use of newer two dimensional (2D) techniques enabling direct assessment of shunt waveforms. Shunt across the PDA was described in an early study by Lundell (77) as initially bidirectional; with right to left flow across the PDA in systole changing to left to right flow in diastole. Left to right shunt is thought to result in a steal of blood from the systemic circulation. This is described as the movement of blood upwards along the descending aorta across the PDA and into the pulmonary artery. This is thought to occur due to increased aortic pressure created by the ejection of blood into the aorta from the left ventricle during systole. From his findings of preferential arterial blood flow to the head and neck associated with both directional shunts, Lundell theorised that systemic steal and shunting of blood away from the lower body in preterm infants with large PDA and CHF may lead to intestinal ischaemia, which may be a factor in the development of necrotising enterocolitis. Lundell's (77) theories relating to systemic steal are supported by the findings of Evans and Kluckow (79) who further proposed that shunting of blood from left to right across a widely patent ductus arteriosus in extremely low birthweight preterm infants may result in an early, rapid fall in systemic pressure accompanied by elevated pulmonary vascular pressure. This is in contrast to Ratner's (121) earlier proposition that VLBW preterm infants may compensate for PDA with large left to right shunt by maintaining arterial pulse pressures similar to control infants without PDA. Evans and Moorcraft (122) similarly compared BP in the first week of life between low birthweight infants with HsPDA classified according to ductal status on daily echocardiography and infants without HsPDA. Systolic and diastolic BP were lower in preterm infants with HsPDA, however infants in the <1000g subgroup with HsPDA maintained higher BP measurements tending to decrease at around 3 days of life. Evans and Moorcraft (122) suggest that the ability of ELBW infants to maintain BP in the initial postnatal period stems from an increase in cardiac output in response to low systemic vascular resistance occurring as a by-product of left to right shunt of blood across the PDA. Subsequent falls in BP were attributed to failure of compensation mechanisms resulting from the inability of ELBW infants to maintain a sustained high output state for a prolonged period. Recent investigations of LV function by Osborn (123) indicate a significant association between low superior vena cava (SVC) blood flow and parameters including; immaturity, large diameter PDA at 12 hours, and high mean airway pressures at 3 hours in the first few

hours of life. Preterms with low SVC flow also had greater upper body SVR, elevated PVR and poor myocardial contractility in the first 3 hours of life. Osborn suggests that the immature myocardium of preterm infants is unable to maintain left ventricular velocity of contraction against the high afterload encountered in the period following birth leading to the development of a low systemic blood flow state. Left to right shunt via a PDA may affect systemic arterial and venous blood flow; however there is some disagreement regarding the response of preterm infants to a possible drop in systemic blood volume, with some suggesting early, sustained hypotension whilst others support the existence of compensatory mechanisms for BP maintenance in the first few days of life.

PDA and pulmonary dysfunction

Respiratory Distress Syndrome (RDS)

As described in Section 2 Patent Ductus Arteriosus, Respiratory Distress Syndrome (RDS) initially develops from surfactant deficiency and lung immaturity with decreasing gestational age, resulting in alveolar atelectasis, pulmonary oedema, and lung tissue injury. Loss of alveolar surface area for gas exchange from alveolar collapse, thickening and injury results in mismatching of the ventilation to perfusion ratio, hypoventilation and inability to maintain normal gaseous exchange.

PDA is commonly observed in preterm infants with RDS. On the other hand, respiratory distress often appears to worsen following PDA diagnosis. Theoretically, increased pulmonary venous flow from a large left to right PDA shunting may lead to pulmonary engorgement. Fluid movement from the vascular space into the alveoli as a result of increased pulmonary pressure interferes with oxygen and CO_2 exchange resulting in worsening hypoxemia and hypercarbia exacerbating RDS and resulting in increased need for ventilation. The simultaneous presence of RDS and PDA in ventilated preterm infants was described in early case reports by Siassi (124). Subsequent investigations implicated PDA as a factor in the development and/or exacerbation of RDS. Preterm infants with severe RDS were noted by Thibeault (81) to have earlier onset of cardiomegaly in addition to left to right ductal shunting associated with clinical signs of heart failure. Similar associations were found by Neal (48) and confirmed in a later study by Thibeault (113). Cotton (100) linked clinically identified PDA with increased requirement for ventilation, risk of CLD and death. Age at extubation correlated with age at clinical evidence of resolution of sPDA and from this it is presumed that PDA resulting from the development of a large left to right shunt of blood from the aorta across the PDA into the pulmonary artery has a role in the development and worsening of RDS. Greater requirement for IPPV was also found in preterm infants with both RDS and PDA, studied by Jacob (125), compared to those with RDS alone. Preterm infants

with both RDS and PDA were also smaller and less mature, a predisposing factor common to both conditions. Increased need for ventilation in ELBW preterm infants with RDS and HsPDA was also indicated in the study by Reller (49) with a greater proportion of ventilated preterms having significant left to right PDA shunt. Together these studies indicate that RDS and large PDA coexist, however the individual contribution of these conditions to ventilation requirements are not clear.

The risk of increased need for ventilation associated with PDA in the observational studies in the previous paragraph may have been distorted by differences in RDS severity between PDA and non-PDA comparison groups. Differences in RDS severity between PDA and non-PDA groups in the studies by Cotton (100), Jacob (125) and Reller (49), in addition to high rates of surgical intervention provided to the infants with persistent PDA in Cotton's study may have distorted risk estimations of need for ventilation. If RDS is more prevalent in preterm infants in the PDA group and RDS increases need for IPPV independently of PDA status, uneven distribution of RDS severity between PDA and non-PDA comparison groups may have confounded the effect of PDA on this outcome. As greater RDS severity often increases the need for ventilation, confounding by RDS severity is likely to overestimate this risk in preterm infants with PDA. Confounding by RDS severity was less likely to have affected the results of a study of VLBW preterm infants by Evans and Iyer (69) in which RDS levels were similar across the cohort. Increasing ductal shunting levels had a negative effect on gas exchange as reflected in the lower mean oxygen indices; however, time on ventilation and oxygen requirement did not vary. This supports RDS severity as a potential confounder in the previous studies of PDA incidence in association with the need for ventilation. RDS may have confounded or modified the relationship between PDA, RDS and clinically relevant outcomes such as length of ventilation, and oxygen, and longer term outcomes including CLD and mortality. Whilst it is likely that there is an association between PDA and RDS, existing observational studies do not demonstrate whether PDA worsens RDS, RDS keeps the PDA open, or a combination of both. Although it remains possible that PDA has an influence on short term respiratory outcomes, the separate contribution of RDS and PDA to these and longer term respiratory outcomes such as CLD and mortality remain difficult to determine from these observational studies. A question to be answered concerns whether one precedes the other or both are equally implicated in pathophysiology.

Bronchopulmonary dysplasia (BPD)/Chronic lung disease (CLD)
Bronchopulmonary dysplasia (BPD) is a term originally used by Northway (126) to describe ongoing damage to the lung resulting from prolonged exposure to positive pressure ventilation (PPV) and high oxygen levels in preterm infants with severe RDS. Northway (126)

defined four stages of BPD occurring in the first 30 days of life: initial respiratory distress, progressive radiographic changes including lung opacification, increasing areas of radiolucency and strands of radiodensity.

Criteria defining BPD and disease concepts have changed since the condition was first described in preterm infants. Bancalari (127) added the following indicators of respiratory failure to Northway's (126) definition; need for IPPV within the first 3 days, continued respiratory symptoms and oxygen dependency in the neonatal period. Shennan (128) demonstrated that the diagnostic criteria of BPD as continued oxygen requirement at 28 days of life compared to 36 weeks corrected age in very preterm infants to be a poor predictor of longer-term respiratory outcomes. The term chronic lung disease (CLD) has replaced BPD which Jobe (129) suggests is characterised by a milder course of respiratory illness from reduced exposure of preterm infants to high airway ventilation pressures and oxygen due to the use of surfactant, antenatal steroids and caffeine for apnoea. According to Rojas (130), in recent times the need for respiratory support in preterm infants more commonly results from apnoea secondary to brain stem immaturity and increased respiratory effort from lung immaturity. Gentler modes of ventilation and the use of nasal-prong CPAP are associated with lower risk of barotrauma. The main pathophysiology associated with CLD is thought to occur due to inflammation as a result of acute lung injury from prolonged ventilation, over-ventilation, hyper-oxygenation, infection and oedema. Airway damage, vascular injury and disruption of lung development lead to airway obstruction, alveolar emphysema, atelectasis, pulmonary edema, pulmonary hypertension, fibrosis and a reduction in the number of alveoli and capillaries. CLD may range from mild to severe and in severe cases is frequently characterized by high airway resistance and reduced lung compliance in the first week of life (131).

A role for PDA in the exacerbation of CLD has been suggested in observational studies. Theoretically, prolonged ventilation and oxygen occurs secondary to pulmonary oedema and impaired gas exchange from increased pulmonary blood flow via ductal shunting (80, 81, 124). Cardiac failure may contribute to pulmonary vascular congestion, exacerbating pulmonary oedema and reduced cardiac output from left to right shunt and poor systemic circulation. Impaired gas exchange and poor systemic circulation may both contribute to hypoxemia with increased need for ventilation. Reller (49) associated PDA with increased risk of CLD at 28 days of life. Odds of CLD were six fold in infants with clinical signs of PDA [OR 6.2 (2.1, 18.4)] compared to those without signs of PDA prospectively studied by Rojas (130). Other factors associated with increased odds of CLD identified by Rojas (130) included lower gestational age and sepsis. Rojas (130) did not confirm all cases by

echocardiogram and all infants with PDA received indomethacin treatment. Considering that some clinical signs have been found to have low sensitivity in detecting PDA, failure to confirm all cases of clinically identified PDA on echocardiogram may have led to some infants with small or no PDA receiving treatment. Indomethacin treatment to close the duct was not examined as a potential confounder or effect modifier in the models examined in logistic regression analyses despite the possibility that indomethacin treatment may have an effect on risk of CLD that is independent of the influence of symptomatic PDA. CLD diagnosis in both studies was based on Bancalari's (127) definition of oxygen requirement at or beyond 28 days which, according to Shennan's (128) definition, may be poorly predictive of poor longer term respiratory outcomes. In a retrospective study by Akram Khan (132), preterm infants developing CLD at 36 weeks postmenstrual age tended to be of lower birthweight and gestational age and have apgar < 5 at 1 minute whilst the presence of PDA and sepsis both increased the odds of CLD. Preterm infants with CLD in this study shared characteristics common in the development of both PDA and RDS. It is possible that increased illness severity associated with RDS and other risk factors including lower gestational age, need for resuscitation at birth, hypoxia and sepsis predisposed some preterm infants to the development of CLD. PDA may also be a factor; however, yet again the relationship between RDS and PDA makes it difficult to determine the role of each with respect to longer term respiratory outcomes such as CLD.

PDA and the preterm brain

Intraventricular haemorrhage (IVH) is common in preterm infants, with up to a third of cases occurring in the antenatal and intrapartum period. The majority of postnatal acquired cases of IVH cases occur in the first few days, and rarely after the first week of life. IVH detected in 36% of preterm infants born at less than 34 weeks gestation studied by Levene (133), occurred in 78% of cases within 72 hours of life. Dolfin (134) reported similar rates. Ment (135) detected IVH in preterm infants from 6 hours of life, with 74% of cases occurring by the 30th hour of life. Beverley (136) similarly reported IVH in 26% of preterm infants with 50% of cases occurring within the first 8 hours of life and a twofold incidence in preterm babies of birthweight < 1500g. Early IVH incidence is further supported by Ment (137) who found the greatest IVH incidence in preterm infants within the first 24 hours of birth and rarely after 4-5 days of life. Considered together these data indicate that the majority of postnatal IVH incidence in infants of lower gestational ages occurs within the first 2-3 days of life and uncommonly after the first week.

The preterm brain is poorly developed; with an immature vascular structure, particularly at the site of cortical integration with the vascular network. The fragile brain is theoretically exposed to greater risk of impaired cerebral blood flow (CBF) regulation and IVH. According to Volpe (138), the ventricular germinal zone and the adjacent germinal matrix within the sub-ependymal region of the brain are key sites of neuronal proliferation within the developing nervous system of the preterm infant. Hambelton and Wigglesworth (139) and Wigglesworth and Pape (140) describe the network of small arteries, capillaries and veins supporting the cerebral vessels within the germinal layer as "poorly developed" and possessing a "simple endothelial wall". Adequate cerebral blood flow is usually maintained by cerebral auto regulation, which alters blood vessel diameter and cerebrovascular resistance in response to metabolic changes such as oxygen and carbon dioxide concentration. Wigglesworth and Pape (140) propose that factors such as hypotension hypoxia, hypercarbia and acidosis may result in impairment of cerebral autoregulation leading to failure of cerebral autoregulation and this may lead to vasodilation and increased cerebral blood flow. This may place stress upon the fragile capillary bed of the germinal matrix, exposing it to greater risk of rupture and subsequent haemorrhage within the ventricular system of the brain. At the other extreme, hypotension with the additive effect of constriction secondary to hypocarbia and hyperoxia may result in ischaemic injury. Merging of the periventricular capillary bed with extension of the arterial networks into the cerebral cortex as gestation approaches term is thought to reduce this risk (138).

Exposure of the cerebral circulation to changing systemic blood pressures combined with impaired auto-regulation of CBF is thought to be central to the pathophysiology of IVH in the preterm infant. Considerable variation in CBF in response to spontaneous changes in blood pressure in preterm infants with hypoxemia and RDS was indicated in an experimental study by Lou (141). The results of a subsequent study correlating low cerebral blood flow (CBF) with increased brain atrophy, abnormal neurological signs and lower developmental scores, caused Lou (142) to further speculate that low CBF exposes the preterm brain to greater risk of ischaemic injury and haemorrhage. In an observational study, Dykes (143) associated HMD severity, alveolar rupture and volume replacement with an increased incidence of IVH. Dykes theorised that IVH occurs as a result of either low cerebral perfusion pressures resulting from high intrathoracic pressure in ventilated preterm infants with severe HMD, alveolar rupture, or high perfusion pressures from overutilisation of volume expanders. A link between cerebral hypoperfusion-hyperperfusion and IVH was also indicated in separate animal studies by Goddard-Finegold (144) and Ment (145). IVH developed following increased blood flow to the germinal matrix of the brain in subjects exposed to cerebral hypoperfusion induced by intentional hypovolaemia then hyperperfusion using blood volume

expanders. A similar relationship between fluctuating cerebral blood flow velocity and subsequent IVH was indicated in cranial Doppler studies by Van Bel (146). These studies support a role for extreme changes in systemic perfusion in the development of IVH in preterm infants, particularly those with birth asphyxia and severe RDS requiring ventilation.

IVH severity has been identified as a major prognostic indicator of long term neurodevelopmental outcome and mortality in preterm infants. Shankaran (147) associated moderate to severe IVH on head ultrasound (HUS) with poor short-term neurodevelopmental outcome. From this, a grading system including mild, moderate and severe IVH was developed. A direct association between severe grades 3 (III) and 4 (IV) IVH and increased risk of major long-term neurodevelopmental disorders, compared to a similar risk between preterm infants with less severe grade 1 (I) – 2 (II) and those without IVH was found by Papile (148). Later studies support Papile's (148) findings of increased morbidity associated with severe grade IVH. For instance, de Vries (149) associated large IVH with increased rates of cerebral palsy in a large cohort of infants born at < 34 weeks gestation with outcome follow-up over 7 years. Severe IVH was also linked with increased risk of poor neurological outcomes in preterm infants prospectively studied by Ment (150). Bozynski (151) also found that abnormal HUS at term in preterm infants born at < 1200g birthweight cohort with previous IVH, was highly predictive of the development of cerebral palsy in survivors at 12-18 months corrected age. Studies have also indicated a strong association between IVH and with increased mortality. Preterm infants with IVH had a greatly increased risk of mortality compared to those without IVH studied by Beverley (136) whilst a combination of IVH and moderately severe to severe HMD increased the risk of death in the study by Dykes (143). Severe grade IVH is likely to be a major contributor to neurodevelopmental disability and mortality in preterm infants.

Observational studies of cerebral blood flow in preterm infants have associated PDA with irregular cerebral blood flow patterns. Abnormal cerebral blood flow patterns including decreased, retrograde or absent diastolic flow, a combination of retrograde and advancing cerebral blood flow, and/or abnormally high pulse amplitudes were identified in doppler imaging of the anterior communicating artery (ACA) in preterm infants with PDA identified by clinical signs or La/Ao from a series of studies by Perlman (152), Martin (153) and Lipman (154). Perlman (152) proposes that the effect of an opening and closing PDA on pulse amplitude within the ACA, is a potential contributor to germinal layer capillary rupture and IVH along with disturbance of auto-regulation by hypoxia and hypercarbia. Magnitude and direction of ductal shunting with respect to CBF and the influence of this on subsequent IVH were not examined in Perlman's study, with ductal shunting confirmed on aortogram in only

20% of preterm infants studied. Lipman (154) suggests an association between PDA and "abnormal cerebral haemodynamics", whilst Martin (153) proposes that low or fluctuating blood flow associated with the presence of a PDA exposes the delicate arterial vessels and developing brain cells to alternating ischaemia and haemorrhagic injury. None of the three studies examined the timing of onset of IVH in relation to abnormal cerebral blood flow and the development of PDA, therefore a temporal relationship was not demonstrated between the timing of PDA, and abnormal CBF with respect to the development of IVH. Similar to the collective results of Perlman (152), Martin (153) and Lipman (154), Van Bel (146) found pulsatility index (PI) was increased in association with PDA ,and there appeared to be a relationship between fluctuating cerebral blood flow and subsequent IVH. However, from his examination of the timing of IVH onset in relation to that symptomatic PDA, Van Bel concluded that PDA is not likely to be implicated in the extension of IVH in the postnatal period as few of the infants with IVH developed symptomatic PDA before day 5. Considered together these studies indicate a suspicion of abnormal cerebral blood flow associated with the presence of a PDA in the causation of IVH, but fail to link this with adequate echocardiographic evidence of the size of ductal shunting and the timing of onset of IVH.

An association between PDA and IVH has been suggested in observational studies; but PDA tends to coexist with a number of other factors in association with IVH. Factors making a statistically significant contribution to IVH in the postnatal period in Dykes' (143) study included; severe RDS, acidosis, hypercarbia, and hypoxia are also predisposing factors to PDA. Considering that RDS and PDA also share many of the same predisposing factors and have been found to be strongly associated with each other, the tendency for preterm infants with a large PDA to also have severe RDS, may at least partly account for the increased IVH incidence. Lack of data supplied by Dykes (143) on comparative RDS severity between preterm infant groups with or without PDA and IVH makes it difficult to ascertain whether PDA independently affects IVH causation. It is possible that RDS or any of the other risk factors may have confounded or modified any effect of PDA on the risk of IVH. PDA may have a role in IVH development with or independent to RDS, or may merely be an accompanying sign of RDS. Dykes (143) does not specify whether PDA was determined according to echocardiographic criteria or clinical signs alone or the postnatal ages at which it was identified, therefore the level of ductal patency and the timing of occurrence with regard to the onset of IVH were not established. As a result, Dykes could not demonstrate a temporal relationship between PDA diameter and IVH development. Numerous other factors including acidosis, hypoxia, hypercarbia, hypotension and RDS may have contributed to the development of both PDA and IVH.

Later studies associated left to right shunting via a large PDA with the development of IVH. Evans and Kluckow (155), hypothesised that irregular CBF secondary to left to right shunting of blood via HsPDA creates a cerebral hypo-perfusion-hyperperfusion cycle with vascular injury culminating in IVH. Large PDA diameter occurring in the absence of clinical signs was associated with a statistically significant increased risk of IVH in studies of early ductal shunting and abnormal cranial ultrasound by Evans and Kluckow (155). In contrast to the findings of Dykes (143), Evans and Kluckow (155) did not find any association between ventilatory parameters and the development of IVH. Similarity in mean airway pressures (MAP) and FIO_2 and between preterm infants groups with no, grades 1-2, or grades 3-4 IVH indicates that RDS severity is likely to be more equally distributed across all groups in the study by Evans and Kluckow (155) in comparison to that of Dyke's. The effect of confounding due to differences in RDS severity on the association between PDA and the risk of IVH presented by Evans and Kluckow (155) is likely to have been minimised by studying preterm infants with similar respiratory severity, however there remains the potential for residual confounding from other factors such as appearance on chest X-ray and need for surfactant. Given the association between PDA and RDS described previously, the effect of large diameter PDA on the risk of IVH may yet have been overestimated due to residual differences in the severity of RDS across the preterm infant cohort. The association between PDA, RDS and IVH implies that the interaction between each component must be taken into account when attempting to examine any relationship between PDA and IVH.

Another factor with the potential to modify the effect of PDA diameter on the risk of IVH is the receipt of antenatal steroids. A protective effect for the maternal receipt of antenatal steroids against the development of severe or any grade IVH was also found by Evans and Kluckow (155). It follows that reduced IVH risk is a function of improvement in lung maturity and surfactant production, both of which are important characteristics of RDS. This suggests a link between risk of IVH and RDS severity. As discussed previously in Section 2 Patent ductus arteriosus (PDA), preterm infants not exposed to effective lung maturation mediated by antenatal steroid administration may be predisposed to the development of both RDS and PDA. It is possible that exposure to antenatal steroids reduces RDS incidence as a predisposing factor to PDA and IVH, reducing PDA incidence and modifying any pathological effect of PDA on the risk of IVH.

Volume expanders also have the potential to confound any relationship between PDA and the risk of IVH. Volume expanders caused cerebral hyperperfusion resulting in IVH during experimental studies by Goddard-Finegold (144) and Ment (145) and were also associated with increased risk of IVH grade 3-4 in the study by Evans and Kluckow (155). In addition,

fluid overload is thought to predispose preterm infants to PDA. Large diameter PDA in Evans and Kluckow's (155) study may have occurred in response to fluid resuscitation of preterm infants with severe RDS and acidosis, both of which are potential factors in the development of IVH. Use of volume expanders may increase cerebral blood flow and IVH risk whilst greater circulating blood volume may increase the risk of fluid overload and the incidence of large diameter PDA, leading to an overestimation of the effect of PDA on IVH. At the same time, use of volume expanders may have modified the risk of IVH incidence resulting in a true increase in the risk of both IVH and PDA. It remains possible that erratic cerebral blood flow associated with increased incidence of large PDA shunt from volume expansion has modified the effect of PDA on risk of IVH leading to a true increase in the risk of IVH.

PDA and renal dysfunction

PDA is thought to exacerbate perennial acute renal failure (ARF) in preterm infants due to a reduction in by lowering the blood pressure beyond the ability of renal vascular autoregulation to maintain renal arterial perfusion and glomerular filtration rate. Preterm infants with large diameter HsPDA had lower renal and mesenteric blood flow than those without HsPDA, which Shimada (156) attributed to abnormal organ flow patterns arising from ductal steal. Studies of ARF in adults by Mason (157) and Brezis (158) indicate that deeper renal structures may sustain the greatest damage during an ischaemic insult. From this Hunley and Kon (159) suggest that preterm infants may be more susceptible to greater renal injury from arterial hypoperfusion due to progressive absence of cortical protection of the inner renal parenchyma in association with lower gestational age. Renal ischaemia from renal arterial blood flow disturbances theoretically associated with a PDA may lead to renal tubular injury and disintegration, with shedding of the cellular debris into the tubular lumen (159). The areas of the nephron unit most affected by prerenal ischaemia in the preterm infant include the proximal tubule and medulla both of which require an adequate oxygen supply to meet high metabolic demand (159). The resulting tubular obstruction increases pressure within the tubules and reduces transcapillary pressure further exacerbating the ischaemia (159). Functional disturbances resulting from tubular injury include: 1) oliguria; 2) protein redistribution resulting in reduction of sodium reabsorption and increased urinary sodium losses; 3) increased permeability of damaged proximal tubular epithelium with re-entry creatinine into the circulation and elevated serum creatinine (159).

Despite the theoretical association between PDA and renal failure frequently referred to in review articles and textbooks, few studies have implied a link between echocardiographically or clinically significant PDA and renal dysfunction. Greater PDA frequency was noted in preterm infants with ARF in a case control study by Cataldi (160), however a greater proportion of infants with ARF had received the non-steroidal inflammatory drug (NSAID) ibuprofen for PDA closure. It is difficult to ascertain the individual contribution of PDA and ibuprofen to ARF in this study, as both PDA diagnosis and ibuprofen administration occurred prior to the development of ARF on day 3 or day 4. A larger proportion of low gestational age preterm infants with low apgar scores, delivered via caesarian section secondary to foetal distress were also more likely to develop ARF. This supports a relationship between ARF; immaturity, hypoxia at birth and PDA, however a causal effect between PDA on ARF remains unclear, and, as will be discussed further in section 4 PDA Management, causal associations between indomethacin targeted at PDA closure and PDA targeted indomethacin treatment in nephrotoxic renal failure have been extensively described.

PDA and Necrotising Enterocolitis

Polin describes necrotising enterocolitis (NEC) as a condition of the bowel most commonly occurring in preterm neonates resulting in inflammation, ischaemia and necrosis. NEC is often of sudden onset, common signs include vomiting, firm and distended abdomen, metabolic acidosis, tachycardia and respiratory failure (161). Untreated NEC is associated with a high mortality rate therefore prevention is a priority (149). Onset of NEC is frequently associated with the commencement of feeding, use of formula feeding, hypoxia and intestinal bacterial colonization (161). High fluid intake has also been indicated as a potential contributor to NEC in a systematic review by Bell and Acarregui (91). Despite intensive research, the mechanisms leading to NEC in the preterm population remain incompletely understood with postulated alternative causes including immune and inflammatory responses and regulation of mesenteric blood flow (161).

It has been suggested that alteration in mesenteric blood flow due to irregularities in blood flow caused by PDA may predispose preterm infants to the development of NEC. Coombs (162) studied the effects of indomethacin and symptomatic PDA on blood velocity in the superior mesenteric artery in preterm neonates. Mesenteric flow in preterm infants with HsPDA was absent, reduced or backwards with a sharp reduction in blood velocity immediately following bolus intravenous indomethacin, returning to normal flow after PDA closure. From this Coombs (162) concluded that indomethacin may exacerbate any PDA-related disruption in mid-gut perfusion. Grosfeld (163) noted an increase in the incidence of NEC in preterm infants with PDA compared to those preterm infants without PDA. It is possible that indomethacin treatment for PDA had an independent effect on mesenteric flow and the development of NEC reported by Grosfeld (163). In contrast to Grosfeld (163), Bellander (164) found no difference in the rates of NEC or feeding tolerance between preterm infants with PDA treated by indomethacin and those without PDA, however this may have been limited by low power from a comparatively smaller study sample size with increased likelihood of altering the effect in the direction of the null or no difference in the risk of NEC between PDA and non-PDA groups. In addition to the effects of PDA on renal function previously mentioned, Shimada (156) found a reduction in mesenteric flow in preterm infants with HsPDA which they attribute to ductal steal. PDA in preterm infants of less than 28 weeks gestation was associated with longer time to commence enteral feeds, however Patole (165) concludes that this outcome may have been influenced by the reluctance of neonatologists to commence enteral feeding in preterm infants with PDA rather than a detrimental effect of PDA on feed tolerance. Whilst it seems likely from the evidence presented that PDA affects mid-gut perfusion, its role in the development of NEC is far less clear, particularly when it is considered that the majority of investigative studies have

included the use of indomethacin for PDA closure which has also been implicated in mesenteric blood flow disturbances and increased NEC incidence. In addition to this traditional thinking on the role of blood flow disturbances in the pathophysiology of NEC is now being challenged, in favour of causation by immune-mediated responses.

PDA and survival

Observational studies indicate an association between PDA and increased risk of death; however these almost exclusively involve treatment to promote ductal closure. PDA was associated with increased mortality rates in a cohort of preterm infants on day 3 of life prospective studied by Dudell and Gersony (166). Similar findings were obtained from a large cohort study of > 7200 preterm infants by Hulsey (167).
In contrast to the findings of Dudell and Gersony (166) and Hulsey (167), there was no association between mortality and PDA in preterm infants ventilated for RDS retrospectively studied by Greenough and Roberton (168). In addition there was no difference in the prevalence of PDA among non-surviving preterm infants in a case control study by Boo (169). Apart from an association between increasing gestational age and survival, Boo (169) found that treatment factors such nasal CPAP and breast-milk also improved survival. These findings highlight the possibility that such supportive treatment may prevent or modify the risk of mortality occurring due to the effects of RDS and possibly PDA on respiratory and gastrointestinal pathology in modern studies.

A proportion of preterm infants in all these studies received treatment for PDA in the form of indomethacin or surgical ligation which may have had an independent effect on survival rates within each cohort. Although Dudell and Gersony (166) measured ductal patency, study infants were treated according to clinical signs of PDA in a separate examination. As clinical signs have low sensitivity for detecting large PDA shunt and a closing duct may have a loud murmur that may be misinterpreted as a large PDA, it is possible that some of the preterm infants treated for PDA in Dudell and Gersony's (166) study did not have a large PDA whilst others that were not treated had a large PDA. It is possible that treatment of infants without PDA, and failure to treat those with a large PDA, or adverse effects of treatment itself may have had an independent effect on mortality within the study cohort which may have altered any association between mortality and PDA detected using contrast aortography. In addition, pharmacological treatment may be independently associated with mortality arising from neurological, respiratory and gastrointestinal morbidity.

Section 4 PDA management

Overview

Management of PDA involves supportive medical management plus the potential for closure using pharmacological and/or surgical approaches. The aim of PDA closure is to reduce left to right shunting of blood from the aorta across the PDA into the pulmonary artery with two main theoretical consequences;

1) Reduced pulmonary arterial blood flow, reversal of pulmonary vascular engorgement and alveolar interstitial oedema, improving gas exchange and decreasing respiratory distress. This may decrease oxygen and ventilation requirements reducing the risk of CLD as a consequence of less exposure to oxygen free radicals and barotrauma. Reduction in pulmonary vascular congestion may also improve cardiac function by decreasing right and left atrial filling pressures.

2) A decrease in systemic circulatory steal from the aorta across the PDA, allowing more regular systemic, cerebral, mesenteric and renal arterial blood flow. Diversion of blood back into the systemic circulation may reduce the risk of acidosis with less need for fluid replacement and inotropes. In addition, stabilization of arterial blood supply to the brain, gut and kidneys from a decreased systolic-diastolic fluctuation may also lower the risk of IVH, NEC and renal ischaemia.

Multiple treatment approaches have evolved with these aims in common. The following sections compare and contrast the relative benefits and disadvantages of each approach.

Medical Management

The aim of medical management is to support cardiac and respiratory function by treating cardiac failure and pulmonary oedema theoretically associated with symptomatic PDA. Such early management techniques include restriction of fluid intake to prevent fluid overload and reduce pulmonary vascular and cardiac congestion (170). In the past, diuretics have been used to treat pulmonary oedema in addition to positive chronotropic agents such as digoxin to help improve cardiac contractility with the aim of increasing systemic perfusion, and reducing pulmonary vascular congestion (171, 172). Cotton (100) reported 71% survival in ventilated preterm infants receiving medical management for symptomatic PDA. There is little data from observational studies performed in the modern context of medically managed sPDA in the absence of extensive use of surgical or pharmacological management within the medically managed cohort. In one of the few studies where efforts were made to avoid active

surgical or pharmacological treatments to close the duct, by Vanhaesebrouck (173), all preterm infants < 30 weeks with clinically important PDA managed conservatively with fluid restriction and a managed ventilation plan underwent spontaneous closure without the need for surgical ligation. Death rates were similar between the conservatively treated cohort and ibuprofen and a comparsion cohort of indomethacin treated preterm infants obtained from the Vermont: Oxford database; however NEC, IVH and CLD were increased in the ibuprofen/indomethacin group. These findings imply that conservatively managed preterms can undergo high rates of spontaneous closure with a possible reduction in the risk of adverse effects associated with indomethacin, ibuprofen and surgical ligation. Conservative management measures such as fluid restriction may reduce the incidence of PDA by preventing cardiac and gastrointestinal overload; however systematic reviews of randomised trials have not so far indicated a difference in the risk of mortality, respiratory and neurological outcomes in association with their use.

Surgical ligation
Another traditional approach to persistent PDA in preterm infants, surgical ligation of PDA was initially performed in older children by Bullock (44) and Gross (174). Cotton (175) compared surgical ligation with conservative medical management of symptomatic PDA in 15 preterm infants with the hypothesis that closing the duct may reduce pulmonary complications. Surgical ligation reduced the time on ventilation and length of hospital stay; however the small number of infants limited the ability of the study to measure morbidity and mortality. Cotton's findings were supported by those of Jacob (125), who reported a marked, rapid decrease in need for ventilation mean airway pressures and oxygen requirement following surgical ligation of PDA in ELBW infants with RDS. Ligation was associated with lower incidence of NEC, shorter duration of ventilation and improved late survival in comparison with supportive medical management in a cohort of >700 preterm infants born at < 37 weeks gestation studied by Mikhail (170). Mikhail (170) suggested that less time on ventilation may limit respiratory disease severity with less BPD and improved survival. Naulty's (176) findings of improved lung compliance following ligation supports the concept of initial post-ligation improvement in ventilation however postoperative improvement was not consistent among preterm infants and did not correlate with survival. Supporting the findings of Naulty (176) , but contradicting those of Cotton (175), Szymankiewicz (177) found that surgical ligation improved pulmonary mechanics preterm infants born at < 30 weeks gestation in terms of compliance, tidal and minute volumes, but did not reduce airway pressures or resistance. These findings suggest that ligation has variable effects on the lung mechanics of preterm infants. Whilst the larger study by Mikhail (170) supports an association between ligation and improved late survival infants, the effect of changes in lung

mechanics on the risk of major outcomes such as mortality is difficult to determine from the studies by Naulty (176), Cotton (175) and Szymankiewicz (177). It is possible that the extremely small sample sizes used in these studies were insufficient to allow detection of a difference in mortality rates between ligated and non-ligated infants.

Although surgical ligation in the management of PDA has been associated with minimal mortality in observational studies such as Trus (178), Little (179), and Mandhan (180), the effectiveness of early ductal ligation on cardiac function, organ perfusion and pulmonary function has been questioned by researchers such as Morrow (181) who found no improvement in these parameters in animal studies. In contrast, Kimball (182) concluded that ventricular performance is generally well maintained in preterm infants receiving ligation for PDA at 24 hours of life despite greater post-ligation SVR and this may be related to the ability of preterm infants to self-regulate afterload. However, more recent studies suggest that extremely low birth weight (ELBW) preterm infants may be unable to maintain cardiac output or regulate afterload.

 Ligation increased cerebral arterial blood flow velocities in preterm infants before and after ductal closure in Doppler studies conducted by Lundell (183). This suggests that ligation may improve brain perfusion; however there may be an attendant increase in the risk of IVH. In addition, increased rates of neurosensory impairment and BPD were found in infants with sPDA undergoing ligation compared with those having medical therapy (as prophylactic indomethacin) in a cohort of preterm infants from the Trial of Indomethacin Prophylaxis in Preterms (TIPP) trial retrospectively studied by Kabra (184). This is supported by Chorne (185) who found greater risk of CLD in preterm infants treated with ligation was independent of the potentially confounding or modifying effect of variables including immature gestation and PDA. Surgical ligation was associated with higher risk of late mortality, oxygen dependence and BPD in preterm infants having received 2 or more courses of indomethacin or ibuprofen studied by Lee (186). Increased risk of BPD may be linked to ligation following previous pharmacological treatment, particularly when it is considered that 83% of preterm infants in Kabra's (184) study had received prophylactic indomethacin prior to undergoing ligation. There is some indication that surgical ligation of the duct does not improve cardiac performance, neurosensory outcomes, and pulmonary mechanics. Risk of pulmonary morbidities such as CLD may be increased by ligation following multiple courses of pharmacological treatment to close the duct.

Early surgical ligation has been associated with an improvement in some short term outcomes and increased risk in others. Early compared to late or no PDA ligation reduced

the risk of NEC in ELBW preterm infants receiving supplemental oxygen in the first 5 days of life in a randomised trial by Cassady (187) however there were no differences in the risk of other studied outcomes including CLD, IVH and mortality. Ligation of more than half of the control group reduced the chances of finding a difference in the incidence of CLD, IVH and death between preterm infants receiving early, late and no ligation. Preterm infants receiving early ligation for failed indomethacin treatment or large HsPDA took less time to reach full feeds and had improved growth at 36 weeks post-conceptual age in a retrospective study by Jaillard (188). However, there were no differences in the risk of BPD and NEC. Early ligation has been associated with increased risk of pulmonary complications. PDA ligation in preterm infants at < 24 hours of life compared to no PDA ligation or ligation for symptomatic PDA was associated with an increased risk of CLD in a re-evaluation of data from the Cassady trial by Clyman (189). Similarly, a Cochrane review by Mosalli (190) of early surgical ligation for PDA prophylaxis in preterm infants was unable to recommend early ligation due to a high possibility of short and long term complications in the light of high rates of spontaneous ductal closure and the existence of other treatment options including later ligation and pharmacological treatment to close the duct. Whilst there is some indication of benefit for early PDA ligation on NEC, feed tolerance and growth, there is little evidence from observational studies, randomised trials or systematic reviews to suggest similar benefit of early ligation on CLD, IVH and mortality with some indication of a potential increase in the risk of CLD.

Considering the findings of studies in relation to the timing of surgical ligation, there may be some benefit for late ligation in terms of reduced mortality and early ligation may reduce NEC. However, these benefits should be balanced against the risk of CLD that has been associated with ligation after several courses of indomethacin or ibuprofen treatment, particularly in babies with persistent PDA requiring oxygen and ventilation. As a proportion of babies having failed medical or pharmacological treatment almost inevitably require ligation, the current evidence gives little direction on optimal timing and which babies are most likely to benefit from surgical intervention..

Pharmacological management to close the PDA

Indomethacin

Description/Action
Pharmacological closure with intravenous indomethacin was introduced as an alternative to surgical ligation. Indomethacin is a cyclooxygenase inhibitor, also referred to as prostaglandin synthase or synthetase inhibitor. As the drug class name suggests, indomethacin inhibits the action of cyclooxygenase 1 and 2 (COX 1 and 2), which are

responsible for the conversion of arachidonic acid into prostaglandins. As explained in section 1, prostaglandins play an important role in immune defence systems and regulation of arterial vessel diameter. Indomethacin lowers prostaglandin levels in the ductal tissue resulting in initial ductal muscle constriction. Such constriction reduces ductal diameter and it becomes smaller, leading to slowing of blood flow and eventual cessation of ductal flow followed by functional closure (refer to Section 1 The Ductus Arteriosus). As indomethacin is a non-selective inhibitor of prostaglandin production, it affects vessel diameter within the entire arterial system resulting in widespread constriction of the cerebral, mesenteric and renal arterial vasculature.

Indomethacin vs. Surgical ligation
Pharmacological treatment evolved as a safer option to the additional risks of air leak and infection associated with surgery in critically ill preterm infants with severe respiratory distress and the technique is relatively simple and far less expensive to provide. Preterm infants with sPDA receiving indomethacin rather than ligation in a quasi-randomised RCT by Merritt (191), had less time on ventilation and need for oxygen however there were no differences in morbidity and mortality between the two treatments in this small trial. Risk of pneumothorax and ROP were increased in preterm infants treated with ligation compared to indomethacin a trial subgroup investigated by Gersony (192); however there were no differences in the major outcomes of CLD, IVH, NEC or death. As only Gersony (192) compared surgical ligation with indomethacin for sPDA in preterm infants, a Cochrane review of surgical ligation vs. medical treatment (including indomethacin) by Malviya (193) concluded that there is insufficient evidence from randomised trials indicating a preference for either approach. Preterm infants with sPDA treated with indomethacin rather than ligation had lower rates of NEC and IVH, both of which were significant predictors of mortality in a retrospective chart review of preterm infants with sPDA by Robie (194). Whilst there is some indication from observational studies that indomethacin compared to surgical ligation reduces morbidity and perhaps mortality, this has not been confirmed in randomised trials, the difference in findings may be due to the small number of randomised trials comparing indomethacin with surgical ligation or an overall lack of difference in effect between pharmacological and surgical approaches.

Symptomatic
As described in Section 1, clinical signs of PDA may include: continuous or systolic murmur, hyperactive praecordium, bounding pulses, cardiomegaly on CXR, peripheral oedema and clinical instability marked by an increased need for respiratory support and/or a metabolic acidosis. The term symptomatic PDA (sPDA) is frequently used to describe PDA that is diagnosed and treated on the basis of the appearance of these signs. Meta-analyses

comparing intravenous indomethacin treatment of sPDA compared to placebo or no treatment are limited in number. In addition the inclusion criteria, methodology and conclusions vary or are unclear. For instance, no significant difference between treatment and control groups for any of the major outcomes of CLD, NEC, IVH, and mortality were found in an early review and meta-analysis of 6 randomized trials, of indomethacin vs. placebo for treatment of symptomatic PDA by Nehgme (195). Apart from increased PDA closure rates for intravenous indomethacin, a review and meta-analysis of 6 different randomized trials of indomethacin or surgical treatment of symptomatic PDA. Knight (196) found no differences between the outcomes of death, NEC, CLD, or retinopathy of prematurity (ROP) .

Author	Included studies
Nehgme (195)	Mahony (197), Hammerman (198), Hammerman (199), Weesner (200), Krauss (201), Mullett (202)
Knight (203)	Cotton (175) , Yeh (204), Yanagi (205), Merritt (206), Rudd (207), Gersony (192)

Table 1. Studies included in meta-analyse indomethacin vs. placebo.

Both Nehgme (195)and Knight (203) selected a different range of trials (refer table 1 above) for their review without specifying any inclusion criteria or methods used to obtain the studies or perform any quality assessment. In addition, both authors directly compared trials of different management strategies for sPDA, for example; conservative vs. surgical treatment as well as those comparing indomethacin vs. placebo or no treatment. Although the primary aim of comparing the effectiveness between conservative, pharmacological and surgical treatments is commendable, as will be more fully explained in Section 5 Indirect comparisons, the limited method used by Nehgme (195) and Knight (203) is of less value in terms of providing a realistic assessment of the effect of indomethacin treatment to close a PDA on the relative risk of major outcomes. Current meta-analyses do not indicate any benefit or adverse effect for indomethacin in the treatment of symptomatic PDA in relation to mortality and morbidity; however the included trials are old, potentially of poor quality, sample sizes are small and the information on methodological quality is incomplete. Meta-analyses comparing intravenous indomethacin treatment of symptomatic PDA compared to placebo or no treatment are limited in number and have small overall sample sizes. In addition the inclusion criteria and methodology vary or are unclearly stated. All of these factors may have affected the ability to demonstrate beneficial or adverse effects for

indomethacin compared to placebo or no treatment, and the impact of these on treatment related outcomes are difficult to ascertain from current meta-analyses.

Prophylaxis

Indomethacin prophylaxis aims to treat preterm infants within the first 24 hours of life and regardless of ductal status. This approach has evolved from a series of randomized trials conducted by Ment (208, 209). These trials (208, 209) indicated a protective effect for intravenous indomethacin administered from 6 hours of life against severe intraventricular haemorrhage in very low birth weight preterm infants without pre-existing IVH. In the initial trial (208), IVH incidence was similar in preterm infants with and or without PDA. From this, Ment (208) proposes that indomethacin protects against IVH by directly acting on the cerebral microvasculature. A subsequent multicentre trial by Ment (209) demonstrated similar findings in relation to severe (grades III/IV) IVH in preterm infants. These findings point to the possibility that indomethacin's capacity to prevent IVH may not be related to its effect on ductal diameter. Despite findings of similar effectiveness of indomethacin in IVH prevention, a large multi-centre RCT of 1202 very low birth weight infants, The Trial of Indomethacin Prophylaxis in Preterms (TIPP) (210), found no difference in long term neurosensory impairment, periventricular leukomalacia (PVL), BPD, mortality or any other outcomes between indomethacin and placebo groups. Similarly, a Cochrane review of early intravenous indomethacin prophylaxis vs. initial placebo by Fowlie and Davis (211), heavily weighted by the TIPP (210) and Ment (212) trials, indicated that the administration of indomethacin within the first 24-48 hours of life was associated with short-term benefit on severe IVH, symptomatic PDA, the need for surgical ligation and ductal reopening. Fowlie and Davis (211) also speculate that the action of indomethacin prophylaxis in IVH reduction arises from a direct neuro-protective effect that is independent of its action in closing the PDA. This review failed to demonstrate any improvement in mortality or longer-term neurosensory outcomes associated with the administration of indomethacin prophylaxis, which Fowlie and Davis (211) relate to high rates of loss of follow-up in relation to longer-term outcomes. Despite short-term benefit on IVH, there remains no evidence of improvement in longer-term neurodevelopmental outcomes associated with indomethacin prophylaxis and short term IVH protection with indomethacin has not yet been associated with early treatment based on ductal status in a randomised trial. As highlighted in earlier discussion, severe IVH has been linked with increased mortality and poor neurodevelopmental outcomes; therefore a reduction in the rate of IVH should have a beneficial effect on both of these outcomes however there is limited evidence from randomised trials of intravenous indomethacin prophylaxis to support this.

Whilst the obvious benefits associated with reducing severe IVH risk in preterm infants are many, indomethacin prophylaxis has the potential to expose a large number of infants with a small or closed duct to the adverse effects of intravenous indomethacin. When the estimated spontaneous closure rates among premature infants born at less than 28 weeks gestation discussed in Section 2 are considered, this represents greater than a third of infants < 28 weeks receiving unnecessary indomethacin treatment. Although the Cochrane review by Fowlie and Davis (211) does not indicate any risk associated with the administration of indomethacin prophylaxis, Ment's pilot trial (208) showed an increase in the rate of GMH/IVH in indomethacin treated preterm infants without PDA at day 5. In support of this finding, the results of Schmidt's secondary analysis of BPD and PDA from the TIPP data (213), demonstrated a similar increase in the rate of BPD in indomethacin treated infants without PDA on follow-up echocardiography. A smaller randomised trial by Kumar (214) was abandoned after recruiting just under 60 infants per intervention group due to high rates of IVH and CLD in an ELBW subgroup randomised to receive intravenous indomethacin prophylaxis. These findings suggest that indomethacin administration in preterm infants without prior knowledge of ductal status, particularly infants in whom the ductus is closing may increase the rate of adverse outcomes such as IVH and CLD.

Presymptomatic
The presymptomatic approach treats preterm infants with PDA identified by echocardiographic criteria including; ductal diameter, magnitude of left to right shunt, left atrial size and degree of cardiac failure prior to the onset of clinical signs. Targeting indomethacin treatment at preterm infants with echo confirmed PDA incorporates the theoretical benefit of early PDA closure in reducing RDS, time on ventilation and CLD, exposing less preterm infants to the risk of adverse effects commonly associated with indomethacin which will be discussed in more detail further in this Section. Later symptomatic PDA and time on oxygen were reduced in otherwise asymptomatic preterm infants with PDA at > 24 hours of life in a Cochrane Review of indomethacin for treatment of presymptomatic PDA by Cooke (215). However, there were no differences in the longer term outcomes of CLD, IVH and mortality. No long term neurodevelopmental outcomes were reported. Failure to find statistically significant differences in major outcomes between presymptomatic indomethacin and placebo may be attributable to small sample sizes, between studies differences in the effectiveness of echocardiographic criteria used to identify PDA or a lack of effectiveness for indomethacin induced ductal closure on outcomes. There is scant evidence from Cochrane systematic reviews supporting the effectiveness of indomethacin on short surrogate outcomes but not long term outcomes in the treatment of presymptomatic PDA.

The terms presymptomatic and "early targeted" are sometimes used interchangeably to describe the use of echocardiographic criteria such as those outlined in the previous paragraph to describe PDA. Somewhat confusingly, the term early targeted has also been used in some studies to describe PDA identified by echo in addition to clinical criteria including gestational age, acid-base balance, requirement for ventilation and oxygen occurring within the first 24-72 hours of life. A Cochrane review of randomized trials by Ohlsson (216) combined both treatment at less than 24 hours and early targeted treatment to close the PDA and is limited to ibuprofen compared with indomethacin. This will be discussed in further detail later in this Section.

Adverse effects

Adverse effects theoretically associated with the administration of intravenous indomethacin are thought to arise from widespread vasoconstriction due to non-selective inhibition of prostaglandins (refer to Section 1).

Pulmonary

Experimental studies have linked intravenous indomethacin with pulmonary vasoconstriction. Prostaglandin inhibition with intravenous indomethacin increased pulmonary vascular resistance which was further exacerbated by hypoxaemia in experimental studies of term and preterm goats and this led Tyler (217) to conclude that indomethacin effectively intervened in pulmonary vasodilation. The benefits of such a reduction in pulmonary vasodilation depend on the extent to which this occurs particularly when it is considered that poor oxygenation may enhance the effect.

It is possible that the dose required for successful ductal closure using intravenous indomethacin is much greater than that required to cause significant pulmonary vasoconstriction. Pulmonary vasoconstriction was achieved at 1/10th the dose of intravenous indomethacin required to produce ductal constriction in preterm lambs in an experimental study by Lock (218). From extrapolation of these results with those from the administration of oral indomethacin 3mg/kg over 3 days, Lock proposes from that the effect of indomethacin on the pulmonary vasculature is transitory, and that preterm infants may adapt to chronic inhibition of PG synthesis by indomethacin. Although Lock proposes that adaptation acts to preserve normal pulmonary vascular tone and responses to hypoxia, cholinergic and immune system mediators, he admits that the consequences of non-selective reduction in the direct pulmonary dilatational effects of PGE on pulmonary function in preterm infants remain unknown. Pulmonary interstitial emphysema (PIE) occurred in 11% of indomethacin treated infants studied by Little (179), however lack of a control group for comparsion means

that this cannot be compared to the baseline risk of PIE in this population. In addition, a secondary analysis of data from the TIPP study by Schmidt (219) indicated increased oxygen requirement and pulmonary oedema in association with early indomethacin administration which Schmidt suggests may counterbalance any beneficial effect of indomethacin on respiratory function arising from PDA closure and offer an explanation for the lack of effect of indomethacin prophylaxis on the incidence of BPD. Intravenous indomethacin may have adverse effects arising from excess pulmonary vasoconstriction including PIE, increased oxygen requirement and CLD.

Renal function
Numerous studies have indicated an association between intravenous indomethacin administration for PDA and impaired renal function. Indomethacin therapy was associated with oliguria, reduced glomerular filtration rate (GFR) and decreased excretion of sodium, potassium and chloride ions in preterm infants with PDA studied by Cifuentes, Olley, Balfe, Radde, and Soldin (220), however renal function returned to normal 1 to 2 weeks post therapy. Halliday (221) demonstrated greater renal function in preterm infants receiving indomethacin for sPDA at 4 to 7 days of life compared to the second week of life, concluding that indomethacin has less effect on renal function in the relatively mature preterm infant. Renal perfusion studies have also associated indomethacin administration with decreased renal arterial blood flow. Renal arterial blood flow velocity was reduced for up to one hour following single IV indomethacin for sPDA in 15 preterm infants studied by Van Bel (222). Pezzati et al. (223) reported similar findings of reduced renal blood flow persisting for up to 2 hours post indomethacin infusion for echo-detected HsPDA in preterm infants < 33 weeks. Kang (224) also found reduced renal blood flow velocity with indomethacin administration in addition to elevated serum creatinine, oliguria and interference in sodium and water balance. Kang (224) suggests that indomethacin treatment for PDA causes a transient reduction in renal function in preterm infants with acute ischaemic renal cell injury but was unable to speculate as study infants were only followed for 3 days post indomethacin dose. In a longer term study by Akima (225), approximately one quarter of preterm infants treated with indomethacin developed acute renal failure with elevated serum creatinine and reduced GFR in the first week of life resolving by day 30 of life. The effect of indomethacin administration on renal function in preterm neonates appears to be well established. Although this effect is generally thought to be transient (226), the effect of indomethacin on long term renal function has not been extensively studied.

Neurological
Indomethacin administration targeted at ductal closure has been associated with changes in cerebral haemodynamics in preterm infants. A single dose of intravenous indomethacin

significantly decreased cerebral blood flow volume (CBFV) for 2 hours in doppler studies by Laudignon (227). All phases of cerebral circulation including systolic, mean, and end-diastolic flow velocities were reduced for at least 2 hours following a rapid injection of intravenous indomethacin for sPDA in a single cohort of preterm infants studied by Van Bel (228). A similar decline in cerebral circulation was found by Colditz (229) in ultrasound studies of anterior cerebral arterial blood flow in preterm infants treated with rapid intravenous indomethacin compared to intravenous indomethacin infused more slowly over 20 minutes in which there was no disruption. In contrast, Edwards (230) and Austin (231) used near-infrared spectroscopy (NIRS) and duplex scanning both found equally severe disruption to cerebral arterial blood flow with either rapid bolus or slow intravenous administration of indomethacin. Oxygen delivery and blood volume changes in response to increased or decreased arterial carbon dioxide were impaired on post intravenous indomethacin infusion NIRS in Edwards' (230) study which he suggests reflects the potential for exacerbation of oxygenation, perfusion and cardiovascular control secondary to intravenous indomethacin administration in the preterm infant. Edwards' proposition is supported by substantial swings in cerebral blood volume on NIRS and a sharp decrease in cytochrome oxidase concentration in association with intravenous indomethacin administration in separate studies of cerebral circulation by Christmann (232) and Benders (233). Cytochrome oxidase activity is thought to be a marker of cerebral oxygenation (233), and a reduction in such activity in response to indomethacin administration for sPDA, suggests that indomethacin may adversely affect cerebral haemodynamics and brain tissue oxygenation.

Use of indomethacin for ductal closure has been associated with prolonged bleeding times in preterm infant that this may influence IVH progression and the development of periventricular leukomalacia. Corazza (234) noted prolongation of bleeding times for up to 48 hours in preterm infants treated with indomethacin for PDA, however bleeding times were not different between those with or without progression of IVH and IVH progression sometimes occurred prior to indomethacin administration. There was no control group of preterm infants without PDA or with untreated PDA to compared incidence of IVH progression and the sample size was small. Both of these factors may have influenced the capacity of Corazza's study to demonstrate an association between indomethacin, bleeding times and IVH progression. Multiple courses of indomethacin administered for ductal closure were associated with a trend toward increased risk of periventricular leukomalacia in a retrospective study of 61 preterm infants born at less than 34 weeks gestation by Sangem (235). Again small sample sizes and lack of comparison with an untreated PDA control group may have contributed to the non-significant finding in this study. An association

between indomethacin, IVH and PVL has not so far been demonstrated in observational studies, however adverse effects of low or fluctuating brain perfusion and prolonged bleeding times associated with indomethacin remain theoretically plausible.

Gastrointestinal

Prostaglandins have a role in protection of normal gastrointestinal (GIT) perfusion and related functions. Studies in animals and adult humans by Elliott (236) and Hawkey (237) suggest that indomethacin interferes in these protective functions by non-selective COX inhibition of the production of GIT specific prostaglandins responsible for maintaining adequate mucosal perfusion, neutral pH and mucous production . Gastric perfusion studies by Coombs (162) found that rapid bolus compared with slow injection of IV indomethacin for PDA closure reduced mesenteric arterial blood flow more than PDA alone, potentially enhancing gut hypoperfusion.

Further evidence of a combined effect of indomethacin and PDA in reducing intestinal blood flow in preterm infants was supplied in a study of near term fetal lambs by Meyers (238). Whilst ductal status alone did not influence oxygen consumption, indomethacin administration with ductal closure changed the relationship between intestinal oxygen consumption and perfusion pressure, indicating that indomethacin may interfere with the autoregulation of intestinal blood flow and oxygen metabolism. From these findings, Meyers proposes that risk factors including PDA, indomethacin and intestinal distension may predispose preterm infants to intestinal ischaemia potentially progressing to NEC and/or gastric perforation. Cases of gastric perforation (GP) following oral indomethacin treatment for sPDA in preterm infants were reported by Alpan (239) and Kuhl (240). A case of GP occurring post intravenous indomethacin treatment for PDA in a VLBW infant was also described by Scholz (241). Observational studies have also associated administration of indomethacin for PDA in preterm infants with an increased risk of spontaneous intestinal perforation (SIP). Early compared to standard administration of indomethacin was associated with increased risk of NEC with intestinal perforation in a retrospective record review of preterm infants with echo-confirmed HsPDA conducted by Fujii (242), whilst 8 and 4% of indomethacin treated preterm infants prospectively studied by Little (179) developed NEC and GP. GP with was associated with greater mortality rates and PVL incidence. From a large database cohort of > 2000 preterm infants, Attridge (243) identified an independent association between early indomethacin administration at < 3 days of life and risk of SIP. Although the retrospective identification of data limits the ability of this study to draw conclusions about causation between indomethacin and SIP, the use of a large sample has improved the power of the study to demonstrate a relationship between the two variables.

The potentially harmful effects of indomethacin exposure on intestinal perfusion in preterm infants may counteract any benefit from ductal closure in improving intestinal blood flow and this may explain why observational studies have failed to clearly demonstrate a reduction in the incidence in NEC or SIP in association with indomethacin treatment for ductal closure.

Mortality

There is some evidence that increased risk of IVH and SIP in association with indomethacin treatment for PDA may be linked to greater mortality in preterm infants. Trus (178) described 3 infant deaths from SIP out of a cohort of 40 preterm infants treated with indomethacin for sPDA, whilst 4 out of 6 preterm infants receiving early indomethacin therapy died from NEC and SIP in the study by Fujii (242). There was a threefold increase in overall mortality in the indomethacin treated PDA group compared to the conservatively managed/late ligation PDA group in a retrospective study of 97 preterm infants by Nagaraj (244) in association with a twofold increase in the risk of IVH and a comparatively high rate of SIP. Due to the retrospective nature of the study, there is a possibility that selection of a particularly high risk case cohort in comparison to the controls may have biased the risk estimate in favour of increased risk for indomethacin-treated preterm infants with PDA. As treatment tends to be targeted at preterm infants with PDA and greater RDS severity and this group are predisposed to higher rates of mortality regardless of the effects of treatment, unless treatment is randomised, the treated group are more likely to have higher risk of poor outcomes. Alternatively, this may indicate that indomethacin for treatment of PDA does not improve overall survival in high risk preterm infants.

Treatment Failure

A proportion of preterm infants treated with indomethacin fail to close the duct or it reopens following initial closure. For example, >40% of preterm infants born at < 25 weeks gestation did not respond to treatment to close or reopened the duct in a randomised trial by Narayanan (115), with up to 37% requiring further treatment or eventual ligation, whilst the recurrence rate of PDA in a recent cohort study by Alexander (245) was as high as 45.9 % following early to moderately-early targeted indomethacin treatment of PDA in preterm infants. The mechanism for indomethacin failure is not completely understood. Alternative theories relate lack of ductal response or reopening to the non-selective action of indomethacin on cyclooxygenase activity. Sodini (246) proposes that deletion of COX by indomethacin increases nitric oxide activity in the walls of the ductus resulting in ductal vasodilatation. This fits with the original theories of Coceani (11, 12, 33) regarding the interference of indomethacin with the mechanism of PGE as a trigger for the independent action of endothelin-1, NO and CO in maintaining or restoring ductal relaxation discussed in Section2: Patent Ductus Arteriosus. Clyman (247) supports an alternative theory that the the

ductal muscle media of very to extremely preterm infants is resistant to the development of hypoxia necessary for cessation of ductal luminal flow and anatomic closure and this is responsible frequent ductal reopening. The success of indomethacin on ductal closure in a proportion of preterm infants may be explained incorporating the theories of Sodini, Coceani and Clyman, as the likelihood of treatment success has been found to increase with down regulation of the in-utero COX-NO activity negative feedback mechanism and increased hypoxia with the ductal muscle as the infant progresses toward term gestation.

Failure of permanent PDA closure following repeated indomethacin treatment occurs more frequently in those preterm infants with risk factors for failure of initial spontaneous ductal closure such as immaturity, severity of respiratory distress, and larger initial ductal diameter. For instance, 21% of preterm infants born at < 33 weeks gestational age treated with indomethacin for asymptomatic PDA had ductal reopening and continued luminal flow in association with lower gestational age in a study by Weiss (248). Higher reopening rates in immature infants even in the absence of luminal flow may indicate deficiency in the normal processes responsible for anatomic closure in such infants. In support of this theory, Narayanan (115), found that 42% of preterm infants born at 24-25 weeks gestation having received indomethacin prophylaxis for echocardiographically detected PDA at <15 hours of life, compared to 22% of infants born at 26-27 weeks treated using the same protocol either failed to close or reopened the duct. The effect of gestational age and birthweight on ductal reopening is supported in retrospective studies of ELBW/VLBW infants by Fendler (249) who found mature gestational age was protective against failure of indomethacin treatment whilst Yang (250) associated increased birthweight with a higher rate of final ductal closure.

The importance of respiratory distress and consequent hypoxaemia as important factors in the persistence of ductal shunting following repeated indomethacin treatment is well recognised. Preterm infants ventilated for severe RDS studied by Seyberth (251) had high PGE levels and increased indomethacin utilization, which may explain the tendency for lower serum indomethacin levels, high rates of ductal reopening and more frequent need for repeat doses or courses of indomethacin in smaller, sicker premature infants. Preterm infants failing to close a PDA required more time on ventilation than those with successful PDA closure following treatment with indomethacin in a retrospective chart review of preterm infants < 35 weeks gestation by Tschuppert (252). These results imply that preterm infants failing to close a PDA following indomethacin treatment require a longer period of ventilation; however it is also possible that RDS severity and gestational age may have contributed to this.

Larger initial ductal diameter and postnatal age at treatment have been associated with an increased likelihood of treatment failure. Initial ductal diameter was a significant predictor of failure of indomethacin treatment in preterm prospectively studied by Boo (253), and retrospectively chart reviewed by Tschuppert (252) and Fendler (249).

Failure of indomethacin treatment has also been linked with age at treatment. Freidman (254) correlated failure of PDA closure with postnatal age at treatment in preterm infants treated with indomethacin at > 2 weeks of life. Narayanan (115) found early administration of indomethacin as PDA prophylaxis resulted in higher initial closure rates than later indomethacin treatment of symptomatic PDA whilst Yang (250) associated early indomethacin with a higher rate of final ductal closure. The preterm infant populations forming the symptomatic cohort in both the Narayanan and Tschuppert studies were historical controls and were drawn from a time period prior to marked changes in respiratory management of preterm infants with the introduction of antenatal steroids and surfactant. Improved respiratory maturation due to greater use of antenatal steroids may have led to a lower incidence of PDA in infants within the more recently studied prophylaxis cohort compared to that of the older symptomatic cohort. Although the possibility remains that indomethacin administration at an earlier postnatal age reduces failure of indomethacin treatment to achieve ductal closure, this has not been conclusively demonstrated in observational studies.

Failure of repeated indomethacin treatment to close the duct in preterm infants has been associated with greater morbidity and mortality. Fendler (249), associated indomethacin treatment failure in preterm infants with an increased risk of CLD. As highlighted in the discussion of the impact of surgical ligation following previous courses of indomethacin or ibuprofen on mortality in Section 3, it is possible that previous indomethacin treatment combined with surgical ligation increases this risk.

Indomethacin treatment to close the PDA is not without risk, and this brings into question the evidence with regard to the safety and the net beneficial effect of indomethacin on outcomes. The use of indomethacin treatment to improve the respiratory, neurological and survival outcomes of preterm infants whilst balancing potential adverse effects of treatment has led to the adoption of numerous different treatment regimes. The following section outlines some commonly used approaches and examines the evidence in the support of these.

Pharmacokinetics

Management protocols for indomethacin dosage commonly constitute a 3-dose regime described as a "course", given at 12 to 24-hour intervals which is based on the serum half-life of intravenous indomethacin of approximately 20 hours in neonates originally established by Thalji (255). Intravenous indomethacin is rapidly distributed within body tissues. However, elimination via the kidney is significantly delayed, taking up to three times longer to occur in neonates than adults, none the less this rate increases with postnatal age (255). Serum half-life and sustained therapeutic action is further prolonged secondary to late entero-hepatic recirculation of indomethacin back into the plasma (255) . Although the long serum half-life of indomethacin allows for less frequent indomethacin administration this increases the risk of adverse effects, particularly in the high risk, very preterm infant with immature renal function.

Current evidence indicates that weight and immature gestational age may contribute less to individual variations in ductal response to conventional methods of indomethacin and ibuprofen dosing between preterm infants than previously thought. Serum indomethacin concentrations in preterm infants achieving permanent ductal closure after a single dose of indomethacin were higher in comparison to infants requiring multiple doses in the study by Thalji (255) whilst a similar study by Yaffe (256) found post indomethacin serum concentrations varied widely among preterm infants. These studies suggest that individual variations in serum uptake among preterm infants despite identical indomethacin dosing by weight occur due to other factors affecting treatment success such as greater illness severity in those preterm infants requiring multiple doses, and postnatal age at treatment. Lack of correlation between gestational age or birthweight and total dose required for permanent PDA closure was reported in a retrospective dose finding analysis by Dumas de la Roque (257) . Similar findings were reported by Shaffer (258) who compared individualised dosage regimes using serum indomethacin concentrations plotted against concentration nomograms, to standard weight-based indomethacin treatment. Collectively this research implies that birthweight and gestational age at birth, despite their common use as such, may not be sufficiently reliable parameters, to calculate dose requirements for successful ductal closure. Postnatal age correlated with the serum distribution of indomethacin in preterm infants studied by Thalji (255). Dose adjustments should be based on postnatal age rather than birthweight as the former has a primary influence on serum distribution and therefore ductal response to treatment of PDA with indomethacin.

Alternative regimes
Various descriptions of dose size and frequency have been reported in the literature with the common aim of closing the duct and preventing it from reopening without increasing the risk

of adverse effects; however there is no single approach that seems to achieve this with any particular advantage with respect to the others.

Individualised dosing

Due to the variability in indomethacin pharmacokinetics between preterm infants as previously described, individualized infant dosing has been proposed as an alternative to the usual 3 dose weight-based course, particularly in preterm infants that have responded poorly to conventional treatment. Preterm infants < 10 days old and having failed conventional indomethacin treatment responded with higher rates of ductal closure to indomethacin dosing based on individual serum indomethacin concentrations according to a regime devised by Shaffer (258), than those infants receiving a further course of standard indomethacin treatment. Smyth (259) determined from a comparison of indomethacin pharmacokinetics between preterm infants responding or not responding with ductal closure, that use of population modelling similar to that proposed by Schaffer may allow the prediction of individualised indomethacin dosing with a higher probability of achieving constant serum levels throughout the regime. The complexity of individualised dosing calculations combined with the requirement for repeated echocardiography may make this approach less practical within the clinical context; particularly in neonatal centres fewer resources.

Prolonged course

Failure of standard treatment to close the ductus arteriosus in extreme preterm infants prolongs exposure to the PDA which increases the need for indomethacin retreatment and surgical ligation with consequent increase in the risk of associated adverse effects. This has have led to investigations of the effect of prolonged courses of indomethacin over 5-7 days on the rate of ductal closure. Lower risk of mild to severe IVH along with initial lower reopening rates in association with prolonged course indomethacin were reported by Rhodes (260), but this did not influence overall closure rates. A Cochrane review by Herrera (261) recommended against the use of prolonged course indomethacin as although transient renal failure was reduced, reopening rates between prolonged and short course indomethacin were no different and there was an increased risk of NEC [RR 1.87(95%CI 1.07, 3.27)] The increased risk of NEC with prolonged course indomethacin reflect a dose response relationship between short and prolonged course indomethacin and adverse effects. Recent evidence that greater exposure to indomethacin may increase the risk of adverse effects is concerning.

Continuous infusion

Rapid infusion of indomethacin has been associated with marked reduction or erratic changes in cerebral, mesenteric and renal blood flow. Continuous intravenous infusion of indomethacin over 36 hours compared to infusion over 15-30 minutes was associated with less marked effect on cerebral, renal and mesenteric arterial blood flow velocities in perfusion studies by Hammerman (262) and Christmann (232). Neither of these studies reported on outcomes such as PDA reopening, NEC, IVH or mortality. A Cochrane review by Gork (263) was unable to locate any further studies or make any recommendations on the clinical usefulness of continuous indomethacin.

Despite the use of indomethacin for greater than 30 years and intensive investigation into alternative methods of administration and different dosages, no single indomethacin regime has been shown to reduce adverse effects whilst preserving the effect on ductal closure. As a result, apart from the investigations and use of different timing strategies, there has been little change in the dose and method of administration.

Ibuprofen vs. indomethacin

The suitability of intravenous ibuprofen in PDA closure was established in animal experiments by investigators such as Coceani (264) at around the same time as indomethacin, however difficulty producing a stable IV preparation prevented ibuprofen from becoming widely used. Adverse effects on pulmonary, renal, and gastrointestinal morbidity and mortality in association with indomethacin administration prompted experimentation with ibuprofen as a potential replacement for indomethacin. An early experimental observational study of animal subjects by Grosfeld (265) indicated that ibuprofen has less effect on renal function, lower incidence of bowel necrosis and may improve gastro-morbidity related survival rates. Perfusion studies almost exclusively show that constrictive effects for ibuprofen on cerebral, mesenteric and renal vasculature are lower than indomethacin and this offers a likely explanation for the lower rate of associated gastrointestinal and renal effects.

Consecutive Cochrane systematic reviews of randomised controlled trials of intravenous indomethacin vs. intravenous or oral ibuprofen by Ohlsson (216, 266, 267) in the treatment of echocardiographically confirmed haemodynamically and/or clinically important PDA have indicated intravenous or oral ibuprofen is equally effective in achieving ductal closure as intravenous indomethacin with less transient renal impairment. The only statistically significant finding, an association between intravenous ibuprofen and an increased risk of chronic lung disease at 28 days with the possibility of a reduction in the effectiveness of ductal closure with oral ibuprofen, indicated in one Cochrane review update (267)

disappeared following the addition of new studies in the following review update (216). Potential for increased risk of CLD with ibuprofen when directly compared to intravenous indomethacin in consideration with cases of pulmonary hypertension and bleeding in association with intravenous ibuprofen administration for PDA prevention in preterm infants at < 24 hours of life reported by Gournay (268) and Bellini (269), although rare, raise concerns regarding the possiblity of increased pulmonary adverse effects in association with intravenous ibuprofen.

Whilst Cochrane reviews (216, 266, 267) have indicated some benefit for intravenous ibuprofen over intravenous indomethacin in terms of less renal failure, use of intravenous ibuprofen in early PDA prophylaxis defined as administration at less than 24 hours of life regardless of PDA status have not so far been associated with a reduction in severe IVH. Early ibuprofen for PDA prevention showed similar benefit to intravenous indomethacin in reducing symptomatic PDA and surgical ligation rates with the notable exception of IVH prevention in a Cochrane Review by Shah (270). Theories surrounding the origins of IVH arising from the hypoperfusion-hyperperfusion cerebral injury cycle originally proposed by Ment (145) and Goddard-Finegold (144) and extended upon by the work of Evans and Kluckow (155), may offer an explanation for the lack of protective effect of ibuprofen on IVH. If, as indicated by perfusion studies, intravenous ibuprofen has less effect on cerebral perfusion, then it may not protect the brain from cerebral blood flow fluctuations theoretically arising from altered systemic circulation in association with left to right shunt via a PDA. This supports the theory that the vasoconstrictive effects of indomethacin in the presence of high ductal flow are responsible for IVH prevention. Lack of neurological improvement with early indomethacin treatment in the TIPP trial (210) may be due to decreased brain perfusion in infants in the presence of smaller ductal fluctuations associated with small or closing PDA. Early targeting of large diameter PDA with indomethacin rather than ibuprofen may prevent IVH; however, as discussed earlier in this section, the dosing required for ductal constriction may increase the risk of CLD.

 More recently, a randomized trial of indomethacin vs. ibuprofen for treatment of presymptomatic PDA at less than 24 hours of life, conducted by Su (271) found no difference in closure or surgical ligation rates, IVH, and CLD between the two medications. In contrast to this finding, administration of ibuprofen from 3 days of life for PDA determined using serial echocardiography compared with treatment of PDA after the onset of clinical signs was associated with a reduction in the incidence of severe IVH in a recent cohort studies by Korhonen and O'Rourke (272, 273). Collection of data over different time-periods for the clinical signs and echo-targeted treatment cohorts in addition to changes in

management may have distorted the comparative effect of diagnostic method and timing of ibuprofen administration on IVH risk should there have been a large difference in IVH incidence between consecutive years. Although ibuprofen may reduce symptomatic PDA and the need for surgical ligation in a similar manner to indomethacin, there is less reliable evidence of effectiveness for ibuprofen in IVH prevention, which, in addition to a suspicion of adverse pulmonary effects with early administration, may diminish its usefulness in IVH prevention in preterm infants in the first few days of life.

Cochrane (216) currently recommends the use of both indomethacin and ibuprofen in the treatment of clinically important PDA at greater than 24 hours of life as there does not appear to be a clinically significant difference between the two medications. Ohlsson (216) compared oral forms of ibuprofen and placebo only and was unable to provide a meta-analysis of ibuprofen vs. placebo or no treatment due to lack of availability of trial data, having located only 1 unpublished trial by Aranda (274), which did not report any unblinded outcomes. The comparison of the relative effectiveness between ibuprofen and indomethacin by Ohlsson (216) does not represent the benefit or risk conferred by either intervention on baseline event rates for mortality and morbidity amongst preterm infants with clinically important PDA. Most importantly, this does not provide an answer to the vital question of whether indomethacin or ibuprofen actually benefits the preterm infant with PDA.

Current practice
Evidence with regard to current clinical practice in the management of PDA is sparse. A comprehensive survey of practice guidelines in Australia conducted by Hollearing (275) in addition to examination of available clinical protocols and guidelines reveal a wide variation in clinician of management of PDA between:
a)   conservative; seldom use indomethacin with rare surgical ligation (173, 276-278),
b)   moderate; Early Targeted Indomethacin (110, 279),
c)   aggressive; Indomethacin prophylaxis and/or early ligation (279, 280).

Such variation in existing practice indicates a distinct lack of consensus between clinicians, not only on treatment approaches to clinically important PDA, but also in defining a PDA in need of intervention. This is supported by the evidence from a web-based survey of neonatal directors of tertiary level Neonatal Units in the US by Amin (281), who found that clinical decision-making with respect to the number of indomethacin courses, retreatment, criteria for contraindications to therapy, and definition of PDA closure based on echocardiographic evidence varied widely between centres with most clinicians preferring early targeted indomethacin or treatment of symptomatic PDA, and 23% using indomethacin prophylaxis

for IVH prevention. Despite lack of effectiveness in the prevention of PDA reopening indicated in successive Cochrane reviews by Herrera (261, 282); prolonged course indomethacin remains an optional therapeutic intervention in some centres. Due to either lack of alternative evidence from Cochrane reviews (263) regarding continuous indomethacin infusion or possibly from convention, many neonatal centres continue to administer intravenous indomethacin as a bolus injection. Given that there is little evidence from current systematic reviews to support indomethacin treatment of PDA in preterm infants at greater than 24 hours of life, the continued wide use of this therapy is cause for concern and further highlights the need for updated systematic reviews of indomethacin treatment for PDA. Whilst it is acknowledged that a subset of infants may benefit from prophylaxis and early treatment, and a portion of infants are likely to require intervention including surgical ligation at some point, despite frequent clinical observation, case reports, a multitude of retrospective and observational cohort studies, the benefits or harm associated with indomethacin administration compared to baseline risk remains undetermined.

Conclusion

Indomethacin and ibuprofen are both currently recommended for use in the treatment of echocardiographically confirmed and/or clinically important PDA as there does not appear to be a clinically important difference between the two medications in terms of effectiveness on ductal closure. Despite the well-established effectiveness of intravenous indomethacin and ibuprofen in PDA closure, there is little evidence from current systematic reviews regarding the baseline benefit or risk profile of early-targeted treatment or treatment of symptomatic PDA using indomethacin or ibuprofen on outcomes in the preterm population. Whilst there is evidence that indomethacin prophylaxis may be beneficial on short term outcomes, particularly with regard to IVH protection, the results of neurological and respiratory outcomes from TIPP, the largest trial of indomethacin prophylaxis to date, do not reflect long term respiratory or neurological improvement arising from the initial reduction in risk of IVH, symptomatic PDA and surgical ligation rates. Investigators have attempted to address the potential significant adverse effects of intravenous indomethacin by conducting numerous studies on timing, slower methods of administration, lower doses, etc. at the same as maximising the effectiveness with regard to PDA closure and reduction in reopening rates; however none of these methods were successful in combining both objectives simultaneously (261). Ibuprofen has been extensively investigated as a potential replacement with less transient renal effects and is now accepted as a replacement for indomethacin in the treatment of PDA, however due to lack of IVH protection and rare cases of pulmonary hypertension, Cochrane reviews (216, 270) continue to recommend against early use of ibuprofen as PDA prophylaxis. Secondary to the potential for an increased risk of CLD arising from indomethacin or ibuprofen treatment in the presence of a small or closing duct and a reduction in reopening rates with spontaneous closure, there may be a clinical indication for allowing time for spontaneous closure to occur.

Current Cochrane reviews and recent randomised trials compare ibuprofen with indomethacin allowing comparison of relative effectiveness and risk/benefit profile, between the two medications, however these do not provide an estimate of the efficacy of ductal closure with respect to the risk/benefit of either medication on outcomes. To date, there has been no published systematic review and meta-analysis of intravenous ibuprofen vs. placebo or intravenous indomethacin vs. placebo for the treatment of echocardiographically confirmed and/or clinically important PDA at greater than 24 hours of life. Although Ohlsson (216) has compared oral forms of ibuprofen and placebo, the reviewers were unable to conduct a meta-analysis of IV ibuprofen vs. placebo as they were only able to locate 1 unpublished trial by Aranda (274), which was still in progress. Direct comparison between

indomethacin and ibuprofen can only provide an indication of the the relative effectiveness of either medication on ductal closure and adverse effects. This comparision cannot yield any information with regard to the benefit or risk of either medication on baseline event rates for mortality and morbidity amongst preterm infants with clinically important PDA. Most importantly, this does not provide an answer to the vital question of whether indomethacin or ibuprofen actually benefits the preterm infant with PDA.

Research Proposal

Rationale

Existing systematic reviews and meta-analyses comparing intravenous ibuprofen or intravenous indomethacin for treatment of echocardiographically and/or clinically important PDA in preterm infants at > 24 hours of life compared separately with placebo provide limited evidence on outcomes and these are currently insufficient to guide practice. At the same time, practice surveys by Hoellering (283) and Amin (281) in addition to clinical practice guidelines (279, 280) indicate that treatment of PDA with indomethacin at greater than 24 hours of life continues to be widely used in Australia and the United States, particularly in centres that do not have access to on call echocardiography services. For this reason it is important to investigate the relative benefit of later treatment with indomethacin or ibuprofen (> 24hours of life) in terms of PDA closure, respiratory, gastrointestinal and neurological outcomes and death compared to baseline risk. Placebo–controlled trials expose the participants to risk of harm, particularly in comparison to an established treatment. Updated systematic reviews and meta-analyses comparing ibuprofen and indomethacin with placebo or no treatment can be used to determine if IV indomethacin or IV ibuprofen administered for PDA at greater than 24 hours of life compared with placebo have benefit on major morbidity and mortality. The incidence rates for each outcomes may then be compared to determine if there is likely to be increased risk of morbidity in the placebo group prior to planning a randomised trial may then be used to inform planning of future randomised controlled trials of intravenous indomethacin or ibuprofen compared to placebo therapy for treatment of echocardiographically and/or clinically important PDA in preterm infants at > 24 hours of life.

A systematic review incorporating documentation of research methodology and quality assessment may assist in providing an overview of the relevant evidence and indicate gaps in the evidence to direct future enquiry. Controlled trials of early intravenous indomethacin vs. placebo or no early intravenous indomethacin are likely to be small. Pooling of these studies, using traditional meta-analyses will assist in increasing the sample size and hence the power to detect any differences in morbidity and mortality attributable to the adverse effects of treatment or non-treatment of PDA. A Cochrane systematic review by Ohlsson (216) located only one abstract by Aranda (284) comparing early intravenous ibuprofen at 1.4 ± 0.7 days of life with placebo or no treatment for PDA. The location of further studies is unlikely; therefore we plan to use network meta-analytic techniques as described by Elliott (285) and Psaty (286), to compare intravenous ibuprofen treatment with placebo or no

treatment. Network meta-analysis (refer to the Research Proposal for a more detailed description of this method) will be used to provide indirect comparisons between intravenous ibuprofen and placebo by combining traditional analyses of targeted intravenous ibuprofen vs. intravenous indomethacin and targeted intravenous indomethacin vs. placebo in the treatment of clinically important PDA. Indirect network data will be combined with all available data from direct comparisons to increase the power and detect any difference in event rates between intravenous ibuprofen and placebo treatment arms for the outcomes of in-hospital death, NEC, IVH, CLD and neurodevelopment. Taking into consideration the outcome of the analyses of mortality and morbidity between treatment and control groups, the results of all meta-analyses will be used to assist in the calculation of event rates for the rarer outcomes of death, NEC and IVH for the purpose of sample size calculations for a postulated.randomized trial.

Aim
We aimed to systematically review the current evidence with regard to baseline mortality and morbidity rates associated with the treatment of clinically important PDA in preterm infants at greater than 24 hours of life between indomethacin and placebo and intravenous ibuprofen and placebo on the outcomes of PDA closure, NEC, IVH, CLD and death.

Objective
The main purpose of this systematic review is to provide an evidenced based overview of the benefit or harm associated with the administration of intravenous indomethacin and ibuprofen for echocardiographically and/or clinically important PDA in preterm infants at greater than 24 hours of life compared separately with placebo on short and longer-term respiratory and neurological outcomes. The information thus derived has been used to highlight evidence-practice gaps for future enquiry and to inform and make recommendations on current clinical practice.

Hypothesis

Decreased time on ventilation and requirement for oxygen in observational and small randomised trials and fewer complications in comparison to surgical ligation led to the use of intravenous indomethacin as standard treatment for the closure of persistent PDA in preterm infants. Many of the predisposing factors associated with the presence of PDA, for instance, hypoxaemia, RDS, and lack of antenatal steroids share a common link with the pathophysiology responsible for major morbidities; IVH, NEC, CLD, poor neurosensory outcomes and mortality. Whilst this association between the presence of PDA and such morbidity and mortality may be causal, it is also possible that these are more refractory to

intensive management of the pathophysiology arising from or contributing to predisposing factors than to treatment aimed at closing the ductus arteriosus. Exogenous surfactant and antenatal steroids interventions have been associated with a reduction in mortality and RDS. In addition, better ventilation, resuscitation and use of nasal CPAP has contributed to improved survival of lower gestational age preterm infants. The benefit of ductal closure with intravenous indomethacin or ibuprofen on morbidity and mortality in the preterm infant with severe respiratory distress is far less obvious. Both intravenous indomethacin and ibuprofen have been associated with adverse pulmonary, GIT and renal effects. In consideration of these effects, and in agreement with Schmidt's (213) attempts to explain the lack of effect of intravenous indomethacin prophylaxis on CLD, it is possible that ductal closure using indomethacin and perhaps ibuprofen does not have any net overall effect on the risk of CLD and NEC commonly attributed to PDA. Another important point concerns the high treatment failure rate for intravenous indomethacin and intravenous ibuprofen in lower gestational age preterm infants and the association between treatment failure and increased mortality in these infants, particularly in those requiring surgical ligation following multiple courses of indomethacin or ibuprofen although this may also define a high-morbidity group at extreme risk of poor outcome. Treatment failure tends to occur in the population of infants in whom ductal closure with indomethacin or ibuprofen is most frequently recommended and this raises the question of whether such treatment is adding to the risk of morbidity/mortality rather than reducing it. We hypothesise that optimal neurological, respiratory and cardiovascular management has rendered ductal closure using intravenous indomethacin or ibuprofen no longer necessary in the modern context and it is possible that such treatment may actually be of harm rather than benefit.

Indirect comparisons

Description

One of the earliest mentions of indirect comparisons in the published literature concerned a comparison of trial outcomes across various breast cancer treatments by Gelber (287). Indirect comparisons have become increasingly popular as a method for comparing direct randomised trials or meta-analyses of two or more interventions in which existing direct evidence of benefit or harm on disease is insufficient or have not been directly compared. A good example of the use of indirect comparisons in determining the comparative benefit or harm of multiple disease interventions is provided by Psaty (286) who combined direct randomised trials of various antihypertensive medications on endpoints including major cardiovascular disease and mortality. Direct studies sharing common intervention arms were combined to obtain indirect comparisons between numerous first line antihypertensive agents. In this way all the effectiveness of all available therapies on cardiovascular outcomes and mortality could be compared across a single meta-analysis as opposed to the need to assemble and review a large amount of patchy and conflicting evidence.

Methods for performing indirect comparisons

Naïve

Numerous methods for performing indirect comparisons have been described in the literature. The "naïve approach" or "simple comparisons" as described by Glenny (288), concerns the pooling of results across individual trial arms from different trials as if they were one study. Knight's (196) meta-analysis is an example of simple comparisons, comparing directly across separate trials including conservative management with fluid restriction and/or digoxin vs. surgical ligation and indomethacin vs. placebo and/or no intervention and/or surgical ligation. Comparing across different interventions from different trials in this way does not take into account between-trial variations in population characteristics that may occur due to the nature of the intervention and the way it is applied in the clinical setting. As the aim of randomisation to specific interventions is to allow equal distribution of population characteristics that may act to confound the effect of the interventions on the outcomes, comparing one intervention arm such as conservative management with fluid restriction directly with another intervention arm such as indomethacin, without adjusting for variance may lead to confounding from between trial variation in population characteristics, for example gestational age, may have led to errors in the estimation of the effect of an intervention on outcomes. With regard to the proposed indirect comparison between ibuprofen and placebo, use of the naïve method may increase the risk of bias due to the pooling of preterm infant population from the ibuprofen and placebo arms of the direct trials (indomethacin vs. placebo and ibuprofen vs. indomethacin) in a non-randomised fashion

allowing between trial differences in the proportion of characteristics such as the severity of respiratory distress syndrome between indomethacin, ibuprofen and placebo groups.

Adjusted

The adjusted method for performing indirect comparisons, originally described by Bucher (289) provides a comparison across trial interventions along with partial preservation of randomisation. This is achieved by deriving a weighted average of the variance between studies sharing a common treatment or placebo arm. A summary relative risk (RR) for the indirect comparison between the two treatments for which there are very few or no studies is provided from analysis of the log RR ratio between the studies within the two treatment arms. The common trial arm used in the adjusted indirect method allows for partial adjustment of any variance in log RR between the two sets of trials resulting in partial preservation of randomization. For this reason the adjusted method is preferred as it does not break randomisation. The adjusted method of indirect comparison will be used for our network meta-analysis in order to allow maximal preservation of randomization.

Multiple treatment comparisons

Mixed treatment comparisons (MTC), also referred to as network meta-analysis, have evolved from health technology assessments. MTC involve comparisons between two or more treatments which can be developed into highly complex networks. The simplest form of MTC, described by Sutton (290), compares 2 treatments and provides both direct and indirect comparisons for one or more of the pairwise comparisons. A combination of indirect comparisons (figure 2) and MTC (figure 3) as described by Bucher (289) and Sutton (290) will be used to compare direct evidence from randomised trials of indomethacin vs. placebo with indirect and direct (where available) comparisons between ibuprofen vs. placebo.
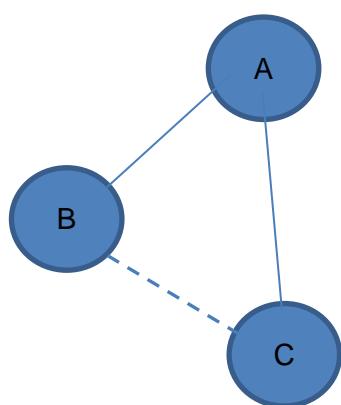
Figure 2 .Simplified diagram of indirect network meta-analysis (adapted from Sutton (290).

In figure 2 above, A, B and C are the treatments for PDA in preterm infants at greater than 24 hours of life to be evaluated in the proposed network meta-analysis. These represent; A) intravenous indomethacin, B) intravenous ibuprofen for treatment, and C) placebo or no treatment.

Available direct trials comparing intravenous indomethacin (A) with placebo or no treatment (C) or B (intravenous ibuprofen) are represented by a solid line between AC and AB respectively. The indirect comparison that we wish to make between intravenous ibuprofen and placebo for PDA in preterm infants at greater than 24 hours of life is indicated on the diagram by the dotted line between B and C.
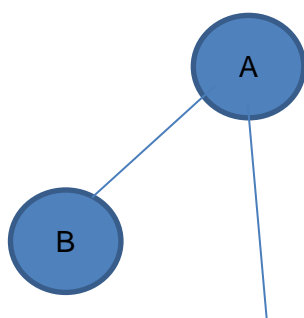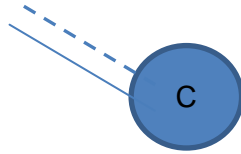
Figure 3. Simplified diagram of indirect network meta-analysis with MTC

Figure 3 above shows the simple MTC. The indirect comparison between ibuprofen and placebo is again shown by the dotted line with the addition of the solid line representing direct evidence between ibuprofen and placebo. The ability to compare results from direct and indirect comparisons will depend on the availability of direct evidence between ibuprofen and placebo.

Apart from traditional methods of assessment, coherence between direct and indirect comparisons can be used to examine the effect of heterogeneity on outcomes resulting from between-study differences in population characteristics in direct meta-analyses within the network. Where a direct randomised trial forms a closed loop in the model and an indirect comparison as seen in the pairwise comparison for ibuprofen vs. placebo (BC) in figure 3 above, this can be used to test the coherence of the effect size between each pair of trial arms within each section of the model. According to Lumley (291), this can be done by calculating the variance for each direct comparison and examining the effect of any incoherence on the consistency of the estimates of log RR between the direct and indirect. The coherence and reliability of the effect estimates supplied by the indirect comparison between ibuprofen vs. placebo will be examined for consistency with the evidence available from direct meta-analyses for ibuprofen vs. indomethacin, indomethacin vs. placebo and ibuprofen vs. placebo.

Interpreting the results of indirect comparisons.

The strength of evidence supplied by indirect comparisons is dependent upon several factors. Mc Alister (292) ranked the strength of evidence from indirect comparisons between drugs from the same class as level 2-4 in the hierarchy of evidence, from observational cohort to case-control depending upon use of subgroups and type of endpoint, i.e. clinically important or validated/unvalidated surrogate. The use of a' priori subgroup analysis and/or clinically important outcomes relating to long term efficacy increased the strength of evidence provided by indirect comparisons in populations with similar and/or different disease risk and factor status compared to those using post hoc subgroups, short term and/or surrogate outcomes. For this reason, we intend to use clinically important endpoints only and provide information where available on patient subgroups where possible as stated in the Methods section.

The incorporation of direct head to head trials with adjusted indirect comparisons may lead to an improvement in statistical power. Song (293) suggests that exaggeration of treatment effect resulting from bias in direct head to head trials introduced by elements of poor methodological quality such as inadequate allocation concealment or lack of blinding may be reduced by the use of indirect comparisons. Further investigation of the use of indirect comparisons to test for bias in direct trials by Song (294) indicated a consistent reduction in effect estimate in indirect compared with direct estimates across all 3 case examples. The effect estimates from indirect comparisons remained similar despite sensitivity analyses including placebo controlled vs. head to head drug comparisons, time-dependent changes and analysis as intention to treat. According to Song (294) indirect comparisons may be less biased than direct comparisons in certain situations, for instance where selection bias may have led to an overestimation of the effect of a newer medication. This may have occurred in randomised trials between ibuprofen and indomethacin, given that ibuprofen is the newer drug with potentially less adverse effects which may influence clinicians to subvert the randomisation process and select it in preference to indomethacin. Poor methodological quality in randomised trials, particularly inadequate blinding of the intervention or difficulty maintaining allocation concealment allowing clinicians to identify which treatment the patients are receiving and can lead to bias in clinical management and/or reporting of outcomes resulting in overestimation of the effect of new treatment. As stated in methods for performing indirect comparisons, use of indirect and direct comparisons may assist in the assessment of consistency in effect estimates between treatment comparisons; however the extent of this assessment will depend upon the availability of studies.

A number of studies underscore the need to consider effect estimates from both direct and indirect comparisons where available. From their evaluation of the use of indirect and direct comparisons between multiple treatments for breast cancer, Gelber (287) proposes that indirect comparisons when used alone are of limited value in defining the "optimal therapeutic regimen" from trials of a number of treatment modalities. Inconsistencies between estimates from direct and indirect comparisons between interventions from randomised trials, prompted Bucher (289) to recommend use of indirect comparisons in situations where direct evidence is limited or absent whilst recognizing the limitations of any inferences drawn from the results. Glenny (295), who also found a degree of incoherence between direct and indirect evidence obtained from simulated meta-analyses of random samples of interventions for stroke prevention, similarly proposes that indirect comparisons should be supported with data from direct comparisons where possible. In addition Glenny (295) suggests that the risk of confounding due to differences between drug classes, action and dose in indirect comparisons is similar to that of observational studies. In support of this finding, Chou (296) found large disparity between indirect and direct comparisons of trials for anti-retroviral drugs. In these trials, many different agents were used, with variation in the type and combination of agents used within individual trials. Patients also varied widely in their prognoses. Song (293) initially argued that the results of indirect comparisons usually agreed with those of direct head to head trials and suggested that indirect comparisons may be a useful source of information when comparing the efficacy of drugs in the absence of any direct evidence but later found from randomised trials of new vs. conventional drugs, that the effect estimates from the direct compared with indirect comparisons consistently overestimated the relative risk of disease outcomes. Song (294) offered the following potential explanations for this overestimation, including; chance, bias in the direct trials, bias in the indirect comparison and clinically meaningful heterogeneity. Lack of consistency between direct and indirect effect estimates have led to the general recommendation that indirect comparisons should preferably be used in conjunction with direct comparison, however it is not known whether this inconsistency is due to bias in either or both of the direct or indirect comparisons or due to the confounding effects of variation in baseline risk of disease within the population included in the meta-analyses.

Indirect comparisons are also subject to bias depending upon the similarity between the patients, treatments and outcomes being investigated. Anti-retroviral drug trials by Chou (296) included patients with a wide variety of disease prognoses, whilst breast cancer trials examined by Gelber (287) are similarly likely to have included women with a range of disease risk. Disparities in effect sizes between indirect and direct comparisons may have

resulted from between trial differences in population disease risk. Ibuprofen and indomethacin are both from the same drug class of COX inhibitors and being used for the same study aim i.e. PDA closure in a similar population of preterm infants. The trials to be included in the proposed network meta-analysis is more likely to represent a set of interventions with a homogenous effect on the disease and a reasonably homogenous population of preterm infants exposed to similar range of pathophysiology. This is likely to improve the consistency of estimates of RR between indirect and direct comparisons, however, similar to standard meta-analyses, Glenny (295) recommends formal assessment of potential confounding from patient characteristics and disease severity between direct meta-analyses on risk of outcomes in the indirect comparison using heterogeneity testing in addition to narrative review. Direct meta-analyses will therefore be examined for heterogeneity prior to the pooling data in order to detect heterogeneity prior to conducting the indirect comparison.

Despite potential limitations with consistency of the effect estimates, indirect comparisons may have a role in examining clinically meaningful heterogeneity and generating hypotheses for future research studies. Song (294) proposes that differences between indirect and direct comparisons may be useful as a means of examining clinically meaningful heterogeneity. Clinically relevant heterogeneity is a potential source of discrepancy in direct comparisons arising from between-study variation in population characteristics and treatments contributing to different patient responses to treatment with corresponding changes in the measured outcomes. In the population of preterm infants with PDA, this may involve population variables such as gestational age, birthweight, and treatment variables such as the method of PDA detection and number of doses of intervention received. Such information may be clinically relevant and allow insight into treatment response and adverse effects between preterm infant subsets. Gelber (287) suggests that indirect comparisons may be useful in generating hypotheses for future research studies. Where traditional systematic reviews and meta-analyses are able to provide recommendations for future trials for the effect of limited range of treatment comparisons on disease-related outcomes, indirect comparisons add depth to this enquiry by forming a network of treatments which can be compared simultaneously.

Chapter 2 – Published version of research paper

Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants

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ABSTRACT

Objectives To evaluate the effects of indomethacin or ibuprofen compared with placebo on closure, morbidity and mortality in preterm infants <37 weeks' gestation with echocardiographically and/or clinically important patent ductus arteriosus (PDA) at >24 h of life.

Data sources MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL, Cochrane Library, clinicaltrials.gov, controlled-trials.com, American Pediatric and European Paediatric Research Societies and Effective Care of the Newborn Infant.

Review methods Systematic review with network meta-analysis of randomised studies comparing intravenous indomethacin, ibuprofen or placebo for PDA in preterm infants at >24 h of life.

Results Ten trials compared intravenous indomethacin versus intravenous ibuprofen, nine intravenous indomethacin versus placebo and one intravenous ibuprofen versus placebo. Both intravenous indomethacin (pooled RR 2.39 (95% CI 2.05 to 2.78)) and intravenous ibuprofen (RR 2.40 (95% CI 2.03 to 2.84)) closed a PDA more effectively than placebo. Intravenous ibuprofen was associated with approximately 30% greater risk of chronic lung disease than intravenous indomethacin (RR 1.28 (95% CI 1.03 to 1.60)) or placebo (RR 1.29 (95% CI 0.99 to 1.70)). Differences in risk or benefit were not significant between any combination of intravenous indomethacin, intravenous ibuprofen or placebo groups for *intraventricular haemorrhage,* necrotising enterocolitis and death. Reporting on neurological outcomes was insufficient for pooling.

Conclusions Intravenous indomethacin or ibuprofen administered to preterm infants for PDA at >24 h of life promoted ductal closure, but other short-term benefits were not seen. Treatment with intravenous ibuprofen may increase the risk of chronic lung disease. Good-quality evidence of treatment effect on morbidity, mortality and improved neurodevelopment is urgently needed.

What is already known on this topic

► Exposure to PDA in preterm infants may increase morbidity and mortality; however, the link between PDA and disease causation has not been clearly demonstrated.
► Intravenous indomethacin administered before 24 h of life regardless of PDA status is the only treatment regime to demonstrate any benefit of protection against severe IVH.
► Ibuprofen is an alternative to indomethacin with equal efficacy in PDA closure and the potential benefit of less renal and gastrointestinal ischaemia.

What this study adds

Administration of intravenous ibuprofen compared with placebo for clinically important PDA beyond 24 h of life:
► is twice as likely to close the PDA compared with placebo;
► was not associated with any benefit or harm on the short-term outcomes of NEC, any IVH and death before hospital discharge;
► may be associated with an increase in the risk of CLD.

Observational studies have suggested an association between echocardiographically and/or clinically important patent ductus arteriosus (PDA) in preterm infants and increased risk of chronic lung disease (CLD), necrotising enterocolitis (NEC), *intraventricular haemorrhage (*IVH), poor neurodevelopmental outcome and mortality; however, a clear role in causation remains elusive.[1 2] In contrast, there is strong evidence of adverse effects arising from the use of intravenous indomethacin to close a PDA within the first 1–3 weeks of life. Examples include brain white matter injury, NEC, intestinal perforation, renal impairment and white cell/platelet dysfunction.[2–6] Intravenous ibuprofen, developed as a potential alternative to

indomethacin, tends to have less vasoconstrictive effect on cerebral, mesenteric and renal arterial beds with improved blood flow.[7]

Recent surveys of preterm infant PDA management in the USA and Australia indicated a wide practice variation; from prophylactic indomethacin or ibuprofen to late pharmacological intervention with indomethacin and/or surgical ligation for persistent PDA.[8 9] Cochrane systematic reviews have indicated that intravenous indomethacin administered to preterm infants at <24 h of life and regardless of PDA status is the only regime associated with a reduction in short-term risk of severe IVH. Such an approach exposes more infants to adverse effects of indomethacin in the absence of any evidence of benefit on longer-term neurological outcomes.[10]

Ibuprofen has been investigated as an alternative to indomethacin with benefits of equal efficacy in PDA closure, less transient renal ischaemia

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and potential reduction in NEC balanced by lack of efficacy in IVH reduction and reports of pulmonary hypertension and haemorrhage with early use.[7] [11] Intravenous ibuprofen compared with placebo in the treatment of PDA at <24 h of life does not reduce IVH and, in case reports, may be associated with pulmonary hypertension and haemorrhage.[7]

In preterm infants >24 h of life, the evidence from Cochrane is limited to a direct comparison between the two medications, intravenous ibuprofen and intravenous indomethacin.[11] Their review findings indicate that intravenous ibuprofen has equal efficacy in PDA closure, with less transient oliguria.[11] This, of course, only represents the comparison of the relative effectiveness of indomethacin versus ibuprofen on PDA closure, related morbidities and mortality; it does not indicate the baseline risks of untreated PDA or potential treatment adverse effects. Previous meta-analyses of intravenous indomethacin versus placebo for echocardiographically and/or clinically important PDA in preterm infants at >24 h of life exist; however, these are in need of updating in light of new trials.[12] [13] Importantly, there are no direct meta-analyses of intravenous ibuprofen versus placebo in this setting.[11]

METHODS
Search strategy
We searched MEDLINE (1966 to August 2008), EMBASE (1982 to August 2008), CINAHL (up to August 2008), The Cochrane Central Register of Controlled Trials, The Cochrane Library (issue 3, 2008), clinicaltrials.gov and controlled-trials.com. We hand searched abstracts of the national and international American Pediatric Society/Pediatric Academic Societies and The European Paediatric Research Societies and the Effective Care of the Newborn Infant. The authors were contacted for further information regarding unpublished trials and reports found in published databases. Search terms included MeSH: infant, newborn AND ductus arteriosus, patent AND, indomethacin OR ibuprofen OR cyclooxygenase inhibitors AND randomised controlled trial (RCT). No search limits were applied.

Selection
We included all randomised and quasi-randomised trials comparing intravenous indomethacin with placebo, intravenous indomethacin with intravenous ibuprofen and intravenous ibuprofen with placebo in preterm (<37 weeks) or low–birth weight infants (<2500 g) with an echocardiographically and/or clinically important PDA at >24 h postnatal age. Thus, studies providing evidence of echocardiographic (ductal size, left to right shunt, atrial enlargement) or clinical (systolic murmur, hyperactive precordium or bounding pulses) criteria for the diagnosis of PDA or both were included.

The primary outcome for all the studies was PDA closure, and the secondary outcomes were (1) death before hospital discharge; (2) NEC in the neonatal period; (3) IVH, including all grades and/or grade 3 to grade 4; (4) CLD at 28 days and/or 36 weeks, corrected and/or at any age reported and (5) neurodevelopment as measured by Bayley Scales of Infant Development.[14] Studies of intravenous indomethacin or intravenous ibuprofen prophylaxis (defined as treatment given at <24 h postnatal age) and regimes including oral forms of indomethacin or ibuprofen were excluded.

Validity assessment
We assessed the methodological quality of all the trials for randomisation, allocation concealment, blinding to intervention and accounting of loss to follow-up using the Jadad Scale with a score of 5 indicating highest quality (table 1)[15].

Data abstraction
Two authors assessed the methodological quality of the trials and extracted the data. Complete articles were used where possible. Disagreements were resolved with the assistance of a third reviewer.

Quantitative data synthesis
Data were pooled separately according to treatment comparison and outcomes using fixed and random effects models. The effects of intravenous ibuprofen versus intravenous indomethacin and intravenous indomethacin versus placebo were directly compared by pooled risk ratio (RR) using the inverse variance method. The 95% CIs were calculated. Planned sensitivity analyses included trials with (1) quality scores of <3 and ≥3, (2) blinding of operators and participants to study medication versus no blinding, (3) mean age of treatment <72 versus ≥72 h and (4) use of clinical versus echocardiographic criteria for primary case identification. Heterogeneity among studies was assessed using I^2 and, where this was significant, was further investigated using sensitivity analyses of post hoc variables mean gestational age at birth <28 versus ≥28 weeks, mean birth weight <1000 versus ≥1000 g and three doses versus one to three doses. Funnel plots were examined for presence of asymmetry indicative of publication bias with further Egger regression testing where appropriate.

This study had two components. First, traditional direct meta-analyses of intravenous indomethacin versus intravenous ibuprofen and intravenous indomethacin versus placebo were performed. Second, these direct meta-analyses were combined using network meta-analysis. Network meta-analysis is a relatively new technique that can be used to indirectly compare the risk or benefit associated with randomly allocated treatments that have not been directly tested against each other. Trials need to have been conducted in populations with similar age and disease profile sharing a common treatment or placebo arm.[15] [16] We chose to use network meta-analysis to estimate the baseline risk or benefit associated with the administration of intravenous ibuprofen compared with placebo.

Figure 1 represents an example of the graph yielded by the three-way network meta-analysis procedure for the outcome of PDA. The natural logarithms of the RR (logRR) of the two direct meta-analyses, intravenous indomethacin versus intravenous ibuprofen and intravenous indomethacin versus placebo, were derived using χ^2 analysis or Fisher exact test (as appropriate) and then fitted into a meta-regression model. A restricted estimation of maximum likelihood function was used in the meta-regression. Indirect estimates of the pooled relative risks (RR) between intravenous ibuprofen versus placebo for the outcomes of PDA closure, death, NEC, IVH and CLD were then estimated. In this manner, we were able to compare the relative benefit or risk of the direct meta-analysis of intravenous indomethacin versus placebo and the indirect network meta-analysis of intravenous ibuprofen versus placebo for the stated outcomes. The incidence of each of these outcomes for the comparators ibuprofen, indomethacin and placebo were pooled and used to calculate the number of preterm infants needed to treat or harm.[17] This information allowed us to estimate the sample sizes required to demonstrate a statistically significant result for each outcome in future randomised trials.

Table 1 Summary of characteristics and methodological quality of the included studies

Study (year)	Participants n	Participants Birth weight (g)	Echo used to identify PDA	Age at treatment (days)	Quality score	Non-randomised indomethacin given as rescue treatment, n (%)	
						Intravenous ibuprofen	**Intravenous indomethacin**
Intravenous ibuprofen versus intravenous indomethacin							
Adamska et al (2005)[23]	35	<1500	Yes	2	5	Unable to translate	
Gimeno Navarro et al (2005)[24]	47	700–1700	To confirm	2–5	2	7 (30)	3 (13)
Lago et al (2002)[34]	175	700–1750	Yes	2–3	2	25 (23)	25 (31)
Mosca et al (1997)[35]	16	600–1620	Yes	29 h†	2	1 (13)	0
Patel et al (2000)[27]	33	450–2800	To confirm	7.5†	5	5 (28)	3 (20)
Pezzati et al (1999)[36]	17	580–1900	Yes	1–2	1	Nil given	Nil given
Plavka et al (2001)[21]	41	<1200	To confirm	2†	1	Not stated	Not stated
Su et al (2003)[37]	63	<1500	Yes	5†	1	Not stated	Not stated
Van Overmeire et al (1996)[22]	28	<1700	Yes	2–3	2	Not stated	Not stated
Van Overmeire et al (1997)[38]	40	<1750	Yes	2–3	1	4 (20)	3 (15)
Van Overmeire et al (2000)[28]	148	800–1700	Yes	2–3	2	12 (16)	9 (12)
Total number	643						
Intravenous indomethacin versus placebo						**Intravenous indomethacin**	**Placebo**
Gersony et al (1983)[26]	410	500–1750	To confirm	1–14	5	28 (21)	176 (65)
Hammerman et al (1987)[31]	24	<1000	Yes	2–3	3	2 (20)	5 (36)
Krauss et al (1987)[33]	27	<1500	Both	>24 h	2	Nil given	Nil given
Mahony et al (1982)[32]	47	700–1700	Yes	3†	4	2 (20)	7 (58)
Merritt et al (1981)[40]	25	700–1300	To confirm	2†	2	3 (30)	11 (85)
Monset-Couchard et al (1983)[25]	24	1100–1800	To confirm	Not stated	2	2 (17)	10 (83)
Van Overmeire et al (1996)[22]	28	<1700	Yes	2–3	2	Not stated	Not stated
Weesner et al (1987)[29]	26	650–1400	Yes	2†	4	0	4 (31)
Yeh et al (1981)[30]	55	800–1700	To confirm	9†	5	3 (12)	21 (78)
Total n	666						
Intravenous ibuprofen versus placebo						**Intravenous ibuprofen**	**Intravenous indomethacin**
Van Overmeire et al (1996)[21]	28	<1700	Yes	2–3	2	Not stated	Not stated

†Estimated mean.

Analyses were performed using the STATA V.10.0 and Revman V.5.0.[18][19] A p≤0.05 was used for statistical significance for all tests except heterogeneity in which 0.10 was used. Sample sizes for future trials were estimated from the event rates for each outcome using a power of 0.8 and α=0.05, with continuity correction where appropriate.

RESULTS

The search yielded a total of 565 citations; the title and abstract of each were screened, and 474 papers were excluded. The remaining 91 papers were examined as potentially relevant RCTs. Twenty-two of these met the inclusion criteria: 3 were later excluded, and 19 RCTs were included across the three meta-analyses (fig 2).

Study characteristics

Table 1 provides details of the characteristics of the 19 trials identified for all three comparisons. Only one trial compared intravenous ibuprofen with placebo; this comparison was thus estimated using indirect network meta-analysis, as described above.

Methodological quality of studies

The methodological quality of the included studies is summarised in table 1. Data for two trials were reported in abstract form only.[20][21] Three trials were translated from foreign language papers with English abstracts.[22–24] Randomisation was adequately described in eight trials; and allocation concealment, in five.[22–31] Six trials adequately described blinding.

Fourteen trials analysed the results according to intention to treat for all outcomes.[20–27][32–37]

FINDINGS OF THE INCLUDED STUDIES
Primary outcome

Intravenous indomethacin and intravenous ibuprofen demonstrated equal effectiveness in preterm infants with echocardiographically and/or clinically important PDA at >24 h of life, with both drugs twice as likely to close the PDA compared with placebo. The robustness of this result is supported by a similar finding of no statistically significant difference in PDA closure rates for the direct meta-analysis intravenous ibuprofen versus intravenous indomethacin.

As indicated by the I^2 values in fig 3, there was a high level of heterogeneity in effect size between the studies included in the direct meta-analysis between indomethacin and placebo for PDA closure. The sensitivity analyses for all the three treatment combinations including studies with the prespecified variables including mean age at treatment and post hoc variables mean birth weight and mean gestational age (supplementary tables 9a and b) did not change the direction or the statistical significance of the effect estimate for PDA closure with the exception of mean gestational age <28 weeks for the comparison intravenous indomethacin versus placebo in which indomethacin was no longer statistically significantly effective. Despite mild funnel plot asymmetry on visual examination for the comparison of intravenous indomethacin versus placebo, Egger regression asymmetry testing (p=0.5) indicates that publication bias

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is unlikely; however, the small number of studies may reduce the accuracy of this assessment.

Secondary outcomes

The direct meta-analysis of intravenous ibuprofen versus intravenous indomethacin indicated a statistically significant increase in the risk of CLD at any age reported (fig 4) associated with the administration of intravenous ibuprofen for closure of echocardiographically and/or clinically important PDA in preterm infants at >24 h of life.

The indirect meta-analysis between ibuprofen and placebo indicated an increase in the risk of CLD of borderline statistical significance. The administration of intravenous indomethacin was not associated with a reduction in the risk of CLD in the direct meta-analysis between intravenous indomethacin versus placebo. There was mild between-study heterogeneity in effect sizes for the outcome of CLD in the direct meta-analysis between indomethacin and placebo, which may have resulted from the use of different definitions of CLD or variations in baseline risk of respiratory morbidity between studies. Risk of CLD for intravenous ibuprofen versus intravenous indomethacin remained statistically significantly increased for all sensitivity analyses with the exception of mean age at treatment <72 h.
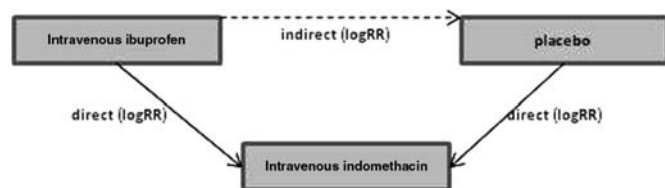
Figure 1   Simplified diagram of indirect network meta-analysis.

Only two studies reported further on neurodevelopmental outcomes at follow-up. Both studies used the Bayley Neurodevelopmental Scales at 1-year corrected age and compared intravenous indomethacin with placebo; however, because data were presented as mean scores in Yeh and incomplete categorical scores in Peckham, the estimates could not be pooled and were analysed separately.[38–40] The mean difference between scores or risk of poorer neurological outcomes
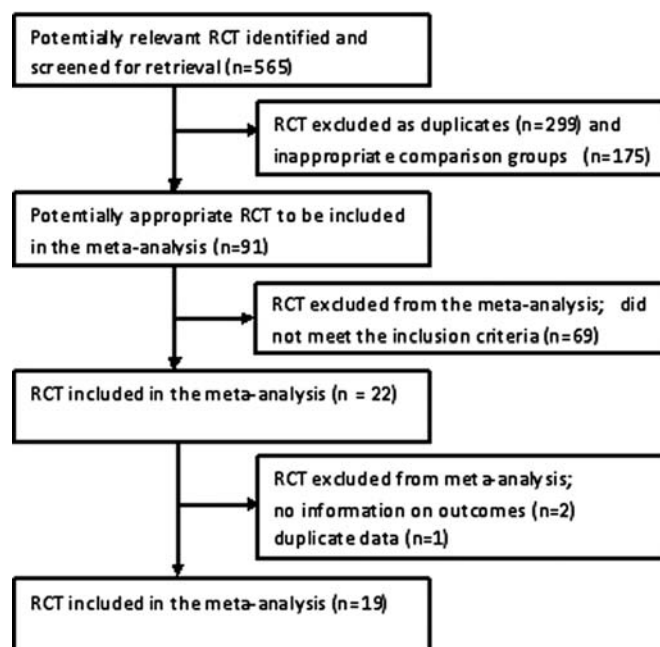
Figure 2   Search results and selection of papers (QUOROM statement flow diagram).

Table 2   Summary of effect estimates, incidence rates, numbers needed to harm or treat and sample sizes

Outcomes	No. of studies	Intravenous indomethacin	Placebo	Pooled RR (95% CI)	Incidence rate (%)† Indomethacin	Placebo	NNH	NNH/100	Sample size‡
PDA closure	9	208/253	121/400	2.39† (2.05 to 2.78)	65.2	27.3	3§	33	21
NEC	5	10/189	17/335	0.97 (0.44 to 2.11)	4.5	4.7	650§	0.2	135657
All IVH	4	25/188	34/334	1.13 (0.70 to 1.82)	19.4	17.1	44	2	3640
All CLD	6	64/214	97/360	1.05 (0.85 to 1.29)	48.7	46.5	46	2	6489
Death	8	38/252	49/401	1.08 (0.72 to 1.62)	13.1	12.2	106	<1	16027

Outcomes	No. of studies	Intravenous ibuprofen	Intravenous indomethacin	Pooled RR (95% CI)*	Difference in incidence rate (%)	Sample size‡
PDA closure	10	243/315	228/300	1.00 (0.93 to 1.08)	0.3	311769
NEC	3	9/243	15/230	0.60 (0.27 to 1.33)	−1.8	1433
All IVH	6	20/253	16/243	1.16 (0.61 to 2.21)	0.3	202662
All CLD	5	93/243	69/230	1.28† (1.03 to 1.60)	13.1	177
Death	5	22/243	22/230	0.99 (0.55 to 1.80)	0.08	2209396

Outcomes	No. of studies	Intravenous ibuprofen	Placebo	Pooled RR (95% CI)	Incidence rate† Ibuprofen	Placebo	NNH	NNH/100	Sample size‡
PDA closure	20	253/329	125/414	2.40† (2.03 to 2.84)	65.5	27.3	3§	33	25
NEC	8	9/243	17/335	0.58 (0.19 to 1.77)	2.7	4.7	50§	2	1199
All IVH	10	22/267	37/348	1.15 (0.56 to 2.36)	19.7	17.1	39	3	2906
All CLD	12	102/257	105/366	1.29† (0.99 to 1.70)	61.8	46.5	7	14	131
Death	13	22/243	49/401	1.07 (0.52 to 2.22)	13.2	12.2	99	1	13640

NNH, number needed to harm.
RR and CI were obtained from metaregression.
†Pooled prevalence.[41]
‡Sample size per intervention group required to show a statistically significant result in a randomised trial.
§NNT, number needed to treat.

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Direct comparison PDA closure intravenous ibuprofen versus intravenous indomethacin								
Mosca 1997	0	0.11	8	8	11.7%	1.00 [0.80, 1.25]	1997	
Van Overmeire 1997	0.06	0.17	20	20	5.2%	1.07 [0.76, 1.49]	1997	
Pezzati 1999	0.006	0.11	9	8	13.0%	1.01 [0.81, 1.24]	1999	
Patel 2000	−0.18	0.14	18	15	7.4%	0.83 [0.63, 1.10]	2000	
Van Overmeire 2000	0.06	0.11	74	74	12.1%	1.06 [0.85, 1.32]	2000	
Plavka 2001	0.008	0.13	21	20	9.1%	1.01 [0.78, 1.30]	2001	
Lago 2002	0.06	0.10	94	81	16.3%	1.06 [0.88, 1.28]	2002	
Su P 2003	0.05	0.12	32	31	11.3%	1.05 [0.83, 1.31]	2003	
Gimeno Navarro 2005	−0.06	0.12	23	24	10.1%	0.94 [0.74, 1.20]	2005	
Adamska 2005	−0.14	0.21	16	19	3.6%	0.87 [0.58, 1.30]	2005	
(95% CI)			**315**	**300**	**100.0%**	**1.00 [0.93, 1.08]**		
Heterogeneity: τ²=0.00; χ²=3.24, df=9 (p=0.95); I²=0%								
Test for overall effect: Z=0.07 (p=0.95)								
Direct comparison PDA closure intravenous indomethacin versus placebo								
Merritt 1981	1.69	0.66	12	13	5.2%	5.42 [1.48, 19.87]	1981	
Yeh 1981	1.39	0.37	28	27	11.3%	4.02 [1.96, 8.23]	1981	
Mahony 1982	0.45	0.18	21	26	18.6%	1.57 [1.10, 2.24]	1982	
Monset-Couchard 1983	2.83	1.40	12	12	1.4%	17.00 [1.09, 265.02]	1983	
Gersony 1983	1.02	0.1	135	270	21.7%	2.78 [2.28, 3.41]	1983	
Hammerman 1987	0.17	0.28	6	10	14.6%	1.19 [0.69, 2.04]	1987	
Weesner 1987	0.69	0.31	13	13	13.3%	2.00 [1.09, 3.67]	1987	
Krauss 1989	1.48	0.70	12	15	4.7%	4.37 [1.11, 17.32]	1989	
Van Overmeire 1996	1.09	0.44	14	14	9.3%	3.00 [1.28, 7.06]	1996	
(95% CI)			**253**	**400**	**100.0%**	**2.41 [1.72, 3.36]**		
Heterogeneity: τ²=0.12; χ²=20.76, df=8 (p=0.008); I²=61%								
Test for overall effect: Z=5.16 (p< 0.00001)								
Indirect comparison PDA closure plus 1 direct study intravenous ibuprofen versus placebo								
Van Overmeire 1996	0.92	0.46	14	14	3.5%	2.50 [1.02, 6.10]	1996	
indirect 2009	0.87	0.09	315	400	96.5%	2.39 [2.02, 2.84]	2009	
(95% CI)			**329**	**414**	**100.0%**	**2.40 [2.03, 2.84]**		
Heterogeneity: τ²=0.00; χ²=0.01, df=1 (p=0.93); I²=0%								
Test for overall effect: Z=10.22 (p< 0.00001)								

0.02 0.1 1 10 50
Favours comparator   Favours intervention

Figure 3 Forest plot of three-way comparison intravenous indomethacin versus intravenous ibuprofen versus placebo, outcome 1: primary outcome: PDA closure (echocardiographically detected and/or clinically important).

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Comparator Total	Weight	Risk Ratio IV, Random, 95% CI	Year	Risk Ratio IV, Random, 95% CI
Direct comparison CLD intravenous ibuprofen versus IV indomethacin								
Van Overmeire 1997	0.35	0.21	20	20	30.1%	1.42 [0.95, 2.12]	1997	
Van Overmeire 2000	0.3	0.18	74	74	38.3%	1.34 [0.94, 1.92]	2000	
Lago 2002	0.42	0.31	94	81	13.0%	1.52 [0.83, 2.81]	2002	
Su P 2003	−0.17	0.45	32	31	6.2%	0.85 [0.35, 2.06]	2003	
Adamska 2005	−0.3	0.45	16	19	6.0%	0.74 [0.30, 1.82]	2005	
Gimeno Navarro 2005	0.04	0.46	23	24	6.3%	1.04 [0.43, 2.51]	2005	
(95% CI)			**259**	**249**	**100.0%**	**1.28 [1.03, 1.60]**		
Heterogeneity: τ²=0.00; χ²=3.09, df=5 (p=0.69); I²=0%								
Test for overall effect: Z=2.20 (p=0.03)								
Direct comparison CLD intravenous indomethacin versus placebo								
Yeh 1981	0.37	0.45	28	27	8.8%	1.45 [0.60, 3.51]	1981	
Merritt 1981	−1.31	0.68	12	13	4.2%	0.27 [0.07, 1.03]	1981	
Gersony 1983	0.2	0.18	140	281	32.5%	1.22 [0.85, 1.76]	1983	
Hammerman 1987	0 05	0.15	10	14	39.4%	1.05 [0.78, 1.41]	1987	
Weesner 1987	−0.6	0.75	10	11	3.5%	0.55 [0.13, 2.38]	1987	
Van Overmeire 1996	−0.24	0.39	14	14	11.6%	0.75 [0.35, 1.60]	1996	
(95% CI)			**214**	**360**	**100.0%**	**1.01 [0.76, 1.34]**		
Heterogeneity: τ²=0.03; χ²=6.66, df=5 (p=0.25); I²=25%								
Test for overall effect: Z=0.06 (p=0.95)								
Indirect comparison plus 1 direct study CLD intravenous ibuprofen versus placebo								
Van Overmeire 1996	0.12	0.31	14	14	0.0%	1.12 [0.62, 2.05]	1996	
indirect 2009	0.29	0.15	0	0	100.0%	1.34 [0.99, 1.82]	2009	
(95% CI)			**0**	**0**	**100.0%**	**1.34 [0.99, 1.82]**		
Heterogeneity: Not applicable								
Test for overall effect: Z=1.90 (p=0.06)								

0.1 0.2 0.5 1 2 5 10
Favours intervention   Favours comparator

Figure 4 Three-way comparison intravenous indomethacin versus intravenous ibuprofen versus placebo, secondary outcome 1: CLD at any age reported.

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Figure 5 Intravenous indomethacin versus placebo, secondary outcome 5: neurodevelopment at 12 months' corrected age. The mean difference in the Bayley Mental Developmental Index/Psychomotor Developmental Index score.
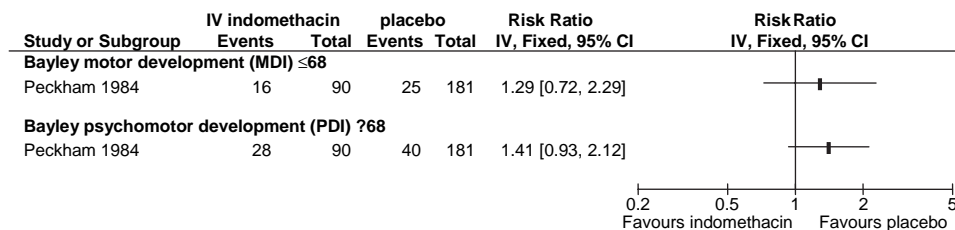
Figure 6 Intravenous indomethacin versus placebo, secondary outcome 5: neurodevelopment at 12 months' corrected age. Poor neurological outcome indicated by the Bayley Mental Developmental Index/Psychomotor Developmental Index ≤68.

indicated by a score of ≤68 was not statistically significant between intravenous indomethacin and placebo (figs 5 and 6).

The risks of NEC, IVH and death (supplementary tables 6, 7 and 8) were not significantly different between comparisons of intravenous ibuprofen versus placebo, intravenous ibuprofen versus intravenous indomethacin and intravenous indomethacin versus placebo. There were inadequate studies for IVH and NEC to perform sensitivity analyses.

Funnel plot asymmetry confirmed by a statistically significant p=0.04 on the Egger test was evident in the direct meta-analysis between ibuprofen and indomethacin for death. This indicated a relative absence of smaller studies showing higher estimates of the risk of death associated with intravenous ibuprofen, which may have arisen due to a tendency for smaller, less precise studies with negative outcomes to remain unpublished. Some funnel plot asymmetry was also noted in the comparison between indomethacin and placebo for the outcomes of CLD and death; however, the Egger test (p=0.5) for both outcomes indicates that publication bias is unlikely. Again, the small number of studies included in each comparison may reduce the accuracy of these assessments.

Analysis of the risk-to-benefit ratios for all the outcomes (table 2) indicates that treating 100 preterm infants at >24 h of life with intravenous ibuprofen or intravenous indomethacin rather than placebo may close an additional 33 PDA cases from which the only associated benefit may be the prevention of one case of NEC. PDA closure with intravenous ibuprofen rather than placebo may be associated with 14 extra cases of CLD per 100 infants, 3 extra cases of IVH and 1 death. The results were similar for intravenous indomethacin versus placebo, substituting an extra two cases each of CLD and IVH.

DISCUSSION

Intravenous ibuprofen administration at >24 h of life in preterm infants was equally effective with intravenous indomethacin in closing an echocardiographically and/or clinically important PDA; however, there was increased risk of CLD at any age reported for intravenous ibuprofen compared with that for indomethacin or placebo. This contrasts with the findings of the most recent Cochrane review, where the differences in the outcome of CLD between ibuprofen and indomethacin

did not reach statistical significance at 28 days, 36 weeks' corrected age or at any age reported. Unlike the Cochrane review, which combined studies of oral ibuprofen or indomethacin with intravenous, this review was restricted to trials of intravenous forms, and it is likely that the increased risk of CLD for ibuprofen seen in this review is associated with administration of intravenous rather than oral ibuprofen for PDA closure. There remains the possibility of a protective effect for intravenous indomethacin rather than an increased risk for intravenous ibuprofen in this meta-analysis, which may account for the comparatively lower risk of CLD for intravenous ibuprofen compared with that for placebo. Considering the small difference in incidence rates of CLD between intravenous indomethacin and placebo in comparison with that between intravenous ibuprofen and placebo (table 2), in addition to the wide differences in sample sizes required to achieve adequate power to detect a difference in a randomised trial between the two comparisons, any protective effect for intravenous indomethacin on CLD is likely to be small. The remaining outcomes of NEC, IVH and death show even smaller differences in the incidence rates between indomethacin, ibuprofen or placebo, which is further reflected in the large sample sizes. Lack of benefit for all the measured outcomes in this meta-analysis may be due to the lack of overall treatment effect of PDA closure with the use of intravenous indomethacin or intravenous ibuprofen or as a result of bias due to the use of non-randomised intravenous indomethacin treatment in the placebo group on which the incidence rates are based. Lack of precision indicated by wide CI surrounding the pooled relative risk for all comparisons for the outcomes of NEC, IVH and death is more than likely because of the small size and number of available studies included in the meta-analyses and may have contributed to the null findings.

A few notes of caution should be added to the findings of our review. There may be variation in baseline risk associated with (1) the inclusion of a range of birth weights, gestational ages and ages at treatment within and between the studies with inadequate reporting of outcomes for low birth weight, low gestational age and age at treatment subgroups and (2) potential differences in baseline incidence of outcomes between the direct meta-analyses of ibuprofen versus indomethacin

and indomethacin versus placebo used to provide the indirect comparison between ibuprofen and placebo. The latter may be due to time-dependent changes in treatment, diagnostic criteria for determination of PDA and study outcomes and survival of lower–gestational age preterm infants. Many of the studies included in this meta-analysis were small, and this may have impacted upon the estimates of pooled RR, particularly for the outcomes of PDA closure, CLD and death. Assessment of funnel plot asymmetry for the direct comparison of intravenous ibuprofen versus intravenous indomethacin indicates a tendency for the inclusion of small studies to overestimate any protective effect of intravenous ibuprofen towards the risk of death. This may have occurred because of the tendency for small studies to demonstrate larger treatment effects, greater tendency for publication of studies showing positive treatment effects or within- and between-study variations in levels of baseline risk of the measured outcomes in the preterm population.

PDA closure with intravenous indomethacin or intravenous ibuprofen administered for echocardiographically and/or clinically important PDA in preterm infants at >24 h of life was not associated with any reduction in the risk of major morbidity and mortality. Administration of non-randomised intravenous indomethacin treatment to the placebo arm was specified in seven of nine studies in the direct meta-analysis (table 1). The resulting lack of trials comparing either intravenous indomethacin or intravenous ibuprofen against placebo implies that the baseline incidence rates of many of the outcomes included in this meta-analysis had never been established in preterm infants before the widespread use of indomethacin for PDA closure. In addition, the diagnostic criteria for outcomes such as CLD, IVH and PDA, survival of extreme preterms and respiratory management have changed substantially since intravenous indomethacin was first introduced >30 years ago. Intravenous ibuprofen, a relative newcomer, has only ever been tested against intravenous indomethacin, and the increased risk of CLD with the administration of intravenous ibuprofen compared with standard intravenous indomethacin treatment or placebo indicated in our own direct and indirect meta-analyses highlights some concerns regarding the exacerbation of early pulmonary disease in preterm infants. The precise mechanism by which these two medications with similar therapeutic action and efficacy in closing the PDA could have different pulmonary outcomes remains unknown. Perfusion studies indicate that compared with intravenous indomethacin, intravenous ibuprofen has less tendency to reduce cerebral, mesenteric and renal arterial blood flow, whereas a recent experimental study in preterm baboons indicated beneficial effects on lung water clearance and alveolar preservation using either medication.[34] [35 38] The effect of intravenous indomethacin and intravenous ibuprofen on pulmonary physiology in preterm neonates has been less well studied.

Future RCTs comparing intravenous ibuprofen or intravenous indomethacin administered for echocardiographically and/or clinically important PDA at >24 h of life to placebo should be (1) of good quality, (2) include complete data on lower–birth weight subgroups, length of exposure to PDA and period of outcome measurement and, (3) examine longer-term respiratory and neurological outcomes. The large sample sizes indicated for most of outcomes in this analysis are difficult to achieve in a neonatal population; therefore, a multi-centre study is recommended with a minimum sample size required to detect a difference in CLD at 36 weeks' corrected age between intravenous ibuprofen and placebo of at least 130 preterm infants per treatment group. Avoidance of treatment in the placebo arm may reduce the sample size required to detect a difference in benefit and harm between intravenous ibuprofen and placebo or intravenous indomethacin and placebo for all outcomes examined in this analysis.

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Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants

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Appendices

Description of contents

1. Extended version of paper

This is an extended version of the network-meta-analysis originally submitted for publication to Perinatal and Pediatric Epidemiology. The paper was written according to the journal style; however we were subsequently advised by the journal that as an epidemiological journal it did not accept papers concerning pharmacological content. The paper was therefore rewritten in a shortened version in accordance with the Archives of Disease of Childhood instructions for authors and comprehensive feedback. Some of the estimates of relative risks in this extended version vary slightly from the published version for two reasons. The full paper by Adamska (297), which became available whilst the second paper was being written, provided additional data on the outcome of CLD. The network meta-analysis was rerun using this data and this was included in the shorter published version. The sensitivity analyses were also re-executed as the journal feedback indicated a simpler method of sensitivity analyses would be preferred to the original method of meta-regression.

2. Original data tables

These are the raw data tables for the network meta-analysis containing the studies included (with the exception of Adamska (297) for the outcome of CLD) and the corresponding estimated relative risks and confidence intervals for each study and the direct and indirect meta-analyses.

3. STATA output for main outcomes

These contain the raw data for the network meta-analyes for the outcomes of PDA closure, CLD, NEC, all IVH and death.

4. Supplementary tables for published version of paper

These include tables referred to as supplementary tables in the published paper.

1. **Extended version of paper**

Systematic review and network meta-analysis of intravenous ibuprofen, or intravenous indomethacin, versus placebo in the management of clinically significant patent ductus arteriosus in preterm infants at greater than 24 hours of life.

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Summary

Patent Ductus Arteriosus (PDA) is common in the neonatal period with an estimated 76% of infants born < 28 weeks gestation developing a clinically significant PDA. There exists great variation in the pharmacological management of PDA between neonatal units in both Australasia and the United States. Echo-targeted or symptomatic-targeted treatment of PDA with a prostaglandin synthetase inhibitor, intravenous (IV) indomethacin, or ibuprofen, at greater than 24 hours of life remains widely used.

We conducted a systematic review of intravenous prostaglandin synthetase inhibitors. Traditional and network meta-analyses were performed to provide direct and indirect comparisons between intravenous (IV) indomethacin, ibuprofen and placebo for the outcomes of PDA closure, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), chronic lung disease (CLD) and neurodevelopmental outcomes.

20 trials of varying quality were identified. Only one trial compared intravenous ibuprofen vs. placebo; this comparison was thus estimated using indirect network meta-analysis.
IV indomethacin and IV ibuprofen demonstrated equal effectiveness in preterm infants with pre-symptomatic or symptomatic PDA at greater than 24 hours of life, with both drugs twice as likely to close the PDA compared to placebo (pooled relative risk (RR) = 2.40 [95% CI 2.03, 2.84] and 2.28 [1.54, 3.39] respectively). Administration of IV ibuprofen compared to IV indomethacin or placebo was associated with a statistically significant increase in the risk of CLD (pooled RR 1.33 [95% CI 1.06, 1.67] and 1.34 [95% CI 1.01, 1.78] respectively; other outcomes were not significantly different between treatments. Neurodevelopmental outcomes at one year were reported in two studies only and were insufficient to be included in the meta-analysis.

Good quality randomized controlled trials of IV indomethacin and IV ibuprofen against placebo are needed to determine whether targeted treatment of an echocardiographically significant or symptomatic PDA with cyclooxygenase inhibitors in preterm infants of greater than 24 hours postnatal age reduce respiratory and neurological morbidity in the modern era.

Introduction

The ductus arteriosus (DA) forms part of the normal in utero circulation connecting the right pulmonary trunk to the descending aorta (298). Normal DA closure is dependent upon alveolar expansion following the commencement of respiration, accompanied by a rise in arterial oxygen and a drop in vena caval oxygen content (298). In addition, the reduced sensitivity to circulating prostaglandins, acts as a stimulus for ductal muscle contraction resulting in ductal closure (247, 299, 300). Patent Ductus Arteriosus (PDA), describes failure of the ductus arteriosus to achieve functional closure within the first few days of life (301, 302).

PDA is especially common in preterm infants, with an estimated incidence of 76% in infants born at less than 28 weeks gestation (49, 51). Other risk factors associated with the development of a clinically significant PDA include the severity of respiratory distress, lack of antenatal steroids, cyclo-oxygenase-2 (COX2) deficiency and infection (303-307).

Pathology attributed to clinically significant PDA is linked to the shunting of blood across the open duct from the aorta into the pulmonary artery (69, 109, 298, 308). The main consequences of this for the preterm infant are; systemic steal with widespread disturbance of arterial blood flow resulting in multi-organ ischemia, and; excessive pulmonary blood flow leading to increased pulmonary vascular pressure (48, 49, 99, 308-315).

A symptomatic PDA is characterised by signs including a systolic murmur, hyperactive precordium, congestive cardiac failure (CCF), respiratory instability, an increased need for ventilatory support and acidosis(166, 316-318). It has been postulated that treating the PDA will reduce the occurrence of co-morbidities such as death, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH) and chronic lung disease (CLD).

Pharmacological treatment to close the PDA was first used in the mid 1970's (191, 319-321). Indomethacin non-selectively inhibits cyclo-oxygenase reducing the synthesis of all prostaglandin subtypes from arachidonic acid, resulting in widespread vasoconstriction and ductal closure(322). Initial studies reported benefits for PDA closure with intravenous indomethacin when compared with surgical ligation in terms of a reduction in time on ventilation, level of oxygen supplementation and improvement in lung compliance (176, 191, 310, 323).

The traditional approach has been IV indomethacin for treating a clinically significant PDA within the first 1-3 weeks of life but this may be associated with adverse events including brain white matter injury, necrotising enterocolitis, gastric bleeding, intestinal perforation, renal impairment, and white cell and platelet dysfunction (162, 183, 222, 228, 230, 238, 242, 324-329).

More recently, neonatal echocardiography has shown that clinical signs and echo-significance are not well correlated leading to earlier treatment of echo-significant in addition to clinically apparent ducts (49, 107, 166). Other treatment approaches include targeting treatment at less than 24 hours of life by ductal size on echocardiography (109, 110, 211). Ibuprofen is postulated to have less effect on the cerebral, mesenteric and renal vasculature and has undergone investigation as a potential alternative to indomethacin.

Recent surveys of PDA management for preterm infants in the United States (US) and Australia indicate a wide variety of practices from prophylactic indomethacin or ibuprofen through to late pharmacological intervention with indomethacin and/or surgical ligation for persistent PDA only (281, 283). The commonest current regimes include IV indomethacin or ibuprofen in the setting of echo-targeted treatment of pre-symptomatic or symptomatic PDA at greater than 24 hours of life. Previous independent meta-analyses of IV indomethacin as treatment of either pre-symptomatic or symptomatic PDA at greater than 24 hours of life versus placebo have been performed, but are currently in need of updating (195, 203). In addition, there are no direct meta-analyses of IV ibuprofen versus placebo in this setting (267, 274).

This study had two components. Firstly traditional direct meta-analyses of IV indomethacin vs. IV ibuprofen and IV indomethacin vs. placebo were performed. Secondly, these direct meta-analyses were combined using the technique of network meta-analysis to provide indirect estimates of relative benefit or risk of IV ibuprofen vs. placebo for the outcomes of death, NEC, IVH, CLD and neurodevelopment. Incidence rates, number of infants needed to treat (NNT) or harm (NNH), and estimates of sample size required to demonstrate a statistically significant result were calculated for each outcome.

Methods

-   The systematic review was conducted according to a pre-defined protocol as outlined below.

Inclusion Criteria

We included all human randomized and quasi-randomized trials comparing IV indomethacin with placebo, IV indomethacin with IV ibuprofen, and IV ibuprofen with placebo. Intervention groups included preterm infants less than 37 weeks and/or birth weights less than 2500g with a significant patent ductus arteriosus at greater than 24 hours postnatal age as determined by: a) Clinical criteria for the diagnosis of a significant PDA including systolic murmur, hyperactive precordium, or bounding pulses. The clinical criteria could be alone or with echocardiographic confirmation, or; b) Studies providing an echocardiographic diagnosis of significant PDA.

The primary outcome for all studies was closure of the PDA and secondary outcomes included: (1) death prior to hospital discharge; (2) necrotizing enterocolitis (NEC) in the neonatal period; (3) intraventricular haemorrhage (IVH), including all grades and/or grade III to IV; (4) chronic lung disease (CLD) at 28 days or at 36 weeks corrected; (5) neurodevelopment as measured by standardized motor and psychological scales.

Exclusion Criteria

We excluded studies of IV indomethacin or IV ibuprofen prophylaxis defined as treatment given at less than 24 hours postnatal age and regimes including oral forms of indomethacin or ibuprofen.

Identification of studies

- We searched MEDLINE (1966 - AUG 2008), EMBASE (1982- AUG 2008), and CINAHL (up to Aug 2008) electronic databases, The Cochrane Central Register of Controlled Trials , The Cochrane Library, issue 3, 2007, clinicaltrials.gov, controlled-trials.com, Blackwell Synergy Online Early and the Journal of Pediatrics Online first. We hand searched abstracts of the national and international American Pediatric/Pediatric Academic (APS/PAS) Society, and The European Paediatric Research Society, the Journal of Pediatric surgery, and the Effective Care of the Newborn Infant. Authors were contacted for further information regarding unpublished trials and technical reports found in published databases. Search terms included Medical Subject Headings (MeSH): infant, newborn AND ductus arteriosus, patent AND, indomethacin OR ibuprofen OR cyclooxygenase inhibitors AND randomized controlled trial. No search limits were applied.

Data collection & abstraction

Two authors assessed the methodological quality of the trials using the Jadad scale and extracted the data (330). Complete articles were used where possible. Disagreements were resolved with the assistance of a third reviewer.

Statistical analysis.

- Data were pooled separately according to treatment comparison and outcomes using fixed and random effects models. The effects of IV ibuprofen versus IV indomethacin and IV indomethacin versus placebo were directly compared by pooling risk ratio using the inverse variance method. 95% confidence intervals (CI) were calculated. Planned sensitivity analyses included trials with: (1) quality scores of <3 and >= 3; (2) blinding of operators and participants to study medication vs. no blinding; (3) mean age of treatment < 72 hours vs. >= 72 hours; (4) use of clinical vs. echocardiographic criteria for primary case identification. Heterogeneity among studies was assessed using the Q test and I^2 and where significant was investigated using random effects and meta-regression modeling. Publication bias was assessed using Egger's test**.**

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Since only one study directly compared the outcomes between intravenous ibuprofen and placebo, network meta-analysis methods were used to estimate the effects of IV ibuprofen versus placebo using information from comparisons of IV ibuprofen versus IV indomethacin, and IV indomethacin versus placebo (Figure 1)(288, 291). The natural logarithms of the risk ratio of these two comparisons were fitted in a meta-regression model. A restricted maximum likelihood function was used in the meta-regression. Pooled relative risks (RR) between IV ibuprofen vs. placebo could then be estimated.

The incidence of each outcome was pooled and numbers needed to treat or harm estimated for the outcomes of PDA closure, IVH, CLD, NEC and death (331). All analyses were performed using STATA 10.0 (Statacorp 2008). A *P*-value of less than or equal to 0.05 was used for statistical significance for all tests except heterogeneity in which 0.10 was used. Event rates were also used to calculate sample sizes needed for future trials using PS-power (Dupont 2003) for each outcome based on power of 0.8, alpha = 0.05(332).

Results

The search yielded a total of 637 RCT's (555 electronic 82 hand search). 507 were not relevant or duplicated. 132 of these were potentially relevant RCT's and 22 met the inclusion criteria.

IV Indomethacin vs. placebo

Nine separate trials were identified for IV indomethacin vs. placebo (192, 197, 199, 206, 323, 333-335).

Quality assessment

Data for two trials were taken from abstracts (333, 334). Three studies adequately described blinding (192, 197, 204). Two studies achieved the highest possible total quality score of 5 with an average quality score of 3.2 across all nine trials (192, 204). Six out of nine trials accounted for losses to follow up; one analyzed these according to intention to treat for all outcomes(192, 197, 199, 204, 206, 335). The remaining three trials did not report losses to follow-up but the numbers analyzed balance those reported at study entry (333, 334, 336).

Primary outcome

All nine studies reported the outcome of initial PDA closure with total sample sizes of 253 for the IV indomethacin group and 400 for the placebo group. Of these, 208/253 and 121/400 subjects initially closed their PDA (Table 1). Neonates receiving IV indomethacin were more than twice as likely to close their PDA as those receiving placebo (pooled RR 2.40 [95% CI 2.03, 2.84]) (Table 1). This estimate showed a high level of heterogeneity (Q test *P*=0.008, I^2 =61.5%). Meta-regression indicated that birthweight and gestational age accounted for most of this variation whilst the contribution of postnatal age at treatment was not significant. There was insufficient reporting of data to examine the effect of other variables, such as ductal status at time of treatment, and total number of doses of IV indomethacin or placebo administered. Pooling using a random effects model gave similar results.

Secondary outcomes

Eight studies reported on the outcome of death in the neonatal period or prior to hospital discharge, four on all IVH, four on NEC, and six on CLD. Two papers reported on the outcome of neurodevelopment at 12 months, but these could not be combined as Peckham provided scores for

all survivors and Yeh reported only the scores of those infants with disability (337, 338).There was no statistically significant increase in IVH, CLD, NEC or death in the indomethacin group compared to placebo (Table 1). All pooled estimates except for CLD (I^2=25%) were homogenous and there was no evidence of publication bias for any outcome.

Sensitivity analyses

Trials with quality scores greater than 3, use of blinding and intention to treat analysis were associated with increased PDA closure rates which remained statistically significant compared to trials with quality scores less than 3, no or inadequate blinding, no intention to treat analysis or all trials combined.

Lower PDA closure rates (pooled RR 1.63 [95% CI 1.26, 2.11]) were associated with studies using echo to identify PDA compared to use of echocardiography to confirm a PDA where clinical signs were initially present (pooled RR 2.94 [95%CI 2.44, 3.57]). Planned sensitivity analyses for age at treatment with indomethacin at less than 72 hours compared to treatment at 72 hours or greater could not be performed due to inconsistent reporting in four studies including the largest trial (192, 206, 333, 336).

Risk to benefit ratio

Numbers needed to treat per 100 infants (NNT/100) calculated from pooled prevalence and incidence rates (Table 4) indicate that treating 100 preterm infants at greater than 24 hours postnatal age with IV indomethacin may close 33 PDA but result in 2 extra cases of CLD, 2 IVH, 1 of NEC and 1 death.

Sample size calculations

Based on the incidence rates for IV indomethacin vs. placebo (Table 4), a sample size of approximately 35 would be needed per intervention group to demonstrate a statistically significantly difference between IV indomethacin and placebo for the primary outcome of PDA closure. Samples sizes of 4918 per intervention group would be required to demonstrate statistically significant differences in risk between IV indomethacin and placebo for the outcome of all IVH, 8181 for CLD, 173251 for NEC and 20292 for death prior to hospital discharge.

IV ibuprofen vs. IV indomethacin

Ten separate trials were identified (339-349). Six of thirteen papers located were abstracts (334, 339-350). Three were from non-English journals with one partly translated from the full report, two represented preliminary reports of the full paper and another did not contain any quantitative data on outcomes (334, 339, 340, 350-352).

Quality assessment

A single trial with a quality score of 5 adequately described blinding, with an average quality score of 2.1 for all ten trials (345). Three trials accounted for losses to follow up and analyzed these according to intention to treat. The numbers analyzed in the remaining five trials balanced those reported at study entry, but did not mention intention to treat analysis (342, 343, 348).

Primary outcome

Nine studies were eligible yielding a total sample size of 315 for IV ibuprofen and 300 for Indomethacin. Of these, 243/315 and 228/300 subjects initially closed their PDA (refer table 1). IV

indomethacin and IV ibuprofen were equally effective in closing the PDA (pooled RR 0.93 [95% CI 0.71, 1.24]. This estimate was homogeneous, with no evidence of publication bias.

Secondary outcomes

-   Five trials reported on death in the neonatal period or prior to hospital discharge, NEC, CLD, severe IVH and 2 on all IVH. No papers reported on neurodevelopmental outcomes. There was a statistically significant increase in the risk of CLD with IV ibuprofen compared to IV indomethacin, with a pooled RR of 1.33 [95% CI 1.06, 1.67]. Other outcomes including IVH, NEC, and death did not differ. These estimates were homogenous and without publication bias with the exception of borderline publication bias (P=0.054) on the Egger test for death.

Sensitivity analyses

There were no differences in the pooled PDA closure rates between IV ibuprofen and IV indomethacin in any of the sensitivity analyses. Sensitivity analyses to assess the effect of blinding and quality on pooled estimates of relative risk were unable to be performed for the remaining outcomes as only one study with a total quality score of greater than 3 described blinding for the outcome of PDA closure.

Sample size calculations

Based on the incidence rates for IV ibuprofen vs. IV indomethacin (Table 4), a sample size of approximately 45479 would be needed per intervention group to demonstrate a statistically significantly difference between IV ibuprofen and indomethacin for the primary outcome of PDA closure. Samples sizes of 50875 per intervention group would be required to demonstrate statistically significant differences in risk between IV ibuprofen and IV indomethacin for the outcome of all IVH, 163 for CLD, 1790 for NEC and 4968291 for death prior to hospital discharge.

IV Ibuprofen vs. placebo

Reported trials

Two trials were identified. Aranda did not report any numeric results and so we undertook an indirect network meta-analysis (274, 334).

Primary outcome

Network meta-analysis indicated that similar to IV indomethacin, neonates receiving IV ibuprofen were approximately twice as likely to close a PDA compared to those receiving placebo (pooled RR 2.24 [95% CI: 1.44, 3.47]) (Table 3). Combining this result with the direct comparison from Van Overmeire yielded similar results (pooled RR 2.28 [95% CI: 1.54, 3.39])(334).

Secondary outcomes

Compared to placebo IV ibuprofen demonstrated a statistically significantly higher pooled RR of 1.39 [95%CI 1.02, 1.89] for the outcome of CLD, representing a potential 34% increase in risk of CLD for IV ibuprofen; this was similar to the increased risk of CLD when we compared IV ibuprofen directly with IV indomethacin. Other outcomes including IVH, NEC, and death did not differ.

Sensitivity analyses

Inclusion of studies with quality scores less than 3 or no blinding reduced the pooled RR of CLD toward the null for the indirect comparison from 1.34 [95%CI 1.01, 1.78] to 1.24 [95%CI 0.87, 1.76]). Inclusion of only those studies analysing with intention to treat or with balanced results increased the relative risk of CLD and this was statistically significant (pooled RR 1.48 [95%CI 1.00, 2.21]). Sensitivity analyses of studies using echo to identify PDA showed lower PDA closure rates (pooled RR 1.49 [95% CI 0.99, 4.91]) compared to those using echo to confirm PDA in which clinical signs were the initial presenting factor (pooled RR 2.75 [95% CI 2.16, 3.50] or all studies combined (pooled RR 2.24 [1.44, 3.47]).

Risk to benefit ratio

From the NNT/100 displayed in Table 4, treating 100 infants with IV ibuprofen rather than placebo may close an additional 33 PDA, prevent up to 2 cases of NEC, result in 17 extra cases of CLD, 3 of IVH and 1 death.

Sample size calculations

Based on the incidence rates for IV ibuprofen vs. placebo (refer table 4) a sample size of approximately 35 would be needed per intervention group to demonstrate a statistically significantly difference between IV ibuprofen and placebo for the primary outcome of PDA closure. Sample sizes of 2889 per intervention group would be required to demonstrate statistically significant differences in risk between IV ibuprofen and placebo for the outcomes of all IVH, 128 for CLD, 1495 for NEC and 23126 for death prior to hospital discharge.

Discussion

This systematic review indicates equal effectiveness between IV indomethacin and IV ibuprofen in closing the patent ductus arteriosus in preterm infants with pre-symptomatic or symptomatic PDA at greater than 24 hours of life, with both drugs about twice as likely to close the PDA compared to placebo. Importantly there was a 33 to 39% increase in the risk of CLD associated with the administration of IV ibuprofen in comparison to IV indomethacin or placebo for the treatment of PDA in preterm infants at greater than 24 hours postnatal age and this reached statistical significance. IVH, NEC and death were rare outcomes in these studies and neither IV indomethacin nor IV ibuprofen were associated with any statistically significant benefit. It is not possible to determine whether this similarity in event rates occurred because of the relatively small number of infants per intervention group in each meta-analysis or the allowance of crossover of infants from placebo to intervention group.

The clinical usefulness of these findings is dependent on the risk to benefit ratio. Treating 100 preterm infants at greater than 24 hours PNA with IV ibuprofen or IV indomethacin rather than placebo may close an additional 33 PDA, from which the only associated benefit may be the prevention of 1 to 2 cases of NEC. PDA closure with IV ibuprofen may be associated with 17 extra cases of CLD per 100 infants, 3 extra cases of IVH and 1 death. The results are similar for IV indomethacin with an extra 2 cases of CLD.

Risk-benefit ratios should be interpreted with caution. There have been dramatic changes in neonatal care over the past 20 years. Increased survival of lower gestational age infants combined with changes in the definition of CLD, NEC and IVH may have altered comparative disease incidence rates. At the same time, the benefit of treating the ductus on major longer-term outcomes remains undemonstrated and increasing the exposure of preterm infants to either IV indomethacin or

IV ibuprofen with the aim of PDA closure is associated with an increase in the risk of major morbidity.

Sensitivity analyses of primary case identification using echocardiography generally showed lower benefits than for clinically significant PDA. Studies with total quality scores greater than 3, adequate blinding and use of intention to treat had similar results indicating that differences in study quality were unlikely to be responsible for the increase in risk of CLD associated with the administration of IV ibuprofen.

Given that both IV indomethacin and IV ibuprofen close the PDA with equal effectiveness, theoretically these medications should reverse the effects of significant PDA leading to improved pulmonary gas exchange, cerebral blood flow, and gut perfusion, culminating in lower rates of CLD, IVH, NEC and death. Our direct and indirect meta-analyses do not support these benefits. This may be a real negative finding or due to methodological issues with the included studies.
Studies in the indirect comparison between IV ibuprofen and placebo had considerable methodological shortcomings likely to result in bias toward the null. The majority were of poor quality and older studies included preterm infants of widely varying gestational ages (25-32 weeks) and birthweight (700-2500g). Not all studies stated the requirement for respiratory support among study entrants and some used a combination of ventilation, nasal CPAP and head box oxygen (339, 345, 347, 352). Heterogeneity testing for PDA closure relative risk between IV indomethacin and placebo also demonstrated birthweight and gestational age variation. In addition, infants initially receiving placebo and failing to close the PDA often crossed over to receive indomethacin. Inadequately reported data such as total doses received, timing and nature of back-up treatment and measurement of outcomes may have contributed to bias in the estimation of pooled relative risk.

Sample size calculations based on the incidence rates in Table 4 indicate that 35 infants per intervention group would be required to demonstrate a statistically significant treatment effect for the outcome of PDA closure for IV indomethacin and IV ibuprofen compared separately with placebo whilst 128 infants per intervention group would be required to demonstrate benefit or harm for the outcome of CLD for IV ibuprofen compared to placebo. The remaining outcomes of NEC, IVH and death would require much larger sample sizes; beyond the scope of most neonatal trials and meta-analyses. For example, 2440 infants per intervention group would be required to demonstrate a statistically significant difference in risk of IVH between IV ibuprofen and placebo and 23126 infants per intervention group for the outcome of death between IV indomethacin and placebo.

These incidence rates may reflect low event rates or crossover of infants may have affected the true incidence of these outcomes in the placebo group. The crossover rate between indomethacin and placebo groups in the included studies was as high as 75%. Avoidance of treatment in the placebo group may decrease the sample size required to show a statistically significant difference in risk for all outcomes in this analysis. Avoidance of crossover or analysis methods to account for crossover for instance those utilising survival analyses should form a vital part of the design and analysis of future randomized trials intending to examine outcomes of IVH, NEC and death.

The increased risk of CLD with IV ibuprofen appears to occur independently of the similarity in effectiveness between IV ibuprofen and IV indomethacin in mediating ductal closure. This may stem from an essential difference in action between IV indomethacin and IV ibuprofen upon the pulmonary vasculature. Perfusion studies have demonstrated that ibuprofen tends to have less vasospastic effect upon the cerebral, mesenteric and renal arterial blood flow than indomethacin (343). Evaluation of the effect of IV indomethacin and IV ibuprofen on pulmonary blood flow in

neonates has been less well studied. In Cochrane reviews of indomethacin for management of PDA, IV ibuprofen compared with IV indomethacin was associated with less transient renal impairment however; the risk of CLD was increased at 28 days postnatal age (216, 267). IV ibuprofen given at less than 24 hours postnatal age compared against placebo performed similarly to IV indomethacin in separate Cochrane reviews (211, 353, 354). The clinical usefulness of IV ibuprofen is still being evaluated due to the lack of positive effect in protecting against early IVH in addition to cases of pulmonary hypertension and pulmonary haemorrhage associated with early administration of both oral and IV forms (216, 268, 269, 339, 355, 356).

The optimal period for clinical benefit arising from pharmacological closure of the PDA remains undetermined. Whether early exposure to untreated PDA predisposes preterm infants to IVH and later CLD, and more importantly, how this affects longer-term neurological and respiratory outcomes has not been demonstrated in randomized trials. It is possible that the increased risk of CLD is linked with earlier administration of IV ibuprofen. IV ibuprofen appears to be associated with greater risk of adverse pulmonary events, however IV indomethacin did not reduce CLD in this analysis and has been implicated in cases of pulmonary haemorrhage therefore the pulmonary effects of both drugs may not be limited to the duct (340, 357).

Many authors acknowledge that the complex interactive nature of the relationship between PDA and CLD is responsible for past failure to demonstrate causality (213, 358-361). The evidence from existing randomized trials is subject to distortion by significant crossover from placebo to treatment. Despite this, the incidence rates of CLD for both IV ibuprofen and IV indomethacin in our direct and indirect meta-analyses were higher in comparison to placebo. Treatment of infants in the placebo arm to close the PDA at different stages may have affected the true incidence of the outcomes in the placebo group; however, there remained a trend toward lower incidence favouring the placebo group for the outcomes of CLD, IVH and death. It is possible had there been fewer crossovers to treatment that the incidence of CLD and other adverse outcomes may be higher than the findings of this review.

Conclusion

Although IV ibuprofen and IV indomethacin were equally effective in closing echocardiographically significant and/or symptomatic PDA at greater than 24 hours of life, neither drug compared to placebo was associated with an improvement in the clinically relevant outcomes of death, NEC, CLD or IVH. Use of IV ibuprofen was associated with a statistically significant increase in the risk of CLD. These findings suggest that the evidence of clinical benefit for IV ibuprofen and IV indomethacin in the management of echocardiographically significant or symptomatic PDA in preterm infants of greater than 24 hours postnatal age on longer-term respiratory and neurological outcomes is lacking and the risks of treatment may outweigh the benefits. Targeting specific infants based on PDA size, clinical signs and at specific times may reverse this risk-benefit analysis. Considering the changes in neonatal respiratory management in the past two decades, well-designed good quality randomized controlled trials comparing indomethacin and ibuprofen to placebo with improved methods of handling crossover from control to intervention groups in the analysis and examining longer term respiratory and neurological outcomes are needed.

Table 1. Direct Meta-analysis: IV indomethacin versus placebo

Author	Year	PDA Closure		IVH		CLD		NEC		Death	
		RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]
Yeh[65]	1981	4.02 [a]	1.96, 8.23	...	...	1.45	0.60, 3.50	1.45	0.26, 7.99	1.16	0.40, 3.35
Merritt[61]	1981	5.42 [a]	1.48, 19.87	...	...	0.27	0.07, 1.03	...	...	0.27	0.04, 2.10
Mahony[60]	1982	1.57 [a]	1.10, 2.24	1.24	0.52, 2.97			0.41	0.05, 3.68	1.86	0.34, 10.11
Gersony[58]	1983	2.78 [a]	2.28, 3.41	0.96	0.46, 1.97	1.23	0.85, 1.76	1.00	0.39, 2.62	1.07	0.61, 1.85
Monset-Couchard[62]	1983	17.00 [a]	1.09, 265.02							7.00	0.4, 122.44
Hammerman[59]	1987	1.19	0.69, 2.04			1.05	0.78, 1.40				
Weesner[64]	1987	2.00 [a]	1.09, 3.67	1.67	0.50, 5.57	0.55	0.13, 2.38			1.00	0.25, 4.07
Krauss[66]	1989	4.38 [a]	1.11, 17.32							1.25	0.31, 5.11
Van Overmeire[63]	1996	3.00 [a]	1.28, 7.06	1.00	0.24, 4.13	0.75	0.35, 1.60			5.00	0.26, 95.61
Pooled RR		2.40 [a]	2.03, 2.84	1.13	0.70, 1.82	1.05	0.85, 1.29	0.97	0.44, 2.11	1.08	0.72, 1.62
Q test (P-value)		***P=0.008		P=0.880		P=0.248		P=0.670		P=0.653	
I^2		61.5		0		24.9		0		0	
Egger test (P-value)		P=0.632		P=0.512		P=0.460		P=0.718		P=0.263	

[a] Statistically significant result

Relative risk (RR) with 95% confidence intervals (95% CI) for studies included in the direct meta-analysis intravenous indomethacin versus placebo with pooled RR for the outcomes of PDA closure, death, IVH, NEC and CLD

Table 2. Direct Meta-analysis: IV ibuprofen versus IV indomethacin

Author	Year	PDA Closure		IVH		CLD		NEC		Death	
		RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]
Van Ovemeire[63]	1996			0.67	0.13, 3.40						
Mosca[73]	1997	1	0.80, 1.25								
Van Overmeire[78]	1997	1.07	0.76, 1.49	...	...	1.42	0.95, 2.12	1.00	0.07,14.90	0.33	0.04, 2.94
Pezzati[74]	1999	1.01	0.81, 1.24	...	...	...	...	...	...	...	...
Patel[75]	2000	0.83	0.63, 1.10	...	...	...	...	...	...	...	...
Van Overmeire[79]	2000	1.06	0.85, 1.32	2.50	0.50, 12.48	1.35	0.94, 1.92	0.50	0.16, 1.59	1.17	0.41, 3.31
Plavka[76]	2001	1.01	0.78, 1.30	...	...	...	...	...	...	...	...
Lago[72]	2002	1.06	0.88, 1.28	1.23	0.49, 3.09	1.52	0.83 ,2.81	0.86	0.12, 5.98	1.35	0.55, 3.33
Su P[77]	2003	1.05	0.83, 1.31	0.48	0.05, 5.07	0.85	0.35, 2.06	0.65	0.12, 3.61	0.24	0.03, 2.05
Gimeno Navarro[70]	2005	0.94	0.74, 1.20	2.09	0.20, 21.48	1.04	0.43, 2.51	0.35	0.02, 8.11	1.04	0.16, 6.80
Adamska[69]	2005	0.87	0.58, 1.30	0.39	0.02,9.01	...	...	...	...	...	...
Pooled RR		0.93	0.71, 1.24	1.16	0.61, 2.21	1.33 [a]	1.06, 1.67	0.60	0.27, 1.33	0.99	0.55, 1.80
Q test (P-value)		P =0.954		P =0.766		P =0.813		P =0.974		P =0.526	
I^2		0		0		0		0		0	
Egger test (P-value)		P =0.177		P =0.708		P =0.190		P =0.322		**P =0.054	

[a] statistically significant result (P <0.05) Relative risk (RR) with 95% confidence intervals (95% CI) for studies included in the direct meta-analysis intravenous ibuprofen versus intravenous indomethacin with pooled RR for the outcomes of PDA closure, death, IVH, NEC and CLD

Table 3. Indirect network meta-analysis: IV ibuprofen versus placebo

Author	Year	PDA Closure		IVH		CLD		NEC		Death	
		RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]	RR	[95% CI]
Van Overmeire[63]	1996	2.50 [a]	1.02, 6.10	0.67	0.14, 3.31	1.13	0.62, 2.05	...	...	...	...
Indirect comparison	2008	2.24 [a]	1.44, 3.47	1.19	0.37, 3.78	1.39 [a]	1.02, 1.89	0.58	0.19, 1.77	1.07	0.52, 2.20
Pooled RR		2.28 [a]	1.54, 3.39	1.17	0.57, 2.40	1.34 [a]	1.01, 1.78	0.58	0.19, 1.77	1.07	0.52, 2.20

[a] Statistically significant result (P <0.05)

Relative risk (RR) with 95% confidence intervals (95% CI) for indirect comparisons obtained from the 2 direct meta-analyses (IV ibuprofen vs. IV indomethacin and IV indomethacin vs. placebo) ,1 direct study and pooled RR for the outcomes of PDA closure, death, IVH, NEC and CLD

Table 4. Incidence and numbers needed to treat or harm: IV indomethacin vs. placebo and IV ibuprofen vs. placebo

	PDA			IVH			CLD		
	I	NNT	NNT/100	I	NNH	NNH/100	I	NNH	NNH/100
Ibuprofen	62.4	3	33	20	35	3	64.6	6	17
Indomethacin	63.3	3	33	19.3	44	2	48.7	46	2
Placebo	27.3	-	-	17.1	-	-	46.5	-	-

	NEC			Death		
	I	NNT	NNT/100	I	NNH	NNH/100
Ibuprofen	2.7	53	2	13.07	114	<1
Indomethacin	4.5	650	<1	13.13	106	<1
Placebo	4.7	-	-	12.2	-	-

Pooled incidence rates (I) and number needed to treat (NNT) or harm (NNH) for comparisons IV ibuprofen vs. IV indomethacin, IV indomethacin vs. placebo, and IV ibuprofen vs. placebo for the outcomes of PDA closure, death prior to hospital discharge, IVH, NEC and CLD.
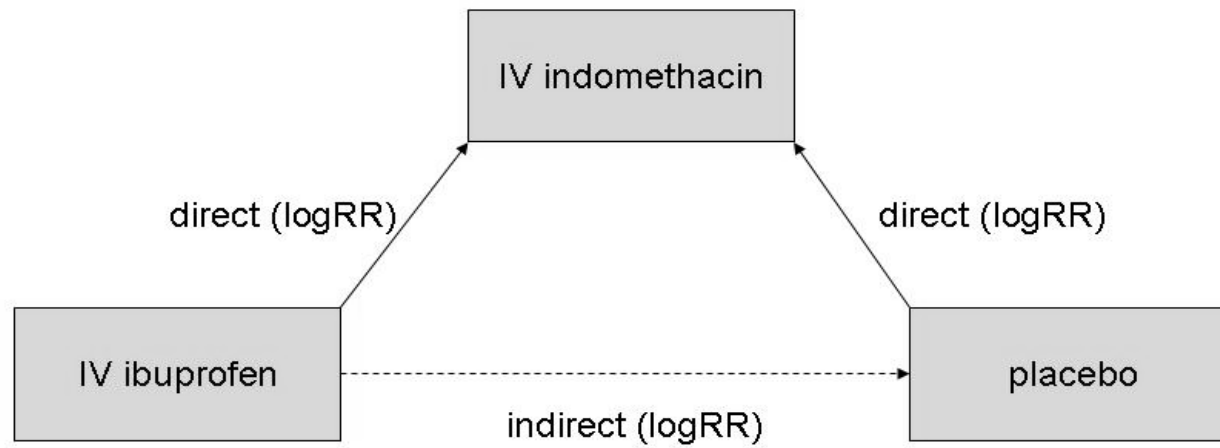
Figure 1.Simplified diagram of indirect network meta-analysis

2. Original data tables

Table 1. Indomethacin versus placebo, and Ibuprofen versus placebo on PDA

Author	Year	Ibuprofen		Indomethacin		RR	95% CI
		PDA closed	PDA open	PDA closed	PDA open		
Mosca	1997	8	0	8	0	1	0.8, 1.25
Van Overmeire	1997	16	4	15	5	1.07	0.76, 1.49
Pezzati	1999	9	0	8	0	1.01	0.81, 1.24
Patel	2000	14	4	14	1	0.83	0.63, 1.1
Van Overmeire	2000	52	22	49	25	1.06	0.85, 1.32
Plavka	2001	18	3	17	3	1.01	0.78, 1.3
Lago	2002	69	25	56	25	1.06	0.88, 1.28
Su	2003	27	5	25	6	1.05	0.83, 1.31
Adamska	2005	11	5	15	4	0.87	0.58, 1.30
Gimeno Navarro	2005	19	4	21	3	0.94	0.74, 1.20
Pooled RR						**1.00**	**0.93, 1.08**
Author	Year	Indomethacin		Placebo			
		PDA closed	PDA open	PDA closed	PDA open		
Merrit	1981	10	2	11	2	5.42	1.48,19.87
Yeh	1981	25	3	21	6	4.02	1.96,8.23
Mahony	1982	19	2	11	15	1.57	1.10, 2.24.
Monset-Couchard	1983	8	4	12	0	17.00	1.09, 265.02
Gersony	1983	110	25	191	79	2.78	2.28, 3.41
Hammerman	1987	5	1	3	7	1.19	0.69, 2.04
Weesner	1987	12	1	7	6	2.00	1.09, 3.67
Krauss	1989	7	5	13	2	4.38	1.11, 17.32
Van Overmeire	1996	12	2	10	4	3.00	1.28, 7.06
Pooled RR						**1.86**	**1.49, 2.41**
`Author	Year	Ibuprofen		Placebo			
		PDA closed	PDA open	PDA closed	PDA open		
Van Overmeire	1996	10	4	4	10	2.50	1.02, 6.10
Indirect comparison	2008					1.85	1.44, 2.38
Pooled RR: direct and indirect data						1.89	1.49, 2.41

Table 2: .Indomethacin versus placebo, and Ibuprofen versus placebo on intraventicular hemorrhage

Author	Year	Ibuprofen		Indomethacin		RR	95% CI
		IVH	Non-IVH	IVH	Non-IVH		
Van Overmeire	1996	2	12	3	11	0.67	0.13, 3.4
Van Overmeire	2000	5	69	2	72	2.5	0.50,12.48
Lago	2002	10	84	7	74	1.23	0.49, 3.09
Su P	2003	1	31	2	29	0.48	0.05, 5.07
Adamska	2005	0	16	1	18	0.39	0.02, 9.01
Gimeno Navarro	2005	2	21	1	23	2.09	0.20, 21.48
Pooled RR						**1.11**	**0.64, 1.97**
Author	Year	Indomethacin		Placebo			
		IVH	Non-IVH	IVH	Non-IVH		
Mahony	1982	7	14	7	19	1.24	0.52, 2.97
Gersony	1983	10	130	21	260	0.96	0.46, 1.97
Weesner	1987	5	8	3	10	1.67	0.5, 5.57
Van Overmeire	1996	3	11	3	11	1.00	0.24, 4.13
Pooled RR						**1.13**	**0.7, 1.82**
Author	Year	Ibuprofen		Placebo			
		IVH	Non-IVH	IVH	Non-IVH		
Van Overmeire	1996	2	12	3	11	0.67	0.14, 3.31
Indirect comparison	2008					1.27	0.60, 2.65
Pooled RR: direct and indirect data						**1.13**	**0.58, 2.23**

Table 3. Studies included in estimation of the effects of Ibuprofen versus Indomethacin, Indomethacin versus placebo, and Ibuprofen versus placebo on bronchopulmonary dysplasia

Author	Year	Ibuprofen		Indomethacin		RR	95% CI
		BD	Non-BD	BD	Non-BD		
Van Overmeire	1997	17	3	12	8	1.42	0.95, 2.12
Van Overmeire	2000	39	35	29	45	1.35	0.94, 1.92
Lago	2002	23	71	13	68	1.52	0.83, 2.81
Su P	2003	7	25	8	23	0.85	0.35, 2.06
Gimeno Navarro	2005	7	16	7	17	1.04	0.43, 2.51
Pooled RR						**1.32**	**1.05, 1.67**
Author	Year	Indomethacin		Placebo			
		BD	Non-BD	BD	Non-BD		
Merritt	1981	2	10	8	5	0.27	0.07, 1.03
Yeh	1981	9	19	6	21	1.45	0.6, 3.5
Gersony	1983	36	104	59	222	1.23	0.85, 1.76
Hammerman	1987	9	1	12	2	1.05	0.78, 1.4
Weesner	1987	2	8	4	7	0.55	0.127, 2.381
Van Overmeire	1996	6	8	8	6	0.75	0.35, 1.6
Pooled RR						**1.05**	**0.85, 1.29**
Author	Year	Ibuprofen		Placebo			
		BD	Non-BD	BD	Non-BD		
Van Overmeire	1996	9	5	8	6	1.13	0.62, 2.05
Indirect comparison	2008					**1.39**	**1.02, 1.89**
Pooled RR: direct and indirect data						1.32	1.01, 1.75

Table 4. Studies included in estimation of the effects of Ibuprofen versus Indomethacin, Indomethacin versus placebo, and Ibuprofen versus placebo on necrotising enterocolitis

Author	Year	Ibuprofen		Indomethacin		RR	95% CI
		NC	Non-NC	NC	Non-NC		
Van Overmeire	1997	1	19	1	19	1.0	0.07, 14.90
Van Overmeire	2000	4	70	8	66	0.5	0.16,1.59
Lago	2002	2	92	2	79	0.86	0.12, 5.98
Su P	2003	2	30	3	28	0.65	0.12, 3.61
Gimeno Navarro	2005	0	23	1	23	0.35	0.02, 8.11
Pooled RR						**0.60**	**0.27, 1.33**
Author	Year	Indomethacin		Placebo			
		NC	Non-NC	NC	Non-NC		
Yeh	1981	3	25	2	25	1.45	0.26, 7.99
Mahony	1982	1	20	3	23	0.41	0.05, 3.68
Gersony	1983	6	134	12	269	1.00	0.39, 2.62
Pooled RR						**0.97**	**0.44, 2.11**
Pooled RR: direct and indirect data						**0.58**	**0.19, 1.77**

Table 5. Studies included in estimation of the effects of Ibuprofen versus Indomethacin, Indomethacin versus placebo, and Ibuprofen versus placebo on death

Author	Year	Ibuprofen		Indomethacin		RR	95% CI
		Death	Alive	Death	Alive		
Van Overmeire	1997	1	19	3	17	0.33	0.04, 2.94
Van Overmeire	2000	7	67	6	68	1.17	0.41, 3.31
Lago	2002	11	83	7	74	1.35	0.55, 3.33
Su P	2003	1	31	4	27	0.24	0.03, 2.05
Gimeno Navarro	2005	2	21	2	22	1.04	0.16, 6.8
Pooled RR						**0.99**	**0.55, 1.8**
Author	Year	Indomethacin		Placebo		RR	95% CI
		Death	Alive	Death	Alive		
Merritt	1981	1	11	4	9	0.27	0.04, 2.10
Yeh	1981	6	22	5	22	1.16	0.4, 3.35
Mahony	1982	3	18	2	24	1.86	0.34, 10.11
Monset-Couchard	1983	3	9	0	12	7.00	0.40, 122.44
Gersony	1983	17	123	32	249	1.07	0.61, 1.85
Weesner	1987	3	10	3	10	1.0	0.25, 4.07
Krauss	1989	3	9	3	12	1.25	0.31, 5.11
Van Overmeire	1996	2	12	0	14	5.0	0.26, 95.61
Pooled RR						**1.17**	**0.73, 1.89**
Pooled RR: direct and indirect data						**1.16**	**0.55, 2.49**

3. STATA output

Main outcomes

Outcome 1: PDA Closure

```
--------------------------------------------------------------------------------
      log:  C:\DATA\do files paper DEC 2009\Ibu Indo Plac PDA CL random direct and indirect 11th Dec
2009.smcl
  log type:  smcl
 opened on:   7 Feb 2010, 17:26:35



***RUN metan direct RR ibu vs plac PDA CL.do FIRST (if ibu plac PDA CL 1 direct study lnrr not already
created)*****************Ibu vs Indo*************************

use "C:\DATA\rpt analysis original data sets 18th August\Ibu Indo PDA CL 18th August.dta", clear

list id author year Ibu_n_PDA Ibu_PDA Ind_n_PDA Ind_PDA mean_ga mean_bw mean_agerx


     +----------------------------------------------------------------------------------------+
     | id         author   year   Ibu_n_~A   Ibu_PDA   Ind_n_~A   Ind_PDA   mean_ga   mean_bw   mean_a~x |
     |----------------------------------------------------------------------------------------|
  1. | 1           Mosca   1997          8         0          8         0        29       837        1.1 |
  2. | 2    VAn Overmeire   1997         16         4         15         5        29      1210        3.1 |
  3. | 3         Pezzati   1999          9         0          8         0      29.3      1277        1.4 |
  4. | 4    Van Overmeire   2000         52        22         49        25        29      1230        3.1 |
  5. | 5           Patel   2000         14         4         14         1        26       838        7.5 |
     |----------------------------------------------------------------------------------------|
  6. | 6          Plavka   2001         18         3         17         3      27.6       902          2 |
  7. | 7            Lago   2002         69        25         56        25      28.5      1214        2.6 |
  8. | 8            Su P   2003         27         5         25         6      28.5      1109        4.5 |
  9. | 9         Adamska   2005         11         5         15         4         .         .        3.5 |
 10. | 10  Gimeno Navarro   2005         19         4         21         3        28      1206          3 |
     +----------------------------------------------------------------------------------------+

.
. list id author if (Ind_n_PDA==0|Ind_PDA==0|Ibu_n_PDA==0|Ibu_PDA==0)
```

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```
      +--------------+
      | id    author |
      |--------------|
  1.  |  1     Mosca |
  3.  |  3   Pezzati |
      +--------------+
```

.
/**Two studies had 0 cell, applying metan would drop these two studies. Thus manually calculate by adding 0.5
to each cell of the two studies would be more appropriate**/

gen ir_Ibu = Ibu_n_PDA/n_Ibu

replace ir_Ibu = (Ibu_n_PDA+0.5)/(n_Ibu+1) if (Ind_n_PDA==0|Ind_PDA==0|Ibu_n
> _PDA==0|Ibu_PDA==0)
(2 real changes made)

gen ir_Ind=Ind_n_PDA/n_Ind

replace ir_Ind=(Ind_n_PDA+0.5)/(n_Ind+1) if (Ind_n_PDA==0|Ind_PDA==0|Ibu_n_PDA==0|Ibu_PDA==0)
(2 real changes made)

gen rr1 =ir_Ibu/ir_Ind

list id rr1 Ibu_*PDA Ind_*PDA if (Ind_n_PDA==0|Ind_PDA==0|Ibu_n_PDA==0|Ibu_PDA==0)

```
      +------------------------------------------------------+
      | id         rr1    Ibu_n_~A    Ibu_PDA    Ind_n_~A    Ind_PDA |
      |------------------------------------------------------|
  1.  |  1           1           8          0           8          0 |
  3.  |  3    1.005882           9          0           8          0 |
      +------------------------------------------------------+
```

gen varlnrr1 = 1/Ind_n_PDA -1/(n_Ind) + 1/Ibu_n_PDA - 1/n_Ibu

replace varlnrr1 =   1/(Ind_n_PDA + 0.5) -1/(n_Ind +1) + 1/(Ibu_n_PDA + 0.5) - 1/(n_Ibu+1) if
(Ind_n_PDA==0|Ind_PDA==0|Ibu_n_PDA==0|Ibu_PDA==0)
(2 real changes made)

```
list id rr1 varlnrr1  Ind_*PDA Ibu_*PDA  if (Ind_n_PDA==0|Ind_PDA==0|Ibu_n_PDA==0|Ibu_PDA==0)

     +--------------------------------------------------------------------+
     | id         rr1    varlnrr1    Ind_n_~A    Ind_PDA    Ibu_n_~A    Ibu_PDA |
     |--------------------------------------------------------------------|
  1. | 1           1    .0130719           8          0           8          0 |
  3. | 3    1.005882    .0117991           8          0           9          0 |
     +--------------------------------------------------------------------+

.
        gen lnrr1 = ln(rr1)

        gen w1  = 1/varlnrr1

        gen wlnrr1 =w1*lnrr1


        egen swlnrr1i=sum(wlnrr1)

        egen sumw1=sum(w1)

        gen lnrr1iv=swlnrr1i/sumw1

        gen rr1iv=exp(lnrr1iv)

        gen varlnrr1iv = 1/sumw1

        gen selnrr1iv = sqrt(varlnrr1iv)

        gen lllnrr1iv  = lnrr1iv -1.96*selnrr1iv

        gen ullnrr1iv = lnrr1iv +1.96*selnrr1iv

        gen llrr1iv = exp(lllnrr1iv)

        gen ulrr1iv = exp(ullnrr1iv)

        gen selnrr1=sqrt(varlnrr1)
```

```
***Q test****
    gen q1 = w1*(lnrr1-lnrr1iv)^2

    egen Q1=sum(q1)

    list Q1


    +----------+
    |       Q1 |
    |----------|
 1. | 3.240104 |
 2. | 3.240104 |
 3. | 3.240104 |
 4. | 3.240104 |
 5. | 3.240104 |
    |----------|
 6. | 3.240104 |
 7. | 3.240104 |
 8. | 3.240104 |
 9. | 3.240104 |
10. | 3.240104 |
    +----------+


    disp $S_7
20.756735


    count
  10

*       gen k =r(N)
    disp chiprob(r(N)-1, Q1)
.95400997

    list Q rr1iv llrr1iv ulrr1iv in 1


    +-------------------------------------------+
    |       Q1      rr1iv    llrr1iv    ulrr1iv |
    |-------------------------------------------|
 1. | 3.240104   1.002693   .9286827   1.082601 |
```

```
            +-------------------------------------------+

              *rr1iv llrr1iv ulrr1iv

          save "C:\DATA\do files paper DEC 2009\Indo Ibu PDA CL random RR 11th Dec 2009.dta",replace
file C:\DATA\do files paper DEC 2009\Indo Ibu PDA CL random RR 11th Dec 2009.dta saved

        keep id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv mean_ga mean_bw mean_agerx

          order id author year rr1 lnrr1 selnrr1 varlnrr1 rr1iv varlnrr1iv mean_ga mean_bw mean_agerx

        list id author year rr1 lnrr1 selnrr1 mean_ga mean_bw mean_agerx

      +---------------------------------------------------------------------------------------+
      | id        author   year        rr1       lnrr1     selnrr1   mean_ga   mean_bw   mean_a~x |
      |---------------------------------------------------------------------------------------|
  1.  | 1         Mosca   1997          1           0    .1143324        29       837       1.1 |
  2.  | 2    VAn Overmeire 1997  1.066667    .0645386    .1707825        29      1210       3.1 |
  3.  | 3       Pezzati   1999   1.005882    .0058651    .1086237      29.3      1277       1.4 |
  4.  | 4   Van Overmeire 2000   1.061224    .0594234    .1123027        29      1230       3.1 |
  5.  | 5         Patel   2000   .8333334   -.1823215    .1436486        26       838       7.5 |
      |---------------------------------------------------------------------------------------|
  6.  | 6         Plavka   2001  1.008403    .0083682    .1294606      27.6       902         2 |
  7.  | 7          Lago   2002    1.06174    .0599091    .0967777      28.5      1214       2.6 |
  8.  | 8          Su P   2003    1.04625    .0452123    .1163141      28.5      1109       4.5 |
  9.  | 9       Adamska   2005   .8708333   -.1383047    .2060198         .         .       3.5 |
 10.  | 10 Gimeno Navarro 2005   .9440994   -.0575239    .1229052        28      1206         3 |
      +---------------------------------------------------------------------------------------+

        gen comparator =1

        lab define comp 1"ibuprofen"

        lab value comparator comp

        save "C:\DATA\do files paper DEC 2009\Indo Ibu PDA CL random lnrr 11th Dec 2009.dta", replace

file C:\DATA\do files paper DEC 2009\Indo Ibu PDA CL random lnrr 11th Dec 2009.dta saved
```

```
*********************************Primary outcome: PDA*********************************************
*********************************************************************************************
**************************generate RR*****************************
  *indo vs. plac

use "C:\DATA\rpt analysis original data sets 18th August\Indo Plac PDA CL 18th August.dta", clear

list id author year Ind_n_PDA Ind_PDA Plac_n_PDA Plac_PDA  mean_ga mean_bw mean_agerx


     +---------------------------------------------------------------------------------------------+
     | id        author   year   Ind_n_~A   Ind_PDA   Plac_n~A   Plac_PDA   mean_ga   mean_bw   mean_a~x |
     |---------------------------------------------------------------------------------------------|
  1. | 1        Merritt   1981         10         2          2         11      27.5      1000         2|
  2. | 2            Yeh   1981         25         3          6         21      31.5      1233       9.9|
  3. | 3         Mahony   1982         19         2         15         11      28.5      1090       2.9 |
  4. | 4  Monset-Couchard 1983          8         4          0         12        31      1398         .|
  5. | 5        Gersony   1983        110        25         79        191      29.5      1045       7.9|
     |---------------------------------------------------------------------------------------------|
  6. | 6      Hammerman   1987          5         1          7          3        28       828       2.5|
  7. | 7        Weesner   1987         12         1          6          7        29       736       1.5|
  8. | 8         Krauss   1989          7         5          2         13         .      1183         4|
  9. | 9  Van Overmeire   1996         12         2          4         10        28      1160       2.5|
     +---------------------------------------------------------------------------------------------+
. metan Ind_n_PDA Ind_PDA Plac_n_PDA Plac_PDA ,randomi nograph label(namevar=author)

         Study      |    RR    [95% Conf. Interval]    % Weight
--------------------+----------------------------------------------------
Merritt             |   5.417    1.477    19.870          5.16
Yeh                 |   4.018    1.961     8.232         11.30
Mahony              |   1.568    1.097     2.242         18.60
Monset-Couchard     |  17.000    1.090   265.024          1.39
Gersony             |   2.785    2.275     3.409         21.75
Hammerman           |   1.190    0.693     2.045         14.58
Weesner             |   2.000    1.089     3.673         13.25
Krauss              |   4.375    1.105    17.320          4.71
Van Overmeire       |   3.000    1.275     7.057          9.26
--------------------+----------------------------------------------------
D+L pooled RR       |   2.408    1.724     3.362        100.00
--------------------+----------------------------------------------------
```

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```
 Heterogeneity chi-squared =  20.76 (d.f. = 8) p = 0.008
 I-squared (variation in RR attributable to heterogeneity) =  61.5%
 Estimate of between-study variance Tau-squared =  0.1228

 Test of RR=1 : z=    5.16 p = 0.000

. gen rr1iv = $S_1

. gen varlnrr1iv =($S_2)^2

. gen rr1 = _ES

. gen lnrr1=ln(rr1)

. gen varlnrr1 = (_selogES)^2

. gen selnrr1 = _selogES

 *no study was dropped, use metan results for overall pooling

 keep id author year rr1 lnrr1 selnrr1 varlnrr1 mean_ga mean_bw mean_agerx

 list id author year rr1 lnrr1 selnrr1 mean_ga mean_bw mean_agerx

     +----------------------------------------------------------------------------+
     | id          author   year       rr1      lnrr1     selnrr1   mean_ga   mean_bw   mean_a~x |
     |----------------------------------------------------------------------------|
  1. | 1          Merritt   1981   5.416667   1.689481   .6631317      27.5      1000         2 |
  2. | 2              Yeh   1981   4.017857   1.390749   .3659444      31.5      1233       9.9 |
  3. | 3           Mahony   1982   1.568254   .4499629   .1822571      28.5      1090       2.9 |
  4. | 4   Monset-Couchard  1983         17   2.833213   1.401357        31      1398         . |
  5. | 5          Gersony   1983    2.78481    1.02418   .1031408      29.5      1045       7.9 |
     |----------------------------------------------------------------------------|
  6. | 6        Hammerman   1987   1.190476   .1743534   .2760262        28       828       2.5 |
  7. | 7          Weesner   1987          2   .6931472   .3100868        29       736       1.5 |
  8. | 8           Krauss   1989      4.375   1.475906   .7020379         .      1183         4 |
  9. | 9    Van Overmeire   1996          3   1.098612   .4364358        28      1160       2.5 |
     +----------------------------------------------------------------------------+
```

```
save "C:\DATA\do files paper DEC 2009\Indo Plac PDA CL RR random 11th Dec 2009.dta", replace
file C:\DATA\do files paper DEC 2009\Indo Plac PDA CL RR random 11th Dec 2009.dta saved

*plac vs indo
 use "C:\DATA\rpt analysis original data sets 18th August\Indo Plac PDA CL 18th August.dta", clear

list id author year Plac_n_PDA Plac_PDA Ind_n_PDA Ind_PDA

    +-------------------------------------------------------------------------+
    | id           author   year   Plac_n~A   Plac_PDA   Ind_n_~A   Ind_PDA  |
    |-------------------------------------------------------------------------|
 1. | 1           Merritt   1981          2         11         10         2  |
 2. | 2               Yeh   1981          6         21         25         3  |
 3. | 3            Mahony   1982         15         11         19         2  |
 4. | 4   Monset-Couchard   1983          0         12          8         4  |
 5. | 5           Gersony   1983         79        191        110        25  |
    |-------------------------------------------------------------------------|
 6. | 6         Hammerman   1987          7          3          5         1  |
 7. | 7           Weesner   1987          6          7         12         1  |
 8. | 8            Krauss   1989          2         13          7         5  |
 9. | 9     Van Overmeire   1996          4         10         12         2  |
    +-------------------------------------------------------------------------+

metan Plac_n_PDA Plac_PDA Ind_n_PDA Ind_PDA,randomi nograph label(namevar=author)

            Study   |    RR     [95% Conf. Interval]     % Weight
--------------------+--------------------------------------------------
Merritt             |   0.185     0.050      0.677         5.16
Yeh                 |   0.249     0.121      0.510        11.30
Mahony              |   0.638     0.446      0.911        18.60
Monset-Couchard     |   0.059     0.004      0.917         1.39
Gersony             |   0.359     0.293      0.440        21.75
Hammerman           |   0.840     0.489      1.443        14.58
Weesner             |   0.500     0.272      0.918        13.25
Krauss              |   0.229     0.058      0.905         4.71
Van Overmeire       |   0.333     0.142      0.784         9.26
--------------------+--------------------------------------------------
D+L pooled RR       |   0.415     0.297      0.580       100.00
```

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```
                   --------------------+---------------------------------------------------

  Heterogeneity chi-squared =   20.76 (d.f. = 8) p = 0.008
  I-squared (variation in RR attributable to heterogeneity) =   61.5%
  Estimate of between-study variance Tau-squared =  0.1228

  Test of RR=1 : z=    5.16 p = 0.000

 gen rr1iv = $S_1

 gen varlnrr1iv =($S_2)^2

 gen rr1 = _ES

 gen lnrr1=ln(rr1)

 gen varlnrr1 = (_selogES)^2

 gen selnrr1 = _selogES

*no study was dropped, use metan results for overall pooling
save "C:\DATA\do files paper DEC 2009\Plac Indo PDA CL RR random 11th Dec 2009.dta", replace
file C:\DATA\do files paper DEC 2009\Plac Indo PDA CL RR random 11th Dec 2009.dta saved

keep id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv  mean_ga mean_bw mean_agerx

order id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv mean_ga mean_bw mean_agerx

         gen comparator =2

         lab define comp 2"placebo"

         lab value comparator comp

save "C:\DATA\do files paper DEC 2009\Plac Indo PDA CL lnrr random 11th Dec  2009.dta", replace
file C:\DATA\do files paper DEC 2009\Plac Indo PDA CL lnrr random 11th Dec 2009.dta saved

*******************************Ibu vs Placebo: Indirect comparison ****************************************
```

```
      use "C:\DATA\do files paper DEC 2009\Indo Ibu PDA CL random lnrr 11th Dec 2009.dta"

       append using "C:\DATA\do files paper DEC 2009\Plac Indo PDA CL lnrr random 11th Dec 2009.dta"
author was str14 now str15
(label comp already defined)

          tab comp


 comparator |      Freq.      Percent        Cum.
------------+-----------------------------------
  ibuprofen |         10        52.63        52.63
          2 |          9        47.37       100.00
------------+-----------------------------------
      Total |         19       100.00


          lab define comp 2"Plac", modify

tab comp


 comparator |      Freq.      Percent        Cum.
------------+-----------------------------------
  ibuprofen |         10        52.63        52.63
       Plac |          9        47.37       100.00
------------+-----------------------------------
      Total |         19       100.00


char comp[omit] 2

xi: metareg lnrr1 i.comp,wsvar(varlnrr1)
i.comparator      _Icomparato_1-2     (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0


Meta-analysis regression                        No of studies =   19
                                                tau^2 method      reml
                                                tau^2 estimate =       0


Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
            |     Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
```

```
-------------+----------------------------------------------------------------
_Icomparat~1 |    .873053   .0870927    10.02   0.000     .7023545    1.043751
       _cons |   -.870364   .0778118   -11.19   0.000    -1.022872   -.7178556
-------------------------------------------------------------------------------

        notes: OR (Ibu vs Indo)

        disp exp(_b[_Icomparato_1]+_b[_cons])
1.0026927

        notes: OR (Placebo vs Indo)

        disp exp(_b[_cons])
.4187991

        disp exp(_b[_cons]-1.96*_se[_cons])
.35955968

        disp exp(_b[_cons]+1.96*_se[_cons])
.48779854

        notes: OR (Indo vs Placebo)

        disp 1/exp(_b[_cons])
2.3877797

        disp 1/exp(_b[_cons]-1.96*_se[_cons])
2.7811795
        disp 1/exp(_b[_cons]+1.96*_se[_cons])
2.0500266


        notes: OR(Ibu vs Placebo)

        disp exp(_b[_Icomparato_1])
2.3942092

        disp exp(_b[_Icomparato_1] - 1.96*_se[_Icomparato_1])
2.0184934
```

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```
        disp exp(_b[_Icomparato_1] + 1.96*_se[_Icomparato_1])
2.8398596

        notes: OR & 95% CI   (Ibu vs indo)

        qui xi: metareg lnrr1  if comp ==1, wsvar(varlnrr1)

        disp exp(_b[_cons])
1.0026927

        disp exp(_b[_cons] - 1.96*_se[_cons])
.92868273

        disp exp(_b[_cons] + 1.96*_se[_cons])
1.0826007

*******************work on here*****************************
******************combine indirect OR with direct OR**********
****Direct OR: Ibuprofen vs Placebo *******

/*     +------------------------------------------+
       |               study     lnrr1    varlnrr1 |
       |------------------------------------------|
   1.  | Van Overmeire 1996   .91629076  .20714286|
       +------------------------------------------+
*/

xi: metareg lnrr1 i.comp , wsvar(varlnrr1)
i.comparator      _Icomparato_1-2     (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                          No of studies =   19
                                                  tau^2 method      reml
                                                  tau^2 estimate =      0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
--------------------------------------------------------------------------
              |     Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
```

```
------------+----------------------------------------------------------------
_Icomparat~1 |    .873053    .0870927     10.02    0.000     .7023545    1.043751
      _cons |   -.870364    .0778118    -11.19    0.000    -1.022872    -.7178556
------------------------------------------------------------------------------

disp _se[_Icomparato_1]
.08709266

disp _b[ _Icomparato_1]
.87305301

***************** combine direct & indirect*********************************

      *A) PDA (Primary outcome)

 /*input indirect results of metareg
lnor=Coef of _Icomparat~1
selnor=Std. Err.
for instance,  results of meta-reg  of Ibu vs placebo are displayed as below


xi: metareg lnrr1 i.comp , wsvar(varlnrr1)
i.comparator     _Icomparato_1-2     (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                         No of studies =   19
                                                  tau^2 method      reml
                                                  tau^2 estimate =  0
Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
             |     Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
------------+----------------------------------------------------------------
_Icomparat~1 |    .873053    .0870927     10.02    0.000     .7023545    1.043751
      _cons |   -.870364    .0778118    -11.19    0.000    -1.022872    -.7178556
------------------------------------------------------------------------------
disp _se[_Icomparato_1]
.08709266

disp _b[ _Icomparato_1]
```

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.87305301

```
open file which contained of one direct study
compared Ibu vs Place. The data had variables as follows:
id author year lnrr1 varlnrr1 */

use "C:\DATA\repeat analyses ibu plac 12th November\Ibu Plac PDA CL 1 direct study lnrr 12th November.dta",
clear

  set obs 2
obs was 1, now 2

 replace id = 2 in 2
(1 real change made)

replace year = 2008 in 2
(1 real change made)

replace author = "Indirect results" in 2
author was str13 now str16
(1 real change made)

replace lnrr1 =  .87305301 in 2
(1 real change made)

replace rr1=exp(.87305301) in 2
(1 real change made)

replace varlnrr1 = (.08709266)^2 in 2
(1 real change made)

replace selnrr1 = .08709266 in 2
(1 real change made)

list
     +----------------------------------------------------------------------------------+
     | id          author    year       rr1      lnrr1   varlnrr1    selnrr 1   rr1iv   varlnr~v |
     |----------------------------------------------------------------------------------|
  1. | 1     Van Overmeire   1996       2.5   .9162908   .2071429   .455129 5     2.5    .2071429 |
```

```
  2. |  2   Indirect results   2008   2.394209    .873053   .0075851   .087092 7        .           . |
      +------------------------------------------------------------------------------------------------+


save "C:\DATA\do files paper DEC 2009\Ibu Plac PDA CL direct and indirect 11th Dec 2009.dta", replace
file C:\DATA\do files paper DEC 2009\Ibu Plac PDA CL direct and indirect 11th Dec 2009.dta saved

xi: metareg lnrr1, wsse(selnrr1)
Iteration 1: tau^2 = 0

Meta-analysis regression                              No of studies =    2
                                                      tau^2 method      reml
                                                      tau^2 estimate =       0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
-----------------------------------------------------------------------------
              |     Coef.    Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+--------------------------------------------------------------
        _cons |   .8745804   .0855406    10.22   0.000    .7069239    1.042237
-----------------------------------------------------------------------------

*meta lnor1 selnor1, or

disp exp(_b[_cons])
2.3978688

disp exp(_b[_cons]-1.96*_se[_cons])
2.0277379

disp exp(_b[_cons]+1.96*_se[_cons])
2.8355613
```

Outcome 2 NEC

```
list id author if ( Ind_NEC==0|Ind_n_NEC== 0|Ibu_NEC==0|Ibu_n_NEC==0)

      +---------------------+
      | id          author  |
      |---------------------|
  5.  | 10   Gimeno Navarro |
      +---------------------+


list id author year Ind_NEC Ind_n_NEC Ibu_NEC Ibu_n_NEC


      +------------------------------------------------------------------------+
      | id            author    year    Ind_NEC    Ind_n_~C    Ibu_NEC    Ibu_n_~C |
      |------------------------------------------------------------------------|
  1.  |  2     Van Overmeire    1997          1          19          1          19 |
  2.  |  4     Van Overmeire    2000          8          66          4          70 |
  3.  |  7             Lago     2002          2          79          2          92 |
  4.  |  8             Su P     2003          3          28          2          30 |
  5.  | 10   Gimeno Navarro    2005          1          23          0          23 |
      +------------------------------------------------------------------------+

 /**Two studies had 0 cell, applying metan would drop these two studies.
Thus manually calculate by adding 0.5 to each cell of the two studies would be more appropriate**/

gen ir_Ibu = Ibu_NEC/n_Ibu

replace ir_Ibu = (Ibu_NEC+0.5)/(n_Ibu+1) if (Ind_NEC==0|Ind_n_NEC== 0|Ibu_NE
> C==0|Ibu_n_NEC==0)
(1 real change made)


gen ir_Ind=Ind_NEC/n_Ind

replace ir_Ind=(Ind_NEC+0.5)/(n_Ind+1) if (Ind_NEC==0|Ind_n_NEC== 0|Ibu_NEC=
> =0|Ibu_n_NEC==0)
(1 real change made)
```

```
gen rr1 =ir_Ibu/ir_Ind

list id rr1 Ibu_*NEC Ind_*NEC if (Ind_NEC==0|Ind_n_NEC== 0|Ibu_NEC==0|Ibu_n_NEC==0)


     +--------------------------------------------------------+
     | id          rr1    Ibu_NEC    Ibu_n_~C    Ind_NEC    Ind_n_~C |
     |--------------------------------------------------------|
  5. | 10    .3472222          0          23          1          23 |
     +--------------------------------------------------------+


gen varlnrr1 = 1/Ind_NEC-1/(n_Ind) + 1/Ibu_NEC- 1/n_Ibu
(1 missing value generated)

replace varlnrr1 =   1/(Ind_NEC+ 0.5) -1/(n_Ind +1) + 1/(Ibu_NEC+ 0.5) - 1/(
> n_Ibu+1) if (Ind_NEC==0|Ind_n_NEC== 0|Ibu_NEC==0|Ibu_n_NEC==0)
(1 real change made)

list id rr1 varlnrr1  Ind_*NEC Ibu_*NEC if (Ind_NEC==0|Ind_n_NEC== 0|Ibu_NEC==0|Ibu_n_NEC==0)


     +-------------------------------------------------------------------+
     | id          rr1    varlnrr1    Ind_NEC    Ind_n_~C    Ibu_NEC    Ibu_n_~C |
     |-------------------------------------------------------------------|
  5. | 10    .3472222       2.585          1          23          0          23 |
     +-------------------------------------------------------------------+



        gen lnrr1 = ln(rr1)

        gen w1  = 1/varlnrr1

        gen wlnrr1 =w1*lnrr1

        egen swlnrr1i=sum(wlnrr1)

        egen sumw1=sum(w1)

        gen lnrr1iv=swlnrr1i/sumw1

        gen rr1iv=exp(lnrr1iv)
```

```
gen varlnrr1iv = 1/sumw1

gen selnrr1iv = sqrt(varlnrr1iv)

gen lllnrr1iv  = lnrr1iv -1.96*selnrr1iv

gen ullnrr1iv = lnrr1iv +1.96*selnrr1iv

gen llrr1iv = exp(lllnrr1iv)

gen ulrr1iv = exp(ullnrr1iv)

gen selnrr1 = sqrt(varlnrr1)

***Q test****
gen q1 = w1*(lnrr1-lnrr1iv)^2

egen Q1=sum(q1)


list Q1

    +----------+
    |       Q1 |
    |----------|
 1. | .4897502 |
 2. | .4897502 |
 3. | .4897502 |
 4. | .4897502 |
 5. | .4897502 |
    +----------+

      disp $S_7
.80021845

      count
    5
```

```
*       gen k =r(N)
          disp chiprob(r(N)-1, Q1)
.97449109


          list Q rr1iv llrr1iv ulrr1iv in 1


       +----------------------------------------+
       |       Q1      rr1iv    llrr1iv   ulrr1iv |
       |----------------------------------------|
    1. | .4897502   .5999438   .2714751   1.32584 |
       +----------------------------------------+


          *rr1iv llrr1iv ulrr1iv

 save "C:\DATA\do files paper DEC 2009\Ibu Indo NEC RR 12th Dec 2009.dta",replace
file C:\DATA\do files paper DEC 2009\Ibu Indo NEC RR 12th Dec 2009.dta saved


          keep id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv ga bw agerx

          order id author year rr1 lnrr1 selnrr1 varlnrr1 rr1iv varlnrr1iv ga bw agerx

 list id author year rr1 lnrr1 selnrr1 ga bw agerx


    +-----------------------------------------------------------------------------+
    | id          author   year         rr1       lnrr1    selnrr1     ga    bwt    agerx |
    |-----------------------------------------------------------------------------|
 1. |  2    Van Overmeire   1997           1           0   1.378405     29   1210    3.1 |
 2. |  4    Van Overmeire   2000          .5   -.6931472   .5898923     29   1230    3.1 |
 3. |  7            Lago   2002    .8617021   -.1488457   .9884412   28.5   1214    2.6 |
 4. |  8            Su P   2003    .6458334   -.4372137   .8773969   28.5   1109    4.5 |
 5. | 10   Gimeno Navarro   2005    .3472222    -1.05779   1.607794     28   1206      3 |
    +-----------------------------------------------------------------------------+


          gen comparator =1

          lab define comp 1"ibuprofen"
```

```
        lab value comparator comp


        save "C:\DATA\do files paper DEC 2009\Ibu Indo NEC lnrr 12th Dec 2009.dta", replace
file C:\DATA\do files paper DEC 2009\Ibu Indo NEC lnrr 12th Dec 2009.dta saved


***********************************Primary outcome: NEC*********************************************
**************************generate RR*****************************
*plac vs indo
 use "C:\DATA\rpt analysis original data sets 18th August\Indo Plac NEC 18ᵗʰ August.dta", clear

 list id author Ind_NEC Ind_n_NEC Plac_NEC Plac_n_NEC


     +------------------------------------------------------------+
     | id    author    Ind_NEC    Ind_n_~C    Plac_NEC    Plac_n~C |
     |------------------------------------------------------------|
  1. | 2       Yeh         3          25          2          25 |
  2. | 3    Mahony         1          20          3          23 |
  3. | 5   Gersony         6         134         12         269 |
     +------------------------------------------------------------+


 metan Plac_NEC Plac_n_NEC Ind_NEC Ind_n_NEC  ,  fixedi nograph label(namevar=author)

            Study     |    RR     [95% Conf. Interval]     % Weight
--------------------+-----------------------------------------------------
Yeh                 |   0.691      0.125     3.820          20.88
Mahony              |   2.423      0.271    21.627          12.74
Gersony             |   0.996      0.382     2.599          66.38
--------------------+-----------------------------------------------------
I-V pooled RR       |   1.034      0.473     2.258         100.00
--------------------+-----------------------------------------------------

   Heterogeneity chi-squared =    0.80 (d.f. = 2) p = 0.670
   I-squared (variation in RR attributable to heterogeneity) =    0.0%

   Test of RR=1: z=    0.08 p = 0.933
```

```
        gen rr1iv = $S_1

        gen varlnrr1iv =($S_2)^2

        gen rr1 = _ES

        gen lnrr1=ln(rr1)

        gen varlnrr1 = (_selogES)^2

        gen selnrr1 = _selogES

         *no study was dropped, use metan results for overall pooling
 save "C:\DATA\do files paper DEC 2009\Plac Indo NEC RR 12th Dec 2009.dta", replace
file C:\DATA\do files paper DEC 2009\Plac Indo NEC RR 12th Dec 2009.dta saved

        keep id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv  ga  bw agerx

         order id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv  ga bw agerx

        list id author year rr1 lnrr1 selnrr1 varlnrr1 ga bw agerx

    +-----------------------------------------------------------------------------------+
    | id    author    year        rr1       lnrr1    selnrr1    varlnrr1     ga    bwt    agerx |
    |-----------------------------------------------------------------------------------|
 1. | 2        Yeh    1981    .691358   -.3690975   .8721135    .760582   31.5   1233     9.9 |
 2. | 3     Mahony    1982   2.423077    .8850381   1.116805   1.247253   28.5   1090     2.9 |
 3. | 5    Gersony    1983   .9964413    -.003565   .4891814   .2392984      .      .       . |
    +-----------------------------------------------------------------------------------+

        gen comparator =2

        lab define comp 2"placebo"

        lab value comparator comp

        save  "C:\DATA\do files paper DEC 2009\Plac Indo NEC lnrr 12th Dec 2009.dta", replace
file C:\DATA\do files paper DEC 2009\Plac Indo NEC lnrr 12th Dec 2009.dta saved
```

```
*******************************Ibu vs Placebo: Indirect comparison *******************************
        use "C:\DATA\do files paper DEC 2009\Ibu Indo NEC lnrr 12th Dec 2009.dta"

         append using "C:\DATA\do files paper DEC 2009\Plac Indo NEC lnrr 12 th Dec 2009.dta"
 (label comp already defined)

           tab comp

 comparator |      Freq.     Percent        Cum.
------------+-----------------------------------
  ibuprofen |          5       62.50       62.50
          2 |          3       37.50      100.00
------------+-----------------------------------
      Total |          8      100.00


   char comp[omit] 2

xi: metareg lnrr1 i.comp,wsvar(varlnrr1)
i.comparator      _Icomparato_1-2    (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                          No of studies =   8
                                                  tau^2 method      reml
                                                  tau^2 estimate =      0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
             |     Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Icomparat~1 |  -.544183    .5679135    -0.96   0.338    -1.657273     .568907
       _cons |  .0332637    .3985542     0.08   0.933    -.7478882    .8144156
------------------------------------------------------------------------------


        notes: OR (Ibu vs Indo)

        disp exp(_b[_Icomparato_1]+_b[_cons])
```

```
.59994379


        notes: OR (Placebo vs Indo)

        disp exp(_b[_cons])
1.0338231

        disp exp(_b[_cons]-1.96*_se[_cons])
.47335836

        disp exp(_b[_cons]+1.96*_se[_cons])
2.2578882

        notes: OR (Indo vs Placebo)

         disp 1/exp(_b[_cons])
.96728346

         disp 1/exp(_b[_cons]-1.96*_se[_cons])
2.1125644

         disp 1/exp(_b[_cons]+1.96*_se[_cons])
.44289173

        notes: OR(Ibu vs Placebo)

        disp exp(_b[_Icomparato_1])
.5803157

        disp exp(_b[_Icomparato_1] - 1.96*_se[_Icomparato_1])
.19065429

        disp exp(_b[_Icomparato_1] + 1.96*_se[_Icomparato_1])
1.7663716

        notes: OR & 95% CI  (Ibu vs indo)

        qui xi: metareg lnrr1  if comp ==1, wsvar(varlnrr1)
```

```
        disp exp(_b[_cons])
.59994379

        disp exp(_b[_cons] - 1.96*_se[_cons])
.27147511

        disp exp(_b[_cons] + 1.96*_se[_cons])
1.32584

    replace id = 1 in 1
(1 real change made)

    replace year = 2009 in 1
(1 real change made)

    replace author = "Indirect results" in 1
(1 real change made)

    replace lnrr1 =  -.544183 in 1
(1 real change made)

    replace varlnrr1 = (.5679135)^2 in 1
(1 real change made)

    replace selnrr1 = .5679135 in 1
(1 real change made)

    replace rr1 = exp(-.544183) in 1
(1 real change made)

 list id author year rr1 lnrr1 selnrr1


     +-----------------------------------------------------------------+
     | id          author   year         rr1        lnrr1    selnrr1 |
     |-----------------------------------------------------------------|
  1. | 1   Indirect results  2009   .5803157     -.544183   .5679135 |
  2. | 4       Van Overmeire  2000          .5    -.6931472   .5898923 |
  3. | 7                Lago  2002   .8617021    -.1488457   .9884412 |
```

```
  4. |  8            Su P   2003   .6458334   -.4372137    .8773969 |
  5. | 10   Gimeno Navarro   2005   .3472222    -1.05779    1.607794 |
     |-----------------------------------------------------------------|
  6. |  2             Yeh   1981    .691358   -.3690975    .8721135 |
  7. |  3          Mahony   1982   2.423077    .8850381    1.116805 |
  8. |  5         Gersony   1983   .9964413    -.003565    .4891814 |
     +-----------------------------------------------------------------+
```

Outcome 3: BPD/CLD at any age reported

```
--------------------------------------------------------------------------
     log:  C:\DATA\do files created 19th November approved by Ammarin 28th November\Ibu Indo Plac CLD added
adamska direct and indirect 14th July.smcl
  log type:  smcl
 opened on:  14 Jul 2009, 16:39:16


************************************Primary outcome: CLD*********************************************
************************************generate RR******************************
*Ind vs indo

  use "C:\DATA\rpt analysis original data sets 18th August\Ibu Indo CLD 14th July 2009.dta", clear

metan Ibu_CLD Ibu_n_CLD Ind_CLD Ind_n_CLD ,  fixedi nograph label(namevar=author)

           Study   |    RR    [95% Conf. Interval]    % Weight
--------------------+-----------------------------------------------------
Van Overmeire      |   1.417     0.947     2.119        29.73
Van Overmeire      |   1.345     0.941     1.921        37.87
Lago               |   1.525     0.827     2.811        12.86
Su P               |   0.848     0.349     2.056         6.13
Gimeno Navarro     |   1.043     0.434     2.510         6.25
Adamska            |   0.781     0.344     1.774         7.16
--------------------+-----------------------------------------------------
I-V pooled RR      |   1.277     1.026     1.591       100.00
--------------------+-----------------------------------------------------

  Heterogeneity chi-squared =    3.06 (d.f. = 5) p = 0.690
  I-squared (variation in RR attributable to heterogeneity) =   0.0%

  Test of RR=1 : z=   2.19 p = 0.029

gen rr1iv = $S_1

gen varlnrr1iv =($S_2)^2

gen rr1 = _ES
```

```
gen lnrr1=ln(rr1)

gen varlnrr1 = (_selogES)^2


 *no study was dropped, use metan results for overall pooling

 save "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo CLD RR 14th July 2009.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo CLD RR 14th July 2009.dta saved

keep id author year rr1 lnrr1 varlnrr1  rr1iv varlnrr1iv


        order id author year rr1 lnrr1 varlnrr1  rr1iv varlnrr1iv


        gen comparator =1

        lab define comp 1"Ibuprofen"

        lab value comparator comp

 save "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo CLD lnrr 14th July 2009.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo CLD lnrr 14th July 2009.dta saved

************************************Primary outcome: CLD*********************************************
 ********************************generate RR******************************
 *plac vs indo

  use "C:\DATA\rpt analysis original data sets 18th August\Indo Plac CLD 18th August.dta", clear

metan  Plac_CLD Plac_n_CLD Ind_CLD Ind_n_CLD ,  fixedi nograph label(namevar =author)

          Study       |    RR    [95% Conf. Interval]    % Weight
---------------------+----------------------------------------------------
Merritt              |   3.692     0.971    14.047         2.43
Yeh                  |   0.691     0.285     1.679         5.52
Gersony              |   0.817     0.569     1.172        33.26
```

```
Hammerman*            |  0.952      0.707      1.282          49.16
Weesner*              |  1.818      0.420      7.872           2.02
Van Overmeire         |  1.333      0.626      2.840           7.60
----------------------+--------------------------------------------------
I-V pooled RR         |  0.955      0.775      1.176         100.00
----------------------+--------------------------------------------------


  Heterogeneity chi-squared =    6.66 (d.f. = 5) p = 0.248
  I-squared (variation in RR attributable to heterogeneity) =   24.9%

  Test of RR=1 : z=    0.43 p = 0.666

 gen rr1iv = $S_1

 gen varlnrr1iv =($S_2)^2

 gen rr1 = _ES

 gen lnrr1=ln(rr1)

 gen varlnrr1 = (_selogES)^2


 *no study was dropped, use metan results for overall pooling

 save "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo CLD RR 14th July 2009.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo CLD RR 14th July 2009.dta saved

keep id author year rr1 lnrr1 varlnrr1  rr1iv varlnrr1iv


        order id author year rr1 lnrr1 varlnrr1  rr1iv varlnrr1iv

        gen comparator =2

        lab define comp 2"placebo"

        lab value comparator comp
```

```
save "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo CLD RR 14th July 2009.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo CLD RR 14th July 2009.dta saved

*******************************Ibu vs Placebo: Indirect comparison *****************************************

     use "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo CLD lnrr 14th July 2009.dta", replace

.
     append using "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo CLD RR 14th July 2009.dta"
(label comp already defined)


     tab comp

comparator |      Freq.     Percent        Cum.
------------+-----------------------------------
 Ibuprofen |         6       50.00       50.00
         2 |         6       50.00      100.00
------------+-----------------------------------
     Total |        12      100.00

     lab define comp 2"Plac", modify

 tab comp

comparator |      Freq.     Percent        Cum.
------------+-----------------------------------
 Ibuprofen |         6       50.00       50.00
      Plac |         6       50.00      100.00
------------+-----------------------------------
     Total |        12      100.00

 char comp[omit] 2

 xi: metareg lnrr1 i.comp,wsvar(varlnrr1)
i.comparator      _Icomparato_1-2      (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                              No of studies =   12
```

```
                                          tau^2 method      reml
                                          tau^2 estimate =     0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
----------------------------------------------------------------------
            |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+---------------------------------------------------------------
_Icomparat~1 |   .2908055   .1544265     1.88   0.060    -.0118649    .5934759
      _cons |  -.0459855   .1063734    -0.43   0.666    -.2544736    .1625025
----------------------------------------------------------------------

        notes: OR (Ibu vs Indo)

        disp exp(_b[_Icomparato_1]+_b[_cons])
1.2773913

        notes: OR (Placebo vs Indo)

        disp exp(_b[_cons])
.95505579

        disp exp(_b[_cons]-1.96*_se[_cons])
.77532156

        disp exp(_b[_cons]+1.96*_se[_cons])
1.1764558

        notes: OR (Indo vs Placebo)

        disp 1/exp(_b[_cons])
1.0470593

        disp 1/exp(_b[_cons]-1.96*_se[_cons])
1.2897874

        disp 1/exp(_b[_cons]+1.96*_se[_cons])
.85001068

        notes: OR(Ibu vs Placebo)
```

```
        disp exp(_b[_Icomparato_1])
1.3375044


        disp exp(_b[_Icomparato_1] - 1.96*_se[_Icomparato_1])
.9881997


        disp exp(_b[_Icomparato_1] + 1.96*_se[_Icomparato_1])
1.8102799


        notes: OR & 95% CI  (Ibu vs indo)

         qui xi: metareg lnrr1  if comp ==1, wsvar(varlnrr1)

        disp exp(_b[_cons])
1.2773913


        disp exp(_b[_cons] - 1.96*_se[_cons])
1.0257283


        disp exp(_b[_cons] + 1.96*_se[_cons])
1.5908001


  *******************work on here*****************************
 ******************combine indirect OR with direct OR**********
****Direct OR: Ibuprofen vs Placebo *******

/*    ------------------------------------------+
      |              study      lnrr1   varlnrr1 |
      |------------------------------------------|
  1.  | Van Overmeire 1996   .91629076  .20714286|
      +------------------------------------------+
*/

xi: metareg lnrr1 i.comp , wsvar(varlnrr1)
i.comparator      _Icomparato_1-2    (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                          No of studies =   12
```

```
                                    tau^2 method       reml
                                    tau^2 estimate =      0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
             |      Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Icomparat~1 |   .2908055    .1544265    1.88    0.060    -.0118649    .5934759
       _cons |  -.0459855    .1063734   -0.43    0.666    -.2544736    .1625025
------------------------------------------------------------------------------
disp _se[_Icomparato_1]
.15442652


disp _b[ _Icomparato_1]
.2908055


***************** combine direct & indirect**************************************
        *A) CLD (Primary outcome)

/*input indirect results of metareg
  lnor=Coef of _Icomparat~1
  selnor=Std. Err.
        for instance,  results of meta-reg  of Ibu vs placebo are displayed as below

xi: metareg lnrr1 i.comp , wsvar(varlnrr1)
i.comparator       _Icomparato_1-2     (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                        No of studies =   11
                                                 tau^2 method      reml
                                                 tau^2 estimate =  0
Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
             |      Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
_Icomparat~1 |   .3287321    .1575254    2.09    0.037     .0199881    .6374762
       _cons |  -.0459855    .1063734   -0.43    0.666    -.2544736    .1625025
------------------------------------------------------------------------------
```

```
disp _se[_Icomparato_1]
.15752538

disp _b[ _Icomparato_1]
.2908055

open file which contained of one direct study
compared Ibu vs Place. The data had variables as follows:
id author year lnrr1 varlnrr1 */

use "C:\DATA\repeat analyses ibu plac 12th November\Ibu Plac CLD 1 direct st
> udy lnrr 12th November.dta", clear

set obs 2
obs was 1, now 2

  replace id = 2 in 2
(1 real change made)

  replace year = 2008 in 2
(1 real change made)

  replace author = "Indirect results" in 2
author was str13 now str16
(1 real change made)

  replace lnrr1 =  .2908055 in 2
(1 real change made)

  replace varlnrr1 = (.15442652)^2 in 2
(1 real change made)

  replace selnrr1 = .15442652 in 2
(1 real change made)

 list

     +----------------------------------------------------------------------------------+
     | id          author    year      rr1     lnrr1   varlnrr1    selnrr1 Lower_~i  Upper_~i |
```

```
         |--------------------------------------------------------------------------------------|
    1.   |  1      Van Overmeire   1996   1.125   .117783   .093254   .3053751  .6183249  2.046861  |
    2.   |  2   Indirect results   2008     .     .2908055  .0238476   .1544265      .        .     |
         +--------------------------------------------------------------------------------------+
```

save "C:\DATA\repeat analyses ibu indo plac 19th November\ Ibu Indo Plac CLD direct and indirect 14th July
2009.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\ Ibu Indo Plac CLD direct and indirect 14th July
2009.dta saved

xi: metareg lnrr1, wsse(selnrr1)
Iteration 1: tau^2 = 0

Meta-analysis regression   No of studies =   2
                                                  tau^2 method   reml
                                                  tau^2 estimate =   0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
----
             | Coef.   Std. Err.   z   P>|z| [95% Conf. Interval]
-------------+--
       _cons | .2555697   .1378079   1.85   0.064   -.0145289   .5256683
----

*meta lnor1 selnor1, or

disp exp(_b[_cons])
1.291197

disp exp(_b[_cons]-1.96*_se[_cons])
.98557126

disp exp(_b[_cons]+1.96*_se[_cons])
1.6915974
```

***Outcome 4: any grade of intraventricular haemorrhage (IVH)***

```
----------------------------------------------------------------------------
      log:  C:\DATA\do files paper Dec 2009\Ibu Indo Plac allIVH 12th Dec 2009.smcl
 log type:  smcl opened on:  13 Dec 2009, 17:28:46


use "C:\DATA\rpt analysis original data sets 18th August\Ibu Indo allIVH 18th August.dta", clear

list id author year Ibu_allIVH Ibu_n_allIVH Ind_allIVH Ind_n_allIVH


    +--------------------------------------------------------------------+
    | id              author  year  Ibu_al~H  Ibu_n_~H  Ind_al~H  Ind_n_~H |
    |--------------------------------------------------------------------|
 1. | 11   Van Overmeire 1996  1996         2        12         3        11 |
 2. |  4         Van Overmeire  2000         5        69         2        72 |
 3. |  7                  Lago  2002        10        84         7        74 |
 4. |  8                  Su P  2003         1        31         2        29 |
 5. |  9               Adamska  2005         0        16         1        18 |
    |--------------------------------------------------------------------|
 6. | 10        Gimeno Navarro  2005         2        21         1        23 |
    +--------------------------------------------------------------------+

list id author if ( Ind_allIVH==0|Ind_n_allIVH== 0|Ibu_allIVH==0|Ibu_n_allIVH==0)


    +--------------+
    | id    author |
    |--------------|
 5. |  9   Adamska |
    +--------------+


/**Two studies had 0 cell, applying metan would drop these two studies. Thus manually calculate by adding 0.5
to each cell of the two studies would be more appropriate**/


gen ir_Ibu = Ibu_allIVH/n_Ibu


replace ir_Ibu = (Ibu_allIVH+0.5)/(n_Ibu+1) if (Ind_allIVH==0|Ind_n_allIVH==0|Ibu_allIVH==0|Ibu_n_allIVH==0)
(1 real change made)
```

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```
gen ir_Ind=Ind_allIVH/n_Ind

replace ir_Ind=(Ind_allIVH+0.5)/(n_Ind+1) if (Ind_allIVH==0|Ind_n_allIVH== 0|Ibu_allIVH==0|Ibu_n_allIVH==0)
(1 real change made)

gen rr1 =ir_Ibu/ir_Ind

list id rr1 Ibu_*allIVH Ind_*allIVH if (Ind_allIVH==0|Ind_n_allIVH== 0|Ibu_allIVH==0|Ibu_n_allIVH==0)


     +-------------------------------------------------------------+
     | id        rr1    Ibu_al~H   Ibu_n_~H    Ind_al~H   Ind_n_~H |
     |-------------------------------------------------------------|
  5. | 9    .3921568          0         16           1         18 |
     +-------------------------------------------------------------+

gen varlnrr1 = 1/Ind_allIVH-1/(n_Ind) + 1/Ibu_allIVH- 1/n_Ibu
(1 missing value generated)

replace varlnrr1 = 1/(Ind_allIVH+ 0.5)-1/(n_Ind +1) + 1/(Ibu_allIVH+ 0.5) -  1/(n_Ibu+1) if
(Ind_allIVH==0|Ind_n_allIVH== 0|Ibu_allIVH==0|Ibu_n_allIVH==0)
(1 real change made)

list id rr1 varlnrr1  Ind_*allIVH Ibu_*allIVH if (Ind_allIVH==0|Ind_n_allIVH ==
0|Ibu_allIVH==0|Ibu_n_allIVH==0)


     +----------------------------------------------------------------------+
     | id        rr1   varlnrr1    Ind_al~H   Ind_n_~H    Ibu_al~H   Ibu_n_~H |
     |----------------------------------------------------------------------|
  5. | 9    .3921568   2.557843           1         18           0         16 |
     +----------------------------------------------------------------------+

        gen lnrr1 = ln(rr1)

        gen w1  = 1/varlnrr1

        gen wlnrr1 =w1*lnrr1

        egen swlnrr1i=sum(wlnrr1)
```

```
egen sumw1=sum(w1)

gen lnrr1iv=swlnrr1i/sumw1

gen rr1iv=exp(lnrr1iv)

gen varlnrr1iv = 1/sumw1

gen selnrr1iv = sqrt(varlnrr1iv)

gen lllnrr1iv  = lnrr1iv -1.96*selnrr1iv

gen ullnrr1iv = lnrr1iv +1.96*selnrr1iv

gen llrr1iv = exp(lllnrr1iv)

gen ulrr1iv = exp(ullnrr1iv)

gen selnrr1 = sqrt(varlnrr1)

***Q test****
gen q1 = w1*(lnrr1-lnrr1iv)^2

egen Q1=sum(q1)

list Q1


     +----------+
     |       Q1 |
     |----------|
  1. | 2.571046 |
  2. | 2.571046 |
  3. | 2.571046 |
  4. | 2.571046 |
  5. | 2.571046 |
     |----------|
  6. | 2.571046 |
     +----------+
```

```
        disp $S_7
.80021845

        count
    6

*       gen k =r(N)

        disp chiprob(r(N)-1, Q1)
.76575939

        list Q rr1iv llrr1iv ulrr1iv in 1

      +------------------------------------------+
      |       Q1      rr1iv    llrr1iv    ulrr1iv |
      |------------------------------------------|
   1. | 2.571046   1.159022   .6089873   2.205844 |
      +------------------------------------------+

        *rr1iv llrr1iv ulrr1iv

save "C:\DATA\do files paper Dec 2009\Ibu Indo allIVH RR 12th Dec 2009.dta",replace
file C:\DATA\do files paper Dec 2009\Ibu Indo allIVH RR 12th Dec 2009.dta saved

  keep id author year rr1 lnrr1 selnrr1  varlnrr1  rr1iv varlnrr1iv  ga bw agerx

  order id author year rr1 lnrr1 selnrr1  varlnrr1 rr1iv varlnrr1iv ga bw agerx

list id author year rr1 lnrr1 selnrr1 ga bw agerx

      +----------------------------------------------------------------------------------+
      | id            author   year        rr1       lnrr1    selnrr1     ga    bwt  agerx |
      |----------------------------------------------------------------------------------|
   1. | 11  Van Overmeire 1996   1996   .6666667   -.4054651   .8309489     28   1160    2.5 |
   2. | 4        Van Overmeire   2000        2.5    .9162906   .8203493     29   1230    3.1 |
   3. | 7                 Lago   2002   1.231003    .2078293   .4689063   28.5   1214    2.6 |
   4. | 8                 Su P   2003    .484375   -.7248959   1.198537   28.5   1109    4.5 |
   5. | 9              Adamska   2005   .3921568   -.9360934   1.599326      .      .    3.5 |
      |----------------------------------------------------------------------------------|
```

```
   6. | 10      Gimeno Navarro   2005   2.086957   .7357068   1.189477   28   1206      3 |
      +---------------------------------------------------------------------------------+

   gen comparator =1

   lab define comp 1"ibuprofen"

   lab value comparator comp

save "C:\DATA\do files paper Dec 2009\Ibu Indo allIVH lnrr 12th Dec 2009.dta", replace
file C:\DATA\do files paper Dec 2009\Ibu Indo allIVH lnrr 12th Dec 2009.dta saved

**********************************Primary outcome: allIVH*****************
**************************generate RR*****************************
*plac vs indo

use "C:\DATA\rpt analysis original data sets 18th August\Indo Plac allIVH 18th August.dta", clear

list author year Ind_allIVH Ind_n_allIVH Plac_allIVH Plac_n_allIVH


      +----------------------------------------------------------------+
      |         author   year   Ind_al~H   Ind_n_~H   Plac_a~H   Plac_n~H |
      |----------------------------------------------------------------|
   1. |         Mahony   1982          7         14          7         19 |
   2. |        Gersony   1983         10        130         21        260 |
   3. |        Weesner   1987          5          8          3         10 |
   4. | Van Overmeire   1996          3         11          3         11 |
      +----------------------------------------------------------------+


metan Plac_allIVH Plac_n_allIVH Ind_allIVH Ind_n_allIVH  ,  fixedi nograph label(namevar=author)

            Study   |    RR     [95% Conf. Interval]    % Weight
--------------------+----------------------------------------------------
Mahony              | 0.808     0.336      1.939         29.72
Gersony             | 1.046     0.507      2.161         43.33
Weesner             | 0.600     0.179      2.007         15.63
Van Overmeire       | 1.000     0.242      4.131         11.33
--------------------+----------------------------------------------------
```

```
I-V pooled RR          |  0.884         0.548      1.424          100.00
--------------------+------------------------------------------------


   Heterogeneity chi-squared =    0.67 (d.f. = 3) p = 0.880
   I-squared (variation in RR attributable to heterogeneity) =    0.0%

   Test of RR=1 : z=    0.51 p = 0.611

gen rr1iv = $S_1

gen varlnrr1iv =($S_2)^2

gen rr1 = _ES

gen lnrr1=ln(rr1)

gen varlnrr1 = (_selogES)^2

gen selnrr1 = _selogES

*no study was dropped, use metan results for overall pooling

save "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo allIVH RR 19th November.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo allIVH RR 19th November.dta saved

keep id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv ga bw agerx

order id author year rr1 lnrr1 selnrr1 varlnrr1  rr1iv varlnrr1iv  ga bw agerx
```

```
list id author year rr1 lnrr1 selnrr1 varlnrr1 ga bw agerx

     +----------------------------------------------------------------------------+
     | id        author  year        rr1       lnrr1   selnrr1   varlnrr1    ga    bwt   agerx |
     |----------------------------------------------------------------------------|
  1. | 3         Mahony  1982   .8076923   -.2135741  .4468039   .1996337  28.5   1090    2.9 |
  2. | 5        Gersony  1983   1.046263    .0452251  .3700236   .1369175     .      .      . |
  3. | 7        Weesner  1987         .6   -.5108256  .6160253   .3794872    29    736    1.5 |
  4. | 9  Van Overmeire  1996          1           0  .7237468   .5238095    28   1160    2.5 |
     +----------------------------------------------------------------------------+

       gen comparator =2

       lab define comp 2"placebo"

       lab value comparator comp


save  "C:\DATA\do files paper Dec 2009\Plac Indo allIVH lnrr 12th Dec 2009.dta", replace
file C:\DATA\do files paper Dec 2009\Plac Indo allIVH lnrr 12th Dec 2009.dta saved

*******************************Ibu vs Placebo: Indirect comparison ***********************************

use "C:\DATA\do files paper Dec 2009\Ibu Indo allIVH lnrr 12th Dec 2009.dta"

append using "C:\DATA\do files paper Dec 2009\Plac Indo allIVH lnrr 12th Dec2009.dta"
(label comp already defined)

tab comp

 comparator |      Freq.      Percent        Cum.
------------+-----------------------------------
  ibuprofen |         6        60.00       60.00
          2 |         4        40.00      100.00
------------+-----------------------------------
      Total |        10       100.00

char comp[omit] 2
```

```
xi: metareg lnrr1 i.comp,wsvar(varlnrr1)
i.comparator      _Icomparato_1-2     (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                          No of studies =   10
                                                  tau^2 method      reml
tau^2 estimate =       0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
-----------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+---------------------------------------------------------------
_Icomparat~1 |   .2712997   .4088096     0.66   0.507    -.5299525    1.072552
       _cons |  -.1237235   .2435617    -0.51   0.611    -.6010956    .3536486
-----------------------------------------------------------------------------


        notes: OR (Ibu vs Indo)

        disp exp(_b[_Icomparato_1]+_b[_cons])
1.1590216

        notes: OR (Placebo vs Indo)

        disp exp(_b[_cons])
.88362416

        disp exp(_b[_cons]-1.96*_se[_cons])
.54820589

        disp exp(_b[_cons]+1.96*_se[_cons])
1.4242672

        notes: OR (Indo vs Placebo)

        disp 1/exp(_b[_cons])
1.1317029

        disp 1/exp(_b[_cons]-1.96*_se[_cons])
```

```
1.8241322

        disp 1/exp(_b[_cons]+1.96*_se[_cons])
.70211546

        notes: OR(Ibu vs Placebo)

        disp exp(_b[_Icomparato_1])
1.3116681

        disp exp(_b[_Icomparato_1] - 1.96*_se[_Icomparato_1])
.58862427

        disp exp(_b[_Icomparato_1] + 1.96*_se[_Icomparato_1])
2.9228716

        notes: OR & 95% CI  (Ibu vs indo)

        qui xi: metareg lnrr1  if comp ==1, wsvar(varlnrr1)

        disp exp(_b[_cons])
1.1590216

        disp exp(_b[_cons] - 1.96*_se[_cons])
.6089873

        disp exp(_b[_cons] + 1.96*_se[_cons])
2.2058442


********************work on here*****************************
******************combine indirect OR with direct OR**********
****Direct OR: Ibuprofen vs Placebo ********
        +-----------------------------------------+
        |              study       lnrr1   varlnrr1 |
        |-----------------------------------------|
    1.  | Van Overmeire 1996    .91629076  .20714286|
        +-----------------------------------------+
*/
```

```
. xi: metareg lnrr1 i.comp , wsvar(varlnrr1)
i.comparator      _Icomparato_1-2    (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                         No of studies =   10
                                                 tau^2 method     reml
                                                 tau^2 estimate =     0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
-----------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+---------------------------------------------------------------
_Icomparat~1 |   .2712997   .4088096     0.66   0.507    -.5299525    1.072552
       _cons |  -.1237235   .2435617    -0.51   0.611    -.6010956    .3536486
-----------------------------------------------------------------------------


disp _se[_Icomparato_1]
.40880964

disp _b[ _Icomparato_1]
.27129968

***************** combine direct & indirect**********************************
*****************************************************************************
        *A) allIVH(Primary outcome)

/*input indirect results of metareg
lnor=Coef of _Icomparat~1
selnor=Std. Err.
     for instance,  results of meta-reg  of Ibu vs placebo
     are displayed as below


xi: metareg lnrr1 i.comp , wsvar(varlnrr1)
 i.comparator      _Icomparato_1-2    (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0
Meta-analysis regression                         No of studies =   10
                                                  tau^2 method     reml
```

```
                                           tau^2 estimate =      0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
              |      Coef.    Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
_Icomparat~1 |   .2712997    .4088096     0.66   0.507    -.5299525    1.072552
       _cons |  -.1237235    .2435617    -0.51   0.611    -.6010956    .3536486
------------------------------------------------------------------------------

disp _se[_Icomparato_1]
 .40880964

disp _b[ _Icomparato_1]
.27129968

open file which contained of one direct study
compared Ibu vs Place. The data had variables as follows:
id author year lnrr1 varlnrr1 */


use "C:\DATA\repeat analyses ibu plac 12th November\Ibu Plac allIVH 1 direct study lnrr 12th November.dta",
clear

set obs 2
obs was 1, now 2

replace id = 2 in 2
(1 real change made)

replace year = 2008 in 2
(1 real change made)

replace author = "Indirect results" in 2
author was str13 now str16
(1 real change made)

replace lnrr1 =  .2712997 in 2
(1 real change made)
```

```
replace varlnrr1 = (.4088096)^2 in 2
(1 real change made)

replace selnrr1 = .4088096 in 2
(1 real change made)

replace rr1 = exp(.2712997) in 2
(1 real change made)

list
```

```
     +----------------------------------------------------------------------------------+
     | id          author   year        rr1      lnrr1   varlnrr1   selnrr1   Lower_~i   Upper_~i |
     |----------------------------------------------------------------------------------|
  1. | 1    Van Overmeire   1996   .6666667   -.4054651   .6904762   .8309489   .1307988   3.397925 |
  2. | 2  Indirect results   2008   1.311668    .2712997   .1671253   .4088096          .          . |
     +----------------------------------------------------------------------------------+
```

```
save "C:\DATA\do files paper Dec 2009\Ibu Indo Plac allIVH direct and indirect 12th Dec 2009.dta",replace
file C:\DATA\do files paper Dec 2009\Ibu Indo Plac allIVH direct and indirect
12th Dec 2009.dta saved

xi: metareg lnrr1, wsse(selnrr1)
Iteration 1: tau^2 = 0

Meta-analysis regression                              No of studies =   2
                                                      tau^2 method      reml
                                                      tau^2 estimate =      0

Successive values of tau^2 differ by less than 10^-4:convergence achieved
------------------------------------------------------------------------------
            |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------+-----------------------------------------------------------------
      _cons |   .139415   .3668197     0.38   0.704    -.5795384    .8583684
------------------------------------------------------------------------------

 *meta lnor1 selnor1, or
```

```
disp exp(_b[_cons])
1.1496011

disp exp(_b[_cons]-1.96*_se[_cons])
.56014946

disp exp(_b[_cons]+1.96*_se[_cons])
2.3593393

log close
        log:  C:\DATA\do files paper Dec 2009\Ibu Indo Plac allIVH 12th Dec 2009.smcl
  log type:  smcl
 closed on:  13 Dec 2009, 17:28:47
----------------------------------------------------------------------------
```

Outcome 5: Death prior to hospital discharge

```
---------------------------------------------------------------------------
      log:  C:\DATA\do files created 19th November approved by Ammarin 28th November\Ibu Indo Plac Dth direct
and indirect 19th November.smcl
 log type:  smcl
 opened on:  16 Jun 2009, 16:45:22


*ibu vs. Ind********


use "C:\DATA\rpt analysis original data sets 18th August\Ibu Indo Dth 18th August.dta", clear


list id author year Ibu_Dth Ibu_n_Dth Ind_Dth Ind_n_Dth


     +------------------------------------------------------------------+
     | id         author   year   Ibu_Dth   Ibu_n_~h   Ind_Dth   Ind_n_~h |
     |------------------------------------------------------------------|
  1. |  2    Van Overmeire   1997         1         19         3         17 |
  2. |  4    Van Overmeire   2000         7         67         6         68 |
  3. |  7             Lago   2002        11         83         7         74 |
  4. |  8             Su P   2003         1         31         4         27 |
  5. | 10   Gimeno Navarro   2005         2         21         2         22 |
     +------------------------------------------------------------------+


metan Ibu_Dth Ibu_n_Dth Ind_Dth Ind_n_Dth , fixedi nograph label(namevar=author)


           Study    |    RR    [95% Conf. Interval]     % Weight
--------------------+-------------------------------------------------
Van Overmeire       |  0.333       0.038      2.939         7.35
Van Overmeire       |  1.167       0.412      3.306        32.09
Lago                |  1.354       0.551      3.330        43.01
Su P                |  0.242       0.029      2.048         7.64
Gimeno Navarro      |  1.043       0.160      6.802         9.91
--------------------+-------------------------------------------------
I-V pooled RR       |  0.995       0.551      1.795       100.00
--------------------+-------------------------------------------------


   Heterogeneity chi-squared =    3.20 (d.f. = 4) p = 0.526
```

```
   I-squared (variation in RR attributable to heterogeneity) =   0.0%

   Test of RR=1: z=    0.02 p = 0.987

gen rr1iv = $S_1

gen varlnrr1iv =($S_2)^2

gen rr1 = _ES

gen lnrr1=ln(rr1)

gen varlnrr1 = (_selogES)^2

*no study was dropped, use metan results for overall pooling

save "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Dth RR 19th November.dta",  replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Dth RR 19th November.dta saved

keep id author year rr1 lnrr1 varlnrr1  rr1iv varlnrr1iv

order id author year rr1 lnrr1 varlnrr1 rr1iv varlnrr1iv

list id author year rr1 lnrr1 varlnrr1

     +--------------------------------------------------------------+
     | id          author   year        rr1       lnrr1   varlnrr1 |
     |--------------------------------------------------------------|
  1. |  2    Van Overmeire   1997   .3333333   -1.098612   1.233333 |
  2. |  4    Van Overmeire   2000   1.166667    .1541506   .2824968 |
  3. |  7            Lago   2002   1.354103    .3031395   .2107823 |
  4. |  8             Su P   2003   .2421875   -1.418043   1.186492 |
  5. | 10   Gimeno Navarro   2005   1.043478    .0425596   .9148551 |
     +--------------------------------------------------------------+

gen comparator =1

lab define comp 1"ibuprofen"
```

```
lab value comparator comp

save "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Dth lnrr19th November.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Dth lnrr19th November.dta saved

**********************************Primary outcome: Dth **********************************
**********************************generate RR******************************
*plac vs indo

use "C:\DATA\rpt analysis original data sets 18th August\Indo Plac Dth 18th August.dta", clear

list id author year Plac_Dth Plac_n_Dth Ind_Dth Ind_n_Dth

     +----------------------------------------------------------------------+
     | id          author   year   Plac_Dth   Plac_n~h   Ind_Dth   Ind_n_~h |
     |----------------------------------------------------------------------|
  1. | 1         Merritt   1981          4          9         1         11 |
  2. | 2             Yeh   1981          5         22         6         22 |
  3. | 3          Mahony   1982          2         24         3         18 |
  4. | 4  Monset-Couchard  1983          0         12         3          9 |
  5. | 5         Gersony   1983         32        249        17        123 |
     |----------------------------------------------------------------------|
  6. | 7         Weesner   1987          3         10         3         10 |
  7. | 8          Krauss   1989          3         12         3          9 |
  8. | 9   Van Overmeire   1996          0         14         2         12 |
     +----------------------------------------------------------------------+

list id author if (Plac_Dth==0|Plac_n_Dth==0|Ind_Dth==0|Ind_n_Dth==0)

     +----------------------+
     | id          author   |
     |----------------------|
  4. | 4   Monset-Couchard  |
  8. | 9     Van Overmeire  |
     +----------------------+
```

/**Two studies had 0 cell, applying metan would drop these two studies.
Thus manually calculate by adding 0.5 to each cell of the two studies would be more appropriate**/

```
gen ir_Plac=Plac_Dth/n_Plac

replace ir_Plac = (Plac_Dth+0.5)/(n_Plac+1) if (Plac_Dth==0|Plac_n_Dth==0|Ind_Dth==0|Ind_n_Dth==0)
(2 real changes made)

gen ir_Ind=Ind_Dth/n_Ind

replace ir_Ind=(Ind_Dth+0.5)/(n_Ind+1) if (Plac_Dth==0|Plac_n_Dth==0|Ind_Dth==0|Ind_n_Dth==0)
(2 real changes made)

gen rr1 =ir_Plac/ir_Ind

list id rr1 Plac_*Dth Ind_*Dth  if (Plac_Dth==0|Plac_n_Dth==0|Ind_Dth==0|Ind_n_Dth==0)

     +---------------------------------------------------------+
     | id        rr1    Plac_Dth    Plac_n~h   Ind_Dth   Ind_n_~h |
     |---------------------------------------------------------|
  4. |  4    .1428571          0          12         3          9 |
  8. |  9         .2          0          14         2         12 |
     +---------------------------------------------------------+

gen varlnrr1 = 1/Plac_Dth -1/(n_Plac) + 1/Ind_Dth - 1/n_Ind
(2 missing values generated)

replace varlnrr1 =   1/(Plac_Dth + 0.5) -1/(n_Plac +1) + 1/(Ind_Dth + 0.5) - 1/(n_Ind+1) if
(Plac_Dth==0|Plac_n_Dth==0|Ind_Dth==0|Ind_n_Dth==0)
(2 real changes made)

list id rr1 varlnrr1  Plac_*Dth Ind_*Dth  if (Plac_Dth==0|Plac_n_Dth==0|Ind_Dth==0|Ind_n_Dth==0)

     +-------------------------------------------------------------------+
     | id        rr1    varlnrr1    Plac_Dth    Plac_n~h   Ind_Dth   Ind_n_~h |
     |-------------------------------------------------------------------|
  4. |  4    .1428571   2.131868          0          12         3          9 |
  8. |  9         .2    2.266667          0          14         2         12 |
     +-------------------------------------------------------------------+

     gen lnrr1 = ln(rr1)
```

```
gen w1  = 1/varlnrr1

gen wlnrr1 =w1*lnrr1

egen swlnrr1i=sum(wlnrr1)

egen sumw1=sum(w1)

gen lnrr1iv=swlnrr1i/sumw1

gen rr1iv=exp(lnrr1iv)

gen varlnrr1iv = 1/sumw1

gen selnrr1iv = sqrt(varlnrr1iv)

gen lllnrr1iv  = lnrr1iv -1.96*selnrr1iv

gen ullnrr1iv = lnrr1iv +1.96*selnrr1iv

gen llrr1iv = exp(lllnrr1iv)

gen ulrr1iv = exp(ullnrr1iv)

***Q test****
gen q1 = w1*(lnrr1-lnrr1iv)^2

egen Q1=sum(q1)

list Q1
```

```
   +----------+
   |       Q1 |
   |----------|
1. | 5.056351 |
2. | 5.056351 |
3. | 5.056351 |
4. | 5.056351 |
5. | 5.056351 |
```

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```
          |----------|
      6.  | 5.056351 |
      7.  | 5.056351 |
      8.  | 5.056351 |
          +----------+

          disp $S_7
3.1951701

          count
      8

*         gen k =r(N)

          disp chiprob(r(N)-1, Q1)
.65308647

          list Q rr1iv llrr1iv ulrr1iv in 1


          +---------------------------------------+
          |       Q1      rr1iv    llrr1iv   ulrr1iv |
          |---------------------------------------|
      1.  | 5.056351   .9284945    .617623   1.395839 |
          +---------------------------------------+

          *rr1iv llrr1iv ulrr1iv

   save  "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo Dth RR 15th November.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo Dth RR  15th November.dta saved

keep id author year rr1 lnrr1 varlnrr1  rr1iv varlnrr1iv

   order id author year rr1 lnrr1 varlnrr1 rr1iv varlnrr1iv

list id author year rr1 lnrr1 varlnrr1


          +-----------------------------------------------------------------+
          | id            author    year         rr1       lnrr1   varlnrr1 |
          |-----------------------------------------------------------------|
```

```
1.  |  1           Merritt  1981  3.692308   1.306252   1.089744 |
2.  |  2               Yeh  1981   .8641975  -.145954    .2939153 |
3.  |  3            Mahony  1982   .5384615  -.6190393   .7472528 |
4.  |  4   Monset-Couchard  1983   .1428571  -1.94591    2.131868 |
5.  |  5           Gersony  1983  1.037517    .0368307   .0789937 |
    |------------------------------------------------------------|
6.  |  7           Weesner  1987         1          0    .5128205 |
7.  |  8            Krauss  1989         .8  -.2231435   .5166667 |
8.  |  9     Van Overmeire  1996         .2  -1.609438   2.266667 |
    +------------------------------------------------------------+

        gen comparator =2

      lab define comp 2"placebo"

       lab value comparator comp

   save  "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo Dth lnrr 15th November.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo Dth lnrr 15th November.dta saved

********************************Ibu vs Placebo: Indirect comparison *****************************************
use "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Dth lnrr 19th November.dta"

append using "C:\DATA\repeat analyses ibu indo plac 19th November\Plac Indo Dth lnrr 15th November.dta"
 (label comp already defined)

        tab comp

 comparator |      Freq.     Percent        Cum.
------------+-----------------------------------
  ibuprofen |          5       38.46       38.46
          2 |          8       61.54      100.00
------------+-----------------------------------
      Total |         13      100.00

       lab define comp 2"Plac", modify


tab comp
```

```
comparator |      Freq.     Percent        Cum.
------------+-----------------------------------
  ibuprofen |          5       38.46       38.46
       Plac |          8       61.54      100.00
------------+-----------------------------------
      Total |         13      100.00


char comp[omit] 2

xi: metareg lnrr1 i.comp,wsvar(varlnrr1)
i.comparator      _Icomparato_1-2     (naturally coded; _Icomparato_2 omitted)
Iteration 1: tau^2 = 0

Meta-analysis regression                          No of studies =    13
                                                  tau^2 method       reml
                                                  tau^2 estimate =      0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
-------------------------------------------------------------------------
             |     Coef.    Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------
_Icomparat~1 |   .0691535    .3659516     0.19   0.850    -.6480985     .7864056
       _cons |  -.0741909    .2080032    -0.36   0.721    -.4818696     .3334879
-------------------------------------------------------------------------


        notes: OR (Ibu vs Indo)

       disp exp(_b[_Icomparato_1]+_b[_cons])
.99497533


        notes: OR (Placebo vs Indo)

        disp exp(_b[_cons])
.92849446


        disp exp(_b[_cons]-1.96*_se[_cons])
.61762297
```

```
        disp exp(_b[_cons]+1.96*_se[_cons])
1.3958386

        notes: OR (Indo vs Placebo)

        disp 1/exp(_b[_cons])
1.0770123

        disp 1/exp(_b[_cons]-1.96*_se[_cons])
1.6191108

        disp 1/exp(_b[_cons]+1.96*_se[_cons])
.71641522

         notes: OR(Ibu vs Placebo)

         disp exp(_b[_Icomparato_1])
1.0716007

        disp exp(_b[_Icomparato_1] - 1.96*_se[_Icomparato_1])
.52303249

        disp exp(_b[_Icomparato_1] + 1.96*_se[_Icomparato_1])
2.1955196

        notes: OR & 95% CI   (Ibu vs indo)

        qui xi: metareg lnrr1   if comp ==1, wsvar(varlnrr1)

        disp exp(_b[_cons])
.99497533

        disp exp(_b[_cons] - 1.96*_se[_cons])
.55146657

        disp exp(_b[_cons] + 1.96*_se[_cons])
1.7951694
```

```
save "C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Plac Dth direct and indirect 15th
November.dta", replace
file C:\DATA\repeat analyses ibu indo plac 19th November\Ibu Indo Plac Dth direct and indirect 15th
November.dta saved

log close
      log:  C:\DATA\do files created 19th November approved by Ammarin 28th November\Ibu Indo Plac Dth direct
and indirect 19th November.smcl
 log type:  smcl
 closed on:  16 Jun 2009, 16:45:22
-------------------------------------------------------------------------------
```

4. Supplementary tables for published version of research paper

Table 6. 3 way comparison IV indomethacin vs. IV ibuprofen vs. placebo, Secondary Outcome 2: Necrotising enterocolitis.

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Comparator Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year	Risk Ratio IV, Fixed, 95% CI
1.4.1 Direct comparison NEC IV ibuprofen vs. IV indomethacin								
Van Overmeire 1997	0	1.378405	20	20	8.6%	1.00 [0.07, 14.90]	1997	
Van Overmeire 2000	-0.6931472	0.5898923	74	74	47.0%	0.50 [0.16, 1.59]	2000	
Lago 2002	-0.1488457	0.9884412	81	94	16.8%	0.86 [0.12, 5.98]	2002	
Su P 2003	-0.4372137	0.8773969	31	32	21.3%	0.65 [0.12, 3.61]	2003	
Gimeno Navarro 2005	-1.05779	1.607794	24	23	6.3%	0.35 [0.01, 8.11]	2005	
Subtotal (95% CI)			230	243	100.0%	**0.60 [0.27, 1.33]**		
Heterogeneity: Chi² = 0.49, df = 4 (P = 0.97); I² = 0%								
Test for overall effect: Z = 1.26 (P = 0.21)								
1.4.2 Direct comparison NEC IV indomethacin vs. placebo								
Yeh 1981	-0.3690975	0.8721135	27	27	20.9%	0.69 [0.13, 3.82]	1981	
Mahony 1982	0.8850381	1.116805	21	26	12.7%	2.42 [0.27, 21.63]	1982	
Gersony 1983	-0.003565	0.4891814	140	281	66.4%	1.00 [0.38, 2.60]	1983	
Subtotal (95% CI)			188	334	100.0%	**1.03 [0.47, 2.26]**		
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%								
Test for overall effect: Z = 0.08 (P = 0.93)								
1.4.3 Indirect comparison NEC IV ibuprofen vs. placebo								
indirect 2009	-0.544183	0.5679135	230	334	100.0%	0.58 [0.19, 1.77]	2009	
Subtotal (95% CI)			230	334	100.0%	**0.58 [0.19, 1.77]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.96 (P = 0.34)								

0.01 0.1 1 10 100
Favours intervention   Favours comparator

Table 7. 3-way comparison IV indomethacin vs. IV ibuprofen vs. placebo, Secondary Outcome 3: Intraventricular haemorrhage GDI-IV.

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Comparator Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year
1.7.1 Direct comparison IVH GD I-IV IV ibuprofen vs. indomethacin							
Van Overmeire 1996	-0.4054651	0.8309489	14	14	15.6%	0.67 [0.13, 3.40]	1996
Van Overmeire 2000	0.9162906	0.8203493	74	74	16.0%	2.50 [0.50, 12.48]	2000
Lago 2002	0.2078293	0.4689063	94	81	49.0%	1.23 [0.49, 3.09]	2002
Su P 2003	-0.7248959	1.198537	32	31	7.5%	0.48 [0.05, 5.07]	2003
Adamska 2005	-0.9360934	1.599326	16	19	4.2%	0.39 [0.02, 9.01]	2005
Gimeno Navarro 2005	0.7357068	1.189477	23	24	7.6%	2.09 [0.20, 21.48]	2005
Subtotal (95% CI)			253	243	100.0%	1.16 [0.61, 2.21]	

Heterogeneity: Chi² = 2.57, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)

1.7.2 Direct comparison IVH GD I-IV IV indomethacin vs. placebo							
Mahony 1982	-0.2135741	0.4468039	21	26	29.7%	0.81 [0.34, 1.94]	1982
Gersony 1983	0.0452251	0.3700236	140	281	43.3%	1.05 [0.51, 2.16]	1983
Weesner 1987	-0.5108256	0.6160253	13	13	15.6%	0.60 [0.18, 2.01]	1987
Van Overmeire 1996	0	0.7237468	14	14	11.3%	1.00 [0.24, 4.13]	1996
Subtotal (95% CI)			188	334	100.0%	0.88 [0.55, 1.42]	

Heterogeneity: Chi² = 0.67, df = 3 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)

1.7.3 Indirect comparison plus 1 direct study IVH GD I-IV IV ibuprofen vs. placebo							
Van Overmeire 1996	-0.4054651	0.8309489	14	14	19.5%	0.67 [0.13, 3.40]	1996
indirect 2009	0.2712997	0.4088096	253	334	80.5%	1.31 [0.59, 2.92]	2009
Subtotal (95% CI)			267	348	100.0%	1.15 [0.56, 2.36]	

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)

0.1 0.2 0.5 1 2 5 10
Favours intervention   Favours control

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Table 8. 3-way comparison IV indomethacin vs. IV ibuprofen vs. placebo, Secondary Outcome 4: in hospital mortality.

Study or Subgroup	log[Risk Ratio]	SE	Intervention Total	Comparator Total	Weight	Risk Ratio IV, Fixed, 95% CI	Year	Risk Ratio IV, Fixed, 95% CI
1.8.1 Direct comparison in hospital mortality IV ibuprofen vs. IV indomethacin								
Van Overmeire 1997	-1.098612	1.110555	20	20	7.4%	0.33 [0.04, 2.94]	1997	
Van Overmeire 2000	0.1541506	0.5315043	74	74	32.1%	1.17 [0.41, 3.31]	2000	
Lago 2002	0.3031395	0.4591103	94	81	43.0%	1.35 [0.55, 3.33]	2002	
Su P 2003	-1.418043	1.089262	32	31	7.6%	0.24 [0.03, 2.05]	2003	
Gimeno Navarro 2005	0.0425596	0.9564806	23	24	9.9%	1.04 [0.16, 6.80]	2005	
Subtotal (95% CI)			**243**	**230**	**100.0%**	**0.99 [0.55, 1.80]**		

Heterogeneity: Chi² = 3.20, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)

1.8.2 Direct comparison in hospital mortality IV indomethacin vs. placebo								
Merritt 1981	1.306252	1.043908	13	12	4.0%	3.69 [0.48, 28.57]	1981	
Yeh 1981	-0.145954	0.5421396	27	28	14.8%	0.86 [0.30, 2.50]	1981	
Mahony 1982	-0.6190393	0.8644378	26	21	5.8%	0.54 [0.10, 2.93]	1982	
Monset-Couchard 1983	-1.94591	1.460092	12	12	2.0%	0.14 [0.01, 2.50]	1983	
Gersony 1983	-0.0641897	0.2817303	281	140	54.7%	0.94 [0.54, 1.63]	1983	
Weesner 1987	0	0.7161149	13	13	8.5%	1.00 [0.25, 4.07]	1987	
Krauss 1989	-0.2231435	0.7187953	15	14	8.4%	0.80 [0.20, 3.27]	1989	
Van Overmeire 1996	-1.609438	1.505545	14	14	1.9%	0.20 [0.01, 3.82]	1996	
Subtotal (95% CI)			**401**	**254**	**100.0%**	**0.88 [0.58, 1.32]**		

Heterogeneity: Chi² = 4.83, df = 7 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)

1.8.3 Indirect comparison in hospital mortality IV ibuprofen vs. placebo								
indirect 2009	0.124654	0.3661063	243	254	100.0%	1.13 [0.55, 2.32]	2009	
Subtotal (95% CI)			**243**	**254**	**100.0%**	**1.13 [0.55, 2.32]**		

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

0.01   0.1   1   10   100
Favours intervention   Favours comparator

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Table 9a. Sensitivity analyses for pre-specified variables

	All studies	Quality score		Blinding	Mean age at treatment		Echo to identify PDA	Echo to confirm PDA
		< 3	≥ 3		< 72 hrs.	≥ 72 hrs.		
PDA closure: IV indomethacin vs. placebo								
Pooled RR (95%CI)	2.41 (1.72, 3.36)	2.98 (1.53, 5.81)	2.26 (1.44, 3.56)	2.46 (1.53, 3.94)	1.71 (1.33, 2.19)	2.88 (2.38, 3.50)	1.69 (1.31, 2.17)	2.95 (2.44, 3.57)
Q test p value[†]	0.008	0.08	0.01	0.009	0.1	0.5	0.2	0.4
$I^{2†}$ (%)	61	53	71	79	42	0%	29	0
Tau^2[†]	0.1	0.3	0.2	0.1	0.07	0	0.04	0
PDA closure: IV ibuprofen vs. placebo								
Pooled RR (95%CI)	2.40 (2.03,2.84)	2.08 (1.54, 2.82)			1.78 (1.37, 2.31)	2.81 (2.23, 3.55)	1.79 (1.38, 2.31)	2.75 (2.16, 3.50)
Tau^2[†]	0	0			0	0	0	0
CLD: IV ibuprofen vs. IV indomethacin								
Pooled RR (95%CI)	1.28 (1.03, 1.60)	0.91 (0.81, 1.01)			1.10 (1.04,1.74)	1.34 (1.04, 1.74)	1.35 (1.07, 1.71)	
Q test p value[†]	0.7				0.8	0.8	0.6	
$I^{2†}$	0				0	0	0	
Tau^2[†]	0				0	0	0	
CLD: IV ibuprofen vs. placebo								
Pooled RR (95%CI)	1.29 (0.99, 1.70)	0.98 (0.77, 1.23)				1.69 (1.11, 2.57)		
Tau^2[†]	0	0				0		

[†] Heterogeneity testing

Unfilled areas represent insufficient studies

Table 9b. Sensitivity analyses for post-hoc variables

	Mean birthweight		Mean Gestational age		Number of doses	
	<1000g	≥ 1000g	≤ 28 wks.	>28 wks.	1-3	3
PDA closure: IV indomethacin vs. placebo						
Pooled RR (95%CI)	1.80 (1.24, 2.61)	2.53 (2.14, 3.00)	1.78 (1.16, 2.74)	2.47 (2.10, 2.91)	2.39 (1.38, 4.45)	2.25 (1.80, 2.82)
Q test p value[†]	0.08	0.02	0.04	0.02	0.17	0.005
$I^{2†}$ (%)	55	66	68	66	46	71
Tau^$2†$	0.2	0.1	0.4	0.1	0.23	0.14
PDA closure: IV ibuprofen vs. placebo						
Pooled RR (95%CI)	1.87 (1.31, 2.66)	2.59 (2.12, 3.17)	1.79 (1.20, 2.70)	2.54 (2.10, 3.09)	2.35 (1.34, 4.12)	2.31 (1.77, 3.03)
Tau^$2†$	0	0	0	0	0	0.02
CLD: IV ibuprofen vs. IV indomethacin						
Pooled RR (95%CI)	1.31 (1.01, 1.77)	1.35 (1.01, 1.80)	0.88 (0.47, 1.65)	1.32 (1.02, 1.71)	1.35 (0.82, 2.22)	1.32 (1.02, 1.71)
Q test p value[†]	0.7	0.8	0.6	0.6	0.5	0.6
$I^{2†}$	0	0	0	0	0	0
Tau^$2†$	0	0	0	0	0	0
CLD: IV ibuprofen vs. placebo						
Pooled RR (95%CI)	1.19 (0.87, 1.64)	1.69 (1.08, 2.63)	0.99 (0.63, 1.55)	1.50 (1.07, 2.10)	1.35 (0.82, 2.20)	1.55 (1.14, 2.12)
Tau^$2†$	0	0	0	0		0

[†] Heterogeneity testing

Chapter 3 –Discussion

Section 1: New Research Directions

1.1.   Pathophysiology of PDA

Academic and clinical understanding of the pathophysiology associated with PDA has made slow progress in the time period that has elapsed since the commencement of this network meta-analysis. A portion of this has arisen from the investigation of adjuvant therapies aimed at management of RDS and cardiac failure rather than those specifically targeting PDA closure. For instance, Abdel-Hady (362) found no change in PDA diameter or shunt severity from using nasal prong continuous positive airways pressure (CPAP) for respiratory support in preterm infants with resolving RDS and HsPDA, signs commonly associated with cardiac failure in preterm infants with HsPDA such as increased right ventricular output and left atrial diameter were reversed. Although small, Abdel-Hady's (362) study implies that nasal CPAP may minimise cardio-respiratory dysfunction associated with HsPDA in preterm infants born at a mean gestational age of 30 weeks without the need for treatment targeted at PDA closure. Although preterm infants with HsPDA receiving nCPAP may require an increased length of time on ventilation compared to those without HsPDA, this gentler form of ventilation may not necessarily translate to an increase in CLD. Although the study was performed in older gestational age infants with resolving RDS, nCPAP may be of use in extreme preterm infants failing to close a PDA despite repeated courses of treatment with indomethacin or ibuprofen. In addition to previous evidence of the effect of treatment failure on mortality in preterm infants previously reported in the literature review, repeated indomethacin treatment to close a PDA was associated with an eight fold increase in mortality in preterm infants born at < 29 weeks in a recent study by Noori (363). This may be related to the susceptibility of the high risk preterm infant to failure of PDA closure and need for repeated indomethacin treatment. An alternative consideration is that increased mortality associated with PDA ligation following repeated courses of indomethacin as discussed in Section 4 PDA Management, arises from adverse treatment effects. It may be beneficial to use nasal CPAP alone, avoid the use of COX inhibitors and reserve late ligation for persistent PDA.

In another example of a supportive therapy with potential to be an effective strategy in preventing and limiting the effects of PDA rather than specifically aiming to close it, fluid restriction is being revisited as a management strategy for PDA. Two new Cochrane systematic reviews are planned; one by Harish Madhava and Settle (364) aims to evaluate the evidence from randomised trials on the use of fluid restriction in preterm infants with symptomatic PDA and the other, by Anabrees and Alfaleh (365) aims to examine the use of fluid restriction as supportive therapy for indomethacin prophylaxis. As the systematic literature search forming part of this review was able to locate only a small number of randomised trials examining the use of fluid restriction for symptomatic PDA, it is likely that currently available randomised trials will provide little evidence to recommend such treatment particularly concerning treatment of symptomatic PDA in the modern era. Consequently, it is envisioned that these new Cochrane Reviews will support the recommendations of this review regarding the need for new trials examining the use of conservative, supportive management of preterm infants with PDA in the context of modern neonatal care.

Investigators have continued to search for improved, more cost-effective methods of identifying haemodynamically significant PDA. One example is NT-pro BNP, a metabolite of brain natruiretic peptide (BNP), a biomarker synthesized by the cardiac muscles in response to over-distension from cardiac overload, to detect clinically important HsPDA. A prospective observational study by Nuntnarumit (366) indicated NT-proBNP to be 100% sensitive and 91% specific in detecting HsPDA at day 2 of life in preterm infants born at < 33 weeks gestation. The added benefits of using the metabolite include longer half-life, lower susceptibility to circadian fluctuation and greater stability of the sample making it more robust for use as a specific marker for ventricular dysfunction in association with HsPDA. Previous studies on BNP indicate a similar timing window for evaluation at 2-3 days, making this test potentially useful for moderately early treatment of PDA in neonatal units with limited access to echocardiography services. Potential disadvantages include affordability and access to testing services in rural and remote areas.

The majority of recent evidence from observational studies continues to suggest similarity in the effectiveness of indomethacin and ibuprofen with less renal failure and a trend toward lower incidence of NEC with ibuprofen. There were no differences in the composite outcome of death, NEC or intestinal perforation between infants treated with intravenous indomethacin compared

with intravenous ibuprofen for symptomatic PDA in a retrospective chart review by Katakam (367), although in keeping with the results of our network meta-analysis, there was a small trend toward lower rates of NEC in those treated with intravenous ibuprofen. Similar to the findings of Katakam (367) there was no difference in intraventricular hemorrhage, necrotizing enterocolitis, or mortality between indomethacin and ibuprofen treated preterm infants with PDA studied by Linder (368) although rising serum creatinine levels were more commonly associated with the use of indomethacin. With the exception of 4 cases of adverse neurological outcome in ibuprofen compared to none in indomethacin treated infants, neurodevelopmental outcomes were not statistically significantly different between infants at 2 years corrected age followed-up retrospectively. This finding is supported by lack of neurological improvement in 165 preterm surviving infants with PDA treated with either intravenous ibuprofen or intravenous indomethacin retrospectively reviewed at 2 years of age by Rheinlaender (369). Studies continue to indicate lack of benefit for indomethacin or ibuprofen on gastrointestinal, respiratory and neurological outcomes; however these are limited by their retrospective design and comparison between PDA treatments rather than conservative vs. pharmacological treatment.

Recent experimental studies continue to indicate a mixture of beneficial and adverse effects associated with both indomethacin and ibuprofen. In support of a therapeutic benefit, an experimental study by McCurnin (370) found that both indomethacin and ibuprofen reduced lung water and improved lung maturation in surfactant treated, ventilated preterm baboons with PDA at 24 hours of life. Although daily echocardiographic examinations of ductal patency were performed, McCurnin (370) did not specify the criteria for determining haemodynamically important PDA or clearly state the PDA screening process for preterm subjects prior to study entry and randomisation. In addition there was no control group treated with indomethacin and ibuprofen in the absence of PDA to evaluate the possibility of a direct pulmonary effect arising from these medications. The degree of ductal patency likely to have benefit on outcomes from administration of indomethacin and ibuprofen for PDA closure is not clear from this study and it remains possible that these may either arise from a direct effect on the lung rather than specifically from ductal closure or depend upon the targeting of a specific ductal diameter beneath which adverse treatment effects may occur.

Additional adverse effects have been associated with the use of both indomethacin and ibuprofen. Gebrekristos (371) found that postnatal growth restriction and elevated cortisol levels in neonatal preterm rats in associated with indomethacin and ibuprofen use, were greater in indomethacin treated rats. Ibuprofen had comparatively transient effects, with a late rebound increase in serum and hepatic growth hormone secretion, whilst indomethacin demonstrated a sustained elevation in corticosteroid levels. These may translate to an alteration in brain growth and stress response with increased risk of long term neurological and endocrine dysfunction. It is possible that adverse effects on neurological development resulting from hormonal dysfunction secondary to the action of COX inhibitors may counterbalance the hypothetical benefit of IVH reduction associated with the early administration of indomethacin on neurological function. This may at least partly explain the failure of the TIPP study to find any improvement in neurobehavioural status in infants receiving indomethacin prophylaxis for IVH prevention.

Further evidence from observational studies indicates that ibuprofen may also have some transient adverse effect on renal function in preterm infants. Increased serum creatinine and reduced PGE2 expression in ibuprofen-treated preterm infants prospectively studied by Antonucci (372) suggests that use of ibuprofen may also impair renal function in the first week of life. PDA may also have contributed to the raised serum creatinine as Antonucci (372) only compared renal function in ibuprofen treated preterm infants with PDA to untreated infants without PDA. This is supported by a retrospective chart review of factors affecting renal function in preterm infants with ibuprofen treated PDA by Iacobelli (373) in which both PDA and ibuprofen were associated with elevated serum creatinine supporting a role for both factors as contributors to renal failure. The transient nature of the effect of indomethacin or ibuprofen treated PDA on renal function, lack of data on long term renal impairment in preterm infants and the inability to provide a comparison with a control group with untreated PDA makes it difficult to determine the overall effect of ibuprofen on this outcome.

A recently completed randomised trial comparing IV ibuprofen with placebo plus rescue by Aranda (374) was only available in abstract form at the time our network meta-analysis was performed and no data on study outcomes was available at that time. A large proportion of the preterm infants in this trial were treated at less than 24 hours of age and therefore this trial does not fit with the inclusion criteria specified in our meta-analysis. Aranda's findings included a

statistically significant reduction in the risk of the composite outcome death/drop out/need for rescue in favour of ibuprofen (rescue 30.9%) compared to placebo (rescue 52.9%) which may indicate that this medication is better tolerated than indomethacin. This supports a previously well-demonstrated lower spontaneous PDA closure rate in preterm infants within the placebo group and reflects the overall aim to close clinically important PDA which has predictably led to an increased need for rescue ibuprofen in the placebo group subject to the lower rate of closure in this group. This outcome is greatly influenced by clinical decision-making on when and who should receive rescue therapy. Omission of the reasons for infants that were dropped from the study and the proportion of drop-outs compared to those rescued or died for ibuprofen compared to placebo may represent the exclusion of important information regarding tolerability of ibuprofen or placebo and prevents an assessment of the impact of differential mortality and withdrawal of high risk preterm infants on outcome measurements. As there is no indication of when the deaths, dropped or rescued occurred in relation to the measurement of single outcomes, it is difficult to ascertain the effect of variation in early vs. late mortality, withdrawals, and use of rescue treatment between ibuprofen and placebo on the risk of NEC, IVH and BPD. Of particular note, referring to table 2 below, a larger proportion of infants continued to have an oxygen requirement at 28 days of life in the ibuprofen compared to the placebo group. This difference was no longer apparent at 36 weeks corrected age, a finding consistent with previous Cochrane reviews of ibuprofen vs. indomethacin and this network meta-analysis. Referring to table 2 below, at the time of CLD diagnosis, a larger number of preterm infants in the placebo (40) compared to the ibuprofen (26) group had died, dropped from the study or had received rescue treatment. The lack of difference in the risk of CLD may be due to improved specificity of the definition of continued oxygen requirement at 36 weeks corrected age rather than at 28 days of life, or it may result from bias of outcome measurement between the two definitions of CLD due to a difference in early vs. late deaths, drop-outs, or use of rescue treatment between preterm infants in the ibuprofen and placebo groups. Aranda (374) has not used analysed the outcome of CLD according to intention to treat and although it appears he has subtracted infants having died or dropped from the denominator of both the ibuprofen and placebo groups, it is difficult to assess the effect of the difference in rates of rescue therapy on the measurement of CLD. Other limitations of Aranda's study (374) include variation in the timing of intervention between early (12 hours) and moderately early (72 hours) which may have contributed to the finding of no significant difference between major outcomes such as

severe IVH and CLD, and the measurement of outcomes to 30 days only with failure to include follow up on longer term neurodevelopmental and respiratory outcomes.

Postnatal age	≤ 14 days	28 days		36 weeks	
	Died, dropped or rescued	Died, dropped or rescued	CLD	Died, dropped or rescued	CLD Dx
Ibuprofen	21/68	26/68	58/65 89.2%	26/68	42/45 91.3%
Placebo	36/68	40/68	53/65 81.5%	40/68	48/52 92.3%
*Died, dropped or rescued.					

Table 2 proportions of deaths, withdrawals and rescue at successive CLD diagnoses.

Updated Cochrane systematic reviews recommend ibuprofen for echo targeted and/or symptomatic PDA due to cumulative evidence of an improved safety profile in comparison to indomethacin. In an update of the Cochrane Review of ibuprofen for PDA in preterm infants, Ohlsson (226) reported that ibuprofen may be safer in terms of a small reduction in the risk of NEC and less transient renal failure whilst maintaining similar efficacy between oral and intravenous formulations. The inconsistency between Cochrane review findings and our network meta-analysis in regard to the outcome of CLD may be due to the combination of both IV and oral ibuprofen in their analysis whereas we compared intravenous formulations only. Sensitivity analyses comparing oral ibuprofen v. intravenous indomethacin and intravenous ibuprofen vs. intravenous indomethacin for the outcome of NEC were not performed in the latest Cochrane review (226) and it is possible that use of different methods to identify PDA there are between trials of oral ibuprofen vs. intravenous ibuprofen compared to intravenous ibuprofen vs. intravenous ibuprofen may have led to difference in baseline risk of NEC at study entry.

The majority of studies comparing intravenous ibuprofen with intravenous indomethacin in the Cochrane review by Ohlsson (226) used echo plus or minus clinical criteria to confirm PDA,

whereas ¾ of studies of oral vs. intravenous used symptomatic criteria to guide echocardiographic detection and all studies treated preterm infants at a later postnatal age. In contrast, a proportion of the studies in the Cochrane review (226) comparing intravenous ibuprofen vs. intravenous indomethacin aimed to treat within the first few days of life. Studies of early treatment are more likely to include lower gestational age preterm infants at high risk of severe outcomes as these infants tend to be predisposed to the early development of large diameter PDA. In contrast, infant populations included in oral vs. intravenous studies treated on the basis of clinical signs at a later postnatal age, may have a lower baseline risk of adverse outcomes associated with PDA at randomisation compared to infants included in trials of intravenous ibuprofen vs. intravenous indomethacin formulations. Addition of newer studies comparing oral ibuprofen vs. intravenous indomethacin to the null result produced by the intravenous ibuprofen and intravenous indomethacin studies previously included in the Cochrane review (226) may indicate a reduction in the risk of NEC, however this can be attributed to the use of oral formulations in the treatment of symptomatic PDA in preterm infants at a later age rather than the use of early treatment to close the PDA in higher risk preterm infants based on echo-targeted treatment alone. It is possible that ibuprofen does reduce the incidence of NEC in comparison to indomethacin, which is supported by the trend incidence rates in our network analysis favouring intravenous ibuprofen over placebo and intravenous indomethacin. As previously discussed, perfusion studies have demonstrated intravenous ibuprofen to have less effect on mesenteric flow than indomethacin. Ibuprofen may have a true effect in reducing the risk of NEC however this has not been demonstrated in studies comparing intravenous formulations for management of echo-targeted PDA.

Updated Cochrane reviews of ibuprofen for PDA in preterm infants (216, 226) no longer indicate an increased risk of CLD in association with oral/intravenous ibuprofen administration when compared to intravenous indomethacin. The change in the direction of the relative risk of CLD toward the null or no difference in risk between ibuprofen and indomethacin in the previous and current Cochrane review updates may have occurred due to the inclusion of a progressively greater number of new studies of oral ibuprofen vs. IV indomethacin treating symptomatic PDA at different ages using clinical signs with echocardiographic confirmation with later age at treatment. Oral formulations may be associated with a reduction in CLD; however sensitivity analyses comparing the effect of including trials of oral ibuprofen vs. intravenous

indomethacin on CLD risk to trials of intravenous ibuprofen vs. intravenous indomethacin alone were not conducted in previous and current Cochrane review updates.

Similar to our review, Cochrane reviews (216, 226) have included studies using a range of criteria for defining PDA, echocardiographic alone, echocardiographic plus clinical criteria and symptomatic with echocardiographic confirmation. In contrast with our review which includes studies of preterm infants treated for PDA at greater than 24 hours of life, Cochrane reviews (216, 226) include studies of preterm infants with PDA treated at any age, from as early as 12 hours of life such as those by Hammerman (375), and Su (376), to 7 - 10 days of life in a study by Salama (377). As our sensitivity analyses of the effect of age at treatment on PDA closure and the literature indicate, age at treatment is likely to be an important factor in the success of PDA closure and any consequent reduction in morbidity and mortality. Parameters relating to the stage of disease, i.e. criteria for establishing PDA such as PDA diameter on echo, and the aetiologically relevant window period for treatment, i.e. age at treatment, need to be similar within each treatment arm in order to exclude any impact of the differences between these on the study outcomes.

Apart from our systematic review and network meta-analysis, there are no available published systematic reviews or randomized trials comparing ibuprofen with placebo or indomethacin with placebo as treatment for PDA in preterm infants at greater than 24 hours of life. There is a particular lack of trials comparing indomethacin to placebo for preterm infants treated for PDA at > 24 hours of life, the most recent study being an abstract by Van Overmeire (334). Treatment, nature of morbidity and survival of preterm infants has changed markedly in 15 years. Resuscitation practices, ventilation including nCPAP, and use of surfactant have made a major impact on infant survival. As discussed in Section 3 of the literature review, the effect of such practice improvements on morbidities such as CLD have led to a milder, more chronic disease course with greater emphasis on the predictive ability of short term outcomes on longer term disability. These changes are likely to have an impact on the risk of PDA pathophysiology and management related morbidity and mortality. Evaluation of previous and current evidence from randomised controlled trials and systematic reviews highlights the need for further randomised trials of PDA treatment at greater than 24 hours of life with indomethacin vs. placebo and ibuprofen vs. placebo in the modern setting of neonatal intensive care.

1.2. Changes in PDA guidelines

Cost, access and experience with use of particular COX 2 inhibitors were the primary motivations directing choice of COX inhibitors and preferred administration route in the management of clinically important PDA indicated in recent surveys. Effectiveness and safety were lesser considerations in some countries. A survey of PDA management across 19 European countries by Guimaraes (378) found that indomethacin was still used in 71% of NICUs despite numerous studies indicating similar effectiveness in PDA closure and a potentially safer profile for ibuprofen. One third of neonatal units surveyed expressed a continued preference for intravenous indomethacin over intravenous ibuprofen as it is far less costly than intravenous ibuprofen, whilst another third (36%) preferred indomethacin as they were experienced in using it. Some neonatal units did not have access to intravenous ibuprofen due to restricttions or lack of availability. Half of survey respondents preferred ibuprofen due to a perceived increase in safety profile. Cost was the primary motivation for choosing oral ibuprofen in 20% of NICU's with an established preference for ibuprofen. Choice of PDA treatment was influenced by economic considerations in 22% of the 45 Neonatal Units surveyed. Oral ibuprofen is rapidly becoming the preference of developing countries due to a combination of a potentially improved safety profile and the lower cost of oral compared with intravenous preparations.

The experience in Australia appears to be similar in terms of a continued preference for intravenous indomethacin largely motivated by cost and greater familiarity with its use. The author of the most recently updated RPA guidelines, Evans (379) asserts that the use of ibuprofen as an alternative to indomethacin is not yet feasible due to its higher cost in comparison to the available intravenous indomethacin formulation and "the absence of any clear benefit in terms of important longer term outcomes". This is cited as the main rationale for lack of formal approval from the Therapeutic Goods Association (TGA) for the use of ibuprofen in Australia, despite its use in Europe, the US and developing countries. Although ibuprofen has recently become available for use in Australia due to a world-wide shortage of indomethacin, this is only under a special-access scheme and the TGA currently advises that this is temporary (380). When it is considered that a beneficial effect on outcomes has not yet been demonstrated in randomized trials of either ibuprofen or indomethacin as treatment for PDA,

this indicates that cost, rather than safety profile remains a major consideration in the selection of pharmacological agents in both developed and developing countries.

Recent surveys of PDA management in Europe, Spain and South America by Golombek (381) and Guimareas (378) suggest that current evidence of the effectiveness of echo-targeting of PDA at < 24 hours on outcomes has not been sufficient motivation to address lack of access to echocardiographic services and adopt early targeted indomethacin treatment at < 24 hours of age in preference to echo targeting PDA at > 24 of life hours or symptomatic PDA. Resources available to individual neonatal intensive care units, particularly the use of echocardiography tend to vary in line with geographical and economic differences. There is considerable variation in preferences for PDA treatment between Neonatal units. Two of 45 European Neonatal units surveyed by Guimareas used early indomethacin as prophylaxis given regardless of PDA status, 25% treat non-HsPDA and 98% treat HsPDA. The criteria defining HsPDA also varied with ductal diameter, La/Ao, retrograde diastolic aortic and other criteria used in 64%, 70%, 55% and 34% of NICU's respectively. Nearly one fifth (18%) of units used symptomatic criteria in the absence of echocardiography to confirm PDA. Due to the variation in criteria defining PDA, methods of detection and treatment timing and management Guimareas recommends the adoption of general guidelines for PDA management.

The Society of Ibero-American Neonatalogists (SIBEN) consensus on PDA management reported by Golombek (381) was formed from the expert opinion of 31 neonatologists from 16 former Spanish-led colonies in the Americas. SIBEN (381) made the recommendation that preterm infants should be treated using ibuprofen or indomethacin for HsPDA identified at 2-5 days of life. The benefit of the approaches underpinning the recommendations of both Guimareas (378) and SIBEN (381) on the risk of outcomes, particularly in regard to later treatment at > 2-5 days of life are not supported by evidence from systematic reviews and randomised trials of PDA closure with indomethacin or ibuprofen. As discussed in the literature review, many of these management approaches, particularly those aimed at providing treatment of PDA at greater than 24 hours of life are poorly supported by observational studies which were subject to bias from confounding by factors, such as RDS, which predispose to PDA, morbidity and mortality, and performed in a different era of neonatal management. The literature, systematic review and network meta-analysis embodied in this thesis point toward the lack of recent evidence from studies of treatment with indomethacin or ibuprofen to close a

PDA at greater than 24 hours of life compared with late ligation or no intervention to close a PDA. Limitations on access to echocardiography services for early PDA management imposed by geographical location, funding allocation for training and service provision, along with the ability to recruit and retain suitably qualified practitioners within the service continues to have a major influence on the treatment approach used by individual neonatal intensive care units. Opinion on PDA management options including; type route and timing of management technique remains divided and the results of randomised trials of indomethacin or ibuprofen for large diameter PDA at < 24 hours of life on morbidity and mortality are eagerly awaited.

1.3.   New trials

Despite the recommendations of Guimareas (378) and SIBEN (381) and some support from US and Australian surveys, there is a relative absence of registered randomized trials investigating indomethacin or ibuprofen compared with placebo for echocardiographically and/or clinically important PDA in preterm infants at greater than 24 hours of life. The majority of randomised trials currently in progress focus on the comparative incidence of PDA closure in lower gestational age, lower birthweight preterm infants using specific echocardiographic detection criteria, in addition to the timing of administration on major outcomes. Chan and Lundbeck (382) propose to evaluate the effect of early vs. late ibuprofen on PDA. A comparison of intravenous vs. oral ibuprofen for PDA closure in preterm infants born at < 28 weeks gestation is planned by Su (383). Evans and Kluckow (384) are proceeding with the much awaited randomised trial "DETECT", in which they plan to test their theories of the effectiveness of indomethacin treatment in preterm infants with PDA at less than 24 hours of life identified via echocardiographic assessment of PDA diameter and flow pattern in on the outcomes of PDA closure, a composite outcome of death and abnormal head ultrasound, and CLD defined as continued oxygen requirement at 36 weeks. Despite a number of new studies and trials, the majority of study investigators have not outlined plans to evaluate longer term respiratory and neurological outcomes.

A single trial plans to evaluate indomethacin compared with placebo for PDA at greater than 24 hours. A pilot trial named "INDUCE" (385) aims to evaluate the efficacy of early targeted indomethacin at 2 to 3 days of life on the outcomes of CLD, IVH and death compared to placebo for echo-detected PDA in preterm infants born at less than 28 weeks gestational age.

The trial investigators plan to avoid the use of rescue treatment in the placebo group, most likely to minimise the effect of this on the tendency toward the null on the risk of outcomes between treatment and placebo groups potentially created by administering treatment to the placebo group.

The proposal to avoid rescue treatment makes recruiting participants ethically and practically difficult as the use of indomethacin is regarded as an established treatment for PDA despite the relative absence of level 1 and II, and recent level III evidence to recommend the efficacy of PDA closure with either indomethacin or ibuprofen on morbidity and mortality. As a consequence, it is likely to take an extended period to recruit even small numbers to the pilot trial, therefore objective examination of any trend toward an increase in adverse events associated with allocation the avoidance of treatment arm considerations and the ability of the pilot for the INDUCE trial to make valid predictions in terms of sample size for potential application to a larger trial are of great importance.

1.4.   Progress in methods and interpretation of network meta-analysis

Formerly reserved for health economic and technology assessments, indirect comparisons are becoming more frequently used to compare the effectiveness between 2 or more interventions on disease-related outcomes where evidence available from head to head randomised trials is sparse or non-existent. Close to 90 separate reports concerning the use of indirect comparisons conducted within the last decade were identified in a recent systematic review by Song (386). More recent reports have used indirect comparisons to rank the effectiveness of drug treatments with no existing direct comparison in a randomised trial, by comparing existing evidence from direct trials of similar interventions. For instance van der Valk.(387) used additional evidence supplied by indirect comparisons, to compare the effect of intraocular pressure reduction across a range of glaucoma treatment.

Other examples where indirect comparisons have been used include investigation of the comparative effectiveness of anti-rheumatoid factor agents in rheumatoid arthritis by Bergman (388), a comparison of anti-thrombolytic agents for acute coronary syndrome by Biondi-Zoccai (389) and an examination of the effect of chemotherapy on progression-free survival in patients with metastatic renal cell carcinoma by Mills (390). The increasing use of indirect comparisons

has led the Cochrane Collaboration to establish some general recommendations for the use of indirect comparisons (391), however due to concerns regarding the comparability of indirect comparisons to direct evidence these do not as yet officially form part of Cochrane methodology for systematic reviews. The Cochrane Collaboration Handbook (391) currently recommends the use of evidence from direct comparisons between trials without methodological issues in precedence to indirect comparisons; with the use of indirect comparisons as supplementary evidence to direct randomised trials when both are available.

Although indirect comparisons have been successfully used to supplement evidence from randomised trials in a number of studies, increased utilization of indirect comparisons has raised concerns regarding the methods used and the potential impact on their consistency with current evidence. Song (386) has provided a more detailed description of the methods of indirect comparisons and these are included as an extension of the explanation provided in the methods section. Despite an overall improvement in the number of studies using recommended methods for indirect comparisons, Song (386) reported that 22% continued to use naïve or informal indirect comparisons, 56% used simple adjusted comparisons and only 20% used network meta-analyses. Naïve or informal indirect comparisons merely compare trial intervention arms across different studies as if they were from the same trial. This method fails to preserve randomisation of baseline characteristics between trial arms leading to the potential for bias in the effect estimates for studied outcomes arising from differences in baseline risk between the populations of infants across the trials being compared. Simple adjusted comparisons are referred to by Song (386) as "classic frequentist methods". These employ simple meta-regression techniques which are useful for comparing a small number of interventions. Song (386) describes network meta-analysis methods as more suitable for use in analysing the comparative effectiveness of treatments across more complex networks. Our method involved network meta-analysis, which, although we only compared two interventions for PDA treatment, may be extended to include other agents, routes, or management approaches which will be further outlined in Section 2 of this chapter.

Other key issues in the methodology of indirect comparisons in recent studies include lack of systematic searching, failure to evaluate or clearly explain the process used to assess population similarity and no investigation of any dissimilarity in patient characteristics. According to Song (386), these flaws are commonly found in studies of indirect comparisons,

therefore the results obtained should be considered with regard to their consistency with combined evidence from randomised trials. Inadequate search methods with failure to search for unpublished work increases the risk of publication bias arising from a tendency to report and publish positive study outcomes rather than null or negative findings which may bias overall effect estimates. Failure to describe or investigate comparative population characteristics and methods for identifying disease and outcomes between studies may lead to a distortion of risk estimates and lack of consideration of the potential effects of any such differences on the risk estimates for disease outcomes. These considerations have been fully addressed within the submitted network meta-analysis by: 1) conducting a systematic search for all relevant randomised trials for the purpose of direct and indirect meta-analysis in accordance within the criteria specified in the Research Proposal; 2) describing any potential influence of dissimilarity between studies on the effect size produced by the indirect comparison; 3) investigating heterogeneity for the outcome of PDA closure for the direct comparison between indomethacin and placebo including a thorough assessment of the likely impact on the effect size for PDA closure and the implications on the comparison between ibuprofen and placebo and the other outcomes. In addition, consistency in the effect estimates for PDA closure and CLD in the 3 way comparison between ibuprofen vs. placebo vs. indomethacin indicates the strength of the relationship between indirect and direct evidence in relation to these outcomes. At the same time, the effect of heterogeneity on the overall effect size for PDA closure in the direct meta-analysis between indomethacin and placebo cannot be entirely discounted.

Section 2: Recommendations for future research

2.1 Sample size

Projected sample sizes for current trials
Randomised trials currently registered or in progress examining indomethacin vs. placebo for the treatment of PDA in preterm infants include INDUCE and DETECT. The pilot trial for INDUCE, with an initial total sample size of 90 infants aims to establish incidence rates for indomethacin vs. placebo with avoidance of treatment for PDA closure administered for echocardiographically important PDA at greater than 24 hours of life. DETECT investigators plan to recruit a total of 300 preterm infants with the aim of detecting a difference in risk/benefit for indomethacin vs. placebo administered at 12 hours of life for echocardiographically important PDA for the outcomes of PDA, abnormal ultrasound/death and CLD. PDA was the most commonly reported outcome in the direct meta-analysis between indomethacin and

placebo in our review, as one in every 3 treated preterm infants underwent primary PDA closure afar 1-2 doses of indomethacin, sample size calculations indicate that for 80% power only 21 preterm infants per intervention group are required to demonstrate a statistically significant difference in the incidence of PDA closure between intravenous indomethacin and placebo. According to the estimated incidence rates in our meta-analysis, both the INDUCE pilot and DETECT trials are sufficiently powered to detect a difference in PDA closure rates between intravenous indomethacin and placebo. On the other hand, from our analysis the outcome of IVH requires 3640 preterm infants to give 80% power to detect a difference in risk or benefit between indomethacin and placebo for PDA, and all CLD requires 6489 infants per group. Further to this, the data for all IVH included all grades, whereas severe grade IVH, a more reliable indicator of later neurological impairment. As severe grade IVH has lower incidence than when all grades of IVH are included, even larger sample sizes are likely to be required. Similarly the limited availability of data using the current definition for CLD of oxygen requirement at 36 weeks corrected age means that all definitions were included in the meta-analysis and larger sample sizes are also likely to be required for this outcome. It is possible that the separate hypotheses of INDUCE and DETECT regarding avoidance of treatment in the placebo arm and early treatment and specific echo-targeting at less than 24 hours postnatal age respectively, may lead to the demonstration of greater difference in incidence rates between indomethacin and placebo for the remaining outcomes of IVH, CLD and death in either trial. Whilst it is acknowledged that INDUCE is a pilot, meta-analysis of the evidence from existing randomised trials indicates that larger sample sizes are required to provide adequate power to demonstrate a risk/benefit on outcomes other than PDA closure for indomethacin compared with placebo in the treatment of echocardiographically and/or clinically important PDA.

Limitations of direct meta-analysis indomethacin vs. placebo and implications of differences in projected sample sizes for ibuprofen vs. placebo.
Sample sizes indicated in the analyses for the comparison intravenous indomethacin vs. placebo may be large as a result of between and within studies variations in baseline characteristics and the use of rescue treatment. Variation in parameters defining baseline morbidity such as echo criteria, gestational age at treatment, age at administration of randomized treatment and age at rescue treatment, in addition to having the capacity to affect the risk of short and long term outcomes, may have reduced the difference in treatment effect

between intravenous indomethacin and placebo. This is likely to cause bias in the measurement of any difference in outcomes between intravenous indomethacin and placebo for PDA closure in the direction of the null or no difference represented by a relative risk that is closer to 1. Larger predicted sample sizes for outcomes in the direct comparison indomethacin vs. placebo compared with those for ibuprofen vs. placebo may have resulted from greater variation in population characteristics and methods for identifying PDA in the studies comparing indomethacin with placebo. Although the outcome of PDA closure in the direct comparison between indomethacin and placebo with an I^2 of 66%, had the greatest level of heterogeneity in the analysis, PDA closure rates across all 3 comparisons; indomethacin vs. placebo and ibuprofen vs. indomethacin and the indirect comparison between ibuprofen vs. placebo were similar. In addition, the PDA closure incidence rates and NNT between indomethacin vs. placebo and ibuprofen vs. placebo were almost identical. Such consistency among PDA closure rates combined with lack of heterogeneity indicated by a tau of 0 following convergence of direct comparisons between intravenous indomethacin vs. placebo and intravenous ibuprofen vs. indomethacin during metaregression (refer meta-regression portions of STATA data output in Chapter 2:Appendices) may reflect the ability of the indirect comparison between intravenous ibuprofen and placebo to accurately predict the sample sizes required to demonstrate a statistically significant risk of harm or benefit for intravenous ibuprofen compared with placebo on the measured outcomes.

With the exception of PDA closure, sample size predictions for the indirect comparison between intravenous ibuprofen and placebo in the network meta-analysis in Chapter 2 (392) were lower than those predicted for the direct comparison between intravenous indomethacin and placebo. Both intravenous indomethacin and intravenous ibuprofen demonstrated equal effectiveness in PDA closure with 1 successful primary PDA closure for every 3 preterm infants treated. Referring again to table 2 in Chapter 2 (392), to obtain to detect such a difference in PDA closure between intravenous ibuprofen and placebo at 80% power, would require a sample size of 25 preterm infants per group. The outcome with the lowest predicted sample size to detect a difference between intravenous ibuprofen and placebo is all CLD, requiring 131 preterm infants per group. CLD is likely to develop in 1 in 7 infants receiving intravenous ibuprofen rather than placebo. Sample size calculations indicate that 1199 preterm infants would be required per treatment group to demonstrate a statistically significant benefit on NEC for ibuprofen with a number needed to treat (NNT) of 50 infants. The measured outcomes all IVH and death had the

smallest difference in incidence rates and therefore the largest predicted sample sizes, with a trend toward harm associated with exposure to intravenous ibuprofen rather than placebo. The tendency for greater differences in the risk or benefit of outcomes reflected in the higher incidence rates and smaller sample sizes for the indirect network meta-analysis intravenous ibuprofen vs. placebo compared with the direct meta-analysis intravenous indomethacin vs. placebo implies that despite initial PDA closure, intravenous ibuprofen has a markedly different risk-benefit profile to intravenous indomethacin. When compared indirectly with placebo, intravenous ibuprofen exhibited a similar risk-benefit profile for outcomes of PDA closure, NEC and CLD to the direct comparison between intravenous ibuprofen and intravenous indomethacin. This supports the consistency of the relationship between ibuprofen, indomethacin and placebo, and suggests there may be some difference in beneficial and adverse effects between intravenous indomethacin and intravenous ibuprofen.

Sample size recommendations for future trials.

In order to provide adequate power to demonstrate a statistically significant difference between treatments on the risk of outcomes other than PDA closure, much larger numbers of preterm infants need to be recruited. Increasing the study sample size is a well-known approach to improving the chance of detecting a difference in the risk of outcomes between two treatments should one exist (393). This chance is referred to as the power of the study to demonstrate such a difference (393). Power is algebraically represented by $(1-\beta)$, which is the probability of correctly deciding that the treatments are different (393). This is dependent on the risk of making a type II error (β) which is the chance of rejecting the alternative hypothesis that there is a difference in treatments when it is in fact true. Figure 4a) represents the normal distributions of the population of preterm infants with PDA, the left distribution represents the null hypothesis that there is no difference in risk of outcomes between treatments for PDA and the right distribution, the alternative hypothesis that such a difference exists. The risk of a type II error is represented by β and α represents the probability of rejecting the normal hypothesis (394).

Figure 4a) Relationship between Power and type II error

Adapted from Centre for Clincial Epidemiology and Biostatistics, University of Newcastle (394).

Comparing figures 4b) and 4c); the effect of small compared to larger sample sizes on the size of the sampling distribution curves for both null and alternate hypotheses can be easily seen. The type II error (β) in figure 4b) is large, taking up almost 50% of the distribution for the alternative hypothesis compared with diagram c) in which the type II error accounts for only 20%. As power = 1-β, studies with small sample sizes have approximately 50% power or chance of correctly detecting a difference in treatments compared to 80% for studies with large sample sizes.

4b) Effect of reduced sample size on power

Figure 4c) The effect of increased sample size on power

Considering the magnitude of the sample sizes predicted by the network analysis between intravenous indomethacin vs. placebo and intravenous ibuprofen vs. placebo required to demonstrate a statistically significant difference in the risk of CLD, IVH, NEC and death, a multi-centre trial is recommended. Depending on whether statistically significant differences or trends in the risk or benefit on outcomes exist between early indomethacin and placebo, study investigators conducting trials such DETECT and INDUCE may expand their trial to include other neonatal centres. The ability to add data from a larger multicentre trial to that collected from an initial trial depends upon the similarity between; population characteristics of preterm infants, and criteria used to define the disease in terms of echocardiographic criteria for the identification of PDA and outcome measurement in the original and subsequent trials. Preterm infants in the populations selected to take part in the multicentre trial should be of similar gestational age (<28 weeks) at birth, ethnicity, risk of IVH and using the same echo criteria and trial methodology. Management of preterm infants should also be similar between treatment centres. Data on outcomes from DETECT can be added to the new data in an expanded multicentre trial if the criteria for outcomes such as CLD and PDA closure remain unchanged. Data from the composite outcome of death and abnormal head ultrasound may not be suitable

for combination with new data on the outcomes of death, severe IVH, and/or PVL unless these outcomes are separately prospectively identified during the original DETECT study (395). INDUCE is subject to similar considerations to DETECT with regard to whether the data from its pilot trial can be expanded to become an internal part of a larger multicentre trial. Unlike DETECT, the pilot trial for INDUCE does not include composite outcomes and this makes data on the stated outcomes of IVH and death more suitable for combination with outcomes from the planned main multicentre trial. It would be possible to use the INDUCE pilot trial as an internal trial within the larger trial which is likely to reduce number of additional preterm infants required to fulfil the sample size as predicted by the pilot trial providing none of the parameters outlined in the previous paragraph vary. It can be argued that given such large predicted samples sizes for the comparison between intravenous indomethacin vs. placebo, perhaps the difference in the outcomes between treated and placebo groups is not clinically relevant and this is certainly reflected in the NNT/NNH in table 2 of the paper (refer Chapter 2). The limitations described previously must be considered when designing future trials comparing PDA management approaches in preterm infants.

Improving the precision of the effect estimate.

Investigation of heterogeneity in the network meta-analysis using sensitivity analyses indicates that primary PDA closure rates in preterm infants receiving indomethacin or placebo across all populations within the study may depend on similarity in gestational age at birth and postnatal age at treatment within and between each study. Whilst the examination of such heterogeneity may yield clinically meaningful data in the context of the influence of potential confounders, it acts to increase the complexity of analysis and reduce the precision of the effect estimates in relation to PDA treatment on the outcomes of CLD, IVH, NEC, and neurosensory impairment. This severely restricts the capacity of evidence from current randomised trials and meta-analyses to adequately direct current clinical practice. For instance, the ability of INDUCE to accurately determine baseline incidence rates between intravenous indomethacin and placebo in order to make sample size recommendations for a larger trial with respect to the outcomes of CLD, IVH, NEC, ROP may depend upon the diagnostic accuracy of echocardiographic targeting of "large PDA" as a guide for indomethacin treatment, the successful promotion of PDA closure in preterm infants at the chosen treatment age of 3 days of life and the existence of any non-duct-related adverse or beneficial effects of indomethacin specific to the age of administration. This may be further addressed by stating more specific diagnostic criteria for PA

and limiting randomised treatment to a specific, narrower postnatal age in a similar manner to the DETECT trial investigators who state specific criteria for PDA diagnosis including PDA diameter and shunt flow to treat preterm infants at a narrowly defined age of treatment at between 12 and 24 hours of life.

Improving the precision of the effect estimate or standard error by minimising variations in potential confounders such as gestational age, age at treatment and method of PDA detection is likely to reduce the risk of a type II error expressed as the likelihood of incorrectly rejecting the alternative hypothesis that there is a difference in risk or benefit for indomethacin or ibuprofen on major morbidity and mortality from PDA in preterm infants. As represented by figure 4c) in the preceding discussion on sample size, reducing type II error may increase the sample size and power of the preterm infant population in the sample without the need to recruit additional infants by reducing the overlap between null and alternate hypotheses. For this reason it is recommended that future randomised trials include preterm infants born at similar gestational ages and further limited to preterm infants commonly requiring treatment for PDA, i.e. < 28 weeks gestation and within a narrow age range i.e. 24-26 or 27-29 weeks rather than a wide range (24-36 weeks). Stratification into age groups is another approach; however this would reduce the power to return any statistically significant differences in treatment effects on outcomes and would necessitate a further increase in sample size (see previous section). Studies within meta-analyses should be combined according to the age at treatment, for instance; treatment at a narrower postnatal age range of 24 hours for early, 48 hours for moderately early. In addition there needs to be an agreement on standardised definitions of timing for treatment of PDA, i.e. early (less than 24 hours), moderately early (1-3 days), moderate (3-5 days), moderately late (5-7days) and late treatment (> 7 days). The use of more specific diagnostic criteria in combination with narrower gestational ages and age at treatment is likely to reduce variation in baseline risk between intervention groups at study entry leading to an increase in precision of the effect estimate and power to detect a difference in risk of outcomes. Whilst quantitative review meta-analyses of randomised trials such as those provided by Cochrane have considered the influence of dependent variables such as gestational age and route of administration, there is a need to further consider the effect of differences in these variables on outcome measurement, particularly with respect to age of treatment, by making a greater effort to investigate and report on subgroup or sensitivity analyses and the addition of a more deeply interpretative narrative review.

2.3 Use of composite outcomes in combination with rigorous survival analysis.

Composite outcomes increase the power of a study to demonstrate a statistically significant difference between outcomes by increasing the likely number of events contributed by each singular outcome to the composite (396). DETECT study investigators have included a composite outcome of death and abnormal head ultrasound instead of the usual outcome of severe IVH alone. Given that severe IVH is a major contributor to death in preterm infants and that the event rates for severe IVH are less frequent than those for the more generalised classification of "abnormal ultrasound" and death is a relatively infrequent outcome, the event rates for death and abnormal head ultrasound combined are likely to be greater than severe IVH or death alone. Consequently the required sample size to detect a difference in risk of the composite outcome death and abnormal ultrasound is likely to be lower than that for death and severe IVH as separate outcomes. On the other hand, as illustrated in Aranda's study (374), using a composite outcome makes it difficult to ascertain which outcome makes the greatest contribution to any statistically significant treatment effect which can limit the clinical relevance of such findings. The classification of "abnormal head ultrasound" also allows for the inclusion of other types of abnormalities than bleeds such as periventricular leukomalacia(396) which may be associated with PDA or treatment; however the inclusion of abnormalities less likely to be related to PDA may make it less specific to the effect of echo-targeted indomethacin treatment for large diameter PDA on severe IVH which formed part of Evans and Kluckow's original hypotheses. We already know from previous studies that preterm infants in the placebo group are likely to have a lower closure rate and require a higher rate of rescue therapy, however a study powered to a composite outcome will not have sufficient sample size to demonstrate a statistically significant difference for the less frequent outcomes of death or severe IVH.

Additional follow-up information on individual outcomes within the composite may provide an indication of the proportion of the result attributed to each outcome. Survivor bias occurs when death, study withdrawal and rescue rates are increased in one group in comparison to another prior to outcome measurement. To assist in the assessment of the potential effect of survivor bias on outcomes such as death and severe IVH, use of survival curves such as the Kaplan Meier survival curve used in Aranda's (374) comparison between intravenous ibuprofen and placebo, a commonly used method for presenting differential time-based information between

interventions on survival and other outcomes, are recommended. In addition to presenting these outcomes for each intervention group in a survival curve, the timing of events such as rescue, died or study withdrawals should be marked separately. Future studies should examine the number and timing of deaths, study withdrawals and receipt of rescue therapy for each intervention in relation to the measured outcomes.

2.4 Limiting the use of rescue treatment.

Limiting and/or establishing similar criteria for the use of rescue treatment administered to provide treatment to all infants failing to close a PDA may improve the ability of studies such as DETECT to demonstrate benefit or harm for PDA closure with intravenous indomethacin or intravenous ibuprofen on outcomes in comparison to placebo. Use of non-randomised rescue treatment for failure to close a PDA in a large proportion of preterm infants (greater than 20%) in the placebo group is likely to alter the comparative risk of study outcomes in preterm infants between the intravenous indomethacin and placebo groups established by initial randomisation. A randomised trial allowing unrestricted use of indomethacin as rescue treatment in the "placebo" arm is effectively comparing the effect of the same treatment administered at multiple time points. If treatment effect is dependent on postnatal age and treatment aimed at PDA closure within a randomised trial is given at different postnatal ages then the administration of rescue indomethacin is likely to reduce the difference in the risk or benefit of outcomes between preterm infants receiving intravenous indomethacin or placebo for PDA. The similarity of risk of outcomes between indomethacin and placebo groups increases in direct proportion with the number of infants in the placebo arm receiving rescue indomethacin or ibuprofen for PDA closure.

 If the age at which infants receive treatment for PDA closure has an effect on outcomes then the benefit or risk of treatment using indomethacin outcomes with longer assessment periods such as CLD administration of rescue treatment is more likely to distort having allowed a greater proportion of infants randomised to initial placebo have received intravenous indomethacin or ibuprofen treatment. The ability of the DETECT trial to demonstrate a difference in IVH (composite abnormal HUS/death) is dependent on the postnatal age at which the investigators intend to scan and provide rescue treatment. As most abnormal HUS events

occur in the first 24-72 hours, provision of rescue after this time would capture the majority of IVH episodes and early deaths theoretically associated with PDA. As a result, measurement of the outcome of CLD at 36 weeks corrected age in accordance with current diagnostic criteria is less likely to reflect a difference in benefit or harm of treatment with intravenous indomethacin on baseline risk. The criteria used to identify PDA across the study, i.e. for both randomised treatment and rescue, are also important factors in improving the likelihood of detecting a difference in risk/benefit of early indomethacin vs. placebo.

Reducing the differences in when, and to whom rescue the treatment is given to close a PDA across a randomised trial is likely to increase the chance of detecting any benefit or harm associated with intravenous indomethacin or ibuprofen treatment for PDA. Administration of study treatment in randomised trials of PDA management generally follows identification of PDA on initial study echo. However, the criteria for further treatment may vary from scheduled follow-up echo to investigation and administration of rescue treatment prompted by changes in clinical condition. This is not always clearly stated in the methods of published studies. Given that large diameter PDA may occur in the absence of any clinical signs and that the importance of this in terms of clinical outcomes has not been clearly demonstrated in large randomised trials, the comparative risk profile of asymptomatic and symptomatic infants remains unknown. For this reason, similar criteria for the use of rescue treatment such as failure to achieve primary PDA closure or development of symptomatic PDA should be used across intervention groups and specified in the trial protocol.

Avoiding the administration of rescue treatment within the placebo arm may reduce the sample size required to demonstrate risk or benefit of indomethacin for PDA on outcomes such as IVH and CLD, however a pilot study is required to provide an indication of the direction of the relative risk. This may favour indomethacin, the control group or continue to demonstrate no difference in outcomes. INDUCE investigators plan to avoid treatment of PDA with the aim of determining the baseline incidence rates of outcomes CLD, IVH, NEC, ROP and death. Close continuous monitoring of comparative adverse event profiles between intravenous indomethacin and the control with avoidance of treatment by an independent body is recommended as a safety precaution. This approach has inherent risks should better echocardiographic targeting of indomethacin therapy prove to be effective in reducing important outcomes and it can be argued that that the investigators await the results of DETECT before

proceeding further. It is likely however, that increasing the sample size to allow for the effect of rescue treatment on study outcomes will result in the exposure of a similar number of infants in the placebo group to the potential risk of later PDA closure as studies such as INDUCE which aim to limit or avoid rescue treatment using smaller sample sizes. Given that recruitment of a sample size of 300 infants for the DETECT trial is anticipated to take several years, the large sample sizes predicted for indomethacin vs. placebo in table 2 of the network meta-analysis in Chapter 2 (392) are not likely to be attainable even in a multi-centre trial.

2.5 Incorporate symptomatic and early targeted treatment for large diameter PDA at greater than 24 hours of life within large multicentre trials of early treatment at less than 24 hours of life.

Comparison between all three treatments: symptomatic at greater than 24 hours of life and early targeted at both less or greater than 24 hours of life is possible within the same multicentre trial. This would also address the issues surrounding the use and timing of rescue or back-up treatment within the placebo group as infants would be randomised to receive rescue treatment according to PDA identified by either echocardiographic or symptomatic treatment. Most importantly, within such a design, it would also be possible to follow-up outcomes in an untreated group of infants with asymptomatic PDA.

Postnatal age (hrs.)	Treatment (Ibuprofen or indomethacin)			Comparator (placebo with rescue)				
0-24	Early intravenous indomethacin			"Placebo"				
24 -36	Rescue [a]	No rescue [a]		Randomised to rescue indomethacin or ibuprofen using **echocardiographic criteria only**		Randomised to rescue indomethacin or ibuprofen using **symptomatic criteria confirmed on echo**		
36 -72		Rescue [a]	No rescue [a]	"rescue" [a]	No rescue required[a]	"rescue" [b]	No rescue required[b]	
72-168			Rescue [a]	No rescue required [a]		Rescue	No rescue required[a]	Rescue	No rescue required[b]

[a] randomised to rescue based on echo criteria
[b] randomised to rescue based on symptomatic criteria

Table 3. Design for randomised trial of early indomethacin vs. placebo @ <24 hours incorporating randomisation of rescue treatment to either early targeted or symptomatic treatments of PDA in preterm infants.

Examining table 4 above, preterm infants within the trial are randomised into two main groups; early targeted indomethacin or ibuprofen administered at less than 24 hours of life and placebo for at least the first 24 hours of life. The placebo group is further randomised into two groups; early targeted "rescue" and symptomatic "rescue". Early targeted "rescue" treatment is based on study echocardiograms performed on all infants at regular intervals within the first 24 hours then daily, ideally for at least the first 7-14 days. Symptomatic "rescue" treatment is based on clinical signs of PDA plus cardiorespiratory condition. Outcomes are also followed for infants within the early targeted and symptomatic "rescue" groups that do not meet the criteria for rescue. The preterm infants within the symptomatic "rescue" group not meeting criteria for symptomatic treatment are of particular interest. A proportion of such infants may have large diameter asymptomatic PDA and this will be detected on routine study echocardiogram. The effect of untreated asymptomatic PDA on IVH, CLD, NEC and mortality has not been examined in a large randomised trial. In addition, such a trial design would compare the three most commonly utilised treatments for PDA in a way that also serves to minimise the effect of rescue treatment on risk of outcomes whilst allowing measurement of the effect of the administration of treatment at different postnatal ages. A limitation of such a design is the need to recruit a larger sample size depending upon the intended period of treatment follow-up. The original sample size of 300 infants for DETECT would require the recruitment of approximately 450 - 750 additional infants to the placebo group bringing the total trial sample size to 600-900 infants.

2.6 Incorporate methods for investigation of pulmonary mechanisms within larger randomised trials.

Current evidence of the comparative effect of intravenous ibuprofen and intravenous indomethacin on pulmonary function in preterm newborns offers insufficient explanation for an increased risk of CLD for intravenous ibuprofen in comparsion to placebo or intravenous indomethacin. Apart from case reports of pulmonary hypertension and bleeding associated with intravenous ibuprofen administration previously mentioned in the literature review, investigation of the direct pulmonary effects of intravenous ibuprofen and intravenous indomethacin remain largely experimental. A small randomised trial of < 30 preterm infants by Yaseen (397) suggests an association between indomethacin prophylaxis and increased oxygen requirement, which is supported by Schmidt's findings from retrospective investigation of data from the

multi-centre TIPP trial described in Section 4 of the Literature Review. A randomised study of early vs. late indomethacin treatment by Van Overmeire (116) also associated increased need for oxygen in preterm infants with PDA randomised to receive indomethacin on day 3 vs. Day 7 of life. In favour of treatment to close the duct, McCurnin (370) found that both intravenous indomethacin and intravenous ibuprofen improved compliance and ventilation index, reduced total lung water and slowed the restriction of alveolar growth in preterm baboons with PDA. McCurnin (370) found that the expression of a subunit of epithelial sodium channel protein (α Enact), thought to be an important factor in the clearance of alveolar fluid after birth, was greater in the lung tissue of ibuprofen treated subjects, which he proposes may suggest a localised effect for ibuprofen on the water content in the lung interstitium. McCurnin's (370) study was limited by a maximum follow-up period of 14 days, which did not allow for the examination of any longer term outcomes such as CLD.

Previous studies have associated changes in the concentration of various pulmonary substances with the use of cyclooxygenase inhibitors for PDA in preterm infants and the development of RDS. Gerdes (398) reported their concerns regarding the potential for indomethacin to increase fibronectin concentration and elastase activity which may worsen pulmonary inflammation and fibrosis for inhibition of bacteria. Lassus (399) identified higher pulmonary concentrations of the vasodilatory prostacyclin metabolite 6-keto-prostaglandinF1alpha in preterm infants with lower levels of respiratory distress and/or of increasing gestational age. Interestingly Lassus (399) also found that indomethacin administered to close a PDA reduced pulmonary PGI_2 levels in the tracheal aspirate of treated preterm infants, which have been found in experimental studies to protect lung tissue against hyperoxic lung injury. This may provide a physiological explanation for the failure of PDA closure to improve respiratory outcomes in preterm infants with respiratory distress.

Studies to date have been largely confined to animal subjects, the few performed in preterm infants small and inadequately powered to detect medium term outcomes such as CLD. PDA targeting has been variable, and although methods of detection have been detailed, no diagnostic criteria for haemodynamically significant PDA were specified. Adequately sized randomised studies examining the potential direct pulmonary effects of indomethacin and ibuprofen administered to close a haemodynamically significant PDA on existing pulmonary

mechanisms in preterm infants are required. Such studies could combine an examination of biochemical changes in ENAC expression, lung water content and alveolar development in addition to surfactant proteins, messenger RNA and cytokine concentrations in the context of the preterm infant with the medium term outcome of CLD and specify longer term neurodevelopmental and respiratory follow-up. It is important that future studies examine the relationship between the haemodynamic significance of PDA according to set criteria (including diameter and age at treatment), and any differences in interactions with pulmonary mechanisms or outcomes between ibuprofen and indomethacin. As many studies neglect to establish a baseline pulmonary biochemical profile it may be useful to study biochemical changes in an untreated control group of preterm infants without HsPDA in addition to the randomised study groups to serve as a reference group.

2.7 Network meta-analysis

Recommendations for the future use of network meta-analysis in summarising evidence from neonatal populations include: 1) expansion of network meta-analysis to include other interventions for PDA related outcomes; 2) provide direction for the investigation of comparative effectiveness of interventions on disease-related outcomes for future randomised trials; 3) incorporation of improved methodological approaches in planning future network meta-analyses.

A complex network of randomised trials of pharmacological, surgical and medical approaches to PDA management incorporating different agents, routes, timing and methods of administration exists for which network meta-analysis would be ideally suited as a method for further investigation of the relative effectiveness of multiple treatments for PDA in preterm infants. In addition to comparing 2 or more treatments, network meta-analysis has the capacity to aid clinical decision making by providing one consistent evidence-based summary of all available treatment comparisons. According to Sutton (290), the validity of this evidence depends on the existence of a connected network with a chain of paired comparisons connecting with other treatments. There are multiple treatment trials concerning PDA management including ligation, and different pharmacological approaches such as; timing, dose, and administration of indomethacin and ibuprofen. For example there is limited evidence from randomised trials comparing conservative treatment with ligation for PDA to provide

direction on the benefit of ligation compared to placebo or no treatment; however, there are a number of trials comparing treatment with indomethacin with ligation. Sutton (290) theorises that expansion of networks may reduce uncertainty due to the increased ability to check consistency between closed loops and increase precision of the effect estimate. This has its own problems with distant extensions more likely to introduce inconsistencies and selectivity of reporting, and the introduction of bias from the inclusion of older studies, such as those examined in this analysis, carried out in different clinical and methodological conditions. There is a need to consider the relative merits of restricted inclusion criteria for preterm populations within the analysis vs. obtaining the biggest possible network for comparison. Criteria for defining PDA, gestational age, and postnatal age at treatment may affect the rate of PDA closure and risk of CLD and these should be considered when planning future MTC and randomised trials.

Figure 5. Expanded network: randomised trials of PDA management

The model depicted in figure 5 above shows the existing trials available concerning treatment of echocardiographically and/or clinically important PDA in preterm infants at any postnatal age for all outcomes. It is apparent from this model that there are randomised trials apart from those compared in this network meta-analysis between intravenous indomethacin and ibuprofen examining a number of management approaches for PDA including surgical ligation, timing, and route of administration of indomethacin and ibuprofen.

In each section of the model where there are two trial arms sharing a common comparator (and more than one trial available for each trial arm), there is potential to compare the three treatments within each section using indirect comparisons. As explained in the Research Proposal, methods for performing indirect comparisons, direct randomised trials forming a closed loop in the model can be compared with indirect comparisons to test the coherence of the effect size between each pair of trial arms within each section of the model.

Network meta-analysis methods can be used to provide direction for further randomised trials of PDA management. This can be in the form of generating a network from which inference regarding the existence and extent of enquiry in regard to PDA management is drawn from assembling models of the network as described above or further extended to analyse the comparative effectiveness between interventions within the network. Examining models of expanded network meta-analysis in the previous paragraphs, it can be easily seen that there are limited connections between the rest of the interventions in the model and randomised trials comparing the benefit of pharmacological management (indomethacin/ibuprofen), fluid restriction and ligation on echocardiographically and clinically important PDA in preterm infants at greater than 24 hours of age. Whilst the model demonstrates some networks with common comparators for the indirect comparison of treatments such as surgical ligation vs. indomethacin treatment by Gersony (192) surgical ligation vs. fluid restriction and/or digoxin by Cotton (100) conservative medical management vs. intravenous indomethacin by Merritt (191) for echocardiographically and/or clinically important PDA at greater than 24 hours of age, there are currently only 1 or 2 randomised trials for each comparator arm of the analysis. The trial by Cotton is small making its inclusion in the network unlikely to yield sufficient data on comparative effect between surgical, medical and pharmacological treatments. Examination of the network also highlights the lack of trials reporting on outcomes other than PDA closure. When only those trials reporting on the outcomes of CLD and NEC are included

(models 2 and 3) the number of trials available for analysis becomes even more limited. This is an example of how building models of interventions using the network meta-analysis method can provide an indication of an area of enquiry where there is little evidence from randomised trials to recommend commonly used treatments such as fluid restriction and surgical ligation. Examination of the existing network of randomised trials indicates a need for further investigation randomised trials of the comparative benefit of oral with IV ibuprofen, surgical ligation and fluid restriction on PDA-related outcomes. Considering the recommendations of the SIBEN conference to treat preterm infants at 2- 5 days of life, the increasing use of oral ibuprofen and recent recommendations of Cochrane that ibuprofen may be more beneficial with respect to reduced rates of NEC in the absence of evidence from current randomised trials and meta-analyses of benefit of any treatment on major respiratory and neurological outcomes

Planning of future network meta-analyses should take into account the methodological considerations informed by recent enquiry outlined in section 1 of this Chapter. According to Song (400), the strength of network meta-analysis relies upon the basic assumption that the population characteristics between trial arms within each meta-analysis are homogeneous. Variation in these characteristics may lead to a distortion of the effect size of the treatment on the disease-related outcome. Before proceeding to combine trials in an indirect meta-analysis Song (386) and Sutton (290) recommend examination for potential differences using subgroup analyses and meta-regression of variables likely to cause confounding or distortion of the effect size using direct meta-analyses. Additional covariates identified in sensitivity analyses of the direct meta-analysis indomethacin vs. placebo as possible components to heterogeneity in PDA closure rates such as gestational age, age at treatment and method of identifying PDA can be included in the model. Song's (400) observation that this approach is open to bias due to problems with sub-group definition is supported by difficulties encountered during attempts to define birthweight and gestational age subgroups for the network meta-analysis ibuprofen vs. indomethacin vs. placebo. Although investigation of the effect of inclusion of birthweight and gestational age as study level variables within the analysis were attempted, data on these covariates were incomplete or inaccurately specified, with insufficient power due to low numbers of lower birthweight or gestational age preterm infants resulting in wide variation in the effect estimates for the many of the subgroup analyses. In addition, data from trials of PDA management regarding criteria such as echocardiographic

vs. clinical identification and timing of treatment for PDA were inadequate to inform subgroup analyses. Larger sample sizes, with adequate information on the covariates birthweight, gestational age, age at treatment and method of identifying PDA, are required to allow for the valid use of subgroups in examining and reducing heterogeneity in PDA closure between future trials comparing intravenous indomethacin with placebo for treatment of echocardiographically and/or clinically important PDA in preterm infants at greater than 24 hours of life.

Conclusion

Patent ductus arteriosus is commonly found in preterm infants and is thought to arise from a multiple of factors interfering with normal functional closure including hypoxia, vascular immaturity and failure of down-regulation of prostaglandins release during the transitional period. PDA is thought to affect cerebral, mesenteric and renal blood flow in addition to causing pulmonary engorgement and low systemic perfusion. The theoretical consequences for the preterm infant include exacerbation of respiratory distress with increased oxygen requirement and prolonged ventilation, cardiac failure, gastrointestinal ischaemia, intracranial bleeds and greater risk of death. Associations were made between increased risk of some of these outcomes and PDA in early observational studies, however the association between PDA and RDS suggested by their coexistence in acutely ill neonates makes it difficult to assess the precise nature of their interaction in altering the risk of outcomes such as IVH, CLD and death. Whilst is likely that PDA increases the risk of RDS, RDS also predisposes to PDA and as this interaction will confound or alter the risk of outcomes, these cannot be accurately determined from an observational study design. Although initial small randomised trials indicated a reduction in time on ventilation and oxygen requirement in preterm infants with PDA treated with indomethacin and/or surgery, later randomised trials examined the effectiveness of PDA closure using different indomethacin regimes on outcomes rather than comparing PDA treatment to spontaneous closure without treatment.

Management approaches to close the PDA including surgical ligation and COX inhibitors; intravenous indomethacin and intravenous ibuprofen, have been associated with detrimental effects on neurological, cardiorespiratory, gastrointestinal and renal function. Indomethacin has been associated with adverse effects on oxygenation and renal function in the first week of life and ibuprofen has been implicated in rare cases of pulmonary hypertension. Dosing

required for ductal constriction with indomethacin is ten times that required to produce pulmonary vasoconstriction which has potential implications for adverse pulmonary effects. Experimental evidence of the pulmonary effects of indomethacin and ibuprofen is conflicting, with some supporting a reduction in lung fluid and improved alveolar growth and others indicating the presence of precursors to lung injury in treated subjects for both medications. This has not been extensively investigated in preterm infants and there is scope for the inclusion of pulmonary measurements as part of randomised trials.

There is a coherent theoretical explanation for the potential effect of early indomethacin administration for large diameter PDA closure on IVH prevention, particularly as there is an indication that indomethacin administration in the absence of echo guidance may be responsible for increased oxygen requirement and risk of CLD. However, both benefit and risk are yet to be tested in a randomised trial. The same cannot be said for ibuprofen as it has not been demonstrated to reduce cerebral fluctuations associated with PDA and meta-analyses of randomised trials do not indicate a protective effect toward IVH with ibuprofen administration at < 24 hours of life. In spite of this, ibuprofen has not been as extensively studied as indomethacin.

This systematic review and network meta-analysis aimed to examine the baseline risk of IVH, CLD, NEC, death and neurodevelopmental deficits between randomised trials of intravenous ibuprofen and intravenous indomethacin compared separately with placebo and make sample size recommendations for future placebo-controlled trials. There was no difference in the risk of IVH, or death for either indomethacin or ibuprofen compared to placebo. Trends toward increased risk of CLD and decreased risk of NEC were associated with ibuprofen compared with placebo; however these were not statistically significant. Neurodevelopmental outcomes were reported in two older trials comparing indomethacin with placebo using different measurement methods. Trials were generally of poor quality, particularly lack of adequate blinding of intervention in some trials and those using symptomatic criteria to identify PDA were older than those using echocardiographic criteria at >24 hours of life. Criteria used to define PDA, IVH and CLD varied among trials and older gestational age preterm infants were included. Rescue treatment was administered to a large proportion of infants within the placebo group of the majority of trials and this is a major stumbling block in the design of these trials. Whilst it is possible that the use of indomethacin or ibuprofen for PDA closure in preterm infants has no net beneficial or harmful effect on the risk of IVH, CLD, NEC and

death, it is likely that these limitations have affected the ability of the trials included in this meta-analysis to demonstrate a benefit or risk for PDA closure using either indomethacin or ibuprofen. Similarly, although the large sample sizes required to provide adequate power to detect such a difference for indomethacin vs. ibuprofen, indomethacin vs. placebo and ibuprofen vs. placebo seen in this analysis may be a reflection of low clinical usefulness for these treatments in mediating PDA closure in preterm infants, it is also possible that the considerable limitations of the included trials have created a null bias which has given the appearance of less difference in risk or benefit of treatment on major outcomes. As this bias has potential to favour treatment or placebo, the true risk of outcomes may demonstrate either benefit or harm for indomethacin or ibuprofen in comparison to placebo.

Randomised trials and meta-analyses have failed to demonstrate a benefit for either indomethacin or ibuprofen administered for PDA at any postnatal age or according to any specific diagnostic criteria (echocardiographic, clinical or combination) on the risk of IVH, CLD death or longer term neurodevelopmental outcomes. This is more than likely due to the use of rescue therapy in the placebo group of almost every trial. It remains possible that there is a small therapeutic window for successful protection against IVH by indomethacin. This is likely to be dependent upon factors such as gestational age and post-natal age at treatment and may have simultaneous direct cerebral and duct-related effects. Despite the theoretical advantages of early treatment with indomethacin for echo-targeted PDA on IVH prevention highlighted in the work of Evans and Kluckow, it remains unknown whether this influences the risk of major outcomes in comparison to echo targeting PDA at > 24 hours of life or when symptoms occur. Although the early echo-targeted approach at < 24 hours of life is being considered for use in major centres, it is clear from surveys of neonatal units in the US, Australia, Europe and South America that many neonatal units without 24 access to echocardiography screening continue to treat echo-targeted and/or clinically important PDA at >24 hours of life using indomethacin or ibuprofen. In addition 20% of neonatal units in the Spanish survey treat infants according to clinical criteria without echo confirmation which has the capacity to expose preterm infants with spontaneous ductal closure to greater risk of CLD. Although there is now a consensus among South American countries to target PDA at 2-5 days of life, there remains no evidence from randomised trials of indomethacin or ibuprofen on risk of IVH, CLD, death or neurodevelopmental outcomes from any approach past or presents to support this decision.

Improved respiratory management of preterm infants including the advent of surfactant, antenatal steroids, gentler ventilation techniques including nasal prong CPAP have contributed to a milder form of CLD. It is possible that these techniques in combination with other approaches including fluid restriction, which may yet be an effective adjunct to PDA management, can be used to reduce the need for PDA treatment with COX inhibitors with late ligation reserved for persistent PDA. Considering that ligation following multiple courses of COX inhibitors has been shown to increase mortality, it may be preferable to avoid COX inhibitor use altogether and use late ligation.

The ability of the current DETECT trial of echo-targeted treatment of PDA at < 24 hours of life to demonstrate a difference in the risk of IVH, NEC , CLD and death is likely to be greatly diminished by the need to administer rescue therapy to preterm infants in the placebo group with failure to close a PDA. Earlier measurement of composite abnormal HUS and death prior to use of rescue therapy may allow a difference in risk to be detected, however the likelihood of detecting a difference in risk between early treatment and placebo for later outcomes such as CLD and late mortality is likely to be obscured by the administration of rescue treatment to progressively greater proportions of the placebo group. Randomised trials which have the capacity to demonstrate a clinically relevant difference in the risk of outcomes between indomethacin and ibuprofen compared separately with placebo in the context of modern neonatal care are needed. There are several conventional approaches to this; 1) increase the sample size, 2) comparison of indomethacin or ibuprofen treatment with avoidance of rescue treatment in the placebo group, 3) use of composite outcomes with survival analysis. The sample sizes required may be beyond those achievable even in a multicentre trial whilst a study such as INDUCE comparing treatment with avoidance of treatment could expose the preterm infant subjects to potential harm and may be difficult to recruit to in terms of obtaining parental consent. Composite outcomes may be useful in determining whether there is any benefit associated with treatment, however it may be difficult to ascertain which outcome within the composite is the main contributor.

Another, less conventional approach involves comparing all three approaches; early targeted at <24 hours, early targeted at > 24 hours and symptomatic with echocardiographic confirmation in a single randomised trial. This design allocates to two main treatment groups; early targeted at <24 hours and placebo, in the same manner as that planned for DETECT, however the influence of non-randomised rescue treatment in reducing treatment effect is

taken into consideration by randomising rescue treatment within the placebo group at study entry to either early targeted at > 24 hours or symptomatic with echocardiographic confirmation. This design also allows for comparison of outcomes between infants with silent PDA allocated to symptomatic treatment as rescue and infants treated with rescue indomethacin at > 24 hours of life or indomethacin at < 24 hours of life which has not thus far been prospectively examined in a randomised trial. Sample sizes within the placebo group would also need to be increased three to four fold to provide adequate power to compare outcomes between those infants receiving or not requiring rescue treatment for each approach. The capacity of such a design to demonstrate a difference in risk between treatment approaches, however, relies on whether treating PDA at a particular age, using echocardiographic or clinical criteria modifies this risk.

Examination of the existing network of randomised trials of indomethacin, ibuprofen, surgical ligation and conservative management indicates the usefulness of network meta-analysis in highlighting areas of need for further trials linking conservative management with indomethacin or ibuprofen and surgical treatment. Investigations have mainly centred on PDA prophylaxis and comparisons between indomethacin and ibuprofen at varying postnatal ages. In order to demonstrate any existing treatment effect for indomethacin or ibuprofen on the risk of IVH, CLD, NEC, death and neurological outcomes, in addition to treating large diameter PDA, it is also necessary to treat preterm infants at similar postnatal ages and unless extremely large sample sizes are recruited this cannot be achieved with conventional randomised trial design that incorporates non-randomised rescue treatment.

If the difference in incidence of outcomes between intravenous indomethacin and intravenous ibuprofen indicated by the sample size calculations in this review are truly so small this calls into the question the clinical use of these interventions. From this network meta-analysis, a randomised trial comparing intravenous ibuprofen with placebo is likely to require smaller sample sizes and may present a more realistic sample size to recruit to, however if the effectiveness of ibuprofen on outcomes is truly similar to indomethacin then the clinical usefulness of this newer, more expensive formulation is also subject to doubt. Should future large multicentre trials return similar null results for indomethacin or ibuprofen treatment of PDA in preterm infants, it can be argued that these treatments may have low clinical utility for reducing the risk of IVH, CLD, NEC, neurodevelopmental deficits and mortality when used in

addition to modern neonatal management and may have harmful effects on respiratory

outcomes if used in the absence of echocardiographic confirmation of PDA status.

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