

CeRebrUm and Cardiac Protection with ALlopurinol in Neonates with Critical Congenital Heart Disease requiring Cardiac Surgery with Cardiopulmonary Bypass



CRUCIAL TRIAL

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Pediatric Cardiology, -Intensive Care, Neonatology

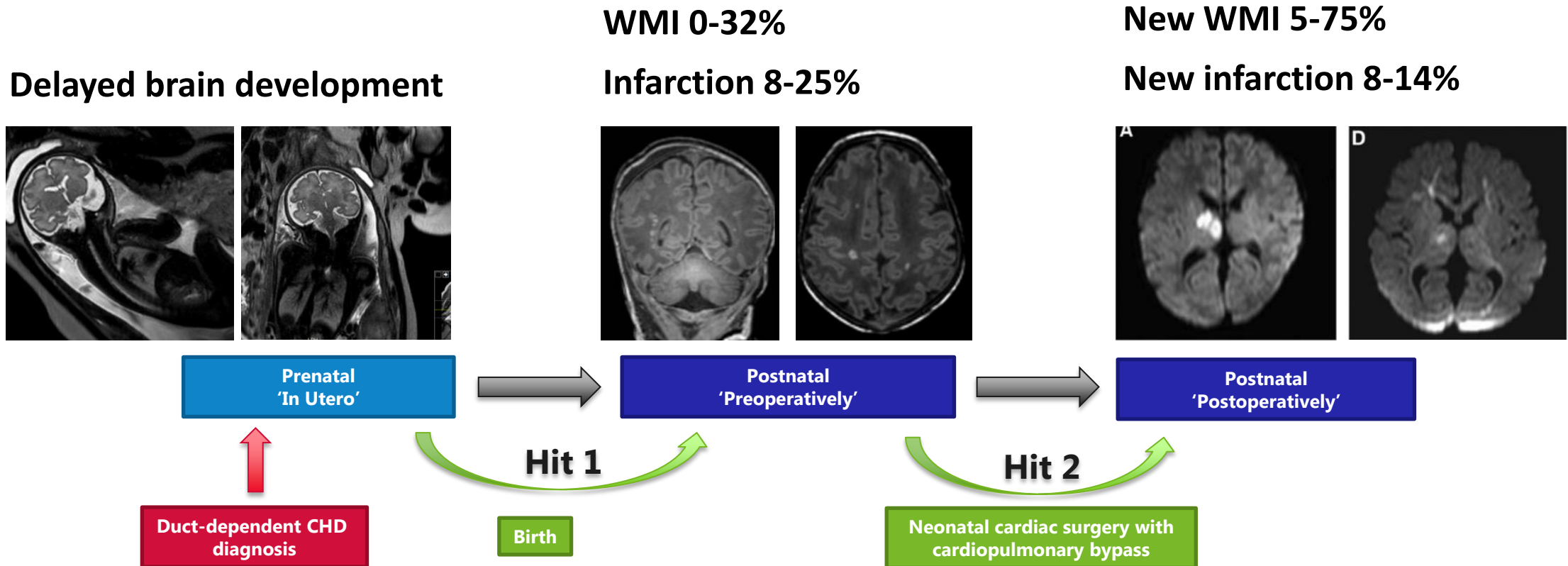


Critical Congenital Heart Disease (CHD)

- Incidence 6/1000 live births
- Survival \geq 90%
- Delayed brain development
- Brain injury
- Longterm neurodevelopmental impairments
- Neuroprotective interventions needed!



Brain Development/Injury



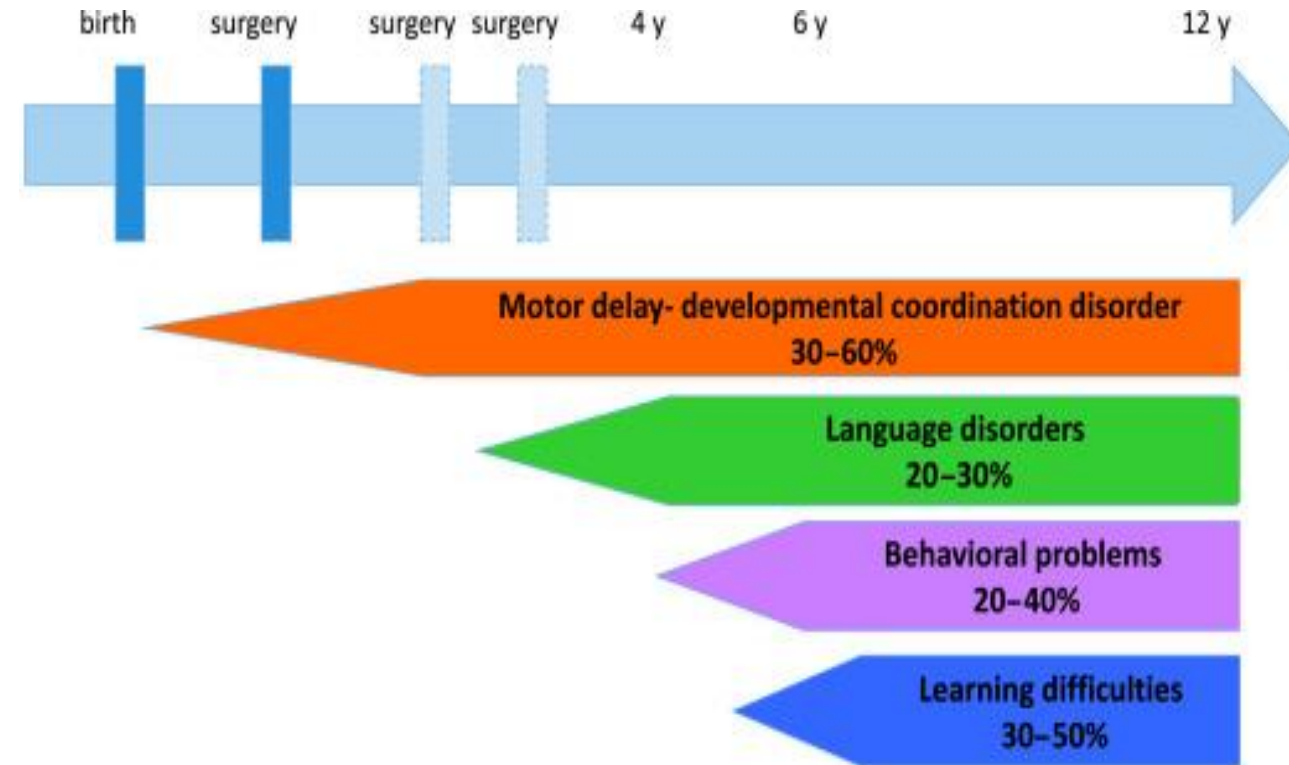
Sun L, et al. *Circulation* 2015

Claessens NHP, et al. *Dev Med Child Neurol* 2017

Algra SO, et al. *Circulation* 2014

Neurodevelopmental Impairments

- BSID-II at 1 year (normal value 100):
 - Motor 78.1 (-1.5 SD)
 - Cognitive 90.3 (-0.7 SD)
- White matter injury:
 - Cognitive 2 year: -11
 - Full scale IQ 6 year: -14
 - Attention problems 6 year: +6
- Involvement posterior limb internal capsule:
 - Motor problems



Snookes SH, et al. Pediatrics 2010

Claessens NHP, et al. Dev Med Child Neurol 2018

Latal B. Perinatol 2016



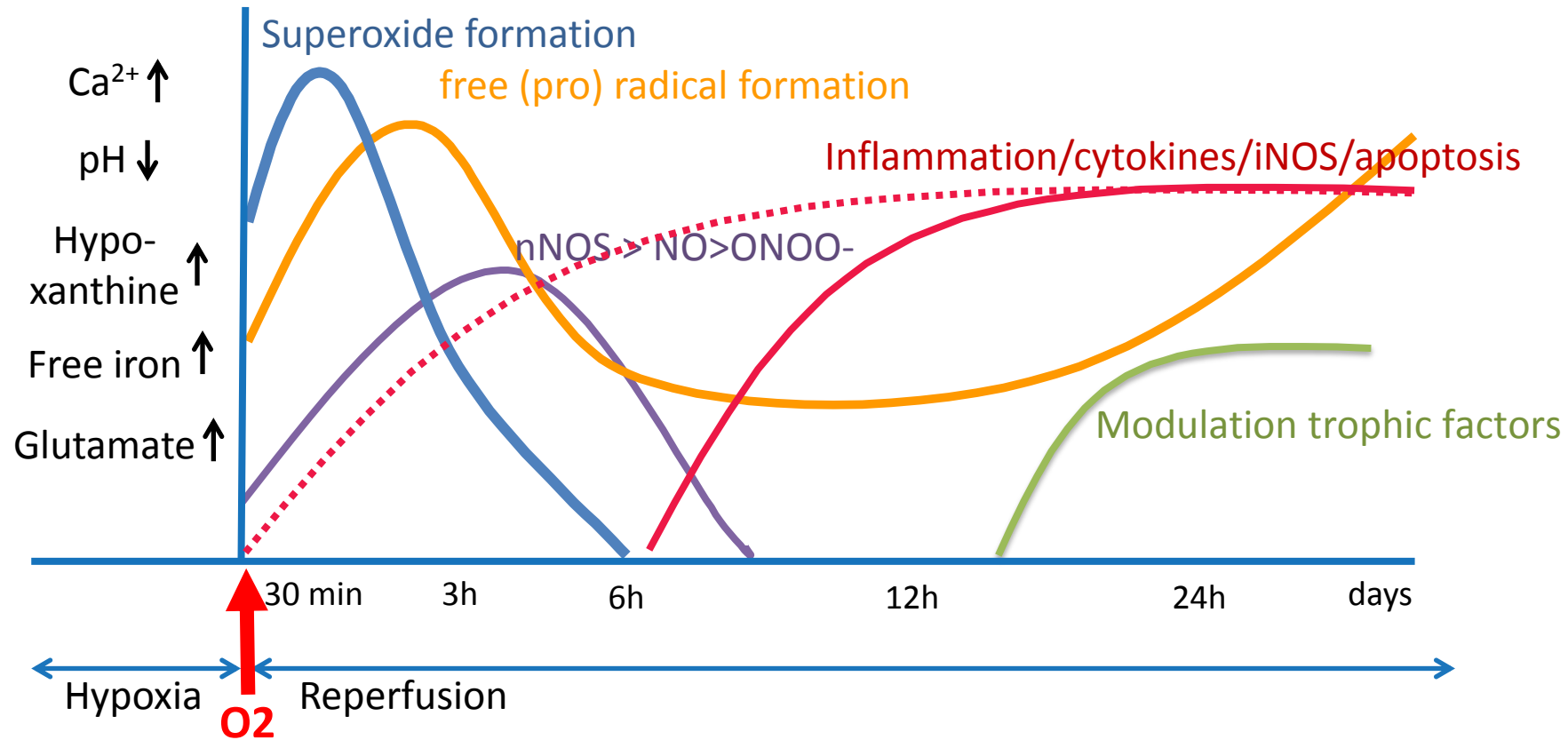
CRUCIAL TRIAL

Neuroprotective Strategies during Cardiac Surgery

- Avoidance of extreme hemodilution during CPB (hematocrit level $\geq 24\%$)
Wypij D, et al. J Thorac Cardiovasc Surg 2009, Jonas RA, et al. J Thorac Cardiovasc Surg 2003
- Deep hypothermia during low-flow CPB
Kern FH, et al. Ann Thorac Surg 1993
- Avoiding hypoglycemia perioperatively
Feranti S, et al. Anesthesiology 2004
- No difference 'deep hypothermic circulatory arrest' and 'antegrade cerebral perfusion'
Algra SO, et al. Circulation 2014

Hirsch J, et al. Ann Thorac Surg 2012

Cascade to Hypoxic-Ischemic Brain Injury

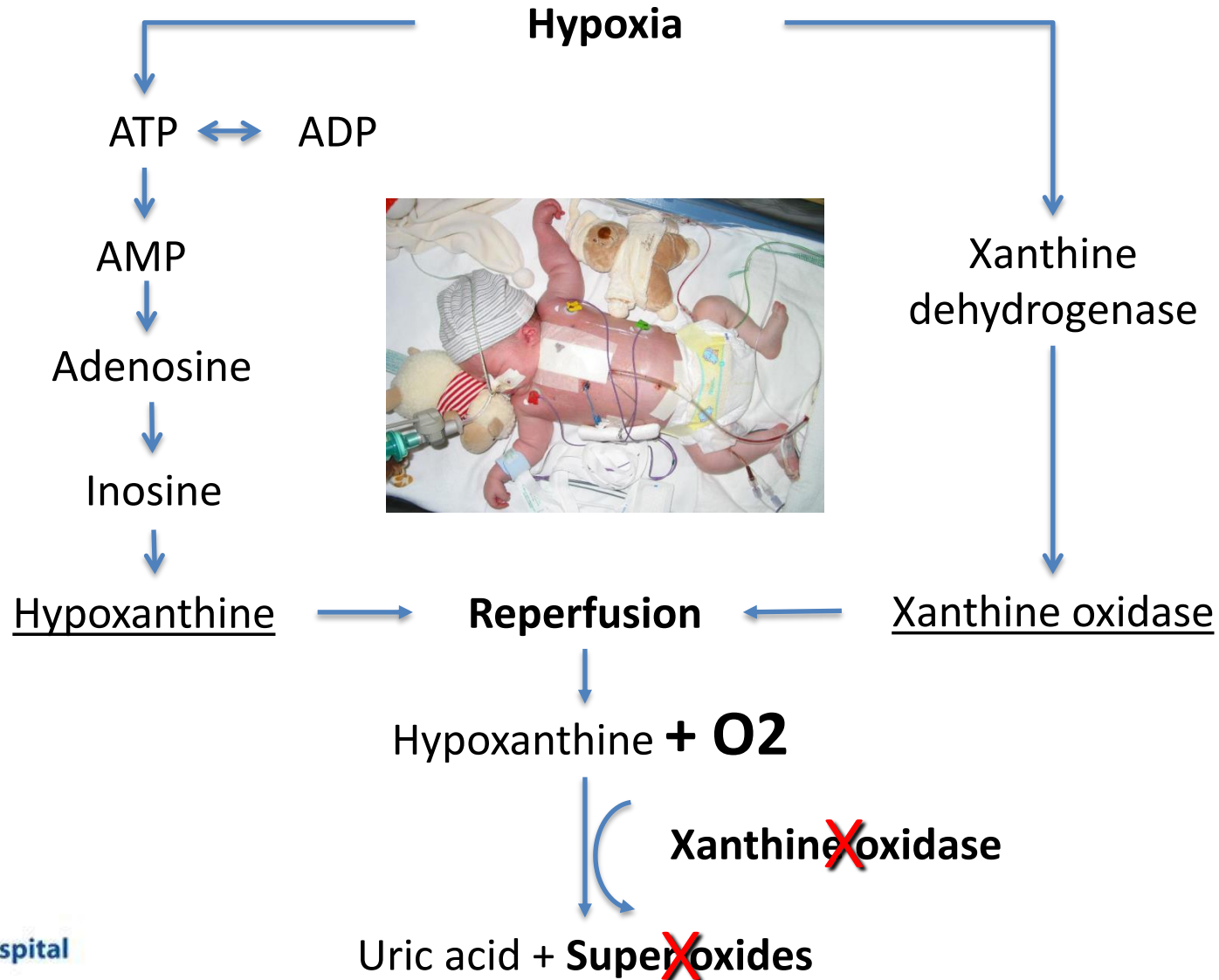


1. Early postnatal phase
2. Perioperative period

Potential Neuroprotective Drugs?

- Current neuroprotective evidence not sufficient for clinical recommendation
 - **Allopurinol**: high quality, neuroprotective effects
 - **Erythropoietin**: high quality, no neuroprotective effects
 - **Sodium nitroprusside, ketamine, dextrometorphan**: low/moderate quality, neuroprotective effects
- Not recommended
 - **Phentolamine** (low quality, neurotoxic effects)
- Larger well-designed trials needed
 - Allopurinol most promising
 - Focusing on both perinatal and perioperative phase
 - Including pre- and postoperative MRI, longterm neurodevelopmental outcome

Allopurinol, Mechanism of Action



Allopurinol, Mechanisms of Action

1. Preventing formation free radicals by **xanthine oxidase inhibition**

- Brain after asphyxia (*Van Bel. Pediatrics 1998, Boda. J Perinat 2011; Ono. Brain Res 2009*)
- Cardiovascular (*McGauran. Pediatrics 1994; Derks. Pediatr Res 2010; Allison. FASEB J 2016; Talwar. J Thorac Cardiovasc Surg 2018*)
- Hypoxic ECMO neonates (*Marro. Pediatr Res 1997*)

2. Scavenger of free radicals

3. Proradical chelator

(*Dirnagel. J Cereb Blood Flow Metabol 1995; Shadid, Neurosci Lett 1998, van Bel. Pediatrics 1998*)

4. Preserves energy metabolism (*Marro. Brain Res 2006*)

5. Anti-inflammatory (*Talwar. J Thorac Cardiovasc Surg 2018*)

Clinical Evidence

- Reduction neuronal damage in neonates suspected of fetal hypoxia

(Torrance. Pediatrics 2009; Kaandorp. Arch Dis Child Fetal Neonatal Ed 2015)

- Improved neurological outcome 12 months in asphyxiated neonates

(Gunes. Pediatr Neurol 2007)

- Beneficial effect on longterm severe adverse outcome in moderate asphyxia

(van Bel. Pediatrics 1998; Benders. Arch Dis Child Fetal Neonatal Ed 2006; Kaandorp. Arch Disc Child Fetal Neonatal Ed 2012)

- Safe, larger studies needed

(Chaudhari. Cochrane Database Syst Rev 2012)

- Neuro- and cardioprotective effects in hypoplastic left heart syndrome infants

(Clancy. Pediatrics 2001)

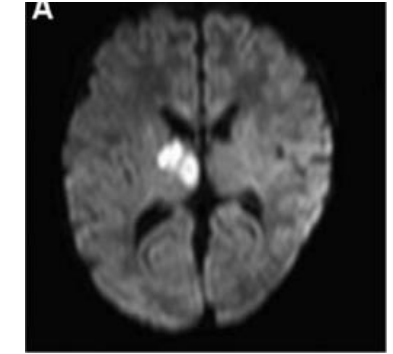
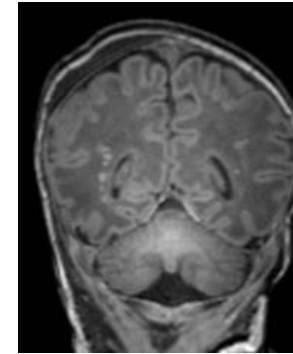
- Reduced inotropics, shorter duration mechanical ventilation, IC and hospital stay

(Talwar. J Thorac Cardiovasc Surg 2018)

Objectives

Primary

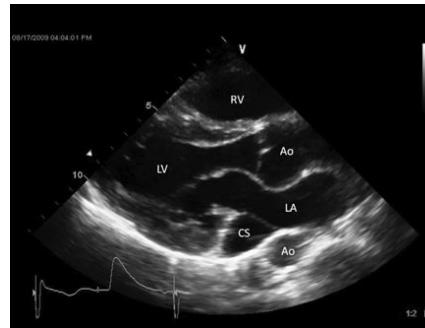
- Reduction of relevant parenchymatous brain injury



Secondary

Improvement of

- Cardiac function
- Brain function and oxygenation
- Neurodevelopmental outcome



Design/population

- Phase III, randomized, double-blinded, placebo-controlled, Dutch multicenter trial
- All 4 Dutch Pediatric Cardiothoracic Surgery Centers
 - 170 per year
 - Prenatal diagnosis 80%, postnatal 20%



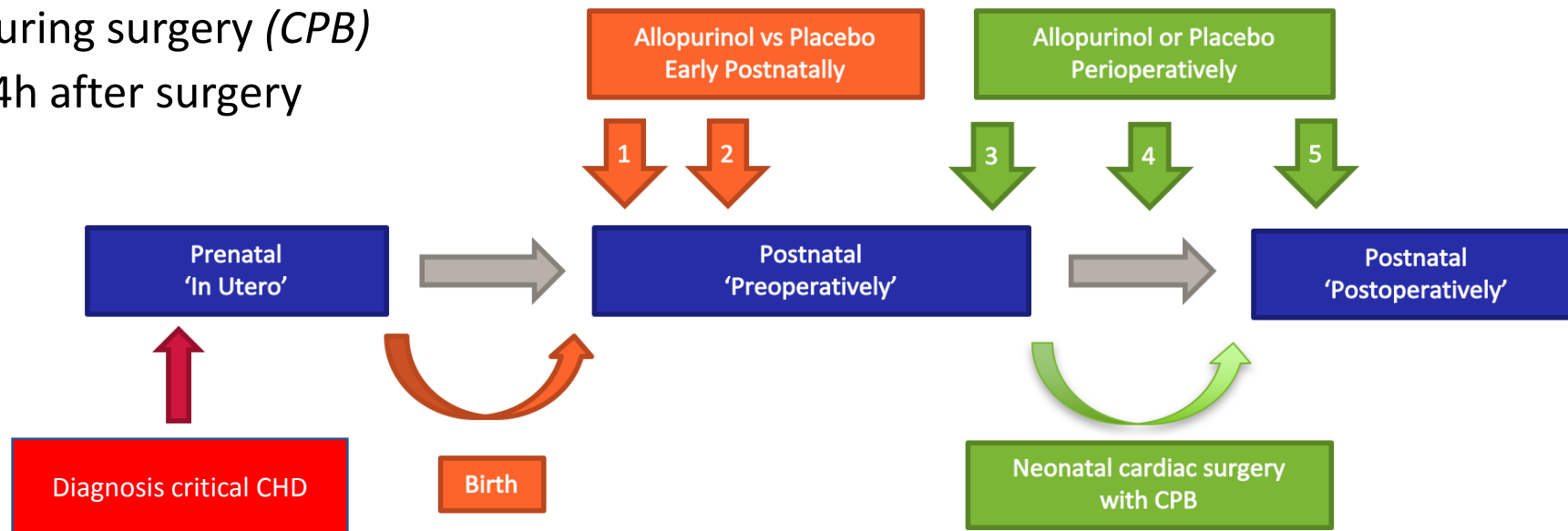
In- and exclusion

- Neonates with a prenatal or postnatal diagnosis of critical CHD requiring cardiac surgery with cardiopulmonary bypass within the neonatal period (expectation \leq 4 weeks)
 - Transposition of the Great Arteries
 - Univentricular Heart Physiology
 - Aortic Arch Anomalies
- Informed consent

- Inability to enroll the patient before start of delivery (*prenatally*) or 24h before surgery (*postnatally*)
- Doubt about severity aortic arch abnormality before birth
- GA < 36 weeks or birth weight < 2000 gram
- Surgery without CPB
- Decision for comfort care only

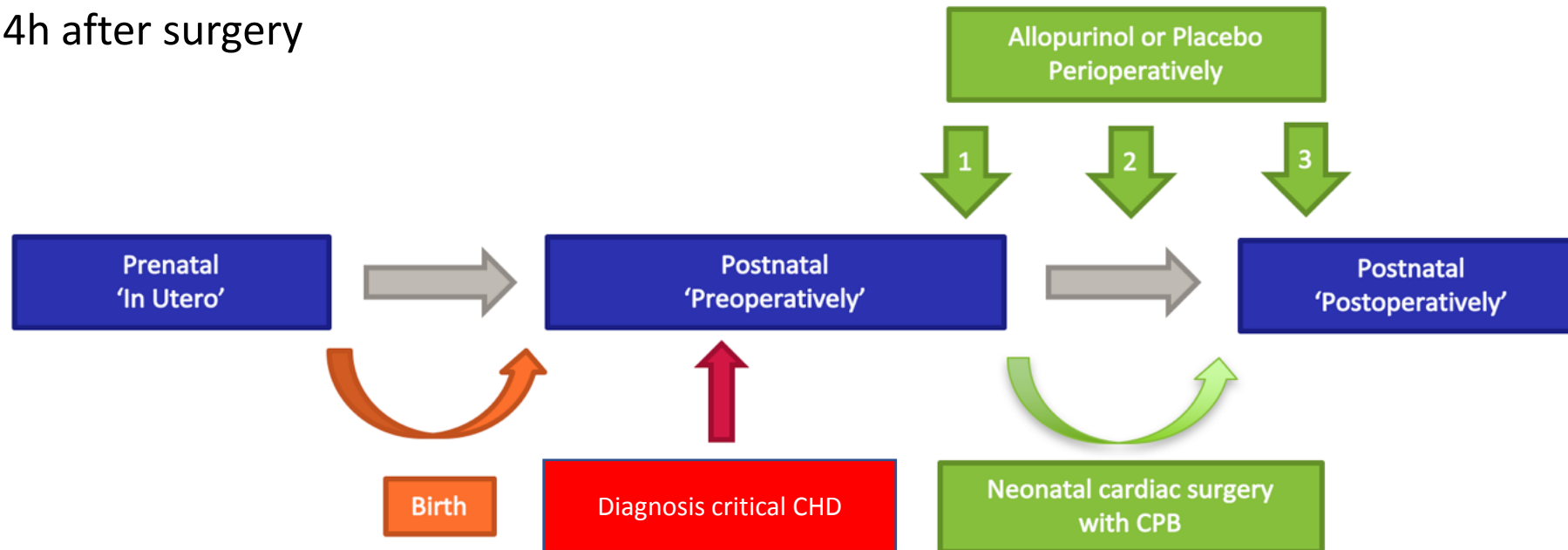
Intervention (in prenatal critical CHD)

- Allopurinol 20 mg/kg or Mannitol-Placebo PFI
 1. ≤ 45 m after birth
 2. 12h after first dose
 3. 12h before surgery
 4. During surgery (CPB)
 5. 24h after surgery



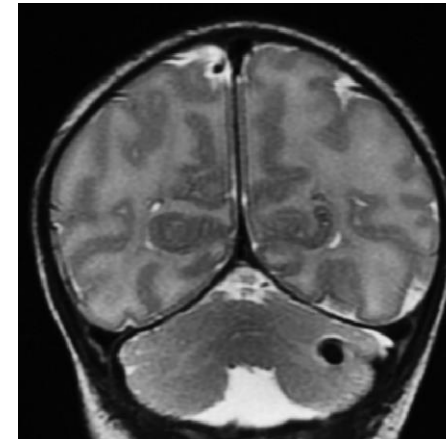
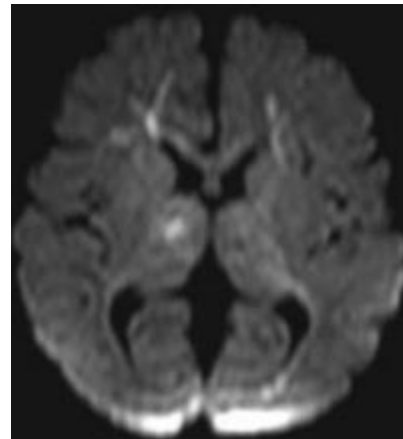
Intervention (in postnatal critical CHD)

- Allopurinol 20 mg/kg or Mannitol-Placebo PFI
 1. 12h before surgery
 2. During surgery (CPB)
 3. 24h after surgery



Primary outcome

- Composite
 - Relevant (moderate/severe) parenchymatous brain injury on postoperative MRI (T1/T2/DWI/SWI)
 - *White matter laesions*
 - *Infarction of the grey matter*
 - *Haemorrhage*
 - *Involvement of motoric/optic tracts*
 - Too instable for postoperative MRI
 - Mortality



Secondary outcomes

- Brain injury severity score
- Volume hypoxic-ischemic brain injury
- Cardiac function
- Cerebral function, oxygenation
- Neurodevelopmental outcome
- Quality of life
- Cost-effectiveness allopurinol

MRI pre- and postoperative

Echocardiography, pre- and postoperative

aEEG/NIRS (postnatal and) perioperative

GMs 3 months

Bayley-III-NL, executive functioning 24 months

TAPQOL questionnaire 24 months

Health technology assessment questionnaires

During hospital stay, at 3 and 24 months

Health Technology Assessment/Questionnaires

During hospital stay, at 3 and 24 months

Echocardiography

4-7 days after birth or preoperatively

Echocardiography

5-10 days after surgery

MRI Brain

4-7 days after birth or preoperatively

MRI Brain

5-10 days or ≤ 1 month after surgery

aEEG, NIRS

24-36 hours after birth

aEEG, NIRS

6 hours before surgery until 48-72 hours postoperatively

GMs

3 months

BSITD-III-NL

Executive functions
TAPQoL
24 months

Study Medication

≤ 30 minutes & 12 hours after birth

Study Medication

12 hours before surgery & during surgery (CPB) & 24 hours after surgery

Informed Consent

Before birth

Birth

Cardiac Surgery with CPB

≤ 28 days after birth

Prenatally

Postnatally & Preoperatively

Peroperatively

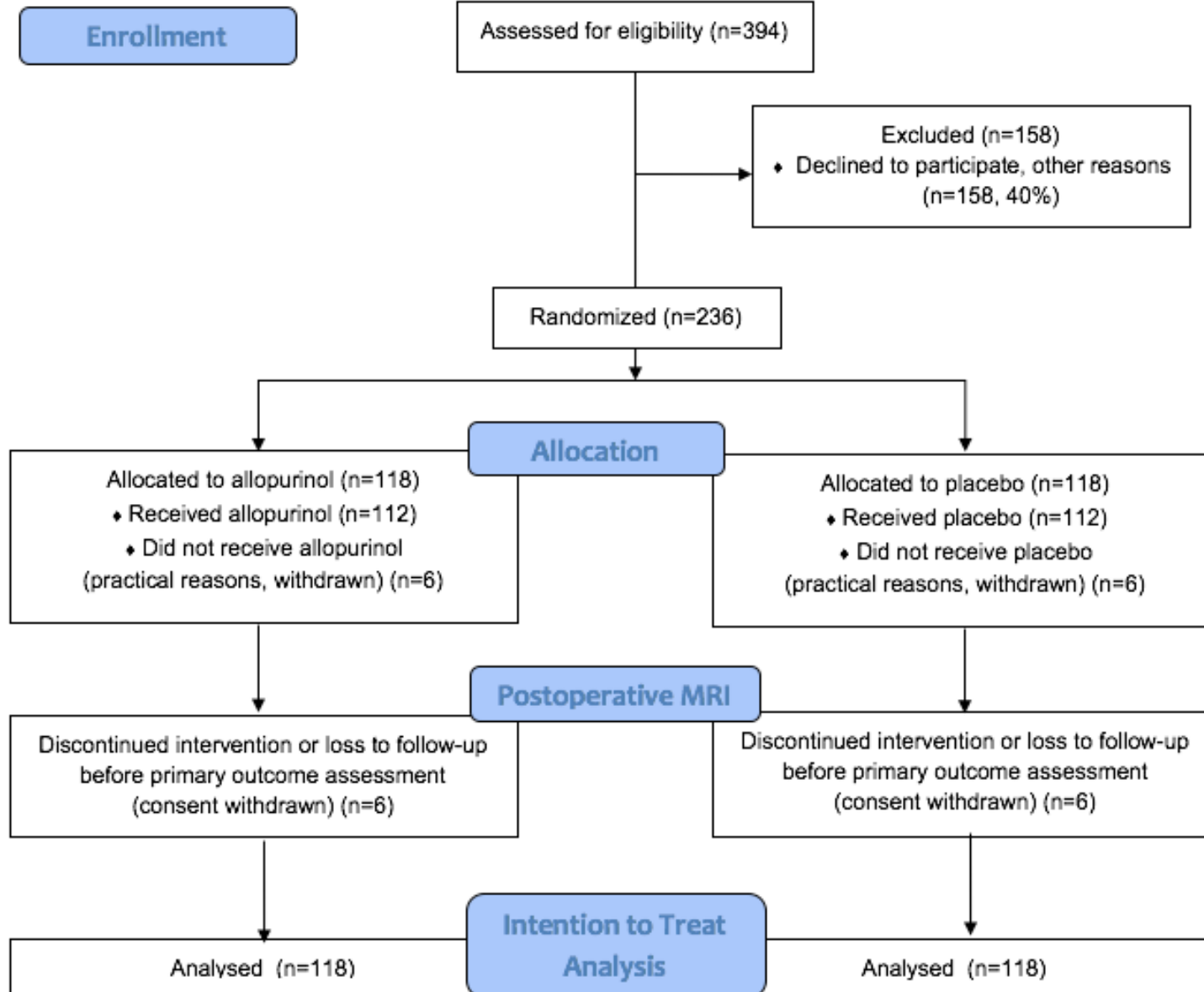
Postoperatively

Follow-up



Sample size and analysis

- 20% reduction in primary outcome (two-sided alpha 5%, power 80%)
- Prenatal diagnosis (n = 188)
 - Primary analysis: 1 interim analysis at n=94 (*efficacy*)
→ 1/2 SD improvement cognitive outcome (IQ +8) at 24 months (with n=140, -25% mortality/syndrome)
 - DSMB interim analysis at defined time points (*safety*)
- Postnatal diagnosis (n = 48)
 - Secondary analysis



Estimated inclusion (*inclusion rate 60%*)

- Prenatal diagnosis 82 a year
- Postnatal diagnosis 20 a year

Duration

- Inclusion period 2.5 years
- Follow-up 2 years
- Total 4.5 years

Dank aan allen!

Kindercardiologie

Neonatologie

Kinder intensive care

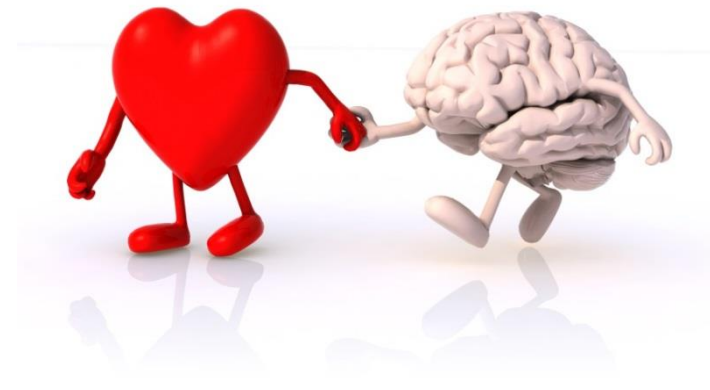
Congenitale thorax chirurgie

Gynaecologie

Kinderanesthesiologie

Kinderfysiotherapie

Kinderpsychologie



Apotheken

Farmaceutisch bedrijf

Statistici

Kwaliteitscoördinator

Datamanagers

Monitor

Veiligheidscommissie

Juridische zaken