PARIS Collaboration: antiplatelets to prevent pre-eclampsia

A review using individual patient data

Askie LM,[1,2,3] Duley L,[4] Henderson-Smart DJ,[1] Farrell B,[4] Stewart L,[5] Clarke M[2], on behalf of the PARIS Collaboration

[1] Centre for Perinatal Health Services Research, University of Sydney
[2] UK Cochrane Centre, Oxford, UK
[3] NHMRC Clinical Trials Centre, University of Sydney, Australia
[4] Resource Centre for Randomised Trials, Oxford, UK
[5] MRC Clinical Trials Unit, London, UK

Background

- pre-eclampsia (hypertension + proteinuria) occurs 2-8% pregnancies
- maternal effects: liver, kidney, brain, clotting system, placental dysfunction
- fetal effects: poor growth, prematurity
- ~ 60,000 women die each year (150/day) due to hypertensive disorders, 99% in low resource countries
- pre-eclampsia consistently leading cause maternal death in high resource countries
- aspirin: mediates abnormal clotting, cheap, safe

Cochrane Review

Antiplatelet agents for preventing pre-eclampsia and its consequences
Duley L, Henderson-Smart DJ, Knight M, King JF

- 51 included trials: ~36,500 women
- 51 excluded trials: >10,000 women
- time period: 1985-2003
- ~ half large (≥ 100), half small trials

Main outcomes

	RR	(95% CI)	N
Pre-eclampsia	0.81	(0.75, 0.88)	33,367
Preterm birth	0.93	(0.88, 0.98)	28,468
Baby death	0.85	(0.74, 0.96)	30,633
SGA baby	0.92	(0.85, 1.00)	24,240

Remaining questions

Targeting the benefits of antiplatelet therapy

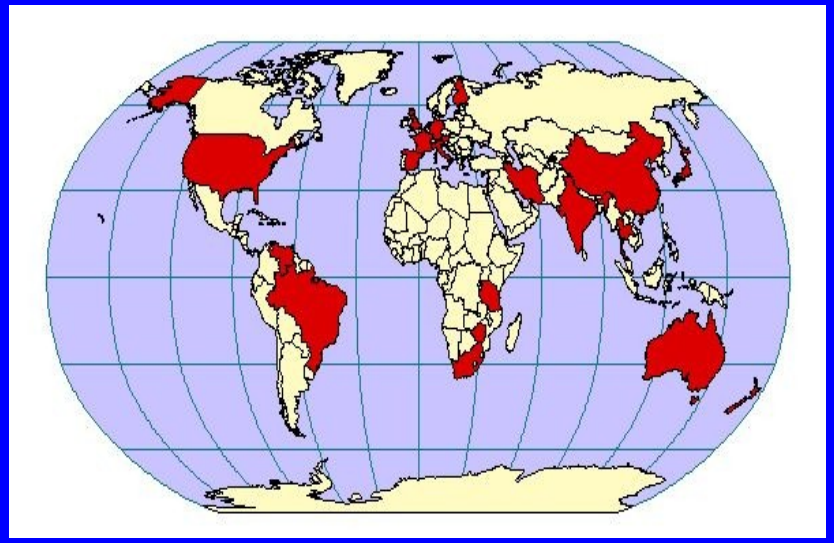
- are there specific high risk women for whom there might be greater benefits?
- what is the best time to initiate treatment?
- what is the best dose?

authors recommended review using individual patient data (IPD)

PARIS Collaboration

Perinatal Antiplatelet Review of International Studies

- 61 eligible trials
  - 51 Cochrane review
  - 6 previously excluded
  - 4 newly identified
- 39,189 women
- 24 countries
- 6 continents



Challenges for PARIS IPD

- IPD approach generally time-to-event data
- PARIS data / outcomes
  - mostly dichotomous
  - numerous
    - 63 data items collected, more for multiple births:
    - 27 enrolment characteristics; 20 maternal, 16 infant outcomes
  - potentially competing outcomes for mother and baby (create composite outcomes)
  - quite complex data management, processing

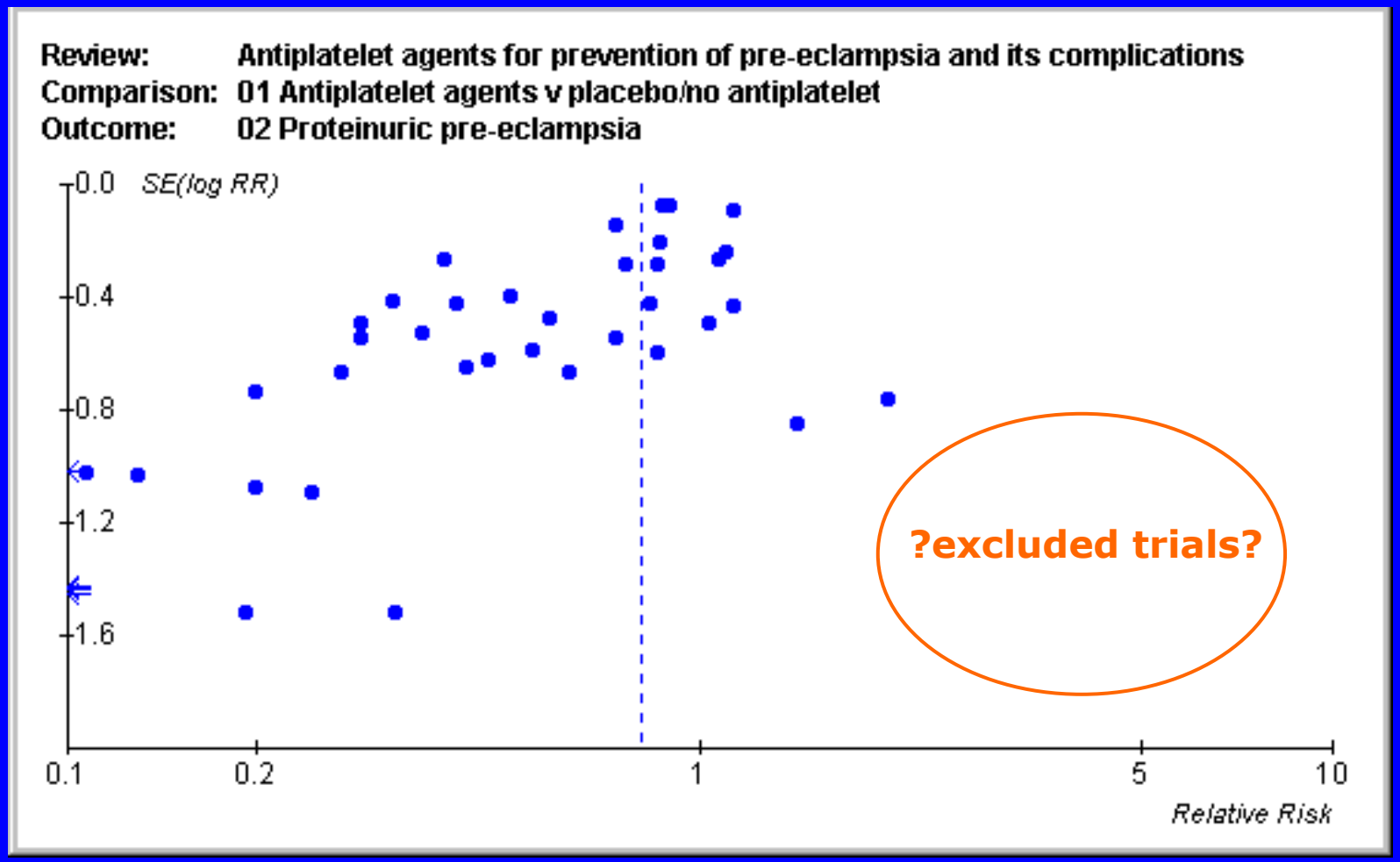
Redefining pre eclampsia outcome

- definition of pre eclampsia differs markedly between trials
- some very ‘strict’, some very ‘loose’ def
- belief that difference in definition might explain difference in results between trials
- IPD allows common outcome definition to be used for all trials
- will explore whether re-definition makes difference to results

Added value to Cochrane review

- inclusion of previously excluded trials
- 51 trials excluded from Cochrane review
  - 20 definitely ineligible
  - 31 trials with no usable data, methods queries
  - mostly early, small trials
  - potential publication bias

Funnel plot asymmetry



Added value to Cochrane review

- inclusion of previously excluded trials
  - 31 trials with no usable data, methods queries
  - able to contact 15 trialists
    - confirm exclusion of 9 trials
    - confirm inclusion of 6 trials (n=1078)
- collect info on all outcomes for all trials
  - help avoid potential selective reporting of outcomes bias

Main outcomes of CC review

	RR	(95% CI)	N
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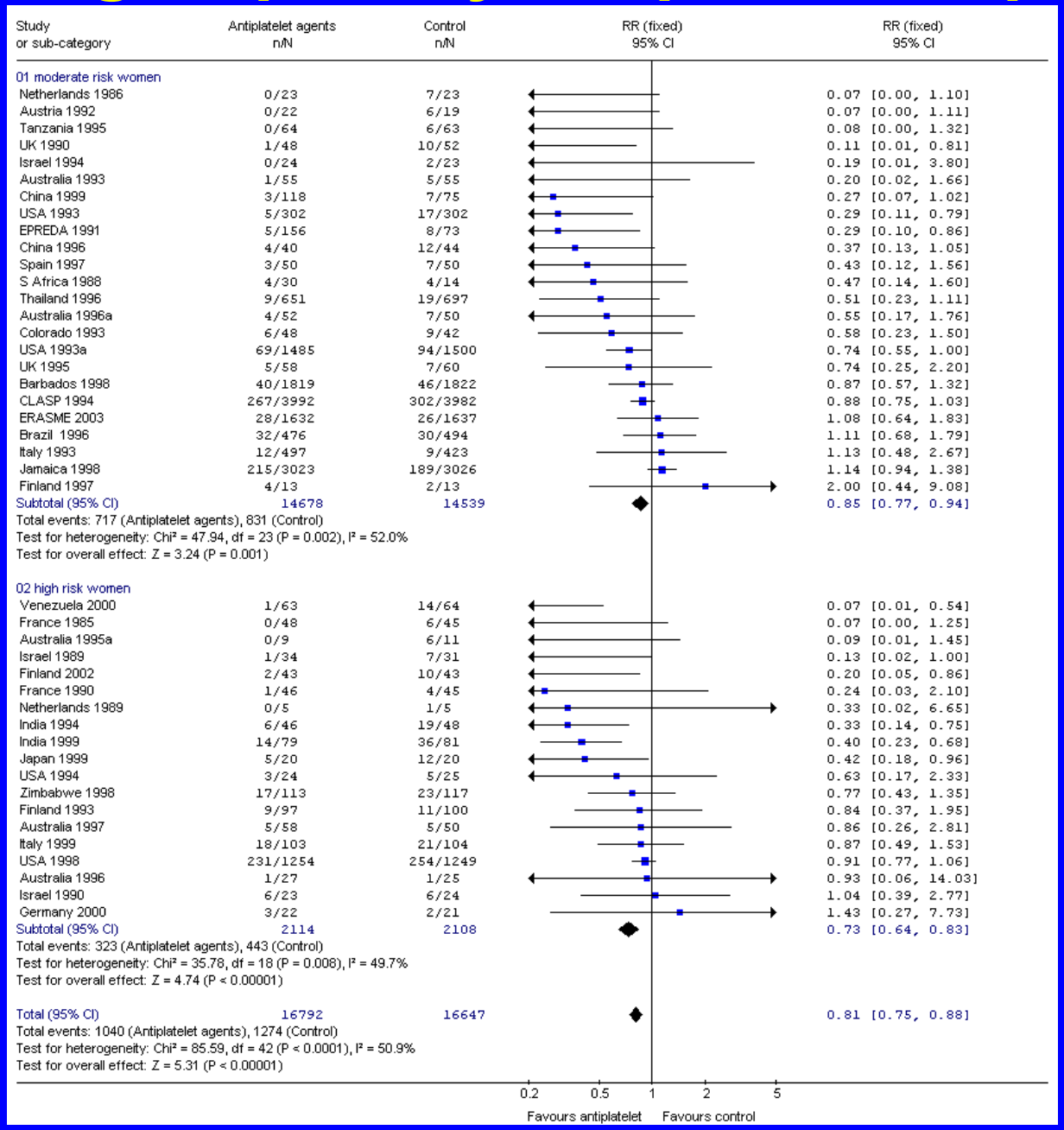
Preterm birth	0.93	(0.88, 0.98)	28,468
Baby death	0.85	(0.74, 0.96)	30,633
SGA baby	0.92	(0.85, 1.00)	**24,310**

Total n = 36,500

Sub group analysis: pre-eclampsia



Analysis by maternal risk

- women normotensive at trial entry
  - previous hypertensive disorder of pregnancy
  - renal disease, diabetes, autoimmune disease
  - multiple pregnancy
  - advanced maternal age
  - previous small for gestational age baby
  - abnormal uterine doppler test
  - primigravida +/- other risk factors

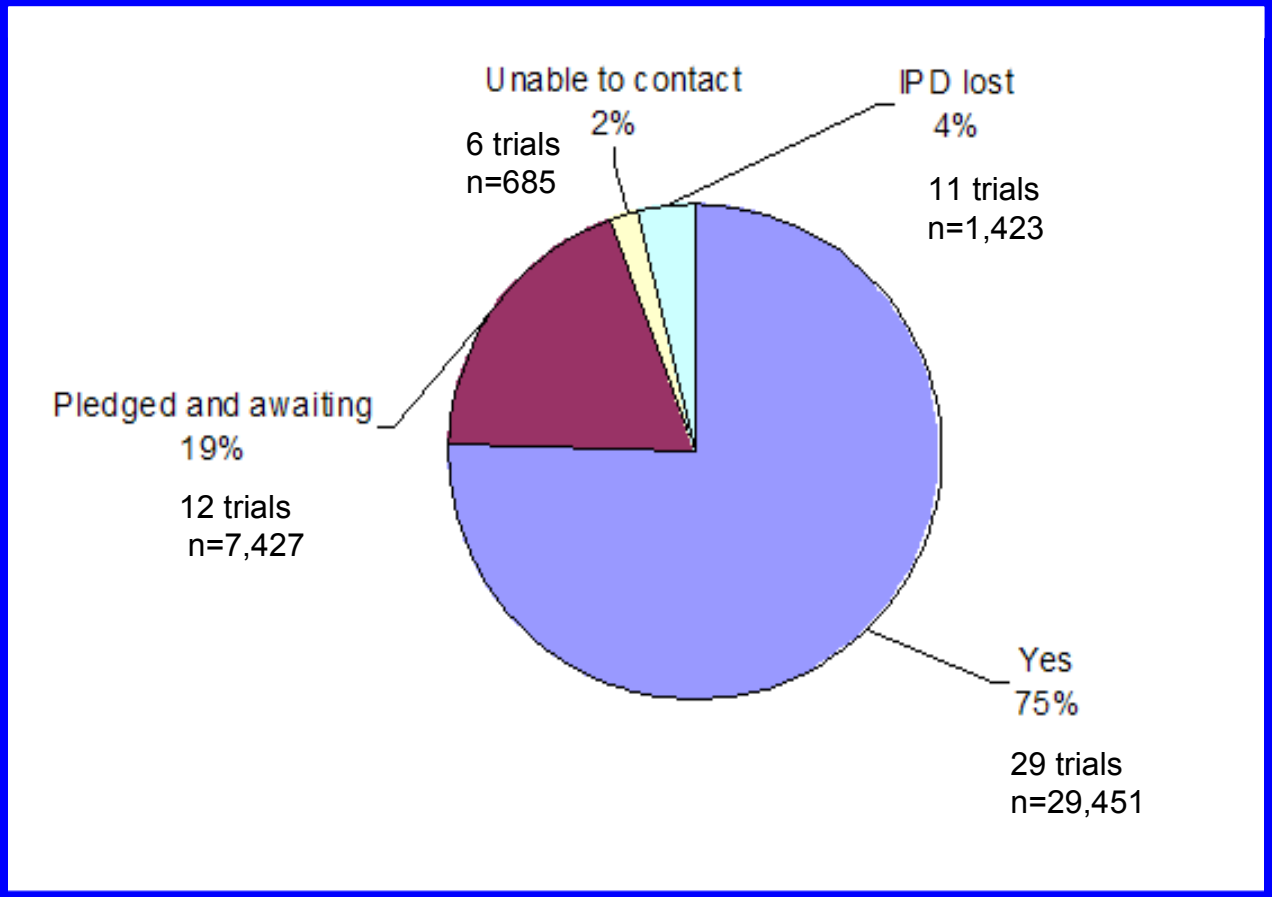
Main analysis approaches

- two stage approach
  - estimate effect within trials, then combine these estimates
  - majority of analyses
  - linkage of mother and baby outcomes
- one stage modelling approach
  - regression analyses for continuous variables
  - exploration of multiple covariates
- further exploratory analyses (later)
  - clinical (rich epidemiological database)
  - methodological

Potential secondary methodological questions?

- What does the data look like at the time of the early, extreme trials?
- How have the results change with the use of IPD compared with aggregate data?
  - correcting data errors
  - including previously excluded trials
  - including previously unavailable data
  - re-instating (erroneously) excluded patients

PARIS progress



Timeline

- data collection complete end 2005
- data analysis first half 2006
- main results in July 2006
- main publication by end 2006
- secondary analyses Cochrane review update in 2007

In conclusion

- important clinical question, unable to be fully answered with aggregate data Cochrane review
- successful IPD collaboration underway
  will have complete dataset by end 2005
- new challenges for IPD methodology with numerous, complex and dichotomous variables
- should provide rich data source for further methodological, epidemiological research
- PARIS Collaboration primary results due July 2006

Thank you ……

Email: paris@perinatal.usyd.edu.au

Phone: +61 (0)2 9351 7318

Fax: +61 (0)2 9351 7742