

“Clinical use of platelets -
therapeutic, prophylactic &
thresholds”

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Aims

- Guidelines for transfusion
- Thinking about the how we develop guidelines
- No answers
- Few other areas to consider

Background

- Platelets are an important blood component
- 216,000 doses/year (England & North Wales)
- Usage stable
- They are expensive (£175/adult dose)



Usage & Developments: risk-benefit analysis

- enhancing clinical effectiveness

- and reducing side-effects

SHOT

Bacterial risks

Guidelines & Consensus Conferences

- 1987 - Consensus Conference, NIH
- 1992 - BCSH guidelines
- 1997 - Consensus Conference, Edinburgh
- 2001 - ASCO guidelines
- 2003 - Revised BCSH guidelines

(Br J Haematol, 2003; www.bcshguidelines.org)

General Indications for platelet transfusions

- for management of bleeding in patients with thrombocytopenia/ plt function defects, e.g.:-
 - » Bone marrow failure
 - » Massive transfusion
 - » DIC - acute
 - » Surgery: cardiac bypass, liver transplant
 - » Inherited/ acquired platelet function disorders
 - » Immune thrombocytopenias: ITP (if haemorrhage), NAIT

Bone marrow failure syndromes

Standard to treat thrombocytopenic bleeding

Also for the prevention of thrombocytopenic bleeding:-

- Common practice was to transfuse if the platelet count $< 20 \times 10^9/L$ in haematology patients, but *currently* lower thresholds

Prophylaxis in adults

Bone marrow failure

Thresholds also vary for different causes:

- Acute leukaemia
- Acute promyelocytic leukaemia
- Haemopoietic stem cell transplantation
- Chronic thrombocytopenia

Prophylaxis for surgery

Guidance includes:-

- *None:* Bone marrow aspiration/biopsy
- $> 50 \times 10^9/l$: LP/epidural, gastroscopy, indwelling-lines, liver biopsy, laparotomy
- $> 100 \times 10^9/l$: Surgery in critical sites e.g. brain

Prophylaxis for interventions in Children

- Guidelines state platelet count between 20-40 x 10⁹/l: LP/ CVL insertion
- Reflects anecdotal experience/ recent observational studies

1. Assessing Responses to Transfusion

Therapeutic: Cessation of bleeding

Prophylactic: Observation of increments

Poor responses (increment $< 10 \times 10^9/l$) to 2 or 3 transfusions should prompt further investigation:

- Identify cause
- Provide more effective platelets

2. Contraindications

- Identify cause of thrombocytopenia as platelet transfusions may be contraindicated

e.g. Heparin-induced thrombocytopenia

Thrombotic thrombocytopenic purpura

Platelet transfusions in massive transfusion

- Platelet count falls to about $50 \times 10^9/\text{L}$ after transfusion of red cells equivalent to about 2 blood volumes
- There is consensus that the platelet count should be maintained above $50 \times 10^9/\text{L}$ in patients with acute bleeding
- A higher target level has been recommended in patients with multiple trauma or central nervous system injury

Platelet transfusions after CPB surgery

- Microvascular bleeding may occur due to thrombocytopenia (platelet count $< 50 \times 10^9/L$) or acquired platelet dysfunction
- Thromboelastography may help decision-making about the need for platelet transfusion
- Platelet transfusions should be reserved to treat excessive bleeding after exclusion of surgical cause
- Combined use of aprotinin & cell salvage may ↓ transfusion rate to 15% in first-time cardiac surgery

Evidence-based practice

- What are guidelines based on?
- How strong is the body of evidence underpinning the guidelines?

What is in the literature?

- Published Research - primary

 - e.g. Controlled trials

 - Other studies

- Review - secondary

 - e.g. Narrative or systematic

Problems with publications

- Many trials started but results never *reported*
- Of trials reported as short abstracts at international cancer meetings, about 45% never reported as full papers (many *negative*)
- Trials with *positive* results published more commonly, sooner, and often more than once: tendency to over-emphasis of benefit

Problems with sources

Databases

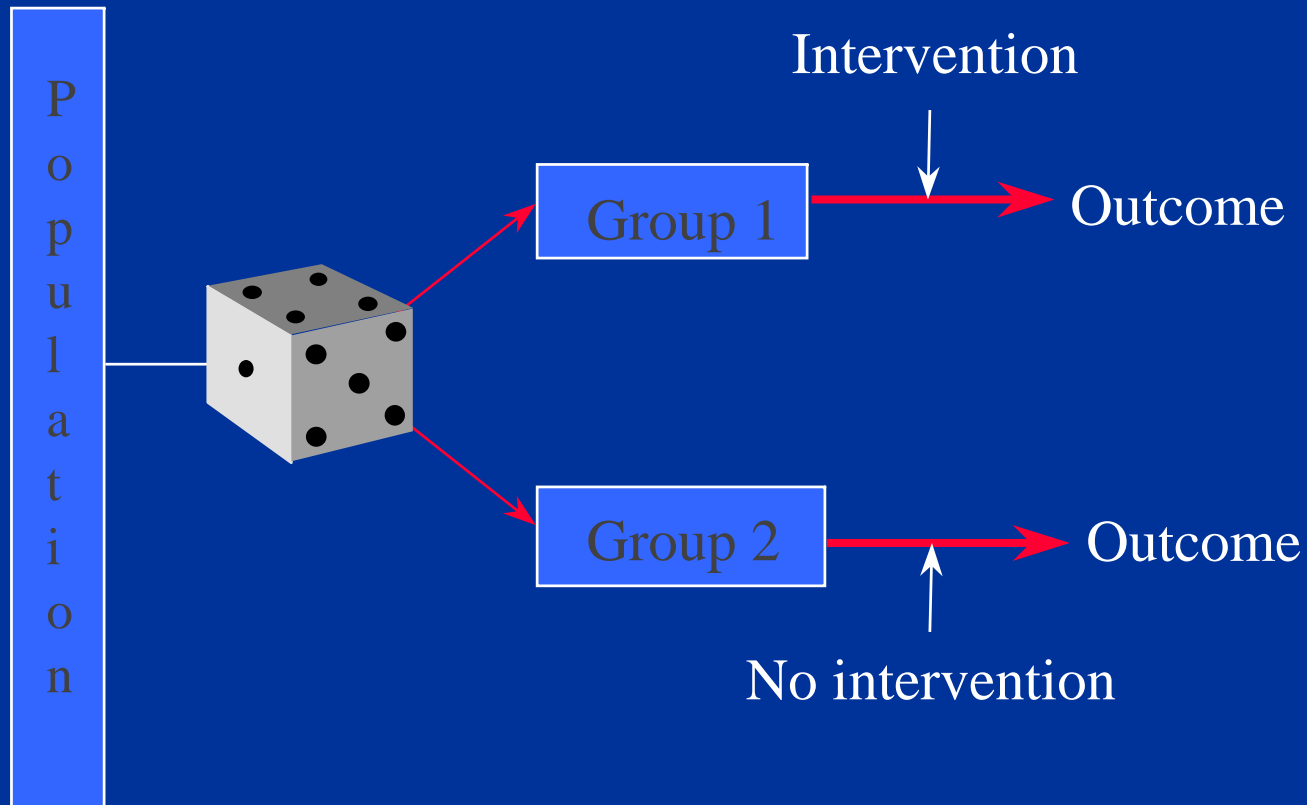
- Medline (4000 journals, 11m citations, US/English, access vendor)
- Embase
- Cochrane
- Others
- Pre-filtered information databases

Need librarian!

'Hierarchy' of primary studies

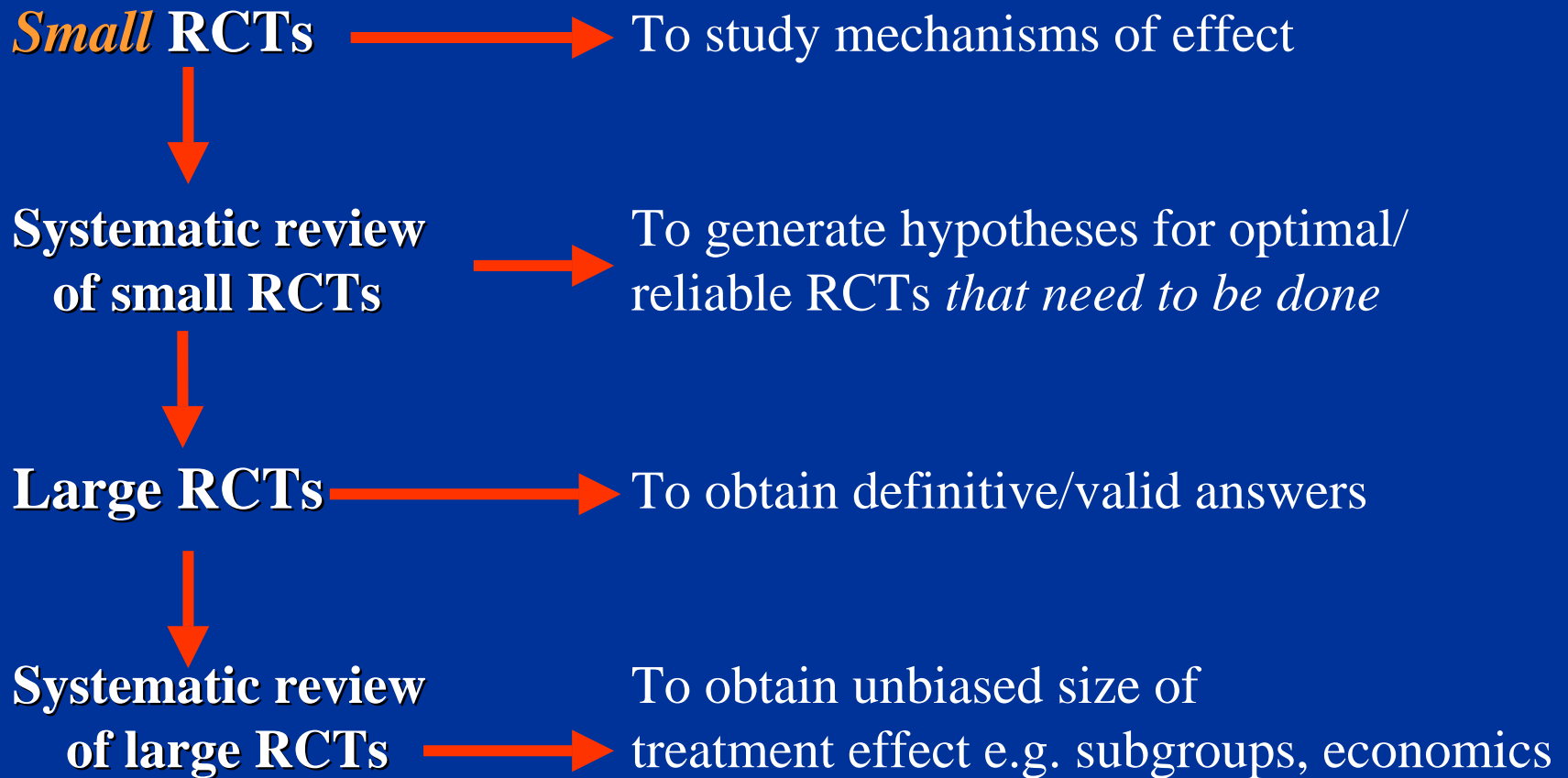
- Anecdotal case reports
- Case series without controls
- Series with literature controls
- Analyses using computer databases
- Case-control observational studies
- Series based on historical control groups
- Randomised controlled trials

To reliably distinguish *moderate treatment* effects from no worthwhile effects



Parallel RCT: Confounding factors

Systematic reviews are not substitutes for RCT



Systematic 'review': process

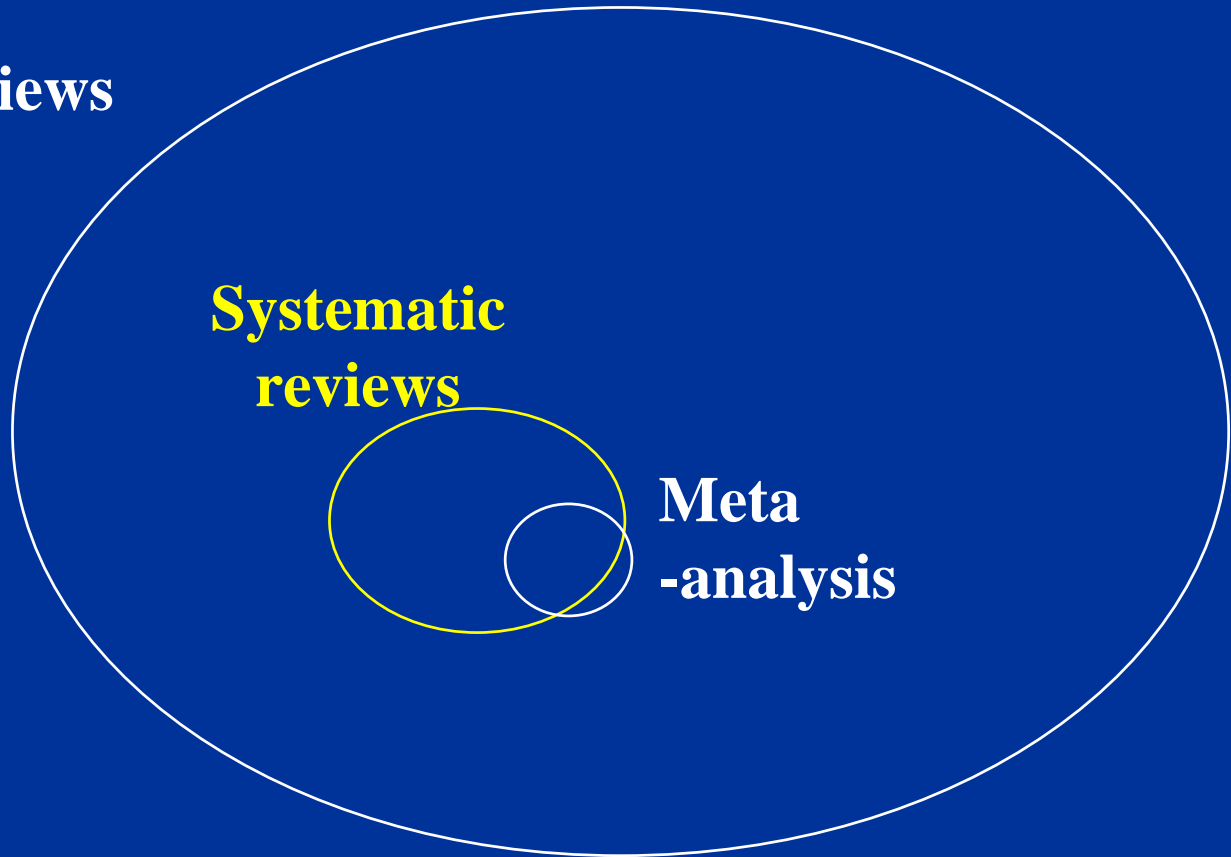
- multi-authorship/different backgrounds
- being transparent to ↓ bias
- explicit methods for inclusions/exclusions
- appraising all studies (& unpublished)
- effect sizes & graphical display to compare

Meta-analysis: quantitatively

All reviews

Systematic reviews

Meta-analysis



Limited evidence about optimal use of platelet transfusions

- Benefit of prophylactic transfusions
- Clinical outcomes
- Dose
- Frequency

1. Prophylactic platelet transfusions

- Prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level
- Prophylactic platelet transfusions vs therapeutic platelet transfusions

A. Platelet transfusion triggers

Prophylactic transfusions - different triggers

- Three RCT
- Contemporary
- Numbers randomised range 78-255
- All compared trigger counts 10 and 20 x 10⁹/L
- 2 trials AML, 1 trial BMT

Prophylactic platelet transfusion trigger RCT in AML

Threshold:	$10 \times 10^9/L^*$	$20 \times 10^9/L$
n	135	120
Major bleeding episodes	21.5%	20%
1	15.6%	15.0%
2-4	5.9%	5.0%
>4	0	0
Days with major bleeding	3.1	2.0
Hemorrhagic deaths (cerebral)	1¶	0



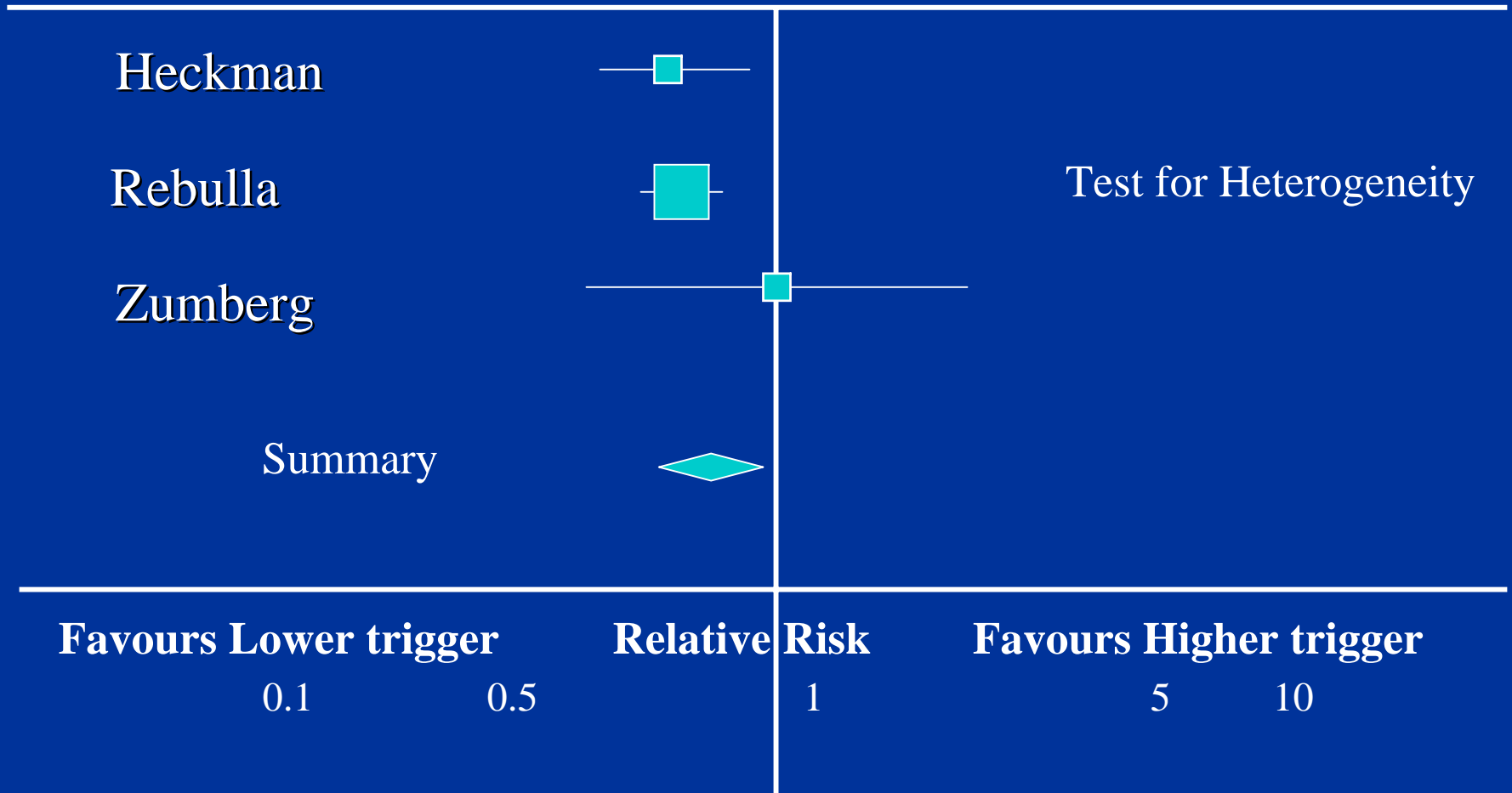
21.5% fewer transfusions

*or $10-20 \times 10^9/L$ and temp $38.0^\circ C$, active bleeding or invasive procedure

¶ Occuring when platelet count = $32 \times 10^9/L$

Rebulla *et al.* *NEJM* 1997;337:1870-5.

Mean platelet transfusions/patient: which results are we confident about?



Revised BCSH guidelines with BMF

- Threshold of $10 \times 10^9/L$ as safe as higher levels for patients without risk factors (& fewer transfusions)
- For patients without any risk factors, an ever lower threshold may be appropriate. But, accurate counting of platelets difficult at threshold $< 10 \times 10^9/l$ (over-estimated)
- A specific threshold may not be appropriate for patients with chronic stable thrombocytopenia who are best managed on an individual basis depending on the degree of haemorrhage

B. Prophylactic vs therapeutic transfusion

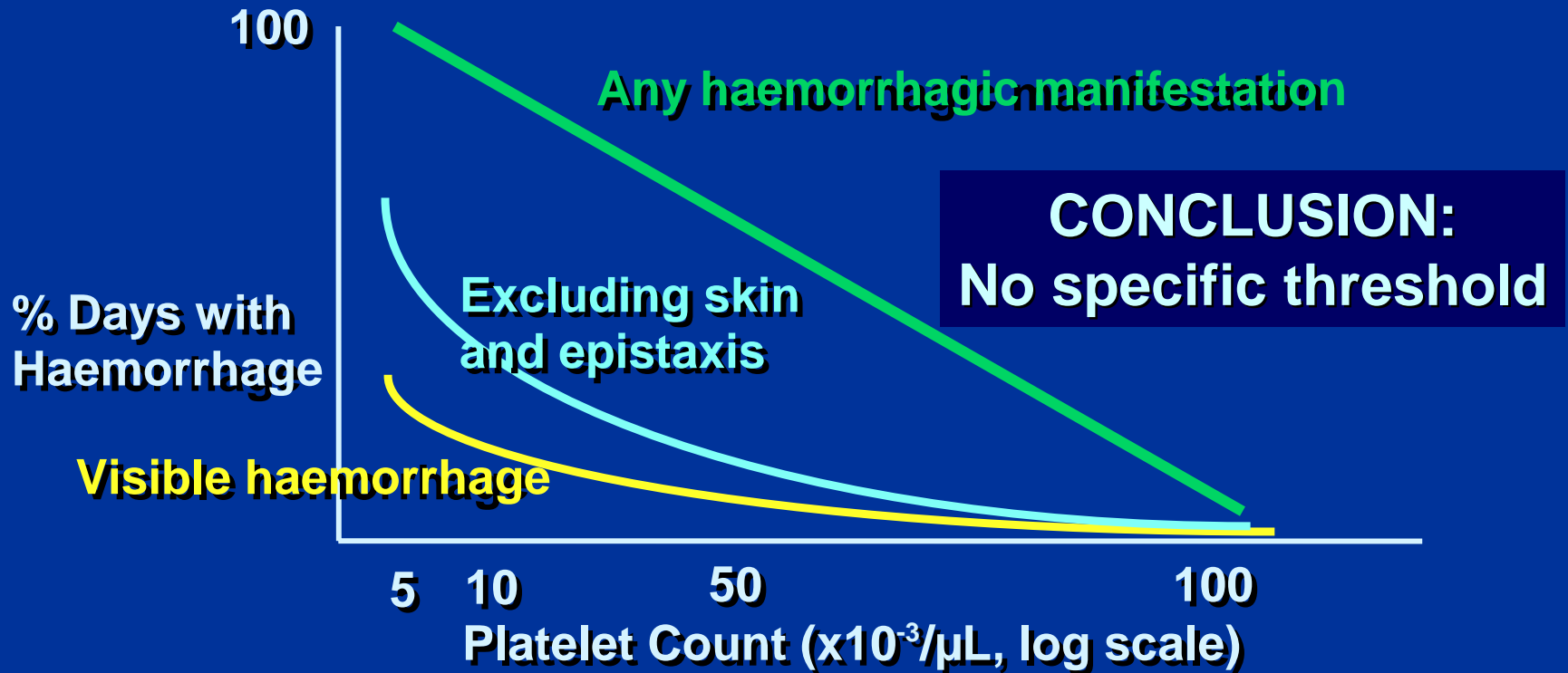
- Three randomised trials
- Dates 1974-1982
- Numbers randomised range 21-56
- 2 trials AML, 1 trial childhood ALL

Heterogeneity in these RCTs

- Inadequately powered/ small numbers
- Dose effect
- Frequency of transfusions
- Control group (population)

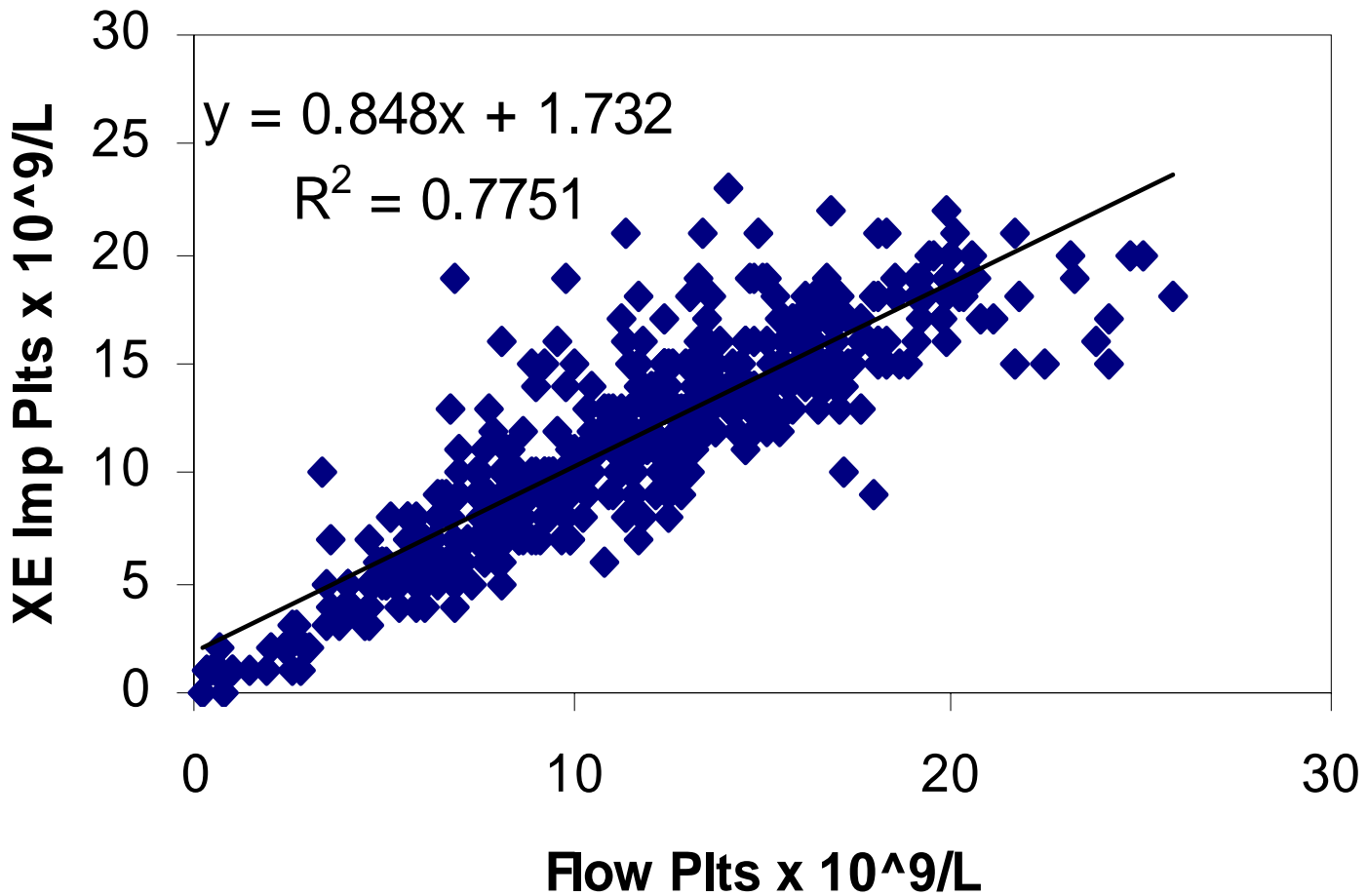
- Either “evidence of no effect”
or “no evidence of effect”

Relationship thrombocytopenia & haemorrhage

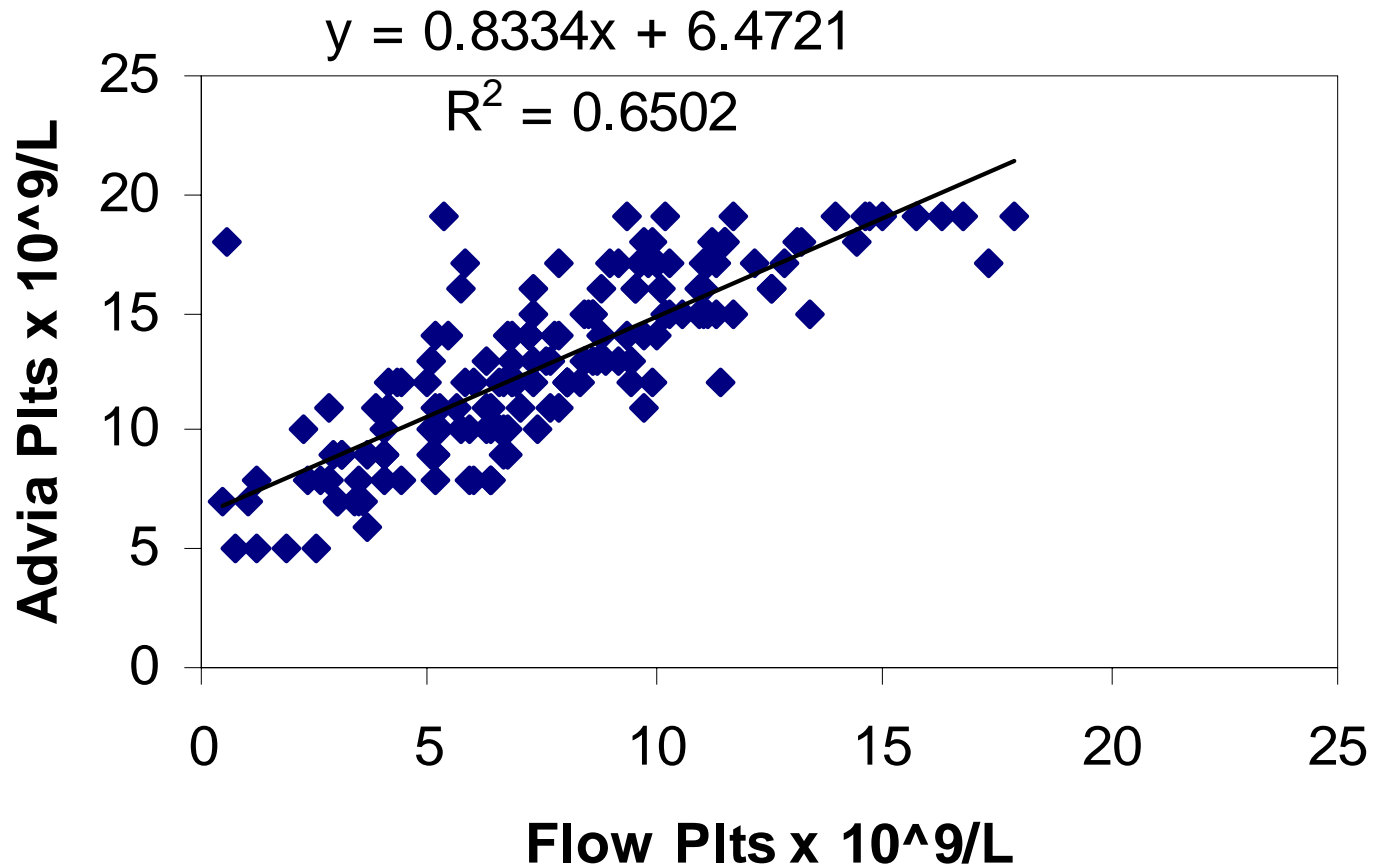


Children & intra-cerebral bleeds: Gaydos *et al.* *NEJM* 1962;266:905-9

Flow Cytometric Plts v XE Impedance Plt counts



Flow plts v Advia Optical Plt counts



Other issues: Platelet dose

- Plt concentrates (adult) from transfusion centres
- mean no. plts/unit 265 (45-472) $\times 10^9$ apheresis
300 (158-439) $\times 10^9$ pooled
- Relate to clinical: single adult dose transfusions
mean plt increment 14 (-6 to 77) $\times 10^9/l$

Platelet function in donors

- Before Plateletpheresis
- PFA-100 testing (simulates high-shear function)
- 100 donors
- Approx 1 in 4 abnormalities
- Reasons varied eg VWF levels, also aspirin-like

Summary points

Limitations of automated analysers in platelet counting when the count is $< 20 \times 10^9/L$

No convincing evidence for prophylactic compared to 'on-demand' platelet transfusions

Recent approach has been to ↓ threshold for prophylaxis, but need to be sure that at these levels platelet transfusions given as therapy to control bleeding will be successful

Conclusion

- Guidelines
- Need to look at the evidence-base
- Accept uncertain results
- Role of prophylactic transfusion
- Different issues eg dose
- Other groups eg neonates

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