

# Systematic Reviews of Epilepsy Monotherapy Trials

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# Evidence Based Guidelines

## Diagnosis and Management of Epilepsy in Adults

A National Clinical Guideline  
recommended for use  
in  
**Scotland**  
by the  
**Scottish Intercollegiate  
Guidelines Network**

Pilot Edition  
November 1997



S I G N

*Getting validated guidelines into local practice*

## Adults with Poorly Controlled Epilepsy

Part I  
Clinical guidelines for treatment

Part II  
Practical tools for aiding  
epilepsy management



Institute of Neurology



Royal College of Physicians



National Society for Epilepsy



*National Institute for  
Clinical Excellence*

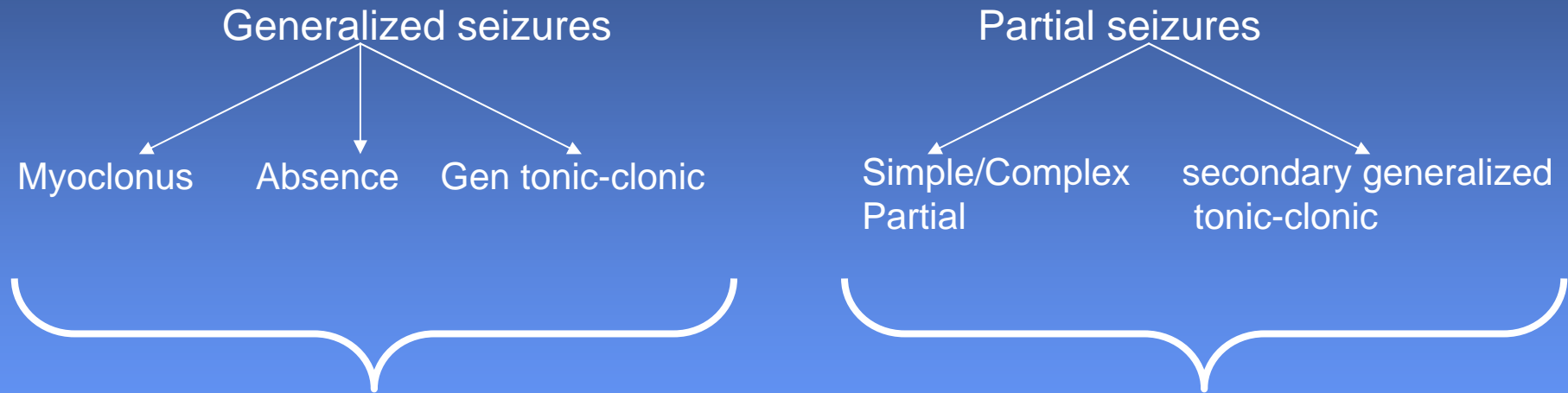
## **The epilepsies**

The diagnosis and management of the  
epilepsies in adults and children in primary  
and secondary care

**Clinical Guideline 20**  
October 2004

Developed by the National Collaborating Centre for  
Primary Care

# First line AEDs and seizure types



**Valproate** **Carbamazepine**

Lamotrigine

Valproate

Topiramate

Lamotrigine

Topiramate

# Systematic review of trials comparing carbamazepine and valproate

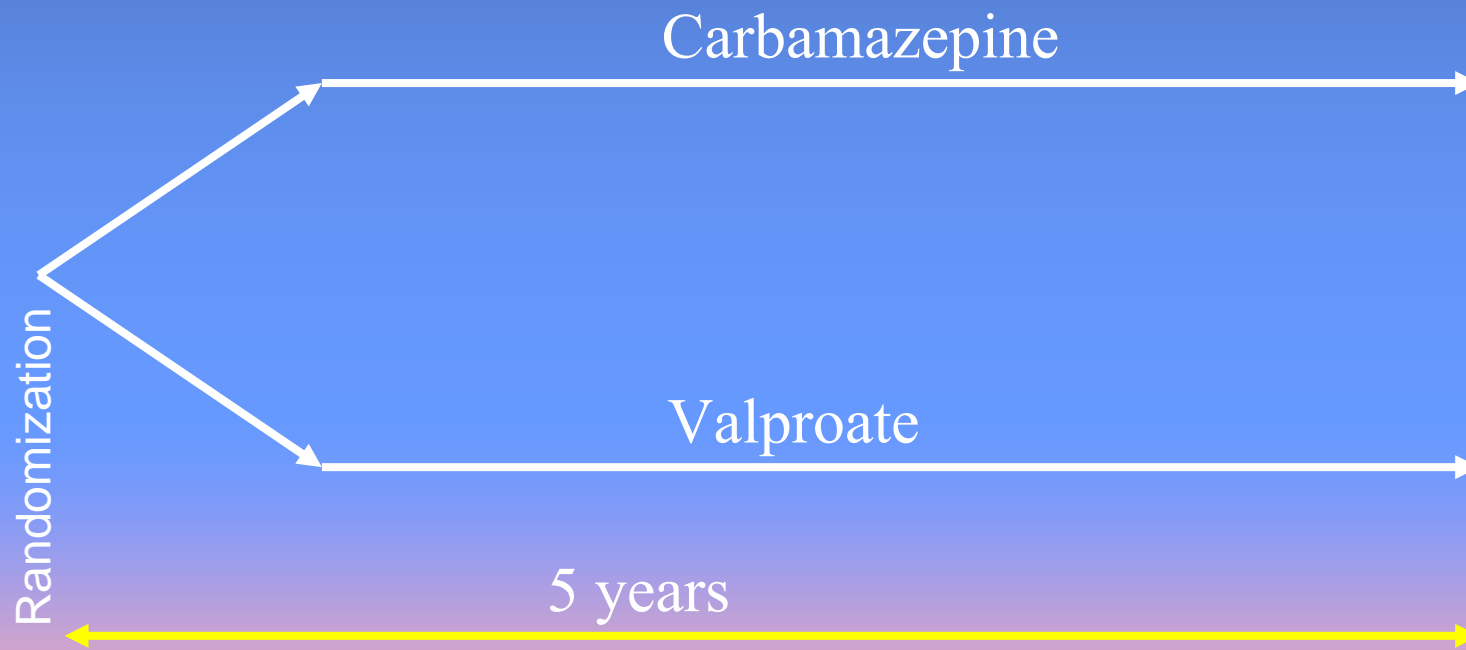


# The protocol

- Describe methods used to minimise bias in the conduct of the review
- Inclusion criteria for studies
- Search strategy
- Data extraction and analysis

# Inclusion criteria 1

- Head to head comparison of carbamazepine and valproate



# Inclusion criteria 2

- Randomized controlled trial with adequate methods of allocation concealment



# Randomization



# Prospective non randomized controlled study



Clinician allocates treatment

Thrombolysis

No  
Thrombolysis

# What are the clinicians prejudices?

- Might be deliberate or subconscious
- Put patients with a worse prognosis in the treatment group
  - Treatment might appear to have no effect when in fact it does
- Put patients with a better prognosis in the treatment group
  - Treatment might appear to have an effect when it does not



# Prospective non randomized controlled study



~~Allocation Bias~~  
Clinician allocates  
treatment

Thrombolysis

No  
Thrombolysis

# Randomization

- Patient allocated to a treatment group using an unpredictable (random) process
- Main aim is to eliminate allocation bias



# Randomization list put on notice board

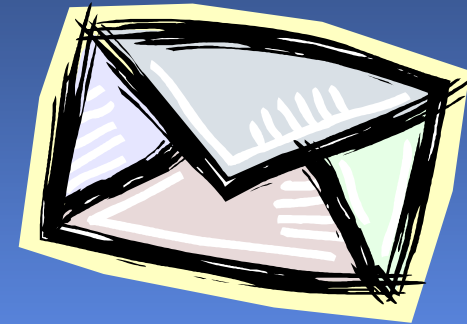


Clinician still decides!



# Allocation concealment

- Sealed opaque envelopes
- Telephone randomization
- Sealed packages



# Randomization – powerful tool

- Used as a basis for statistical inference
  - If a treatment effect is found we assume that this was due to the treatment
- Empirical evidence that failure to properly conceal allocation is the largest source of bias in RCTs (Schulz 1995)



# Allocation concealment $\neq$ Blinding

- All RCTs should have allocation concealment
- Not all RCTs need to be blinded



# Inclusion criteria 3

- Trials may be blinded or unblinded



# Bias and measuring outcomes

- Will the measurement of outcome be affected by knowledge of the treatment taken?
  - Patient tries to please doctor
  - Doctor over optimistic about new treatment
- Depends on the outcome
  - Death → Very unlikely
  - Seizure counts
    - Simple partial seizures > Tonic clonic
  - Quality of life questionnaires....

# Blinding – Trade offs

- Not always possible – e.g. surgery
- Patient / clinician may guess what is being taken especially with side effects in a placebo controlled trial
- Expensive
  - Blinding versus larger cohort....
- Departs from usual clinical practice
  - Not ‘real world’ which pragmatic trials try to emulate
- Compliance (adherence), especially double dummy.



# Inclusion 4 - Outcomes

- Time to treatment withdrawal
  - Global outcome reflecting seizure control and tolerability
  - Patient participates in decision to withdraw treatment
- Time to 12-month remission
  - Longer term seizure outcome
  - In UK patient allowed to drive if 12 months seizure free
- Time to first seizure
  - Less clinically meaningful but more powerful statistically.

# Time to event data

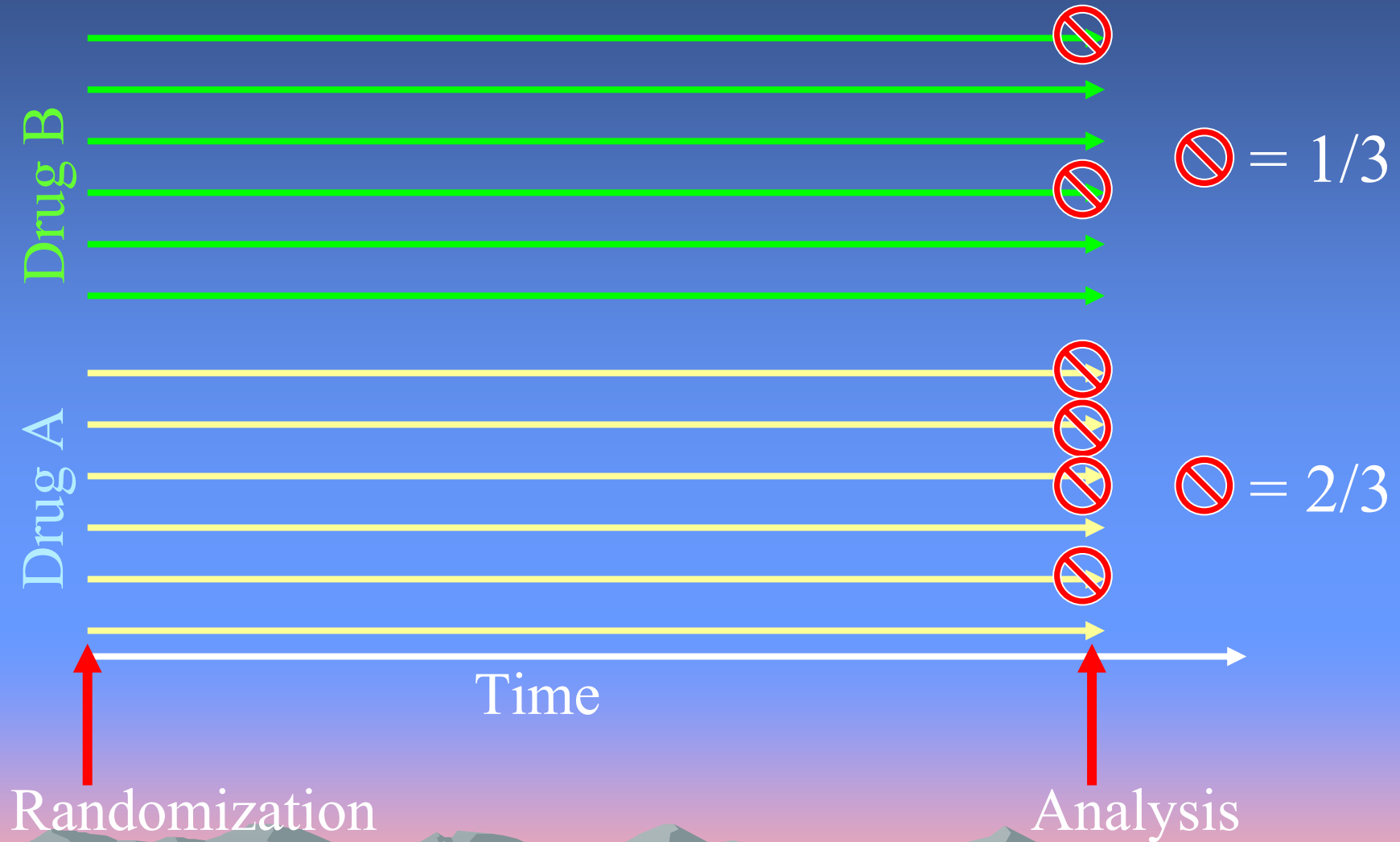


# 'Traditional' Cochrane Review

- Use summary / aggregate data from:
- Published reports
- Original trialists



# Follow-up for a uniform time period



## 2 Treatment group trial

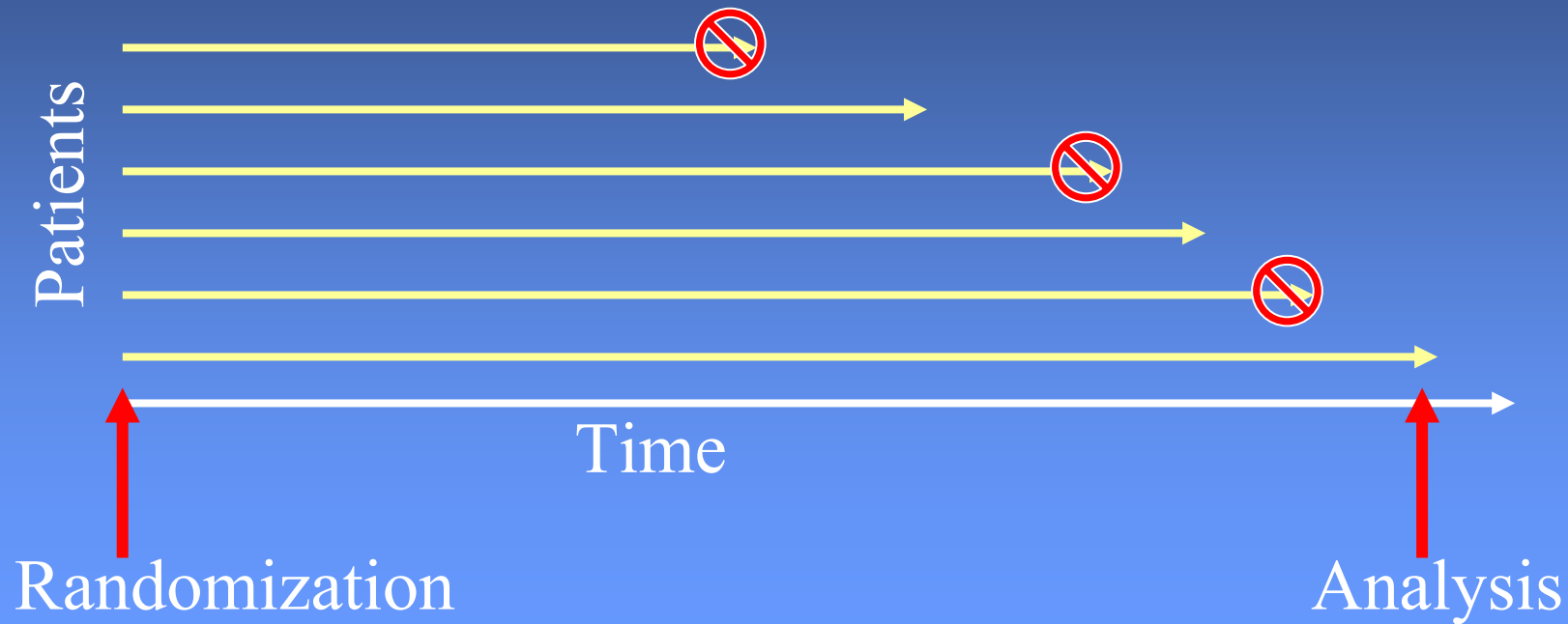
	<b>S u c c e s s</b>	<b>F a i l u r e</b>	<b>T o t a l</b>
<b>T r e a t m e n t 1</b>	a	b	a + b
<b>T r e a t m e n t 2</b>	c	d	c + d

Risk of success: Treatment 1 =  $a/a+b$   
Treatment 2 =  $c/c+d$

Relative risk (trt 1/trt 2) =  $a(c+d)/c(a+b)$

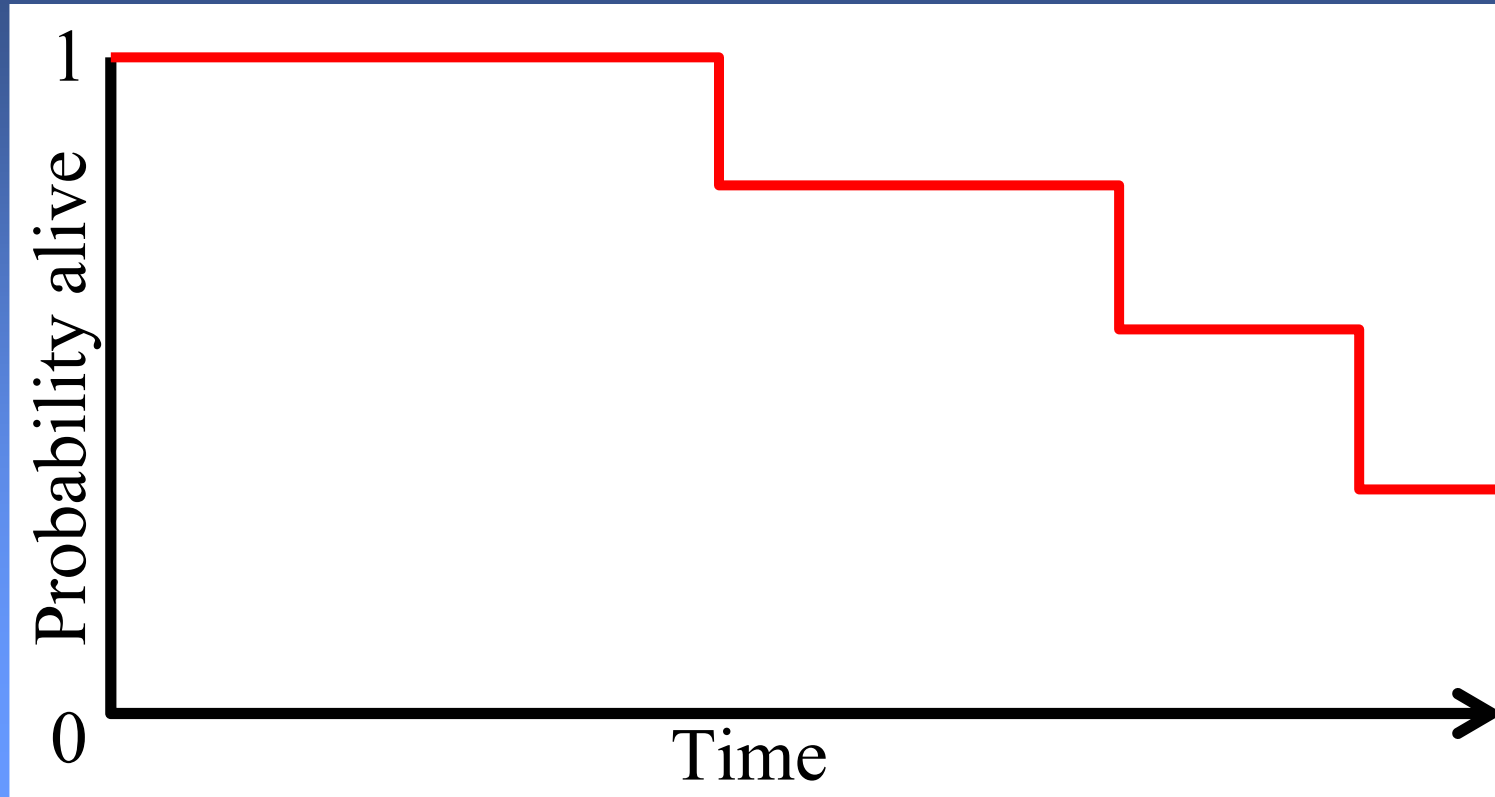
# Time to event data

## Variable follow-up

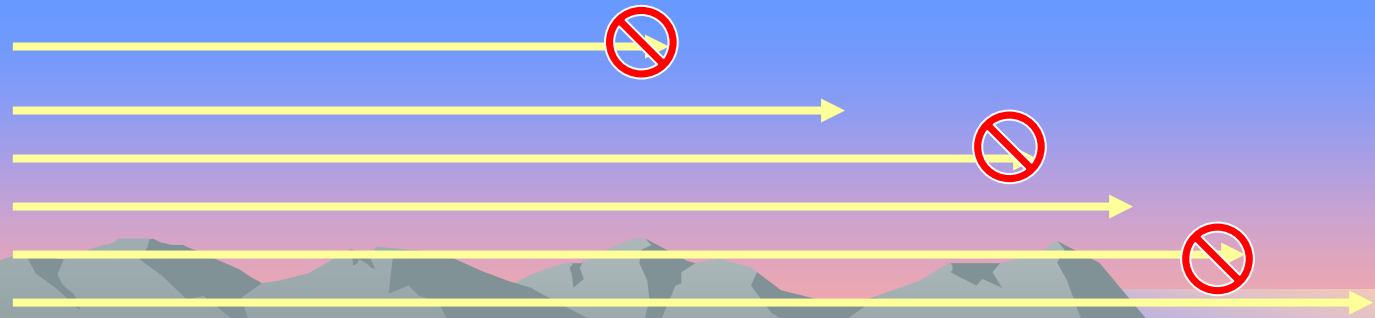


- Analysis requires survival techniques
- Actuarial, Kaplan-Meier

# Kaplan Meier



Patients



# Meta-analysis using individual patient data

- Allows thorough investigation of time to event data
- Requires access to original trial data-sets
- Increased power
- Overcome reporting of different outcomes
- Thorough investigation of treatment epilepsy type interaction

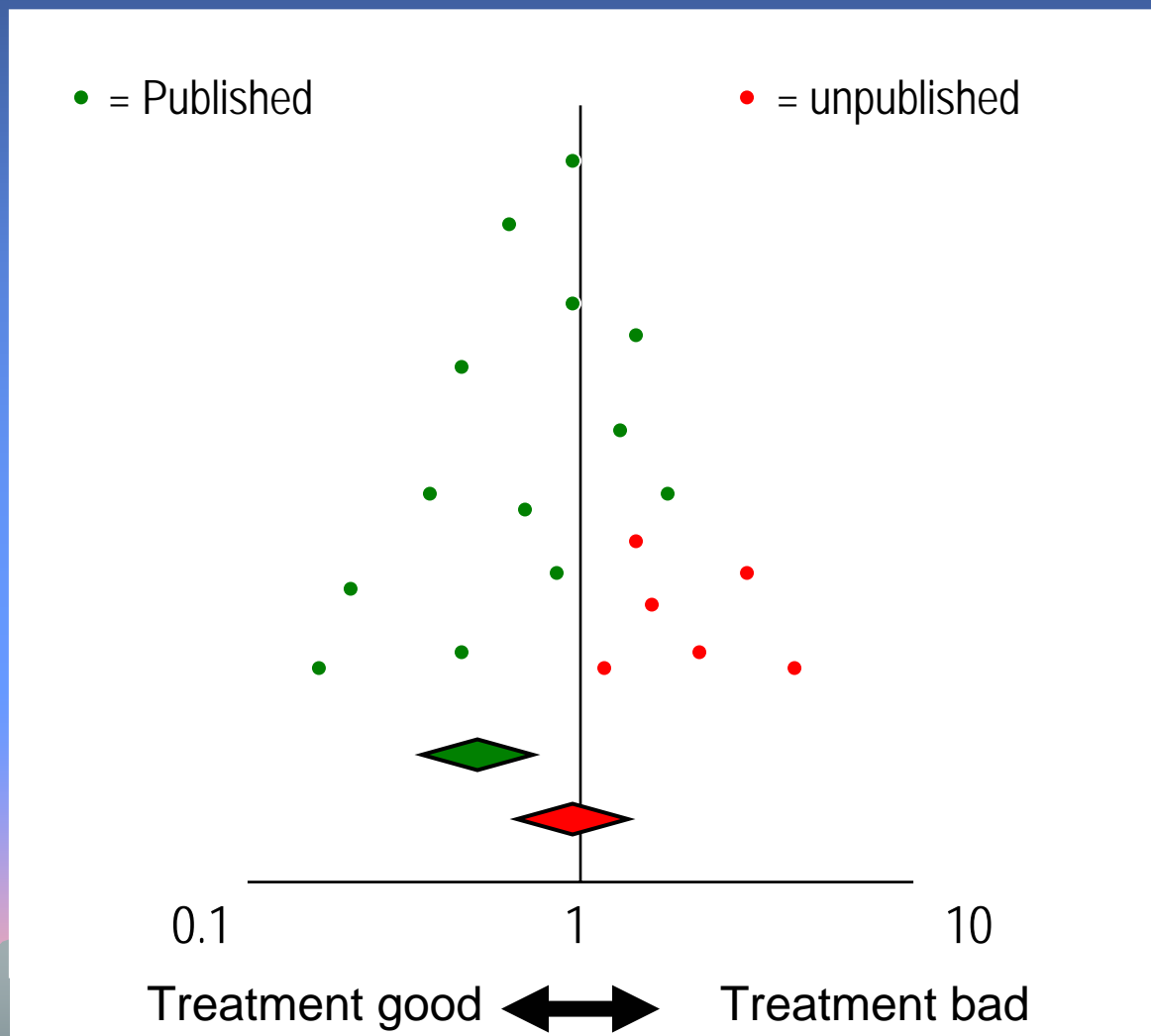
# Outcomes reported

	Treatment withdrawal	12 month remission	First seizure
Heller 1995	N	Y	Y
De Silva 1996	N	Y	Y
Richens 1994	Y	Y	N
Verity 1995	Y	Y	N
Mattson 1992	Y	N	Y
Callaghan 1985	N	N	N
Loiseau 1984	N	N	N
Czapinski 1997	N	N	N

# Search strategy

- Medline 1966 - 2003
- The Cochrane Controlled Trials Register 2003
- Hand searching journals
  - Epilepsy group
  - Collaboration

# Publication Bias



# Results



# Trials comparing carbamazepine and valproate

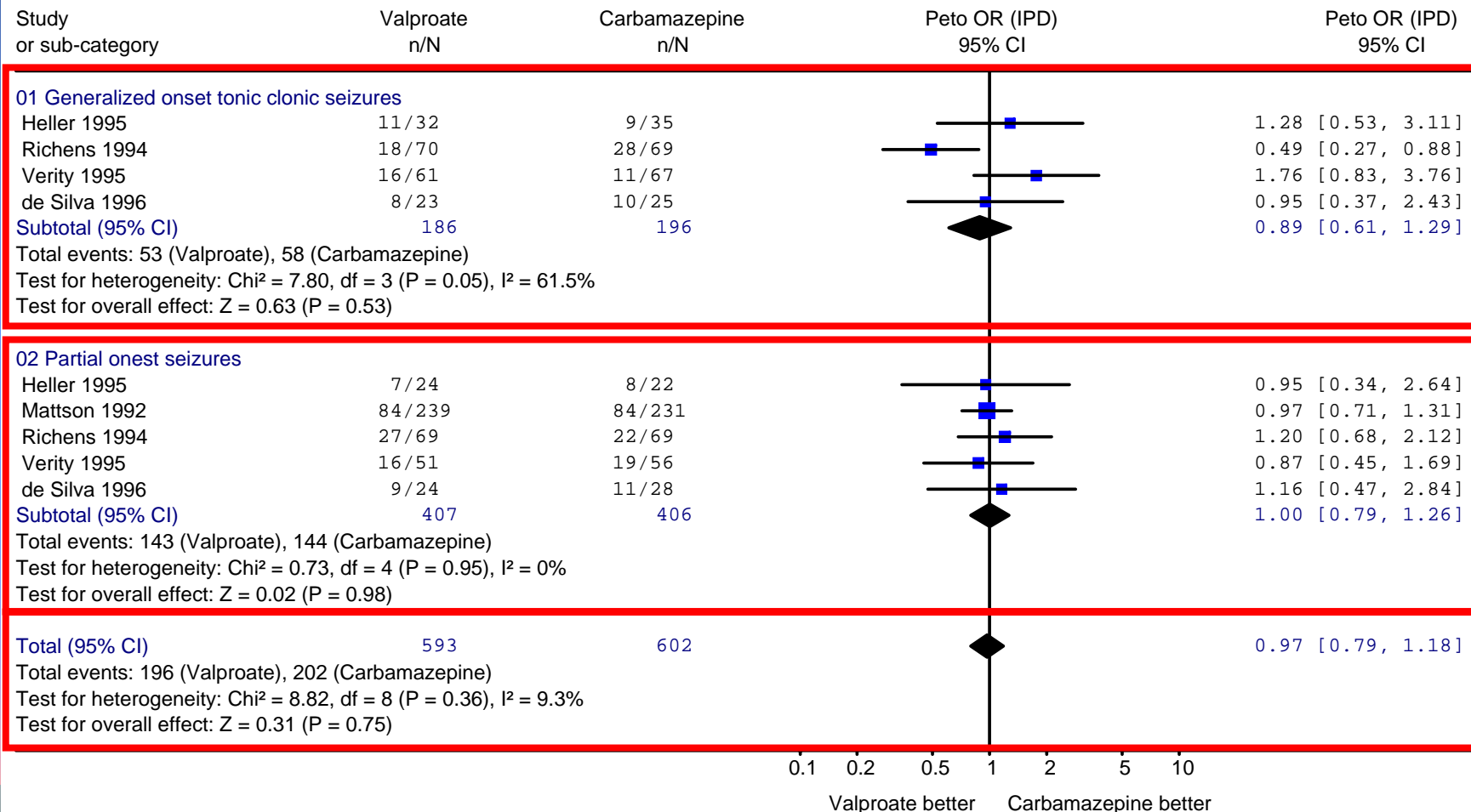
	Randomized	% Partial epilepsy	Age range
<b>Data available</b>			
Heller 1995	122	40	13-70
De Silva 1996	103	55	3-16
Richens 1994	300	51	16-79
Verity 1995	260	46	5-16
Mattson 1992	480	100	18-83
<b>No data available</b>			
Callaghan 1985	123	47	4-75
Czapinski 1997	60	100	18-40
Loiseau 1984	31	100	5-70

# Outcomes reported

	Treatment withdrawal	12 month remission	First seizure
Heller 1995	N	Y	Y
De Silva 1996	N	Y	Y
Richens 1994	Y	Y	N
Verity 1995	Y	Y	N
Mattson 1992	Y	N	Y
Callaghan 1985	N	N	N
Loiseau 1984	N	N	N
Czapinski 1997	N	N	N

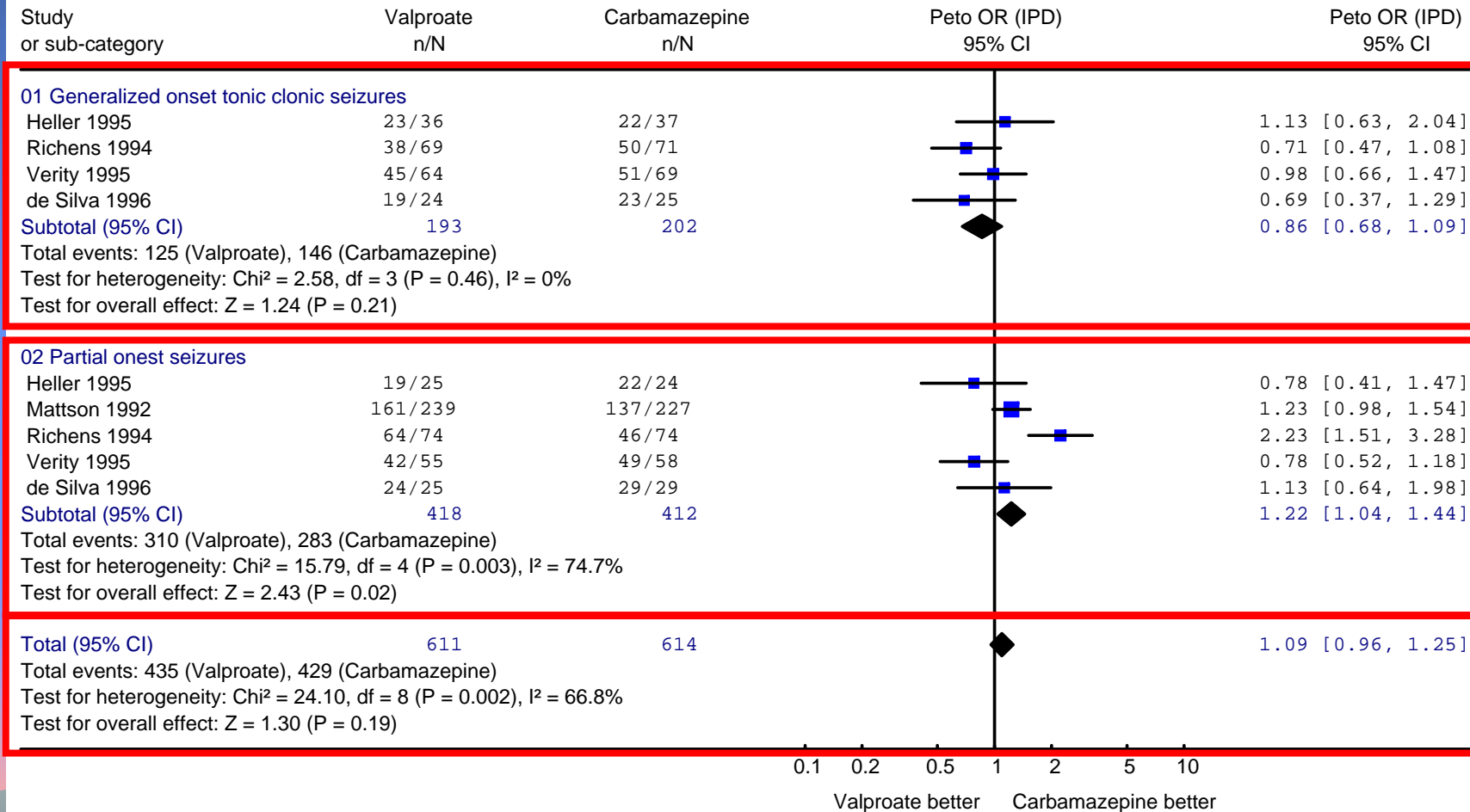
# Time to treatment withdrawal

Review: Carbamazepine vs valproate monotherapy for epilepsy  
 Comparison: 01 Carbamazepine versus valproate  
 Outcome: 01 Time to treatment withdrawal



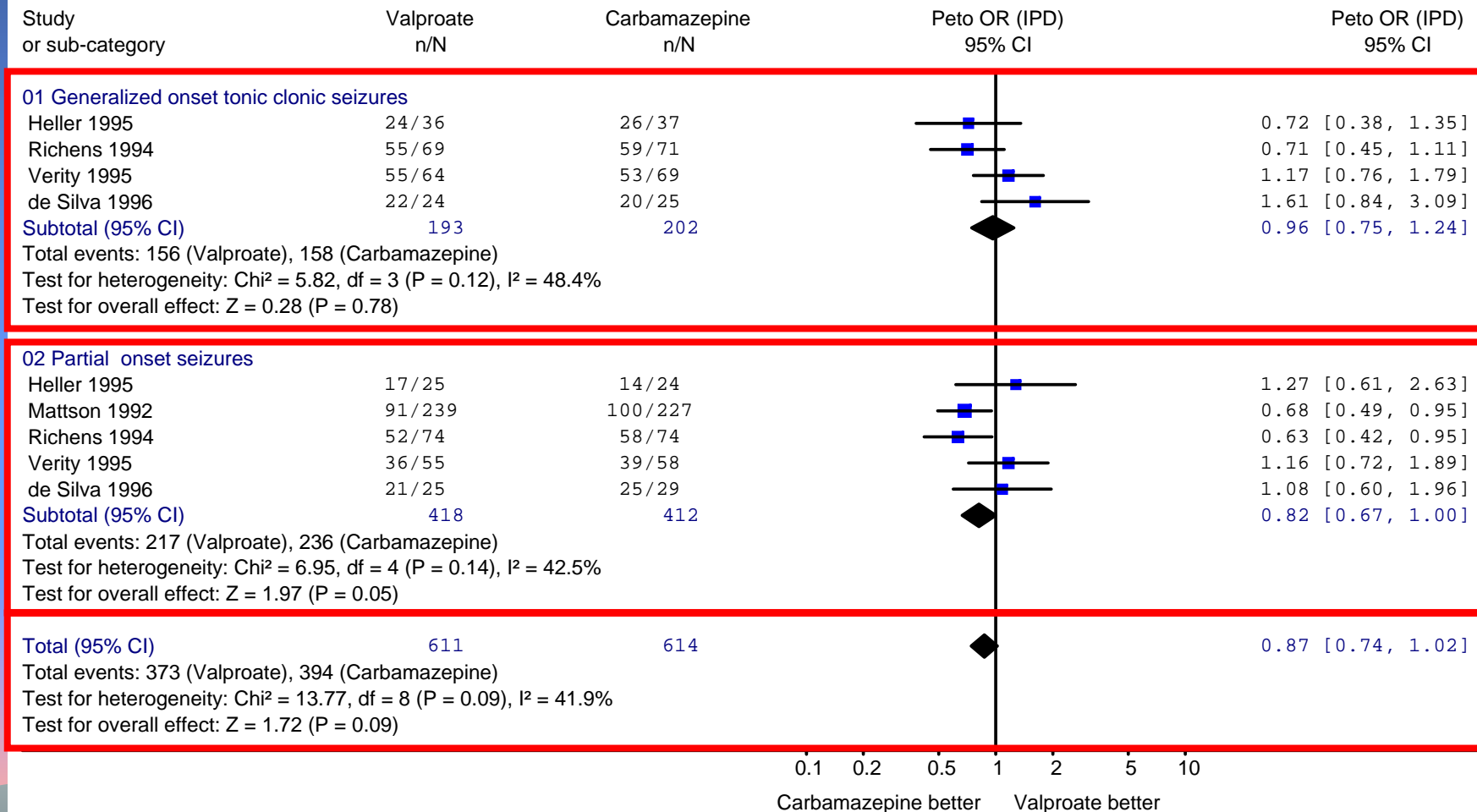
# Time to first seizure

Review: Carbamazepine vs valproate monotherapy for epilepsy  
 Comparison: 01 Carbamazepine versus valproate  
 Outcome: 03 Time to first seizure post randomization



# Time to 12 month remission

Review: Carbamazepine vs valproate monotherapy for epilepsy  
 Comparison: 01 Carbamazepine versus valproate  
 Outcome: 02 Time to 12 month remission from seizures

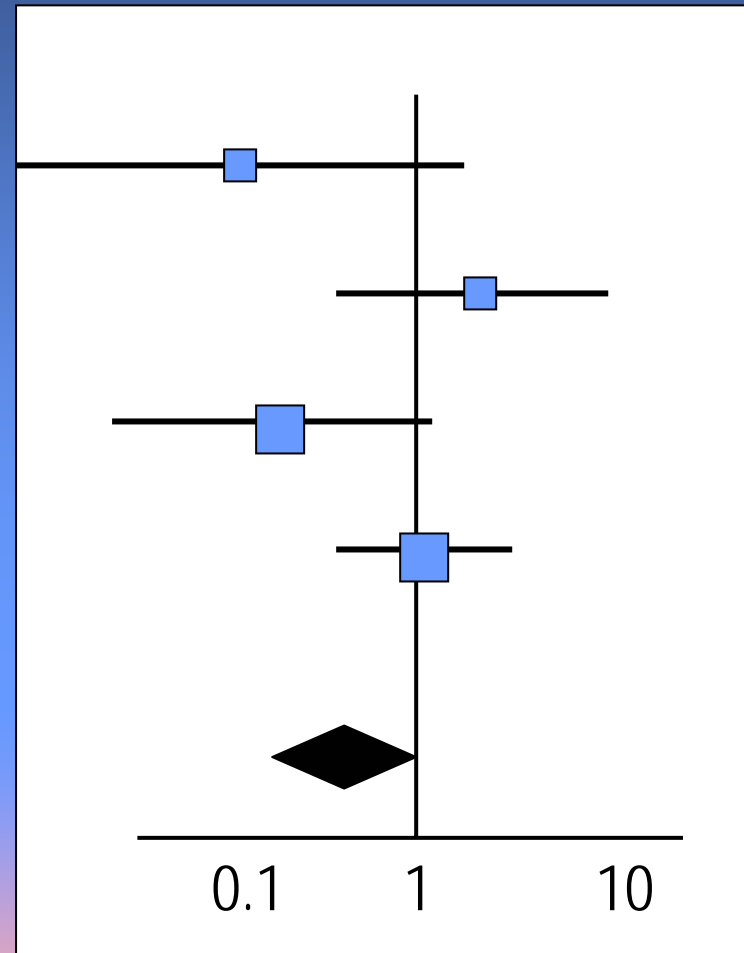
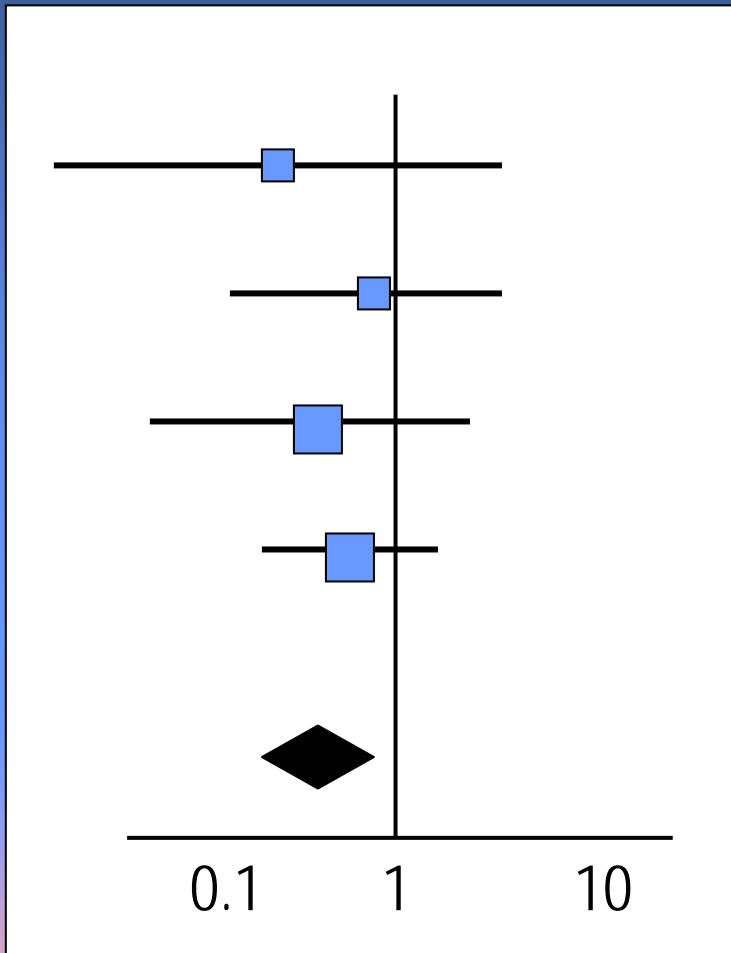


# Heterogeneity for 12 month remission

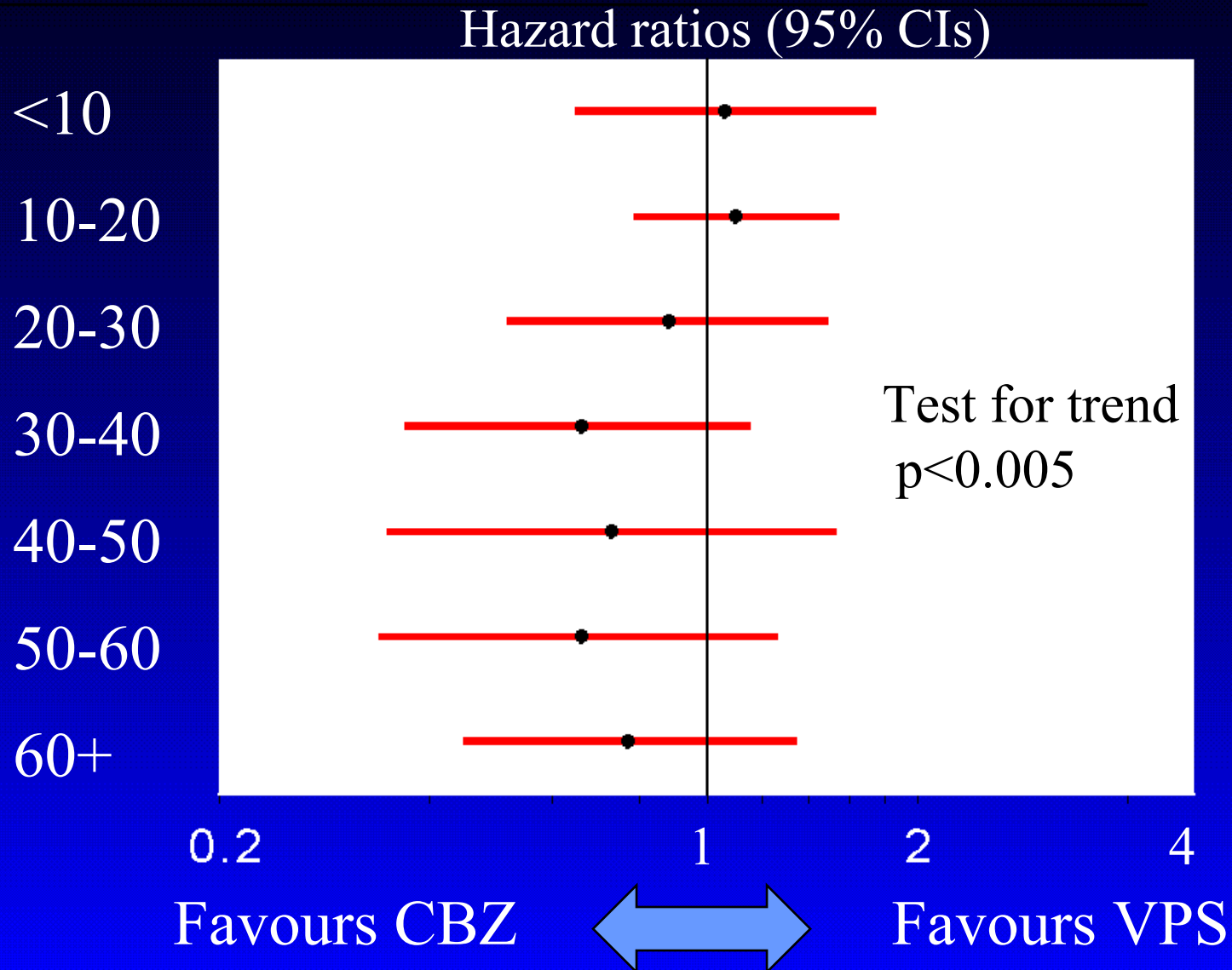
- Some evidence for heterogeneity
- Chi squared  $p=0.09$
- I squared = 41.9%



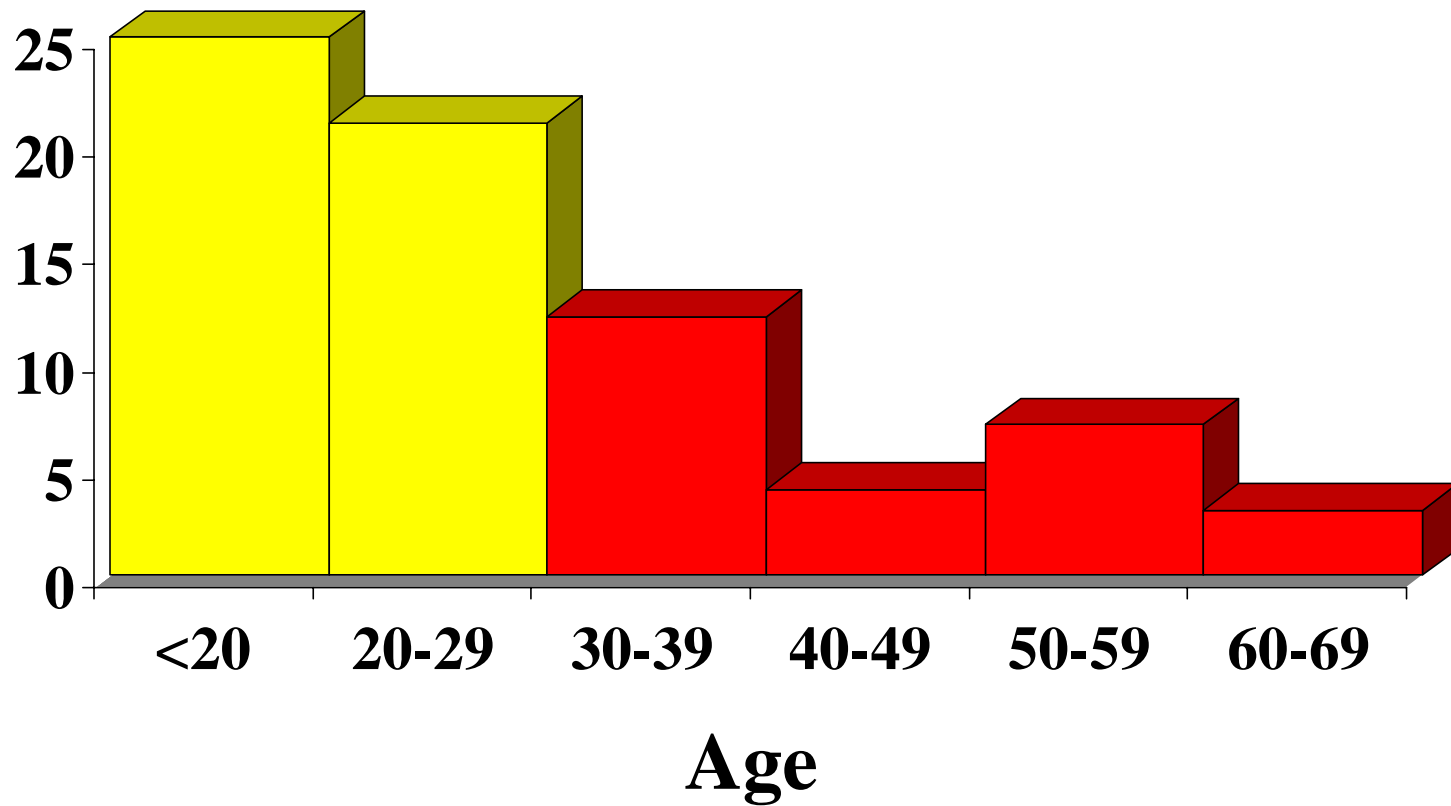
# Heterogeneity



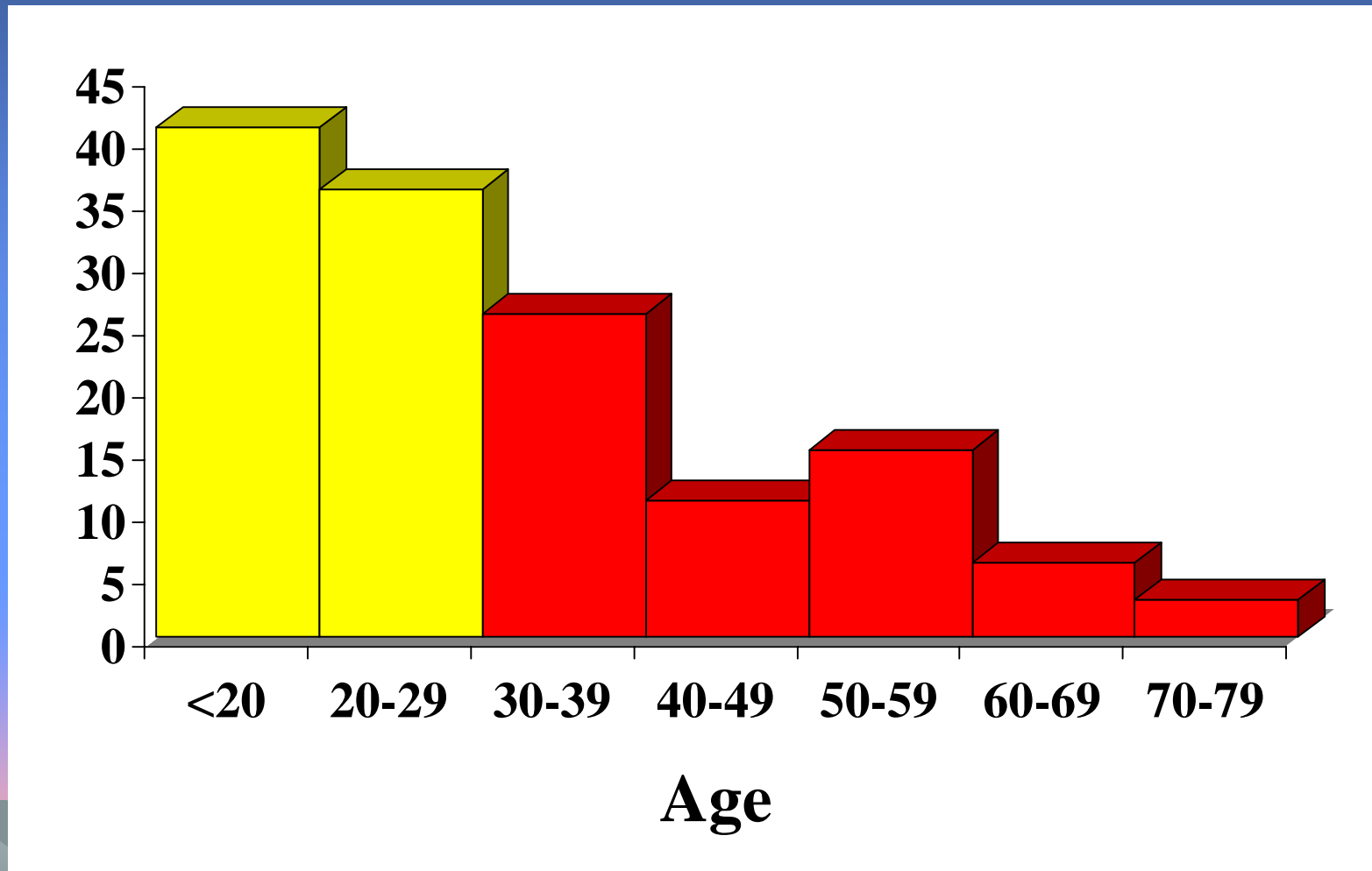
# Hazard ratios for 12 month remission at differing ages



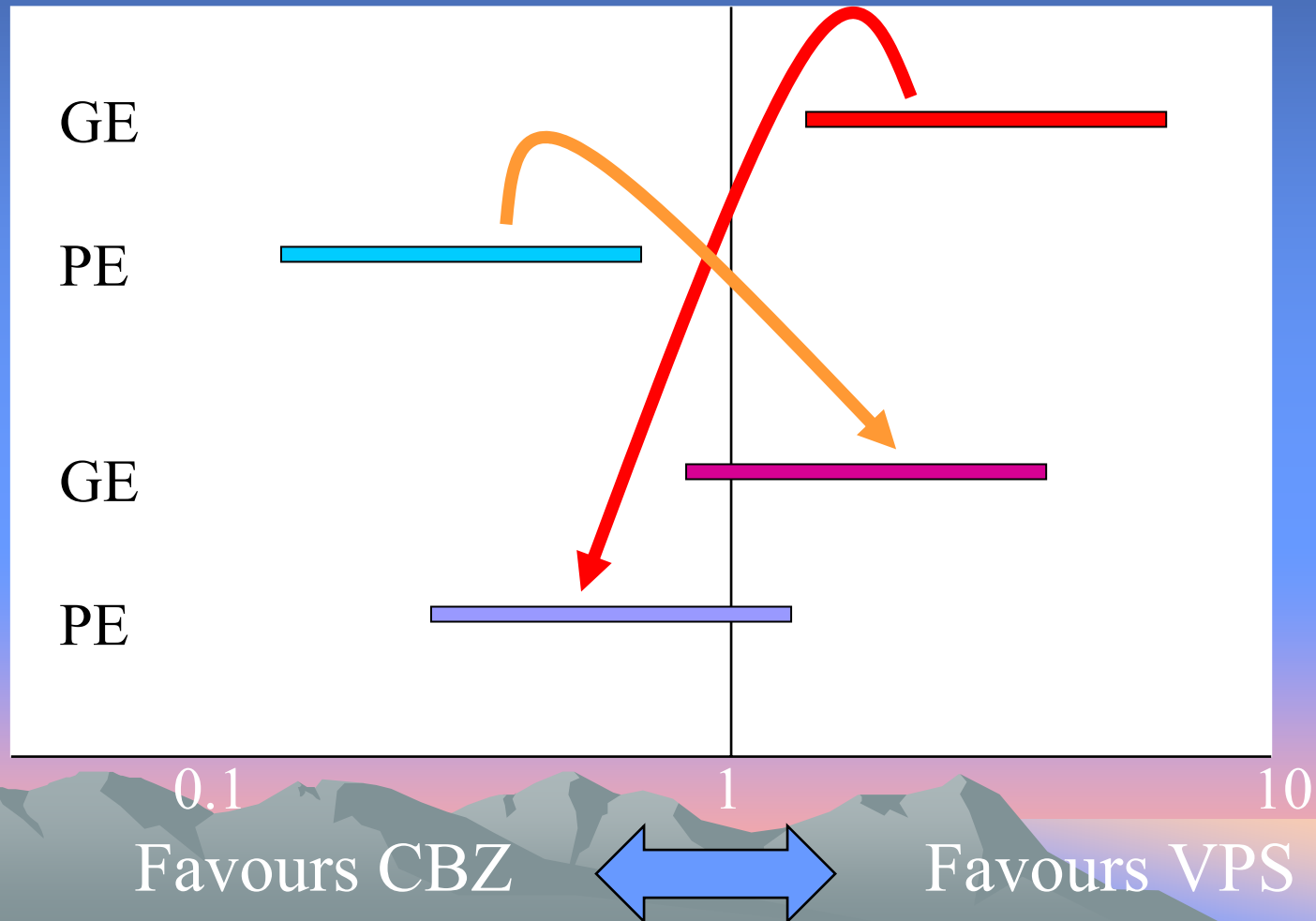
# Age at randomization for patients with GTCS Heller 1995



# Age at randomization for patients with GTCS Richens 1994



# Consequences of misclassification



# Consequences for practice

- Evidence to support the use of carbamazepine for patients with partial onset seizures
- No evidence to support or overthrow current use of valproate for patients with generalized onset tonic clonic seizures



# Lessons for designing future trials

- Differences between antiepileptic drugs are likely to be small
- Large trials needed to detect those differences
- Consider designing to detect equivalence



# More lessons for future trials

- Test for interactions between treatments and epilepsy types
- Patients will need to be adequately classified and systems established to check this
- Clinicians must be allowed to express uncertainty about classification at randomization



# Questions?



# Summary

- Trial methods
  - Randomization and blinding
- Systematic review methods
  - Defining inclusion criteria
  - Search
  - Individual patient data approach
  - Meta-analysis plots
  - Heterogeneity

# Summary

- Systematic review of trials comparing carbamazepine and valproate
- Summarises existing best evidence in one place
- Provides evidence to inform practice
- Highlights issues that must be dealt with in future trials