

お招きいただきまして
ありがとうございます

Can We Trust the Clinical Trials?

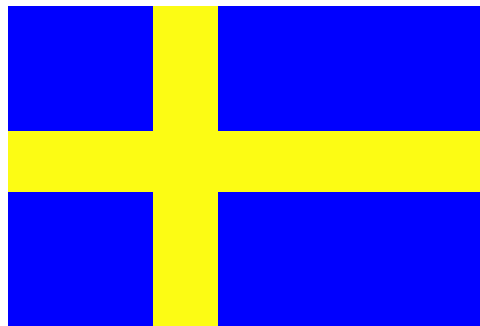
Björn Beermann,

MD, PhD, Professor

Medical Products Agency

Uppsala

Sweden



Can We Trust the Clinical Trials?

Yes, if they are performed
according to GCP etc
BUT

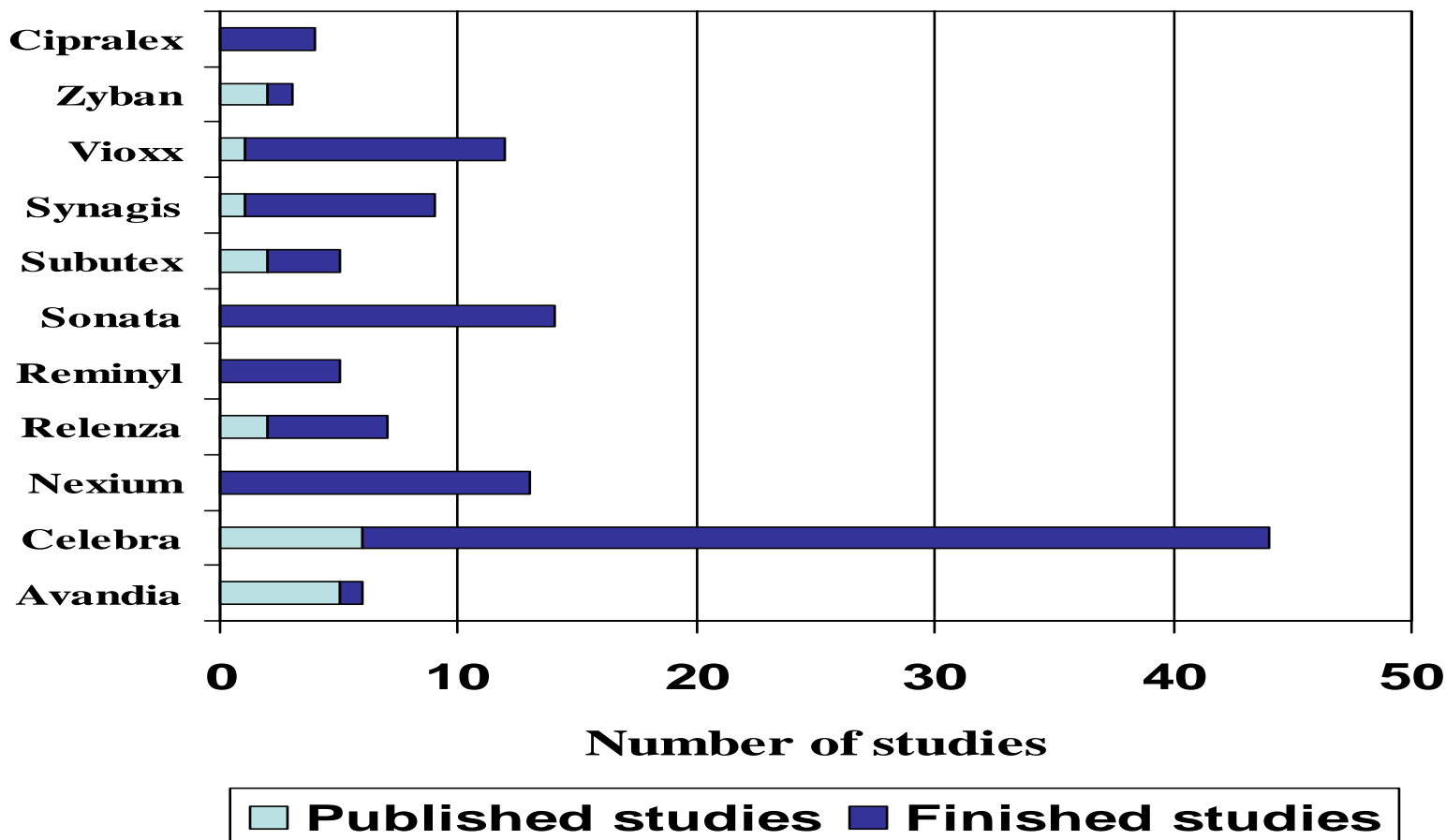
But do we get the results of all of
them?

**Publication bias,
a clinical, scientific and ethical
problem**

New Drugs

**To which extent are the results of finished
Clinical trials of new drugs available for the
Health care system at the time of approval?**

Very Few Studies Have Been Published at the Time of Approval!

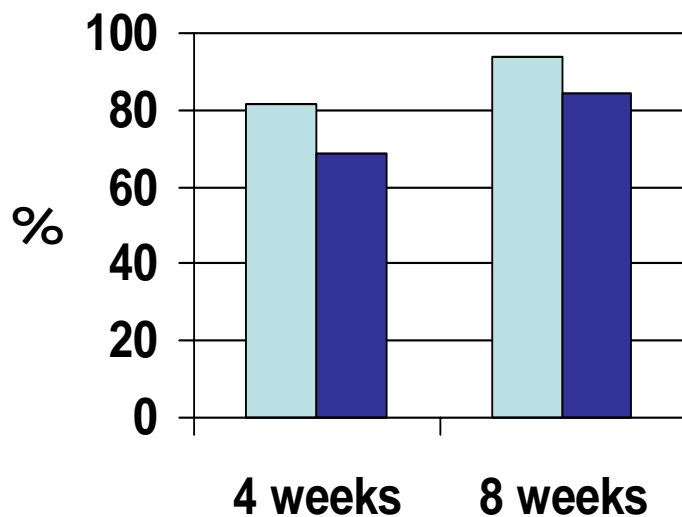


How are clinical studies published?

- Timing of publishing?
- What is published?
 - Positive/negative studies
- How are the results presented?
- Influence of the sponsor?
- Influence of the language?

Timing of publication

Healing of esophageal ulcer



 Nexium 40 mg  Losec 20 mg

4_v VS 8_v

Nexium 40 mg i 4 veckor ger total utläkning för drygt 80 % av patienterna vid refluxesofagit⁽¹⁾.


20 mg omeprazol i 8 veckor ger total utläkning för drygt 80 % av patienterna vid refluxesofagit⁽¹⁾.

Våra forskare har lyckats separera den mest potenta isomeren i omeprazol⁽²⁾; Nexium. Detta innebär att vi nu kan presentera den första protonpumpshämmaren som utnyttjar sin fulla potential.

Detta i sin tur gör det möjligt för dina refluxpatienter att bli läkta på 4 i stället för 8 veckor jämfört med den vanligaste protonpumpshämmaren från slutet av 1900-talet⁽¹⁾. Möjligheten till kortare behandlingstid innebär i praktiken att både patienterna och samhället kan spara pengar. Ännu ett argument för Nexium.

För komplett katalogtext se denna plats i denna tidning.

Ref. 1. Richter J et al. Gastroenterology 2000;118(suppl 3):A1035.
2. Anderson T et al. Gastroenterology 2000;118(suppl 3):A1035.



NexiumTM

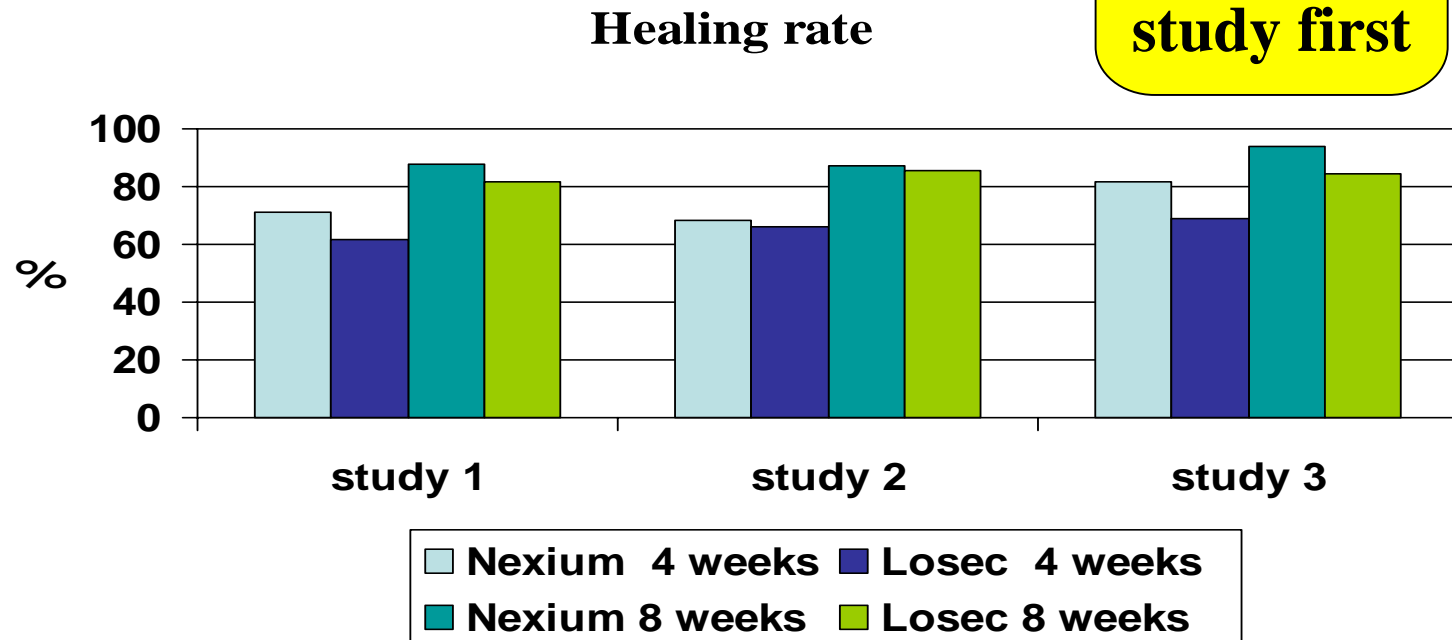
esomeprazol

– full potential

Hässel Läkemedel AB, 431 86 Mölndal. Tel 031-776 35 00. Fax 031-776 35 01. www.nexium.nu

Nexium 40 mg vs Losec 20 mg in the treatment of esophageal ulcers

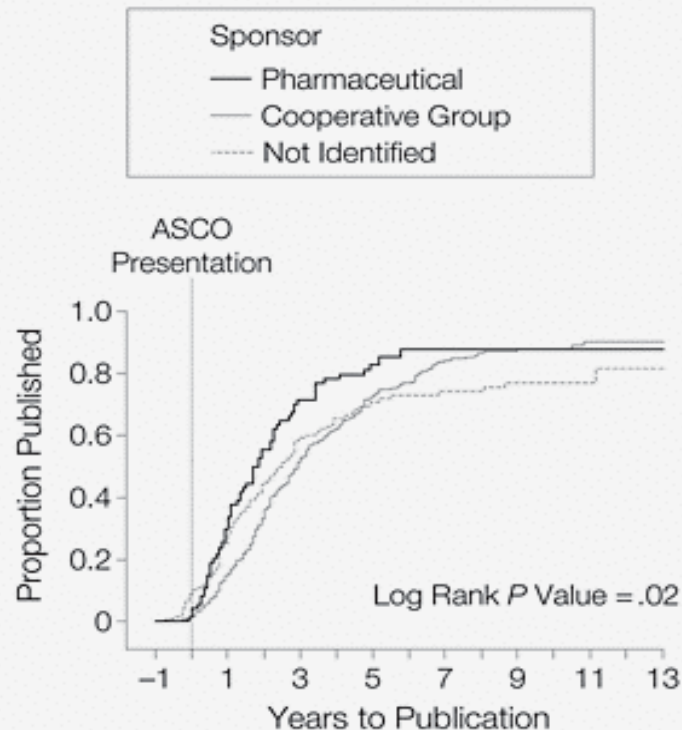
**We publish
this
study first**



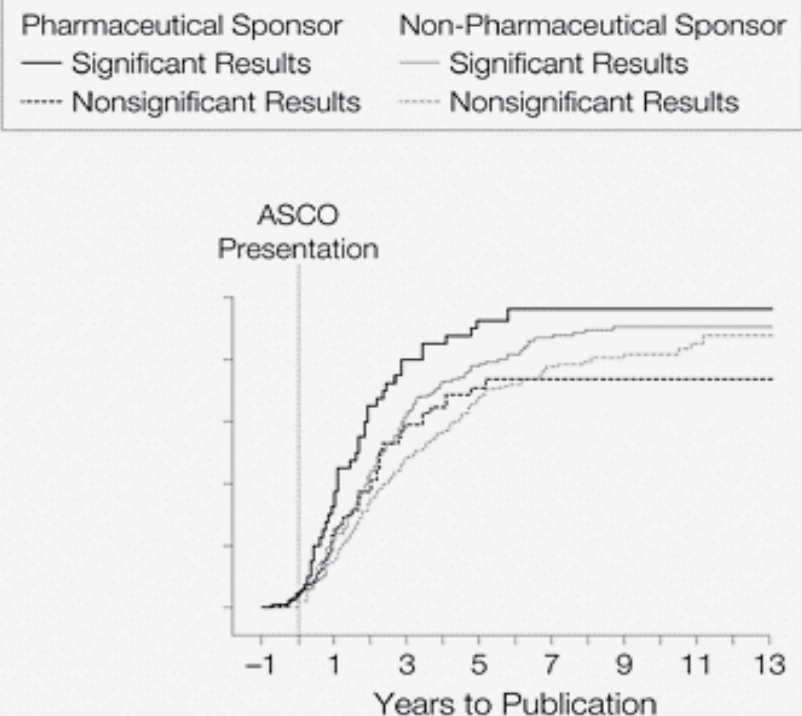
Time pattern of publication of RCT:s presented at ASCO 1989-1998

JAMA 2003;(290) 495-501

A Time to Publication by Sponsorship



B Time to Publication by Type of Result and Sponsorship

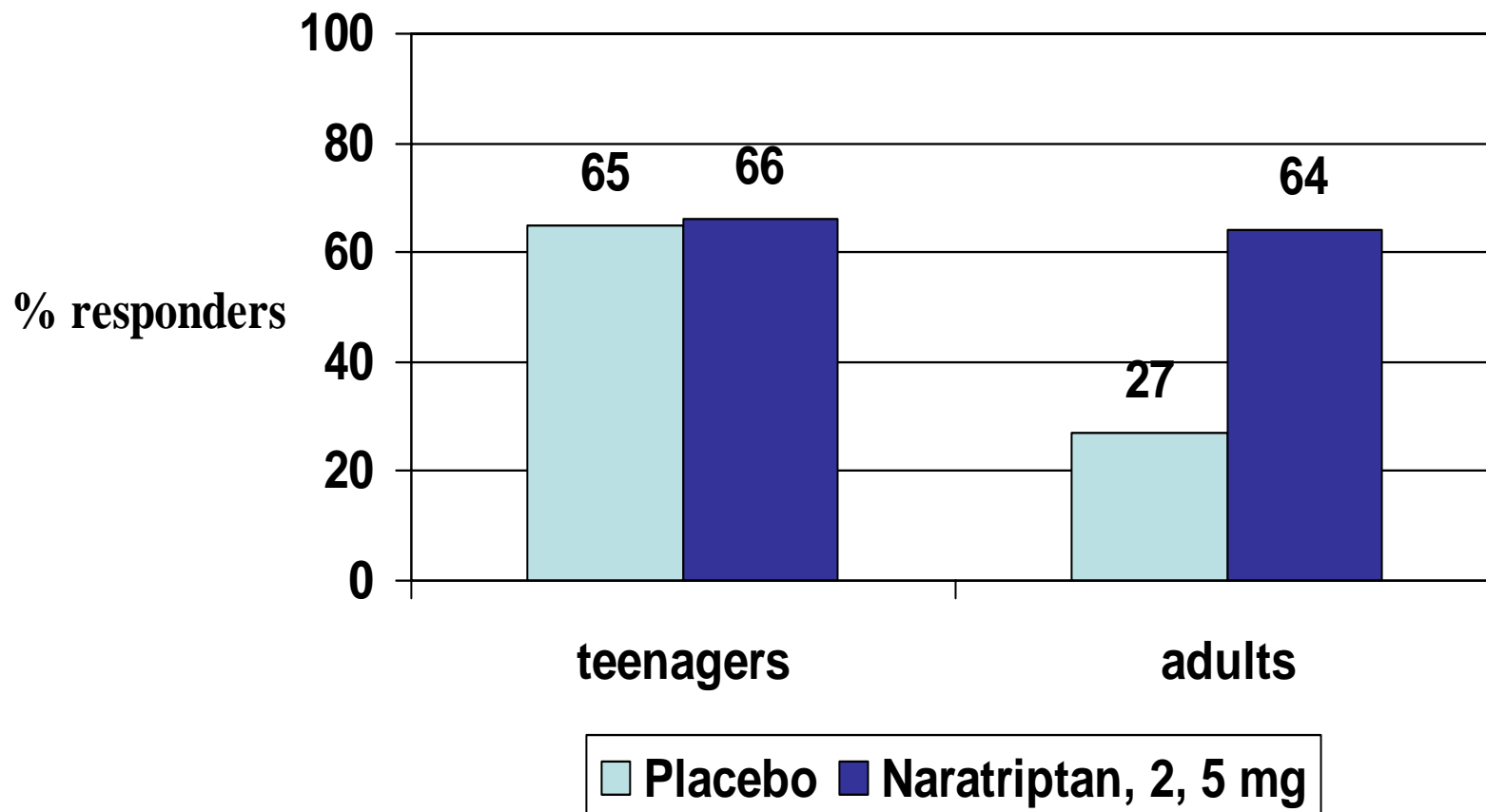


Publication of positive/negative trials

The case of triptans.

- **Neurologists at an expert meeting about migraine:**
 - **Triptans can be recommended to teenagers even if it stated i PDR that the age group has not been studied.**

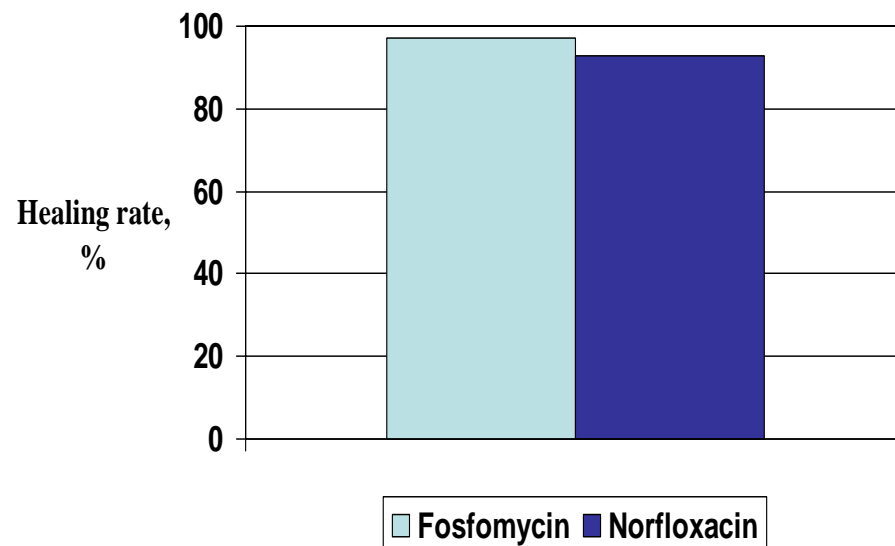
Response rate at two hours in teenagers and adults when treating attacks of migraine with naratriptan (unpublished data)



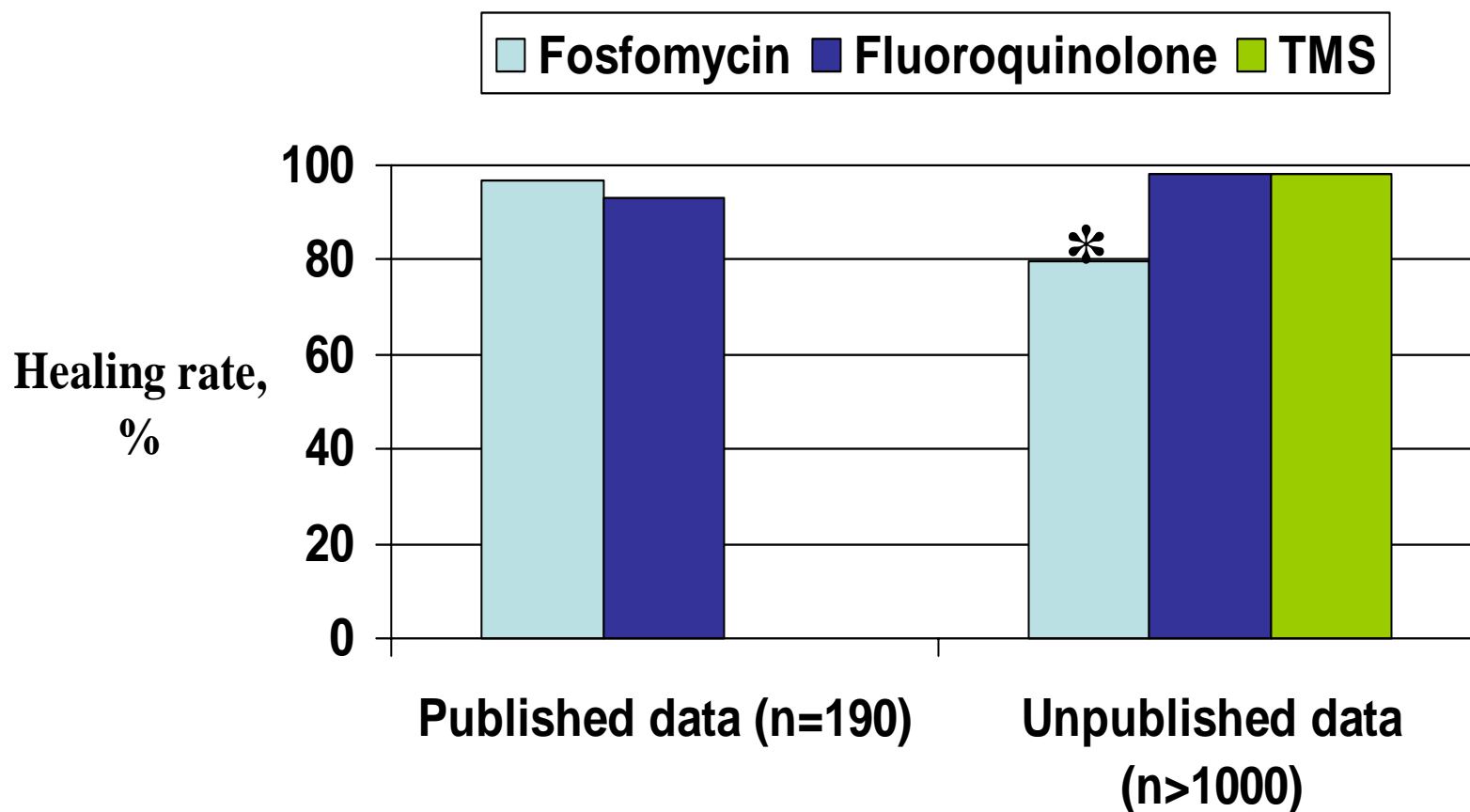
The Case of fosfomycin, treatment of lower urinary tract infection (LUTI) in women

Three reviews:

- “.suggest....is as clinically effective as...”
- “It is as effective and safe as...”
- “..99% clinically cured or improved..”

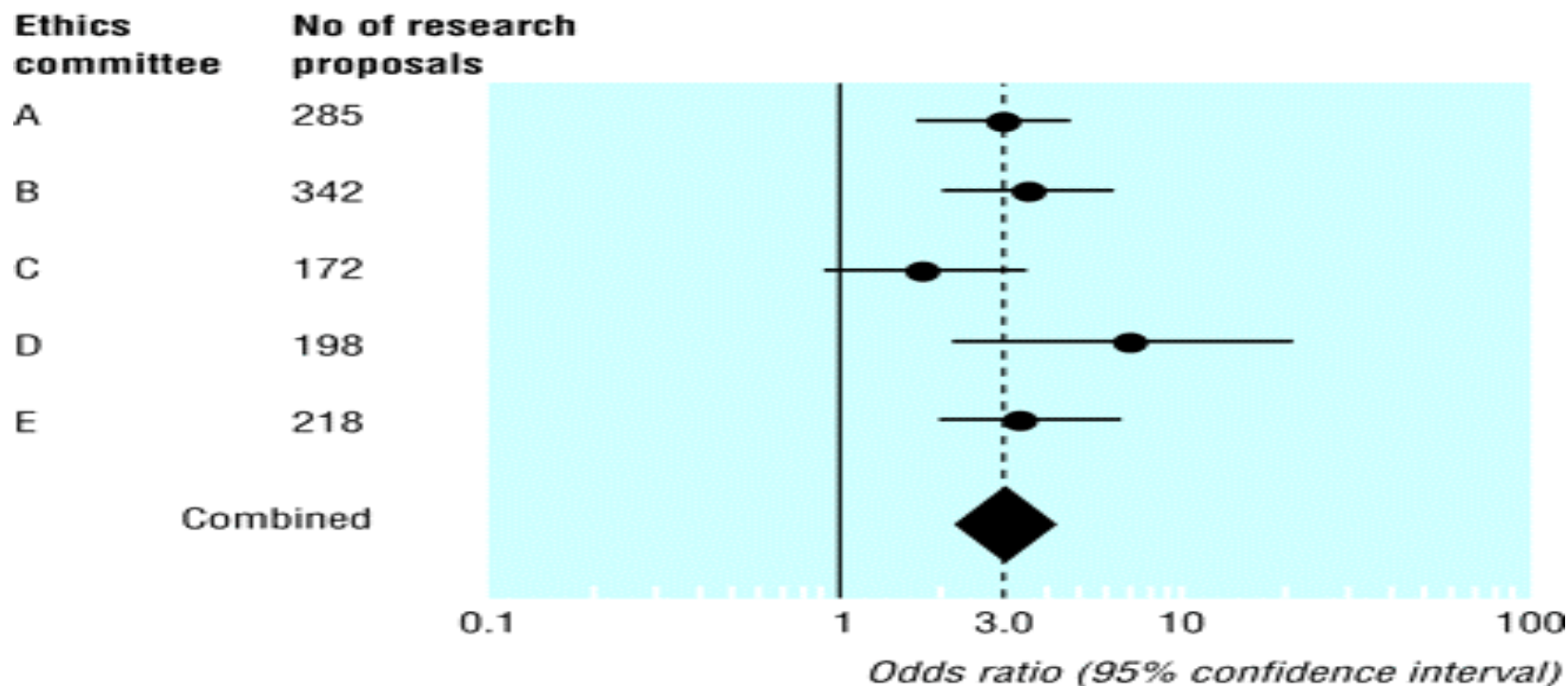


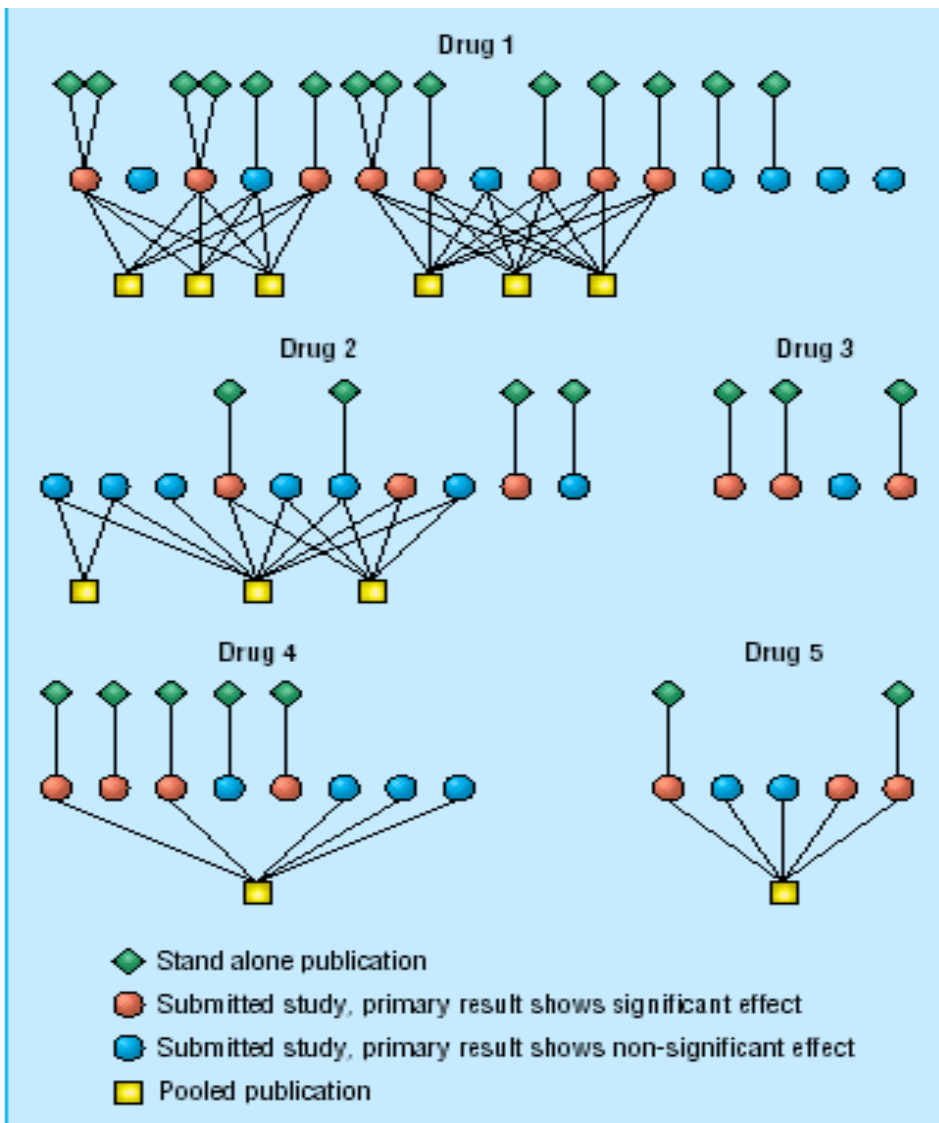
Fosfomycin in LUTI



Odds ratios for publication of studies with positive result vs negative result approved by 5 ethics committees

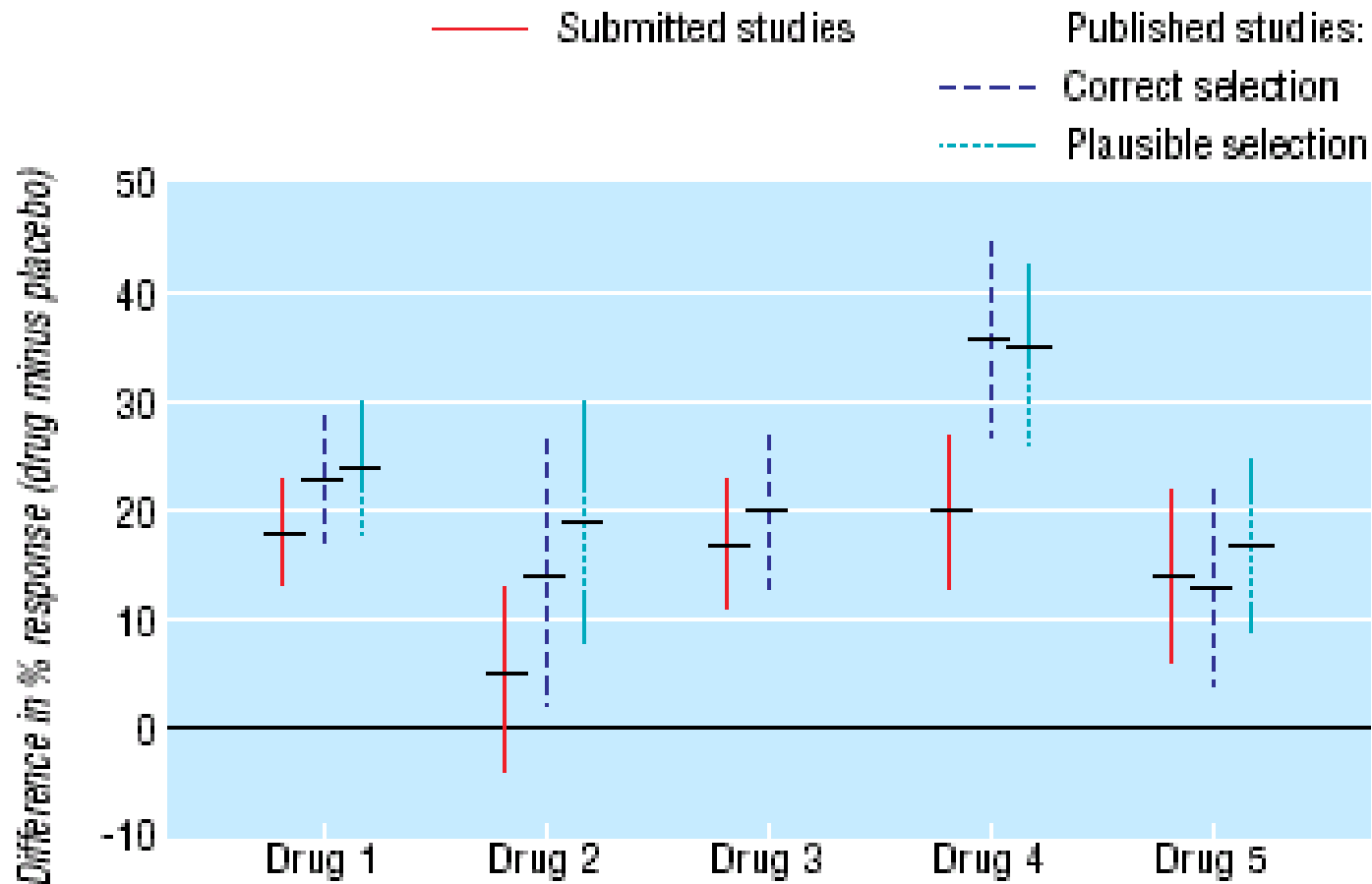
Egger et al 2001, BMJ Books





Publication pattern for studies of the five selective serotonin reuptake inhibitors approved in Sweden between 1989 and 1994 for treating major depression

BMJ 2003; 326: 1171-1173

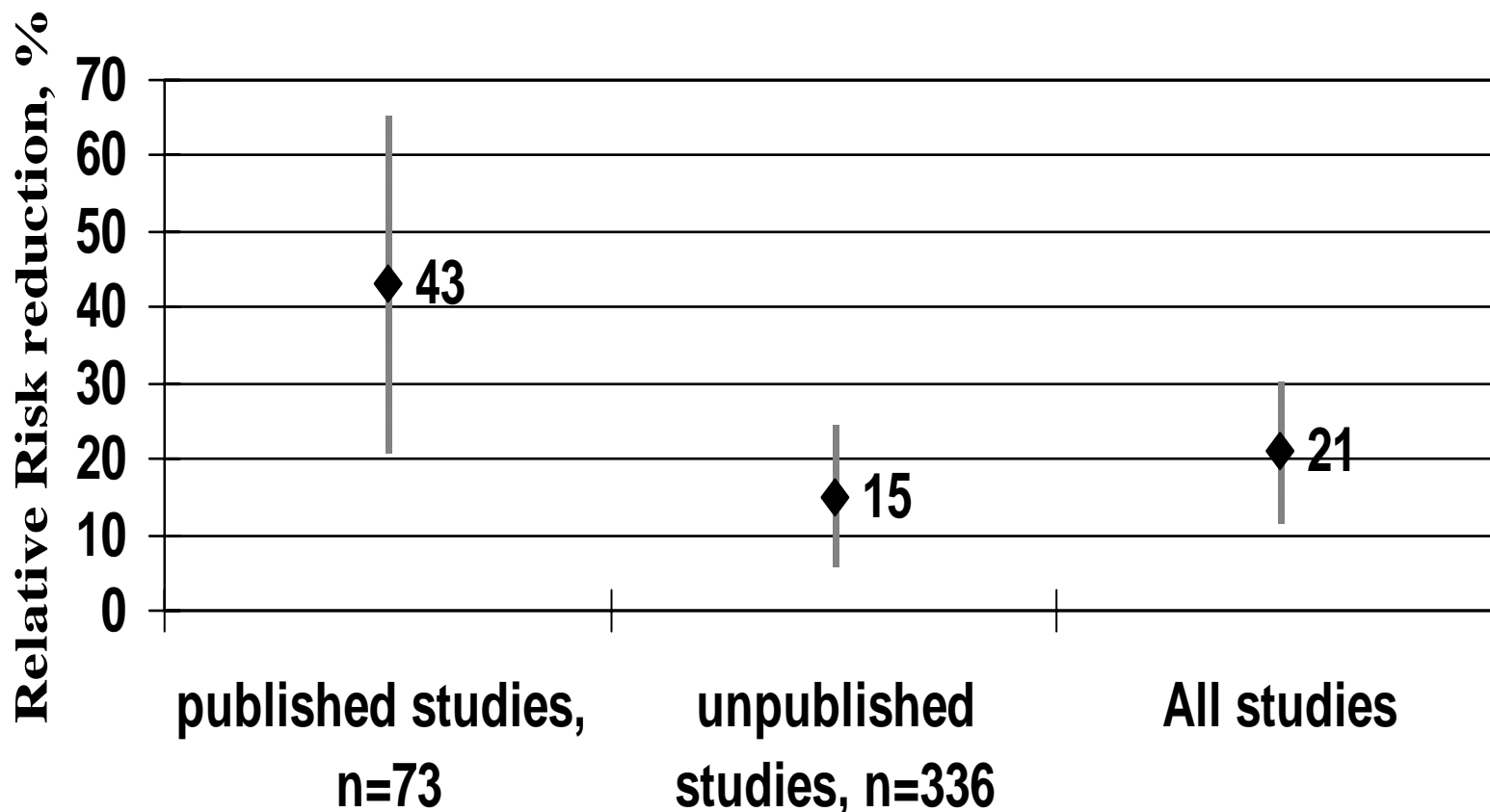


Differences (95% confidence intervals) in response rate (% response to drug minus response to placebo). Results from pooled analyses of all submitted studies, correct selection of published studies (duplicates excluded), and plausible selection of published studies (including probably undetectable duplicates) *BMJ 2003; 326: 1171-1173*

Quinine in the Treatment of Leg Cramps

Relative Risk Reduction (95%CI)

J Gen Int Med 1998;13;600

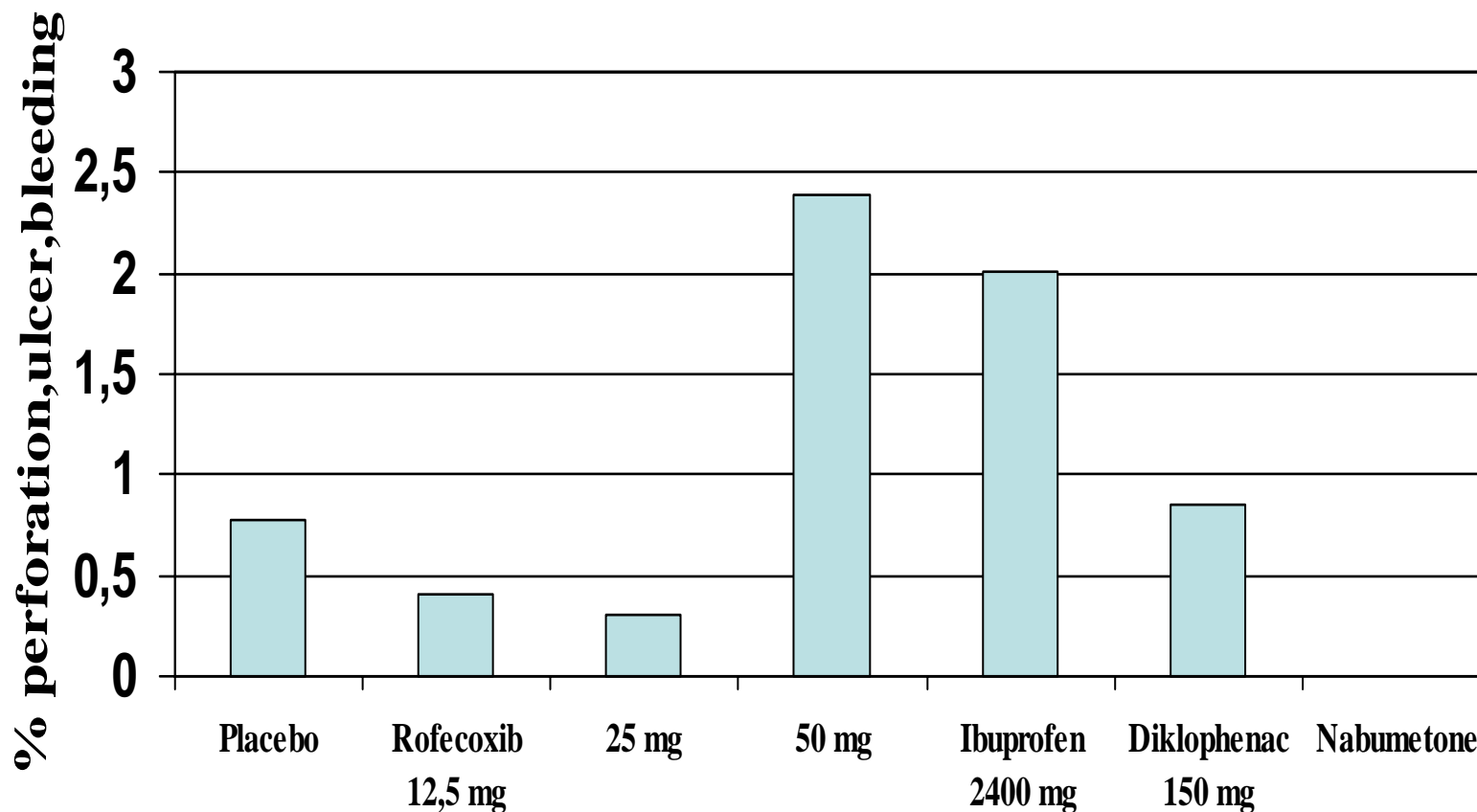


Anti-inflammatory and Upper Gastrointestinal Effects of Celecoxib in Rheumatoid Arthritis

Results The incidence of PUB (*perforation, ulcer, bleeding*) over 12 months was significantly lower with rofecoxib vs NSAIDs (rate per 100 patient-years, 1.33 vs 2.60; relative risk, 0.51; 95% confidence interval, 0.26-1.00).

Conclusion In a combined analysis of 8 trials of patients with osteoarthritis, treatment with rofecoxib was associated with a significantly lower incidence of PUBs than treatment with NSAIDs.

The truth behind the study in JAMA

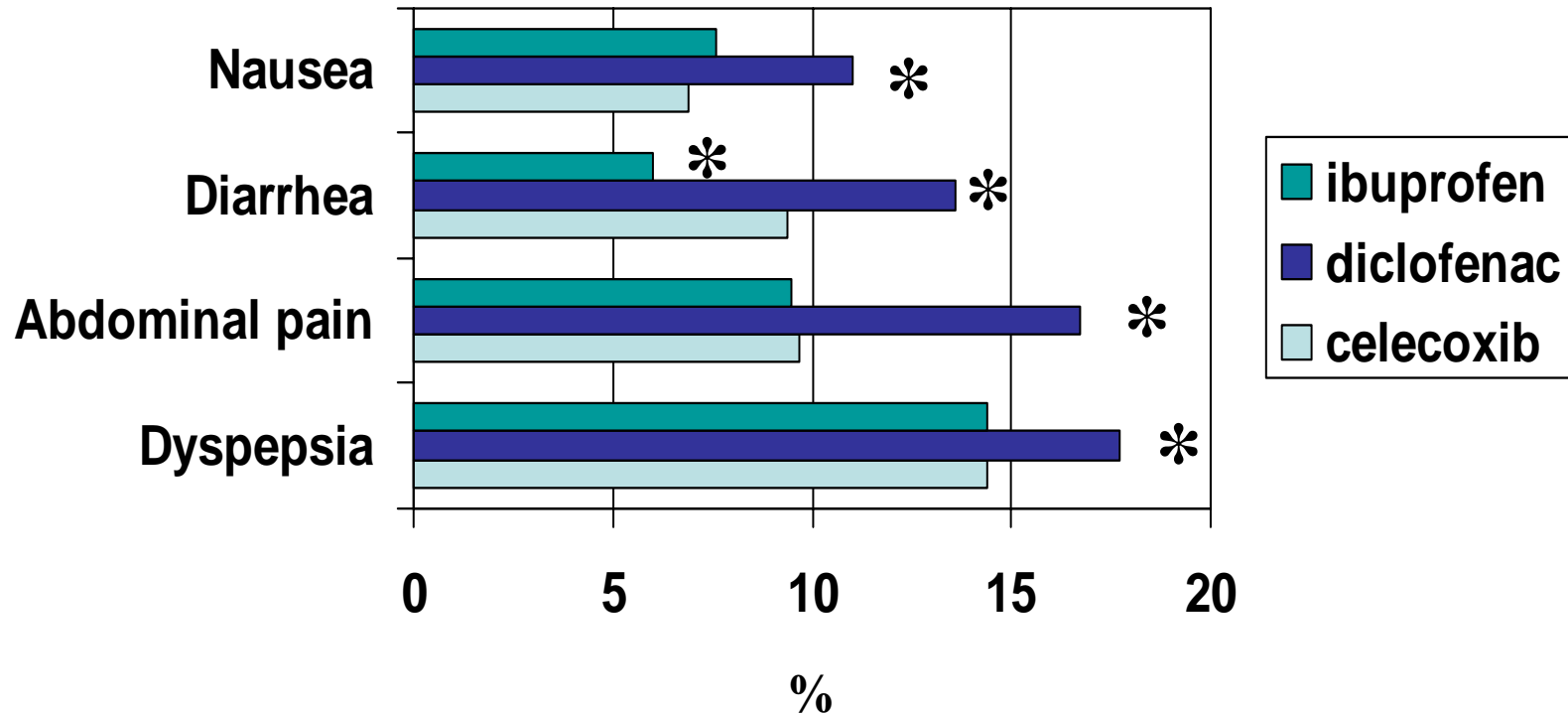


The CLASS study

JAMA 2000;284;1247-1255

- Combination of two studies (4000 patients each)
 - Celecoxib vs diclofenac
 - Celecoxib vs ibuprofen
- Primary endpoint in the two studies
 - Gastric ulcer bleeding and/or perforation at 12 months
- CONCLUSIONS: In this study, **celecoxib**, at dosages greater than those indicated clinically, was associated with a **lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages.**

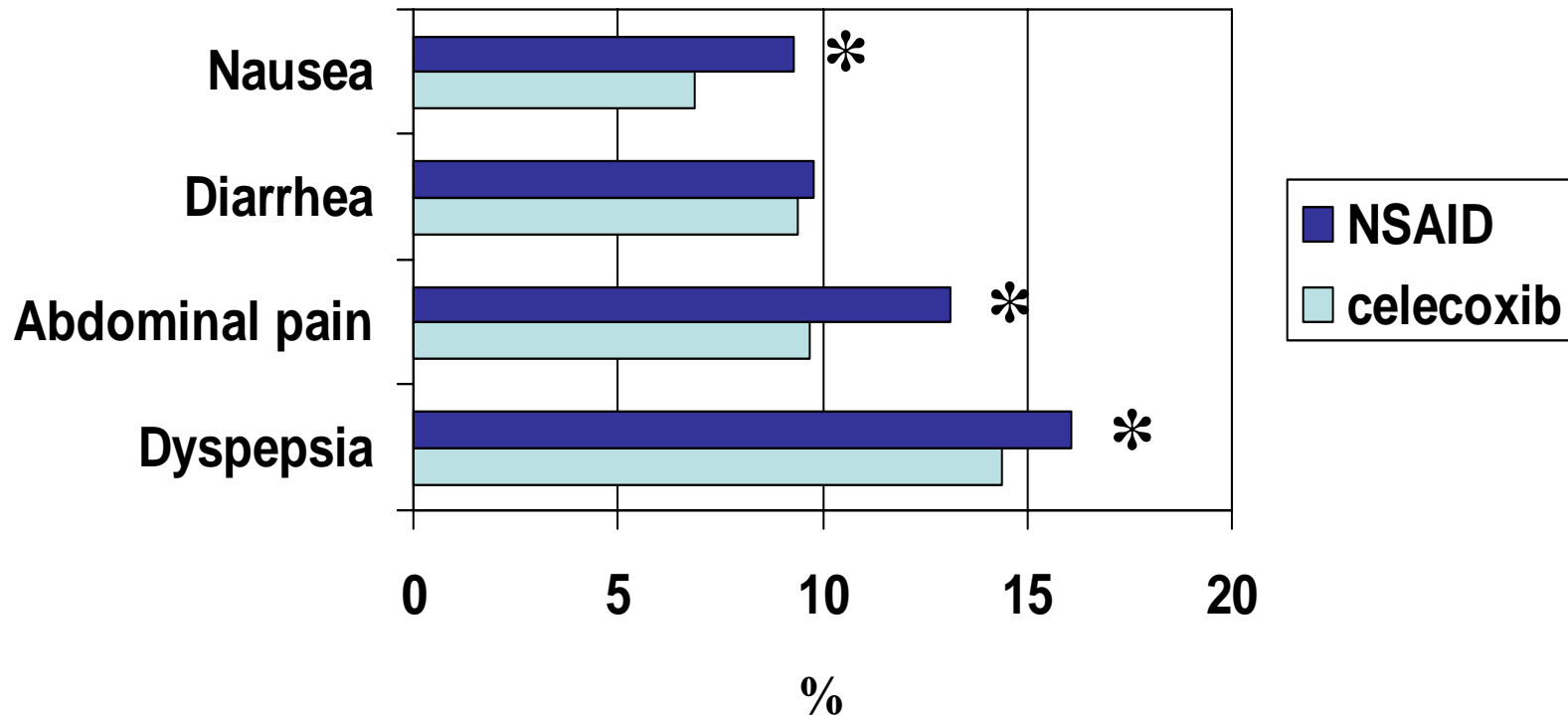
The Class study - Follow up at 6 Months Submitted Documentation to MPA



The CLASS study as presented in JAMA

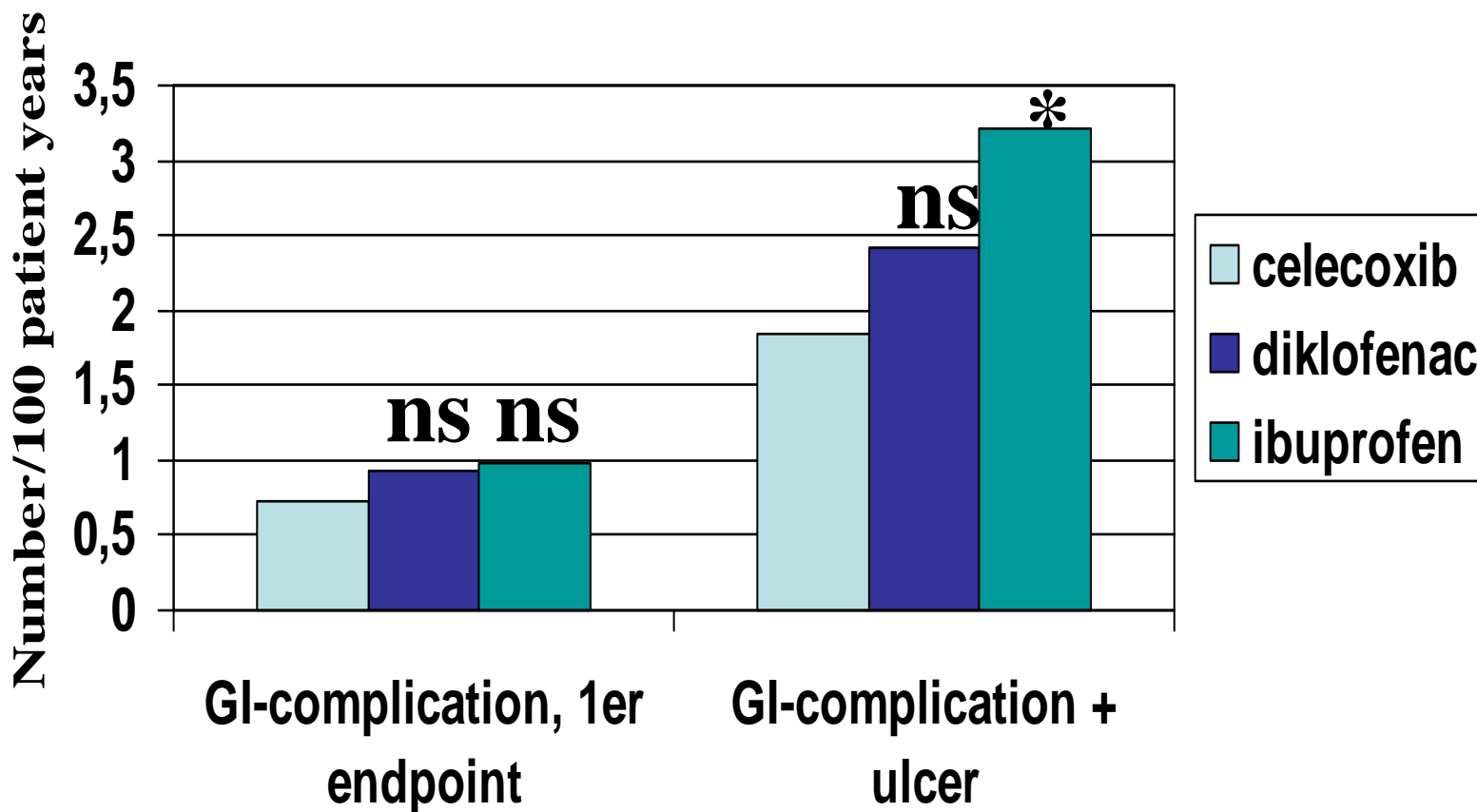
NSAID=Diklofenac + ibuprofen, 6 months data

JAMA 2000;284;1247-1255



The Class Study -12 Months Outcome

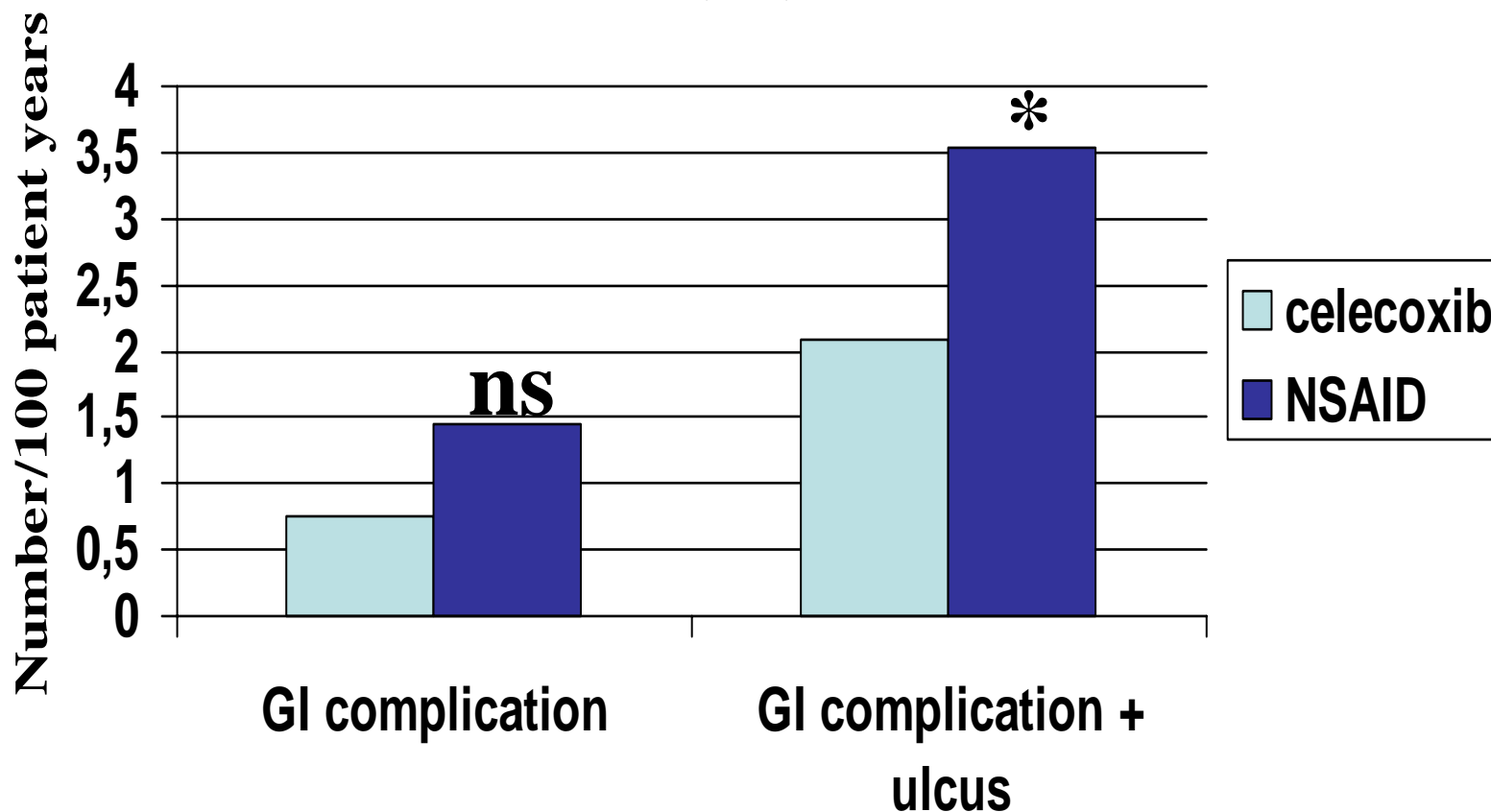
Submitted Documentation to MPA



The CLASS Study As Presented in JAMA

6 Months Data

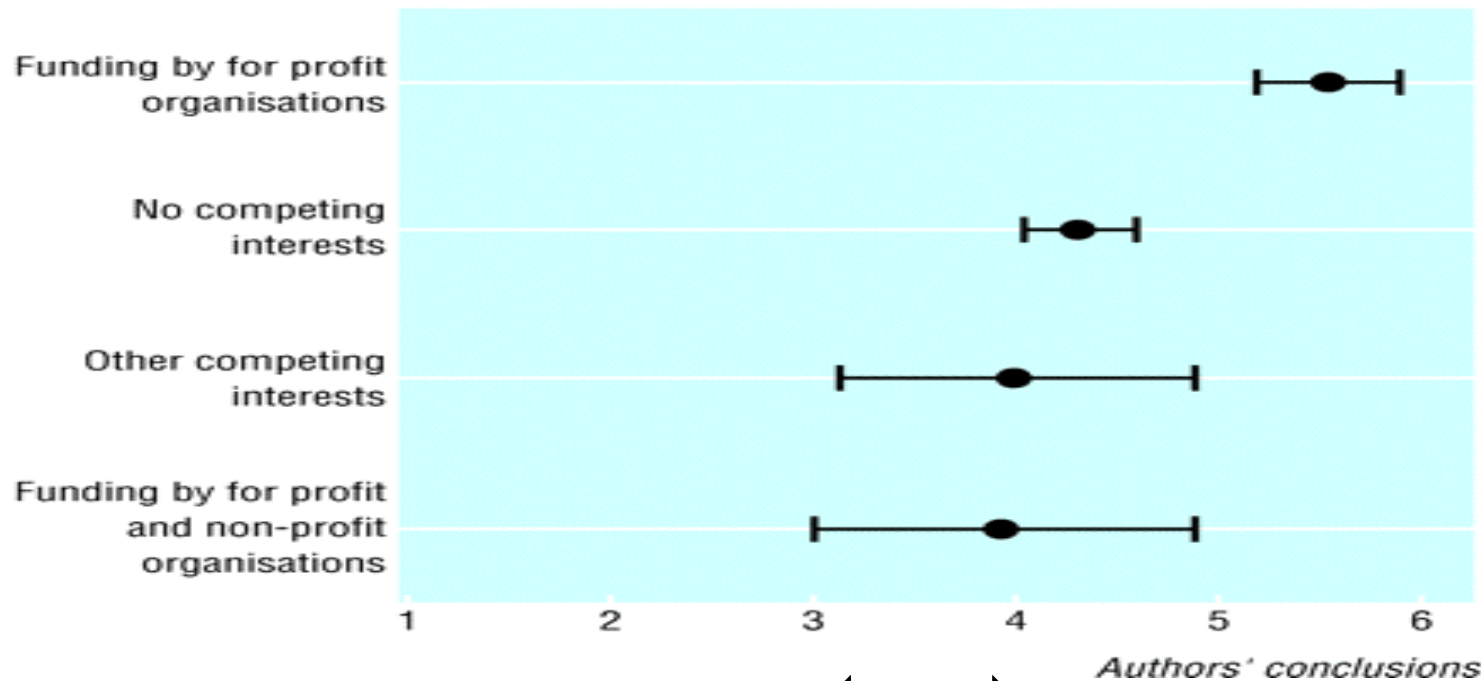
JAMA 2000;284;1247-1299



The influence of sponsors

“Profit organisations, by skill or by chance, may fund only those trials in which the experimental intervention is significantly better than the control intervention”.

BMJ 2002 325(7358):249



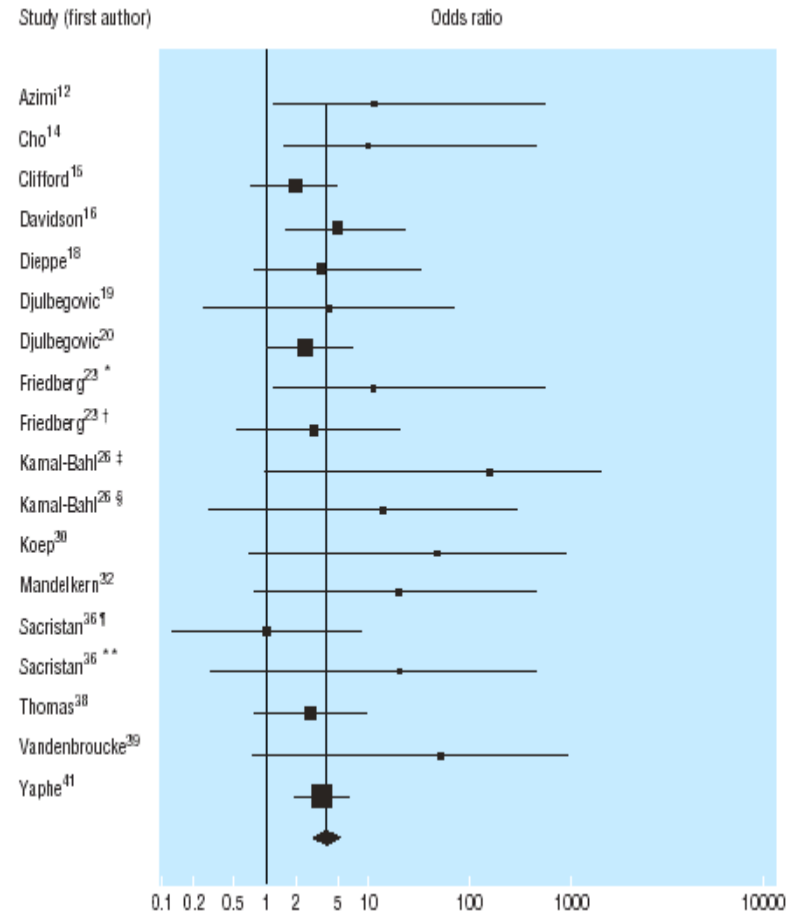
Negative outcome



Positive outcome

Outcome of pharmacoeconomic studies, clinical trials and meta-analysis- commercial vs non-commercial funding *BMJ 2003;326;1167*

Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons).



Language Bias

Egger Et Al Lancet 1997;350 (326-9)

35% + results in
German journals

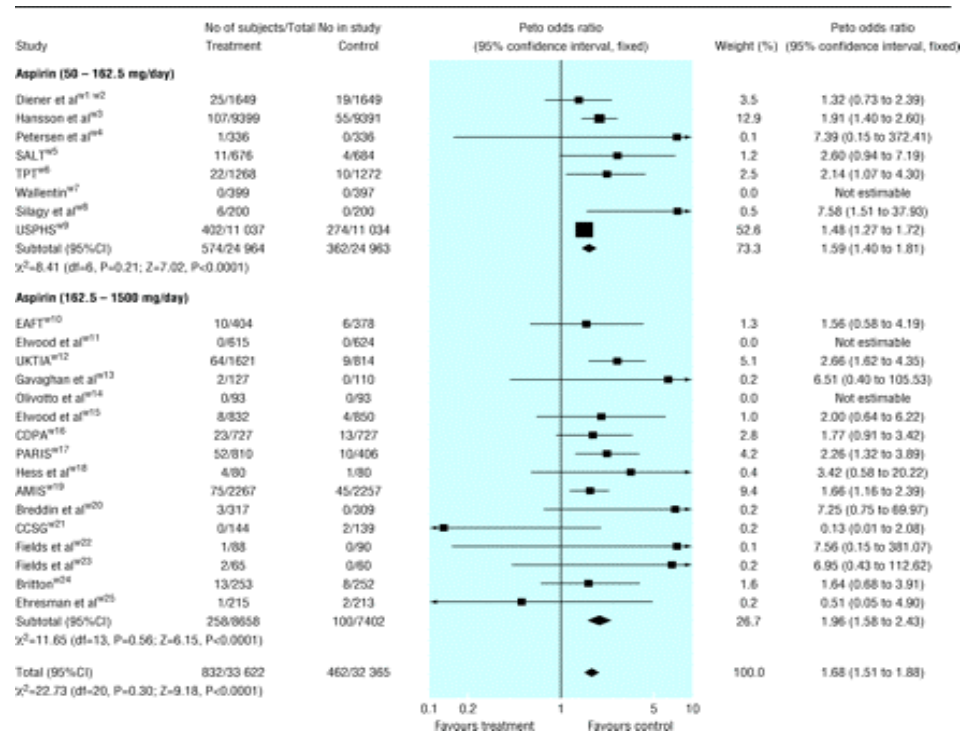
63%+ results in English
journals



**Choose
English
journals
and you
get better
results**

Meta analyses of systematic Reviews

- Golden standard in evidence based medicine.
- Any problems with publication bias?
- How to find the problems?



Magnesium in Acute Myocardial Infarction, a Meta Analysis

Role of magnesium in reducing mortality in acute myocardial infarction. A review of the evidence.

Teo KK, Yusuf S.

A systematic overview of mortality and serious morbidity data from all the available randomised controlled trials of magnesium conducted in a total of nearly 4000 patients with AMI indicates that there were 123 deaths in 1974 patients allocated magnesium, and 193 deaths in 1949 controls (**odds ratio 0.61**, 95% confidence interval 0.48 to 0.76, $p < 0.0001$). *Drugs* 1993 46(3):347

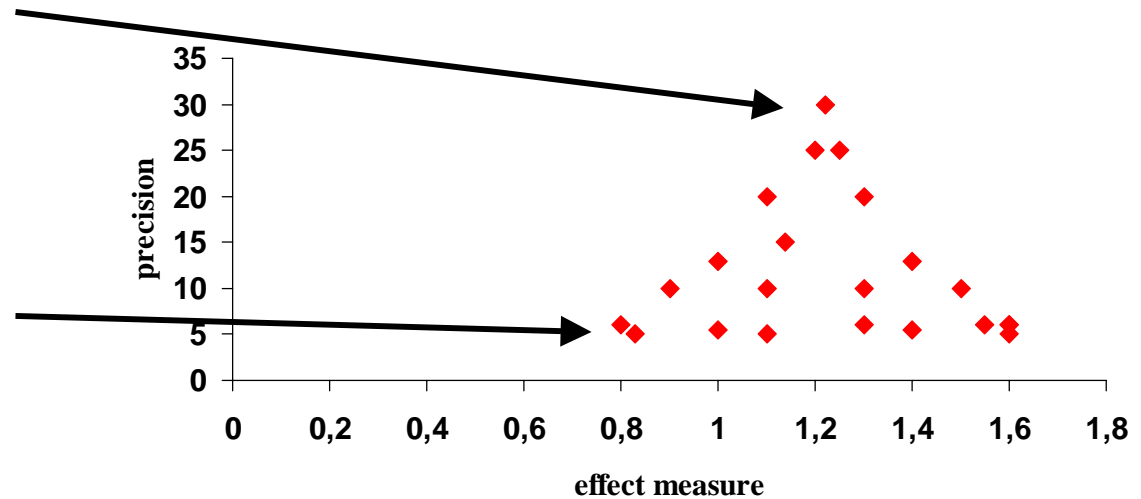
Magnesium in acute myocardial infarction, two large RCT:s

- ISIS 4. 69 000 patients. *Lancet 1995; 345, 669*
 - RR = 1,04
- MAGIC 6200 patients. *Lancet 2002; 360: 1189*
 - OR = 1,0
- Why the discrepancy compared with the meta analysis?

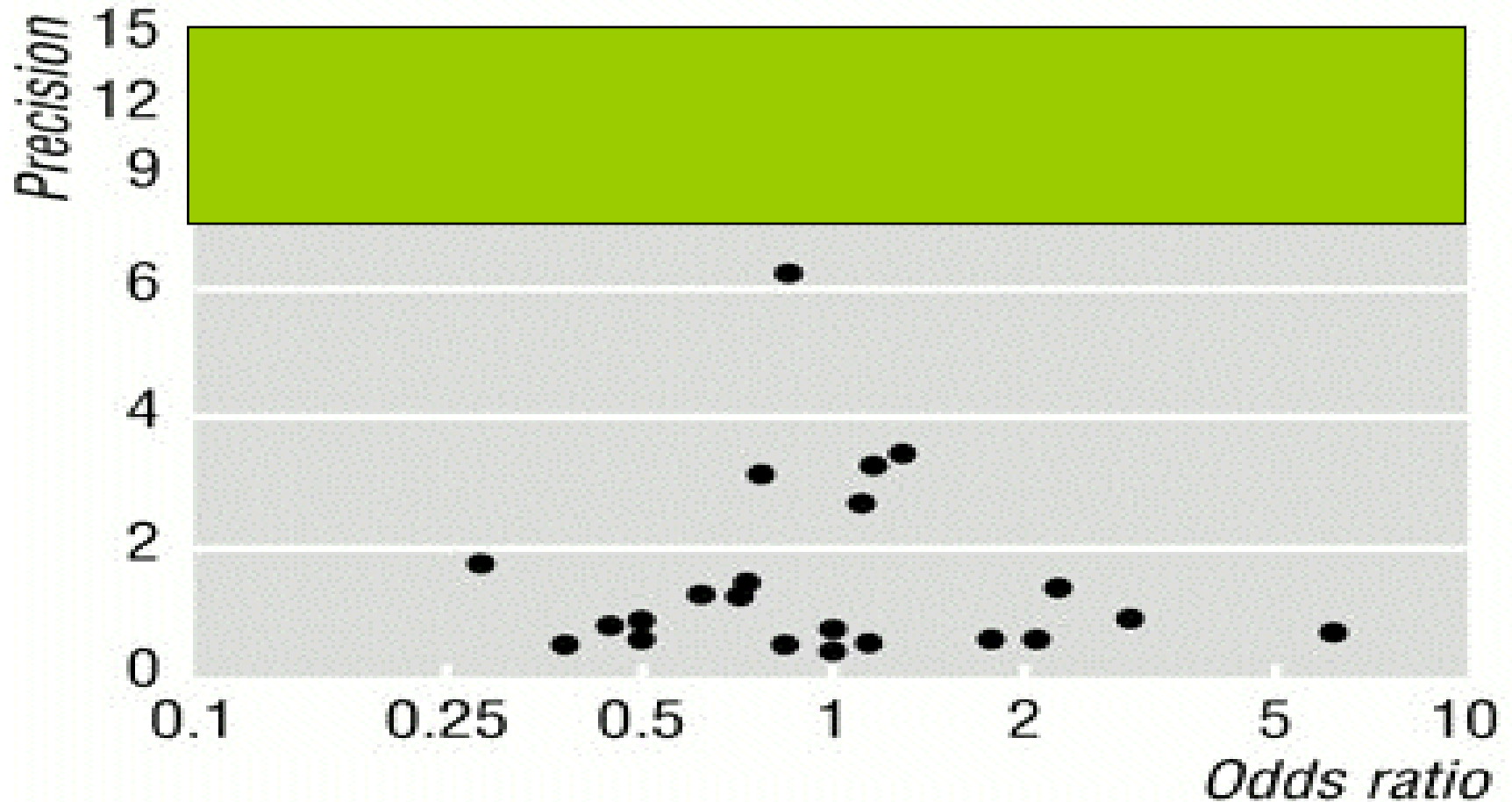
Funnel Plots and Meta Analyses

(*BMJ* 1997;315:629-634)

- Large studies-
high precision-
small variation
- Small studies-
low precision-
large variation

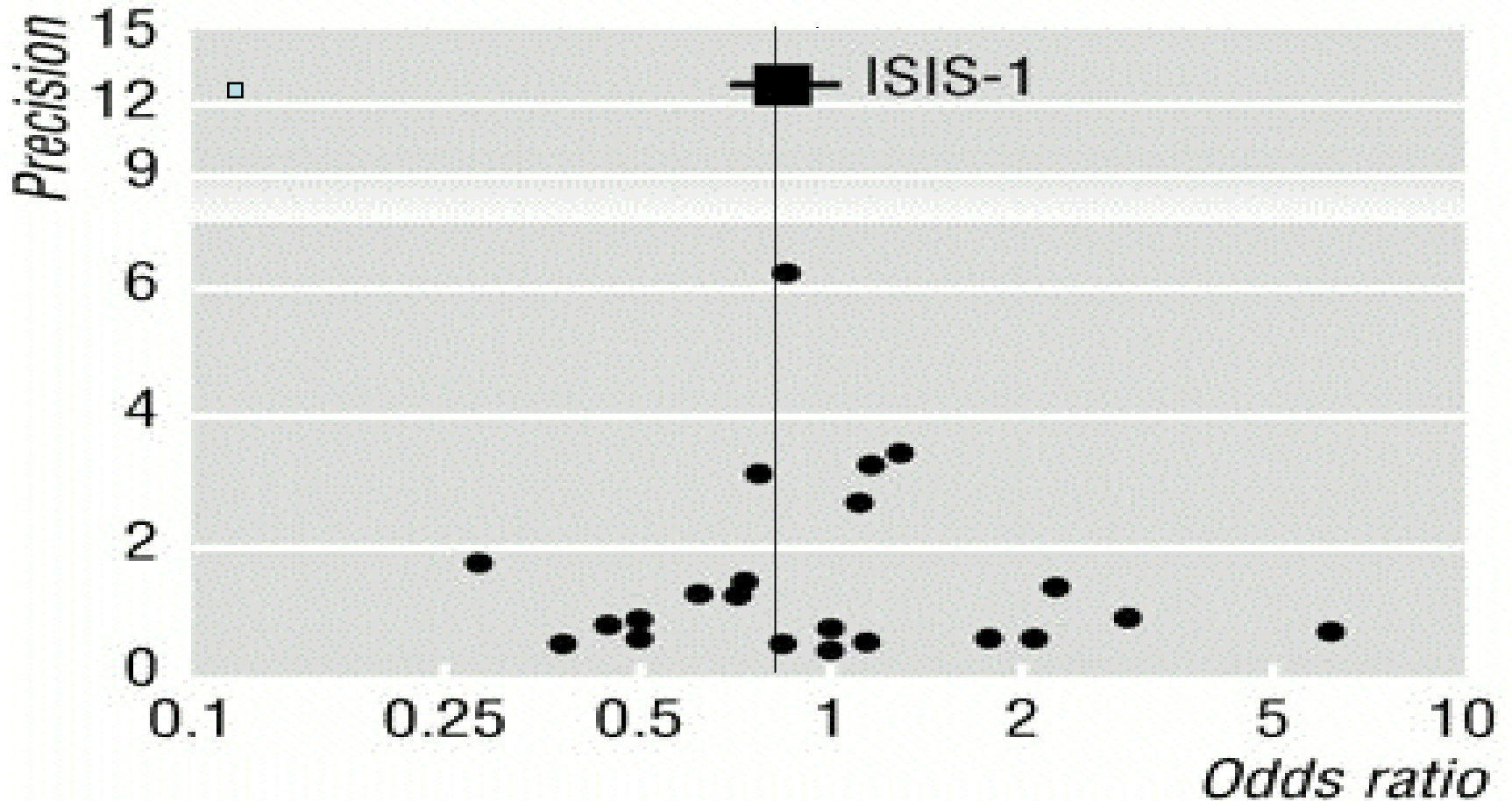


β Blockers in myocardial infarction

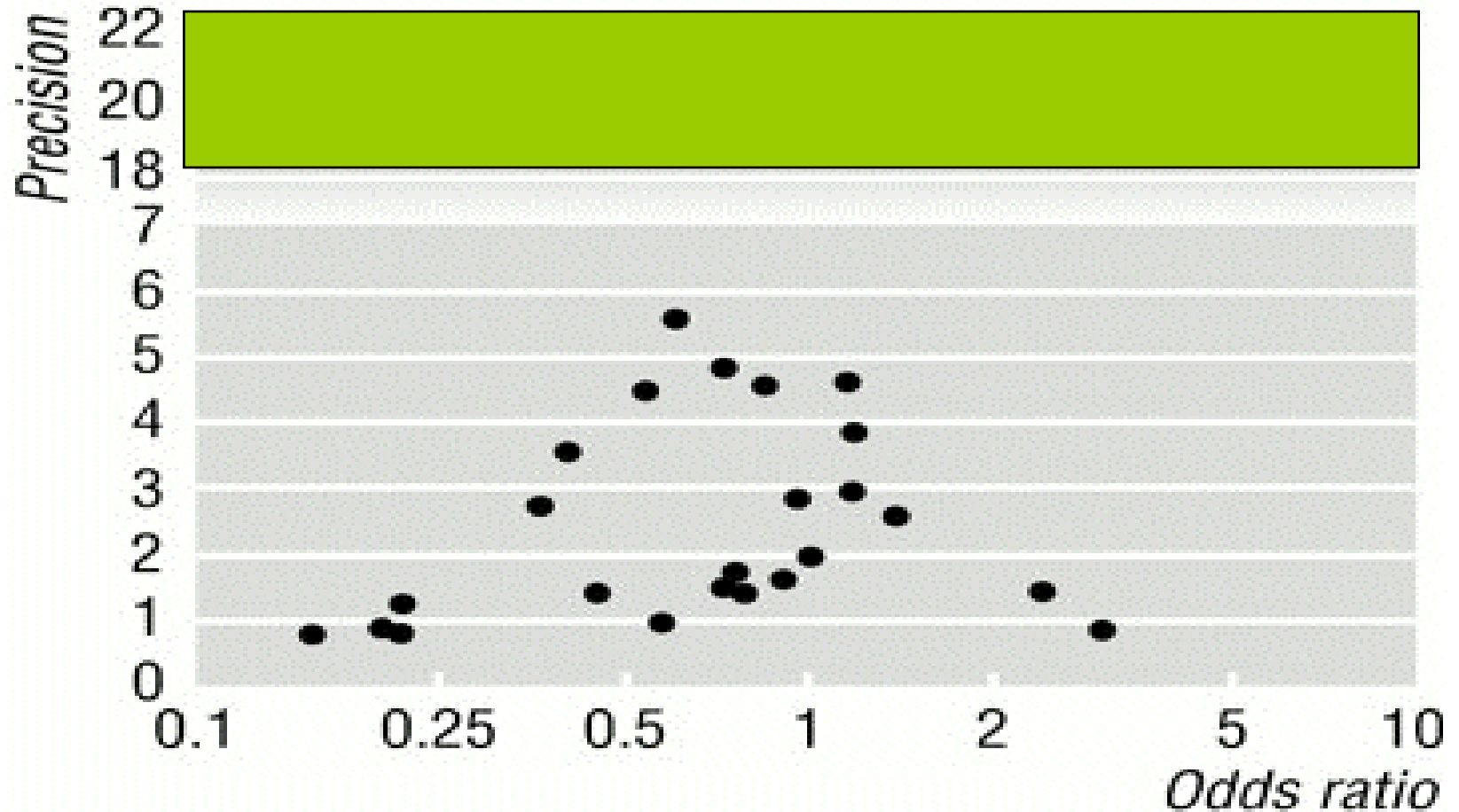


BMJ 1997;315:629-634

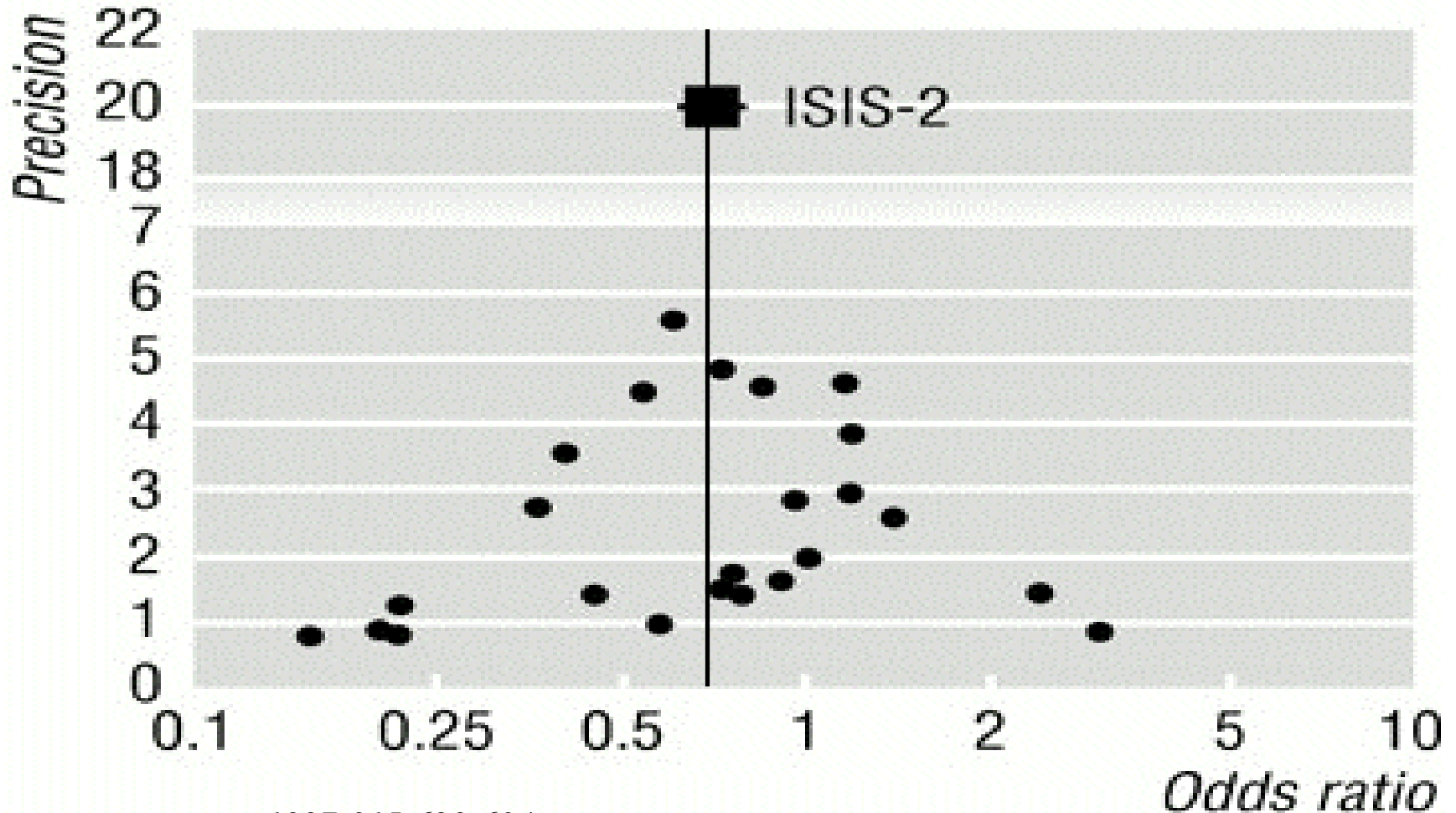
β Blockers in myocardial infarction



Streptokinase in myocardial infarction



Streptokinase in myocardial infarction



Nitrates in Acute Myocardial Infarction

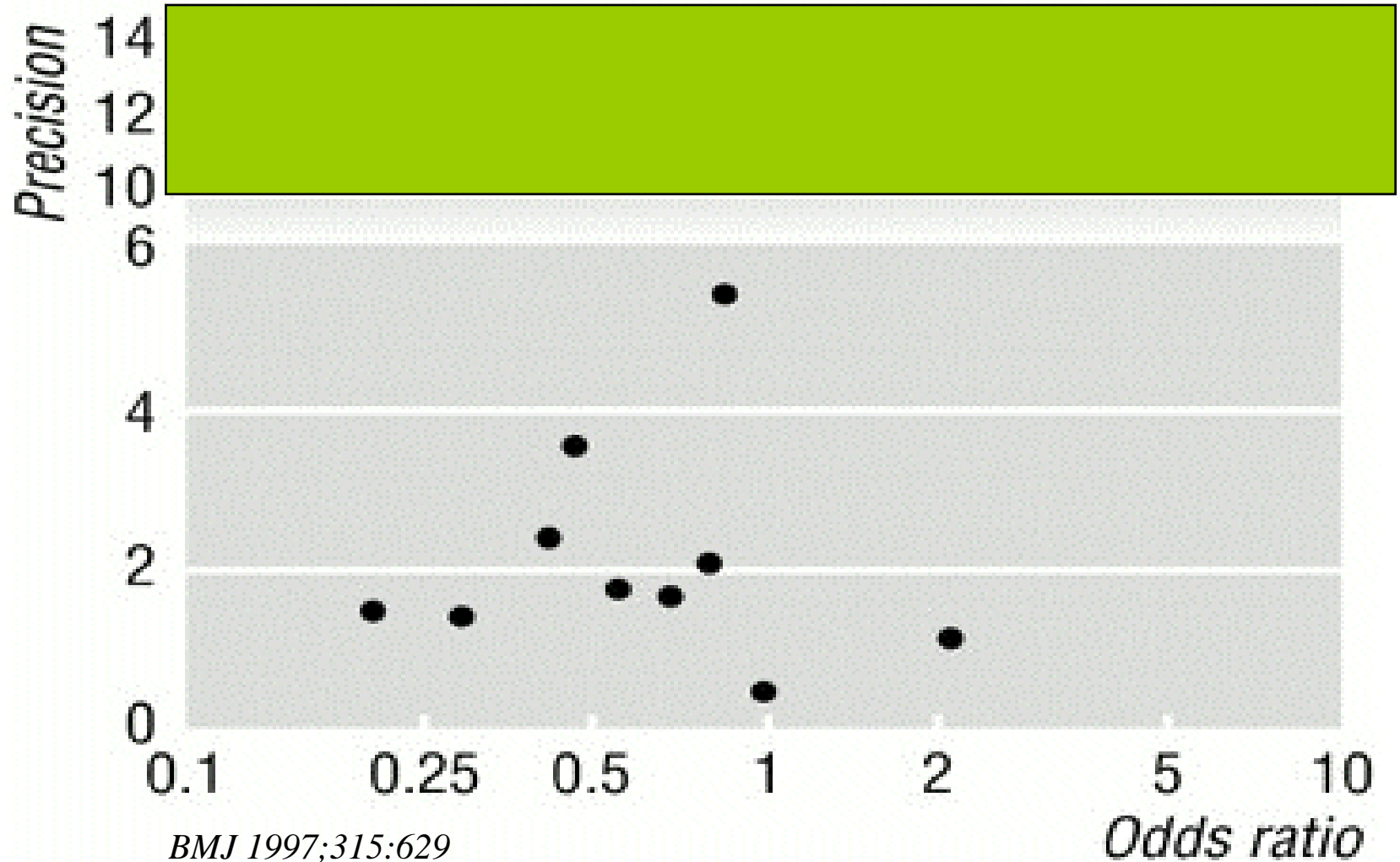
Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials.

Yusuf S, Collins R, MacMahon S, Peto R.

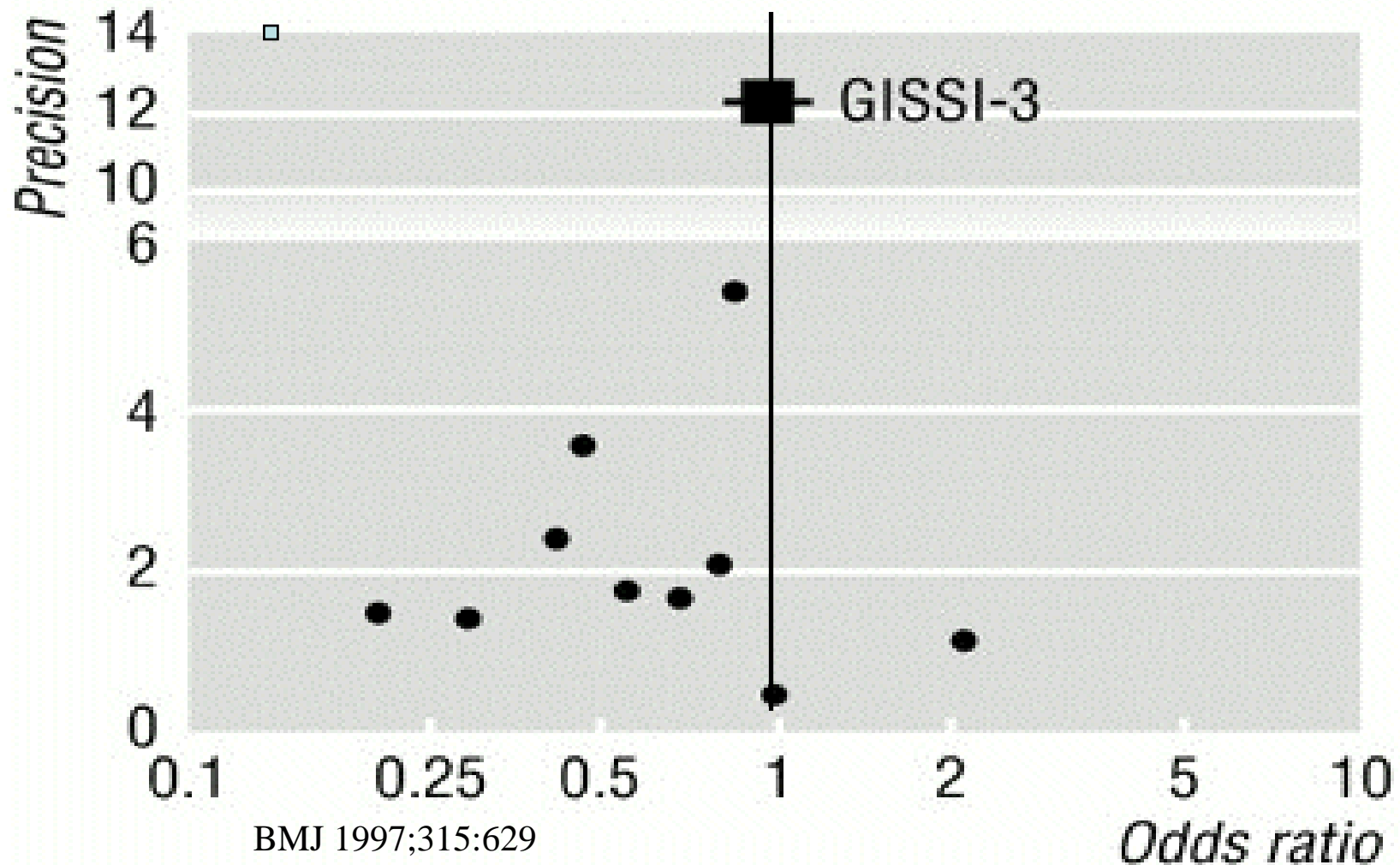
About 2000 patients have been .. **"typical" reduction of 35% (SD 10) in the odds of death** (2p less than 0.001)

Lancet 1988 (8594):1088

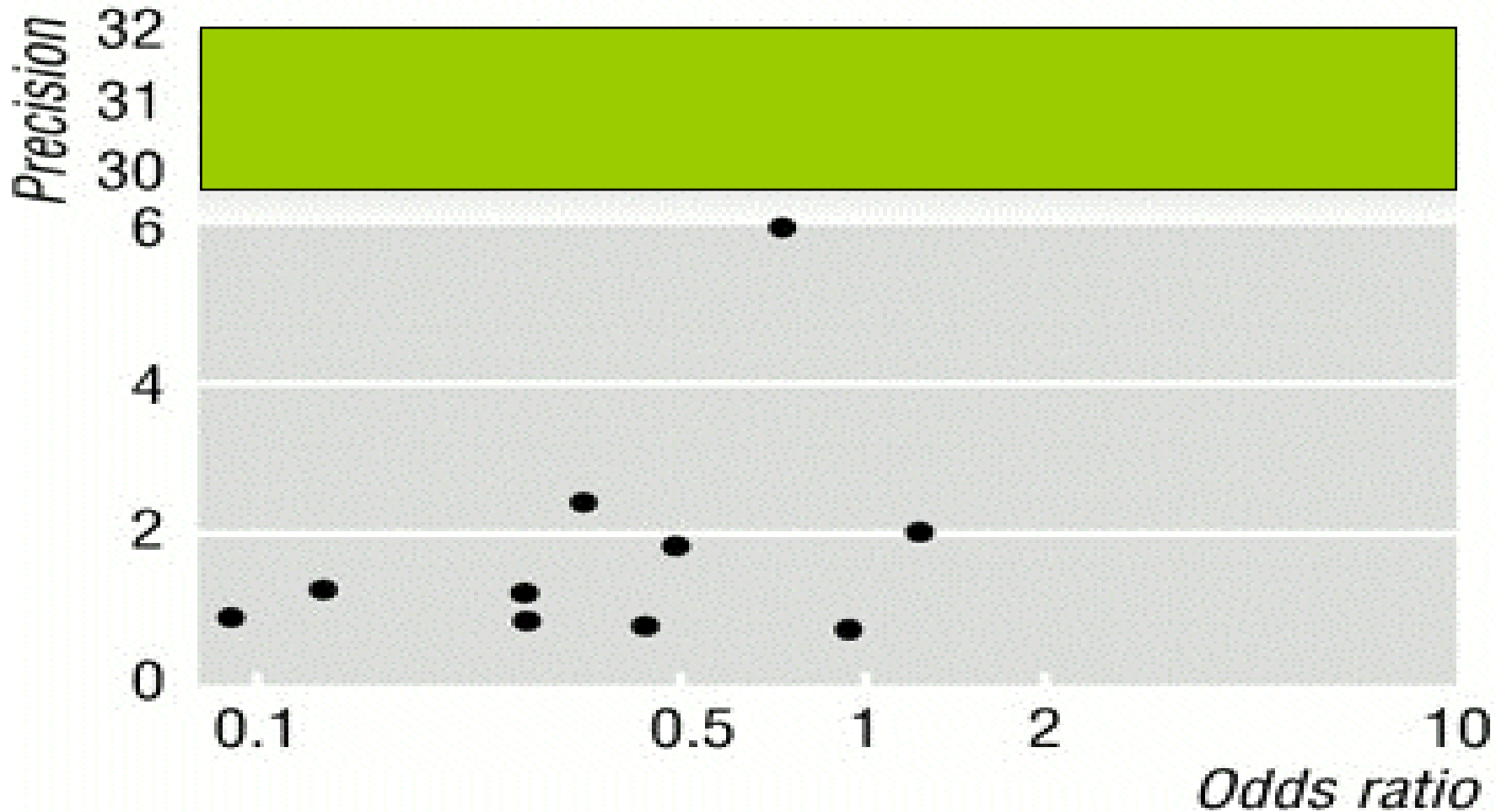
Nitrates in myocardial infarction



Nitrates in myocardial infarction

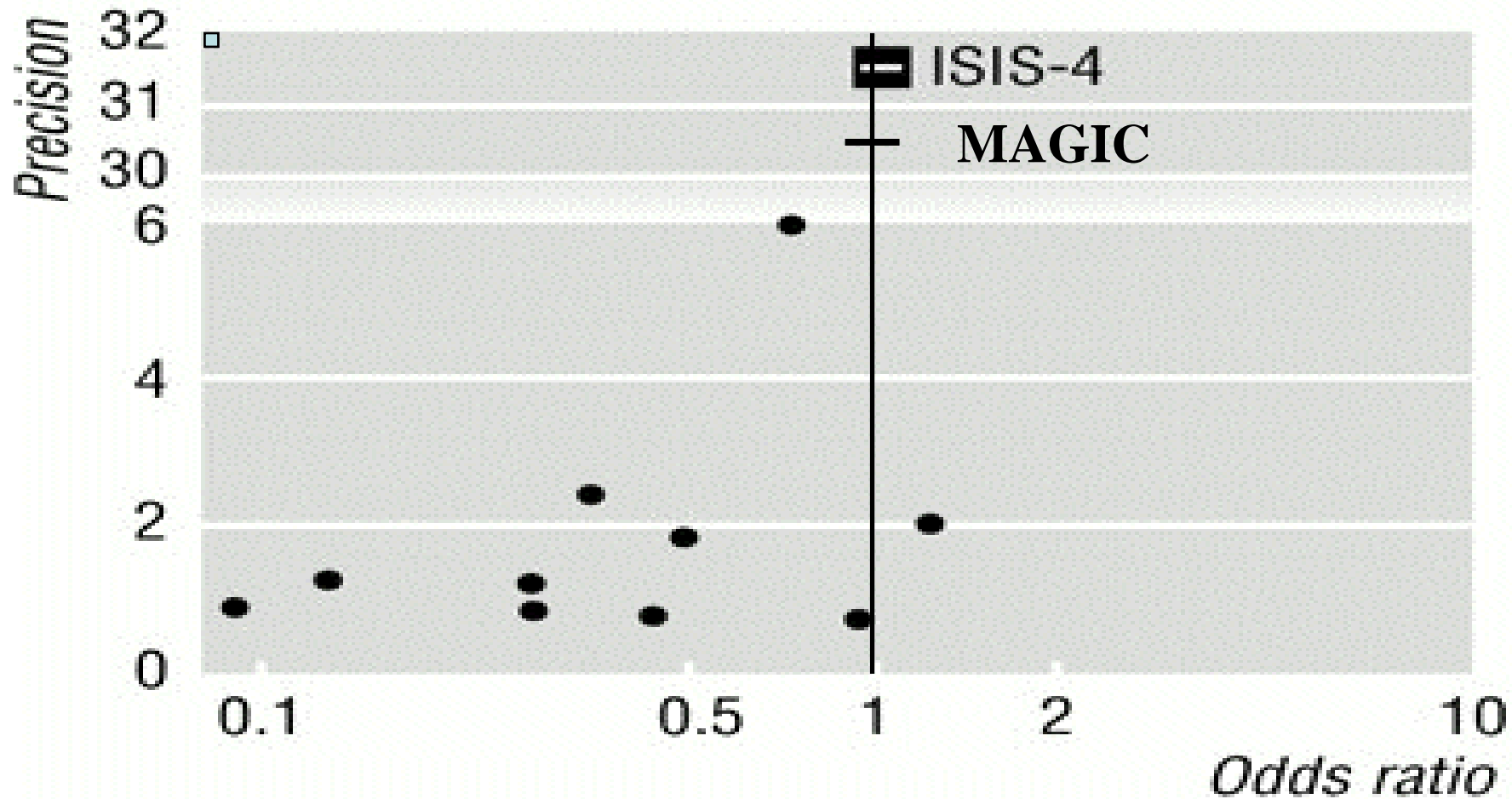


Magnesium in myocardial infarction



BMJ 1997;315:629

Magnesium in myocardial infarction

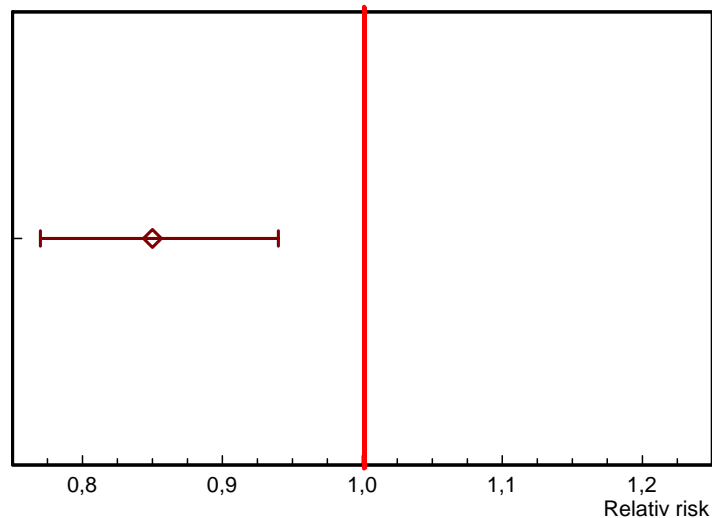


BMJ 1997;315:629

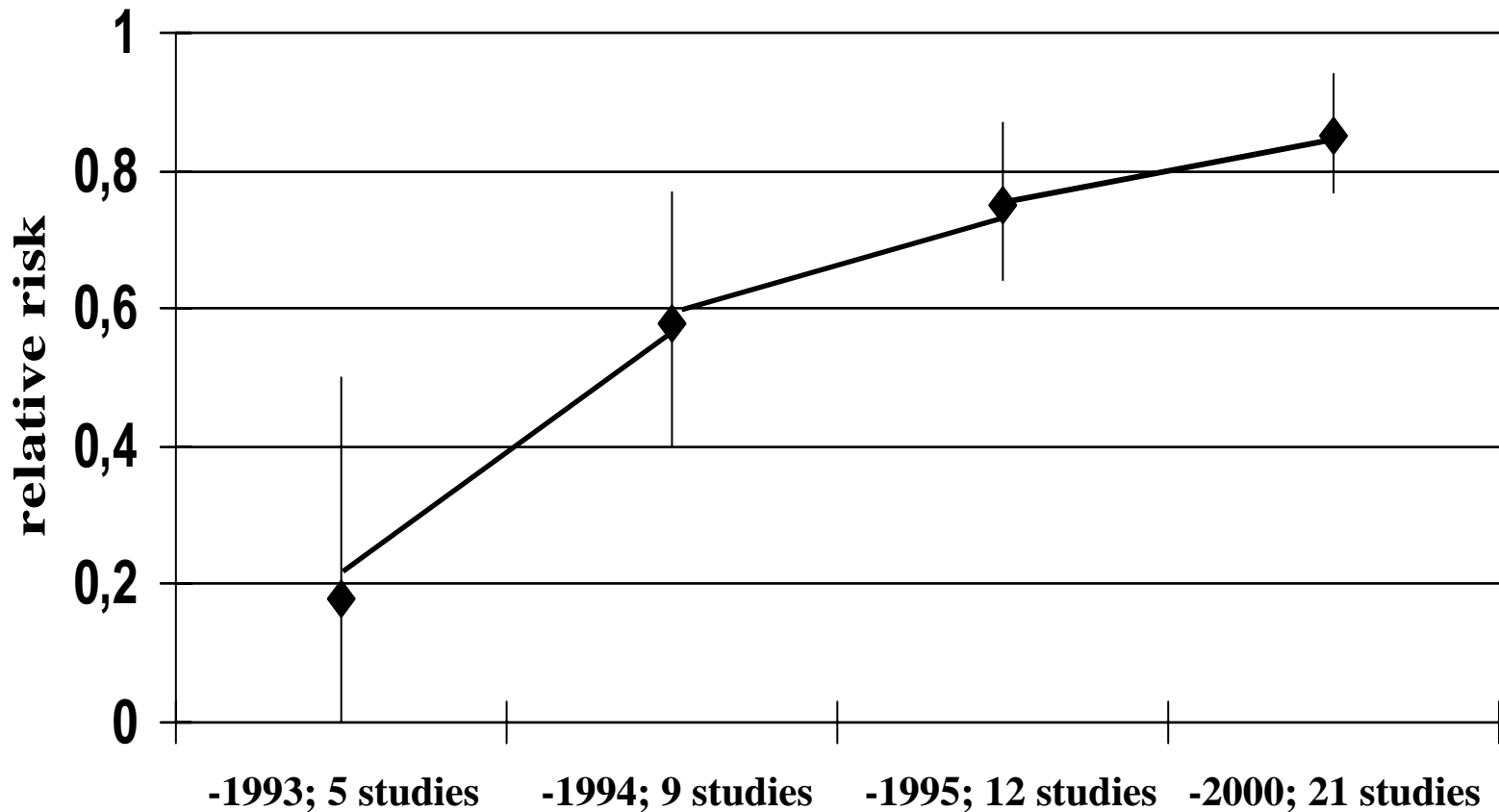
Antiplatelet Drugs for Prevention of Pre-eclampsia and Its Consequences: Systematic Review

BMJ 2001;322:329

Conclusions: Antiplatelet drugs, largely low dose aspirin, have small to moderate benefits when used for prevention of pre-eclampsia



Aspirin As preeclampsia prophylaxis in Moderate Risk Women



Concordance between 19 meta- analyses och 12 large RCT:s with 40 outcomes *NEJM 1997, 337(536-542)*

**Result of
meta
analysis**

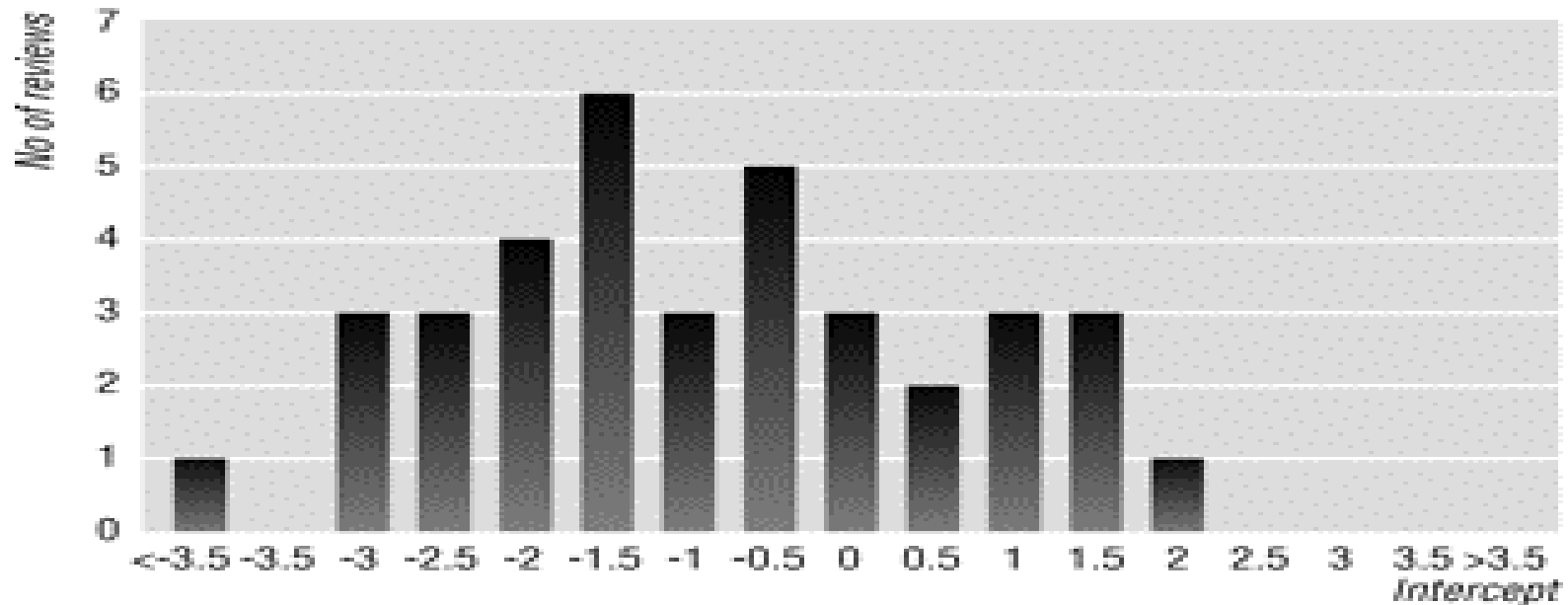
Result of RCT

Positive *Negative* *Total*

<i>Positive</i>	13	6	19
<i>Negative</i>	7	14	21

Meta Analyses in BMJ, Lancet Etc

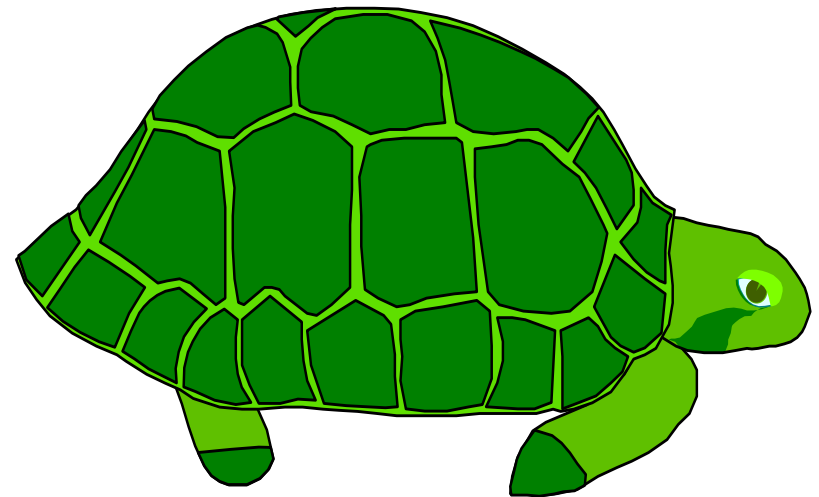
Regression Analyses of Funnel Plot Symmetry



Expected-symmetry around 0

Publication Delay

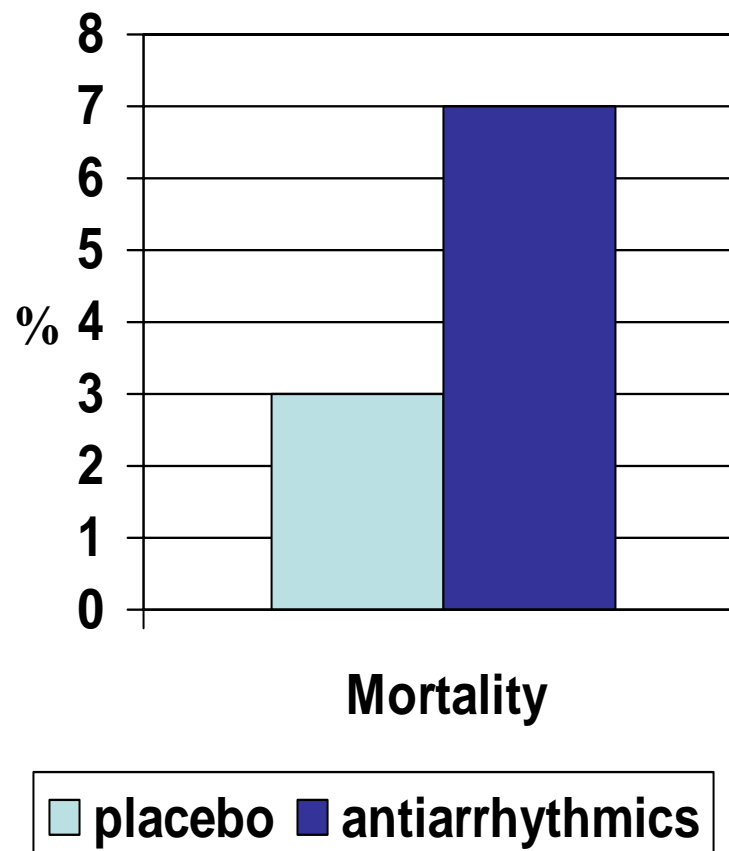
- What is the main problem?
- Trials with harmful outcome may be repeated!



Cast-flecainide and encainide Vs Placebo Post AMI

- Mortality;
 - RR 2.5 (1.6-4.5)
- Published in NEJM **1989**; 321(406-412)

Big surprise!

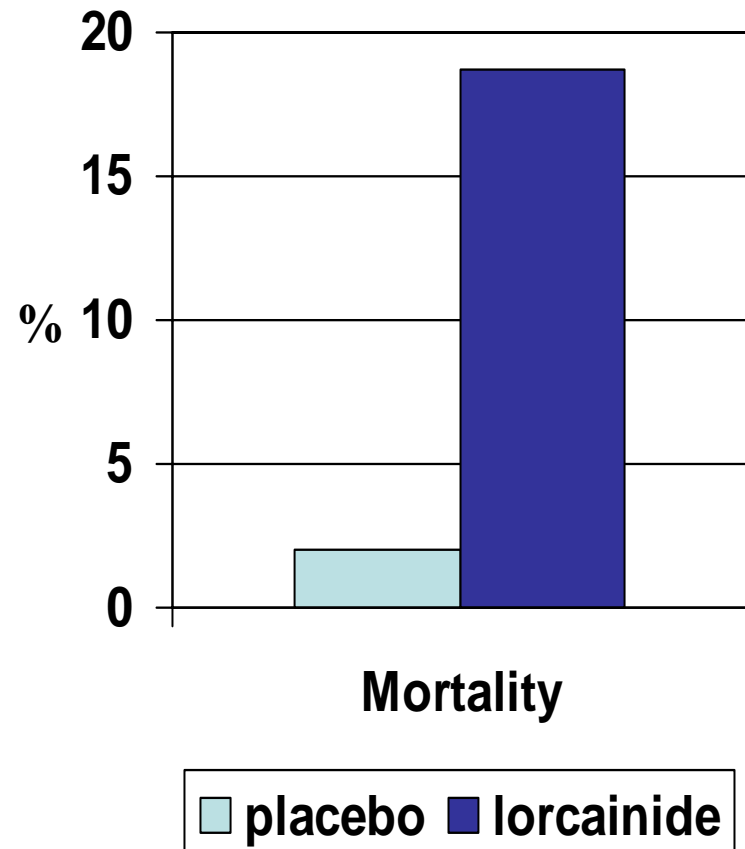


Lorcainide Vs Placebo Post AMI

Int J Cardiol 1993;40 (161-6)

- Mortality;
 - RR 9 (3.3-14.7)
- Published in
 - *Int J Cardiol 1993;40 (161-6)*

The trial was
finished **1980!**



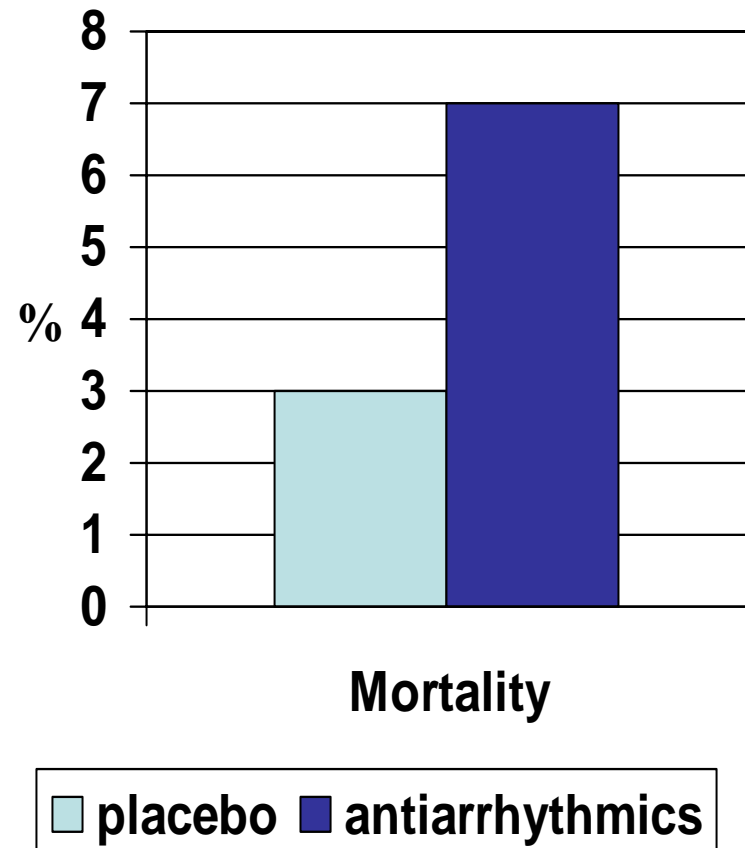
Cast-flecainide and encainide Vs Placebo Post AMI

- Mortality;
 - RR 2.5 (1.6-4.5)
- Published in NEJM **1989**; 321(406-412)

Big surprise!

Not at all!

Knowledge since 1980!!



Aptiganel, a NMDA Receptor Antagonist

- Diminishes the brain damage after cerebral ischemia with 40-70% in the rat
- Diminishes the brain edema after skull damage in animal models

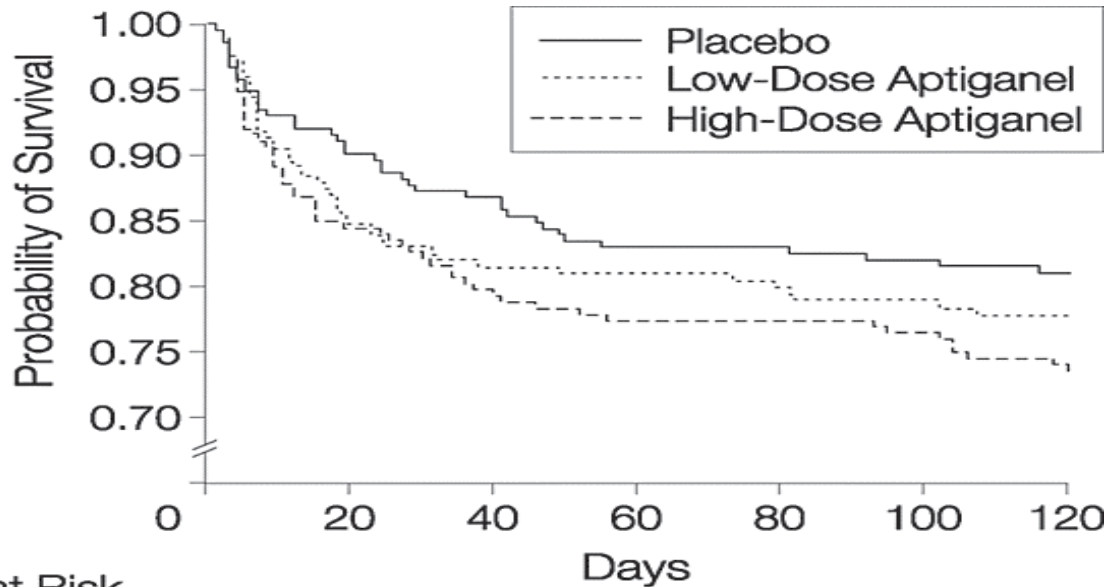
Aptiganel, a NMDA Receptor Antagonist

- Internationell RCT - ischemic stroke
- Placebo, low dose, high dose
- 628 patients
- Interim analysis 300 patients 7 days
- 1. End point- modified Rankin scale day 90
- 2. End point - mortality and performance day 7

Aptiganel, a NMDA Receptor Antagonist

- Interim analysis, mortality day 7
 - Placebo 3,1%
 - Apriganel low dose 8,6%
 - Apriganel high dose 9,9%
- } p=0,03

Aptiganel- Outcome, All Patients



No. at Risk	0	20	40	60	80	100	120
Placebo	214	190	179	170	170	168	166
Low-Dose Aptiganel	200	168	158	156	154	152	150
High-Dose Aptiganel	213	178	166	161	161	159	154

Aptiganel- Outcome All Patients

Table 6. Number of Patients With Severe Adverse Events*

WHO Organ Class and Preferred Term	Placebo (n = 214)	Aptiganel Hydrochloride		P Value†	
		Low Dose (n = 200)	High Dose (n = 214)	Low Dose	High Dose
Central and peripheral nervous system					
Cerebral edema	4 (1.9)	11 (5.5)	16 (7.5)	.05	.01
Stupor	4 (1.9)	2 (1.0)	13 (6.1)	.46	.03
Respiratory Phenomena	8 (3.7)	11 (5.5)	12 (5.6)	.39	.36
Vascular (extracardiac)					
Cerebral hemorrhage	5 (2.3)	7 (3.5)	11 (5.1)	.48	.13
Cerebrovascular	18 (8.4)	15 (7.5)	15 (7.0)	.73	.59
Total With Any Severe Adverse Event	86 (40.2)	87 (43.5)	114 (53.3)	.29	.01

*Values are expressed as number (percentage). Serious adverse events occurring among 5% or greater in any treatment group.

†Comparison is with placebo.

Apriganel

- The study was stopped September 1997 after the interim analysis.
- Published in JAMA December 2001!
- How many hazardous trials started because of the publication delay?

Consequences of Publication Bias

- Wrong picture of the effect size
- Effect, despite that it is probably lacking
- Wrong picture of the adverse drug reactions
- Negative studies are repeated by other researchers/companies

The Reality

- The drug companies often give very scarce information on which trials have been done on a certain drug
- The drug companies often do not present study reports asked for

The Helsinki Declaration 2000

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. **Negative as well as positive results should be published or otherwise publicly available.**

A Solution?

- A condition for approval by ethics committees/the drug regulatory authorities is that the drug company:
 - Will inform the society that the study has been done
 - Will present the results of the study whether published or not

**Many thanks for
Listening**

