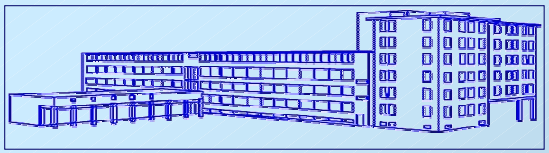
CONVEGNO NAZIONALE
I PRONTUARI OSPEDALIERI COME STRUMENTO DI GOVERNO CLINICO

24 – 25 maggio 2007

E’ ottimale la scelta dei comparatori nelle sperimentazioni registrative dei nuovi farmaci?

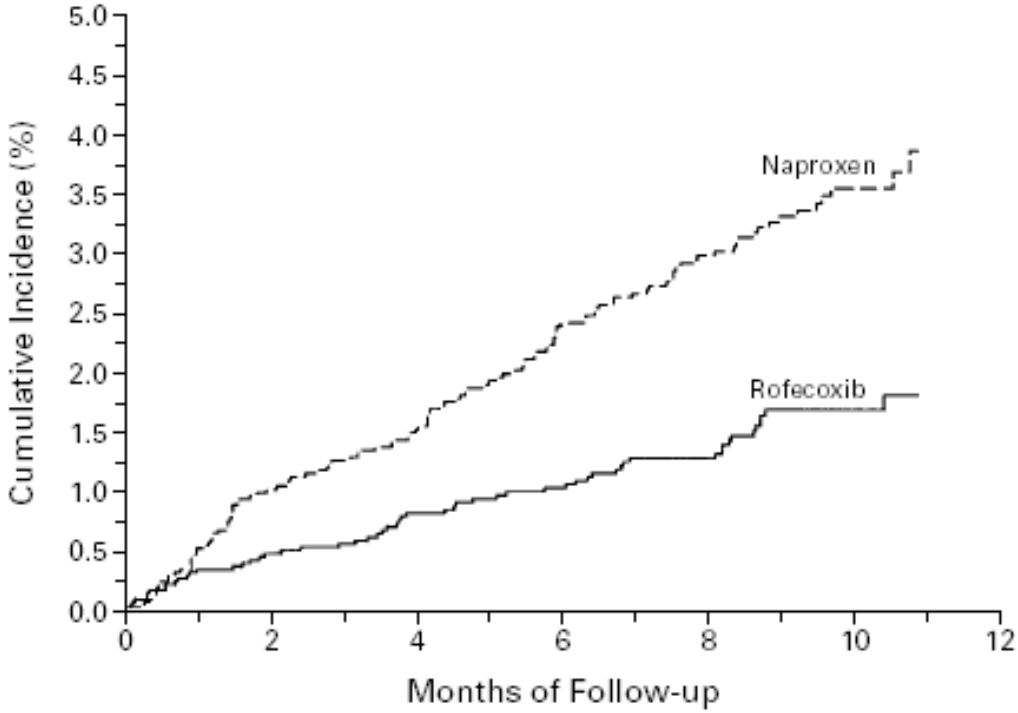


Vittorio BERTELE’
Head, Regulatory Policies Lab
Mario Negri Instutite for Pharmacological Research

…solo un anello di una lunga catena di bias

- Scelta inappropriata dell'ipotesi (domanda vera per il paziente, non per il farmaco)
- Scelta inappropriata dei criteri di valutazione (test di superiorità vs non-inferiorità)
- Scelta inappropriata delle misure di outcome (endpoint surrogati vs sopravvivenza e qualità della vita)
- **Scelta inappropriata del comparatore o delle sue dosi**
- Ricerca selettiva di alcuni eventi avversi soltanto (sintomi GI vs MI per i coxib)
- Pubblicazione selettiva degli studi o dei dati
- Conflitti di interesse

Comparator

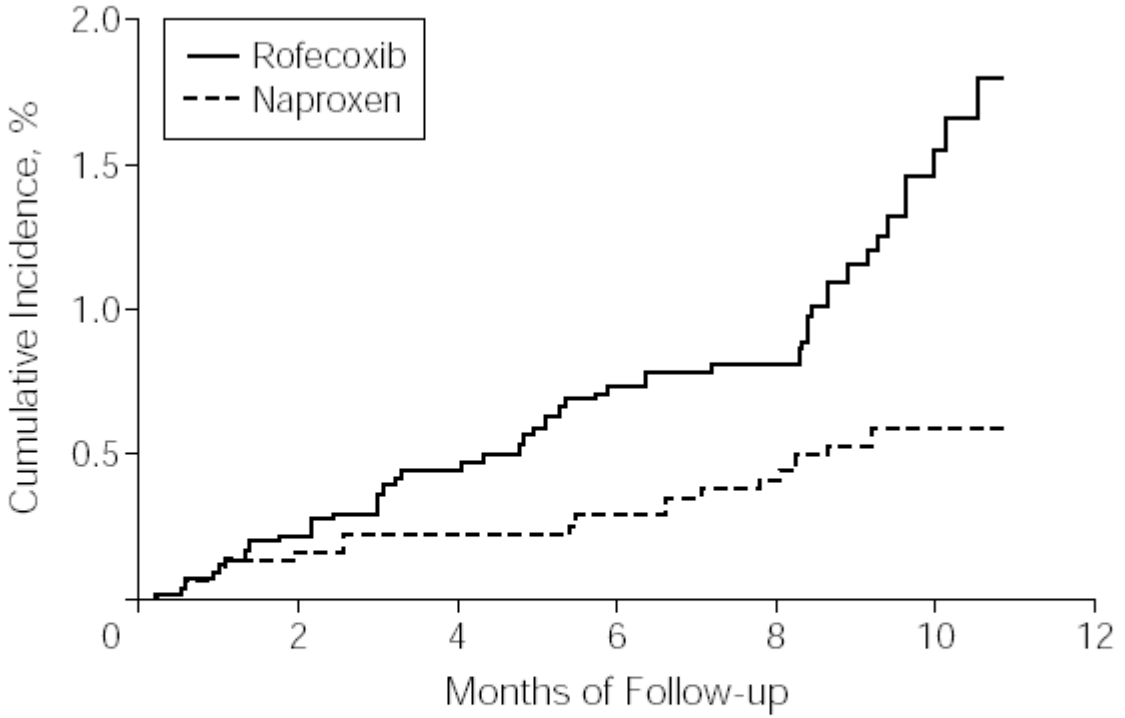


No. at Risk							
Rofecoxib	4047	3641	3402	3180	2806	1073	533
Naproxen	4029	3644	3389	3163	2796	1071	513

Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.

Vigor Study Group. N Engl J Med 2000

Time to cardiovascular adverse events in the VIGOR trial



No. at Risk							
Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514

Relative risk (95% confidence interval)=2.38 (1.39-4.00); $P<.001$. VIGOR indicates Vioxx Gastrointestinal Outcomes Research.

Mukherjee et al, JAMA, 2001

Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison

*Christopher P Cannon, Sean P Curtis, Garret A FitzGerald, Henry Krum, Amarjot Kaur, James A Bolognese, Alise S Reicin, Claire Bombardier, Michael E Weinblatt, Désirée van der Heijde, Erland Erdmann, Loren Laine, for the MEDAL Steering Committee**

Lancet 2006; 368: 1771–81

Summary

Background Cyclo-oxygenase-2 (COX-2) selective inhibitors have been associated with an increased risk of thrombotic cardiovascular events in placebo-controlled trials, but no clinical trial has been reported with the primary aim of assessing relative cardiovascular risk of these drugs compared with traditional non-steroidal anti-inflammatory drugs (NSAIDs). The MEDAL programme was designed to provide a precise estimate of thrombotic cardiovascular events with the COX-2 selective inhibitor etoricoxib versus the traditional NSAID diclofenac.

Methods We designed a prespecified pooled analysis of data from three trials in which patients with osteoarthritis or rheumatoid arthritis were randomly assigned to etoricoxib (60 mg or 90 mg daily) or diclofenac (150 mg daily). The primary hypothesis stated that etoricoxib is not inferior to diclofenac, defined as an upper boundary of less than 1·30 for the 95% CI of the hazard ratio for thrombotic cardiovascular events in the per-protocol analysis. Intention-to-treat analyses were also done to assess consistency of results. These trials are registered at http://www.clinicaltrials.gov with the numbers NCT00092703, NCT00092742, and NCT00250445.

Findings 34701 patients (24913 with osteoarthritis and 9787 with rheumatoid arthritis) were enrolled. Average treatment duration was 18 months (SD 11·8). 320 patients in the etoricoxib group and 323 in the diclofenac group had thrombotic cardiovascular events, yielding event rates of 1·24 and 1·30 per 100 patient-years and a hazard ratio of 0·95 (95% CI 0·81–1·11) for etoricoxib compared with diclofenac. Rates of upper gastrointestinal clinical events (perforation, bleeding, obstruction, ulcer) were lower with etoricoxib than with diclofenac (0·67 *vs* 0·97 per 100 patient-years; hazard ratio 0·69 [0·57–0·83]), but the rates of complicated upper gastrointestinal events were similar for etoricoxib (0·30) and diclofenac (0·32).

Interpretation Rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs.

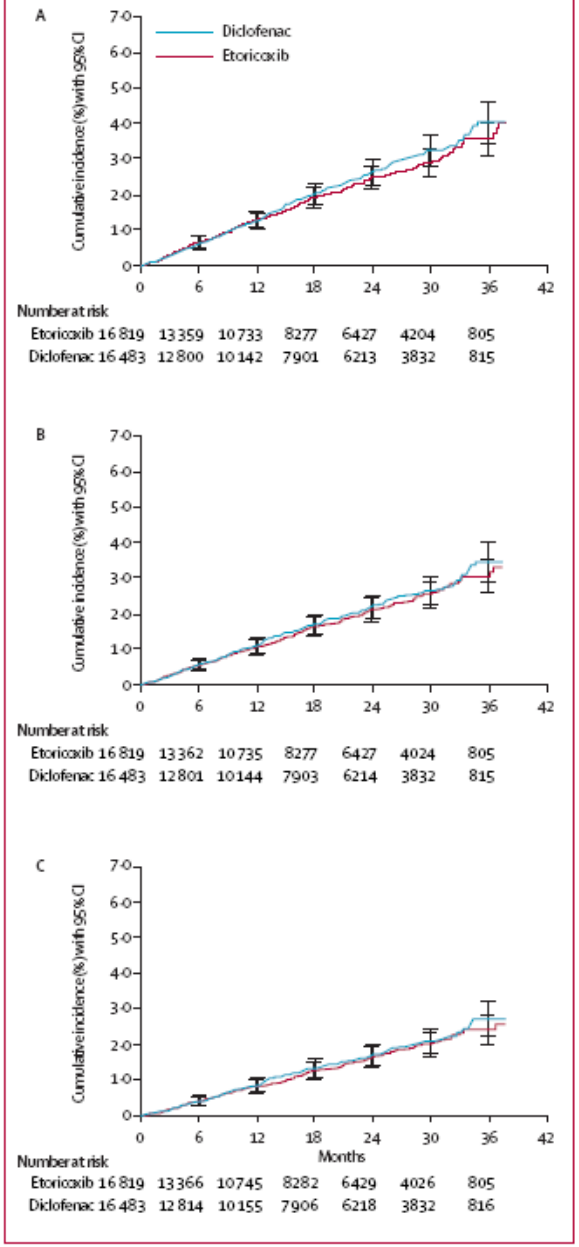


Figure 2: Time-to-event per-protocol analysis
(A) Cumulative incidence of thrombotic cardiovascular events. (B) Cumulative incidence of arterial thrombotic events. (C) Cumulative incidence of APTC[21] events (myocardial infarction, stroke, or vascular death).

Interpretation **Rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs.**

MEDAL Trial, Lancet 2006

	CARDIOVASCULAR TOXICITY
PLACEBO	1
COXIBs	1.42*
	(1.13-1.76)

* 121 RCT

Psaty and Weiss, 2007

	CARDIOVASCULAR TOXICITY
NAPROXEN	1
COXIBs	1.57*
	(1.21-2.03)

Psaty and Weiss, 2007

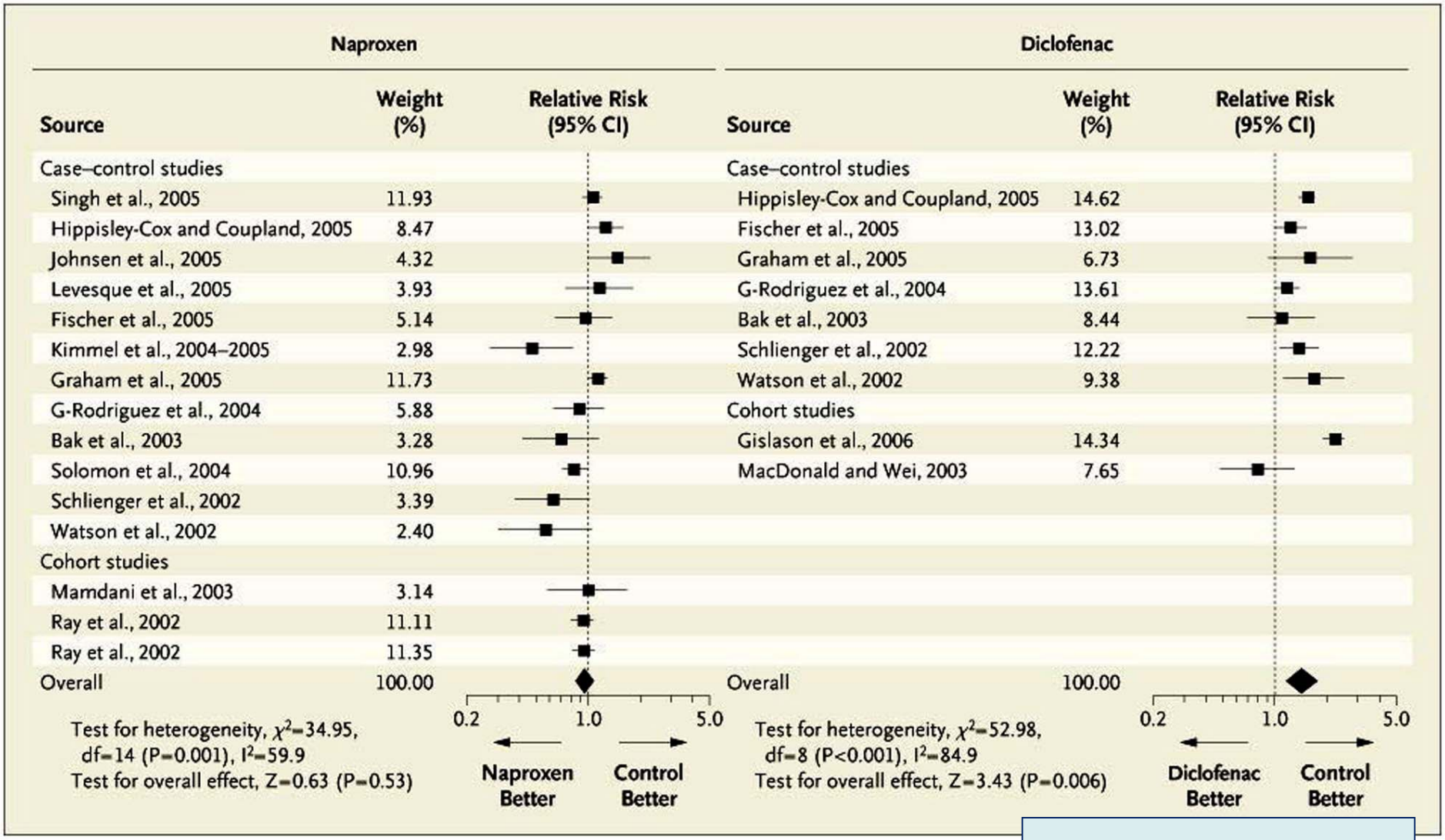
* 42 RCT

	CARDIOVASCULAR TOXICITY
DICLOFENAC	1
COXIBs	0.92*
	(0.81-1.05)

* 26 RCT

Psaty and Weiss, 2007

POINT ESTIMATES AND SUMMARY RELATIVE RISKS OF CARDIOVASCULAR EVENTS ASSOCIATED WITH NAPROXEN AND DICLOFENAC



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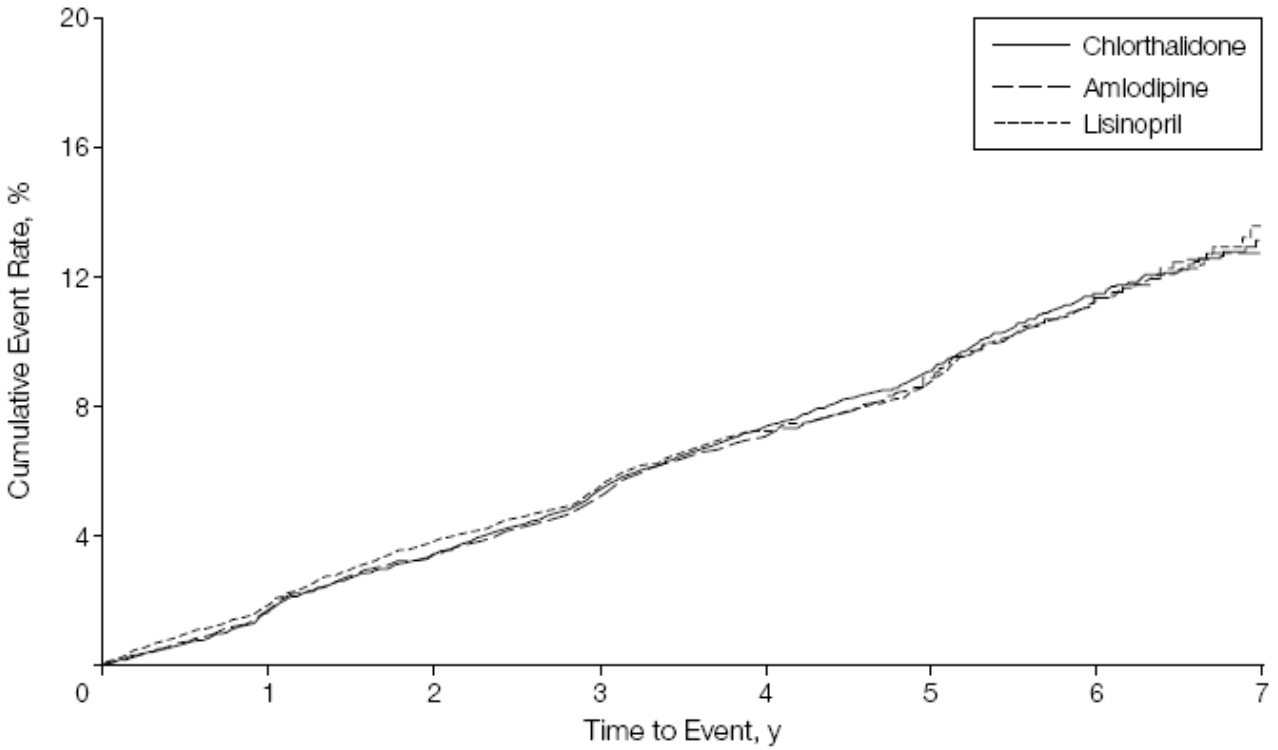
Psaty and Weiss, 2007

ALLHAT, JAMA 2002

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Figure 3. Cumulative Event Rates for the Primary Outcome (Fatal Coronary Heart Disease or Nonfatal Myocardial Infarction) by Treatment Group



No. at Risk								
Chlorthalidone	15255	14477	13820	13102	11362	6340	2956	209
Amlodipine	9048	8576	8218	7843	6824	3870	1878	215
Lisinopril	9054	8535	8123	7711	6662	3832	1770	195

No significant difference was observed for amlodipine (relative risk [RR], 0.98; 95% confidence interval [CI], 0.90-1.07; $P = .65$) or lisinopril (RR, 0.99; 95% CI, 0.91-1.08; $P = .81$) vs chlorthalidone with a mean follow-up of 4.9 years.

Low-dose diuretics associated with reduced risks of all the major outcomes, including

- stroke (relative risk [RR], 0.66; 95% confidence interval [CI], 0.55-0.78),
- coronary heart disease (RR, 0.72; 95% CI, 0.61-0.85),
- heart failure (RR, 0.58;95% CI, 0.44-0.76), and
- total mortality (RR, 0.90; 95% CI,0.81-0.99).

Controls in anti-hypertensive trials

Table. Summary of the Design and Primary Results of Recent Comparative Trials in Hypertension[17-20]

	Trial			
	LIFE,[17] 2002	VALUE,[18] 2004	INVEST,[19] 2003	ASCOT,[20] 2003
Intervention				
Active group	Losartan	Valsartan	Verapamil	Amlodipine
Comparison group	Atenolol	Amlodipine	Atenolol	Atenolol
No. of participants	9193	15 245	22 579	19 257
Heart failure in primary composite outcome?	No	Yes	No	No
Primary outcome, RR (95% CI)	0.87 (0.77-0.98)	1.04 (0.94-1.15)	0.98 (0.90-1.06)	0.90 (0.79-1.02)

Abbreviations: CI, confidence interval; RR, relative risk.

Psaty et al, JAMA, 2006; 295:1704-6

Low-dose diuretics associated with reduced risks of all the major outcomes, including

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- heart failure (RR, 0.58;95% CI, 0.44-0.76), and
- total mortality (RR, 0.90; 95% CI,0.81-0.99).

Beta-blockers, primarily atenolol, associated with reduced risks of

- **stroke (RR, 0.71; 95% CI, 0.59-0.86) and**
- **heart failure (RR, 0.58; 95% CI, 0.40-0.84)**
- **but not of coronary heart disease (RR, 0.93; 95% CI,0.80-1.09) or**
- **total mortality (RR, 0.95; 95% CI, 0.84-1.07).**

Beta-blocker therapy

-

Different effect on diseases

▸ clear mortality benefit in the treatment of patients with coronary heart disease regardless of hypertension status

■ apparent inability to prevent coronary heart disease in the treatment of patients with high blood pressure

Different effects within the class

patients with coronary heart disease, strong evidence of a mortality benefit associated with the use of

▸**metoprolol** (RR, 0.80; 95% CI, 0.66-0.90),
▸**propranolol** (RR, 0.71; 95% CI, 0.59-0.85), and
▸**timolol** (RR, 0.59; 95% CI, 0.46-0.77)

whereas the mortality in patients assigned to receive **atenolol** was similar to the mortality in those assigned to receive placebo (RR, 1.02; 95% CI, 0.51-1.99)

N.Freemantle, et al, BMJ 1999; 318:1730-7

Comparator and doses

Exenatide is an incretin mimetic such as glucagon like peptide 1 (GLP-1), facilitate insulin secretion following its release from the gut into the circulation in response to food intake.

http://www.emea.europa.eu/humandocs/PDFs/EPAR/byetta/H-698-en6.pdf

Table 1: Summary of Efficacy Results for Exenatide Long-Term Placebo- and Active-Comparator Controlled Studies (Intent-to-Treat Subjects)

Study	N	Change From Baseline to Endpoint (LOCF) (Least Squares Mean ± Standard Error)		
		Haemoglobin A_{1c} (%)	Fasting Glucose (mmol/L)	Body Weight (kg)
H8O-MC-GWAA (Metformin + Sulphonylurea) – 26 Weeks of Treatment				
Insulin glargine	[1]	-1.10 ± 0.07	-2.86 ± 0.19	1.85 ± 0.23
Exenatide 10 µg	[1]	-1.13 ± 0.07	-1.22 ± 0.19***	-1.92 ± 0.22***
H8O-MC-GWAD (Metformin + Sulphonylurea) – 52 Weeks of Treatment				
Biphasic insulin aspart	[1]	-0.86 ± 0.08	-1.64 ± 0.19	2.92 ± 0.17
Exenatide 10 µg	[1]	-1.01 ± 0.08	-1.75 ± 0.19	-2.54 ± 0.17***
112 (Metformin) – 30 Weeks of Treatment				
Placebo	113	-0.00 ± 0.106	0.79 ± 0.26	-0.2 ± 0.42
Exenatide 5 µg	110	-0.46 ± 0.112**	-0.29 ± 0.28*	-1.3 ± 0.45*
Exenatide 10 µg	113	-0.86 ± 0.110**	-0.56 ± 0.27*	-2.6 ± 0.44*
113 (Sulphonylurea) – 30 Weeks of Treatment				
Placebo	123	0.06 ± 0.115	0.32 ± 0.29	-0.8 ± 0.32
Exenatide 5 µg	125	-0.51 ± 0.111**	-0.29 ± 0.28	-1.1 ± 0.30
Exenatide 10 µg	129	-0.91 ± 0.110**	-0.60 ± 0.28*	-1.6 ± 0.30*
115 (Metformin + Sulphonylurea) – 30 Weeks of Treatment				
Placebo	247	0.12 ± 0.079	0.72 ± 0.20	-0.9 ± 0.21
Exenatide 5 µg	245	-0.66 ± 0.079**	-0.60 ± 0.20*	-1.6 ± 0.21*
Exenatide 10 µg	241	-0.88 ± 0.080**	-0.68 ± 0.20*	-1.6 ± 0.21*

[1] The primary endpoint, change in haemoglobin A1c, is presented for the Per-Protocol Subjects (GWAA: exenatide N=228, insulin glargine N=228; GWAD: exenatide N=243, biphasic insulin aspart N=240);

Exenatide, Byetta, EPAR

In both long-term active-comparator controlled studies, the change in HbA_{1c} in the exenatide treated group was statistically non-inferior to that of insulin glargine or biphasic insulin aspart. The mean insulin doses were 24.9 IU/day, (range 4-95 IU/day), at the end of study GWAA with insulin glargine and mean insulin dose 24.4 IU /day, (range 3-78 IU/day), at the end of study GWAD with biphasic insulin aspart. In study GWAD the biphasic insulin aspart group had a reduction of HbA1c with 0.86 %, and 8.5 % of the subjects reached HbA1c below 6.5 %. Based on the non-blinded nature of the insulin-comparator studies, a potential bias towards lower insulin doses cannot be fully excluded; however, the Applicant has tried to minimise this potential bias.

http://www.emea.europa.eu/humandocs/PDFs/EPAR/byetta/H-698-en6.pdf

European Tacrolimus *vs* Ciclosporin Microemulsion Renal Transplantation trial, *Lancet* 2002; 359:741–46

	tacrolimus	ciclosporin
Acute renal rejection	32.5%	51.3%
	mean trough concentrations were 10-20 ng/mL: within this range efficacy is optimum and toxic effects at a minimum.	mean blood concentration was lower than 300 ng/mL while the risk of acute renal rejection is at a minimum when trough concentrations are 330–430 ng/mL

…subtherapeutic ciclosporin concentrations were compared with therapeutic tacrolimus concentrations!!

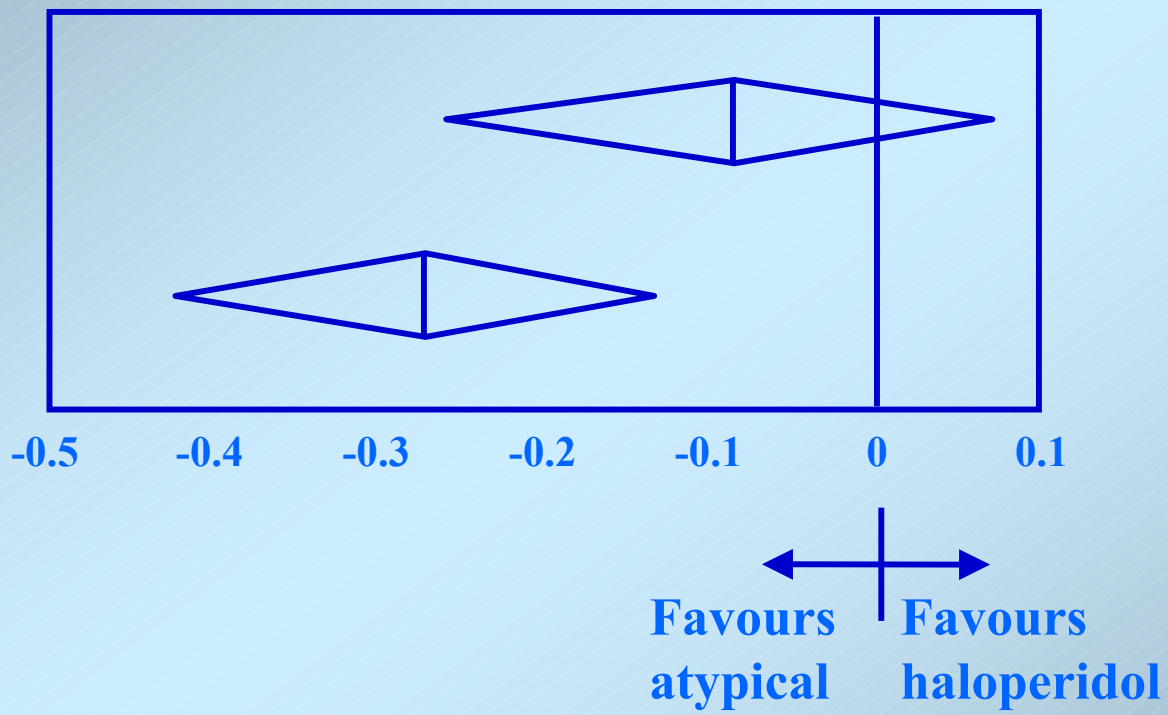
Comparator and doses

fluoxetine	average doses > 30 mg/day in	benefit in
as a test drug	43%	70%
as a reference drug	13%	58%

Barbui C, Hotopf M, Garattini S. Fluoxetine dose and outcome in antidepressant drug trials. Eur J Clin Pharmacol 2002; 58:379-86

≤ 12 mg haloperidol

> 12 mg haloperidol

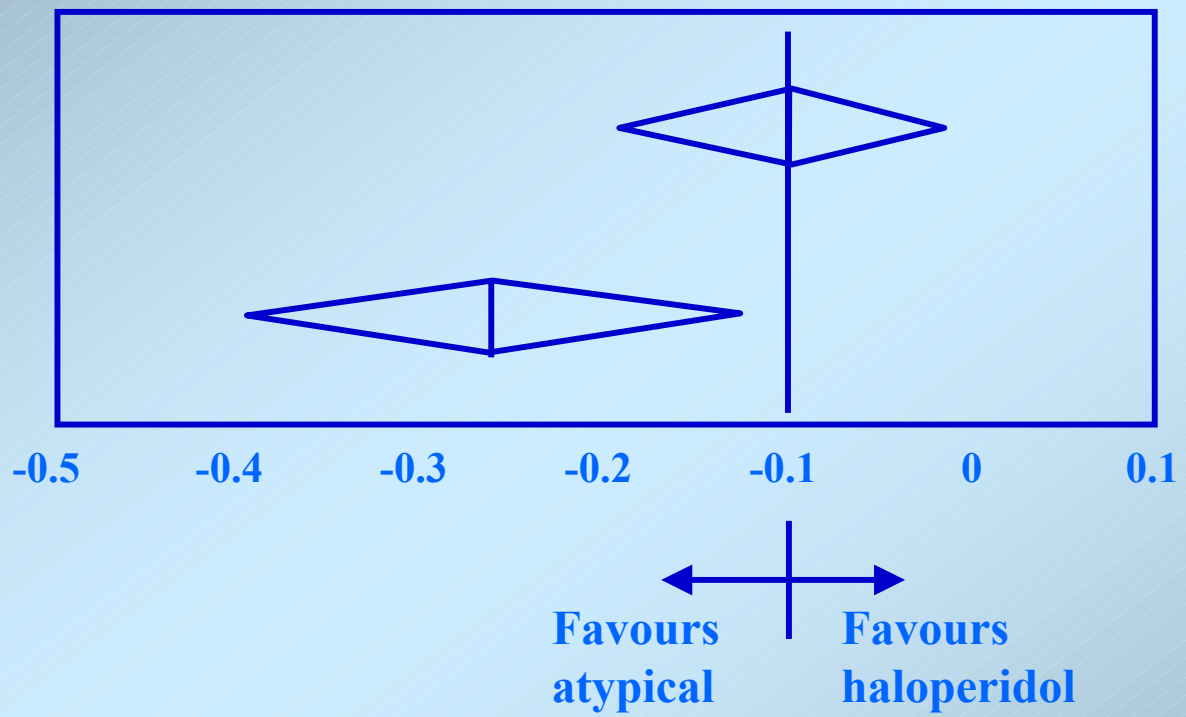


Overall symptom score by dose of comparator drug in trials of patients with schizophrenia or related disorders (standardised weighted mean difference and 95 % confidence intervals)

Geddes et al., 2000

≤ 12 mg haloperidol

> 12 mg haloperidol



Drop out rates by dose of comparator drug in trials of patients with schizophrenia or related disorders (risk difference and 95 % confidence intervals)

Geddes et al., 2000

Comparator and co-treatment

Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial

Lancet 2004; 364: 503–12

*Giuseppe Remuzzi, Mariadomenica Lesti, Eliana Gotti, Maria Ganeva, Borislav D Dimitrov , Bogdan Ene-Iordache, Giulia Gherardi, Donato Donati, Maurizio Salvadori, Silvio Sandrini, Umberto Valente, Giuseppe Segoloni, Georges Mourad, Stefano Federico, Paolo Rigotti, Vito Sparacino, Jean-Louis Bosmans, Norberto Perico, Piero Ruggenenti, for the MYSS Study Group**

Summary

Background Mycophenolate mofetil has replaced azathioprine in immunosuppression regimens worldwide to prevent graft rejection. However, evidence that its antirejection activity is better than that of azathioprine has been provided only by registration trials with an old formulation of ciclosporin and steroid. We aimed to compare the antirejection activity of these two drugs with a new formulation of ciclosporin.

Methods The mycophenolate steroids sparing multicentre, prospective, randomised, parallel-group trial compared acute rejections and adverse events in recipients of cadaver-kidney transplants over 6-month treatment with mycophenolate mofetil or azathioprine along with ciclosporin microemulsion (Neoral) and steroids (phase A), and over 15 more months without steroids (phase B). The primary endpoint was occurrence of acute rejection episodes. Analysis was by intention to treat.

Findings 168 patients per group entered phase A. 56 (34%) assigned mycophenolate mofetil and 58 (35%) assigned azathioprine had clinical rejections (risk reduction [RR] on mycophenolate mofetil compared with azathioprine 13·7% [95% CI –25·7% to 40·7%], p=0·44). 88 patients in the mycophenolate mofetil group and 89 in the azathioprine group entered phase B. 14 (16%) taking mycophenolate mofetil and 11 (12%) taking azathioprine had clinical rejections (RR –16·2%, [–157·5% to 47·5%], p=0·71). Average per-patient costs of mycophenolate mofetil treatment greatly exceeded those of azathioprine (phase A €2665 [SD 586] *vs* €184 [62]; phase B €5095 [2658] *vs* €322 [170], p<0·0001 for both).

Interpretation In recipients of cadaver kidney-transplants given ciclosporin microemulsion, mycophenolate mofetil offers no advantages over azathioprine in preventing acute rejections and is about 15 times more expensive. Standard immunosuppression regimens for transplantation should perhaps include azathioprine rather than mycophenolate mofetil, at least for kidney grafts.

Comparator and sponsorship

A Long-Term Comparison of Galantamine and Donepezil in the Treatment of Alzheimer's Disease

Gordon Wilcock,[1] Ian Howe,[2] Hilary Coles,[3] Sean Lilienfeld,[4] Luc Truyen,[5] Young Zhu,[5] Roger Bullock[6] and Members of the GAL-GBR-2 Study Group

1 Department of Care of the Elderly, University of Bristol, Frenchay Hospital, Bristol, UK
2 Shire Pharmaceuticals, Ltd., Chineham, Basingstoke, Hampshire, UK
3 Janssen-Cilag UK, Saunderton, High Wycombe, Buckinghamshire, UK
4 Janssen Pharmaceutica Products, L.P., Titusville, New Jersey, USA
5 Johnson & Johnson Pharmaceutical Research & Development, LLC, Titusville, New Jersey, USA
6 Department of Old Age Psychiatry, Kingshill Research Centre, Victoria Hospital, Swindon, UK

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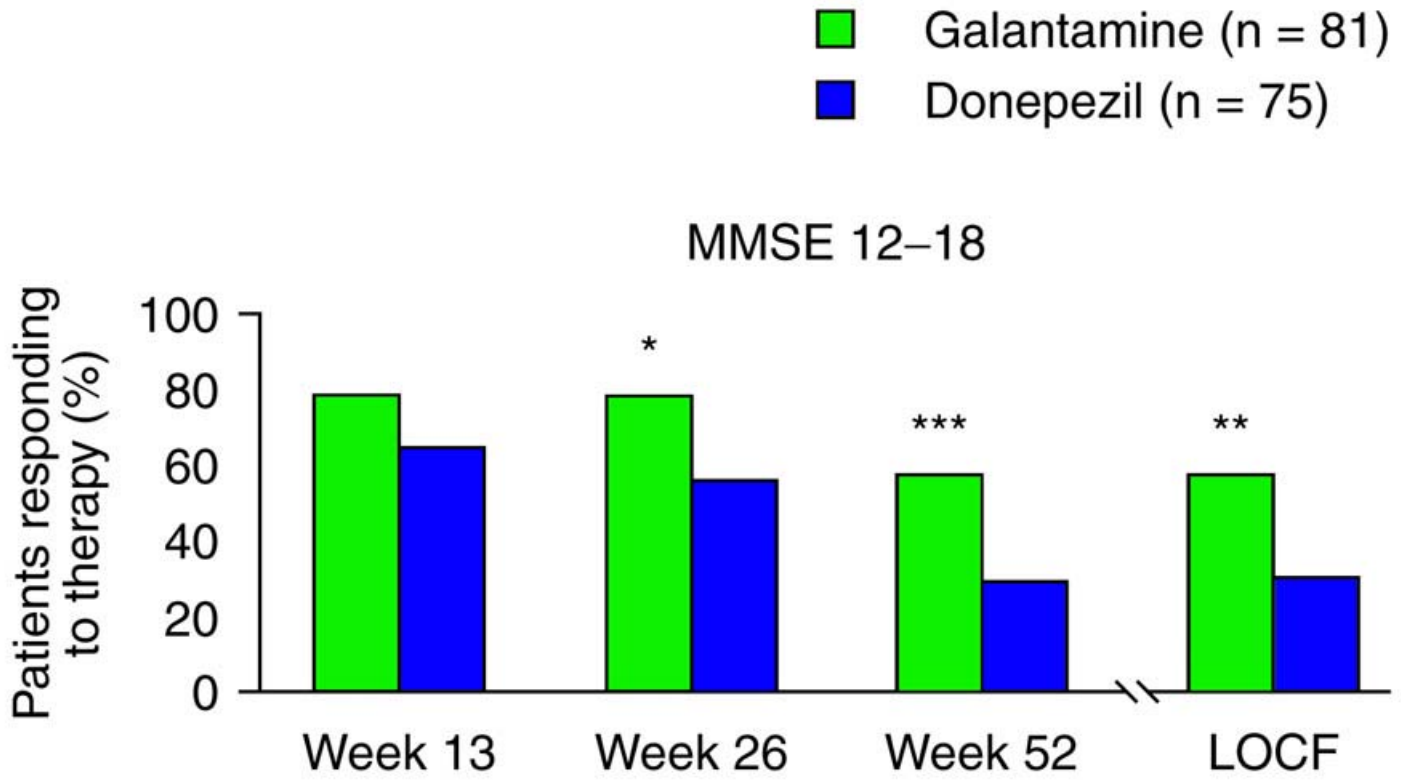

Proportion of galantamine and donepezil recipients responding to therapy (improvement or no change in MMSE score vs baseline); results in the total population and subgroup with baseline MMSE scores of 12–18. **LOCF** = last observation carried forward; **MMSE** = Mini-Mental State Examination; * $p \leq 0.01$, ** $p \leq 0.005$, *** $p < 0.001$ vs donepezil.

Wilcock et al., 2003

A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease

Roy W. Jones[1]*, Hilkka Soininen[2], Klaus Hager[3], Dag Aarsland[4], Peter Passmore[5], The DONGAL Study Group, Anita Murthy[6], Richard Zhang[7] and Ranbir Bahra[7]

[1]*Research Institute for the Care of the Elderly, St Martin's Hospital, Bath, UK*
[2]*Department of Neurology, Kuopio University Hospital, Finland*
[3]*Department of Medical Rehabilitation and Geriatrics Henriettenstiftung, Hannover, Germany*
[4]*Rogaland Psykiatriske Sykehus, Stavanger, Norway*
[5]*Department of Geriatric Medicine, Queen's University, Belfast, UK*
[6]*Eisai Inc., Teaneck, New Jersey, USA*
[7]*Pfizer Inc., New York, USA*

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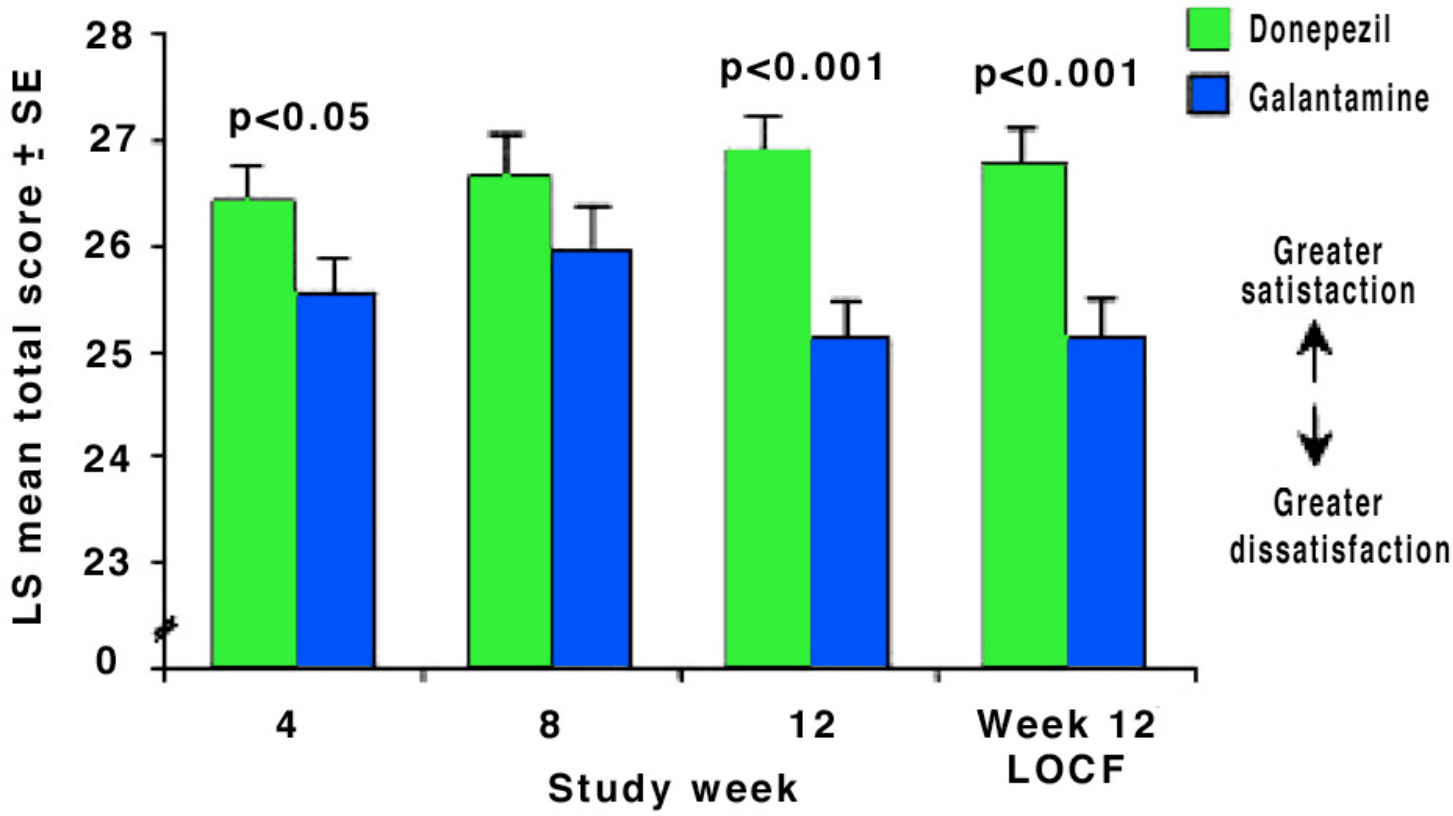
Physician's Satisfaction/Ease of Use Questionnaire Total Score (ITT population)



Donepezil n=60	60	60	(64)
Galantamine n=54	53	52	(56)

Score renges from a minimum of 6 to a maximum of 30

Jones et al., 2003

…solo un anello di una lunga catena di bias

- Scelta inappropriata dell'ipotesi (domanda vera per il paziente, non per il farmaco)
- Scelta inappropriata dei criteri di valutazione (test di superiorità vs non-inferiorità)
- Scelta inappropriata delle misure di outcome (sopravvivenza e qualità della vita vs endpoint surrogati)
- Scelta inappropriata del comparatore o delle sue dosi
- Ricerca selettiva di alcuni eventi avversi soltanto (sintomi GI vs MI per i coxib)
- Pubblicazione selettiva degli studi o dei dati
- Conflitti di interesse

	PAIN RELIEF	CARDIOVASCULAR TOXICITY	GASTROINTESTINAL EVENTS
DICLOFENAC	1	1	0.32/100
ETORICOXIB	1	1.05 (0.93-1.19)	0.30/100

Psaty and Weiss, 2007

GI RISK FACTORS	WITHOUT cv RISK	WITH cv RISK
NO GI RISK	NSAID	SELECTED NSAID (NO COXIB)
INTERMEDIATE GI RISK	NSAID + MISOPROSTOL	SELECTED NSAID + MISOPROSTOL
HIGH GI RISK (PREVIOUS ULCER COMPLICATION)	NO COXIB and NO NSAID IF NECESSARY COXIB + PPI	NO COXIB and NO NSAID IF NECESSARY SELECTED NSAID + PPI OR MISOPROSTOL

	Outcome		
	Favourable	Neutral	Unfavourable
Sponsorship v. outcome favouring SSRIs over TCAs: industry v. non-industry studies			
Industry sponsor	13	4	0
Non-industry sponsor	1	2	3
Sponsorship v. outcome favouring newest antidepressant: industry v. non-industry studies			
Industry sponsor	25	7	1
Non-industry sponsor	1	2	4
Sponsorship v. outcome favouring newest antidepressant: industry v. non-industry modelling studies			
Industry sponsor	18	0	1
Non-industry sponsor	1	1	3

Baker et al., 2003

Recent Trials in Hypertension
Compelling Science or Commercial Speech?

Table. Summary of the Design and Primary Results of Recent Comparative Trials in Hypertension[17-20]

	Trial			
	LIFE,[17] 2002	VALUE,[18] 2004	INVEST,[19] 2003	ASCOT,[20] 2003
Intervention				
Active group	Losartan	Valsartan	Verapamil	Amlodipine
Comparison group	Atenolol	Amlodipine	Atenolol	Atenolol
No. of participants	9193	15 245	22 579	19 257
Heart failure in primary composite outcome?	No	Yes	No	No
Primary outcome, RR (95% CI)	0.87 (0.77-0.98)	1.04 (0.94-1.15)	0.98 (0.90-1.06)	0.90 (0.79-1.02)

Psaty et al, Jama 2006

TACROLIMUS VS CYCLOSPORINE

32.5 %　　51.3 %

ACUTE REJECTIONS

MARGREITER et al., 2002 TRIAL
CYCLOSPORINE < 300 ng/ml

ACUTE RENAL REJECTIONS ARE MINIMIZED WHEN TROUGH LEVELS ARE KEPT BETWEEN 330 - 430 ng/ml

PATIENTS WITH EVENTS ON PHASE A

	Mycophenolate mofetil	Azathioprine	p
Acute rejection episodes			
Clinical diagnosis	56 (34%)	58 (35%)	0·91
Biopsy proven	30 (18%)	38 (23%)	0·34
Steroid resistant	9 (5%)	18 (11%)	0·11
Refractory*	2 (1%)	2 (1%)	0·99
Banff score ⩾2	28 (17%)	38 (23%)	0·22

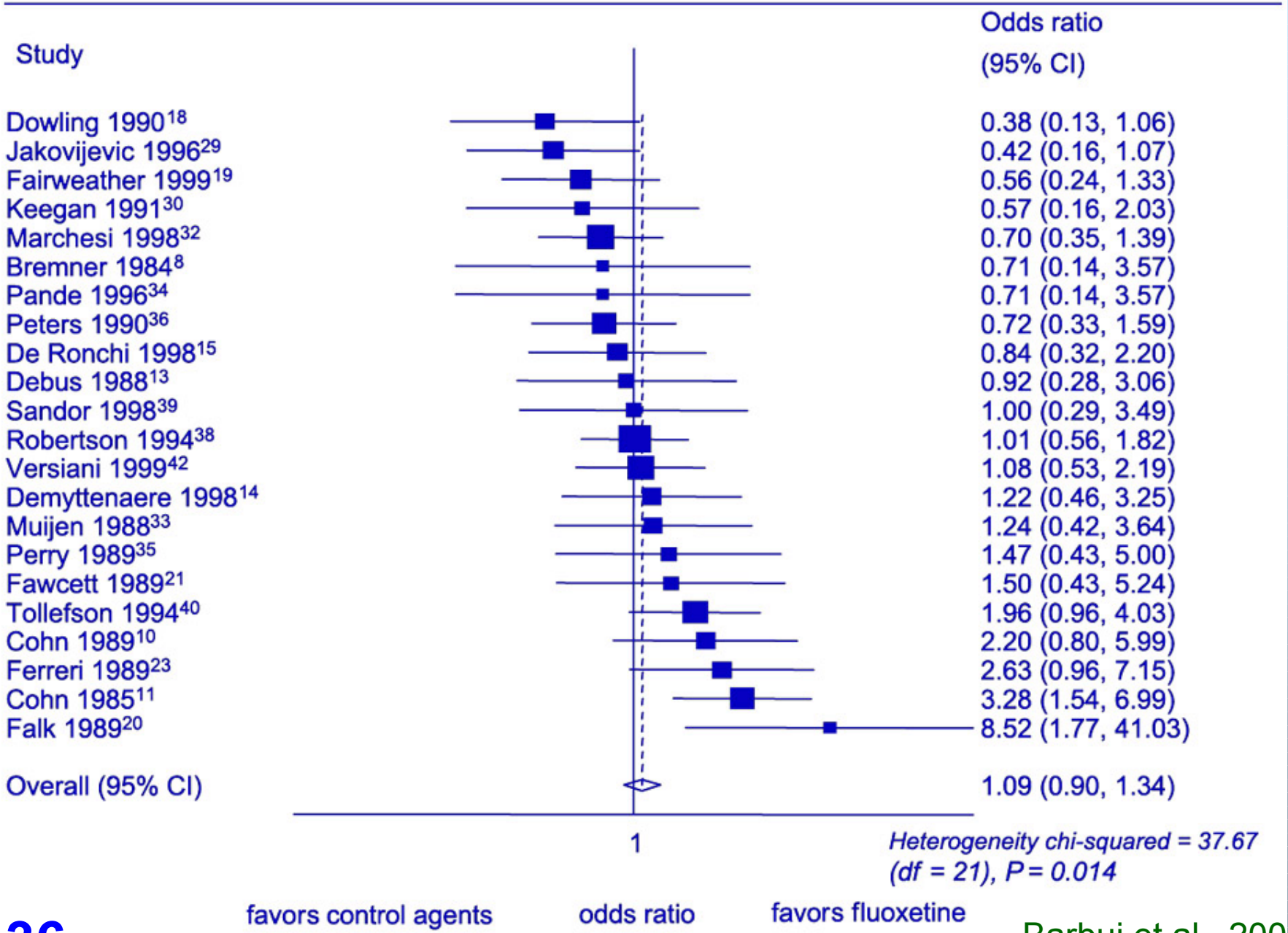
Remuzzi et al, 2004

PATIENTS WITH EVENTS ON PHASE A

	Mycophenolate mofetil	Azathioprine	p
Adverse events			
Deaths	4 (2%)	4 (2%)	0·99
Delayed graft function	52 (31%)	59 (35%)	0·49
White blood-cell count $<3{\cdot}5\times10^9$/L	32 (19%)	22 (13%)	0·18
Platelet count $<60\times10^9$/L	2 (1%)	5 (3%)	0·45
Anaemia	10 (6%)	12 (7%)	0·82
Diarrhoea	3 (2%)	1 (1%)	0·99
Urinary tract infection	11 (7%)	6 (4%)	0·32
CMV reactivations	43 (26%)	42 (25%)	0·99
Ganciclovir-treated	40 (24%)	39 (23%)	0·99

2027

Outcome of RCTs where fluoxetine was the experimental agent.



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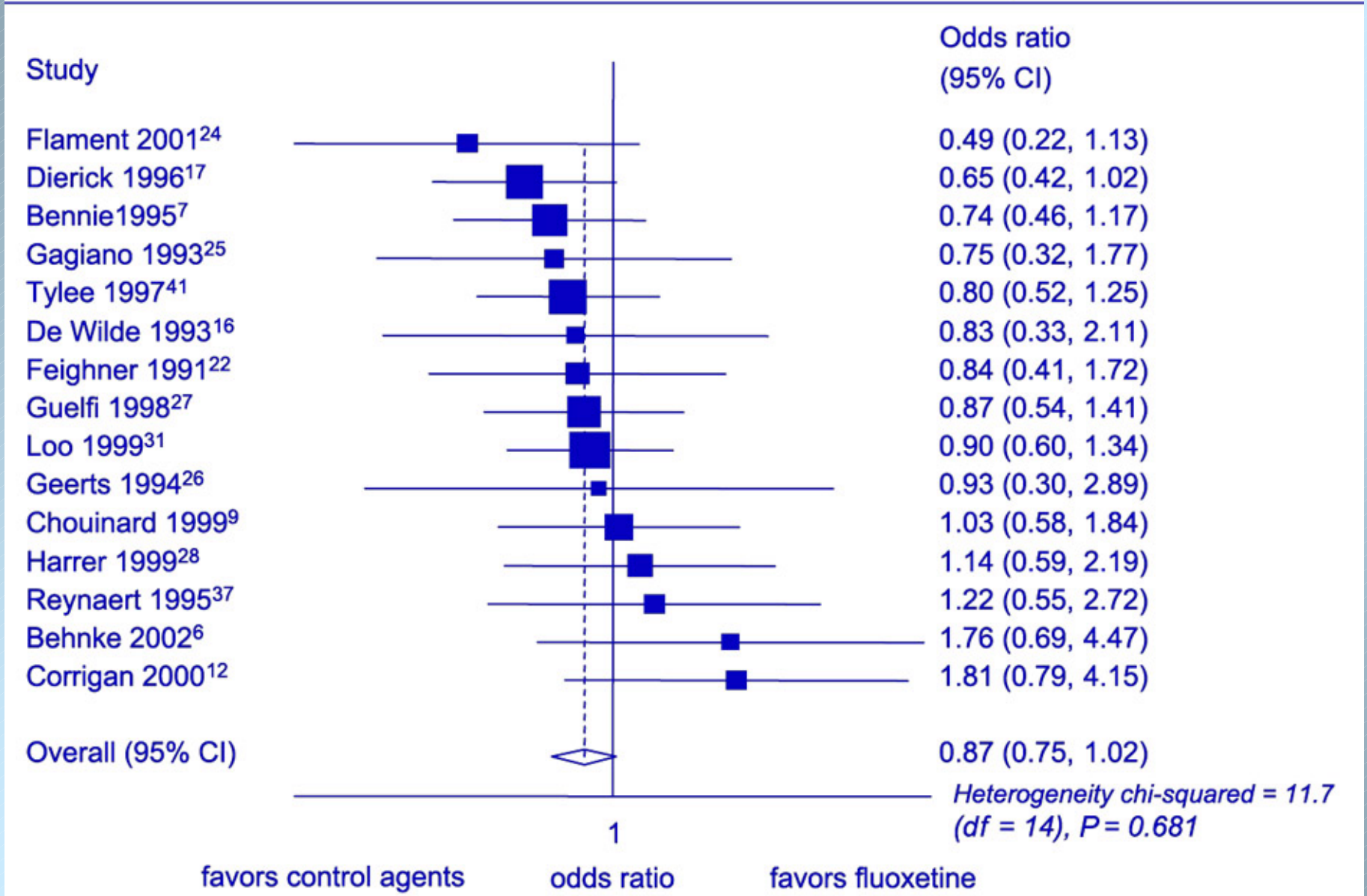
Barbui et al., 2004

Outcome of RCTs where fluoxetine was the comparator agent.



3435

Barbui et al., 2004

- **ATYPICAL ANTIPSYCHOTICS HAVE A SIMILAR EFFECT ON SYMPTOMS TO CONVENTIONAL ANTIPSYCHOTICS AT AN AVERAGE DOSE OF ≤ 12 mg HALOPERIDOL OR EQUIVALENT**

- **ATYPICAL ANTIPSYCHOTICS CAUSE FEWER EXTRAPYRAMIDAL SIDE EFFECTS, BUT OVERALL TOLERABILITY IS SIMILAR TO CONVENTIONAL DRUGS.**

GEDDES et al., 2000

Quality of Reporting of Noninferiority and Equivalence Randomized Trials

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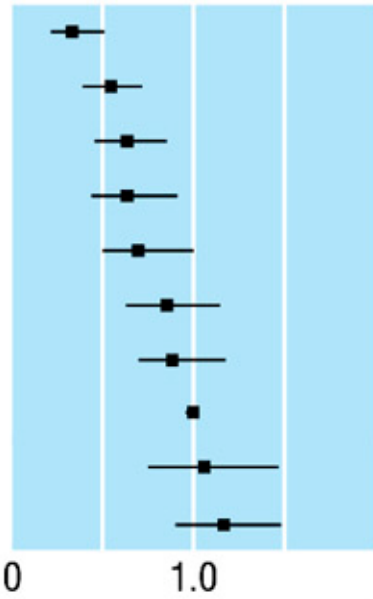
Bruno Giraudeau, PhD
Gabriel Baron, MSc

JAMA, March 8, 2006—Vol 295, No. 10 1147

Results

A total of 162 reports were included in the analysis (116 reports of noninferiority and 46 of equivalence). The margin defining noninferiority or equivalence was described in most reports (156 [96.3%]), with justification of the margin in only 33 (20.4%). Almost one quarter of the reports (35 [21.6%]) did not describe a sample size calculation, and an additional 11 (6.8%) did not take into account a prespecified noninferiority or equivalence margin.

	No of relapses	Person years	Incidence	Fully adjusted relative risk (95% CI)
Perphenazine depot	53	187	0.28	0.32 (0.22 to 0.49)
Olanzapine	329	822	0.40	0.54 (0.41 to 0.71)
Clozapine	336	804	0.42	0.64 (0.48 to 0.85)
Chlorprothixene	79	146	0.54	0.64 (0.45 to 0.91)
Thioridazine	115	201	0.57	0.70 (0.51 to 0.96)
Perphenazine oral	155	327	0.47	0.85 (0.63 to 1.13)
Risperidone	343	651	0.53	0.89 (0.69 to 1.16)
Haloperidol oral	73	107	0.68	1.00
Chlorpromazine	82	127	0.64	1.06 (0.76 to 1.47)
No antipsychotic drugs	2248	3362	0.67	1.16 (0.91 to 1.47)



Relative risk of rehospitalisation by treatment. Adjusted for sex, calendar year, age at onset of follow-up, number of previous relapses, duration of first hospitalisation, and length of follow-up by a multivariate regression model alone (adjusted column) and by multivariate regression and the propensity score method

Tiihonen et al., 2006

What this study adds

The effectiveness of first and second generation antipsychotics varies greatly in a real world setting

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Patients treated with perphenazine depot, clozapine, or olanzapine have a lower risk of rehospitalisation or all cause discontinuation of their initial treatment than patients treated with haloperidol

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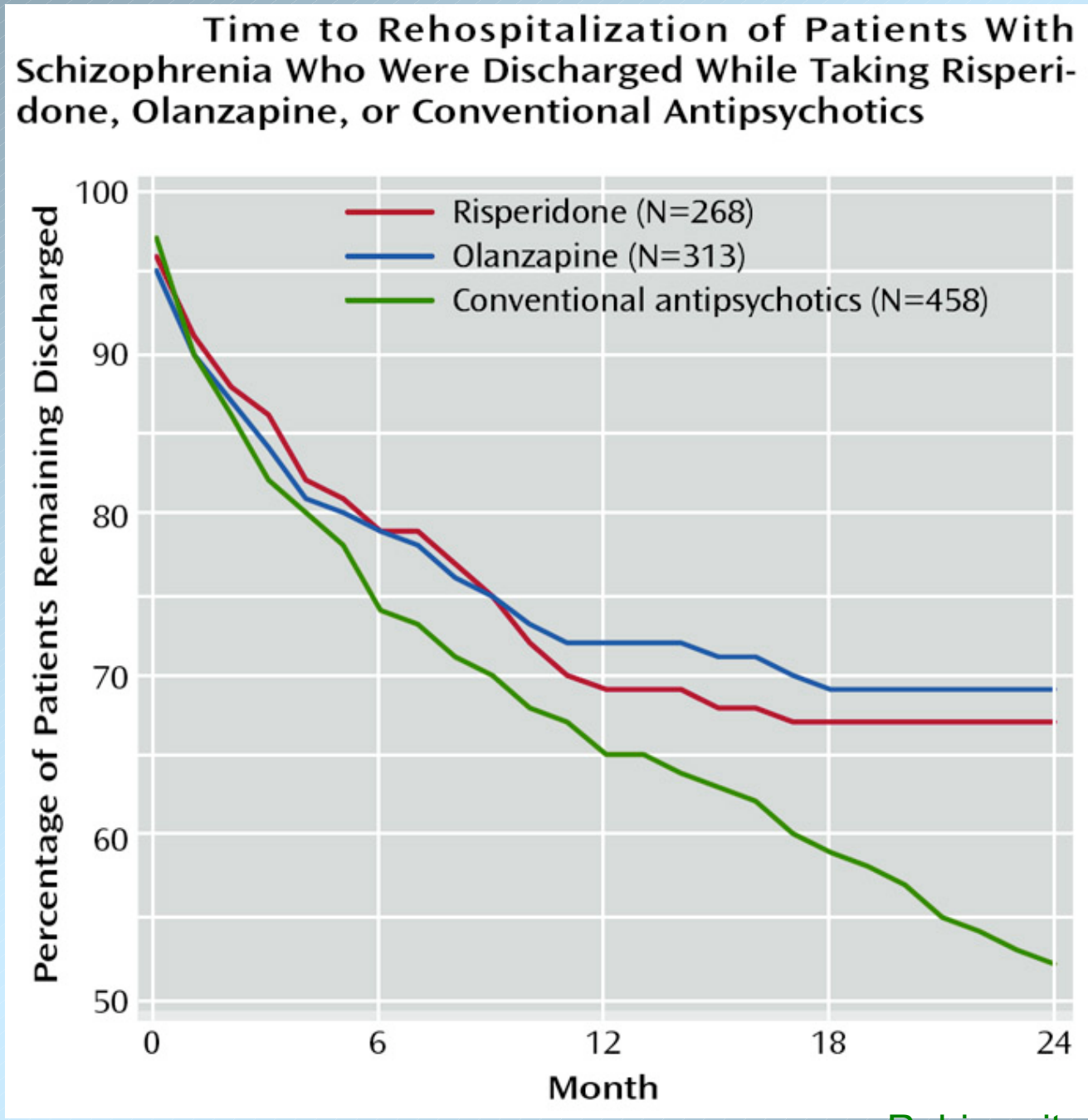
Excess mortality is seen mostly in patients not taking antipsychotic drugs

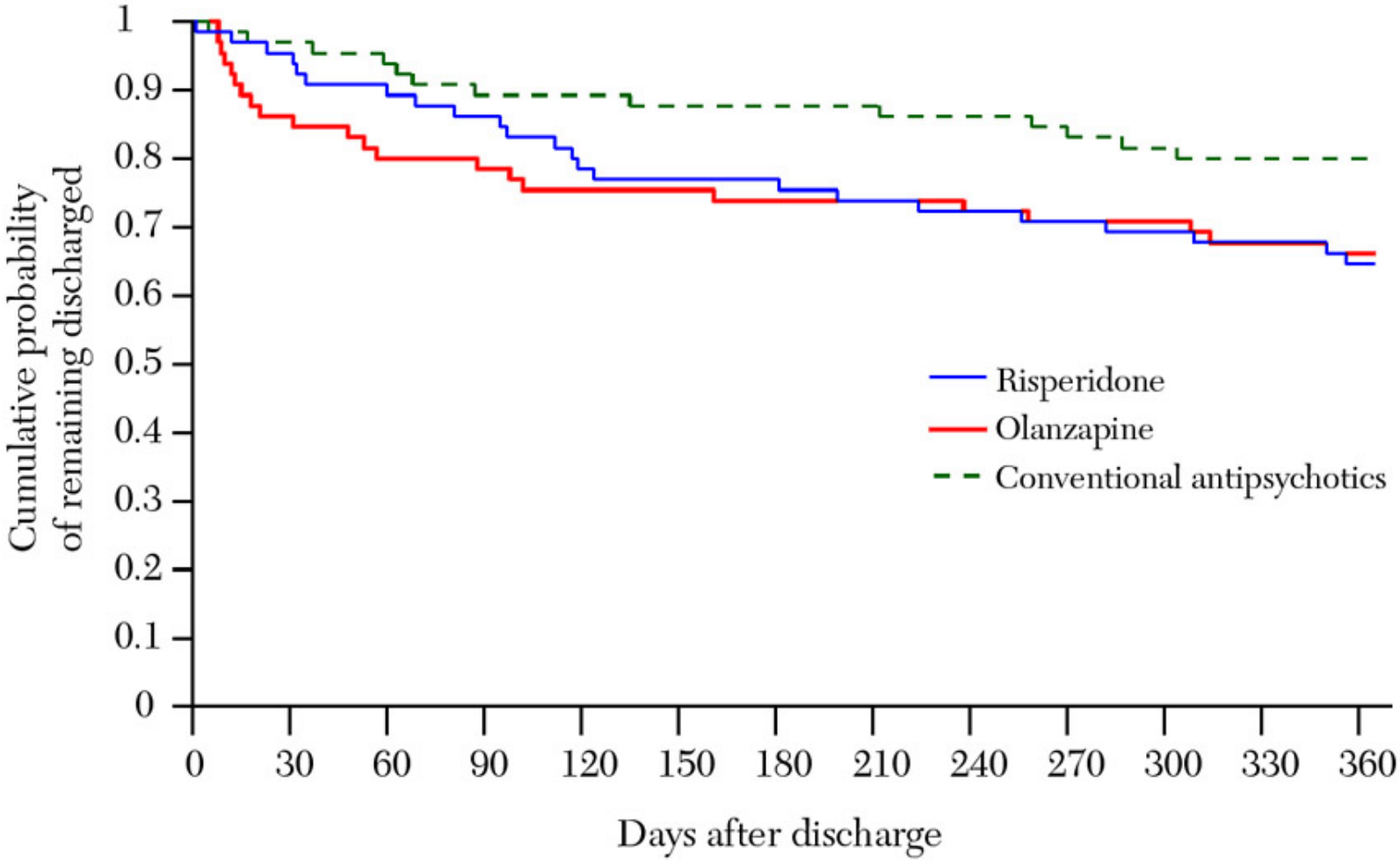
Tiihonen et al., 2006



3640

Rabinowitz et al., 2001

Time to rehospitalization among patients who were discharged from the hospital with a prescription for olanzapine, risperidone, or a conventional antipsychotic[a]

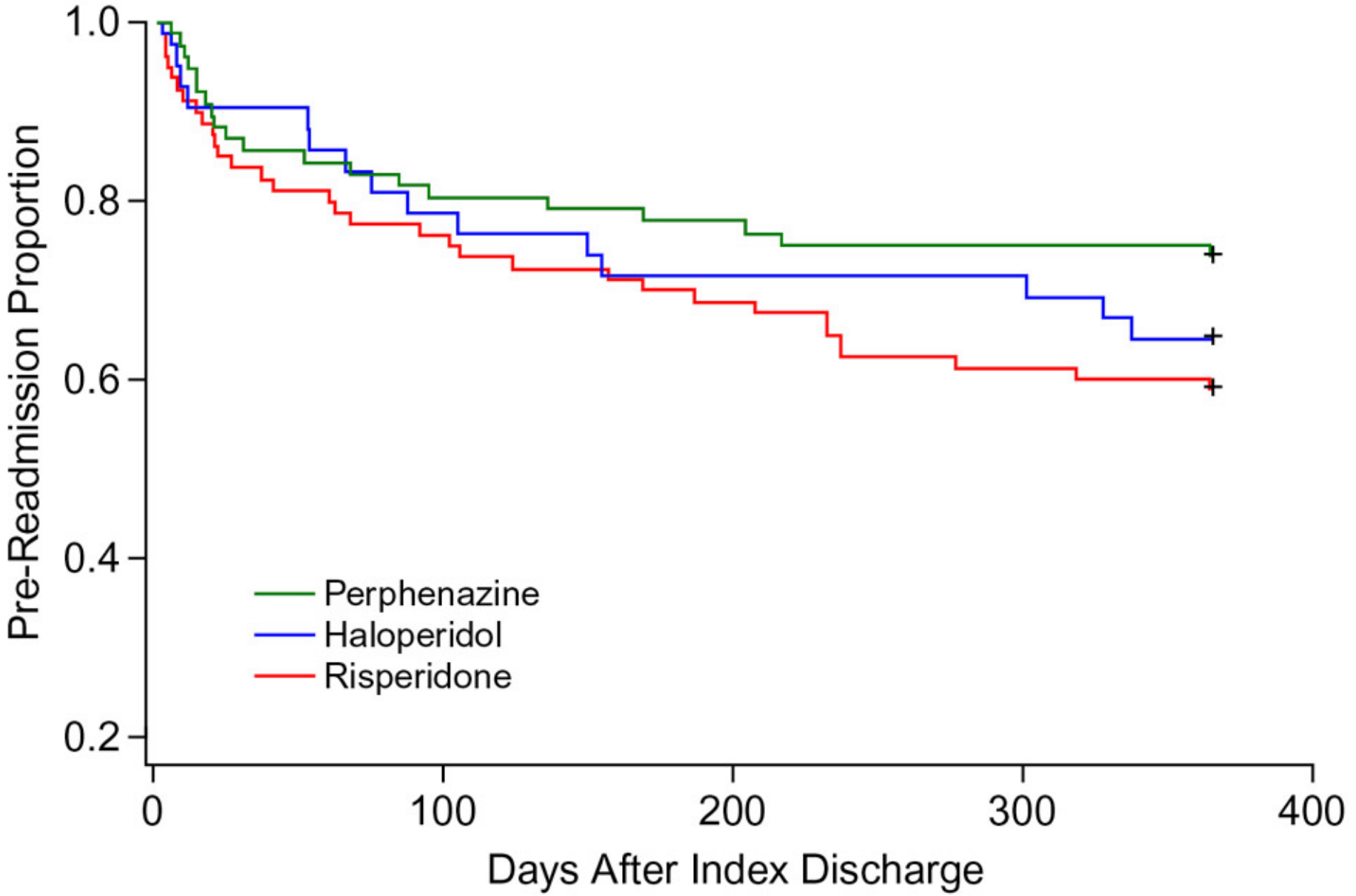


[a] Significant difference between olanzapine and conventional antipsychotic groups at 180 days (Mantel-Haenszel χ^2=3.981, df=1, p=.046).

3641

Patel et al., 2002

Time to First Readmission by Index Drug



3642

Coley et al., 1999

Outcome of Studies by Support of Research

Outcome of Study	Studies Supported by a Drug Company (n = 40)	Studies Not Supported by a Drug Company (n = 112)
	n(%)	
Favorable	39 (98)	89 (79)
Not favorable	1 (2)	23 (21)

Cho and Bero, 1996

WITH DOSES OF CHLORPROMAZINE < 600 mg

NO DIFFERENCE WITH ATYPICAL ANTIPSYCHOTICS
IN TERMS OF EPS

NO DIFFERENCE FOR 9/10 OF PATIENTS
IN TERMS OF EFFICACY

LEUCHT et al., 2003