Abwägung zwischen Schaden und Nutzen medizinischer Interventionen

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Outline

- Wall Street, New York, Sept 30, 2004
  - Rofecoxib: harms → benefits
- Barcelona, Sept 2, 2006
  - Drug-eluting stents: benefits → harms
- *Disclaimer: costs not taken into account*

Sept 30, 2004


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Nov03
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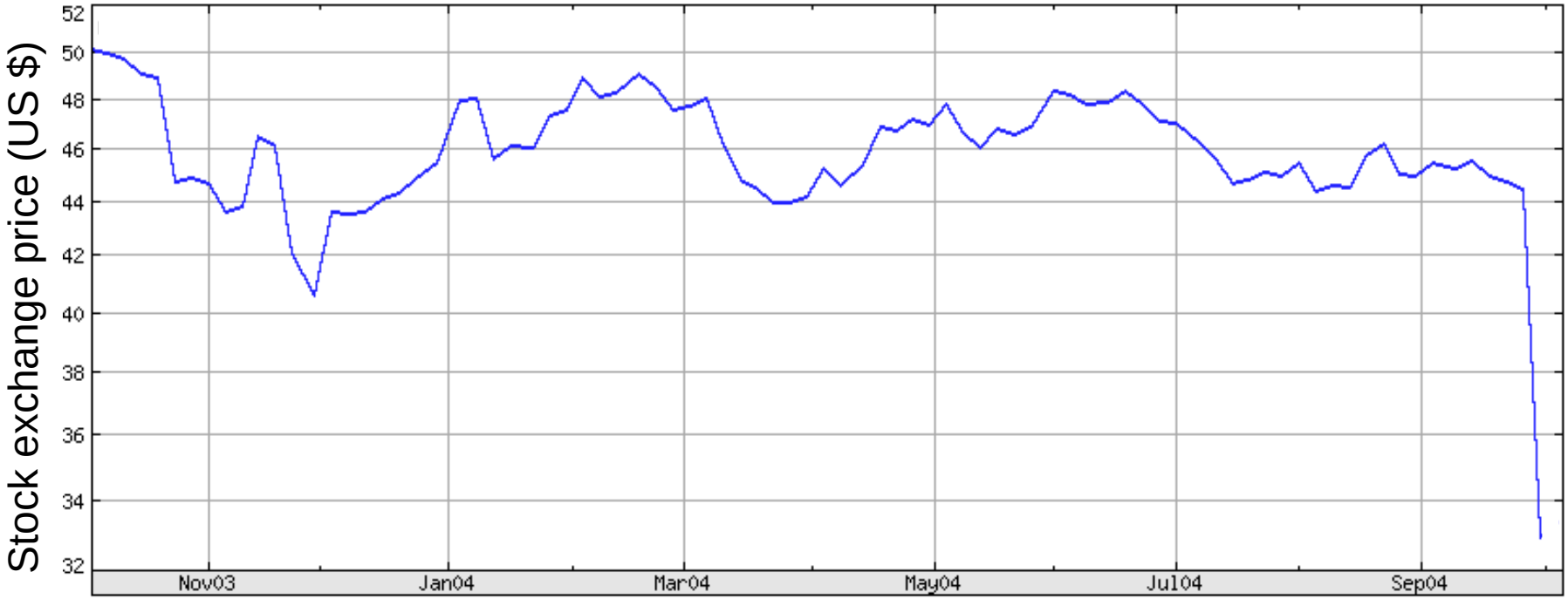
Mar04
May04
Jul04
Sep04

Merck, Sharp & Dohme: New York Stock Exchange



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

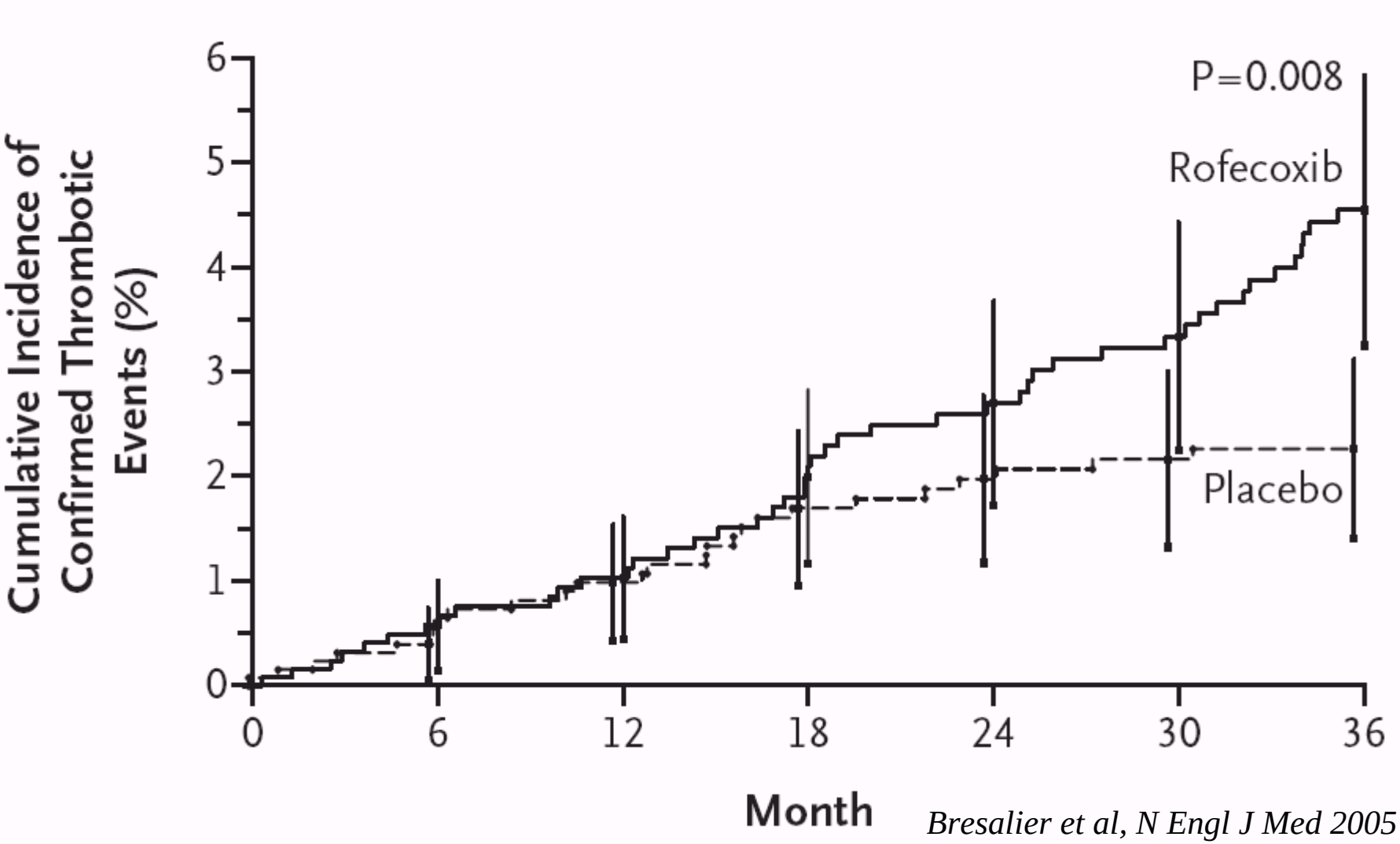
Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators*

ABSTRACT

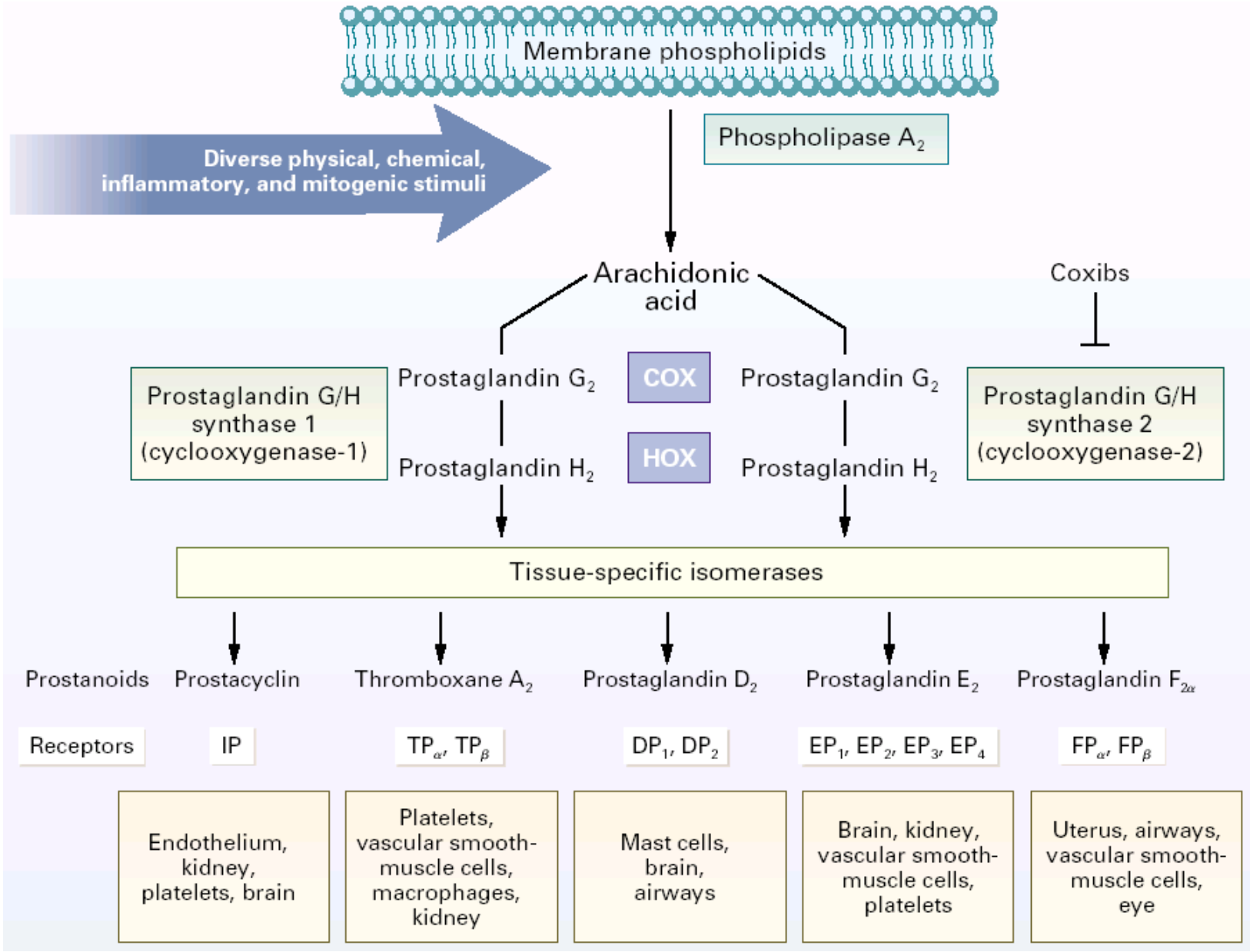
BACKGROUND

Selective inhibition of cyclooxygenase-2 (COX-2) may be associated with an increased risk of thrombotic events, but only limited long-term data have been available for analysis. We report on the cardiovascular outcomes associated with the use of the selective

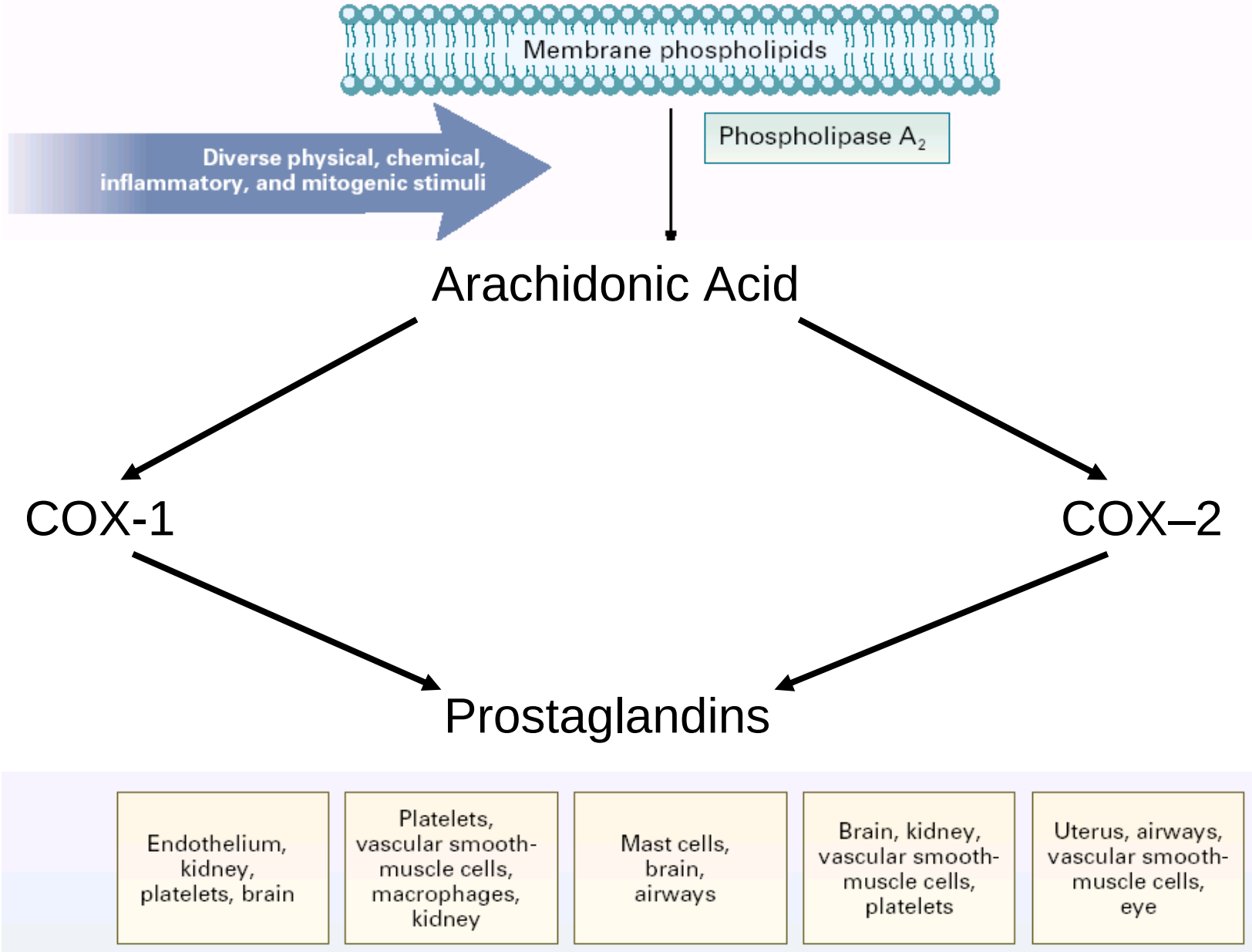
Bresalier et al, N Engl J Med 2005



Bresalier et al, N Engl J Med 2005



FitzGerald, N Engl J Med 2001



FitzGerald, N Engl J Med 2001

Thrombotic risk

	COX-2	COX-1	Thrombotic Risk
Low-Dose Aspirin	=	⇓⇓	⇓
Conventional NSAIDs	⇓	⇓	Unclear
COX-2 Specific Inhibitors	⇓	=	Unclear

Catella-Lawson, Am J Med 2001

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 272–277, January 1999
Pharmacology

Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2

(prostaglandins/platelets/monocytes/ibuprofen/celecoxib)

(...) trials much larger than those necessary to detect efficacy (...) in arthritis will be necessary to determine whether cardiovascular consequences (...) will modulate the anti-inflammatory benefit to be derived from chronic administration of COX-2 inhibitors in humans.

McAdam et al, Proc Natl Acad Sci U S A. 1999

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

ABSTRACT

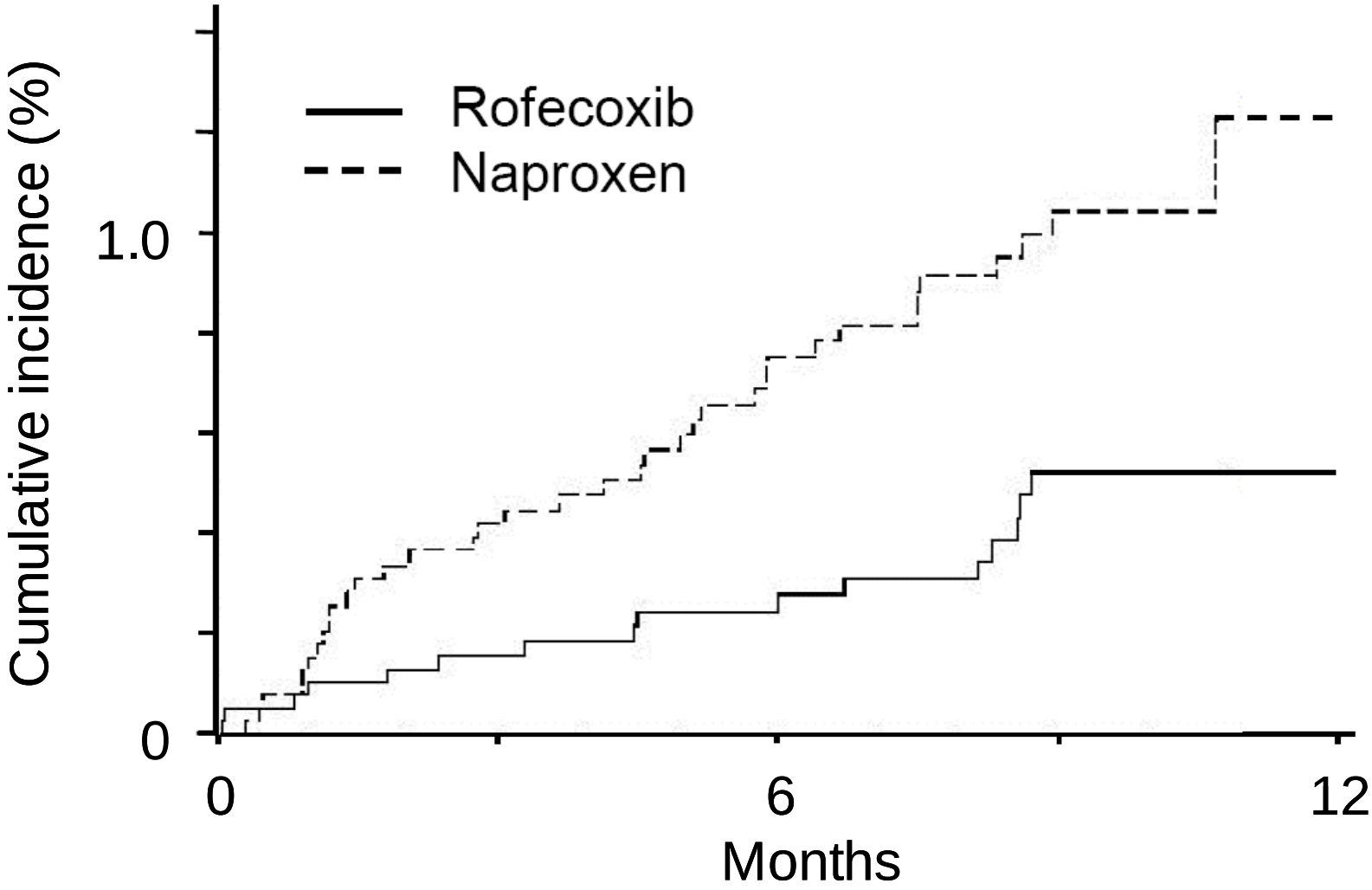
Background Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods We randomly assigned 8076 patients who were at least 50 years of age (or at least 40 years of age and receiving long-term glucocorticoid therapy) and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. The primary end point was confirmed clinical

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs,[2] the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events.[3,4]

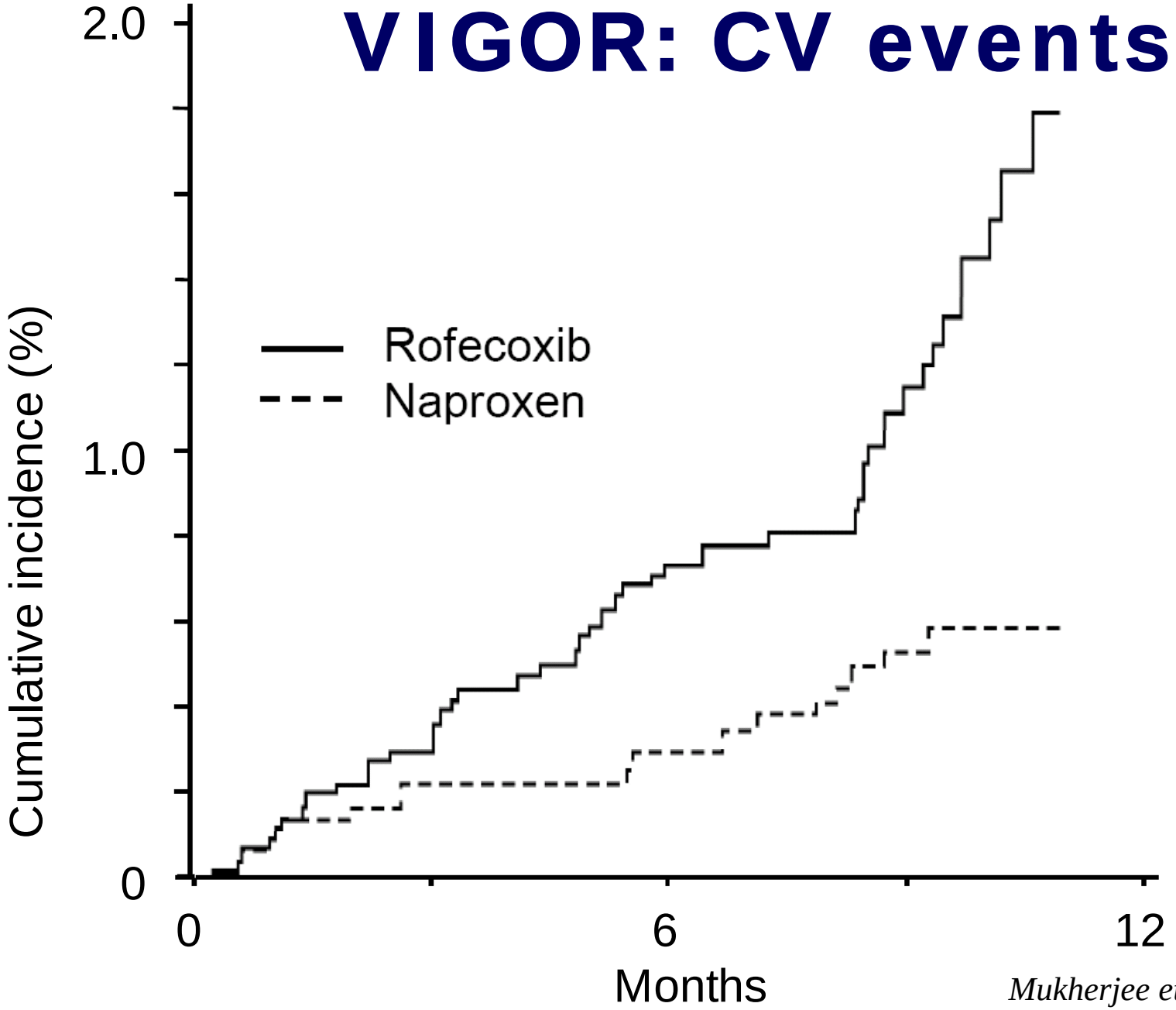
Most NSAIDs inhibit both cyclooxygenase-1 and cyclooxygenase-2, isoenzymes involved in the synthesis of prostaglandins.[5] Cyclooxygenase-1 is constitu-

VIGOR: Ulcer complications



Bombardier et al, N Engl J Med 2000

VIGOR: CV events



Mukherjee et al, JAMA 2002

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Relative risk of myocardial infarction: 5.0 (95% CI 1.7 to 14.5)

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Bombardier et al, N Engl J Med 2000

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Our results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection owing to its selective inhibition of cyclooxygenase-2 at its therapeutic dose and at higher doses.

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Bombardier et al, N Engl J Med 2000


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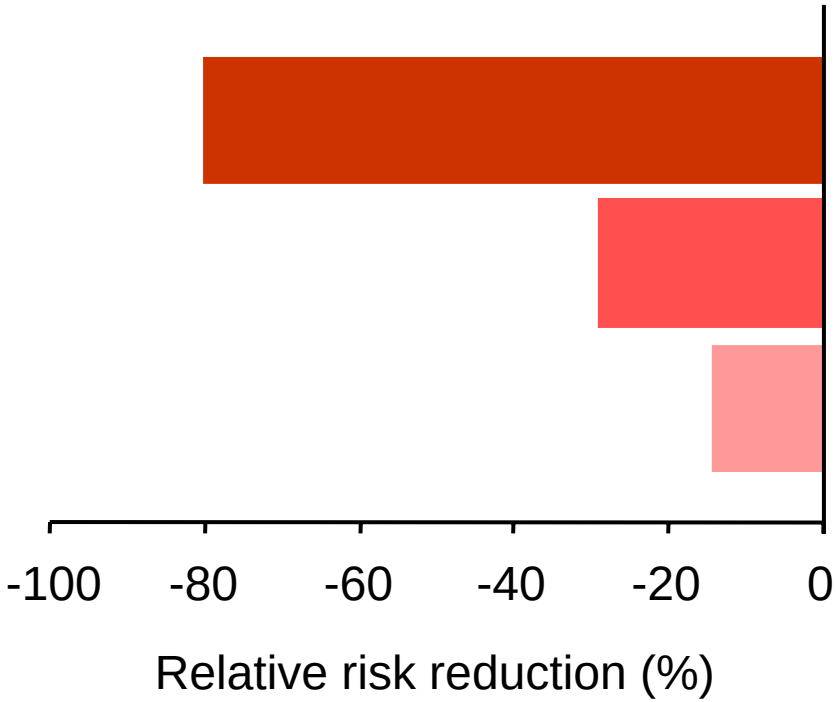
PAS 493

Naproxen‘s «cardioprotective potential» in VIGOR

- Rofecoxib‘s relative risk for MI: 5.0
- Naproxen‘s relative risk for MI: 1/5=0.2
- Naproxen‘s relative risk reduction: 1-0.2 → 80%

Magnitude of cardio-protective potential



Naproxen versus rofecoxib in VIGOR trial

Aspirin in RCTs

Naproxen in observational studies

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Peter Jüni, Linda Nartey, Stephan Reichenbach, Rebekka Sterchi, Paul A Dieppe, Matthias Egger

Lancet 2004; 364: 2021–29

Published online November 5, 2004 http://image.thelancet.com/extras/04art10237web.pdf

See Comment page 1995

Department of Social and Preventive Medicine, University of Berne, Berne, Switzerland (P Jüni MD, L Nartey DipMed, S Reichenbach MD, R Sterchi, Prof M Egger MD); Department of Rheumatology and Clinical Immunology, Inselspital, University of Berne, Berne, Switzerland (P Jüni, S Reichenbach); and MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol, UK (P Jüni,

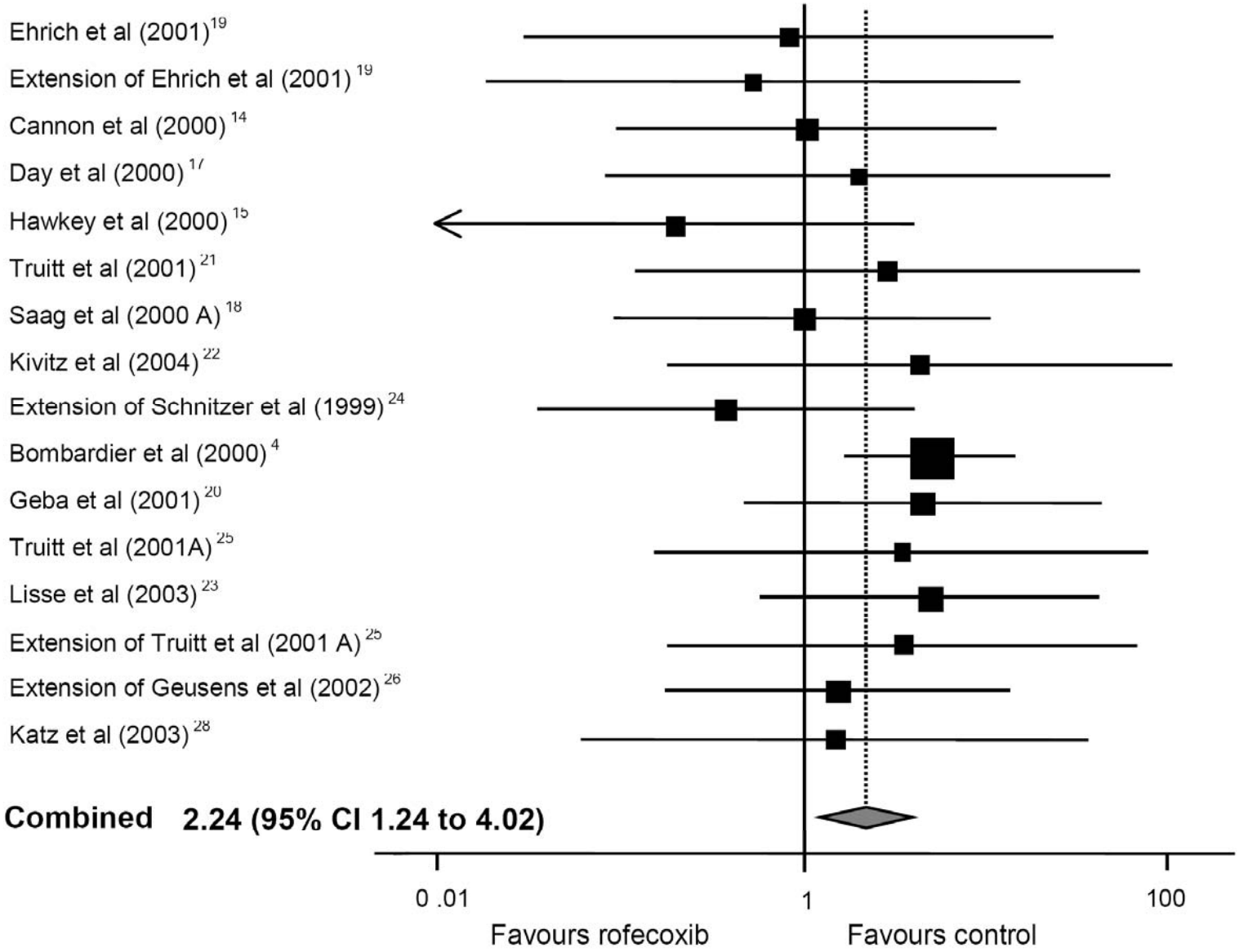
Summary

Background The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint.

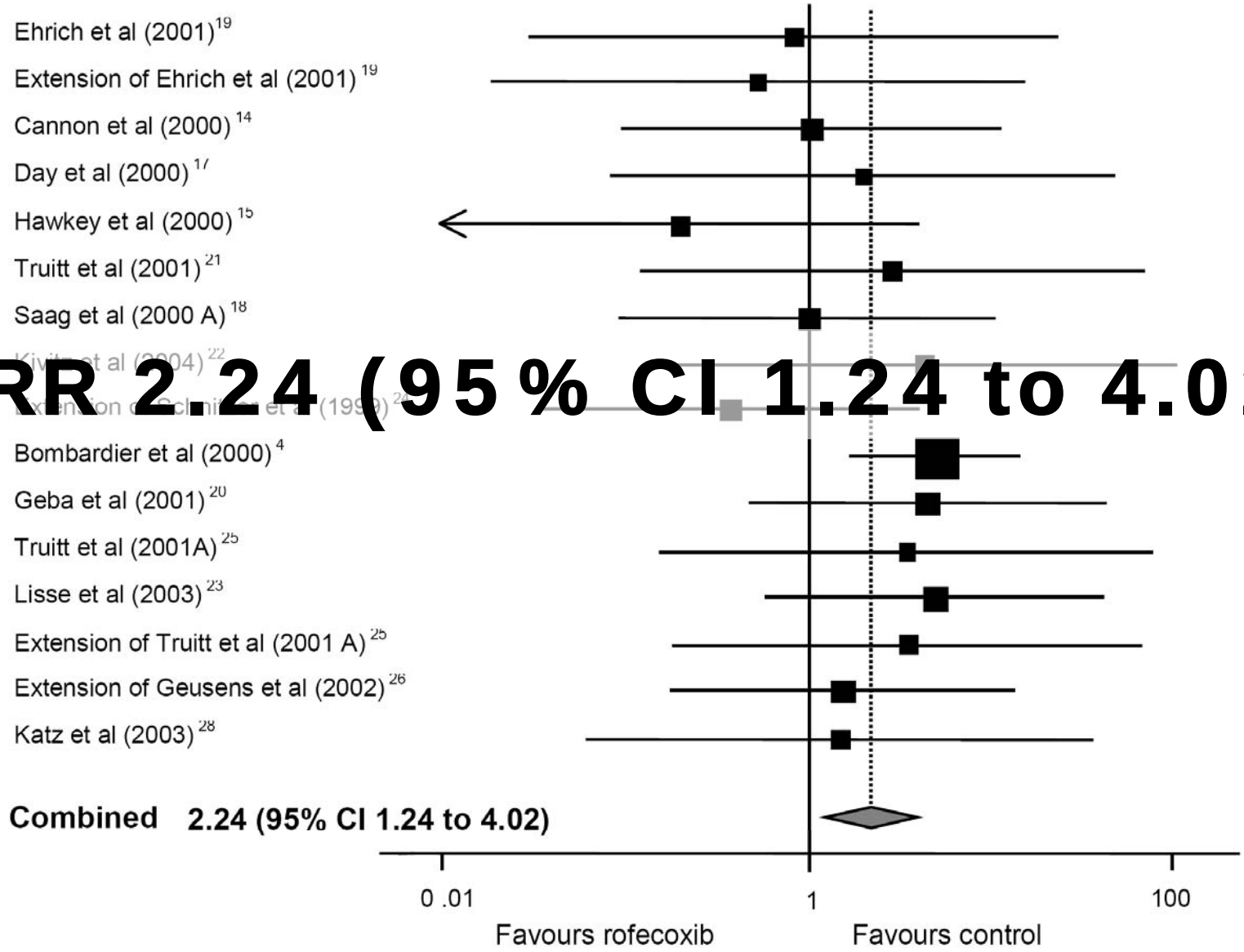
Findings We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20 742 patients) the relative risk from randomised controlled trials was 2·30 (95% CI 1·22–4·33, p=0·010), and 1 year later (64 events, 21 432 patients) it was 2·24 (1·24–4·02, p=0·007). There was little

Jüni et al, Lancet 2004



Relative risk of myocardial infarction

Jüni et al, Lancet 2004



RR 2.24 (95% CI 1.24 to 4.02)

Relative risk of
myocardial infarction

Jüni et al, Lancet 2004

Bottom line regarding harm

- Theory: rofecoxib may harm
- Basic research: rofecoxib may harm
- RCT vs naproxen: rofecoxib harms
- ...
- **RCT vs placebo: rofecoxib harms!**

MERCK

ONCE DAILY VIOXX® (rofecoxib)

PRINT THIS PAGE

Press Release

Prescribing Information

Patient Product Information

Information for Patients

Information for Healthcare Professionals

Information for Direct and Indirect Pharmacy Wholesaler and Retailer Customers

Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004—Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

Observational studies of any help?

RESEARCH

Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies

Panagiotis N. Papanikolaou, Georgia D. Christidi, John P.A. Ioannidis

∞ See related article page 645

Abstract

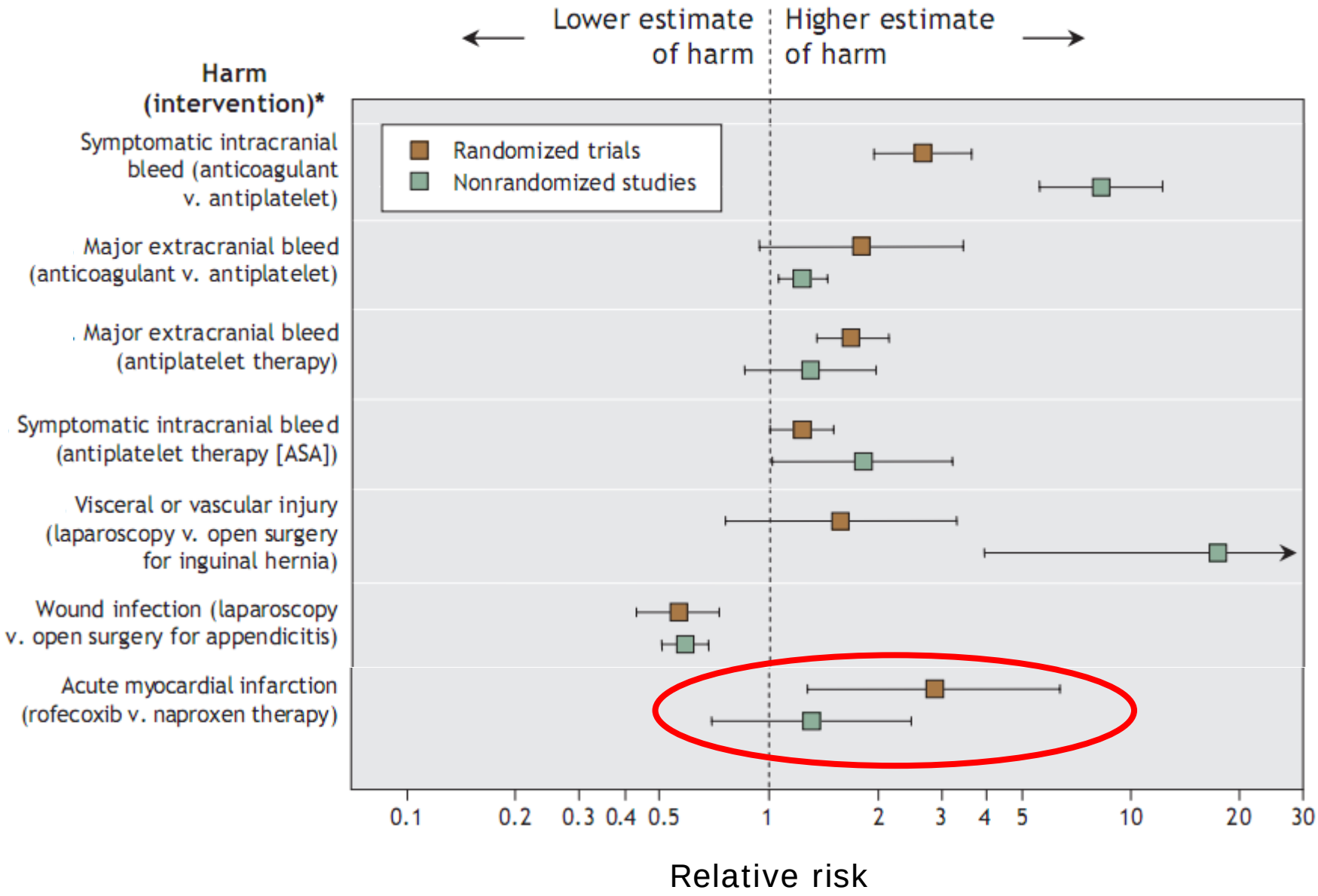
Background: Information on major harms of medical interventions comes primarily from epidemiologic studies performed after licensing and marketing. Comparison with data from large-scale randomized trials is occasionally feasible. We compared evidence from randomized trials with that from epidemiologic studies to determine whether they give different estimates of risk for important harms of medical interventions.

Methods: We targeted well-defined, specific harms of various medical interventions for which data were already avail-

the safety profile is incomplete, and some treatments are occasionally withdrawn from the market because of the emergence of toxic side effects that were either missed or suppressed during clinical development.[3,4]

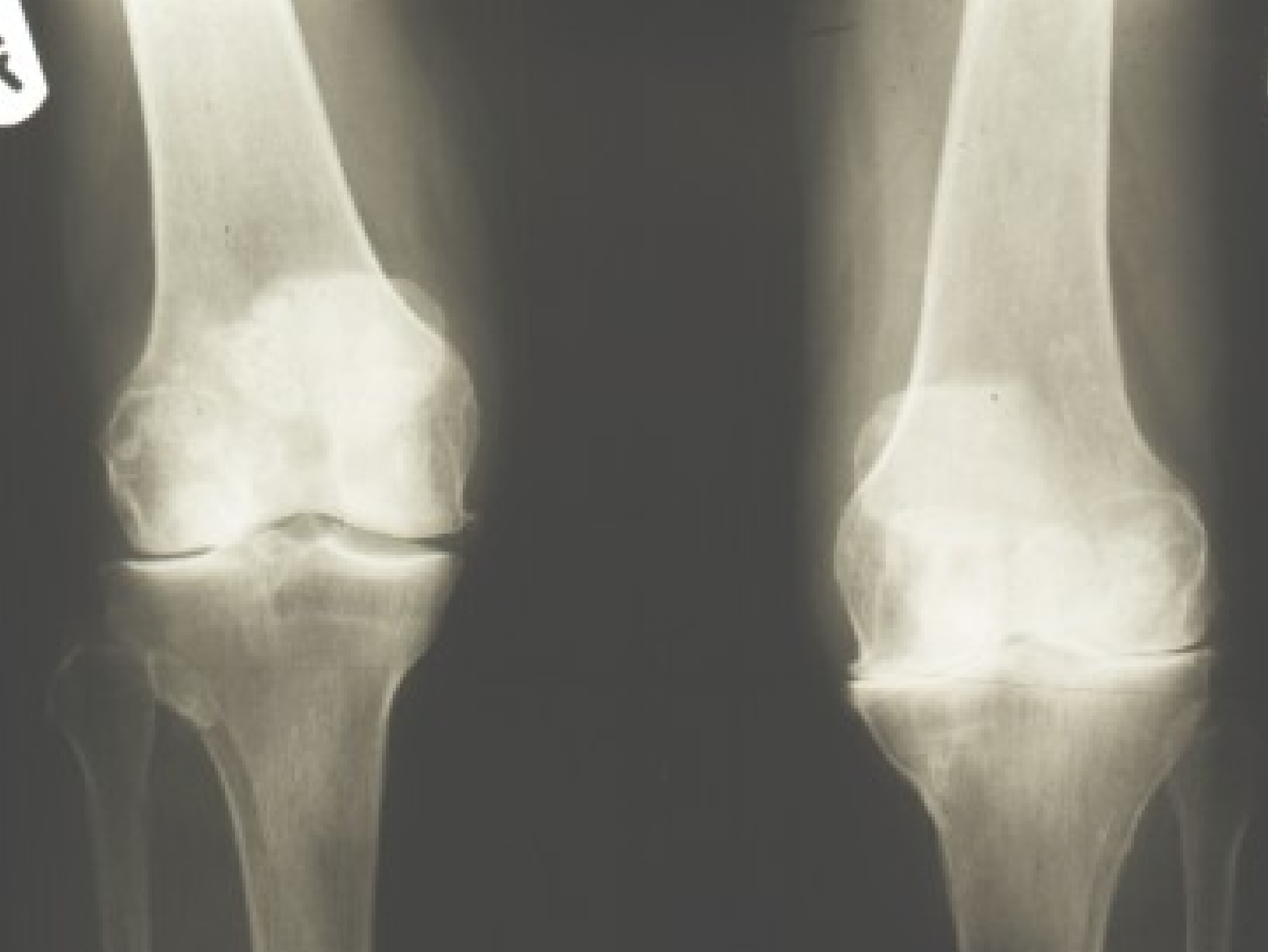
Considerable evidence on the harms of medical interventions is accumulated through epidemiologic studies performed after licensing and marketing.[5–8] Recently, there has been an effort to improve the recording and reporting of information on harms derived from clinical trials.[2,9] Although single trials are usually underpowered to address adequately the absolute and relative risks of adverse events, especially uncommon ones, large trials or meta-analyses may achieve adequate power for this purpose. Previously we examined

Papanikolaou et al, CMAJ 2006



Papanikolaou et al, CMAJ 2006

And the benefits?



EDITORIALS

Knee Pain Is the Malady – Not Osteoarthritis

Osteoarthritis is a well-defined pathoanatomic entity readily demonstrable by modern imaging techniques. For a century, the pathology that is this disease has been ingrained in the mind of every medical student.

10 cm Visual Analogue Scale
Time point: 0 days

No Pain

Extreme Pain

10 cm Visual Analogue Scale
Time point: 180 days

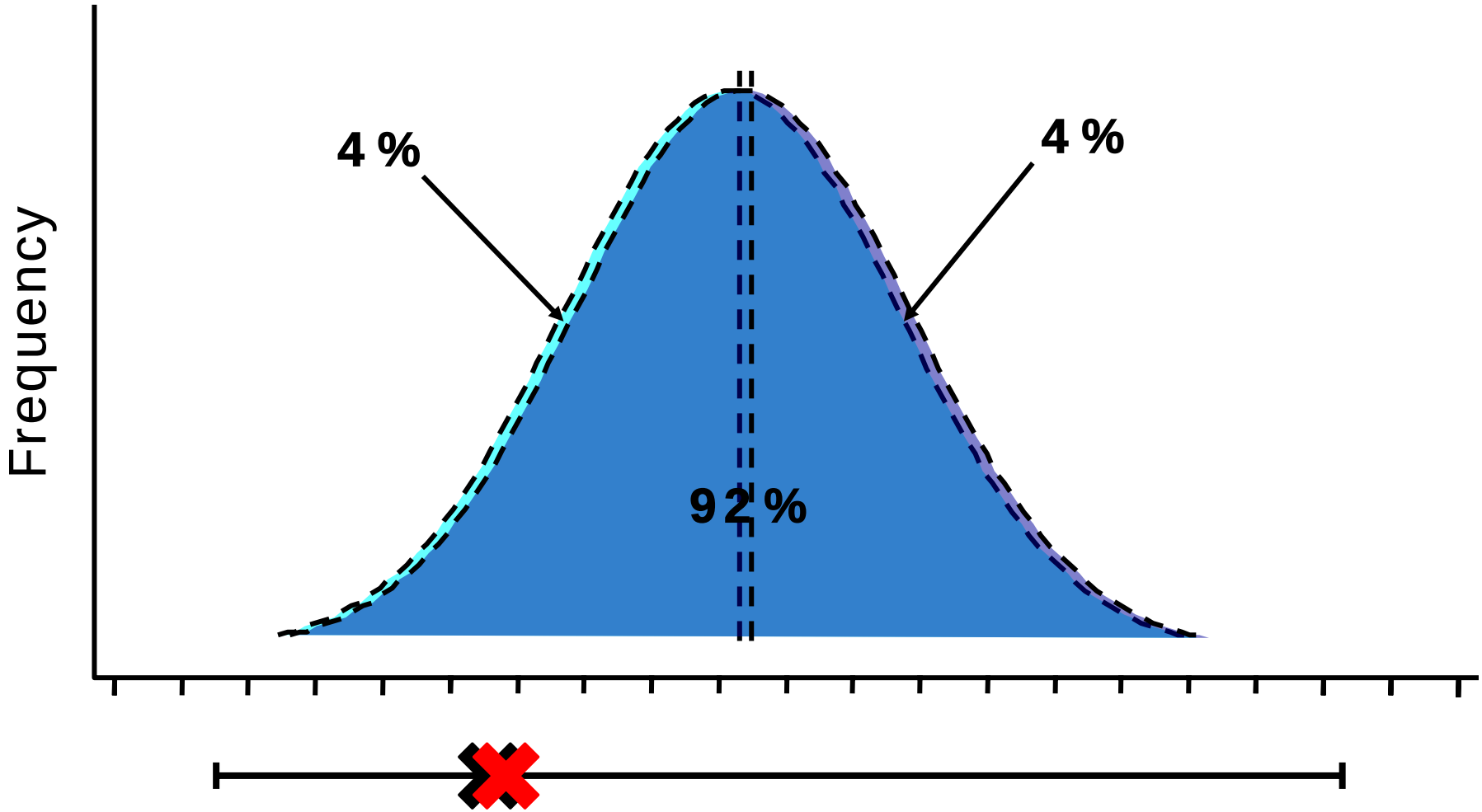
No Pain

Extreme Pain

Effect size

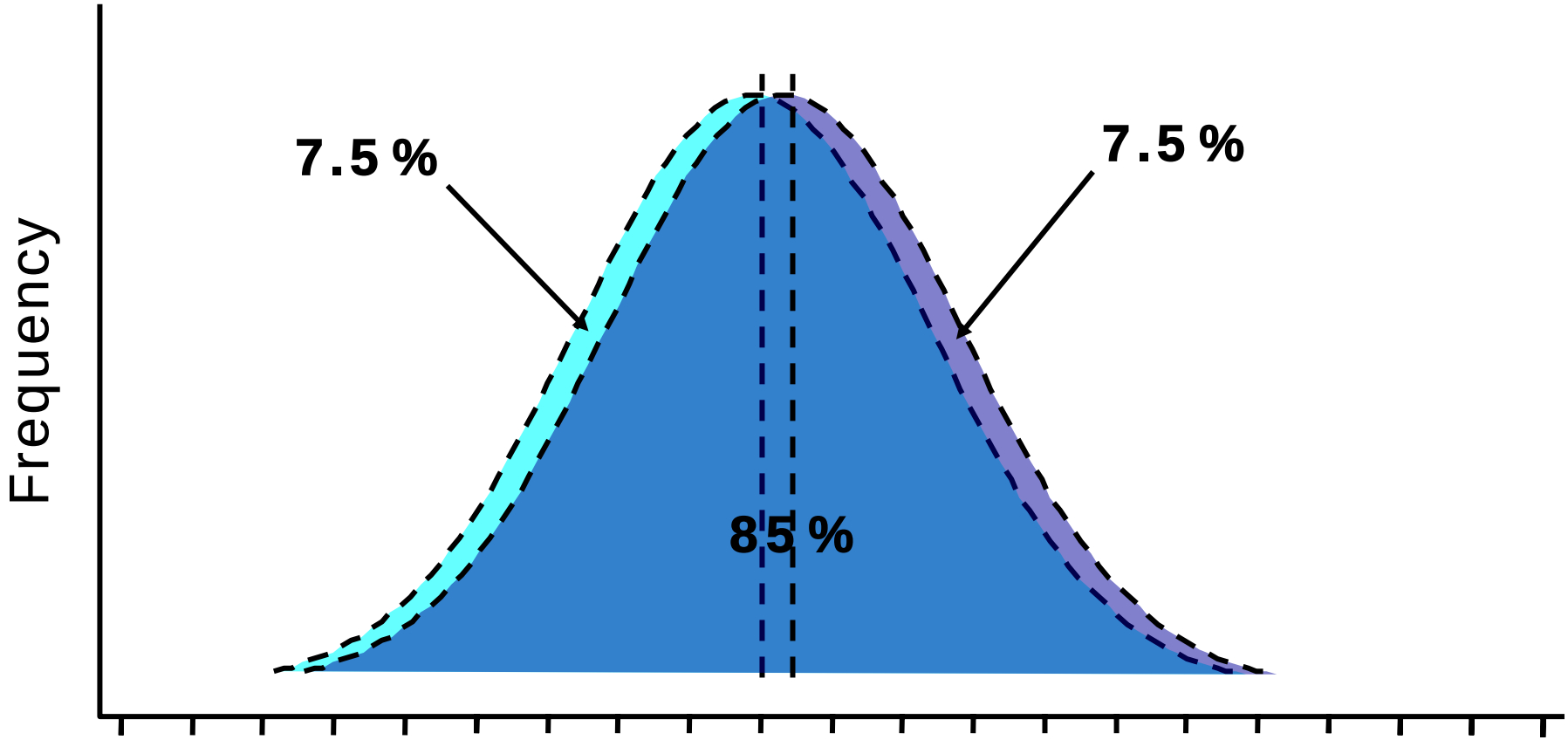
$$\frac{\text{Difference in pain scores}}{\text{Pooled standard deviation}}$$

Effect size -0.10



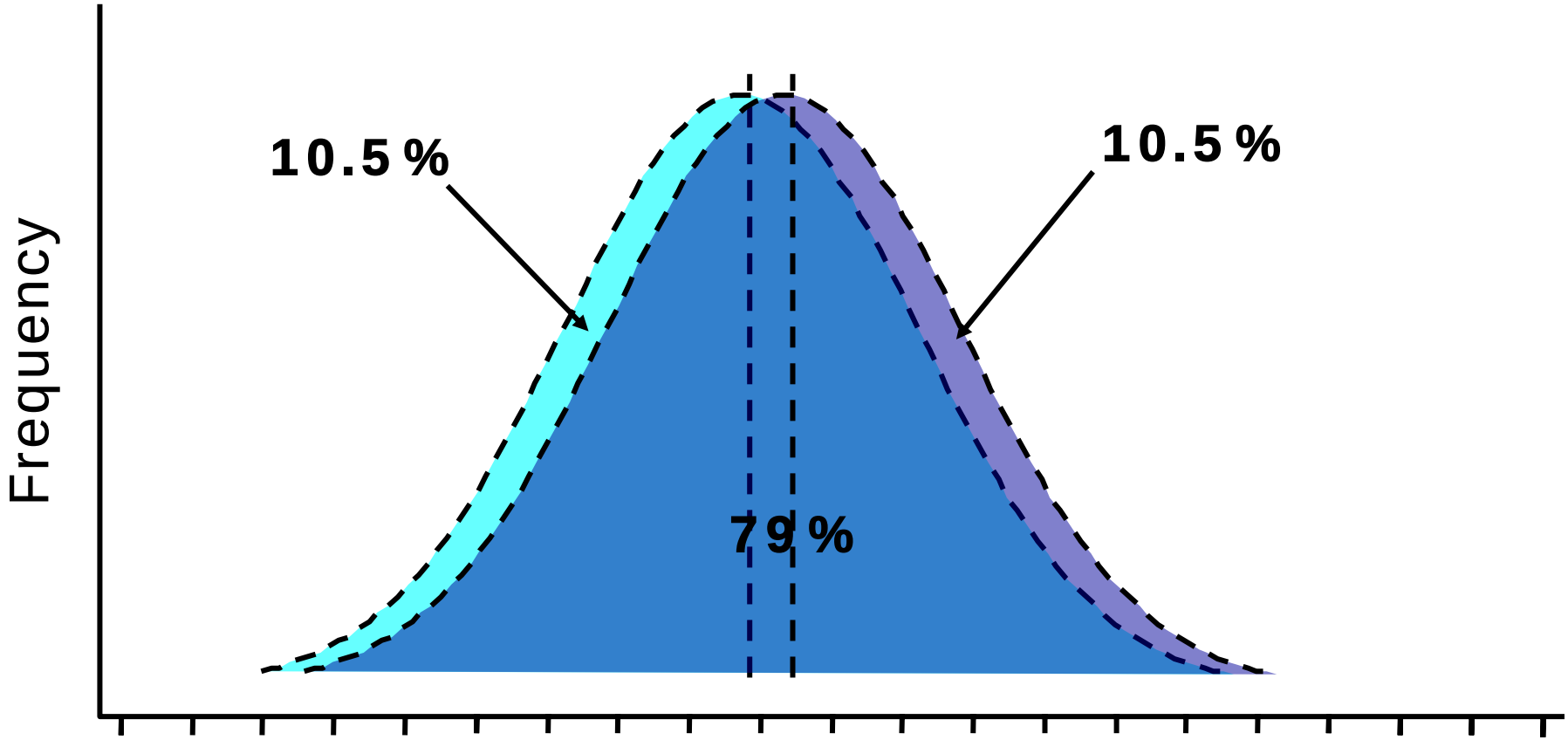
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.20



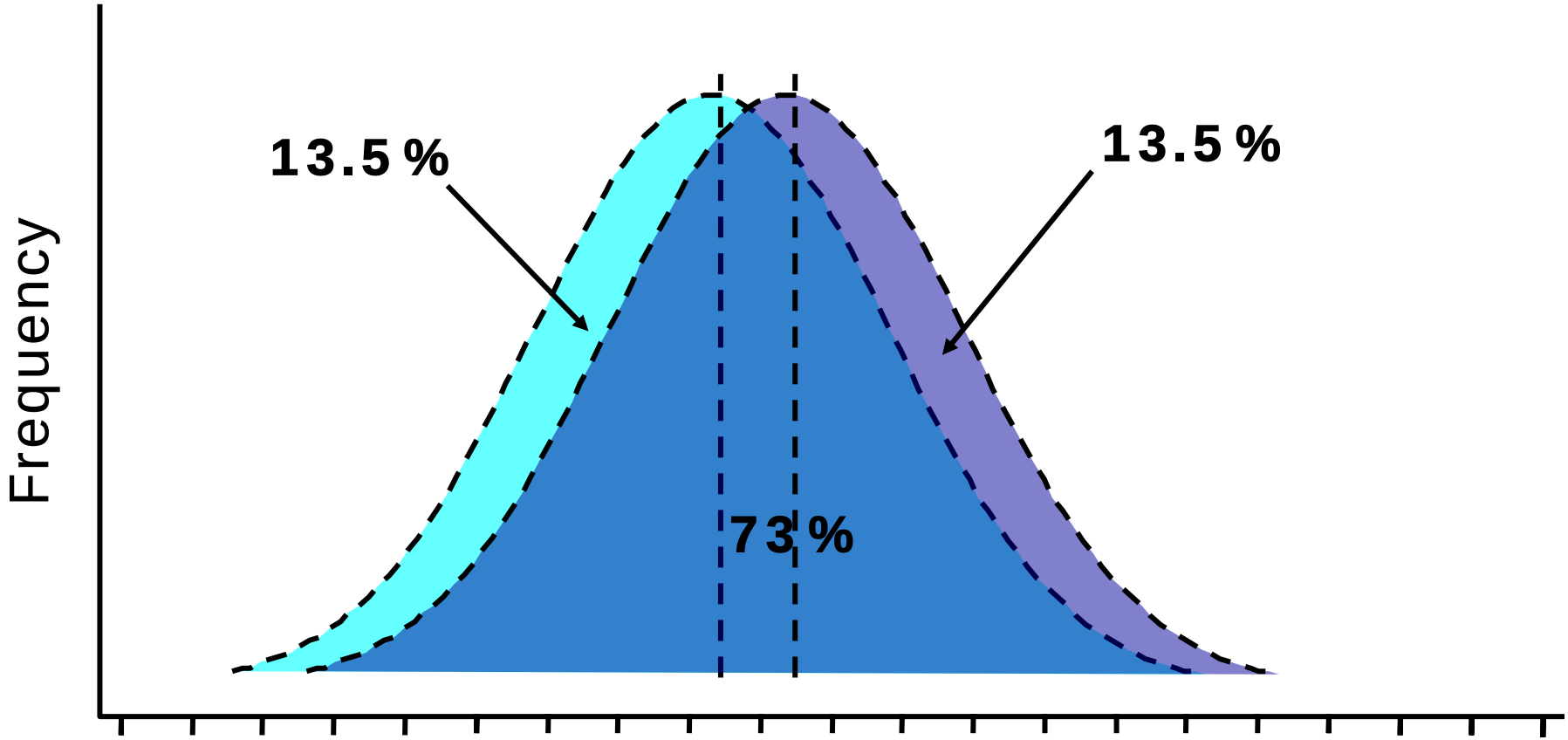
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.30



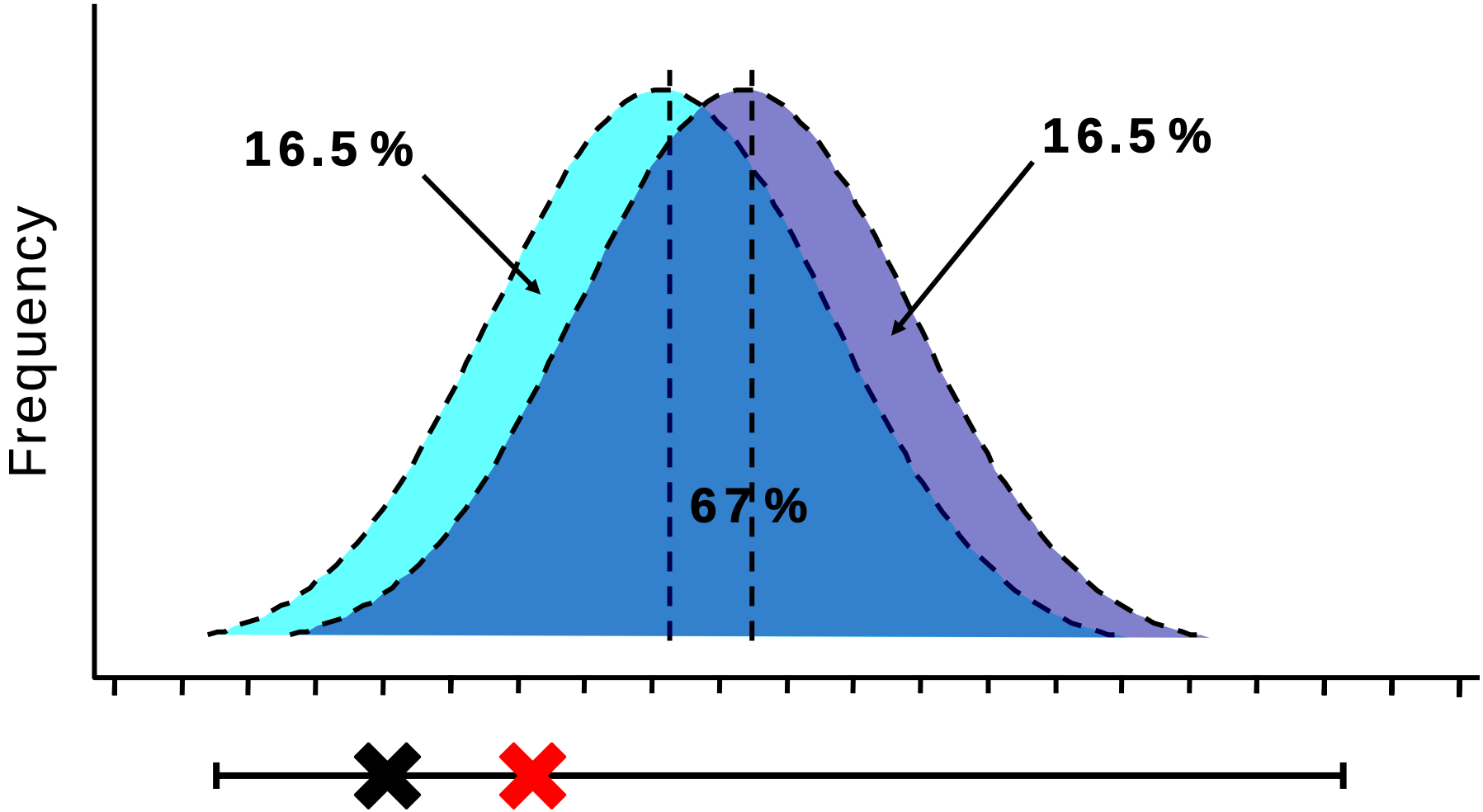
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.40



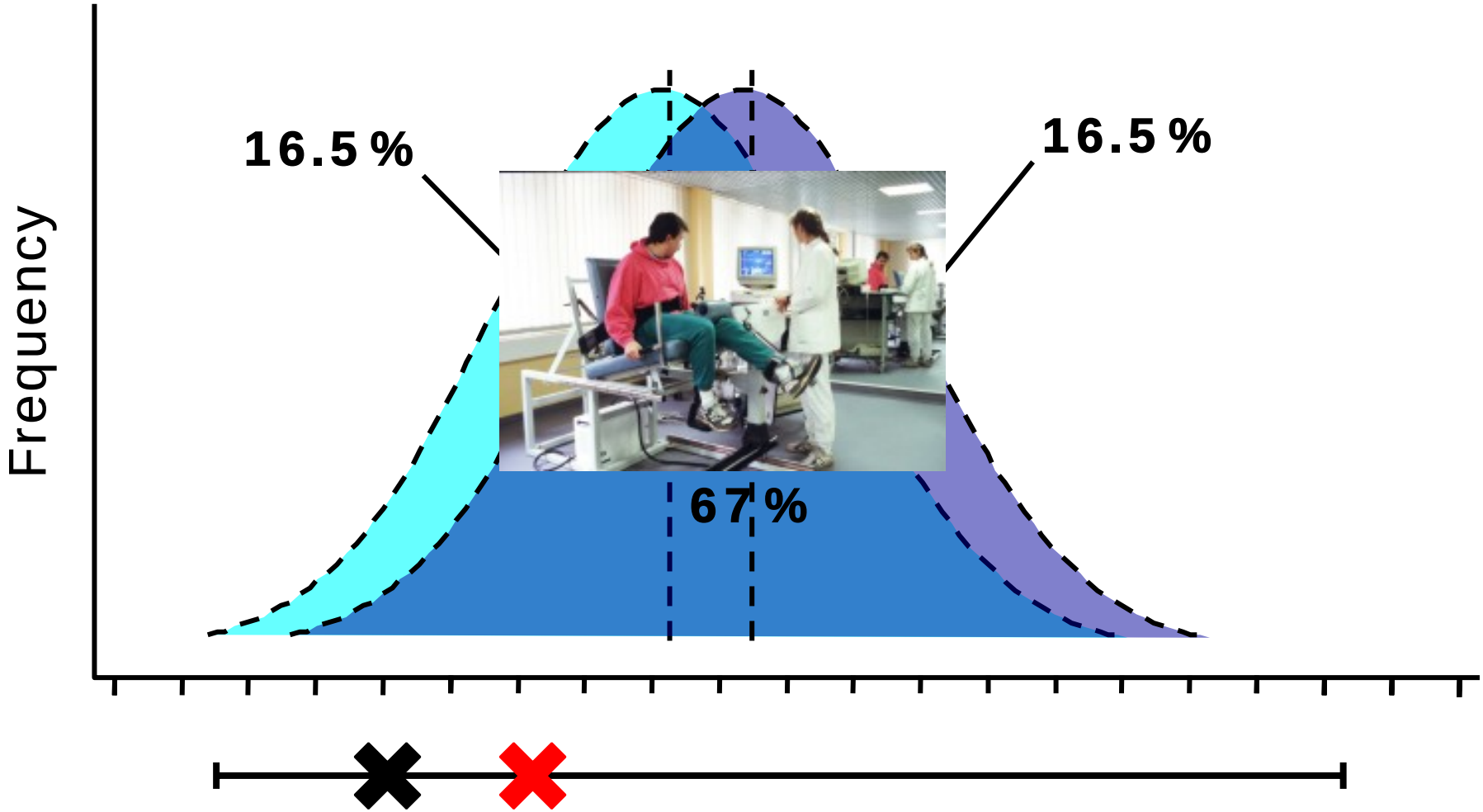
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.50



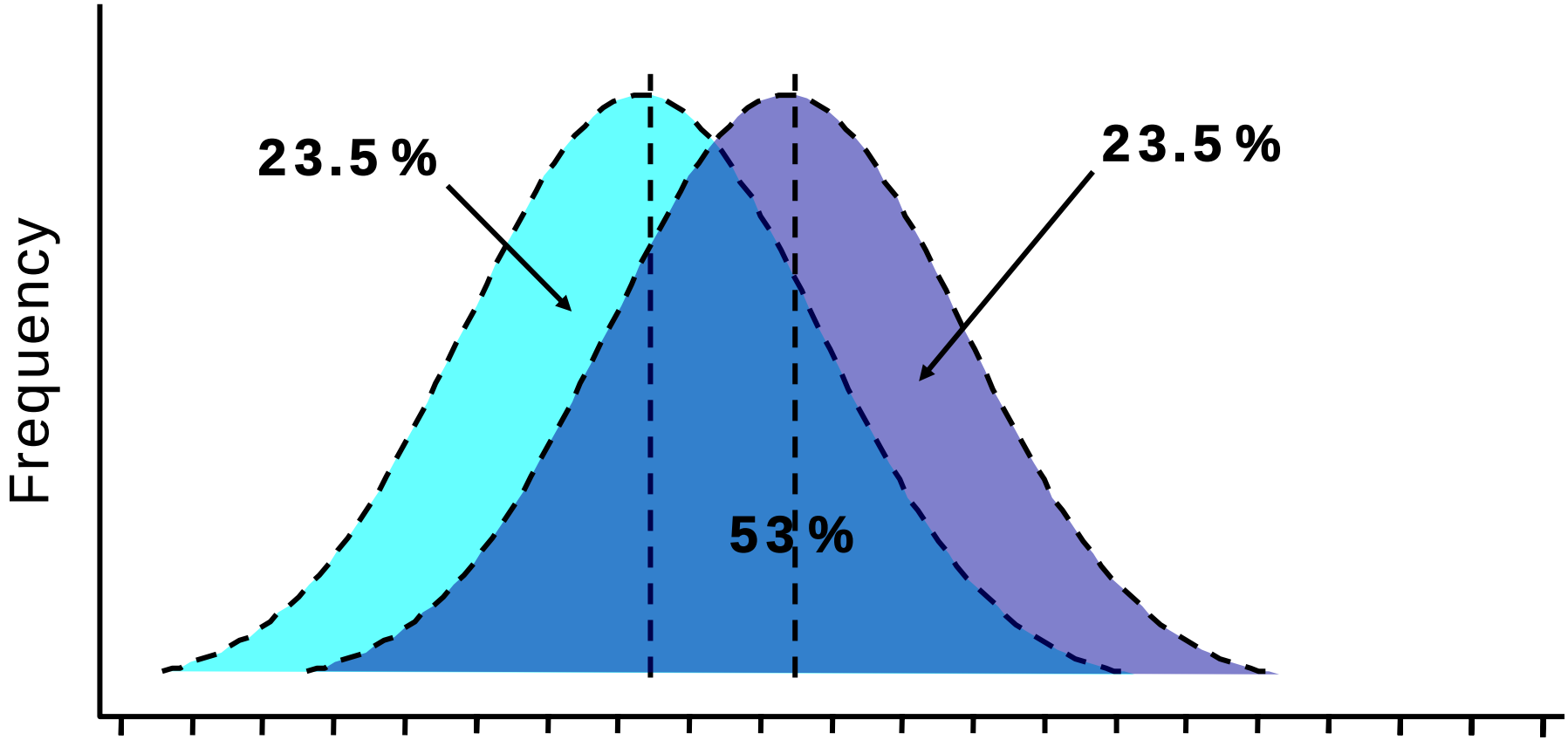
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.50



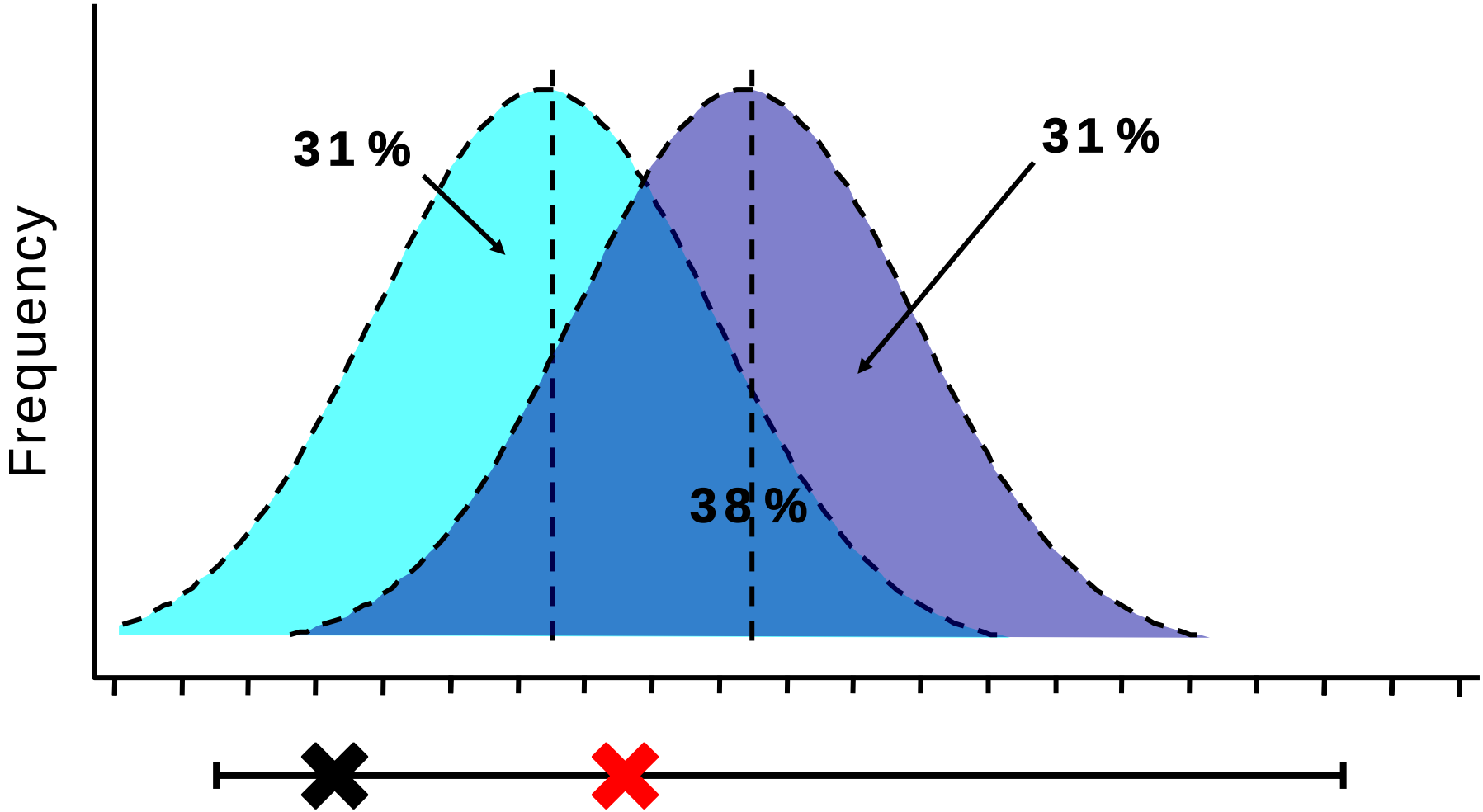
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -0.80



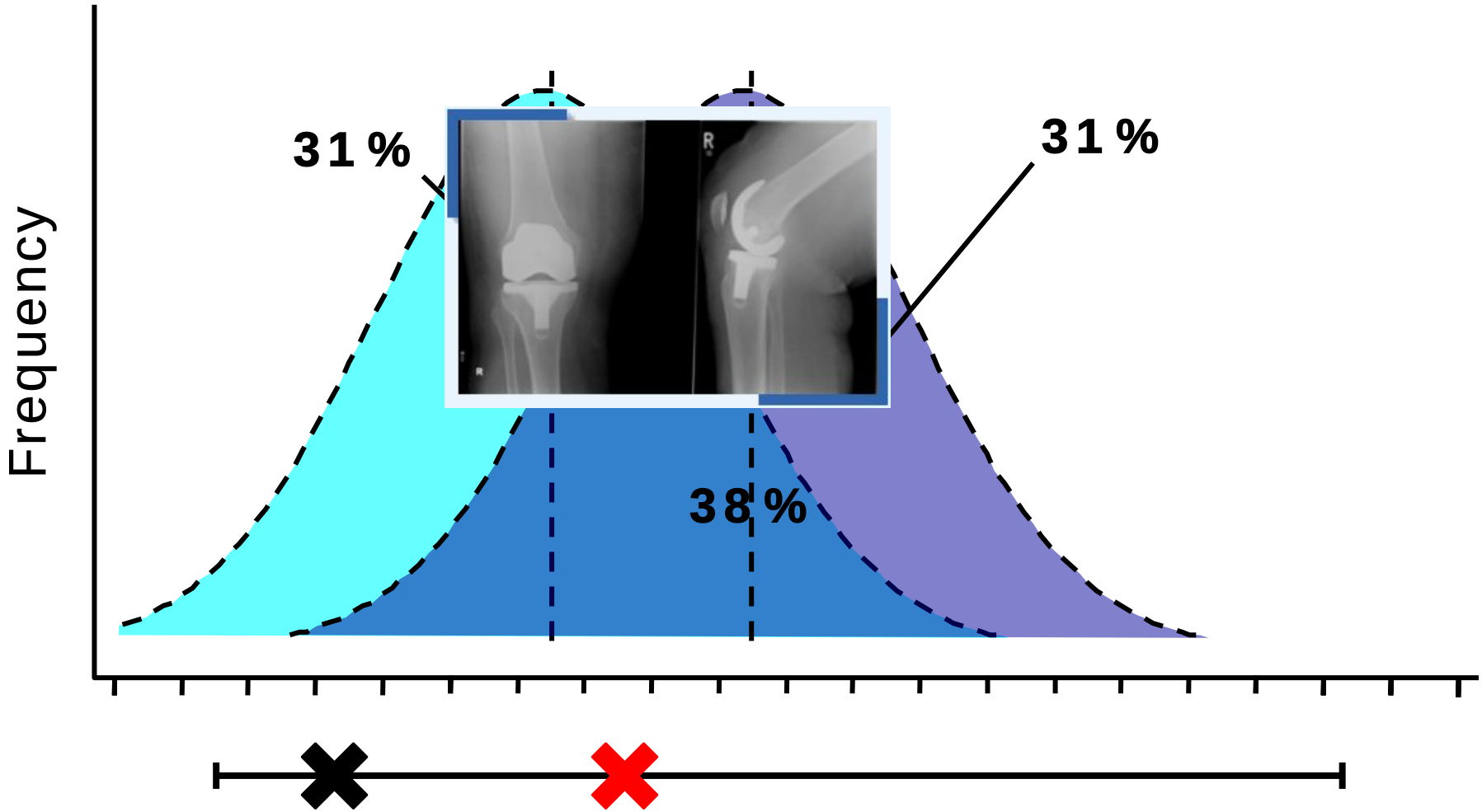
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -1.20



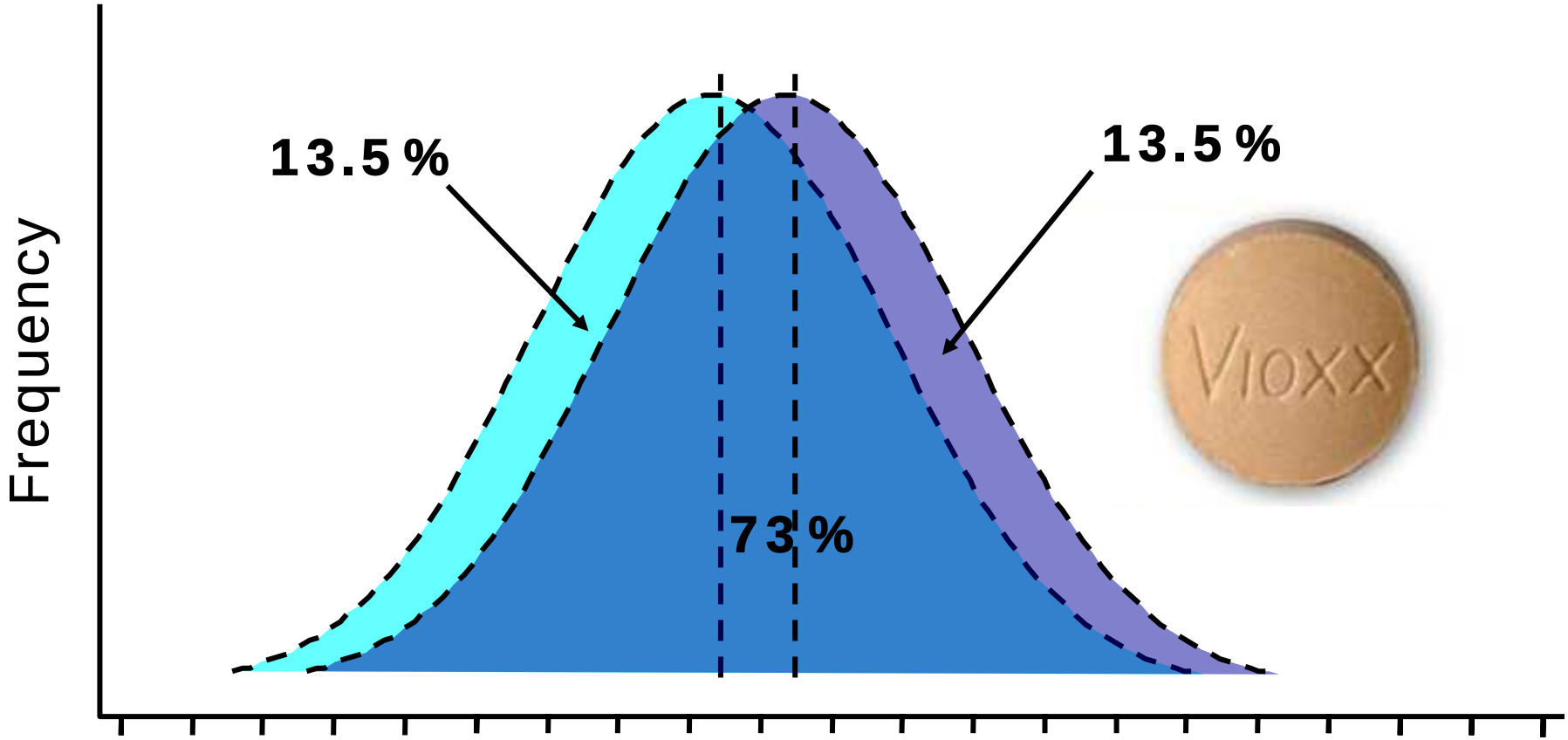
Jüni et al, Best Pract Res Clin Rheumatol 2006

Effect size -1.20



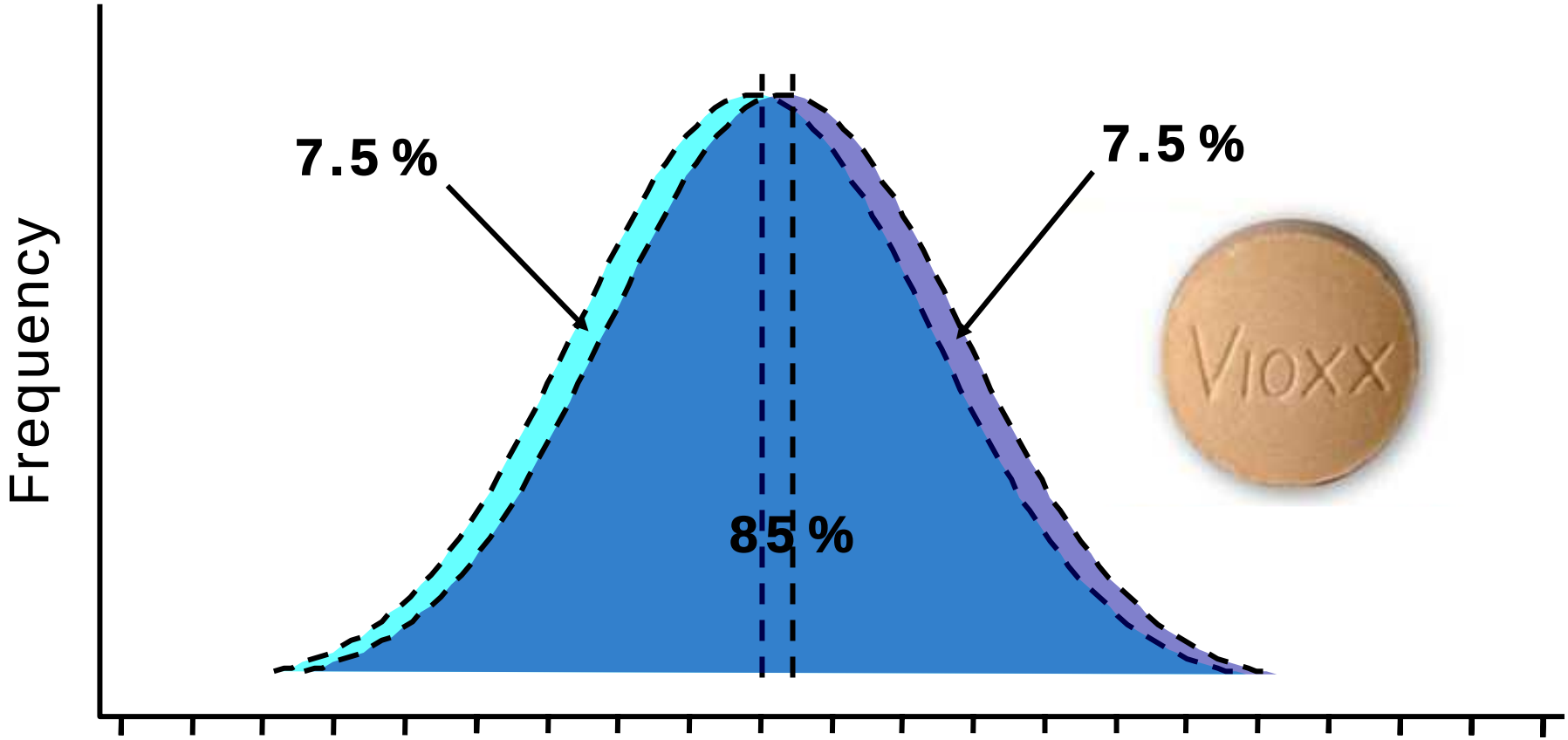
Jüni et al, Best Pract Res Clin Rheumatol 2006

Rofecoxib versus placebo
Effect size ~ -0.40



Jüni et al, Best Pract Res Clin Rheumatol 2006

Rofecoxib versus paracetamol
Effect size ~ -0.20



Jüni et al, Best Pract Res Clin Rheumatol 2006

NNH & NNT

- Myocardial infarction: NNH ~610
- Ulcer complications, versus naproxen: NNT ~130

Observational studies of any help?

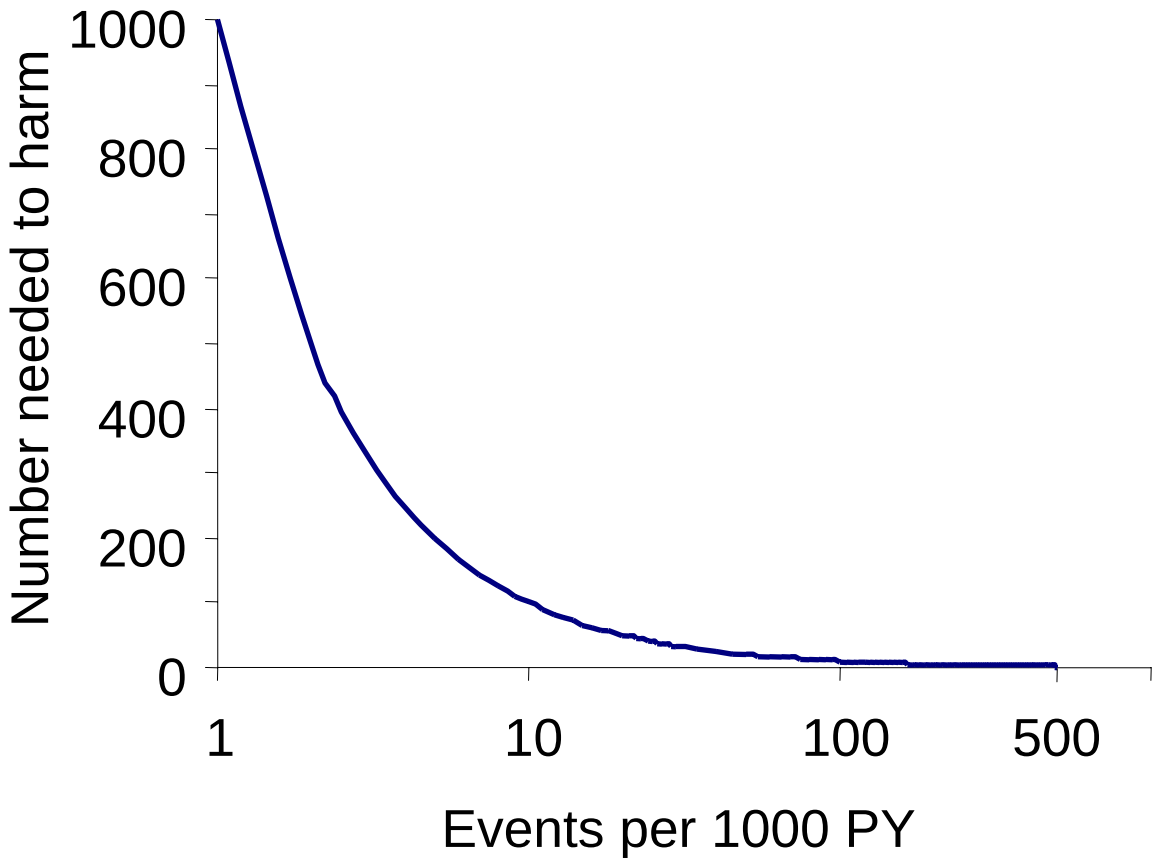
	Non-user (n=202 916)	Rofecoxib ⩽25 mg (n=20 245)	Rofecoxib >25 mg (n=3887)
Age (mean, SD) (years)	61·8 (9·0)	63·2 (8·8)	60·6 (8·1)
Women	127 458 (63%)	14 830 (73%)	2552 (66%)
White	151 568 (75%)	15 561 (77%)	2998 (77%)
TennCare enrolment, uninsured†	74 718 (37%)	5884 (29%)	1184 (31%)
Treatment for cardiovascular	155 681 (77%)	17 618 (87%)	3350 (86%)
Oestrogen use among women	54 574 (27%)	7723 (38%)	1510 (39%)
Smoking-related illness‖	8281 (4%)	953 (5%)	197 (5%)
Hospital admission for non-cardiovascular illness	21 564 (11%)	2946 (15%)	578 (15%)
Number of prescriptions, any drug (mean, SD) because of non-cardiovascular illness	49·9 (43·3)	91·0 (60·1)	94·2 (66·8)
Number of visits to doctor (mean, SD)	2·5 (1·6)	3·3 (1·5)	3·3 (1·5)

Major cardiovascular disease 42%

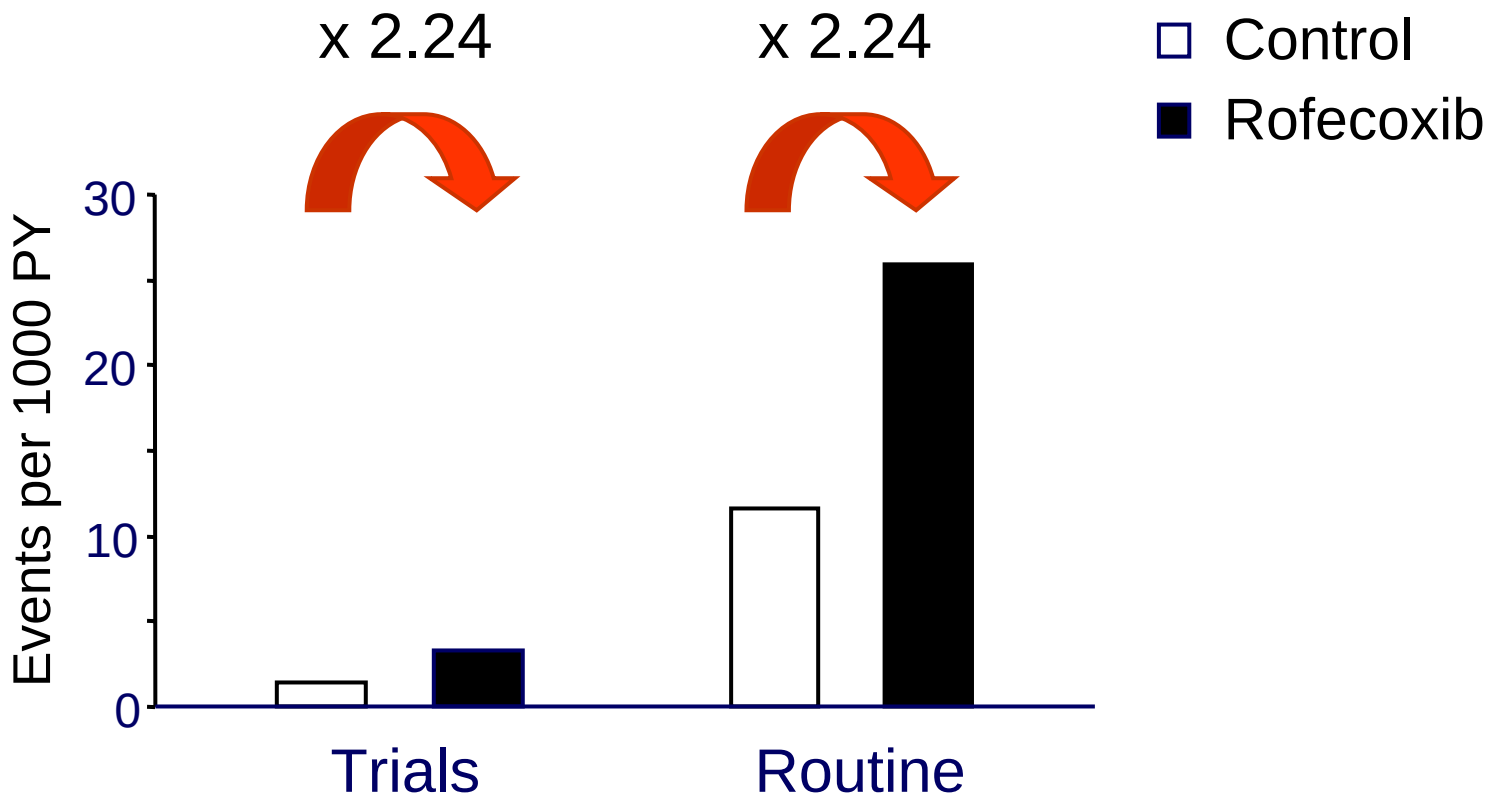
Peptic ulcer or gastrointestinal bleeding 3%

Ray et al, Lancet 2002

Baseline Risk and NNT/NNH

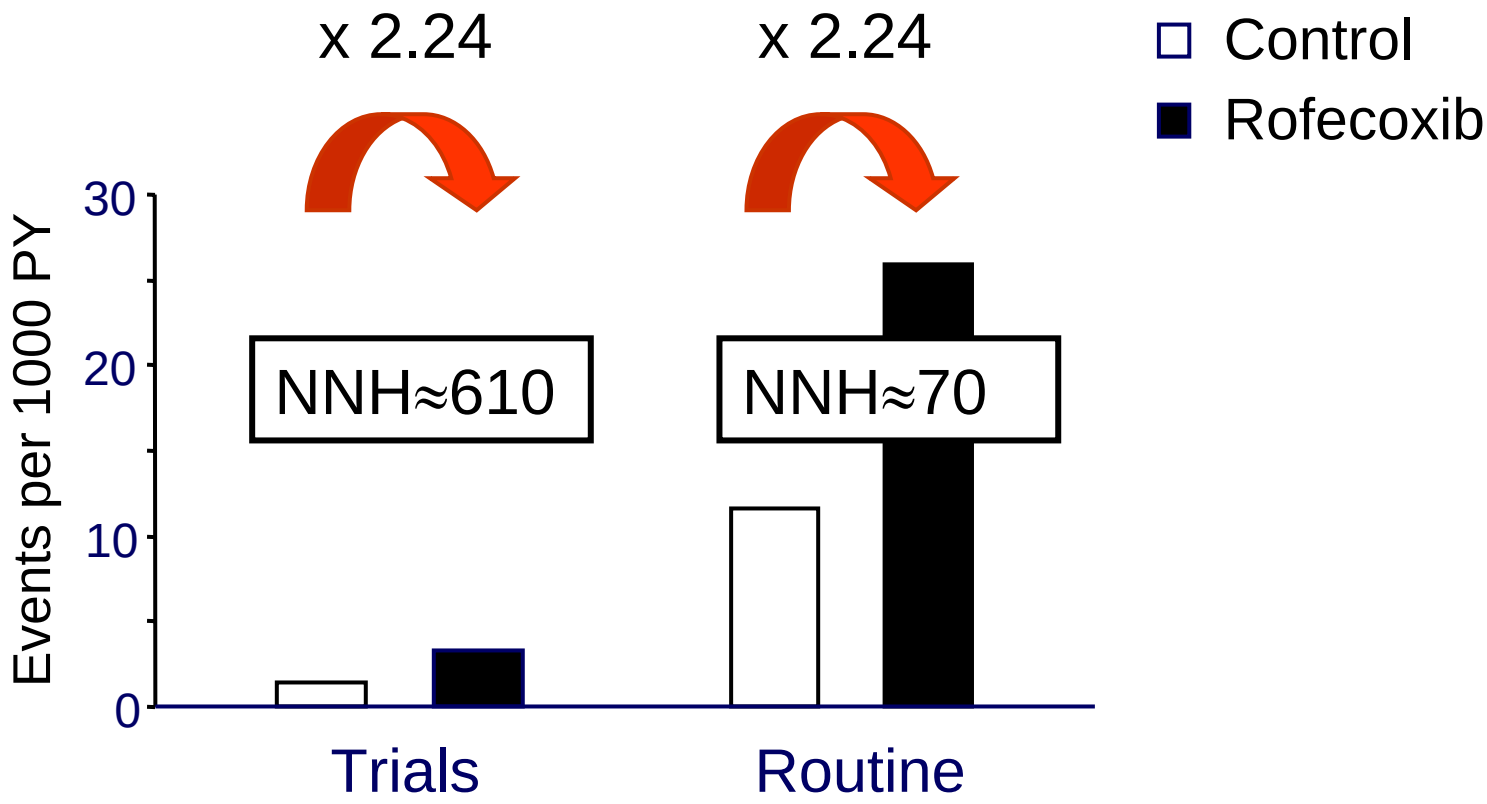


Extrapolation to routine settings: rofecoxib & myocardial infarction



Jüni et al, Lancet 2005

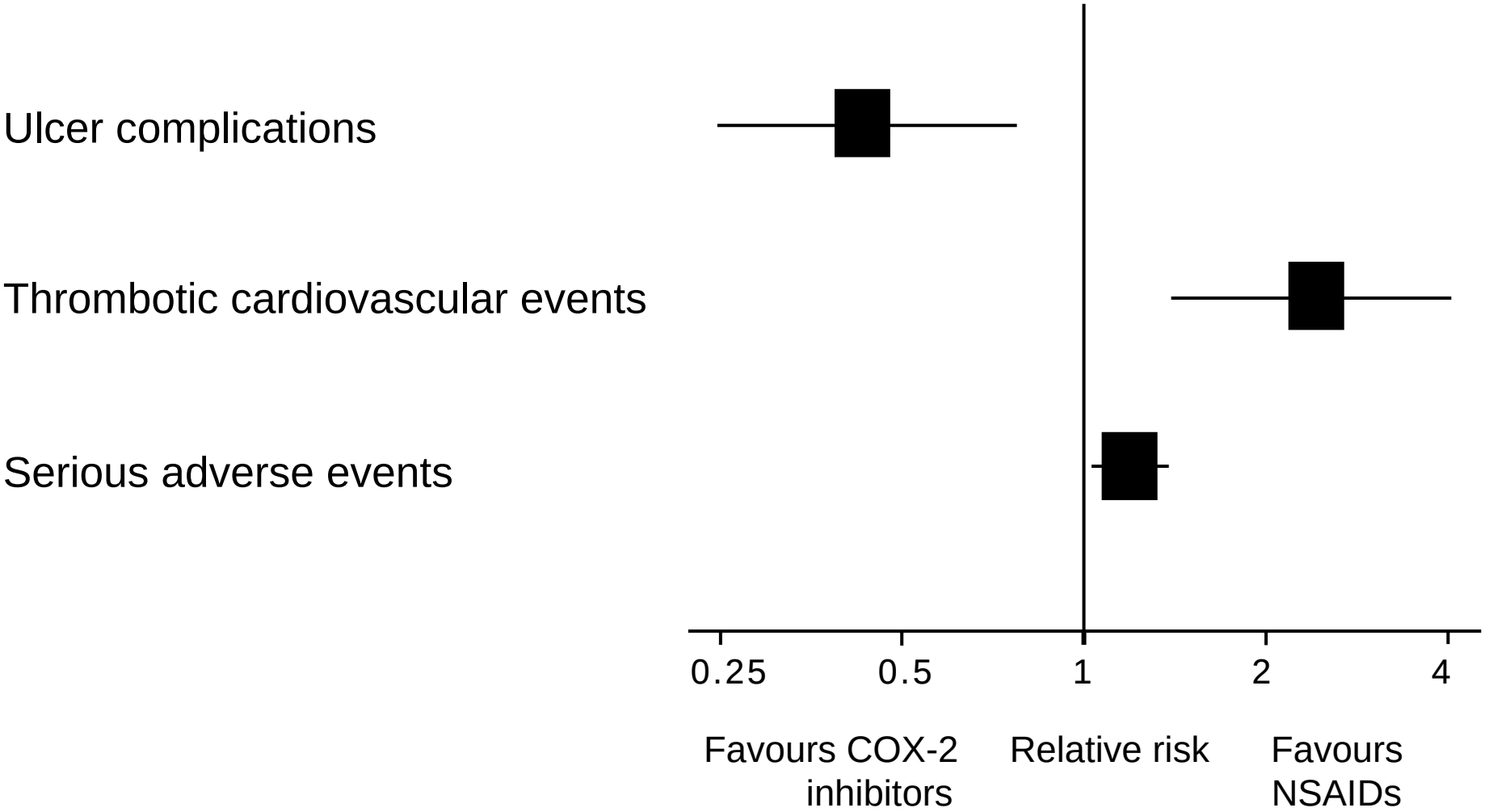
Extrapolation to routine settings: rofecoxib & myocardial infarction



Jüni et al, Lancet 2005

Risk patterns and serious adverse events overall

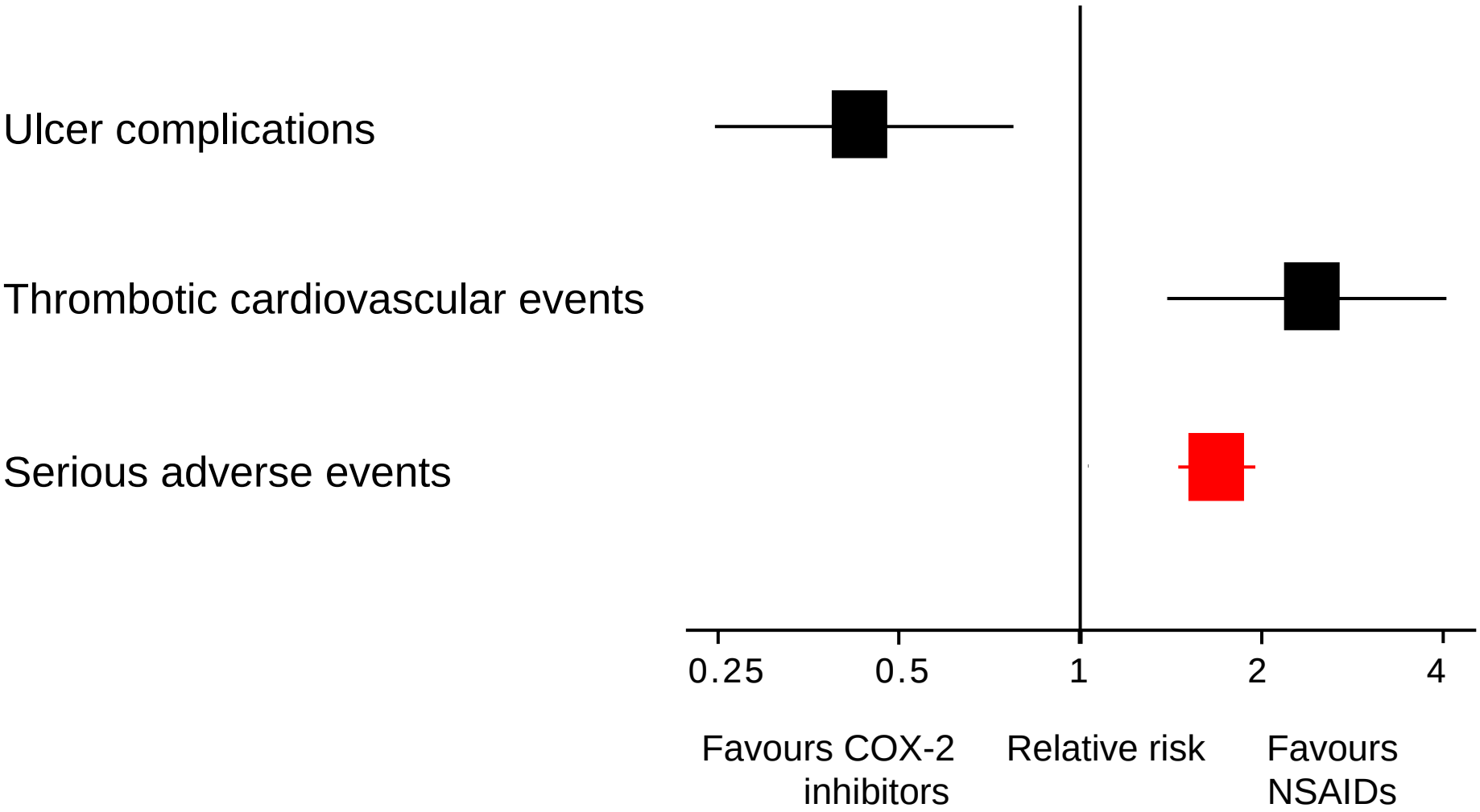
Rofecoxib versus Naproxen



Bombardier et al, N Engl J Med 2000

Risk patterns and serious adverse events overall

Rofecoxib versus Naproxen



Bombardier et al, N Engl J Med 2000

Sept 2, 2006

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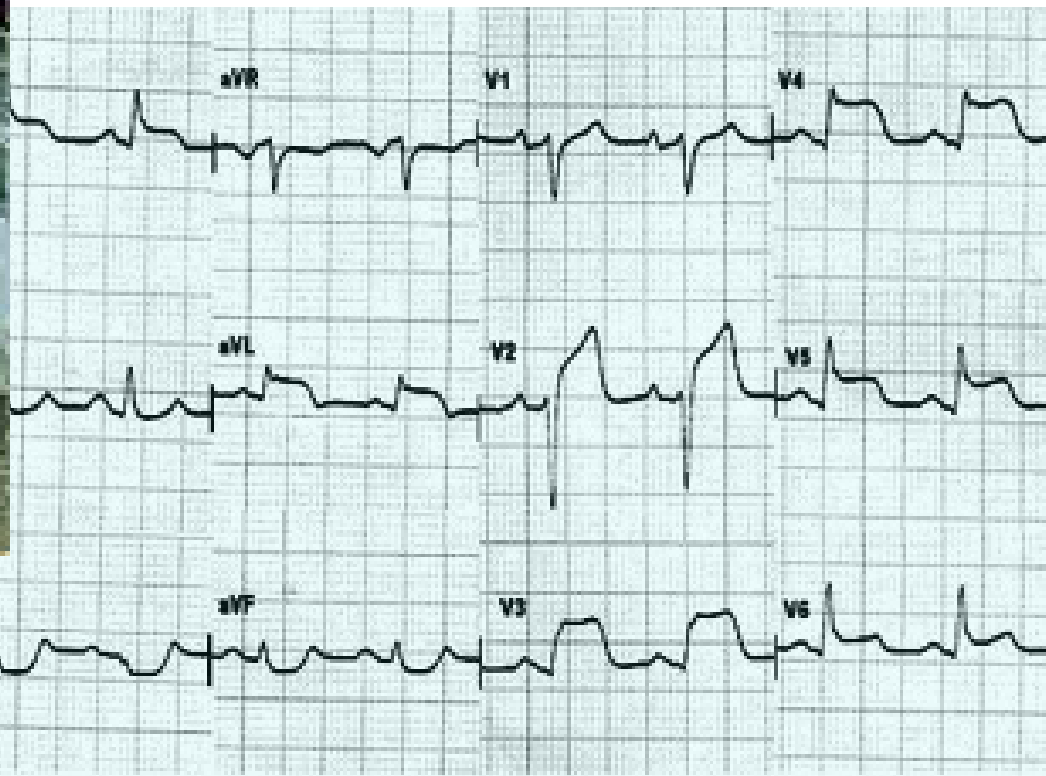
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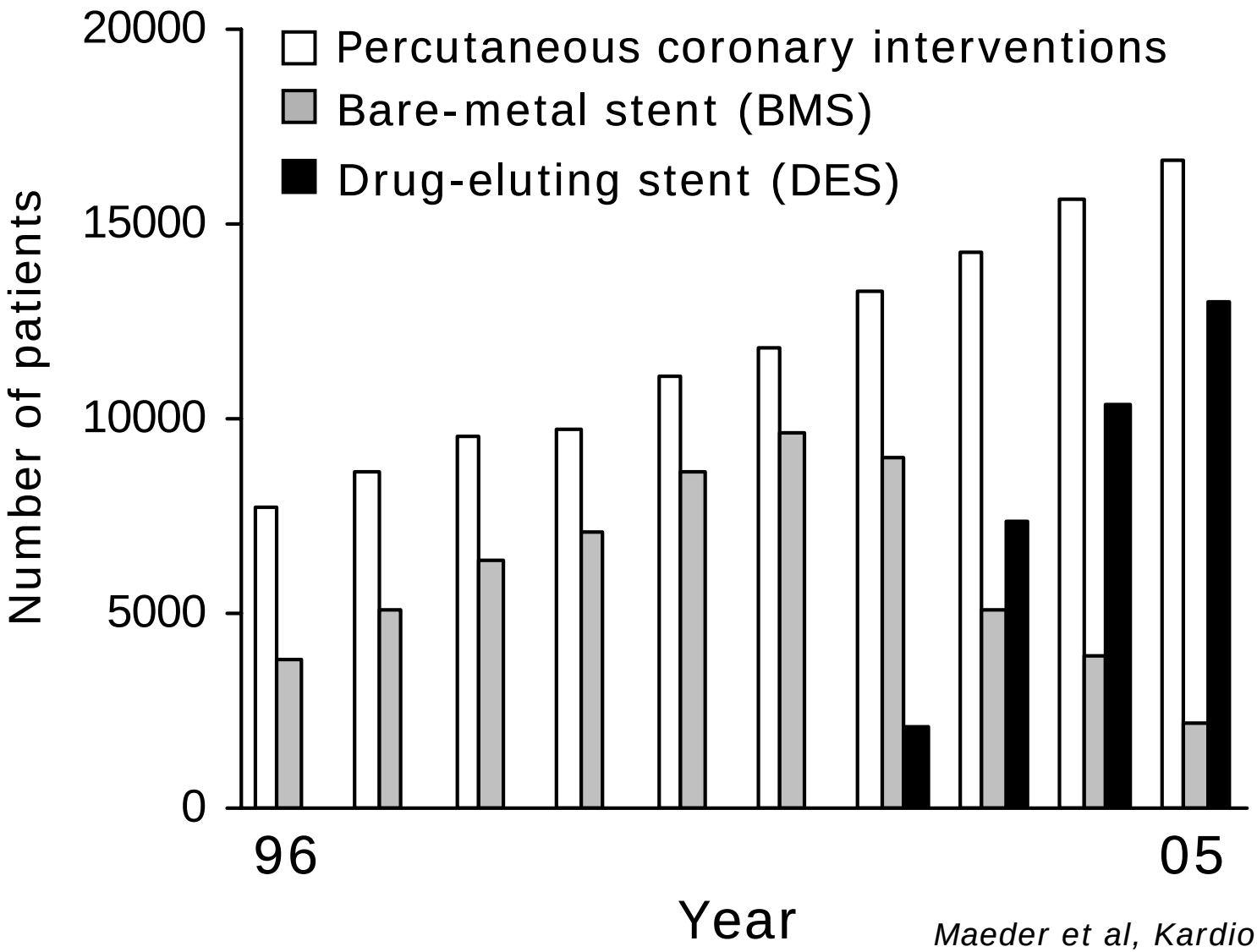
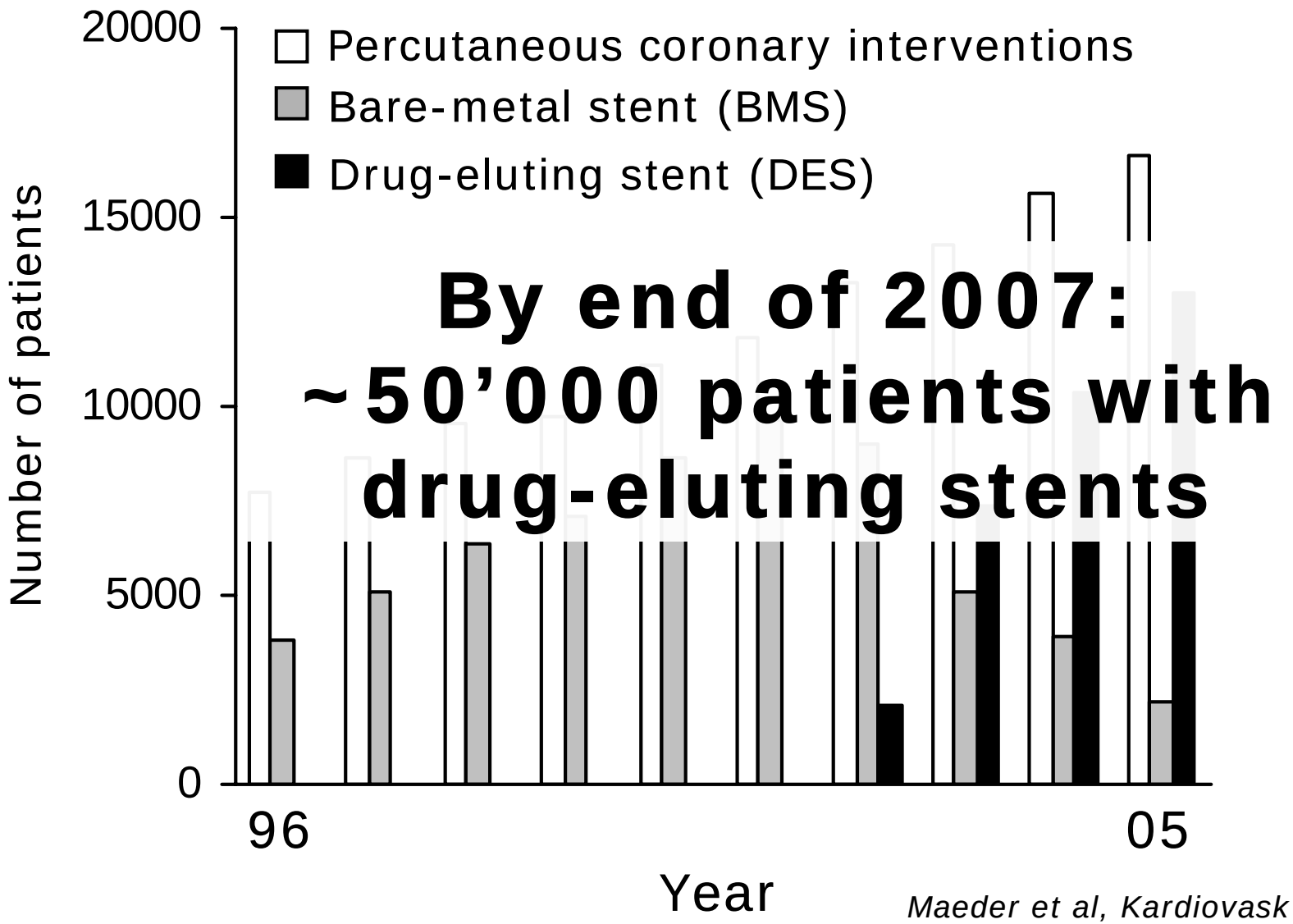
Percutaneous coronary interventions in Switzerland



Maeder et al, Kardiovask Med 2007

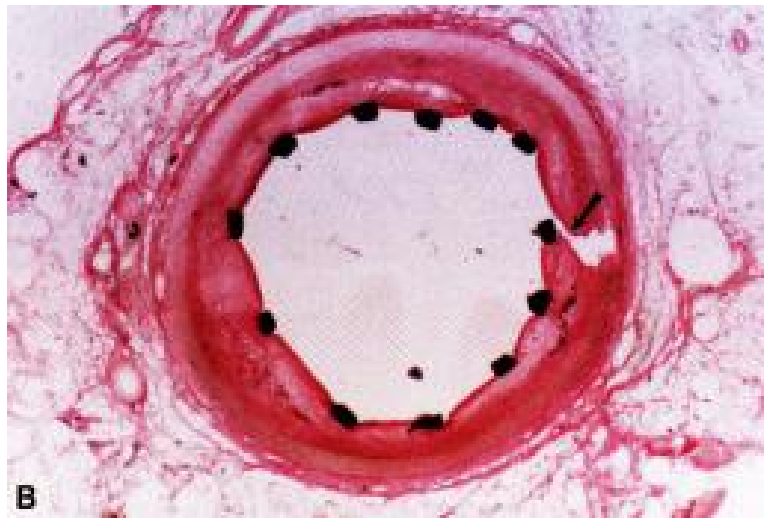
Percutaneous coronary interventions in Switzerland



Maeder et al, Kardiovask Med 2007

Two FDA approved drug-eluting stents

- Paclitaxel-eluting stents (PES)
- Sirolimus-eluting stents (SES)



Estimated NNT to avoid one revascularisation over 1 year

- **Bare metal stents versus PTCA**
  - NNT 14
- **Drug-eluting versus bare metal stents**
  - NNT 10

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Safety and Efficacy of Drug-Eluting Stents Reaffirmed in New England Journal of Medicine Articles and Editorial
Boston Scientific Press Release September 13, 2006
Two-year data suggest different rates of blood clots and heart attacks between the Cypher sirolimus-eluting coronary stent and the Taxus stent
Cordis Press Release
September 5, 2006
New York Times September 5, 2006
HEALTH AND MEDICINE
Cardiologists question the risks in using drug-coated stents
The data we currently have do not allow us to fully characterize the mechanism, risks, and incidence of DES thrombosis
FDA Statement
September 14, 2006

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

MARCH 8, 2007

Unanswered Questions — Drug-Eluting Stents and the Risk of Late Thrombosis

William H. Maisel, M.D., M.P.H.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden

Bo Lagerqvist, M.D., Ph.D., Stefan K. James, M.D., Ph.D., Ulf Stenestrand, M.D., Ph.D., Johan Lindbäck, M.Sc., Tage Nilsson, M.D., Ph.D., and Lars Wallentin, M.D., Ph.D., for the SCAAR Study Group*

ABSTRACT

BACKGROUND

Recent reports have indicated that there may be an increased risk of late stent thrombosis with the use of drug-eluting stents, as compared with bare-metal stents.

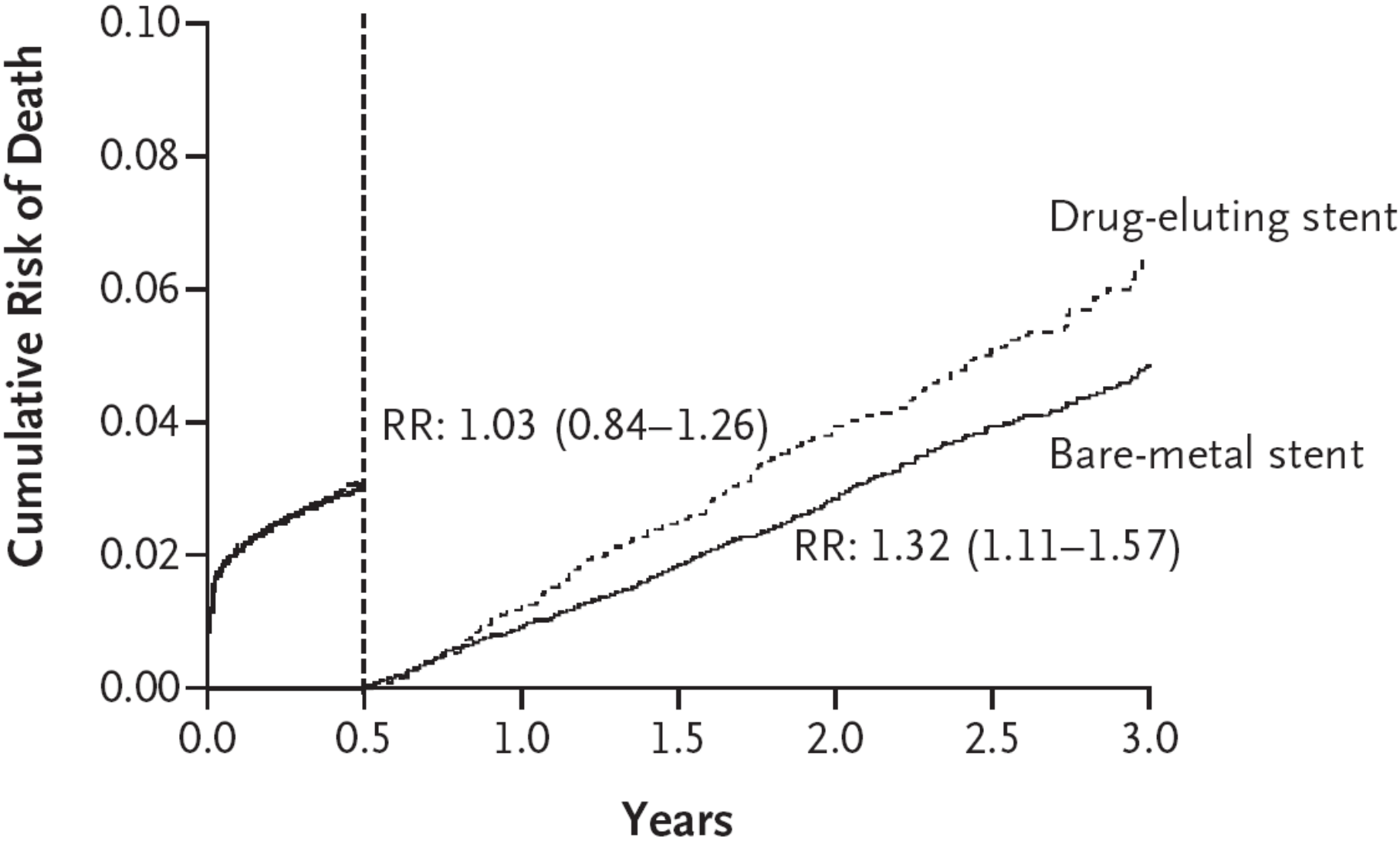
METHODS

We evaluated 6033 patients treated with drug-eluting stents and 13,738 patients treated with bare-metal stents in 2003 and 2004, using data from the Swedish Coronary Angiography and Angioplasty Registry. The outcome analysis covering a period of up to 3 years was based on 1424 deaths and 2463 myocardial infarctions and was adjusted for differences in baseline characteristics.

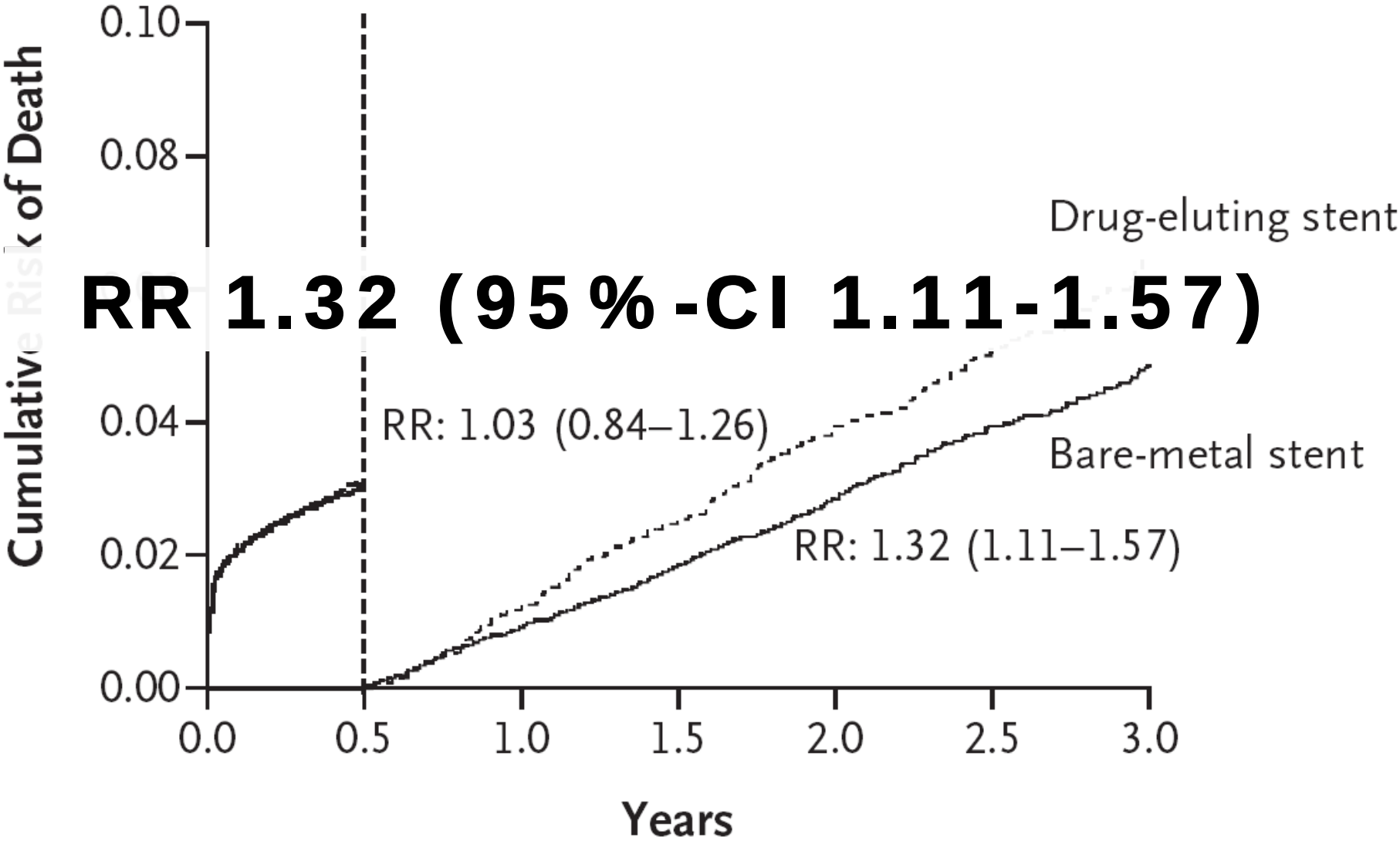
From the Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala (B.L., S.K.J., J.L., T.N., L.W.); and Linköping University Hospital, Linköping (U.S.) — both in Sweden. Address reprint requests to Dr. Lagerqvist at the Uppsala Clinical Research Center, Uppsala University Hospital, 751 85 Uppsala, Sweden, or at bo.lagerqvist@ucr.uu.se.

Lagerqvist et al, N Engl J Med 2007

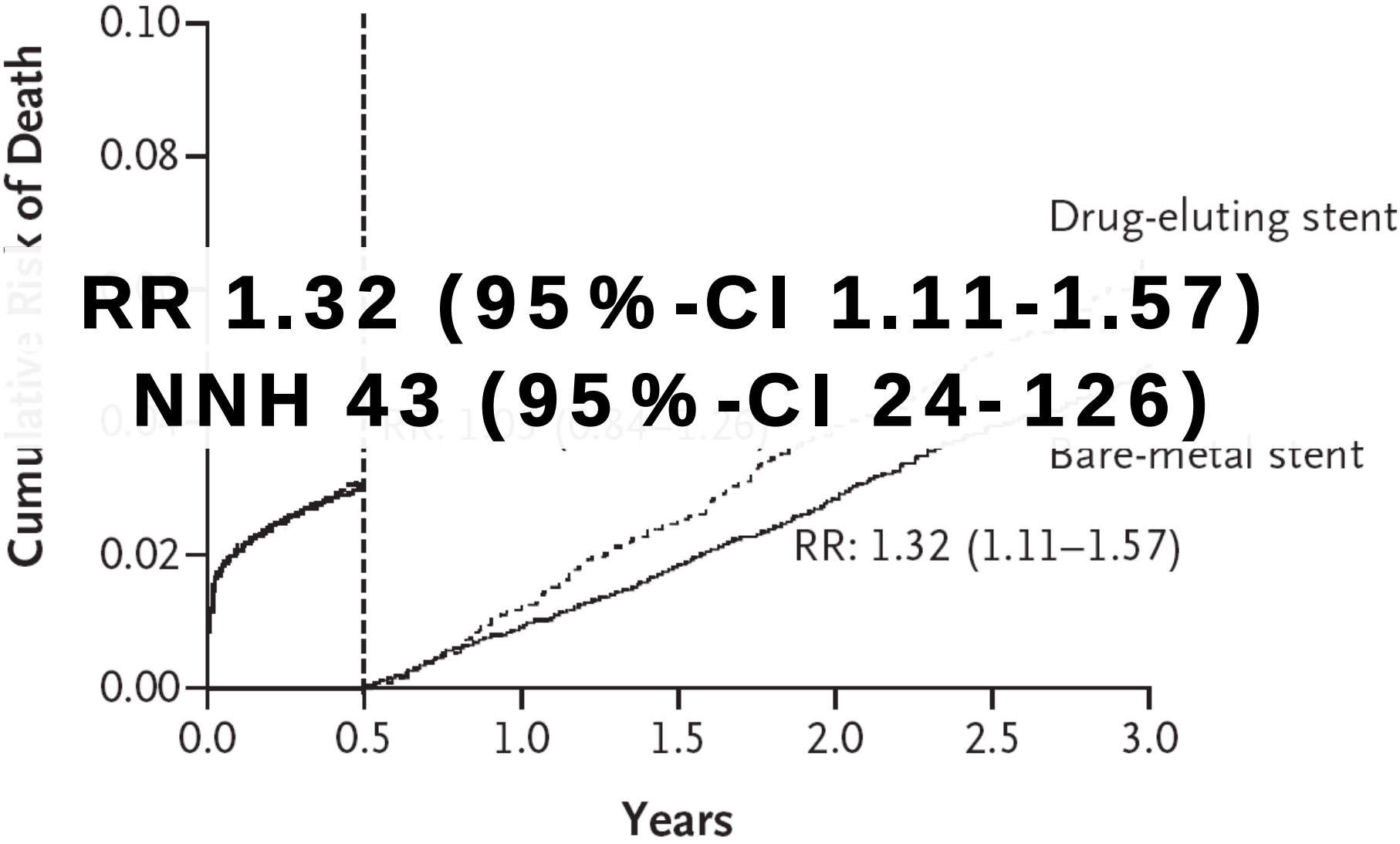
Swedish Registry: overall mortality



Swedish Registry: overall mortality



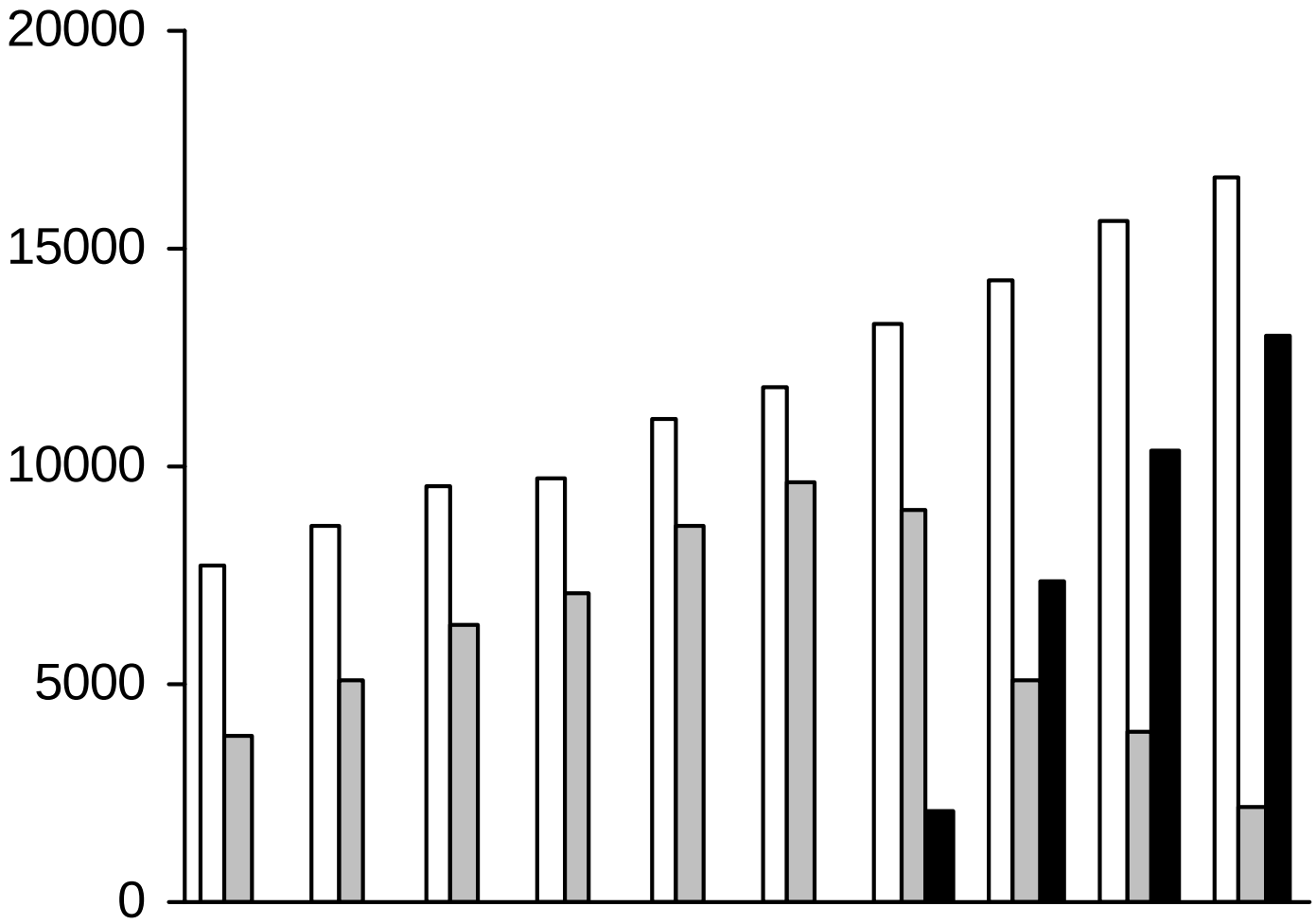
Swedish Registry: overall mortality



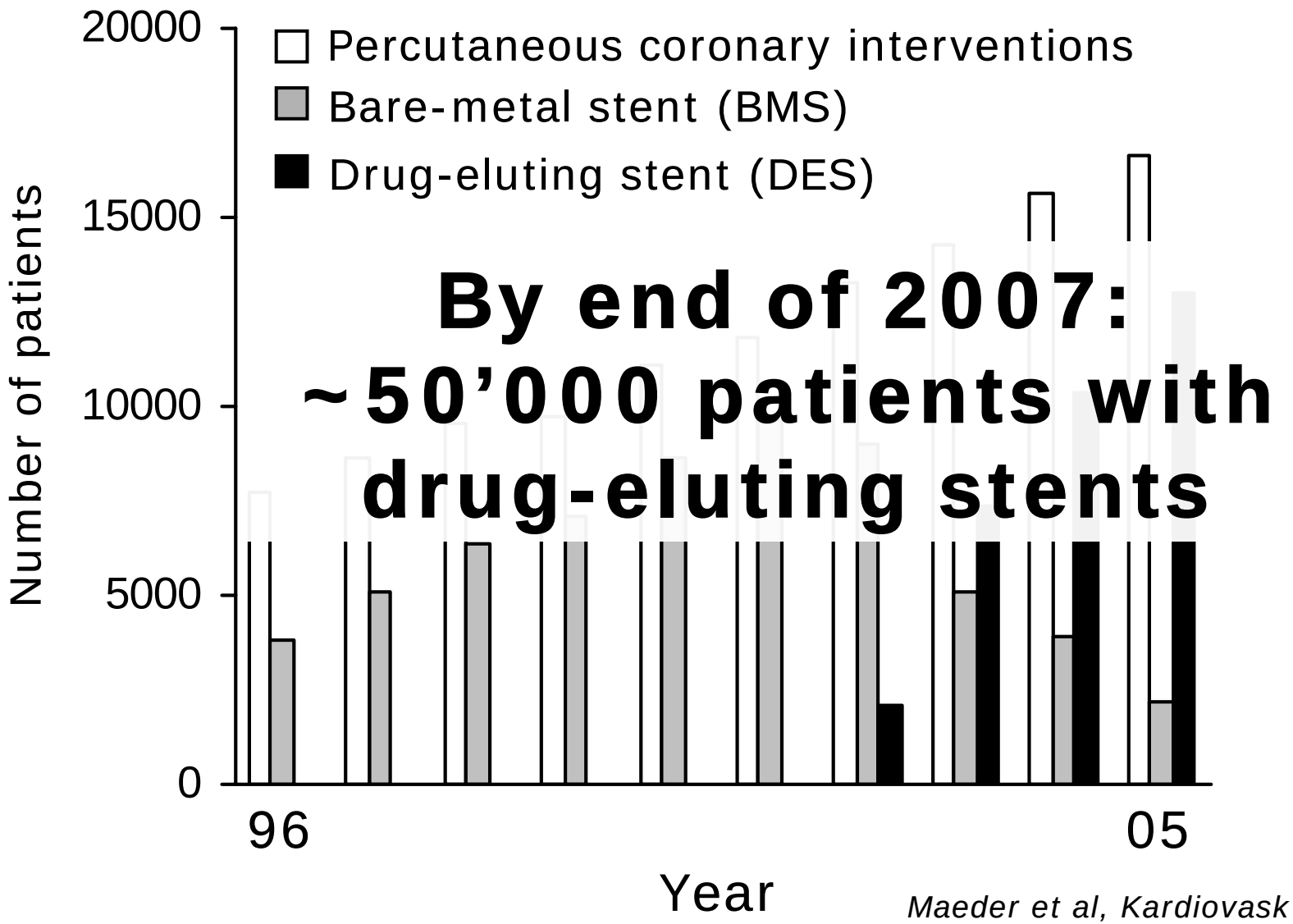
RR 1.32 (95%-CI 1.11-1.57)

NNH 43 (95%-CI 24-126)

Percutaneous coronary interventions in Switzerland



Percutaneous coronary interventions in Switzerland



Maeder et al, Kardiovask Med 2007

Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis

Christoph Stettler, Simon Wandel,* Sabin Allemann, Adnan Kastrati, Marie Claude Morice, Albert Schömig, Matthias E Pfisterer, Gregg W Stone, Martin B Leon, José Suarez de Lezo, Jean-Jacques Goy, Seung-Jung Park, Manel Sabaté, Maarten J Suttorp, Henning Kelbaek, Christian Spaulding, Maurizio Menichelli, Paul Vermeersch, Maurits T Dirksen, Pavel Cervinka, Anna Sonia Petronio, Alain J Nordmann, Peter Diem, Bernhard Meier, Marcel Zwahlen, Stephan Reichenbach, Sven Trelle, Stephan Windecker, Peter Jüni*

Summary

Background Whether the two drug-eluting stents approved by the US Food and Drug Administration—a sirolimus-eluting stent and a paclitaxel-eluting stent—are associated with increased risks of death, myocardial infarction, or stent thrombosis compared with bare-metal stents is uncertain. Our aim was to compare the safety and effectiveness of these stents.

Methods We searched relevant sources from inception to March, 2007, and contacted investigators and manufacturers to identify randomised controlled trials in patients with coronary artery disease that compared drug-eluting with bare-metal stents, or that compared sirolimus-eluting stents head-to-head with paclitaxel-eluting stents. Safety outcomes included mortality, myocardial infarction, and definite stent thrombosis; the effectiveness outcome was target lesion revascularisation. We included 38 trials (18 023 patients) with a follow-up of up to 4 years. Trialists and manufacturers provided additional data on clinical outcomes for 29 trials. We did a network meta-analysis with a mixed-treatment comparison method to combine direct within-trial comparisons between stents with indirect evidence from other trials while maintaining randomisation.

Findings Mortality was similar in the three groups: hazard ratios (HR) were 1·00 (95% credibility interval 0·82–1·25) for sirolimus-eluting versus bare-metal stents, 1·03 (0·84–1·22) for paclitaxel-eluting versus bare-metal stents, and 0·96 (0·83–1·24) for sirolimus-eluting versus paclitaxel-eluting stents. Sirolimus-eluting stents were associated with the lowest risk of myocardial infarction (HR 0·81, 95% credibility interval 0·66–0·97, p=0·030 *vs* bare-metal stents;

Lancet 2007; 370: 937–48

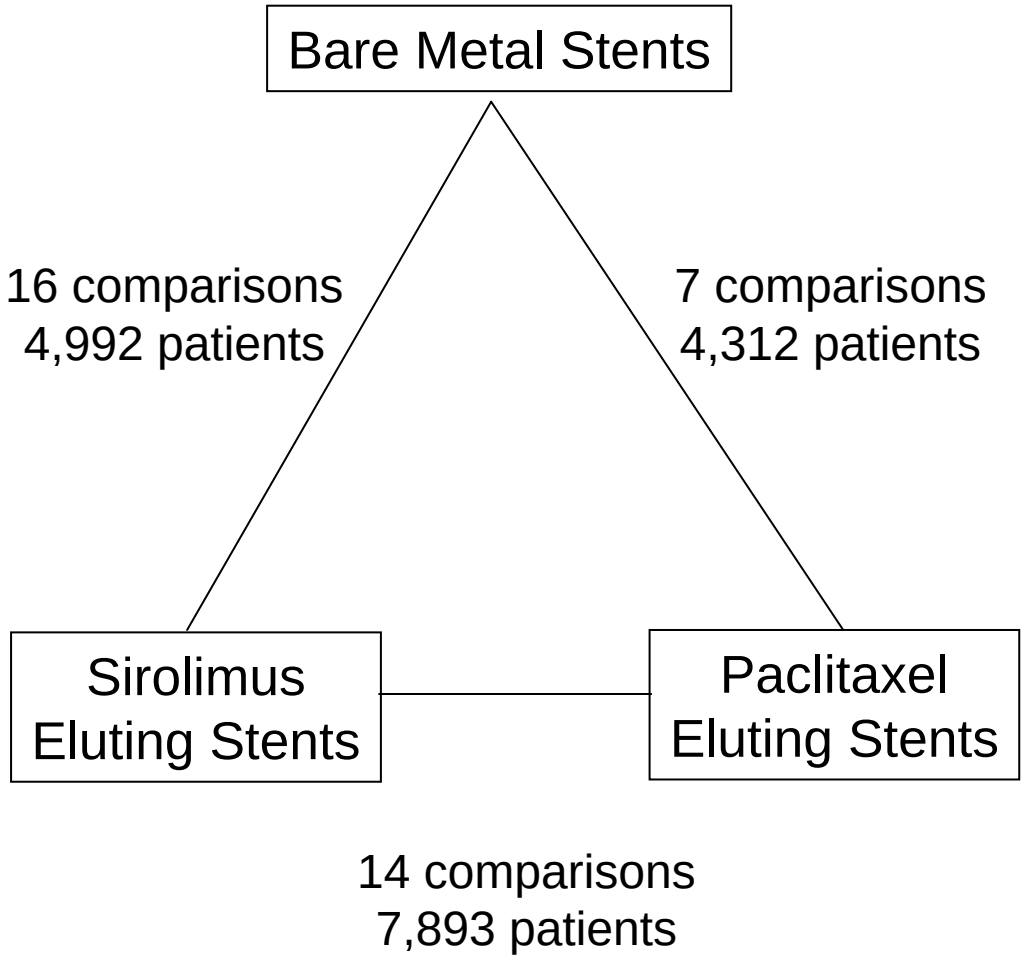
See Comment page 914

*Contributed equally to this report

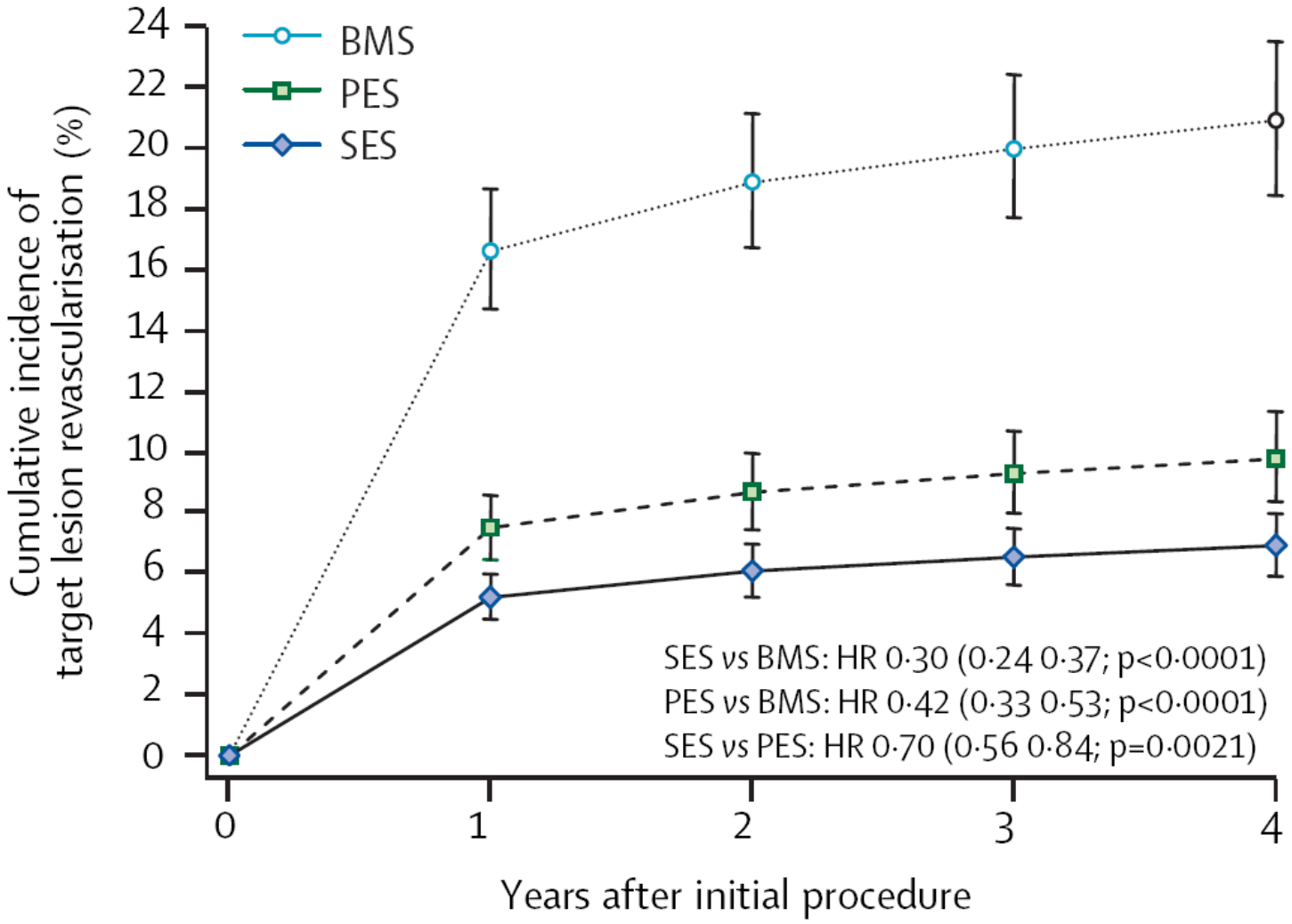
Institute of Social and Preventive Medicine (ISPM) (C Stettler MD, S Wandel MSc, S Allemann PhD, M Zwahlen PhD, S Reichenbach MD, S Trelle MD, P Jüni MD), **and CTU Bern** (Prof S Windecker MD, P Jüni), **University of Bern, Bern, Switzerland; Division of Endocrinology, Diabetes and Clinical Nutrition** (C Stettler, S Allemann, Prof P Diem MD) **and Division of Cardiology** (Prof B Meier MD, S Windecker), **University Hospital, Bern, Switzerland; International Centre for Circulatory Health,**

Stettler et al, Lancet 2007

38 randomised controlled trials in 18,023 patients

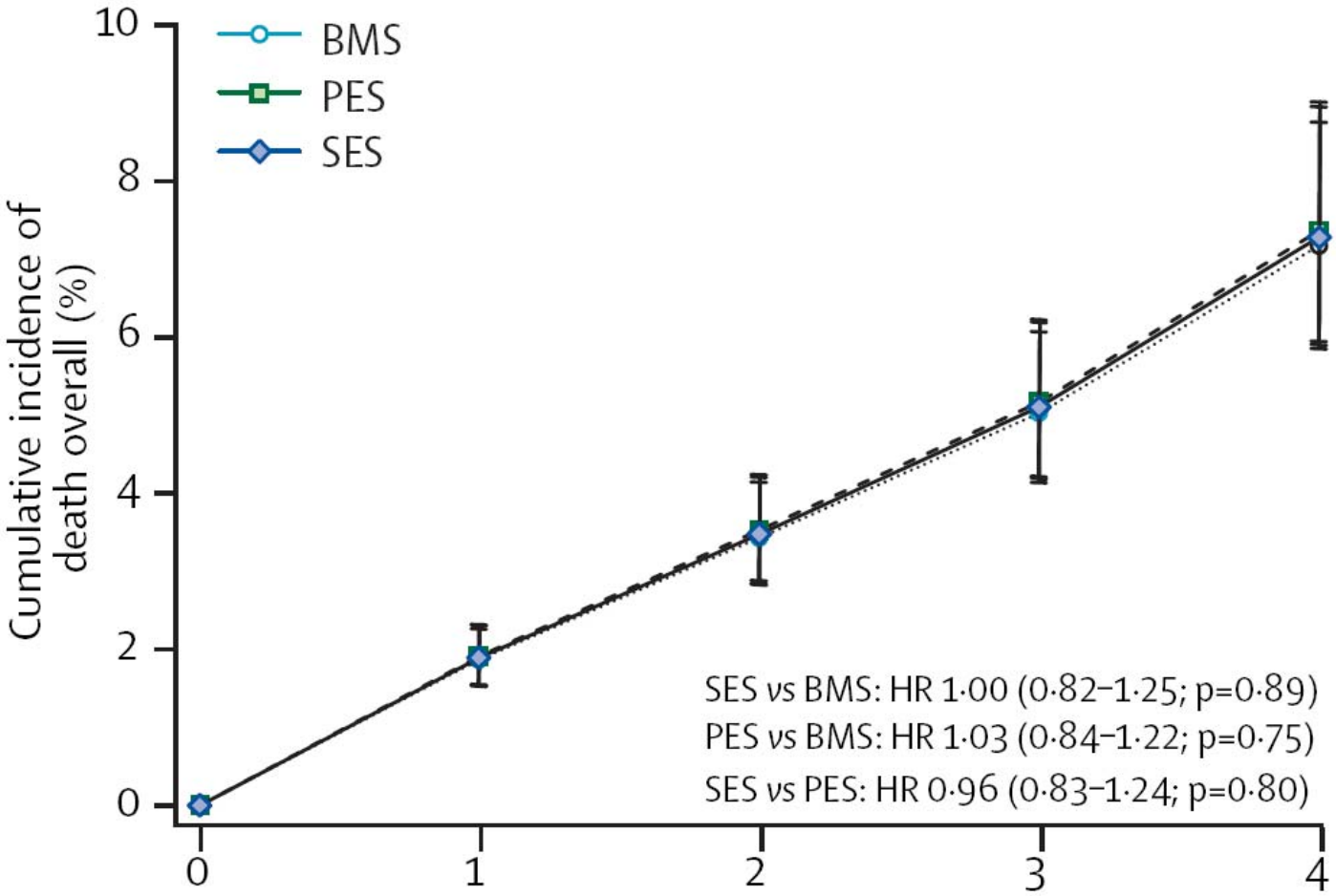


Revascularisation



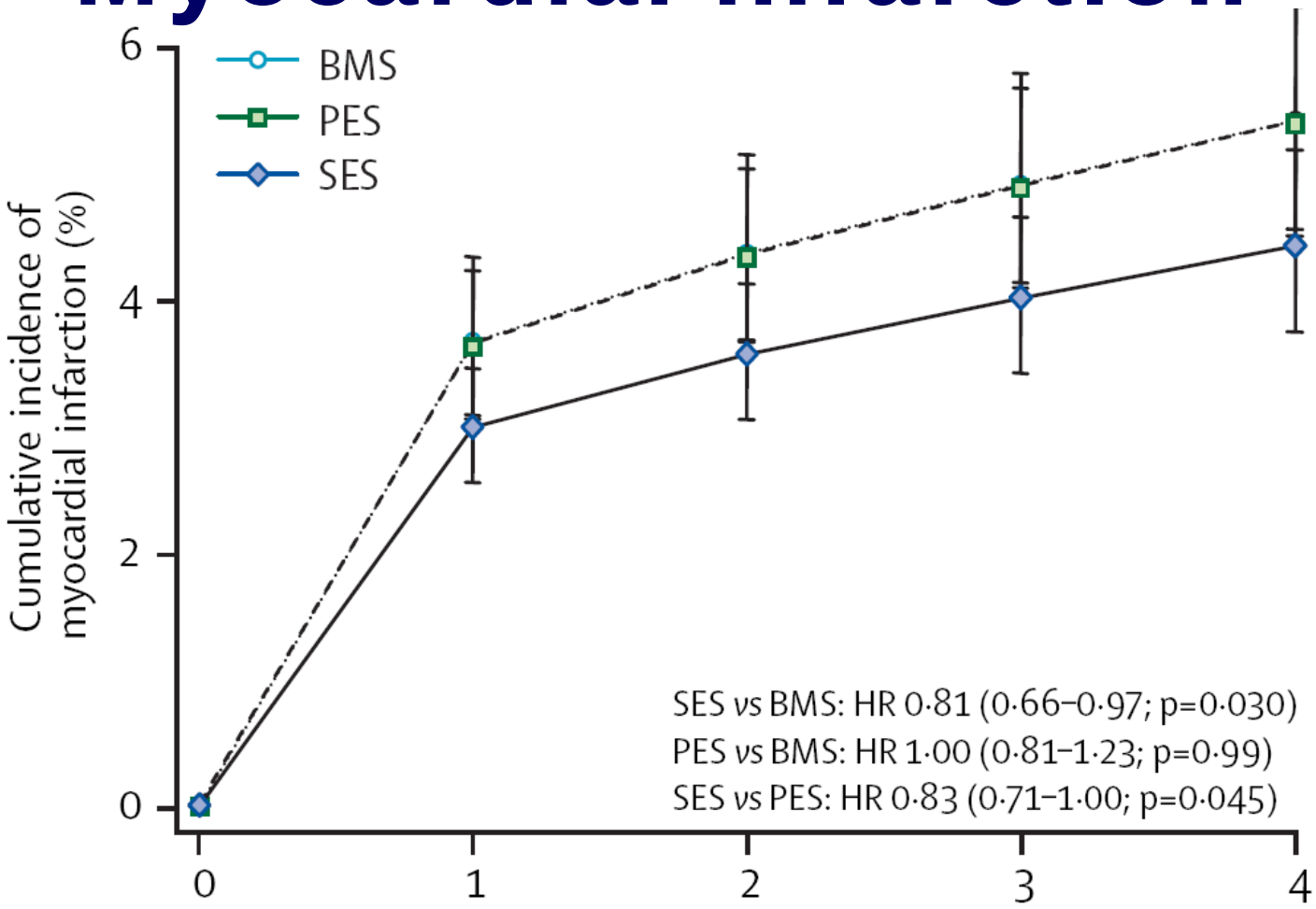
4763	820/4746	53/2795	22/1871	10/1543
6328	448/6280	98/3950	15/1999	6/832
6621	356/6580	68/3801	16/2153	14/999

Overall mortality



BMS	4921	109/4904	48/3340	31/2264	44/1875
PES	6331	138/6283	78/4263	32/2187	15/869
SES	6771	139/6730	72/4041	38/2340	24/10810

Myocardial infarction



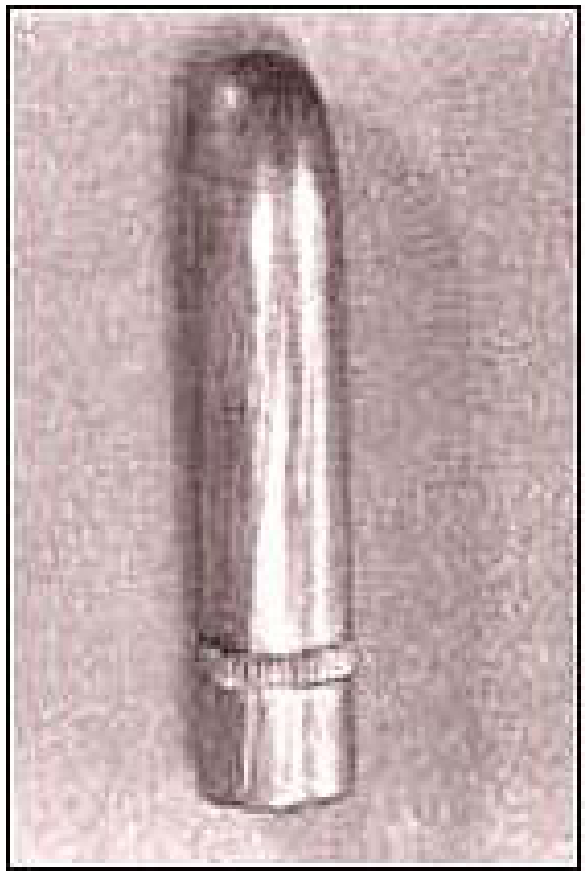
BMS	4891	210/4874	20/3174	17/2129	9/1745
PES	6300	249/6252	47/4057	15/2054	8/805
SES	6771	232/6730	25/3884	11/2236	7/1025

Bottom line regarding harm

- Theory: DES may harm
- Basic research: DES may harm
- RCTs vs BMS: DES do not harm
- Observational studies: DES harm
- **Network of RCTs: DES do not harm!**

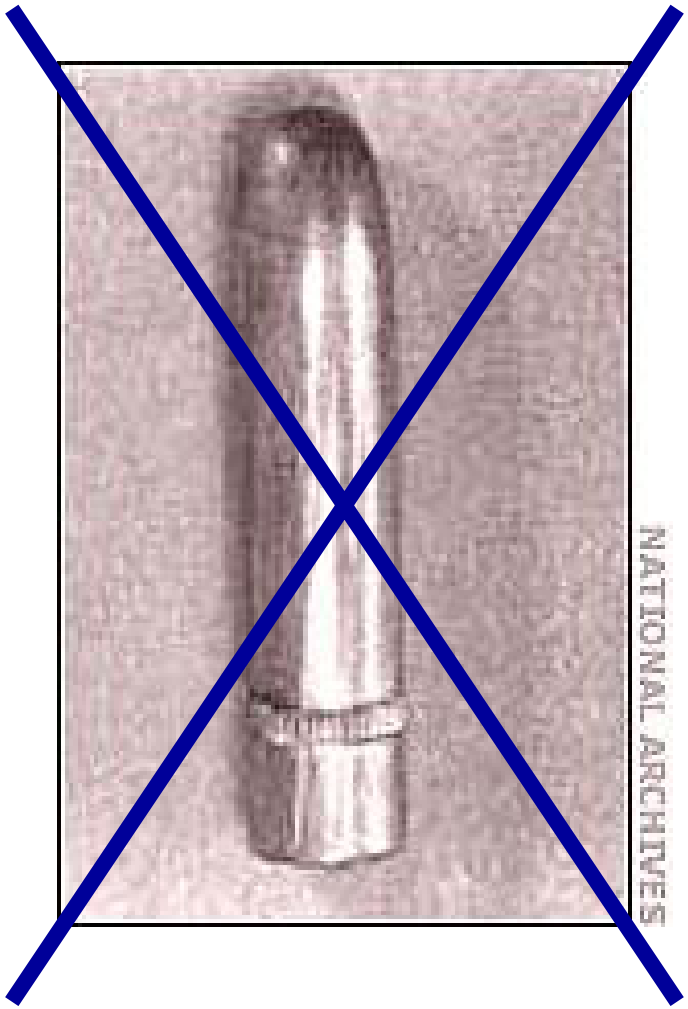
Conclusions

Magic Bullets



NATIONAL ARCHIVES

No Magic Bullets



Balance of benefit and harms

- We need an understanding of the magnitude of
  - benefits
  - harms

  in patients who take the drug in clinical routine
- The balance of benefit and harms will vary according to the spectrum of patients

Final common pathways of relevant benefits and harms

- Overall mortality
- Serious adverse events
- Quality-adjusted life-years (?)

Extrapolations from

- Relative risks from RCTs and, for harms, observational studies
- Event rates observed in routine populations from observational studies

To understand the full spectrum of ***adverse effects*** *— those that occur* ***late****, that* ***were not known*** *beforehand, and that are* ***rare*** *but nevertheless serious — and to be able to investigate the* ***true incidence*** *of known adverse effects* ***in circumstances of actual prescribing****, well-designed observational studies will always be necessary.*

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tinually improve a systematic approach to risk-benefit analysis for use throughout the [Food and Drug Administration] in the preapproval and postapproval settings" specifically ac-

ways be necessary. It follows that systematic reviews of drug treatments must include not only the results of randomized trials on benefits but also evidence from observational

Vandenbroucke & Psaty, JAMA 2008

Simple Principles of Clinical Trials Remain Powerful

Robert M. Califf, MD

IN THIS ISSUE OF *JAMA*, 2 ARTICLES FROM THE CLINICAL Trial (Myoc ATE) ment of a (STEMI). raises new considera

The fac (1) low-m chemic ev glucose, i to rest— CREATE However, thoughts about several questions.

teractions among them. Given the increasing evidence that the drug and device research and development system is not producing the evidence that is needed to guide practice,[6] regulators would be well served to encourage factorial-

ed use- nt, per- global a forms ne, and y mak- rs, the l broad oday's data- nts and . More

A drug simply cannot be declared "safe" without measuring the balance of benefits and risks in a ***randomized controlled trial*** *over an appropriate period of time* ***in a large population representing*** *those who will use the treatment in* ***practice****.*

Califf, JAMA 2005

Thank you

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PLoS MEDICINE

Essay

Observational Research, Randomised Trials, and Two Views of Medical Science

Jan P. Vandenbroucke

Summary

Two views exist of medical science: one emphasises discovery and explanation, the other emphasises evaluation of interventions. This essay analyses in what respects these views differ, and how they lead to opposite research hierarchies, with randomisation on top for evaluation and at bottom for discovery and explanation. The two views also differ strongly in their thinking about the role of prior specification of a research hypothesis. Hence, the essay explores the controversies surrounding subgroup analyses and multiplicity of analyses in observational research. This exploration leads to a rethinking of the universally accepted hierarchy of strength of study designs, which has the randomised trial on top: this hierarchy may be confounded by the prior odds of the research hypothesis. Finally, the strong opinions that are sometimes displayed in pitting the two types of medical science against each other may be explained

soon as there is a hint of confirmation, a paper is submitted. The next wave of researchers immediately tries to check this idea, using their own existing data or their trusted lab experiments. They will look at different subgroups of diseased persons, vary the definition of exposures, take potential bias and confounding into account, or vary the lab conditions, in attempts to explain why the new idea holds—or why it is patently wrong. In turn, they swiftly submit their results for publication. These early exchanges may lead to strong confirmation or strong negation. If not, new studies are needed to bring a controversy to resolution.

The other view is that of medical researchers whose aim is to set up studies to evaluate whether the patient's lot is really improved by the new therapies or diagnostics that looked so wonderful initially. The most developed branch of evaluation research is randomised trials of drug research loops that are a burden to the public purse.

In contrast, the discovery type of researcher is convinced that too much emphasis on evaluation actually hampers the progress of science—precisely because everything is preplanned. For discovery you need chance and one-sided views. You need to look at the literature in a slanted way, to examine the data of others as well as your own to see them in a different light. To discoverers, evaluation is mainly a form of "quality control" that society needs for financial reimbursement by third party payers. Finally, numbers are not explanations; they do not give insight upon which you can build the next step of your reasoning or your next investigation.

Co-existence in the mind of an individual? Yet, these two views of medical science can exist simultaneously in the mind of one person. Over the past decades, I

Vandenbroucke, PLoS Medicine 2008