Netzwerk-Meta-Analysen und indirekte Vergleiche: Erhöhte (Un)Sicherheit?

Prof. Peter Jüni MD FESC

Institute of Social and Preventive Medicine
and CTU Bern, University of Bern

b
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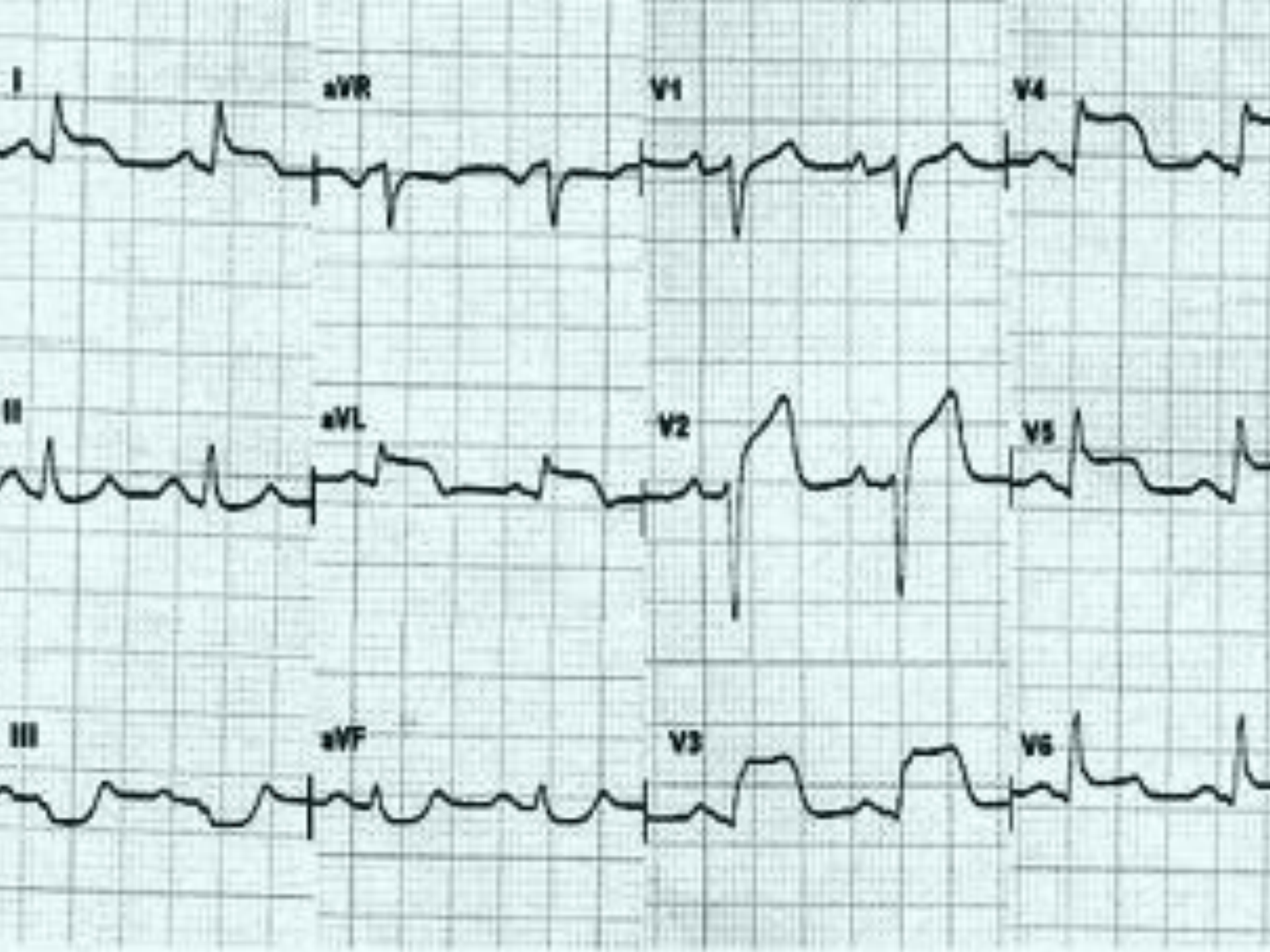
BERN

Is there increased certainty?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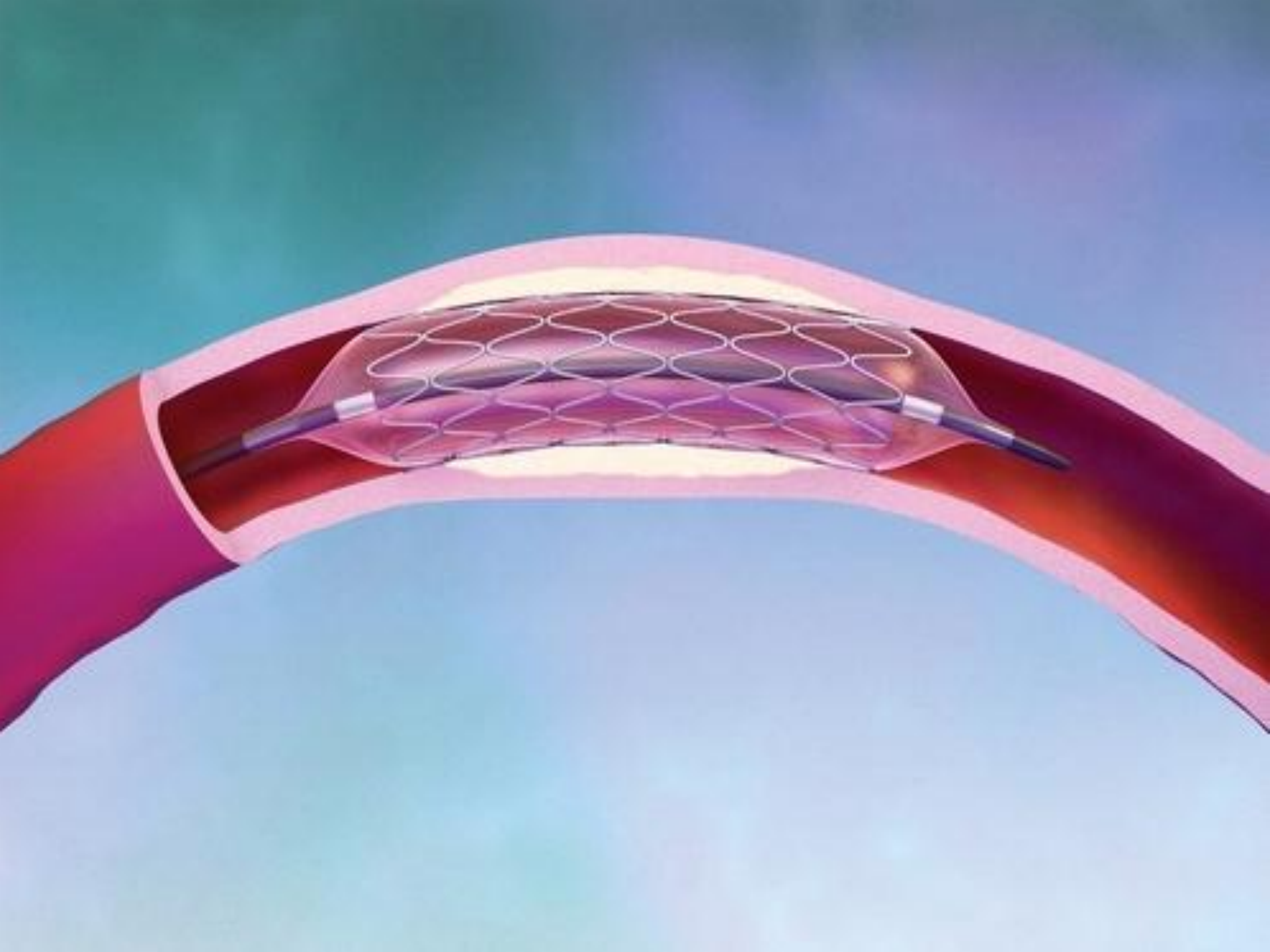


EUROPEAN SOCIETY OF CARDIOLOGY®


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

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

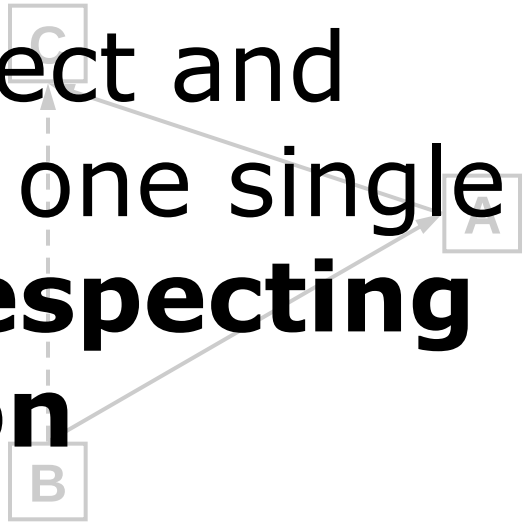
Institute of Social and Preventive Medicine (ISPM) (C Stettler MD, S Wandel MSc, S Allemann PhD, M Zwahlen PhD, S Reichenbach MD, S Trelle MD, P Jüni MD), and CTU Bern (Prof S Windecker MD, P Jüni), University of Bern, Bern, Switzerland; Division of Endocrinology, Diabetes and Clinical Nutrition (C Stettler, 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

Network meta-analysis (NWMA)

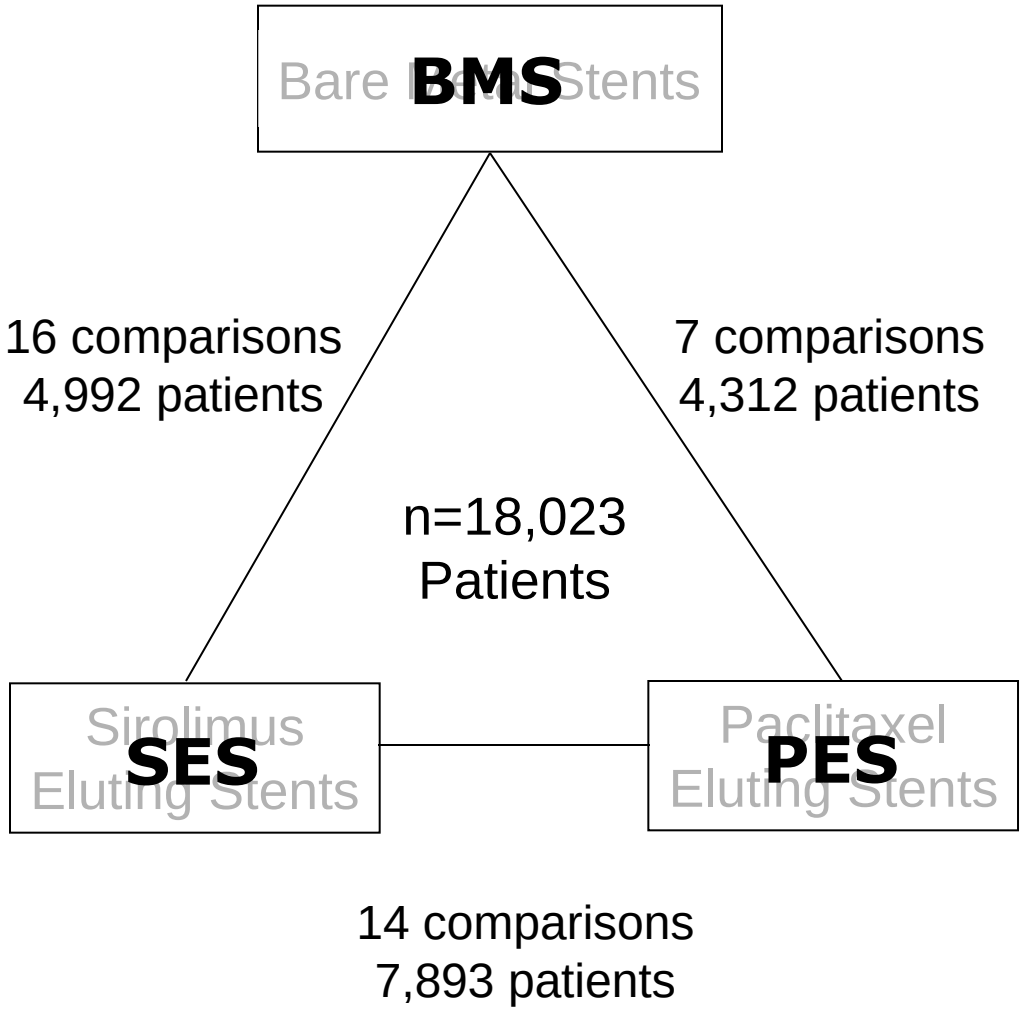
Direct evidence

Indirect evidence



An integration of direct and indirect comparisons in one single analysis **while fully respecting randomisation**

38 randomised controlled trials in 18,023 patients



Myocardial infarction

Comparison	HR (95% CI)	I^2
SES vs BMS	0.86 (0.67–1.09)	0%
PES vs BMS	1.06 (0.83–1.34)	0%
SES *vs* PES	0.84 (0.69–1.02)	0%

Myocardial infarction

SES vs BMS (indirect)

$$HR_{SES\text{-}BMS} = \frac{HR_{SES\text{-}PES}}{HR_{PES\text{-}BMS}}$$

$$= \frac{0.84}{1.06}$$

$$= 0.80$$

Myocardial infarction

Comparison	HR (95% CI)	I^2
SES vs BMS	**0.86** (0.67–1.09)	0%
PES vs BMS	1.06 (0.83–1.34)	0%
SES *vs* PES	0.84 (0.69–1.02)	0%

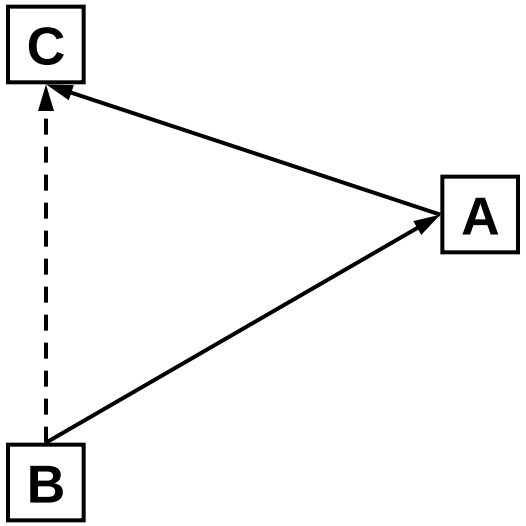
Myocardial infarction

Comparison	**RR (95% CI)**	**I^2**
SES vs BMS	0.86 **(0.67–1.09)**	0%
PES vs BMS	1.06 (0.83–1.34)	0%
SES *vs* PES	0.84 (0.69–1.02)	0%

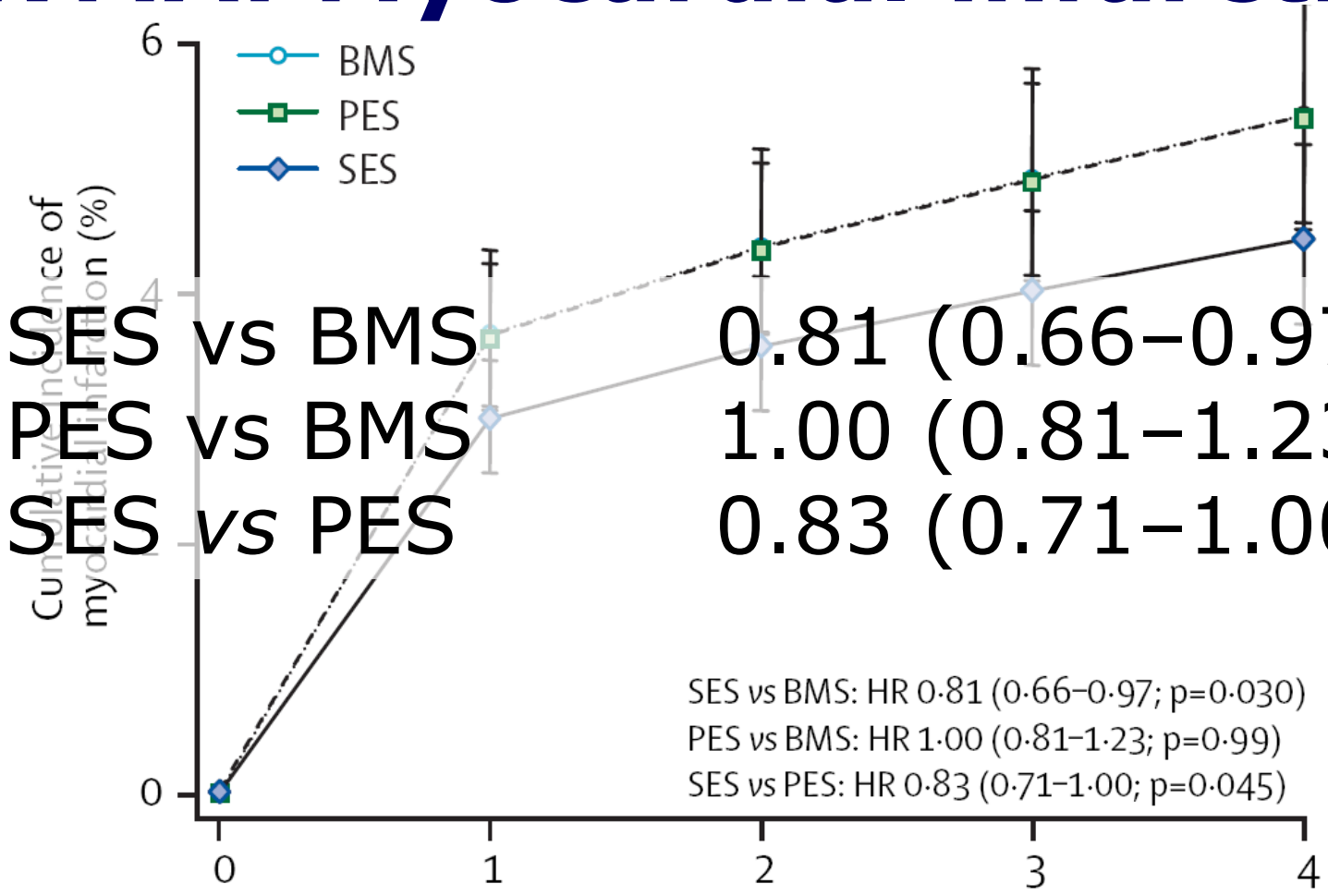
NWMA to integrate direct and indirect comparisons

Direct evidence

Indirect evidence



NWMA: Myocardial infarction



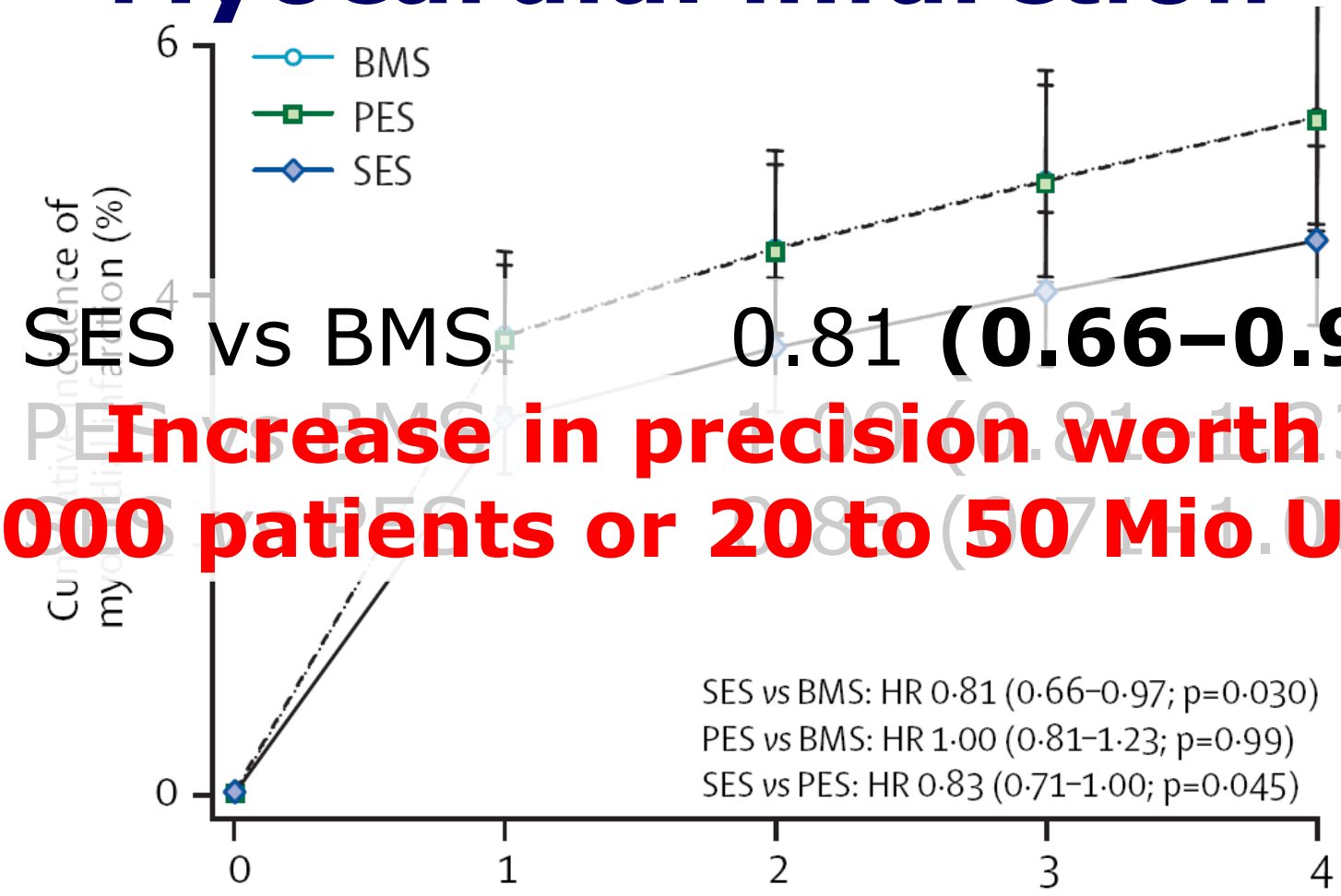
BMS	4891	210/4874	20/3174	17/2129	9/1745
PES	6300	249/6252	47/4057	15/2054	8/805
SES	6771	232/6730	25/3884	11/2236	7/1025

SES vs BMS 0.81 (0.66–0.97)

PES vs BMS 1.00 (0.81–1.23)

SES *vs* PES 0.83 (0.71–1.00)

Myocardial infarction



SES vs BMS 0.81 **(0.66–0.97)**

Increase in precision worth
3000 patients or 20 to 50 Mio US $

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 8, 2007 VOL. 356 NO. 10

A Pooled Analysis of Data Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

Christian Spaulding, M.D., Joost Daemen, M.D., Eric Boersma, Ph.D., Donald E. Cutlip, M.D., and Patrick W. Serruys, M.D., Ph.D.

ABSTRACT

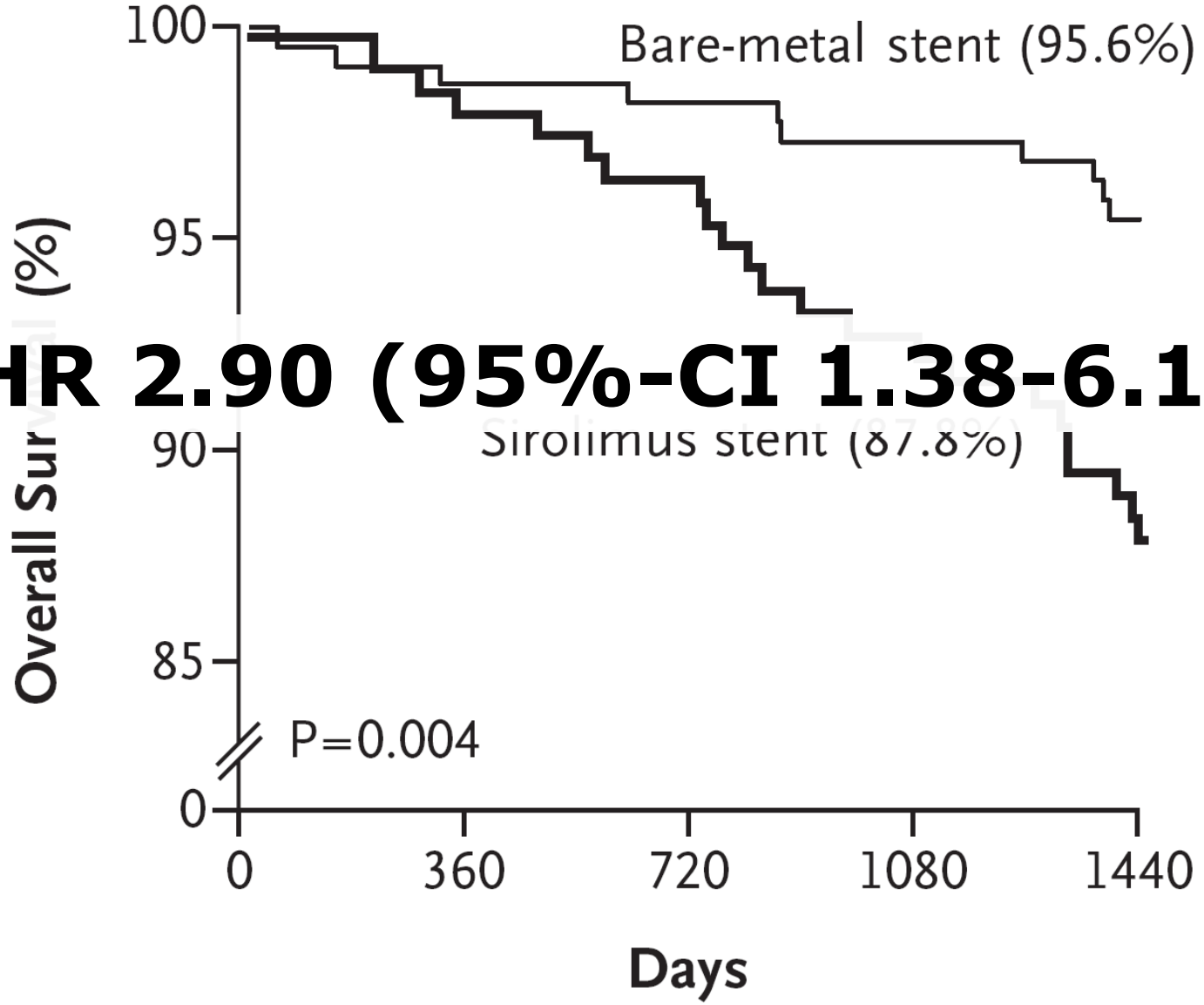
BACKGROUND

Although randomized studies have shown a beneficial effect of drug-eluting stents in reducing the risk of repeated revascularization, these trials were underpowered to compare rates of death and myocardial infarction. The long-term safety of drug-eluting stents has been questioned recently.

From Assistance Publique–Hôpitaux de Paris Cochin Hospital, Paris 5 Medical School René Descartes University and INSERM Unité 780 Avenir, Paris (C.S.); Erasmus Medical Center, Rotterdam, the Netherlands (J.D., E.B., P.W.S.); and Har-

Spaulding et al, N Engl J Med 2007

SES versus BMS in diabetic patients: overall mortality



HR 2.90 (95%-CI 1.38-6.10)

DES versus BMS in diabetic patients: mortality

Comparison	HR	(95% CI)
SES vs BMS	2.90	(1.38–6.10)
PES vs BMS	0.88	(0.55–1.40)

Overall mortality

SES vs PES (indirect)

$$HR_{SES\text{-}PES} = \frac{HR_{SES\text{-}BMS}}{HR_{PES\text{-}BMS}}$$

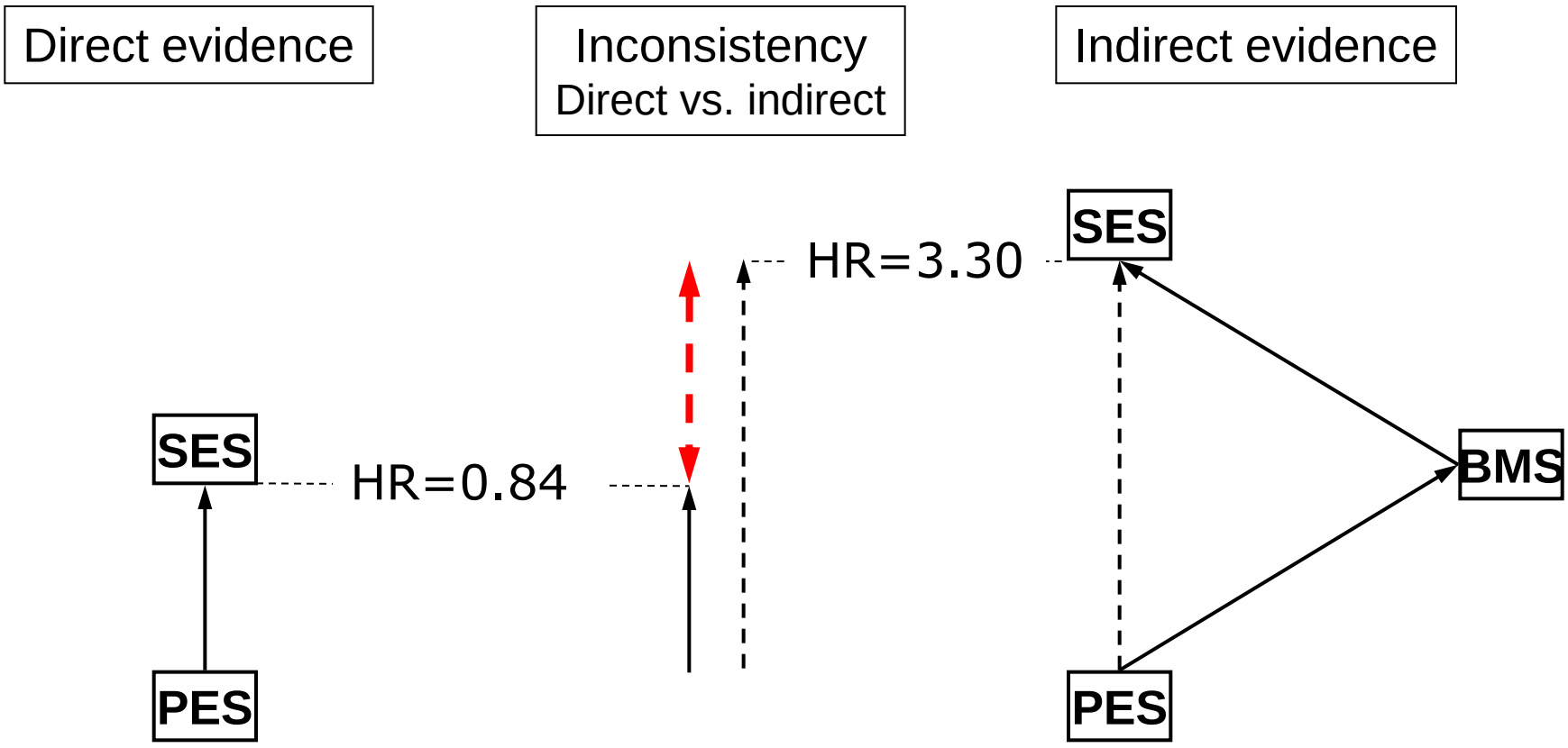
$$= \frac{2.90}{0.88}$$

$$= 3.30$$

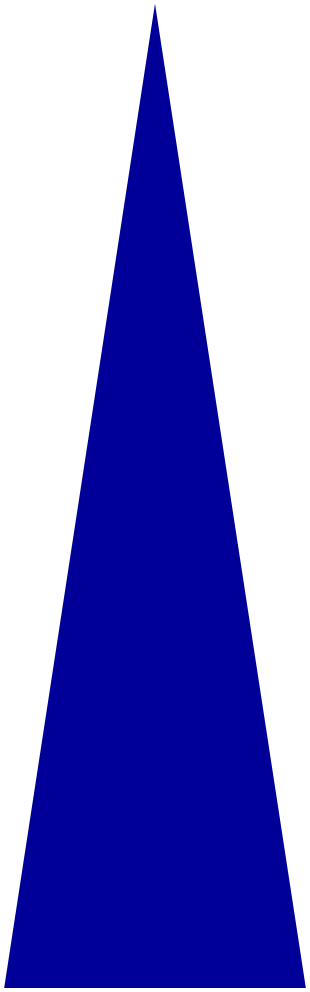
SES versus BMS in diabetic patients: mortality

Comparison	HR	(95% CI)
SES vs BMS	2.90	(1.38–6.10)
PES vs BMS	0.88	(0.55–1.40)
SES vs PES	**0.84**	(0.58–1.22)

Inconsistency

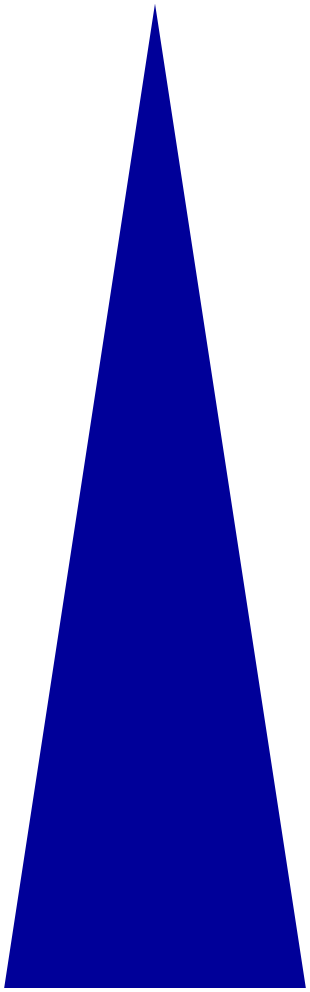


Inconsistency of the network



0%	No inconsistency
25%	Low inconsistency
50%	Moderate inconsistency
100%	High inconsistency

Inconsistency of the network using Spaulding et al's data



← >100%

BMJ

RESEARCH

Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis

Christoph Stettler, senior research fellow,[1,2,3] Sabin Allemann, research fellow,[1,2] Simon Wandel, research fellow,[1] Adnan Kastrati, professor of cardiology,[4] Marie Claude Morice, professor of cardiology,[5] Albert Schömig, professor of medicine,[4] Matthias E Pfisterer, professor of cardiology,[6] Gregg W Stone, professor of medicine,[7] Martin B Leon, professor of medicine ,[7] José Suárez de Lezo, professor of cardiology,[8] Jean-Jacques Goy, professor of interventional cardiology,[9] Seung-Jung Park, professor of cardiology,[10] Manel Sabaté, associate professor of cardiology,[11] Maarten J Suttorp, head of department ,[12] Henning Kelbaek, associate professor of cardiology ,[13] Christian Spaulding, professor of cardiology ,[14] Maurizio Menichelli, interventional cardiologist,[15] Paul Vermeersch, interventional cardiologist,[16] Maurits T Dirksen, training fellow in cardiology,[17] Pavel Cervinka, cardiologist,[18] Marco De Carlo, vice director,[19] Andrejs Erglis, associate professor of cardiology,[20] Tania Chechi, interventional cardiologist,[21] Paolo Ortolani, interventional cardiologist,[22] Martin J Schalij, professor of cardiology,[23] Peter Diem, head of division ,[2] Bernhard Meier, professor of cardiology,[24] Stephan Windecker, head of invasive cardiology ,[24,25] Peter Jüni, head of division [1,25]

[1]Institute of Social and Preventive Medicine, University of Bern, 3012 Bern, Switzerland

[2]Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital, Bern, Switzerland

ABSTRACT

Objective To compare the effectiveness and safety of three types of stents (sirolimus eluting, paclitaxel eluting, and bare metal) in people with and without diabetes mellitus.

Design Collaborative network meta-analysis.

Data sources Electronic databases (Medline, Embase, the

eluting stents were associated with a decrease in revascularisation rates compared with bare metal stents in people both with and without diabetes.

Conclusion In trials that specified a duration of dual antiplatelet therapy of six months or more after stent implantation, drug eluting stents seemed safe and

Stettler et al, BMJ 2008

Table 2 | Overall mortality in patients with diabetes: evaluation of variation in network according to different trial characteristics

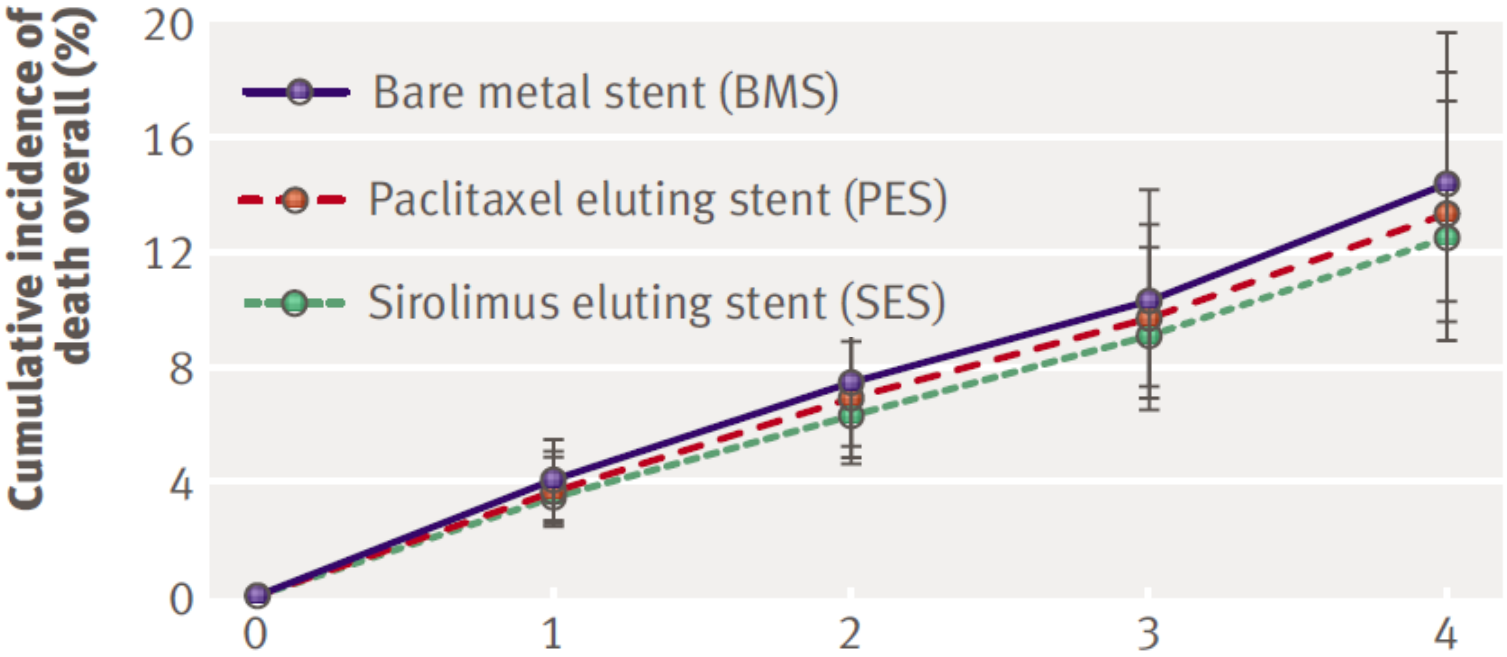
Characteristic	SES *v* bare metal stent		PES *v* bare metal stent		SES *v* PES	
	Relative risk (95% CI)	P value for interaction	Relative risk (95% CI)	P value for interaction	Relative risk (95% CI)	P value for interaction
Concealment of allocation:						
Adequate	1.30 (0.86 to 2.02)	0.16	1.22 (0.74 to 1.99)	0.72	1.06 (0.69 to 1.67)	—
Unclear	0.32 (0.03 to 2.27)		0.93 (0.21 to 4.33)		—	
Blind adjudication:						
Yes	1.30 (0.84 to 2.16)	0.37	1.17 (0.67 to 1.96)	0.96	1.11 (0.69 to 2.04)	0.78
No	0.72 (0.17 to 2.46)		1.24 (0.10 to 11.76)		0.94 (0.26 to 2.64)	
Intention to treat analysis:						
Yes	1.25 (0.81 to 2.02)	0.71	1.13 (0.65 to 1.92)	0.92	1.11 (0.71 to 1.87)	Not estimable*
No or unclear	0.97 (0.26 to 3.82)		1.08 (0.37 to 3.23)		0.14 (0.01 to 3.10)*	

Characteristic	SES *v* bare metal stent	
	Relative risk (95% CI)	P value for interaction
Dual antiplatelet therapy:		
≥6 months	0.89 (0.58 to 1.40)	0.02
<6 months	2.37 (1.18 to 5.12)	

Stettler et al, BMJ 2008

Restricted network: overall mortality

SES *v* BMS: hazard ratio 0.88 (0.55 to 1.30)
PES *v* BMS: hazard ratio 0.91 (0.60 to 1.38)
SES *v* PES: hazard ratio 0.95 (0.63 to 1.43)



		No of events/No of patients			
BMS	904	37/904	15/632	7/358	10/224
PES	1162	35/1162	40/1020	11/535	3/158
SES	1078	39/1078	26/830	12/497	1/73

BMJ

BMJ 2011;343:d4909 doi: 10.1136/bmj.d4909

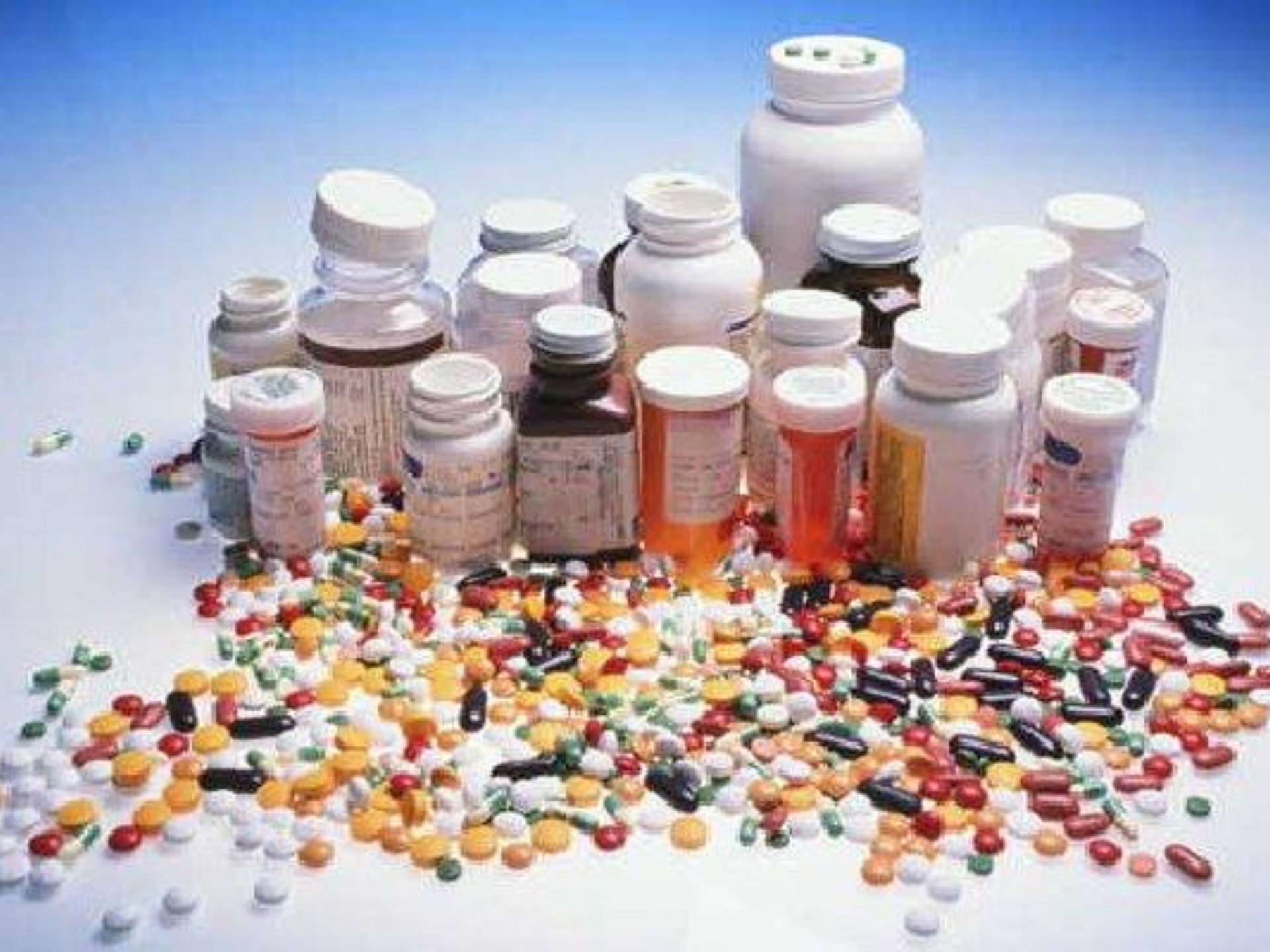
RESEARCH

Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study

Inconsistency between the direct and indirect comparison was statistically significant in 16 cases (14%, 95% CI 9% to 22%).

University of Cambridge, Cambridge, UK; [3]NIHR Trials and Studies Coordinating Centre, University of Southampton, Southampton, UK; [4]Department of Health Science, University of Leicester, Leicester, UK; [5]Centre for Reviews and Dissemination, University of York, York, UK; [6]Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK; [7]School of Dentistry, University of Manchester, Manchester, UK; [8]Centre for Statistics in Medicine, University of Oxford, Oxford, UK

Song et al, BMJ 2011



BMJ

RESEARCH

Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis

Sven Trelle, senior research fellow,[1,2] Stephan Reichenbach, senior research fellow,[1,4] Simon Wandel, research fellow,[1] Pius Hildebrand, clinical reviewer,[3] Beatrice Tschannen, research fellow,[1] Peter M Villiger, head of department and professor of rheumatology,[4] Matthias Egger, head of department and professor of epidemiology and public health,[1] Peter Jüni, head of division and professor of clinical epidemiology[1,2]

[1]Institute of Social and Preventive Medicine, University of Bern, Switzerland

[2]CTU Bern, Inselspital, and University of Bern, Switzerland

[3]Swissmedic (Swiss Agency for Therapeutic Products), Bern

[4]Department of Rheumatology and Clinical Immunology/ Allergology, Inselspital, and University of Bern

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juni@ispm.unibe.ch

Cite this as: *BMJ* 2011;342:c7086
doi:10.1136/bmj.c7086

ABSTRACT

Objective To analyse the available evidence on cardiovascular safety of non-steroidal anti-inflammatory drugs.

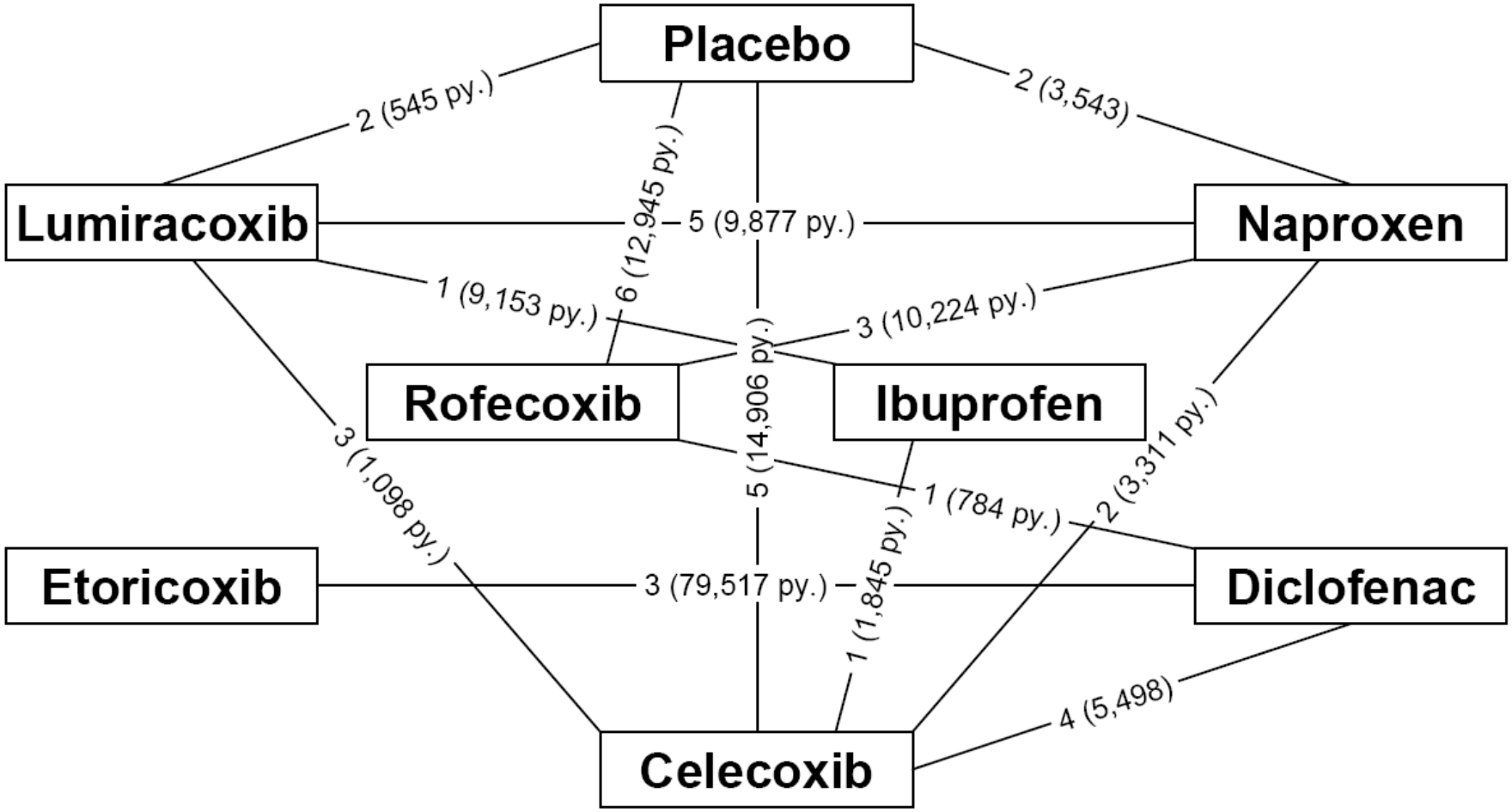
Design Network meta-analysis.

Data sources Bibliographic databases, conference proceedings, study registers, the Food and Drug Administration website, reference lists of relevant articles, and reports citing relevant articles through the Science Citation Index (last update July 2009). Manufacturers of celecoxib and lumiracoxib provided additional data.

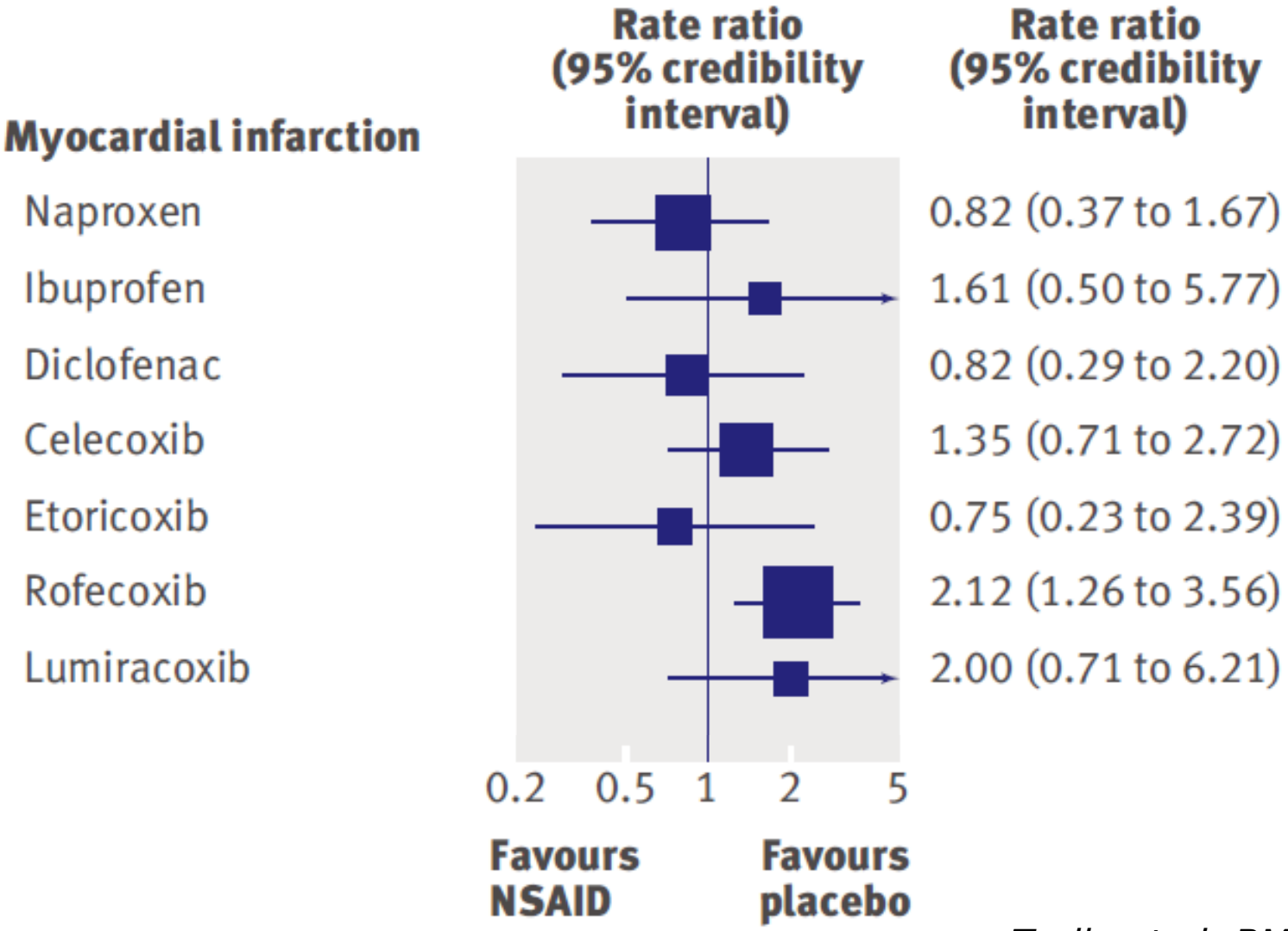
Study selection All large scale randomised controlled trials comparing any non-steroidal anti-inflammatory drug with other non-steroidal anti-inflammatory drugs or

with osteoarthritis and other painful conditions. In the United States an estimated 5% of all visits to a doctor are related to prescriptions of non-steroidal anti-inflammatory drugs and they are among the most commonly used drugs.[1 2] In 2004, rofecoxib, marketed as a cyclo-oxygenase-2 (COX 2) selective inhibitor, was withdrawn from the market after the results of a randomised placebo controlled trial[3] showed an increased risk of cardiovascular events associated with the drug. This finding was confirmed in other trials and a cumulative meta-analysis.[4] Since then debate has surrounded the cardiovascular safety of cyclo-oxygenase-2 selective inhibitors, followed by similar concerns about traditional non-steroidal anti-inflammatory drugs.[5] More recently, the US Food and Drug Administration

Trelle et al, BMJ 2008


Placebo
Lumiracoxib
Naproxen
Rofecoxib
Ibuprofen
Etoricoxib
Diclofenac
Celecoxib
2 (545 py.)
2 (3,543)
6 (12,945 py.)
5 (9,877 py.)
1 (9,153 py.)
3 (10,224 py.)
5 (14,906 py.)
3 (1,098 py.)
2 (3,311 py.)
1 (784 py.)
1 (1,845 py.)
3 (79,517 py.)
4 (5,498)

RR of myocardial infarction



Trelle et al, BMJ 2011

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winbugs

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BUGS

Patch to upgrade to WinBUGS version 1.4.3 now available!
(this patch is cumulative and contains minor fixes over 1.4.2)

Click here for details

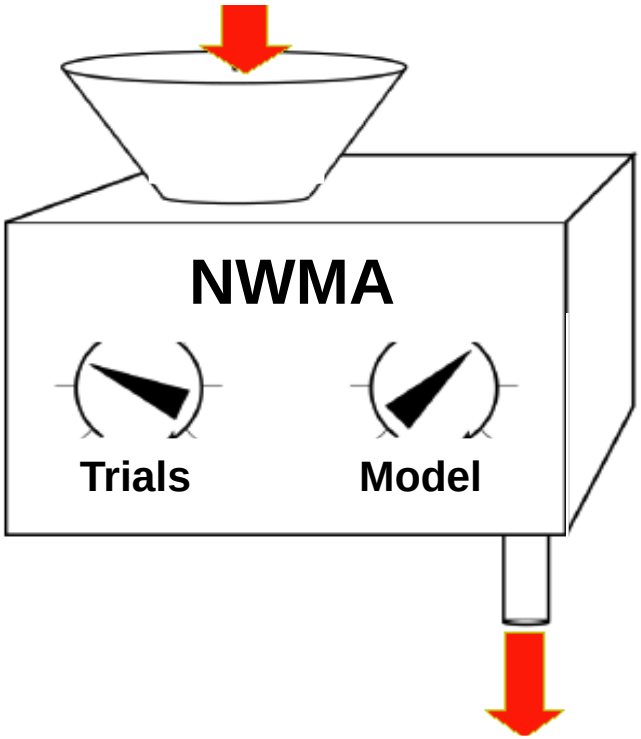
Quick start

- Download and install WinBUGS14.exe
- If installing on a 64-bit machine, you should download a zipped version of the whole file structure and unzip it into Program Files or wherever you want it.
- Download and install the patch for 1.4.3
- Get the free key for unrestricted use by filling in the registration form - the same key can be used for multiple installations. If your key has expired, you should have been sent a link to the new key. If this hasn't happened please register again.
- See the main BUGS page for a summary of the different versions of BUGS available.

Contents

WinBugs

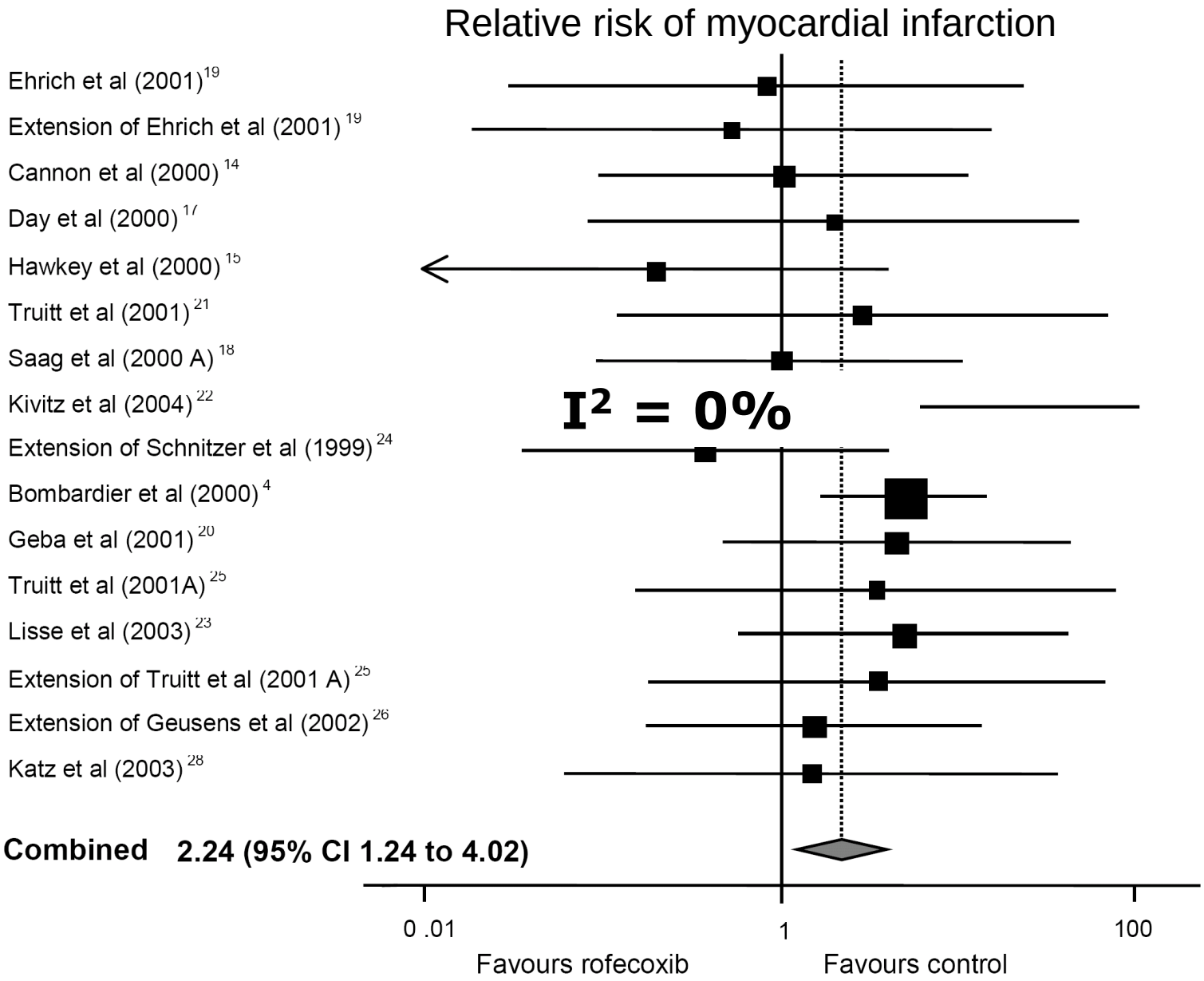
Prior distribution



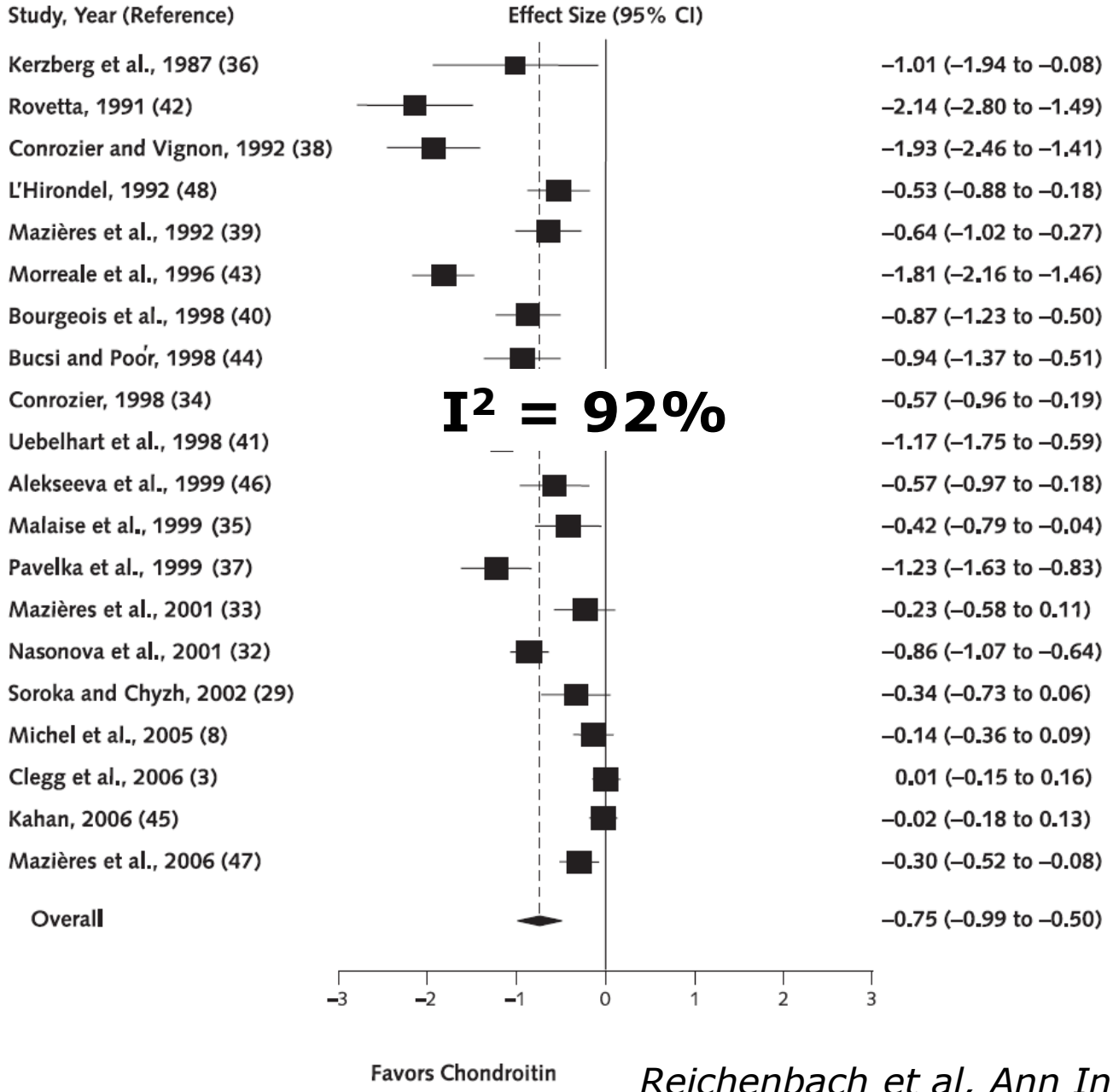
Posterior distribution

Prerequisites

	NWMA	Random-effects MA
Log RR behave additively	**Yes**	**Yes**
Log RR from same common distribution	**Yes**	**Yes**
Model fits the data	**Yes**	**Yes**
Heterogeneity between trials low	**Yes**	**Yes**
Inconsistency of network low	**Yes**	**-**



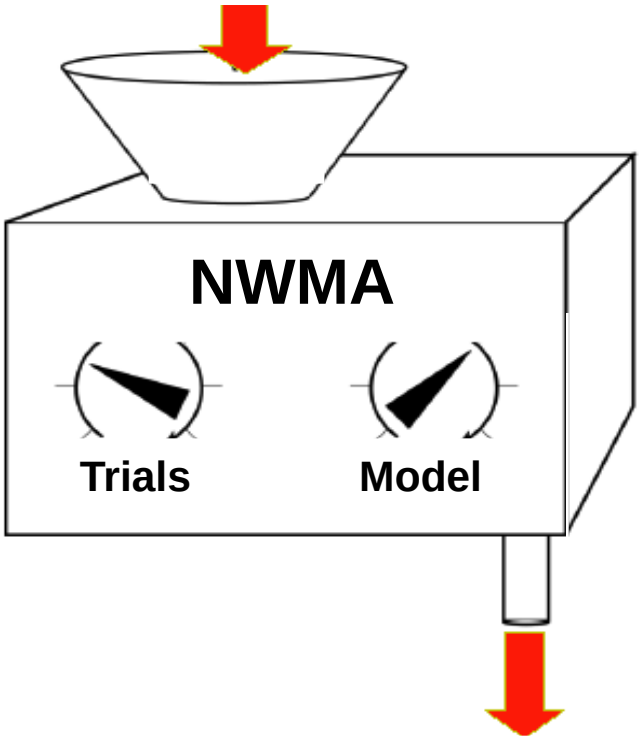
Jüni et al, Lancet 2004



Reichenbach et al, Ann Intern Med 2007

WinBugs

Prior distribution



Posterior distribution

Trials

id[]	t[,1]	t[,2]	r[,1]	py[,1]	r[,2]	py[,2]	r[,3]	py[,3]
1	1	2	40	31	21	54	NA	NA
2	1	3	85	49	NA	NA	75	45
3	2	3	NA	NA	52	158	67	124
4	2	3	NA	NA	22	46	18	65
5	1	2	15	77	21	85	NA	NA
6	1	2	7	25	8	21	NA	NA
7	1	2	3	26	6	13	NA	NA
8	1	2	49	59	44	54	NA	NA
9	2	3	NA	NA	70	210	81	189
10	1	2	41	26	44	31	NA	NA
11	1	3	12	13	NA	NA	14	17
12	1	3	64	389	NA	NA	75	450
13	2	3	NA	NA	32	78	15	44
14	1	2	27	16	30	18	NA	NA
15	2	3	NA	NA	3	14	5	15
16	1	3	281	201	NA	NA	250	235
17	1	2	109	73	150	88	NA	NA
18	1	2	16	10	8	16	NA	NA
19	2	3	NA	NA	12	45	12	66
20	1	2	284	200	389	304	NA	NA
21	2	3	NA	NA	25	89	23	103
22	1	2	203	112	210	104	NA	NA
23	2	3	NA	NA	38	105	39	103

END

Model

$$r_{jk} \sim Poisson(\lambda_{jk})$$

$$\log(\lambda_{jk}) = \begin{cases} \log(py_{jk}/1000) + \mu_{jb} & \text{if treatment } k = \text{treatment } b \\ \log(py_{jk}/1000) + \mu_{jb} + \delta_{jbk} & \text{if treatment } k \neq \text{treatment } b \end{cases}$$

$$\delta_{jbk} \sim N(d_{bk}, \tau^2)$$

Prior distributions were chosen to be vague: $d_{bk} \sim N(0, 1000)$

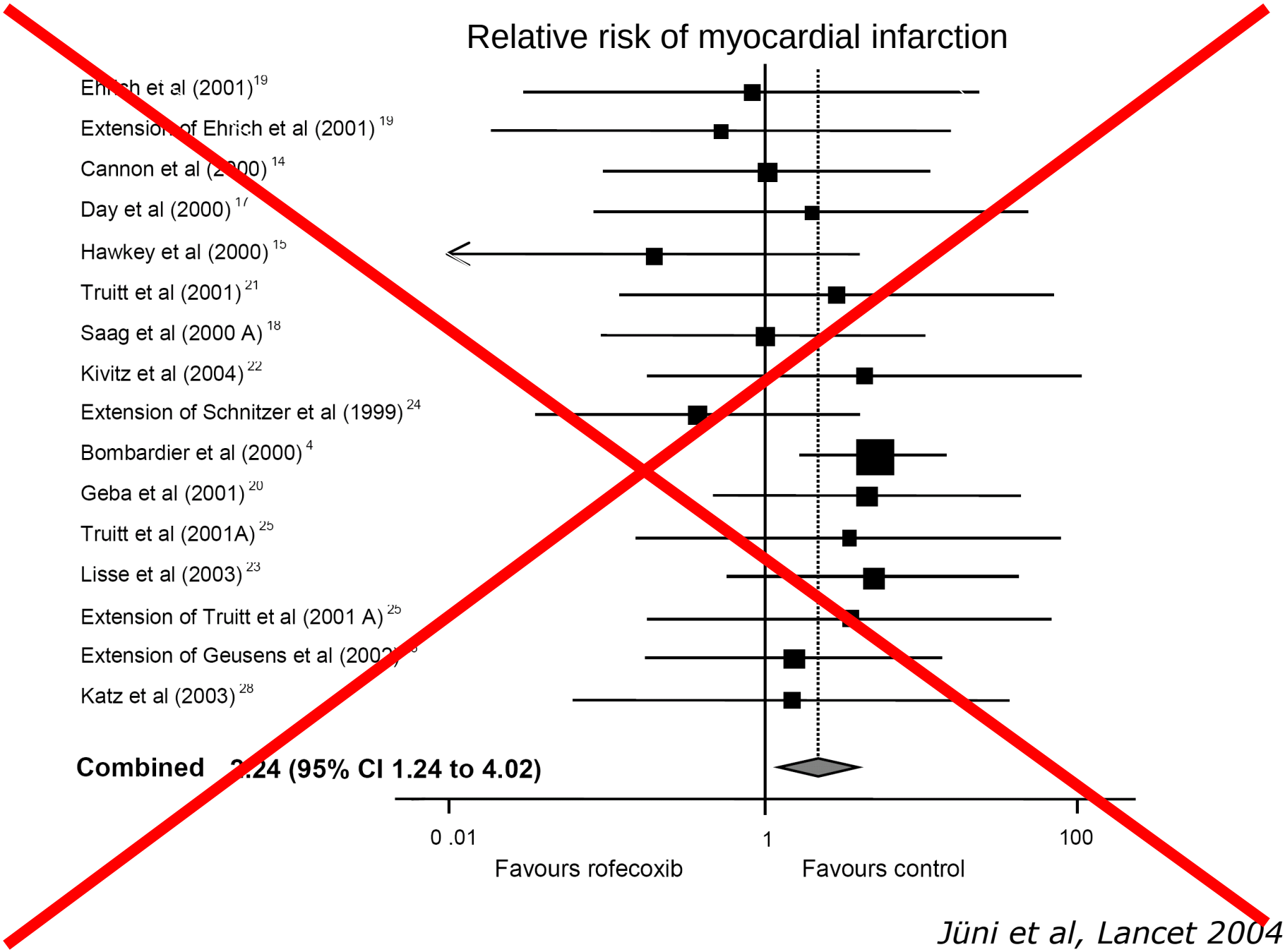
$\tau \sim U(0, 2)$

WinBUGS Code

```
model{
for(i in 1:23) {

    # likelihood
    r[i,t[i,1]] ~ dpois(lambda[i,t[i,1]])
    r[i,t[i,2]] ~ dpois(lambda[i,t[i,2]])

    # evidence synthesis model
    log(lambda[i,t[i,1]]) <- log(py[i,t[i,1]]/1000) + mu[i]
    log(lambda[i,t[i,2]]) <-
        log(py[i,t[i,2]]/1000) + mu[i] + delta[i,t[i,2]]

    # trial specific log rate ratio
    delta[i,t[i,1]] <- 0
    delta[i,t[i,2]] ~ dnorm(md[i,t[i,2]],tau)

    # mean of log rate ratio distribution
    md[i,t[i,2]] <- d[t[i,2]] - d[t[i,1]]
}
```

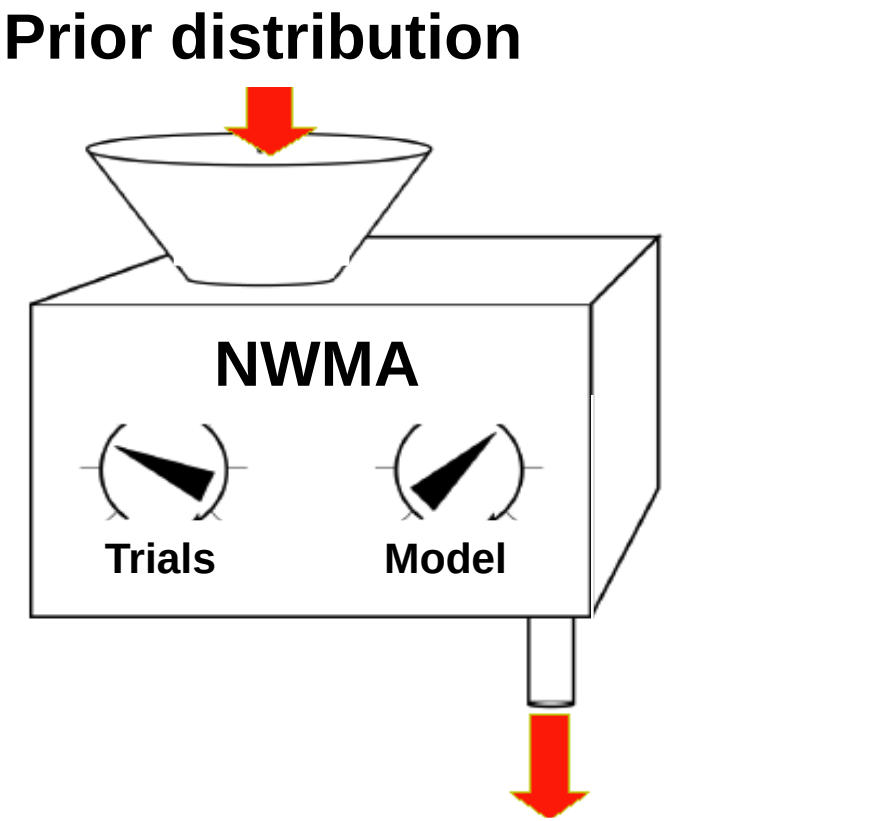
WinBUGS Code

```
    # vague priors for trial baselines
    for (i in 1:23){
      mu[i] ~ dnorm(0,0.001)
    }

    # vague priors for basic parameters
    d[1] <- 0
    d[2] ~ dnorm(0,0.001)
    d[3] ~ dnorm(0,0.001)

    # vague prior for random effects standard deviation
    sd ~ dunif(0,2)
    tau <- 1/pow(sd,2)
    tau2 <- 1/tau

}
```



Jüni et al, Lancet 2004

WinBUGS=Black box



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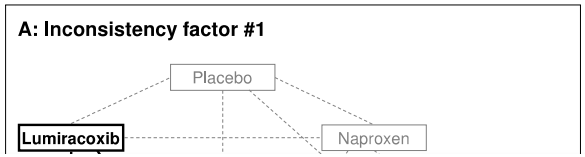
Inconsistency factors



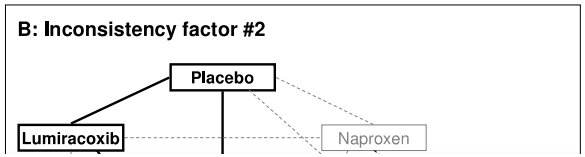
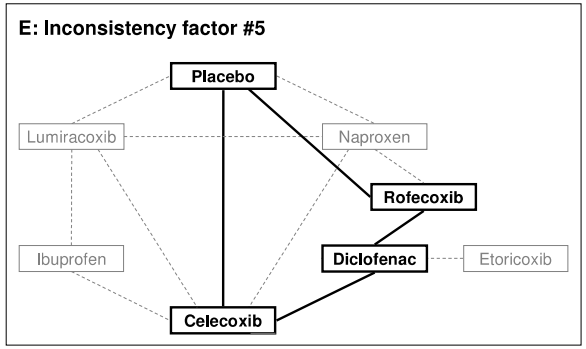
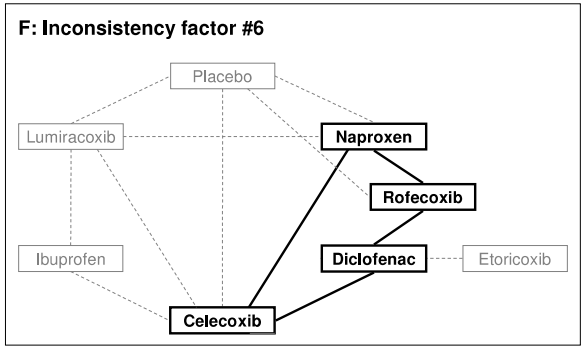


Table 4: Assessment of inconsistency

Outcome	ICF #1 (95%-CI)	ICF #2 (95%-CI)	ICF #3 (95%-CI)	ICF #4 (95%-CI)	ICF #5 (95%-CI)	ICF #6 (95%-CI)
Myocardial infarction	5% (0-144%)	0% (0-293%)	16% (0-276%)	7% (0-135%)	4% (0-201%)	29% (0-257%)
Stroke	0% (0-210%)	3% (0-285%)	1% (0-127%)	3% (0-116%)	1% (0-252%)	3% (0-257%)
Cardiovascular death	3% (0-248%)	28% (0-1409%)	2% (0-390%)	11% (0-194%)	11% (0-545%)	13% (0-867%)
Death from any cause	12% (0-253%)	45% (0-3075%)	23% (0-1101%)	23% (0-203%)	110% (0-1522%)	35% (0-1217%)
APTC outcome	9% (0-72%)	11% (0-310%)	3% (0-122%)	5% (0-102%)	3% (0-125%)	33% (0-447%)

APTC, Antiplatelet Trialist Collaboration

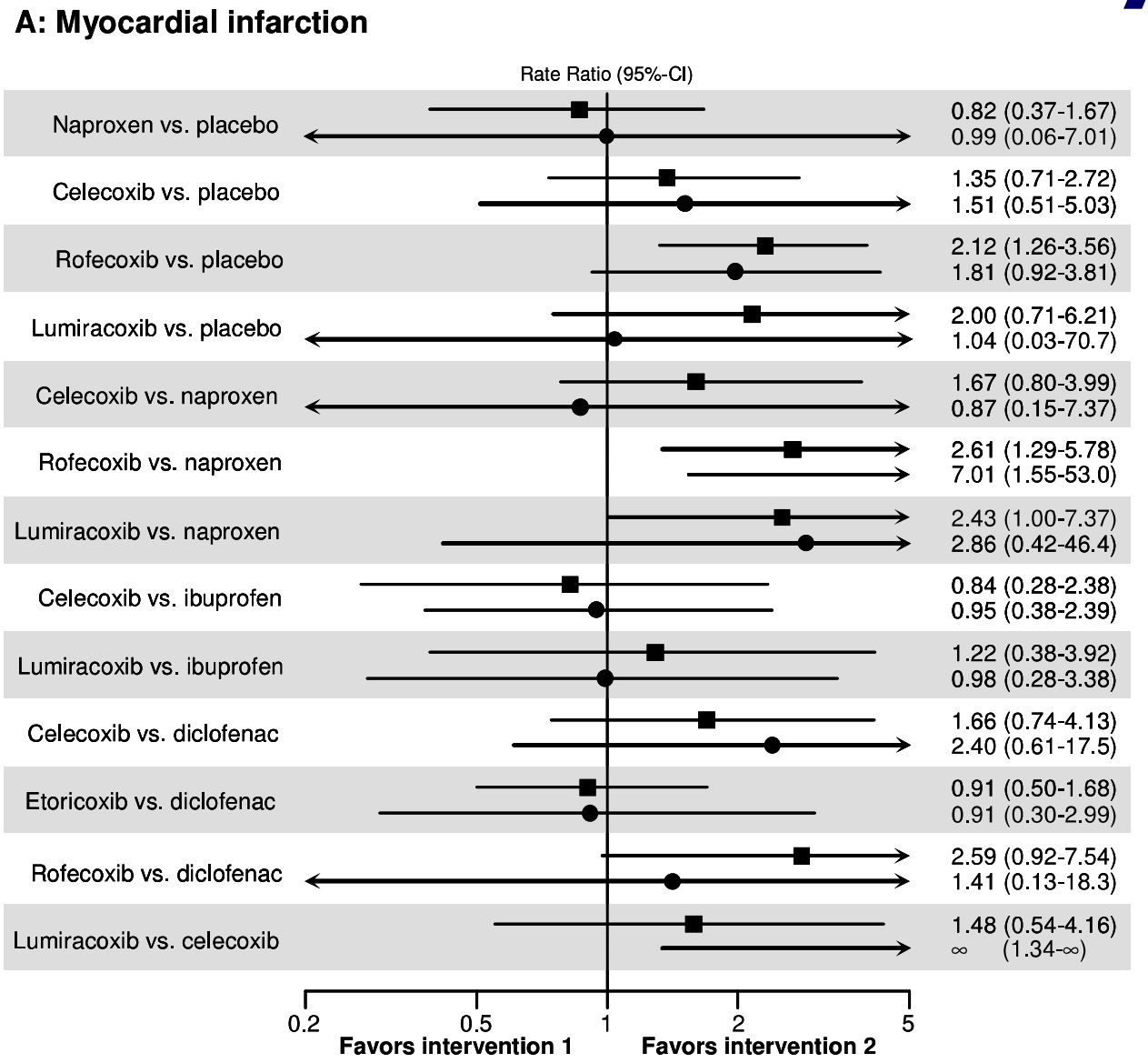




Heterogeneity between trials

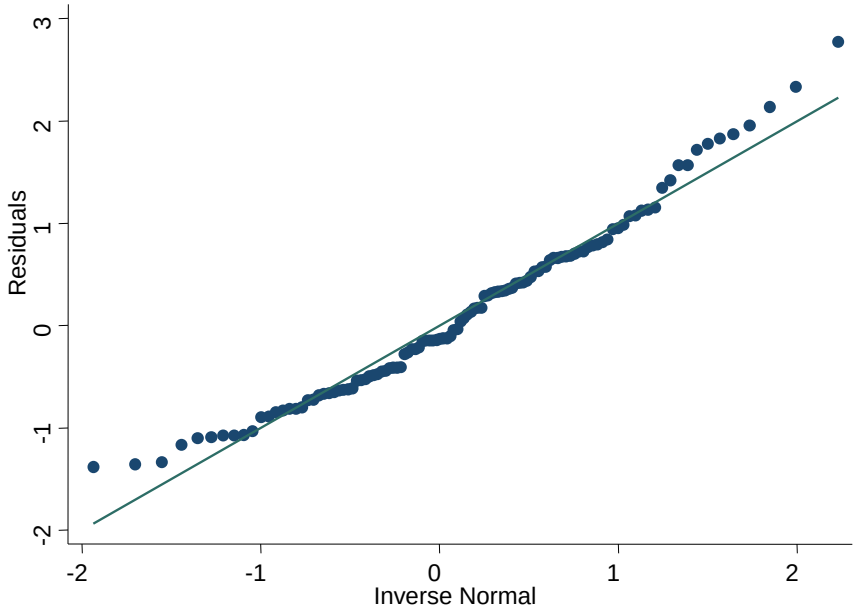
Outcome	Network meta-analysis (τ^2)		
	SES vs BMS	PES vs BMS	SES vs PES
Death overall	0.001	0.001	0.001
Cardiac death	0.005	0.003	0.007
Myocardial infarction	0.01	0.01	0.02
Death or myocardial infarction	0.002	0.003	0.006
Definite stent thrombosis	0.02	0.01	0.02
Target lesion revascularisation	0.15	0.06	0.007

Comparision of network and conventional meta-analysis

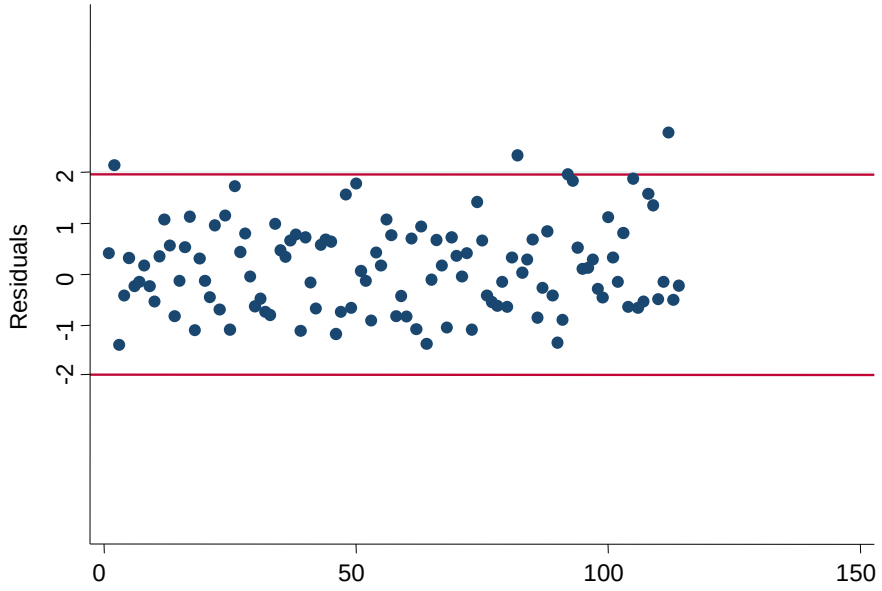


Goodness of fit

Q-Q plot



Residuals



Is there increased uncertainty?

Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis

Tullio Palmerini, Giuseppe Biondi-Zoccai, Diego Della Riva, Christoph Stettler, Diego Sangiorgi, Fabrizio D'Ascenzo, Takeshi Kimura, Carlo Briguori, Manel Sabatè, Hyo-Soo Kim, Antoinette De Waha, Elvin Kedhi, Pieter C Smits, Christoph Kaiser, Gennaro Sardella, Antonino Marullo, Ajay J Kirtane, Martin B Leon, Gregg W Stone

Summary

Background The relative safety of drug-eluting stents and bare-metal stents, especially with respect to stent thrombosis, continues to be debated. In view of the overall low frequency of stent thrombosis, large sample sizes are needed to accurately estimate treatment differences between stents. We compared the risk of thrombosis between bare-metal and drug-eluting stents.

Methods For this network meta-analysis, randomised controlled trials comparing different drug-eluting stents or drug-eluting with bare-metal stents currently approved in the USA were identified through Medline, Embase, Cochrane databases, and proceedings of international meetings. Information about study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted.

Findings 49 trials including 50 844 patients randomly assigned to treatment groups were analysed. 1-year definite stent thrombosis was significantly lower with cobalt-chromium everolimus eluting stents (CoCr-EES) than with bare-metal stents (odds ratio [OR] 0·23, 95% CI 0·13–0·41). The significant difference in stent thrombosis between CoCr-EES and bare-metal stents was evident as early as 30 days (OR 0·21, 95% CI 0·11–0·42) and was also significant between 31 days and 1 year (OR 0·27, 95% CI 0·08–0·74). CoCr-EES were also associated with significantly lower rates of 1-year definite stent thrombosis compared with paclitaxel-eluting stents (OR 0·28, 95% CI 0·16–0·48), permanent polymer-based sirolimus-eluting stents (OR 0·41, 95% CI 0·24–0·70), phosphorylcholine-based zotarolimus-eluting stents (OR 0·21, 95% CI 0·10–0·44), and Resolute zotarolimus-eluting stents (OR 0·14, 95% CI 0·03–0·47).

Lancet 2012; 379: 1393–402

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See Comment page 1368

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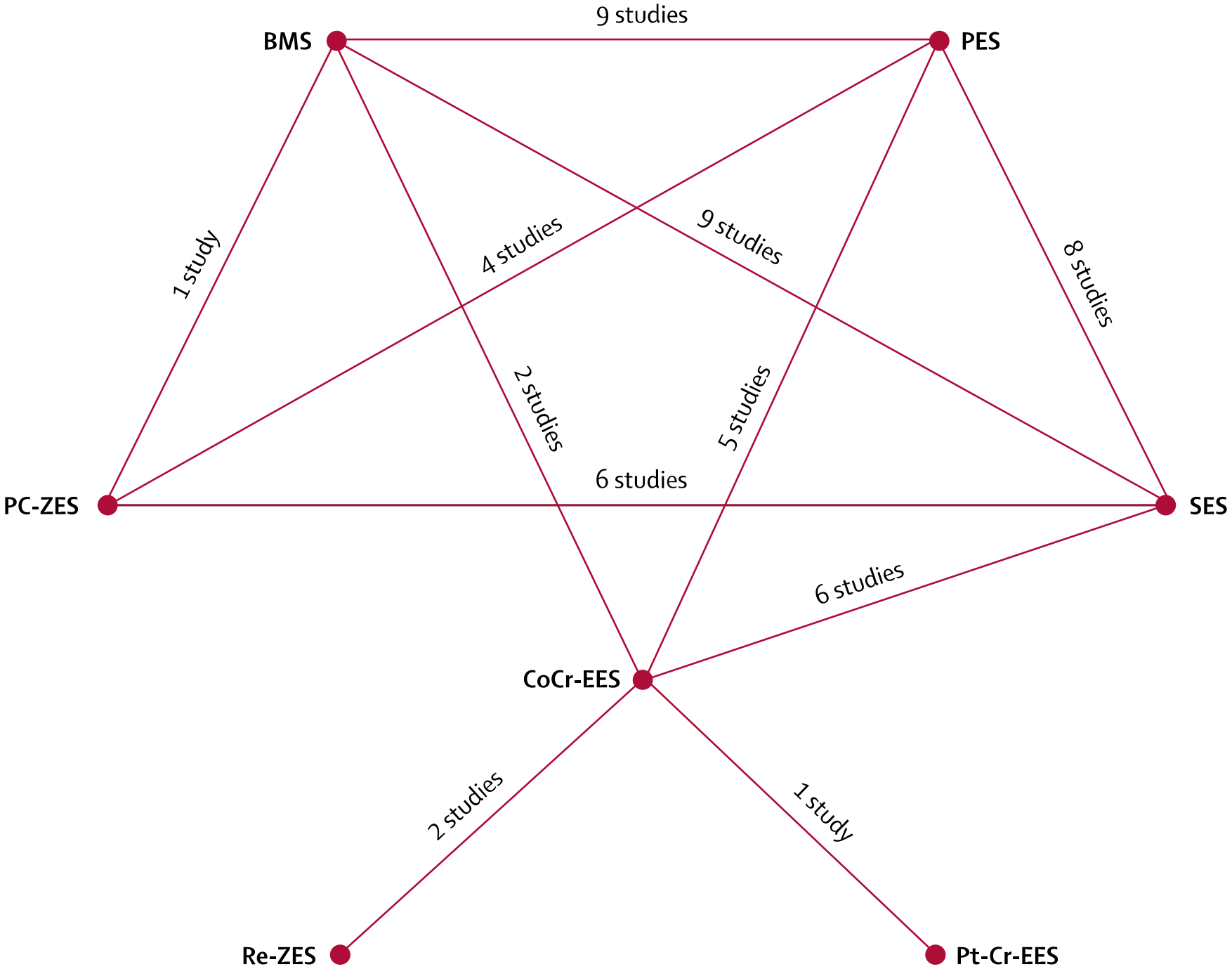
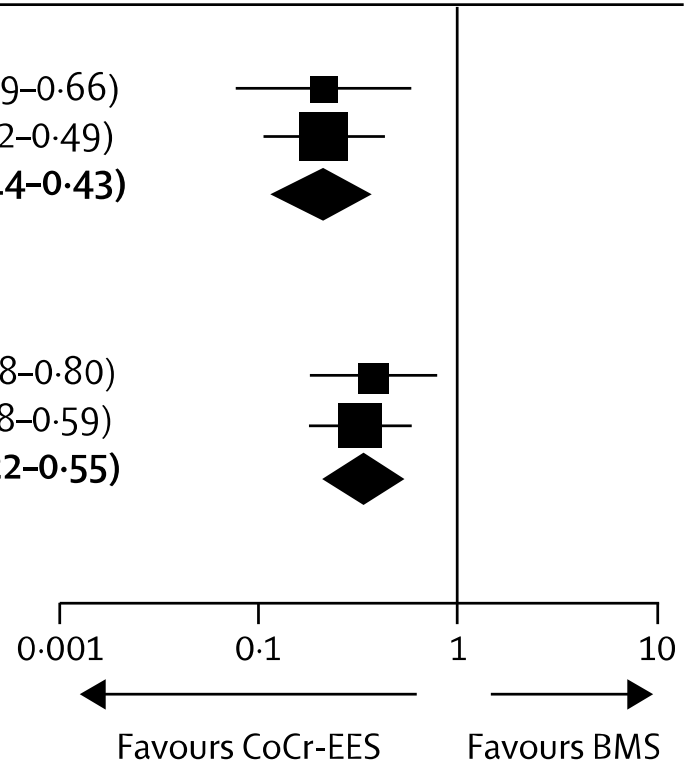
Palmerini et al, Lancet 2012


BMS
PES
PC-ZES
SES
CoCr-EES
Re-ZES
Pt-Cr-EES
9 studies
1 study
4 studies
9 studies
8 studies
2 studies
5 studies
6 studies
6 studies
2 studies
1 study

1 estimate of inconsistency

	log (odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
(A) Definite thrombosis				
Direct estimate	–1·427	0·519	32·4%	0·24 (0·09–0·66)
Indirect estimate	–1·421	0·359	67·6%	0·24 (0·12–0·49)
Total (95% CI)			**100·00%**	**0·24 (0·14–0·43)**
Test for overall effect Z=4·82 (p<0·00001)				
(B) Definite or probable thrombosis				
Direct estimate	–0·968	0·377	39·4%	0·38 (0·18–0·80)
Indirect estimate	–1·122	0·304	60·6%	0·33 (0·18–0·59)
Total (95% CI)			**100·00%**	**0·35 (0·22–0·55)**
Test for overall effect Z=4·48 (p<0·00001)				



Not reported

- Inconsistency for remaining loops
- Heterogeneity in the network
- Goodness of fit
- Sensitivity analyses according to methodological quality and sample size

BMJ

RESEARCH

Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published

Table 3 | Consistency assumption when direct and indirect evidence were compared or combined

Compared or combined direct and indirect evidence	Consistency assumption		Total
	Explicit	Not explicit	
Yes	12	18	30
No	0	10	10
Total	12	28	40

Oxford
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Cite this as: *BMJ* 2009;338:b1147
doi:10.1136/bmj.b1147

2000 and 2007 in which an indirect approach had been explicitly used.

Data extraction Identified reviews were assessed for comprehensiveness of the literature search, method for indirect comparison, and whether assumptions about similarity and consistency were explicitly mentioned.

Results The survey included 88 review reports. In 13 reviews, indirect comparison was informal. Results from different trials were naively compared without using a common control in six reviews. Adjusted indirect

ted head to head randomised controlled trials provide the most rigorous and valid research evidence on the relative effects of different interventions.[1] Evidence from head to head comparison trials is often limited or unavailable, however, and indirect comparison may therefore be necessary.[2 3]

Indirect comparison may be done narratively—for example, by discussing the results of separate systematic reviews of different interventions for a given condition. A simple but inappropriate statistical method is to

Song et al, BMJ 2009

Diabetologia (2012) 55:566–578
DOI 10.1007/s00125-011-2398-8

META-ANALYSIS

Reno-protective effects of renin–angiotensin system blockade in type 2 diabetic patients: a systematic review and network meta-analysis

P. Vejakama · A. Thakkinstian · D. Lertrattananon · A. Ingsathit · C. Ngarmukos · J. Attia

A network meta-analysis was performed to compare indirectly all treatment effects.

renal outcomes between ACE inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and other antihypertensive drugs or placebo in type 2 diabetes.

Methods Publications were identified from Medline and Embase up to July 2011. Only randomised controlled trials comparing ACEI/ARB monotherapy with other active drugs

cations, microalbuminuria, macroalbuminuria and albuminuria regression were extracted. Risk ratios were pooled using a random-effects model if heterogeneity was present; a fixed-effects model was used in the absence of heterogeneity.

Results Of 673 studies identified, 28 were eligible (n=13–4,912). In direct meta-analysis, ACEI/ARB had significantly lower risk of serum creatinine doubling (pooled RR=0.66 [95% CI 0.52, 0.83]), macroalbuminuria (pooled RR=0.70 [95% CI 0.50, 1.00]) and albuminuria regression (pooled RR 1.16 [95% CI 1.00, 1.39]) than other antihypertensive drugs, mainly calcium channel blockers (CCBs). Although the risks

Electronic supplementary material The online version of this article (doi:10.1007/s00125-011-2398-8) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

P. Vejakama · A. Thakkinstian (✉) · A. Ingsathit

Vejakama et al, Diabetologia 2012

Not reported

- Everything …!

OPEN ACCESS Freely available online

PLoS one

Impact of Reporting Bias in Network Meta-Analysis of Antidepressant Placebo-Controlled Trials

Ludovic Trinquart[1,2,3,4.], Adeline Abbé[1,2,3,4.], Philippe Ravaud[1,2,3,4,5*]

1 French Cochrane Centre, Paris, France, 2 Université Paris Descartes - Sorbonne Paris Cité, Paris, France, 3 INSERM U738, Paris, France, 4 Assistance Publique-Hôpitaux de Paris, Hôpital Hôtel-Dieu, Centre d'Epidémiologie Clinique, Paris, France, 5 Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York, United States of America

Abstract

Background: Indirect comparisons of competing treatments by network meta-analysis (NMA) are increasingly in use. Reporting bias has received little attention in this context. We aimed to assess the impact of such bias in NMAs.

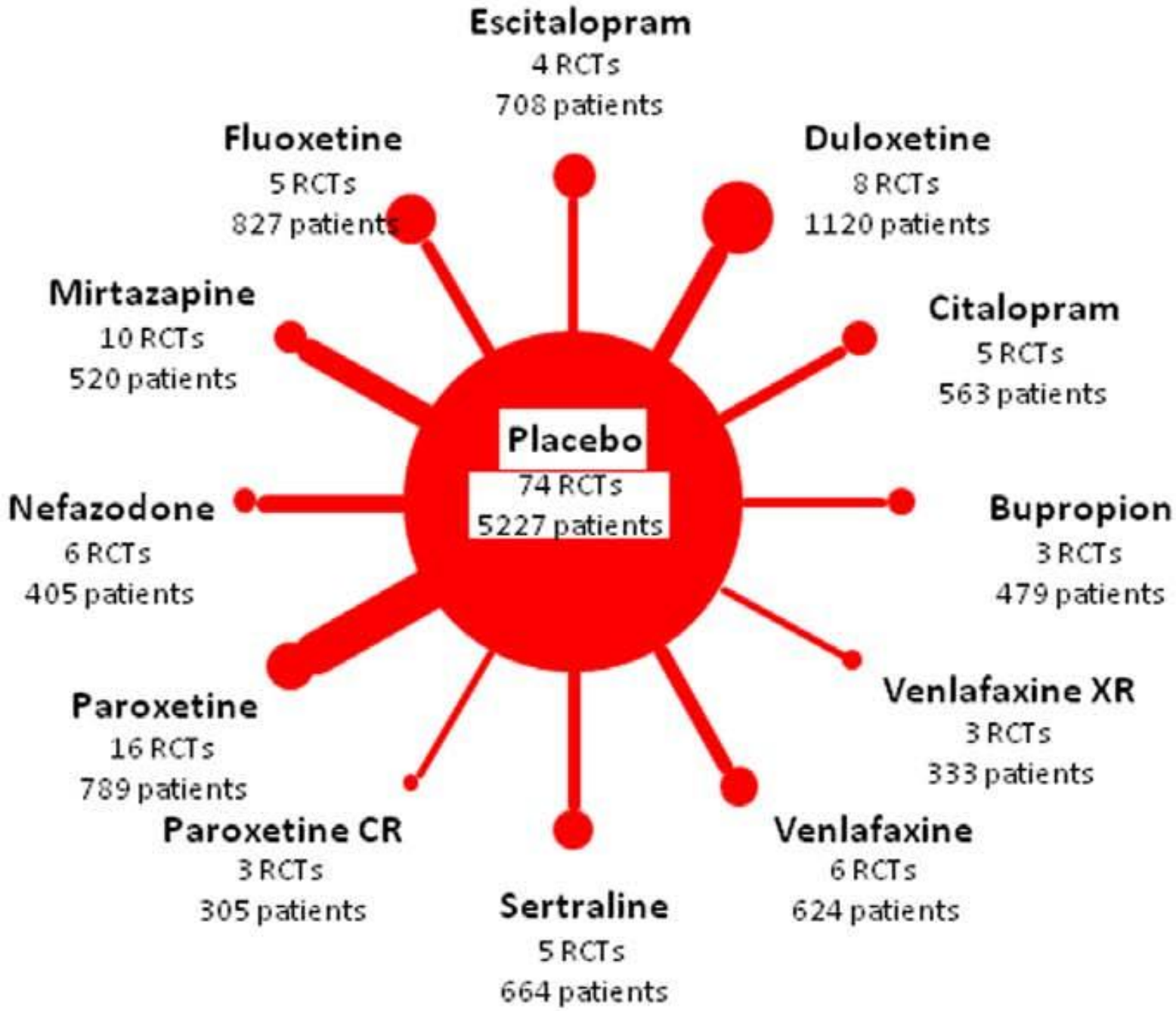
Methods: We used data from 74 FDA-registered placebo-controlled trials of 12 antidepressants and their 51 matching publications. For each dataset, NMA was used to estimate the effect sizes for 66 possible pair-wise comparisons of these drugs, the probabilities of being the best drug and ranking the drugs. To assess the impact of reporting bias, we compared the NMA results for the 51 published trials and those for the 74 FDA-registered trials. To assess how reporting bias affecting only one drug may affect the ranking of all drugs, we performed 12 different NMAs for hypothetical analysis. For each of these NMAs, we used published data for one drug and FDA data for the 11 other drugs.

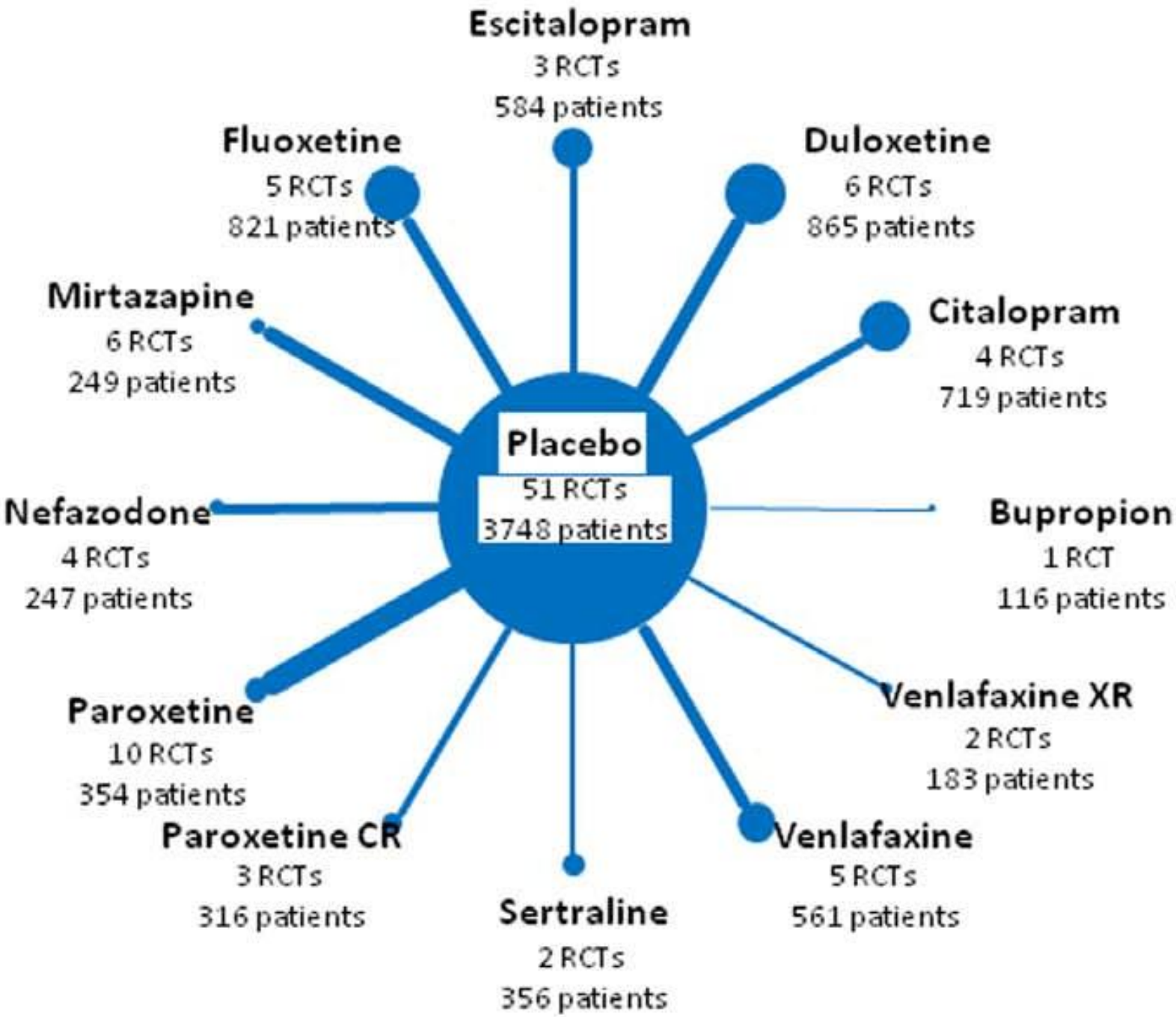
Findings: Pair-wise effect sizes for drugs derived from the NMA of published data and those from the NMA of FDA data differed in absolute value by at least 100% in 30 of 66 pair-wise comparisons (45%). Depending on the dataset used, the top 3 agents differed, in composition and order. When reporting bias hypothetically affected only one drug, the affected drug ranked first in 5 of the 12 NMAs but second (n = 2), fourth (n = 1) or eighth (n = 2) in the NMA of the complete FDA network.

Conclusions: In this particular network, reporting bias biased NMA-based estimates of treatments efficacy and modified ranking. The reporting bias effect in NMAs may differ from that in classical meta-analyses in that reporting bias affecting only one drug may affect the ranking of all drugs.

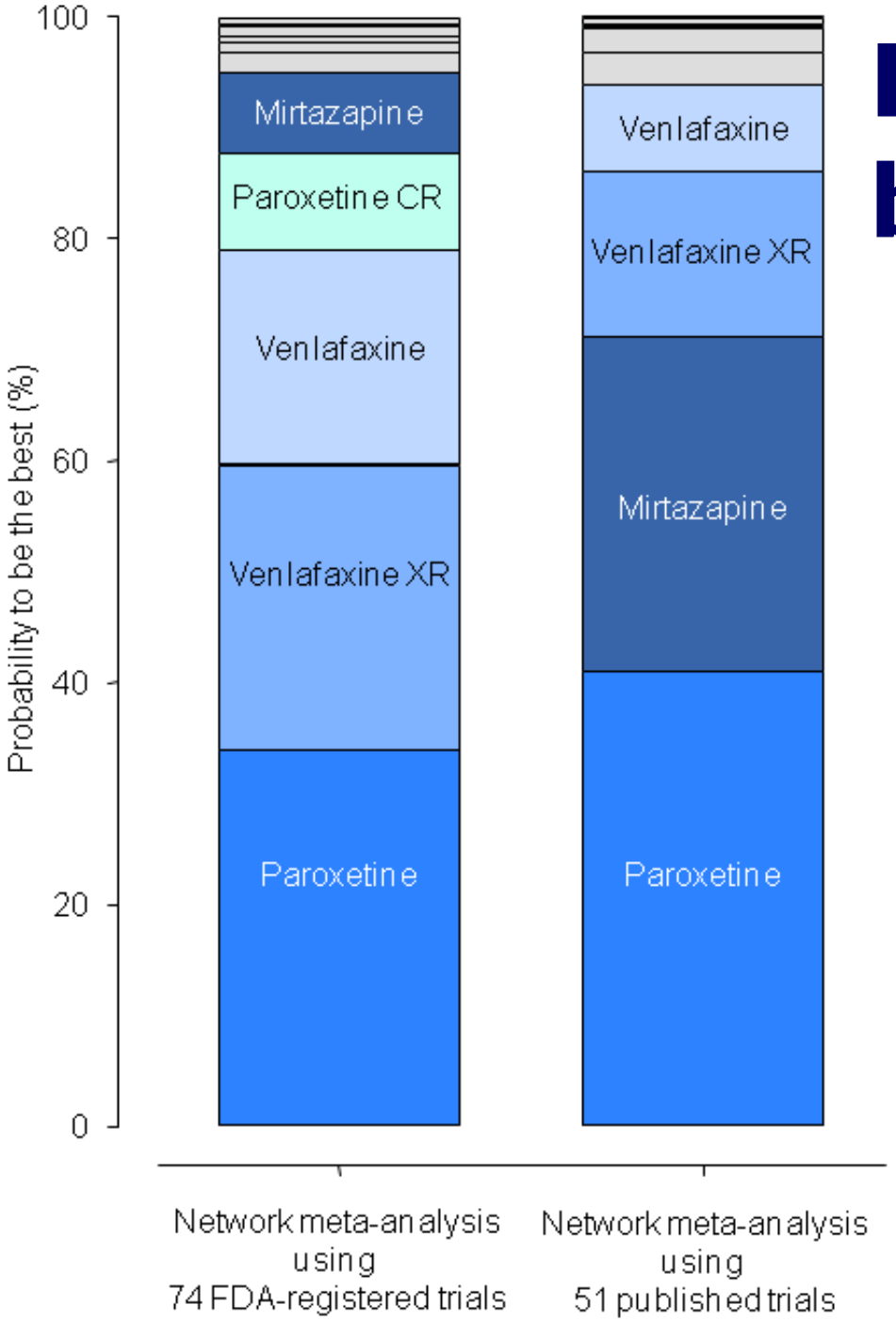
Citation: Trinquart L, Abbé A, Ravaud P (2012) Impact of Reporting Bias in Network Meta-Analysis of Antidepressant Placebo-Controlled Trials. PLoS ONE 7(4): e35219. doi:10.1371/journal.pone.0035219

Trinquart et al, PLoS ONE 2012

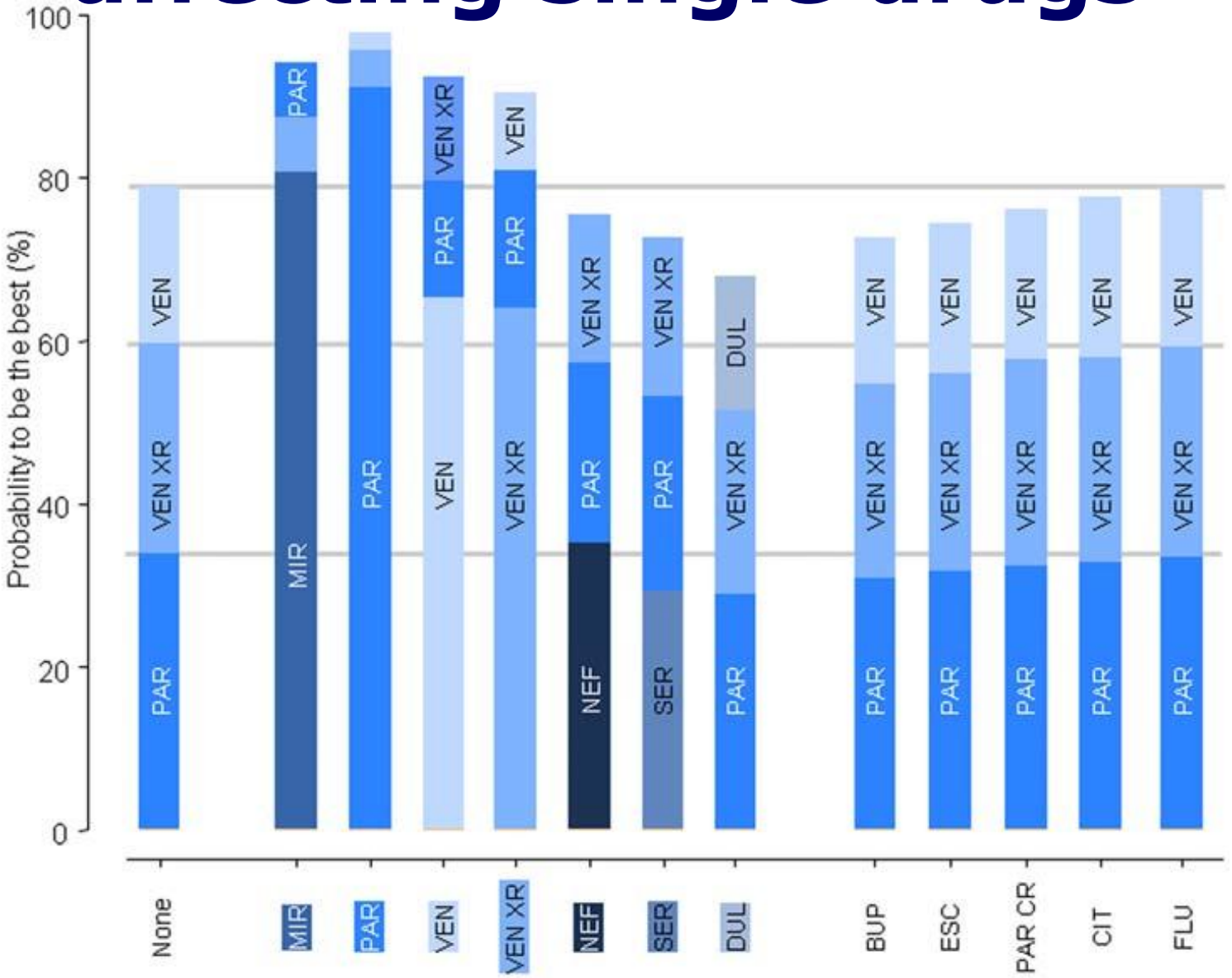

Escitalopram
4 RCTs
708 patients
Fluoxetine
5 RCTs
827 patients
Duloxetine
8 RCTs
1120 patients
Mirtazapine
10 RCTs
520 patients
Citalopram
5 RCTs
563 patients
Placebo
74 RCTs
5227 patients
Nefazodone
6 RCTs
405 patients
Bupropion
3 RCTs
479 patients
Paroxetine
16 RCTs
789 patients
Venlafaxine XR
3 RCTs
333 patients
Paroxetine CR
3 RCTs
305 patients
Venlafaxine
6 RCTs
624 patients
Sertraline
5 RCTs
664 patients


Escitalopram
3 RCTs
584 patients
Fluoxetine
5 RCTs
821 patients
Duloxetine
6 RCTs
865 patients
Mirtazapine
6 RCTs
249 patients
Citalopram
4 RCTs
719 patients
Placebo
51 RCTs
3748 patients
Nefazodone
4 RCTs
247 patients
Bupropion
1 RCT
116 patients
Paroxetine
10 RCTs
354 patients
Venlafaxine XR
2 RCTs
183 patients
Paroxetine CR
3 RCTs
316 patients
Venlafaxine
5 RCTs
561 patients
Sertraline
2 RCTs
356 patients

Probability to be best



Effect of reporting biases affecting single drugs



Conclusions

- Potential of clinically useful syntheses of evidence
- Same pitfalls as in traditional meta-analyses … and a few more
- Quality of reporting even more crucial than in traditional meta-analysis
- Beware of star-shaped NWMAs!