META-ANALISI

Maria Cecilia Giron
Dipartimento di Scienze del Farmaco
Edificio di Farmacologia
Email: cecilia.giron@unipd.it
Tel. 049-8275091

META-ANALISI

Centre for Evidence-Based Medicine
Oxford-Centre for Evidence Based Medicine

LEVELS OF EVIDENCE:

1A Systematic Review/Meta-analysis of RCTs;

1B Individual RCT;

2A Systematic Review of Cohort Studies;

2B Individual Cohort Study, Low-quality RCT;

2C Ecological Studies;

3A Systematic Review of Case-control Studies;

3B Individual Case-control Study;

4 Case Series, Poor-quality Studies.

http://www.cebm.net/levels_of_evidence.asp

REVISIONI SISTEMATICHE e META-ANALISI

- A **Systematic Review** is a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.

- **Statistical methods** (*meta-analysis*) **may or may not be used** to analyze and summarize the results of the included studies.

Revisioni Sistematiche vs Revisioni Narrative

Feature	Narrative Review	Systematic Review
Question	Often broad in scope	Often a focused clinical question
Sources and search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Often a qualitative summary	Quantitative summary*
Inferences	Sometimes evidence-based	Usually evidence-based

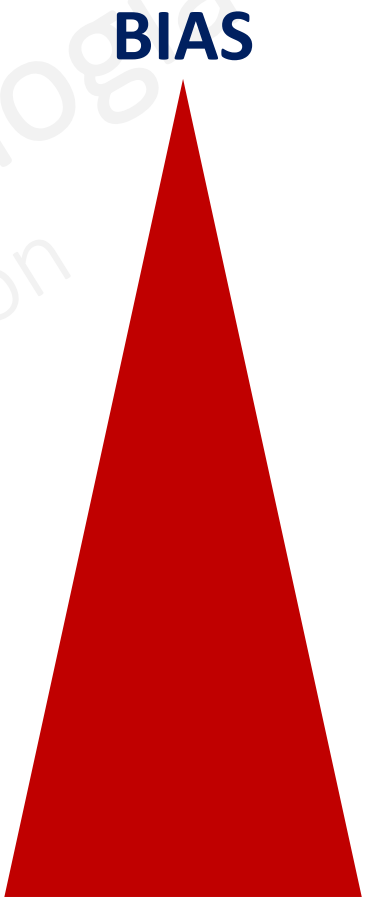
* A quantitative summary that includes a statistical synthesis is a meta-analysis.

Cook, D. J. et. al. Ann Intern Med 1997;126:376-380

BIAS

Tutti, anche se in misura diversa, sono soggetti a bias

- Systematic Reviews of Randomized Controlled Trials
- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations
- Expert Opinion



https://catalogofbias.org/

Le sperimentazioni cliniche controllate

(Randomized Double Blind Controlled Trials)

Gold standard degli studi di efficacia di una terapia

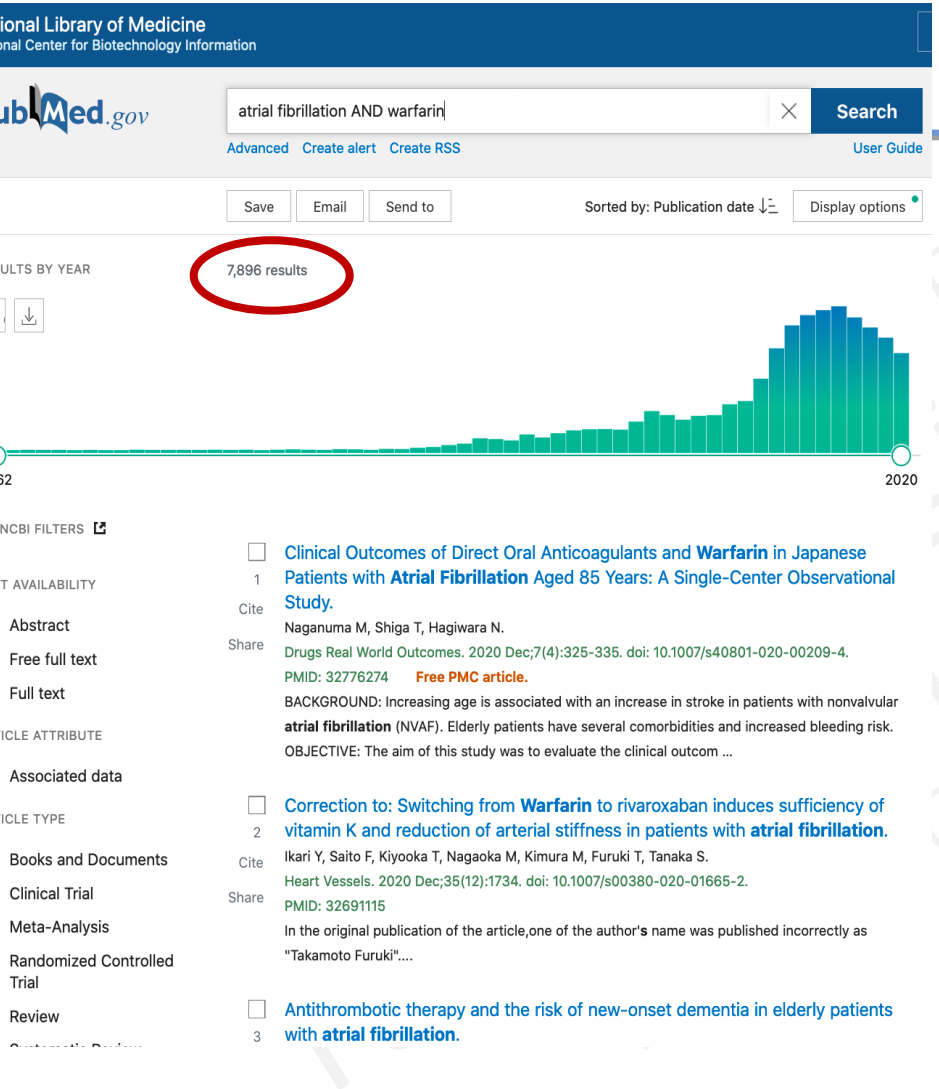
- Randomizzazione
- Doppio cieco
- Consenso informato
- Intention to Treat
- Descrizione della casistica e dei criteri di inclusione/esclusione
- Accuratezza ed affidabilità della valutazione diagnostica
- Descrizione dettagliata della procedura e dei risultati
- …

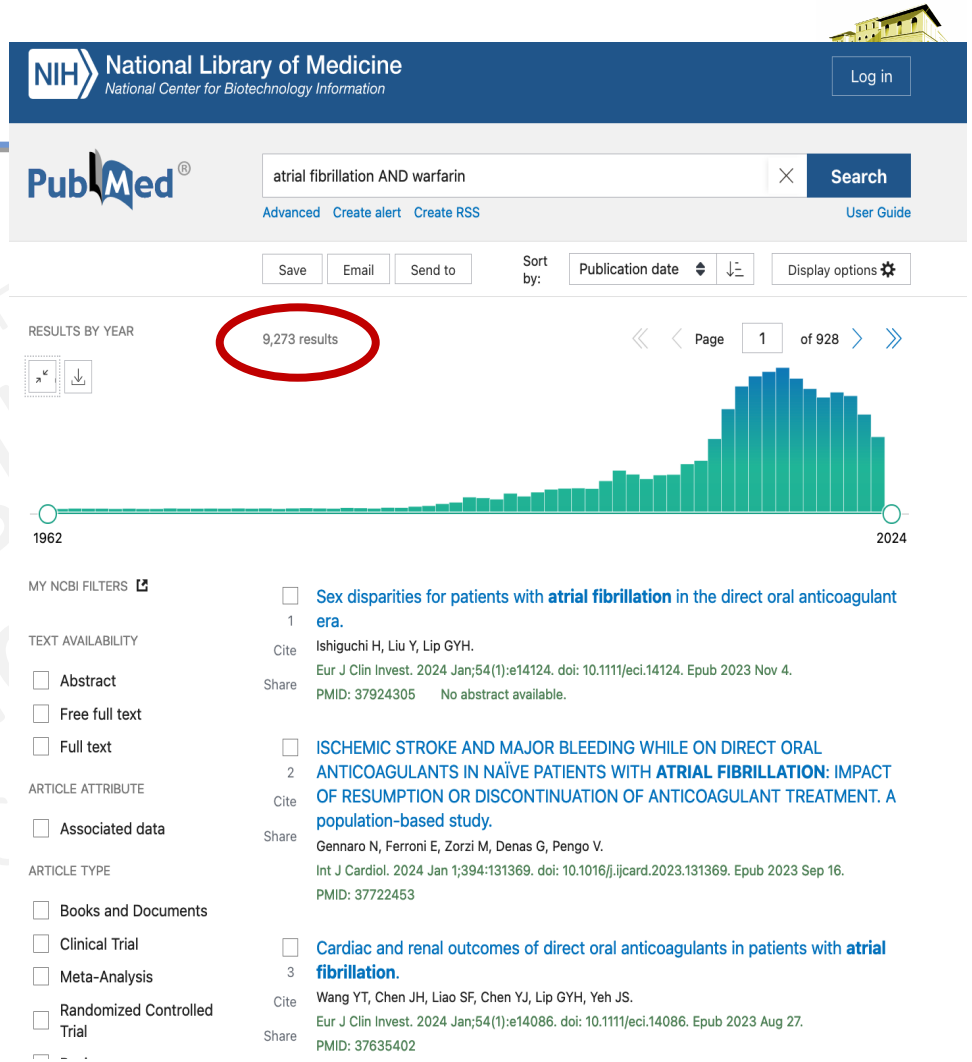
Le sperimentazioni cliniche controllate

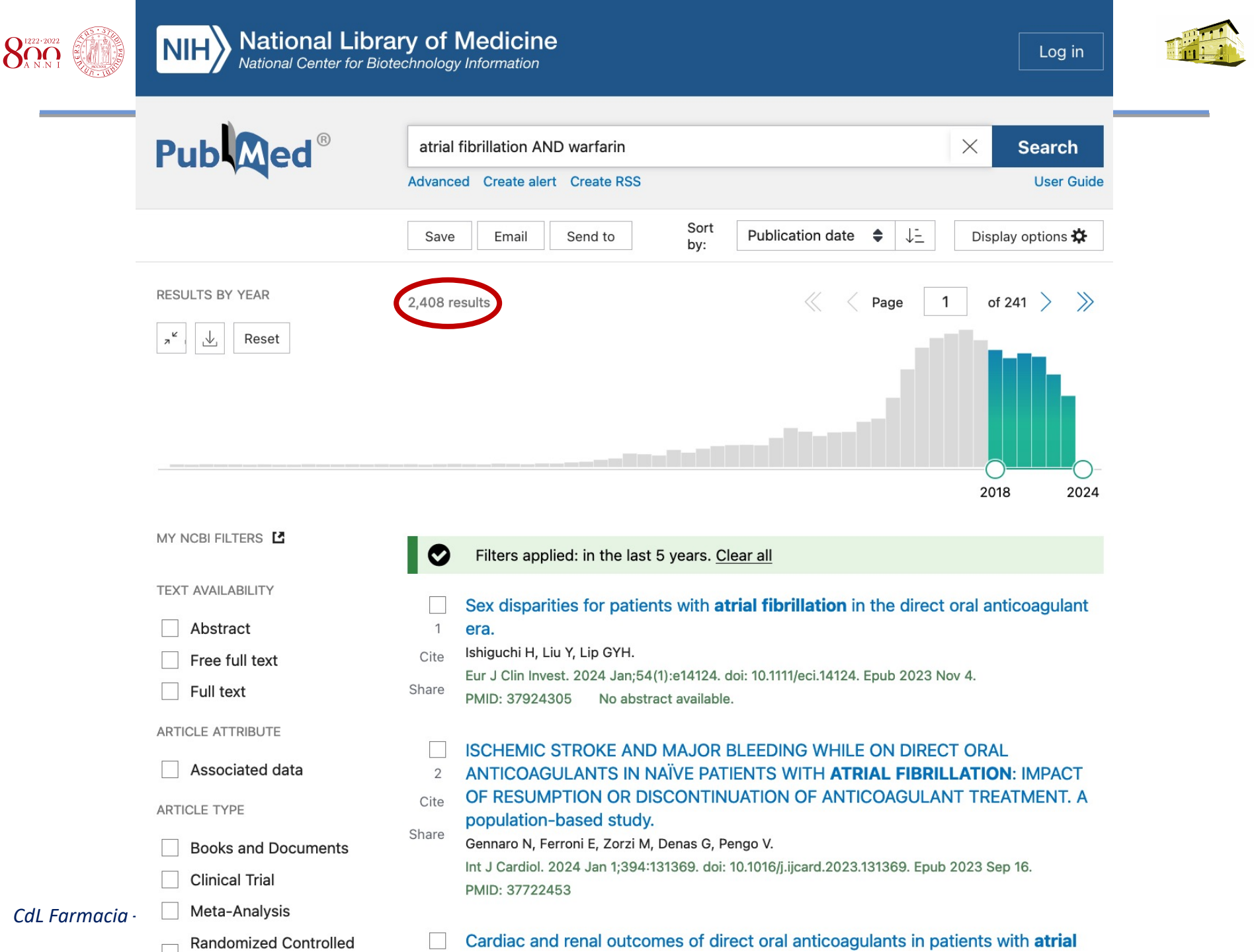
(Randomized Double Blind Controlled Trials)

CRITICITÀ

- Molteplici studi con risultati contrastanti
- Studi di qualità non omogenea (falsi positivi e falsi negativi)
- Studi di dimensioni insufficienti (falsi negativi)
- Pubblication bias


ional Library of Medicine
onal Center for Biotechnology Information
ubMed.gov
atrial fibrillation AND warfarin
Search
Advanced Create alert Create RSS
User Guide
Save Email Send to
Sorted by: Publication date
Display options
ULTS BY YEAR
7,896 results
62
2020
NCBI FILTERS
T AVAILABILITY
Abstract
Free full text
Full text
ICLE ATTRIBUTE
Associated data
ICLE TYPE
Books and Documents
Clinical Trial
Meta-Analysis
Randomized Controlled Trial
Review
1 Cite Share
Clinical Outcomes of Direct Oral Anticoagulants and Warfarin in Japanese Patients with Atrial Fibrillation Aged 85 Years: A Single-Center Observational Study.
Naganuma M, Shiga T, Hagiwara N.
Drugs Real World Outcomes. 2020 Dec;7(4):325-335. doi: 10.1007/s40801-020-00209-4.
PMID: 32776274 Free PMC article.
BACKGROUND: Increasing age is associated with an increase in stroke in patients with nonvalvular atrial fibrillation (NVAF). Elderly patients have several comorbidities and increased bleeding risk. OBJECTIVE: The aim of this study was to evaluate the clinical outcom ...
2 Cite Share
Correction to: Switching from Warfarin to rivaroxaban induces sufficiency of vitamin K and reduction of arterial stiffness in patients with atrial fibrillation.
Ikari Y, Saito F, Kiyooka T, Nagaoka M, Kimura M, Furuki T, Tanaka S.
Heart Vessels. 2020 Dec;35(12):1734. doi: 10.1007/s00380-020-01665-2.
PMID: 32691115
In the original publication of the article,one of the author's name was published incorrectly as "Takamoto Furuki"....
3
Antithrombotic therapy and the risk of new-onset dementia in elderly patients with atrial fibrillation.


NIH National Library of Medicine
National Center for Biotechnology Information
Log in
PubMed®
atrial fibrillation AND warfarin
Search
Advanced Create alert Create RSS
User Guide
Save Email Send to
Sort by: Publication date
Display options
RESULTS BY YEAR
9,273 results
Page 1 of 928
1962
2024
MY NCBI FILTERS
TEXT AVAILABILITY
Abstract
Free full text
Full text
ARTICLE ATTRIBUTE
Associated data
ARTICLE TYPE
Books and Documents
Clinical Trial
Meta-Analysis
Randomized Controlled Trial
1 Cite Share
Sex disparities for patients with atrial fibrillation in the direct oral anticoagulant era.
Ishiguchi H, Liu Y, Lip GYH.
Eur J Clin Invest. 2024 Jan;54(1):e14124. doi: 10.1111/eci.14124. Epub 2023 Nov 4.
PMID: 37924305 No abstract available.
2 Cite Share
ISCHEMIC STROKE AND MAJOR BLEEDING WHILE ON DIRECT ORAL ANTICOAGULANTS IN NAÏVE PATIENTS WITH ATRIAL FIBRILLATION: IMPACT OF RESUMPTION OR DISCONTINUATION OF ANTICOAGULANT TREATMENT. A population-based study.
Gennaro N, Ferroni E, Zorzi M, Denas G, Pengo V.
Int J Cardiol. 2024 Jan 1;394:131369. doi: 10.1016/j.ijcard.2023.131369. Epub 2023 Sep 16.
PMID: 37722453
3 Cite Share
Cardiac and renal outcomes of direct oral anticoagulants in patients with atrial fibrillation.
Wang YT, Chen JH, Liao SF, Chen YJ, Lip GYH, Yeh JS.
Eur J Clin Invest. 2024 Jan;54(1):e14086. doi: 10.1111/eci.14086. Epub 2023 Aug 27.
PMID: 37635402


NIH National Library of Medicine
National Center for Biotechnology Information
Log in
PubMed®
atrial fibrillation AND warfarin
Search
Advanced Create alert Create RSS
User Guide
Save Email Send to
Sort by: Publication date
Display options
RESULTS BY YEAR
2,408 results
Page 1 of 241
Reset
2018
2024
MY NCBI FILTERS
TEXT AVAILABILITY
Abstract
Free full text
Full text
ARTICLE ATTRIBUTE
Associated data
ARTICLE TYPE
Books and Documents
Clinical Trial
Meta-Analysis
Randomized Controlled
Filters applied: in the last 5 years. Clear all
1
Cite
Share
Sex disparities for patients with atrial fibrillation in the direct oral anticoagulant era.
Ishiguchi H, Liu Y, Lip GYH.
Eur J Clin Invest. 2024 Jan;54(1):e14124. doi: 10.1111/eci.14124. Epub 2023 Nov 4.
PMID: 37924305 No abstract available.
2
Cite
Share
ISCHEMIC STROKE AND MAJOR BLEEDING WHILE ON DIRECT ORAL ANTICOAGULANTS IN NAÏVE PATIENTS WITH ATRIAL FIBRILLATION: IMPACT OF RESUMPTION OR DISCONTINUATION OF ANTICOAGULANT TREATMENT. A population-based study.
Gennaro N, Ferroni E, Zorzi M, Denas G, Pengo V.
Int J Cardiol. 2024 Jan 1;394:131369. doi: 10.1016/j.ijcard.2023.131369. Epub 2023 Sep 16.
PMID: 37722453
Cardiac and renal outcomes of direct oral anticoagulants in patients with atrial

"È causa di grande preoccupazione constatare come la professione medica non abbia saputo organizzare un sistema in grado di rendere disponibile, e costantemente aggiornate, revisioni critiche sugli effetti dell'assistenza sanitaria"

Cochrane A.
Effectiveness and efficacy. Random reflections on health service.
London: Nuffield Provincial Hospital Trust, 1972

META-ANALISI

- **Analisi combinata di informazioni quantitative** ottenute in due o più studi indipendenti e selezionati – sulla base di definiti criteri – dall'insieme, possibilmente completo, di studi volti ad indagare uno stesso fenomeno di interesse.

- I risultati di una meta-analisi rafforzano la conoscenza al di là del contributo della molteplicità dei singoli studi, accumulando evidenze circa gli effetti di un trattamento o una procedura.

META-ANALISI

- **E' un'alternativa statistica e quindi quantitativa alla tradizionale rassegna di letteratura.**

- La meta-analisi è nota soprattutto come tecnica di sintesi degli studi clinici controllati, ma è stata sviluppata anche per la sintesi di studi osservazionali in epidemiologia.

META-ANALISI

- **CONSORT Statement (1996)** presenta le linee guida per riportare i risultati e valutare la qualità degli **studi clinici controllati** (e di conseguenza programmarli) http://www.consort-statement.org/
- **QUORUM Statement** (1999, Quality of reporting meta-analysis) queste comprende una checklist per programmare e riportare una **meta-analisi** e un modello di diagramma di flusso per descrivere l'inclusione degli studi nella meta-analisi.
- **PRISMA Statement (2009)** help authors improve the reporting of systematic reviews and meta-analyses

  http://www.prisma-statement.org/index.htm

PRISMA

TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES

History

Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field [1,2], and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research [3], and some health care journals are moving in this direction [4]. As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.

Several early studies evaluated the quality of review reports. In 1987, Mulrow examined 50 review articles published in four leading medical journals in 1985 and 1986 and found that none met all eight explicit scientific criteria, such as a quality assessment of included studies [5]. In 1987, Sacks and colleagues [6] evaluated the adequacy of reporting of 83 meta-analyses on 23 characteristics in six domains. Reporting was generally poor; between one and 14 characteristics were adequately reported (mean = 7.7; standard deviation = 2.7). A 1996 update of this study found little improvement [7].

In 1996, to address the suboptimal reporting of meta-analyses, an international group developed a guidance called the QUOROM Statement (*QU*ality *O*f *R*eporting *O*f *M*eta-analyses), which focused on the reporting of meta-analyses of randomized controlled trials [8].

In 2009, the guideline was updated to address several conceptual and practical advances in the science of systematic reviews, and was renamed PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses).

Learn more:

- Evolving from QUOROM to PRISMA – conceptual issues
- Developing the PRISMA Statement
- Developing the PRISMA Explanatory Document

Cd

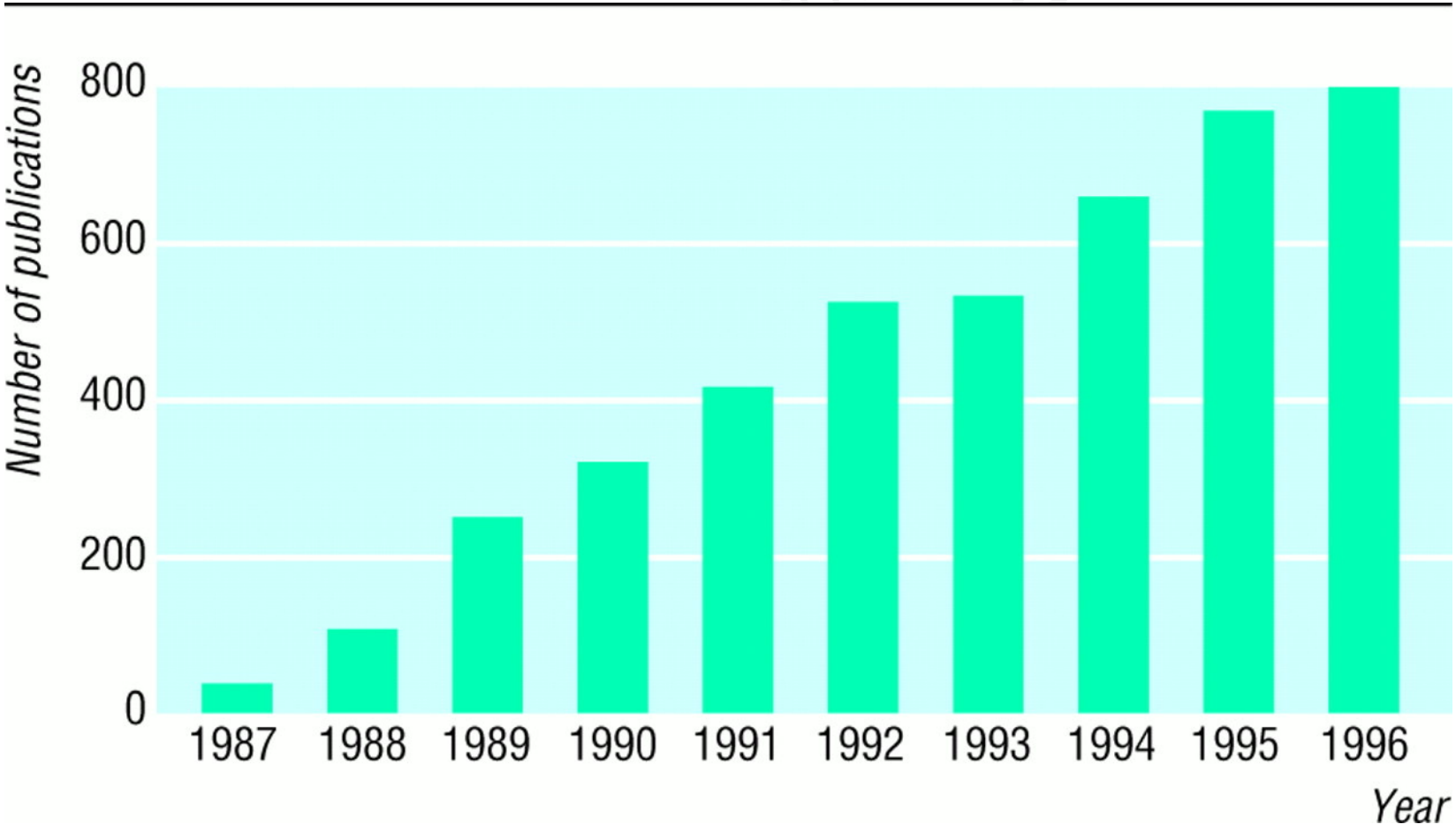
META-ANALISI

- È una tecnica clinico-statistica, che consente di assemblare i risultati di più trial di uno stesso trattamento in un unico risultato cumulativo.

- **Cochrane Collaboration**. È questo un mega-network internazionale non-profit costituito da numerosi gruppi collaborativi che producono e diffondono meta-analisi di trattamenti relativi a specifici problemi sanitari.

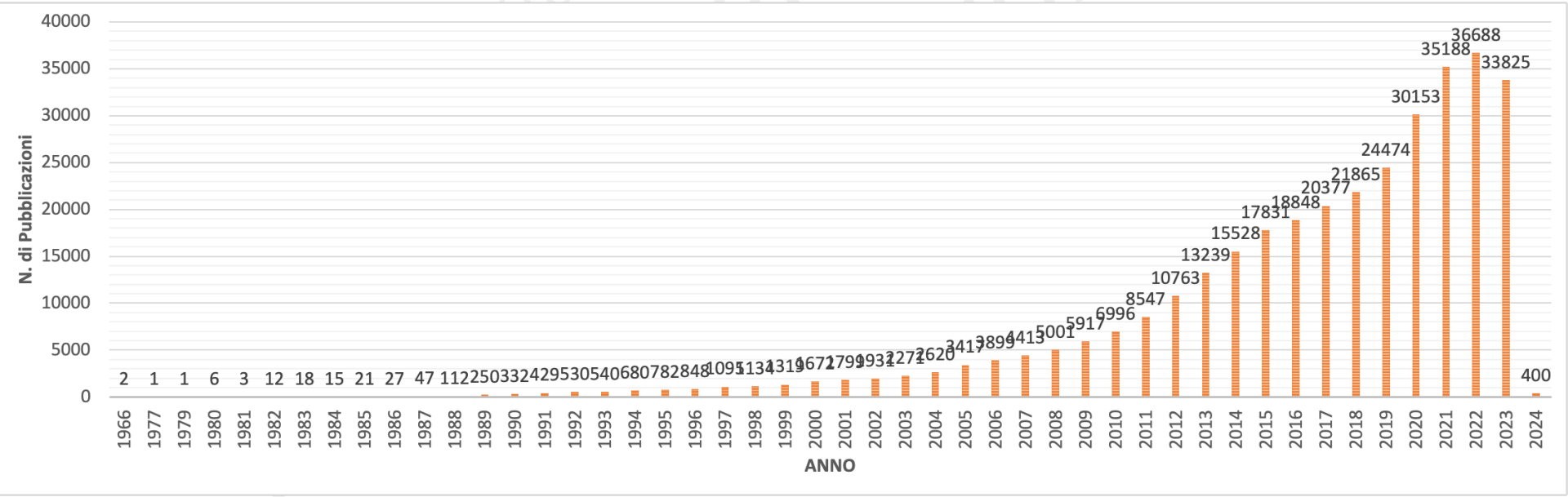
- Le meta-analisi della Cochrane Collaboration sono raccolte nella Cochrane Library. Sono elaborate con criteri metodologici rigorosi (peer review).

Number of publications about meta-analysis, 1987–96 (results from Medline search using text word and medical subject heading "meta-analysis").



Egger M , and Smith G D BMJ 1997;315:1371-1374

META-ANALISI



META-ANALISI

The Cochrane Collaboration

Trusted evidence. Informed decisions. Better health.

Cochrane is for anyone interested in using high-quality information to make health decisions.

https://www.cochrane.it/it/la-nostra-storia

META-ANALISI

Tabella 1. Numero di RCTs di alcuni trattamenti

Trattamento	Applicazione	N. di RCTs (voce bibl.)
Interferone alfa	Epatite cronica C	66 (3)
Trombolisi con streptochinasi	Infarto miocardico acuto	33 (4)
Profilassi antibiotica	Chirurgia colorettale	21 (4)
Scleroterapia endoscopica	Varici esofagee nella cirrosi per la prevenzione della prima emorragia	19 (5)
Ac. Aminosalicilico	Colite ulcerosa, per indurre una remissione	19 (6)

BIF Mar-Apr 2000 - N. 2

META-ANALISI

Gli autori scrivono... “Il confronto dei calcio-antagonisti con altri farmaci nel trattamento dell’ipertensione arteriosa ha **identificato 2406 articoli…”**

THE LANCET

Volume 356, Issue 9246, 9 December 2000, Pages 1949–1954

Articles

Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials

Prof Marco Pahor, MD[a], Prof Bruce M Psaty, MD[c], Prof Michael H Alderman, MD[d], Prof William B Applegate, MD[a], Jeff D Williamson, MD[a], Chiara Cavazzini, MD[a], Prof Curt D Furberg, MD[b]

[a] Sticht Center on Aging, Department of Internal Medicine

[b] Department of Public Health Sciences

[c] Wake Forest University, Winston Salem, NC; Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA

[d] Albert Einstein College of Medicine, Department of Epidemiology and Social Medicine, Bronx, NY, USA (Prof M H Alderman

C

Tabella 2. Gradi di raccomandazione (A-C) e livelli di evidenza (1-5)

	Tipi di studi da cui si è ottenuta l'evidenza
Grado A	
Livello 1a	• Megatrial (*large RCTs*); o meta-analisi di più RCTs che abbiano un numero cumulativo di dati almeno pari a quelli di un megatrial.
Livello 1b	• Almeno uno studio di coorte di qualità elevata, nel quale ebbero un esito sfavorevole *tutti* i pazienti trattati con terapia convenzionale mentre ebbero esito favorevole una parte dei pazienti trattati con la nuova terapia; oppure nel quale ebbero un esito sfavorevole *molti* dei pazienti trattati con terapia convenzionale, e nessuno di quelli trattati con la nuova terapia.
Livello 1c	• Almeno un RCT con numero di pazienti medio, o una meta-analisi di piccoli RCTs con un numero cumulativo di pazienti non elevato.
Livello 1d	• Almeno un RCT (non specificate le caratteristiche).
Grado B	
Livello 2	• Almeno uno studio di qualità elevata, non randomizzato, di coorti che ricevevano e (rispettivamente) non ricevevano la nuova terapia.
Livello 3	• Almeno uno studio caso-controllo di qualità elevata.
Livello 4	• Almeno una serie di casi di qualità elevata.
Grado C	
Livello 5	• Opinioni di esperti, senza riferimento a una delle evidenze precedenti (cioè su base fisio-patologica, ricerca non clinica [*bench research*] o principi generali).

META-ANALISI: origine

R. A. Fisher (1944)

- When a number of quite independent tests of significance have been made, it sometimes happens that although few or none can be claimed individually as significant, yet the aggregate gives an impression that the probabilities are on the whole lower than would often have been obtained by chance".
- Source of the idea of cumulating probability values

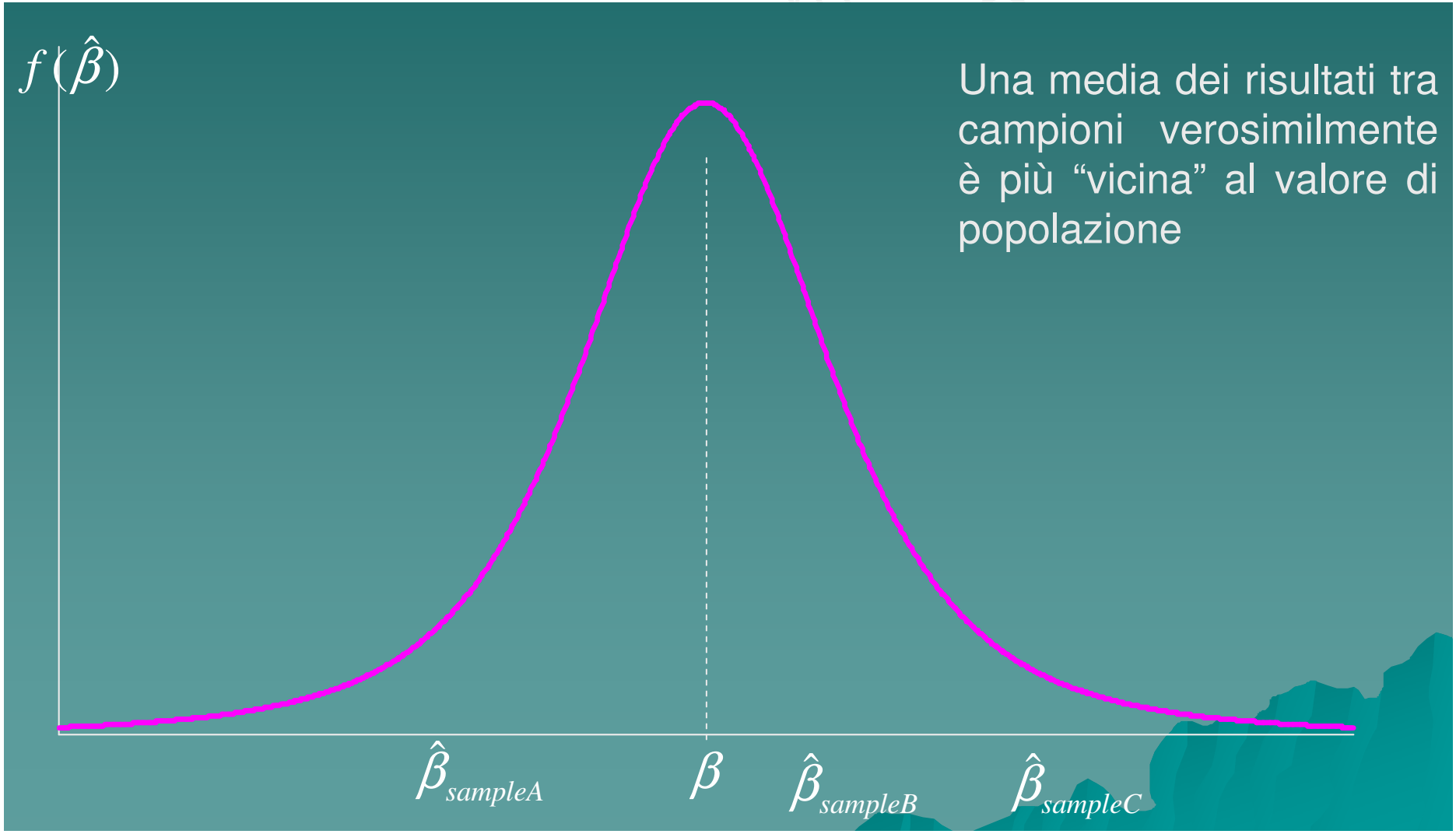
W. G. Cochrane (1953)

- Discusses a method of averaging means across independent studies
- Laid-out much of the statistical foundation that modern meta-analysis is built upon (e.g., inverse variance weighting and homogeneity testing)

META-ANALISI: obiettivi

- Aumentare la potenza statistica
- Risolvere controversie quando gli studi mostrano risultati contrastanti
- Migliorare le stime
- Rispondere a quesiti non considerati nei singoli studi

META-ANALISI: obiettivi



Una media dei risultati tra campioni verosimilmente è più "vicina" al valore di popolazione

META-ANALISI: fasi

- Metodi di ricerca degli studi effettuati sul fenomeno di interesse (Medline, Index medicus, Data base specifici)
- Criteri di ammissione degli studi
- Variabili di risposta
- Disegno dello studio
- Risultati usati per la combinazione
- Metodi statistici
- Studio della eventuale eterogeneità

META-ANALISI: fasi

Tabella 3. Sequenza di operazioni di una meta-analisi

1. Definizione di un obiettivo (per esempio: nella trombosi venosa profonda, è efficace il trattamento con eparina a basso peso molecolare, o sarà necessario un trattamento con eparina non frazionata in infusione continua [8]?).

2. Definizione di criteri di inclusione ed esclusione dei trial (per esempio, si possono escludere trial che non valutano un end point che rientra nell'obiettivo della meta-analisi).

3. Ricerca dei trial di interesse, il più possibile esaustiva.

4. Analisi critica dei trial che, in base ai criteri in precedenza definiti, sono stati inclusi nella meta-analisi (caratteristiche dei pazienti, modalità di somministrazione del trattamento, end point, follow up, qualità metodologica). Di particolare interesse è la ricerca di una eventuale eterogeneità qualitativa inter-trial, cioè con trial che dimostrano un vantaggio terapeutico del trattamento sperimentale e altri che dimostrano un vantaggio terapeutico del trattamento di controllo.

5. Se i trial sono simili per caratteristiche cliniche e senza eterogeneità significativa, combinazione dei risultati dei trial (*pooling*), spesso presentata anche in forma grafica.

6. Interpretazione, che tiene conto di eventuale eterogeneità inter-trial e del *pooling* (differenza fra i trattamenti, sua significatività statistica, sua entità).

BIF Mar-Apr 2000 - N. 2

META-ANALISI: stime degli effetti

- Risk ratio, rate ratio, relative risk
- Hazard ratio
- Odds ratio
- Standardized mortality ratio(SMR)
- Differenze tra rischi, NNT
- Differenze tra medie (standardizzate)
- Dose-risposta (coeff di regress.)
- Sensibilità, specificità, curve ROC

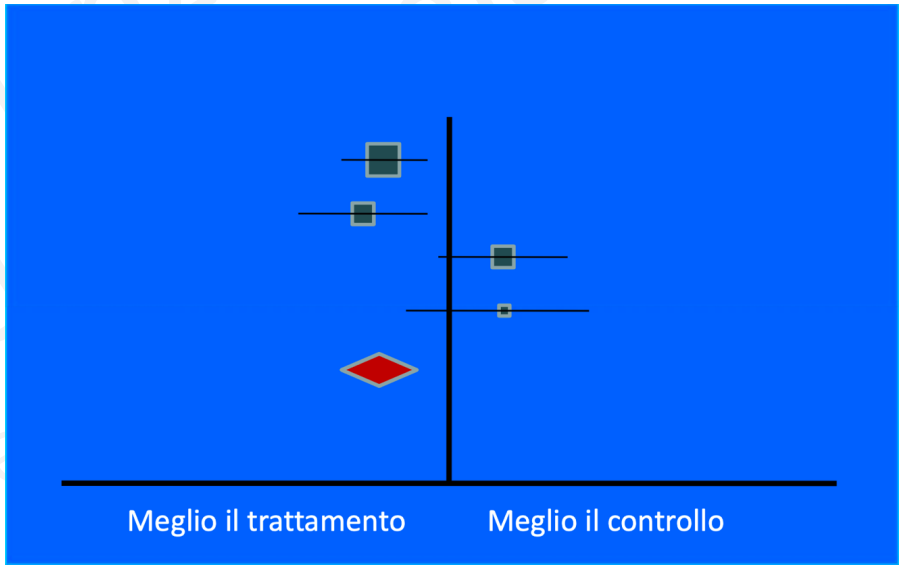
META-ANALISI: dati

- Dati grezzi

- Risultati delle singole analisi (odds ratio, effetti di trattamento)

META-ANALISI: il Forest Plot

- Il **Forest Plot** è una rappresentazione grafica in cui sono riportati, per ogni studio primario incluso nella meta-analisi, i valori relativi **all'effect size e all'intervallo di confidenza**.
- Nel **Forest Plot** viene anche riportato l'effect size medio e il suo relativo intervallo di confidenza.
- **L'intervallo di confidenza rappresenta il range entro cui è probabile che si collochi il vero effect size.**
- **L'intervallo di confidenza** esprime il livello di **precisione** associato alla stima di un parametro: tanto più è piccolo, tanto più indica che la stima è precisa.
- Solitamente vengono calcolati intervalli di confidenza con una probabilità di contenere il vero effect size pari al 95%.



META-ANALISI: dati

Table I. Prophylactic use of lidocaine after a heart attack: evaluating mortality from prophylactic use of lidocaine in acute myocardial infarction. Source: reference 1

Source	Number randomized		Number dead	
	Lidocaine	Control	Lidocaine	Control
1. Chopra *et al.*	39	43	2	1
2. Mogensen	44	44	4	4
3. Pitt *et al.*	107	110	6	4
4. Darby *et al.*	103	100	7	5
5. Bennett *et al*	110	106	7	3
6. O'Brian *et al.*	154	146	11	4
Total	557	549	37	21

S. T. Normand "Meta analysis, formulating, evaluating, combining, and reporting" Statistics in Medicine, 1999, 18, 321-359

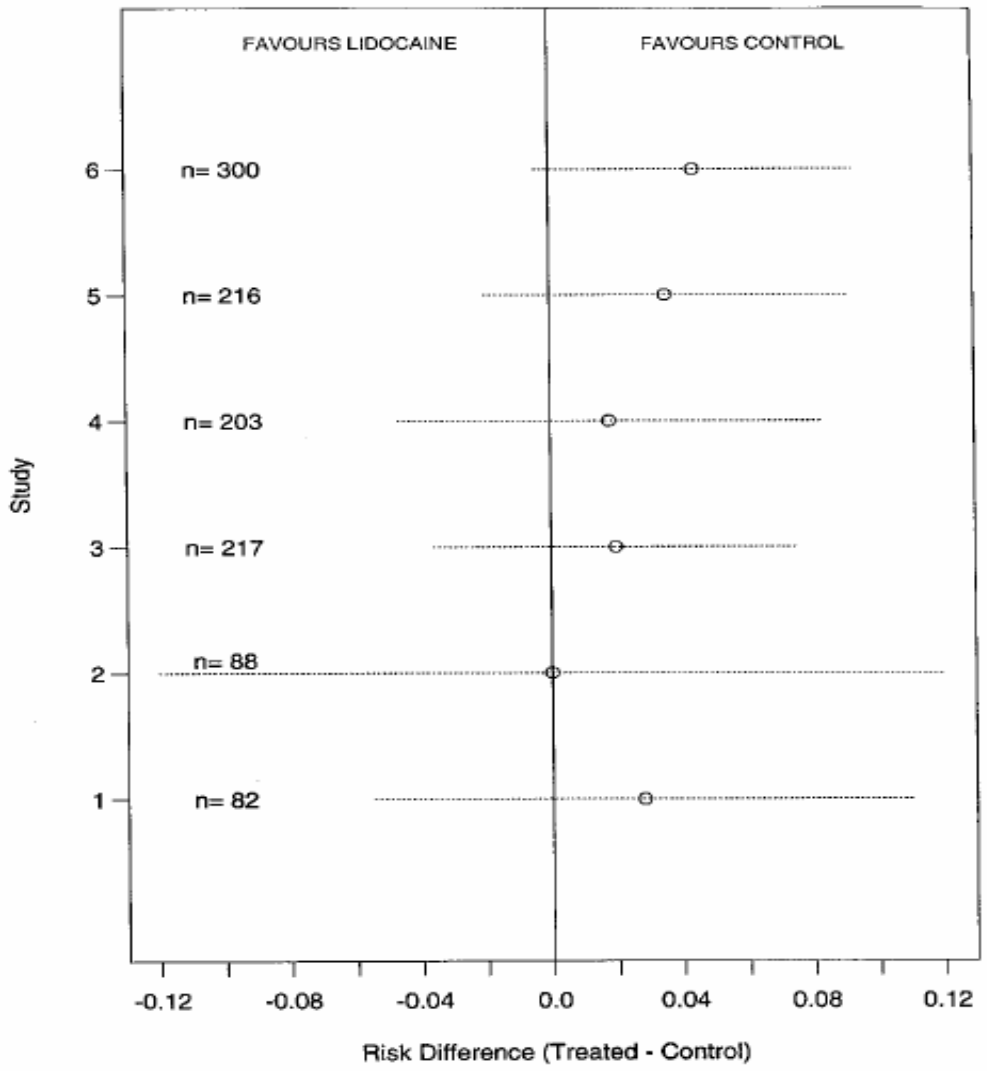
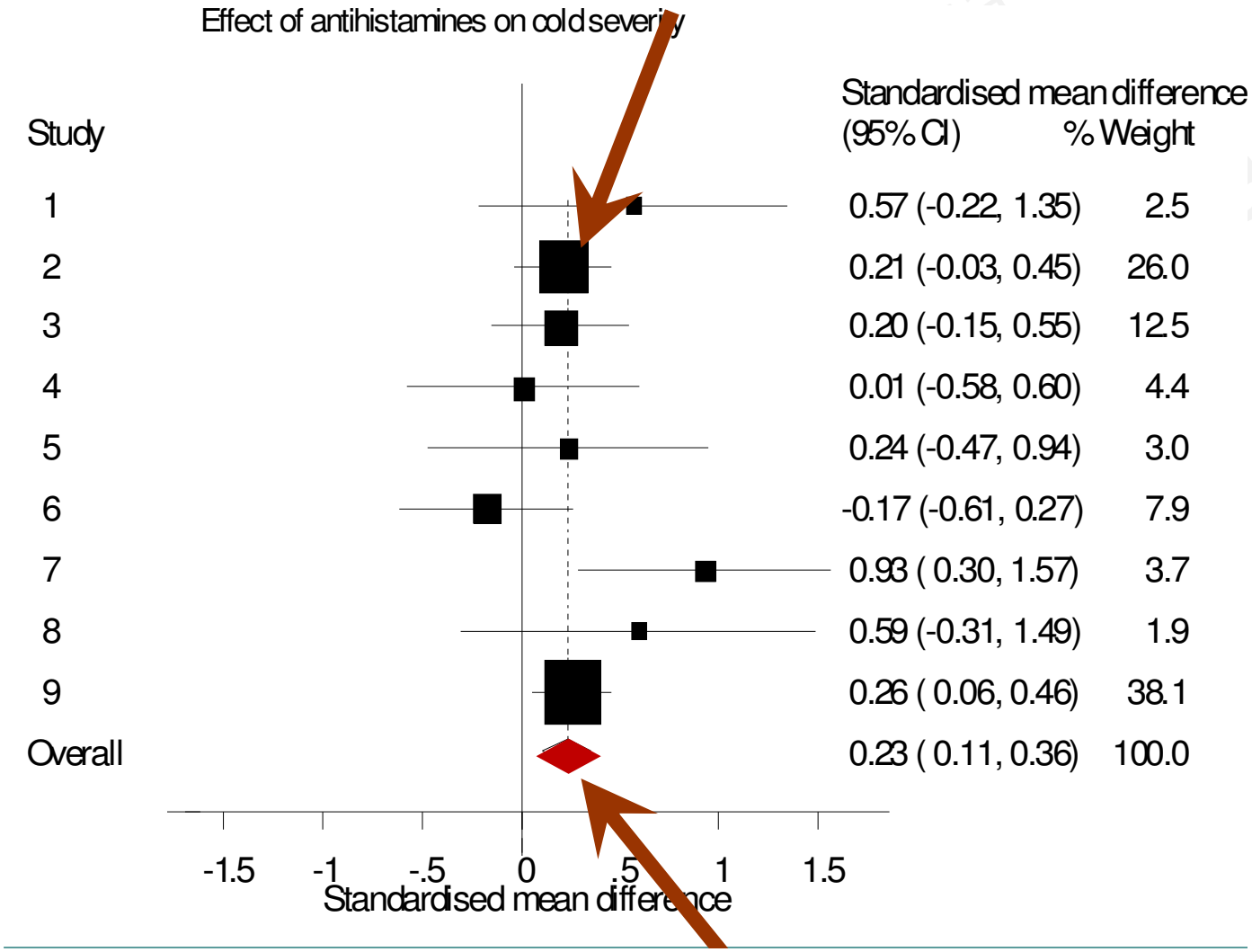


Figure 1. Prophylactic lidocaine after a heart attack. The x-axis displays the risk difference, $d_i = \hat{p}_{Ti} - \hat{p}_{Ci}$, and corresponding 95 per cent confidence intervals $\left(s^2_{d_i} = \frac{\hat{p}_{Ti}\hat{q}_{Ti}}{n_{Ti}} + \frac{\hat{p}_{Ci}\hat{q}_{Ci}}{n_{Ci}} \right)$; the y-axis indicates the study and total sample size

FOREST PLOT

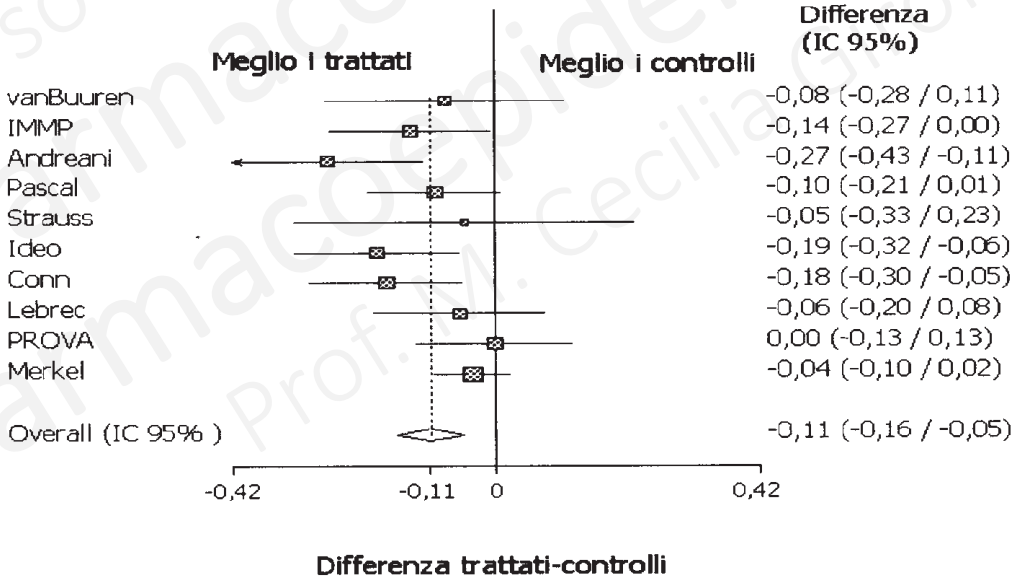
Area proporzionale al peso dello studio



il rombo è la stima della differenza totale col relativo IC

META-ANALISI: grafico

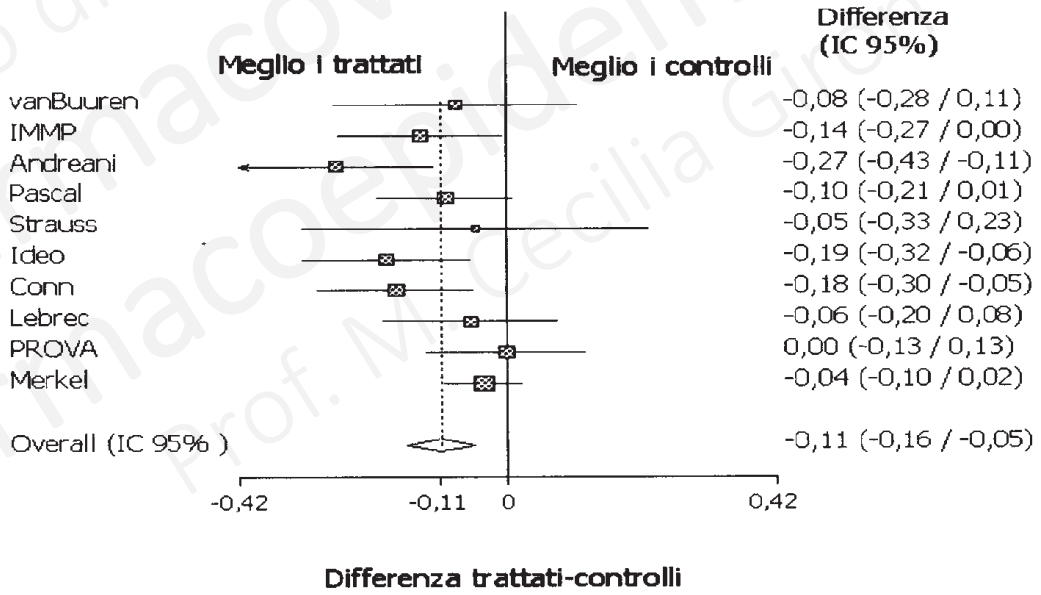
- **La linea orizzontale** rappresenta le differenze fra l'incidenza di eventi nei pazienti che ricevono la terapia sperimentale e quella nei controlli;
- Al centro della linea orizzontale è segnata **la differenza zero**, che indica l'equivalenza fra i due trattamenti.
- I risultati dei singoli trial e della loro combinazione (overall), con i rispettivi intervalli di confidenza, sono ordinati perpendicolarmente alla linea verticale di equivalenza.
- A destra di ognuno dei trial e della loro combinazione sono segnate le corrispondenti differenze e, in parentesi, i loro intervalli di confidenza.



Beta-bloccanti per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incidenza di emorragie nei pazienti trattati con beta-bloccanti e nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; in parentesi i rispettivi intervalli di confidenza.

META-ANALISI: grafico

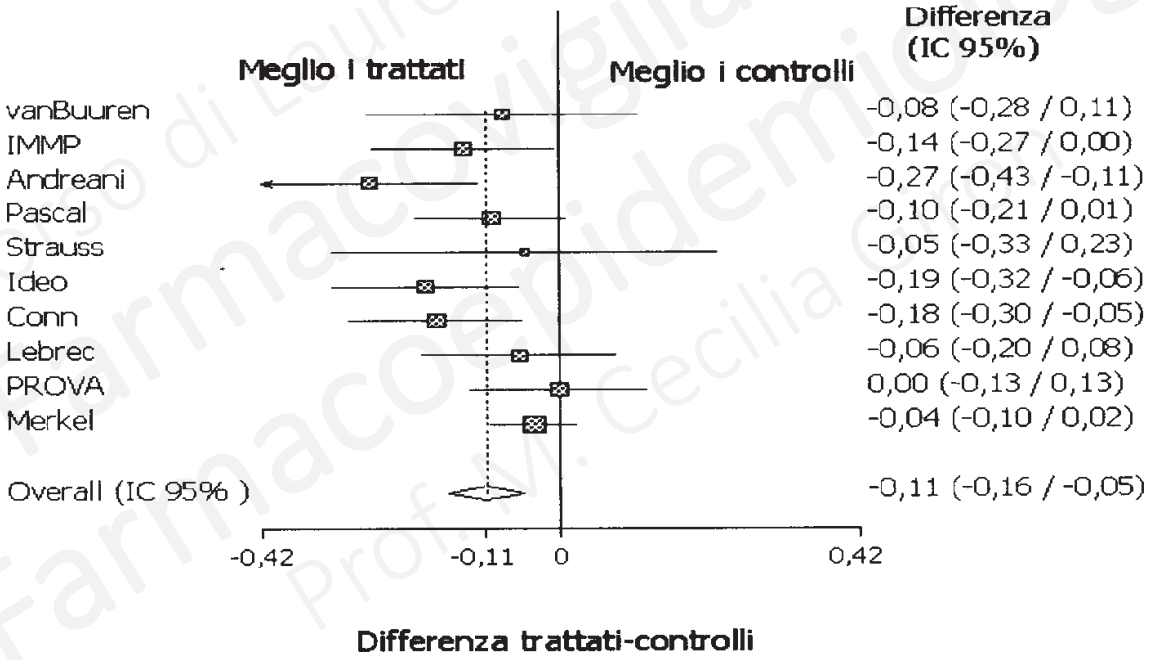
- Le differenze con segno negativo (a sinistra della verticale di equivalenza) indicano una **più alta incidenza di eventi nei controlli**, e pertanto **un vantaggio terapeutico** del trattamento sperimentale
- l'effetto terapeutico **non è statisticamente significativo** se l'intervallo di confidenza attraversa la linea di equivalenza.



Beta-bloccanti per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incidenza di emorragie nei pazienti trattati con beta-bloccanti e nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; in parentesi i rispettivi intervalli di confidenza.

META-ANALISI: grafico

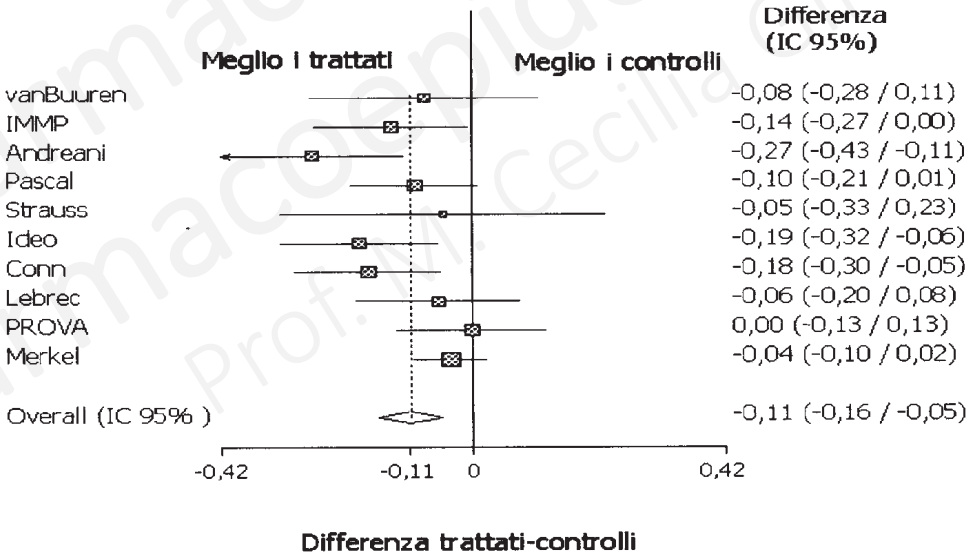
- La precisione e la riproducibilità della misura dell'effetto terapeutico sono inversamente proporzionali all'ampiezza dell'intervallo di confidenza



Beta-bloccanti per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incidenza di emorragie nei pazienti trattati con beta-bloccanti e nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; in parentesi i rispettivi intervalli di confidenza.

META-ANALISI: grafico

- Non c'è eterogeneità qualitativa inter-trial; nessuno dei trial ha risultati favorevoli ai controlli: nessuna delle differenze dei singoli trial è a destra della verticale di equivalenza .
- Sono significativi a favore del trattamento i risultati di 3 singoli trial (il 3° , il 6° e il 7°): gli intervalli di confidenza non attraversano la linea di equivalenza.
- E' significativa a favore del trattamento la combinazione dei trial (overall).



Beta-bloccanti per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incidenza di emorragie nei pazienti trattati con beta-bloccanti e nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; in parentesi i rispettivi intervalli di confidenza.

META-ANALISI: grafico

- La precisione e la riproducibilità della misura dell'effetto terapeutico sono inversamente proporzionali all'ampiezza dell'intervallo di confidenza

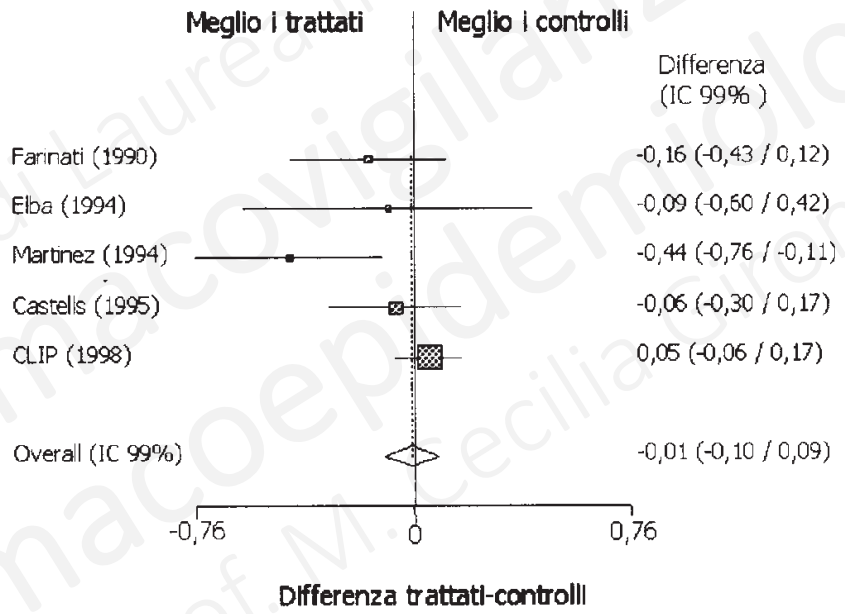


Figura 4. Tamoxifene per il trattamento del carcinoma epatocellulare. Differenze fra mortalità nei pazienti trattati con tamoxifene e mortalità nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; tra parentesi i rispettivi intervalli di confidenza.

META-ANALISI: grafico

- I trial sono assai diversi per numerosità di pazienti, come mostra la differente ampiezza degli intervalli di confidenza; non c'è una vera eterogeneità; la differenza relativa di un solo trial (CLIP, il più numeroso) è appena a destra della verticale di equivalenza, ma ad essa vicinissima.
- E' significativo a favore del trattamento il risultato di un singolo trial (il 3°).
- La combinazione dei trial mostra che non c'è differenza fra tamoxifene e trattamento non attivo.

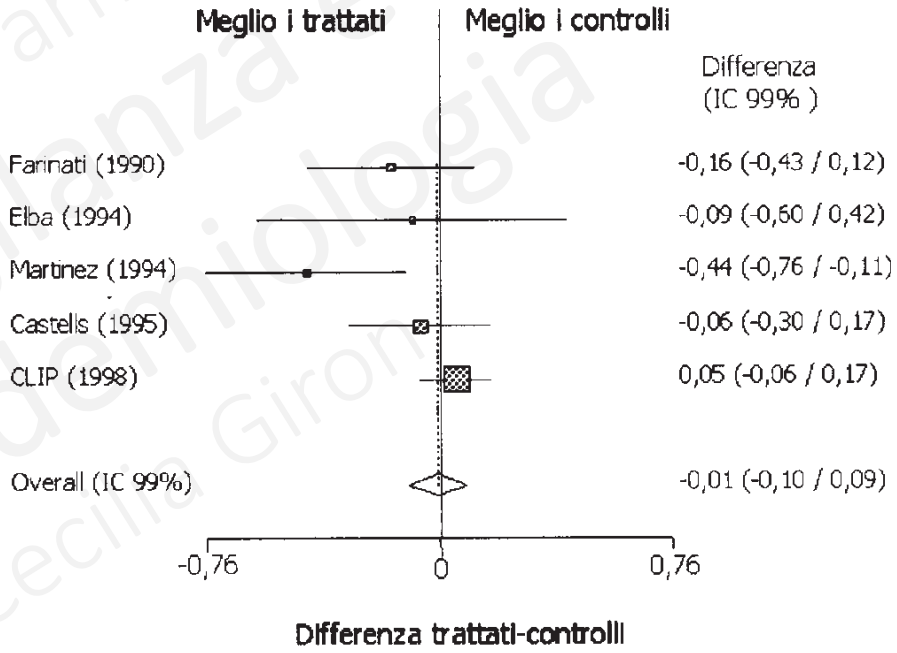
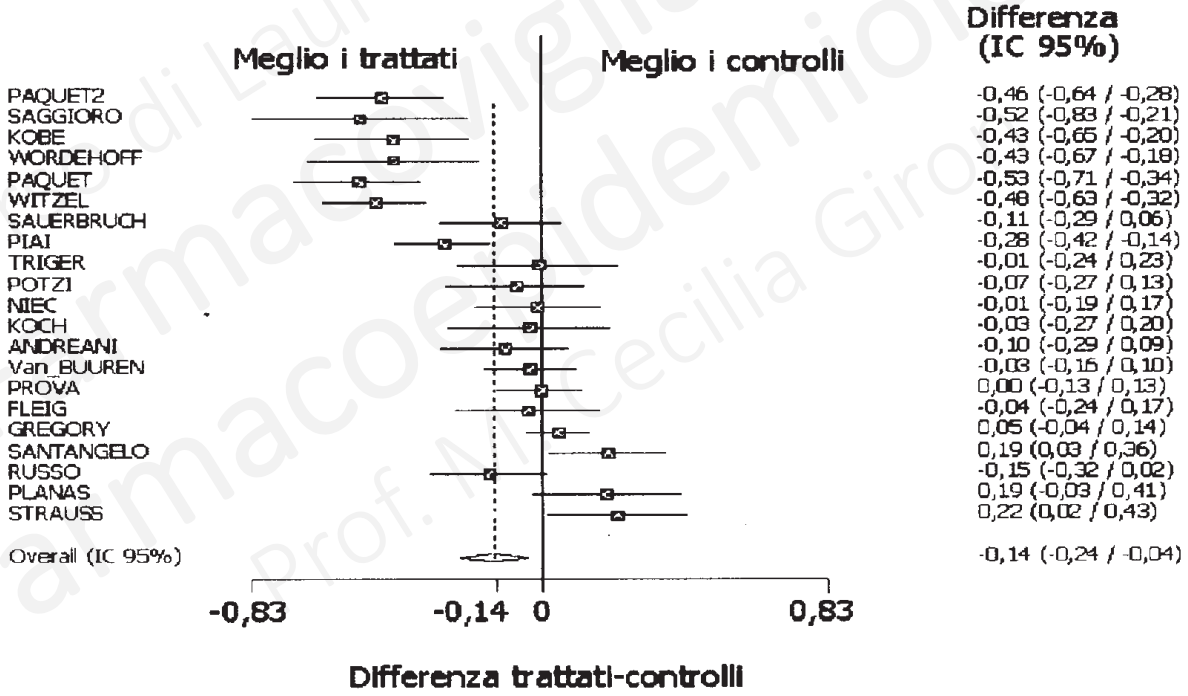


Figura 4. Tamoxifene per il trattamento del carcinoma epatocellulare. Differenze fra mortalità nei pazienti trattati con tamoxifene e mortalità nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; tra parentesi i rispettivi intervalli di confidenza.

META-ANALISI: grafico

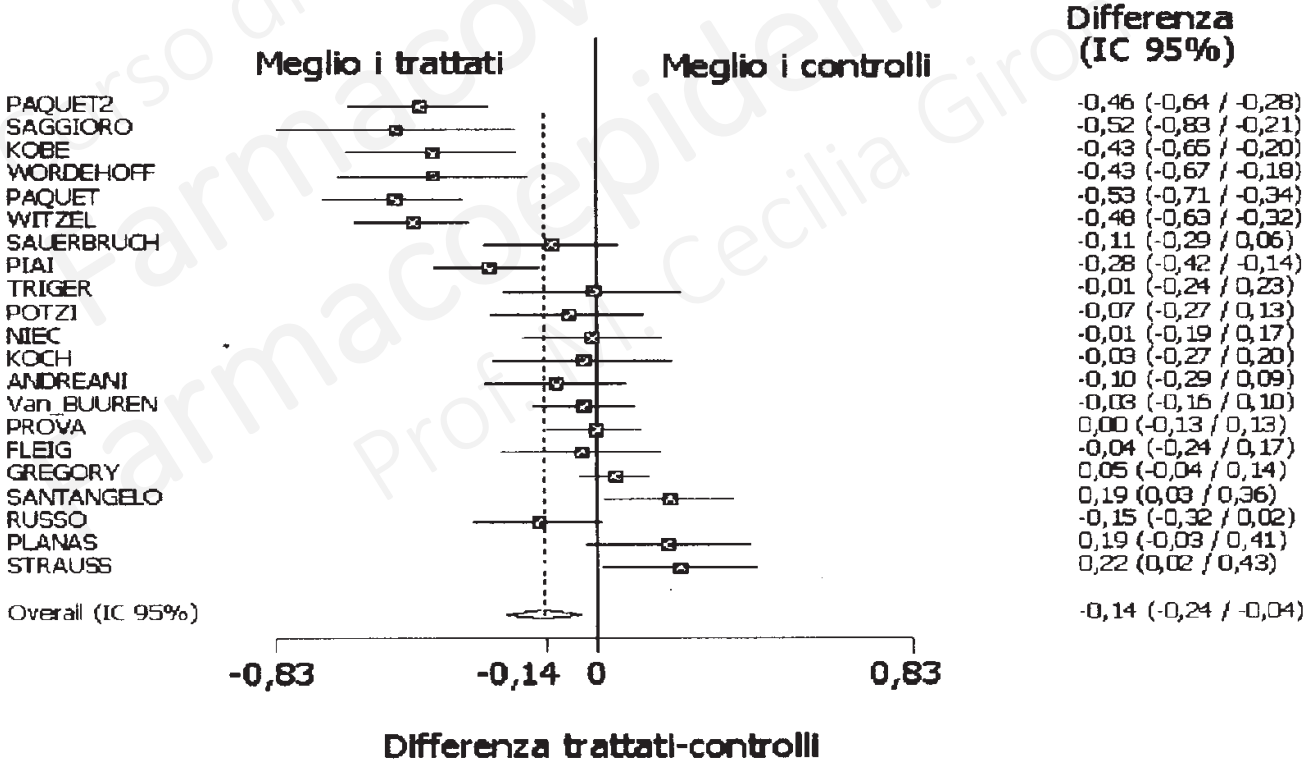
- il Forrest plot dimostra **chiaramente l'eventuale eterogeneità qualitativa inter-trial**, quando alcune delle differenze relative ai singoli trial sono a sinistra della verticale di equivalenza, e altre a destra, **specie se i rispettivi intervalli di confidenza sono per lungo tratto non sovrapposti**



. Scleroterapia endoscopica per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incidenza di emorragie nei pazienti trattati con scleroterapia e nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; tra parentesi i rispettivi intervalli di confidenza. I trial sono in ordine decrescente dall'alto in basso secondo l'incidenza di emorragie nei controlli.

META-ANALISI: grafico

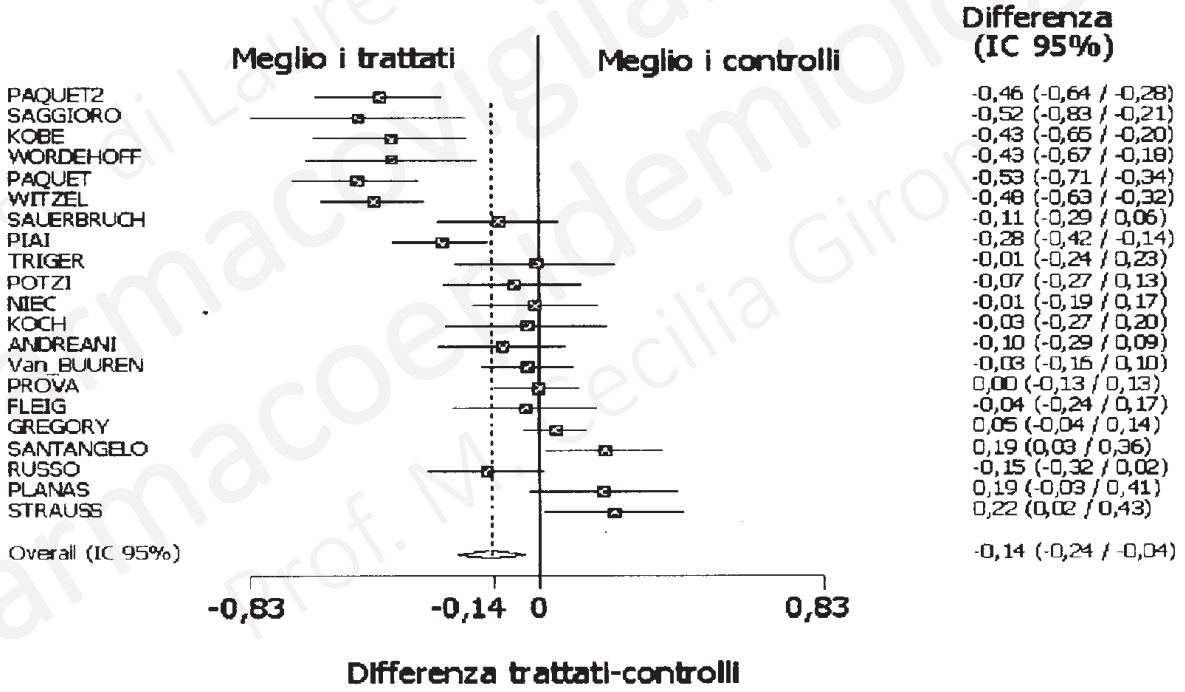
- La caratteristica principale è l'eterogeneità qualitativa inter-trial: 4 trial (17° , 18° , 20° e 21) hanno risultati sfavorevoli al trattamento, e due di essi raggiungono la significatività statistica.
- I trial presentati nella parte alta della figura hanno risultati favorevoli al trattamento, significativi in sette. Quelli nella parte intermedia tendono all'equivalenza.



. Scleroterapia endoscopica per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra inciden-

META-ANALISI: grafico

- In presenza di una eterogeneità così forte la combinazione in un'unica misura dei risultati dei trial (pooling), benché statisticamente significativa a favore del trattamento, sarebbe clinicamente inappropriata. Applicato nella pratica corrente, il trattamento potrebbe esporre una parte dei pazienti agli effetti sfavorevoli osservati nei trial negativi.

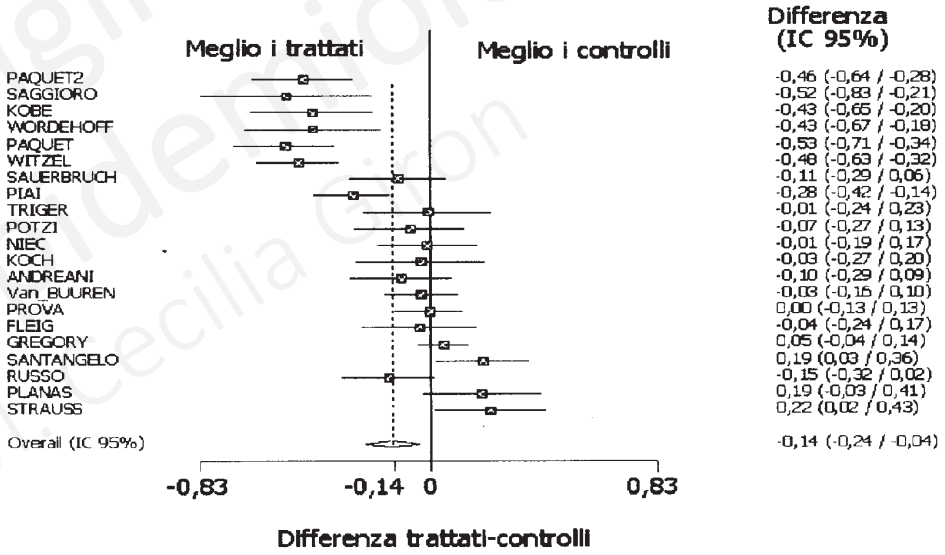


. Scleroterapia endoscopica per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incidenza di emorragie nei pazienti trattati con scleroterapia e nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; tra parentesi i rispettivi intervalli di confidenza. I trial sono in ordine decrescente dall'alto in basso secondo l'incidenza di emorragie nei controlli.

META-ANALISI: grafico

- La figura è costruita disponendo i trial in ordine decrescente secondo l'incidenza di emorragie nei controlli non trattati: dato che i trial sono randomizzati, tale incidenza equivale al rischio di base dei pazienti dei trial (trattati e controlli).

- I risultati (favorevoli per i trial disposti nella parte più alta della figura, indifferenti nella parte media, negativi nella parte inferiore**) sono coerenti con l'ipotesi, avanzata nell'articolo, che gli effetti del trattamento siano correlati all'entità del rischio di base**; potrebbero essere giustificati pertanto studi successivi in pazienti ad alto rischio.



. Scleroterapia endoscopica per la prevenzione delle emorragie da varici esofagee nella cirrosi. Differenze fra incider za di emorragie nei pazienti trattati con scleroterapia e nei controlli non trattati [EER – CER]; le differenze dei sir goli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; tra parentesi i rispettivi intervalli confidenza. I trial sono in ordine decrescente dall'alto in basso secondo l'incidenza di emorragie nei controlli.

META-ANALISI: grafico

- Le differenze con segno negativo (a sinistra della verticale di equivalenza) indicano una **più alta incidenza di eventi nei controlli**, e pertanto **un vantaggio terapeutico** del trattamento sperimentale;

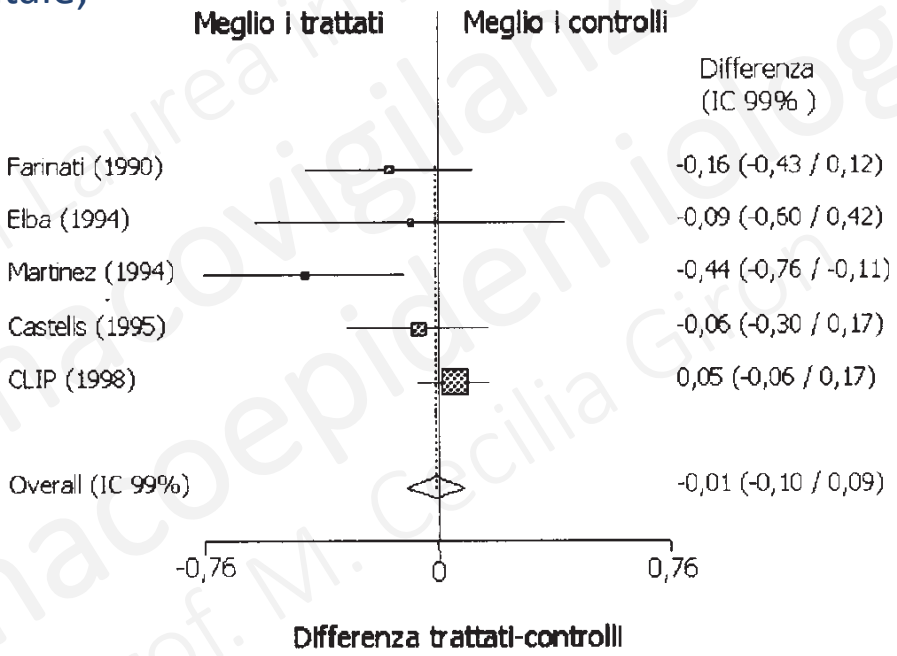
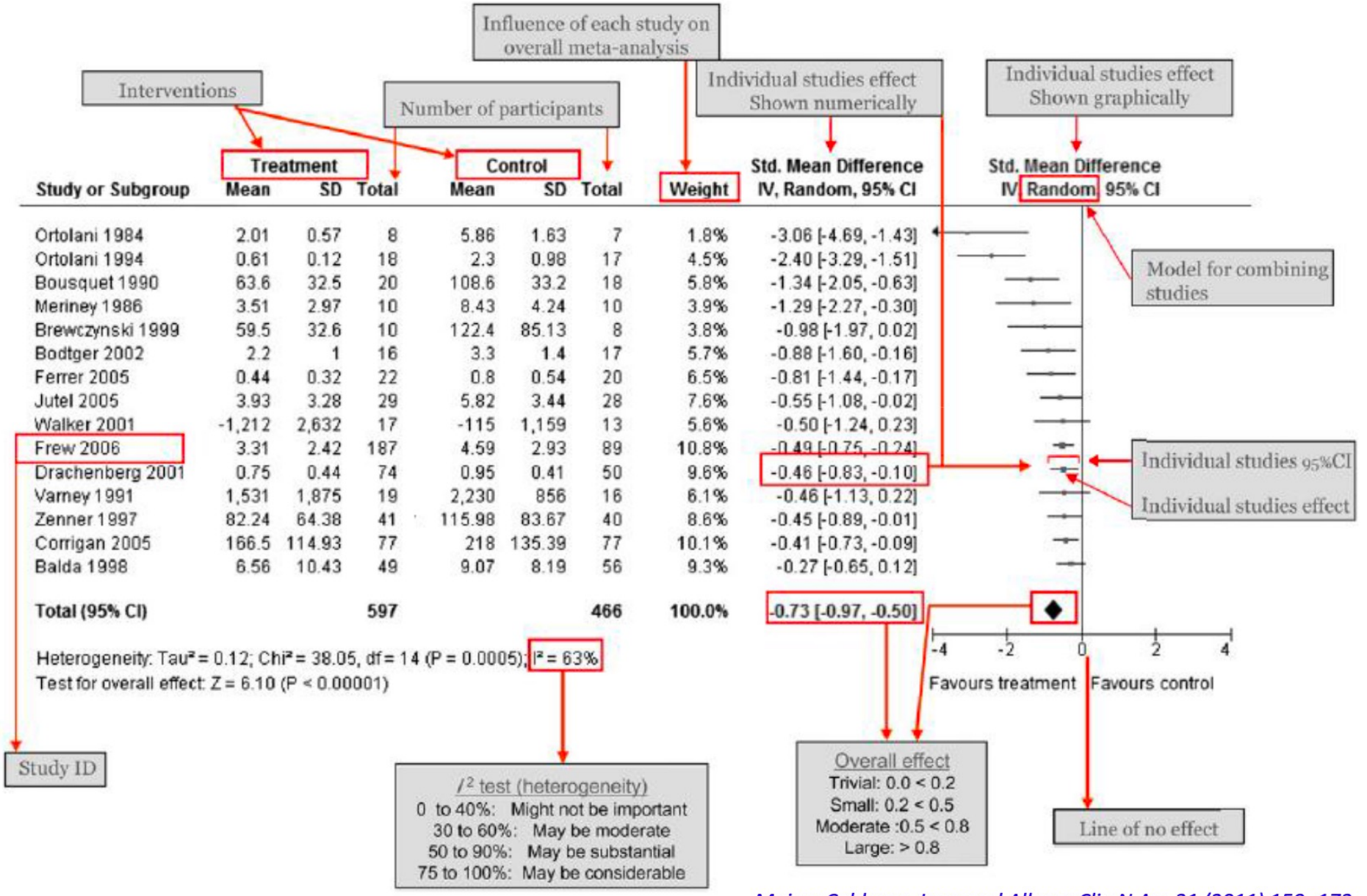


Figura 4. Tamoxifene per il trattamento del carcinoma epatocellulare. Differenze fra mortalità nei pazienti trattati con tamoxifene e mortalità nei controlli non trattati [EER – CER]; le differenze dei singoli trial e della loro combinazione (*overall*) sono riportate a destra del grafico; tra parentesi i rispettivi intervalli di confidenza.

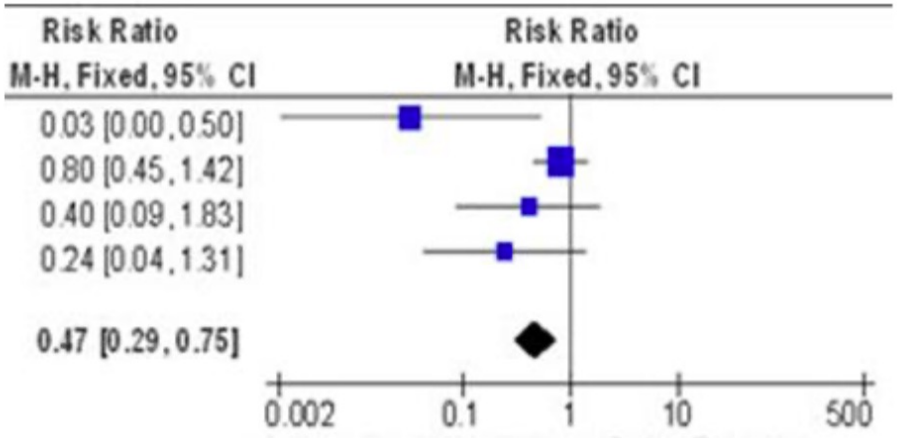
META-ANALISI: grafico



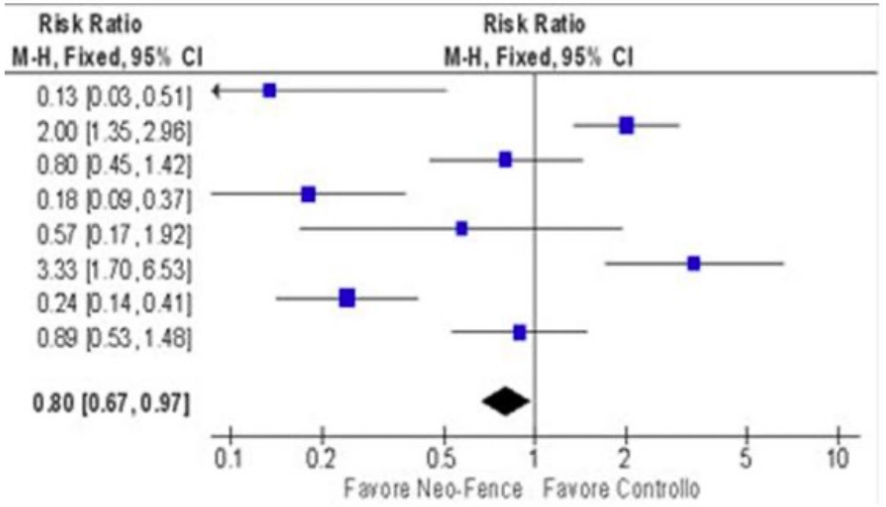
Moises Calderon, Immunol Allergy Clin N Am 31 (2011) 159–173

META-ANALISI: eterogeneità

...quando non è riportato I^2 o Chi^2



le stime puntuali (i quadratini) sono molto diverse per dimensione ma coerenti per direzione

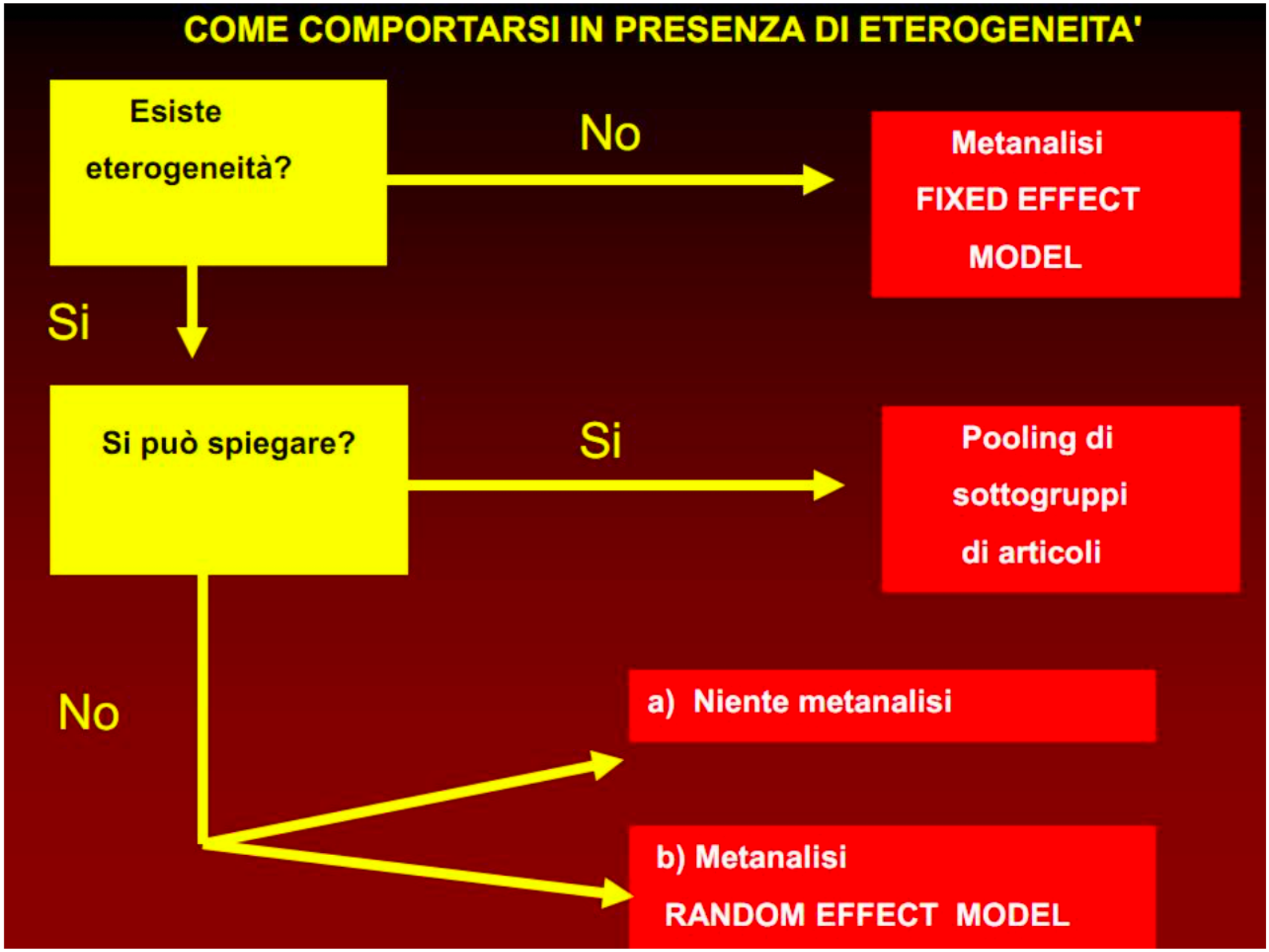


le stime puntuali (i quadratini) sono differenti sia in direzione che in grandezza

i "baffi" degli IC non si sovrappongono = alta eterogeneità

META-ANALISI: publication bias

- Studi che dimostrino un'efficacia del trattamento tendono a essere pubblicati con maggiore facilità rispetto ai cosiddetti studi negativi
- Di conseguenza, le meta-analisi che includono solo gli studi pubblicati tendono a sovrastimare l'effetto, introducendo un errore sistematico (bias) a favore dell'efficacia dei trattamenti.
- Se il bias di pubblicazione è presente e tutti gli studi hanno una stessa direzione di effetto (come probabile), le stime prodotte con la meta-analisi saranno viziate, ma precise, e quindi erroneamente convincenti.
- Possibili soluzioni a questo problema possono essere:
  - La pubblicazione di tutti i lavori metodologicamente corretti, anche quelli non dimostrativi di efficacia
  - Reperimento e inclusione nelle meta-analisi di studi anche non pubblicati (banche dati di clinical trials, comunicazioni a congressi)
  - Approcci statistici o quasi statistici volti a correggere il bias


COME COMPORTARSI IN PRESENZA DI ETEROGENEITA'
Esiste eterogeneità?
No
Metanalisi FIXED EFFECT MODEL
Si
Si può spiegare?
Si
Pooling di sottogruppi di articoli
No
a) Niente metanalisi
b) Metanalisi RANDOM EFFECT MODEL

META-ANALISI: metodi per combinare i risultati

- Effetti fissi: l'interesse è circoscritto agli studi che sono stati inclusi nella meta- analisi

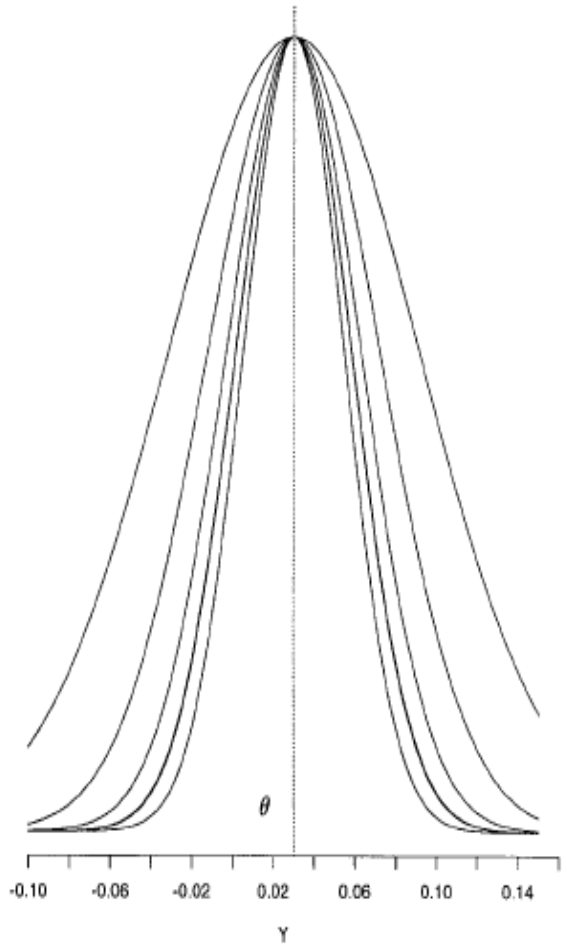
- Effetti variabili: gli studi analizzati costituiscono un campione estratto da una popolazione più ampia di possibili studi

META-ANALISI: metodi per combinare i risultati

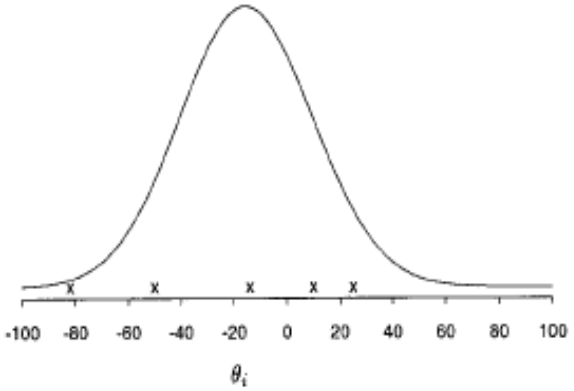
- Modello ad effetti fissi: ogni studio offre una stima di un medesimo parametro le differenze osservate sono dovute ad errori casuali

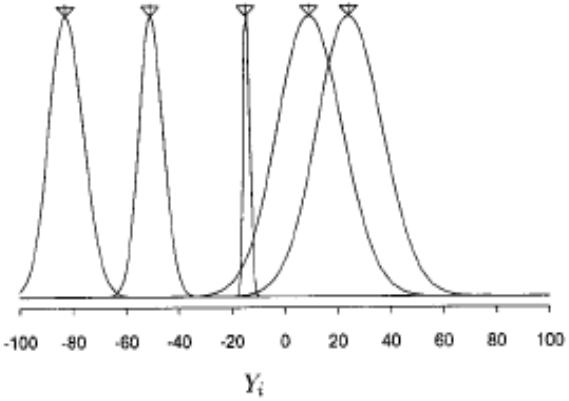
- Modello ad effetti variabili: le differenze nei risultati tratti da ciascuno studio sono sia casuali sia dovute a differenze tra le popolazioni studiate o legate alle caratteristiche dei singoli studi.

META-ANALISI: metodi per combinare i risultati



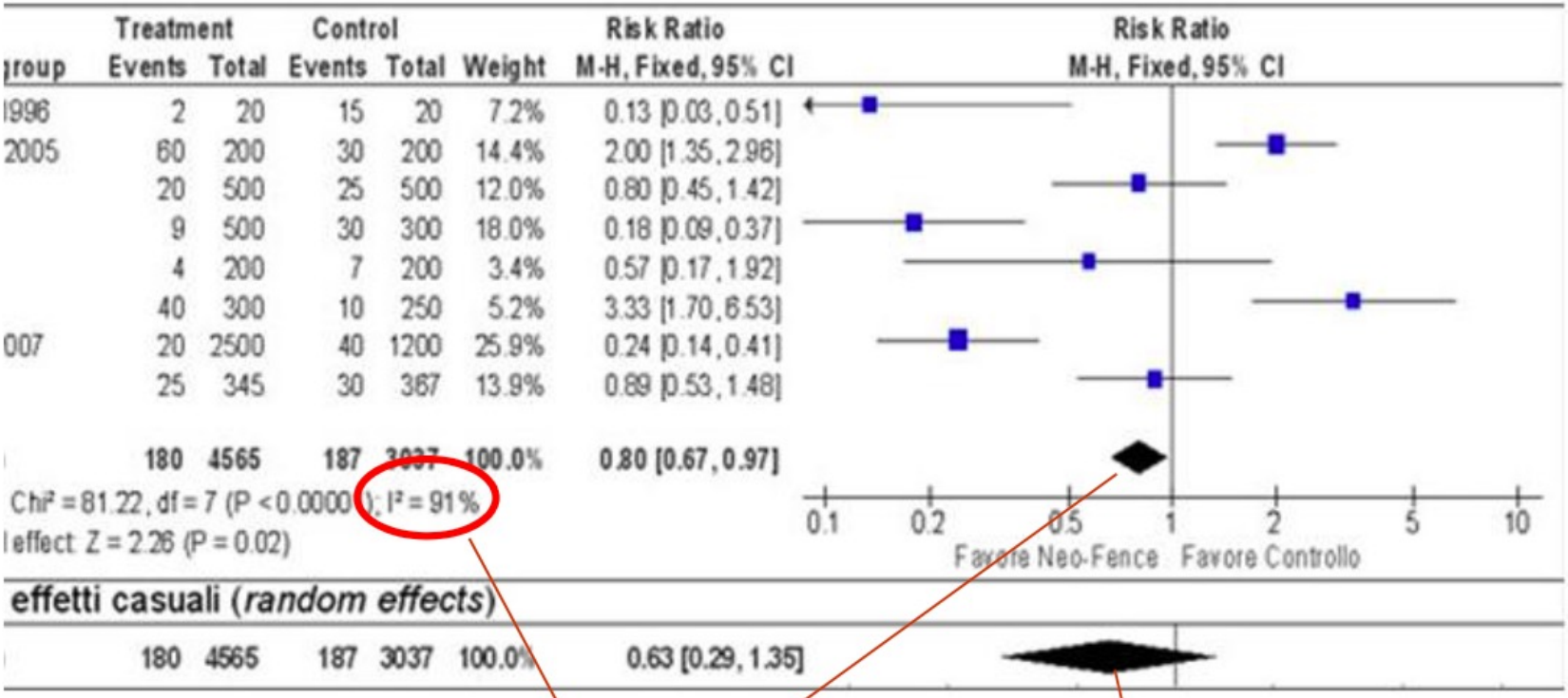
Modello ad effetti fissi





Modello ad effetti variabili

META-ANALISI: effetti fissi e variabili



L'analisi condotta con il modello ad effetti fissi (*fixed effects*) produce una stima complessiva di efficacia statisticamente significativa

se viene applicato il modello ad effetti casuali (*random effects*) si osserva che la losanga nera interseca la linea verticale

non vi è evidenza di efficacia, a causa della grande eterogeneità

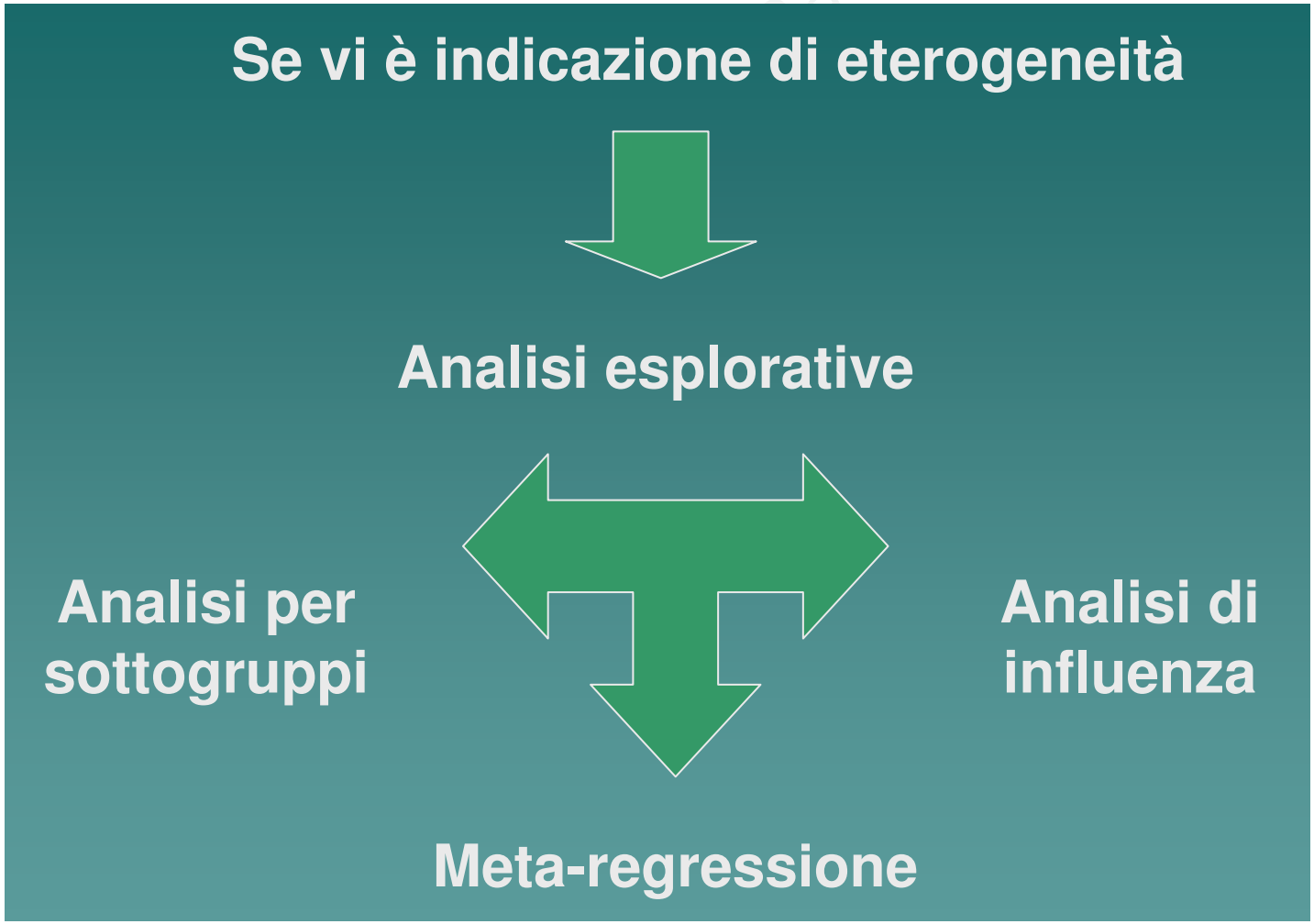
META-ANALISI: metodi per combinare i risultati

In base all'ipotesi che le stime dei coefficienti provengano da studi tra loro indipendenti e siano realizzazioni di variabili casuali normali con stessa media e varianza, **la stima sintetica ad effetti fissi massimizza la verosimiglianza per il parametro di interesse** , che rappresenta l'effetto unico sottostante il fenomeno osservato (Bohning, 1999)

META-ANALISI: metodi per combinare i risultati

In base all'ipotesi che le stime dei coefficienti provengano da studi tra loro indipendenti e siano realizzazioni di variabili casuali normali con stessa media e varianza, **la stima sintetica ad effetti fissi massimizza la verosimiglianza per il parametro di interesse** , che rappresenta l'effetto unico sottostante il fenomeno osservato (Bohning, 1999)

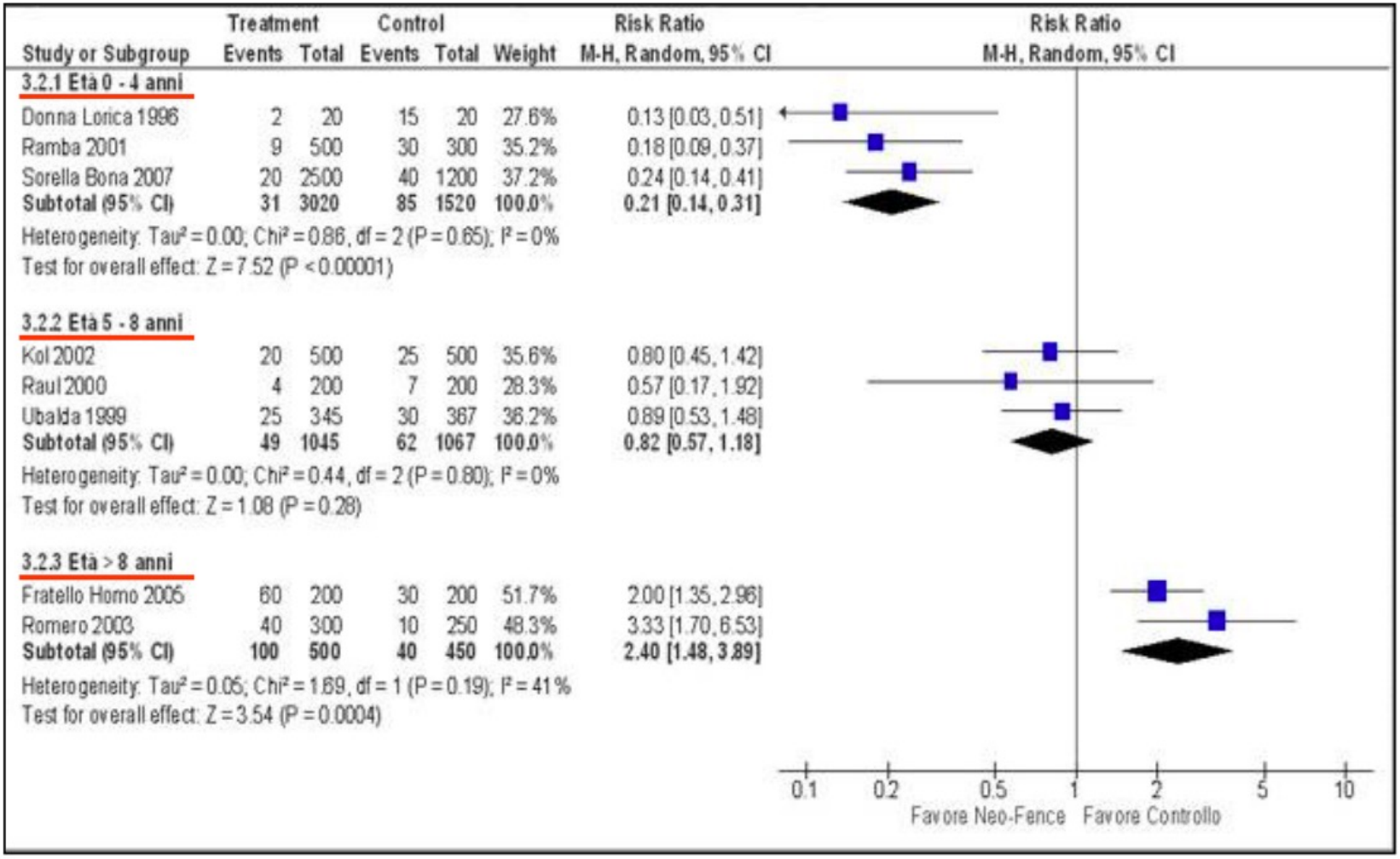
META-ANALISI: metodi per combinare i risultati



META-ANALISI: eterogeneità

- La presenza di eterogeneità pone il problema di indagarne le cause. Infatti, quando gli studi differiscono in direzione e/o grandezza della stima questo dovrebbe suggerire che possono esistere dei fattori importanti che influenzano l'efficacia dell'intervento.
- L'esempio della slide successiva chiarisce l'importanza dell'analisi per sottogruppi in presenza di una importante eterogeneità

META-ANALISI: eterogeneità per sottogruppi



analisi ripetuta tenendo conto che gli studi differivano fra loro principalmente per le età dei soggetti

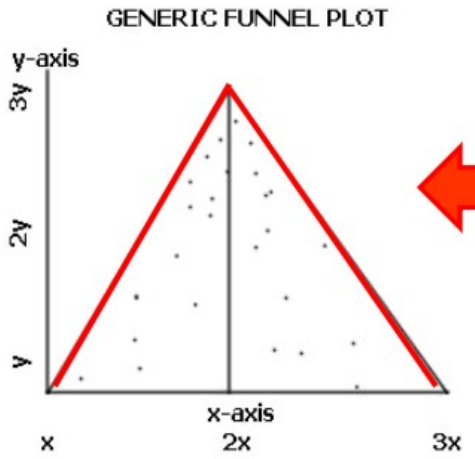
META-ANALISI: eterogeneità per sottogruppi

- Caratteristiche dei partecipanti: criteri di inclusione/esclusione dei partecipanti, età, presenza/assenza di patologie concomitanti.
- Caratteristiche del trattamento o dell'intervento: tipo di intervento, modalità e vie di somministrazione, dosaggio, presenza di co-somministrazioni, presenza di co-interventi, presenza di eventuali effetti collaterali.
- Modalità di conduzione dello studio: tipo definizione e modalità di rilevazione degli eventi di interesse (end-point principali), lunghezza del periodo di osservazione.
- Qualità metodologica della conduzione dello studio: qualità delle procedure di randomizzazione, dimensione campionaria, numero di persi di vista, esclusi o ritirati dopo l'inizio dello studio.
- Conflitto di interesse

META-ANALISI: Publication bias e Funnel Plot

- Gli studi negativi, soprattutto se di piccole dimensioni, tendono ad essere meno pubblicati.
- Per stimare l'entità del publication bias si può ricorrere al **metodo dell'imbuto rovesciato**, basato sul fatto che le misure dell'effetto dovrebbero essere distribuite casualmente attorno all'effetto medio con meno variazioni negli studi con un grande campione di soggetti rispetto a quelli di piccole dimensioni.
- Se si riportano in **un diagramma cartesiano la misura dell'effetto sull'ascissa e la dimensione dello studio sull'ordinata**, **i vari punti**, ciascuno corrispondente a uno studio, **dovrebbero disegnare una specie di imbuto rovesciato**. Il publication bias fa sì che siano più o meno rari i punti da un lato in basso, cioè quelli corrispondenti agli studi più piccoli e con risultati più sfavorevoli per il trattamento di interesse.

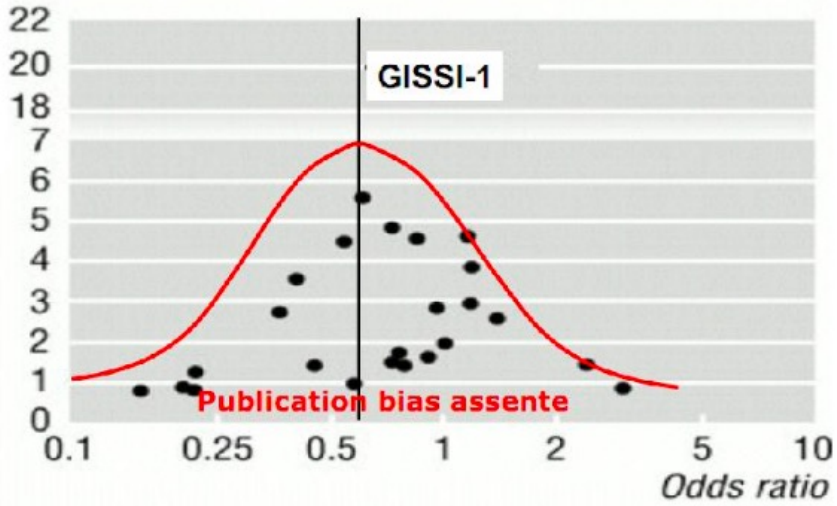
META-ANALISI: Publication bias e Funnel Plot

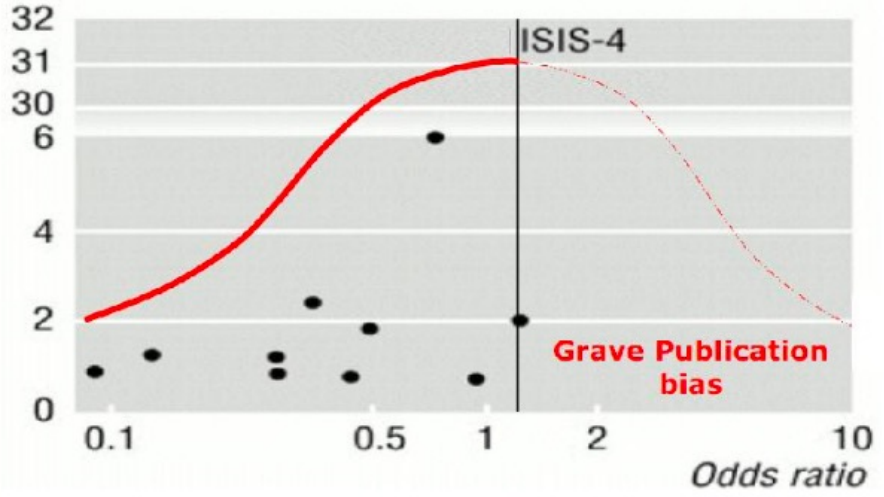


Study size

Effect size

Un'immagine a imbuto rovesciato, simmetrica, testimonia la presenza di un buon "data set", con assenza di *publication bias*





META-ANALISI: analisi per sottogruppi

The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

Passive Smoking and the Risk of Coronary Heart Disease — A Meta-Analysis of Epidemiologic Studies

Jiang He, M.D., Ph.D., Suma Vupputuri, M.P.H., Krista Allen, M.P.H., Monica R. Prerost, M.S., Janet Hughes, Ph.D., and Paul K. Whelton, M.D.

N Engl J Med 1999; 340:920-926 | March 25, 1999 | DOI: 10.1056/NEJM199903253401204

Share:

Abstract | Article | References | Citing Articles (148) | Letters

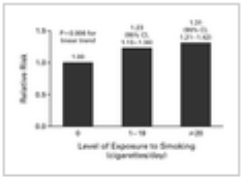
BACKGROUND

The effect of passive smoking on the risk of coronary heart disease is controversial. We conducted a meta-analysis of the risk of coronary heart disease associated with passive smoking among nonsmokers.

Full Text of Background...

MEDIA IN THIS ARTICLE

FIGURE 2



Pooled Relative Risks of Coronary Heart Disease Associated

STUDY (YEAR)	EXPOSURE	NO EXPOSURE
	no. of events/no. at risk	
Cohort		
Hirayama[7,8] (1984)	376/69,645	118/21,895
Garland et al.[9] (1985)	17/492	2/203
Svendsen et al.[10] (1987)	5/286	8/959
Butler[11] (1988)	4/430	60/6077
Butler[11] (1988)	50/2802	95/3630
Sandler et al.[12] (1989)	673/10,799	685/8236
Hole et al.[13] (1989)	54/1538	30/917
Humble et al.[14] (1990)	49/296	27/217
Steenland et al.[15] (1996)	571/67,369	2574/164,831
Kawachi et al.[16] (1997)	135/25,959	17/6087
	CASE PATIENTS	CONTROLS
	no. with exposure/no. without exposure	
Case–control		
Lee et al.[17] (1986)	70/48	269/182
He et al.[18] (1989)	25/9	30/38
Jackson[19] (1989)	18/21	87/148
Dobson et al.[20] (1991)	65/278	133/692
La Vecchia et al.[21] (1993)	24/66	37/157
He et al.[22] (1994)	48/11	76/50
Muscat and Wynder[23] (1995)	63/51	70/88
Ciruzzi et al.[24] (1998)	131/205	117/329
Overall		

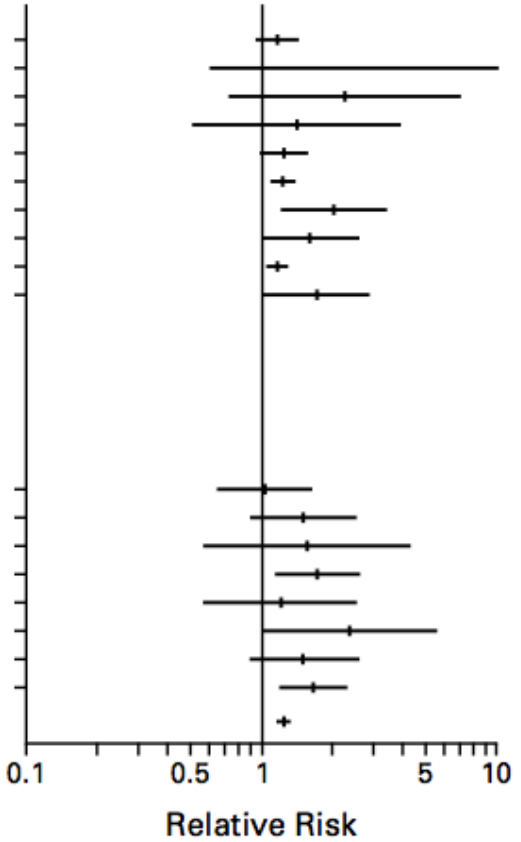


Figure 1. Relative Risks of Coronary Heart Disease Associated with Passive Smoking among Nonsmokers in 18 Epidemiologic Studies. The horizontal bars represent the 95 percent confidence intervals. The relative risk in the study by Garland et al.[9] was 14.9.

META-ANALISI: analisi per sottogruppi

Stratificazione per sottogruppi e calcolo della stima dell'effetto per ogni sottogruppo

TABLE 3. OVERALL RELATIVE RISK OF CORONARY HEART DISEASE ASSOCIATED WITH PASSIVE SMOKING AMONG NONSMOKERS IN STUDIES THAT USED DIFFERENT EXCLUSION CRITERIA.*

STUDIES INCLUDED IN ANALYSIS	NO. OF STUDIES	RELATIVE RISK (95% CI)	P VALUE
All studies	18	1.25 (1.17–1.32)	<0.001
All studies except one outlier study†	17	1.24 (1.17–1.32)	<0.001
Peer-reviewed studies‡	15	1.25 (1.17–1.33)	<0.001
Studies that used death from MI or CHD as an outcome measure§	14	1.24 (1.17–1.32)	<0.001
Studies that controlled for important CHD risk factors¶	10	1.26 (1.16–1.38)	<0.001

META-ANALISI: analisi per sottogruppi

Stratificazione per sottogruppi e calcolo della stima dell'effetto per ogni sottogruppo

TABLE 4. OVERALL RELATIVE RISK OF CORONARY HEART DISEASE ASSOCIATED WITH PASSIVE SMOKING AMONG NONSMOKERS, ACCORDING TO THE DESIGN OF THE STUDY AND THE CHARACTERISTICS OF THE PARTICIPANTS.

VARIABLE	NO. OF STUDIES	RELATIVE RISK (95% CI)*	P VALUE
Study design			
Cohort	10	1.21 (1.14–1.30)	<0.001
Case–control	8	1.51 (1.26–1.81)	<0.001
Sex†			
Male	9	1.22 (1.10–1.35)	<0.001
Female	15	1.24 (1.15–1.34)	<0.001
Passive exposure to smoking			
Home	18	1.17 (1.11–1.24)	<0.001
Workplace	8	1.11 (1.00–1.23)	0.05

*CI denotes confidence interval.

†Two studies did not report results according to sex.

META-ANALISI: tipologie

❑ Meta-analisi standard:

I risultati sono combinati in un'unica analisi

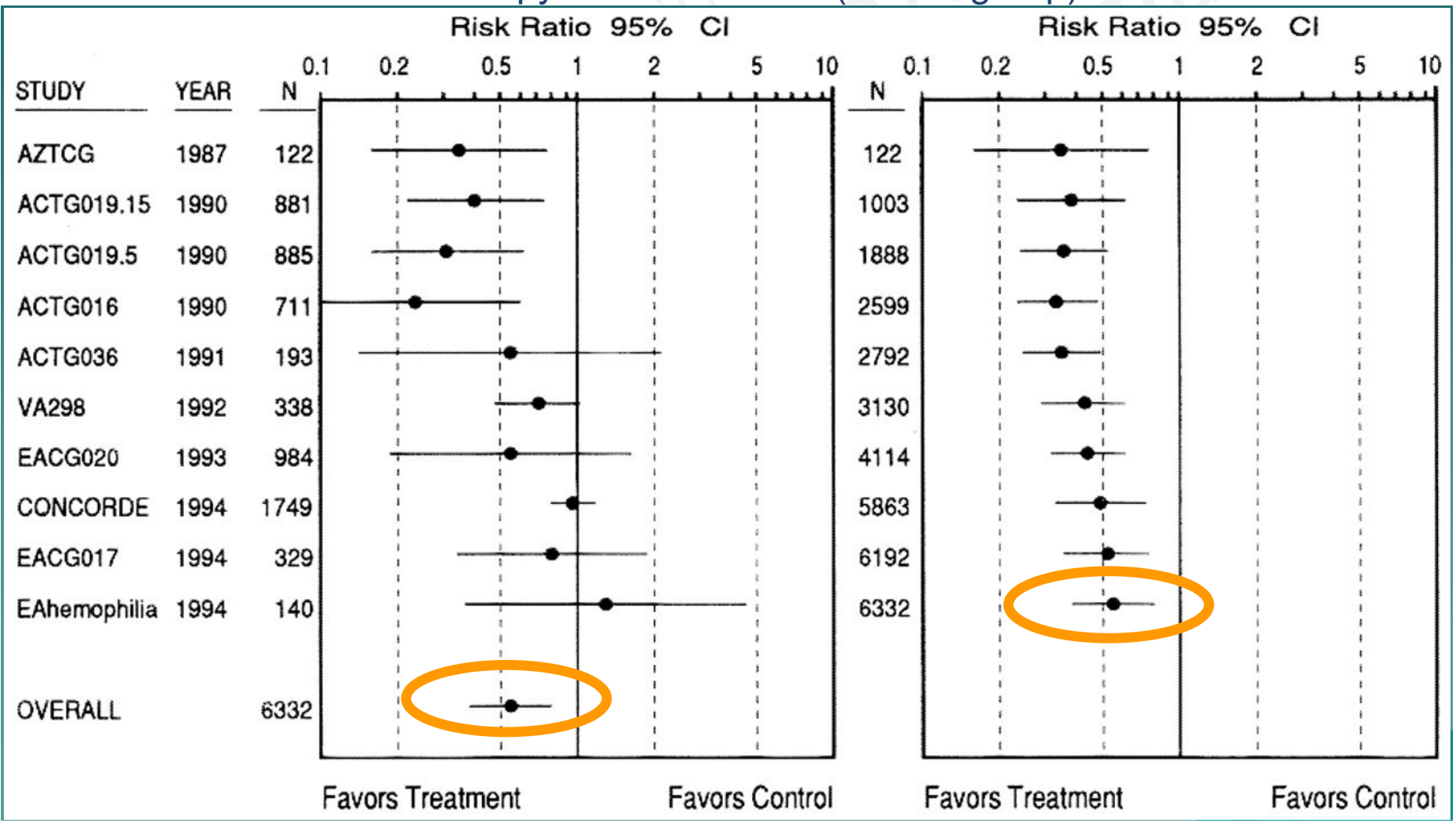
❑ Meta-analisi cumulativa:

I risultati dei singoli studi vengono combinati sequenzialmente.

Può evidenziare trend emergenti

Meta-analisi standard e meta-analisi cumulativa

Risk ratios for progression to AIDS or death
in a comparison of early therapy with zidovudine (treatment group) or deferred therapy with zidovudine (control group).



THE LANCET

Volume 364, Issue 9450, 4–10 December 2004, Pages 2021–2029

Fast track — Articles

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

Peter Jüni, MD[a, b, c], Linda Nartey, DipMD[a], Stephan Reichenbach, MD[a, b, c], Rebekka Sterchi[a], Prof Paul A Dieppe, MD[c], Prof Matthias Egger, MD[a, c]

[a] Department of Social and Preventive Medicine, University of Berne, Berne, Switzerland

[b] Department of Rheumatology and Clinical Immunology, Inselspital, University of Berne, Berne, Switzerland

[c] MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Bristol, UK

Refers To Richard Horton

Vioxx, the implosion of Merck, and aftershocks at the FDA

The Lancet, Volume 364, Issue 9450, 4–10 December 2004, Pages 1995-1996

PDF (105 K)

Referred to by Richard Horton

Vioxx, the implosion of Merck, and aftershocks at the FDA

The Lancet, Volume 364, Issue 9450, 4–10 December 2004, Pages 1995-1996

PDF (105 K)

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, S Reichenbach, Prof P A Dieppe MD, Prof M Egger)

Correspondence to: Prof M Egger, Department of Social and Preventive Medicine, University of Berne, CH-3012 Berne, Switzerland **egger@ispm.unibe.ch**

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 evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; p=0·41) or trial duration (p=0·82). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0·86 [95% CI 0·75–0·99]) and could not have explained the findings of the VIGOR trial.

Interpretation Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

Meta-analisi standard e meta-analisi cumulativa

Vioxx and Relative Risk of Myocardial Infarction

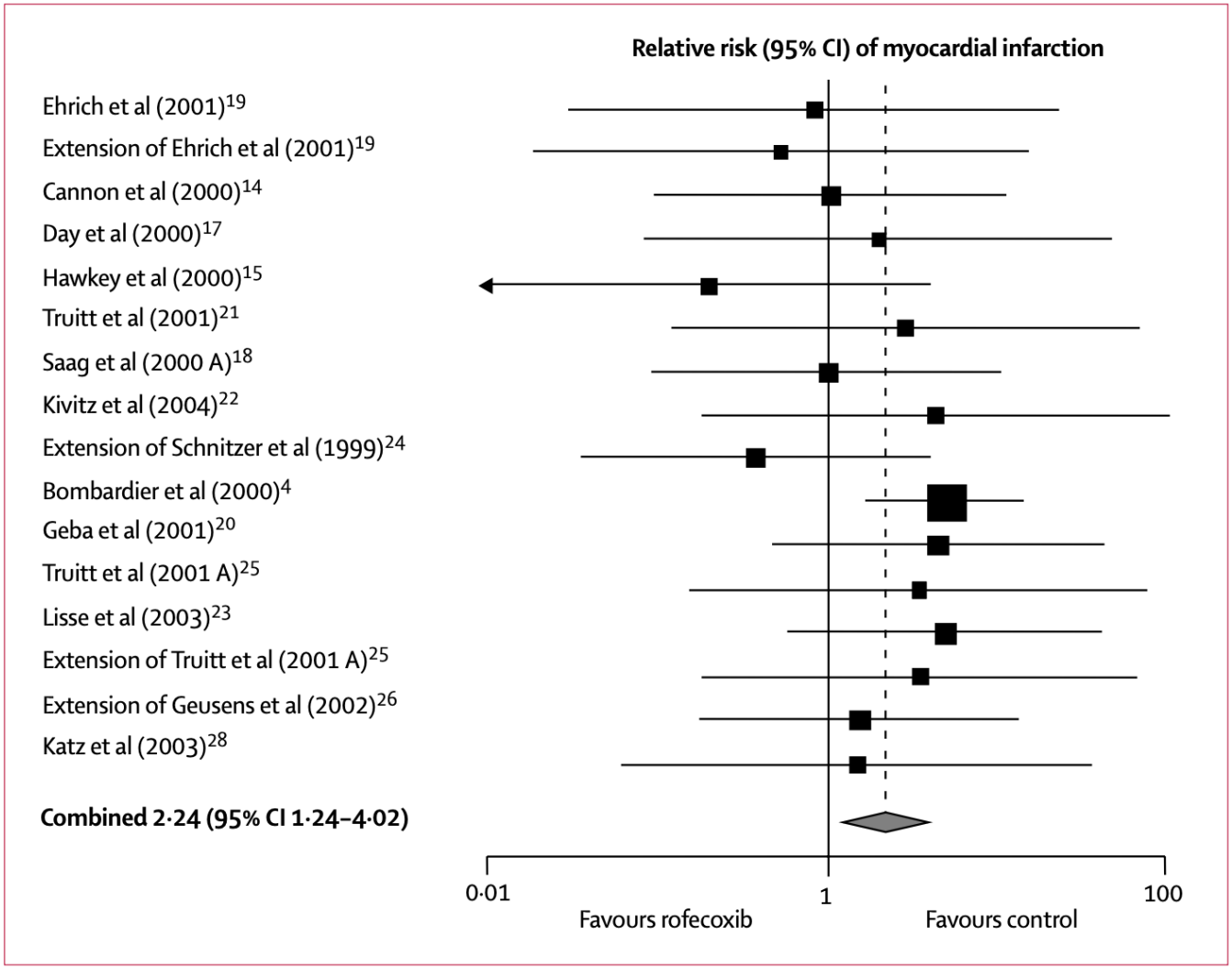


Figure 2: **Meta-analysis of randomised trials comparing rofecoxib with control**

Meta-analisi standard e meta-analisi cumulativa

Vioxx and Relative Risk of Myocardial Infarction

As figure 2 shows, the combined relative risk was 2·24 (95% CI 1·24–4·02), with little evidence of between trial heterogeneity (I^2=0%, p for heterogeneity=0·82). Table 2 presents results from stratified analyses. Estimates of relative risk varied depending on whether rofecoxib had been compared with placebo, an NSAID other than naproxen, or naproxen, but 95% CIs were wide and a test of interaction was not significant (p=0·41). Similarly, there was little evidence that relative risks differed depending on the dose of rofecoxib or the duration of trials. The estimated relative risk of myocardial

	Relative risk (95% CI)	p for interaction
All comparisons	2·24 (1·24–4·02)	..
Type of control		
Placebo	1·04 (0·34–3·12)	0·41
Non-naproxen NSAIDs	1·55 (0·55–4·36)	
Naproxen	2·93 (1·36–6·33)	
Daily dose		
12·5 mg	2·71 (0·99–7·44)	0·69
25 mg	1·37 (0·52–3·61)	
50 mg	2·83 (1·24–6·43)	
Trial duration		
⩾6 months	2·17 (1·03–4·59)	0·82
<6 months	2·33 (0·90–6·03)	
Concealment of allocation		
Adequate	2·04 (0·32–12·93)	0·96
Unclear	2·26 (1·22–4·19)	
External endpoint committee		
Yes	3·88 (1·88–8·02)	0·011
No or unclear	0·79 (0·29–2·13)	

Table 2: **Relative risk of myocardial infarction comparing rofecoxib with control, from stratified meta-analyses**

Meta-analisi standard e meta-analisi cumulativa

Vioxx and Relative Risk of Myocardial Infarction

Year	Patients	Events	p
1997	523	1	0·916
1998	615	2	0·736
	1399	5	0·828
	2208	6	0·996
	2983	8	0·649
	3324	9	0·866
1999	4017	12	0·879
	5059	13	0·881
2000	5193	16	0·855
	13 269	40	0·070
	14 247	44	0·034
	15 156	46	0·025
	20 742	52	0·010
2001	20 742	58	0·007
	20 742	63	0·007
	21 432	64	0·007

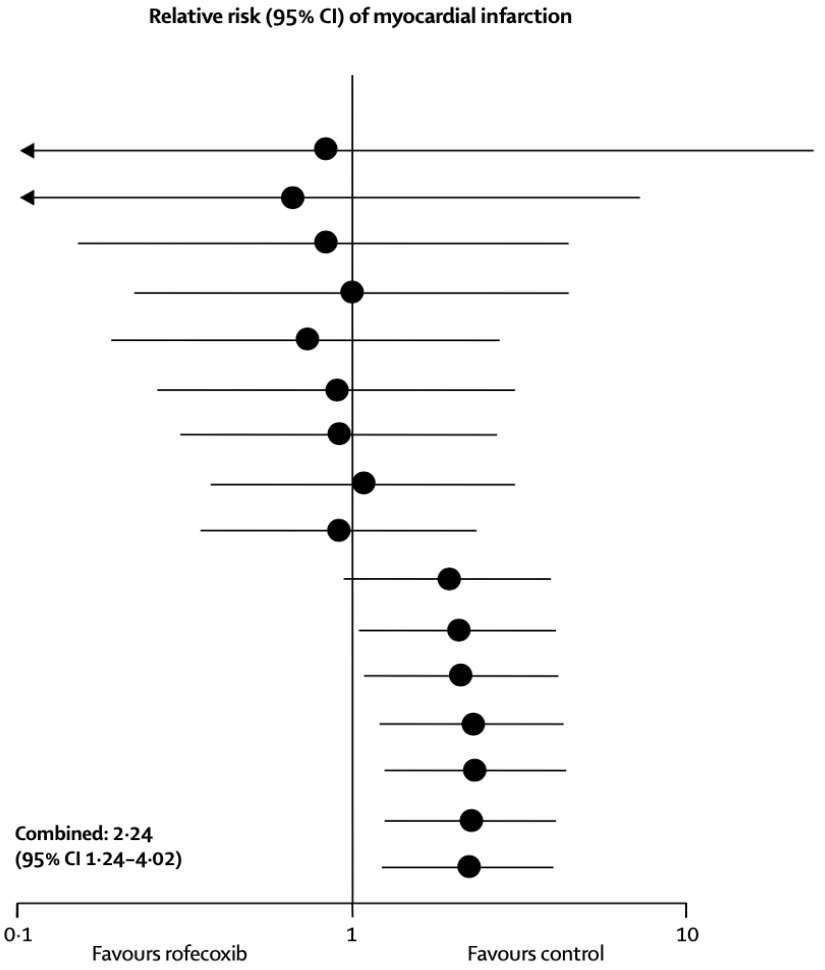


Figure 3: **Cumulative meta-analysis of randomised trials comparing rofecoxib with control**
See figure 2 for sequence of trials.

Meta-analisi standard e meta-analisi cumulativa

Vioxx and Relative Risk of Myocardial Infarction

Cumulative meta-analysis (figure 3) showed that an increased risk of myocardial infarction became evident in 2000, when 14 247 patients had been randomised and 44 events had occurred. At the end of 2000 (52 myocardial infarctions, 20 742 patients) the relative risk was 2·30 (95% CI 1·22–4·33, p=0·010). Subsequent trials brought the number of patients to 21 432 and the number of events to 64. Although this resulted in a narrowing of the CI, point estimates remained similar. The most recent data became available in October, 2001; later trials did not report on cardiovascular outcomes.

A total of 44 strokes were recorded in 11 comparisons, with 25 events in rofecoxib groups and 19 in control groups. The combined relative risk was 1·02 (95% CI 0·54–1·93). Nine comparisons contributed to the analysis of cardiovascular death, with 18 deaths in rofecoxib groups and 13 in control groups and a pooled relative risk of 0·79 (0·29–2·19). Finally, 17 comparisons contributed to the analysis of serious cardiovascular events, with 85 events in rofecoxib groups and 38 in control groups (combined relative risk 1·55 [95% CI 1·05–2·29]). Again, there was little evidence of between-trial heterogeneity for these outcomes (I^2 0%, 27%, and 0%, respectively).

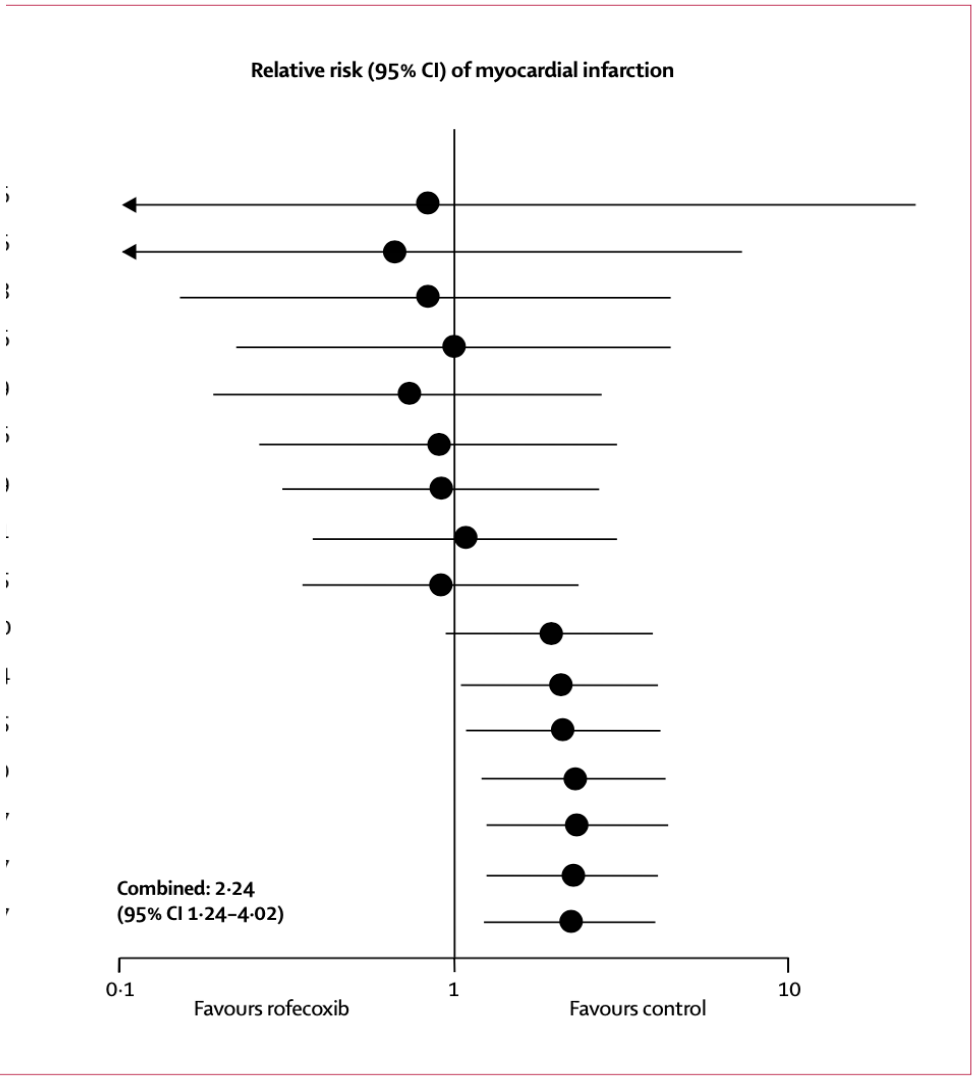


Figure 3: **Cumulative meta-analysis of randomised trials comparing rofecoxib with control**
See figure 2 for sequence of trials.

Meta-analisi standard e meta-analisi cumulativa

Naproxen and Relative Risk of Myocardial Infarction

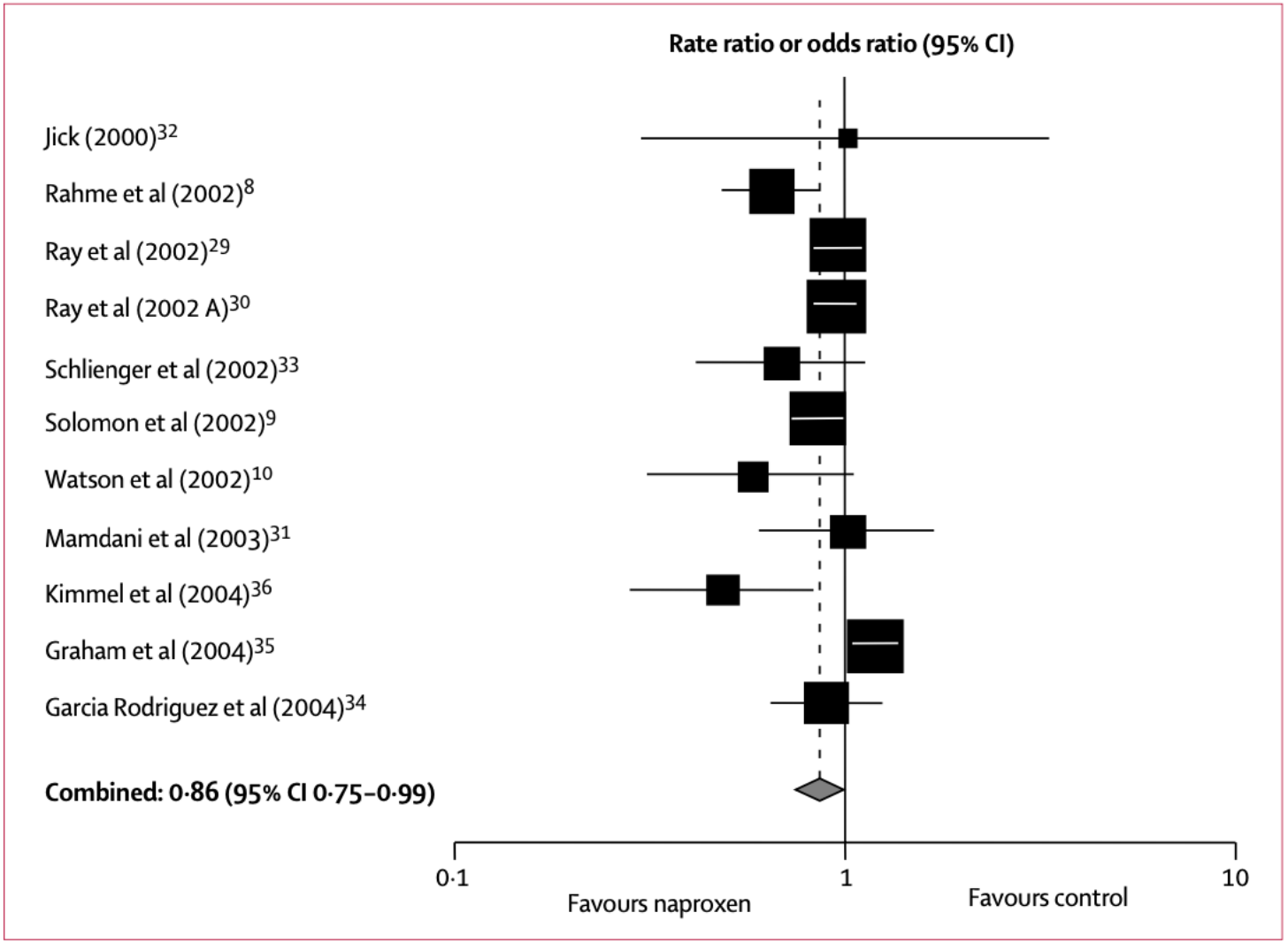


Figure 4: **Meta-analysis of observational studies of naproxen and risk of myocardial infarction**

Meta-analisi standard e meta-analisi cumulativa

Naproxen and Relative Risk of Myocardial Infarction

Cardioprotective effect of naproxen

For the analysis of naproxen there were eight case-control studies and three retrospective cohort studies (table 3). All studies except one[36] used data from large administrative or clinical databases. Four studies were based on the UK General Practice Research Database. Figure 4 shows the meta-analysis of results from primary analyses. The combined estimate was 0·86 (95% CI 0·75–0·99). Almost identical results were obtained when analyses were based on comparisons with non-naproxen NSAIDs (0·86 [0·75–0·99]). In both analyses, there was considerable between-study hetereogeneity (I^2 68% and 43%, respectively). Meta-regression analysis indicated that the funding source largely explained between-study heterogeneity, with studies funded by Merck indicating larger cardioprotective effects of naproxen (p=0·001 and p=0·056, respectively, by test of interaction). There was little evidence for an association with study design or adjustment for aspirin use (p>0·30).

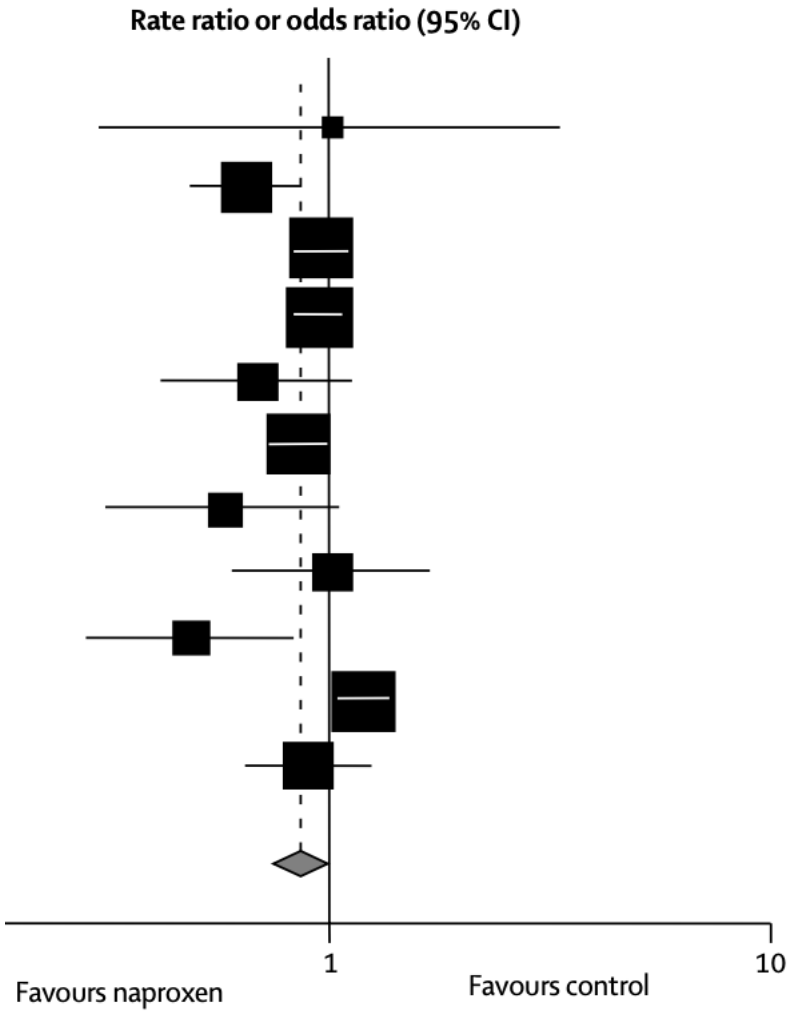


Figure 4: **Meta-analysis of observational studies of naproxen and risk of myocardial infarction**

Meta-analisi standard e meta-analisi cumulativa

Vioxx and Relative Risk of Myocardial Infarction

Discussion

The voluntary withdrawal of rofecoxib by its manufacturer, Merck, on the basis of a fairly small trial that was designed for a different purpose raises several questions.[37] In particular, we must establish whether the drug should have been withdrawn earlier. Our cumulative meta-analysis of randomised controlled trials indicates that an increased risk of myocardial infarction was evident from 2000 onwards. At the end of 2000, the effect was both substantial and unlikely to be a chance finding.

We found an increased risk of myocardial infarction in trials of both short and long duration, which is in contrast to the unpublished results from the APPROVe trial.[1] Our findings thus indicate that patients are at risk even if rofecoxib is taken for a few months only. Therefore, the reassuring statement by Merck, that there is no excess risk in the first 18 months,[1] is not supported by our data. Similarly, we recorded no evidence to support the notion that rofecoxib's cardiovascular toxicity is dose-dependent.[35,38] The reported increase in risk was greater in trials with an external endpoints committee (relative risk 3·9), suggesting that misclassification of coronary events could have biased results in trials that did not include external appraisal of safety outcomes. The inclusion of an independent endpoints committee should be the rule, and exceptions to this rule should be justified.

The difference in coronary risk in the VIGOR trial has been widely interpreted as being due to a cardioprotective effect of naproxen, rather than an adverse effect of rofecoxib.[4,39,40] We examined this hypothesis by stratifying results from randomised trials according to the control intervention and found that the increase in risk was indeed greater in trials comparing rofecoxib with naproxen, but that this finding was probably attributable to chance (p=0·41). The possible cardioprotective effect of naproxen has also been examined in several observational, pharmaco-epidemiological studies. Taken together, the data from these studies indicate that if a protective effect of naproxen exists, it is probably small, and, as pointed out earlier,[6,29] not large enough to explain the findings of VIGOR.[4]

By contrast to our findings, two earlier meta-analyses from Merck Research Laboratories showed no evidence of a rise in cardiovascular risk[41] or an increase in risk that was restricted to trials comparing rofecoxib with naproxen.[7] Possible explanations for these discrepant results include: confounding by trial, in analyses inadequately pooling individual patients' data; use of composite cardiovascular endpoints, which will have diluted any increase in risk of myocardial infarction; and inclusion of safety data that had not undergone independent adjudication. Pooled analyses of industry-sponsored drug trials, undertaken by the company manufacturing the drug in question, are becoming increasingly common. To clarify the reasons behind the

Failing the Public Health — Rofecoxib, Merck, and the FDA

Eric J. Topol, M.D.

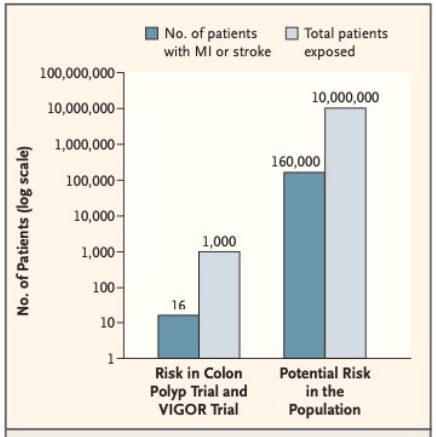
ardial Infarction

On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this medicine and annual sales had topped $2.5 billion, the company withdrew the drug because of an excess risk of myocardial infarctions and strokes. This represents the largest prescription-drug withdrawal in history, but had the many warning signs along the way been heeded, such a debacle could have been prevented.

Neither of the two major forces in this five-and-a-half-year affair — neither Merck nor the FDA — fulfilled its responsibilities to the public. The pivotal trial for rofecoxib involved 8076 patients with rheumatoid arthritis and demonstrated that this coxib had lower gastrointestinal toxicity than naproxen.[1] Even though the drug was approved in 1999 on the basis of data submitted to the FDA, the data were not submitted to a peer-reviewed journal until the following year and did not appear in print until November 23, 2000, one and a half years after commercial approval had been granted. The cardiovascular data reported in that article were incomplete, in part because of incomplete ascertainment: the design and execution of the trial had not anticipated that untoward cardiovascular events might occur.[1]

It was not until February 8, 2001, that the FDA Arthritis Advisory Committee met to discuss concern about the potential cardiovascular risks associated with rofecoxib. It remains unclear why the FDA waited two years after its review and approval of rofecoxib to conduct this meeting. My colleagues and I reviewed the data from the meeting that were made publicly accessible and published an analysis of all the available data on rofecoxib and celecoxib on August 22, 2001.[2] Our primary conclusion, based on the clear-cut excess number of myocardial infarctions associated with rofecoxib and the numerical, albeit not statistically significant, excess associated with celecoxib, was that "it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents."[2] Such a trial needed to be conducted in patients with established coronary artery disease, who frequently have coexisting osteoarthritis requiring medication and have the highest risk of further cardiovascular events. Given the very high coincidence of coronary disease and arthritis, this group may represent the largest segment of the population for whom rofecoxib was prescribed. In light of the insight that arterial inflammation is the basis for myocardial infarction and stroke and the knowledge that coxibs reduce the production of biomarkers of inflammation such as C-reactive protein and improve endothelial function, such a trial would also have been quite attractive from the standpoint of potential benefit. The trial would have prospectively determined the incidence of cardiovascular events, whose possible association with coxib treatment had not been anticipated in the early and pivotal trials of these drugs.

Unfortunately, such a trial was never done. The FDA has the authority to mandate that a trial be conducted, but it never took the initiative. Instead of conducting such a trial at any point — and especially after the FDA advisory committee meeting in 2001 — Merck issued a relentless series of publications, beginning with a press release on May 22, 2001, entitled "Merck Reconfirms Favorable Cardiovascular Safety of Vioxx" and complemented by numerous papers in peer-reviewed medical literature by Merck employees and their consultants. The company sponsored countless continuing medical "education" symposiums at national meetings in an effort to debunk the concern about adverse cardiovascular effects. The message that was duly re-



Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.

Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

inforced was that rofecoxib had no cardiovascular toxicity: rather, naproxen was cardioprotective. Only by happenstance, in a trial involving 2600 patients with colon polyps who could not have been enrolled if they had had any cardiovascular disease, was it discovered that 3.5 percent of the patients assigned to rofecoxib had myocardial infarction or stroke, as compared with 1.9 percent of the patients assigned to placebo ($P<0.001$), necessitating premature cessation of the trial and the decision to discontinue treatment with rofecoxib.

Over the course of the five-and-a-half-year saga, many epidemiologic studies confirmed and amplified the concern about the risk of myocardial infarction and serious cardiovascular events associated with rofecoxib.[3] These studies considered large populations, up to 1.4 million patients, tracking the use of various nonsteroidal antiinflammatory medications or coxibs to determine the risk of adverse events. Each time a study was presented or published, there was a predictable and repetitive response from Merck, which claimed that the study was flawed and that only randomized, controlled trials were suitable for determining whether there was any risk. But if Merck would not initiate an appropriate trial and the FDA did not ask them to do so, how would the truth ever be known?

Meanwhile, Merck was spending more than $100 million per year in direct-to-consumer advertising — another activity regulated by the FDA and a critical mechanism in building the "blockbuster" status of a drug with annual sales of more than $1 billion. For the past few years, every month has seen more than 10 million prescriptions for rofecoxib written in the United States alone. At any point, the FDA could have stopped Merck from using direct-to-consumer advertising, especially given the background concern that the cardiovascular toxicity was real and was receiving considerable confirmation in multiple studies conducted by investigators who were independent of Merck. The only significant action taken by the FDA occurred on April 11, 2002, when the agency instructed Merck to include certain precautions about cardiovascular risks in its package insert. The FDA also sponsored one of the large epidemiologic studies performed in a cohort of Kaiser Permanente patients.

Considering the tens of millions of patients who were taking rofecoxib, we are dealing with an enormous public health issue. Even a fraction of a percent excess in the rate of serious cardiovascular events would translate into thousands of affected people. Given the finding in the colon-polyp trial in low-risk patients without known cardiovascular disease — an excess of 16 myocardial infarctions or strokes per 1000 patients — there may be tens of thousands of patients who have had major adverse events attributable to rofecoxib (see Figure).

I believe that there should be a full Congressional review of this case. The senior executives at Merck and the leadership at the FDA share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health. Sadly, it is clear to me that Merck's commercial interest in rofecoxib sales exceeded its concern about the drug's potential cardiovascular toxicity. Had the company not valued sales over safety, a suitable trial could have been initiated rapidly at a fraction of the cost of Merck's direct-to-consumer advertising campaign. Despite the best efforts of many investigators to conduct and publish meaningful independent research concerning the cardiovascular toxicity of rofecoxib, only the FDA is given the authority to act. In my view, the FDA's passive position of waiting for data to accrue is not acceptable, given the strong signals that there was a problem and the vast number of patients who were being exposed. Furthermore, the tradeoff here involved a drug for symptoms of arthritis, for which many alternative medications are available, in the

Meta-analisi: guidelines

The Cochrane Collaboration
Trusted evidence. Informed decisions. Better health.

COCHRANE 20 years
GO TO THE 20TH ANNIVERSARY SITE

to The Cochrane Library

Home | About us | Cochrane Reviews | News & Events | Training | Multimedia | Contact | Community | Search site | go

Home › About us › Webliography of evidence-based health care resources › Books, articles & online resources › Reporting guidelines

About us
- Our principles
- Our policies
- History
- Newcomers' guide
- Reports
- Relations with the World Health Organization
- Evidence-based health care
- Webliography of evidence-based health care resources
  - Books, articles & online resources
    - Clinical guidelines
    - Clinical studies
    - Critical appraisal
    - Epidemiology & statistics

Reporting guidelines

This selection of resources does not aim to be comprehensive, but it is updated regularly, and we welcome suggestions for additions at web@cochrane.org.

MECIR - Methodological Expectations of Cochrane Intervention Reviews

Equator Network - Enhancing the QUAlity and Transparency Of health Research

The EQUATOR Network maintains the *Library for health research reporting* providing direct links to the following key reporting guidelines, also including their bibliographic references, lists of all relevant literature, and links to all available translations.

CONSORT Consolidated Standards Of Reporting Trials
Full Record | Checklist | Flow Diagram

STROBE STrengthening the Reporting of OBservational studies in Epidemiology
Full Record | Checklist

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Full Record | Checklist | Flow Diagram

STARD Standards for Reporting Studies of Diagnostic Accuracy
Full Record | Checklist | Flow Diagram

Meta-analisi: guidelines

Equator Network - Enhancing the QUAlity and Transparency Of health Research

The EQUATOR Network maintains the *Library for health research reporting* providing direct links to the following key reporting guidelines, also including their bibliographic references, lists of all relevant literature, and links to all available translations.

CONSORT Consolidated Standards Of Reporting Trials
Full Record | Checklist | Flow Diagram

STROBE STrengthening the Reporting of OBservational studies in Epidemiology
Full Record | Checklist

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Full Record | Checklist | Flow Diagram

STARD Standards for Reporting Studies of Diagnostic Accuracy
Full Record | Checklist | Flow Diagram

COREQ Consolidated criteria for reporting qualitative research
Full Record

ENTREQ Enhancing transparency in reporting the synthesis of qualitative research
Full Record

SQUIRE Publication guidelines for quality improvement in health care
Full Record | Checklist

CHEERS Consolidated Health Economic Evaluation Reporting Standards
Full Record | Checklist

CARE Consensus-based Clinical Case Reporting Guideline Development
Full Record | Checklist

SAMPL Basic Statistical Reporting for Articles Published in Biomedical Journals: The "Statistical Analyses and Methods in the Published Literature"
Full Record

Meta-analisi: dispositivi medici

BMJ

RESEARCH

Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis

The most commonly used methods for skin closure after orthopaedic surgery are metal staples or nylon sutures.[1 3] Both methods act to hold the skin edges together while healing occurs. Metal staples are said to be superior as they are regarded as quicker and easier than sutures.[6-8] Other authors have suggested that use of metal staples or clips has a greater risk of wound infection[4] and might be less acceptable cosmetically than sutures.[2] Metal staples might also be more expensive.[2 9 10]

Objective To compare the clinical outcomes of staples versus sutures in wound closure after orthopaedic surgery.

BMJ 2010;340:c1199

Meta-analisi: dispositivi medici

BMJ

RESEARCH

Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis

Data sources Medline, CINAHL, AMED, Embase, Scopus, and the Cochrane Library databases were searched, in addition to the grey literature, in all languages from 1950 to September 2009. Additional studies were identified from cited references.

Selection criteria Two authors independently assessed papers for eligibility. Included studies were randomised and non-randomised controlled trials that compared the use of staples with suture material for wound closure after orthopaedic surgery procedures. All studies were included, and publications were not excluded because of poor methodological quality.

Review methods Two authors independently reviewed studies for methodological quality and extracted data from each paper. Final data for analysis were collated through consensus. The primary outcome measure was the assessment of superficial wound infection after wound closure with staples compared with sutures. Relative risk and mean difference with 95% confidence intervals were calculated and pooled with a random effects model. Heterogeneity was assessed with I^2 and χ^2 statistical test.

CdL

BMJ 2010;340:c1199

BMJ

Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis

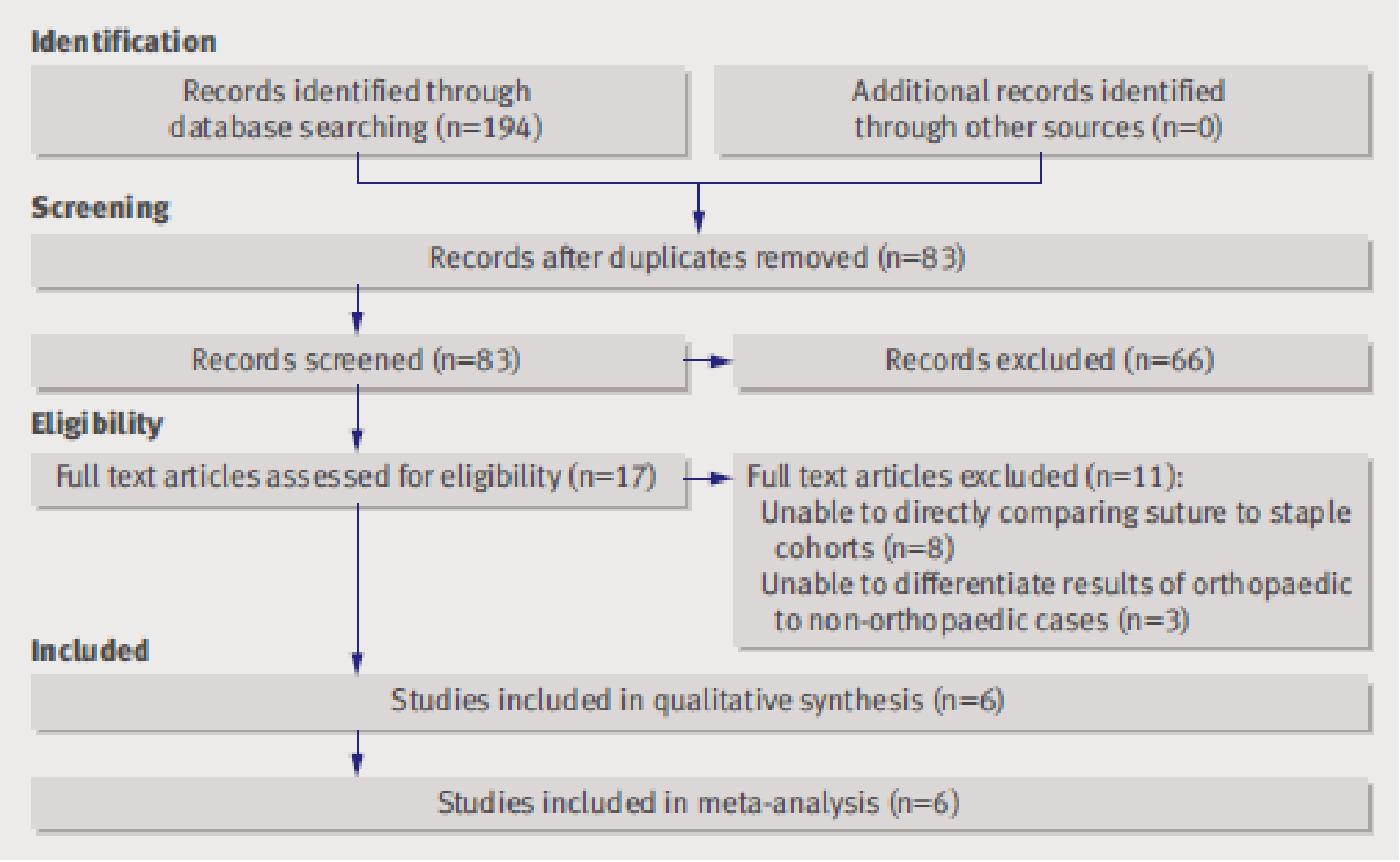
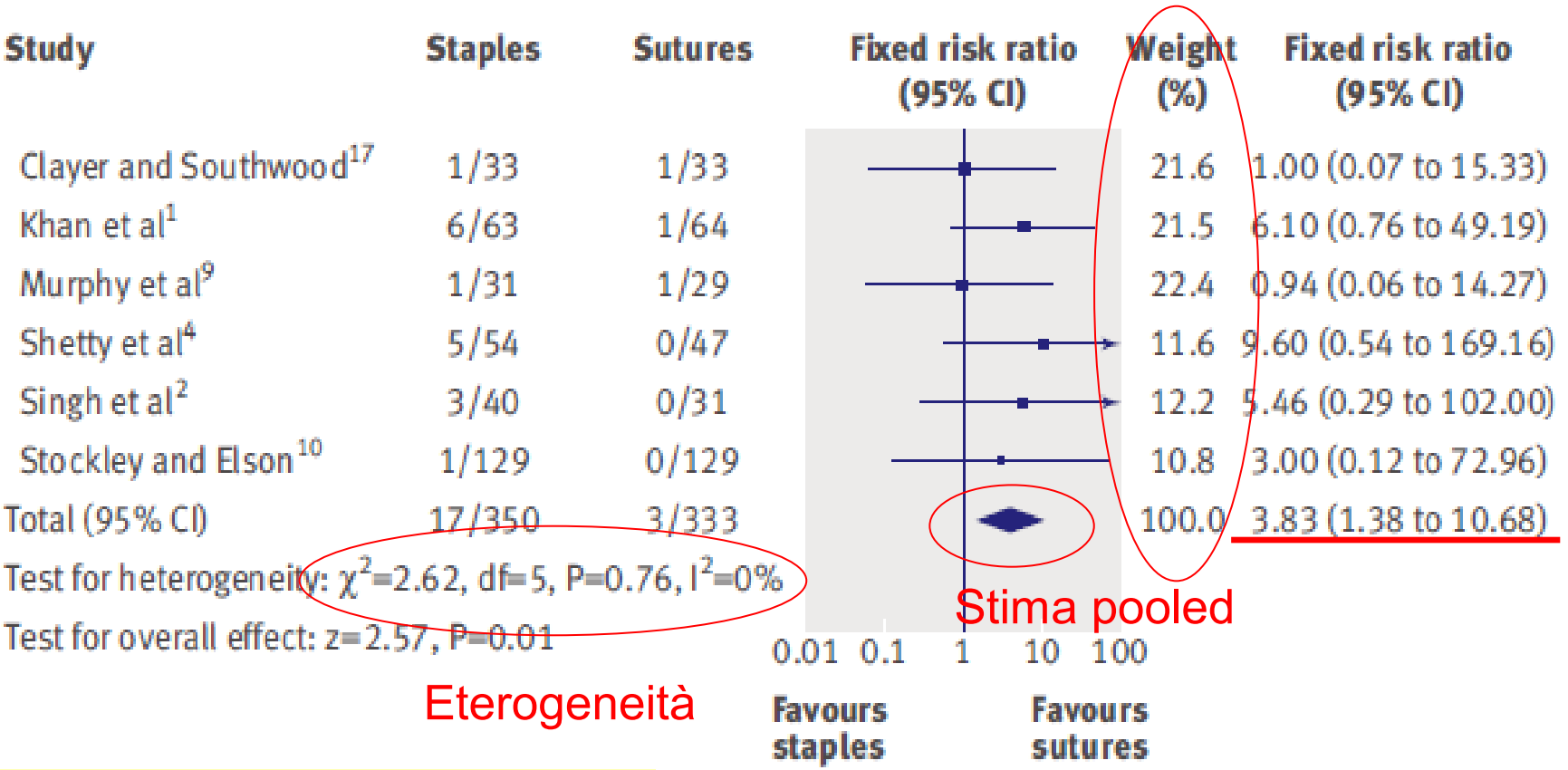


Fig 1| Flow of identified studies

Forest plot

Peso degli studi



Stima pooled

Eterogeneità

È dovuta a fattori clinici o metodologici, e viene calcolata con i seguenti test:
Cochran's Q (eterog. se P < 0,10)
Higgins I^2 (eterog. se I^2 > 50%)

Risultato numerico della metanalisi (non è una media; dà maggior peso agli studi che forniscono maggiori informazioni)

BMJ 2010;340:c1199

BMJ

Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis

Results Six papers, which included 683 wounds, were identified; 332 patients underwent suture closure and 351 staple closure. The risk of developing a superficial wound infection after orthopaedic procedures was over three times greater after staple closure than suture closure (relative risk 3.83, 95% confidence interval 1.38 to 10.68; P=0.01). On subgroup analysis of hip surgery

Meta-analisi: pros & cons

VANTAGGI

- ✓ quadro riassuntivo di quell'argomento
- ✓ dimensione campione più grossa e maggiore potenza
- ✓ possibilità di effettuare analisi di sottogruppi

SVANTAGGI

- ✓ publication bias
- ✓ selection bias
- ✓ eterogeneità degli studi