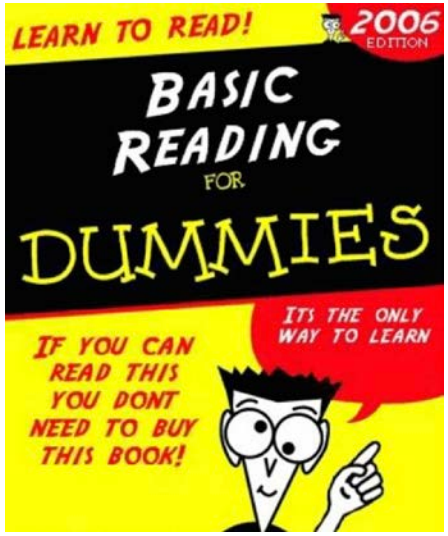


Come (e Perchè) Leggere una Meta-Analisi.

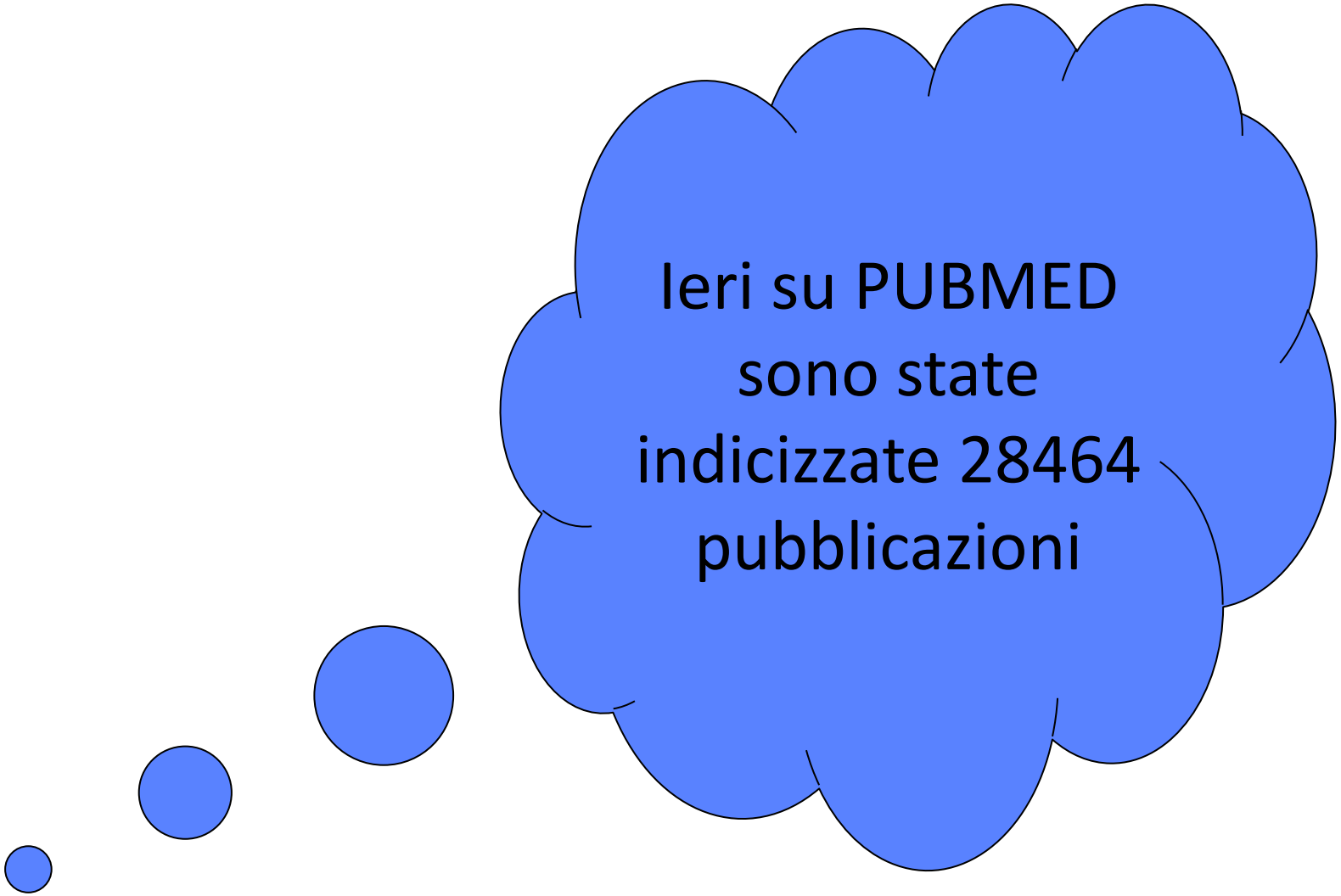
(e quando non leggerla…)

Francesco Dentali
Dipartimento di Medicina Clinica
Università dell' Insubria, Varese

Conflitti di Interesse

Letture
Protocolli di Ricerca
Advisory Boards

- Bayer
- BMS/Pfizer
- Boehringer
- Daiichi
- Sanofi
- Alfa Wasserman


Ieri su PUBMED
sono state
indicizzate 28464
pubblicazioni

THE
LITERATURE
OF
MEDICINE

How to Keep Up with the Medical Literature: V. Access by Personal Computer to the Medical Literature

R. BRIAN HAYNES, M.D., Ph.D.; K. ANN McKIBBON, M.L.S.; DOROTHY FITZGERALD, M.L.S.; GORDON H. GUYATT, M.D., M.Sc.; CYNTHIA J. WALKER, M.L.S.; and DAVID L. SACKETT, M.D., M.Sc.Epid.; Hamilton, Ontario, Canada

Access to the medical literature through personal computers is now readily available and can greatly reduce logistical barriers to using recently published journal articles to support clinical decisions. In this article, we describe many of the options available to clinicians who wish to do their own computer searching of MEDLINE, the largest of the electronic services for the biomedical literature. The "bare bones" computer equipment needed includes a terminal or personal computer, a modem and telephone line, and a printer. Access to MEDLINE is then gained through subscribing to any of a burgeoning number of database vendors. A comparison of 17 permutations and combinations of software and vendors shows that the software and vendors vary substantially in efficiency, cost, and ease of use. Direct subscription to MEDLINE is least expensive, PaperChase is the simplest service to use, and Colleague and Medis provide both MEDLINE access plus full-text journals online. Basic search techniques are illustrated for three clinical problems.

IN PREVIOUS ARTICLES in this series, we have discussed critical appraisal of published medical literature (1), methods for regular surveillance of the literature (2), and ways to search the literature to find the best published evidence concerning specific clinical problems (3). In this article, we describe how to gain fingertip access to the medical literature through a personal computer. Let's start with a clinical example.

Your patient, a 23-year-old college student with insulin-dependent diabetes, is developing early signs of retinopathy. She asks whether further retinopathy could be prevented if she were to keep her blood sugar levels under very tight control with an insulin pump. Although you know that insulin pumps can achieve close to normal blood sugar levels, you cannot recall having read anything definitive about their value in slowing or reversing retinopathy.

You excuse yourself from the patient and step into the room that contains your office computer. You interrupt its billing routine and type in four letters that stand for the computer program that connects you with the National Library of Medicine's (NLM) current MEDLINE file (*see* the Appendix for addresses and telephone numbers for all computer information services mentioned in this article). The system gives you a polite computer welcome, and then you type in the terms *diabetic retinopathy and insulin infusion systems*. MEDLINE replies that 38 articles are classified with both these descriptors. You then type in *1 and random allocation* (the *1* stands for the first search statement you typed in). MEDLINE replies that just 4 articles meet all three criteria you have indicated (4-7). You ask for a printout of the titles, authors, and abstracts of these articles. The online search time for the session was less than 2 minutes, and the search charge was just $0.93.

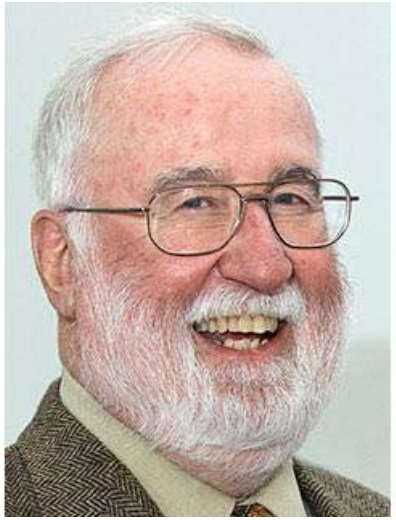
One of the articles (6) that MEDLINE selected is in a recent issue of *The New England Journal of Medicine*, so you direct your computer to contact the Colleague full-text service of BRS/Saunders and ask for a printout of the complete article. You scan the abstracts of the articles retrieved from the first search and then the methods section of the full-text article as your high-speed printer churns it out. One article reports a trial that is in progress (5), and the others provide the results of controlled trials. The findings of these studies are in accordance. They report greater deterioration in retinal structure in patients treated with infusion pumps, though the studies are small and none reports on major outcomes such as blindness. Thus, although the findings are not definitive, these initial studies give rise to caution.

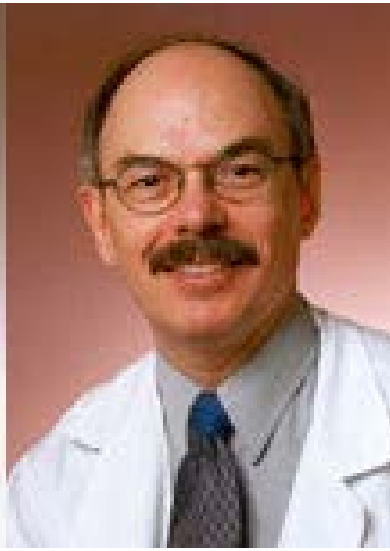
You return to the patient, whose mild annoyance at having been kept waiting for 10 minutes turns to amazed admiration when you hand her a copy of the abstracts and indicate that you do not feel pump therapy has yet shown that it can be helpful in controlling diabetic retinopathy. You inform her that her retinopathy is mild as far as you can discern and that you are referring her to an ophthalmologist for further assessment. You reassure her that there are well-established and effective treatments for retinopathy and that the ophthalmologist will arrange for these should they be required.

Romancing the Literature Electronically

If you think that the clinical scenario just described is far-fetched, then you have not been keeping track of recent developments in user-friendly electronic access to medical information. It is now possible and reasonably straightforward for clinicians (called "end-users" in computer-speak) to retrieve highly pertinent information from huge literature databases in order to support clinical decisions that must be made immediately (that is, in "real time" in computer jargon). For example, two surgeons recently reported consulting the medical literature on line in the midst of an operation (8). One of the surgeons was doing an exploratory laparotomy on a patient with an undiagnosed abdominal mass that proved, on frozen section, to be sclerosing mesenteritis. Not being conversant with this condition, he notified his partner who

► From the Program for Educational Development, Departments of Clinical Epidemiology and Biostatistics and of Medicine, and the Health Sciences Library, McMaster University Faculty of Health Sciences; Hamilton, Ontario, Canada.





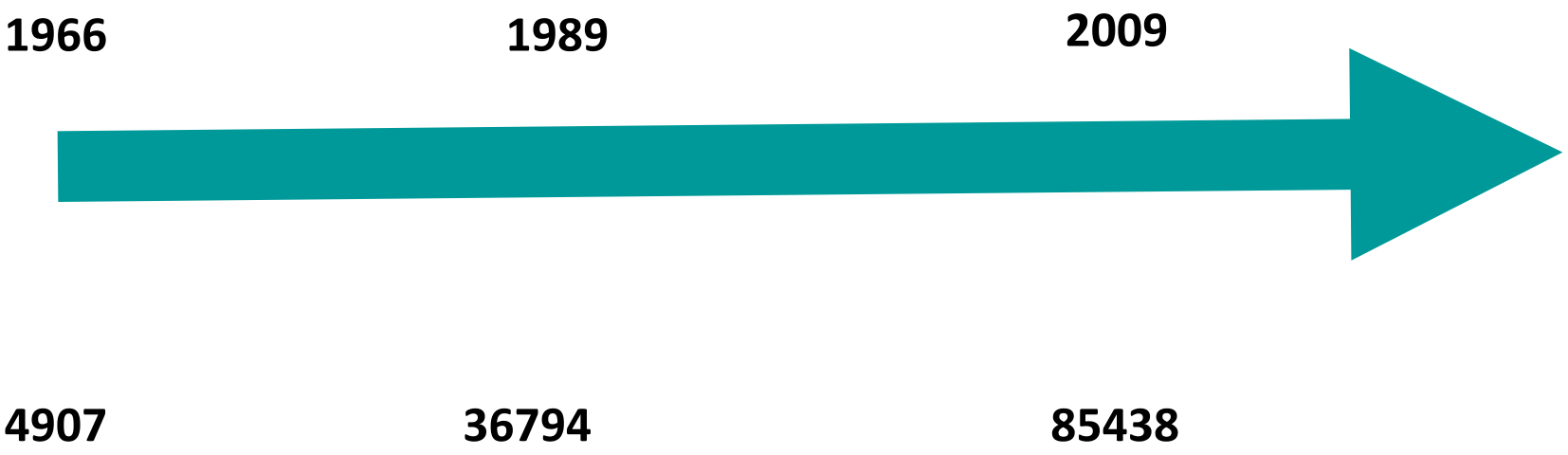
Tempo Medio per leggere un articolo scientifico

Minuti

PubMed
www.pubmed.gov

A service of the National Library of Medicine
and the National Institutes of Health

Revisioni



Article types clear
Clinical Trial
✓ Meta-Analysis
Review
Customize ...

Text availability
Abstract
Free full text
Full text

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Clear all

Show additional filters

Search results

Items: 1 to 20 of 175

« First ‹ Prev Page 1 of 9 Next › Last »

Filters activated: Meta-Analysis. Clear all to show 4227 items.

1. Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation.
   Kahale LA, Hakoum MB, Tsolakian IG, Matar CF, Barba M, Yosuico VED, Terrenato I, Sperati F, Schünemann H, Akl EA.
   Cochrane Database Syst Rev. 2017 Dec 29;12:CD006466. doi: 10.1002/14651858.CD006466.pub6. Review.
   PMID: 29285754
   Similar articles

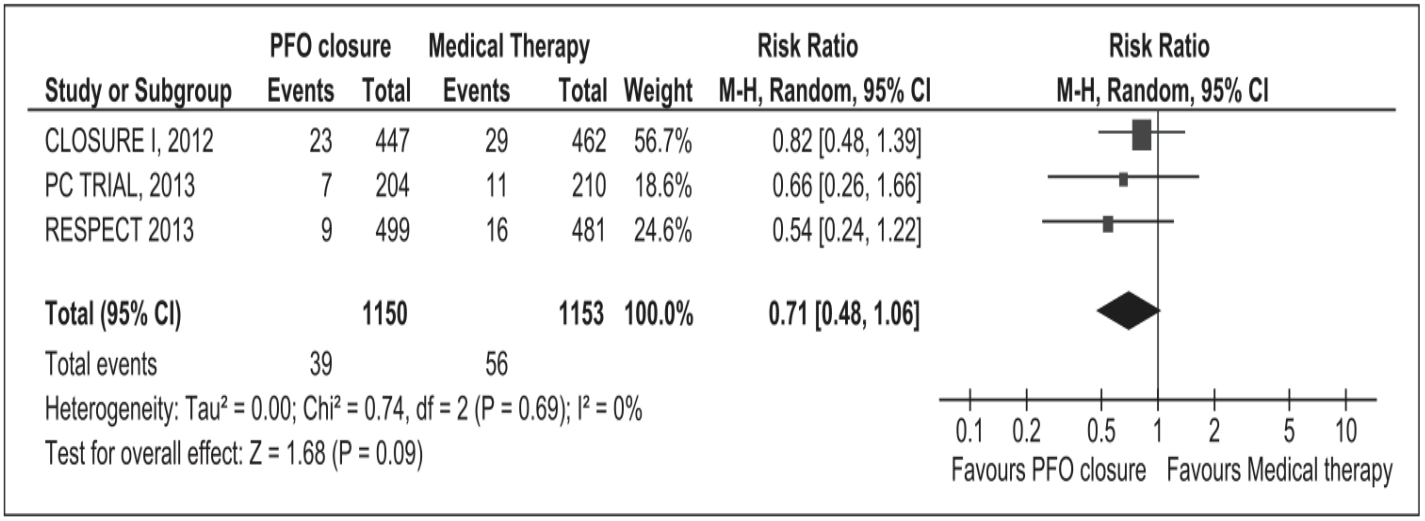
2. Secondary prevention of recurrent **venous thromboembolism** after initial oral anticoagulation therapy in patients with unprovoked **venous thromboembolism**.
   Robertson L, Yeoh SE, Ramli A.
   Cochrane Database Syst Rev. 2017 Dec 15;12:CD011088. doi: 10.1002/14651858.CD011088.pub2. Review.
   PMID: 29244199
   Similar articles

3. Comparative efficacy and safety of anticoagulants for prevention of **venous thromboembolism** after hip and knee arthroplasty.
   Hur M, Park SK, Koo CH, Jung ED, Kang P, Kim WH, Kim JT, Jung CW, Bahk JH.
   Acta Orthop. 2017 Dec;88(6):634-641. doi: 10.1080/17453674.2017.1361131. Epub 2017 Aug 8. Review.
   PMID: 28787226 Free PMC Article
   Similar articles

4. Oral anticoagulants for prevention of stroke in **atrial fibrillation**: systematic review, network **meta-analysis**, and cost effectiveness analysis.
   López-López JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, Davies PA, Bodalia PN, Bryden PA, Welton NJ, Hollingworth W, Caldwell DM, Savović J, Dias S, Salisbury C, Eaton D, Stephens-Boal A, Sofat R.
   BMJ. 2017 Nov 28;359:j5058. doi: 10.1136/bmj.j5058. Review. Erratum in: BMJ. 2017 Dec 4;359:j5631.
   PMID: 29183961 Free PMC Article

Efficacy and safety of patent foramen ovale closure in patients with a cryptogenic stroke: Systematic review and meta-analysis

Francesco Dentali[1]; Monica Gianni[2]; Nicola Mumoli[3]; Marco Cei[3]; Andrea Bertolini[1]; Luigina Guasti[1]; Walter Ageno[1]



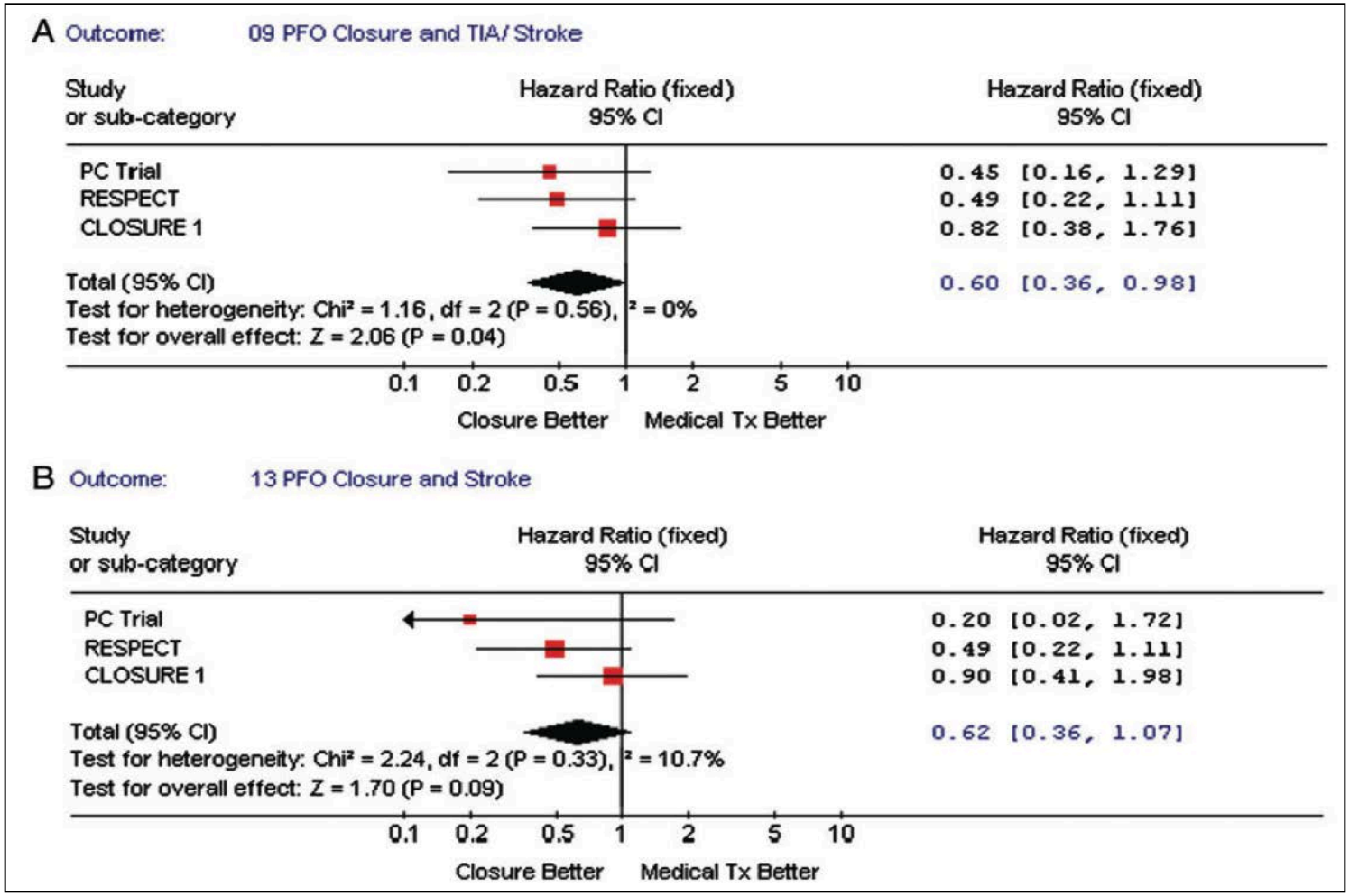
Study or Subgroup	PFO closure Events	Total	Medical Therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CLOSURE I, 2012	23	447	29	462	56.7%	0.82 [0.48, 1.39]
PC TRIAL, 2013	7	204	11	210	18.6%	0.66 [0.26, 1.66]
RESPECT 2013	9	499	16	481	24.6%	0.54 [0.24, 1.22]
Total (95% CI)		**1150**		**1153**	**100.0%**	**0.71 [0.48, 1.06]**
Total events	39		56			

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 1.68 (P = 0.09)

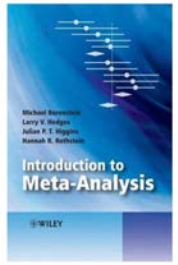
Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials

Pablo Rengifo-Moreno[1], Igor F. Palacios[2], Parichart Junpaparp[3], Christian F. Witzke[1], D. Lynn Morris[1,4], and Abel Romero-Corral[1,5]*



- Review Narrativa
- Review Sistematica
- Meta-analisi (Network,IPMA)

Meta-Analysis



Meta-analysis refers to the statistical synthesis of results from a series of studies. While the statistical procedures used in a **meta-analysis can be applied to any set of data**, the **synthesis** will be **meaningfu**l only if the studies have been collected **systematically.**

If a treatment effect (or effect size) is **consistent** across the series of studies, these procedures enable us to report that the **effect is robust across the kinds of populations** sampled, and also to estimate the **magnitude of the effect more precisely** than we could with any of the studies alone.

Borenstein et al; Introduction to Meta-Analysis

Storia

- Il primo tentativo di combinare mediante tecniche statistiche dati diversi risale al 1904
- La prima meta-analisi che ha valutato l'effetto di un intervento terapeutico (vs placebo) risale al 1955
- Il termine meta-analisi è stato coniato da Glass nel 1976
- Dal 1988 i medici ricercatori hanno riscoperto l'utilizzo delle meta-analisi

Scopi

- Uno studio singolo spesso non ha la capacità di trovare o escludere con sicurezza una differenza clinica tra due diversi trattamenti

  (Errore di tipo II)

Scopi

- Nella meta-analisi dati provenienti da “piccoli” studi che valutano un trattamento uguale o simile vengono combinati

- La meta-analisi può essere quindi una valida e più economica alternativa a studi grandi e molto costosi

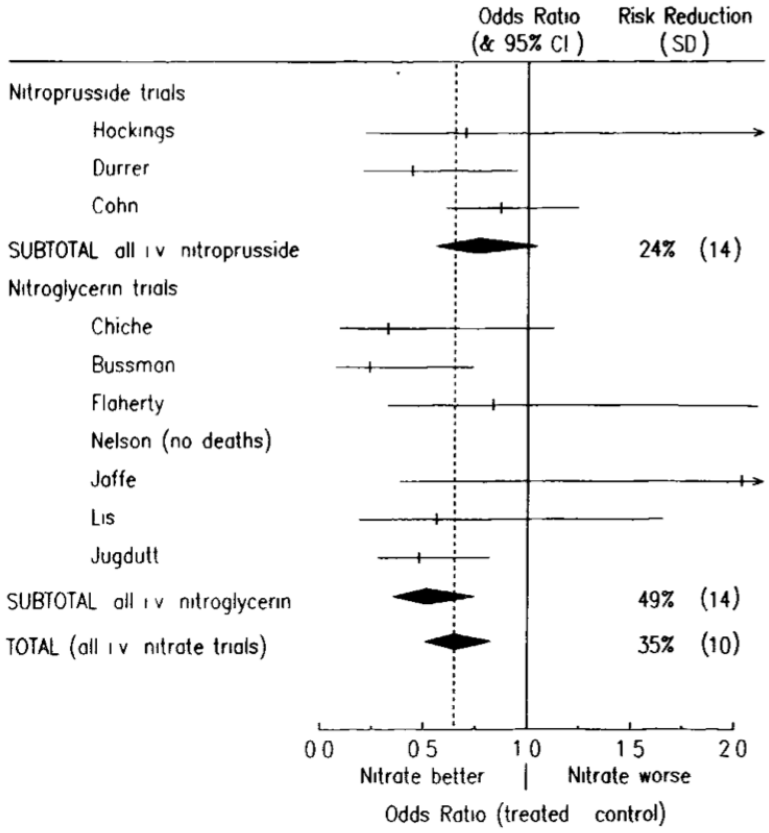
Therapeutics

EFFECT OF INTRAVENOUS NITRATES ON MORTALITY IN ACUTE MYOCARDIAL INFARCTION: AN OVERVIEW OF THE RANDOMISED TRIALS

SALIM YUSUF[1,2] RORY COLLINS[1,3]
STEPHEN MACMAHON[1,2] RICHARD PETO[1]

ISIS Trials Office, Clinical Trial Service Unit, Radcliffe Infirmary, Oxford OX2 6HE;[1] Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20892, USA;[2] Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford[3]

THE LANCET, MAY 14, 1988



Apparent effects of intravenous nitroprusside and nitroglycerin on mortality in the randomised trials of the treatment of acute myocardial infarction.

Vertical stroke = odds ratio.

Horizontal line = 95% CI; a 95% CI that does not include 1·0 indicates a statistically significant difference ($2p < 0{\cdot}05$) in mortality between the treatment groups,

Broken line = "Typical" odds ratio indicated by an overview of all intravenous nitrate trials.

Evoluzione

- Inizialmente, venivano considerate accettabili solo meta-analisi di RCT

- Attualmente vengono considerate accettabili anche MA di studi osservazionali, anche se tale opinione non è condivisa da tutti (garbage in, garbage out)

- I metodi utilizzati nello sviluppo della MA sono però fondamentali nella valutazione della stessa

Punto di Partenza

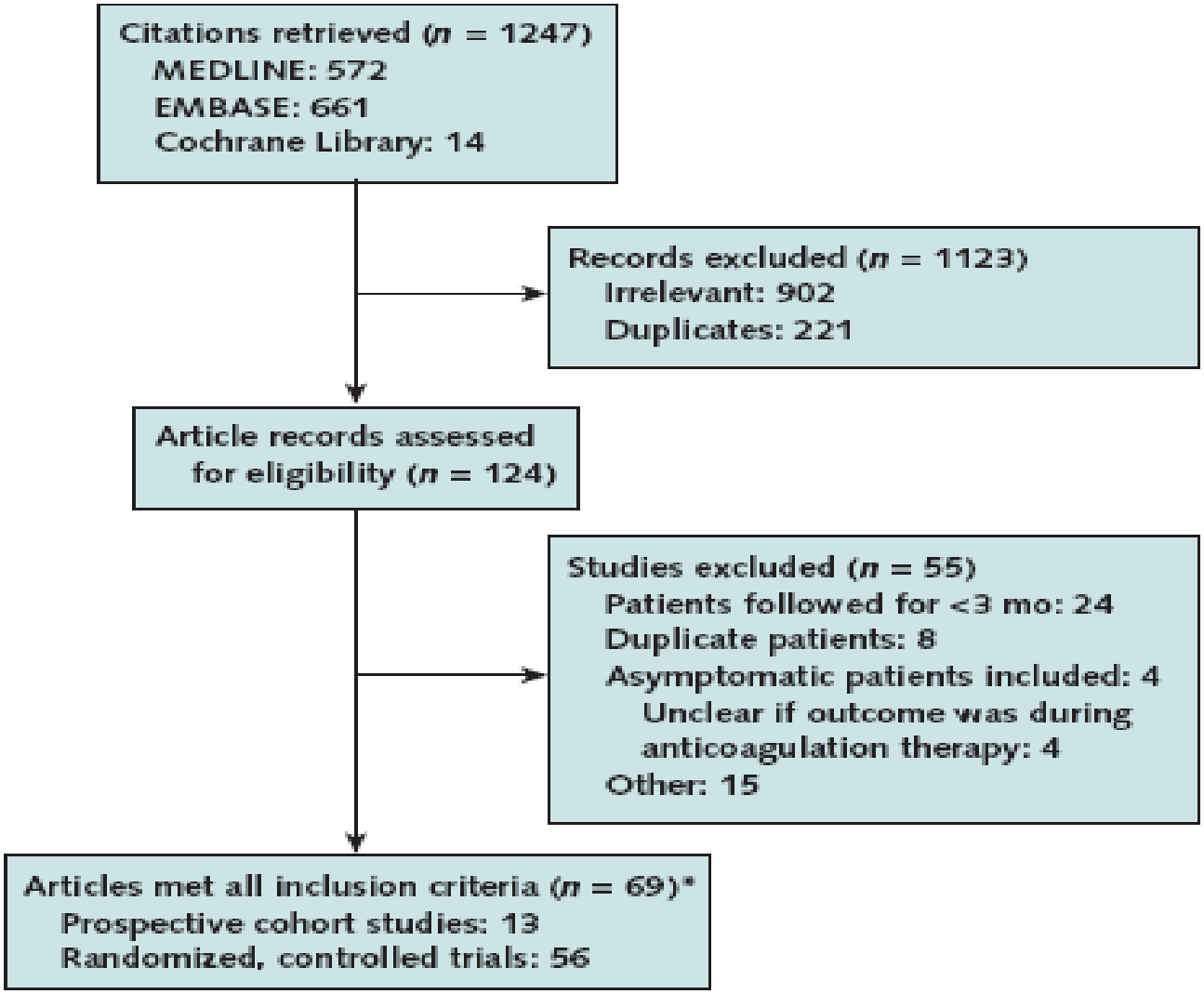
Le MA sono generate per rispondere ad una specifica domanda che deve essere formulata secondo 4 variabili

- Popolazione scelta (popolazione anziana ambulatoriale)
- Condizione di interesse (ipertensione)
- Esposizione ad un test o ad un trattamento (terapia con ace-inibitori)
- Uno o più outcomes (eventi cerebrovascolari, mortalità)

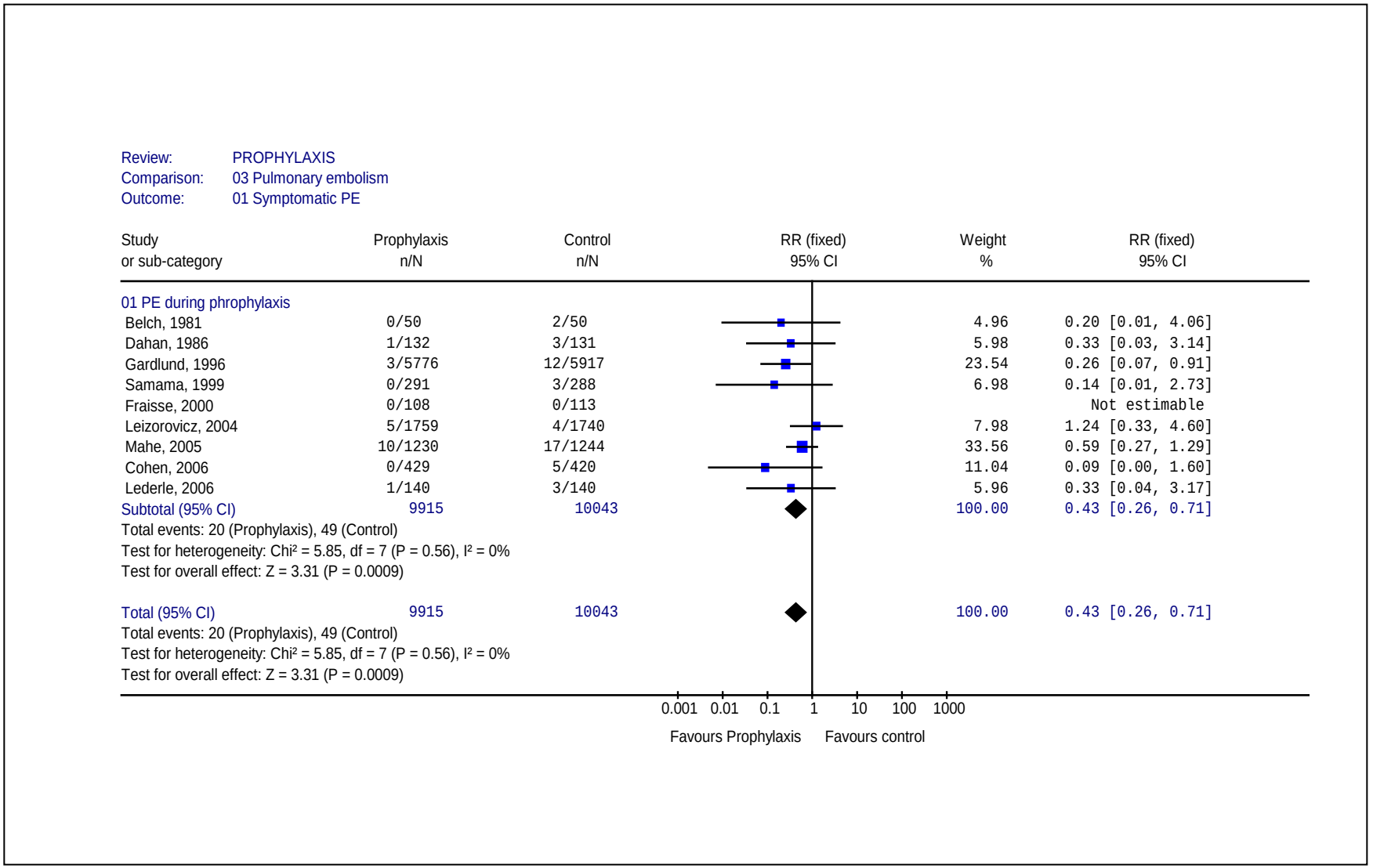
Appendix Table 1. **Systematic Search Strategy**

1	exp Thrombosis/
2	exp Venous Thrombosis/
3	Thromb$.ti,ab.
4	phlebothrombosis.mp.
5	Deep vein thrombosis.mp.
6	or/1–5
7	exp Therapeutics/
8	Treat$.ti,ab.
9	treatment.mp.
10	exp Drug therapies/
11	exp Therapies, Investigational/
12	exp Anticoagulant/
13	exp Heparin/
14	exp Heparin, low-molecular-weight/
15	Pentassacharide$.mp
16	Fondaparinux.mp
17	Ximelagatran.mp
18	Direct thrombin inhibitor.mp
19	or/7–18
20	6 and 19.

Appendix Figure. Study flow diagram.

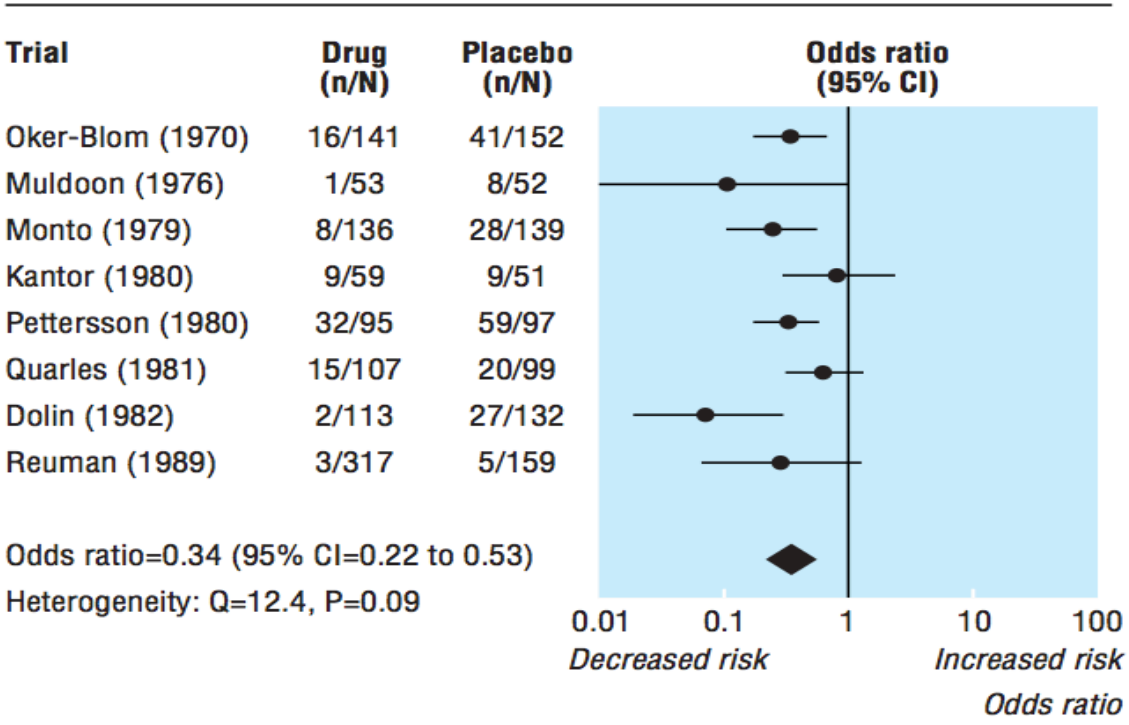


Forrest Plot



Measuring inconsistency in meta-analyses

Julian P T Higgins, Simon G Thompson, Jonathan J Deeks, Douglas G Altman

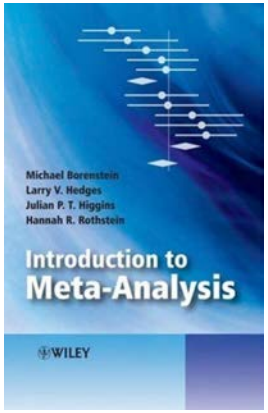


Advantages of I^2

- Focuses attention on the effect of any heterogeneity on the meta-analysis
- Interpretation is intuitive—the percentage of total variation across studies due to heterogeneity
- Can be accompanied by an uncertainty interval
- Simple to calculate and can usually be derived from published meta-analyses
- Does not inherently depend on the number of studies in the meta-analysis
- May be interpreted similarly irrespective of the type of outcome data (eg dichotomous, quantitative, or time to event) and choice of effect measure (eg odds ratio or hazard ratio)
- Wide range of applications

$$I^2 = 100\% \times (Q - df)/Q$$

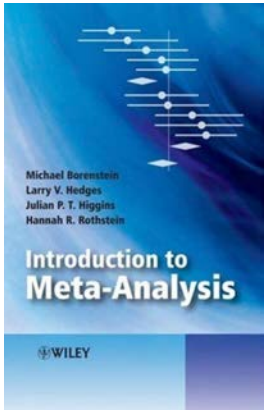
Fixed effect model



SUMMARY POINTS

- Under the fixed-effect model all studies in the analysis share a common true effect.
- The summary effect is our estimate of this common effect size, and the null hypothesis is that this common effect is zero (for a difference) or one (for a ratio).
- All observed dispersion reflects sampling error, and study weights are assigned with the goal of minimizing this within-study error.

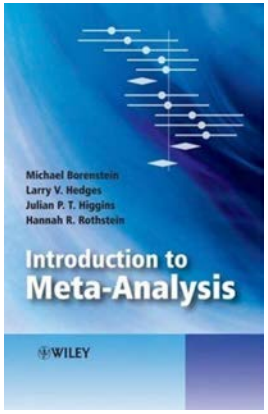
Random effect model



SUMMARY POINTS

- Under the random-effects model, the true effects in the studies are assumed to have been sampled from a distribution of true effects.
- The summary effect is our estimate of the mean of all relevant true effects, and the null hypothesis is that the mean of these effects is 0.0 (equivalent to a ratio of 1.0 for ratio measures).
- Since our goal is to estimate the mean of the distribution, we need to take account of two sources of variance. First, there is within-study error in estimating the effect in each study. Second (even if we knew the true mean for each of our studies), there is variation in the true effects across studies. Study weights are assigned with the goal of minimizing both sources of variance.

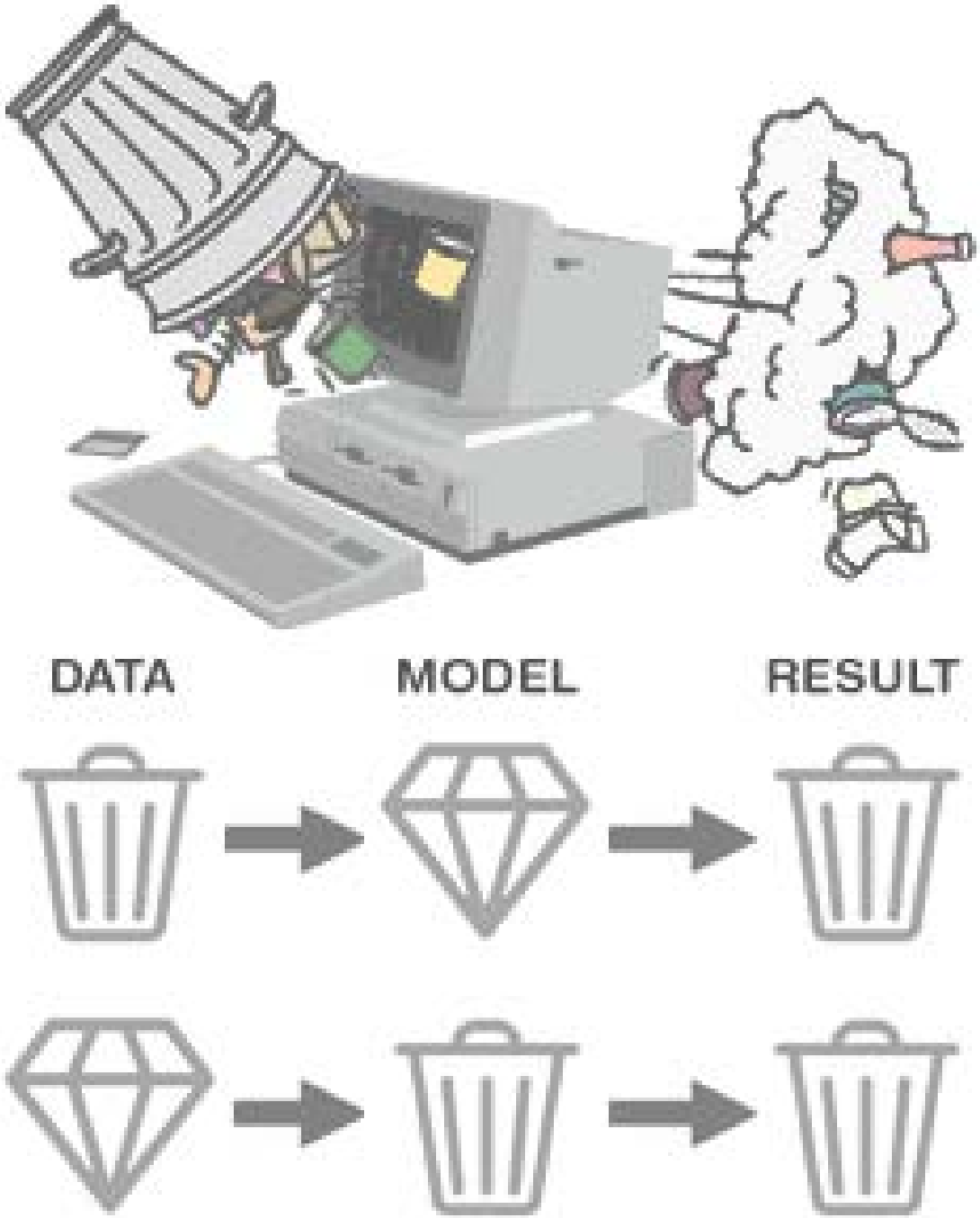
Fixed vs Random



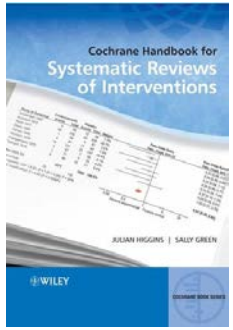
MODEL SHOULD NOT BE BASED ON THE TEST FOR HETEROGENEITY

This test is based on the amount of between-studies variance observed, relative to the amount we would expect if the studies actually shared a common effect size.

Some have adopted the practice of starting with a fixed-effect model and then switching to a random-effects model if the test of homogeneity is statistically significant. This practice should be strongly discouraged because the decision to use the random-effects model should be based on our understanding of whether or not all studies share a common effect size, and not on the outcome of a statistical test (especially since the test for heterogeneity often suffers from low power).


DATA
MODEL
RESULT

Chapter 8: Assessing risk of bias in included studies



Editors: Julian PT Higgins and Douglas G Altman on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group.

Domain	Description	Review authors' judgement
Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Analisi Dati

(Endpoint binario)

- Rischio assoluto (RA)
- Rischio relativo (RR)
- Riduzione del rischio assoluto (RRA)
- Number needed to treat (NNT) or number needed to harm (NNH)
- Odds, odds ratio (OR)

Sintesi dei Dati

- Rischio assoluto: probabilità che un evento si verifichi
- Rischio relativo: rischio nel gruppo di trattamento relativo al gruppo di controllo (R_1/R_2)
- Riduzione del rischio assoluto: rischio nel gruppo di trattamento – il rischio nel gruppo di controllo
- NNT: reciproco della riduzione del rischio assoluto di un particolare trattamento (1/RRA). Esprime il numero dei pazienti che devono essere trattati per prevenire un evento

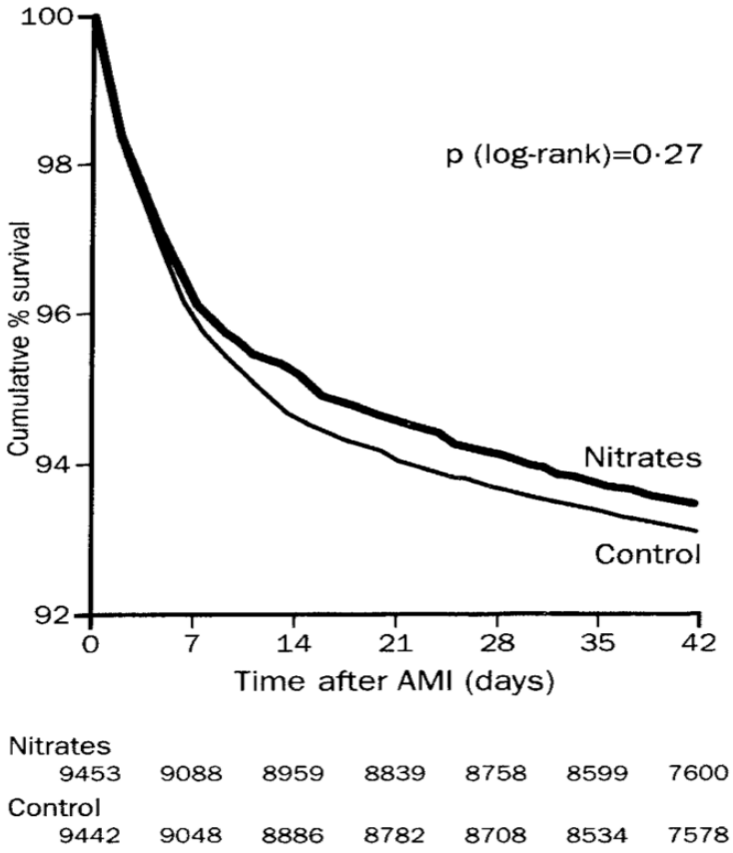
Attenzione!!!
RR di raggiungere l'end-point è 0.30 con il farmaco rispetto al placebo

- Eventi nel gruppo placebo 10/10000
- Eventi nel gruppo farmaco 3/10000
- RRA: 0.07/100 pz
- NNT: 1429

- Eventi nel gruppo placebo 10/100
- Eventi nel gruppo farmaco 3/100
- RRA: 7/100 pz
- NNT: 14

GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction

*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico**



	Nitrates (n=9453)	Controls (n=9442)	OR (95% CI)	2p*
No of deaths (%)	617 (6 5)	653 (6 9)	0 94 (0 84–1 05)	0 28
Combined endpoint events (%)	1502 (15 9)	1580 (16 7)	0 94 (0 87–1 02)	0 12
Deaths	617 (6 5)	653 (6 9)		
Clinical heart failure	357 (3 8)	363 (3 8)		
EF ⩽35%	483 (5 1)	498 (5 3)		
AD score ⩾45%	45 (0 5)	66 (0 7)		

Individual patient Meta-analysis

- Ricerca della letteratura simile alle meta-analisi tradizionali.
- Dati originali dai singoli studi (creazione di un unico database)
- Analisi per sottogruppi/endpoints singoli

Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials

	All trials			Multicentre trials			Single-centre trials		
	LMWH (n=480)	No LMWH (n=483)	Absolute difference (95% CI), p value	LMWH (n=288)	No LMWH (n=291)	Absolute difference (95% CI), p value	LMWH (n=192)	No LMWH (n=192)	Absolute difference (95% CI), p value
Primary composite outcome of early-onset or severe pre-eclampsia, or SGA <5th percentile, or placental abruption, or pregnancy loss ≥ 20 weeks' gestation*	62/444 (14%)	95/433 (22%)	−8·0% (−17·3 to 1·4), p=0·09	47/263 (18%)	47/255 (18%)	−0·6% (−10·4 to 9·2), p=0·91	15/181 (8%)	48/178 (27%)	−18·7% (95% CI −21·6 to −15·7), p<0·0001
Secondary outcomes									
Placental abruption	15/469 (3%)	31/474 (7%)	−3·3% (−6·7 to −0·1), p=0·0491	5/277 (2%)	7/282 (2%)	−0·7% (−4·0 to 2·6), p=0·69	10/192 (5%)	24/192 (13%)	−7·3% (−9·0 to −5·6), p<0·0001
Placental abruption leading to delivery	5/469 (1%)	10/474 (2%)	−1·0% (−2·4 to 0·3), p=0·14	3/277 (1%)	5/282 (2%)	†	2/192 (1%)	5/192 (3%)	†
Any pregnancy loss*	46/477 (10%)	64/478 (13%)	−3·8% (−9·5 to 2·0), p=0·20	30/285 (11%)	37/286 (13%)	−2·4% (−11·3 to 6·5), p=0·60	16/192 (8%)	27/192 (14%)	−5·7% (−7·8 to −3·7), p<0·0001
Pre-eclampsia§	41/444 (9%)	67/433 (15%)	−6·2% (−13·1 to 0·6), p=0·08	29/263 (11%)	32/255 (13%)	−1·5% (−10·0 to 7·0), p=0·73	12/181 (7%)	35/178 (20%)	−13·0% (−16·4 to −9·6), p<0·0001
Severe pre-eclampsia§	22/442 (5%)	43/433 (10%)	−5·0% (−11·2 to 1·3), p=0·12	19/261 (7%)	19/255 (7%)	−0·2% (−6·4 to 6·0), p=0·96	3/181 (2%)	24/178 (13%)	−11·8% (−16·6 to −7·1), p<0·0001
Early-onset pre-eclampsia§	18/444 (4%)	32/433 (7%)	−3·3% (−7·9 to 1·2), p=0·15	11/263 (4%)	14/255 (5%)	−1·3% (−7·5 to 4·9), p=0·68	7/181 (4%)	18/178 (10%)	−6·2% (−10·5 to −2·0), p=0·0037
Severe or early-onset pre-eclampsia§	31/444 (7%)	51/433 (12%)	−4·8% (−11·6 to 2·0), p=0·17	24/263 (9%)	22/255 (9%)	0·5% (−6·8 to 7·8), p=0·89	7/181 (4%)	29/178 (16%)	−12·4% (−16·5 to −8·4), p<0·0001
HELLP syndrome§	2/384 (1%)	11/370 (3%)	−2·5% (−4·4 to −0·6)(p=0·0112)	1/203 (<1%)	3/192 (2%)	†	1/181 (1%)	8/178 (4%)	†
SGA <10th percentile§	61/444 (14%)	94/429 (22%)	−8·2% (−14·3 to −2·0), p=0·0094	47/263 (18%)	53/251 (21%)	−3·2% (−9·6 to 3·1), p=0·32	14/181 (8%)	41/178 (23%)	−15·3% (−19·1 to −11·5), p<0·0001
SGA <5th percentile§	27/443 (6%)	38/429 (9%)	−2·8% (−5·4 to −0·1), p=0·0417	22/262 (8%)	23/251 (9%)	−0·8% (−3·7 to 0·2), p=0·61	5/181 (3%)	15/178 (8%)	−5·7% (−6·1 to −5·2), p<0·0001
SGA <3rd percentile§	13/443 (3%)	12/429 (3%)	−0·1% (−1·9 to 2·2, p=0·89	13/262 (5%)	9/251 (4%)	1·4% (−1·3 to 4·1), p=0·32	0/181	3/178 (2%)	†
Pregnancy loss ≥20 weeks' gestation§	13/444 (3%)	18/432 (4%)	−1·2% (−4·2 to 1·8), p=0·42	8/263 (3%)	5/254 (2%)	1·1% (−2·1 to 4·2), p=0·50	5/181 (3%)	13/178 (7%)	−4·5% (−7·0 to −2·1), p=0·0003
Preterm delivery <37 weeks' gestation§	131/431 (30%)	136/414 (33%)	−2·5% (−9·7 to 4·5), p=0·49	58/255 (23%)	48/249 (19%)	3·5% (−1·3 to 8·2), p=0·15	73/176 (41%)	88/165 (53%)	−11·9% (−13·5 to −10·3), p<0·0001
Preterm delivery <34 weeks' gestation§	28/431 (6%)	45/414 (11%)	−4·4% (−9·0 to 0·3), p=0·07	17/255 (7%)	19/249 (8%)	−1·0% (−4·7 to 2·8), p=0·61	11/176 (6%)	26/165 (16%)	−10·0% (−14·6 to −4·4), p=0·0003
Neonatal death within 28 days of birth§	3/423 (1%)	9/406 (2%)	−1·5% (−3·1 to 0·1), p=0·07	1/247 (<1%)	2/241 (1%)	†	2/176 (1%)	7/165 (4%)	†

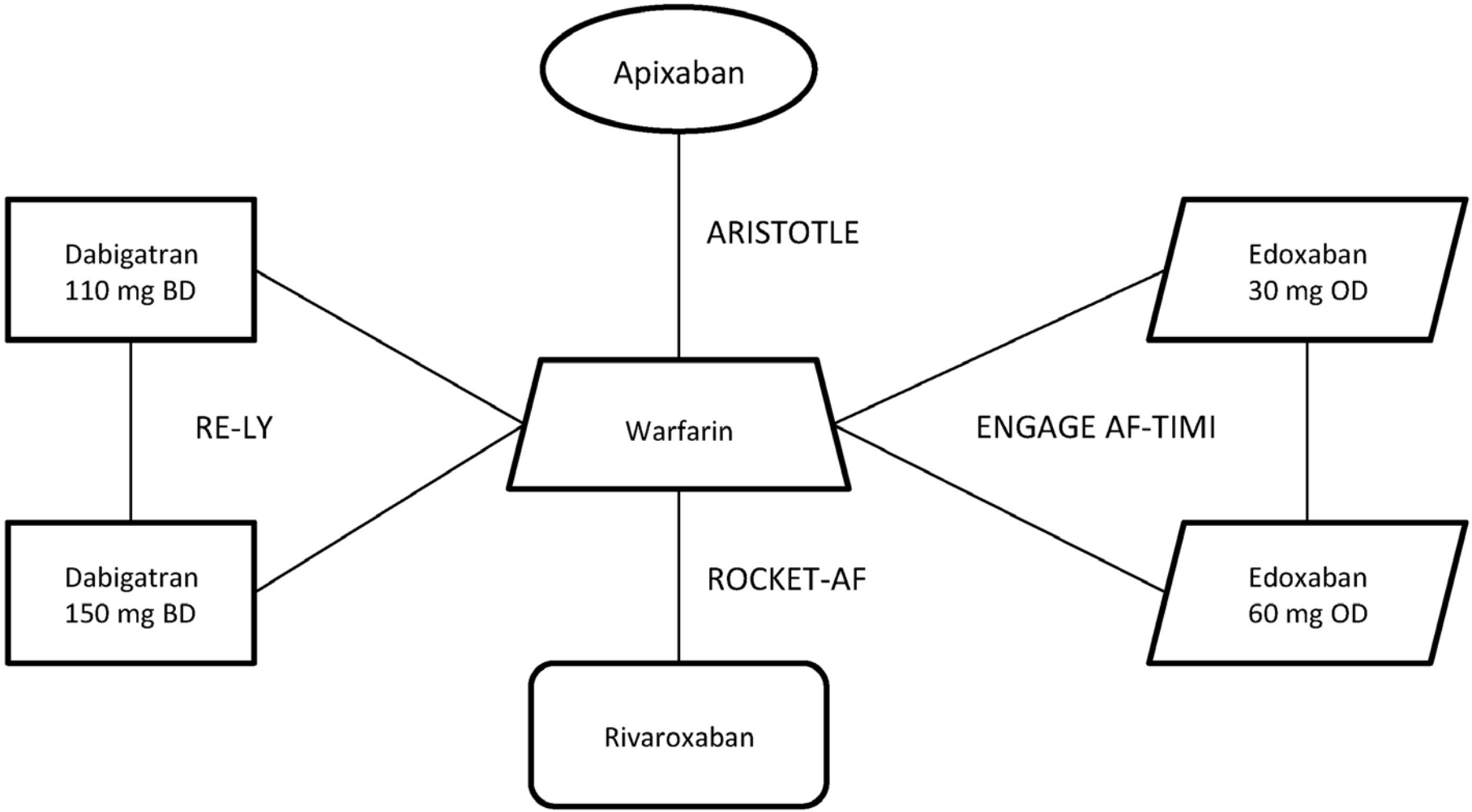
Rodger MA et al, Lancet 2006

Network meta-analyses

- Stesse caratteristiche di base
- Stesso tipo di analisi
- Stessi endpoints

Un farmaco è superiore all'altro?

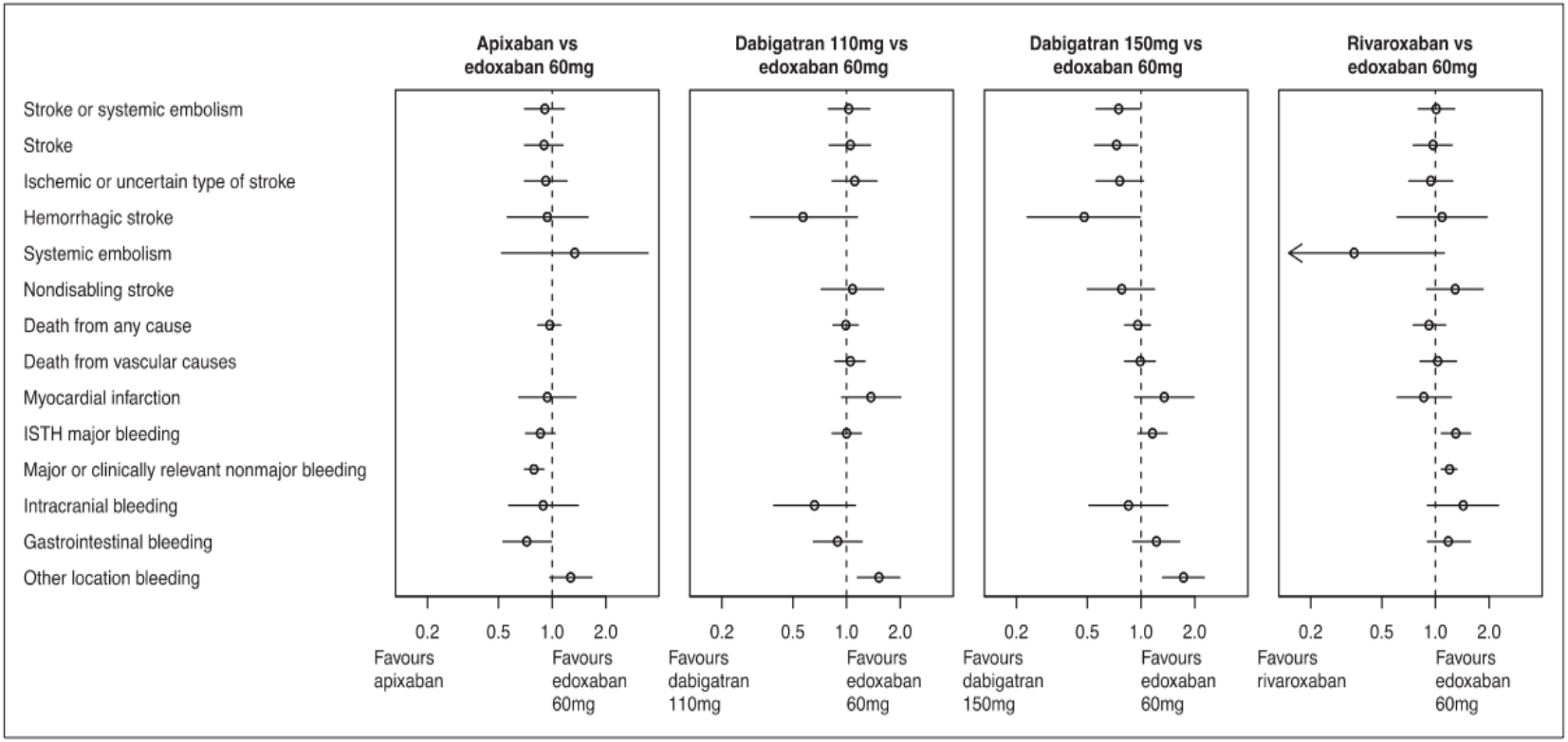
Network Meta-analyses



Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation

An indirect comparison analysis

Flemming Skjøth[1,2]; Torben Bjerregaard Larsen[1,2]; Lars Hvilsted Rasmussen[1,2]; Gregory Y. H. Lip[1,3]



RCTs

Baseline characteristics

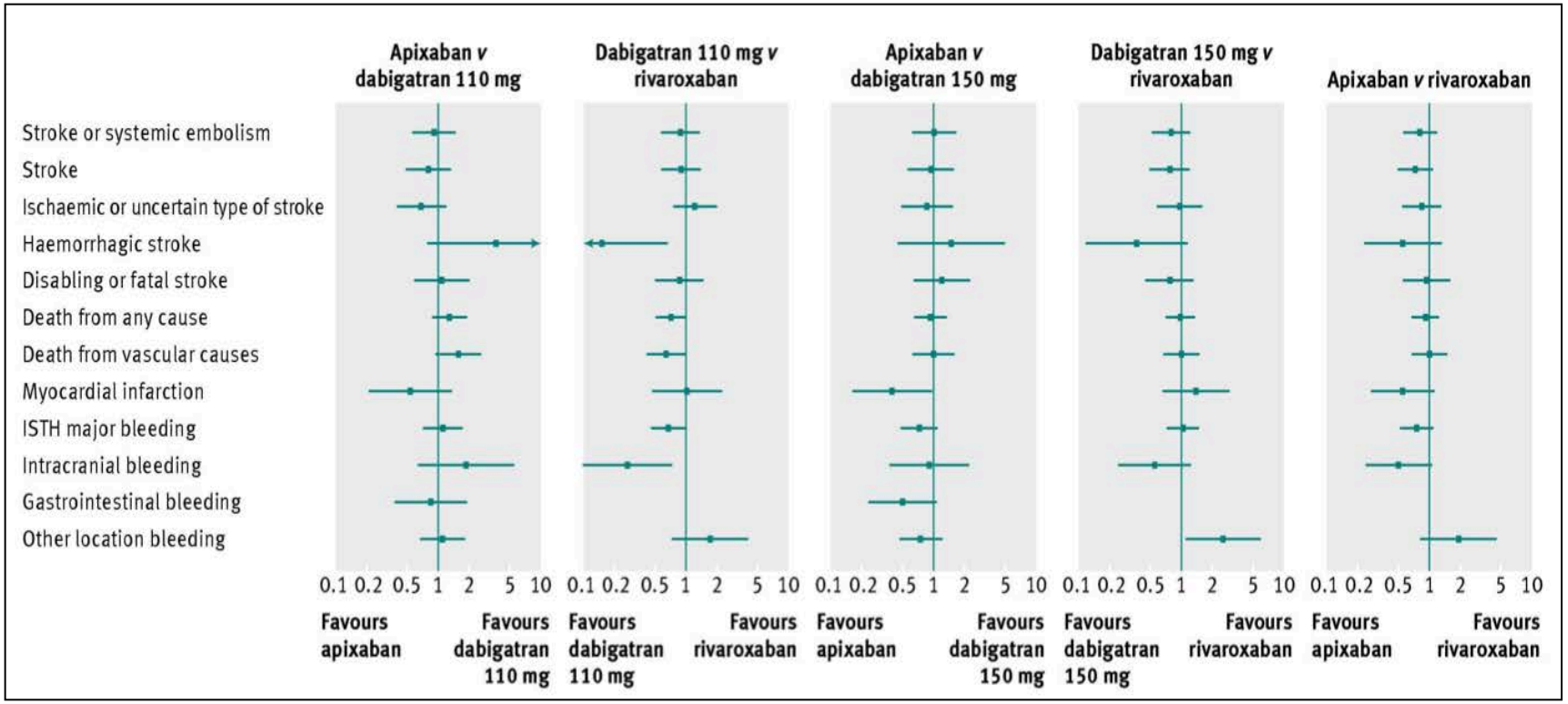
	Rocket AF	Aristotele	Rely	Engage
Mean Age (SD)	71 (64-77)[ç]	70 (9.7)	70 (9)	72
Mean CHADS2	3.5	2.1	2.1	2.8
Female (%)	39	37	37	38
Hypertension (%)	85	87	77	93.5
Previous Stroke/TIA (%)	52	19	20	28.3
DM (%)	40	25	23	36
CHF (%)	62	35	32	57
Previous MI	17.3	14	16.5	
ASA (%)	36.3	24	40	29
CrCl < 50 ml/min (%)	21	15	20	20

Connolly et al, NEJM 2009 ; Patel et al, NEJM 2011
Giugliano et al, NEJM 2013; Granger et al, NEJM 2011

Network meta-analyses

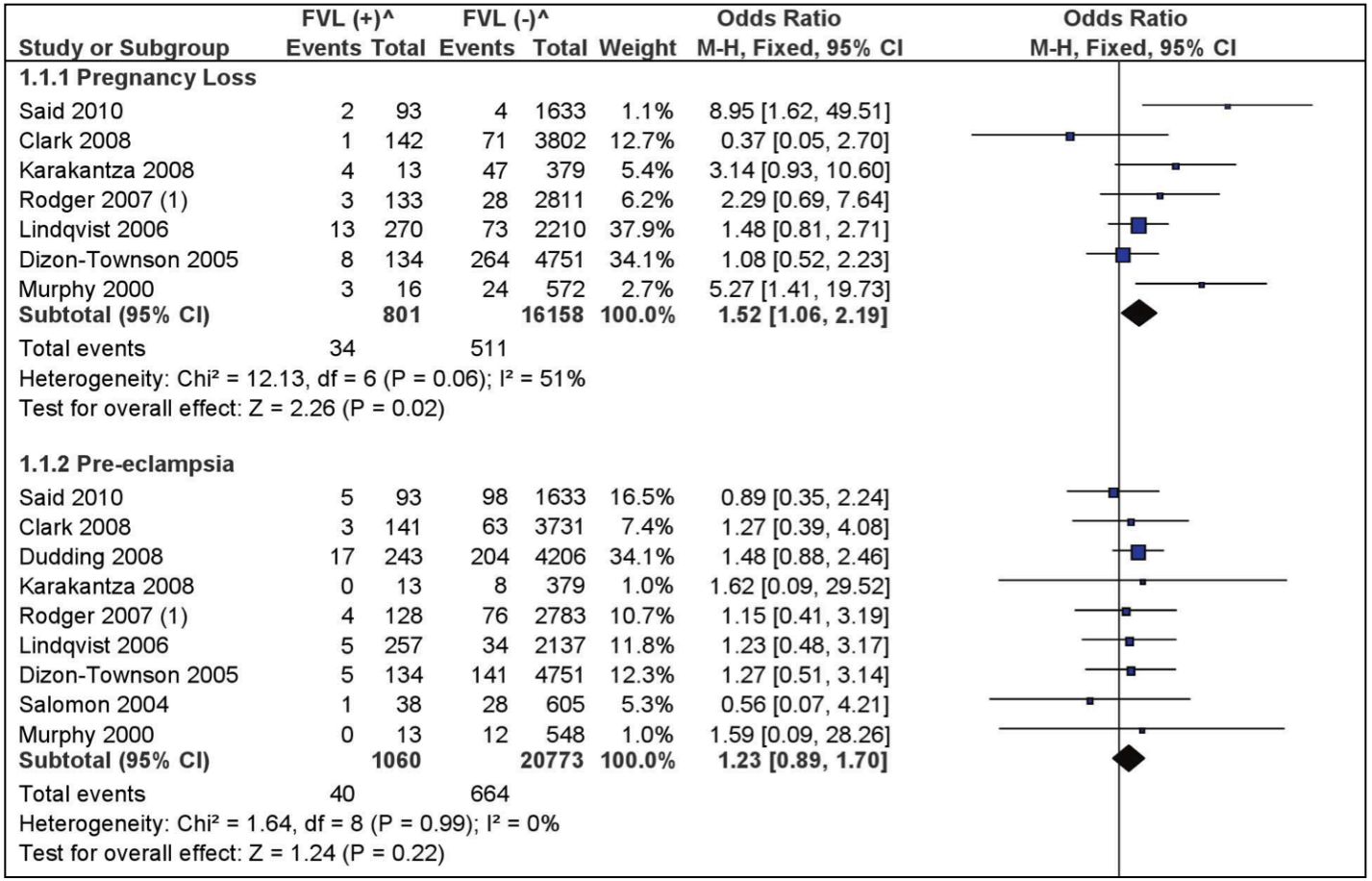
- Stesse caratteristiche di base (?)
- Stesso tipo di analisi (?)
- Stessi endpoints

Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis



Rasmussen et al, BMJ 2012

The Association of Factor V Leiden and Prothrombin Gene Mutation and Placenta-Mediated Pregnancy Complications: A Systematic Review and Meta-analysis of Prospective Cohort Studies



Study or Subgroup	FVL (+)^ Events	Total	FVL (-)^ Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Pregnancy Loss						
Said 2010	2	93	4	1633	1.1%	8.95 [1.62, 49.51]
Clark 2008	1	142	71	3802	12.7%	0.37 [0.05, 2.70]
Karakantza 2008	4	13	47	379	5.4%	3.14 [0.93, 10.60]
Rodger 2007 (1)	3	133	28	2811	6.2%	2.29 [0.69, 7.64]
Lindqvist 2006	13	270	73	2210	37.9%	1.48 [0.81, 2.71]
Dizon-Townson 2005	8	134	264	4751	34.1%	1.08 [0.52, 2.23]
Murphy 2000	3	16	24	572	2.7%	5.27 [1.41, 19.73]
Subtotal (95% CI)		**801**		**16158**	**100.0%**	**1.52 [1.06, 2.19]**
Total events	34		511			
Heterogeneity: Chi² = 12.13, df = 6 (P = 0.06); I² = 51%						
Test for overall effect: Z = 2.26 (P = 0.02)						
1.1.2 Pre-eclampsia						
Said 2010	5	93	98	1633	16.5%	0.89 [0.35, 2.24]
Clark 2008	3	141	63	3731	7.4%	1.27 [0.39, 4.08]
Dudding 2008	17	243	204	4206	34.1%	1.48 [0.88, 2.46]
Karakantza 2008	0	13	8	379	1.0%	1.62 [0.09, 29.52]
Rodger 2007 (1)	4	128	76	2783	10.7%	1.15 [0.41, 3.19]
Lindqvist 2006	5	257	34	2137	11.8%	1.23 [0.48, 3.17]
Dizon-Townson 2005	5	134	141	4751	12.3%	1.27 [0.51, 3.14]
Salomon 2004	1	38	28	605	5.3%	0.56 [0.07, 4.21]
Murphy 2000	0	13	12	548	1.0%	1.59 [0.09, 28.26]
Subtotal (95% CI)		**1060**		**20773**	**100.0%**	**1.23 [0.89, 1.70]**
Total events	40		664			
Heterogeneity: Chi² = 1.64, df = 8 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						

Rodger MA et al; Plos One 2010

L’utilizzo della terapia anticoagulante aumenta il rischio di recidiva di emorragia intracranica nei pazienti con pregressa emorragia intracranica?

(Domanda con risposta ovvia?)

Restarting Anticoagulant Therapy After Intracranial Hemorrhage

A Systematic Review and Meta-Analysis

Santosh B. Murthy, MD, MPH; Ajay Gupta, MD; Alexander E. Merkler, MD; Babak B. Navi, MD, MS; Pitchaiah Mandava, MD, PhD, MSEE; Costantino Iadecola, MD; Kevin N. Sheth, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH; Hooman Kamel, MD

Background and Purpose—The safety and efficacy of restarting anticoagulation therapy after intracranial hemorrhage (ICH) remain unclear. We performed a systematic review and meta-analysis to summarize the associations of anticoagulation resumption with the subsequent risk of ICH recurrence and thromboembolism.

Methods—We searched published medical literature to identify cohort studies involving adults with anticoagulation-associated ICH. Our predictor variable was resumption of anticoagulation. Outcome measures were thromboembolic events (stroke and myocardial infarction) and recurrence of ICH. After assessing study heterogeneity and publication bias, we performed a meta-analysis using random-effects models to assess the strength of association between anticoagulation resumption and our outcomes.

Results—Eight studies were eligible for inclusion in the meta-analysis, with 5306 ICH patients. Almost all studies evaluated anticoagulation with vitamin K antagonists. Reinitiation of anticoagulation was associated with a significantly lower risk of thromboembolic complications (pooled relative risk, 0.34; 95% confidence interval, 0.25–0.45; Q=5.12, P for heterogeneity=0.28). There was no evidence of increased risk of recurrent ICH after reinstatement of anticoagulation therapy, although there was significant heterogeneity among included studies (pooled relative risk, 1.01; 95% confidence interval, 0.58–1.77; Q=24.68, P for heterogeneity <0.001). No significant publication bias was detected in our analyses.

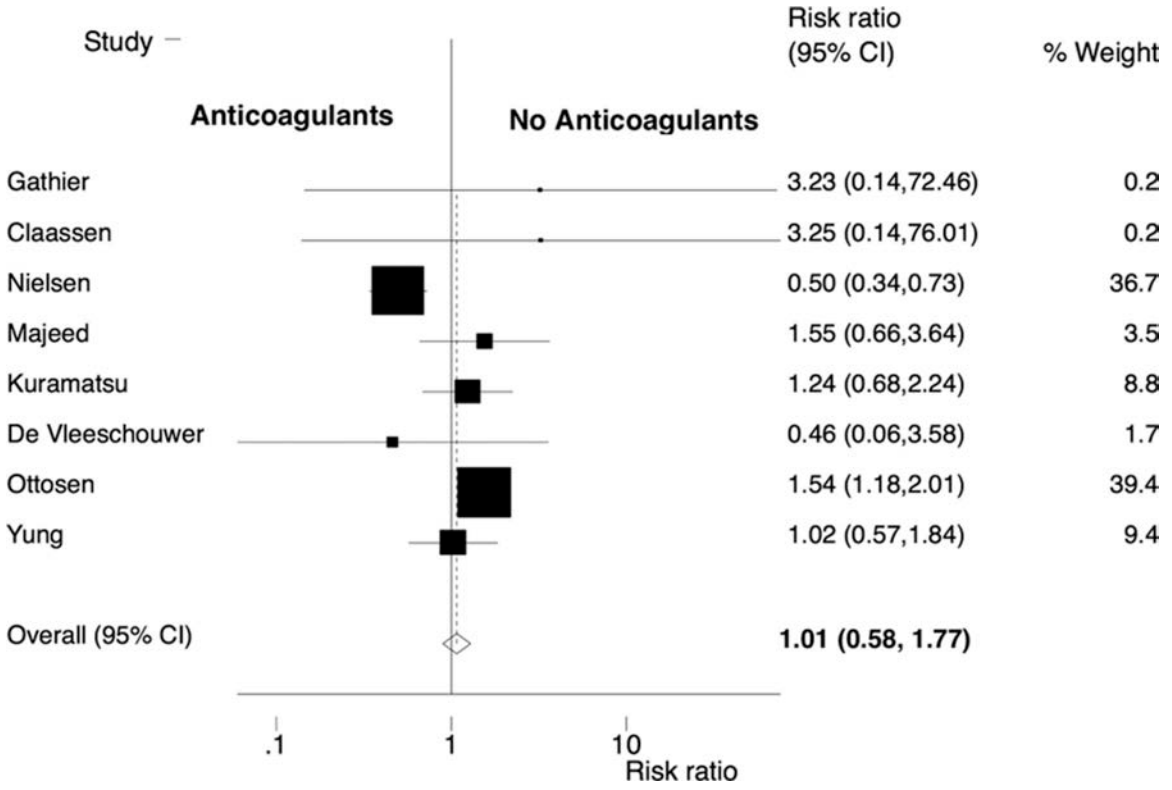
Conclusions—In observational studies, reinstitution of anticoagulation after ICH was associated with a lower risk of thromboembolic complications and a similar risk of ICH recurrence. Randomized clinical trials are needed to determine the true risk–benefit profile of anticoagulation resumption after ICH. **(*Stroke*. 2017;48:1594-1600. DOI: 10.1161/STROKEAHA.116.016327.)**

Key Words: anticoagulation ■ atrial fibrillation ■ myocardial infarction ■ stroke ■ thromboembolism

Restarting Anticoagulant Therapy After Intracranial Hemorrhage

A Systematic Review and Meta-Analysis

FOREST PLOT OF THE ASSOCIATION BETWEEN OAT RESUMPTION AND ICH-RECURRENCE



Murthy SB et al; Stroke 2017

Conclusioni

- Molto utili per i clinici
- Attenzione alla qualità!
- Non tutto può/deve essere “Meta-analizzato” (e letto!)

“Garbage in, garbage out”

Your analysis is as good as your data.