EVIDENCE BASED MEDICINE (EBM)

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ULB Certificate in Translational Medicine
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An old topic …

Pierre Jean Georges Cabanis *Du degré de la certitude de la médecine* (1797)

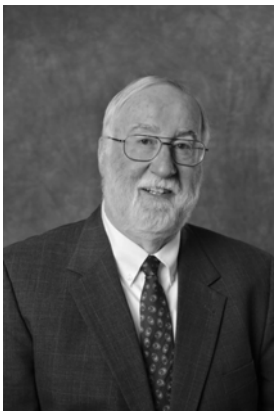
Pierre Charles Alexandre Louis :- Médecine numérique (1835)

Evidence Based Medicine (EBM): what it is?

- EBM is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

- The practice of EBM means integrating individual clinical expertise and patient's choice with the best available external clinical evidence from systematic research.

Br Med J 1996;312:71-72.



D.L. Sackett

Born in Chicago in 1934, David Sackett went on to Lawrence University (1952) and then to the University of Illinois College of Medicine for his MD and post-graduate training in Internal Medicine and Nephrology. After 2 years in the service and a year at Harvard, he moved to **McMaster University in Canada in 1967** to help start a **new medical school and a new way of training physicians -- no courses, no lectures, but working with and for patients from day one**. In 25 years, he has held a number of positions from founding chair of a department, to a medical researcher, to physician-in-chief at the university hospital, and to head of general internal medicine for the region. In fact, he and his colleagues were the first to show that aspirin could prevent strokes and heart attacks. In 1994 Oxford University created a chairmanship position, enabling him to found the world's first Centre for Evidence-Based Medicine. Along the way, he has written eight books, chapters for about 60 others, and published over 300 papers

Evidence-Based Medicine

- Begins in North America in 1992 (David Sackett and his team – co-founder of the « clinical epidemiology »)
- Is an approach combining the update of the medical knowledge and its application.
- Proposes searching methods to retrieve the knowledge, develops critical appraisal of this knowledge for consecutive application (with more or less delay) to the patient

Evidence-Based Medicine Principles

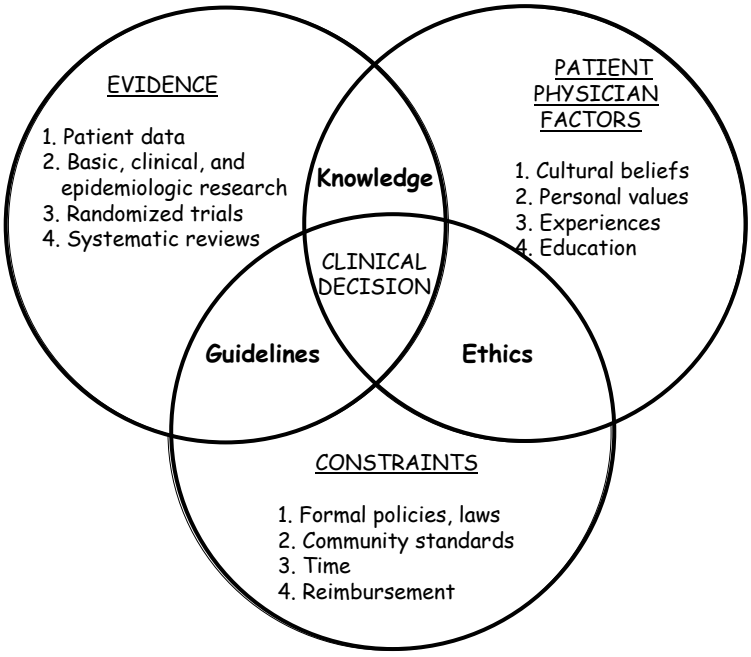
- At the beginning is the question:

What must we do with this patient who presented with…?

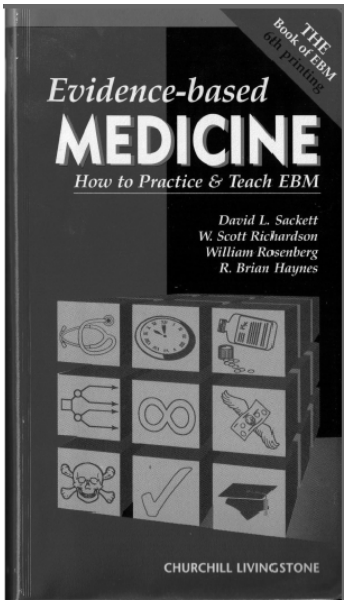
- The physician explores the databases containing bibliographical data (EBM websites, Pubmed, …)
- He retrieves several synthesis' papers (systematic reviews, meta-analyses) and/or original articles

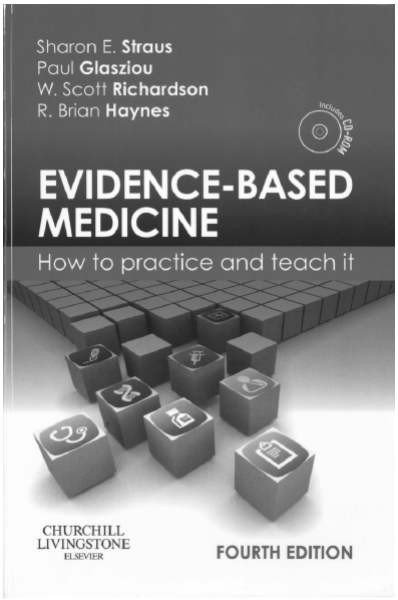
Evidence-Based Medicine Principes

- He reads these articles using a grid for reading with a priority given to systematic reviews and to original articles with high level of evidence
- He receives (or not) an answer to the initial question.
- At the end, a decision is taken concerning the patient for which he asks the question.



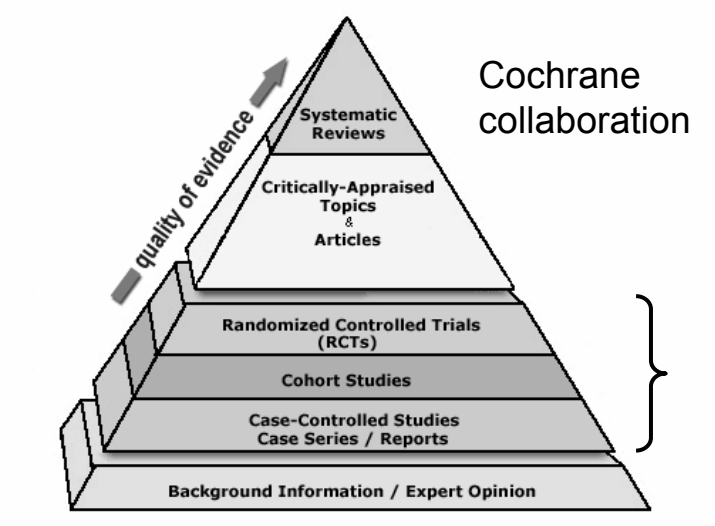
Mulrow CD, Cook DJ, Davidoff F, Ann. Int. Med. 1997;126:389-391





2011

Quality of evidence

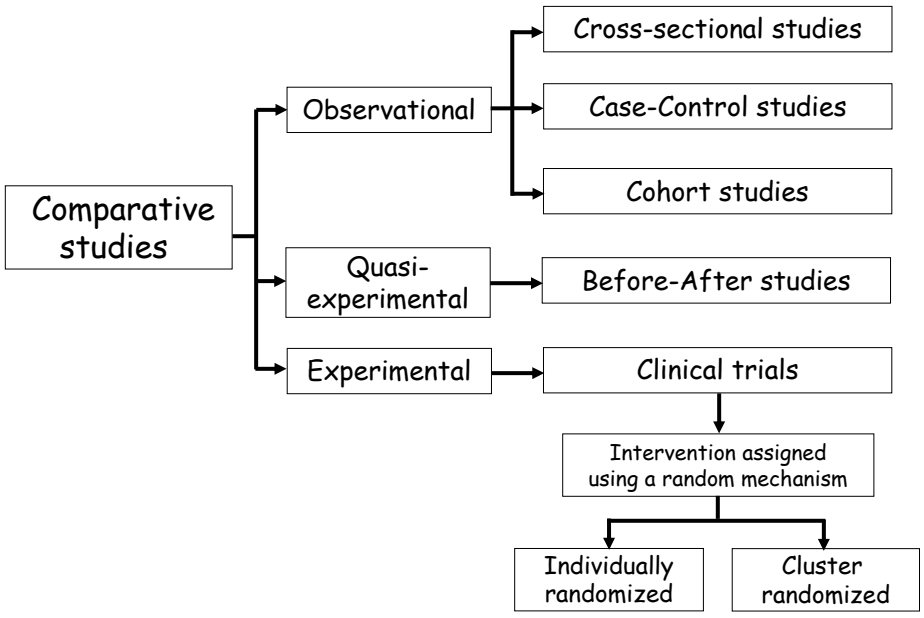


Cochrane collaboration

Original papers

How to classify the individual publications?

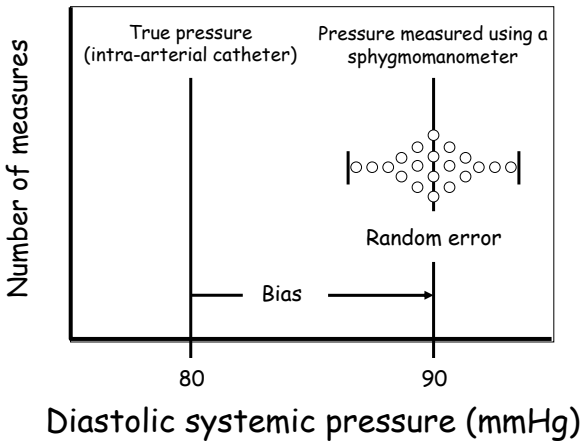
Comparative studies



Bias and Chance

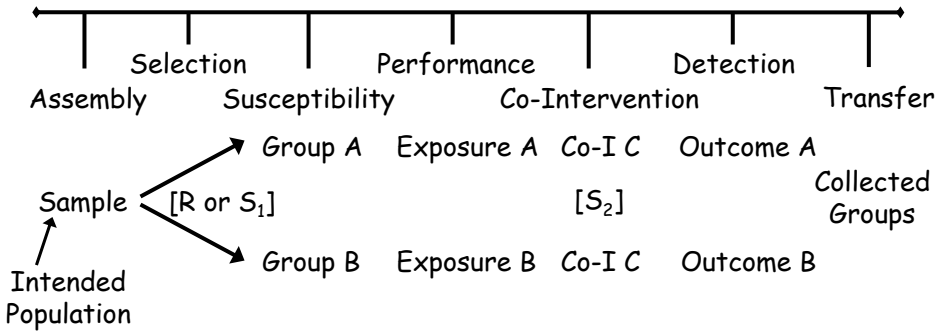
Observed effect
=
True effect
+
Random error ⇐ Power (sample size)
+
Systematic error ⇐ Biases (RCT)

Bias and Random Error: an example



Biases in a clinical trial

Main biases in a clinical trial



- Goal: Comparability of the groups who did and did not receive the active treatment (exposure)

Adapted from Feinstein (Five key aspects)

Bias in Estimating Effects

- Distorted Assembly (biased sample)*
- Selection bias
- Susceptibility bias
- Performance bias
- Co-Interventions (opportunity for selection)
- Outcome or Detection bias
- Transfer bias*
- Accidental bias

RANDOMIZATION

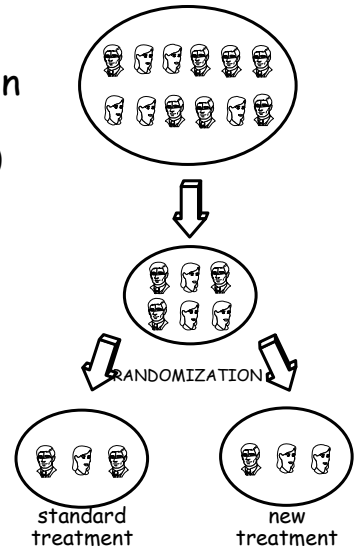
- The clinical trial situation:

loosely defined population
(unknown response rate, uncomplete list of patients)

non random sample
(e.g. hospitalized patients only)

comparison of the results among randomized groups

randomized groups



Intent-to-treat analysis (transfer bias)

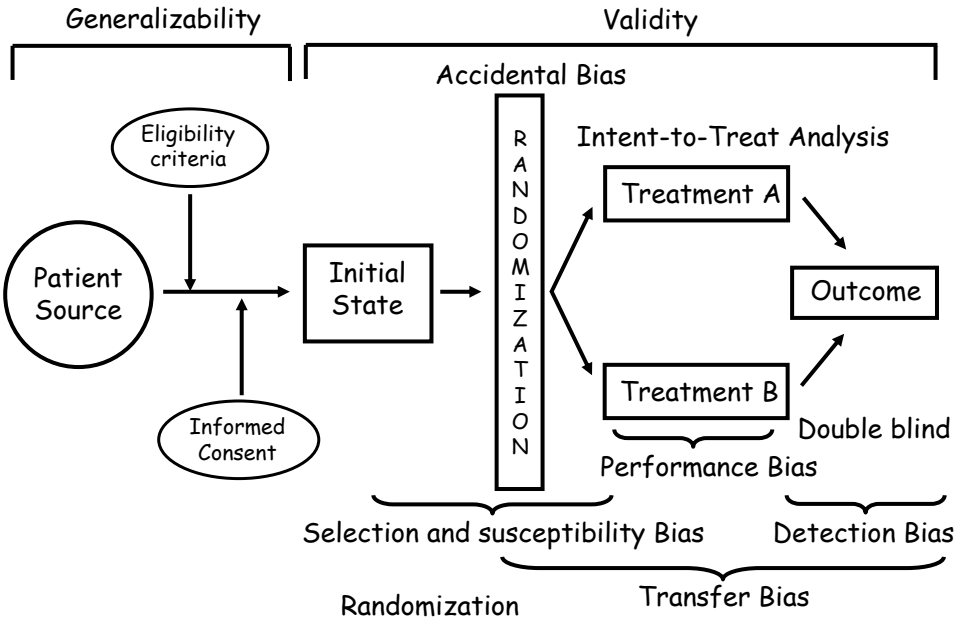
	Randomization	End of the trial	Number of positive responses	Per protocol	Intent-to-treat
Group 1	200	104	40	= 40/104 38 %	=40/200 20 %
Group 2	200	160	20	=20/160 12.5 %	=20/200 10 %

« Efficacy »

« Effectiveness »

- The intent to treat analysis is the best way to report the result because it corresponds to the caveat of the real life (lost to follow up, lack of compliance,…)

Randomized Controlled Trial (RCT)

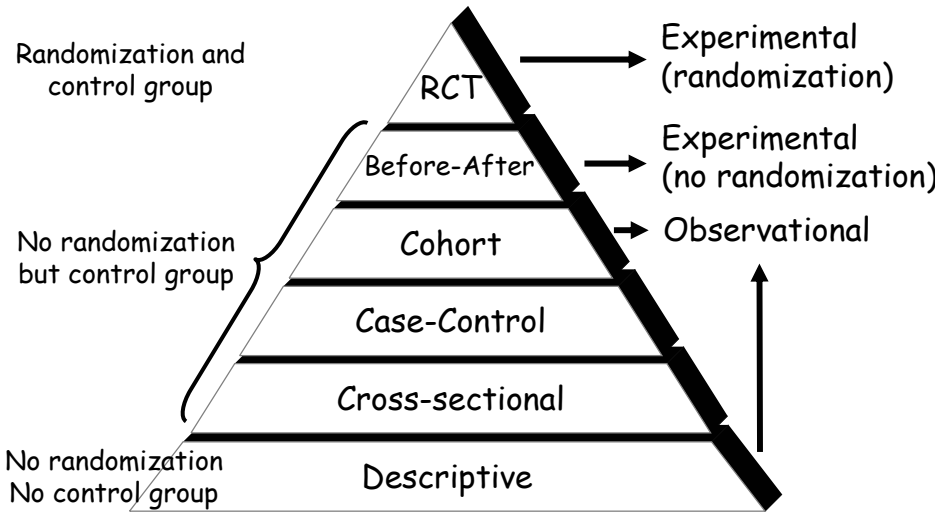


Hierarchy of the clinical trials

Randomized Controlled Trial - RCT

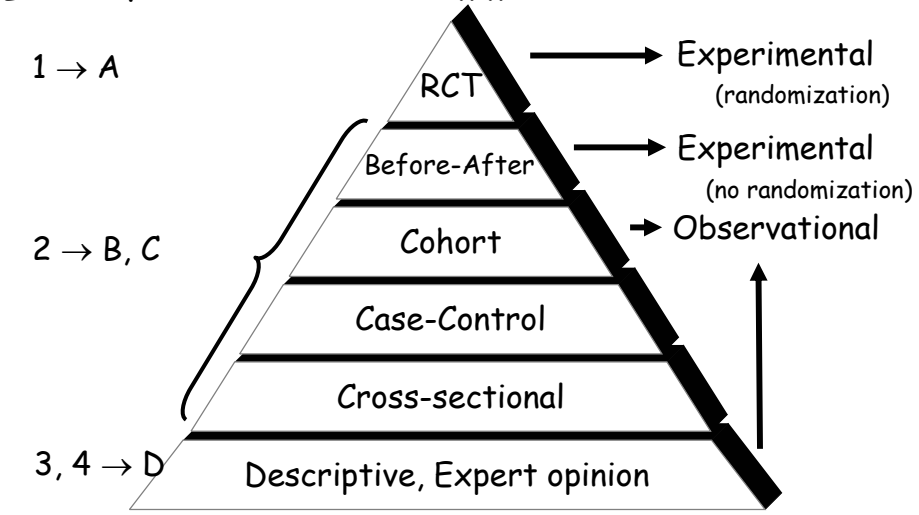
- Randomization:
  - Validates the statistical tests used to compare treatments.
  - Eliminates all sources of bias except for accidental bias.
  - Tends to ensure balance among treatments with respect to known (gender, weight, …) and unknown factors (?).
- Control group:
  - A contemporary control group is necessary to control:
    - for the spontaneous evolution of the disease
    - for the regression to the mean.

HIERARCHY OF THE CLINICAL STUDIES



HIERARCHY OF THE CLINICAL STUDIES

Level of evidence → Recommendation



LEVEL OF EVIDENCE IN CLINICAL STUDIES

A new system for grading recommendations in evidence based guidelines . *BMJ* 2001;323:334-336

GRADING OF RECOMMENDATIONS GIVEN THE LEVEL OF EVIDENCE

A new system for grading recommendations in evidence based guidelines . *BMJ* 2001;323:334-336

Example of search in Pubmed

Table: results of a PubMed search for "atrial fibrillation AND warfarin" with some filters

Type	Term used	Number of articles
All articles	(no filter)	2175
RCT	"random allocation" [MeSH]	7
cohort	"cohort studies" [MeSH]	366
Case-control	"Case-Control Studies"[Mesh]	234
Case report	Case Reports [Publication Type]	196

Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review (s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

http://www.cebm.net/index.aspx?o=1025

http://www.cebm.net

How to apply the published results to an individual patient?

ESTIMATING THE IMPACT OF A VALID, IMPORTANT TREATMENT RESULT ON AN INDIVIDUAL PATIENT

- Do the results apply to the patient?
- How great would be the potential benefit of therapy for the individual patient?

Evidence Based Medicine, DL Sackett et al, Churchill Livingstoone, 1998.

ESTIMATING THE IMPACT OF A VALID, IMPORTANT TREATMENT RESULT ON AN INDIVIDUAL PATIENT

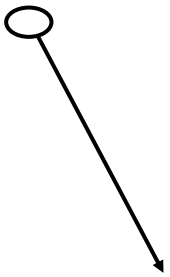
- Do the results apply to the patient?
  - Eligibility criteria for the trial
  - How can we extrapolate from the external evidence to the individual patient ("generalizability of the trial")?
  - Is the patient so different from those in the trial?

Evidence Based Medicine, DL Sackett et al, Churchill Livingstoone, 1998.

Example

PROGRESS, Lancet 2001;358:1033-1041

Example



Relative Risk Reduction
(0.10-0.14)/0.14 = - 0.28 (-28 %)

PROGRESS, Lancet 2001;358:1033-1041

Relative reduction vs Absolute risk reduction

- Absolute reduction:
  - Risk difference (RD or ARR):
    (307/3051) – (420/3054) = 0.10 – 0.14 = - 0.04 (- 4 %)

- Relative reduction:
  - Relative Risk (RR) ou Hazard ratio (HR):
    0.10/0.14 = 0.72
  - Relative Risk Reduction (RRR):
    (0.10-0.14)/0.14 = - 0.28 (- 28 %)

Risk Difference (RD) and NNT

- NNT: number needed to treat to avoid a harm effet or to have a beneficial effect.

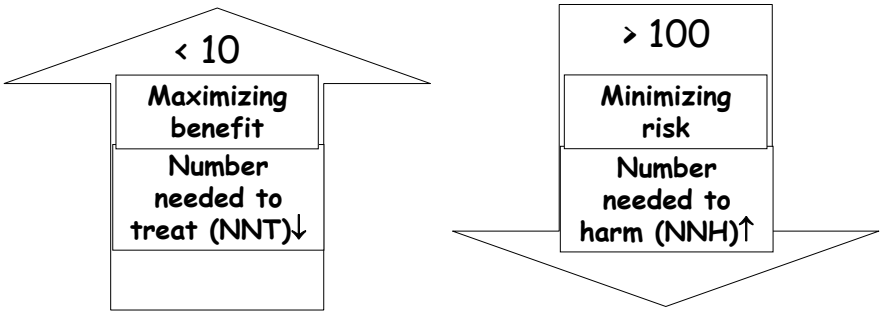
- NNT = 1/RD

- Example: RD = - 4 % (- 0.04)
  NNT = 1/0.04 = 25

NNH

- NNH: number needed to harm (side effects)
- NNH = 1/ difference of side effects (SE) rate
- Drop-out due to side effect:
  - SE rate in treated group = 5%
  - SE rate in placebo group = 3%
  - Risk Difference = 2%
  - NNH = 1/0.02 = 50
- 1 "drop-out" due to SE every 50 treated patients.

Benefit-to-risk ratio: maximizing the benefits, minimizing the risks



$$\text{Benefit Risk ratio} = \frac{\text{NNH}}{\text{NNT}}$$

$$\text{Benefit Risk ratio} = \frac{50}{25} = 2$$

How to estimate the expected individual benefit?

ESTIMATING THE IMPACT OF A VALID, IMPORTANT TREATMENT RESULT ON AN INDIVIDUAL PATIENT

- How great would be the potential benefit of therapy for the individual patient?

  - Estimation of the "susceptibility" or the "baseline risk" of patient (F):

    $$F = 2$$

    (the individual patient is estimated twice as susceptible as the average control patient patient in the trial)

  - NNTi for the individual patient:

    $$NNTi = \frac{NNT}{F} = \frac{25}{2} = 12.5 \quad \text{or (13 patients)}$$

Evidence Based Medicine, DL Sackett et al, Churchill Livingstoone, 1998.

Exercise

- Patient 80 y/o with diabetes

Example

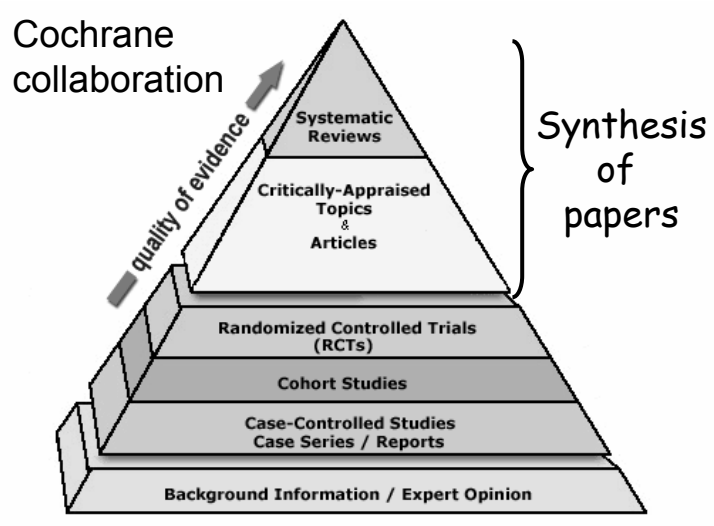
PROGRESS, Lancet 2001;358:1033-1041

Exercise

- Patient 80 y/o with diabetes
- Progress study:
  - Mean age 64 yrs
  - Diabetes 13 %
- Estimation of susceptiblity:

  F = 80/64 * 100/13 = 9.6
- NNTindividual: NNTi = 25/10 = 2.5

Quality of evidence



What is GRADE?

- GRADE is a systematic and explicit approach to making judgements about quality of evidence and strength of recommendations.

- It was developed by the **Grading of Recommendations, Assessment, Development and Evaluations (GRADE)** Working Group, and it is now widely seen as the most effective method of linking evidence-quality evaluations to clinical recommendations.

How GRADE system does it work?

- GRADE addresses many of the perceived shortcomings of existing models of evidence evaluation. Crucially, when using GRADE, we rate evidence not study by study, but across studies for specific clinical outcomes.

GRADE scoring system

- GRADE scoring
  - Type of evidence
  - Quality
  - Consistency
  - Directness (limitation of generalisability)
  - Effect size
- Strength of recommendation
- Cost-effectiveness

Type of evidence		
Initial score based on type of evidence	+4	RCTs/ SR of RCTs, +/– other types of evidence
	+2	Observational evidence (e.g., cohort, case-control)

Quality		
Based on	Blinding and allocation process	
	Follow-up and withdrawals	
	Sparse data	
	Other methodological concerns (e.g., incomplete reporting, subjective outcomes)	
Score	0	No problems
	–1	Problem with 1 element
	–2	Problem with 2 elements
	–3	Problem with 3 or more elements

Consistency		
Based on	Degree of consistency of effect between or within studies	
Score	+1	Evidence of dose response across or within studies (or inconsistency across studies is explained by a dose response); also 1 point added if adjustment for confounders would have increased the effect size
	0	All/most studies show similar results
	–1	Lack of agreement between studies (e.g., statistical heterogeneity between RCTs, conflicting results)

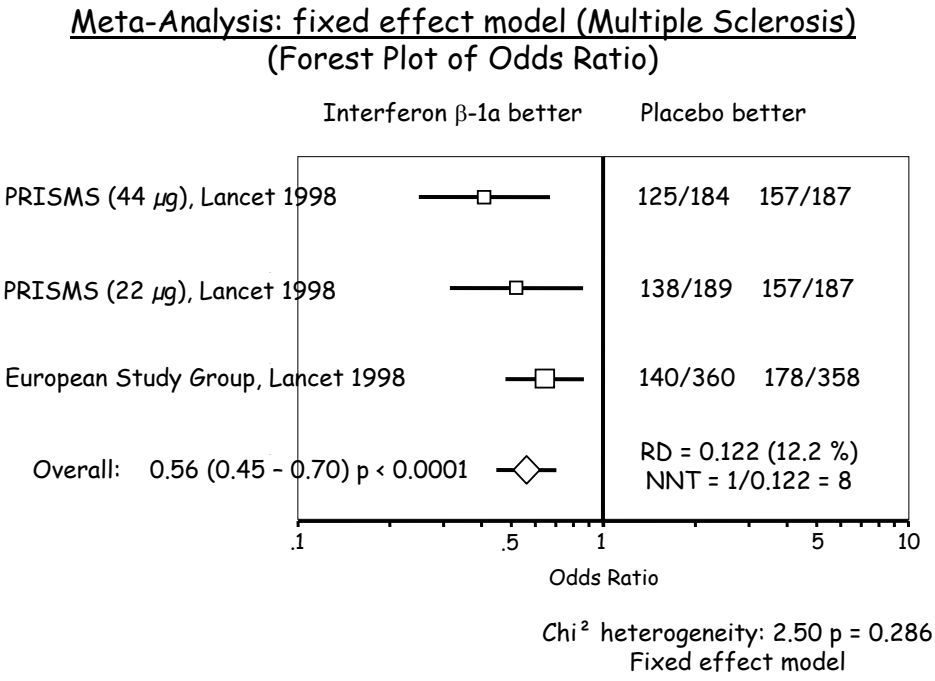
Directness		
Based on	The generalisability of population and outcomes from each study to our population of interest	
Score	0	Population and outcomes broadly generalisable
	–1	Problem with 1 element
	–2	Problem with 2 or more elements

Effect size		
Based on	The reported OR/RR/HR for comparison	
Score	0	Not all effect sizes >2 or <0.5 and significant; or if OR/RR/HR not significant
	+1	Effect size >2 or <0.5 for all studies/meta-analyses included in comparison and significant
	+2	Effect size >5 or <0.2 for all studies/meta-analyses included in comparison and significant

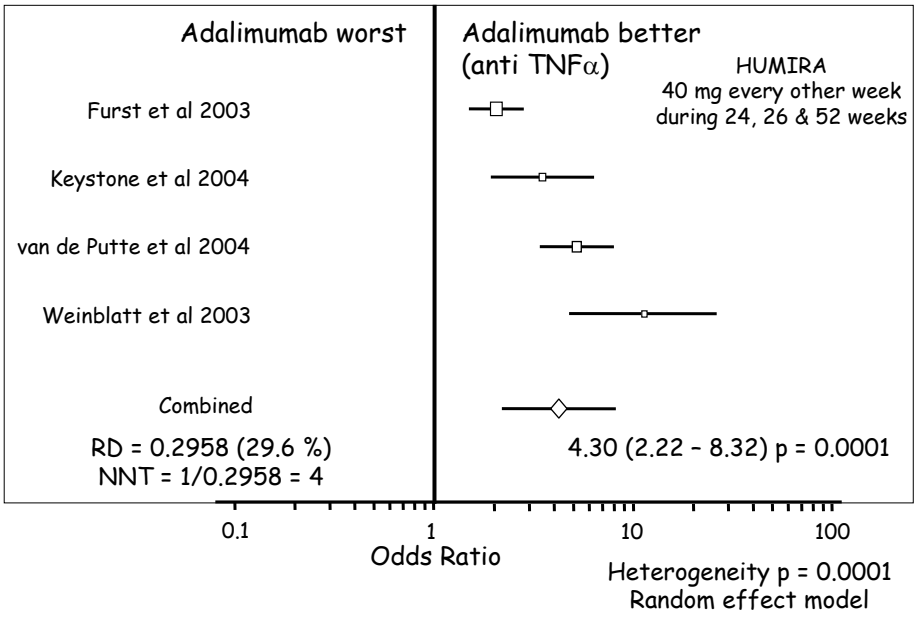
- The final GRADE score used 4 categories of evidence quality based on the overall GRADE scores for each comparison:
  - High (at least 4 points overall)
  - Moderate (3 points)
  - Low (2 points)
  - Very low (≤ 1 point)

for a <u>specific clinical outcome</u>.

Meta-Analysis of clinical trials



Meta-Analysis: random effect model (Rheumatoid arthritis)
(Forest Plot of Odds Ratio)



Meta-analysis: truth or lie?
(comparison of meta-analysis with a single huge clinical trial)

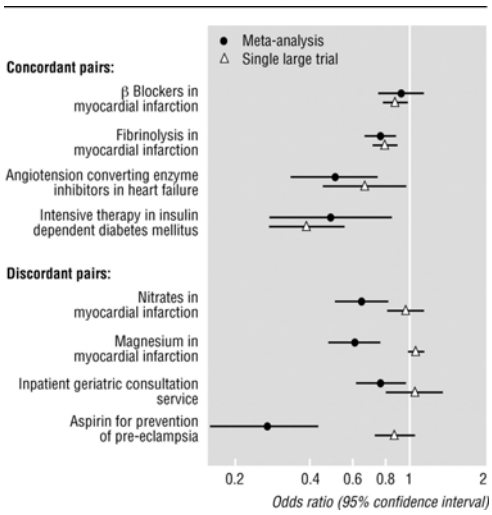
Table 1 Characteristics of nine pairs of meta-analyses and corresponding large trials

Topic	Typical end point	Large trial (year of publication)	Meta-analysis (year of publication)
Concordant pairs,			
ß Blockers in myocardial infarction	Mortality in hospital	ISIS-1 (1986)[20]	Yusuf et al (1985)[19]
Streptokinase in myocardial infarction	Mortality in hospital	GISSI-1 (1986)[18]	Yusuf et al (1985)[17]
Angiotensin converting enzyme inhibitors in heart failure	Mortality at 3 months	SOLVD (1991)[15]	Mulrow et al (1988)[26]
Intensive therapy in insulin-dependent diabetes mellitus	Progression of retinopathy over several years	DCCT (1993)[22]	Wang et al (1993)[21]
Discordant pairs			
Magnesium in myocardial infarction	Mortality in hospital	ISIS-4 (1995)[28]	Teo et al (1993)[27]
Nitrates in myocardial infarction	Mortality in hospital	GISSI-3 (1994)[25]	Yusuf et al (1988)[24]
Inpatient geriatric consultation service	Mortality at 6 months	HMO (1995)[23]	Stuck et al (1993)[14]
Aspirin for preventing pre-eclampsia	Development of pre-eclampsia	CLASP (1994)[30]	Imperiale and Stollenwerk (1991)[29]

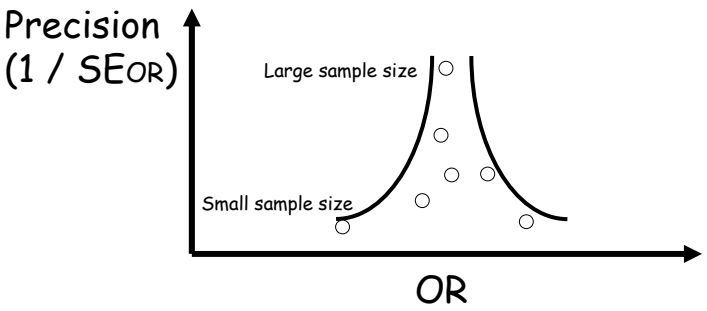
GISSI=Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico; ISIS=International Study of Infarct Survival; DCCT=Diabetes Control and Complications Trial; HMO=Health Maintenance Organisation study; SOLVD=Studies of Left Ventricular Dysfunction; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy.

Egger M, et al.
Bias in meta-analysis detected by a simple, graphical test.
BMJ 1997;315:629-645

Meta-analysis: truth or lie?



The funnel plot



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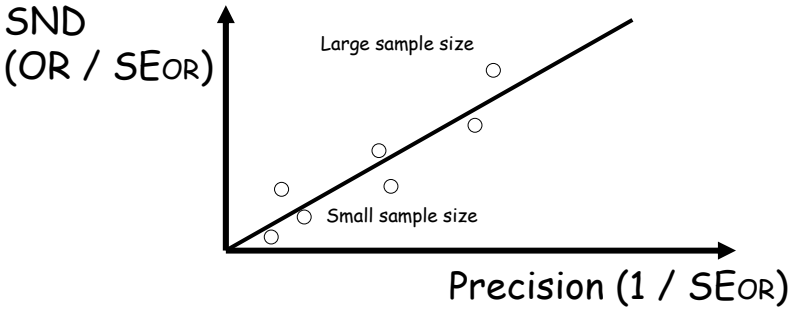
BMJ 1997;315:629-645

The asymetry of the funnel plot



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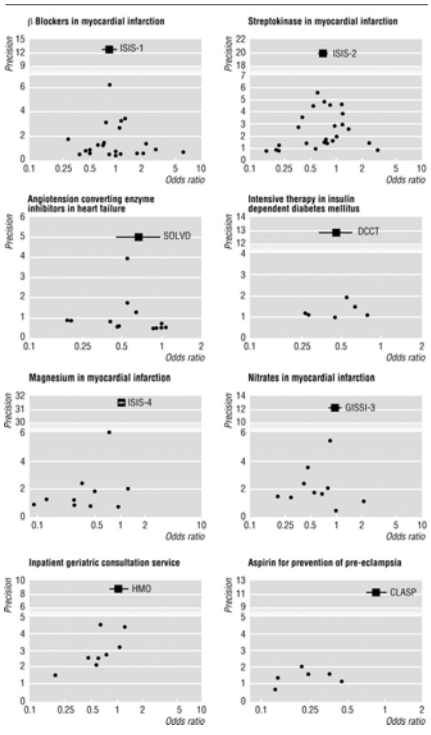
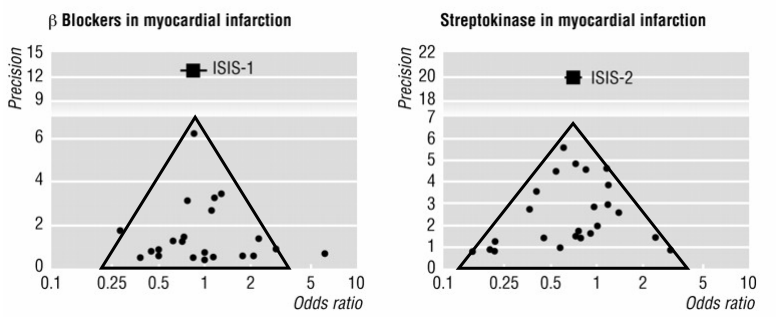
Concordant pair

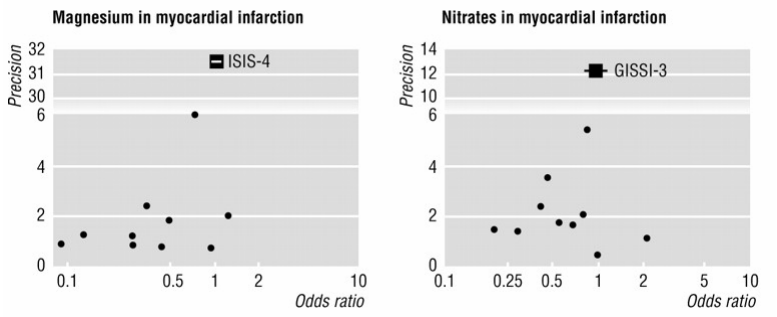
Discordant pair



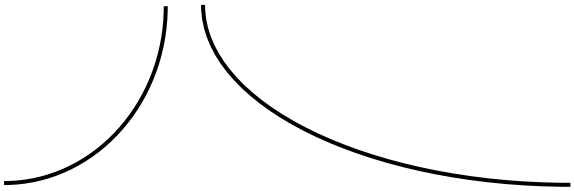
Concordant meta-analysis



Discordant meta-analysis



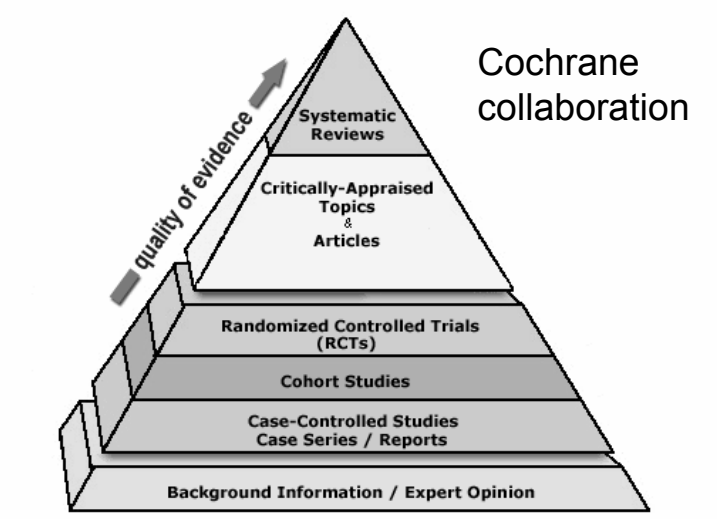
Meta-analysis in homeopathy



Lancet 1997;350:834-843

http://www.cochrane.org

Evidence-Based Medicine is the integration of best research evidence with clinical expertise and patient values.



Cochrane collaboration

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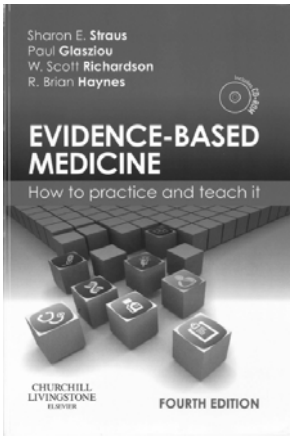
Books:
- Straus SE, Glasziou P, Richardson WS, Haynes RB. Evidence-Based Medicine. How to pratice and teach it. 4th edition. Churchill Livingstone, Oxford, 2011



Revue:
- BMJ Clin. Evid.

ClinicalEvidence

Essential tremor

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ABSTRACT

INTRODUCTION: Essential tremor is one of the most common movement disorders in the world, with prevalence in the general population of 0.4% to 3.9%. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of drug treatments in people with essential tremor of the hand? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 56 studies. After deduplication and removal of conference abstracts, 31 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 18 studies and the further review of 13 full publications. Of the 13 full articles evaluated, two RCTs were added at this update. We performed a GRADE evaluation for 11 PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for 13 interventions based on information about the effectiveness and safety of alprazolam, beta-blockers other than propranolol, botulinum A toxin-haemagglutinin complex, clonazepam, diazepam, gabapentin, levetiracetam, lorazepam, phenobarbital, primidone, propranolol, sodium oxybate, and topiramate.

QUESTIONS

INTERVENTIONS

DRUG TREATMENT

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

END