# EBM: Le evidenze e le loro implicazioni per le politiche sanitarie

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# Di che cosa vorrei parlarvi

- EBM
- Perchè oggi non creiamo vantaggio rispetto alla letteratura scientifica
- Orientamento della ricerca
- Orientamento della pratica
- DIfficoltà di un approccio sistemico
- Conclusioni

# EBM 2014

- ‘Chi può essere contro le evidenze nel 21 sec.?’



UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE BIOMEDICHE PER LA SALUTE

# EBM in 2013

## Diade medico-paziente: prendere decisioni informate

- Better and more evidence
- Public and social perspective
- Access

- Maturazione dei metodi (epidemiologia e biostatistica)

"So it's a combination of the evidence, the clinical expertise and the patient's views that come together."

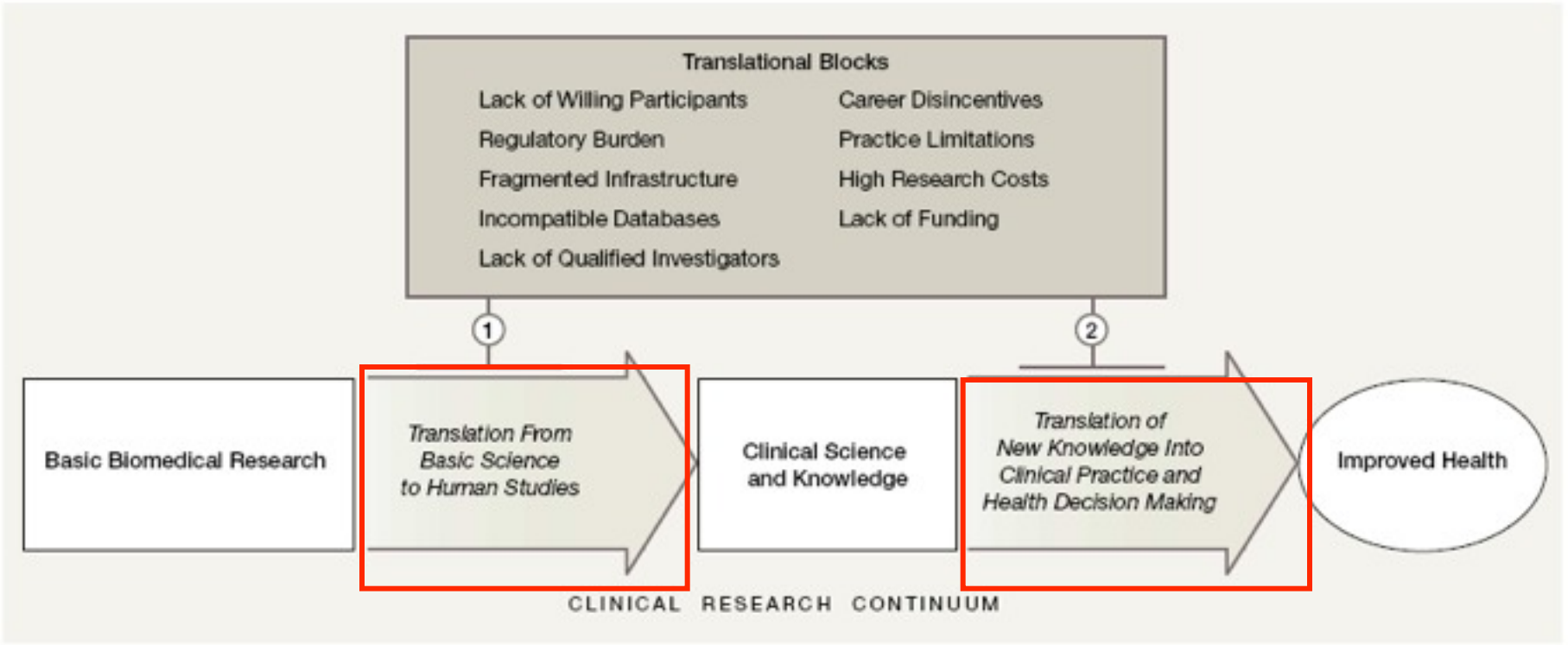


# Epidemiology

- Originally study of epidemics (comunicable diseases)
- Modern def: the study of the distribution and determinants of health-related states and events in populations, and the application of this study to control health problems [empasis add to control]
- Clinical epidemiology: marriage between quantitative concepts used by epidmiologists to study disease populations and decision-making in the individual case which is the daily fare of clinical medicine (John Paul)

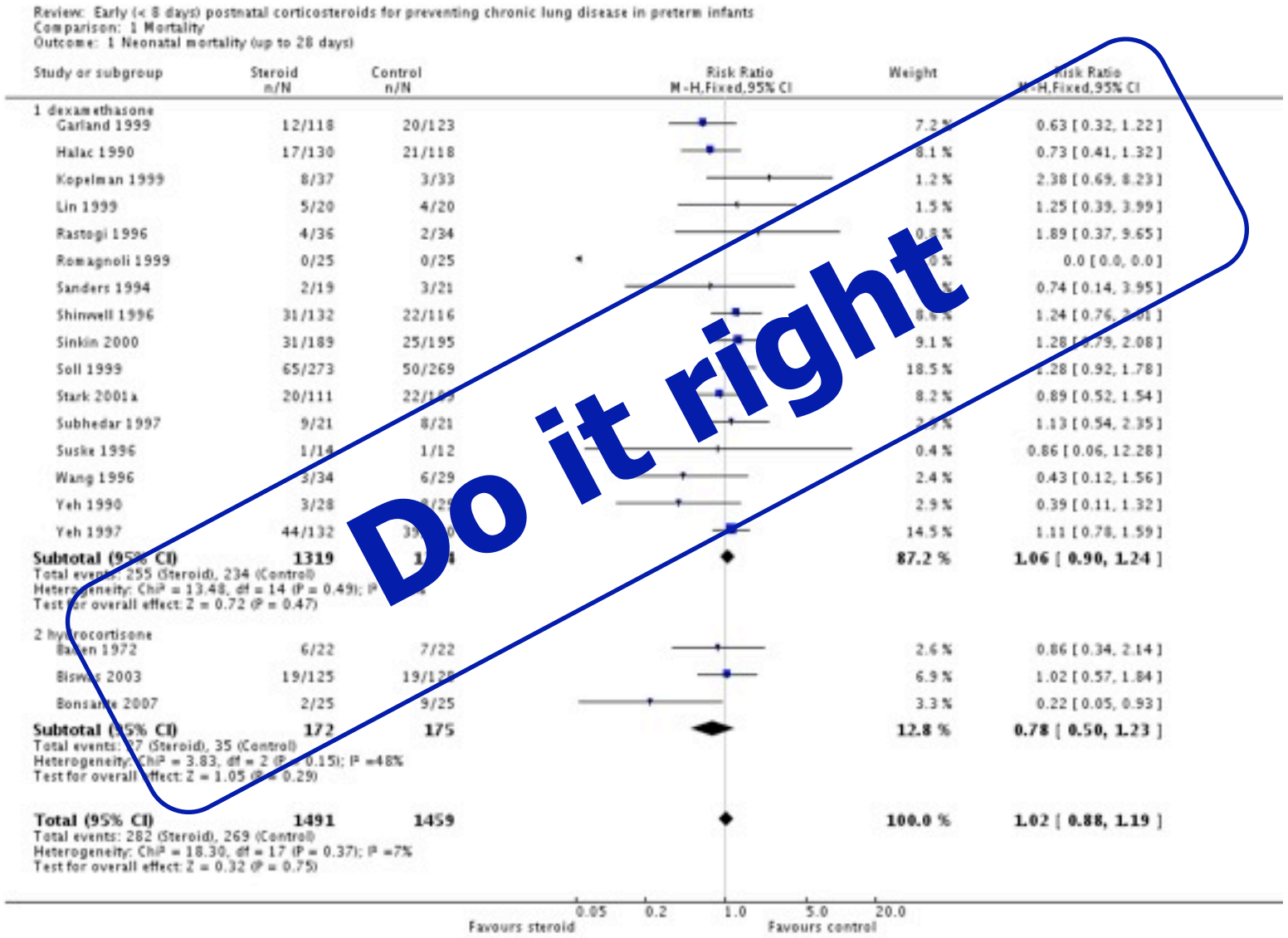
# Knowledge translation blocks

**Figure 1.** The 2 Translational Blocks in the Clinical Research Continuum




Institute of Medicine; Clinical Research Roundtable,
Sung et al. JAMA 289:1278,2003

# Knowledge synthesis



Al-Shahi R, Will RG, Warlow CP. Amount of research interest in rare and common neurological conditions: bibliometric study. *Bmj* 2001;323(7327):1461-2.

# Amount of research interest in rare and common neurological conditions: bibliometric study

Rustam Al-Shahi, Robert G Will, Charles P Warlow

Neurologists are often accused of being interested in only rare incurable diseases. Although this may have been true in the past, today's neurologists claim to be more concerned with common disorders—but are they really?

## Methods and results

death, economic hardship, and loss of quality of life. It is recognised that funding for research into a disease should be proportional to that disease's burden on society[2]; however, conditions that account for 90% of the global burden of disease receive less than one tenth of the world's health budget.[3]

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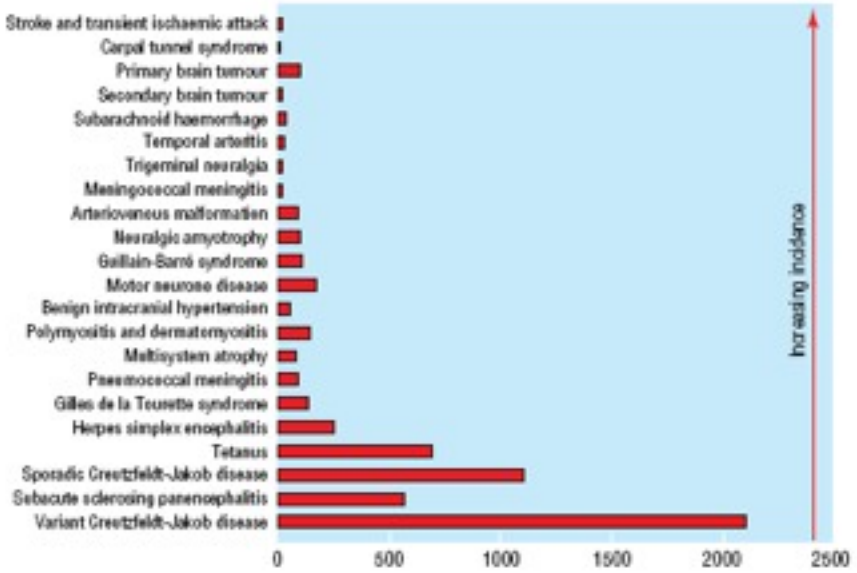
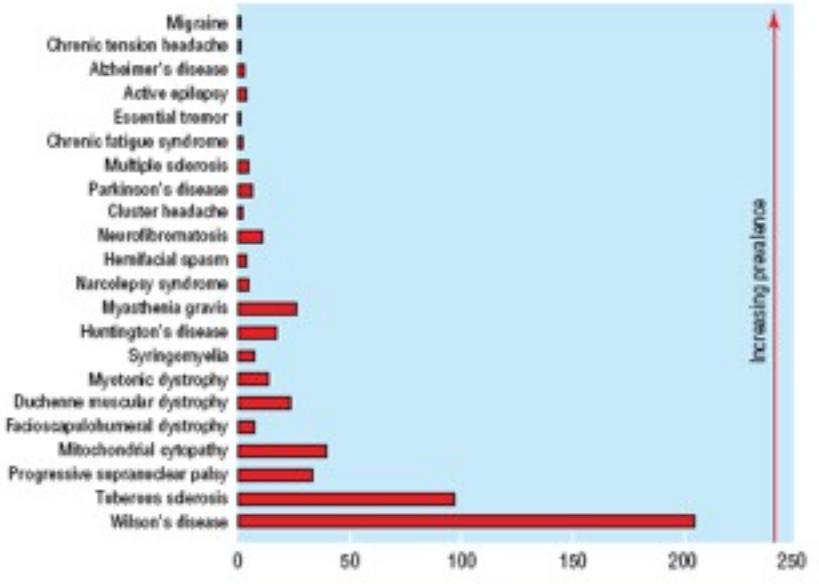
continued over

*BMJ* 2001;323:1461–2

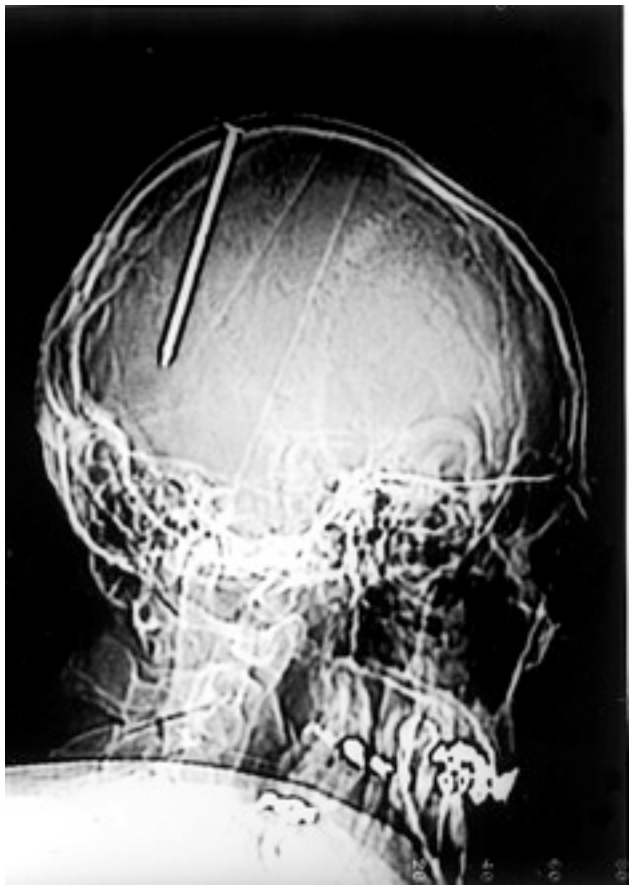



Overall, there were 42 papers about variant Creutzfeldt-Jakob disease and 4562 about stroke and transient ischaemic attack. If the publication ratio for stroke and transient ischaemic attack had been equal to that of variant Creutzfeldt-Jakob disease, clinicians and researchers interested in stroke would have had to read 525 000 papers in 1998 (about 10 000 per week)—an insufferable burden!




Publication ratios for 44 neurological conditions ordered by their incidence (top) and prevalence (bottom)

# BMJ Vol. 320 8 April 2000



This 38 year old man attended his local hospital with an apparently minor head injury after a work colleague dropped a nail gun on his head. His small scalp wound was dressed, and he was discharged. Ten days later he had a grand mal fit. On examination he had no neurological deficit but a positive Babinski's sign on the left. A computed tomogram of the head showed a 7 cm nail embedded in the right cerebral hemisphere. It was removed via a burr hole, and he made a full recovery.

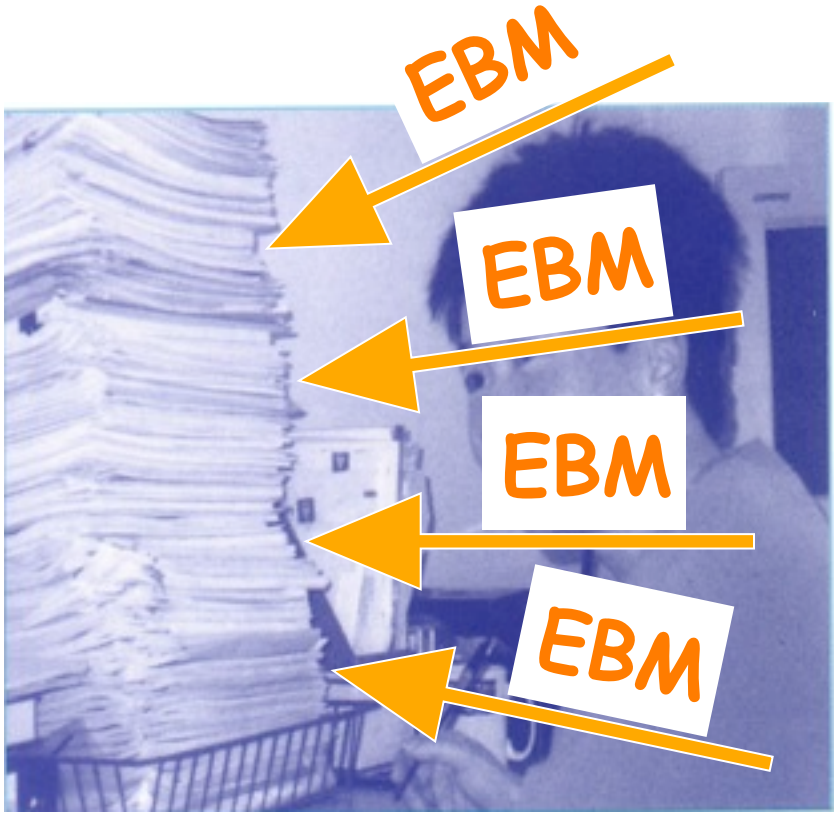
Arup Ray, registrar, Aloke Sen, senior house officer, A T King, consultant, John Thorne, registrar, department of neurosurgery, Hope Hospital, Manchester M6 8HD

# A comment on medical journals from Drummond Rennie deputy editor (west) JAMA

- There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print.

# New York Times (16 Febbraio 1988)

"…. the number of scientific articles and journal being published has grown so large that it is starting to confuse researchers, overwhelm the quality control system of science, encourage fraud and distort the dissemination of important findings."




Pila di articoli pubblicati ogni otto ore

# Evidence to recommendations

Misconceptions when going from synthesis to results to discussion

Potential solutions

- Structured framework (GRADE)
- Useful presentation to readers (Abstract, Summary of Findings Tables and Evidence Profiles, Plain Language Summaries)

# Treatments for precancerous cervical lesions

- WHO guidelines
- 10 systematic reviews

Question 1:
*What are the effects of cryotherapy compared to no treatment?*

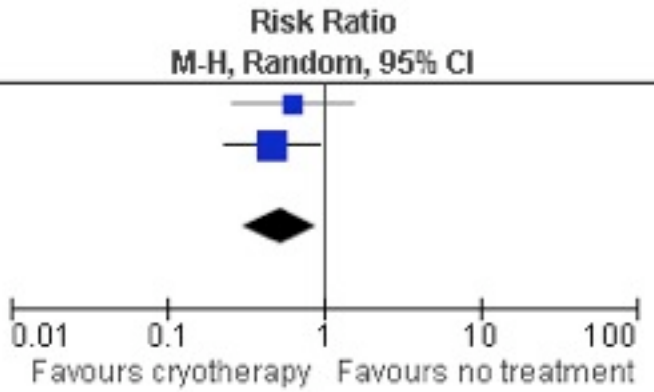
Outcome 1:
*Recurrence of lesion*

# Does cryotherapy reduce the risk of recurrence?

| Study or Subgroup | cryotherapy Events | Total | no therapy Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Poomtavorn 2009 | 6 | 38 | 12 | 49 | 38.8% | 0.64 [0.27, 1.56] |
| Siadi 1977 | 8 | 44 | 23 | 60 | 61.2% | 0.47 [0.23, 0.96] |
| **Total (95% CI)** | | **82** | | **109** | **100.0%** | **0.53 [0.31, 0.93]** |
| Total events | 14 | | 35 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.28$, $df = 1$ ($P = 0.59$); $I^2 = 0\%$

Test for overall effect: $Z = 2.23$ ($P = 0.03$)



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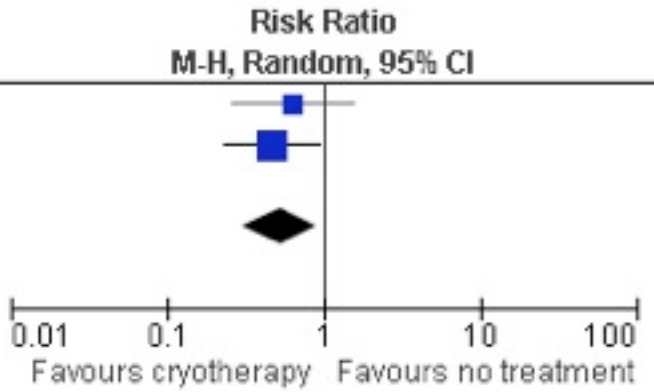
Test for overall effect: Z = 2.23 (P = 0.03)




Result:

The risk ratio for recurrence was 0.53 (95% CI 0.31, 0.93)

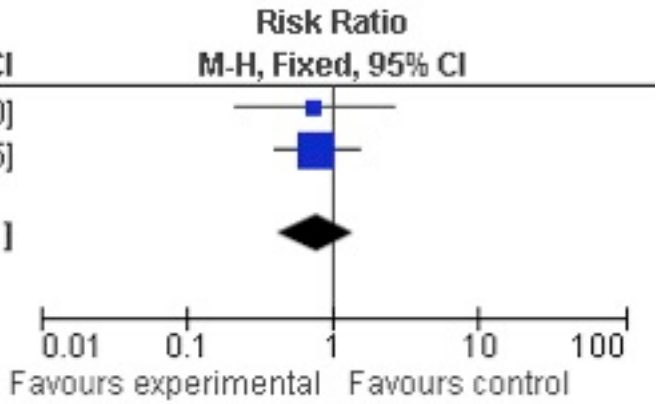
Conclusion:

Cryotherapy reduces the risk of recurrence.

# Does cryotherapy reduce the risk of recurrence?

| Study or Subgroup | cryotherapy Events | Total | no therapy Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Poomtavorn 2009 | 4 | 53 | 5 | 49 | 26.8% | 0.74 [0.21, 2.60] |
| Siadi 1977 | 10 | 44 | 16 | 55 | 73.2% | 0.78 [0.39, 1.55] |
| **Total (95% CI)** | | **97** | | **104** | **100.0%** | **0.77 [0.42, 1.41]** |
| Total events | 14 | | 21 | | | |

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)




Result:
The risk ratio for recurrence was 0.77 (95% CI 0.42, 1.41)

Conclusion:
There was a non-significant difference in the risk of recurrence.
OR
There was no effect of cryotherapy on the risk of recurrence.

# Questions to ask yourself

- Do I believe the results from these studies? Risk of bias
- Are the results consistent across studies? Heterogeneity
- Are these all of the studies? Reporting/publication bias
- Is this effect size precise? Imprecision
- How do these results apply? Applicability, directness

# Risk of bias

- ‘quality of the studies’

- Selection bias
- Performance bias
- Detection bias
- Attrition
- Reporting bias

RCT:
Cochrane Risk of Bias

Observational studies:
Newcastle-Ottawa Scale; Downs & Black

# Questions to ask yourself

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- Is this effect size precise? Imprecision
- How do these results apply? Applicability, directness

# GRADE criteria – a framework

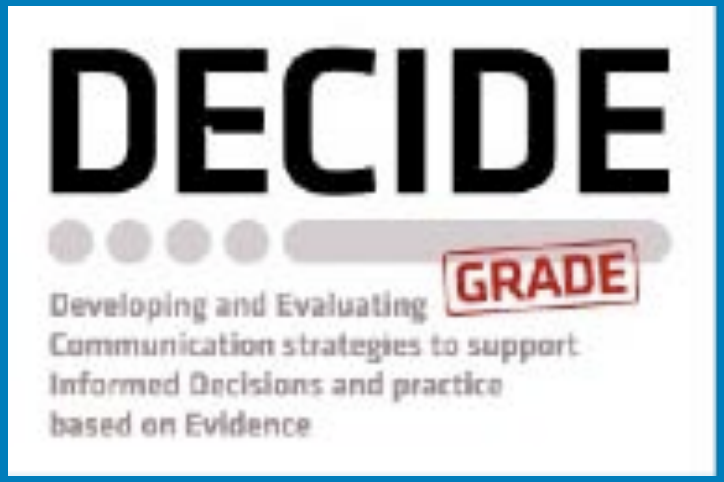
- Risk of bias
- Inconsistency
- Publication bias
- Imprecision
- Indirectness

GRADE

# Evidence profiles

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | Importance |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | oral leukotriene receptor antagonists | placebo | Relative (95% CI) | Absolute | | |
| **Daytime nasal symptoms (change from baseline) (follow-up 6 weeks; Better indicated by less)** | | | | | | | | | | | | |
| 2 | randomised trial | no serious limitations | no serious inconsistency | serious | no serious imprecision | none | 1632 | 1603 | - | SMD -0.09 (-0.11 to -0.05) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Nighttime symptoms (change from baseline) (follow-up 6 weeks; measured with: 4-point scale (0 - none; 3 - severe)range of scores: 0-3; Better indicated by less)** | | | | | | | | | | | | |
| 1 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1002 | 990 | - | mean -0.06 (-0.02 to -0.1)[1] | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Quality of life (follow-up 6 weeks; measured with: rhinoconjunctivitis quality-of-life questionnaire range of scores: 0-6; Better indicated by more)** | | | | | | | | | | | | |
| 2 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1632 | 1603 | - | not pooled[2] | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Quality of life (% with meaningful improvement) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 570/977 | 514/960 | RR 1.1 (1.02 to 1.19) | 53 more per 1000 (from 11 more to 101 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Daytime eye symptoms (follow-up 6 weeks; Better indicated by less)** | | | | | | | | | | | | |
| 1 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3,4] | none | 630 | 613 | - | not pooled[4] | ⊕⊕⊕O MODERATE | IMPORTANT |
| **Adverse effects (Upper respiratory infection) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 63/1632 | 45/1603 | RR 1.37 (0.94 to 2) | 10 more per 1000 (from 2 fewer to 28 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Adverse effects (Headache) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 61/1632 | 72/1603 | RR 0.83 (0.6 to 1.16) | 8 fewer per 1000 (from 18 fewer to 7 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
| **Adverse effects (other) (follow-up 6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | –/1632 | –/1603 | not pooled[5] | not pooled | ⊕⊕⊕⊕ HIGH | IMPORTANT |

[1] A second trial reported only that there was no statistically significant difference between the groups
[2] change in RQLQ from baseline was -0,15 (95% CI: -0.06 to -0.24) in one study, and -0,13 (95% CI: 0.00 to -0,25) in another.
[3] one trial
[4] authors stated only that there was no difference between the groups
5 There were many different adverse effects of uncertain relation to treatment and importance to patients; it was also uncertain how many occurred per patient.

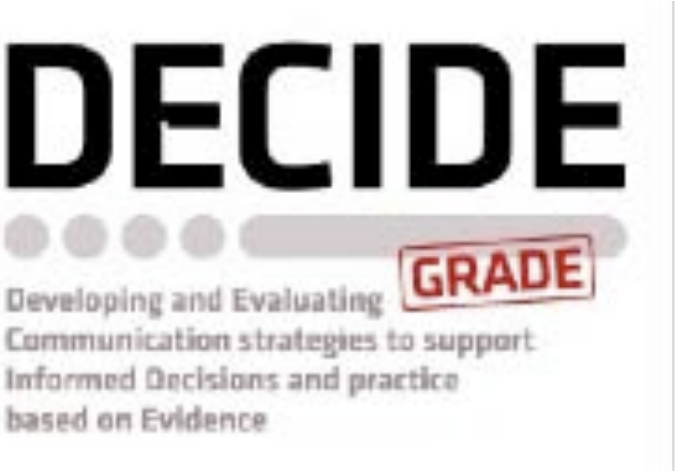



This research program has received funding from the European Union Seventh Framework Programme (*FP7 – HEALTH. 2010.3.1-1 – two stage)*

Healthcare decision makers face challenges in understanding guidelines, including the quality of the evidence upon which recommendations are made. Guideline are also typically developed as one-size-fits all package.

**Aim of the Research Program:** to improve the communication of evidence-based recommendations produced using the GRADE System to develop and evaluate methods that address the targeted dissemination of guidelines.

# GRADE




- **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation

- a consistent, rigorous, **transparent** grading system for evidence and recommendations to use when producing clinical practice guidelines

# Scenario

## Should apixaban, dabigatran or rivaroxaban be covered for patients with atrial fibrillation?

**Patients:** Patients with atrial fibrillation

**Intervention:** Apixaban, Dabigatran, Rivaroxaban

**Comparison:** Warfarin

**Background:** ***Warfarin*** reduces the risk of ischemic stroke in patients with atrial fibrillation, but increases the risk of hemorrhage and requires frequent blood tests and clinic visits to monitor the international normalized ratio (INR) and to adjust the dose. Moreover, warfarin interferes with some foods and many drugs.

***Apixaban, Dabigatran and Rivaroxaban*** are newer fixed-dose, oral anti-coagulants, each of which has been compared to Warfarin in randomized trials. There are no head-to-head comparisons of the three drugs. Their efficacy is not inferior to that of warfarin in preventing ischemic stroke. Their use requires no INR monitoring and is associated with less drug-drug interactions than warfarin.

# Should apixaban, dabi… rivaroxaban be covered for … atrial fibrillatio…

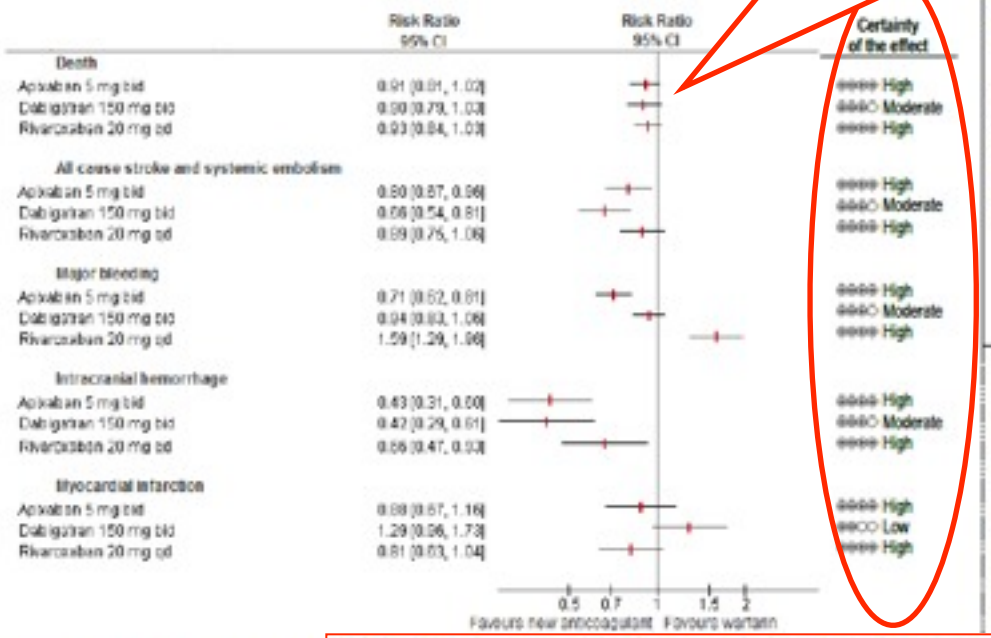
No difference in Death.
Favour to Apixaban and Dabigatran for Stroke.
Favour to Apixaban for Major Bleed

| CRITERIA | JUDGEMENT | EVIDENCE |
|---|---|---|
| Overall, are the anticipated desirable effects large? | Favours apixaban ☐ Favours dabigatran ☐ Favours rivaroxaban ☐ Uncertain ☐ | |
| Overall, are the anticipated undesirable effects small? | Favours apixaban ☐ Favours dabigatran ☐ Favours rivaroxaban ☐ Uncertain ☐ | |
| Overall, what is the certainty of the anticipated effects (in our setting)? | Favours apixaban ☐ Favours dabigatran ☐ Favours rivaroxaban ☐ Uncertain ☐ | |

BENEFITS & HARMS

**Summary of overall results**

(Link to summary of finding for apixaban, dabigatran, rivaroxaban)




anticoagulant. The certainty of differences in the effects is lower because these are indirect (between study) comparisons.

**Subgroup considerations**

Consideration should also be given to restricting coverage to patients with poor INR control with warfarin despite documented adequate medication compliance, CHADS2>2 and <=2 and age <75 and >75.

Compliance might potentially be more of a problem with dabigatran than warfarin since monitoring and frequent clinic visits are not needed, but there is not evidence to support or refute this.

There is currently no antidote for apixaban, dabigatran or rivaroxaban. This is a concern for healthcare providers who have to manage bleeding patients receiving these drugs and might lead to worse outcomes in such patients.

Average effects for all patients in the trial. Eff… subgroups with different levels of warfarin co…

*Other potential undesirable effects*: The r… rivaroxaban is uncertain.

*Burden of treatment*:
*Warfarin*: daily medication, lifestyle limitations
*Apixaban*: twice daily medication
*Dabigatran*: twice daily medication
*Rivaroxaban*: daily medication

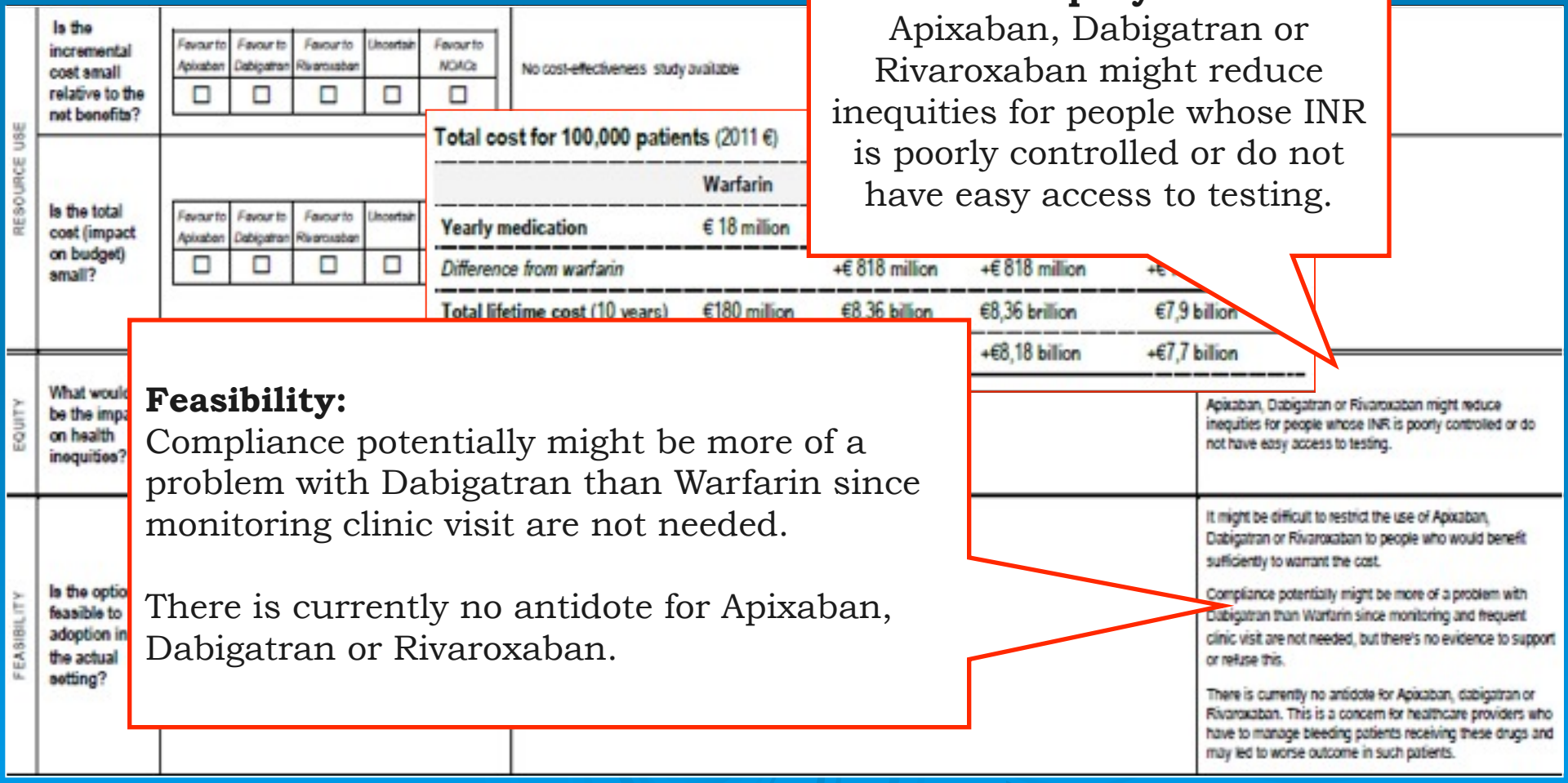
**Subgroup considerations**: Consideration should be given to restricting coverage to patients with poor INR control with warfarin despite documented adequate medication compliance.

# Should apixaban, dabigatran or rivaroxaban be covered for patients with atrial fibrillation?

**Equity:**
Apixaban, Dabigatran or Rivaroxaban might reduce inequities for people whose INR is poorly controlled or do not have easy access to testing.

**Feasibility:**
Compliance potentially might be more of a problem with Dabigatran than Warfarin since monitoring clinic visit are not needed.

There is currently no antidote for Apixaban, Dabigatran or Rivaroxaban.



# Decision Summary

| | | | | | |
|---|---|---|---|---|---|
| **Balance of desireable and undesirable consequences of covering the intervention** | Undesirable consequences *clearly outweigh* desirable consequences | Undesirable consequences *probably outweigh* desirable consequences | The balance between desirable and undesirable consequences is *closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences | Desirable consequences *clearly outweigh* undesirable consequences |
| | ☐ | ☐ | ✗ | ☐ | ☐ |
| **Decision** | **Do not cover** | | **Coverage with evidence development (which Drug/s?)** | | **Cover (which Drug/s?)** |
| | ☐ | | ☐ | | ✗ |
| **Comments** | | | | | **Apixaban** |
| **Restriction** (any restriction on coverage of the intervention) | Just for patients with a proven bad control of INR with Warfarin | | | | |
| **Justification** (reason for deciding the intervention should be covered, covered with evidence development or not covered) | | | | | |
| **Implementation considerations** (details regarding the decision, including any restrictions on coverage and conditions for coverage with evidence development) | Monitoring of compliance and control of INR to be sure that only the patients that would really benefit from the new drug will receive it. Expecially due to the difference in costs. | | | | |

# Health system and public health evidence to decision framework

| Factors to consider |
| --- |
| Quality of the evidence |
| Balance between benefits and harms |
| Patient values and preferences |
| Resource use (cost, human resources, etc.) |

| Strength of recommendation | Wording |
| --- | --- |
| **Strong** recommendation for | We recommend... |
| **Strong** recommendation against | We recommend not... |
| **Weak/conditional** recommendation for | We suggest... |
| **Weak/conditional** recommendation against | We suggest not.... |

GRADE DECIDE

# Grazie per l'attenzione

## I miei contatti

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