Handout L1

Why do we need systematic reviews and meta-analyses?

Matthias Egger

NETHERLANDS INSTITUTE FOR HEALTH SCIENCES | ERASMUS MC ERASMUS UNIVERSITY MEDICAL CENTER ROTTERDAM

SUMMER PROGRAMME 2016

WWW.NIHES.NL

A heart attack in Burgdorf 1981

- 55-year old man
- Anterior myocardial infarction
- Regular heart beat
- Overweight
- No signs of cardiac failure
- No obstructive lung disease

A heart attack in Burgdorf 1982

- **55-year old man**
- **Anterior myocardial infarction**
- **Regular heart beat**
- **Overweight**
- **No signs of cardiac failure**
- **No obstructive lung disease**
- ***BETA-BLOCKER ?***

The New England
Journal *of* Medicine

Volume 304 APRIL 2, 1981 Number 14

TIMOLOL-INDUCED REDUCTION IN MORTALITY AND REINFARCTION IN PATIENTS SURVIVING ACUTE MYOCARDIAL INFARCTION

THE NORWEGIAN MULTICENTER STUDY GROUP

We conclude that long-term treatment with timolol in patients surviving acute myocardial infarction reduces mortality and the rate of reinfarction. (N Engl J Med 1981;304:801-7).

The New England
Journal *of* Medicine

Volume 307 NOVEMBER 18, 1982 Number 21

A LONG-TERM PREVENTION STUDY WITH OXPRENOLOL IN CORONARY HEART DISEASE

S.H. Taylor, Ph.D., M.D., B. Silke, M.D., A. Ebbutt, Ph.D., G.C. Sutton, M.D., B.J. Prout, Ph.D., M.D., and D.M. Burley, M.B., Ch.B

Abstract We carried out a randomized double-blind (P<0.001). In 274 patients with treatment

between 1 and 90 months previously. ***Overall, there was no difference in mortality or cardiac events between the placebo and oxprenolol groups.*** The

infarction oxprenolol increased the six-year cumulative survival rate from 77 to 95 per cent

relatively soon after myocardial infarction. (N Engl J Med 1982;307:1293-1301.

Reduction in mortality after myocardial infarction with long-term beta-adrenoceptor blockade

Multicentre international study: supplementary report

British Medical Journal, 1977; 2: 419-421

Until the results of further trials are reported long-term ***beta-adrenoceptor blockade*** (possibly up to two years) ***is recommended after uncomplicated anterior myocardial infarction.***

The figures for non-fatal reinfarction (97 in the placebo group, and 75 in the practolol group) were not significantly different. Patients with pre-entry

Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy, and Yugoslavia

N S Baber, D Wainwright Evans, G Howitt, M Thomas, C Wilson, J A Lewis, P M Dawes, K Handler, R Tuson

From ICI Pharmaceuticals Division, Macclesfield; Papworth Hospital, Cambridge; Manchester Royal Infirmary; Midhurst Medical Research Institute; and Waveney Hospital, Ballymena

SUMMARY A multicentre study of survivors of an anterior myocardial infarction is reported. The trial consisted of 720 patients and was a double-blind, placebo-controlled study with propranolol 40 mg three times a day. Trial entry was at two to 14 days (mean 8.5 days) and follow-up at one, three, and in most centres, six and nine months. ***The trial was designed to detect a 50 per cent reduction in mortality and this was not shown.*** The non-fatal reinfarction rate was similar in both groups. interacted with treatment.

Information overload

In 1995 the most important internal medicine journals published

7000 articles

7000 : 365 = 19 articles / day

“ … we still have no clear evidence that beta-blockers improve long-term survival after infarction despite almost 20 years of clinical trials ”

Mitchell. *BMJ* 1981;282:1565-70

“ … it seems perfectly reasonable to treat patients who have survived a myocardial infarction with timolol ”

Hampton. *Eur Heart J* 1981;2:259-268

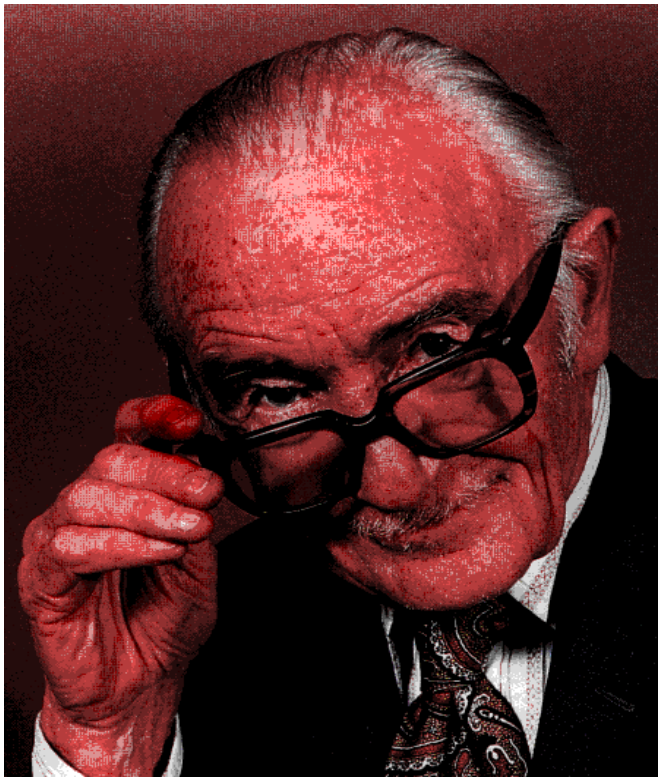

h. Daumier

Traditional reviews

- Subjective
- Methods not transparent
- Results not reproducible
- No quantitative summary
- Uncertainty remains

Mulrow. *Ann Intern Med* 1987

Archie Cochrane (1979)



“ It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials ”

Systematic reviews

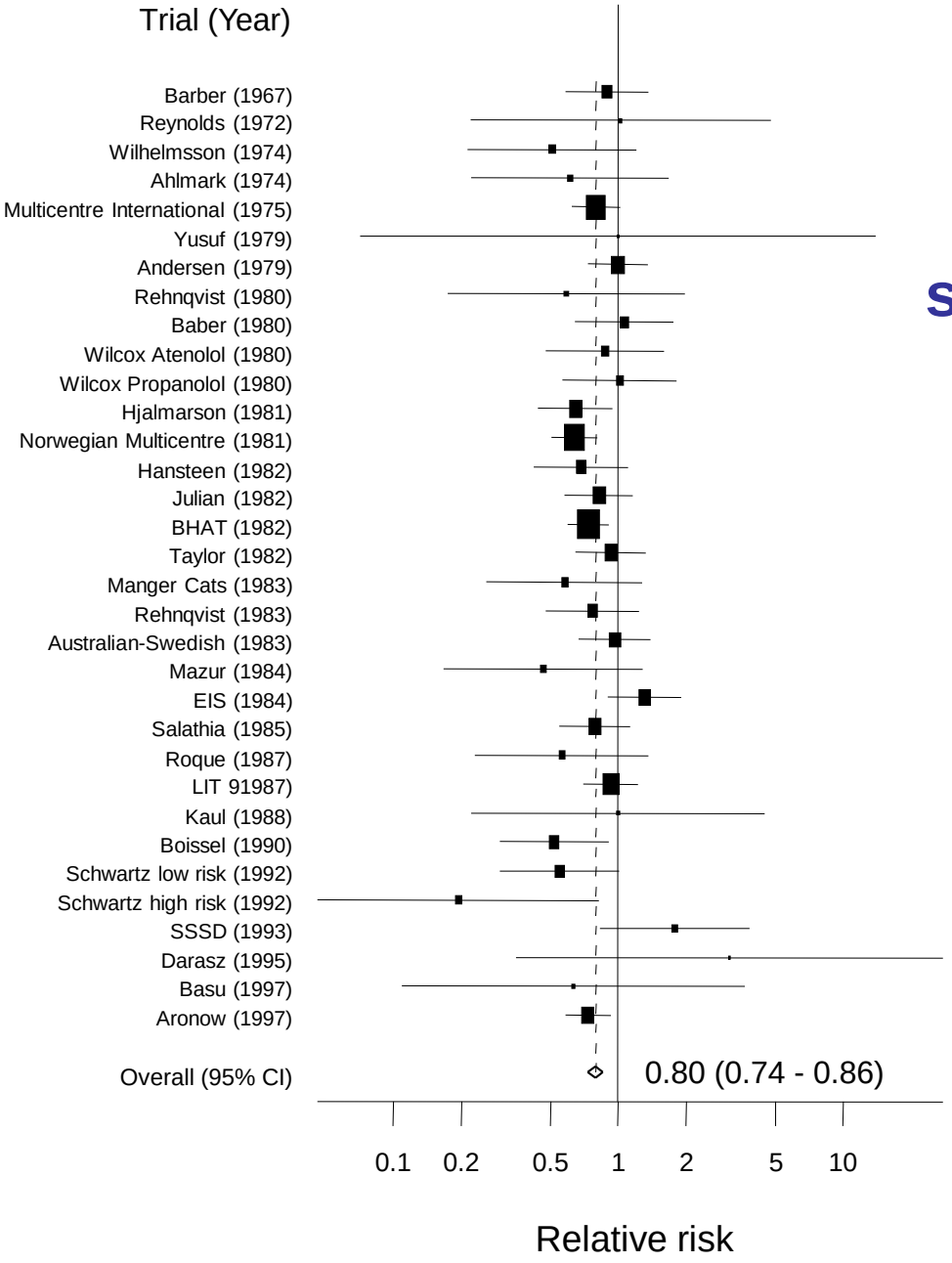
- Systematic approach to minimize biases and random errors
- Always includes materials and methods section
- May include meta-analysis

Chalmers and Altman 1994

Meta-analysis

- A statistical analysis which combines the results of several independent studies considered by the analyst to be ‘combinable’

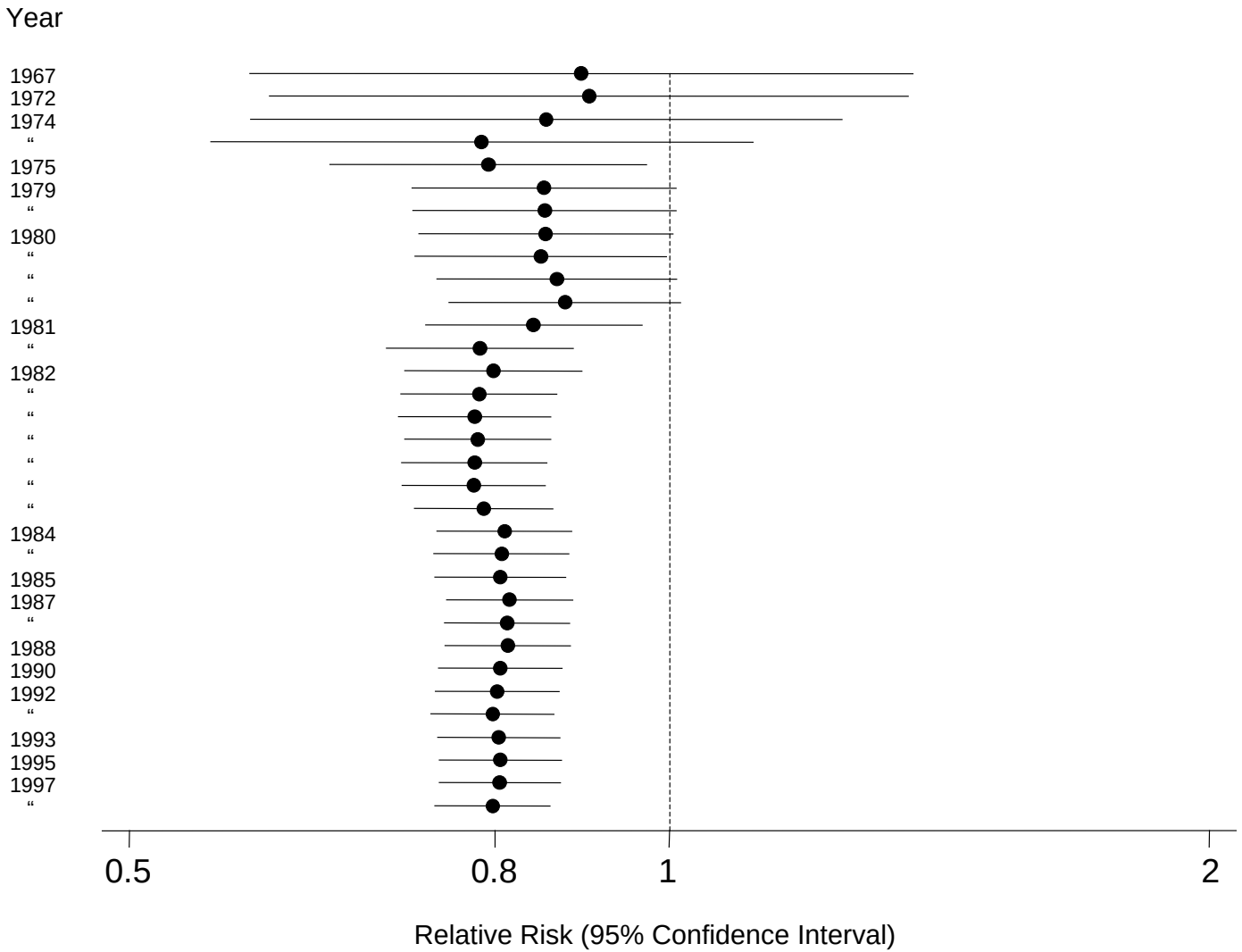
Huque 1988



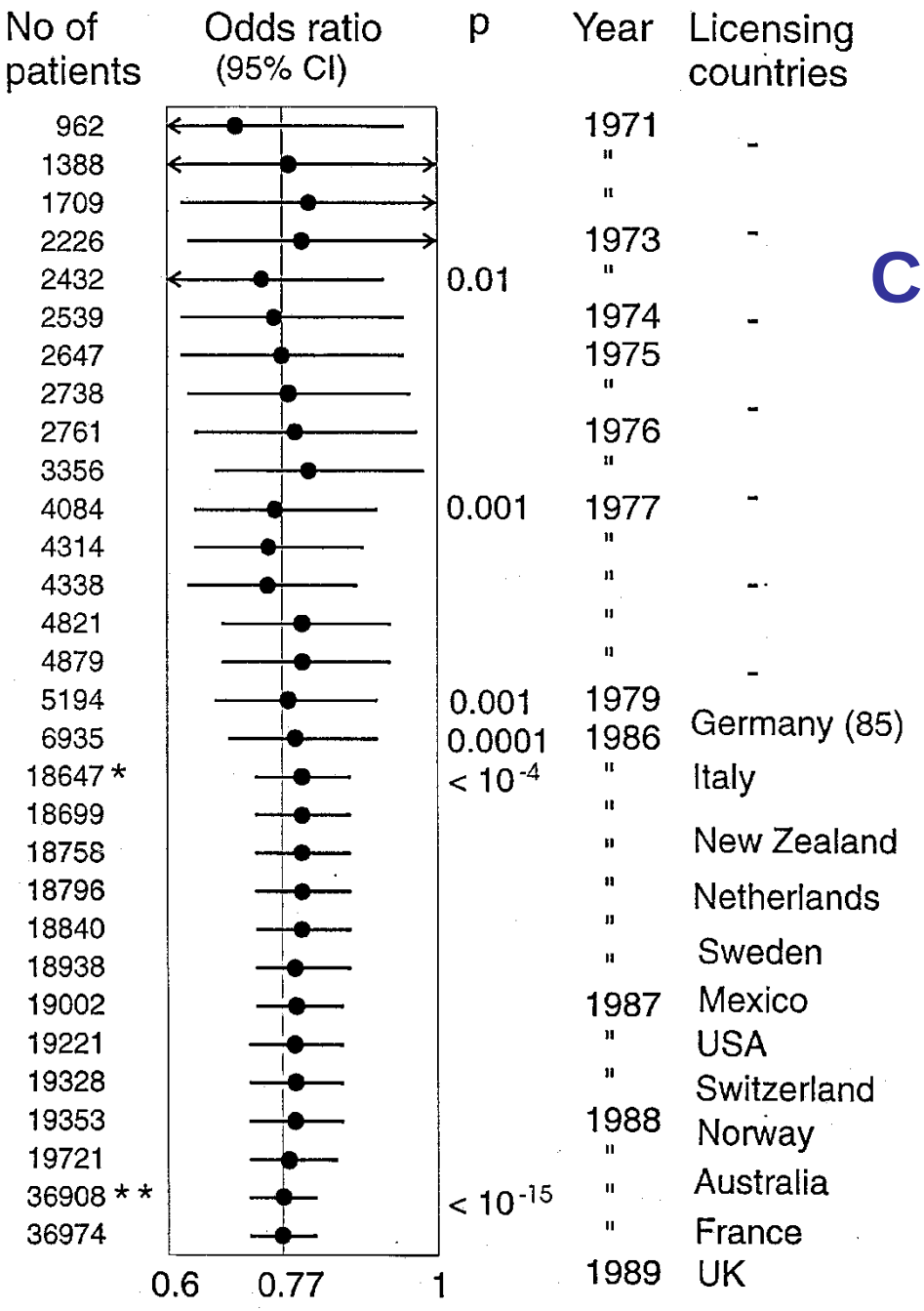
Mortality results from 33 trials of beta-blockers in secondary prevention after myocardial infarction

Adapted from Freemantle et al *BMJ* 1999

Cumulative meta-analysis of 33 trials of beta-blockers in secondary prevention after myocardial infarction



Calculated from Freemantle et al *BMJ* 1999



Streptokinase in acute myocardial infarction: Cumulative meta-analysis

"Newtonian"

Mann, *Science,* 1990

* includes GISSI-1, ** ISIS-2

So why are up-to-date systematic reviews so necessary?

“Because the results of a particular research study cannot be interpreted with any confidence unless they have been synthesised, systematically, with the results of all other relevant studies.

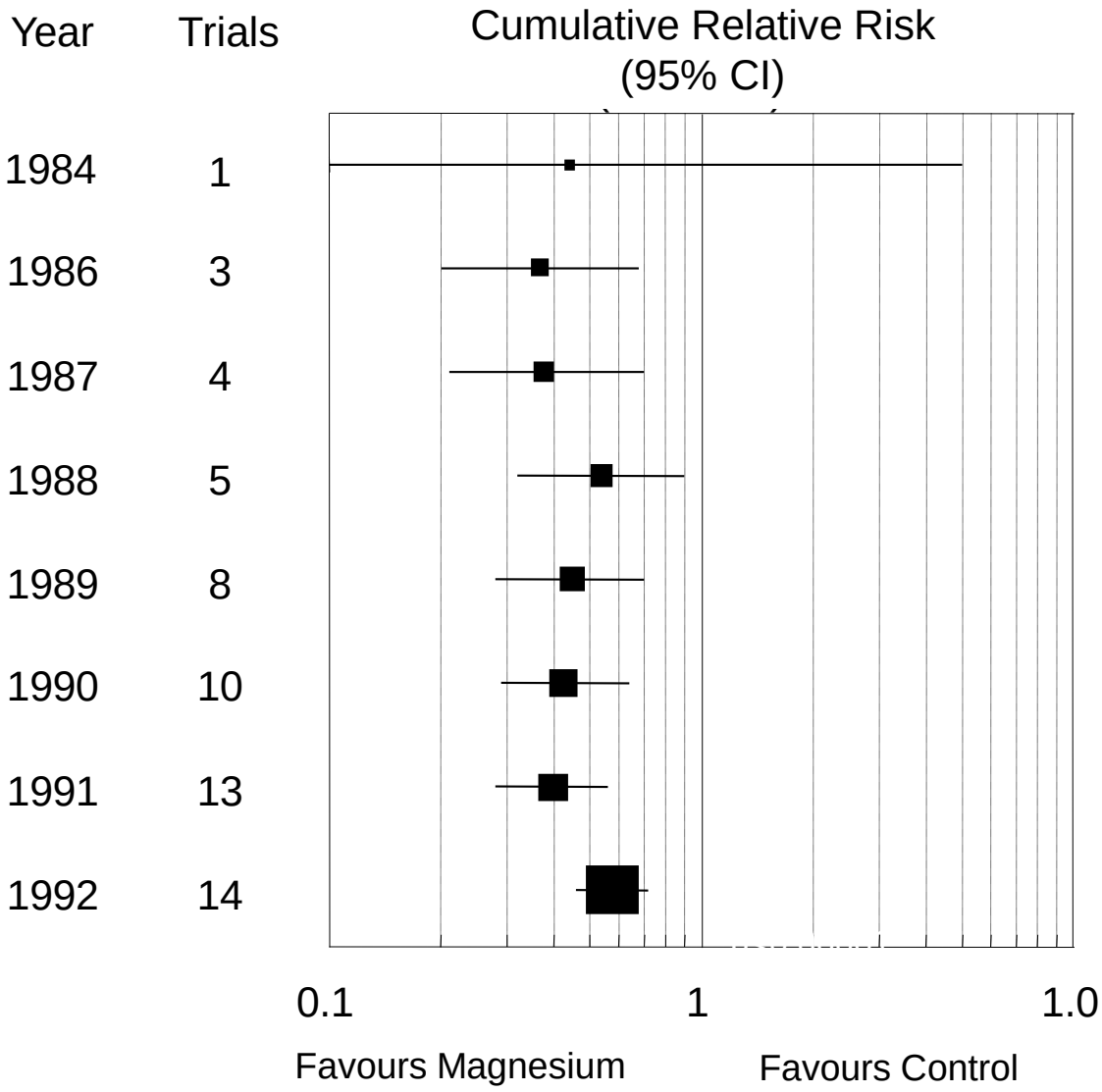
Science is meant to be cumulative, but researchers usually don’t cumulate scientifically…”

Iain Chalmers

Potentials of Systematic Reviews

- Objective appraisal of the evidence
- Enhanced precision of pooled estimate
- Timely introduction of effective treatments
- Promising future research questions

Magnesium in acute myocardial infarction: Cumulative meta-analysis



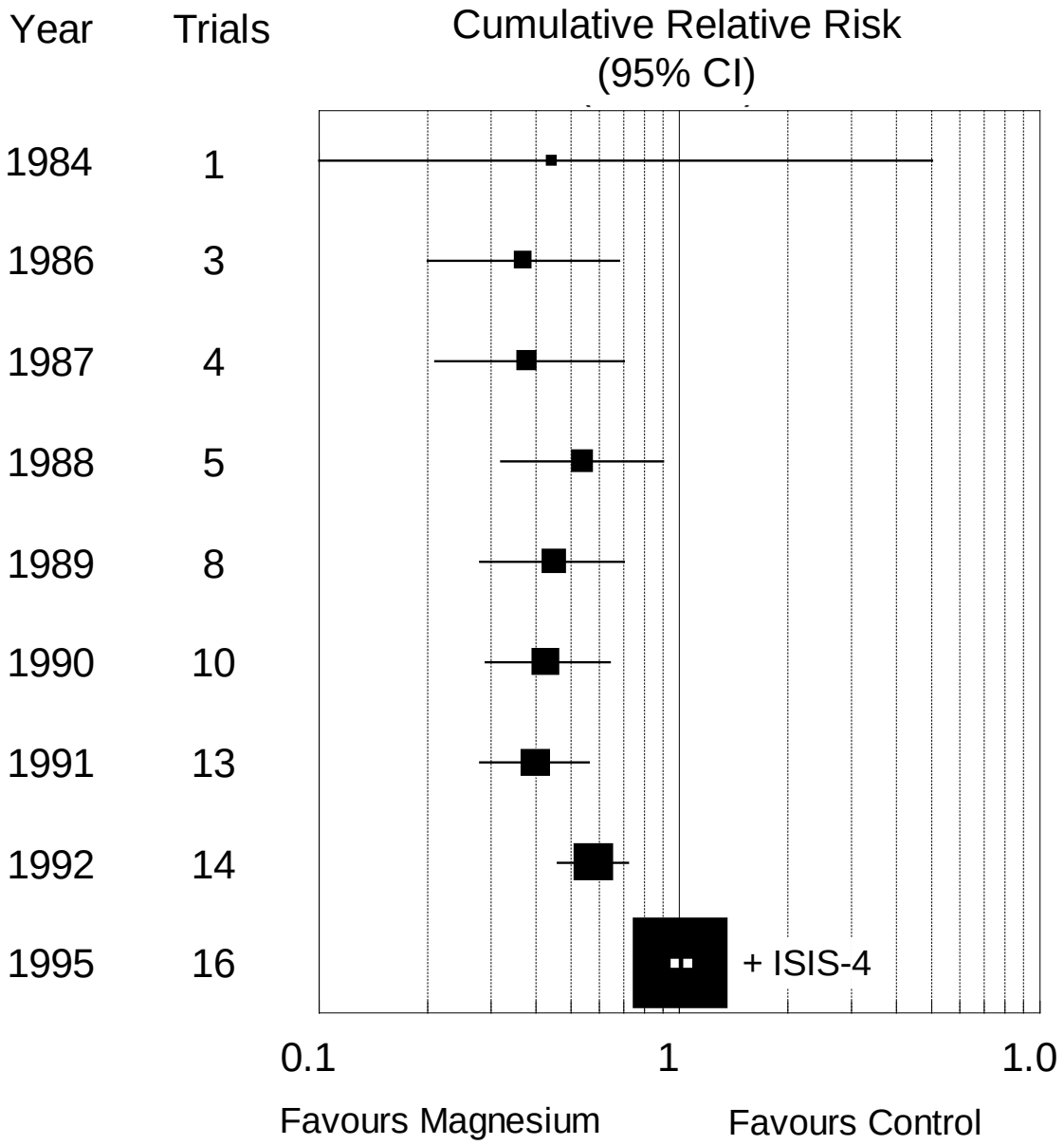
Editorial

Intravenous Magnesium in Acute Myocardial Infarction

An Effective, Safe, Simple and Inexpensive Intervention

Salim Yusuf FRCP, DPhil; Koon Teo, FRCPC, PhD; and Kent Woods, MD, FRCP

Circulation *Vol 87, No 6 June 1993*



Egger and Davey Smith, *Lancet* 1994

- ‘An exercise in mega-silliness’
- ‘Meta-analysis … should be stifled at birth’
- ‘… an obstetrical Baader-Meinhof gang’
- ‘A tool has become a weapon’
- ‘I still prefer the conventional narrative review article’

Publication is an ethical imperative !

“Nine patients died in the lorcainide group and one in the placebo group…”

“The development of lorcainide was abandoned for commercial reasons, and this study was therefore never published…”

“The results described here ….might have provided an early warning of trouble ahead.”

Cowley et al. *Int J Cardiol* 1993

Principles and procedures

- Formulate the question
- Locate and select studies
- Critically appraise studies
- Analyse and interpret results

Formulate review question

P - Who is the **p**atient or **p**articipant?

I - What is the **i**ntervention or exposure?

C - What is the **c**omparison group?

O - What is the **o**utcome or endpoint?

+ study design

Locate studies

Develop search strategy considering the following sources:

- MEDLINE, EMBASE, other databases
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Trials registers
- Hand searching of key journals
- Personal communication with experts in the field

Select studies

- Have eligibility checked by >1 observer
- Develop strategy to resolve disagreements
- Keep log of excluded studies, with reasons for exclusions

Extract data

- Design and pilot data extraction form
- Consider data extraction by >1 observer
- Consider blinding of observers to

  authors,

  institutions and journals

Analyse and present results

- Tabulate results from individual studies
- Examine forest plot
- Explore possible sources of heterogeneity
- Consider meta-analysis of all trials or subgroups of trials
- Perform sensitivity analyses
- Make list of excluded studies available to interested readers

Interpret results

- Consider limitations, including publication and related biases
- Consider strength of evidence
- Consider applicability

Write up and publish

- PRISMA Statement
- MOOSE proposal
- See www.equator-network.org for current reporting guidelines

OPEN ACCESS Freely available online

PLoS MEDICINE

Guidelines and Guidance

*P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement

David Moher[1,2]*, Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

1 Ottawa Methods Centre, Ottawa Health Research Institute, Ottawa, Ontario, Canada, **2** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **3** Università di Modena e Reggio Emilia, Modena, Italy, **4** Centro Cochrane Italiano, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy, **5** Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

Introduction

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

clinicians, medical editors, and a consumer. The objective of the Ottawa meeting was to revise and expand the QUOROM checklist and flow diagram, as needed.

The executive committee completed the following tasks, prior to the meeting: a systematic review of studies examining the quality of reporting of systematic reviews, and a comprehensive literature search to identify methodological and other articles that might inform the meeting, especially in relation to modifying checklist items. An international survey of review authors, consumers, and groups commissioning or using systematic reviews and meta-analyses was completed, including the International Network of Agencies for Health Technology Assessment (INAHTA) and the Guidelines International Network (GIN). The survey aimed to ascertain views of QUOROM, including the merits of the existing checklist items. The results of these activities were presented during the meeting and are summarized on the PRISMA Web site (http://www.prisma-statement.org/).

Table 1. Checklist of items to include when reporting a systematic review or meta-analysis.

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	