
We are
Knowledge
Brokers

LEARNING OBJECTIVES

1.explain, apply, and interpret basic biostatistical analytic techniques, and their appropriate applications;

2.identify and differentiate between study designs currently used in the evaluation of pharmaceuticals;

3.critically evaluate published research to make judgments about the validity, value, and applicability of the findings to patient care;

4.identify, analyze, interpret, and appropriately apply the literature to clinical practice.

OVERALL OBJECTIVEs
Develop your Ability to Assess Health Claims

Popular drugs for colds, allergies, sleep linked to dementia

The NEW ENGLAND JOURNAL of MEDICINE

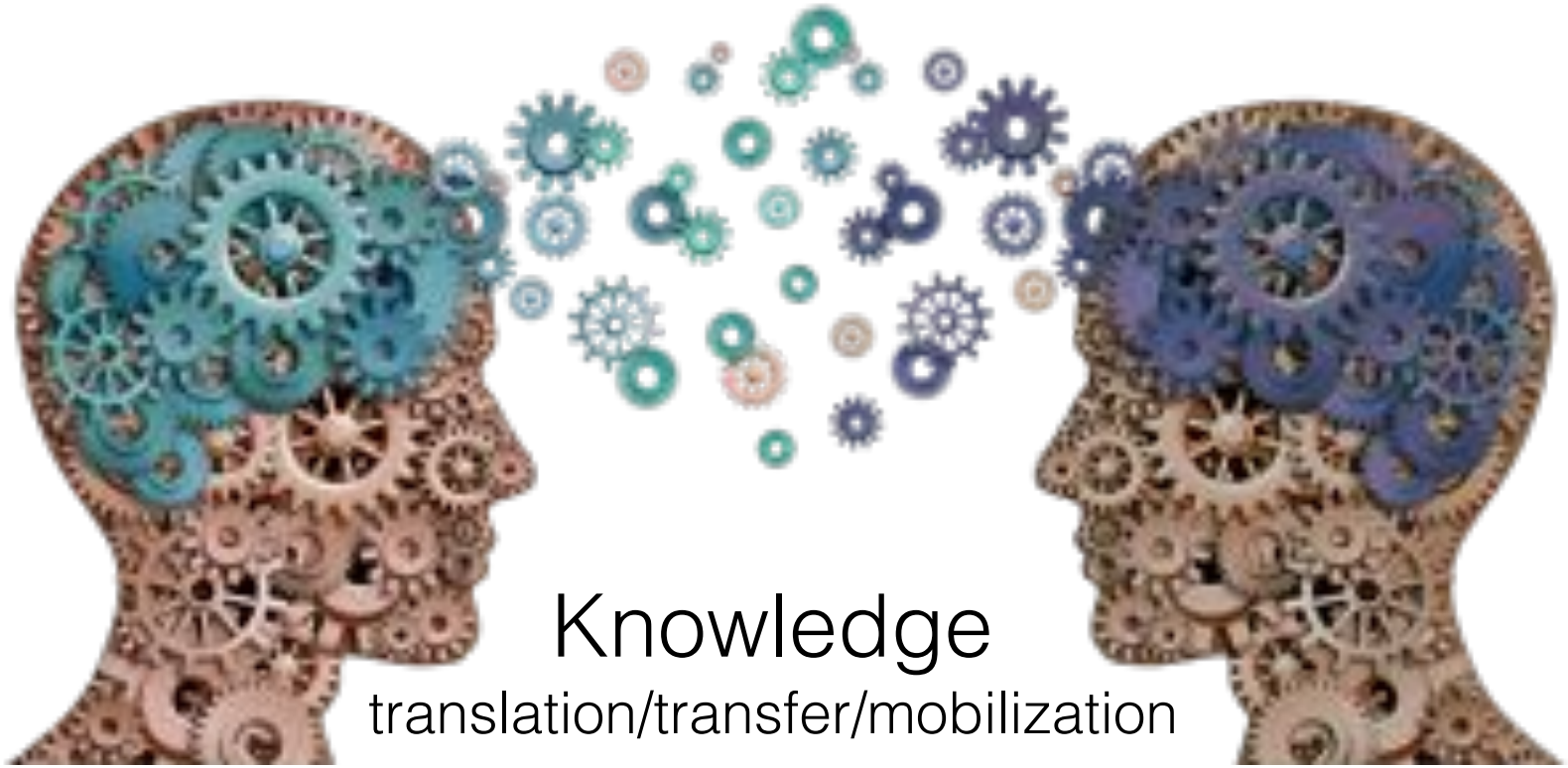
ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease (Review)

Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M, Stranges S

THE COCHRANE COLLABORATION®



Knowledge

translation/transfer/mobilization

BELIEF

All Health Care Providers should have their practice underpinned by the best available evidence

IT'S NOT ABOUT GUIDELINES

140/90
< 6.5%
< 2.0

GUIDELINES RARELY CONSIDER
PATIENT PREFERENCES

IT'S NOT ABOUT RCTs

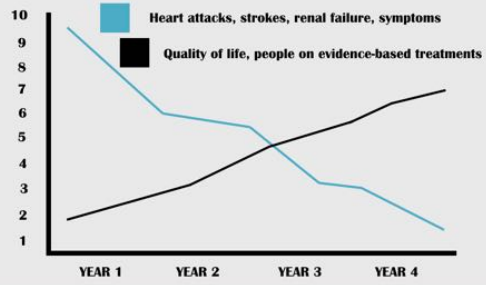
RCTs ARE USEFUL
BUT THEY ONLY
HELP
INFORM DECISIONS

p<0.05 ≠ GOOD p>0.05 ≠ BAD

IT'S NOT CHECKBOX MEDICINE

PEOPLE
DON'T
FIT
INTO BOXES

IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES



IT'S NOT SOMETHING "NEW"

DOING THE RIGHT THING
IS NOT A
NEW IDEA

IT'S NOT ABOUT IGNORING BASIC SCIENCE

WE NEED TO UNDERSTAND
HOW IT WORKS

IT'S NOT ABOUT SAVING MONEY

RATIONING
IS NOT THE
MOTIVE

IT'S NOT ABOUT ZERO COMPETING INTERESTS

RESEARCH
COSTS MONEY
SOMEBODY HAS TO PAY FOR IT

WE NEED TO UNDERSTAND
BIAS IS
EVERYWHERE

WHAT IT IS

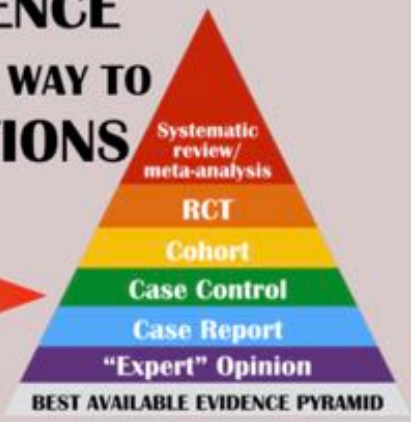
IT'S A WAY OF THINKING

EVIDENCE-BASED PRACTICE

BEST AVAILABLE EVIDENCE

USED IN A **HIERARCHICAL** WAY TO ANSWER **CLINICAL QUESTIONS**

Patient
Intervention
Comparator
Outcome



USING CLINICAL EXPERTISE

Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful

INFORMING PATIENTS & ELICITING & INTEGRATING PREFERENCES

Wrong guidelines: why and how often they occur

Primiano Iannone,[1] Nicola Montano,[2] Monica Minardi,[3] James Doyle,[3] Paolo Cavagnaro,[4] Antonino Cartabellotta[5]

"Unfortunately, depending on how their reliability is measured, up to 50% of guidelines can be considered untrustworthy. This carries serious consequences for patients' safety, resource use and health economics burden."

EBM 2017;22:1-3

Wrong guidelines: why and how often they occur

Primiano Iannone,[1] Nicola Montano,[2] Monica Minardi,[3] James Doyle,[3] Paolo Cavagnaro,[4] Antonino Cartabellotta[5]

"guideline reliability is largely over-stated, and guidelines still suffer methodological flaws, limited panel composition and conflicts of interests, making their conclusions often untrustworthy. Even when evidence-based methodology is claimed, it is often not fully adopted and the 'evidence-based quality mark' gets misappropriated by vested interests"

EBM 2017;22:1-3

We recommend

- those involved in the conduct of clinical research (universities/research institutions/ industry), should provide training in research methods and the use of statistics in evaluating the benefits and harms of medicines for research staff across all career stages as part of their continuing professional development
- similar courses should be provided for healthcare professionals by universities or CPD programmes
- existing courses should also be reviewed and, where necessary, new courses should be established to accommodate the full range of evidence-generating approaches for assessing the benefits and harms of medicines

Universities and research institutions should play a greater role in ensuring that the research they host is portrayed accurately in the media.

“It’s a statistically significant finding”

There are always 3 possibilities that must be considered:

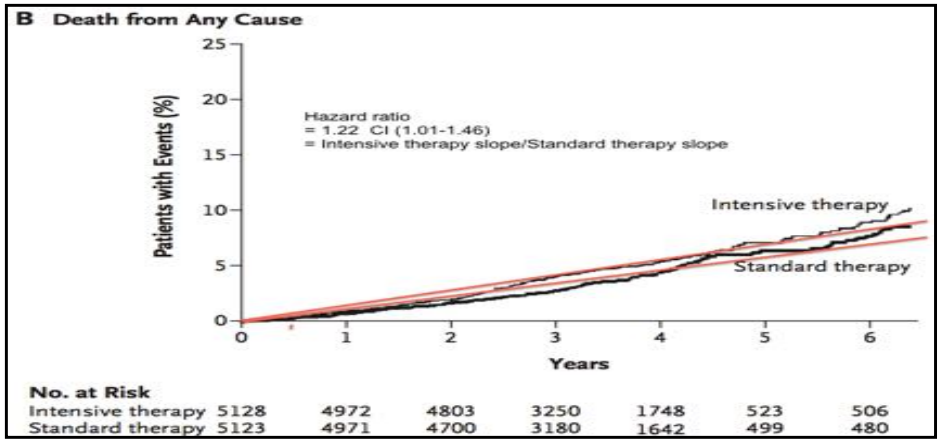
1. The observed difference was due to chance
2. The observed difference was due to confounding or other source of bias
3. If neither 1 nor 2 is believed to have caused the difference, then by simple elimination, it is inferred that the treatment caused it

Similar but different relatives

Relative risk/risk ratio (RR) - ratio of two probabilities (%) at one point in time - treatment/control

- eg 8% vs 10% - RR = 8/10 = 0.8
- most useful in low probability events

Hazards ratio (HR) - ratio of two hazard rates (slopes) over a time period



Odds ratio (OR) - ratio of two odds (25/1) - typically used in case-control studies - typically the incidence is not known

OR is a reasonable estimate of the **RR** if a disease is "rare" <~15% but treating an **OR** as if it were an accurate estimate of the **RR** will typically overestimate both the likely benefits and harms of treatment

Course Material

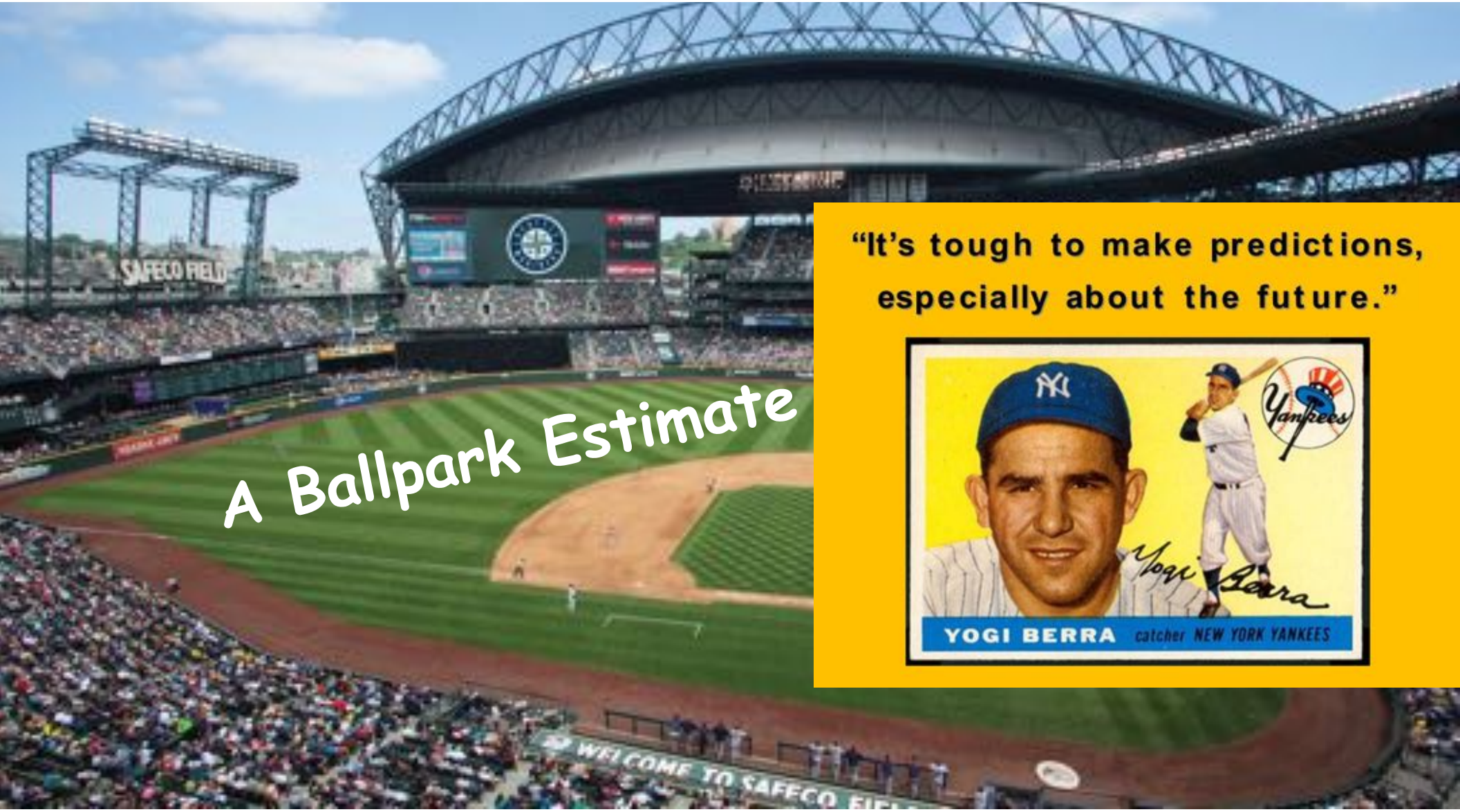
1. Evidence Appraisal Content
2. Evidence Appraisal Work Book

For Course Material Please Go To
https://therapeuticseducation.org/boot-camp

Healthcare should be all about
Figuring out AND Explaining about

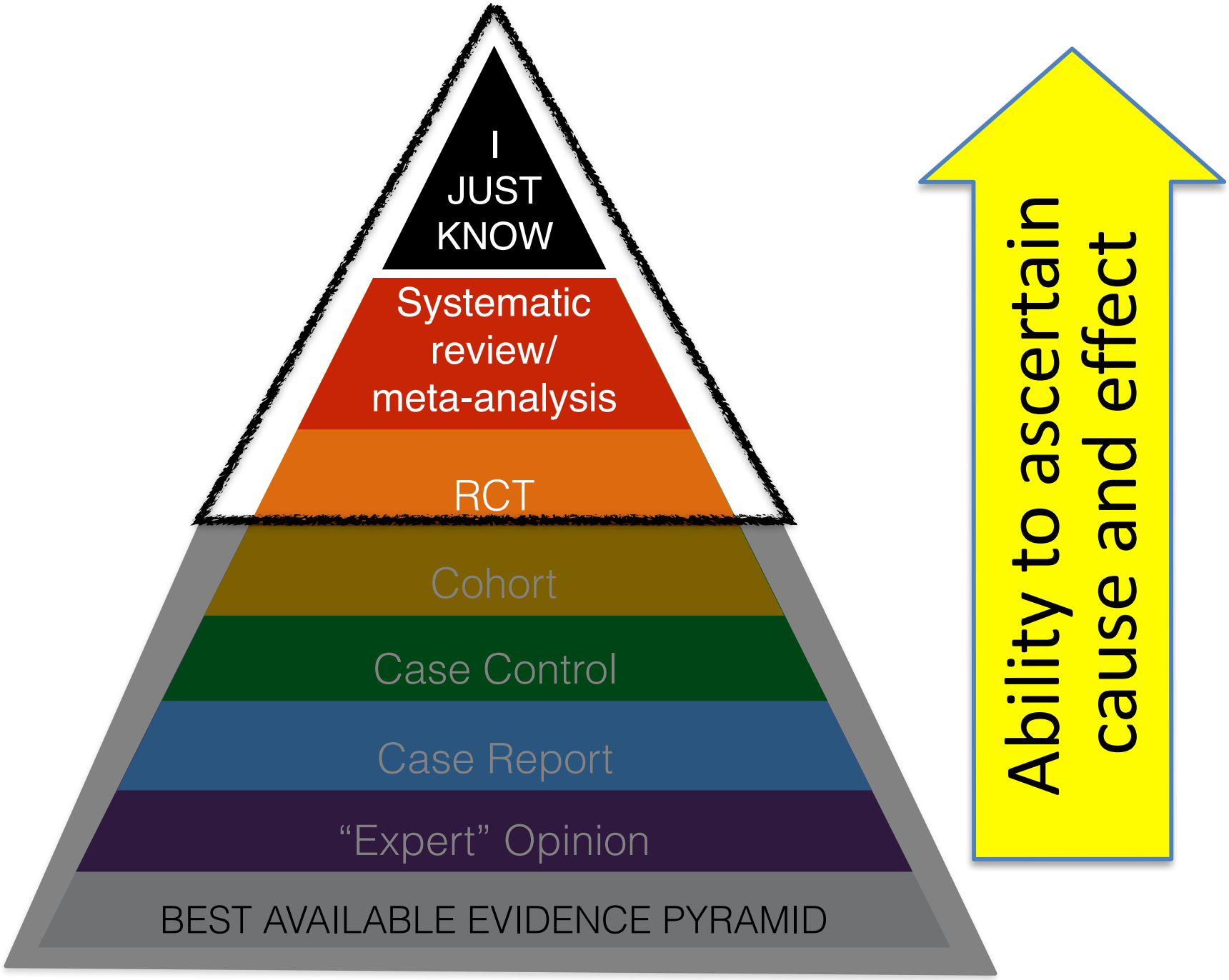
The Chance of Something Happening
WITH NO TREATMENT
VS
The Chance of Something Happening
WITH TREATMENT
over a period of time

It's really THAT simple



Trials almost never include people exactly like the person in front of you - genetic mongrels

All results from individual trials or meta-analyses are by definition ballpark estimates



Need different evidence for different questions

It’s a Mindset

SCIENCE: NOT JUST FOR SCIENTISTS

We believe *that science is a human endeavour; it’s a way to ask questions about the world and test them out. It’s not just a list of facts;* ***it’s a mindset*** *owned by anyone who approaches the world in an* ***open-minded, sceptical, logical, systematic, empirically-oriented, tentative and curious way.*** *It applies in the natural and social sciences, as well as technology, engineering and mathematics.*

How To Critically Appraise

an RCT in 10 minutes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

ABSTRACT

in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 99% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

*Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in the Appendix.

This article (10.1056/NEJMoa0802743) was published at www.nejm.org on June 9, 2008.

N Engl J Med 2008;358:2545-59.

TYPE 2 DIABETES MELLITUS IS A METABOLIC disease that is diagnosed on the basis of sustained hyperglycemia. People with type 2 diabetes are at elevated risk for a number of serious health problems, including cardiovascular disease, premature death, blindness, kidney failure, amputations, fractures, frailty, depression, and cognitive decline.[1] In prospective epidemiologic studies, the incidence of many of these outcomes is directly associated with the degree of hyperglycemia, as measured by the plasma glucose or the glycated hemoglobin level, a measure of the mean blood glucose level during the previous 2 to 3 months. Thus, after adjustment for other risk factors, an increase of 1% in the glycated hemoglobin level is associated with an increase of 18% in the risk of cardiovascular events,[2] an increase of 12 to 18% in the risk of death,[3,4] and an increase of 37% in the risk of retinopathy or renal failure.[5]

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and were provided with glucose-lowering medications (from a study-supervised formulary) and glucose-monitoring supplies. Any marketed antihyperglycemic therapy that was not provided by the formulary could also be prescribed to any patient but was not provided by study investigators. Therapeutic regimens were individualized at the discretion of the investigators and patients on the basis of study-group assignment and the response to therapy. Adverse effects of therapy were carefully audited both locally and centrally to ensure the safety of the patients.[12]

Patients in the intensive-therapy group attended monthly visits for the first 4 months and then every 2 months thereafter, with at least one interim phone call, with the aim of rapidly and safely reducing glycated hemoglobin levels to below 6.0%. Additional visits were scheduled as needed to achieve glycemic goals, as described previously.[6,13] Patients in the standard-therapy group had glycemic management visits every 4 months

monitor the primary outcome and deaths from any cause, ensure the safety of patients, make recommendations to continue or alter the study design, and advise the NHLBI if there was clear evidence of benefit or harm. After reviewing mortality trends for several months (and as part of a preplanned safety analysis), on January 8, 2008, the committee concluded that the harm associated with the intensive regimen and the excess risk of death from any cause in the intensive-therapy group, as compared with that in the standard-therapy group, outweighed any potential benefits and recommended that the intensive regimen be discontinued for safety reasons. This recommendation was accepted by the NHLBI. Patients were informed of this decision on February 5, 2008, and were subsequently switched to standard glycemic therapy. The public was informed of the decision in a press release on February 6, 2008. This report is based on data that were submitted to the coordinating

Table 1. Characteristics of the Patients at Baseline.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)
Age (yr)	62.2±6.8	62.2±6.8
Female sex (%)	38.7	38.4
Median duration of diabetes (yr)	10	10
Previous cardiovascular event (%)	35.6	34.8
Previous congestive heart failure (%)	4.9	4.8
Race or ethnic group (%)†		
White	64.4	64.5
Black	19.7	18.9
Hispanic	7.0	7.4
Education (%)		
Less than high school	15.7	14.0
High-school graduate	26.1	26.7
Some college	32.7	32.9
College degree or higher	25.5	26.4
Cigarette-smoking status (%)		
Current	14.3	13.7

Table 1. (Continued.)

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)
Potassium (mg/dl)	4.5±0.4	4.5±0.7
Serum creatinine (mg/dl)	0.9±0.2	0.9±0.2

* Plus–minus values are means ±SD. There were no significant differences between the two study groups at baseline. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for glucose to millimoles per liter, multiply by 0.0555. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
† Race was self-reported, and patients could check multiple categories.

outcomes — including severe hypoglycemia, heart failure, motor vehicle accidents in which the patient was the driver, fluid retention, elevated aminotransferase levels, and weight gain — were compared with the use of Fisher's exact test.

Analyses of primary and secondary outcomes were performed with the use of time-to-event methods according to the intention-to-treat principle, and occurrences of these outcomes in the two study groups were compared with the use of hazard ratios and 95% confidence intervals. Two-sided P values were obtained from likelihood-ratio tests from Cox proportional-hazards regression analyses. Our inspection of plots of survival estimates versus follow-up time indicated that the assumption of proportional hazards for the glycemia interventions appeared to be valid. The Cox models contained a term representing study-group assignments plus terms accounting for the following prespecified stratifying variables: assignment to either the blood-pressure trial or the lipid trial, assignment to the intensive blood-pressure intervention in the blood-pressure trial, assignment to receive fibrate in the lipid trial, the seven clinical-center networks, and the presence or absence of a previous cardiovascular event. An analysis of how sensitive the results were to inclusion of these variables as stratifying factors rather than as covariates in the Cox model was also performed. Event rates are expressed as the percentage of events per follow-up year, taking into account censoring of follow-up data. Kaplan–Meier estimates were used to obtain the proportion of patients who had an event during follow-up.

We assessed the consistency of the effect of study-group assignment on total mortality and the primary outcome among prespecified subgroups using statistical tests of interactions between the treatment effect and the subgroup within the Cox model. We report all nominal P values, unadjusted for the multiplicity associated with the various tests performed for this study or monitoring of the primary and mortality end points by the data and safety monitoring committee. Since we conducted 15 statistical tests of hypotheses related to secondary and post hoc subgroups, there was a 54% chance (i.e., 1−[1−0.05]^{15}) that at least one of these tests would be statistically significant at an alpha level of 0.05, assuming independence between tests.

Post hoc exploratory analyses to identify factors associated with higher mortality in the intensive-therapy group examined baseline characteristics, hypoglycemic events, risk factors for hypoglycemic events, single medications prescribed, combinations of medications prescribed, cointerventions, changes in weight, achieved blood pressure, achieved glycated hemoglobin levels, and occurrence of a cardiovascular event during follow-up. Detailed analyses of these and other potential causal factors or mechanisms will be reported separately.

RESULTS

PATIENTS

A total of 10,251 men and women with a mean (±SD) age of 62.2±6.8 years and a median glycated hemoglobin level of 8.1% (interquartile range, 7.6 to 8.9) were randomly assigned to either the intensive-therapy group or the standard-therapy group (see the figure in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Approximately 38% of the entire cohort of patients were women. Recruitment occurred in two phases: 1174 patients were recruited during a 20-week period from January to June 2001, and 9077 patients were recruited from February 2003 to October 2005.[14] Key baseline characteristics were similar in the two study groups (Table 1). The mean duration of follow-up

at the time the data and safety monitoring committee recommended the discontinuation of the intensive regimen was 3.5 years (median, 3.4).

The two therapeutic strategies rapidly achieved different glycated hemoglobin levels (Fig. 1), was 1.1% in the intensive-therapy group and 1.0% in the standard-therapy group, and the mean weight gain at 1 years was 3.5 kg and 0.4 kg in the two groups, respectively. One death in each

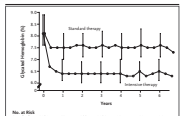

Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.
I bars denote interquartile ranges.

groups were lost to follow-up, and 362 patients (1.0%, including 84 in the intensive-therapy group and 78 in the standard-therapy group) withdrew consent. The mean follow-up time for patients who either withdrew consent or were lost to follow-up was 1.2 years in the intensive-therapy group and 1.0 year in the standard-therapy group (P=0.22). There were fewer occurrences of the composite primary outcome in the intensive-therapy group, with rates of the primary outcome beginning to separate in the two study groups after 3 years (Table 4 and Fig. 2A). This trend was not significant, with rates of 6.9% in the intensive-therapy group and 7.2% in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). In the intensive-therapy group, the rate of nonfatal myocardial infarction was lower than in the standard-therapy group (3.0% vs. 4.0%; hazard ratio, 0.76; 99% CI, 0.62 to 0.92; P=0.004), and the rate of death from cardiovascular causes was higher (2.0% vs. 1.8%; hazard ratio, 1.35; 99% CI, 1.04 to 1.76; P=0.02); there was no significant difference in the rate of nonfatal stroke (1.7% vs. 1.7%; hazard ratio, 1.06; 99% CI, 0.75 to 1.50; P=0.74).

The rate of death from any cause was higher

cant increase in cardiovascular events and no difference in mortality, and in the University Group Diabetes Program,[15,16] the group that received a sulfonylurea had a higher mortality.

Our findings indicate that a comprehensive, customized, therapeutic strategy targeting glycated hemoglobin levels below 6.0% increased the rate of death from any cause after a mean of 3.5 years, as compared with a strategy targeting levels of 7.0 to 7.9% in patients with a median glycated hemoglobin level of 8.1% and other previous cardiovascular events or multiple cardiovascular risk factors. Patients in both groups had lower mortality than reported in epidemiologic studies of similar patients.[17,18] However, as compared with the standard-therapy group, the intensive-therapy group had a relative increase in mortality of 22% and an absolute increase of 1.0% during this follow-up period, with similar differences in death from cardiovascular causes. This increase in mortality is equivalent to one extra death for every 95 patients who were treated for 3.5 years.

This study was not designed to test the components of the intervention strategy. Analyses that we have performed to date have not identi-

Table 4. Primary and Secondary Outcomes.*

Outcome	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per yr	no. of patients (%)	% per yr		
Fatal stroke†			9 (0.2)	11 (0.2)		
Fatal cardiovascular disease†			8 (0.2)	10 (0.2)		
Cancer			65 (1.3)	63 (1.2)		
Condition other than cancer or cardiovascular disease‡			50 (1.0)	35 (0.7)		
Undetermined			7 (0.1)	11 (0.2)		

* The primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Data are shown for the first event in each category; a patient could report more than one event. Hazard ratios are for the intensive group as compared with the standard-therapy group. P values are not listed for the relevant categories. Hazard ratios are for the intensive group as compared with the standard-therapy group.
† This condition was a component of the outcome of fatal cardiovascular disease.
‡ Additional details are provided in the Supplementary Appendix.

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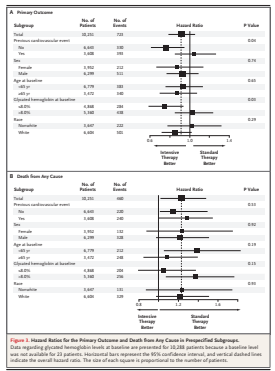

Figure 2. Hazard Ratios for the Primary Outcome and Death from Any Cause in Prespecified Subgroups.
Data regarding glycated hemoglobin levels at baseline are presented for 10,248 patients because a baseline level was not available for 23 patients. Horizontal bars represent the 95% confidence interval, and vertical dashed lines indicate the overall hazard ratio. The size of each square is proportional to the number of patients.

vascular disease or additional cardiovascular out cardiovascular disease raises the possibility risk factors. Indeed, the suggestion of a greater that certain subgroups of patients may benefit benefit in the primary outcome for patients with from intensive glucose lowering. However, our a lower glycated hemoglobin level or those with- study was not designed to test these possibili-

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Members of the ACCORD data and safety monitoring committee were A.M. Gotto (chair), R. Bailey, D. Cutler, S. Haffner, R. Hess, K. Ismaeva, K. Lee, D. Nathan, D. Neuwen, L. Wallace, Members of the ACCORD study group were as follows. **Steering Committee:** W.T. Hradenthal (chair), J.B. Buse (vice chair), J.T. Bigger, R.P. Byington, W.C. Cushman, H.C. Gerstein, H.N. Ginsberg, D.C. Goff, Jr., R. H. Grimm, Jr., J. Somes-Kelly, L. Probstfield, D.G. Simons-Morton, Scientific director persons who are no longer affiliated with the study unit, and daggers persons who are deceased. **Clinical Center Networks and Clinical Sites — Canada:** Population Health Research Institute, Hamilton Hospital, Canadian Diabetes Outcome Evaluation, Hamilton, ON: A.G. Gerstein, S. Yusuf, J. Pogue-Geile, R. Ramos, A. Rosen, R. Crutchfield, T. Calderwood-Tuffs, A. Gula, G. Guyatt,* S. Hall, J. Kanjeva, N. Lane,* D. McLeod, R. Read,* T. Redding, M. Shehelich, M. Sheridan, M. Sivaskandarajah, Canadian Diabetes Outcome Evaluation, Vancouver, BC: P. Hanelin, K. Hunter, C. Pearkhaker, A. Smith, J. Stanton, S. Cujec,* S. Dahl, W. Harper, P. Harvey, D. Hunt, P. Mayer,* A. Moreno, K. Otto, A. Pearkhaker, T. Valle, Six Nations Health Service, Ohsweken, ON: Z. Pearkhaker, A. Stein, S. Cujec,* K.C. Hill, T. McCarthy, Diabetes, Hypertension and Cholesterol Centre, University of Calgary, Calgary, AB: A.L. Edwards, D.J. Mitchell, M.A. Clearenkow, C. Dakhoura, M. Gillies, R. Hammond,* H. Jensen,* A. Khawaji, D. Lee, T. Pringle, D. Katz, R. Sigal, G. Smith,* M. Wallen.* **Williams:** University of Newfoundland, St. John's, NL: B. Tomlinson, M. Bungay, M. Dicker, J. Hollett, J. Morgan, D. Parsons, M. Power, S. Vaughan, University of Alberta, Edmonton: L. Brown, J. Ryan, F. Seaton, J. Kolkmeyer, J. Abe,* K. Dahlen, W. Goodell, J. Gottesbuhel,* D. Huntman,* A. Jeffries,* C. MacDonald, H. Makhani, S. Marwaha,* P. Morales, B. Pate,* M. Pelz,* K. Schroeder, A. Stark, M. Tennant, S. Varma,* P. Wankadia-Wood, R. Wakeenah, W. Zimmerman.* **Centre de Recherche Clinique de Laval, Laval, QC:** A. Bélanger, S. Gauthier, G. Rabasah, C. Rudnicki, S. Capozzi, R. Duchesneau,* R. Dumas, P. Gauthier, J. Giovanni, M. Kandalaft, M. Labbé, J. Pelardy, M. Pilon, J. Raymond, A. Schiffrin. **St. Joseph's Health Care London, London, ON:** J. Hramiuk, S. Trimarchi, M. Driscoll, M. Gerlsaag, J. Gendre, C. Lancaster, W. Mellenthi, C. McDonald, T. McDonald,* P. Pauli,* T. Peel, S. Powers,* N. Russell, V. Trinh, L. Vincer, D. Wallis.* **Ottawa Hospital Research Institute, Ottawa, ON:** K. Beaudoin, M. Bernier, M. Bourque, J. Brière, M. Brousseau, J. Cameron, M. Chiasson, J. Dubois, M. Gilchrist, B. Hendry, M. Hurley, K. Jay,* S. Leach, J. Malcolm, M. McLaren,* S. Parker, M. Sigal,* M. Sullivan. **Royal Victoria Hospital, Montreal, QC:** Yale, A.A. Sagal, N. Kouwal, N. Allaire,* M.A.M.A. Alamuddin,* B. Bellis,* G.W. Blank, F. Bouchard, S. Bray-Phang,* J. Cantor, L. Coppins,* D. Dalpe,* S. Delpuch,* P.M. Dumas, F. Emmanuel,* S. Fortin,* N. Gaudard, M. Gonzalez,* A. Hassa,* M. Kalengia,* S. Kosmikas,* C. Légaré, A. Lombardo, J.A. Morais, M. Quigley, N. Renaud, C. Riopel,* I. Rioux, J.A. Rivera, G. Rochon,* M. Roy, M. Serri, and William C. Knowler, M.D., Columbia University Mailman School of Public Health, New York: outcome responsibility for the overall content and integrity of this article. Address reprint requests to Dr. Byington at the Division of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157, or at rbyington@wfubmc.edu.

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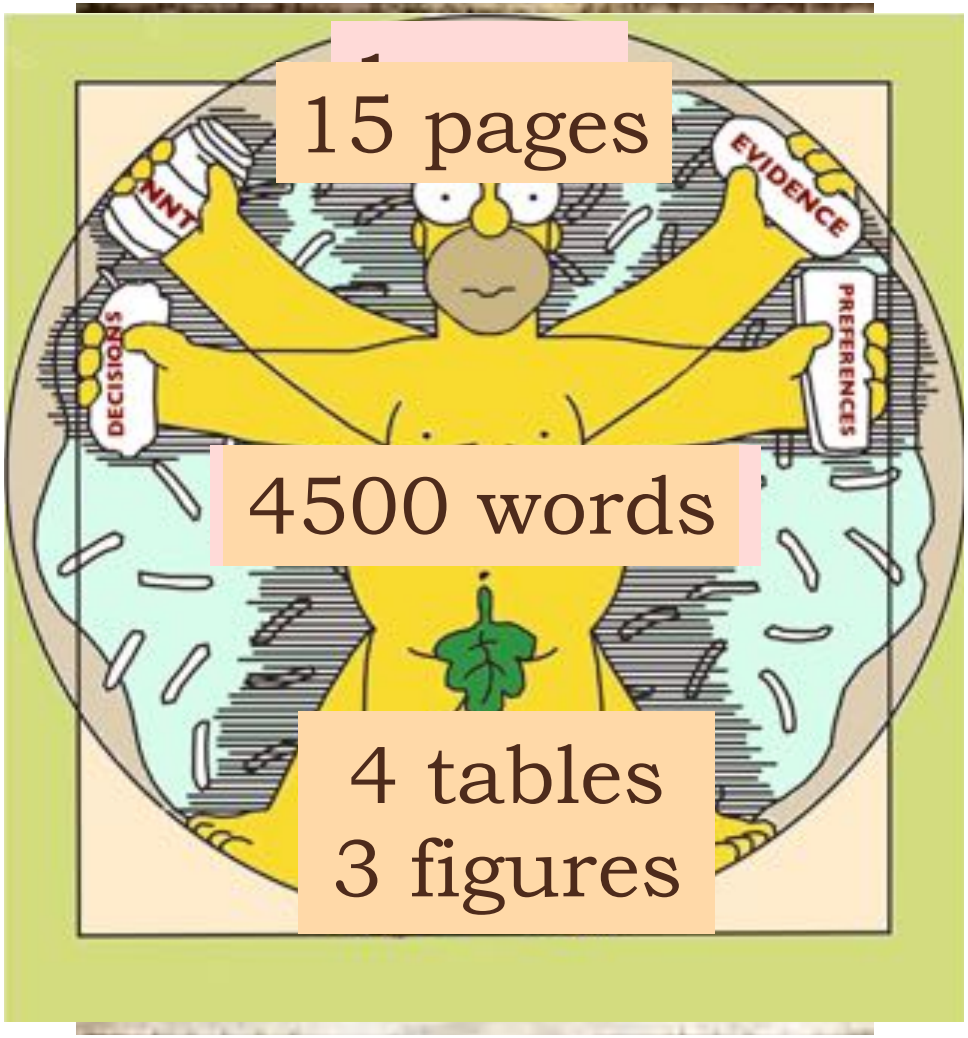
“Simplicity is the ultimate sophistication”




WHO CARES !!!

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

ABSTRACT

BACKGROUND

Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

METHODS

In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of

therapy after a mean of 3.5 years of follow-up.

therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously

Let's recap

- Look at the Abstract
- Read the title
- Look at what was studied
- Look at the outcomes
- Read the conclusions

random

All 10,251 patients were randomly assigned

blind

premature death, blindness, kidney failure

allocation

∅

intent

Analyses of primary and secondary outcomes were performed with the use of time-to-event methods according to the intention-to-treat principle, and occurrences of these outcomes in the

follow

of patients within the previous 12 months; 50 patients (0.5%, including 26 patients in the intensive-therapy group and 24 in the standard-therapy group) were lost to follow-up, and 162 patients

✗

?

✓

✓

Supported by grants (N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184, IAA-Y1-HC-9035, and IAA-Y1-HC-1020) from the National Heart, Lung, and Blood Institute; by other components of the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute; by the

Abbott
GE Healthcare
SOLVAY
ALLERGAN
Roche
Baxter
JANSSEN PHARMACEUTICAL LTD
sanofi aventis
BD
MERCK SHARP & DOHME
SCHWARZ PHARMA
NOVARTIS
élan
Pfizer
Bristol-Myers Squibb
Lilly
Schering-Plough
Wyeth

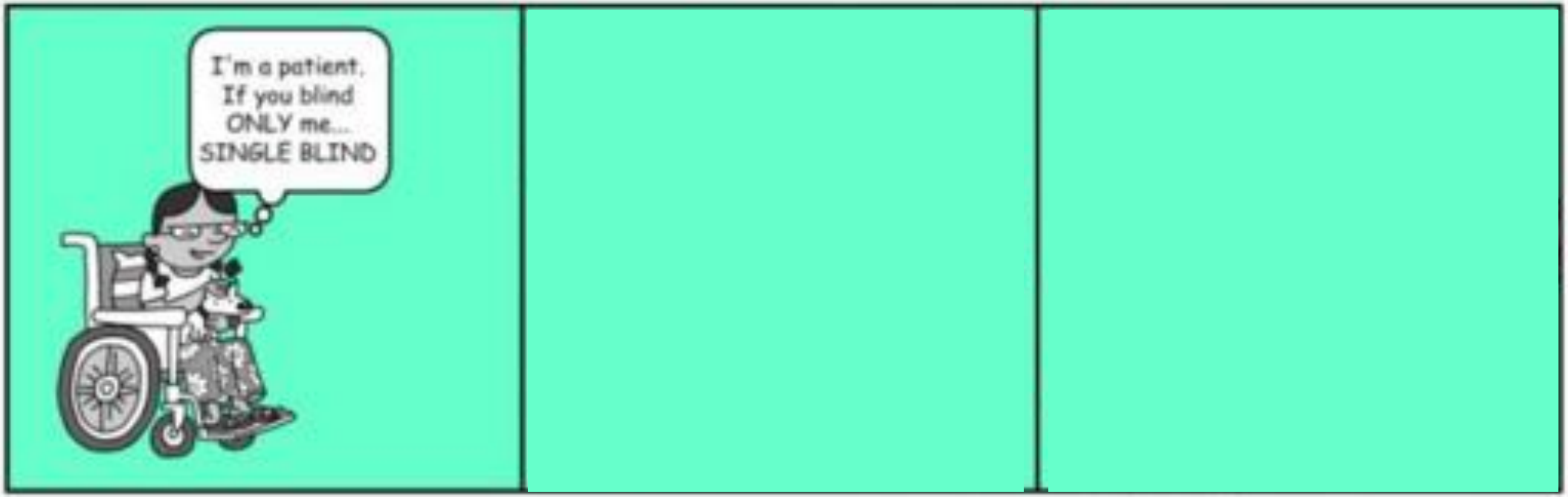
tis, King, Takeda, and Sanofi-Aventis, lecture fees from Novartis, and grant support from Novartis, Hamilton Health, and Abbott; Dr. Genuth, receiving consulting fees from Merck, Mannkind, Sanofi-Aventis, and Novartis and lecture fees from Lilly and having an equity interest in Bristol-Myers Squibb; Dr. Grimm, receiving lecture fees from Merck, Pfizer, and Novartis; and Dr. Probstfield, receiving consulting fees from King and grant support from King and Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

Primarily funded by the National Institutes of Health

Let's recap

- Randomized
- Blinded
- Allocation concealment
- Intention to treat
- Follow-up
- Conflicts of interest

Blinding



Cartoon created by Terry Shaneyfelt

Morphine or Physiotherapy?

Morphine

OR

Physiotherapy

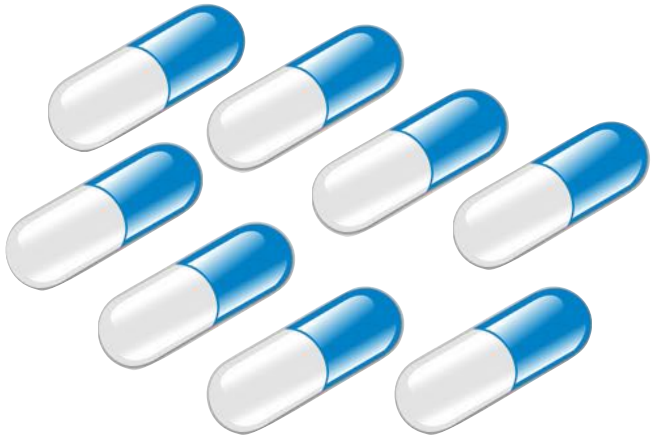
ALLOCATION CONCEALMENT and UNBLINDED

Morphine

Placebo

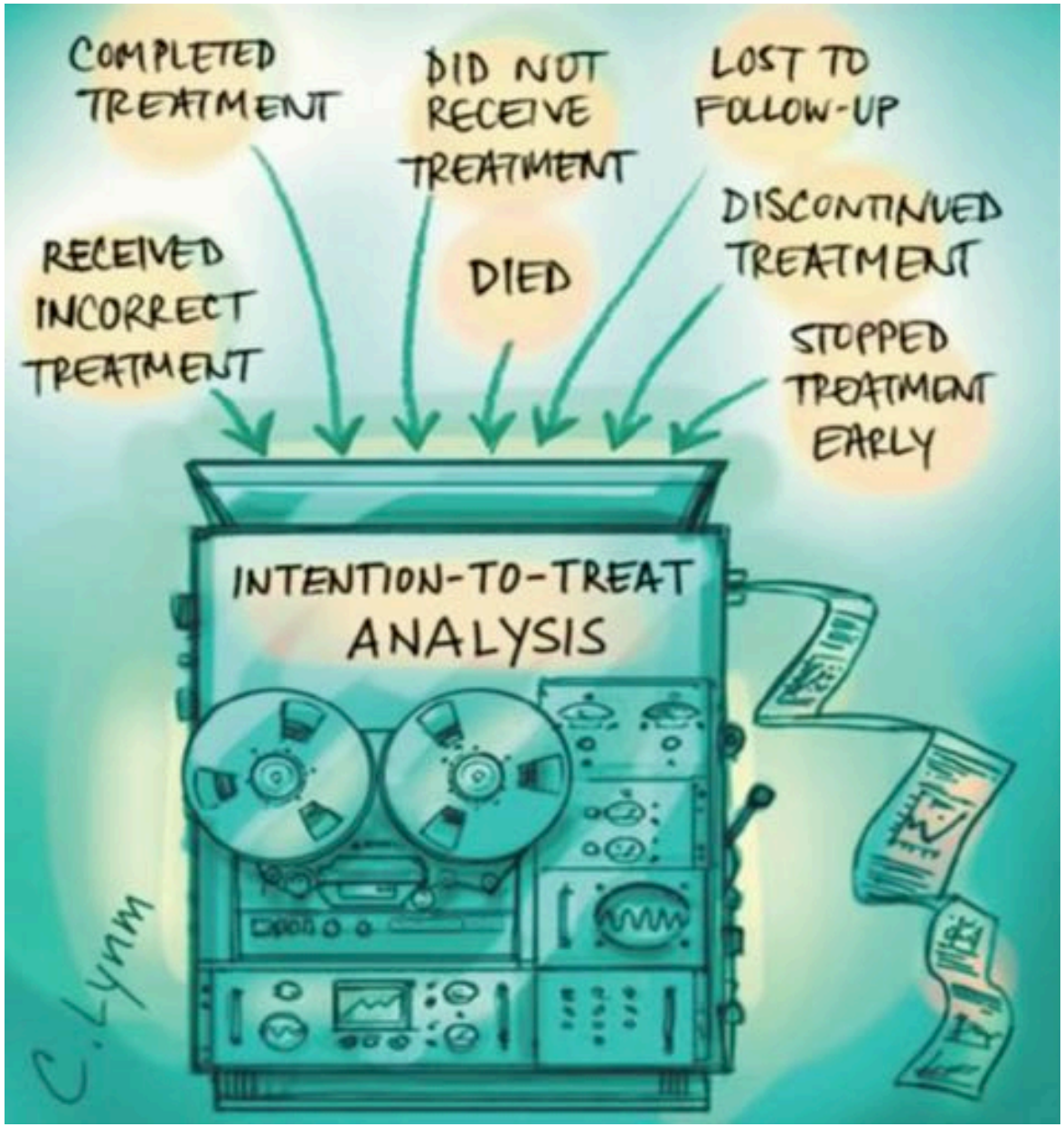
OR

Morphine or Placebo?



ALLOCATION CONCEALMENT and BLINDED

PROTOCOL VIOLATIONS



ITT analysis

(if randomized then analyzed)

- intuitively one would want to exclude these people from the evaluation BUT
- excluding these people could lead to a randomization issue - now it is no longer truly randomized
- the protocol violations may be **secondary to the intervention or disease severity**
- you lose power if you exclude people
- exclusions could lead to a bias
- including all people is **more like practice**
- a per-protocol analysis - only analyze those who adhered to the protocol - is actually **closer to the true efficacy** of the treatment HOWEVER an **ITT is a more conservative estimate**

Lost to follow-up

Could be a problem if:

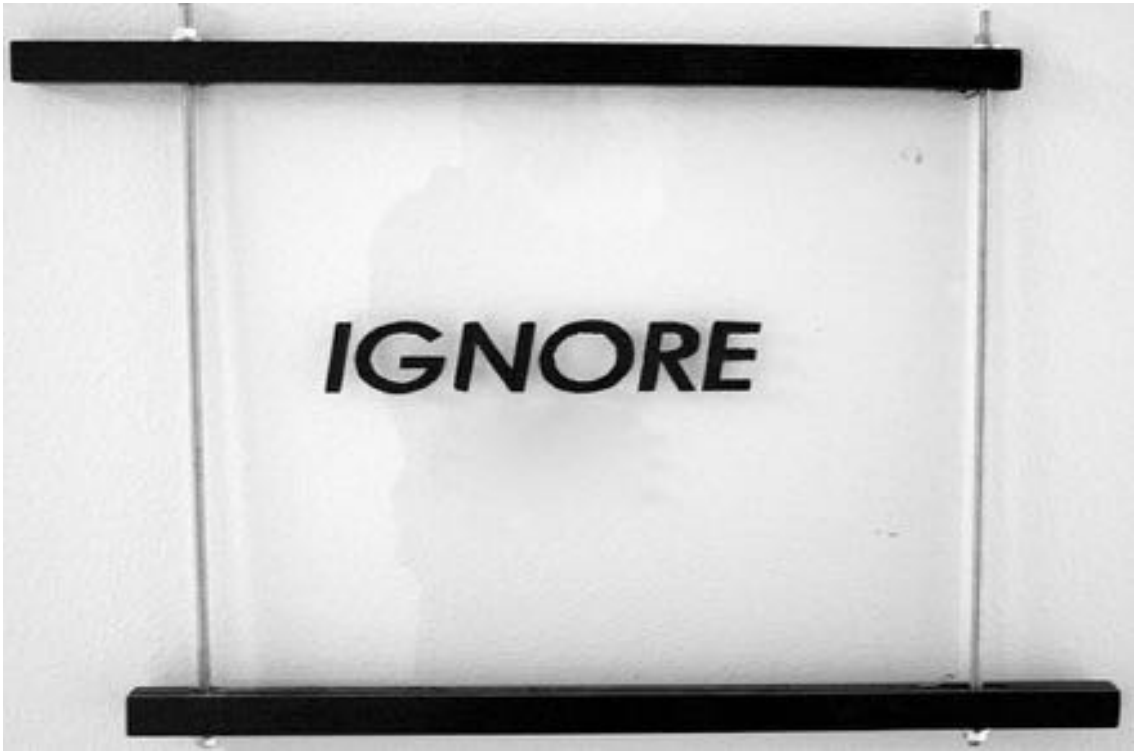
the % of people lost to follow-up is greater than the absolute effect

OR

the % lost is quite different in one arm

MUCH OF THE REST OF THE TEXT

- INTRODUCTION
- "MOST" OF THE METHODS
- STATISTICAL TESTS
- DISCUSSION



Patient Characteristics

Table 1. Characteristics of the Patients at Baseline.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)
Age (yr)	62.2±6.8	62.2±6.8
Female sex (%)	38.7	38.4
Median duration of diabetes (yr)	10	10
Previous cardiovascular event (%)	35.6	34.8
Previous congestive heart failure (%)	4.9	4.8
Race or ethnic group (%)†		
White	64.4	64.5
Black	19.7	18.9
Hispanic	7.0	7.4
Education (%)		
Less than high school	15.7	14.0
High-school graduate	26.1	26.7
Some college	32.7	32.9
College degree or higher	25.5	26.4
Cigarette-smoking status (%)		
Current	14.3	13.7
Former	44.4	44.0
Never	41.3	42.3
Weight (kg)	93.5±18.7	93.6±18.7
Body-mass index	32.3±5.5	32.2±5.5
Waist circumference (cm)	106.8±14.3	106.8±13.8
Blood pressure (mm Hg)		
Systolic	136.2±17.0	136.5±17.2
Diastolic	74.8±10.6	75.0±10.7
Medications (%)		
Insulin	34.1	35.7
Metformin	59.7	60.0
Any sulfonylurea	50.8	49.4
Any thiazolidinedione	19.5	19.2
Any antihypertensive agent	84.9	86.0
Angiotensin-converting-enzyme inhibitor	53.0	53.0
Aspirin	54.8	54.1
Beta-blocker	28.7	29.9
Any thiazide diuretic	26.5	26.4
Statin	61.7	62.4
Glycated hemoglobin (%)		
Mean	8.3±1.1	8.3±1.1
Median	8.1	8.1
Fasting serum glucose (mg/dl)	174.9±56.0	175.7±56.5
Cholesterol (mg/dl)		
Total	183.1±42.1	183.1±41.8
Low-density lipoprotein	104.9±34.0	104.9±33.8
High-density lipoprotein		
Women	47.2±13.0	46.9±12.2
Men	38.4±9.5	38.8±9.8
Median triglyceride (mg/dl)	156	154

No "clinical" differences

N = 5,100

Age 62
Female 38%
Diabetes 10 years
Previous CV event 35%
White 65%
Smoker 14%
BMI 32
BP 136/75
A1C 8.3%
Total Chol 183 or 4.7

Let's recap

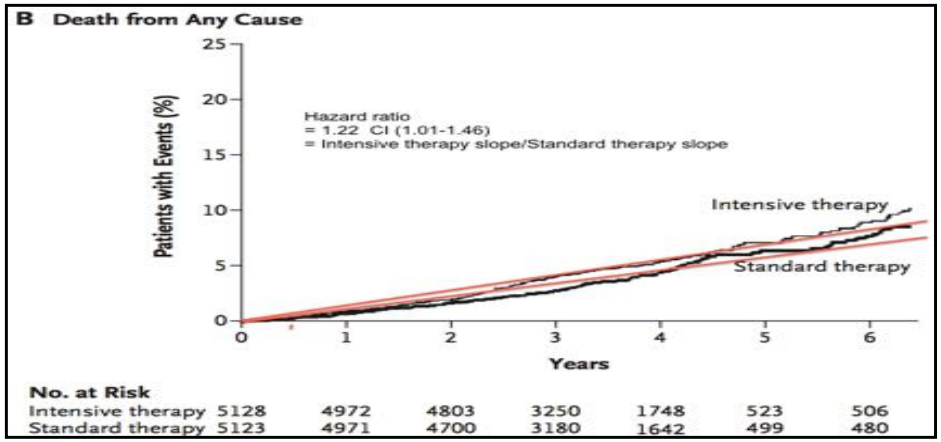
- Differences between groups
- Baseline characteristics

Similar but different relatives

Relative risk/risk ratio (RR) - ratio of two probabilities (%) at one point in time - treatment/control

- eg 8% vs 10% - RR = 8/10 = 0.8
- most useful in low probability events

Hazards ratio (HR) - ratio of two hazard rates (slopes) over a time period



Odds ratio (OR) - ratio of two odds (25/1) - typically used in case-control studies - typically the incidence is not known

OR is a reasonable estimate of the **RR** if a disease is "rare" <~15% but treating an **OR** as if it were an accurate estimate of the **RR** will typically overestimate both the likely benefits and harms of treatment

Main Patient Outcomes

Table 4. Primary and Secondary Outcomes.*

Outcome	A1c = 6.4% no. of patients (%)	A1c = 6.4% % per yr	A1c = 7.5% no. of patients (%)	A1c = 7.5% % per yr	Hazard Ratio (95% CI)	P Value
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.33 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease‡	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			

Primary outcome = nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI	Relative Risk
Primary outcome (%)	6.9	7.2	0.9	0.78-1.04	0.96
Death (%)	5	4	1.22	1.01-1.46	1.25
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92	0.78
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50	1.08
CHF (%)	3	2.4	1.18	0.93-1.49	1.25

INITIAL COST

Baseline risk

25% OFF SALE

Relative benefit

NOW COSTS

New risk

YOU SAVE

Absolute benefit

Let's recap

- Primary outcomes
- Other outcomes
- Differences
  - Absolute numbers
  - Relative numbers
  - Confidence intervals

Adverse Events

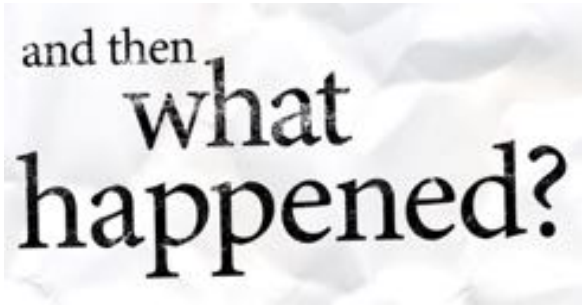


Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124 (2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±3		
Blood pressure — mm Hg¶			
Systolic	126.4±2		
Diastolic	66.9±1		

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI
Primary outcome (%)	6.9	7.2	0.9	0.78-1.04
Death (%)	5	4	1.22	1.01-1.46
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50
CHF (%)	3	2.4	1.18	0.93-1.49
Hypoglycemia (%)	10.5	3.5		
Serious adverse event	2.2	1.6		
Weight gain >10kg	27. 8	14.1		

Let's recap

- Adverse outcomes
- Any other outcomes
- Differences
  - Absolute numbers
  - Relative numbers
  - Confidence intervals

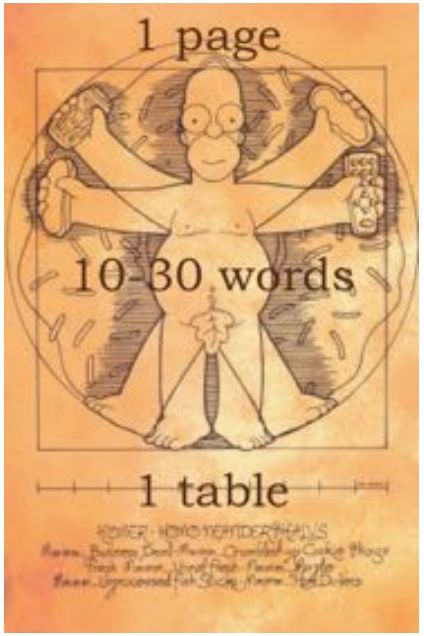
Randomised

Non-blinded

Allocation concealment?

Intention-to-treat

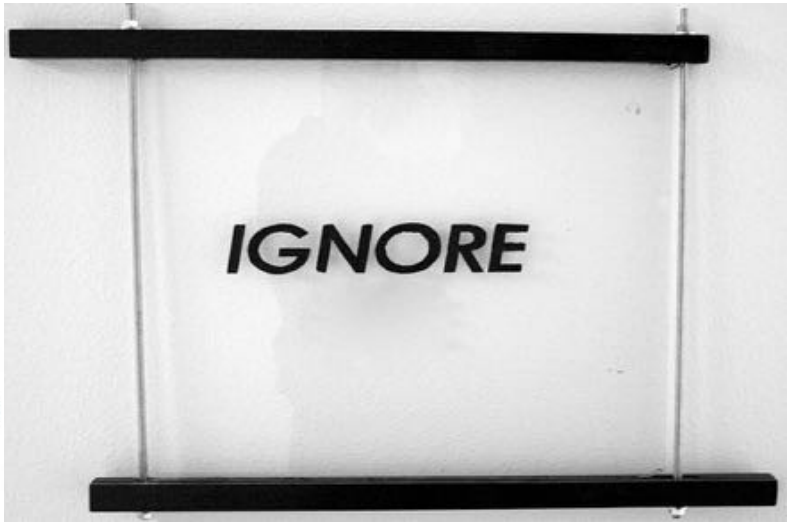
Follow-up



N=10,251 - 3.5 years

Age 62, Female 38%, Diabetes 10 years, Previous CV event 35%, White 65%, Smoker14%, BMI 32, BP136/75, A1C 8.3, Total Chol 183

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI
Primary outcome (%)	6.9	7.2	0.9	0.78-1.04
Death (%)	5	4	1.22	1.01-1.46
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50
CHF (%)	3	2.4	1.18	0.93-1.49
Hypoglycemia (%)	10.5	3.5		
Serious adverse event	2.2	1.6		
Weight gain >10kg	27.8	14.1		



Critical appraisal

Meta-Analysis

Meta-Analysis

MA’s “started” in 1976

Critics - “An exercise in Mega-Silliness”

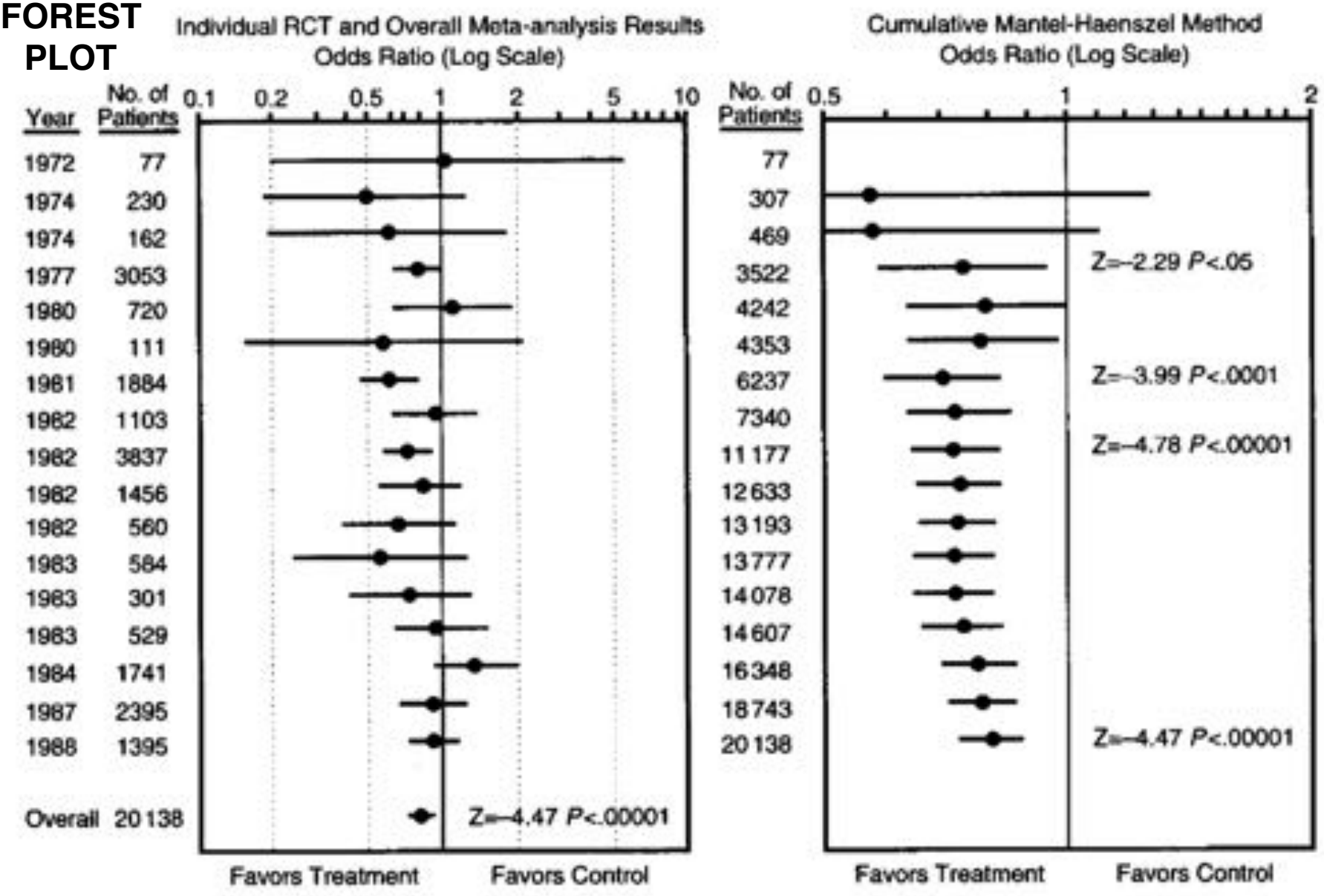
“Garbage in = Garbage out"

"Anybody who publishes a high-quality large scale meta-analysis should in my opinion, receive a **gold medal, a large promotion, and a long, fully paid vacation.** Such a research synthesis can be an immensely valuable scholarly contribution that brings **order to confusion**, helps set a future research agenda, and at the same time gives the **best evidence-based practice advice**"

Geoff Cumming

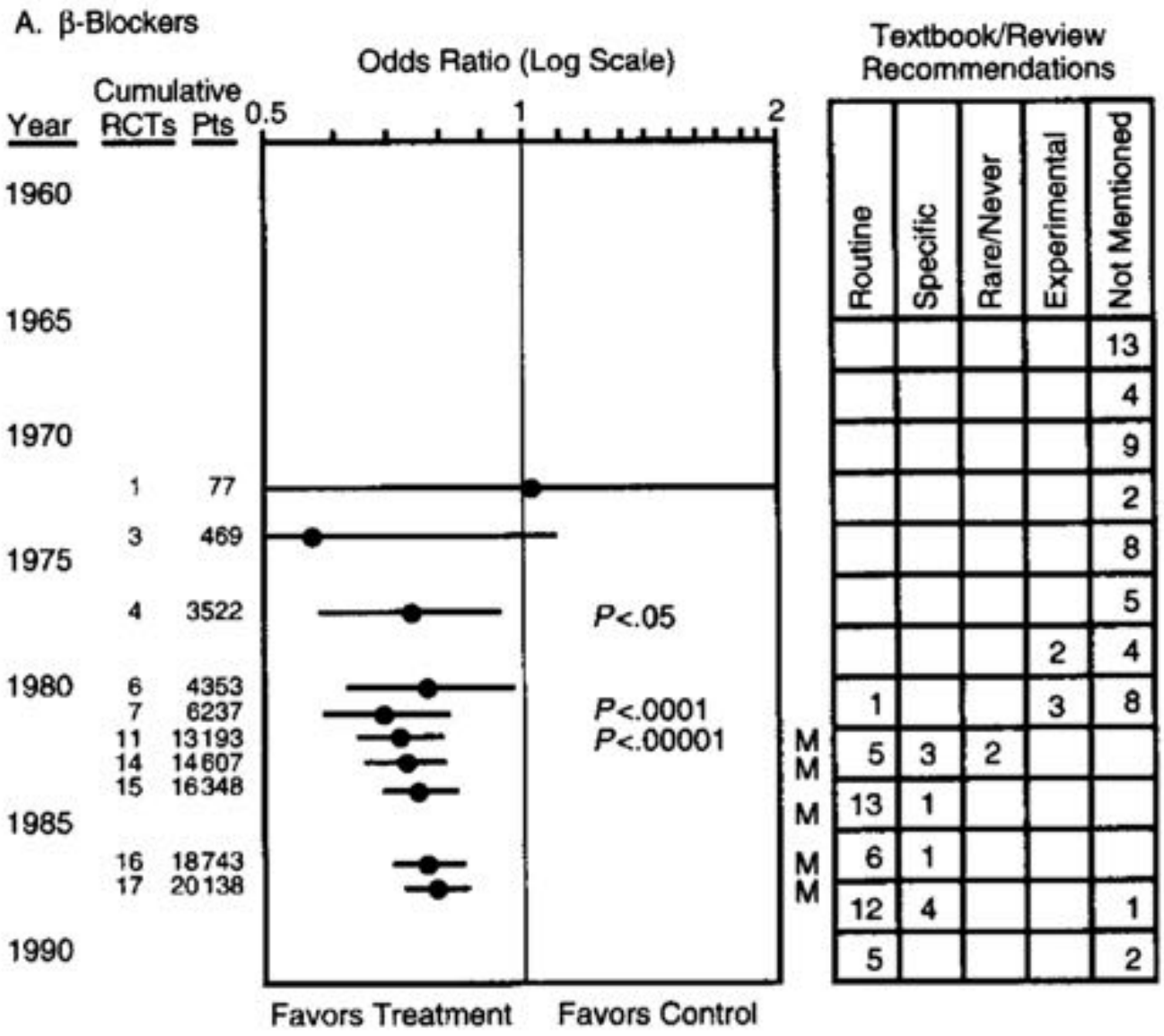
Effect of beta-blockers on mortality after a heart attack

FOREST PLOT



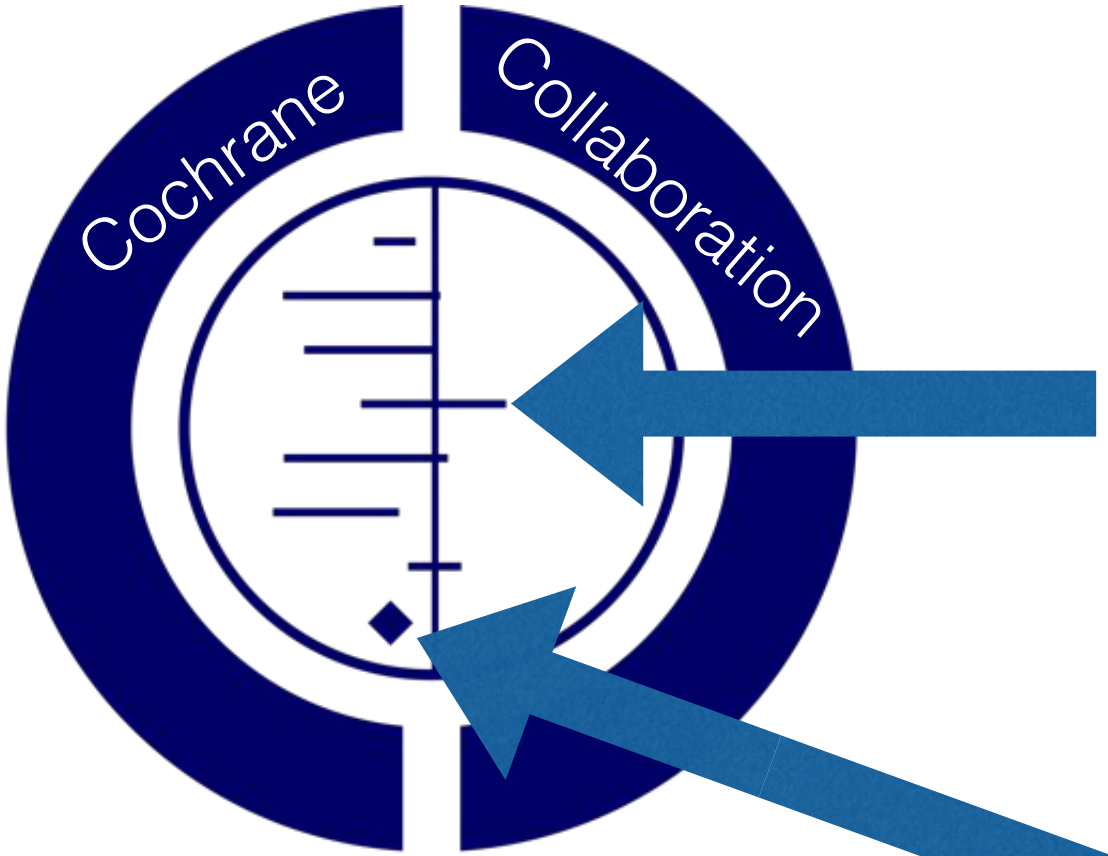
JAMA 1992;268:240-248

Effect of beta-blockers on mortality after a heart attack



JAMA 1992;268:240-248

Started in 1993



THE COCHRANE COLLABORATION

Systematic review of RCTs of a short, inexpensive course of a corticosteroid given to women about to give birth too early.
7 studies

Neonatal death reduced by 31% - RR 0.69
Absolute difference 5%

Number of Cochrane Reviews

TOTAL

2016/17	Total reviews	Total protocols	Total reviews and protocols
Issu12 '17	7510	2542	10052
Issu11 '17	7469	2565	10034
Issu10 '17	7442	2560	10002
Issue 9 '17	7415	2572	9987
Issue 8 '17	7399	2470	
Issue 7 '17			
Issue 6 '17			9890
Issue 5 '17		2539	9855
Issue 4 '17	7284	2548	9832
Issue 3 '17	7258	2543	9801
Issue 2 '17	7201	2542	9743
Issue 1 '17	7169	2526	9695

~7500

NEW

2016/2017	New reviews	Updated reviews	Withdrawn reviews	Conclusions changed
Issu12 '17	26	20	0	
Issu11 '17	41	23		
Issu10 '17				
Is				6
Issu			2	9
Issue4	37	25	2	11
Issue3 '17	45	20	3	3
Issue2 '17	33	34	4	10
Issue1 '17	28	21	0	8

Each issue
~35 new reviews
~25 updated
~2-3 withdrawn
~10 conclusions changed

Table of Contents

Included and excluded

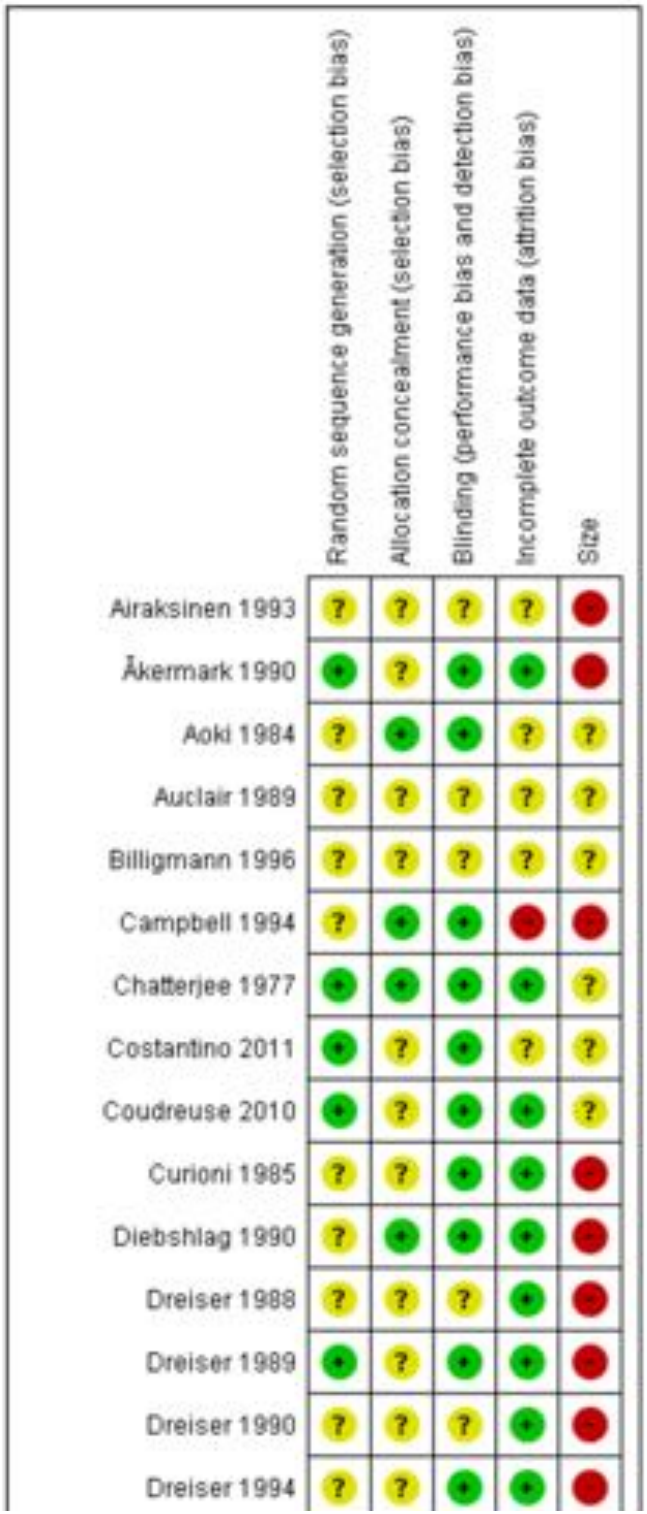
Summary of Findings

Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults

Patient or population: adults with strains, sprains, or muscle pull
Settings: community
Intervention: topical NSAID (topical diclofenac, ibuprofen, and ketoprofen gels only shown here for efficacy)
Comparison: topical placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR, NNT, NNTp, or NNH (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Topical diclofenac gel (as Emulgel) Clinical success (eg 50% reduction in pain)	780 in 1000	200 in 1000	RR 3.4 (2.7 to 55) NNT 1.8 (1.5 to 2.1)	2 studies 314 participants	High	Consistent results in 2 moderately sized recent studies of high quality
Topical ibuprofen gel Clinical success (eg 50% reduction in pain)	420 in 1000	160 in 1000	RR 2.7 (1.7 to 4.2) NNT 3.9 (2.7 to 6.7)	2 studies 241 participants	Moderate	Modest effect size and numbers of participants
Topical ketoprofen gel Clinical success (eg 50% reduction in pain)	720 in 1000	330 in 1000	RR 2.2 (1.7 to 2.8) NNT 2.5 (2.0 to 3.4)	5 studies 348 participants	Moderate	Modest effect size and numbers of participants, but studies small, with none recent
All topical NSAIDs Local adverse events	46 in 1000	50 in 1000	RR 1.0 (0.80 to 1.2) NNH not calculated	42 studies 6125 participants	High	Large number of studies and participants with consistent results
All topical NSAIDs Systemic adverse events	32 in 1000	35 in 1000	RR 1.0 (0.7 to 1.3) NNH not calculated	38 studies 5372 participants	High	Large number of studies and participants with consistent results
All topical NSAIDs Withdrawals - adverse events	11 in 1000	11 in 1000	RR 1.0 (0.7 to 1.7) NNH not calculated	42 studies 5790 participants	High	Large number of studies and participants with consistent results

Author's assessment of the risk of bias



Characteristics of Studies

WOSCOPS

Methods	Randomised trial.	
Participants	6595 men with hypercholesterolaemia based in Scotland aged 45-64 (mean age 55). < 10% with clinical evidence of CVD	
Interventions	40 mg pravastatin versus placebo; follow-up 4.9 years.	
Outcomes	Primary outcome: composite of non-fatal MI and CHD death. Single outcomes included total mortality, fatal CVD events, cholesterol, revascularisations, non-fatal MI and CHD death and adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocks of random numbers and treatment assigned randomly
Allocation concealment (selection bias)	Low risk	All trial personnel remained unaware of the participant's treatment assignment throughout the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: participants and personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT used, 30% drop-outs reported
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funded by pharmaceutical industry

Data and Analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Mortality	13	48060	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.94]
2 Total Number of CHD Events	14	48049	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.67, 0.80]
3 Number of Fatal CHD Events	10	46094	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.96]
4 Number of Non-fatal CHD Events	11	40977	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.59, 0.76]
5 Total Number of CVD Events	9	23805	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.70, 0.81]
6 Number of Fatal CVD Events	5	34012	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.96]
7 Number of Non-fatal CVD Events	2	8696	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
8 Total Number of Stroke Events	10	40295	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.68, 0.89]
9 Number of Fatal Stroke Events	3	27238	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.18, 2.23]
10 Number of Non-fatal Stroke Events	5	28097	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.58, 0.83]
11 Total Number of Fatal and Non-fatal CHD, CVD and Stroke Events	4	35254	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.58, 0.73]
12 Number of Study Participants who underwent Revascularisation	7	42403	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.54, 0.72]

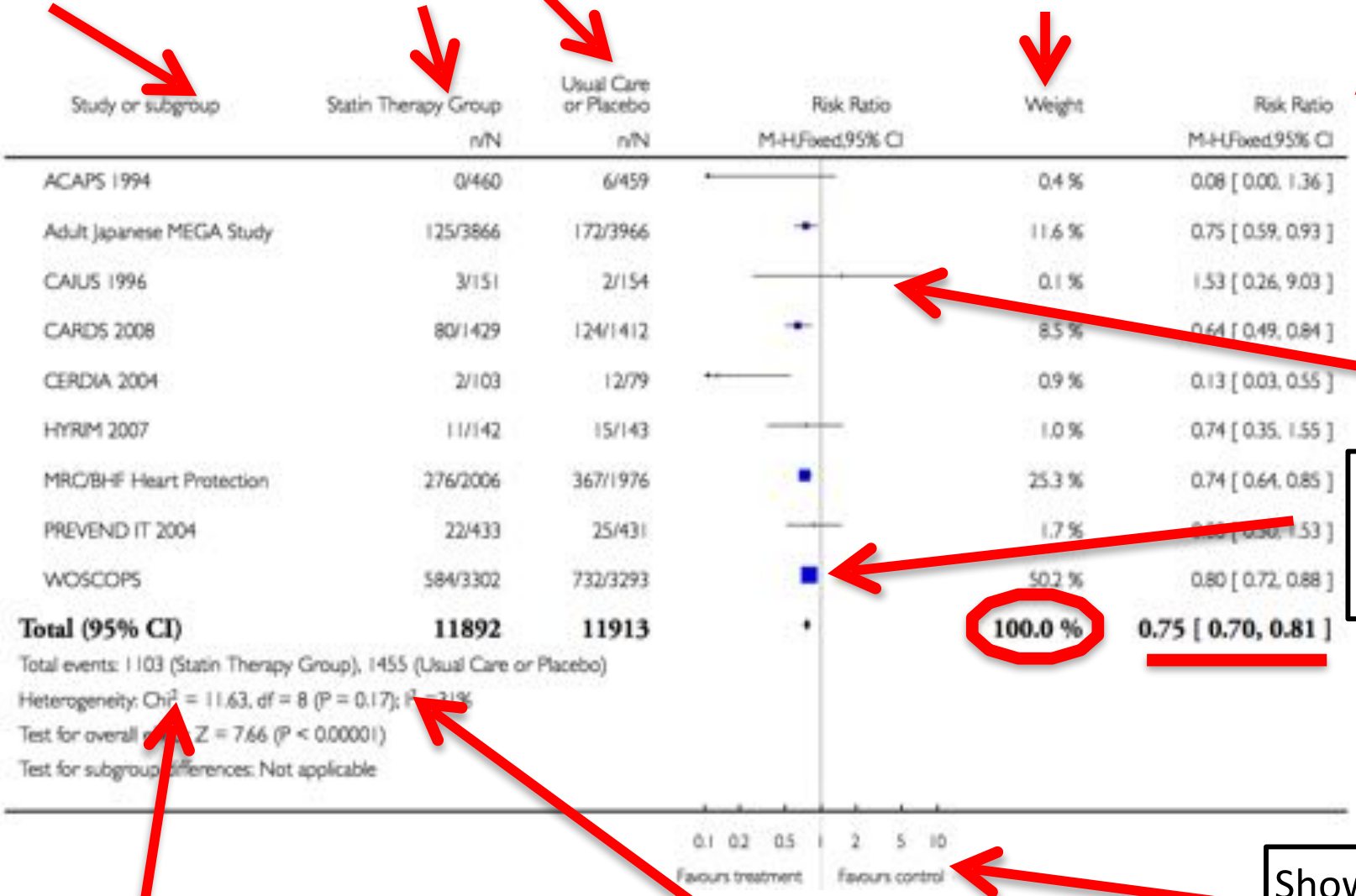
Mantel–Haenszel - statistical method
Random (assumes the studies are different) is more conservative than fixed (assumes trials are the same)

Included studies (ideally would have citation)

Includes the number of events & total included in each group

How much each study contributes (weight)

The actual (numeric) results for each study



Tiny square= small study

Big square= Big study and/or lots of events

Heterogeneity given & I^2 stat available

Final numbers of events and total included in each arm (can do “cheater” NNT)

Shows what side is “better” for treatment or control

CD004816 2013

McCormack et al. BMC Medical Research Methodology 2013, 13:134
http://www.biomedcentral.com/1471-2288/13/134

BMC
Medical Research Methodology

DEBATE Open Access

How confidence intervals become confusion intervals

James McCormack[1], Ben Vandermeer[2] and G Michael Allan[3*]

BMC Medical Research Methodology 2013;13:134

Do statins reduce mortality in primary prevention?

Studer et al.: “reduced risks of overall and cardiac mortality”**YES**

Thavendiranathan et al.: [does not decrease]”overall mortality”**NO**

Mills et al.: “an important role in preventing all-cause mortality”**YES**

Brugts et al.: “associated with significantly improved survival”**YES**

Ray et al.: “did not find evidence for the benefit … on all-cause mortality”**NO**

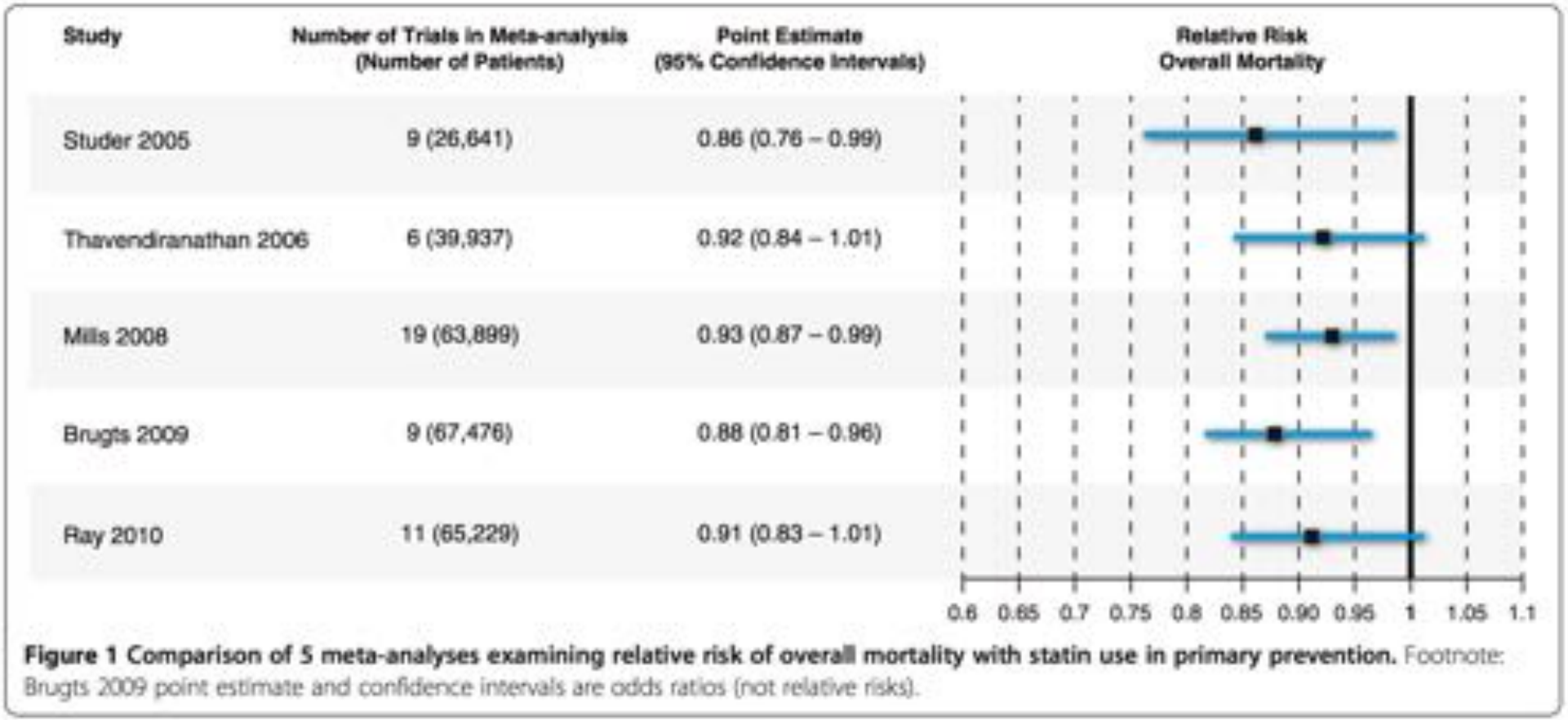


Figure 1 Comparison of 5 meta-analyses examining relative risk of overall mortality with statin use in primary prevention. Footnote: Brugts 2009 point estimate and confidence intervals are odds ratios (not relative risks).

Effect size

Can refer to unstandardized effect sizes - the difference between group means, relative risk or odds ratio

Standardized effect sizes - such as ‘correlation’ or ‘Cohen’s d’ for when using different measurement scales

Often used as a summary statistic in meta-analysis when trials looked at the same outcome but used different scales to measure that outcome

Effect Sizes

Comparison: 1 TCAs versus placebo

Outcome: 1 Depression symptoms at post-treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Barge-Schaapveld 2002	23	8.9 (6.2)	26	12.5 (6.3)		6.1 %	-0.57 [-1.14, 0.01]
Blashki (150 mg) 1971	14	5.1 (4.9)	9	11.4 (9.6)		3.3 %	-0.86 [-1.74, 0.02]
Blashki (75mg) 1971	13	6.4 (5.4)	9	11.4 (9.6)		3.3 %	-0.65 [-1.53, 0.22]
Brink 1984	24	8.8 (7.3)	25	11.1 (6.9)		6.3 %	-0.32 [-0.88, 0.25]
Doogan 1994	96	14.2 (4.5)	90	15.3 (4)		11.8 %	-0.26 [-0.55, 0.03]
Feighner 1979	53	15.2 (7.3)	30	21 (9.6)		7.9 %	-0.70 [-1.16, -0.24]
Hollyman 1988	67	5.4 (3.8)	74	8.7 (3.5)		10.4 %	-0.90 [-1.25, -0.55]
Lecrubier 1997	74	10.4 (4.5)	76	10.2 (4)		11.0 %	0.05 [-0.27, 0.37]
Malt 1999	120	11.3 (4.5)	129	14 (4)		12.7 %	-0.63 [-0.89, -0.38]
Mynors-Wallis 1995	27	8.1 (7.1)	26	11.8 (7.3)		6.5 %	-0.51 [-1.05, 0.04]
Philipp 1999	105	8 (4.2)	46	10.6 (4)		10.2 %	-0.62 [-0.98, -0.27]
Thompson 1989	20	9 (7.3)	21	10 (9.6)		5.6 %	-0.11 [-0.73, 0.50]
Thomson 1982	21	4.9 (4.9)	15	7.93 (4.2)		4.9 %	-0.64 [-1.32, 0.04]
Total (95% CI)	**657**		**576**			**100.0 %**	**-0.49 [-0.67, -0.32]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 24.09$, df = 12 (P = 0.02); $I^2 = 50\%$

Test for overall effect: Z = 5.45 (P < 0.00001)

Test for subgroup differences: Not applicable

(Continued . . .)

A Type of Effect Size

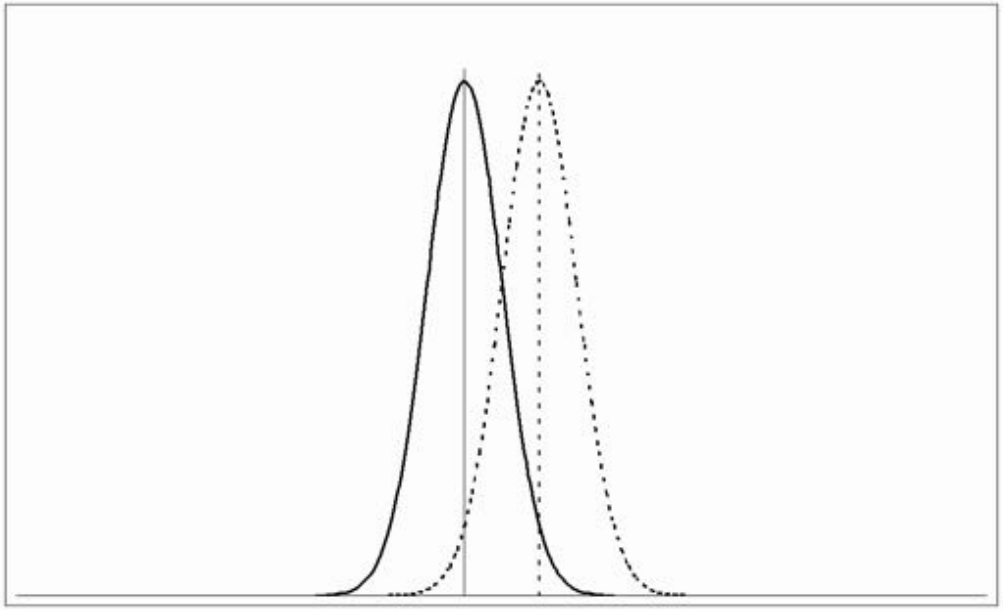
AKA Standardized Mean Difference

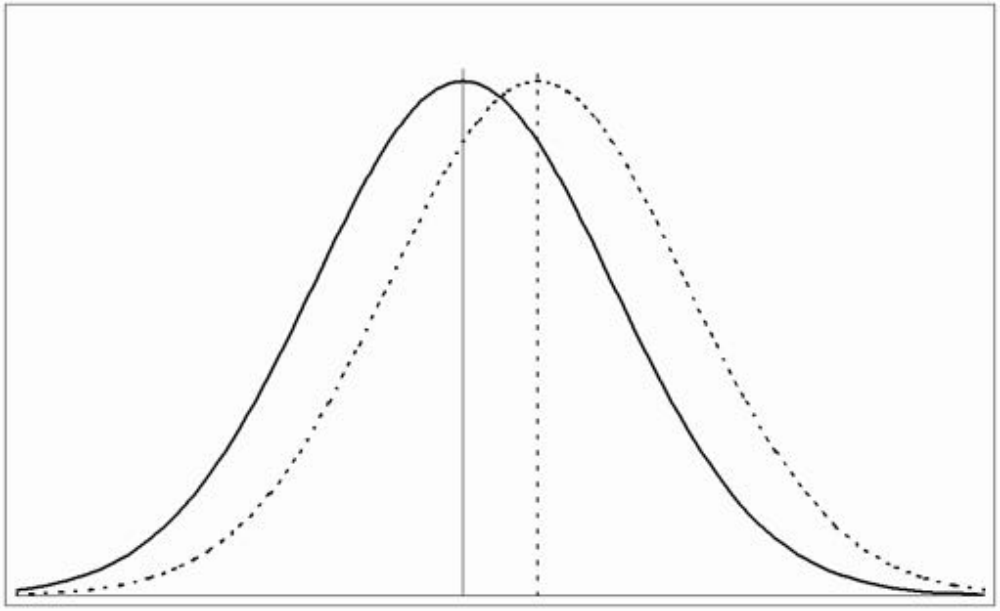
'Effect size' is simply a way of quantifying the size of the difference between two groups

Is an interpretation of the overlap of the results

An effect size of 0.5 means that the score of the AVERAGE person in the experimental group is 0.5 SD above the AVERAGE person in the control group

Effect size = $\frac{\text{(Mean of the experimental group - Mean of the control group)}}{\text{Standard Deviation}}$





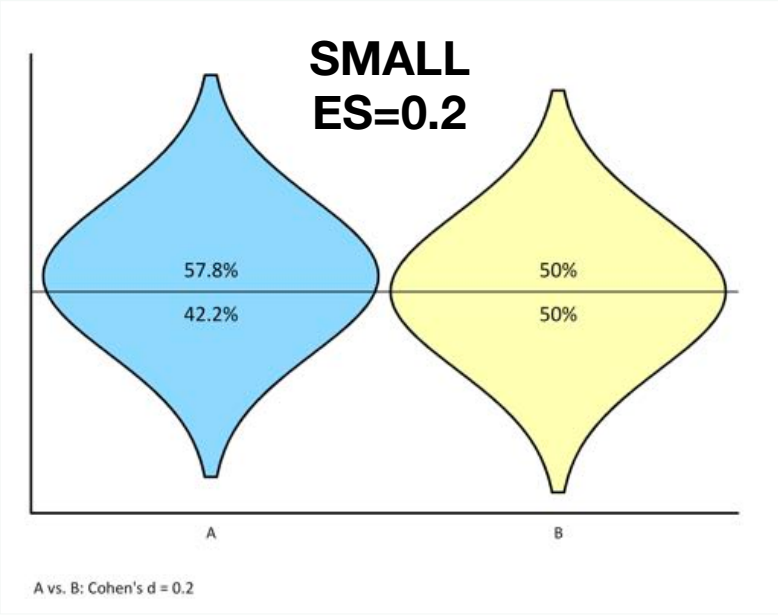
Effect Size or SD above	Description	Percentage of control group who would be below average person in experimental group
0.0		50%
0.1		54%
0.2	SMALL	58%
0.3		62%
0.4		66%
0.5	MEDIUM	69%
0.6		73%
0.7		76%
0.8	LARGE	79%
0.9		82%
1.0		84%
1.2	VERY LARGE	88%
1.4		92%
1.6		95%
1.8		96%
2.0	HUGE	98%

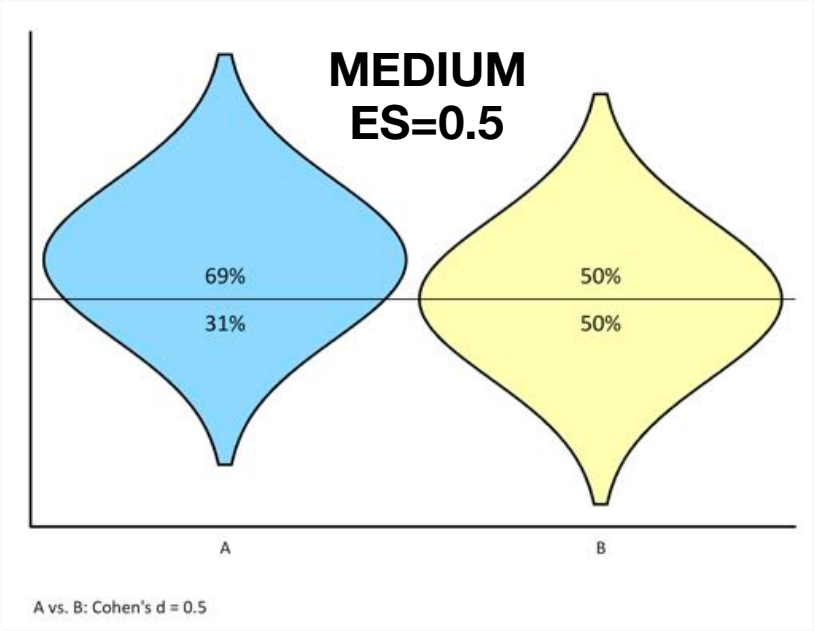
Interpreting effect sizes

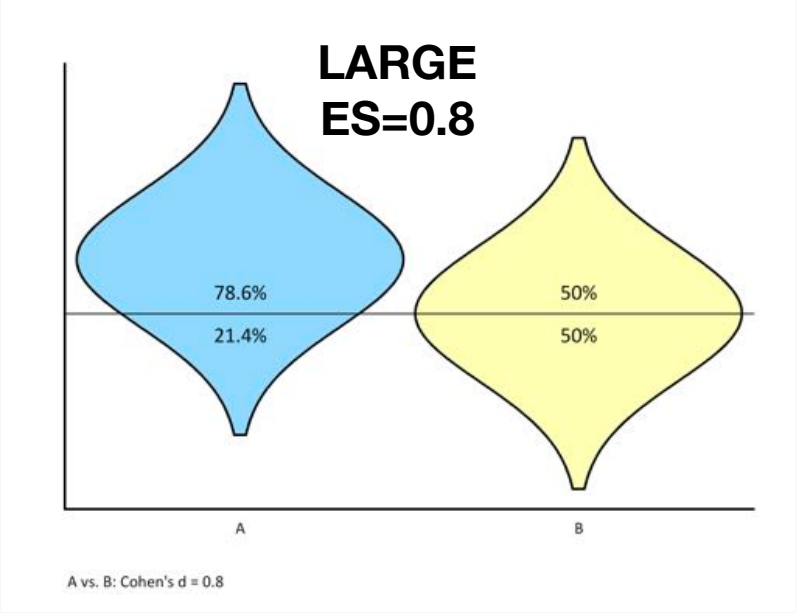
Jacob Cohen - reluctantly suggested thresholds of 0.2, 0.5, and 0.8 as indicators of small, medium, and large effects - however he warns:

"The terms 'small', 'medium', and 'large' are relative . . . to each other . . . the definitions are arbitrary . . . these proposed conventions were set forth throughout with much diffidence, qualifications, and invitations not to employ them if possible. … The values chosen had no more reliable a basis than my own intuition."

Gardner's effect size illustrator http://esi.medicine.dal.ca


SMALL
ES=0.2
57.8%
42.2%
50%
50%
A
B
A vs. B: Cohen's d = 0.2


MEDIUM
ES=0.5
69%
31%
50%
50%
A
B
A vs. B: Cohen's d = 0.5


LARGE
ES=0.8
78.6%
21.4%
50%
50%
A
B
A vs. B: Cohen's d = 0.8

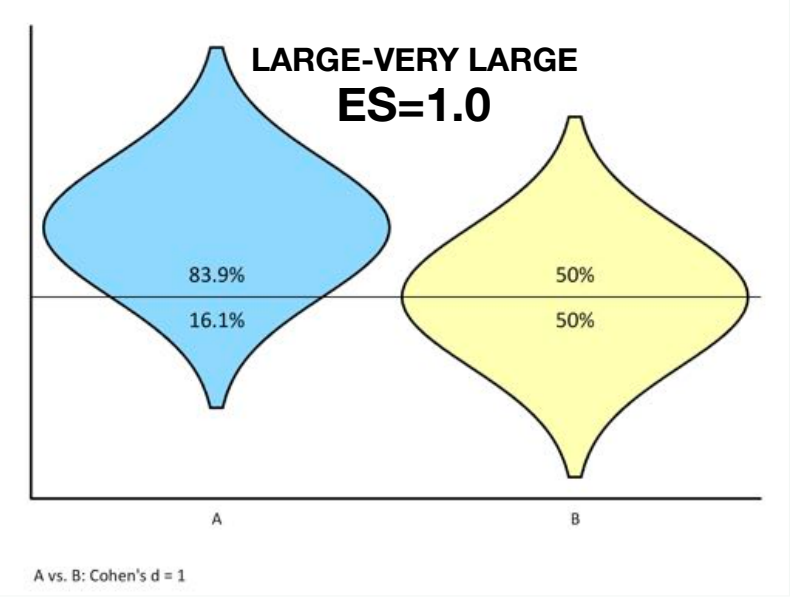
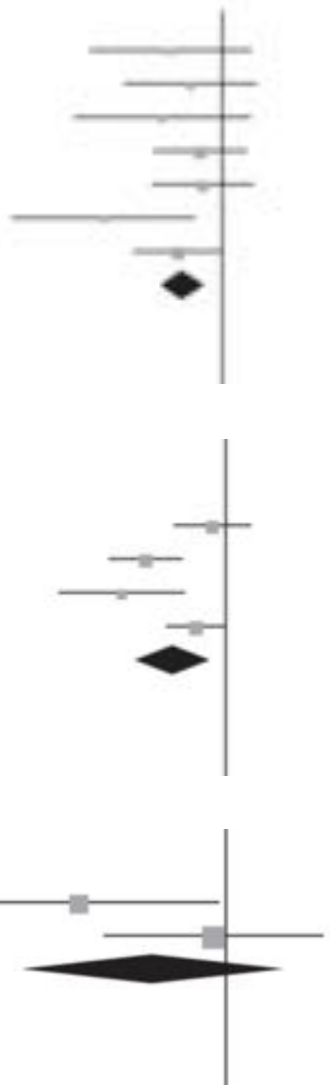

LARGE-VERY LARGE
ES=1.0
83.9%
16.1%
50%
50%
A
B
A vs. B: Cohen's d = 1

Figure 1. Standardized mean differences for posttreatment depression scores of psychological treatments compared with control (usual care or placebo).

Study or Subgroup	Psychological Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Face-to-face CBT								
Laidlaw 2008[a]	9.4	8.56	20	13.25	10.3	20	7.8	−0.40 (−1.03, 0.23)
Scott 1992[a]	6.7	6.1	29	8.4	7.5	29	11.4	−0.25 (−0.76, 0.27)
Scott 1997[a]	17.7	10	18	22.7	11.2	16	6.5	−0.46 (−1.14, 0.22)
Serfaty 2009[a]	18.4	10.8	64	20.3	11.3	55	23.4	−0.17 (−0.53, 0.19)
Smit 2006[a]	12.5	9.88	40	13.92	8.95	63	19.4	−0.15 (−0.55, 0.25)
Teasdale 1984[a]	8	11.18	17	18.5	11.18	17	6.0	−0.92 (−1.63, −0.21)
Ward 2000[b]	14.3	10.8	63	18.3	12.4	67	25.4	−0.34 (−0.69, 0.01)
Subtotal (95% CI)			251			267	100	−0.30 (−0.48, −0.13)
Heterogeneity: $T^2 = 0.00$; $\chi^2 = 4.33$; df = 6 ($P = 0.63$); I2 = 0%								
Test for overall effect: Z = 3.37 ($P = 0.0007$)								
1.1.7 Guided self-help CBT								
Joling 2011[c]	16.6	6.41	86	17.27	6.53	84	26.1	−0.10 (−0.40, 0.20)
Proudfoot 2004[b]	12.1	9.3	95	18.4	10.9	100	26.8	−0.62 (−0.91, −0.33)
Watkins 2012[b]	18.36	15.21	33	29.06	11.06	37	17.8	−0.80 (−1.29, −0.31)
Williams 2013[b]	21.1	13.3	141	24	11.9	140	29.4	−0.23 (−0.46, 0.01)
Subtotal (95% CI)				355		361	100	−0.40 (−0.69, −0.11)
Heterogeneity: $T^2 = 0.06$; $\chi^2 = 10.24$; df = 3 ($P = 0.02$); I2 = 71%								
Test for overall effect: Z = 2.74 ($P = 0.006$)								
1.1.6 Remote therapist-led problem-solving therapy								
Lynch 1997[c]	12.9	7.9	7	22.4	7.9	9	44.5	−1.14 (−2.22, −0.05)
Lynch 2004[c]	9	5.4	9	9.7	7.8	13	55.5	−0.10 (−0.95, 0.75)
Subtotal (95% CI)				16		22	100	−0.56 (−1.57, 0.45)
Heterogeneity: $T^2 = 0.29$; $\chi^2 = 2.18$; df = 1 ($P = 0.14$); I2 = 54%								
Test for overall effect: Z = 1.08 ($P = 0.28$)								



Heterogeneity

If confidence intervals for the results of individual studies have poor overlap, this generally indicates the presence of statistical heterogeneity

Thresholds for the interpretation of I^2 can be misleading but

0% - no heterogeneity

25% - low heterogeneity

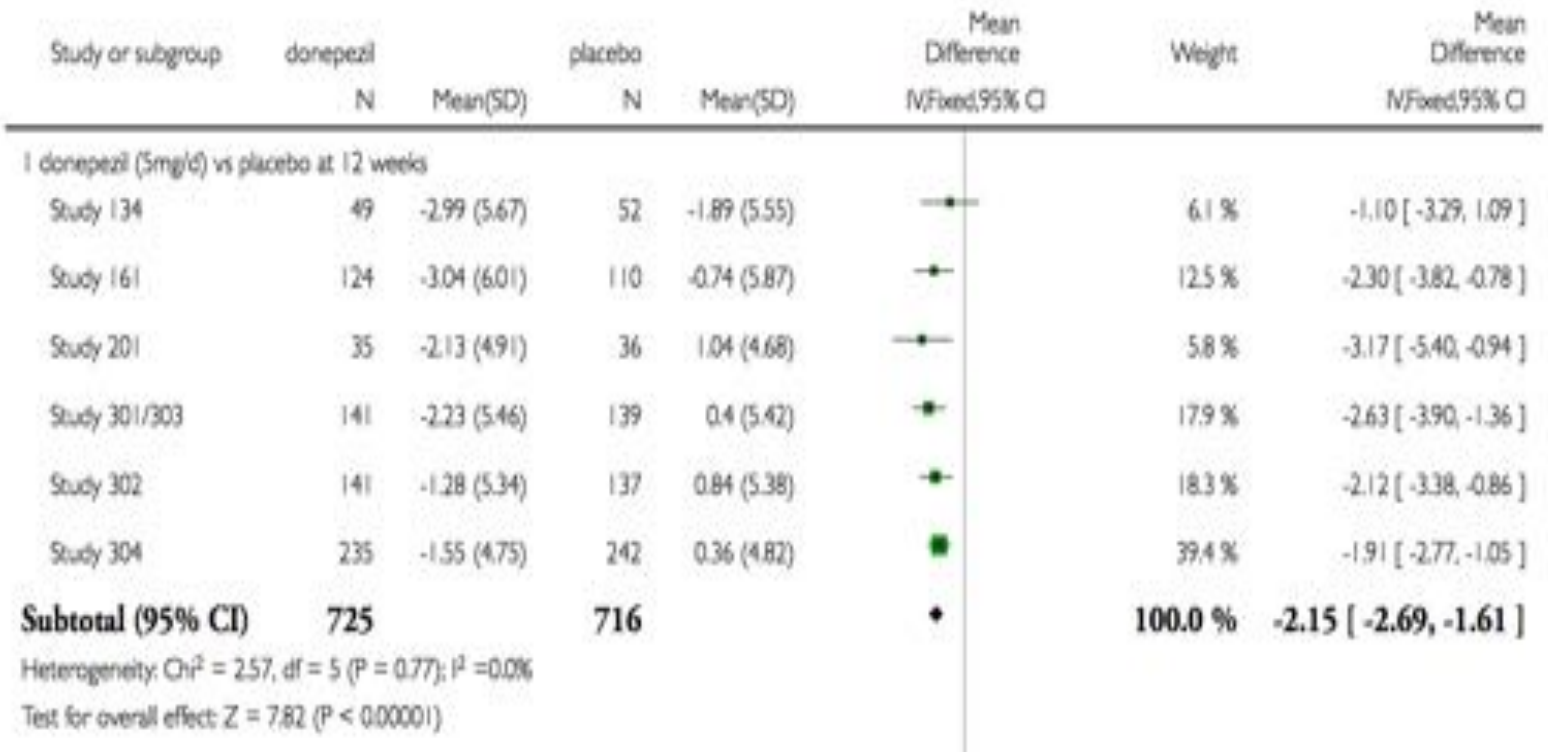
50% - moderate heterogeneity

75% - high heterogeneity

Significant heterogeneity

- differences between studies seem to exist
- it may be invalid to pool the results and generate a single summary result
- look for the variation in the studies
- investigate sources of heterogeneity - do subgroup analysis, look at characteristics of the studies
- account for heterogeneity

Statistical significance Yes; Heterogeneity No

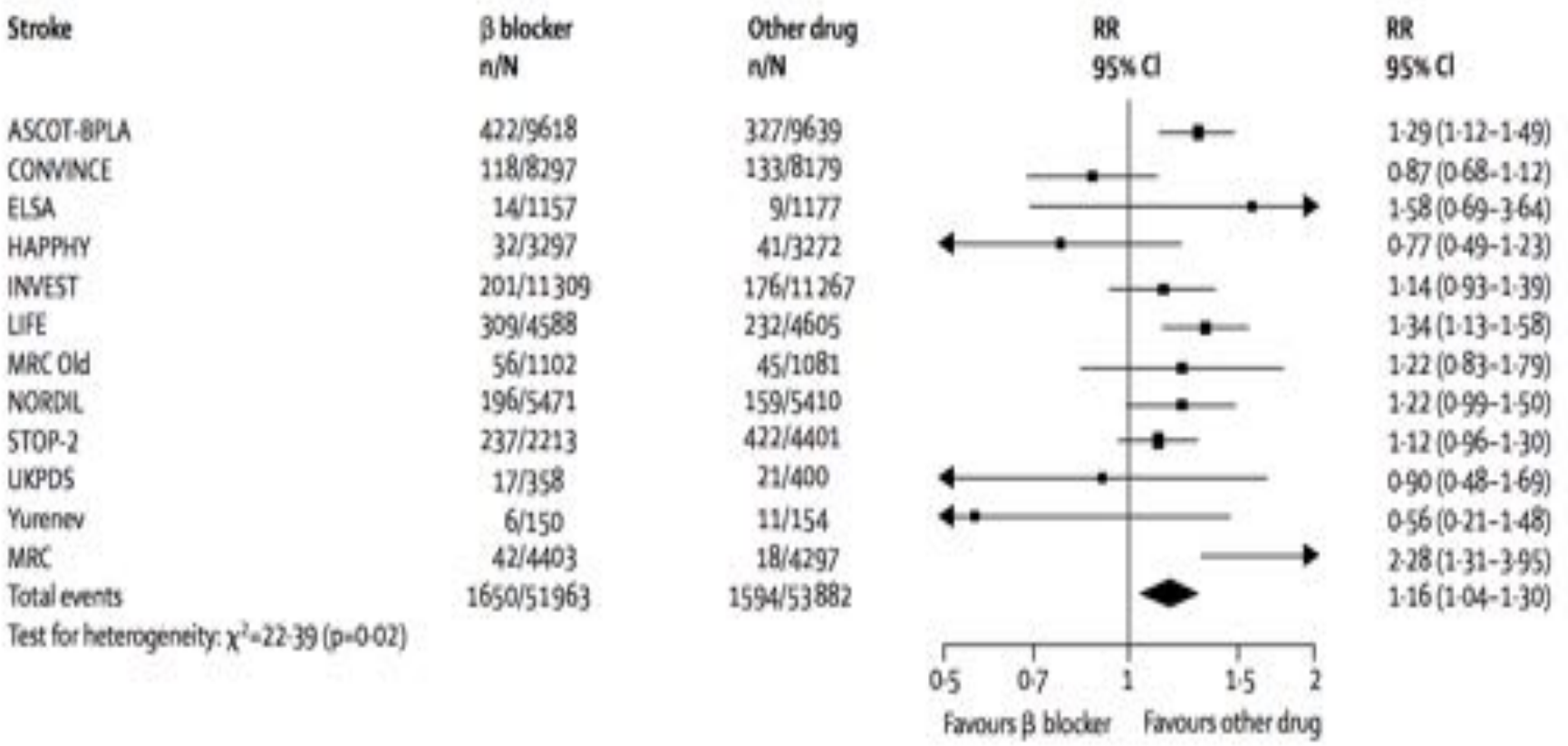


Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5mg/d) vs placebo at 12 weeks							
Study 134	49	-2.99 (5.67)	52	-1.89 (5.55)		6.1 %	-1.10 [-3.29, 1.09]
Study 161	124	-3.04 (6.01)	110	-0.74 (5.87)		12.5 %	-2.30 [-3.82, -0.78]
Study 201	35	-2.13 (4.91)	36	1.04 (4.68)		5.8 %	-3.17 [-5.40, -0.94]
Study 301/303	141	-2.23 (5.46)	139	0.4 (5.42)		17.9 %	-2.63 [-3.90, -1.36]
Study 302	141	-1.28 (5.34)	137	0.84 (5.38)		18.3 %	-2.12 [-3.38, -0.86]
Study 304	235	-1.55 (4.75)	242	0.36 (4.82)		39.4 %	-1.91 [-2.77, -1.05]
Subtotal (95% CI)	**725**		**716**			**100.0 %**	**-2.15 [-2.69, -1.61]**
Heterogeneity: Chi^2 = 2.57, df = 5 (P = 0.77); I^2 =0.0%							
Test for overall effect: Z = 7.82 (P < 0.00001)							

ADAS-cog changes with donepezil in dementia

Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001190.

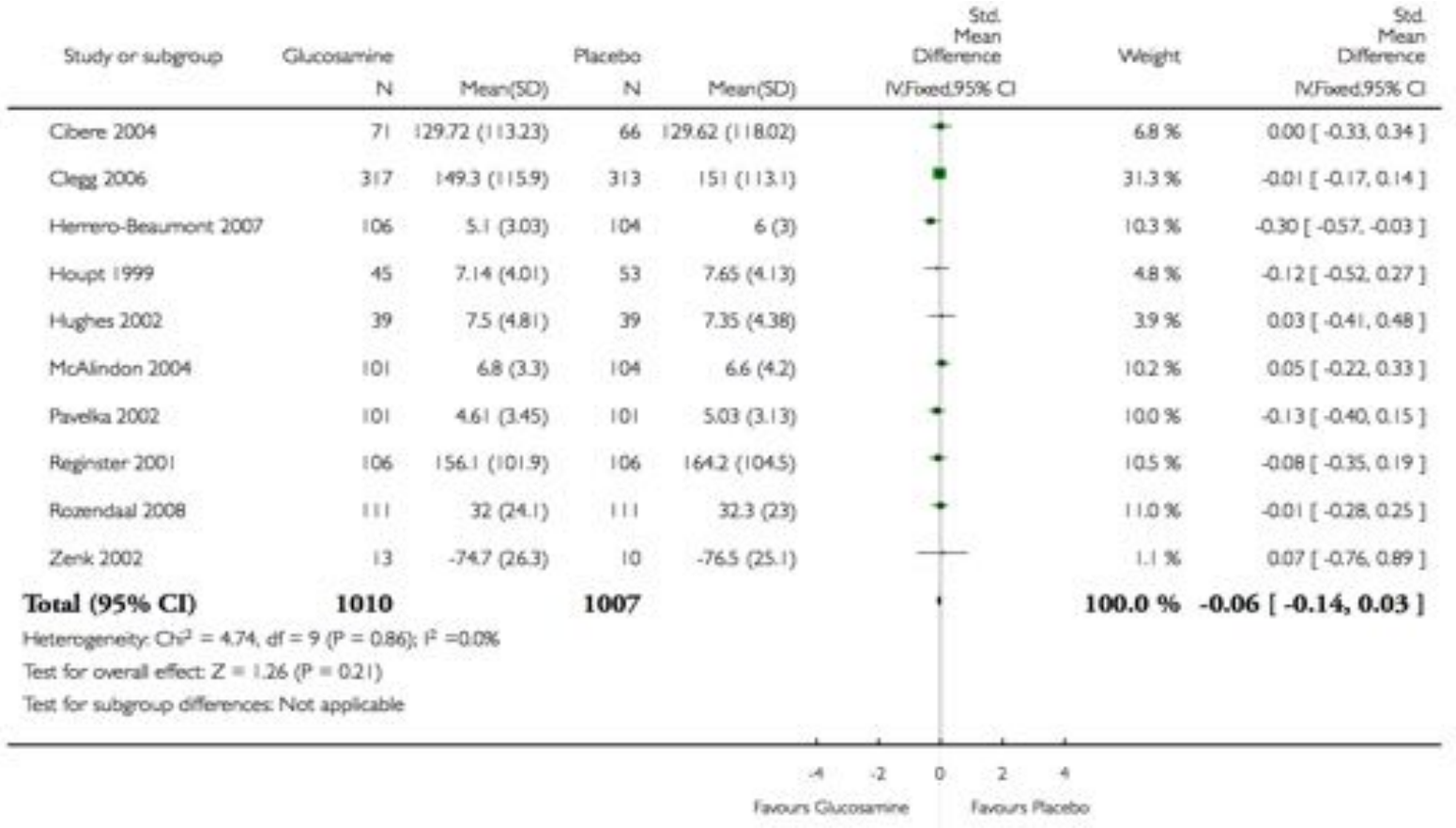
Statistical significance Yes; Heterogeneity Yes



Beta-blockers vs other drugs in hypertension for stroke

Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53.

Statistical significance No; Heterogeneity No

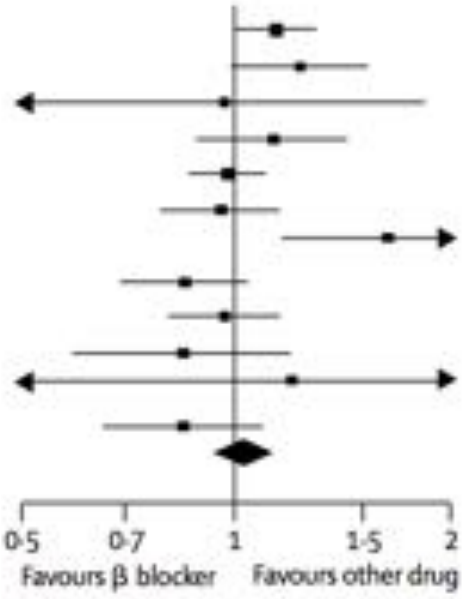


Glucosamine vs Placebo for OA pain, high quality studies

Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002946.

Statistical significance No; Heterogeneity Yes

Myocardial infarction	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
ASCOT-BPLA	444/9618	390/9639		1·14 (1·00–1·30)
CONVINCE	166/8297	133/8179		1·23 (0·98–1·54)
ELSA	17/1157	18/1177		0·96 (0·50–1·85)
HAPPHY	132/3297	116/3272		1·13 (0·88–1·44)
INVEST	441/11309	452/11267		0·97 (0·85–1·11)
LIFE	118/4588	198/1081		0·95 (0·78–1·16)
MRC Old	80/1102	48/4605		1·63 (1·15–2·32)
NORDIL	157/5471	183/5410		0·85 (0·69–1·05)
STOP-2	154/2213	318/4401		0·96 (0·80–1·16)
UKPDS	46/358	61/400		0·84 (0·59–1·20)
Yurenev	7/150	6/154		1·20 (0·41–3·48)
MRC	103/4403	119/4297		0·84 (0·65–1·10)
Total events	1935/51963	2042/53882		1·02 (0·93–1·12)
Test for heterogeneity: χ^2=20·67 (p=0·04)				



Beta-blockers vs other drugs in hypertension for MI

Lancet. 2005 Oct 29-Nov 4;366(9496):1545-53.

What is in those Vitamin D trials?

Study	Country	Endpoint	Age
Camargo (2012)	Mongolia	Acute RI	10
Jorde (2012)	Norway	Influenza	63
Laaksi (2010)	Finland	URTI	18-28
Li-Ng (2009)	USA	URI*	59
Manaseki-Holland (2010)	Afghanistan	pneumonia	0-3
Manaseki-Holland (2012)	Afghanistan	pneumonia	0-1
Murdoch (2012)	New Zealand	Colds	47
Urashima (2010)	Japan	Flu	10.2

URI* = 2 or more of fever, cough, productive sputum or change in sputum color and quantity, muscle aches, nausea or vomiting

What is in those Vitamin D trials?

Let's look specifically at Urashima (Am J Clin Nutr 2010;91:1255-60)

	Vitamin D		Placebo		Relative Risk*
	n (167)	%	n (167)	%	
Influenza A	18	11%	31	19%	0.58 (0.34-0.996)
Influenza B	39	23%	28	17%	1.39 (0.90-2.15)
Influenza Like Illness	8	5%	9	5%	-
Total	65	38.9%	68	40.7%	0.96 (0.73-1.24)

* Using http://www.hutchon.net/ConfidRR.htm for RR (& CI) estimation