PHRM 451
Evidence Appraisal Boot Camp

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Some bootcamp material (work book) developed by

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Professor, Faculty of Medicine
University of Alberta, Edmonton, Alberta

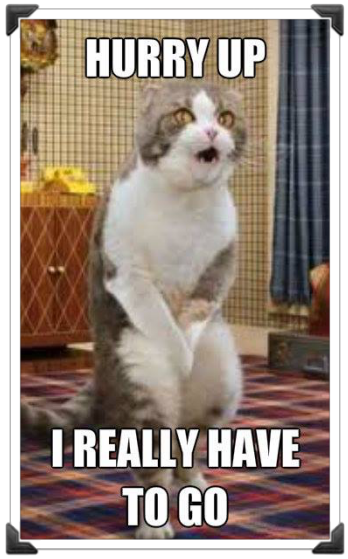
For Course Material Please Go To Canvas PHRM 451

Course Material

1. Evidence Appraisal Content
2. Evidence Appraisal Work Book

The Schedule

- Philosophy
- How to critically appraise an RCT in 10 minutes
- You do “it” - in groups
- Homework review
- Meta-analyses
- Numbers, numbers, numbers workbook
- Meta-analysis workbook
- Lab tests and evidence
- Please ask questions at any time - this is your chance to make mistakes/have things clarified/ OK to go off topic somewhat




We are
Knowledge
Brokers

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®

Everyday you will give lot's of health recommendations

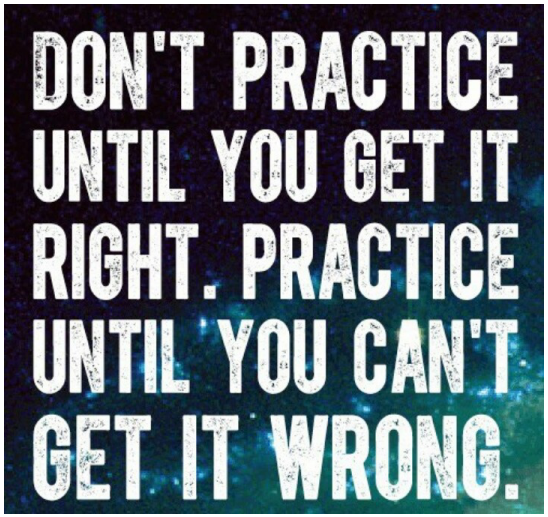
a. How to take a pill (TID, BID, DAILY)

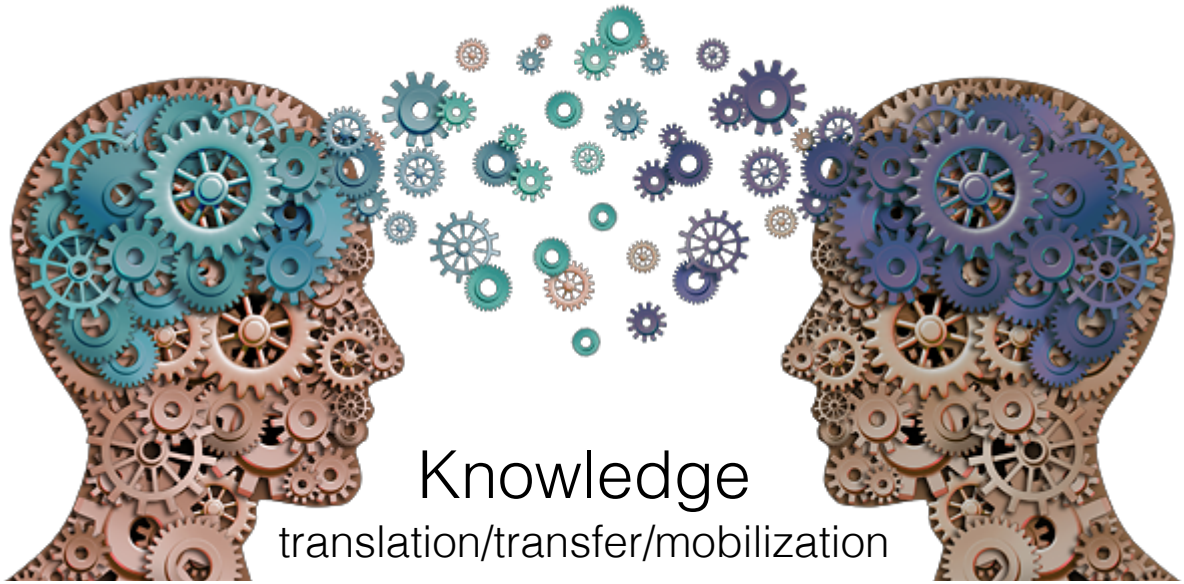
b. With food, on an empty stomach, take until all gone

c. Try this vitamin, pain killer, stomach remedy, cough remedy, cold remedy

d. What do you think of "X"

e. Low, medium, high dose



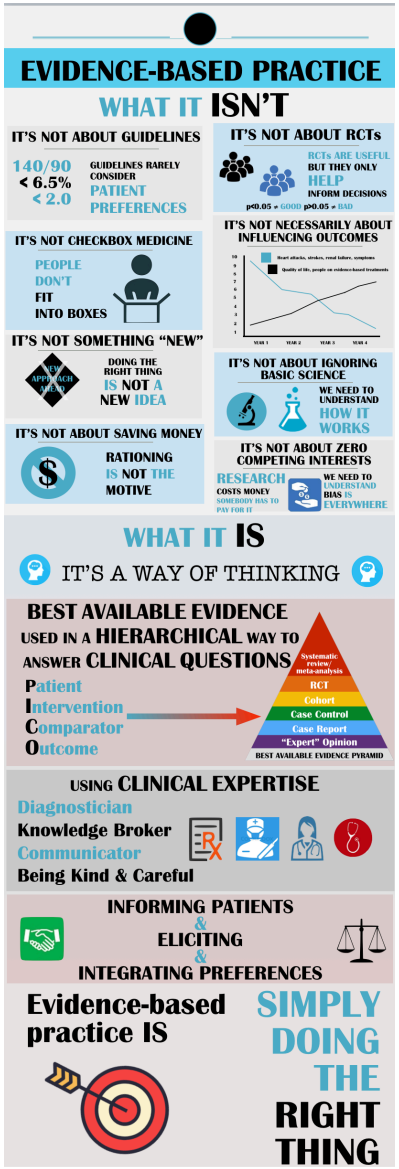


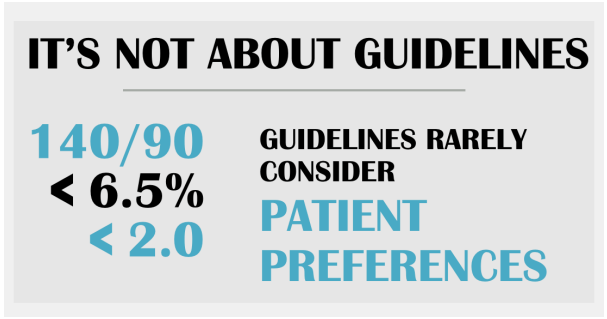
Knowledge

translation/transfer/mobilization

BELIEF

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


EVIDENCE-BASED PRACTICE
WHAT IT ISN'T
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
Heart attacks, strokes, renal failure, symptoms
Quality of life, people on evidence-based treatments
YEAR 1
YEAR 2
YEAR 3
YEAR 4
IT'S NOT SOMETHING "NEW"
NEW APPROACH AHEAD
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
BEST AVAILABLE EVIDENCE
USED IN A HIERARCHICAL WAY TO ANSWER CLINICAL QUESTIONS
Patient
Intervention
Comparator
Outcome
Systematic review/ meta-analysis
RCT
Cohort
Case Control
Case Report
"Expert" Opinion
BEST AVAILABLE EVIDENCE PYRAMID
USING CLINICAL EXPERTISE
Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful
INFORMING PATIENTS
&
ELICITING
&
INTEGRATING PREFERENCES
Evidence-based practice IS
SIMPLY DOING THE RIGHT THING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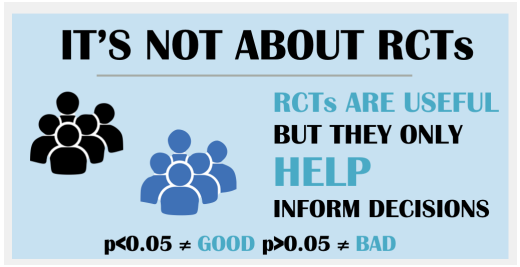
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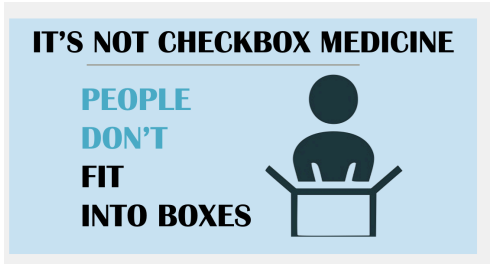
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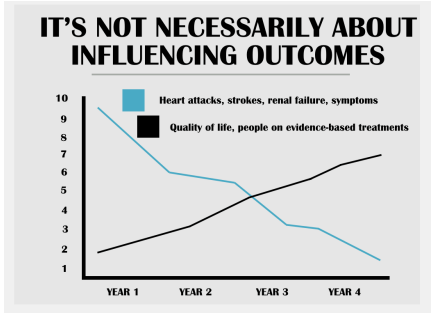
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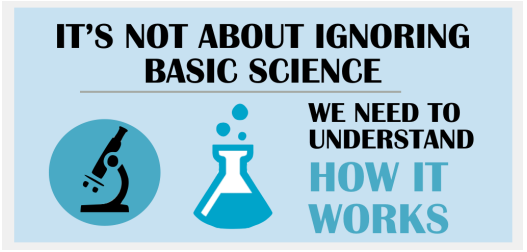
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WHAT IT IS

IT'S A WAY OF THINKING

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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:

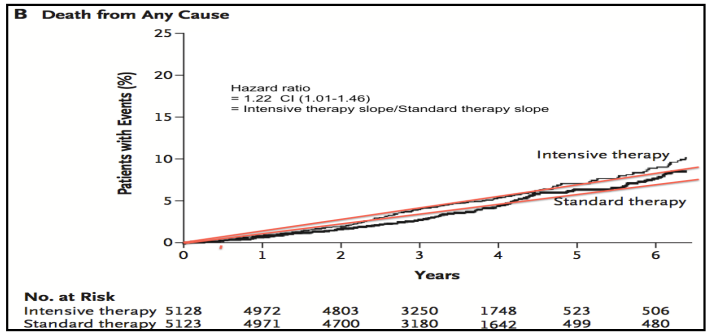
1. The observed difference was due to chance
2. The observed difference was due to confounding or other source of bias
3. If neither 1 nor 2 is believed to have caused the difference, then by simple elimination, it is inferred that the treatment caused it

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



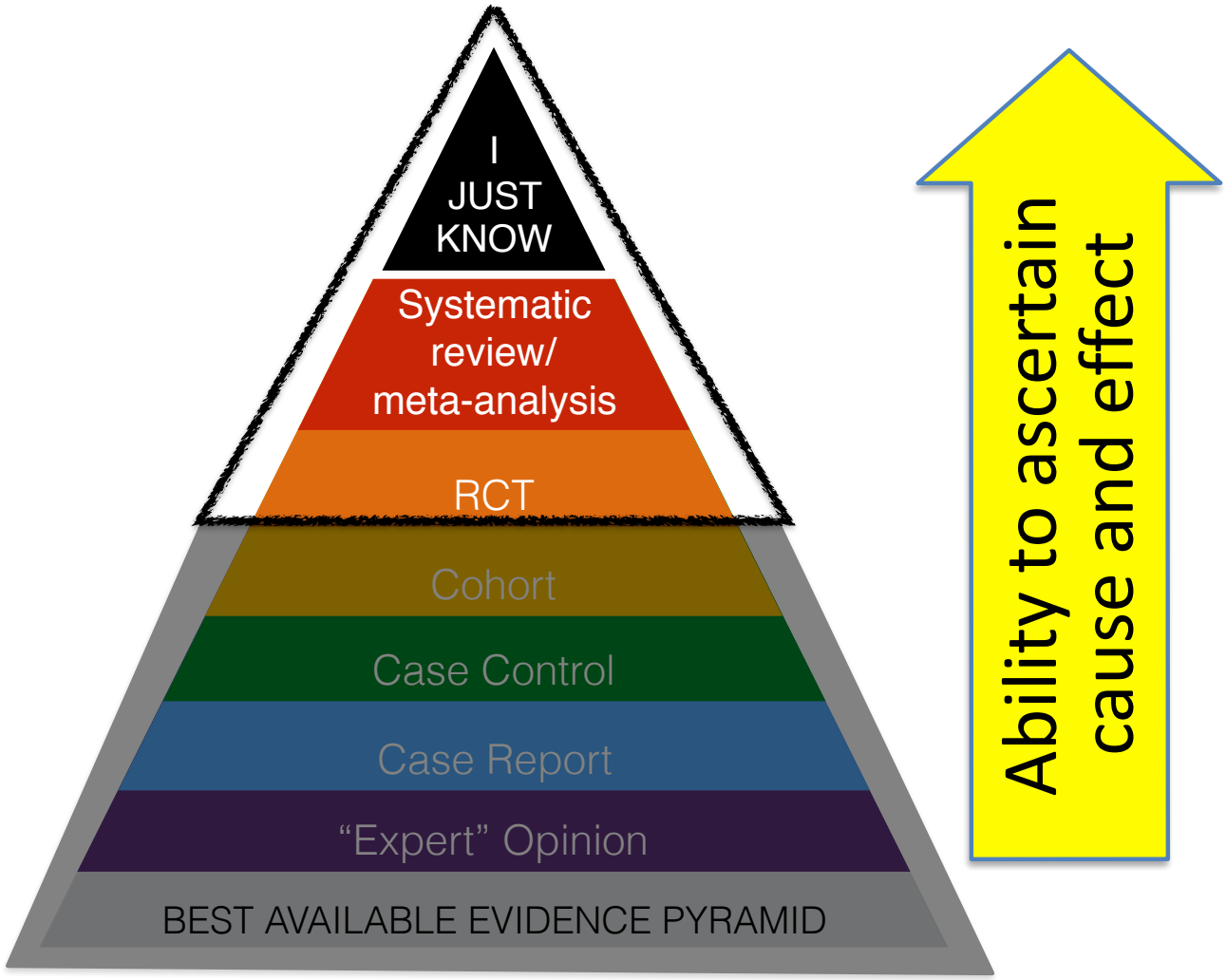
Odds ratio (OR) - ratio of two odds (25/1) - typically used in case-control studies - typically the incidence is not known

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

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



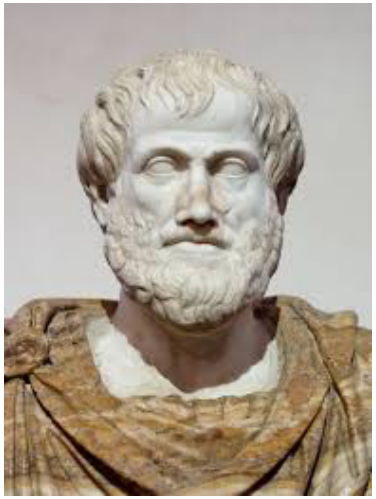
Need different evidence for different questions

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.*

“For the things we have to learn before we can do them, we learn by doing them.”
— Aristotle, The Nicomachean Ethics



You may already know many of the concepts, which is great, because you will get to practice them and maybe learn some interesting therapeutics

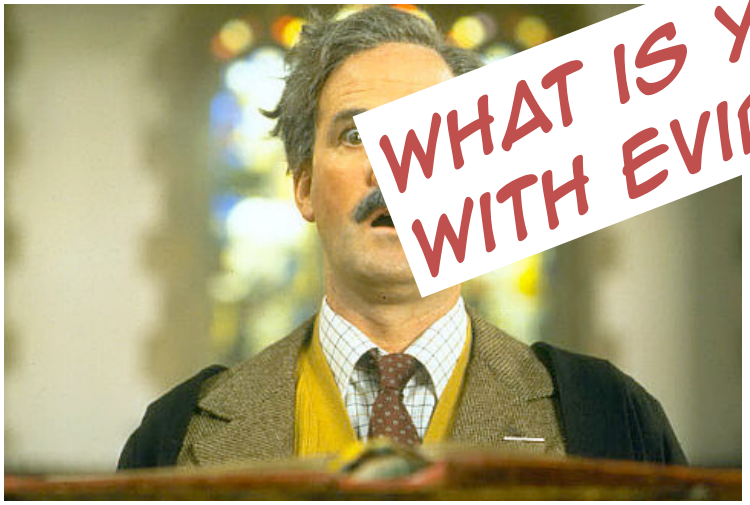
Clinical Questions (PICO)

Patient
  Description of the most important characteristics of the patient or target disorder
Intervention
  What do you want to do for the patient?
  Could include exposure, diagnostic test, prognostic factor, surgery, therapy or patient's perception
Comparator(s)
  Relevant alternative(s) most often considered for this type of patient
Outcome
  Clinical outcome of interest to you and your patient

EVIDENCE APPRAISAL CONTENT

How To Critically Appraise

WHAT IS YOUR EXPERIENCE WITH EVIDENCE APPRAISAL?



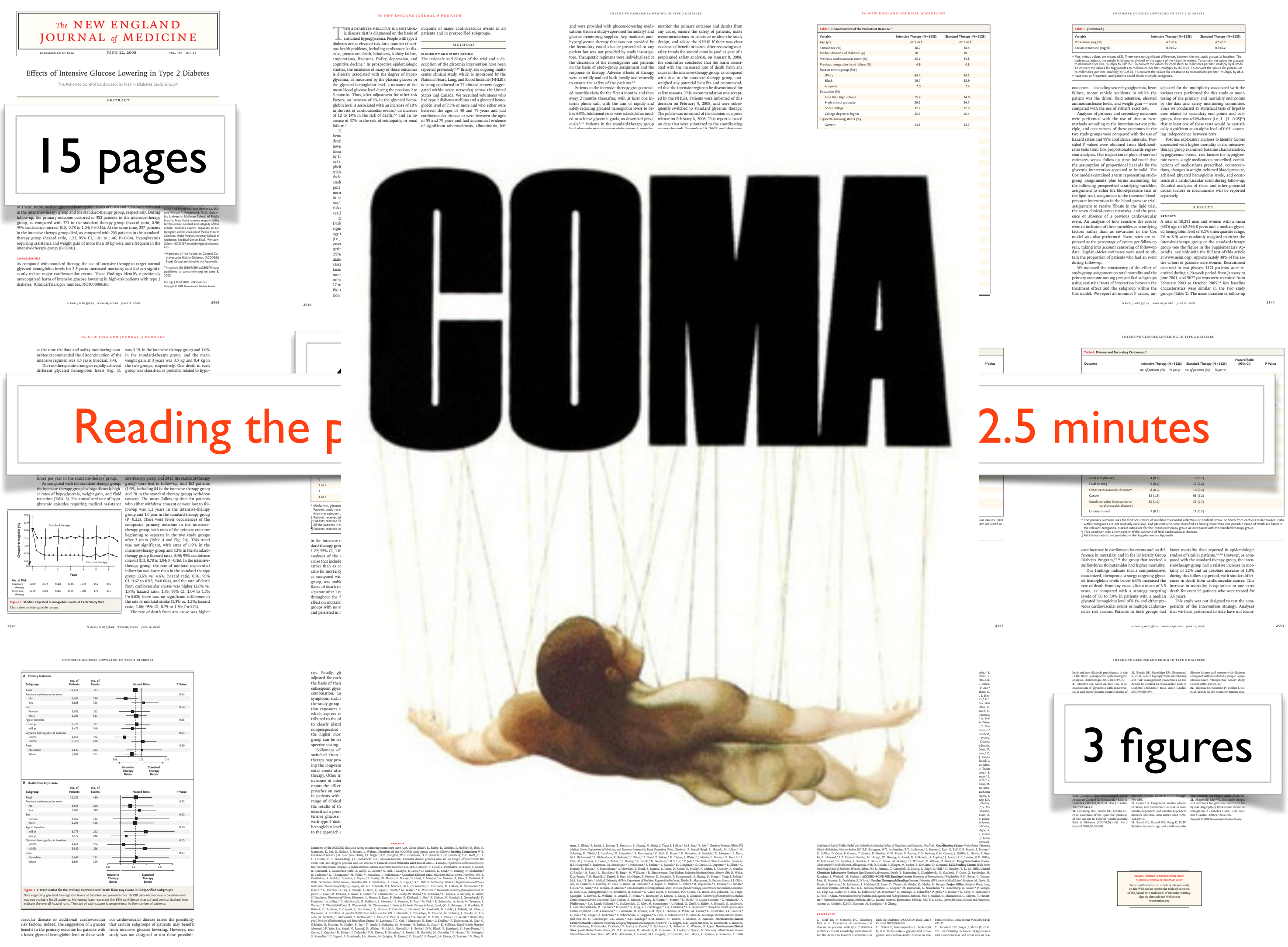
an RCT in
10 minutes

The NEW ENGLAND JOURNAL of MEDICINE

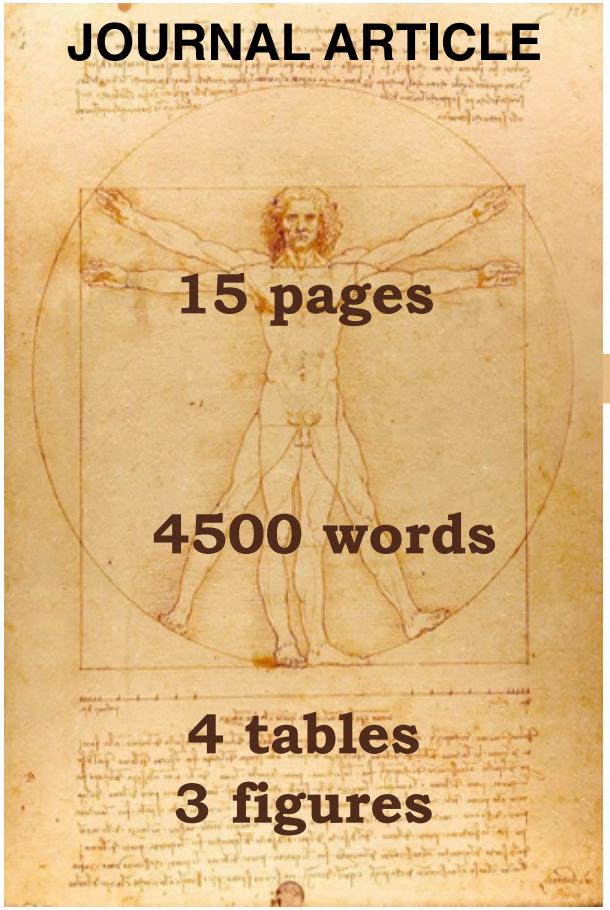
ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

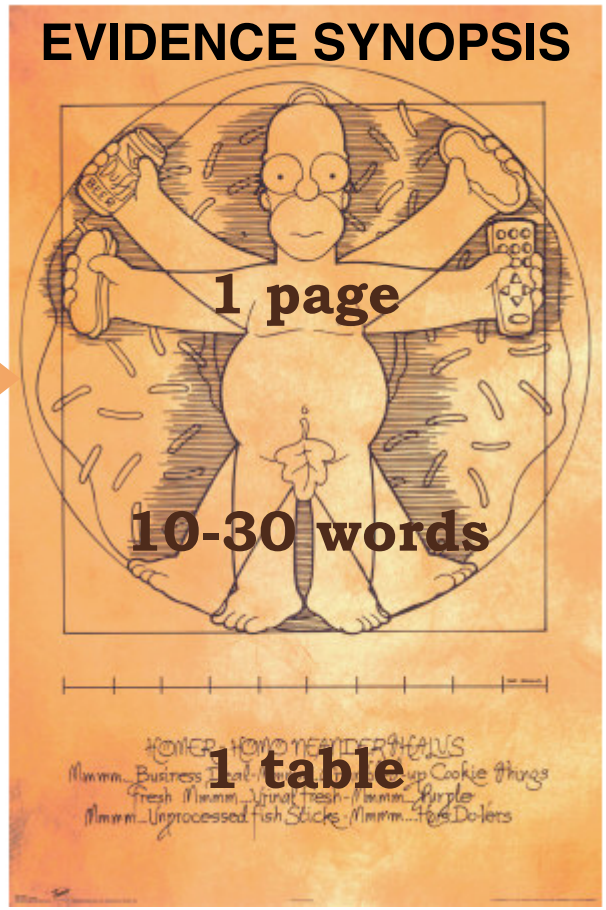
Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*


The NEW ENGLAND JOURNAL of MEDICINE
Effects of Intensive Glucose Lowering in Type 2 Diabetes
15 pages
COMA
Reading the p
2.5 minutes
3 figures

“Simplicity is the ultimate sophistication”





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

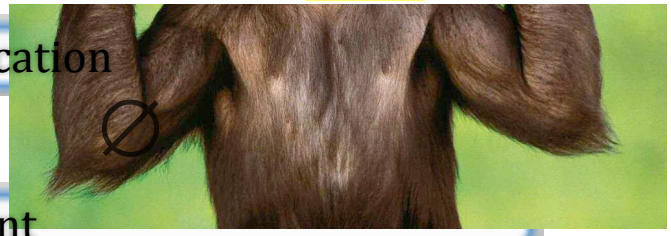
- Look at the Abstract
- Read the title
- Look at what was studied
- Look at the outcomes
- Read the conclusions

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

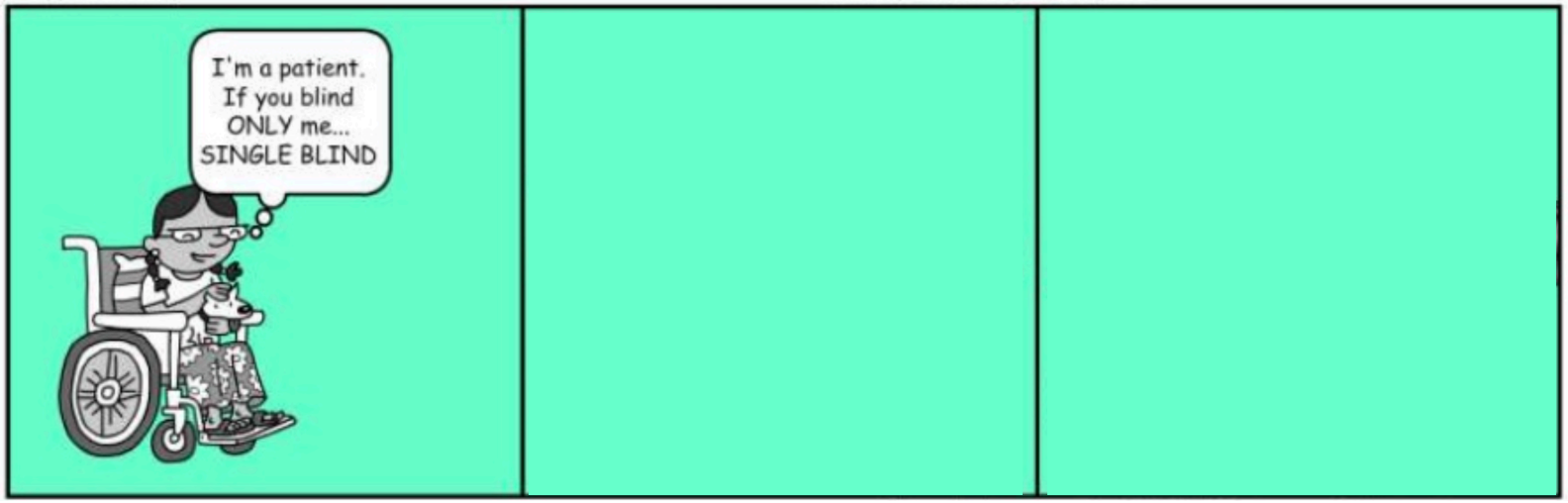
Supported by grants (N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184, IAA-Y1-HC-9035, and IAA-Y1-HC-1010) from the National Heart, Lung, and Blood Institute; by other components of the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute; by the

Abbott A Promise for Life
GE Healthcare
SOLVAY
ALLERGAN
gsk GlaxoSmithKline
Roche
Baxter
JANSSEN PHARMACEUTICAL LTD
sanofi aventis
BD
MERCK SHARP & DOHME
Boots
NOVARTIS
SCHWARZ PHARMA
A member of the UCB group
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

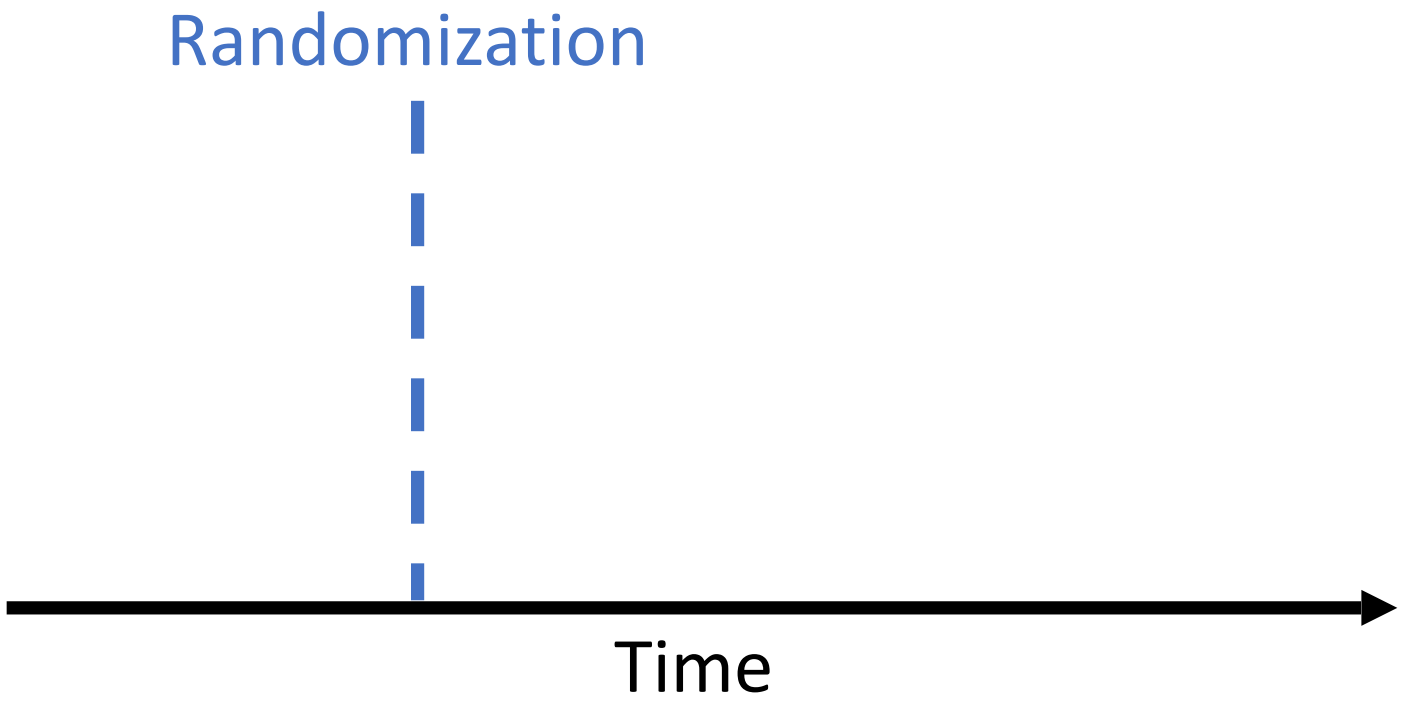
Blinding



Cartoon created by Terry Shaneyfelt

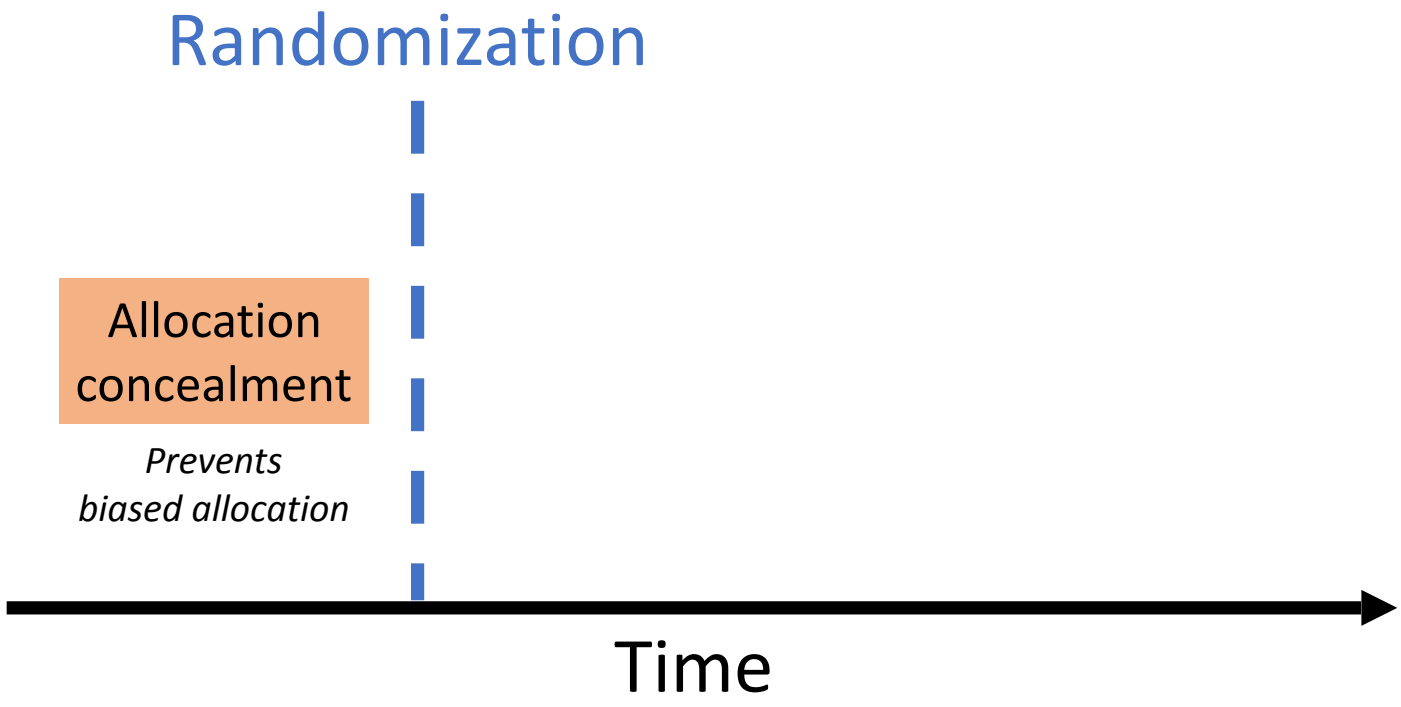
Allocation Concealment

Allocation Concealment vs. Blinding



Modified from slide 22 of https://www.slideshare.net/ciscogiii/assessment-of-bias-presentation

Allocation Concealment vs. Blinding



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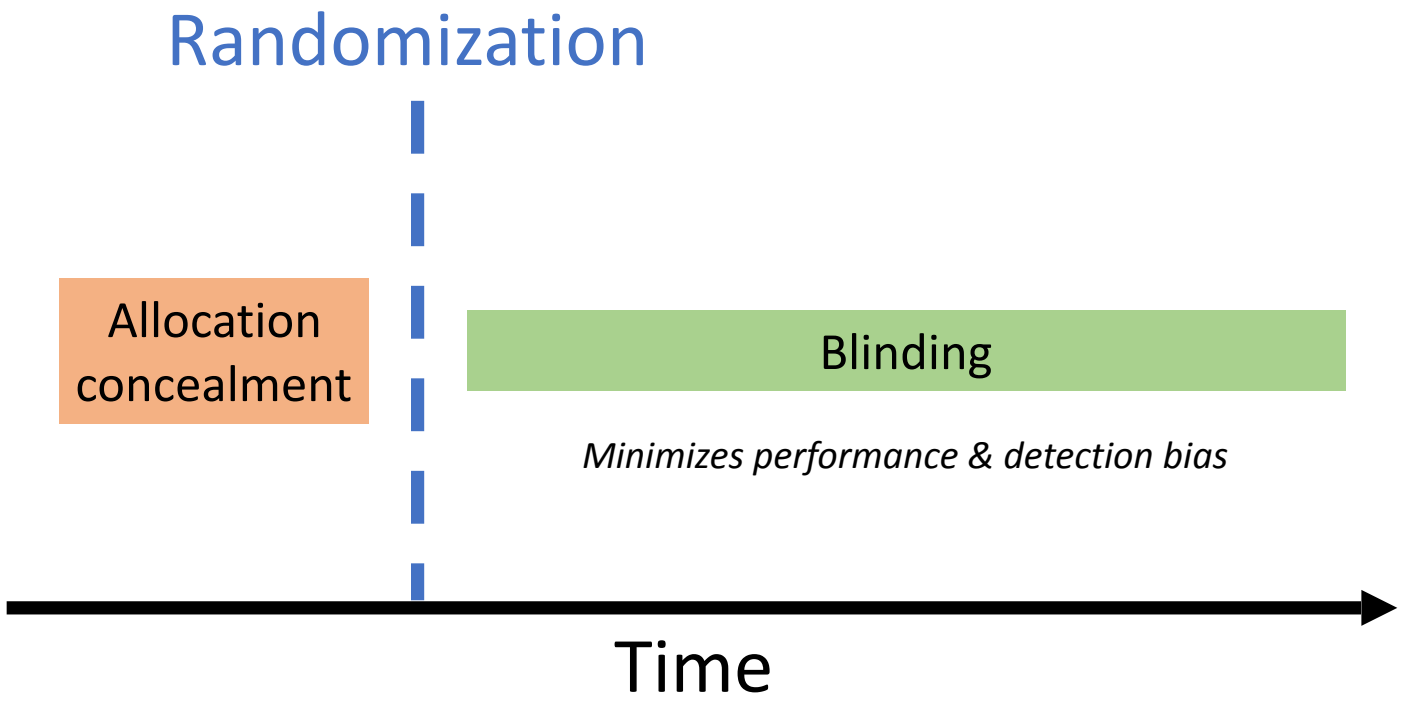

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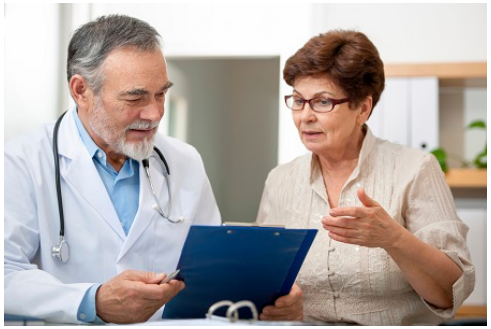
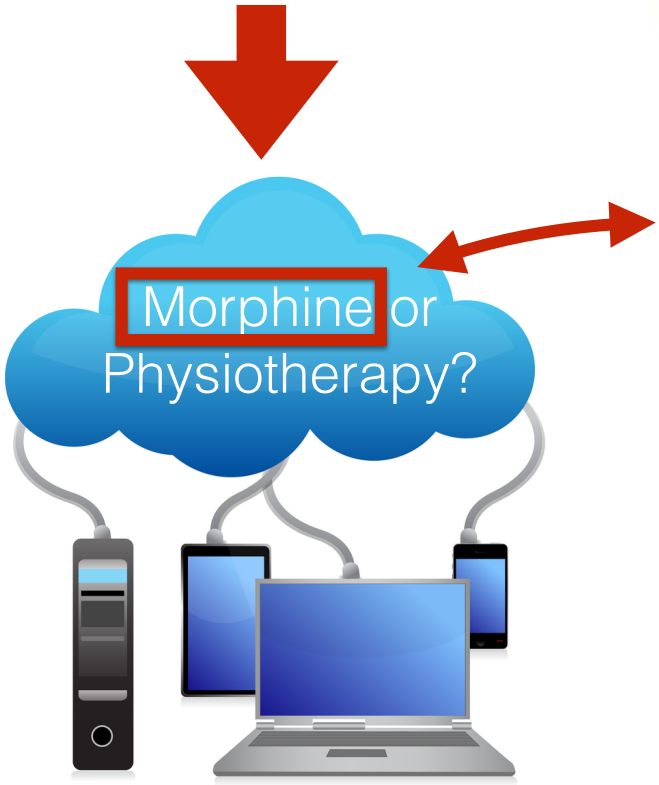
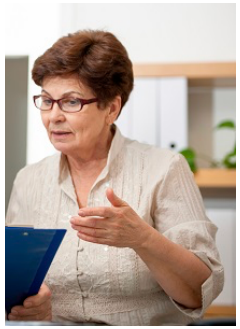


Morphine

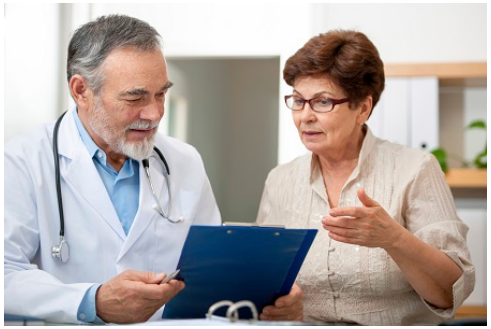
OR

Physiotherapy





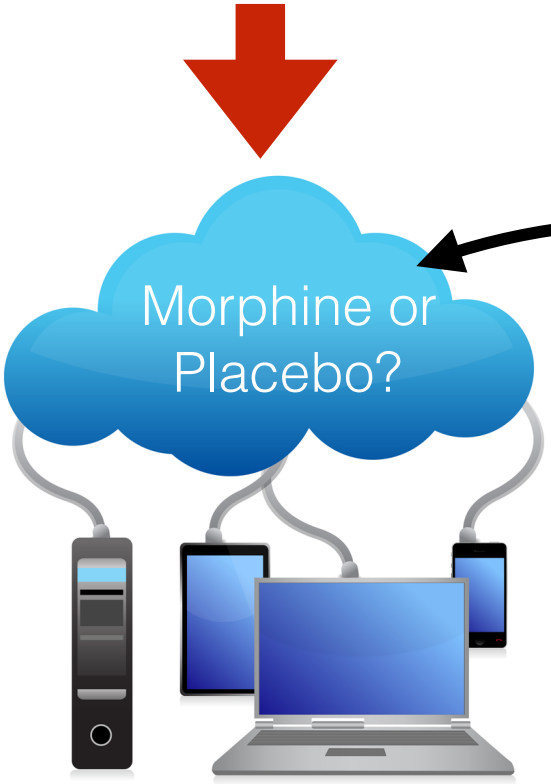
ALLOCATION CONCEALMENT and UNBLINDED

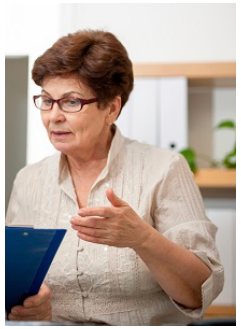


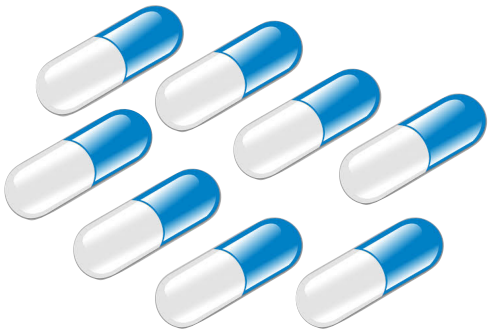
Morphine

Placebo

OR







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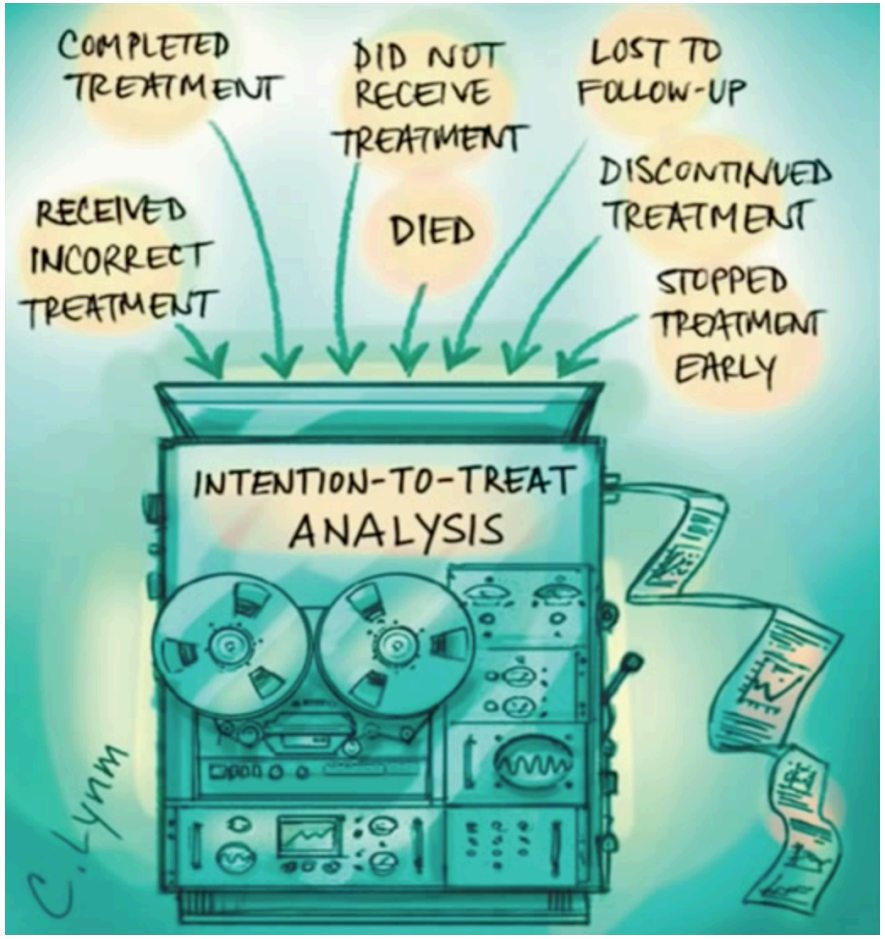
and
BLINDED



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

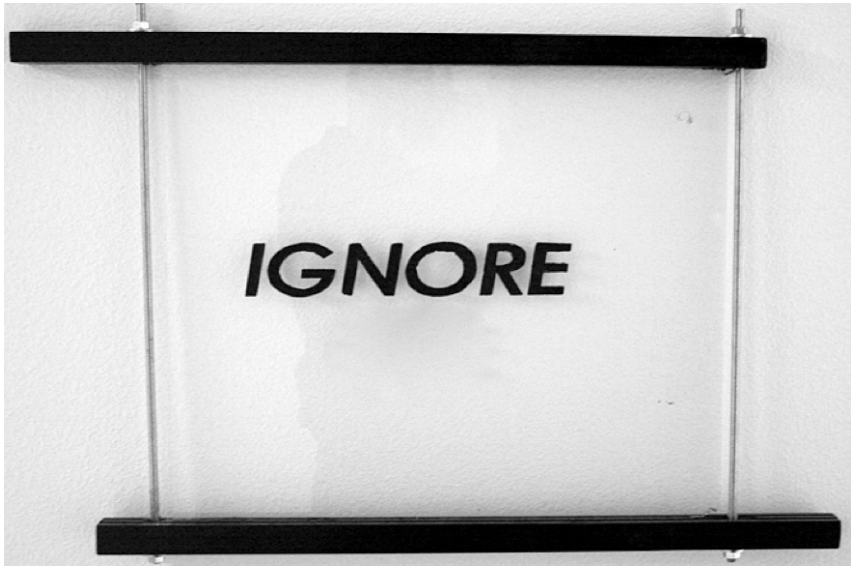
the % lost is quite different in one arm

Let's recap

- Random
- Blind
- Allocation
- Intent
- Follow
- Conflicts

MUCH OF THE REST OF THE TEXT

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



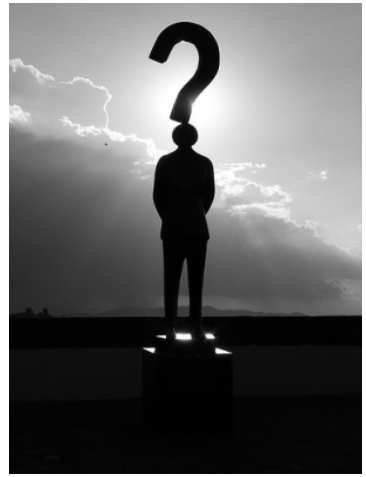
Patient Characteristics

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	32.2±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	183.3±42.1	183.3±41.6
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

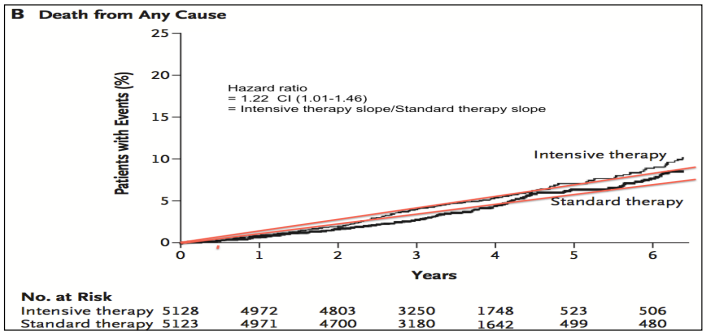
- Differences between groups
- Baseline characteristics

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 (%)	% per yr	A1c = 7.5% no. of patients (%)	% 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	1.35 (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		
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

Hazard ratio is the ratio of the slopes of the hazard curve

The CI represents a plausible range of values for the effect but not a probability of its magnitude

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI	Rela
Primary outcome (%)	6.9	7.2	0.9	.78-1.04	0.95
Death (%)	5	4	1.22	1.01-1.46	1.25
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92	0.79
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50	1.1
CHF (%)	3	2.4	1.18	0.93-1.49	1.22

22% relative increase
1.22 minus 1.00 = 0.22
1% relative increase
1.01 minus 1.00 = 0.01
46% relative increase
1.46 minus 1.00 = 0.46

5 is 25% greater than 4
RR - 1.25

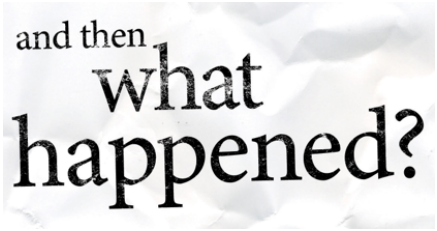
Let's recap

- 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±33.5	90.6±34.0	0.74
Blood pressure — mm Hg¶			
Systolic	126.4±16.7	127.4±17.2	0.002
Diastolic	66.9±10.5	67.7±10.6	<0.001



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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

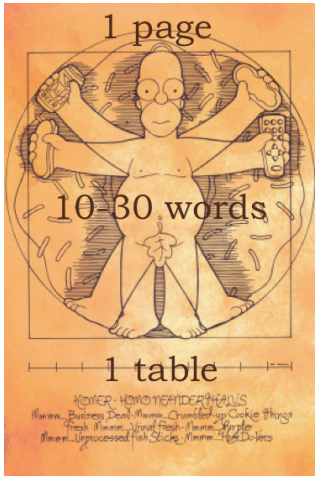
Randomised

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

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Randomised
Non-blinded
Allocation concealment?
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Weight gain >10kg	27.8	14.1		

Combined CVD (death, MI, CHF, angina, stroke)

	Combined CVD	No CVD	Total (n)
Doxazosin	1592 a	7475 b	9067 a+b
Chlorthalidone	2245 c	13023 d	15268 c+d

Chlorthalidone = Control
Doxazosin = Experimental

Control event rate (CER) = c/c+d = 2245 / 15268 = **0.147 = 14.7%**

Experimental event rate (EER) = a/a+b = 1592 / 9067 = **0.176 = 17.6%**

Relative Risk (RR) * = EER / CER = (a/a+b) / (c/c+d) = **17.6%** / **14.7%** = **1.20**

Relative Risk Increase (RRI) = EER – CER/CER = (**17.6%** - **14.7%**) / **14.7%** = **20%**

Risk Difference (RD) = Absolute Risk Increase (ARI) = EER – CER = **17.6 – 14.7 = 2.9%**

NNH = 100/ARR = **100 / 2.9 = 34.5 ≈ 35**

Therefore, you would harm one person for every **35** you treat with Doxazosin instead of Chlorthalidone.

The effect of Risedronate on the risk of hip fracture in elderly women

- 6197 randomized to Risedronate and 137 had a hip fracture.
- 3134 randomized to Placebo and 95 had a hip fracture.

EER: 137/6197 = 2.21%

CER: 95/3134 = 3.03%

- **Note**: Or use the Kaplan-Meier survival curves to estimate which were CER 3.9% & EER 2.8%.

- What is the relative risk reduction of hip fracture for those on Risedronate?

RR: 2.8 / 3.9 = 0.72
RRR: 1-0.72 = 0.28 = 28%

- What is the number of patients who would have to receive Risedronate (the NNT) to prevent one hip fracture in high risk women over three years?

AR: 3.9 – 2.8 = 1.1%
NNT: 100 / 1.1 = 91

RR : 2.21 / 3.03 = 0.73, RRR = 1 – 0.73 = 0.27 or 27%
AR: 3.03 – 2.21 = 0.82, NNT: 100 / 0.82 = 122

Meta-Analysis

Meta-Analysis

“Started” in 1976

Critics

- “An exercise in Mega-Silliness”
- “Garbage in = Garbage out"
- “Are MAs a form of medical fake news?”

"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

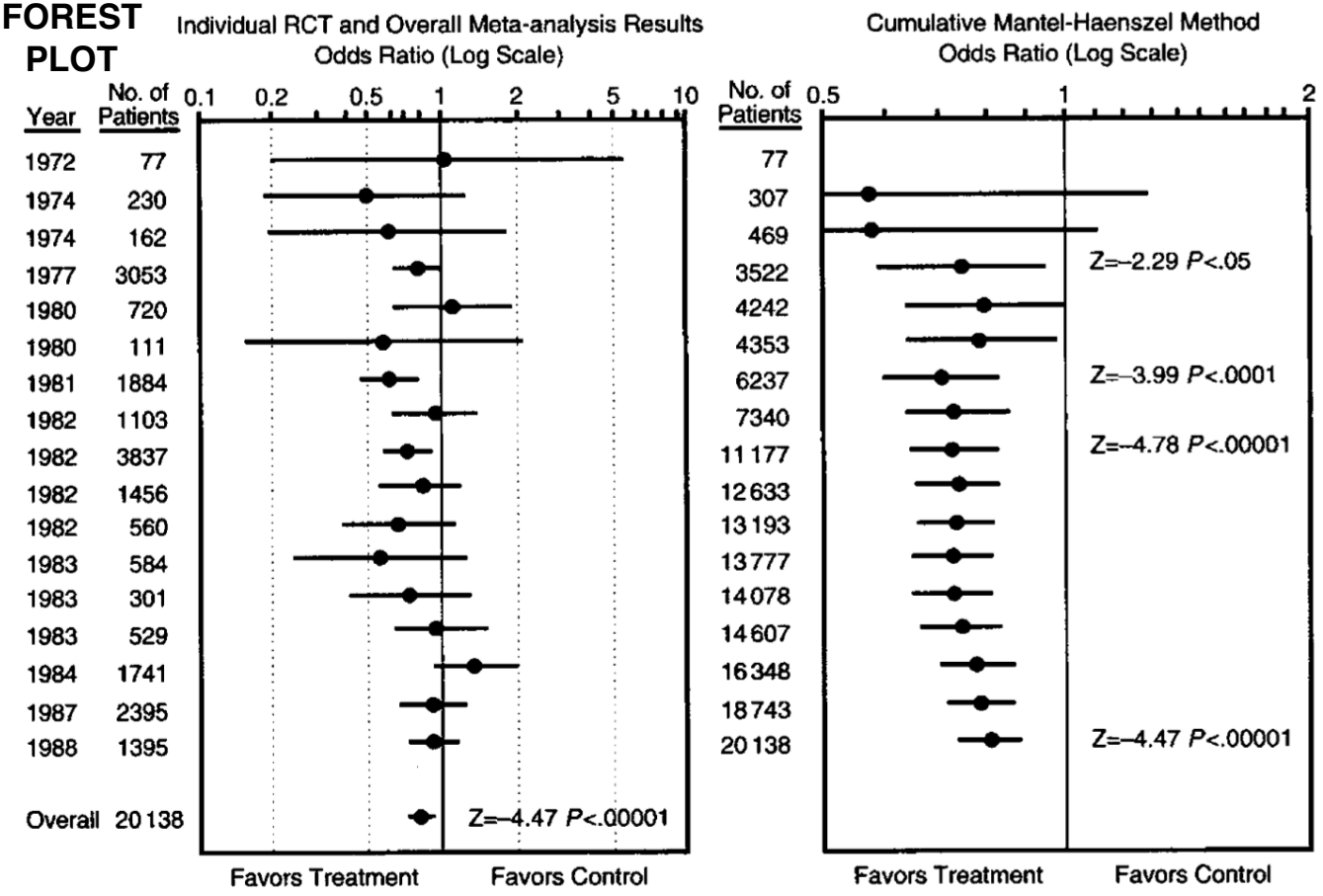
Meta-Analyses Should Not Tell Us What We Already Know or Obscure What We Should Remember

Meta-analyses should provide insights that are superior to those provided by a narrative summary of the data. If large-scale trials of 3 different β-blockers (bisoprolol, carvedilol, and metoprolol) for heart failure each report a nearly identical 35% reduction of all-cause mortality, little purpose would be served by performing a meta-analysis of the 3 trials. Not only would such a meta-analysis not add any new information, but also its results would not necessarily apply to other β-blockers (eg, bucindolol and nebivolol). Many meta-analyses only confirm existing knowledge and may conceal meaningful differences that can best be understood descriptively, rather than mathematically.

Packer M. Circulation 2017;136:2097-9

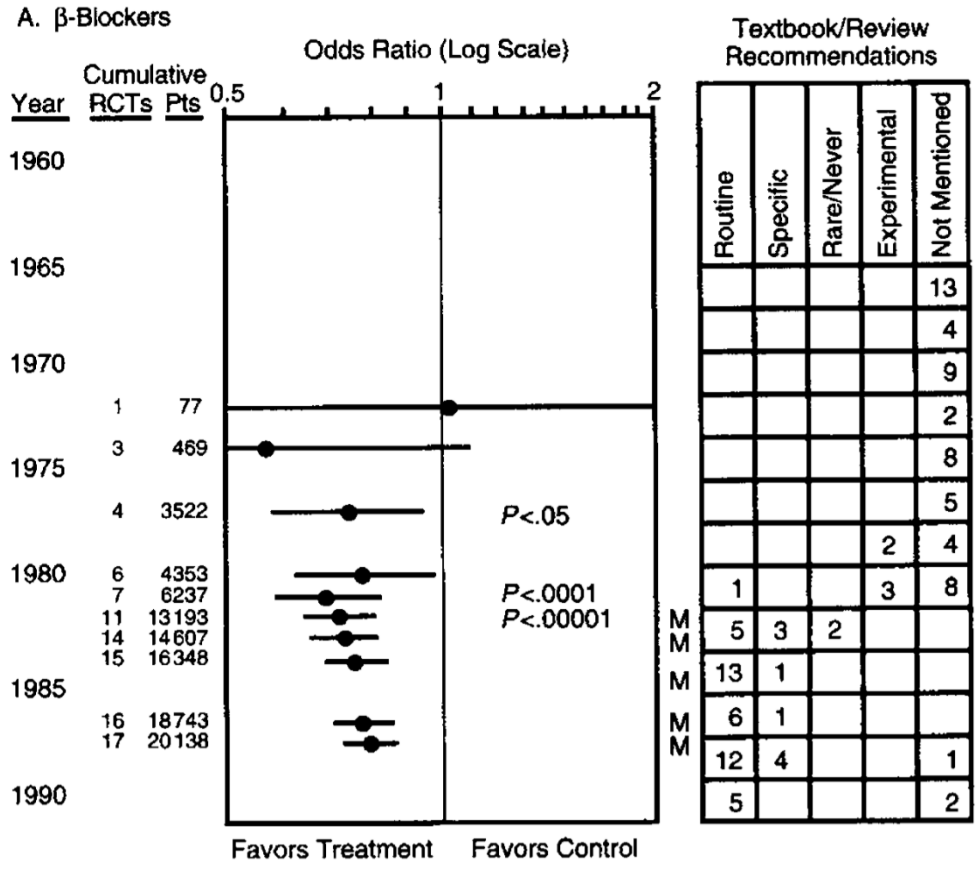
Effect of beta-blockers on mortality after a heart attack

FOREST PLOT



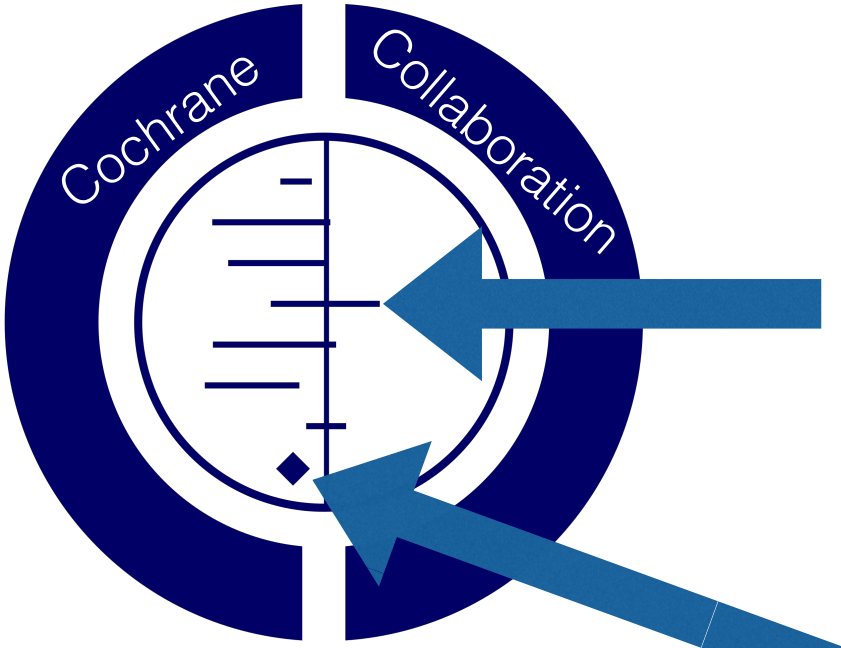
JAMA 1992;268:240-248

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	9
Issue 7 '17	7386		9832
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				
Issue 9 '17				6
Issue 8 '17			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

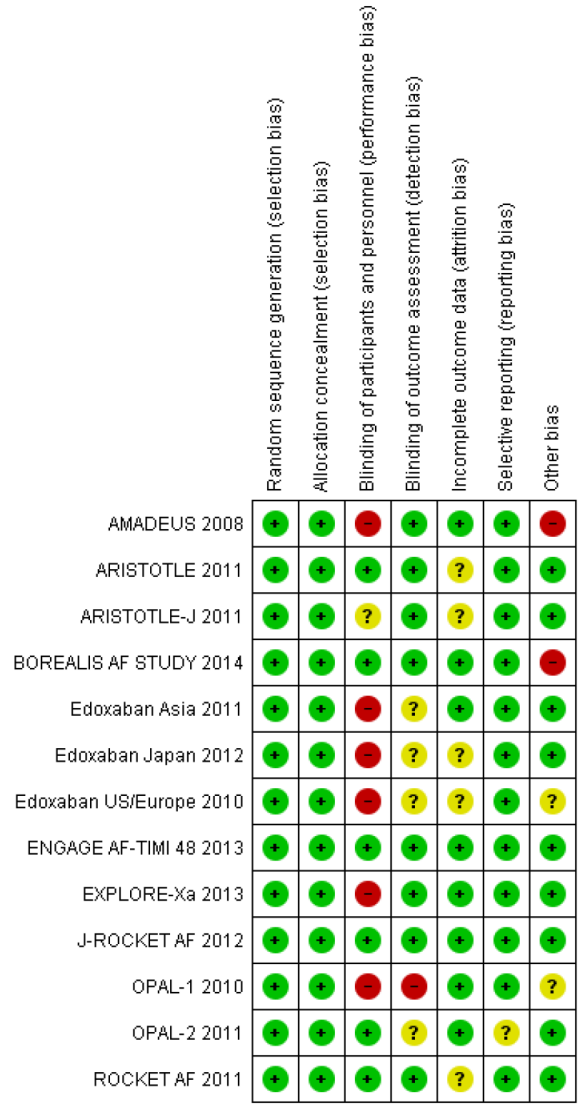
Summary of Findings

Factor Xa inhibitors compared with vitamin K antagonists for preventing stroke and other systemic embolic events in patient with atrial fibrillation

Patient or population: people with atrial fibrillation deemed eligible for long-term anticoagulant treatment
Settings: hospital-based setting
Intervention: factor Xa inhibitor[1]
Comparison: dose-adjusted vitamin K antagonist[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Warfarin	Factor Xa inhibitors				
Stroke and other systemic embolic events Follow-up: 12 weeks to 2.8 years	**34 per 1000**	**32 per 1000** (33 to 28)	**OR 0.89** (0.82 to 0.97)	67477 (13)	⊕⊕⊕⊕ **high**	Most data (90%) from studies of apixaban, edoxaban and rivaroxaban
All strokes Follow-up: 12 weeks to 2.8 years	**30 per 1000**	**28 per 1000** (29 to 24)	**OR 0.89** (0.81 to 0.97)	67449 (13)	⊕⊕⊕⊕ **high**	Most data (90%) from studies of apixaban, edoxaban rivaroxaban
Major bleedings Follow-up: 12 weeks to 2.8 years	**51 per 1000**	**41 per 1000** (43 to 38)	**OR 0.78** (0.73 to 0.84)	67396 (13)	⊕⊕⊕◯ **moderate**[3]	Most data (90%) from studies of apixaban, edoxaban and rivaroxaban
Intracranial haemorrhages Follow-up: 12 weeks to 2.8 years	**13 per 1000**	**7 per 1000** (8 to 6)	**OR 0.50** (0.42 to 0.59)	66259 (12)	⊕⊕⊕⊕ **high**[4]	Most data (90%) from studies of apixaban, edoxaban and rivaroxaban

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]

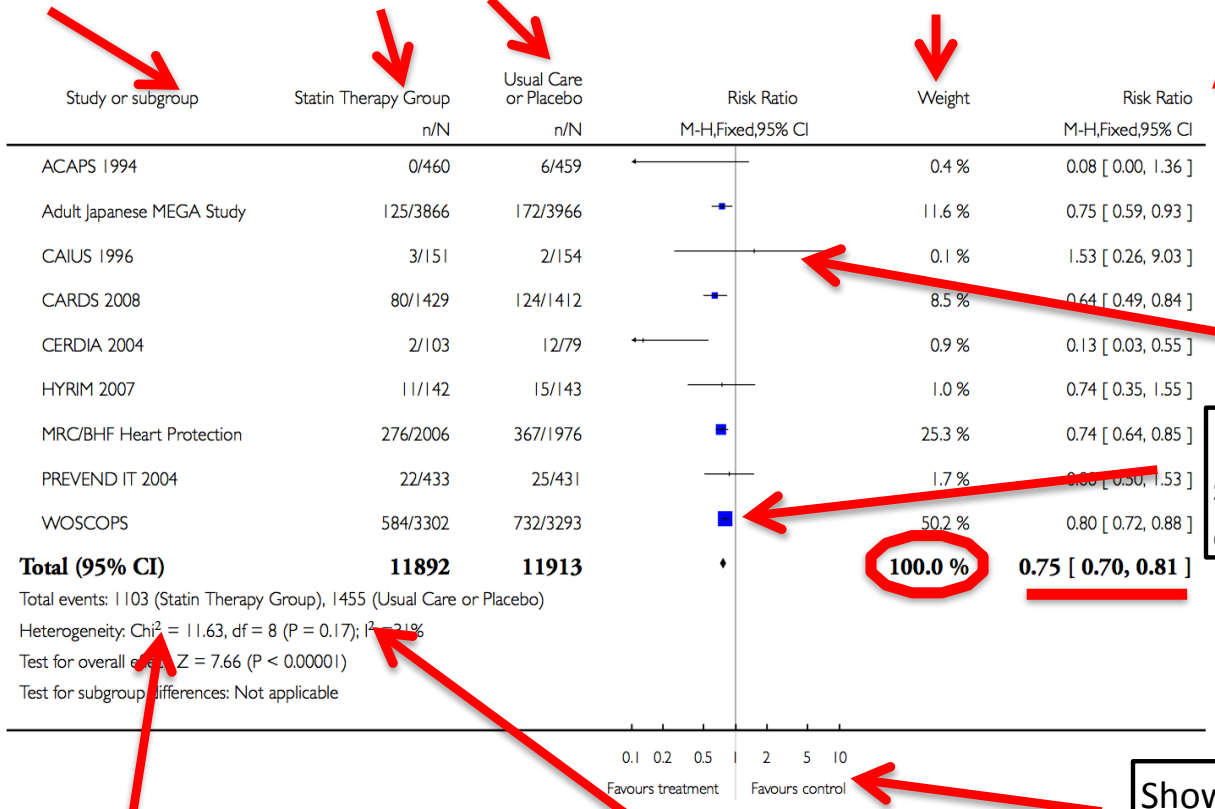
Mantel–Haenszel - statistical method
Random (assumes the studies are different) is more conservative than fixed (assumes trials are the same)

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

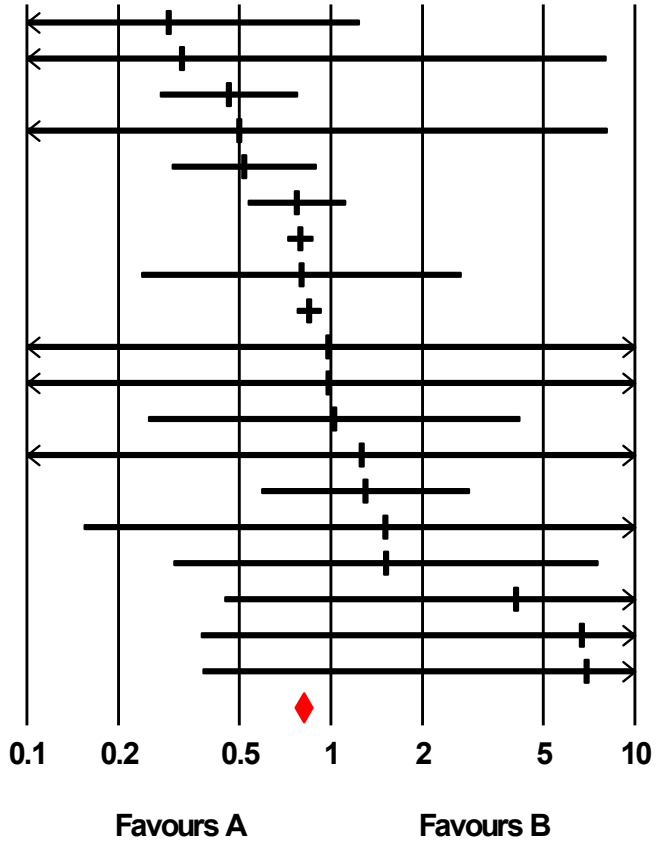
Final numbers of events and total included in each arm (can do “cheater” NNT)

Shows what side is “better” for treatment or control

CD004816 2013

Another common Forest plot “look”

Odds ratio	Lower limit	Upper limit	p-Value
0.293	0.069	1.241	0.095
0.324	0.013	8.039	0.491
0.462	0.275	0.776	0.004
0.500	0.031	8.110	0.626
0.519	0.301	0.895	0.018
0.773	0.535	1.117	0.170
0.793	0.721	0.872	0.000
0.800	0.239	2.683	0.718
0.849	0.775	0.929	0.000
0.981	0.061	15.891	0.989
0.982	0.088	10.988	0.988
1.025	0.251	4.180	0.973
1.263	0.060	26.676	0.881
1.300	0.592	2.855	0.513
1.511	0.154	14.785	0.723
1.518	0.304	7.565	0.611
4.066	0.448	36.895	0.213
6.694	0.375	119.570	0.196
6.940	0.380	126.777	0.191
0.813	0.763	0.866	0.000



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*]

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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**

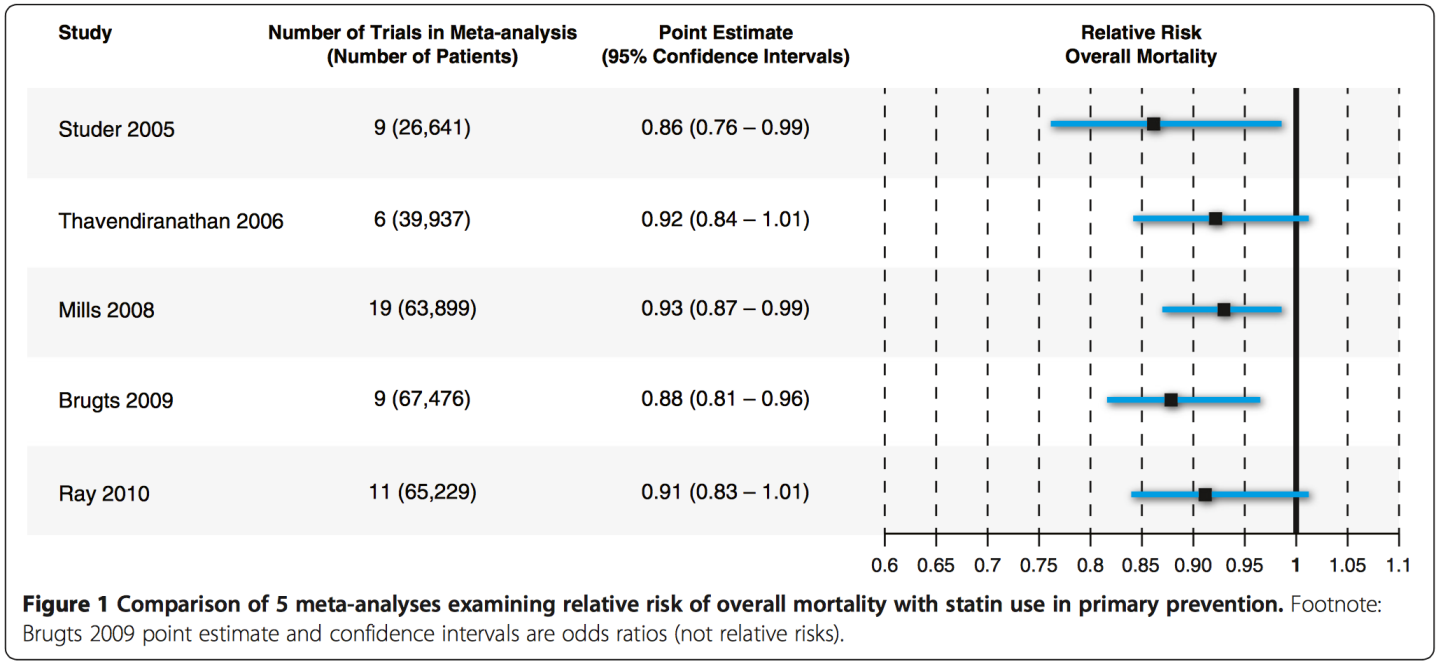


Figure 1 Comparison of 5 meta-analyses examining relative risk of overall mortality with statin use in primary prevention. Footnote: Brugts 2009 point estimate and confidence intervals are odds ratios (not relative risks).

Statistical Heterogeneity

Poor overlap in confidence intervals of individual generally indicates the presence of statistical heterogeneity

Best way to test: I^2

Rule of thumb to interpreting I^2:

- 0% - no heterogeneity
- 25% - low
- 50% - moderate
- 75% - high

Significant Heterogeneity

Differences between studies seem to exist

May be invalid to pool results and generate a single summary result

Need to explore sources of heterogeneity:

- Did they pool the correct effect measure?
  - Relative effect measure (HR, OR, RR) best for meta-analysis
- Sensitivity & subgroup analysis
- May be from differences in: Methods, patient inclusion/exclusion, intervention, control, outcome definition, duration

Statistical significance Yes; Heterogeneity No

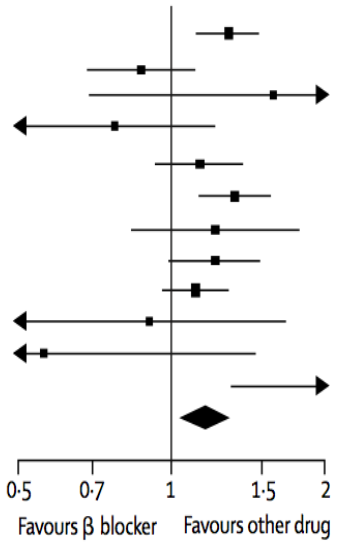
Study or subgroup	donepezil N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 donepezil (5mg/d) vs placebo at 12 weeks							
Study 134	49	-2.99 (5.67)	52	-1.89 (5.55)		6.1 %	-1.10 [-3.29, 1.09]
Study 161	124	-3.04 (6.01)	110	-0.74 (5.87)		12.5 %	-2.30 [-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

Stroke	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
ASCOT-BPLA	422/9618	327/9639		1·29 (1·12–1·49)
CONVINCE	118/8297	133/8179		0·87 (0·68–1·12)
ELSA	14/1157	9/1177		1·58 (0·69–3·64)
HAPPHY	32/3297	41/3272		0·77 (0·49–1·23)
INVEST	201/11309	176/11267		1·14 (0·93–1·39)
LIFE	309/4588	232/4605		1·34 (1·13–1·58)
MRC Old	56/1102	45/1081		1·22 (0·83–1·79)
NORDIL	196/5471	159/5410		1·22 (0·99–1·50)
STOP-2	237/2213	422/4401		1·12 (0·96–1·30)
UKPDS	17/358	21/400		0·90 (0·48–1·69)
Yurenev	6/150	11/154		0·56 (0·21–1·48)
MRC	42/4403	18/4297		2·28 (1·31–3·95)
Total events	1650/51963	1594/53882		1·16 (1·04–1·30)
Test for heterogeneity: χ^2=22·39 (p=0·02)				



Beta-blockers vs other drugs in hypertension for stroke

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

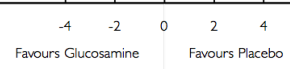
Statistical significance No; Heterogeneity No

Study or subgroup	Glucosamine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Cibere 2004	71	129.72 (113.23)	66	129.62 (118.02)		6.8 %	0.00 [-0.33, 0.34]
Clegg 2006	317	149.3 (115.9)	313	151 (113.1)		31.3 %	-0.01 [-0.17, 0.14]
Herrero-Beaumont 2007	106	5.1 (3.03)	104	6 (3)		10.3 %	-0.30 [-0.57, -0.03]
Houpt 1999	45	7.14 (4.01)	53	7.65 (4.13)		4.8 %	-0.12 [-0.52, 0.27]
Hughes 2002	39	7.5 (4.81)	39	7.35 (4.38)		3.9 %	0.03 [-0.41, 0.48]
McAlindon 2004	101	6.8 (3.3)	104	6.6 (4.2)		10.2 %	0.05 [-0.22, 0.33]
Pavelka 2002	101	4.61 (3.45)	101	5.03 (3.13)		10.0 %	-0.13 [-0.40, 0.15]
Reginster 2001	106	156.1 (101.9)	106	164.2 (104.5)		10.5 %	-0.08 [-0.35, 0.19]
Rozendaal 2008	111	32 (24.1)	111	32.3 (23)		11.0 %	-0.01 [-0.28, 0.25]
Zenk 2002	13	-74.7 (26.3)	10	-76.5 (25.1)		1.1 %	0.07 [-0.76, 0.89]
Total (95% CI)	**1010**		**1007**			**100.0 %**	**-0.06 [-0.14, 0.03]**

Heterogeneity: $Chi^2 = 4.74$, df = 9 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 1.26 (P = 0.21)

Test for subgroup differences: Not applicable

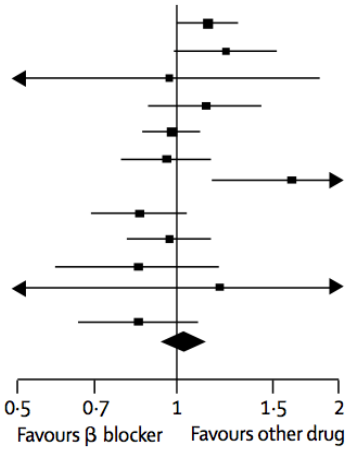


Glucosamine vs Placebo for OA pain, high quality studies

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.

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

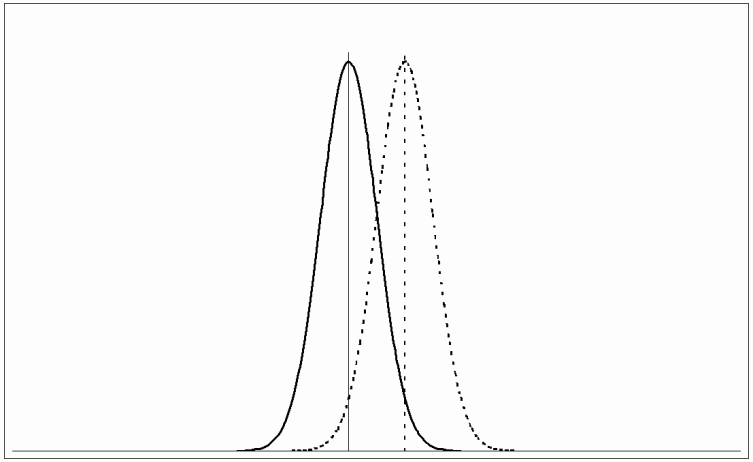
AKA Standardized Mean Difference

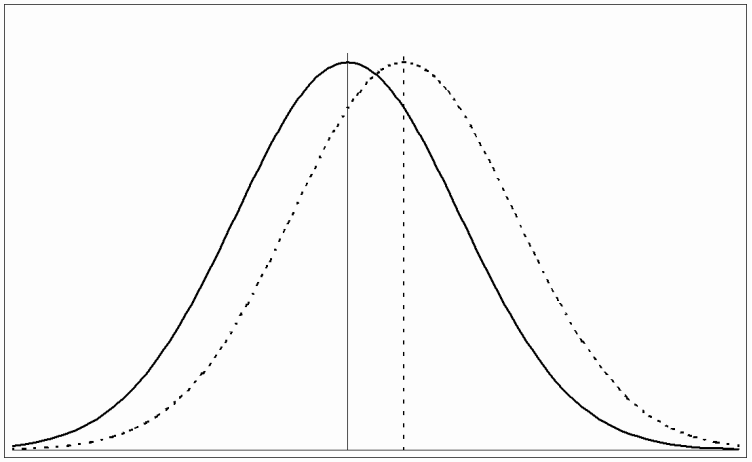
'Effect size' is simply a way of quantifying the size of the difference between two groups

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

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





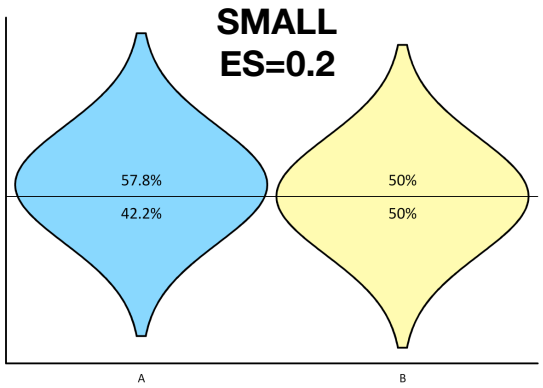
Effect Size or SD above control	Description	Percentage of control group who would be below average person in experimental group
0.0		50%
0.1		54%
0.2	SMALL	58%
0.3		62%
0.4		66%
0.5	MEDIUM	69%
0.6		73%
0.7		76%
0.8	LARGE	79%
0.9		82%
1.0		84%
1.2	VERY LARGE	88%
1.4		92%
1.6		95%
1.8		96%
2.0	HUGE	98%

Interpreting effect sizes

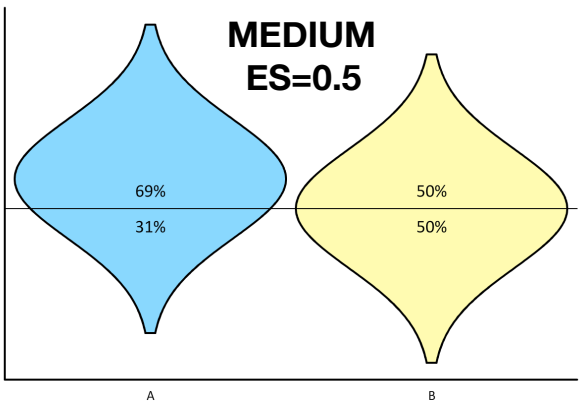
Jacob Cohen - reluctantly suggested thresholds of 0.2, 0.5, and 0.8 as indicators of small, medium, and large effects - however he warns:

"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."

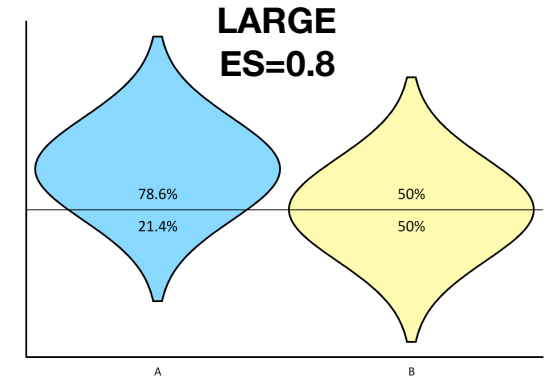
Gardner's effect size illustrator http://esi.medicine.dal.ca



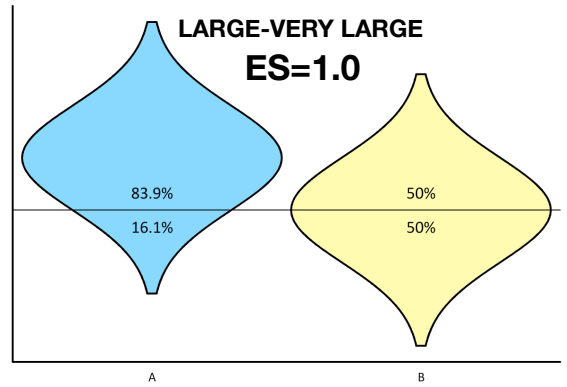
A vs. B: Cohen's d = 0.2



A vs. B: Cohen's d = 0.5



A vs. B: Cohen's d = 0.8



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[b]	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 ($P = 0.28$)