

Introduction to Evidence-Based Medicine: question formulation

Dr Kamal R. Mahtani
BSc PhD MBBS PGDip MRCGP
GP and Clinical Lecturer
Centre for Evidence Based Medicine
University of Oxford

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NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES



Outline of the EBM Thread

Today	
9 to 9.45am	Why we need EBM Question formulation Assignment
10 to 11 am	Critical appraisal of RCTS
11 to 12 am	Systematic Reviews
12-12.30pm	Searching the evidence
4pm to 5pm	Searching session (optional) (Cairns library/ private study)
Tues	
3.00-5.00pm	Presentations (see back of workbook)

Assignment

- Assigned to work in pairs
- 7 minute presentation
- 3 minutes for questions

Assignment (criteria)

- Turning up
- Clinical Question – using PICO
- Search strategy
- Appraisal
- Interpretation of findings
- Clear recommendation
- Overall Impression

The Question

Mr. X is a 58 year old obese gentleman suffering from non-insulin-dependent diabetes mellitus.

We want to know whether the drug metformin could be used to improve his condition, as measured by lowering his glycosylated haemoglobin.

P	Obese adults suffering from NIDDM
I	Metformin
C	Placebo
O	Change in glycosylated haemoglobin

The Search

Searched PubMed for the following terms

- Non-insulin-dependent diabetes mellitus (MeSH)
 - Metformin
 - Glycosylated haemoglobin
 - Placebo
 - Obese
-
- Out of the 8 trials that appeared through the search, we selected the DeFronzo 1995 trial as it's abstract suggested it was the most relevant to our question.

The Study appraisal

Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus.

- Critical appraisal
 - Randomisation: **the paper did not disclose the method of randomisation**, therefore **we cannot eliminate the possibility of the introduction of bias** through inappropriate methods of randomisation. However, the baseline demographics appeared satisfactory.
 - Ascertainment: there was a **follow up** of 78% in the metformin group and 72% in the placebo group, which could be better.
 - Measurements: our chosen outcome of glycosylated haemoglobin is an **objective measurement**, and not operator dependent, therefore is less open to bias from the technicians involved.
 - Blinding: full **double blinding** was carried out throughout the trial, again reducing possibilities for the introduction of biases.

The Results (interpretation of findings)

- The measurements for mean glycosylated haemoglobin (\pm SE) in the two groups were as follows.
 - In the metformin group: 7.1% (\pm 0.1%)
 - In the placebo group 8.6% (\pm 0.2%)
- There was a mean absolute reduction in glycosylated haemoglobin of 1.5% in the metformin group, bringing the patients closer to the ideal of under 7%.
- However, there were more side effects in the metformin group (14) than the placebo group (2).
 - The side effects were digestive symptoms, primarily diarrhoea.

The Implications

- Based on these results, we would feel happy to recommend that Mr. X be treated with metformin for his non-insulin-dependent diabetes mellitus. We would also warn him of the risk of adverse digestive side effects.
- Given time, we would like to look at more papers to see how metformin compares to other drugs for treatment of NIDDM, such as glicazide and insulin.



EBM can (amongst other things!)

- Help you make clinical decisions
- Share decision making with patients
- Provide better diagnostic reasoning
- Understanding benefits versus harms
- Allow you to practice more safely

Practicing EBM – the 4 A's

Step 1

Ask a
clinical
question

Step 2

Acquire
the best
evidence

Step 3

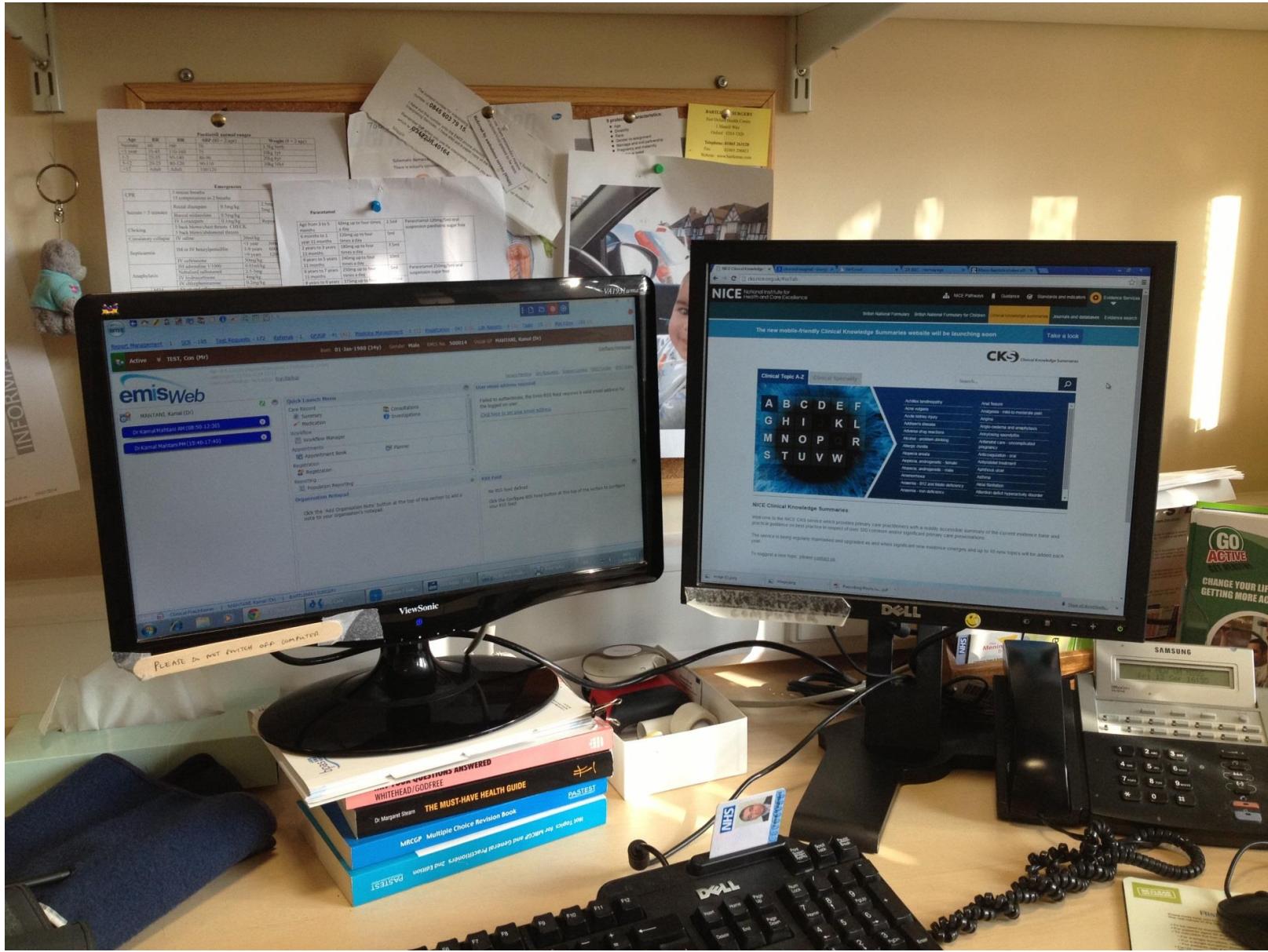
Appraise
the
evidence

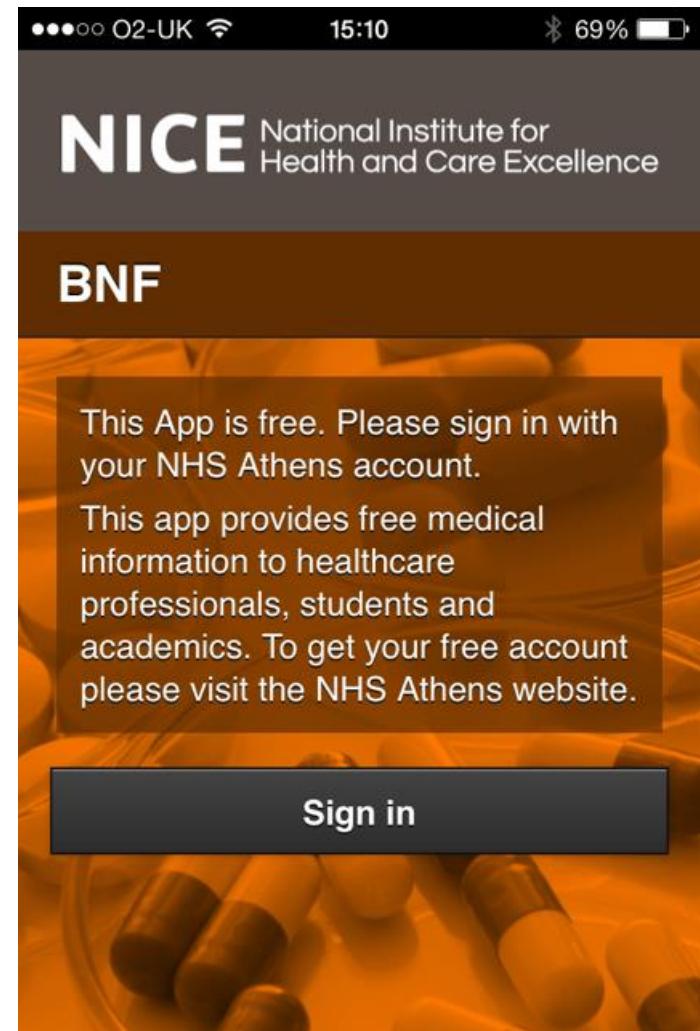
Step 4

Apply
the
evidence

The EBM “cart”...in the old days







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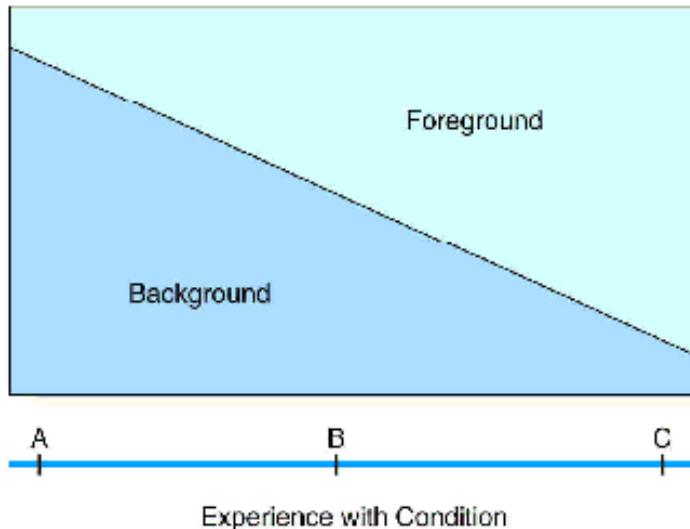
Appraise
the
evidence

Step 4

Apply
the
evidence

Types of questions

- More general
- Whole condition, symptoms, signs
- Pathophysiology
- Textbooks/online



- Specific clinical decisions
- Primary/pre assessed studies
- Patient centred
- Diagnosis, prognosis, management of disease

Question formulation using PICO

Element	Tips	Example
Patient or Problem	Starting with your patient ask “How would I describe a group of patients similar to mine?” Balance precision with brevity.	“In patients with heart failure from dilated cardiomyopathy who are in sinus rhythm...”
Intervention	Ask “Which main intervention am I considering?” Be Specific	“...would adding anticoagulation with warfarin to standard heart failure therapy,...”
Comparison (Intervention)	Ask “ What is the main alternative to compare with the intervention?” Be specific	“...when compared with standard therapy alone,...”
Outcomes	Ask “What can I hope to accomplish?” or “What could this exposure really affect?” Be specific	“...lead to lower mortality or morbidity from thromboembolism.”

Types of question

- | | |
|--|-------------------|
| 1. How common is the problem | <i>Prevalence</i> |
| 2. Is early detection worthwhile | <i>Screening</i> |
| 3. Is the diagnostic test accurate | <i>Diagnosis</i> |
| 4. What will happen if we do nothing | <i>Prognosis</i> |
| 5. Does this intervention help | <i>Treatment</i> |
| 6. What are the harms of an intervention | <i>Harms</i> |

Clinical scenario

- Mrs Whish, is a 28 y solicitor. She comes to see you today as she is frustrated by the symptoms of his irritable bowel syndrome. She feels that they have got worse and despite trying numerous things that you have suggested nothing has helped. She read an article in The Daily Mail suggesting that probiotic drinks help and wonders what you think?

Daily Mail



Framing questions: using PICO

**Patient/
Population**

Intervention

Comparison

Outcome

Scenario 2

CHILDHOOD SEIZURES

- Childhood seizures are common and frightening for the parents, and the decision to initiate treatment is a difficult one. What is the risk of further recurrences following a single seizure of unknown cause?



Scenario 3

VACCINATION AND NEEDLE LENGTH

- You are the practice nurse and one of your colleagues tells you it is better to use a short needle than a long needle when immunising babies for their first ever vaccinations, as it reduces the swelling and decreases the parents anxiety about further vaccinations. You wonder if your colleague is correct?



Scenario 4 – p9

CHILDREN AND ANTIVIRALS

- You are the GP and the next patient brings their 3 year old child who is unwell with a fever, the mother wants to know whether she should give the child tamiflu?



Angela is a patient on the general medical ward who recently moved to the area to be closer to her son and his family.

She is 72 years old and has a history of congestive heart failure. She was admitted 2 days ago having presenting with non specific chest pain, shortness of breath, an enlarged liver, swollen ankles and has been diagnosed with a Non –ST elevation MI.

She has been hospitalized twice within the last 6 months for worsening of heart failure.

At the present time she says she is pain free and is extremely diligent about taking her medications (lisinopril and aspirin), and wants desperately to stay out of the hospital. She reports being mobile and lives alone with several cats.

She also tells you she is a bit hard of hearing, has a slight cough, is a smoker of 20 cigs a day for 40 years. When you examine her: BP is 170/90, her ankles are slightly swollen, her pulse is 80 and irregular, her Hb is 10.5g/dL and her Na is 132.

She is about to be discharged home on her previous medications plus 25mg spironolactone od. She is happy to be going home and asks you if this new medication will help her stay out of hospital?



**What are
your
questions?**



	Patient or Problem	Intervention	Comparison intervention	Outcomes
	Describe a group of patients similar to your own	What intervention are you considering	What is the main alternative to the intervention	What do you hope to accomplish with the intervention

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evidence

Types of evidence



Levels of evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard"**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

	Patient or Problem	Intervention	Comparison intervention	Outcomes
	Describe a group of patients similar to your own	What intervention are you considering	What is the main alternative to the intervention	What do you hope to accomplish with the intervention
	“In elderly patients with congestive heart failuredoes treatment with spirinolactonewhen compared with standard therapy alone...	...lead to a decrease in hospitalization ”

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N Engl J Med. 1999 Sep 2;341(10):709-17.

The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J.

Department of Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, USA.

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Abstract

BACKGROUND AND METHODS: Aldosterone is important in the pathophysiology of heart failure. In a doubleblind study, we enrolled 1663 patients who had severe heart failure and a left ventricular ejection fraction of no more than 35 percent and who were being treated with an angiotensin-converting-enzyme inhibitor, a loop diuretic, and in most cases digoxin. A total of 822 patients were randomly assigned to receive 25 mg of spironolactone daily, and 841 to receive placebo. The primary end point was death from all causes.

RESULTS: The trial was discontinued early, after a mean follow-up period of 24 months, because an interim analysis determined that spironolactone was efficacious. There were 386 deaths in the placebo group (46 percent) and 284 in the spironolactone group (35 percent; relative risk of death, 0.70; 95 percent confidence interval, 0.60 to 0.82; $P < 0.001$). This 30 percent reduction in the risk of death among patients in the spironolactone group was attributed to a lower risk of both death from progressive heart failure and sudden death from cardiac causes. The frequency of hospitalization for worsening heart failure was 35 percent lower in the spironolactone group than in the placebo group (relative risk of hospitalization, 0.65; 95 percent confidence interval, 0.54 to 0.77; $P < 0.001$). In addition, patients who received spironolactone had a significant improvement in the symptoms of heart failure, as assessed on the basis of the New York Heart Association functional class ($P < 0.001$). Gynecomastia or breast pain was reported in 10 percent of men who were treated with spironolactone, as compared with 1 percent of men in the placebo group ($P < 0.001$). The incidence of serious hyperkalemia was minimal in both groups of patients.

CONCLUSIONS: Blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with severe heart failure.

Apply the evidence...



- We can tell Angela that her new drug could reduce her risk of being rehospitalised by 35% as well as improving some the symptoms of her heart failure

Analysis of abstracts

Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial

The Telmisartan Randomised AssessmeNt Study in ACE iNTolerant subjects with cardiovascular Disease (TRANSCEND) Investigators*

Summary

Background Angiotensin-converting enzyme (ACE) inhibitors reduce major cardiovascular events, but are not tolerated by about 20% of patients. We therefore assessed whether the angiotensin-receptor blocker telmisartan would be effective in patients intolerant to ACE inhibitors with cardiovascular disease or diabetes with end-organ damage.

Methods After a 3-week run-in period, 5926 patients, many of whom were receiving concomitant proven therapies, were randomised to receive telmisartan 80 mg/day ($n=2954$) or placebo ($n=2972$) by use of a central automated randomisation system. Randomisation was stratified by hospital. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00153101.

Findings The median duration of follow-up was 56 (IQR 51–64) months. All randomised patients were included in the efficacy analyses. Mean blood pressure was lower in the telmisartan group than in the placebo group throughout the study (weighted mean difference between groups 4·0/2·2 [SD 19·6/12·0] mm Hg). 465 (15·7%) patients experienced the primary outcome in the telmisartan group compared with 504 (17·0%) in the placebo group (hazard ratio 0·92, 95% CI 0·81–1·05, $p=0·216$). One of the secondary outcomes—a composite of cardiovascular death, myocardial infarction, or stroke—occurred in 384 (13·0%) patients on telmisartan compared with 440 (14·8%) on placebo (0·87, 0·76–1·00, $p=0·048$ unadjusted; $p=0·068$ after adjustment for multiplicity of comparisons and overlap with primary outcome). 894 (30·3%) patients receiving telmisartan were hospitalised for a cardiovascular reason, compared with 980 (33·0%) on placebo (relative risk 0·92, 95% CI 0·85–0·99; $p=0·025$). Fewer patients permanently discontinued study medication in the telmisartan group than in the placebo group (639 [21·6%] vs 705 [23·8%]; $p=0·055$); the most common reason for permanent discontinuation was hypotensive symptoms (29 [0·98%] in the telmisartan group vs 16 [0·54%] in the placebo group).

Interpretation Telmisartan was well tolerated in patients unable to tolerate ACE inhibitors. Although the drug had no significant effect on the primary outcome of this study, which included hospitalisations for heart failure, it modestly reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke.

Funding Boehringer Ingelheim.

1. ***What is the question (PICO) of the study?***
2. ***What is the purpose of the study?***
3. ***Which study type would give the highest quality evidence to answer the question?***
4. ***Which is the best study type that is also feasible?***
5. ***What is the study type used?***
6. ***What do the results mean?***

Analysis of abstracts

Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study)

P M Rothwell, A J Coull, L E Silver, J F Fairhead, M F Giles, C E Lovelock, J N E Redgrave, L M Bull, S J V Welch, F C Cuthbertson, L E Binney, S A Gutnikov, P Anslow, A P Banning, D Mant, Z Mehta, for the Oxford Vascular Study

Summary

Background Acute coronary, cerebrovascular, and peripheral vascular events have common underlying arterial pathology, risk factors, and preventive treatments, but they are rarely studied concurrently. In the Oxford Vascular Study, we determined the comparative epidemiology of different acute vascular syndromes, their current burdens, and the potential effect of the ageing population on future rates.

Methods We prospectively assessed all individuals presenting with an acute vascular event of any type in any arterial territory irrespective of age in a population of 91 106 in Oxfordshire, UK, in 2002–05.

Findings 2024 acute vascular events occurred in 1657 individuals: 918 (45%) cerebrovascular (618 stroke, 300 transient ischaemic attacks [TIA]); 856 (42%) coronary vascular (159 ST-elevation myocardial infarction, 316 non-ST-elevation myocardial infarction, 218 unstable angina, 163 sudden cardiac death); 188 (9%) peripheral vascular (43 aortic, 53 embolic visceral or limb ischaemia, 92 critical limb ischaemia); and 62 unclassifiable deaths. Relative incidence of cerebrovascular events compared with coronary events was 1·19 (95% CI 1·06–1·33) overall; 1·40 (1·23–1·59) for non-fatal events; and 1·21 (1·04–1·41) if TIA and unstable angina were further excluded. Event and incidence rates rose steeply with age in all arterial territories, with 735 (80%) cerebrovascular, 623 (73%) coronary, and 147 (78%) peripheral vascular events in 12 886 (14%) individuals aged 65 years or older; and 503 (54%), 402 (47%), and 105 (56%), respectively, in the 5919 (6%) aged 75 years or older. Although case-fatality rates increased with age, 736 (47%) of 1561 non-fatal events occurred at age 75 years or older.

Interpretation The high rates of acute vascular events outside the coronary arterial territory and the steep rise in event rates with age in all territories have implications for prevention strategies, clinical trial design, and the targeting of funds for service provision and research.

1. ***What is the question (PICO) of the study?***
2. ***What is the purpose of the study?***
3. ***Which study type would give the highest quality evidence to answer the question?***
4. ***Which is the best study type that is also feasible?***
5. ***What is the study type used?***
6. ***What do the results mean?***

PICO exercise...

- Think of clinical question/scenario you have come across.
- Frame it in a PICO format
- What type of question is it?
 - Aetiology/cause?
 - Prognosis?
 - Diagnosis?
 - Treatment/intervention
- How will you answer the question?

Practicing EBM – the 4 A's

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clinical
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Appraise
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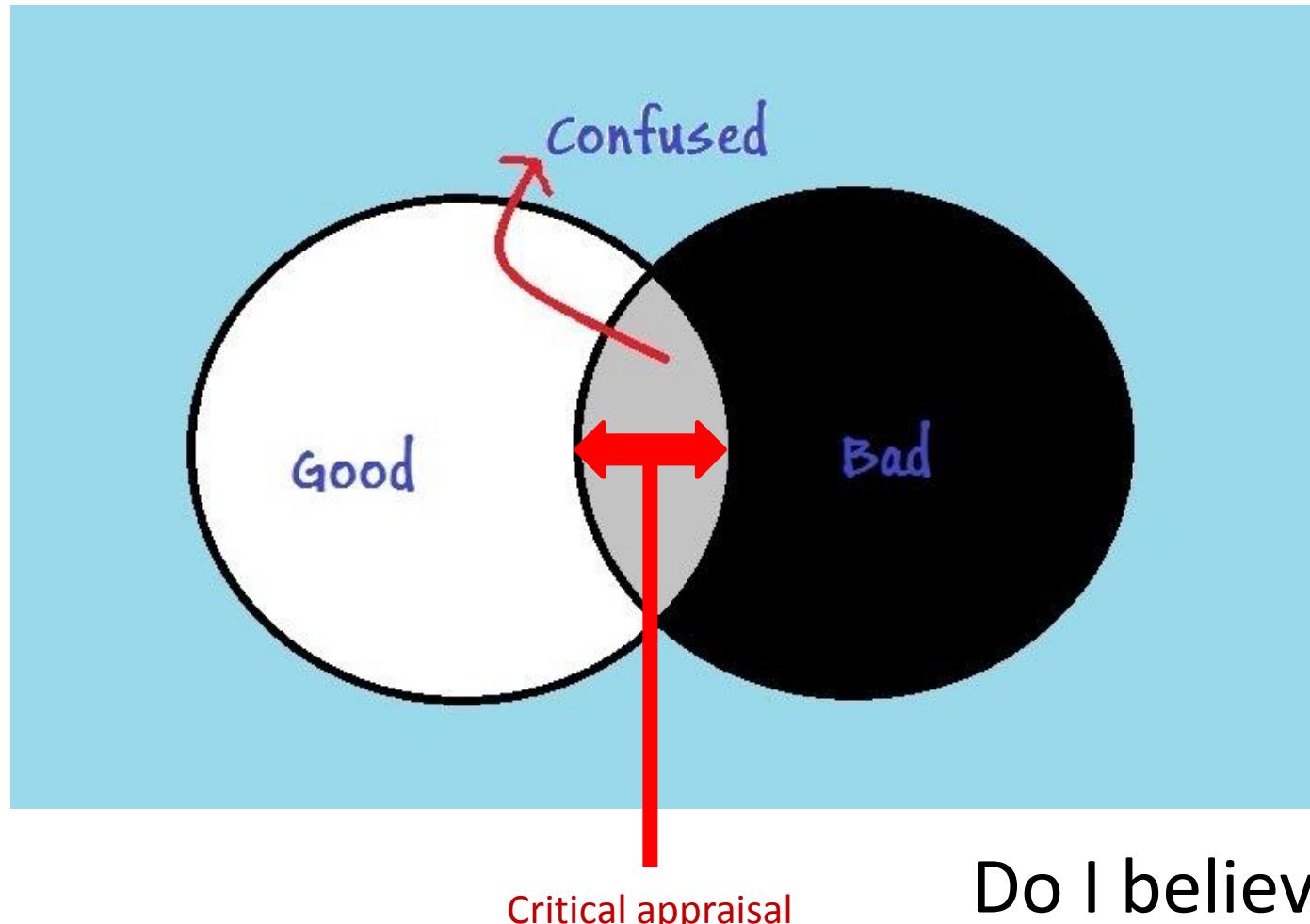
Step 4

Apply
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Risk of bias – assessment of internal validity



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External validity...

- Will it change the way I manage this patient?



Assignment

- Assigned to work in pairs
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- 3 minutes for questions

Assignment (criteria)

- Turning up
- Clinical Question – using PICO
- Search strategy
- Appraisal
- Interpretation of findings
- Clear recommendation
- Overall Impression

Does cinnamon reduce fasting blood glucose in Type II diabetics?

The Question

Miss S. has poorly managed Type II diabetes and asks if taking cinnamon would improve her fasting blood glucose levels.

P	57 year old lady with poorly managed Type II diabetes
I	Eating cinnamon in addition to prescribed medication
C	Diabetic medication without cinnamon
O	Fasting blood glucose levels

The Search

- We searched the MEDLINE database:
 - Cinnamon AND diabetes
 - Cinnamon AND Type II diabetes AND fasting blood glucose
- We selected:

Leach MJ, Kumar S. **Cinnamon for diabetes mellitus.** *Cochrane Database of Systematic Reviews* 2012, Issue 9

 - This article systematically reviewed papers investigating whether cinnamon affected diabetic management, using fasting blood glucose as its primary outcome.
 - The paper's recent publication suggests that the latest evidence collected will have been included in their review.
 - The mean age range of participants in trials reviewed included that of Miss S.

The Study appraisal

Leach MJ, Kumar S. **Cinnamon for diabetes mellitus.** *Cochrane Database of Systematic Reviews* 2012, Issue 9

- **The authors' search:**
 - 14 search engines were used to find relevant papers, including:
 - The Cochrane Library (issue 12, 2011).
 - MEDLINE (until January 2012).
 - EMBASE (until January 2012).
- **Selection:**
 - 2 reporters independently scanned the abstract of every paper retrieved by the search to ensure inclusion criteria were met:
 - Randomised controlled trials
 - Orally administered monopreparations of cinnamon
 - Placebo/ active medication/ no treatment.
 - Type I or II diabetes
 - Potential limitation – only papers published in English were selected. Pertinent reports published in other languages may have been missed.

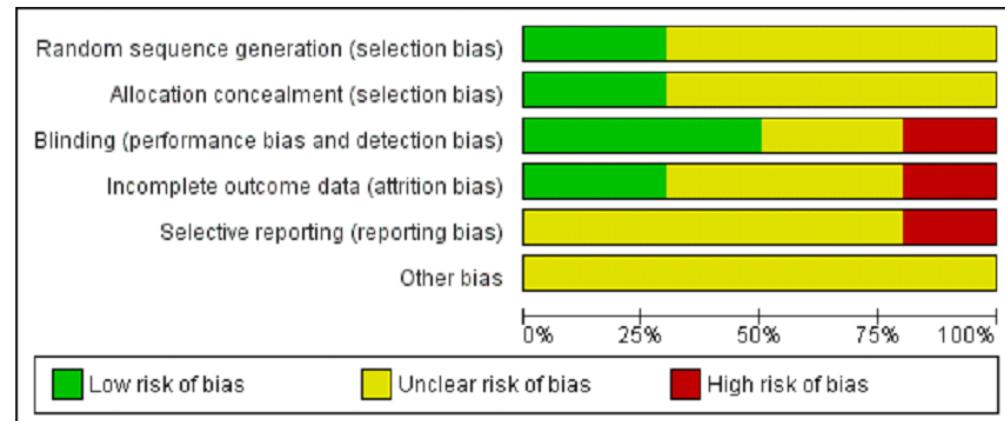
RANDOMISATION

- 10 prospective, parallel-group design, randomised control trials, involving a total of 577 participants with either Type 1 or 2 diabetes were included.
- 1 of the 10 studies didn't use a placebo control.
- 6 studies were double-blinded, 2 single-blinded and 2 undefined with respect to blinding.
 - However, the precise blinding protocol was not clearly described in many trials included in the review.

ALLOCATION

- Gender was approximately distributed evenly in most trials.
- The mean age of participants ranged from 52-63 years.
- Bias was assessed independently by two reviewers using a pre-defined criteria (*Higgins, 2008*).
- Risk of bias was high or unclear in 8/10 trials, with the remaining 2 assessed as having a moderate risk.

Figure 3. Risk of bias graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



MAINTENANCE

- All studies used oral monopreparation of cinnamon in tablet or capsule form.
- 3 studies were excluded after careful evaluation of the full publication – primarily due to failure to meet the diagnostic criteria for Type 1 or 2 diabetes.
- Where possible, any relevant missing information on the trial was sought from the original author(s) of the article – e.g. reasons for drop-outs were inconsistently reported.

MEASUREMENT

- Heterogeneity was assessed by visual inspection of the forest plots and by using a standard Chi² test:
 - Cinnamon vs. Placebo; Outcome – fasting blood glucose level (mmol/L) Chi²=0.97.
- If one of the primary outcome parameters showed significant differences between the intervention groups subgroup analysis was performed:
 - Cinnamon species
 - Cinnamon dosage
 - Treatment duration
 - Type of diabetes (I or II)

The Results (interpretation of findings)

- There were 8 studies reporting data on fasting blood glucose for 388 participants.
 - These showed significant heterogeneity ($\text{Chi}^2=0.82$).
- Visual inspection of the funnel plot and subgroup analysis led the authors to exclude 2 out of these 8 studies as outliers.
- **Analysis of the 6 remaining studies found no statistically significant difference in fasting blood glucose between cinnamon and placebo groups ($P=0.55$; 95%CI -0.34 to 0.18).**
- Adverse effects were recorded in 4 trials.
 - 3 events in intervention groups:
 - Rash
 - Hives
 - Hypoglycaemic episode
 - 4 events in control groups.
 - Nausea
 - Stomach ache
 - Other frequent illness
 - Overall, there was no significant difference between adverse effects in the intervention and control group.

The Implications

- Based upon this systematic review there is no statistically significant evidence to support a doctor advising a patient like Miss S to take cinnamon in an attempt to lower their fasting blood glucose levels.
- Miss S. should be warned that if she does take cinnamon there is a small possibility of her experiencing some mild side effects.
- It would also be worthwhile to suggest she checks she is not allergic to cinnamon before embarking on a treatment programme.



Timetable

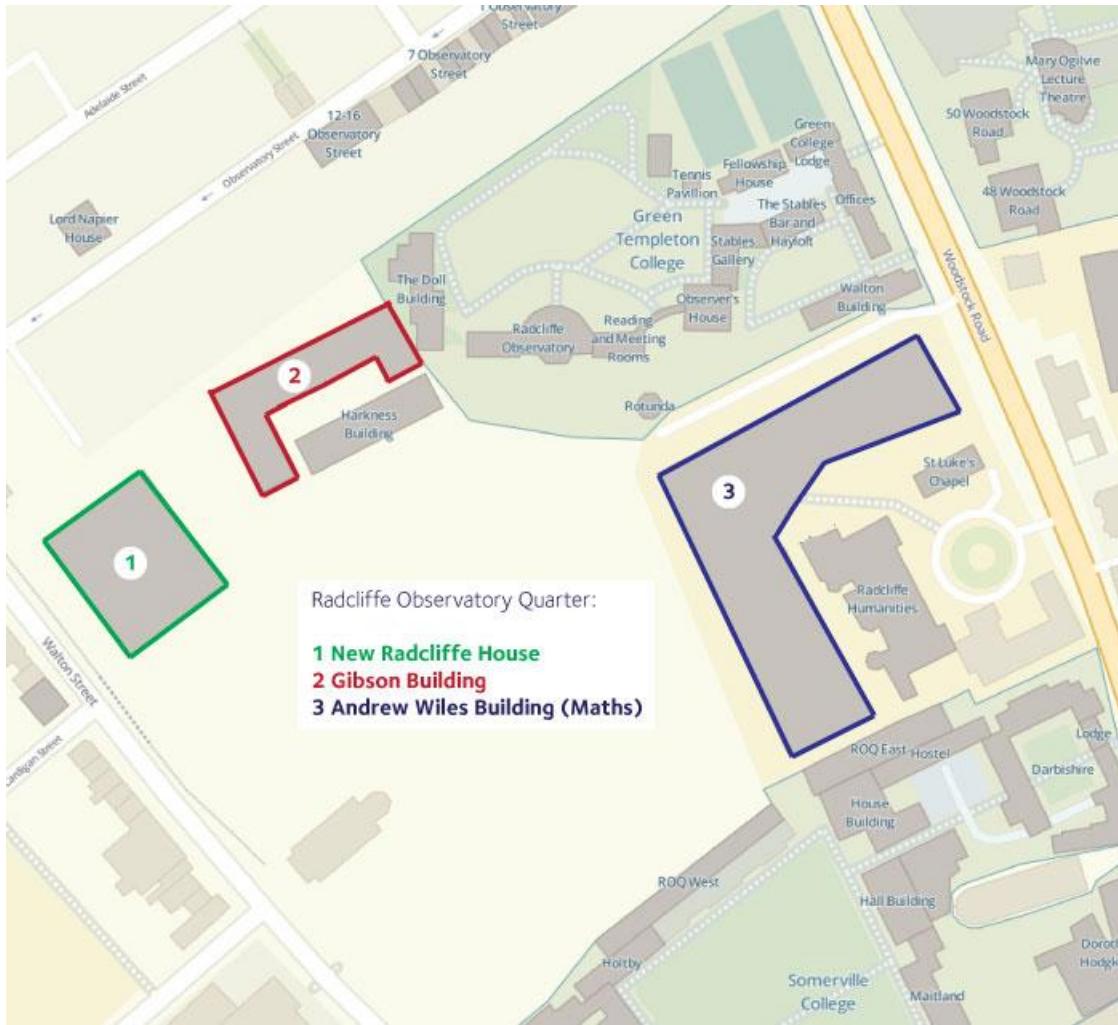
Monday 6th October 9.00 - 12:30	09:00 - 09:45	Introduction to Evidence-Based Medicine, Question Formulation Dr Kamal Mahtani
	10:00 - 11:00	Formulation/Rapid Appraisal/RCTs Dr Daniel Lasserson
	11:00 - 12:00	Systematic Reviews Dr Rafael Perera
	12:00 - 12:30	Advanced Searching Tatjana Petrinic/Owen Coxall
Monday 6th October 16:00 - 17:00	16:00 - 17:00	Searching Session CAIRNS LIBRARY/Private study (optional)
Tuesday 7th October 15:00 - 17:00		Tutorials/Presentations

ALL Lectures and Tutorial on day 1 to be held in Lecture Theatre 1 level 3 of the JR Hospital

Day 2: Check your Group Number and room Presentations will take place at various class rooms at the Radcliffe Observatory Quarter, Woodstock Road Oxford.

Tutorial Rooms

Tutor Group	Tutor Tuesday 7th October	Room
1	Beth Shinkins/ Sian Harrison	Room C2 Maths Institute
2	Duncan Keeley	Meeting Room 1 NRH
3	Jamie Hartman-Boyce/James Sheppard	Meeting Room 3 NRH
4	David Nunan	Room C3 Maths Institute
5	Paul Aveyard	Room C5 Math Institute
6	Susannah Fleming/Gail Hayward	Meeting Room 1 Gibson Building
7	Annette Pluddemann & Niklas Bobrovitz	Room C4 Maths Institute





kamal.mahtani@phc.ox.ac.uk