

# Introduction to Evidence- Based Medicine: question formulation

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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.

<b>P</b>	Obese adults suffering from NIDDM
<b>I</b>	Metformin
<b>C</b>	Placebo
<b>O</b>	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

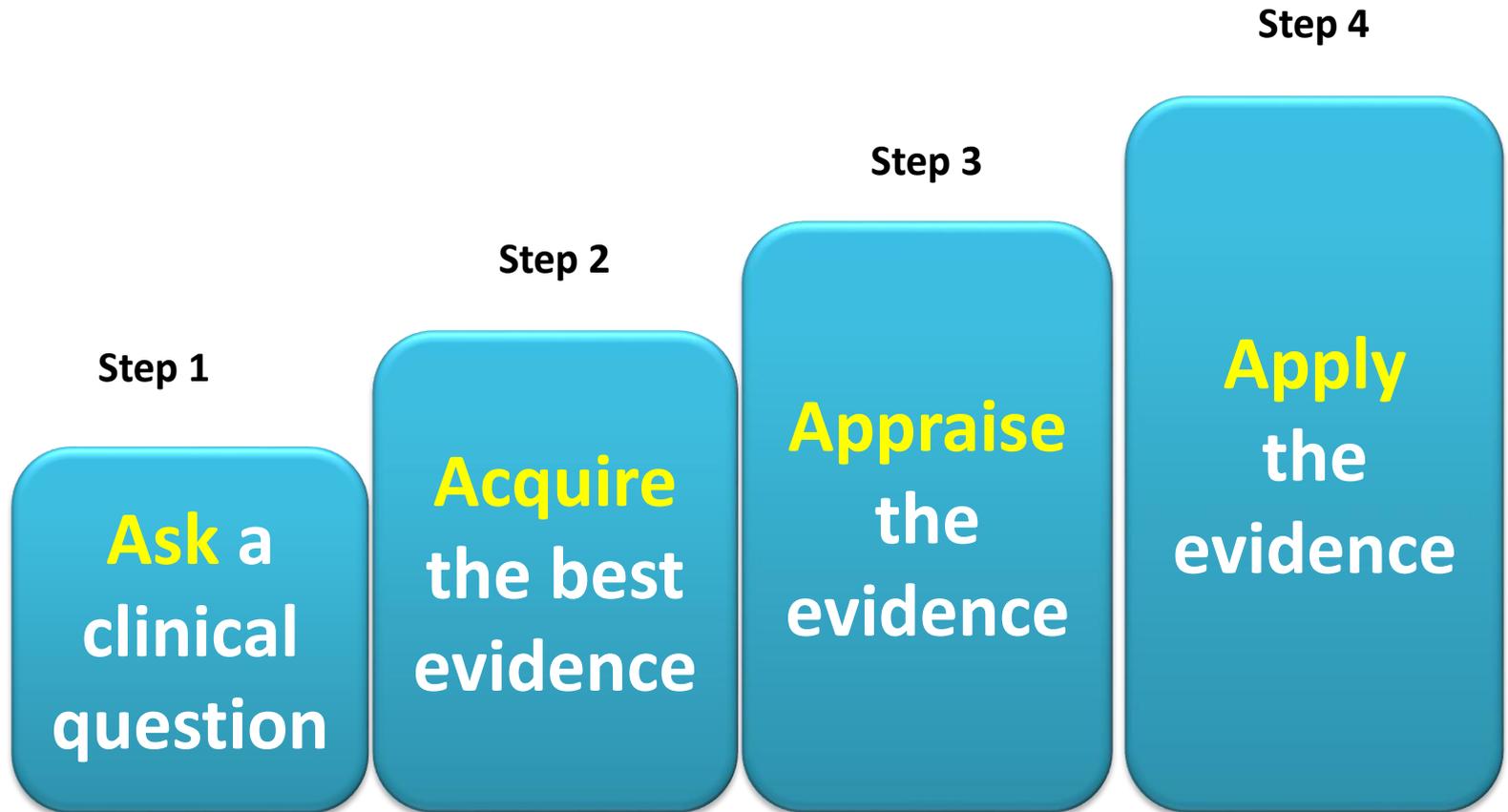
- Based on these results, we would feel happy to recommend that Mr. X be treated with metformin for his non-insulin-dependent diabetes mellitus. We would also warn him of the risk of adverse digestive side effects.
- Given time, we would like to look at more papers to see how metformin compares to other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



The EBM “cart”...in the old days



Personal normal ranges

Age	HR	RR	SBP (mmHg)	DBP (mmHg)	Weight (kg)
1-3 years	80-130	20-30	90-110	60-80	15-20
4-12 years	70-130	20-30	90-110	60-80	20-30
13-17 years	60-100	12-20	110-130	70-90	45-65
18-30 years	60-100	12-20	110-130	70-90	55-75
31-50 years	60-100	12-20	110-130	70-90	65-85
51-70 years	60-100	12-20	110-130	70-90	75-95
71+ years	60-100	12-20	110-130	70-90	85-105

Emergency

Emergency	1st line	2nd line	3rd line
Respiratory distress	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Respiratory arrest	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Cardiac arrest	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Stroke	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Seizure	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Diabetes	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Low blood pressure	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
High blood pressure	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Low oxygen saturation	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
High oxygen saturation	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Low heart rate	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
High heart rate	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
Low respiratory rate	12 oxygen via 2-4 litres	2-4 litres	2-4 litres
High respiratory rate	12 oxygen via 2-4 litres	2-4 litres	2-4 litres

Paracetamol

Age	1st line	2nd line	3rd line
0-11 months	100mg	100mg	100mg
12-23 months	120mg	120mg	120mg
24-35 months	150mg	150mg	150mg
36-47 months	180mg	180mg	180mg
48-59 months	200mg	200mg	200mg
60-71 months	220mg	220mg	220mg
72-83 months	240mg	240mg	240mg
84-95 months	260mg	260mg	260mg
96-107 months	280mg	280mg	280mg
108-119 months	300mg	300mg	300mg
120-131 months	320mg	320mg	320mg
132-143 months	340mg	340mg	340mg
144-155 months	360mg	360mg	360mg
156-167 months	380mg	380mg	380mg
168-179 months	400mg	400mg	400mg
180-191 months	420mg	420mg	420mg
192-203 months	440mg	440mg	440mg
204-215 months	460mg	460mg	460mg
216-227 months	480mg	480mg	480mg
228-239 months	500mg	500mg	500mg
240-251 months	520mg	520mg	520mg
252-263 months	540mg	540mg	540mg
264-275 months	560mg	560mg	560mg
276-287 months	580mg	580mg	580mg
288-299 months	600mg	600mg	600mg
300-311 months	620mg	620mg	620mg
312-323 months	640mg	640mg	640mg
324-335 months	660mg	660mg	660mg
336-347 months	680mg	680mg	680mg
348-359 months	700mg	700mg	700mg
360-371 months	720mg	720mg	720mg
372-383 months	740mg	740mg	740mg
384-395 months	760mg	760mg	760mg
396-407 months	780mg	780mg	780mg
408-419 months	800mg	800mg	800mg
420-431 months	820mg	820mg	820mg
432-443 months	840mg	840mg	840mg
444-455 months	860mg	860mg	860mg
456-467 months	880mg	880mg	880mg
468-479 months	900mg	900mg	900mg
480-491 months	920mg	920mg	920mg
492-503 months	940mg	940mg	940mg
504-515 months	960mg	960mg	960mg
516-527 months	980mg	980mg	980mg
528-539 months	1000mg	1000mg	1000mg
540-551 months	1020mg	1020mg	1020mg
552-563 months	1040mg	1040mg	1040mg
564-575 months	1060mg	1060mg	1060mg
576-587 months	1080mg	1080mg	1080mg
588-599 months	1100mg	1100mg	1100mg
600-611 months	1120mg	1120mg	1120mg
612-623 months	1140mg	1140mg	1140mg
624-635 months	1160mg	1160mg	1160mg
636-647 months	1180mg	1180mg	1180mg
648-659 months	1200mg	1200mg	1200mg
660-671 months	1220mg	1220mg	1220mg
672-683 months	1240mg	1240mg	1240mg
684-695 months	1260mg	1260mg	1260mg
696-707 months	1280mg	1280mg	1280mg
708-719 months	1300mg	1300mg	1300mg
720-731 months	1320mg	1320mg	1320mg
732-743 months	1340mg	1340mg	1340mg
744-755 months	1360mg	1360mg	1360mg
756-767 months	1380mg	1380mg	1380mg
768-779 months	1400mg	1400mg	1400mg
780-791 months	1420mg	1420mg	1420mg
792-803 months	1440mg	1440mg	1440mg
804-815 months	1460mg	1460mg	1460mg
816-827 months	1480mg	1480mg	1480mg
828-839 months	1500mg	1500mg	1500mg
840-851 months	1520mg	1520mg	1520mg
852-863 months	1540mg	1540mg	1540mg
864-875 months	1560mg	1560mg	1560mg
876-887 months	1580mg	1580mg	1580mg
888-899 months	1600mg	1600mg	1600mg
900-911 months	1620mg	1620mg	1620mg
912-923 months	1640mg	1640mg	1640mg
924-935 months	1660mg	1660mg	1660mg
936-947 months	1680mg	1680mg	1680mg
948-959 months	1700mg	1700mg	1700mg
960-971 months	1720mg	1720mg	1720mg
972-983 months	1740mg	1740mg	1740mg
984-995 months	1760mg	1760mg	1760mg
996-1007 months	1780mg	1780mg	1780mg
1008-1019 months	1800mg	1800mg	1800mg
1020-1031 months	1820mg	1820mg	1820mg
1032-1043 months	1840mg	1840mg	1840mg
1044-1055 months	1860mg	1860mg	1860mg
1056-1067 months	1880mg	1880mg	1880mg
1068-1079 months	1900mg	1900mg	1900mg
1080-1091 months	1920mg	1920mg	1920mg
1092-1103 months	1940mg	1940mg	1940mg
1104-1115 months	1960mg	1960mg	1960mg
1116-1127 months	1980mg	1980mg	1980mg
1128-1139 months	2000mg	2000mg	2000mg
1140-1151 months	2020mg	2020mg	2020mg
1152-1163 months	2040mg	2040mg	2040mg
1164-1175 months	2060mg	2060mg	2060mg
1176-1187 months	2080mg	2080mg	2080mg
1188-1199 months	2100mg	2100mg	2100mg
1200-1211 months	2120mg	2120mg	2120mg
1212-1223 months	2140mg	2140mg	2140mg
1224-1235 months	2160mg	2160mg	2160mg
1236-1247 months	2180mg	2180mg	2180mg
1248-1259 months	2200mg	2200mg	2200mg
1260-1271 months	2220mg	2220mg	2220mg
1272-1283 months	2240mg	2240mg	2240mg
1284-1295 months	2260mg	2260mg	2260mg
1296-1307 months	2280mg	2280mg	2280mg
1308-1319 months	2300mg	2300mg	2300mg
1320-1331 months	2320mg	2320mg	2320mg
1332-1343 months	2340mg	2340mg	2340mg
1344-1355 months	2360mg	2360mg	2360mg
1356-1367 months	2380mg	2380mg	2380mg
1368-1379 months	2400mg	2400mg	2400mg
1380-1391 months	2420mg	2420mg	2420mg
1392-1403 months	2440mg	2440mg	2440mg
1404-1415 months	2460mg	2460mg	2460mg
1416-1427 months	2480mg	2480mg	2480mg
1428-1439 months	2500mg	2500mg	2500mg
1440-1451 months	2520mg	2520mg	2520mg
1452-1463 months	2540mg	2540mg	2540mg
1464-1475 months	2560mg	2560mg	2560mg
1476-1487 months	2580mg	2580mg	2580mg
1488-1499 months	2600mg	2600mg	2600mg
1500-1511 months	2620mg	2620mg	2620mg
1512-1523 months	2640mg	2640mg	2640mg
1524-1535 months	2660mg	2660mg	2660mg
1536-1547 months	2680mg	2680mg	2680mg
1548-1559 months	2700mg	2700mg	2700mg
1560-1571 months	2720mg	2720mg	2720mg
1572-1583 months	2740mg	2740mg	2740mg
1584-1595 months	2760mg	2760mg	2760mg
1596-1607 months	2780mg	2780mg	2780mg
1608-1619 months	2800mg	2800mg	2800mg
1620-1631 months	2820mg	2820mg	2820mg
1632-1643 months	2840mg	2840mg	2840mg
1644-1655 months	2860mg	2860mg	2860mg
1656-1667 months	2880mg	2880mg	2880mg
1668-1679 months	2900mg	2900mg	2900mg
1680-1691 months	2920mg	2920mg	2920mg
1692-1703 months	2940mg	2940mg	2940mg
1704-1715 months	2960mg	2960mg	2960mg
1716-1727 months	2980mg	2980mg	2980mg
1728-1739 months	3000mg	3000mg	3000mg
1740-1751 months	3020mg	3020mg	3020mg
1752-1763 months	3040mg	3040mg	3040mg
1764-1775 months	3060mg	3060mg	3060mg
1776-1787 months	3080mg	3080mg	3080mg
1788-1799 months	3100mg	3100mg	3100mg
1800-1811 months	3120mg	3120mg	3120mg
1812-1823 months	3140mg	3140mg	3140mg
1824-1835 months	3160mg	3160mg	3160mg
1836-1847 months	3180mg	3180mg	3180mg
1848-1859 months	3200mg	3200mg	3200mg
1860-1871 months	3220mg	3220mg	3220mg
1872-1883 months	3240mg	3240mg	3240mg
1884-1895 months	3260mg	3260mg	3260mg
1896-1907 months	3280mg	3280mg	3280mg
1908-1919 months	3300mg	3300mg	3300mg
1920-1931 months	3320mg	3320mg	3320mg
1932-1943 months	3340mg	3340mg	3340mg
1944-1955 months	3360mg	3360mg	3360mg
1956-1967 months	3380mg	3380mg	3380mg
1968-1979 months	3400mg	3400mg	3400mg
1980-1991 months	3420mg	3420mg	3420mg
1992-2003 months	3440mg	3440mg	3440mg
2004-2015 months	3460mg	3460mg	3460mg
2016-2027 months	3480mg	3480mg	3480mg
2028-2039 months	3500mg	3500mg	3500mg
2040-2051 months	3520mg	3520mg	3520mg
2052-2063 months	3540mg	3540mg	3540mg
2064-2075 months	3560mg	3560mg	3560mg
2076-2087 months	3580mg	3580mg	3580mg
2088-2099 months	3600mg	3600mg	3600mg
2100-2111 months	3620mg	3620mg	3620mg
2112-2123 months	3640mg	3640mg	3640mg
2124-2135 months	3660mg	3660mg	3660mg
2136-2147 months	3680mg	3680mg	3680mg
2148-2159 months	3700mg	3700mg	3700mg
2160-2171 months	3720mg	3720mg	3720mg
2172-2183 months	3740mg	3740mg	3740mg
2184-2195 months	3760mg	3760mg	3760mg
2196-2207 months	3780mg	3780mg	3780mg
2208-2219 months	3800mg	3800mg	3800mg
2220-2231 months	3820mg	3820mg	3820mg
2232-2243 months	3840mg	3840mg	3840mg
2244-2255 months	3860mg	3860mg	3860mg
2256-2267 months	3880mg	3880mg	3880mg
2268-2279 months	3900mg	3900mg	3900mg
2280-2291 months	3920mg	3920mg	3920mg
2292-2303 months	3940mg	3940mg	3940mg
2304-2315 months	3960mg	3960mg	3960mg
2316-2327 months	3980mg	3980mg	3980mg
2328-2339 months	4000mg	4000mg	4000mg
2340-2351 months	4020mg	4020mg	4020mg
2352-2363 months	4040mg	4040mg	4040mg
2364-2375 months	4060mg	4060mg	4060mg
2376-2387 months	4080mg	4080mg	4



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# NICE

 National Institute for Health and Care Excellence

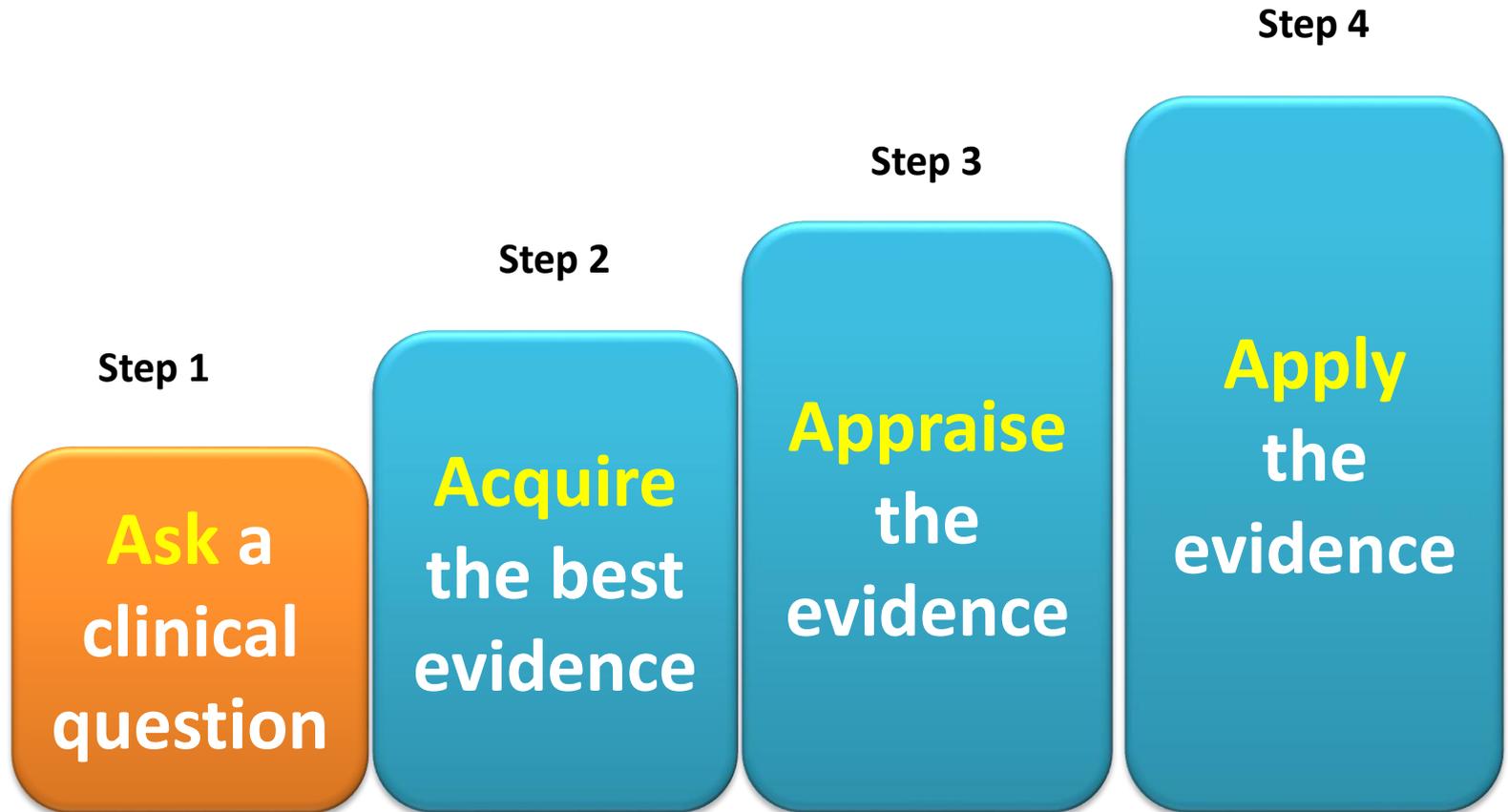
## BNF

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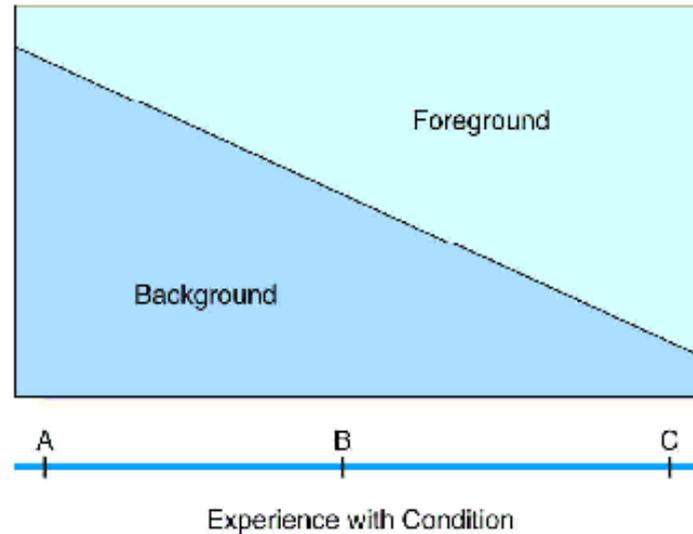
This app provides free medical information to healthcare professionals, students and academics. To get your free account please visit the NHS Athens website.

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# Practicing EBM – the 4 A's



# 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
<b>Patient or Problem</b>	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...”
<b>Intervention</b>	Ask “Which main intervention am I considering?” Be Specific	“...would adding anticoagulation with warfarin to standard heart failure therapy,...”
<b>Comparison (Intervention)</b>	Ask “What is the main alternative to compare with the intervention?” Be specific	“...when compared with standard therapy alone,...”
<b>Outcomes</b>	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

**P**atient/  
Population

**I**ntervention

**C**omparison

**O**utcome

# 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

# Practicing EBM – the 4 A's



# Types of evidence

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# 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)
<b>How common is the problem?</b>	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
<b>Is this diagnostic or monitoring test accurate?</b> (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
<b>What will happen if we do not add a therapy?</b> (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
<b>Does this intervention help?</b> (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -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
<b>What are the COMMON harms?</b> (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -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
<b>What are the RARE harms?</b> (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile?</b> (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 failure ...	...does treatment with spirinolactone ...	...when compared with standard therapy alone...	...lead to a decrease in hospitalization”

Display Settings: Abstract

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.

Display Settings: Abstract

Send to:

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.

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?

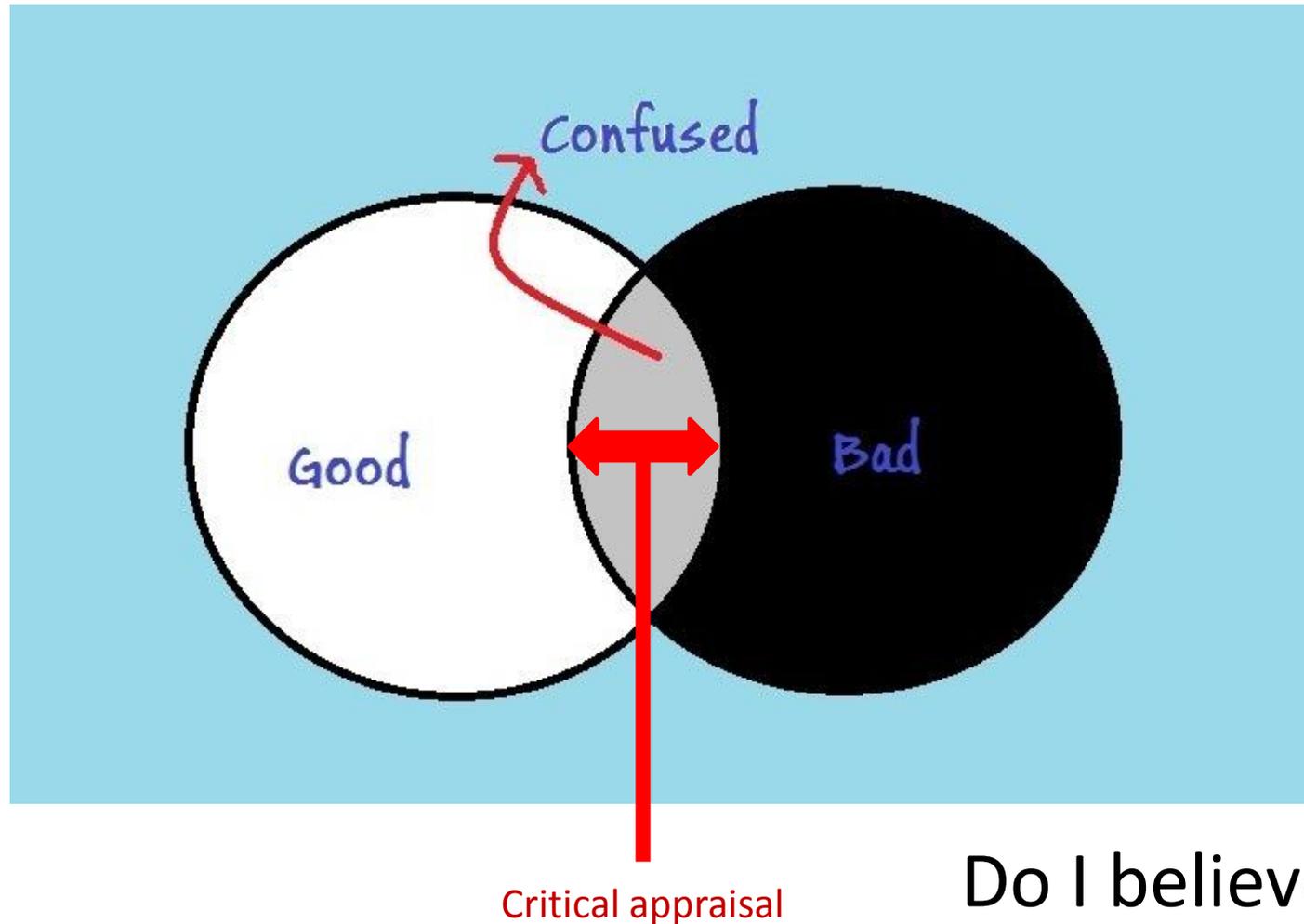
# Practicing EBM – the 4 A's



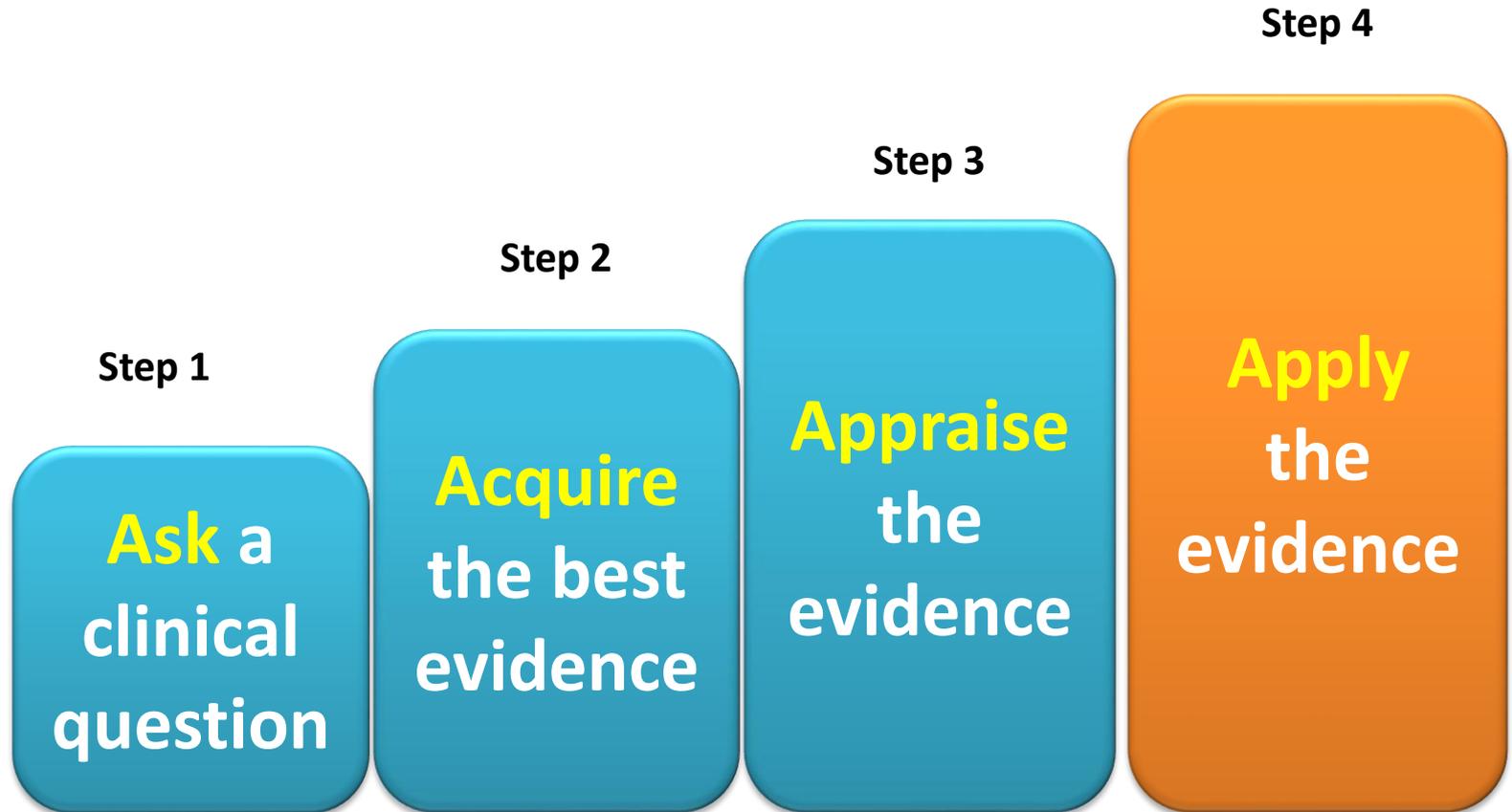
# Outline of the EBM Thread

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)

# Risk of bias – assessment of internal validity



# Practicing EBM – the 4 A's



# External validity...

- Will it change the way I manage this patient?



# 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

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.

<b>P</b>	57 year old lady with poorly managed Type II diabetes
<b>I</b>	Eating cinnamon in addition to prescribed medication
<b>C</b>	Diabetic medication without cinnamon
<b>O</b>	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.

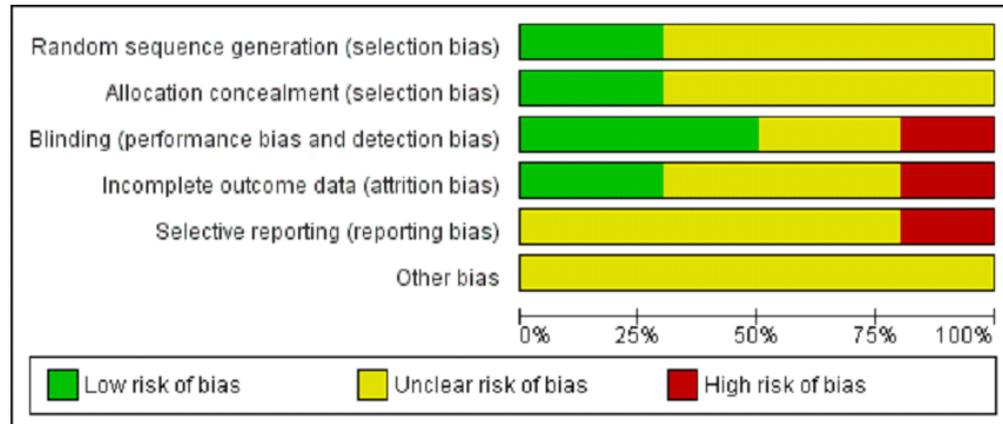
## RANDOMISATION

- 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 Chi<sup>2</sup> test:
  - Cinnamon vs. Placebo; Outcome – fasting blood glucose level (mmol/L) Chi<sup>2</sup>=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

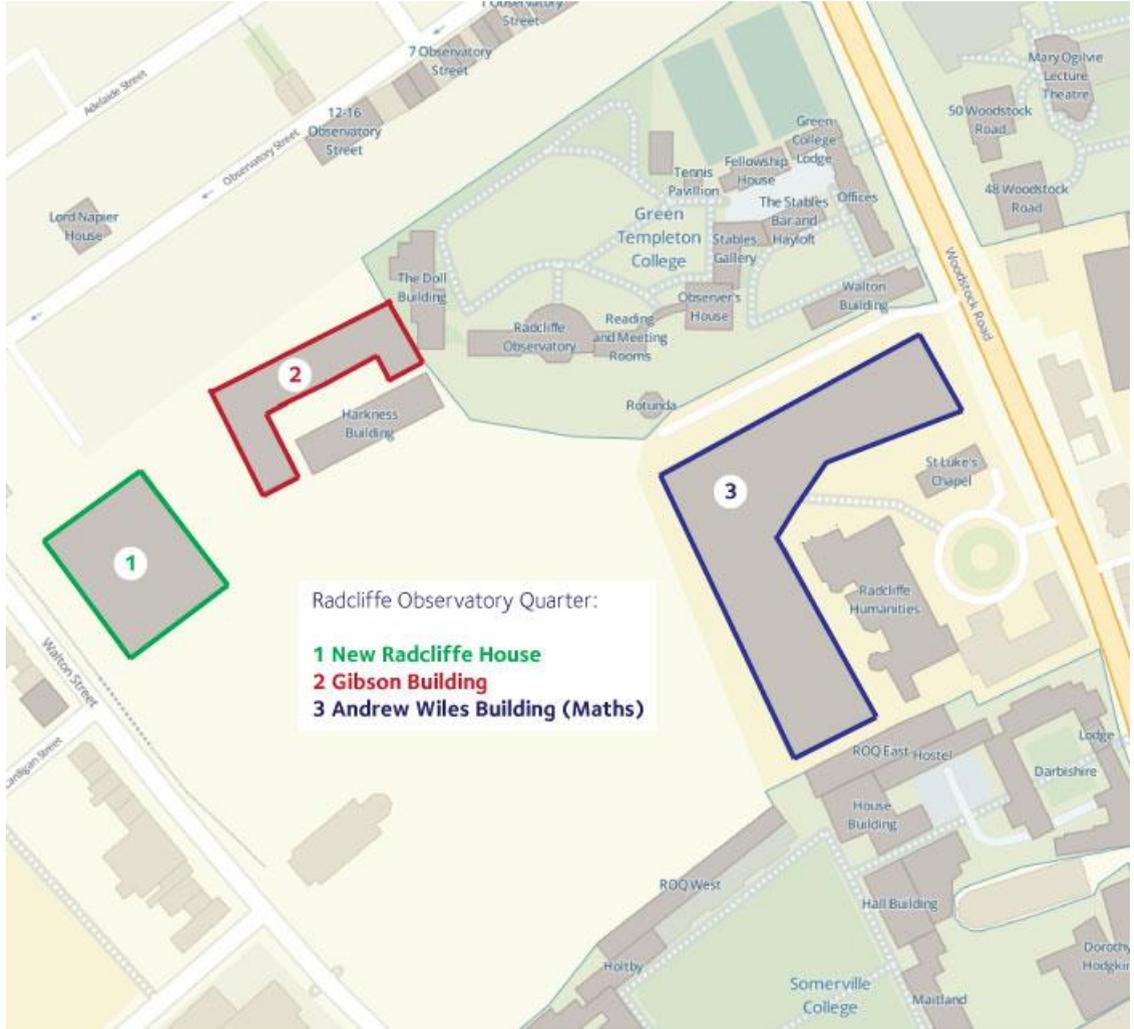
<b>Monday 6<sup>th</sup> October</b> <b>9.00 - 12:30</b>	09:00 – 09:45	Introduction to Evidence-Based Medicine, Question Formulation Dr Kamal Mahtani
	10:00 – 11:00	Formulation/Rapid Appraisal/RCTs Dr Daniel Lasserson
	11:00 – 12:00	Systematic Reviews Dr Rafael Perera
	12:00 – 12:30	Advanced Searching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



Radcliffe Observatory Quarter:

- 1 New Radcliffe House**
- 2 Gibson Building**
- 3 Andrew Wiles Building (Maths)**



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