Introduction to Evidence-Based Medicine

Prof. Carl Heneghan
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Practising EBM
This section contains all of our tools to help you practice and teach Evidence-Based Medicine, including asking focused questions, finding the evidence, critical appraisal worksheets, CAMmaker and planning a study.

EDUCATION AND TRAINING
Confused about confidence intervals? Frantic about forest plots? One of our courses can sort you out, whether it’s a one-day refresher or a two-year MSc.

EBM RESOURCES
Practical tools for asking focused questions, searching the literature, critically appraising the evidence, making a decision and evaluating your performance. You can even design your own study. No excuses then! Get cracking.

CEBM BLOGS
Up-to-date comment and review of current issues in Evidence-Based Medicine, brought to you by our team of bloggers.

CEBM PROJECTS
We like to get ourselves involved in projects about developing and implementing EBM. You can find out about them in this section, and hold of all of our publications.

RECOMMENDED CONTENT
Deadly Devices & Dangerous Drugs
Improving the evidence that underpins devices and drugs used for routine clinical care. Saturday 20th September 2014 10:30 – 16:00 Oxford Museum of Natural History - Read More

OCEBM Levels of Evidence
The Levels of Evidence help you to target your search at the type of evidence that is most likely to provide a reliable answer.

TWITTER FEED
Getting ready for Evidence Live 2015, please refer to http://www.cebmblog.co.uk
What is Evidence-Based Medicine?

“Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values”
Why do we need EBM?
Do You Know Who Frances Kelsey Is?

by Ed Silverman // September 30th, 2010 / 12:35 pm

The odds are that you don’t, but her actions a half-century ago helped transform the way prescription drugs are tested and approved. Kelsey, you see, was a new FDA employee in 1960, when she was assigned to review Kevadon, which was the brand name for thalidomide. The drug caused severe birth defects in thousands of babies born overseas after being prescribed to help women sleep or manage morning sickness. But babies often had limbless arms, malformed legs or extra appendages.

A physician and pharmacologist, Kelsey questioned its safety. “It just came with so many extravagant claims that I didn’t believe,” Kelsey, now 96, tells The Washington Post. Her decision set in motion a lot of intrigue as the manufacturer, Merrell, pushed back by complaining about her to the FDA. But Kelsey held her ground and after the scandal became known, President John Kennedy gave her the Federal Civilian Service award.

Congress, meanwhile, amended the Food, Drug & Cosmetic Act to require safety and effectiveness testing and informed consent in clinical trials. What did informed consent have to do with it? As the paper notes, Merrell gave the drug to more than 1,000 US docs to distribute to 20,000 patients as part of a 100-called investigational trial, but some patients were not informed they were participating in a trial. The upshot about 40 babies in US were born with deformities.

To honor Kelsey on the 50th anniversary of her groundbreaking effort, FDA commissioner Margaret Hamburg yesterday gave her the agency’s first Kelsey Award, which in the future, will be given to an FDA employee to “celebrate courage and scientific decision-making.” Want to know more? Read this and this.
Why do we need RANDOMIZED CONTROLLED TRIALS?

In the early 1980s newly introduced antiarrhythmics were found to be highly successful at suppressing arrhythmias.

Not until a RCT was performed was it realized that, although these drugs suppressed arrhythmias, they actually increased mortality.

The CAST trial revealed Excess mortality of 56/1000.

By the time the results of this trial were published, at least 100,000 such patients had been taking these drugs.
Bad Pharma
Ben Goldacre
Bestselling author of Bad Science

How drug companies mislead doctors and harm patients

INTRO

Medicine is broken. And I genuinely believe that if patients and the public ever fully understand what has been done to them – what doctors, academics and regulators have permitted – they will be angry. On this, only you can judge.

We like to imagine that medicine is based on evidence, and the results of fair tests. In reality, those tests are often profoundly flawed. We like to imagine that doctors are familiar with the research literature, when in reality much of it is hidden from them by drug companies. We like to imagine that doctors are well-educated, when in reality much of their education is funded by industry. We like to imagine that regulators only let effective drugs onto the market, when in reality they approve hopeless drugs, with data on side effects casually withheld from doctors and patients.
EBM and management of Common Cardiovascular conditions

Myocardial infarction with ST-segment elevation (STEMI):

Immediate management

i) Ambulance
   - Arrange for an emergency ambulance if acute myocardial infarction is suspected.

ii) Aspirin
    - Give 150mg of aspirin in the absence of contraindications.

Hospital management – acute management

i) Aspirin
   - In the absence of contraindications, give 300mg of aspirin.

ii) Reperfusion therapy
    - See NICE guideline CG167.
    - Immediate access to eligibility (irrespective of age, ethnicity, or sex) for coronary reperfusion therapy (either primary PCI or fibrinolysis) in people with acute STEMI.

iii) Additional antplatelet agents
     - Consider adding additional antplatelet agents to aspirin-based therapy (e.g., clopidogrel or prasugrel) in selected patients with high-risk features.

iv) Drug therapy
     - See NICE Guidance (G172)
     - Offer all patients aspirin, clopidogrel, and a statin.

Diabetes only

Insulin-glucose infusion

Post discharge

i) Smoking
   - Advise all who smoke to stop and offer smoking cessation services.

ii) Aspirin
    - Continue aspirin indefinitely unless there is a contraindication or an indication for antiplatelet therapy.

iii) Beta-blocker
     - Offer a beta-blocker as soon as possible after discharge, and continue for at least 12 months.

iv) ACE inhibitor
    - Offer an ACE inhibitor to all patients after an MI, unless there is a contraindication.

v) Urapidil
    - Consider rapid-acting antihypertensive agents in patients with severe hypertension.

vi) Hypertension
    - Offer antihypertensive therapy to control hypertension.

vii) Exercise and
     - Avoid-disease
     - Offer regular physical activity to improve exercise capacity and reduce mortality.
Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour

Eric Boersma, MSc, Arthur CP Maas, MD, Prof Jaap W Deckers, MD, Prof Maarten L Simoons, PhD

• For every 1000 patients treated 65 more will be alive at 1 month if treatment is administered in the first hour – the ‘golden hour’ – after symptom onset, compared with not giving thrombolysis;
  • 37 lives are saved for every 1000 patients treated in the 1–2 hour interval after symptom onset;
  • 26 lives are saved for every 1000 patients treated in the 2–3 hour interval after symptom onset;
  • 29 lives are saved for every 1000 patients treated in the 3–6 hour interval after symptom onset;
  • 20 lives are saved for every 1000 patients treated in the 7–12 hour interval after symptom onset.
Allocation to antiplatelet therapy produced a highly significant reduction (P<0.00001) of 38 per 1000 in the risk of suffering a subsequent vascular event
Pain relief

Usual distribution of pain with myocardial ischemia

Right side
Jaw
Epygastrum
Back

Less common sites of pain with myocardial ischemia
Beware of text books

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**Immediate treatment of Myocardial Infarction (MI):**

- Morphine
- Oxygen
- Aspirin
- Nitroglycerine

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**Cochrane Library**

**OXYGEN THERAPY IN ACUTE MYOCARDIAL INFARCTION – GOOD OR BAD?**

By: Pascal Meier, Shah Ebrahm, Catherine Otto & Juan Pablo Casas

**On:** August 21, 2013, 13:00

Read comments on the editorial

Most patients with acute coronary syndromes (ACS) receive oxygen therapy as part of their emergency treatment, initiated by paramedics during transfer and before their first contact with a physician. A survey among physicians involved with acute myocardial infarction cases found that 96% of their patients with ACS received oxygen therapy. About 50% of all responders believed that oxygen decreases mortality, 25% thought it helps to relieve pain and 25% thought it has no effect.[1] Many therapies and interventions are not based on proven benefit, but on anecdotal evidence, expert opinion and tradition. This is especially true for oxygen therapy, which is usually not questioned and has been used for over 100 years. We could argue that as long as it does no harm, it does not really matter whether we continue to provide oxygen in these situations. However, is it really harmless?

From a physiological perspective, treating ACS patients with oxygen may seem reasonable. In ACS there is a lack of myocardial perfusion and consequently a lack of oxygenation of the myocardium. Therefore, it seems logical to increase the oxygenation of the blood reaching the jeopardised myocardium by administering oxygen therapy. However, another theory argues that oxygen may increase microvascular resistance, leading to reduced coronary blood flow thus reducing cardiac output and increasing radical oxygen species, which can have multiple negative effects including increased risk for arrhythmias and cell damage leading to heart failure.[2,3]

Randomised trial data on oxygen delivery in acute myocardial infarction (AMI) are also conflicting. A systematic review is therefore very useful. In the August 2013 issue of the Cochrane Database of Systematic Reviews Cabelló et al report a systematic review including a total of 4 randomised trials and 426 patients. All these trials randomised patients to placebo oxygen at 4 to 6 litres/min versus 20 litres/min of inspired oxygen.

In conclusion, we do not know whether routine oxygen administration in patients with an acute MI has any impact on outcome. Nonetheless, this systematic review challenges the status quo predicated by international guidelines on the treatment of acute coronary syndromes and highlights the need for large-scale trials.

Pascal Meier¹, Shah Ebrahm², Catherine M Otto³, Juan P Casas⁴
“A 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system.”

BMJ 2008:337:704-705
EBM as a medical student?
Be aware that treatment options should be based on clinical need and the effectiveness of treatment options, and that decisions should be arrived at through assessment and discussion with the patient.
Must be aware of their responsibility to maintain their knowledge and skills throughout their careers.

Students are expected to keep up to date and to apply knowledge necessary for good clinical care.

17 Students must be aware of their responsibility to maintain their knowledge and skills throughout their careers.

18 Students are expected to keep up to date and to apply knowledge necessary for good clinical care. They should understand that as doctors they will have to participate in audit, assessments and performance reviews throughout their careers as part of revalidation and licensing.

19 In order to demonstrate that they are fit to practise, students should:

(a) reflect regularly on standards of medical practice in accordance with Good medical practice and Tomorrow’s Doctors
(b) attend compulsory teaching sessions or make other arrangements with the medical school
(c) complete and submit course work on time
(d) be responsible for their own learning
(e) reflect on feedback about their performance and achievements and respond constructively
(f) be familiar with guidance from the GMC and other organisations, such as medical schools, hospitals, trusts and health boards
(g) respect the knowledge and skills of those involved in their education
(h) make sure they can be contacted and always respond to messages in relation to care of patients or their own education.
What skills will you need to keep up to date with the best evidence?

- to find the evidence more efficiently
- to appraise the quality of the evidence more effectively
- to use good quality evidence more systematically

Must be aware of their responsibility to maintain their knowledge and skills throughout their careers.

Students are expected to keep up to date and to apply knowledge necessary for good clinical care.
about 1/2 of ‘valid’
evidence today is out of
date in 5 years

about 1/2 of valid
evidence is not
implemented

"...and, as you go out into the world, I predict
that you will, gradually and imperceptibly,
forget all you ever learned at this university."
the steps of practicing EBM

1. Ask a focused question.
2. Track down the evidence
3. Critically appraise evidence for its validity, effect size, precision
4. Apply the evidence in practice:
   a. *amalgamate* the valid evidence with other relevant information (values & preferences, clinical/health issues, & system issues)
   b. implement the decision in practice
1. **Ask a focused question.**

Patient presenting with MI
‘Background’ Questions

About the disorder, test, treatment, etc.

a. Root* + Verb: “What causes …”
b. Condition: “HIV?”
   * Who, What, Where, When, Why
Patient presenting with MI

1. What are the symptoms and signs of someone presenting with MI?
2. What are the diagnostic tests for MI?
3. What are the causes of MI?
4. What are the treatments of MI?
Signs and symptoms

The onset of symptoms in myocardial infarction (MI) is usually gradual, over several minutes, and rarely instantaneous. Chest pain is the most common symptom of acute myocardial infarction and is often described as a sensation of tightness, pressure, or squeezing. Chest pain due to ischemia (a lack of blood and hence oxygen supply) of the heart muscle is termed angina pectoris. Pain radiates most often to the left arm, but may also radiate to the lower jaw, neck, right arm, back, and epigastrium, where it may mimic heartburn. Levine's sign, in which the patient localizes the chest pain by clenching their fist over the sternum, has classically been thought to be predictive of cardiac chest pain, although a prospective observational study showed that it had a poor positive predictive value.

Shortness of breath (dyspnea) occurs when the damage to the heart limits the output of the left ventricle, causing left ventricular failure and consequent pulmonary edema. Other symptoms include diaphoresis (an excessive form of sweating), weakness, light-headedness, nausea, vomiting, and palpitations. These symptoms are likely induced by a massive surge of catecholamines from the sympathetic nervous system which occurs in response to pain and the hemodynamic abnormalities that result from cardiac dysfunction. Loss of consciousness (due to inadequate cerebral perfusion and cardiogenic shock) and sudden death (frequently due to the development of ventricular fibrillation) can occur in myocardial infarctions.

Female, elderly, and diabetic patients report atypical symptoms more frequently than their male and younger counterparts. Women also report more numerous symptoms compared with men (2.6 on average vs 1.8 symptoms in men). The most common symptoms of MI in women include dyspnea (shortness of breath), weakness, and fatigue. Fatigue, sleep disturbances, and dyspnea have been reported as frequently occurring symptoms that may manifest as long as one month before the actual clinically manifested ischemic event. In women, chest pain may be less predictive of coronary ischemia than in men.

At least one-fourth of all myocardial infarctions are silent, without chest pain or other symptoms. These cases can be discovered later on electrocardiograms, using blood enzyme tests or at autopsy without a prior history of related complaints. Estimates of the prevalence of silent myocardial infarctions vary between 22 and 64%. A silent course is more common in the elderly, in patients with diabetes mellitus and after heart transplantation, probably because the donor heart is not fully innervated by the nervous system of the recipient. In people with diabetes, differences in pain threshold, autonomic neuropathy, and psychological factors have been cited as possible explanations for the lack of symptoms.

Any group of symptoms compatible with a sudden interruption of the blood flow to the heart are called an acute coronary syndrome.

The differential diagnosis includes other catastrophic causes of chest pain, such as pulmonary embolism, aortic dissection, pericardial effusion causing cardiac tamponade, tension pneumothorax, and esophageal rupture. Other non-catastrophic differentials include gastroesophageal reflux and Tietze's syndrome.

Causes

[edit source | edit beta]
Myocardial Infarction (Heart Attack)

A heart attack (myocardial infarction) is usually caused by a blood clot, which stops the blood flowing to a part of your heart muscle. You should call for an
Know your background

The human heart can squirt blood as far as 30 feet...
Patient presenting with MI

Foreground’ Questions

About actual patient care decisions and actions

For treatment
4 (or 3) components:

In Patients with a MI
Does (I) cholesterol lowering therapy
Compared to placebo
reduce mortality (O)
During the scheduled treatment period, there were 3832 (8.5%) deaths among the 45 054 participants allocated a statin compared with 4354 (9.7%) among the 45 002 controls. This difference represents a 12% proportional reduction in all-cause mortality per mmol/L LDL cholesterol reduction (RR 0.88, 95% CI 0.84–0.91; p<0.0001; figure 1).
Secondary Prevention

Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study

9,014 patients with a history of MI or hospitalization for unstable angina randomized to pravastatin (40 mg) or placebo for 6.1 years

Statins provide significant benefit across a broad range of cholesterol levels

CHD=Coronary heart disease, MI=Myocardial infarction, RRR=Relative risk reduction

Patient presenting with MI

1. How common is the problem  
   Prevalence

2. Is early detection worthwhile  
   Screening

3. Is the diagnostic test accurate  
   Diagnosis

4. What will happen if we do nothing  
   Prognosis

5. Does this intervention help  
   Treatment

6. What are the common harms of an intervention  
   Treatment

7. What are the rare harms of an intervention  
   Treatment
Figure 1.1 Background and foreground questions.
Size of Medical Knowledge

• NLM MetaThesaurus
  – 875,255 concepts
  – 2.14 million concept names

• Diagnosis Pro
  – 11,000 diseases
  – 30,000 abnormalities (symptoms, signs, lab, X-ray,)
  – 3,200 drugs (cf FDAs 18,283 products)

To cover the vast field of medicine in four years is an impossible task.
- William Olser
why do we need to use evidence efficiently?

EBP: informing decisions with the best up-to-date evidence
Median minutes/week spent reading about my patients

Self-reports at 17 Grand Rounds:

- Medical Students: 90 minutes
- House Officers (PGY1): 0 (up to 70%=none)
- SHOs (PGY2-4): 20 (up to 15%=none)
- Registrars: 45 (up to 40%=none)
- Sr. Registrars: 30 (up to 15%=none)
- **Consultants:**
  - Grad. Post 1975: 45 (up to 30%=none)
  - Grad. Pre 1975: 30 (up to 40%=none)
clinical evidence increasing so rapidly we need better skills to keep up-to-date more efficiently than previous generations of clinicians
the steps of practicing EBM

1. ask a focused question.
2. Track down the evidence
3. Critically appraise evidence for its validity, effect size, precision
4. apply the evidence in practice:
   a. amalgamate the valid evidence with other relevant information (values & preferences, clinical/health issues, & system issues) and make an evidence-based decision; and
   b. implement the decision in practice
Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators*

Summary

Background Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug’s ability to prevent type 2 diabetes in individuals at high risk of developing the condition.

Methods 5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00095654.

Findings At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11·6%) individuals given rosiglitazone and 686 (26·0%) given placebo developed the composite primary outcome (hazard ratio 0·40, 95% CI 0·35–0·46; p<0·0001); 1330 (50·5%) individuals in the rosiglitazone group and 798 (30·3%) in the placebo group became normoglycaemic (1·71, 1·57–1·87; p<0·0001). Cardiovascular event rates were much the same in both groups, although 14 (0·5%) participants in the rosiglitazone group and two (0·1%) in the placebo group developed heart failure (p=0·01).

Interpretation Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.
Prevention of diabetes

Drug trials show promising results, but have limitations

Diabetes affects one in 20 adults worldwide and 333 million cases are projected worldwide by 2030.\(^1\) Treatment can prevent some of the complications of diabetes. \(^2\) Ramipril did not reduce the risk of diabetes. \(^3\) These results are promising, but they should be viewed cautiously.

BMJ helping doctors make better decisions

Editorial

Prevention of diabetes

Carl Heneghan (carl.heneghan@dphtc.ox.ac.uk), deputy director, M Thompson, clinical lecturer, R Perera, senior statistician

Drug trials show promising results, but have limitations

Diabetes affects one in 20 adults worldwide and 333 million cases are projected worldwide by 2025. \(^4\) Treatment can prevent some of the microvascular and macrovascular complications of diabetes.
DRUG REGULATION

ROSIGLITAZONE WHAT WENT WRONG

Over 10 years after the diabetes drug rosiglitazone was approved by regulators, and despite studies on tens of thousands of people, questions remain about its cardiovascular safety. An investigation by Deborah Cohen looks at why this happened.
the steps of practicing EBM

1. Ask a focused question.

2. Track down the evidence

3. Critically appraise evidence for its validity, effect size, precision

(NEXT month)

4. Apply the evidence in practice:
   a. *amalgamate* the valid evidence with other relevant information
      (values & preferences, clinical/health issues, & system issues)
   b. implement the decision in practice
In the next 4 weeks

• Try to ask for one patient you have seen:

1. What causes the disease?
2. How was the disease diagnosed?
3. How was the patient treated?
4. What is the natural history of the disease?
5. Consider formulating a PICO

And try to find some evidence