Please sit beside someone from whom you would like help in solving a problem related to practicing evidence-based health care.
Plan

- a little more about Dave Sackett
- EBHC process of answering clinical questions
- introduce a patient
  - apply process
- review an EBM principle

Why did EBHC succeed so well?

- Commitment to excellence
- Dedication and hard work
- Innovation
- Scepticism, challenge authority
- Collaboration
- Generosity
- Caring
- Fun and mischievousness
CLINICAL EPIDEMIOLOGY ROUNDS

How to read clinical journals:
IV. To determine etiology or causation

DEPARTMENT OF CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS,
McMASTER UNIVERSITY HEALTH SCIENCES CENTRE

CMA JOURNAL/APRIL 15, 1981/VOL. 124

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Evidence Arc

Patient

Ask
Acquire
Appraise
Act
Apply
Type 2 diabetes epidemic
- occurs in older, often obese and sedentary individuals
- associated with macrovascular (MI, CV death, stroke) and microvascular (neuropathy, retinopathy, nephropathy) complications
- diagnosis by fasting glucose (> 125 mg/dl, 7 mm/l), GTT, increasingly HbA1C
Our patient’s presentation

- 57 year old man, + family history of CV disease, doesn’t smoke, moderate regular exercise, not obese, balanced diet
- thinking of taking aspirin or statins for CV protection
- routine testing shows no hypertension, lipid profile normal, FBG 117/6.5
- should we consider glucose lowering tx?

Question

- patient
  - middle-aged man with borderline sugar
- intervention
  - rosiglitazone
- comparator
  - no rosiglitazone
- outcome?
Evidence Arc

Ask

Act

Acquire: what sort of study?

Appraise

Apply

Patient

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.

September 15, 2006
oral GTT
fasting glucose > 6.1, < 7.0 mmol/l
2 hr > 7.8, < 11.1

> 80% meds taken over 17 days

all participants received
healthy diet and lifestyle advice
Risk of bias

- randomization
  - concealed
- blinding
  - patients
  - caregivers
  - data collectors
  - adjudicators
  - data analysts
- loss to follow-up

Eligible patients were randomly assigned (stratified by site) by a concealed, computerised telephone randomisation system to receive either rosiglitazone (4 mg once daily for the first 2 months and then 8 mg once daily) or matching placebo. The dose of 8 mg per day was chosen
Risk of bias

- randomization
  - concealed
- blinding
  - patients
  - caregivers
  - data collectors
  - adjudicators
  - data analysts
- loss to follow-up

individuals who die than in those who survive. Diabetes was diagnosed if (1) a locally measured fasting plasma glucose concentration of 7·0 mmol/L or greater or 2-h plasma glucose concentration of 11·1 mmol/L or greater during a 75 g oral glucose tolerance test was confirmed by a second test on a different day; (2) a single test was consistent with diabetes, no confirmatory test was done, and the masked adjudicator had no reason to reject the diagnosis; or (3) a physician diagnosed diabetes outside the study and the diagnosis was supported by the
Risk of bias

- randomization
  - concealed
- blinding
  - patients
  - caregivers
  - data collectors
  - adjudicators
  - data analysts
- *loss to follow-up*
Risk of bias

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone group (n=2635)</th>
<th>Placebo group (n=2634)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary outcome*</td>
<td>306 (11.6%)</td>
<td>686 (26.0%)</td>
<td>0.40 (0.35-0.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>280 (10.6%)</td>
<td>658 (25.0%)</td>
<td>0.38 (0.33-0.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnosed by FPG/OGTT</td>
<td>231 (8.8%)</td>
<td>555 (21.1%)</td>
<td>0.38 (0.33-0.44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physician diagnosed</td>
<td>49 (1.9%)</td>
<td>103 (3.9%)</td>
<td>0.47 (0.33-0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>30 (1.1%)</td>
<td>33 (1.3%)</td>
<td>0.91 (0.55-1.49)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Assignment

- using evidence in practice
- issue of whether to give rosiglitazone to patient arises in outpatient clinic
- summarize the study
- goals
  - remind resident/yourself of risk of bias criteria
  - summarize results using approximate numbers
    - include notion of confidence intervals
  - applicability to our patient
An Indispensable Skill: Study Synopsis

The Problem:
- immediately after reading an article few learners can provide a synopsis.
- several days after reading an article, hardly any clinicians can do this.
- some EBM teachers can’t do this either
- clinicians and teachers need to practice creating the verbal study synopsis of an article
- One element left out: should we prescribe rosiglitazone?

This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes. The absolute risk difference between treatment groups of 14.4% means that for every seven people with impaired fasting glucose or impaired glucose tolerance who are prescribed rosiglitazone for 3 years, one will be prevented from developing diabetes. Moreover, rosiglitazone significantly increased the likelihood of regression to normoglycaemia by about 70–80% compared with placebo. The reduction in diabetes reported here is of much the same magnitude as the reduction achieved with lifestyle approaches and greater than the reductions reported previously with drugs such as metformin or acarbose. The effect on regression is
several chronic diseases. The results of this study suggest that the addition of rosiglitazone to basic lifestyle recommendations substantially reduces the risk of developing diabetes by about two-thirds, offering a novel preventive approach that could be as, or more, effective and sustained than previously reported lifestyle approaches alone.\textsuperscript{45} Balancing both the benefits and risks suggests that for every 1000 people treated with rosiglitazone for 3 years, about 144 cases of diabetes will be prevented, with an excess of four to five cases of congestive heart failure. Finally, the observation that rosiglitazone increased the likelihood of regression to normoglycaemia by about 70–80\% suggests that it is treating dysglycaemia as well as reducing the frequency of diabetes. Further work is needed.

What is the authors’ message?

- rosiglitazone to prevent diabetes:
  - strong indication (for all)
  - weak indication (for some)
  - not indicated
Doctor, what do I gain by taking rosiglitazone?

- Doc: less chance of diabetes
- Pt: what happens if I get diabetes
- Doc: you have to take a drug
- Pt: the same drug I’m taking to prevent diabetes?
- Doc: I could give you a drug with less problems
- Pt: I’ll take a drug every day for 3 years to lower my risk of taking the same or a less toxic drug from 25 to 10%???

Waking up from the DREAM of preventing diabetes with drugs

A drug to prevent diabetes would be attractive. But despite promotion of recent research evidence, Victor Montori, William Isley, and Gordon Guyatt argue that we are not there yet.
Modeling exercise

- 10,000 patients with pre-diabetes
- what would happen if:
  - lifestyle advice only, drugs when they develop diabetes
  - rosiglitazone for 3 years, stop, resume drug if develop diabetes

<table>
<thead>
<tr>
<th></th>
<th>drug</th>
<th>no drug</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes medication 3 years</td>
<td>30000</td>
<td>3650</td>
<td>26350</td>
</tr>
<tr>
<td>new diagnosis of diabetes</td>
<td>1060</td>
<td>2500</td>
<td>HR 0.38 (CI, 0.33-0.44)</td>
</tr>
<tr>
<td>Anxiety about diabetes</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Costs inconvenience self-monitoring</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Costs and inconvenience HbA1c, lipoprotein testing, retinal exam, etc.</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>MI, stroke, CV death at 3 years</td>
<td>120</td>
<td>90</td>
<td>HR 1.39 (CI 0.81-2.37)</td>
</tr>
<tr>
<td>Heart failure, at 3 years</td>
<td>50</td>
<td>10</td>
<td>HR 7.03 (CI 1.6-30.9)</td>
</tr>
<tr>
<td>kidney, eyes, neuropathy</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
<tr>
<td>Peripheral edema, at 3 years</td>
<td>680</td>
<td>490</td>
<td>RR 1.4 (CI 1.1-1.8)</td>
</tr>
<tr>
<td>Weight gain (kg), at 3 years</td>
<td>+ 1.1</td>
<td>-1.1</td>
<td>+ 2.2</td>
</tr>
<tr>
<td>Rare (fractures, macular edema)</td>
<td>??</td>
<td>??</td>
<td>??</td>
</tr>
</tbody>
</table>
What is your view?

- rosiglitazone to prevent diabetes:
  - strong indication (for all)
  - weak indication (for some)
  - not indicated
- investigators very smart people
  - what has gone wrong here?

What is the problem?

- development of diabetes is a surrogate
- surrogate for:
  - mortality
  - cardiovascular events (stroke, MI)
  - renal failure
  - visual impairment and blindness
  - anxiety
  - inconvenience
Patient-important and surrogates

- **patient important outcomes**
  - change might mandate treatment
- **surrogate outcomes**
  - associated with patient-important
  - change in surrogate leads to change in pt-important
- **often biologically compelling**
  - observational studies show association suggesting causal relationship between surrogate and pt-important
- **often practically compelling**
  - markedly ↓ duration, sample size, cost of RCTs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surrogate</th>
<th>Patient-important</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Bone density</td>
<td>Fracture</td>
<td>Sodium fluoride</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Hemodynamic function</td>
<td>Mortality</td>
<td>Flosequinan, milrinone, ibopamine, venzarainone, xamotol, epoprostanol</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Nasty looking arrhythmia</td>
<td>Sudden death</td>
<td>Encaimide/flecaimide</td>
</tr>
<tr>
<td>Coronary risk</td>
<td>Cholesterol</td>
<td>Mortality</td>
<td>Clofibrate</td>
</tr>
<tr>
<td>Coronary risk</td>
<td>LDL, HDL</td>
<td>Coronary events</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>Coronary risk, disease</td>
<td>HDL, triglycerides</td>
<td>Coronary events</td>
<td>High dose extended release niacin, fenofibrate, torcetrapib</td>
</tr>
</tbody>
</table>
Surrogate or patient-important?

- blood pressure
  - (stroke, MI, death)
- heart failure exacerbation
- cardiac output
  - (QOL, exacerbations, death)
- hip fracture
- vertebral fracture
  - (pain, deformity)
- development/increase in albuminuria
  - (dialysis)
- asymptomatic DVT
  - (symptomatic DVT, PE)
- development of diabetes

Conclusion

- beware surrogate outcomes
- if intervention harmless, no cost, can rely on surrogate
- if intervention has harms or costs, demand evidence of effect on patient-important outcomes
## Suggestions for the course

- clarify your learning objectives
- take responsibility for ensuring objectives met
- Remember Dave Sackett - Have fun!