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

How To Practice and Teach Evidence Based Health Care: An Attempt at a Tantalizing Introduction to the Workshop

Gordon Guyatt

Plan

- EBHC process of answering clinical questions
- introduce a patient
  - apply process
- review an EBM principle

How to spend your time at this workshop?

all on learning
EBHC fundamentals

all on teaching

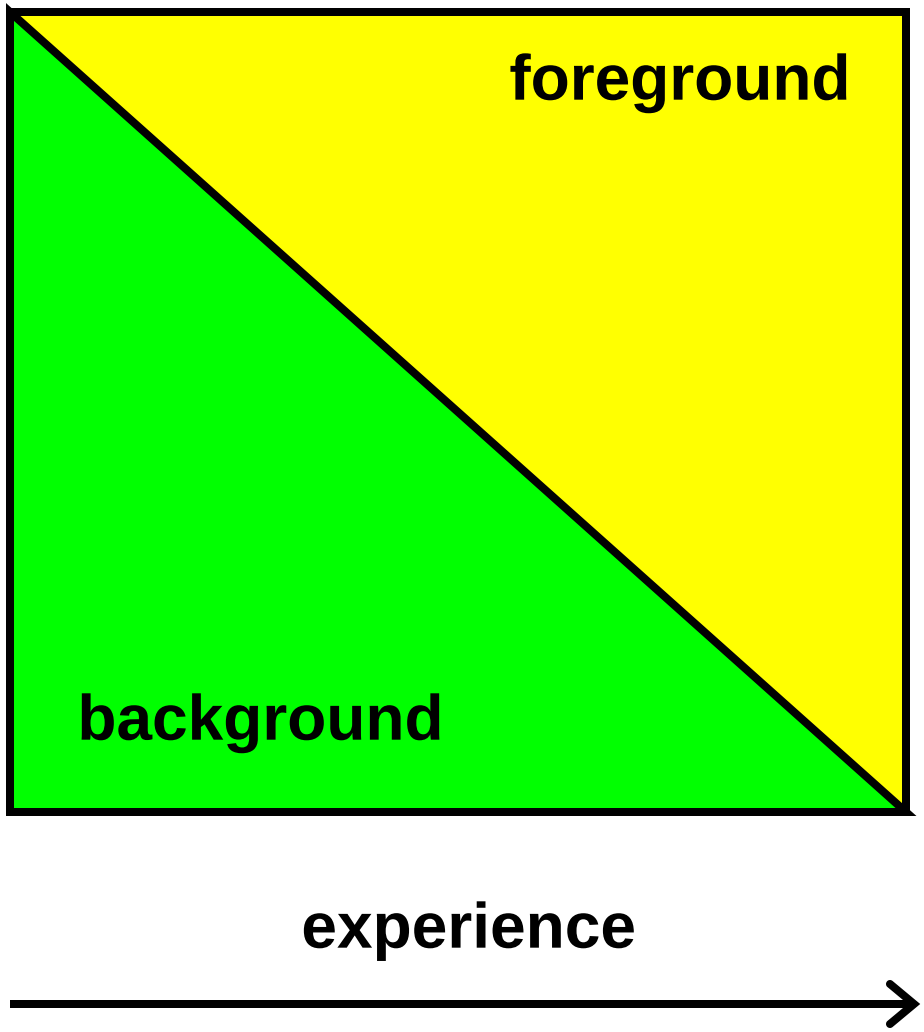
0

10

What are your EBHC teaching opportunities?

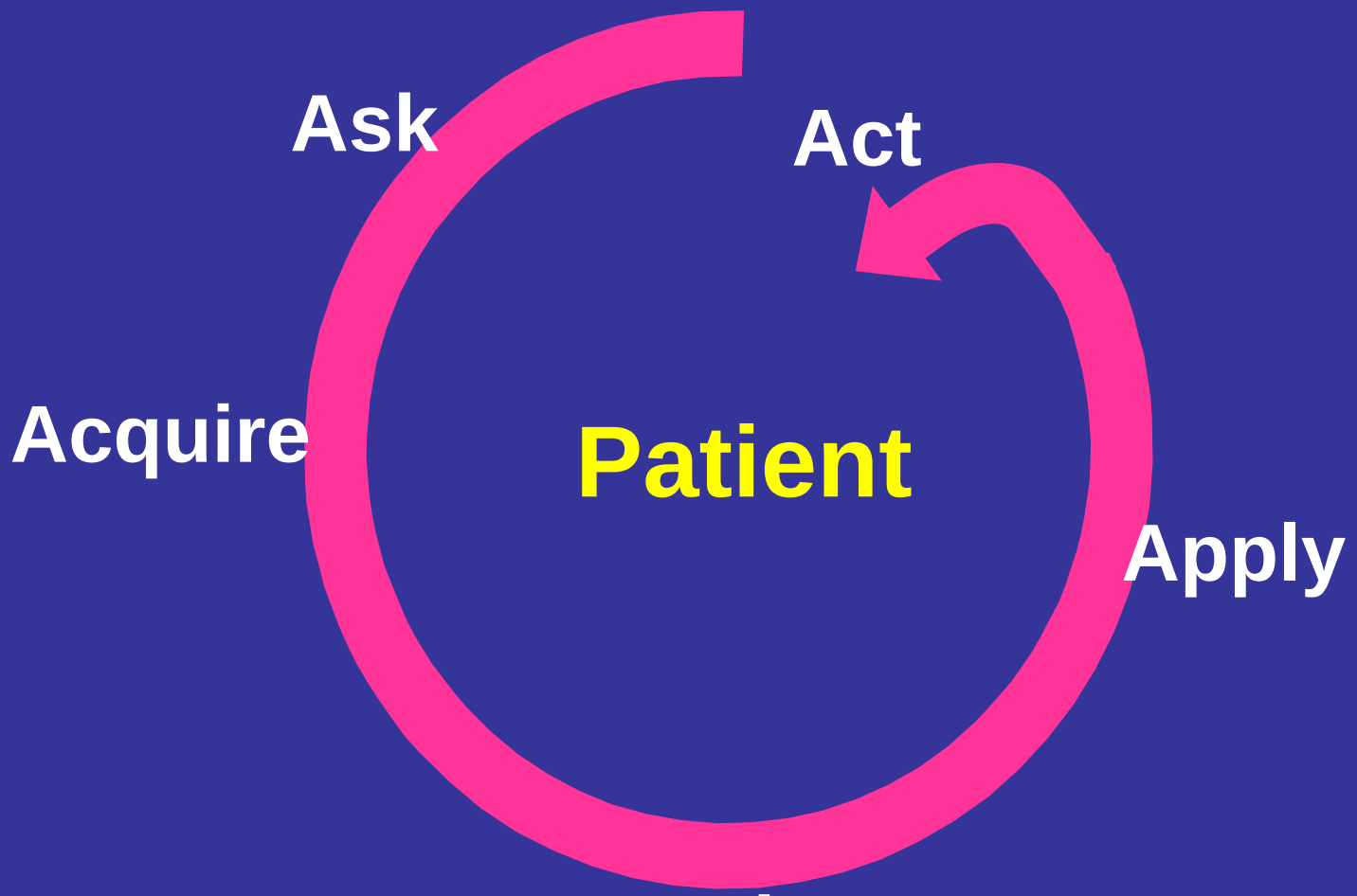
- large-group lectures?
- half to one hour small-group sessions?
  - morning report
  - journal club
  - course tutorials
- on the ward and outpatient
  - 30 second, 2 minute, 5 minute, 20 minute
- other?

Formulating Clinical Questions

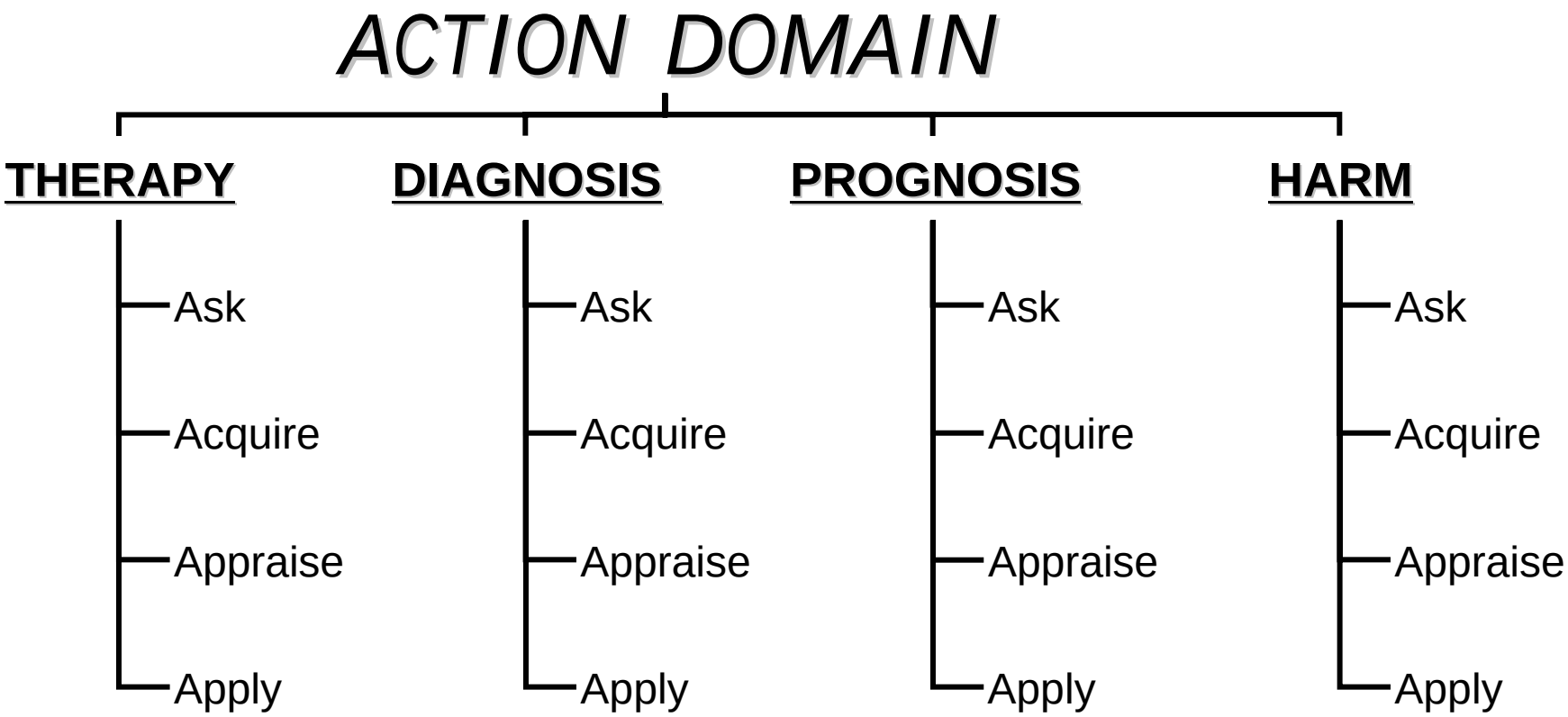


Richardson et al, ACPJC 2000

Evidence Arc



The Action Domains



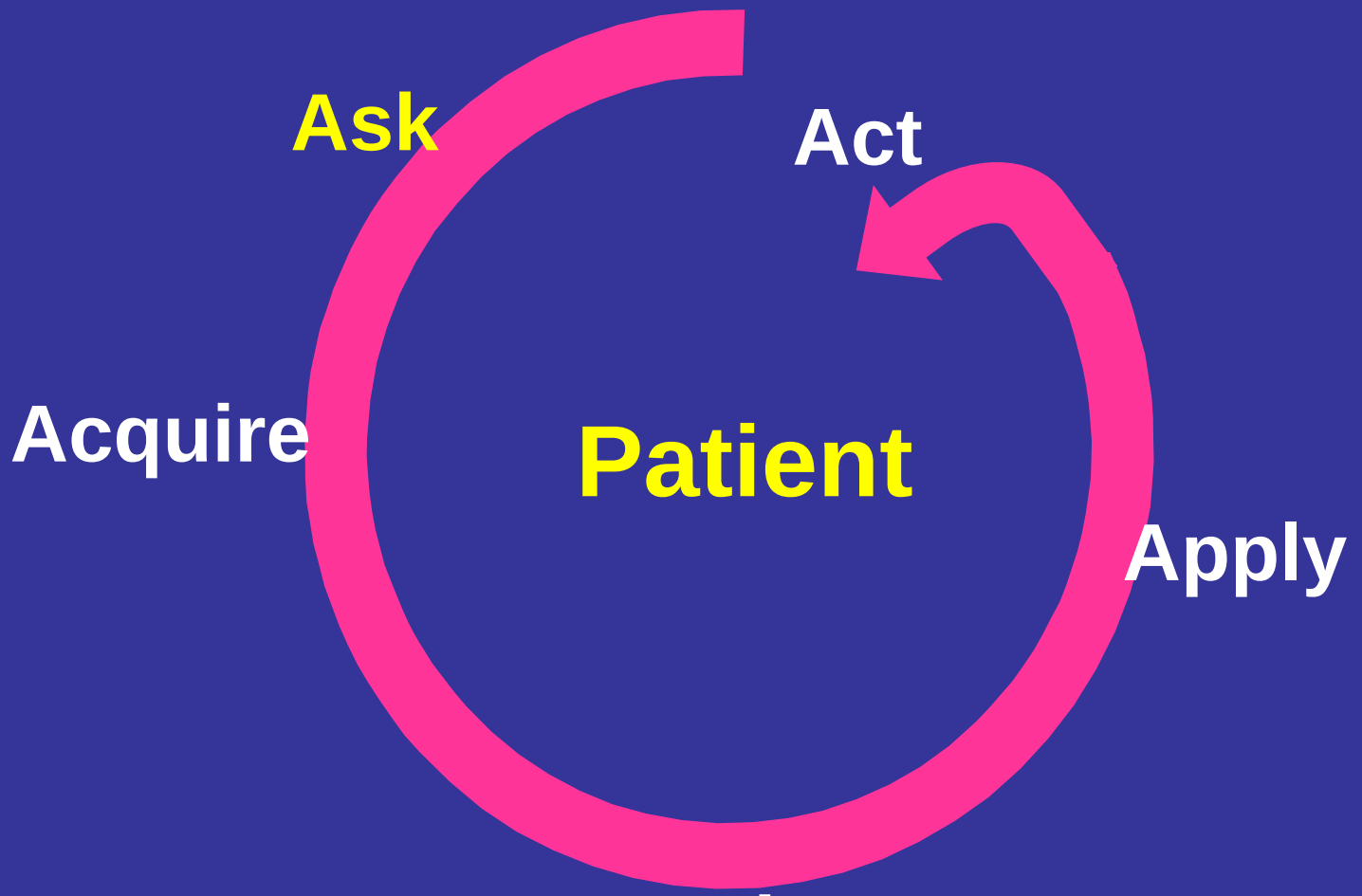
Background to our patient

- 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

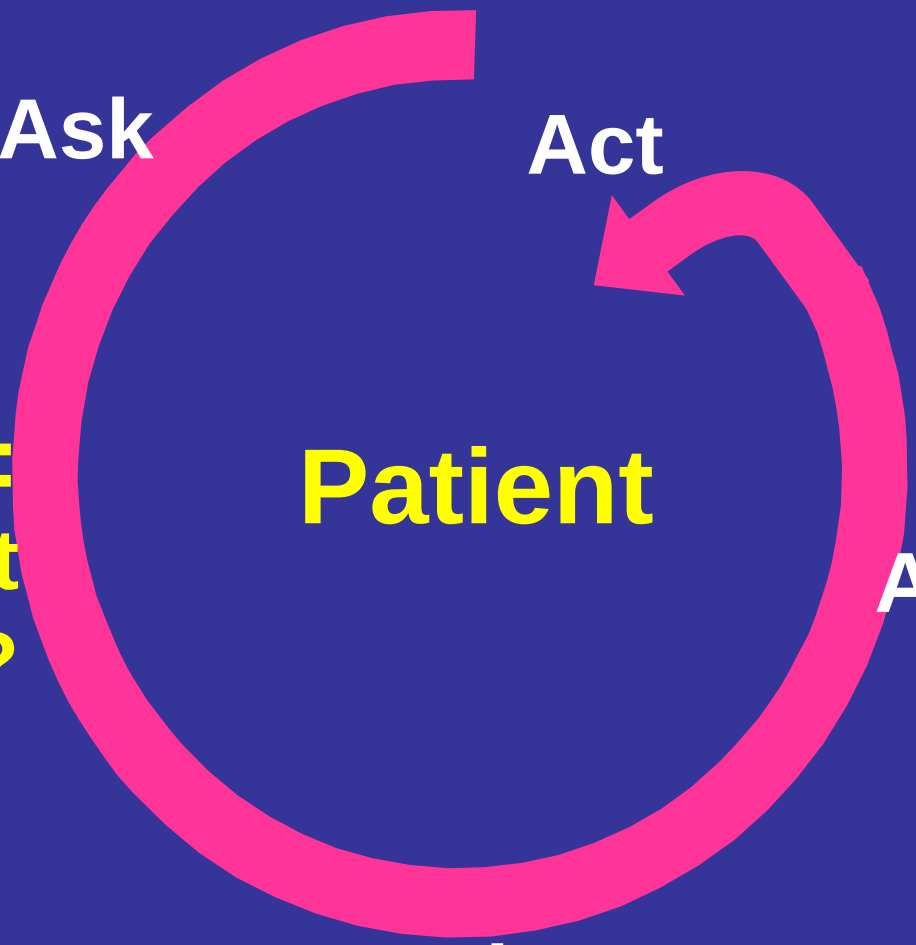
Our patient's presentation

- 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
- any questions about patient management?

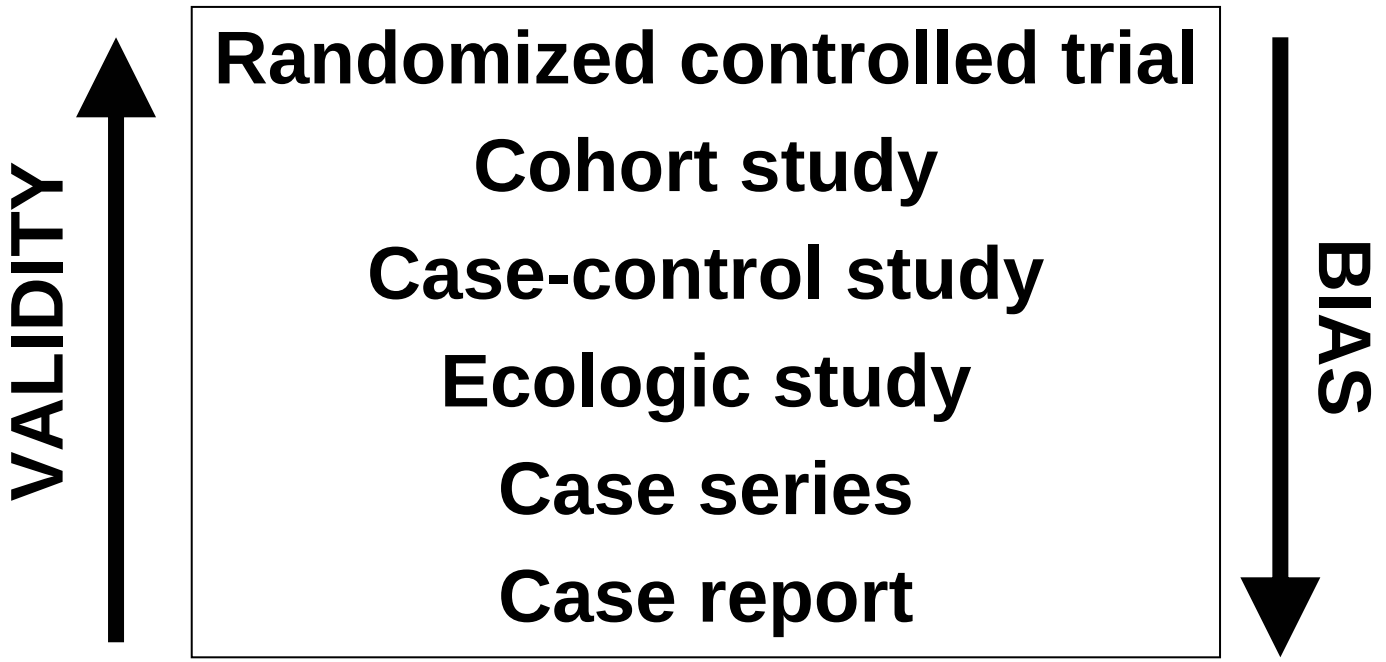
Evidence Arc

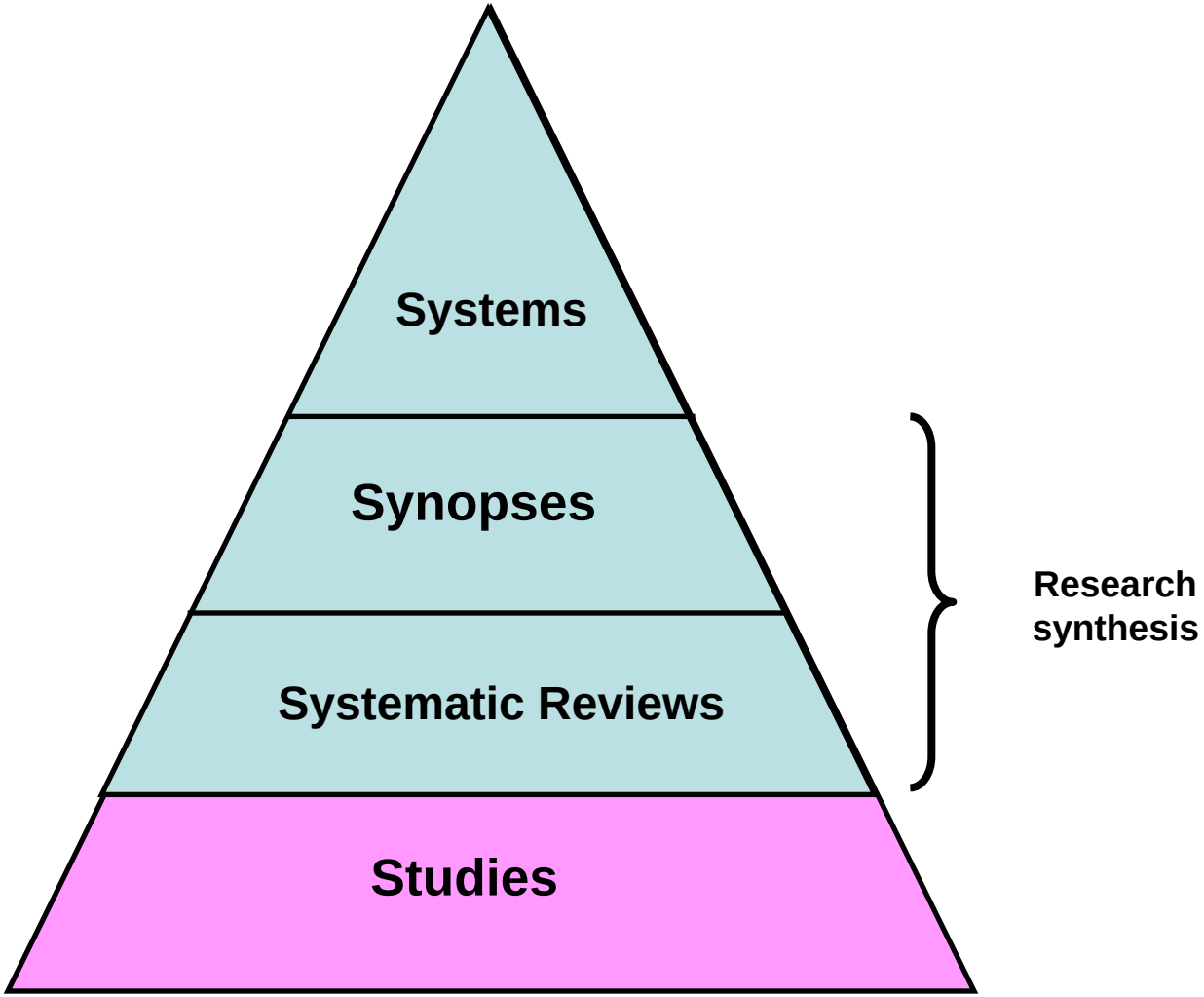


Evidence Arc



Study Designs For Best Evidence on Prevention and Treatment




Systems
Synopses
Systematic Reviews
Studies
Research synthesis

DREAM

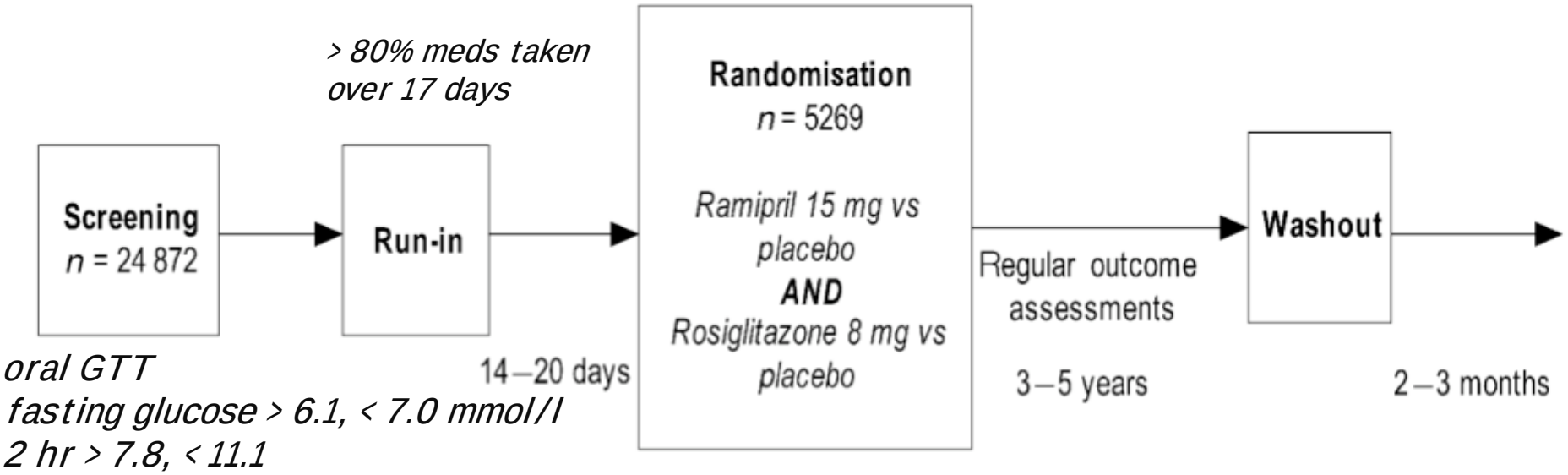
Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

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

Summary

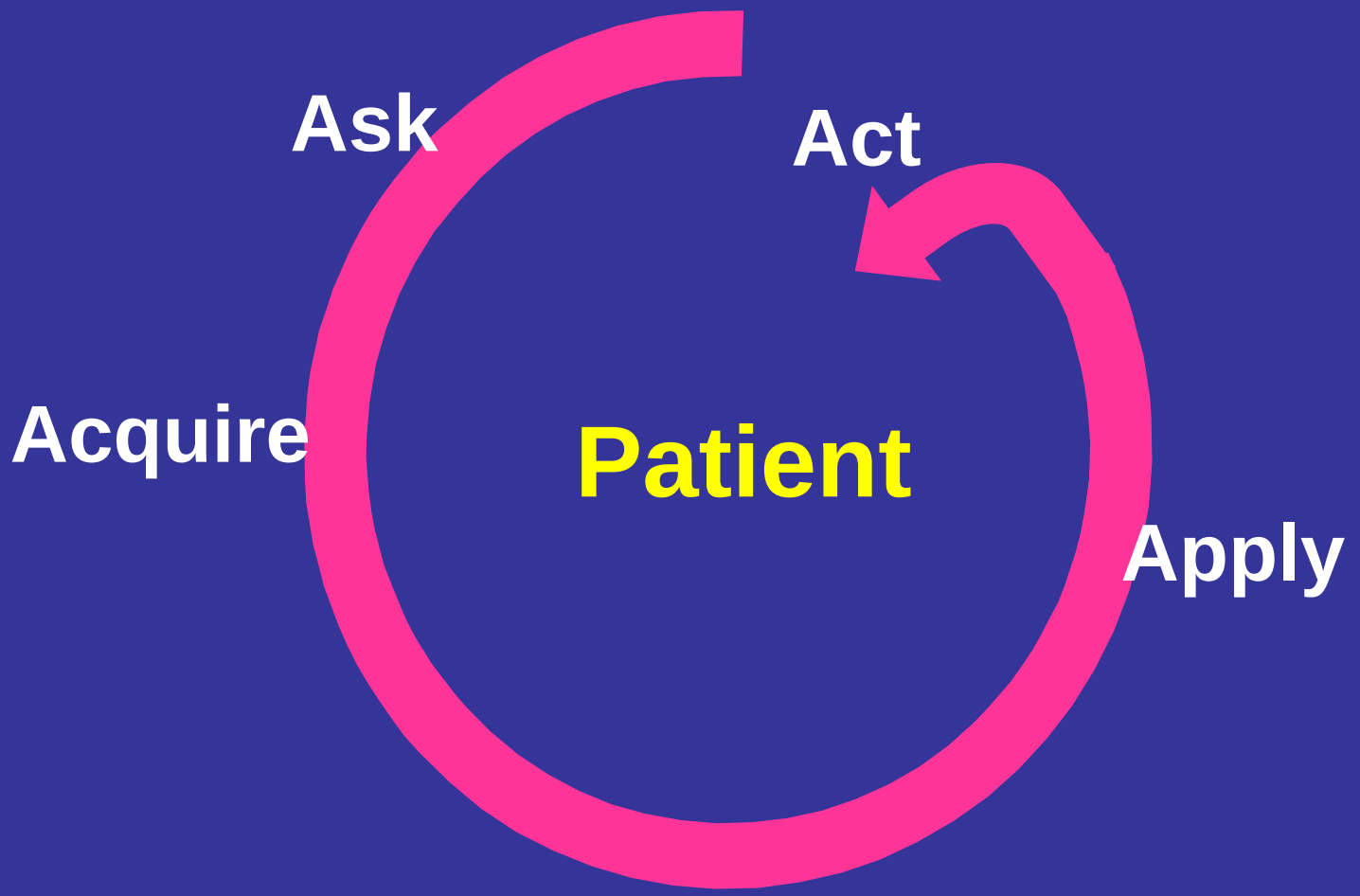
Background **Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.**

September 15, 2006



all participants received
healthy diet and lifestyle advice

Evidence Arc



Validity (likelihood 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 to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose. Patients

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The composite primary outcome was incident diabetes or death from any cause during the active treatment period; death was included to account for the possibility that diabetes might develop at a different rate in 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 prescription of an antidiabetic agent and either a fasting plasma glucose concentration of 7·0 mmol/L or greater or any glucose concentration of 11·1 mmol/L or more. Diabetes status and date of diagnosis were established by masked adjudication of all relevant data.

Validity (likelihood of bias)

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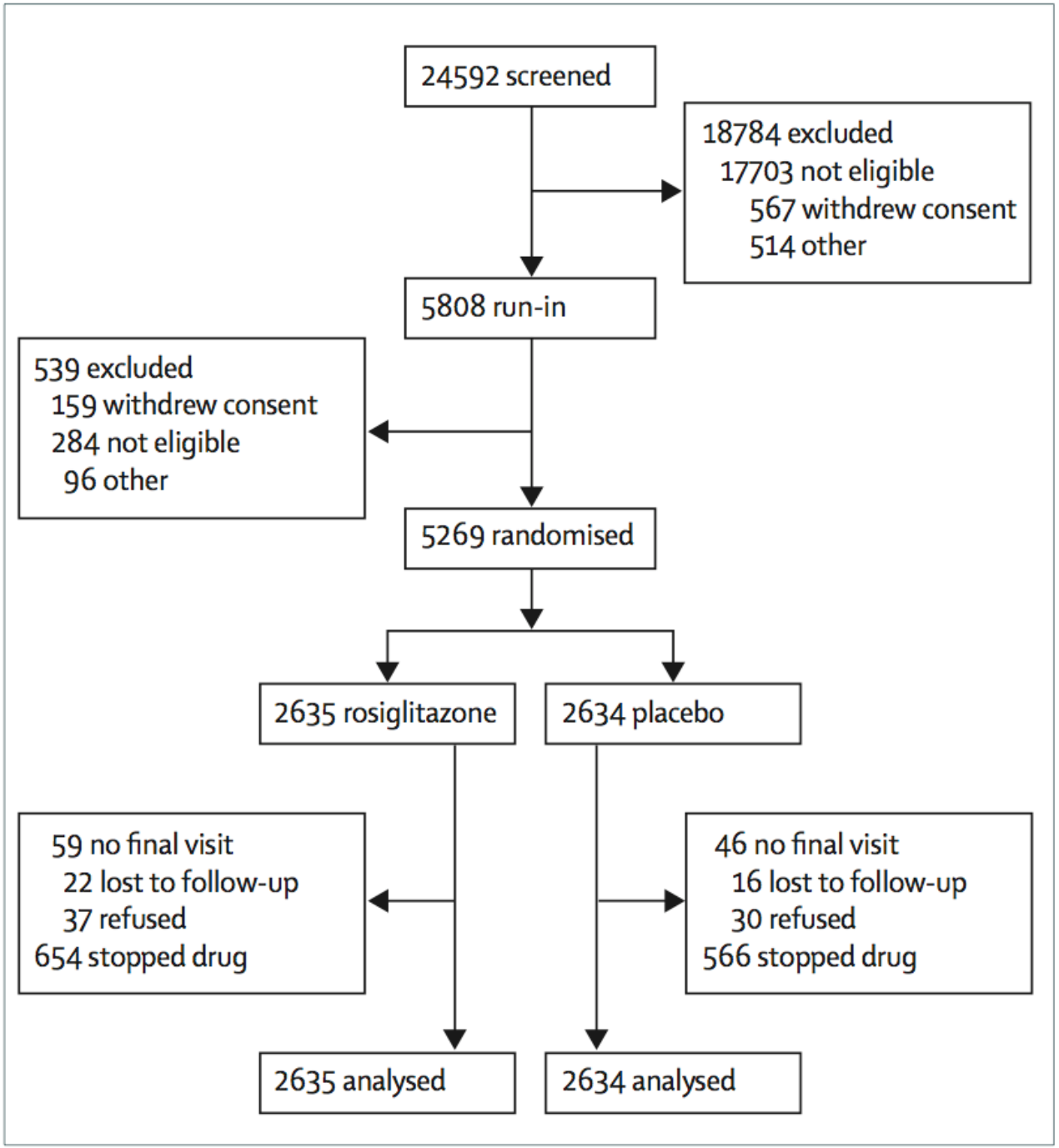
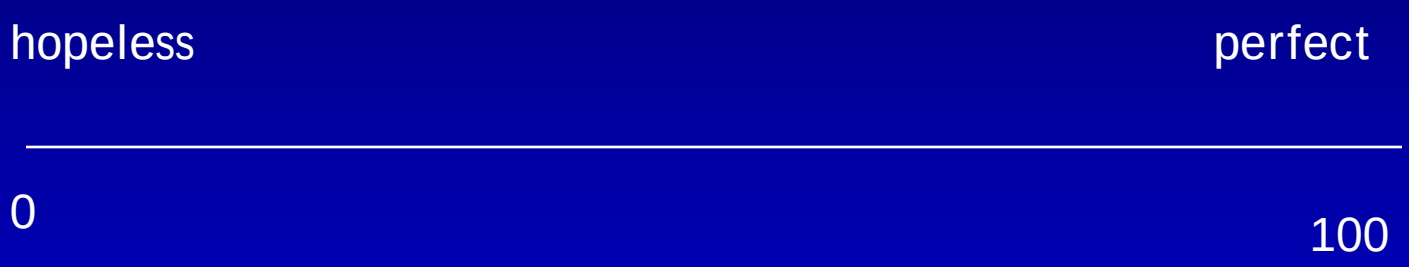

24592 screened
18784 excluded
17703 not eligible
567 withdrew consent
514 other
5808 run-in
539 excluded
159 withdrew consent
284 not eligible
96 other
5269 randomised
2635 rosiglitazone
2634 placebo
59 no final visit
22 lost to follow-up
37 refused
654 stopped drug
46 no final visit
16 lost to follow-up
30 refused
566 stopped drug
2635 analysed
2634 analysed

Validity – risk of bias



	Rosiglitazone group (n=2635)	Placebo group (n=2634)	HR (95% CI)	p
Composite primary outcome*	306 (11·6%)	686 (26·0%)	0·40 (0·35–0·46)	<0·0001
Diabetes	280 (10·6%)	658 (25·0%)	0·38 (0·33–0·44)	<0·0001
Diagnosed by FPG/OGTT	231 (8·8%)	555 (21·1%)	0·38 (0·33–0·44)	<0·0001
Physician diagnosed	49 (1·9%)	103 (3·9%)	0·47 (0·33–0·66)	<0·0001
Death	30 (1·1%)	33 (1·3%)	0·91 (0·55–1·49)	0·7

Cardiovascular events composite*	75 (2·9%)	55 (2·1%)	1·37 (0·97–1·94)	0·08
Myocardial infarction	15 (0·6%)	9 (0·3%)	1·66 (0·73–3·80)	0·2
Stroke	7 (0·3%)	5 (0·2%)	1·39 (0·44–4·40)	0·6
Cardiovascular death	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·7
Confirmed heart failure‡	14 (0·5%)	2 (0·1%)	7·03 (1·60–30·9)	0·01
New angina	24 (0·9%)	20 (0·8%)	1·20 (0·66–2·17)	0·5
Revascularisation	35 (1·3%)	27 (1·0%)	1·29 (0·78–2·14)	0·3
Myocardial infarction, stroke, or cardiovascular death	32 (1·2%)	23 (0·9%)	1·39 (0·81–2·37)	0·2

Assignment

- using evidence in practice
  - 30 second teaching opportunity
- issue of whether to give rosiglitazone to patient arises in outpatient clinic
- summarize the study
- educational goals
  - remind resident 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.

The Solution:

- clinicians and teachers need to practice creating the verbal study synopsis of an article.

Study Synopsis

1) context (patient problem, question)

2) content (validity, results, application)

3) editorial emphasis (features, findings)

Example

- *There's a long standing debate about whether we should use colloids or crystalloids for fluid resuscitation. Recently, a randomized blinded 7,000 patient RCT with 100% follow-up showed no difference (RR 0.99) in patients resuscitated with albumin versus crystalloid. It is hard to justify using albumin in this situation, given the lack of benefit and higher costs compared to crystalloids.*

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[4,5] and greater than the reductions reported previously with drugs such as metformin[4] or acarbose.[3] 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.[4,5] 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

Modelling 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

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

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
  - cardiovascualar events (stroke, MI)
  - renal failure
  - visual impairment and blindness
  - anxiety
  - inconvenience

Patient-important and surrogtes

- 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

Condition	Surrogate	Patient-important	Intervention
Osteoporosis	Bone density	Fracture	Sodium fluoride
Heart failure	Hemodynamic function	Mortality	Flosequinan, milrinone, ibopamine, vesnarinone, xamoterol, epoprostanol
Myocardial infarction	Nasty looking arrhythmia	Sudden death	Encainide/flecainide
Coronary risk	Cholesterol	Mortality	Clofibrate
Coronary risk	LDL, HDL	Coronary events	Hormone replacement therapy
Coronary risk, disease	HDL, triglycerides	Coronary events	High dose extended release niacin, fenofibrate, torcetrapib

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
- Have fun!