

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

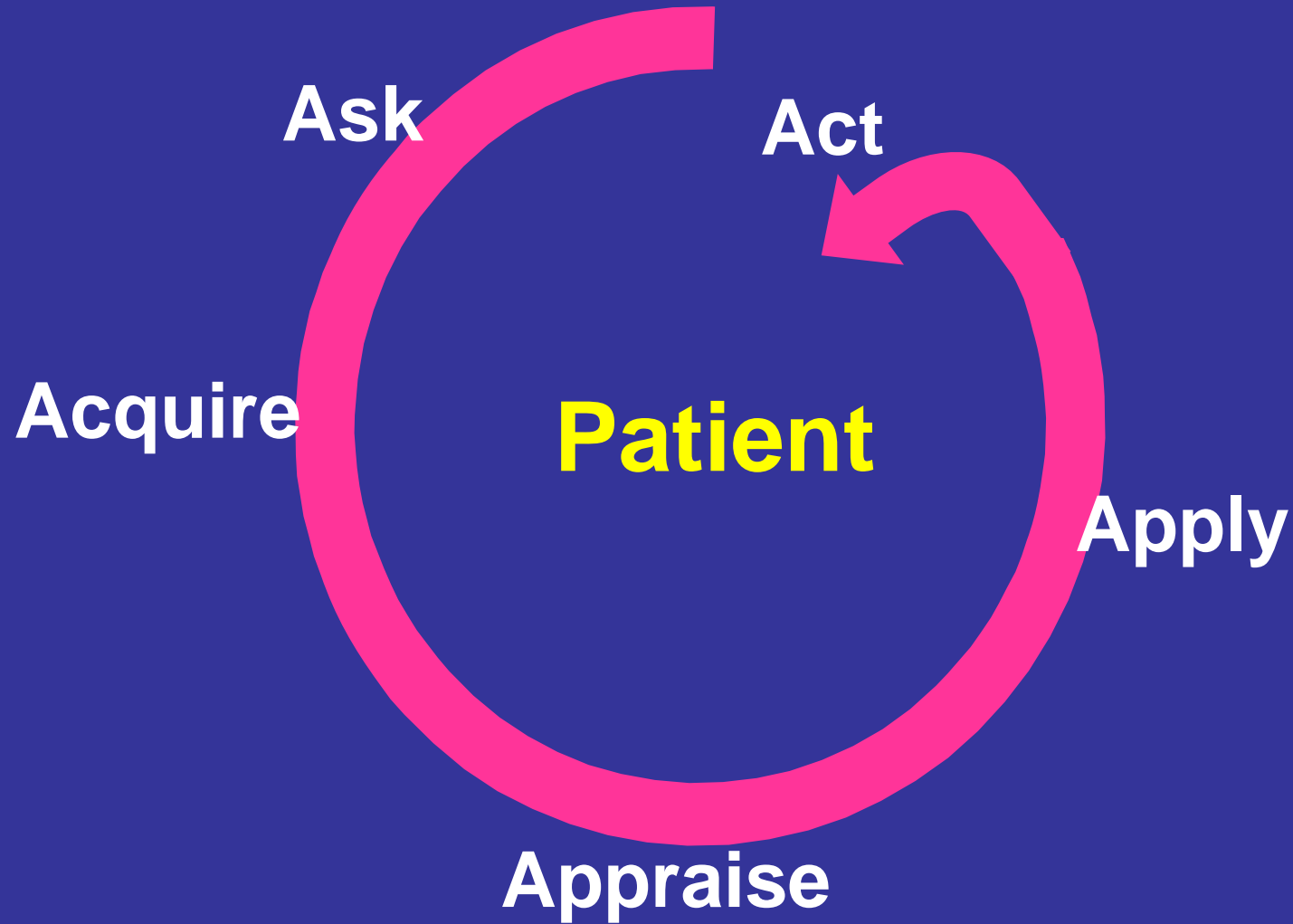
Gordon Guyatt



Plan

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

Evidence Arc



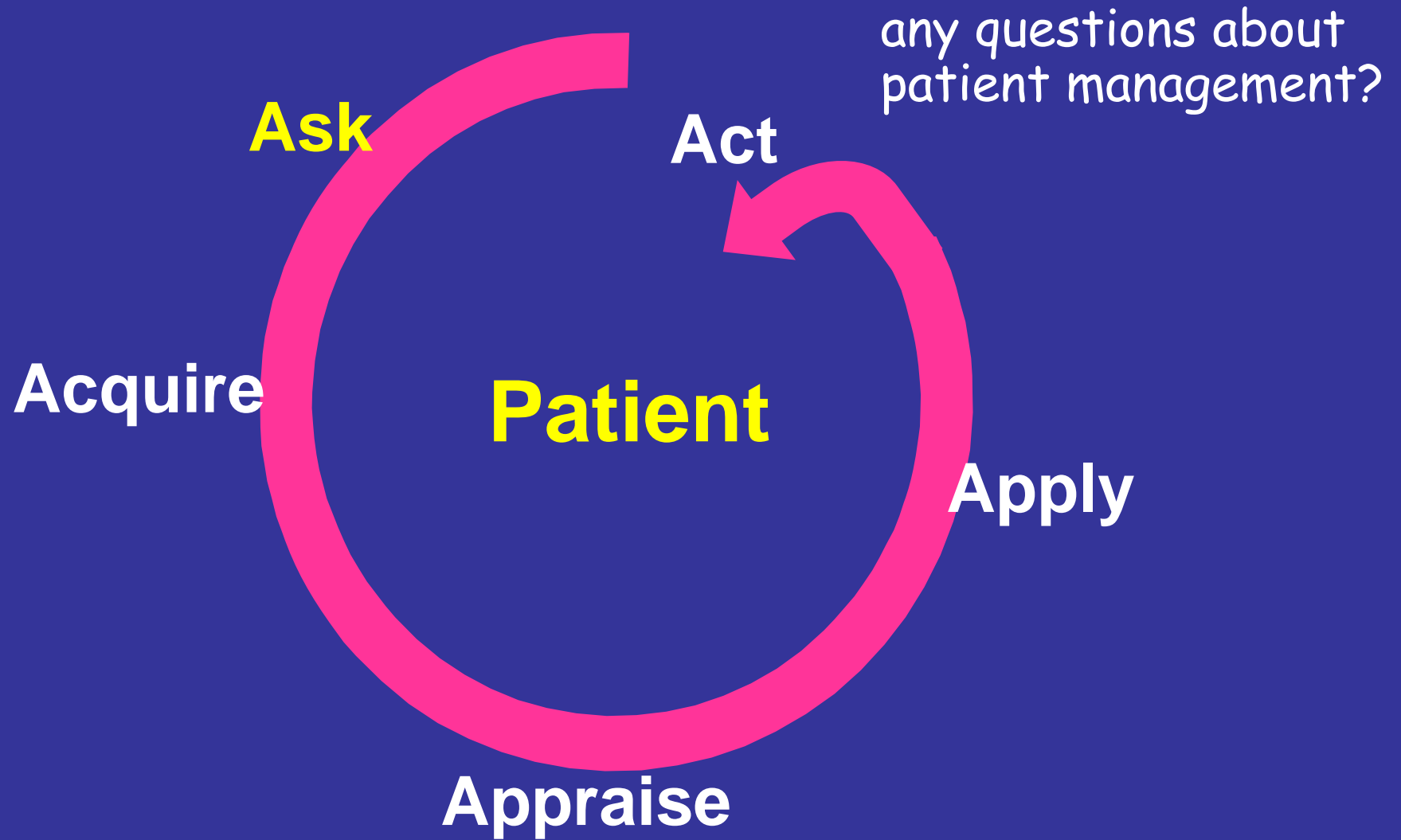
Background to our patient

- 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
- routine testing shows no hypertension, lipid profile normal, FBG 117/6.5

Evidence Arc



Our patient's presentation

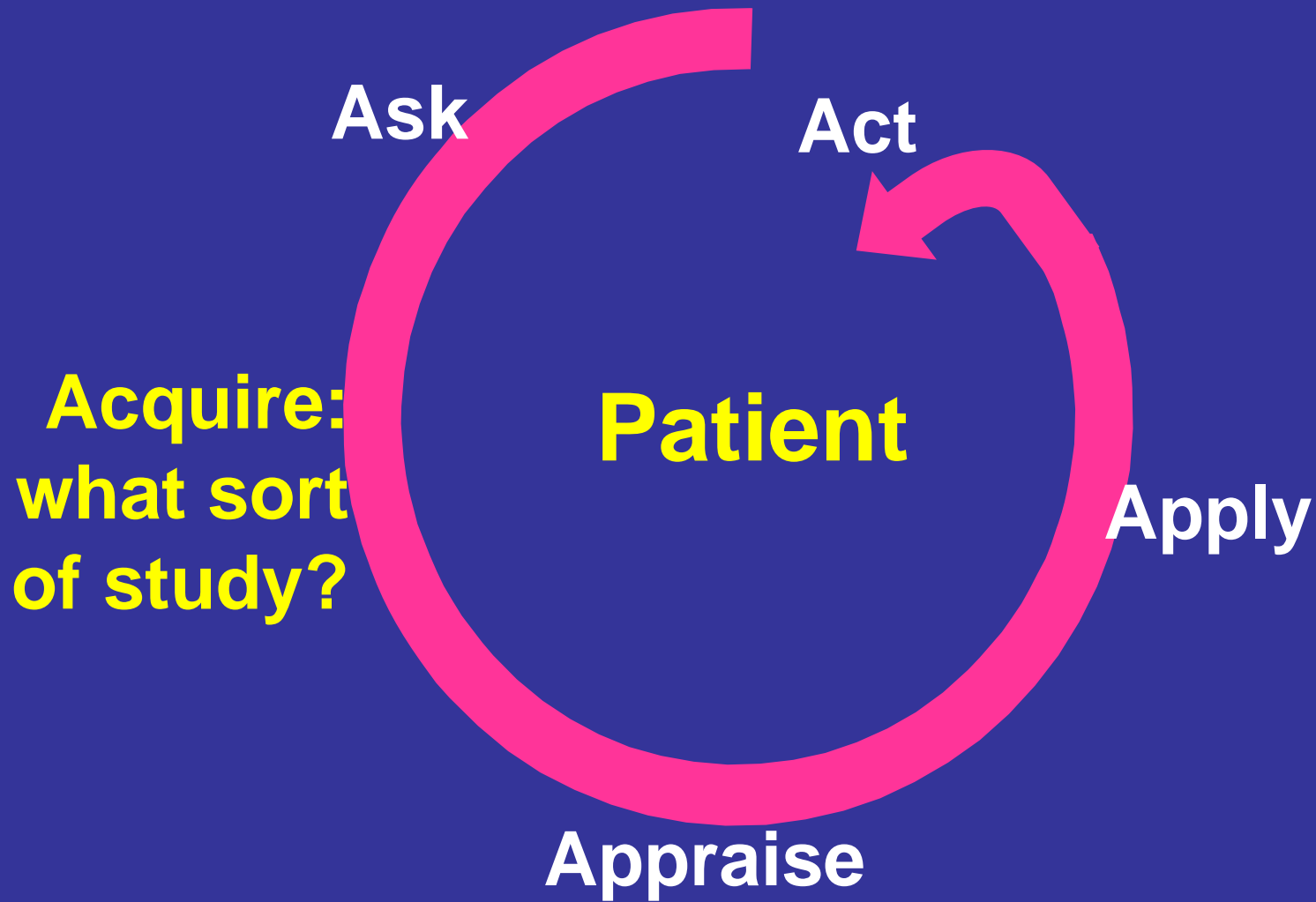
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Question

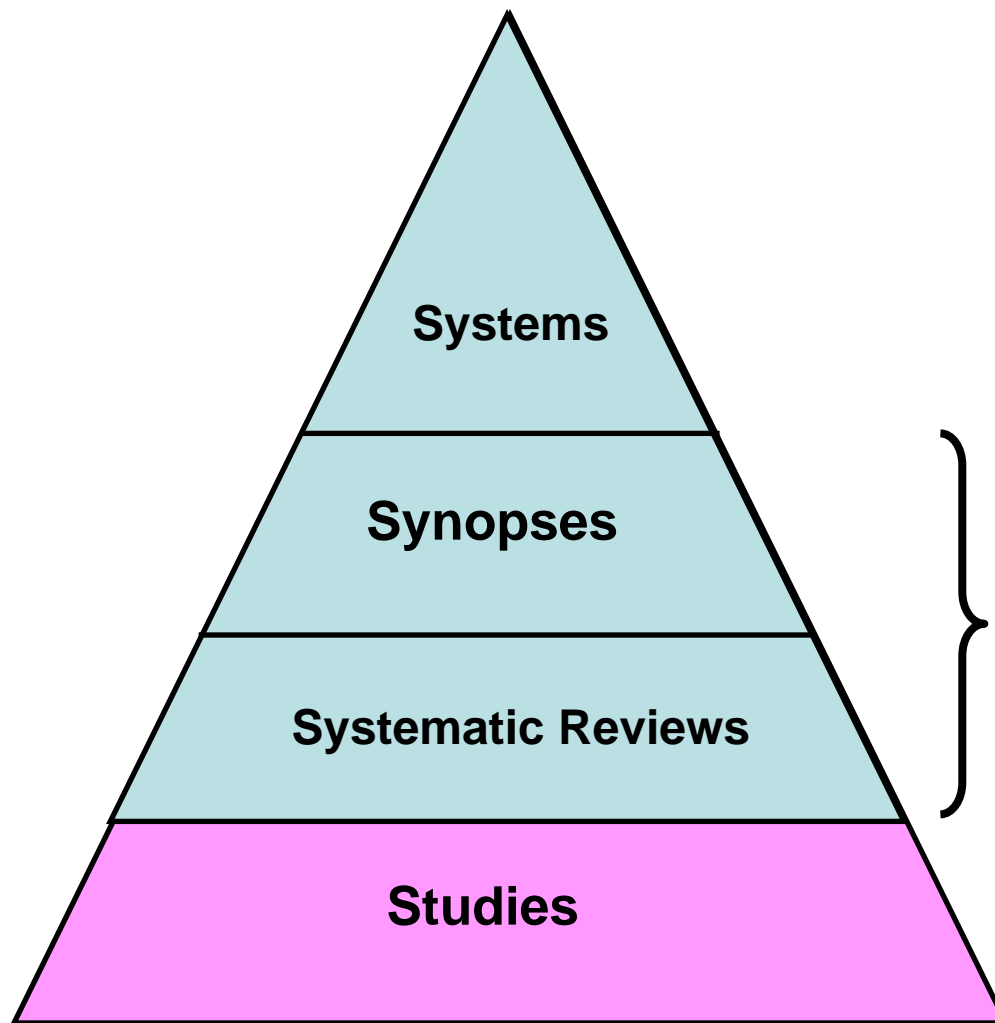
- patient
 - middle-aged man with borderline sugar
- intervention
 - rosiglitazone
- comparator
 - no rosiglitazone
- outcome?

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

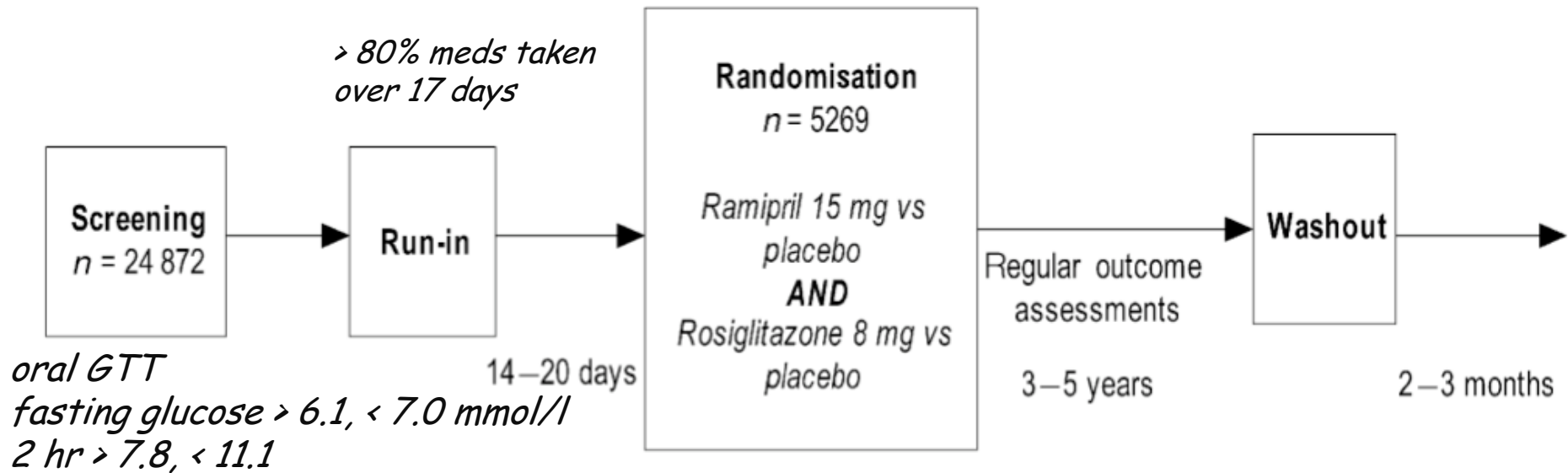
*The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators**

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.

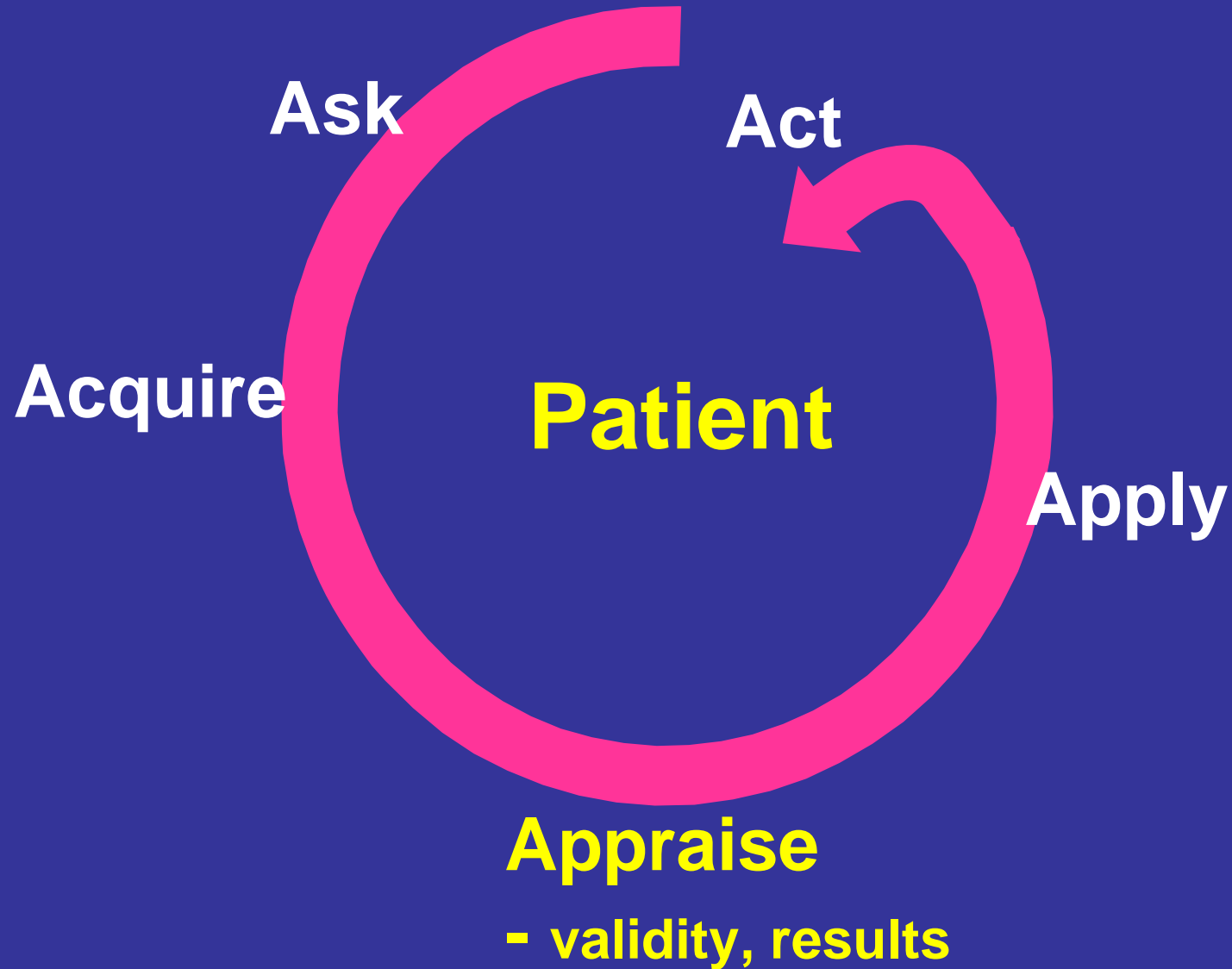
September 15, 2006

Warning: You will be asked to summarize



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

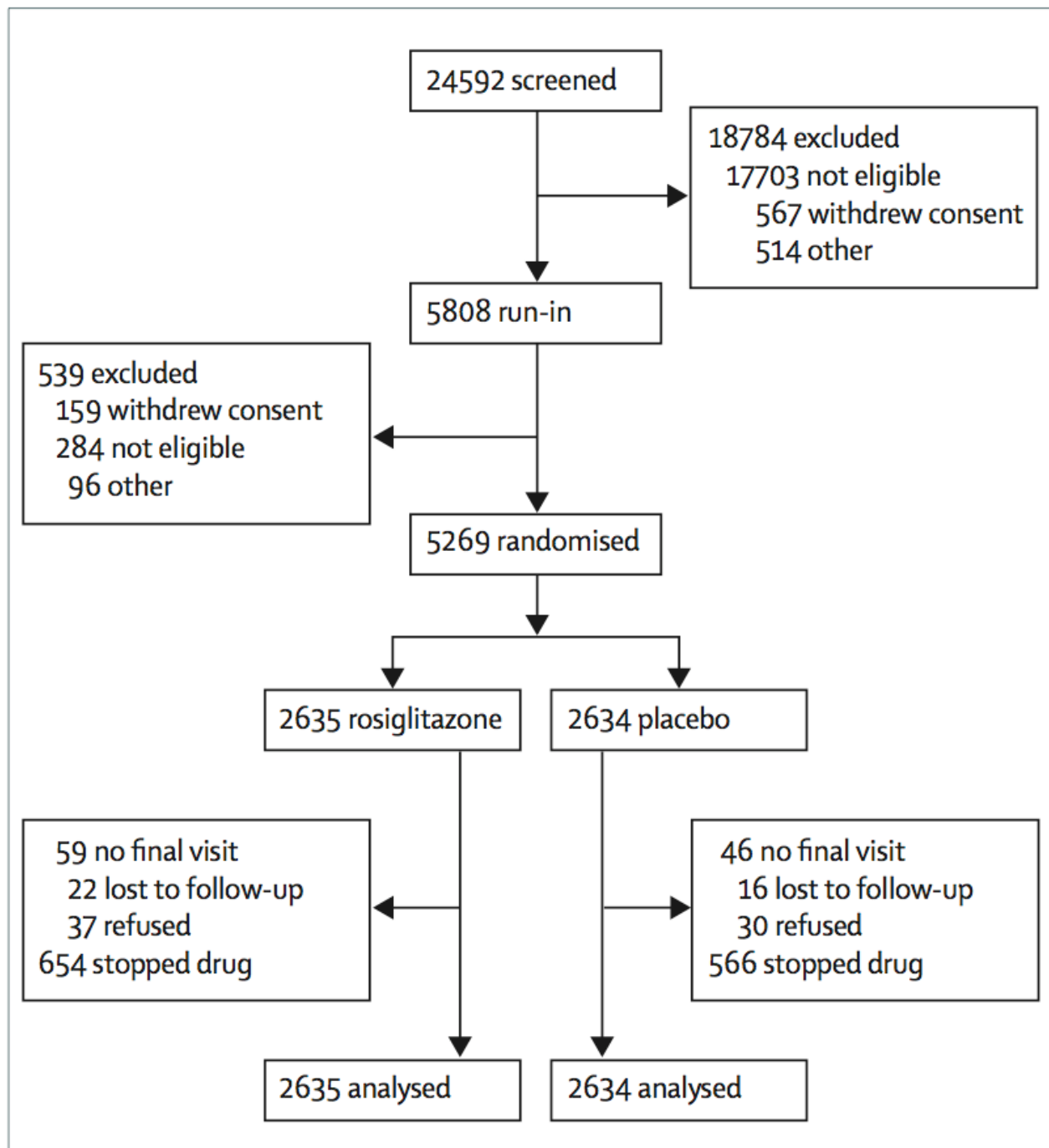
Eligible patients were randomly assigned (stratified by site) by a concealed, computerised telephone randomisation system to receive either rosiglitazone (4 mg once daily for the first 2 months and then 8 mg once daily) or matching placebo. The dose of 8 mg per day was chosen to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose. Patients

Validity (likelihood of bias)

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Validity (likelihood of bias)

- randomization
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Validity - risk of bias

hopeless

perfect

0

100



	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.

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 metformin⁴ 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
 - 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

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!