Contribution to clinicians of the last revision of the UKPDS study

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Salamanca 29th January 2010. IV congress on Diabetes and obesity

The Oxford Centre

for Diabetes, Endocrinology and Metabolism

- Title: Contribution to clinicians of the last revision of the UKPDS study Given where: Salamanca, Spain
- Based on: Florence , Teneriffe
- Keywords: Glycaemia, trials, Advance, Record, Adopt,UKPDS,Proactive

- Date: 29/01/2010
- Occasion: IV congress on Diabetes and Obesity
- Sponsor:
- Contact: academic
- Feedback:
- Duration: 45mins
- Timing:
- Notes:
- Discussion:
- Thoughts:
- Revisions necessary

Risks of complications in type 2 diabetes

- Glycaemia *
- Hypertension *
- Dyslipidaemia
- Smoking
- Obesity

- Age
- Sex
- Race
- Genes (within race)
- Competing risks

The problem

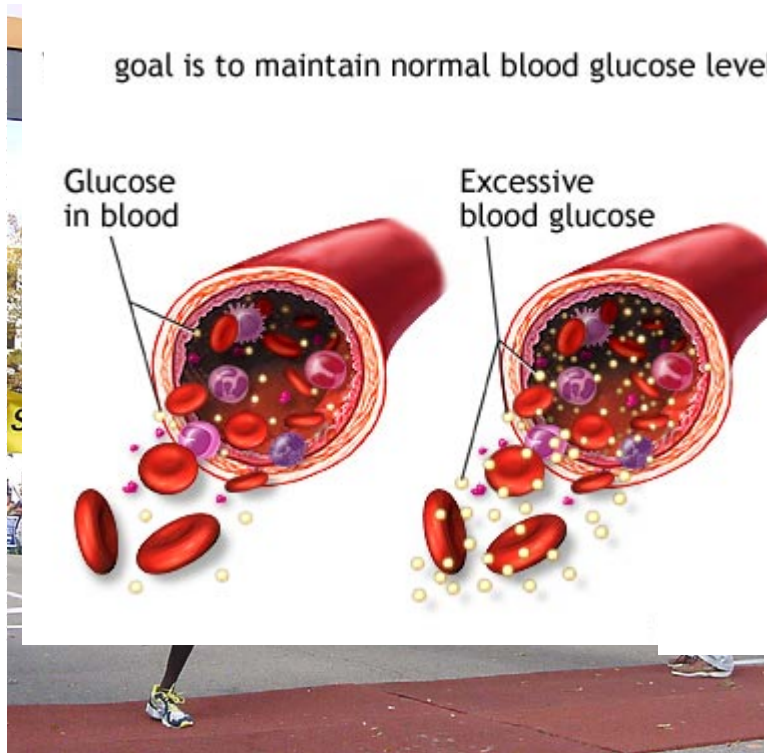
- We utilise glucose as our main metabolic fuel
- Glucose can be stored and mobilised in seconds
- A fit person can run on glucose energy for about 15miles

BUT

Glucose is very osmotically active

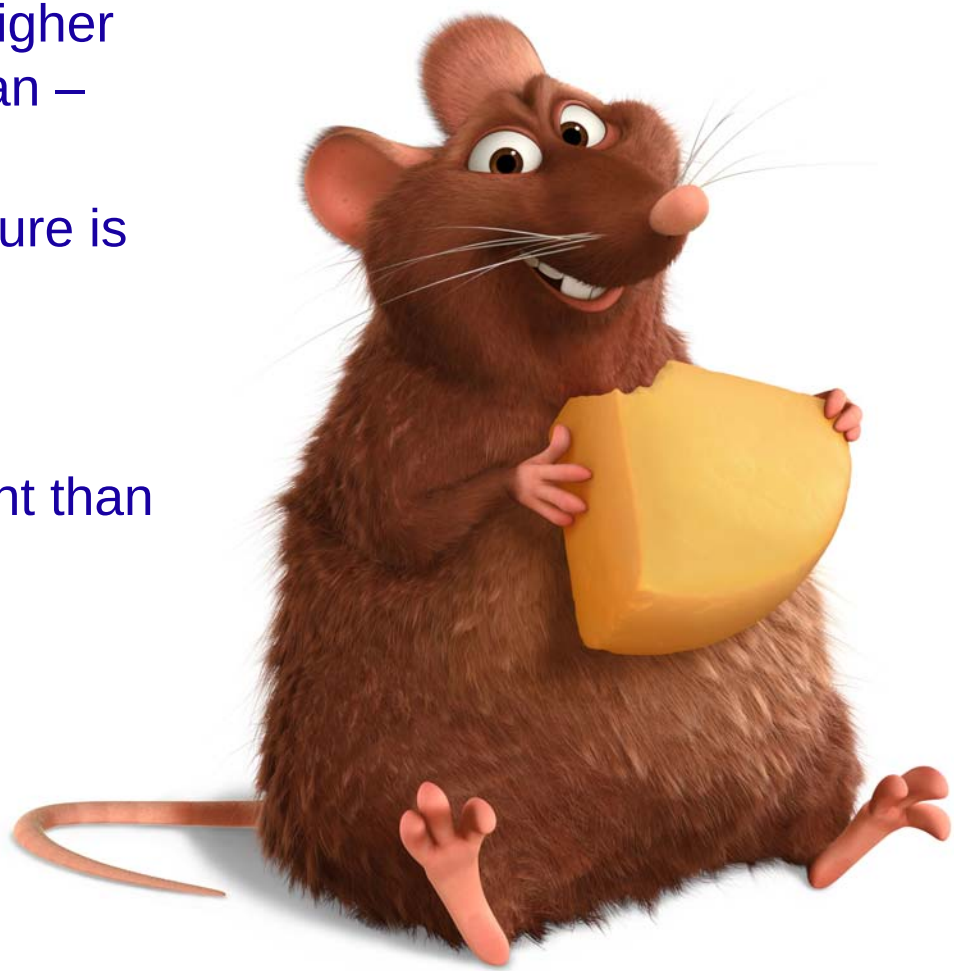
Even 8mmol/l will damage vessels

If we could survive with glucose at just 12mmol/l most diabetes would be irrelevant



How do we know that high glucose is dangerous?

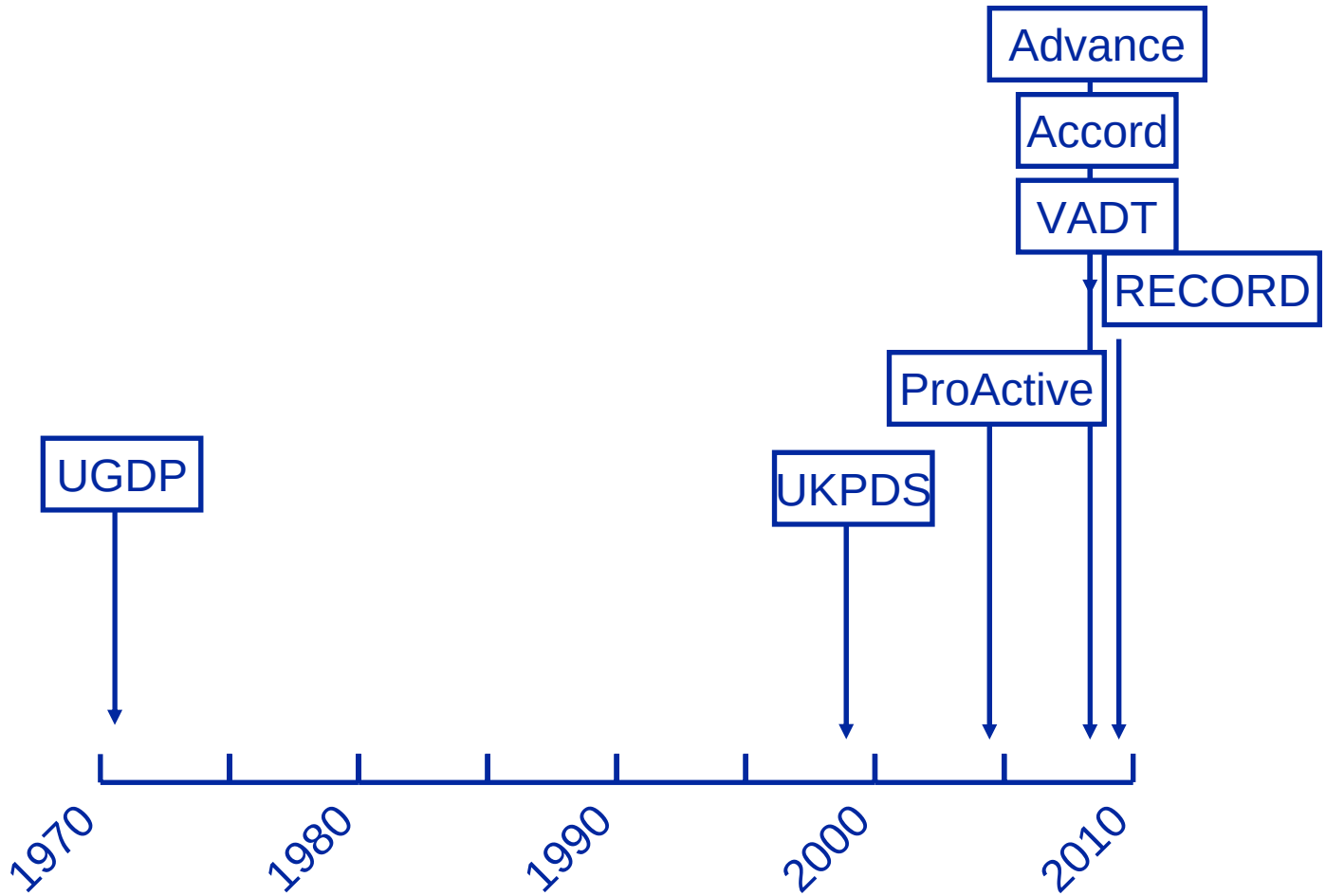
- Rats and mice run a higher blood glucose than man – typically 8mmol/l
  - Evolutionary pressure is not about 70-year survival but 3 year survival
  - Fuel more important than glucose risk
- *In man we have trial evidence of the risk*



Trials relating to glycaemia and outcomes

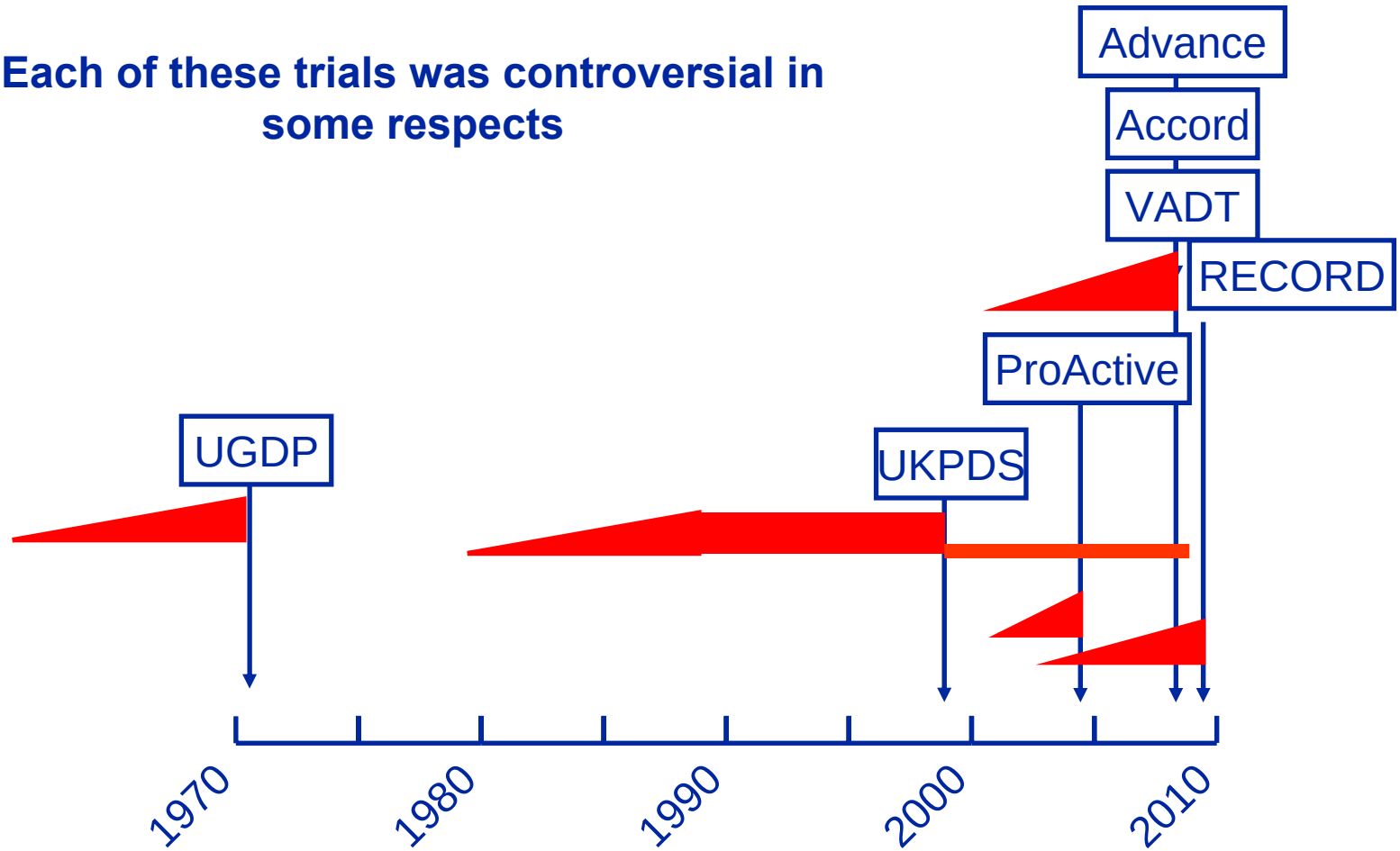
- UGDP
- UKPDS
- PROactive
- (ADOPT)
- (Nissen et al meta-analysis)
- RECORD
- ACCORD
- ADVANCE
- UKDPS PTM
- VADT

Glycaemic outcome trials

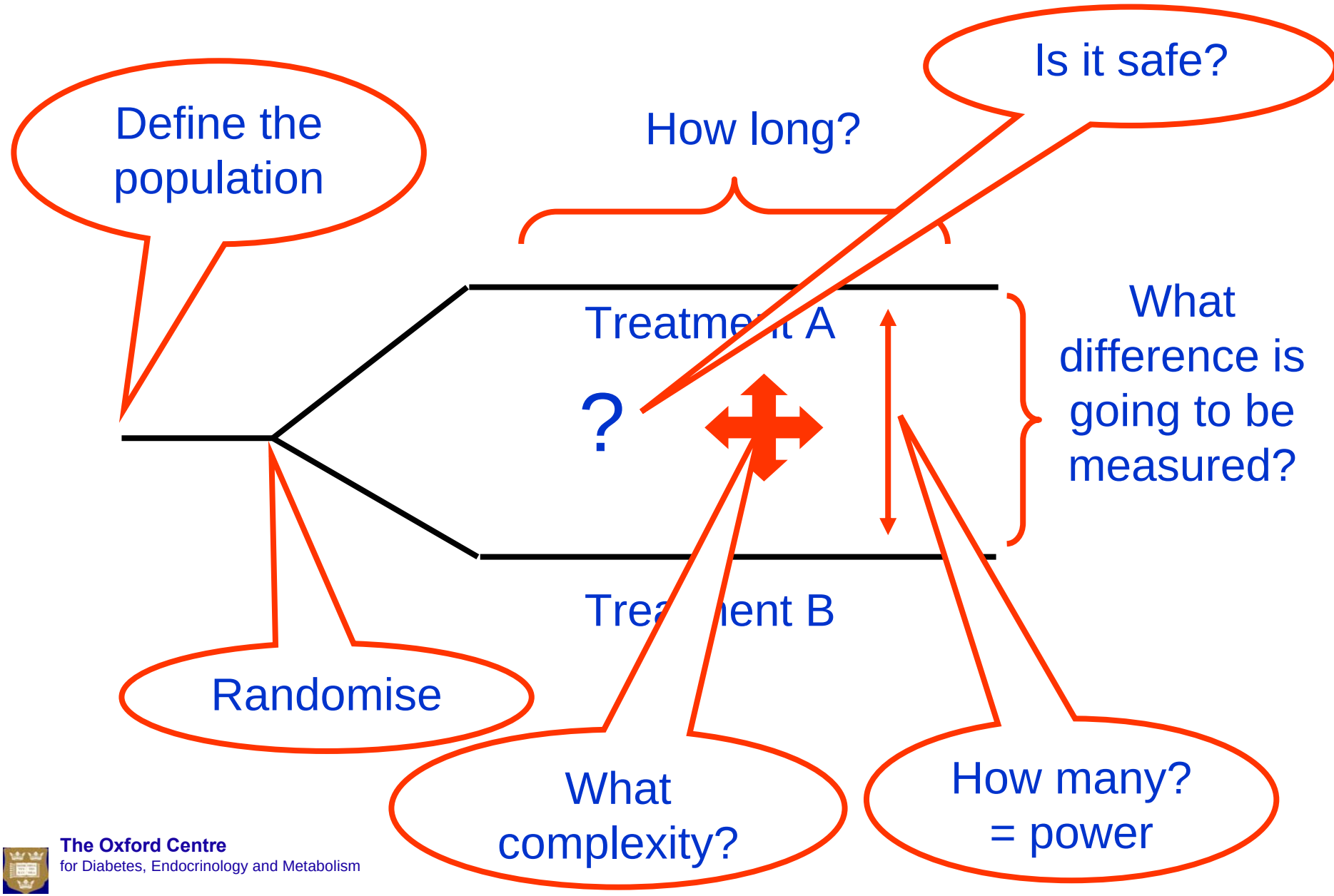


Glycaemic outcome trials

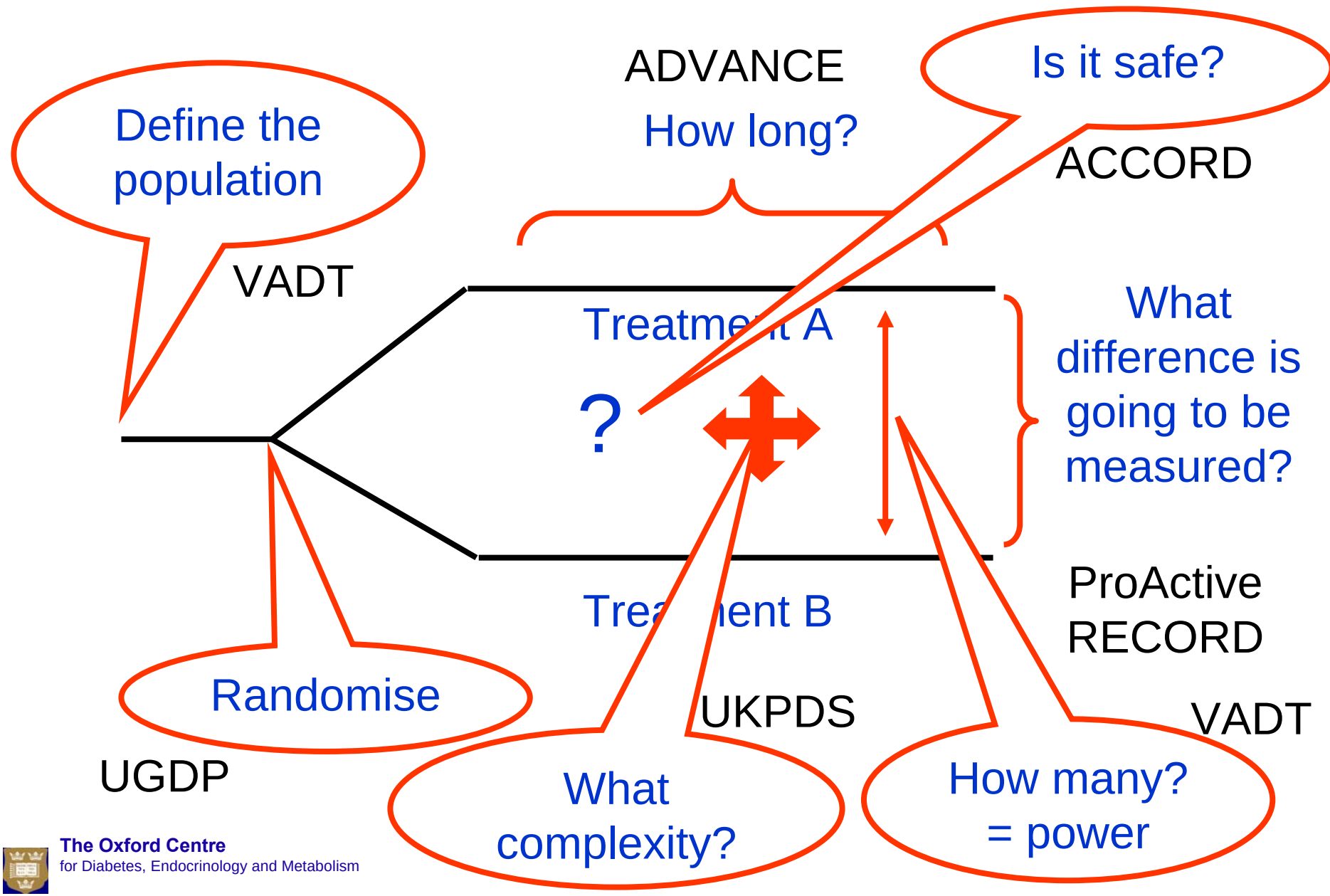
Each of these trials was controversial in some respects



Randomised controlled trials



Problems in trials



UGDP – perhaps tolbutamide was dangerous?

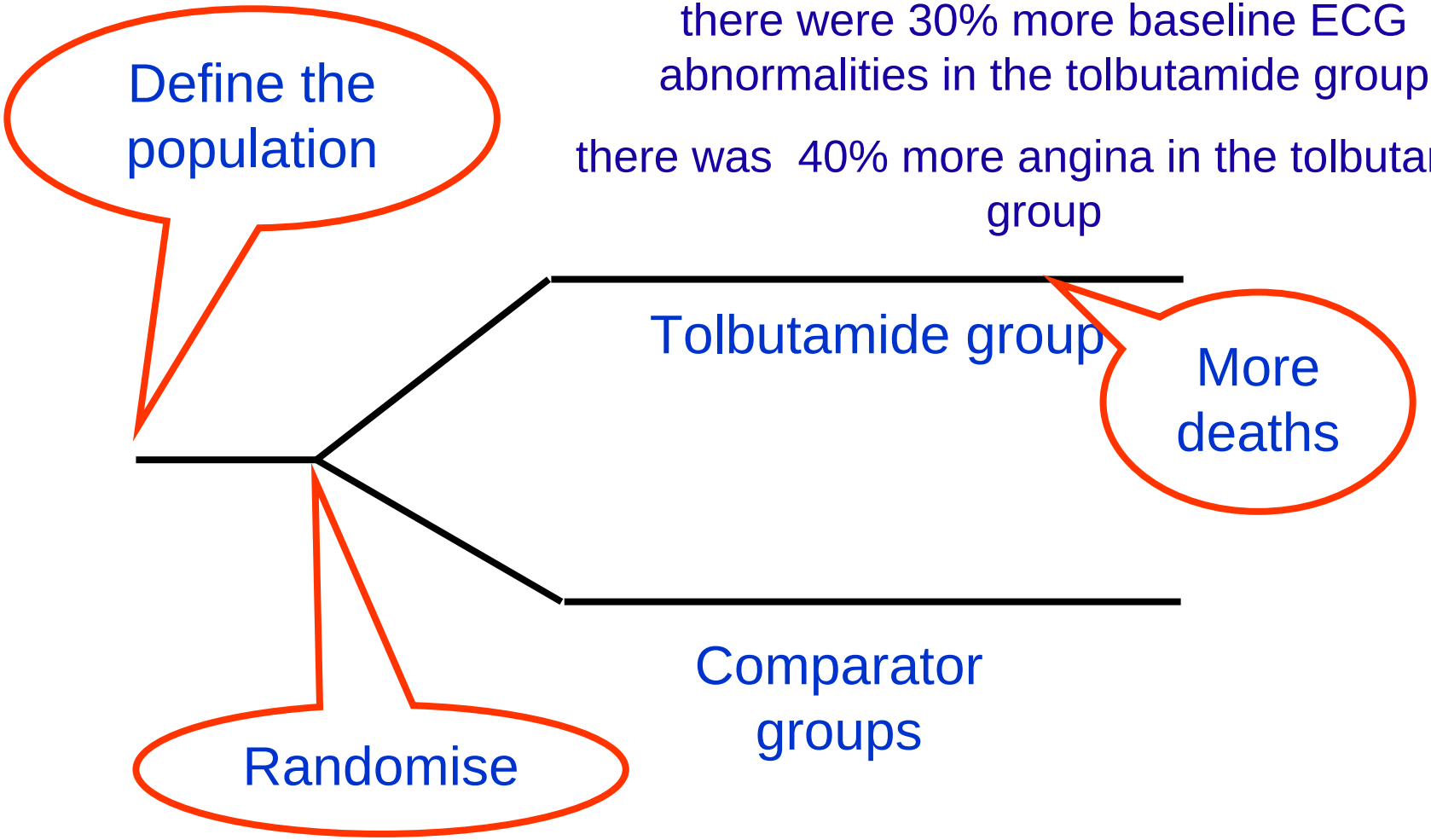
More people died in the tolbutamide group

Leibel B. An analysis of the UGDP. Can Med Assoc J. 1971 Aug 7;105(3):292-4.

UGDP

there were 30% more baseline ECG abnormalities in the tolbutamide group

there was 40% more angina in the tolbutamide group

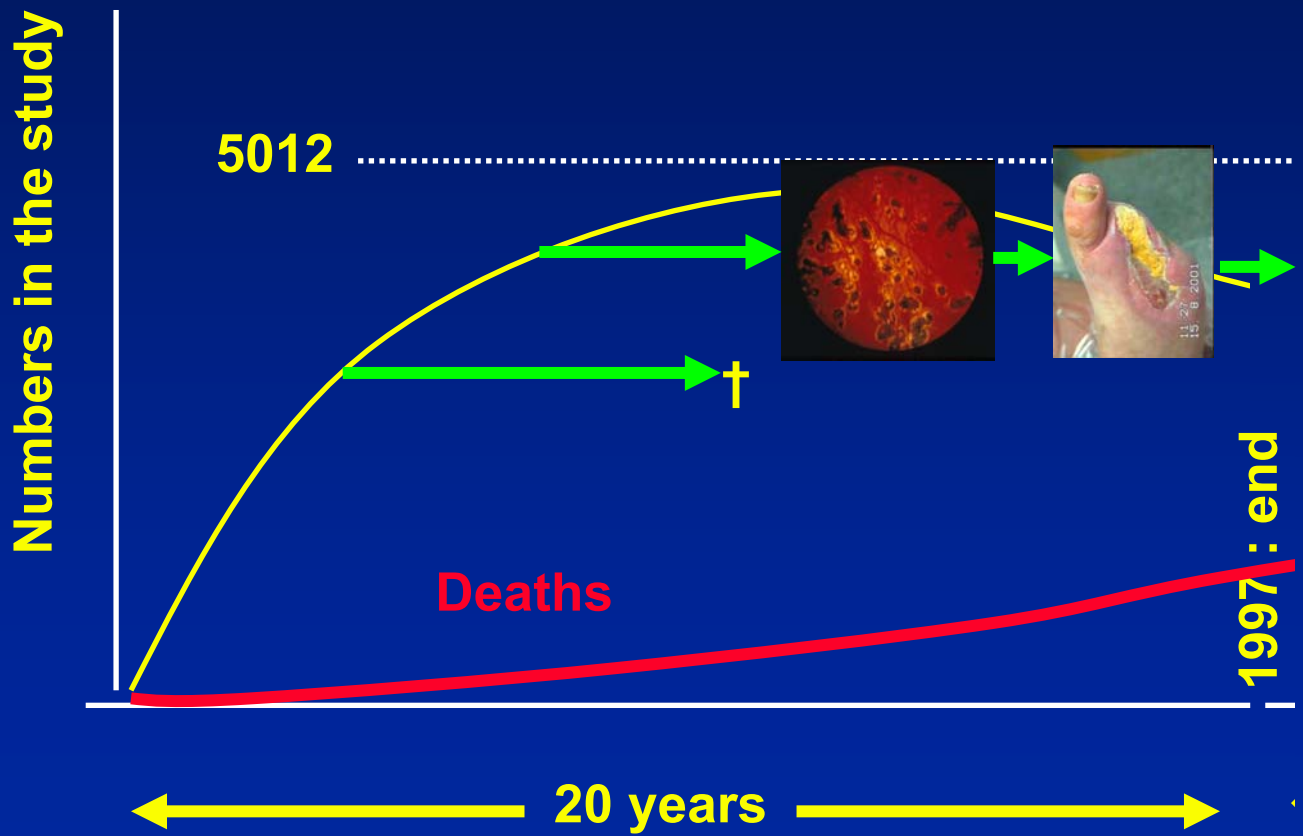


UKPDS

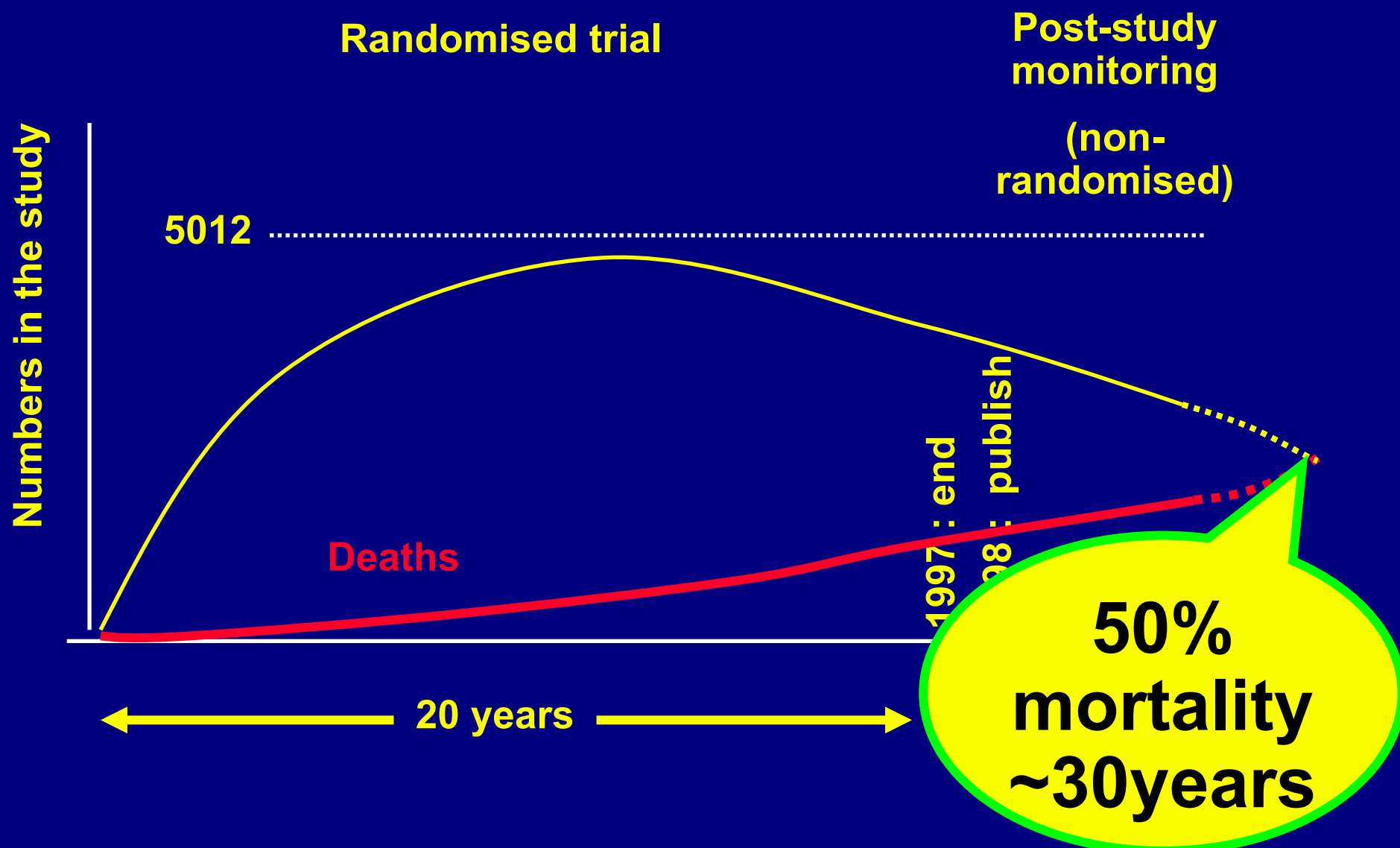
- Primary intervention randomised controlled outcome trial
- Used sulphonylureas
  - mainly glibenclamide and chlorpropamide
  - small number of patients used gliclazide and acarbose (not formally part of the trial)
- Used metformin in the overweight (120% Ideal body weight)
- Used insulin as primary intervention
- Recruited patients with fasting glucose greater than 6mmol/l

UKPDS assessment design (end-point counting)

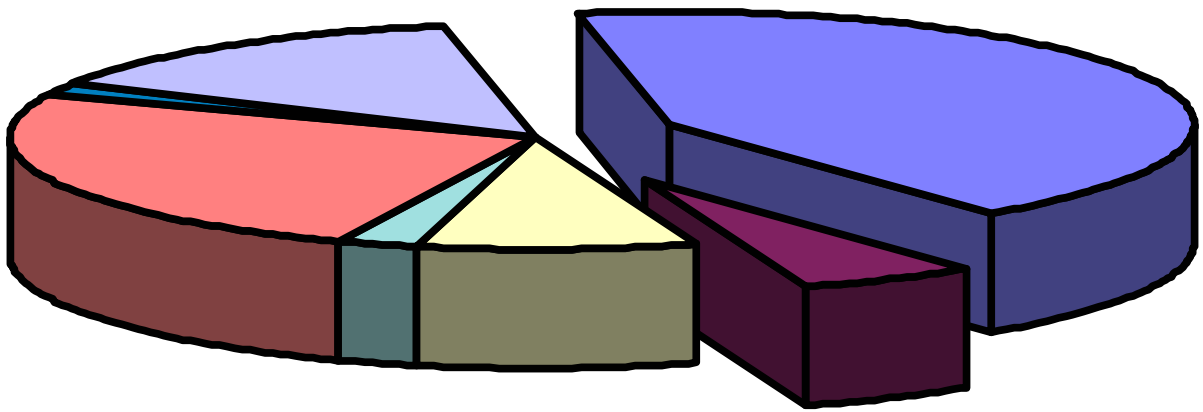
Randomised trial



UKPDS design



Mortality in the UKPDS (1997)



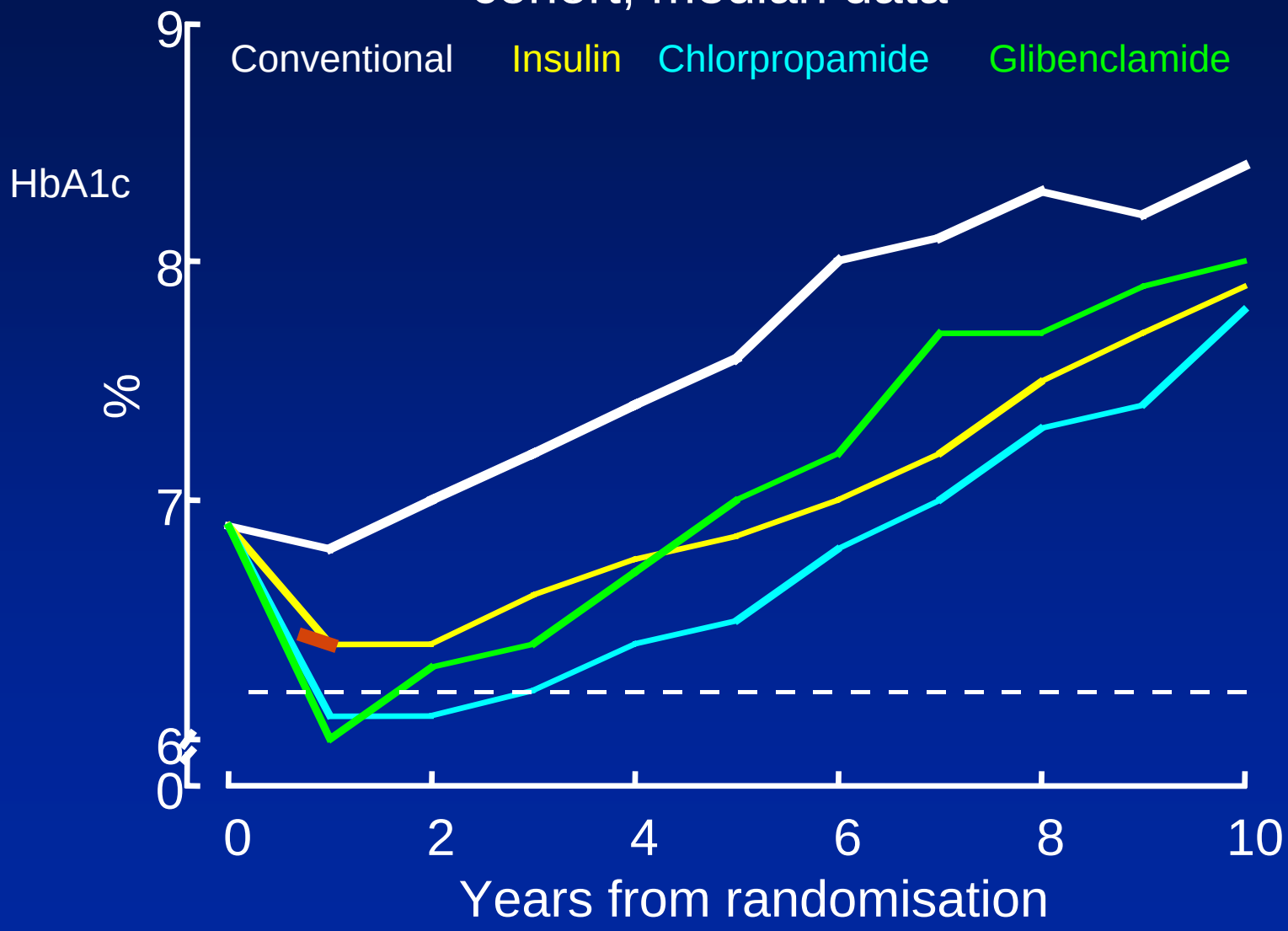
End of the trial (1997): 1/7 of all the patients had died (20y)

By 2000: 1/4 of all the patients had died

End of Post Study Monitoring: 1/2 of all the patients had died (30y)

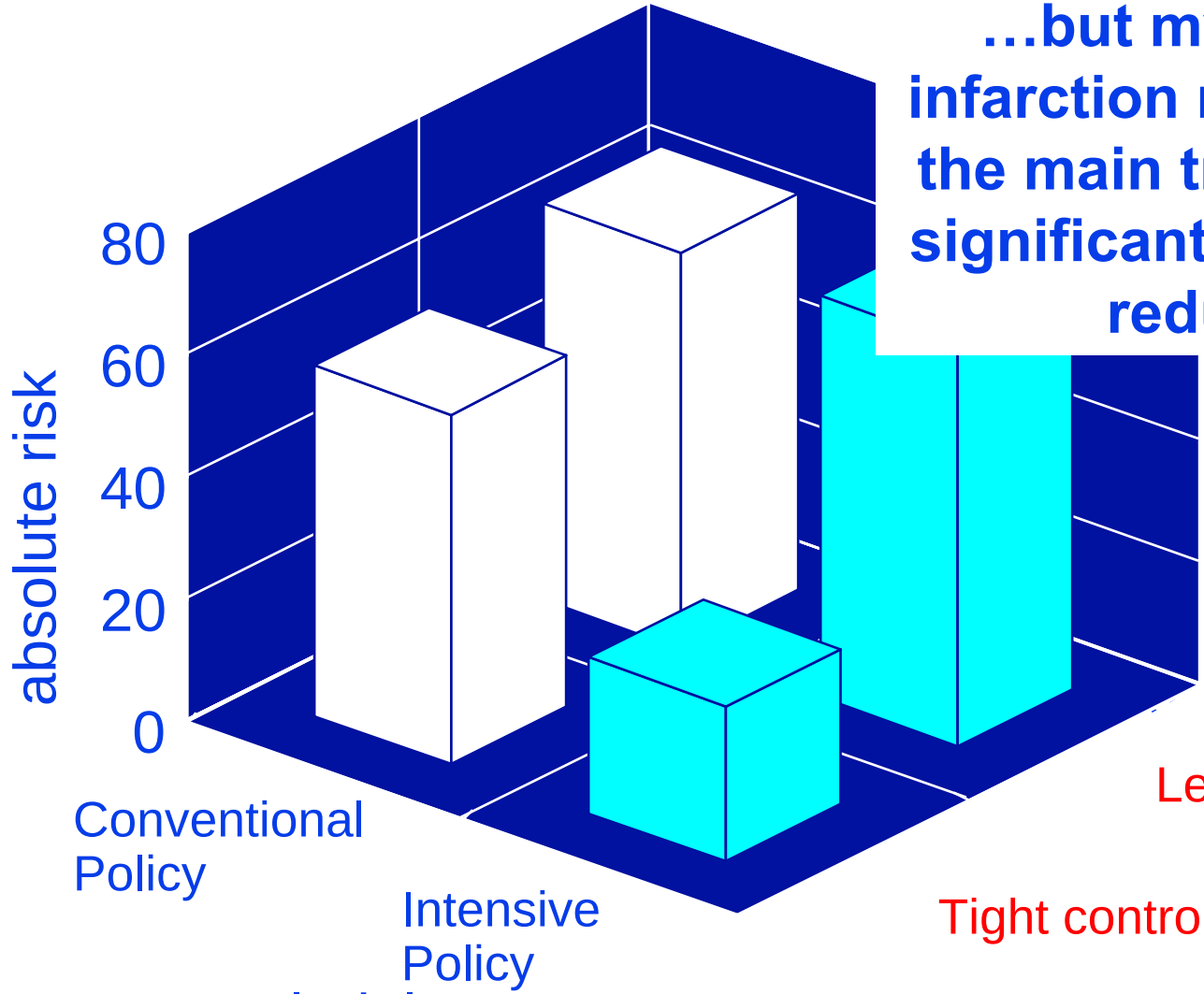
HbA_{1c}

cohort, median data



ukpds

UKPDS: Any Diabetes Related endpoints



…but myocardial infarction reduction in the main trial was not significantly (p=0.052) reduced

Less tight control

Tight control

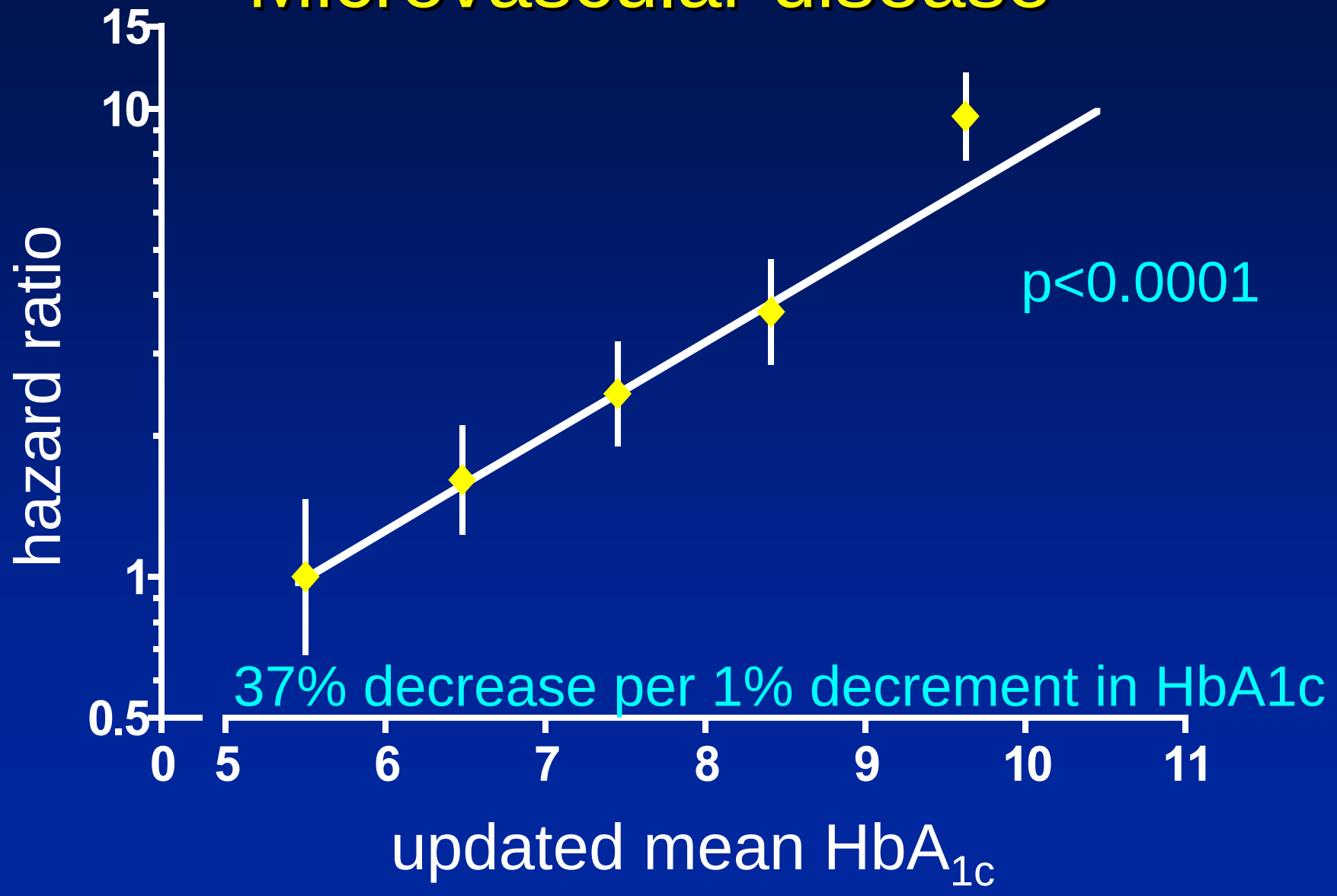
Glucose control trial

Blood pressure control trial

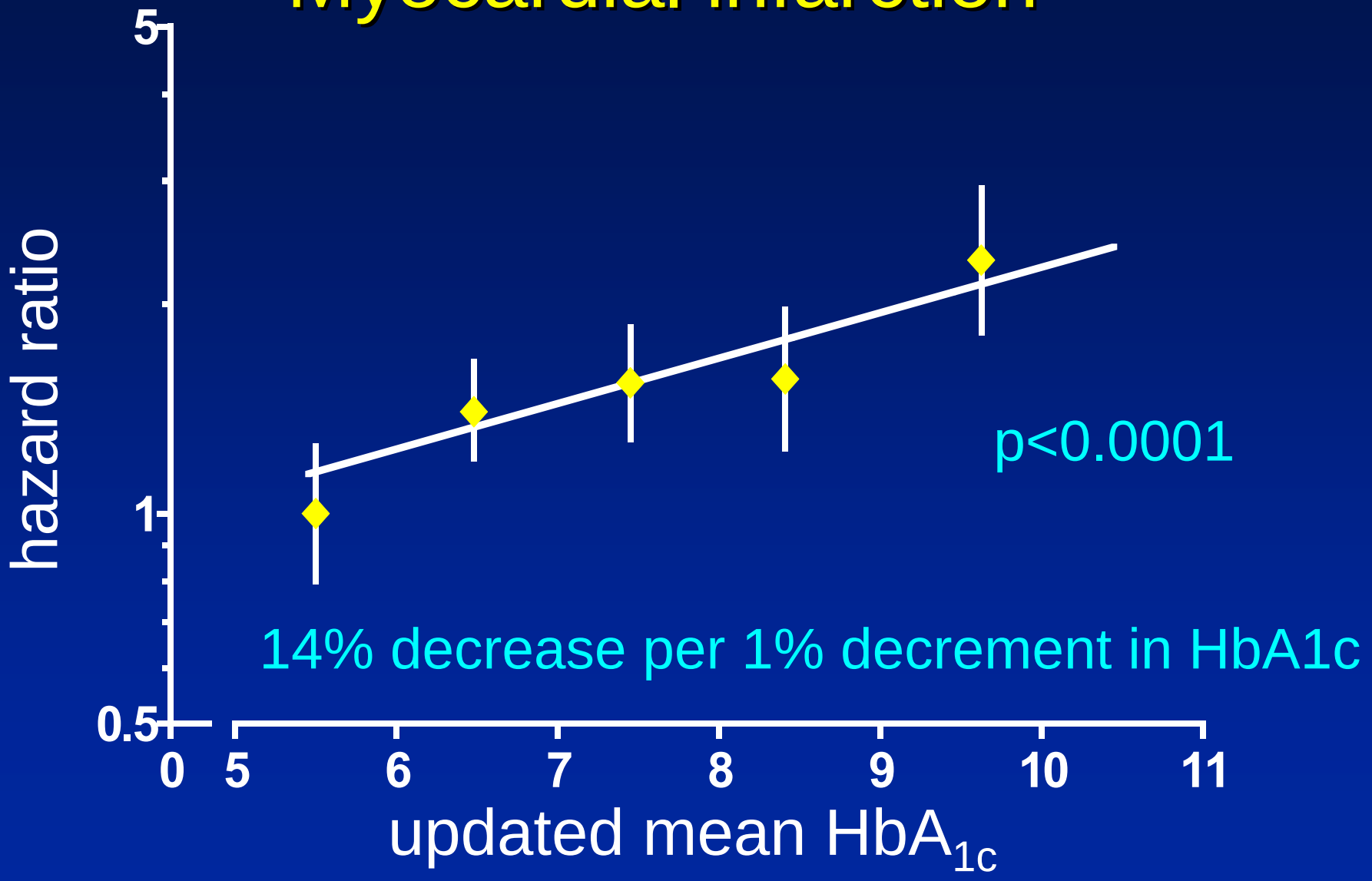
Epidemiology vs trial

- Trials randomise patients and examine the outcome on the basis of the randomised intervention.
- Epidemiological analyses examine a surrogate marker within the trial (e.g. the glucose or the blood pressure) and examine the outcome based on *what was achieved rather than what was administered*.

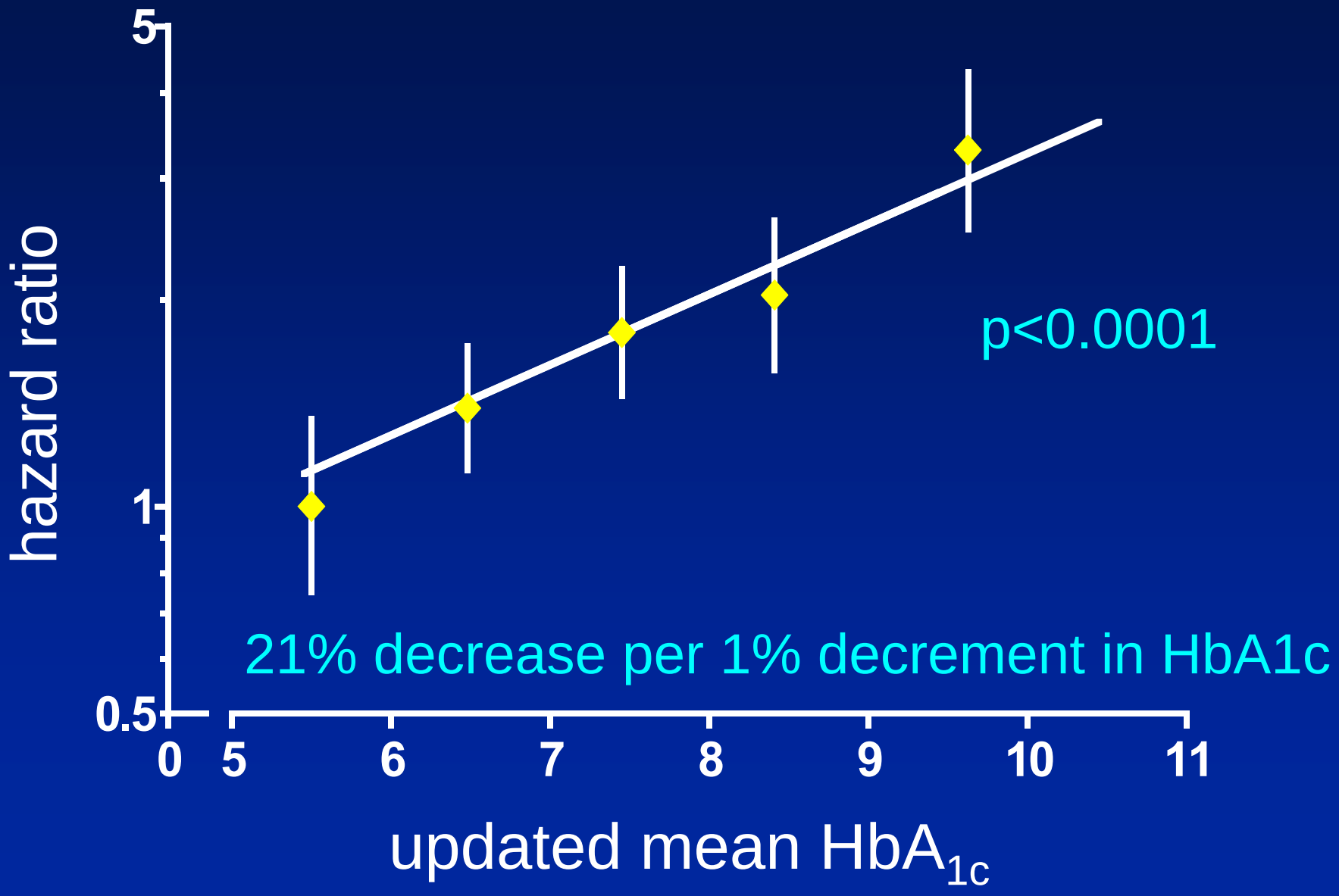
Microvascular disease



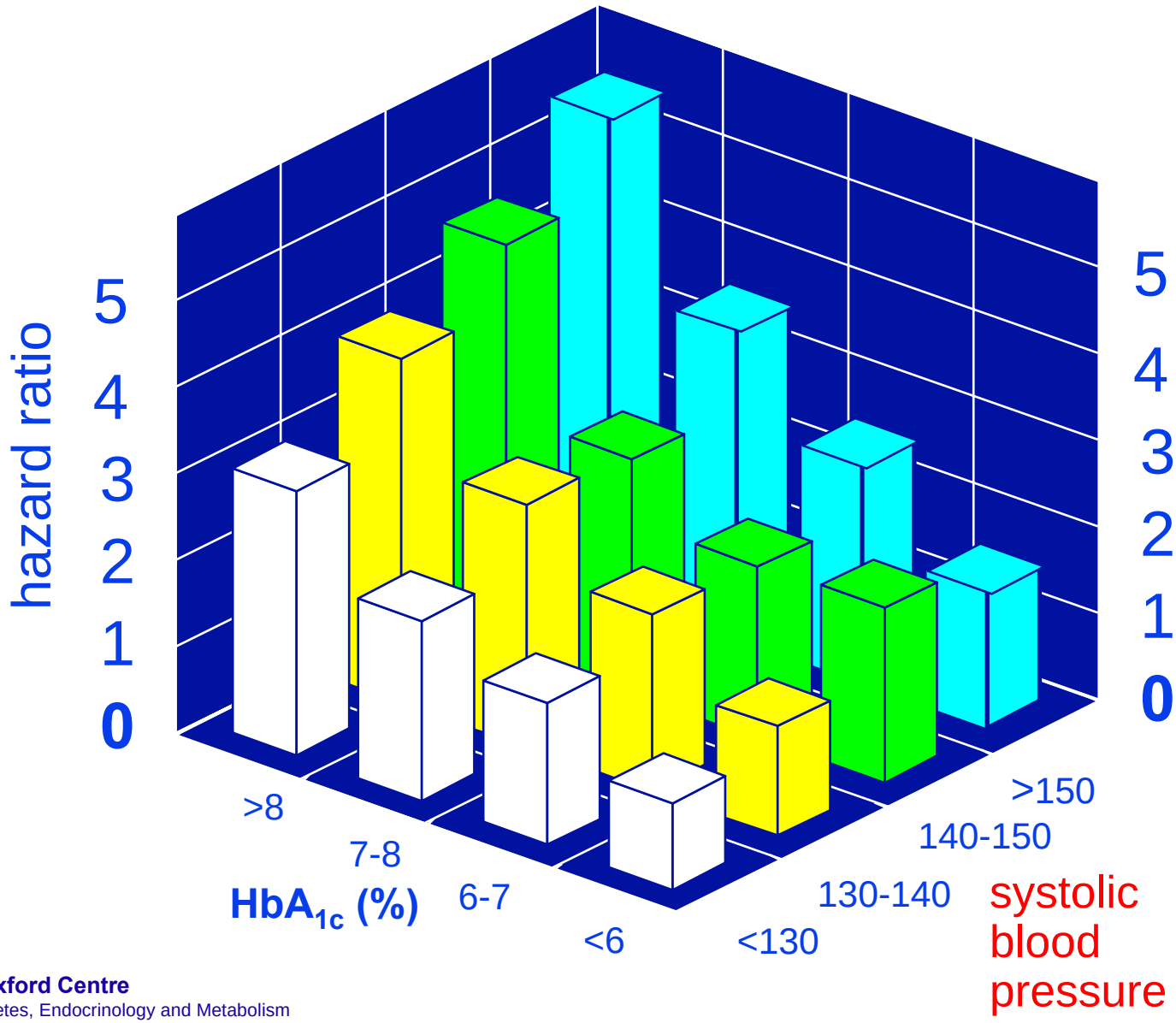
Myocardial infarction



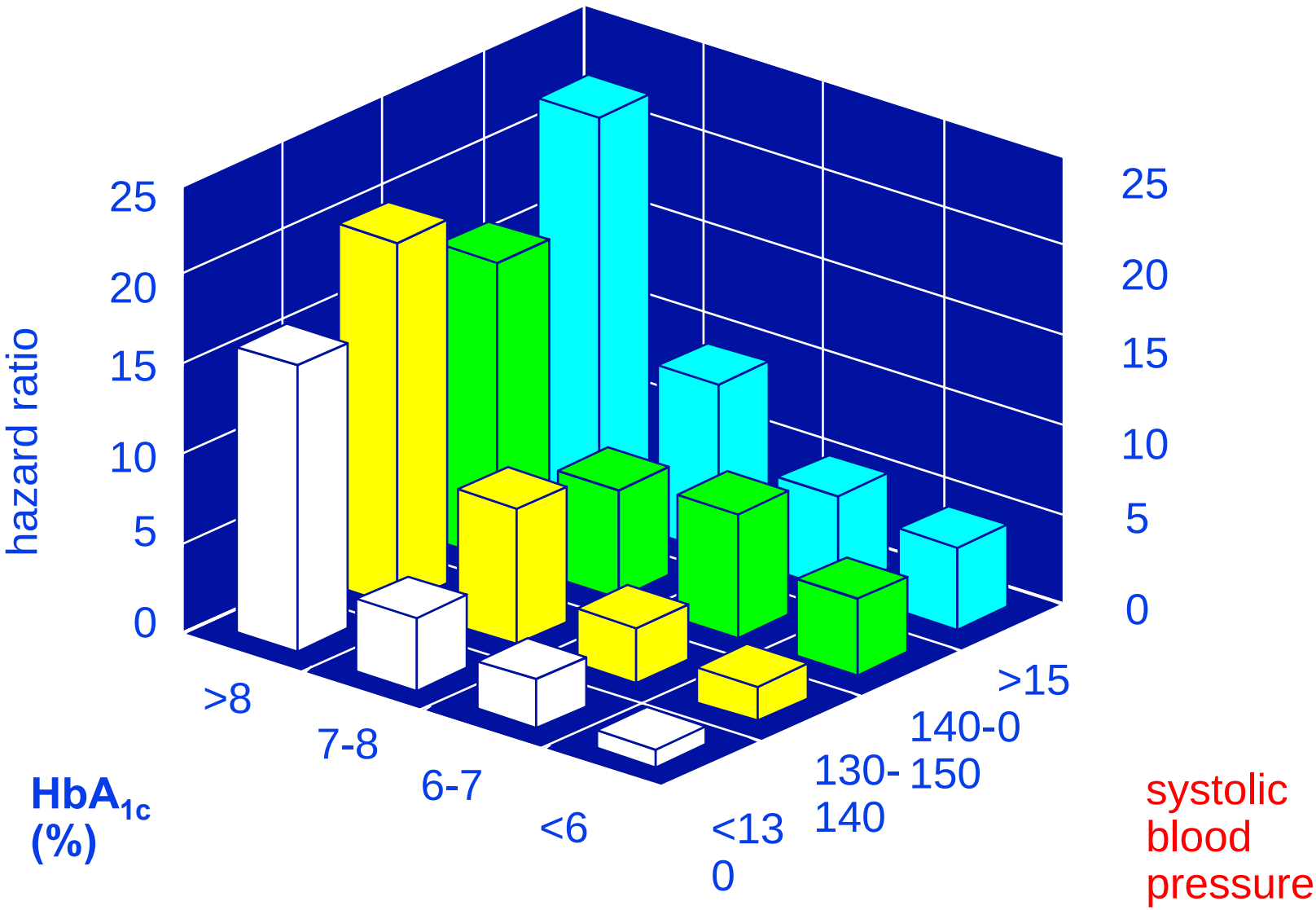
Diabetes related deaths



Any Diabetes Related endpoints



Microvascular endpoints



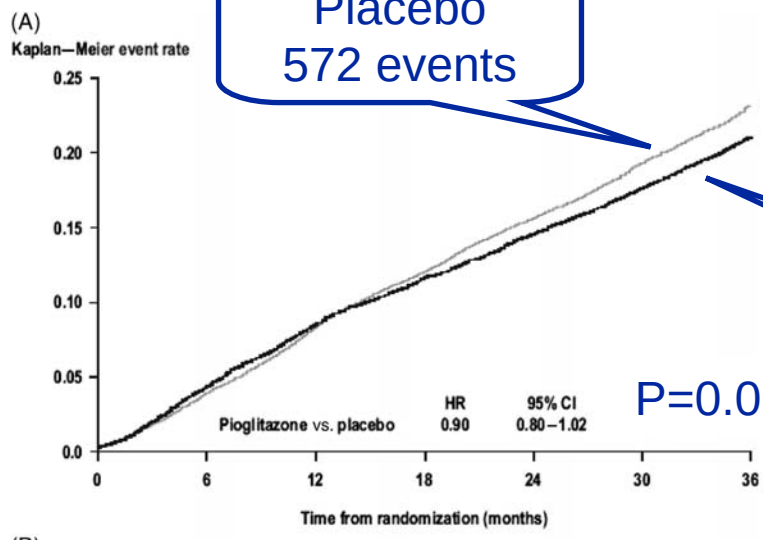
PROactive

PROactive

- Pioglitazone
- Secondary prevention in type 2 diabetes and macrovascular disease
- N=5238 Duration 34.5 months
- Primary outcome: composite of all-cause mortality, non-fatal MI (including silent MI), non-fatal stroke, major leg amputation, ACS, cardiac intervention (bypass graft or percutaneous coronary intervention), and leg revascularization

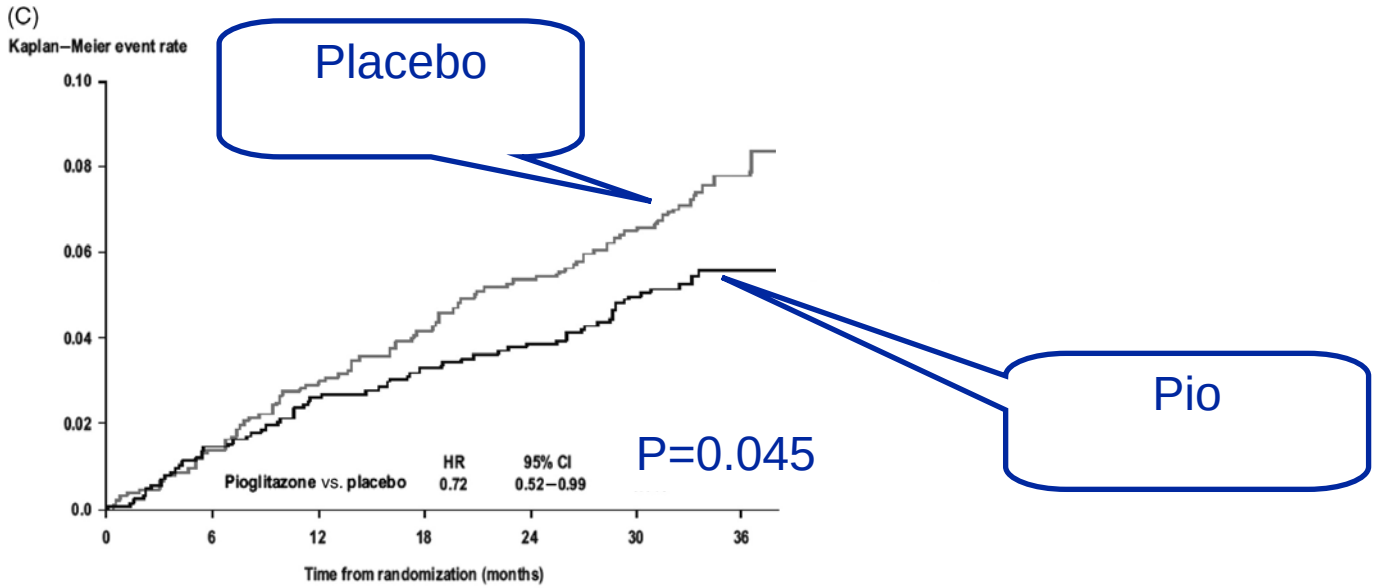
Proactive composite outcome

Primary composite event rate



Betteridge, D. J. et al. Eur Heart J 2008 29:969-983

Fatal and non-fatal MI



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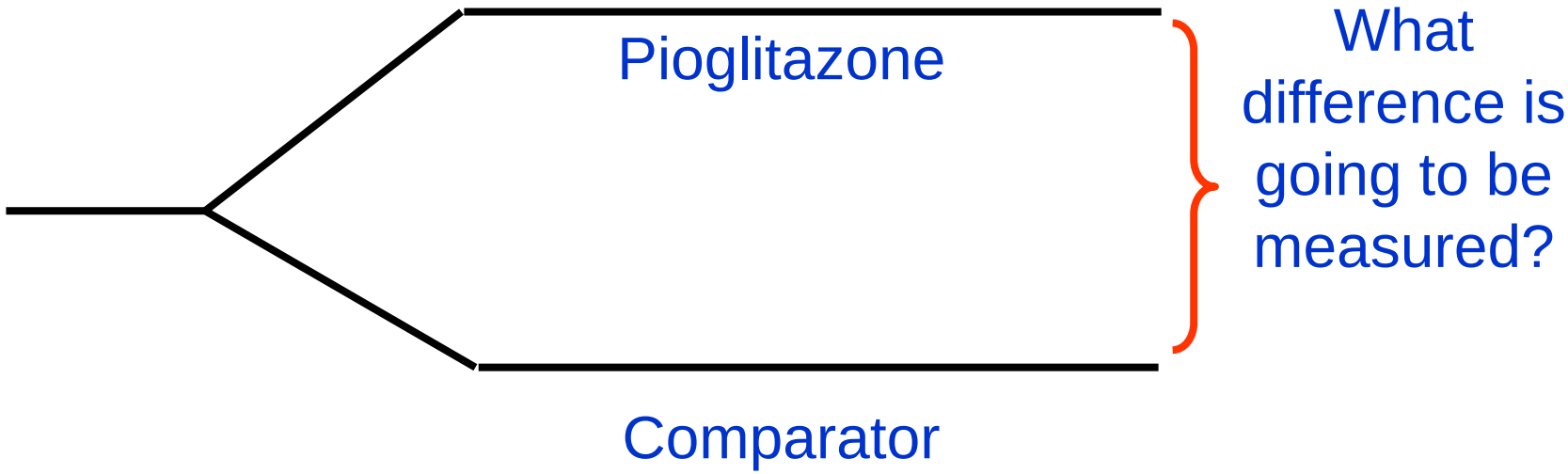
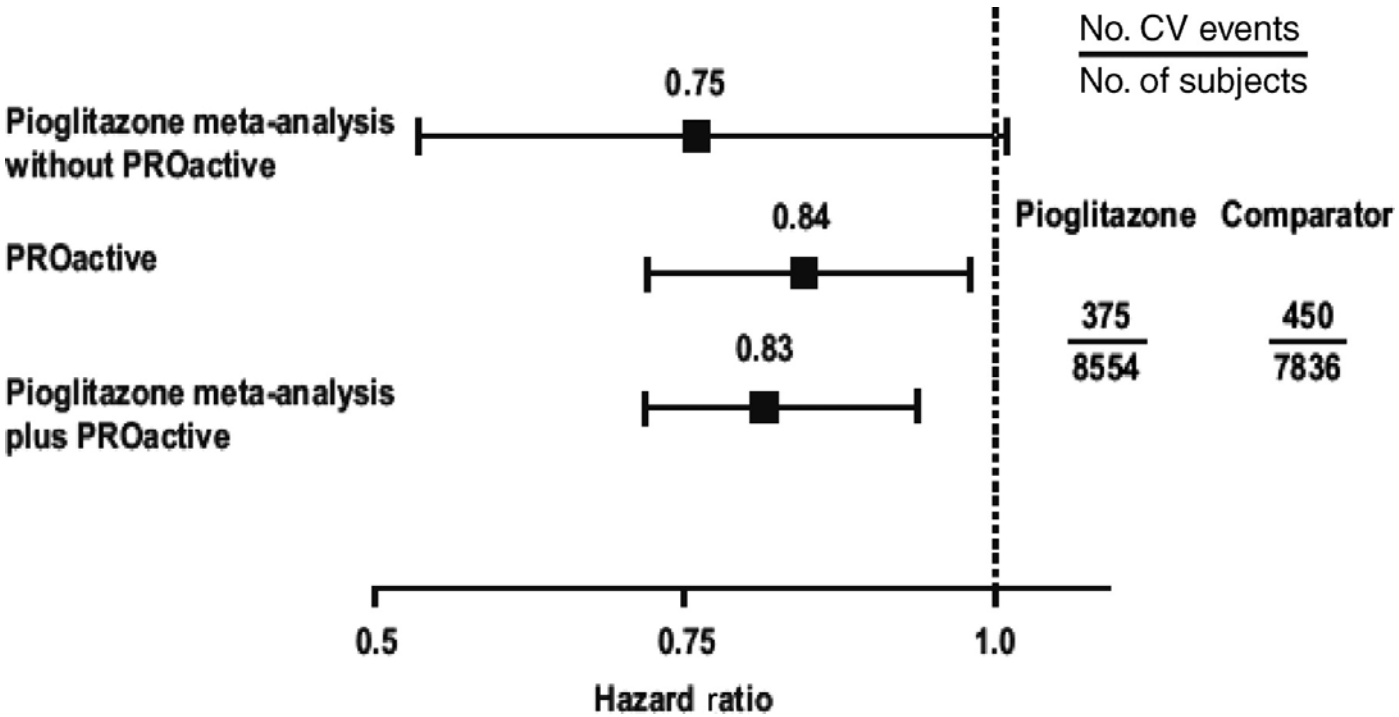
ProActive


Pioglitazone
Comparator
What difference is going to be measured?

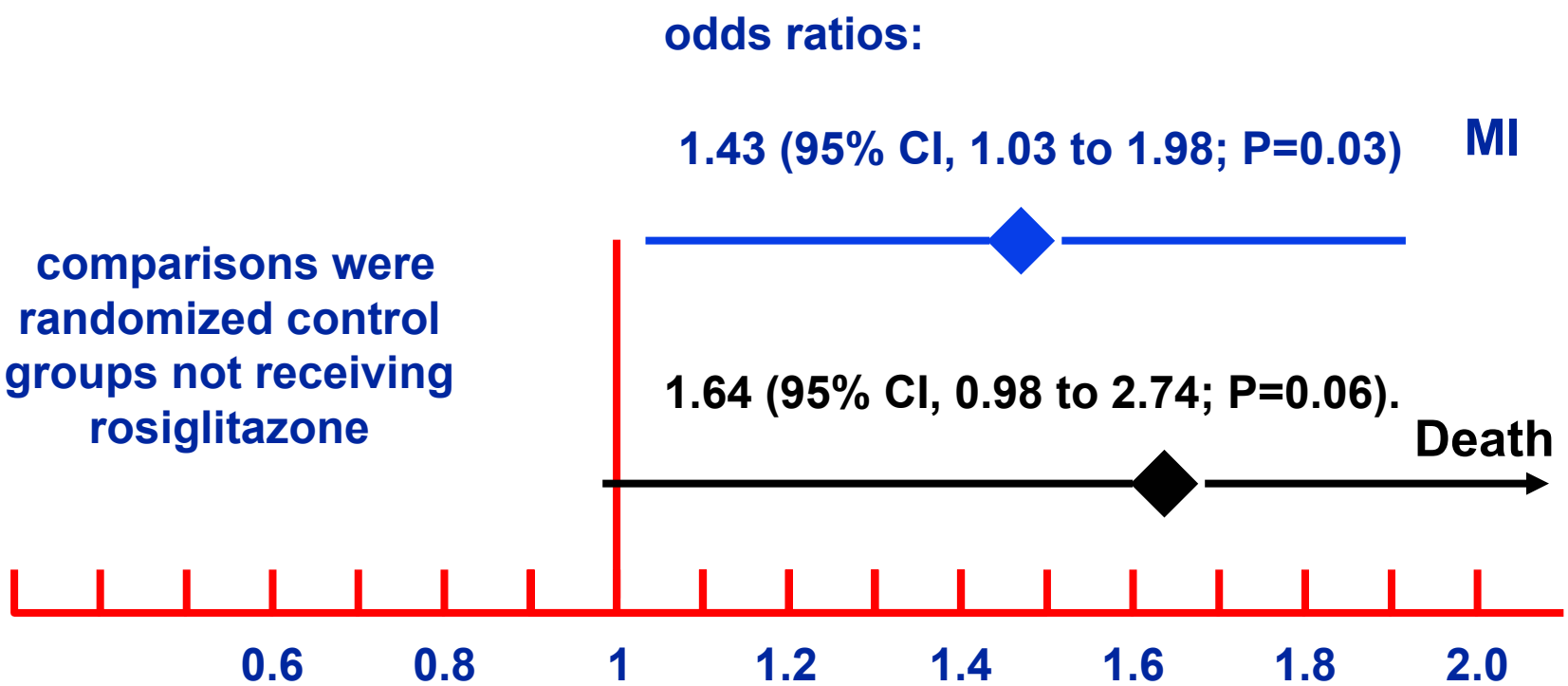
Pioglitazone meta-anlyses



Betteridge, D. J. et al. Eur Heart J 2008 29:969-983

Rosiglitazone Meta-analysis

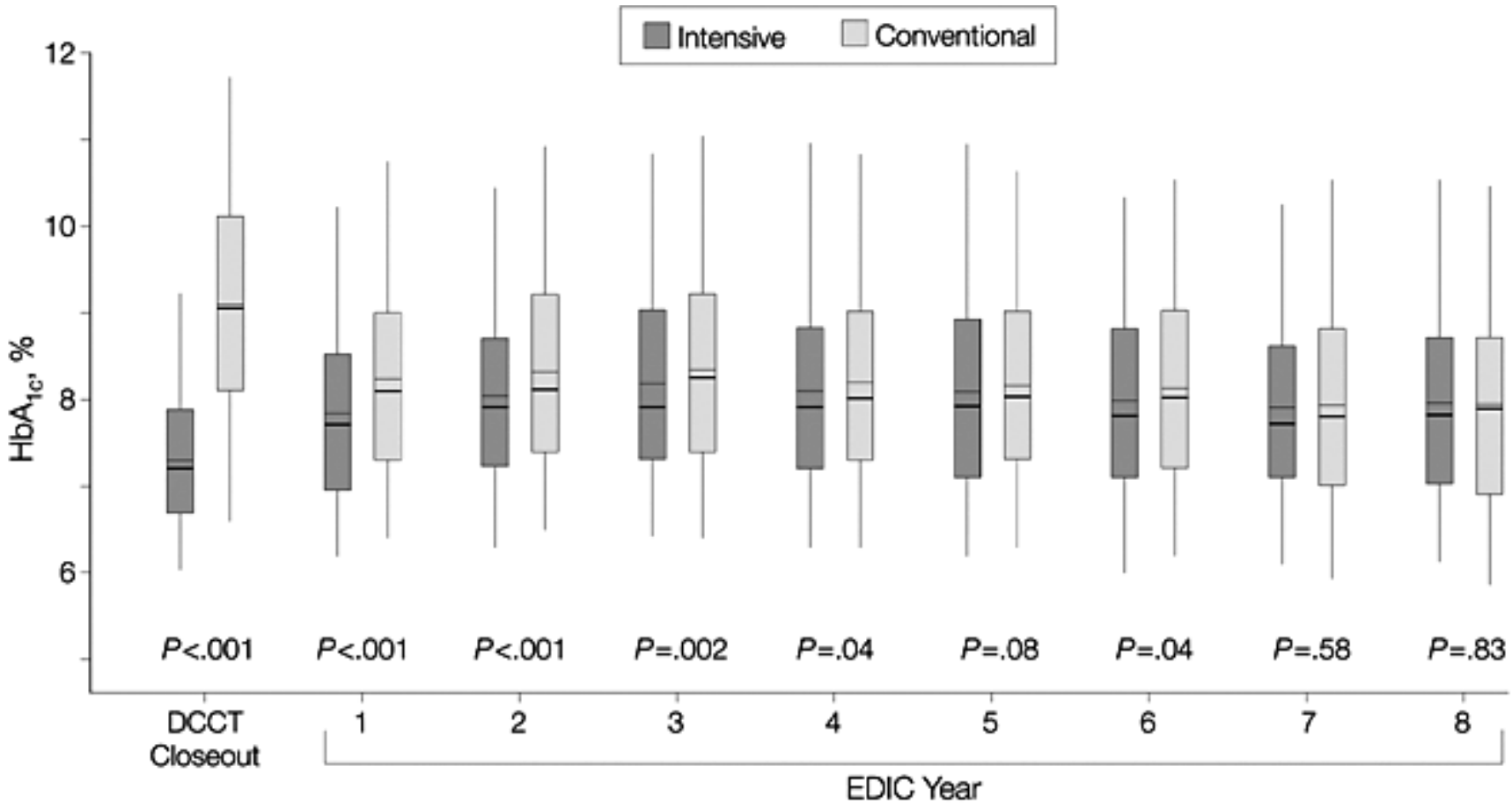
42 trials
study duration of more than 24 weeks
mean age 56 years; baseline HbA1c 8.2%



Nissen N Engl J Med. 2007 Jun 14;356(24):2457-71.

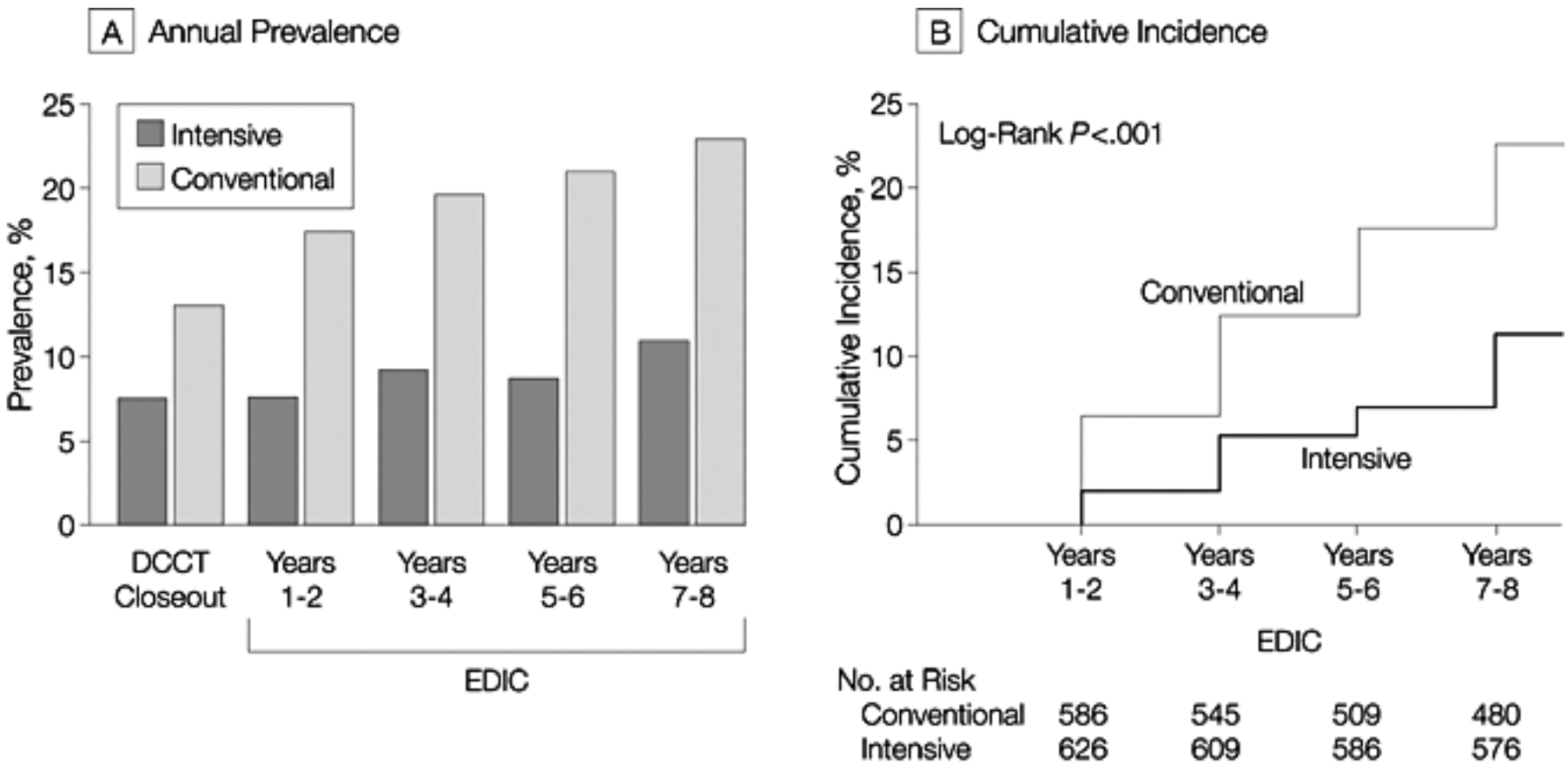
EDIC
(DCCT post trial monitoring)

Distribution of HbA1c Concentration by Randomized Treatment Group at the End of the DCCT and in Each Year of the EDIC Study



JAMA 2003;290:2159-2167.

Prevalence and Cumulative Incidence of Microalbuminuria



JAMA 2003;290:2159-2167.

JAMA

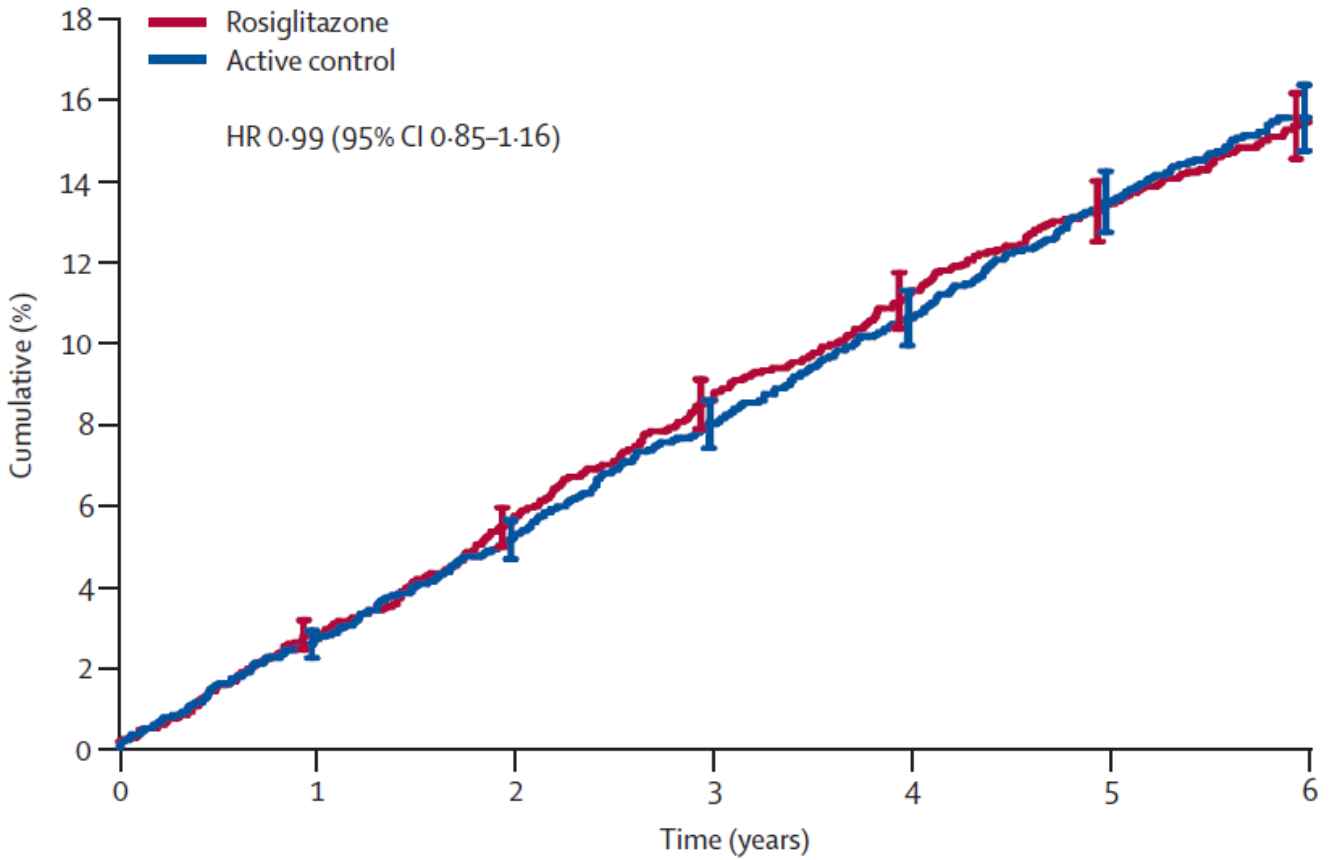
RECORD

RECORD

- An outcome trial of Rosiglitazone: interim results
- The interim results for the primary end point were inconclusive
- a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) on the basis of events adjudicated by the committee reviewing clinical end points.
- In any interim trial report, there are inevitably some potential primary events pending adjudication. Adding in these pending events increased the hazard ratio to 1.11 (95% CI, 0.93 to 1.32).

Home, P.D. et al

RECORD

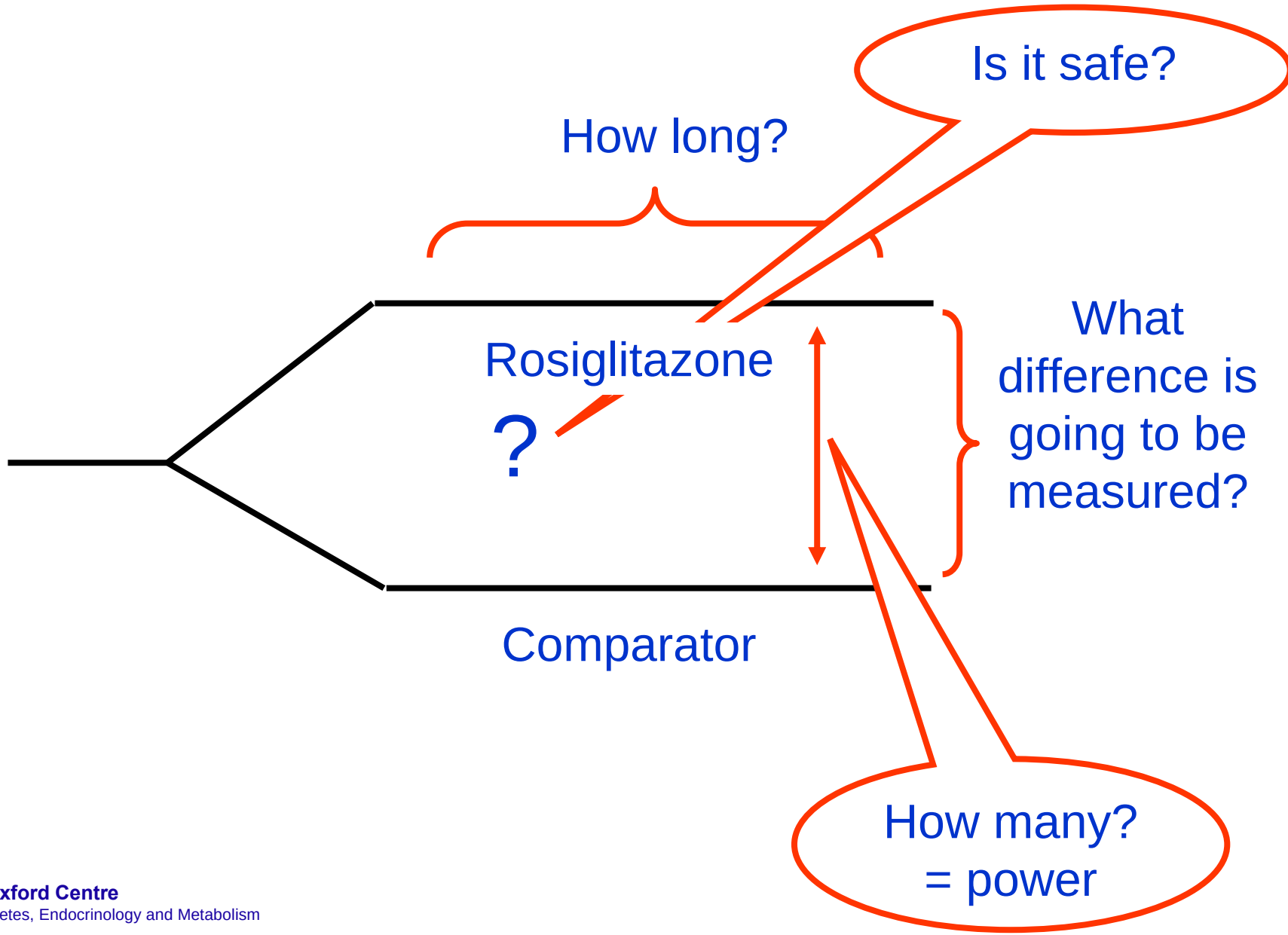


Number at risk

Rosiglitazone	2220	2086	1981	1883	1795	1720	918
Active control	2227	2101	1995	1895	1798	1697	908

Figure 2: **Kaplan-Meier plots of time to the primary endpoint (cardiovascular death or cardiovascular hospitalisation)**
HR=hazard ratio.

RECORD


Is it safe?
How long?
Rosiglitazone
?
What difference is going to be measured?
Comparator
How many? = power

ACCORD

ACCORD (Action to Control Cardiovascular Risk in Diabetes) Design

to determine whether intensively lowering blood sugar would reduce the risk of cardiovascular events such as heart attack, stroke, or death from cardiovascular disease, specifically in people with type 2 diabetes who are at particularly high risk for a cardiovascular event

Accord Study design

- 77 sites USA and Canada,
- includes adults
- ages of 40 – 82y at enrolment
- type 2 diabetes,
- PLUS:
  - two or more other risk factors for heart disease
  - or had been diagnosed with heart disease before entering the study.

Enrolment

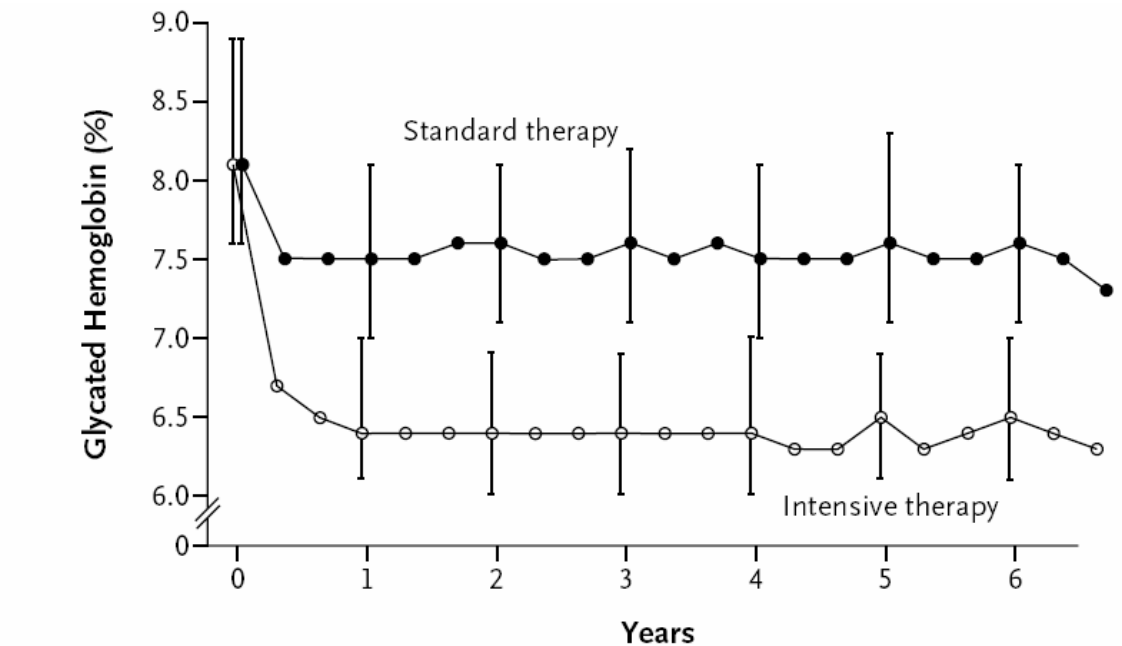
- average diabetes duration of 10 years at enrolment,
- randomly assigned to either standard (n=5,123 participants) or intensive (n=5,128) blood sugar treatment goals.
- also enrolled in one of two other ACCORD randomized clinical trials examining effects of treatments for blood pressure or blood lipids.

ACCORD: Patient Characteristics

Table 1. Characteristics of the Patients at Baseline.*

Variable	Intensive Therapy (N = 5128)	Standard Therapy (N = 5123)
Age (yr)	62.2±6.8	62.2±6.8
Median duration of diabetes (yr)	10	10
Previous cardiovascular event (%)	35.6	34.8
Previous congestive heart failure (%)	4.9	4.8

Glucose control in ACCORD



No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Treatments in intensive control group

Insulin 77%

TZD 92%

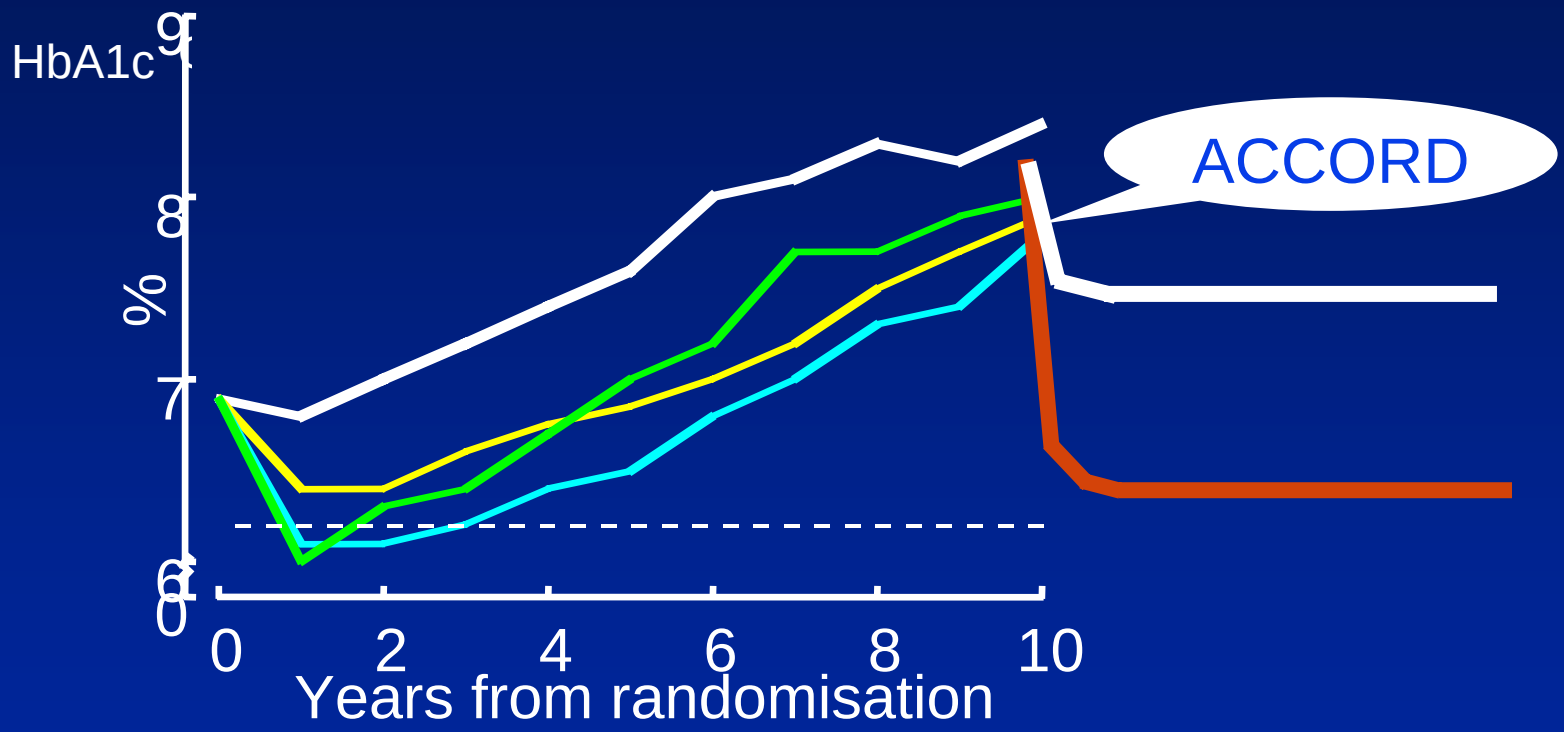
SU 78%

Metformin 95%

N Engl J Med 2008;358:2545-59

UKPDS and ACCORD

cohort, median data



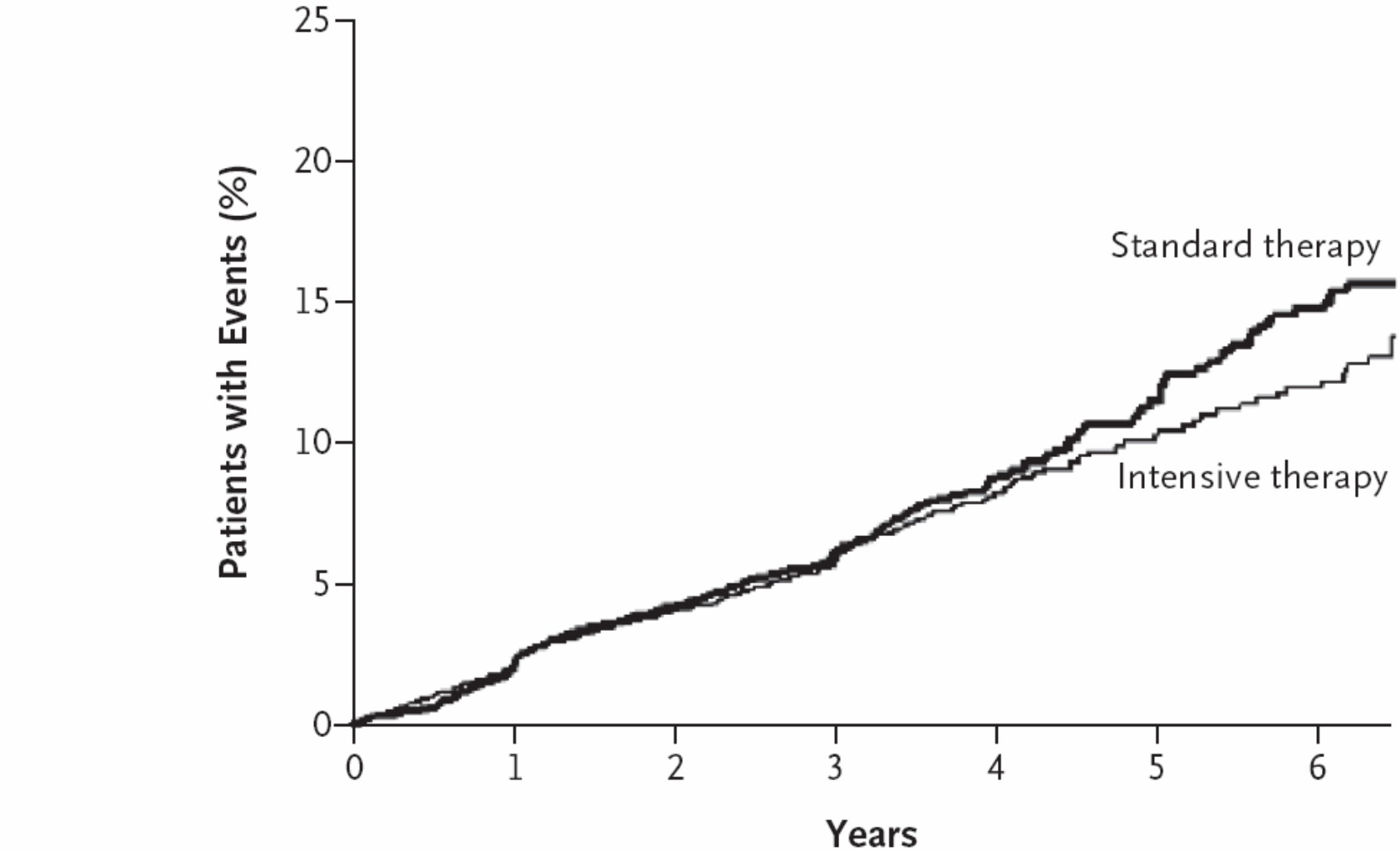
ACCORD

Primary outcome

The first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes.

The latter included death from myocardial infarction, heart failure, arrhythmia, invasive cardiovascular interventions, cardiovascular causes after noncardiovascular surgery, stroke, unexpected death presumed to be from ischaemic cardiovascular disease occurring within 24 hours after the onset of symptoms, and death from other vascular diseases.

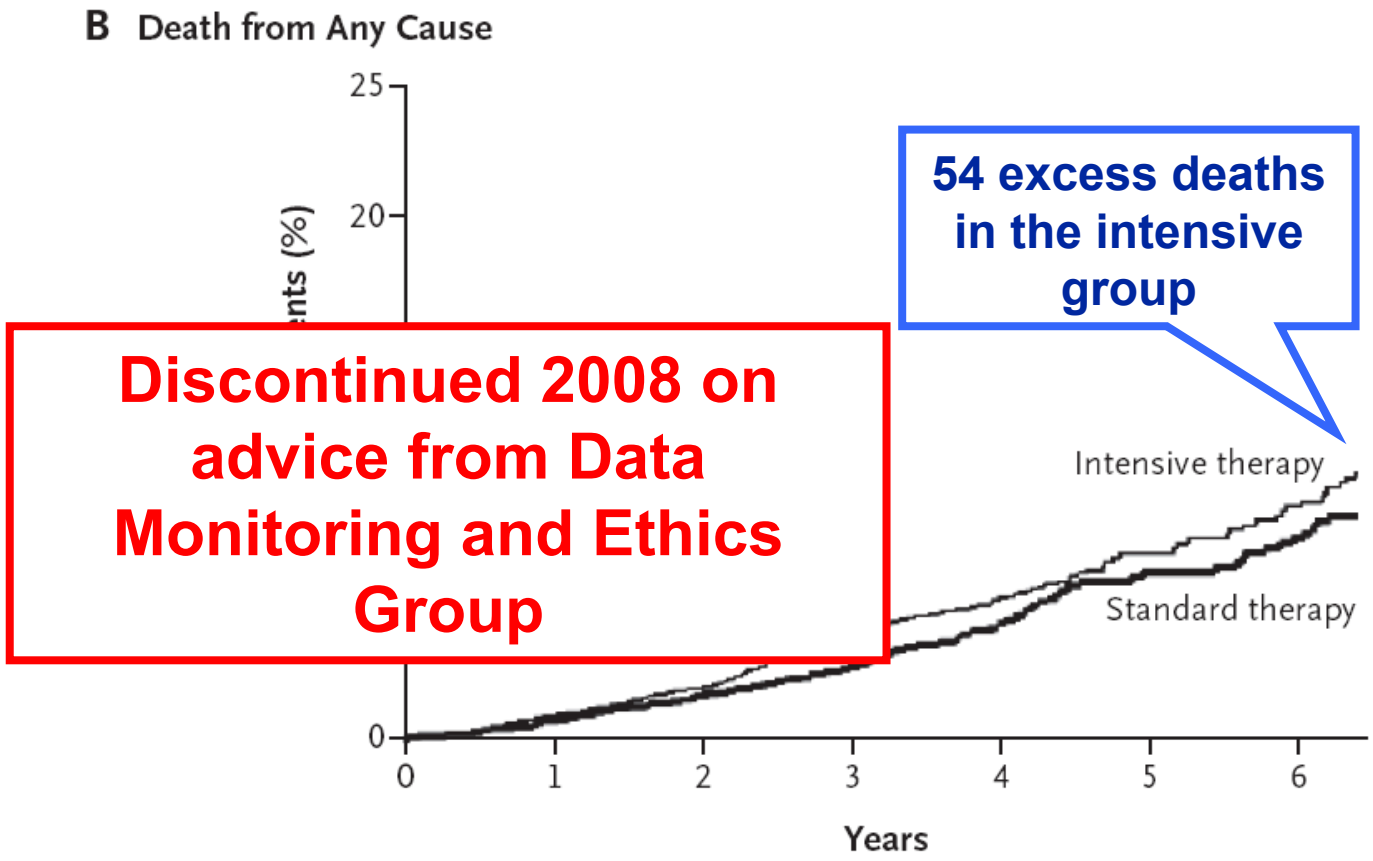
ACCORD



No. at Risk

Intensive therapy	5128	4843	4390	2839	1337	475	448
Standard therapy	5123	4827	4262	2702	1186	440	395

ACCORD



54 excess deaths in the intensive group

Discontinued 2008 on advice from Data Monitoring and Ethics Group

257 deaths

203 deaths

Figure 2. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.

Risk profile high

Participants were included in the ACCORD trial because they were at especially high risk—more risk than is associated with diabetes alone—for having a heart attack, stroke, or of dying from cardiovascular disease.

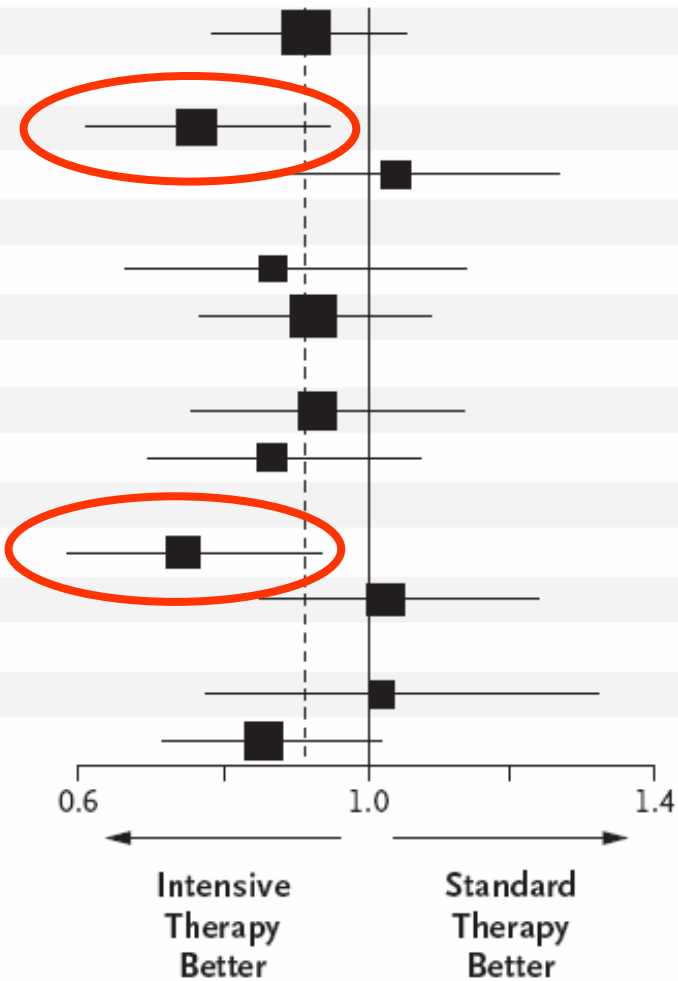
HbA1c

- intensive treatment group participants achieved, on average, A1C values lower than standard treatment group participants.
- half of the participants in the intensive treatment group achieved an A1C of less than 6.4 percent
- half of the participants in the standard treatment group achieved an A1C of less than 7.5 percent.
- The average blood sugar levels for both groups were lower than when they entered the study

ACCORD Primary outcome

A Primary Outcome

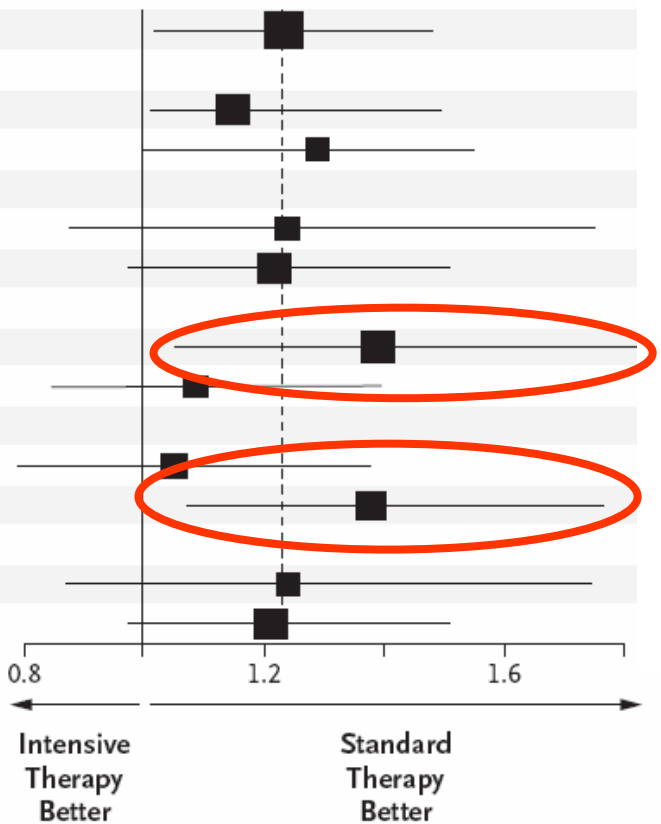
Subgroup	No. of Patients	No. of Events	P Value
Total	10,251	723	
Previous cardiovascular event			0.04
No	6,643	330	
Yes	3,608	393	
Sex			0.74
Female	3,952	212	
Male	6,299	511	
Age at baseline			0.65
<65 yr	6,779	383	
≥65 yr	3,472	340	
Glycated hemoglobin at baseline			0.03
≤8.0%	4,868	284	
>8.0%	5,360	438	
Race			0.29
Nonwhite	3,647	222	
White	6,604	501	



ACCORD death from any cause

B Death from Any Cause

Subgroup	No. of Patients	No. of Events
Total	10,251	460
Previous cardiovascular event		
No	6,643	220
Yes	3,608	240
Sex		
Female	3,952	132
Male	6,299	328
Age at baseline		
<65 yr	6,779	212
≥65 yr	3,472	248
Glycated hemoglobin at baseline		
≤8.0%	4,868	204
>8.0%	5,360	256
Race		
Nonwhite	3,647	131
White	6,604	329



Younger

Higher A1c

ACCORD

Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

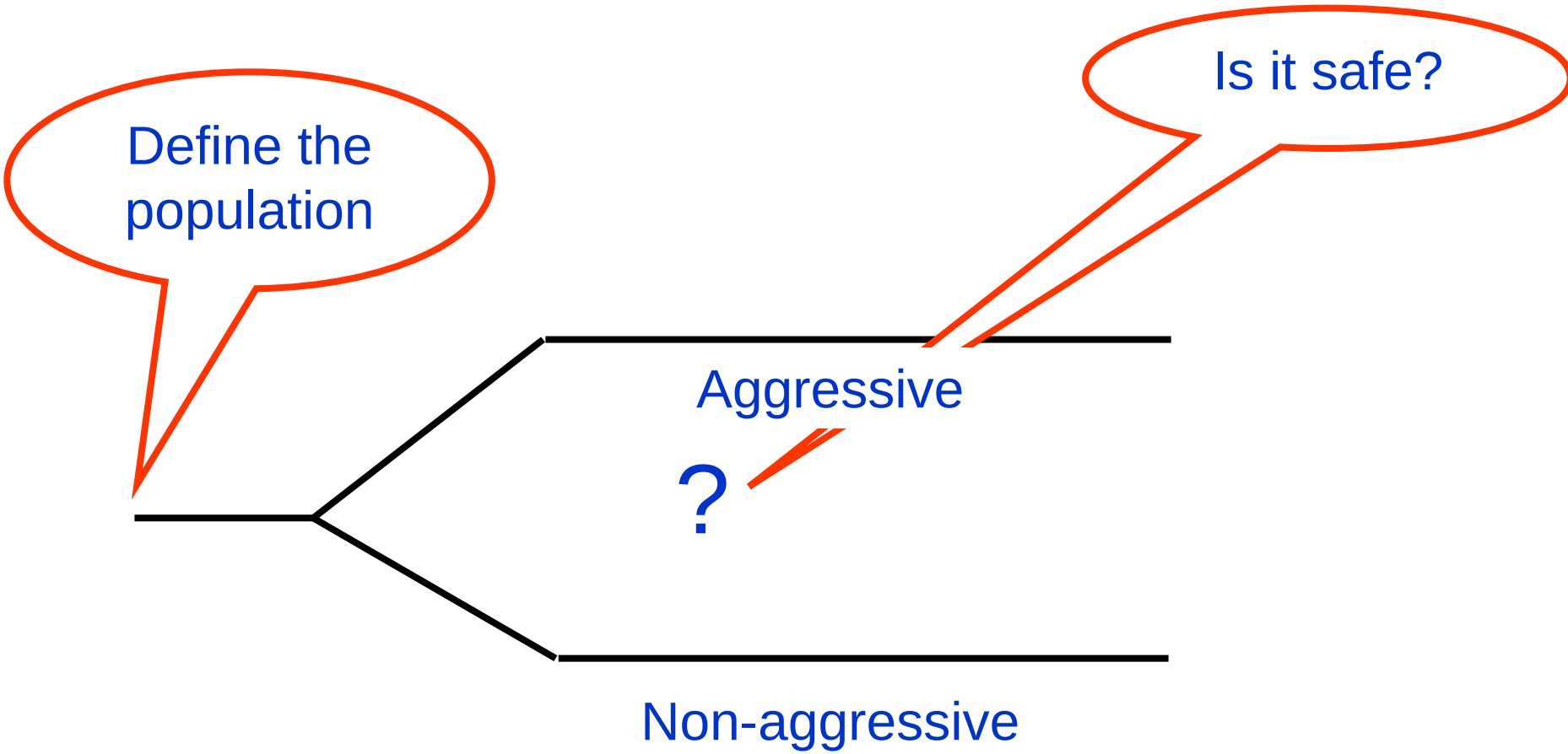
Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001

The problem

- enrolled
- Of thes
  compar
  group.
- This is a differe ,000 participants each year, over an average of almost four years of treatment.
- Participants had been followed for 2 years to 7 years at the time the intensive blood sugar control treatment was stopped
- The death rates in both groups were lower than seen in similar populations in other studies.

(14 deaths per 1000 patients per year versus 11 per 1000 patients per year in the standard treatment program; a difference of 0.3 deaths per 100 patients per year).

ACCORD


Define the population
Is it safe?
Aggressive
?
Non-aggressive

ADVANCE

ADVANCE Inclusion criteria

- Type 2 diabetes mellitus
- Age 55 years or older
- Additional risk of vascular event
  - Age ≥ 65 years
  - History of major macrovascular disease
  - History of major microvascular disease
  - First diagnosis of diabetes >10 years prior to entry
  - Other major risk factor
- Any level of blood pressure
- Any level of glucose control but no definite indication for long-term insulin

ADVANCE: Patient Characteristics

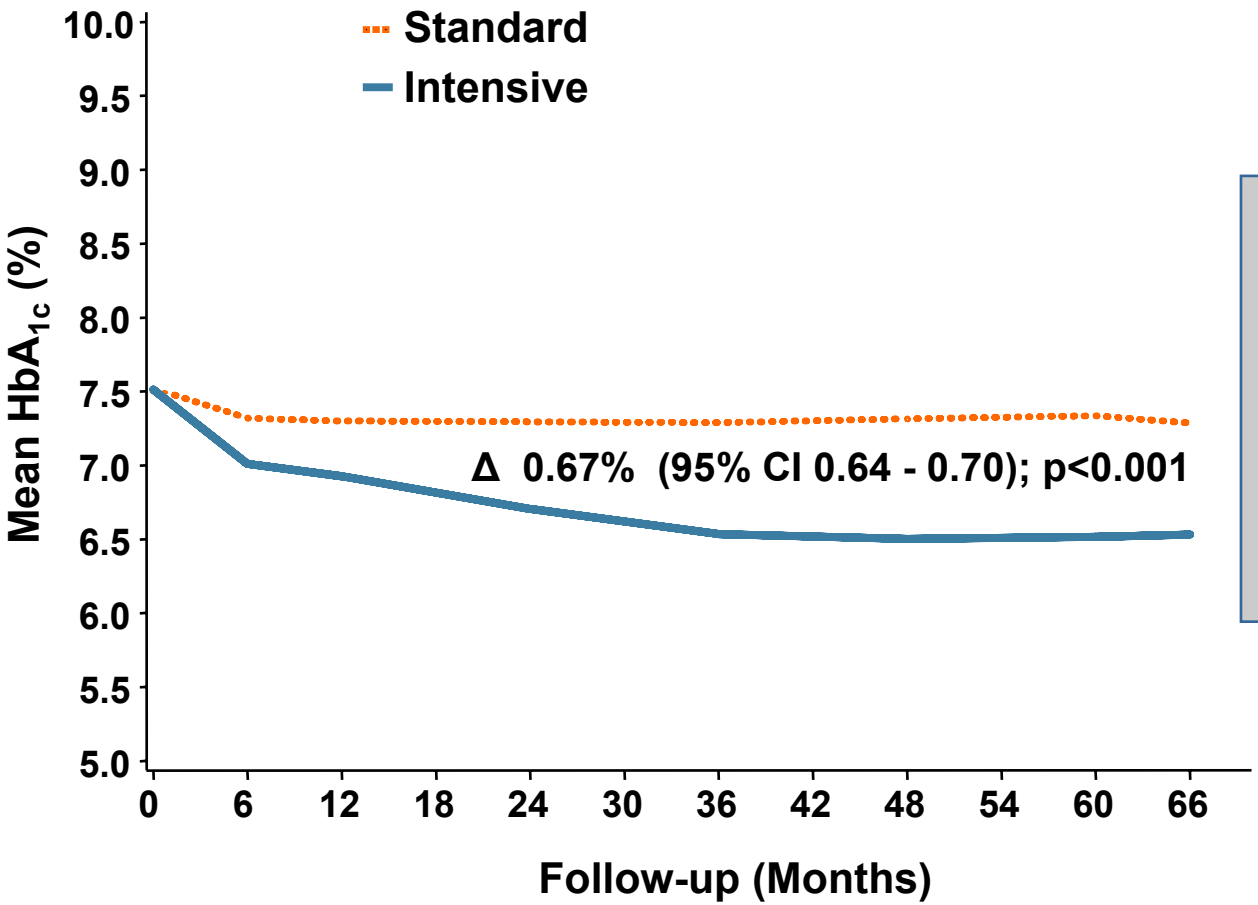
	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Age (years), mean (SD)	66 (6)	66 (7)
Age when diabetes first diagnosed (years), mean (SD)	58 (9)	58 (9)
Previous vascular disease		
History of major macrovascular disease, n (%)	1798 (32%)	1792 (32%)
History of myocardial infarction, n (%)	678 (12%)	656 (12%)
History of stroke, n (%)	502 (9%)	520 (9%)
History of major microvascular disease, n (%)	568 (10%)	584 (10%)
History of macroalbuminuria†, n (%)	197 (4%)	204 (4%)
History of microvascular eye disease‡, n (%)	389 (7%)	404 (7%)
Blood pressure control		
Systolic blood pressure (mm Hg), mean (SD)	145 (22)	145 (21)
Diastolic blood pressure (mm Hg), mean (SD)	81 (11)	81 (11)
History of currently treated hypertension, n (%)	3802 (68%)	3853 (69%)

8 Years

ADVANCE
Intensive glucose control strategy

- More frequent visits
- Emphasis on lifestyle management
- Drug titration at physician's discretion based on HbA_{1c} and FBG levels:
  - Maximize gliclazide MR dose
  - Add other oral agents
  - Add long-acting insulin
  - Use multiple insulin injection therapy

ADVANCE Hemoglobin A_{1c}

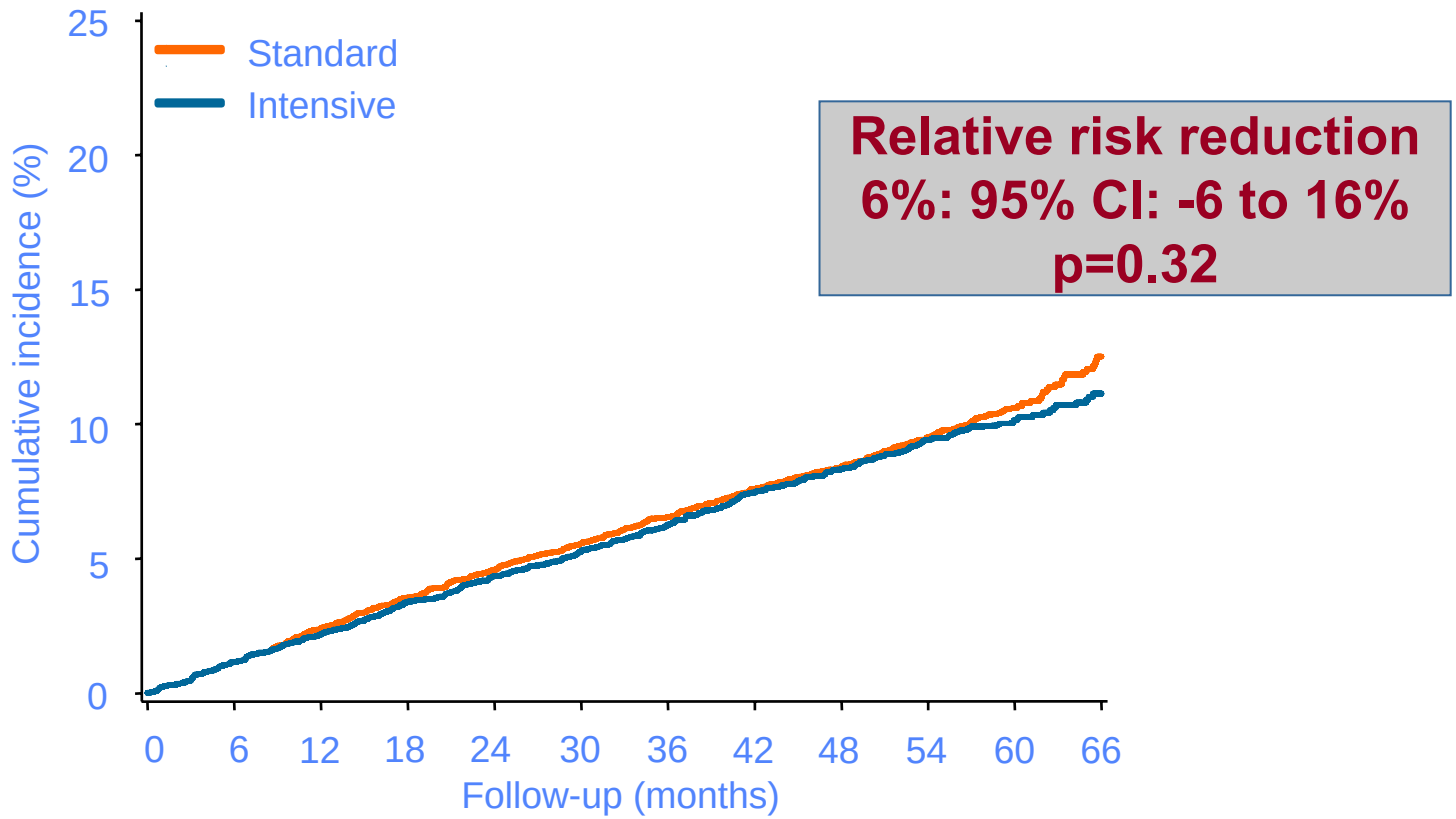


Mean HbA_{1c} at final visit

7.3 %

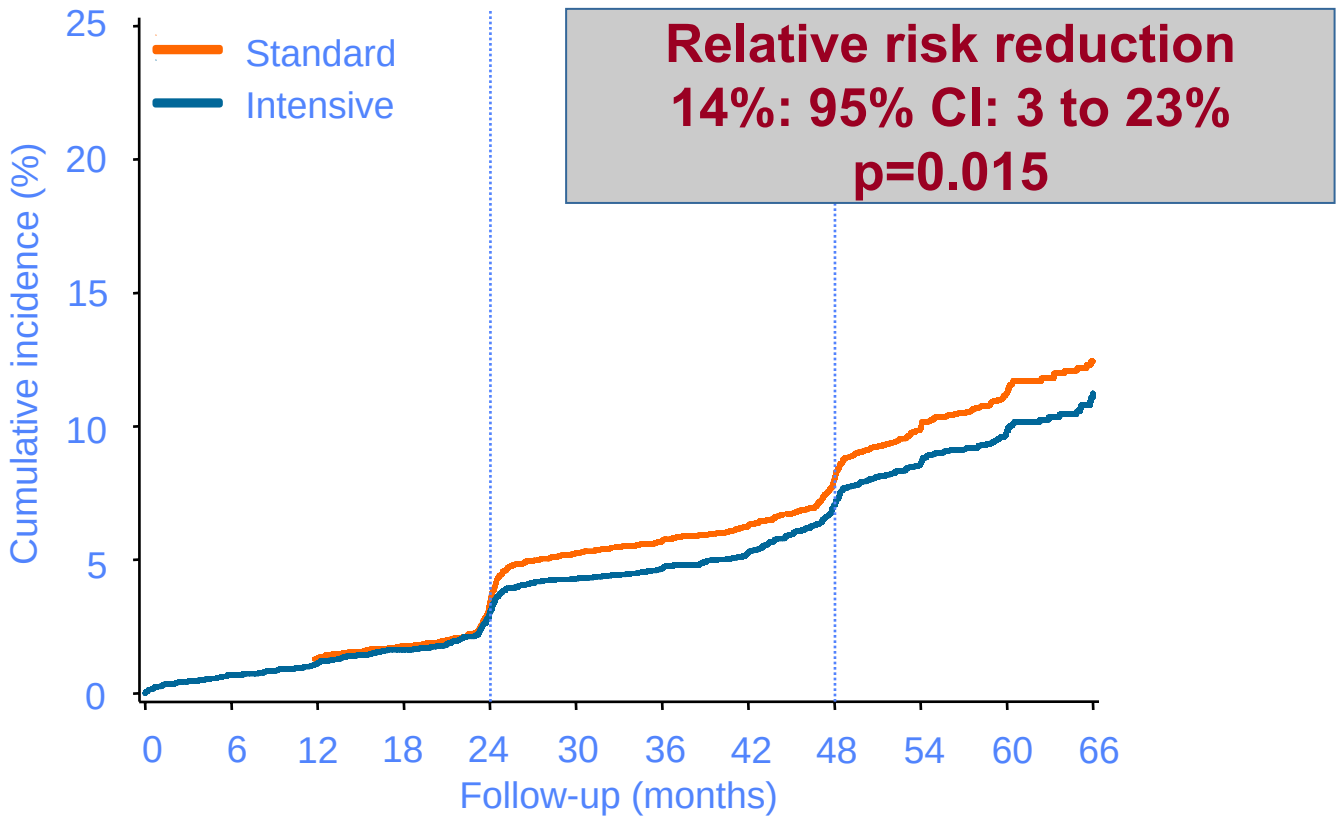
6.5%

ADVANCE
Major macrovascular events

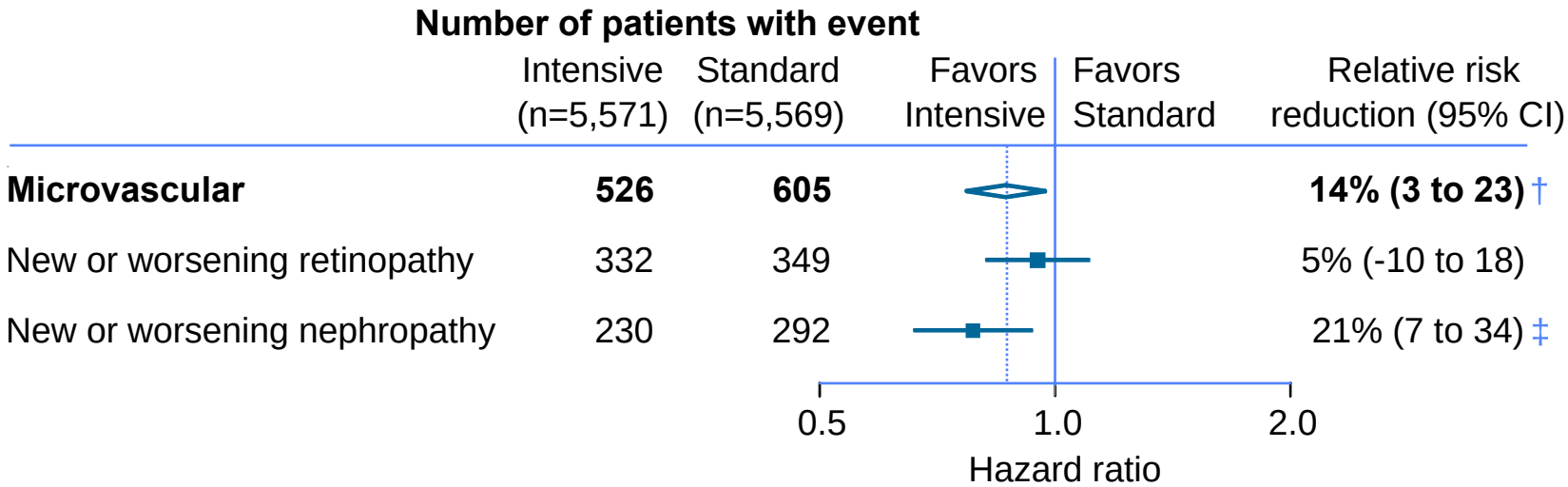


Relative risk reduction
6%: 95% CI: -6 to 16%
p=0.32

ADVANCE
Major microvascular events



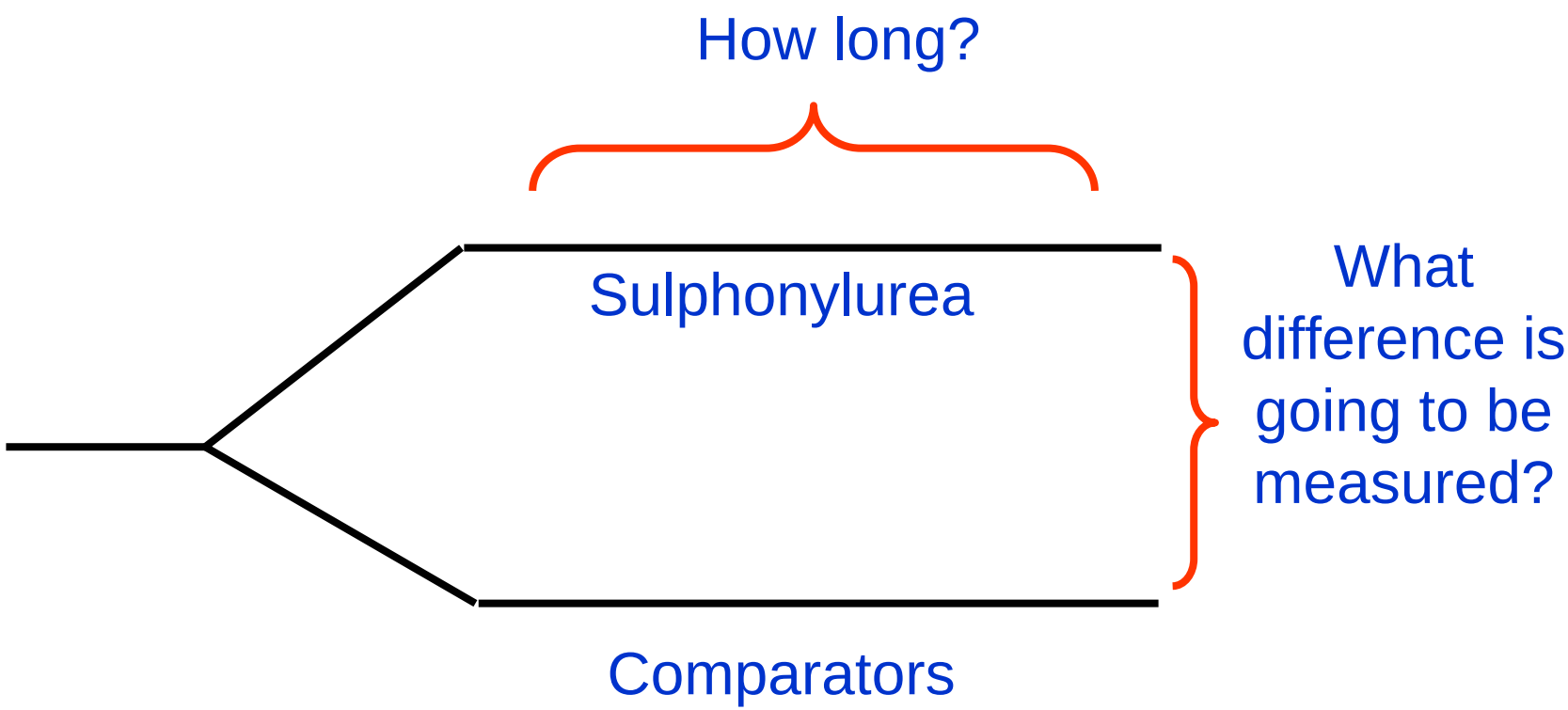
ADVANCE
Major microvascular events



†P=0.01

‡P=0.006

ADVANCE


How long?
Sulphonylurea
What difference is going to be measured?
Comparators

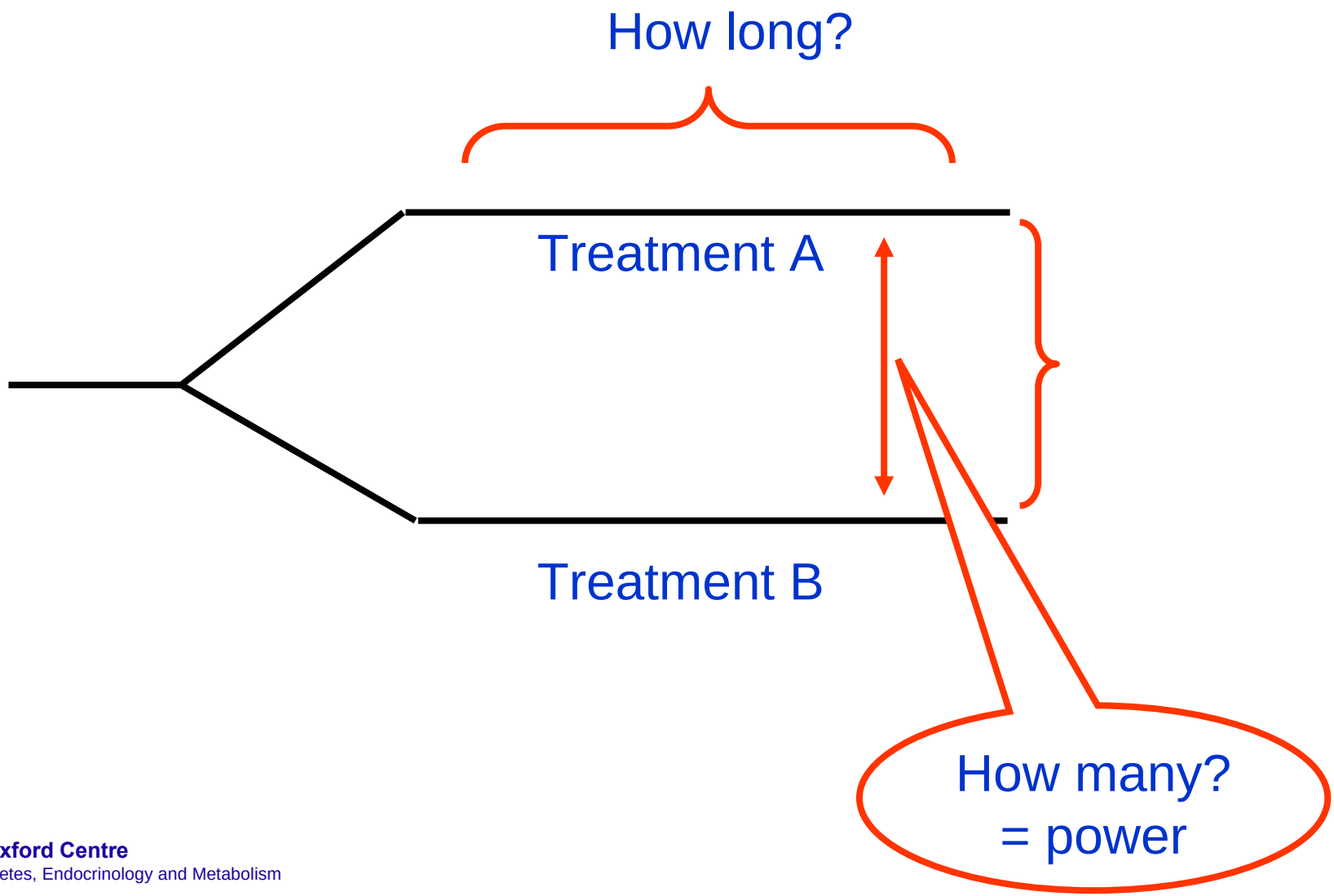
VADT

VADT

- 20 centres
- 1791 patients
- Major CVD events
- 97% male
- Duration 7.5 years
- median f-up 6 years
- Median 7% vs 8.4% HbA1c in groups
- No difference in cardiovascular outcome

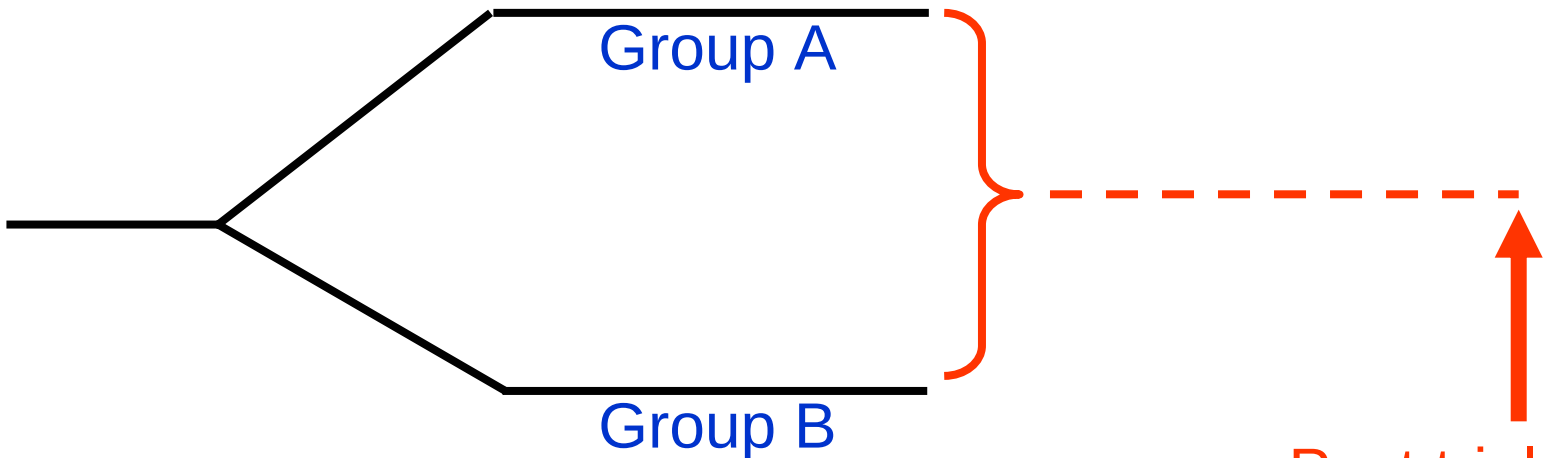
Underpowered trial

VADT



At the end of a trial
all subjects are
treated with the best
option

Trial



Did being in Group A or B
years ago make a difference
to what is happening now?

UKPDS Post Trial Monitoring

UK Prospective Diabetes Study

20-year Interventional Trial from 1977 to 1997

- 5,102 patients with newly-diagnosed type 2 diabetes recruited between 1977 and 1991
- Median follow-up 10.0 years, range 6 to 20 years
- Results presented at the 1998 EASD Barcelona meeting

10-year Post-Trial Monitoring from 1997 to 2007

- Annual follow-up of the survivor cohort
- Clinic-based for first five years
- Questionnaire-based for last five years

Median overall follow-up 17.0 years, range 16 to 30 years

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Post-Trial Monitoring: Aims

- To observe HbA_{1c} levels after cessation of the intervention trial
- To observe glucose therapy regimens after cessation of the intervention trial
- To determine the longer-term impact of earlier improved glucose control on microvascular and on macrovascular outcomes
- To evaluate the health economic implications with a projected 50% mortality at ten years post trial

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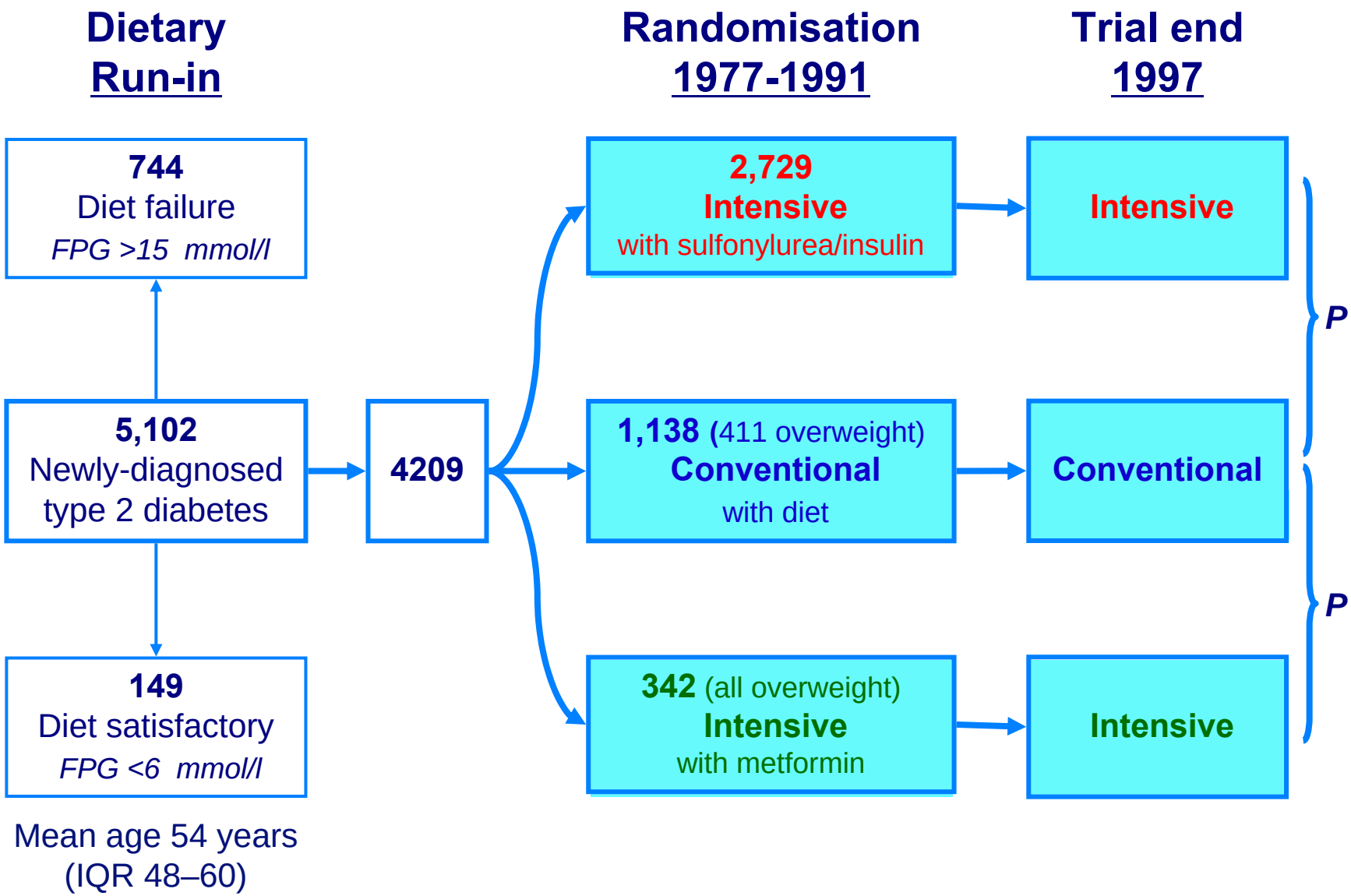
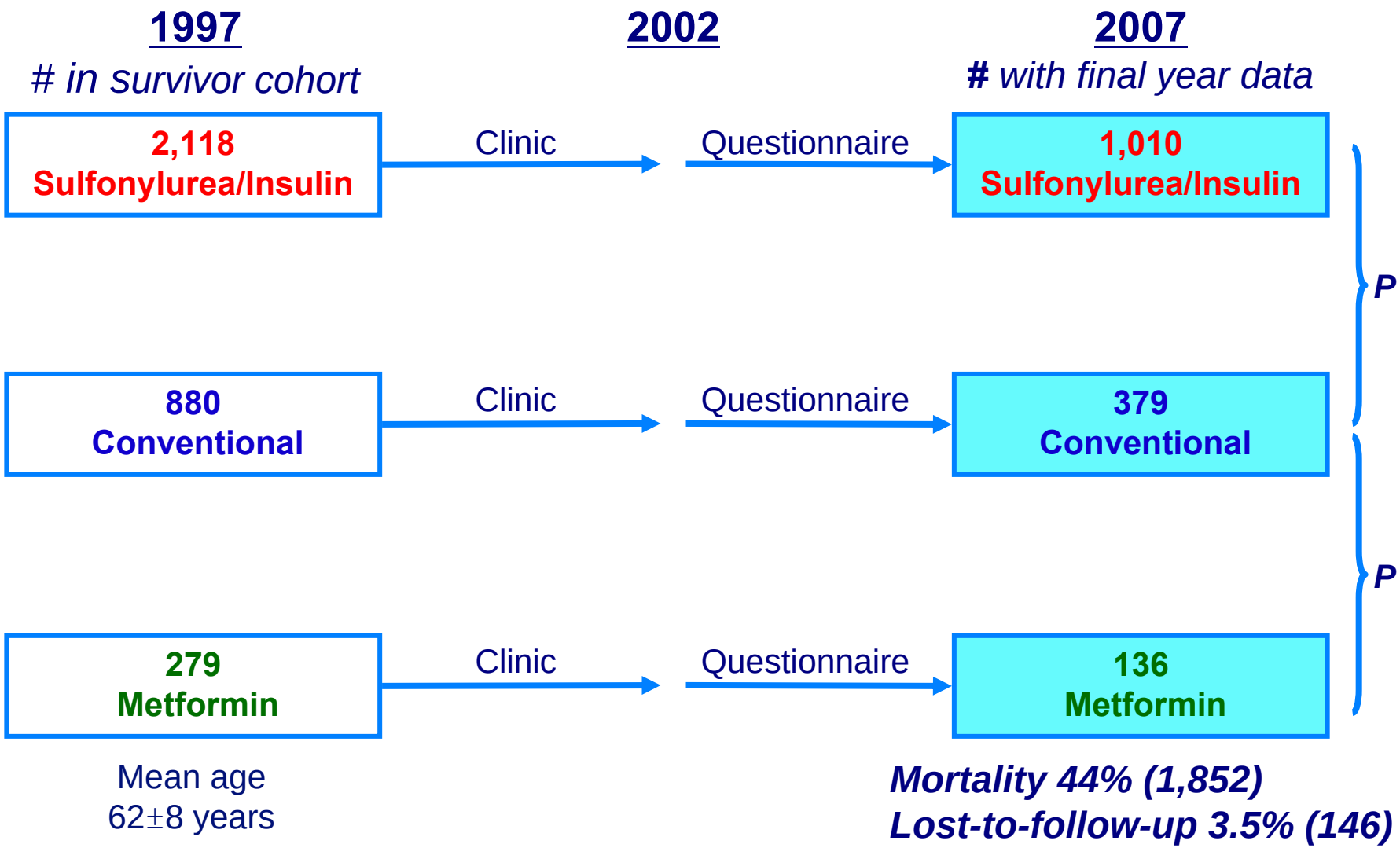
Glucose Interventional Trial



*UKPDS 8. Diabetologia 1991; **34**: 877-89*

Post-Trial Monitoring: Patients



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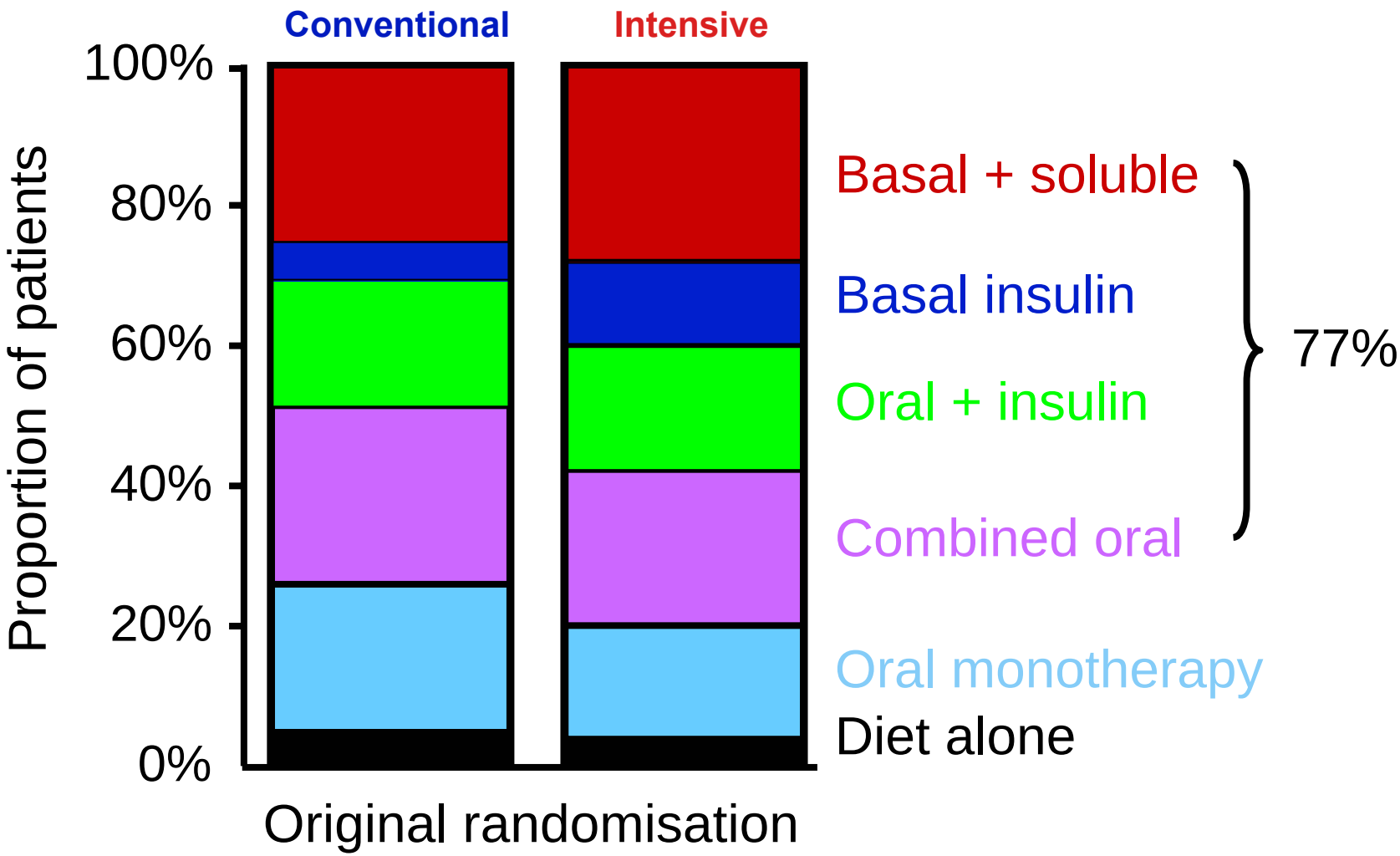
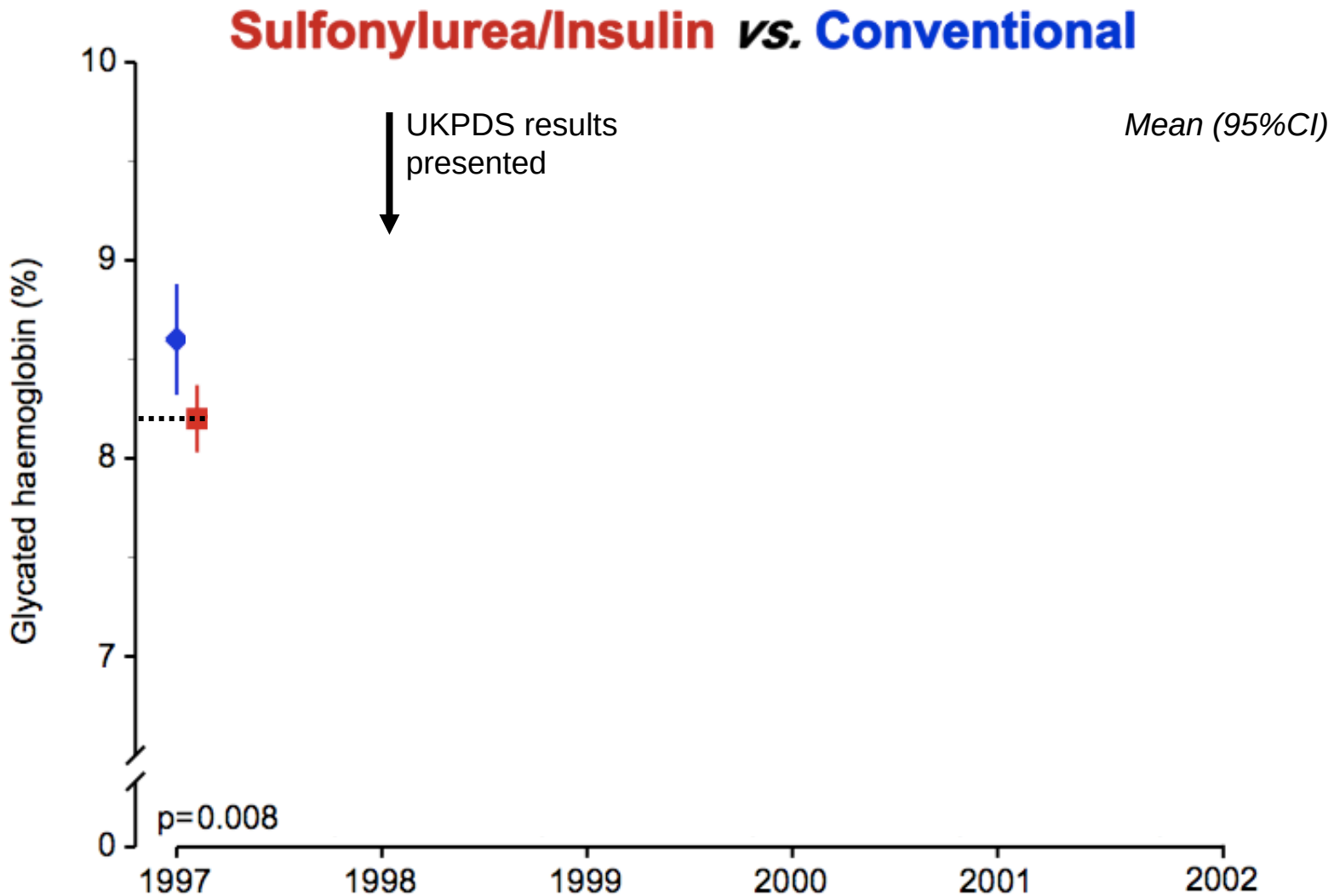
Therapy for Glycaemia at 5 Years



Post-Trial Changes in HbA_{1c}



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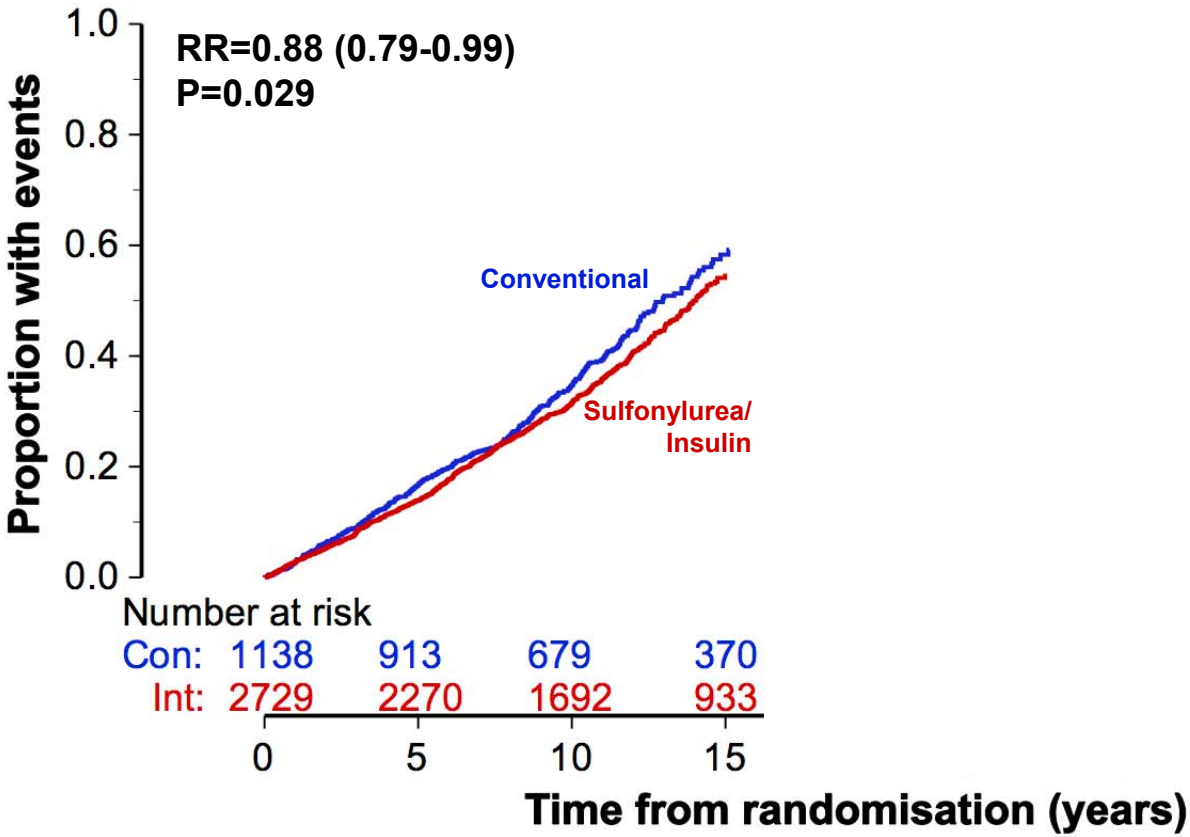
Any Diabetes-related Endpoint

A “legacy effect” of prior improved glucose control



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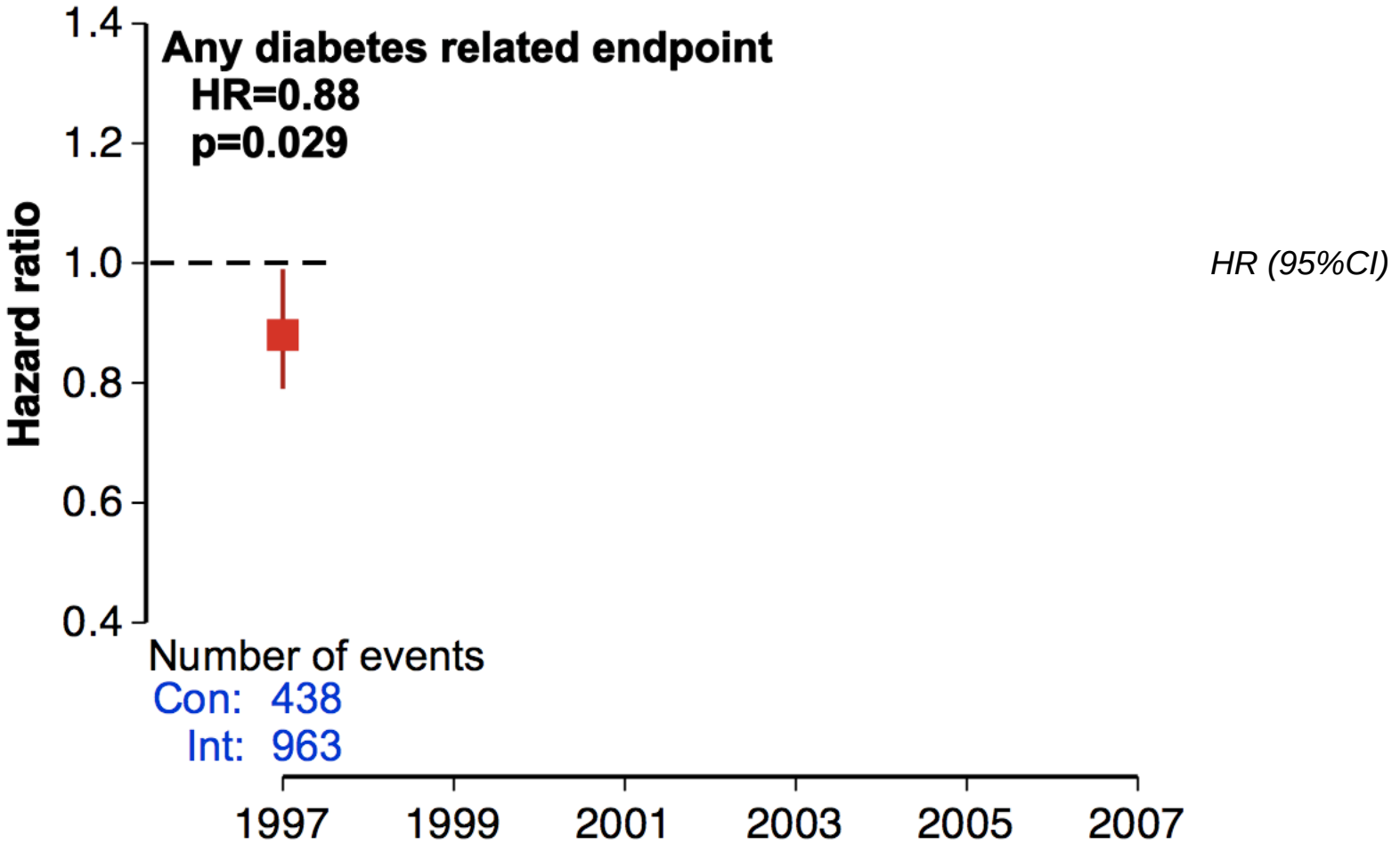
Any Diabetes Related Endpoint Hazard Ratio

Intensive (SU/Ins) *vs.* Conventional glucose control



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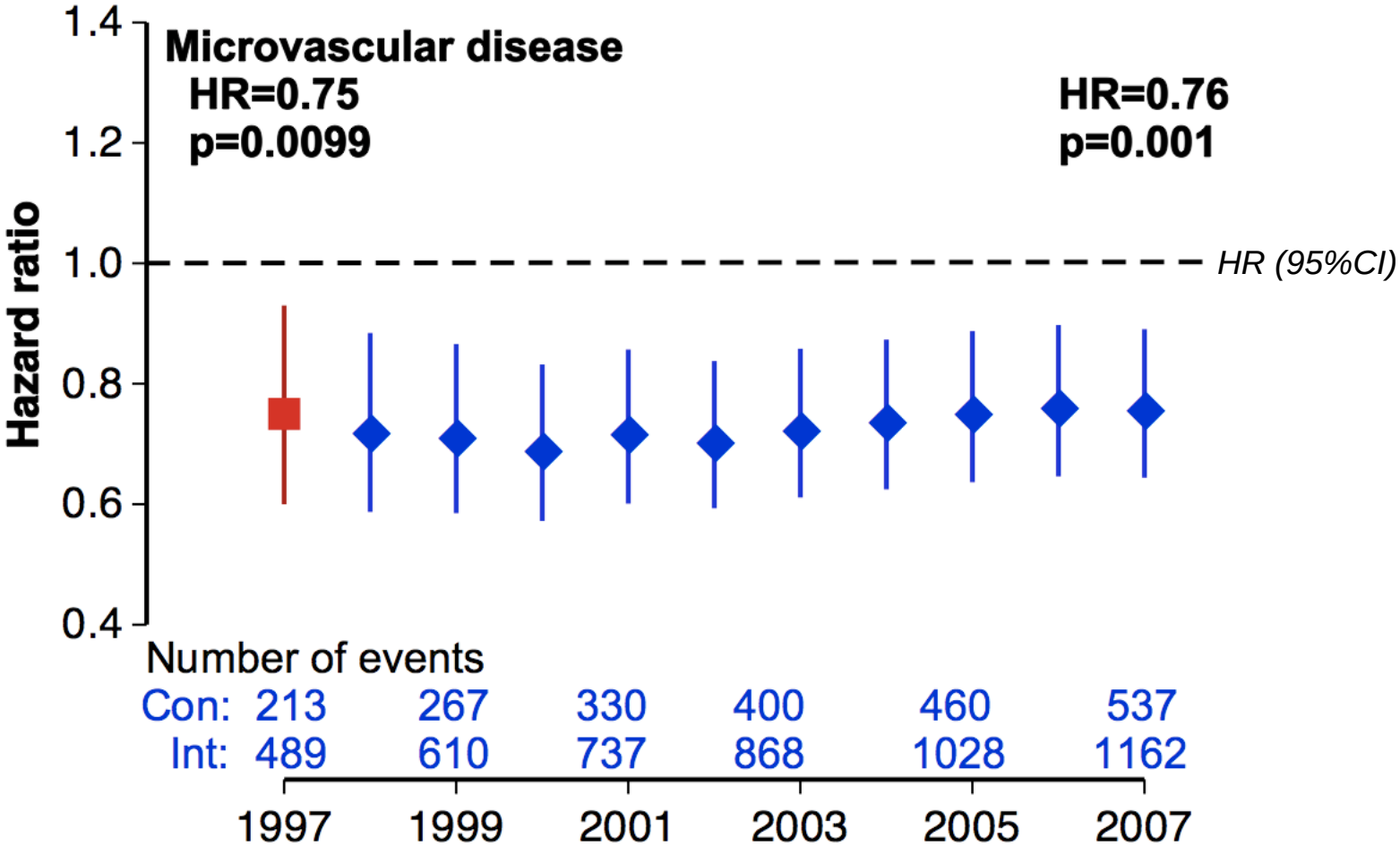
Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

Intensive (SU/Ins) *vs.* Conventional glucose control



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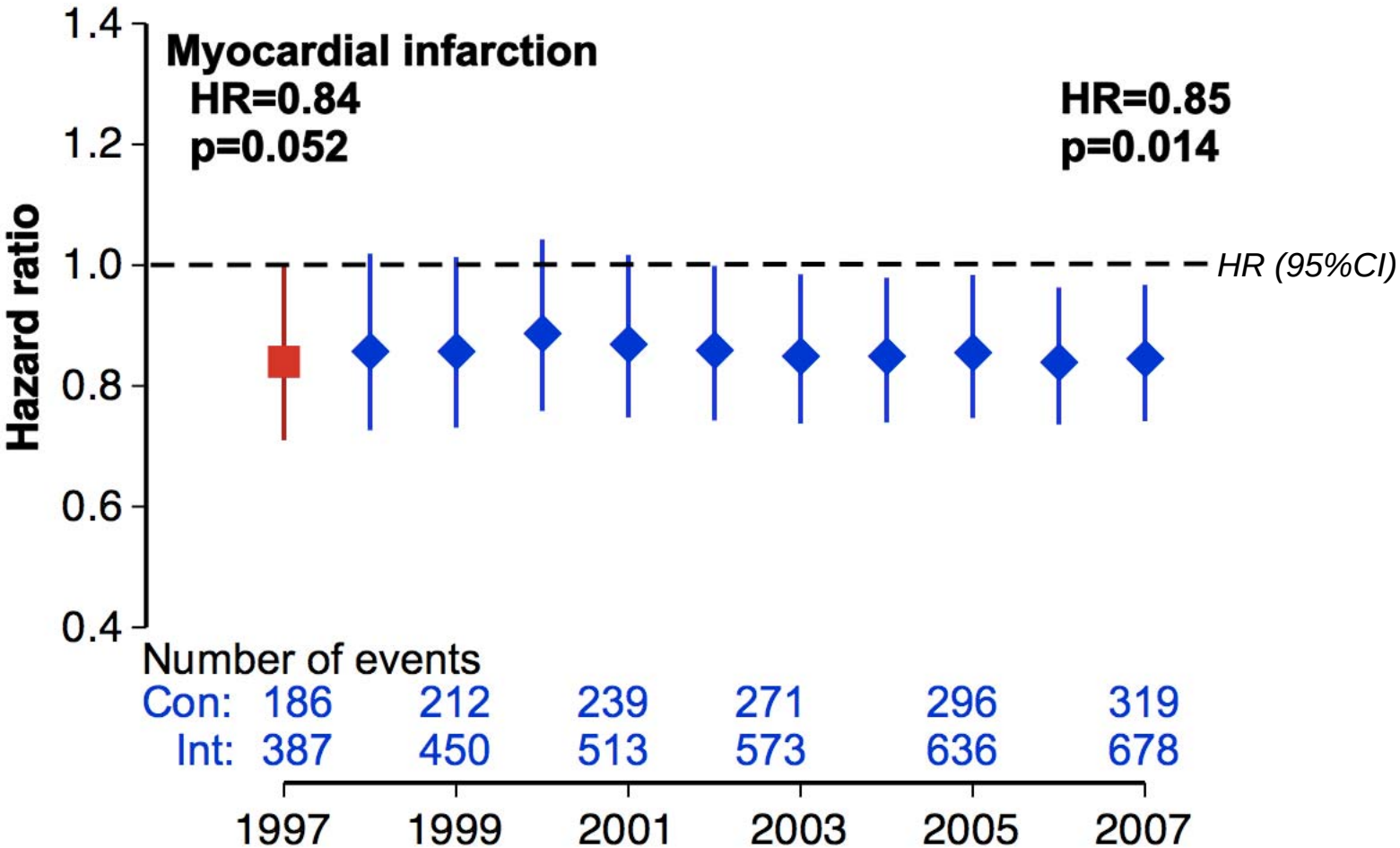
Myocardial Infarction Hazard Ratio

(fatal or non-fatal myocardial infarction or sudden death)

Intensive (SU/Ins) *vs.* Conventional glucose control



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Post-Trial Monitoring: Protocol

- At trial end, patients were returned to usual physician care for their diabetes management
- No attempt was made to maintain them in randomised groups, or to influence their therapy
- All endpoints were adjudicated in an identical manner by the same Adjudication Committee as during the trial

From 1997 to 2002:

- Patients were seen annually in UKPDS clinics for standardised collection of clinical and biochemical data

From 2002 to 2007:

- Clinical outcomes were ascertained remotely by questionnaires sent to patients and GPs

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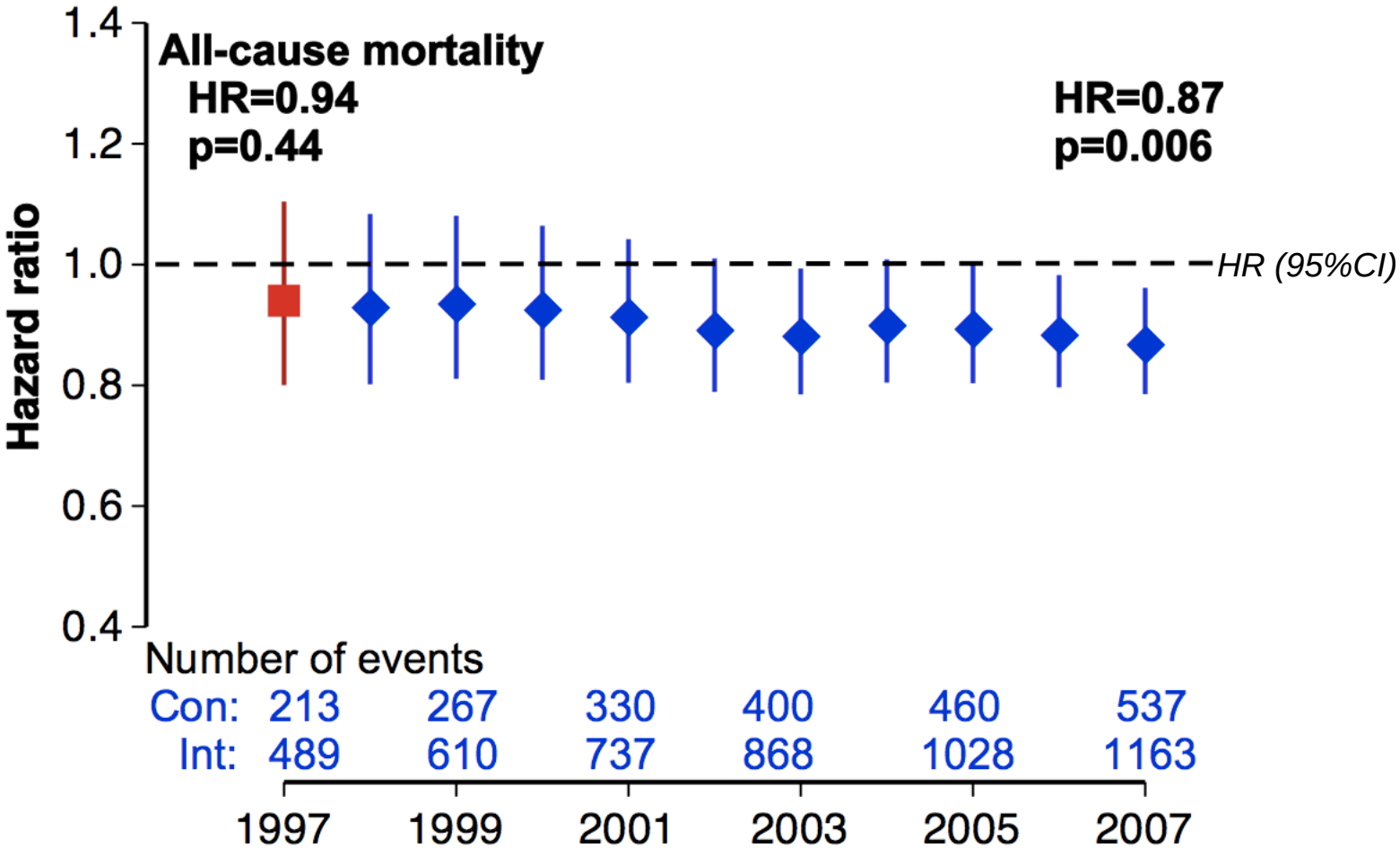
All-cause Mortality Hazard Ratio

Intensive (SU/Ins) *vs.* Conventional glucose control



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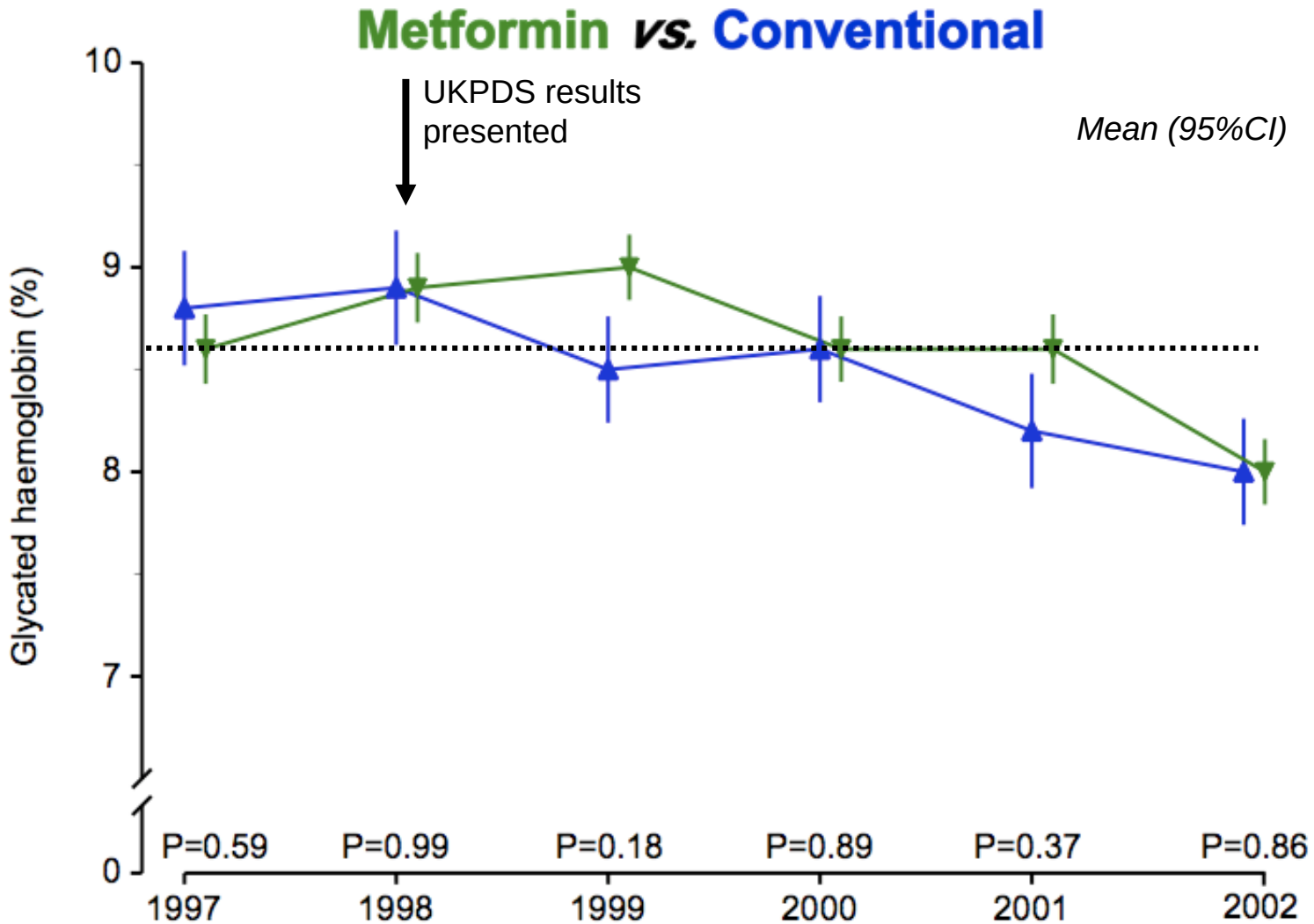
Post-Trial Changes in HbA_{1c}



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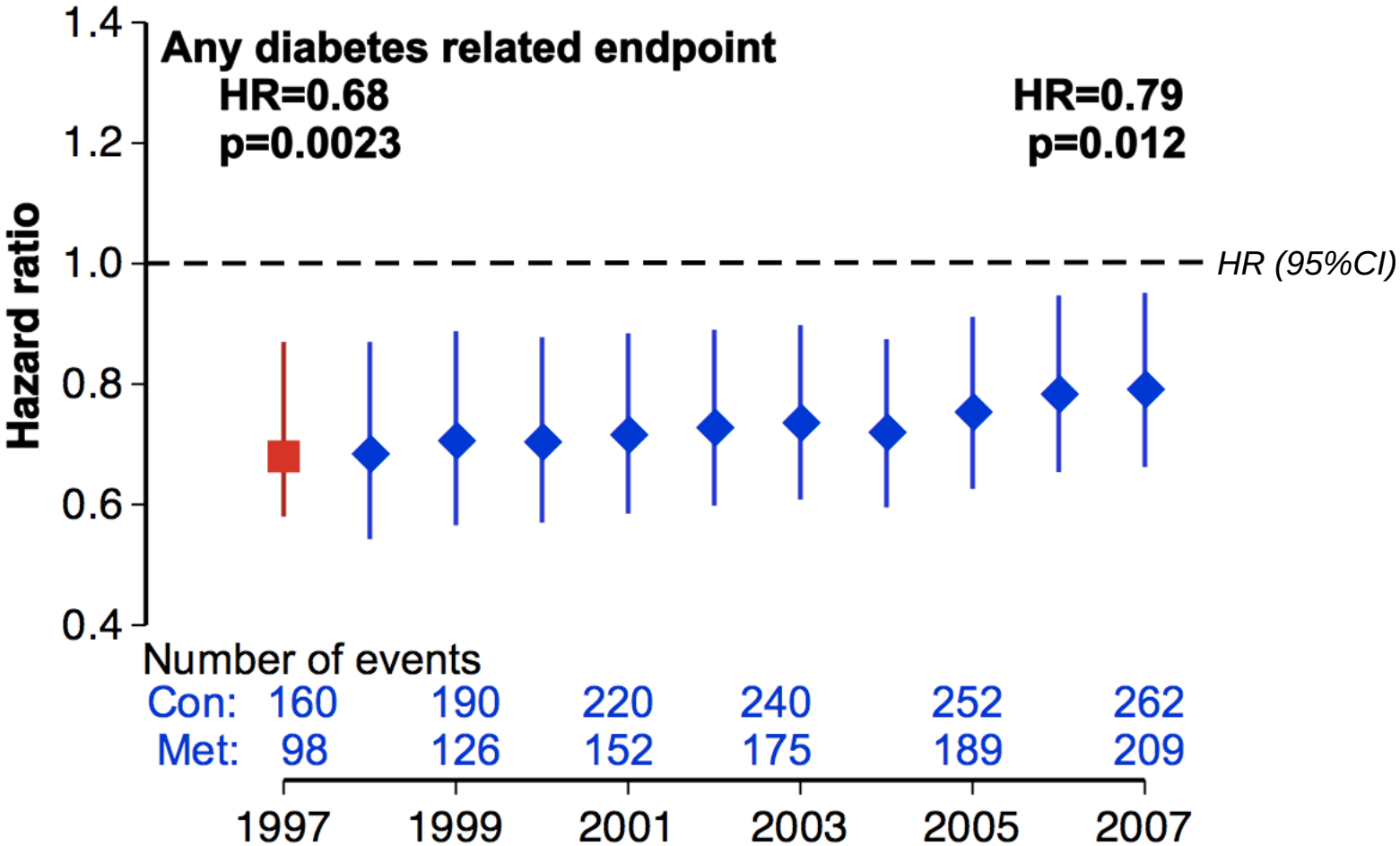
Any Diabetes Related Endpoint Hazard Ratio

Intensive (metformin) *vs.* Conventional glucose control



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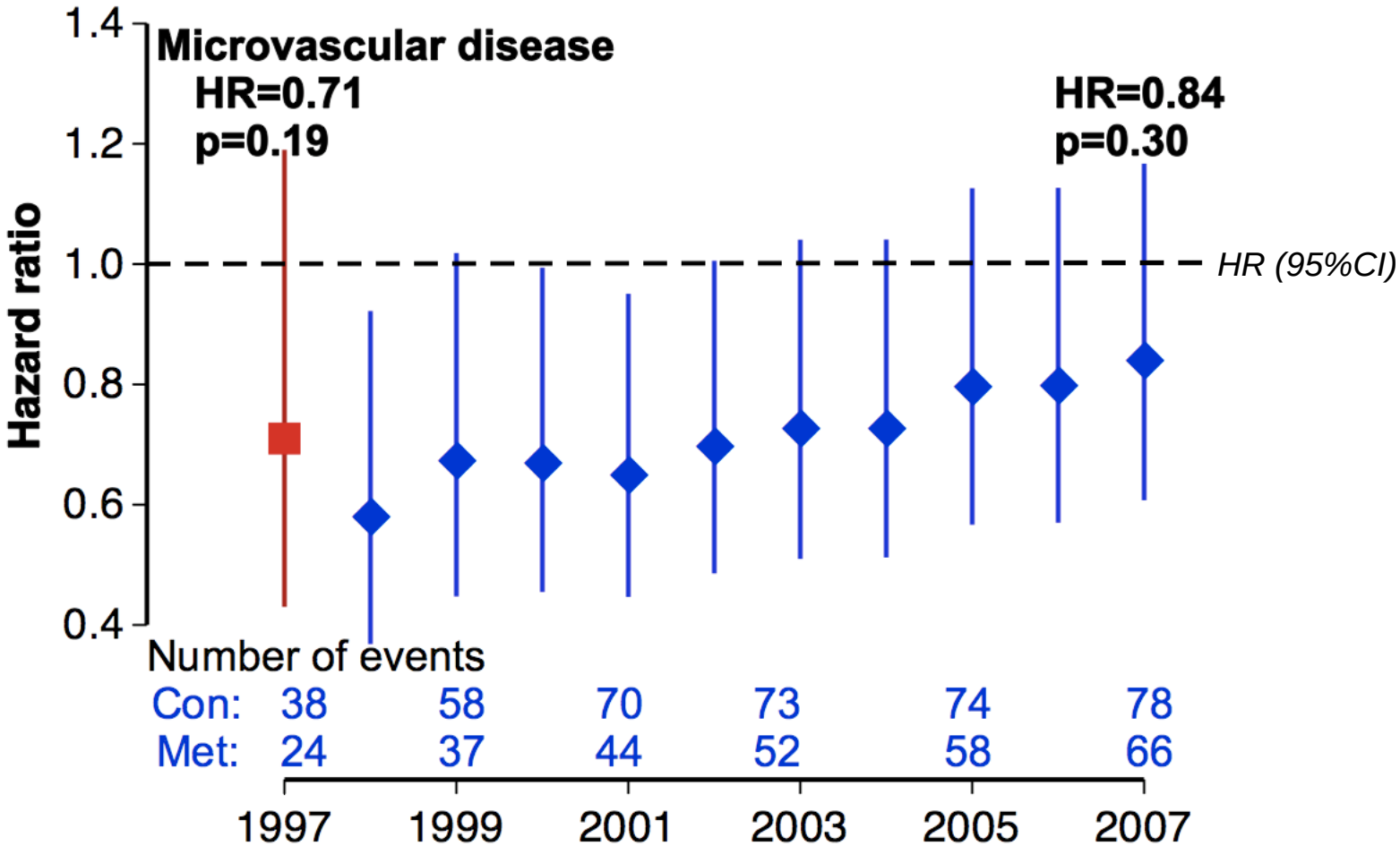
Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

Intensive (metformin) *vs.* Conventional glucose control



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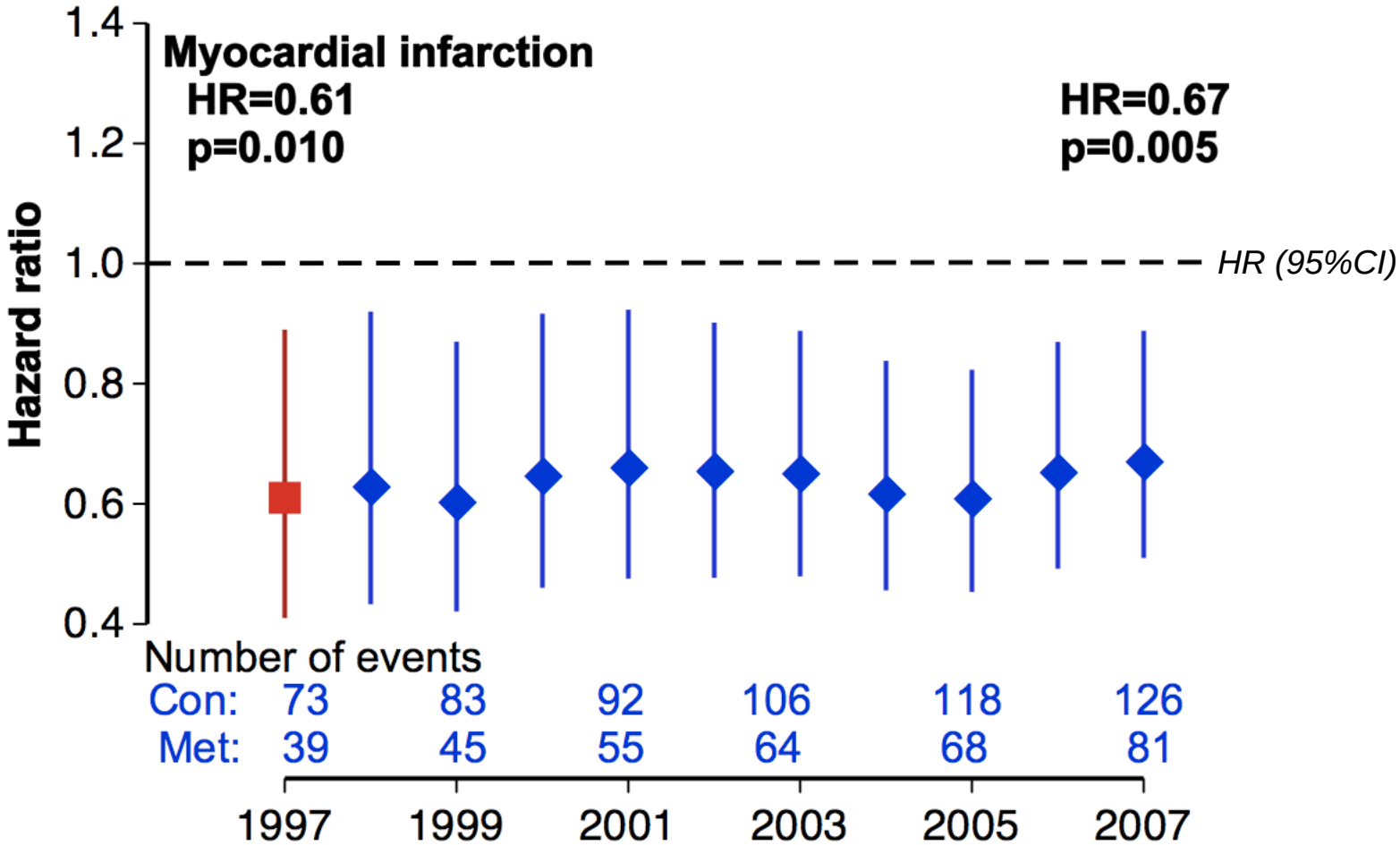
Myocardial Infarction Hazard Ratio

(fatal or non-fatal myocardial infarction or sudden death)

Intensive (metformin) *vs.* Conventional glucose control



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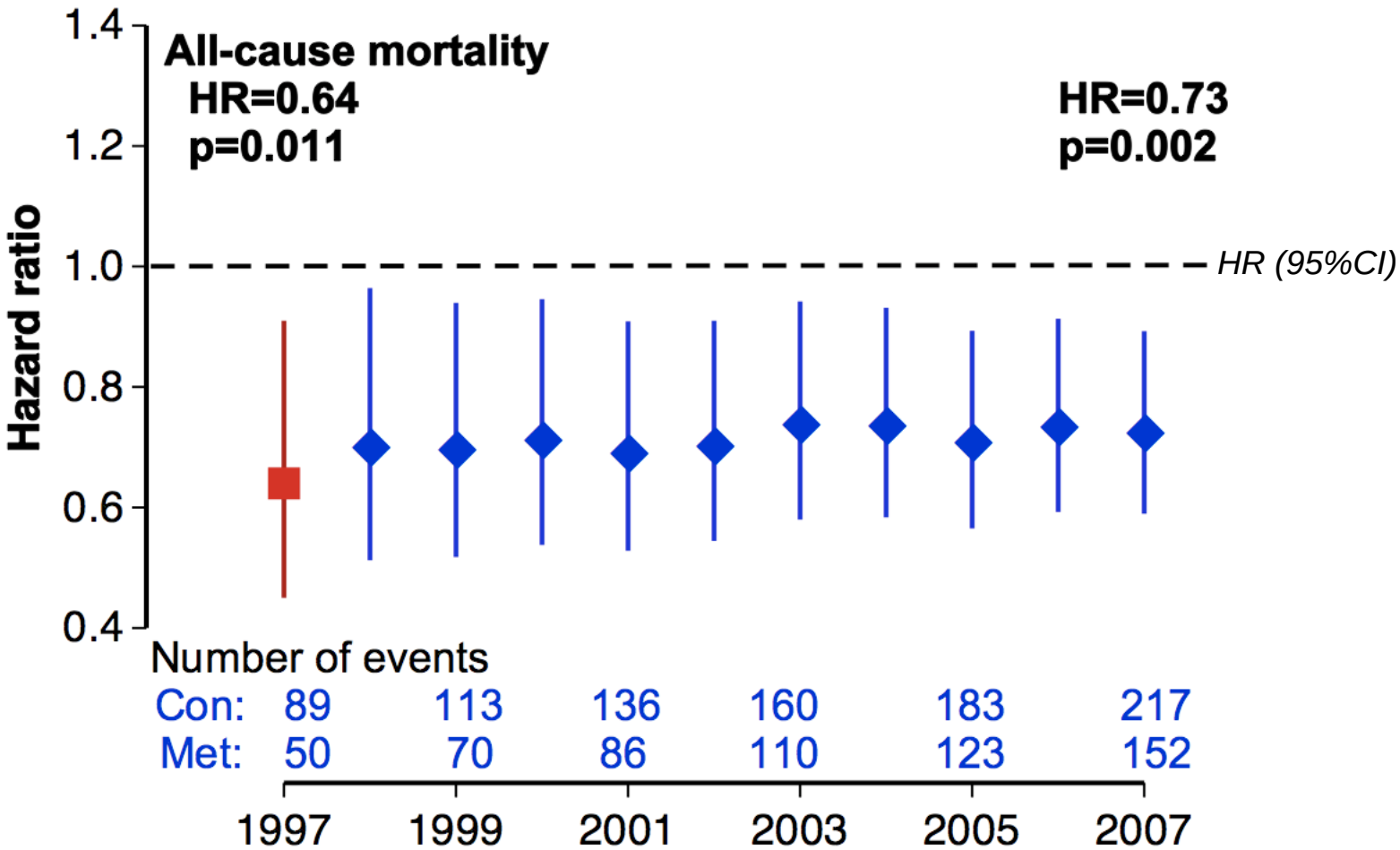
All-cause Mortality Hazard Ratio

Intensive (metformin) *vs.* Conventional glucose control



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Are there Blood Pressure Therapy Legacy Effects?

Hypertension in Diabetes Study (HDS)

10-year Intervention Trial 1987-1997

- 1,148 patients with blood pressure ≥160/90 mm Hg, or ≥150/85 mm Hg if receiving antihypertensive treatment, enrolled over four years from 1987
- Median follow-up 8.4 years, range 6 to 10 years
- Results presented at the 1998 EASD Barcelona meeting

10-year Post-trial Monitoring 1997-2007

- Annual follow-up of the survivor cohort
- Clinic-based for first five years
- Questionnaire-based for last five years

Median overall follow-up 14.6 years, range 16 to 20 years

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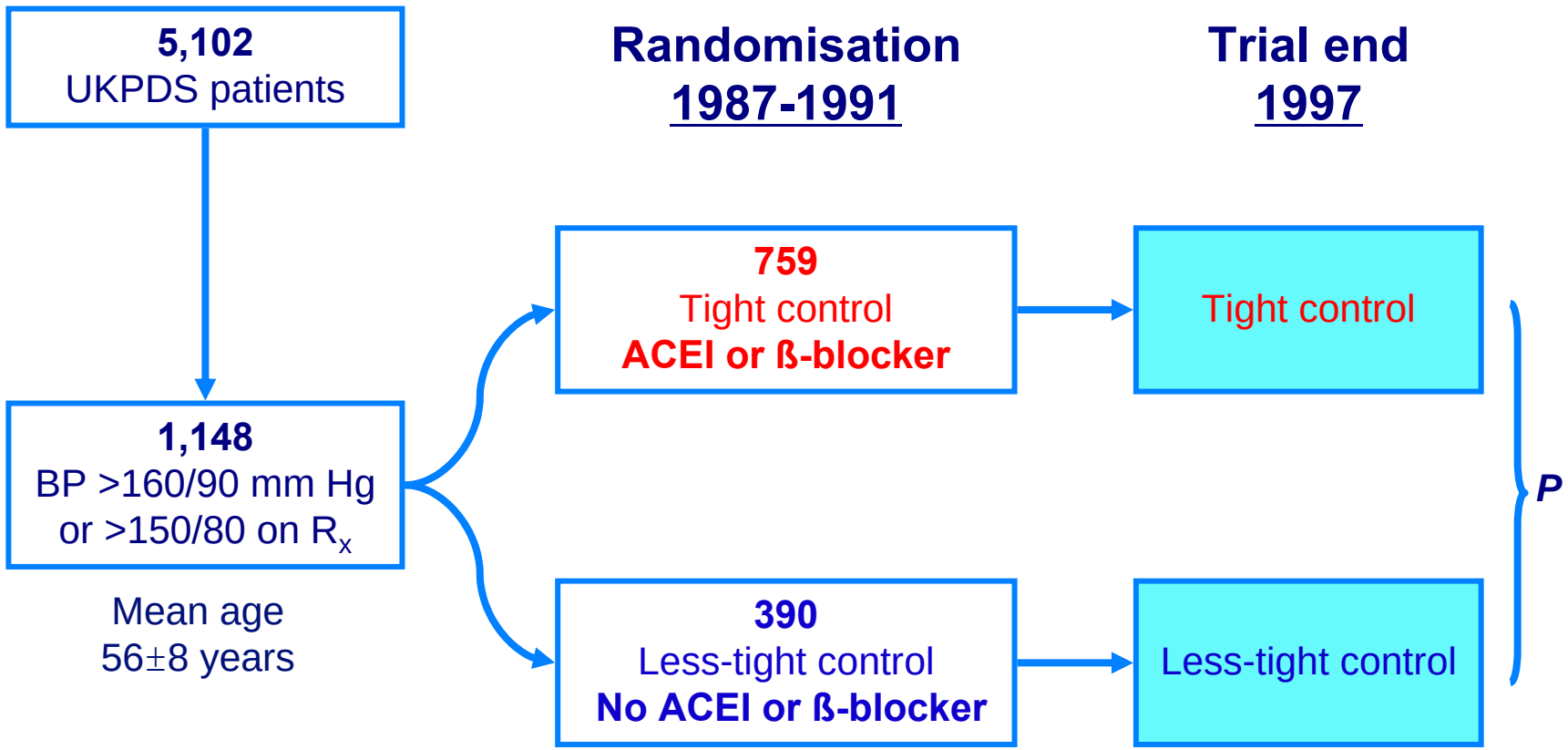
Blood Pressure Interventional Trial



*UKPDS 8. Diabetologia 1991; **34**: 877-89*

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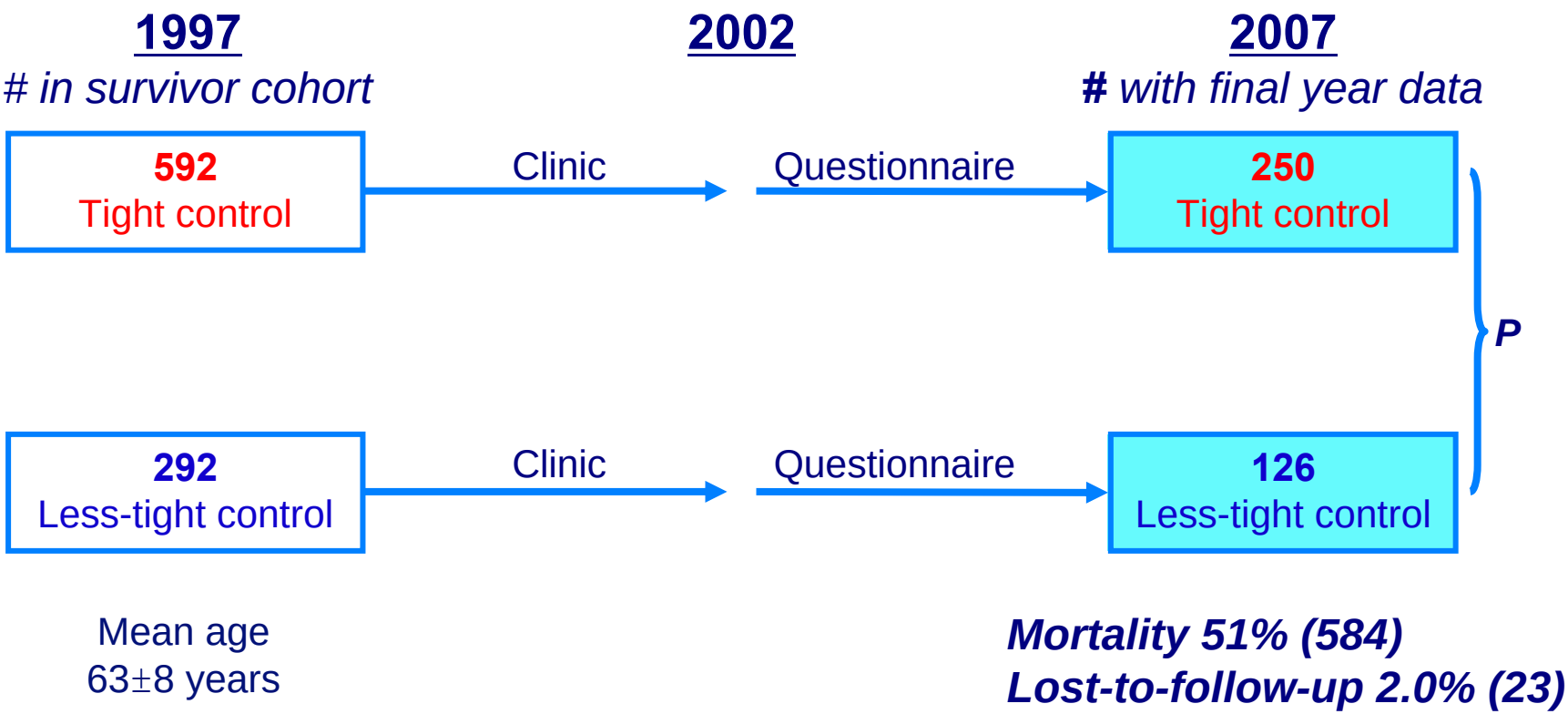
Post-Trial Monitoring: Patients



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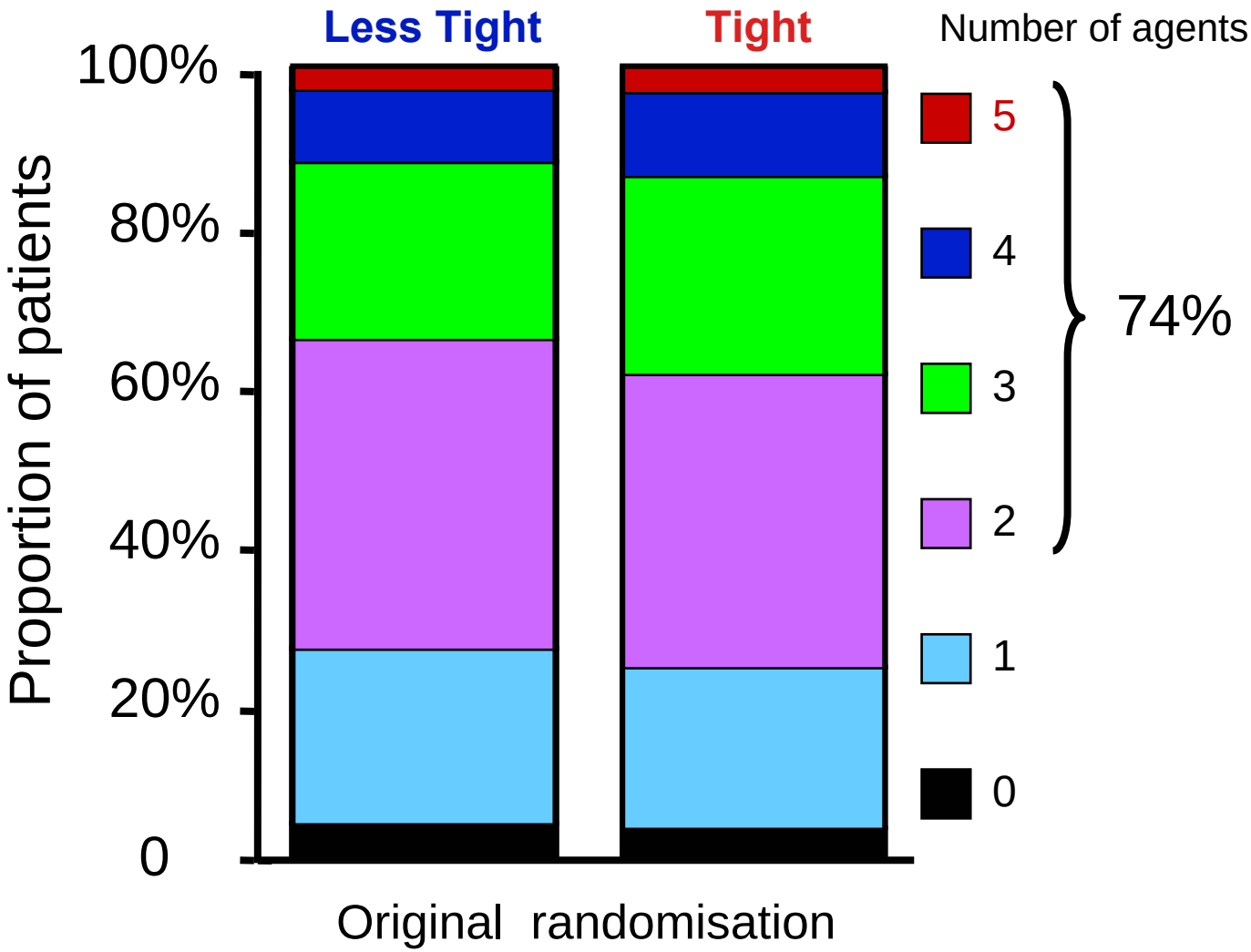
Antihypertensive Therapy at 5 years



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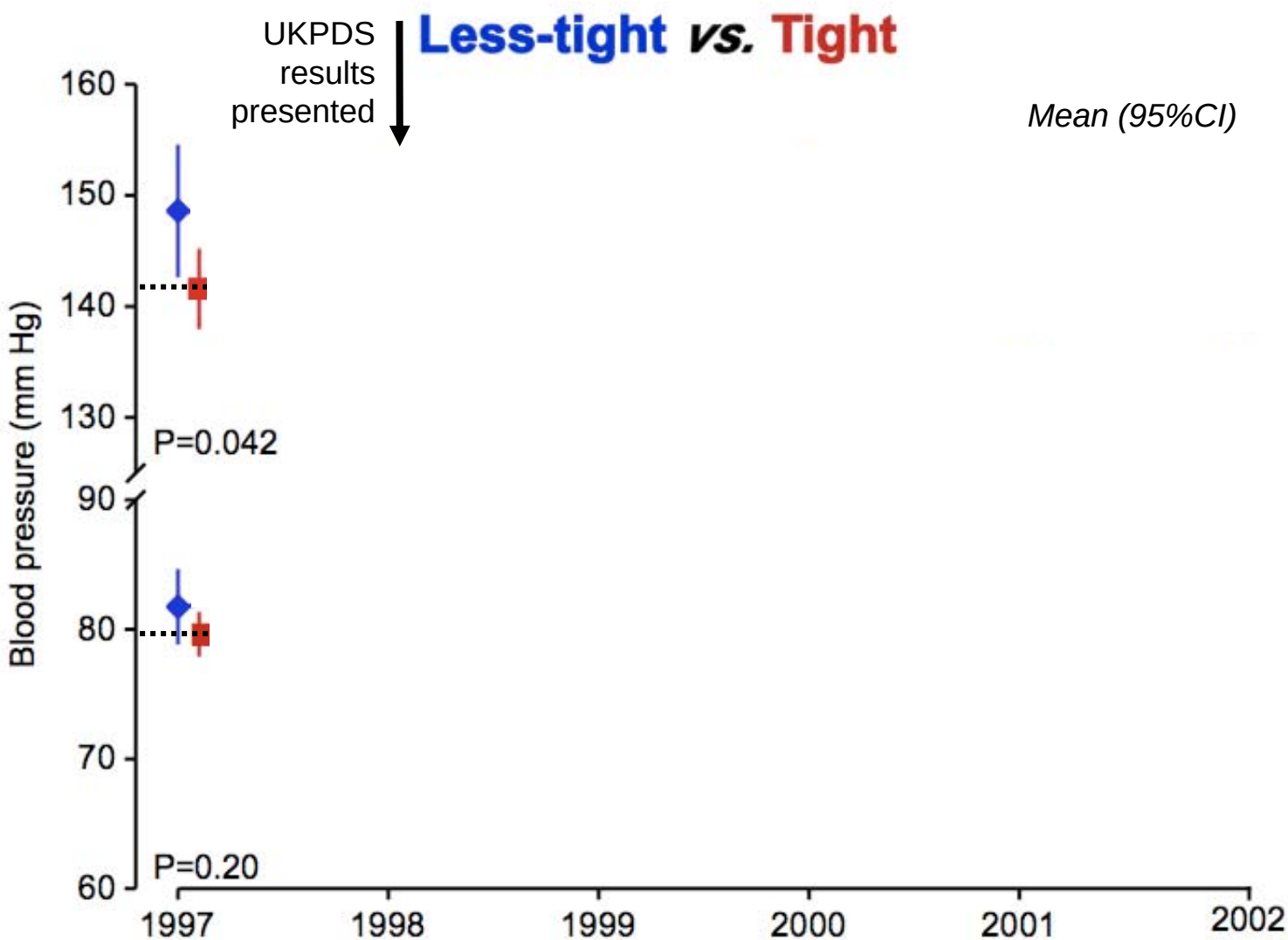
Post-Trials Changes in Blood Pressure



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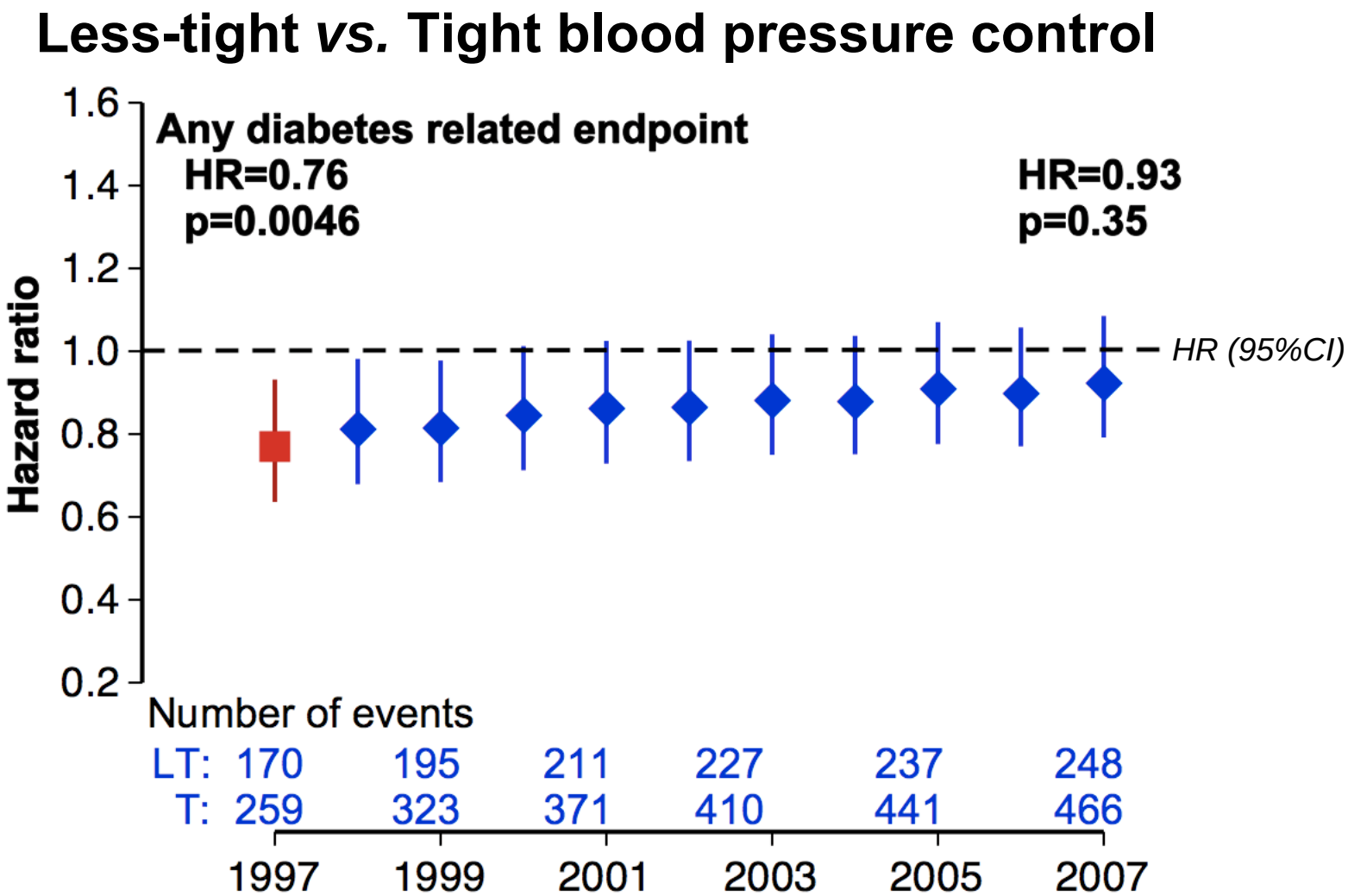
Any Diabetes Related Endpoint Hazard Ratio



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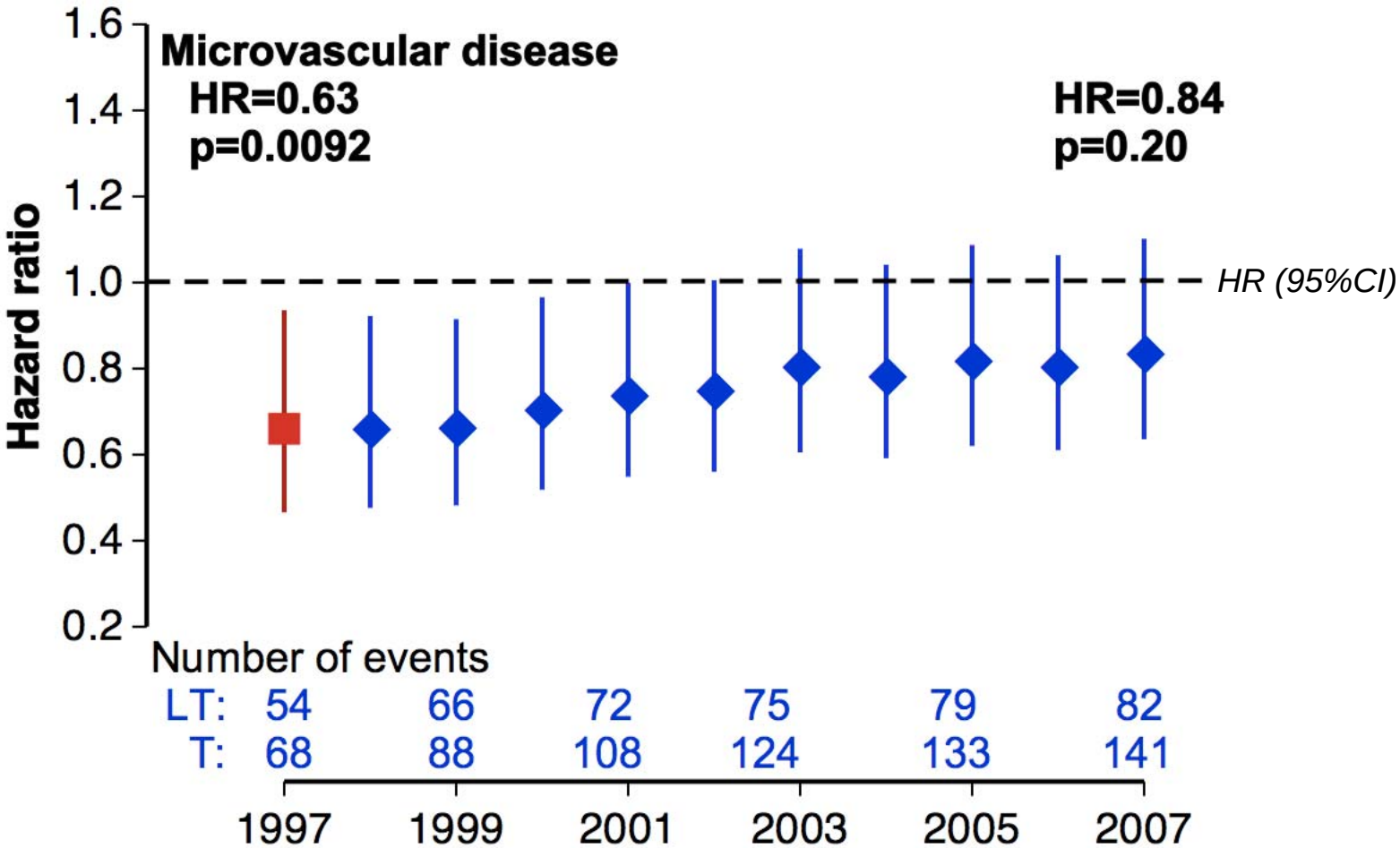
Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

Less-tight *vs.* Tight blood pressure control



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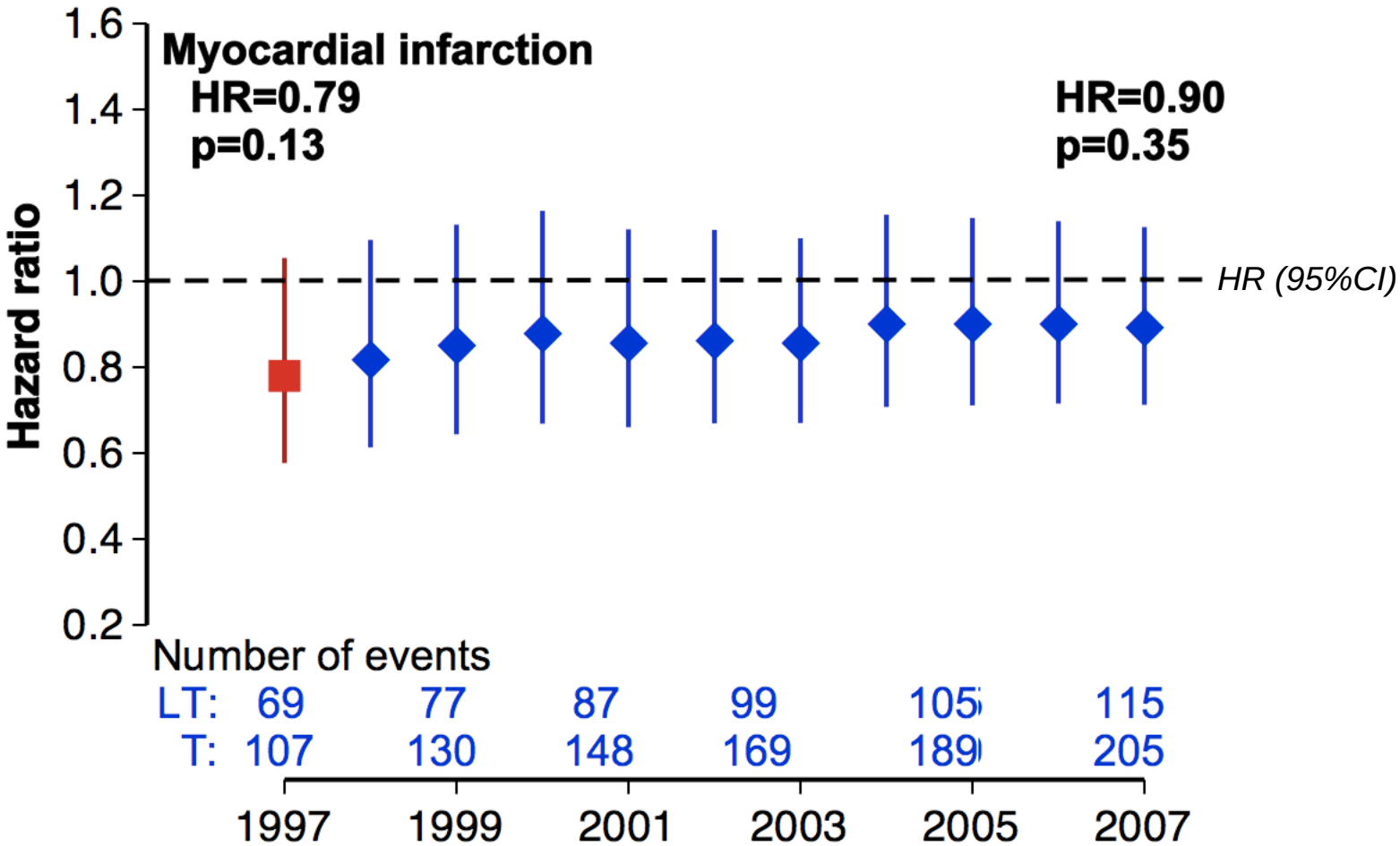
Myocardial Infarction Hazard Ratios

(fatal or non-fatal myocardial infarction or sudden death)

Less-tight *vs.* Tight blood pressure control



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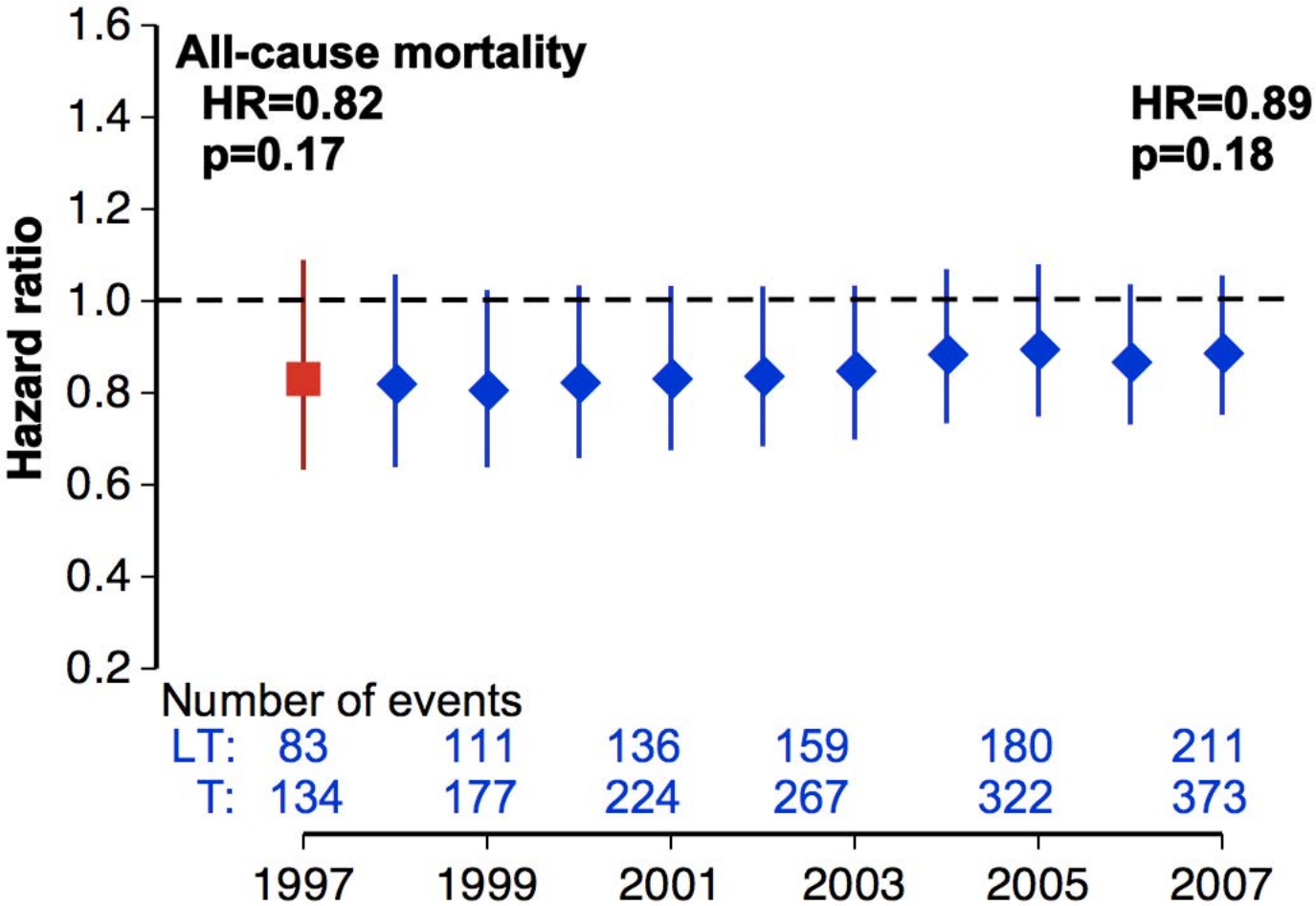
All-cause Mortality Hazard Ratios

Less-tight *vs.* Tight blood pressure control



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Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	
	P:	0.029	
Microvascular disease	*RRR:*	25%	
	P:	0.0099	
Myocardial infarction	*RRR:*	16%	
	P:	0.052	
All-cause mortality	*RRR:*	6%	
	P:	0.44	

RRR = Relative Risk Reduction, P = Log Rank

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Legacy Effect of Earlier Metformin Therapy

After median 8.8 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	32%	
	P:	0.0023	
Microvascular disease	*RRR:*	29%	
	P:	0.19	
Myocardial infarction	*RRR:*	39%	
	P:	0.010	
All-cause mortality	*RRR:*	36%	
	P:	0.011	

RRR = Relative Risk Reduction, P = Log Rank

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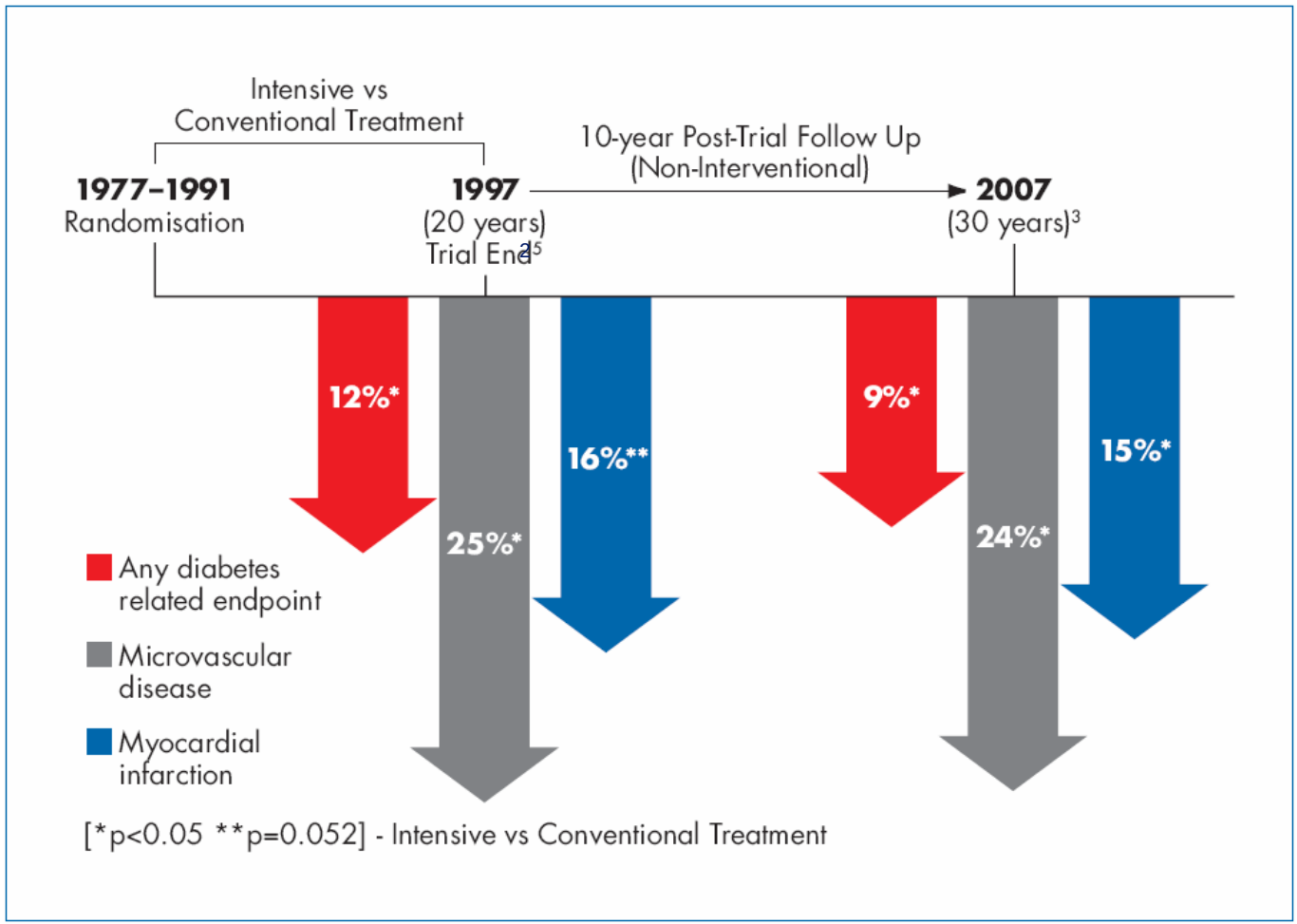
The Benefits of Early Tight Control- UKPDS 10 year Post-Trial Follow-Up



1.Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89.
2. UKPDS 33. Lancet, 1998: 352; 837

No Legacy Effect of Earlier BP Control

After median 8.0 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	24%	
	P:	0.0046	
Microvascular disease	*RRR:*	37%	
	P:	0.0092	
Myocardial infarction	*RRR:*	21%	
	P:	0.13	
All-cause mortality	*RRR:*	18%	
	P:	0.17	

RRR = Relative Risk Reduction, P = Log Rank

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Legacy effects

- Legacy: "something handed on by or left unfinished by a predecessor or previous owner"*
- More likely to be gradually developing pathology than "metabolic memory"

*Chambers Dictionary 10th edition

The performance of this machine may depend on its previous history as well as standards of care today.

Accidents likely to happen

The rust on this machine today is the result of what has happened in the distant past

The air pressure in the tyres of this machine is the result of what has happened in the recent past

Glycaemic control in the distant past reduces the risks of events today

Blood pressure control in the recent past reduces the risks of events today

What do we change in clinical practice?

- Evidence is strongly in favour of intensive treatment for glycaemia early in T2DM
- Evidence suggests that in those with established CVD that a rapid lowering of glycaemia to aggressive targets may cause excess mortality.
- Rosiglitazone needs further evidence for its safety in established T2DM
- Sulphonylureas may be appropriate for preventing microvascular disease (nephropathy)

With thanks to…

…Robert Turner
died August 1999

…Carole Cull
died June 2007

1998 EASD Investigator Meeting in Barcelona

Aberdeen	John Stowers, Lilian
Belfast City	Randal Hayes
Belfast Royal	David Hadden
Birmingham	David Wright
Carshalton	Steve Hyer, Memo S
Derby	Ian Peacock
Dundee	Ray Newton, Roland
Exeter	Kenneth McLeod, Jo
Hammersmith	Anne Dornhorst, Eva
Ipswich	John Day
Leicester	Felix Burden
Manchester	Andrew Boulton
Northampton	Charles Fox
Norwich	Richard Greenwood
Oxford	Robert Turner, Rury
Peterborough	Jonathan Roland
Salford	Tim Dornan, Martin
Scarborough	Phil Brown
St George's	Nigel Oakley, Arshia
Stevenage	Les Borthwick
Stoke on Trent	John Scarpell, Lione
Torbay	Richard Paisey
Whittington	John Yudkin

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Funding

1997 to 2002

- UK Medical Research Council
- UK Department of Health
- Diabetes UK
- British Heart Foundation
- National Institutes for Health (NEI, NIDDK)

2002 to 2007

- Bristol-Myers Squibb
- GlaxoSmithKline
- Merck Serono
- Novartis
- Novo Nordisk
- Pfizer

MEGA-trials

(No cardiovascular outcomes assessable in diabetes without mega-trials)

Defined (by me) as a randomised interventive trial with outcomes where greater than about 5,000,000 patient days are reported

(e.g. 1,000 patients for 3 years…or greater)

AND they need to last longer than 5 years

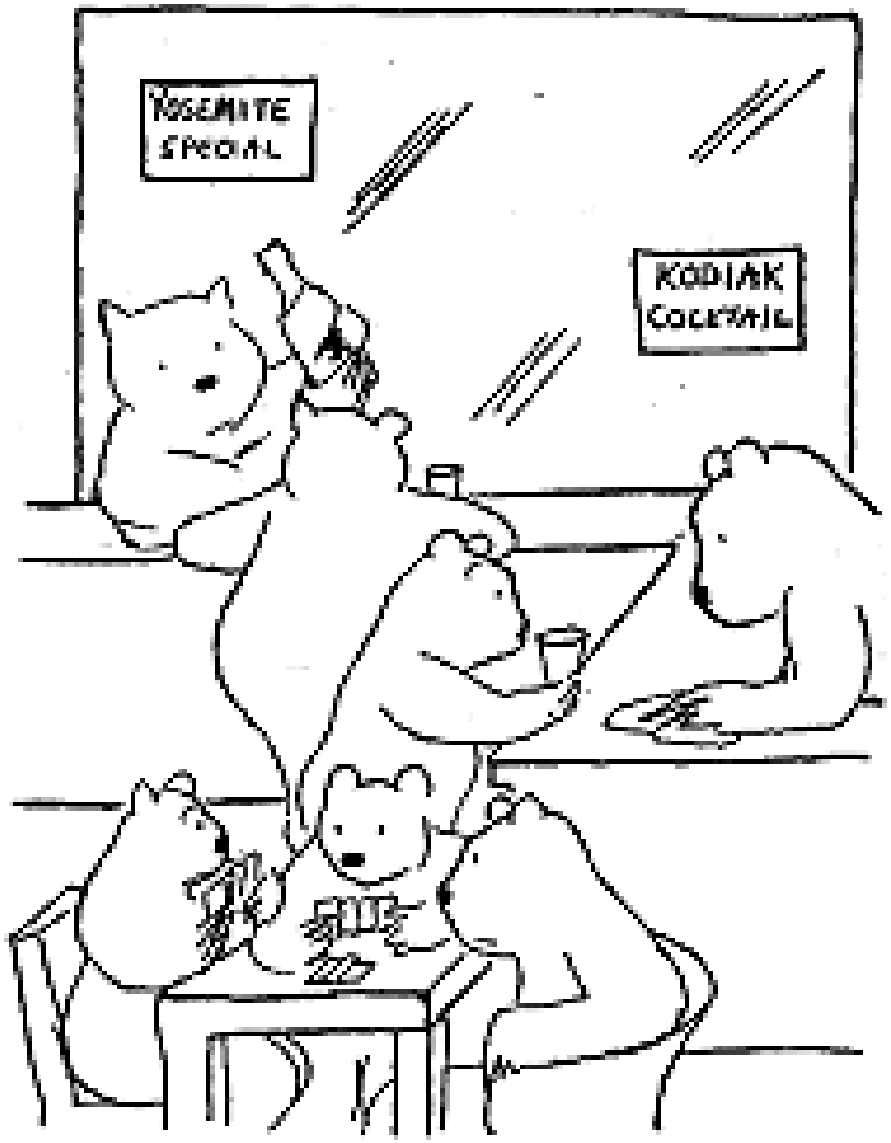
AND the glycaemic difference needs to be >0.5% Hba1c.

What do we change in clinical practice (1)?

- Evidence is strongly in favour of intensive treatment for glycaemia early in T2DM
- Evidence suggests that in those with established CVD that a rapid lowering of glycaemia to aggressive targets may cause excess mortality.
- Rosiglitazone needs further evidence for its safety in established T2DM
- Gliclazide MR use may be appropriate for preventing microvascular disease (nephropathy)

What do we change in clinical practice (2)?

- Evidence suggests that recent blood pressure control is protective, while a past history of good control is less significant.
- Evidence suggests that MULTIPLE risk-factor intervention is important.
  - (Steno studies – not reviewed today, but suggest that a well-delivered package of intervention has beneficial outcome)

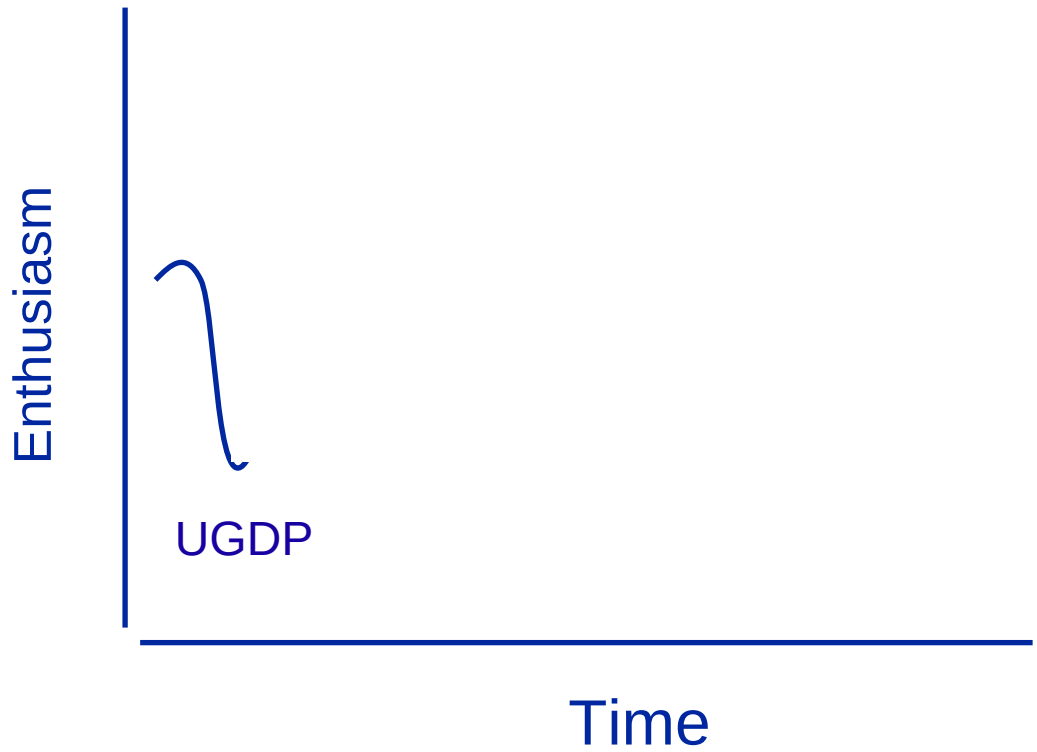


"You might as well fall flat on your face, as lean over too far backwards"

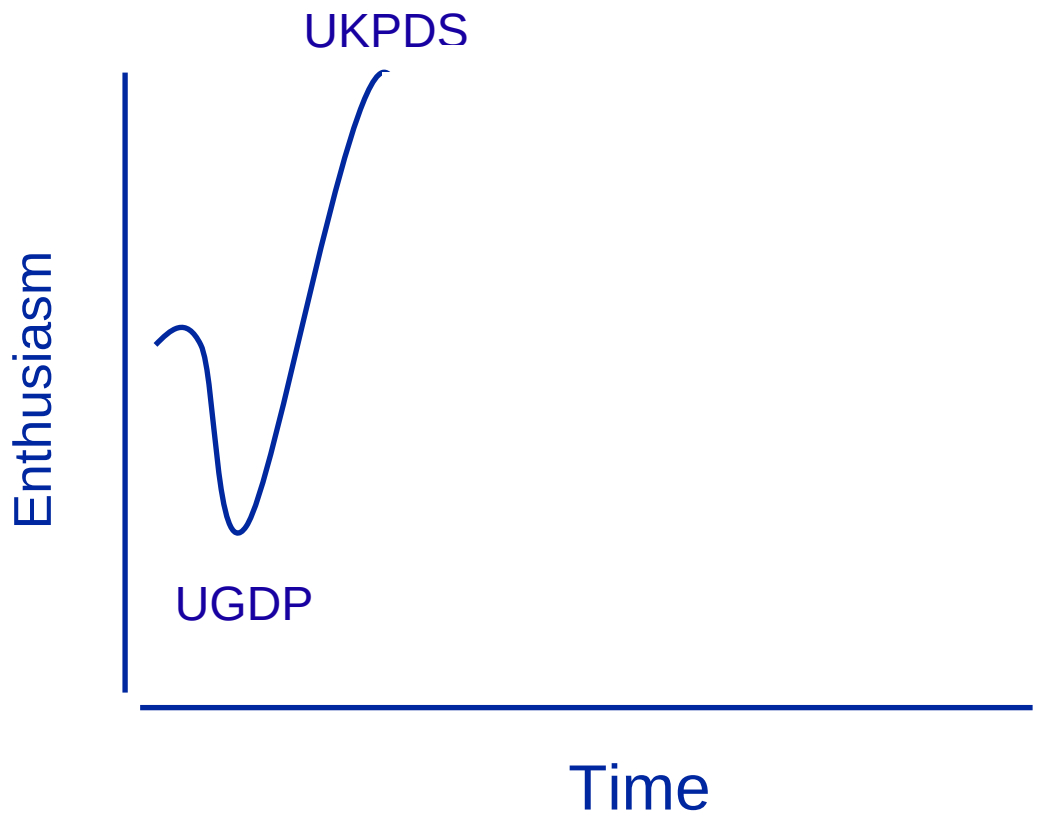
James Thurber.

Fl. 1945

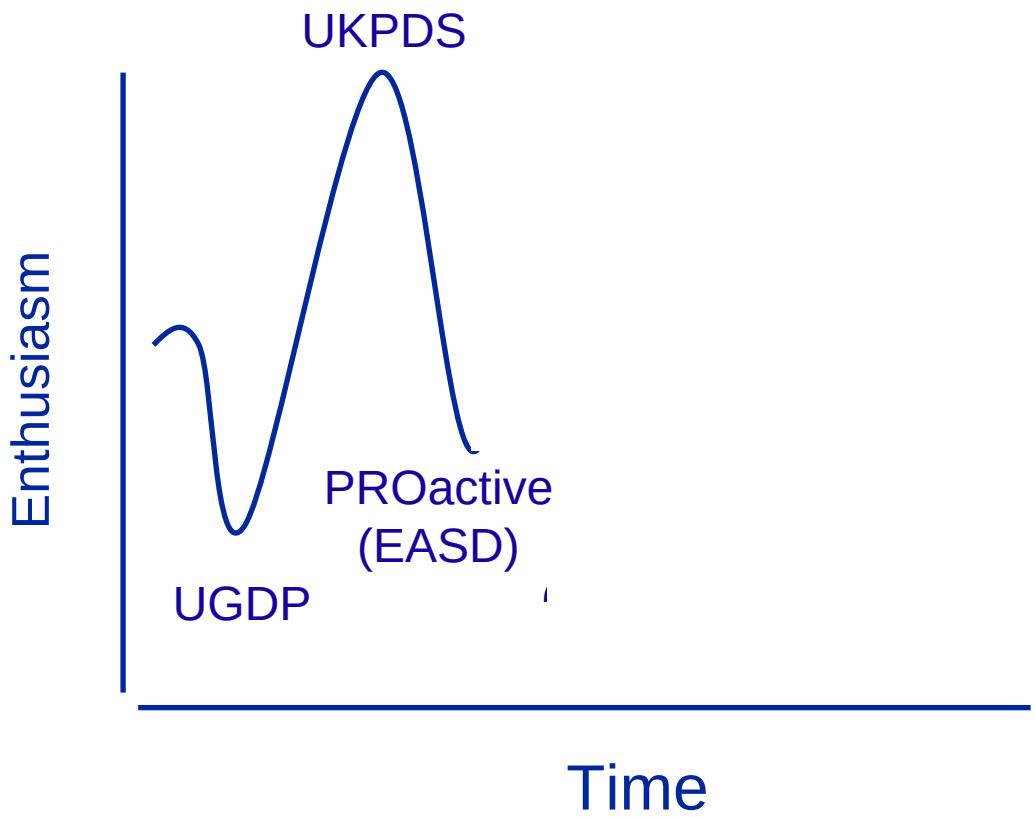
The roller-coaster: trials relating to glycaemia



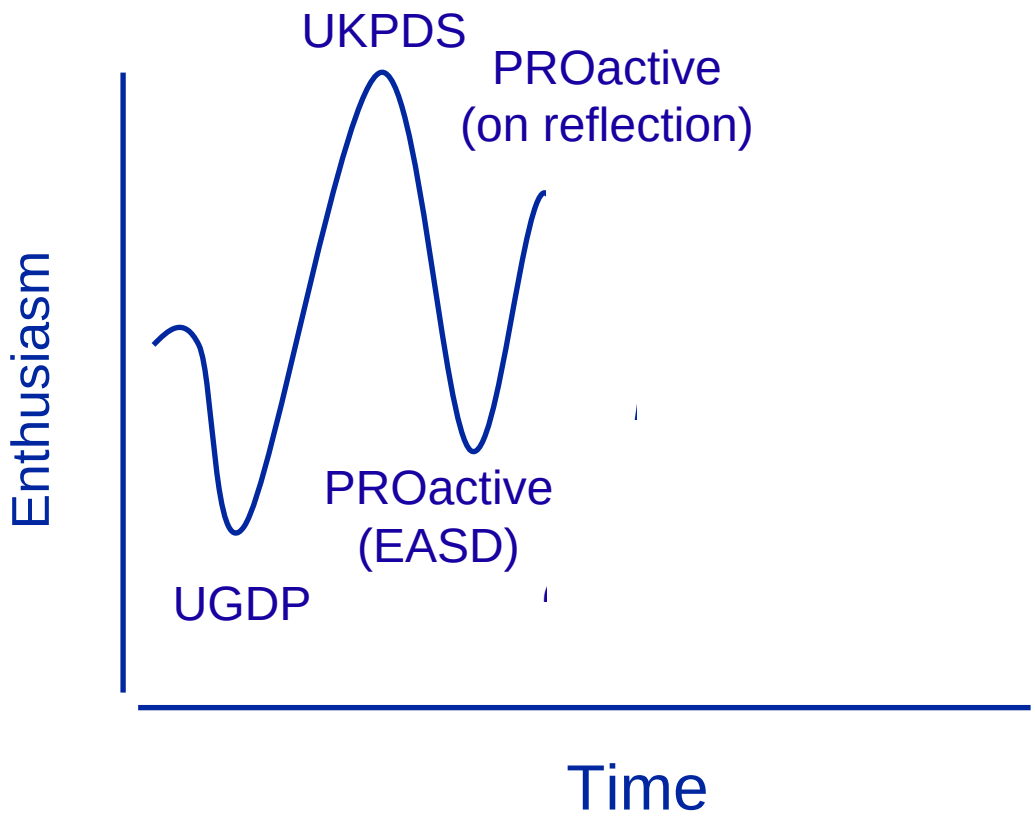
The roller-coaster: trials relating to glycaemia



The roller-coaster: trials relating to glycaemia



The roller-coaster: trials relating to glycaemia



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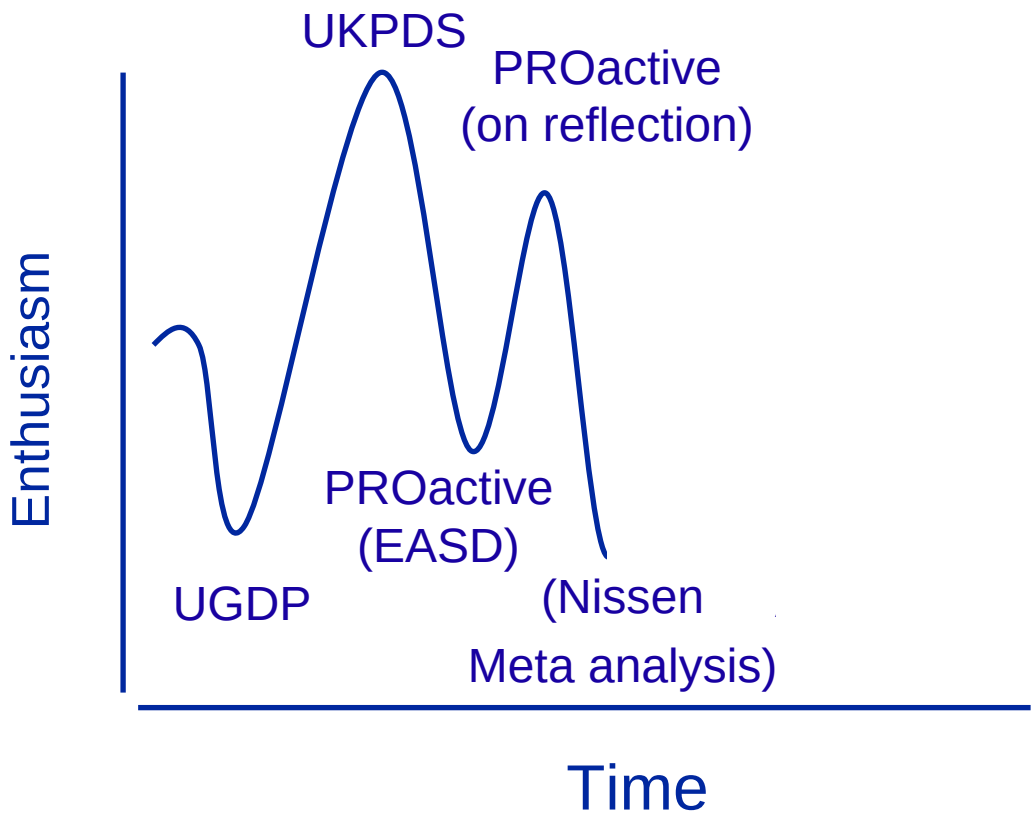
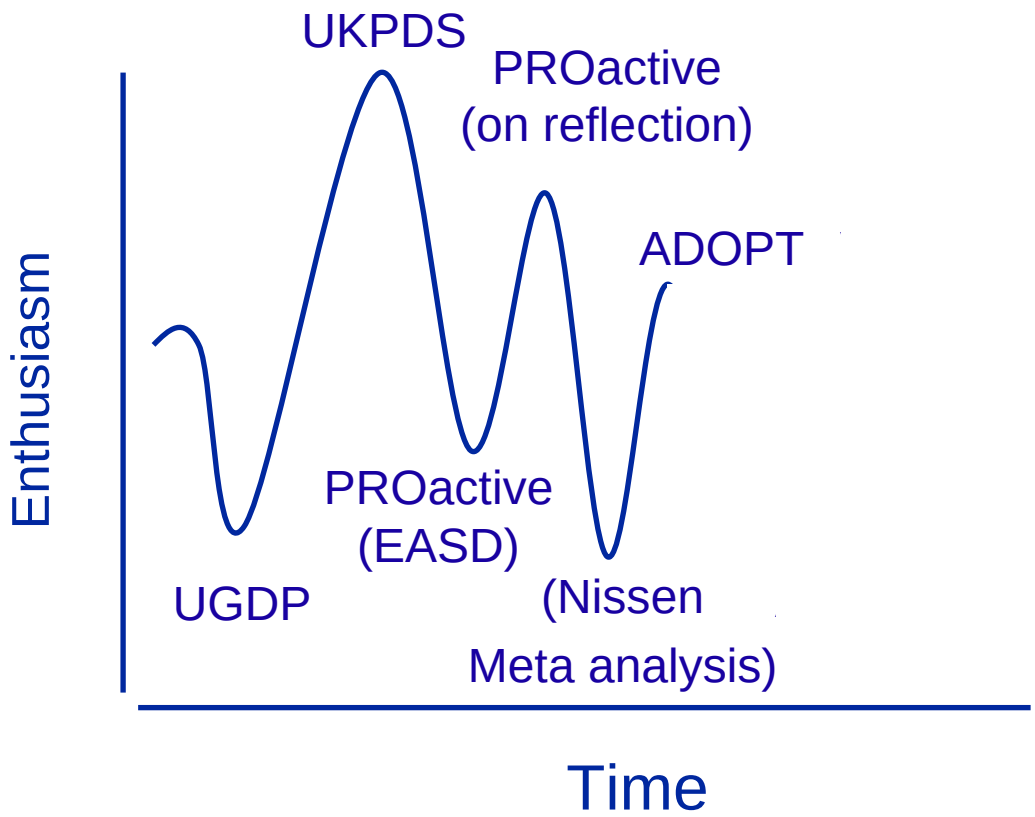
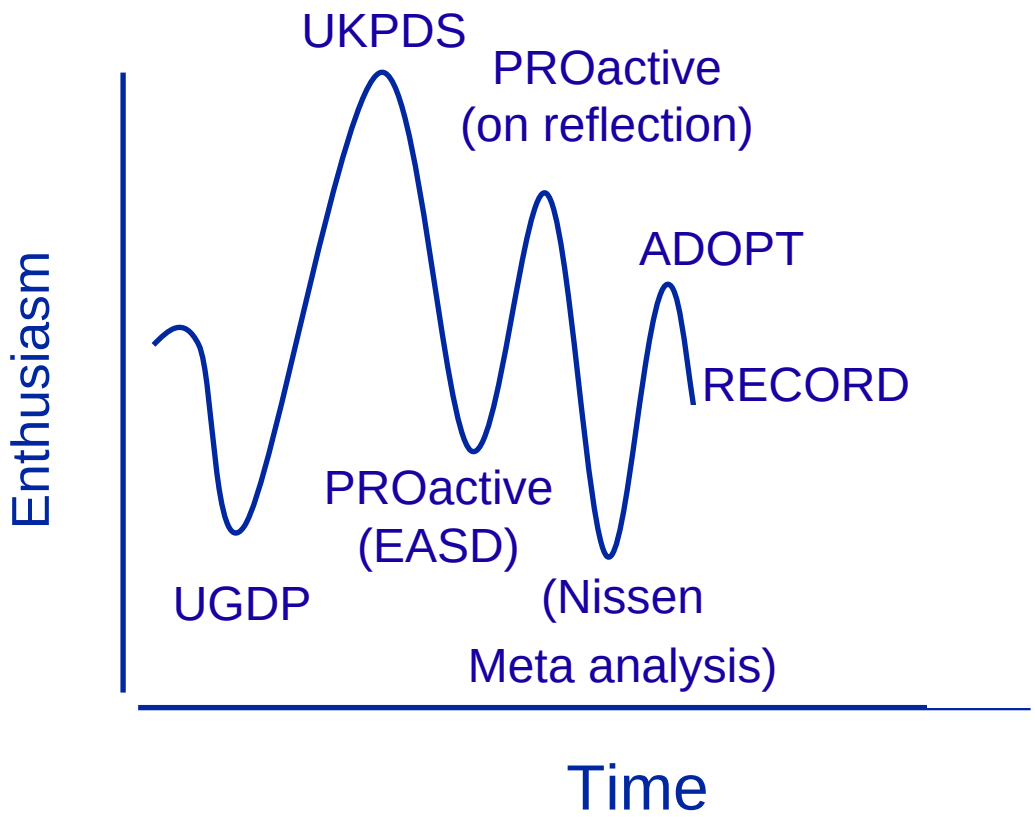


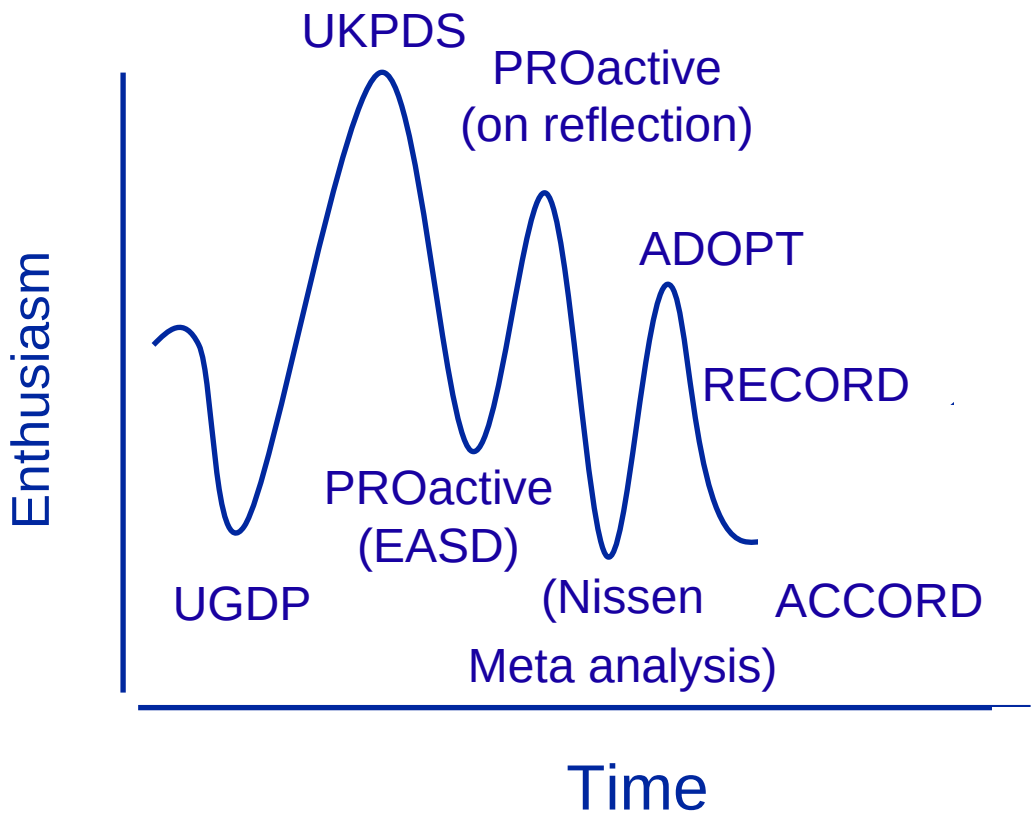
The roller-coaster: trials relating to glycaemia



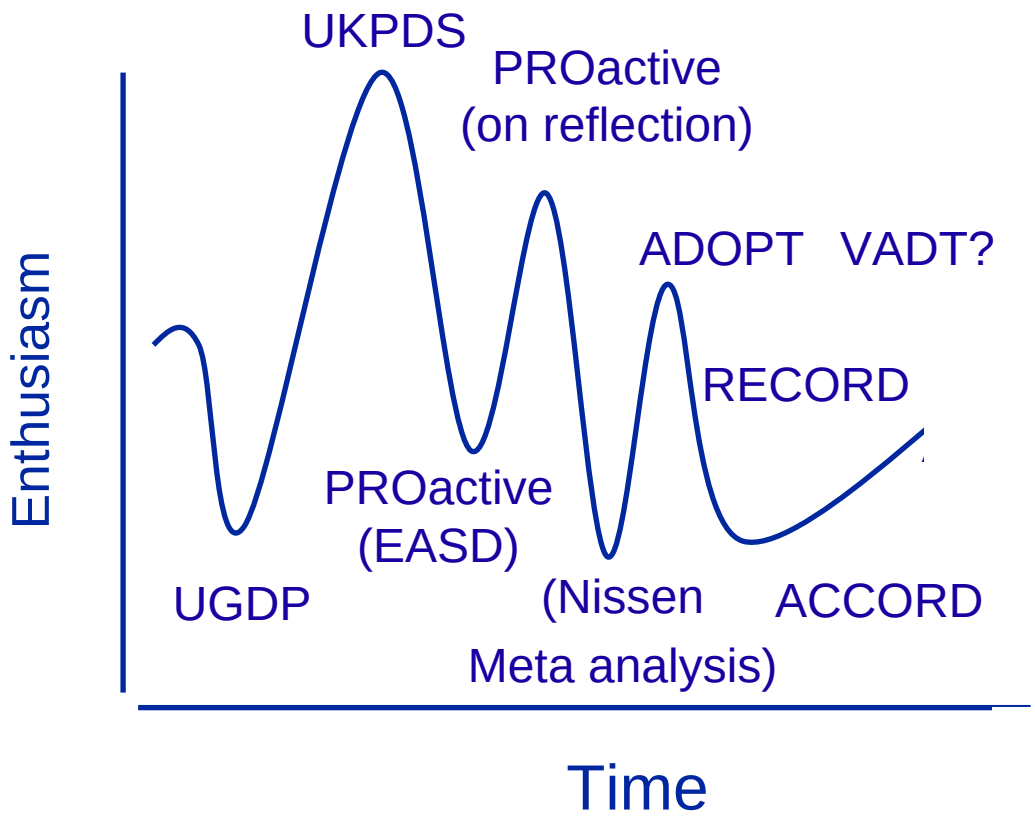
The roller-coaster: trials relating to glycaemia



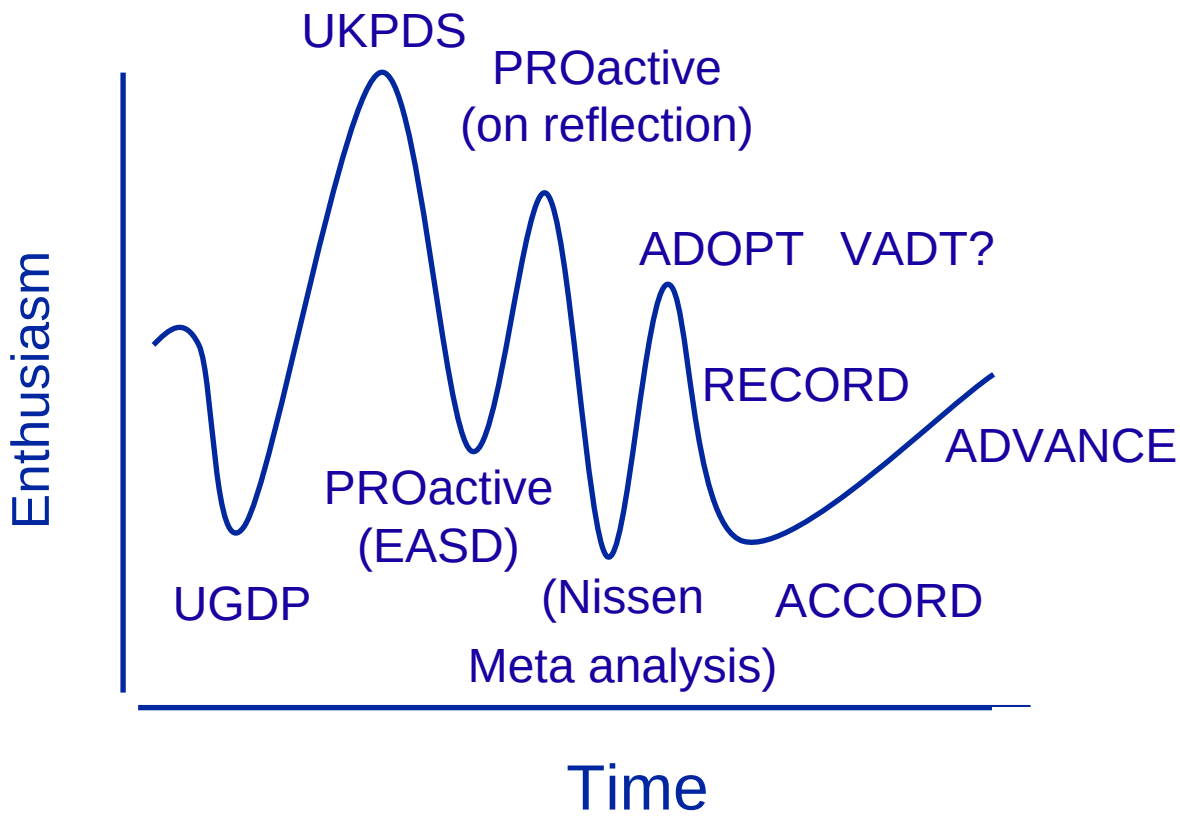
The roller-coaster: trials relating to glycaemia



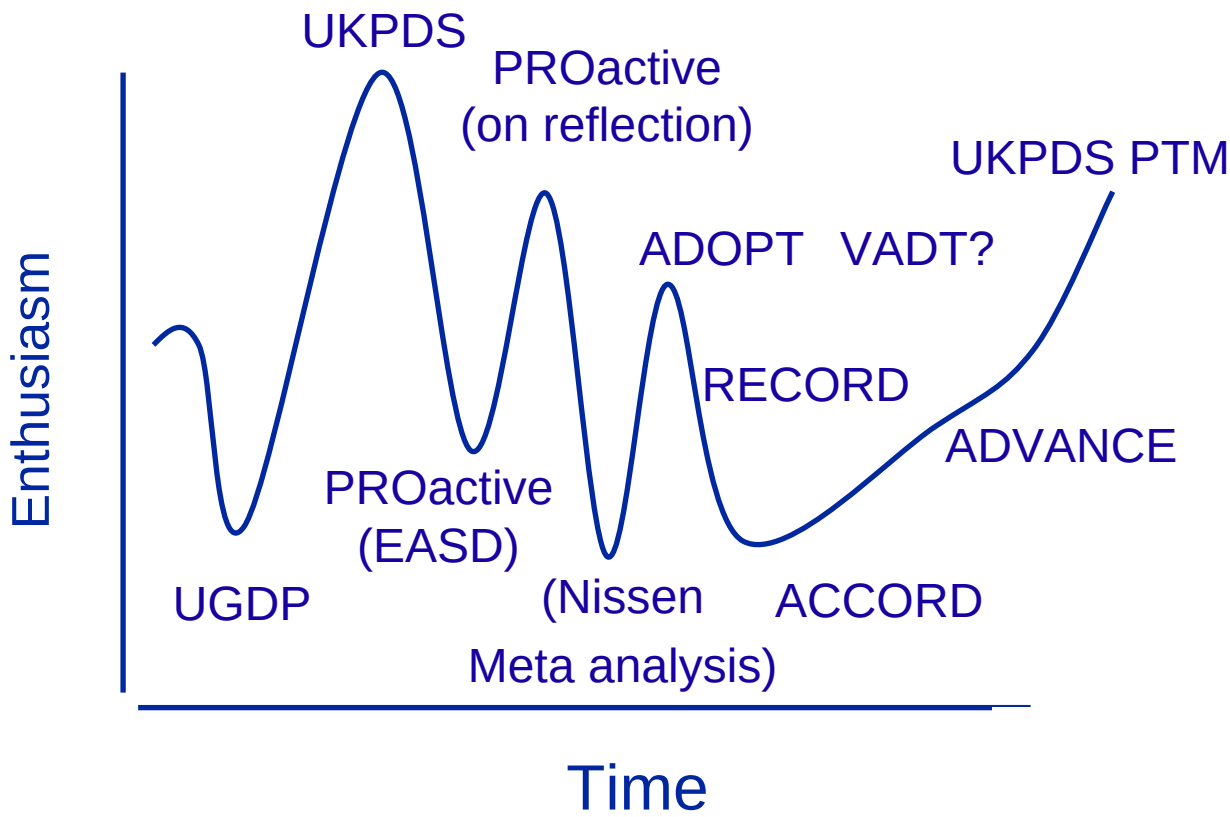
The roller-coaster: trials relating to glycaemia



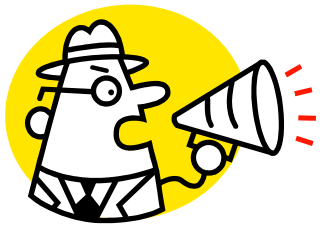
The roller-coaster: trials relating to glycaemia



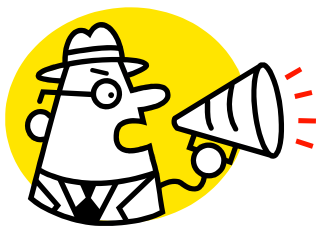
The roller-coaster: trials relating to glycaemia



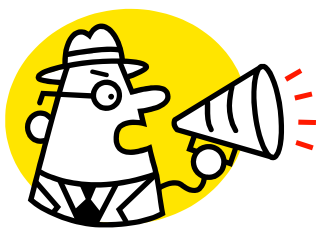
Some cautions



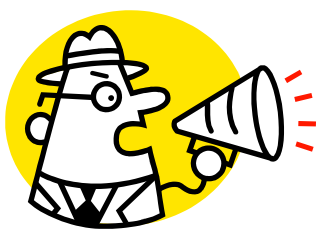
- There will be those who say that glucose lowering is not cost effective



- There will be those who say that the target of 7.5% is adequate, without saying for whom

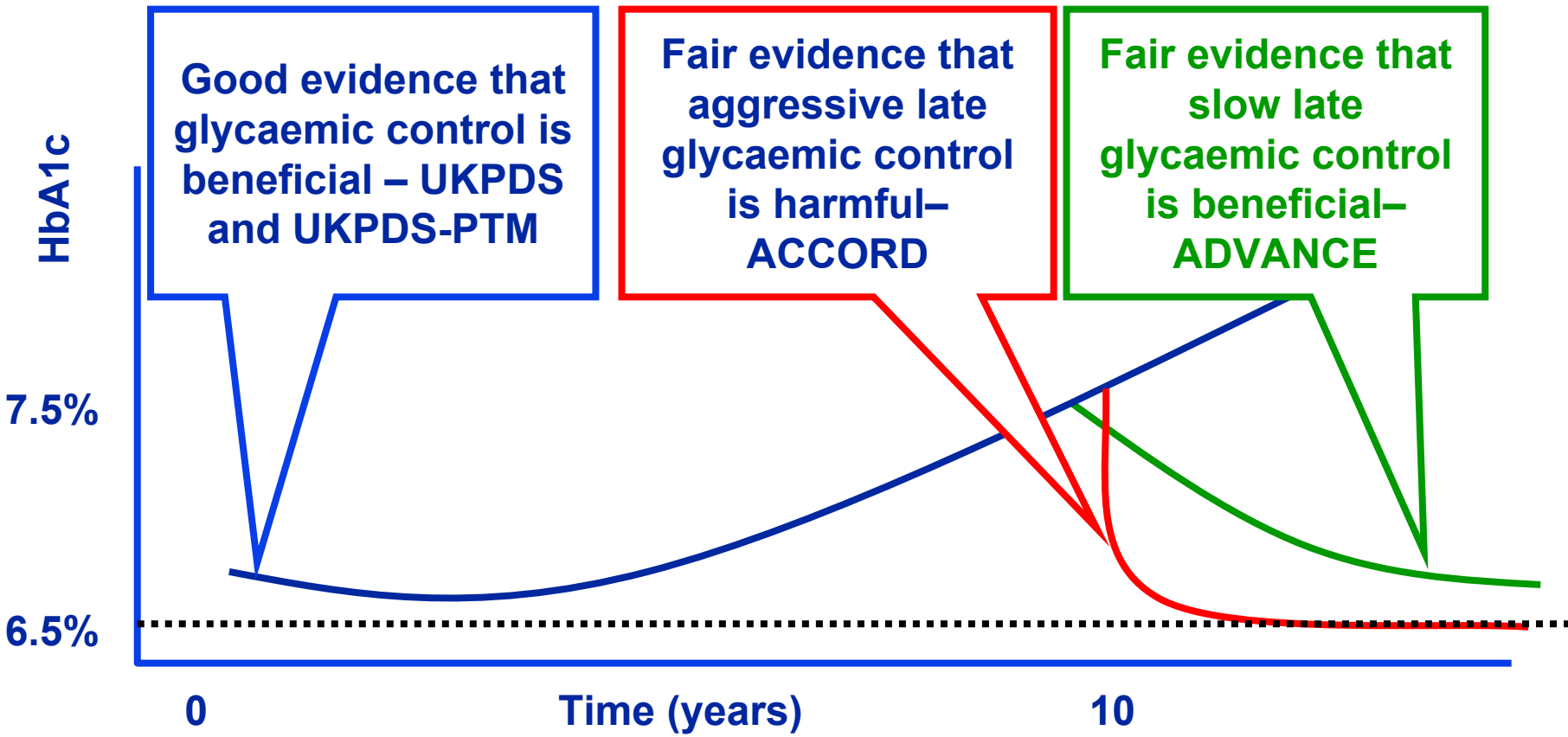


- There will be those who say that we should just lower cholesterol and blood pressure



- There will be those who will become famous for saying almost anything, but loudly

Summary of evidence



- Good evidence for metformin (UKPDS)
- Fair evidence for gliclazide and pioglitazone (ADVANCE and ProACTIVE)
- Poor evidence for rosiglitazone (ACCORD and RECORD)

If you have been…

…thank you for listening