New Therapies for Type 2 Diabetes Have Added Little to Improve Glycaemic Control Compared with Conventional Therapies

Against the motion:

Mark Savage

Glycaemic Control

- We must take glycaemic control to mean control of diabetes
- Pure “Glucocentric” approach is not control
- We can all control glucose with U500 insulin if required!

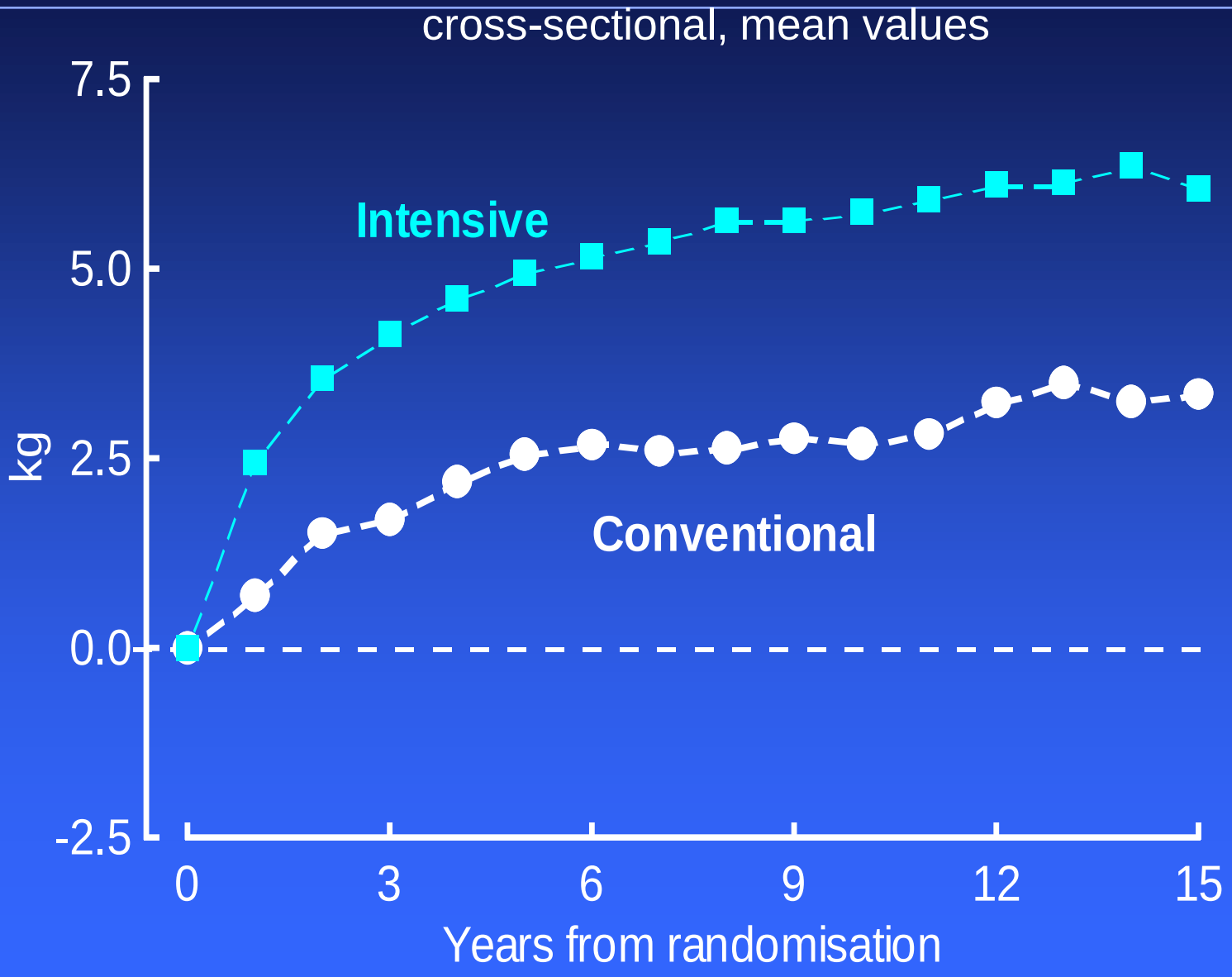
- So what we need is value added and fewer side effects

The Problems

Weight and hypoglycaemia

Weight

Change in Body Weight



Aberdeen Study

- 263 T2DM who died in 85/86.
- Mean age 65 yrs at diagnosis and 72 and 75 for men and women at death.
- Life expectancy at age 65 was 35% less than published figures for the general population.
- For each 1 kg weight loss there was 3-4 months prolonged survival

Surgical Weight Loss and Diabetes

- Australia (Melbourne)

- 2008 Surgical Study, Lap Banding.
- T2DM <2 yrs. 60 patients, 30 in each group (surgical and conventional lifestyle)
- Remission rate 73%(22) in surgical group and 13%(4) in standard care group
- Weight loss in surgical group was 21% and 1.7% in standard group

- Remission: HbA1c <6.2% and FBG <7mmol/l

Severe Hypoglycaemia

People *in Tayside with diabetes and number of severe hypoglycemic events*

	Type 1 diabetes	Type 2 diabetes
n	977 (57% male)	7,678 (52% male)
Mean age (years)	33.1	65.8
Mean diabetes dur^{n} (yrs)	17.0	8.0
Number of episodes	112	132
Number of patients	69	91

Conclusion (Leese et al.)

- “Hypoglycemia requiring emergency assistance from health service personnel is as common in people with type 2 diabetes treated with insulin as in people with type 1 diabetes. It is associated with considerable NHS resource use that has a significant economic and personal cost.”

- For severe hypo if MF is 1 likelihood for SU is 18 and for insulin 236

Today's Diabetes Care

- Albert Einstein:
  - "the definition of insanity is doing the same thing over and over again and expecting different results".
- Anthony Robins:
  - "If you always do what you've always done you'll always get what you've always got"

Agents

- OLD:
  - Metformin
  - Sulfonylureas
  - Meglitinides
  - Acarbose
  - Insulin
- NEWISH: Glitazones
- NEW: DPP-4s/GLP-1s

  Insulin analogues

Ideal Anti Glycaemic Agent

- Controls glucose
- Does not cause weight gain
- Does not affect, or at least does not raise BP
- Does not affect, or at least does not raise lipids
- Easy administration
- No/Few side effects

Ideal Agent?

- Metformin
  - Advantages
    - Small sub-study of UKPDS suggested benefit, not been observed since
    - Weight neutral
    - cheap
  - Disadvantages
    - Makes you sick
    - Twice daily
    - ?Lactic acidosis risk

Ideal Agent?

- SUs (lumped together)
  - Advantages
    - Once daily
    - Lowers blood glucose
    - cheap
  - Disadvantages
    - Hypos
    - Still query over CV safety

Ideal Agent?

- Meglitinides
  - Advantages
    - Occasional benefit for T2DM patient with hectic lifestyle
  - Disadvantages
    - Multiple doses per day
    - No end point data

Ideal Agents?

- TZDs
  - Advantages
    - Once daily
    - Some evidence of CV benefit/no harm
    - Soon to be cheap
  - Disadvantages
    - Heart failure an issue
    - Fractures an issue

Ideal Agents?

- FartAbose
  - Advantages
    - Cheap
    - Some evidence of secondary end point improvement
  - Disadvantages
    - Poor tolerability
    - Multiple dosing

Insulin?

- Advantage
  - Its what's missing
- Disadvantages
  - Therapeutic index very narrow
  - Requires intensive education
  - Requires DSN follow up
  - Hypos
  - Stigma
  - Lipohypertrophy
  - Bruising
  - Resistance
  - Pens difficult for those with poor vision
  - Often require help in elderly
  - Death
  - Etc.etc.

A Tale of 2 Studies

Summary of ACCORD and ADVANCE studies

- Both ACCORD and ADVANCE include patients of similar ages with T2DM of 8–10 years' duration
- Both had >10,000 patients
- HbA_{1c} targets
  - ACCORD: <6% (few attained it anyway)
  - ADVANCE: <6.5% (most met it)

Table 1. **Differences between the ACCORD and ADVANCE Studies.**

Characteristic	ACCORD	ADVANCE
Baseline data		
No. of participants	10,251	11,140
Mean age (yr)	62	66
Duration of diabetes (yr)*	10	8
Median glycated hemoglobin at baseline (%)	8.1	7.2
History of macrovascular disease (%)	35	32
Intervention		
Target glycated hemoglobin value (%)	<6.0	≤6.5
Median duration (yr)	3.4	5.0
Medical treatment at study completion (intensive vs. standard) (%)		
Insulin	77 vs. 55	41 vs. 24
Metformin	95 vs. 87	74 vs. 67
Secretagogue (sulfonylurea or glinide)	87 vs. 74	94 vs. 62
Thiazolidinedione	92 vs. 58	17 vs. 11
Incretin	18 vs. 5	Not reported
Statin	88 vs. 88	46 vs. 48
Any antihypertensive drug	91 vs. 92	89 vs. 88
Angiotensin-converting–enzyme inhibitor	70 vs. 72	Not reported
Aspirin	76 vs. 76	57 vs. 55
Outcome (intensive vs. standard)		
Median glycated hemoglobin at study end (%)	6.4 vs. 7.5†	6.4 vs. 7.0†
Death		
From any cause (%)	5.0 vs. 4.0†	8.9 vs. 9.6
From cardiovascular causes (%)	2.6 vs. 1.8†	4.5 vs. 5.2
Nonfatal myocardial infarction (%)	3.6 vs. 4.6†	2.7 vs. 2.8
Nonfatal stroke (%)	1.3 vs. 1.2	3.8 vs. 3.8
Major hypoglycemia requiring assistance (ACCORD), or severe hypoglycemia (ADVANCE) (%/yr)	3.1 vs. 1.0†	0.7 vs. 0.4
Weight gain (kg)	3.5 vs. 0.4	0.0 vs. −1.0†
Current smoking (%)	10 vs. 10	8 vs. 8

* Duration of diabetes is the median for the ACCORD trial and the mean for the ADVANCE trial.
† The comparison of the intervention with the standard therapy was significant.

ACCORD and ADVANCE

- “Traditional” agents used almost exclusively
- No evidence of benefit in favour of aggressive glucocentric approach to diabetes

Can traditional agents do any good for CV disease?

UKPDS

- 80!!!

UKPDS 80

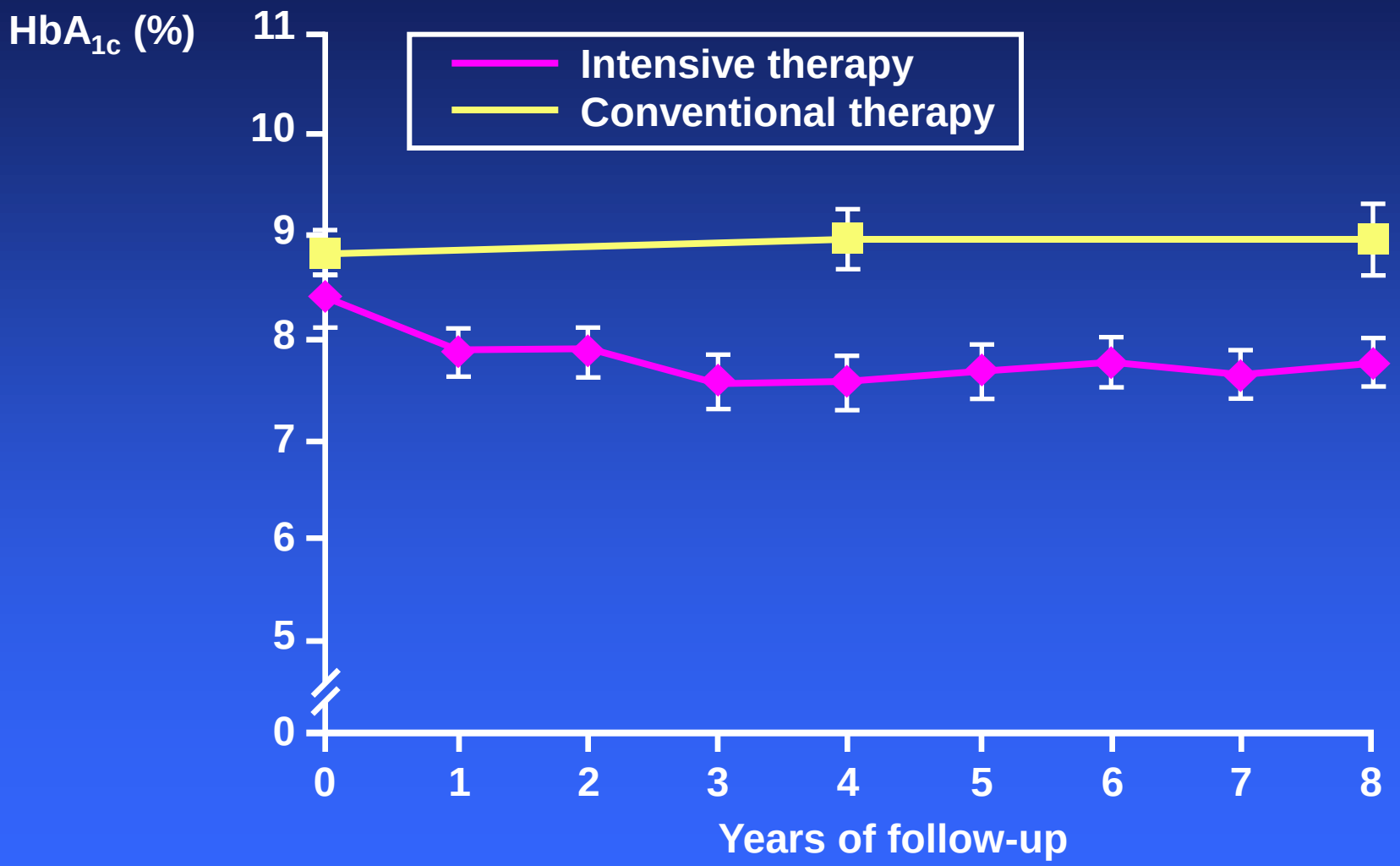
- In the intensive group, relative reductions in risk persisted at 10 years for
  - any diabetes-related end point (9%, P=0.04)
  - microvascular disease (24%, P=0.001)
  - myocardial infarction (15%, P=0.01)
  - death from any cause (13%, P=0.007).

STENO-2

- Aim
  - to compare the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for CVD in 160 patients with Type 2 diabetes and microalbuminuria
- Design:
  - conventional treatment from their GP in accordance with Danish guidelines (n=80)
  - intensive multifactorial intervention targeting hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria, overseen by a doctor, nurse and dietician (n=80)

Gaede *et al*. NEJM 2003; 348: 383–393

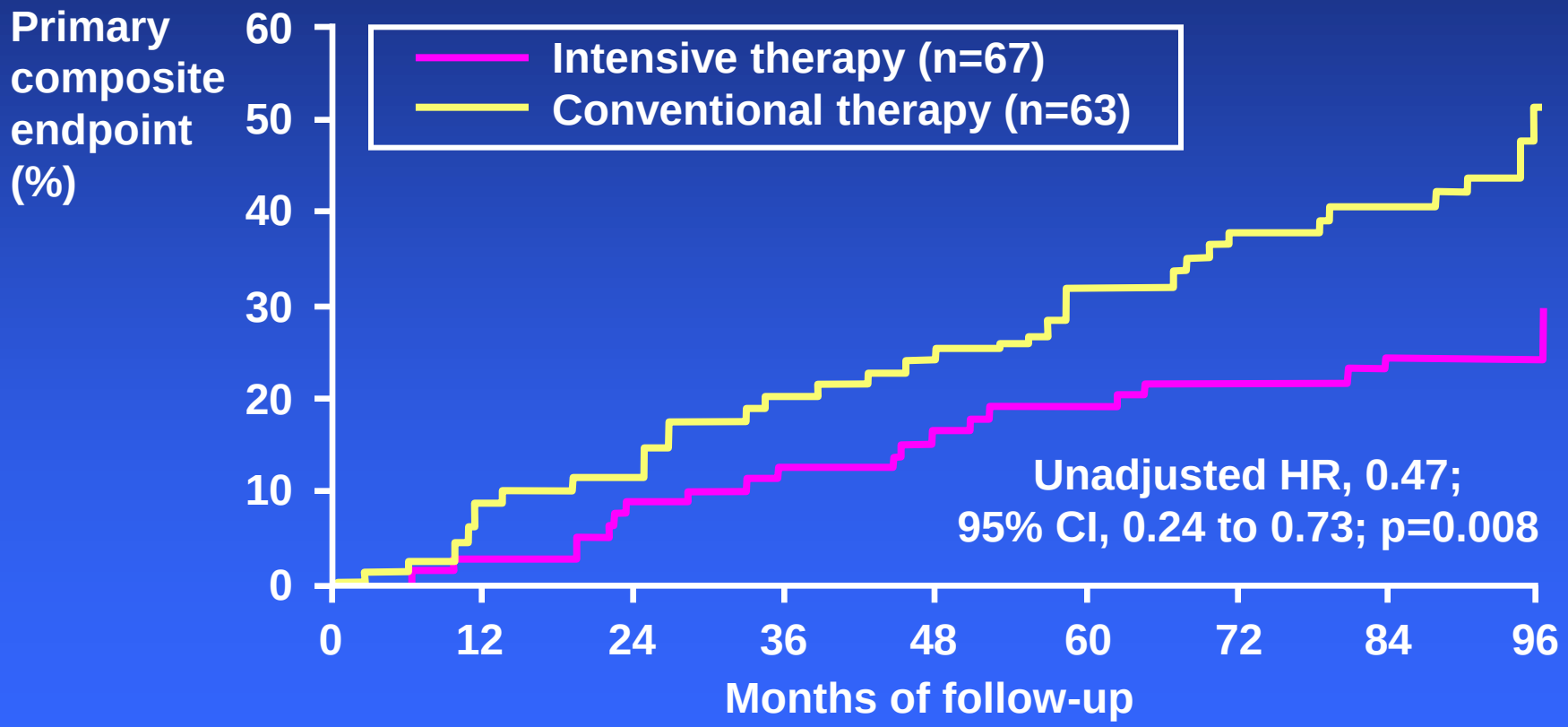
STENO-2: Mean change in HbA_{1c}



Gaede *et al*. NEJM 2003; 348: 383–393

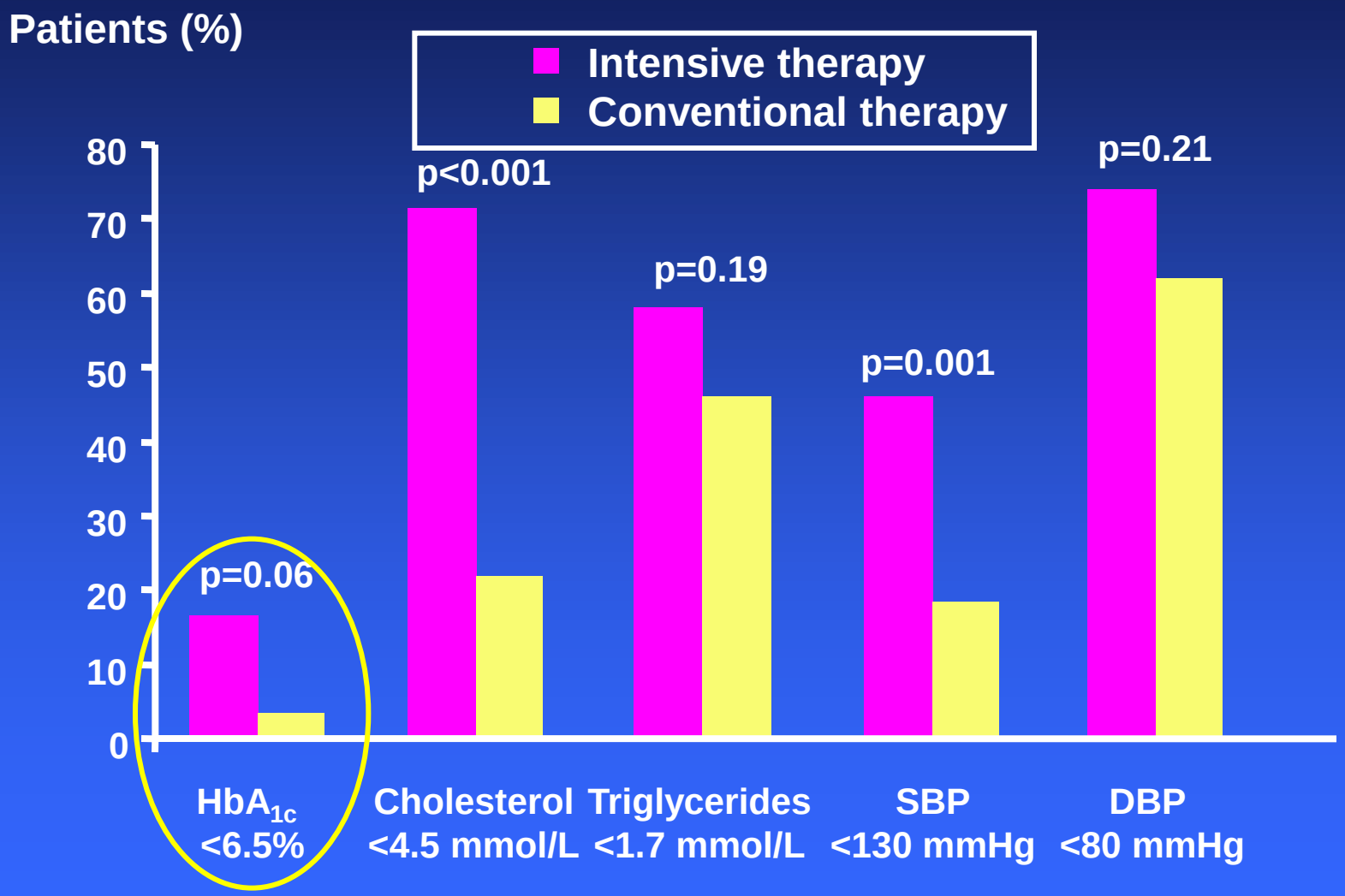
STENO-2

Primary endpoint: composite of death from CV causes, non-fatal MI, coronary artery bypass surgery, percutaneous intervention, non-fatal stroke, vascular surgery for peripheral vascular disease and amputation as a result of ischaemia



Adapted from Gaede *et al*. NEJM 2003; 348: 383–393

STENO-2: % of patients reaching intensive treatment goals



Gaede *et al*. NEJM 2003; 348: 383–393

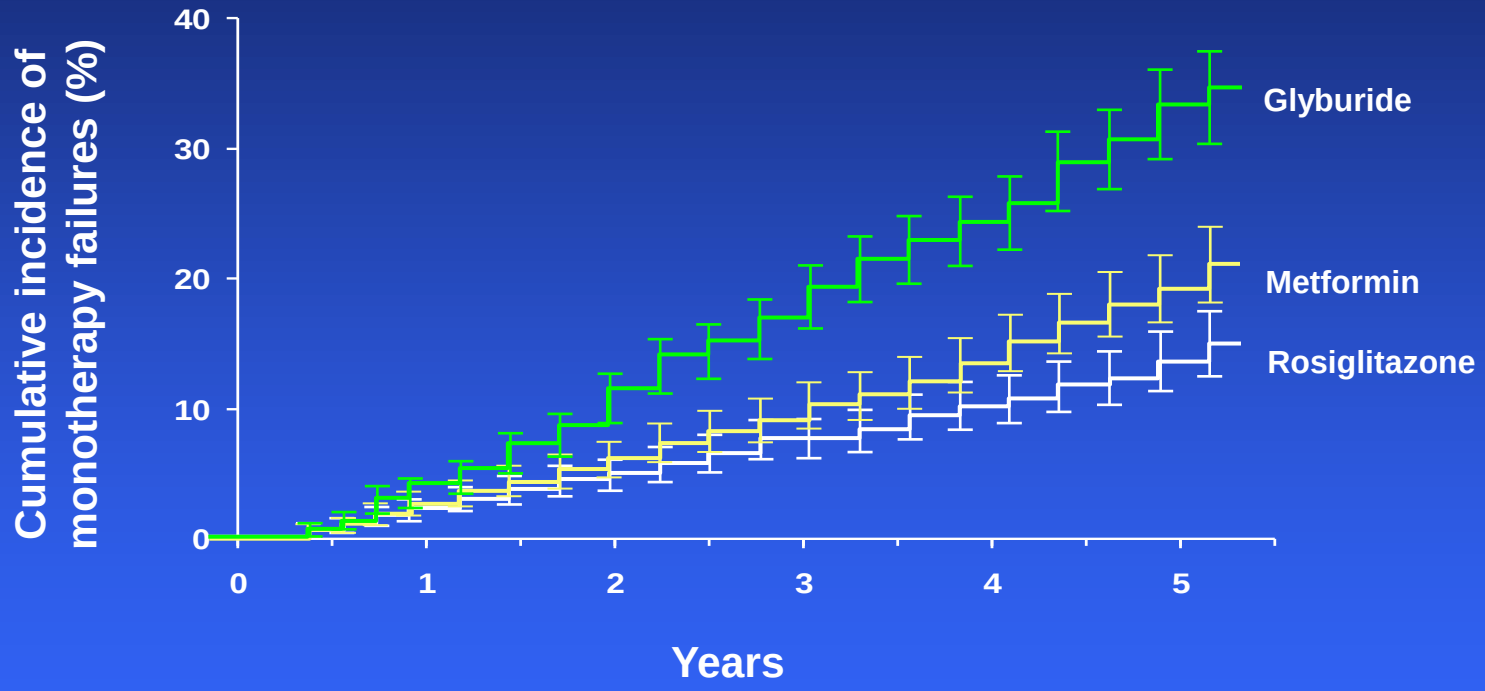
STENO-2

- Long-term intensified multifactorial intervention in patients with Type 2 diabetes and microalbuminuria reduced the risk of cardiovascular and microvascular events by around 50%
- HbA1c very difficult to treat

Gaede *et al*. NEJM 2003; 348: 383–393

ADOPT:

Kaplan-Meier estimates of the cumulative incidence of monotherapy failures (FPG>10 mmol/l) at 5 years



FPG = fasting plasma glucose

6. Kahn SE et al. *N Engl J Med* 2006;355:2427-2443. Reproduced with permission from reference 6.

“What have the Romans Done For Us?”

Got us half way there?

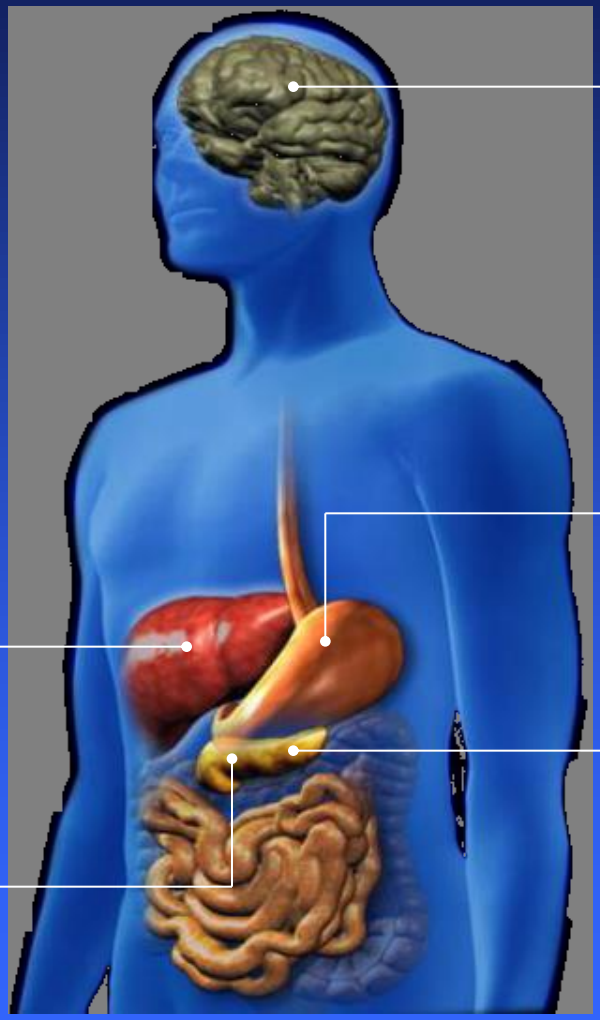
Surely we can do better?

What do patients (and Doctors) want?

- Efficacy
- Few side effects
- Particularly
  - No or few hypos
  - No weight gain

New Kids on the Block

The Multiple Modes of Action of GLP-1



CNS:
Promote satiety and reduction of appetite

Stomach:
Slow gastric emptying

β-cell:
Stimulate glucose-dependent insulin secretion; increase gene expression of key β-cell genes; and increase β-cell mass (in animal models)

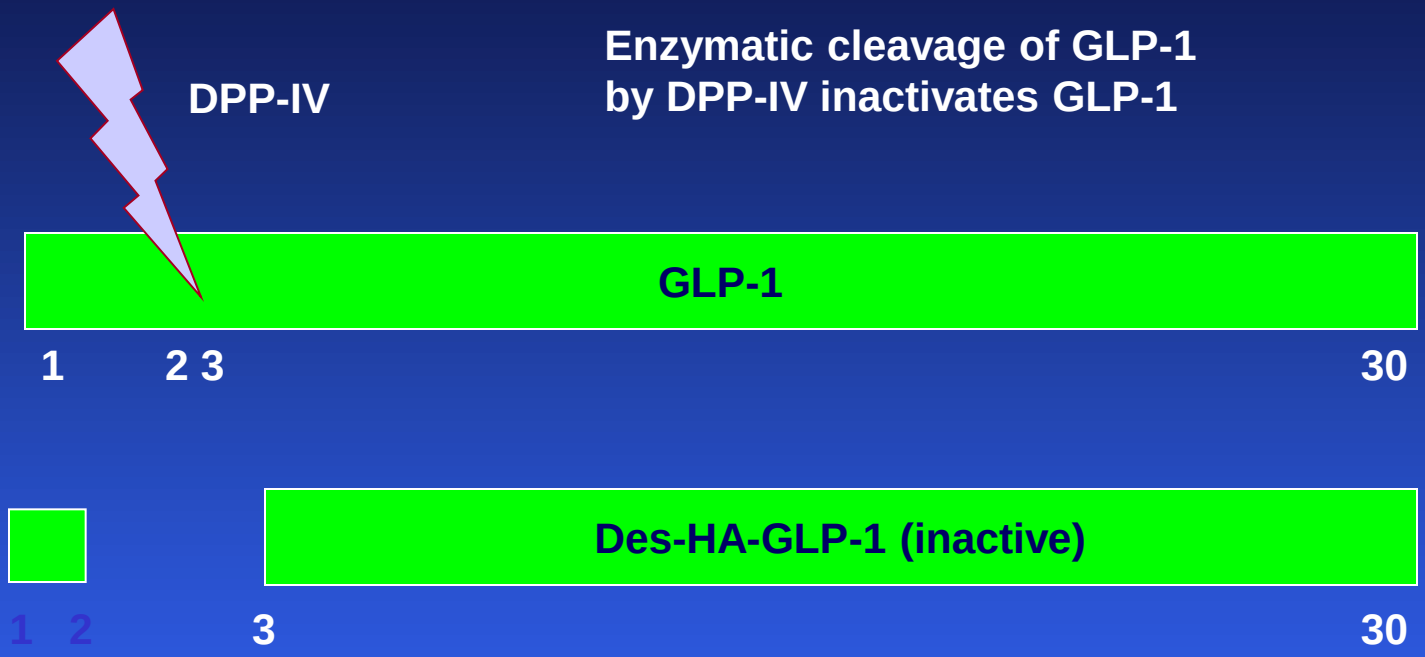
Liver:
Reduce hepatic glucose output by inhibiting α-cell secretion of glucagon

α-cell:
Inhibit glucagon secretion

CNS: Central nervous system

Flint A, et al. *J Clin Invest.* 1998;101:515-520; Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422; Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553; Drucker DJ. *Diabetes.* 1998;47:159-169.

Degradation of GLP-1



Two possible solutions to utilize GLP-1 action therapeutically

- Long-acting DPP-IV resistant GLP-1 analogs/incretin mimetics
- DPP-IV inhibitors

DPP-IV: Dipeptidyl peptidase-IV

Adapted from: Mentlein R, et al. *Eur J Biochem.* 1993;214:829-835; Gallwitz B, et al. *Eur J Biochem.* 1994;225:1151-1156.

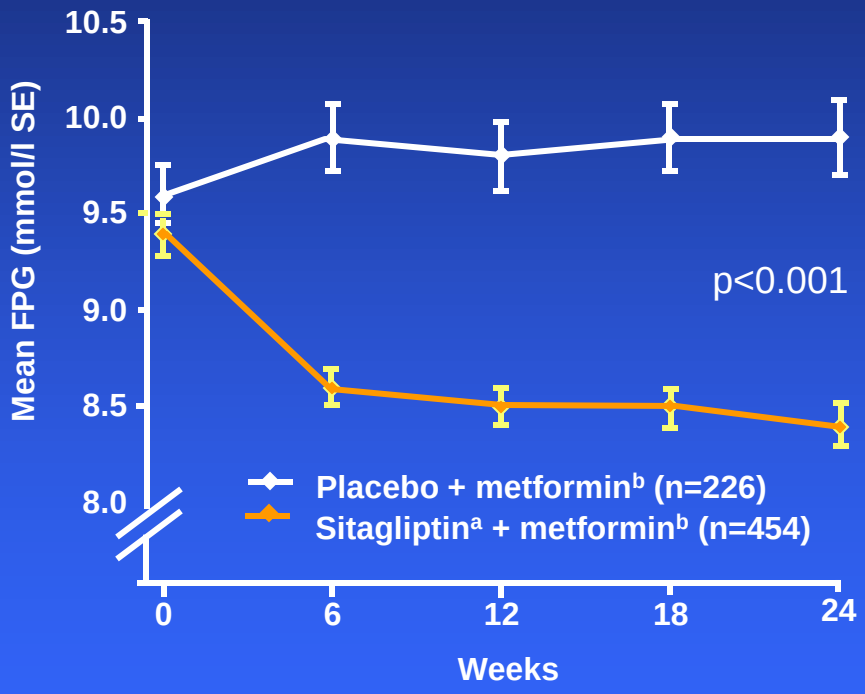
New Kids

- DPP4s
  - Sitagliptin
  - Vildagliptin
  - Saxagliptin
- GLP-1 Mimetics
  - Exenatide
  - Liraglutide

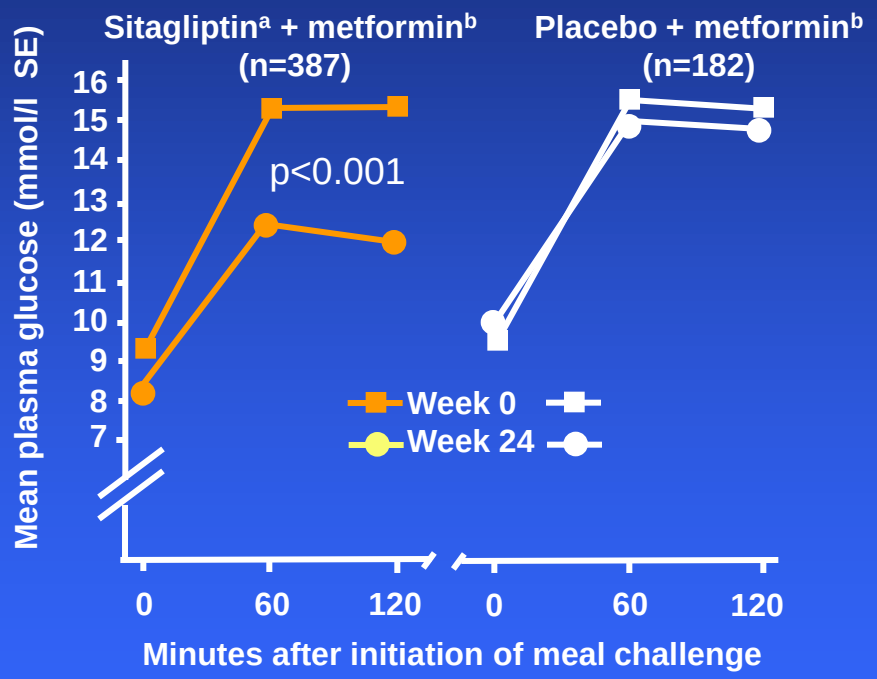
Sitagliptin: Add-on therapy to metformin

Significantly improved fasting and post-meal glucose

Fasting plasma glucose



Post-meal glucose



LSM between-group differences at week 24 (95% CI) change in FPG vs placebo = 1.4 mmol/l [-1.7, -1.1] (p<0.001).

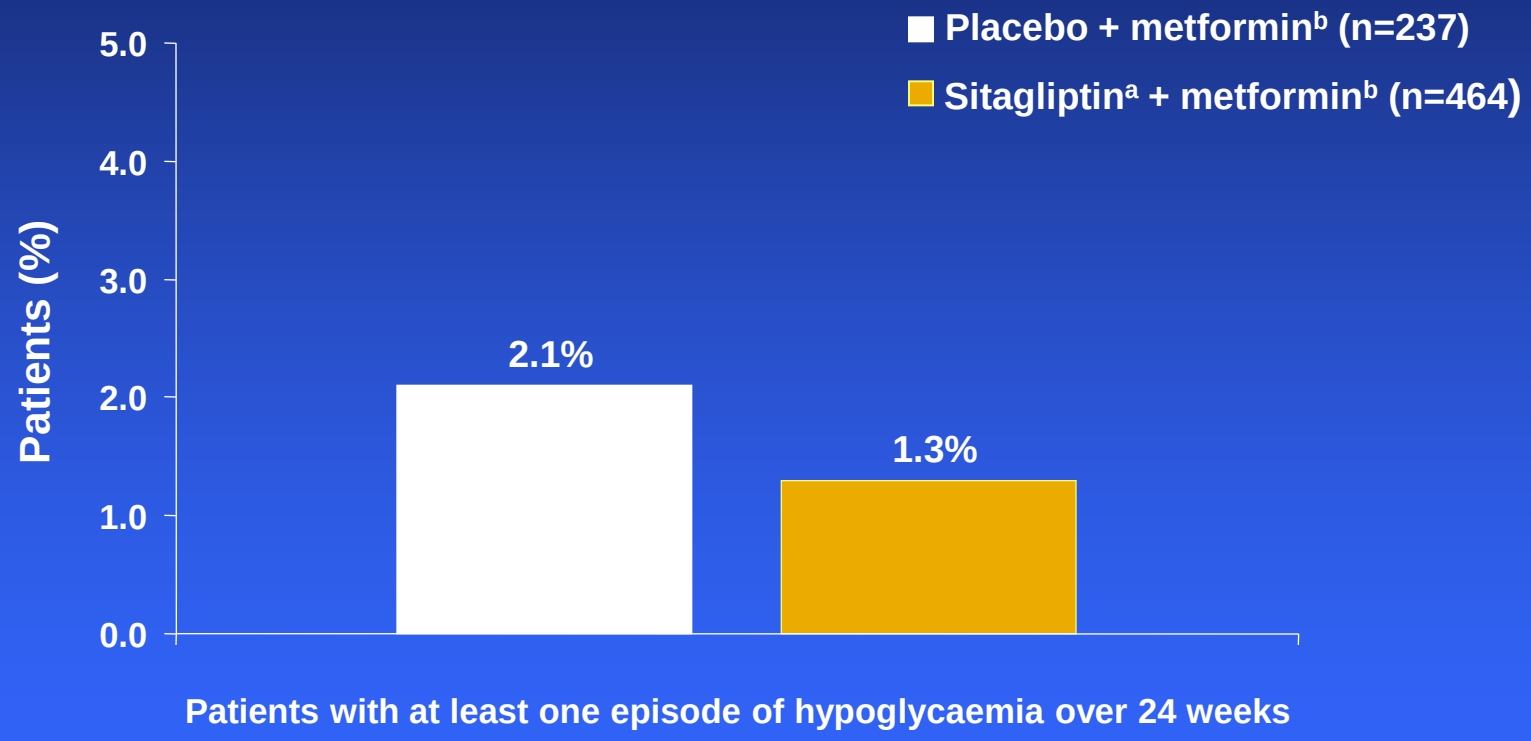
[a]Sitagliptin 100 mg o.d.; [b]Metformin ≥1,500 mg/day

Charbonnel B et al for the Sitagliptin Study 020 Group. *Diabetes Care* 2006;29:2638-2643.

Sitagliptin clinical studies: Add-on therapy to metformin

Incidence of hypoglycaemia

% patients with at least one episode of hypoglycaemia over 24 weeks



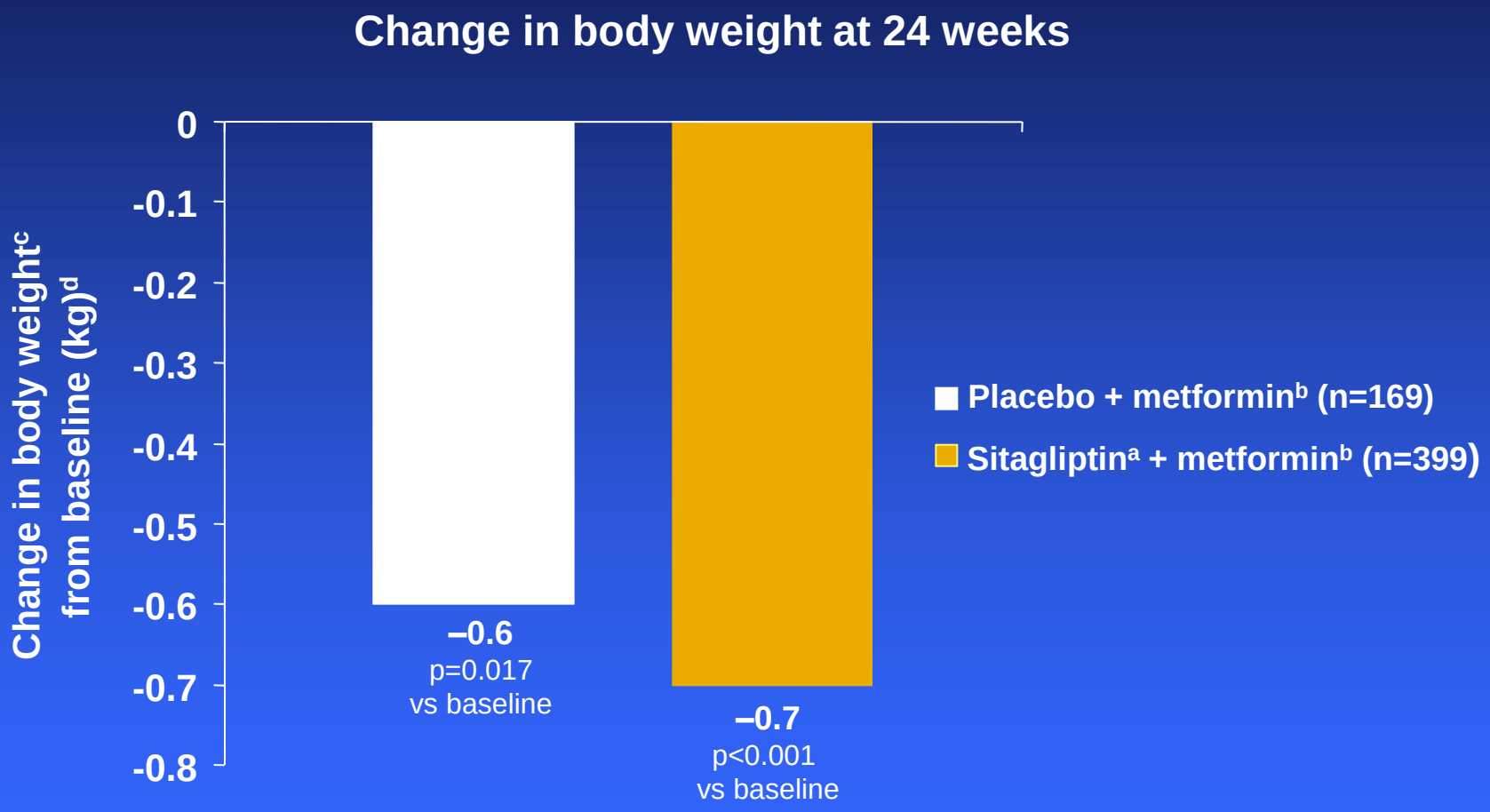
All-patients-as-treated population

[a]Sitagliptin 100 mg o.d.; [b]Metformin ≥1,500 mg/day

Charbonnel B et al for the Sitagliptin Study 020 Group. *Diabetes Care* 2006;29:2638-2643.

Sitagliptin clinical studies: Add-on therapy to metformin

Change in body weight

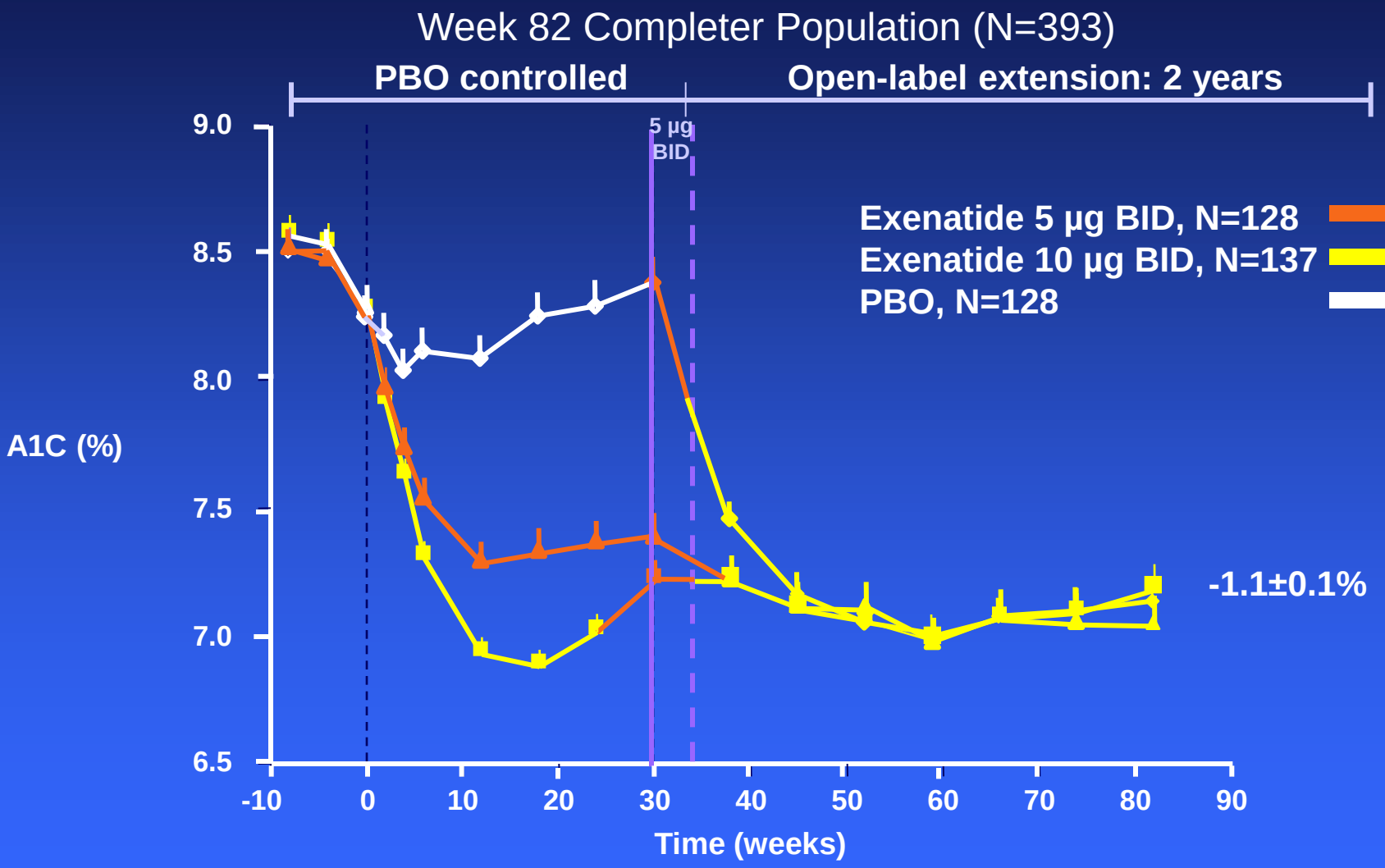


[a]Sitagliptin 100 mg o.d.; [b]Metformin ≥1,500 mg/day; [c]Excluding data after initiation of glycaemic rescue therapy; [d]least squares means

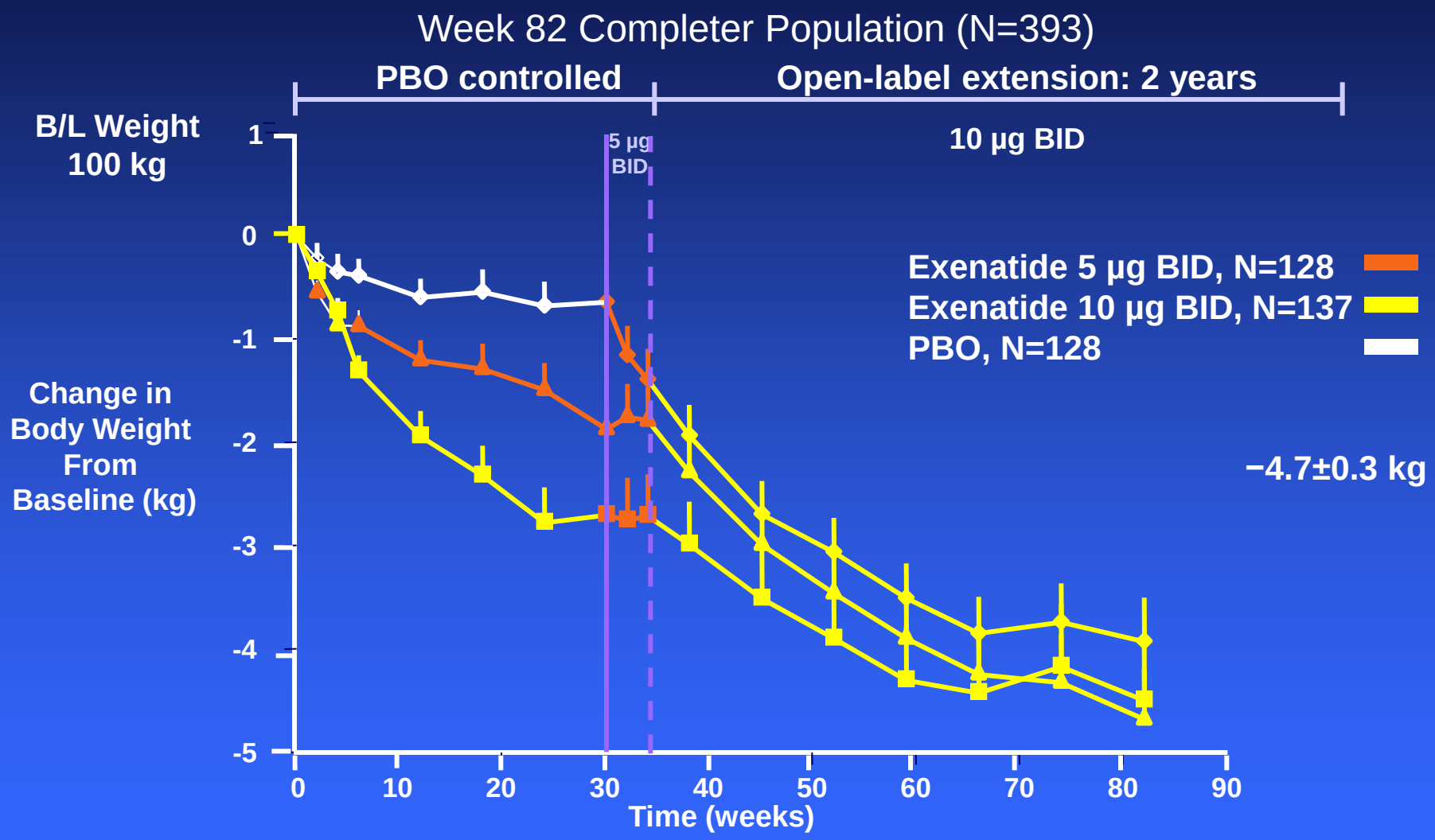
Charbonnel B et al for the Sitagliptin Study 020 Group. *Diabetes Care* 2006;29:2638-2643.

Data on file, Merck Sharp & Dohme Limited.

PBO-controlled/Open-label Extension (Combined): Exenatide Sustained HbA1c Reduction



PBO-controlled/Open-label Extension (Combined): Exenatide Continued to Reduce Weight



New, or false, Dawn?

- Unclear at present
- Agents new

- However……

Remember:

- Albert Einstein:
  - “the definition of insanity is doing the same thing over and over again and expecting different results”.
- Anthony Robins:
  - “If you always do what you’ve always done you’ll always get what you’ve always got”
- Savage:
  - “If we treat out patient they way we always have, we will not improve on UKPDS”

Be Brave

Vote Against the Motion

Metformin and SUs: the UKPDS

Treatment Policies in 3867 patients

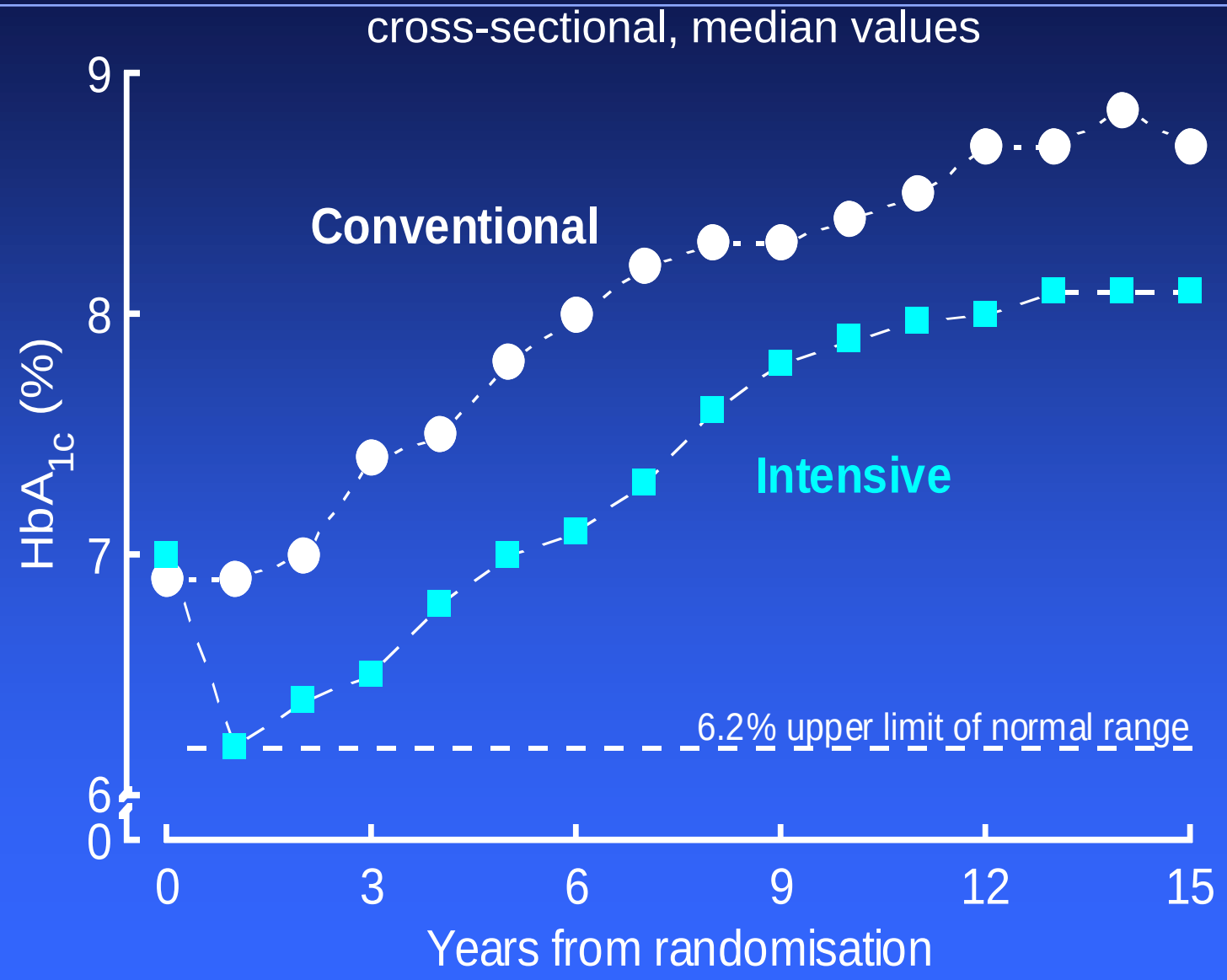
Intensive Policy with sulphonylurea or insulin

n = 2729

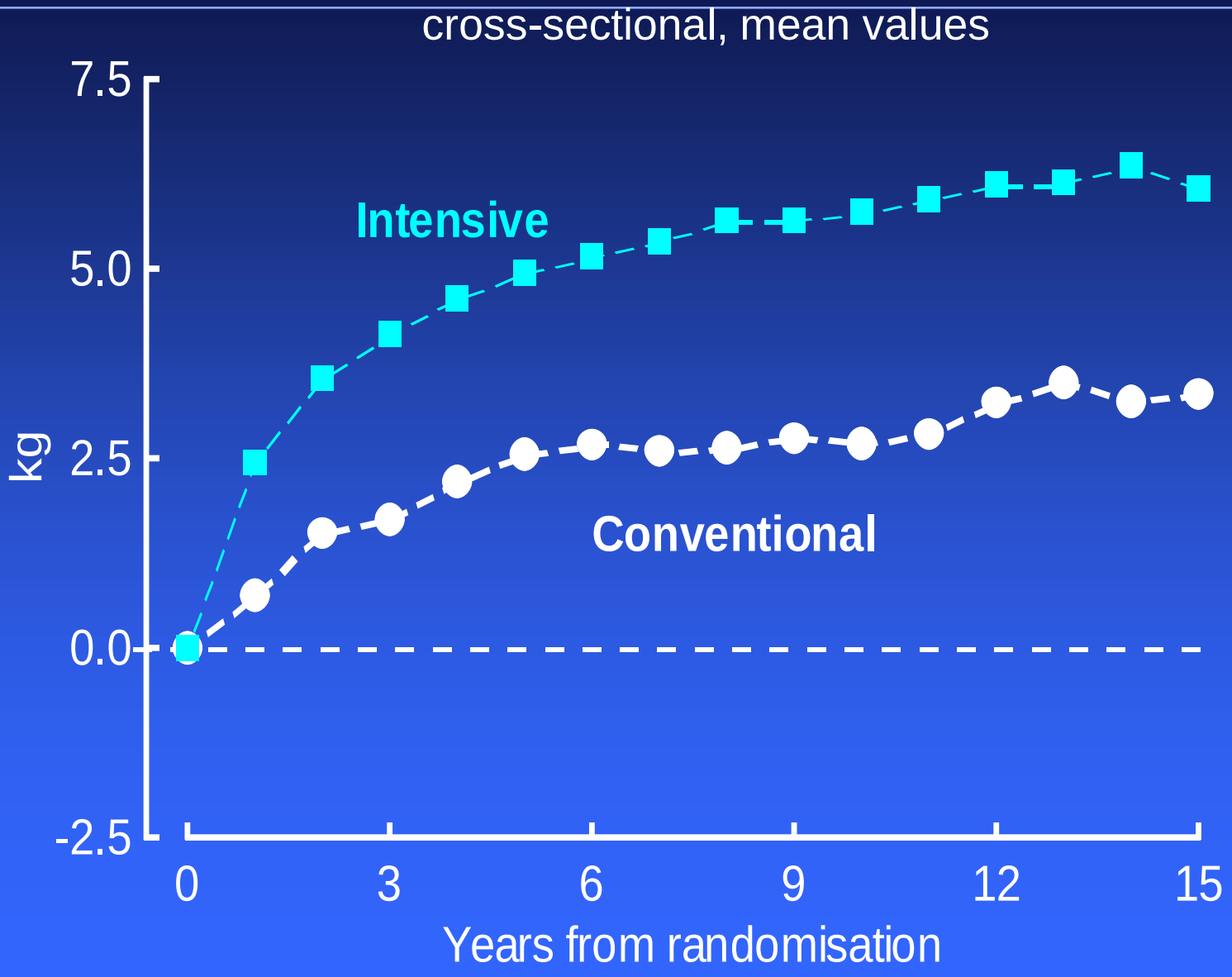
- aim for
  fasting plasma glucose < 6 mmol/L
  asymptomatic

- when marked hyperglycaemia develops
  on sulphonylurea
    add metformin
    move to insulin therapy
  on insulin, transfer to complex regimens

HbA_{1c}

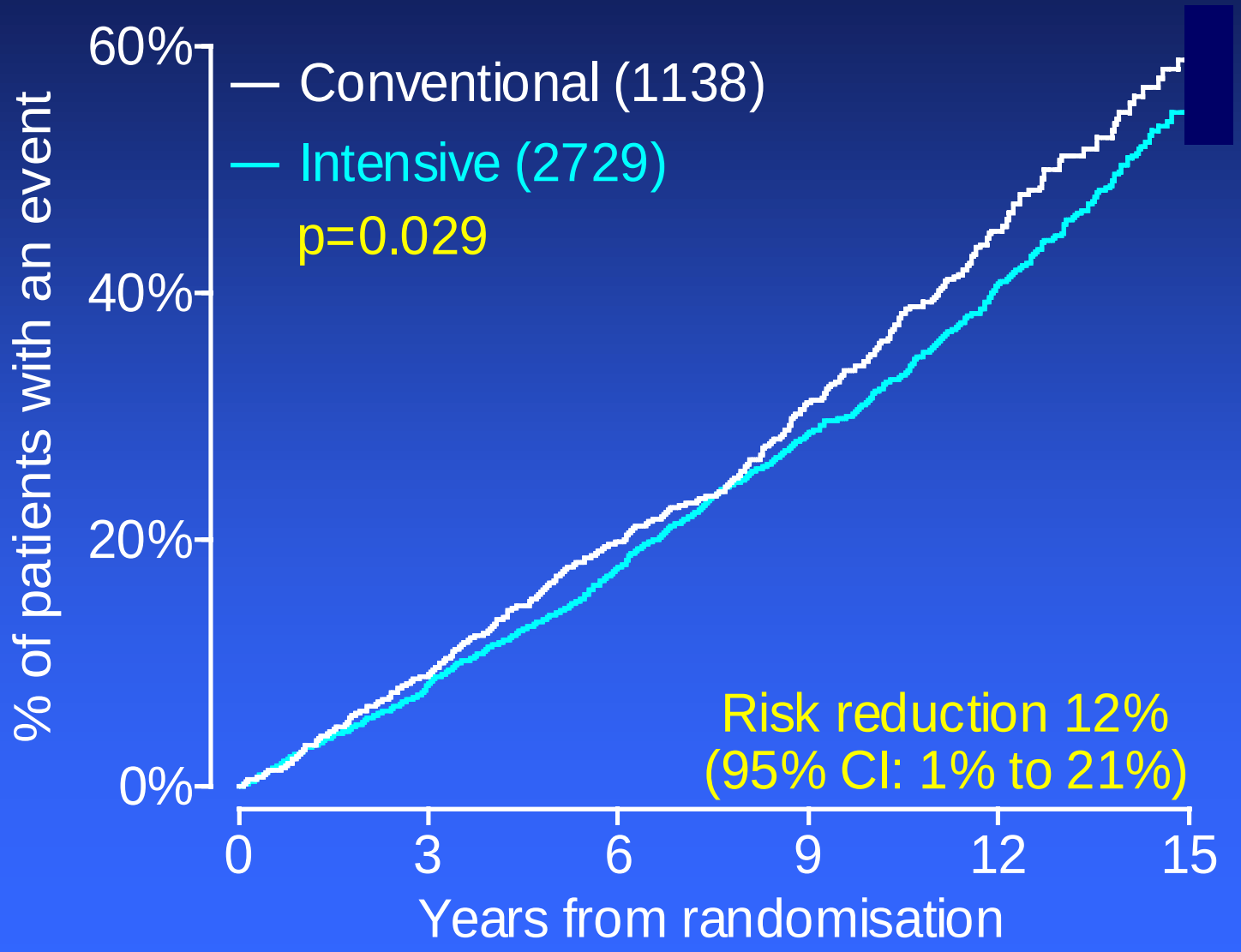

cross-sectional, median values
9
8
7
6
0
HbA_{1c} (%)
Conventional
Intensive
6.2% upper limit of normal range
0
3
6
9
12
15
Years from randomisation

Change in Body Weight



Any Diabetes Related Endpoint (cumulative)

1401 of 3867 patients (36%)



Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA_{1c} by 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints	p=0.0099
16%	for myocardial infarction	p=0.052
24%	for cataract extraction	p=0.046
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years p=0.000054	

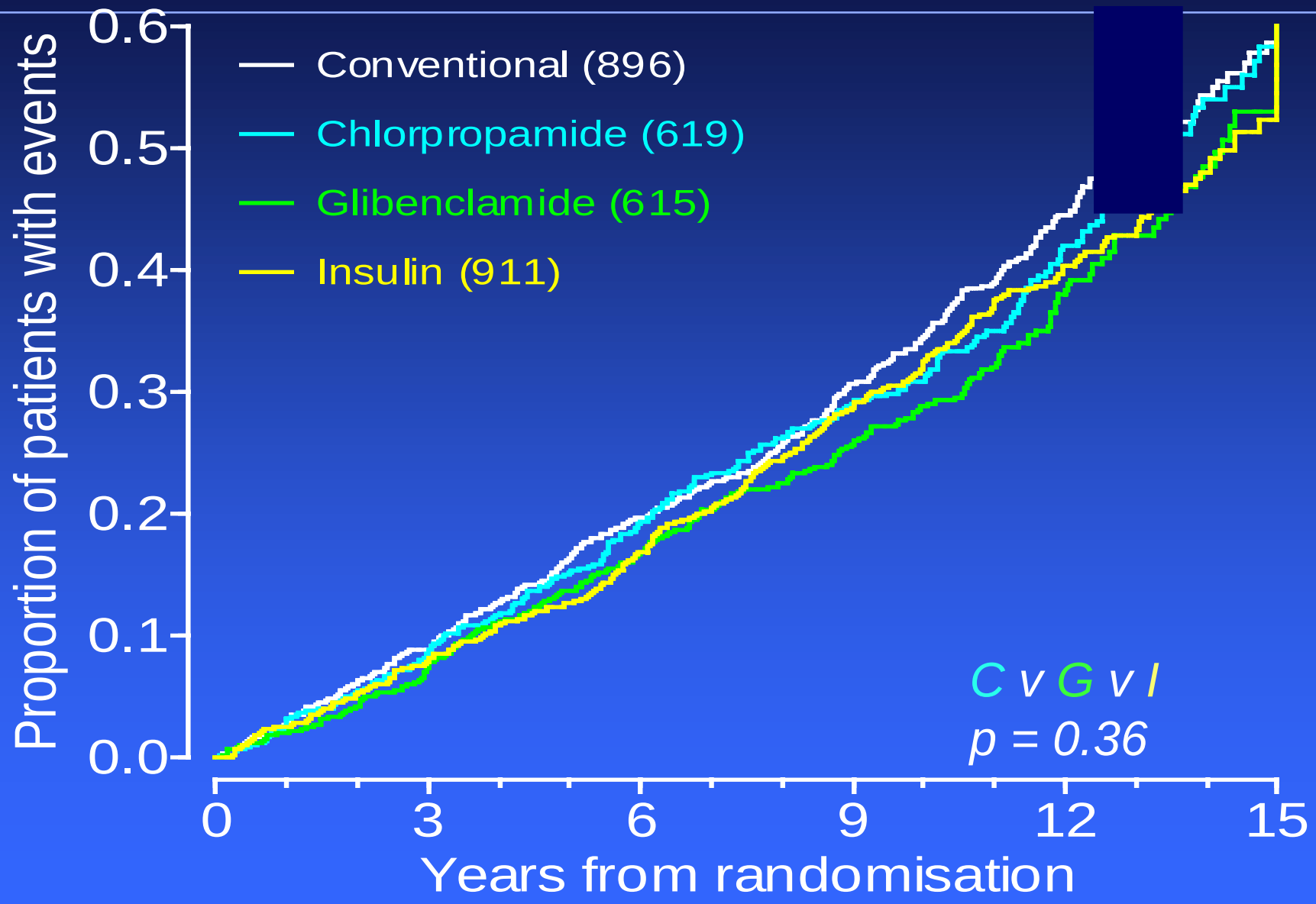
Conclusion

The UKPDS has shown that intensive blood glucose control reduces the risk of diabetic complications, the greatest effect being on microvascular complications

UK Prospective Diabetes Study

Does insulin or sulphonylurea therapy have specific advantages or disadvantages?

Any diabetes-related endpoints



Sulphonylurea or Insulin : Summary 1

- all three therapies were similarly effective in reducing HbA_{1c}
- all three therapies had equivalent risk reduction
  for major clinical outcomes
  compared with conventional policy
- in those allocated to chlorpropamide there was equivalent reduction of risk of microalbuminuria but no reduction of risk of progression of retinopathy

Sulphonylurea or insulin : Summary 2

Sulphonylurea therapy

- no evidence of deleterious effect on myocardial infarction, sudden death or diabetes related deaths

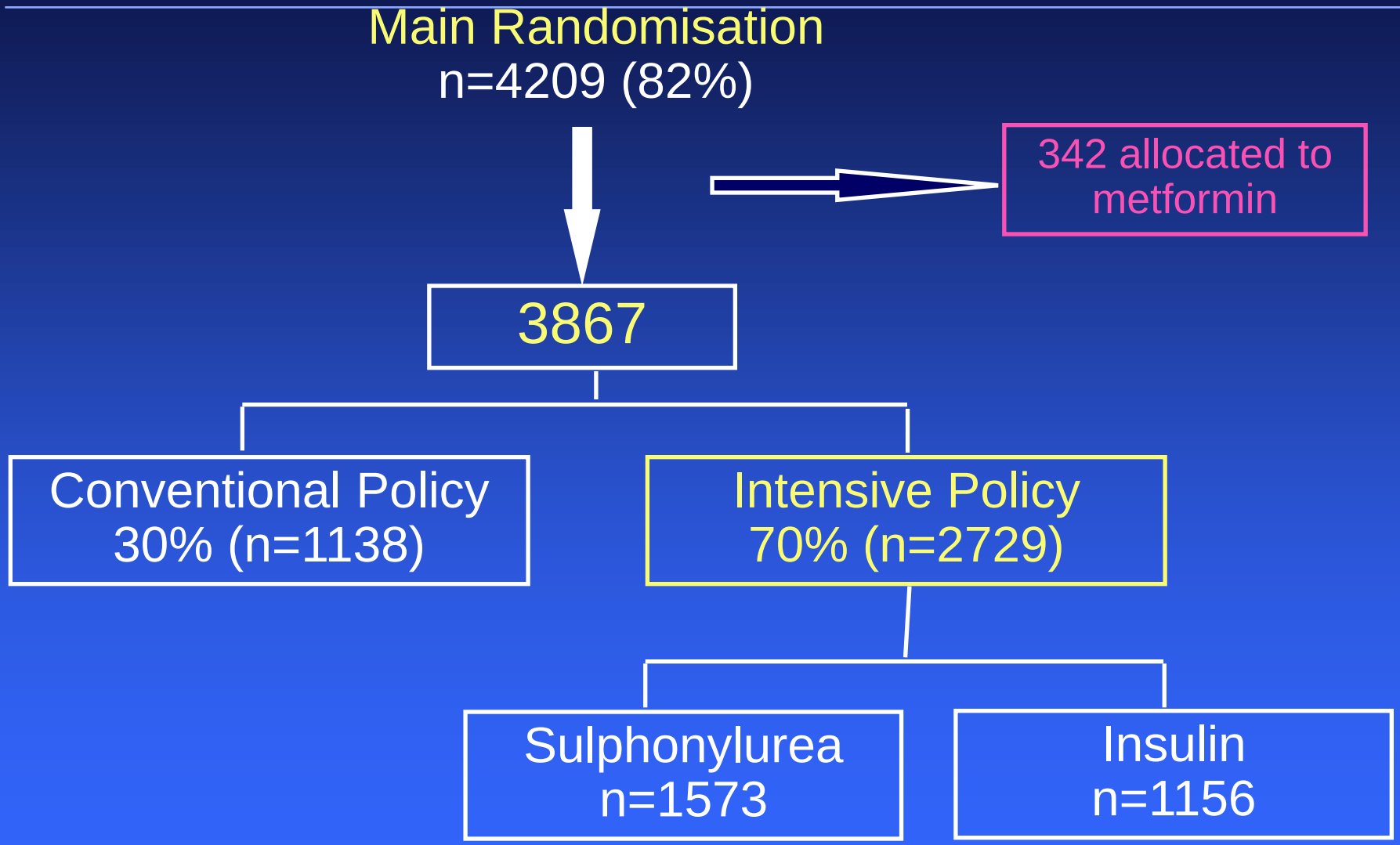
Insulin therapy

- no evidence for more atheroma-related disease

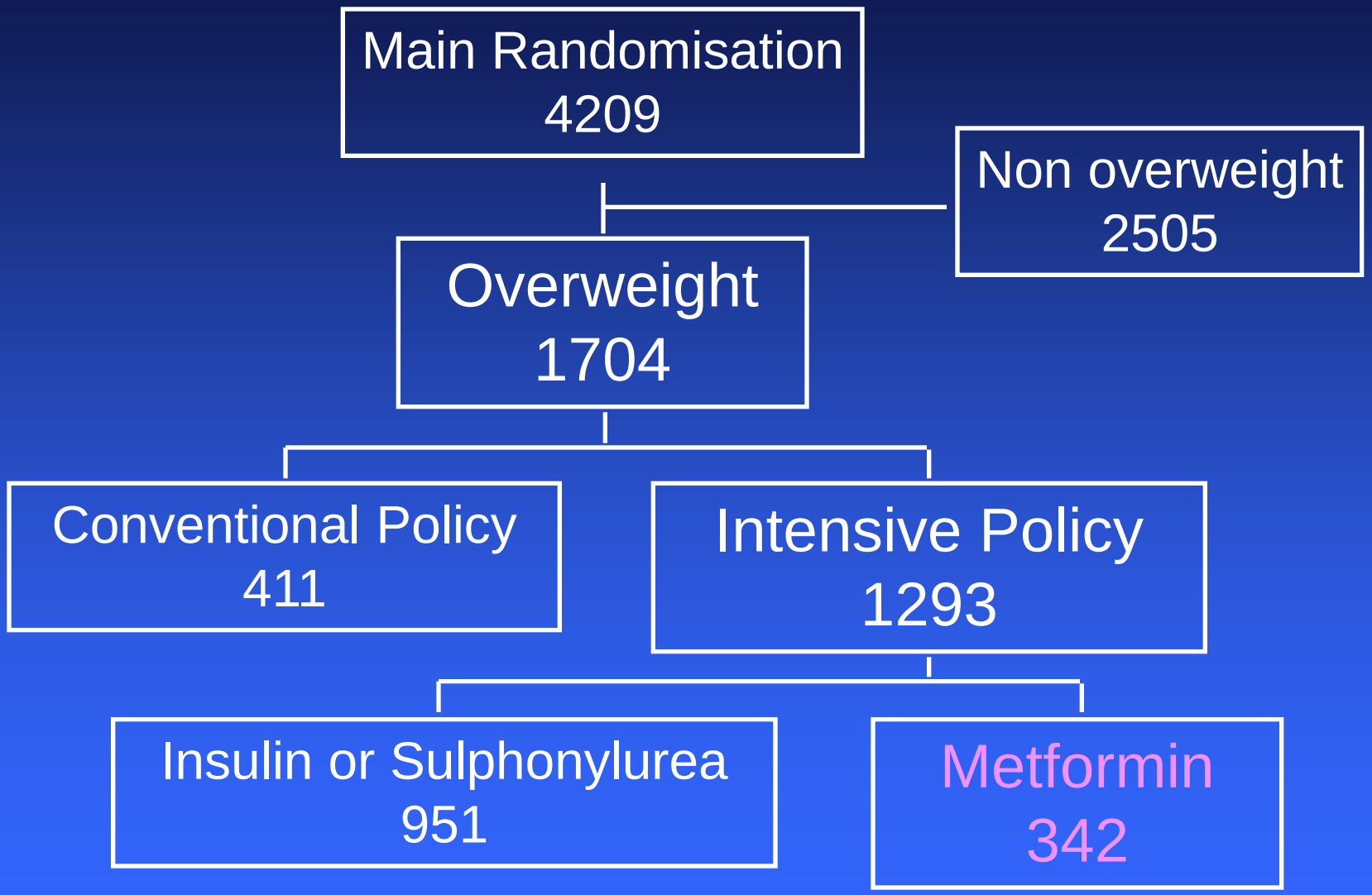
UK Prospective Diabetes Study

Does metformin in overweight diabetic patients have any advantages or disadvantages?

Randomisation of Treatment Policies



Randomisation



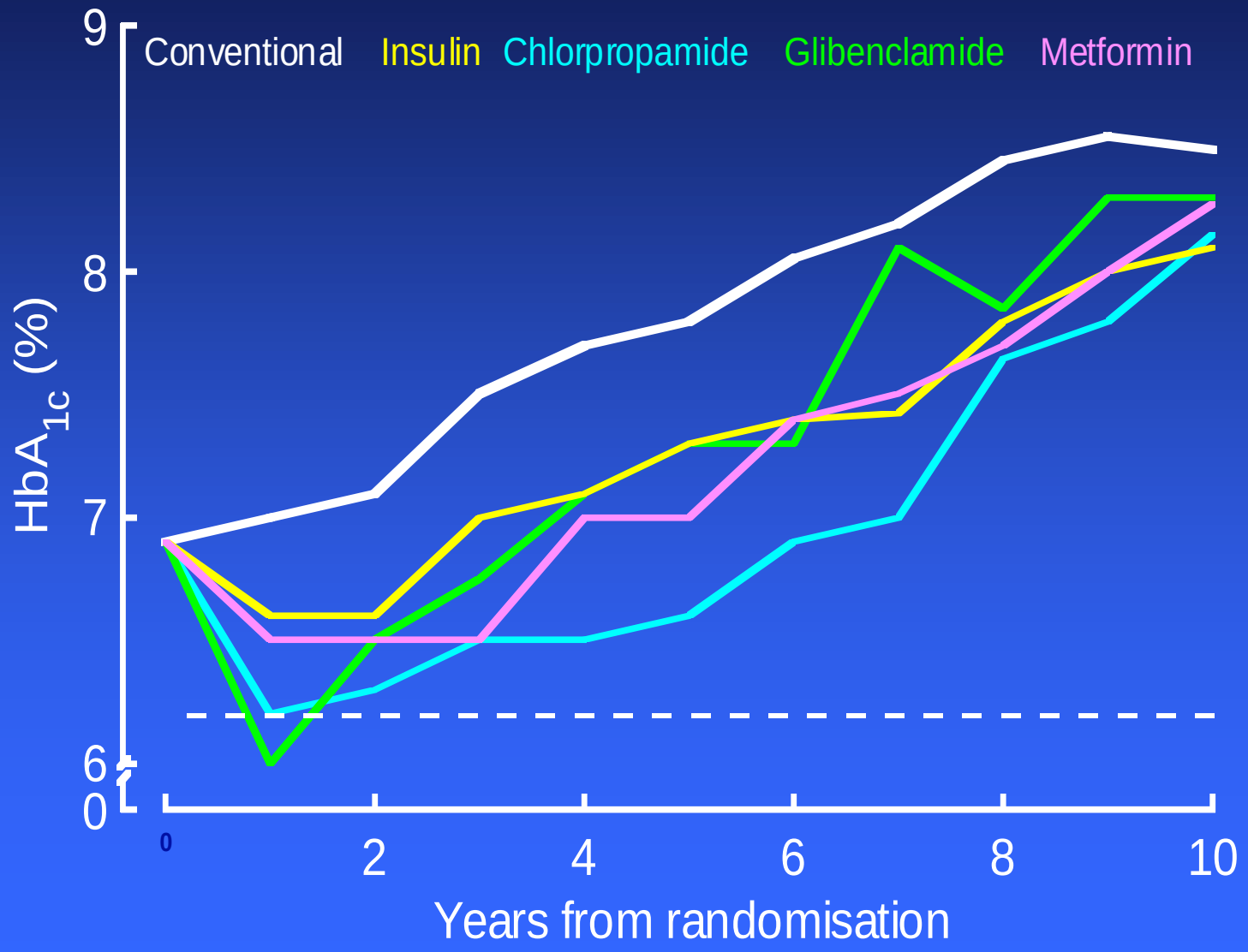
Patient Characteristics

overweight patients > 120% ideal body weight
after three months' diet therapy

age	*mean*	53 years
gender	male / female	46% / 54%
ethnic groups	Caucasian	86%
	Asian	6%
	African-Caribbean	8%
Body Mass Index	*mean*	31 kg/m^2
fasting plasma glucose	*median*	8.1 mmol/L
HbA_{1c}	*mean*	7.2 %

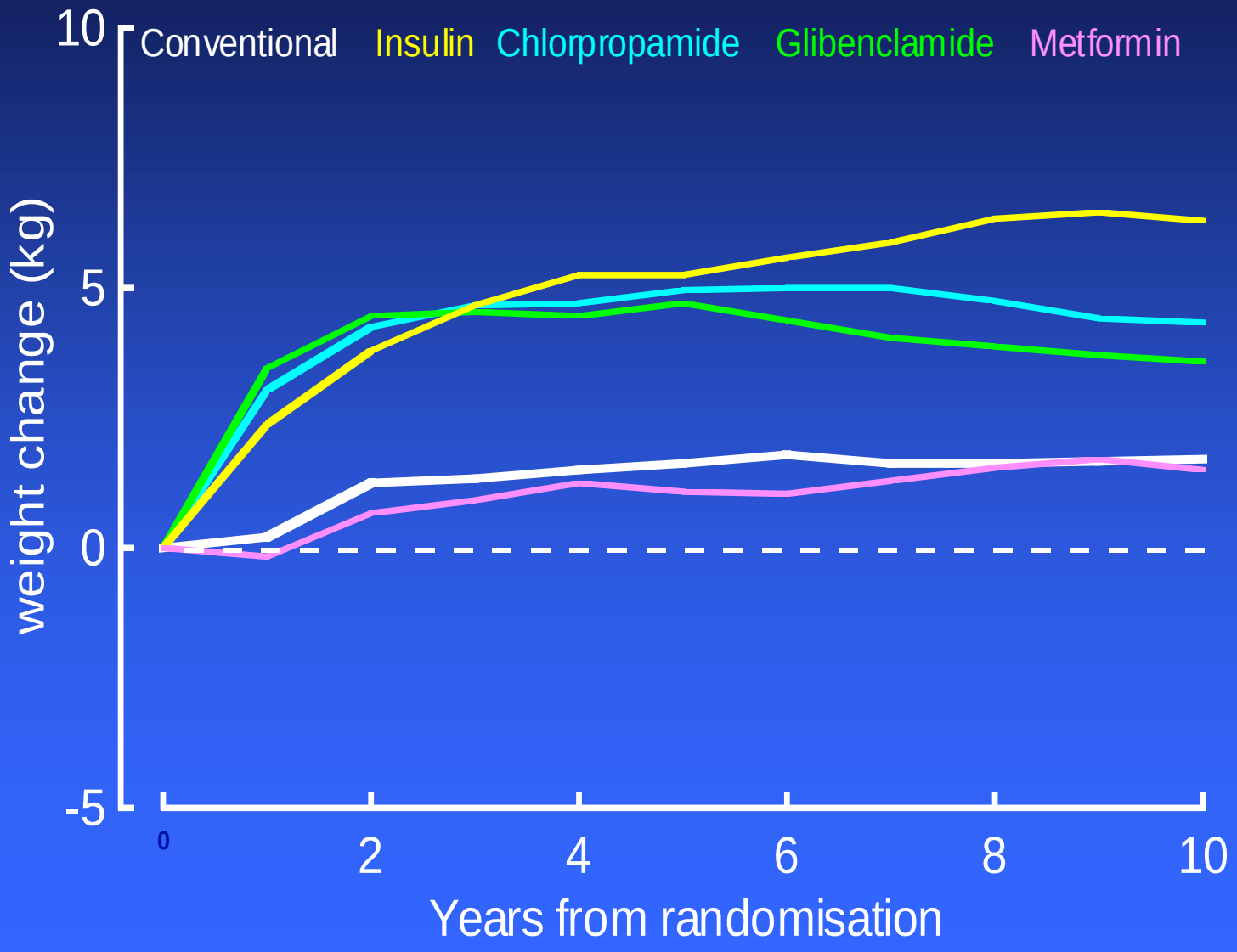
HbA_{1c}

overweight patients cohort, median values

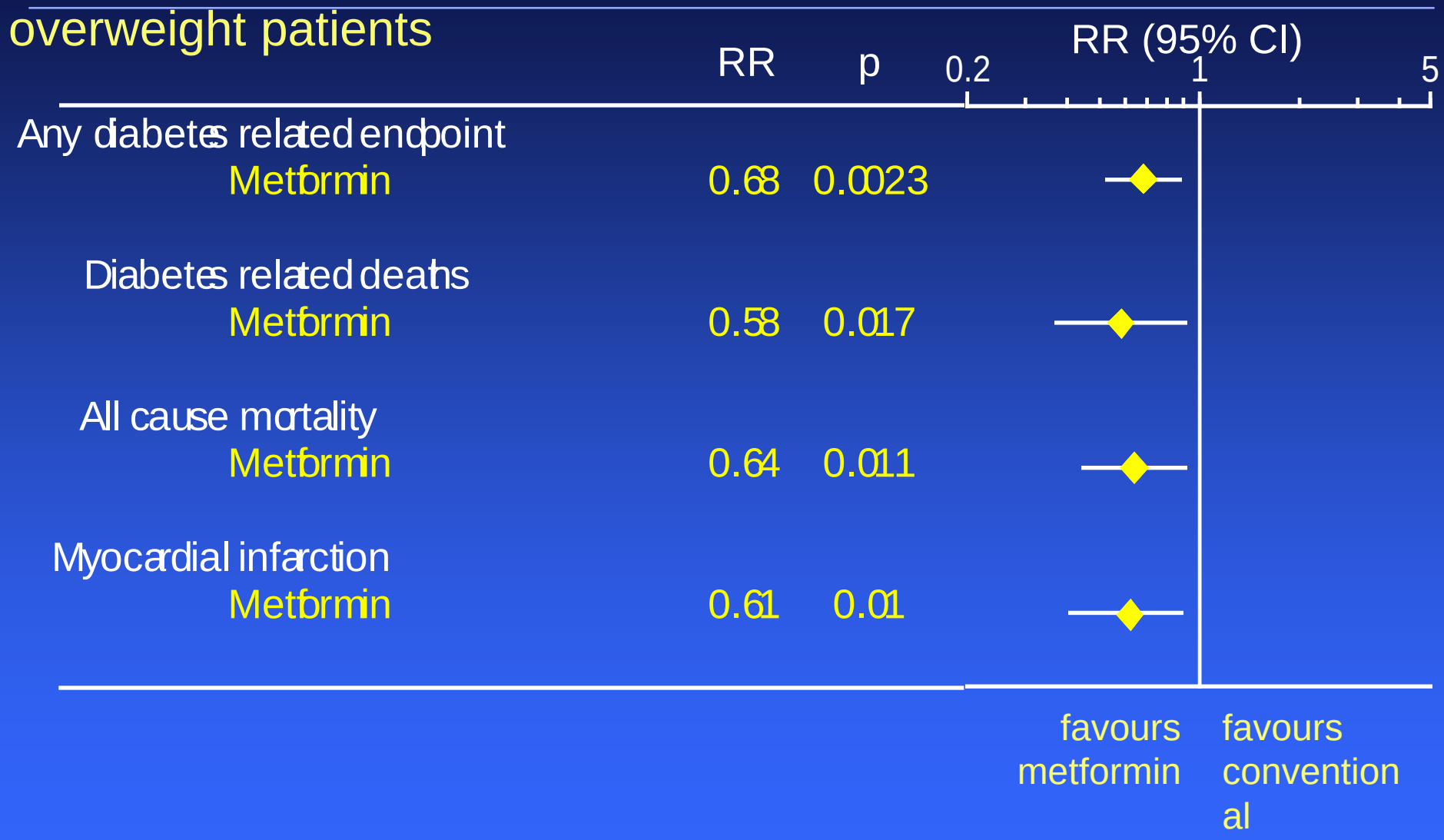


Change in Weight

overweight patients cohort, mean values



Metformin Comparisons



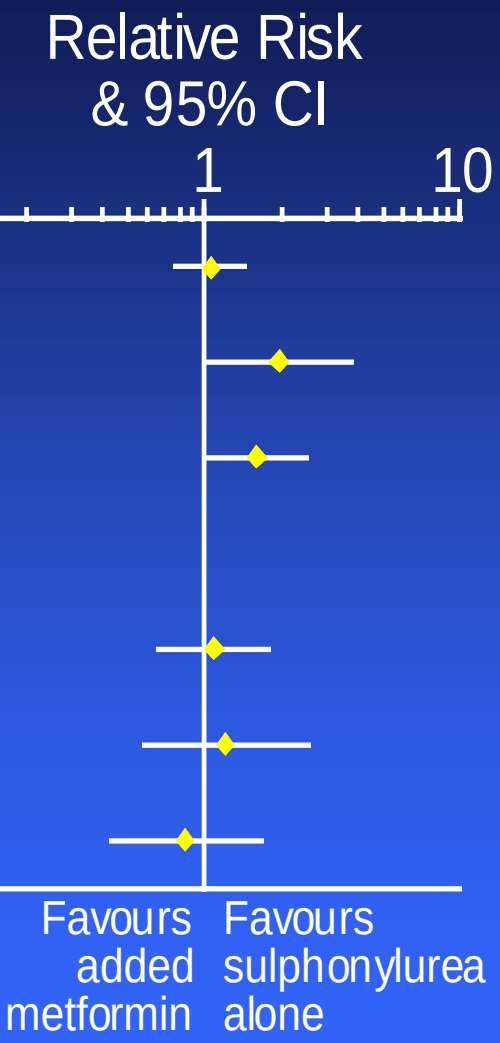
Sulphonylurea plus Metformin

- patients primarily randomised to intensive therapy with sulphonylurea were not given additional metformin until their fpg was >15 mmol/L or they developed hyperglycaemic symptoms

- in view of the progressive hyperglycaemia in these patients, a protocol modification was made to randomise secondarily the subset of patients who were on maximum sulphonylurea therapy and had fpg >6 mmol/L to earlier addition of metformin

Aggregate Endpoints

Median follow up 6.6 years	RR	p
Any diabetes related endpoint	1.04	0.78
Diabetes related deaths *	1.96	0.039
All cause mortality	1.60	0.041
Myocardial infarction	1.09	0.73
Stroke	1.21	0.61
Microvascular	0.84	0.62



* interpret with caution in view of small numbers : 26 deaths on sulphonylurea plus metformin versus 14 deaths on sulphonylurea alone

Metformin and SU UKPDS: Summary

- “the addition of metformin in patients already treated with sulphonylurea requires further study”
- (NOT HAPPENED in RCT)

- “on balance”, metformin treatment would appear to be advantageous as primary pharmacological therapy in diet-treated overweight patients

Metformin: problems with UKPDS Evidence

- 342 patients in UKPDS
- Hardly a large number
- Weight gain was less…how much of a factor (google!)
- Now:
  - Statins not included (study started in the 70’s)
  - Antihypertensive agents better

So what other dtudies do we have?

- Some Notable Studies
  - STENO-2
  - DREAM
  - ADOPT
  - ProActive
  - Record

Outcomes

- Weight….up
- HbA1c….down a bit, then up again, or maintained…for a bit
- Blood Pressure….only controlled with antihypertensives
- Lipids….statins required
- Cardiovascular Outcomes….improved if you do everything well….in a clinical trial

"I won it in a competition, honest!!"

"Pfft! C'mon scouser, you can come up with a better story than that!"