New therapies for type 2 diabetes have added little to improve glycaemic control compared to conventional therapies.

Charles Fox

ABCD 20/11/09

Last week's debate

I was opposing the motion:

Do attitudes need to change for people with diabetes to have real treatment choice?

Last week's debate

I was opposing the motion:

Do attitudes need to change for people with diabetes to have real treatment choice?

Against Simon Heller

- At Insulin Dependent Diabetes Trust
- How many votes??

This time

I’m replacing Simon Heller – and he really believes in the motion:

New therapies for type 2 diabetes have added little to improve glycaemic control compared to conventional therapies.

In a debate

- Know your audience
- Know your opponent
- Know your subject

MY AUDIENCE

My Opponent

MARK LEADING YOU TO THE PROMISED LAND

Fox in a blue funk

Who do we represent

- Manchester
- Northampton

Jan 24 2004, Sixfields Stadium
Chris Hargreaves scoring an own goal.
Manchester United 3 – Northampton Town 0

Things were even worse

- April 1970
  5th round FA cup
  County Ground

- Final score
  Best 6 / Cobblers 0
  Man U 8 / N’ton 2

New therapies for type 2 diabetes have added little to improve glycaemic control compared to conventional therapies.

New therapies for type 2 diabetes have added little to improve glycaemic control compared to conventional therapies.

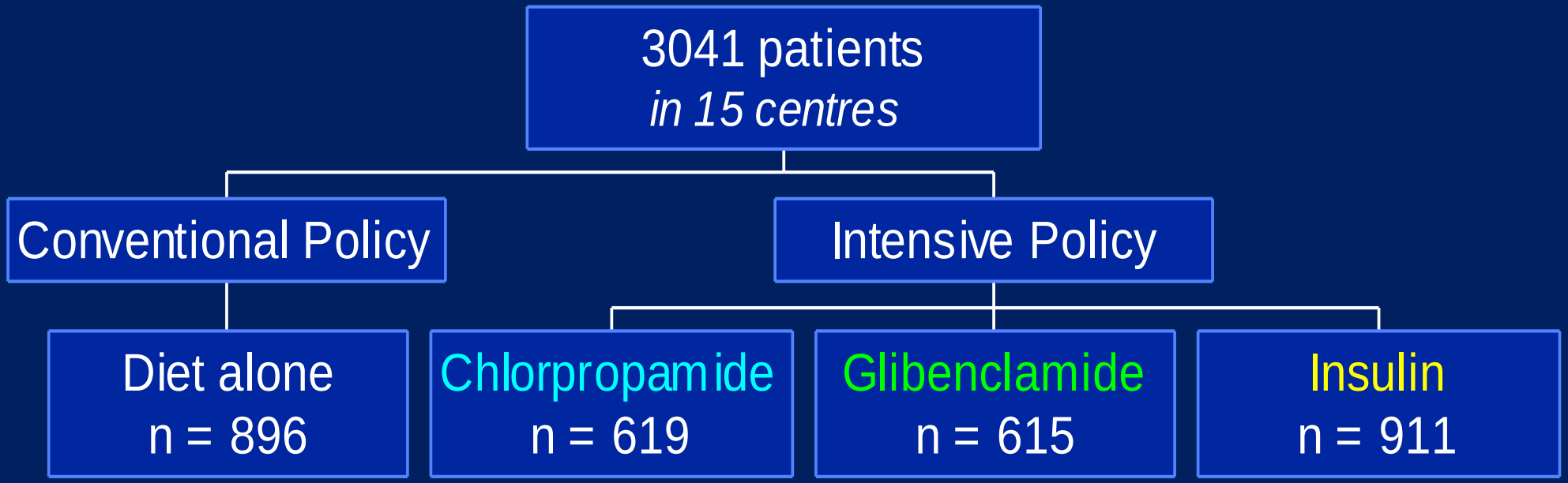
So what about the old drugs

- Insulin
- Metformin
- Sulphonylureas

Old evidence for old drugs

UKPDS

Randomisation

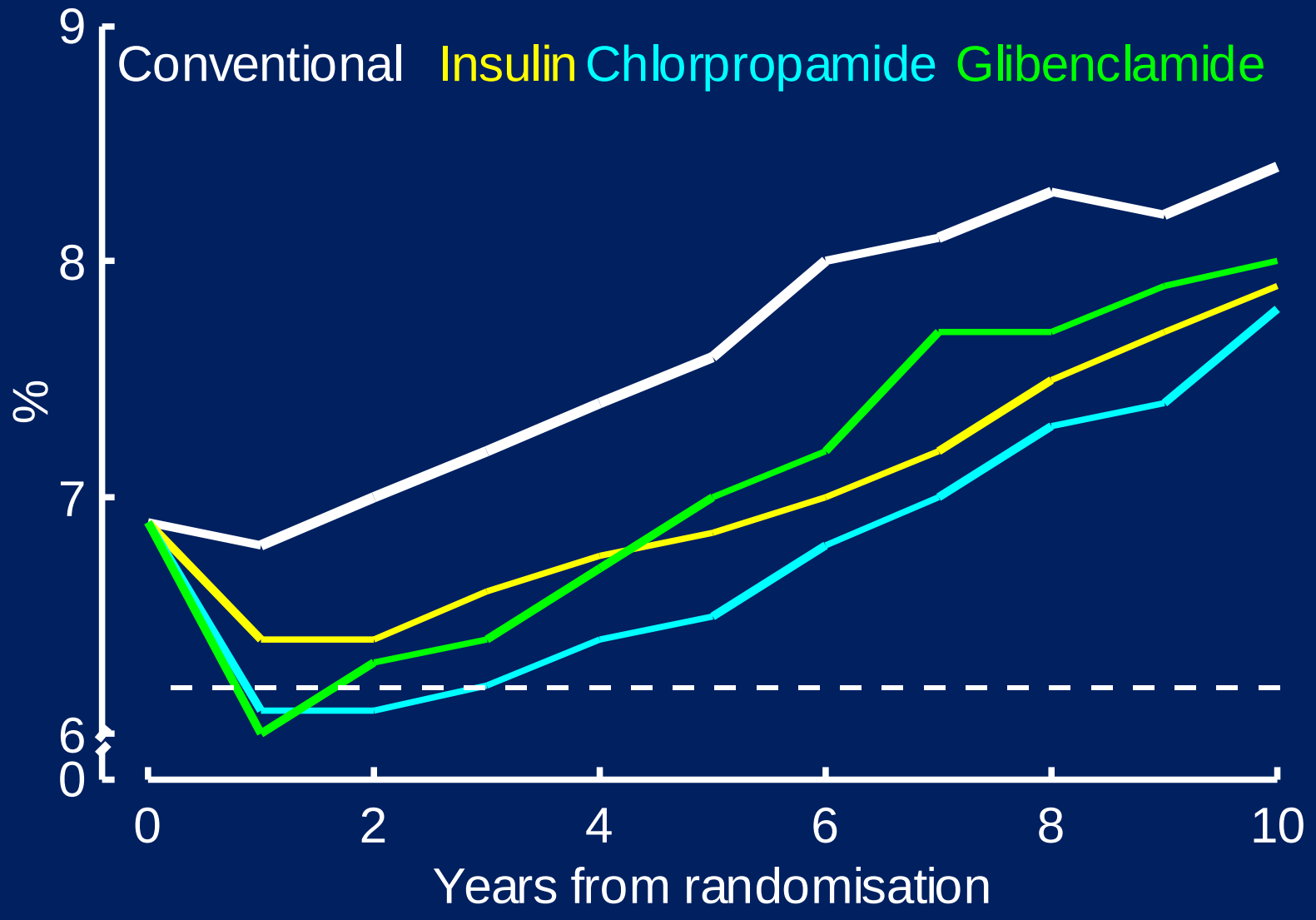


comparison between three intensive therapies

compare each with conventional policy

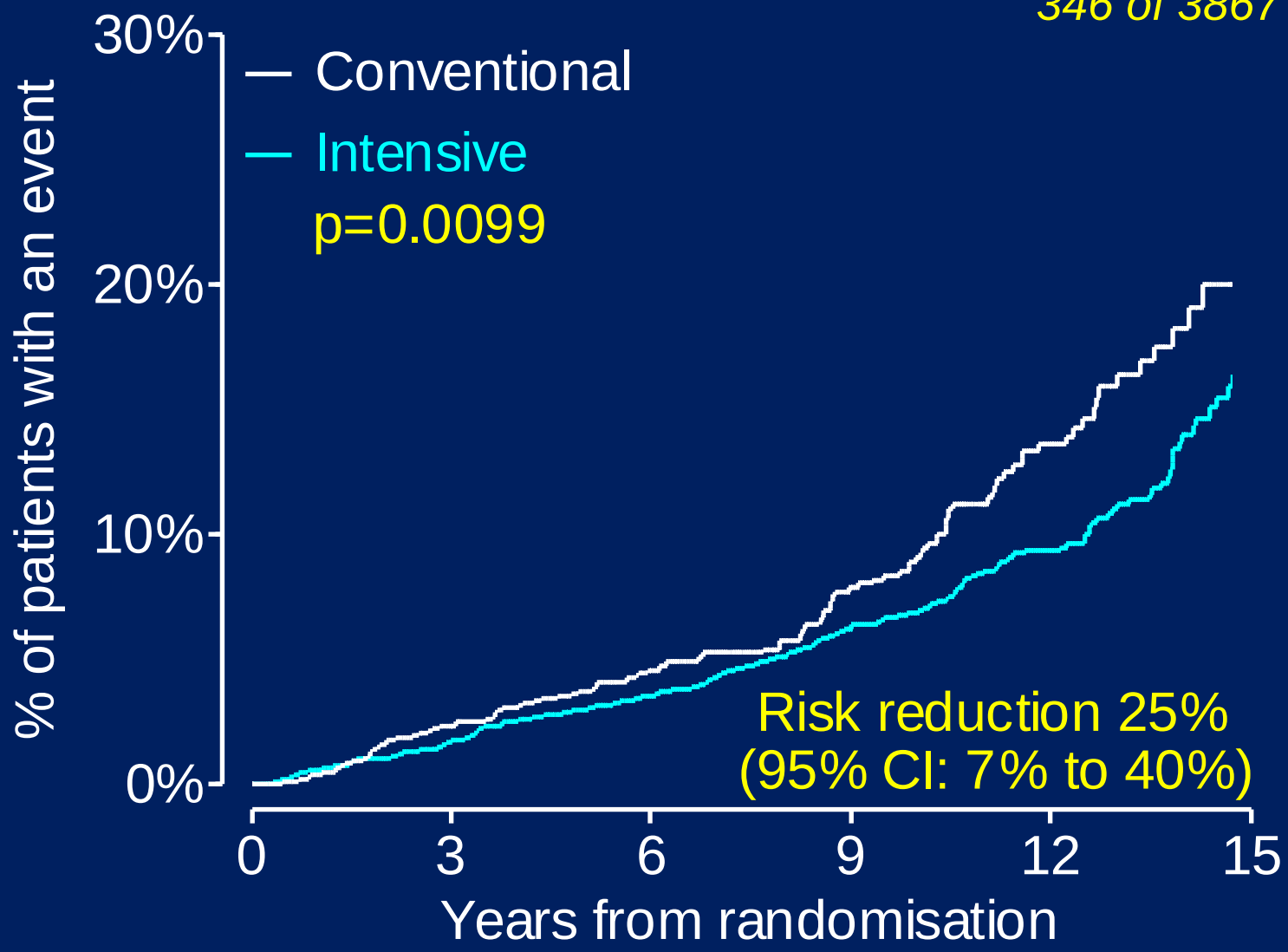
HbA_{1c}

cohort, median data



Microvascular Endpoints (cumulative)

renal failure or death, vitreous haemorrhage or photocoagulation
346 of 3867 patients (9%)



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

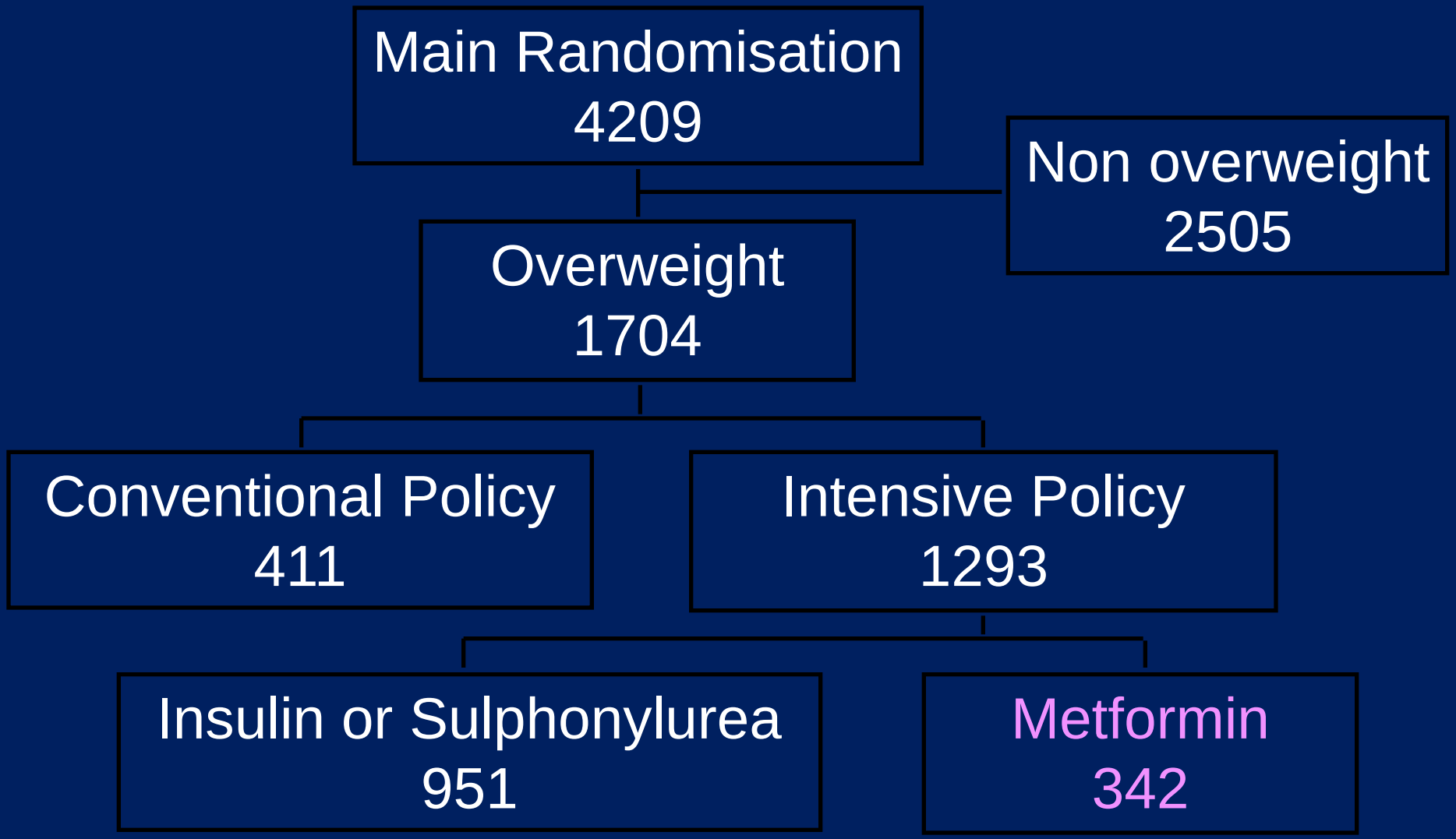
Sulphonylurea therapy

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

Insulin therapy

- no evidence for more atheroma-related disease

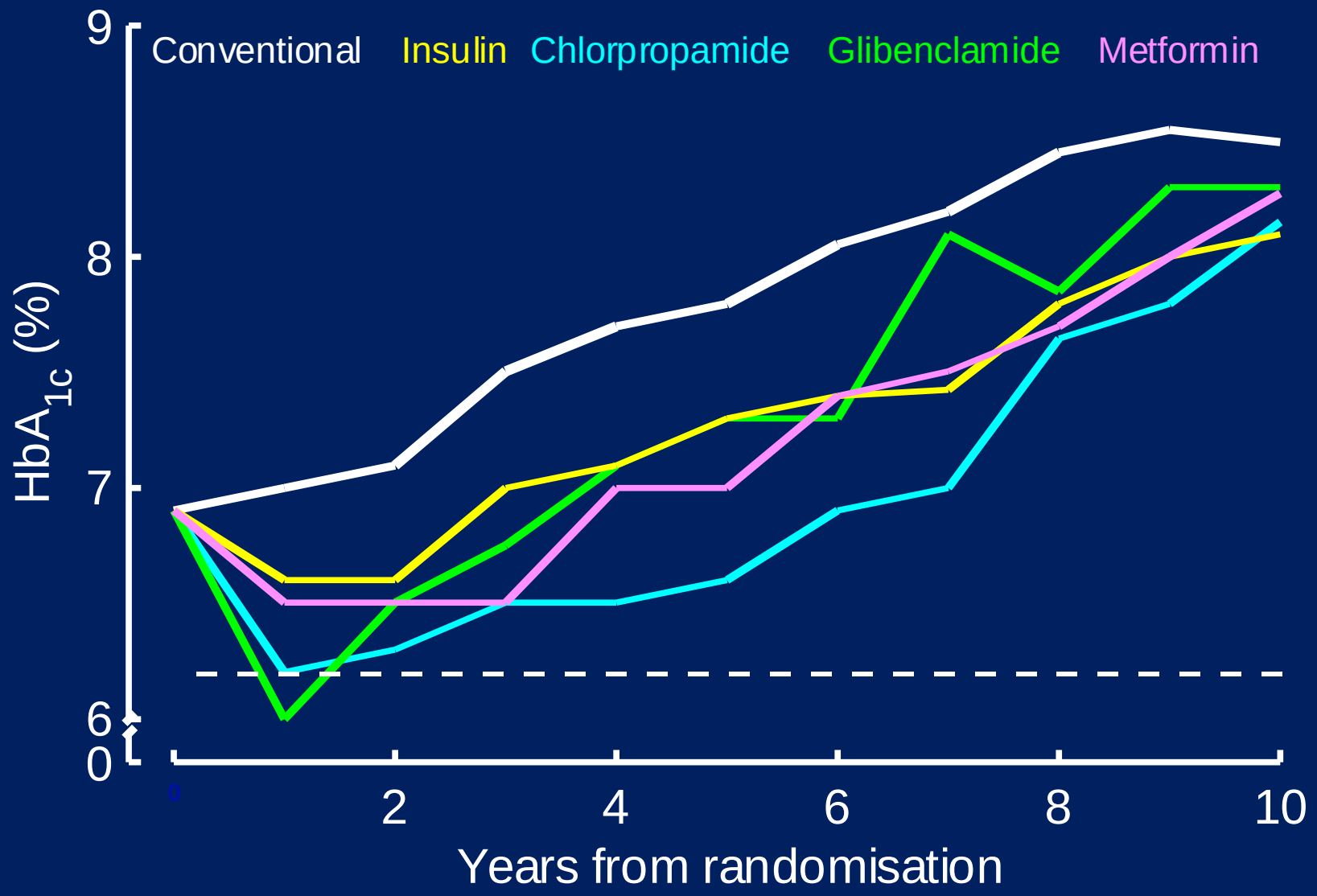
Randomisation



HbA_{1c}

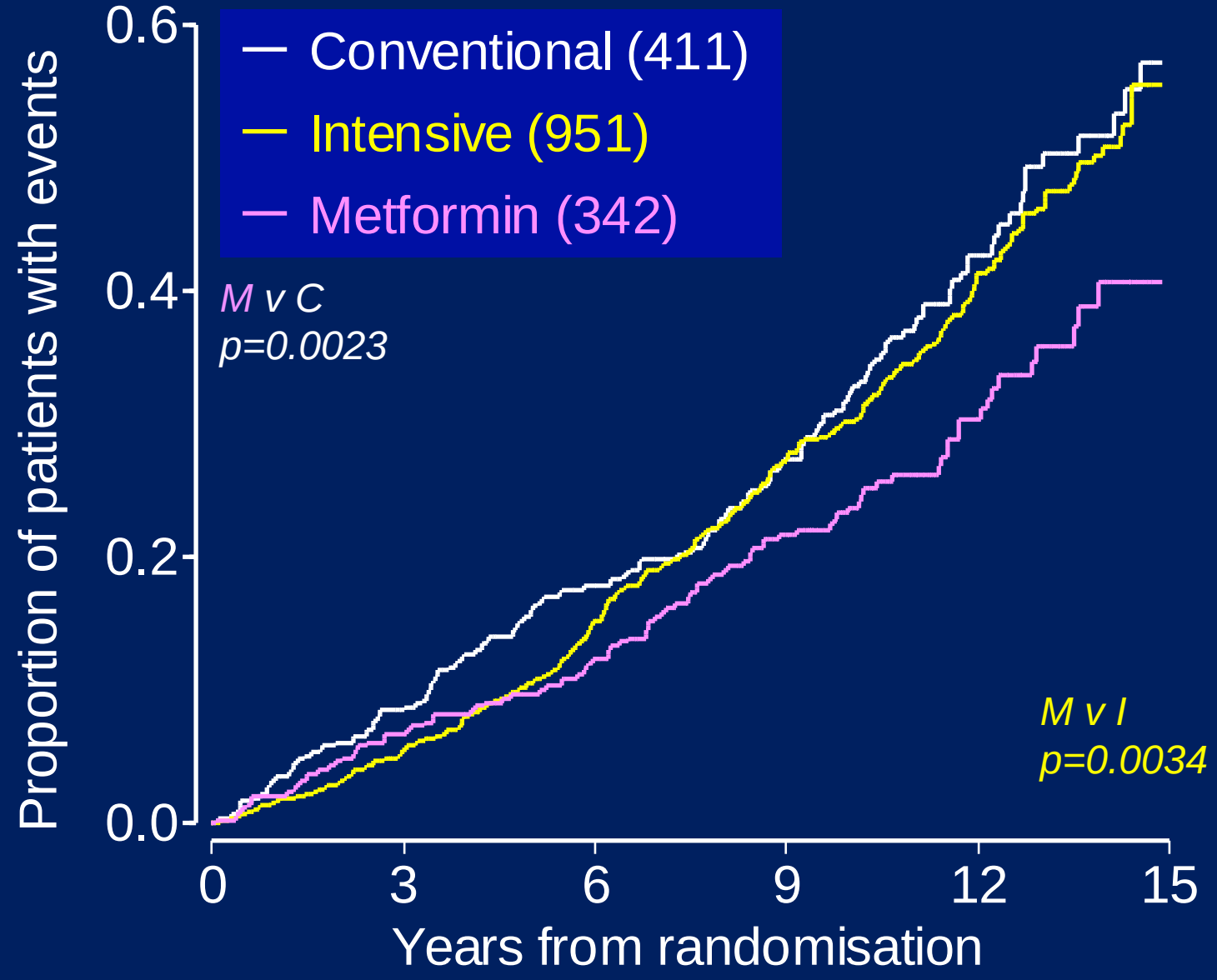
overweight patients

cohort, median values



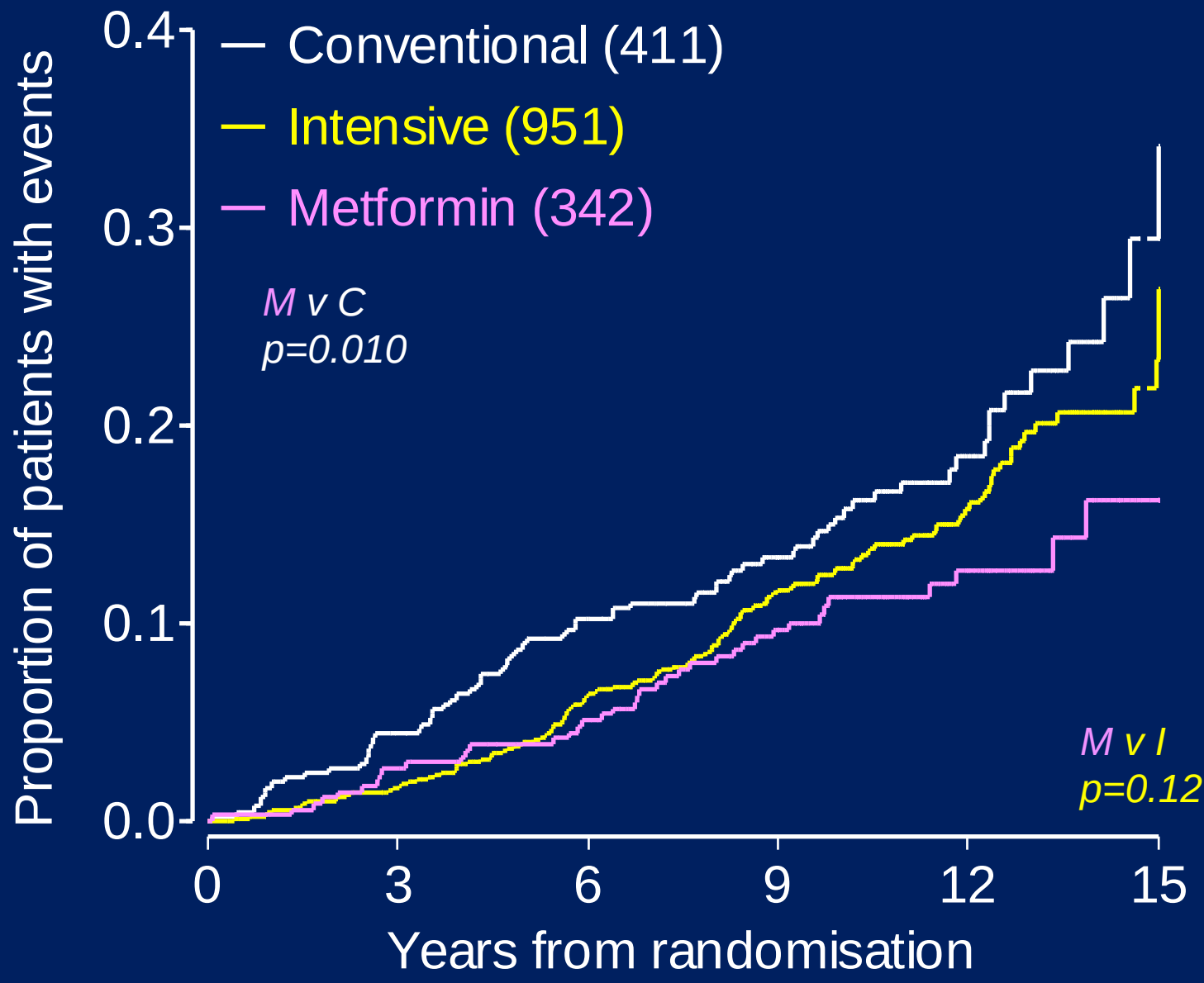
Any diabetes related endpoint

overweight patients



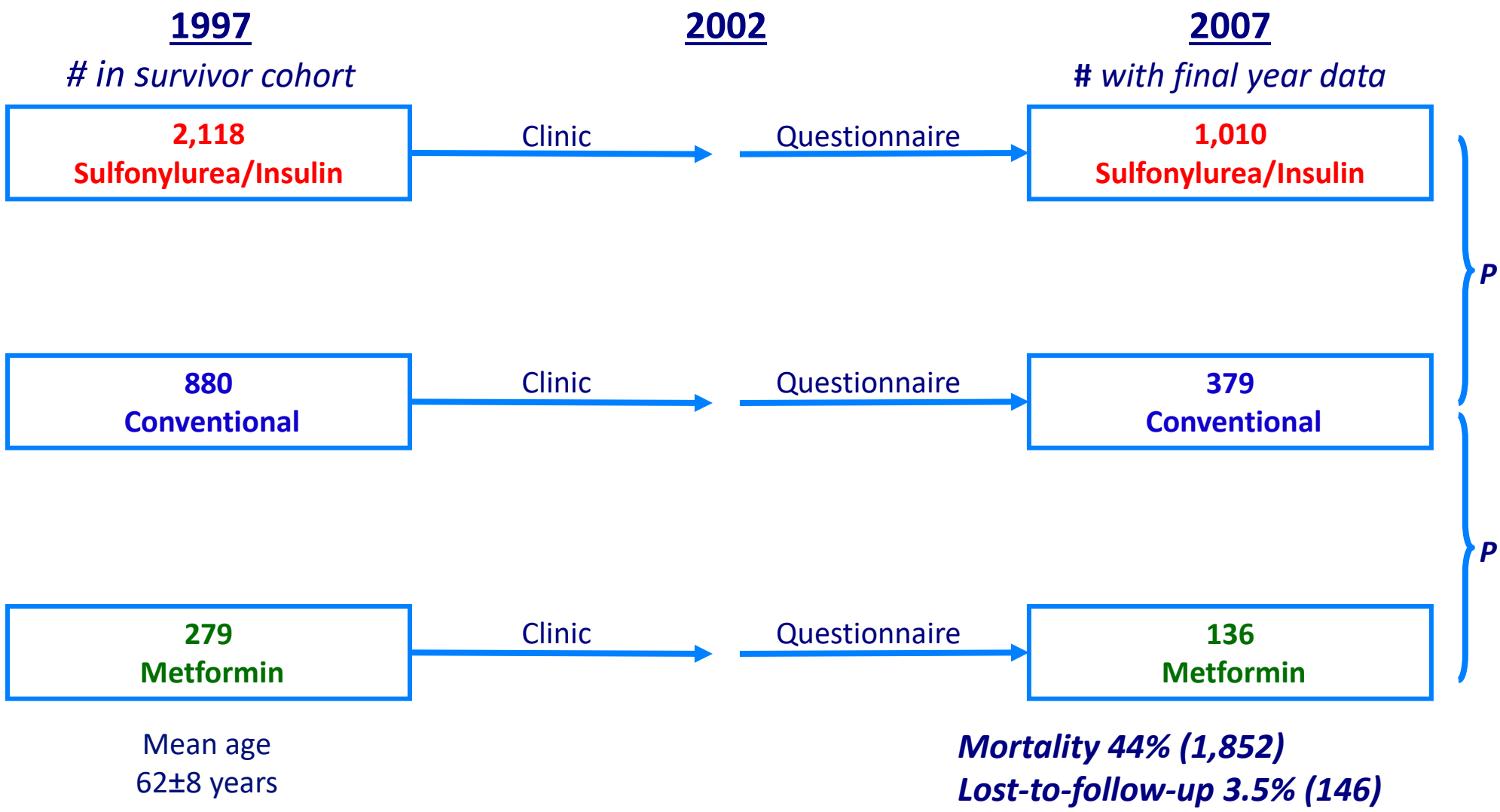
Myocardial Infarction

overweight patients

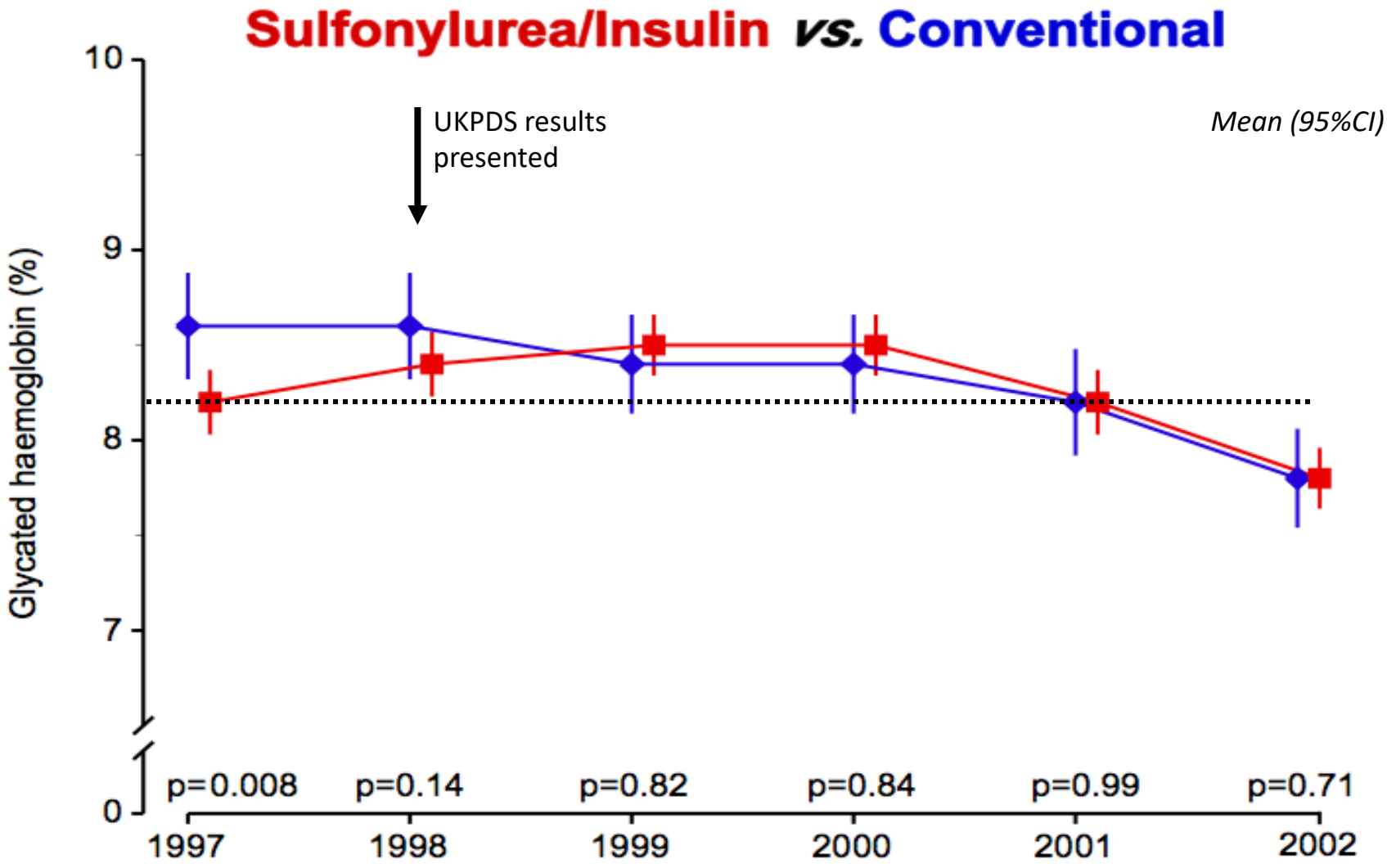


New evidence for old drugs

Post-Trial Monitoring: Patients



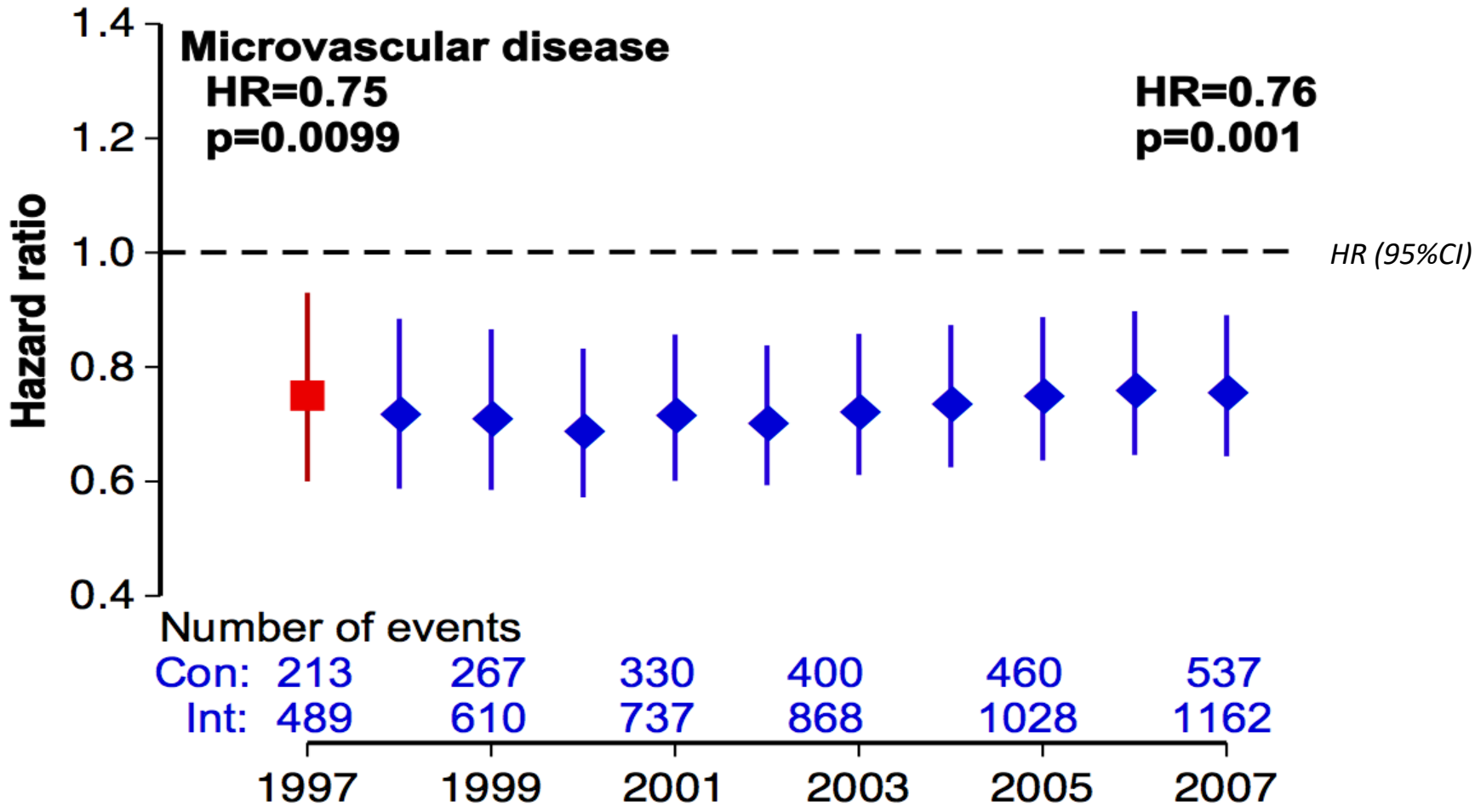
Post-Trial Changes in HbA_{1c}



Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

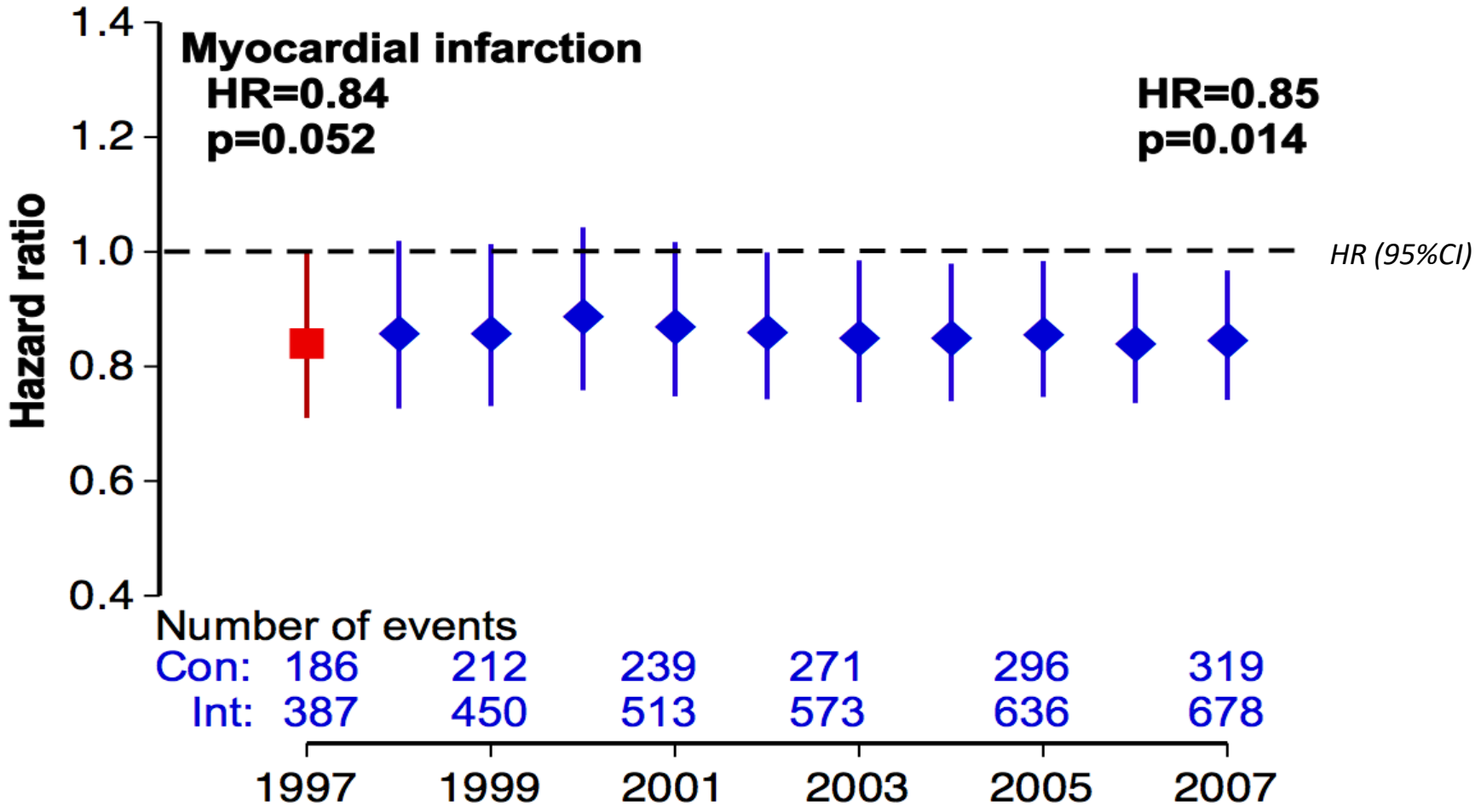
Intensive (SU/Ins) *vs.* Conventional glucose control



Myocardial Infarction Hazard Ratio

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

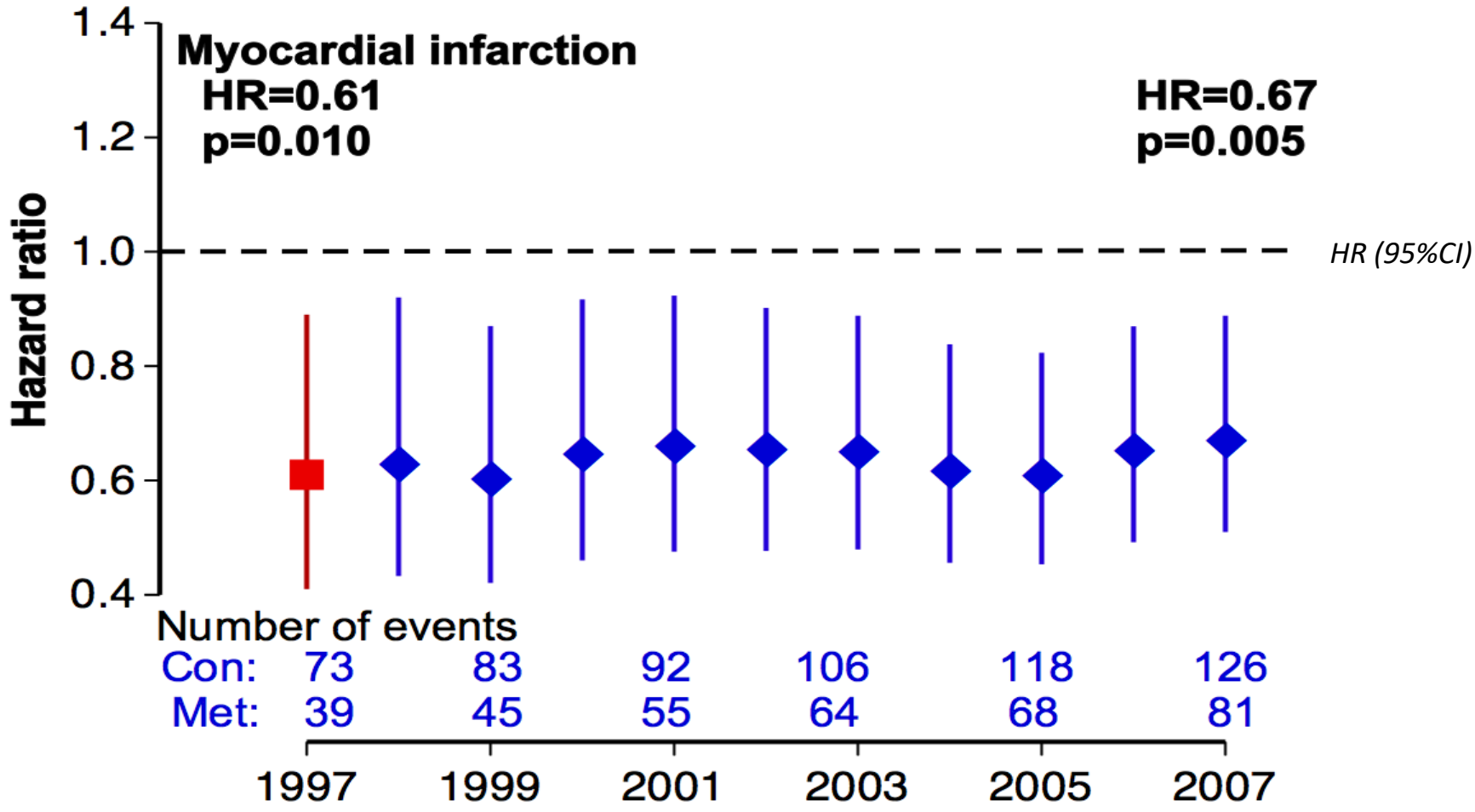
Intensive (SU/Ins) *vs.* Conventional glucose control



Myocardial Infarction Hazard Ratio

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

Intensive (metformin) *vs.* Conventional glucose control



A New study using Old drugs

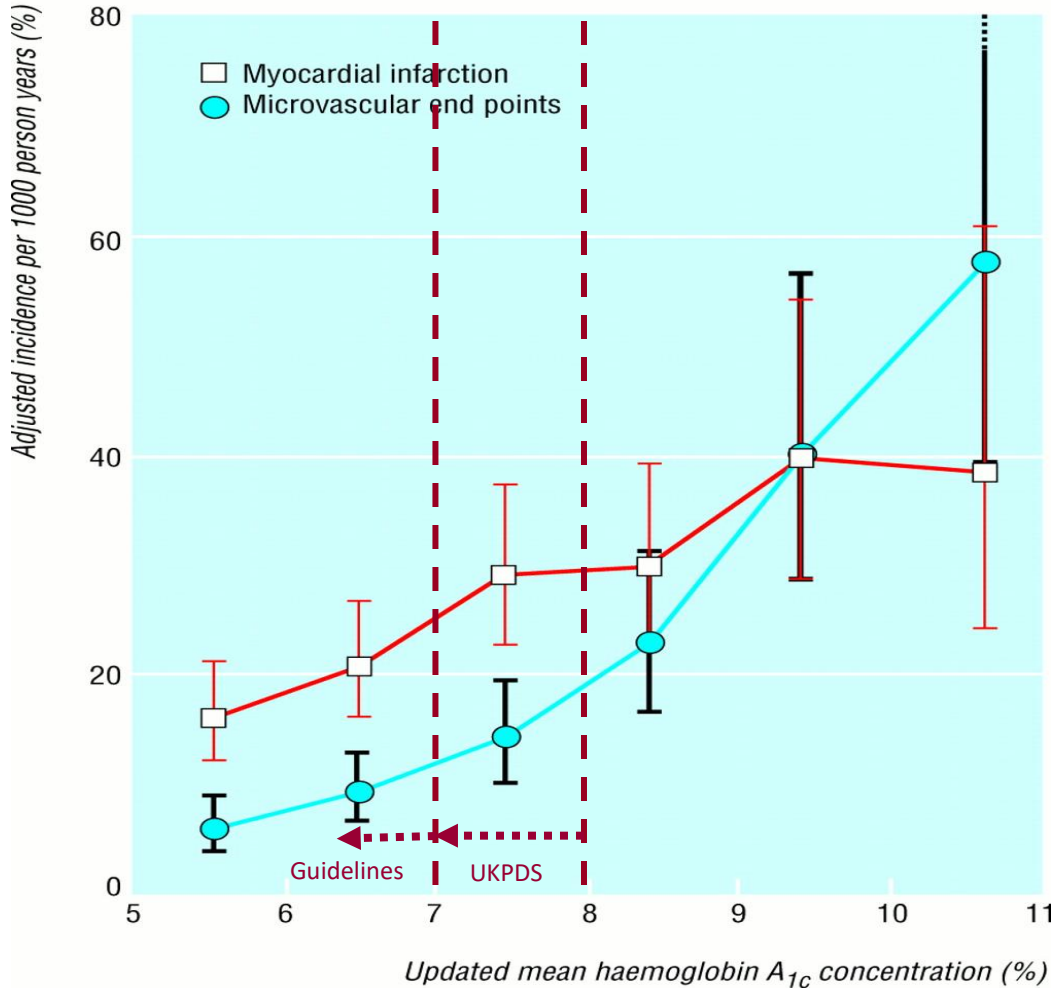
Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group

New England Journal Med, 2008. 358:2560-2572

Blood glucose and vascular risk in diabetes

Best evidence: 2000



BMJ VOLUME 317 12 SEPTEMBER 1998

UK Prospective Diabetes Study

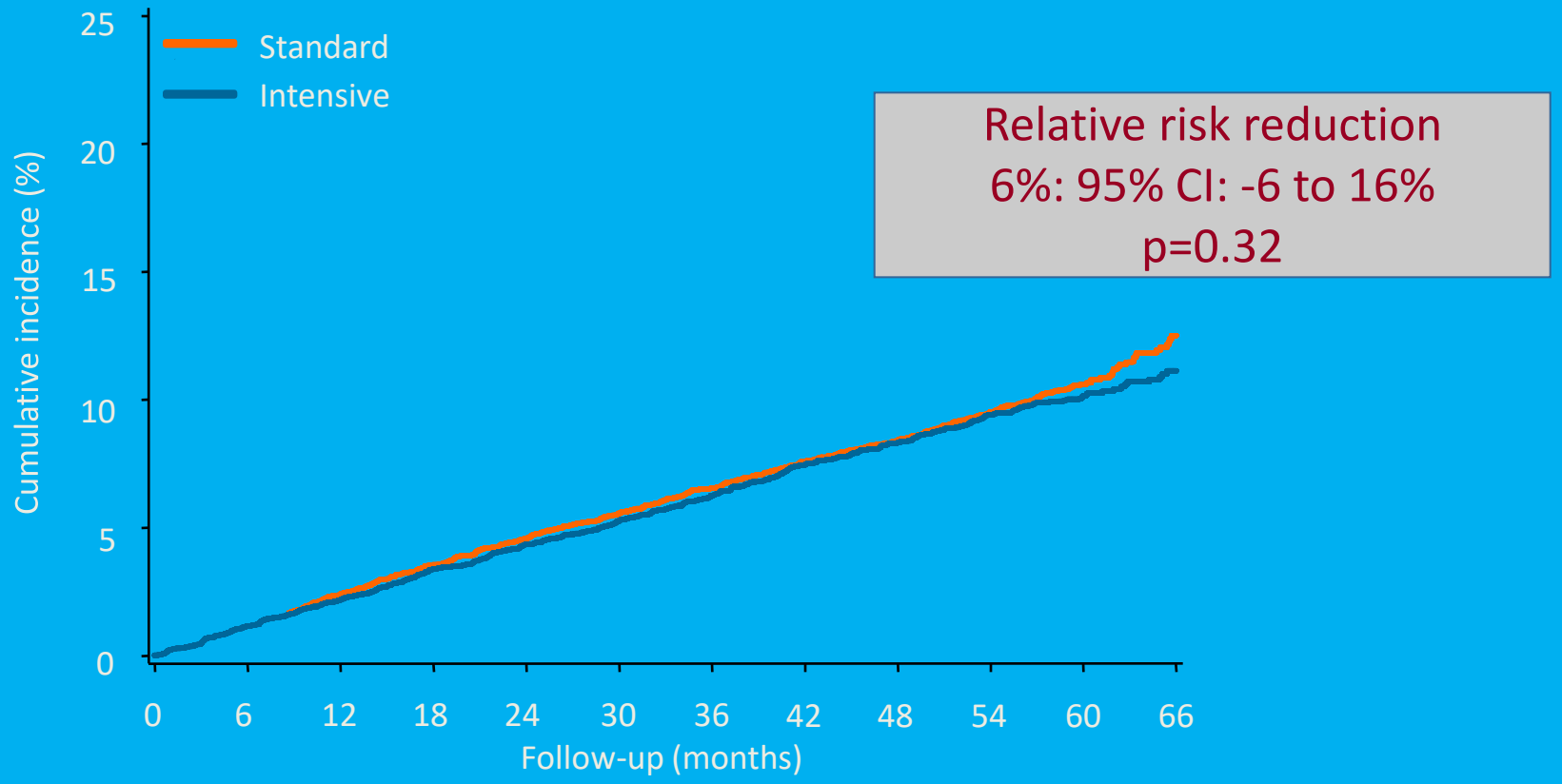
Blood glucose lowering in diabetes:
Unresolved issues 2000

- *Among patients with diabetes, does blood glucose lowering therapy:*

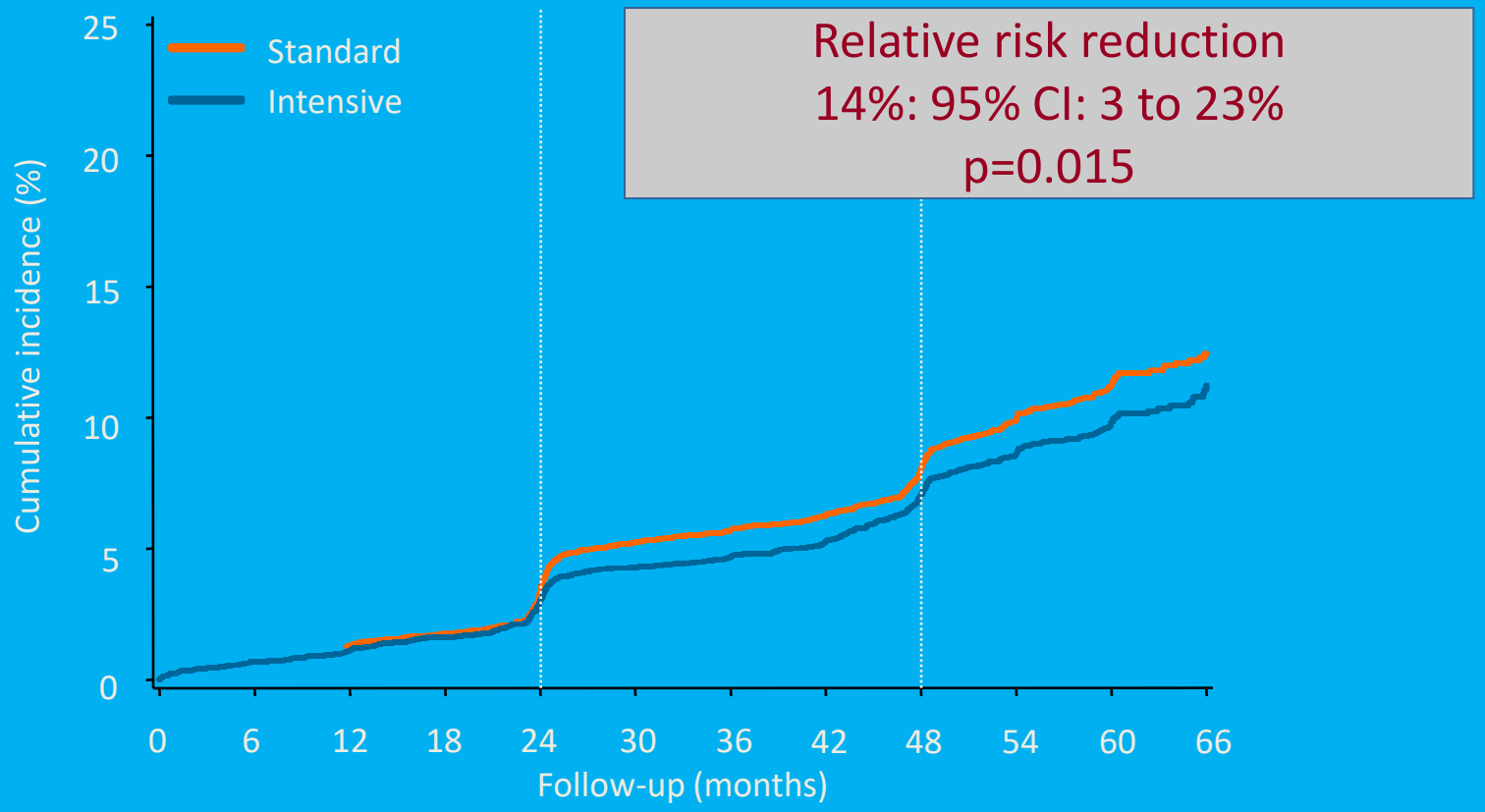
  - Produce additional microvascular benefits when hemoglobin A1c is reduced to 6.5% or lower?

  - Produce macrovascular benefits when hemoglobin A1c is reduced to 6.5% or lower?

Major macrovascular events-ADVANCE



Major microvascular events-ADVANCE



Randomized glucose lowering strategies -ADVANCE

Intensive control arm

- Gliclazide MR (sulfonylurea) in all participants
- Unrestricted additional therapy to achieve target $HbA_{1c} \leq 6.5\%$

Standard control arm

- Sulfonylurea other than Gliclazide MR
- Unrestricted additional therapy according to standard local guidelines

All other treatment

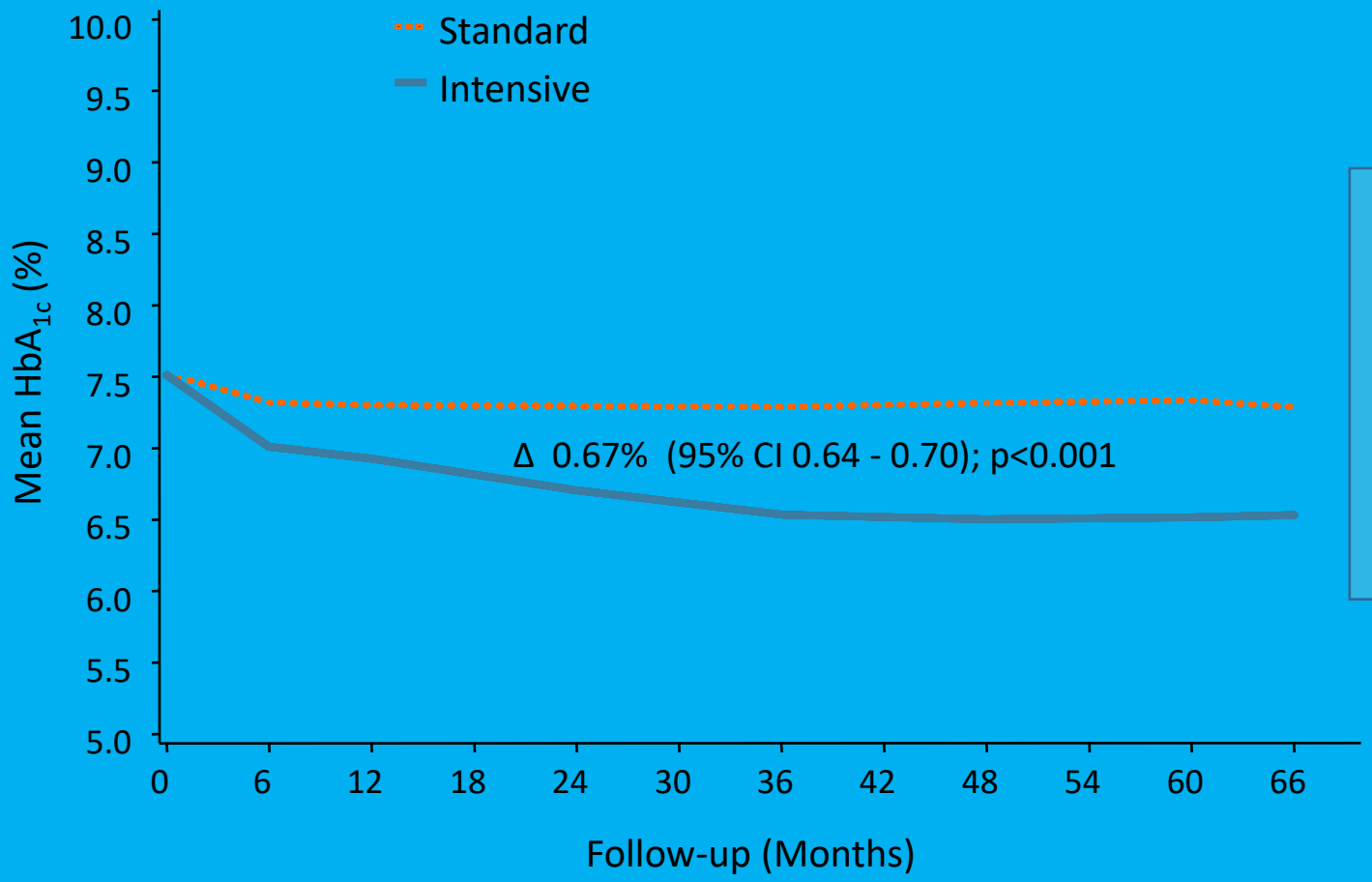
- At discretion of treating physician

Glucose control drugs-ADVANCE

At end of follow-up

	Randomized treatment	
	Intensive (n=4828)	Standard (n=4741)
Sulfonylurea	91%	59%
Metformin	74%	67%
Thiazolidinediones	17%	11%
Acarbose	19%	13%
Glinides	1%	3%
Insulin	40%	24%

Haemoglobin A_{1c}-ADVANCE



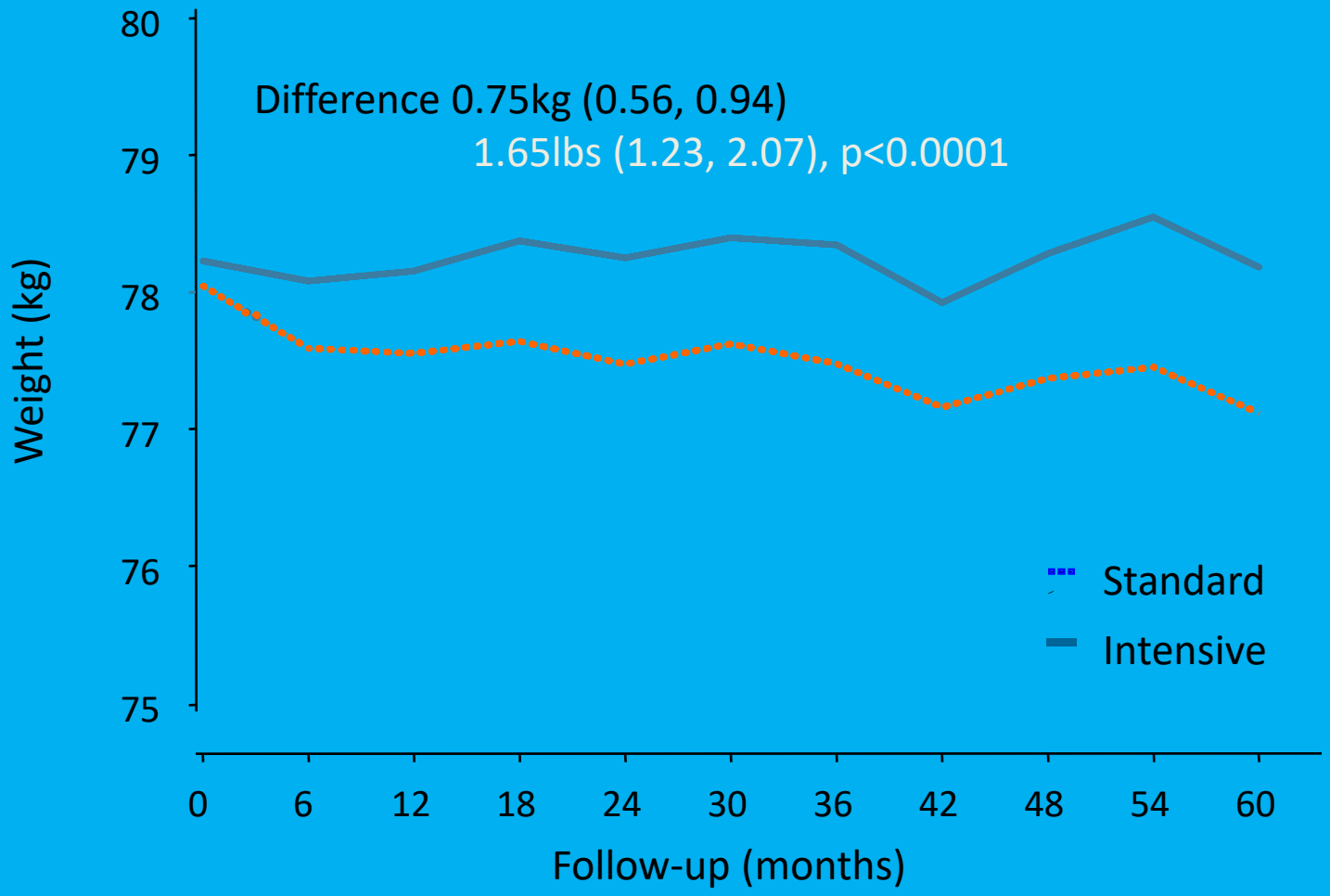
Mean HbA_{1c} at final visit

7.3 %

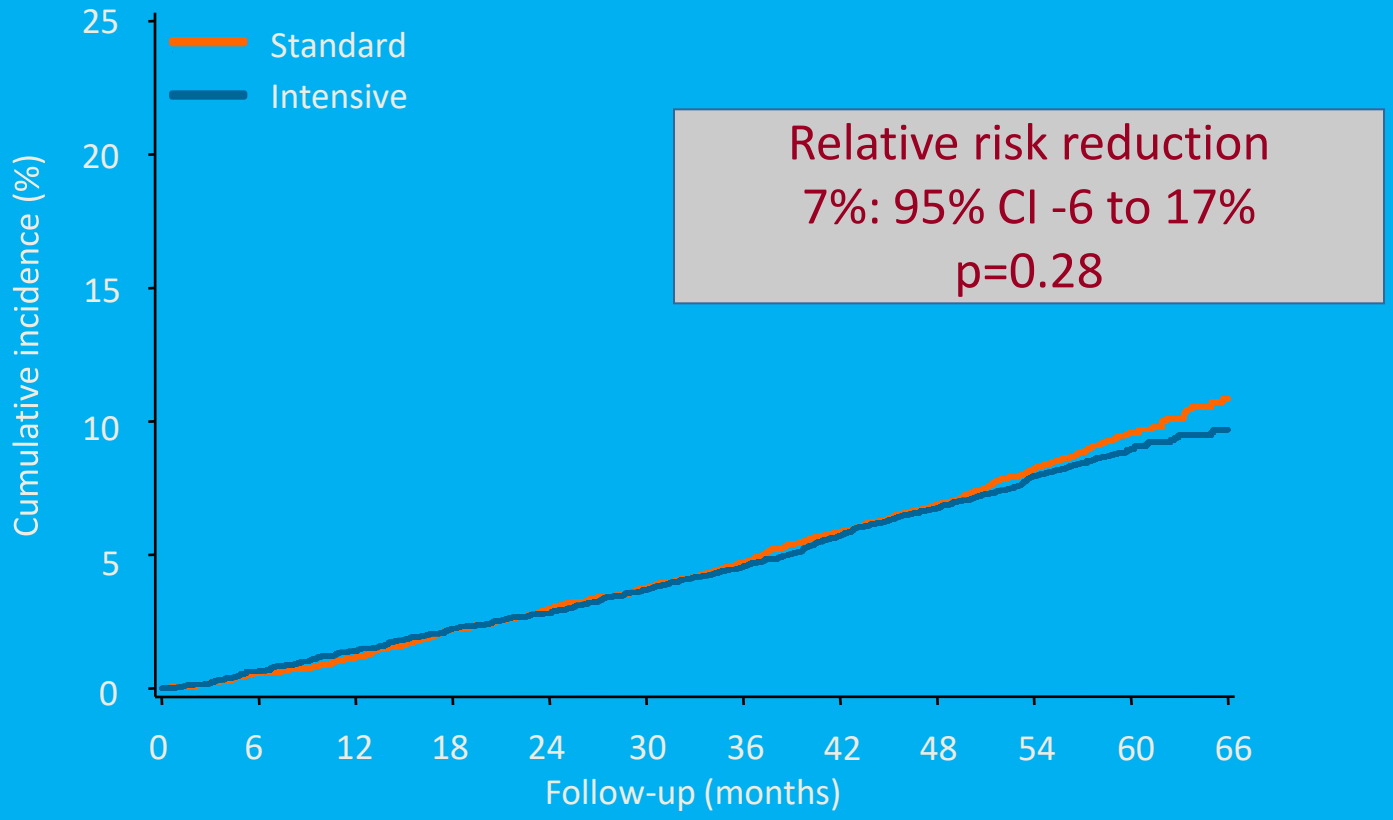
6.5%

AND WHAT DID THESE OLD-FASHIONED TREATMENTS DO TO THE BODY WEIGHT??

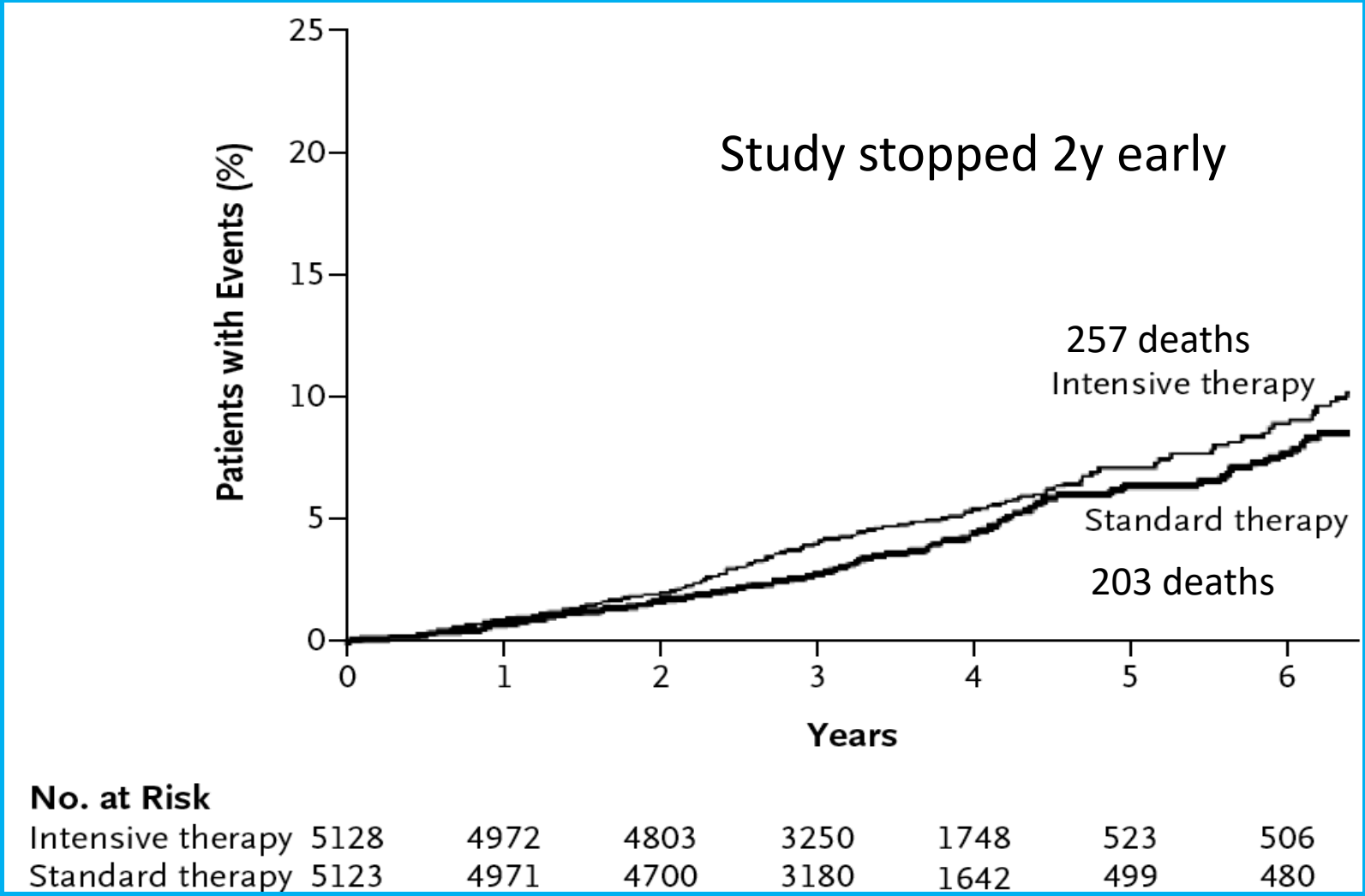
Difference in body weight-ADVANCE



All-cause mortality-ADVANCE



All-cause mortality-ACCORD



No. at Risk

Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

Glucose control drugs-ADVANCE

At end of follow-up

	Randomized treatment	
	Intensive (n=4828)	Standard (n=4741)
Sulfonylurea	91%	59%
Metformin	74%	67%
Thiazolidinediones	17%	11%
Acarbose	19%	13%
Glinides	1%	3%
Insulin	40%	24%

Glucose control drugs-ACCORD

At end of follow-up

	Randomized treatment	
	Intensive (n=5128)	Standard (n=5123)
Sulfonylurea	78%	74%
Metformin	95%	87%
Rosiglitazone	92%	58%
Acarbose	23%	5%
Glinides	50%	18%
Insulin	77%	55%
Bolus Insulin	55%	35%

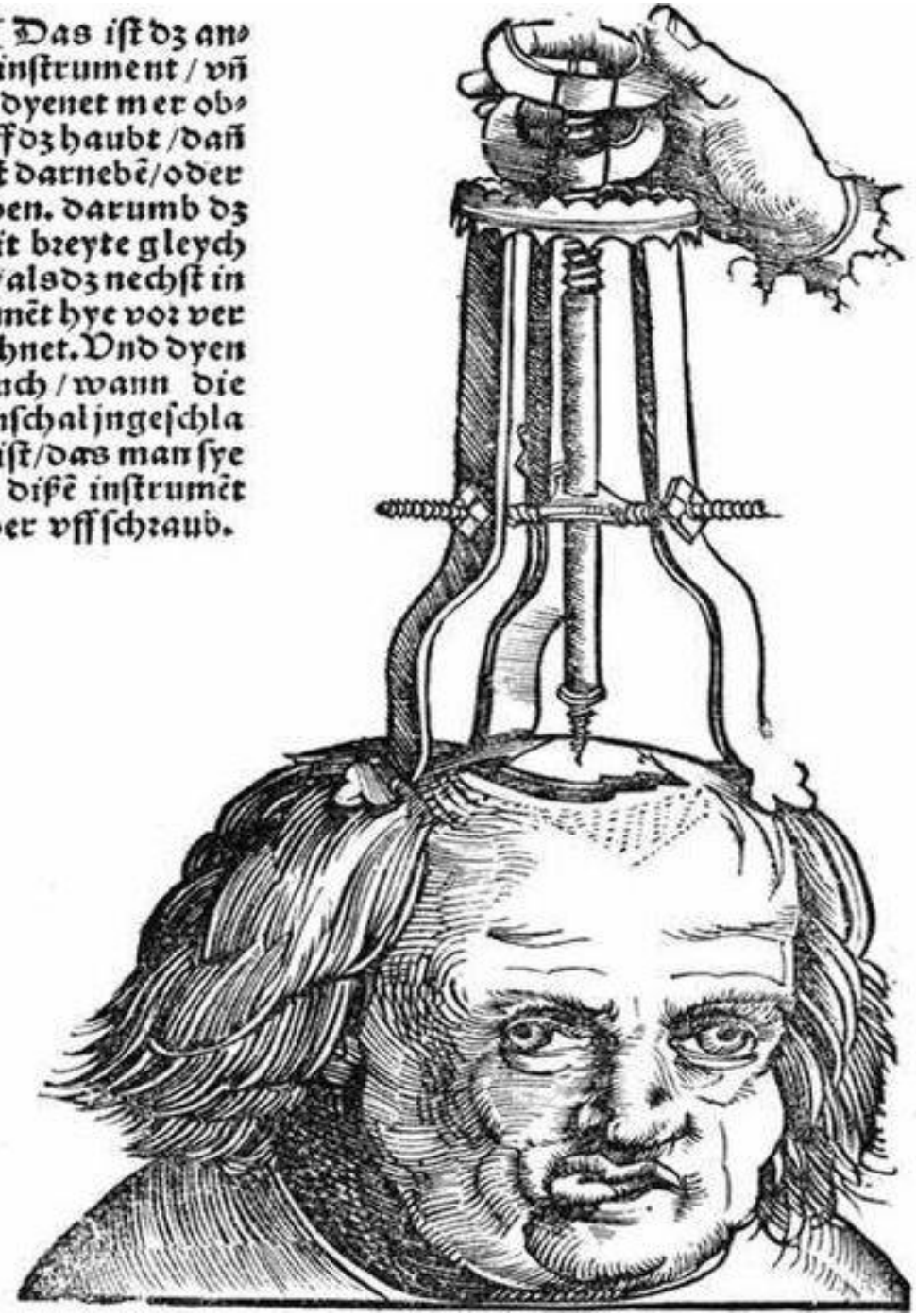
New therapies for type 2 diabetes have added little to improve glycaemic control compared to conventional therapies.

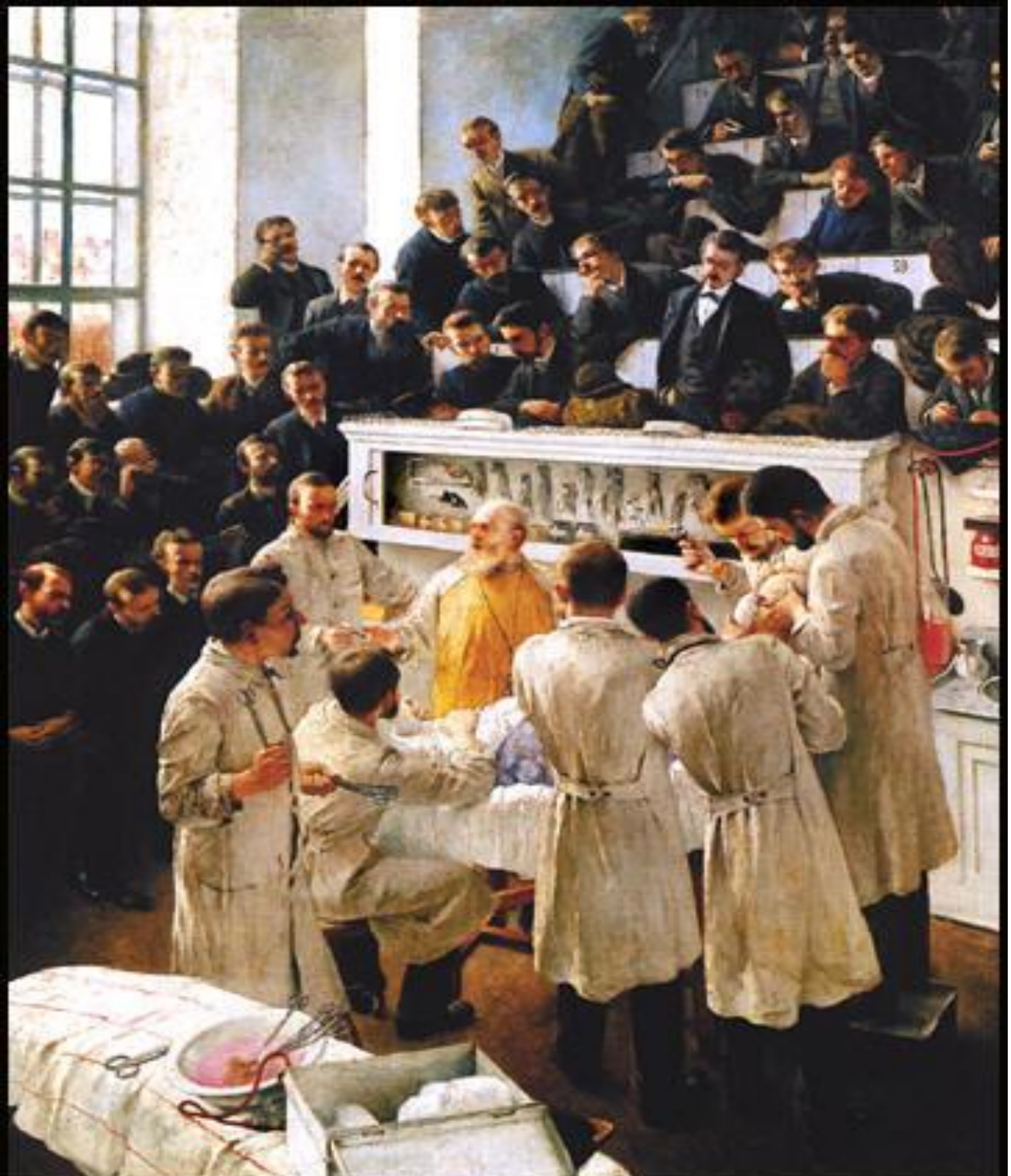
So what about the old therapies

- Insulin
- Metformin
- Sulphonylureas

- Surgery

¶ Das iſt dz ander inſtrument / vñ das dyenet mer oben vff dz haubt / dañ ſunſt darnebē / oder hinden. darumb dz es nit breyte gleych hat / alsdz nechſt inſtrumēt hye vor verzeychnet. Vnd dyenet auch / wann die hyrnſchal jngeſchlagen iſt / das man ſye mit diſē inſtrumēt wider vff ſchraub.





Christian Albert Theodor Billroth, MD
(1829-1894)

Picture by Seligmann 1889
Allegemeines Krankenhause, Vienna

Bariatric surgery

This does / can cure type 2 diabetes

Roux-en-Y Gastric Bypass (RYGBP)

- General Features
  - Pouch size: 1 oz
  - Pouch opening: 0.5 in
  - Roux-en-Y limb
    - Standard: 2 ft
- Average Weight Loss
  - 70 % of excess weight
- "The Pouch-Tool"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Mortality after Gastric Bypass Surgery

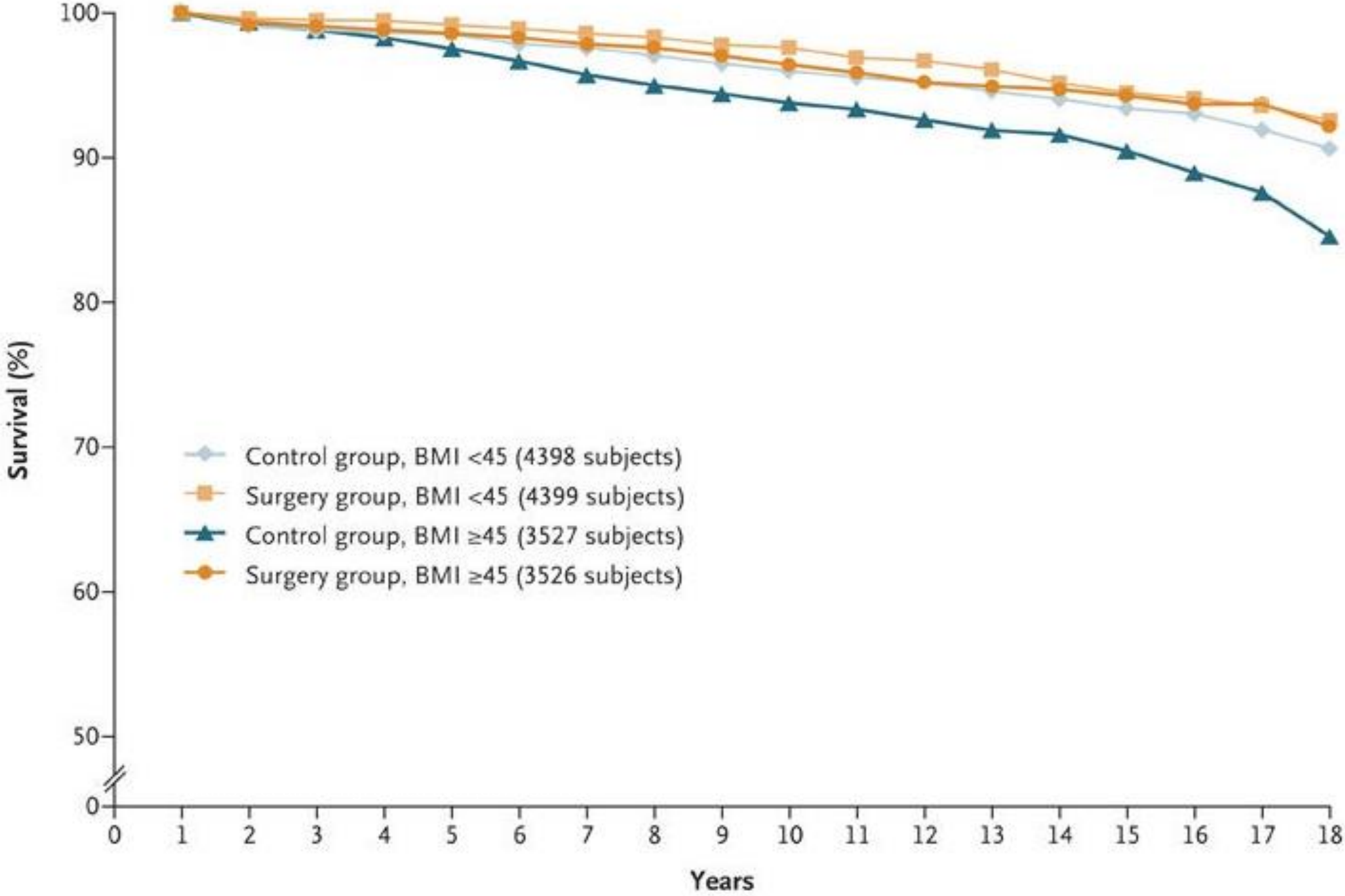
Ted D. Adams, Ph.D., M.P.H., Richard E. Gress, M.A., Sherman C. Smith, M.D., R. Chad Halverson, M.D., Steven C. Simper, M.D., Wayne D. Rosamond, Ph.D., Michael J. LaMonte, Ph.D., M.P.H., Antoinette M. Stroup, Ph.D., and Steven C. Hunt, Ph.D.

N Engl J Med 2007;357:753-61.

Does surgery save your life?

Adams TD et al 2007 N Engl J Med; 357:753

- A single centre in Utah, USA, looked back at 7925 patients who had surgery and were matched with the same number of people who were overweight and applied for driving licences.
- The groups were (pretty) well matched but of course these are retrospective data


Survival (%)
100
90
80
70
60
50
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
Years
Control group, BMI <45 (4398 subjects)
Surgery group, BMI <45 (4399 subjects)
Control group, BMI ≥45 (3527 subjects)
Surgery group, BMI ≥45 (3526 subjects)

Does surgery save your life?

Adams TD et al 2007 N Engl J Med; 357:753

	Surgery group	Control group
numbers	7925	7925
Female %	84	84
age	39.5	39.2
BMI	45.3	46.7
Follow up - years	7.1	7.1
Deaths	213	321

How does surgery save your life?

Adams TD et al 2007 N Engl J Med; 357:753

	Surgery group	Control group	P value
Cardiovascular deaths	55	104	<0.001
Cancer	31	73	<0.001
Suicide	15	5	NS ???

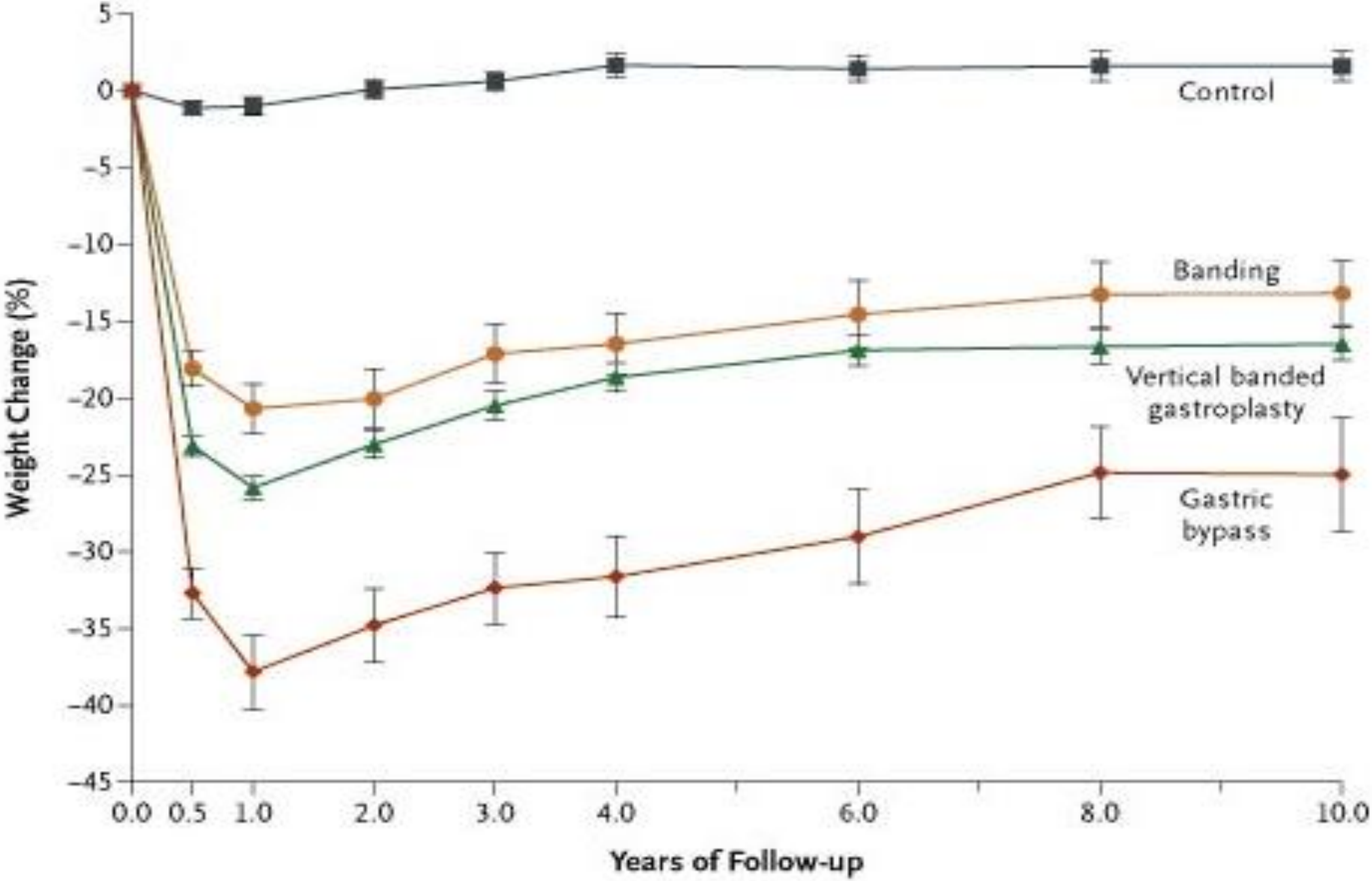
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 23, 2007 VOL. 357 NO. 8

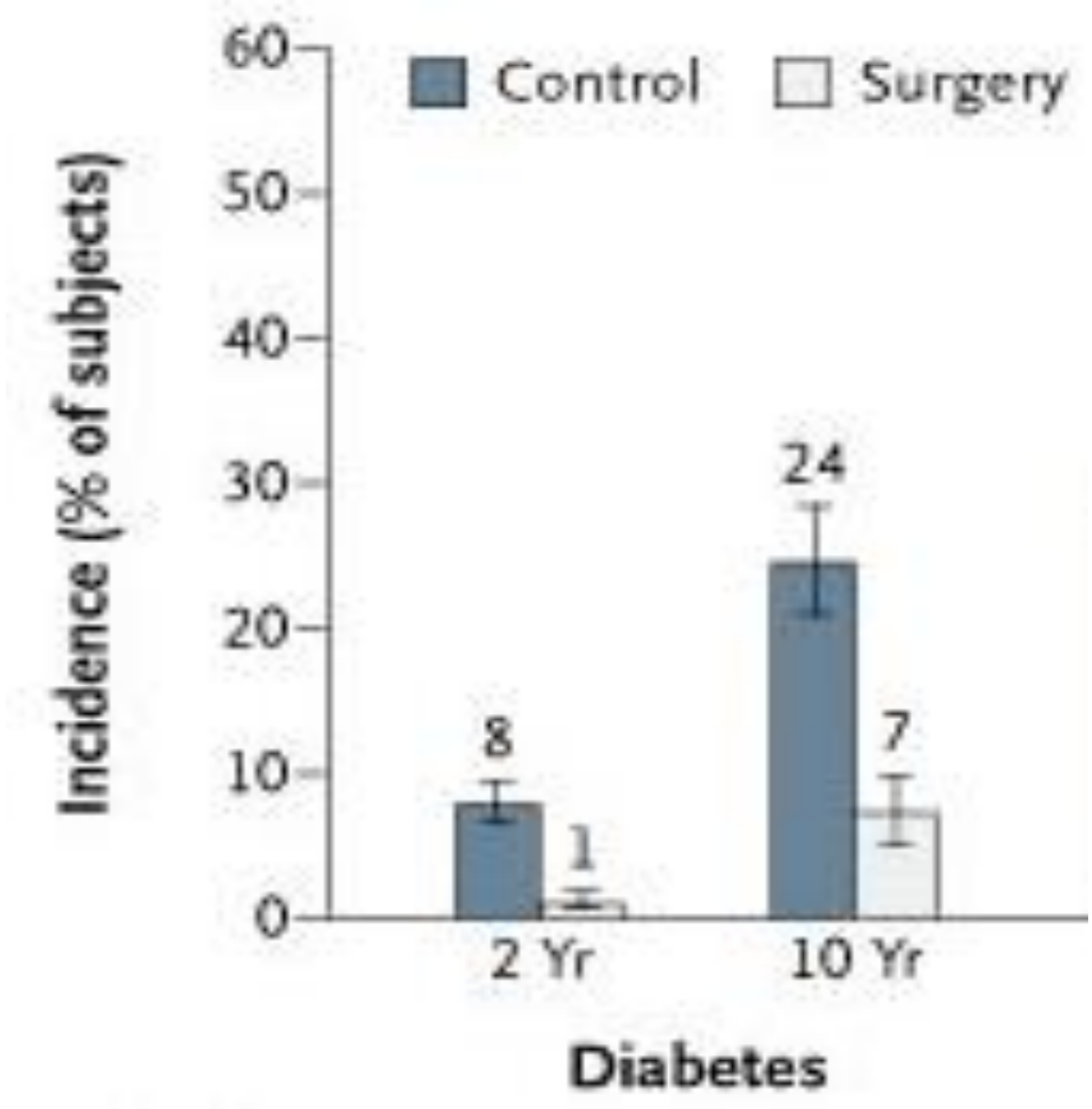
Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects

Lars Sjöström, M.D., Ph.D., Kristina Narbro, Ph.D., C. David Sjöström, M.D., Ph.D., Kristjan Karason, M.D., Ph.D., Bo Larsson, M.D., Ph.D., Hans Wedel, Ph.D., Ted Lystig, Ph.D., Marianne Sullivan, Ph.D., Claude Bouchard, Ph.D., Björn Carlsson, M.D., Ph.D., Calle Bengtsson, M.D., Ph.D., Sven Dahlgren, M.D., Ph.D., Anders Gummesson, M.D., Peter Jacobson, M.D., Ph.D., Jan Karlsson, Ph.D., Anna-Karin Lindroos, Ph.D., Hans Lönroth, M.D., Ph.D., Ingmar Näslund, M.D., Ph.D., Torsten Olbers, M.D., Ph.D., Kaj Stenlöf, M.D., Ph.D., Jarl Torgerson, M.D., Ph.D., Göran Ågren, M.D., and Lena M.S. Carlsson, M.D., Ph.D., for the Swedish Obese Subjects Study

N= 4047


5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
Weight Change (%)
Control
Banding
Vertical banded gastroplasty
Gastric bypass
0.0
0.5
1.0
2.0
3.0
4.0
6.0
8.0
10.0
Years of Follow-up

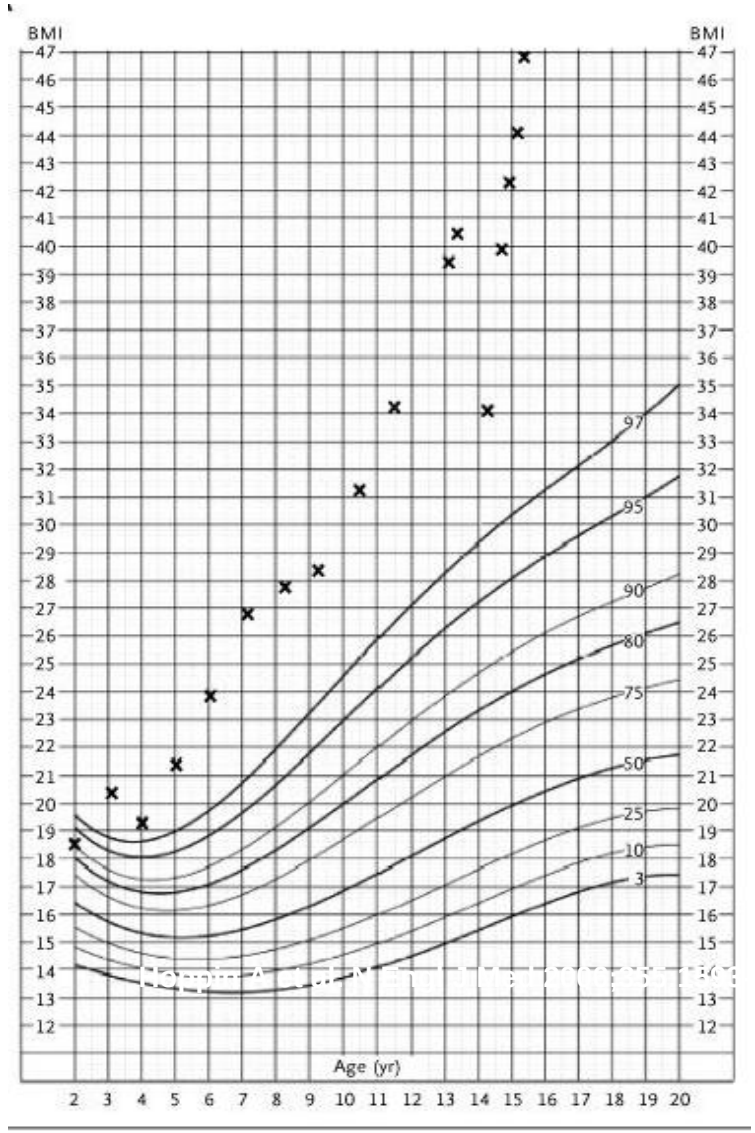
Incidence of Diabetes

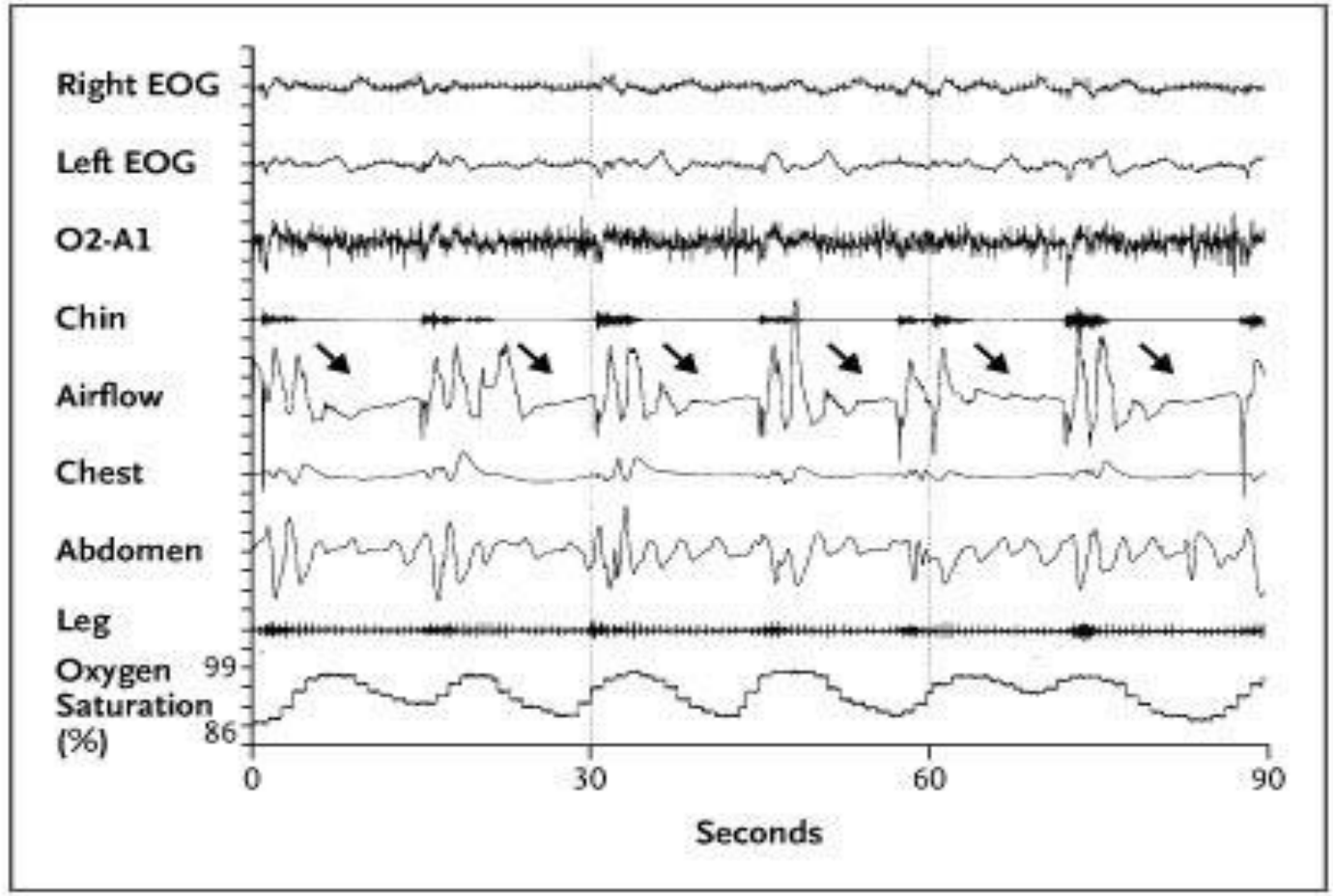


Sophie’s story

Case report

Change in BMI over time





One month after surgery

Weight 122.5 – 109.6 kg
Metformin and lisinopril discontinued.

All blood glucose measurements normal
BP 138/79 mmHg

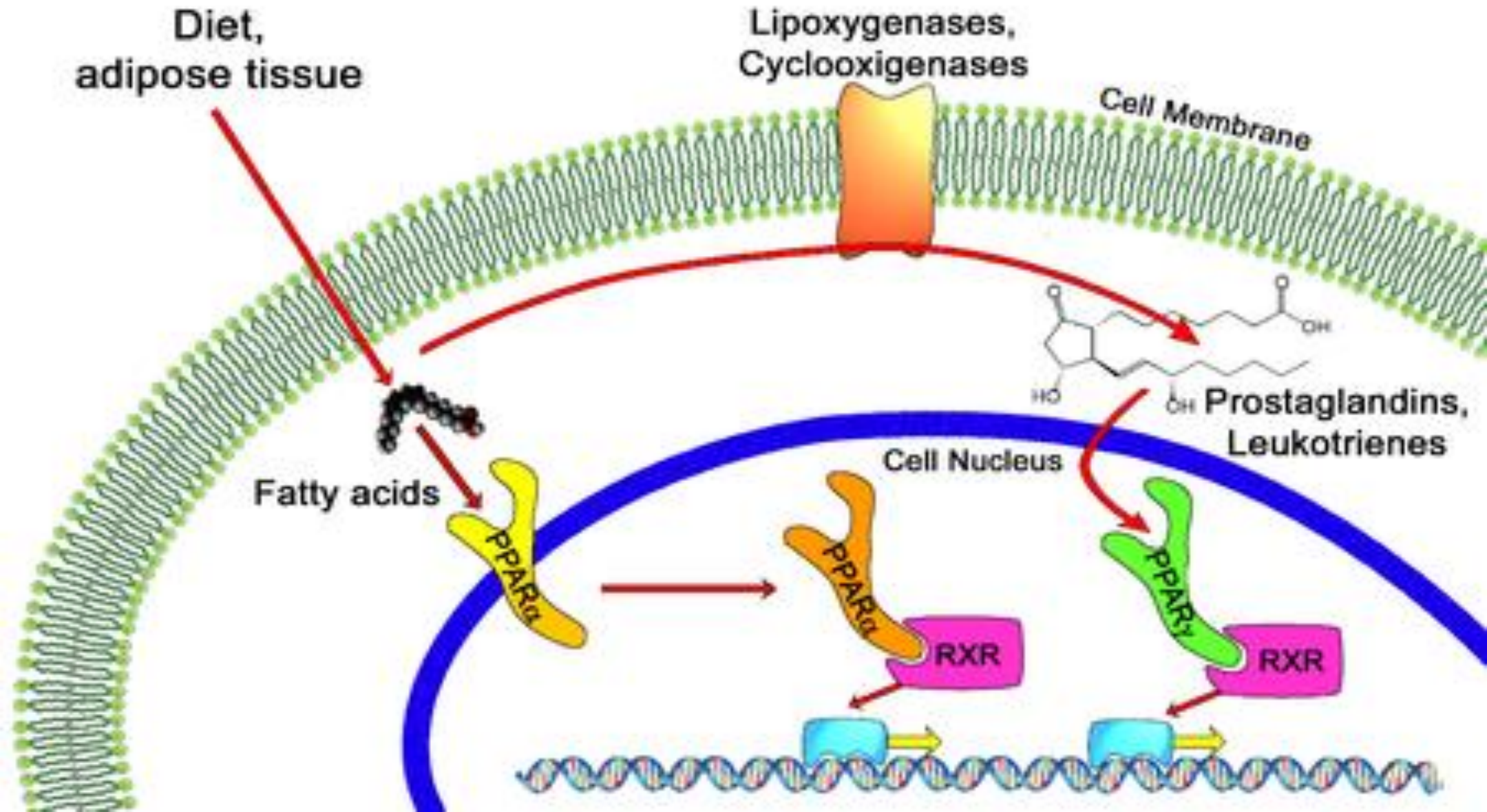
Acanthosis nigricans on wrists and ankles disappeared, but remained on neck

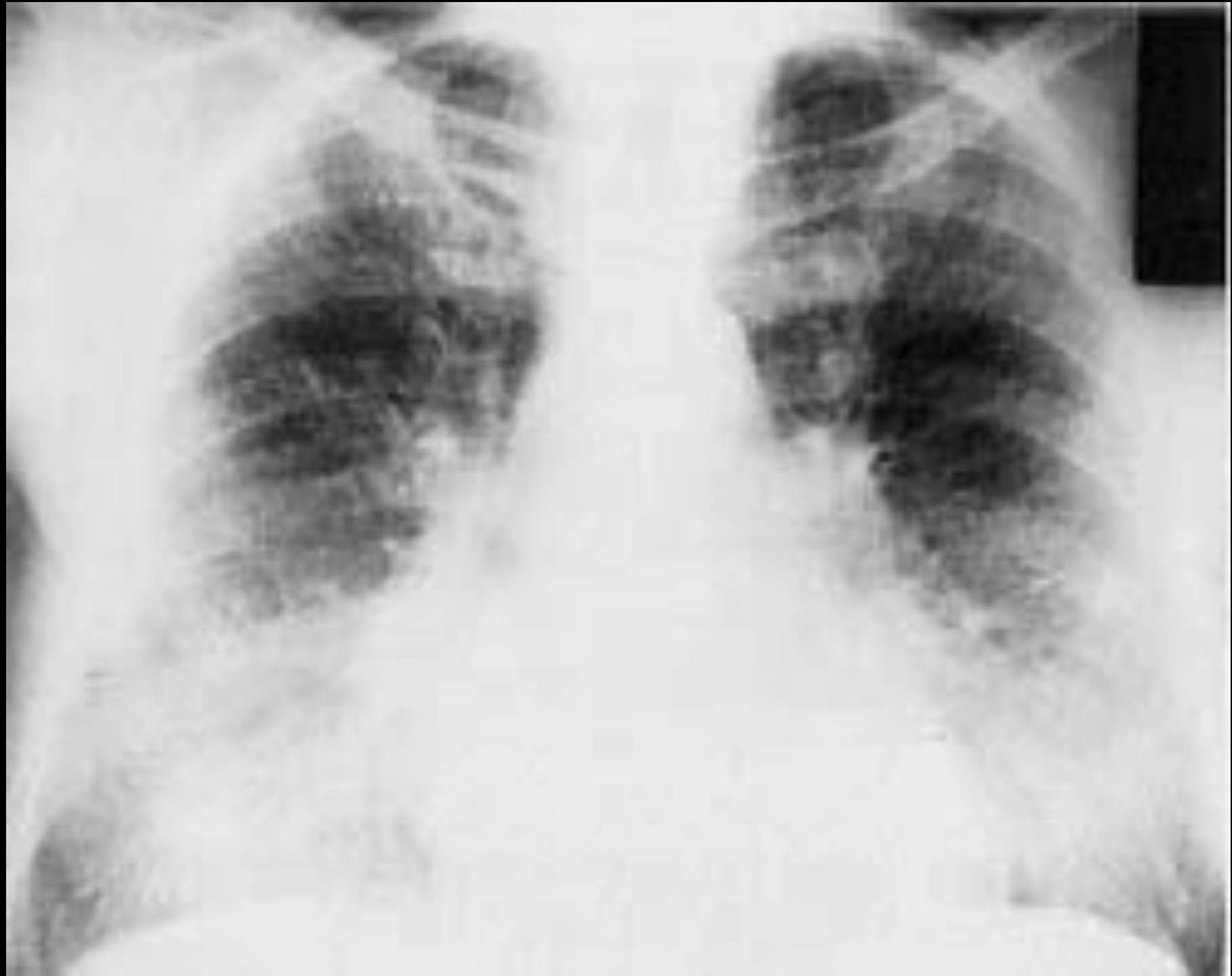
So ….

- Diabetes can be prevented **BEFORE** it happens
- Surgery can **CURE** type 2 diabetes

What about new treatments?

peroxisome proliferator-activated receptors



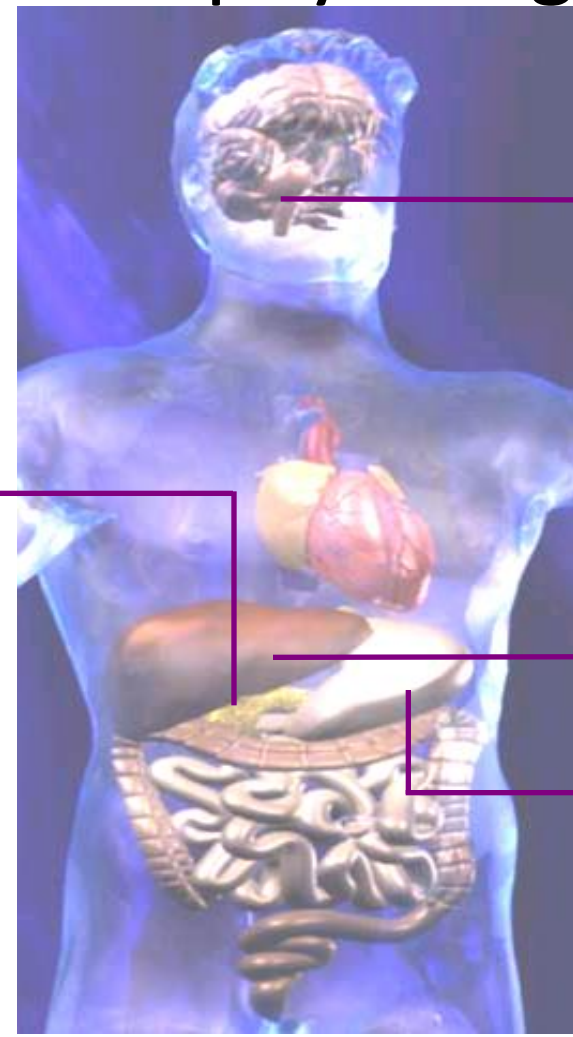


Are TZDs finished?

- ScienceDaily (9th April 2008) — There is no convincing evidence that the glitazones, offer real advantages over other diabetes drugs, when used on their own, concludes the Drug and Therapeutics Bulletin (DTB).

GLP-1 agonists

Native GLP-1 has multiple direct effects on human physiology



Pancreas

- ↑ insulin secretion (glucose-dependent)
- ↑ Insulin synthesis
- ↑ (Beta-cell mass*)
- ↓ Glucagon secretion

Brain

- ↓ Food intake

Liver

- ↓ glucose output

GI tract

- ↓ motility

Baggio & Drucker, 2007; Drucker *et al,* 1987; Bulotta *et al,* 2002; Farilla *et al*, 2003; Nauck *et al*, 1993; Zander *et al,* 2002; Gutzwiller *et al*, 1999; Kieffer & Habener, 1999; Wettergren *et al,* 1993 *animal data

Exenatide sequence

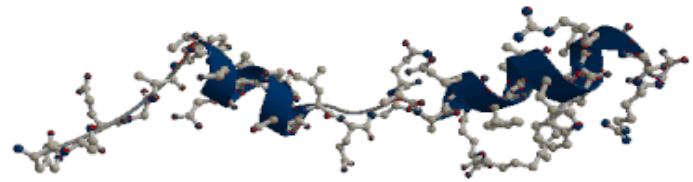
H **G** E G T F T S D **L** S

K Q M E **E E** A **V R L**

F I **E** W L **K N** G **G P**

S S G A P P P S – NH_2

Liraglutide molecule



Exenatide sequence

H **G** E G T F T S D **L** S

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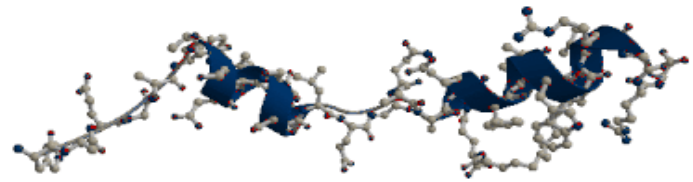
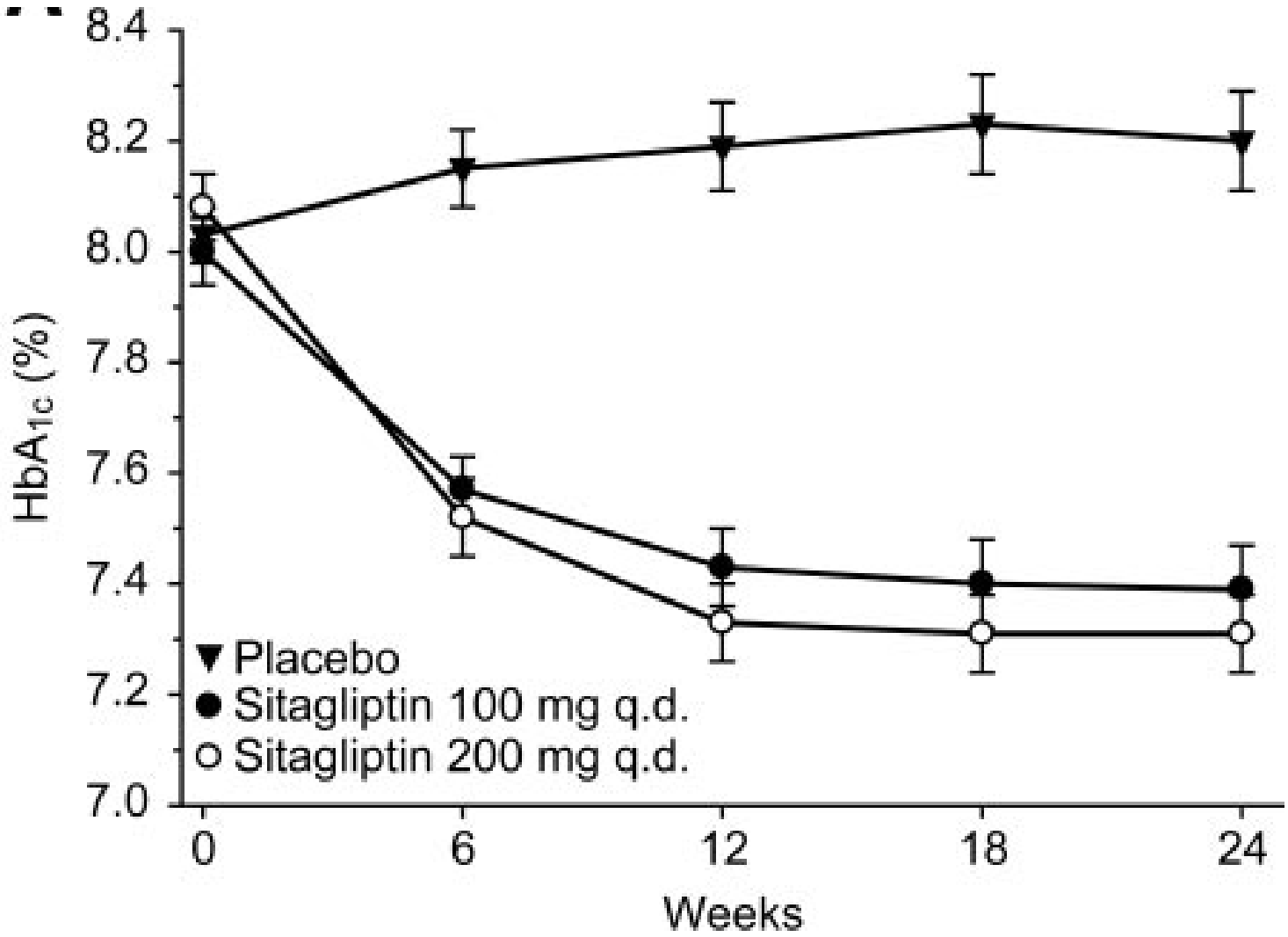
S S G A P P P S – NH_2

Liraglutide molecule

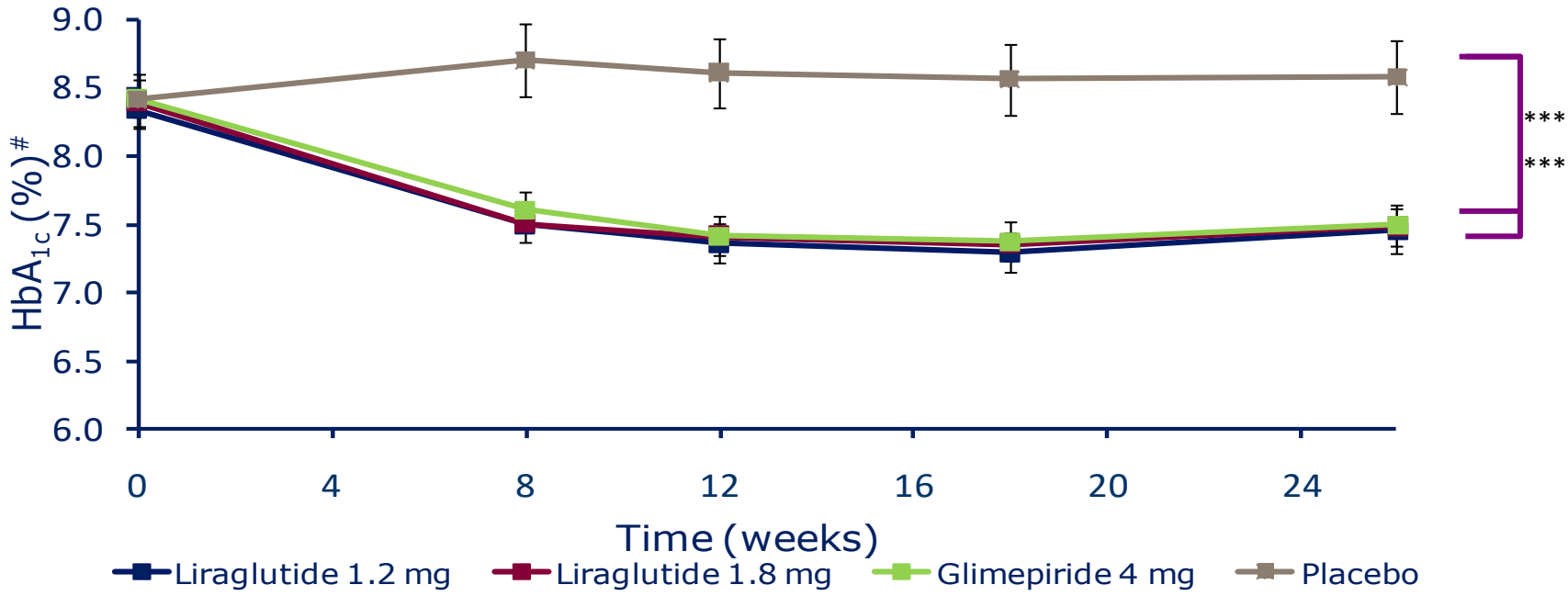


THESE DON'T LOOK LIKE THE SORT OF DRUGS WE SHOULD BE GIVING OUR PATIENTS

Gliptins are pretty feeble agents



HbA_{1c} over time (LEAD-2, add-on to MET)



#Vertical axis range selected for clinical relevance

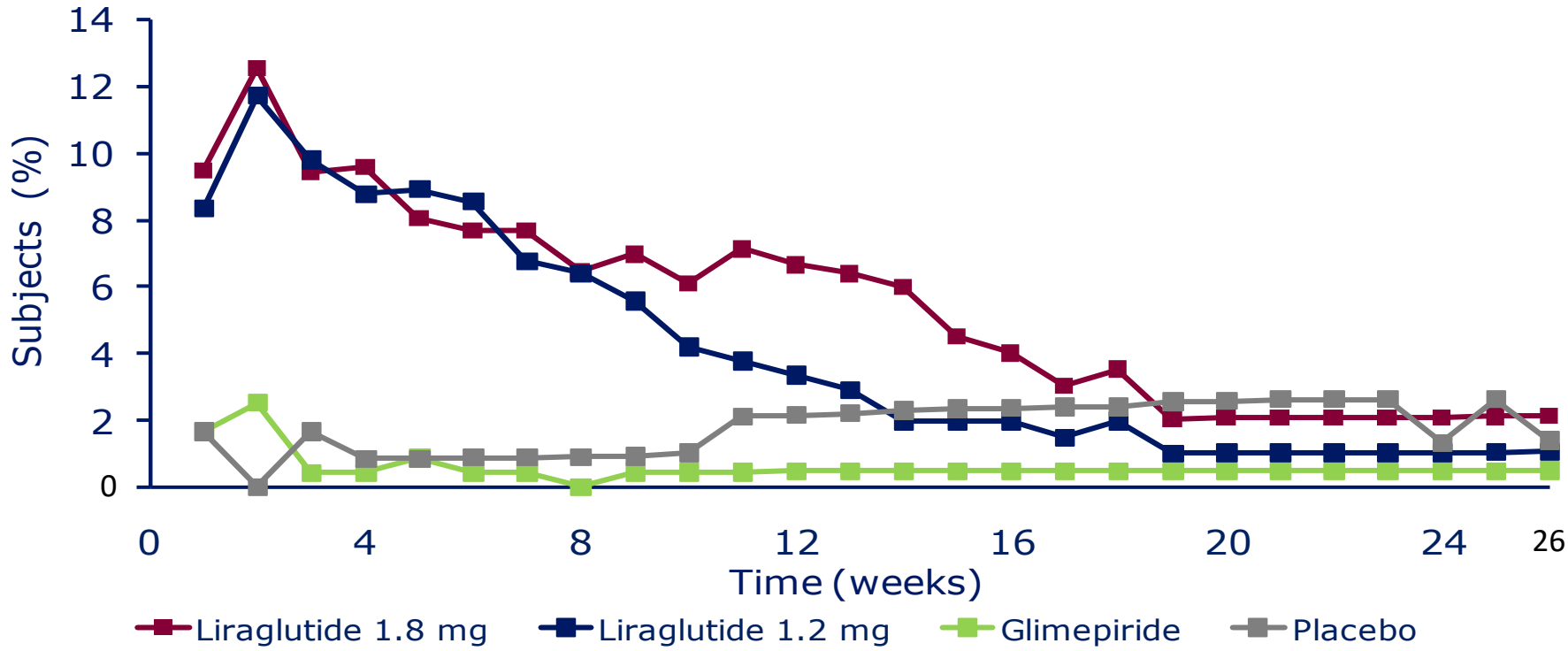
***Estimated treatment difference for changes from baseline. Liraglutide 1.2 mg and 1.8 mg both $p<0.0001$ *versus* placebo

Adapted from Nauck *et al. Diabetes Care* 2009;32:84–90 (LEAD-2)

Frequency of nausea (LEAD-2)

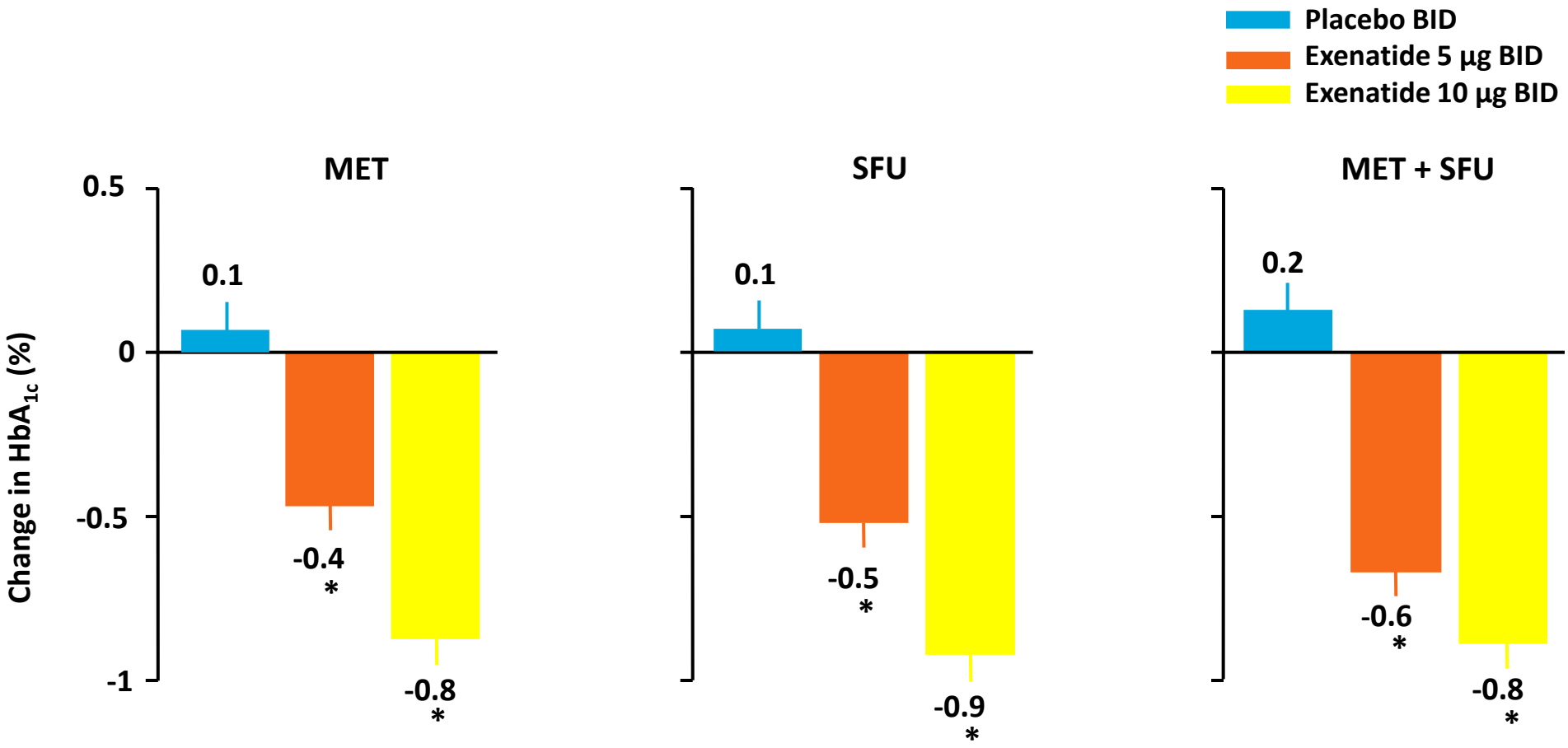
Proportion of subjects with nausea by week and treatment – safety population

Treatment difference in changes not analysed



Data on file (LEAD2/01), Novo Nordisk

Exenatide Lowered HbA_{1c} at 30 Weeks



DeFronzo RA, et al

Buse JB, et al

Kendall DM, et al


BEWARE THE MONSTER

And stick with your old and trusted friends