HbA1c-how low should we go? Evidence from recent trials

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Humour.com

Treatment targets for people with diabetes[1,2]

Blood pressure	**<130/80**
Glycaemic control	
– HbA_{1c}(%)[a]	≤6.5%
Lipid profile, mmol/L	
Total cholesterol	<4.5
– LDL-cholesterol	≤1.8
– HDL-cholesterol	M >1.0 /F >1.2
Triglycerides[b]	<1.7
– TC/HDL[b]	<3
Smoking cessation	**Obligatory**
Regular physical activity, mins/day	**>30–35**
Weight control	
– BMI, kg/m^2	<25*
– For overweight, weight reduction, %	10
Waist (optimum, cm)	**Men <94/Women <80**

[a]DCCT-standardised[3]

[b]Not recommended for guiding treatment but for metabolic/risk assessment

*Not often achieved; BMI maintenance may more relevant

1. De Backer G, et al. Eur J Cardiovasc Prev Rehab. 2003;10:S1-78. 2. Rydén L, et al. Eur Heart J. 2007; 28:88-136.
3. Jeppsson JO, et al. Diabetes Care. 1996;19:142-5.

Glycaemic targets for the management of type 2 diabetes

Organisation	HbA_{1c} (%)	FPG (mmol/L)	PPG (mmol/L)
ADA-EASD[1]	<7	—	—
IDF-Europe[2]	<6.5	5.5	7.8
AACE[3]	≤6.5	6.1	7.8
NICE[4]	6.5[a]	—	—

1. Nathan DM, et al. Diabetologia . 2009;52:17–30; 2. IDF-European Guidelines. 2007. Available at: http://www.idf.org/webdata/docs/Guideline_PMG_final.pdf. Accessed on 26 May 2009.
3. American College of Endocrinology. Endocr Pract 2007;13 (Suppl. 1):1-68. 4. NICE short clinical guideline 87 (partial update). 2009. Available from: http://www.nice.org.uk/CG87. Accessed on 23 June 2009.


I BEAT
ANOREXIA

Meta-analysis of RCTs on macrovascular outcomes and death (1)

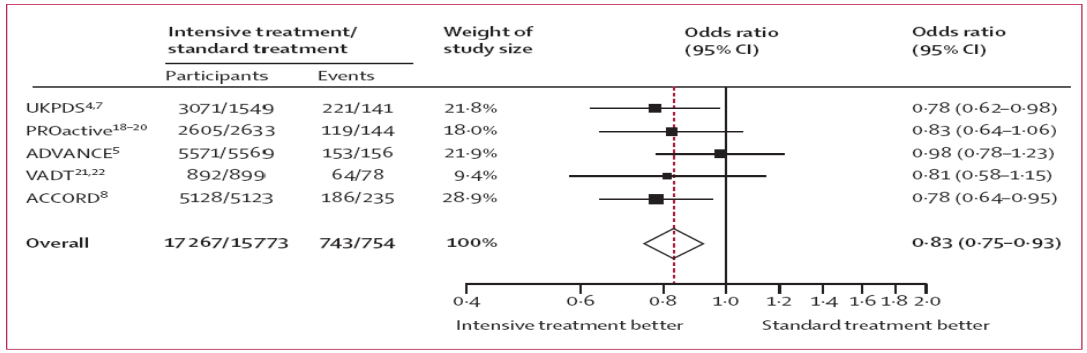


Figure 1: **Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment**

Non-fatal MI
-18% for -1% HbA1c

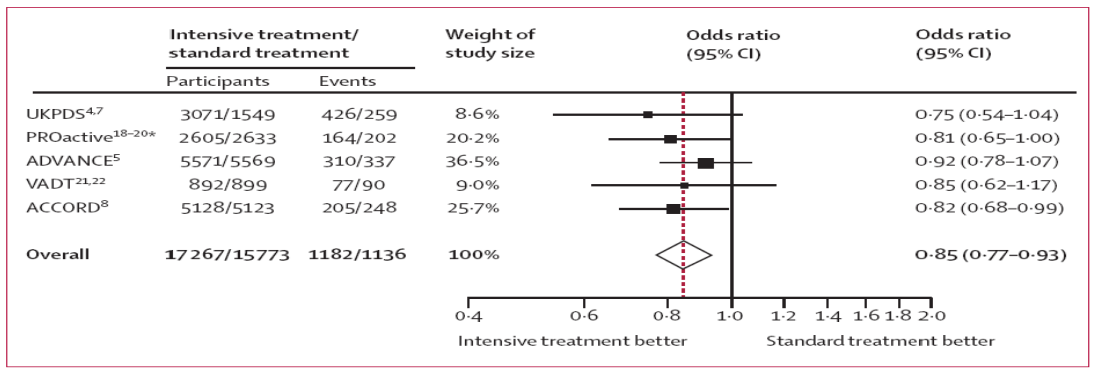


Figure 2: **Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment**
*Included non-fatal myocardial infarction and death from all-cardiac mortality.

Coronary events

All-cause mortality

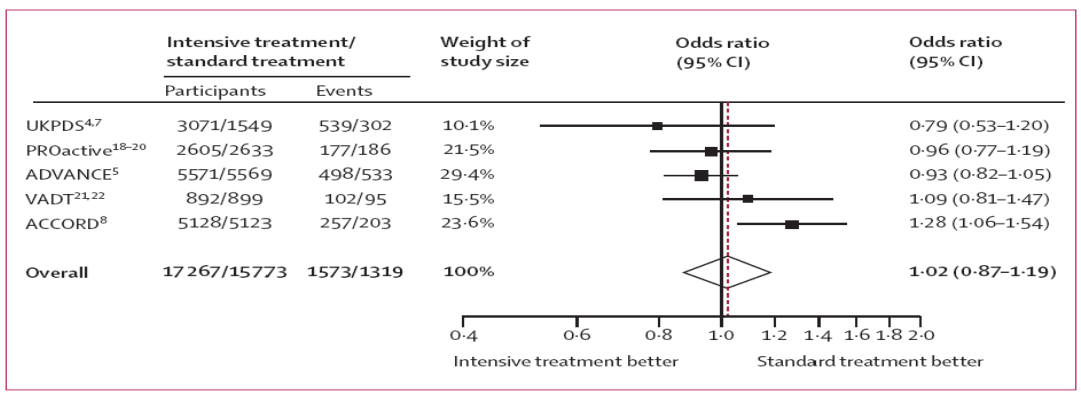
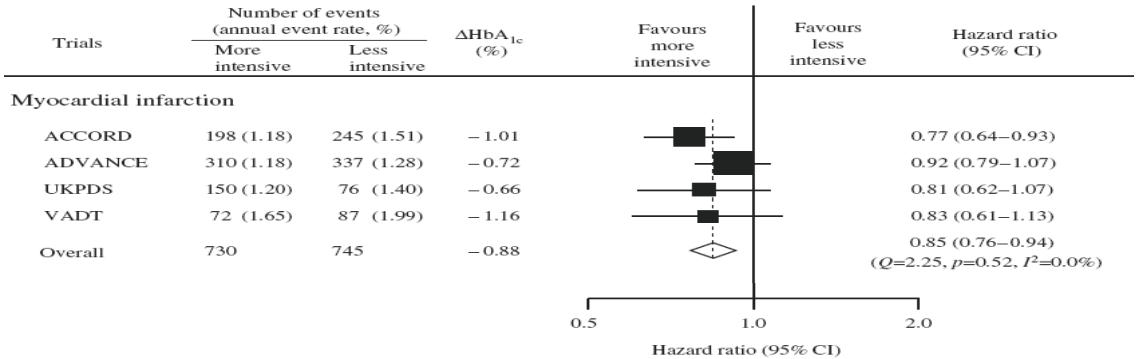


Figure 4: **Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment**

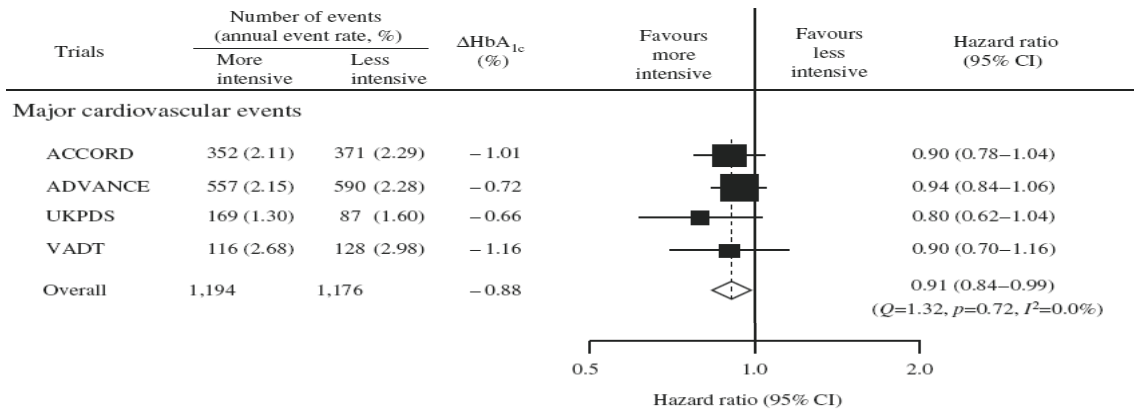
Ray, et al. Lancet. 2009;373:1765

Meta-analysis of RCTs on macrovascular outcomes and death (2)



Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA1c (%)	Hazard ratio (95% CI)
Myocardial infarction				
ACCORD	198 (1.18)	245 (1.51)	−1.01	0.77 (0.64–0.93)
ADVANCE	310 (1.18)	337 (1.28)	−0.72	0.92 (0.79–1.07)
UKPDS	150 (1.20)	76 (1.40)	−0.66	0.81 (0.62–1.07)
VADT	72 (1.65)	87 (1.99)	−1.16	0.83 (0.61–1.13)
Overall	730	745	−0.88	0.85 (0.76–0.94) (Q=2.25, p=0.52, I^2=0.0%)

Fatal and non-fatal MI

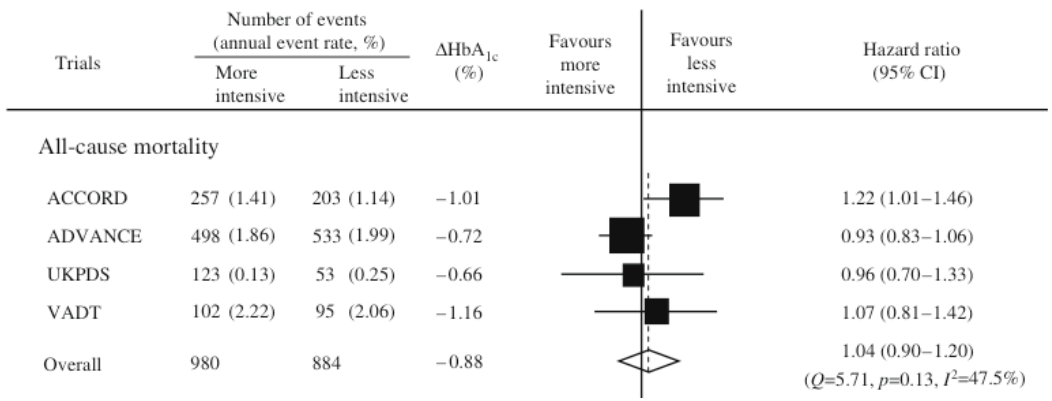


Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA1c (%)	Hazard ratio (95% CI)
Major cardiovascular events				
ACCORD	352 (2.11)	371 (2.29)	−1.01	0.90 (0.78–1.04)
ADVANCE	557 (2.15)	590 (2.28)	−0.72	0.94 (0.84–1.06)
UKPDS	169 (1.30)	87 (1.60)	−0.66	0.80 (0.62–1.04)
VADT	116 (2.68)	128 (2.98)	−1.16	0.90 (0.70–1.16)
Overall	1,194	1,176	−0.88	0.91 (0.84–0.99) (Q=1.32, p=0.72, I^2=0.0%)

Major CV events*

*CV Death, Non-Fatal Stroke, Non-Fatal MI

All-cause mortality



Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA1c (%)	Hazard ratio (95% CI)
All-cause mortality				
ACCORD	257 (1.41)	203 (1.14)	−1.01	1.22 (1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	−0.72	0.93 (0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	−0.66	0.96 (0.70–1.33)
VADT	102 (2.22)	95 (2.06)	−1.16	1.07 (0.81–1.42)
Overall	980	884	−0.88	1.04 (0.90–1.20) (Q=5.71, p=0.13, I^2=47.5%)

Turnbull, et al. Diabetologia 2009; Epub August 5

Review of recent studies investigating intensive glycaemic control

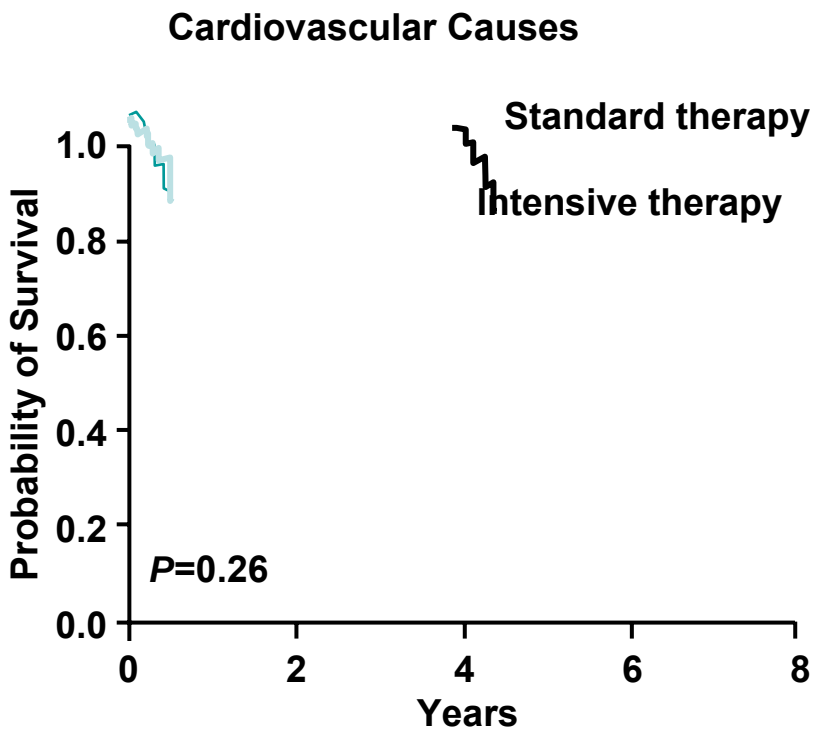
Variable	VADT (n=1,700)	ACCORD (n=10,250)	ADVANCE (n=11,140)
HbA_{1c} (%)[a]	8.4 vs 6.9	7.5 vs 6.4	7.3 vs 6.5
Primary outcome	MI, stroke, death from CV causes, new or worsening CHF, revascularisation[b] and inoperable CAD, amputation for ischaemic gangrene	Non-fatal MI, non-fatal stroke, CVD death	Non-fatal MI, non-fatal stroke, CVD death
HR (95% CI) for primary outcome	0.87 (0.730–1.04)	0.90 (0.78–1.04)	0.94 (0.84–1.06)
HR (95% CI) for mortality	1.065 (0.801–1.416)	1.22 (1.01–1.46)[b]	0.93 (0.83–1.06)

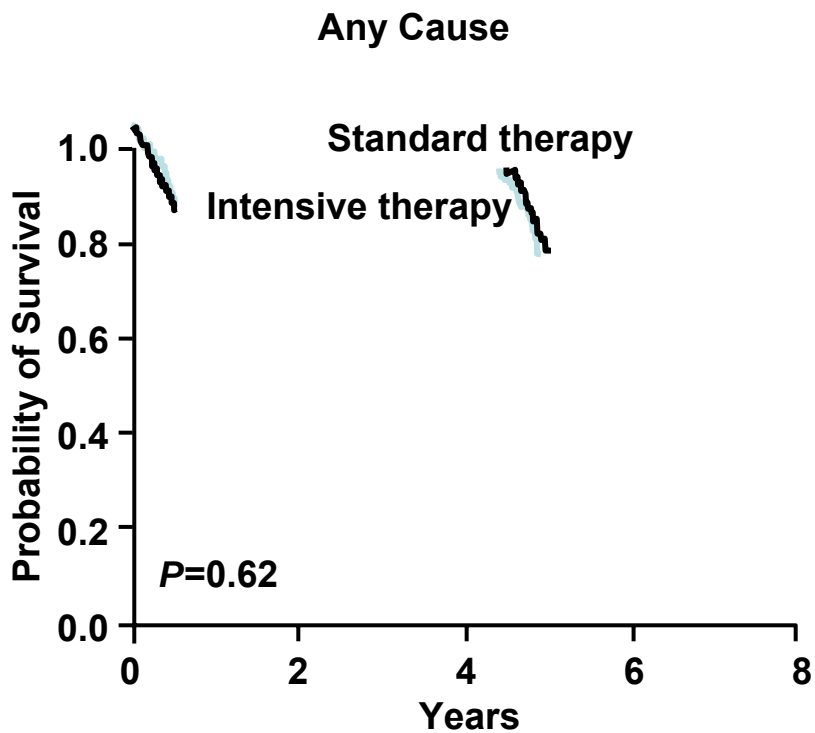
[a] Conventional vs intensive

[b] p=0.04

CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction

No significant difference in time to death from cardiovascular causes or death from any cause





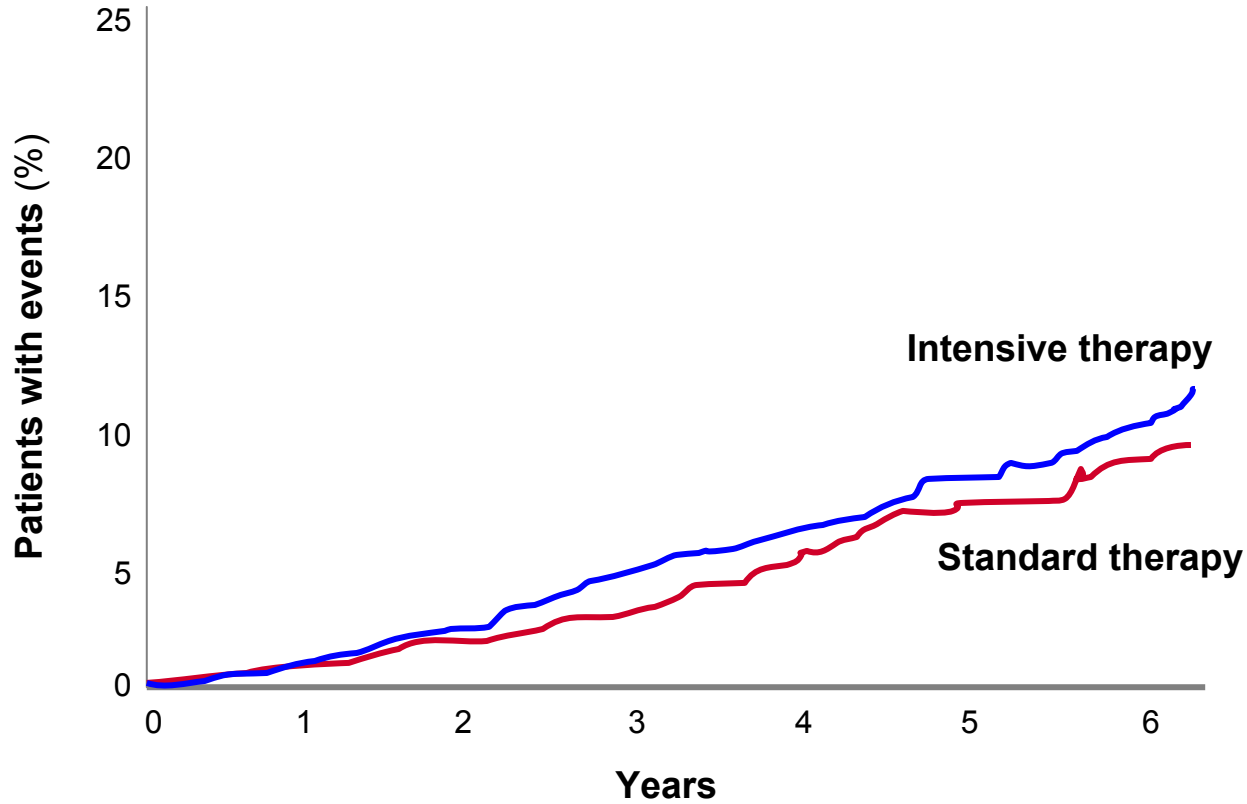
No. at Risk								
Standard therapy 899	833	767	767	724	635	320	75	0
Intensive therapy 892	828	786	746	713	646	337	85	0

No. at Risk								
Standard therapy 899	836	801	772	727	637	322	76	0
Intensive therapy 892	832	791	752	720	650	341	86	0

Duckworth W et al; the VADT Study Investigators. *N Engl J Med* 2009;360:129-139.

ACCORD

- Mortality Rate for Intensive vs Standard Tx: Death From Any Cause



No. at Risk

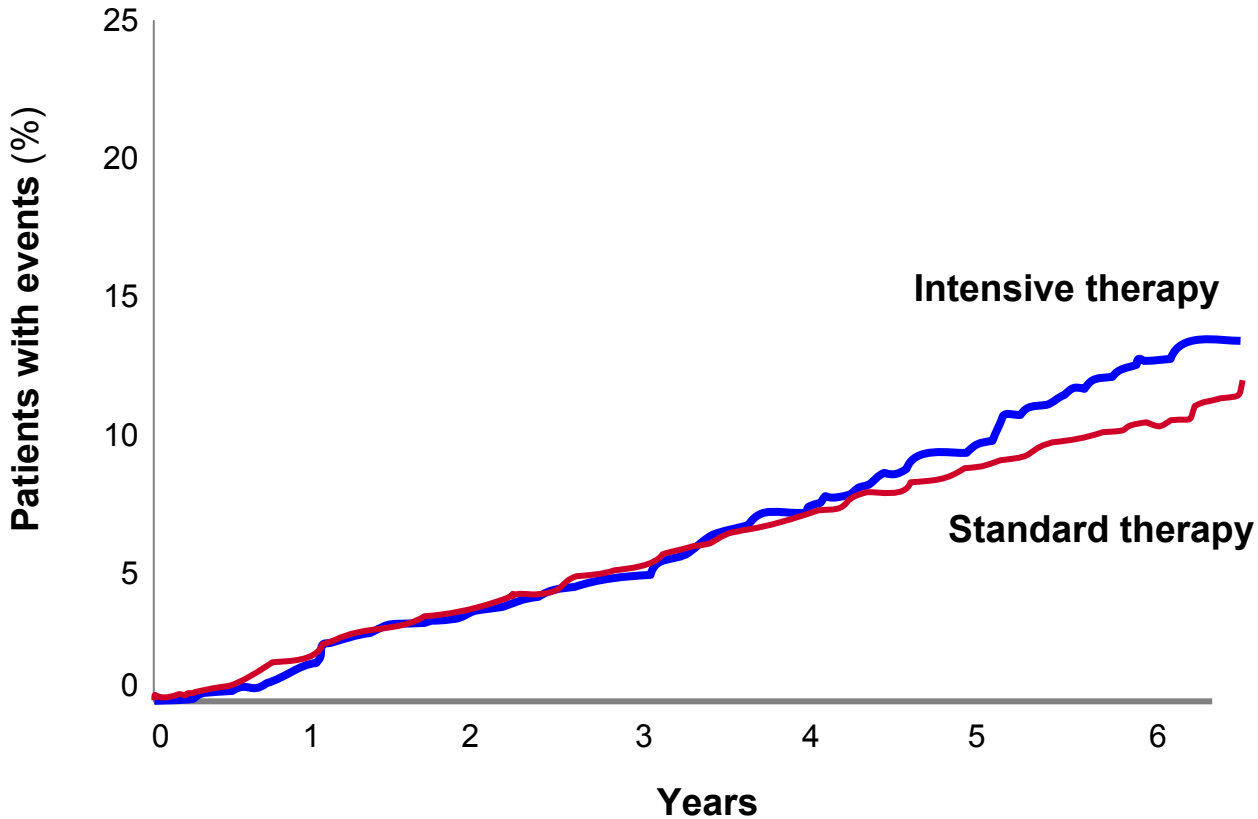
Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

22% relative increase in mortality for intensive Tx over standard Tx

N Engl J Med 2008;358:2545-59.

ACCORD

- Mortality Rate for Intensive vs Standard Tx: Death From CV Events



No. at Risk							
Intensive therapy	5128	4843	4390	2839	1337	475	448
Standard therapy	5123	4827	4262	2702	1186	440	395

Primary Outcome

Conclusions

- **Intensive glucose lowering can be *harmful* in patients at high CV risk**

N Engl J Med 2008;358:2545-59.

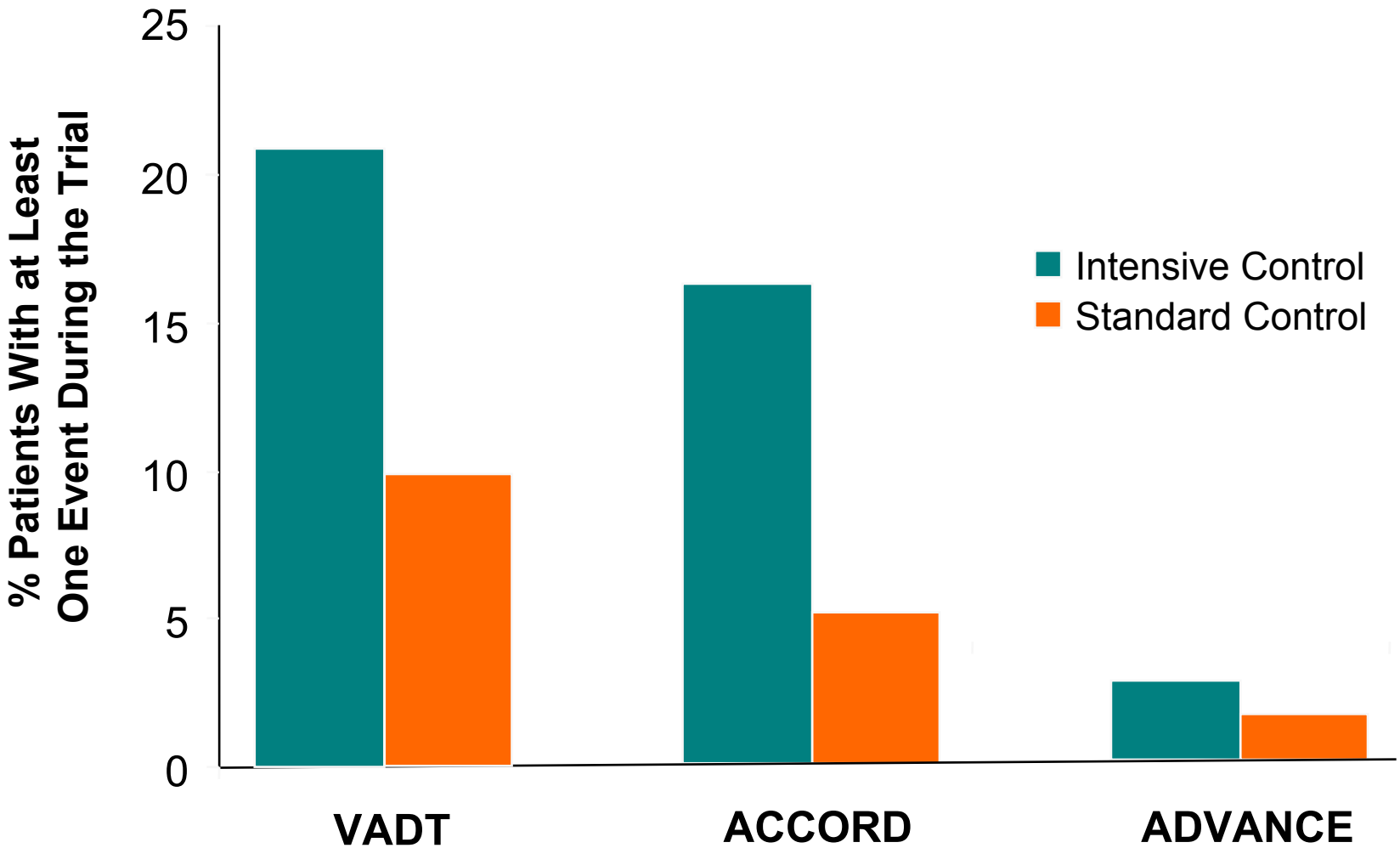
Possible causes of increased mortality during intensified therapy

Specific medication

Weight gain

Hypoglycaemia

Severe hypoglycaemia in the three recent trials of intensive glucose control in Type 2 diabetes

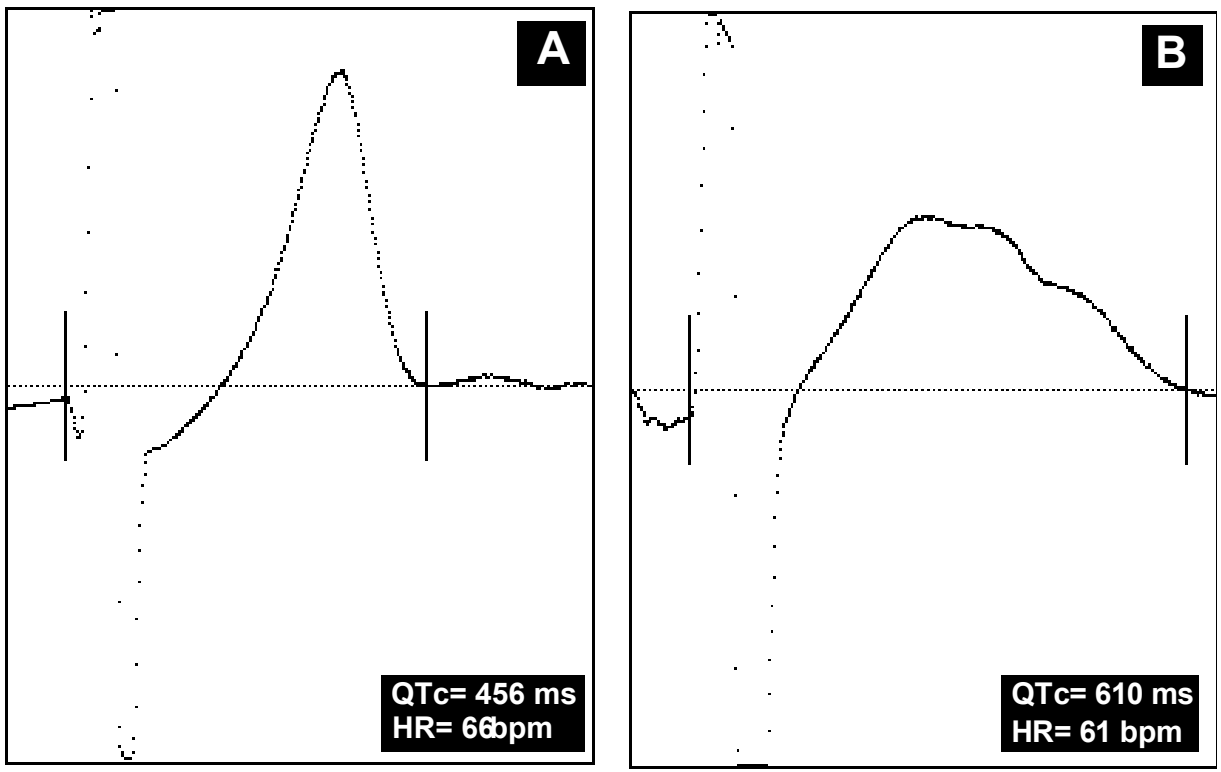


ACCORD: Higher Mortality in Participants who Experienced Severe Hypoglycaemia (SH)

Potential Mechanisms of Hypoglycaemia Induced Mortality

- Cardiac arrhythmias due to abnormal cardiac repolarization in high-risk patients (IHD, cardiac autonomic neuropathy)
- Increased thrombotic tendency/decreased thrombolysis
- Cardiovascular changes induced by catecholamines
  - *Increased heart rate*
  - *Silent myocardial ischaemia*
  - *Angina and myocardial infarction*

Effect of experimental hypoglycaemia on QT interval



5.0mM

2.5mM

The ACCORD Study

- Intensive therapy to lower HbA1c to normal target levels for 3.5 years was associated with higher mortality but with no significant reduction of major cardiovascular events

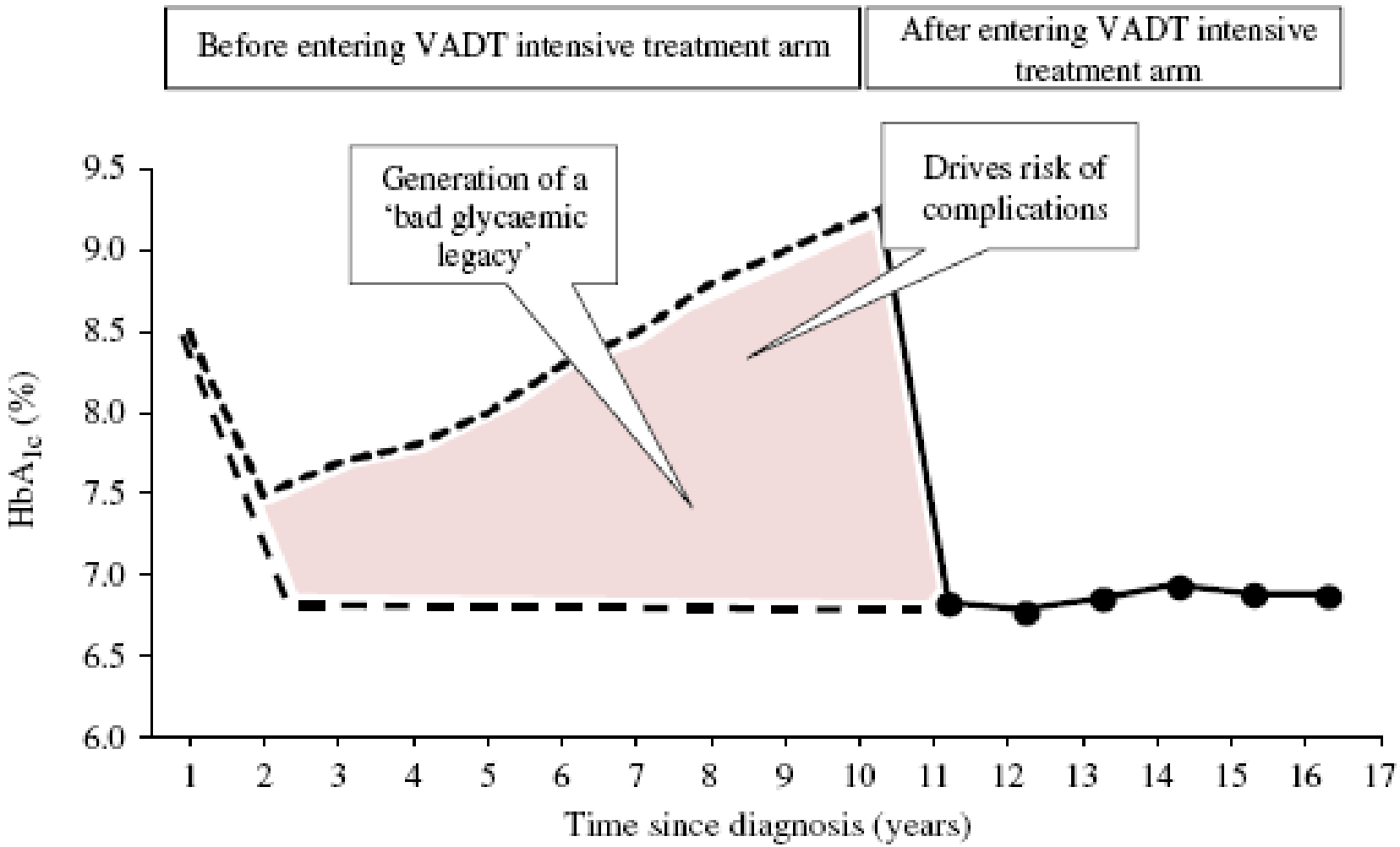
- The cause of the increased mortality *could not be proven*; severe hypoglycaemia was implicated

- This study demonstrated the potential harm of using intensive treatment to lower glucose in high-risk patients with Type 2 diabetes

- The outcome raises questions about targets for glycaemic control in type 2 diabetes and how they should be achieved

ACCORD Study Group (2008) N Engl J Med;358:2545

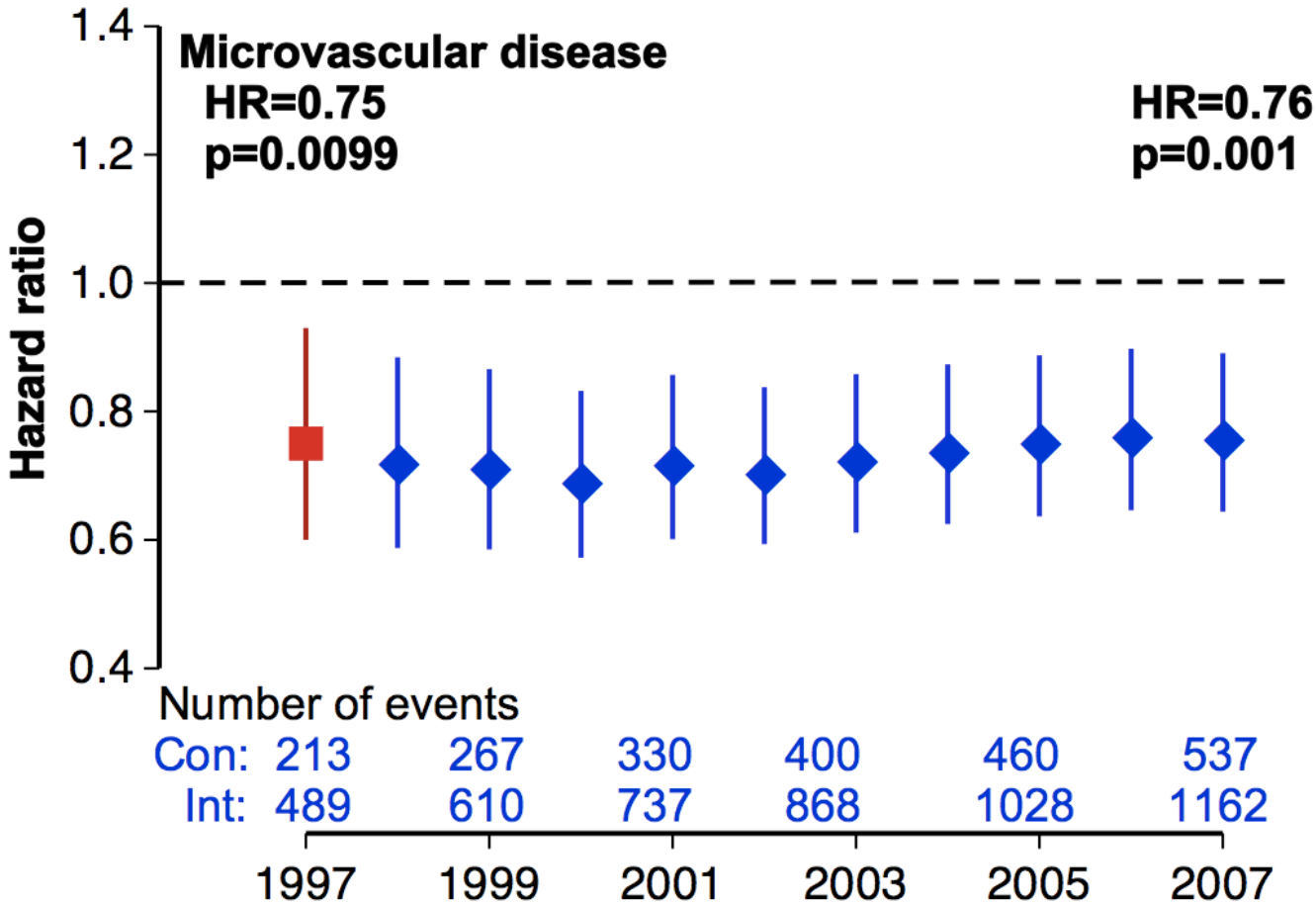
“Bad Glycaemic Legacy”



Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

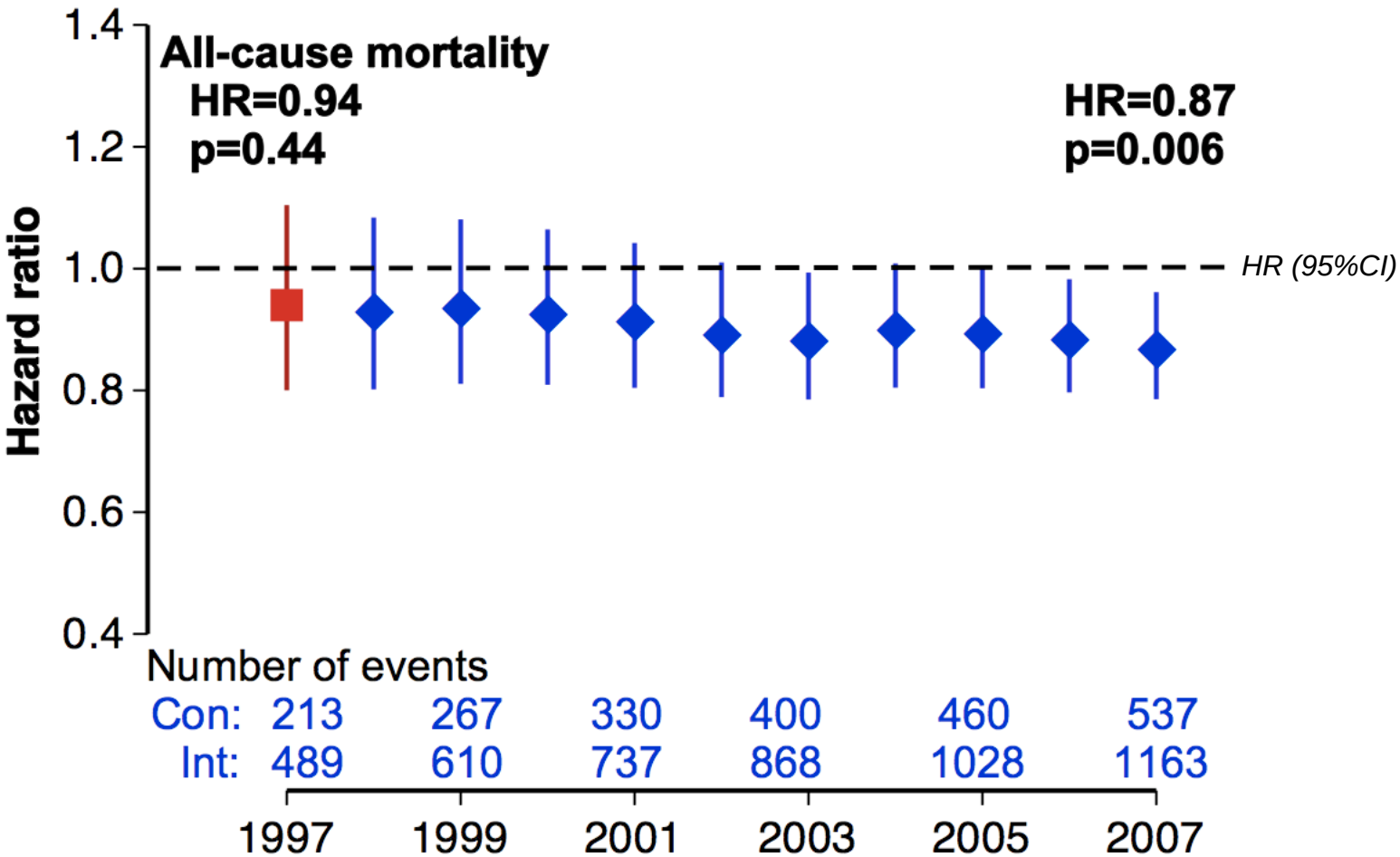
Intensive (SU/Ins) *vs.* Conventional glucose control



Holman RR et al. N Engl J Med 2008;359:1577-89.

All-cause Mortality Hazard Ratio

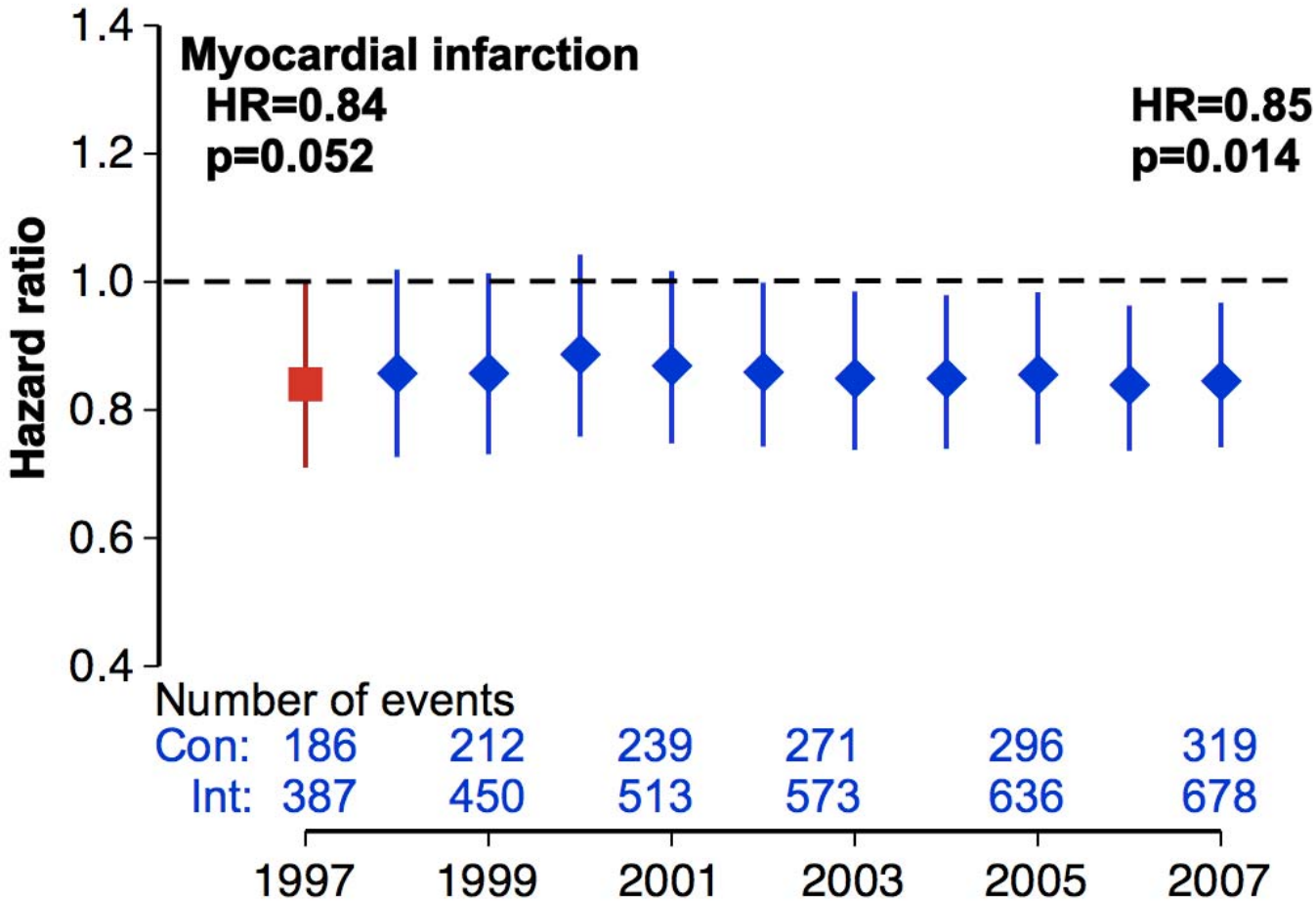
Intensive (SU/Ins) *vs.* Conventional glucose control



Myocardial Infarction Hazard Ratio

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

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

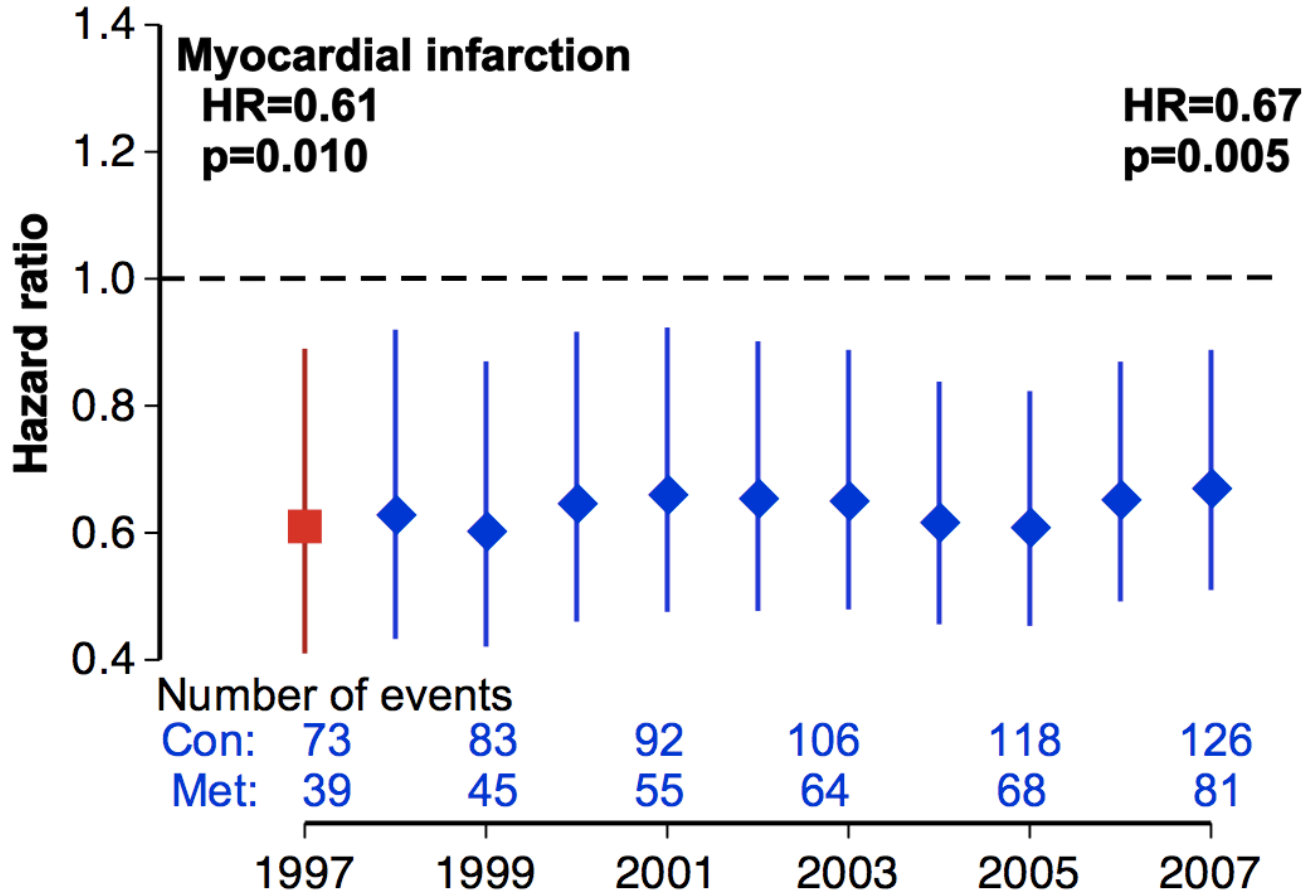


Holman RR et al. N Engl J Med 2008;359:1577-89.

Myocardial Infarction Hazard Ratio

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

Intensive (metformin) *vs.* Conventional glucose control



Holman RR et al. N Engl J Med 2008;359:1577-89.

Conclusions from UKPDS
10 years post-trial follow-up

Despite an early loss of glycaemic differences there was a continued reduction in microvascular risk and emergent risk reductions for MI and death from any cause during 10 years of post-trial follow-up.

Continued benefit after metformin among overweight patients.

GOOD GLYCAEMIC CONTROL IN THE EARLY YEARS OF DIABETES IS VITAL TO REDUCE VASCULAR EVENTS AND MORTALITY LONGTERM.

"... within the timeframe of the intensive treatment period of recent trials, there is less opportunity to influence the development and/or progression of complications in individuals with longstanding diabetes. Conversely, in both type 1 and type 2 diabetic patients, early strict glycaemic control generates a legacy that may confer protection against, or delay, long term diabetic complications"

"... no form of mild diabetes exists, and no excuse exists to postpone appropriate and effective treatment"

S. Del Prato Diabetologia 2009;52:1219-1226

Overall conclusions from recent trials

- Tight diabetes control in the early years after diagnosis associated with significant reduction in total and CV mortality and vascular events.

- Caution re “too tight” and “too rapid tightening of” control in longer duration, high risk patients possibly because of increased chance of hypoglycaemia precipitating arrhythmias/CV events and death

HYPOGLYCAEMIA

A major limiting factor to achieving intensive glycaemic control for people with type 2 diabetes

Briscoe VJ et al Clin Diab 2006;24:115-121

Hypoglycaemia in type 2 diabetes

- Hypoglycaemia symptoms common in type 2 diabetes – 38% of patients[1]
- Associated with reduced –

    quality of Life

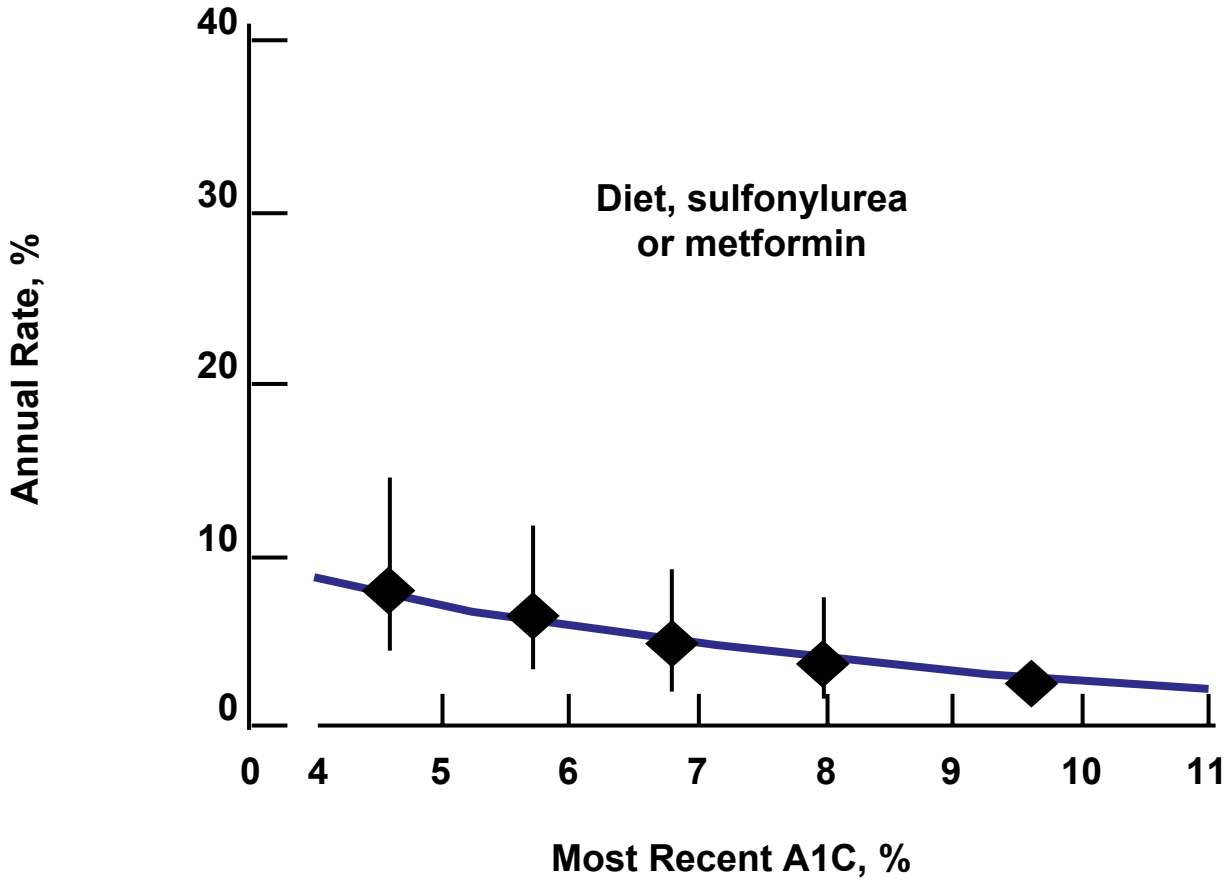
    treatment satisfaction

    therapy adherence

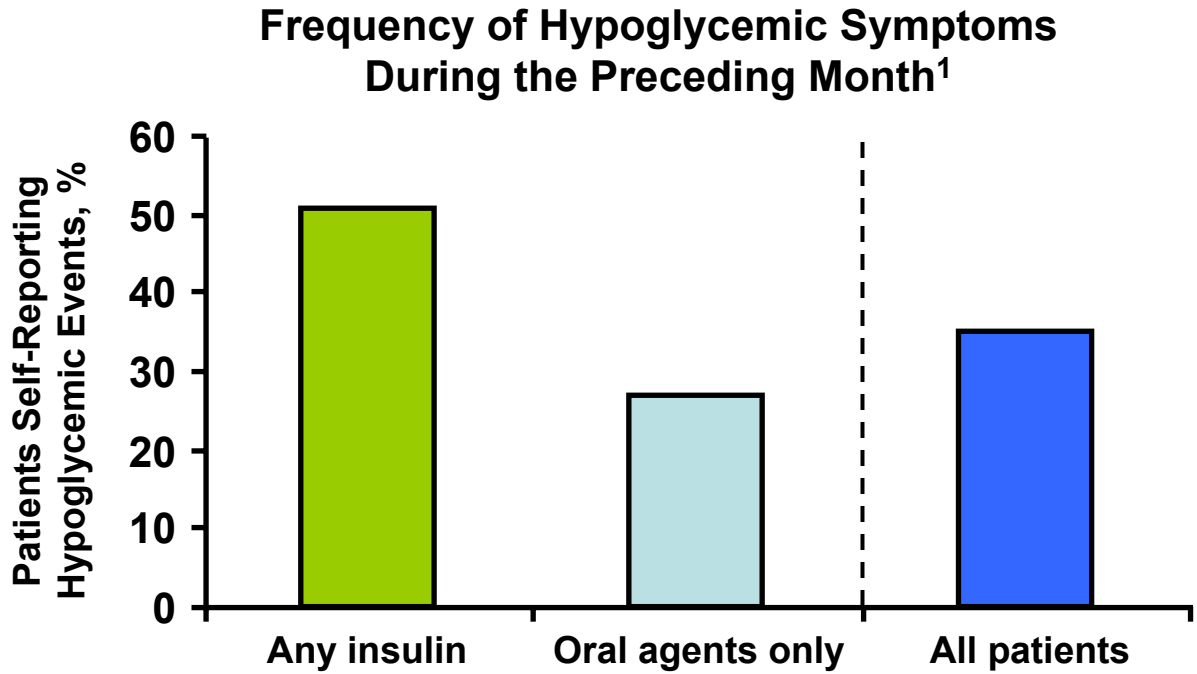
More common at HbA1c < 7%

1. Diabetes Obesity and metabolism 2008 Jun;10 Suppl 1:25-32.

Rates of Hypoglycemia Increase as A1C Levels Decrease in type2 diabetes patients



Frequency of Hypoglycemic Symptoms Among Patients With Type 2 Diabetes



Other studies in Asia and Europe report similar prevalence of hypoglycemia in patients with type 2 diabetes treated with oral agents.[2,3]

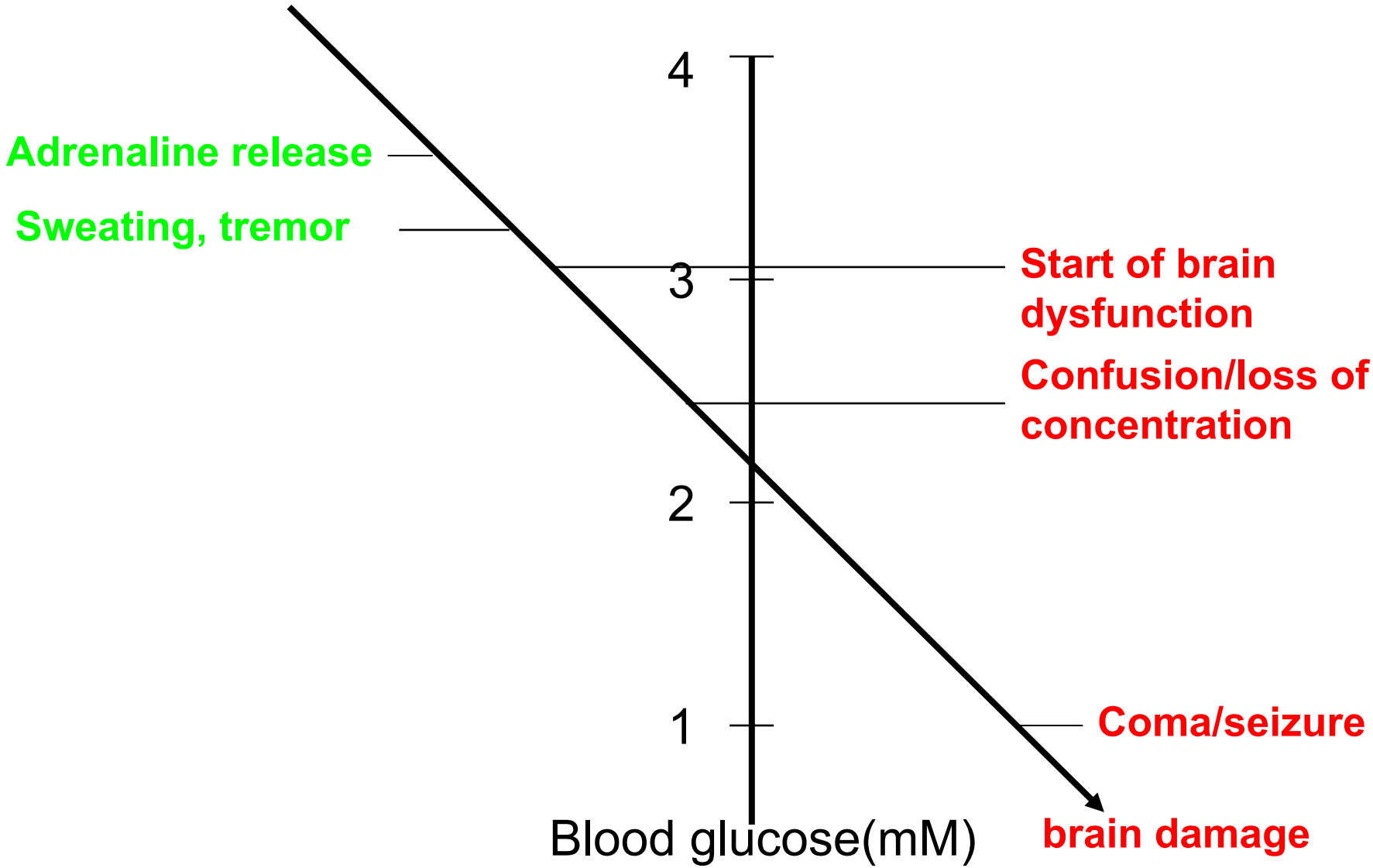
1. Reproduced with permission of Springer Verlag. Lundkvist J et al. *Eur J Health Econom*. 2005;6(3):197–202. Permission conveyed through Copyright Clearance Center, Inc.
2. Asia RECAP-DM Study Group. 7th IDF Western Pacific Region Congress, Wellington, New Zealand. Poster No. P45.
3. Álvarez Guisasola F et al. *Diabetes Obes Metab*. 2008;10(suppl 1):25–32.

Awareness of hypoglycaemia

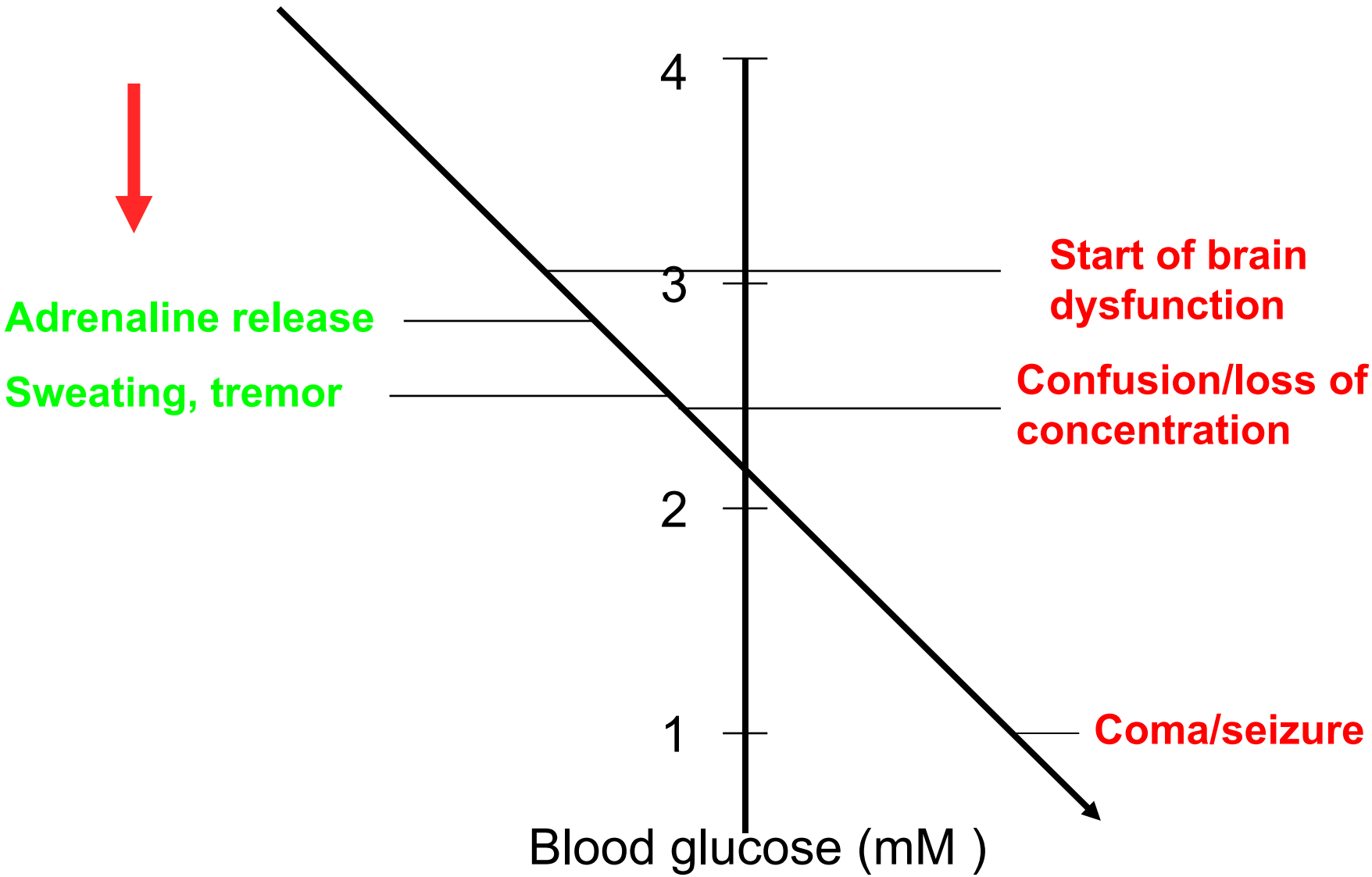
- Recognition of warning symptoms fundamental for self-treatment and prevent progression to severe hypo[1]
- Even mild hypoglycaemia induces defects in counterregulatory responses and impaired awareness[2]
- Impaired awareness predisposes to six-fold increase in the frequency of severe hypoglycaemia[3]
- Only 15% of type 2 diabetes patients who experienced a hypoglycaemic event reported the incident to their doctor[1,4]

1. McAulay V *et al. Diabet Med.* 2001; **18**: 690–705.
2. Amiel SA et al. Diabetic Medicine 2008; **25**: 245–254.
3. Gold AE *et al*. *Diabetes Care* 1994; **17**: 697–703.
4. Leiter LA *et al. Can J Diab.* 2005; **29**(3): 186–192.

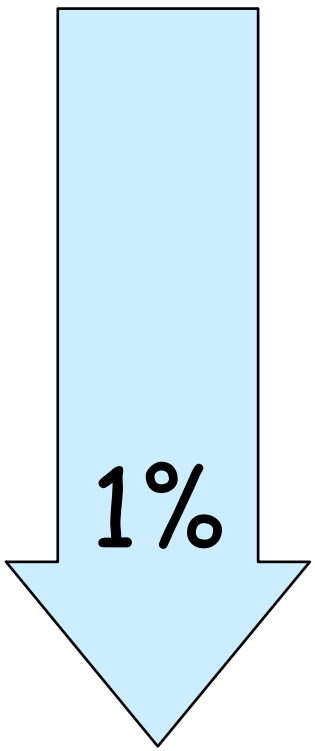
Normal physiological response to hypoglycaemia



Impaired physiological responses and unawareness



Lessons from UKPDS: better control means fewer complications

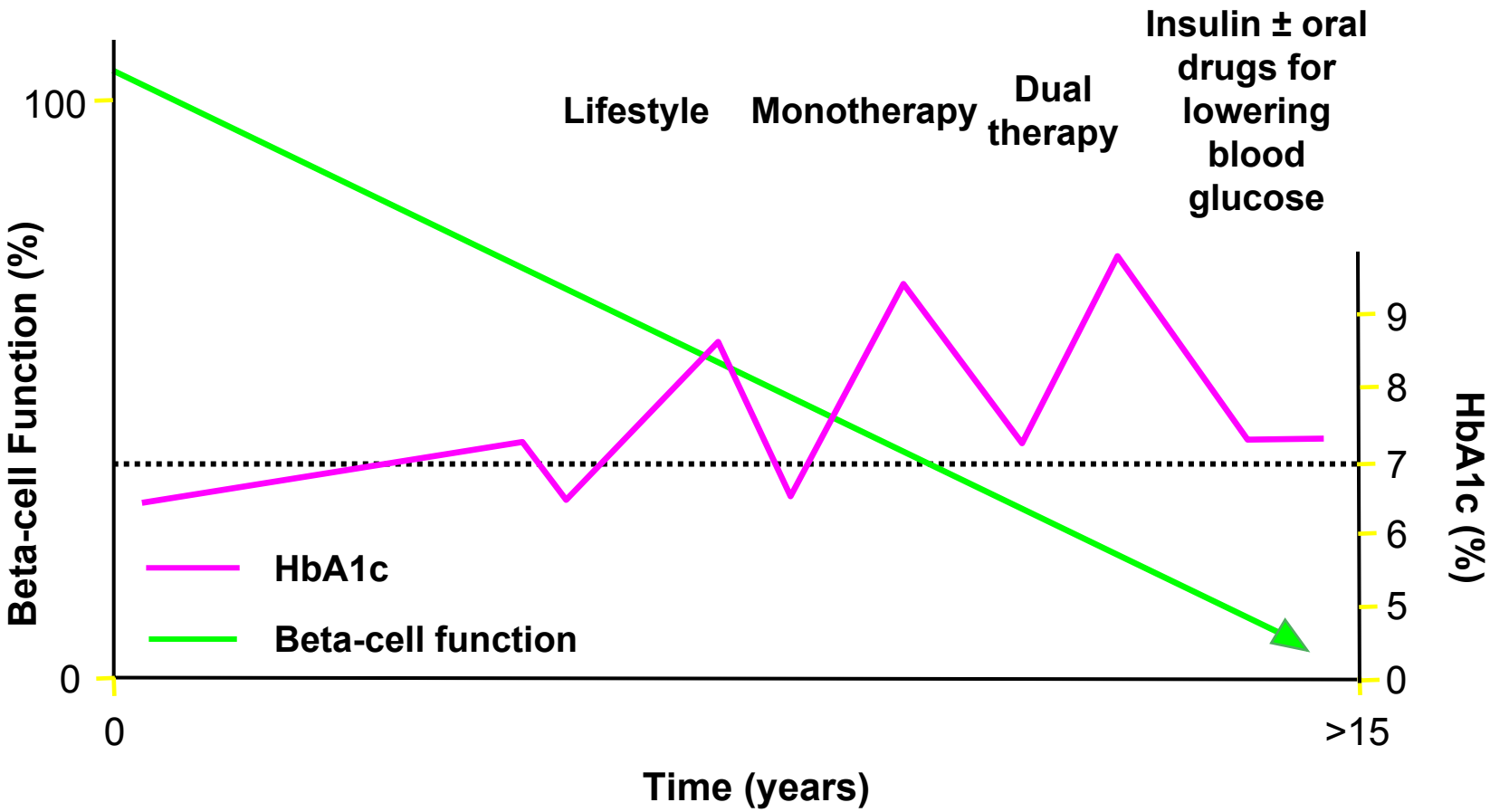


	REDUCED RISK*
Deaths from diabetes	21%
Heart attacks	14%
Microvascular complications	37%
Peripheral vascular disorders	43%

UKPDS 35. BMJ 2000;321:405ñ12

*p<0.0001

Progressively Declining Beta-cell Function in T2DM-"waiting for failure"



Heine RJ, et al. *BMJ*. 2006;333:1200–1204.

Anti-Diabetes Agents

Insulin Secretion

Sulphonylureas

Insulin secretagogues (rapid)

Incretin-mimetics

DPP4 - inhibitors

Glucose Absorption

Alpha-glucosidase inhibitors

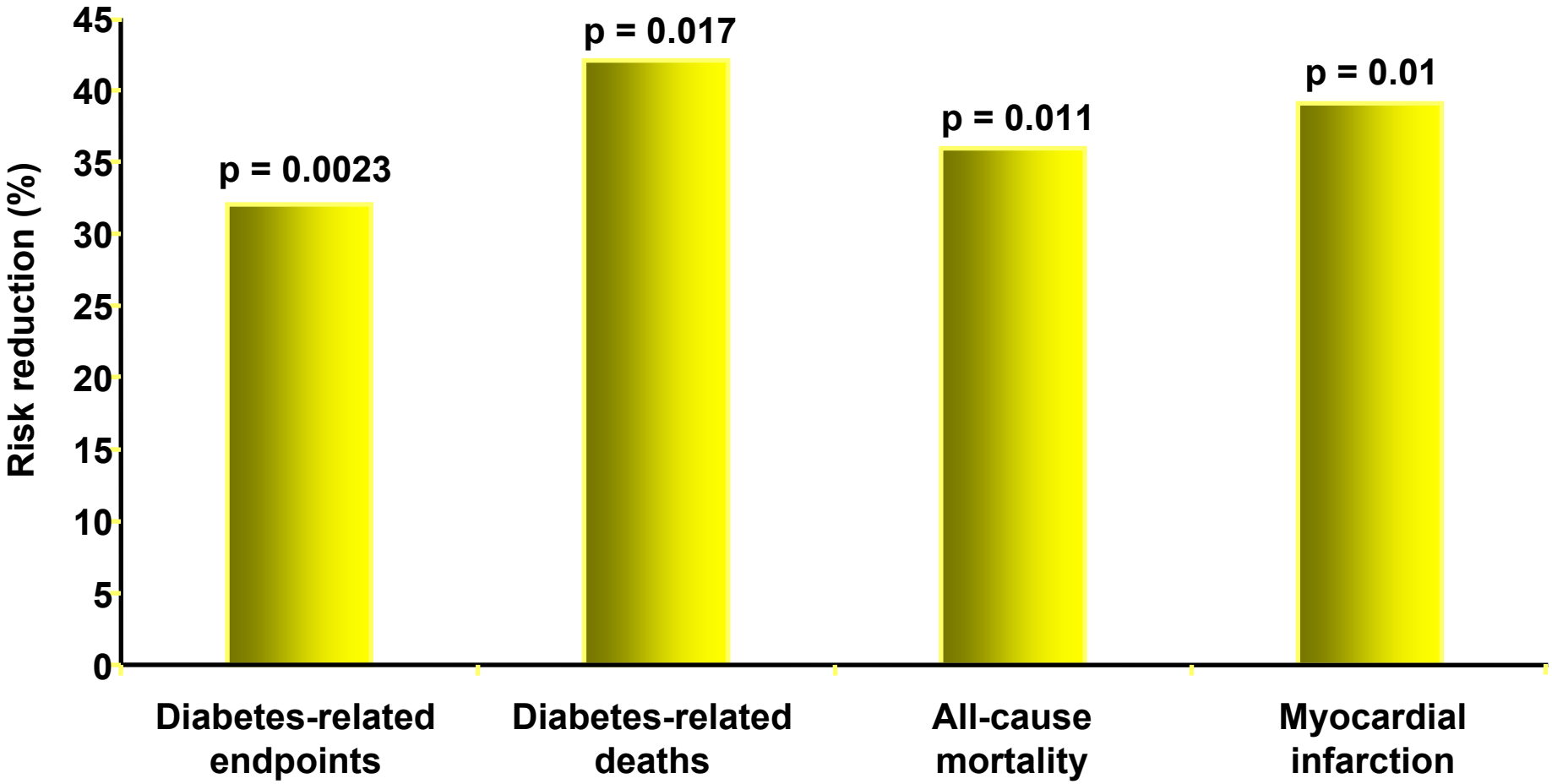
Insulin Action

Thiazolidinediones (Glitazones)

Metformin

Insulin

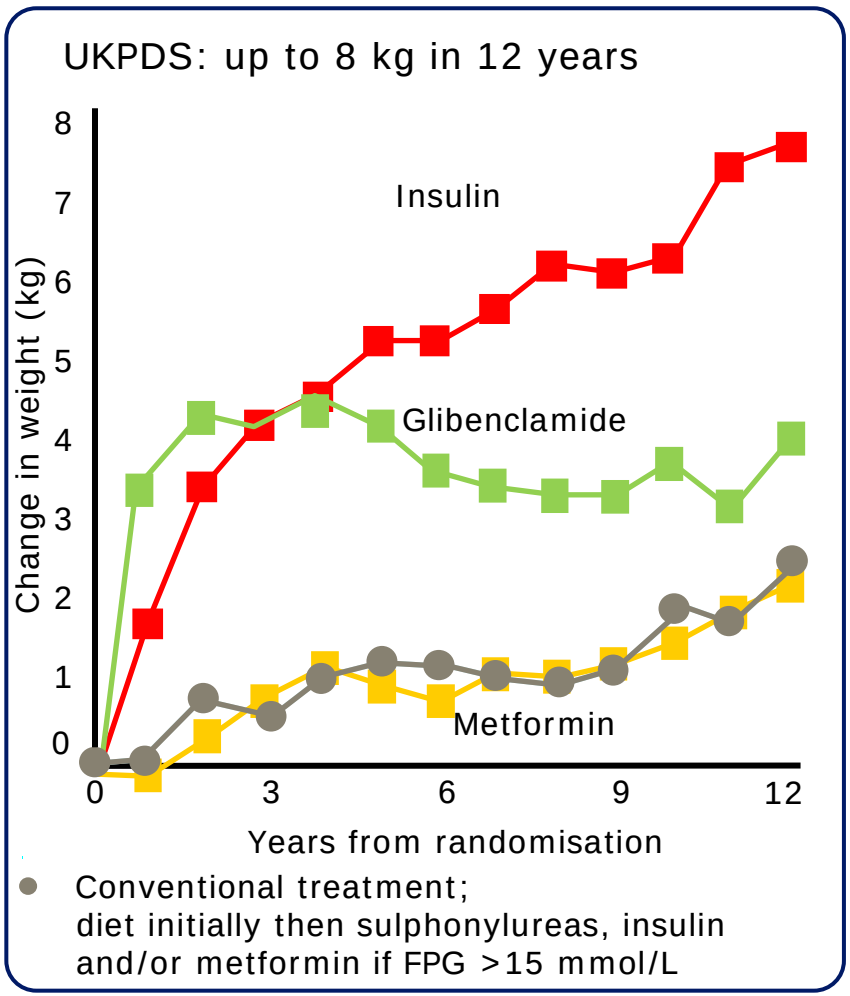
UKPDS: benefit of metformin in overweight Type 2 diabetes patients*

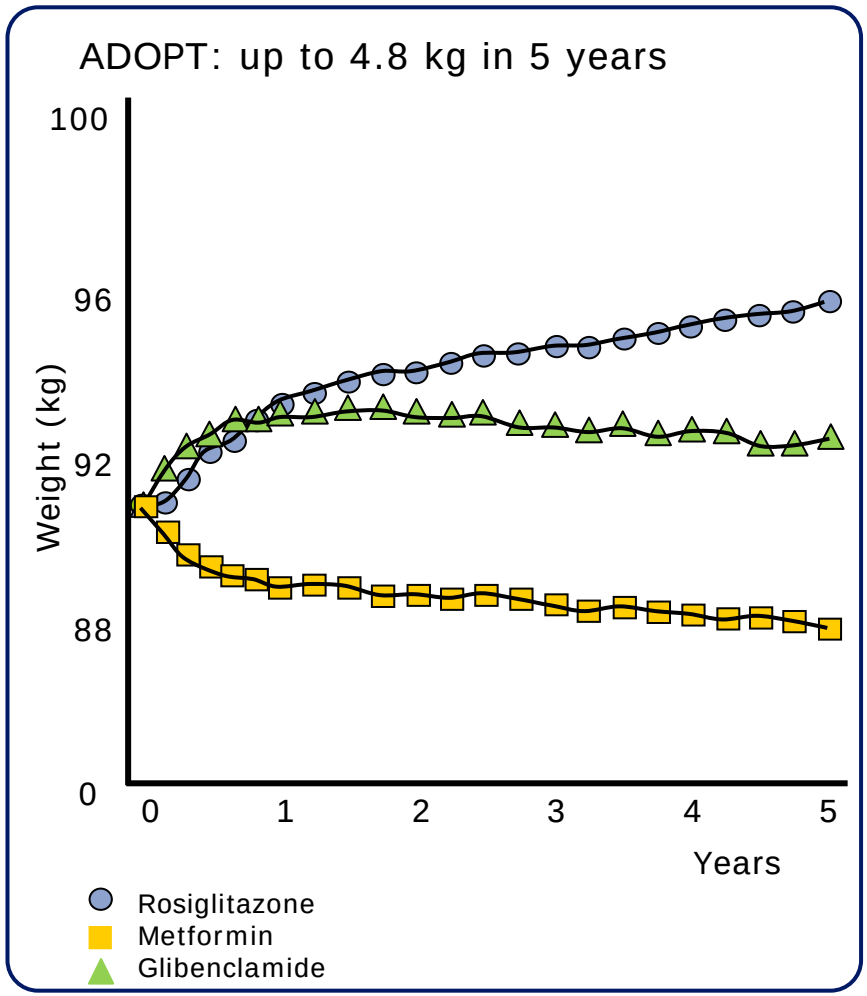


*Compared to conventional treatment group

United Kingdom Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352: 854–865.

Most current therapies result in weight gain





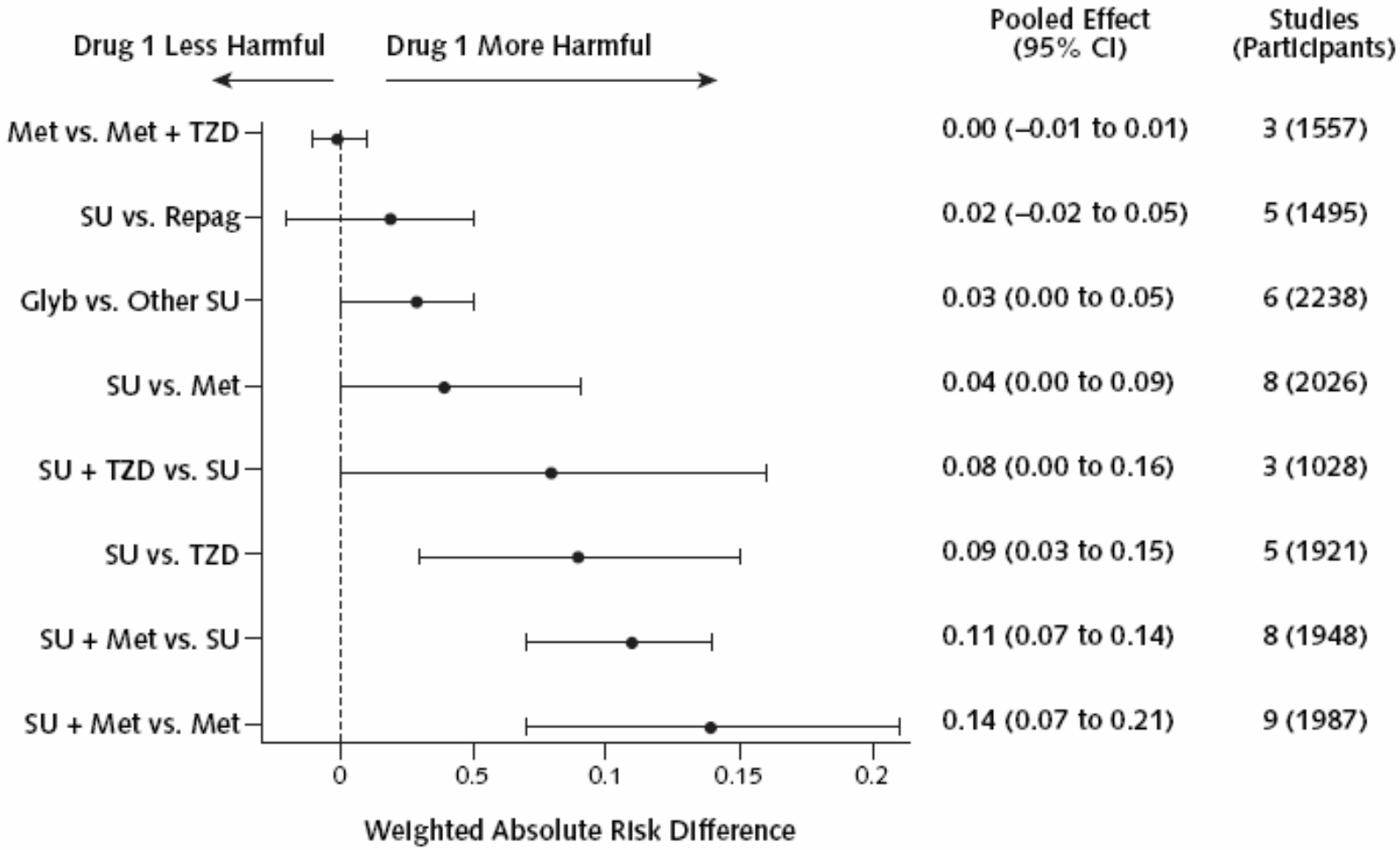
UKPDS 34. *Lancet* 1998:352:854–65. n=at baseline; Kahn *et al* (ADOPT). *NEJM* 2006;355(23):2427–43

Obstructive Sleep Apnoea (OSA),type 2 diabetes and obesity

- In the US, ~17% of adults 30–69 years have OSA[1]
- Excess weight is an important factor for OSA[1]
- About 86% of obese people with type 2 diabetes have OSA[2]
- OSA is an independent marker of type 2 diabetes[1]
- OSA is a significant risk factor for CV disease and mortality[1]

1. Tasali E, et al. Chest. 2008;133;496-506. 2. Foster GD, et al. Diabetes Care. 2009;32:1017-9.

Pooled hypoglycaemia results for randomized trials, by drug comparison



Bolen S, et al. Ann Intern Med 2007; 147:386-399.

UK Hypoglycaemia Group Study

Multicentre study funded by Dept for Transport

Determine the frequency of hypoglycaemia in type 2 diabetes treated with SUs and insulin for differing duration

Compare frequencies with type 1 diabetes

Prospective study over 9-12 months of patients with good glycaemic control

Documented severe and mild hypoglycaemia prospectively, supplemented with CGM x 2

Hypoglycaemia in Type 2 DM: Sulphonylureas vs Insulin

In patients treated for < 2 years, no difference in the proportion of patients experiencing:

- severe hypoglycaemia (7% v 7%)
- mild symptomatic (39% v 51%)
- interstitial glucose < 2.2 mol/L (22% v 20%)

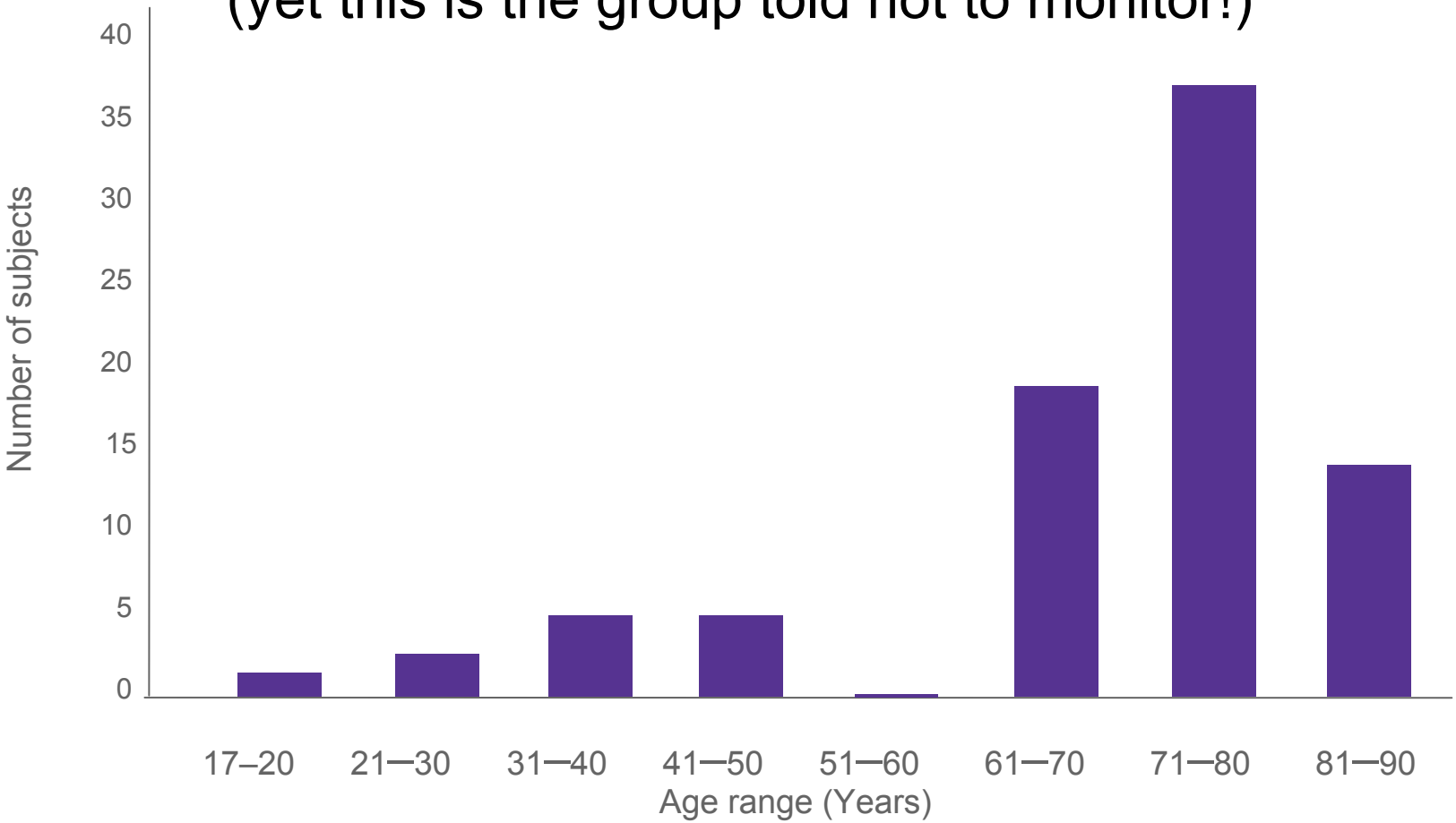
UK Hypoglycaemia Study Group. Diabetologia 2007; 50:1140-1147.

Clinical consequences

- Hospital admissions:
  - Prospective study[1] of well-controlled elderly T2D patients- 25% of hospital admissions for diabetes for severe hypo
- Increased mortality:
  - 9% in a study[2] of severe SU-associated hypoglycaemia
- Road accidents caused by hypos[3]:
  - 45 serious events per month

1. *Diab Nutr Metab* 2004; **17**:23–26
2. *Horm Metab Res Suppl* 1985; **15**: 105–111
3. *BMJ* 2006; **332**: 812

Drug-induced hypoglycaemic coma is more common in elderly people with type 2 diabetes- (yet this is the group told not to monitor!)



Retrospective medical record review of individuals with diabetes who were admitted with DIHC or developed DIHC during hospitalisation.

Ben-Ami H, et al. Arch Intern Med. 1999;159:281-4.

Lack of awareness and education

- Patient receive little information on the adverse events of oral medication, including hypos:
  - In a UK survey, only 10% of people treated with an SU knew that it could cause hypos[1]
- GPs and practice nurses may not be aware of the prevalence of hypos with SUs

1. Diabet Med 2000; **17**:528–531

SUs and severe hypoglycaemia in the UK

- >5000 patients pa on SUs experience at least one severe hypo requiring hospital admission

Amiel SA et al.Diab Med 2008;25:245-254

Newer agents for blood glucose control in type 2 diabetes

NICE guideline overview

Publication date: 27 May 2009

Current targets recommended by NICE[1]

- HbA_{1c} 6.5% - for first 2 treatment steps
- HbA_{1c} 7.5% - beyond this

DPP-4 inhibitors

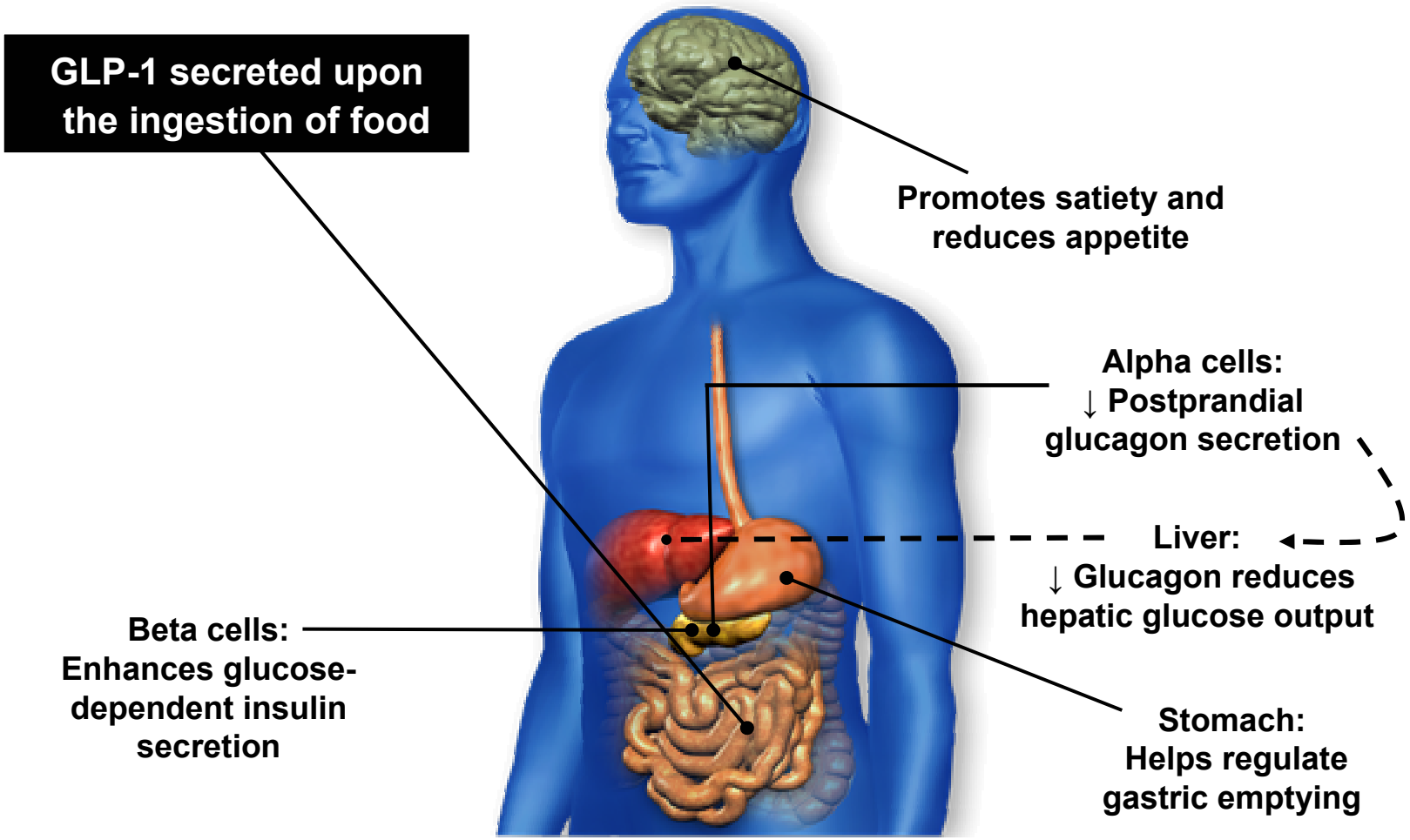
Recommendation 1.1.1

- **Consider adding a DPP-4 inhibitor second-line instead of SU when blood glucose control inadequate (HbA_{1c} ≥6.5%) with metformin if:**
  - **Significant risk of hypoglycaemia. This may include older people and those in certain occupations (eg working at heights or with heavy machinery) or those in certain social circumstances (eg living alone)**
  - **SU not tolerated or containdicated**

HbA_{1c}=glycated haemoglobin A_{1c}
DPP-4=dipeptidyl peptidase-4

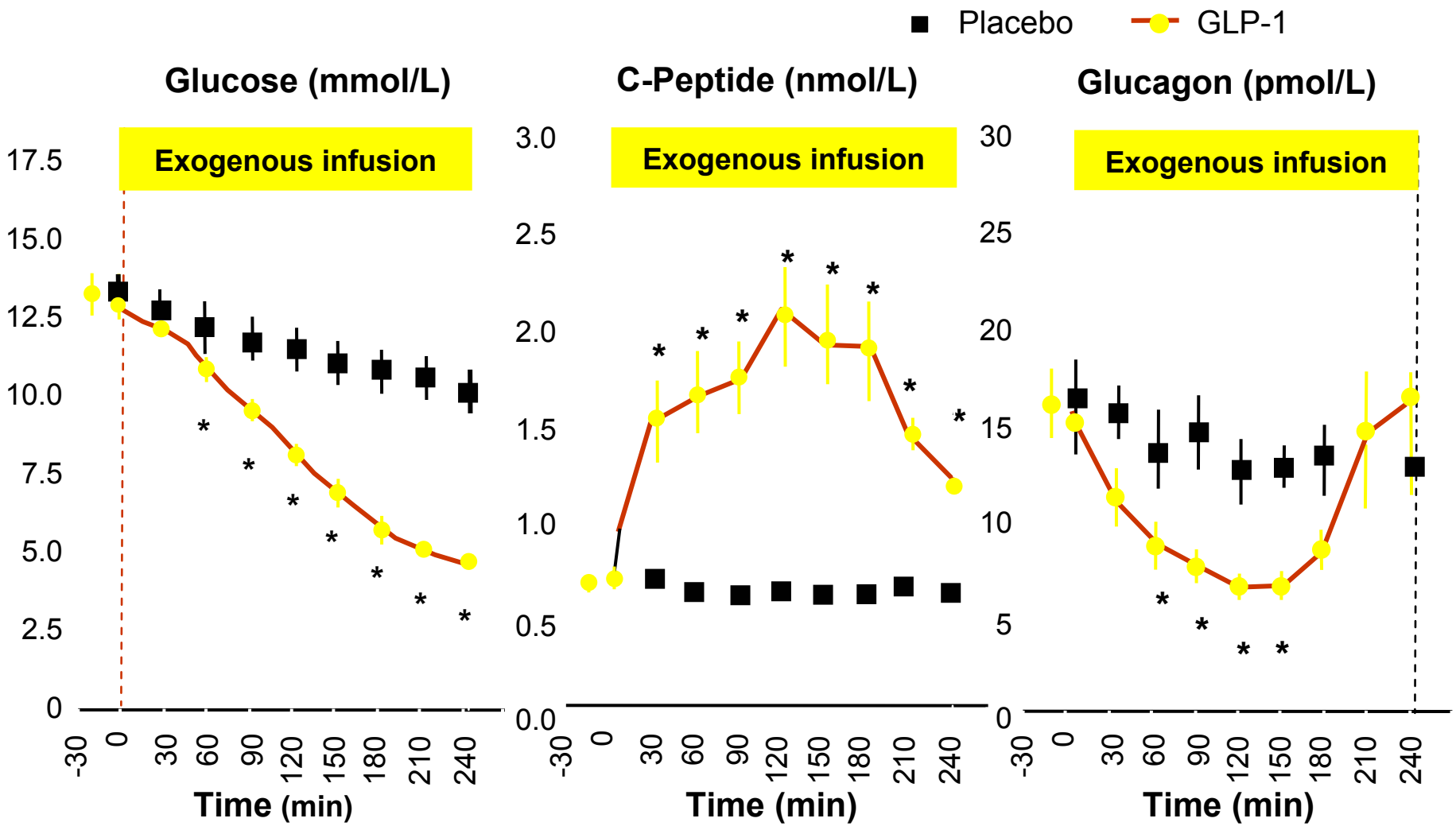
1. National Institute for Health and Clinical Excellence. *Type 2 diabetes newer agents*. Clinical guideline. London; May 2009

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



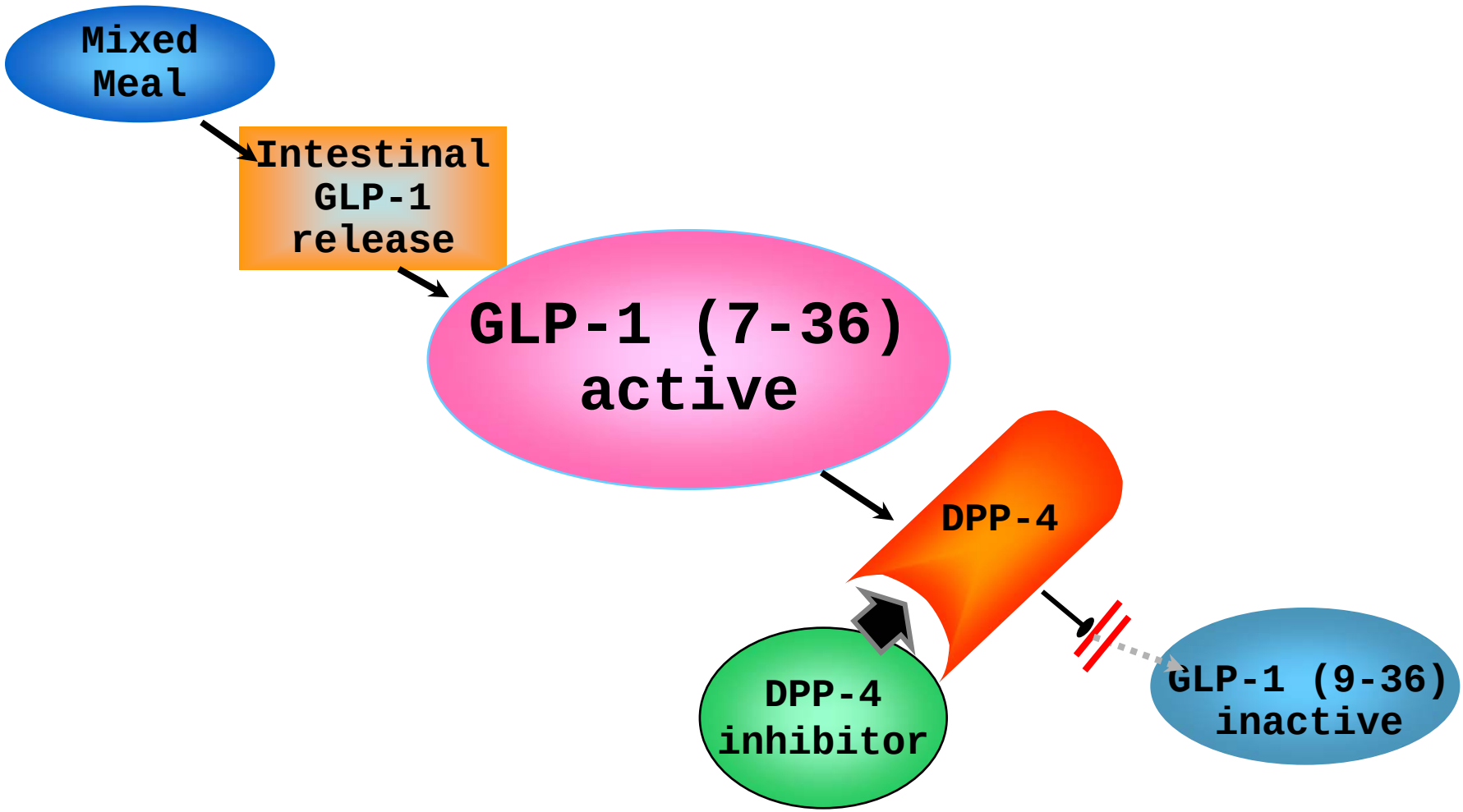
Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

GLP-1 Infusion Has Beneficial Effects in T2DM



*p<0.05; (n=10); data presented as mean ± SEM.
Adapted from Nauck MA, et al. *Diabetologia*. 1993;36:741–744.

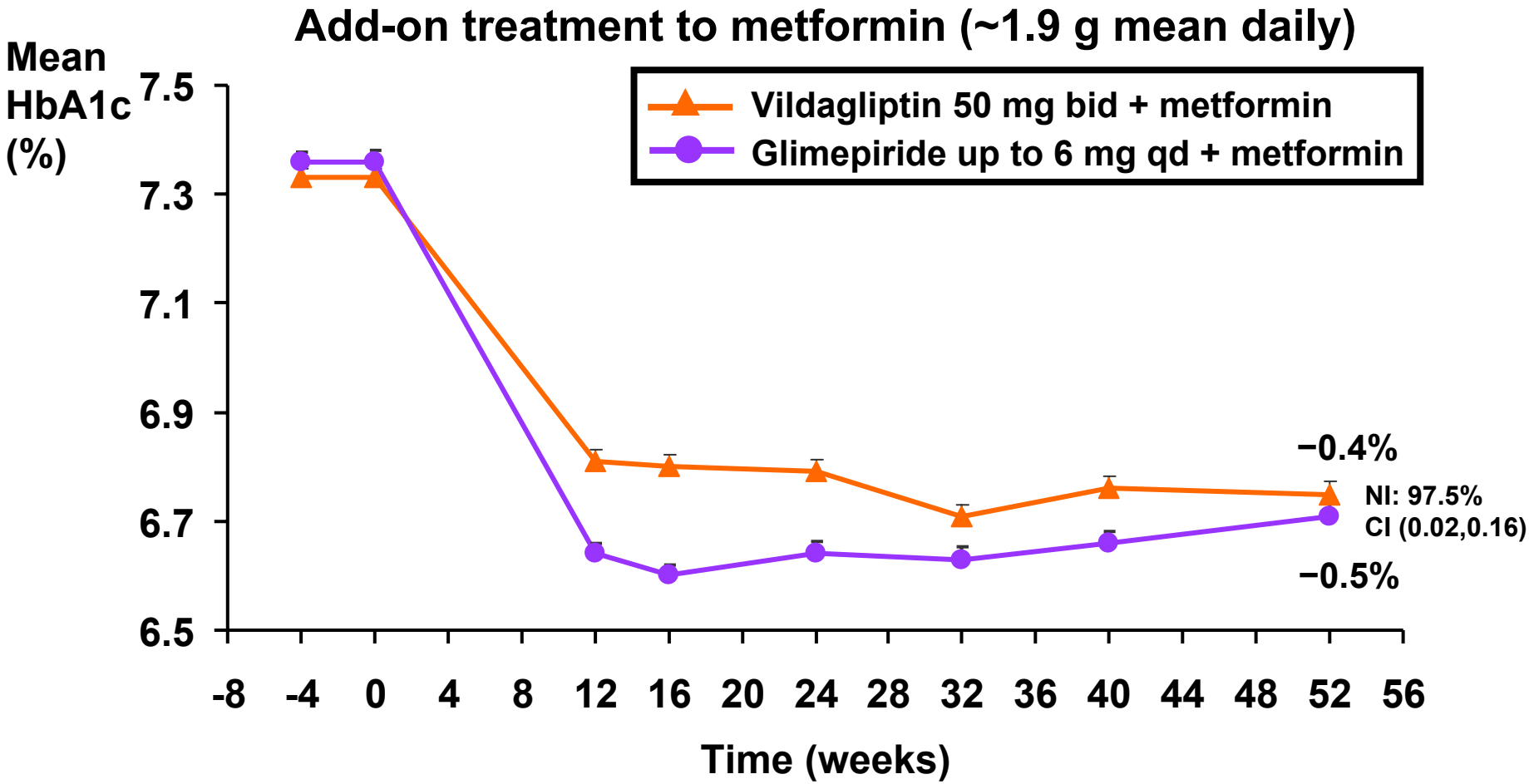
DPP-4 Inhibitors: Rationale



DPP-IV=dipeptidyl peptidase IV

Adapted from Drucker DJ *Expert Opin Invest Drugs* 2003;12(1):87–100; Ahrén B *Curr Diab Rep* 2003;3:365–372.

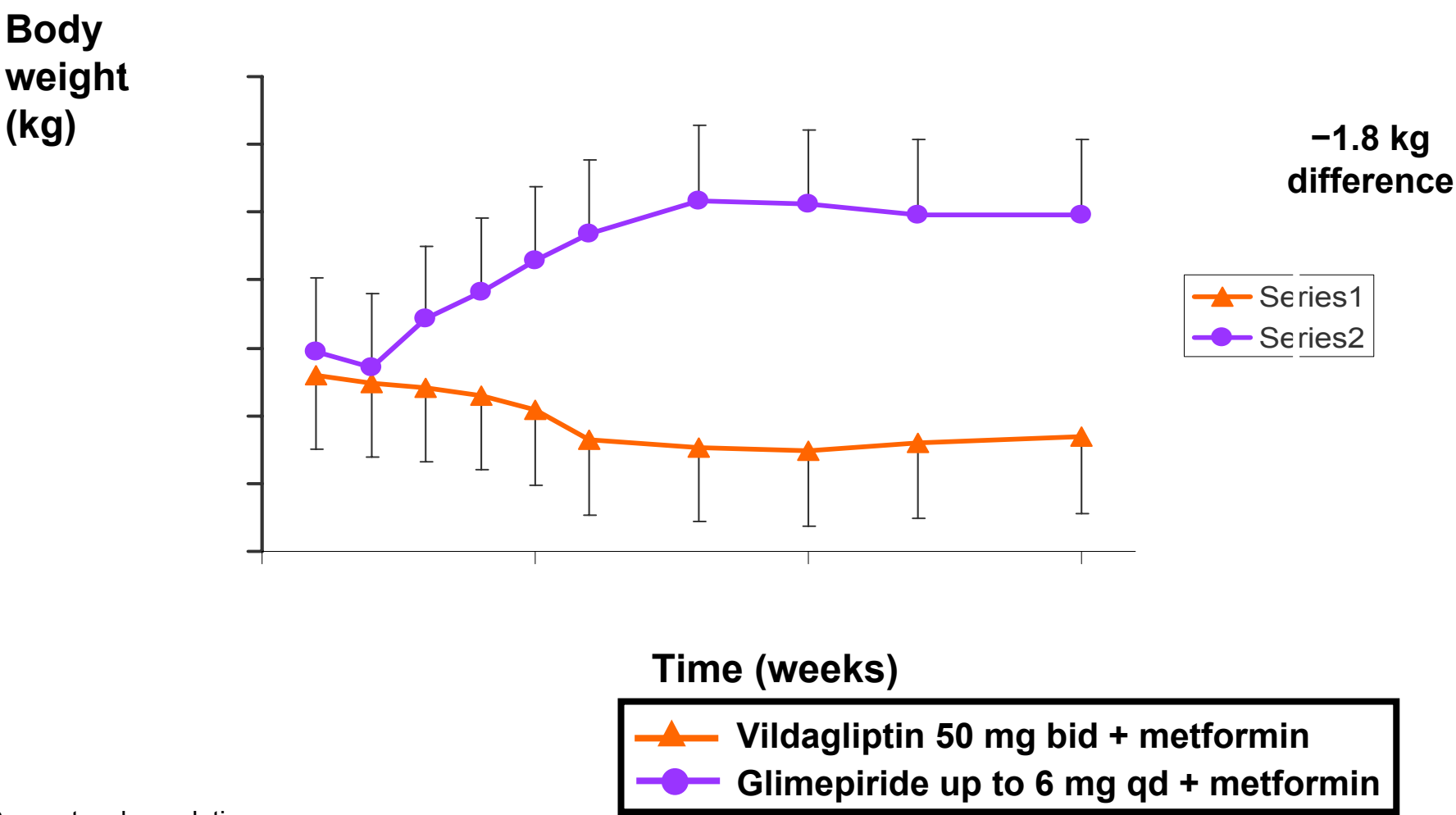
Vildagliptin: as effective as glimepiride when added to metformin at 52 weeks



Per protocol population.
Data on file, Novartis Pharmaceuticals, LAF237A2308 52-week interim analysis.

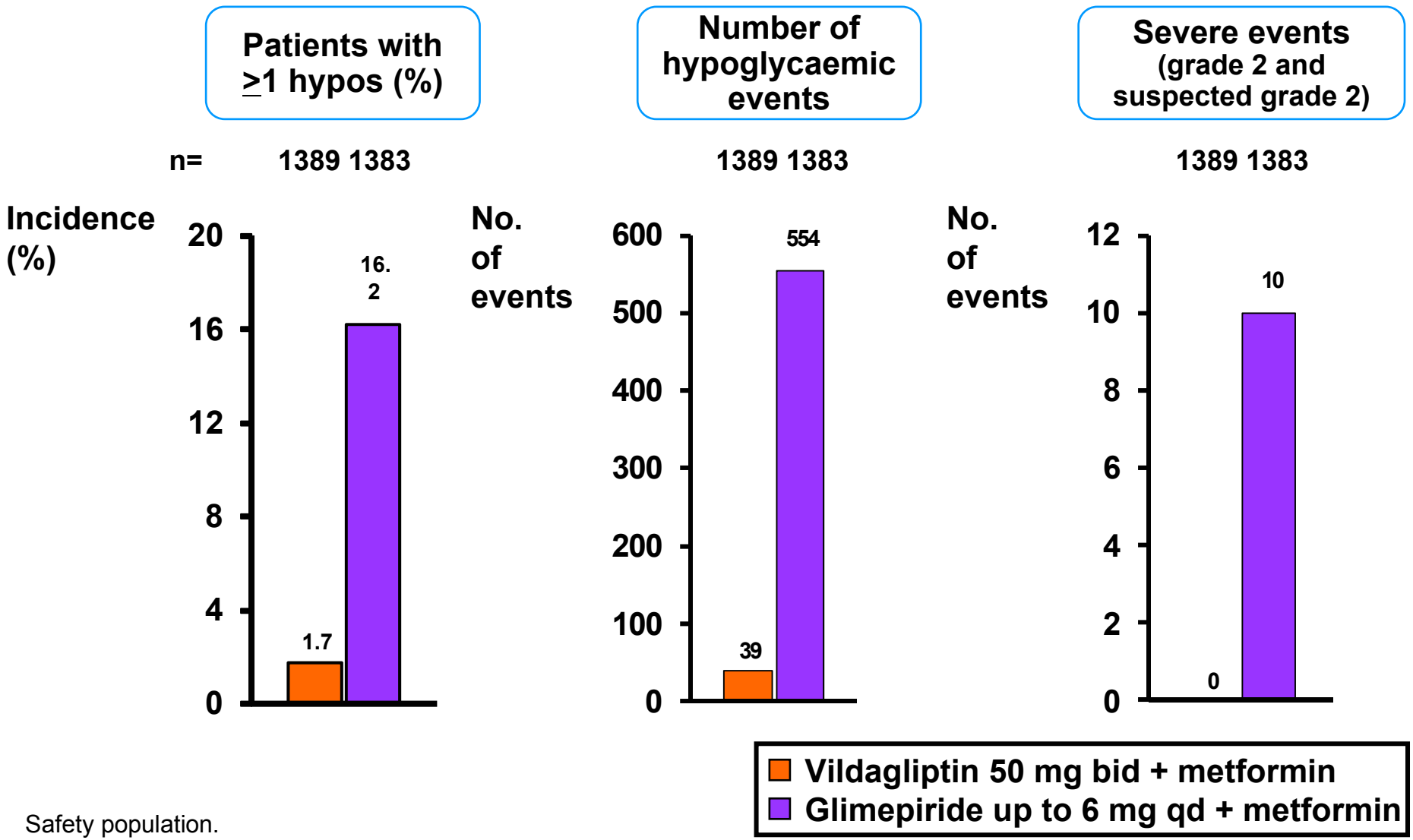
Vildagliptin: no weight gain

Add-on treatment to metformin (~1.9 g mean daily)



Per protocol population.
Data on file, Novartis Pharmaceuticals, LAF237A2308 52-week interim analysis.

Vildagliptin vs glimepiride: hypoglycaemic events in add-on to metformin treatment



Safety population.
Data on file, Novartis Pharmaceuticals, LAF237A2308 52-week interim analysis.

Pooled placebo-controlled safety population: Hypoglycaemia

Short-term period (excludes RT)	Percentage	SAXA 2.5 mg	SAXA 5 mg	SAXA 10 mg	SAXA All	PBO
Pooled Monotherapy (-011, -038)	Reported	4.0	5.6	8.2	5.4	4.1
	Confirmed	*0*	*0*	*0*	*0*	*0*
Add-on Combination + MET (-014)	Reported	7.8	5.2	3.9	5.7	5.0
	Confirmed	0.5	0.5	0.6	0.5	0.6
+ SU (-040)	Reported	13.3	14.6	–	14.0	10.1
	Confirmed	2.4	0.8	–	1.6	0.7
+ TZD (-013)	Reported	4.1	2.7	–	3.4	3.8
	Confirmed	0.5	0	–	0.3	0
Placebo-controlled pooled population*	Reported	7.6	7.8	5.4	7.4	6.8
	Confirmed	0.8	0.5	0.4	0.6	0.4

		SAXA 5 mg + MET	SAXA 10 mg + MET	SAXA 10 mg	SAXA All	MET
Initial combination with MET (-39)	Reported	3.4	5.0	1.5	3.3	4.0
	Confirmed	*0*	*0.6*	*0*	*0.2*	*0.3*

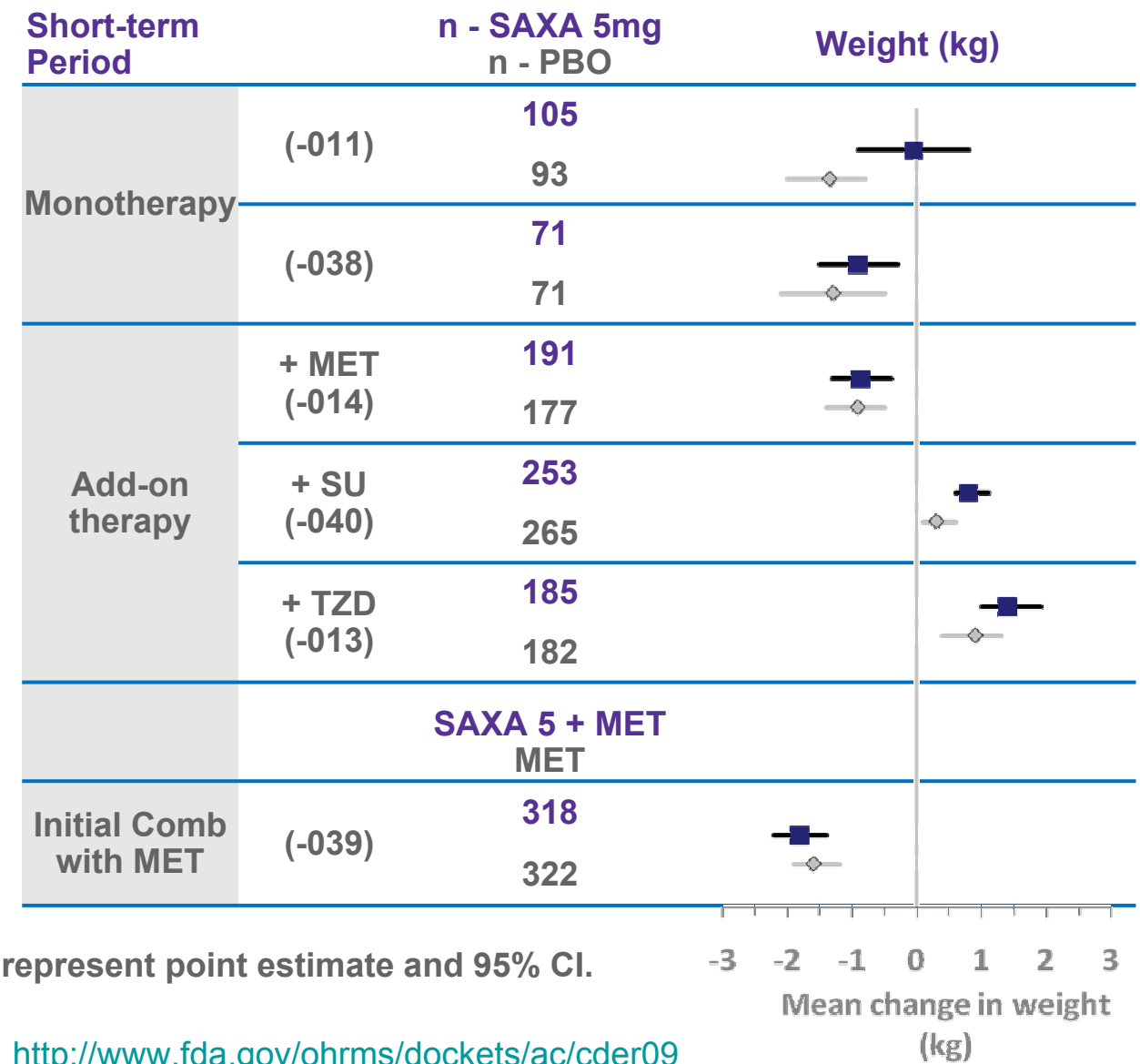
MET: Metformin; SAXA: Saxagliptin; AE: adverse event.

Saxagliptina es un producto en investigación clínica.

No está aún comercializado para uso clínico.

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm149225.htm. Accessed: 14 Nov, 09

Pivotal phase 3 studies/ST period excluding RT
Change from baseline in weight (saxagliptin 5 mg)



Data represent point estimate and 95% CI.

http://www.fda.gov/ohrms/dockets/ac/cder09

Saxagliptina es un producto en investigación clínica. No está aún comercializado para uso clínico.

DPP-4 Inhibitors

- Effective as mono- and combination therapy
- Oral dosing
- Low risk of hypoglycaemia
- Weight neutral
- Well tolerated
- Theoretical possibility that they could preserve and even reverse progressive loss of insulin secretory capacity

Pros and cons of Diabetes Therapies

	Metformin	**SU**	**Glitazone**	**Insulin**	**GLP-1 agonist**	**Gliptins**
Efficacy	++	++	++	+++	++	++
Influence Disease Progression	No	No	(?)	No	(?)	(?)
Outcome Studies	Yes	Yes	Yes	Yes	No	No
Tolerability	Moderate	Moderate	Moderate	Moderate	Moderate	Excellent
Weight gain	No	Yes	Yes	Yes	Weight loss	No
Hypos	No	Yes	No	Yes	(No?)	No

Personalised Care is Paramount

- When dealing with a complex chronic disease such as type 2 diabetes:

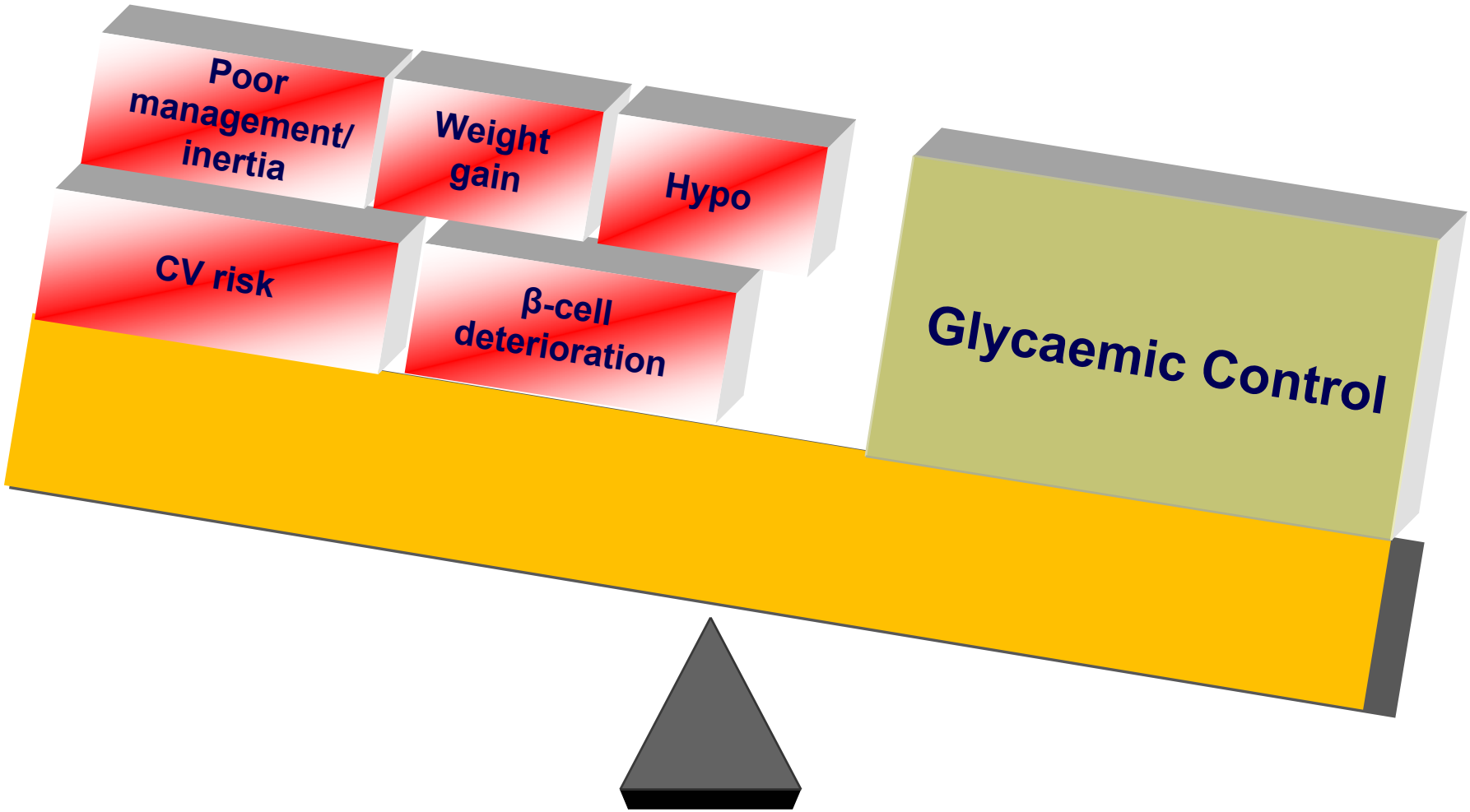
  . . . “ the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drug they are considering”

NICE clinical guidelines for the management of type 2 diabetes, May 2009

The Health Professional MUST agree with the individual patient both their glycaemic target and how best to achieve this.

Guidelines are guidelines NOT absolutes!

Need for Personalised Care: The Benefits *vs.* Risks of Diabetes Therapy Must be Assessed for Each Patient



Conclusions

- Tight diabetes control in the early years after diagnosis associated with significant reduction in total and CV mortality and vascular events.

- Caution re “too tight” and “too rapid tightening of” control in longstanding, high risk patients possibly because of increased chance of hypoglycaemia precipitating arrhythmias/CV events and death

- Individualisation of targets and therapies vital

- New drugs, including incretin based therapies, have the potential to improve glycaemic control with low risk of hypoglycaemia and weight gain