What's New in Type 2?

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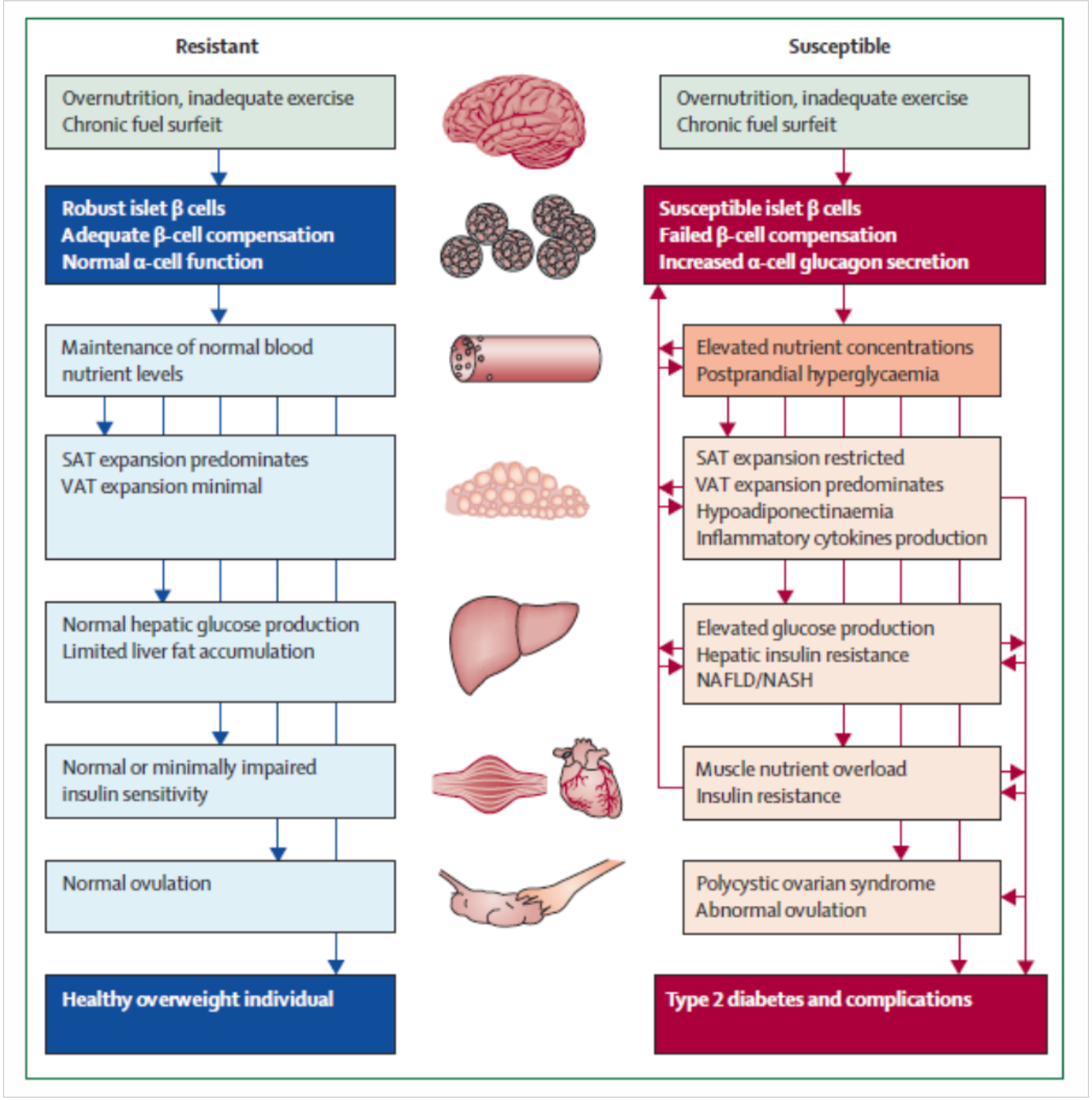
Therapy considerations in T2DM

- Thiazoledinediones
- DPP IV inhibitors
- GLP 1 agonists
- Insulin
  - Type
  - Delivery
- Horizon scanning



Nolan CJ et al. *Lancet* 2011;378:169-181

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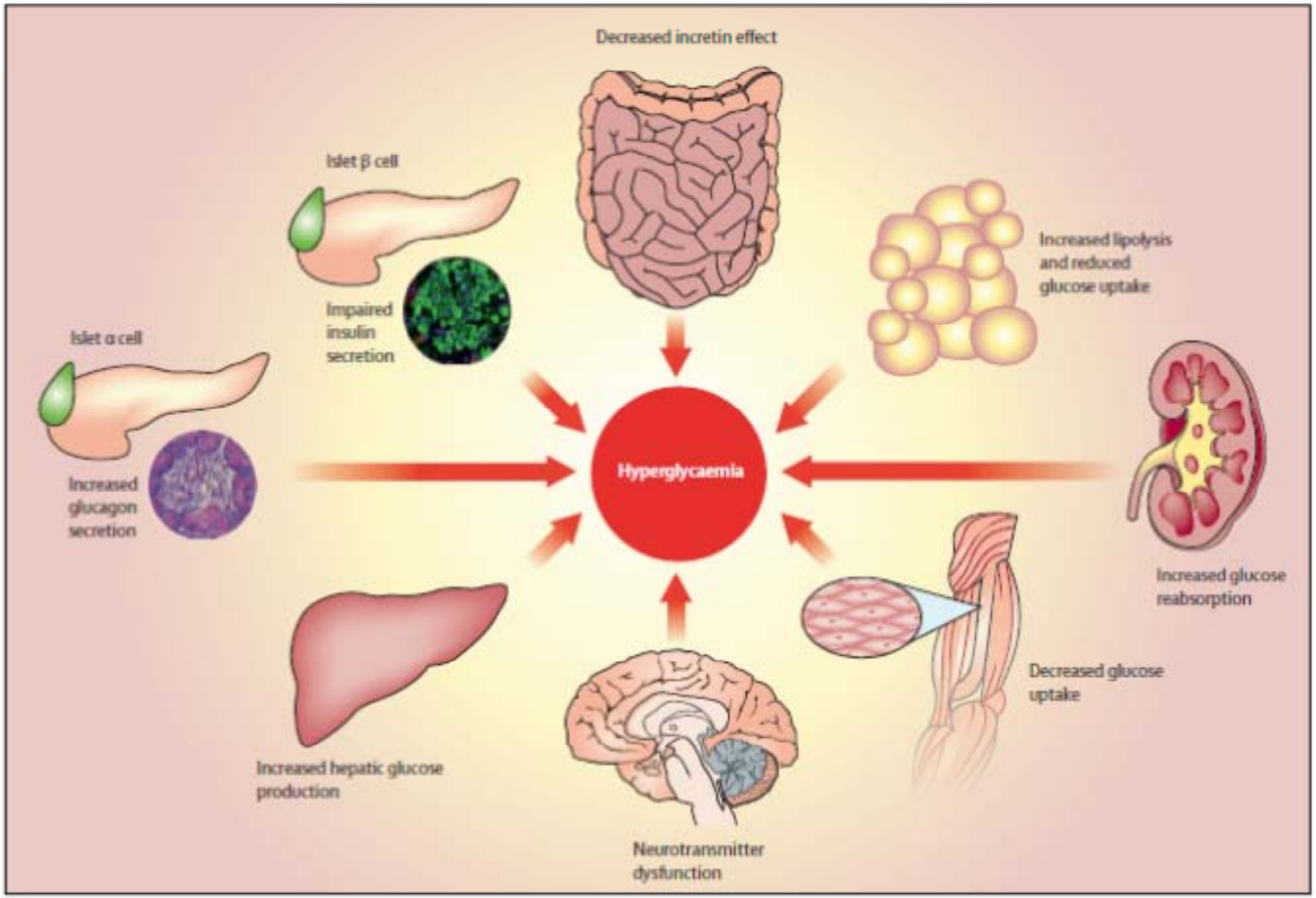
Therapeutic targets



Tahrani A et al. *Lancet* 2011;378:182-197

Panel 2: Desired characteristics of glycaemic control therapies in type 2 diabetes

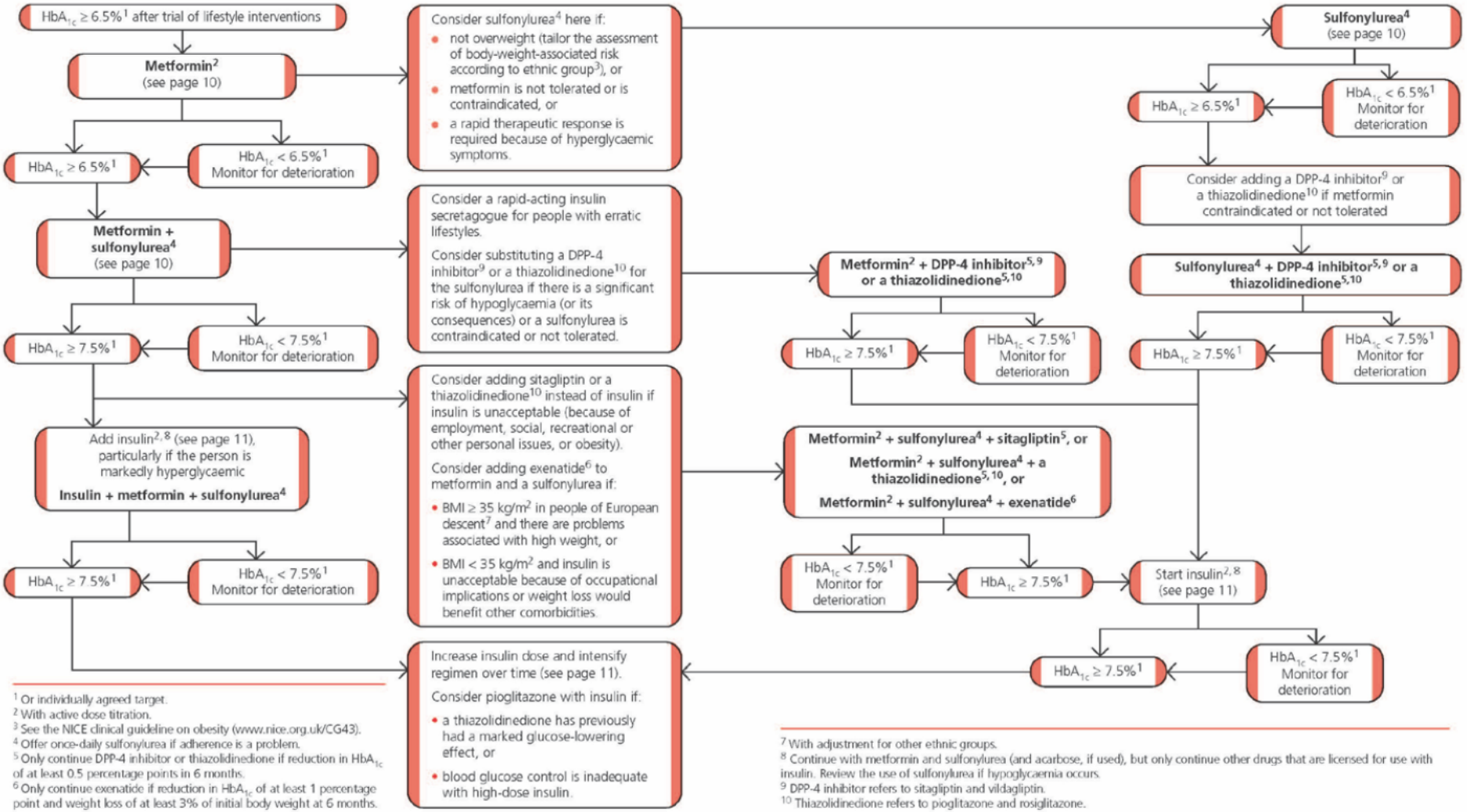
The therapy, in addition to achieving target HbA_{1c}, should:

- Be disease modifying (ie, reverse one or more of the underlying pathophysiological processes)
  - (i) Reduce chronic fuel surfeit
  - (ii) Protect islet β-cells from progressive failure
  - (iii) Prevent adipose tissue dysfunction, including abnormal fat distribution and inflammation
  - (iv) Restore normal islet α-cell function and incretin physiology
  - (v) Restore normal regulation of hepatic glucose production
  - (vi) Enhance skeletal muscle mitochondrial function/oxidative metabolism
  - (vii) Enhance energy expenditure and thermogenesis
- Sustain good metabolic control with low therapy-associated unwanted effects
- Enhance quality of life of patients
- Reduce diabetes microvascular and macrovascular complications
- Reduce diabetes-related mortality (includes cardiovascular disease-related), and all-cause mortality

HbA_{1c}=glycated haemoglobin A_{1c}.

Nolan CJ et al. *Lancet* 2011;378:169-181

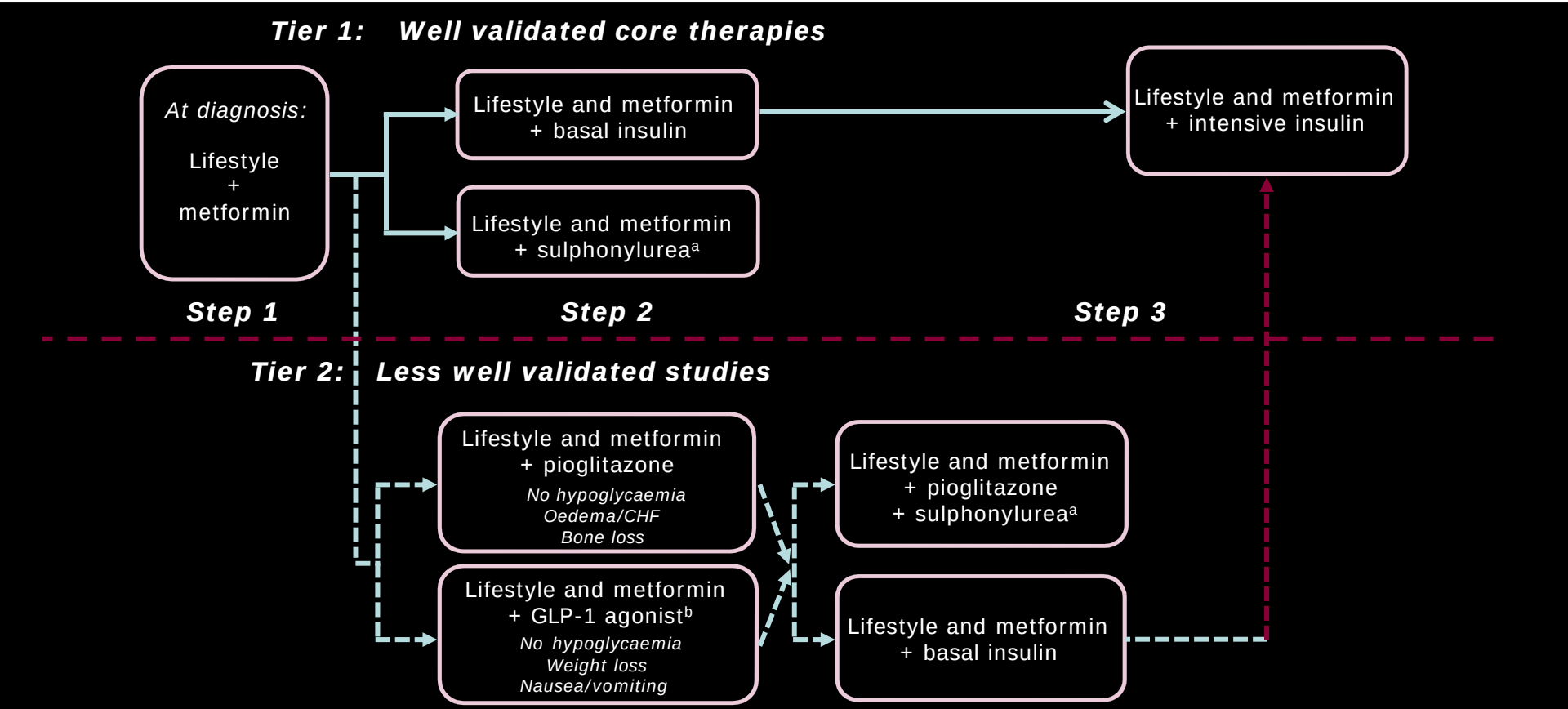
Blood-glucose-lowering therapy



[1] Or individually agreed target.
[2] With active dose titration.
[3] See the NICE clinical guideline on obesity (www.nice.org.uk/CG43).
[4] Offer once-daily sulfonylurea if adherence is a problem.
[5] Only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA_{1c} of at least 0.5 percentage points in 6 months.
[6] Only continue exenatide if reduction in HbA_{1c} of at least 1 percentage point and weight loss of at least 3% of initial body weight at 6 months.
[7] With adjustment for other ethnic groups.
[8] Continue with metformin and sulfonylurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulfonylurea if hypoglycaemia occurs.
[9] DPP-4 inhibitor refers to sitagliptin and vildagliptin.
[10] Thiazolidinedione refers to pioglitazone and rosiglitazone.

ADA and EASD algorithm

- *Reinforce lifestyle interventions at every visit and check HbA_{1C} every 3 months until HbA_{1C} is <7% and then at least every 6 months. The interventions should be changed if HbA_{1C} is ≥7%.*

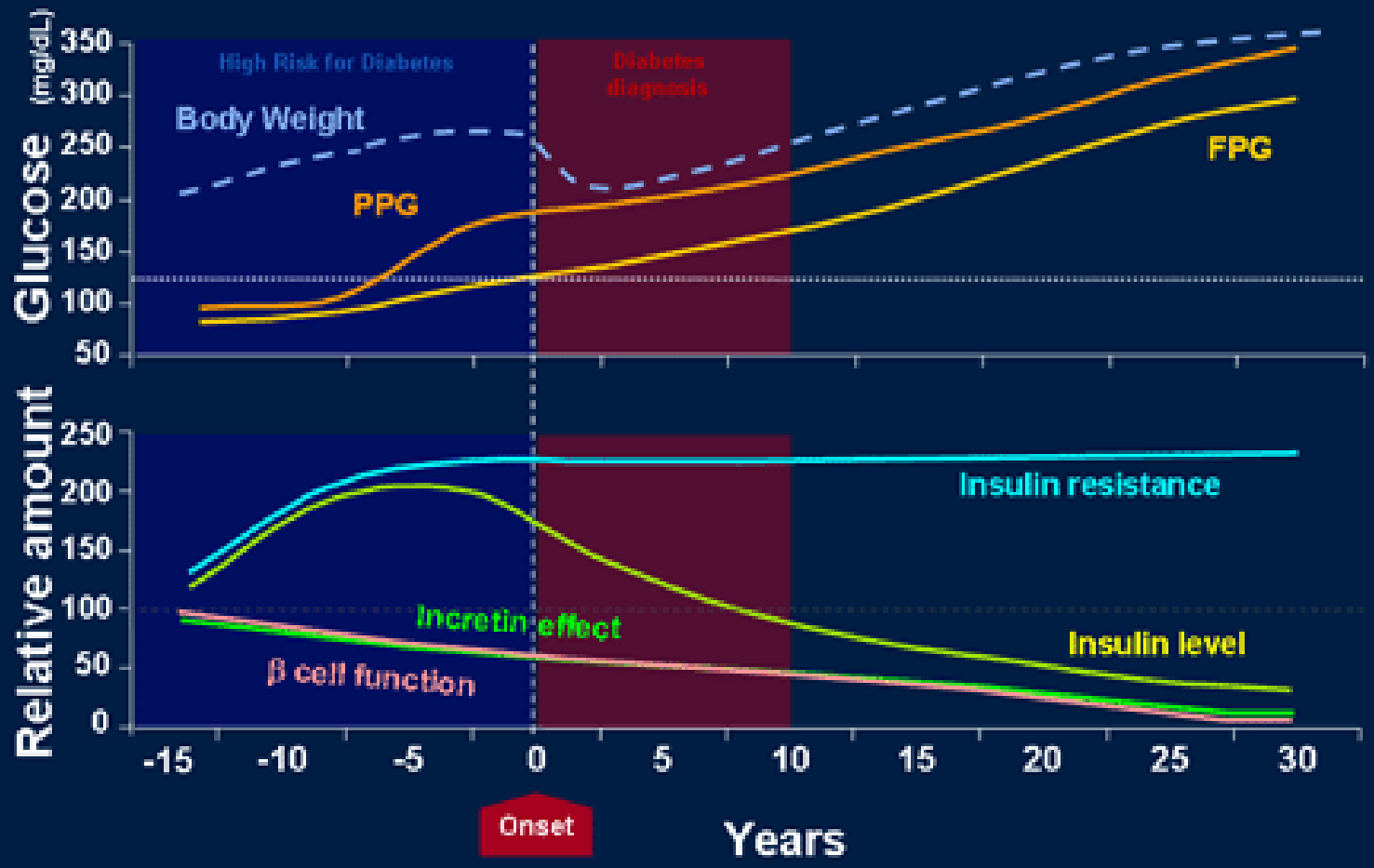


[a]*Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.*

[b]*Insufficient clinical use to be confident regarding safety.*

Nathan *et al. Diabetes Care* 2008;31:1–11

Natural History of Type 2 Diabetes



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%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.0099	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

RRR = Relative Risk Reduction, P = Log Rank

UKPDS 80. N Engl J Med 2008 359

There is no place for pioglitazone in the management of type 2 diabetes

Pioglitazone – pros and cons

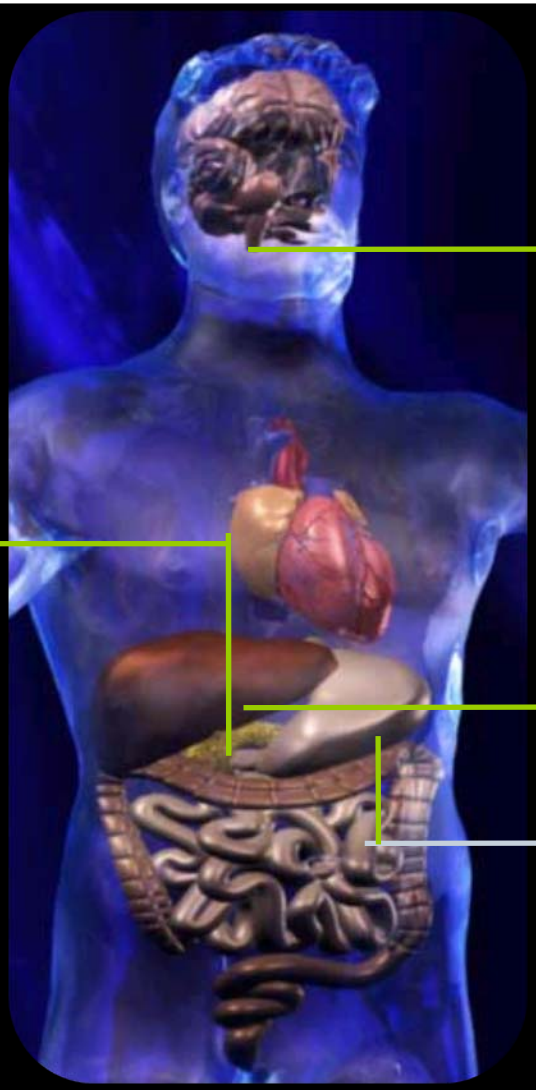
- Bladder cancer: RR 1.12-1.33
  - Avoid if active or PH of bladder ca, or if have uninvestigated haematuria
  - Consider risk factors: smoking, age
- Osteoporosis
- PROACTIVE study: 16% RR in all-cause mortality, non-fatal MI and stroke

MHRA Safety Update August 2011

Pioglitazone – case study

- PH, 78 M
- Jan’ 11: wt 90.1 kg, HbA1c 72 mmol/mol (8.7%)
  - Glargine 20 u am, 50 u pm
  - Metformin 850 mg tds
  - Sitagliptin 100 mg od
- Added pioglitazone 30 mg od
  - Glargine dose reduced to 16 u am, 44 u pm
- July ’11: wt 98.1 kg, HbA1c 57.5 mmol/mol (7.4%)
  - Lows during the night

Physiological effects of GLP1



Pancreas

- ↑ Insulin secretion (glucose-dependent) and beta-cell sensitivity
- ↑ Insulin synthesis
- ↓ Glucagon secretion (glucose-dependent)
- ↑ Beta-cell mass*

Brain

- ↓ Energy intake*

Liver

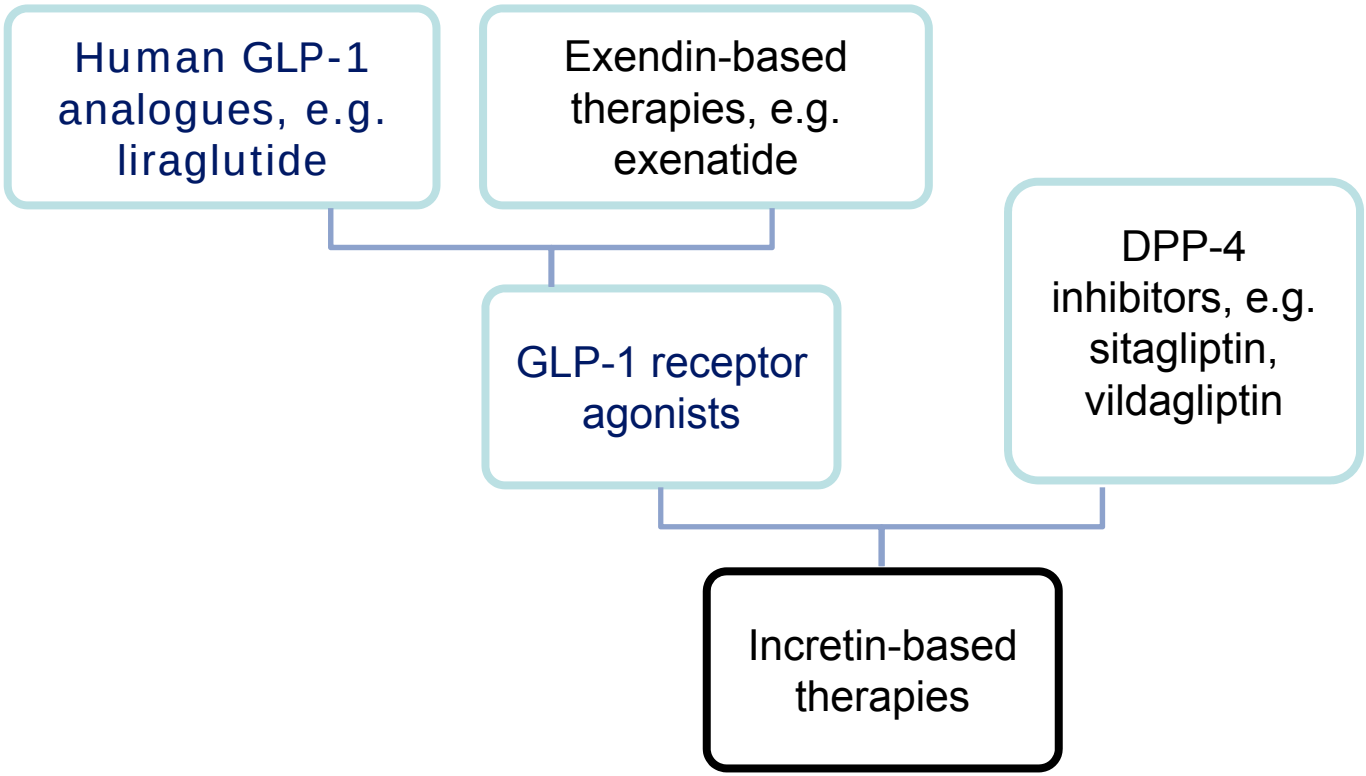
- ↓ Hepatic glucose output

GI tract

- ↓ Decreased motility

*in animal studies

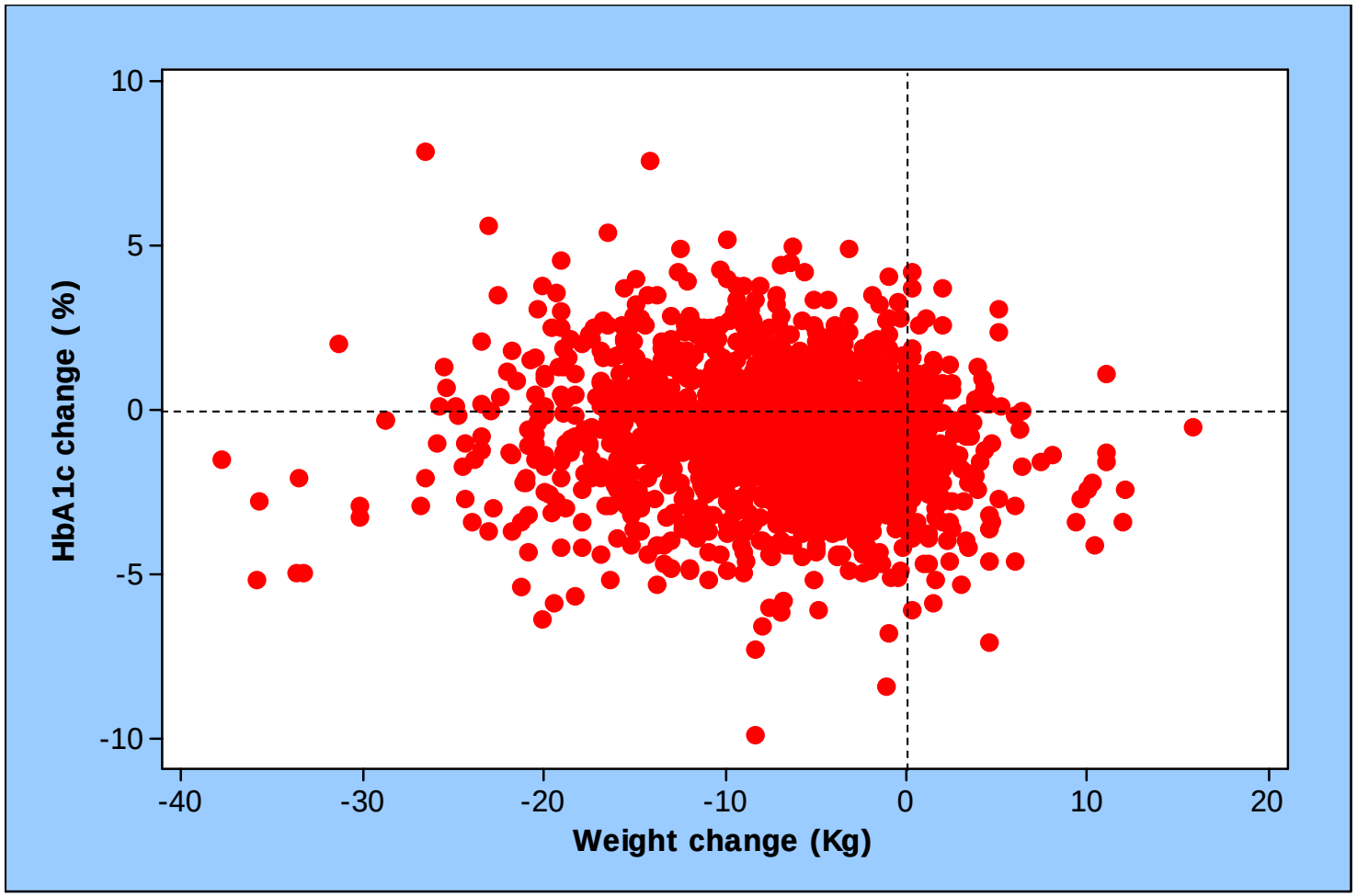
The family of incretin-based therapies



DPP IV inhibitors

- Comparable improvement in glycaemic control to SUs but with much less hypoglycaemia and weight neutral
- Useful in renal failure
  - Saxagliptin: renal dose 2.5 mg od
  - Linagliptin: biliary excretion, no dose adjustment needed
- CV outcome trials in progress

Exenatide – national audit



6 months after exenatide start in 1959 patients

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Exenatide in real clinical use - conclusion

- 60% of patients achieve the ideal of both weight loss and fall in HbA1c
- However many patients experience a predominant response to only one of weight or HbA1c with more minimal response to the other
- Hence only 28% achieve the NICE guideline
- The NICE guideline should change to acknowledge that significant weight loss or significant HbA1c response may represent a beneficial response

Composite end points that matter

HbA_{1c} <7.0%

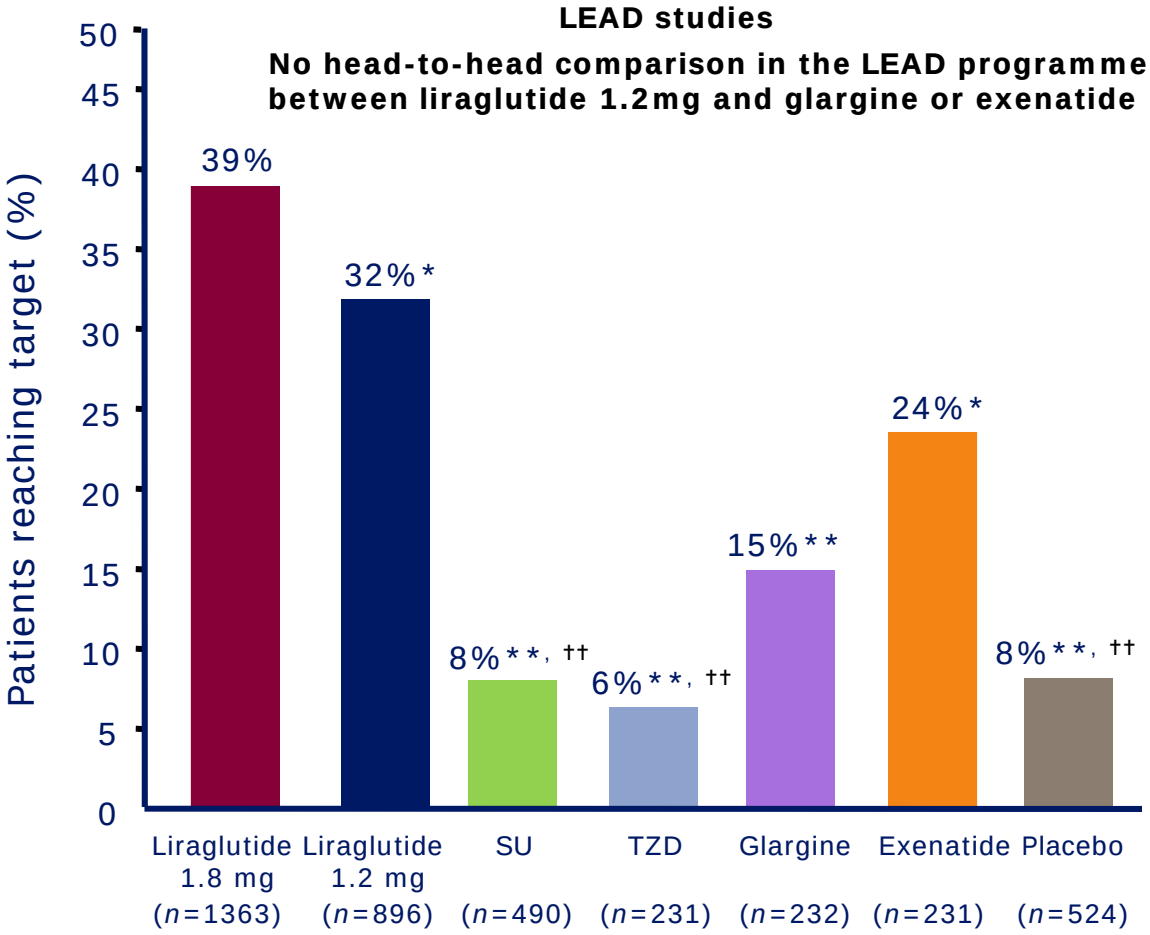
+

No weight gain

+

No hypoglycaemia

Composite endpoint: HbA_{1c}<7.0%, no weight gain and no hypos



Liraglutide 1.8 mg is superior (*p<0.01; ** p<0.0001)
Liraglutide 1.2 mg is superior (†† p<0.0001)
Percentages are from logistic regression model adjusted for trial, previous treatment and with baseline HbA_{1c} and weight as covariates

Zinman B et al. *Diabetologia* 2009; **52**(Suppl 1): S292 (A743);

Prately RE et al. *Lancet* 2010; **375**:1447−56

Comparative odds ratio for achieving the composite endpoint

HbA_{1c} <7.0%, no weight gain, no minor or major hypoglycaemia

Comparison	Odds ratio favouring liraglutide
Liraglutide 1.8 mg vs TZD	10.3***
Liraglutide 1.2 mg vs. TZD	7.5***
Liraglutide 1.8 mg vs SU	7.3***
Liraglutide 1.2 mg vs. SU	5.3***
Liraglutide 1.8 mg vs glargine	3.7***
Liraglutide 1.8 mg vs sitagliptin	3.4***
Liraglutide 1.2 mg vs sitagliptin	2.6***
Liraglutide 1.8 mg vs exenatide	2.0**

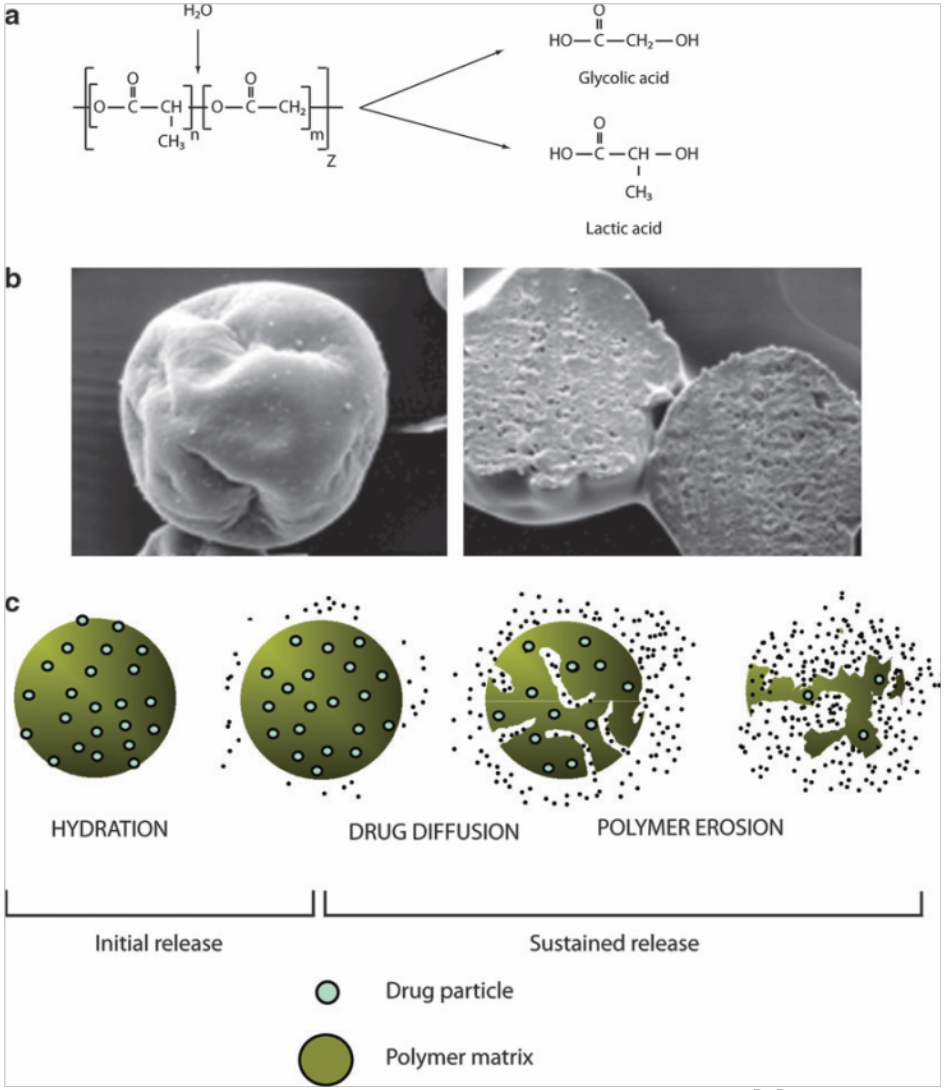
**p<0.005; ***p<0.0001 in favour of liraglutide 1.8 mg

Based on meta-analysis of LEAD 1–6. Adjusted for previous treatment, baseline values and randomisation. LOCF, ITT

Zinman B et al. *Diabetologia* 2009; **52**(Suppl 1): S292 (A743);

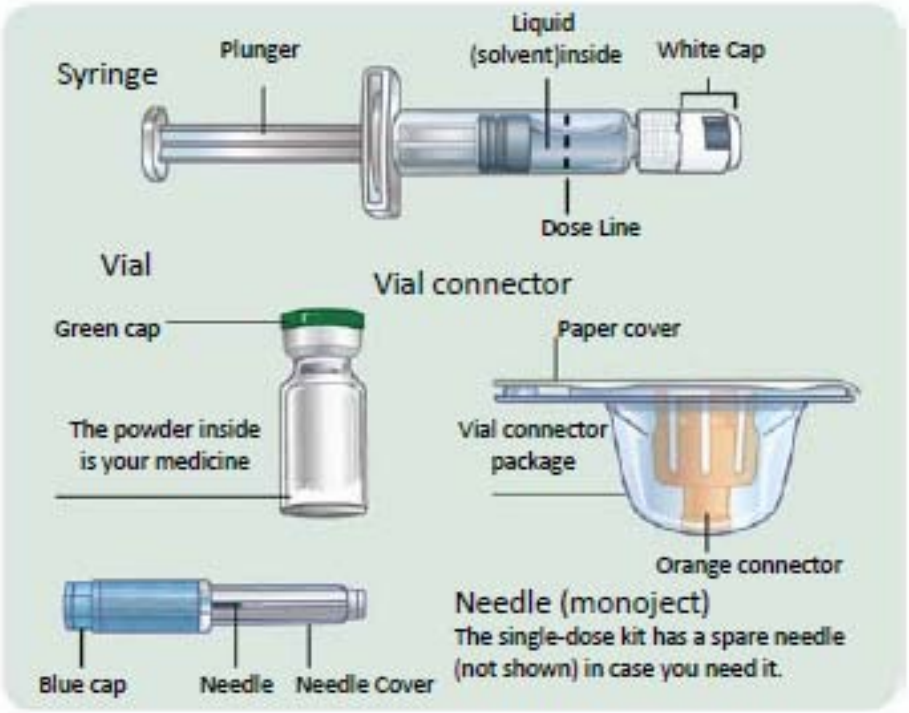
Prately RE et al. *Lancet* 2010; **375**:1447−56

Exenatide ER

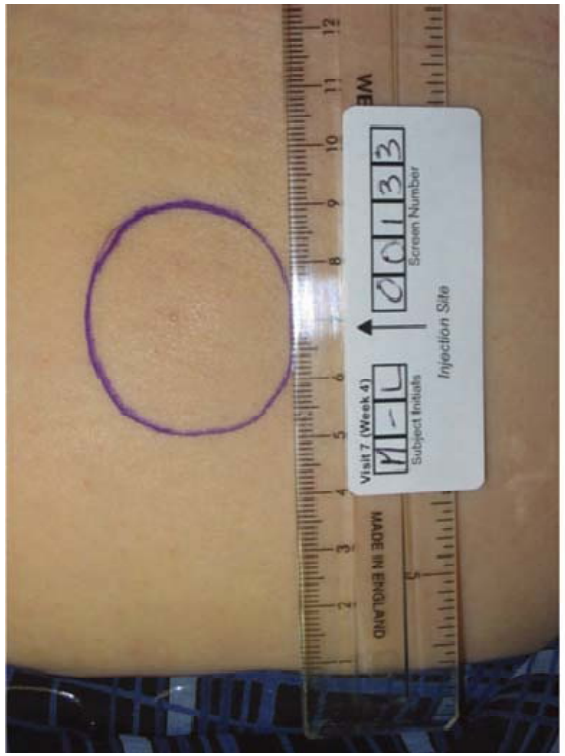


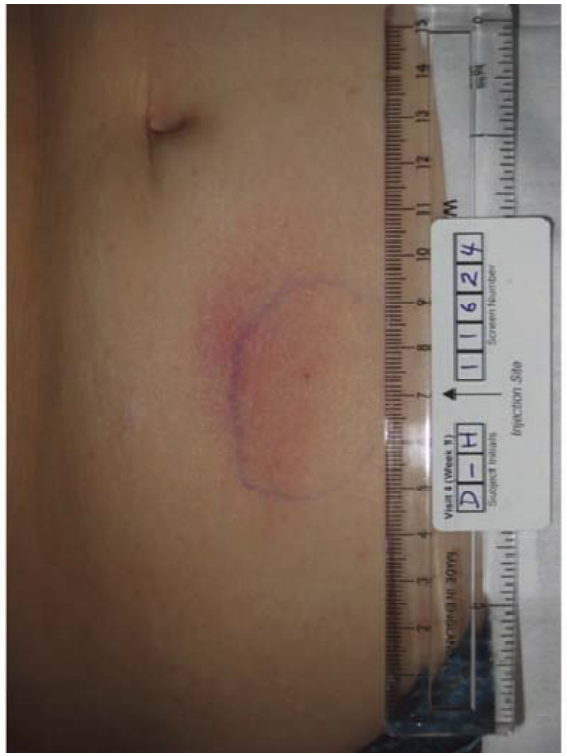
DeYoung MB et al. *Diab Tech Ther* 2011;13:1145-54

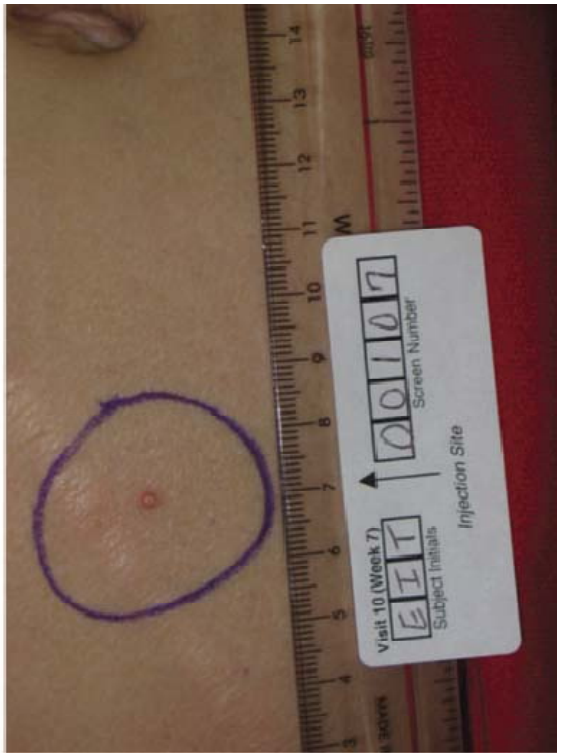
Exenatide ER (Bydureon)



Microsphere deposits







DeYoung MB et al. *Diab Tech Ther* 2011;13:1145-54

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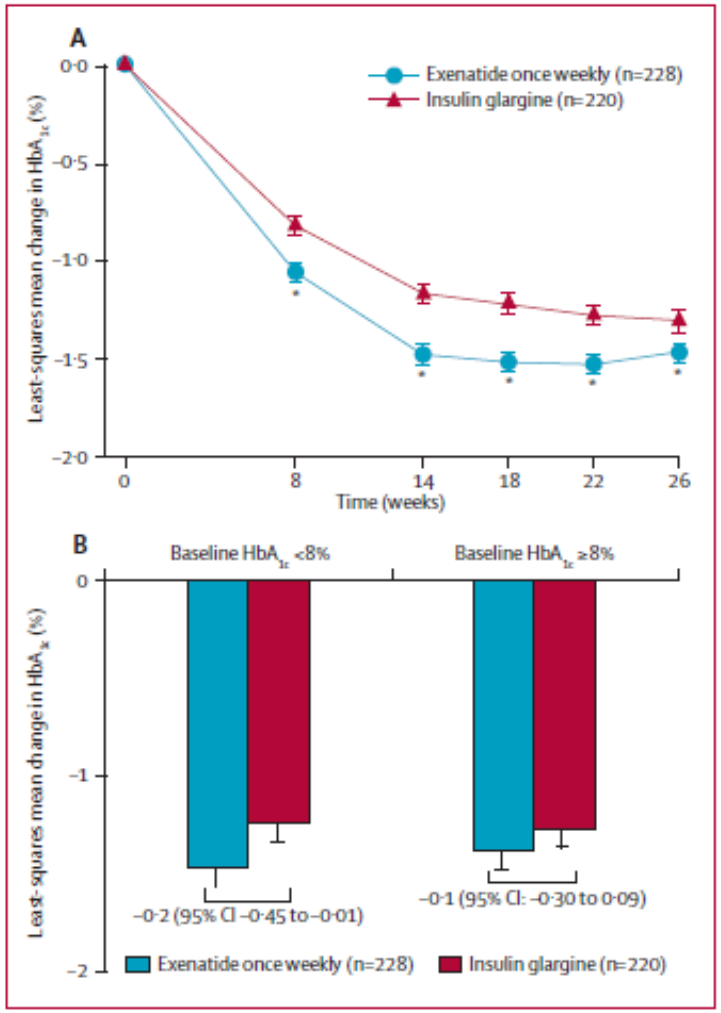
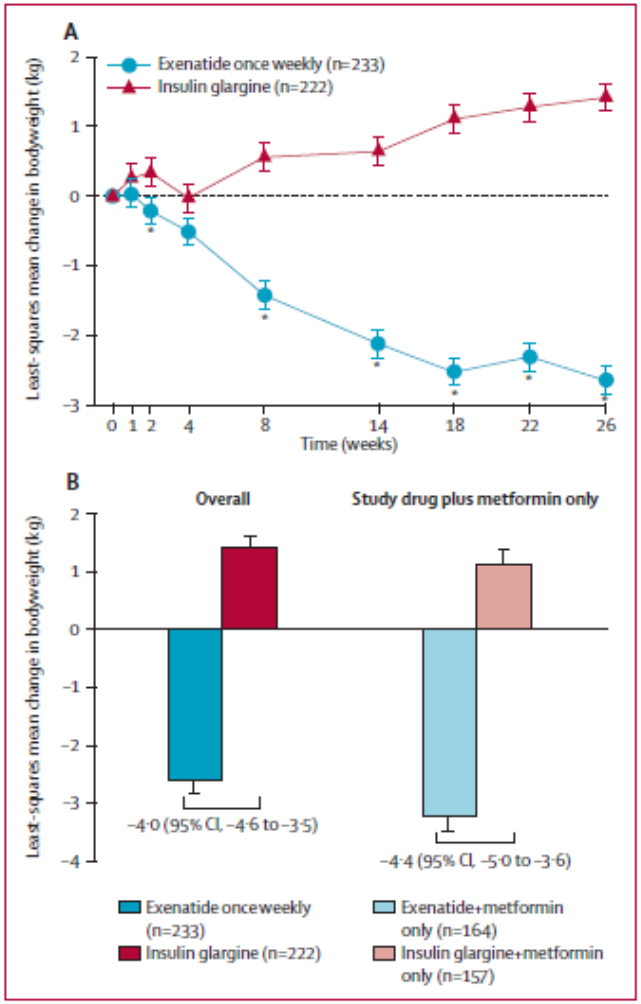
Exenatide ER vs Glargine





DURATION 3 *Lancet* 2010;375:2234-43

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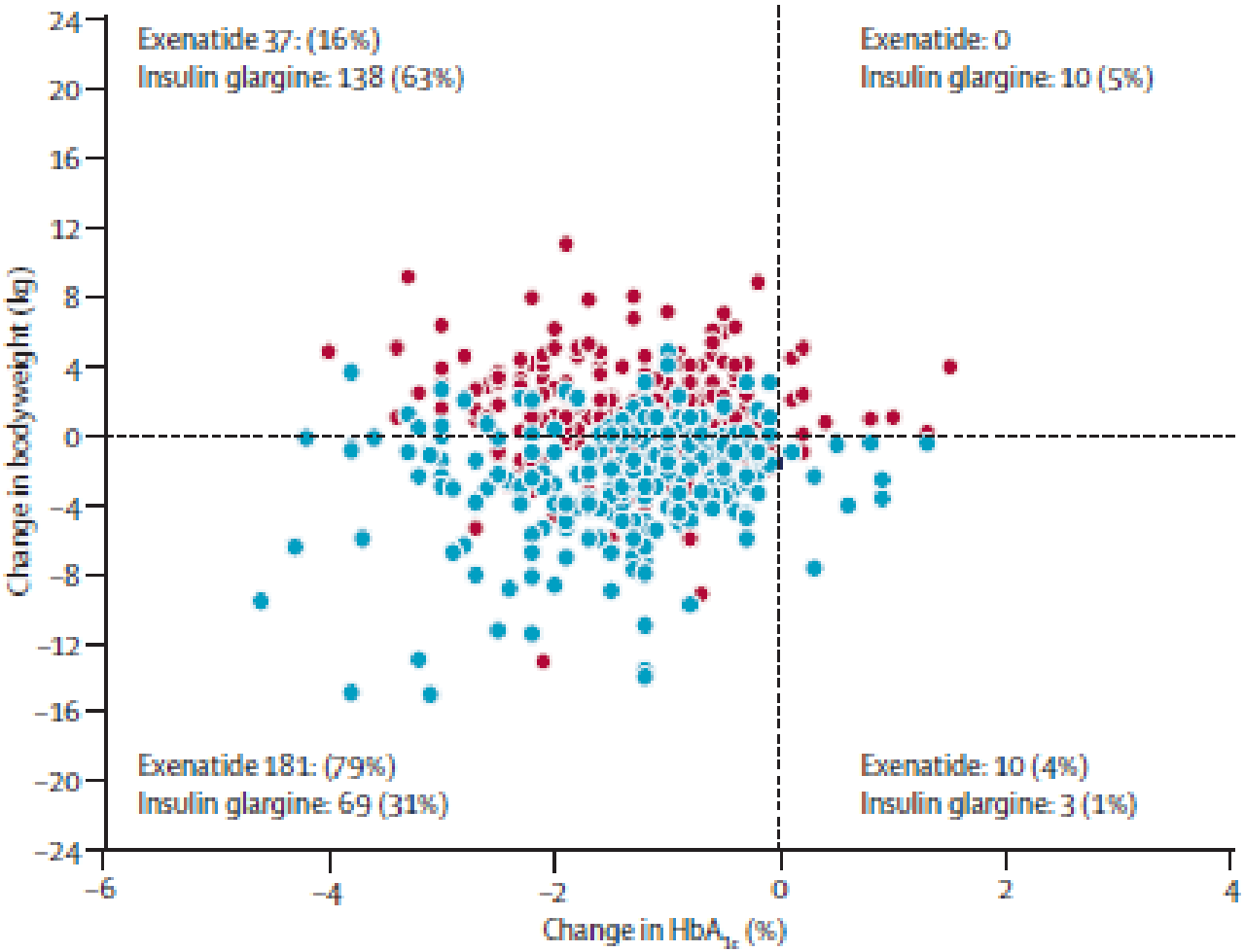
Exenatide ER vs glargine: targets



DURATION 3 *Lancet* 2010;375:2234-43

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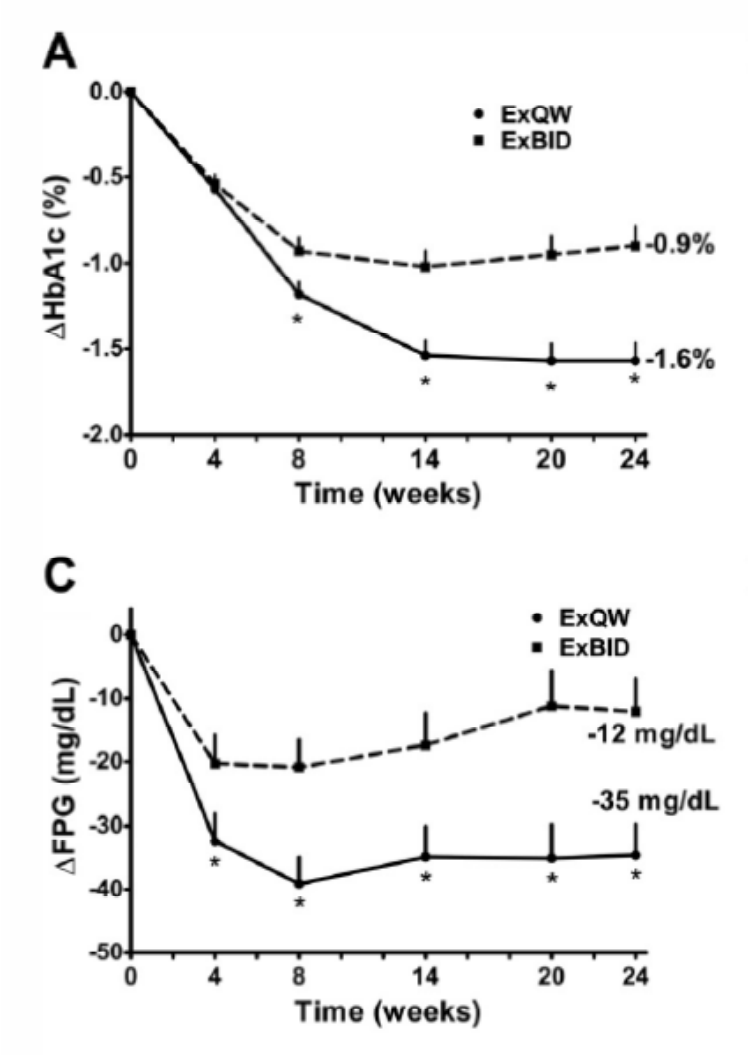
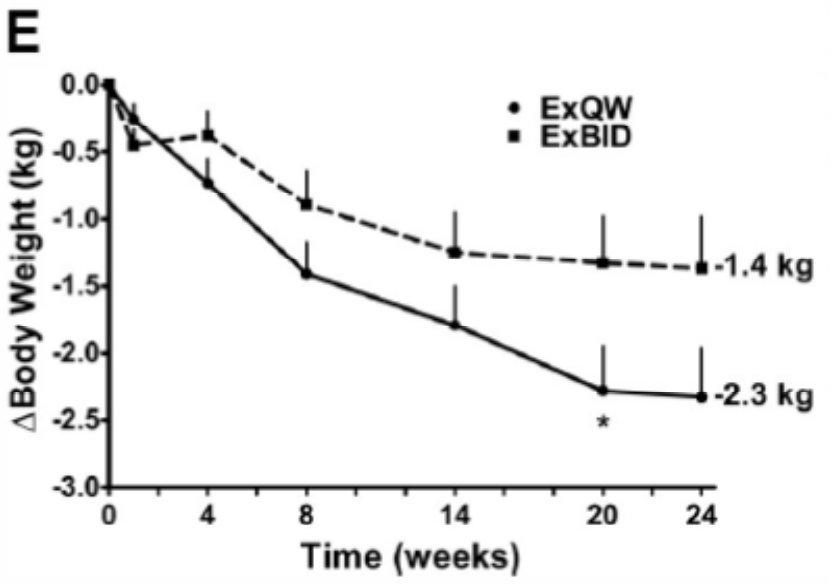
Exenatide ER vs BD





DURATION 5 ***J Clin End Met*** **2011;96:1301-10**

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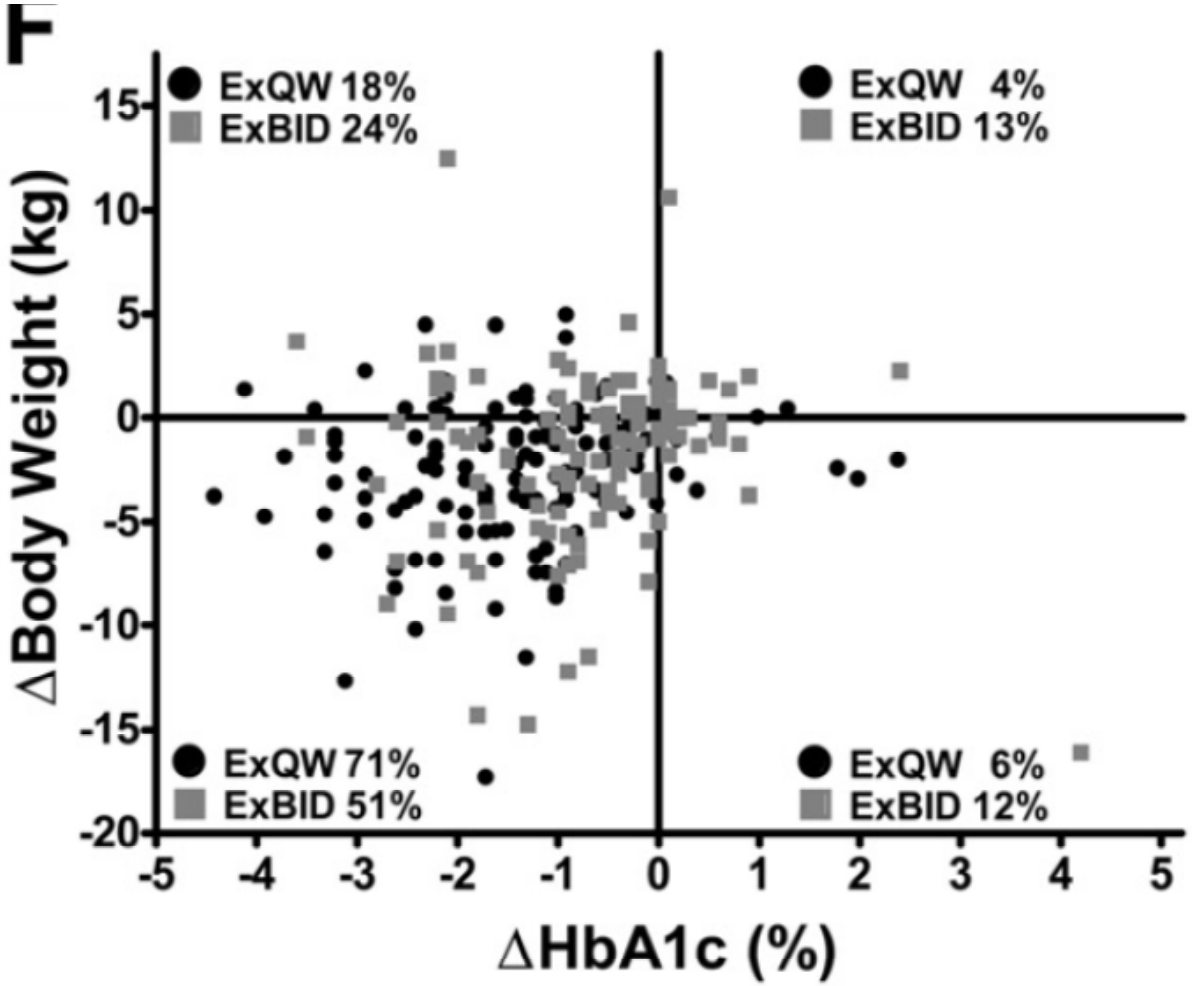
Exenatide ER vs BD: targets



DURATION 5 ***J Clin End Met*** **2011;96:1301-10**

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Long vs short-acting GLP 1 agonists

- Advantages:
  - Better glycaemic control
  - Better tolerated
  - ?Better adherence
- Disadvantages:
  - ?Less weight loss
  - Slower onset of action
  - More difficult to stop

GLP1 agonists and insulin

Figure 2. Change in HbA_{1c} over 30 weeks.

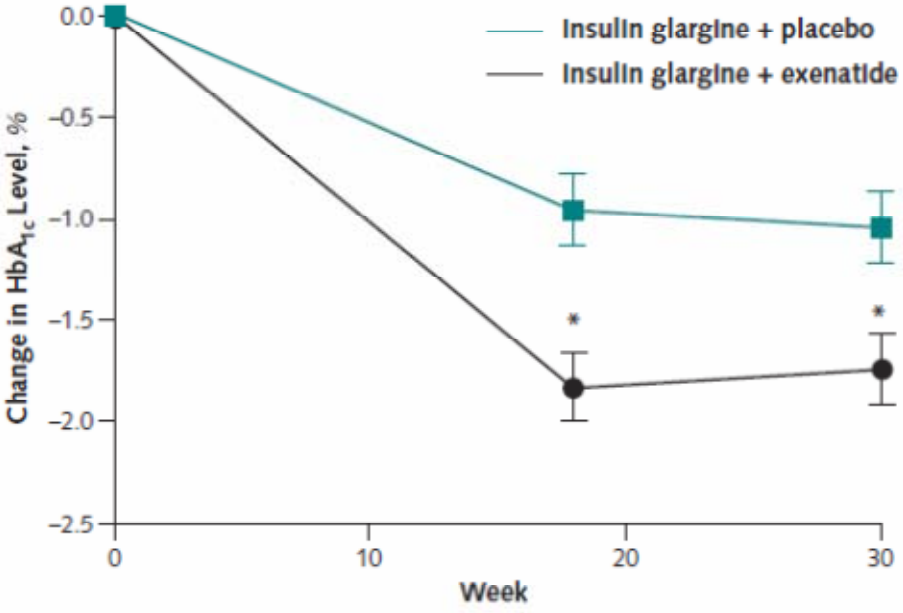
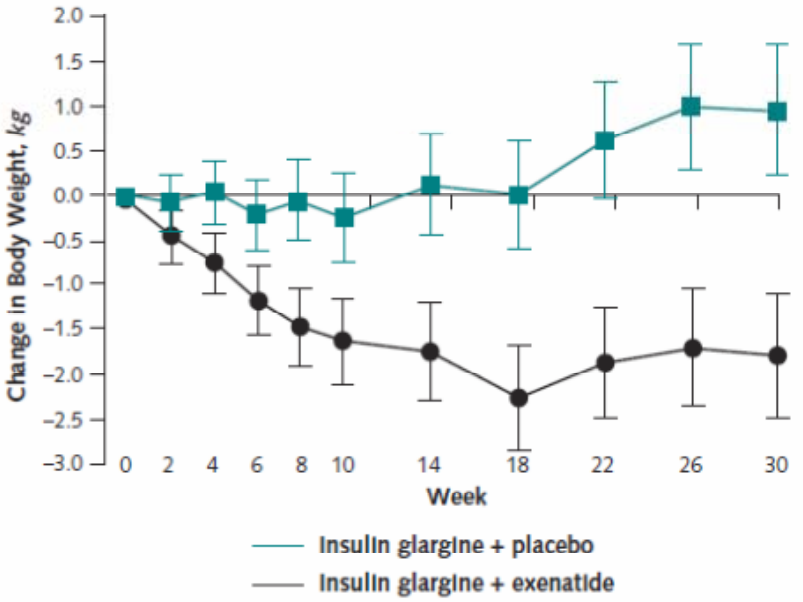


Figure 3. Changes in body weight and glucose levels over 30 weeks.



Buse JB et al. *Ann Intern Med* 2011;154:103-12

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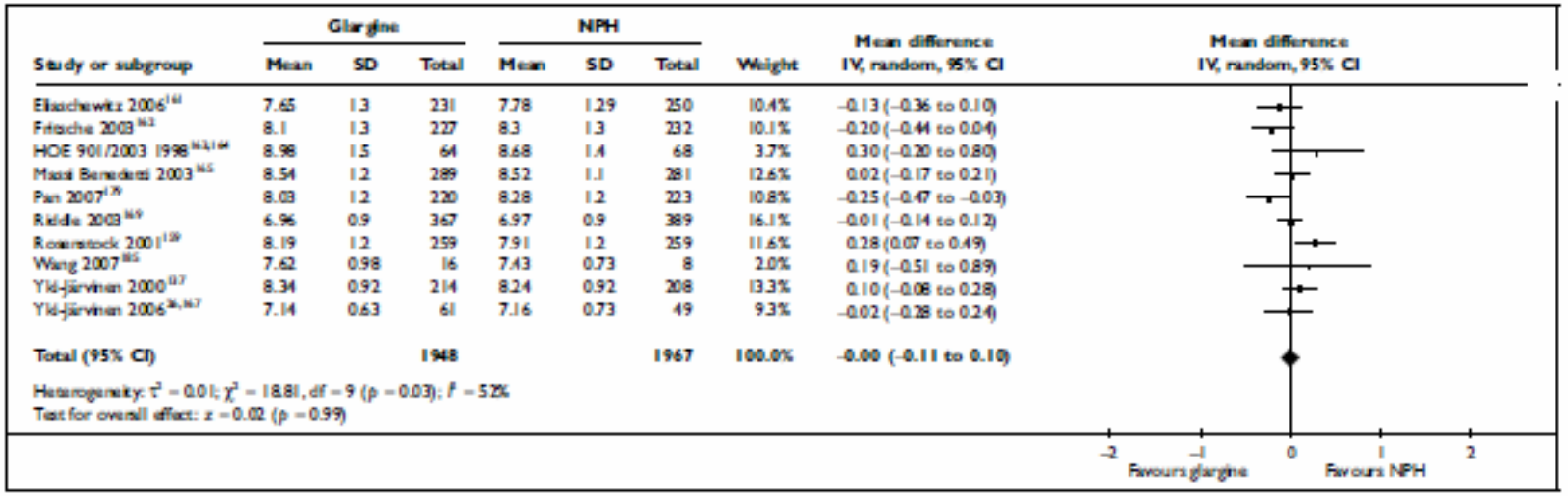
GLP1 and insulin – case study

- PC, 52 M
- Jan ’10: wt 135.6 kg HbA1c 86 mmol/mol (10.0%)
  - On 256 units insulin/d
  - Started liraglutide: titrated to 1.8 mg od
  - Treatment costs injectable therapy £5.84/day
- April ’11: wt 129.0 kg HbA1c 62 mmol/mol (7.8%)
  - On 68 units insulin/d
  - Treatment costs injectable therapy £5.69/day

NPH/isophane insulin should be first choice for initiation in type 2 diabetes

Glycaemic control



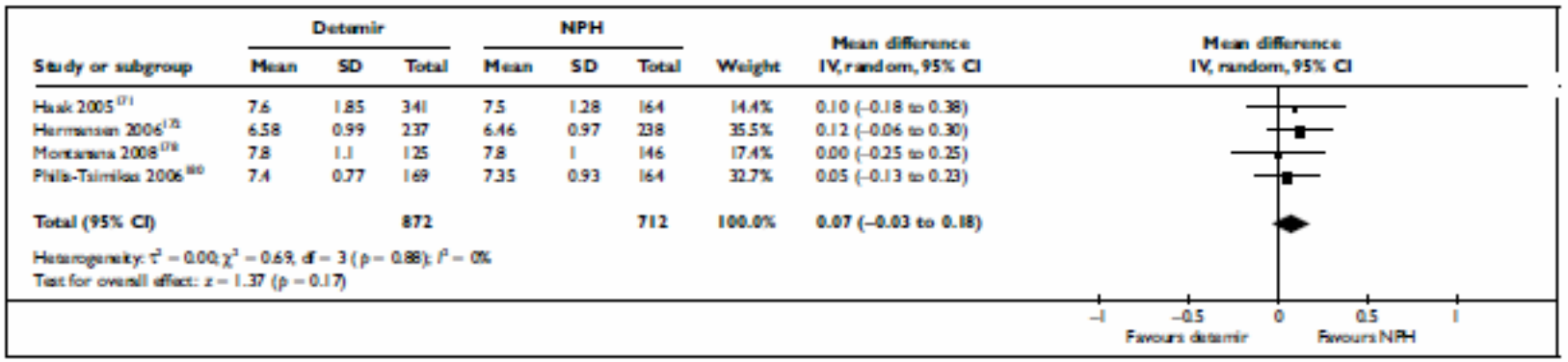
Study or subgroup	Glargine Mean	Glargine SD	Glargine Total	NPH Mean	NPH SD	NPH Total	Weight	Mean difference IV, random, 95% CI
Eliaschewitz 2006[161]	7.65	1.3	231	7.78	1.29	250	10.4%	−0.13 (−0.36 to 0.10)
Fritsche 2003[163]	8.1	1.3	227	8.3	1.3	232	10.1%	−0.20 (−0.44 to 0.04)
HOE 901/2003 1998[163,164]	8.98	1.5	64	8.68	1.4	68	3.7%	0.30 (−0.20 to 0.80)
Massi Benedetti 2003[165]	8.54	1.2	289	8.52	1.1	281	12.6%	0.02 (−0.17 to 0.21)
Pan 2007[179]	8.03	1.2	220	8.28	1.2	223	10.8%	−0.25 (−0.47 to −0.03)
Riddle 2003[169]	6.96	0.9	367	6.97	0.9	389	16.1%	−0.01 (−0.14 to 0.12)
Rosenstock 2001[159]	8.19	1.2	259	7.91	1.2	259	11.6%	0.28 (0.07 to 0.49)
Wang 2007[185]	7.62	0.98	16	7.43	0.73	8	2.0%	0.19 (−0.51 to 0.89)
Yki-Järvinen 2000[137]	8.34	0.92	214	8.24	0.92	208	13.3%	0.10 (−0.08 to 0.28)
Yki-Järvinen 2006[36,167]	7.14	0.63	61	7.16	0.73	49	9.3%	−0.02 (−0.28 to 0.24)
Total (95% CI)			**1948**			**1967**	**100.0%**	**−0.00 (−0.11 to 0.10)**

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 18.81$, $df = 9$ ($p = 0.03$); $I^2 = 52\%$
Test for overall effect: $z = 0.02$ ($p = 0.99$)

Mean difference IV, random, 95% CI

−2 −1 0 1 2
Favours glargine Favours NPH

FIGURE 2 HbA_{1c} *glargine versus Neutral Protamine Hagedorn.*



Study or subgroup	Detemir Mean	Detemir SD	Detemir Total	NPH Mean	NPH SD	NPH Total	Weight	Mean difference IV, random, 95% CI
Hask 2005[171]	7.6	1.85	341	7.5	1.28	164	14.4%	0.10 (−0.18 to 0.38)
Hermansen 2006[175]	6.58	0.99	237	6.46	0.97	238	35.5%	0.12 (−0.06 to 0.30)
Montanana 2008[178]	7.8	1.1	125	7.8	1	146	17.4%	0.00 (−0.25 to 0.25)
Philis-Tsimikas 2006[180]	7.4	0.77	169	7.35	0.93	164	32.7%	0.05 (−0.13 to 0.23)
Total (95% CI)			**872**			**712**	**100.0%**	**0.07 (−0.03 to 0.18)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.69$, $df = 3$ ($p = 0.88$); $I^2 = 0\%$
Test for overall effect: $z = 1.37$ ($p = 0.17$)

Mean difference IV, random, 95% CI

−1 −0.5 0 0.5 1
Favours detemir Favours NPH

FIGURE 3 HbA_{1c} *detemir versus Neutral Protamine Hagedorn.*

Waugh N et al. *HTA assessment* 2010;14:No 6

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ACCORD – intensive BG lowering

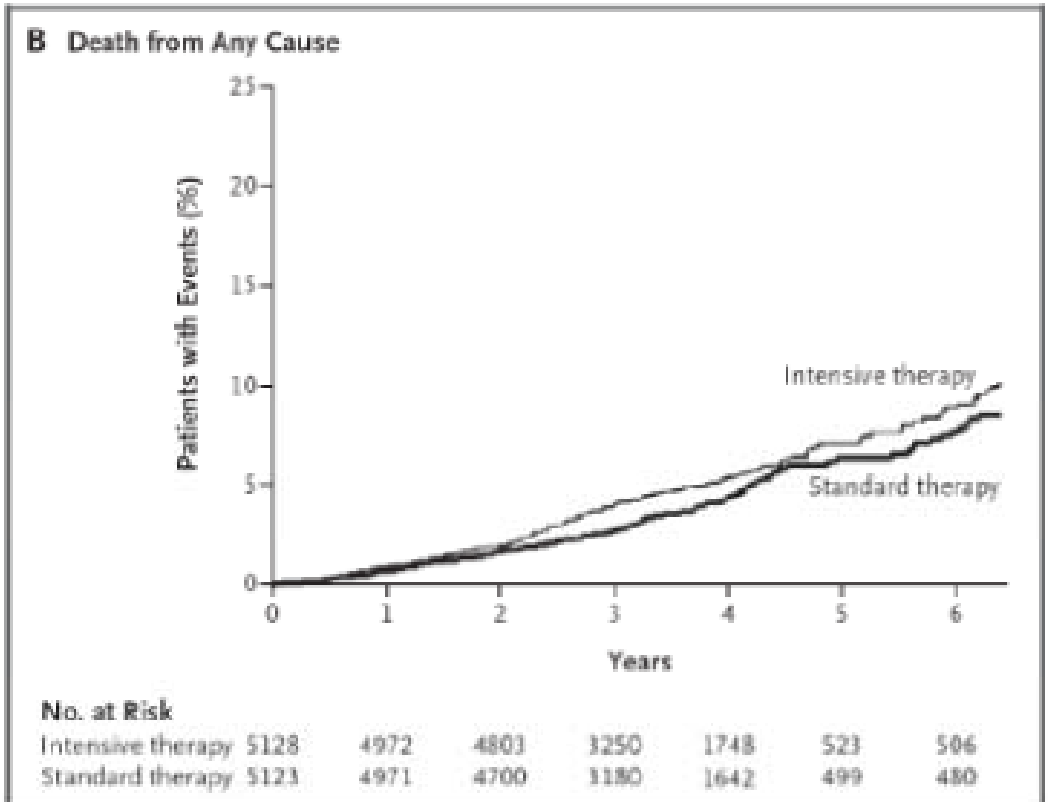

Figure 2. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.

The ACCORD study group. *N Eng J Med* 2008;358:2545-59

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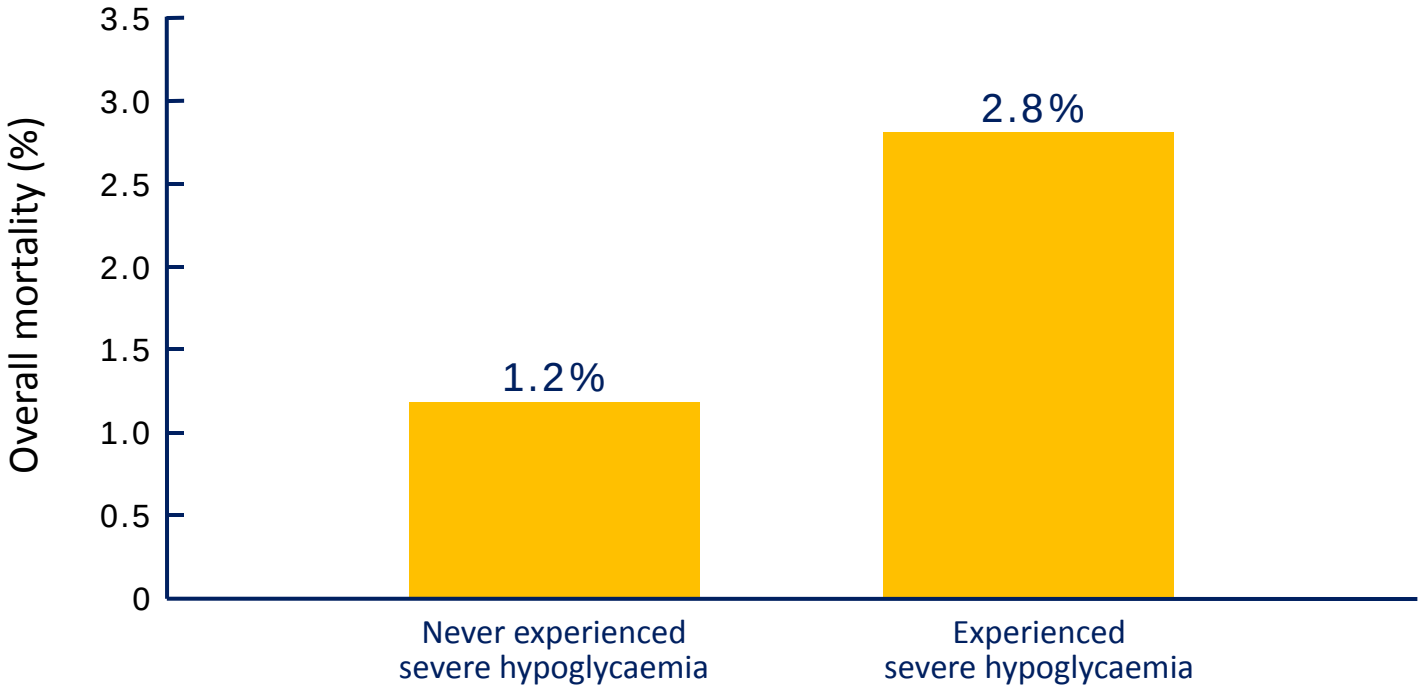
Hypoglycaemia and mortality: The ACCORD experience



Bonds DE et al. *BMJ* 2010; **340**: b4909

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Hypoglycaemia and mortality: The ADVANCE experience

Events	Severe Hypoglycemia (N=231)	No Severe Hypoglycemia (N=10,909)	Hazard Ratio (95% CI)
	no. of patients with events (%)		
Major macrovascular events	33 (15.9)	1114 (10.2)	
Unadjusted model			4.05 (2.86–5.74)
Adjusted model			3.53 (2.41–5.17)
Major microvascular events	24 (11.5)	1107 (10.1)	
Unadjusted model			2.39 (1.60–3.59)
Adjusted model			2.19 (1.40–3.45)
Death from any cause	45 (19.5)	986 (9.0)	
Unadjusted model			4.86 (3.60–6.57)
Adjusted model			3.27 (2.29–4.65)
Cardiovascular disease	22 (9.5)	520 (4.8)	
Unadjusted model			4.87 (3.17–7.49)
Adjusted model			3.79 (2.36–6.08)
Noncardiovascular disease	23 (10.0)	466 (4.3)	
Unadjusted model			4.82 (3.16–7.35)
Adjusted model			2.80 (1.64–4.79)

Zoungas S et al. *N Engl J Med* 2010; **363**: 1410−8

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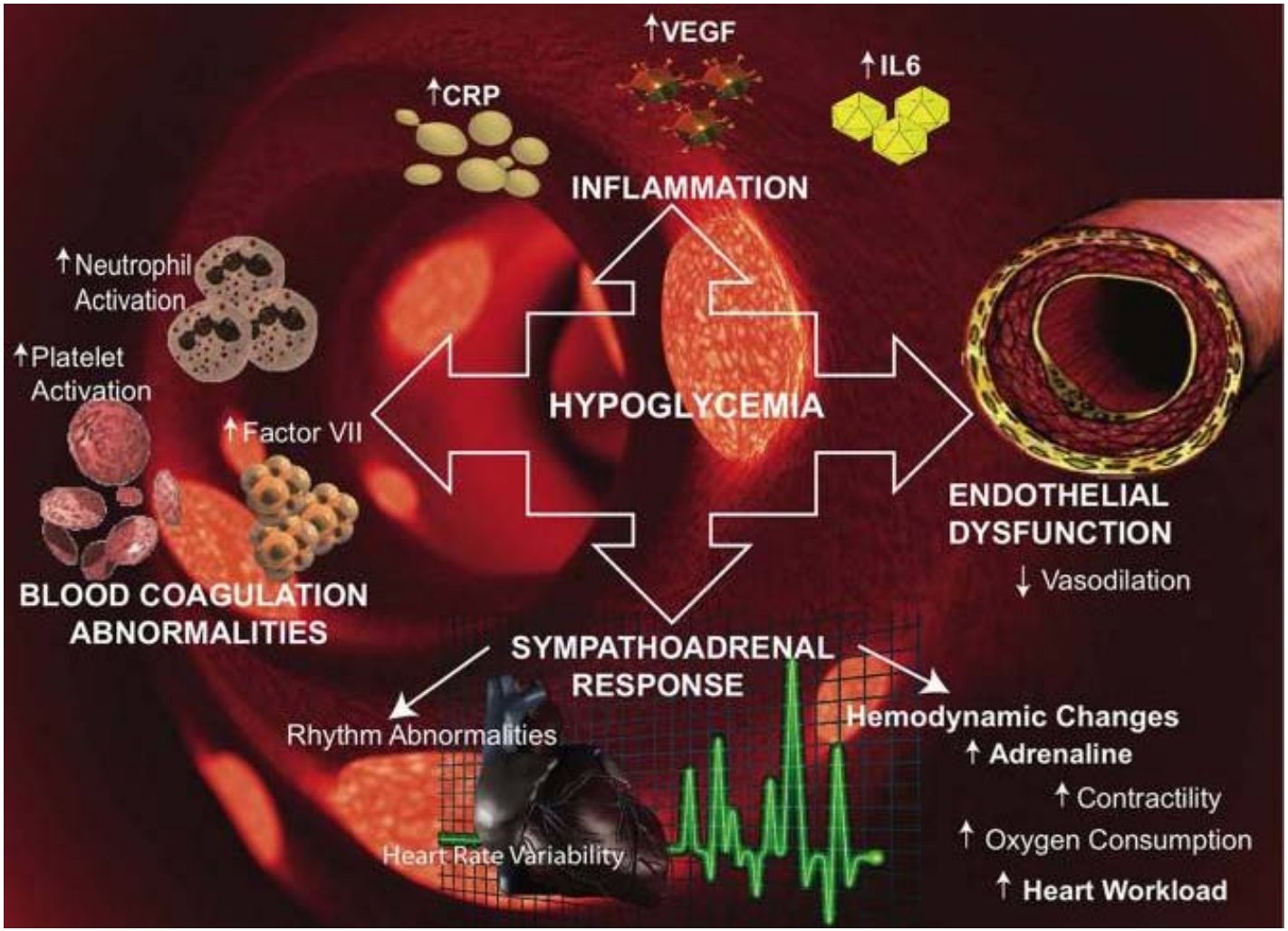
Pathophysiological cardiovascular consequences of hypoglycaemia



CRP, C-reactive protein; IL-6, interleukin 6; VEGF, vascular endothelial growth factor

Desouza *et al. Diabetes Care* 2010;33:1389–94

Hypoglycaemia in clinical practice

- 3% of people with type 2 diabetes experienced severe hypoglycaemia over a 12 month period
- People of all ages who experienced severe hypoglycaemia had a 79% increased risk of suffering an acute cardiovascular event
- Hypoglycaemia directly preceded an acute cardiovascular event in over 25% of people
- People who experienced severe hypoglycaemia incurred a 2 fold greater health related expenditure

Johnston et al. Diabetes care March 2011

Nocturnal hypoglycaemia

- Almost 50% of all episodes of severe hypoglycaemia occur at night during sleep[1]
- Nocturnal hypoglycaemia is a major concern to patients and family, and is a particular barrier to insulin dose titration[2,3]
- Nocturnal hypoglycaemia has a major detrimental effect on mood and well being the following day[1]
- Nocturnal hypoglycaemia is linked to 'dead in bed' syndrome[4]
- Recurrent nocturnal hypoglycaemia is linked to development of hypoglycaemia unawareness[5]
- Avoiding nocturnal hypoglycaemia is a key clinical imperative

1. Allen KV. *Endocr Pract* 2003; **9**: 530–43
2. Frier BM. *Diabetes Metab Res Rev* 2008; **24**: 87–92
3. Yale JF. *Diabetes Res Clin Pract* 2004; **65** Suppl 1: S41–6
4. Tanenburg RJ et al. *Endocr Pract* 2010; **16**: 244–8
5. Veneman T et al. *Diabetes* 1993; **42**: 1233–7

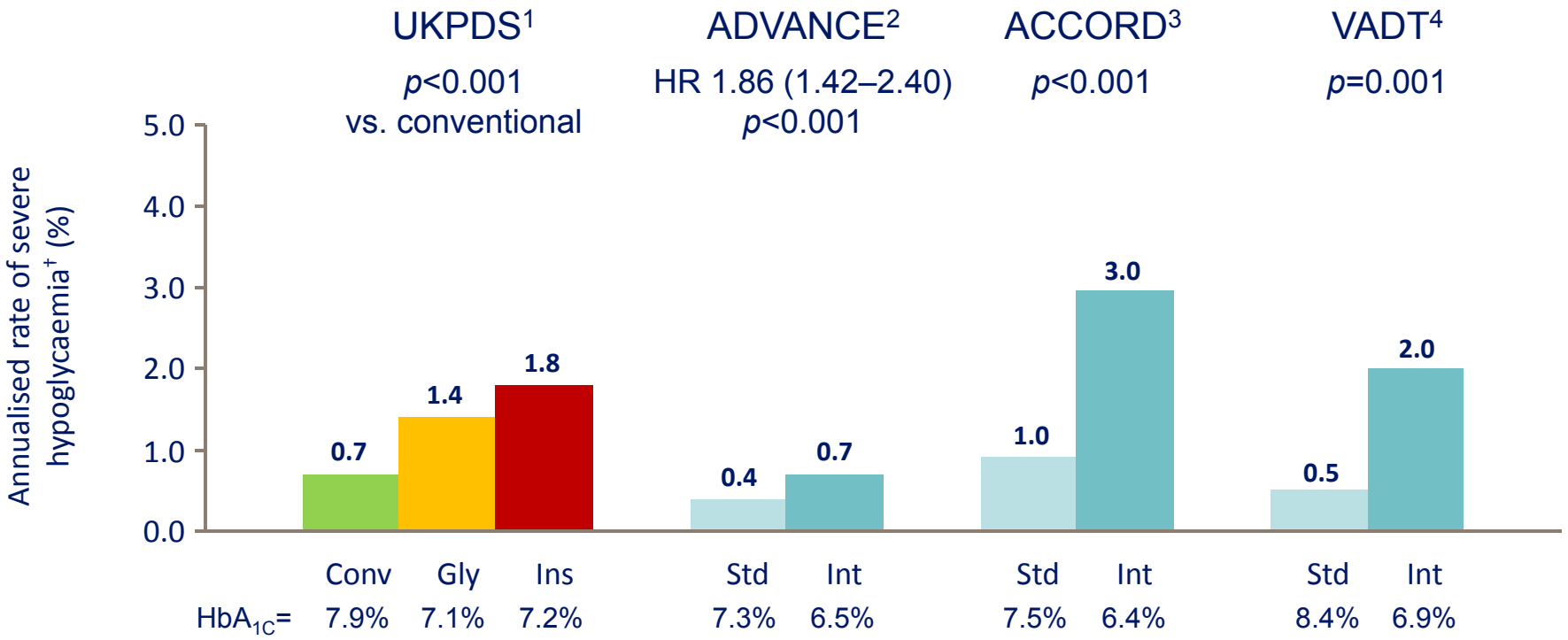
Consequences of hypoglycaemia for driving in the UK

Patients managed by insulin, **must** inform the DVLA of their treatment and **also if the following apply**:

- You suffer more than one episode of disabling hypoglycaemia (low blood sugar) within 12 months, or if you or your carer feels you are at high risk of developing disabling hypoglycaemia
- You develop impaired awareness of hypoglycaemia (difficulty in recognising the warning symptoms of low blood sugar)
- You suffer disabling hypoglycaemia while driving

DVLA guidance. Available at: http://www.dft.gov.uk/dvla/medical/ataglance.aspx

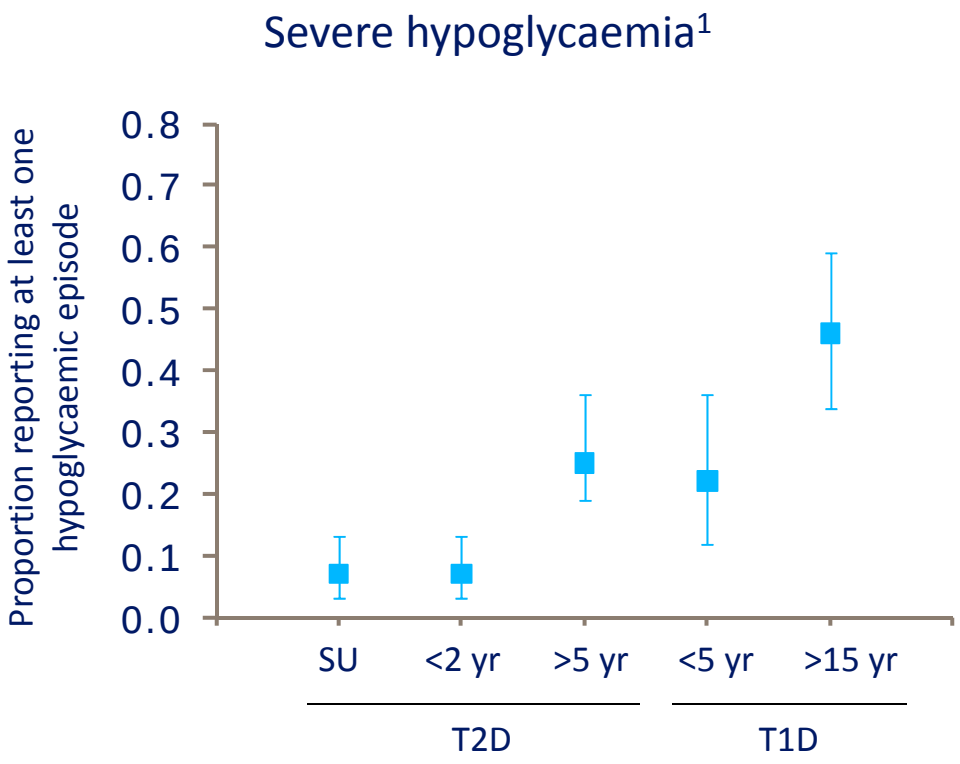
Higher rate of severe hypoglycaemia with intensive glycaemic control*

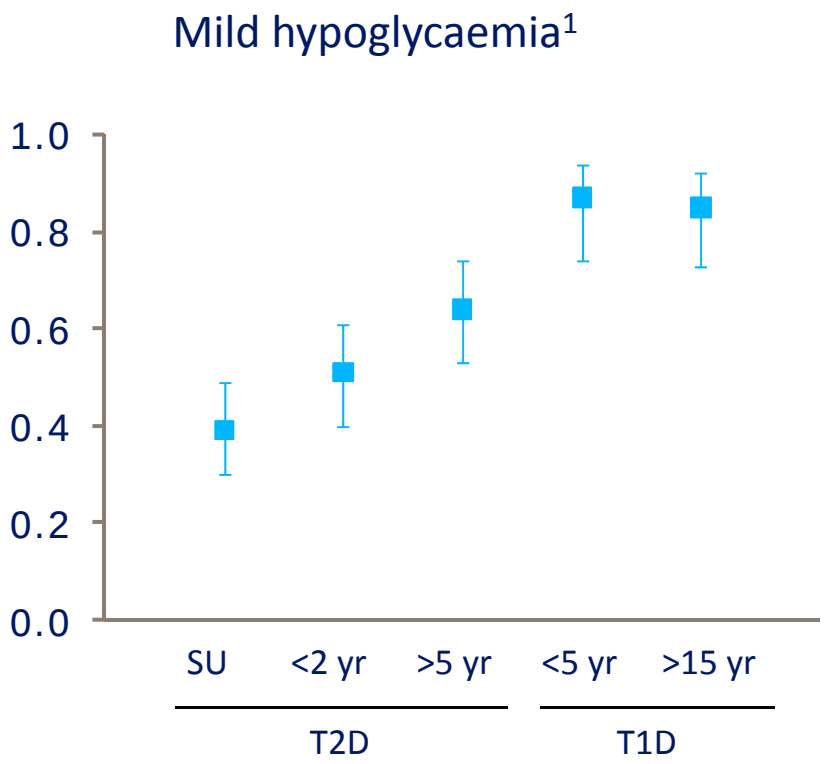


*Intensive glycaemic control was defined differently in these trials. †Hypoglycaemia requiring any assistance in glucose-lowering trials. Conv, conventional therapy; Gly, glibenclamide; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; Ins, insulin; Int, intensive therapy; Std, standard therapy

[1]UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53; [2]Patel *et al;* ADVANCE Collaborative Group [ADVANCE]. *N Engl J Med* 2008;358:2560–72; [3]Gerstein *et al*; Action to Control Cardiovascular Risk in Diabetes Study Group [ACCORD]. *N Engl J Med* 2008;358:2545–59; [4]Duckworth *et al. N Engl J Med* 2009;360:129–39

Myth 1: hypoglycaemia does not occur in T2DM





- T1D
  - 55% of severe and 43% of all hypoglycaemic episodes occur during sleep in T1D[2]
  - 36% of severe episodes that occurred while awake had no warning signs[2]

SU, sulphonylurea

[1]UK Hypoglycaemia Study Group *Diabetologia* 2007;50:1140–7;
[2]DCCT. *Am J Med* 1991;90:450–9

Myth 2: hypoglycaemia does not have major consequences in T2DM

- Similar clinical (CV and neurological) consequences to T1D

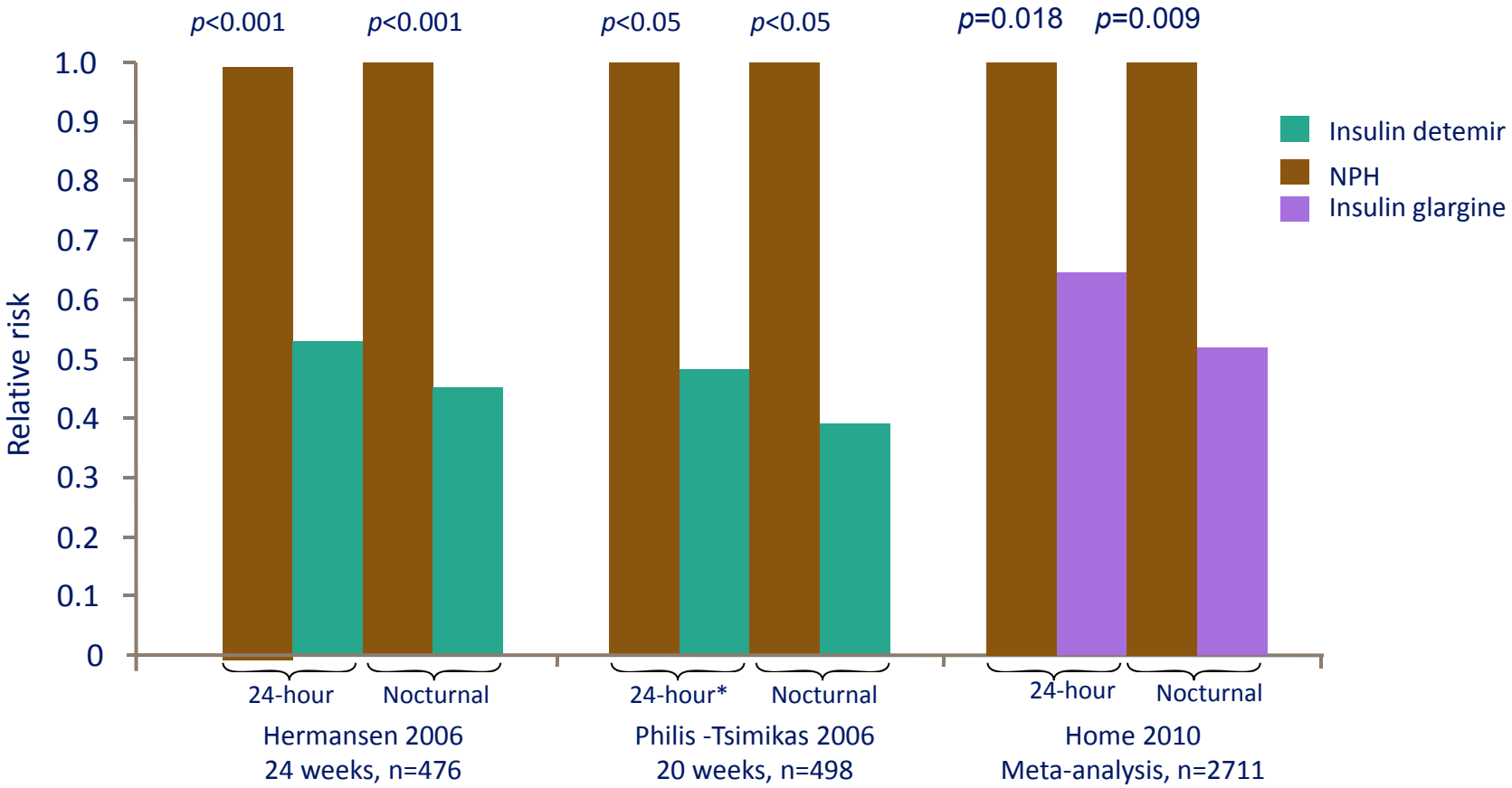
However:

- T2D population is older
  - Symptoms can be different
  - Hypoglycaemia unawareness
  - More comorbidities
    - high frequency of CVD
    - osteoporosis – higher fracture risk
    - longer hospital stay duration
- Event rate increases with disease duration – progressive disease

CV, cardiovascular; CVD, CV disease

Chelliah *et al*. *Drugs Aging* 2004;21:511–30; Lebovitz *Diab Rev* 1999;7:139–53

Hypoglycaemic event rates are reduced with basal analogue insulins vs. NPH in T2DM



* PM dose

Threshold of <3.1 mmol/L for confirmed hypoglycaemia

Threshold of <3.9 mmol/L for confirmed hypoglycaemia

Home *et al. Diabetes Obes Metab 2010*;12;772–9; Hermansen *et al. Diabetes Care* 2006;29:1269–74; Philis-Tsimikas *et al. Clin Ther* 2006;28:1569–81

Hypoglycaemia and basal analogues

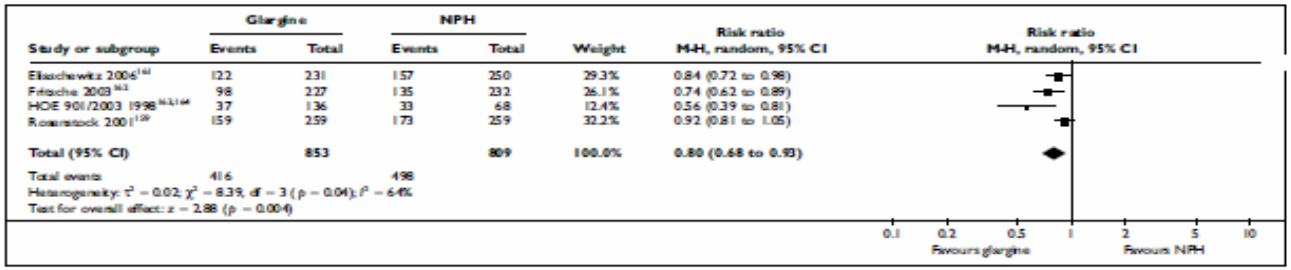


FIGURE 8 *Symptomatic hypoglycaemia glargine versus Neutral Protamine Hagedorn.*

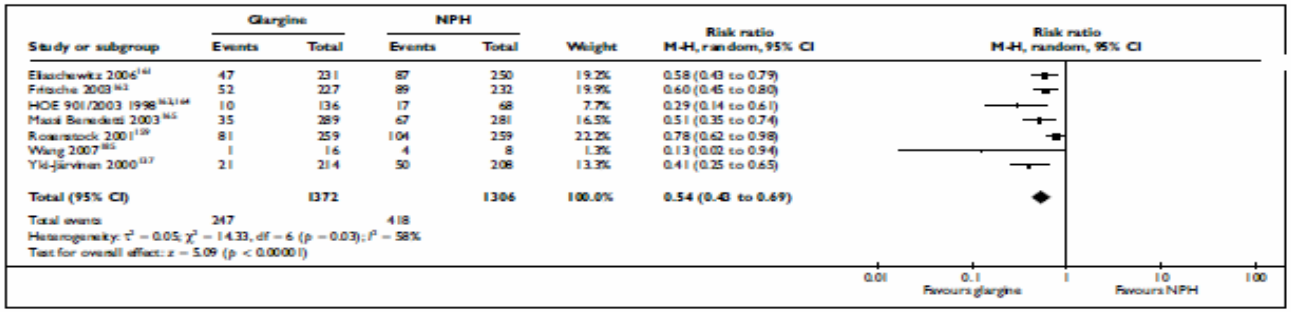


FIGURE 9 *Nocturnal hypoglycaemia glargine versus Neutral Protamine Hagedorn.*

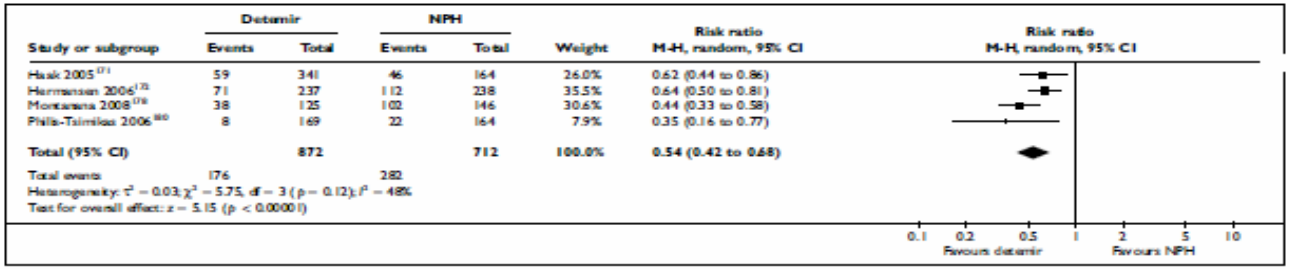
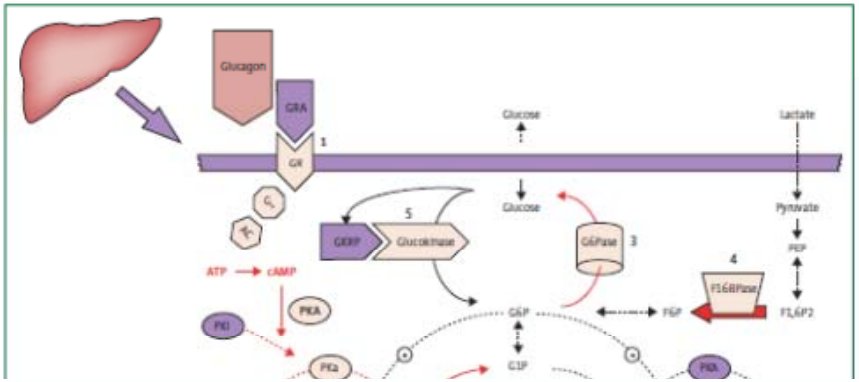
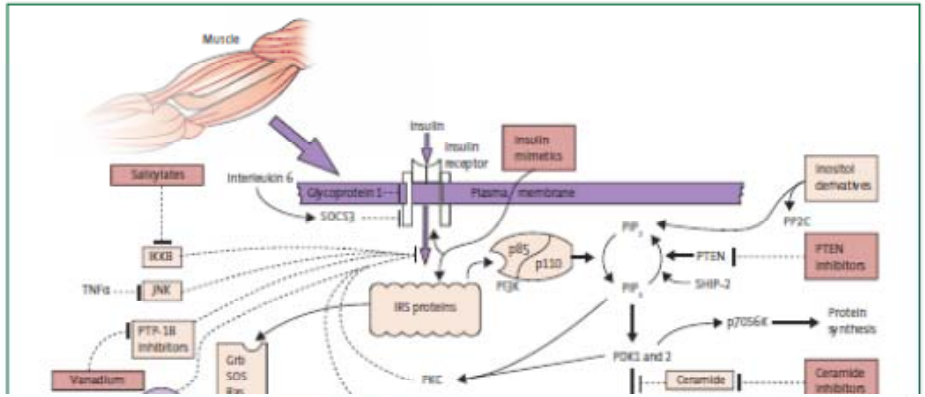


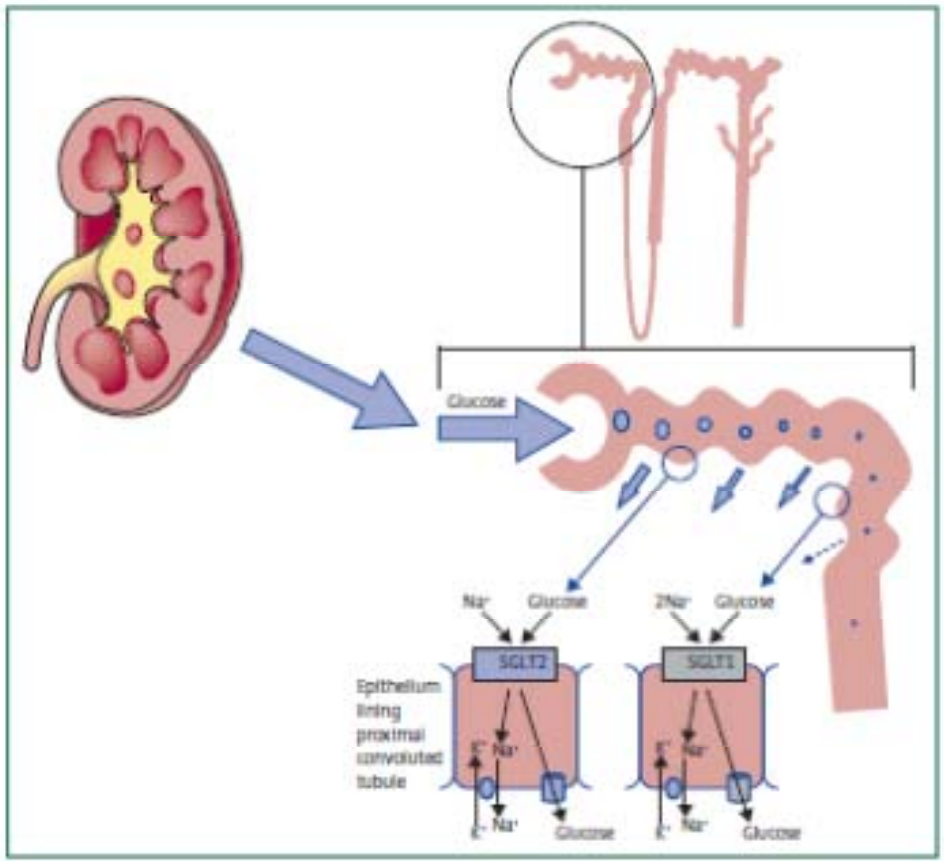
FIGURE 10 *Nocturnal hypoglycaemia detemir versus Neutral Protamine Hagedorn.*

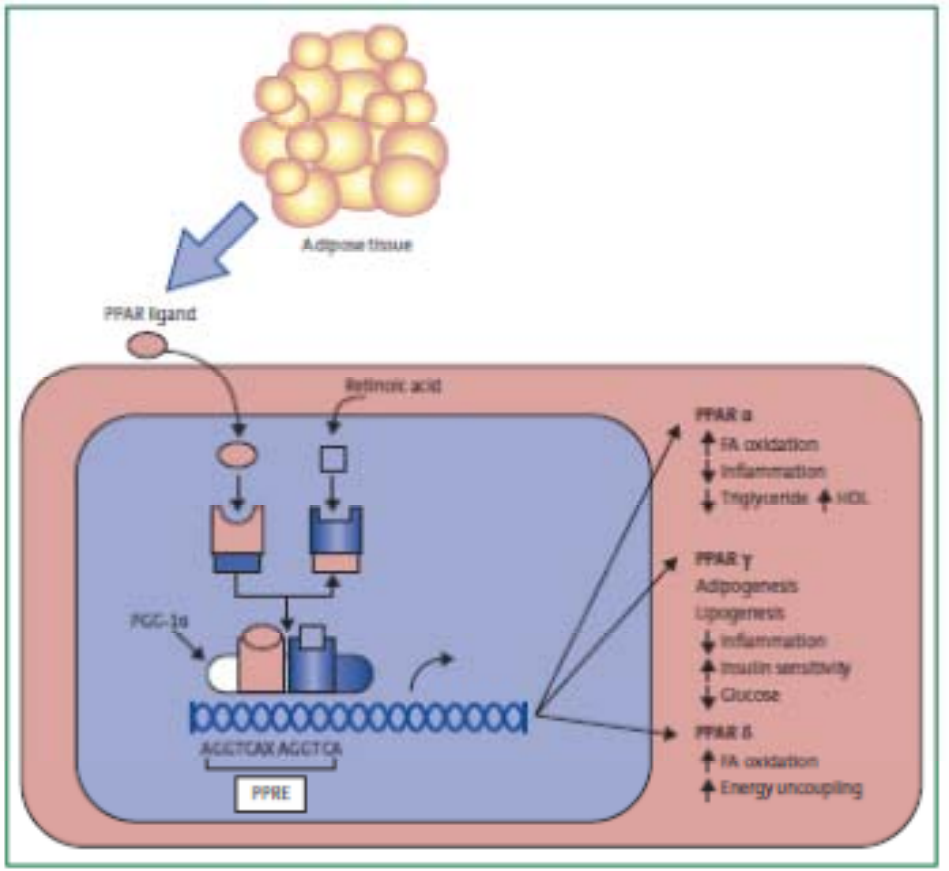
Waugh N et al. *HTA assessment* 2010;14:No 6

Harrogate and District NHS Foundation Trust







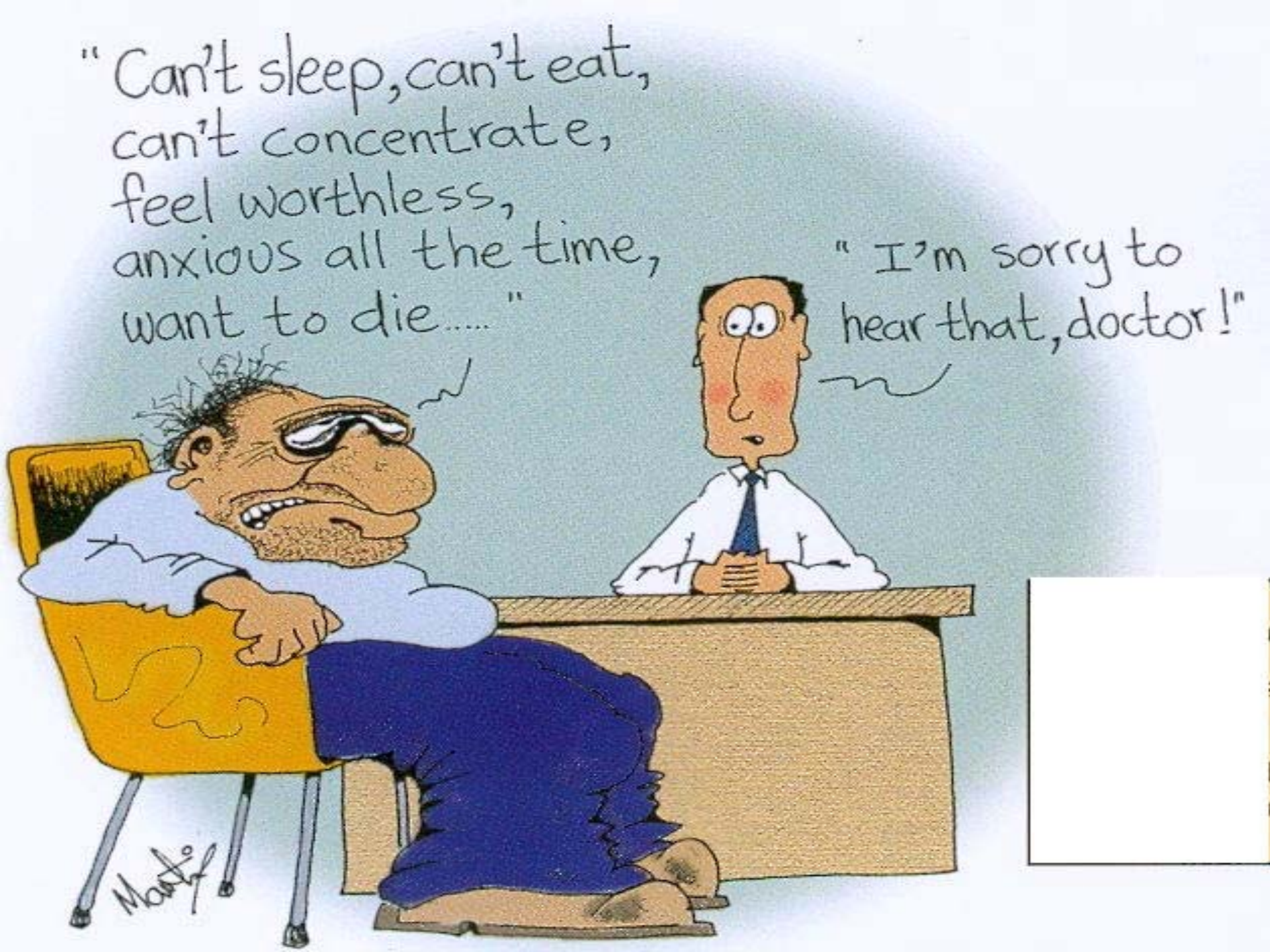


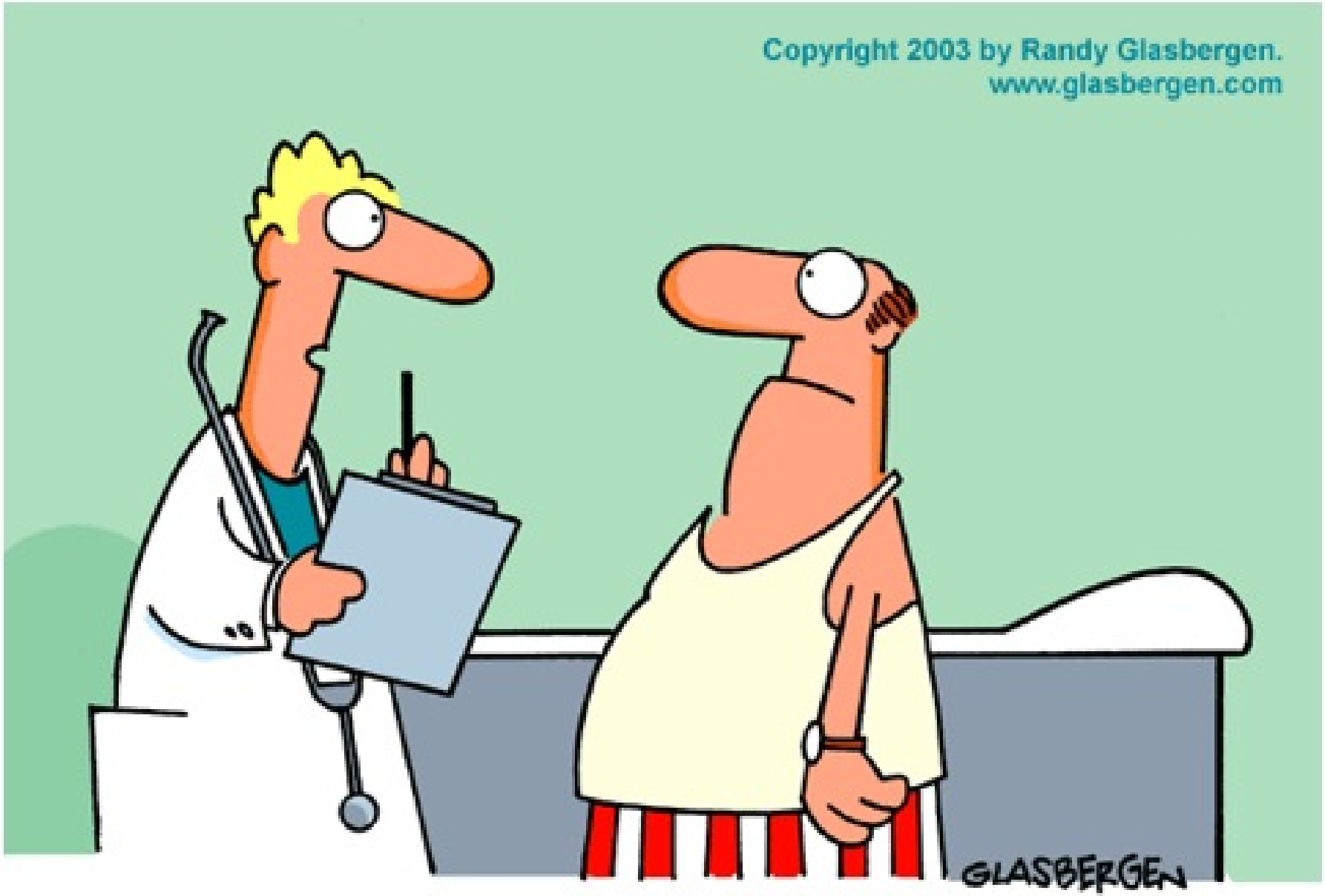
Tahrani A et al. *Lancet* 2011;378:182-197

Harrogate and District NHS
NHS Foundation Trust

Bullet Points for New Clinical Solutions

- There is a legacy effect of good glycaemic control so NICE targets are essential and combination drug therapy is inevitable
- The ideal drug combination therapy for glucose control combines low risk of hypoglycaemia, weight reduction and CV safety
- Newer agents, particularly those targeting the GLP1 receptor show potential but CV safety data is awaited


"Can't sleep, can't eat, can't concentrate, feel worthless, anxious all the time, want to die....."
"I'm sorry to hear that, doctor!"



"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"