The ABCD Debate: This house believes that the unlicensed use of GLP-1's is unethical, unaffordable and should stop

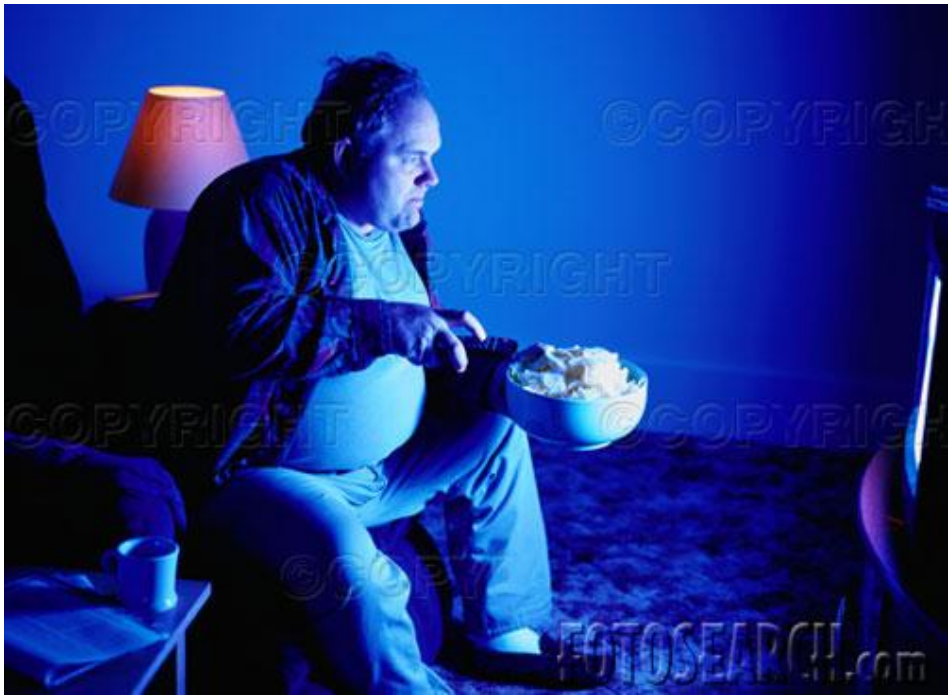
Against the motion:
Dr Bob Ryder, Consultant Physician and Diabetologist, City Hospital, Birmingham

Sandwell and West Birmingham Hospitals NHS
NHS Trust

Where EVERYONE Matters

- Off licence GLP1 RA
  - –unethical
  - –unaffordable

Obese person with diabetes



- I would like to convince you:
  - Losing weight a good thing
  - (Increasing weight a bad thing)

Mr PH, age 61, type 2 diabetes 20 years, on insulin 14 years

Treating to Target

Emerging Treatments and Technologies
ORIGINAL ARTICLE

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

MATTHEW C. RIDDLE, MD[1]
JULIO ROSENSTOCK, MD[2]
JOHN GERICH, MD[3]
ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

OBJECTIVE — To compare the abilities and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA_{1c}.

RESEARCH DESIGN AND METHODS — In a randomized, open-label, parallel, 24-week multicenter trial, 756 overweight men and women with inadequate glycemic control (HbA_{1c} >7.5%) on one or two oral agents continued prestudy oral agents and received bedtime glargine or NPH once daily, titrated using a simple algorithm seeking a target fasting plasma glucose (FPG) ≤100 mg/dl (5.5 mmol/l). Outcome measures were FPG, HbA_{1c}, hypoglycemia, and percentage of patients reaching HbA_{1c} ≤7% without documented nocturnal hypoglycemia.

RESULTS — Mean FPG at end point was similar with glargine and NPH (117 vs. 120 mg/dl [6.5 vs. 6.7 mmol/l]), as was HbA_{1c} (6.96 vs. 6.97%). A majority of patients (~60%) attained HbA_{1c} ≤7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (≤72 mg/dl [4.0 mmol/l]) with glargine (33.2 vs. 26.7%, $P < 0.05$). Moreover, rates of other categories of symptomatic hypoglycemia were 21–48% lower with glargine.

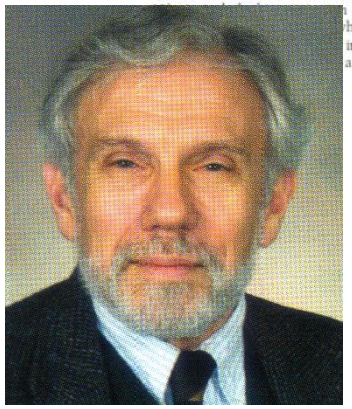
CONCLUSIONS — Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% HbA_{1c} in a majority of overweight patients with type 2 diabetes with HbA_{1c} between 7.5 and 10.0% on oral agents alone. In doing this, glargine causes significantly less nocturnal hypoglycemia than NPH, thus reducing a leading barrier to initiating insulin. This simple regimen may facilitate earlier and effective insulin use in routine medical practice, improving achievement of recommended standards of diabetes care.

Diabetes Care 26:3080–3086, 2003

Type 2 diabetes is a progressive disorder of β-cell dysfunction. Patients using oral therapy for it seldom achieve and maintain the recommended 7% HbA_{1c} goal (1,2) for glycemic control and are exposed to increasing risks of diabetic complications as control worsens over time (3–5). The U.K. Prospective Diabetes Study (UKPDS) (6) showed that intensive treatment can reduce these clinical risks, and a recently reported substudy of the UKPDS (7) confirmed that early addition of insulin to oral therapy can safely keep HbA_{1c} close to 7% in the first 6 years after diagnosis.

However, the majority of patients with a longer duration of diabetes remain poorly controlled with oral agents, and use of insulin, which could improve glycemic control, is often long delayed and not aggressive enough. The reluctance to initiate insulin therapy seems partly due to its perceived complexity, the belief that insulin is not effective for type 2 diabetes (8), and fear of hypoglycemia, which may be the greatest barrier (9).

A regimen that may make initiation of insulin simpler and more effective has been tested in several small studies (10–



Julio Rosenstock

Matthew Riddle

Riddle et al, Diabetes Care 2003; 26: 3080-3086

Diabetologia (2006) 49: 442–451
DOI 10.1007/s00125-005-0132-0

ARTICLE

H. Yki-Järvinen · R. Kauppinen-Mäkelin · M. Tiikkainen · M. Vähätalo · H. Virtamo · K. Nikkilä · T. Tulokas · S. Hulme · K. Hardy · S. McNulty · J. Hänninen · H. Levänen · S. Lahdenperä · R. Lehtonen · L. Ryysy

Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study

Received: 4 May 2005 / Accepted: 7 November 2005 / Published online: 3 February 2006

Abstract *Aims/hypothesis:* In type 2 diabetic patients we compared 9 months of combination therapy with insulin glargine and metformin with 9 months of NPH insulin combined with metformin. The primary focus was changes in HbA_{1c}; secondary focus was diurnal glucose profiles and symptomatic hypoglycaemia. *Methods:* In this investigator-initiated open, parallel-group clinical trial involving seven centres, 110 insulin-naive type 2 diabetic patients with poor glycaemic control (HbA_{1c} ≥8.0%) on oral hypoglycaemic agents (90% using sulfonylurea plus metformin) were randomised to receive bedtime insulin glargine with metformin (G+MET) or bedtime NPH with metformin (NPH+MET) for 36 weeks. The patients were taught how to self-adjust their insulin dose and use a modem to send the results of home glucose monitoring to treatment centres. The goal was to achieve a fasting plasma glucose (FPG) of 4.0 to 5.5 mmol/l in both groups. *Results:* During the last 12 weeks, FPGs averaged 5.75±0.02 and 5.96±0.03 mmol/l ($p<0.001$) and insulin doses were 68±5 and 70±6 IU/day (0.69±0.05 and 0.66±0.04 IU kg^{-1} day^{-1}, NS) in the G+MET and NPH+MET groups, respectively. At 36 weeks, mean HbA_{1c} was 7.14±0.12 and 7.16±0.14%, respectively (NS). Symptomatic, but not confirmed symptomatic, hypoglycaemia was significantly lower during the first 12 weeks in the G+MET group (4.1±0.8 episodes/patient-year) than in the NPH+MET group (9.0±2.3 episodes/patient-year, $p<0.05$), but not significantly different thereafter. Glucose levels before dinner were higher in the NPH+MET group (10.1±0.3 mmol/l) than in the G+MET group (8.6±0.3 mmol/l, $p=0.002$) throughout the 36-week study. With regard to baseline characteristics such as initial glycaemia or C-peptide, there was no difference between patients who achieved good glycaemic control (HbA_{1c} <7.0%) and those who did not. Differences were seen in the following: between study centres, weight gain during the run-in period and insulin therapy, and FPG during the last 12 weeks (5.7±0.2 vs 6.7±0.3 mmol/l for patients reaching vs those not reaching target, $p<0.01$). *Conclusions/interpretation:* Good glycaemic control can be achieved with both G+MET and NPH+MET. Use of G+MET reduces symptomatic hypoglycaemia during the first 12 weeks and dinnertime hyperglycaemia compared with NPH+MET.

Keywords Glucose · Insulin analogues · Insulin therapy · Metformin · Type 2 diabetes

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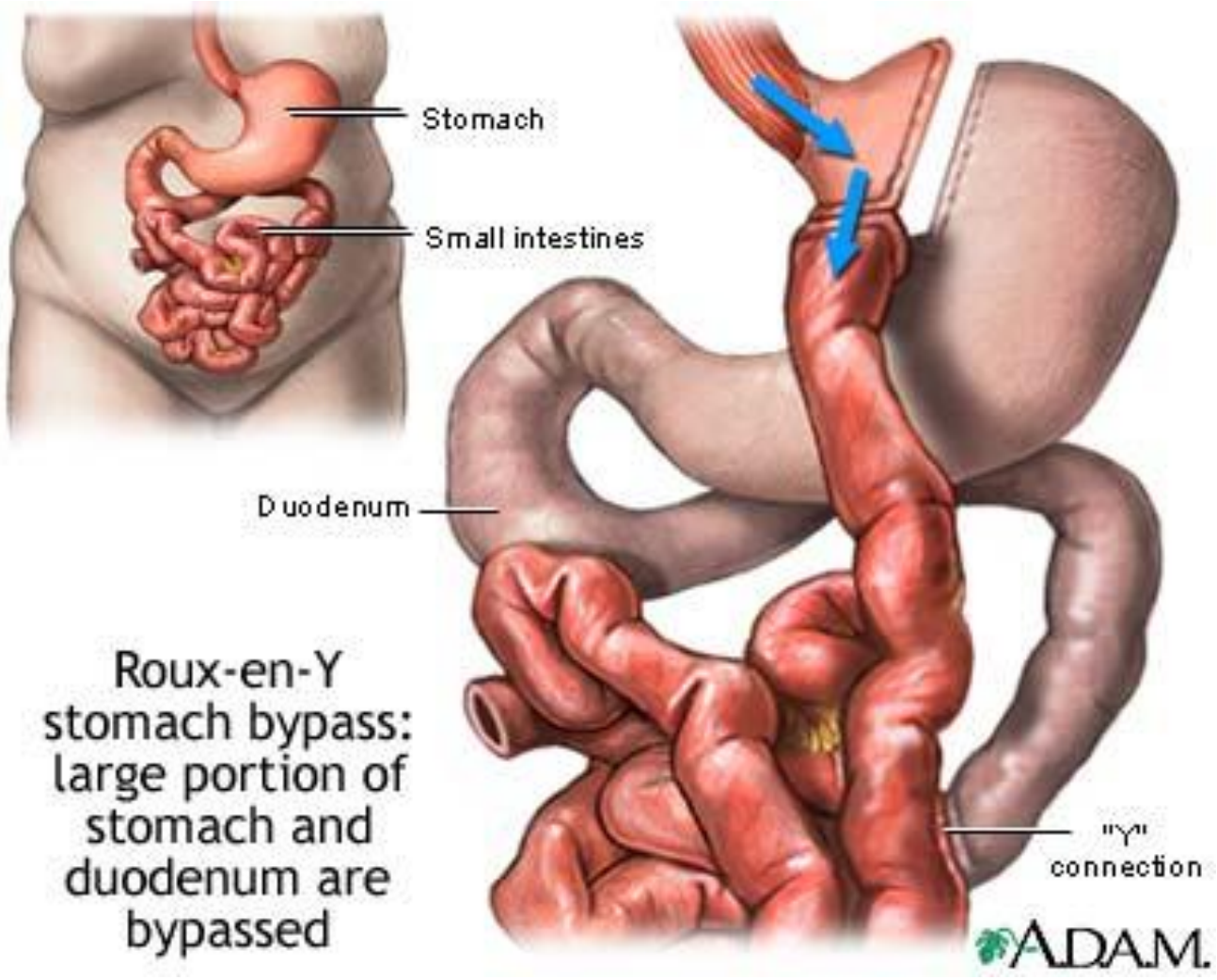
Yki-Jarvinen et al, Diabetologia 2006; 49: 442-451

Mr PH, age 61, type 2 diabetes 20 years, on insulin 14 years (attendee at Dr Ryder “Treat to Target” clinic)

- May 2006
- Wt = 160 kg
- BMI = 53
- 325 units insulin daily (NR + I) with pioglitazone
- A1c = 6.7%
- BP 162/75 on 3-4 antihypertensive agents

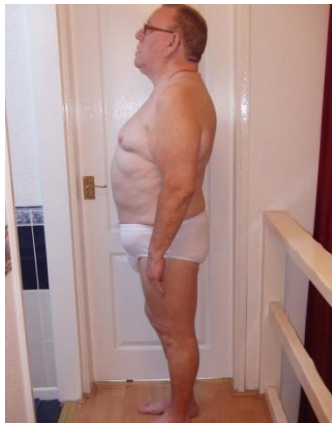
Roux-en-Y stomach surgery for weight loss



Roux-en-Y stomach bypass: large portion of stomach and duodenum are bypassed

Diabetes Cured?

- May 2006
- Wt = 160 kg
- BMI = 53
- 325 units insulin daily (NR + I) with pioglitazone
- A1c = 6.7%
- BP 162/75 on 3-4 antihypertensive agents

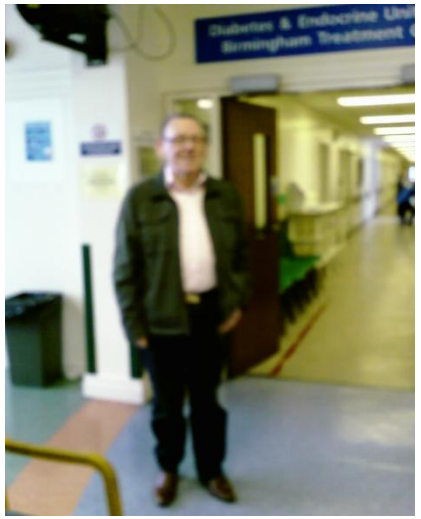


- September 2007
- Wt = 105 kg
- BMI = 35
- No insulin

- A1c = 5.5%
- BP 112/70 - no anti-hypertensives

NB GTT

- May 2006
- Wt = 160 kg
- BMI = 53
- Trouser size = 54 inch
- 325 units insulin daily (NR + I) with pioglitazone
- A1c = 6.7%



- April 2008
- Wt = 83 kg
- BMI = 27
- Trouser size = 32 inch
- No insulin, only metformin

- A1c = 7% (NB GTT still DM)

The patient and his partner
- both inside his old belt

Sunday, June 1, 2008

- **May 2006**
  - **Wheelchair**
- **June 2008**
  - **Sky-diving**

“Curing” diabetes through weight loss

- Do you need bariatric surgery?
- Can it be done by diet alone?

Dr PD, age 43, newly diagnosed type 2 diabetes

November 1995

- 27 Stone (173Kg)
- BMI 58.3
- Fasting glucose 13.7 mmol/L
- Glycoylated Hb = 12.7%

Ryder, REJ, Desai, PM.
Diabetes and Vascular Disease 2004; 4: 281-282

Ryder, REJ, Desai, PM.
Diabetes and Vascular Disease 2004; 4: 281-282

January 1997

- 14.5 Stone
- (93.1Kg)
- BMI = 31.3

Ryder, REJ, Desai, PM.
Diabetes and Vascular Disease 2004; 4: 281-282

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January 1997

- 14.5 Stone
- (93.1Kg)
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Ryder, REJ, Desai, PM.
Diabetes and Vascular Disease 2004; 4: 281-282

January 97 Glucose Tolerance Test

- Fasting glucose 3.9 mmol/l
- 2 hour value 6.6 mmol/l

ie normal by |WHO criteria

Ryder, REJ, Desai, PM. Diabetes and Vascular Disease 2004; 4: 281-282

Glucose Tolerance Test, 1997:

- Fasting glucose 3.9 mmol/l
- 2 hour value 6.6 mmol/l

ie normal by |WHO criteria

Diabetes cured?

- 1995

Wt. = 27stone (173Kg)
BMI = 58.3
Fasting glucose 13.7 mmol/l
Glycosylated haemoglobin 12.7%

- 1997

Wt. = 14.5 stone (93.1Kg)
BMI = 31.5
Random glucose 4.4 mmol/l
Glycosylated haemoglobin 4.4%

Ryder, REJ, Desai, PM. Diabetes and Vascular Disease 2004; 4: 281-282

Nov 1995	Wt. = 173 Kg
Jan 1997	Wt. = 93.1 Kg
May 1998	Wt. = 112.2 Kg
Nov 2000	Wt. = 173 Kg

Ryder, REJ, Desai, PM. Diabetes and Vascular Disease 2004; 4: 281-282

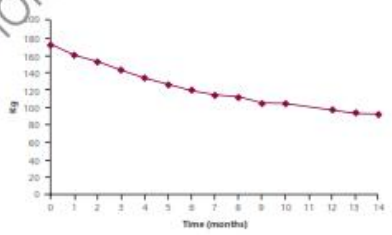
A patient 'cured' of type 2 diabetes mellitus

ROBERT EJ RYDER, PRAKASH M DESAI

Figure 1. Prior to losing weight through diet and exercise the patient weighed 27 stone

Figure 2. The patient and his wife and daughter after losing 12.5 stone. The trousers that he used to wear are displayed

Figure 3. Weight loss over 14 months through strict diet and exercise



Case report

A 43-year-old South-Asian man weighing 172.8 kg (BMI 58.3 kg/m^2) (figure 1) presented with a history of thirst, fatigue and nocturia. Investigation revealed FPG 13.7 mmol/L and HbA_1 12.7%. He was commenced on a sugar free, weight reducing diet. As part of his diabetes education he was told about the anecdote of another patient who in losing 25 kg had gone from diabetes by WHO criteria to IGT. He was very motivated by this story. Over the subsequent 14 months, through a combination of strict dieting and exercise, he managed to lose 80 kg in weight (BMI 31.5 kg/m^2) (figures 2 and 3). At the start of this time he had difficulty walking far, but 14 months later he was walking six miles a day. After the weight loss he had a random blood glucose of 4.4 mmol/L and HbA_1 4.4% (ref. range 3.5–6%) (table 1). A GTT showed that the patient no longer had diabetes (fasting glucose 3.9 mmol/L, two-hour glucose 6.6 mmol/L). Other investigations at this time were (urine albumin/creatinine ratio 1.63 mg/mmol/L, serum cholesterol 3.4 mmol/L, TG 0.59 mmol/L and HDL cholesterol 1.3 mmol/L) within the normal range.

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Br J Diabetes Vasc Dis 2004;**4**:281–2

Prakash Desai

Bob Ryder

Ryder, REJ, Desai, PM. Diabetes and Vascular Disease 2004; 4: 281-282

Diabetologia
DOI 10.1007/s00125-011-2204-7

ARTICLE

Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

E. L. Lim · K. G. Hollingsworth · B. S. Aribisala · M. J. Chen · J. C. Mathers · R. Taylor

Received: 22 March 2011 / Accepted: 5 May 2011

Abstract
Aims/hypothesis Type 2 diabetes is regarded as inevitably progressive, with irreversible beta cell failure. The hypothesis was tested that both beta cell failure and insulin resistance can be reversed by dietary restriction of energy intake.
Methods Eleven people with type 2 diabetes (49.5±2.5 years, BMI 33.6±1.2 kg/m^2, nine male and two female) were studied before and after 1, 4 and 8 weeks of a 2.5 MJ (600 kcal)/day diet. Basal hepatic glucose output, hepatic and peripheral insulin sensitivity and beta cell function were measured. Pancreas and liver triacylglycerol content was measured using three-point Dixon magnetic resonance imaging. An age-, sex- and weight-matched group of eight non-diabetic participants was studied.
Results After 1 week of restricted energy intake, fasting plasma glucose normalised in the diabetic group (from 9.2±0.4 to 5.9±0.4 mmol/l; p=0.003). Insulin suppression of hepatic glucose output improved from 43±4% to 74±5% (p=0.003 vs baseline; controls 68±5%). Hepatic triacylglycerol content fell from 12.8±2.4% in the diabetic group to 2.9±0.2% by week 8 (p=0.003). The first-phase insulin response increased during the study period (0.19±0.02 to 0.46±0.07 nmol min^{-1} m^{-2}; p<0.001) and approached control values (0.62±0.15 nmol min^{-1} m^{-2}; p=0.42). Maximal insulin response became supranormal at 8 weeks (1.37±0.27 vs controls 1.15±0.18 nmol min^{-1} m^{-2}). Pancreatic triacylglycerol decreased from 8.0±1.6% to 6.2±1.1% (p=0.03).
Conclusions/interpretation Normalisation of both beta cell function and hepatic insulin sensitivity in type 2 diabetes was achieved by dietary energy restriction alone. This was associated with decreased pancreatic and liver triacylglycerol stores. The abnormalities underlying type 2 diabetes are reversible by reducing dietary energy intake.

Keywords Insulin secretion · Liver fat · Low energy diet · Pancreatic fat · Type 2 diabetes

Abbreviation
ffm Fat-free mass

Introduction

Type 2 diabetes has long been regarded as a chronic progressive condition, capable of amelioration but not cure. A steady rise in plasma glucose occurs irrespective of the degree of control or type of treatment [1]. Beta cell function declines linearly with time, and after 10 years more than 50% of individuals require insulin therapy [2]. The underlying changes in beta cell function have been well

E. L. Lim · K. G. Hollingsworth · B. S. Aribisala · M. J. Chen · R. Taylor (✉)
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Roy Taylor

Lim EL, et al Diabetologia 2011; 54: 2506-2514

11 patients diabetes <4years duration 600 kcal diet/day diet for 8 weeks:

Variable	**Baseline**	**Week 8**
Weight (kg)	101.5±3.4	88.4±4.3
BMI (Kg/m^2)	33.4±0.9	28.7±1.3
Fat mass (kg)	36.2±2.7	26.3±4.0
Waist circumference (cm)	105.0±1.5	94.2±2.5

Lim EL, et al Diabetologia 2011; 54: 2506-2514

11 patients diabetes <4years duration 600 kcal diet/day diet for 8 weeks:

Fasting concentration	**Baseline**	**Week 8**
HbA1c (%)	7.4±0.3	6.0±0.2
Plasma glucose (mmol/l)	9.2±0.4	5.7±0.5
Plasma insulin (pmol/l)	151±31	65±15
Plasma C-peptide (nmol/l)	1.21±0.20	0.86±0.11
Cholesterol (mmol/l)	4.0±0.3	3.2±0.3
LDL-cholesterol (mmol/l)	1.7±0.2	1.3±0.2
HDL-cholesterol (mmol/l)	1.1±0.1	1.1±0.1
ALT (U/l)	46±7	33±3
Gamma GT (U/l)	62±12	26±5

Lim EL, et al Diabetologia 2011; 54: 2506-2514

11 patients diabetes <4years duration 600 kcal diet/day diet for 8 weeks:

Variable	Baseline	Week 8	
Hepatic insulin sensitivity normalised			
Hepatic triacylglycerol (%)	12.8±2.4	2.9±0.2	p=0.003
Insulin suppression of hepatic glucose output (%)	43±4%	74±5	p=0.003
Beta cell function normalised			
Pancreatic triacylglycerol (%)	8.0±1.6	6.2±1.1	p=0.03
The first-phase insulin response (nmol min-.1 m-2)	0.19±0.02	0.46±0.07	p<0.001
Maximal insulin response (nmol min-.1 m-2)	0.72±0.11	1.37±0.27	p<0.03

Lim EL, et al Diabetologia 2011; 54: 2506-2514

11 patients diabetes <4years duration 600 kcal diet/day diet for 8 weeks:

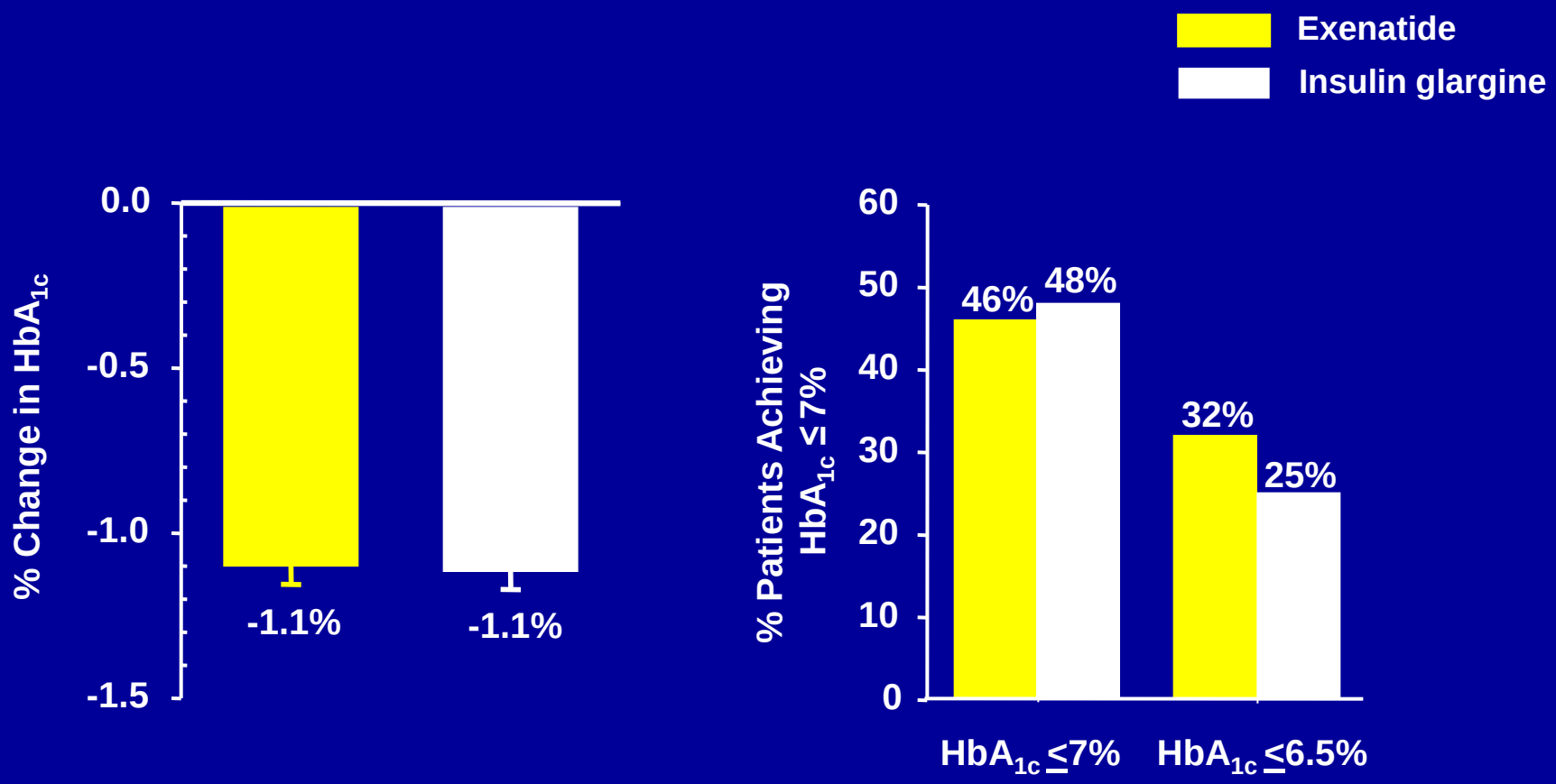
- Decreased liver fat
- Decreased pancreatic fat
- Normalisation of beta cell function
- Normalisation hepatic insulin sensitivity
- Normalisation glucose metabolism
    - ie **“Cure” of type 2 diabetes!**

Lim EL, et al Diabetologia 2011; 54: 2506-2514

Conclusion

- Obesity intimately involved in aetiology of mainstream type 2 diabetes
- In treatment
  - weight loss is a good thing
  - weight increase is a bad thing

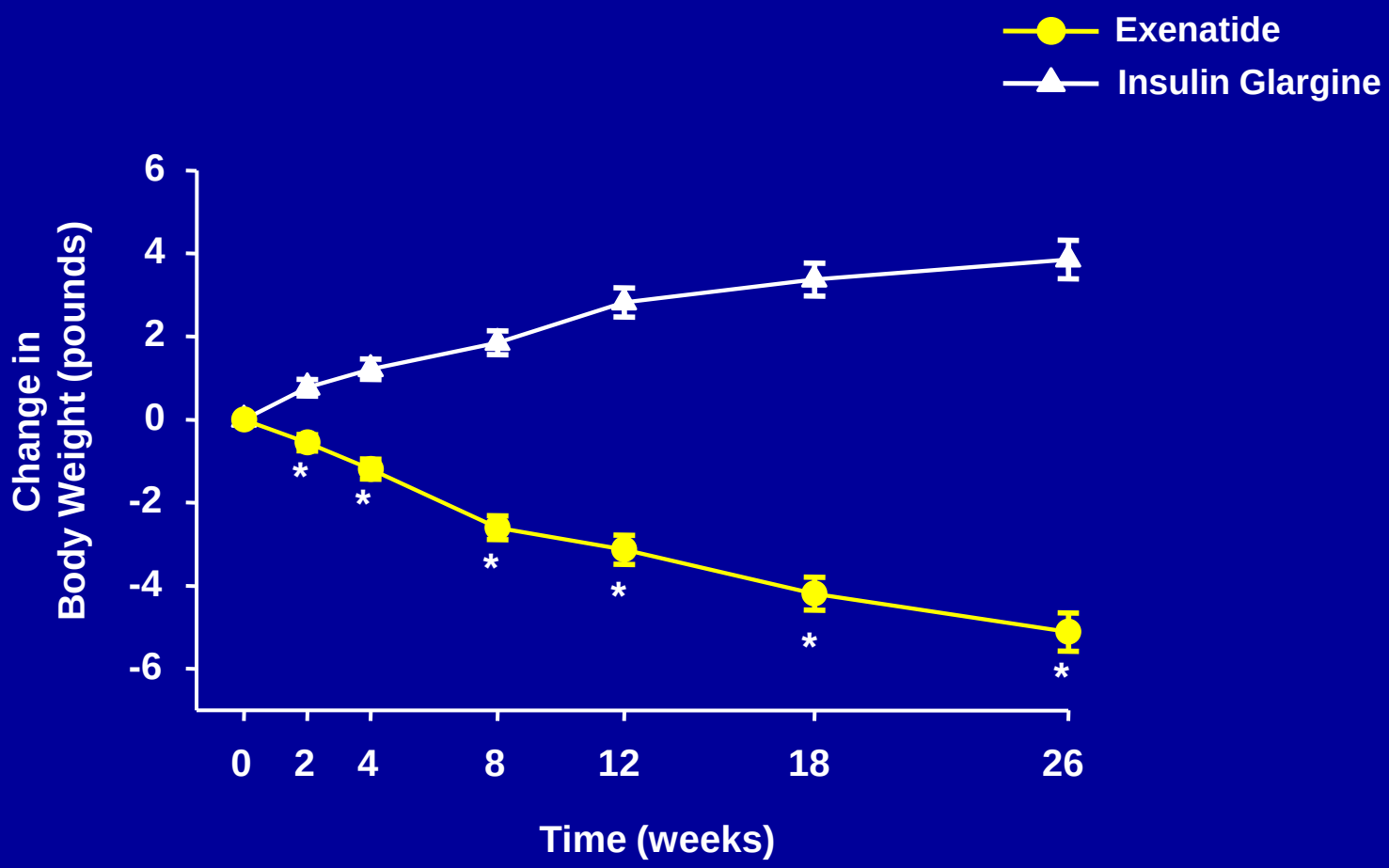
Exenatide/Insulin Glargine Comparator Trial: Achieved Equivalent Reductions in HbA_{1c}



ITT population; Mean ± SE shown.

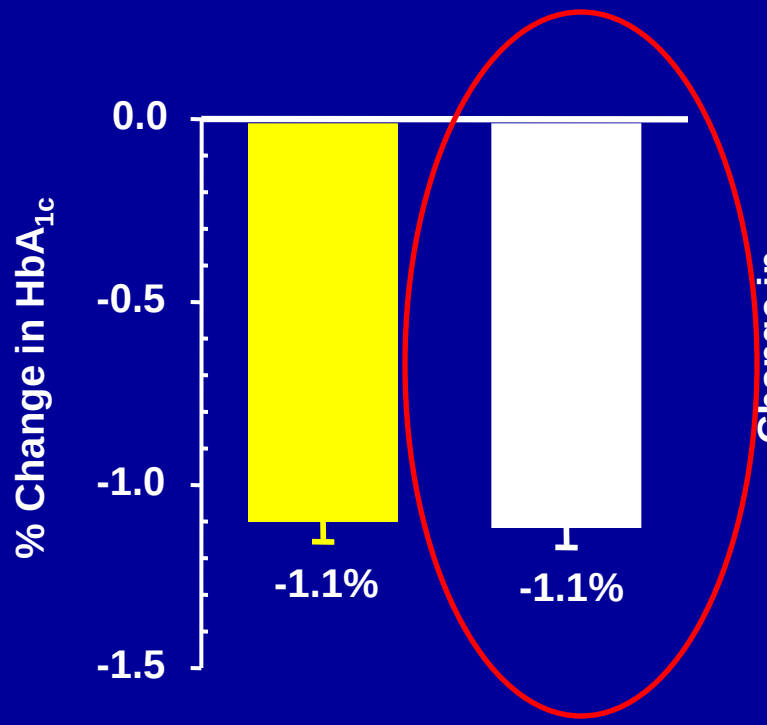
Heine RJ, et al. *Ann Intern Med.* 2005;143:559-569.

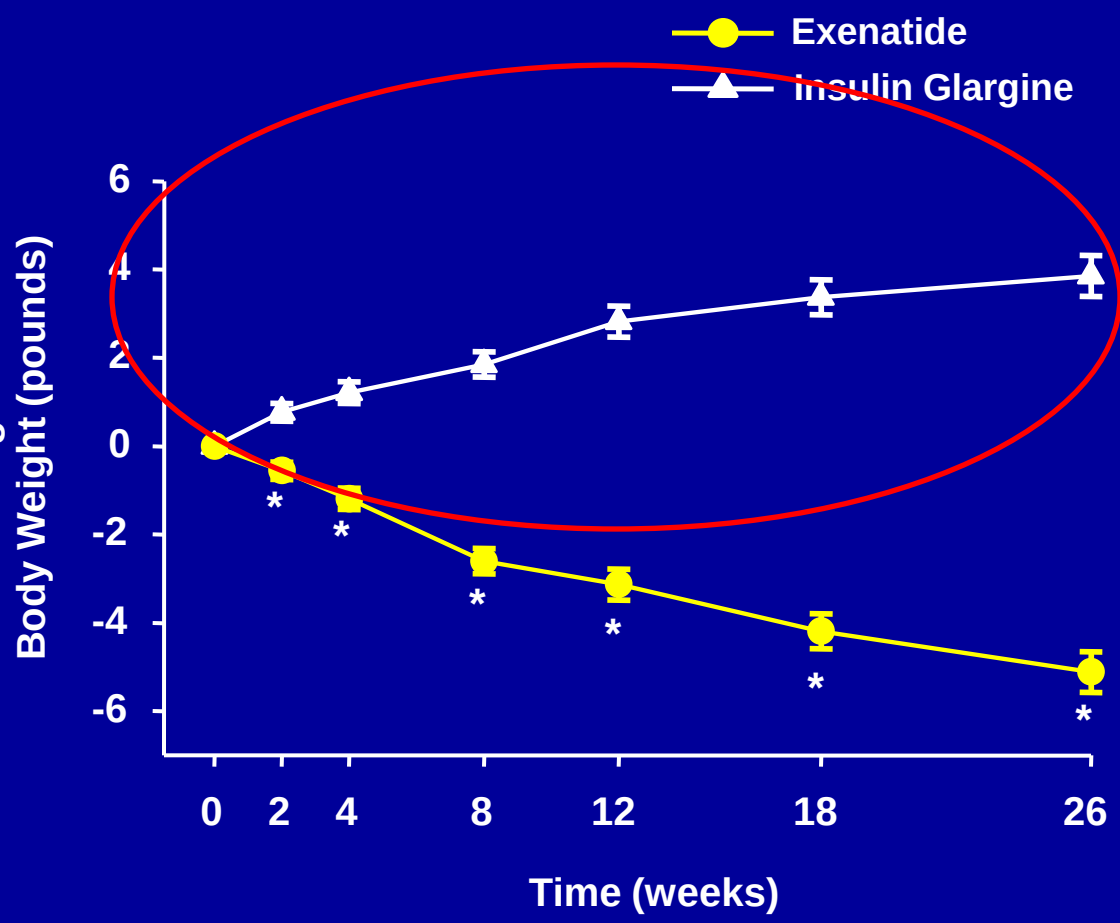
Exenatide/Insulin Glargine Comparator Trial: Exenatide Resulted in Progressive Weight Reductions



ITT population; Mean ± SE shown; *P <0.0001, exenatide vs insulin glargine at same time point.
Heine RJ, et al. *Ann Intern Med*. 2005;143:559-569. Reprinted with permission from The American College of Physicians.

Using insulin in type 2 diabetes (HbA1c down but weight up)





Heine RJ, et al. *Ann Intern Med.* 2005;143:559-569.

- Off licence GLP1 RA
  - unethical
  - unaffordable

"**Exenatide** is licensed in combination with metformin or a sulfonylurea, or both, or with pioglitazone, or with both metformin and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination."

"**Liraglutide** is licensed for the treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. Liraglutide is also licensed for use in combination with both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control.

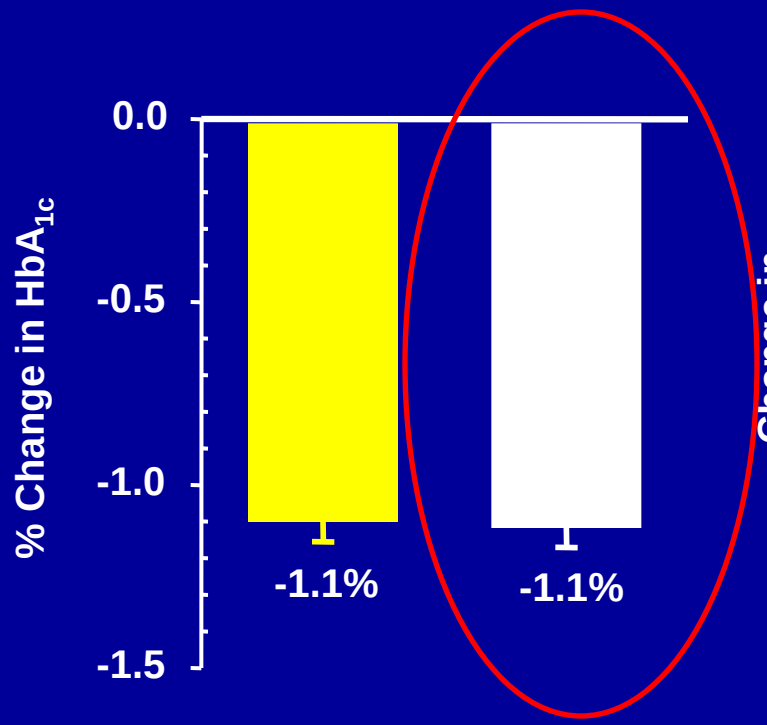
ie neither licensed to add onto triple oral therapy

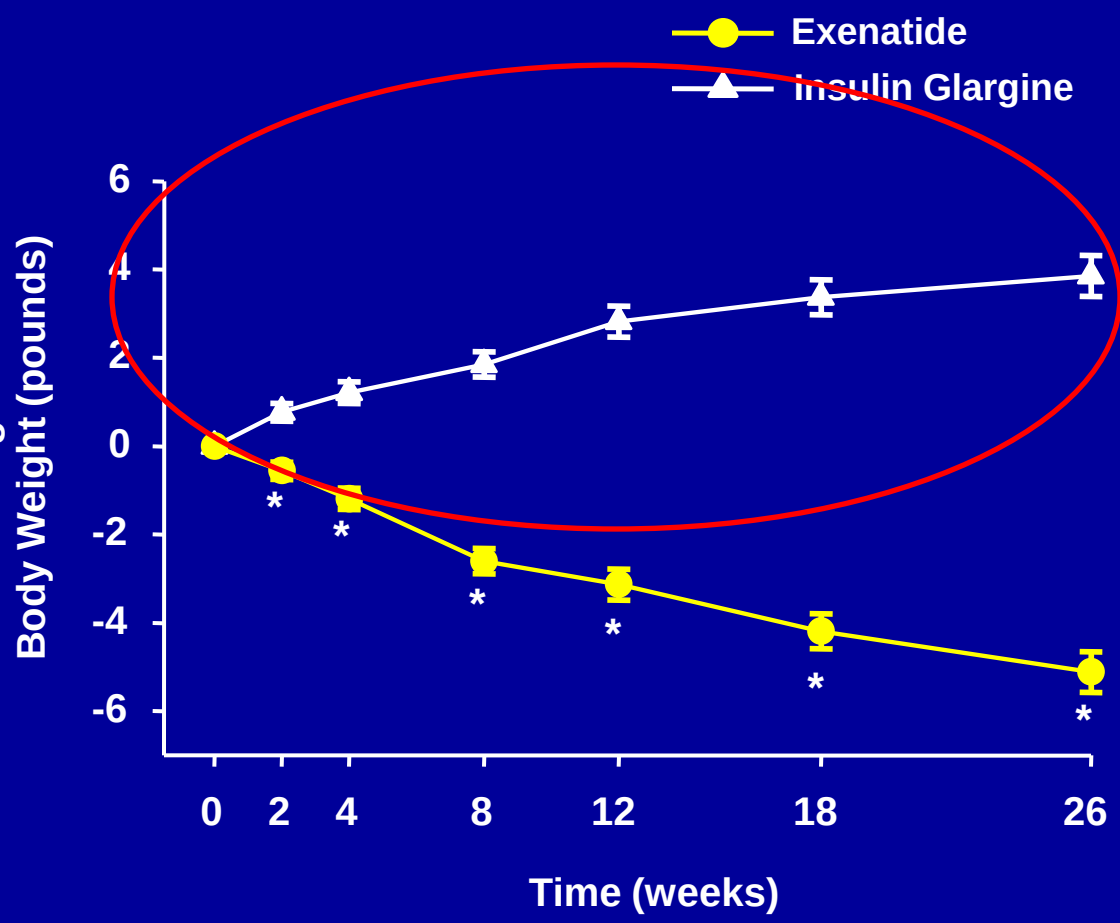
Patient on maximal metformin, sulphonylurea and pioglitazone but HbA1c still elevated

Only licensed option is insulin

What will happen if we use insulin?

Using insulin in type 2 diabetes (HbA1c down but weight up)





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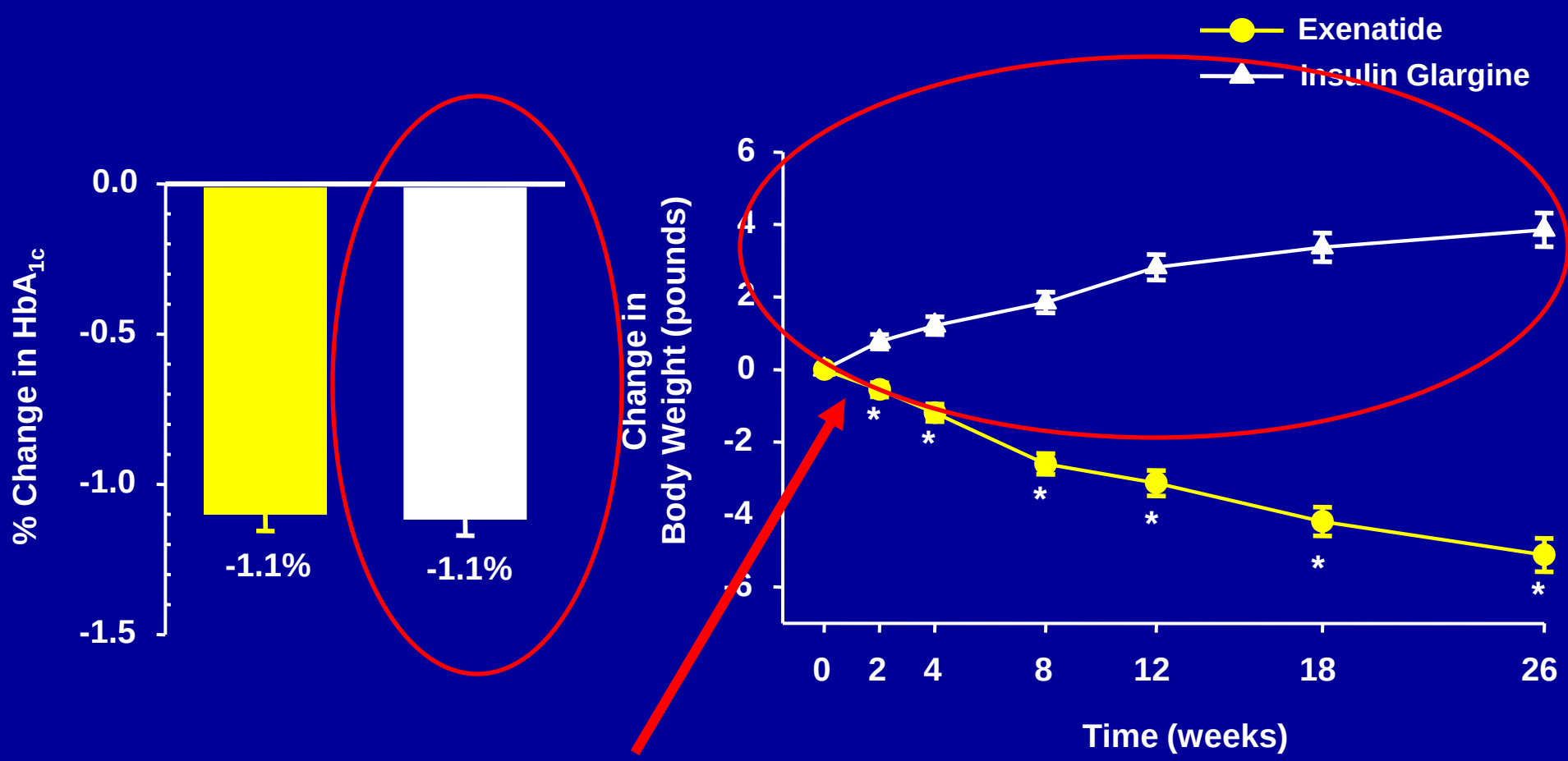
Using insulin in type 2 diabetes (HbA1c down but weight up)



If there is an alternative, this is not ethical!

Heine RJ, et al. *Ann Intern Med.* 2005;143:559-569.

- Off licence GLP1 RA
  - –unethical
  - –unaffordable

- ~~Off licence GLP1 RA~~
- On licence insulin
  - Unethical if alternative available
  - unaffordable

Is there an alternative?

Association of British Clinical Diabetologists

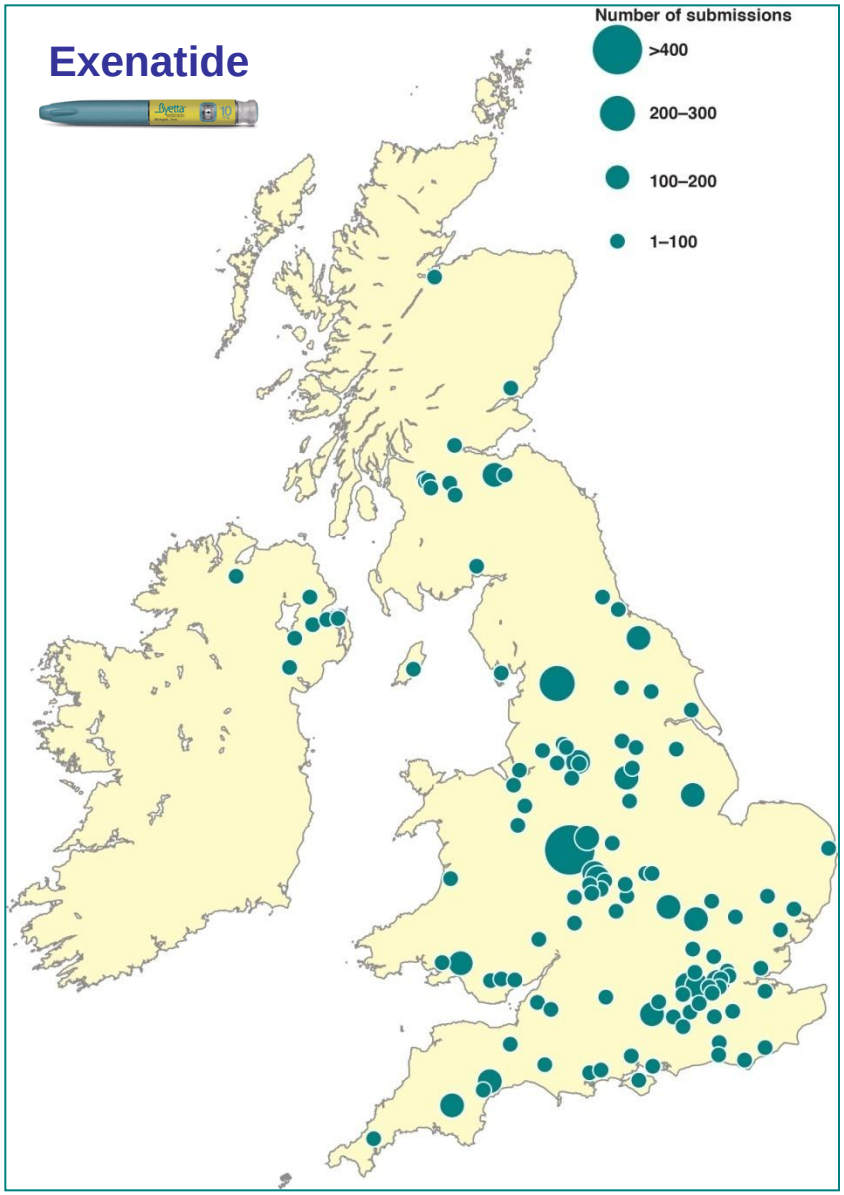
ABCD nationwide exenatide and liraglutide audits

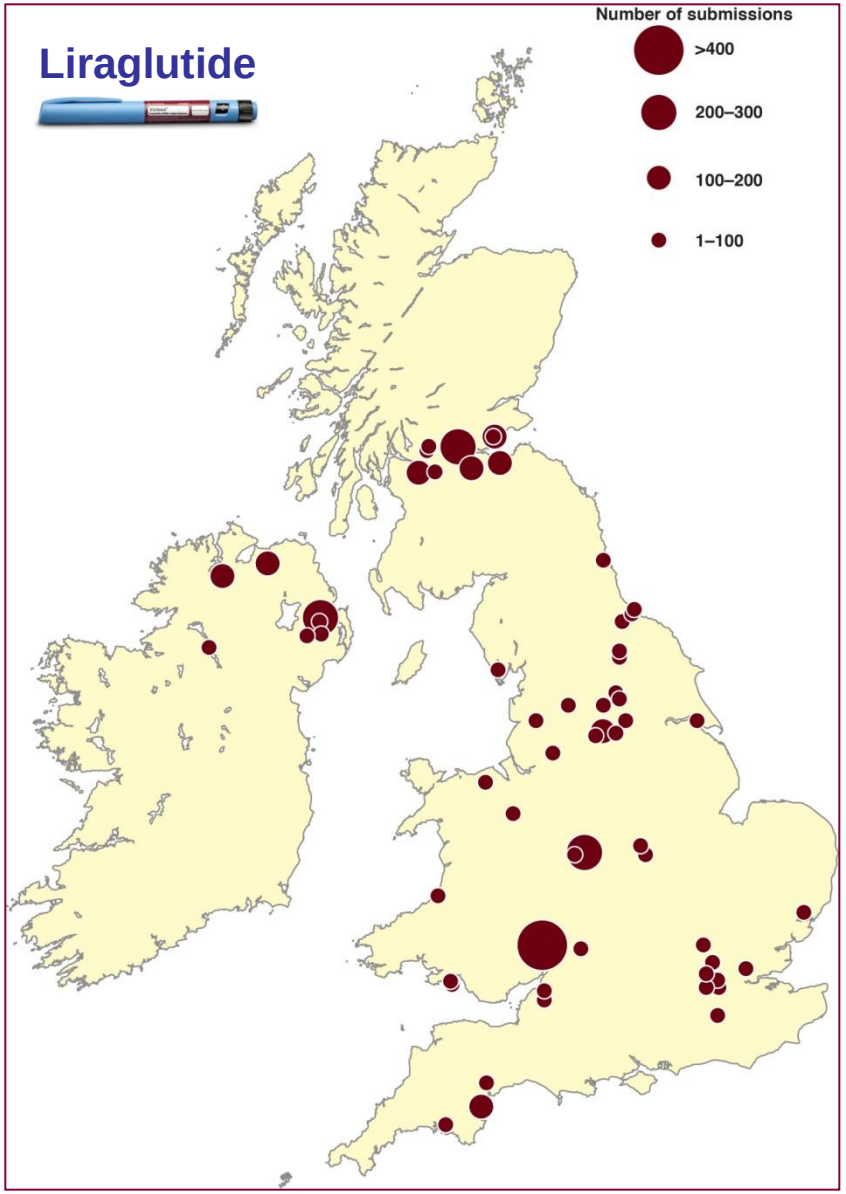
	Exenatide	Liraglutide
Dates of data	2007-2009	2009-2011
Centres	126	77
Contributors	315	265
Patients	6717	4129
Duration of follow-up, median (range)	26 (0 – 159) weeks	26 (0 – 103) weeks

Exenatide audit – final datacut July 2009
Liraglutide audit is ongoing – latest datacut September 2011

ABCD
Association of British Clinical Diabetologists

Nationwide contribution to exenatide and liraglutide national audit





Baseline characteristics

	Exenatide	Liraglutide
n	6717	3247 (from 4129)
Male (%)	54.9	54.6
Caucasian (%)	84.4	90.8
Age (yrs)	54.9 (10.6)	55.5 (11.1)
Diabetes duration (yrs)	8 (5-13)	9 (5-13)
HbA_{1c} (%)	9.47 (1.69)	9.40 (1.73)
Weight (kg)	113.8 (23.4)	110.9 (22.8)
BMI (kg/m^2)	39.8 (8.0)	39.0 (7.4)

Results with mean (SD) and median diabetes duration (inter-quartile range)

Results for exenatide adapted from Ryder *et al. Pract Diab Int* 2010;27:352-357b

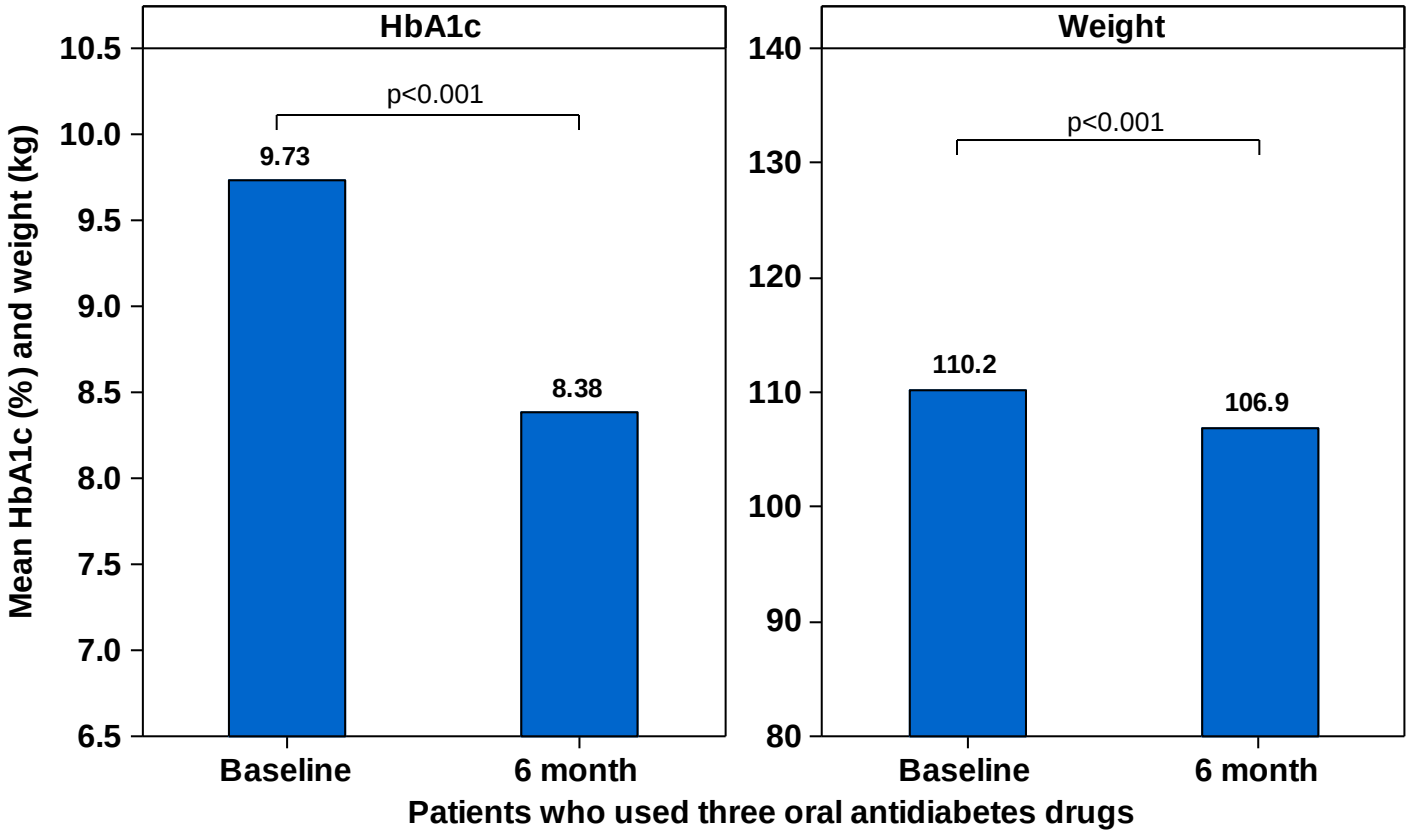
Association of British Clinical Diabetologists

Baseline characteristics – clinical trials versus real clinical use in UK

	Clinical trials combined	Real clinical use in UK (ABCD audit)
	Baseline HbA_{1c} (%)	
Exenatide	8.37	9.47
Liraglutide	8.5	9.40
	Baseline BMI (kg/m^2)	
Exenatide	32.72	39.8
Liraglutide	31	39.0

ABCD
Association of British Clinical Diabetologists

Exenatide or liraglutide added to three oral anti-diabetic medications (combined data from both nationwide audits) (n=142)



-1.35% **-3.3 kg**

Result of off licence use of exenatide and liraglutide in the UK

- Off licence GLP1 RA
  - –unethical
  - –unaffordable

Add on to triple OHA:

- Off licence GLP1 RA
  - ~~Unethical~~
  - The ethical choice
  - unaffordable

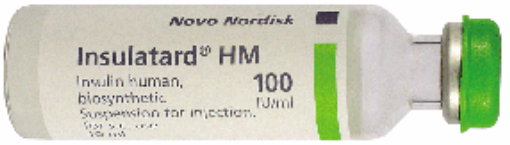
- Off licence GLP1 RA
  - –unethical
  - –unaffordable

Cost equivalence, pens, needles and drug

- Lantus 86 units OD

- Byetta 10ug BD

- Insulatard penfill cartridges
  74 units BD (157 units total)



Treating to Target

Mean HbA1c fell from 9.13% to 7.14% by 9months
Mean dose insulin approximately 70 units

Diabetologia (2006) 49: 442–451
DOI 10.1007/s00125-005-0132-0

ARTICLE

H. Yki-Järvinen · R. Kauppinen-Mäkelin · M. Tikkanen · M. Vähätalo · H. Virtamo · K. Nikkilä · T. Tulokas · S. Hulme · K. Hardy · S. McNulty · J. Hänninen · H. Levänen · S. Lahdenperä · R. Lehtonen · L. Ryysy

Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study

Received: 4 May 2005 / Accepted: 7 November 2005 / Published online: 3 February 2006

Abstract *Aims/hypothesis:* In type 2 diabetic patients we compared 9 months of combination therapy with insulin glargine and metformin with 9 months of NPH insulin combined with metformin. The primary focus was changes in HbA_{1c}; secondary focus was diurnal glucose profiles and symptomatic hypoglycaemia. *Methods:* In this investigator-initiated open, parallel-group clinical trial involving seven centres, 110 insulin-naive type 2 diabetic patients with poor glycaemic control (HbA_{1c} ≥8.0%) on oral hypoglycaemic agents (90% using sulfonylurea plus metformin) were randomised to receive bedtime insulin glargine with metformin (G+MET) or bedtime NPH with metformin (NPH+MET) for 36 weeks. The patients were taught how to self-adjust their insulin dose and use a modem to send the results of home glucose monitoring to treatment centres. The goal was to achieve a fasting plasma glucose (FPG) of 4.0 to 5.5 mmol/l in both groups. *Results:* During the last 12 weeks, FPGs averaged 5.75±0.02 and 5.96±0.03 mmol/l ($p<0.001$) and insulin doses were 68±5 and 70±6 IU/day (0.69±0.05 and 0.66±0.04 IU kg^{-1} day^{-1}, NS) in the G+MET and NPH+MET groups, respectively. At 36 weeks, mean HbA_{1c} was 7.14±0.12 and 7.16±0.14%, respectively (NS). Symptomatic, but not confirmed symptomatic, hypoglycaemia was significantly lower during the first 12 weeks in the G+MET group (4.1±0.8 episodes/patient-year) than in the NPH+MET group (9.0±2.3 episodes/patient-year, $p<0.05$), but not significantly different thereafter. Glucose levels before dinner were higher in the NPH+MET group (10.1±0.3 mmol/l) than in the G+MET group (8.6±0.3 mmol/l, $p=0.002$) throughout the 36-week study. With regard to baseline characteristics such as initial glycaemia or C-peptide, there was no difference between patients who achieved good glycaemic control (HbA_{1c} <7.0%) and those who did not. Differences were seen in the following: between study centres, weight gain during the run-in period and insulin therapy, and FPG during the last 12 weeks (5.7±0.2 vs 6.7±0.3 mmol/l for patients reaching vs those not reaching target, $p<0.01$). *Conclusions/interpretation:* Good glycaemic control can be achieved with both G+MET and NPH+MET. Use of G+MET reduces symptomatic hypoglycaemia during the first 12 weeks and dinnertime hyperglycaemia compared with NPH+MET.

Keywords Glucose · Insulin analogues · Insulin therapy · Metformin · Type 2 diabetes

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Hannele Yki-Jarvinen

Yki-Jarvinen et al, Diabetologia 2006; 49: 442-451

Treating to Target

Emerging Treatments and Technologies
ORIGINAL ARTICLES

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

MATTHEW C. RIDDLE, MD[1]
JULIO ROSENSTOCK, MD[2]
JOHN GERICH, MD[3]

ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

OBJECTIVE — To compare the abilities and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA_{1c}.

RESEARCH DESIGN AND METHODS — In a randomized, open-label, parallel, 24-week multicenter trial, 756 overweight men and women with inadequate glycemic control (HbA_{1c} >7.5%) on one or two oral agents continued prestudy oral agents and received bedtime glargine or NPH once daily, titrated using a simple algorithm seeking a target fasting plasma glucose (FPG) ≤100 mg/dl (5.5 mmol/l). Outcome measures were FPG, HbA_{1c}, hypoglycemia, and percentage of patients reaching HbA_{1c} ≤7% without documented nocturnal hypoglycemia.

RESULTS — Mean FPG at end point was similar with glargine and NPH (117 vs. 120 mg/dl [6.5 vs. 6.7 mmol/l]), as was HbA_{1c} (6.96 vs. 6.97%). A majority of patients (~60%) attained HbA_{1c} ≤7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (≤72 mg/dl [4.0 mmol/l]) with glargine (33.2 vs. 26.7%, $P < 0.05$). Moreover, rates of other categories of symptomatic hypoglycemia were 21–48% lower with glargine.

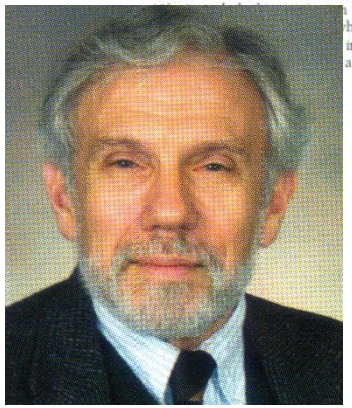
CONCLUSIONS — Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% HbA_{1c} in a majority of overweight patients with type 2 diabetes with HbA_{1c} between 7.5 and 10.0% on oral agents alone. In doing this, glargine causes significantly less nocturnal hypoglycemia than NPH, thus reducing a leading barrier to initiating insulin. This simple regimen may facilitate earlier and effective insulin use in routine medical practice, improving achievement of recommended standards of diabetes care.

Diabetes Care 26:3080–3086, 2003

Type 2 diabetes is a progressive disorder of β-cell dysfunction. Patients using oral therapy for it seldom achieve and maintain the recommended 7% HbA_{1c} goal (1,2) for glycemic control and are exposed to increasing risks of diabetic complications as control worsens over time (3–5). The U.K. Prospective Diabetes Study (UKPDS) (6) showed that intensive treatment can reduce these clinical risks, and a recently reported substudy of the UKPDS (7) confirmed that early addition of insulin to oral therapy can safely keep HbA_{1c} close to 7% in the first 6 years after diagnosis.

However, the majority of patients with a longer duration of diabetes remain poorly controlled with oral agents, and use of insulin, which could improve glycemic control, is often long delayed and not aggressive enough. The reluctance to initiate insulin therapy seems partly due to its perceived complexity, the belief that insulin is not effective for type 2 diabetes (8), and fear of hypoglycemia, which may be the greatest barrier (9).

A regimen that may make initiation of insulin simpler and more effective has been tested in several small studies (10–



Julio Rosenstock Matthew Riddle

58% achieved HbA1c =< 7%

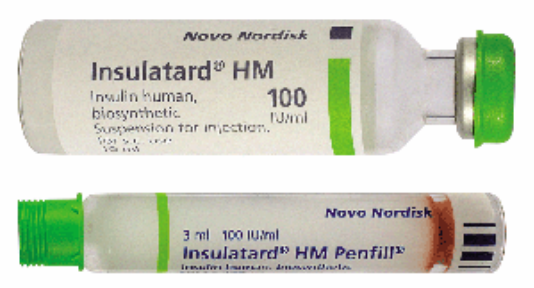
This means 42% didn't – what happens to those who don't:

Riddle et al, Diabetes Care 2003; 26: 3080-3086

- 325 units insulin daily (insulin aspart and isophane) with pioglitazone and metformin
- HbA1c = 6.7%

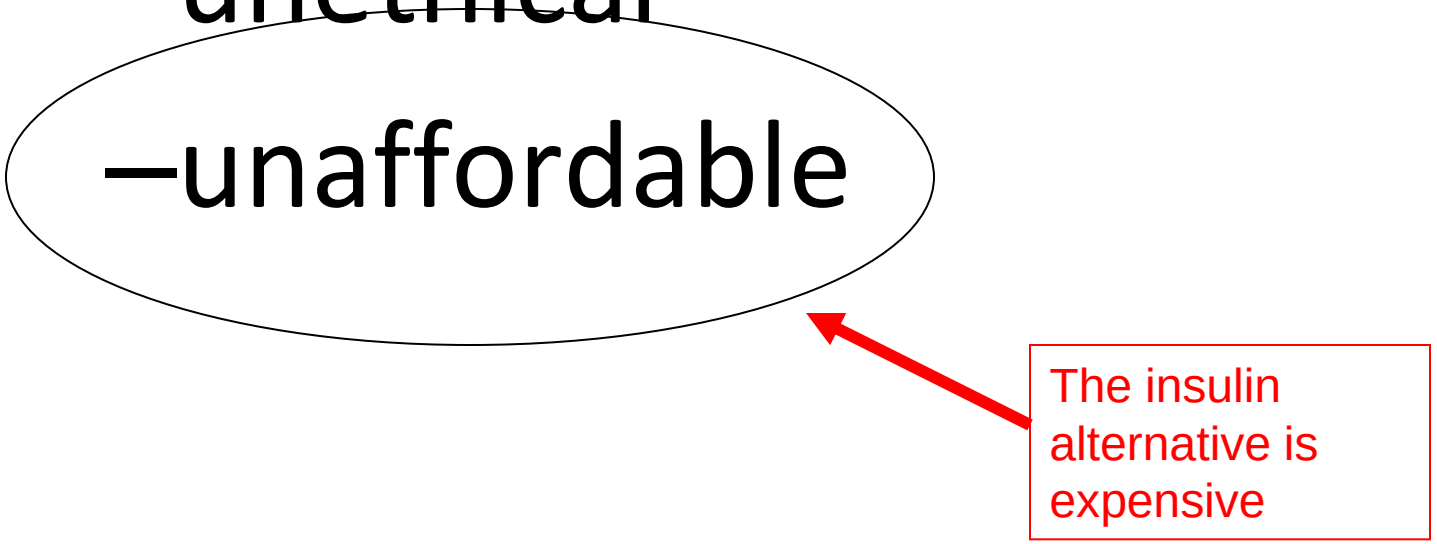
Can easily get onto very high doses of insulin in overweight, insulin resistant patients

True cost of insulin



- The insulin and needles
- Home blood glucose monitoring (may not be required with GLP1)
- Regular, often frequent, consultations with health care professionals (very expensive)

- Off licence GLP1 RA
  - –unethical
  - –unaffordable



"**Exenatide** is licensed in combination with metformin or a sulfonylurea, or both, or with pioglitazone, or with both metformin and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination."

"**Liraglutide** is licensed for the treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. Liraglutide is also licensed for use in combination with both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control.

ie not licensed to use with insulin as of March 2012

Chris Walton

Peter Winocour

Patrick Sharp

Rob Gregory

Ketan Dhatariya

Yoon Loke

Conscientious doctor

Overweight patient on insulin who might have responded to GLP1 receptor agonist

Chris Walton

Peter Winocour

Patrick Sharp

Rob Gregory

Ketan Dhatariya

Yoon Loke

Conscientious doctor

Overweight patient on insulin who might have responded to GLP1 receptor agonist

What should the conscientious doctor do?

One possibility is to switch from insulin to GLP1 receptor agonist in order to stay within licence

- Some doctors in the ABCD nationwide audits did this
- Especially the exenatide audit
- What happened? :

ABCD nationwide exenatide audit

original article

Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit*

K. Y. Thong[1], B. Jose[1], N. Sukumar[1], M. L. Cull[1], A. P. Mills[1], T. Sathyapalan[2], W. Shafiq[2], A. S. Rigby[2], C. Walton[2] & R. E. J. Ryder[1] on behalf of the ABCD nationwide exenatide audit contributors†

[1]Department of Diabetes, City Hospital, Birmingham, UK
[2]Department of Diabetes, Hull Royal Infirmary, Hull, UK

ORIGINAL ARTICLE

Aim: To assess the extent, safety, efficacy and tolerability of reported off-licence exenatide use through a nationwide audit.

Methods: The Association of British Clinical Diabetologists hosted a password-protected, online collection of anonymized data of exenatide use in real clinical practice. Three hundred and fifteen contributors from 126 centres across UK provided data on 6717 patients. HbA1c and weight changes, exenatide discontinuation, adverse events and treatment satisfaction were compared between non-insulin and insulin-treated patients.

Results: Four thousand eight hundred and fifty-seven patients had baseline and follow-up treatment status with mean (±s.d.) baseline HbA1c 9.45 ± 1.69% and BMI 40.0 ± 8.2 kg/m². Of the 4857 patients, 1921 (39.6%) used exenatide with insulin. Comparing patients who continued insulin with exenatide with non-insulin-treated patients, mean (±s.e.) latest HbA1c and weight reduction (median 26 weeks) were 0.51 ± 0.06 versus 0.94 ± 0.04% ($p < 0.001$) and 5.8 ± 0.2 versus 5.5 ± 0.1 kg ($p = 0.278$). Insulin-treated patients had higher rates of exenatide discontinuation (31.0 vs. 13.9%, $p < 0.001$), hypoglycaemia (8.9 vs. 6.1%, $p < 0.001$), gastrointestinal side effects (28.4 vs. 25.0%, $p = 0.008$) and treatment dissatisfaction (20.8 vs. 5.7%, $p < 0.001$). However, 34.2% of the patients continuing insulin still achieved HbA1c reduction ≥1%. There was significant insulin discontinuation, dose reduction and greater sulphonylurea discontinuation among insulin-treated patients.

Conclusions: Addition of exenatide to obese, insulin-treated patients can improve glycaemia and weight. Adverse events were statistically but probably not clinically significantly higher, but combination treatment was less well tolerated. Overall, exenatide was less effective in lowering HbA1c among insulin-treated patients, although significant number of insulin-treated patients still achieved significant HbA1c, weight and insulin reductions. Further research into identifying obese, insulin-treated patients who will tolerate and benefit from exenatide treatment is urgently needed.

Keywords: exenatide, GLP-1 analogue, incretin therapy, insulin therapy, type 2 diabetes

Date submitted 29 December 2010; date of first decision 7 February 2011; date of final acceptance 9 March 2011

Introduction

Exenatide, a GLP-1 agonist, has proven efficacy in combination with various oral diabetes treatment in the management of type 2 diabetes [1–4]. In the UK, the National Institute for Health and Clinical Excellence has endorsed its use mainly as third-line treatment in patients with BMI ≥35 kg/m² [5]. However, exenatide is not licensed for use in combination with insulin, with insulin treatment being, in essence, considered a surrogate marker of significant β-cell decline [6]. With as many as 27.4% of patients with type 2 diabetes treated with insulin in a population-based study [7], this potentially excludes exenatide

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E-mail: kythong@gmail.com

*The intention-to-treat HbA1c and weight data of patients analysed in this article were presented as a poster in the 46th EASD 2010 Annual Meeting in Stockholm.

†See Appendix for list of contributors to the ABCD nationwide exenatide audit.

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International Diabetes Federation

Brief report

Response at 3 months to insulin dose decisions made at exenatide initiation in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit

K.Y. Thong[a,1,*], B. Jose[a,1], A.D. Blann[a,1], M.L. Cull[a,1], A.P. Mills[a,1], T. Sathyapalan[b,1], C. Walton[b,1], R.E.J. Ryder[a,1]

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ABSTRACT

It is uncertain what should be done with insulin dose if starting exenatide. In the ABCD nationwide exenatide audit, many patients with type 2 diabetes had worsened glycaemia when insulin was stopped. If starting exenatide, insulin should not be stopped but weaned off only if there is significant glycaemic response.

made at exenatide initiation on treatment response at three months.

2. Subjects and methods

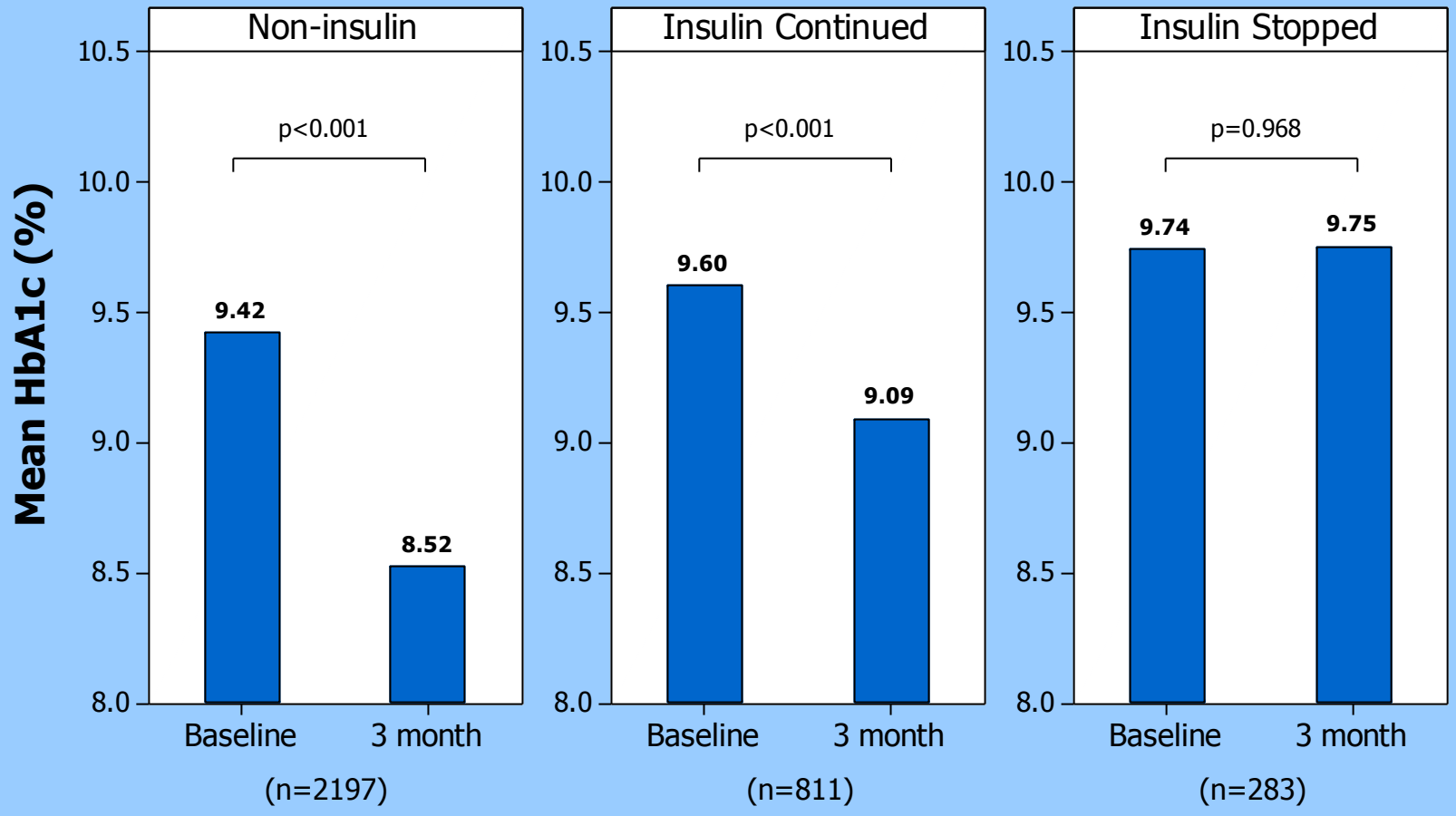
ABCD is a national diabetes specialist society. From December 2008 to December 2009, diabetes physicians across UK submitted anonymised audit data electronically on patients commenced on exenatide therapy. 315 contributors from 126 centres submitted data on 6717 patients. Among other

Ken Thong Bob Ryder

Thong KY et al. Diabetes, Obesity and Metabolism 2011; 13(8): 703-720

Thong KY et al. Diabetes Research and Clinical Practice 2011; 93(2): e87-e91

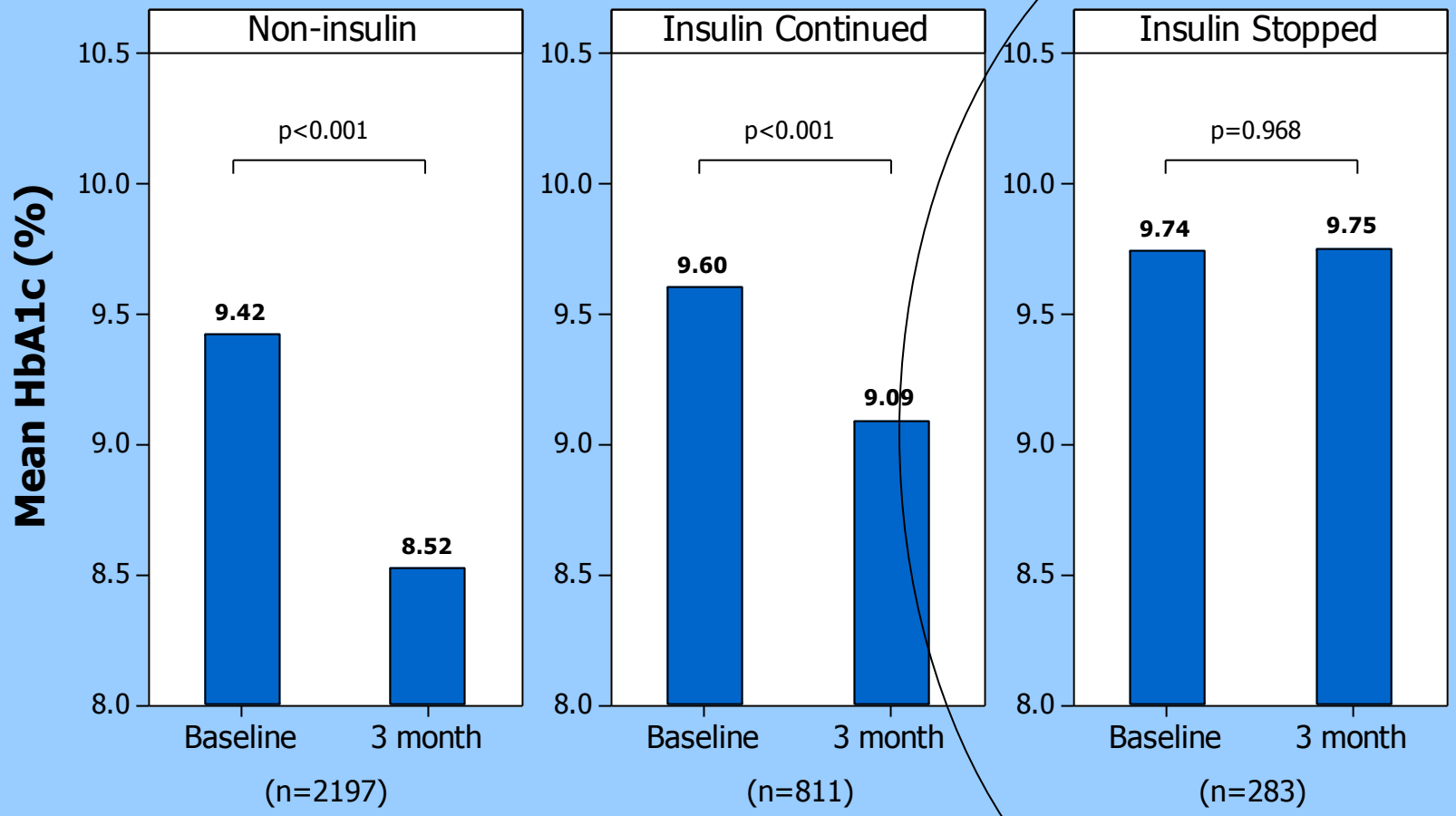
Baseline vs 3 month HbA1c with exenatide treatment comparing groups of insulin use



Mean change

-0.90% **-0.51%** **+0.00%**

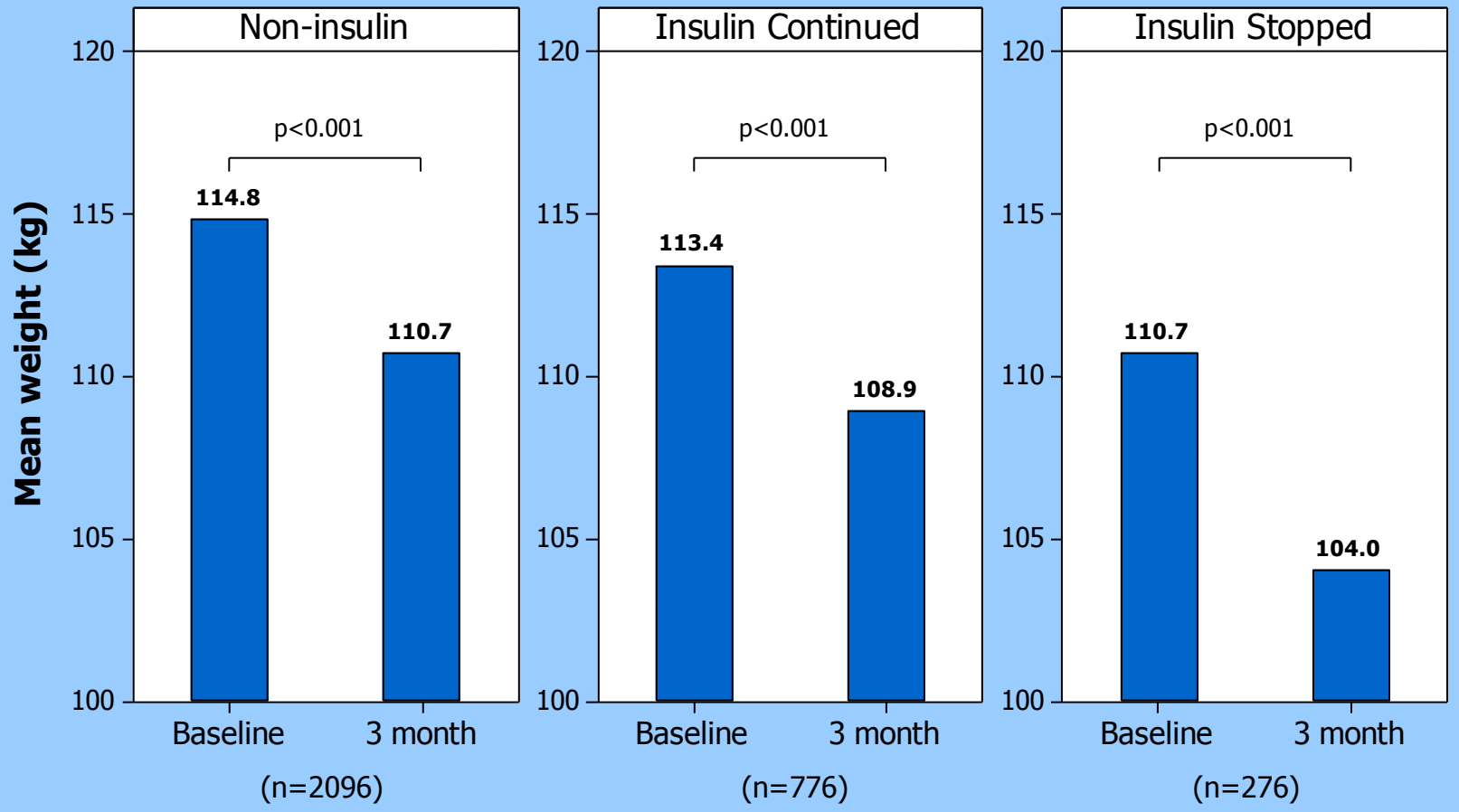
Baseline vs 3 month HbA1c with exenatide treatment comparing groups of insulin use



Mean change

-0.90% **-0.51%** **+0.00%**

Baseline vs 3 month weight with exenatide treatment comparing groups of insulin use



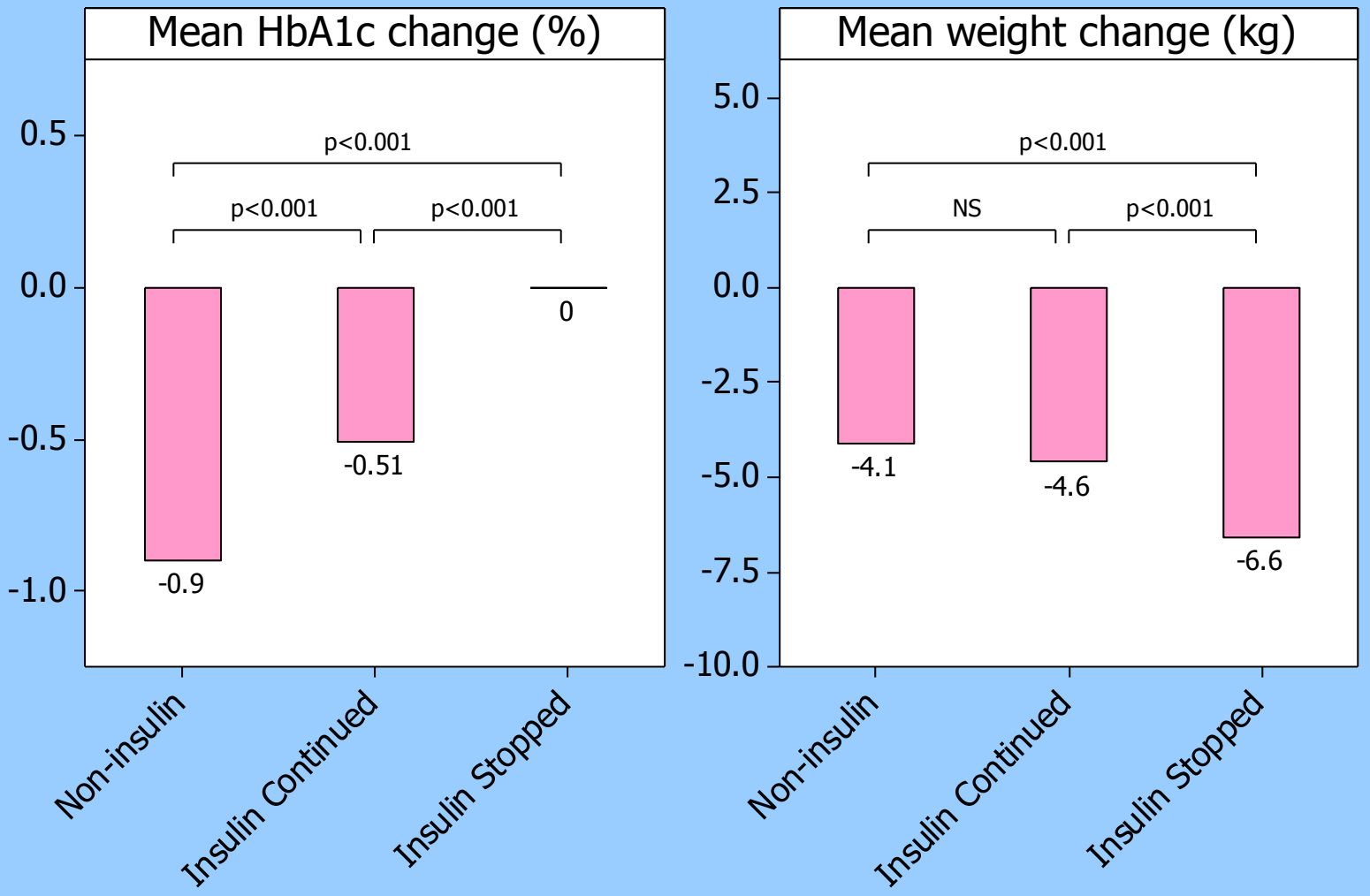
Mean change

-4.1 kg

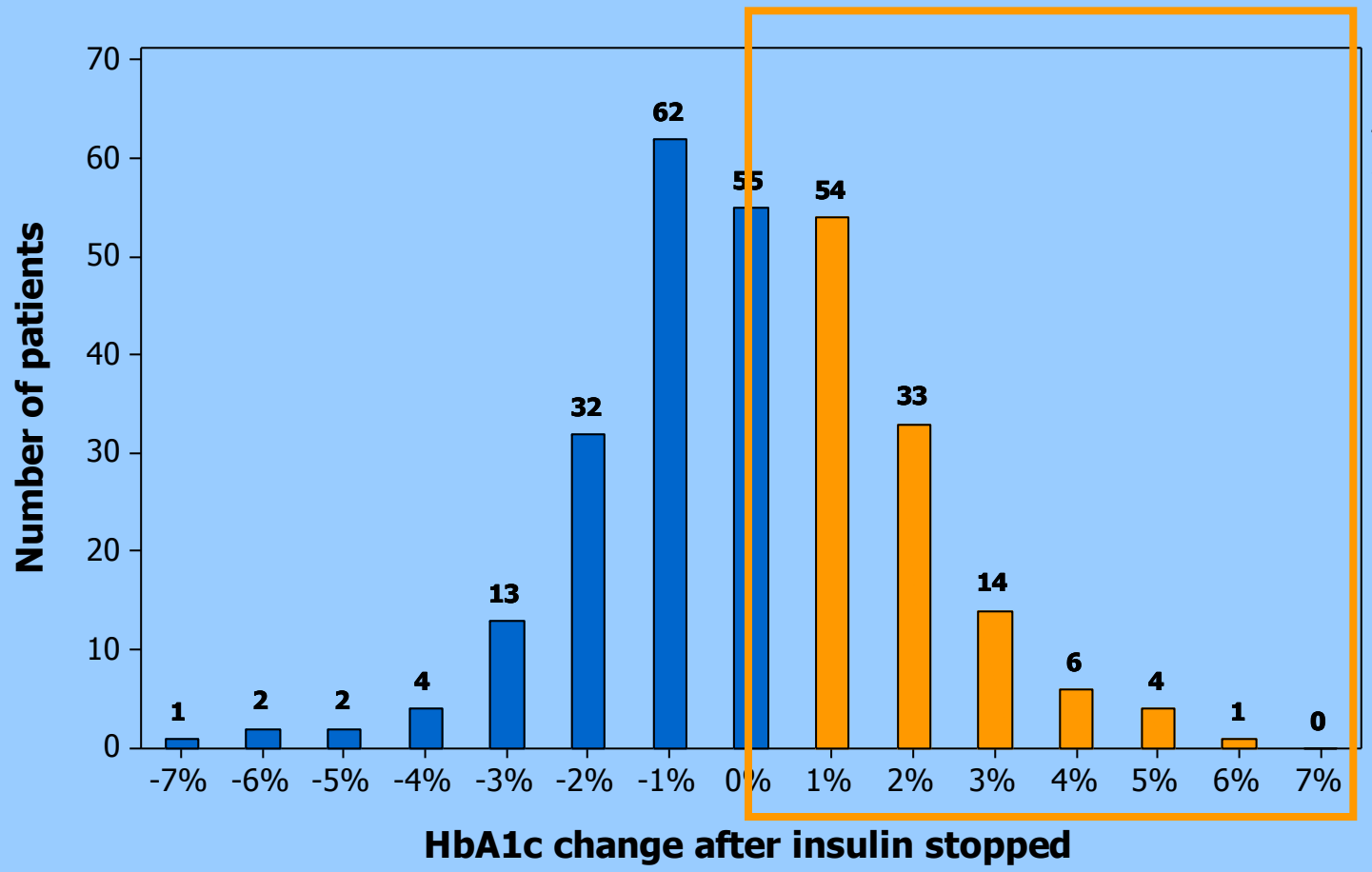
-4.6 kg

-6.6 kg

HbA1c and weight changes at 3 months with exenatide comparing groups of insulin use



HbA1c change at 3 months after exenatide start in insulin stopped group



Total number of patients who stopped insulin at exenatide initiation with HbA1c = 283

Increased HbA1c>0% = 137 (48.4%)

Increased HbA1c≥1% = 82 (29.0%)

Increased HbA1c≥2% = 43 (15.2%)

Groups of HbA1c represent changes of ±0.5%

ABCD nationwide exenatide audit

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Keywords:
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ABSTRACT

It is uncertain what should be done with insulin dose if starting exenatide. In the ABCD nationwide exenatide audit, many patients with type 2 diabetes had worsened glycaemia when insulin was stopped. If starting exenatide, insulin should not be stopped but weaned off only if there is significant glycaemic response.

1. Introduction

Exenatide, a GLP-1 agonist, is not licensed for use in insulin-treated patients with type 2 diabetes [1]. In the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit, many physicians stopped patients' insulin when starting exenatide to stay within licensing restriction. Some reduced insulin to facilitate weight loss or avoid hypoglycaemia. However, these risked worsening glycaemic control in patients. We examined the effects of insulin dose decisions made at exenatide initiation on treatment response at three months.

2. Subjects and methods

ABCD is a national diabetes specialist society. From December 2008 to December 2009, diabetes physicians across UK submitted anonymised audit data electronically on patients commenced on exenatide therapy. 315 contributors from 126 centres submitted data on 6717 patients. Among other

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[1] On behalf of the ABCD nationwide exenatide contributors (see Appendix A).
0168-8227/$ – see front matter
doi:10.1016/j.diabres.2011.05.015

- "There were 11 reported cases of ketosis or diabetic ketoacidosis in the audit, seven of these cases occurred in patients who stopped insulin at exenatide initiation."

Thong KY et al. Diabetes Research and Clinical Practice 2011; 93(2): e87-e91

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- "There were 11 reported cases of ketosis or diabetic ketoacidosis in the audit, seven of these cases occurred in patients who stopped insulin at exenatide initiation."
- Stopping insulin to stay within licence is unethical

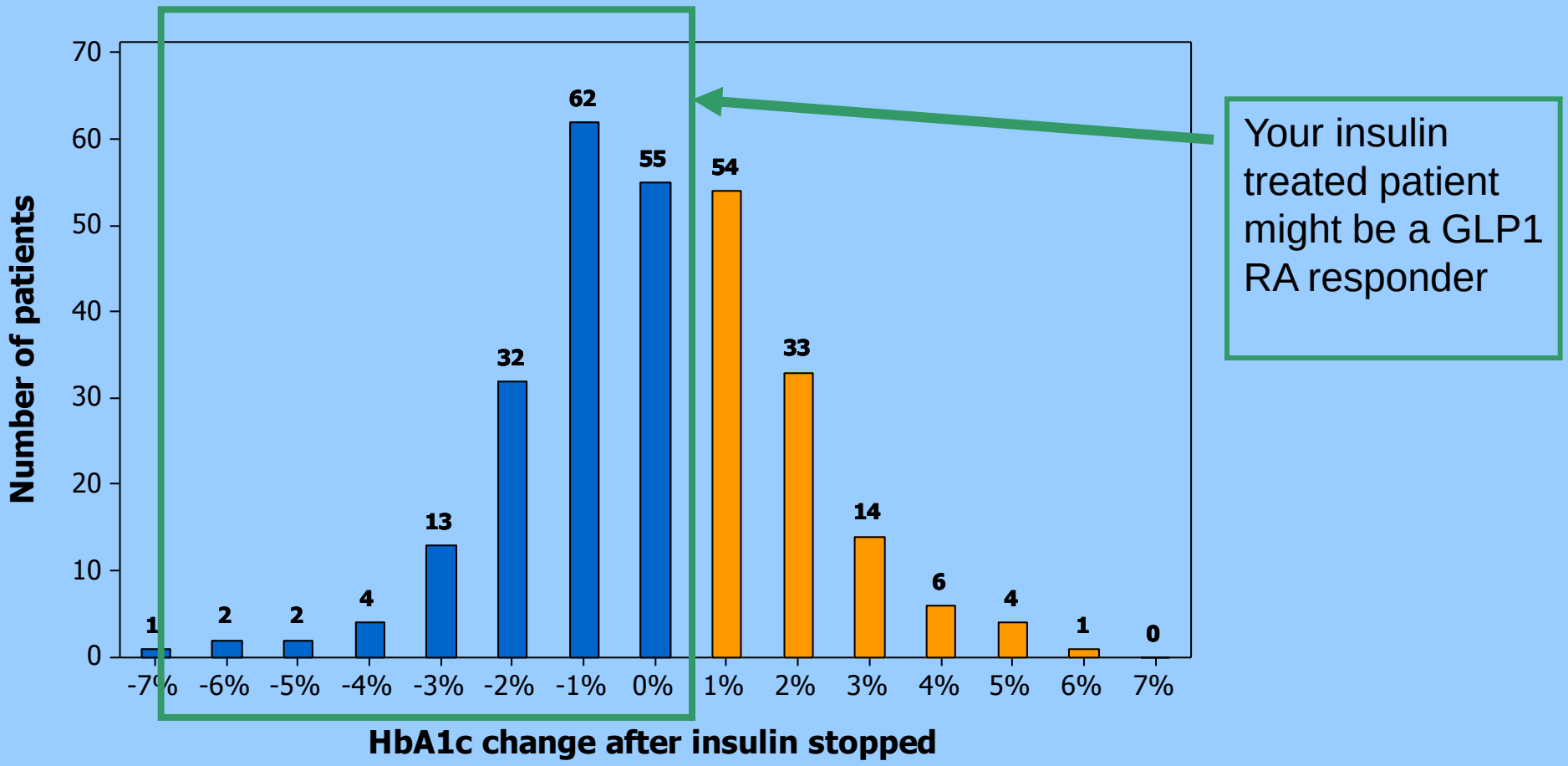
Thong KY et al. Diabetes Research and Clinical Practice 2011; 93(2): e87-e91

- Off license GLP1 RA
  - –unethical
  - –unaffordable

Insulin treated patients:

- ~~Off license GLP1 RA~~
- Stopping insulin to stay in licence
  - Unethical
  - unaffordable

HbA1c change at 3 months after exenatide start in insulin stopped group



Your insulin treated patient might be a GLP1 RA responder

Groups of HbA1c represent changes of ±0.5%

ABCD nationwide exenatide audit

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doi:10.1016/j.diabres.2011.05.015

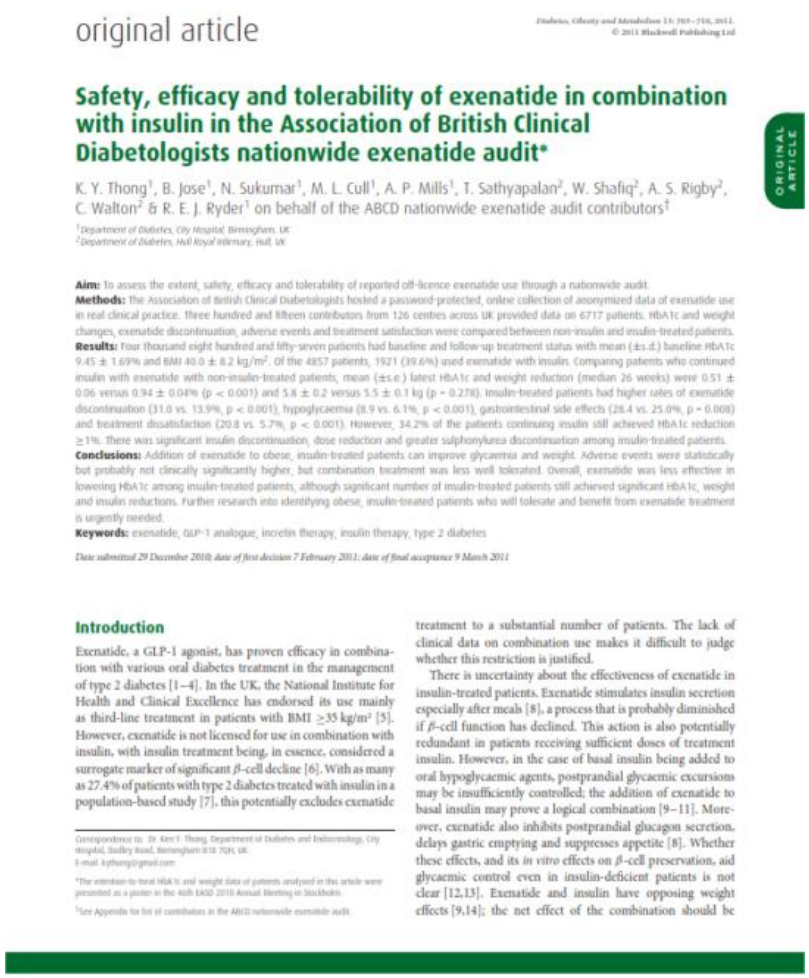
- "The glycaemic response of stopping insulin when starting exenatide is heterogeneous; many patients had worsening glycaemic control when insulin was stopped.
- If starting exenatide in insulin-treated patients, it appears prudent in most patients to continue insulin, and only to wean patients off insulin if there was significant glycaemic response."

Thong KY et al. Diabetes Research and Clinical Practice 2011; 93(2): e87-e91

Insulin treated patients:

- Off licence GLP1 RA
  - –Adding GLP1 RA to insulin the ethical choice
  - –unaffordable

ABCD nationwide exenatide audit



original article

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Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit*

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ORIGINAL ARTICLE

Aim: To assess the extent, safety, efficacy and tolerability of reported off-licence exenatide use through a nationwide audit.
Methods: The Association of British Clinical Diabetologists hosted a password-protected, online collection of anonymized data of exenatide use in real clinical practice. Three hundred and fifteen contributors from 126 centres across UK provided data on 6717 patients. HbA1c and weight changes, exenatide discontinuation, adverse events and treatment satisfaction were compared between non-insulin and insulin-treated patients.
Results: Four thousand eight hundred and fifty-seven patients had baseline and follow-up treatment status with mean (±s.d.) baseline HbA1c 9.45 ± 1.69% and BMI 40.0 ± 8.2 kg/m². Of the 4857 patients, 1921 (39.6%) used exenatide with insulin. Comparing patients who continued insulin with exenatide with non-insulin-treated patients, mean (±s.e.) latest HbA1c and weight reduction (median 26 weeks) were 0.51 ± 0.06 versus 0.94 ± 0.04% ($p < 0.001$) and 5.8 ± 0.2 versus 5.5 ± 0.1 kg ($p = 0.278$). Insulin-treated patients had higher rates of exenatide discontinuation (31.0 vs. 13.9%, $p < 0.001$), hypoglycaemia (8.9 vs. 6.1%, $p < 0.001$), gastrointestinal side effects (28.4 vs. 25.0%, $p = 0.008$) and treatment dissatisfaction (20.8 vs. 5.7%, $p < 0.001$). However, 34.2% of the patients continuing insulin still achieved HbA1c reduction ≥1%. There was significant insulin discontinuation, dose reduction and greater sulphonylurea discontinuation among insulin-treated patients.
Conclusions: Addition of exenatide to obese, insulin-treated patients can improve glycaemia and weight. Adverse events were statistically but probably not clinically significantly higher, but combination treatment was less well tolerated. Overall, exenatide was less effective in lowering HbA1c among insulin-treated patients, although significant number of insulin-treated patients still achieved significant HbA1c, weight and insulin reductions. Further research into identifying obese, insulin-treated patients who will tolerate and benefit from exenatide treatment is urgently needed.
Keywords: exenatide, GLP-1 analogue, incretin therapy, insulin therapy, type 2 diabetes

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Introduction

Exenatide, a GLP-1 agonist, has proven efficacy in combination with various oral diabetes treatment in the management of type 2 diabetes [1–4]. In the UK, the National Institute for Health and Clinical Excellence has endorsed its use mainly as third-line treatment in patients with BMI ≥35 kg/m² [5]. However, exenatide is not licensed for use in combination with insulin, with insulin treatment being, in essence, considered a surrogate marker of significant β-cell decline [6]. With as many as 27.4% of patients with type 2 diabetes treated with insulin in a population-based study [7], this potentially excludes exenatide treatment to a substantial number of patients. The lack of clinical data on combination use makes it difficult to judge whether this restriction is justified.

There is uncertainty about the effectiveness of exenatide in insulin-treated patients. Exenatide stimulates insulin secretion especially after meals [8], a process that is probably diminished if β-cell function has declined. This action is also potentially redundant in patients receiving sufficient doses of treatment insulin. However, in the case of basal insulin being added to oral hypoglycaemic agents, postprandial glycaemic excursions may be insufficiently controlled; the addition of exenatide to basal insulin may prove a logical combination [9–11]. Moreover, exenatide also inhibits postprandial glucagon secretion, delays gastric emptying and suppresses appetite [8]. Whether these effects, and its *in vitro* effects on β-cell preservation, aid glycaemic control even in insulin-deficient patients is not clear [12,13]. Exenatide and insulin have opposing weight effects [9,14]; the net effect of the combination should be

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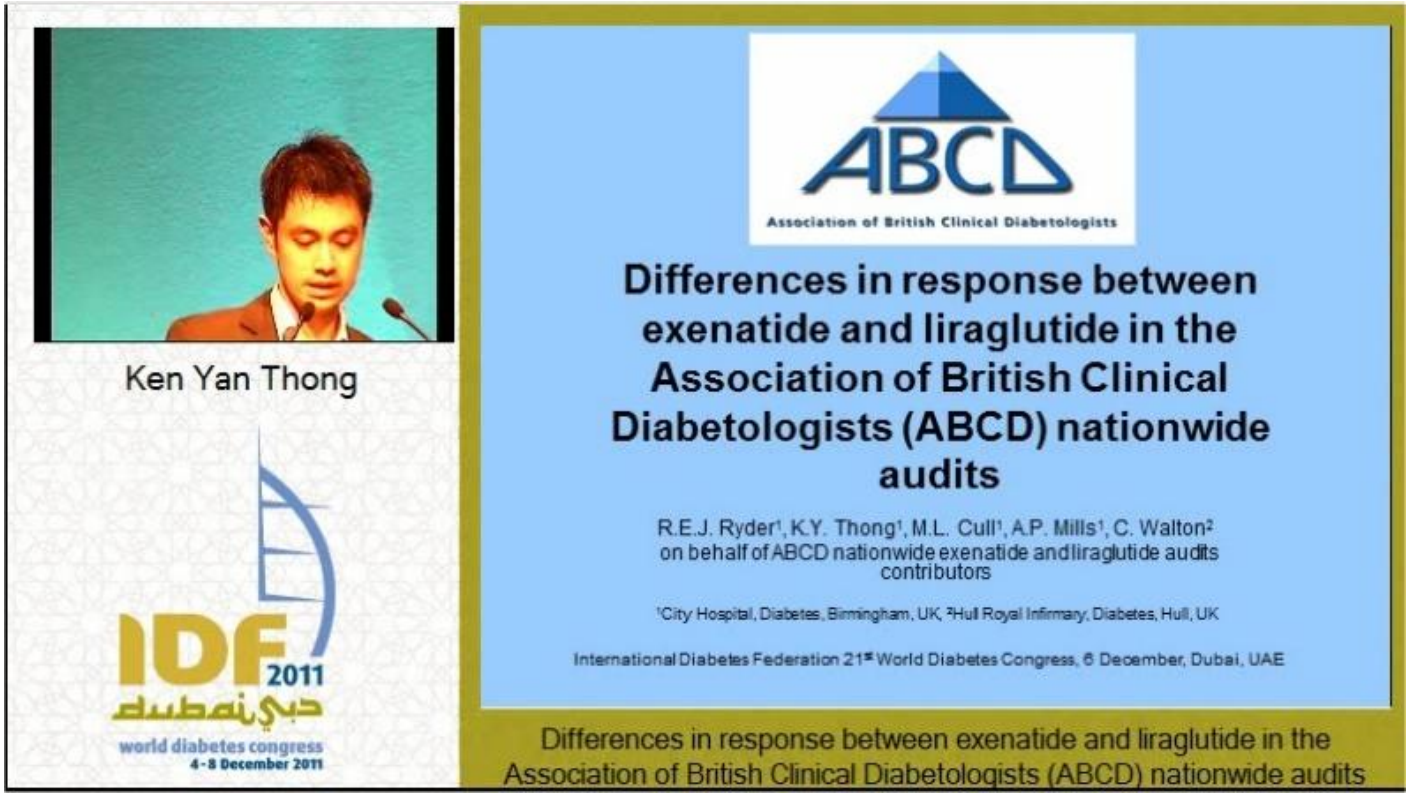
*The attention-to-treat HbA1c and weight data of patients analysed in this article were presented as a poster in the 46th EASD 2010 Annual Meeting in Stockholm.

†See Appendix for list of contributors in the ABCD nationwide exenatide audit.

- More than 1/3 of insulin-treated patients achieved an HbA1c reduction of ≥1%
- 1 in 6 discontinued insulin alongside HbA1c reduction
- Insulin dose reduction from 1.0 ± 0.8 U/kg/day to 0.7 ± 0.7 U/kg/day ($p<0.001$)

Thong KY et al. Diabetes, Obesity and Metabolism 2011; 13(8): 703-720

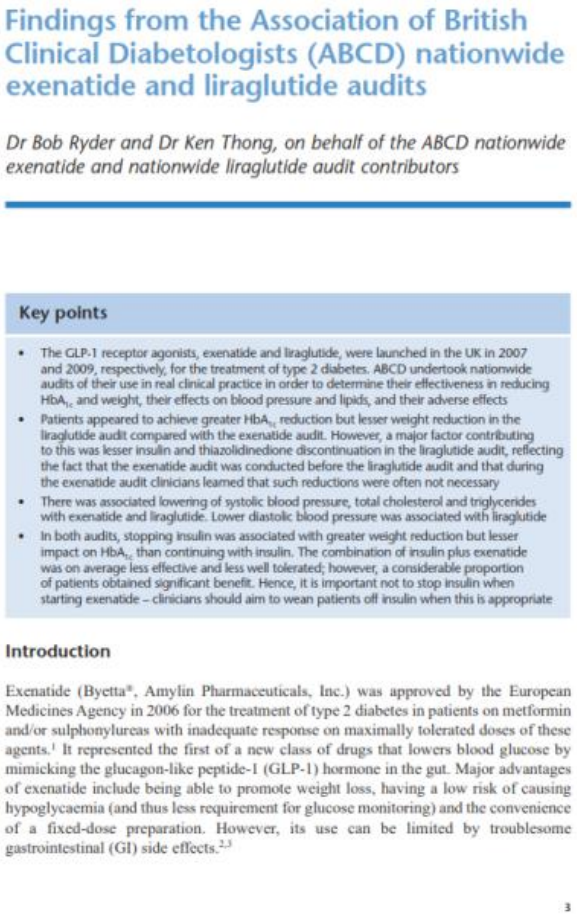
ABCD nationwide liraglutide audit



- **Clinicians learned during the era of the exenatide audit how to use GLP1's with insulin so that by the time of the liraglutide audit:**

R. E. J. Ryder, K. Y. Thong. Findings from the ABCD nationwide exenatide and liraglutide audits. In Hot topics in diabetes, Vora J, ed. Synergy, London, 2012

ABCD nationwide liraglutide audit



Findings from the Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audits

Dr Bob Ryder and Dr Ken Thong, on behalf of the ABCD nationwide exenatide and nationwide liraglutide audit contributors

Key points

- The GLP-1 receptor agonists, exenatide and liraglutide, were launched in the UK in 2007 and 2009, respectively, for the treatment of type 2 diabetes. ABCD undertook nationwide audits of their use in real clinical practice in order to determine their effectiveness in reducing HbA_{1c} and weight, their effects on blood pressure and lipids, and their adverse effects
- Patients appeared to achieve greater HbA_{1c} reduction but lesser weight reduction in the liraglutide audit compared with the exenatide audit. However, a major factor contributing to this was lesser insulin and thiazolidinedione discontinuation in the liraglutide audit, reflecting the fact that the exenatide audit was conducted before the liraglutide audit and that during the exenatide audit clinicians learned that such reductions were often not necessary
- There was associated lowering of systolic blood pressure, total cholesterol and triglycerides with exenatide and liraglutide. Lower diastolic blood pressure was associated with liraglutide
- In both audits, stopping insulin was associated with greater weight reduction but lesser impact on HbA_{1c} than continuing with insulin. The combination of insulin plus exenatide was on average less effective and less well tolerated; however, a considerable proportion of patients obtained significant benefit. Hence, it is important not to stop insulin when starting exenatide – clinicians should aim to wean patients off insulin when this is appropriate

Introduction

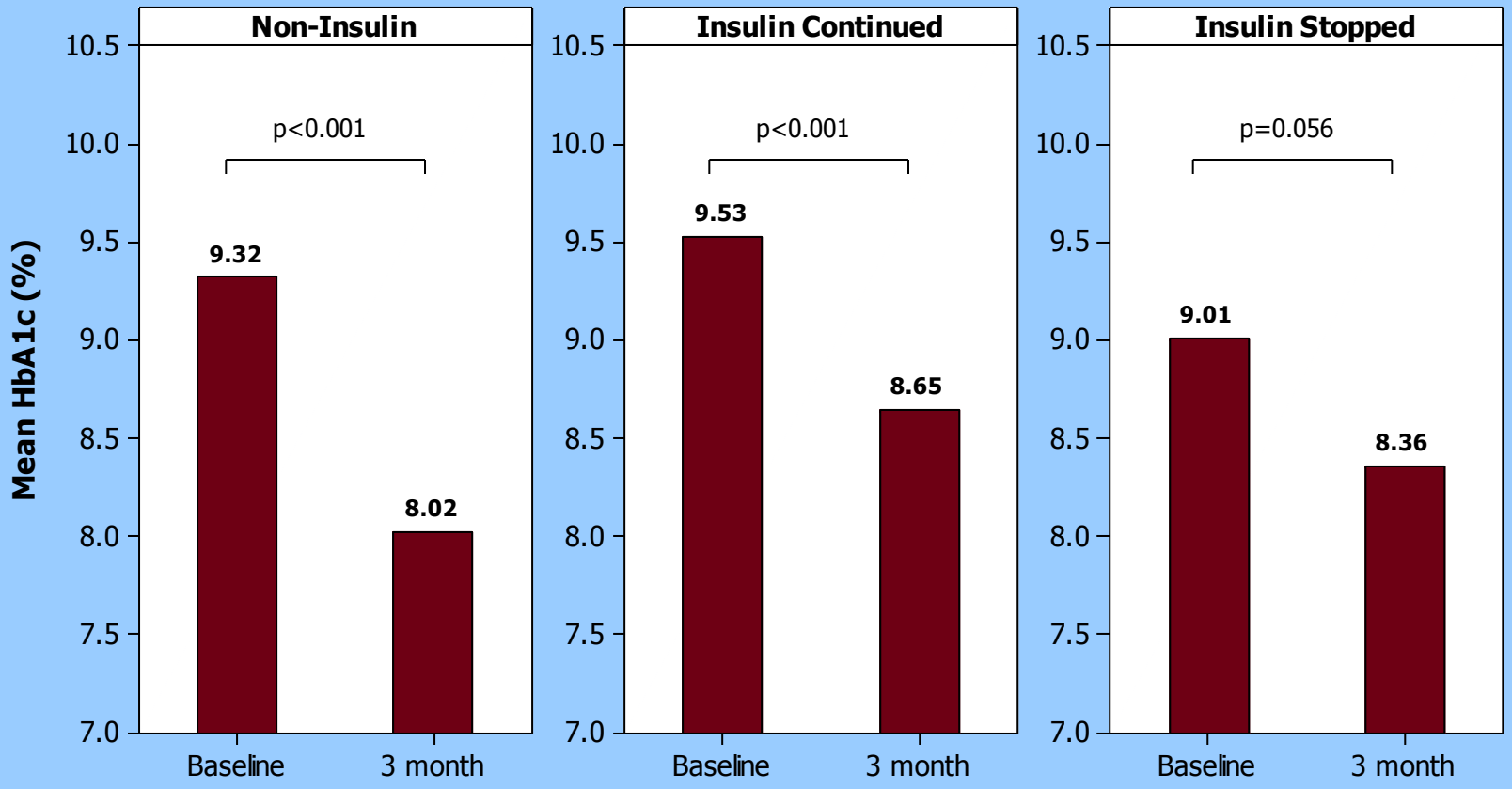
Exenatide (Byetta®, Amylin Pharmaceuticals, Inc.) was approved by the European Medicines Agency in 2006 for the treatment of type 2 diabetes in patients on metformin and/or sulphonylureas with inadequate response on maximally tolerated doses of these agents.[1] It represented the first of a new class of drugs that lowers blood glucose by mimicking the glucagon-like peptide-1 (GLP-1) hormone in the gut. Major advantages of exenatide include being able to promote weight loss, having a low risk of causing hypoglycaemia (and thus less requirement for glucose monitoring) and the convenience of a fixed-dose preparation. However, its use can be limited by troublesome gastrointestinal (GI) side effects.[2,3]

3

- Clinicians learned during the era of the exenatide audit how to use GLP1 receptor agonists with insulin so that by the time of the liraglutide audit:

R. E. J. Ryder, K. Y. Thong. Findings from the ABCD nationwide exenatide and liraglutide audits. In Hot topics in diabetes, Vora J, ed. Synergy, London, 2012

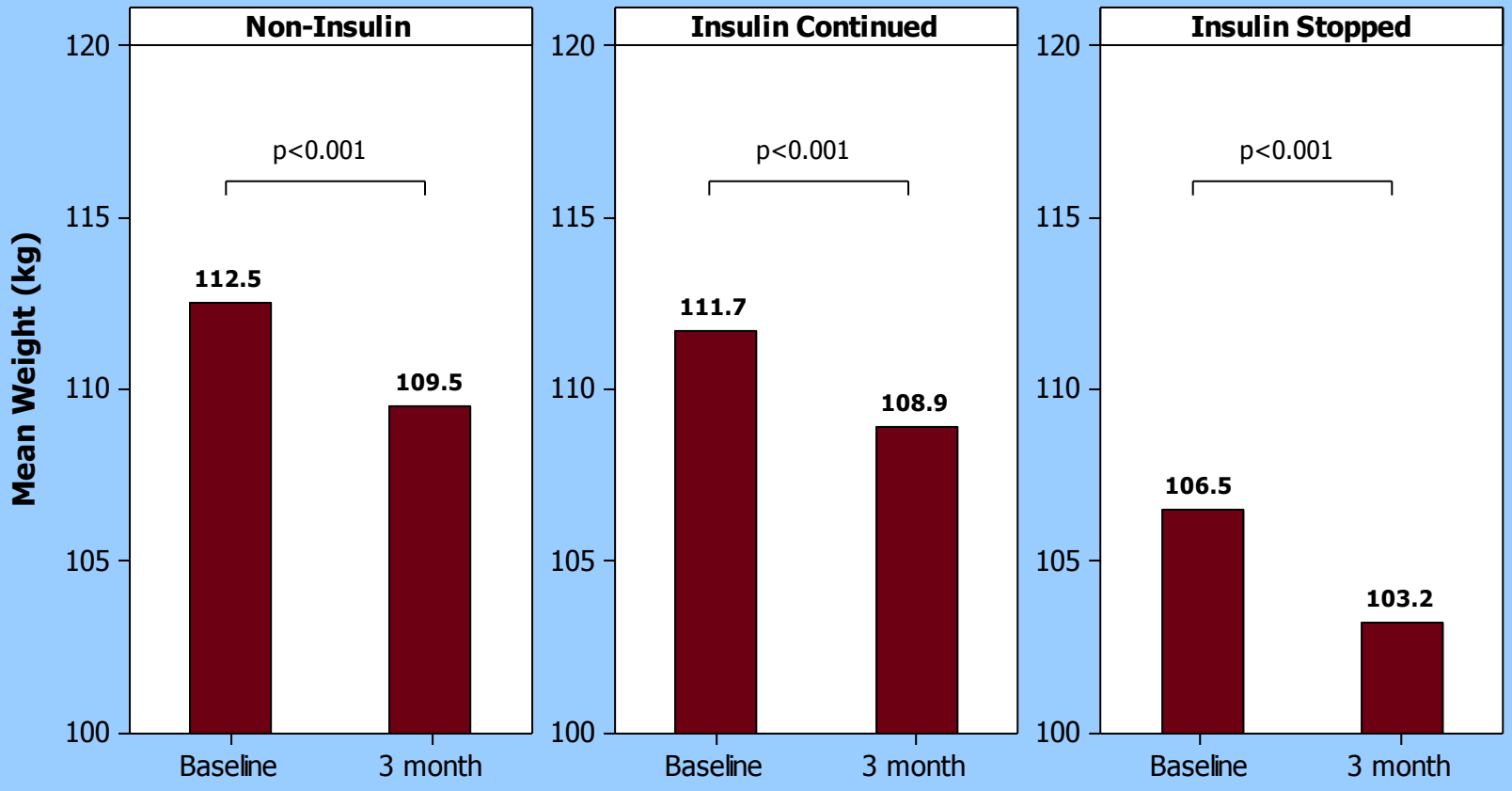
Baseline vs 3 month HbA1c with liraglutide treatment comparing patient groups



(n=740) (n=463) (n=36)

Mean change **-1.30%** **-0.88%** **-0.65%**

Baseline vs 3 month Weight with liraglutide treatment comparing patient groups



(n=733) (n=488) (n=36)

Mean change

-3.0 kg **-2.8 kg** **-3.3 kg**

Conclusions

- Losing weight is at the heart of optimum management of mainstream type 2 diabetes and GLP1 RAs facilitate weight loss which can be considerable in some patients
- Adding the on-licence treatment (insulin) to patients on triple OHA who are overweight is the unethical choice
- Adding a GLP1 RA (off licence) is the ethical choice
- Many patients already on insulin will respond to a GLP1 RA with significant glycaemic and weight improvement
- Stopping insulin to start a GLP1 RA in order to stay on licence is the unethical choice
- A trial of adding a GLP1 RA to insulin (even if off licence) in patients who overweight and inadequately controlled is the ethical choice
- The true cost of insulin use is very high when one takes into account the high doses of insulin in overweight, insulin resistant patients, the cost of home blood glucose monitoring and the considerable cost of multiple consultations with health care professionals

Summing up

- Two of my patients invited me to share their experiences:
  - One from the ABCD nationwide exenatide audit
  - One from the ABCD nationwide liraglutide audit

Mrs KU, age 55, type 2 diabetes 18 years, on insulin 8 years

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

Prediction if stay within guidelines – keep titrating the insulin

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

- April 2011
- Wt = 93 kg
- BMI = 37.7
- A1c = 8.2%
- Insulin 132 units, Repaglinide 4mg tds, Metformin 1gm BD

Exenatide – coming off insulin, improving control, and losing weight

- June 2008
- Wt = 87 kg
- BMI = 35.3
- A1c = 9.0%
- Insulin 82 units, Repaglinide 4mg tds, Metformin 1gm BD

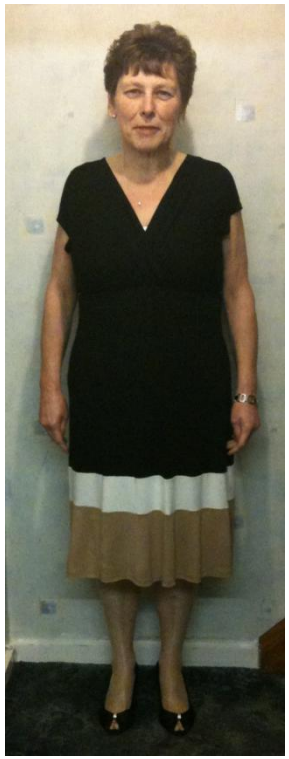
- April 2011
- Wt = 65 kg
- BMI = 26.7
- A1c = 7.2%
- Exenatide 10ug BD, Metformin 1gm BD

Mrs SH, age 53, type 2 diabetes 13 years, on insulin 8 years

- September 2009
- Wt = 93.9 kg
- BMI = 36.7
- A1c = 9.3%
- Insulin 60 units, Metformin 1gm BD

Liraglutide – coming off insulin, improving control, losing weight and “never felt so good”

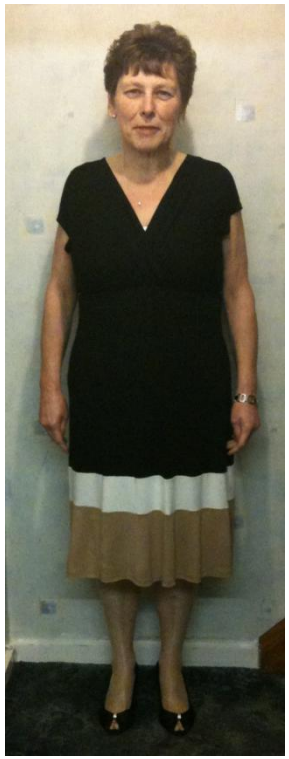
- September 2009
- Wt = 93.9 kg
- BMI = 36.7
- A1c = 9.3%
- Insulin 60 units, Metformin 1gm BD



- February 2012
- Wt = 70 kg
- BMI = 26.3
- A1c = 7.2%
- Liraglutide 1.2mg daily, Metformin 1gm BD

Liraglutide – coming off insulin, improving control, losing weight and “never felt so good”

“I would like to add that since I was prescribed liraglutide and started a healthy eating diet I have never felt so good. Yes I had a couple of weeks at the start of Liraglutide when I had stomach upsets and nausea but I am so glad I persevered as I haven't looked back since September 2009. The icing on the cake is that I no longer have to take insulin. Although you have to accept that taking insulin is part of your life and you obviously have no choice there is definitely no feeling like it when you realize you are 'insulin free‘ ”



- September 2009
- Wt = 93.9 kg
- BMI = 36.7
- A1c = 9.3%
- Insulin 60 units, Metformin 1gm BD

- February 2012
- Wt = 70 kg
- BMI = 26.3
- A1c = 7.2%
- Liraglutide 1.2mg daily, Metformin 1gm BD