

# ABCD Nationwide Exenatide and Liraglutide Audits

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

DUK APC, London, 1 April 2011

# ABCD Nationwide Exenatide and Liraglutide Audits

- Exenatide and Liraglutide in real clinical use in the UK
  - Real (too busy) doctors and nurses in the real NHS
  - Real cancelled clinics and appointments
  - Real patients compliant, non compliant …
  - Real DNA's
  - Real chaos, poor communication and misunderstandings
  - Real enthusiasm for a new and different form of treatment



### **Important**



- The slides in this presentation show data from large scale real-life audits not from head-to-head clinical trials
- Data from the exenatide and liraglutide audits are shown together not for the purposes of comparison of the effectiveness of the two drugs, but to ...
- Serve to illustrate trends in clinical practice re the use of these two agents

### **Important**

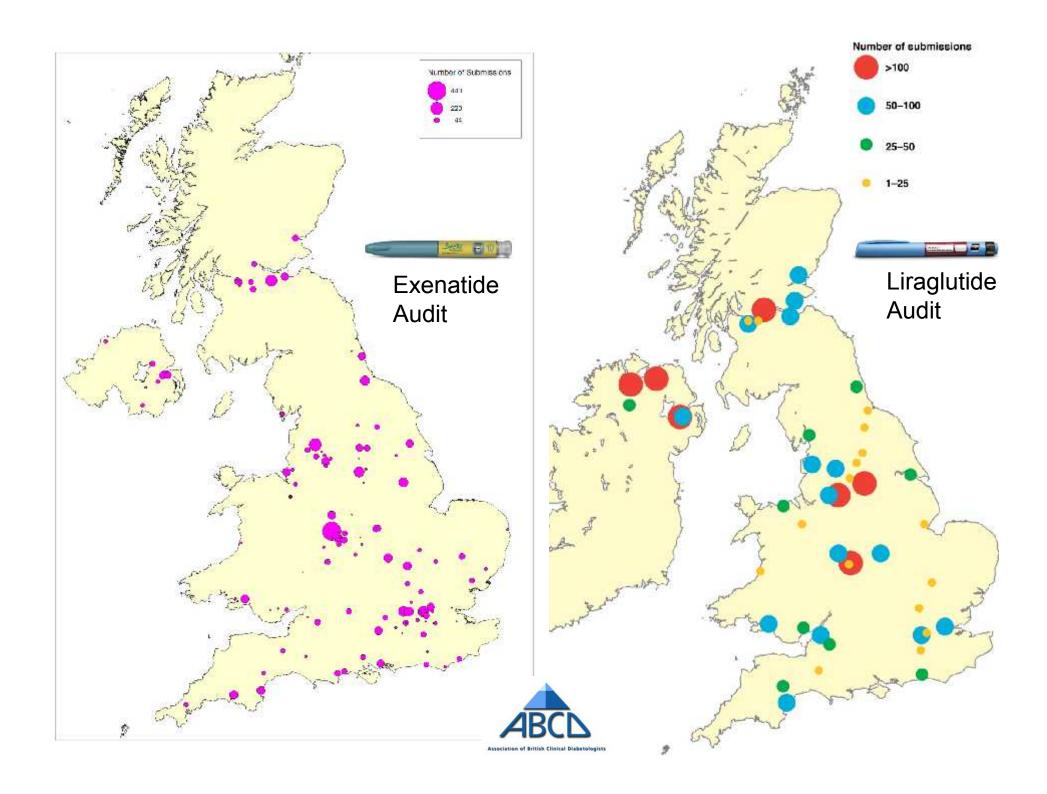


- To prepare you:
  - As a rule of thumb the following data tends to show a bigger HbA1c effect for liraglutide but bigger weight effect for exenatide.
  - We suspect this is mostly due to increased confidence of clinicians with time in continuing and/or reducing less other medications, in particular insulin, when using GLP1 receptor agonists
  - Exenatide data = 2007-2009
  - Liraglutide data = 2009-2010

### Audit characteristics



	Exenatide Audit	Liraglutide Audit
Launch date	December 2008	November 2009
Data collection	Online questionnaire or emailed spreadsheet	Downloaded audit tool, email of csv files
Contributors	315	210
Centres	126	64
Patients	6717	3010
Duration of follow-up: median (range)	32 (0.1-175) weeks	Ongoing
Status	Primary analyses completed, long term follow-up planned	This audit has just started



#### Baseline diabetes treatment use and discontinuation



	Exenatide Audit	Liraglutide Audit
Metformin	84.0% (0.9%)	82.7% (0.7%)
Sulphonylurea	49.5% (6.5%)	42.8% (5.3%)
Thiazolidinedione	27.1% (13.4%)	20.5% (7.5%)
Meglitinide	2.0% (0.6%)	1.0% (0.2%)
Acarbose	0.9% (0.3%)	0.7% (0.3%)
DPPIV Inhibitor	2.2% (1.4%)	10.9% (9.3%)
Exenatide	-	21.9% (21.9%)
Insulin	33.9% (8.1%)	39.6% (2.6%)

Proportion of 6717 and 3010 patients respectively

 Relevant data presented for liraglutide audit excluded patients who have been previously on exenatide or switched from exenatide to liraglutide



#### Baseline characteristics



	Exenatide Audit	Liraglutide Audit	p value
n	6717	2303 (from 3010)	
Male (%)	54.9	54.1	0.491
Caucasian (%)	84.4	90.4	<0.001
Age (yrs)	54.9 (10.6)	55.4 (11.2)	0.033
Diabetes duration (yrs)	8 (5-13)	9 (5-13)	0.424
HbA1c (%)	9.47 (1.69)	9.32 (1.72)	0.001
Weight (kg)	113.8 (23.4)	111.1 (23.0)	<0.001
BMI (kg/m <sup>2</sup> )	39.8 (8.0)	39.1 (7.5)	<0.001
Single oral therapy (%)	12.7	12.0	0.371
Dual oral therapy (%)	28.1	28.1	0.969
≥3 oral therapy (%)	15.6	17.9	0.012
On insulin (%)	33.9	39.8	<0.001

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

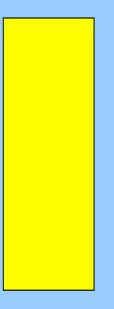
## HbA1c and Weight changes



### Colour scheme for results

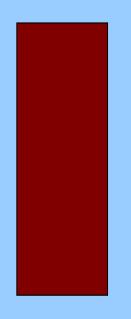






#### Liraglutide

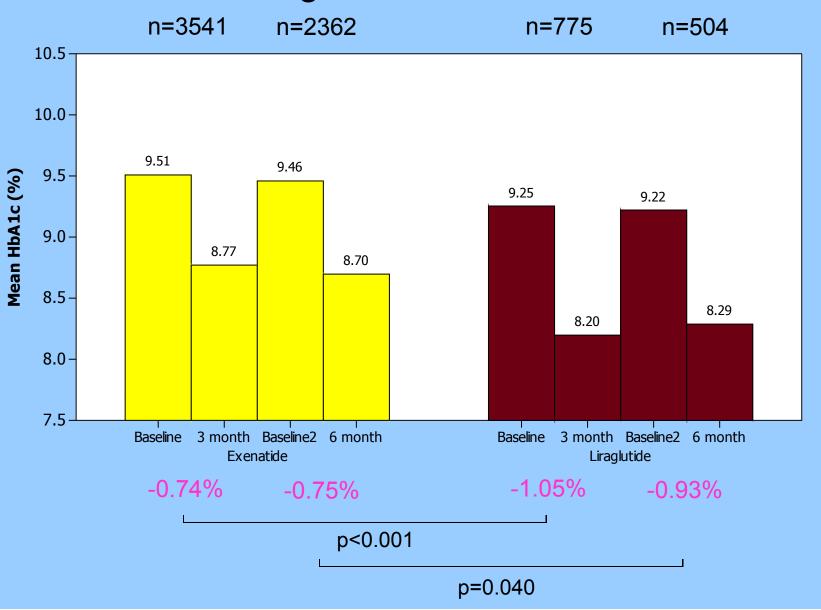






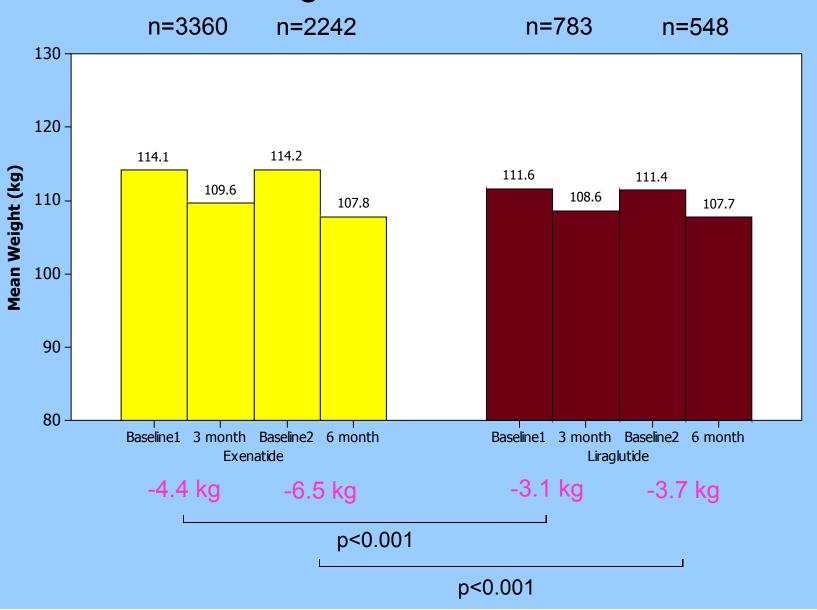
## ABCD Association of British Clinical Diabetologists

## HbA1c results at 3 and 6 months: exenatide and liraglutide



## ABCL Association of British Clinical Diabetologists

## Weight results at 3 and 6 months: exenatide and liraglutide



### Findings 1

- Patients appear to achieve greater HbA1c reduction but lesser weight reduction in the liraglutide audit as compared with the exenatide audit
- However, there were lesser insulin and TZD discontinuation but greater DPPIV inhibitor discontinuation in the liraglutide audit
- Contributors might have learnt from the previous use of exenatide to avoid over-reduction of diabetes treatment when initiating liraglutide

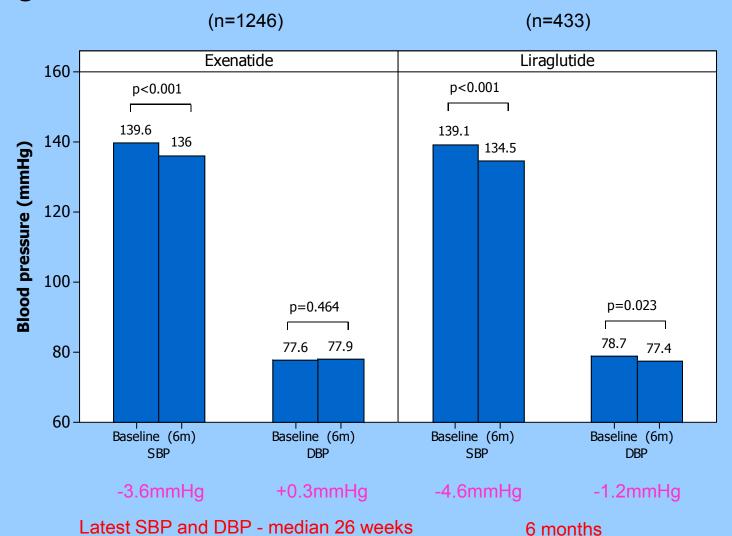


### **Blood Pressure and Lipids**



## Blood pressure results: exenatide and liraglutide

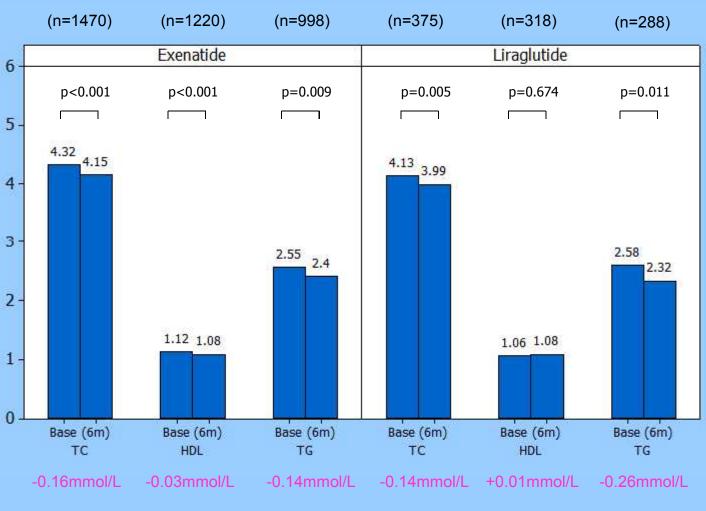




Results for exenatide adapted from Ryder et al. Pract Diab Int 2010; 27:352-357b

#### Lipid results: exenatide and liraglutide





Latest TC, HDL, TG - median 26 weeks

6 months

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

### Findings 2

- Consistent lowering of SBP, total cholesterol and triglycerides with exenatide and liraglutide
- Diastolic blood pressure also lowered with liraglutide



#### Adherence to NICE guidelines/guidance



National Institute for Health and Clinical Excellence

esue date: May 2009

#### Type 2 diabetes

The management of type 2 diabetes

This guideline partially updates NICE clinical guideline 66 and replaces it

Recommendations 1 1423, 11424, 1 1575 and 1 1576 in this guideline have been updated and replaced by Hourogathia pair: the pharmacological management of neuropathic pain in adults in non-specialist settings" (NICC stimical guideline 56), available from www.nberg.guideline 5656.

in September 2310 the European Medicines Agency (EMA), the European Union (EU) body isoparable to monitoring the safety of moditions, essemmented the suspension of the marking authorization for feeding supportation. Avaidance and Avaiding from Glaudardington. The EMA has conduced by the benefits of realigitazione no longer outwigh its risks and the marketing authorisation should be expended across the EU.

The FMA has artifact that patients with are currently taking realigitazione containing medicines enculd make an appointment with their doctor at a

convenient time to discuss suitable afternative treatments. Patients are advised no. It stop that healther's without speaking to their Jocoth fract these not accommend the use of drugs without markeling authorisation. Therefore, as a securit of the EMAP decision, MICE has temporarily without with the accommendations on the use of magiltazume in this guidalin

NICE clinical guideline 87 Developed by the National Collaborating Centre for Chronic Conditions are the Centre for Chronic Practice at NID≣

National Institute for Health and Clinical Excellence turus date: October 2010: Liraglutide for the treatment of type 2 diabetes mellitus This guidance was developed using the single technology appraisal process MCE technology appraisal guidance 203

### Patients excluded by NICE



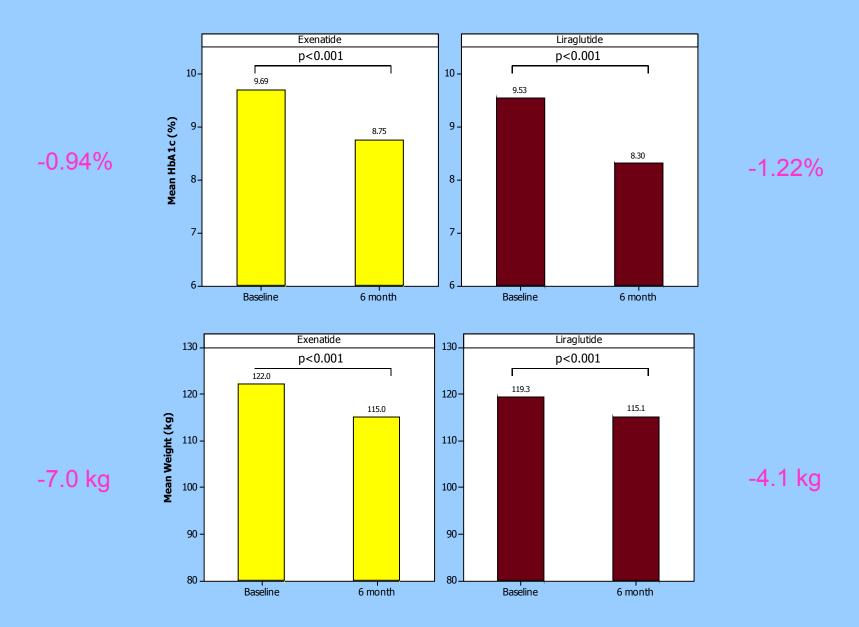
	Starting Exenatide	Starting Liraglutide
NICE compliant	21.7%	28.6%
NICE non-compliant	46.5%	66.6%
HbA1c <7.5%	9.4%	11.7%
BMI <35 kg/m <sup>2</sup>	14.6% (*1.3%)	28.6% (*3.7%)
3 OHA	6.6%	6.6%
Insulin	22.9%	37.1%
Lacked details	31.8%	4.8%

NICE adherence for number of OHA and insulin use was judged after treatment changes made at GLP-1 initiation. Patients on 1.8mg dose of liraglutide was accepted as NICE compliant for this preliminary analysis

\*percentage of 6717 and 2303 patients who had BMI <35 kg/m² but who were of South Asian or Afro Caribbean ethnicity, or held professional driving licences

## 6 month HbA1c and Weight results among patients meeting NICE criteria on starting exenatide and liraglutide







#### Patients excluded by NICE



#### GLP-1 mimetic (exenatide)

- 1.1.14 Consider adding a GLP 1 mimetic (exenatide) as third line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA<sub>16</sub>≥ 7.5%, or other higher level agreed with the individual), and the person has.
  - a body mass index (BMI) ≥ 35.0 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or

NICE short clinical guideline 87 - Type 2 diabetes: newer agents

11

- a BMI < 35.0 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.
- 1.1.15 Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA<sub>1s</sub> and a weight loss of at least 3% of initial body weight at 6 months).
- 1.1.16 Discuss the potential benefits and risks of treatment with a GLP 1 mimetic (exenatide) with the person to enable them to make an intermed decision.

- 1.1 Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has:
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At the time of publication pipglitazone was the only thiazol directione with UK marketing authorisation for use with insuln.



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NICE short clinical guideline 87 - Type 2 diabetes, newer agents

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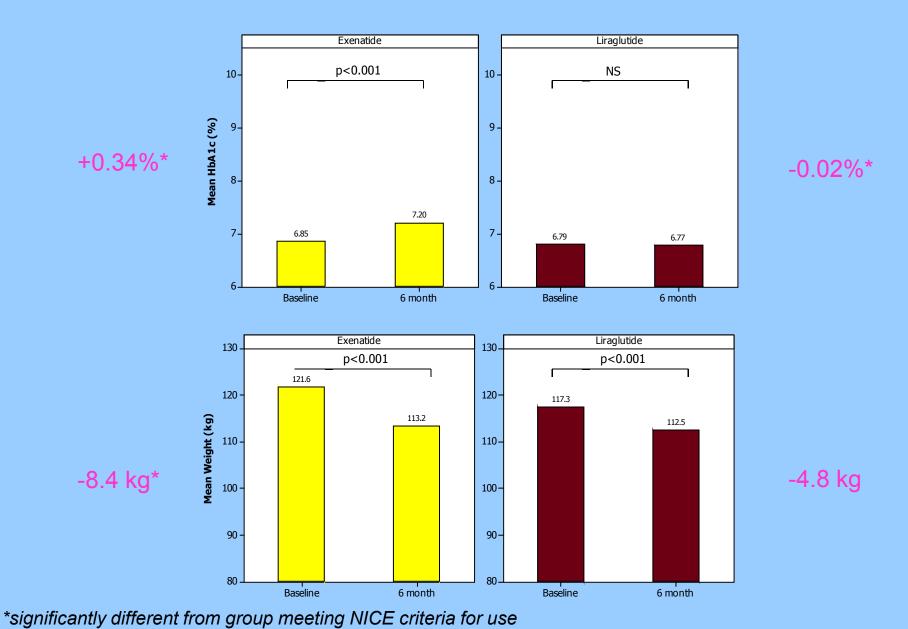
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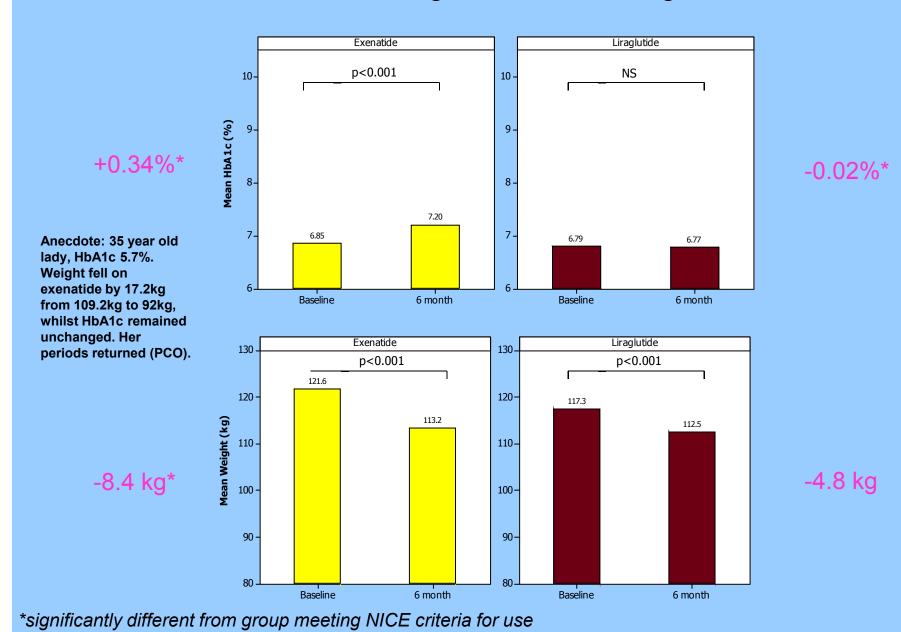
## 6 month HbA1c and Weight results among patients with baseline HbA1c<7.5% starting exenatide and liraglutide





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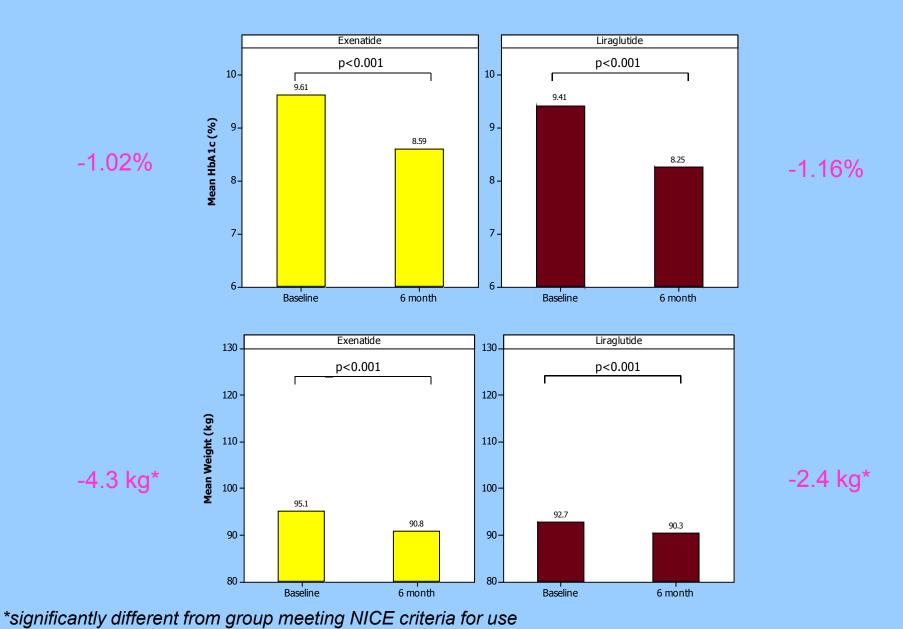
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## 6 month HbA1c and Weight results among patients with baseline BMI<35 kg/m<sup>2</sup> starting exenatide and liraglutide







#### Patients excluded by NICE



#### GLP-1 mimetic (exenatide)

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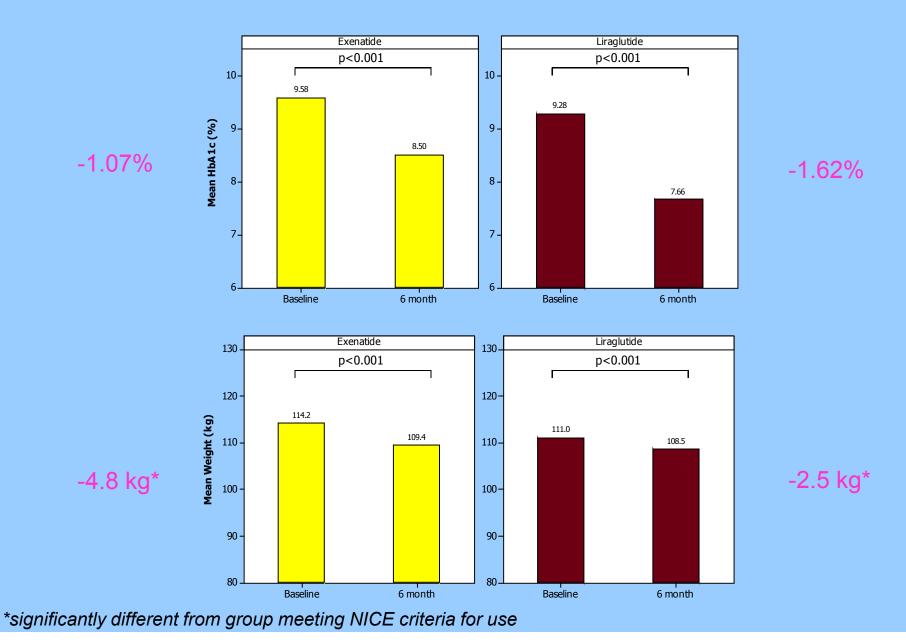
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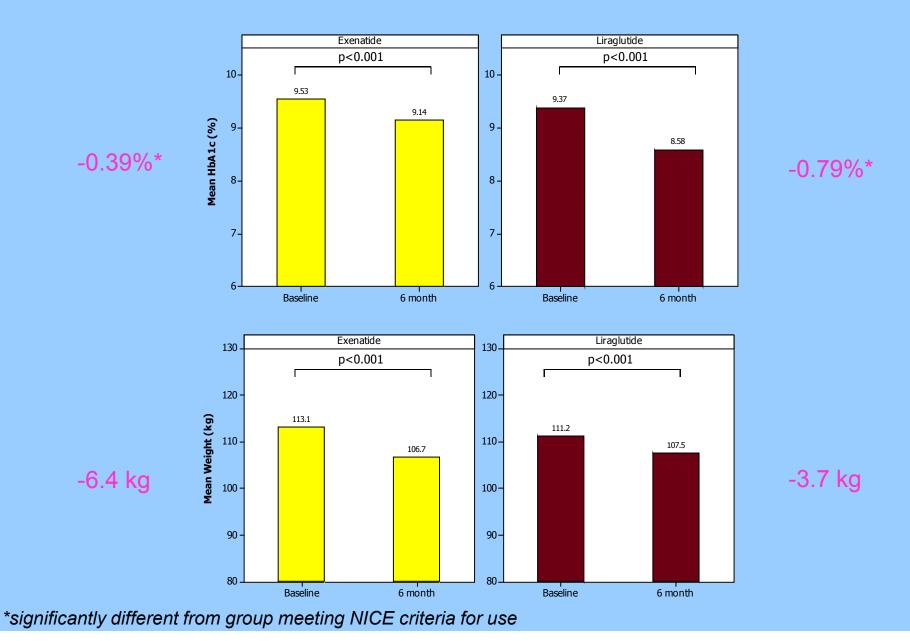
## 6 month HbA1c and Weight results among patients on triple oral therapy starting exenatide and liraglutide





## 6 month HbA1c and Weight results among patients on insulin starting exenatide and liraglutide





### Findings 3

• Exenatide and liraglutide were commonly used outside that of NICE guidelines with considerable benefits to patients in terms of glycaemic control and weight loss



#### NICE: Only continue if beneficial metabolic response





1.1.15 Only continue GLP-1 mimetic (exenatide) therapy if the person has

had a beneficial metabolic response (a reduction of at least 1.0 percentage point in  $HbA_{1c}$  and a weight loss of at least 3% of initial body weight at 6 months).

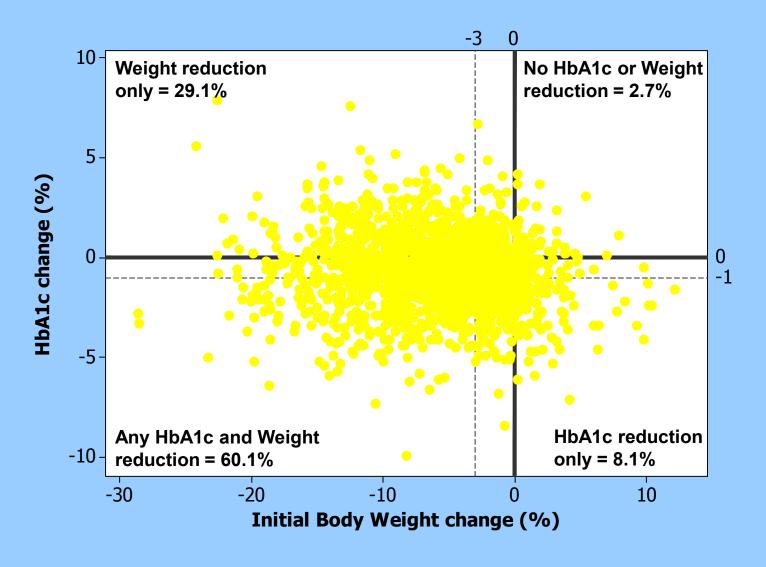


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- •At 6 months:
  - ✓ HbA1c fall by ≥ 1%
  - ✓Weight loss ≥ 3% initial body weight

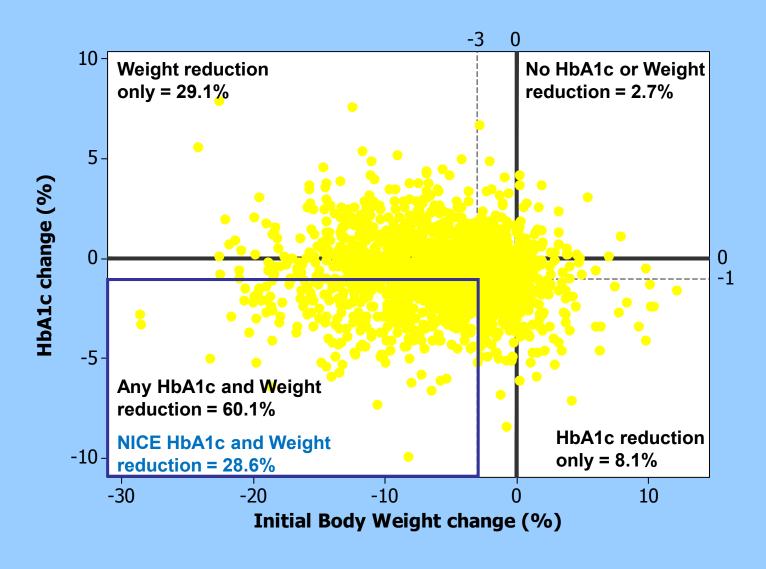
## HbA1c and IBW changes at 6 months in 1882 patients on exenatide





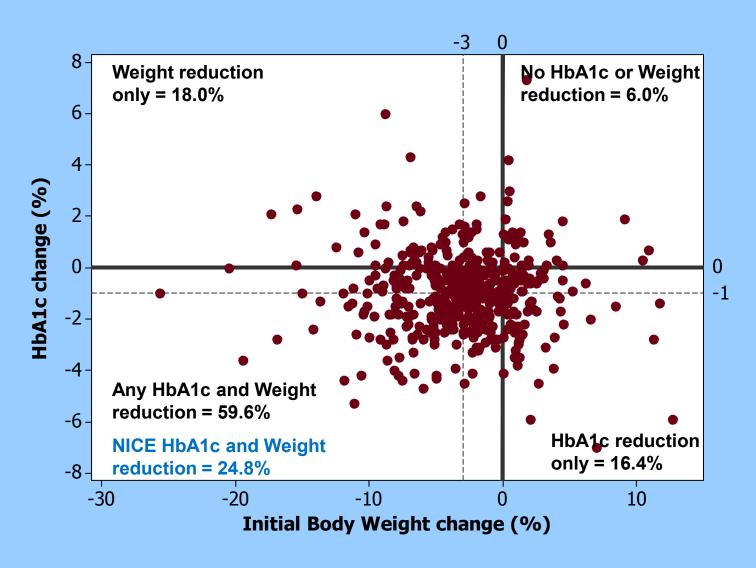
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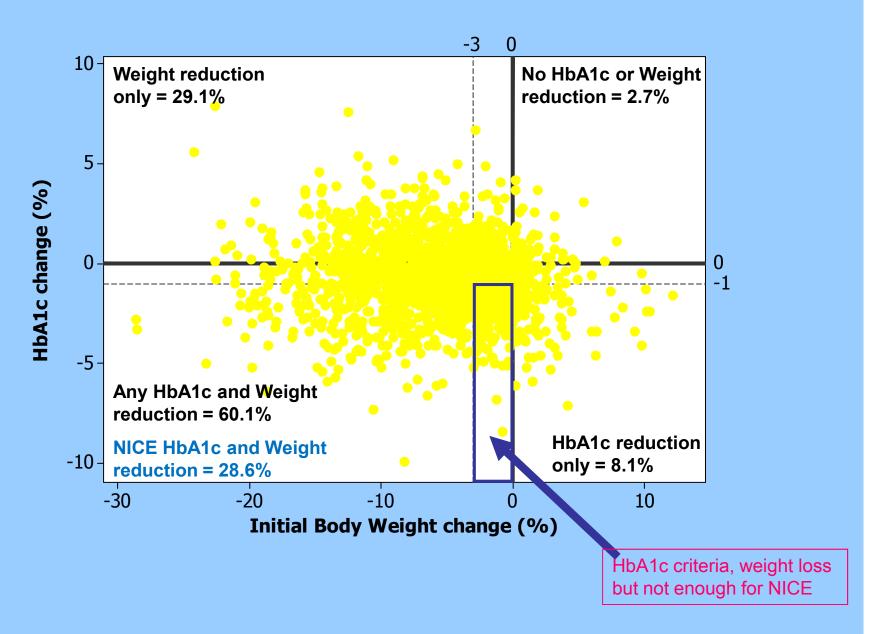
## HbA1c and IBW changes at 6 months in 451 patients on liraglutide (excluding those who were on exenatide)



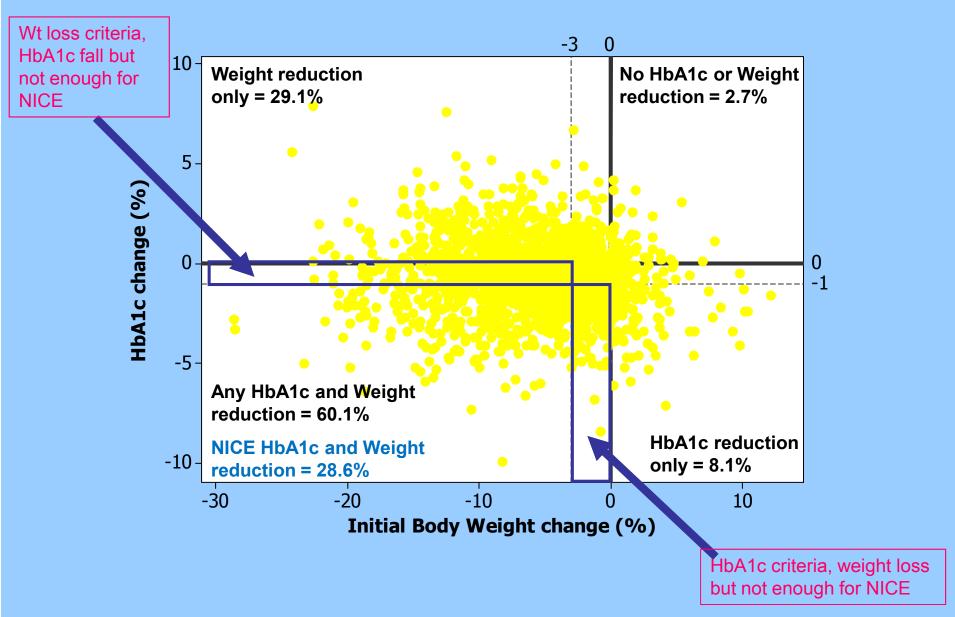


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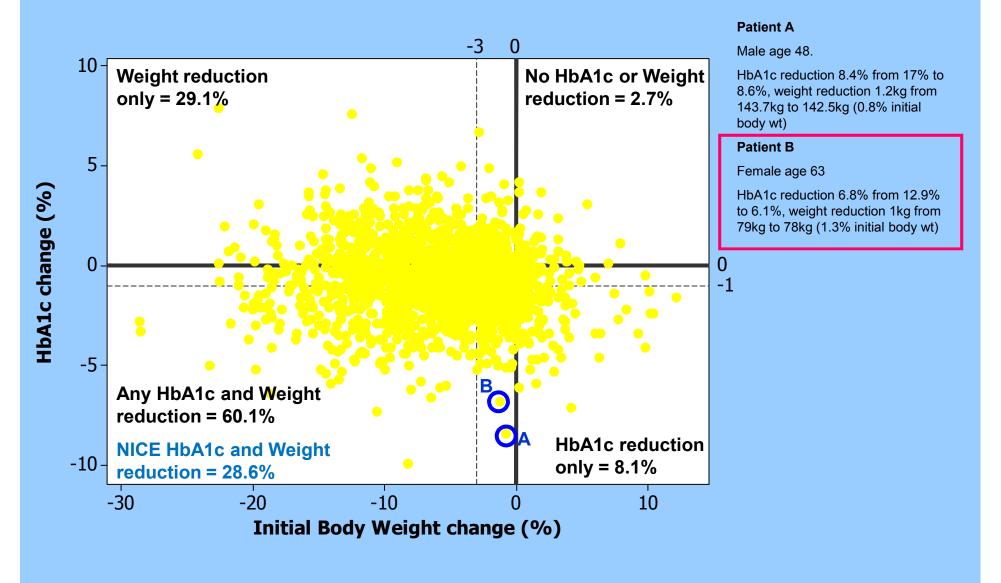




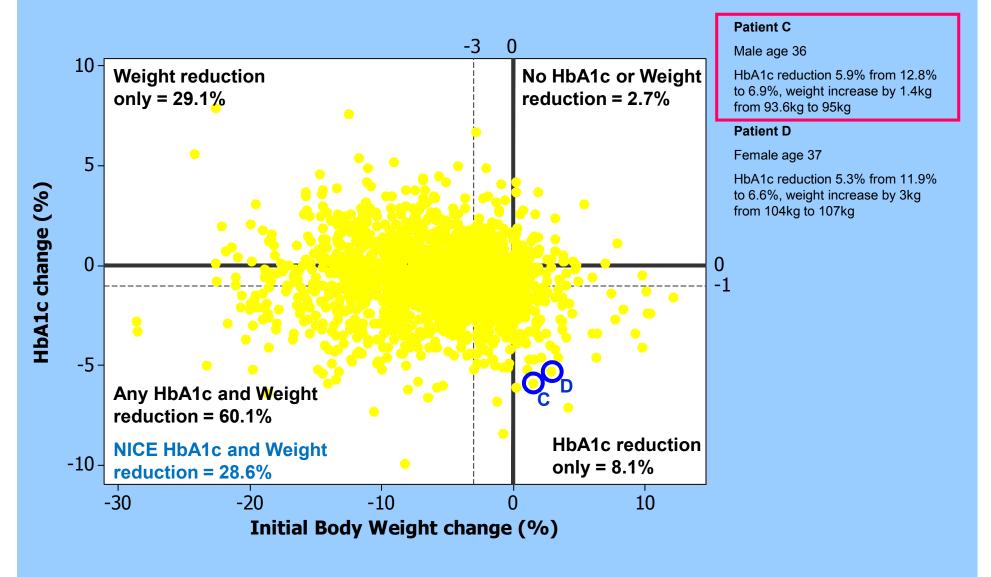




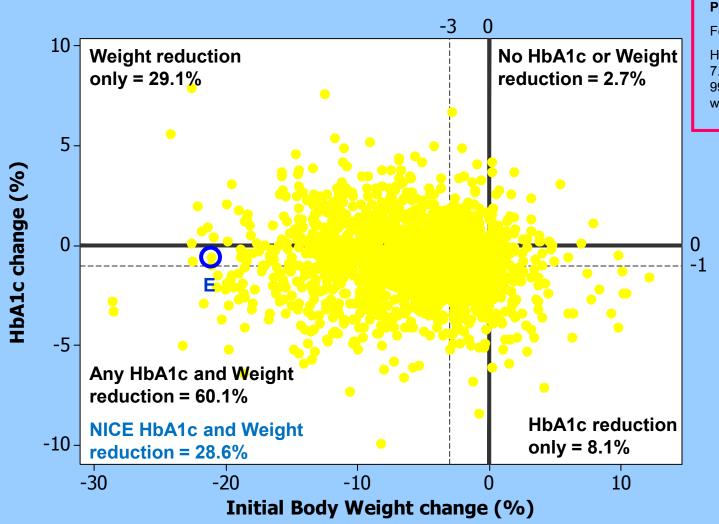










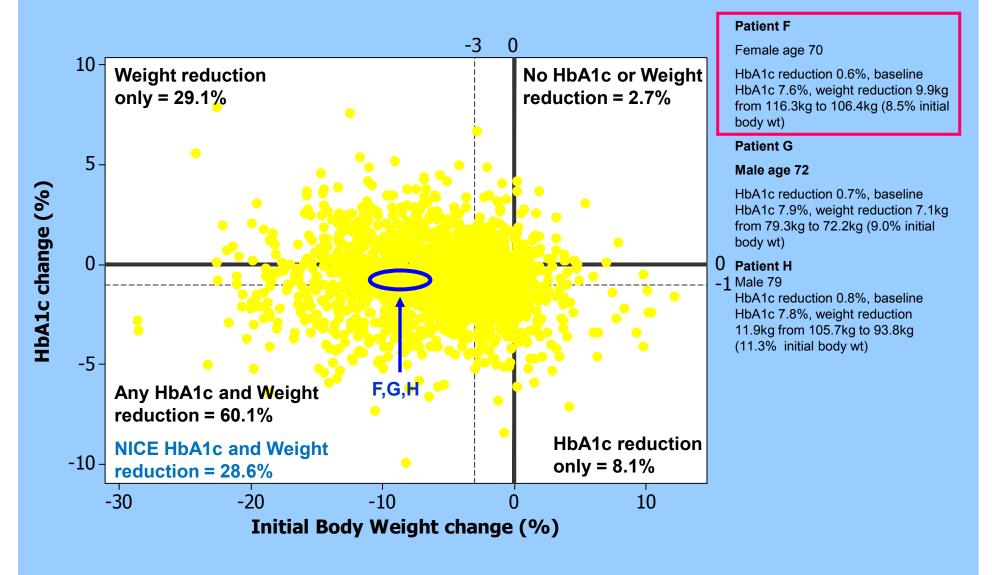


### Patient E

Female age 63

HbA1c reduction 0.6% from 8.1% to 7.5%, weight reduction 21kg from 99.4kg to 78.4kg (21.1% initial body wt)





### Findings 4

- Around 60% of patients starting on exenatide or liraglutide achieve both HbA1c and Weight reduction but less than 30% achieve NICE criteria for a metabolic success
- Many patients achieved significant HbA1c or Weight response, but not both
- Perhaps the Scottish SIGN guidelines are more appropriate than those of NICE





## Sign Guideline





#### REVIEW AND SET GLYCAEMIC TARGET: HbA1c <7% (53 mmol/mol) OR INDIVIDUALISED AS AGREED

1st LINE OPTIONS in addition to lifestyle measures; START ONE OF

Metformin (MF)

### Sulphonylurea\* (SU)

- · If intolerant of metformin or
- If weight loss/osmotic symptoms

Review and if not reaching target move to 2nd line

2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF

Sulphonylurea\* (SU)

#### Thiazolidinedione\*

- If hypos a concern (eg driving, occupational hazards, at risk of falls) and
- If no congestive heart failure

#### DPP-IV inhibitor\*

- If hypos a concern (eg driving, occupational hazards, at risk of falls)
- If weight gain a concern

Review and if not reaching target move to 3rd line

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD OR SUBSTITUTE WITH ONE OF

ORAL (continue MF/SU if tolerated)

INJECTABLE (if willing to self inject; continue MF/SU if tolerated)

Thiazolidinedione\*

If no congestive heart failure

### DPP-IV inhibitor\*

If weight gain a concern

#### Insulin\* (inject before bed)

- · If osmotic symptoms/rising HbA1c; NPH insulin initially
- · If hypos a concern, use basal analogue insulin as an alternative
- · Add prandial insulin with time if required

#### GLP-1 agonists\*

- If BMI >30 kg/m<sup>2</sup>
- · If a desire to lose weight
- Usually <10 years from diagnosis</li>

Prescribers should refer to the British National Formulary (www.brif.org) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk) for updated guidence on licensed indications, full contraindications and monitoring requirements.

Usual approach

этипинати прегоден преста соплативного

Continue medication if ETTHER individualised target achieved OR HbATc falls >0.5% (5.5 mmol/mol) in 3-6 months

Management of diabetes quick reference guide • 7



## SIGN Guideline

### GLP-1 agonists\*

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- · If a desire to lose weight
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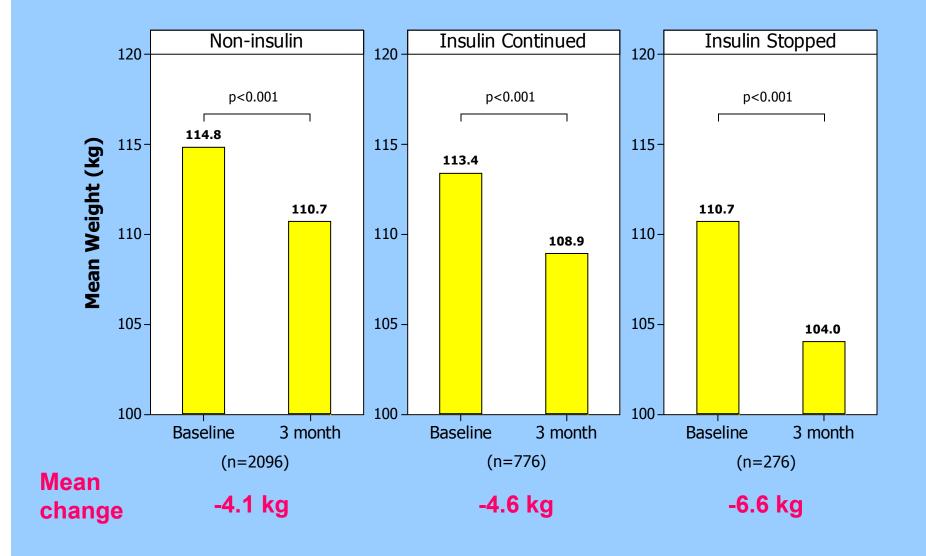
Continue medication if EITHER individualised target achieved OR HbA1c falls > 0.5% (5.5 mmol/mol) in 3.6 months

## GLP-1 treatment with Insulin



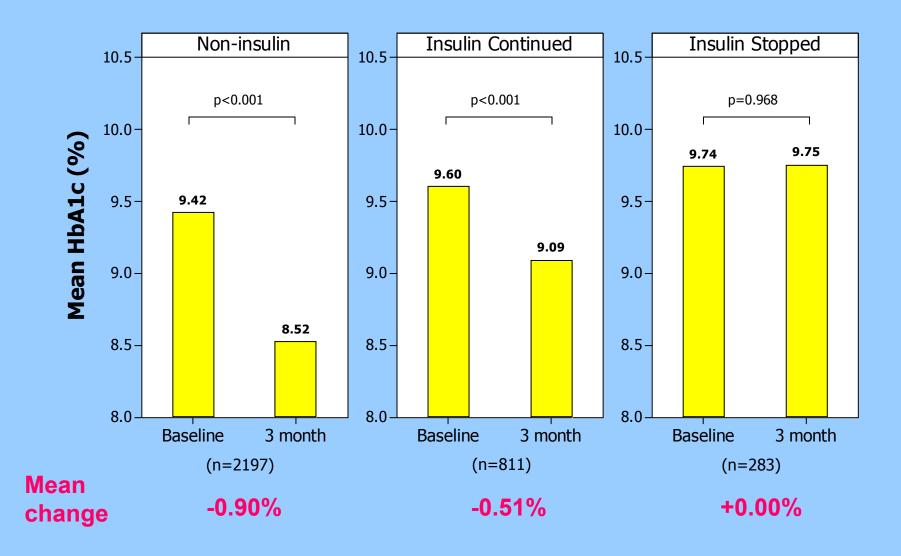
## Baseline vs 3 month Weight with exenatide treatment comparing patient groups





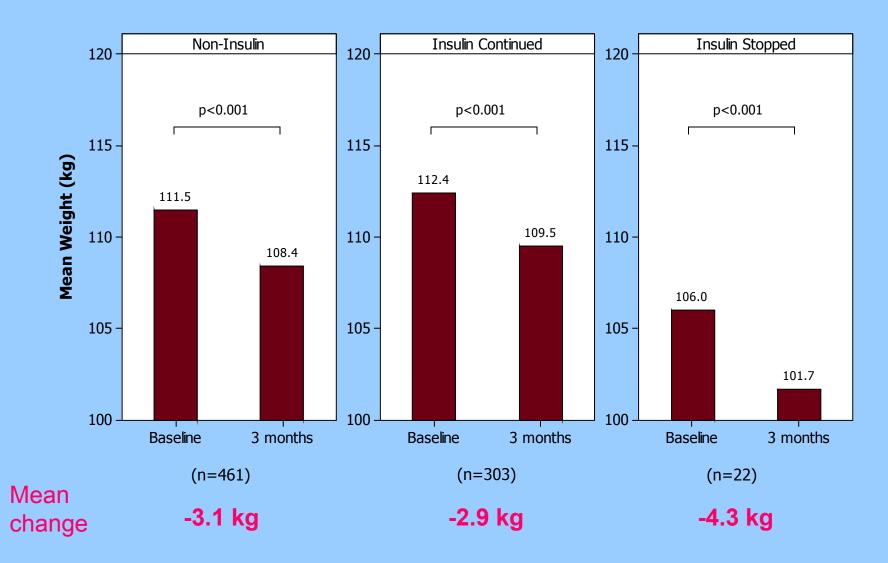
# Baseline vs 3 month HbA1c with exenatide treatment comparing patient groups





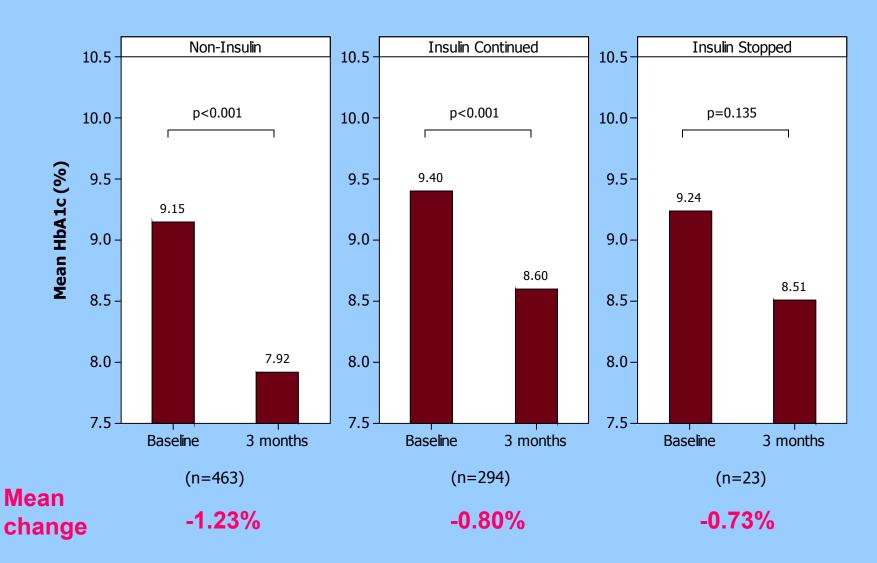
## Baseline vs 3 month Weight with liraglutide treatment comparing patient groups





## Baseline vs 3 month HbA1c with liraglutide treatment comparing patient groups



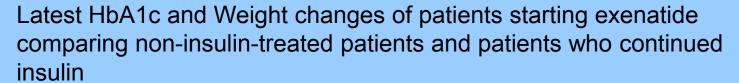


## Exenatide discontinuation, adverse events and exenatide treatment satisfaction comparing non-insulin and insulin-treated patients



	Non-insulin-treated % (95% CI)	Insulin-treated % (95% CI)	P value
Exenatide discontinuation			
Whole audit	13.9 (12.7,15.2)	31.0 (28.9,33.1)	<0.001
Lack of efficacy	33.6 (29.0,38.4)	41.0 (37.0,45.1)	0.017
GI side effect	31.9 (27.3,36.6)	35.8 (31.9,39.8)	0.197
Before 3 months	3.5 (2.9,4.3)	12.8 (11.3,14.4)	<0.001
Adverse events			
Pre-exenatide hypo	2.9 (2.3,3.6)	6.6 (5.5,7.8)	<0.001
Post-exenatide hypo	6.1 (5.3,7.1)	8.9 (7.7,10.2)	<0.001
All GI side effects	25.0 (23.4,26.6)	28.4 (26.4,30.5)	0.008
Acute renal failure	0.2 (0.1,0.4)	0.3 (0.1,0.7)	0.459
Patient satisfaction			
Positive response	74.4 (71.7,77.0)	58.0 (53.6,62.3)	<0.001 (group)
Neutral response	19.8 (17.5,22.0)	21.2 (17.7,25.0)	
Negative response	5.7 (4.5,7.3)	20.8 (17.3,24.6)	

adapted from Thong et al accepted for print, Diabetes, Obesity and Metabolism





	Non-insulin-treated	Continued insulin	p-value
N	2016	839	
Baseline HbA1c %	9.42 (1.68)	9.55 (1.70)	0.058
Latest HbA1c %	8.48 (1.74)	9.04 (1.90)	
HbA1c change %	-0.94 (0.04)	-0.51 (0.06)	<0.001
HbA1c reduction ≥1%	49.0%	34.2%	<0.001
N	1957	802	
Baseline Weight <i>kg</i>	114.1 (23.9)	112.7 (22.5)	0.161
Latest Weight <i>kg</i>	108.6 (23.2)	106.9 (22.6)	
Weight change <i>kg</i>	-5.5 (0.1)	-5.8 (0.2)	0.278
Weight loss ≥3% IBW	59.0%	61.1%	0.613

### **Exenatide and Insulin**

 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)</li>



# GLP-1 (Exenatide) and Insulin – should we and how?

- No evidence of safety concerns despite statistically higher rates of hypoglycaemia (from background insulin)
- Combination on average less effective and less well tolerated BUT
- \*\*A significant proportion of patients obtained significant benefit
- If starting exenatide don't stop insulin when starting exenatide – aim to wean off the insulin in the appropriate patients instead

# GLP-1 treatment with Insulin - Who?



- Exenatide insulin stoppers
  - Mean total daily insulin dose = 0.8 U/kg/day
  - Median diabetes duration 10 (6-15) years

- Liraglutide insulin stoppers
  - Mean total daily insulin dose = 0.6 U/kg/day
  - Median diabetesduration 9 (6-13) years



## Stepwise regression analyses-factors influencing HbA1c and Weight changes among patients treated with exenatide and liraglutide



	HbA1c reduction, stepwise regression among 3982 patients		Weight reduction, stepwise regression in 3089 patients	
Factor	Adjusted T- value	Adjusted p- value	Adjusted T- value	Adjusted p- value
Baseline HbA1c	30.44	<0.001	-5.94	<0.001
Baseline Weight	-3.79	<0.001	13.29	<0.001
HbA1c change	-	-	-	NS
Weight change	-	NS	-	-
Age	-	-	2.06	0.040
Diabetes duration	-4.16	<0.001	3.25	0.001
Ethnicity	-	-	-	NS
TZD reduction	-7.96	<0.001	7.02	<0.001
Insulin use	-10.02	<0.001	7.06	<0.001
	Stepwise regression among 1134 patients		Stepwise regression among 1002 patients	
Total insulin dose (log)	-3.6	<0.001	-	NS
Insulin dose reduction	-3.5	<0.001	9.21	<0.001

Models of HbA1c change and weight change has been altered to HbA1c reduction and weight reduction, with appropriate changes to T-values to aid interpretation

### GLP-1 and Insulin – Who?

 The data from the GLP-1 audits suggests that patients on insulin who do well are the ones with smaller total daily insulin dose and shorter diabetes duration



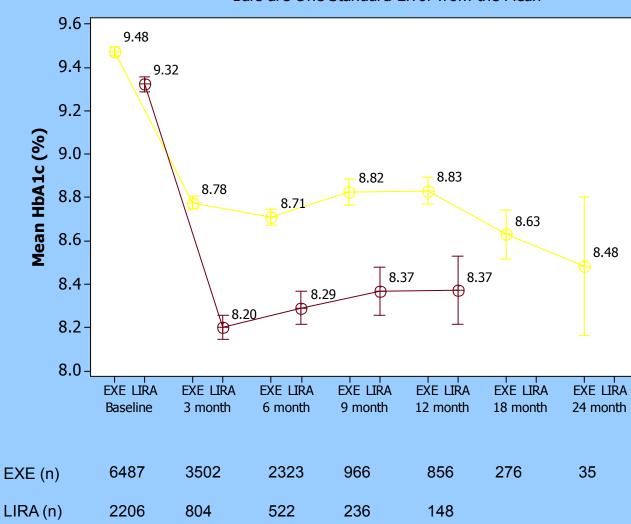
# HbA1c and Weight changes - effects with time



# HbA1c changes with time: exenatide and liraglutide









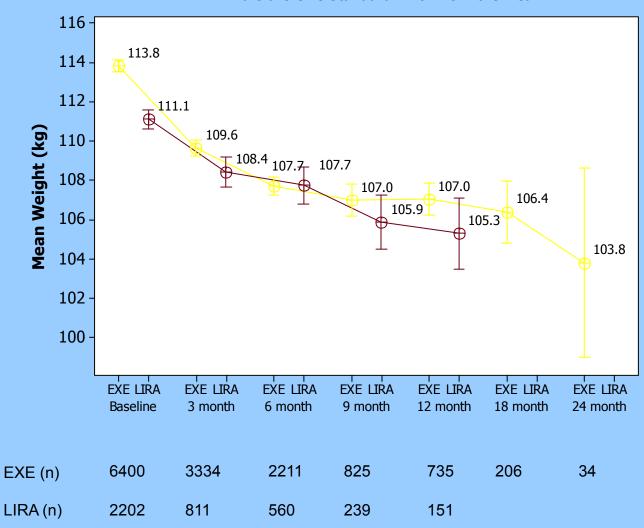
All pairwise HbA1c comparisons with baseline for exenatide and liraglutide were p<0.001, except exenatide 0v24m, p=0.021

Liraglutide data may include patients who have stopped liraglutide

# Weight changes with time: exenatide and liraglutide







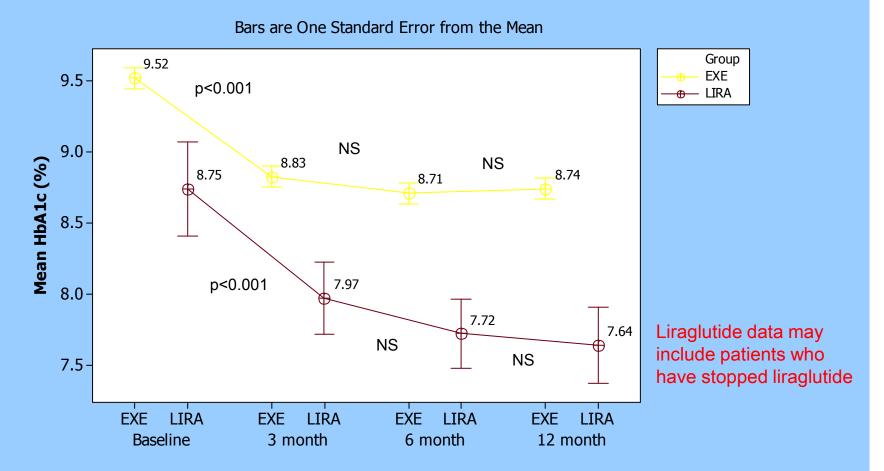


All pairwise Weight comparisons with baseline for exenatide and liraglutide were p<0.001

Liraglutide data may include patients who have stopped liraglutide

# General Linear Model of 584 and 31 patients with baseline, 3 month, 6 month and 12 month HbA1c after exenatide and liraglutide

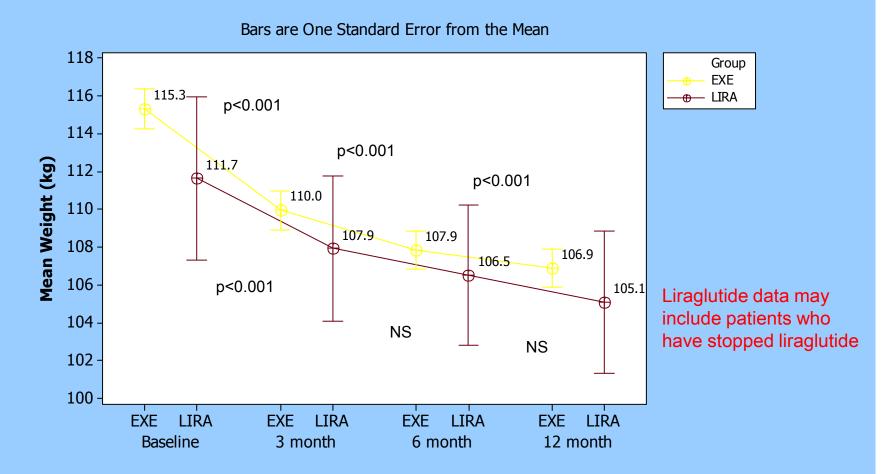




HbA1c changes were significant between baseline and 3 months but not between 3 and 6 months, or 6 and 12 months

# General Linear Model of 481 and 30 patients with baseline, 3 month, 6 month and 12 month Weight after exenatide and liraglutide





Weight changes were significant between all time intervals for exenatide; and baseline v 3 month for liraglutide

## **Findings**

- Both GLP-1 agents showed remarkably similar HbA1c and Weight effects over time
- HbA1c reduction occur predominantly in the first 3 months after GLP-1 agonist start and then plateauxs
- Weight reduction continued to occur until 12 months and appears to continue until 24 months

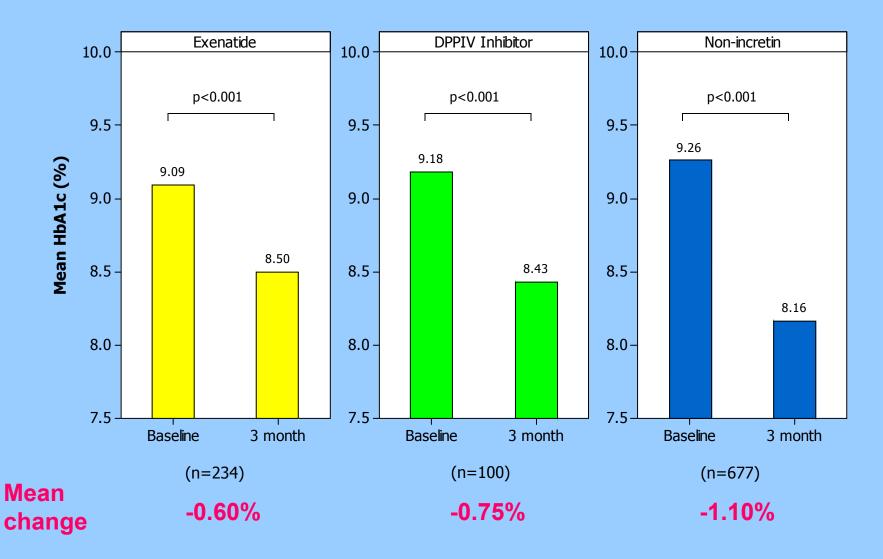


# Effects of exenatide and gliptin switch to liraglutide



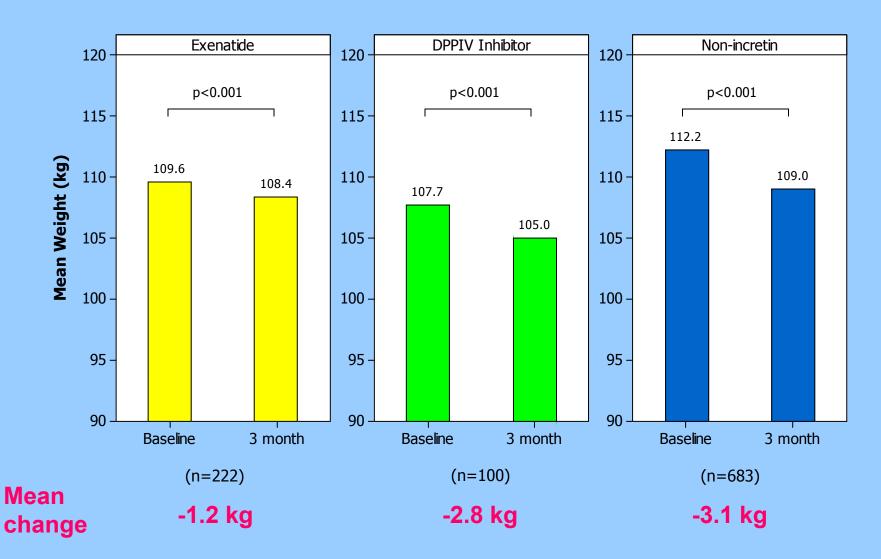
# Baseline vs 3 month HbA1c among patients on Exenatide, DPPIV inhibitors and Non-incretin therapies starting liraglutide





# Baseline vs 3 month Weight among patients on Exenatide, DPPIV inhibitors and Non-incretin therapies starting liraglutide





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2.	Bob Ryder, Hisham Ibrahim, Peter Davies et al, SWBH NHS Trust	231
3.	Shenaz Ramtoola & Geraint Jones et al, Royal Blackburn Hospital, Blackburn	209
4.	Karen Adamson, Ferelith Green et al, St John's Hospital, Livingston	182
5.	Laila King, Ralph Abraham et al, London Medical, London	180
6.	David Dove et al, Wexham Park Hospital, Slough	163
7.	Jackie Elliott et al, Sheffield Teaching Hospitals, Sheffield	154
8.	Mark Edwards, Helen Doolittle et al, The Hillingdon Hospital, Uxbridge	136
9.	Keith Sands, Lincoln County Hospital, Lincoln	132
10.	Julie Mehaffy Jean MacLeod et al, North Tees General Hospital, Stockton-on-Tees	125
11.	Zin Zin Htike, Anne Kilvert, Brian Mtemererwa et al, Northampton General Hospital	115
12.	Roland Guy et al, Basingstoke and North Hampshire NHS Foundation Trust, Hampshire	111
13.	Jeffrey W Stephens et al, Morriston Hospital, Swansea	110
14.	Richard Paisey et al, Torbay Hospital, Torquay	106
15.	Patrick English et al, Derriford Hospital, Plymouth	104
16.	Alison Melvin, Julia Pledger & Nick Morrish et al, Bedford Hospital, Bedford	103
17.	Phil Coates, Peter Daggett, Gill Green et al, Staffordshire DGH, Stafford	102
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5.	Chris Kelly, Alison Mackenzie, Linda Buchanan et al, NHS Forth Valley, Stirling	177
6.	Saiful Kassim, Adele Kennedy et al, Northern HSC, County Antrim	146
7.	John Lindsay, Maurice O'Kane, Kenneth Moles et al, Altnagelvin Hospital, Derry	130
8.	Karen Adamson, Nicola Zammit et al, NHS Lothian, Edinburgh	89
9.	lan Lawrence, Zin Zin Htike, Marie-France Kong et al, University Hospitals of Leicester	86
10.	Shenaz Ramtoola, Manoj Mishra, Amar Ali et al, East Lancashire Hospitals, Blackburn	82
11.	Cartriona Duncan, John Chalmers, Victoria Hospital, Kirkcaldy	73
12.	Gayle Richards, Simon Croxson et al, University Hospitals Bristol	71
13.	Colin Semple, Brian Kennon et al, Southern General Hospital, Glasgow	69
14.	Satyan Rajbhandari, Lancashire Teaching Hospitals	69
15.	Maneesh Udiawar, Singleton Hospital, Swansea	66
16.	Priya George, Ninewells Hospital, Dundee	60
17.	Richard Paisey, Jamie Smith, Kate Lissett et al, Torbay Hospital	60
18.	Gul Bano, Natasha Patel, Fahad Ahmed et al, St Georges Hospital, London	59
19.	Steven Hunter, Barbara Cooke, Royal Victoria Belfast	58
20.	Baldev M Singh et al, New Cross Hospital, Wolverhampton	56
21.	Michael Mulcahy et al, Basildon University Hospital	56
22.	R Welby Henry et al, Belfast City Hospital	52
23.	W P Stephens, A George et al, Trafford General Hospital	50

