ABCD Nationwide Exenatide Audit

Dr Bob Ryder

on behalf of the ABCD nationwide exenatide audit contributors

ABCD Spring Meeting, Newcastle, May 7 2010

Acknowledgment

- The ABCD nationwide exenatide audit is an independent audit supported by an unrestricted grant from Eli Lilly Ltd

ABCD
Association of British Clinical Diabetologists

Disclaimer

- The following presentation represents a provisional analysis of the data as of early May 2010. Further analyses are on going on a database which is still being improved as Centres respond to queries about possible typographical errors etc. Furthermore the below is an “intention to treat analysis” of the data - analyses taking into account patients who discontinued exenatide will be undertaken as information is returned from Centres on the patients concerned

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- *Exenatide 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*

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- Headlines from the data analysis to be presented in a trilogy of events:
  - DUK satellite symposium March 2 2010
  - DUK main meeting March 3 2010
  - ABCD Spring meeting, Newcastle May 7 2010

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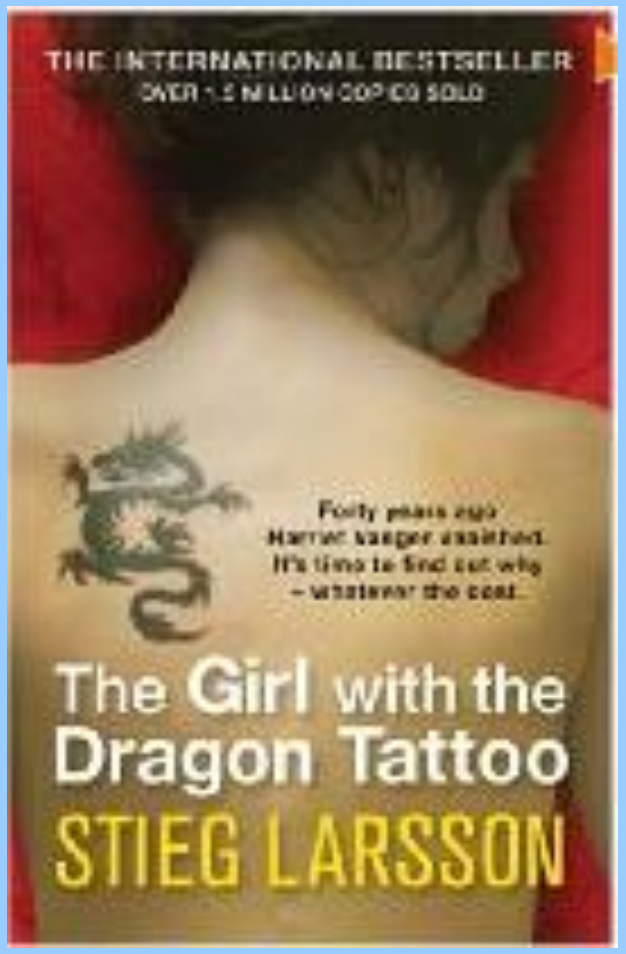
Association of British Clinical Diabetologists

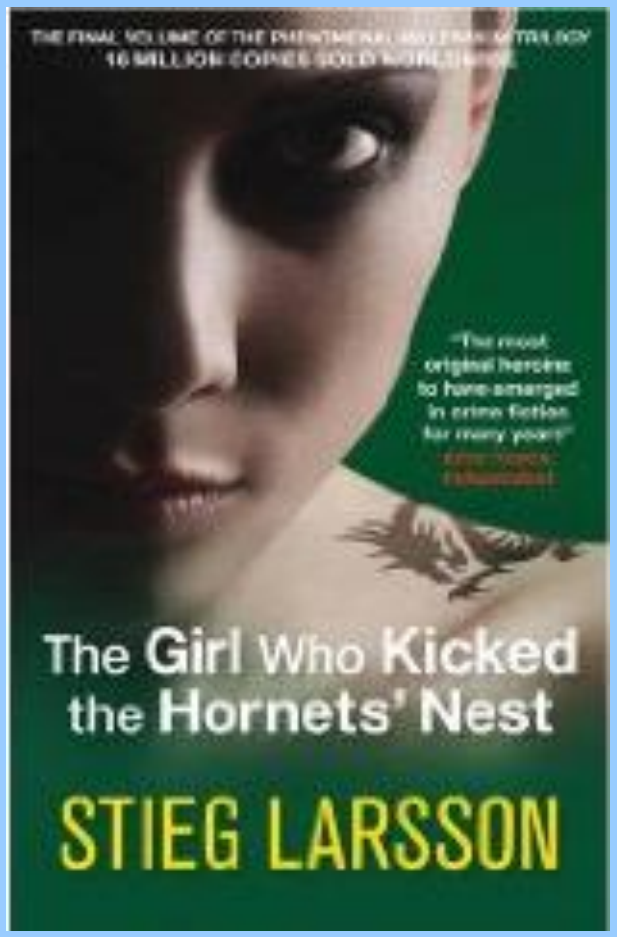
A Trilogy?

The Leaders Trilogy

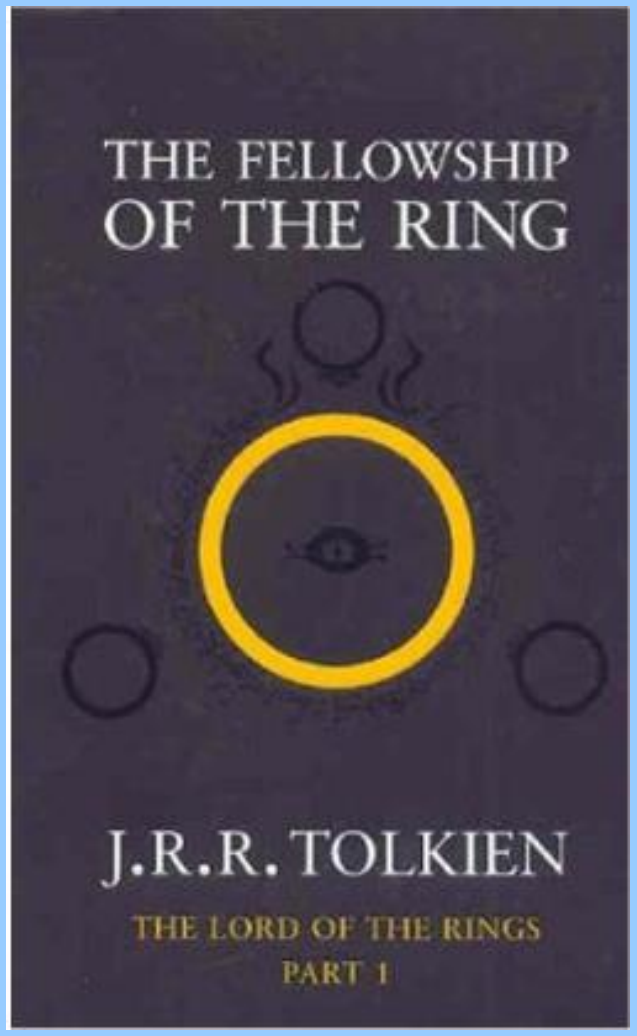
The Leaders Trilogy

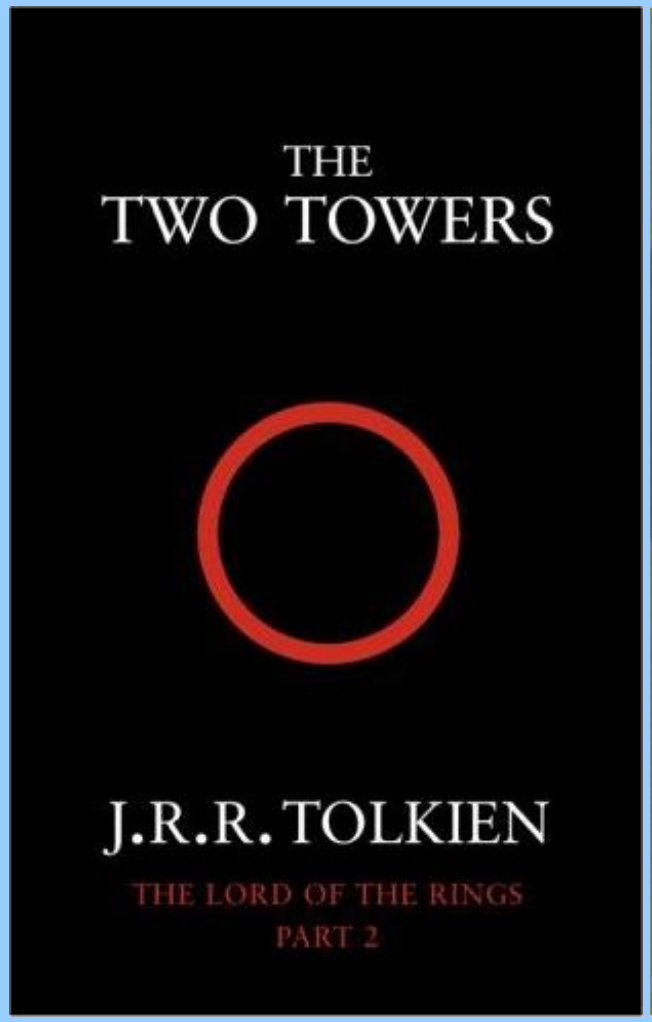
The Millennium Trilogy

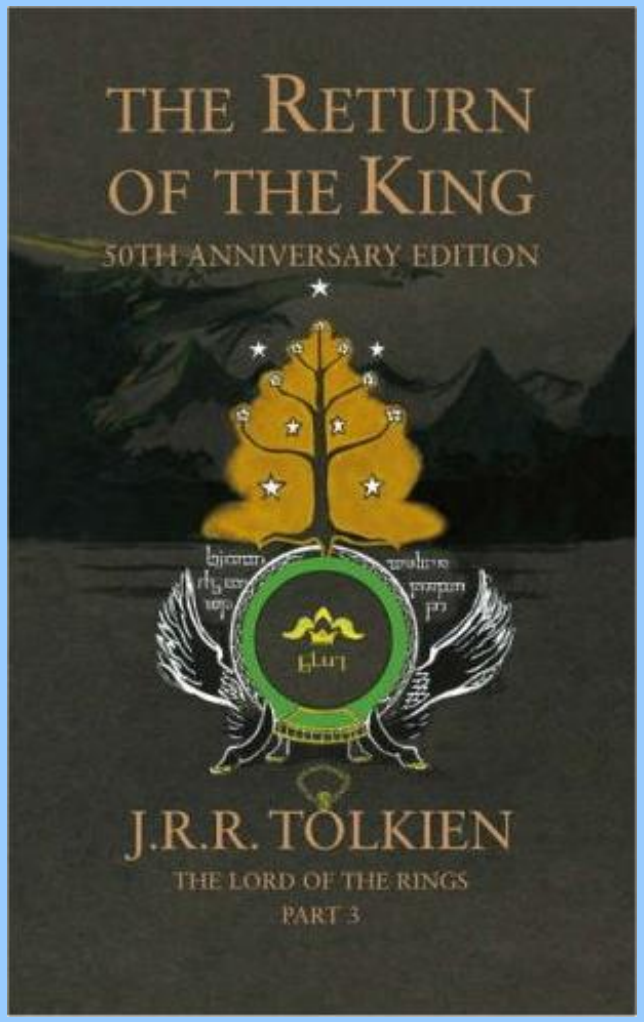


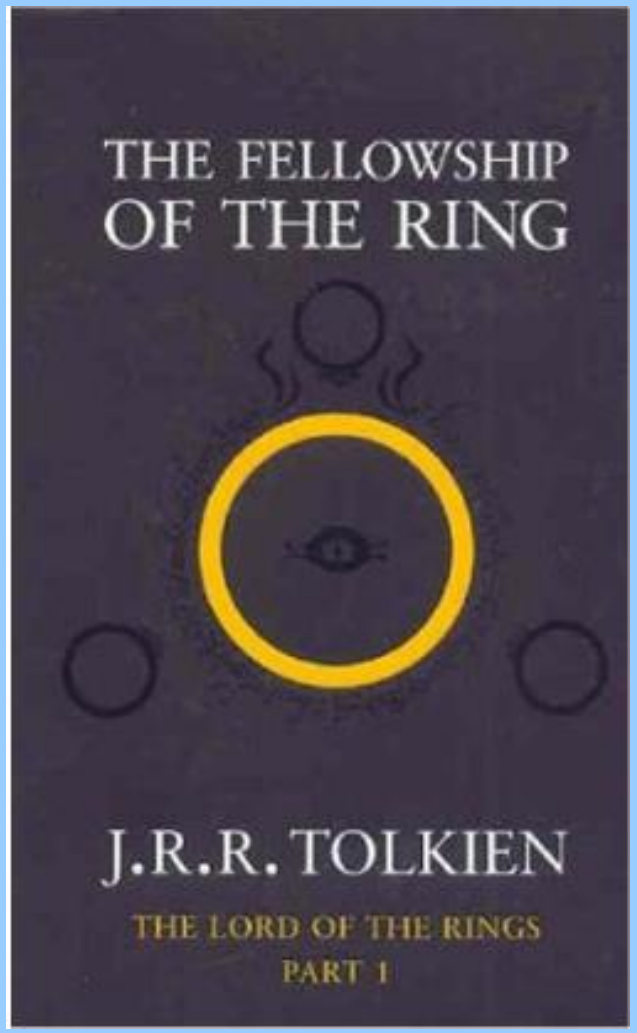


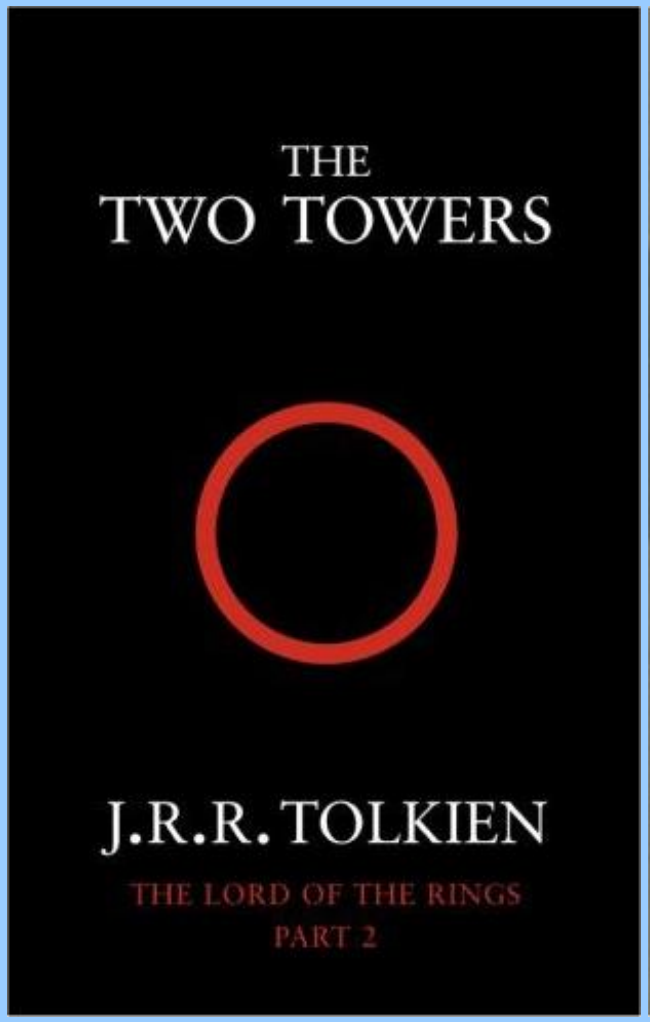
The Lord of the Rings

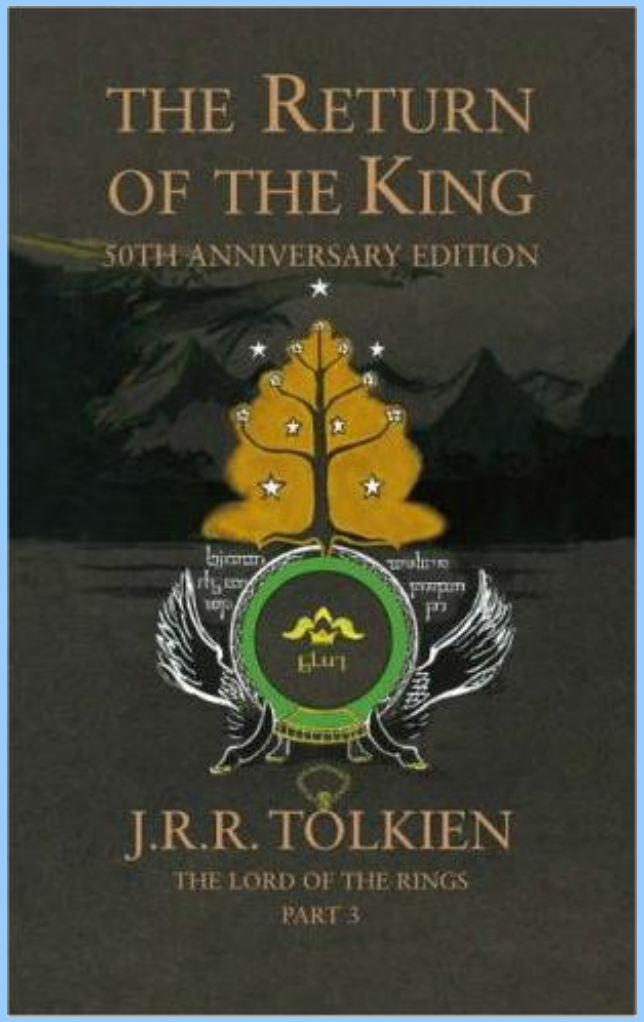







THE FELLOWSHIP
OF THE RING
J.R.R. TOLKIEN
THE LORD OF THE RINGS
PART 1


THE
TWO TOWERS
J.R.R. TOLKIEN
THE LORD OF THE RINGS
PART 2


THE RETURN
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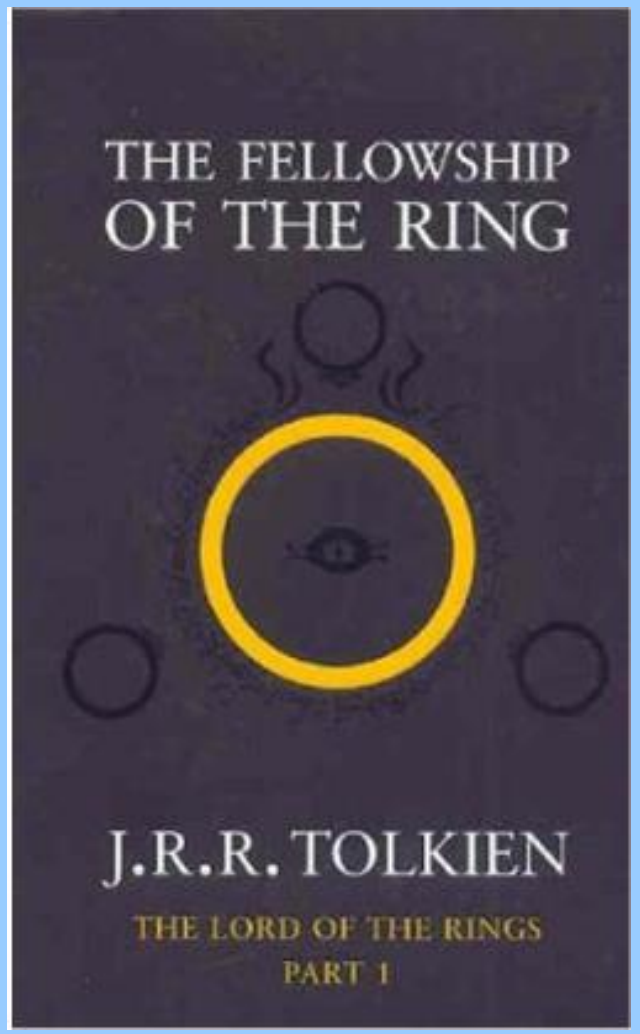
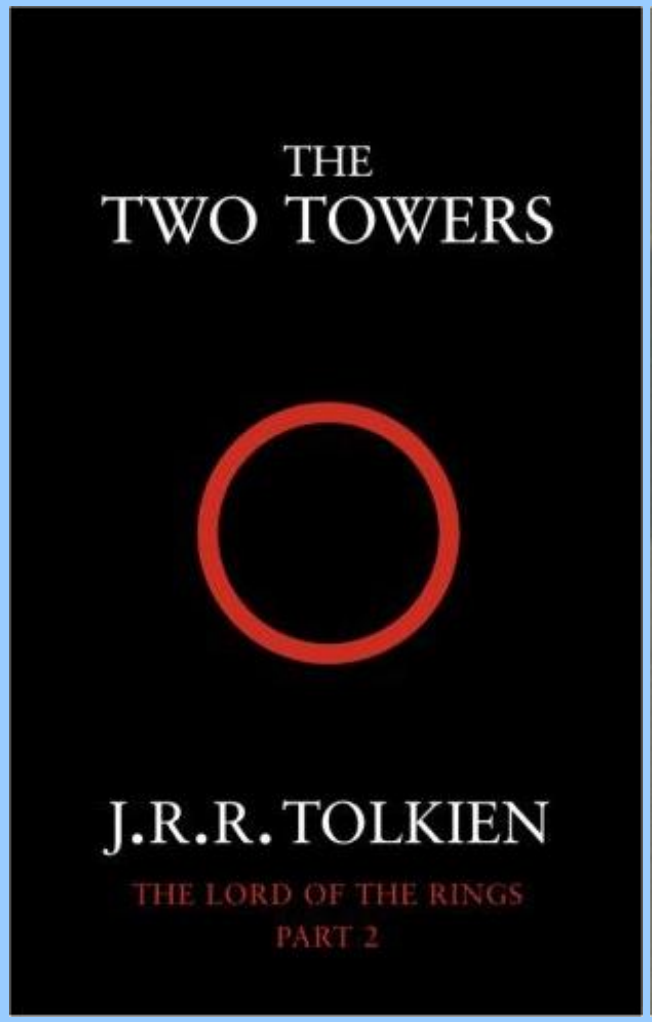
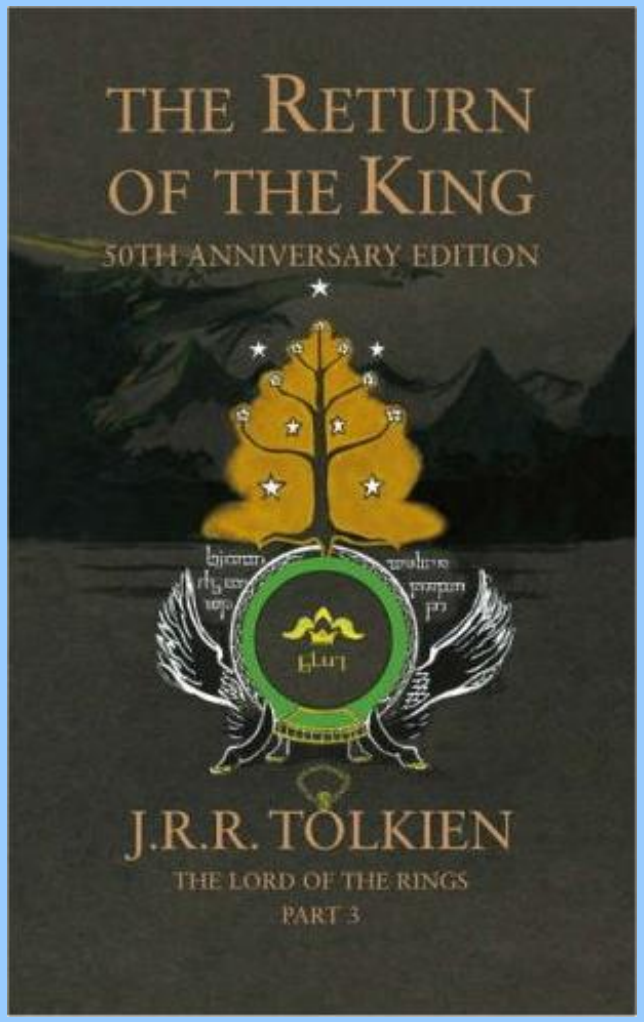
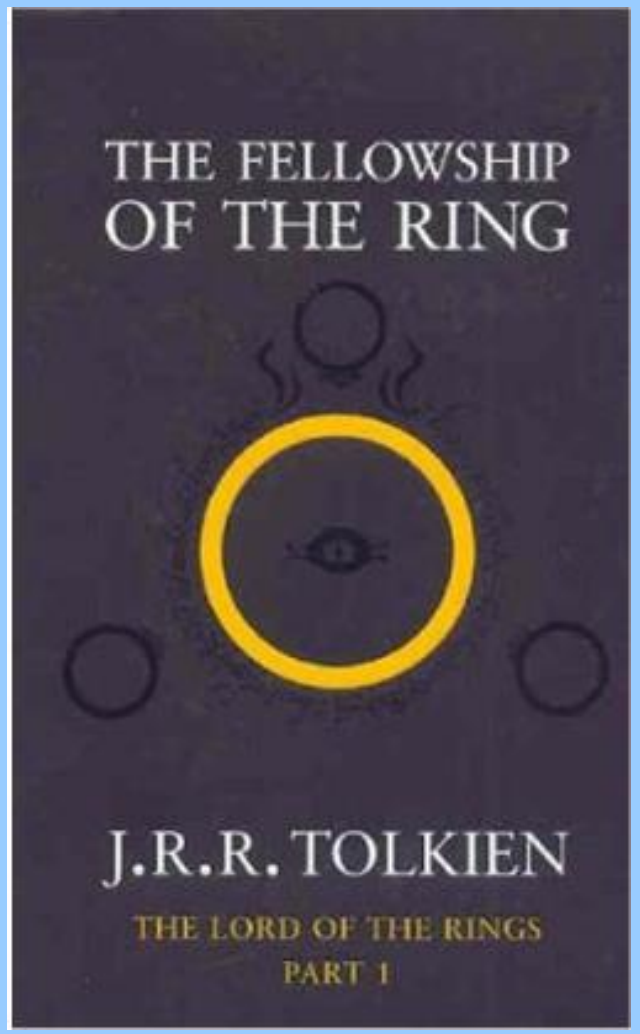
50TH ANNIVERSARY EDITION
J.R.R. TOLKIEN
THE LORD OF THE RINGS
PART 3

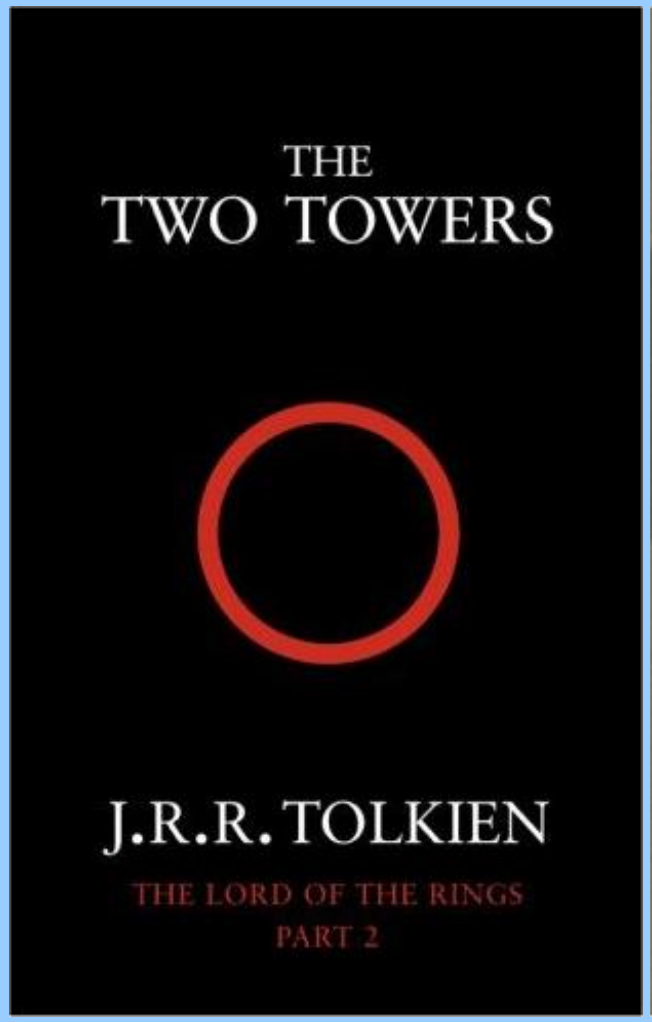


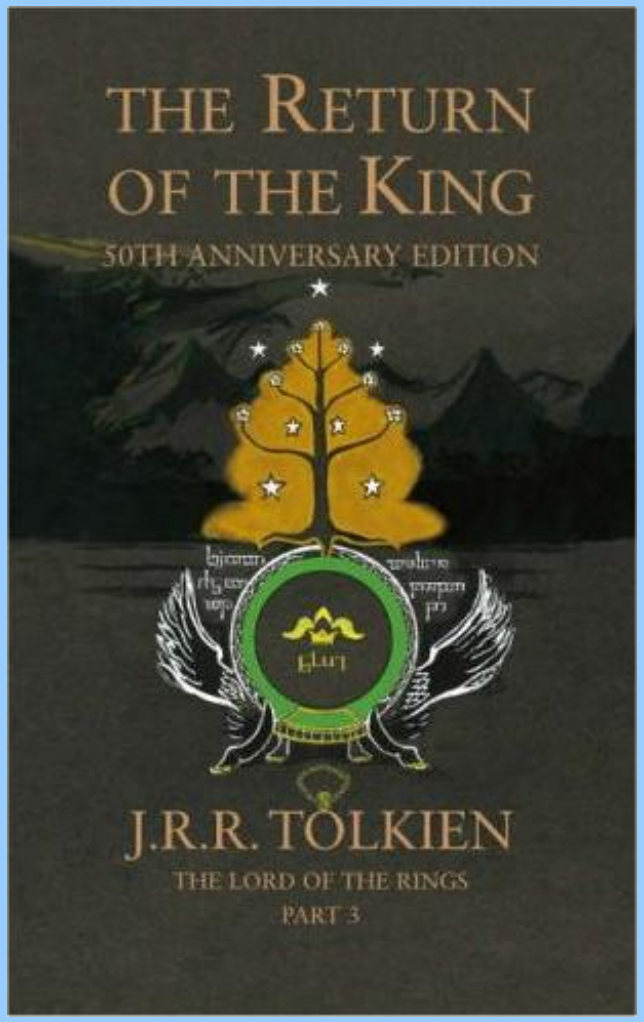




March 2 2010:
Main findings
Detailed data
at 6 months







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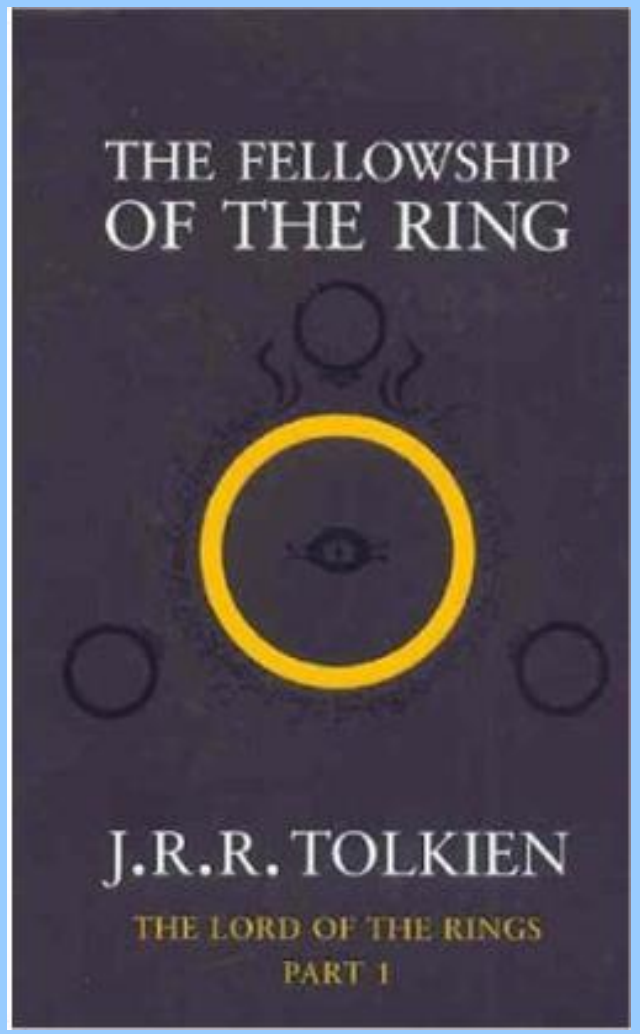

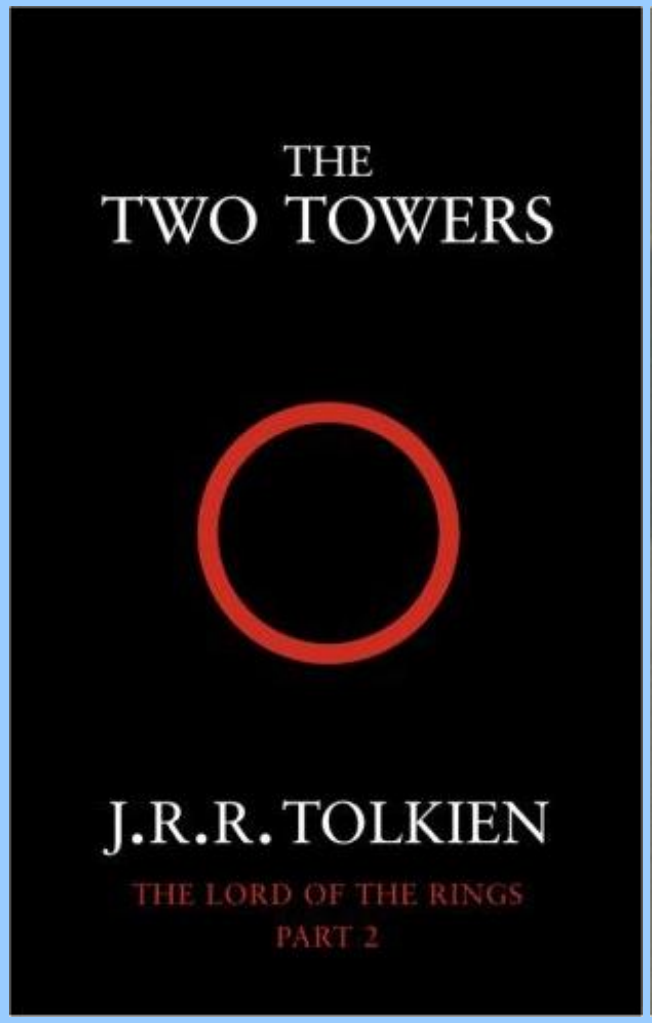

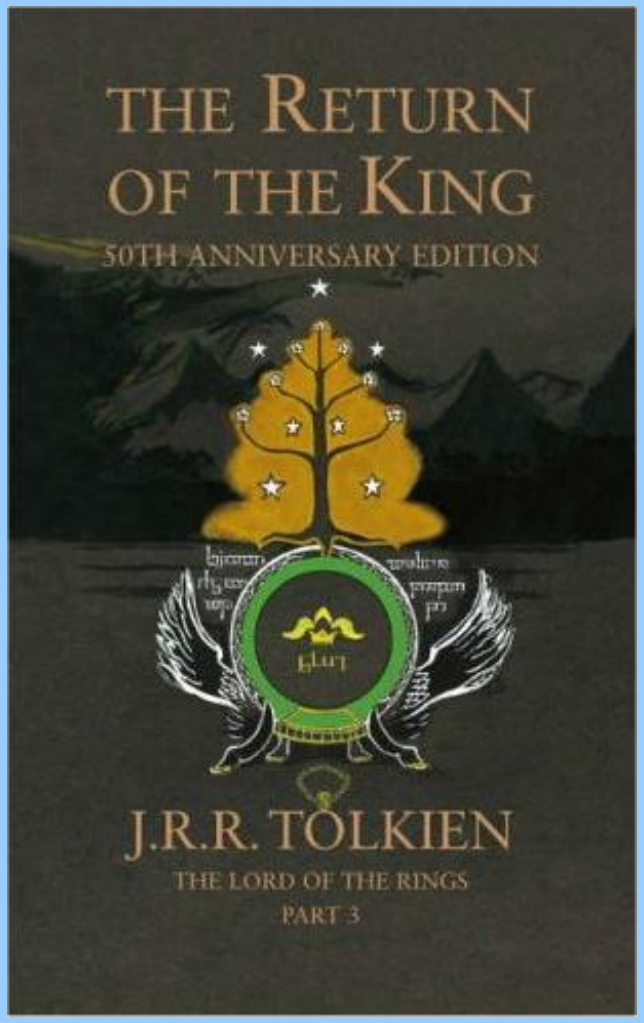

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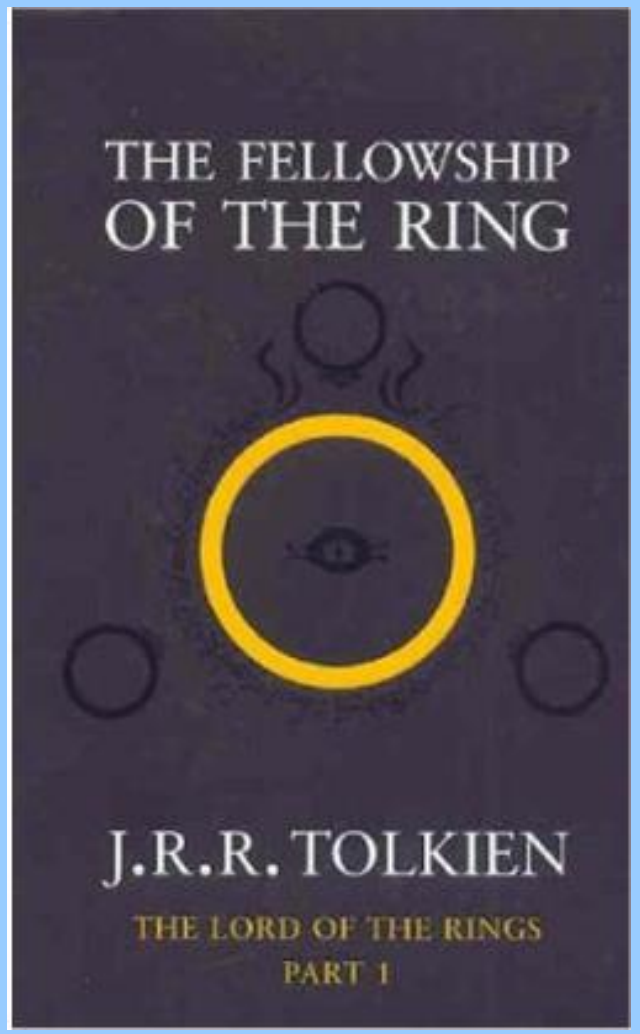
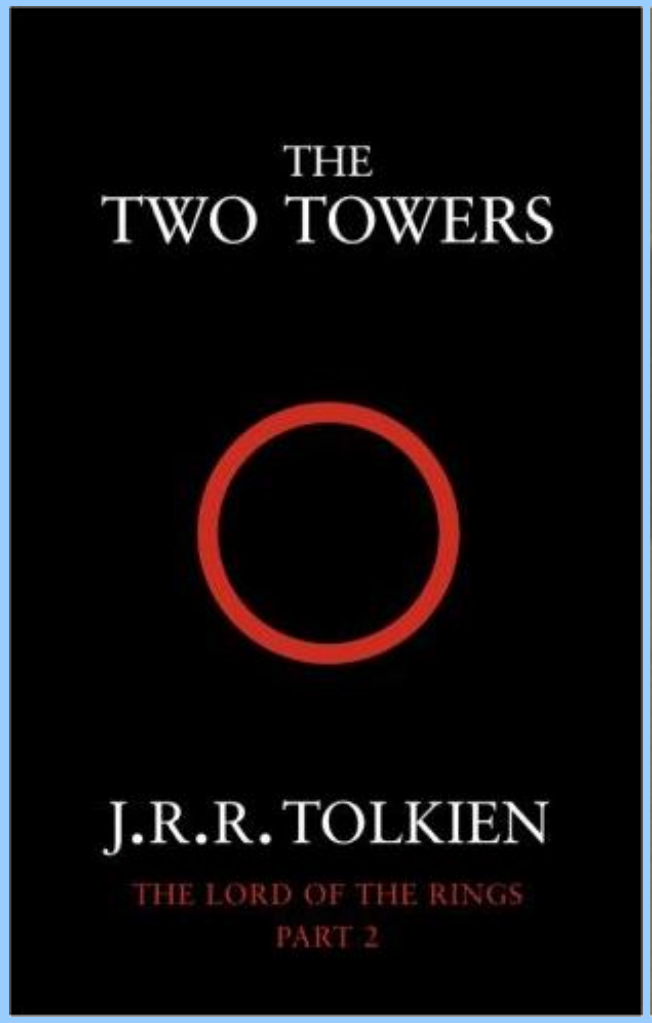
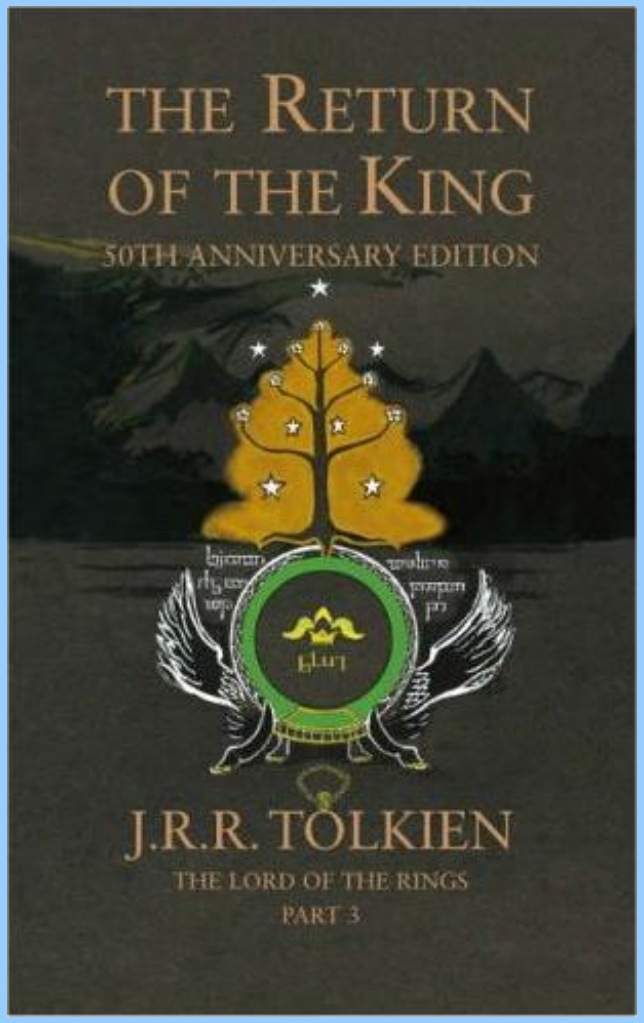
March 3 2010:
NICE 6 month targets
Response with time







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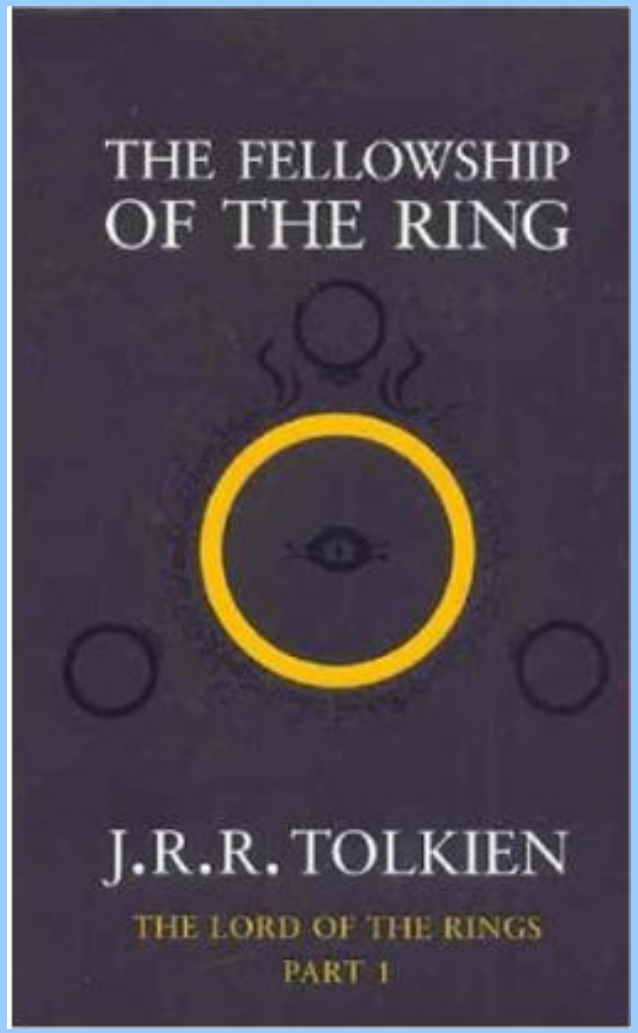

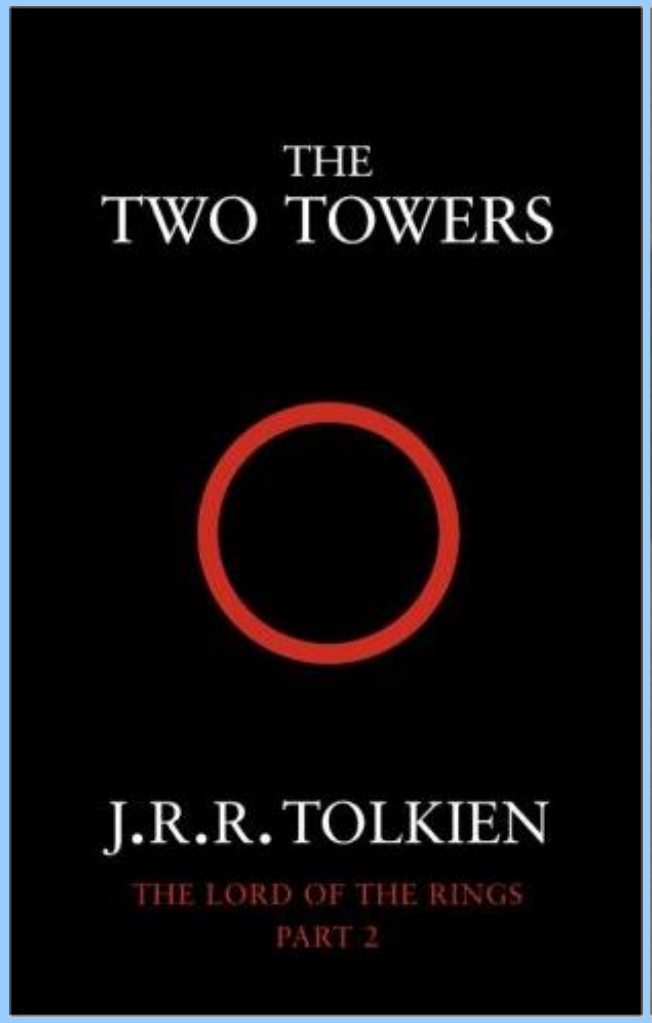

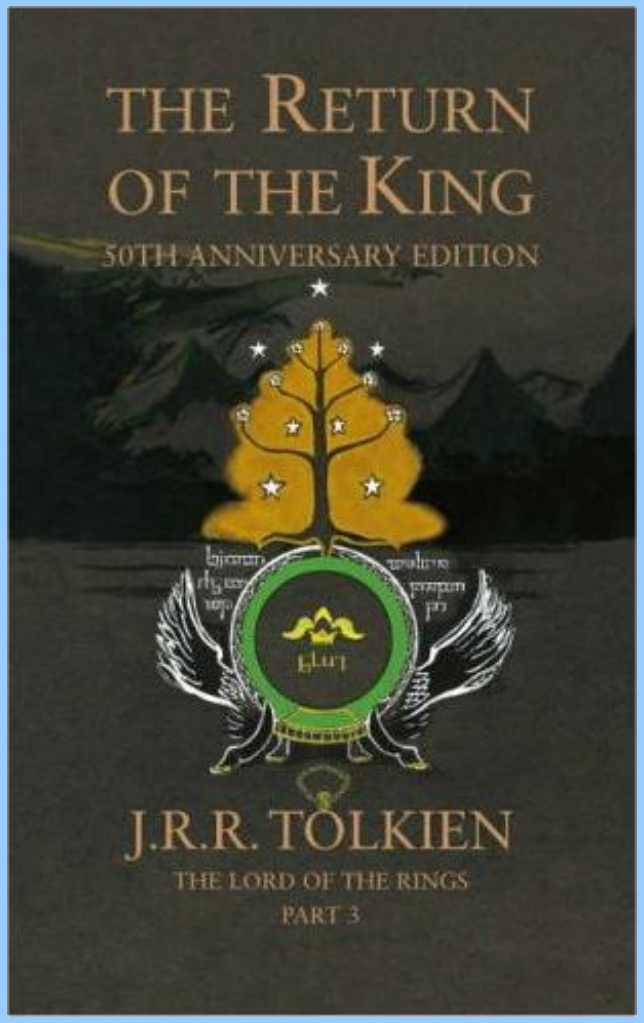

March 2 2010:
Main findings
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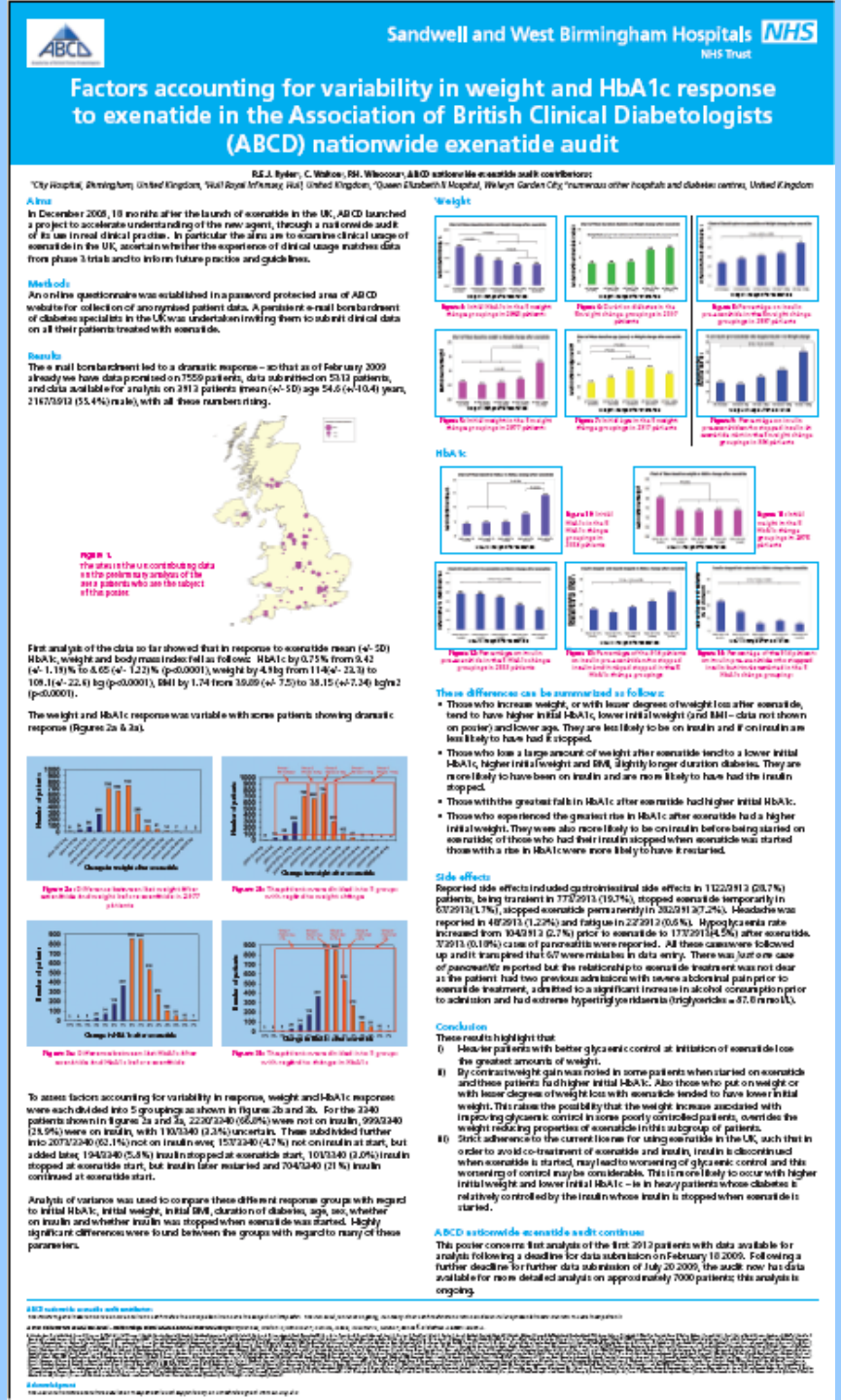
March 3 2010:
NICE 6 month targets
Response with time

May 7 2010:
With insulin



Sandwell and West Birmingham Hospitals NHS
NHS Trust

Factors accounting for variability in weight and HbA1c response to exenatide in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit

R.E.J. Ryder, C. Walton, P.H. Wilcocson, ABCD nationwide exenatide audit contributors:
City Hospital, Birmingham, United Kingdom, Royal Infirmary, Hull, United Kingdom, Queen Elizabeth II Hospital, Welwyn Garden City, Numerous other hospitals and diabetes centres, United Kingdom

Aims

In December 2008, 18 months after the launch of exenatide in the UK, ABCD launched a project to accelerate understanding of the new agent, through a nationwide audit of its use in real clinical practice. In particular the aims are to examine clinical usage of exenatide in the UK, ascertain whether the experience of clinical usage matches data from phase 3 trials and to inform future practice and guidelines.

Methods

An online questionnaire was established in a password protected area of ABCD website for collection of anonymised patient data. A persistent e-mail bombardment of diabetes specialists in the UK was undertaken inviting them to submit clinical data on all their patients treated with exenatide.

Results

The e mail bombardment led to a dramatic response – so that as of February 2009 already we have data promised on 7559 patients, data submitted on 5313 patients, and data available for analysis on 3913 patients (mean (+/- SD) age 54.6 (+/-10.4) years, 2167/3913 (55.4%) male), with all these numbers rising.

FIGURE 1.
The areas in the UK contributing data as to the position at the analysis of the 3913 patients who are the subject of this poster.

First analysis of the data so far showed that in response to exenatide mean (+/- SD) HbA1c, weight and body mass index fell as follows: HbA1c by 0.75% from 9.42 (+/- 1.19)% to 8.65 (+/- 1.22)% (p<0.0001), weight by 4.1kg from 114(+/- 23.3) to 108.1(+/- 22.6) kg (p<0.0001), BMI by 1.74 from 39.89 (+/- 7.5) to 38.15 (+/-7.34) kg/m2 (p<0.0001).

The weight and HbA1c response was variable with some patients showing dramatic response (figures 2a & 3a).

To assess factors accounting for variability in response, weight and HbA1c responses were each divided into 5 groupings as shown in figures 2b and 3b. For the 3340 patients shown in figures 2a and 3a, 2220/3340 (66.8%) were not on insulin, 999/3340 (29.9%) were on insulin, with 119/3340 (3.3%) uncertain. These subdivided further into 2073/3340 (62.1%) not on insulin ever, 153/3340 (4.7%) not on insulin at start, but added later, 194/3340 (5.8%) insulin stopped at exenatide start, 101/3340 (2.0%) insulin stopped at exenatide start, but insulin later restarted and 704/3340 (21 %) insulin continued at exenatide start.

Analysis of variance was used to compare these different response groups with regard to initial HbA1c, initial weight, initial BMI, duration of diabetes, age, sex, whether on insulin and whether insulin was stopped when exenatide was started. Highly significant differences were found between the groups with regard to many of these parameters.

Weight

HbA1c

These differences can be summarized as follows:

- Those who increase weight, or with lesser degrees of weight loss after exenatide, tend to have higher initial HbA1c, lower initial weight (and BMI – data not shown on poster) and lower age. They are less likely to be on insulin and if on insulin are less likely to have had it stopped.
- Those who lose a large amount of weight after exenatide tend to a lower initial HbA1c, higher initial weight and BMI, slightly longer duration diabetes. They are more likely to have been on insulin and are more likely to have had the insulin stopped.
- Those with the greatest fall in HbA1c after exenatide had higher initial HbA1c.
- Those who experienced the greatest rise in HbA1c after exenatide had a higher initial weight. They were also more likely to be on insulin before being started on exenatide, of those who had their insulin stopped when exenatide was started those with a rise in HbA1c were more likely to have it restarted.

Side effects

Reported side effects included gastrointestinal side effects in 1122/3913 (28.7%) patients, being transient in 777/3913 (19.7%), stopped exenatide temporarily in 67/3913(1.7%), stopped exenatide permanently in 382/3913(9.8%). Headache was reported in 487/3913 (1.23%) and fatigue in 223/3913 (0.6%). Hypoglycaemia rate increased from 104/3913 (2.7%) prior to exenatide to 177/3913(4.5%) after exenatide. 7/3913 (0.18%) cases of pancreatitis were reported. All these cases were followed up and it transpired that 6/7 were mistakes in data entry. There was just one case of pancreatitis reported but the relationship to exenatide treatment was not clear as the patient had two previous admissions with severe abdominal pain prior to exenatide treatment, admitted to a significant increase in alcohol consumption prior to admission and had extreme hypertriglyceridaemia (triglycerides = 87.8 mmol/L).

Conclusion

These results highlight that:

i) Heavier patients with better glycaemic control at initiation of exenatide lose the greatest amounts of weight.

ii) By contrast weight gain was noted in some patients when started on exenatide and these patients had higher initial HbA1c. Also those who put on weight or with lesser degrees of weight loss with exenatide tended to have lower initial weight. This raises the possibility that the weight increase associated with improving glycaemic control in some poorly controlled patients, overrides the weight reducing properties of exenatide in this subgroup of patients.

iii) Strict adherence to the current license for using exenatide in the UK, such that in order to avoid co-treatment of exenatide and insulin, insulin is discontinued when exenatide is started, may lead to worsening of glycaemic control and this worsening of control may be considerable. This is more likely to occur with higher initial weight and lower initial HbA1c – ie in heavy patients whose diabetes is relatively controlled by the insulin whose insulin is stopped when exenatide is started.

ABCD nationwide exenatide audit continues:

This poster concerns first analysis of the first 3913 patients with data available for analysis following a deadline for data submission on February 18 2009. Following a further deadline for further data submission of July 20 2009, the audit now has data available for more detailed analysis on approximately 7000 patients; this analysis is ongoing.

ABCD nationwide exenatide audit contributors:

Acknowledgments

Association of British Clinical Diabetologists

- So what were those presentations at
  - DUK satellite symposium March 2009
  - ABCD Spring meeting May 2009
  - Poster EASD Vienna September 2009
  - Poster IDF Montreal October 2009

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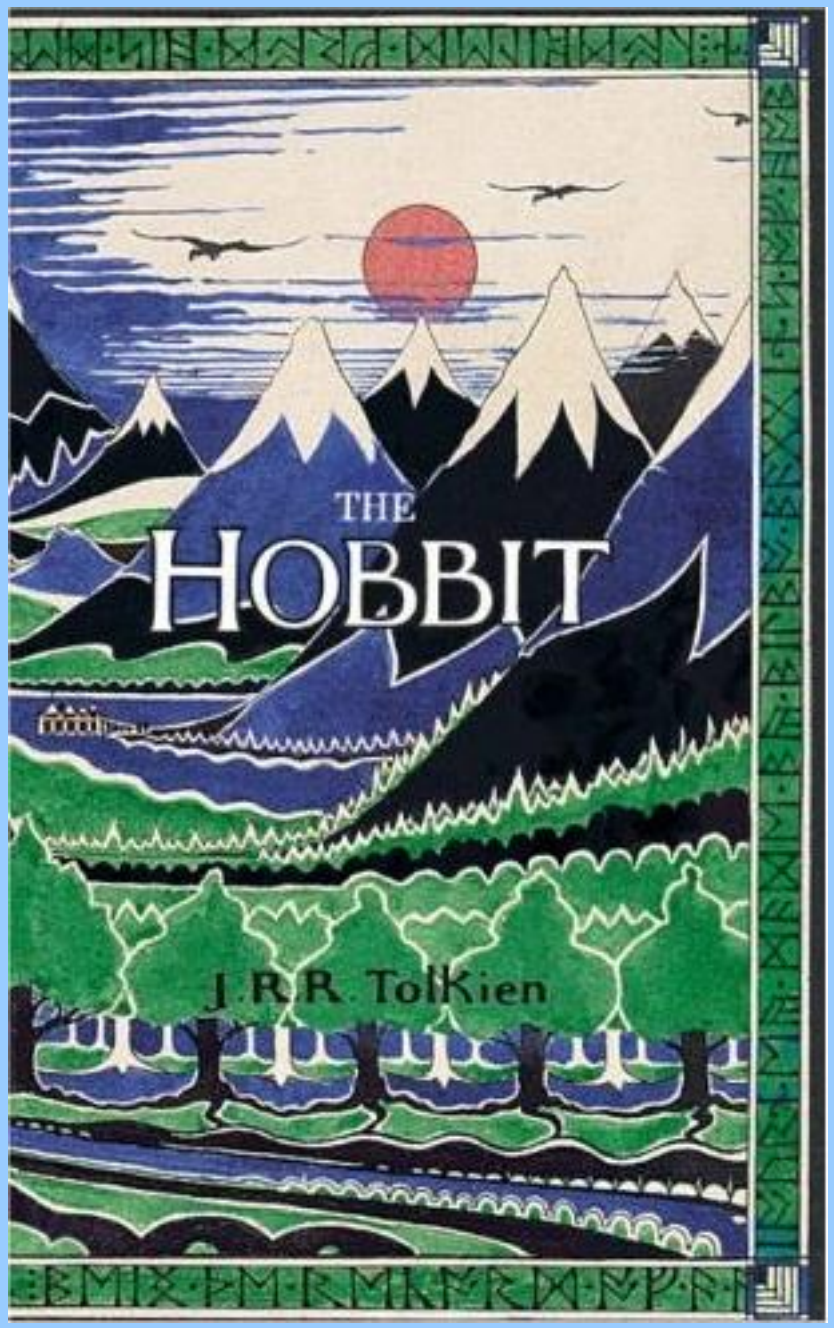
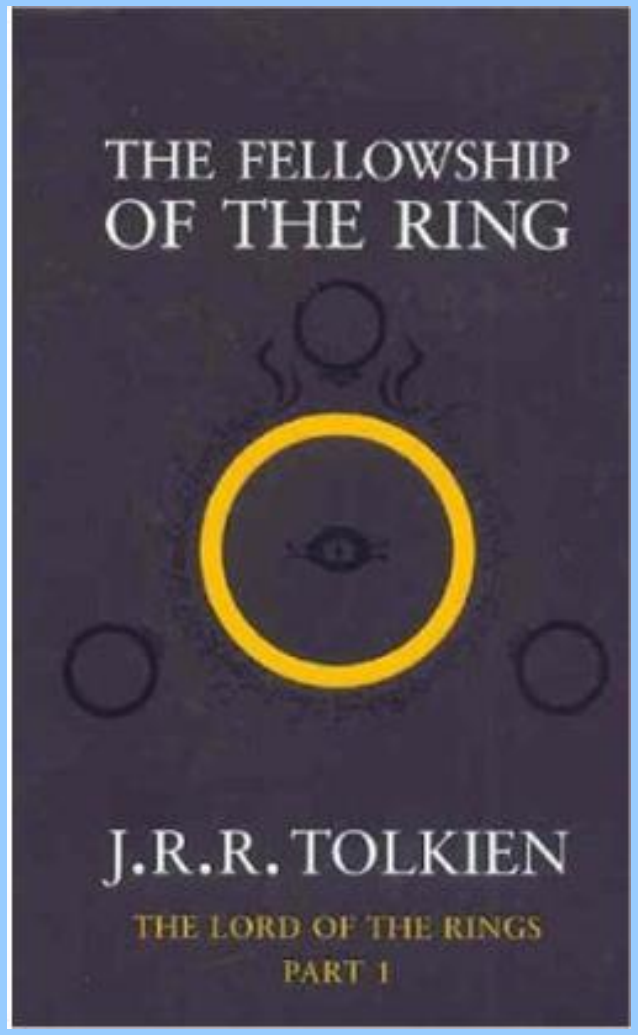


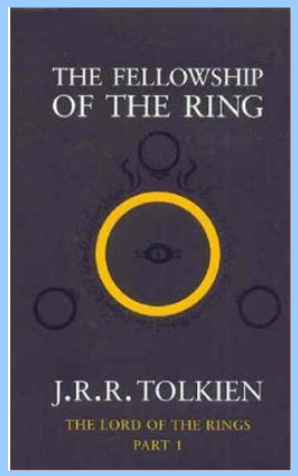
n=3913



March 2 2010:
Main findings
Detailed data
at 6 months

The Fellowship of the ABCD nationwide exenatide audit

- 315 contributors
- 126 centres



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ABCD nationwide exenatide audit contributors

The following are those whom we know about.

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ABCD nationwide exenatide audit – initial setup, maintenance and nationwide analysis: *Ryder REJ, Walton C, Winocour P, Cull ML, Jose B, Sukumar N, Mills AP, Sands K, Shafiq W, Rigby A, Thozhukat S, Thong K. Statistician: Blann A.*

Addenbrookes Hospital: Adler A, Evans M, Simmons D, O'Rahilly S, Coll T, Farooqi S, Park A. **Altnagelvin Area Hospital:** Lindsay J, Kelly J. **Antrim Area Hospital:** Kennedy A, Rooney D. **Barnsley Hospital:** Uchegbu E. **Basildon University Hospital:** Mulcahy M, Krishnan L. **Basingstoke and North Hampshire NHS Foundation Trust:** Guy R, Turner B, Akester K, Lewis G, Harrison O, Tombling S, Lloyd G, Hughes C, Lowe C. **Bedford Hospital:** Morrish N, Melvin A, Pledger J, Barron R. **Bedfordshire & Hertfordshire PGMS, Luton:** Rehman T, Sinclair A. **Belfast City Hospital:** Henry W. **Bolton Diabetes Centre:** Palin S, Kenz R. **Bristol Royal Infirmary:** Raghavan R, Phillips S, Bradley K. **Bronglais Hospital:** Kotonya C, Premawardhana LDKE. **Chesterfield Royal Hospital:** Mohammad M, Robinson RTCE, MacInerney RM. **Chorley & South Ribble Hospital:** Rajbhandari SM, Acharya S. **City Hospital, Birmingham:** Ryder REJ, Basu A, De P, Lee BC, Jose B, Sukumar N, McAloon CJ, Blann A, Mills AP, Cull ML, Lee A, Rawcliffe C, Ryder B, Burbridge W, Irwin S, Cutler J, Zzizinger A, Mehrali T, Bedi T, Stevenson-Mort J. **CMMC Foundation Trust, Manchester:** Jinadev P, Watts R, Abul-Ainine S, Salahuddin S. **Colchester General Hospital:** Bodmer C. **Conquest Hospital, St Leonards on Sea:** Dashora U, Castro E. **Countess of Chester:** Shulwalia R,, Ewins D, Goenka N. **County Hospital, Hereford:** Lloyd J. **Craigavon Area Hospital, Co Armagh:** Ritchie C. **Daisy Hill hospital, Newry:** Adil MM. **Derriford Hospital, Plymouth:** English P, Viney T, Laird O, Rigley R, Babu A, Blackmore M. **Dumfries & Galloway Royal Infirmary:** Bell E., Green F, Banerjee S. **East Surrey Hospital, Redhill:** Foster K, Natarajan G. **Eastbourne District Diabetes Centre:** Bending J, Afolayan J, Sheppard P. **Fairfield Hospital, Bury:** Rowles S, Smithurst HJ. **Falkirk and District Royal Infirmary:** Kelly C, Peden N, Currie J., Buchanan L. **Frimley Park Hospital:** Eliwe MH, Bingham E, Tringham JR. **Furness General, Barrow In Furness:** Chuni P, Hay C, Narayan S, Krishnan S. **Gartnavel General Hospital:** Small M, Jones G, McGrane D, Sainsbury G. **George Eliot Hospital Nuneaton:** Shaikh S, Patel V. **Good Hope Hospital, Sutton Coldfield:** Jones SL, Milles JJ, Griffiths U, Colloby M, Harold C**,** Rangan S, Morrison J. **Glasgow Royal Infirmary**, Fisher M, McGrane D. **Great Western, Swindon:** Govindan J, Price P, Ahmed S, Gardner A. **Guys & St Thomas Hospital, London:** Brackenbridge A, Reid A, Piper-Smith J, Preston J. **Hammersmith and Charing Cross:** Field BCT, Dornhorst A. **Harrogate Hospital:** Hammond P, Thirumurugan E,. **Heartlands Hospital, Birmingham:** John R, Patel M, Ulnaf S, Begum S. **Hillingdon Hospital, Uxbridge:** Edwards M, Doolittle H, Currie A, O'Sullivan S, Lillystone R. **Hinchinbrooke Hospital, Huntingdon:** Mathews AA. **Hull Royal Infirmary:** Walton C, Ng B, Kumar BK, Bosomworth A. **Ipswich Hospital:** Srinath A, Parkinson C, 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EG, Krishnan A, Clark J, Thondam S. **North Manchester General Hospital:** Rathur H, Savage M, Wiles P, Prakash P. **North Tees & Hartlepool Trust:** MacLeod J, Anthony S, Mehaffy J. **North Wales NHS Trust, Wrexham:** White H. **Northampton General Hospital** Htike ZZ, Kilvert A, Mtemererwa B, Nisal K, Fox C, Rippin J. **Bromley PCT:** Casiglia D. **Pinderfields General, Wakefield:** Nagi DK. **Poole Hospital NHS Foundation Trust:** Masding M, Osborne K, Wallace P. **PRH, Haywards Heath:** Smith A, Mabrook J. **Prince Philip Hospital, Llanelli:** Williams M, Aggarwal N. **Princess Royal, Bromley:** Lulsegged A. **Queen Alexandra, Portsmouth:** Cranston I, Darzy K. **Queen Elizabeth II Hospital, Welwyn Garden City:** Winocour PH. **Queen's Hospital, Burton:** Benn J. **Raigmore Hospital, Inverness:** McLaren L. **Rotherham General:** Franke B. **Royal Berkshire Hospital, Reading:** Simpson H, Reddy N, Barber T. **Royal Blackburn Hospital:** Astin J, Faina J, Whalley G, Ramtoola S, Jones G, Wilkinson R. **Royal Bournemouth:** Richards J, Richardson T. **Royal Cornwall Hospital, Treliske:** Fox T., Foote J, Browne D, Pinkney J **Royal Devon & Exeter:** Bowman P, Hattersley A, Vadiya B. **Royal Glamorgan Hospital, Llantrisant:** Evans P. **Royal Gwent Hospital, Newport:** Obuobie K. **Royal Infirmary of Edinburgh:** Jaap A, Noh R, Richards M. **Royal Liverpool University Hospital:** Vora J, Brake J. **Royal Oldham Hospital:** Mishra BM. **Royal Surrey County Hospital, Guildford:** Hordern V. **Royal United Hospitals, Bath:** Higgs E, Gouni R, Taylor P, Wylie S, Hall B, Hillier N, Neathercote D. **RSCH, Brighton:** Quin J, Robinson N. **Sandwell Hospital, West Bromwich:** Ibrahim H, Robertson D, Davies P, Banerjee P, Li YK, Wong KH, Barker N, Dhallu J, Farell D., R.M. Iqbal **Scunthorpe General:** Moisey R, Malik M, Dromgoole P, Elmalti A. **Selly Oak Hospital, Birmingham:** Creely S, Gough S, Hanif W. **Sheffield Teaching Hospitals:** Elliott J, Scott A. **Smethwick Health Centre:** Pall N, Harrington J. **South East CHCP, Glasgow:** Carson L-A. **Southampton General Hospital:** Sharp P, Brown B. **Southern General Hospital, Glasgow:** Semple C. **St John's Hospital, Livingston:** Adamson K, Green F. **St Mary's Hospital, Isle of Wight:** Kaklamanou M, Al-Mrayat M. **St Peter's Hospital, Chertsey:** Sennik D, Baxter M, Naqvi S, Suresh D, Miras A. **Staffordshire DGH, Stafford:** Coates P**,** Daggett P, Green F. **Stirling Royal Infirmary:** Kelly C, Mackenzie A, Peden N. **Bronglais Hospital, Aberystwyth:** Kotonya CA. **Sunderland Royal:** Nayar R, Carey P, Aspray T. **Taunton & Somerset:** Close C, Andrews R, Douek I, Watson J., Lambert P. **Torbay Hospital, Torquay:** Paisey R. **University Hospital Coventry Warwickshire:** Anderson S. **Ulster Hospital, Belfast:** Brennan U, Satti N, Harper R, Harding J. **Victoria Infirmary, Glasgow:** Stewart A. **Warwick Hospital** Rao RK, Gopinathan, Horrocks P. **Watford General Hospital:** Tharakan G, Simpson K. **West Suffolk Hospital, Bury St. Edmunds:** Majeed J, Clark J, Wijenaike N, Gurnell E, Hartley L, Abdullah H, Marath H. **Western General Hospital, Edinburgh:** Aniello L, McKnight JA, Strachen M, Reynolds R, Nyrenda M. **Berkshire East PCT:** Dove D, Aung T. **Whipps Cross University Hospital, London:** Lakhdar A, Manogaraan B. **Wirral Teaching Hospital, Upton Wirral:** Leong KS, Leong K, Lorains J, Joseph P, Leach J, Fenna I. **Whiteabbey Hospital:** Andrews J, Strrezlecka A. **Wishaw General, Lanarkshire:** O'Brien I, Davidson E. **Worcestershire Acute Hospitals, Worcester:** Newrick P, Jenkins D. **Wrexham Maelor:** Dixon AN, Munigoti S, Stanaway S, Harvey JN. **Wythenshawe Hospital, Manchester:** Younis N. **Yeovil District Hospital:** Bickerton AST, Crocker M, Down S. **York Hospital:** Jennings P, Hudson N.

Acknowledgment

The ABCD nationwide exenatide audit is an independent audit supported by an unrestricted grant from Eli Lilly Ltd

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The Fellowship of the ABCD nationwide exenatide audit

- 315 contributors
- 126 centres
- 6717 patients
  - 2154 (32.1%) submitted by ABCD members
  - 4563 (67.9%) submitted by non members
  - 2659 (39.6%) submitted by subweb
  - 4058 (60.4%) via spreadsheet
- 570945 data items

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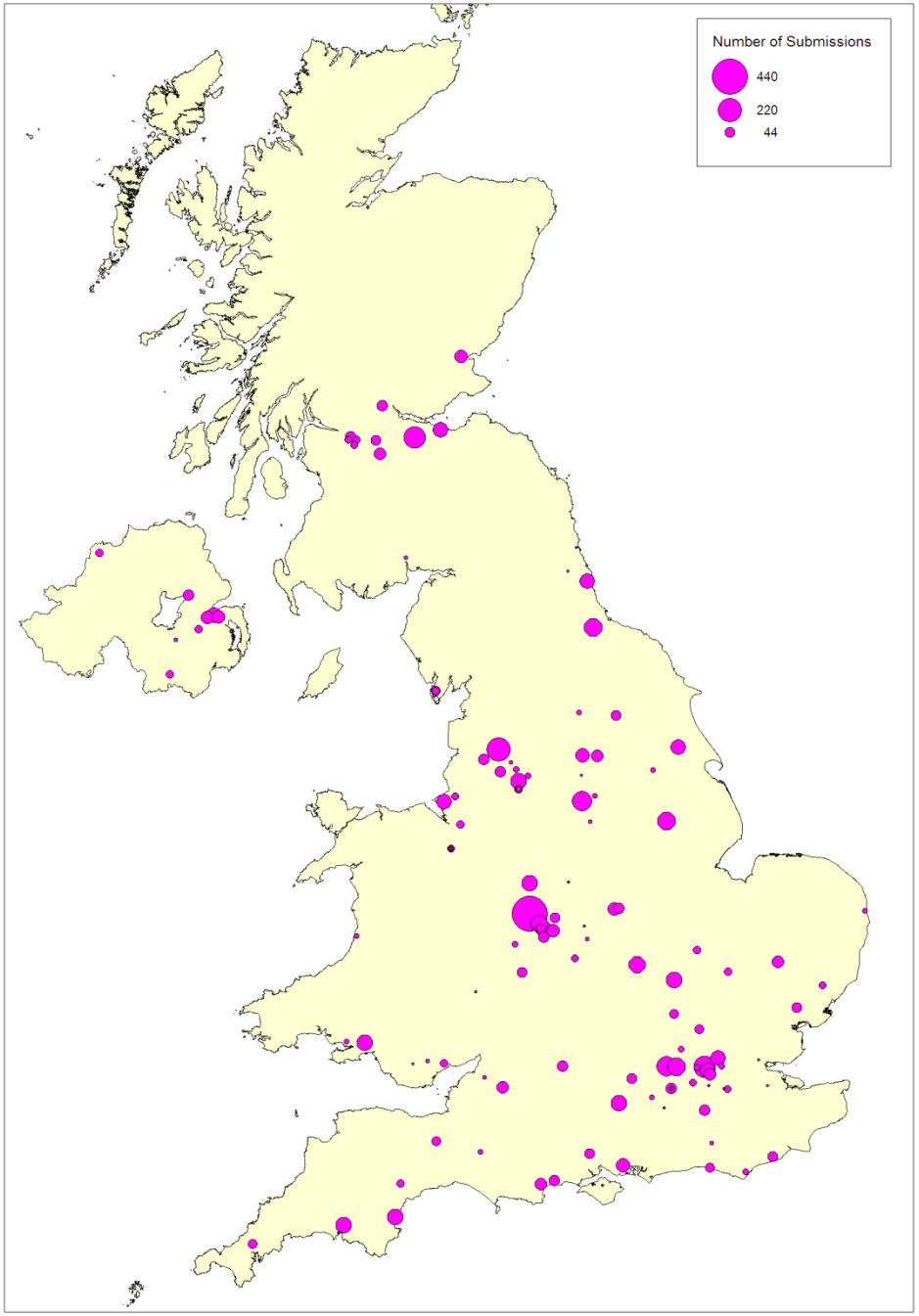

Association of British Clinical Diabetologists

Top contributors > 100 patients

1.	B.M. Singh, U. A. Nayak, J. Govindan, D.N.Kalupahana, New Cross Hospital, Wolverhampton	438
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
18.	Mark Savage, Phil Wiles & Parmeshwara Prakash et al, North Manchester General	101

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Premier league

1.	Wolverhampton Wonderers		438
2.	West Bromwich Albion		231
3.	Blackburn Rovers		209
4.	Livingston FC		182
5.	Tottenham Hotspurs	180	
6.	Slough Town FC		163
7.	Sheffield Wednesday		154
8.	Uxbridge FC		136
9.	Lincoln County		132
10.	Middlesbrough		125
11.	Northampton		115
12.	Basingstoke Town		111
13.	Swansea		110
14.	Torquay United		106
15.	Plymouth Argyle		104
16.	Bedford Town		103
17.	Stafford Town		102
18.	Manchester United		101

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Baseline

Male	55.5%	n=6375
Caucasian	84.4%	n=5099
Age (mean, years)	54.9	n=6234
Duration of diabetes (median (interquartile range), years)	8 (5-13)	n=5025
HbA1c (mean, %)	9.47	n=6597
Weight (mean, kg)	113.83	n=6509
BMI (mean, kg/m2)	38.9	n=3614
Systolic BP (mean, mmHg)	139.52	n=3112
Diasolic BP (mean, mmHg)	78.49	n=3112
Cholesterol (mean, mmol/L)	4.35	n=3002
HDL cholesterol (mean, mmol/L)	1.11	n=2497
Triglycerides (mean, mmol/L)	2.57	n=2115

n= number from the 6717 patients with this data item submitted

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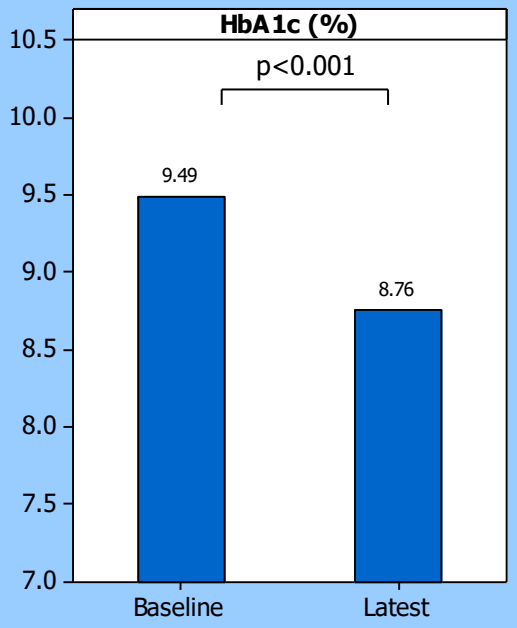
Main findings

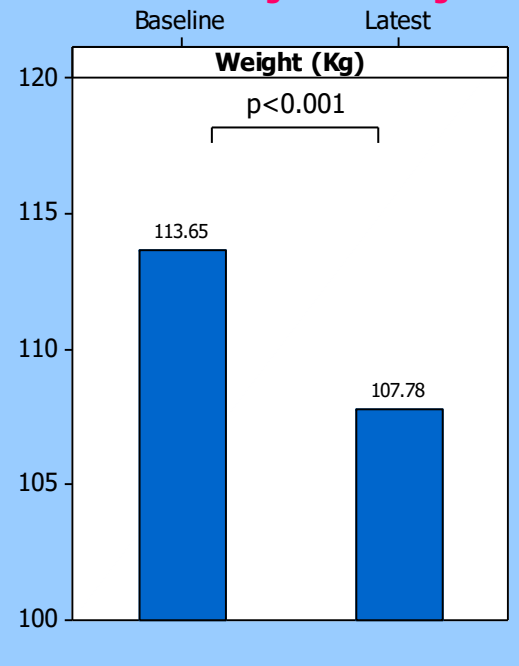
Baseline versus latest following exenatide

	N	Weeks after exenatide start (median (range))
HbA1c	4691	26.3 (6.6 – 164.1)
Weight	4506	26.1 (6.6 – 159.0)
BMI	2396	26.1 (6.6 – 150.6)
Waist circumference	512	25 (6.0 – 146.0)

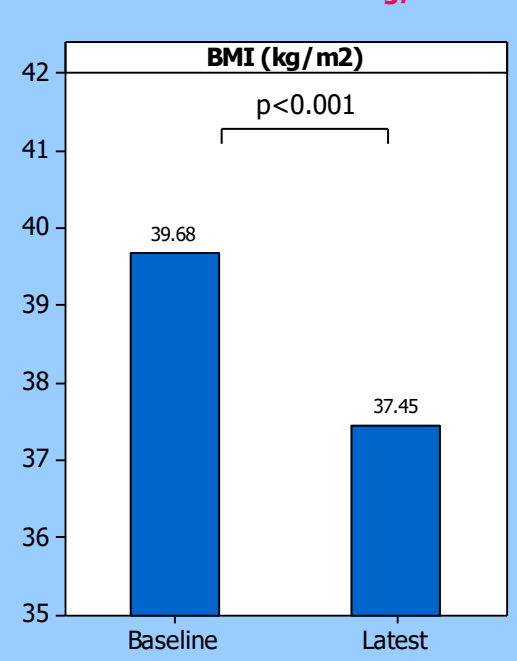
Fall in HbA1c = 0.73%



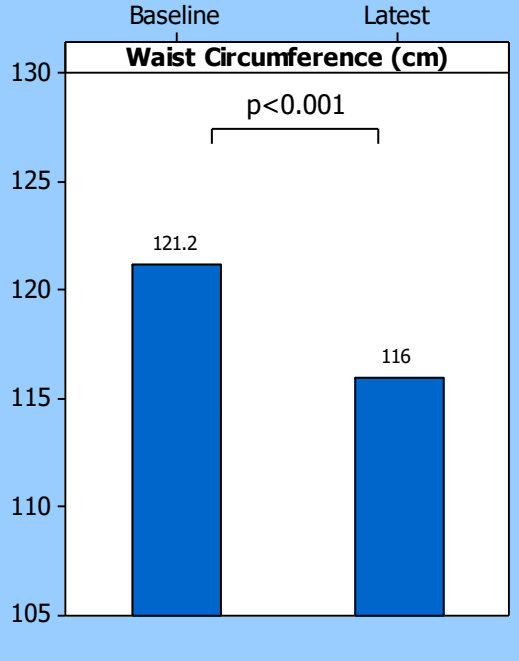
Fall in weight = 5.87 Kg



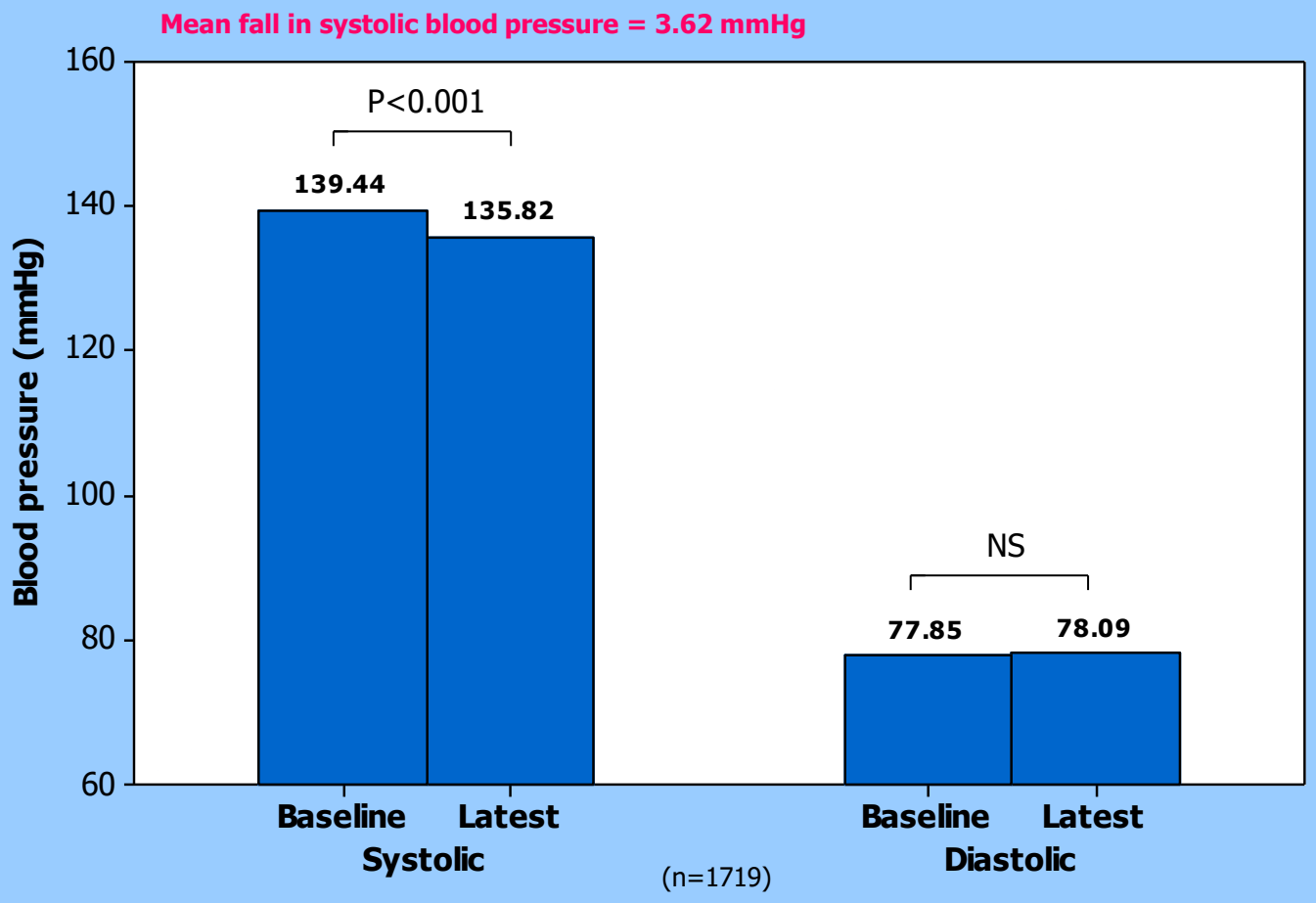
Fall in BMI = 2.23 kg/m²



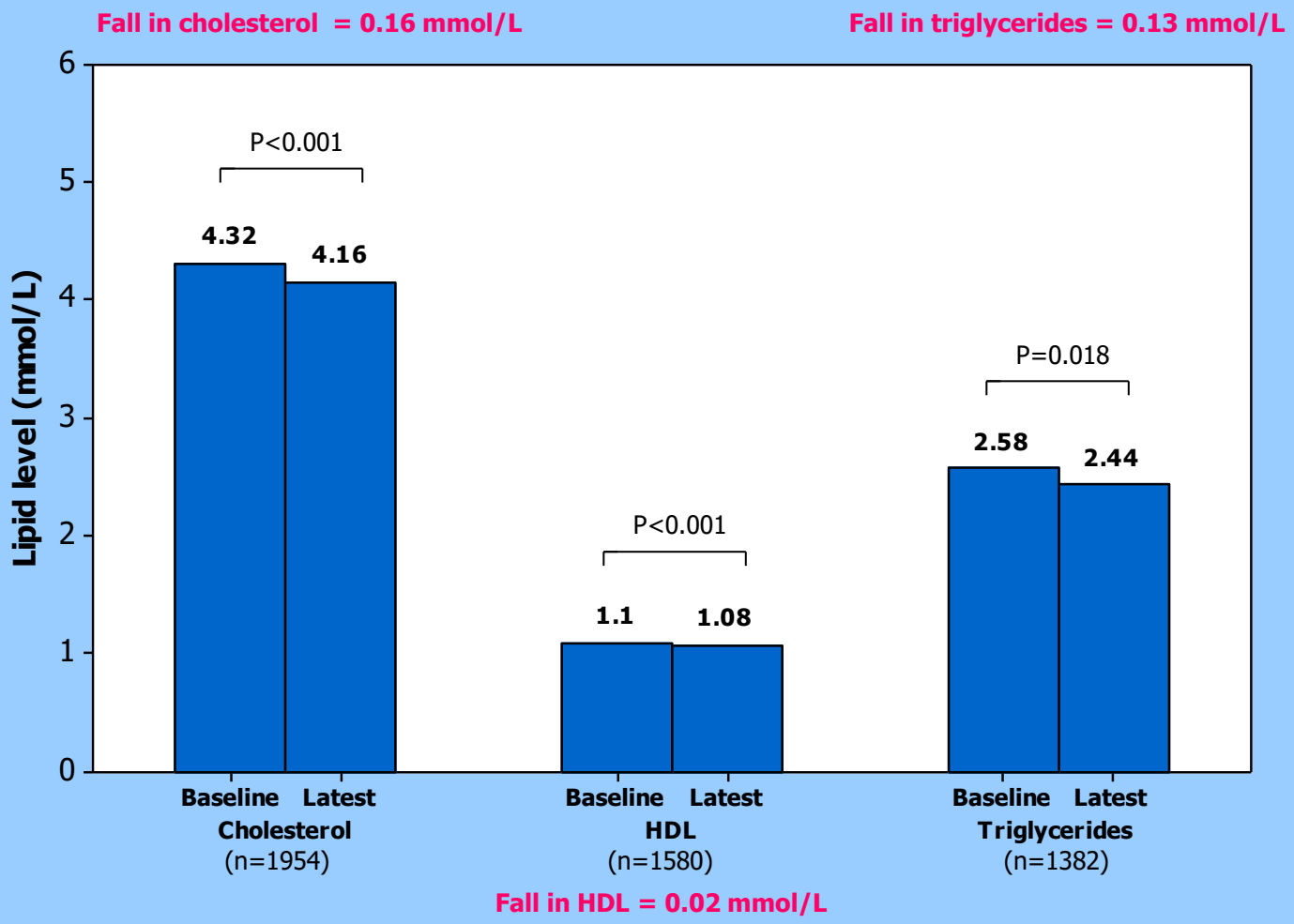
Fall in waist circumference = 5.2cm



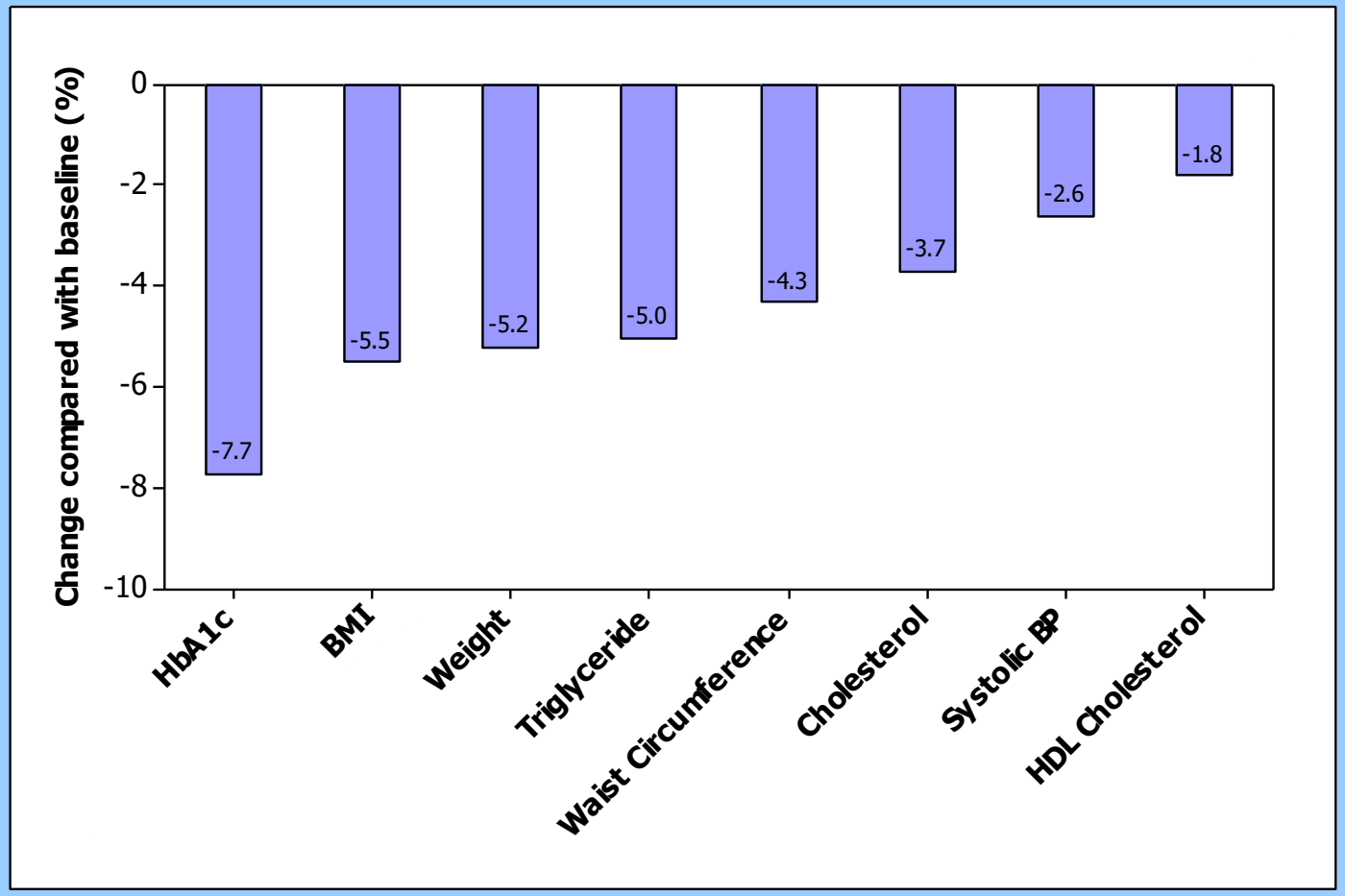
Baseline versus latest blood pressure following exenatide



Baseline versus latest lipids following exenatide



Magnitude of change among various parameters after exenatide use



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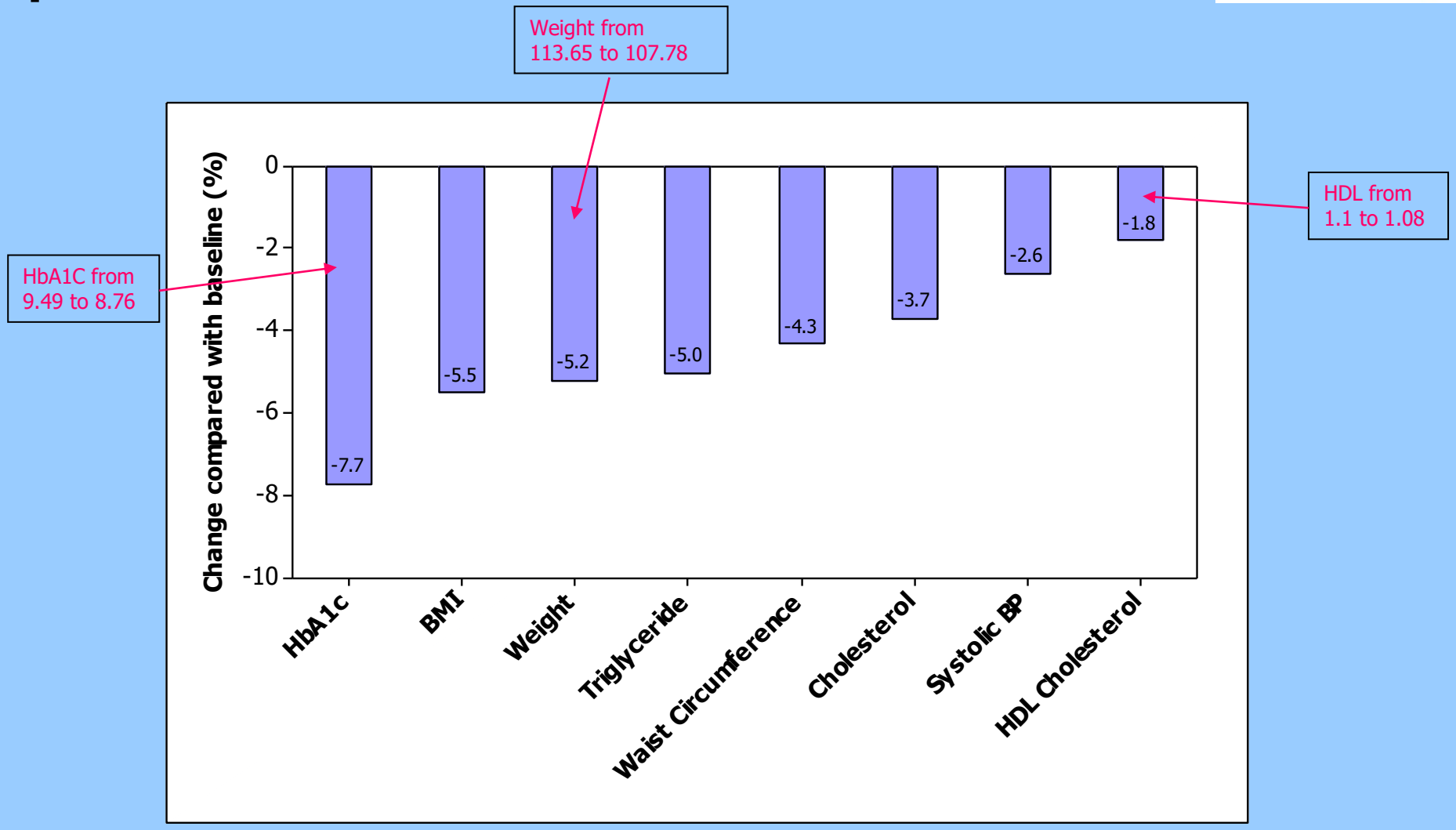
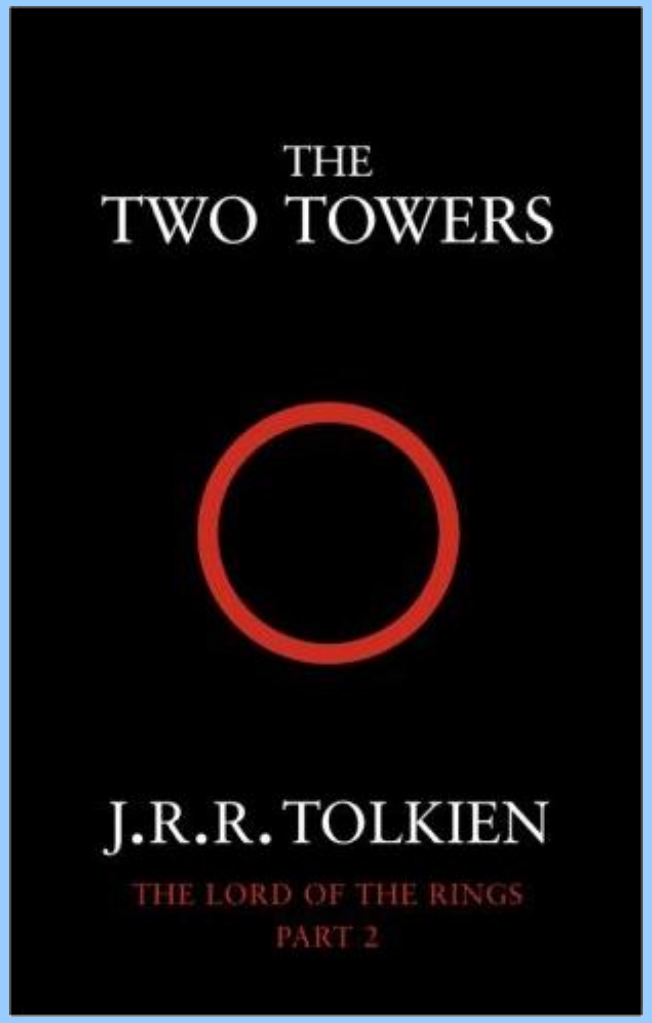
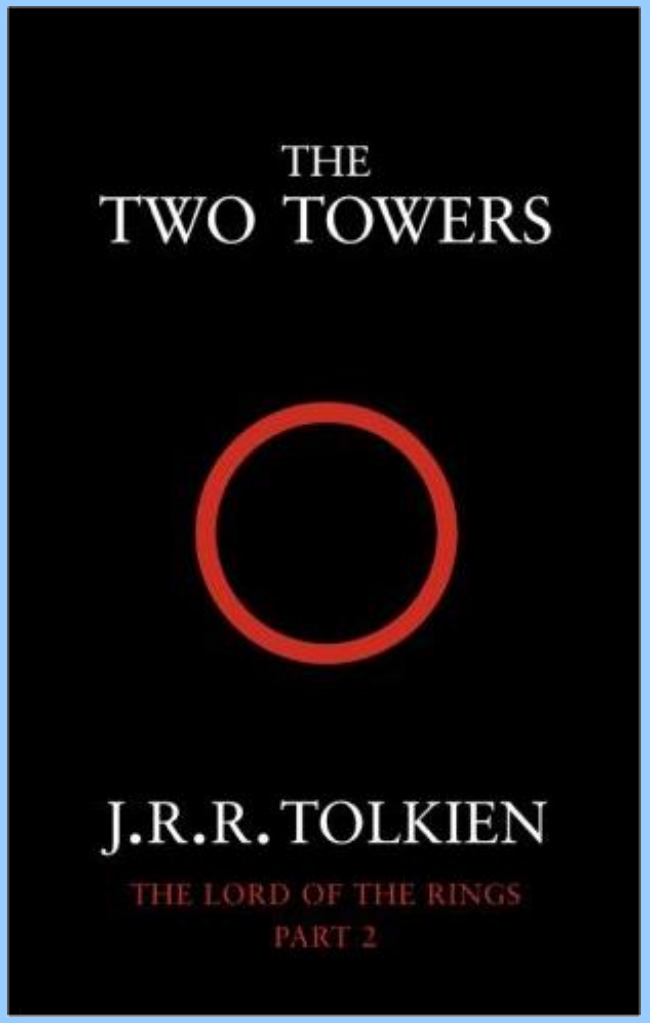




March 3 2010:
NICE 6 month targets
Response with time



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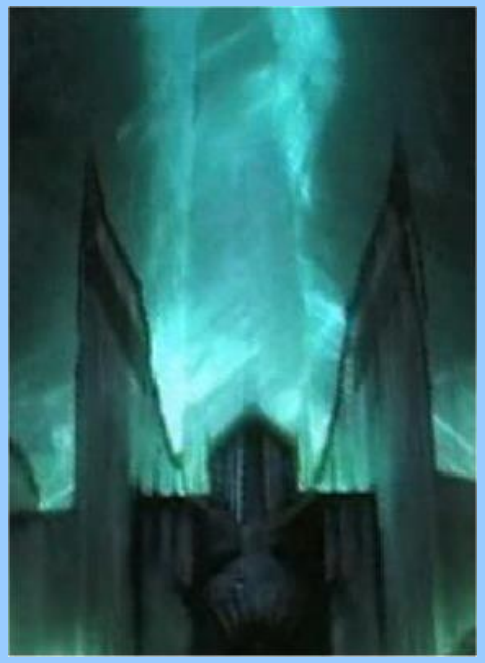
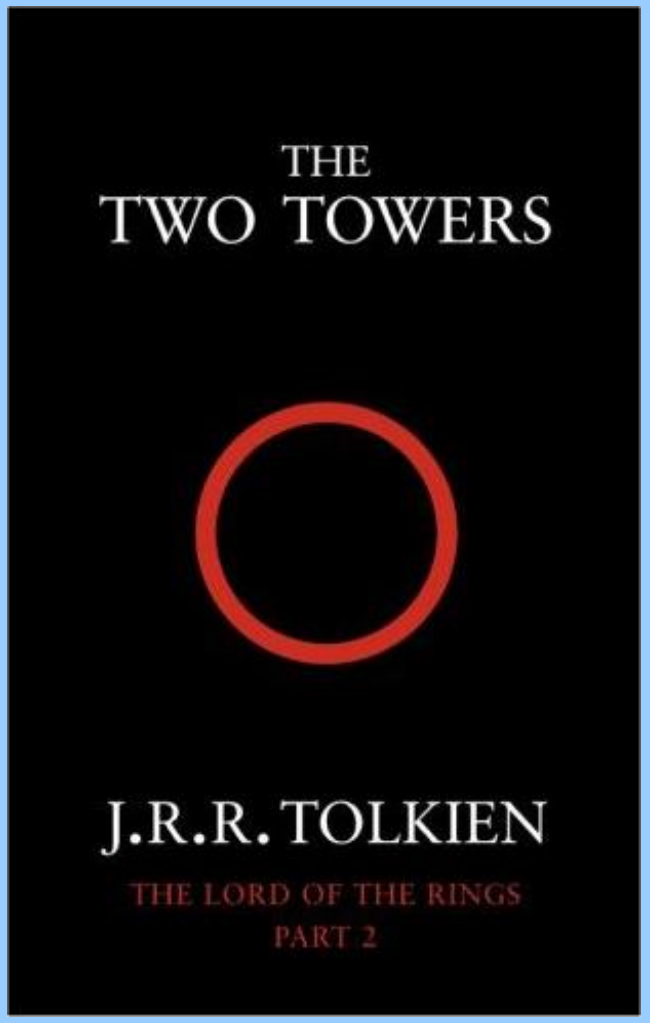


Minas Morgul

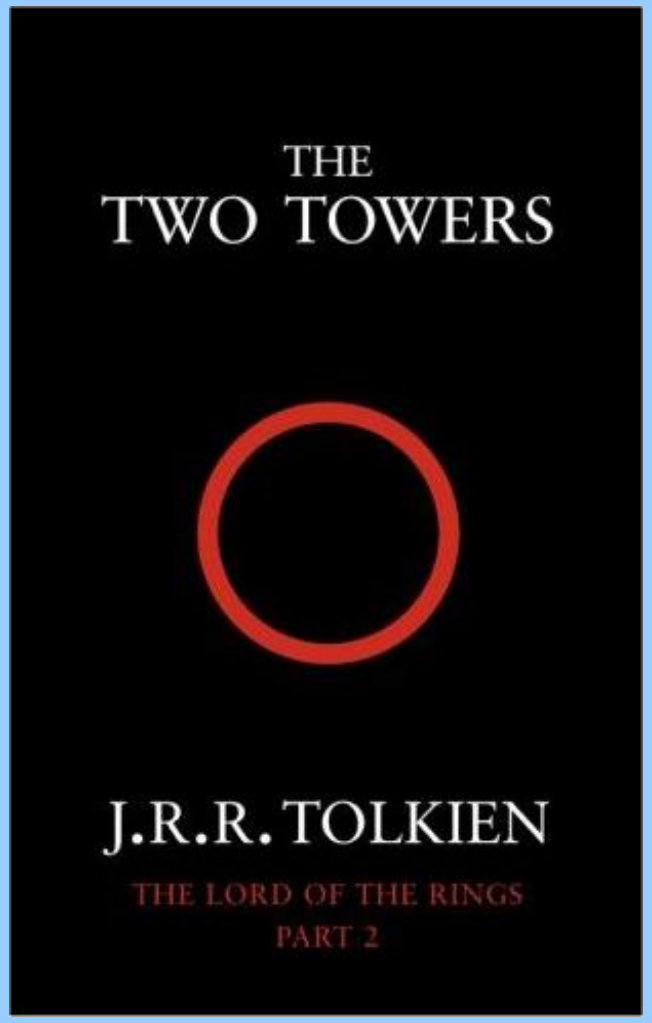


Orthanc

The Two Towers

Could be any two of: The Tower of Cirith Ungol, Orthanc, Minas Tirith, Barad-dûr and Minas Morgul

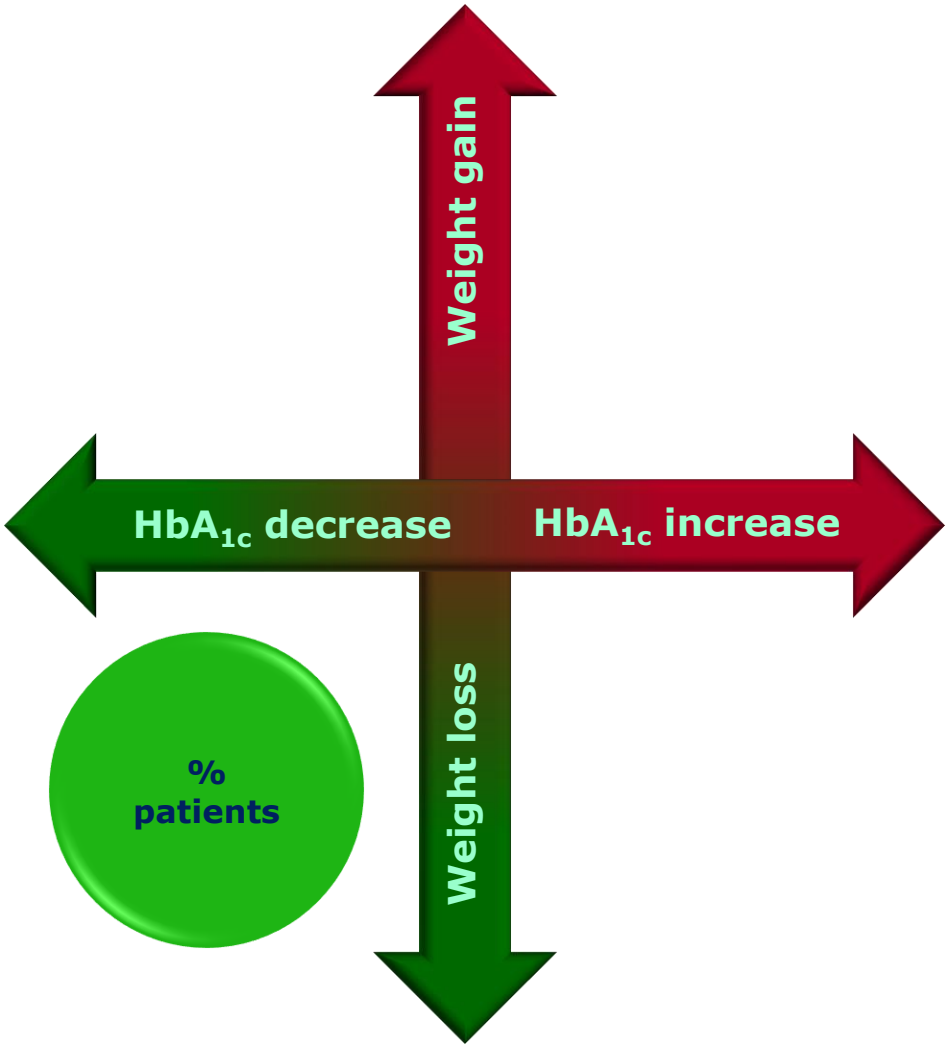
Weight



HbA1c

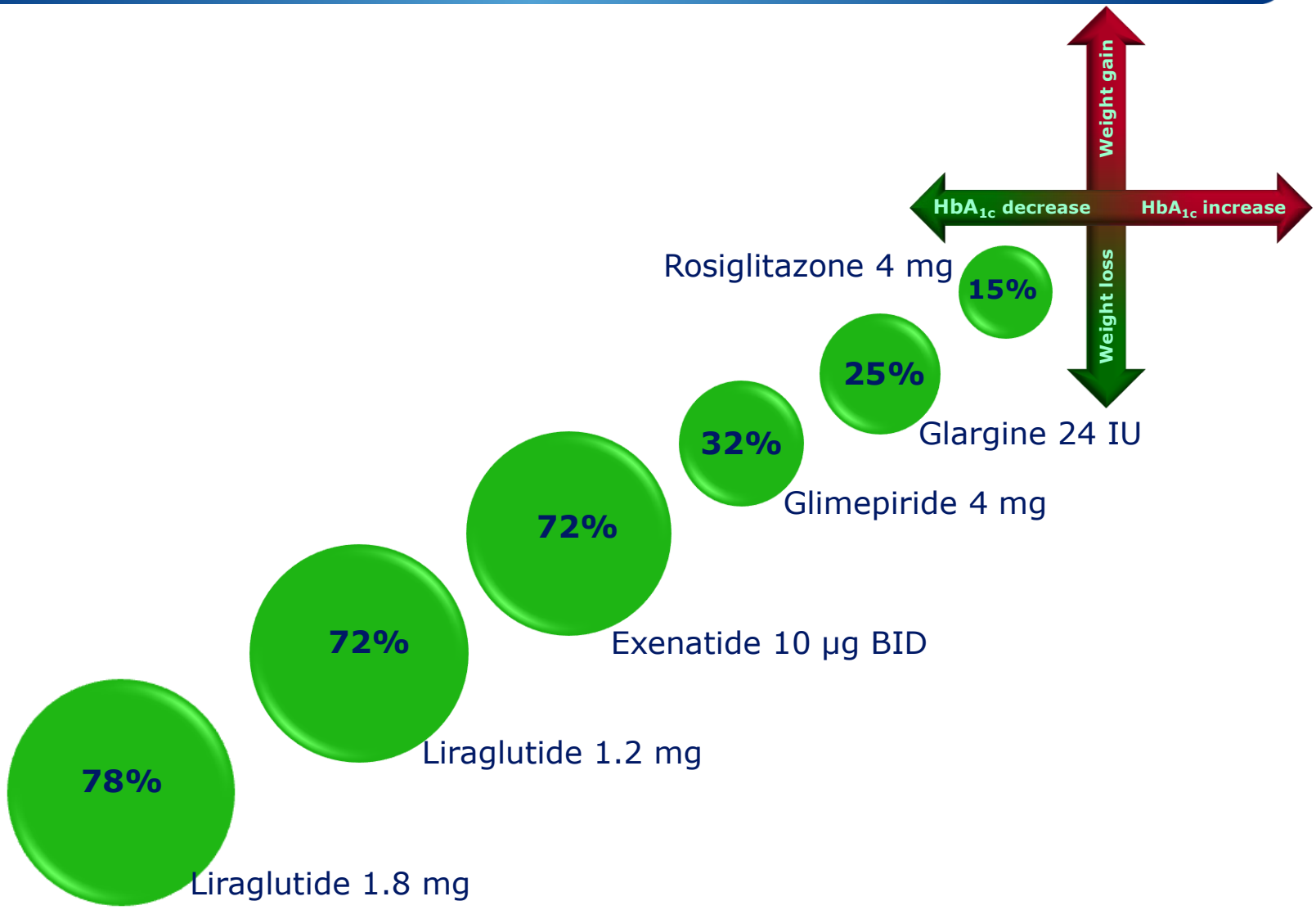
The Two Towers

Composite endpoint HbA_{1c} and weight loss: analysis by individual LEAD trials 1–6[1-6]



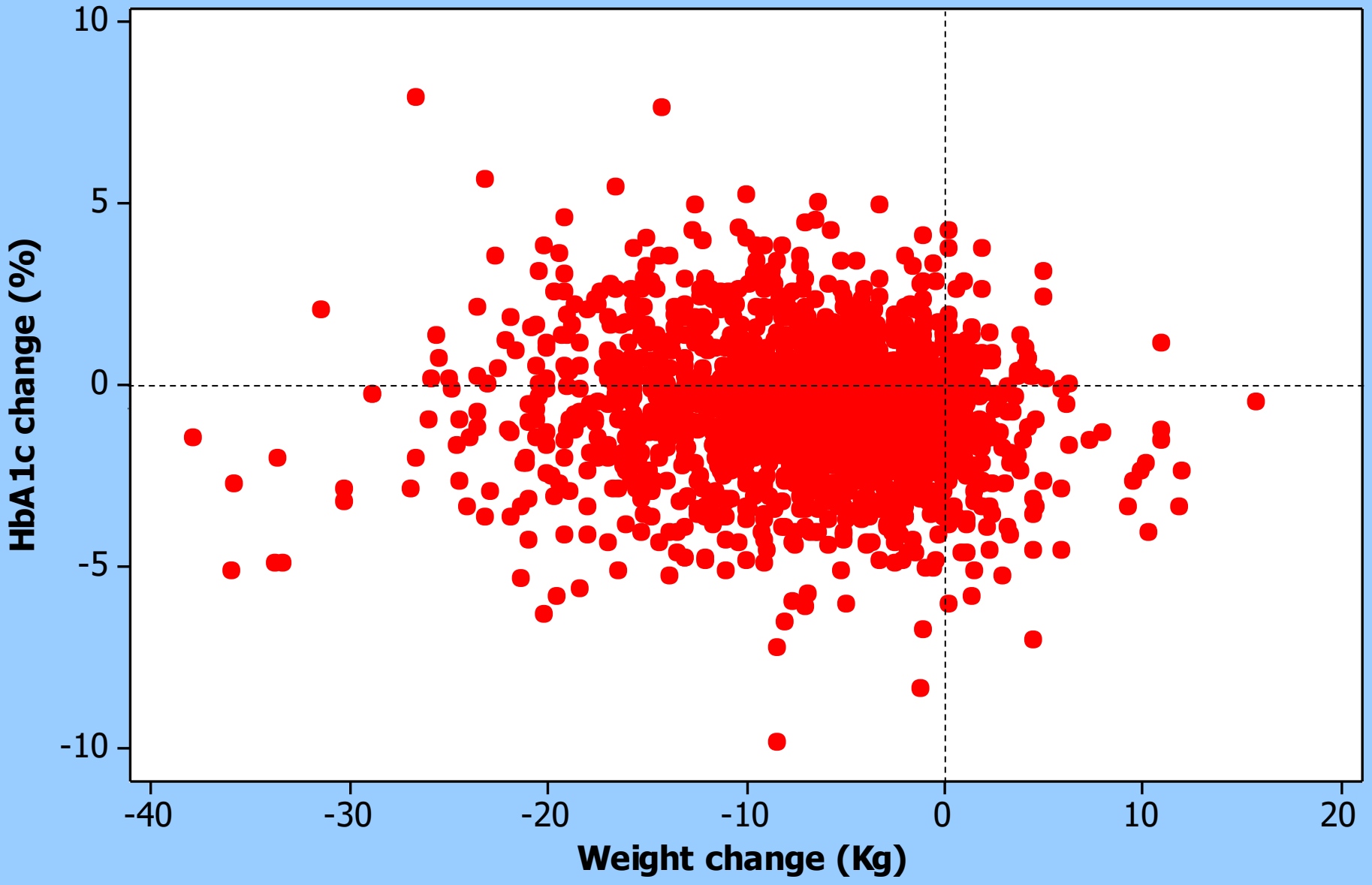
[1]Marre M *et al*. *Diabet Med* 2009; 26:268-78; [2]Nauck M *et al*. *Diabetes Care* 2009;32:84-90; [3]Garber A *et al*. *Lancet* 2009; 373:473–481; [4]Zinman B *et al*. *Diabetes Care* 2009;32:1224–1230; [5]Russell-Jones D *et al*. *Diabetologia* 2009;52:2046-55; [6]Buse J *et al*. *Lancet* 2009;374:39–47

Summary: shifting the paradigm

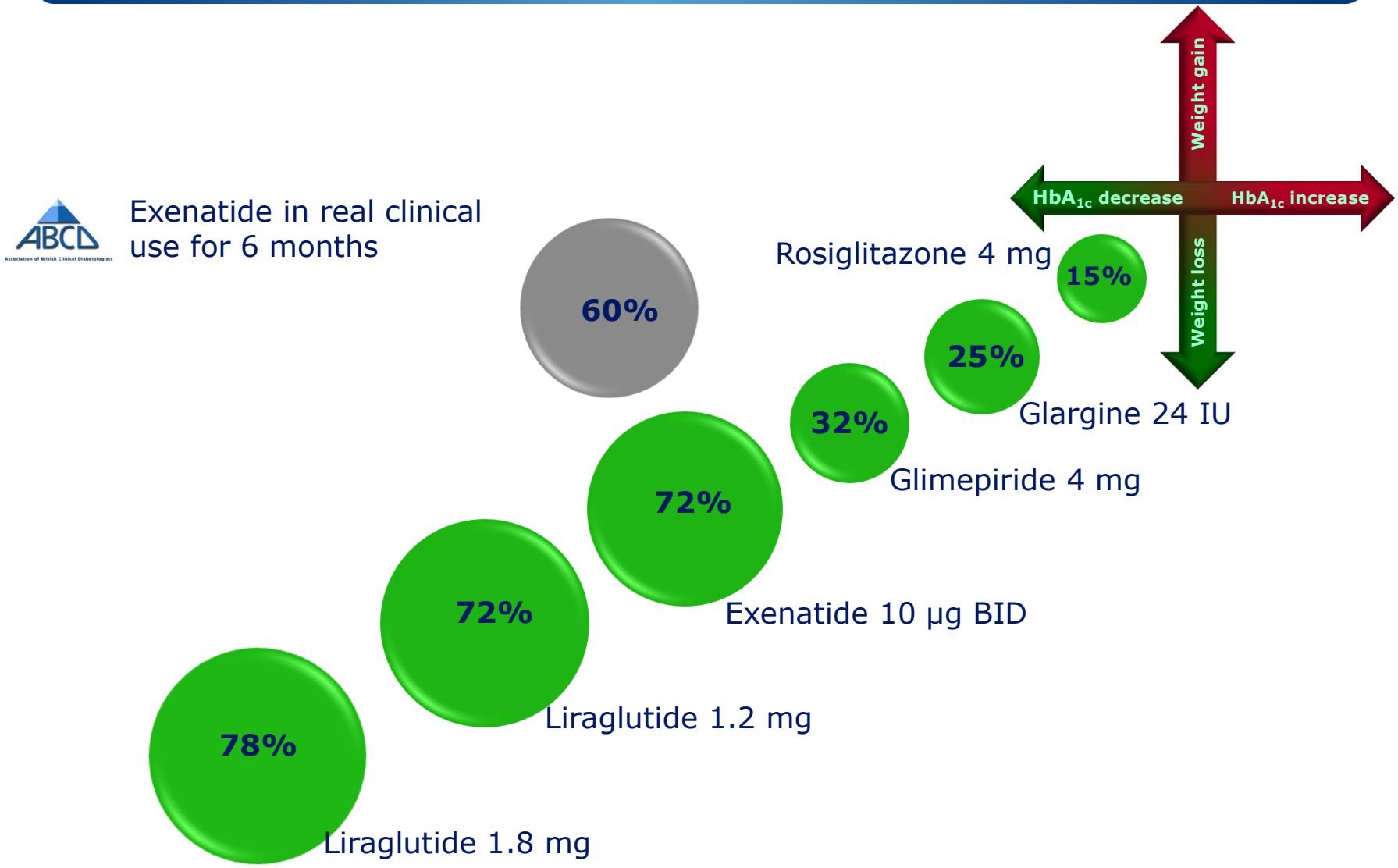


Data on file (Composite Endpoint/01/02), Novo Nordisk

6 months after exenatide start in 1959 patients



Summary: shifting the paradigm



Data on file (Composite Endpoint/01/02), Novo Nordisk

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 ($HbA_{1c} \geq 7.5\%$, or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) ≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or

[5] At the time of publication pioglitazone was the only thiazolidinedione with UK marketing authorisation for use with insulin.

- a BMI < 35.0 kg/m^2, 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_{1c} 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 informed decision.

Insulin therapy

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Insulin therapy

Achieving NICE criteria

- NICE:
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Association of British Clinical Diabetologists

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- 1959 patients with both HbA1c AND Weight data at 6 months

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- 1319/1959 (67.3%) achieved weight loss criteria

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- 1319/1959 (67.3%) achieved weight loss criteria
- 863/1959 (44.1%) achieved HbA1c reduction criteria

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- 1959 patients with both HbA1c AND Weight data at 6 months
- 1319/1959 (67.3%) achieved weight loss criteria
- 863/1959 (44.1%) achieved HbA1c reduction criteria
- 547/1959 (27.9%) achieved both

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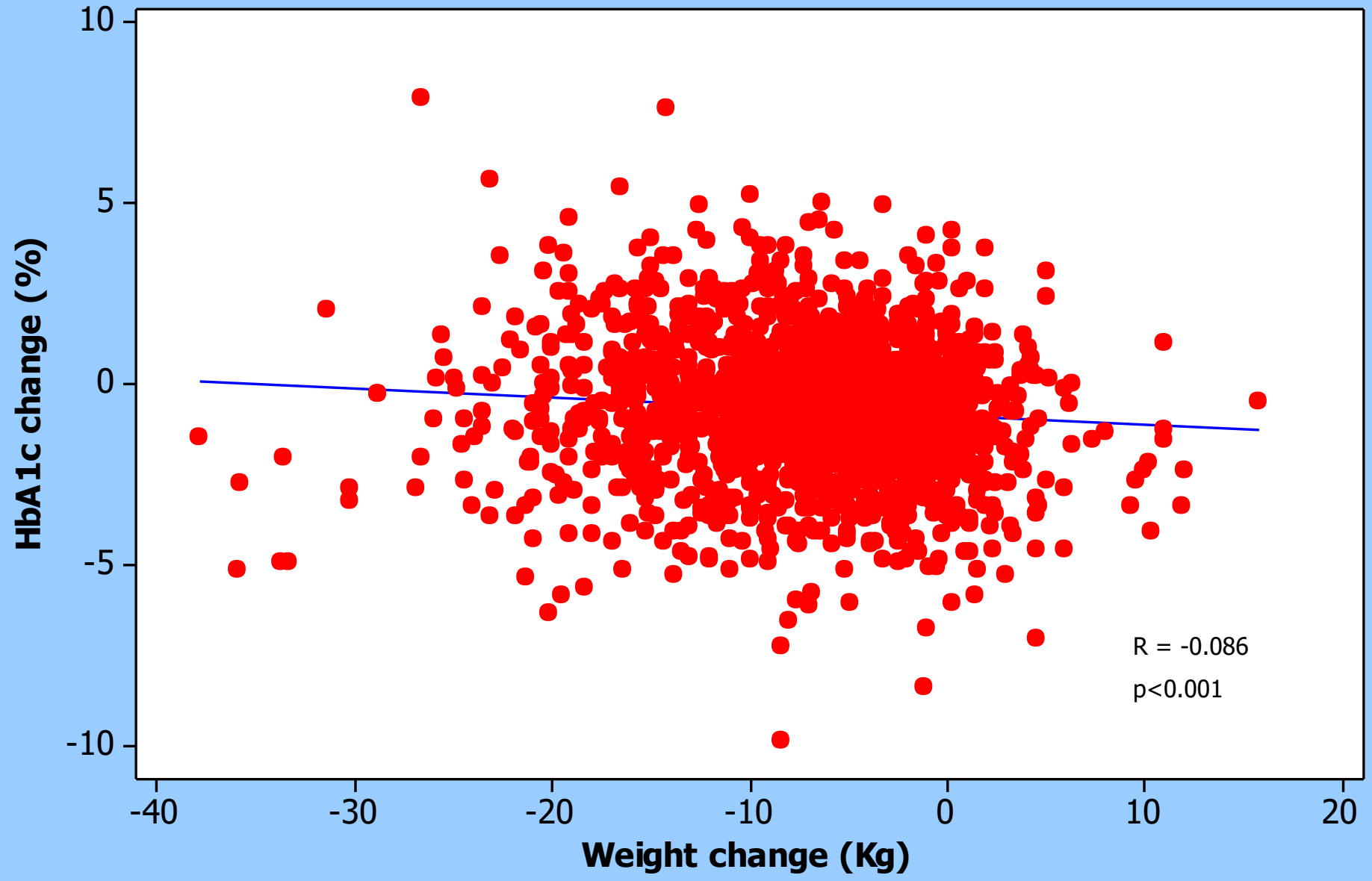
- ie
  - Some people have a good weight response but more minimal HbA1 response
  - Some people have a good HbA1c response but more minimal weight response

6 months after exenatide start in 1959 patients



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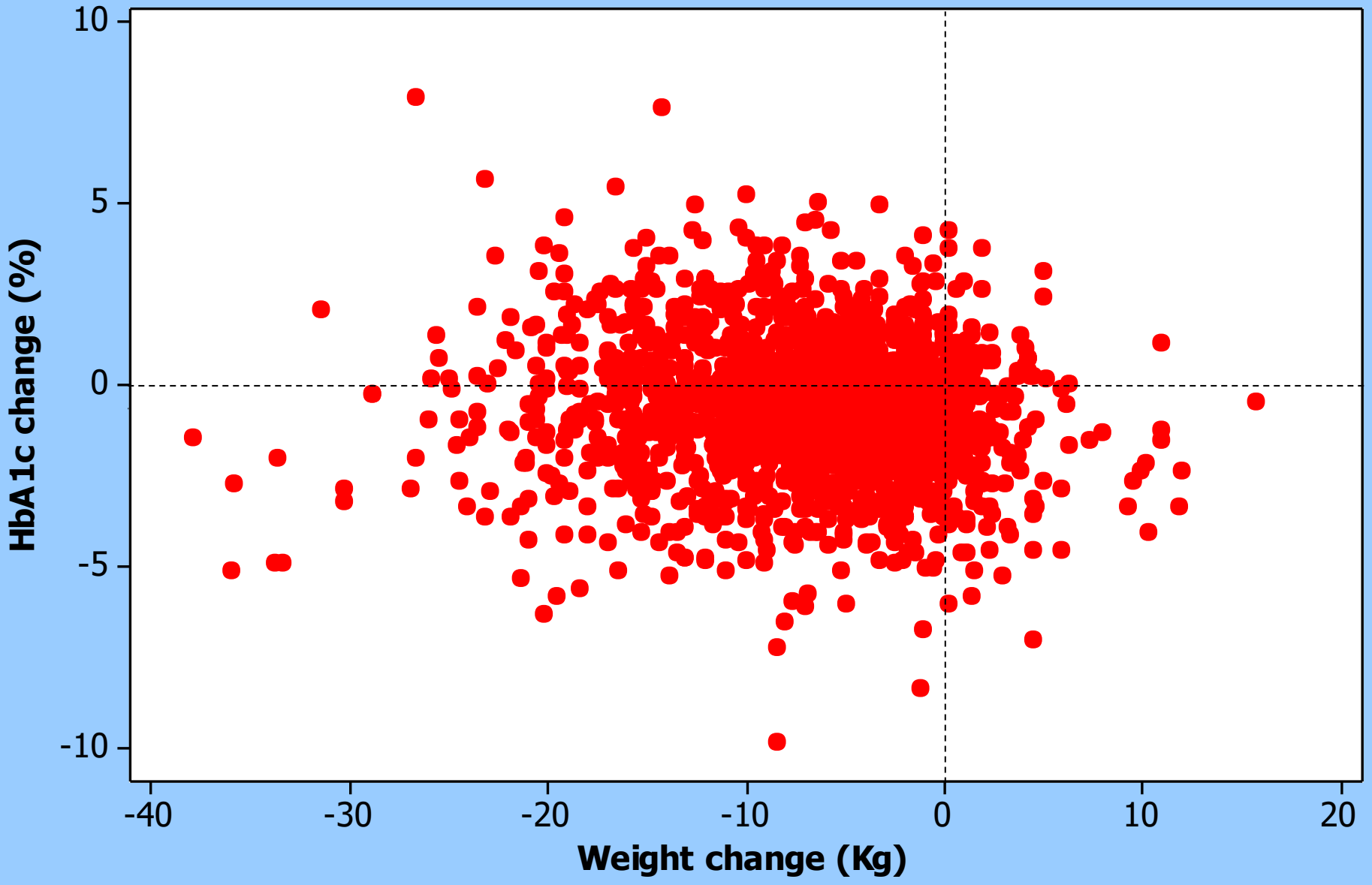

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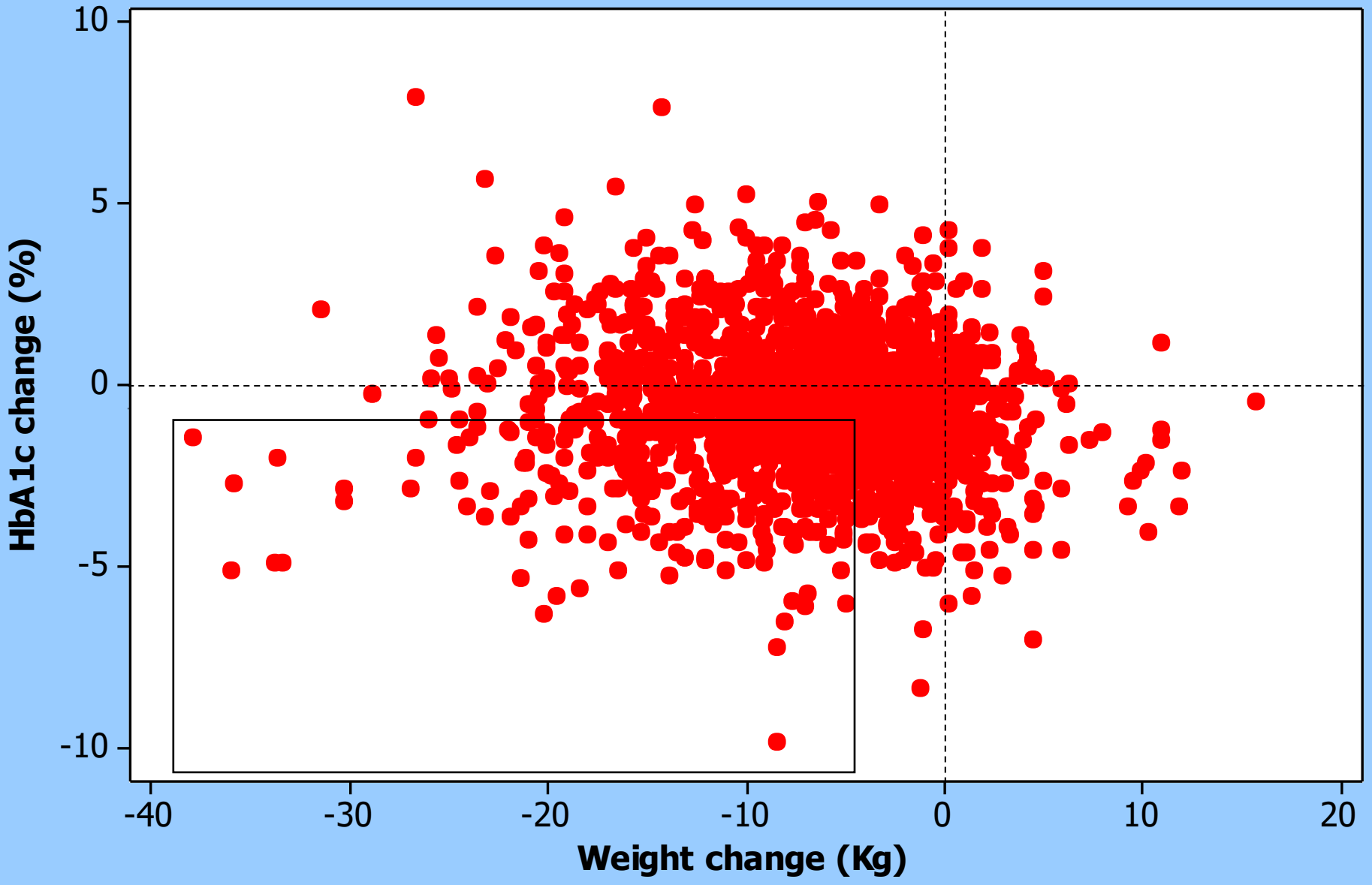

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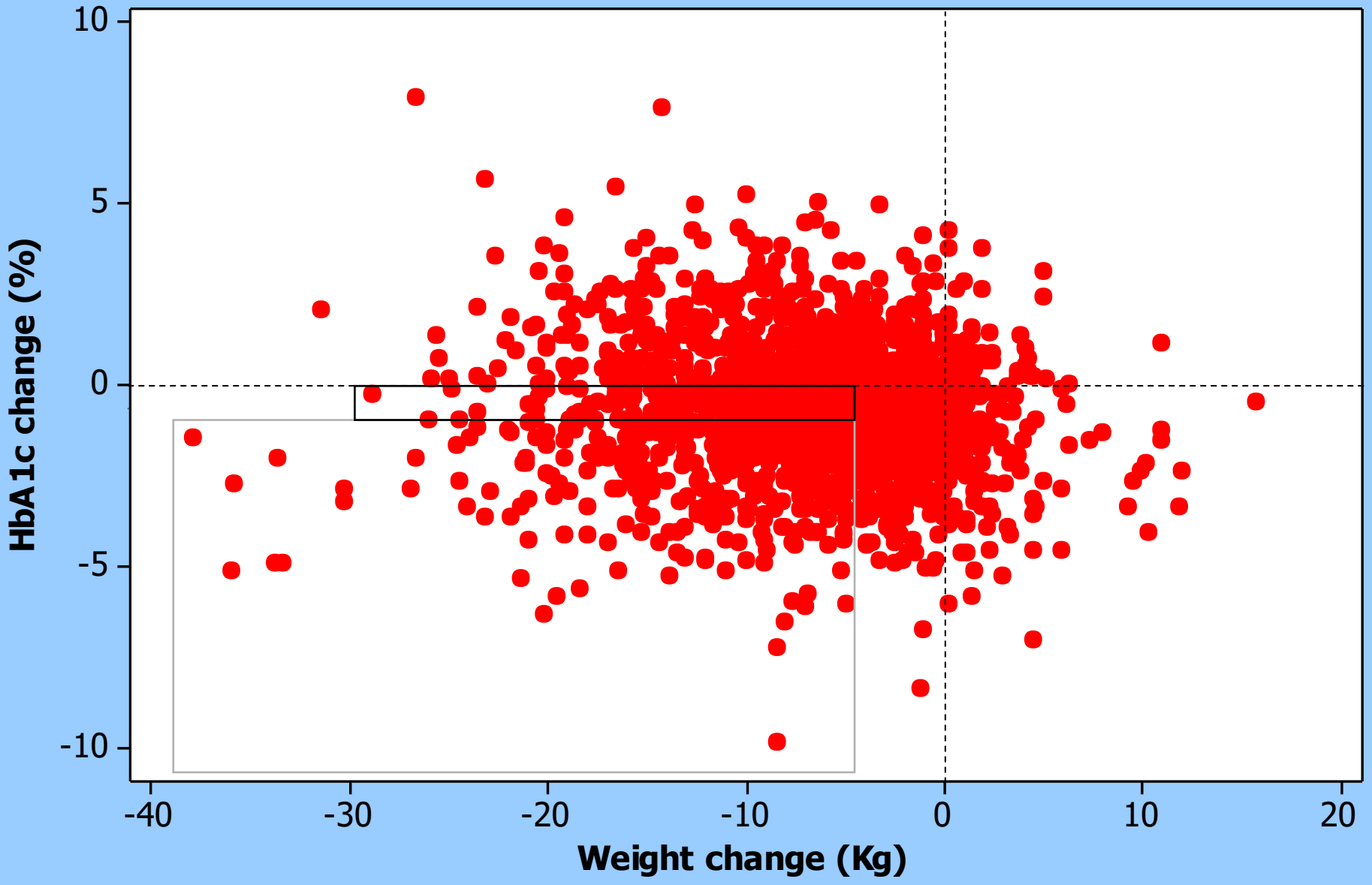

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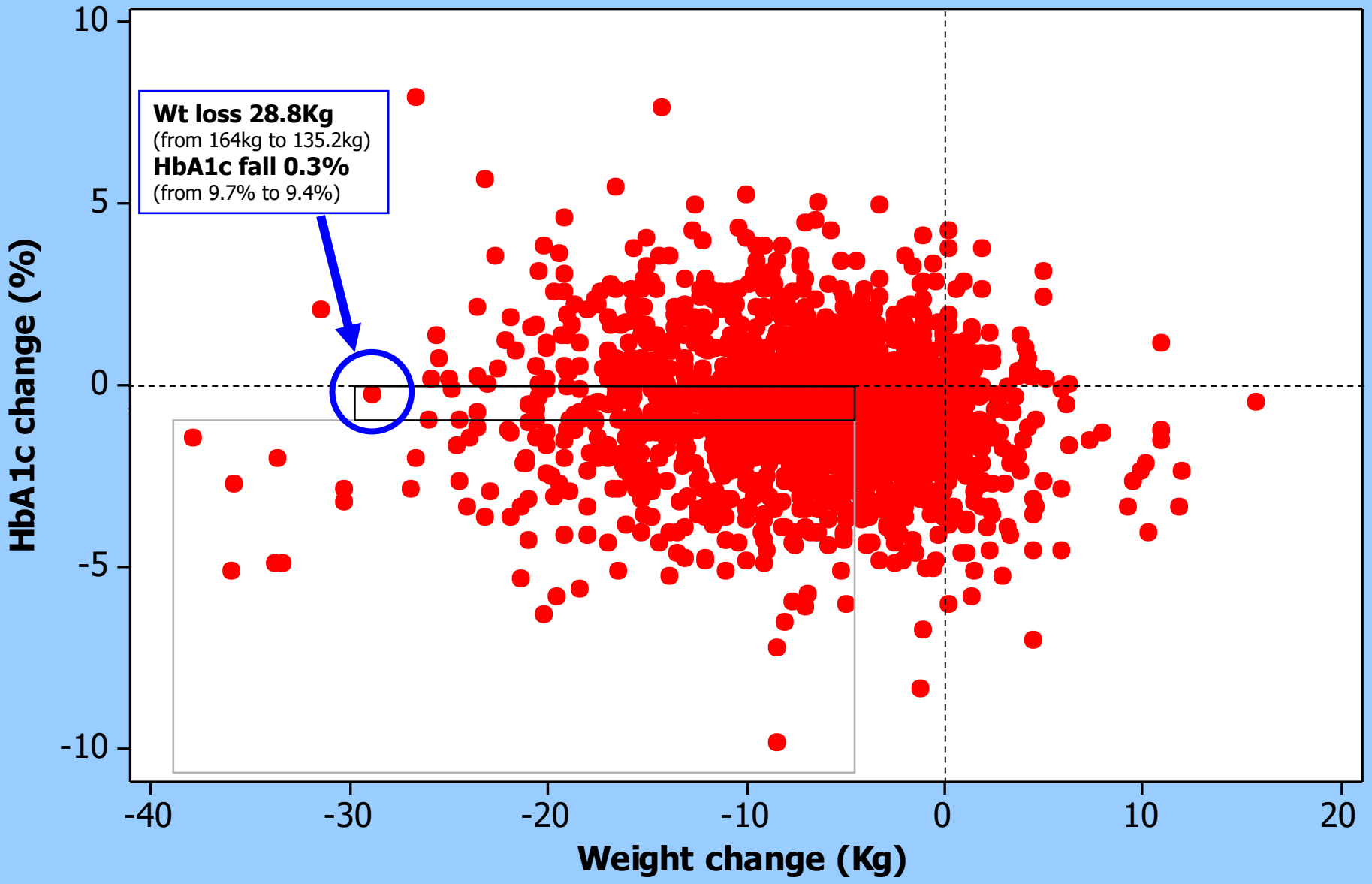

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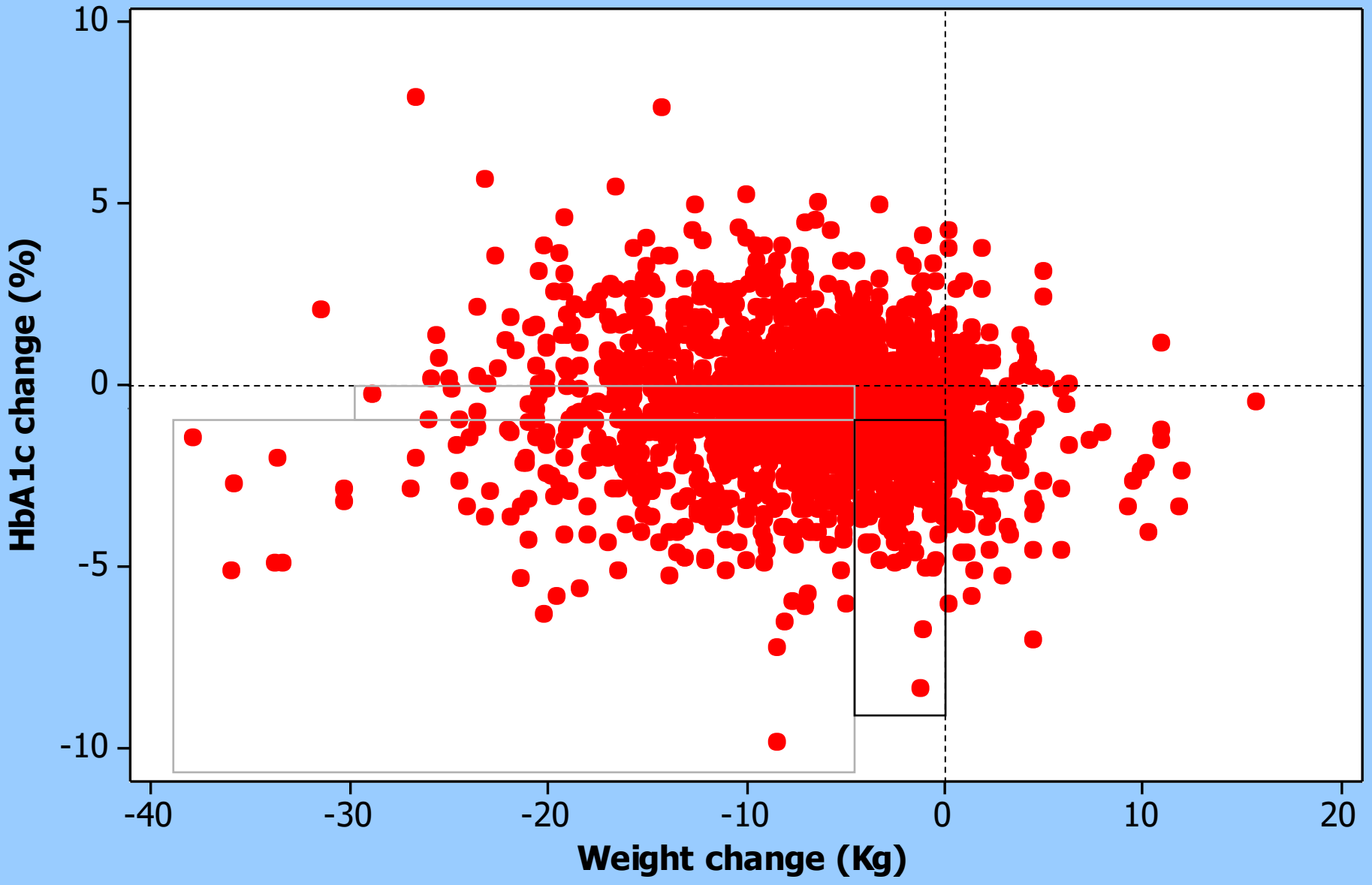
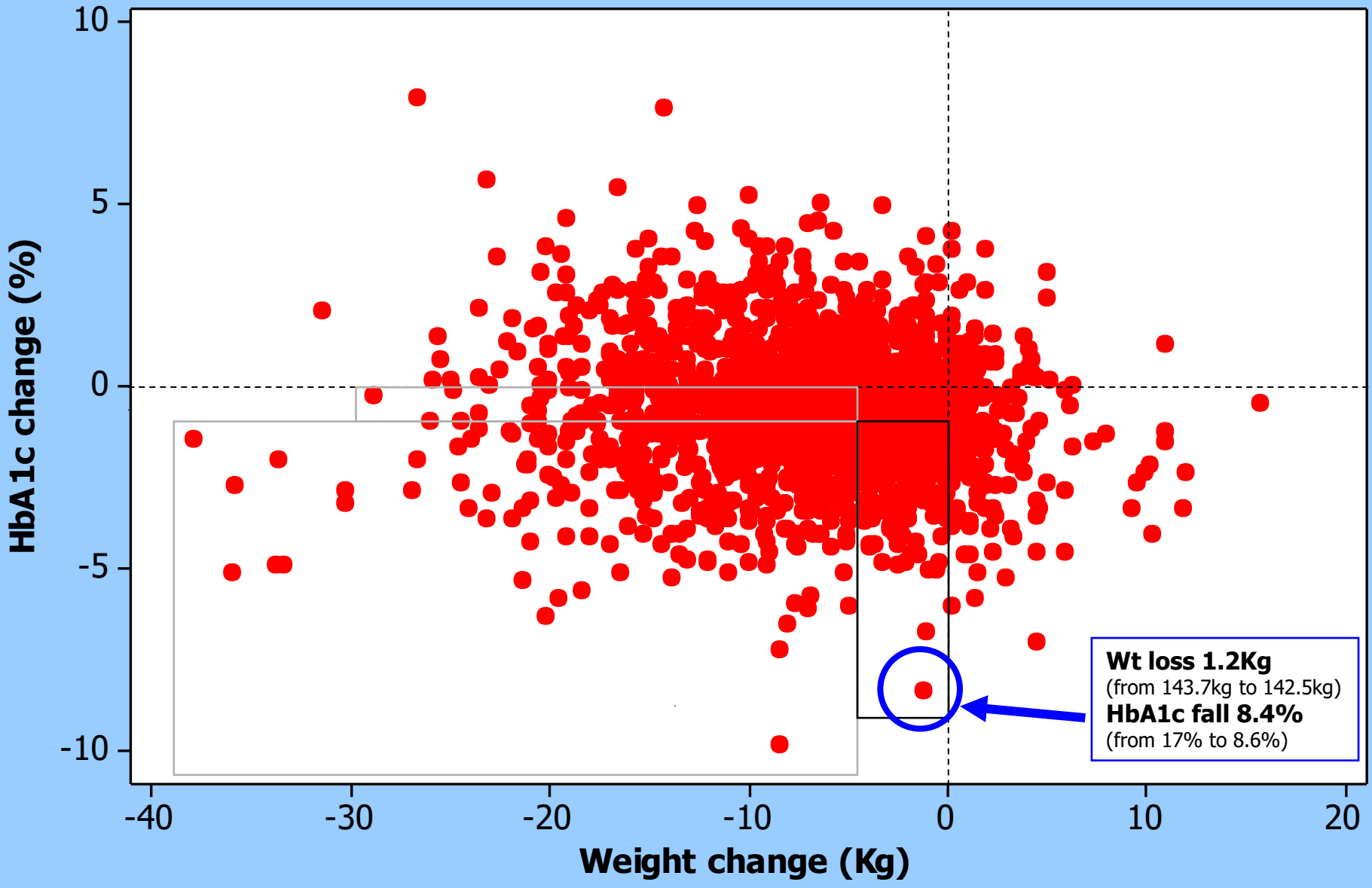
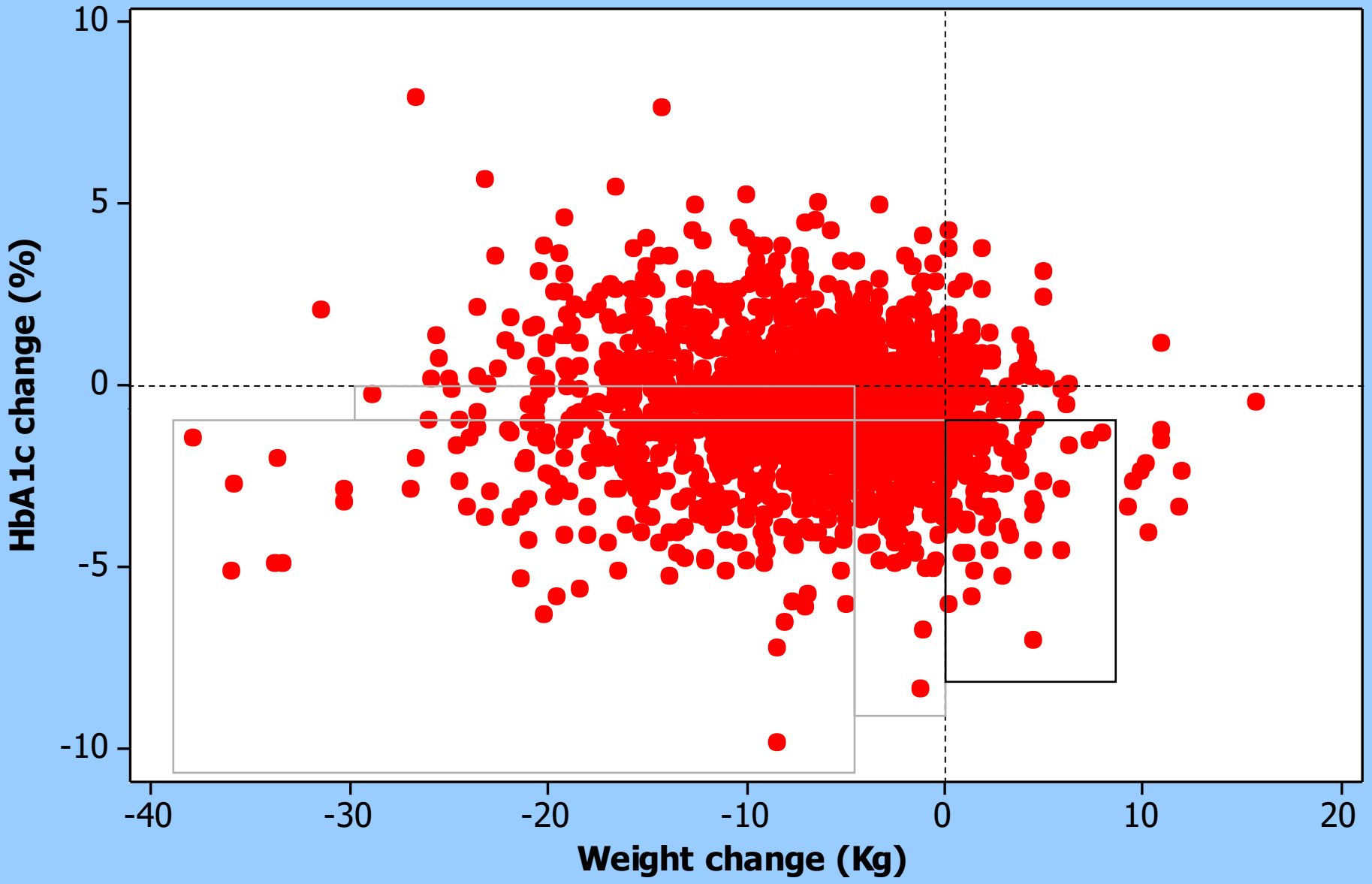


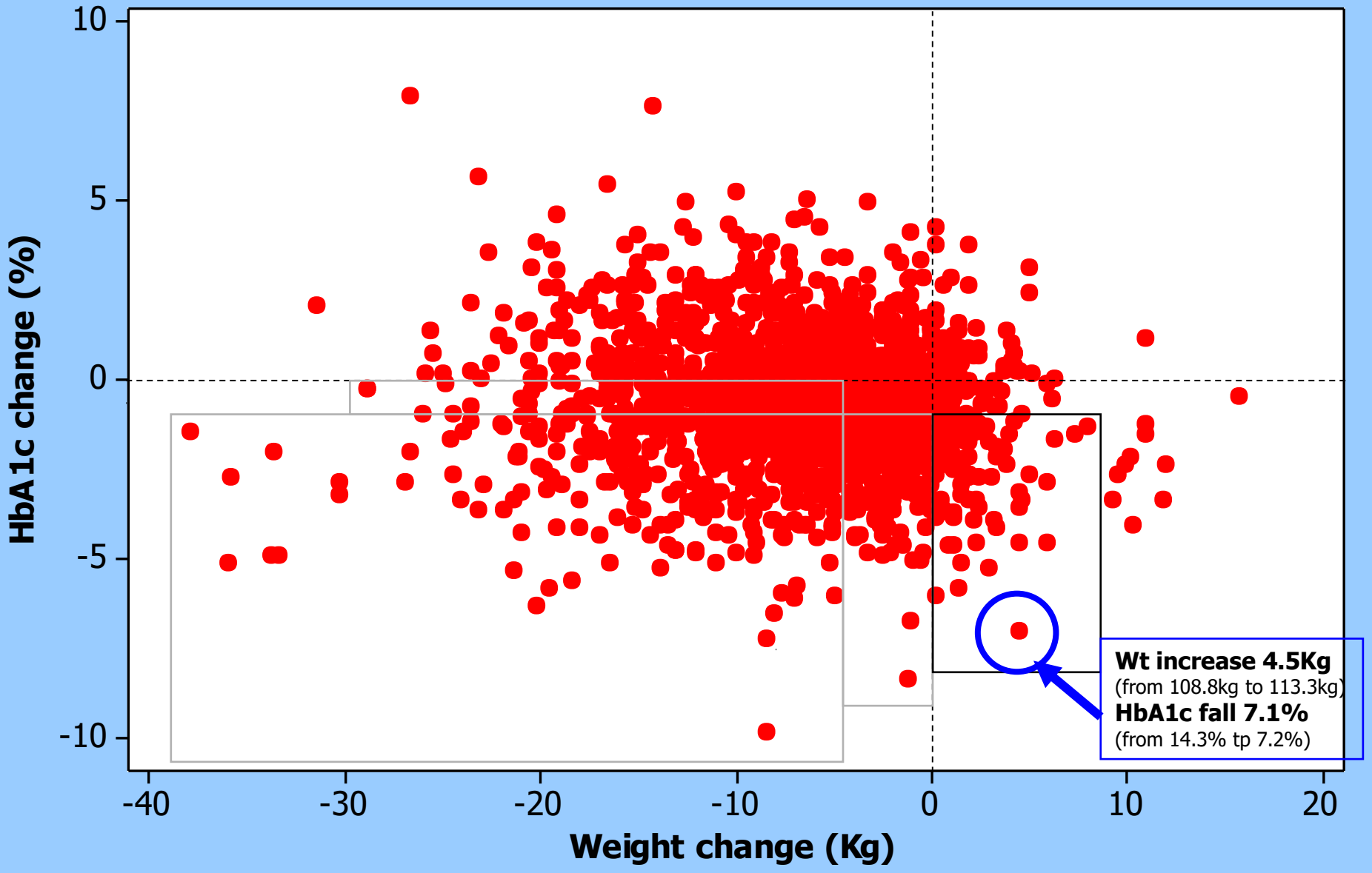
6 months after exenatide start in 1959 patients



6 months after exenatide start in 1959 patients



6 months after exenatide start in 1959 patients



Conclusion 1 – exenatide in real clinical use

- 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

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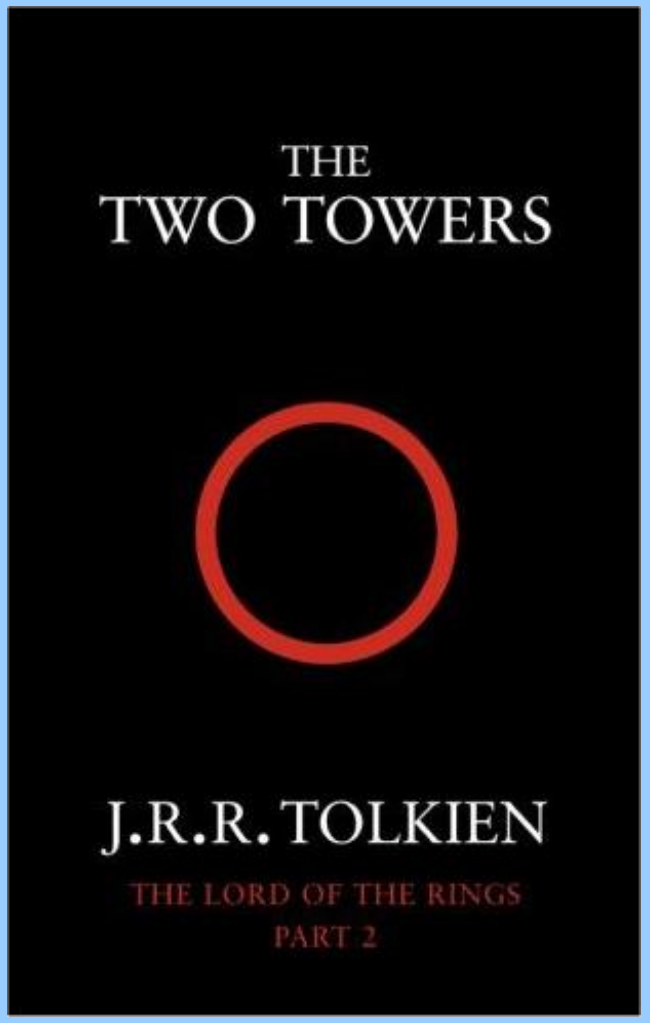
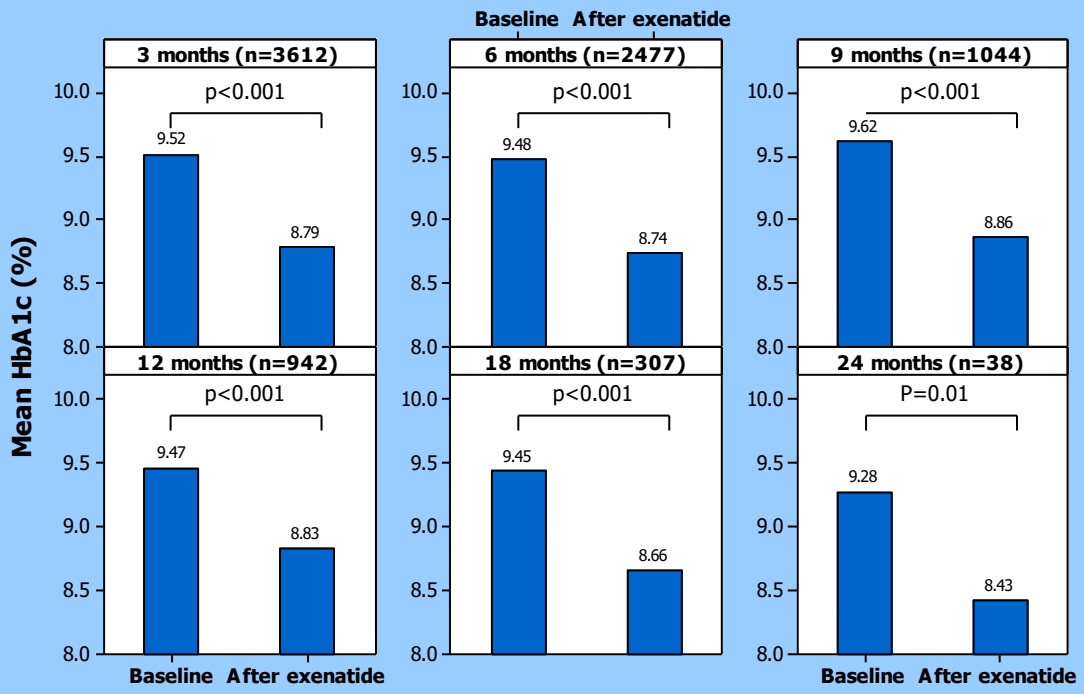
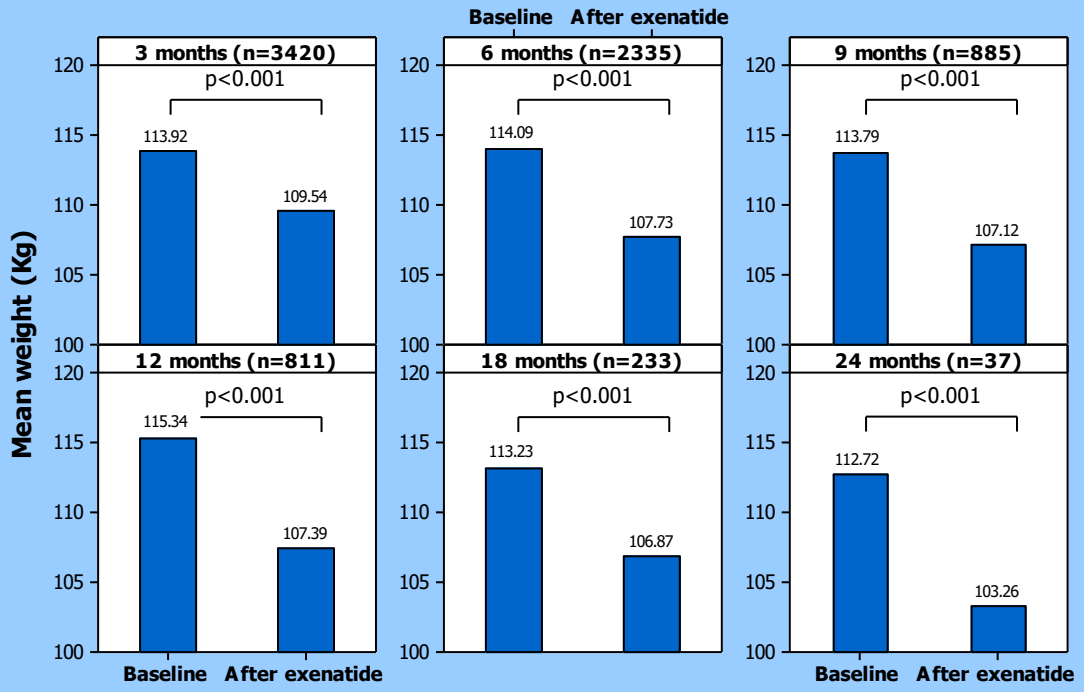


March 3 2010:
NICE 6 month targets
Response with time

Paired baseline and follow up HbA1c and weight at various timepoints after exenatide



HbA1c



Weight

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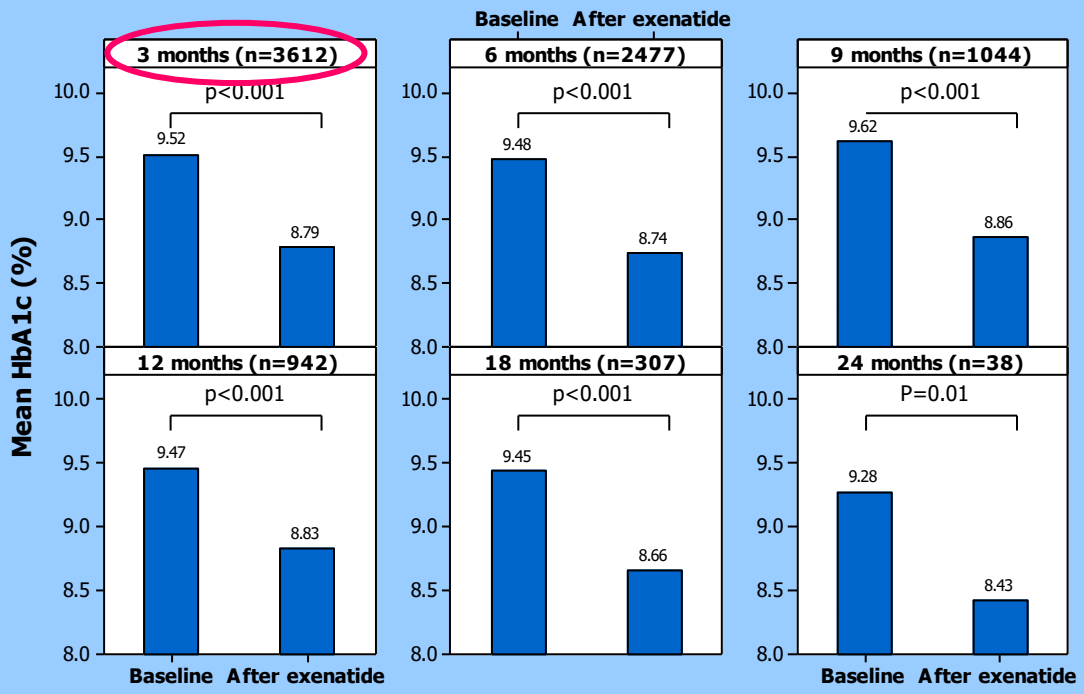
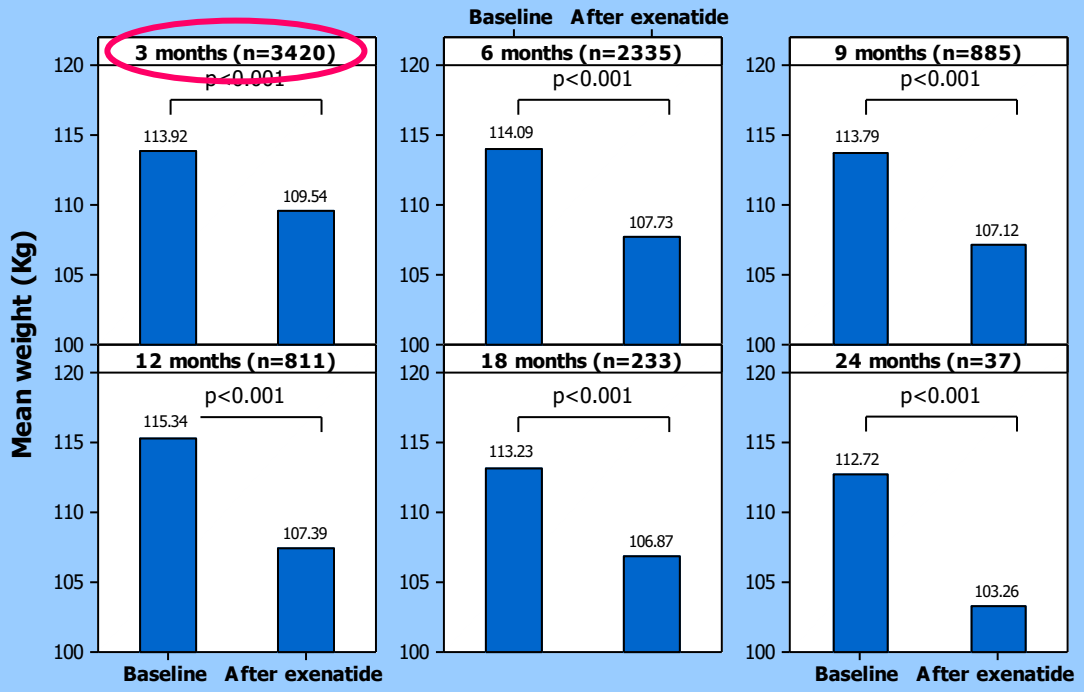
Paired baseline and follow up HbA1c and weight at various timepoints after exenatide



HbA1c



Weight

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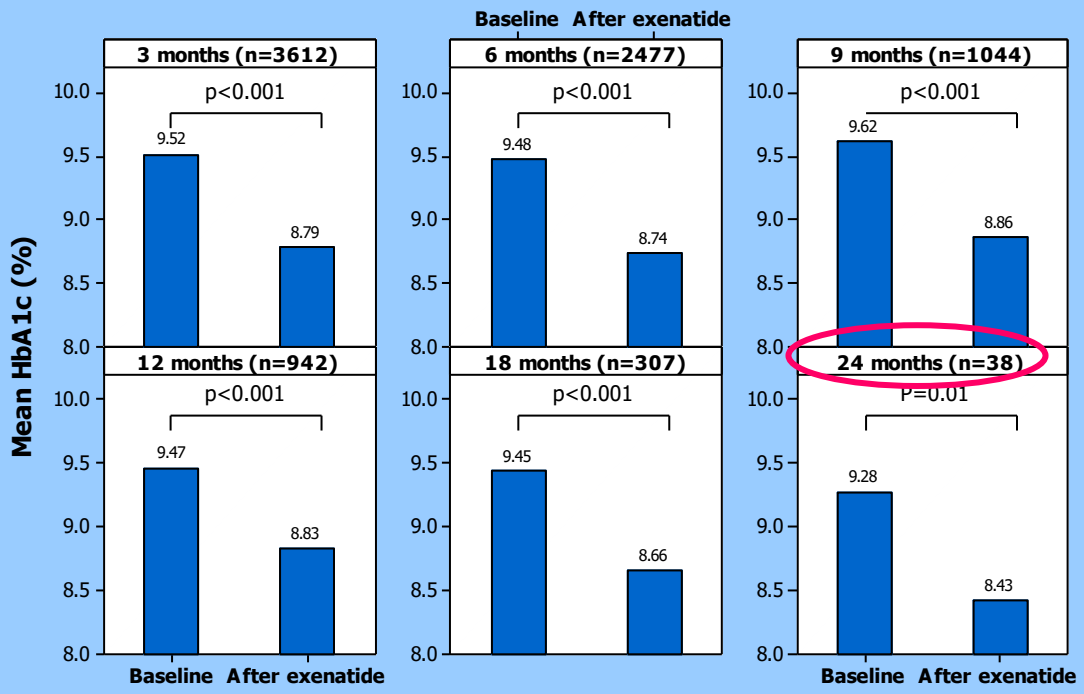
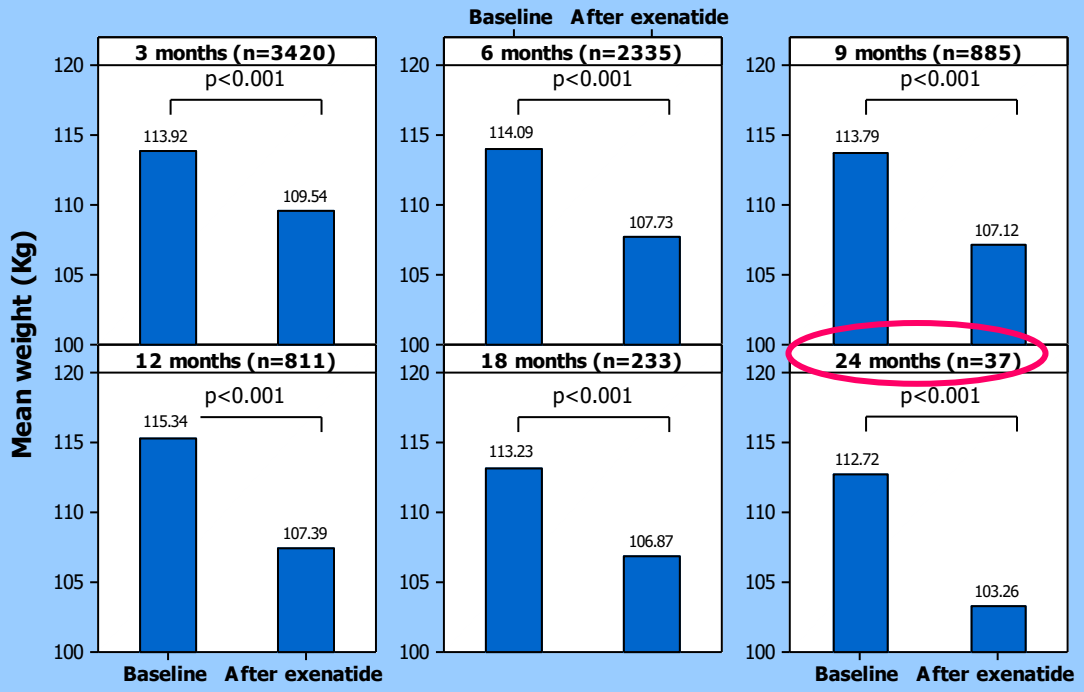
Paired baseline and follow up HbA1c and weight at various timepoints after exenatide



HbA1c



Weight

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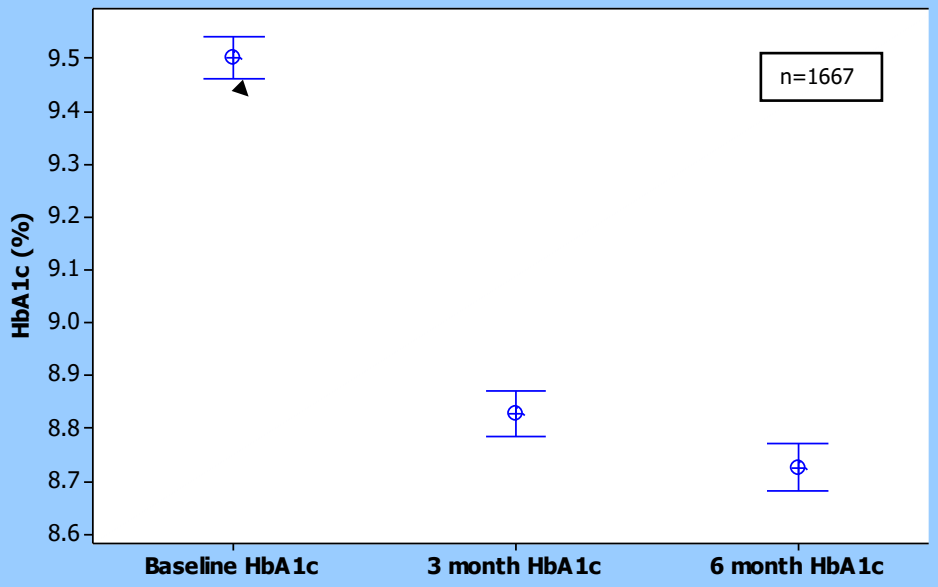
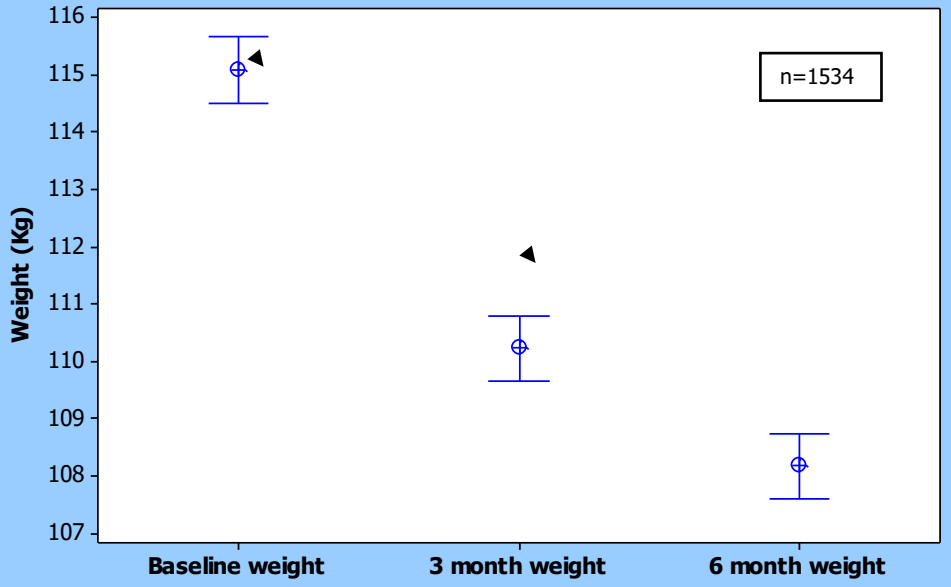
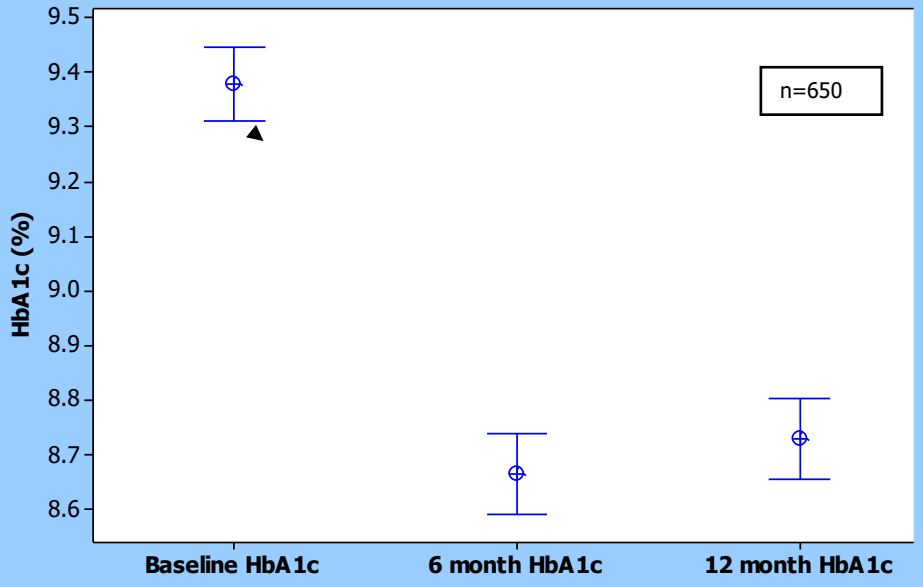
Interval plots after exenatide

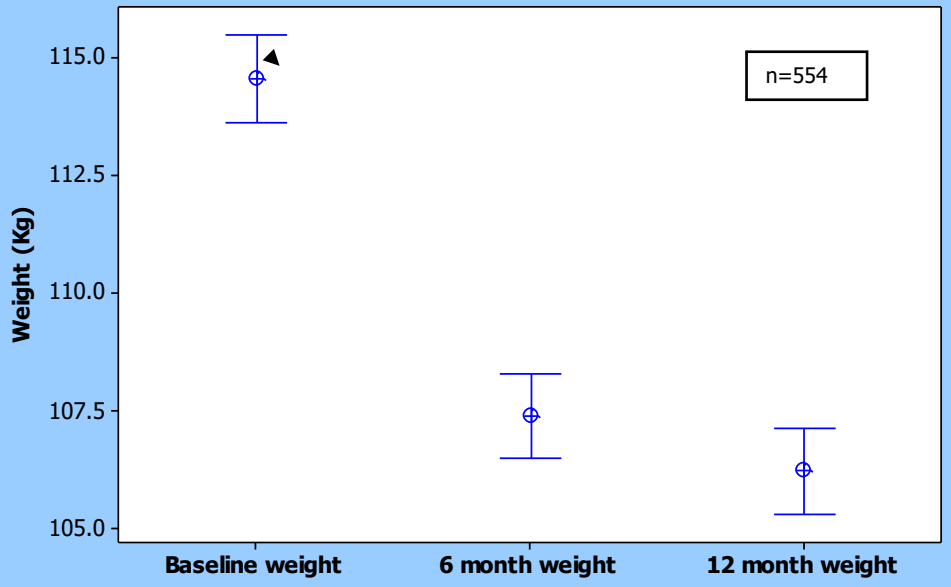
HbA1c



Weight

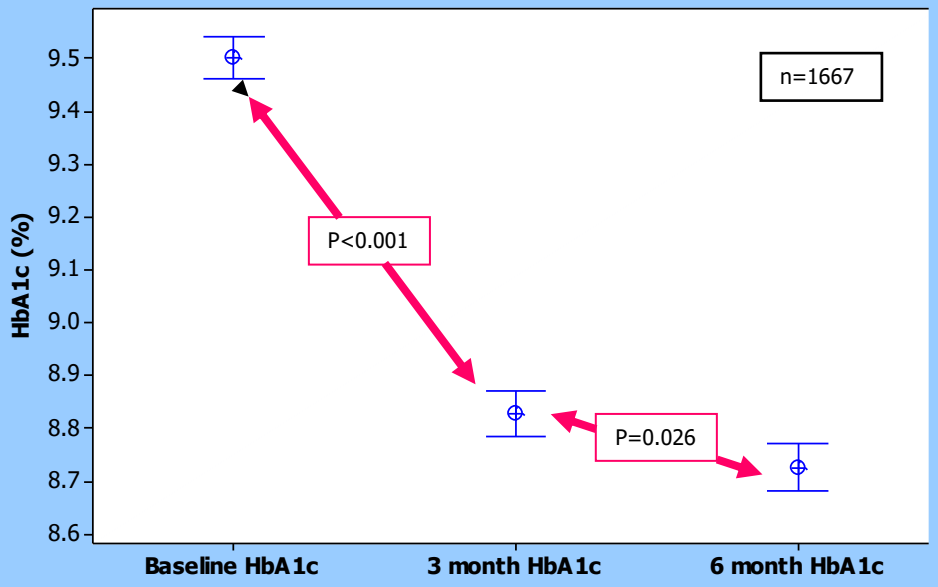




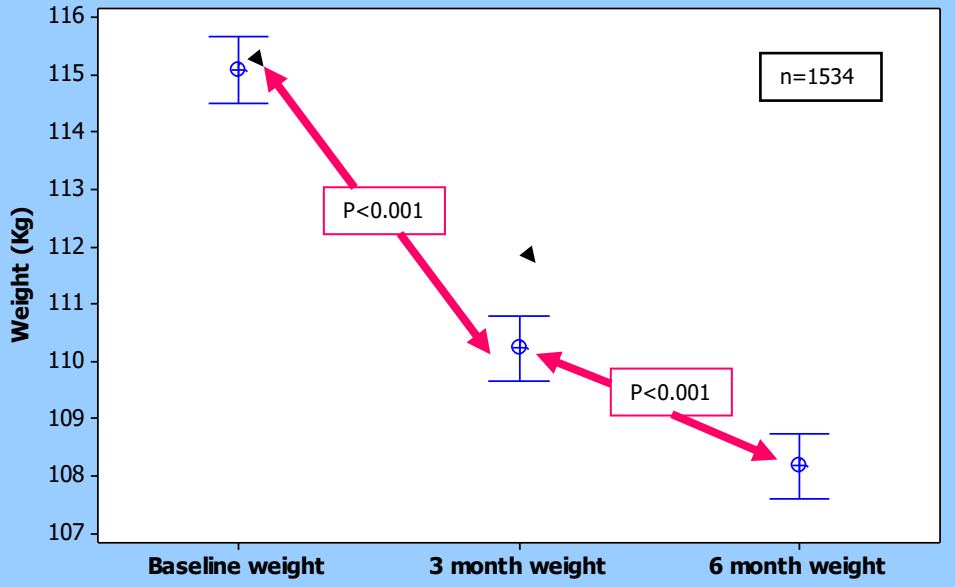


Interval plots after exenatide

HbA1c

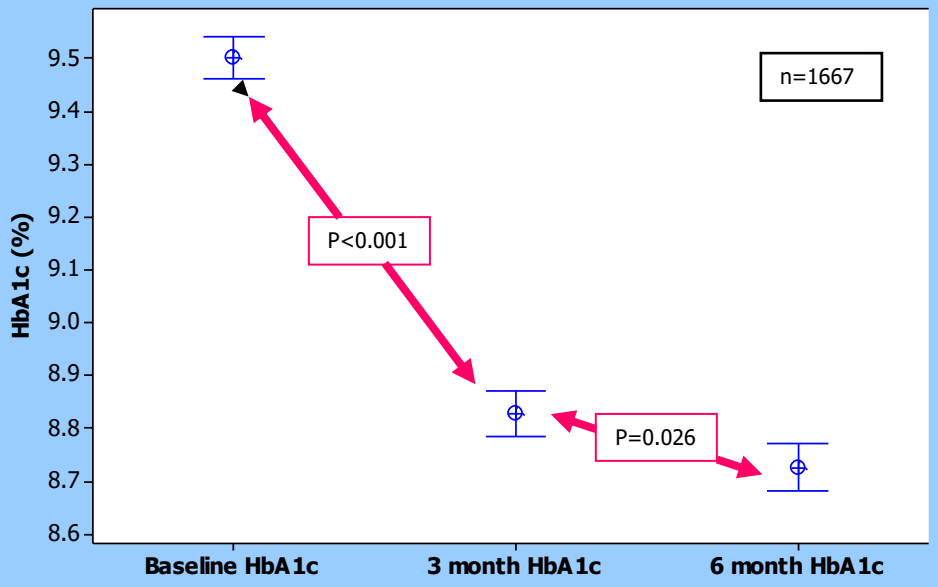


Weight

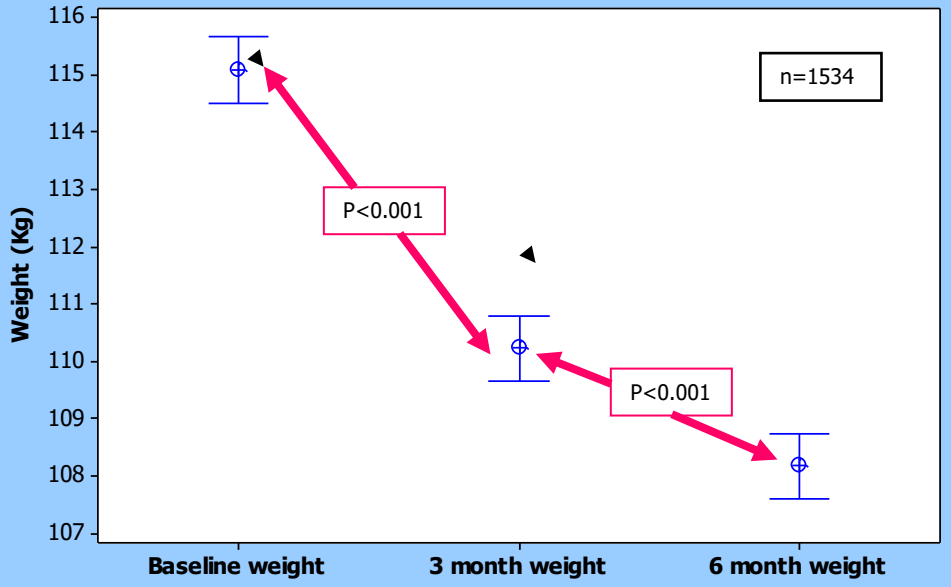


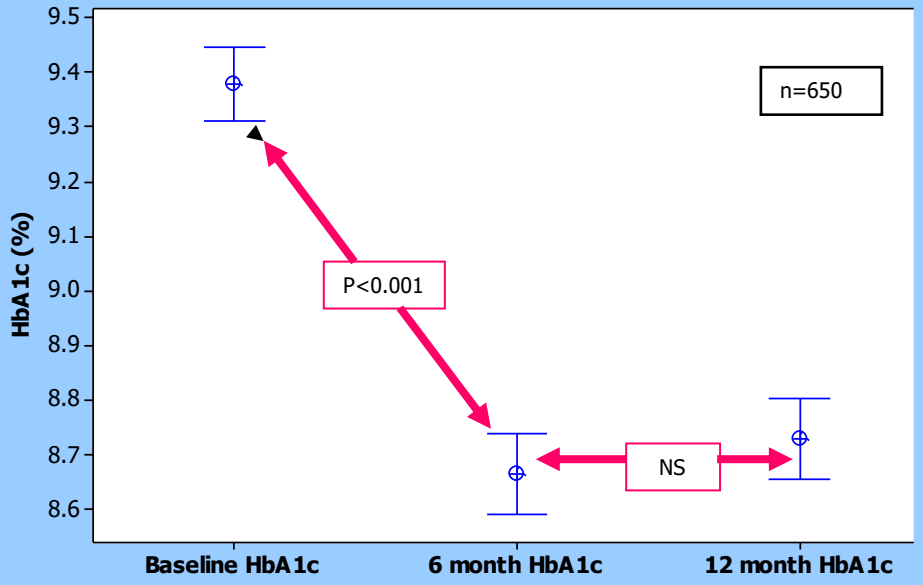
Interval plots after exenatide

HbA1c



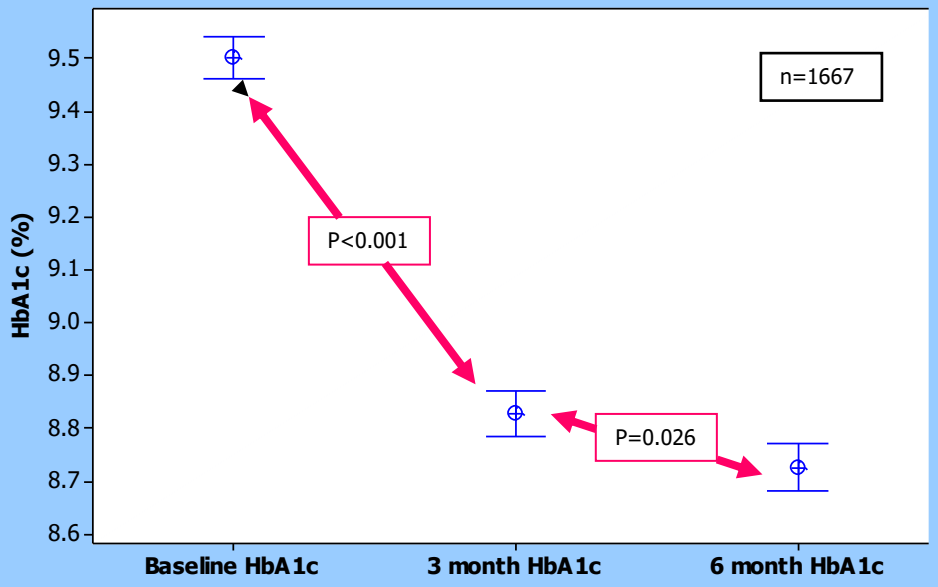
Weight



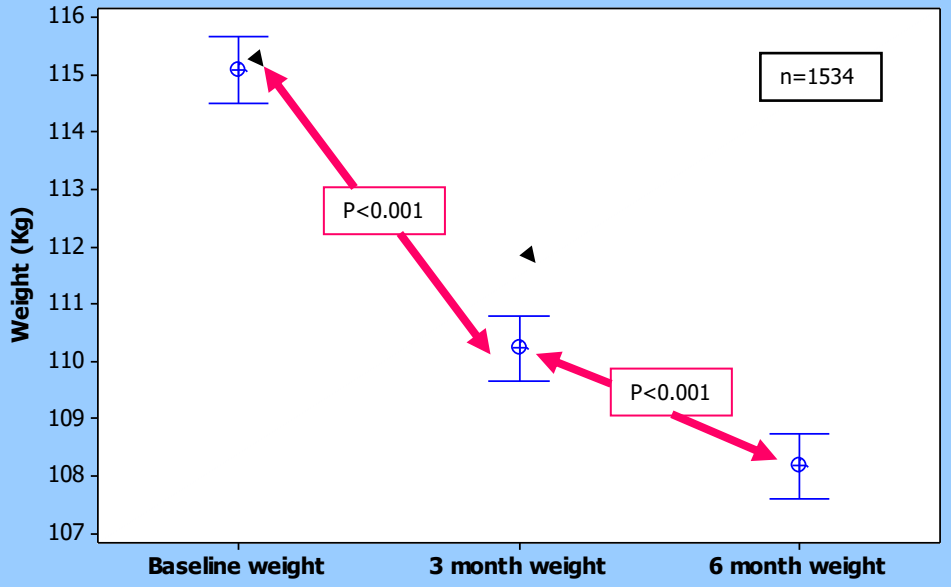


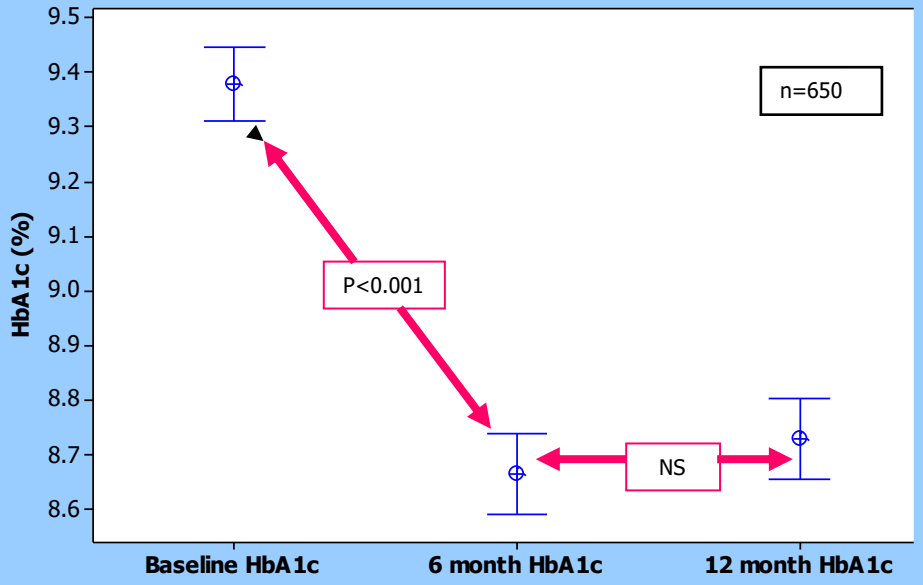
Interval plots after exenatide

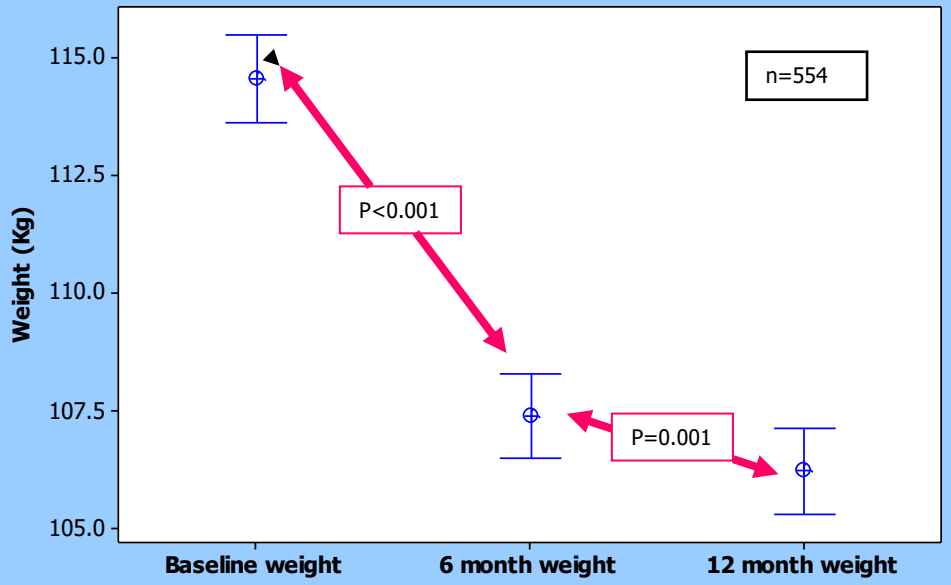
HbA1c



Weight







After 12 months?

- Maintenance of the reduced level of HbA1c and weight extending out to 24 months but no significant further fall at 18 or 24 months

Conclusion 2 – exenatide in real clinical use

- **Weight** loss continues to reduce for the first 12 months but then levels off
- The weight loss is sustained out to 24 months
- **HbA1c** continues to reduce for the first 6 months but then levels off
- Reduction in HbA1c is sustained out to 24 months

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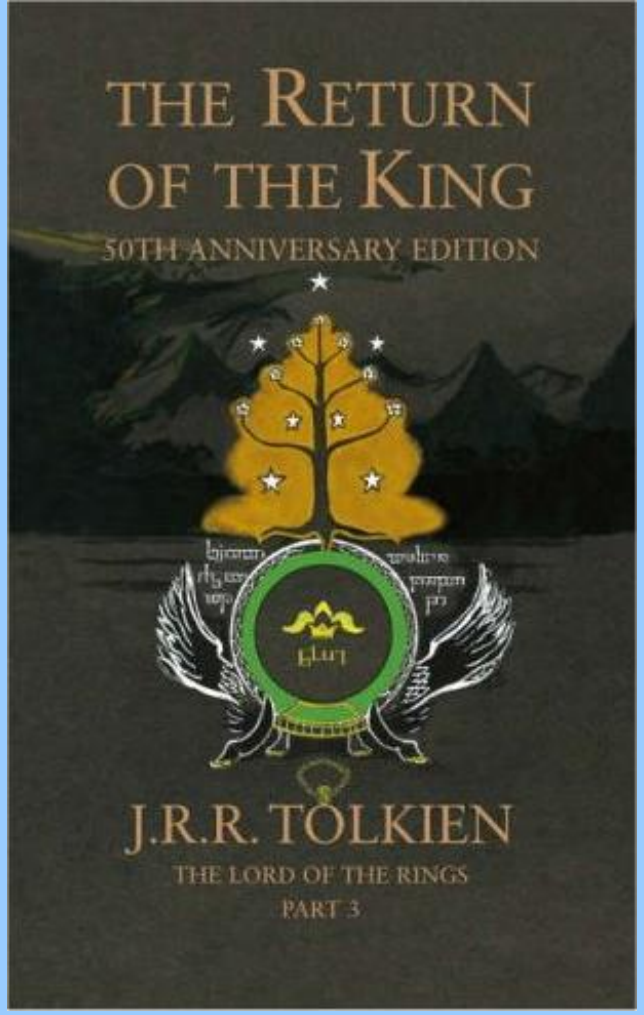
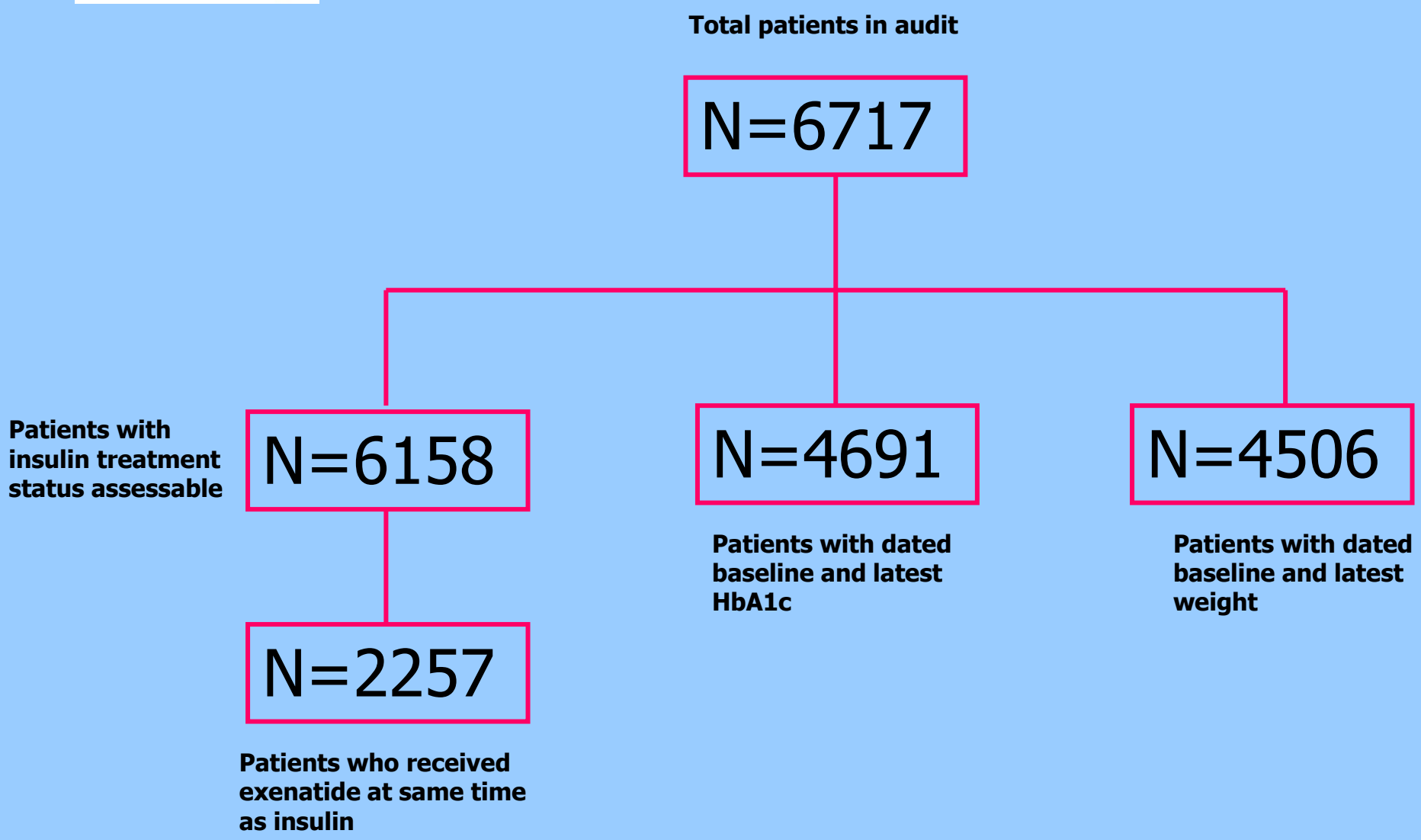
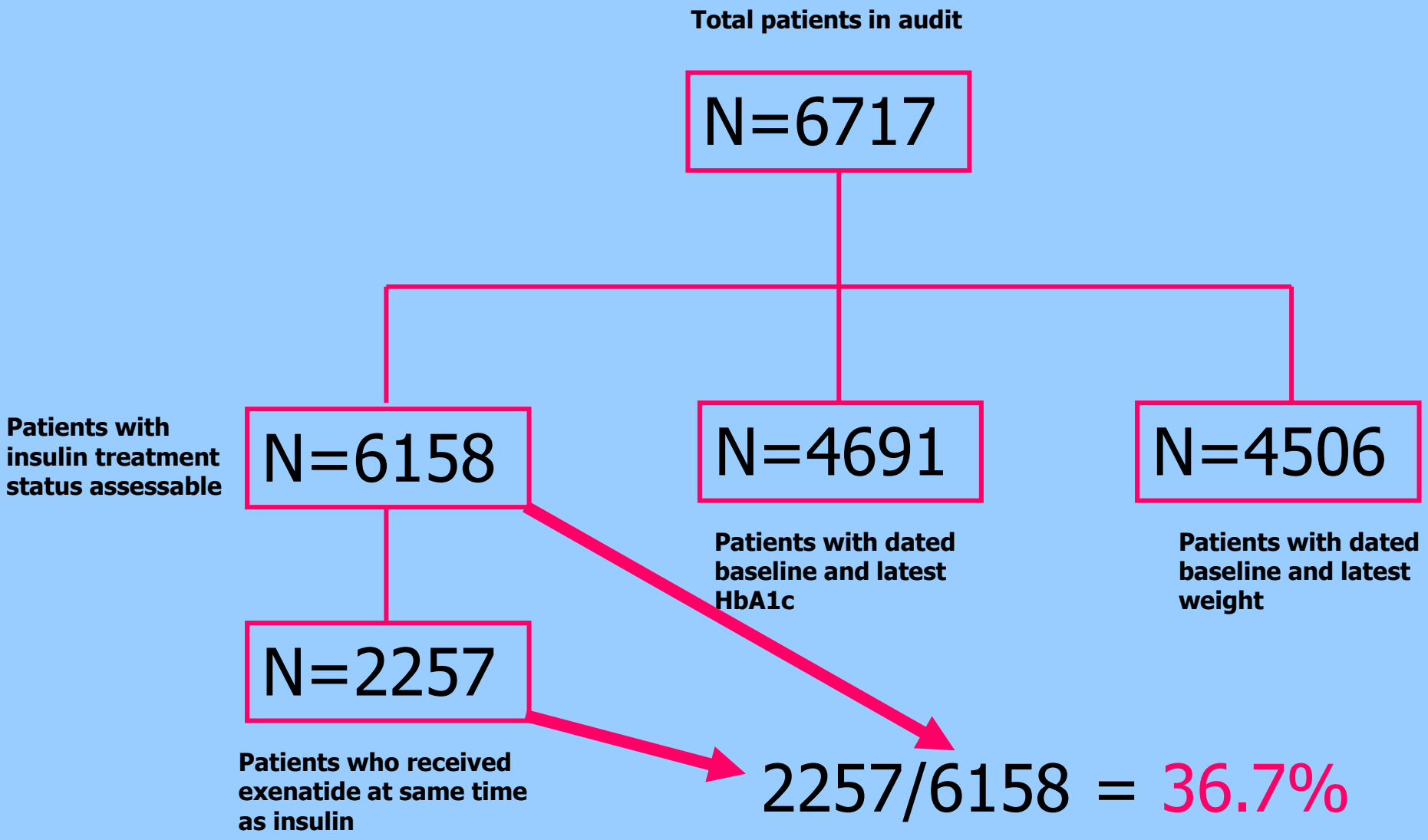


May 7 2010:
With insulin

Safety and efficacy of using exenatide in combination with insulin


Total patients in audit
N=6717
Patients with insulin treatment status assessable
N=6158
N=4691
N=4506
Patients with dated baseline and latest HbA1c
Patients with dated baseline and latest weight
N=2257
Patients who received exenatide at same time as insulin

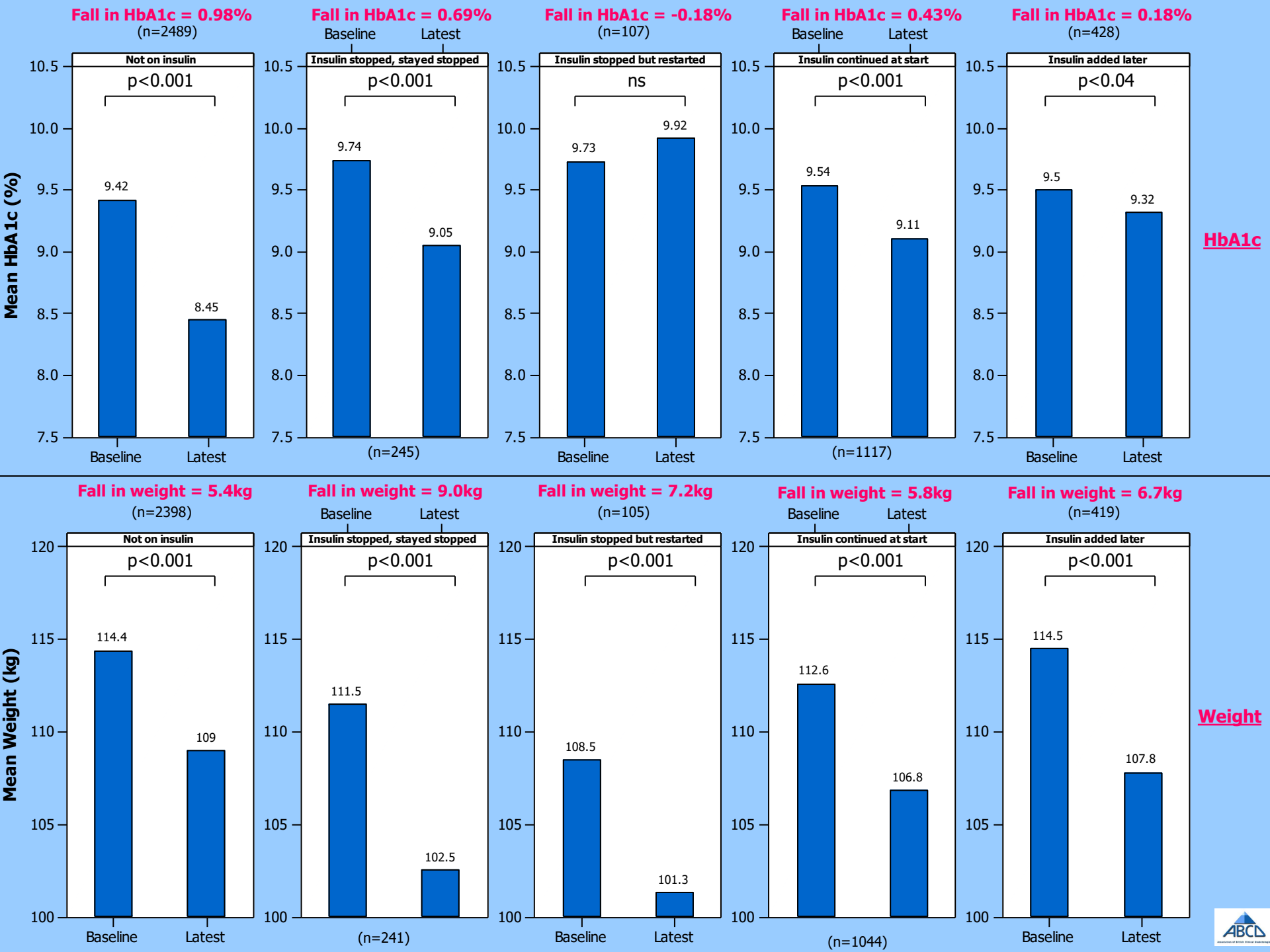

Total patients in audit
N=6717
Patients with insulin treatment status assessable
N=6158
N=4691
N=4506
Patients with dated baseline and latest HbA1c
Patients with dated baseline and latest weight
N=2257
Patients who received exenatide at same time as insulin
2257/6158 = 36.7%

Insulin Treatment groups

1. Not on insulin
2. Insulin stopped at start and stayed stopped
3. Insulin stopped at start but restarted
4. Insulin continued at start
5. Not on insulin at start but added later
6. All insulin and exenatide in combination
7. Insulin stopped whilst on exenatide

Insulin Treatment groups

1. *Not on insulin*
2. *Insulin stopped at start and stayed stopped*
3. *Insulin stopped at start but restarted*
4. *Insulin continued at start*
5. *Not on insulin at start but added later*
6. All insulin and exenatide in combination
7. Insulin stopped whilst on exenatide


Fall in HbA1c = 0.98%
(n=2489)
Not on insulin
p<0.001
9.42
8.45
Fall in HbA1c = 0.69%
Baseline
Latest
Insulin stopped, stayed stopped
p<0.001
9.74
9.05
(n=245)
Fall in HbA1c = -0.18%
(n=107)
Insulin stopped but restarted
ns
9.73
9.92
Fall in HbA1c = 0.43%
Baseline
Latest
Insulin continued at start
p<0.001
9.54
9.11
(n=1117)
Fall in HbA1c = 0.18%
(n=428)
Insulin added later
p<0.04
9.5
9.32
Mean HbA1c (%)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
Baseline
Latest
HbA1c
Fall in weight = 5.4kg
(n=2398)
Not on insulin
p<0.001
114.4
109
Fall in weight = 9.0kg
Baseline
Latest
Insulin stopped, stayed stopped
p<0.001
111.5
102.5
(n=241)
Fall in weight = 7.2kg
(n=105)
Insulin stopped but restarted
p<0.001
108.5
101.3
Fall in weight = 5.8kg
Baseline
Latest
Insulin continued at start
p<0.001
112.6
106.8
(n=1044)
Fall in weight = 6.7kg
(n=419)
Insulin added later
p<0.001
114.5
107.8
Mean Weight (kg)
120
115
110
105
100
Baseline
Latest
Weight

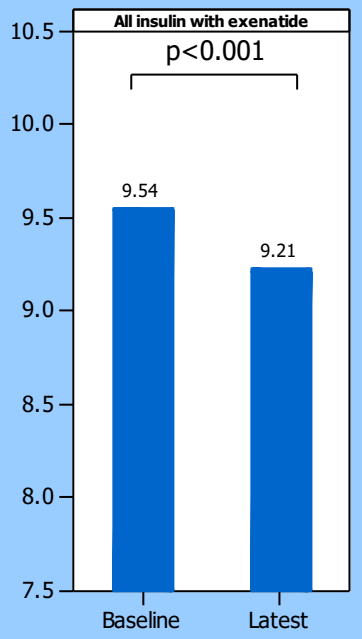
Insulin Treatment groups

1. Not on insulin
2. Insulin stopped at start and stayed stopped
3. *Insulin stopped at start but restarted*
4. *Insulin continued at start*
5. *Not on insulin at start but added later*

36.7%

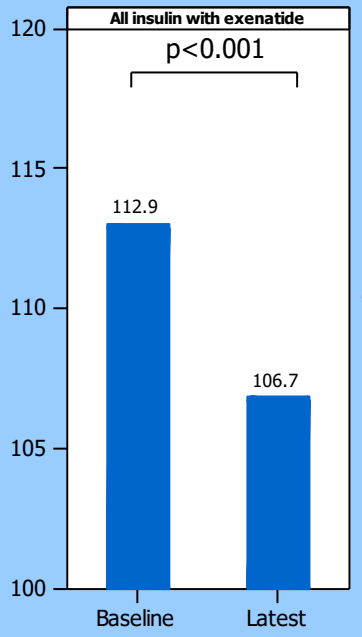
6. **All insulin and exenatide in combination**
7. Insulin stopped whilst on exenatide

Fall in HbA1c = 0.33%
(n=1652)

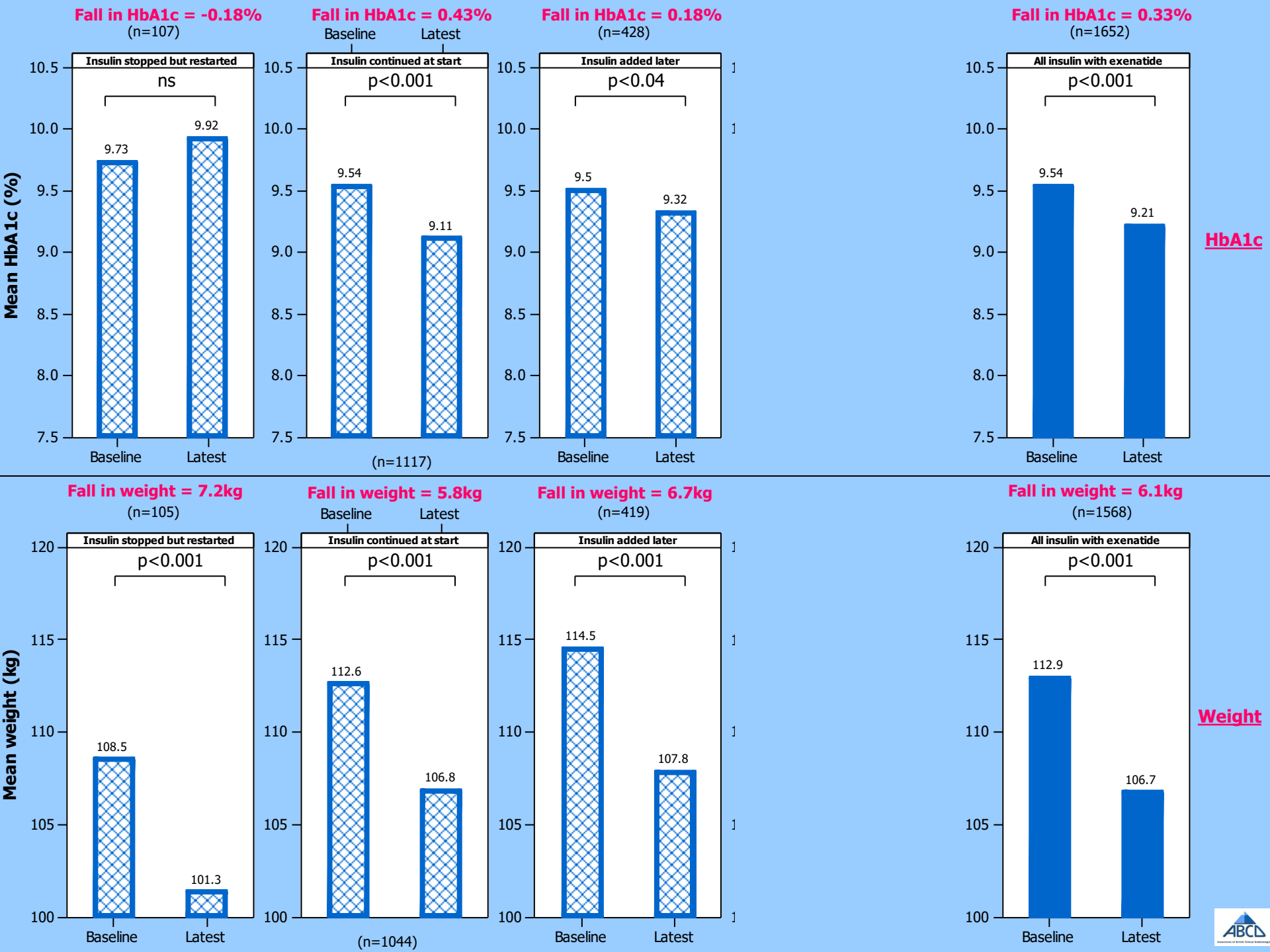


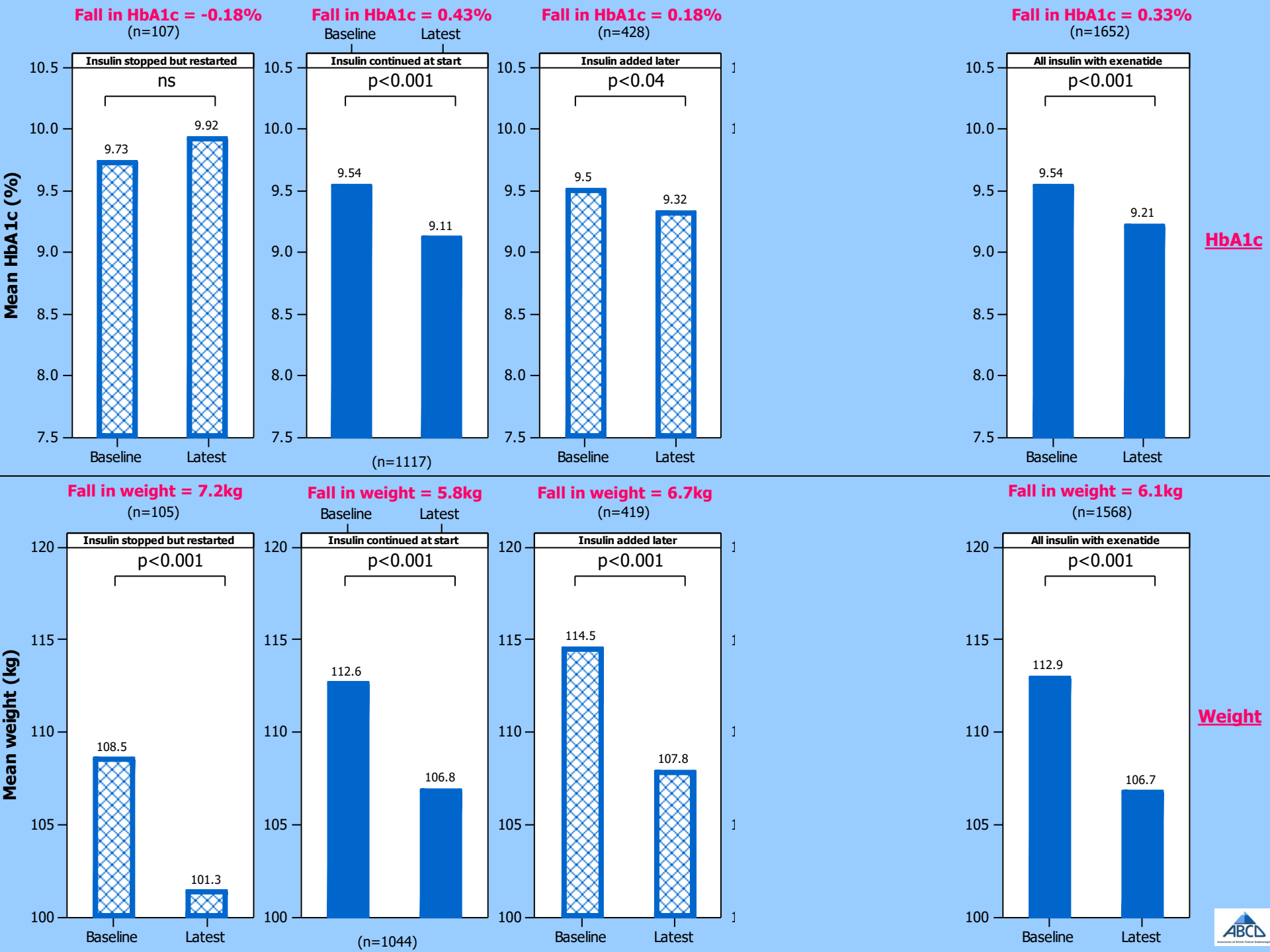
HbA1c

Fall in weight = 6.1kg
(n=1568)



Weight


Fall in HbA1c = -0.18%
(n=107)
Insulin stopped but restarted
ns
9.73
9.92
Fall in HbA1c = 0.43%
Baseline
Latest
Insulin continued at start
p<0.001
9.54
9.11
(n=1117)
Fall in HbA1c = 0.18%
(n=428)
Insulin added later
p<0.04
9.5
9.32
Fall in HbA1c = 0.33%
(n=1652)
All insulin with exenatide
p<0.001
9.54
9.21
Mean HbA1c (%)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
Baseline
Latest
HbA1c
Fall in weight = 7.2kg
(n=105)
Insulin stopped but restarted
p<0.001
108.5
101.3
Fall in weight = 5.8kg
Baseline
Latest
Insulin continued at start
p<0.001
112.6
106.8
(n=1044)
Fall in weight = 6.7kg
(n=419)
Insulin added later
p<0.001
114.5
107.8
Fall in weight = 6.1kg
(n=1568)
All insulin with exenatide
p<0.001
112.9
106.7
Mean weight (kg)
120
115
110
105
100
Baseline
Latest
Weight


Fall in HbA1c = -0.18%
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Insulin stopped but restarted
ns
9.73
9.92
Fall in HbA1c = 0.43%
Baseline
Latest
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Mean HbA1c (%)
10.5
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8.5
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Baseline
Latest
HbA1c
Fall in weight = 7.2kg
(n=105)
Insulin stopped but restarted
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Baseline
Latest
Insulin continued at start
p<0.001
112.6
106.8
(n=1044)
Fall in weight = 6.7kg
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Insulin added later
p<0.001
114.5
107.8
Fall in weight = 6.1kg
(n=1568)
All insulin with exenatide
p<0.001
112.9
106.7
Mean weight (kg)
120
115
110
105
100
Baseline
Latest
Weight

Insulin Treatment groups

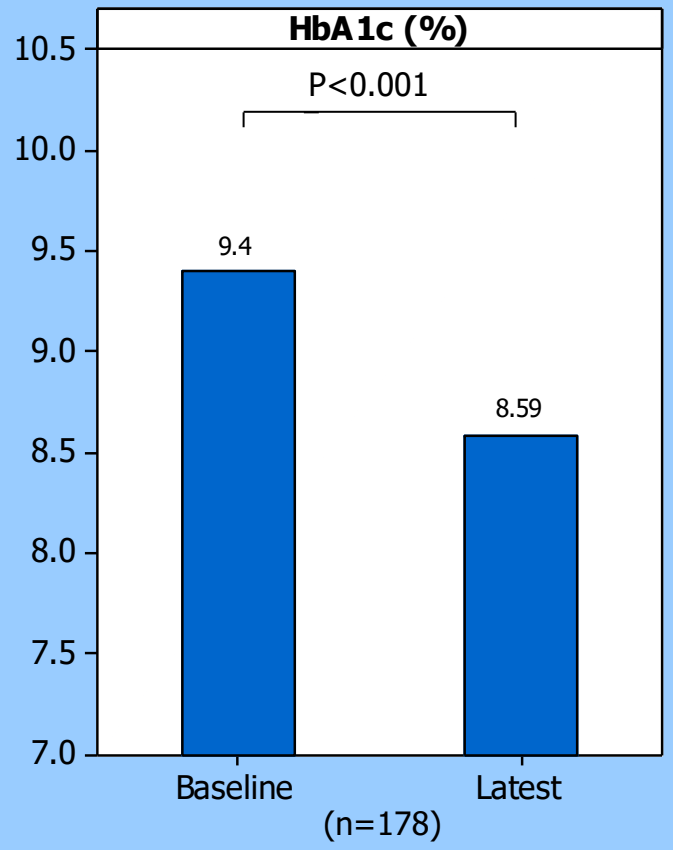
1. Not on insulin
2. Insulin stopped at start and stayed stopped
3. Insulin stopped at start but restarted
4. Insulin continued at start
5. Not on insulin at start but added later
6. All insulin and exenatide in combination
7. **Insulin stopped whilst on exenatide**

Insulin stopped during exenatide treatment

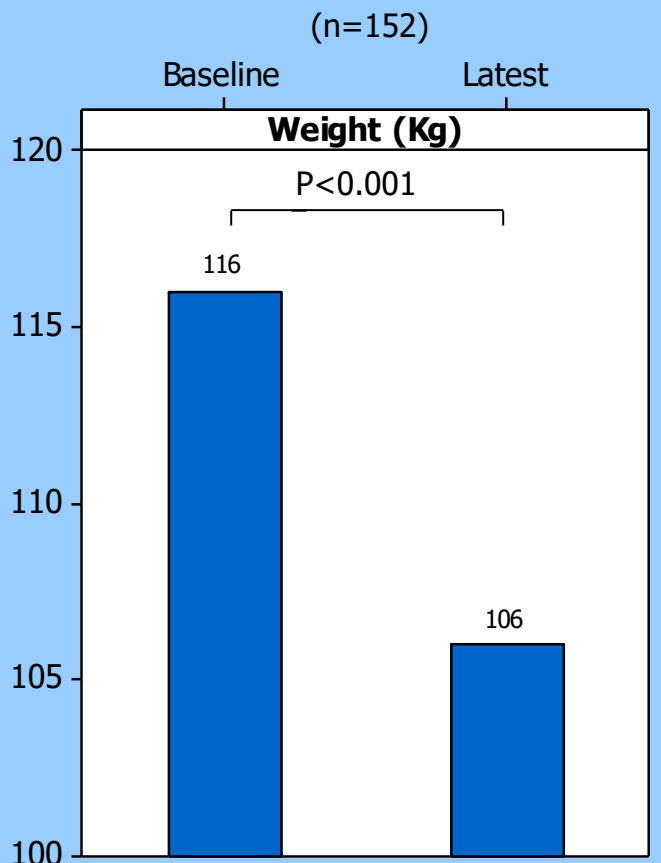
- 1584 patients continued insulin at time of exenatide start
- Of these 201/1584 (12.7%) came off insulin during exenatide treatment
- This group did particularly well:

Baseline versus latest HbA1c and Weight insulin stopped during exenatide treatment

Fall in HbA1c = 0.81 %



Fall in weight = 10.0 kg



Hypoglycaemia

INSULIN EXENATIDE Co-Administration HYPOGLYCAEMIA	N = 2257	
Hypoglycaemia before exenatide start (80 of these had none after exenatide start!)	133/2257	5.9%
Hypoglycaemia after exenatide start (140 hypo-naive; 53 used to have hypo before)	193/2257	8.6%

*The difference in rate of hypoglycaemia was significant, p = 0.001

Severe Hypoglycaemia

- Only one case reported
  - 1/2257 (0.04%)
  - (Unlikely to have been related to exenatide)

Conclusion 3 – exenatide in real clinical use

- The combination of insulin with exenatide was used in 36.7% (2257/6158) patients in the ABCD nationwide exenatide audit
- Exenatide with insulin in real clinical use in the UK has been both safe and effective with significant reductions in both weight and HbA1c and only one reported case of severe hypoglycaemia
- Exenatide allowed some patients to be weaned off insulin and this group experienced a considerable improvement in glycaemic control and weight

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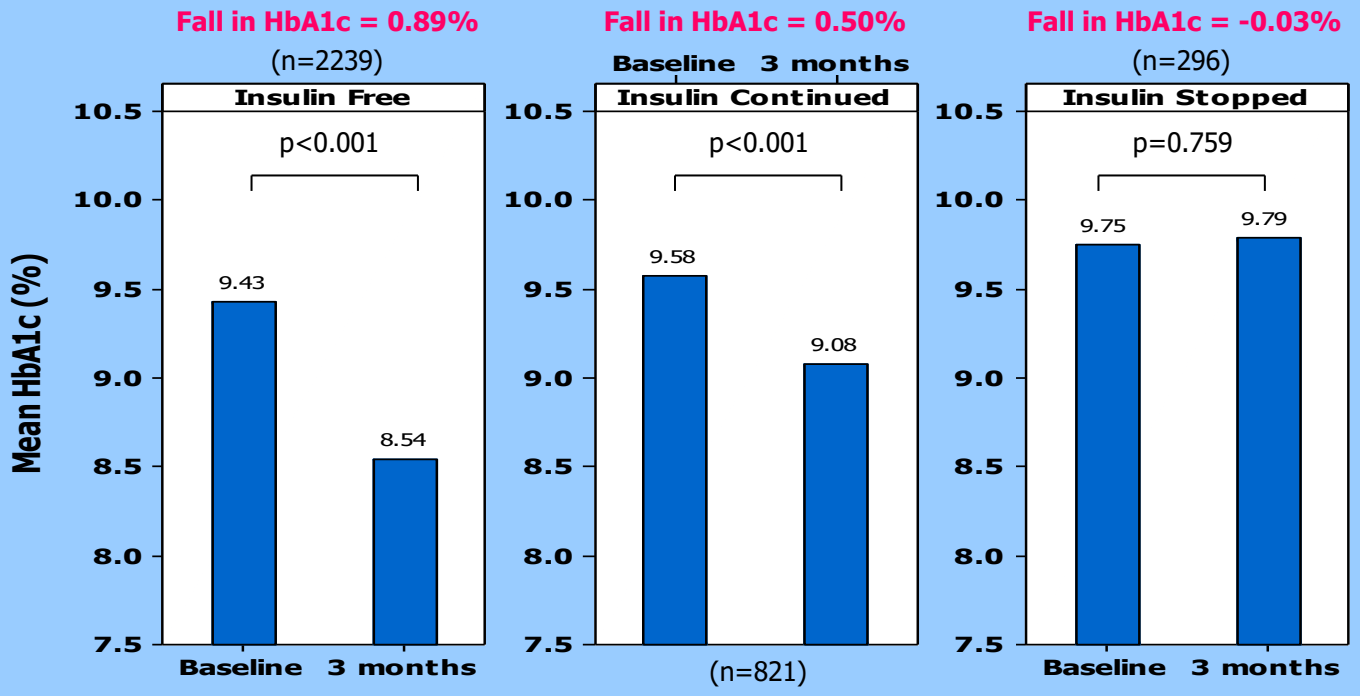
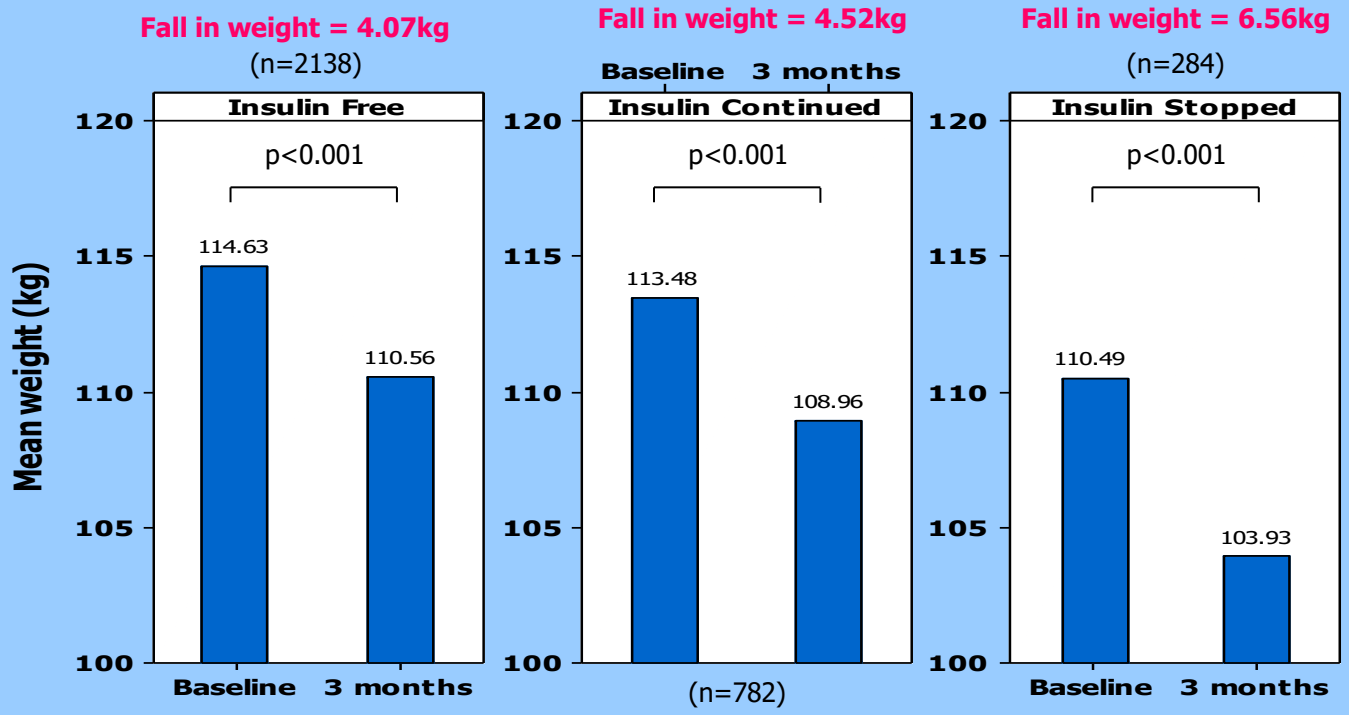
Response at 3 months to insulin dose decisions made at exenatide initiation

Insulin Treatment Groups

1. Insulin free
2. Insulin continued
3. Insulin stopped

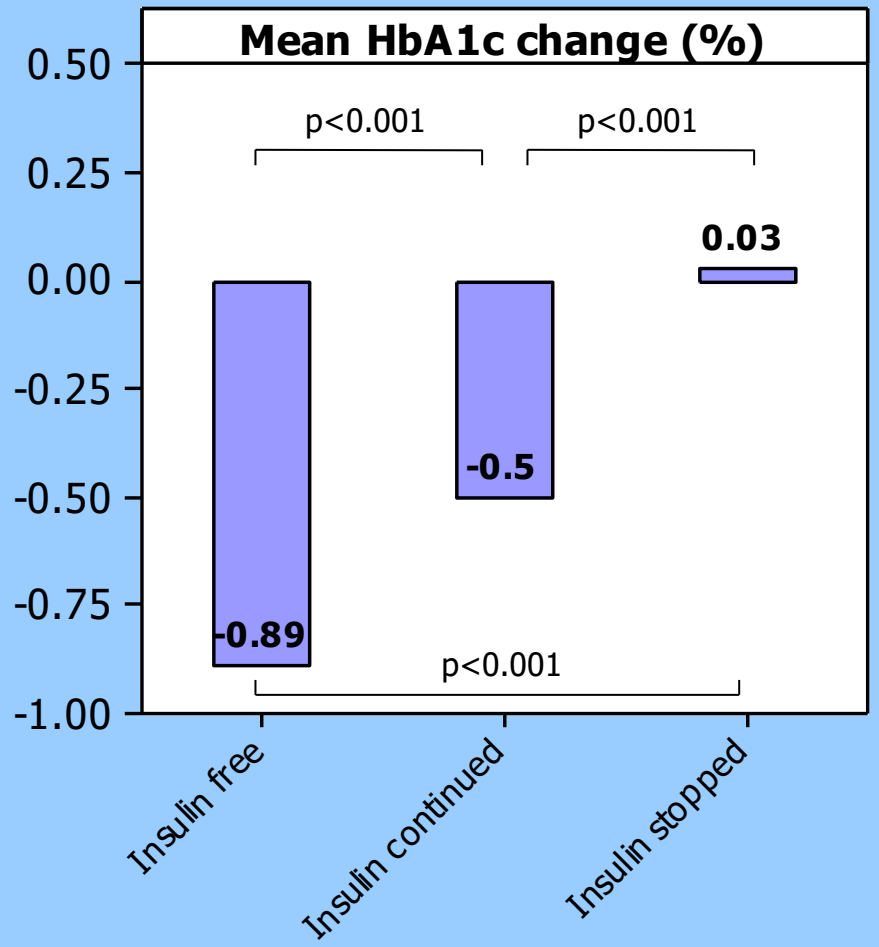


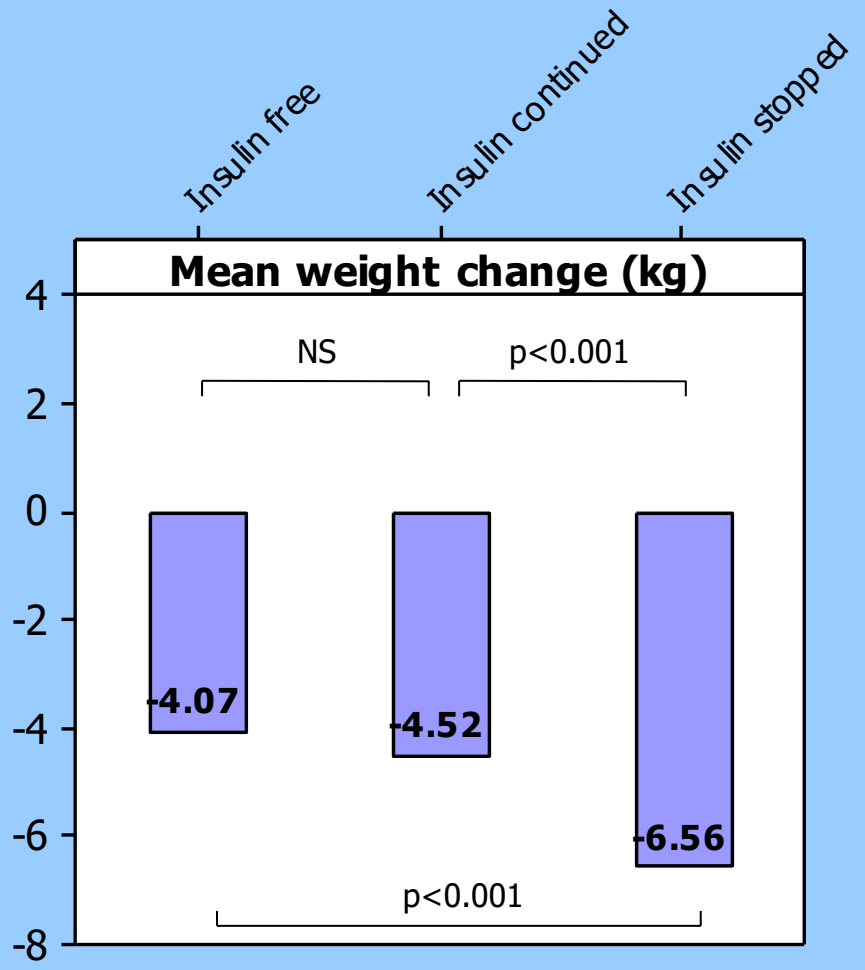
HbA1c



Weight

HbA1c and weight changes at 3 months by groups of insulin use





Conclusion 4 – exenatide in real clinical use

- Non-insulin users derived the most Hba1c benefit but the least weight benefit, while those who stopped insulin had the least (none) HbA1c benefit but the most weight benefit. Those who continued using insulin had intermediate results between the former two groups.
- With the addition of exenatide, weight loss occurred (4.5kg) even with insulin use
- Substituting insulin with exenatide facilitated further weight loss but at the expense improving HbA1c

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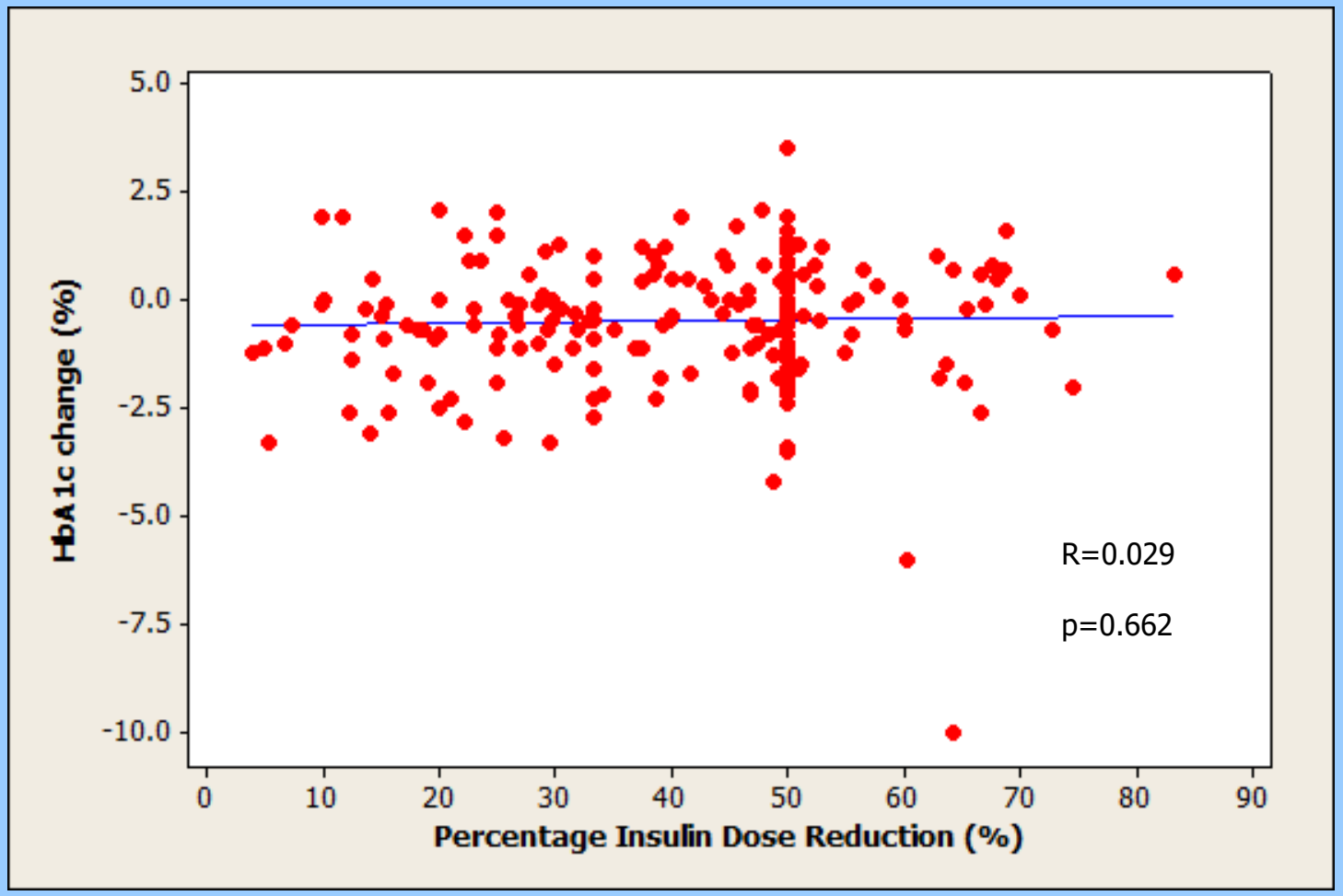
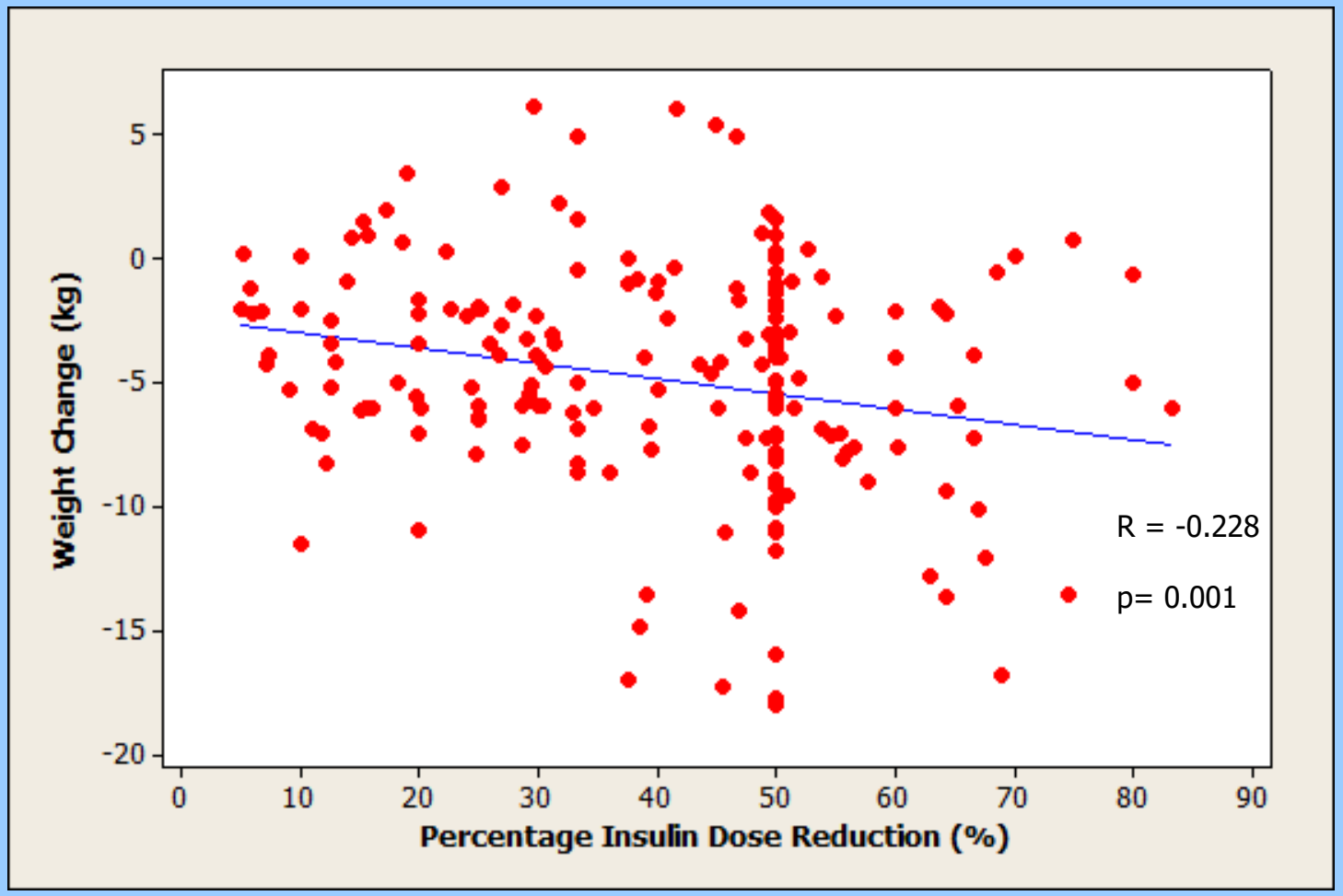
Does the degree of insulin dose reduction influence HbA1c and weight?

Correlation between insulin dose reduction and HbA1c change



Correlation between insulin dose reduction and weight change



Insulin Treatment Groups

1. Insulin free
2. Insulin continued
   a) No insulin dose reduction
   b) 1-40% insulin dose reduction (mean 25.3%)
   c) 41-80% insulin dose reduction (mean 52.2%)
3. Insulin stopped

Insulin Treatment Groups

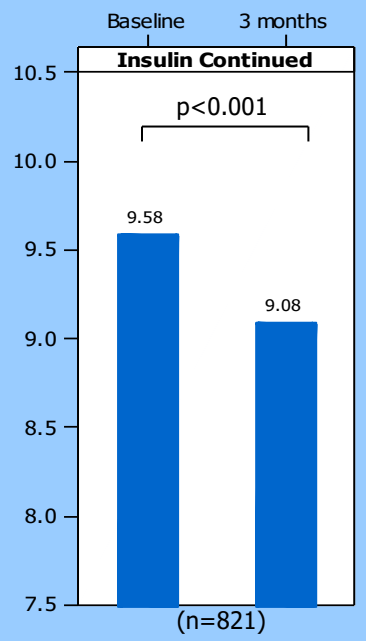
1. Insulin free
2. Insulin continued
   a) No insulin dose reduction
   b) 1-40% insulin dose reduction (mean 25.3%)
   c) 41-80% insulin dose reduction (mean 52.2%)
3. Insulin stopped

"Insulin not reduced"

"Insulin reduced 25%"

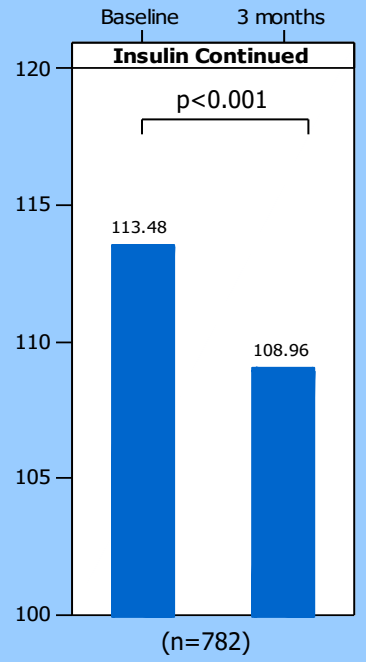
"Insulin reduced 50%"

Fall in HbA1c = 0.50%

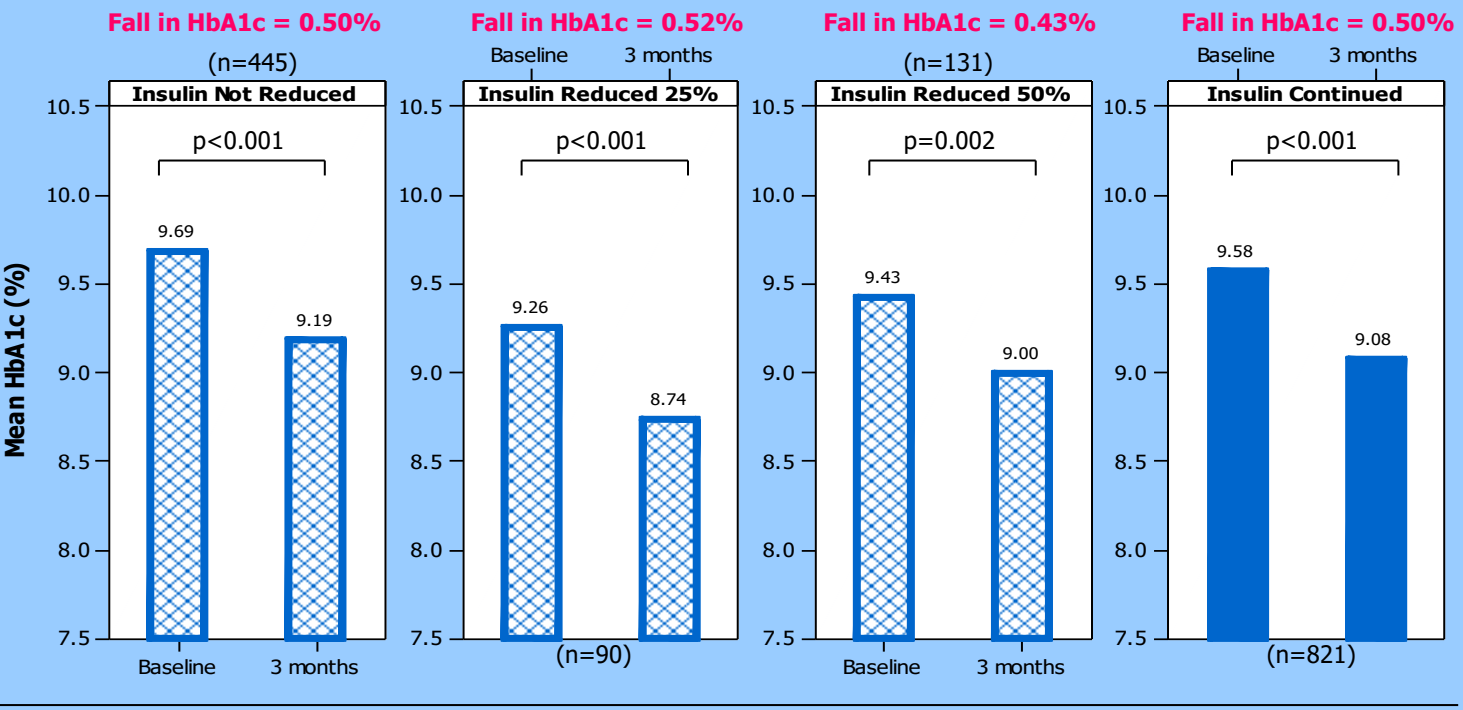


HbA1c

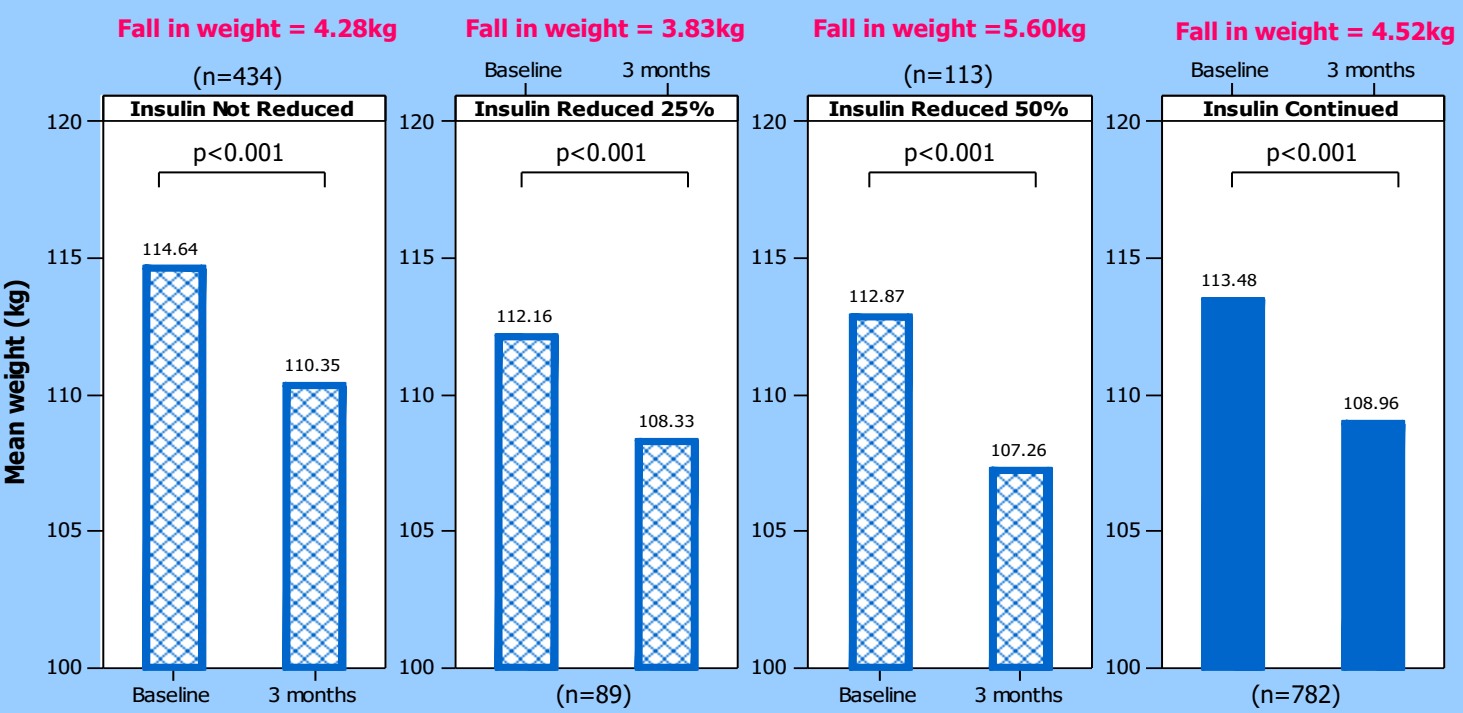
Fall in weight = 4.52kg



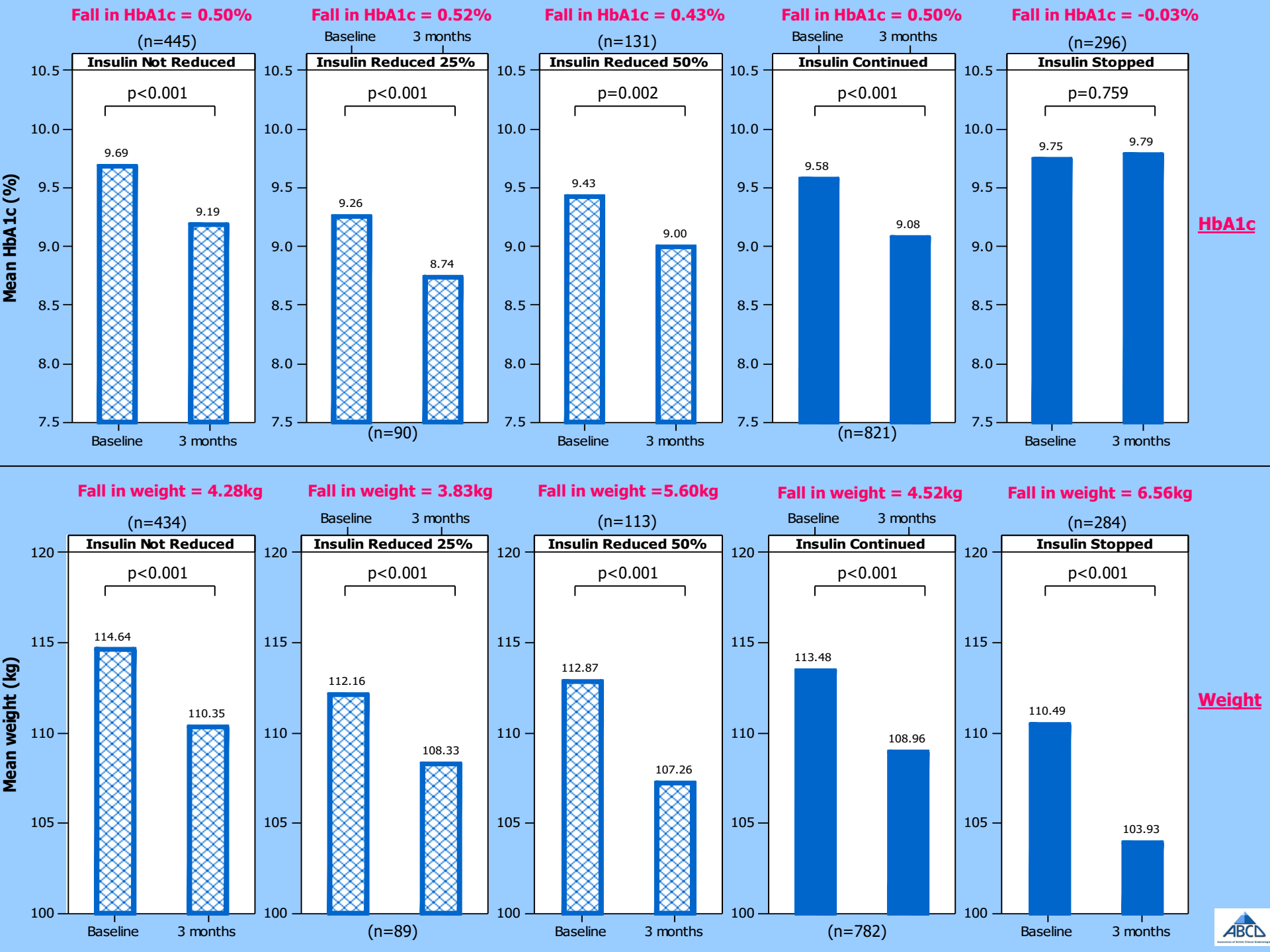
Weight



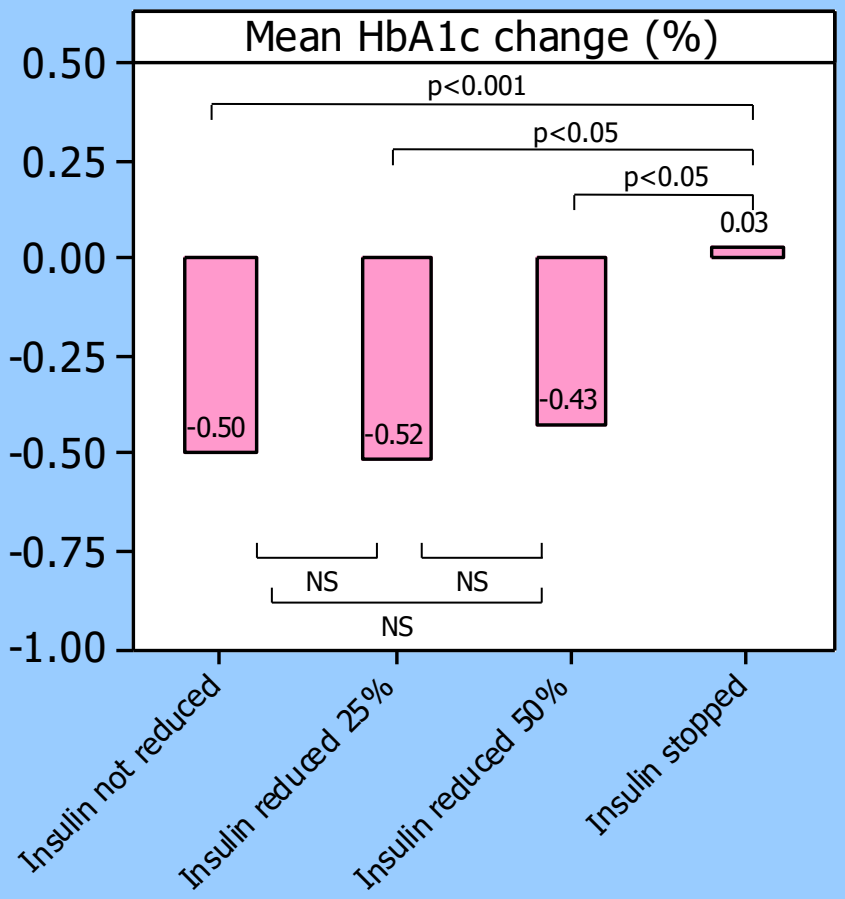
HbA1c

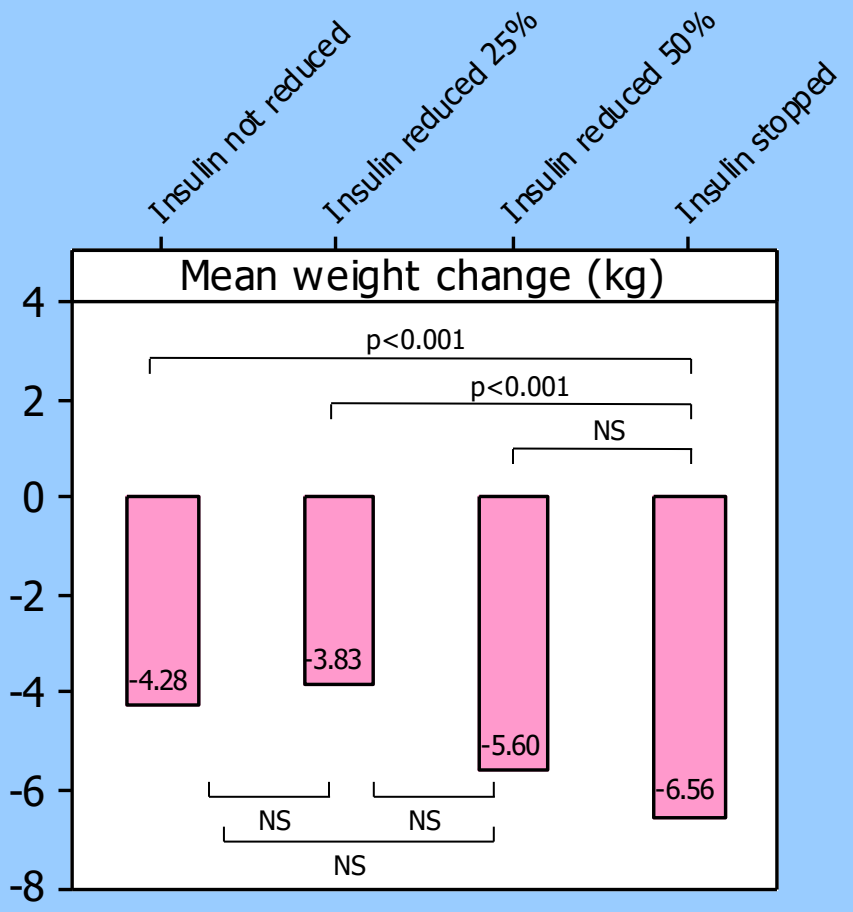


Weight


Fall in HbA1c = 0.50%
(n=445)
Insulin Not Reduced
p<0.001
9.69
9.19
Fall in HbA1c = 0.52%
Baseline
3 months
Insulin Reduced 25%
p<0.001
9.26
8.74
(n=90)
Fall in HbA1c = 0.43%
(n=131)
Insulin Reduced 50%
p=0.002
9.43
9.00
Fall in HbA1c = 0.50%
Baseline
3 months
Insulin Continued
p<0.001
9.58
9.08
(n=821)
Fall in HbA1c = -0.03%
(n=296)
Insulin Stopped
p=0.759
9.75
9.79
Mean HbA1c (%)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
Baseline
3 months
HbA1c
Fall in weight = 4.28kg
(n=434)
Insulin Not Reduced
p<0.001
114.64
110.35
Fall in weight = 3.83kg
Baseline
3 months
Insulin Reduced 25%
p<0.001
112.16
108.33
(n=89)
Fall in weight =5.60kg
(n=113)
Insulin Reduced 50%
p<0.001
112.87
107.26
Fall in weight = 4.52kg
Baseline
3 months
Insulin Continued
p<0.001
113.48
108.96
(n=782)
Fall in weight = 6.56kg
(n=284)
Insulin Stopped
p<0.001
110.49
103.93
Mean weight (kg)
120
115
110
105
100
Baseline
3 months
Weight

HbA1c and weight changes at 3 months by insulin dose reduction groups





Conclusion 5 – exenatide in real clinical use

- Weight reduction, but not HbA1c change, correlated with insulin dose reduction
- There was no clear threshold of insulin dose reduction when HbA1c or weight was affected, except when compared with insulin being stopped completely

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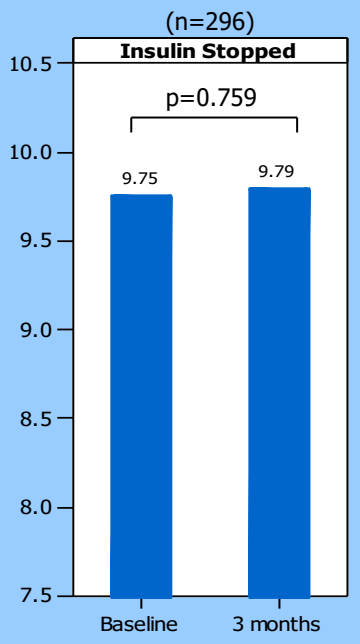
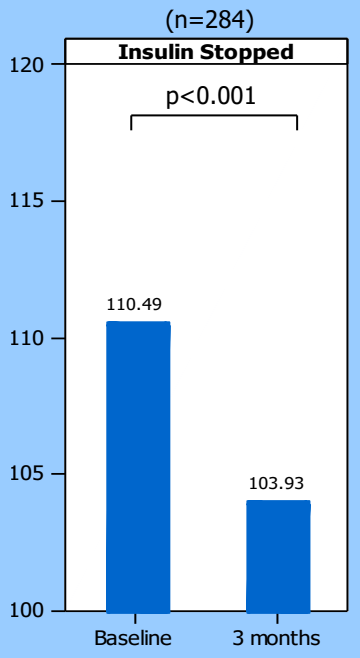
Are there predictors of glycaemic deterioration when insulin is substituted by exenatide?

Fall in HbA1c = -0.03%



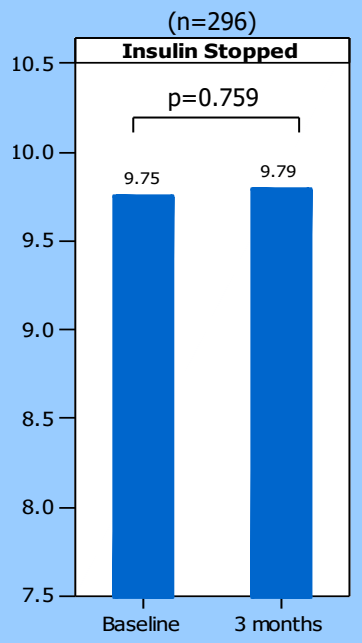
HbA1c

Fall in weight = 6.56kg



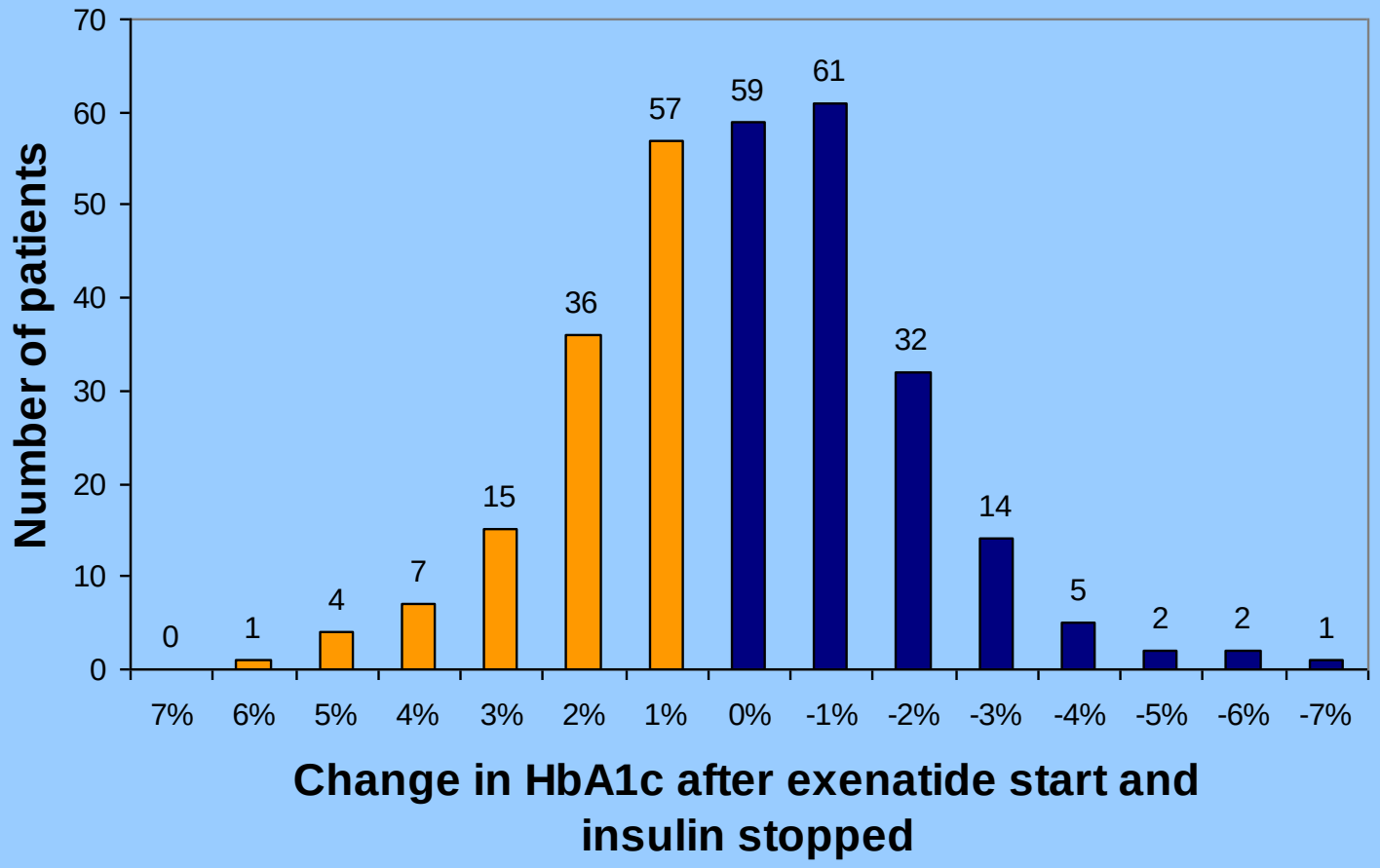
Weight

Fall in HbA1c = -0.03%



HbA1c

HbA1c change at 3 month among patients who stopped insulin



Total number of patients who stopped insulin at exenatide initiation = 296

Increased HbA1c>0% = 146 (49.3%)

Increased HbA1c>1% = 82 (27.7%)

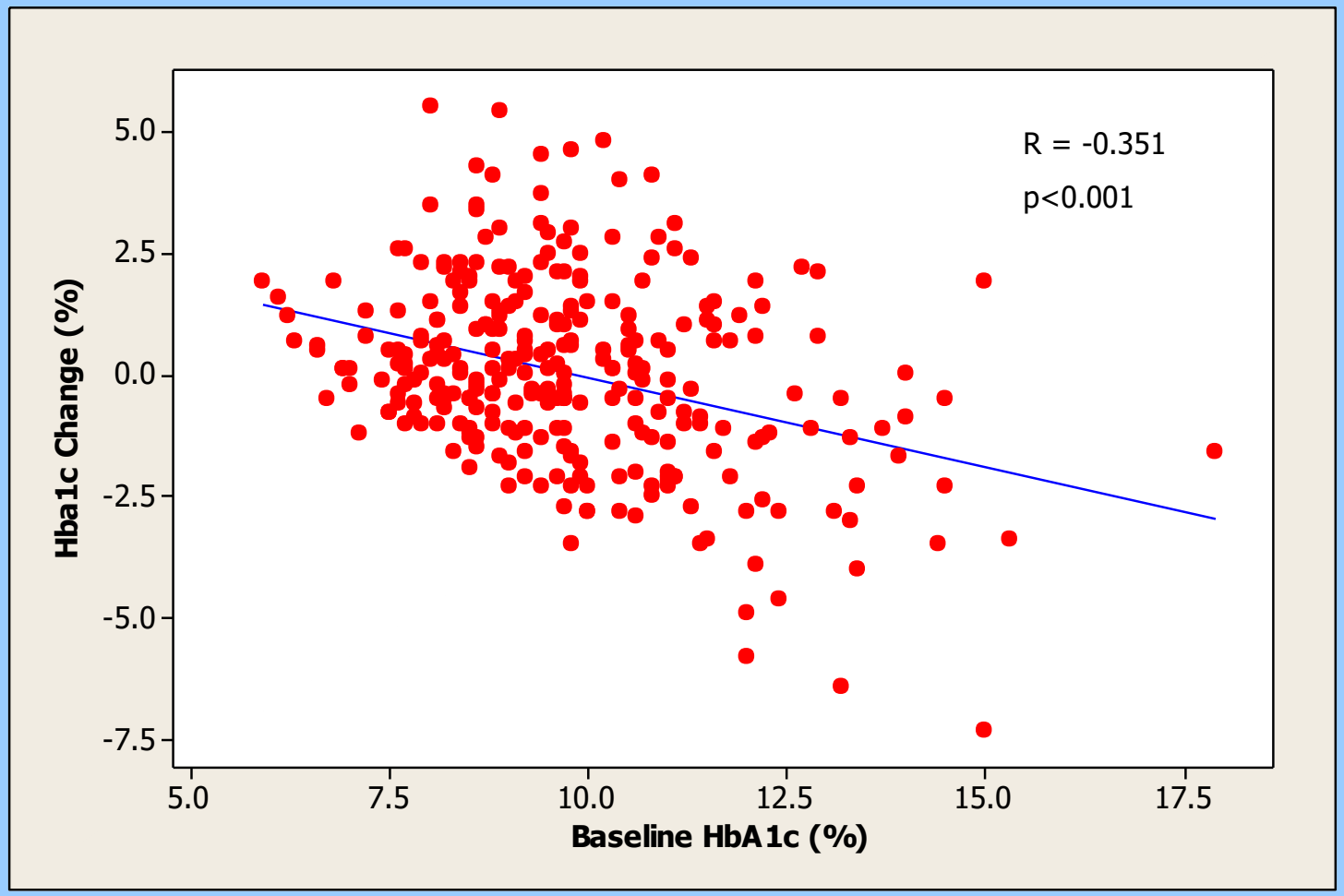
Increased HbA1c>2% = 42 (14.2%)

Predictors of worsening HbA1c in patients who stop insulin – multivariate analysis

	p value
Higher weight loss at 3 months	***<0.001***
Lower baseline HbA1c	***<0.001***
Insulin Dose	0.124*

**p=0.082 with age and diabetes duration removed from regression analysis*

Baseline HbA1c predicts HbA1c change in patients stopping insulin

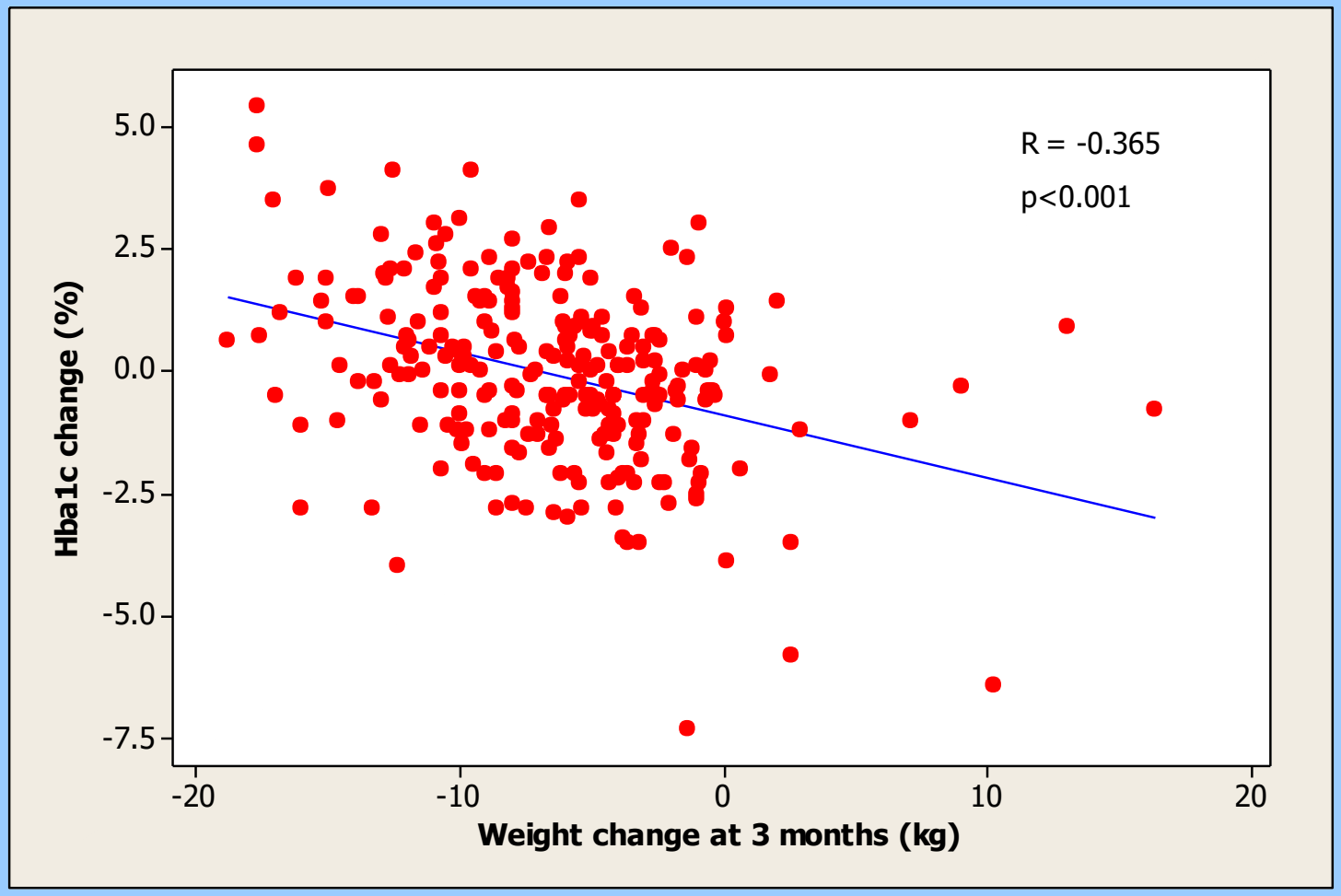


Lower baseline HbA1c predicts worsening HbA1c

or

Higher baseline HbA1c predicts Hba1c improvement

Weight change at 3 months predicts HbA1c change in patients stopping insulin

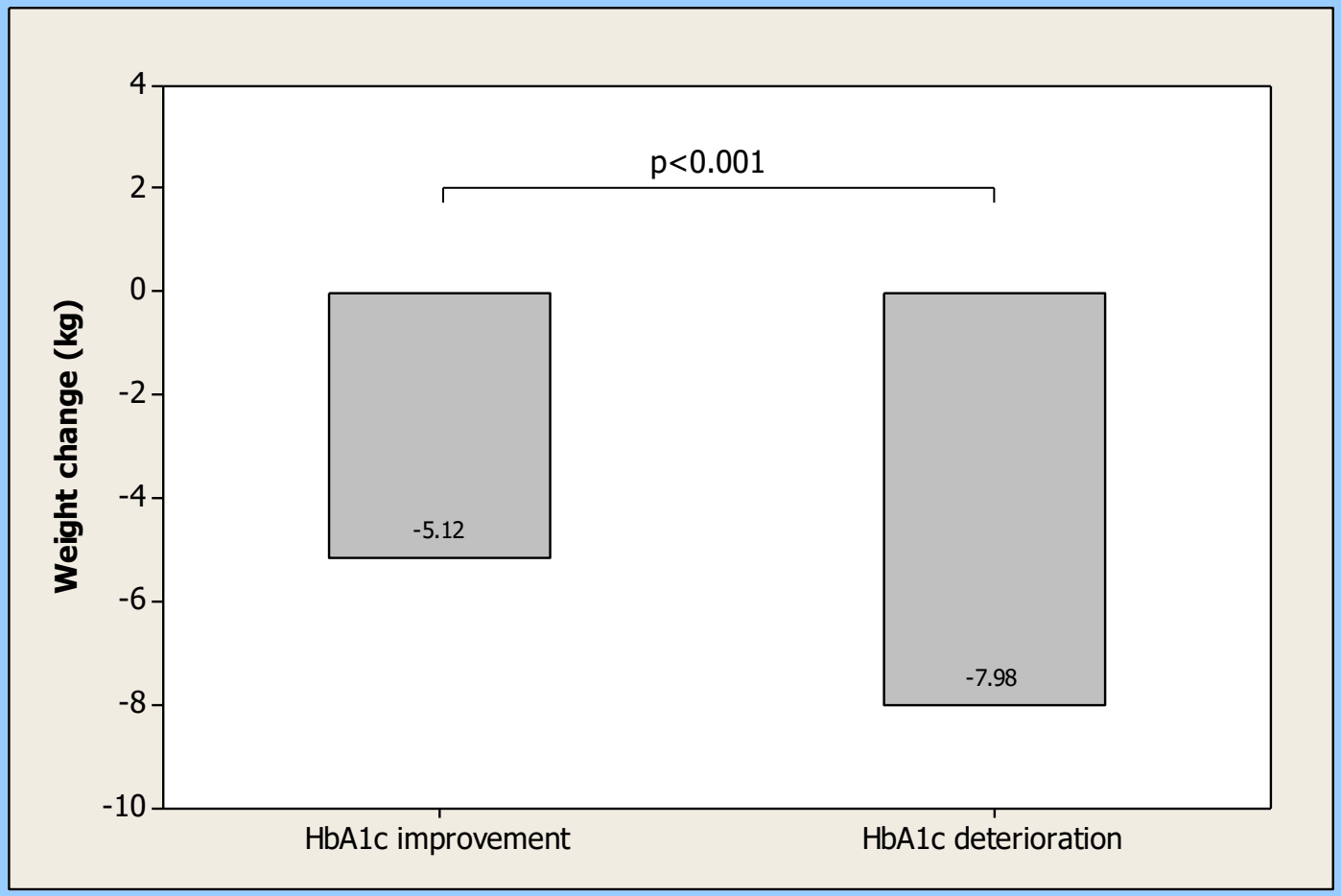


Higher weight loss predicts worsening HbA1c

or

Less weight loss predicts HbA1c improvement

Difference in weight loss between patients who had worsening vs improving HbA1c



Conclusion 6 – exenatide in real clinical use

- When insulin was substituted by exenatide nearly half of patients had worsening of their HbA1c
  - this is in the background of already suboptimal glycaemic control
- Predictors of worsening HbA1c was a lower baseline HbA1c and higher amount of weight loss after 3 months of exenatide treatment
- Practical conclusion – don't stop insulin when starting exenatide – aim to wean off the insulin in the appropriate patients instead

Association of British Clinical Diabetologists

Exenatide and Insulin: *where to from here?*

- The heterogenous, even opposing, response of HbA1c vs weight when insulin was stopped warrants further investigation
- Correlation of response to exenatide with markers of endogenous β cell function such as c-peptide levels would be of great interest

ABCD Prospective Nationwide Liraglutide Audit

http://www.diabetologists.org.uk/liraglutide.htm

Association of British Clinical Diabetologists

Registered Charitable Trust No. 1074491

ABCD Prospective Nationwide Liraglutide Audit

Following the success of the nationwide exenatide audit, ABCD has set up a nationwide ***prospective*** audit of liraglutide in real clinical use in the UK. The audit has a number of objectives.

An audit tool to facilitate data entry has been created specifically for the audit. The tool has inbuilt the following facilities:

- A calculations page summarizing data on ***your*** patients
- A chart page which automatically presents the data in ***your*** patients in graphical form
- A facility to export the data and the charts automatically and automatically create a PowerPoint presentation of ***your*** data
- A button to export the data to a file to send the anonymized data to the ABCD Audit

Register to take part in the audit and download the tool

To facilitate data collection during clinics there are two paper forms which exactly match the data that can be entered into the audit tool. You can download and print these forms locally or order preprinted data entry forms.

To download use ***right click, "save target as"*** to save the files to your hard disk. Use ***left click to open the files*** in a new window - depending on the speed of your internet connection there may be a delay before the file opens

Download first visit data entry form
Download follow up visit data entry form

Further information will be found on the ABCD members only website at:
http://www.diabetologists.org.uk/liraglutide_audit/

Non ABCD members are welcome to take part in the audit and will be given access to the above subweb when they register for the audit.

Register to take part in the audit and download the tool

Further enquiries may be made to the ABCD nationwide audits database administrator of the project, Melissa Cull

Download liraglutide clinical slideset (Powerpoint)

The ABCD prospective nationwide liraglutide audit is an independent audit supported by an unrestricted grant from Novo Nordisk Ltd