ABCD Nationwide Exenatide Audit

Dr Bob Ryder

on behalf of the ABCD nationwide exenatide audit contributors

DUK APC, Liverpool, March 3 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

ABCD Nationwide Exenatide Audit

- *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 will 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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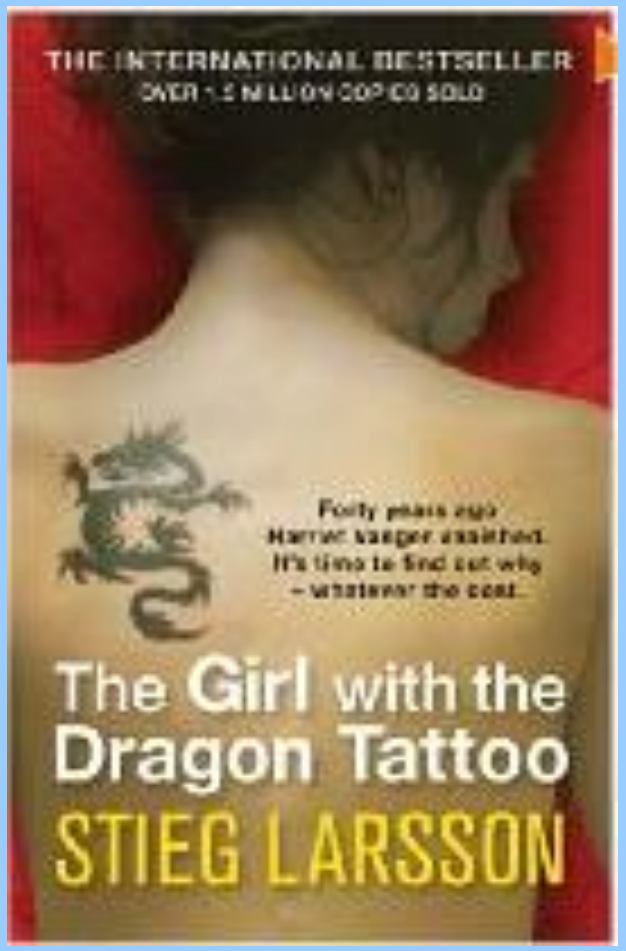
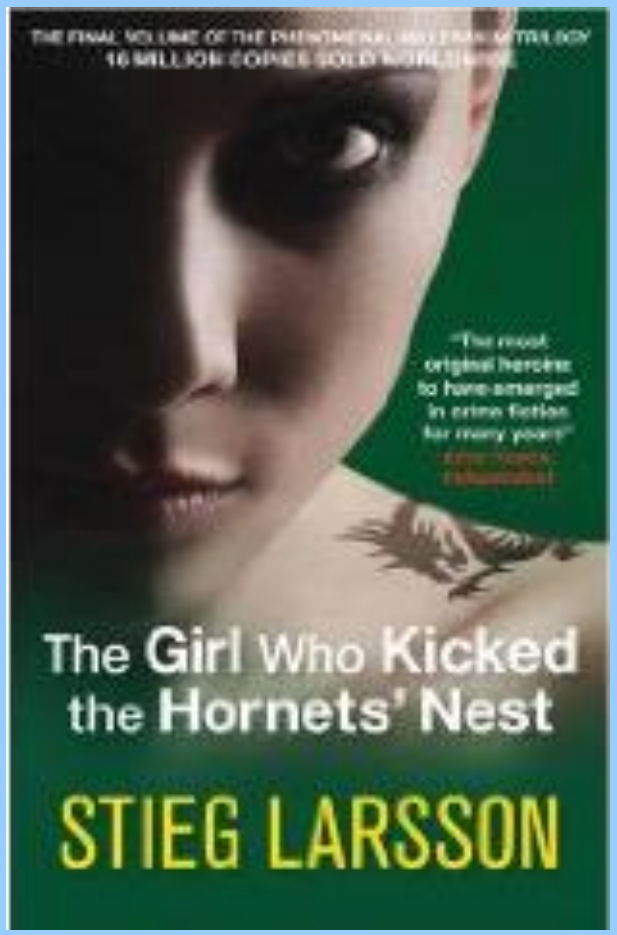
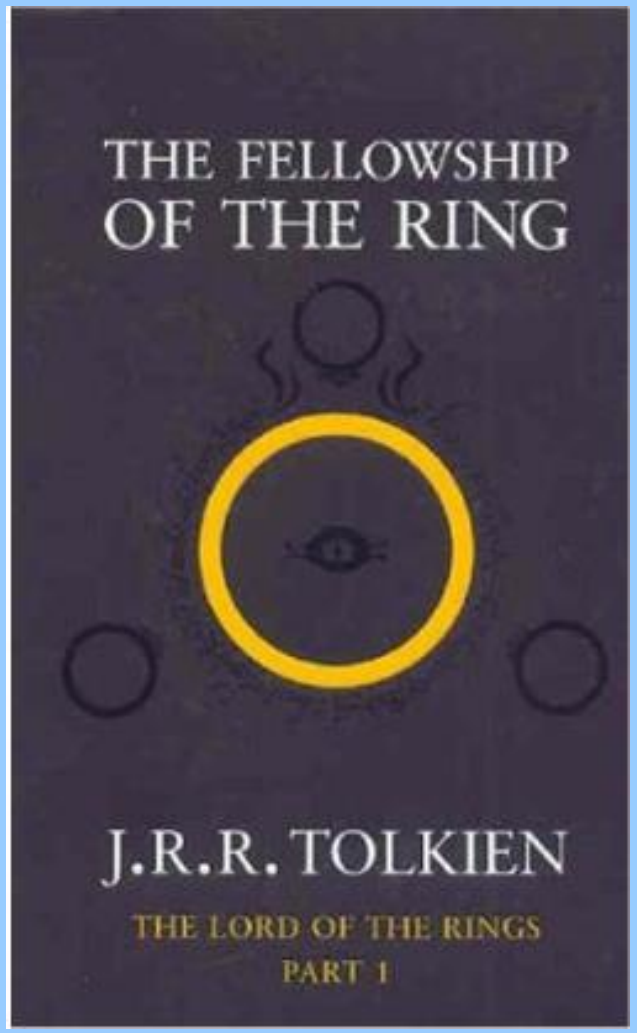
A Trilogy?

The Millennium Trilogy



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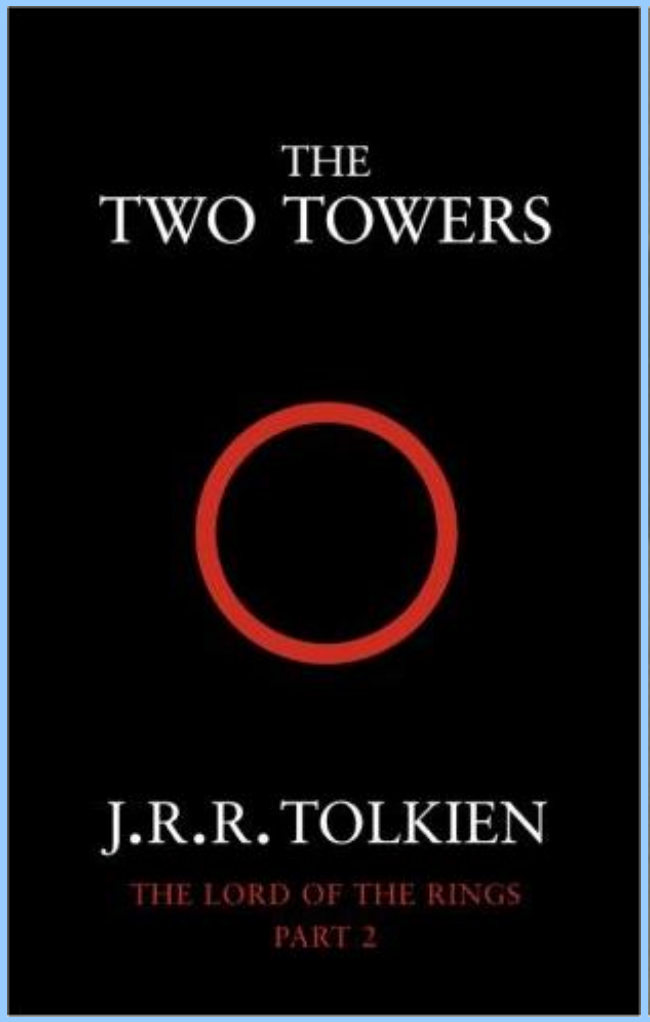
THE
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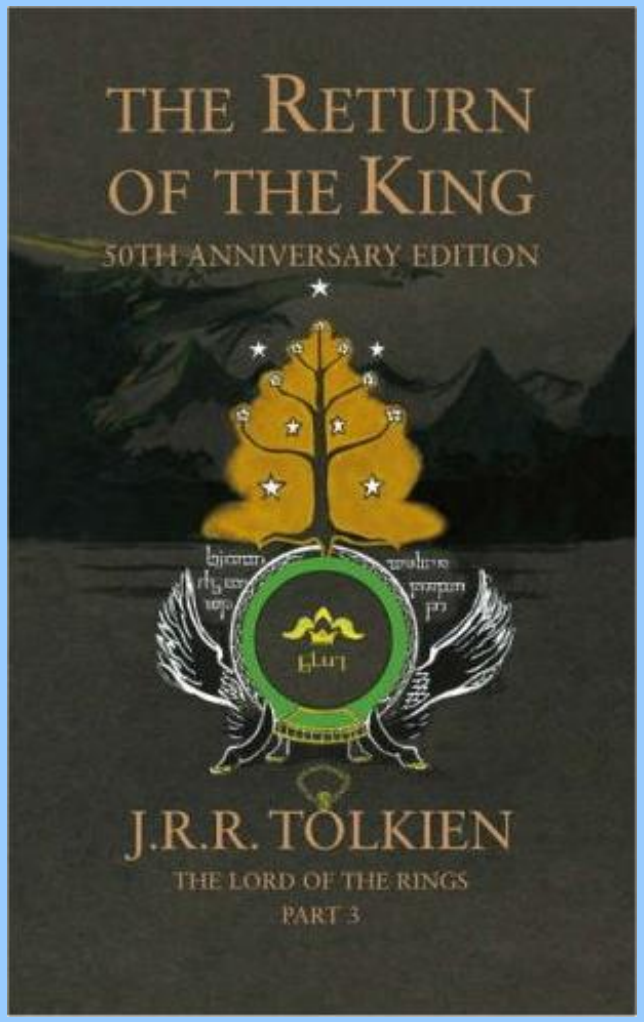
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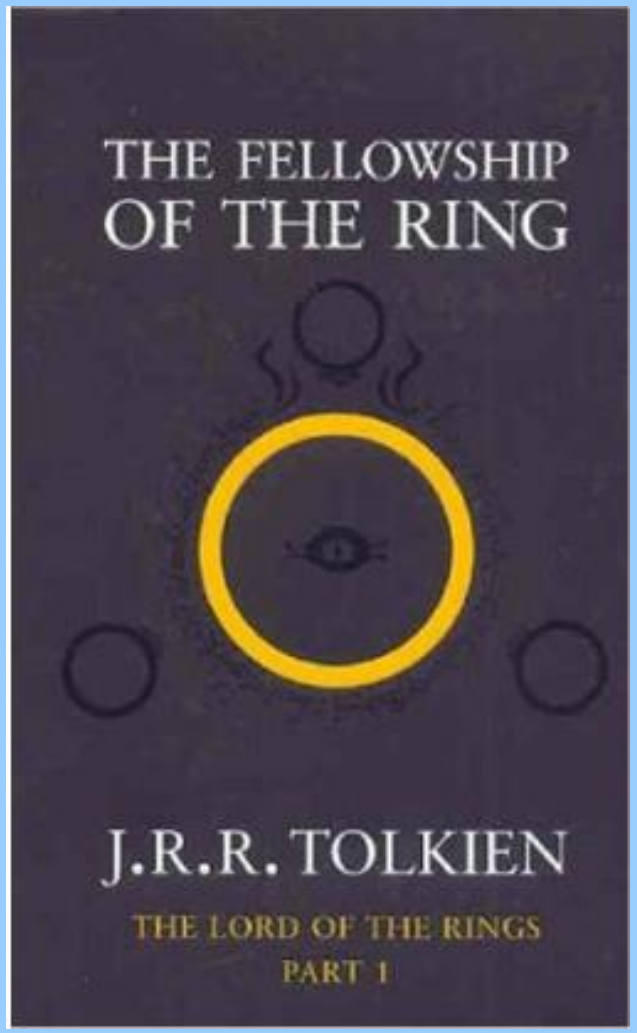
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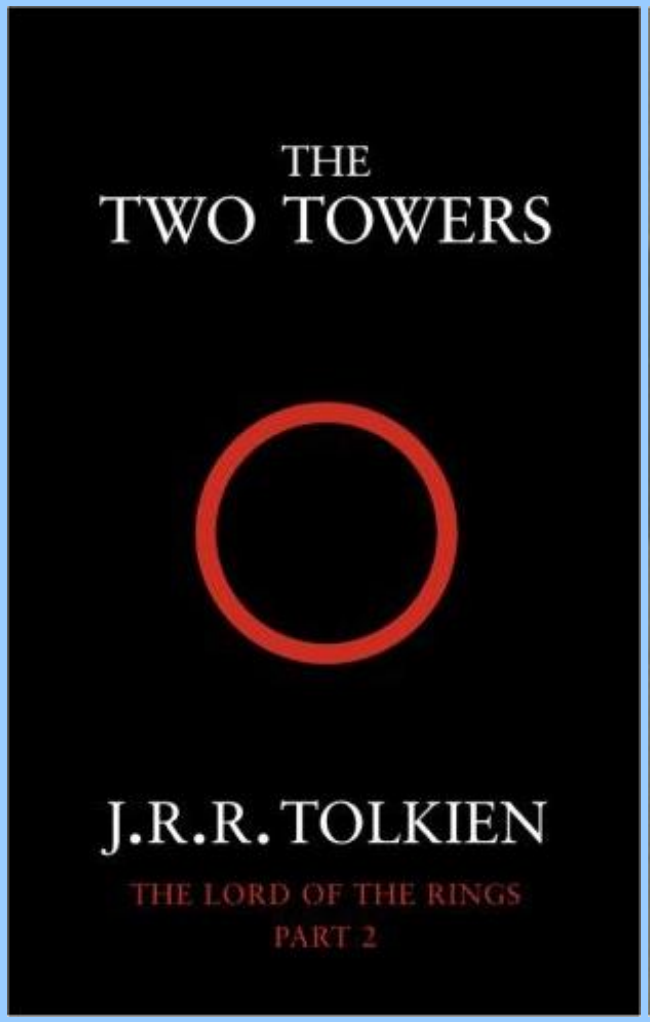
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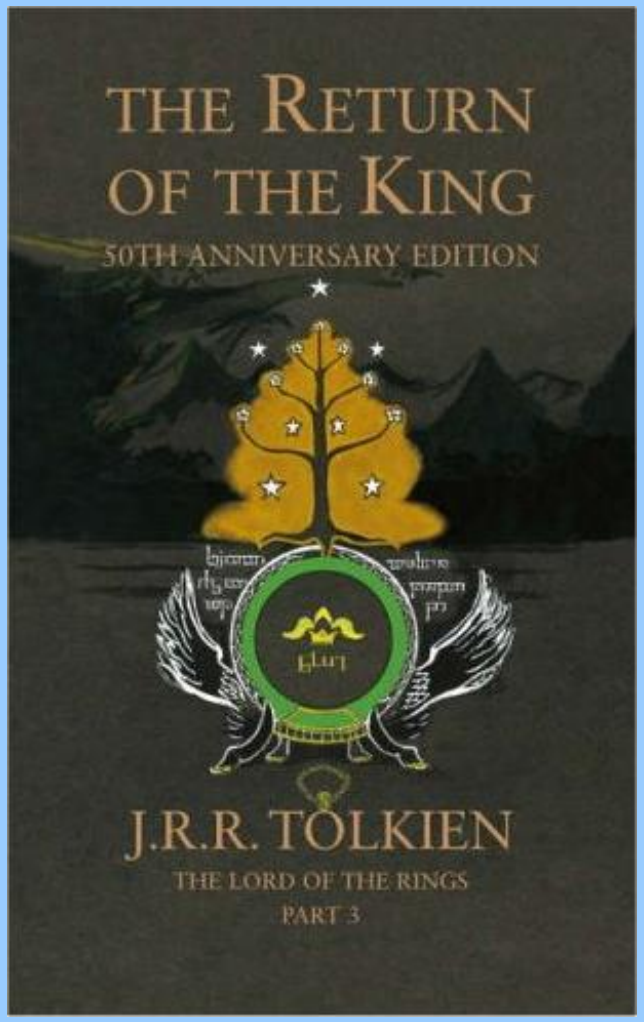
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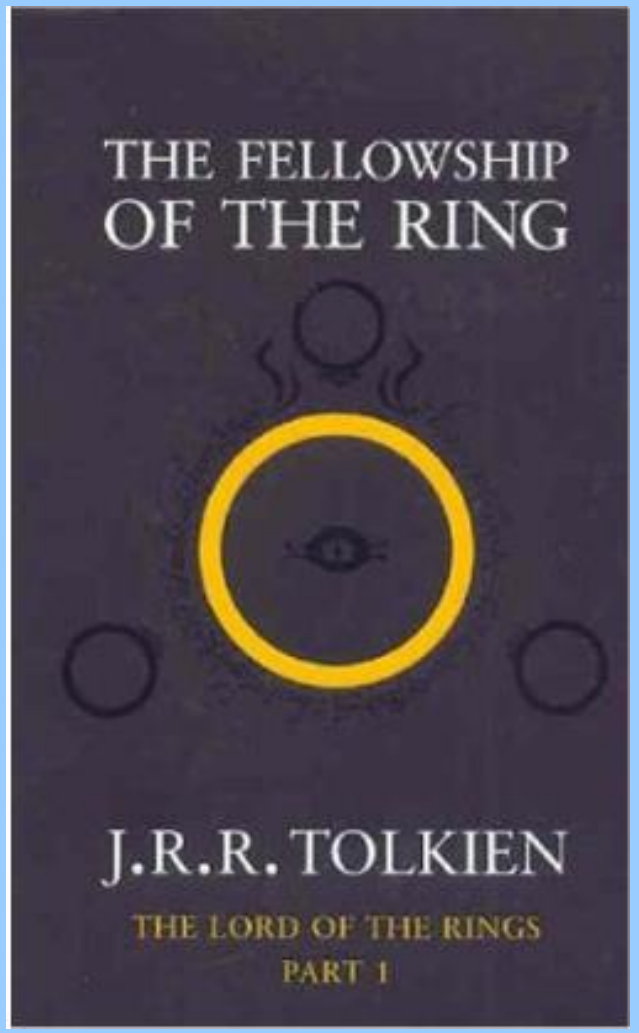
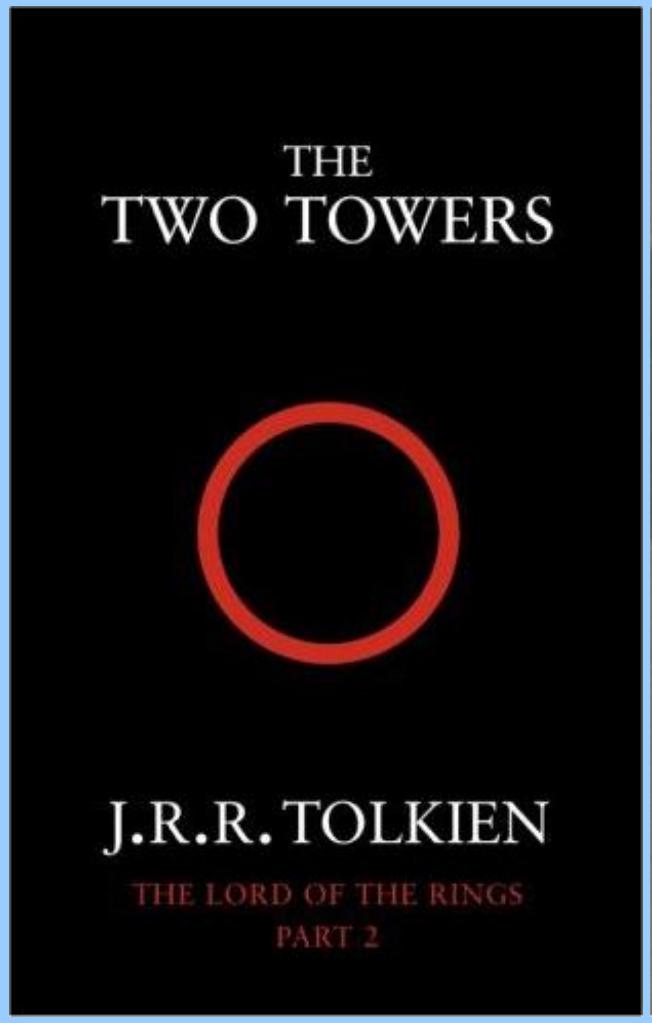
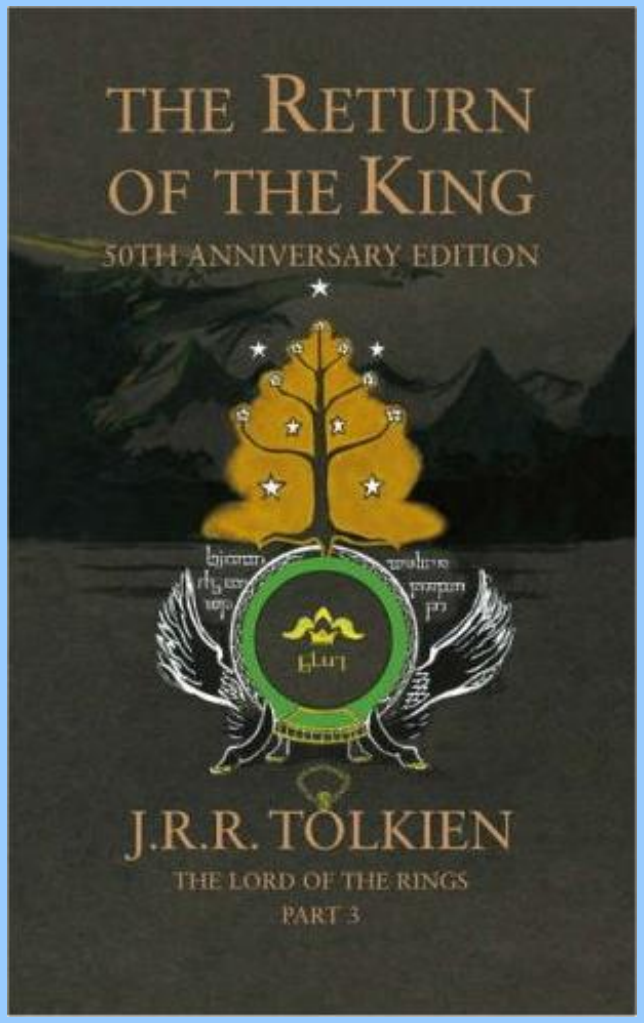
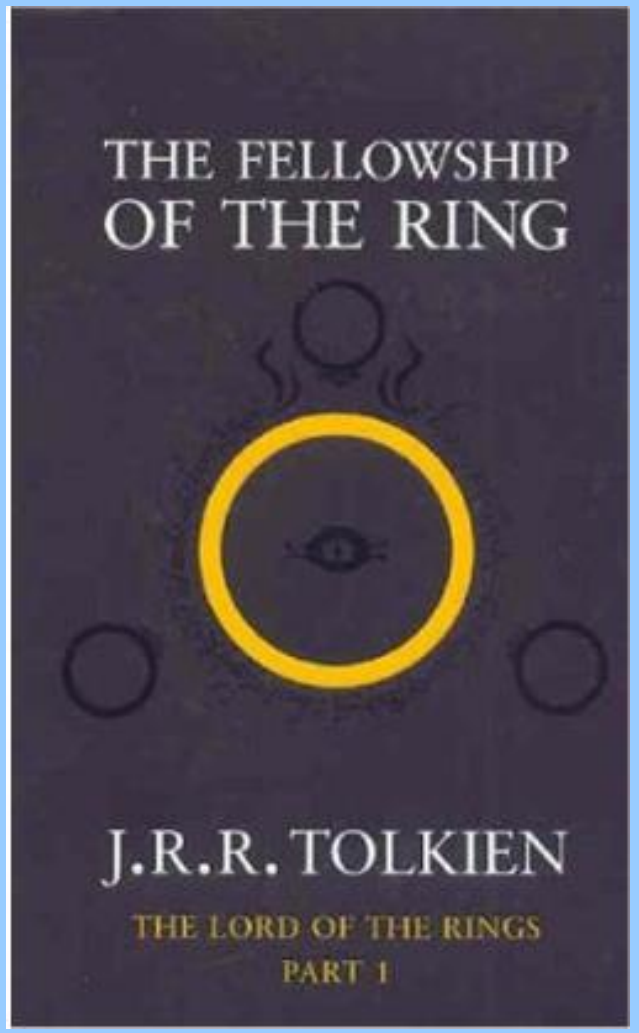
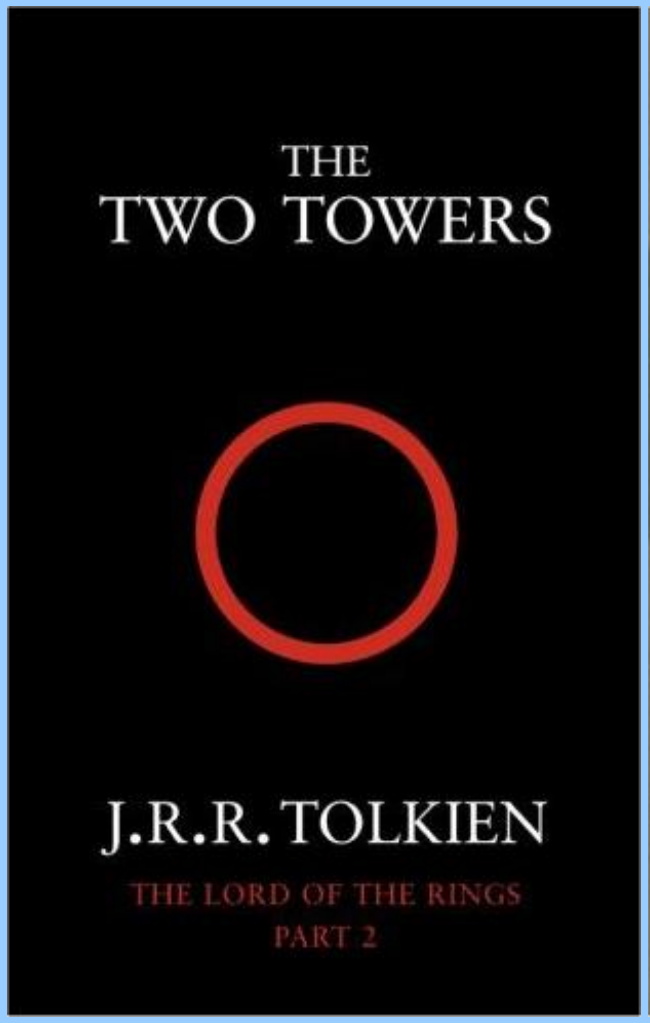


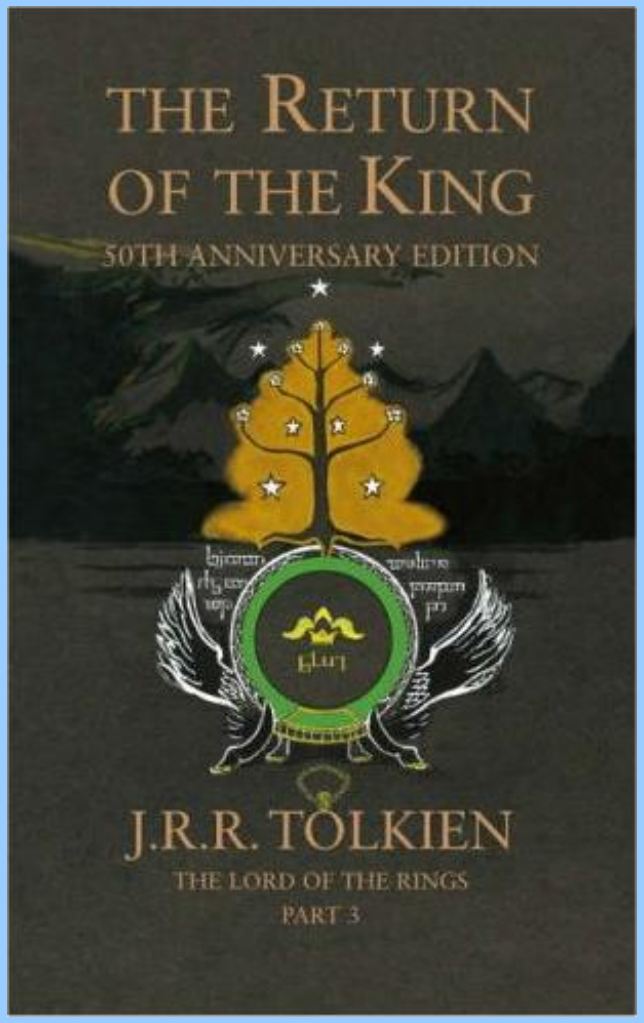




March 2 2010:
Data at 6 months

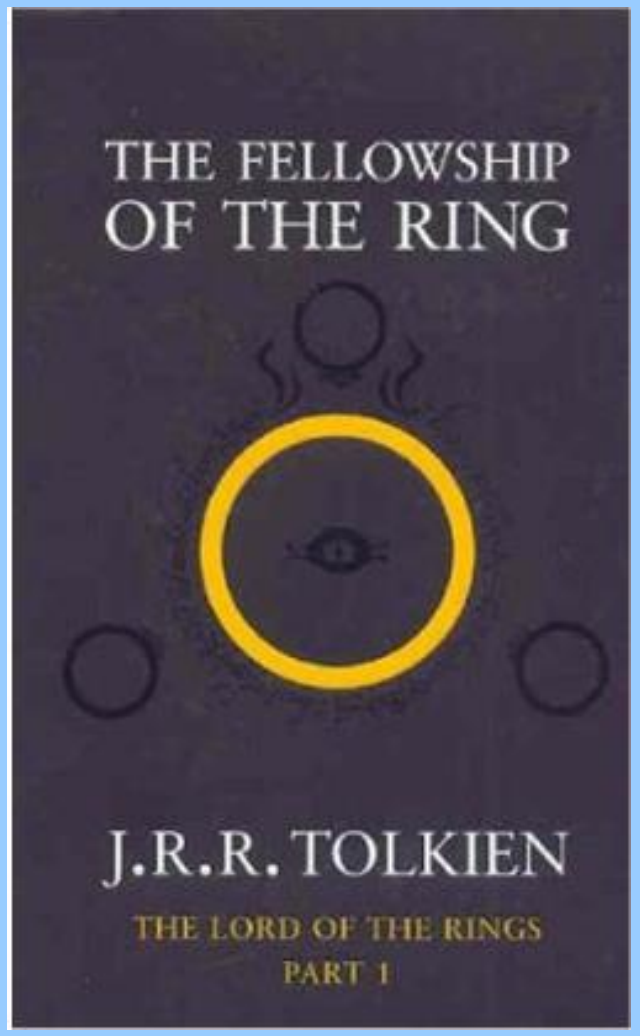


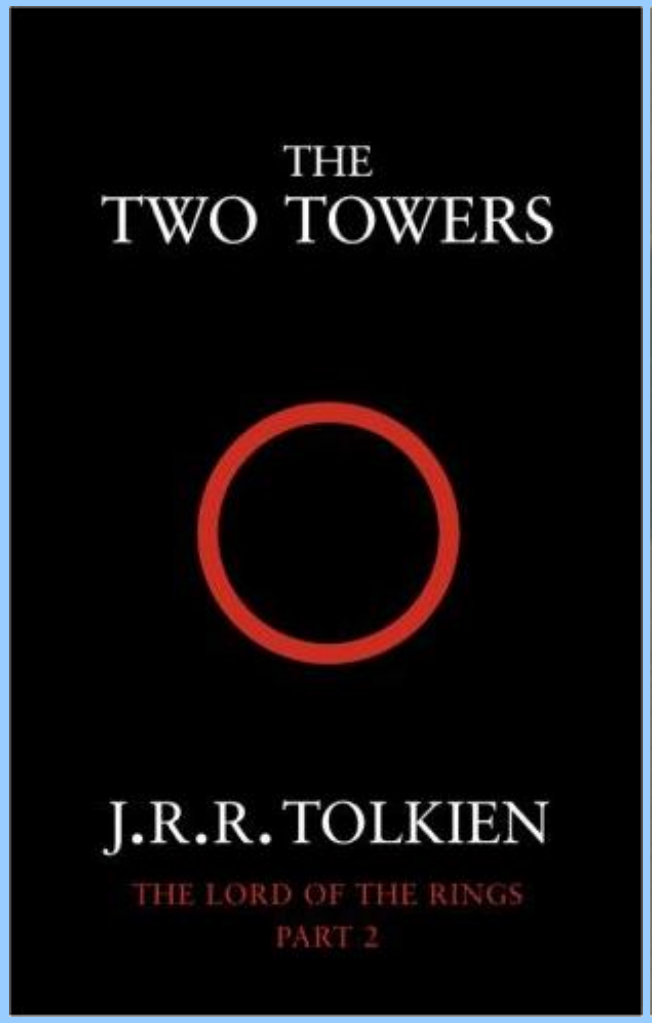


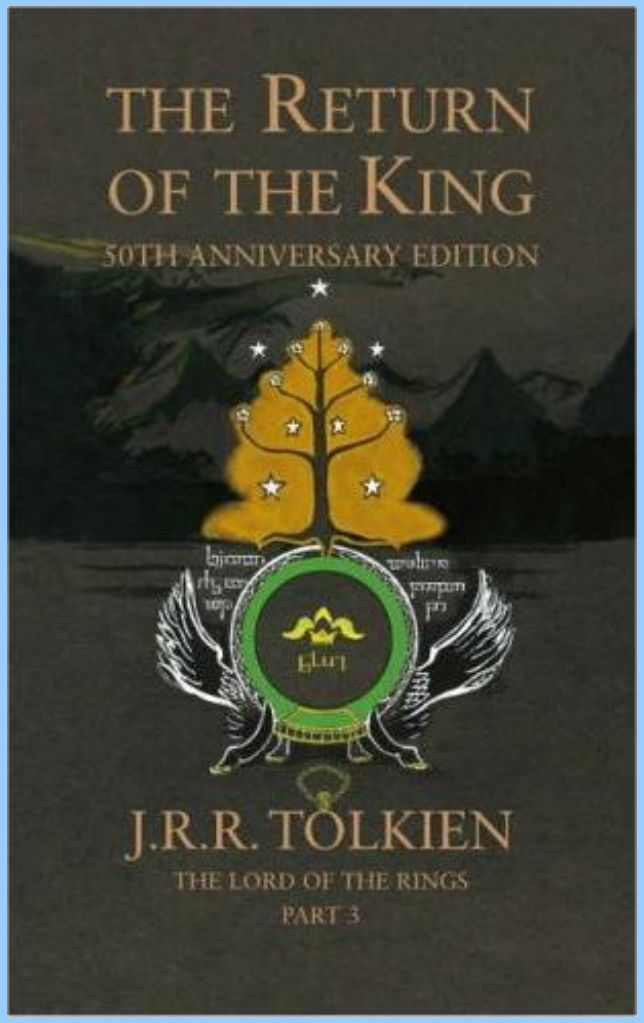


March 2 2010:
Data at 6 months

March 3 2010:
Response with time



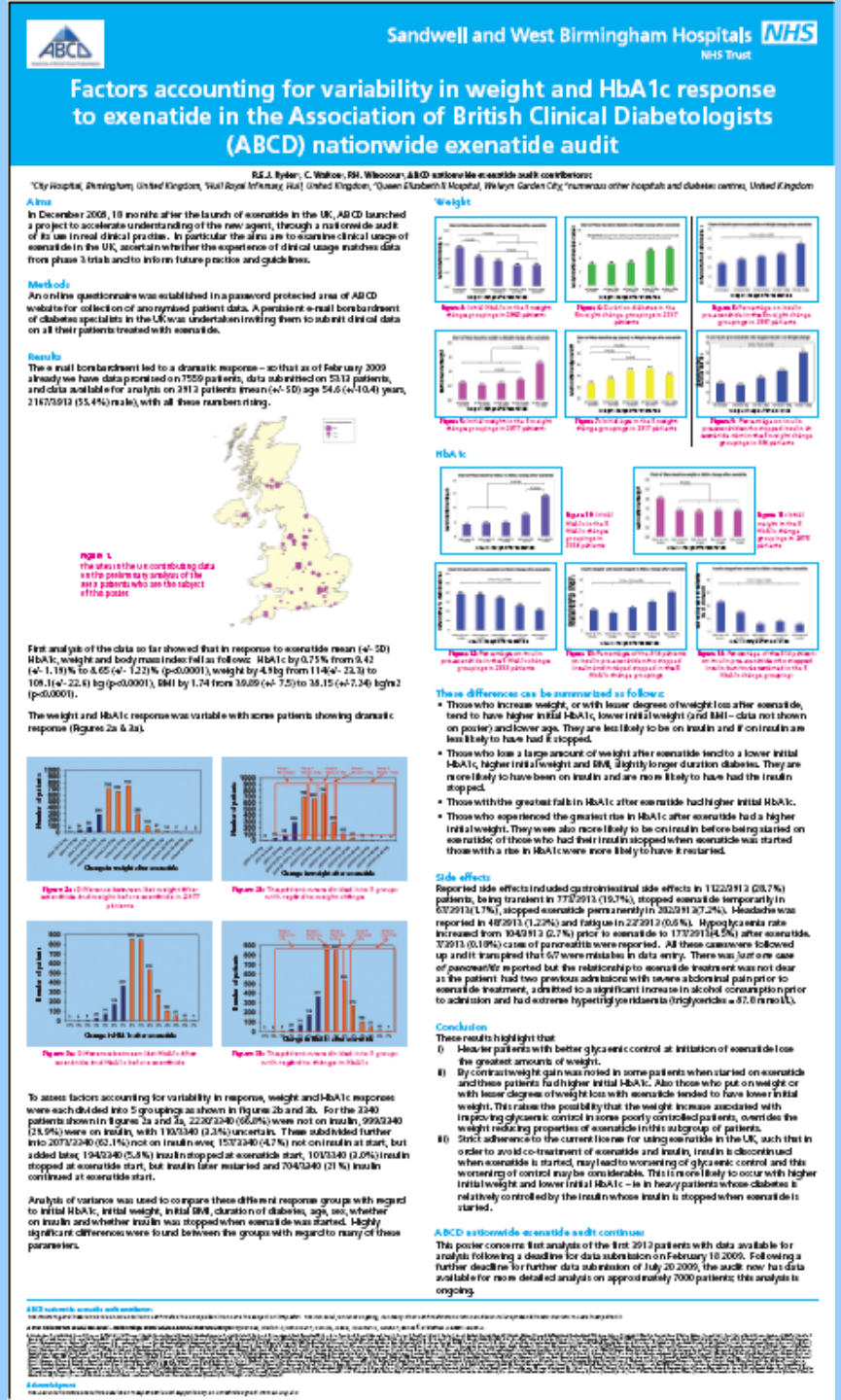




March 2 2010:
Data at 6 months

March 3 2010:
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. Wilcocks, ABCD nationwide exenatide audit contributors
City Hospital, Birmingham, United Kingdom, Hull 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 2913 patients (mean (+/- SD) age 54.6 (+/-10.4) years, 2167/2913 (55.4%) male), with all these numbers rising.

FIGURE 1.
The sites in the UK contributing data as at the preliminary analysis of the 2913 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 2340 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 falls 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 1122/2913 (38.7%) patients, being transient in 777/2913 (19.7%), stopped exenatide temporarily in 67/2913(1.7%), stopped exenatide permanently in 382/2913(7.3%). Headache was reported in 487/2913 (1.23%) and fatigue in 22/2913 (0.6%). Hypoglycaemia rate increased from 104/2913 (2.7%) prior to exenatide to 177/2913(4.5%) after exenatide. 7/2913 (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 the first analysis of the first 2913 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:

Acknowledgements

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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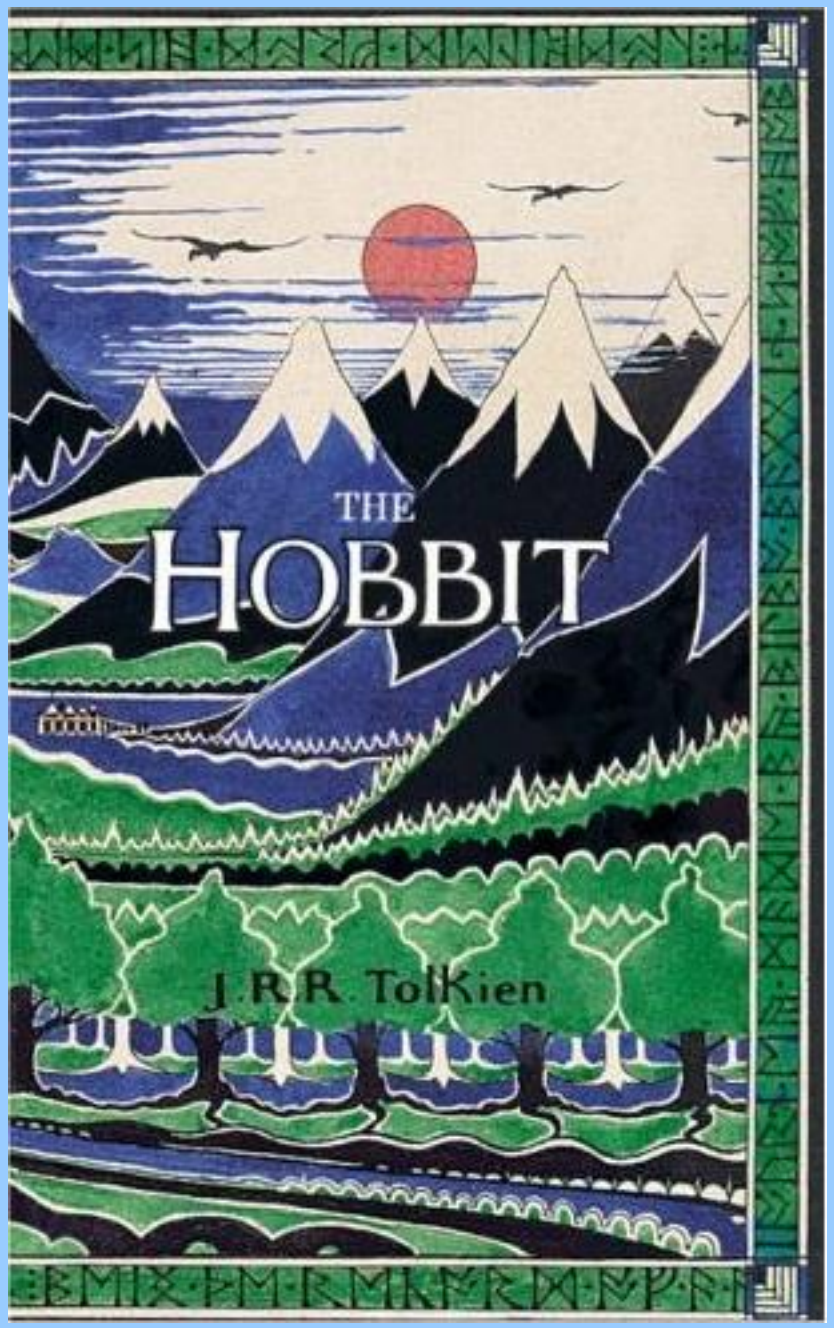

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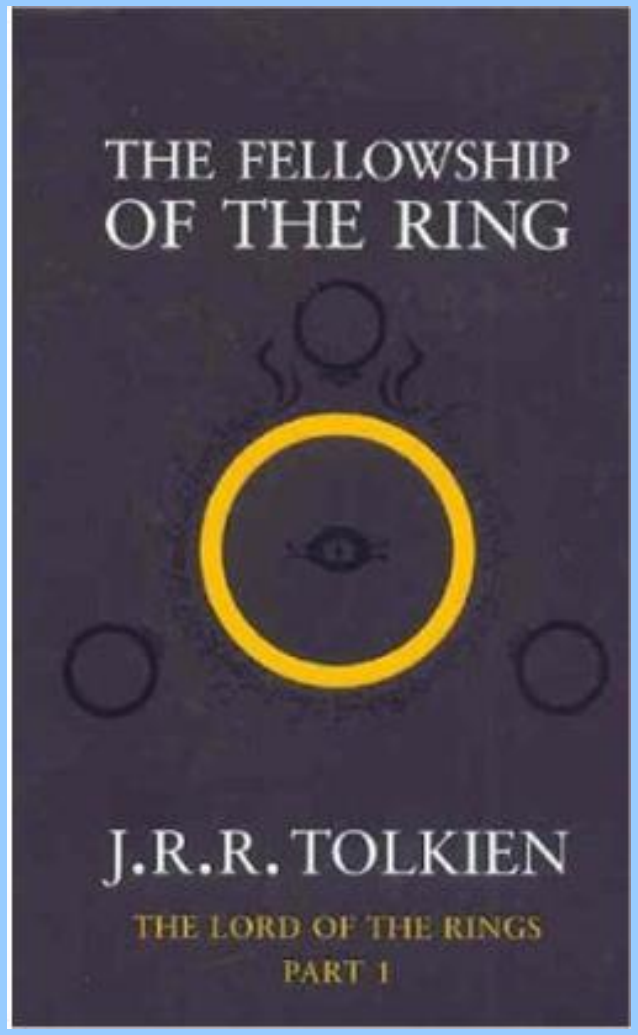
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PART 1

n=6717

The Fellowship of the ABCD Nationwide Exenatide Audit

- 315 contributors
- 126 centres

Association of British Clinical Diabetologists

ABCD nationwide exenatide audit contributors

The following are those whom we know about.

ABCD nationwide exenatide audit project steering group: *Ryder REJ, Walton C, Rowles S, Adamson K, Dove D, Thozhukat S*

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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. 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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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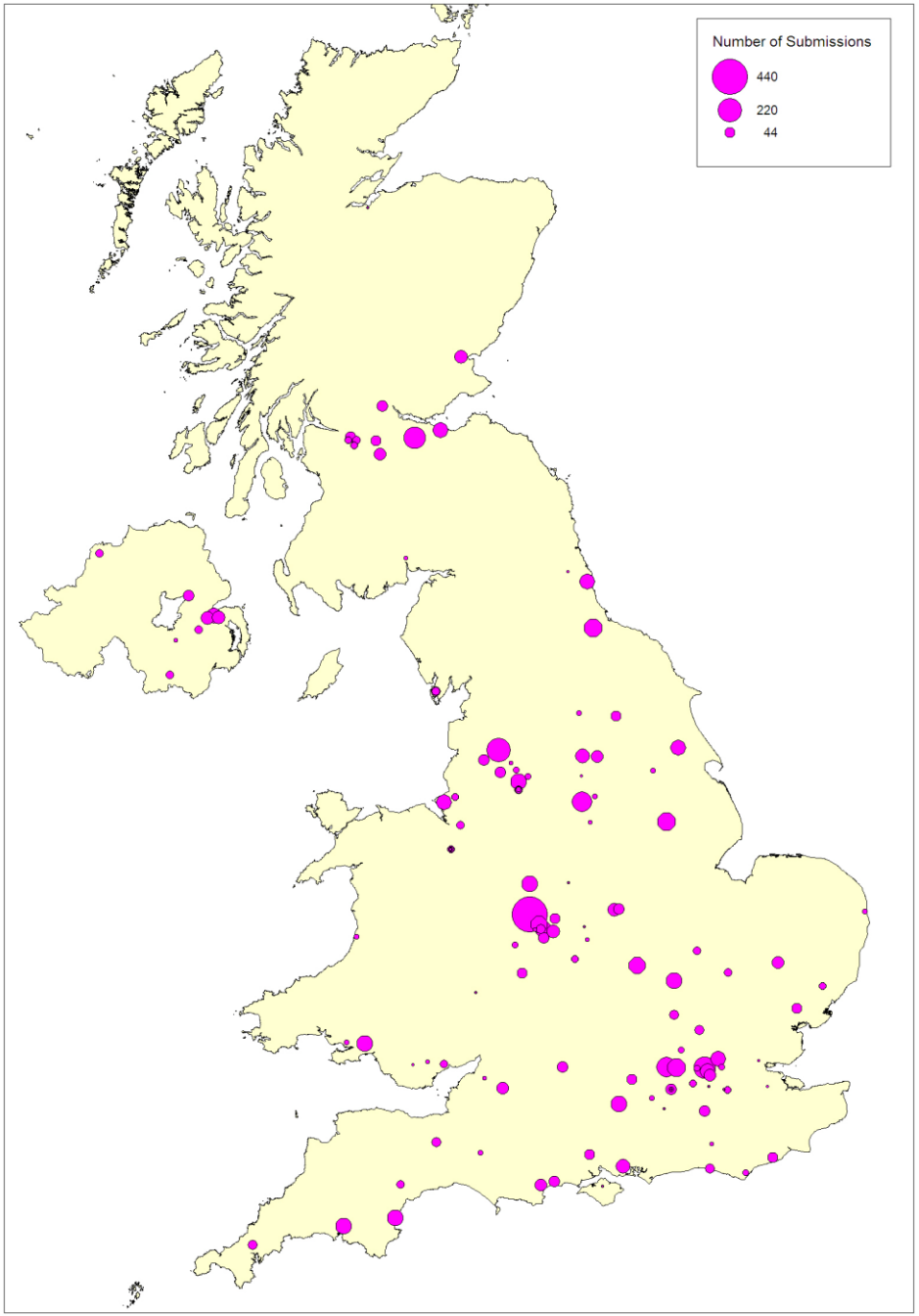

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Top contributors > 100 patients

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
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8.	Mark Edwards, Helen Doolittle et al, The Hillingdon Hospital, Uxbridge	136
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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

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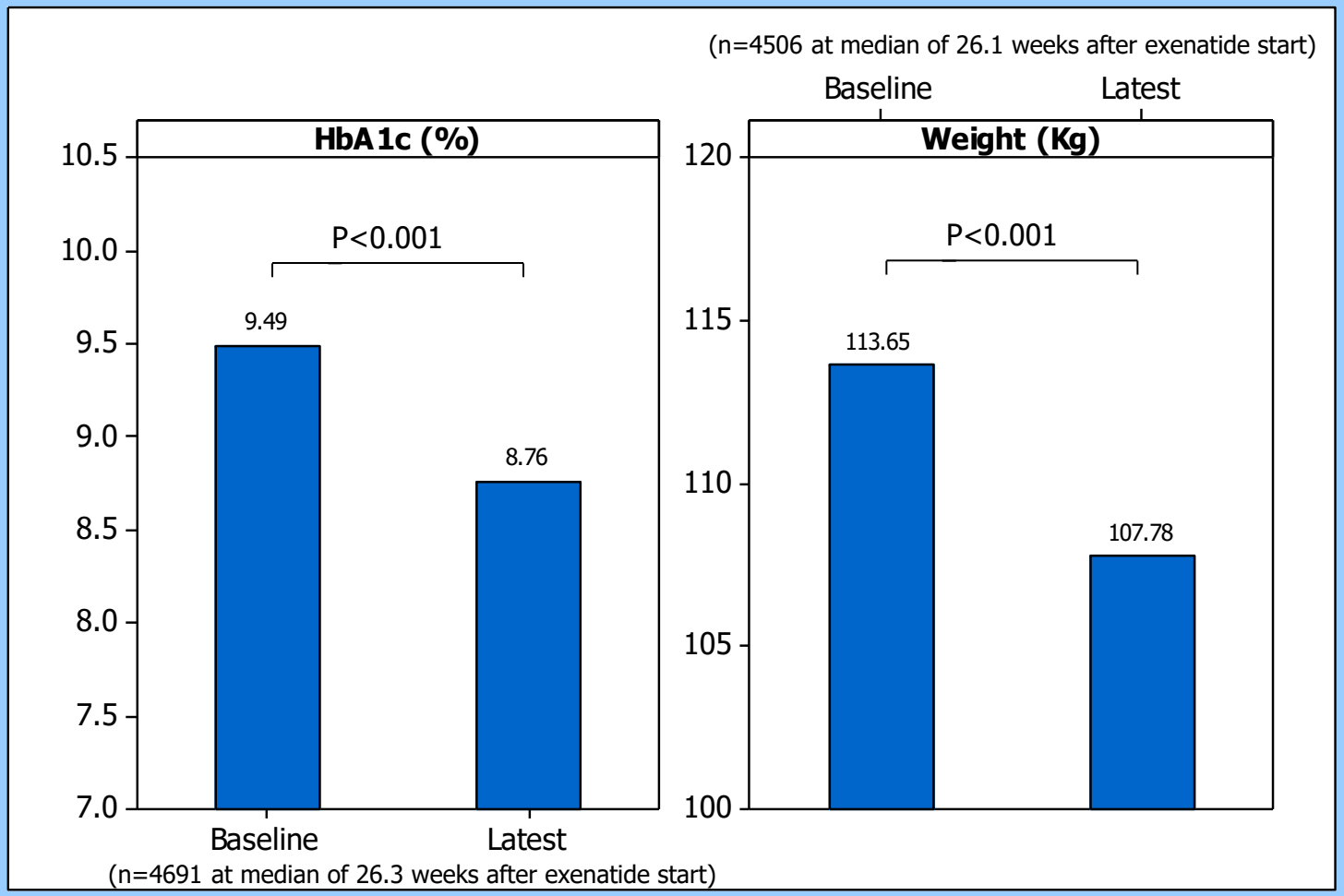
n= number from the 6717 patients with this data item submitted

Main findings

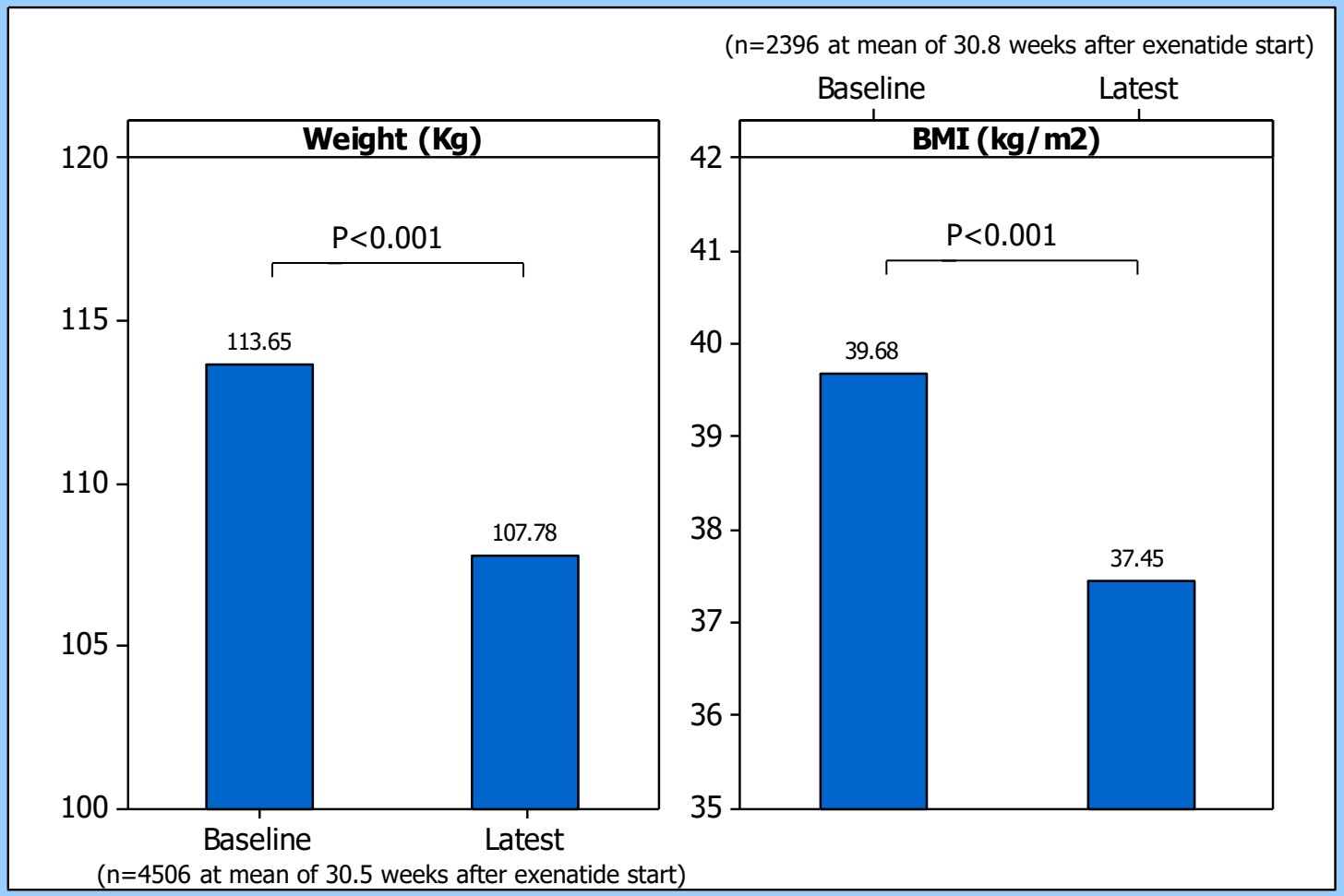
Baseline versus latest HbA1c and Weight following exenatide



Mean fall in HbA1c = 0.73 %

Mean fall in weight = 5.87 kg

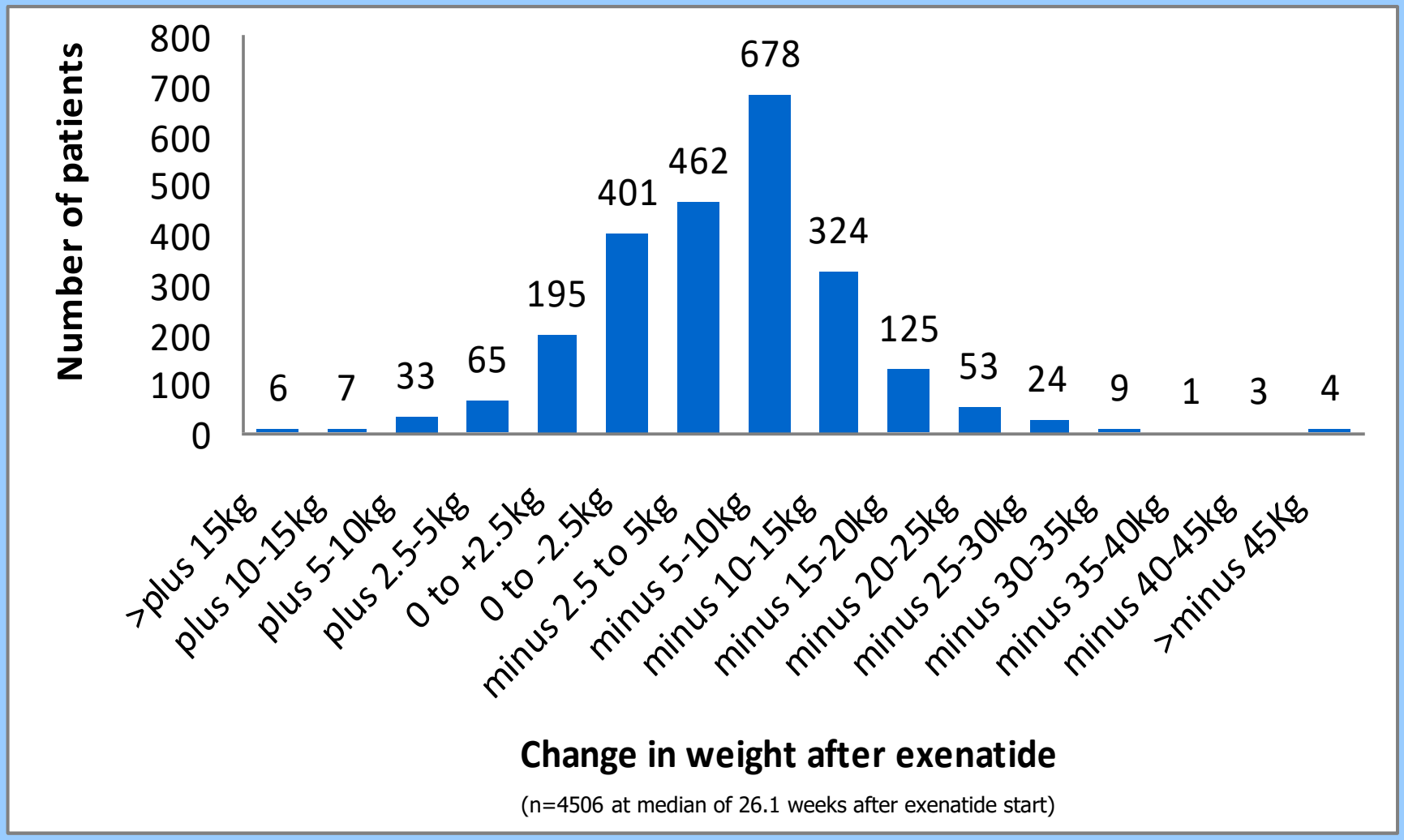
Baseline versus latest weight and BMI following exenatide



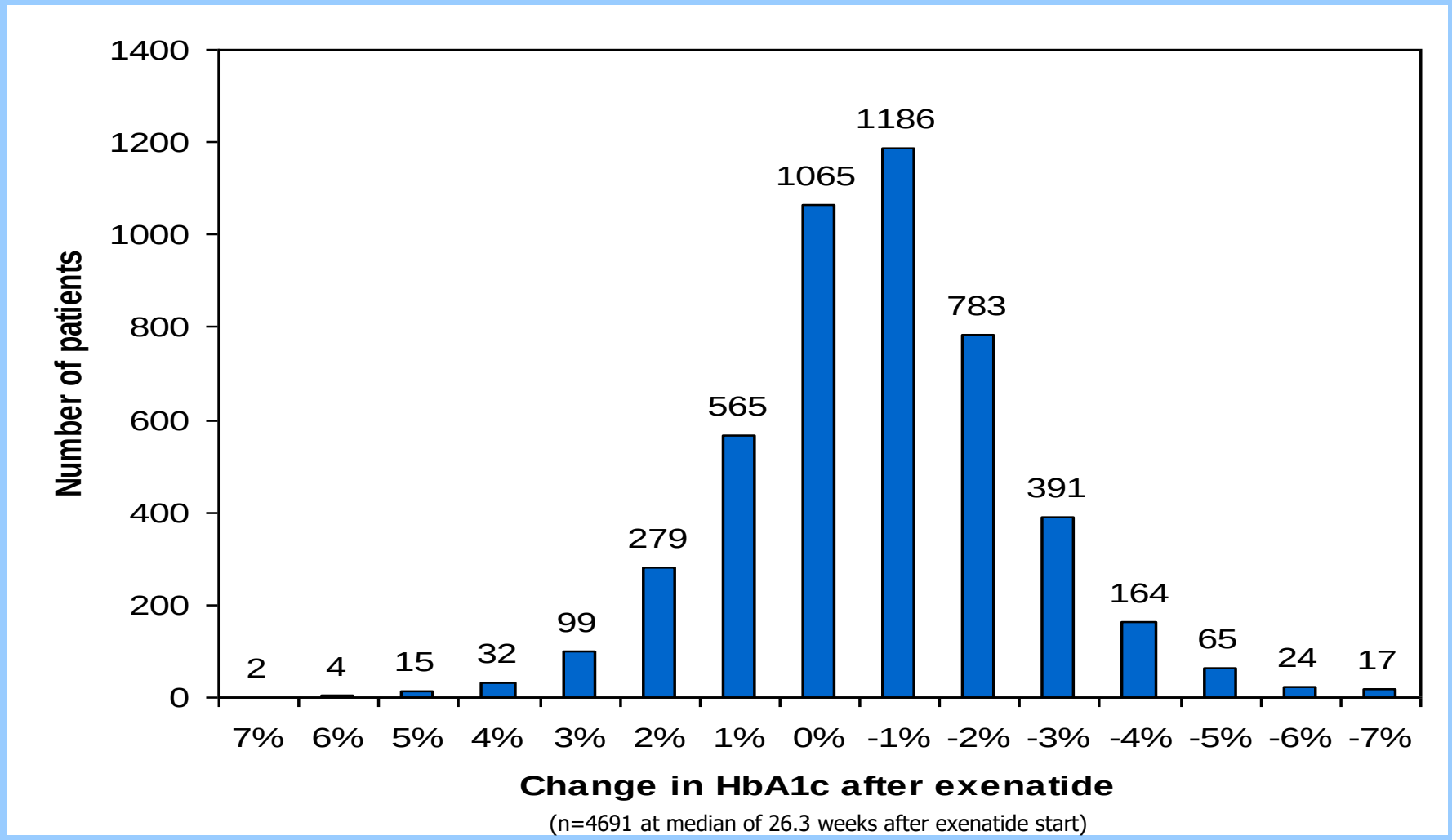
Mean fall in BMI = 2.23 kg/m^2

Mean fall in weight = 5.87 kg

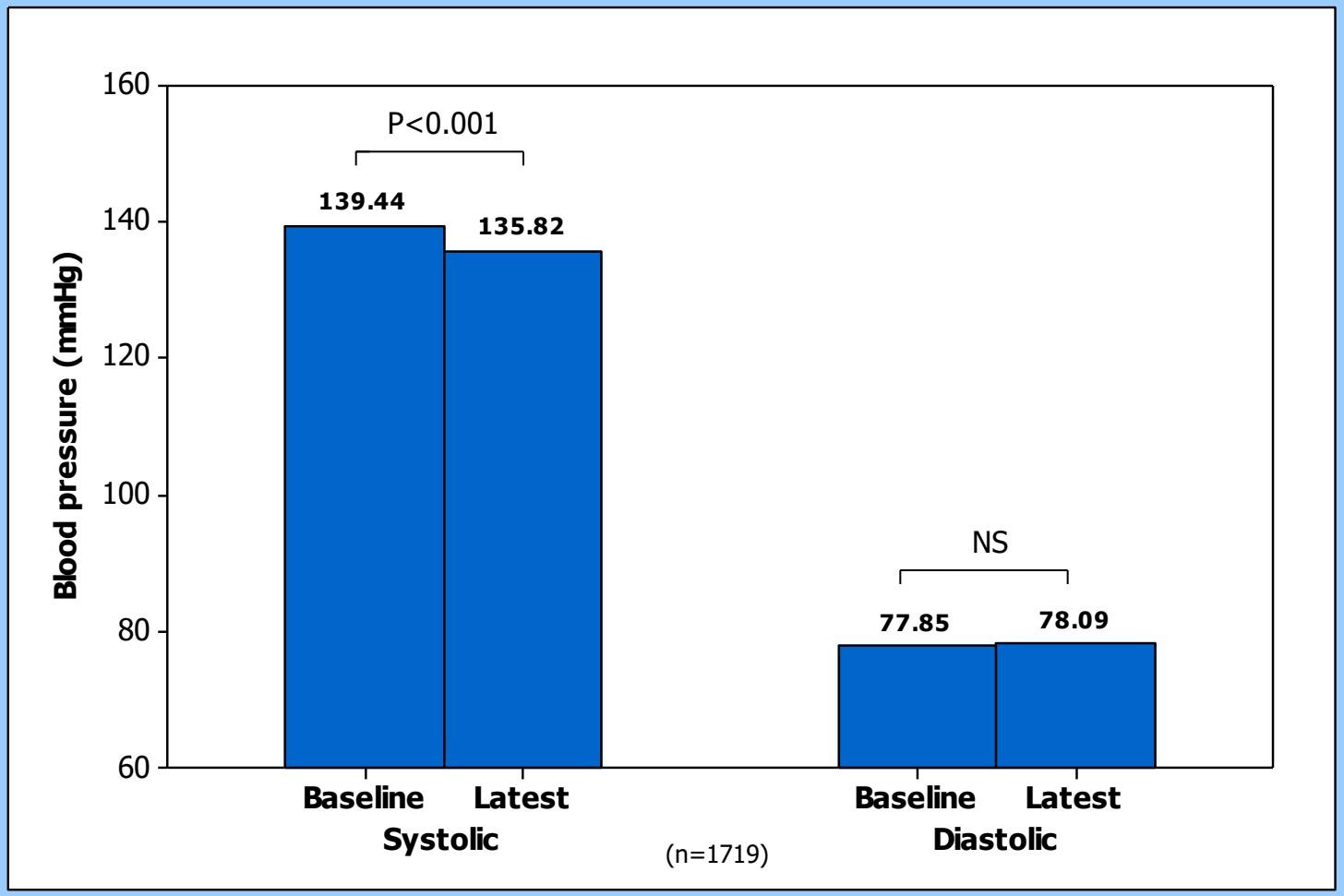
Difference between last weight after exenatide and weight before exenatide – range of responses



Difference between last HbA1c after exenatide and HbA1c before exenatide – range of responses

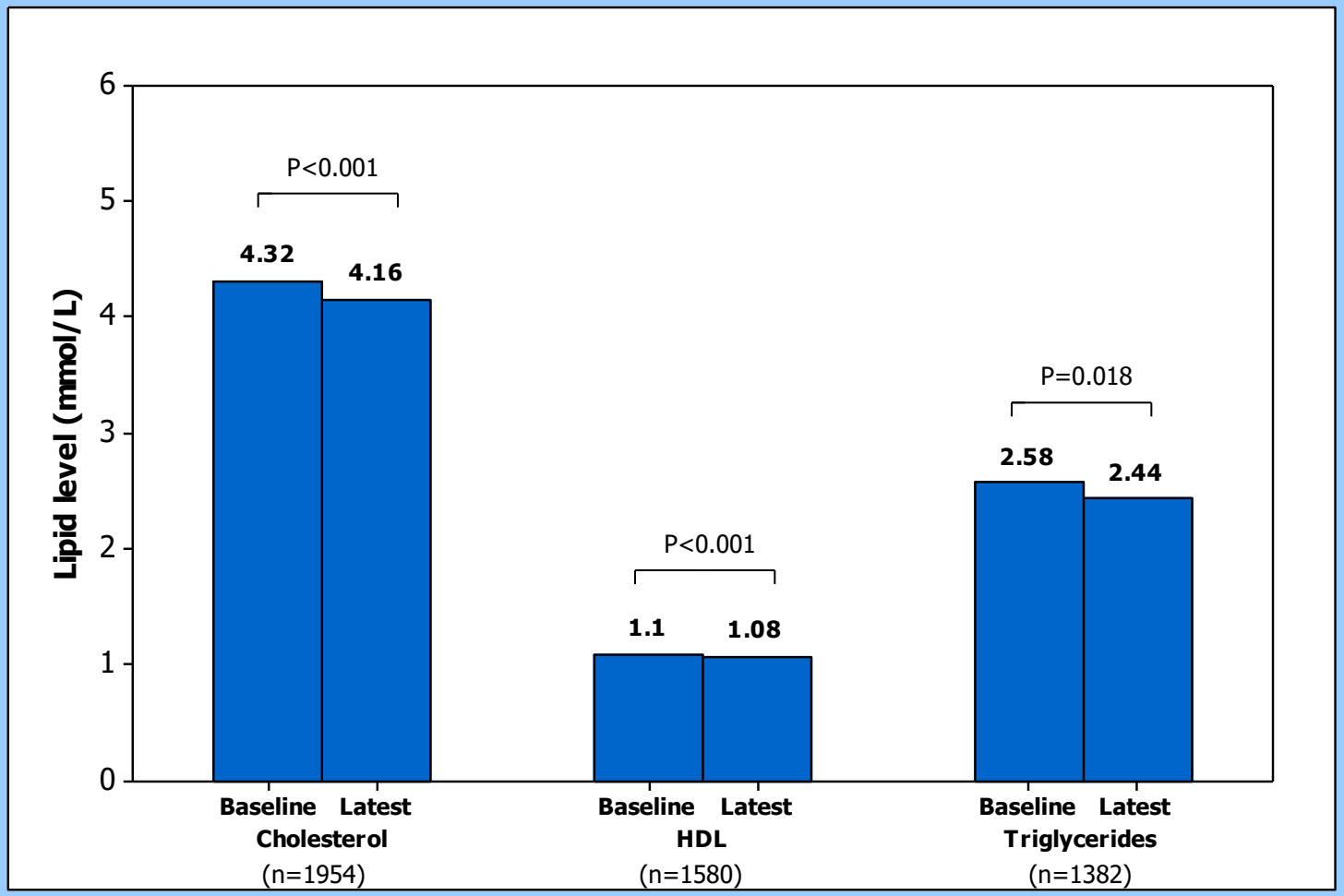


Baseline versus latest blood pressure following exenatide in 1719 patients

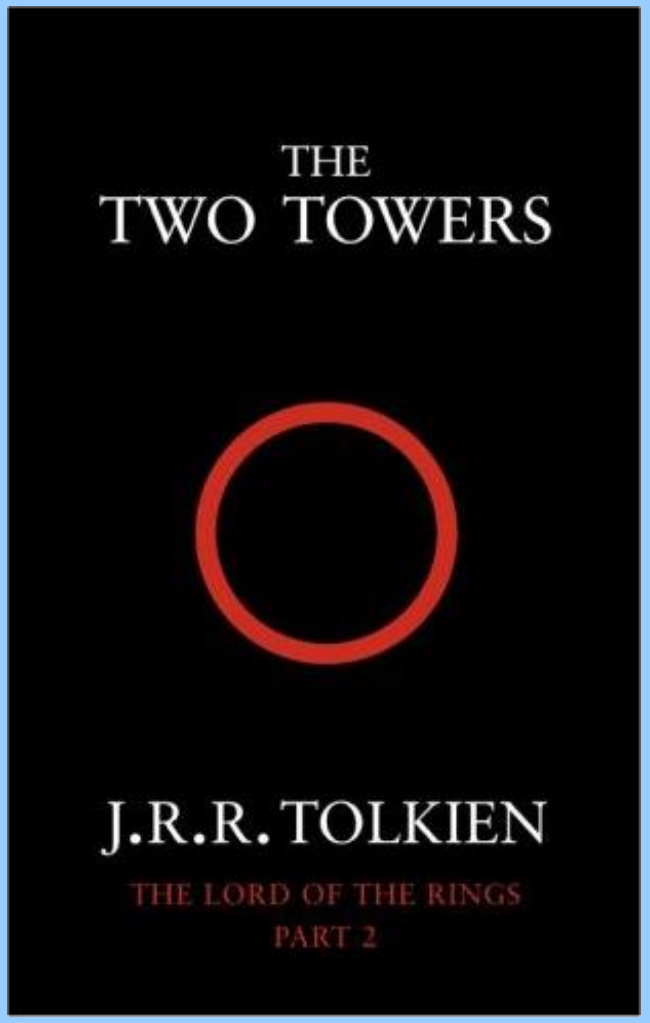


Mean fall in systolic blood pressure = 3.62 mmHg

Baseline versus latest lipids following exenatide



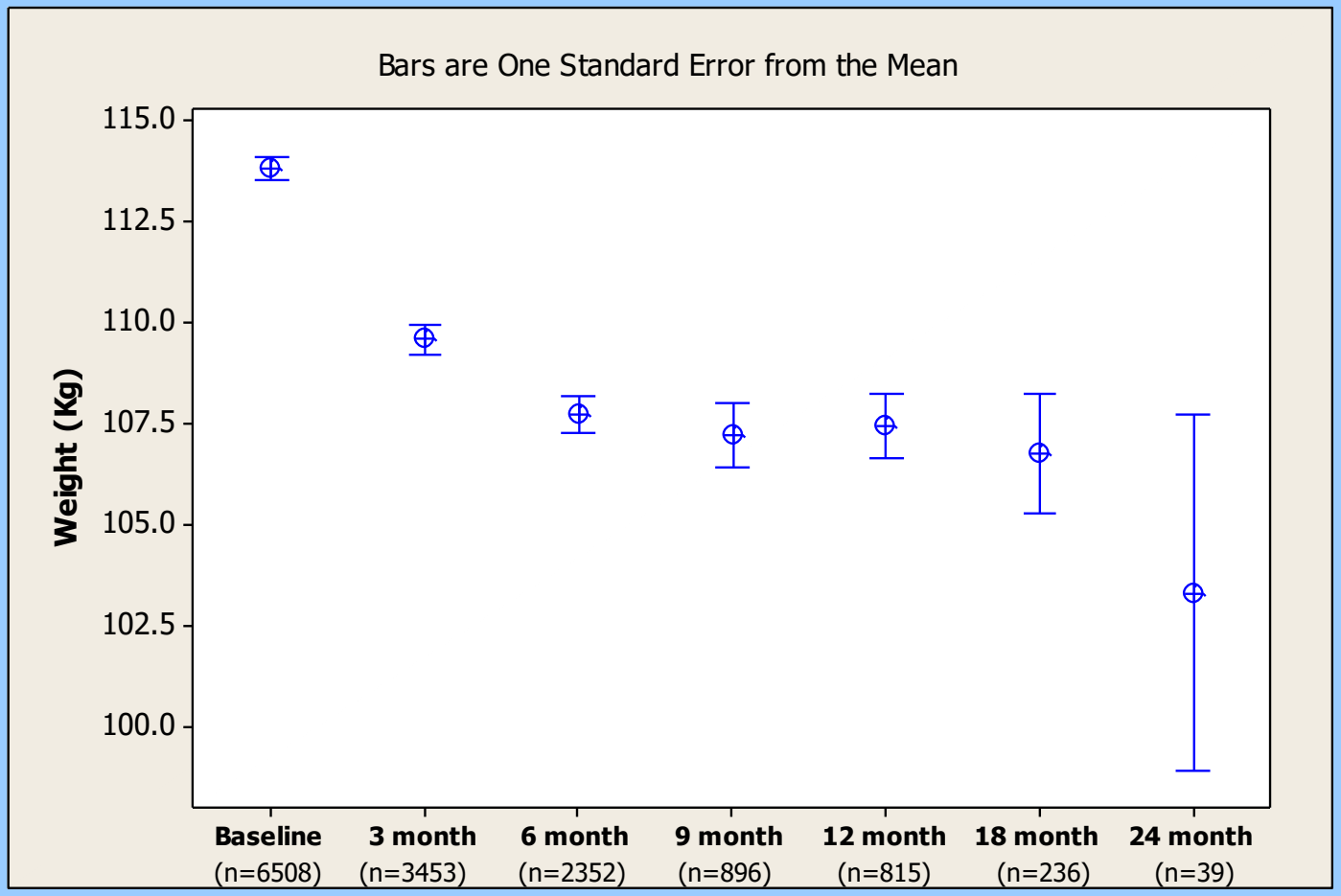
Mean fall in cholesterol = 0.16 mmol/L
Mean fall in HDL = 0.02 mmol/L
Mean fall in triglycerides = 0.13 mmol/L



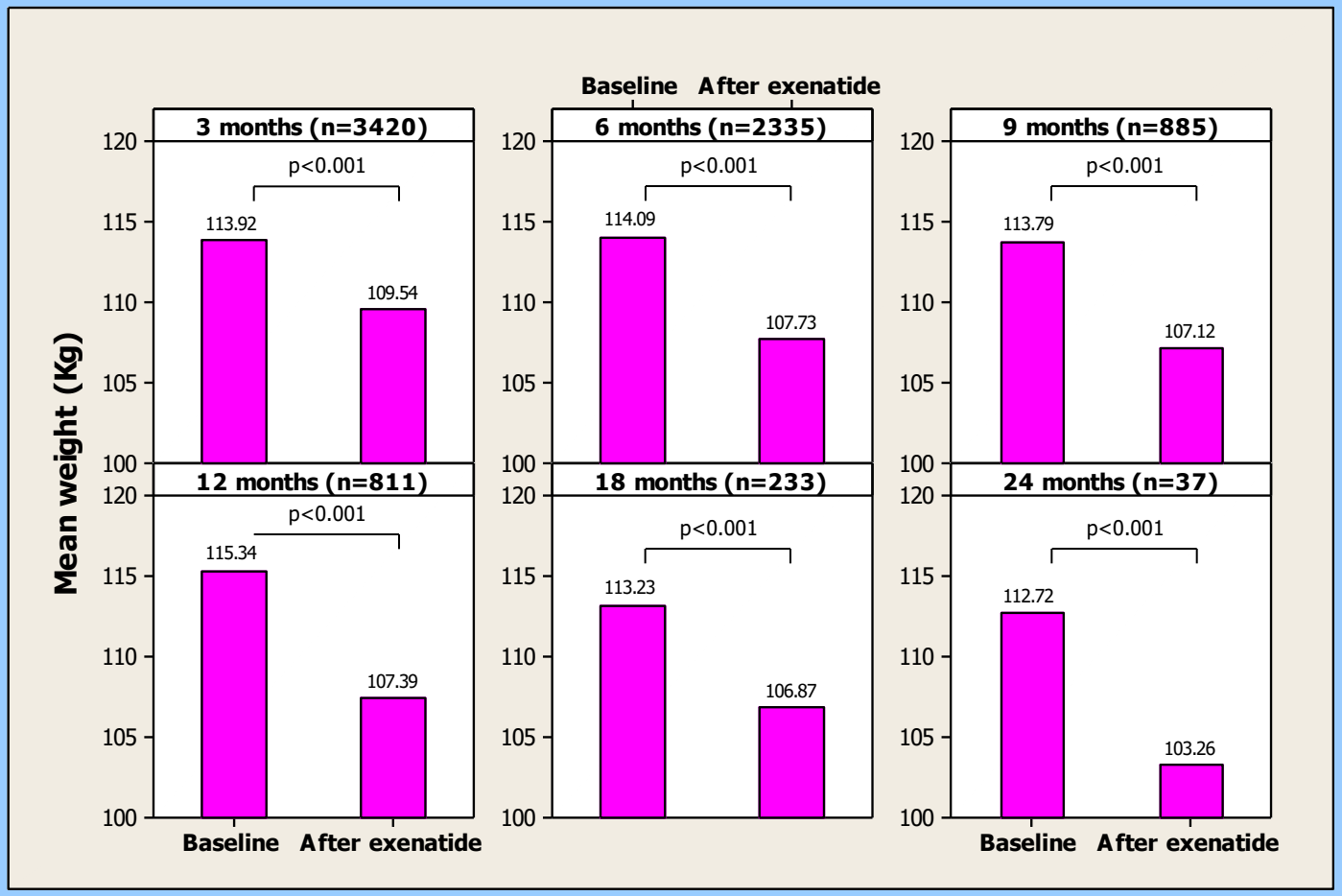
March 3 2010:
Response with time

Weight with time

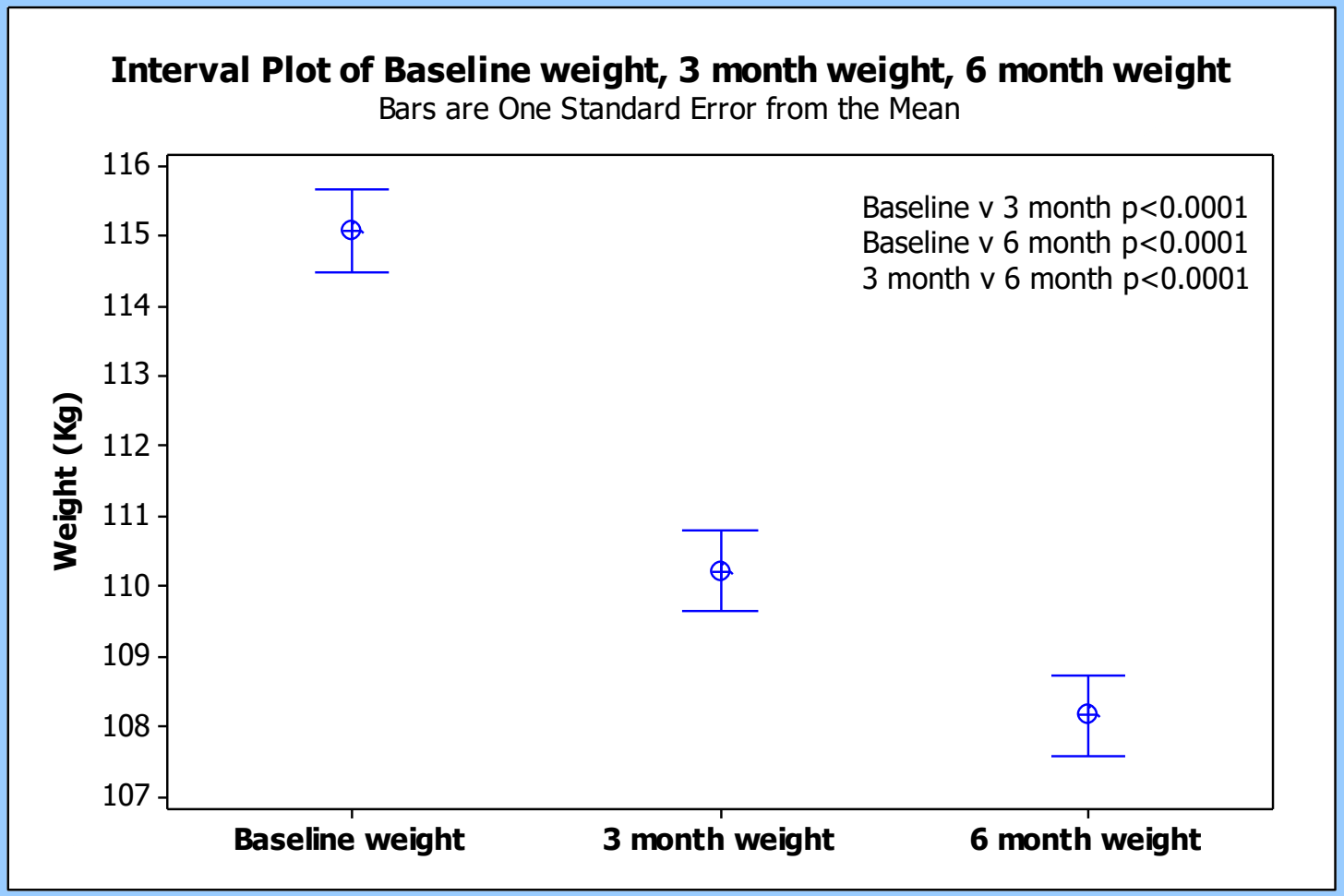
Weight after exenatide in 6508 patients



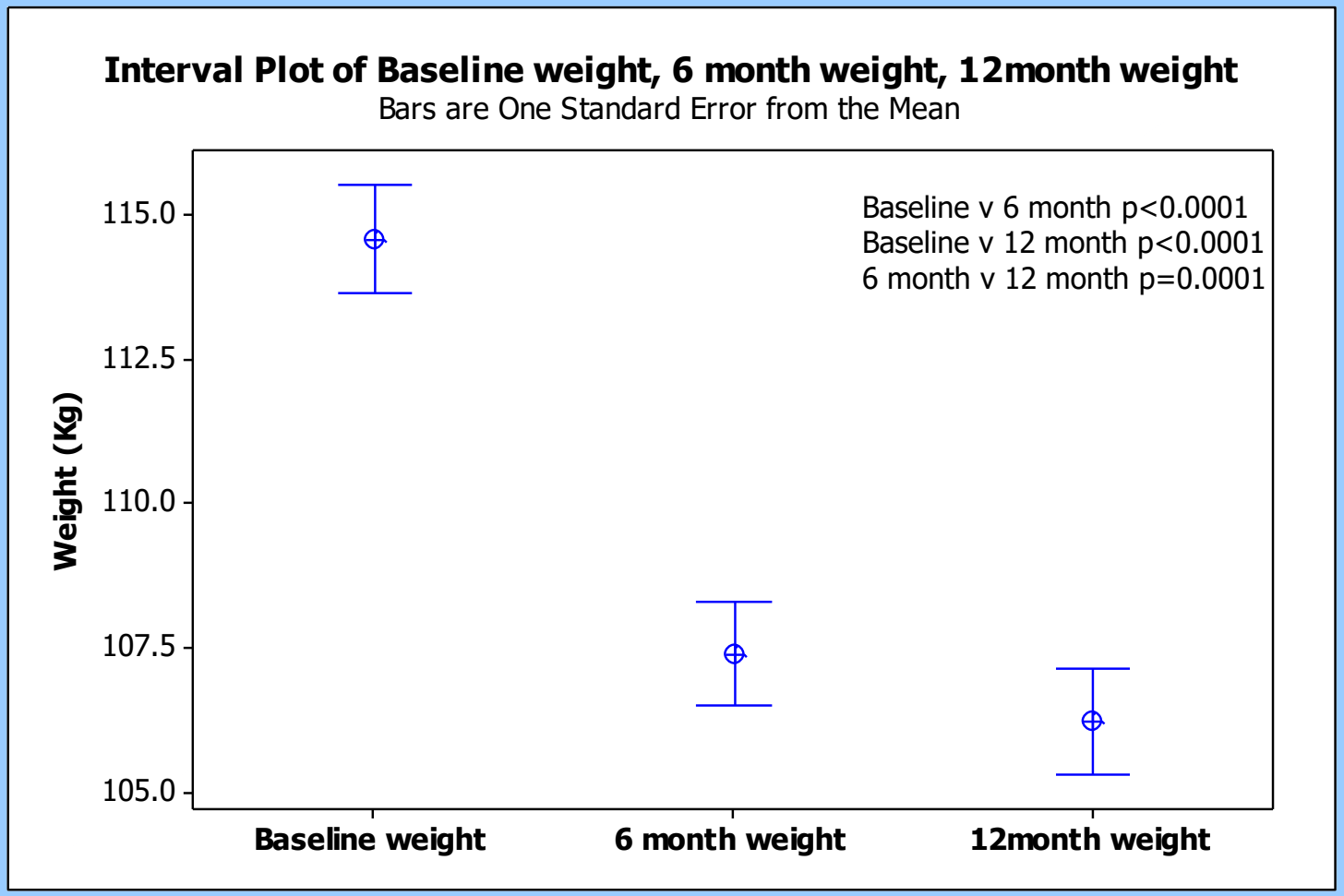
Paired baseline and follow up weights at various timepoints after exenatide



Weight at 3 and 6 months after exenatide in 1534 patients



Weight at 6 and 12 months after exenatide in 554 patients

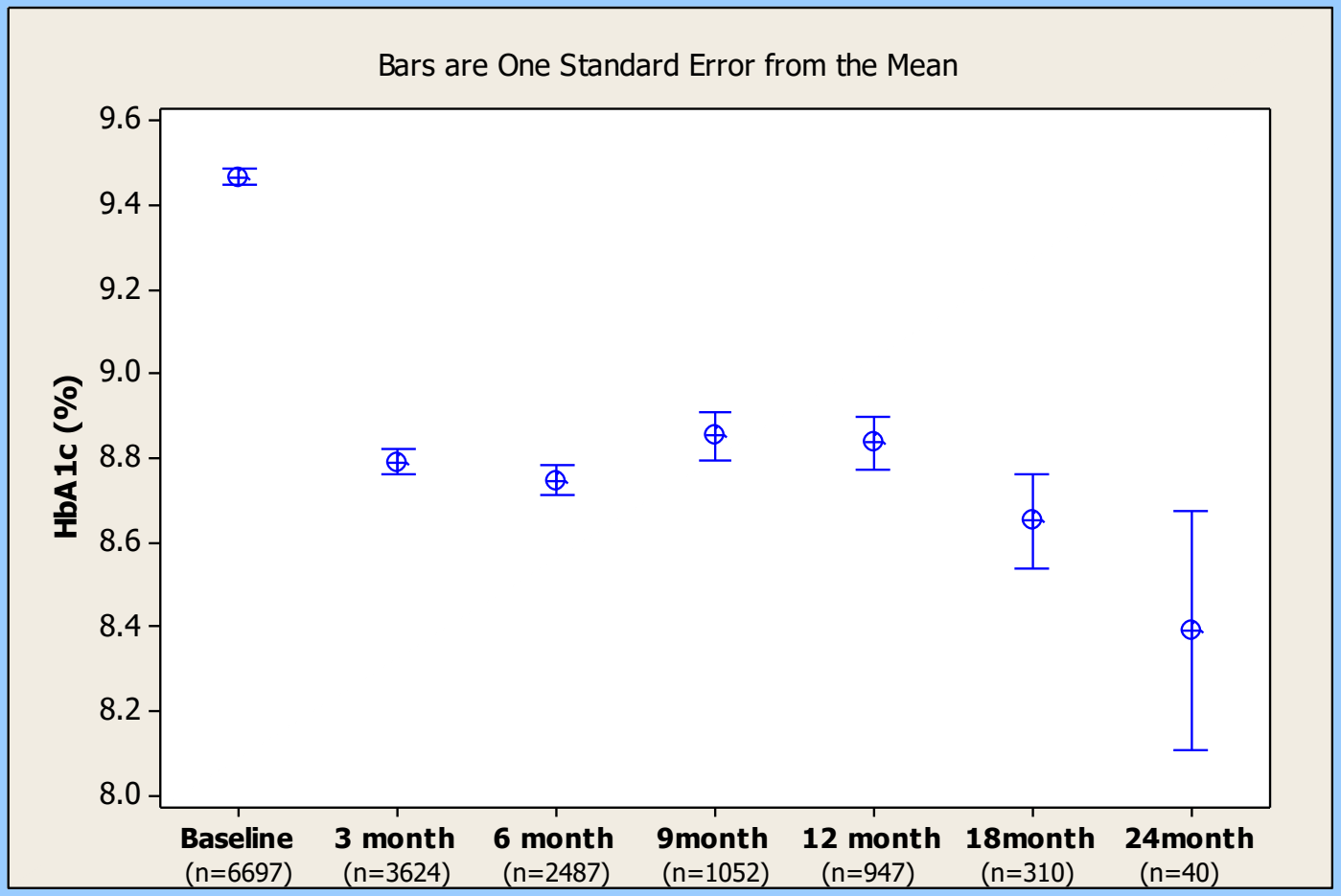


After 12 months?

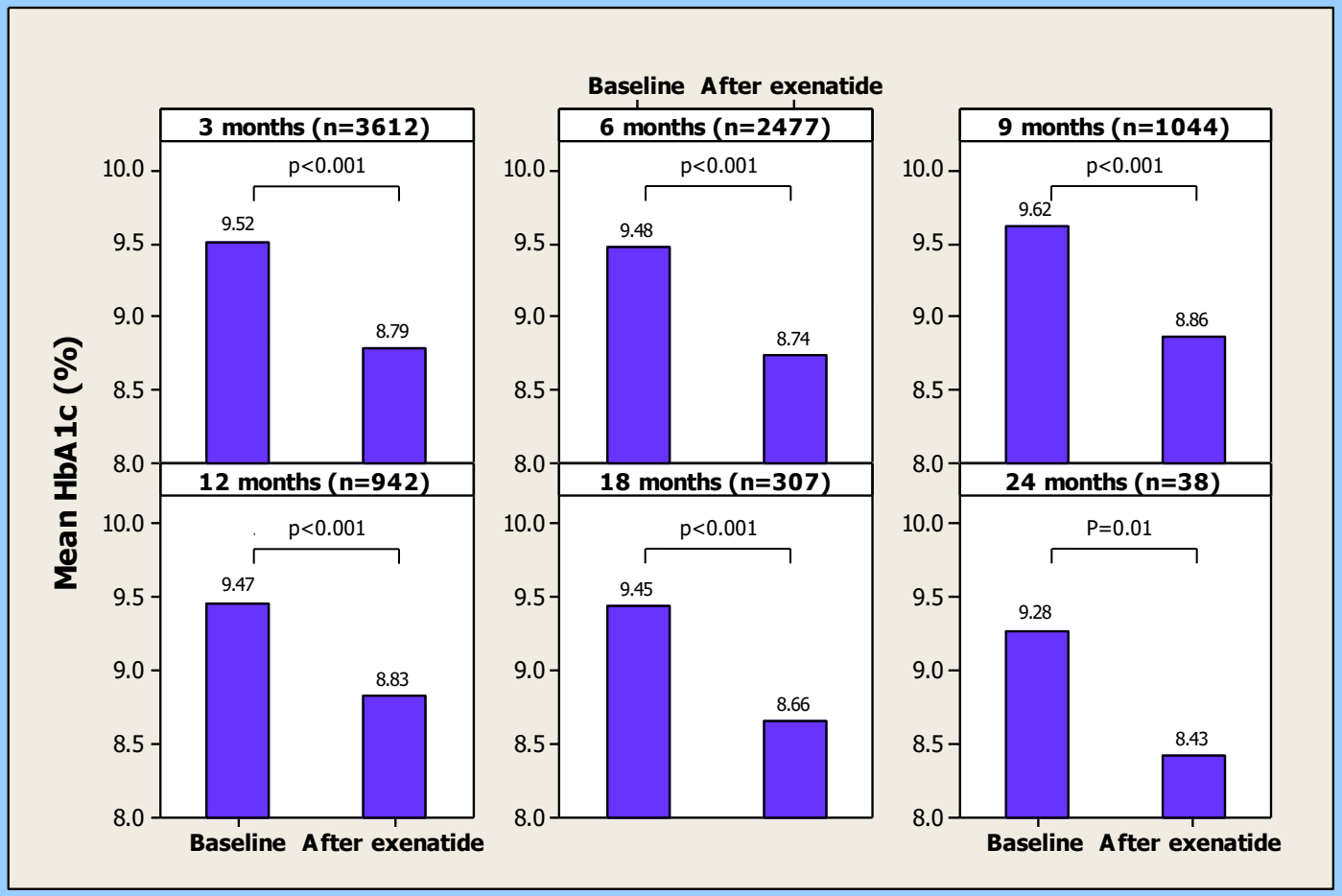
- Weight loss maintained compared to baseline but no significant further fall at 18 or 24 months

HbA1c with time

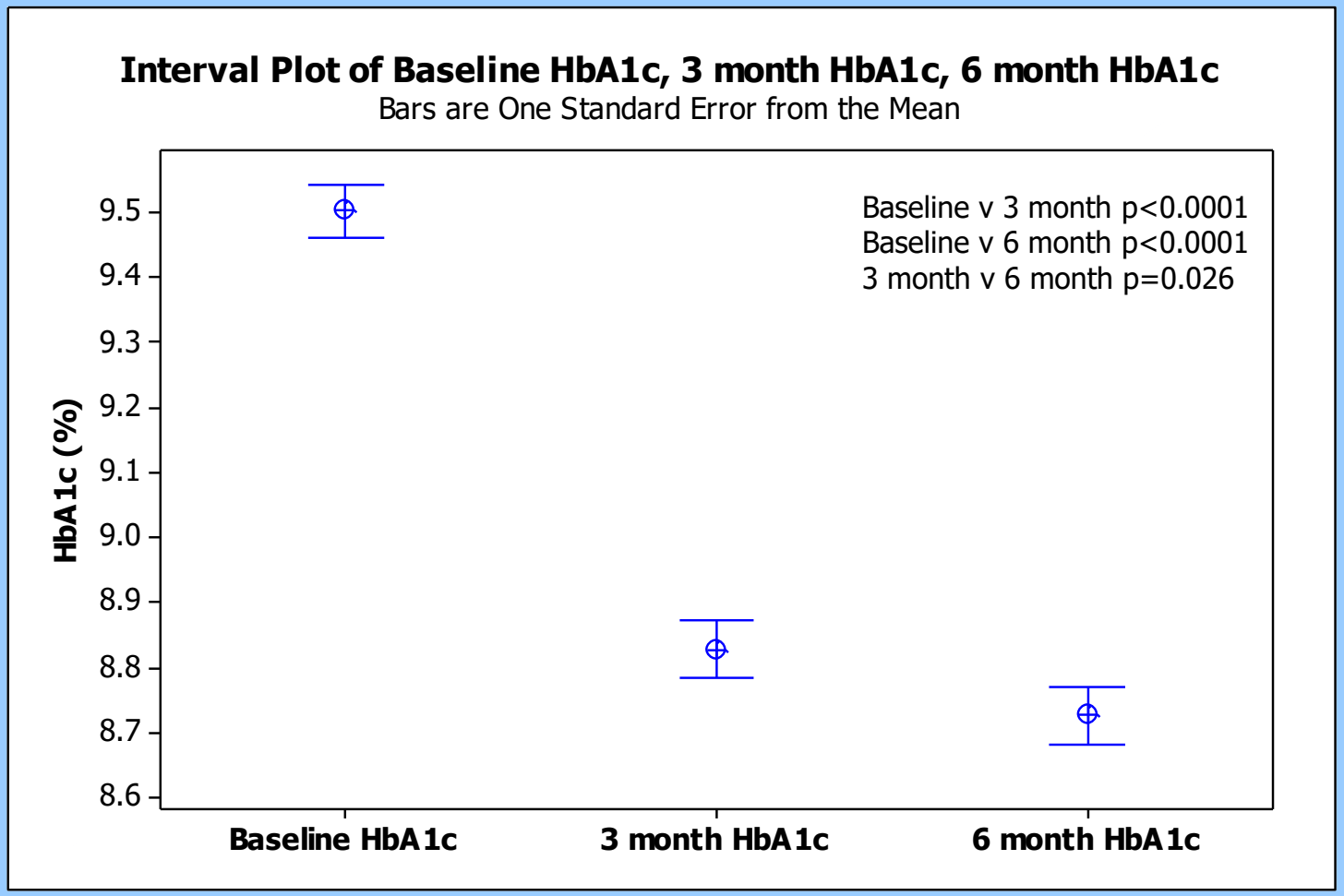
HbA1c after exenatide in 6597 patients



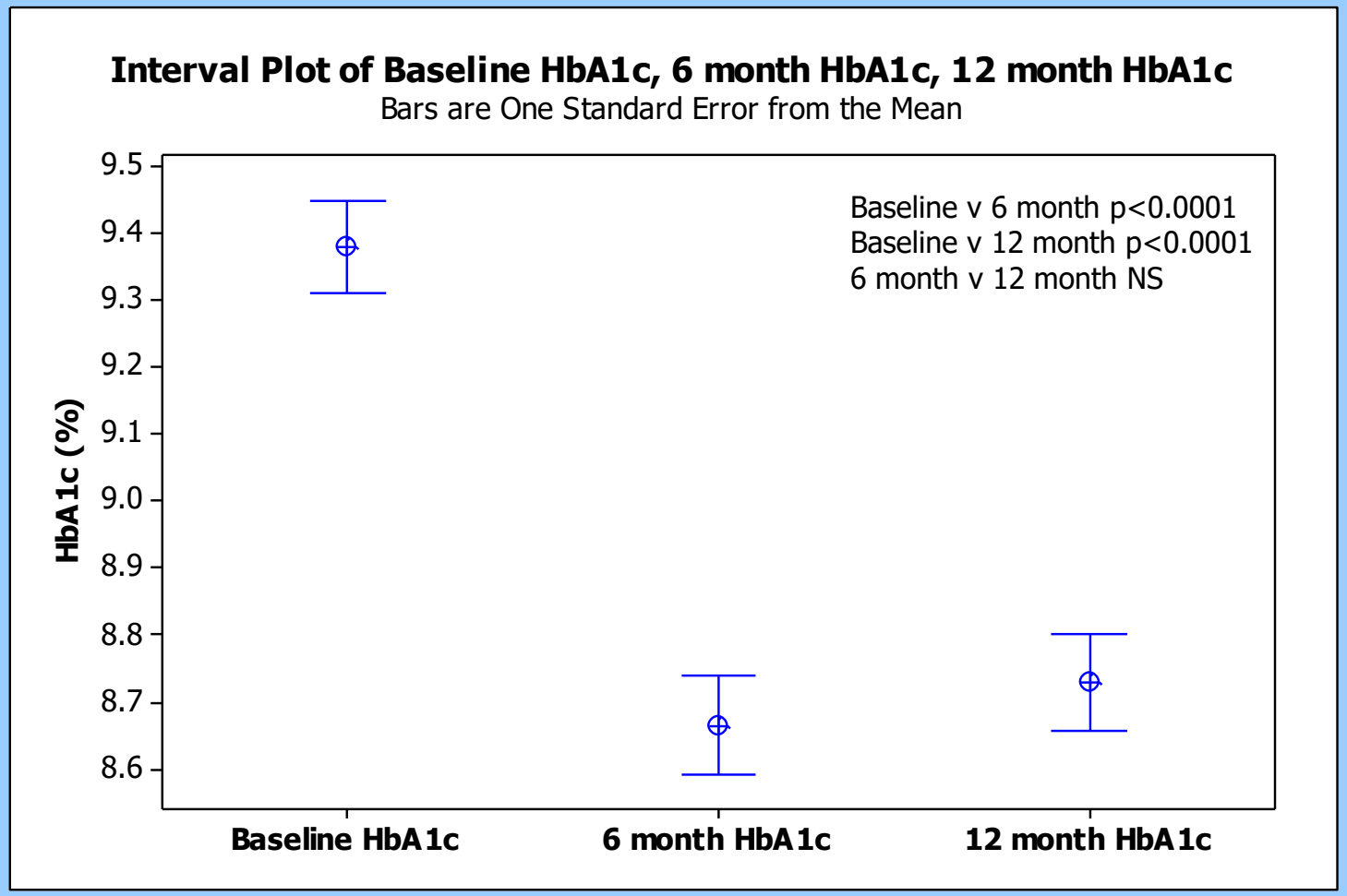
Paired baseline and follow up HbA1c levels at various timepoints after exenatide



HbA1c at 3 and 6 months after exenatide in 1667 patients

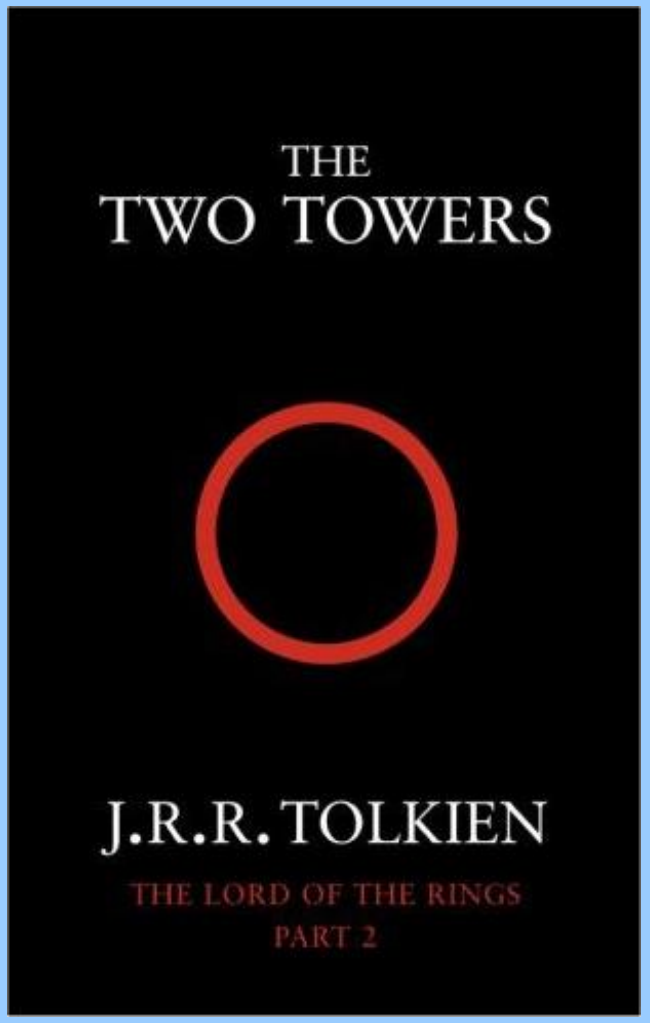


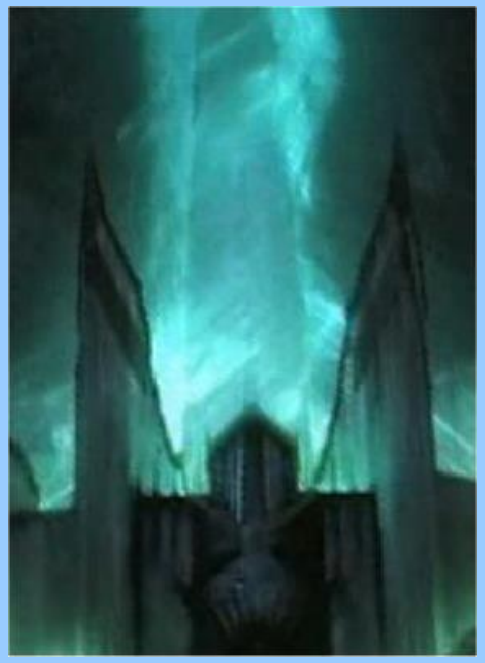
HbA1c at 6 and 12 months after exenatide in 650 patients



After 12 months?

- Reduction in HbA1c compared to baseline maintained but no significant further reduction at 18 or 24 months


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

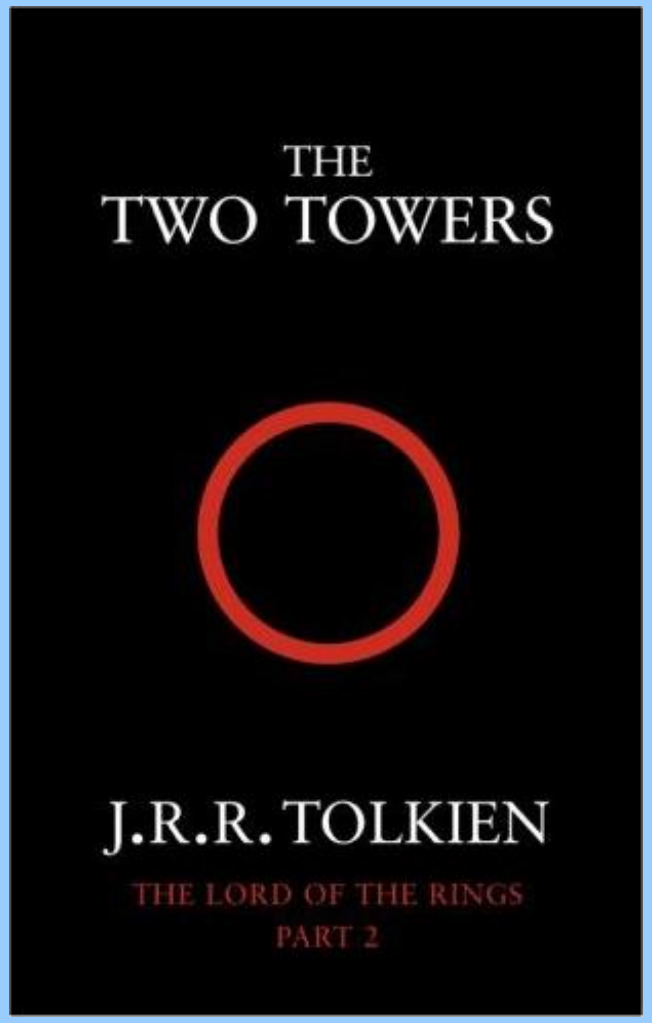


THE
TWO TOWERS

J.R.R. TOLKIEN

THE LORD OF THE RINGS
PART 2

Weight



HbA1c

The Two Towers

Achieving NICE criteria

- NICE:
  - 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 HbA1c and a weight loss of at least 3% of initial body weight at 6 months).

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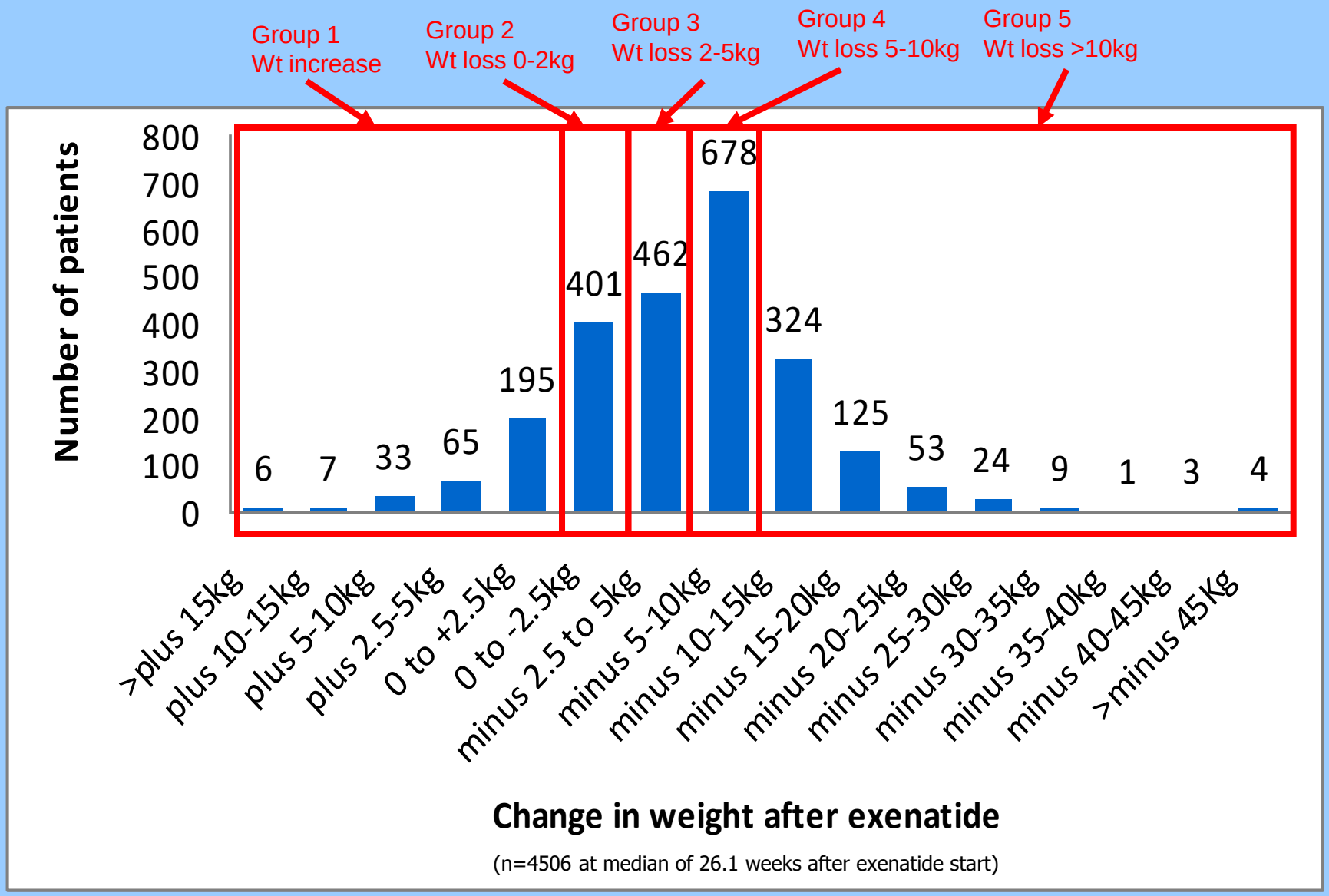
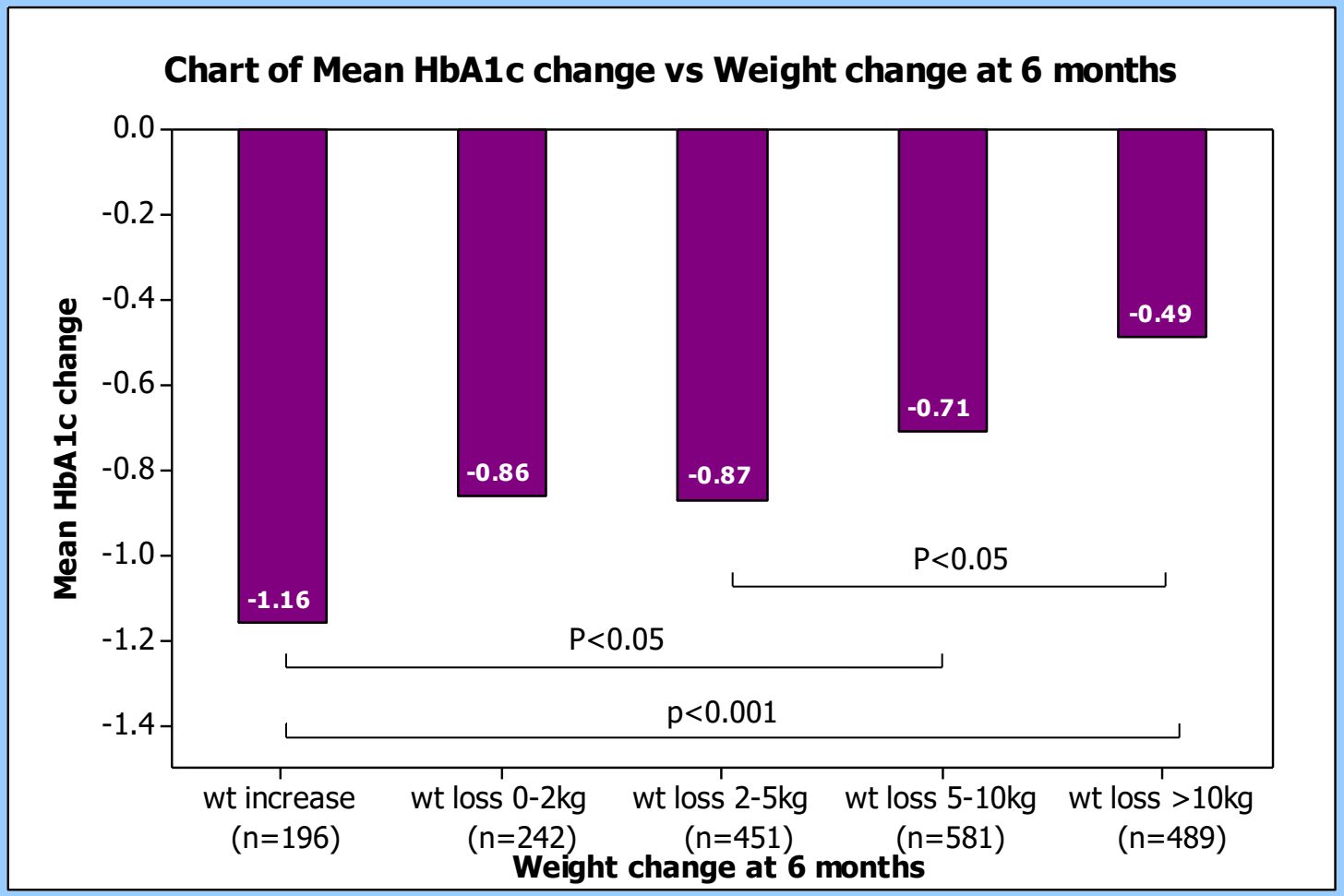
- ie
  - Some people have a good weight response but more minimal HbA1 response
  - Some people have a good HbA1c response but more minimal weight response

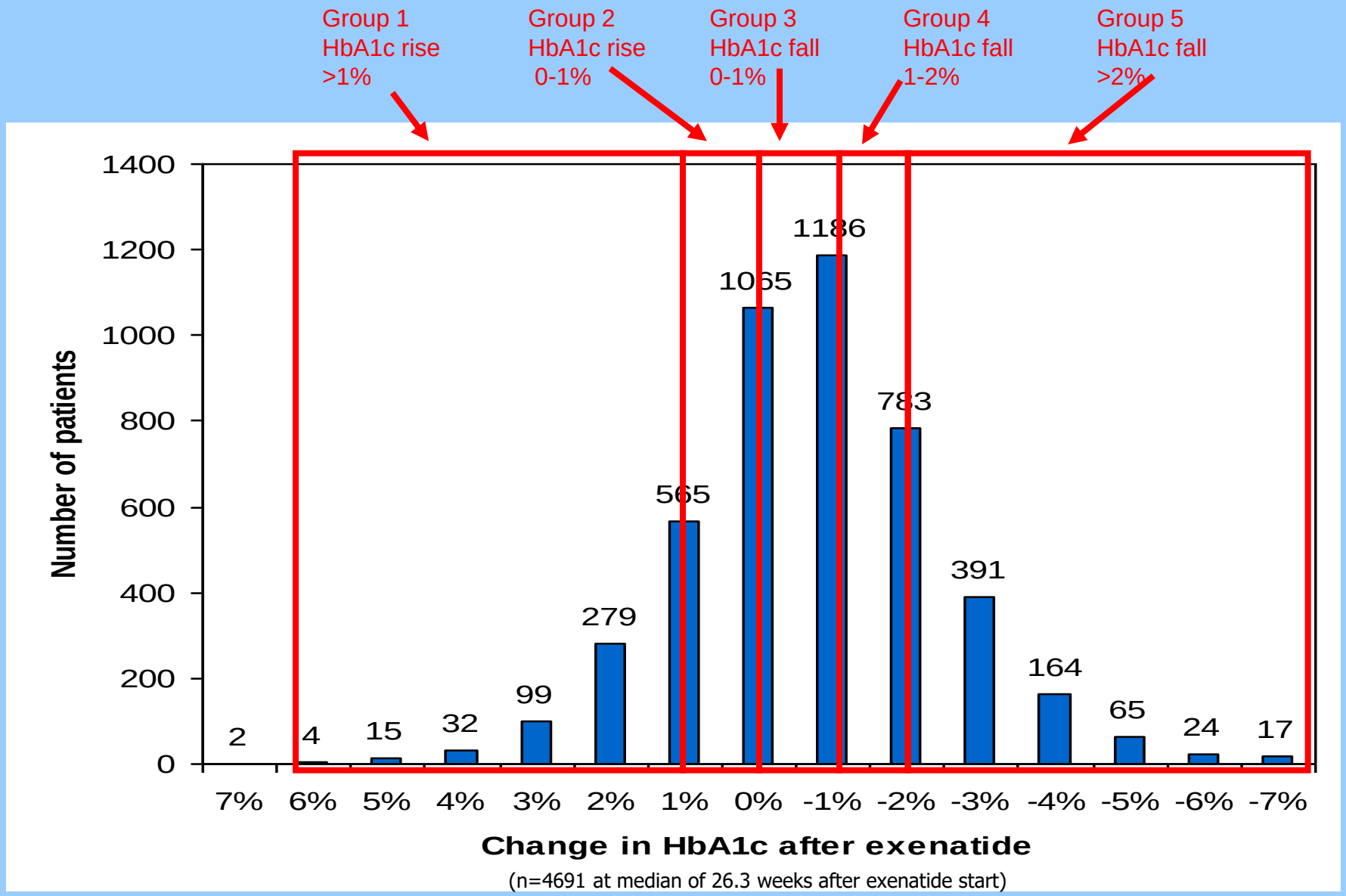
Dividing the range of weight responses



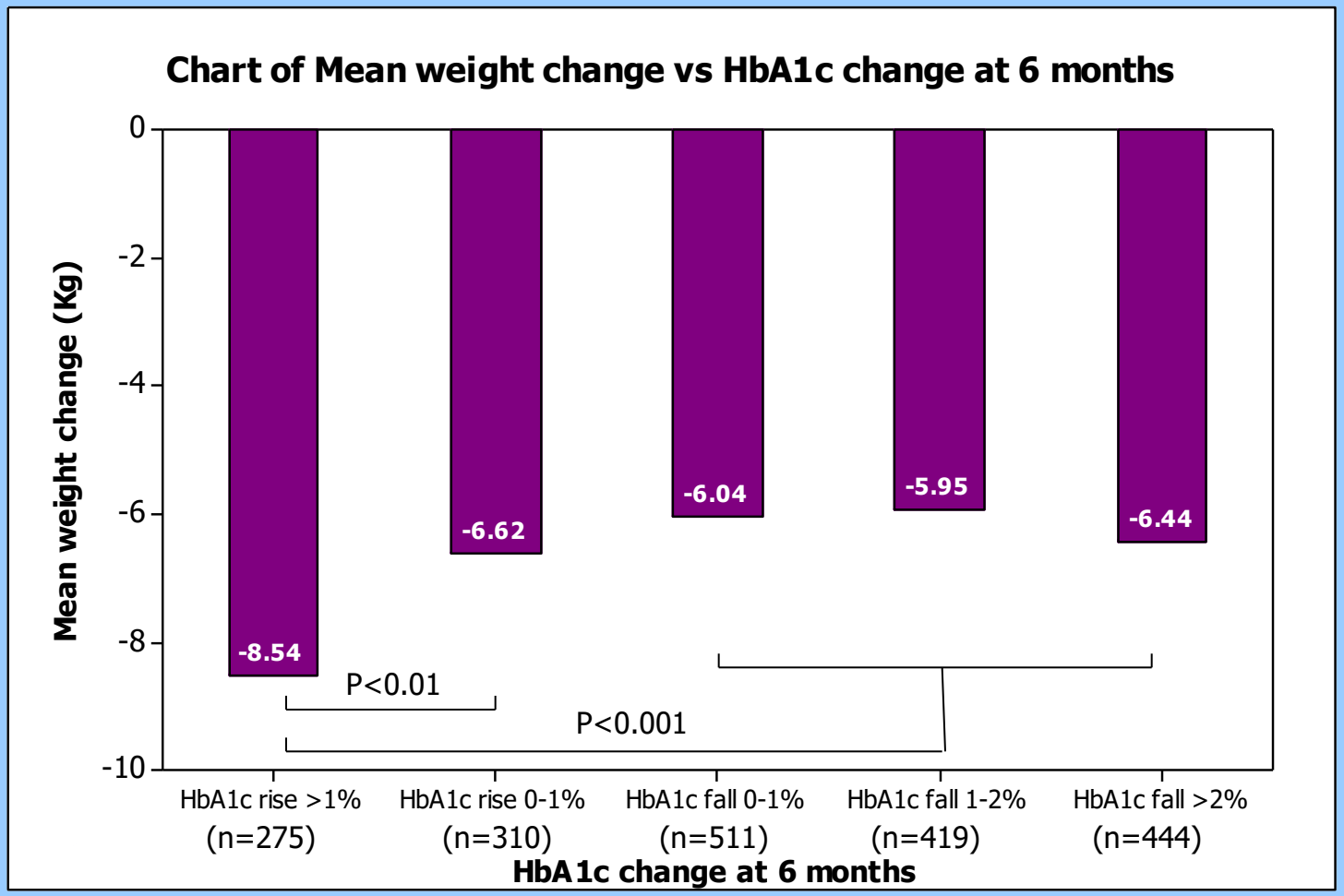
HbA1c change in the 5 weight change groupings at 6 months in 1959 patients



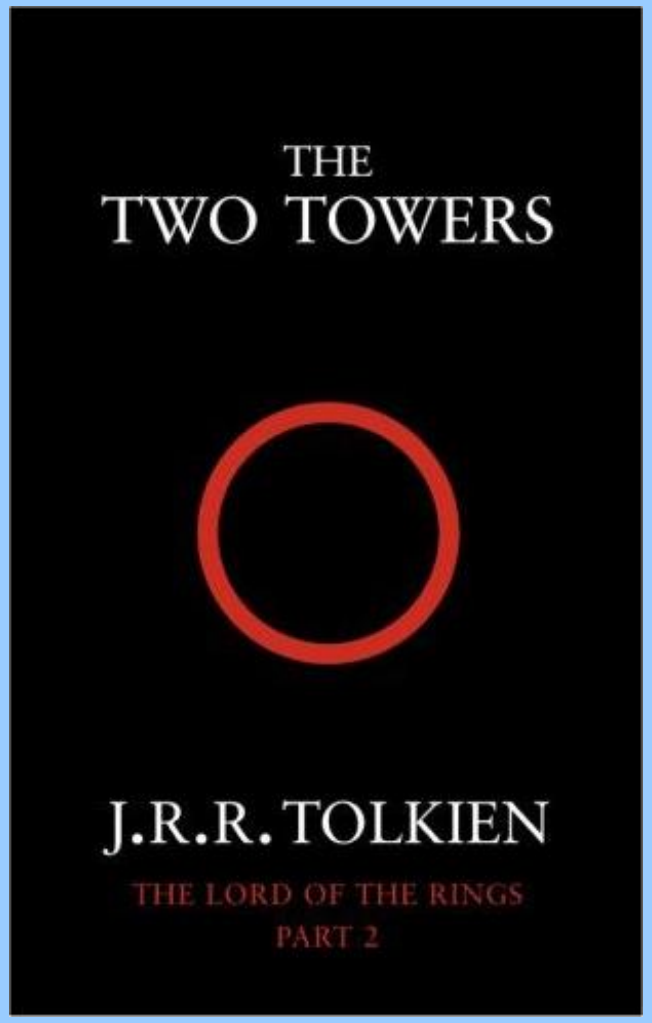
Dividing the range of HbA1c responses



Weight change in the 5 HbA1c change groupings at 6 months in 1959 patients



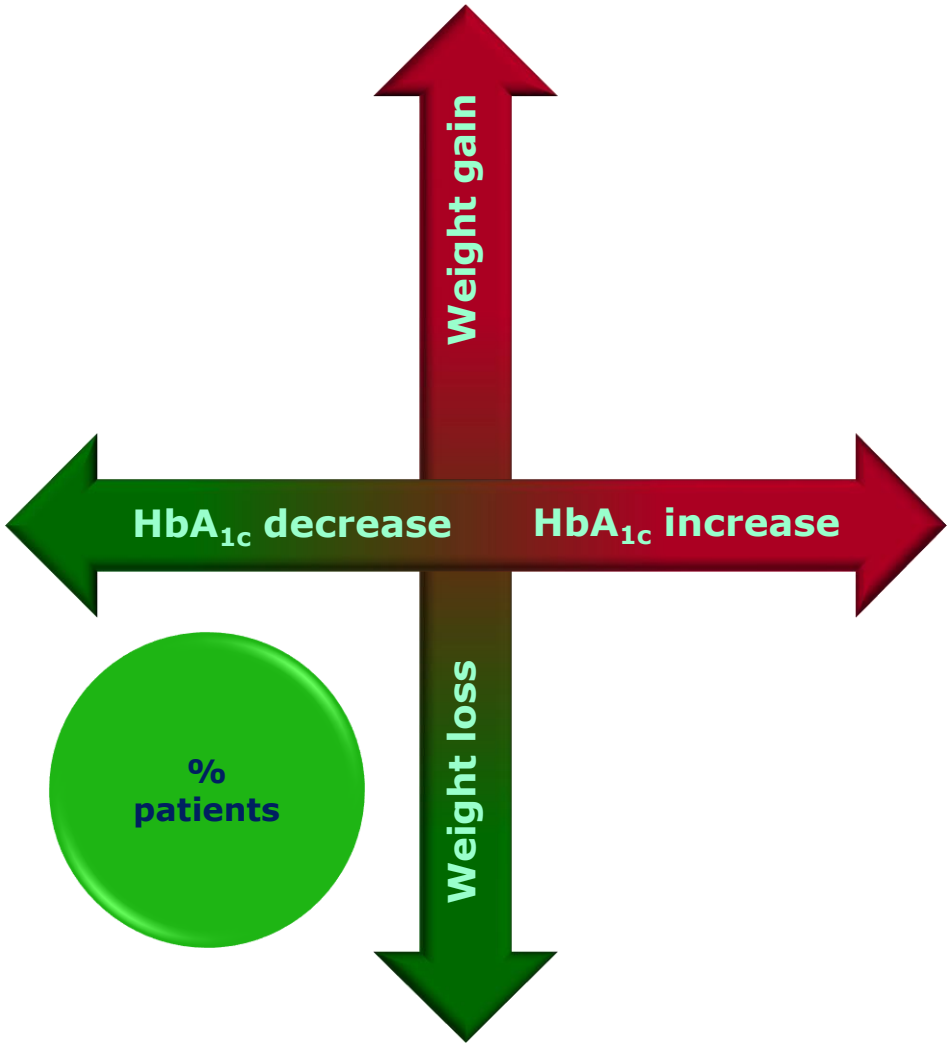
Weight



HbA1c

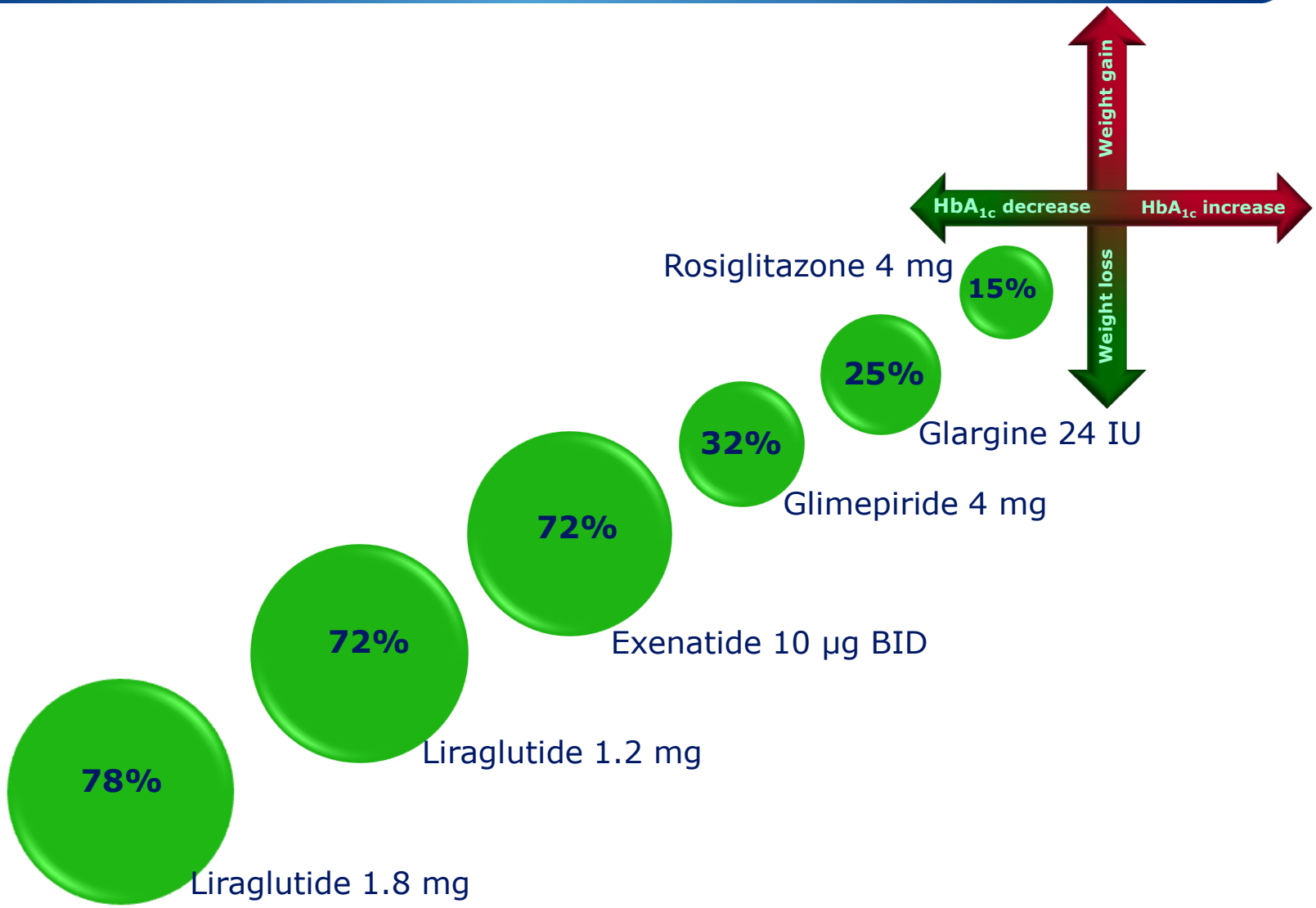
The Two Towers

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



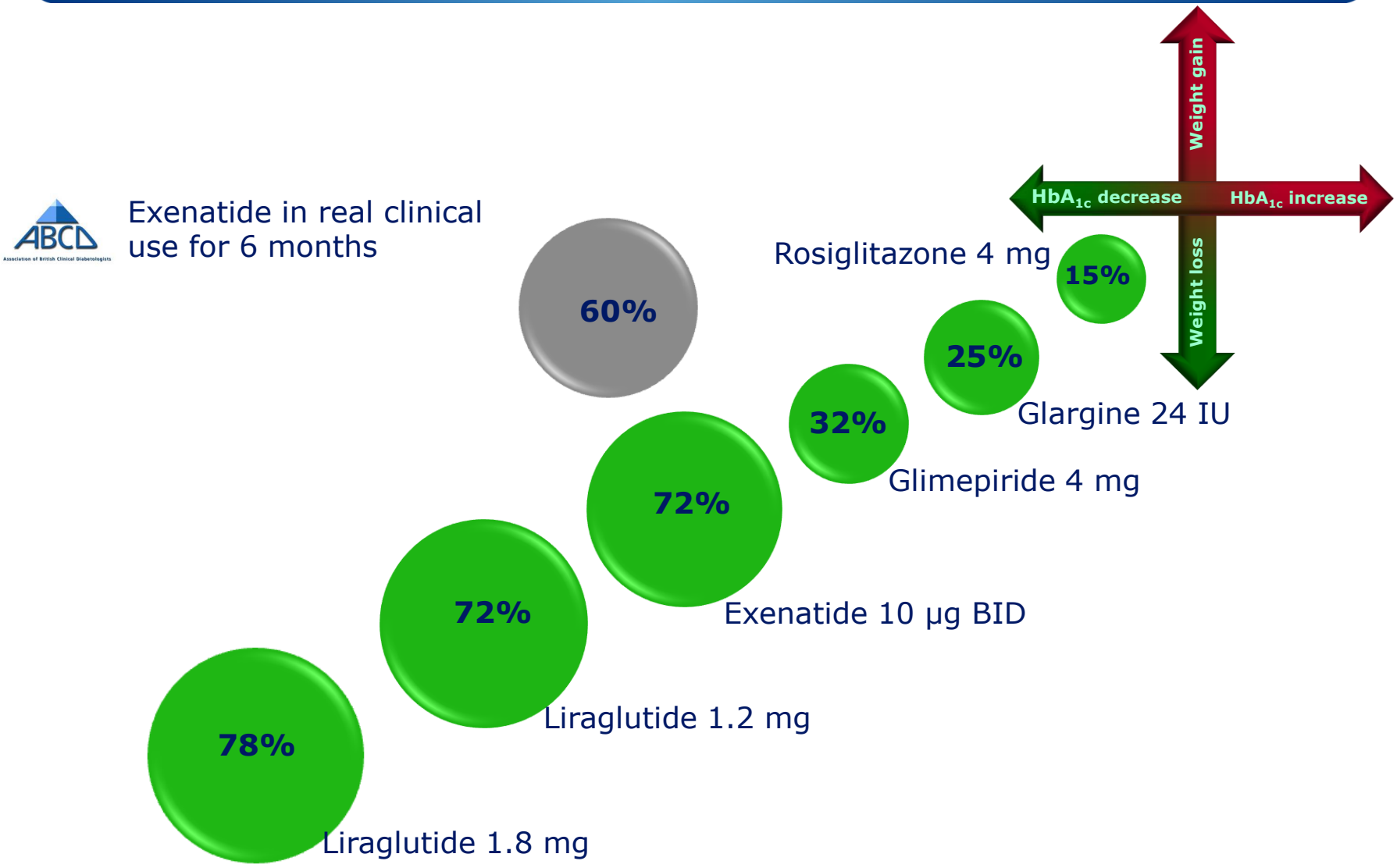
[1]Marre M *et al*. *Diabet Med* 2009; 26:268-78; [2]Nauck M *et al*. *Diabetes Care* 2009;32:84-90; [3]Garber A *et al*. *Lancet* 2009; 373:473–481; [4]Zinman B *et al*. *Diabetes Care* 2009;32:1224–1230; [5]Russell-Jones D *et al*. *Diabetologia* 2009;52:2046-55; [6]Buse J *et al*. *Lancet* 2009;374:39–47

Summary: shifting the paradigm



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

Summary: shifting the paradigm



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

Conclusion 1 – exenatide in real clinical use

- Weight loss continues to reduce for the first 9-12 months but then levels off
- The weight loss is sustained up to 24 months
- HbA1c continues to reduce for the first 6 months but then levels off
- Reduction in HbA1c is sustained up to 24 months

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Conclusion 2 – 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 represent a beneficial response

Association of British Clinical Diabetologists

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