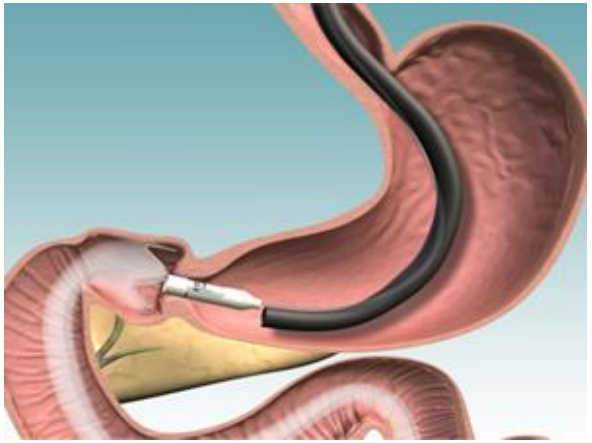
1-year outcomes of REVISE-Diabesity clinical trial

Randomisation to Endobarrier alone Versus with Incretin analogue in Sustained Diabesity



Dr Bob Ryder, Birmingham City
Dr Barbara McGowan, Guys, London
Dr Piya Sen Gupta, Kings, London and Birmingham City
Dr Russell Drummond, Glasgow Royal
Prof Stephanie Amiel, Kings, London

ABCD Meeting, Manchester, Spring 2016

Sandwell and West Birmingham Hospitals NHS Trust
King's College London
King's College Hospital NHS Foundation Trust
Guy's and St Thomas' NHS Foundation Trust
NHS Greater Glasgow and Clyde

Introduction – Bob Ryder

- Prologue
- Concept
- Aims
- Methods

Prologue

Diabetologia
DOI 10.1007/s00125-011-2204-7

ARTICLE

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

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

Received: 22 March 2011 / Accepted: 5 May 2011

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

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

Abbreviation
ffm Fat-free mass

Introduction

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

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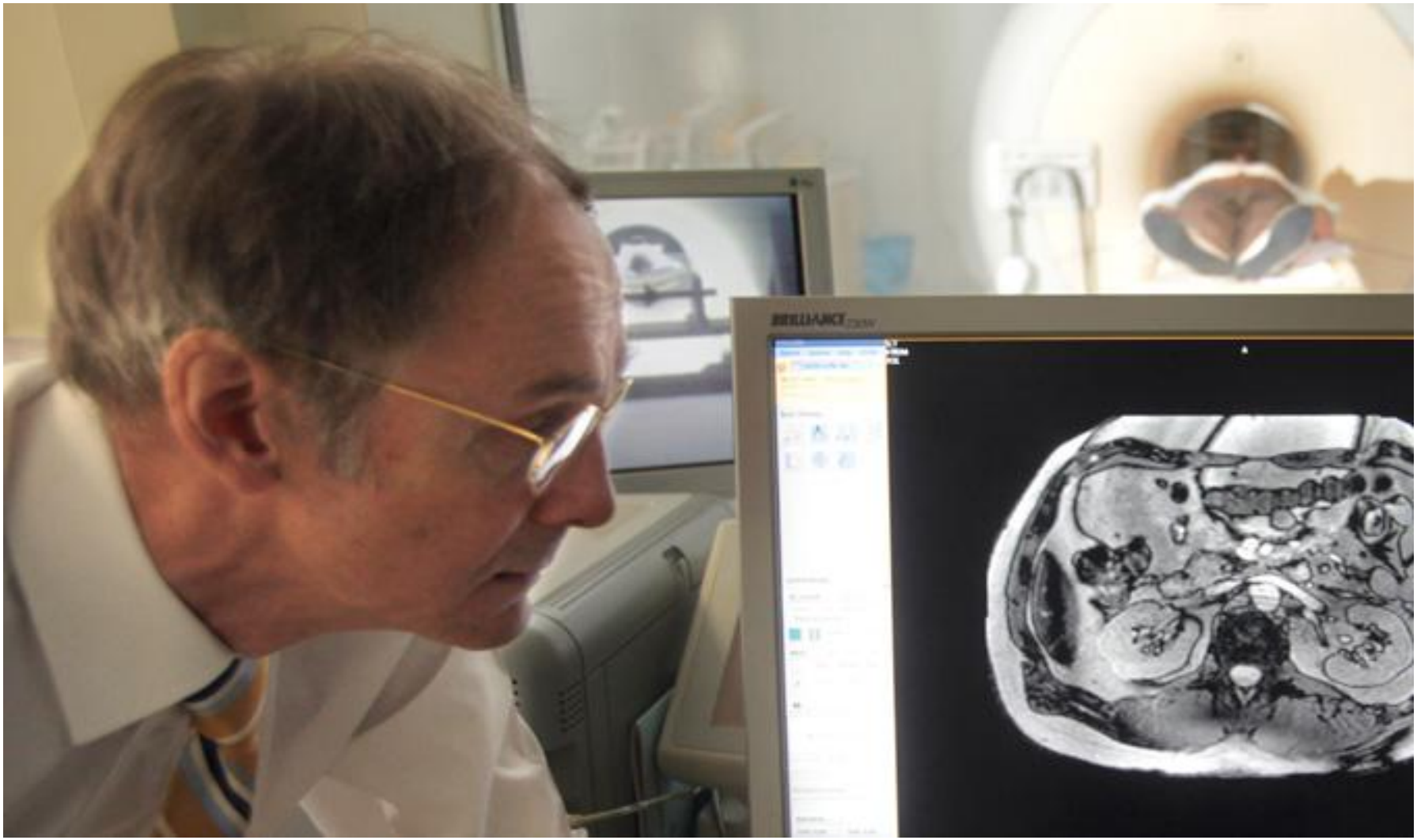
Magnetic Resonance Centre, Institute of Cellular Medicine,

Ee Lim

Roy Taylor

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

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



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

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

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

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

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

- Decreased liver fat
- Decreased pancreatic fat
- ?Decreased coronary artery fat
- ?Decreased carotid artery fat

Treating to Target

Emerging Treatments and Technologies
ORIGINAL ARTICLE

The Treat-to-Target Trial

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

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JULIO ROSENSTOCK, MD[2]
JOHN GERICH, MD[3]

ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

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

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

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

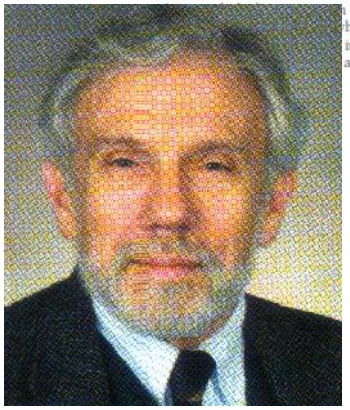
CONCLUSIONS — Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% HbA_{1c} in a majority of overweight patients with type 2 diabetes with HbA_{1c} between 7.5 and 10.0% on oral agents alone. In doing this, glargine causes significantly less nocturnal hypoglycemia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

Diabetes Care 26:3080–3086, 2003

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

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

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



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Diabetologia (2006) 49: 442–451
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Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study

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

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

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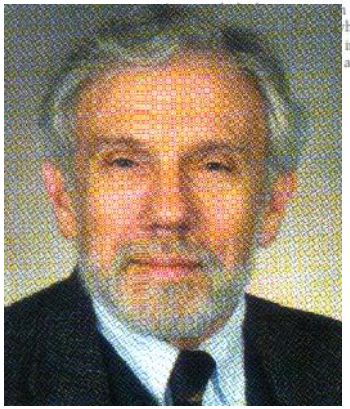

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Espoo, Finland

Hannele Yki-Jarvinen

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Keep increasing the insulin to drive down the HbA1c

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Emerging Treatments and Technologies
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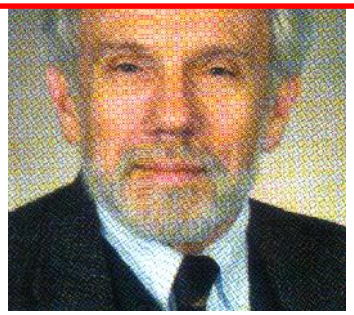
But ….

Julio Rosenstock



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to drive down the HbA1c
But ….
increasing the insulin increases
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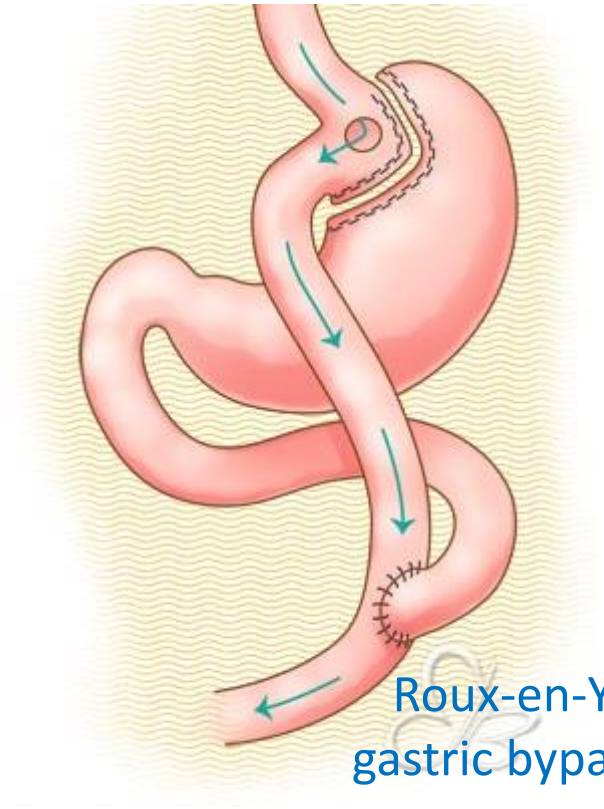
A patient in Dr Ryder's clinic who followed the treat to target approach

- May 2006
- Wt = 160 kg
- BMI = 53
- 325 units insulin daily with pioglitazone
- HbA1c = 6.7%

Roux-en-Y stomach gastric bypass surgery



Roux-en-Y gastric bypass surgery

Roux-en-Y gastric bypass surgery

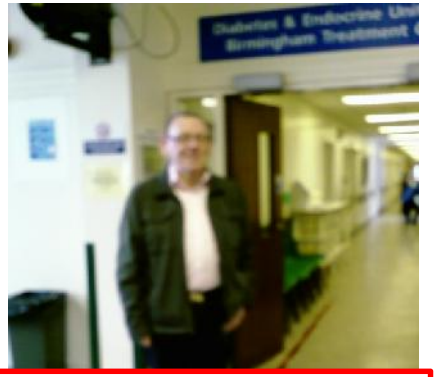
- May 2006
- Wt = 160 kg
- BMI = 53
- Trouser size = 54 inch
- 325 units insulin daily with pioglitazone etc
- HbA1c = 6.7%
- BP 162/75 on 3-4 antihypertensive agents

- April 2008
- Wt = 83 kg
- BMI = 27
- Trouser size = 32 inch
- No insulin;
  no OHAs
- HbA1c = 7%
- BP 112/70 - no anti-hypertensives

Roux-en-Y gastric bypass surgery

- May 2006
- April 2008

Roux-en-Y gastric bypass surgery



Spent 1 month in intensive care unit post op because of post op complications

- 325 units insulin daily with pioglitazone etc
- HbA1c = 6.7%
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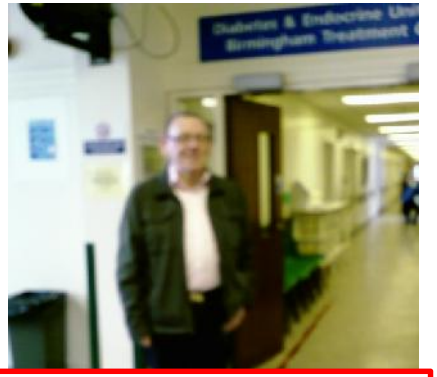

Wouldn't it be great if there was a less invasive procedure?

- 325 units insulin daily with pioglitazone etc
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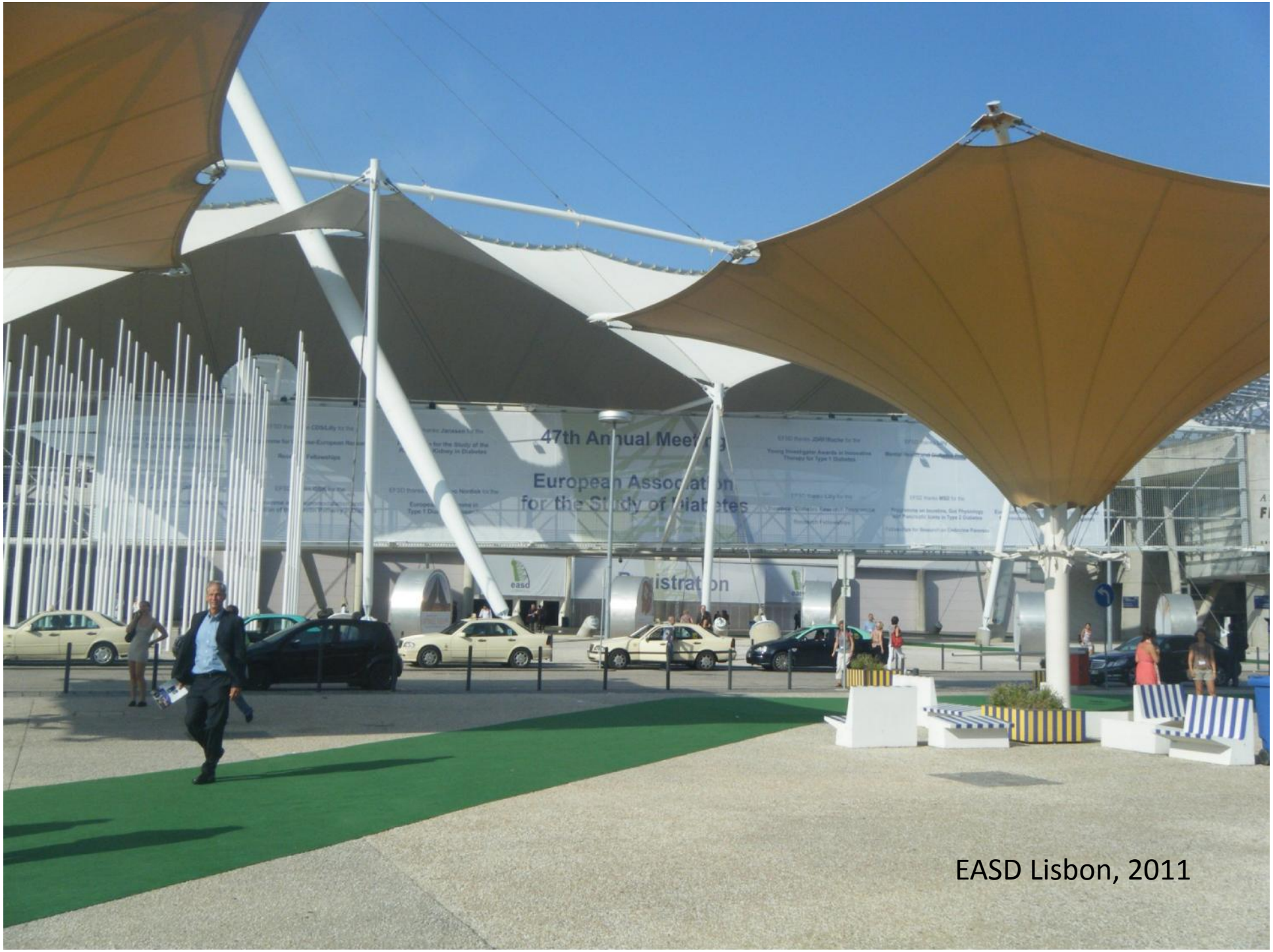
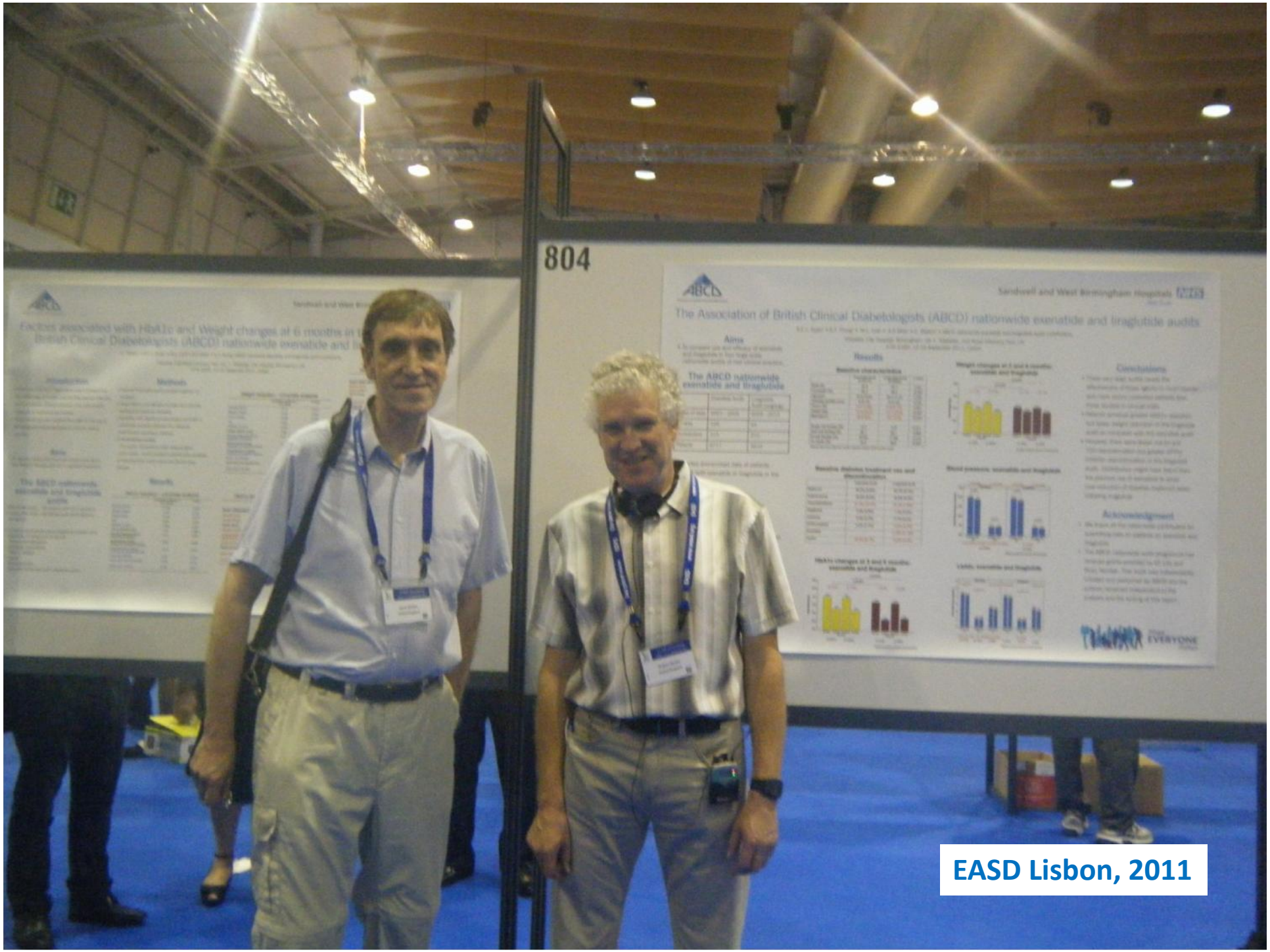


EASD Lisbon, 2011


804
The Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audits
EASD Lisbon, 2011

Lisbon 2011

watch

Roma Hall

15 Sep 2011
16:00 - 16:15

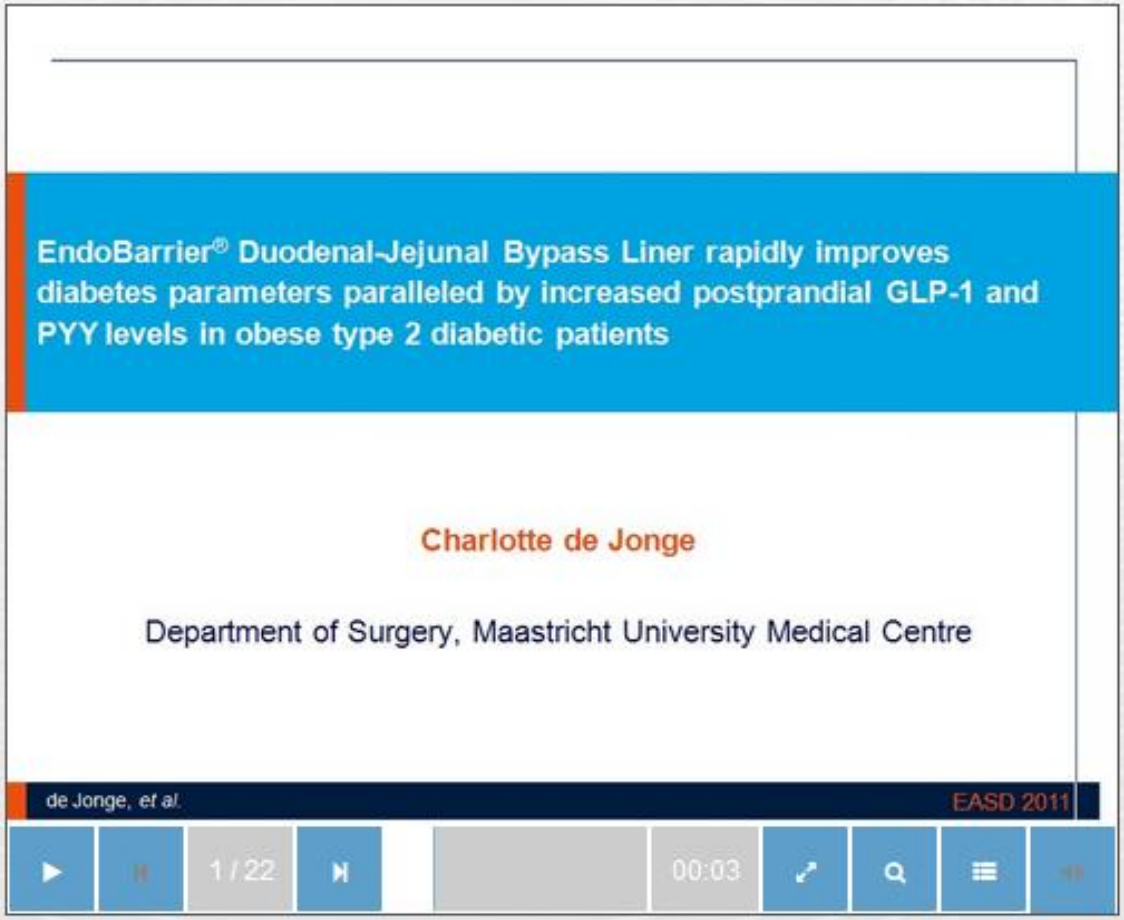
92 viewers

View Session Outline

OP 31 Metabolic effect of bariatric surgery

Charlotte de Jonge

EndobarrierTM duodenal-jejunal bypass liner rapidly improves diabetes parameters paralleled by increased postprandial GLP-1 and PYY levels in obese type 2 diabetic patients



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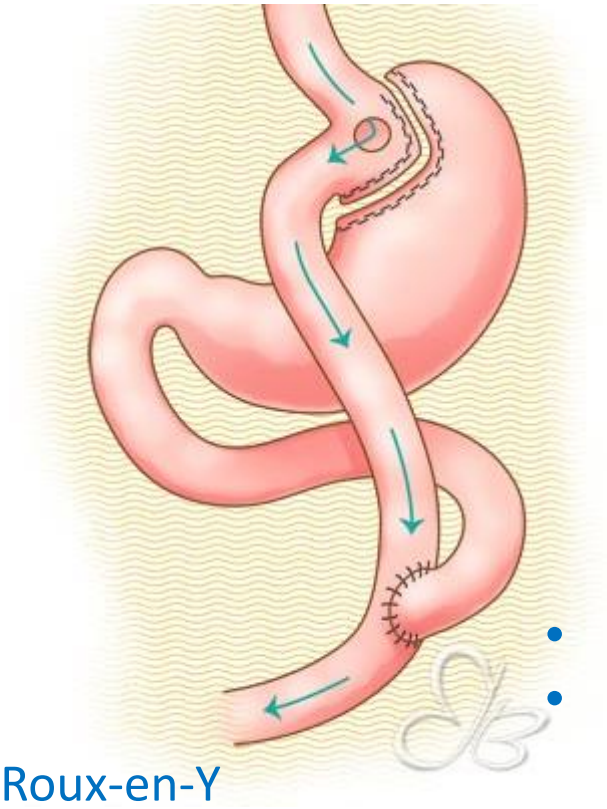
Endobarrier – implantable duodenal-jejunal liner

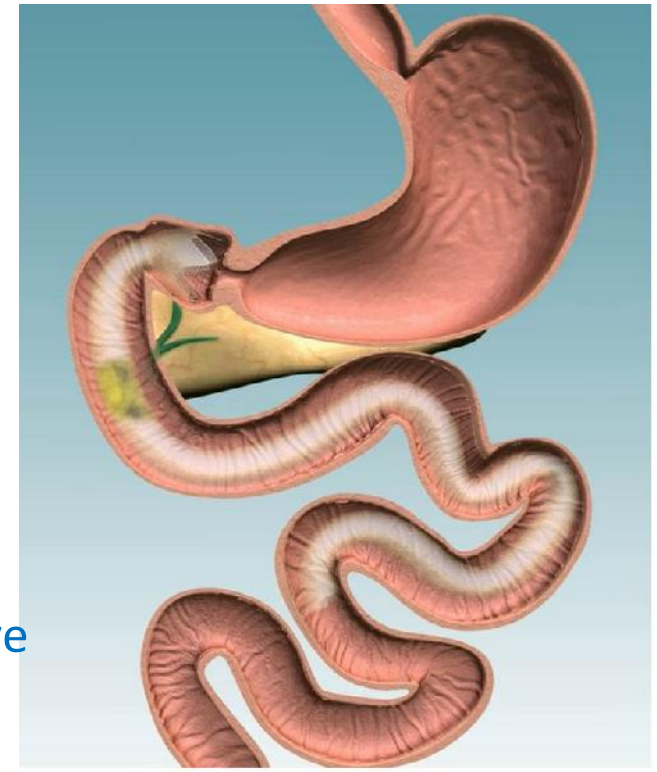


Roux-en-Y gastric bypass surgery

Fluoropolymer wall

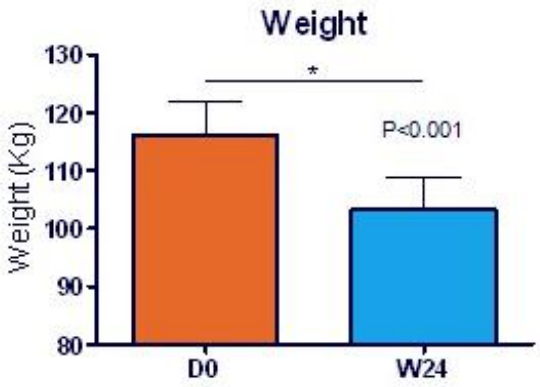
Nitinol Anchor

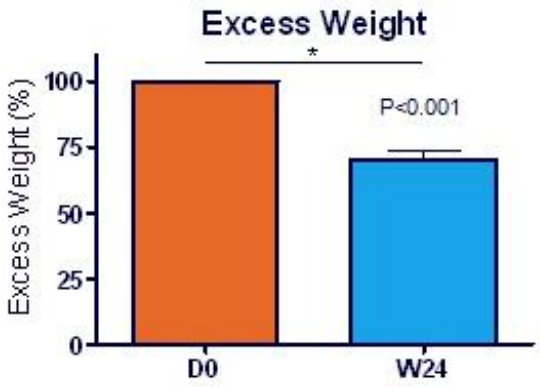
- 60 cm impermeable sleeve
- Minimally invasive



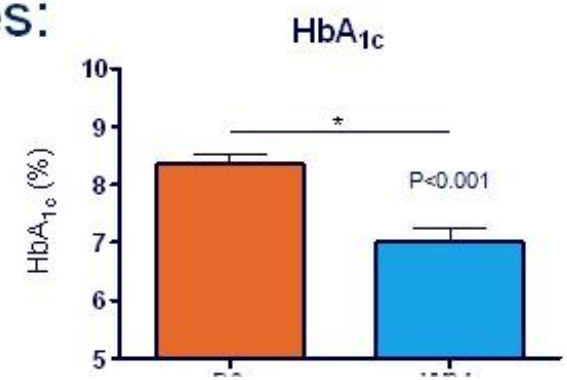
Weight loss and diabetic improvement

Weight:



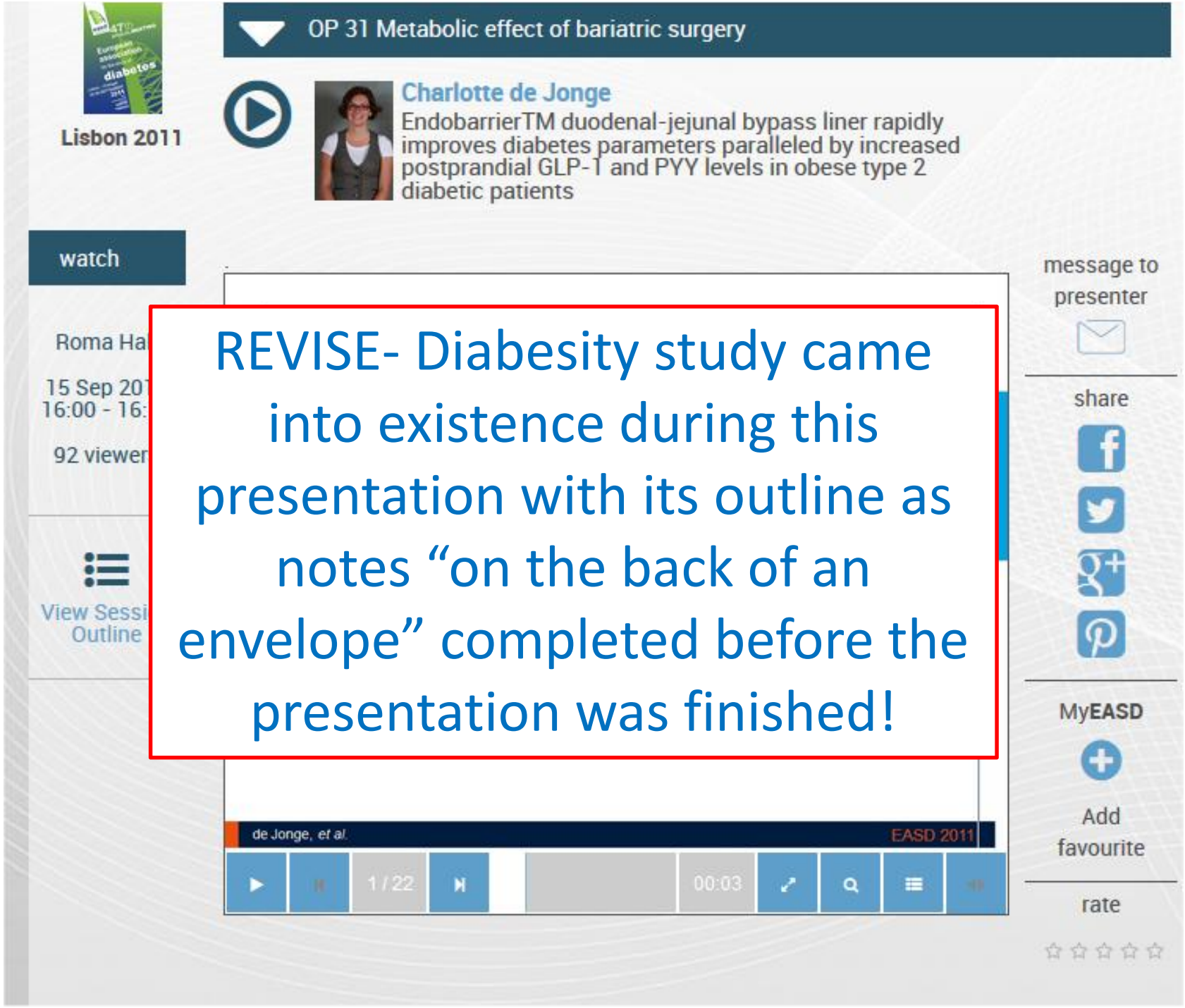


Diabetes:



Reduction of anti-diabetic medication in 16/17 patients

de Jonge et al. EASD Lisbon, 2011



REVISE- Diabesity study came into existence during this presentation with its outline as notes “on the back of an envelope” completed before the presentation was finished!

2 year endobarrier

ABCD Liraglutide audit [illegible]

BMI > 35

HbA1c > 8%

6 big centres

1 Research Fellow

Ultra long barrel

Group 0 "usual care"

Group 1 titrate Lira up to 3mg or max tolerated

Group 2 Endobarrier followed by best + usual

Group 3 " " Lira 3mg

Group 4 " + Lira 3mg + Contrave 3mg

Ryder REJ – notes on proposed study made during EASD endobarrier presentation, 2011

2 year endpoints ✓

ABCD Lira audit features ✓

BMI > 35 ✓

HbA1c > 8% ← Became ≥7.5%

6 big contributing centres

1 Research Fellow

Algorithm

Ultra long basal

Group 0 "usual care"

Group 1 titrate Lira up to 3mg or max tolerated

Group 2 Endocarer " " "

Group 3 " " " Lira 3mg

Group 4 " + Lira 3mg + Canagliflozin 3mg

2 year endotoxaemia

ABCD Liraglutide audit failures

6 big contributing centres

1 Research Fellow

Became 4 contributing centres

HbA1c > 8%

Group 0 "usual care"

Group 1 titrate Lira up to 3mg or max tolerated

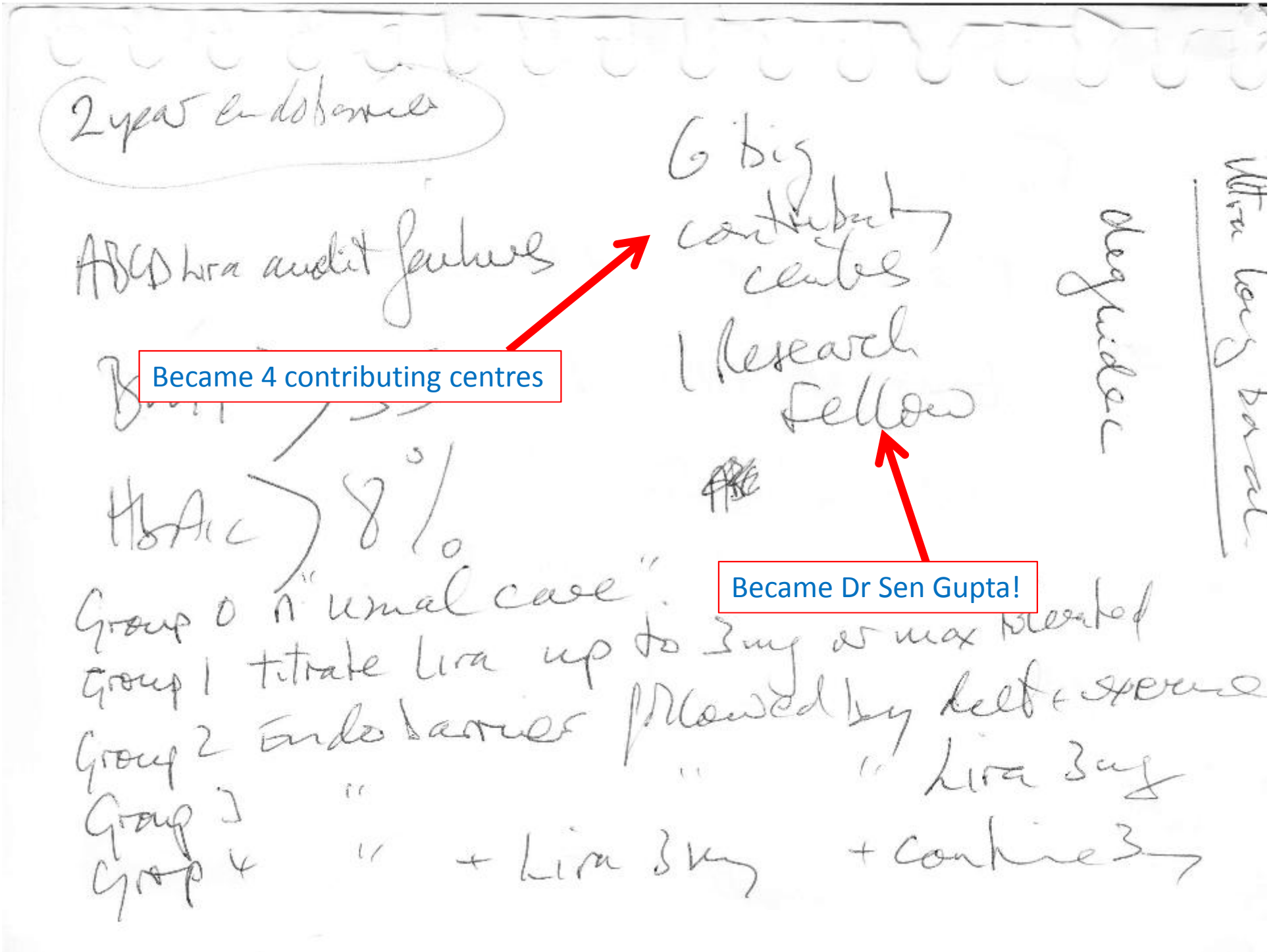
Group 2 Endotoxaemia followed by Lira 3mg

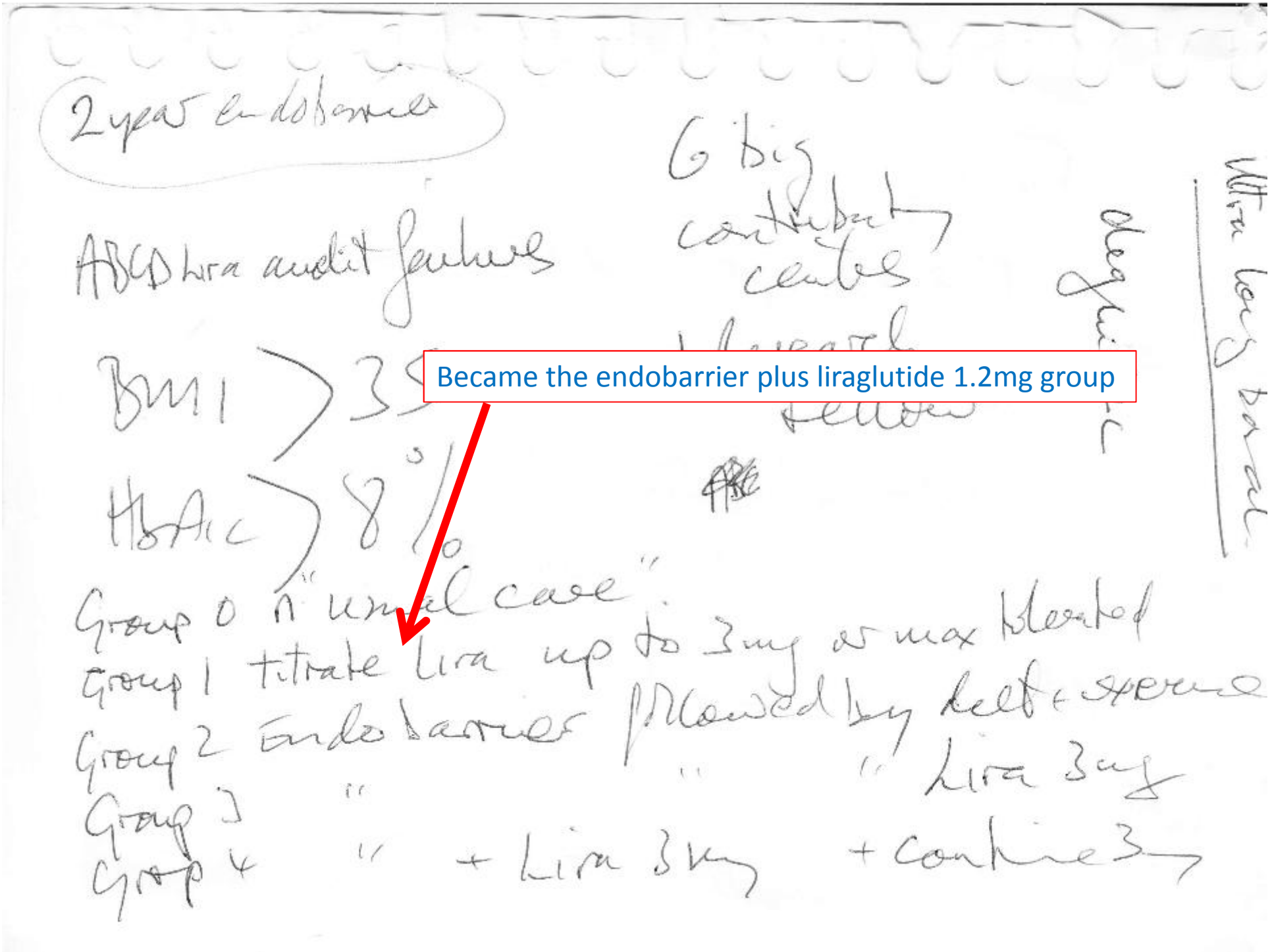
Group 3 " "

Group 4 " + Lira 3mg + Combine 3mg

Ultra long basal

degludec


2 year endotrance
ABCD Lira audit feature
6 big contributing centres
1 Research Fellow
Became 4 contributing centres
Became Dr Sen Gupta!
HbA1c > 8%
Group 0 "usual care"
Group 1 titrate Lira up to 3mg as max tolerated
Group 2 Endotrance
Group 3
Group 4 + Lira 3mg + Canagliflozin 300mg


2 year endobarrier
ABCD liraglutide audit feature
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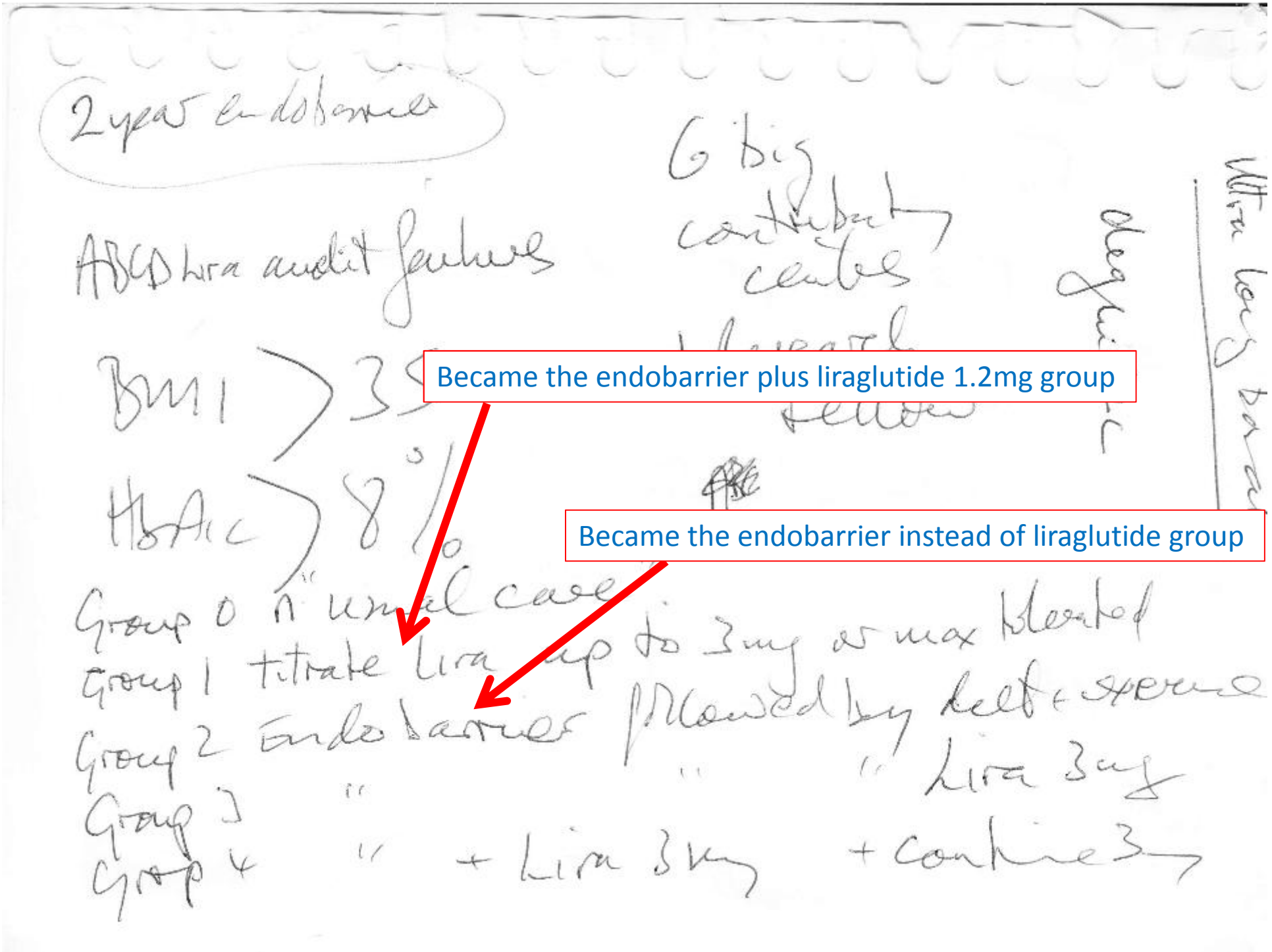
Group 2 Endobarrier followed by best + optimal
Group 3 " " lira 3mg
Group 4 " + Lira 3mg + continue 3mg
6 big contributing centres
Ultra long basal
Became the endobarrier plus liraglutide 1.2mg group


2 year endobarrier
ABCD Lira audit feature
BMI > 35
HbA1c > 8%
Group 0 "usual care"
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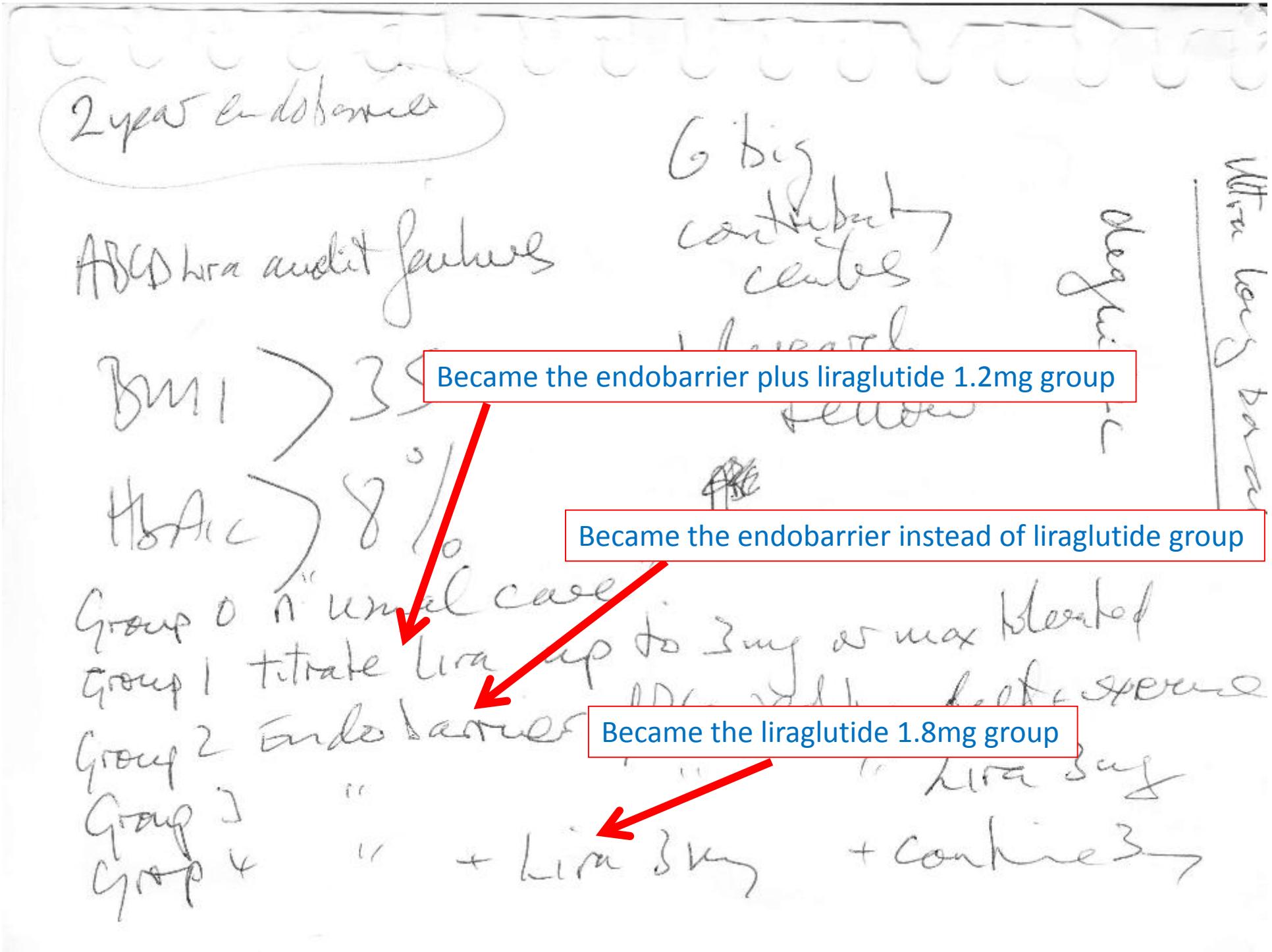
Group 2 Endobarrier followed by best + optimal
Group 3 " " Lira 3mg
Group 4 " + Lira 3mg + continue 3mg
6 big contributing centres
Ultra long barrier
Became the endobarrier plus liraglutide 1.2mg group
Became the endobarrier instead of liraglutide group


2 year endobarrier
ABCD Lira audit feature
BMI > 35
HbA1c > 8%
Group 0 "usual care"
Group 1 titrate lira up to 3mg or max tolerated
Group 2 Endobarrier
Group 3 "
Group 4 " + Lira 3mg + Contrave 3mg
6 big contributing centres
Ultra long barrier
Became the endobarrier plus liraglutide 1.2mg group
Became the endobarrier instead of liraglutide group
Became the liraglutide 1.8mg group

Friday

ABCD pay for endobronchus ✓

Nova provides here X

Gastroenterologists are collaborators. ✓

N? – ask Goldstein ✓

Concept & timelines for the trial

- EASD 2011
- 2012-3 grant, ethics, R&D approval
- July 2013 – first patient treated
- April 2016 – 1-year complete for all patients
- March 2017 – 2-year results

Aim

To investigate the effects of adding proximal intestinal exclusion to GLP-1RA therapy not achieving targets, on weight and HbA1c compared to either treatment alone

Study design: Selection Criteria

INCLUSION CRITERIA:

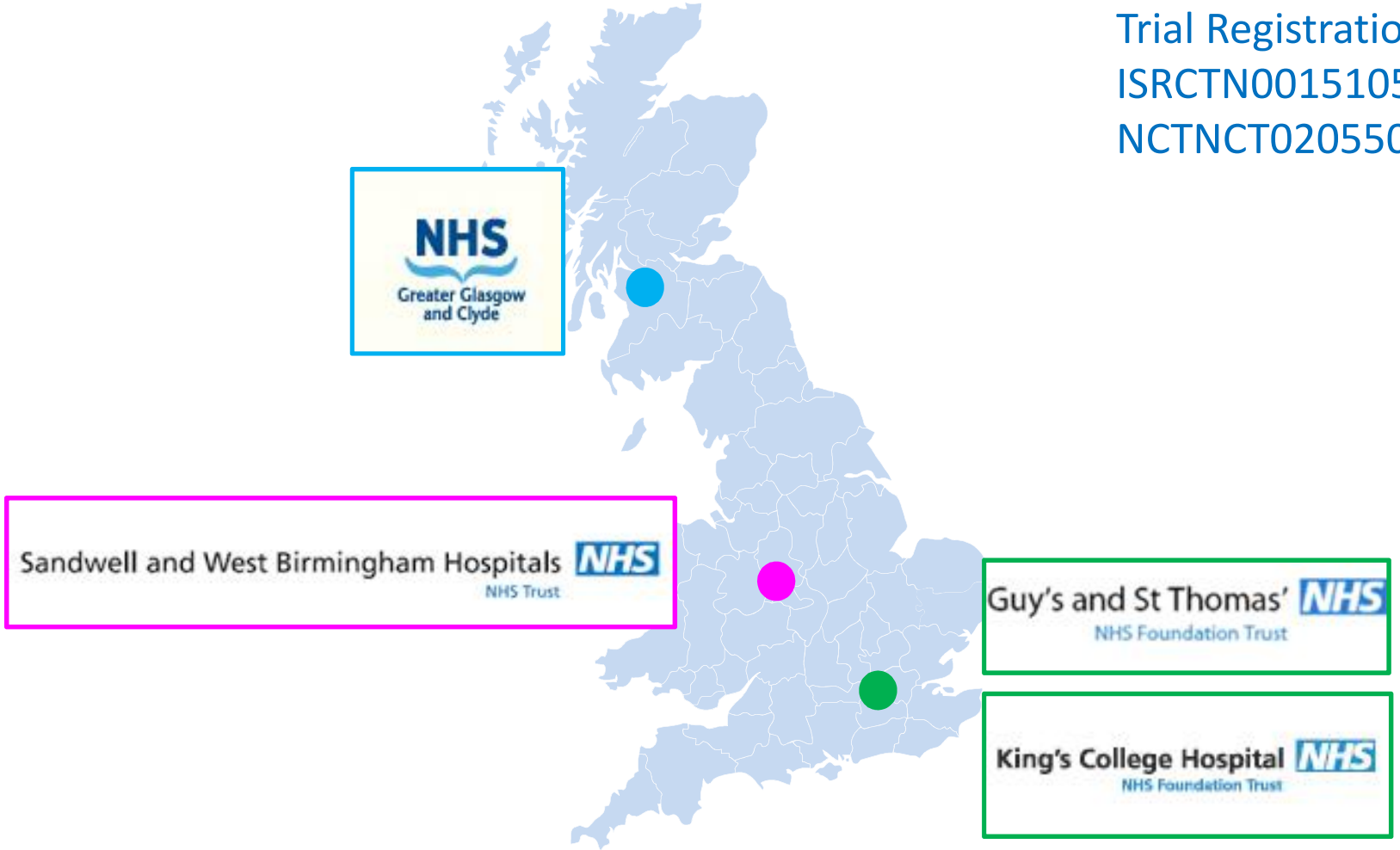
- Type 2 diabetes
- Liraglutide treated for ≥6 months
- HbA1c ≥58mmol/mol (7.5%)
- Obesity, BMI ≥35kg/m^2
- Stable weight, HbA1c (3 months)

EXCLUSION CRITERIA:

- Safety considerations:
- Bleeding risk: aspirin, warfarin
- Infection
- Pregnancy
- Conditions interfering with endobarrier placement/ findings

Study design:

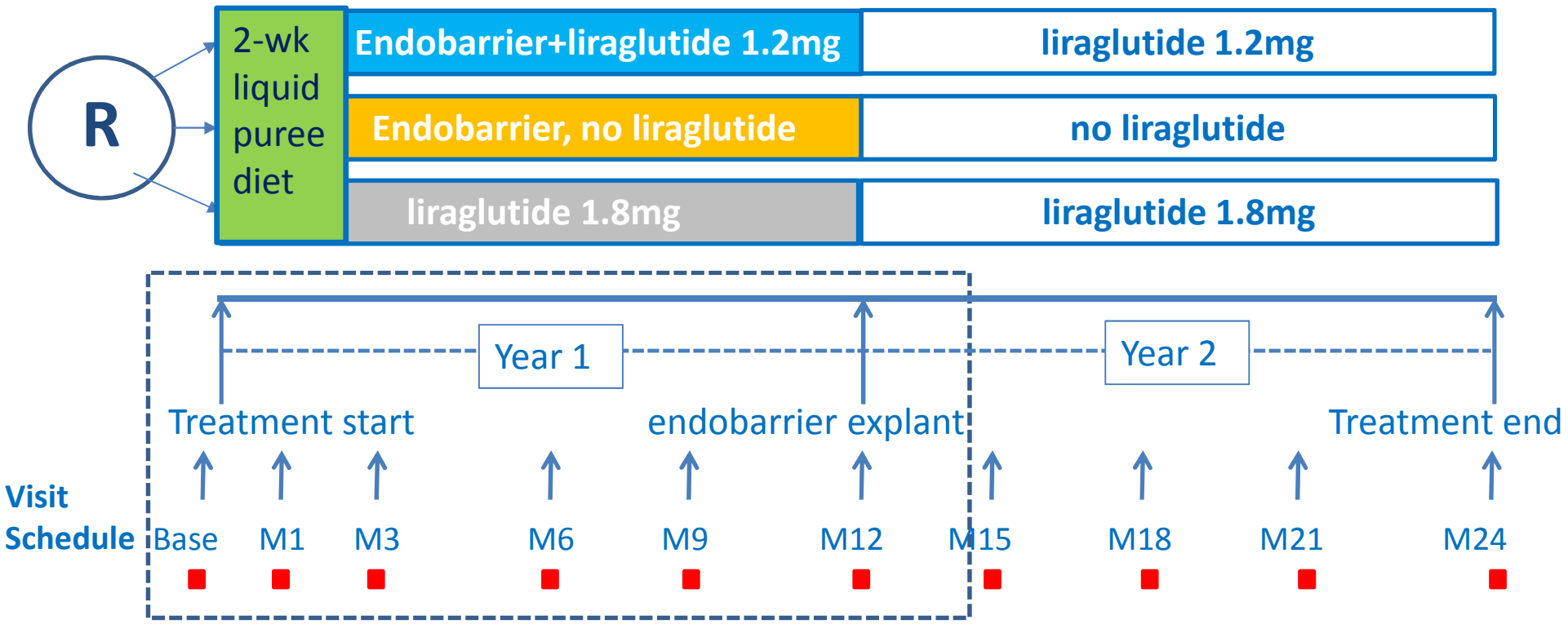
Open label, multicentre, parallel group, randomised controlled trial



Trial Registrations:
ISRCTN00151053
NCTNCT02055014

Study design:

Open label, multicentre, parallel group, randomised controlled trial



- 3-monthly visits: interview, anthropometry, blood tests (fbc, u&e, lft, amylase, lipids, HbA1c)
- Primary outcome: HbA1c at 2 years
- Subgroup MRI liver and pancreas – baseline and 4 months

Results – Piya Sen Gupta

- Flowsheet of study subjects

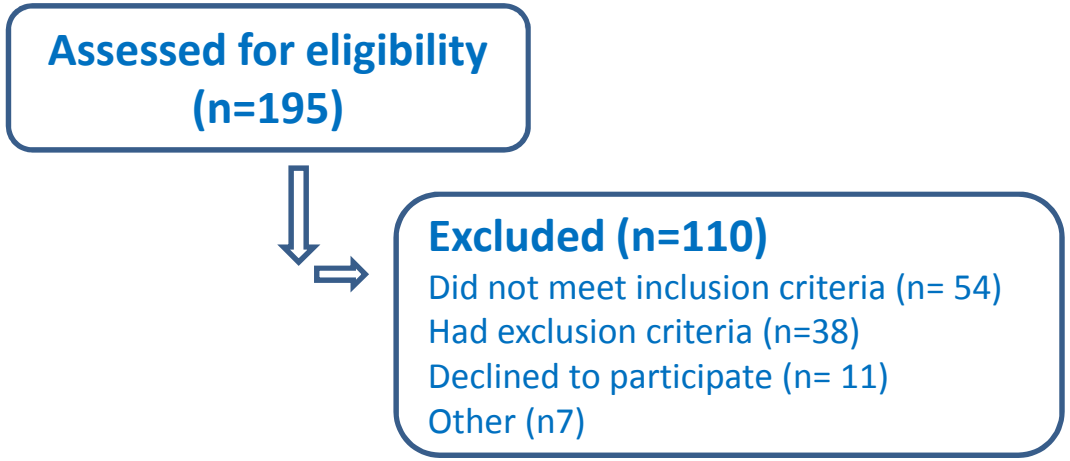
- Baseline characteristics

- Efficacy:
- weight
- HbA1c and diabetes medications
- Cardiovascular risk
- Liver fat

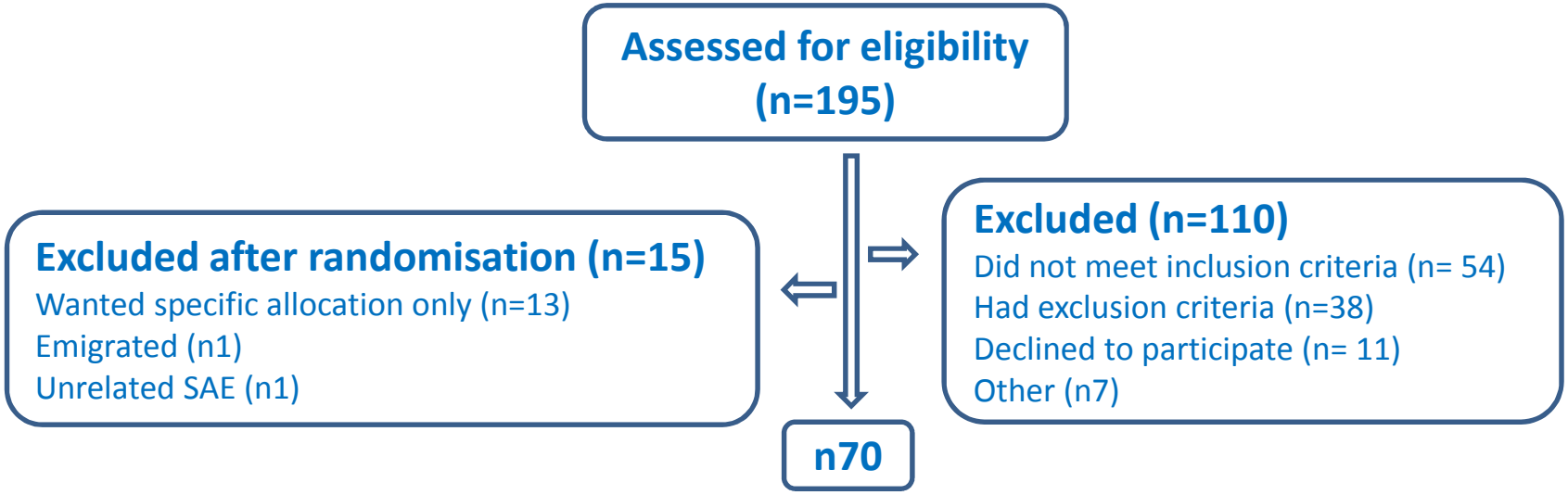
Flowsheet of study subjects (n70)

Assessed for eligibility
(n=195)

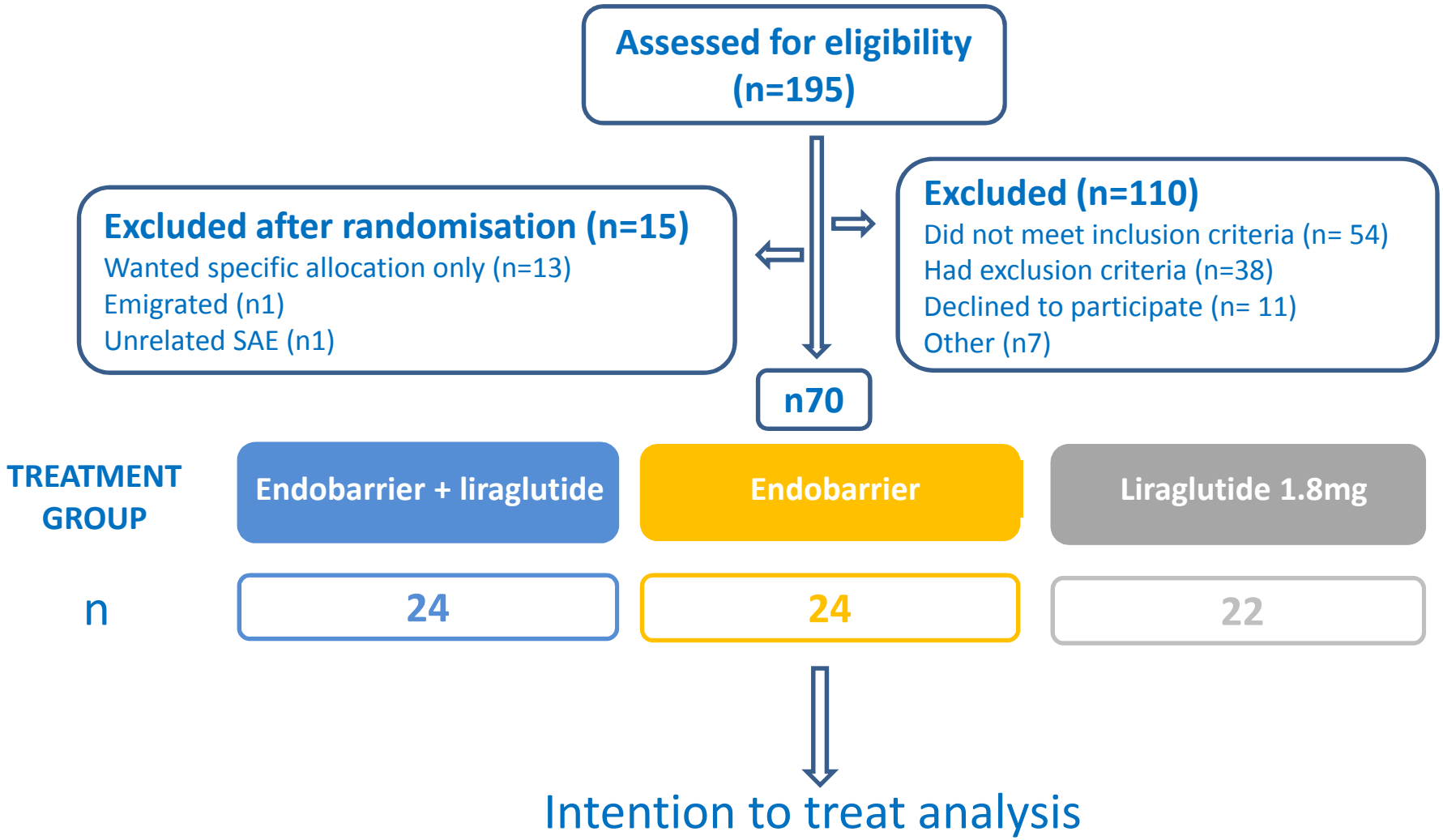
Flowsheet of study subjects (n70)



Flowsheet of study subjects (n70)



Flowsheet of study subjects (n70)



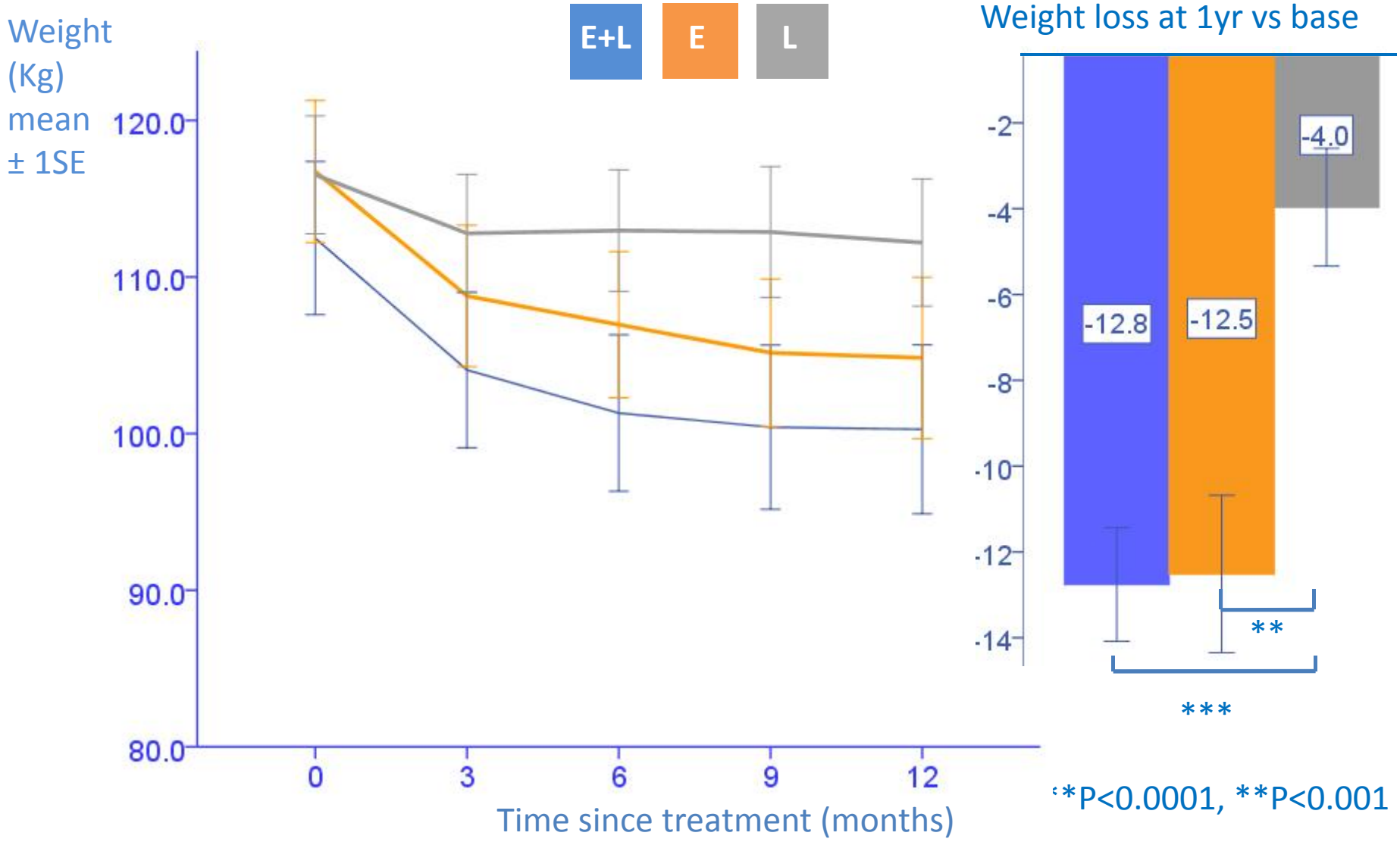
Baseline characteristics

Parameter	Endobarrier +liraglutide N=24	Endobarrier N=24	Liraglutide N=22
Age (years)	52.0±11.7	50.7±8.4	54.0±10.1
Sex (% male)	41.7	29.2	36.4
Ethnicity (% Caucasian)	66.7	70.8	72.7
*Diabetes duration (yrs)	11.2 (6.7-17.1)	10.3 (7.8-12.7)	13.3 (9.0-18.4)
Taking insulin (%)	58.3	25.0	45.5
BMI (kg/m^2)	40.3±4.8	41.7±4.9	40.6±4.4
Weight (kg)	112.8±20.4	115.6±19.4	113.9±14.9
HbA1c (mmol/mol)	81.5±14.9	78.1±19.0	82.5±18.8
HbA1c (%)	9.6±1.4	9.3±1.7	9.7±1.7

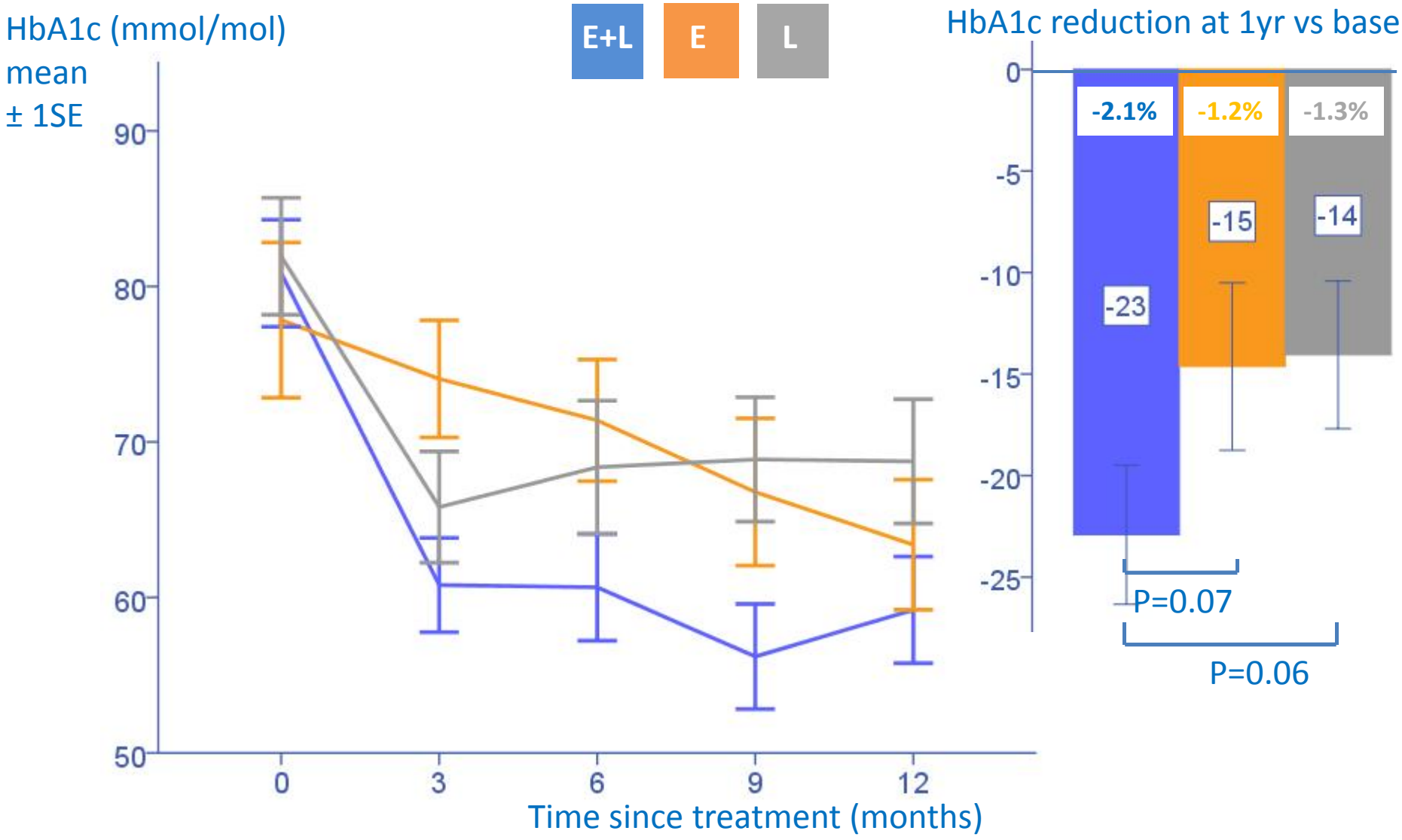
**interquartile range*

No significant differences between groups

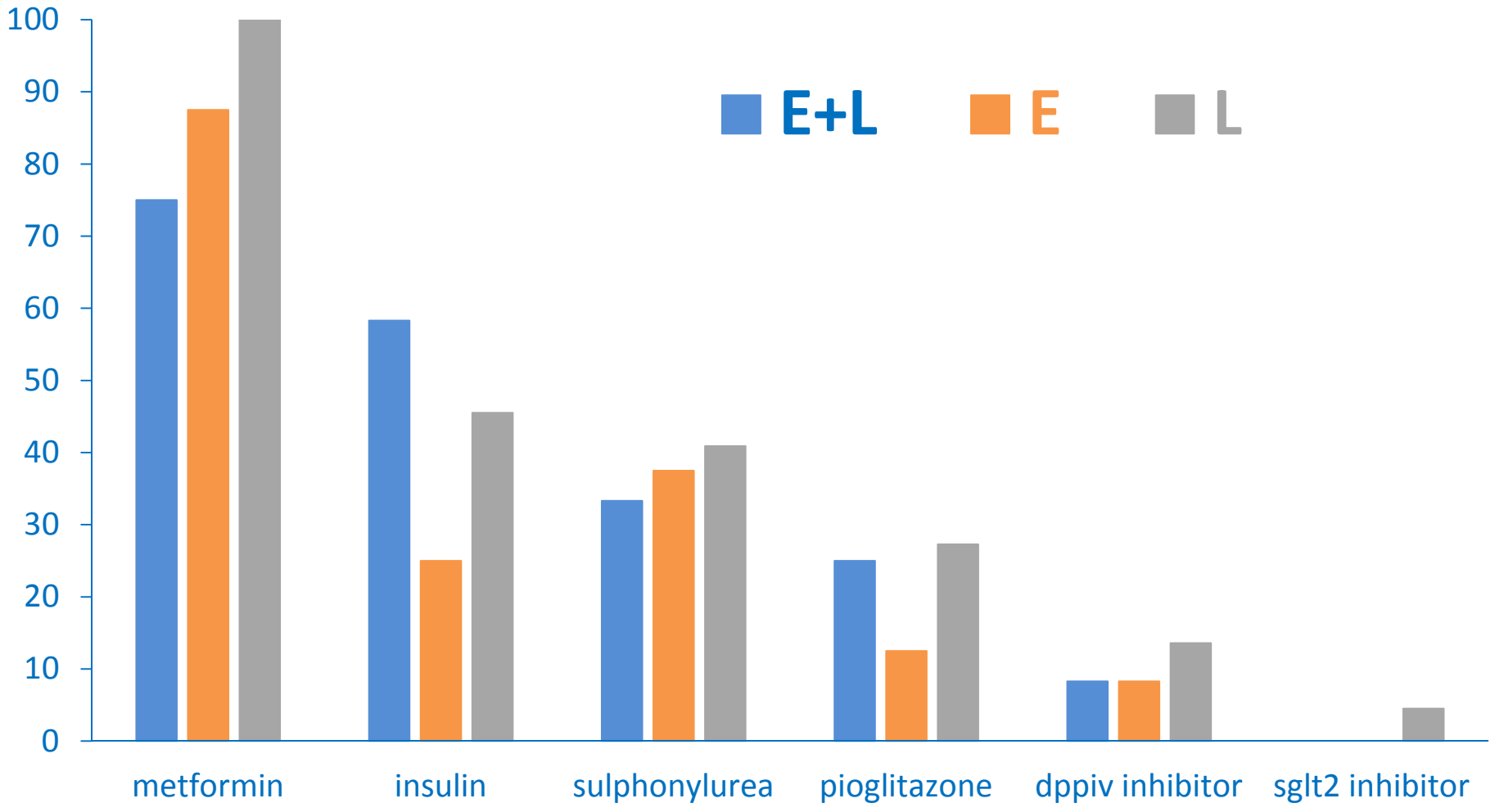
Impact of treatment on weight over 1 year



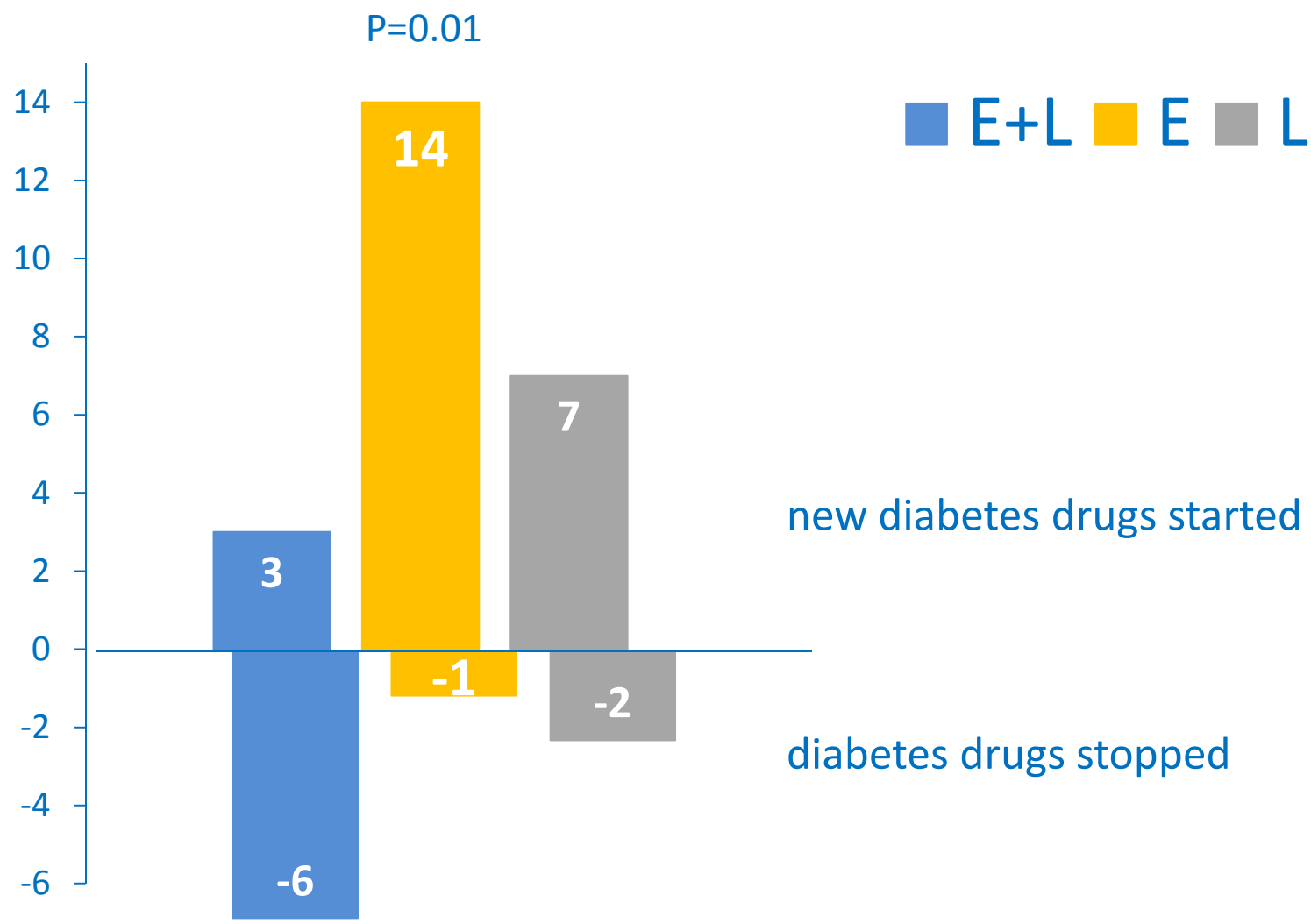
Impact of treatment on HbA1c over 1 year



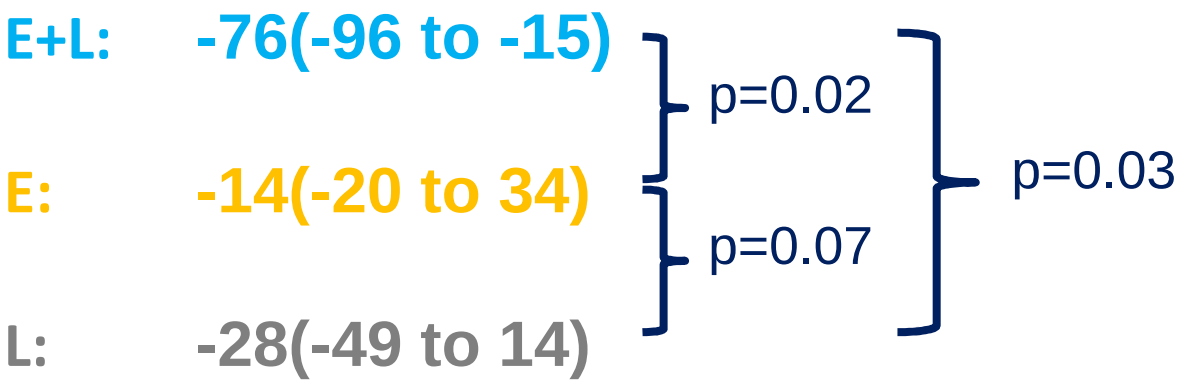
% frequency of diabetes medications at baseline by treatment group



Number of new/ stopped diabetes medications started in each intervention group



Change in total daily dose of insulin by treatment group



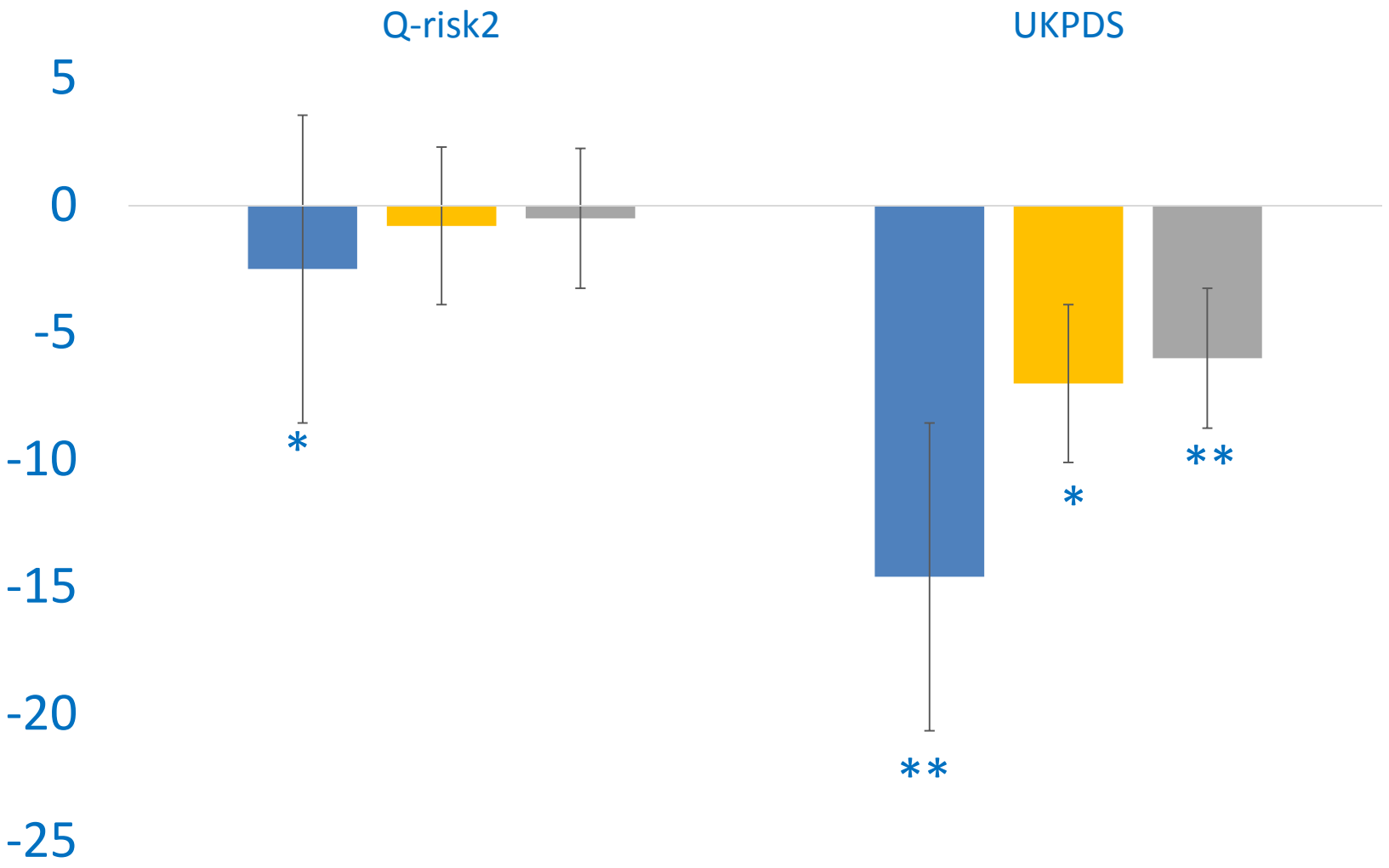
Impact of treatment on 10-year cardiovascular risk

10-Year CV risk score parameters	Q-risk2	UKPDS
Age, Sex, Ethnicity, Smoking status	✓	✓
Postcode	✓	
Diabetes status	✓	
Duration of diabetes, HbA1c		✓
Hypertension status, Rheumatoid arthritis, CKD IV-V	✓	
Atrial fibrillation	✓	✓
Cholesterol:HDL	✓	✓
Systolic BP	✓	
Diastolic BP		✓
BMI	✓	

Q-risk2 at baseline

- 38.7% intermediate (10-20%) risk
- 40.0% high (>20%) risk

Impact of treatment on 10-year cardiovascular risk

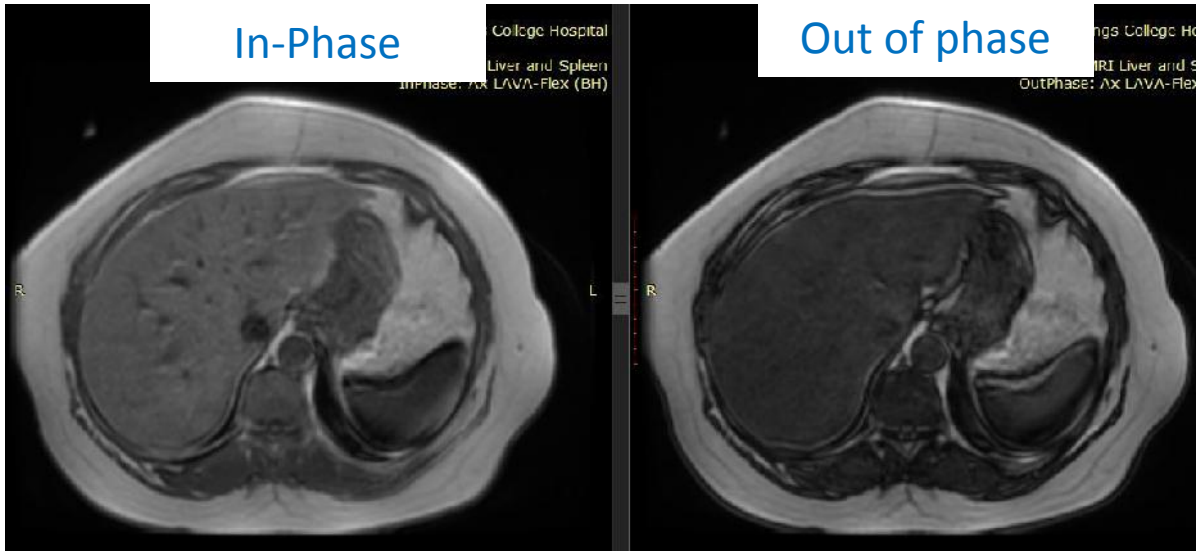


Liver fat pre- and post-MR images

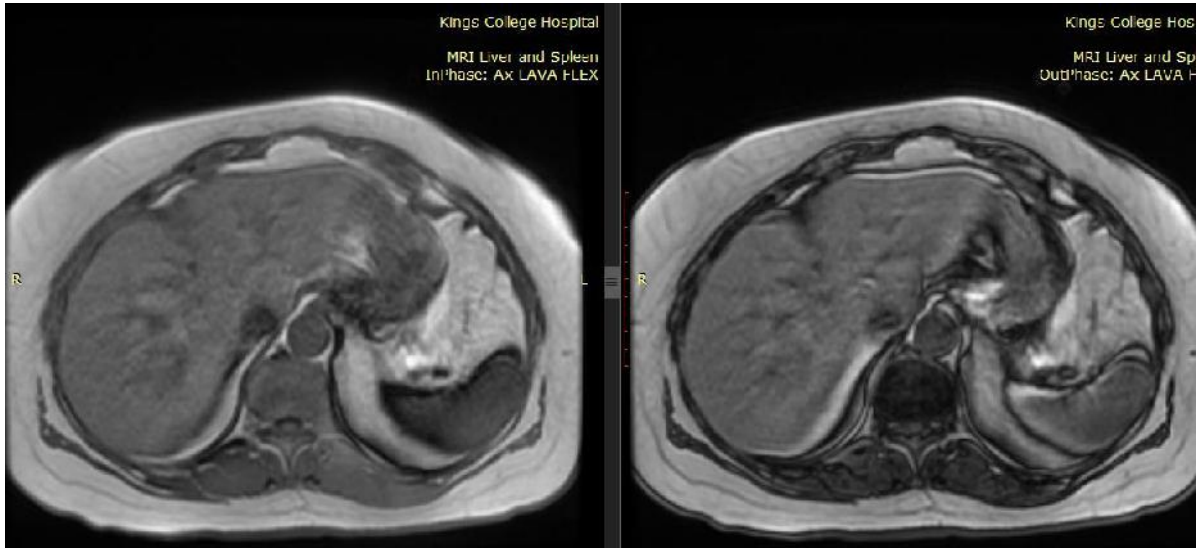
In-Phase

Out of phase

Pre-endobarrier

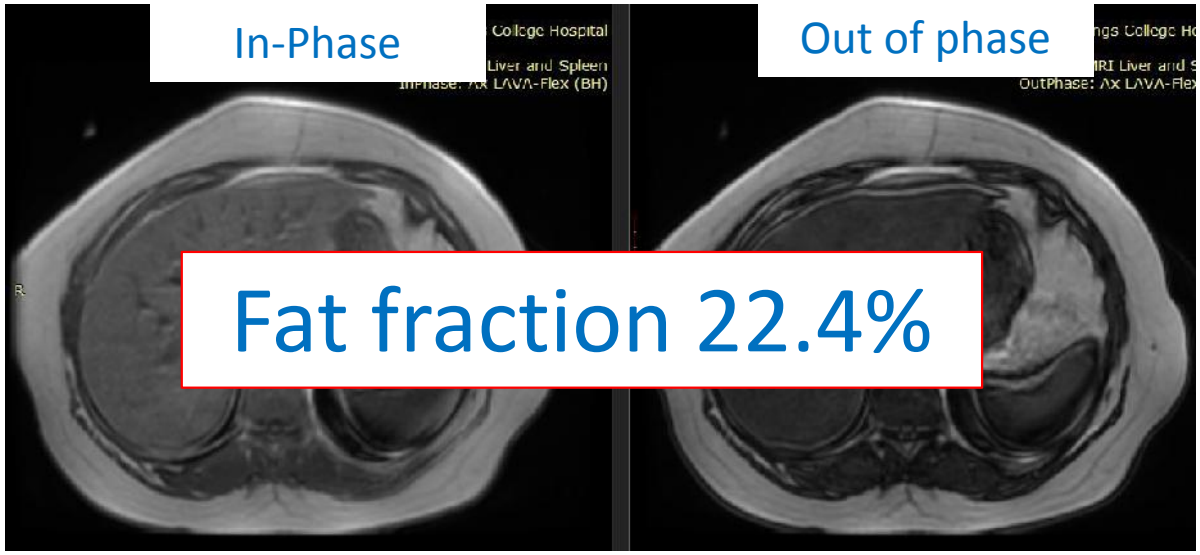


4-months later

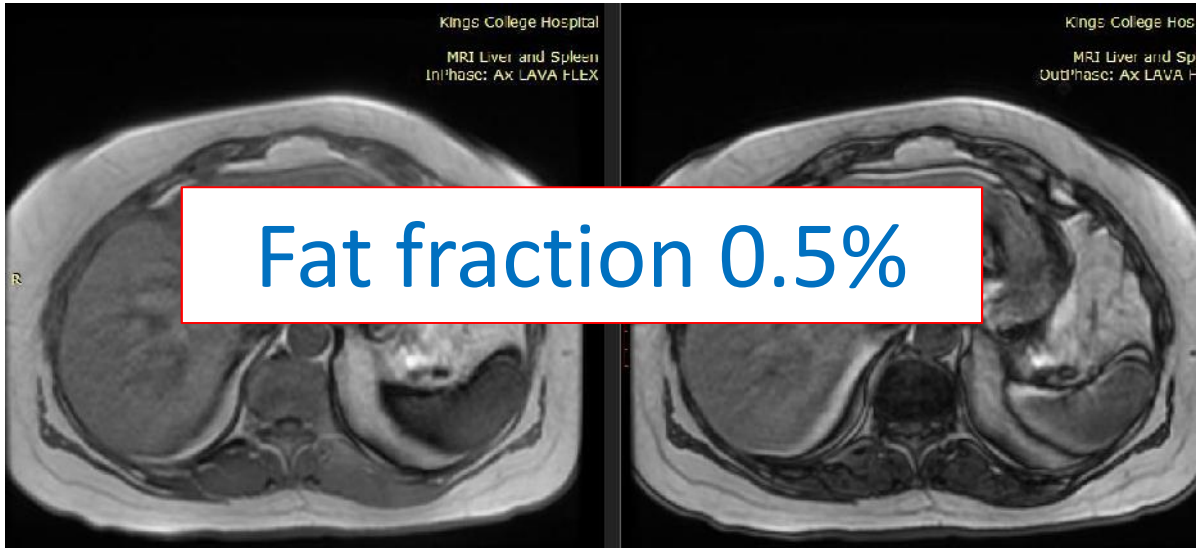


Liver fat pre- and post-MR images

Pre-endobarrier



4-months later



Liver fat – n8

Mean hepatic fat fraction fell from 15.9±9.4% to 2.9±4.5% post-endobarrier (87.5±25.2% reduction), P=0.0026

Pancreatic fat – n8

Mean pancreatic fat fraction fell from 6.9% to 1.3% post-endobarrier, P=0.02

Safety and tolerability – Barbara McGowan

- Serious adverse events
- Quality of life
- Satisfaction scores

Safety Data

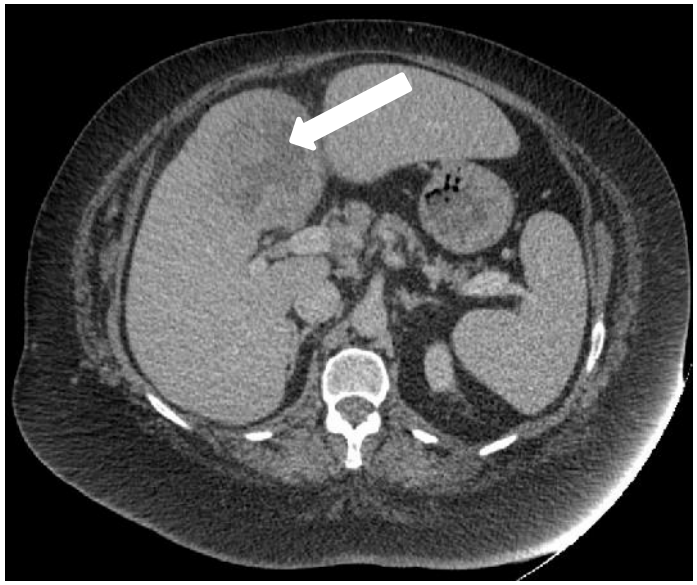
Table of Serious Adverse Events (related)

	Early removal ✓ or X	Endobarrier +liraglutide	Endobarrier	Liraglutide
Gastrointestinal symptoms	✓	3	2	---
Symptomatic cholelithiasis	✓	---	2	---
GI Bleed	✓	---	1	---
Obstruction	✓	1	1	---
Complicated removal	n/a	---	1	---
Liver abscess	X	---	2	---

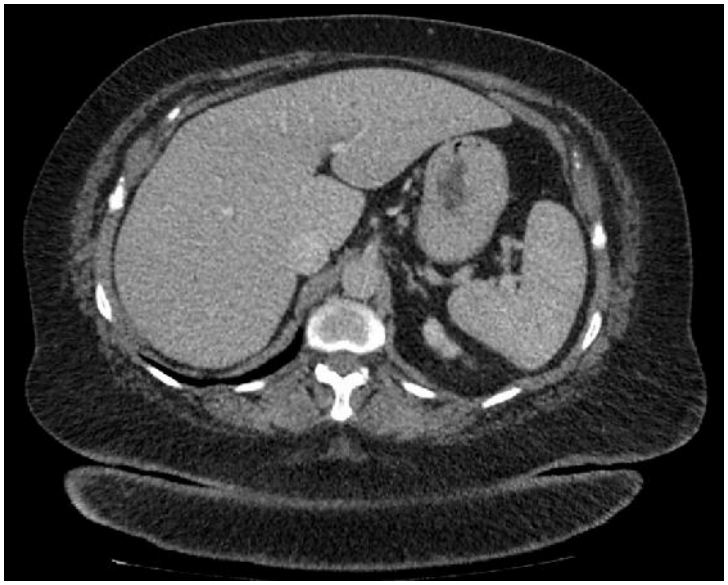
5/48 (10.4%) cases had serious complications and all had a full recovery following endobarrier removal

Liver abscess - case 1

- 51yr Caucasian female
- Base BMI 53.9kg/m^2, HbA1c 73mmol/mol (8.8%)
- 01/07/2014 – Endobarrier implant
- 6 weeks later – admitted to a local hospital while on holiday with nausea, vomiting, fevers and abdominal pain
- → Glasgow CT abdomen:



After 10 weeks antibiotics



- Attempted US-guided drainage was unsuccessful
- IV Tazocin 12 days, PO ciprofloxacin 16 weeks as she refused removal
- At 1-year Endobarrier removed – weight loss 18.9kg, HbA1c +0.9%

Liver abscess – case 2

- 48yr Afrocaribbean male
- Base BMI 44.3kg/m^2, HbA1c 67mmol/mol (8.3%)
- 30/09/2013 – Endobarrier implant
- At 1-year – DNA'd planned removal, seen at 14 months
- 10 days later – Admitted with septic shock, hyperosmolar hyperglycaemic state glucose 47.4mmol/l, Ur42, Cr348, bili 28, ALT100, AlP140, CRP 239
- 10/12/2014 CT abdomen – 13x10x12cm right lobe hepatic abscess
- Abscess drained twice – 500mls pus removed and IV then PO antibiotics
- Abscess improved
- Feb 2015 – Endobarrier removal

Liver abscesses

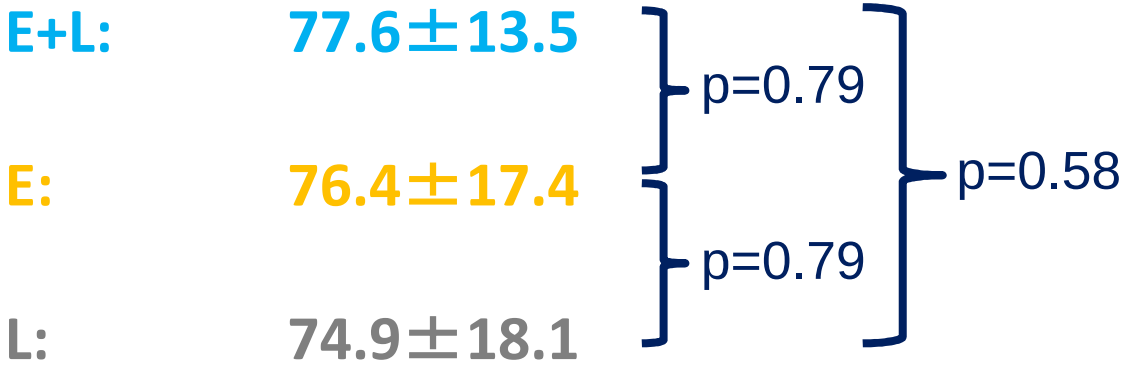
- FDA pivotal trial in USA – ENDO trial
- Design: RCT double blind, sham control, 500 patients, 25 centres
- July 2015, ENDO trial was terminated early (325/500 enrolled) due to 7 /217 (3.2%) cases of hepatic abscess (exceeded safety threshold 2%)
- Liver abscesses occurred 40-424 days after implant

- 3000 cases worldwide since 2009 – liver abscess rate ~ 0.73%

- Recommendations under consideration:
- Antibiotic cover for implant and explant procedures
- Shortened implant period (9 months)

EQ-5D quality of life – health state at 1-year

"Indicate how good or bad your health state is today in your opinion (the best state you can imagine is marked 100, the worst state you can imagine is marked 0.)"



Patient satisfaction – NHS friends and family test

"How likely would you be to recommend the treatment you have had in this research study to family and friends based on your experience?"

Very likely	*likely*	*neither likely/unlikely*	*unlikely*	*very unlikey*	*don't know*
☐	☐	☐	☐	☐	☐

E+L: **89.5%**

E: **85.7%**

L: **88.9%**

Summary

- In E+L group HbA1c fell by 22.8 mmol/mol (2.1%) from 81.5 (9.6%) to 58.7 mmol/mol (7.5%) and weight fell by 12.4 kg from 112.8kg to 100.4 kg
- Both endobarrier groups produced reduction in weight with a reduction in liver and pancreatic fat
- E+L group demonstrated a trend towards superiority with HbA1c reduction at 1-year, achieved with:
  - reduction in other diabetes medications
  - reduction in 10-year cardiovascular risk
- Safety profile is reasonable – ongoing clinical vigilance during the implant period is advised
- Patient satisfaction levels are high

Conclusion

These data suggest that adding proximal intestinal exclusion in patients with suboptimally performing GLP1-RA therapy rather than switching to it or increasing GLP-1RA dose, has a useful role in the management of refractory diabetes and obesity.

Acknowledgements

All study participants

Endoscopy team: Mark Anderson, Louise Bensaid, Ross Carter, Ed Fogden, David Galloway, Bu Hayee, Lesley Sadler

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Administration: Melissa Cull, Rosa DaCosta, Vikram Johal, Ben Stothard, Melanie Wyres

R&D: Jocelyn Bell, Sinead Collinge

Statistician: Andrew Blann

Data monitoring committee: Cliff Bailey, John McClure, Parth Narendran

Association of British Clinical Diabetologists

NIHR/ Wellcome Trust King's Clinical Research Facility