University Hospital Galway
Ospidéal na h-Ollscoile, Gaillimh
GALWAY UNIVERSITY HOSPITALS

Bariatric Medicine

"Understanding The Clinical Trials of Drugs Aimed at Diabetes and Obesity"

Dr. Francis Finucane MD FRCPI

15th June 2016

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

SCOPE
SPECIALIST CERTIFICATION OF OBESITY
PROFESSIONAL EDUCATION

Declaration of Interests:

- **Research Contracts:**
  - Novo Nordisk
- **Travel Grants/ Advisory Boards:**
  - Novo Nordisk
  - Astra Zeneca
- **Unrestricted Educational Grants:**
  - Bristol Myers Squibb
  - Sanofi Aventis
  - Eli Lilly
- **Other Grants**
  - HRB
  - IRC

Bariatric Medicine

Bariatric Medicine

Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

W. Philip T. James, M.D., D.Sc., Ian D. Caterson, M.D., Ph.D., Walmir Coutinho, M.D., D.Sc., Nick Finer, M.B., B.S.,

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 2, 2010 VOL. 363 NO. 10

	RCT Components:
P	Population
I	Intervention
C	Control
O	Outcome(s)
T	Timeframe

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	RCT Components:
P	>55, DM, CVD or Both
I	Sibutramine (after run-in)
C	Lifestyle advice
O	MACE
T	**6 years** **

58% M
n 10,744
63 years
96% white
96 kg
34 kg/m2
3.4 years
HbA1c **7.5**%

Bariatric Medicine

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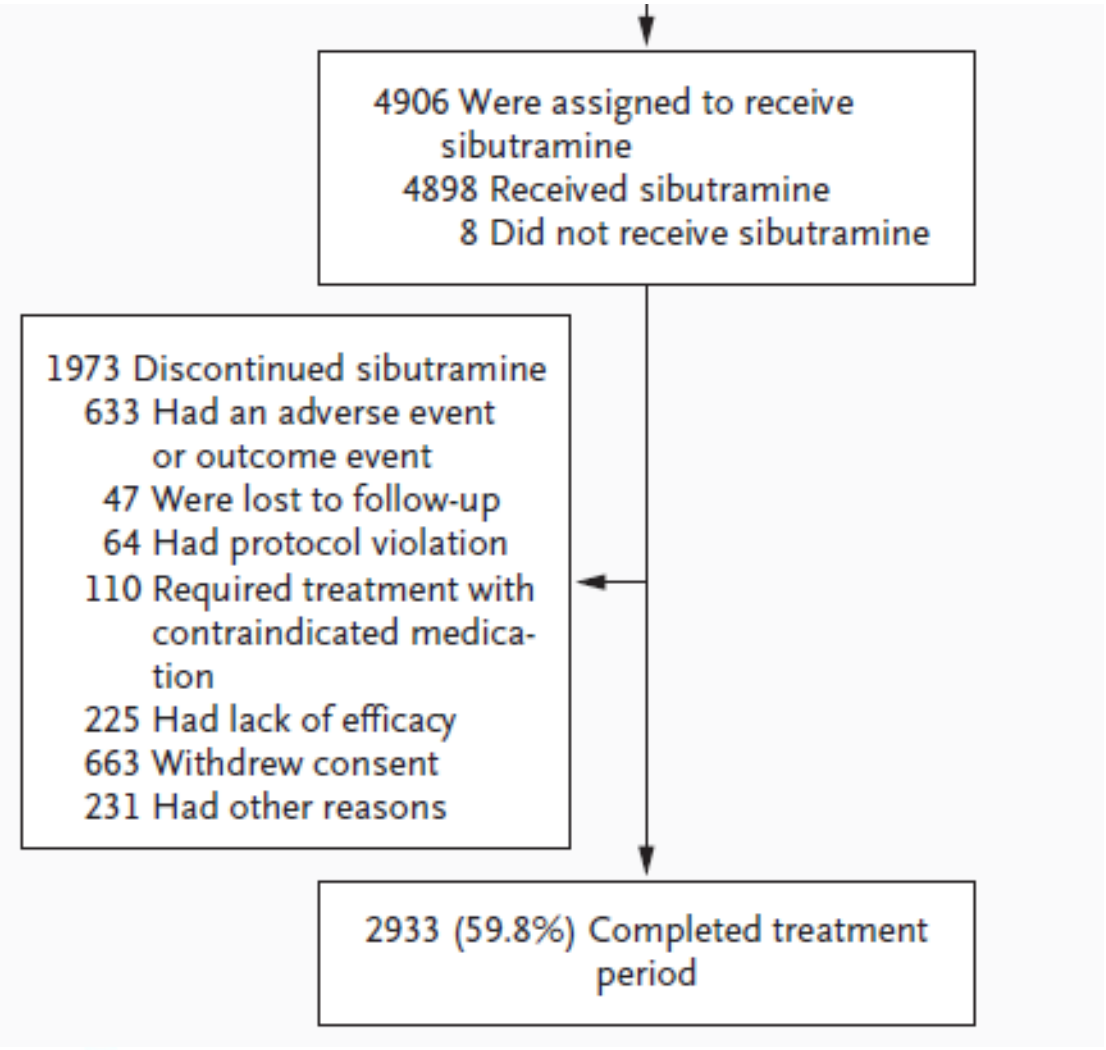

ΔWeight:

-2.6kg, then
-1.7 v. +0.7kg

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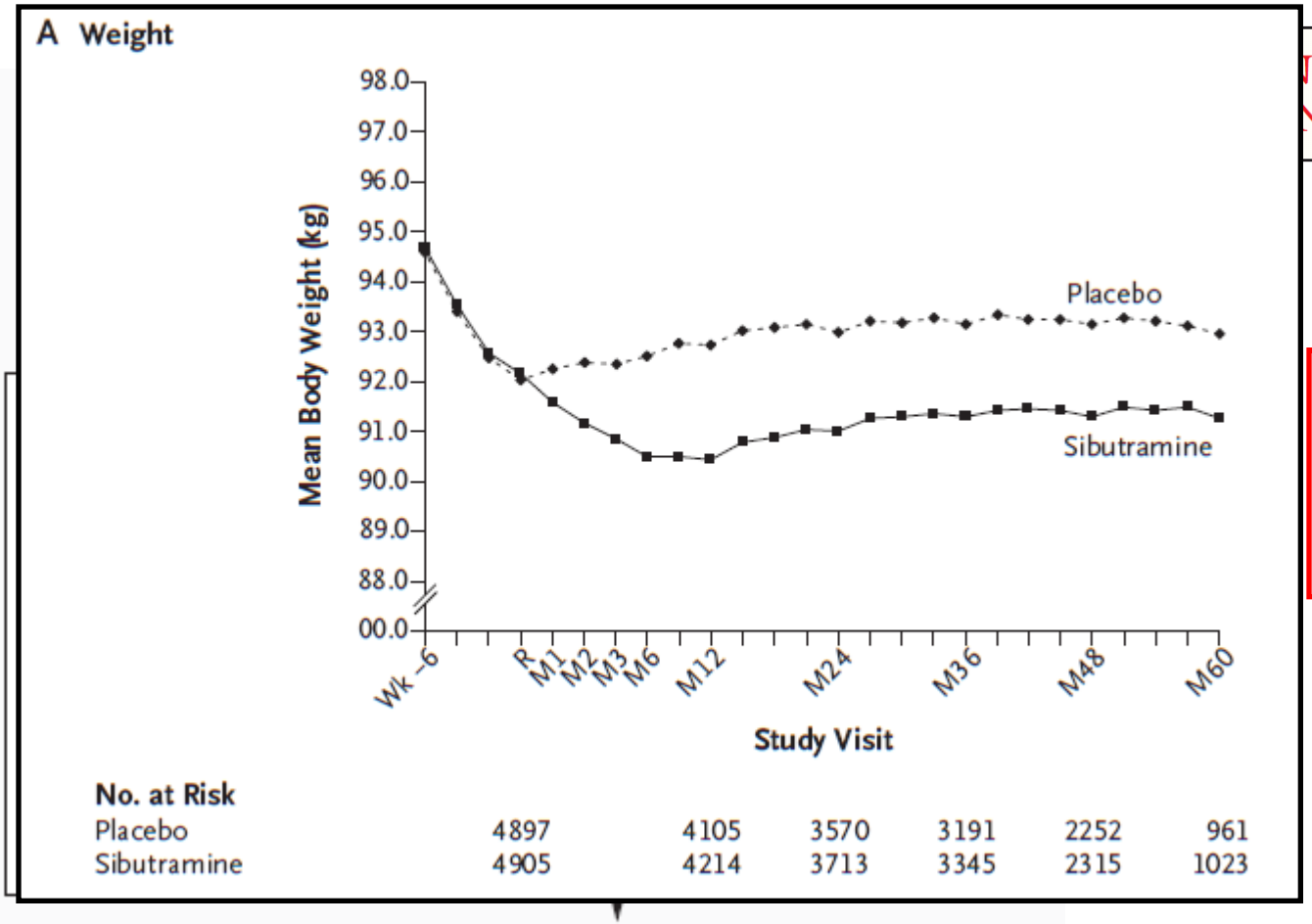

ΔWeight:

-2.6kg, then
-1.7 v. +0.7kg

2933 (59.8%) Completed treatment period

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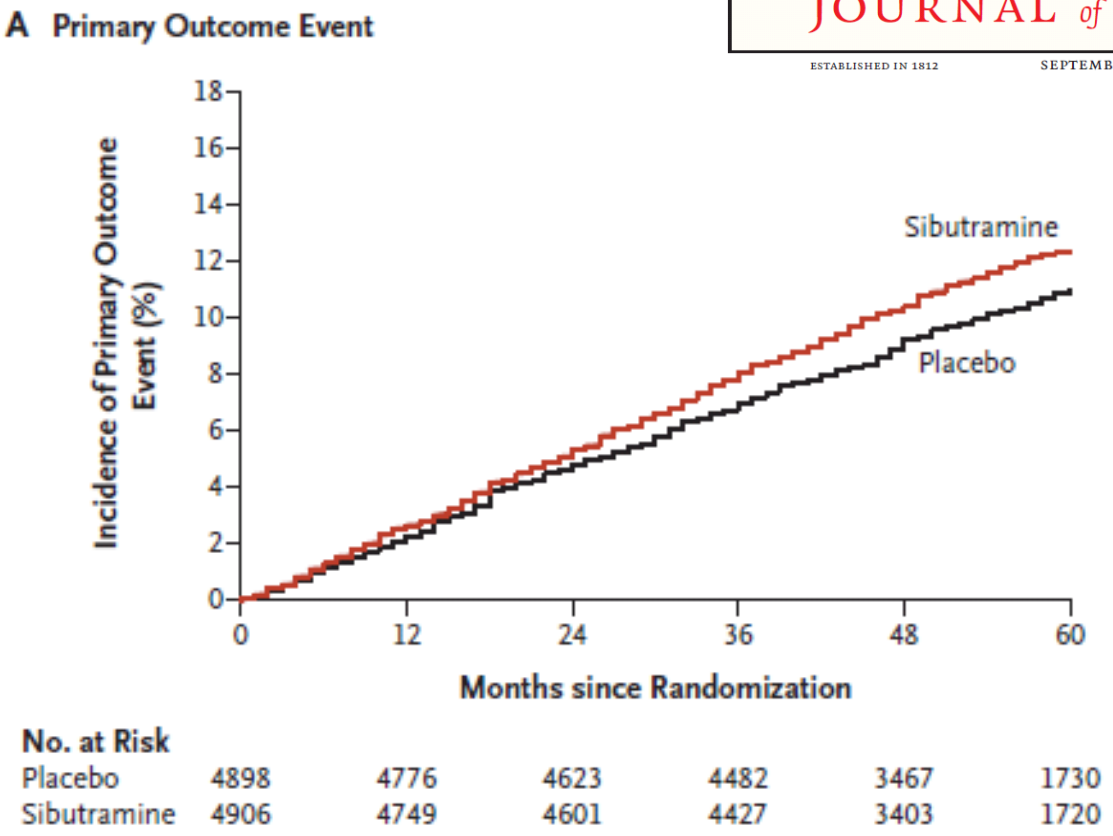

MACE:

11.4 v 10%
HR 1.16

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EDITORIALS

Sibutramine — Another Flawed Diet Pill

Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

health. But given that sibutramine has minimal efficacy for weight loss, no apparent benefit for clinical outcomes, a worrisome cardiovascular risk profile, and a plausible mechanism to explain the cardiovascular risk, it is difficult to discern a credible rationale for keeping this medication on the market.

Bariatric Medicine

Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study

André J Scheen, Nick Finer, Priscilla Hollander, Michael D Jensen, Luc F Van Gaal, for the RIO-Diabetes Study Group*

Lancet 2006; 368: 1660–72
Published Online October 27, 2006
DOI:10.1016/S0140-6736(06)69571-8

Summary

Background Rimonabant, a selective cannabinoid type 1 receptor blocker, reduces bodyweight and improves cardiovascular and metabolic risk factors in non-diabetic overweight or obese patients. The aim of the RIO-Diabetes trial was to assess the efficacy and safety of rimonabant in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylureas.

Bariatric Medicine

Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study

Rimonabant: obituary for a wonder drug

La
Publish
October
DOI:10.101
67?6/06

th type 2 diabetes that was

The story of rimonabant might be tarnished by low public and regulatory acceptance for a drug designed to counteract the consequences of our abundant lifestyle. Focus should now return to motivating patients to control their caloric intake and increase physical activity. Although cumbersome, this approach is causal and safe.[9] New strategies to more effectively achieve these lifestyle changes are needed.

*S Matthijs Boekholdt, Ron J G Peters

Bariatric Medicine

PAFTT!

Push away from the table

JELEM!

Just eat less and exercise more

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

N=5145
BMI 36
63% White
60% female
A1c 7.3%

	RCT Components:
P	Adult T2DM, BMI >25
I	Weekly counselling. “7%”
C	Support/ education “ELEM”
O	MACE
T	9.6 years

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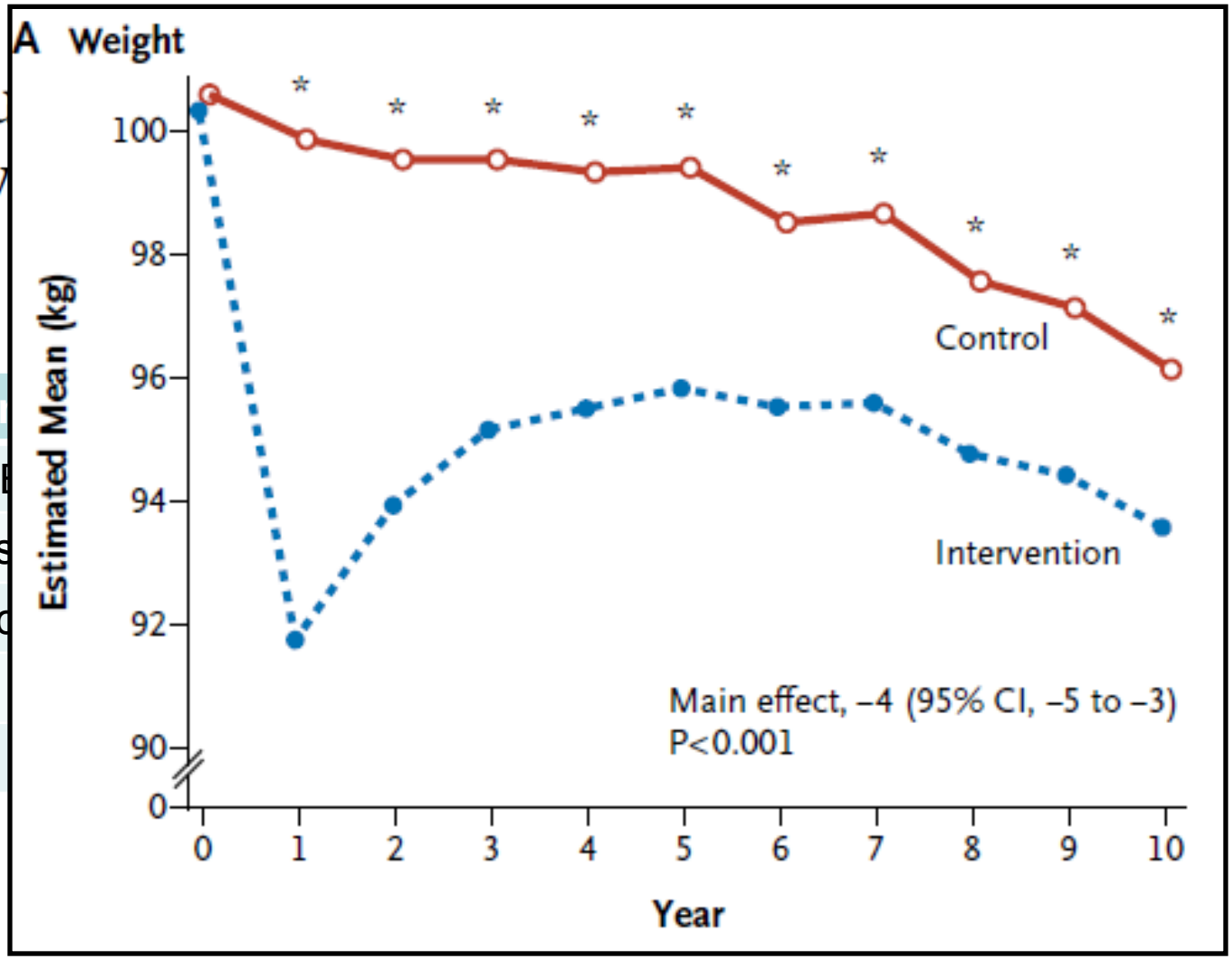
ORIGINAL ARTICLE

Cardiovascu
Interv

	RCT Compor
P	Adult T2DM,
I	Weekly couns
C	Support/ educ
O	MACE
T	9.6 years



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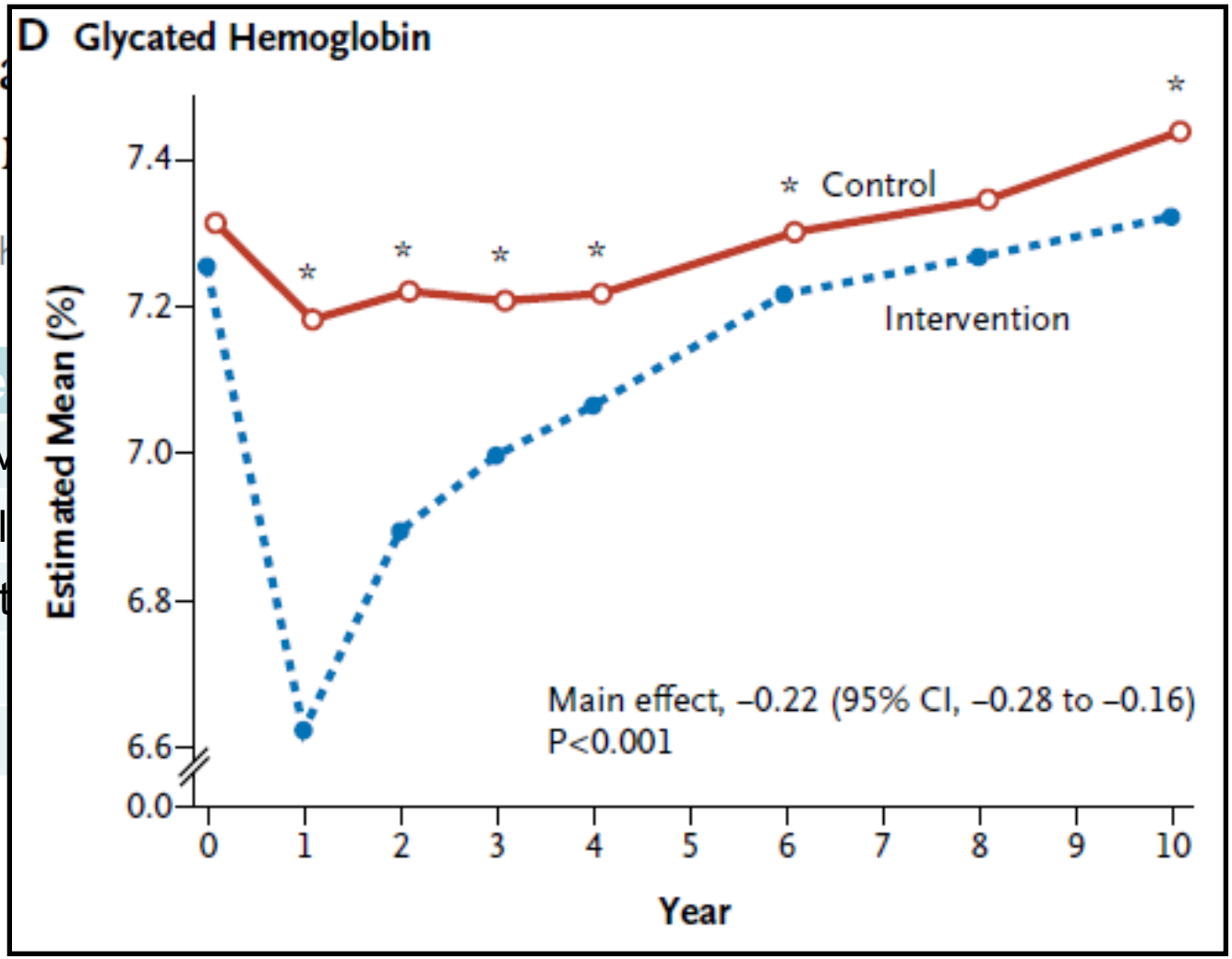
ORIGINAL ARTICLE

Cardiovascula
Interve

Th

	RCT Compone
P	Adult T2DM, BM
I	Weekly counsel
C	Support/ educat
O	MACE
T	9.6 years



Cardiovascular
Interventi

The L

	RCT Components
P	Adult T2DM, BMI >
I	Weekly counselling
C	Support/ education
O	MACE
T	9.6 years

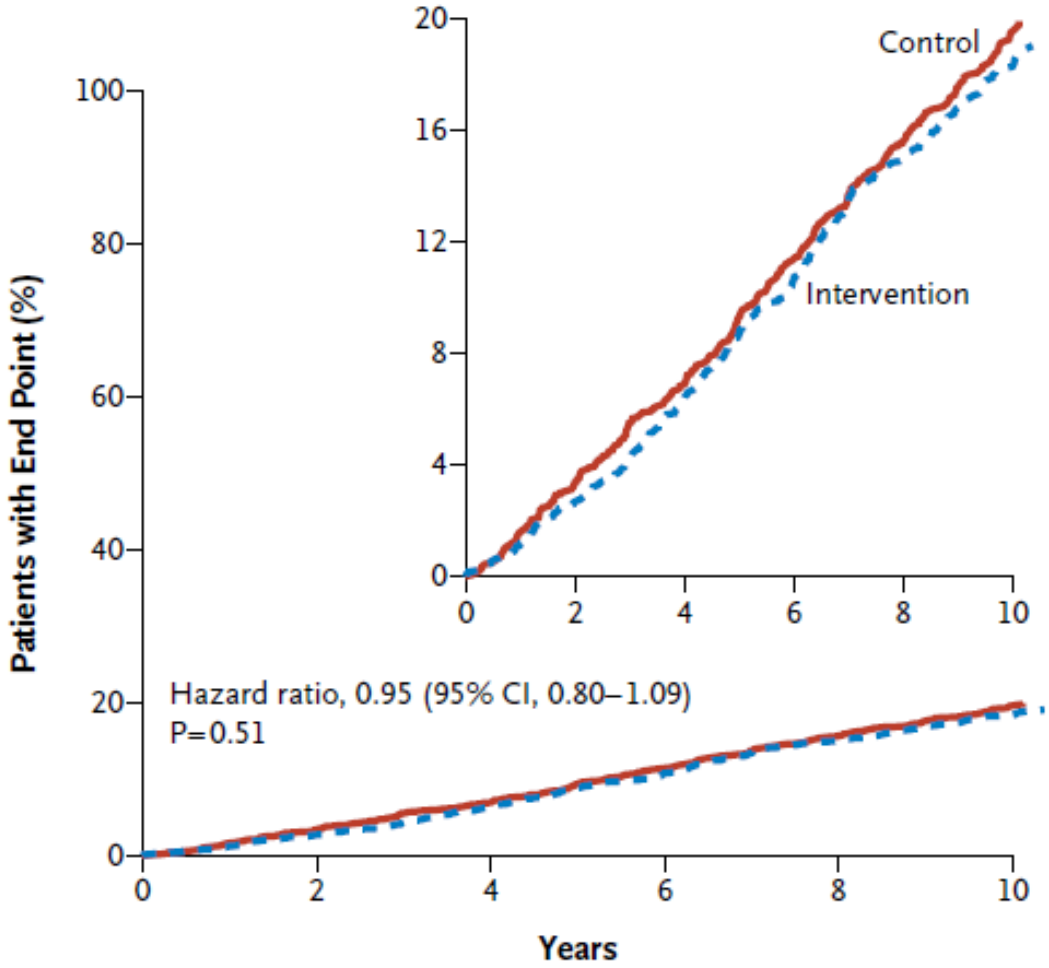


Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.

BMJ

BMJ 2014;348:g2646 doi: 10.1136/bmj.g2646 (Published 14 May 2014)

Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials

OPEN ACCESS

S U Dombrowski *lecturer in health psychology*[1 2], K Knittle *health psychology research associate*[1 3],

45 studies:

10 had robust allocation concealment
17 described some form of blinding
25 handled incomplete data well

Bariatric Medicine

British Journal of Nutrition (2013), **110**, 1178–1187
© The Authors 2013

Very-low-carbohydrate ketogenic diet *v.* low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

Nassib Bezerra Bueno*, Ingrid Sofia Vieira de Melo, Suzana Lima de Oliveira and Terezinha da Rocha Ataide

Table 2. Risk of bias of the included studies

Source	Sequence generation	Allocation concealment	Blinding	Missing data	Selective report	Overall
Brinkworth *et al.*[28]	Low	High	Unclear	Low	Low	High
Dansinger *et al.*[50]	Low	Low	Low	Low	Low	Low
Davis *et al.*[51]	Low	High	Unclear	Low	Low	High
Dyson *et al.*[52]	Low	Low	Low	High	Low	Low
Foster *et al.*[53]	Low	Unclear	Unclear	Low	Low	Low
Foster *et al.*[27]	Low	Unclear	Unclear	Low	Low	Low
Gardner *et al.*[30]	Low	Low	Low	Low	Low	Low
Iqbal *et al.*[29]	Low	Unclear	Unclear	Low	Low	Low
Lim *et al.*[54]	Unclear	Unclear	Unclear	High	Low	High
McAuley *et al.*[55]	Low	Low	Unclear	High	Low	Low
Shai *et al.*[49]	Low	Unclear	Low	Low	Low	Low
Stern *et al.*[26]	Low	Unclear	Unclear	Low	Low	Low
Truby *et al.*[56]	Low	Unclear	High	High	Low	High

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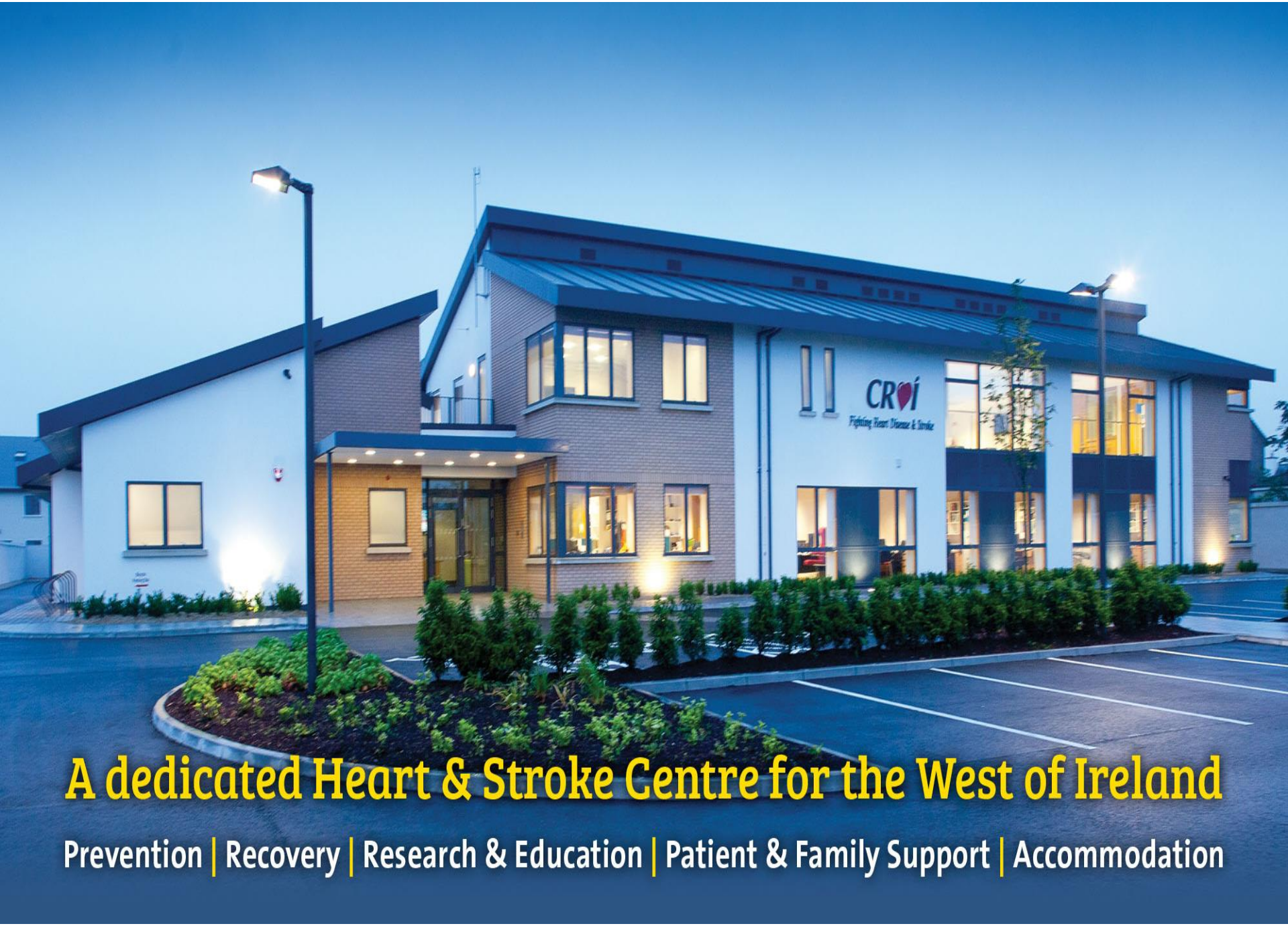
CROÍ
Fighting Heart Disease & Stroke
A dedicated Heart & Stroke Centre for the West of Ireland
Prevention | Recovery | Research & Education | Patient & Family Support | Accommodation

MyAction: an innovative approa to the prevention of cardiovascu disease in the community

The CRÍ CLANN Programme

Change your Lifestyle with Activity and Nutrition

Crowe *et al. BMC Endocrine Disorders* (2015) 15:37
DOI 10.1186/s12902-015-0038-x

BMC Endocrine Disorders

RESEARCH ARTICLE Open Access

Effects of an eight-week supervised, structured lifestyle modification programme on anthropometric, metabolic and cardiovascular risk factors in severely obese adults

Catherine Crowe[1], Irene Gibson[2], Katie Cunningham[1,2], Claire Kerins[2], Caroline Costello[2], Jane Windle[2], Paula M. O'Shea[3], Mary Hynes[1,4], Brian McGuire[4], Katriona Kilkelly[1], Helena Griffin[1], Tim O'Brien[1,5], Jenni Jones[5,6] and Francis M Finucane[1,5*]

Mechanisms of Diabetes Improvement Following Bariatric/Metabolic Surgery

Rachel L. Batterham[1,2,3]
David E. Cummings[4]

Diabetes Care 2016;39:893–901 | DOI: 10.2337/dc16-0145

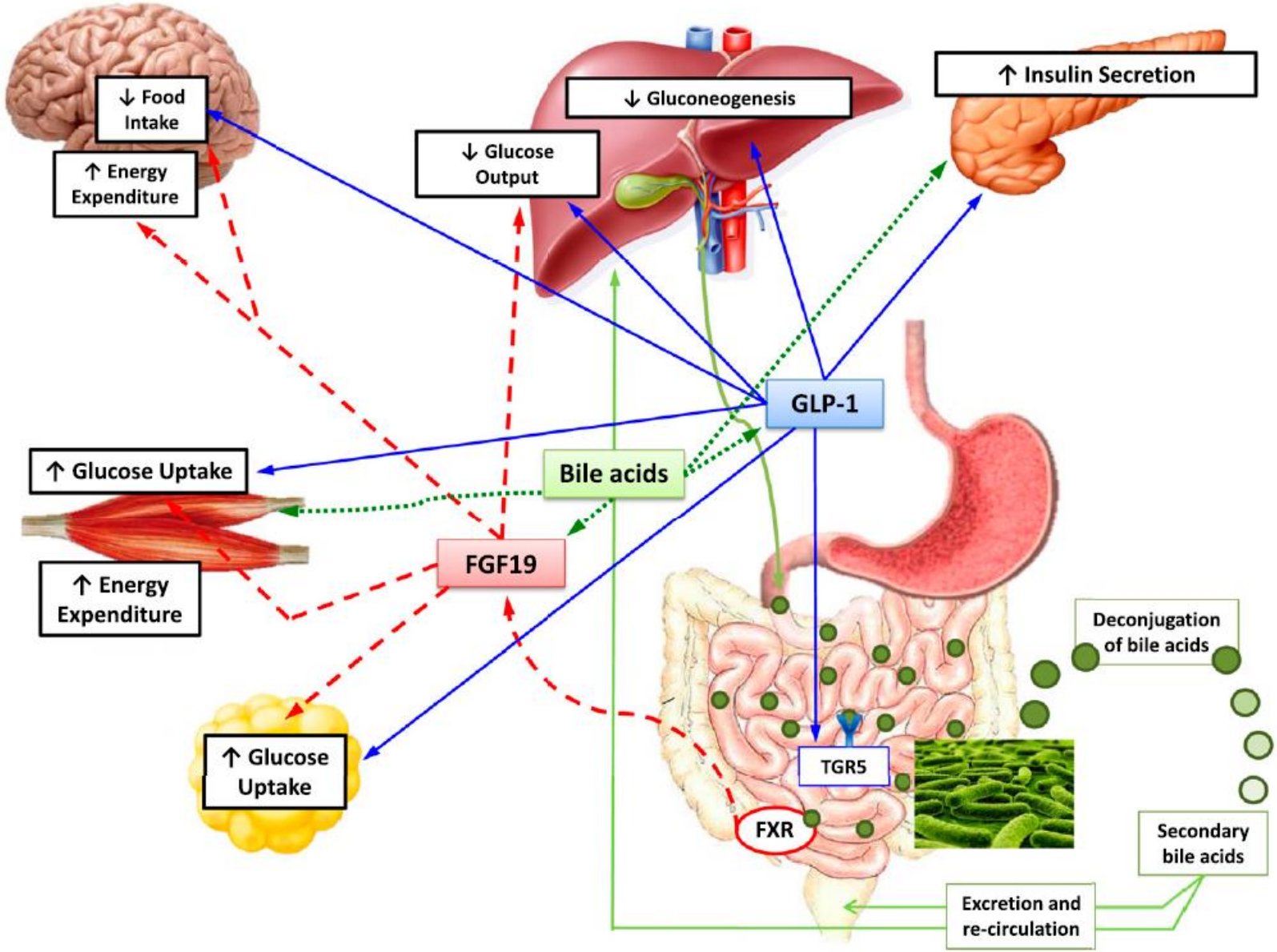

Figure 2—Diagram of some of the metabolic effects and cross talk among BAs, GLP-1, and FGF-19.

5% weight loss at 1 year:

- ***Khera et al, 2016***
- 28 trials
- N=29,018
- 46 y
- 74% female
- Wt=100.5kg
- BMI=36.1kg/m2
- Drop out 30-45%

JAMA®
The Journal of the American Medical Association

Bariatric Medicine

5% weight loss at 1 year:

JAMA® The Journal of the American Medical Association

Drug	%>5%	OR	Δ Weight	OR D/C
Placebo	23	-	-	-
Phentermine Topiramate	75	9.22	8.8	-
Liraglutide	63	5.54	5.3	2.95
Naltrexone Bupropion	55	3.96	5.0	2.63
Lorcaserin	49	3.1	3.2	-
Orlistat	44	2.7	2.6	-

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

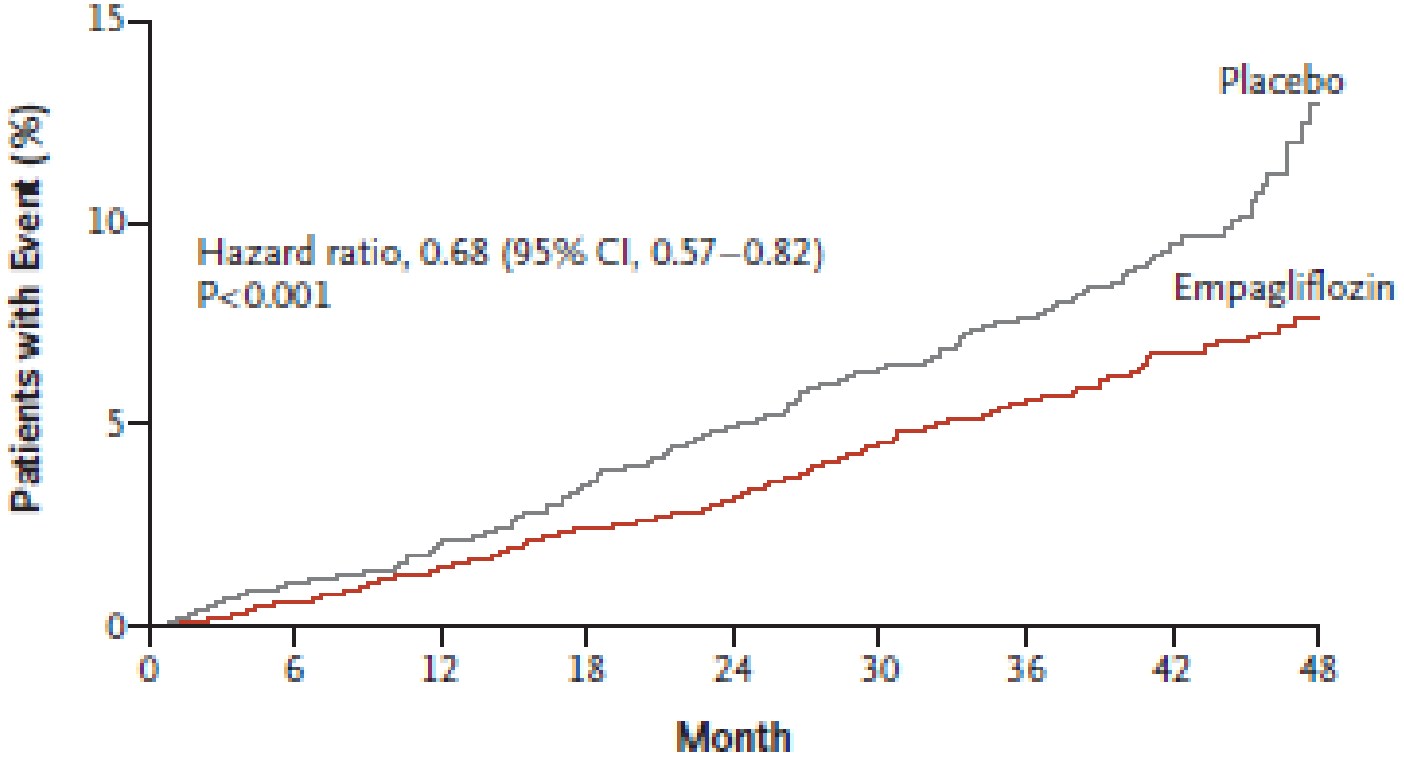
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Bariatric Medicine

ORIGINAL ARTICLE

C Death from Any Cause



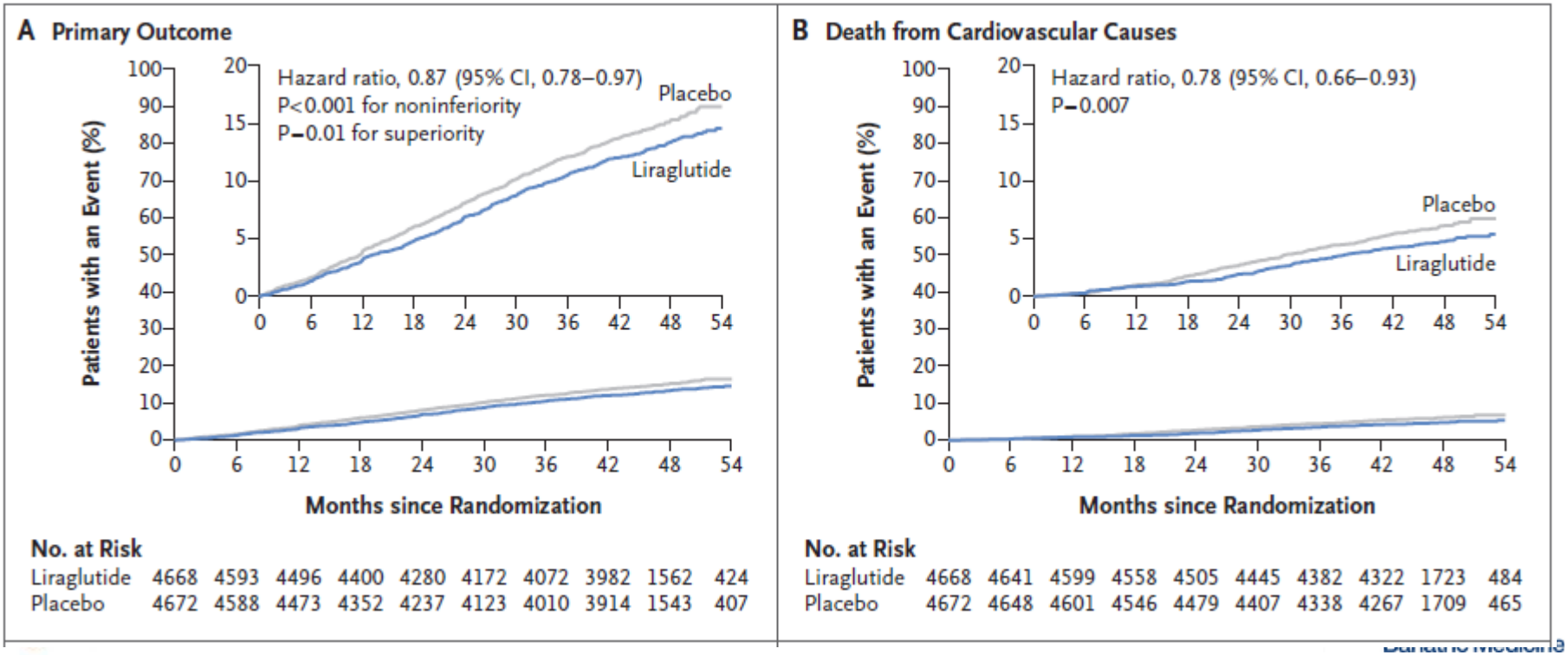
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

The NEW ENGLAND JOURNAL of MEDICINE

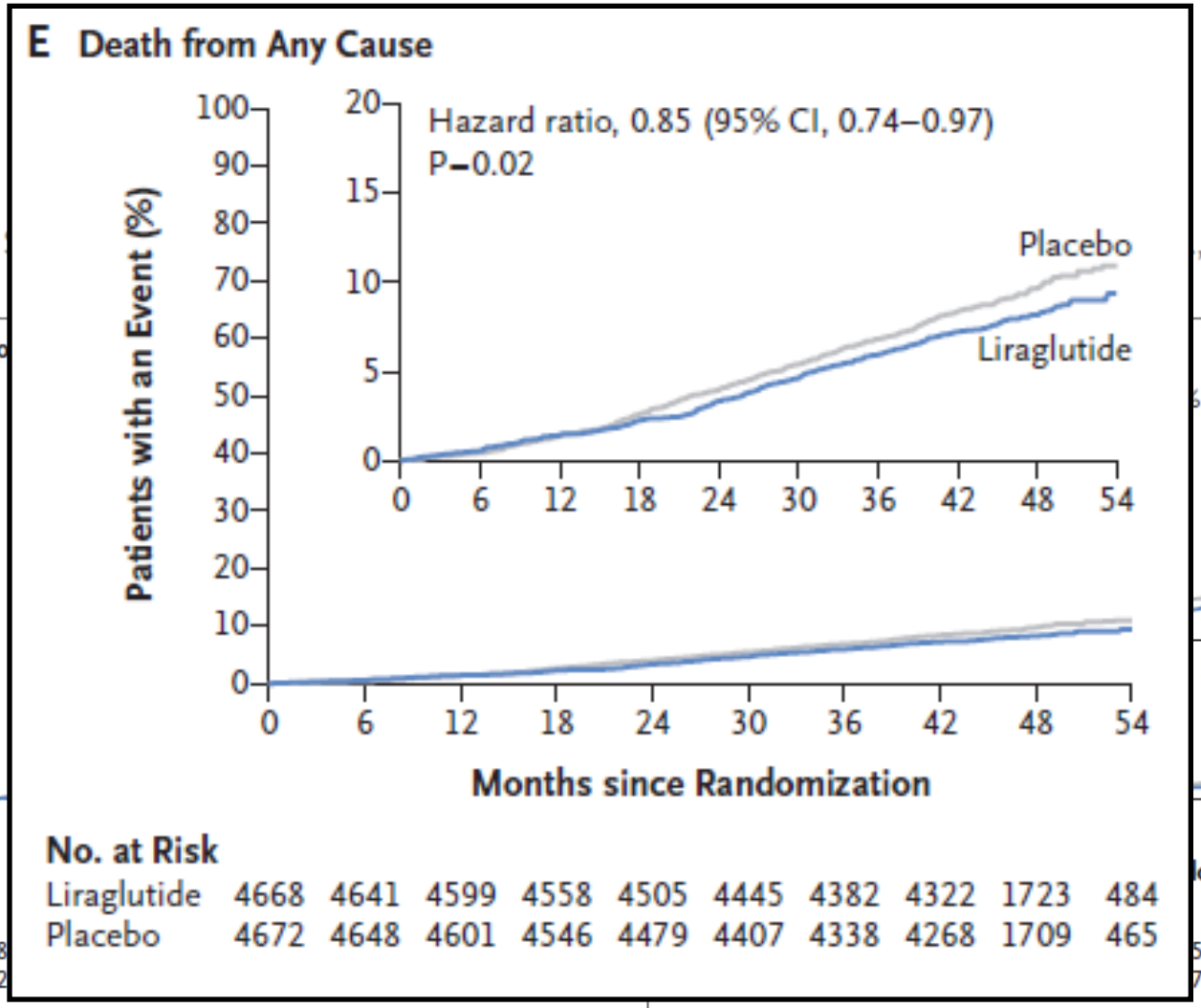
ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D.,



ORIGINAL ARTICLE



Original Investigation

Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial

Melanie J. Davies, MD; Richard Bergenstal, MD; Bruce Bode, MD; Robert F. Kushner, MD; Andrew Lewin, MD; Trine Vang Skjøth, MD; Arne Haahr Andreasen, MSc; Christine Bjørn Jensen, MD; Ralph A. DeFronzo, MD; for the NN8022-1922 Study Group

JAMA®
The Journal of the American Medical Association

	RCT Components:
P	T2DM, BMI >27, HbA1c 7-10%
I	Liraglutide 1.8 or 3.0 mg
C	Placebo (all got lifestyle advice)
O	%Δ Weight, how many at -5%, -10%?
T	56 weeks

M:F 1:1, n 846
55 years
84% white
106 kg
37 kg/m2
85% obese
55% 'bariatric'
HbA1c 8%
T2DM x 7 yr
70% ↑BP
70% ↑Lipids

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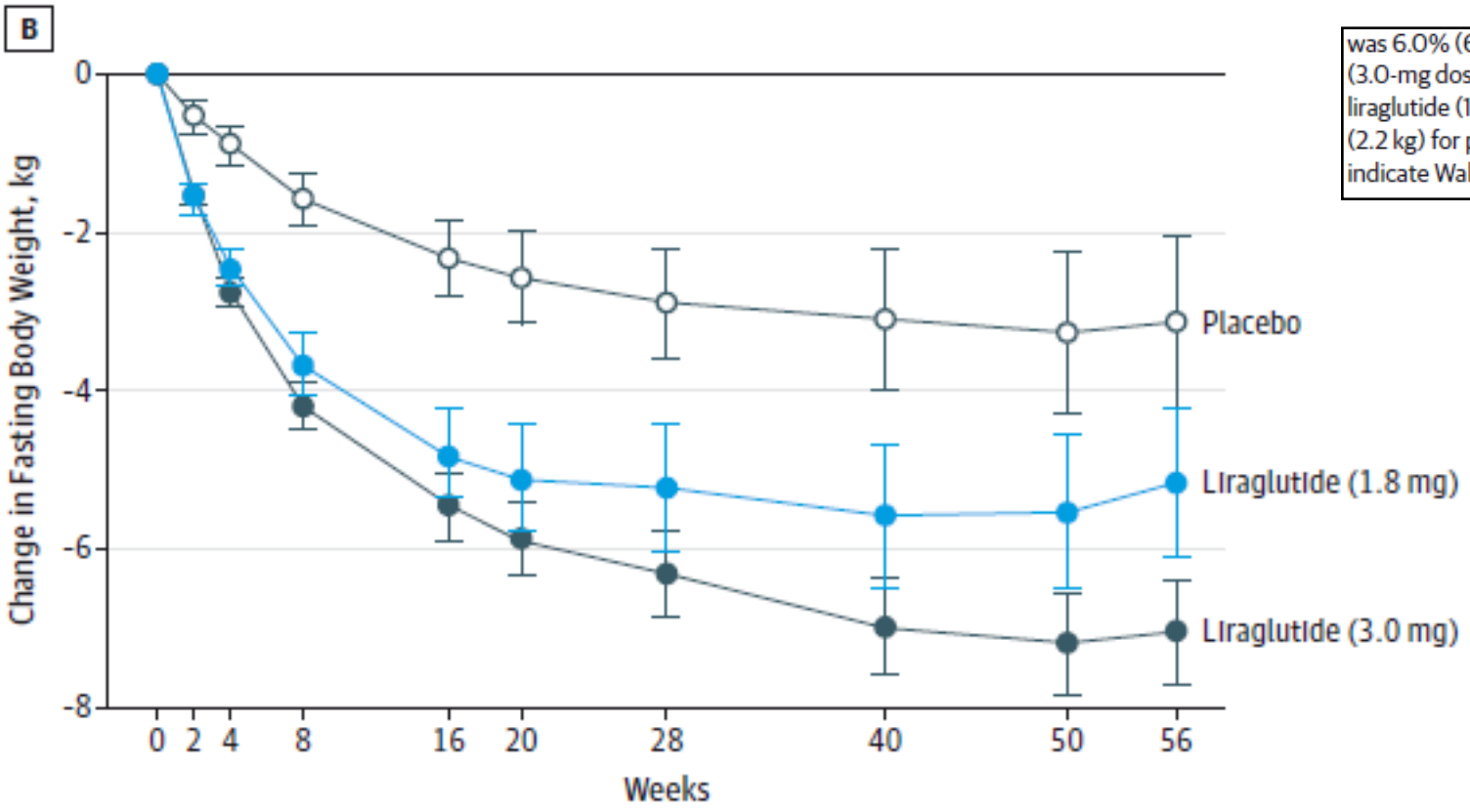
Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial

Figure 2. Time Course of Body Weight Loss From Baseline to Week 56 for Liraglutide (3.0 mg), Liraglutide (1.8 mg), and Placebo



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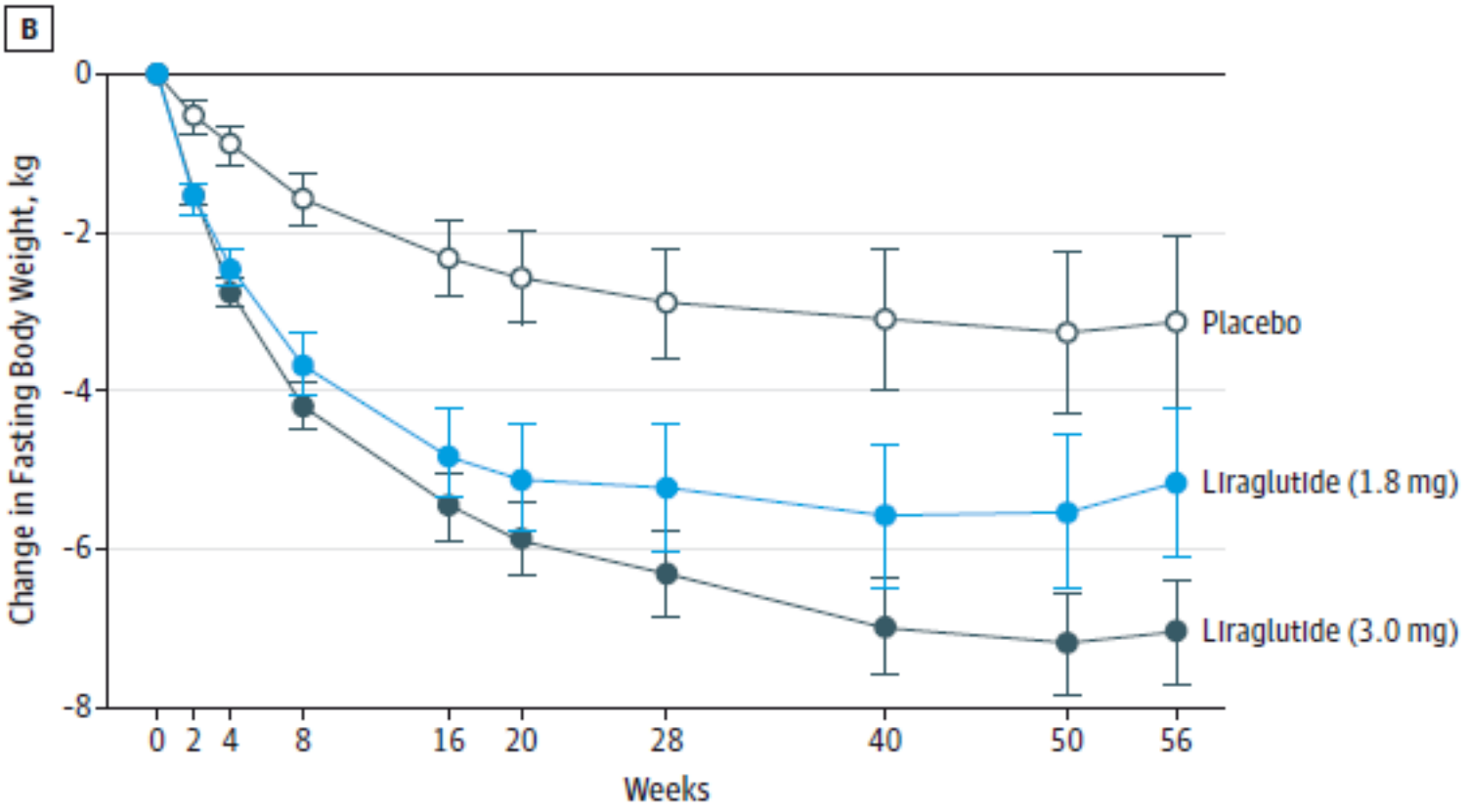

Δ5%:
21.4%
40.4%
54.3%

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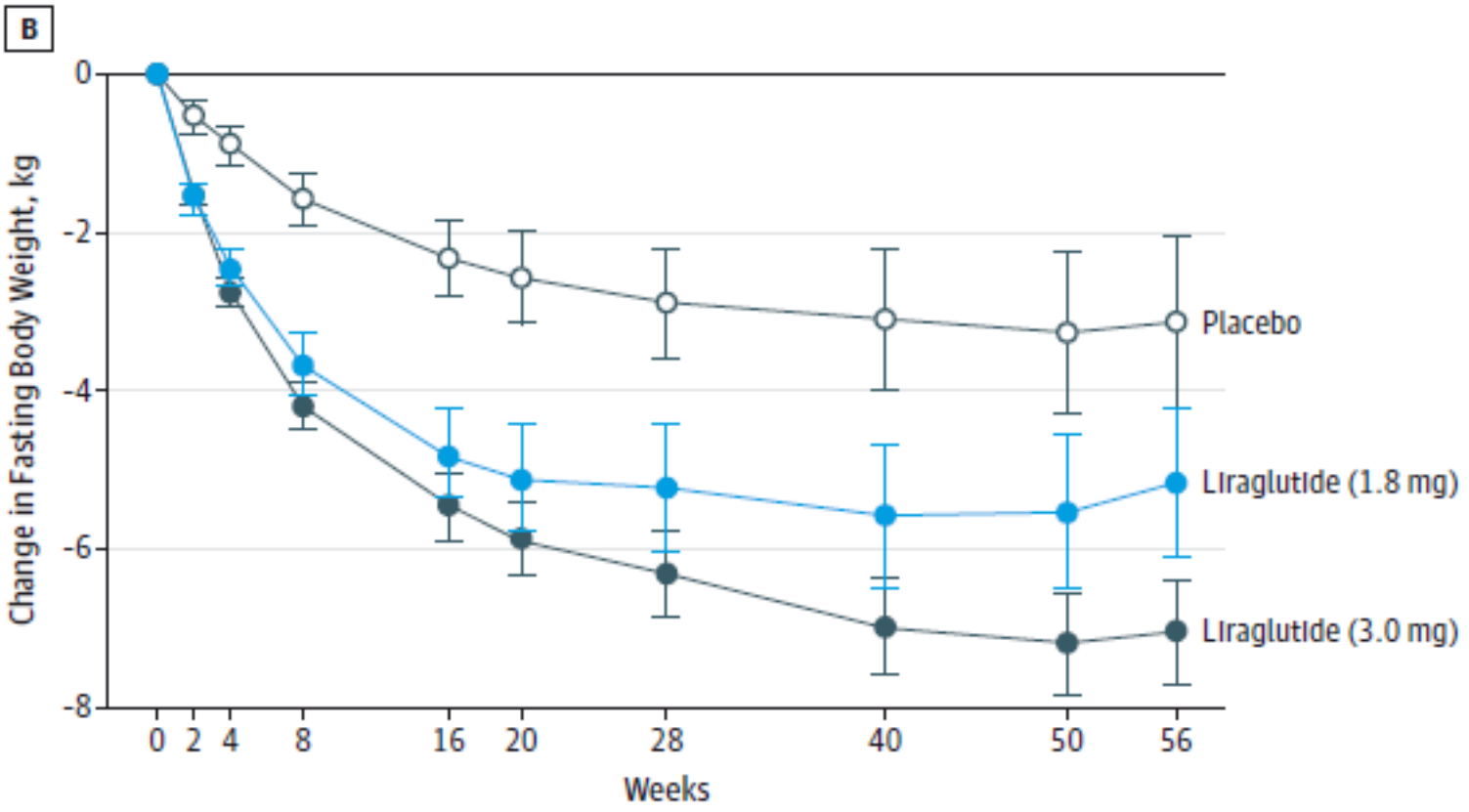

Δ10%:
6.7%
15.9%
25.2%

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The NEW ENGLAND JOURNAL of MEDICINE

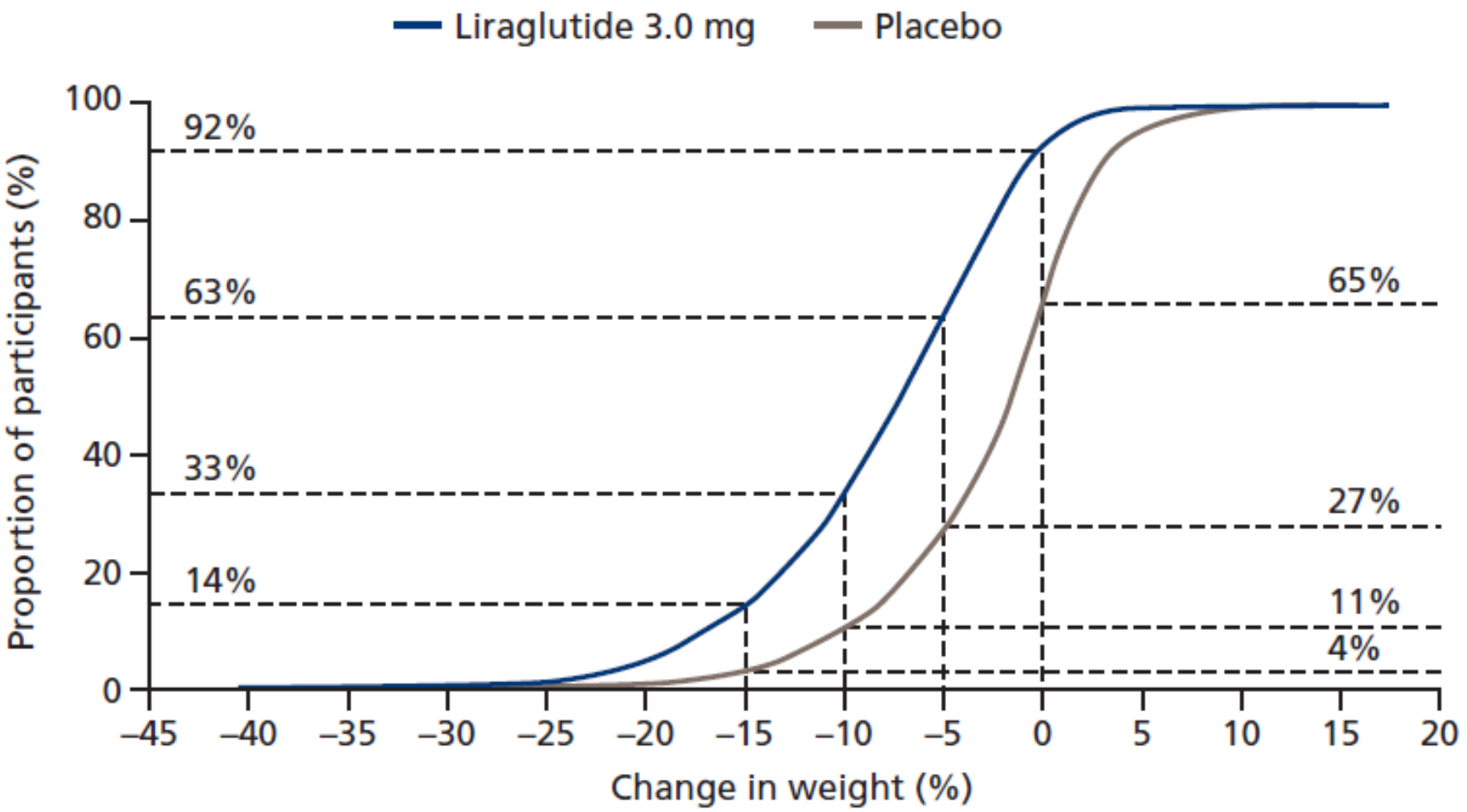
ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, M.D., Arne Astrup, M.D., D.M.Sc., Ken Fujioka, M.D., Frank Greenway, M.D., Alfredo Halpern, M.D., Michel Krempf, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carel W. le Roux, F.R.C.P., Ph.D., Rafael Violante Ortiz, M.D., Christine Bjørn Jensen, M.D., Ph.D., and John P.H. Wilding, D.M., for the SCALE Obesity and Prediabetes NN8022-1839 Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

Figure 1 Distribution of weight loss for all participants at Week 56.



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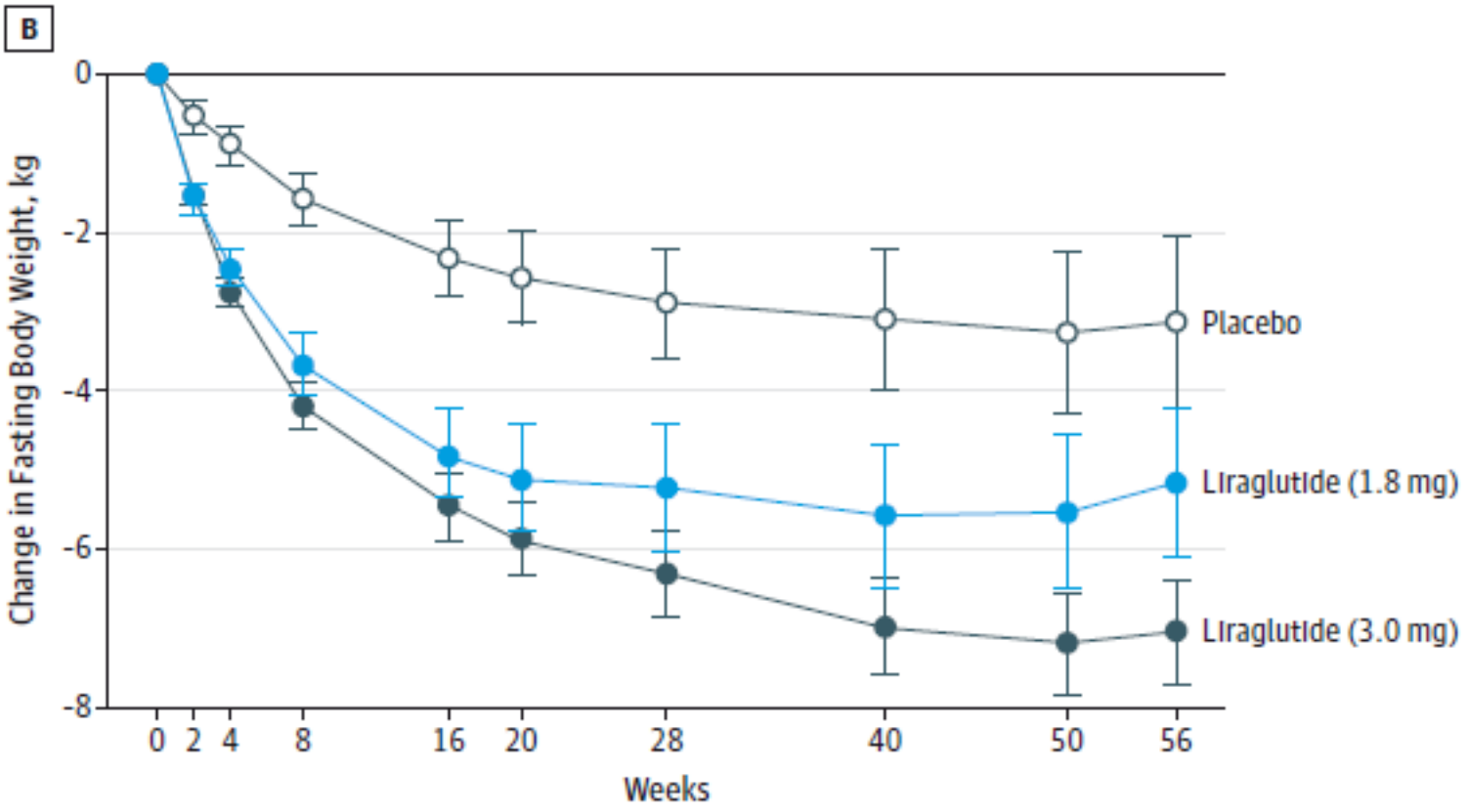

A1c<6.5%
15%
46%
57%

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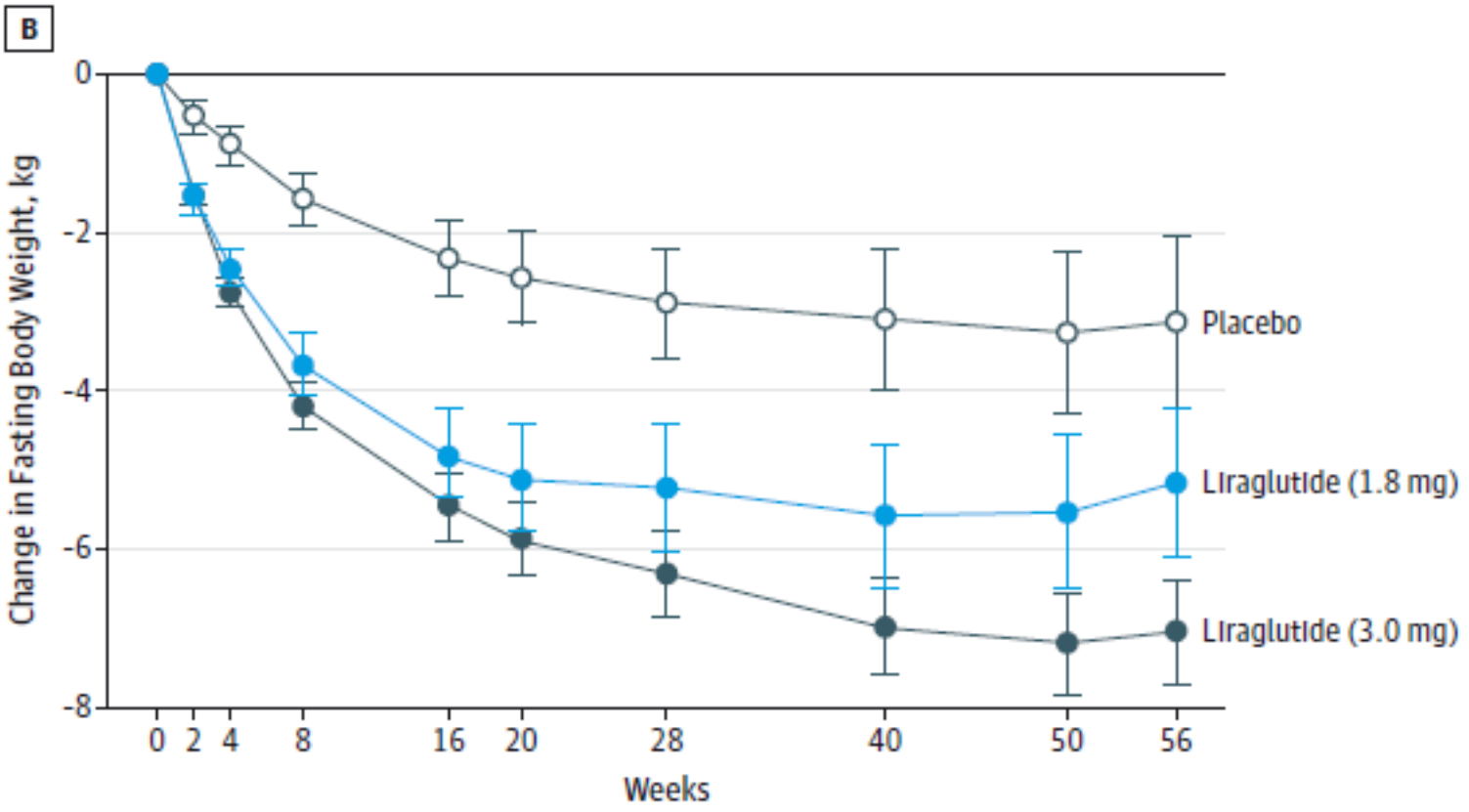

New OHA

27%

9.3%

5.1%

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Original Investigation

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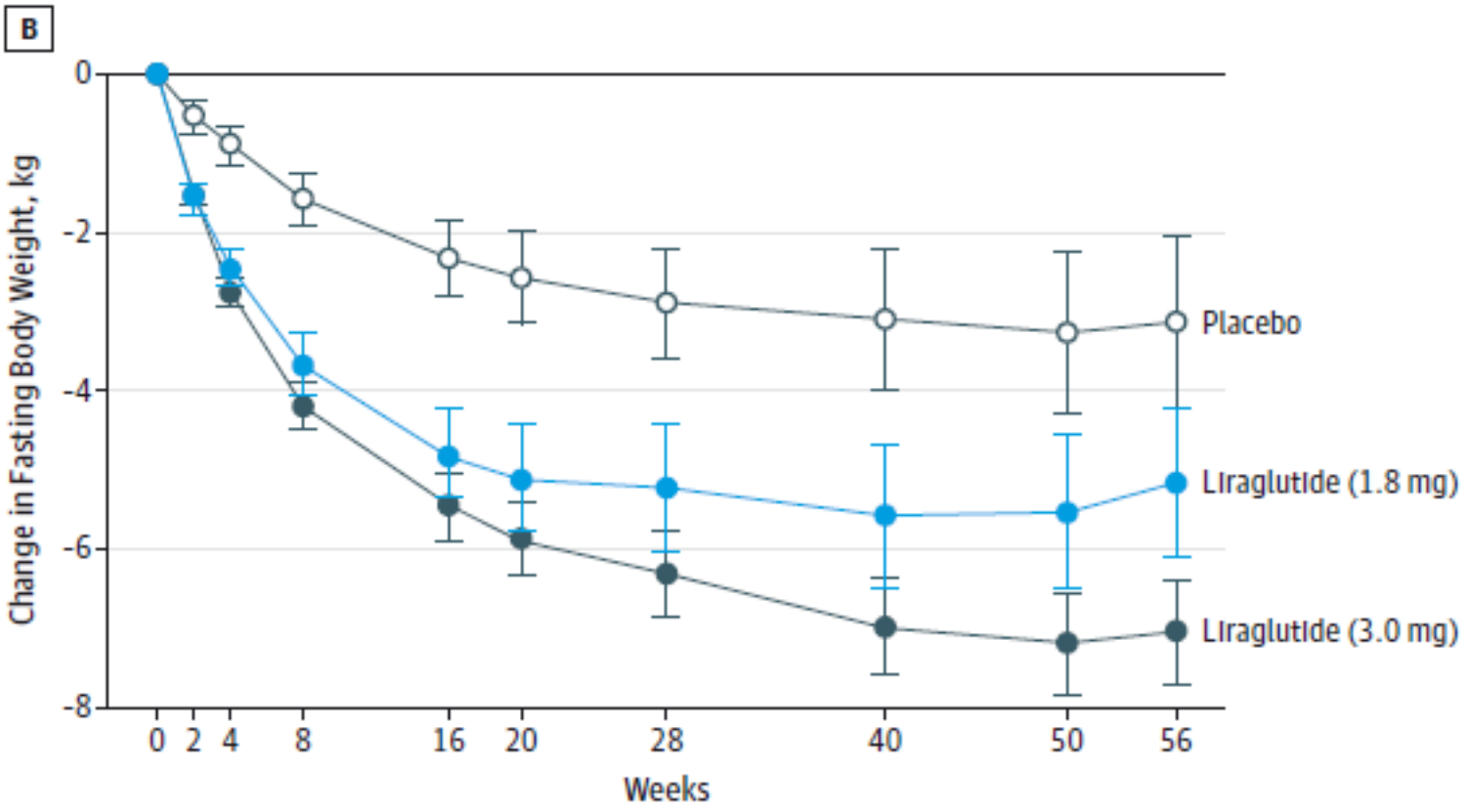

Nausea
(/100 py)

19

44

55

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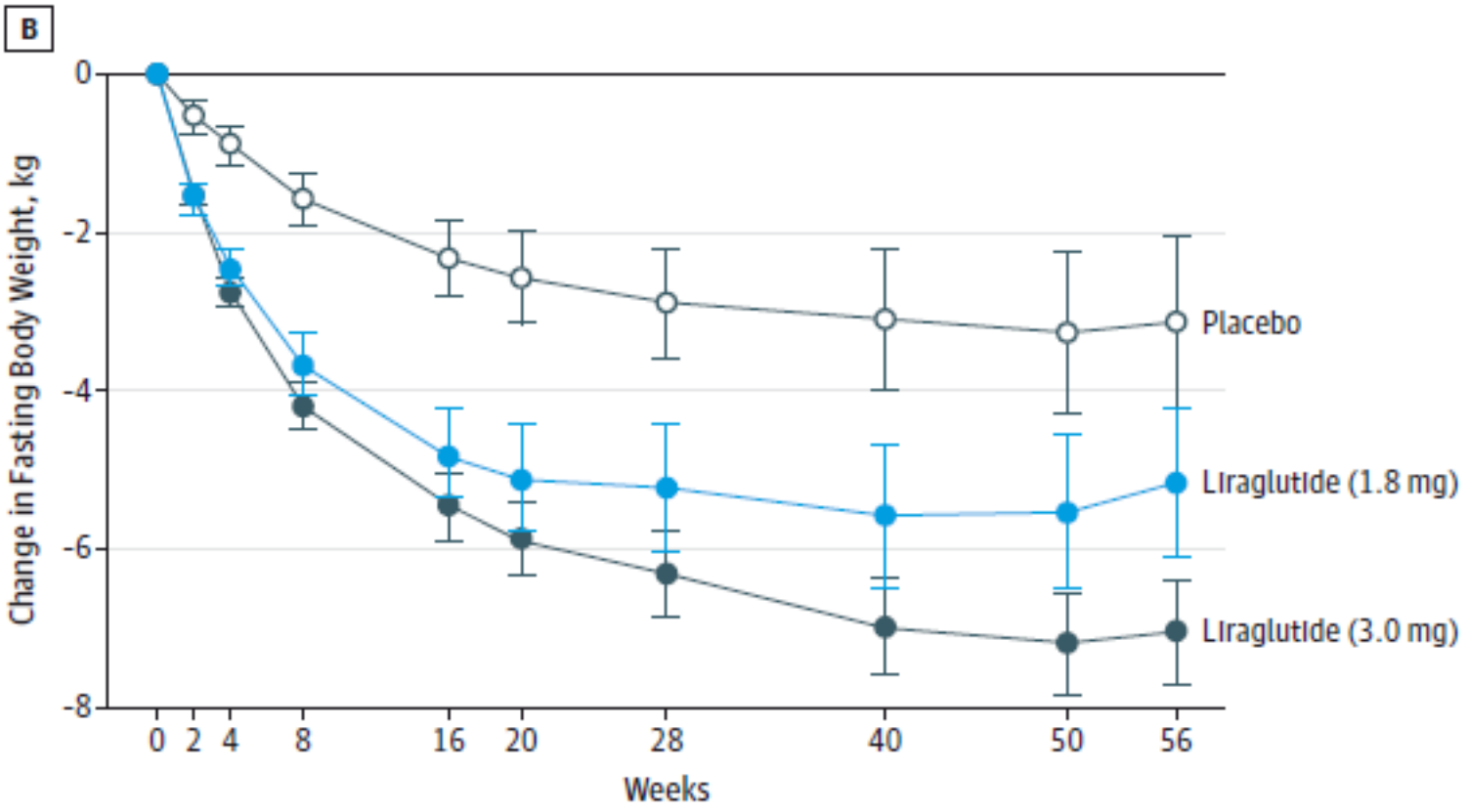

Vomiting
(/100 py)

8

14

30

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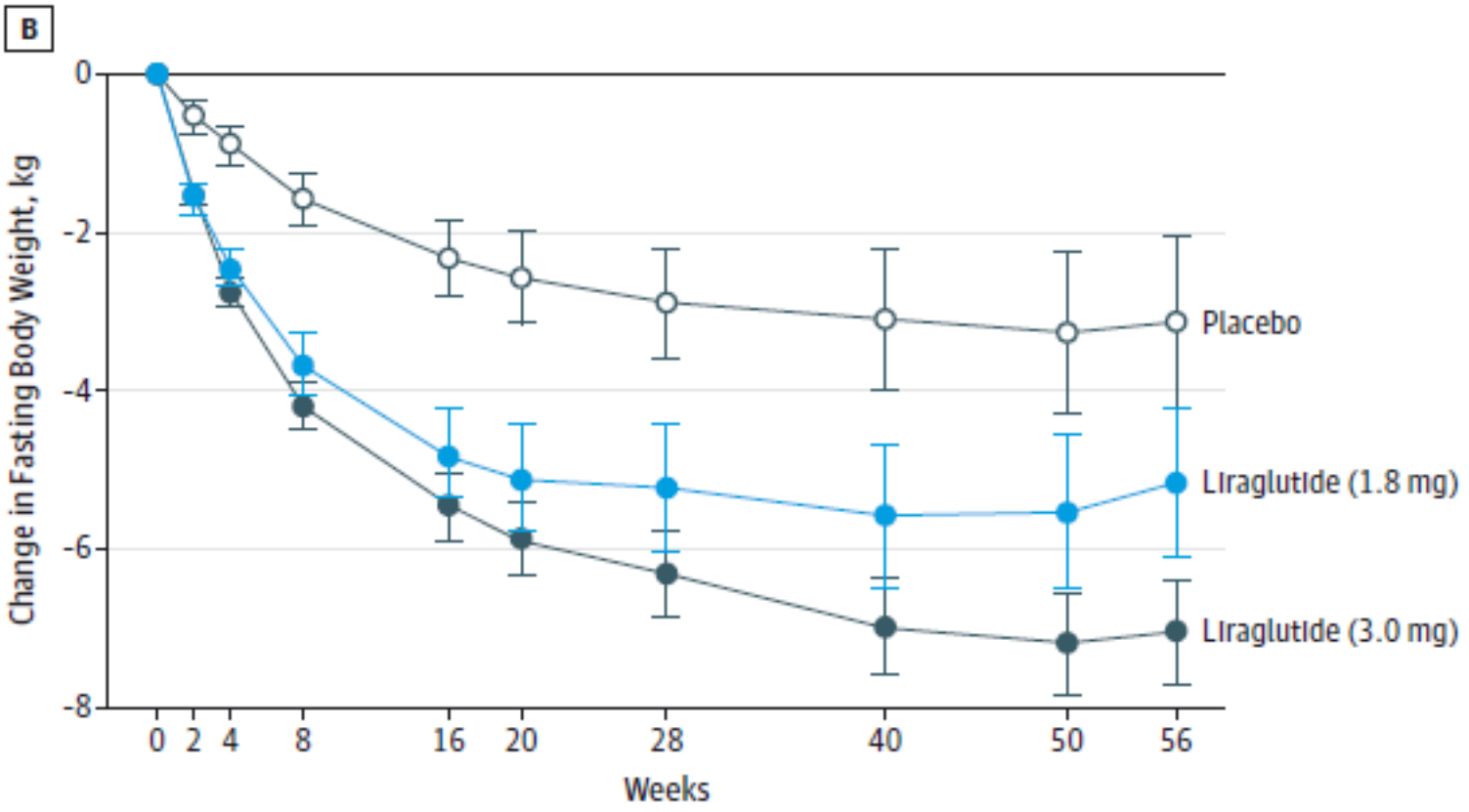

Diarrhoea (/100 py)
19
26
46

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Original Investigation

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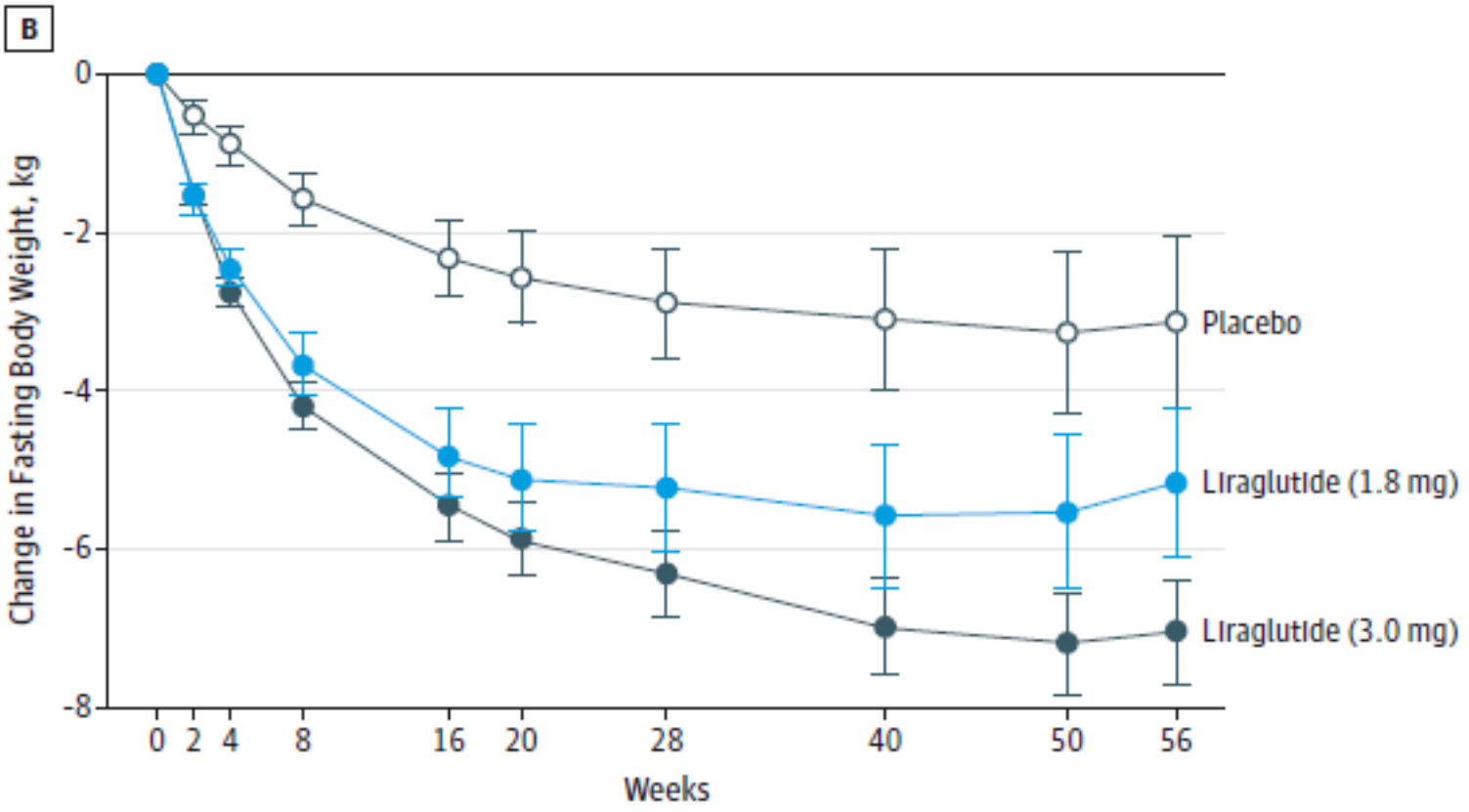

Constipation
(/100 py)

8

13

21

Bariatric Medicine

Original Investigation

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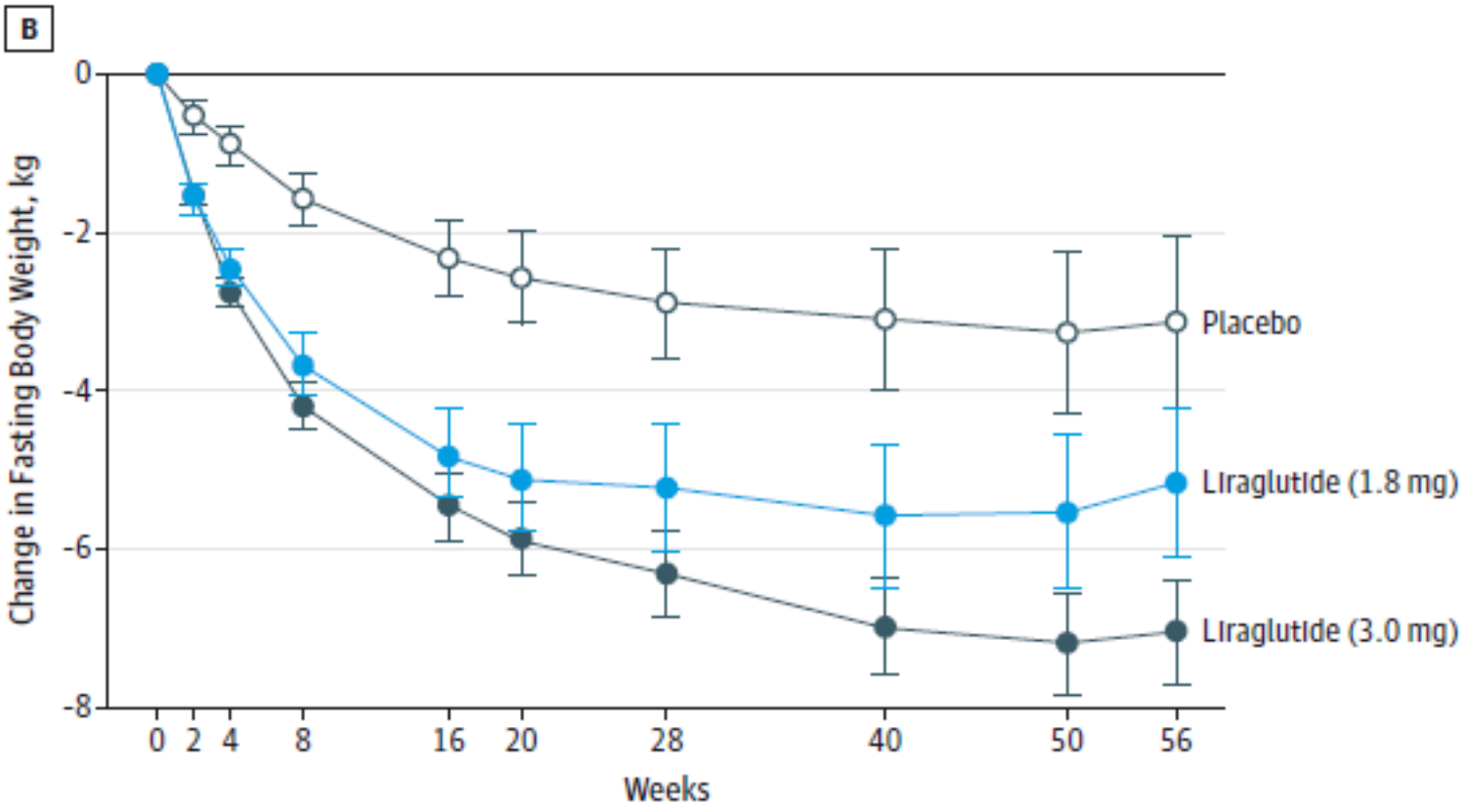

Hypos
(/100 py)

31

95

87

Bariatric Medicine

Original Investigation

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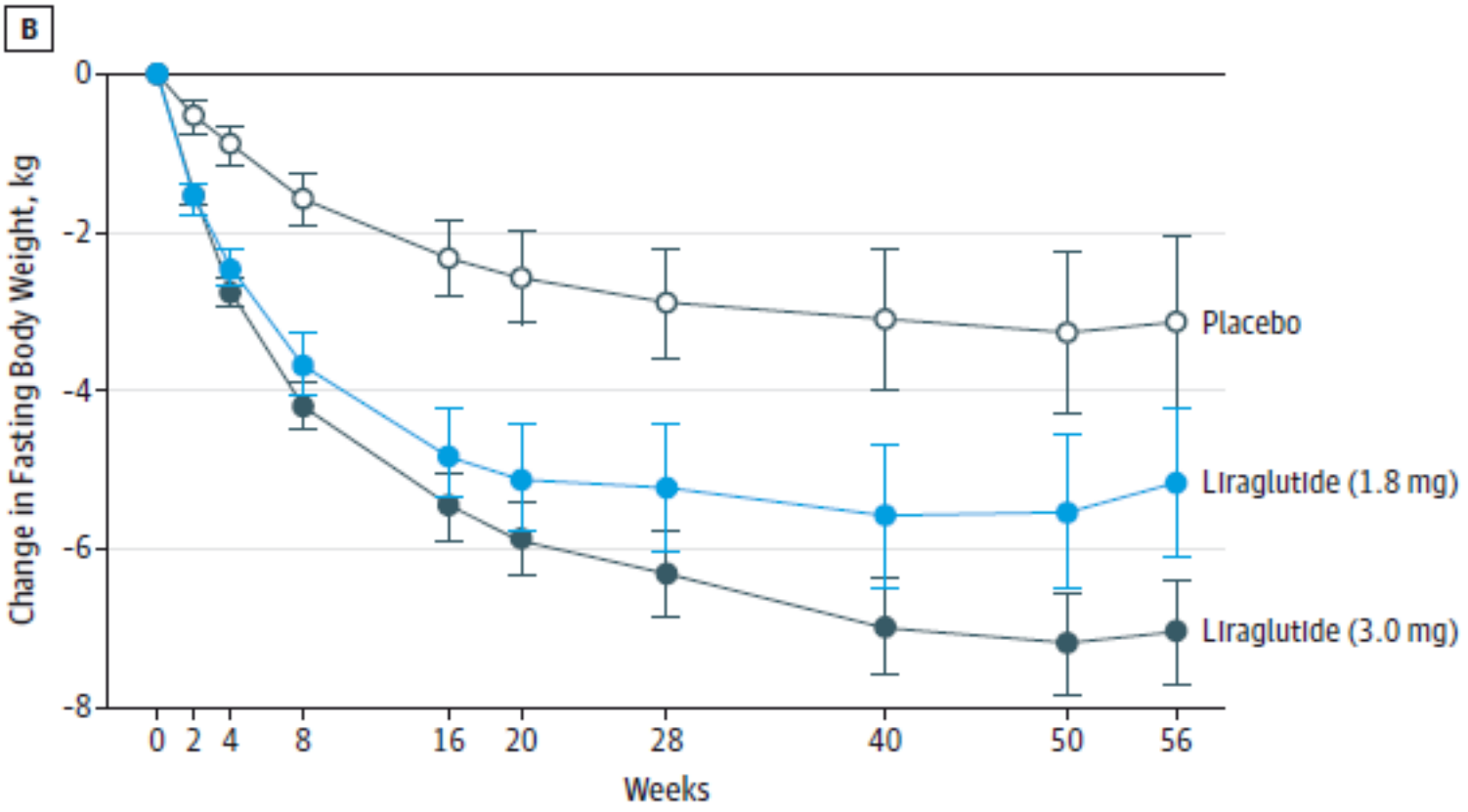
The SCALE Diabetes Randomized Clinical Trial

Figure 2. Time Course of Body Weight Loss From Baseline to Week 56 for Liraglutide (3.0 mg), Liraglutide (1.8 mg), and Placebo



SAEs

6.1%

8.6%

8.8%

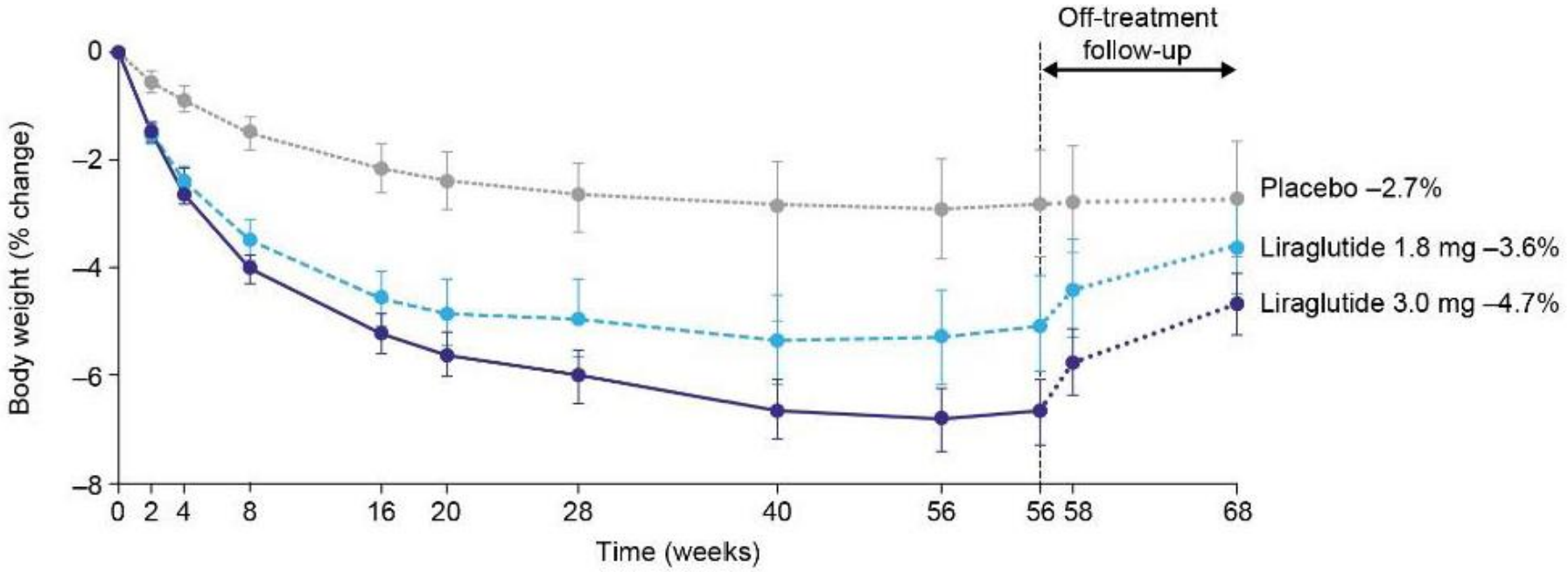
Bariatric Medicine

Original Investigation

Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes

The SCALE Diabetes Randomized Clinical Trial

Melanie J. Davies, MD; Richard Bergenstal, MD; Bruce Bode, MD; Robert F. Kushner, MD; Andrew Lewin, MD; Trine Vang Skjøth, MD; Arne Haahr Andreasen, MSc; Christine Bjørn Jensen, MD; Ralph A. DeFronzo, MD; for the NN8022-1922 Study Group



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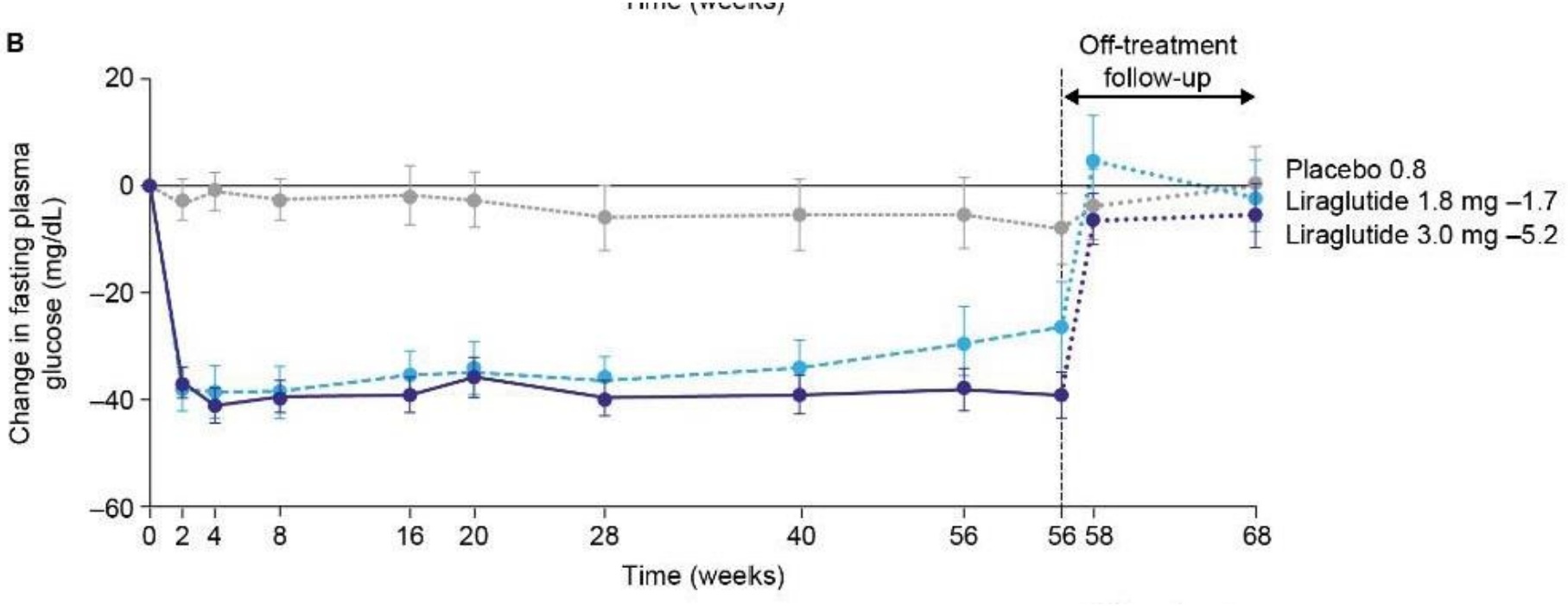

Bariatric Medicine

Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study

John B Buse, Michael Nauck, Thomas Forst, Wayne H-H Sheu, Sylvia K Shenouda, Cory R Heilmann, Byron J Hoogwerf, Aijun Gao, Marilyn K Boardman, Mark Fineman, Lisa Porter, Guntram Schernthaner

	RCT Components:
P	912 adults, T2DM
I	Exenatide 2mg weekly
C	Liraglutide 1.8mg daily
O	Change in A1c
T	26 weeks

ΔHbA1c:

1.48 v 1.28%
(But more AEs)

Bariatric Medicine

Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study

Richard E Pratley, Michael A Nauck, Anthony H Barnett, Mark N Feinglos, Fernando Ovalle, Illana Harman-Boehm, June Ye, Rhona Scott, Susan Johnson, Murray Stewart, Julio Rosenstock, for the HARMONY 7 study group

	RCT Components:
P	841 adults with T2DM
I	Albiglutide 50mg weekly
C	Liraglutide 1.8mg daily
O	Change in HbA1c
T	32 weeks

ΔHbA1c:

0.99 v 0.78%
(But more AEs)

Bariatric Medicine

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