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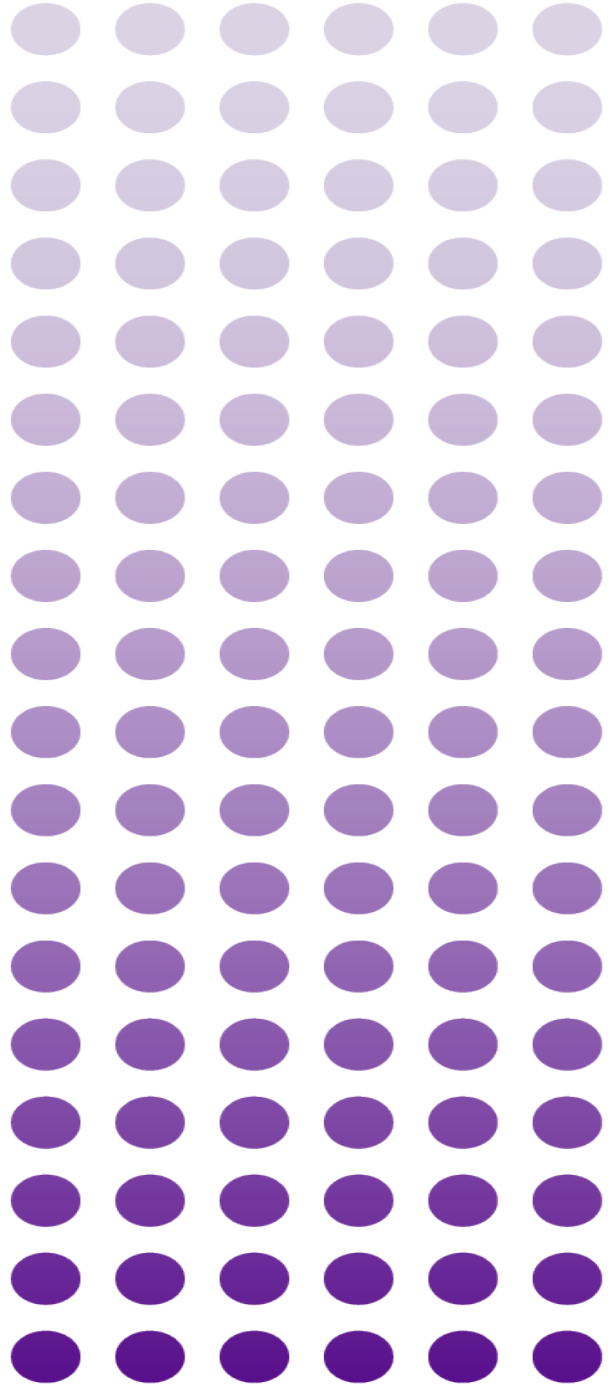
Implementing the Newer Anti-Obesity Medications into a Comprehensive Low Calorie Diet (LCD) Program

Holly F. Lofton, MD, DABOM
Clinical Associate Professor of Surgery and Medicine
NYU Grossman School of Medicine
Director, NYU Langone Health Medical Weight Management Program



Objectives

- Review study design and outcomes data and for GLP-1 and GIP receptor agonists' weight management trials
- Discuss the role proper nutrition and behavior education plays in conjunction with anti-obesity medication therapy
- Illustrate effective integration of an LCD to embody a comprehensive approach in patients on GLP-1 receptor agonists

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THE PAST

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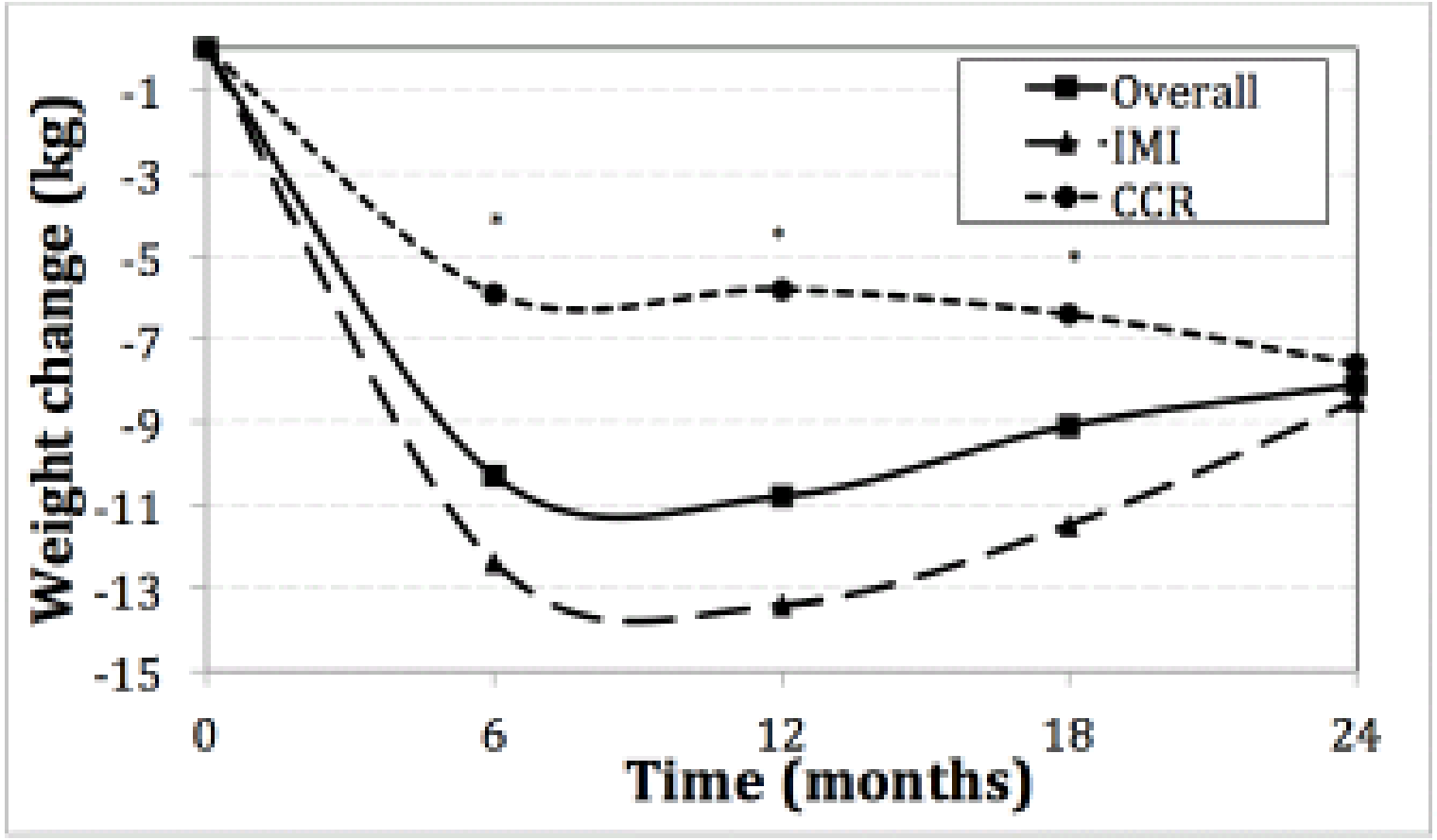

Figure 1: Mean Weight Loss at 6, 12, 18, and 24 Months. Mean weight loss was higher in the IMI group at 6, 12, and 18 months, but the difference between groups was not significant at 24 months.
*p-value < 0.05 for IMI versus CCR
IMI: Intensive Medical Intervention; CCR: Conventional Carbohydrate Restriction

Sethi M, Youn H, Ren-Fielding C, Lofton H (2015) Clinical Efficacy of a Medically Supervised Low-Calorie Diet Program versus a Conventional Carbohydrate-Restricted Diet. J Obes Weight Loss Ther 5: 267. doi:10.4172/2165-7904.1000267

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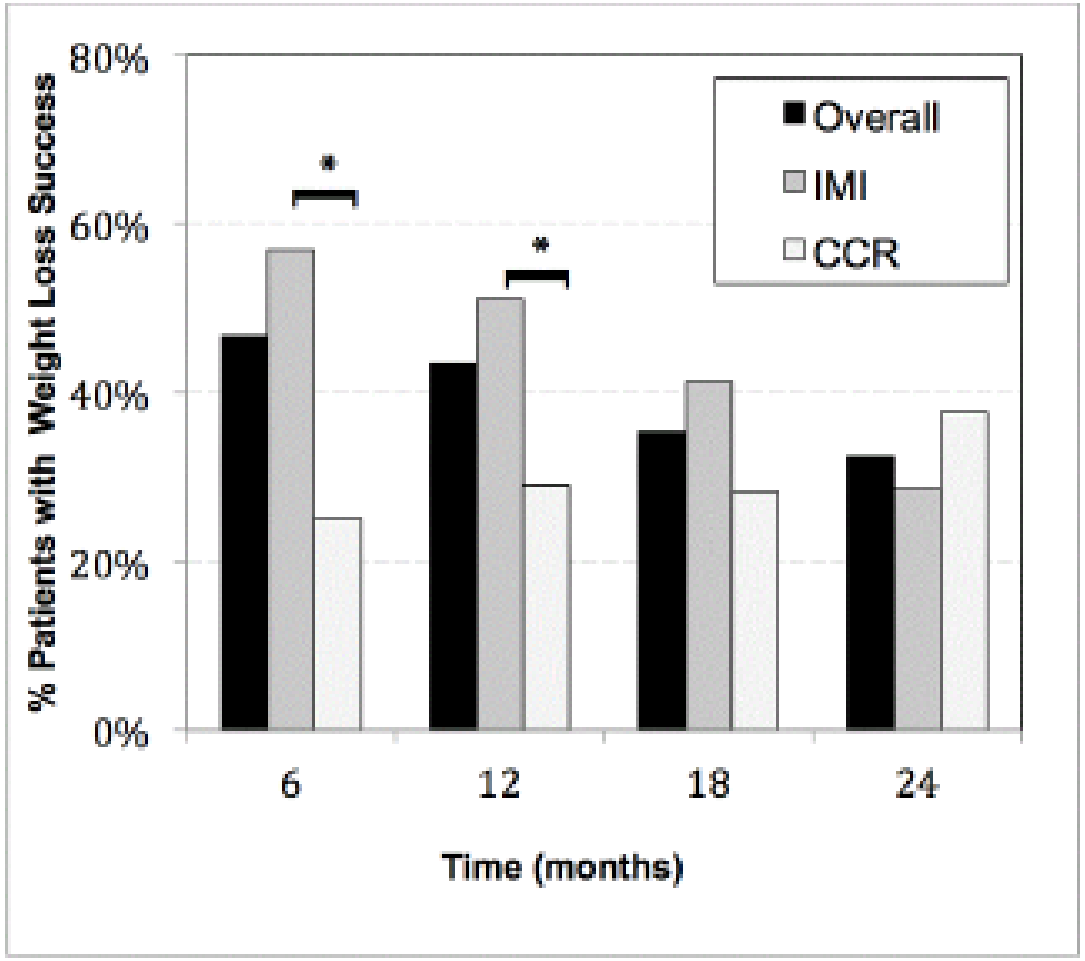

Figure 2: Percent of Patients with Weight Loss Success (>10% BWL) at 6, 12, 18, and 24 Months. The percent of patients with >10% BWL was higher in the IMI group at 6 months and 12 months, but differences between groups were not significant at 18 months or 24 months.
*p-value < 0.05 for IMI versus CCR
BWL: body weight loss; IMI: Intensive Medical Intervention; CCR: Conventional Carbohydrate Restriction

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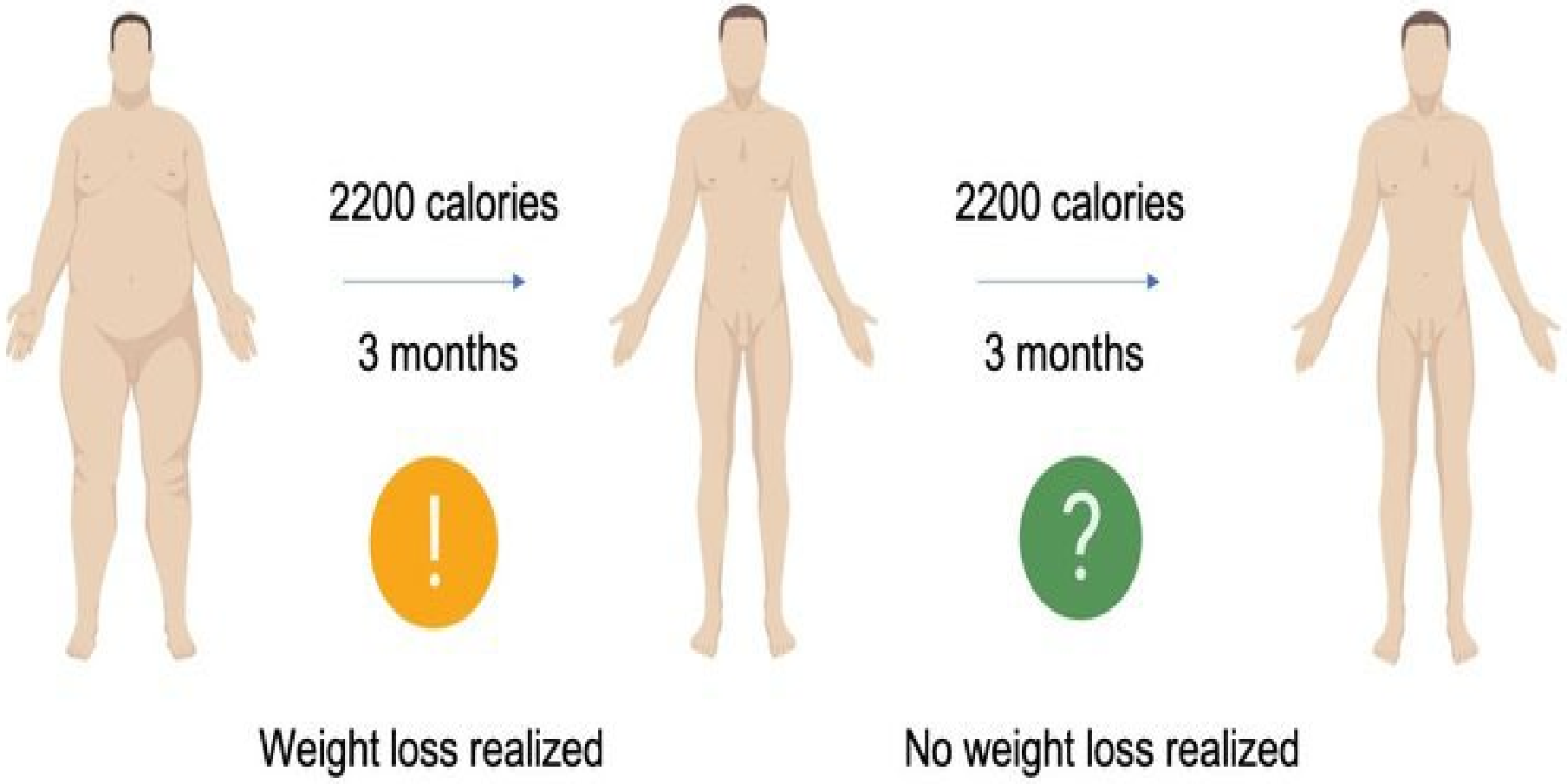
Sethi M, Youn H, Ren-Fielding C, Lofton H (2015) Clinical Efficacy of a Medically Supervised Low-Calorie Diet Program versus a Conventional Carbohydrate-Restricted Diet. J Obes Weight Loss Ther 5: 267. doi:10.4172/2165-7904.1000267

Metabolic adaptation



https://piphd.com/nutrition-and-fitness/2019/2/28/what-is-metabolic-adaptation

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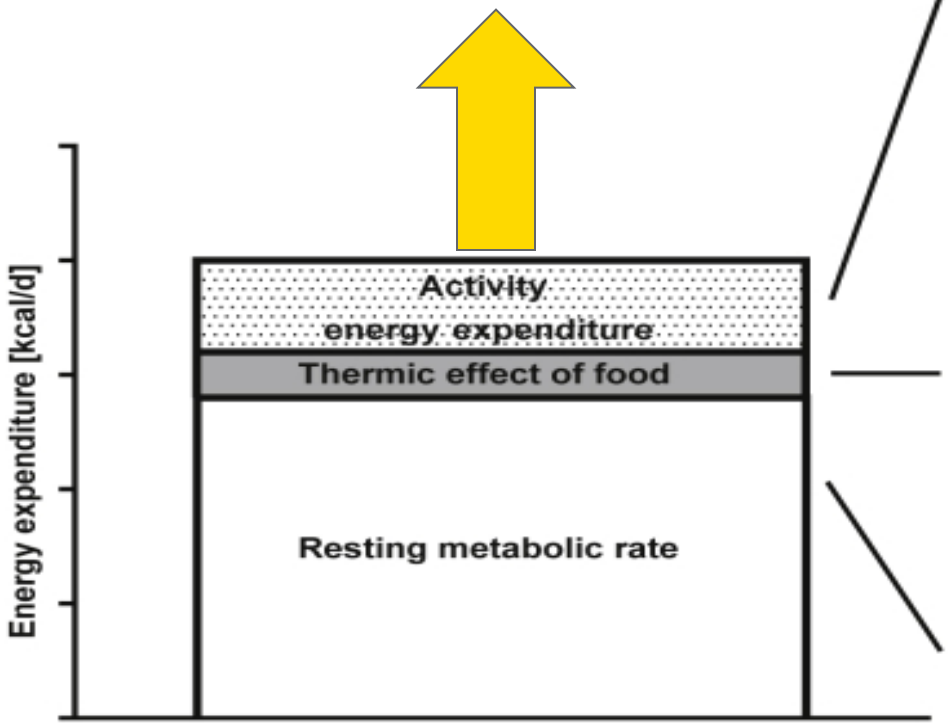
Determinants of Total Energy Expenditure

Weight loss can decrease RMR by about 15% which decreases TEE



Key determinants

- Genetic traits
- Age
- Sex
- Environmental stimuli

- Diet composition
- Age
- Physical activity
- Obesity
- Insulin resistance

- Fat-free mass
- Fat mass
- Sex
- Age
- Genetic traits

Lam YY, Ravussin E. Analysis of energy metabolism in humans: A review of methodologies. Mol Metab. 2016 Sep 20;5(11):1057-1071. doi: 10.1016/j.molmet.2016.09.005. PMID: 27818932; PMCID: PMC5081410.

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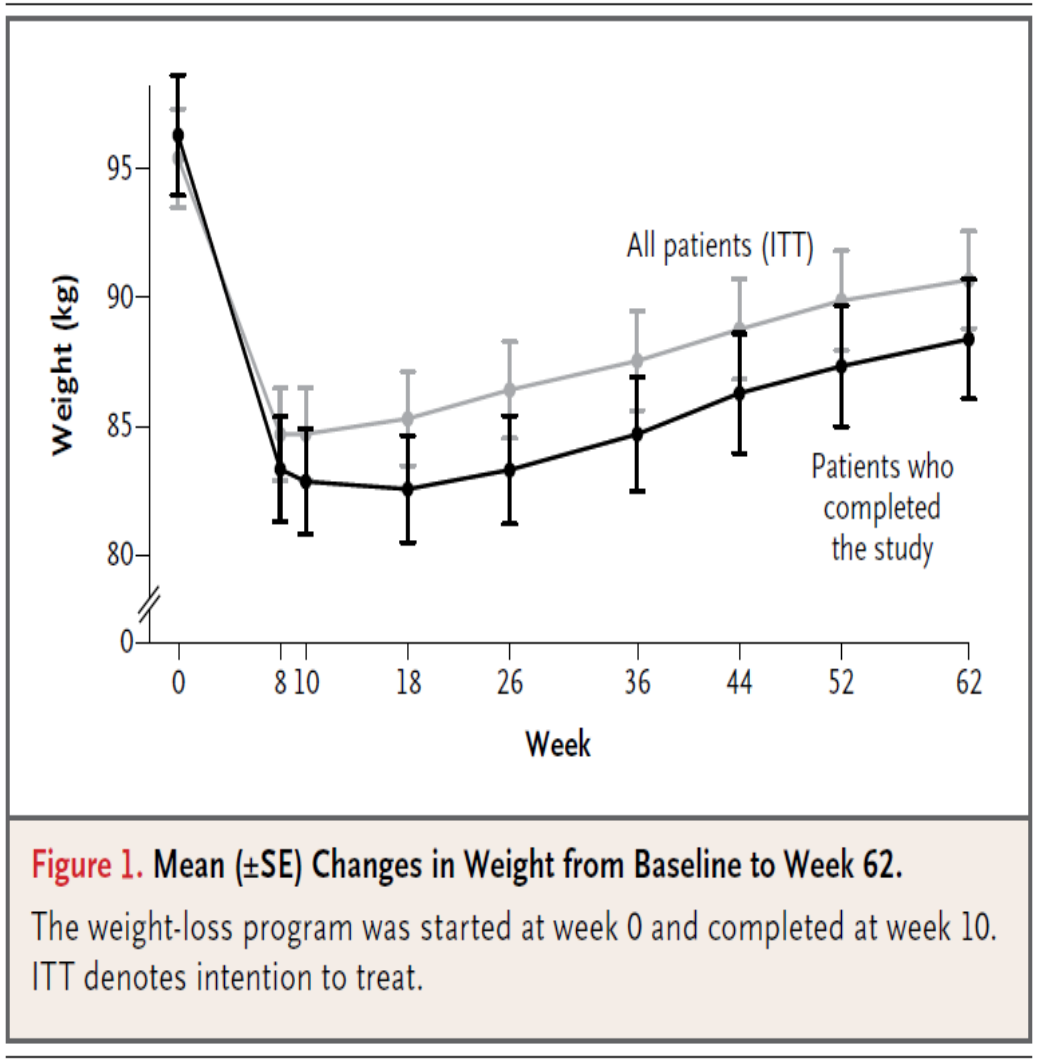

Figure 1. Mean (±SE) Changes in Weight from Baseline to Week 62.

The weight-loss program was started at week 0 and completed at week 10. ITT denotes intention to treat.

Orexigenic (appetite stimulation)

Ghrelin

Anorexigenic (appetite suppression)

Peptide YY
Amylin
Cholecystokinin

Sumithran et al. Long-Term Persistence of Hormonal Adaptations to Weight Loss.NEJM.2011 Vol. 365 Issue 17.1597-1604

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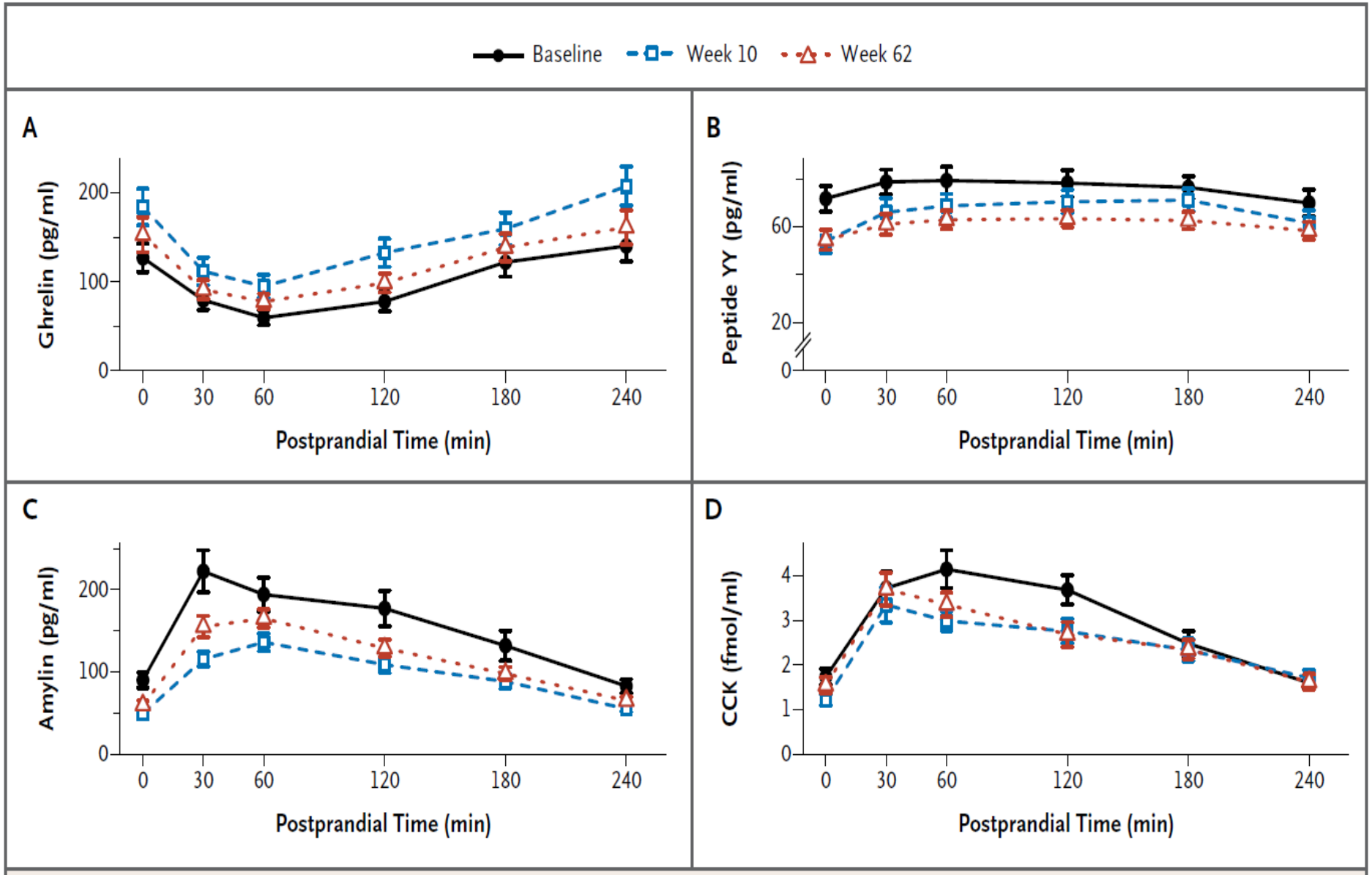

Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

THE PRESENT

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NIH Consensus Statement on Pharmacotherapy for Weight Management

- Adjunct to **comprehensive weight loss program, including dietary therapy and physical activity**
- BMI of 30 kg/m^2
- BMI of 27 kg/m^2 with concomitant obesity-related risk factors or diseases

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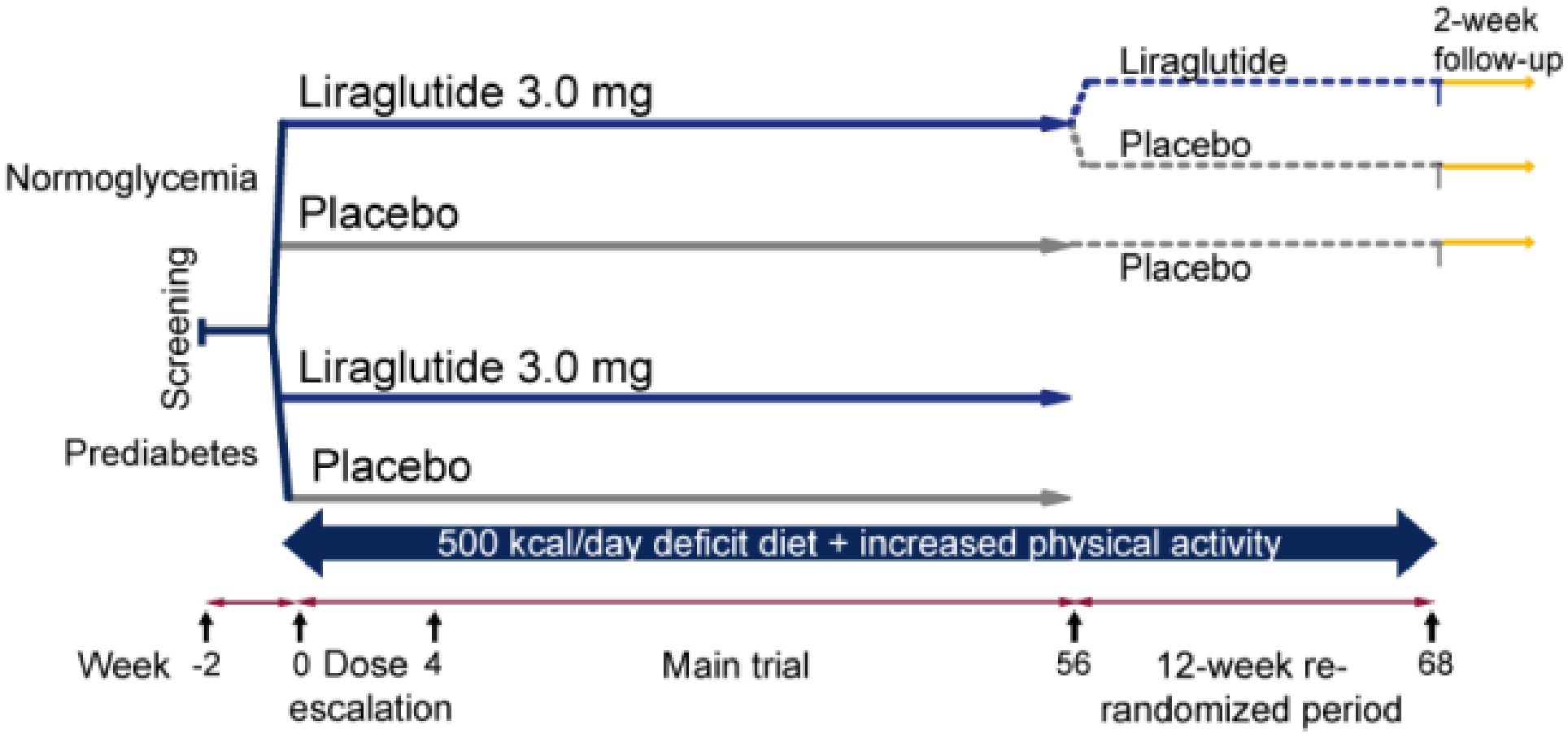
SCALE – LIRAGLUTIDE 3 MG



Pi-Sunyer, X etal. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management (SCALE). New England Journal of Medicine 2015 Vol. 373 Issue 1 Pages 11-22

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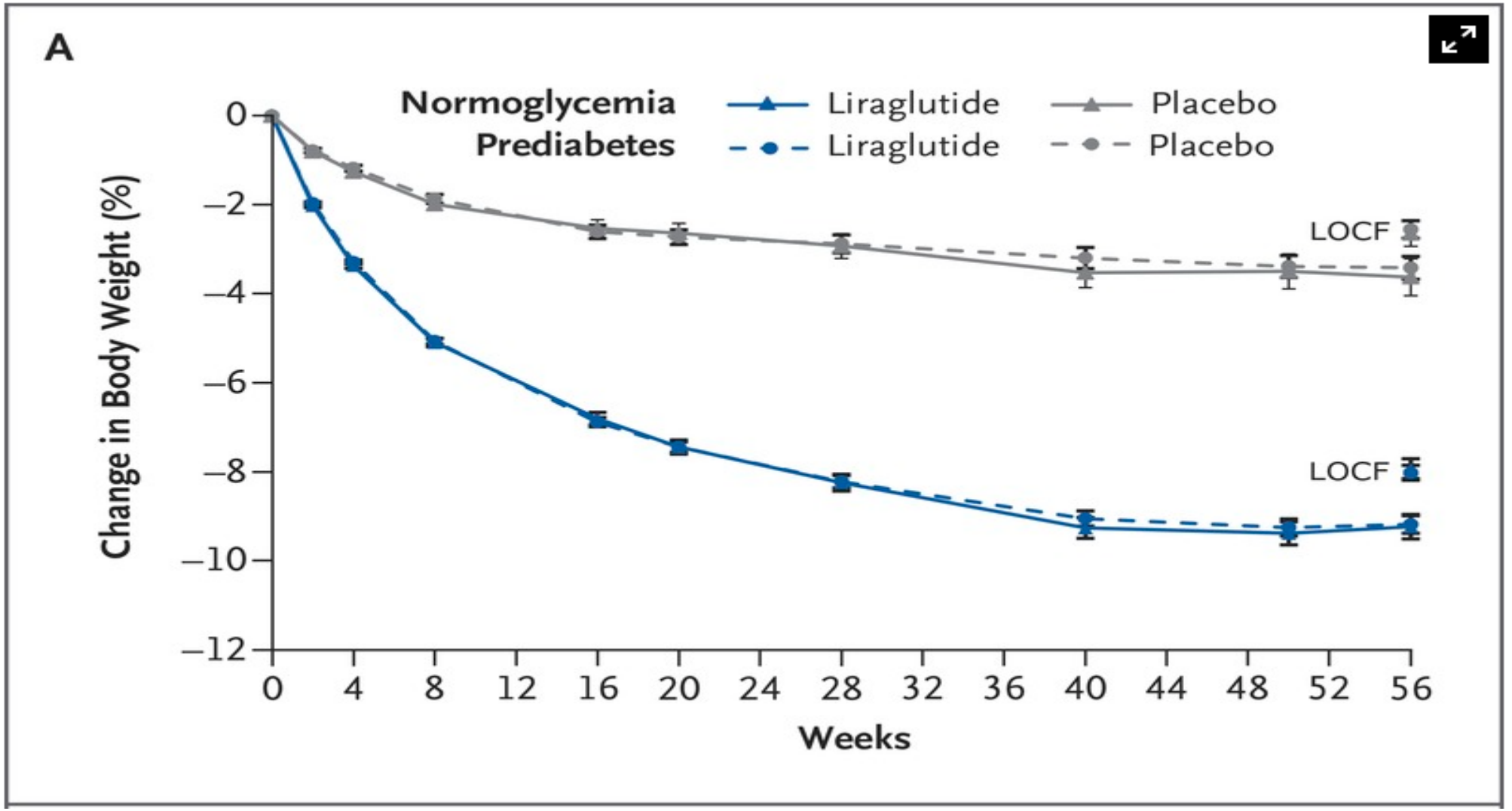

Pi-Sunyer, X etal. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management (SCALE). New England Journal of Medicine 2015 Vol. 373 Issue 1 Pages 11-22

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Liraglutide 3 mg

- **Potential Adverse Experiences**
  - **Nausea**
  - **Hypoglycemia**
  - **Diarrhea**
  - **Constipation**
  - **Vomiting**
  - Headache
  - Decreased appetite
  - Dyspepsia
  - Fatigue
  - Dizziness
  - Abdominal pain
  - Increased lipase

Contra-indications

- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2
- Hypersensitivity to liraglutide or any product components
- Contra-indicated during pregnancy or nursing mothers (pregnancy category X)

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Semaglutide –STEP 3 TRIAL

Placebo	Semaglutide 2.4 mg
8 week LCD 1000-1200 kcal with MR	8 week LCD 1000-1200 kcal with MR
Hypocaloric conventional plan for 68 weeks	Hypocaloric conventional plan for 68 weeks
100 minutes PA/wk (spread across 4-5 days), which increased by 25 minutes every 4 weeks, to reach 200 min/wk	100 minutes PA/wk (spread across 4-5 days), which increased by 25 minutes every 4 weeks, to reach 200 min/wk

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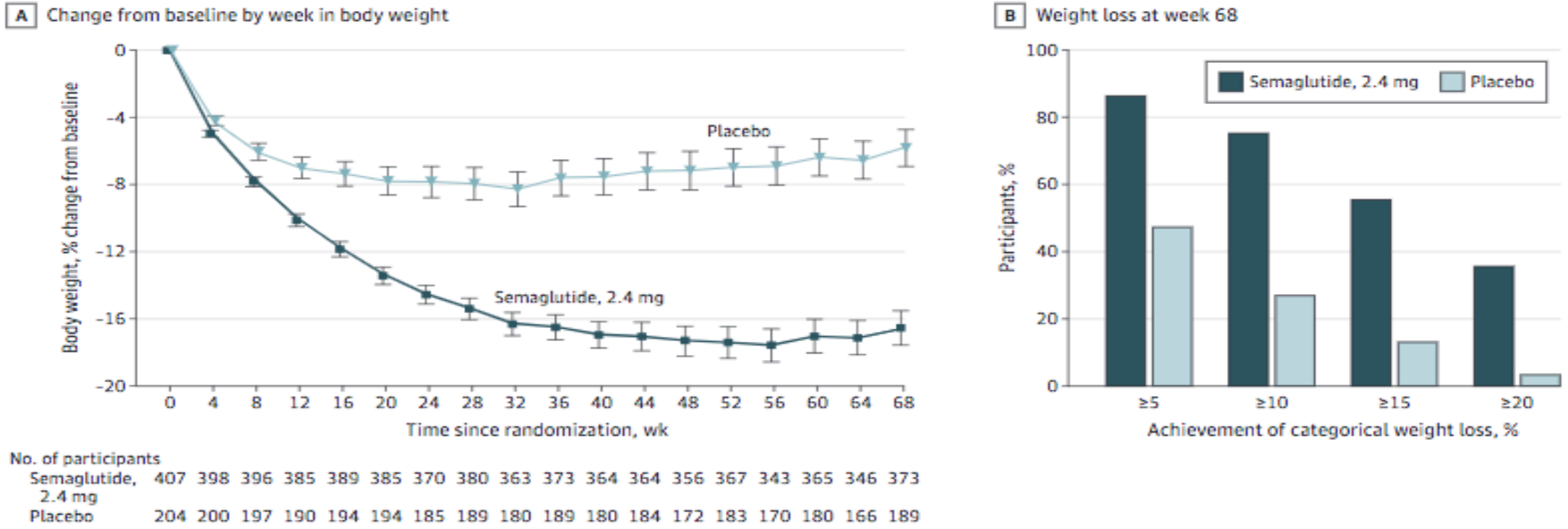
Semaglutide 2.4 mg

Figure 2. Body Weight–Related Efficacy End Points



Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al.. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity. JAMA. JAMA; 2021;325(14):1403.

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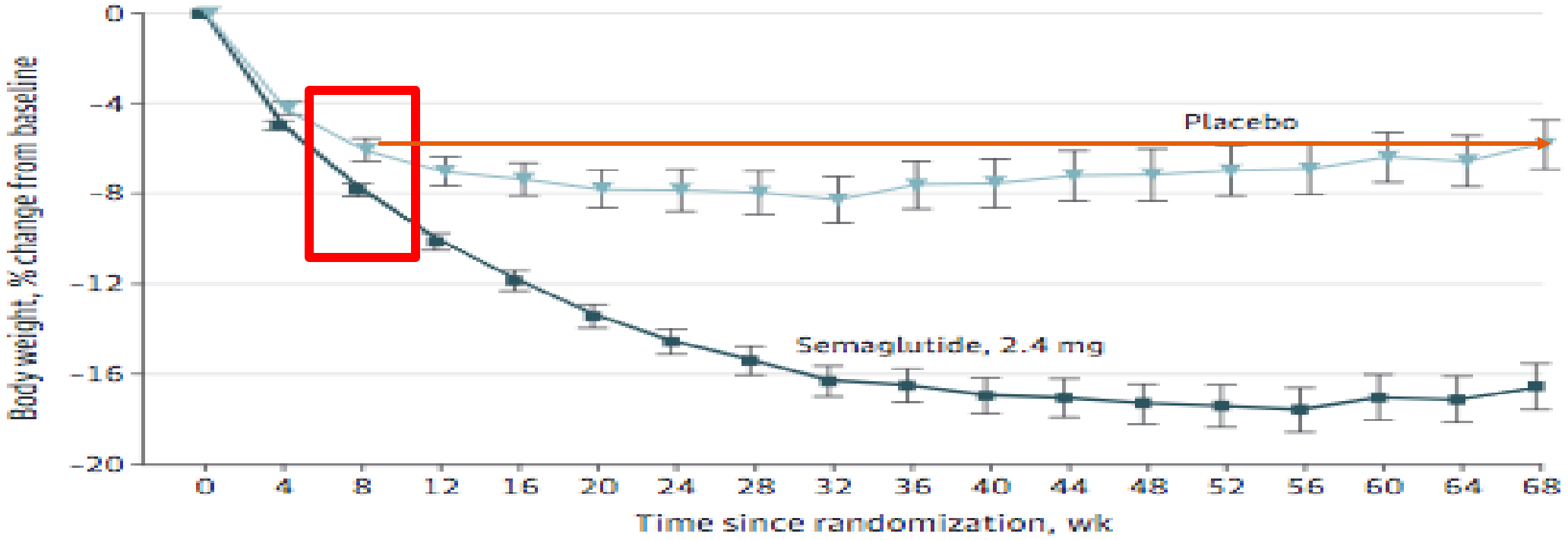
Figure 2. Body Weight–Related Efficacy End Points

A Change from baseline by week in body weight



No. of participants

Semaglutide, 2.4 mg	407	398	396	385	389	385	370	380	363	373	364	364	356	367	343	365	346	373
Placebo	204	200	197	190	194	194	185	189	180	189	180	184	172	183	170	180	166	189

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Body Composition: Semaglutide 2.4 mg vs. Placebo

- 140 subjects (95 semaglutide, 45 placebo)

	Semaglutide	Placebo
BL Total Fat Mass	43.4%	44.6%
BL Regional Visceral Fat Mass	33.8%	36.3%
Week 68 Total Fat	-19.3%	-
Week 68 RVF	-27.4%	-
Change in TLBM	-9.7% *	-

*** Proportion lean body mass: total body mass increased 3%**

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Wilding J, et al. Impact of Semaglutide on Body Composition in Adults with Overweight or Obesity:Exploratory Analysis of STEP 1 Study

THE FUTURE

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

"Lifestyle intervention included regular lifestyle counseling sessions, delivered by a dietitian or a qualified health care professional, to help the participants adhere to healthful, balanced meals, with a **deficit of 500 calories per day, and at least 150 minutes of physical activity per week"**

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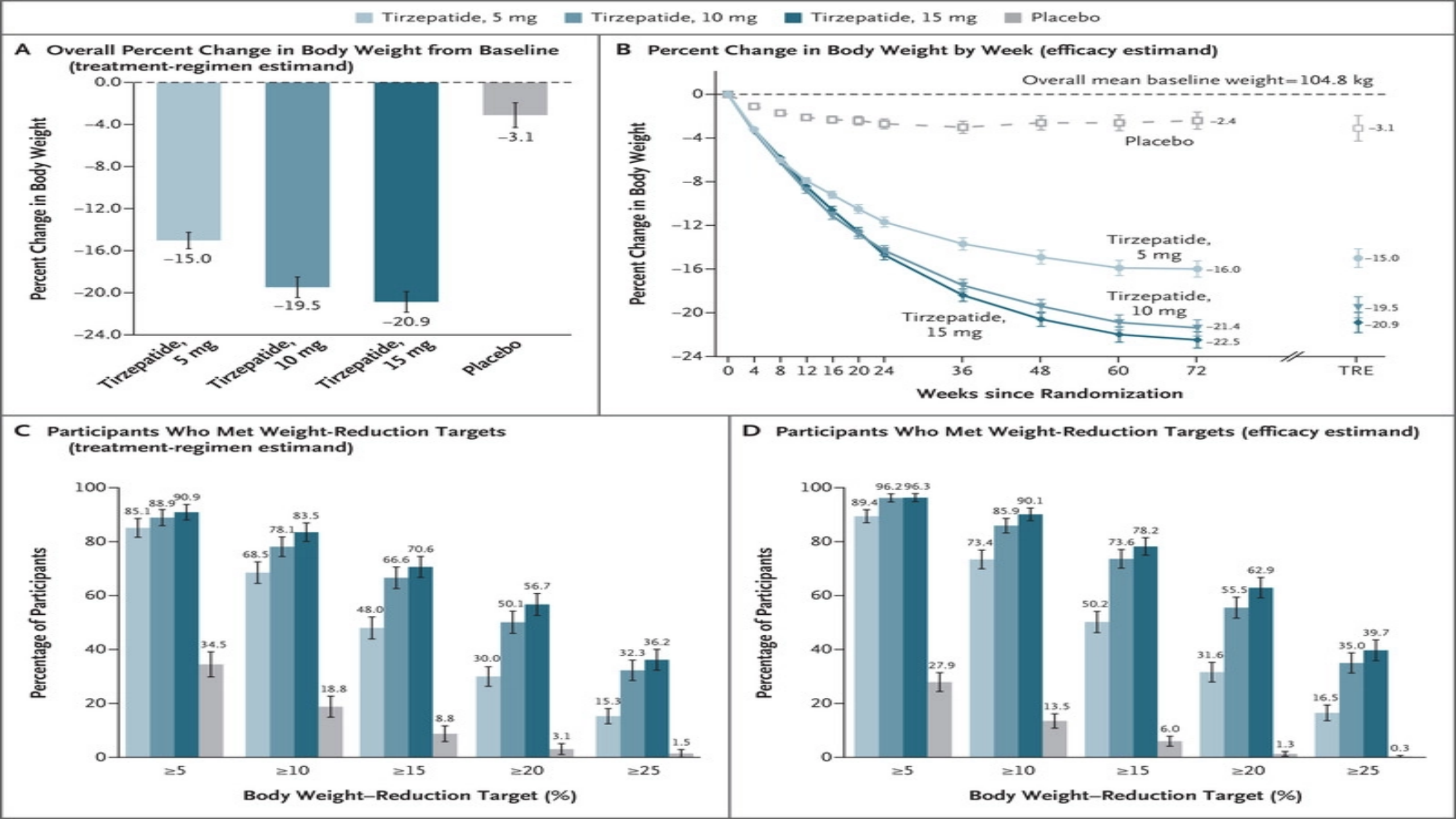
Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
Placebo
A Overall Percent Change in Body Weight from Baseline (treatment-regimen estimand)
Percent Change in Body Weight
0.0
−4.0
−8.0
−12.0
−16.0
−20.0
−24.0
−15.0
−19.5
−20.9
−3.1
Tirzepatide, 5 mg
Tirzepatide, 10 mg
Tirzepatide, 15 mg
Placebo
B Percent Change in Body Weight by Week (efficacy estimand)
Overall mean baseline weight=104.8 kg
Placebo
−2.4
−3.1
Tirzepatide, 5 mg
−16.0
−15.0
Tirzepatide, 10 mg
−21.4
−19.5
Tirzepatide, 15 mg
−22.5
−20.9
0 4 8 12 16 20 24 36 48 60 72 TRE
Weeks since Randomization
C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)
Percentage of Participants
85.1 88.9 90.9 34.5
68.5 78.1 83.5 18.8
48.0 66.6 70.6 8.8
30.0 50.1 56.7 3.1
15.3 32.3 36.2 1.5
≥5 ≥10 ≥15 ≥20 ≥25
Body Weight–Reduction Target (%)
D Participants Who Met Weight-Reduction Targets (efficacy estimand)
Percentage of Participants
89.4 96.2 96.3 27.9
73.4 85.9 90.1 13.5
50.2 73.6 78.2 6.0
31.6 55.5 62.9 1.3
16.5 35.0 39.7 0.3
≥5 ≥10 ≥15 ≥20 ≥25
Body Weight–Reduction Target (%)

% Body Weight Change

Placebo **-3.1**

Tirz 5 **-15**

Tirz 10 **-19.5**

Tirz 15 **-20.9**

Table 2. Primary and Secondary End Points for the Treatment-Regimen Estimand.*

End Points	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	least-squares mean (95% CI)			
Coprimary end points†				
Percentage change in body weight‡	−15.0 (−15.9 to −14.2)	−19.5 (−20.4 to −18.5)	−20.9 (−21.8 to −19.9)	−3.1 (−4.3 to −1.9)
Difference from placebo in percentage change in body weight — percentage points‡	−11.9 (−13.4 to −10.4)	−16.4 (−17.9 to −14.8)	−17.8 (−19.3 to −16.3)	—
Weight reduction of 5% or more at week 72 — percentage of participants‡§	85.1 (81.6 to 88.6)	88.9 (85.9 to 91.9)	90.9 (88.0 to 93.8)	34.5 (29.8 to 39.2)
Key secondary end points†				
Weight reduction of 10% or more at week 72 — percentage of participants§¶	68.5 (64.5 to 72.5)	78.1 (74.4 to 81.7)	83.5 (80.0 to 86.9)	18.8 (14.9 to 22.7)
Weight reduction of 15% or more at week 72 — percentage of participants§¶	48.0 (43.9 to 52.1)	66.6 (62.6 to 70.6)	70.6 (66.7 to 74.5)	8.8 (5.9 to 11.7)
Weight reduction of 20% or more at week 72 — percentage of participants§¶	30.0 (26.4 to 33.6)	50.1 (46.0 to 54.2)	56.7 (52.6 to 60.8)	3.1 (1.1 to 5.1)
Change in waist circumference — cm¶	−14.0 (−14.9 to −13.1)	−17.7 (−18.7 to −16.8)	−18.5 (−19.3 to −17.6)	−4.0 (−5.1 to −2.8)
Difference from placebo in change in waist circumference — cm ¶	−10.1 (−1.6 to −8.6)	−13.8 (−15.2 to −12.3)	−14.5 (−15.9 to −13.0)	—
Additional secondary end point				
Weight reduction of 25% or more at week 72 — percentage of participants §‖	15.3 (12.5 to 18.1)	32.3 (28.5 to 36.1)	36.2 (32.3 to 40.1)	1.5 (0.1 to 2.9)

* All changes are from baseline to week 72.
† The primary and key secondary end points were tested under a type 1 error–control procedure, and all comparisons with placebo were significant at P<0.001.
‡ The change in body weight in the tirzepatide 5-mg group was not a coprimary end point and was analyzed as a key secondary end point.
§ The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.
¶ The specified weight-reduction targets and the change in waist circumference in the tirzepatide 5-mg group were not key secondary end points and were analyzed as additional secondary end points. Hypothesis testing was not conducted; confidence intervals were not adjusted for multiplicity, and no definite conclusions can be drawn.
‖ This was an exploratory end point not controlled for type 1 error; therefore, hypothesis testing was not conducted. Confidence intervals were not adjusted for multiplicity, and no definite conclusions can be drawn.

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Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

* All changes are from baseline to week 72, unless otherwise indicated. VLDL denotes very-low-density lipoprotein.
† "Pooled tirzepatide groups" refers to pooled data for the 5-mg, 10-mg, and 15-mg groups unless otherwise indicated.
‡ The key secondary end points were tested under type 1 error–control procedure, and all tests had $P<0.001$ versus placebo.
§ Data are for the pooled 10-mg and 15-mg tirzepatide groups.
¶ The change from baseline in the SF-36 physical function score was assessed with use of an analysis of covariance model, with terms for baseline SF-36 physical function score, treatment, and stratification factors.
‖ The estimated treatment differences from placebo in the percentage changes in levels are expressed as percentage-points. Lipid and fasting insulin levels were analyzed with the use of log transformation. Data shown represent model-based estimates and 95% confidence intervals.
** Results of absolute values for the change in fasting insulin, fasting glucose, and glycated hemoglobin are included in Table S4.
†† For additional secondary end points, the widths of confidence intervals were not adjusted for multiplicity, and these may not be used in place of hypothesis tests.

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Table 4. Adverse Events and Safety.

Variable	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)
	number (percent)			
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0
Adverse events occurring in at least 5% of participants in any treatment group†				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
Covid-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection-site reaction‡	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)
Adverse events of special interest				
Hepatic events§	2 (0.3)	2 (0.3)	0	0
Cancer	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)
Pancreatitis (adjudication-confirmed)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Major adverse cardiovascular events (adjudication-confirmed)	4 (0.6)	5 (0.8)	0	5 (0.8)
Cardiac disorders¶	0	1 (0.2)	2 (0.3)	1 (0.2)
Severe or serious gastrointestinal events	11 (1.7)	20 (3.1)	21 (3.3)	7 (1.1)
Gallbladder disease§	5 (0.8)	11 (1.7)	6 (1.0)	5 (0.8)
Renal events§	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Major depressive disorder or suicidal ideation§	1 (0.2)	2 (0.3)	2 (0.3)	0
Hypersensitivity‖	0	1 (0.2)	1 (0.2)	0
Hypoglycemia (blood glucose <54 mg/dl)	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)
Other adverse events of interest that emerged during treatment period†				
Cholelithiasis	7 (1.1)	9 (1.4)	4 (0.6)	6 (0.9)
Cholecystitis	4 (0.6)	3 (0.5)	0	0
Acute cholecystitis	1 (0.2)	4 (0.6)	1 (0.2)	0
Chronic cholecystitis	1 (0.2)	1 (0.2)	3 (0.5)	3 (0.5)

* All deaths were adjudicated by an external committee of physicians, who determined whether the death was cardiovascular-related.
† Adverse events are listed according to *Medical Dictionary for Regulatory Activities*, version 24.1, preferred terms.
‡ None of the events were reported as severe or serious.
§ Events were classified as severe or serious adverse events.
¶ Events were classified as severe or serious supraventricular arrhythmias and cardiac conduction disorders.
‖ Hypersensitivity includes immediate (≤24 hours after administration of tirzepatide or placebo) and nonimmediate (>24 hours after administration of tirzepatide or placebo) severe or serious hypersensitivity events.

Adverse Events

- Nausea *
- Diarrhea *
- Abdominal Pain *
- Vomiting *
- COVID- 19
- Constipation
- Dyspepsia

* Lead to discontinuation

Other Considerations favoring Meal Replacement

- Decrease in gastric acid production

- Improved compliance with avoidance of high fat foods that trigger nausea, vomiting

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IMPLEMENTATION

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Sample Visit Schedule

Sema 0.25
- RD week 2
- RD week 4

Sema 0.5
- RD week 6
- RD week 8

Sema 1
- RD week 10
- RD week 12

Sema 1.7
- Repeat 12 week program
- Transition to hypocaloric

Sema 2.4
- Follow up with medical provider

Maintenance dose
- Medical Provider q 1 -3 months

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CASES

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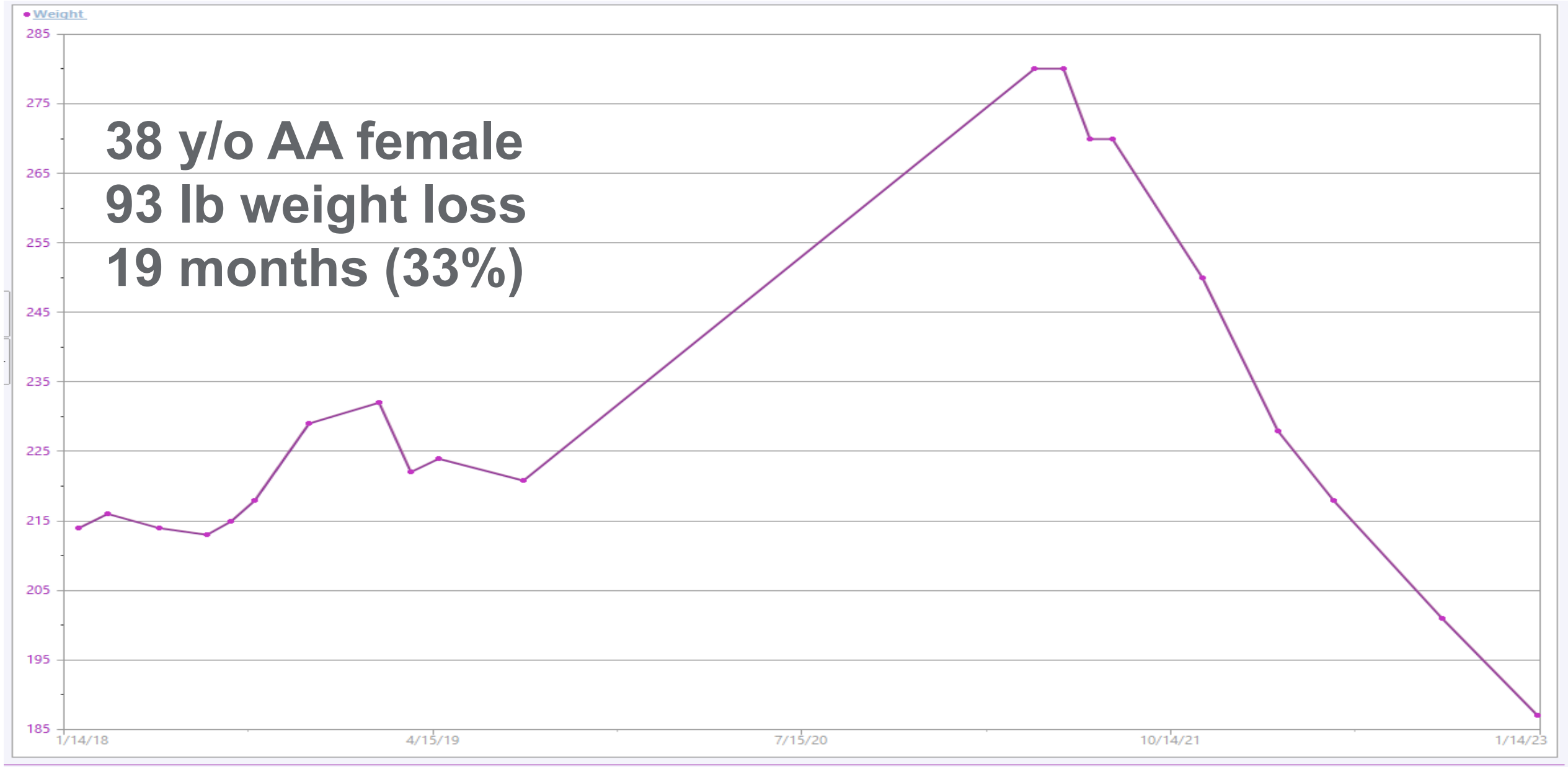

38 y/o AA female
93 lb weight loss
19 months (33%)

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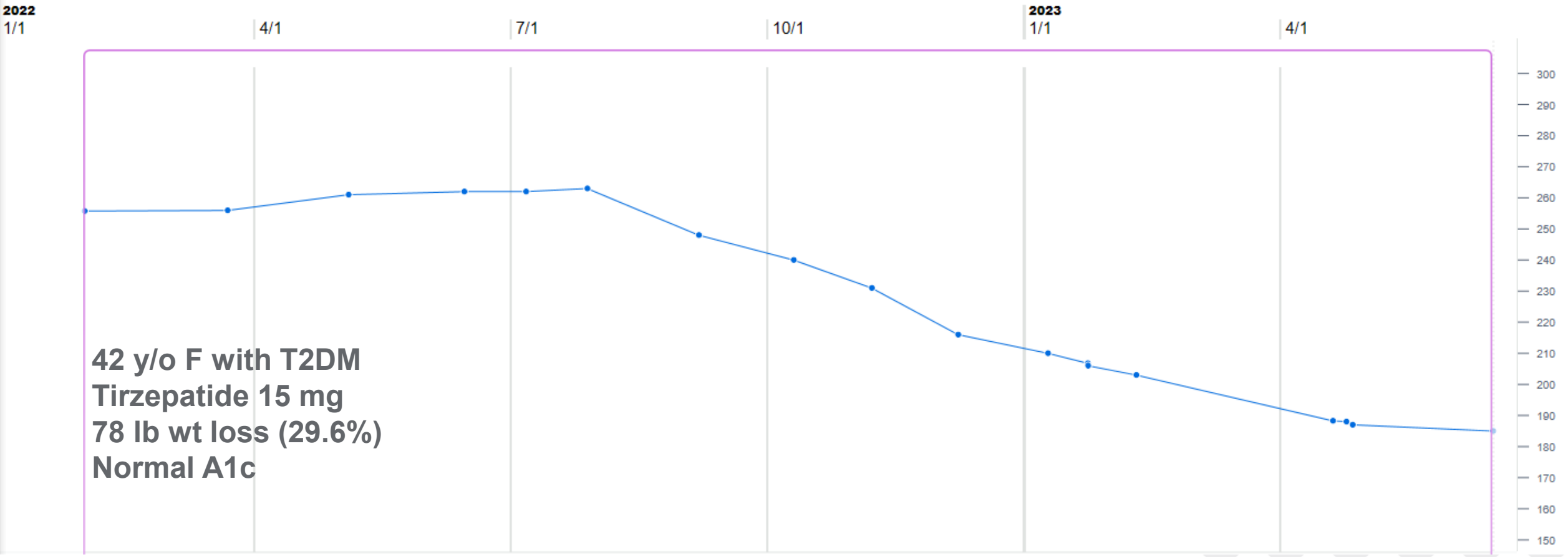
Tirzepatide



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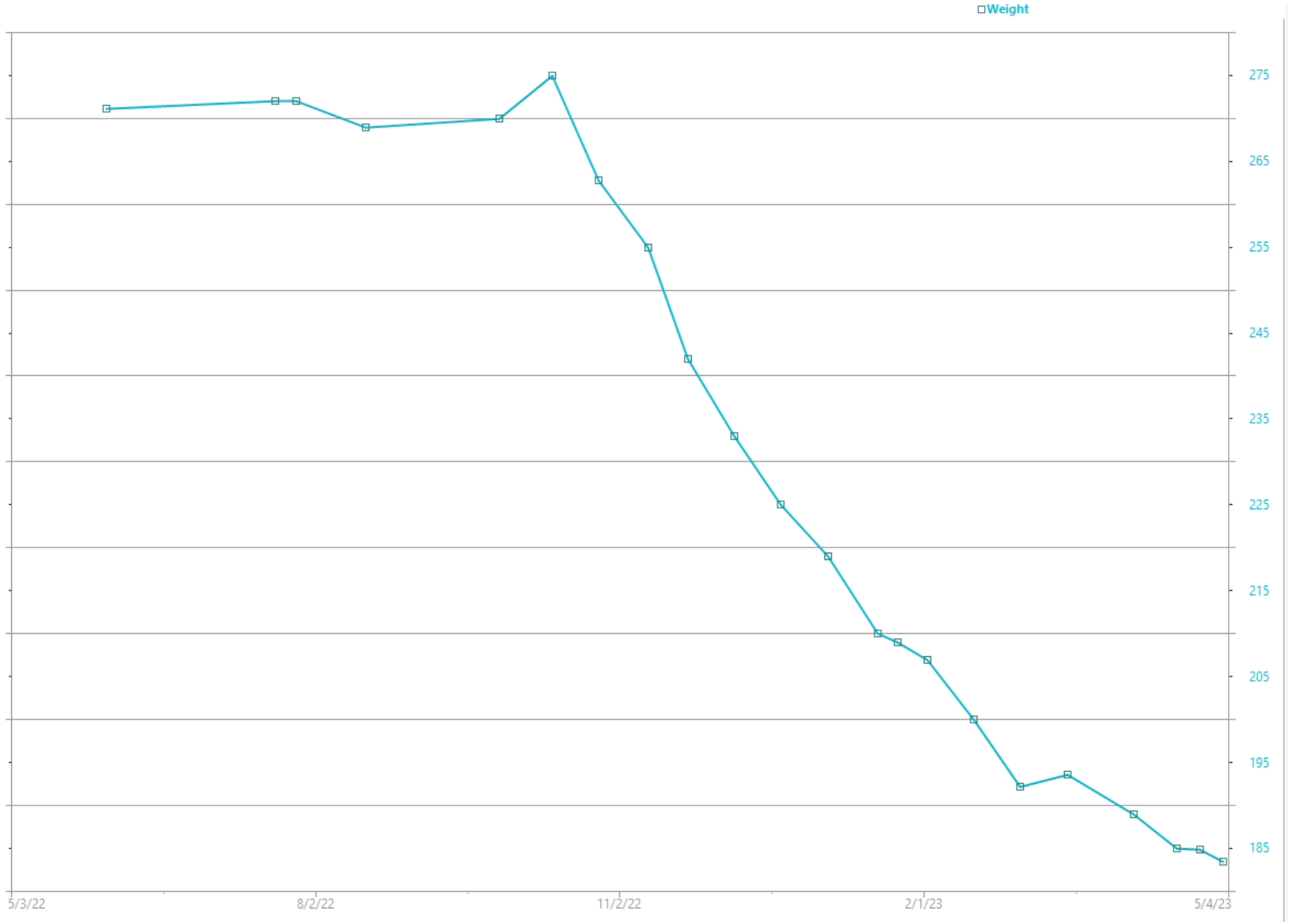
63 M with HOCM
Semaglutide 2.4
And LCD
33% wt loss
7 months



Take – Home Messages

- Obesity is a chronic, progressive disease, thus patients often regain weight

- Anti-obesity medications have demonstrated safety and additional efficacy as an ADJUNCT to lifestyle recommendations
- Both hypocaloric and structured hypocaloric nutrition plans have been used in clinical obesity trials

- Lean body mass and adipose tissue are targeted in the process of weight loss with diet, exercise, and medications
- Adequate protein intake is essential to minimize lean body mass loss
- Meal replacements can be utilized to maximize protein intake when appetite is suppressed and to decrease diet-induced medication side effects

- Medical monitoring of lifestyle intervention is necessary long-term (life-long) for patients with obesity and overweight even if they are taking anti-obesity medications