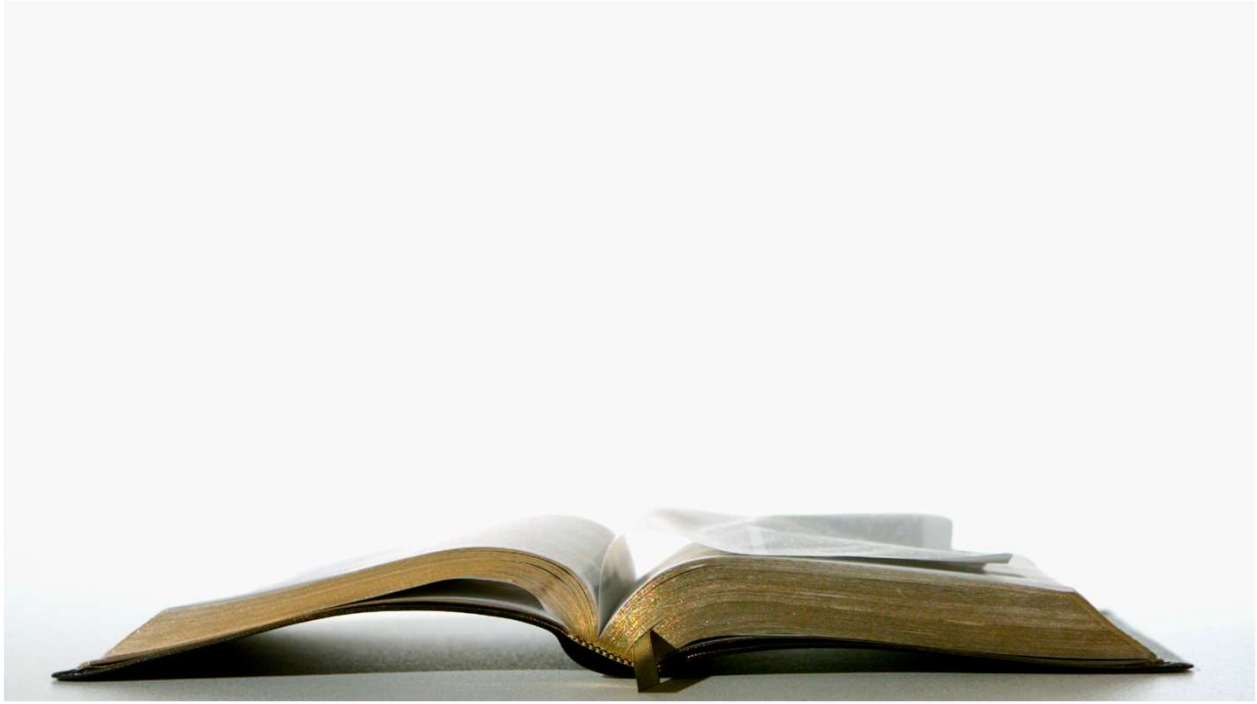
Journal Club Presentation

Semaglutide Treatment Effect in People with Obesity (STEP 1) Study

Jeayoung Park, IM-PGY2



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Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

Contents

TL; DR:
(before you lose focus)

This is a study about semaglutide, a diabetes drug, being useful for obesity treatment in **non-diabetics**.

About **50%** of participants lost **15%** of body weight after **68 weeks** of treatment, when combined with diet/exercise.

Study is limited by skewed population towards white females and the high cost of medication.

All right, class dismissed.

All right, class dismissed.

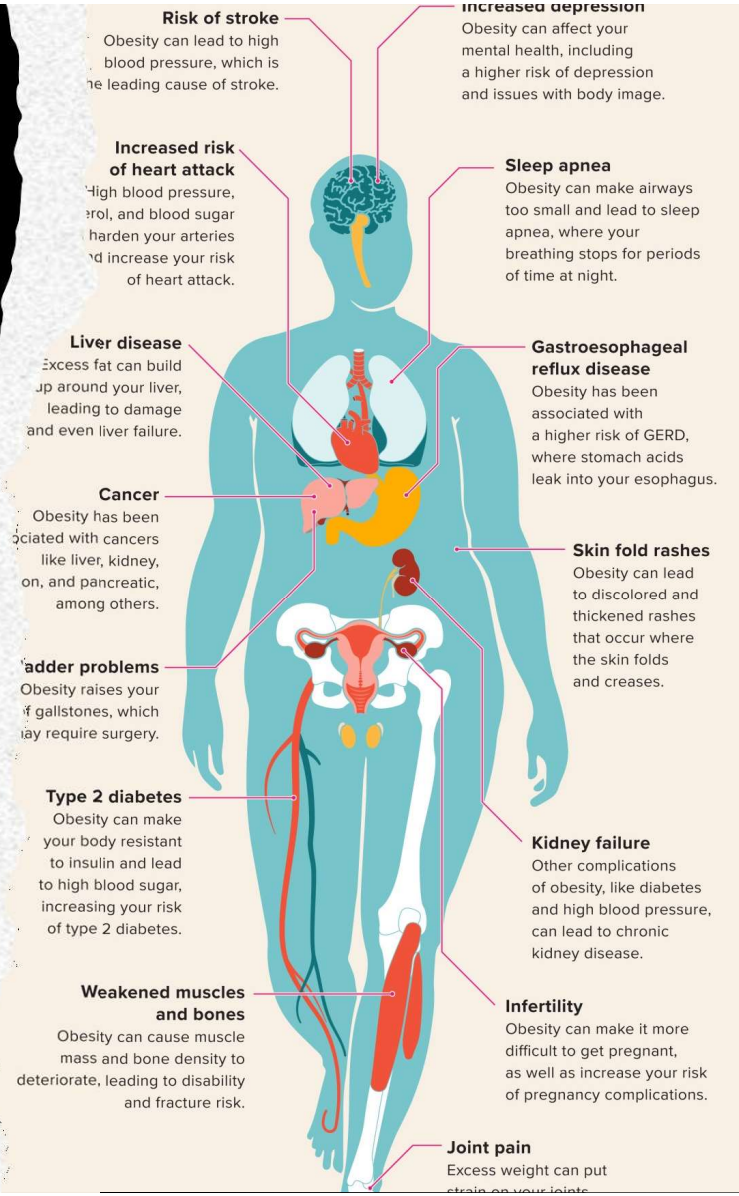
(Just kidding.)

Background

Obesity and GLP-1 agonists

Obesity is a global public health challenge.

- Obesity is associated with complications such as type 2 DM, CV disease, fatty liver disease, and reduces life expectancy.
- Obesity is associated with increased rate of hospitalizations, mechanical ventilation, death with persons with COVID-19.

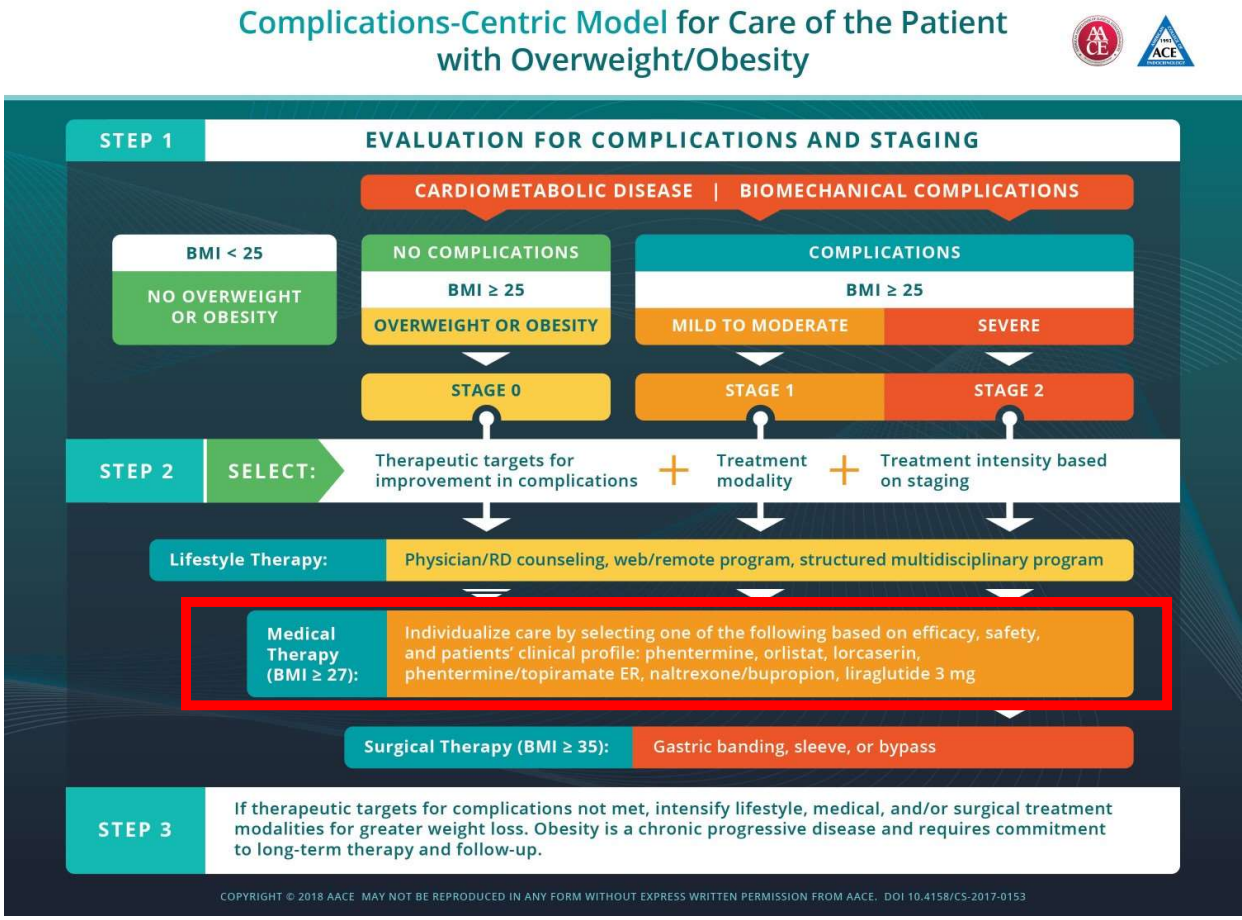


Sustaining long-term weight loss is challenging.

Adjunctive pharmacotherapy is recommended for

- Patients with BMI >=30
- Patients with BMI >=27 with comorbid conditions

(AACE 2016 guidelines)



Sustaining long-term weight loss is challenging.

- Available medications and options are currently limited due to modest efficacy, safety concerns, and cost.

Table 2. Pharmacotherapies for Chronic Weight Loss Management

Medication	Approved	Mechanisms of action	Mean weight loss (drug-placebo) at 1 year	
Orlistat	1999; 2007 (OTC)	Gastrointestinal lipase inhibitor causes excretion of approximately 25% to 30% of ingested fat in stool	–2.5 kg with 60 mg –3.4 kg with 120 mg	
Bupropion/naltrexone	2014	Bupropion: Inhibitor of neuronal reuptake of dopamine and norepinephrine Naltrexone: opioid antagonist	–6.2 kg	$300
Liraglutide	2014	Glucagon-like peptide 1 (GLP-1) agonist	–6.2 kg	$1400
~~Lorcaserin~~	~~2012~~	~~Selective serotonergic 5-HT2C~~	~~–3.2 kg~~	
Phentermine and topiramate extended release	2012	Phentermine: Sympathomimetic amine anorectic Topiramate: precise MOA is unknown. May be due to increased GABA activity, inhibition of AMPA/kainite excitatory glutamate receptors, inhibition of carbonic anhydrase	–6.7 kg with 7.5 mg P/46 mg T –8.9 kg with 15 mg P/92 mg T	$250

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABA, gamma-aminobutyrate, OTC, over the counter

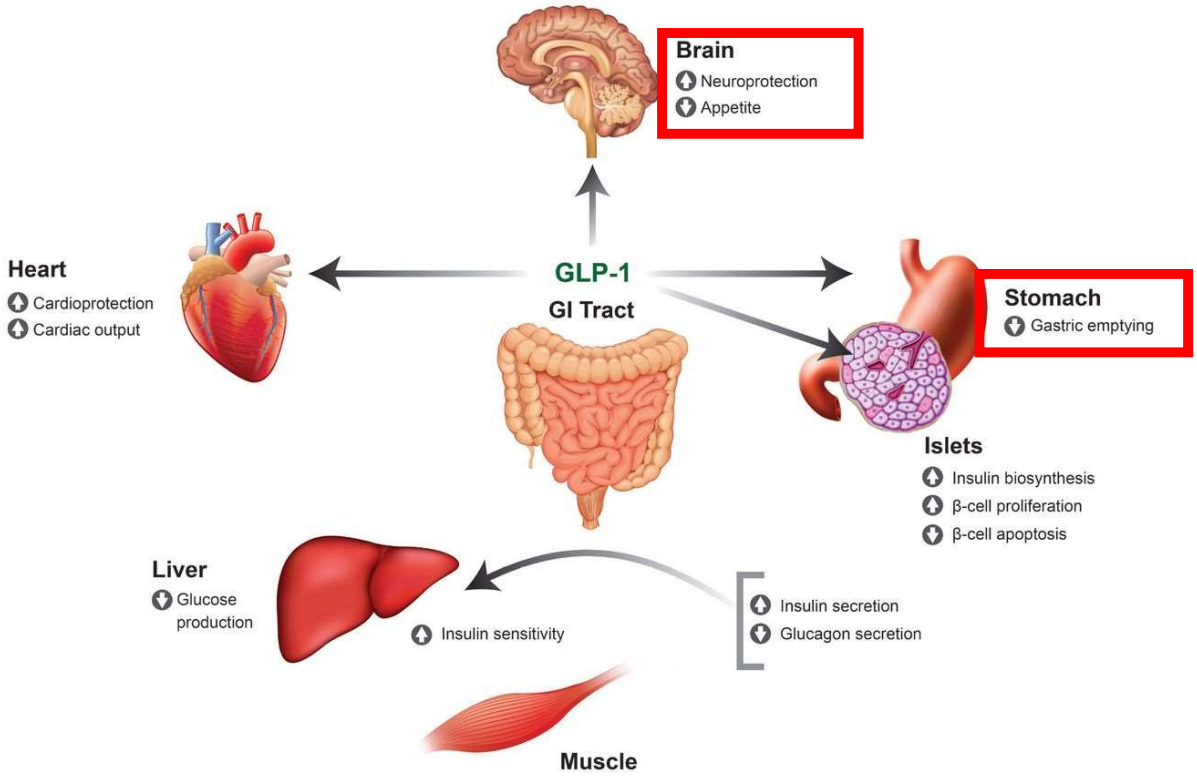
Data extracted from Yanovski SZ, et al.[4]

Modified from Powell AG, et al.[5]

GLP-1 agonists on obesity

MoA:

- Appetite suppression (hypothalamus)
- Decreased gastric emptying
- Early satiety.



GLP-1 agonists on obesity

Common forms:

-O***zem***pic (***Sem***aglutide IM weekly)

-***Trul***icity (***Dul***aglutide IM weekly)

-Victoza, Saxenda (Liraglutide IM qD)

-Rybelsus (Semaglutide PO)

-Soliqua (Glargine/Lixisenatide)

Previous Studies

- SCALE study (2015)- Liraglutide SQ 3.0mg qD + Lifestyle intervention vs Placebo + lifestyle. 63.2% vs 27.1% (P<0.001) of patients losing at least 5% of body weight.
    - Lead to FDA approval of liraglutide for obesity.
    - Once daily injection limits widespread use.

Previous Studies

- Semaglutide Phase 2 (2018)- Semaglutide SQ 0.1 – 0.4mg qD + Lifestyle intervention vs Placebo + lifestyle.
  - 13.8% vs 2.3% ($P<0.001$) weight loss from baseline.
  - 0.4mg qD equivalent to 2.4mg qWeekly.

Present study (2021): Semaglutide STAGE 3 trial (STEP 1)

- Does ***weekly*** semaglutide injection provide significant weight loss benefit in overweight or obese patients without diabetes?
  - Population = overweight or obese patients ***without*** diabetes
  - Intervention = ***weekly*** semaglutide injection + lifestyle modification
  - Outcome = presence of significant weight loss benefit over placebo

Methods

Inclusion/Exclusion Criteria
Study Procedure
Randomization
Endpoints
Statistical Analysis

Key Inclusion Criteria

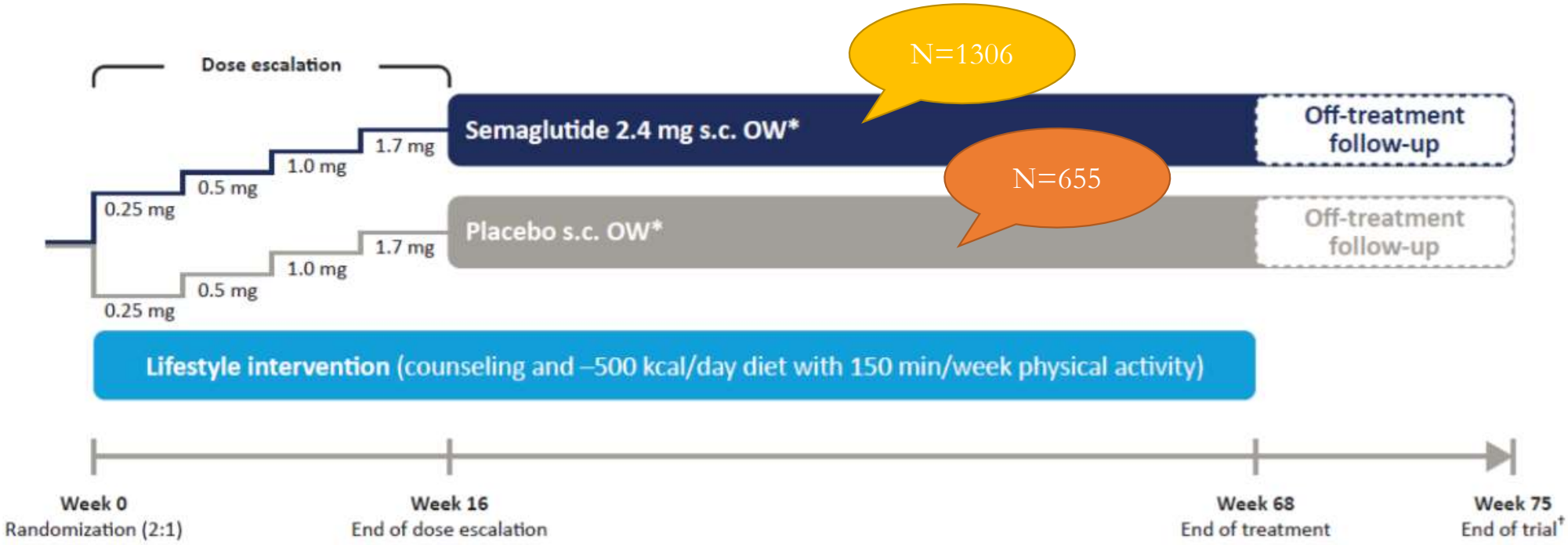
-Overweight or obese adults (BMI>27, Mean BMI 37.8)

-One or more self-reported unsuccessful dietary efforts

-One or more weight-related coexisting conditions (HTN, HLD, OSA, CVD)

Key Exclusion Criteria

- **Without history** of diabetes **(but including pre-diabetes, Mean A1c 5.7)**
- A1c > 6.5
- Hx of chronic pancreatitis, or acute pancreatitis within 180 days before enrollment
- Previous surgical obesity treatment
- Use of antiobesity medication within 90 days



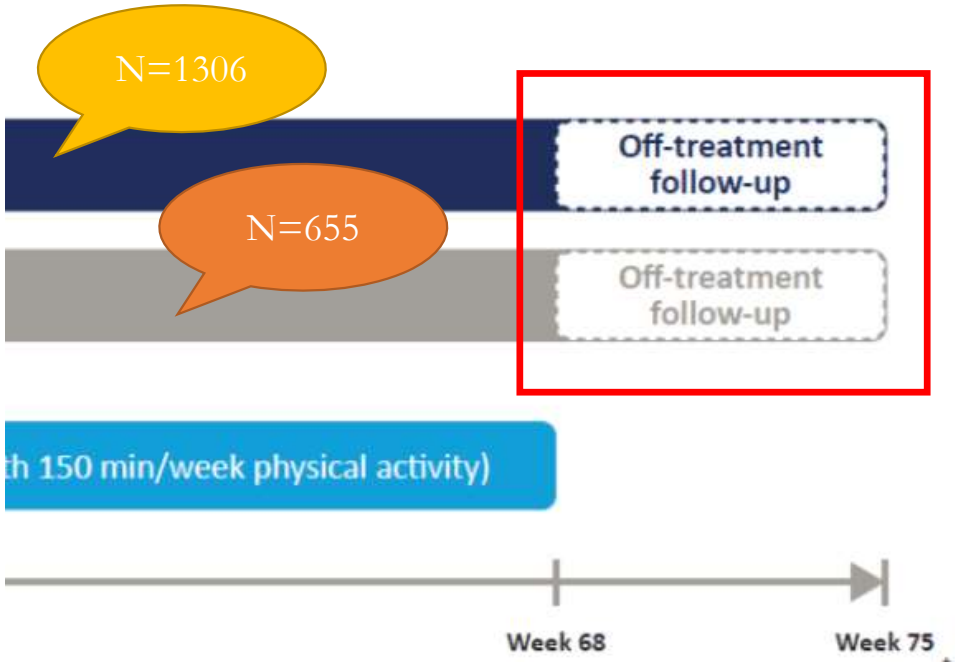
*As an adjunct to lifestyle intervention (–500 kcal/day diet with 150 min/week physical activity).

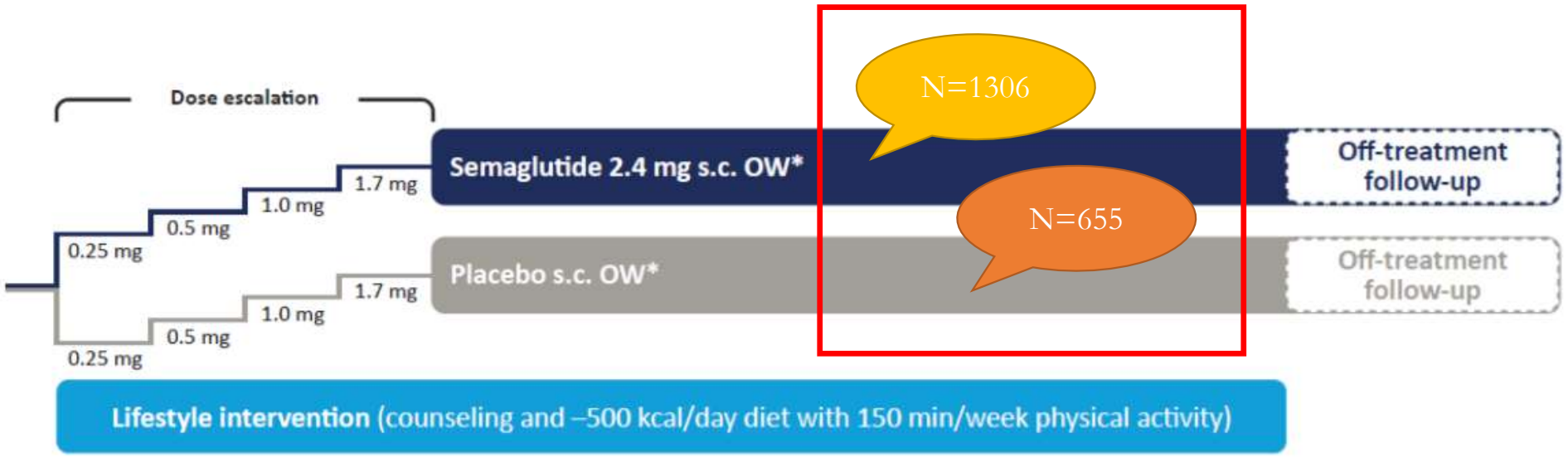
†End of trial for the main phase.

Semaglutide 2.4mg was pharmacokinetically equivalent to 0.4mg daily dose that was testing during Phase 2 of trial

Washout Period:

-Period of time after the intervention where all treatment is held off.
-Helps affirm that effects seen in a clinical trial are attributable to the investigational drug, not a chronic medication patient is on.





Treatment group N = 1306 VS **Placebo group N = 655**

…….Why?

2:1 (unequal) Randomization

Sometimes performed for the following purposes:

- If one arm is cheaper than the other arm.
- If a higher drop-out rate is expected in one arm.
- **Gathering additional safety information**
- Early phase trials where different dosing are being tested.
- If the intervention (such as surgery or new technology) has a learning curve
- **Increase patient recruitment.**

2:1 (unequal) Randomization

Problems of unequal randomization-

1. Patients are **aware** that they will more likely receive the treatment than not– which can introduce behavorial biases.

   "Therapeutic misrepresentation."

2. Attempting to increase patient turnout by giving them higher expectations of receiving treatment– can have ethical issues.

3. Causes loss of power rather than gaining power– 2:1 randomizations need 12% more patients to be equivalent. (for 3:1 randomizations, 33% more patients)

Hey SP, Kimmelman J. The questionable use of unequal allocation in confirmatory trials. *Neurology*. 2014

Endpoints

1) Co-primary End Points
2) Confirmatory Secondary End Points
3) Supplementary Secondary End Points (Cholesterol, Diastolic BP, glycemic control, etc)

Coprimary end points assessed in the overall population
Percent body-weight change from baseline to wk 68
Participants with body-weight reduction ≥5% at wk 68 — %‡
Confirmatory secondary end points assessed in the overall population
Participants with body-weight reduction ≥10% at wk 68 — %‡
Participants with body-weight reduction ≥15% at wk 68 — %‡
Change from baseline to wk 68
Waist circumference — cm
Systolic blood pressure — mm Hg
SF-36 physical functioning score
IWQOL-Lite-CT physical function score

‡ Denominators for the percentages of participants observed to have body-weight reduction of ≥5%, ≥10%, ≥15%, and ≥20% at week 68 are the numbers of participants for whom data were available at the week 68 visit — 1212 participants in the semaglutide group and 577 participants in the placebo group.

Co-primary End Points

Coprimary end points assessed in the overall population
Percent body-weight change from baseline to wk 68
Participants with body-weight reduction ≥5% at wk 68 — %‡

- **In order for the study to be "significant," both of these end points have to be significant.**
- Co-primary endpoints should preferably be used when the two endpoints are truly independent of another.

Co-primary End Points

If endpoints are not independent of one another---
Type I error (false positive) adjustment needed: When independent **co-primary endpoints** are used, each **primary endpoint** is tested at significance level (α) of 0.05.

=> However, is "Percent body-weight change from baseline to wk 68" and "Participants with body-weight reduction >=5% at wk 68" truly independent?
=> Significance level adjustment needed.

Co-primary End Points

Also, Type II error (false negative) adjustment needed: If you need more than one condition to "win," the false negative rate rises. The more hypotheses you test, the harder it is for you to prove that all of the hypotheses are correct. This is addressed by increasing **power (β).**

Intention to Treat?

Difference between the two co-primary endpoints regarding treatment of **drop-outs**

- Percent body-weight change from baseline to week 68

  -> includes the entire study population regardless of if they dropped out (**intention-to-treat analysis**)

- Participants with body-weight reduction >=5% at week 68‡

  -> does not include the numbers of participants whose data was not available at the week 68 visit– 94 (7.1% dropout) in semaglutide group and 78 (11.9%) participants in placebo group (**per-protocol analysis**)

‡ Denominators for the percentages of participants observed to have body-weight reduction of ≥5%, ≥10%, ≥15%, and ≥20% at week 68 are the numbers of participants for whom data were available at the week 68 visit — 1212 participants in the semaglutide group and 577 participants in the placebo group.

Why is this a problem?

Benefits of Randomization is Lost Without Intention-To-Treat Analysis

- The problem arises because **the reasons for nonadherence to the protocol may be related to prognosis**.
- Empirical evidence suggests that participants who adhere tend to do better than those who do not adhere, even after adjustment for all known prognostic factors and irrespective of assignment to active treatment or placebo.

Montori VM, Guyatt GH. Intention-to-treat principle. *CMAJ*. 2001;165(10):1339-1341.

Why is this a problem?

Benefits of Randomization is Lost Without Intention-To-Treat Analysis

- Excluding nonadherent participants from the analysis leaves those who may be destined to have a better outcome and destroys the unbiased comparison afforded by randomization.

Montori VM, Guyatt GH. Intention-to-treat principle. *CMAJ*. 2001;165(10):1339-1341.

Two Types of...
Secondary End Points

- Hard to justify why some are confirmatory and some are supportive; assumption is due to concerns of study power.

Confirmatory secondary end points assessed in the overall population
Participants with body-weight reduction ≥10% at wk 68 — %‡
Participants with body-weight reduction ≥15% at wk 68 — %‡
Change from baseline to wk 68
Waist circumference — cm
Systolic blood pressure — mm Hg
SF-36 physical functioning score
IWQOL-Lite-CT physical function score

Supportive secondary end points assessed in the overall population§
Participants with body-weight reduction ≥20% at wk 68 — %‡
Change from baseline to wk 68
Body weight — kg
Body-mass index
Glycated hemoglobin — percentage points
Fasting plasma glucose — mg/dl
Diastolic blood pressure — mm Hg
Lipid levels, ratio of wk 68 value to baseline¶
Total cholesterol
HDL cholesterol
LDL cholesterol
VLDL cholesterol
Free fatty acids
Triglycerides
C-reactive protein, ratio of wk-68 value to baseline¶

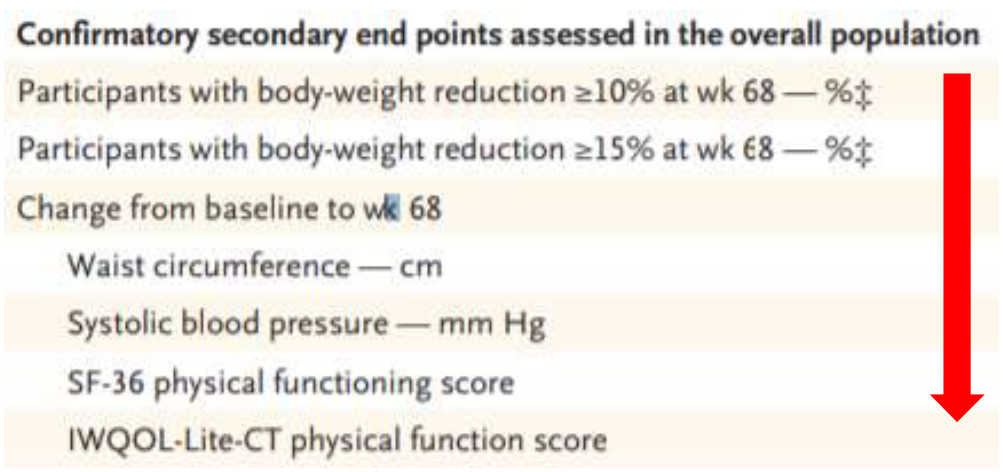
Statistical Analysis

- A study population of 1950 provided enough power for primary and secondary outcomes.
- All results from statistical analysis were accompanied by a two-sided 95% confidence interval and corresponding P values
- Confirmatory secondary endpoints were evaluated with Hierarchical Testing rather than Bonferroni Correction for Multiple Comparisons.
- Supplementary endpoints were not corrected for multiple comparisons

Multiple Comparisons Problem:

The more endpoints you evaluate, the more likely that you will have a positive test, thereby increasing false positive (Type I) error rate.

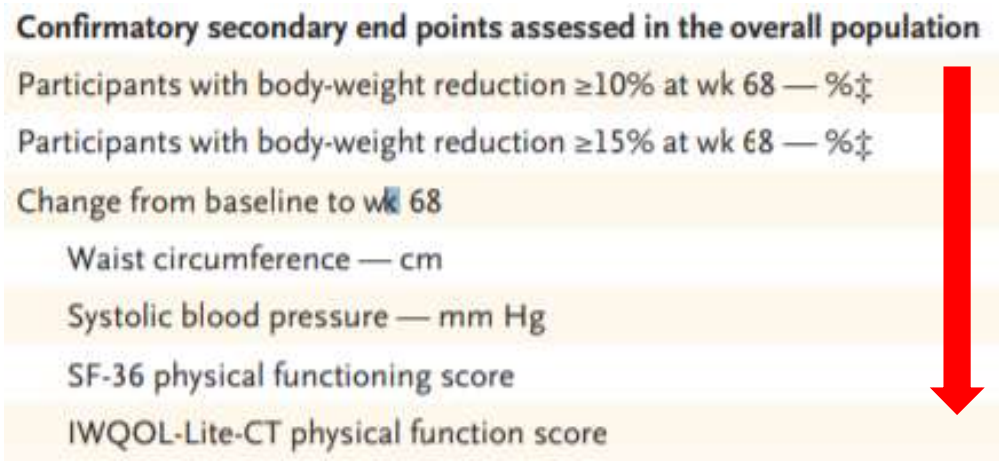
=> correct the α value (the cutoff for the P value, typically 0.05)



Bonferroni Correction	Hierarchical Testing
Each of the secondary end points will be considered to have the same false positive rate. ⇒ Correct the p-value cutoff by dividing it by the number of endpoints (α/n) ⇒ If there are 10 endpoints, P value cutoff is 0.05/10 = 0.005	Keep the p-value cutoff at the default (0.05), but only test the next hypothesis if the previous hypothesis is true. => Only if "# of patients with Body Weight Reduction >=15%" has a significant difference, test "Waist circumference"

Problem with Hierarchical Testing

- If hierarchical testing were to be used, it should be justified that the previous hypothesis is more important than the next hypothesis



Is waist circumference more important than systolic blood pressure?

Is systolic blood pressure more important than the physical functioning scores?

Safety Assessment

- Safety assessments included the number of adverse events occurring during the on-treatment period **(the time during which participants received any dose of semaglutide or placebo within the previous 49 days, with any period of temporary interruption of the regimen excluded)** and serious adverse events occurring between baseline and week 75.

=> If the patient had an adverse event during the time patient was off the regimen (or not compliant), this was not included in study.

Despite the issues regarding--

- Unequal randomization
- Co-primary end points
- Hierarchical testing
- Safety assessments,

…the results were still nonetheless promising.

Results

- Patient Characteristics/Randomization
- Primary and Secondary Endpoints
- Adverse Outcomes

<Patient Characteristics>

Characteristic	Semaglutide (N=1306)	Placebo (N=655)
Age — yr	46±13	47±12
Female sex — no. (%)	955 (73.1)	498 (76.0)
Race or ethnic group — no. (%)†		
White	973 (74.5)	499 (76.2)
Asian	181 (13.9)	80 (12.2)
Black or African American	72 (5.5)	39 (6.0)
Other	80 (6.1)	37 (5.6)
Hispanic or Latino ethnic group — no. (%)†	150 (11.5)	86 (13.1)
Body weight — kg	105.4±22.1	105.2±21.5
Body-mass index‡		
Mean	37.8±6.7	38.0±6.5
Distribution — no. (%)		
<30	81 (6.2)	36 (5.5)
≥30 to <35	436 (33.4)	207 (31.6)
≥35 to <40	406 (31.1)	208 (31.8)
≥40	383 (29.3)	204 (31.1)
Waist circumference — cm	114.6±14.8	114.8±14.4
Glycated hemoglobin — %	5.7±0.3	5.7±0.3
Prediabetes — no. (%)§	593 (45.4)	263 (40.2)

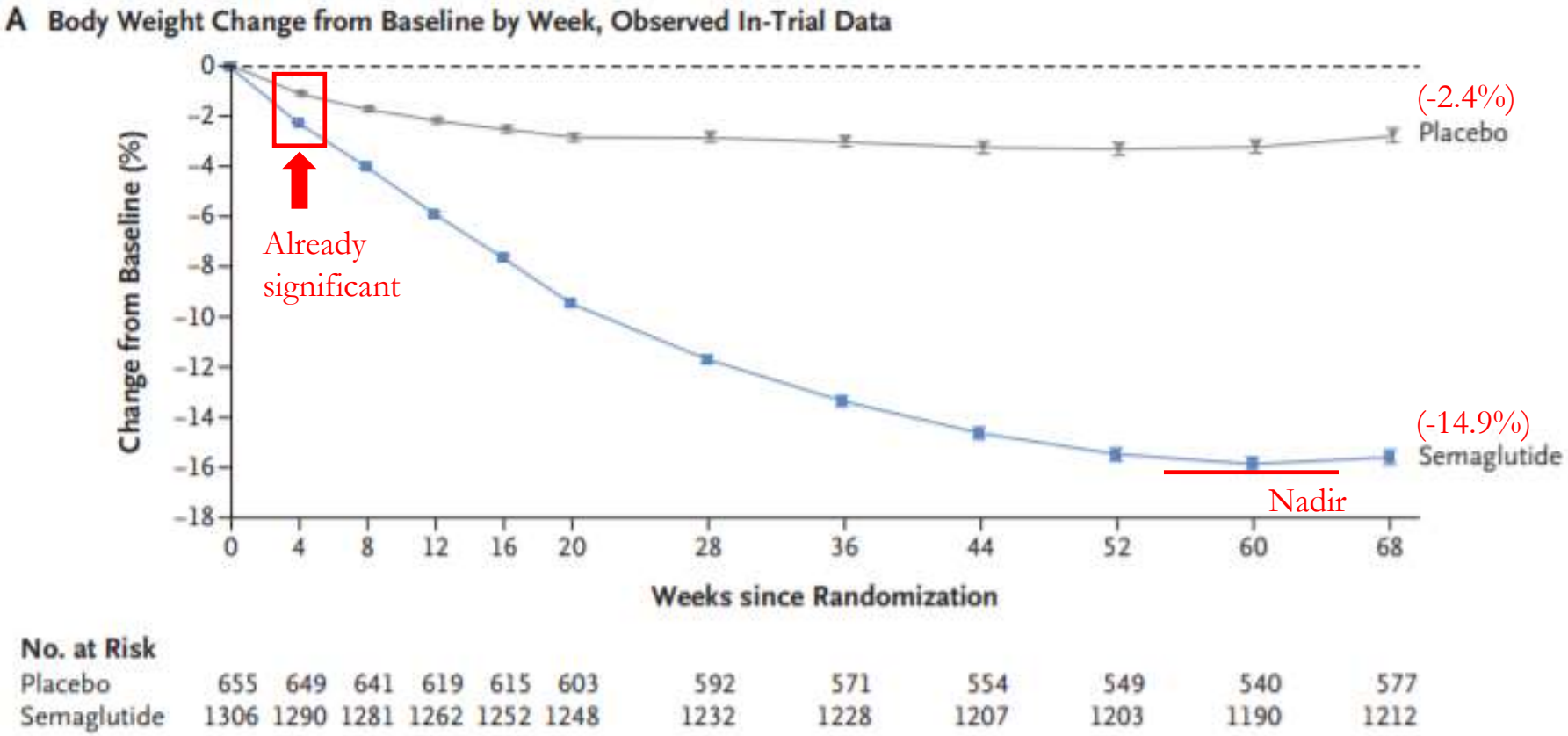
<- A disproportionate number of

-Female (73%)

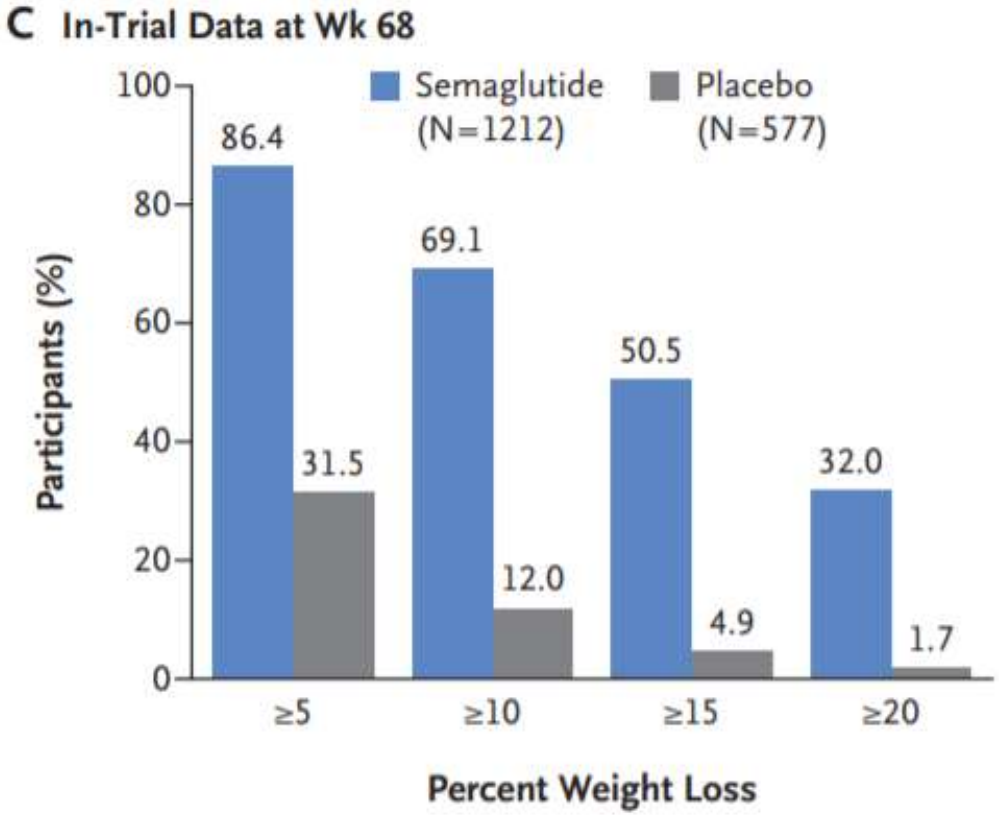
-White (74.5%)

-Patients with prediabetes (45.4%)

<Co-Primary Endpoint 1: % body weight change>



<Co-Primary Endpoint 2: % of patients reaching 5% weight loss>



<Confirmatory Secondary Endpoints>

End Point	Semaglutide (N=1306)	Placebo (N=655)	Difference between Semaglutide and Placebo (95% CI)†	Odds Ratio	P Value
Coprimary end points assessed in the overall population					
Percent body-weight change from baseline to wk 68	−14.85	−2.41	−12.44 (−13.37 to −11.51)		<0.001
Participants with body-weight reduction ≥5% at wk 68 — %‡	86.4	31.5		11.2 (8.9 to 14.2)	<0.001
Confirmatory secondary end points assessed in the overall population					
Participants with body-weight reduction ≥10% at wk 68 — %‡	69.1	12.0		14.7 (11.1 to 19.4)	<0.001
Participants with body-weight reduction ≥15% at wk 68 — %‡	50.5	4.9		19.3 (12.9 to 28.8)	<0.001
Change from baseline to wk 68					
Waist circumference — cm	−13.54	−4.13	−9.42 (−10.30 to −8.53)		<0.001
Systolic blood pressure — mm Hg	−6.16	−1.06	−5.10 (−6.34 to −3.87)		<0.001
SF-36 physical functioning score	2.21	0.41	1.80 (1.18 to 2.42)		<0.001
IWQOL-Lite-CT physical function score	14.67	5.25	9.43 (7.50 to 11.35)		<0.001

In all of the endpoints, the difference is very big and also statistically significant, whether Bonferroni Correction (α/n) or Hierarchical Testing is used.

<Supportive Secondary Endpoints>

However,
No P value reported

Supportive secondary end points assessed in the overall population§				
Participants with body-weight reduction ≥20% at wk 68 — %‡	32.0	1.7		26.9 (14.2 to 51.0)
Change from baseline to wk 68				
Body weight — kg	−15.3	−2.6	−12.7 (−13.7 to −11.7)	
Body-mass index	−5.54	−0.92	−4.61 (−4.96 to −4.27)	
Glycated hemoglobin — percentage points	−0.45	−0.15	−0.29 (−0.32 to −0.26)	
Fasting plasma glucose — mg/dl	−8.35	−0.48	−7.87 (−9.04 to −6.70)	
Diastolic blood pressure — mm Hg	−2.83	−0.42	−2.41 (−3.25 to −1.57)	
Lipid levels, ratio of wk 68 value to baseline¶				
Total cholesterol	0.97	1.00	0.97 (0.95 to 0.98)	
HDL cholesterol	1.05	1.01	1.04 (1.02 to 1.05)	
LDL cholesterol	0.97	1.01	0.96 (0.94 to 0.98)	
VLDL cholesterol	0.78	0.93	0.84 (0.81 to 0.87)	
Free fatty acids	0.83	0.93	0.89 (0.83 to 0.94)	
Triglycerides	0.78	0.93	0.84 (0.81 to 0.87)	
C-reactive protein, ratio of wk-68 value to baseline¶	0.47	0.85	0.56 (0.51 to 0.61)	

95% confidence interval for difference does not include 0.

95% confidence interval for ratio does not include 1.

Statistical significance **NOT reported** as these endpoints were not corrected for multiple comparisons with either Bonferroni or Hierarchical Testing **(therefore, no P value reported)**

<Safety Assessment>

Adverse Event	Semaglutide (N=1306)			Placebo (N=655)		
	No. of participants (%)	No. of events	Events/100 person-yr	No. of participants (%)	No. of events	Events/100 person-yr
Any adverse event	1171 (89.7)	9658	566.1	566 (86.4)	3302	398.0
Serious adverse events	128 (9.8)	164	9.6	42 (6.4)	53	6.4
Adverse events leading to discontinuation of drug or placebo	92 (7.0)	123	7.2	20 (3.1)	23	2.8
Gastrointestinal disorders	59 (4.5)	78	4.6	5 (0.8)	5	0.6
Fatal events†‡	1 (0.1)	1	0.1	1 (0.2)	3	0.3
Safety focus areas¶						
Gastrointestinal disorders‖	969 (74.2)	4309	252.6	314 (47.9)	739	89.1
Gallbladder-related disorders	34 (2.6)	42	2.5	8 (1.2)	8	1.0
Hepatobiliary disorders‖	33 (2.5)	40	2.3	5 (0.8)	5	0.6
Cholelithiasis	23 (1.8)	24	1.4	4 (0.6)	4	0.5
Hepatic disorders	31 (2.4)	37	2.2	20 (3.1)	24	2.9
Acute pancreatitis**	3 (0.2)	3	0.2	0	—	—
Cardiovascular disorders†	107 (8.2)	134	7.2	75 (11.5)	96	10.5
Allergic reactions	96 (7.4)	108	6.3	54 (8.2)	63	7.6
Injection-site reactions	65 (5.0)	99	5.8	44 (6.7)	82	9.9
Malignant neoplasms†	14 (1.1)	14	0.8	7 (1.1)	7	0.8
Psychiatric disorders‖	124 (9.5)	160	9.4	83 (12.7)	113	13.6
Acute renal failure	3 (0.2)	4	0.2	2 (0.3)	2	0.2
Hypoglycemia	8 (0.6)	15	0.9	5 (0.8)	7	0.8

‡ In the semaglutide group, sudden cardiac death occurred in one participant with a medical history of hypertension and obstructive sleep apnea who had discontinued semaglutide. In the placebo group, death due to glioblastoma, aspiration pneumonia, and severe sepsis occurred in one participant each who had discontinued placebo.

Discussion

- Strengths
- Limitations

Strengths

- The study had enough power to account for the two co-primary end points and the multiple secondary end points.
- The effect of the intervention was very significant ($P<0.001$) enough even when the following are considered:
  - Co-primary end points that are unlikely to be truly independent of one another
  - Hierarchical Analysis of secondary end points that are difficult to justify its hierarchy
  - 2:1 Randomization

Limitations- Population selection

- Study had a disproportionate number of Female (73%), White (74.5%)– does not represent the overall US population and hurts generalizability.
- The significant inclusion of patients with prediabetes (45.4%) without stratification of prediabetes status, makes it difficult to interpret results in patients with obesity ***without*** diabetes.*

=> **Regression analysis to find confounding vs effect modification would be useful.**

*Ingelfinger JR, Rosen CJ. STEP 1 for Effective Weight Control - Another First Step? N Engl J Med. 2021

Limitations- Study design

- 68 weeks in duration is still not long enough to truly address long-term efficacy. Obesity is a chronic medical illness.
- Many of the study's endpoints are evaluated in Per-protocol analysis rather than Intention-to-treat (ITT).
- 2:1 randomization can be helpful with studying medication side effects, but can raise concerns of therapeutic misrepresentation (patients are aware that they will more likely receive the treatment than not)– which is a statistical AND ethical concern.
- Study results during/after washout period (68-75 week) not reported.

Limitations- Study design

- Study compares semaglutide with placebo.
- Head-to-head trials comparing semaglutide with
  - GLP-1 agonists
  - SGLT-2 antagonists
  - Weight loss medications
  - Bariatric surgery

will be necessary to evaluate true benefit.

(Both semaglutide and liraglutide produced by Novo Nordisk, unlikely to publish comparative studies)

Limitations- Net Clinical Benefit

- Once-weekly subcutaneous injection is likely more tolerable compared to daily injections; however, still difficult to justify its use when there are daily oral preparations of GLP-1 agonists.
- Cost-effectiveness of the solution is still unclear.

  2.4mg Ozempic = $195.06. 1.5mg Trulicity = $168.28.
- Study results show increased risk of GI and gallbladder disease.

Summary

- In participants with overweight or obesity, 2.4 mg of weekly subcutaneous semaglutide plus lifestyle intervention was associated with decrease in body weight.

- Study had enough power to show statistical significance in co-primary/confirmatory secondary endpoints

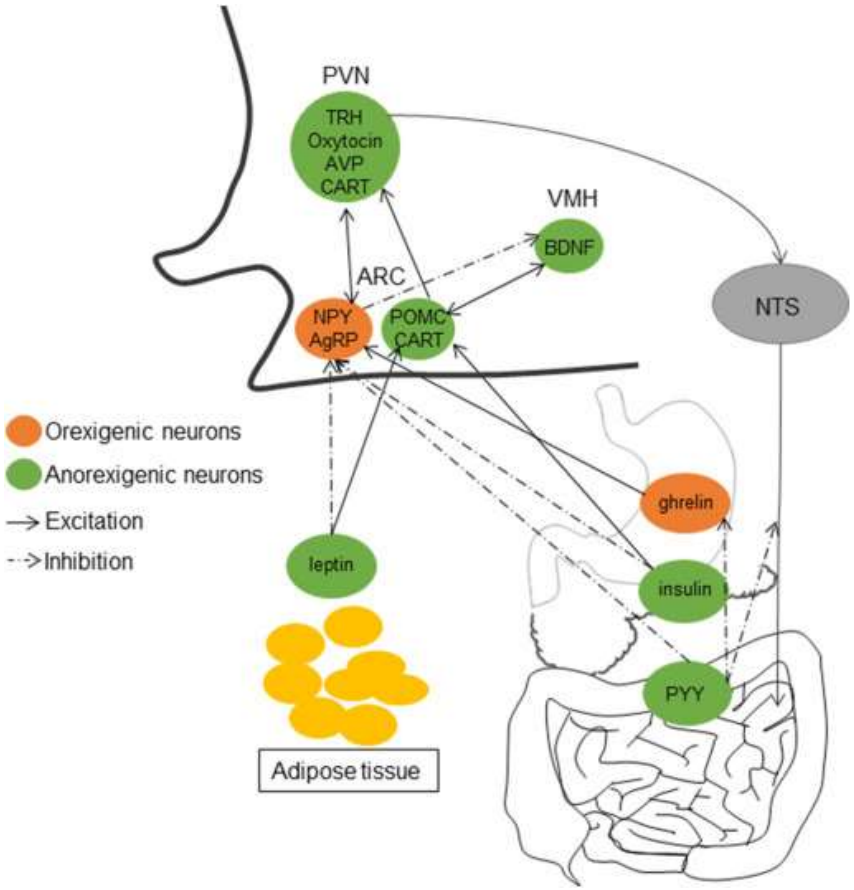
- Limitations include skewed population towards white females, inclusion of pre-diabetics, duration of study, analysis methods.

- Cost of medication and side effect profile may decrease net clinical benefit

- Head-to-head trials with other obesity treatment modalities are needed.

Thank you

- … Any questions?



[Pharmacotherapy of obesity: Available medications and drugs under investigation - Metabolism - Clinical and Experimental (metabolismjournal.com)]

TABLE 1. Summary of therapeutic options for weight loss (WL) approved by the United States Food and Drug Administration (FDA)

NAME (TRADE)	MECHANISM OF ACTION	EFFICACY*	SIDE EFFECTS**	COST***
Phentermine	Sympathomimetic—suppresses appetite	(a) 46% (b) 4.5kg	Anxiety, dizziness, hypertension, constipation	(a) $34.78 (b) $1.16
Orlistat (Alli)	Lipase inhibitor—reduces fat absorption	(a) 33% (b) 2.0kg	Vitamin deficiencies, fatty stools, flatulence	(a) $39.94 (b) $0.67
Lorcaserin (Belviq)	Selective 5-HT2C receptor agonist—promotes satiety	(a) 50% (b) 3.6kg	Headache, dizziness, nausea	(a) $322.27 (b) $7.86
Phentermine/ Topiramate (Osymia)	Sympathomimetic + antiepileptic—suppresses	(a) 67% (b) 7.5kg	Topiramate: numbness/tingling of hands or paresthesias; Phentermine: see above	(a) $235.94 (b) $7.86
Naltrexone/buproprion (Contrave)	Norepinephrine reuptake inhibitor + pure opioid antagonist—suppresses appetite	(a) 56% (b) 4.6kg	Nausea	(a) $310.30 (b) $2.59
Liraglutide (Saxenda)	GLP-1 agonist—suppresses appetite + glucose homeostasis	(a) 76% (b) 4.4kg	Nausea, vomiting	(a) $1,405.38 (b) $46.85

* (a) Percentage of patients on intervention that lost >5 percent weight in randomized, controlled trial; (b) Absolute intervention weight loss minus placebo weight loss in randomized, controlled trial
** See text section on risks for contraindications
*** (a) Average retail cost; (b) Cost per dose

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