Evidence-Based Medicine: Semaglutide for Weight Loss in Overweight or Obese Patients

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CUSOM

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CAMPBELL UNIVERSITY | Jerry M. Wallace School of Osteopathic Medicine

Our patient . . .

A 46-year-old woman presents to her primary care physician to discuss strategies for weight loss. She has steadily gained weight over the last five years. She is 5’9”, now weights 240 lbs with a BMI of 35.

She has tried multiple diet strategies on her own with little success. She tries to walk two or three times per week but her knees bother her.

PMH:

- OA of knees
- OSA
- HTN
- No known CAD
- No known diabetes

Medications:

- Lisinopril 20 mg po daily
- Chlorthalidone 25 mg po daily
- Acetaminophen 1000 mg po tid prn knee pain

Social history: She is married and lives with her husband. She has a sedentary job at a local retail store. There is no hx of tobacco, alcohol or drug use. She has no health insurance so she takes generic medications whenever possible.

Family hx is significant for obesity and HTN but is otherwise negative.

Her vital signs and weight are stable today and her exam is otherwise without new findings.

She wants to know her options for weight loss moving forward . . .
She has also heard of a new weekly injectable medication for weight loss . . .

Clinical question:
What are the efficacy and safety of semaglutide in the treatment of overweight or obesity among patients without diabetes?

Source:
Wilding JPH, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. **New Engl J. Med** 2021;384(11):989-1002

DIET AND EXERCISE

GLUCAGON-LIKE PEPTIDE RECEPTOR AGONIST

("-glutides")

- Acts in gut
- Reduces glucagon secretion
- Slows gastric emptying and improves satiety

Glucagon-like peptide-1 receptor agonist (GLP-1) RA Semaglutide

Mechanism	•Reduces glucagon secretion •Slows gastric emptying and improves satiety
Dose, Route, Frequency	0.25 mg SQ weekly; increase by 0.25 mg every for weeks to target dose of 2.4 mg
Class Side effects	Pancreatitis; GI upset; slight increase in HR; thyroid cancer
Contraindications	Multiple endocrine neoplasia; hx pancreatitis; personal or family hx medullary thyroid cancer

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Was the assignment of patients to treatment randomized? And was the randomization list concealed?

2. Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

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1. Were the patients and clinicians kept “blind” to which treatment was being received?

2. Aside from the experimental treatment, were the groups treated equally?

3. Were the groups similar at the start of the trial?

If the study satisfies these criteria, then it has *internal validity.*

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

Do these results apply to your patient?

(ie. Do the results have *external validity*?)

- Is the patient so different from those in the trial that its results cannot help you?
- How great would the potential benefit of therapy actually be for your individual patient?

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

- Are your patient's values and preferences satisfied by the regimen and its consequences?
  - Do your patient and you have a clear assessment of their values and preferences?
  - Are they met by this regimen and its consequences?

Semaglutide for Weight Loss

Design: Randomized, double-blind, placebo-controlled multicenter trial

Setting: 129 clinical sites in 16 countries

Was the assignment of patients treatment randomized?
And was the randomization list concealed?

Were the patients and clinicians kept “blind” to which treatment was being received?

Semaglutide for Weight Loss: Patients included

Semaglutide for Weight Loss: Patients included

- Adults 18 years or older
- One or more self-reported unsuccessful dietary efforts to lose weight.
- BMI $\geq$ 30 OR BMI $\geq$ 27 with one or more comorbidity:
  - HTN
  - HLD
  - OSA
  - ASHD
- Written informed consent

Semaglutide for Weight Loss: Patients excluded

Semaglutide for Weight Loss: Patients excluded

- Diabetes
- Hx chronic pancreatitis
- Acute pancreatitis within the last 180 days prior to enrollment
- Previous bariatric surgery
- Use of antiobesity medication within the last 90 days prior to enrollment

Semaglutide for Weight Loss: Interventions

Semaglutide for Weight Loss: Interventions

- Patients randomized in 2:1 fashion:
  - Semaglutide 2.4 mg SQ weekly
  - Placebo SQ weekly
- 68-week study period
- Followed by 7-week period without semaglutide or placebo

- Semaglutide dosing:
  - Starting dose : 0.25 mg SQ weekly
  - Increased by 0.25 mg every four weeks until target dose of 2.4 mg SQ weekly by week 16 OR until side effects occurred

Semaglutide for Weight Loss: Interventions

- All patients had dietary counseling every four weeks to create a caloric deficit of 500 cal daily
- All patients encouraged to perform moderate-level physical activity about 150 minutes per week (ie. 30 minutes five days per week), such as walking

Semaglutide for Weight Loss: Interventions

- Intention-to-treat analysis: every subject included in data analysis once randomization has occurred.

Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Semaglutide for Weight Loss: Outcomes

Semaglutide for Weight Loss: Efficacy Outcomes

- Primary:
  - Percentage change in body weight from baseline to week 68
  - Achievement of weight loss of 5% or more by week 68

- Secondary:
  - Reduction in baseline body weight $\geq$ 10%
  - Reduction in baseline body weight $\geq$ 15%

Semaglutide for Weight Loss: Safety Outcomes

- All adverse events occurring from baseline to week 68 among all patients receiving at least one dose either semaglutide or placebo

- Serious adverse events occurring from baseline to week 75

- Independent external adjudication for selected adverse events:
  - Cardiovascular events
  - Acute pancreatitis

Semaglutide for Weight Loss : Study Power

Study Power: Why it is important

- To design a trial with a sample size which *optimizes* the opportunity to demonstrate a true treatment effect between two study groups (for example, between a medication compared to placebo)

- The probability of successfully demonstrating a true treatment effect is the *power of the study*

- It is also important to decide what probability investigators are willing accept that the treatment effect demonstrated is due to *chance* alone rather than a true treatment effect

Estimating the Necessary Sample Size based on the following assumptions. . Semaglutide for Weight Loss

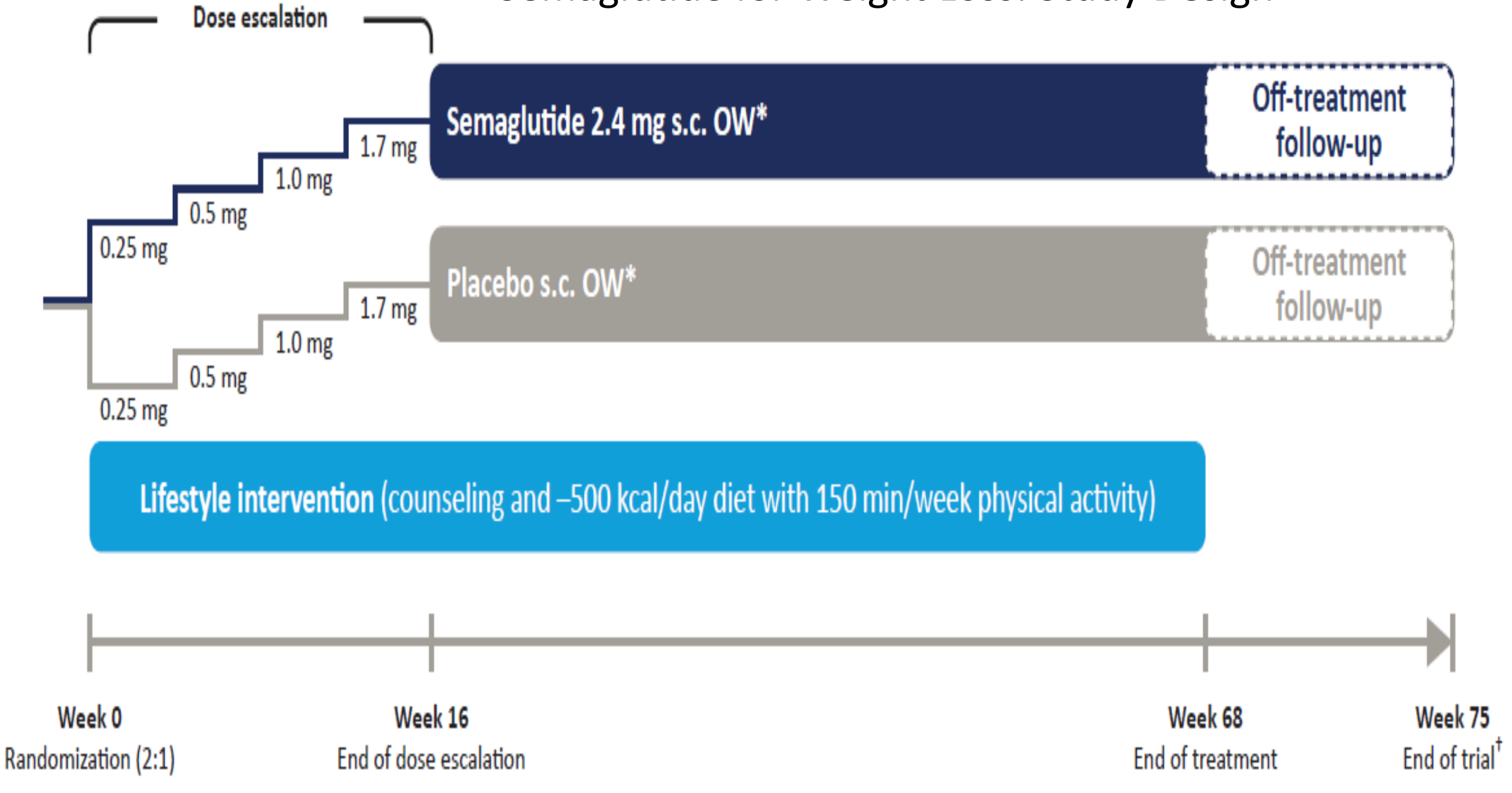
- IF investigators want a 99% probability of demonstrating a statistically significant difference with semaglutide compared to placebo with respect to:
  - Loss from baseline weight
  - % of patients losing at least 5% of weight from baseline

- AND investigators are willing to accept a 5% probability that the difference demonstrated is not a true treatment effect but instead is due to chance alone (ie. 5% chance of type 1 error, or $p < 0.05$)

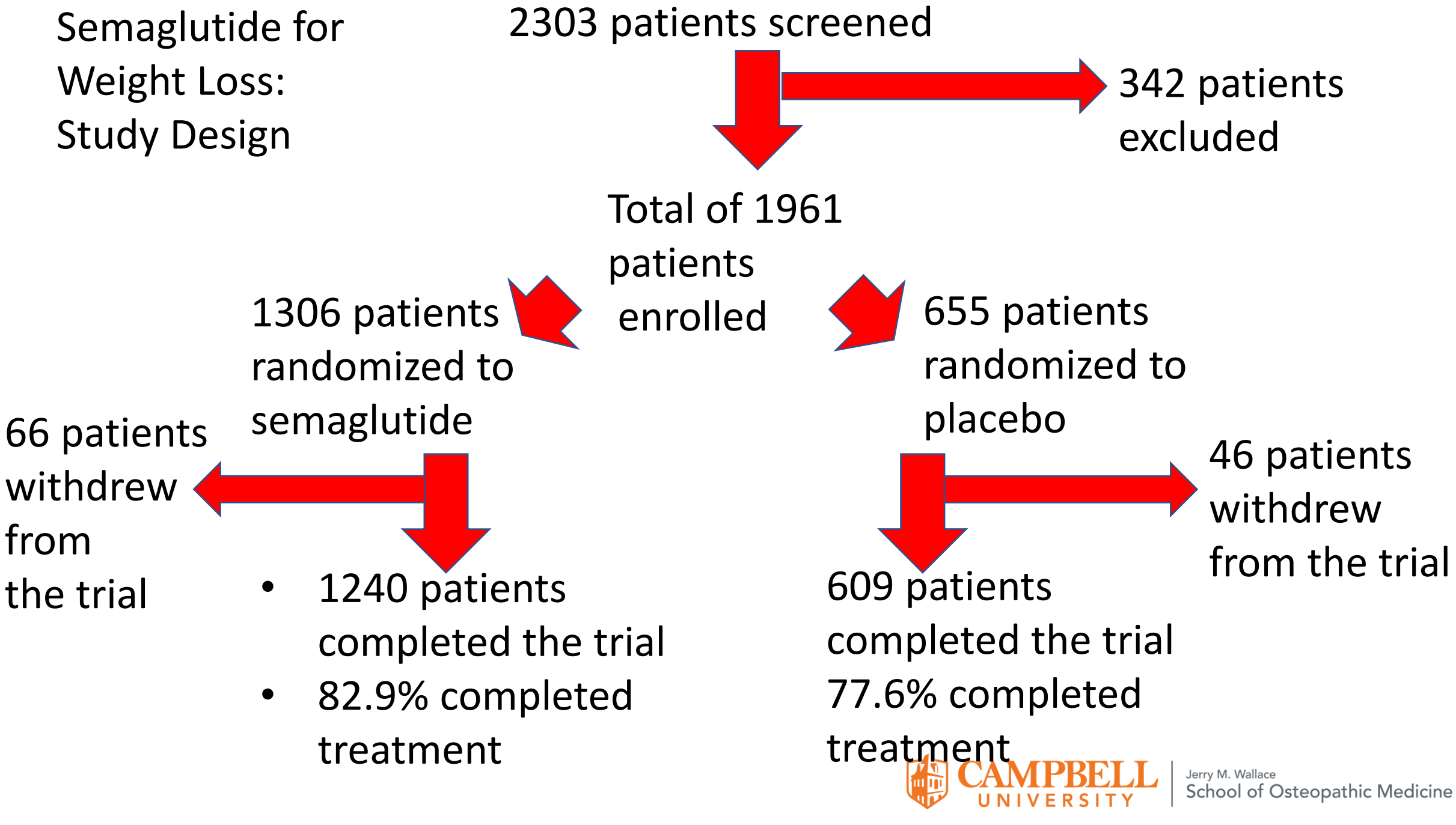
- THEN a sample size of 1950 patients is needed . . .

Semaglutide for Weight Loss: Main Results

Semaglutide for Weight Loss: Study Design



Semaglutide for Weight Loss: Study Design



Semaglutide for Weight Loss: Baseline Patient Characteristics

Characteristic	**Semaglutide (N=1306)**	**Placebo (N=655)**
Age (years)	46	47
Female sex (%)	73.1	76.0

Semaglutide for Weight Loss: Baseline Patient Characteristics

Race/Ethnic Group (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
White	74.5	76.2
Asian	13.9	12.2
Black or African American	5.5	6.0

Semaglutide for Weight Loss: Baseline Patient Characteristics

Race/Ethnic Group (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Hispanic or Latino	11.5	13.1
Other	6.1	5.6

Semaglutide for Weight Loss: Baseline Patient Characteristics

Characteristic	**Semaglutide (N=1306)**	**Placebo (N=655)**
BMI (kg/m2), mean	37.8	38.0

Semaglutide for Weight Loss: Baseline Patient Characteristics

BMI (kg/m2) Distribution (%)	Semaglutide (N=1306)	Placebo (N=655)
< 30	6.2	5.5
≥ 30 to < 35	33.4	31.6
≥ 35 to < 40	31.1	31.8
≥ 40	29.3	31.1

Semaglutide for Weight Loss: Baseline Patient Characteristics

Characteristic	**Semaglutide (N=1306)**	**Placebo (N=655)**
Waist circumference (cm)	114.6 (45.1 inches)	114.8 (45.3 inches)
GFR ml/min/1.73m2 BSA	96.3	95.9

Semaglutide for Weight Loss: Baseline Patient Characteristics

Comorbidity(%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Dyslipidemia	38.2	34.5
HTN	36.1	35.7
Knee OA	13.2	15.6
OSA	12.2	10.8

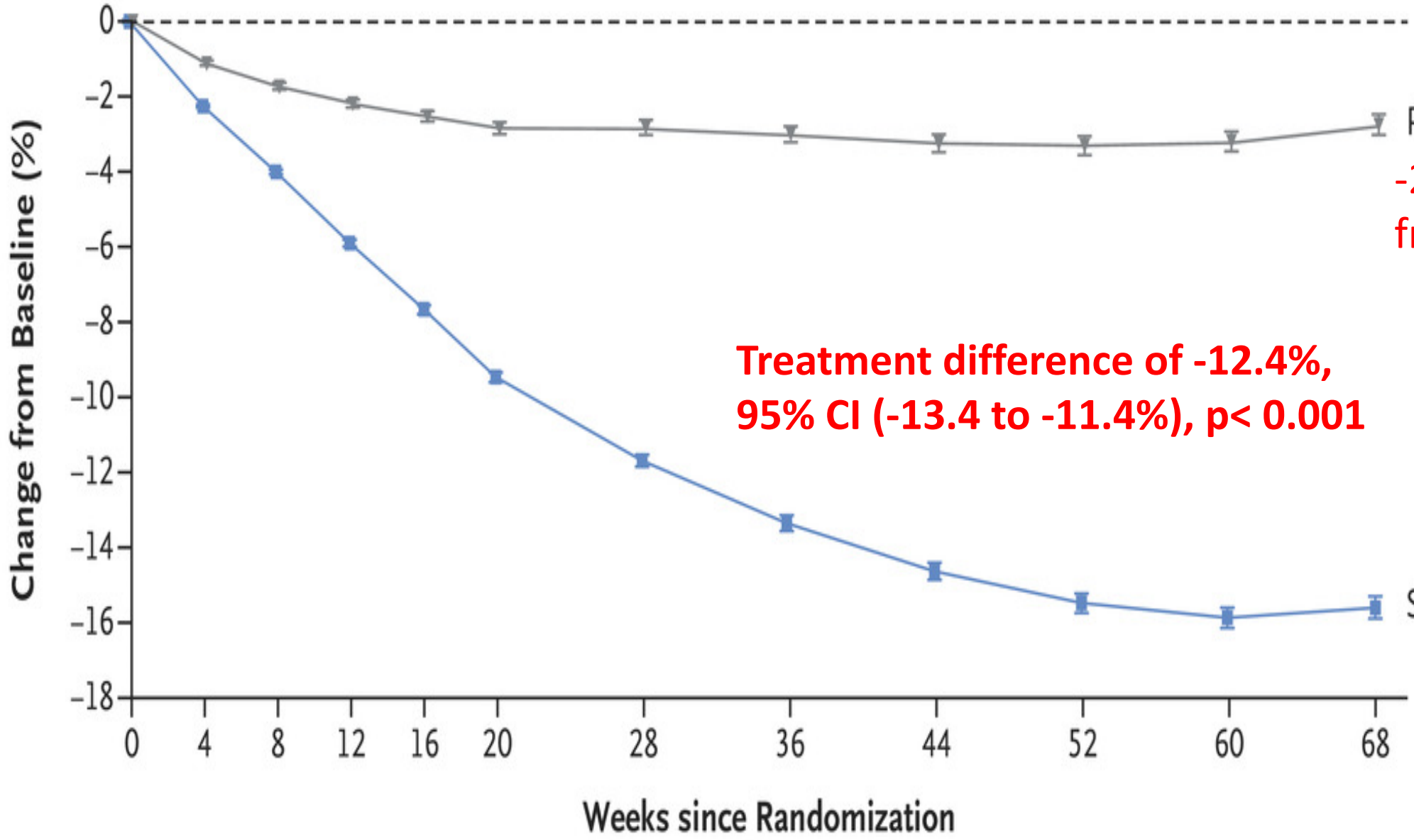
Semaglutide for Weight Loss: Baseline Patient Characteristics

Comorbidity (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Asthma or COPD	11.3	12.2
NASH	7.7	9.5
PCOS	6.5	6.8
CAD	2.5	2.6

- Aside from the experimental treatment, were the groups treated equally?
- Were the groups similar at the start of the trial?

Semaglutide for Weight Loss: Primary Efficacy Outcomes

Body Weight Change from Baseline by Week, Observed In-Trial Data

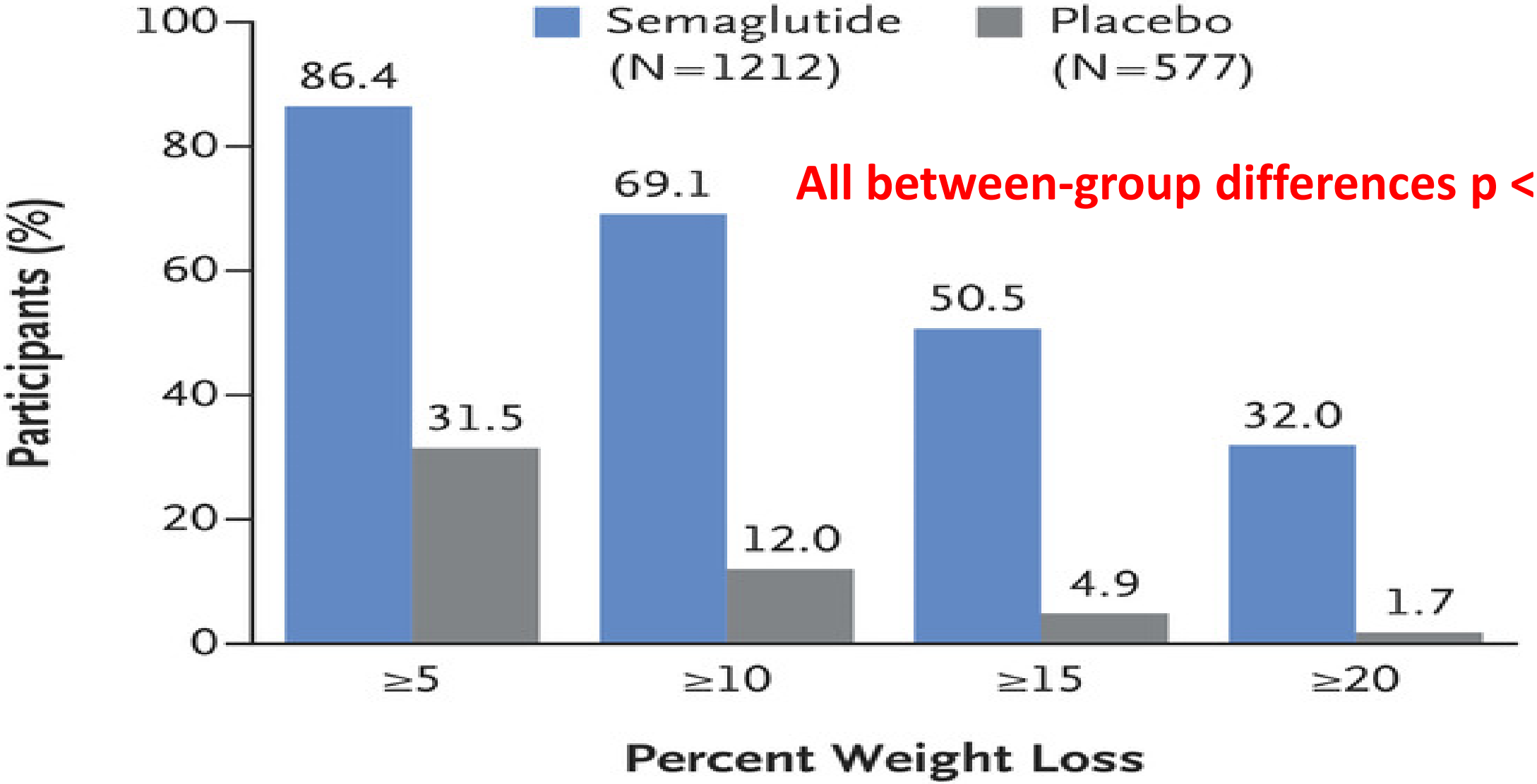


-2.4% change from baseline

Treatment difference of -12.4%, 95% CI (-13.4 to -11.4%), p< 0.001

-14.9% change from baseline

In-Trial Data at Wk 68



All between-group differences p < 0.001

Semaglutide for Weight Loss: Proportion of Patients with Significant Weight Loss from Baseline

Weight Loss from Baseline	Semaglutide (%)	Placebo (%)	Relative Risk of given weight loss with semaglutide vs placebo
≥ 5%	86.4	31.5	1.74
≥ 10%	69.1	12.0	4.76
≥ 15%	50.5	4.9	10.3

Semaglutide for Weight Loss: Safety Outcomes

Semaglutide for Weight Loss: Safety Outcomes

Side effects reported by ≥ 10% of patients (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Nausea	44.2	17.4
Diarrhea	31.5	15.9
Vomiting	24.8	6.6

Semaglutide for Weight Loss: Safety Outcomes

Side effects reported by ≥ 10% of patients (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Constipation	23.4	9.5
Nasopharyngitis	21.5	20.3
Headache	15.2	12.2

Semaglutide for Weight Loss: Safety Outcomes

Side effects reported by ≥ 10% of patients (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Dyspepsia	10.3	3.5
Abdominal pain	10.0	5.5
Upper respiratory tract infection	8.7	12.2

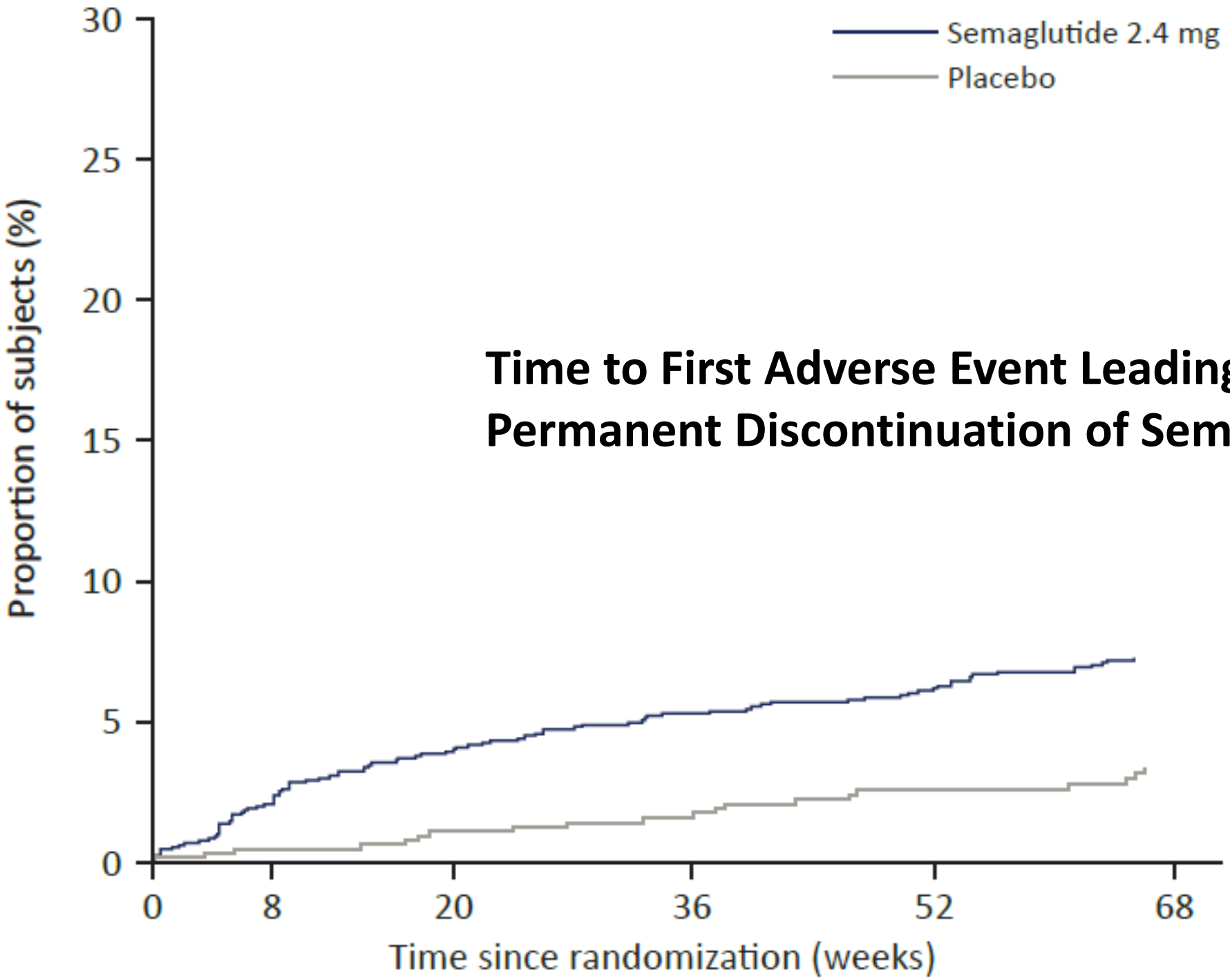
Semaglutide for Weight Loss: Safety Outcomes

Outcome (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Any adverse event	89.7	86.4
Serious adverse event	9.8	6.4
Fatal events	0.1	0.2

Semaglutide for Weight Loss: Safety Outcomes

Outcome (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Total adverse events leading to discontinuation of semaglutide or placebo	7.0	3.1
Gastrointestinal disorders leading to discontinuation of semaglutide or placebo	4.5	0.8

Time to First Adverse Event Leading to Permanent Discontinuation of Semaglutide or Placebo



Semaglutide for Weight Loss: Safety Outcomes

Prespecified Safety Outcome (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Any gastrointestinal disorder	4.5	0.8
Acute pancreatitis	0.2	0
Gallbladder disorder	2.6	1.2

Semaglutide for Weight Loss: Safety Outcomes

Prespecified Safety Outcome (%)	**Semaglutide (N=1306)**	**Placebo (N=655)**
Cardiovascular disorders	8.2	11.5
Allergic reactions	7.4	8.2
Hypoglycemia	0.6	0.8

Semaglutide for Weight Loss: Main Conclusions

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- Among patients *without diabetes*, with overweight (BMI > 27) with at least one related comorbidity or among obese patients (BMI > 30) who follow a reduced-calorie diet and a moderate exercise regimen, semaglutide titrated up to 2.4 mg SQ weekly compared to placebo:
  - Led to a mean 14.9% loss in baseline body weight after 68 weeks (about 1.5 years)
  - Increased the chance of a ≥ 5% weight loss by a factor of about 2; a ≥ 10% weight loss by a factor of about 5 and a > 15% weight loss by a factor of about 10.

Semaglutide for Weight Loss: Main Conclusions

- Among patients *without diabetes* overweight (BMI > 27) with at least one related comorbidity or among obese patients (BMI > 30) who follow a reduced-calorie diet and a moderate exercise regimen, semaglutide titrated up to 2.4 mg SQ weekly compared to placebo:
  - Most common side effects were gastrointestinal including nausea, vomiting, abdominal pain, dyspepsia, diarrhea and constipation. About 5% of patients discontinued semaglutide due to gastrointestinal side effects
  - Led to a higher incidence of gastrointestinal disorders, specifically gallbladder disorders but the risk of acute pancreatitis was < 0.5%

Semaglutide for Weight Loss: Main Conclusions

- Among patients *without diabetes* with overweight (BMI > 27) with at least one related comorbidity or among obese patients (BMI > 30) who follow a reduced-calorie diet and a moderate exercise regimen, semaglutide titrated up to 2.4 mg SQ weekly compared to placebo:
  - No fatal events attributed to semaglutide
  - No significant increase in risk of hypoglycemia

Semaglutide for Weight Loss: Strengths of this study

- Large sample size
- High degree of completion of trial over 90%
- High degree of adherence to study medication about 80%

Semaglutide for Weight Loss: Limitations of this study

- Sample not diverse: > 75% white patients, > 75% women
- Patients with diabetes excluded from this trial
- Short follow up of only about 1.5 years
- Some post marketing reports of rebound weight gain after semaglutide is stopped

Glucagon-like peptide-1 receptor agonist (GLP-1) RA Semaglutide

Mechanism	•Reduces glucagon secretion •Slows gastric emptying and improves satiety
Dose, Route, Frequency	0.25 mg SQ weekly; increase by 0.25 mg every for weeks to target dose of 2.4 mg
Class Side effects	Pancreatitis; GI upset; slight increase in HR; thyroid cancer
Contraindications	Multiple endocrine neoplasia; hx pancreatitis; personal or family hx medullary thyroid cancer

How does the efficacy of semaglutide compare to other FDA-approved medications for weight loss?

Weight loss outcomes with FDA-approved medications

Perreault, UpToDate 2023

But there is one big problem . . .

Semaglutide burns a hole in your wallet!!!

Cost/month	**$1,407 per month at Walmart *with Good Rx discount***

Many insurers refuse to cover semaglutide for weight loss

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Monthly Cost of FDA-approved weight loss drugs

Medication	**Approximate Monthly Cost at Walmart through Good Rx**
Phentermine	$15
Phentermine-topiramate	$200
Bupropion-naltrexone	$500
Orlistat	$600
Semaglutide	**$1,400**

Back to our patient. . .

Is the patient so different from those in the trial that its results cannot help you?

NO—the patients in this trial are similar enough to our patient; therefore, we can apply the trial's result to our patient . . .

A 46-year-old woman presents to her primary care physician to discuss strategies for weight loss. She has steadily gained weight over the last five years. She is 5’9”, now weights 240 lbs with a BMI of 35.

She has tried multiple diet strategies on her own with little success. She tries to walk two or three times per week but her knees bother her.

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Social history: She is married and lives with her husband. She has a sedentary job at a local retail store. There is no hx of tobacco, alcohol or drug use. She has no health insuranceso she takes generic medications whenever possible.

Family hx is significant for obesity and HTN but is otherwise negative.

Her vital signs and weight are stable today and her exam is otherwise without new findings.

She wants to know her options for weight loss moving forward . . .
She has also heard of a new weekly injectable medication for weight loss . . .

You recommend a dietician consultation with the goals of surveying her daily diet and starting a reduced calorie diet with a 500-calorie daily deficit for weight loss. You also encourage her to walk at her own pace for 30 minutes at least four times per week.

You also counsel her that she meets criteria for weight loss medication. Unfortunately, she currently has no health insurance.

You discuss the options of generic phentermine or semaglutide if she can enroll in a patient assistance program.

You counsel her that there are good data for weekly semaglutide for weight loss and that she meets criteria to use the medication if she can afford it. You discuss the starting dose, and the titration schedule over several months to a target dose of 2.4 mg SQ weekly. You counsel her that semaglutide would give her the best chance of achieving at least a 5% weight loss from baseline when combined with reduced-calorie diet and exercise.

You also counsel her that the most common side effects of semaglutide include stomach upset with nausea vomiting, abdominal pain, or changes in bowel function and that about 5% of patients have to stop semaglutide due to side effects. You discuss the rare side effect of acute pancreatitis with this class of drug. You review the symptoms and signs of acute pancreatitis.

You also discuss the rare side effect of thyroid cancer with use of medications similar to semaglutide.

The patient agrees to a dietician referral and with a walking program. She will try these lifestyle changes and return in four to six weeks for reevalution and to discuss medication options . . .

Questions?

Thank you!

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