Cagrilintide–Semaglutide in Adults with Overweight or Obesity and Type 2 Diabetes

Mentor: Dr mansouri

Presented by: Reza Rahimzdeh

Background

- Obesity & Type 2 diabetes are closely linked.
- Weight loss improves glycemic control & reduces complications.
- Semaglutide & cagrilintide individually induce weight loss.
- CagriSema combines both drugs for potentially greater efficacy.
- This study assessed CagriSema in patients with Type 2 diabetes.
- Trial aimed at evaluating efficacy & safety.

Objective

- Evaluate the efficacy and safety of CagriSema (2.4 mg each) vs placebo in overweight/obese adults with T2DM.
- Primary endpoints:
  - % change in body weight
  - % achieving ≥5% weight loss
- Also assessed glycemic outcomes, QoL, and adverse events.

Methods - Study Design

- Phase 3a, double-blind, randomized, placebo-controlled trial.
- Conducted across 12 countries; 68-week duration.
- Participants: Age >18, BMI ≥27, HbA1c 7-10%, Type 2 diabetes.
- CagriSema 2.4 mg each or placebo weekly + lifestyle intervention.
- Primary endpoints: % change in body weight & ≥5% weight loss.
- Secondary endpoints: glycemic control, safety, other health metrics.

Methods - Key Procedures

- Dose escalation every 4 weeks to 2.4 mg maintenance dose.
- Submaximal doses allowed if side effects occurred.
- Continuous glucose monitoring in selected patients.
- Outcome assessed via treatment-policy estimand (ITT principle).
- Additional trial-product estimand analyzed on-treatment effects.
- Multiple imputation for missing data; hierarchical testing approach.

Baseline Characteristics

- 1206 patients randomized: 904 CagriSema, 302 placebo.
- Mean age: 56 years; 52.8% male.
- Mean weight: 102.2 kg; Mean BMI: 36.2.
- HbA1c: 8.0%; Duration of diabetes: 8.5 years.
- Most common drugs: Metformin (85.9%), SGLT2i (33.4%), SU (26.9%).
- Groups well balanced at baseline.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

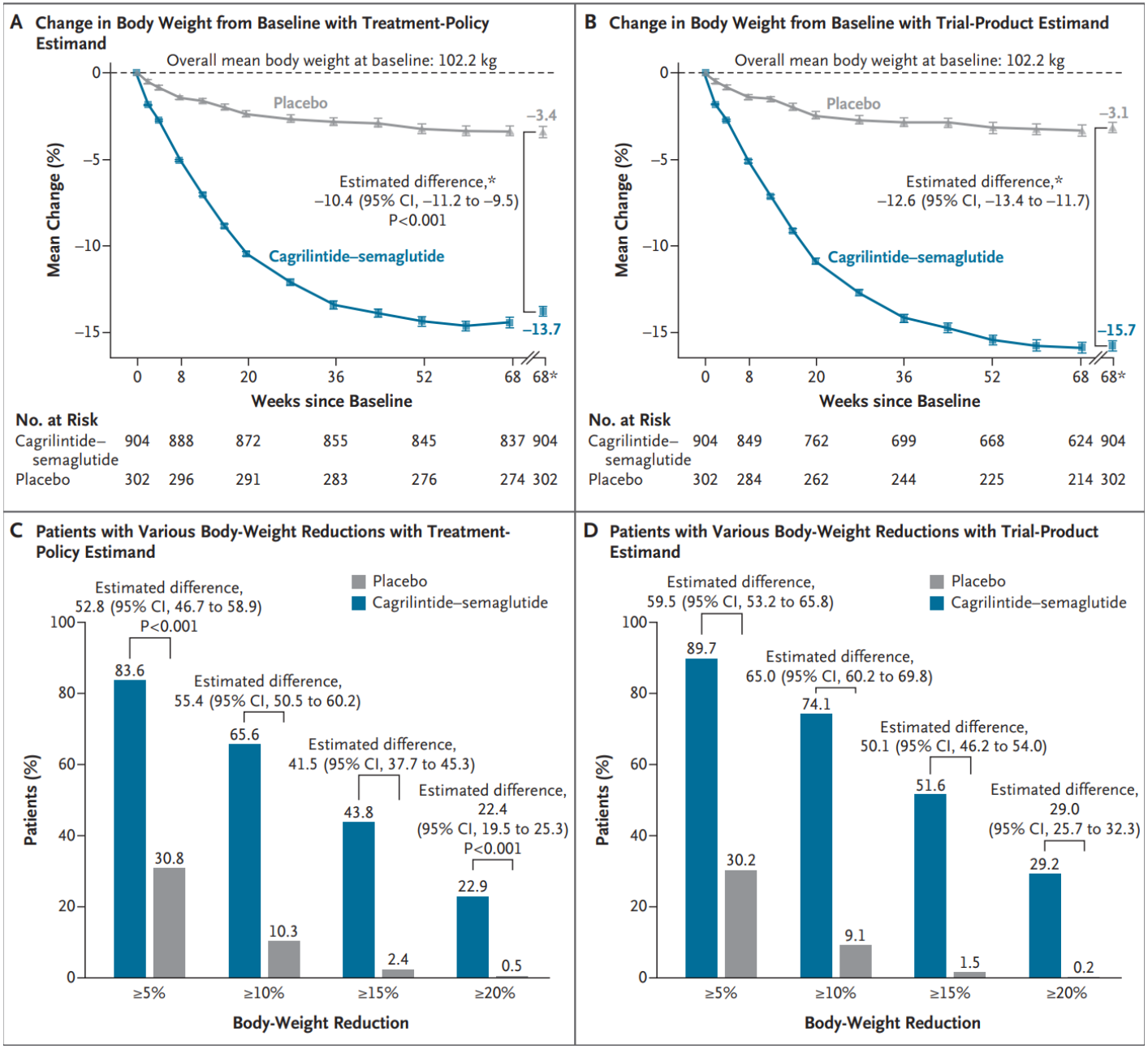
Characteristic	Cagrilintide–Semaglutide (N=904)	Placebo (N=302)
Age — yr	55.9±11.8	56.5±10.7
Female sex — no. (%)	429 (47.5)	140 (46.4)
Race or ethnic group — no. (%)†		
White	597 (66.0)	204 (67.5)
Asian	262 (29.0)	84 (27.8)
Black	33 (3.7)	10 (3.3)
Other‡	12 (1.3)	4 (1.3)
Body weight — kg	101.9±22.6	103.3±23.5
Body-mass index	36.1±6.7	36.4±7.1
Waist circumference — cm	115.6±14.7	116.4±15.2
Glycated hemoglobin level — %	8.0±0.8	8.0±0.8
Fasting plasma glucose level — mmol/liter	9.3±2.4	9.5±2.8
Blood pressure — mm Hg		
Systolic	130.2±14.0	130.2±13.8
Diastolic	80.4±9.6	80.4±9.3
Estimated glomerular filtration rate — ml/min/per 1.73 m^2	94.2±19.3	93.4±17.2
Duration of diabetes — yr	8.5±6.3	8.7±5.9
Oral glucose-lowering medication — no. (%)		
Metformin	773 (85.5)	263 (87.1)
SGLT2 inhibitor	305 (33.7)	98 (32.5)
Sulfonylurea	238 (26.3)	87 (28.8)
Thiazolidinedione	41 (4.5)	15 (5.0)
None	64 (7.1)	18 (6.0)
Physical function		
IWQOL-Lite-CT score§	59.0±24.3	59.7±24.0
SF-36v2 score¶	44.8±9.8	44.6±9.6

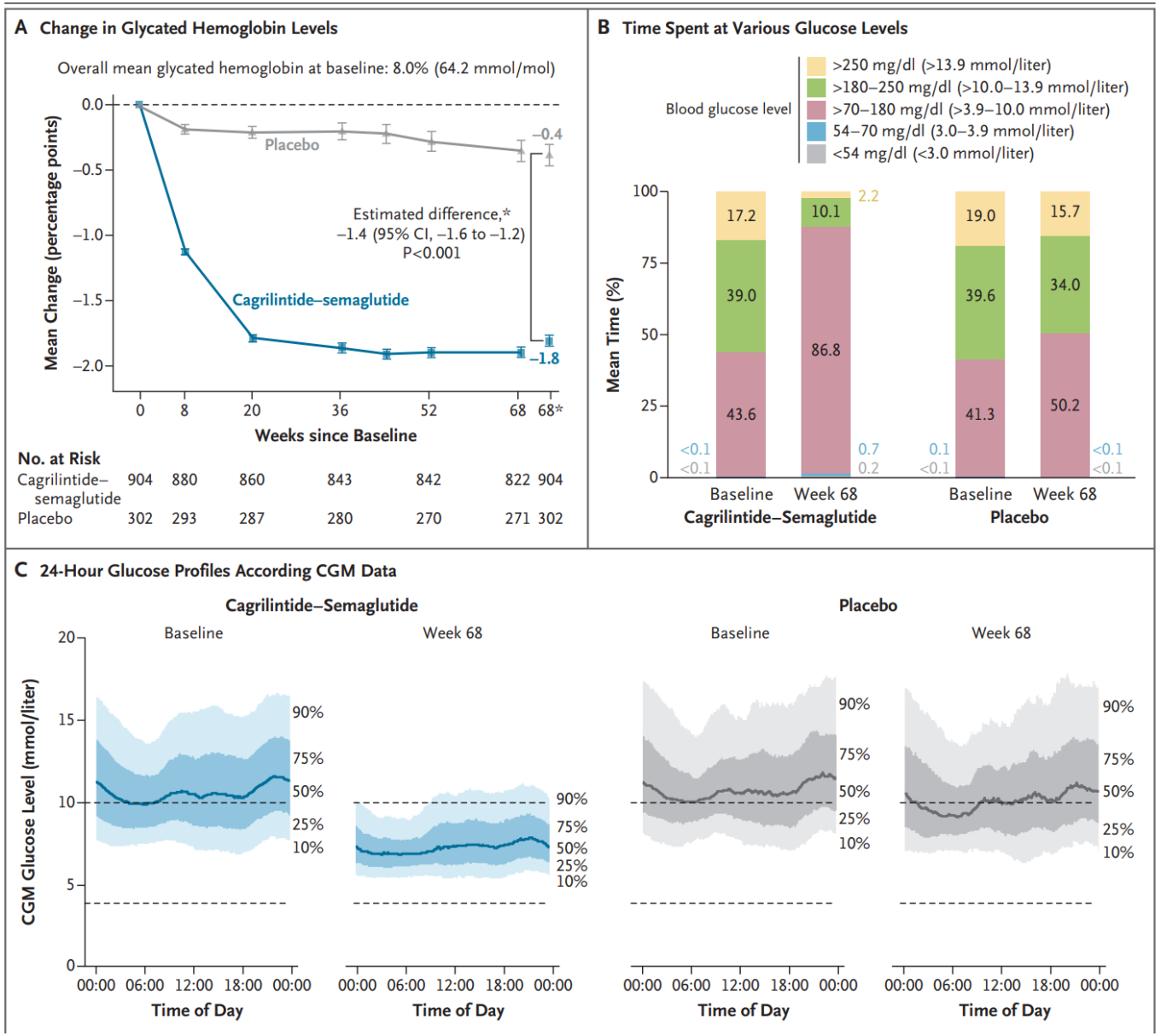
Results - Primary Endpoints

- Body weight change: -13.7% (CagriSema) vs -3.4% (Placebo).
- Difference: -10.4 percentage points ($P<0.001$).
- ≥5% weight loss: 83.6% (CagriSema) vs 30.8% (Placebo).
- Higher proportions achieved ≥10%, ≥15%, ≥20% weight loss.
- Waist circumference & glycemic measures also improved.
- Results consistent across both estimands.

Table 2. Primary and Confirmatory Secondary End Points.*

End Point	Cagrilintide–Semaglutide (N=904)	Placebo (N=302)	Treatment Difference (95% CI)	P Value
Primary end points				
Percent change in body weight	−13.7	−3.4	−10.4 (−11.2 to −9.5)	<0.001
Patients with body-weight reduction of ≥5% — %	83.6	30.8	52.8 (46.7 to 58.9)	<0.001
Confirmatory secondary end points				
Patients with body-weight reduction of ≥20% — %	22.9	0.5	22.4 (19.5 to 25.3)	<0.001
Percent change in body weight from baseline to week 20	−10.1	−2.3	−7.8 (−8.3 to −7.3)	<0.001
Change in waist circumference — cm	−11.9	−3.6	−8.3 (−9.3 to −7.3)	<0.001
Change in glycated hemoglobin level — percentage points	−1.8	−0.4	−1.4 (−1.6 to −1.2)	<0.001
Change in systolic blood pressure — mm Hg	−6.5	−2.4	−4.1 (−6.0 to −2.1)	<0.001
Change in IWQOL-Lite-CT physical-function score				
All patients	16.1	10.4	5.8 (3.2 to 8.4)	<0.001
Patients with poor physical function at baseline†	21.8	12.0	9.8 (2.1 to 17.6)	0.01
Change in SF-36v2 physical-function score				
All patients	5.0	3.1	1.9 (0.9 to 3.0)	<0.001
Patients with poor physical function at baseline†	7.6	3.8	3.8 (0.5 to 7.1)	0.02


A Change in Body Weight from Baseline with Treatment-Policy Estimand
Overall mean body weight at baseline: 102.2 kg
Placebo
Cagrilintide–semaglutide
Estimated difference,*
–10.4 (95% CI, –11.2 to –9.5)
P<0.001
–3.4
–13.7
Mean Change (%)
0
–5
–10
–15
0
8
20
36
52
68
68*
Weeks since Baseline
No. at Risk
Cagrilintide–semaglutide 904 888 872 855 845 837 904
Placebo 302 296 291 283 276 274 302
B Change in Body Weight from Baseline with Trial-Product Estimand
Overall mean body weight at baseline: 102.2 kg
Placebo
Cagrilintide–semaglutide
Estimated difference,*
–12.6 (95% CI, –13.4 to –11.7)
–3.1
–15.7
Mean Change (%)
Weeks since Baseline
No. at Risk
Cagrilintide–semaglutide 904 849 762 699 668 624 904
Placebo 302 284 262 244 225 214 302
C Patients with Various Body-Weight Reductions with Treatment-Policy Estimand
Placebo
Cagrilintide–semaglutide
Estimated difference, 52.8 (95% CI, 46.7 to 58.9) P<0.001
Estimated difference, 55.4 (95% CI, 50.5 to 60.2)
Estimated difference, 41.5 (95% CI, 37.7 to 45.3)
Estimated difference, 22.4 (95% CI, 19.5 to 25.3) P<0.001
83.6
30.8
65.6
10.3
43.8
2.4
22.9
0.5
Patients (%)
100
80
60
40
20
0
≥5%
≥10%
≥15%
≥20%
Body-Weight Reduction
D Patients with Various Body-Weight Reductions with Trial-Product Estimand
Placebo
Cagrilintide–semaglutide
Estimated difference, 59.5 (95% CI, 53.2 to 65.8)
Estimated difference, 65.0 (95% CI, 60.2 to 69.8)
Estimated difference, 50.1 (95% CI, 46.2 to 54.0)
Estimated difference, 29.0 (95% CI, 25.7 to 32.3)
89.7
30.2
74.1
9.1
51.6
1.5
29.2
0.2
Patients (%)
≥5%
≥10%
≥15%
≥20%
Body-Weight Reduction


A Change in Glycated Hemoglobin Levels
Overall mean glycated hemoglobin at baseline: 8.0% (64.2 mmol/mol)
Mean Change (percentage points)
0.0
−0.5
−1.0
−1.5
−2.0
Placebo
−0.4
Estimated difference,*
−1.4 (95% CI, −1.6 to −1.2)
P<0.001
Cagrilintide–semaglutide
−1.8
0
8
20
36
52
68
68*
Weeks since Baseline
No. at Risk
Cagrilintide–semaglutide 904 880 860 843 842 822 904
Placebo 302 293 287 280 270 271 302
B Time Spent at Various Glucose Levels
Blood glucose level
>250 mg/dl (>13.9 mmol/liter)
>180–250 mg/dl (>10.0–13.9 mmol/liter)
>70–180 mg/dl (>3.9–10.0 mmol/liter)
54–70 mg/dl (3.0–3.9 mmol/liter)
<54 mg/dl (<3.0 mmol/liter)
Mean Time (%)
100
75
50
25
0
17.2
39.0
43.6
<0.1
<0.1
10.1
2.2
86.8
0.7
0.2
19.0
39.6
41.3
0.1
<0.1
15.7
34.0
50.2
<0.1
<0.1
Baseline
Week 68
Cagrilintide–Semaglutide
Baseline
Week 68
Placebo
C 24-Hour Glucose Profiles According CGM Data
Cagrilintide–Semaglutide
Placebo
Baseline
Week 68
Baseline
Week 68
CGM Glucose Level (mmol/liter)
20
15
10
5
0
90%
75%
50%
25%
10%
00:00 06:00 12:00 18:00 00:00
Time of Day

Discussion

CagriSema (combination of cagrilintide and semaglutide) led to:

- Significant, clinically meaningful weight loss in adults with overweight or obesity and Type 2 diabetes.
- Near normalization of blood glucose levels in many patients.
- Improvements in cardiovascular risk factors (BP, lipids, inflammation) and physical functioning.

The weight loss effect is likely due to:

- Complementary mechanisms of the two drugs affecting appetite and energy regulation.
- Enhanced control over eating and glucose metabolism.

Discussion

Efficacy Comparison:

- Weight loss magnitude similar to other advanced treatments with lower dose (like tirzepatide).
- Higher proportions achieved significant weight-loss thresholds (≥5%, ≥10%, ≥15%, ≥20%) compared to placebo.
- Achieving substantial weight loss is generally harder in Type 2 diabetes due to medications promoting weight gain.

The trial demonstrated benefits even though:

Many participants were on drugs causing weight gain (e.g., sulfonylureas, thiazolidinediones).

Weight loss was slightly less than in non-diabetic populations (a typical pattern seen in obesity trials).

Discussion

Glycemic Control:

- Achieved excellent glycemic outcomes with low hypoglycemia risk.
- High percentage of patients reached HbA1c ≤6.5%.
- Improved time in target glucose ranges in those using continuous glucose monitoring.

Physical Function:

- Notable improvements in quality of life and physical functioning, especially in those with poor baseline function.

Dosing Flexibility:

- Flexible dose adjustment helped minimize side effects and treatment discontinuation.
- Even with dose adjustments, significant benefits were maintained.

Discussion

Safety Profile:

- Mostly mild to moderate GI adverse events.
- Low discontinuation rate due to side effects.
- Low rates of hypoglycemia and serious adverse events

Table 3. Adverse Events.*

Adverse Events	Cagrilintide–Semaglutide (N=904)			Placebo (N=302)		
	Patients	Events	Event Rate†	Patients	Events	Event Rate†
	no. (%)	*no.*		*no. (%)*	*no.*	
Any	815 (90.2)	6088	477.4	258 (85.4)	1275	301.6
Serious	94 (10.4)	138	10.8	39 (12.9)	51	12.1
Leading to permanent discontinuation						
Any adverse event	76 (8.4)	97	7.6	9 (3.0)	13	3.1
Gastrointestinal adverse event	43 (4.8)	49	3.8	2 (0.7)	3	0.7
Fatal event‡	4 (0.4)	4	0.3	0	—	—
Hypoglycemic episode§						
Alert value: level 1¶	108 (11.9)	328	27.8	24 (7.9)	61	15.6
Clinically significant: level 2¶	54 (6.0)	85	7.2	10 (3.3)	11	2.8
Severe: level 3¶	2 (0.2)	2	0.2	0	—	—
Selected safety event						
Gastrointestinal disorder¶	655 (72.5)	2742	232.4	104 (34.4)	227	58.0
Retinal disorder	75 (8.3)	94	7.4	24 (7.9)	29	6.9
Neoplasm	63 (7.0)	80	6.3	20 (6.6)	26	6.1
Allergic reaction¶	46 (5.1)	55	4.7	18 (6.0)	19	4.9
Injection-site reaction¶	44 (4.9)	65	5.5	0	—	—
Gallbladder-related disorder¶	18 (2.0)	24	2.0	2 (0.7)	2	0.5
Malignant neoplasm‖	14 (1.5)	16	1.3	4 (1.3)	4	0.9
Pancreatitis¶	3 (0.3)	3	0.3	0	—	—
Suicidal ideation or behavior**	8 (0.9)	—	—	4 (1.4)	—	—

Discussion

Strengths of the Study:

- Large sample size.
- Long duration.
- Use of continuous glucose monitoring.

Limitations:

- No monotherapy comparator arms (no separate cagrilintide or semaglutide arms).
- Mostly White participants, limiting generalizability.
- Limited use of continuous glucose monitoring (only 16.5% of patients).

Conclusion

- CagriSema highly effective for weight loss & glycemic control in Type 2 diabetes.
- Clinically meaningful reductions in HbA1c, body weight, and cardiometabolic risk.
- Safe with mainly GI-related adverse events.
- Promising treatment option requiring long-term use.