Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes (SURPASS-2)

報告藥師：**陳嬿宇 藥師**

指導藥師：**簡佳穎 藥師**

2022/5/18

OUTLINE

Background

- ADA Guideline 2022
- Tirzepatide

Journal

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes.
Frías JP, et al. N Engl J Med. 2021 Aug 5;385(6):503-515.

Appraisal

CASP Checklist for RCTs

1

Background

ADA guideline 2022
Introduction of Tirzepatide

ADA Guideline 2022 Updates

- Principle: consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy.
- Recommendation removed from 2021 guideline:

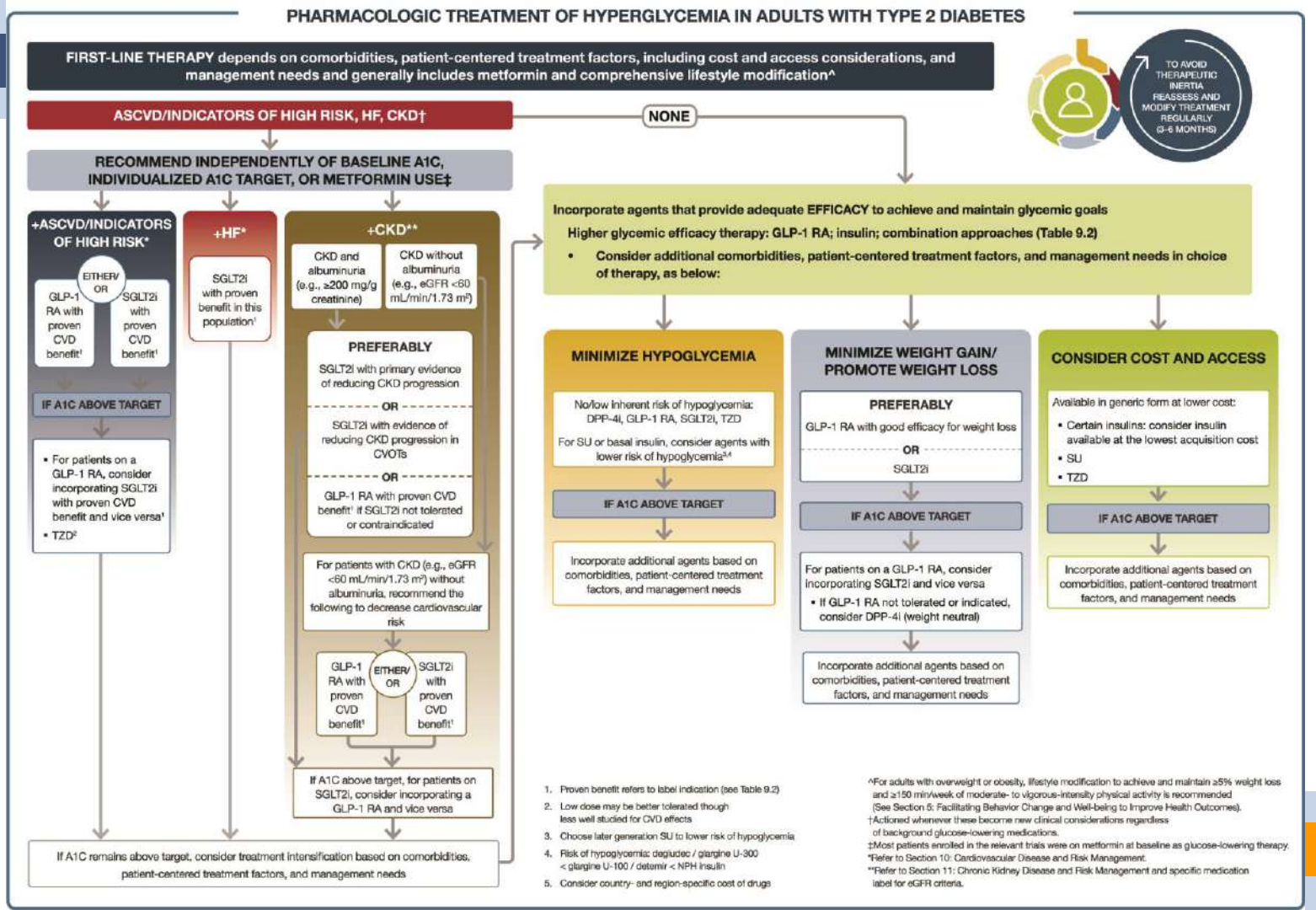
  If the HbA1C target is not achieved after approximately 3 months, metformin can be combined with any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin.

ADA Guideline 2022 Updates

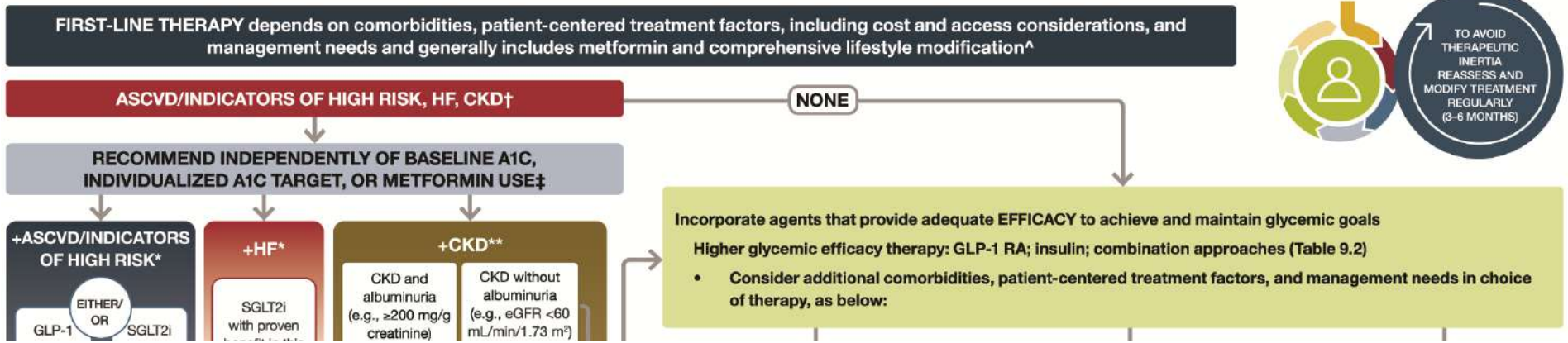
- First line therapy
  - ✓ Depends on **comorbidities, patient-centered treatment factors, and management**. (Recommendation 9.4a)
  - ✓ **Atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease**: **GLP-1 RA** or **SGLT2i** with or without metformin as appropriate initial therapy . (Recommendation 9.4b)
- Combination therapy
  - ✓ **Initial combination therapy** should be considered in patients presenting with **HbA1c levels 1.5–2.0% above target**.
  - ✓ Treatment intensification may not necessarily follow a pure sequential addition.

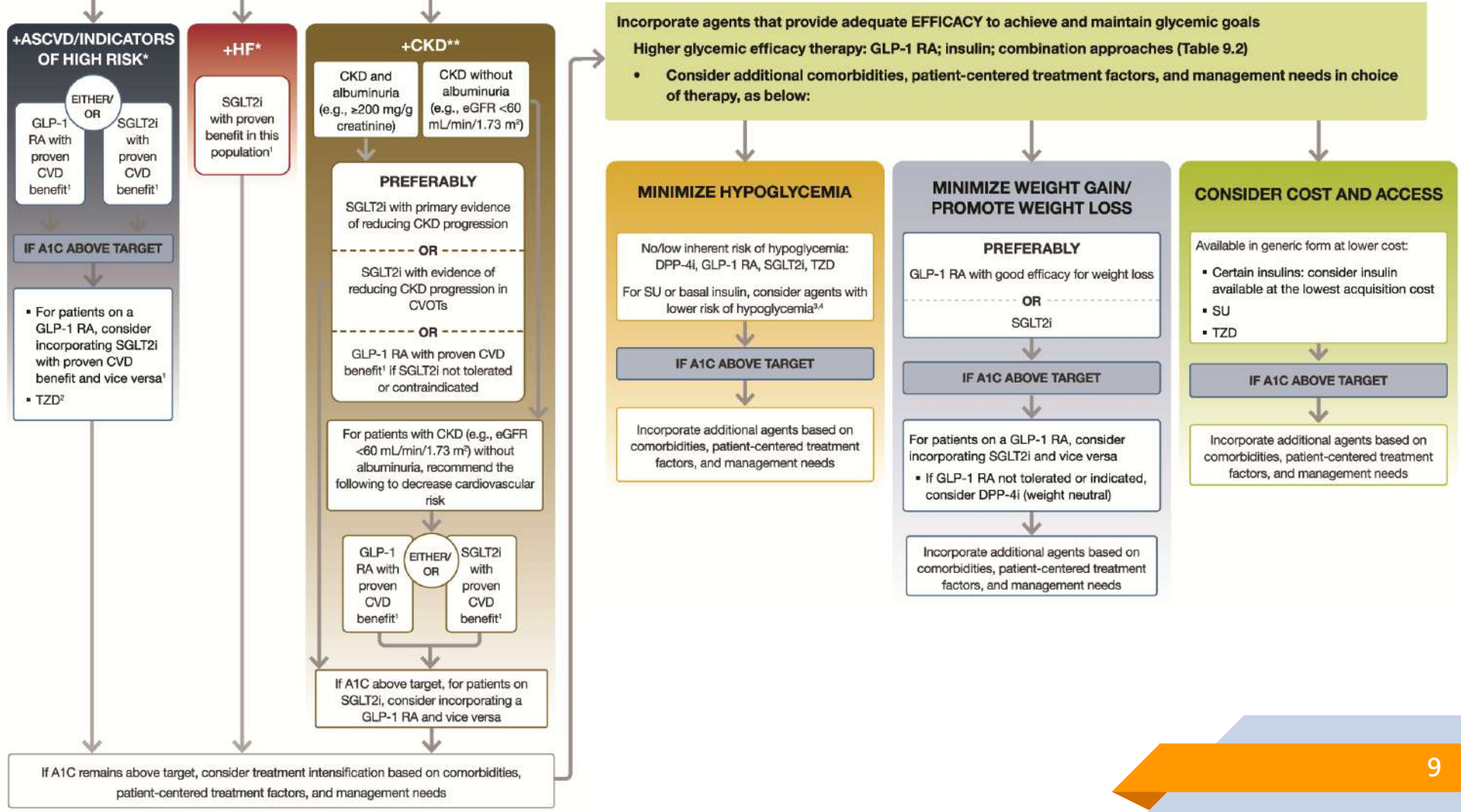
ADA Guideline 2022 Updates

- Injectable therapy
  - ✓ If **insulin** is used, **combination** therapy with a **glucagon-like peptide 1 receptor agonist** is recommended for greater efficacy and durability of treatment effect. (Recommendation 9.11)
  - ✓ When initiating combination injectable therapy, **metformin** therapy should be maintained, while **sulfonylureas and DPP-4 inhibitors** are typically weaned or discontinued.
  - ✓ Adjunctive use of a **thiazolidinedione or an SGLT2 inhibitor** may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered.


PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
IF A1C ABOVE TARGET
• For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa[1]
• TZD[2]
+HF*
SGLT2i with proven benefit in this population[1]
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk
GLP-1 RA with proven CVD benefit[1]
EITHER/ OR
SGLT2i with proven CVD benefit[1]
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa
If A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia[3,4]
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
PREFERABLY
GLP-1 RA with good efficacy for weight loss
OR
SGLT2i
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
• If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
CONSIDER COST AND ACCESS
Available in generic form at lower cost:
• Certain insulins: consider insulin available at the lowest acquisition cost
• SU
• TZD
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
3. Choose later generation SU to lower risk of hypoglycemia
4. Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs
^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes).
†Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
‡Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.
*Refer to Section 10: Cardiovascular Disease and Risk Management.
**Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

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GLP-1/GIP Comparison

Incretin	Glucagon-Like Peptide (GLP-1)	Glucose-Dependent Insulinotropic Polypeptide (GIP)
Composition	30 amino acid peptide	4 amino acid peptide
Receptor Expression	Pancreas, gastrointestinal tract, kidney, heart, brain	Pancreas, adipose tissue, gastric mucosa, heart, adrenal cortex, bone, brain
Metabolism	Half-life: 1-2 mins Metabolised by DPP-4	Half-life: 4-7 mins Metabolised by DPP-4

Glucagon-like Peptide-1 Receptor Agonism

Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

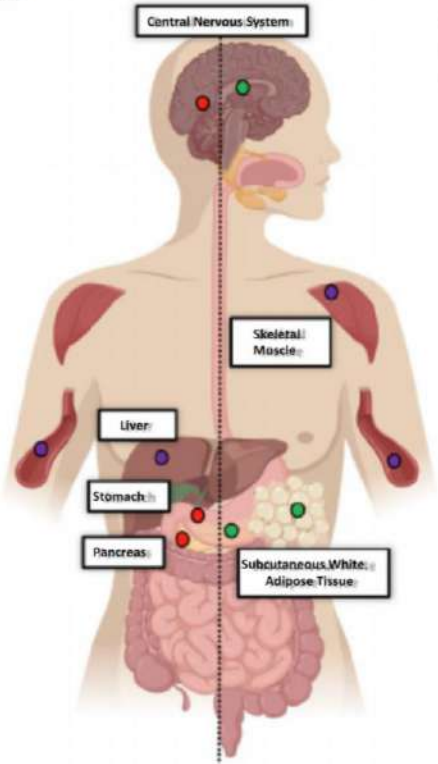
Central Nervous System
- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↑ Glucagon

Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

Skeletal Muscle
- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation



Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
Glucagon-like Peptide 1 Receptor Agonism
Indirect Action

Samms, Ricardo & Coghlan, Matthew & Sloop, Kyle. (2020). How May GIP Enhance the Therapeutic Efficacy of GLP-1?. Trends in Endocrinology & Metabolism. 31. 10.1016/j.tem.2020.02.006.

GLP-1/GIP Comparison

Incretin	GLP-1	GIP
Hypoglycaemic State	-	Glucagon↑
Normoglycaemic State	Glucagon↓	Glucagon↑
Hyperglycaemic State	Glucagon↓	Glucagon↑/-
Glucose-dependent insulin secretion	Insulin↑	Insulin↑↑

Safeguarding against hypoglycemia

Insulinotropic potency is restored if the hyperglycaemia is first reduced by another agent

Tirzepatide

- Dual GIP and GLP-1 receptor agonist
- 39 amino acid peptide based on the native GIP sequence which attached to fatty diacid
- Albumin binding: prolonged half-life (5 days) →QW dosing
- Synergic effect:
  - ✓ Significantly increased insulin response
  - ✓ Glucagonostatic response
  - ✓ Central satiety and anorexigenic effect; weight loss

Table 3 Overview of the SURPASS phase 3 clinical trials of tirzepatide for the treatment of T2DM

Trial/ Identifier	Estimated enrolment	Concomitant therapy	TZP groups	Comparator group	Primary outcome	Treatment duration (weeks)	Primary outcome completion date
SURPASS-1 NCT03954834	472	None	5 mg 10 mg 15 mg	Placebo	Change from baseline in HbA1c	40	Oct 2020
SURPASS-2 NCT03987919	1881	Metformin	5 mg 10 mg 15 mg	Semaglutide	Change from baseline in HbA1c	40	Feb 2021
SURPASS-3 NCT03882970	1420	Metformin or metformin plus SGLT2i	5 mg 10 mg 15 mg	Insulin degludec	Change from baseline in HbA1c	52	Jan 2021
SURPASS-4 NCT03730662	1878	1–3 OAMs of metformin, SGLT2i or SU	5 mg 10 mg 15 mg	Insulin glargine	Change from baseline in HbA1c	52	June 2021
SURPASS-5 NCT04039503	472	Insulin glargine once daily with or without metformin	5 mg 10 mg 15 mg	Placebo	Change from baseline in HbA1c	40	Feb 2021
SURPASS-6 NCT04537923	1182	Insulin glargine once daily with or without metformin	5 mg 10 mg 15 mg	Insulin lispro	Change from baseline in HbA1c	52	Aug 2022

Trial/Identifier	Estimated Enrollment	Concomitant Therapy	TZP groups	Comparator Group	Primary Outcome	Treatment Duration (weeks)	Primary Outcome Completion Date
SURPASS-J mono NCT 03861052	Japanese	OAM-naïve or OAM monotherapy	5/10/15 mg	Dulaglutide 0.75 mg	Change from baseline in HbA1c	52	April 2021
SURPASS-J combo NCT 03861039		OAM monotherapy		N/A	Number of participants with ≥ 1 SAE	52	Mar 2021
SURPASS-AP combo NCT 04093752	Asian-pacific	Metformin with or without SU		Insulin glargine	Change from baseline in HbA1c	40	Feb 2022
SURPASS-CVOT NCT04255433	12,500	Oral or injectable anti-hyperglycaemic medications	Maximum tolerated dose up to 15 mg	Dulaglutide 1.5 mg	Cardiovascular outcomes	Event driven	Oct 2024
SURMOUNT-1 NCT04184622	Obesity or Overweight	N/A	5/10/15 mg	Placebo	Percent change from baseline in body weight	72	April 2022

2. Journal

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*

Frías JP, Davies MJ, Rosenstock J, *et al*. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021 Aug 5;385(6):503-515. doi: 10.1056/NEJMoa2107519. Epub 2021 Jun 25. PMID: 34170647.

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ABSTRACT

BACKGROUND

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown.

METHODS

In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to 40 weeks.

END POINTS

The primary end point was the change in the glycated hemoglobin level from baseline to week 40. The key secondary end points (in a graphical testing scheme, described in the Statistical Analyses Methods section in the Supplementary Appendix, Figs. S2 through S6, and Table S2) were the change in body weight from baseline to week 40 and the attainment of glycated hemoglobin level targets of less than 7.0% and less than 5.7%. Other end points were attainment of a glycated hemoglobin level of 6.5% or less and weight loss of at least 5%, 10%, or 15%; the mean change from baseline in the fasting serum

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O

Trial Design

- 40-week, open-label, parallel-group, randomized, active-controlled, phase 3 trial.
- 1,879 patients with type 2 diabetes were randomly assigned in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg; or semaglutide 1 mg.
- Funded by Eli Lilly.

Trial Design-Inclusion Criteria

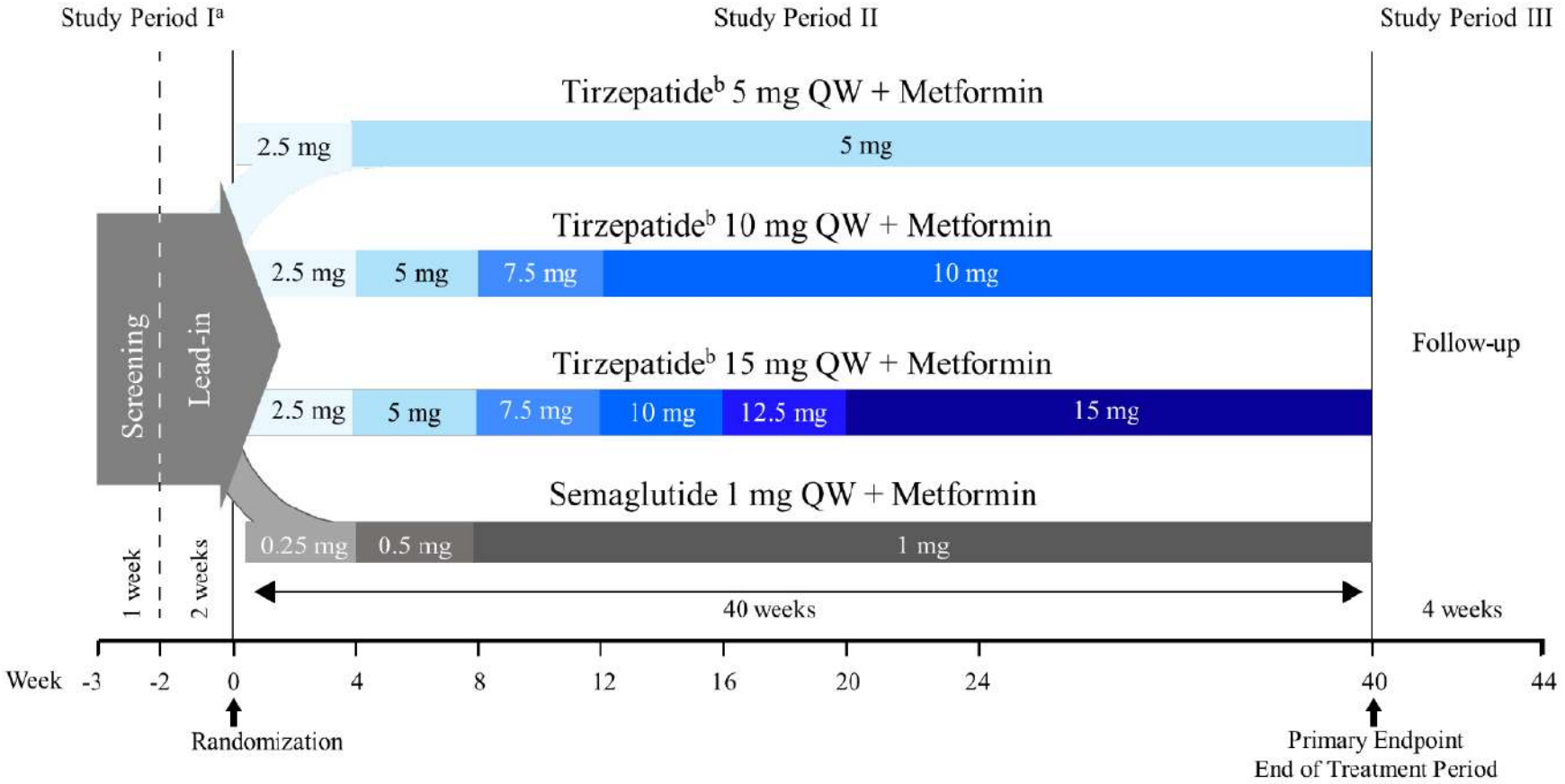
- Type 2 diabetes
- HbA1c ≥7.0% (≥53 mmol/mol) to ≤10.5% (≤91 mmol/mol)
- Are of stable weight (±5%) ≥3 months with body mass index (BMI) ≥25 kg/m^2
- Have been on stable diabetes treatment with metformin ≥1500 mg/day

Trial Design-Exclusion Criteria

- Type 1 diabetes
- eGFR < 45 ml/minute/1.73 m2
- History of chronic or acute pancreatitis
- History of diabetic retinopathy or diabetic maculopathy
- History of ketoacidosis or sever hypoglycemia
- Acute myocardial infarction, cerebrovascular accident; hospitalization due to congestive heart failure or NYHA Classification IV CHF.

Method

- Once weekly subcutaneous injection of tirzepatide (dose were double-blinded) or semaglutide.
- Dose escalated every 4 week until randomly assigned dose was reached (associated to gastrointestinal-related side-effect.)
- 40 weeks of treatment period+4 weeks of safety follow-up.


Study Period I[a]
Study Period II
Study Period III
Tirzepatide[b] 5 mg QW + Metformin
2.5 mg
5 mg
Tirzepatide[b] 10 mg QW + Metformin
2.5 mg
5 mg
7.5 mg
10 mg
Tirzepatide[b] 15 mg QW + Metformin
2.5 mg
5 mg
7.5 mg
10 mg
12.5 mg
15 mg
Semaglutide 1 mg QW + Metformin
0.25 mg
0.5 mg
1 mg
Screening
Lead-in
1 week
2 weeks
40 weeks
Follow-up
4 weeks
Week -3 -2 0 4 8 12 16 20 24 40 44
Randomization
Primary Endpoint
End of Treatment Period

Endpoints

- Primary endpoint: change in the HbA1c from baseline to week 40.
- Secondary endpoints:
  - ✓ Change in body weight from baseline to week 40
  - ✓ Lipid level
- Safety endpoints: adverse events, hypersensitivity reactions…

Statistical Analysis

- Modified intention-to-treat population
- At least 90% power to show noninferiority of tirzepatide compare with semaglutide; with two-side alpha value of 0.025.
- 1,872 patients would be eligible, assuming a dropout rate of 28%.

Result-Flow Chart

Figure S7. Patient Disposition

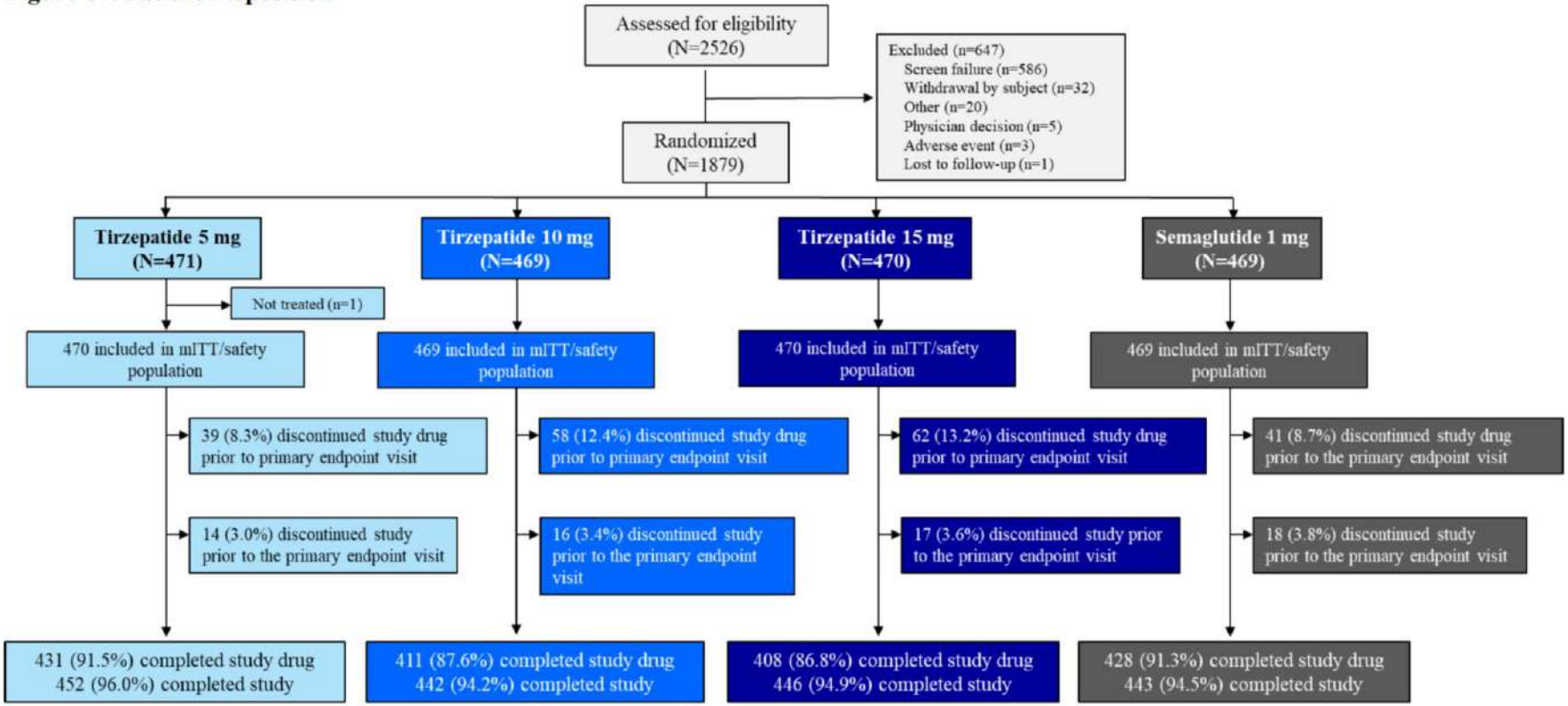


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline in the Modified Intention-to-Treat Population.*

Characteristic	Tirzepatide			Semaglutide	Total (N=1878)
	5 mg (N=470)	10 mg (N=469)	15 mg (N=470)	1 mg (N=469)	
Age — yr	56.3±10.0	57.2±10.5	55.9±10.4	56.9±10.8	56.6±10.4
Female sex — no. (%)	265 (56.4)	231 (49.3)	256 (54.5)	244 (52.0)	996 (53.0)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	53 (11.3)	53 (11.3)	57 (12.1)	45 (9.6)	208 (11.1)
Asian	6 (1.3)	11 (2.3)	5 (1.1)	3 (0.6)	25 (1.3)
Black	28 (6.0)	21 (4.5)	15 (3.2)	15 (3.2)	79 (4.2)
White	382 (81.3)	376 (80.2)	392 (83.4)	401 (85.5)	1551 (82.6)
Hispanic	325 (69.1)	322 (68.7)	334 (71.1)	336 (71.6)	1317 (70.1)
Non-Hispanic	145 (30.9)	147 (31.3)	136 (28.9)	133 (28.4)	561 (29.9)
Glycated hemoglobin level					
Glycated hemoglobin level — %	8.32±1.08	8.30±1.02	8.26±1.00	8.25±1.01	8.28±1.03
≤8.5% — no. (%)	293 (62.3)	294 (62.7)	303 (64.5)	302 (64.4)	1192 (63.5)
>8.5% — no. (%)	177 (37.7)	175 (37.3)	167 (35.5)	167 (35.6)	686 (36.5)
Glycated hemoglobin level — mmol/mol	67.46±11.84	67.20±11.20	66.78±10.97	66.69±10.99	67.03±11.25
Fasting serum glucose level					
In mg/dl	173.8±51.87	174.2±49.79	172.4±54.37	171.4±49.77	172.9±51.46
In mmol/liter	9.65±2.88	9.67±2.76	9.57±3.02	9.51±2.76	9.60±2.86
Duration of diabetes — yr	9.1±7.16	8.4±5.90	8.7±6.85	8.3±5.80	8.6±6.46

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Characteristic	Tirzepatide			Semaglutide	Total (N=1878)
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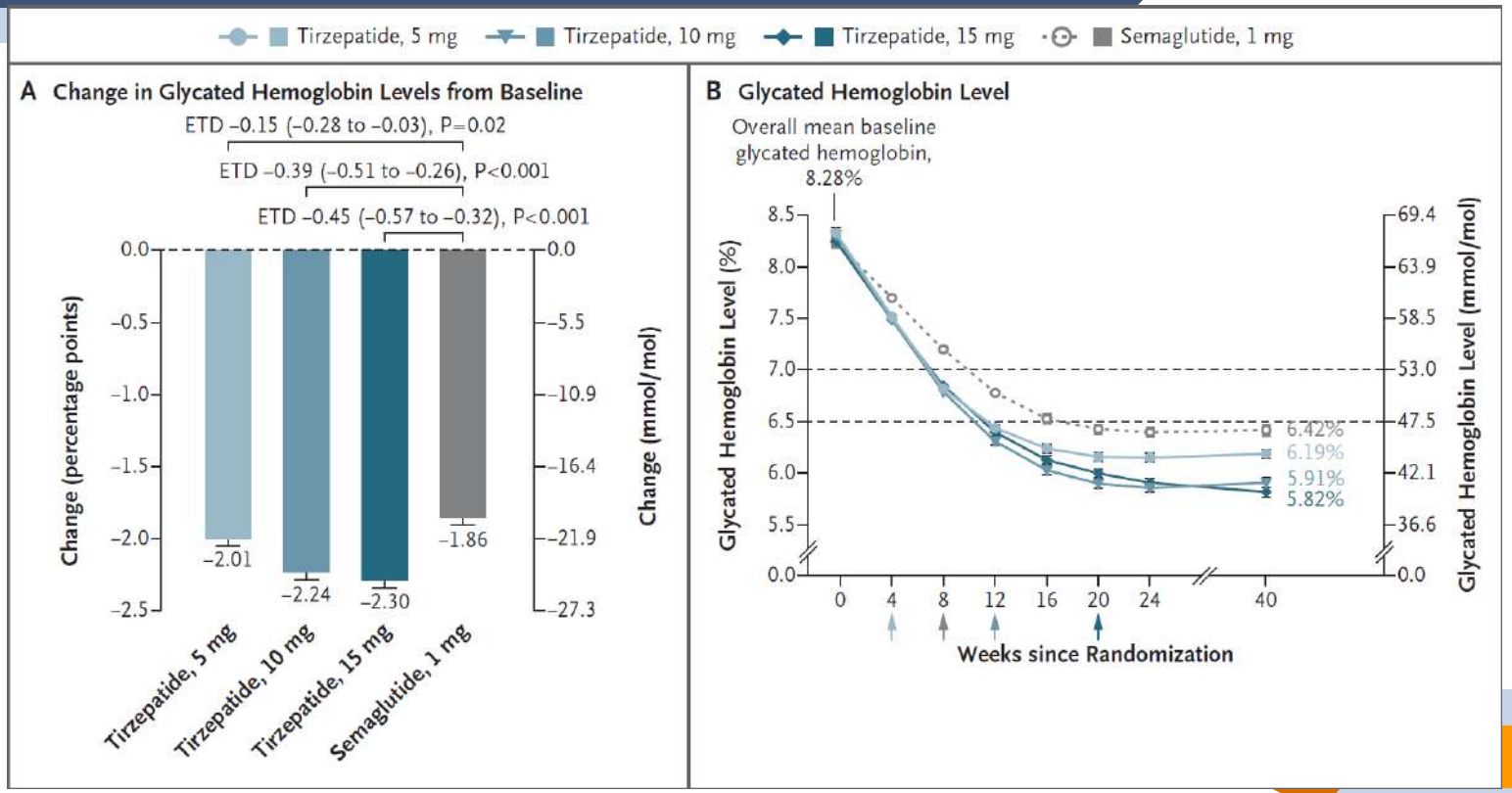
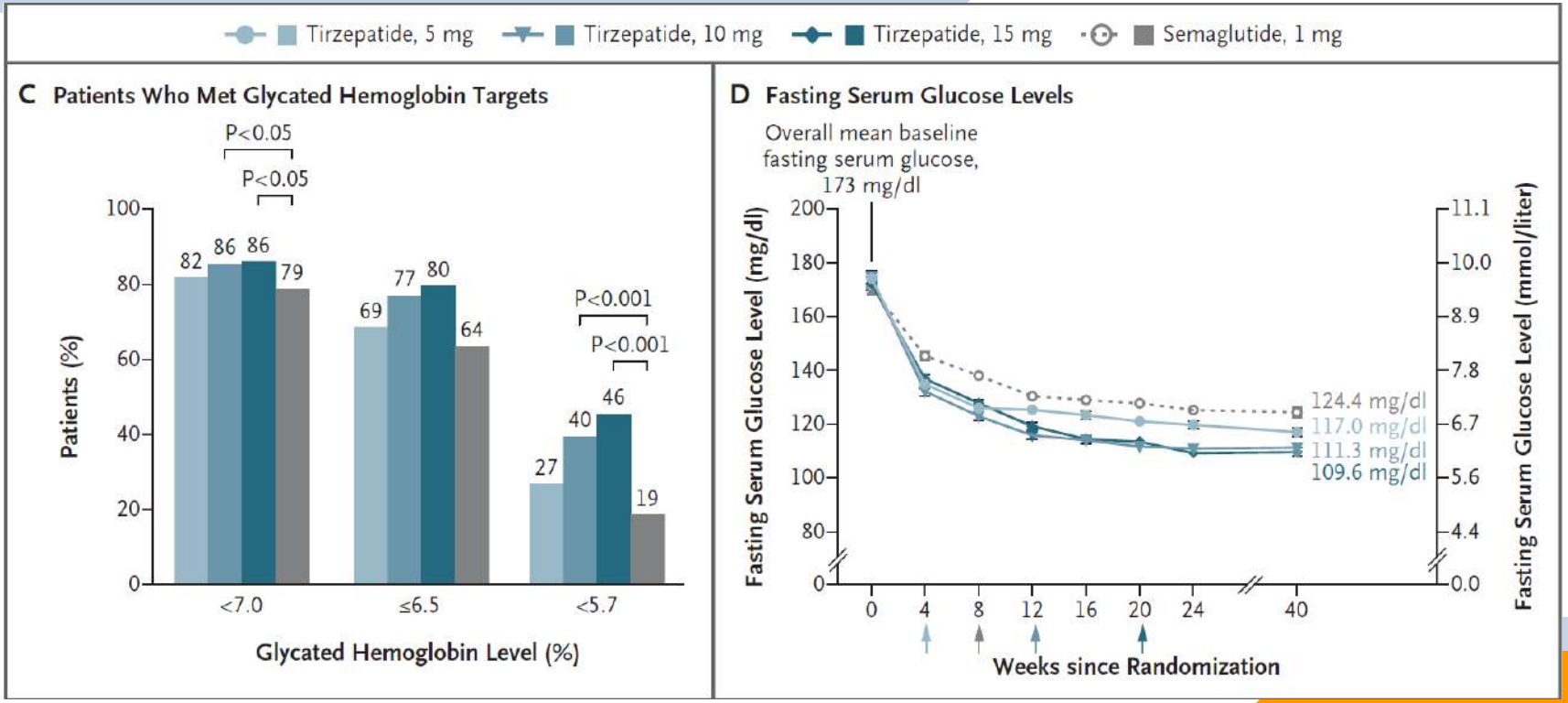
BMI‡	33.8±6.85	34.3±6.60	34.5±7.11	34.2±7.15	34.2±6.93
Weight — kg	92.5±21.76	94.8±22.71	93.8±21.83	93.7±21.12	93.7±21.86
Waist circumference — cm	108.06±14.81	110.55±16.05	109.55±15.60	109.04±14.90	109.30±15.36
Estimated GFR§					
Mean value — ml/min/1.73 m^2	96.6±17.51	95.5±16.62	96.3±16.92	95.6±17.25	96.0±17.07
Value <60 ml/min/1.73 m^2 — no. (%)	19 (4.0)	15 (3.2)	11 (2.3)	19 (4.1)	64 (3.4)
Value ≥60 ml/min/1.73 m^2 — no. (%)	451 (96.0)	454 (96.8)	459 (97.7)	450 (95.9)	1814 (96.6)
Urinary albumin-to-creatinine ratio — no. (%)¶					
<30	340 (72.3)	353 (75.3)	357 (76.0)	364 (77.6)	1414 (75.3)
30 to ≤300	111 (23.6)	87 (18.6)	85 (18.1)	90 (19.2)	373 (19.9)
>300	18 (3.8)	29 (6.2)	27 (5.7)	15 (3.2)	89 (4.7)
Use of metformin — no. (%)	470 (100.0)	469 (100.0)	470 (100.0)	469 (100.0)	1878 (100.0)
Blood pressure — mm Hg					
Systolic	130.53±14.11	131.47±13.77	130.45±14.32	129.96±12.99	130.60±13.81
Diastolic	78.61±8.89	80.03±9.59	78.97±8.97	79.33±8.61	79.23±9.03
Pulse rate — bpm	74.88±9.37	74.55±10.75	74.46±9.86	75.10±10.25	74.75±10.07

Result-Primary Endpoint

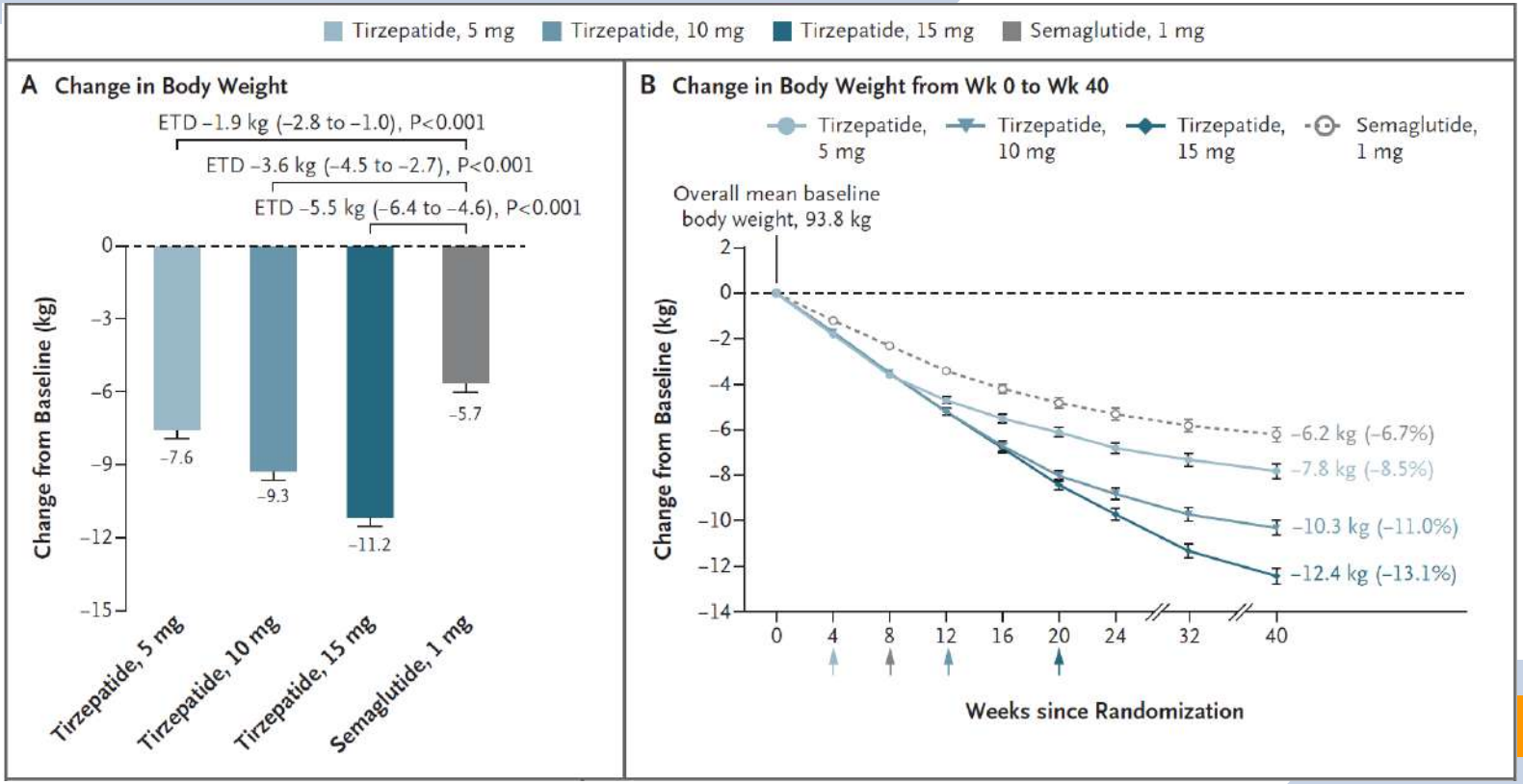


ETD: estimated treatment difference

Result-Primary Endpoint



Result-Secondary Endpoints



Result-Secondary Endpoints

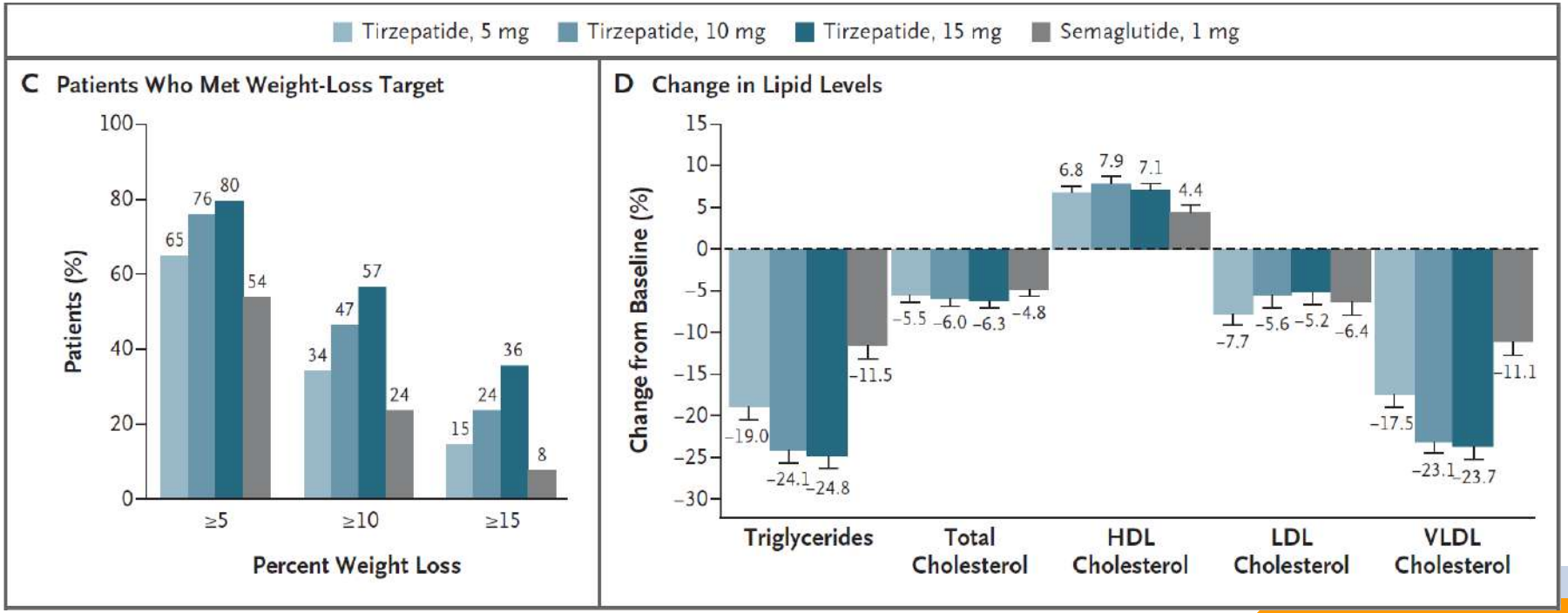


Table 2. Adverse Events and Safety.*

Event	Tirzepatide						Semaglutide		Total (N=1878)	
	5 mg (N=470)		10 mg (N=469)		15 mg (N=470)		1 mg (N=469)			
	No. of patients (%)	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*
Adverse events occurring in ≥5% of patients in any treatment group, according to preferred term										
Nausea	82 (17.4)	111	90 (19.2)	124	104 (22.1)	136	84 (17.9)	126	360 (19.2)	497
Diarrhea	62 (13.2)	120	77 (16.4)	99	65 (13.8)	102	54 (11.5)	68	258 (13.7)	389
Vomiting	27 (5.7)	35	40 (8.5)	56	46 (9.8)	61	39 (8.3)	53	152 (8.1)	205
Dyspepsia	34 (7.2)	—	29 (6.2)	—	43 (9.1)	—	31 (6.6)	—	137 (7.3)	—
Decreased appetite	35 (7.4)	—	34 (7.2)	—	42 (8.9)	—	25 (5.3)	—	136 (7.2)	—
Constipation	32 (6.8)	—	21 (4.5)	—	21 (4.5)	—	27 (5.8)	—	101 (5.4)	—
Abdominal pain	14 (3.0)	—	21 (4.5)	—	24 (5.1)	—	24 (5.1)	—	83 (4.4)	—
All gastrointestinal adverse events	188 (40.0)	—	216 (46.1)	—	211 (44.9)	—	193 (41.2)	—	808 (43.0)	—
Other adverse events										
Hypoglycemia, blood glucose level <54 mg/dl	3 (0.6)	3	1 (0.2)	2	8 (1.7)	10	2 (0.4)	2	14 (0.7)	17
Severe hypoglycemia	1 (0.2)	1	0	0	1 (0.2)‡	1‡	0	0	2 (0.1)	2
Injection-site reaction	9 (1.9)	—	13 (2.8)	—	21 (4.5)	—	1 (0.2)	—	44 (2.3)	—
Adjudicated pancreatitis	0	—	2 (0.4)	—	2 (0.4)	—	3 (0.6)	—	7 (0.4)	—
Cholelithiasis	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	2 (0.4)	—	14 (0.7)	—
Hypersensitivity§	9 (1.9)	—	13 (2.8)	—	8 (1.7)	—	11 (2.3)	—	41 (2.2)	—
Diabetic retinopathy¶	0	—	2 (0.4)	—	0	—	0	—	2 (0.1)	—

Result-Conclusion

- All tirzepatide doses were found to be superior to semaglutide regarding to reduction in the mean HbA1c and body weight.
- More patients at the tirzepatide arm reached a composite end point of a HbA1c level <6.5% or with at least 10% weight loss.
- Reduction in body weight with tirzepatide were dose-dependent.
- Weight reduction did not plateau in any of the four treatment groups at week 40.

Discussion

- Strengths
  - Large sample size with low dropout rate
  - The results on the semaglutide arm were consistent with former semaglutide trials. (SUSTAIN clinical trials and STEP 2 trial)
- Limitations
  - Not blinded because of difference in devices and dose-escalation schemes
  - Relatively short duration of 40 weeks.

3

Appraisal

Question 1

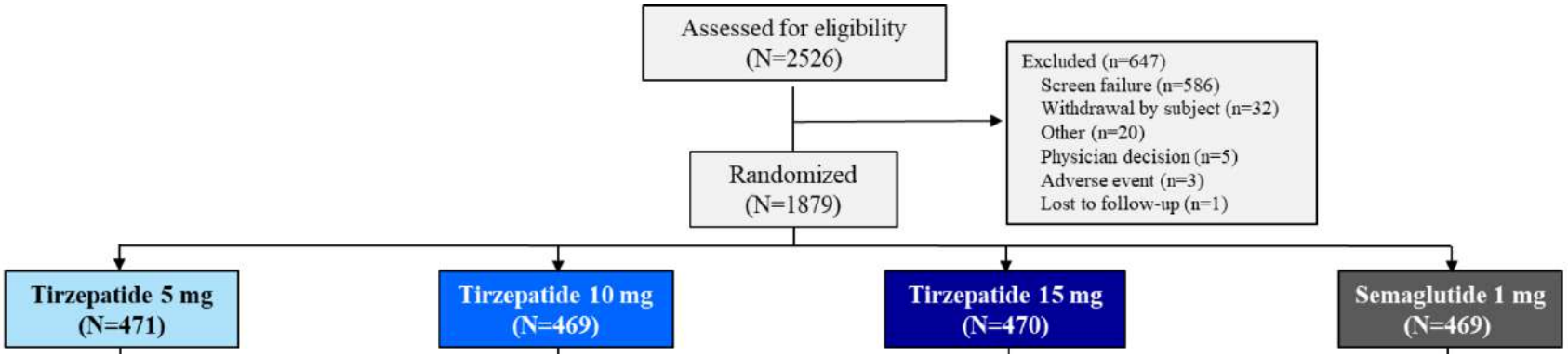
Did the study address a clearly focused research question?

P	Patients with type 2 Diabetes, treated with ≥1500 mg Metformin/day
I	Tirzepatide 5 mg, 10 mg, 15 mg QW SC
C	Semaglutide 1 mg QW SC
O	Change in the HbA1c level and body weight from baseline to 40 weeks

Question 2

Was the assignment of participants to interventions randomized?

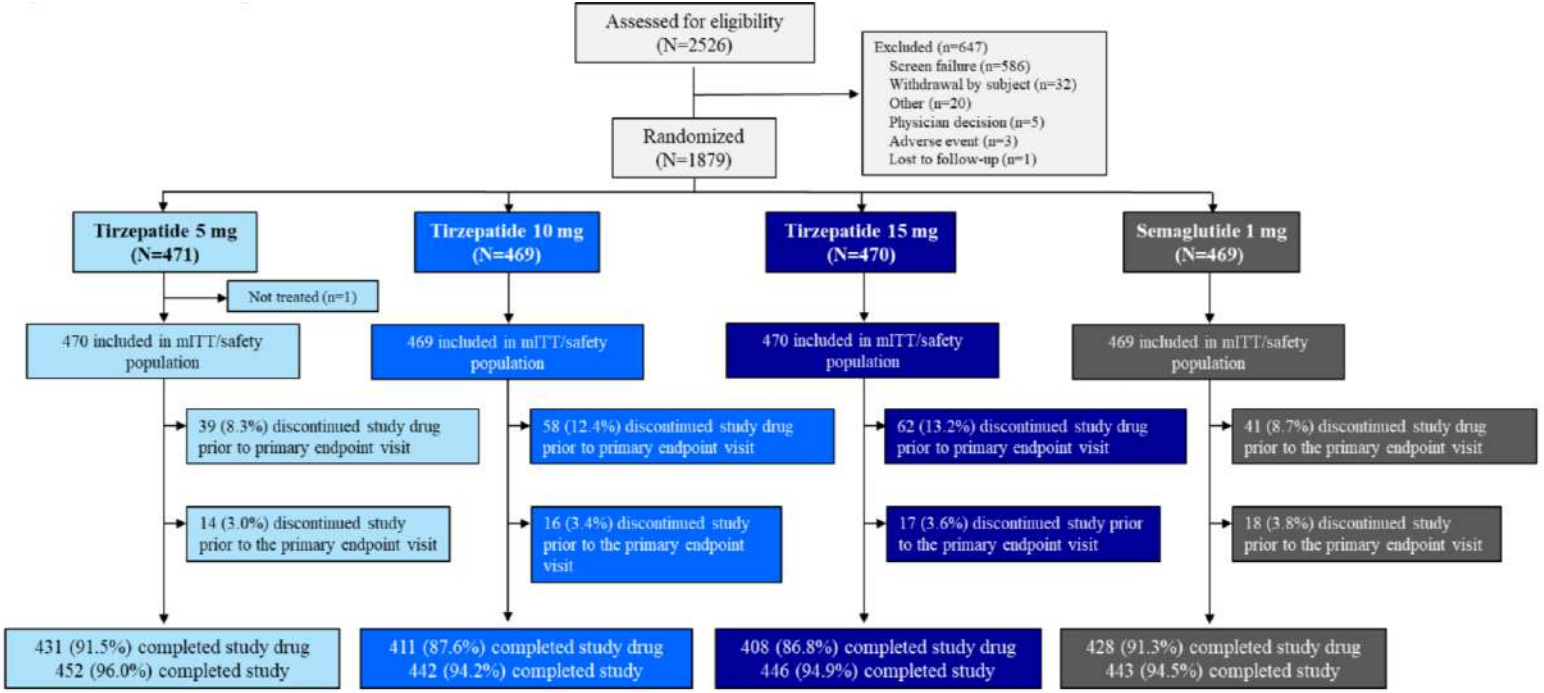
YES



Question 3

Were all participants who entered the study accounted for at its conclusion?

YES



Question 4-a

Were the participants "blind" to intervention they were given?

PROCEDURES

The patients were randomly assigned in a 1:1:1:1 ratio to receive a once-weekly subcutaneous injection of either tirzepatide (at a dose of 5 mg, 10 mg, or 15 mg; the doses were double-blinded) or semaglutide (1 mg) for a 40-week treatment period, followed by a 4-week safety follow-up period (Fig. S1). The patients were stratified at randomization according to country and baseline glycated hemoglobin level (≤8.5% or >8.5% [≤69 or >69 mmol per mol]).

The limitations of our trial were that treatments could not be blinded because of differences in devices and dose-escalation schemes (tirzepatide doses were blinded) and the relatively short duration of 40 weeks, which allowed only 16 weeks at a steady state for the assessment of the highest tirzepatide dose. In addition, the number of Black patients was low. Higher doses of semaglutide were not available as comparators at the time of this trial.

Question 4-b

Were the investigators "blind" to intervention they were giving to participants?

PROCEDURES

The patients were randomly assigned in a 1:1:1:1 ratio to receive a once-weekly subcutaneous injection of either tirzepatide (at a dose of 5 mg, 10 mg, or 15 mg; the doses were double-blinded) or semaglutide (1 mg) for a 40-week treatment period, followed by a 4-week safety follow-up period (Fig. S1). The patients were stratified at randomization according to country and baseline glycated hemoglobin level (≤8.5% or >8.5% [≤69 or >69 mmol per mol]).

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Question 4-c

Were the people assessing/ analysing outcomes "blinded?"

PROCEDURES

The patients were randomly assigned in a 1:1:1:1 ratio to receive a once-weekly subcutaneous injection of either tirzepatide (at a dose of 5 mg, 10 mg, or 15 mg; the doses were double-blinded) or semaglutide (1 mg) for a 40-week treatment period, followed by a 4-week safety follow-up period (Fig. S1). The patients were stratified at randomization according to country and baseline glycated hemoglobin level (≤8.5% or >8.5% [≤69 or >69 mmol per mol]).

The limitations of our trial were that treatments could not be blinded because of differences in devices and dose-escalation schemes (tirzepatide doses were blinded) and the relatively short duration of 40 weeks, which allowed only 16 weeks at a steady state for the assessment of the highest tirzepatide dose. In addition, the number of Black patients was low. Higher doses of semaglutide were not available as comparators at the time of this trial.

Question 5

Were the study groups similar at the start of the randomized controlled trial?

Characteristic	Tirzepatide			Semaglutide	Total (N=1878)
	5 mg (N=470)	10 mg (N=469)	15 mg (N=470)	1 mg (N=469)	
Age — yr	56.3±10.0	57.2±10.5	55.9±10.4	56.9±10.8	56.6±10.4
Female sex — no. (%)	265 (56.4)	231 (49.3)	256 (54.5)	244 (52.0)	996 (53.0)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	53 (11.3)	53 (11.3)	57 (12.1)	45 (9.6)	208 (11.1)
Asian	6 (1.3)	11 (2.3)	5 (1.1)	3 (0.6)	25 (1.3)
Black	28 (6.0)	21 (4.5)	15 (3.2)	15 (3.2)	79 (4.2)
White	382 (81.3)	376 (80.2)	392 (83.4)	401 (85.5)	1551 (82.6)
Hispanic	325 (69.1)	322 (68.7)	334 (71.1)	336 (71.6)	1317 (70.1)
Non-Hispanic	145 (30.9)	147 (31.3)	136 (28.9)	133 (28.4)	561 (29.9)

Question 5

Were the study groups similar at the start of the randomized controlled trial?

Characteristic	Tirzepatide			Semaglutide	Total (N=1878)
	5 mg (N=470)	10 mg (N=469)	15 mg (N=470)	1 mg (N=469)	
Glycated hemoglobin level					
Glycated hemoglobin level — %	8.32±1.08	8.30±1.02	8.26±1.00	8.25±1.01	8.28±1.03
≤8.5% — no. (%)	293 (62.3)	294 (62.7)	303 (64.5)	302 (64.4)	1192 (63.5)
>8.5% — no. (%)	177 (37.7)	175 (37.3)	167 (35.5)	167 (35.6)	686 (36.5)
Glycated hemoglobin level — mmol/mol	67.46±11.84	67.20±11.20	66.78±10.97	66.69±10.99	67.03±11.25
Fasting serum glucose level					
In mg/dl	173.8±51.87	174.2±49.79	172.4±54.37	171.4±49.77	172.9±51.46
In mmol/liter	9.65±2.88	9.67±2.76	9.57±3.02	9.51±2.76	9.60±2.86
Duration of diabetes — yr	9.1±7.16	8.4±5.90	8.7±6.85	8.3±5.80	8.6±6.46
BMI‡	33.8±6.85	34.3±6.60	34.5±7.11	34.2±7.15	34.2±6.93
Weight — kg	92.5±21.76	94.8±22.71	93.8±21.83	93.7±21.12	93.7±21.86
Waist circumference — cm	108.06±14.81	110.55±16.05	109.55±15.60	109.04±14.90	109.30±15.36

Question 6

Apart from the experimental intervention, did each study group receive the same level care?

If any additional interventions were given (e.g. tests or treatments, were they similar between the study group?

Inclusion Criteria

5. Have been on stable diabetes treatment with metformin ≥1500 mg/day during the 3 months prior to Visit 1 and between Visits 1 and 3

Exclusion Criteria

Monotherapy: Metformin 1500-2550 mg/day

Prior/Concomitant Therapy

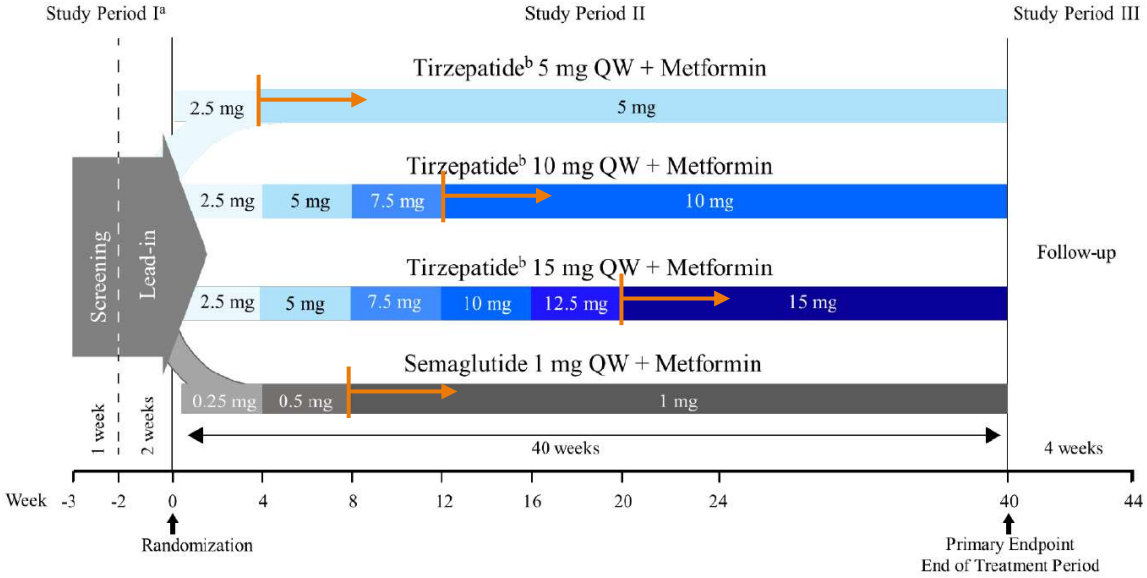
28. Have been treated with any antihyperglycemic medication (other than metformin) within the 3 months prior to Visit 1. An exception is for the use of insulin for gestational diabetes or short-term use (<14 days) for acute conditions such as acute illness, hospitalization, or elective surgery

Question 6

UNCLEAR

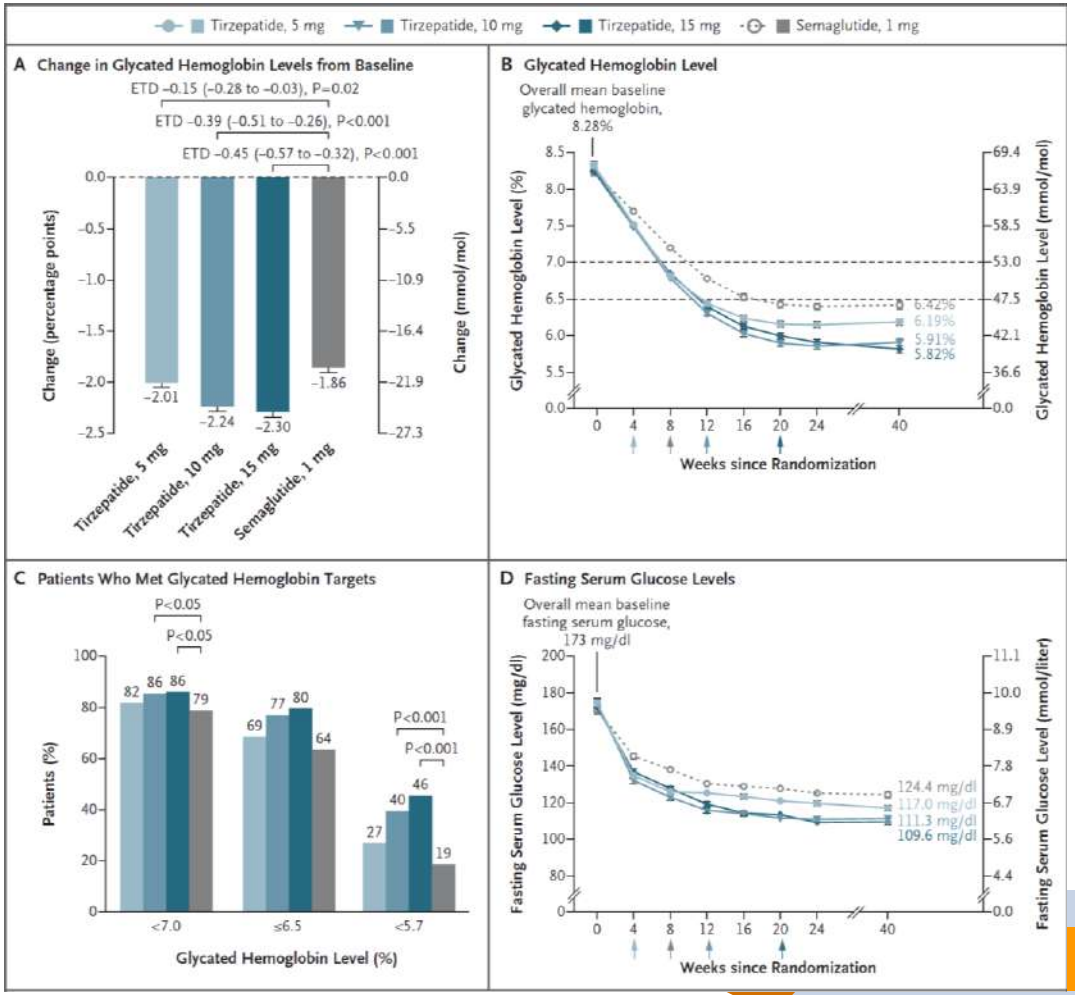
Apart from the experimental intervention, did each study group receive the same level care?

Were the follow-up intervals the same for each study group?



Question 7

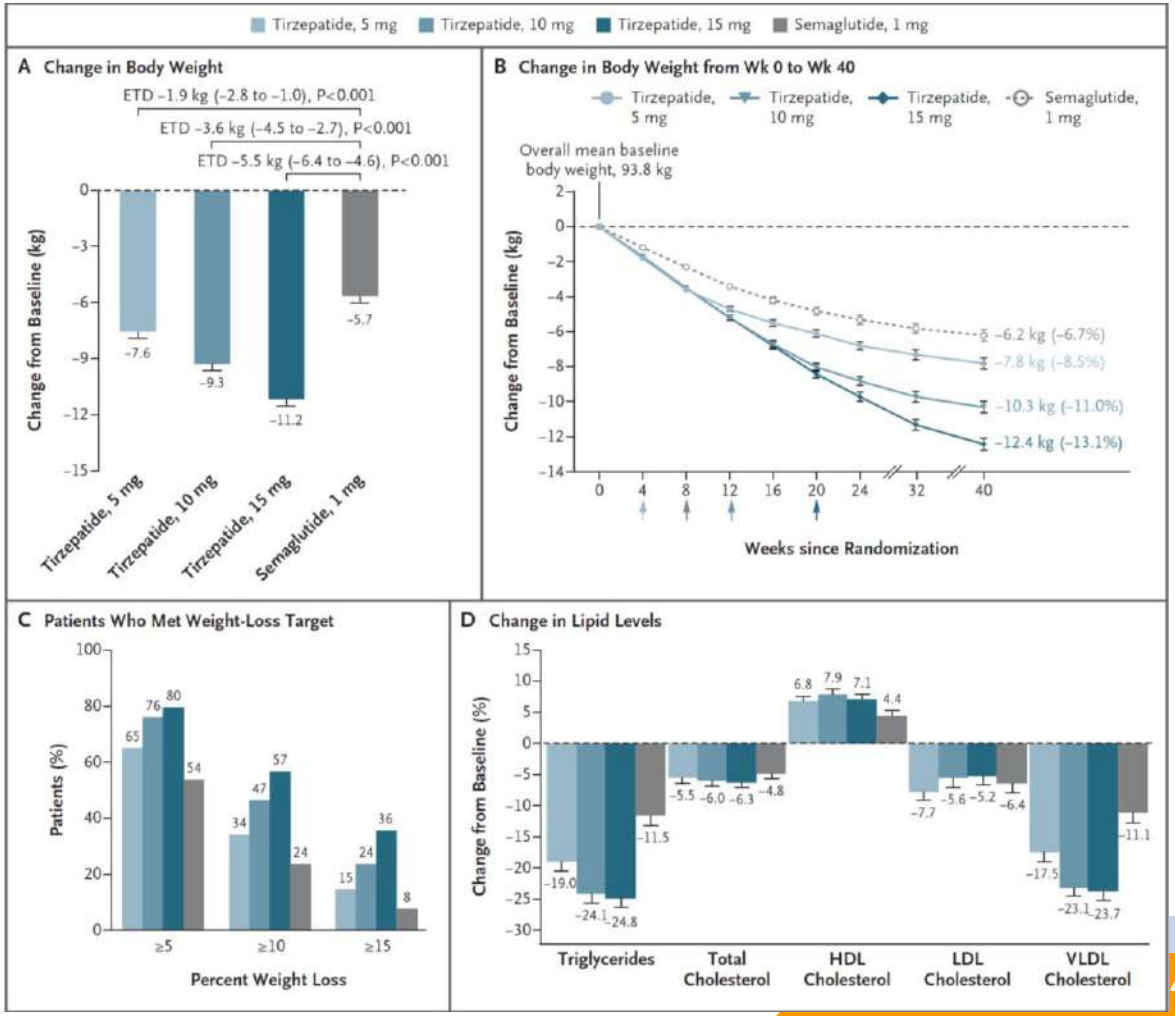
Were the effects of intervention reported comprehensively?



Question 7

Were the effects of intervention reported comprehensively?

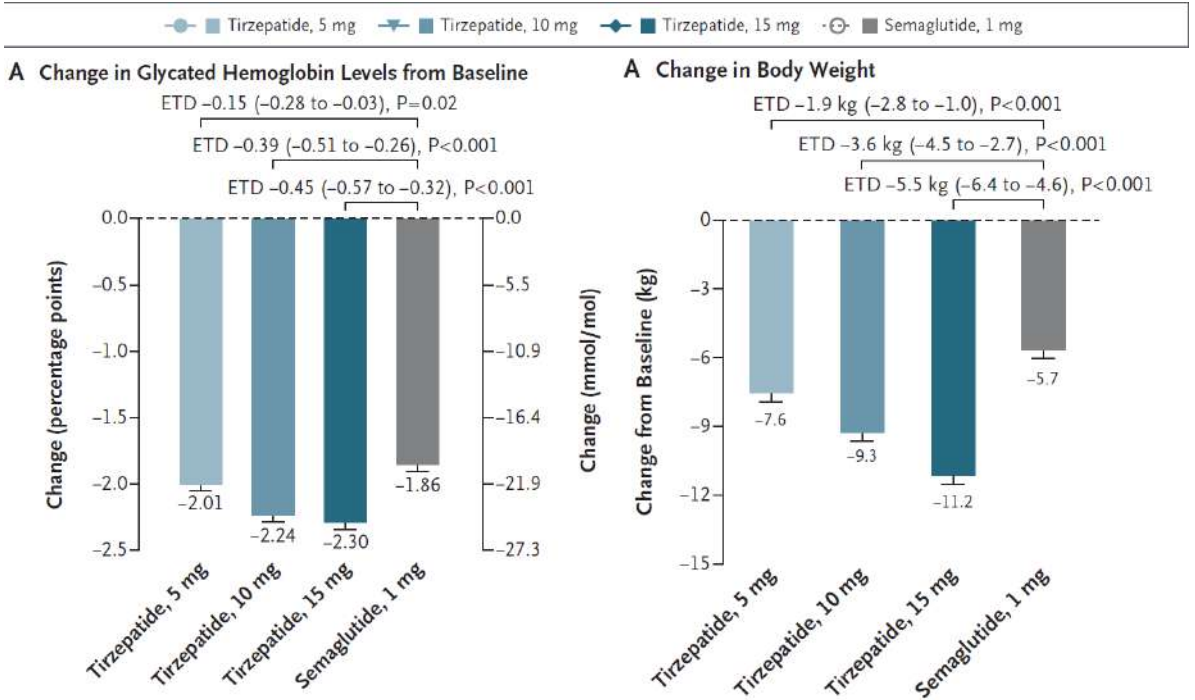
YES



Question 8

Was the precision of the estimate of the intervention or treatment effect reported?

YES



Question 9

Treatment effect (Primary endpoint)

Reduction in the HbA1c level (compare with semaglutide 1 mg, %):

Tirzepatide 5 mg	-0.15 [-0.28 to -0.03, p=0.02]
Tirzepatide 10 mg	-0.39 [-0.51 to -0.26, p<0.001]
Tirzepatide 15 mg	-0.45 [-0.57 to -0.32, p<0.001]

Treatment effect (Secondary endpoint)

Reduction in body weight (compare with semaglutide 1 mg, kg):

Tirzepatide 5 mg	-1.9 [-2.8 to -1.0, p<0.001]
Tirzepatide 10 mg	-3.6 [-4.5 to -2.7, p<0.001]
Tirzepatide 15 mg	-5.5 [-6.4 to -4.6, p<0.001]

Question 9

Do the benefits of the experimental intervention outweigh the harm and costs?

Adverse effect	Nausea Diarrhea Vomiting Dyspepsia Decreased appetite Constipation Abdominal pain
Cost-effectiveness analysis	N/A (still under investigation)

Question 10

Can the results be applied to your local population/in your context?

Characteristic	Tirzepatide			Semaglutide	Total (N=1878)
	5 mg (N=470)	10 mg (N=469)	15 mg (N=470)	1 mg (N=469)	
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Non-Hispanic	145 (30.9)	147 (31.3)	136 (28.9)	133 (28.4)	561 (29.9)

Question 11

Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

- Potential treatment option to reach a HbA1c goal of less than 5.7% without an increased risk of hypoglycemia.
- Possess similar cardiovascular benefits as in semaglutide.
- Long-term safety profiles are to be discussed in other on-going trials.

Final Remarks

	Question	Yes	No	Can't tell
1	Did the study address a clearly focused research question?	✓		
2	Was the assignment of participants to interventions randomized?	✓		
3	Were all participants who entered the study accounted for at its conclusion?	✓		
4	Were the participants, investigators, and analyzer blinded?		✓	

Final Remarks

	Question	Yes	No	Can't tell
5	Were the study groups similar at the start of the randomized controlled trial?	✓		
6	Apart from the experimental intervention, did each study group receive the same level care?			✓
7	Were the effects of intervention reported comprehensively?	✓		
8	Was the precision of the estimate of the intervention or treatment effect reported?	✓		

Final Remarks

	Question	Yes	No	Can't tell
9	Do the benefits of the experimental intervention outweigh the harm and costs?	✓		
10	Can the results be applied to your local population/in your context?		✓	
11	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?			✓

Final Remarks

- According to the baseline characteristics (BMI 33-34 kg/m^2, Body weight 92-94 kg,) the study group may not be able to apply on Taiwanese population.
- Did not discuss the comorbidity of the participants, which is a key factor on medication choice for type 2 diabetes.
- The trial design and the analyzing methods could be described more discretely in the paper (i.e noninferiority and superiority.)
- Many data were only found in the appendix, the confidential interval and statistical significancy of some results could be stated as well.

Final Remarks

- As a first-in-class medication, tirzepatide can provide better effect on reducing HbA1c level and body weight than semaglutide.
- Long-term safety profile and application on Asian population are to be discussed in the future.
- Weight loss potential on overweight adults without type 2 diabetes is also to be discussed in the future.

Take Home Message

- According to ADA Guideline 2022, the management of type 2 diabetes depends on comorbidities and patient-centered treatment factors.
- Tirzepatide, a dual GIP and GLP-1 receptor agonist, is a potential treatment for T2DM noninferior and superior to 1 mg of semaglutide on the aspect of reducing HbA1c level and weight loss.

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Thank you for your attention.