Terapia incretinica multirecettoriale: oltre il controllo glicemico e il peso

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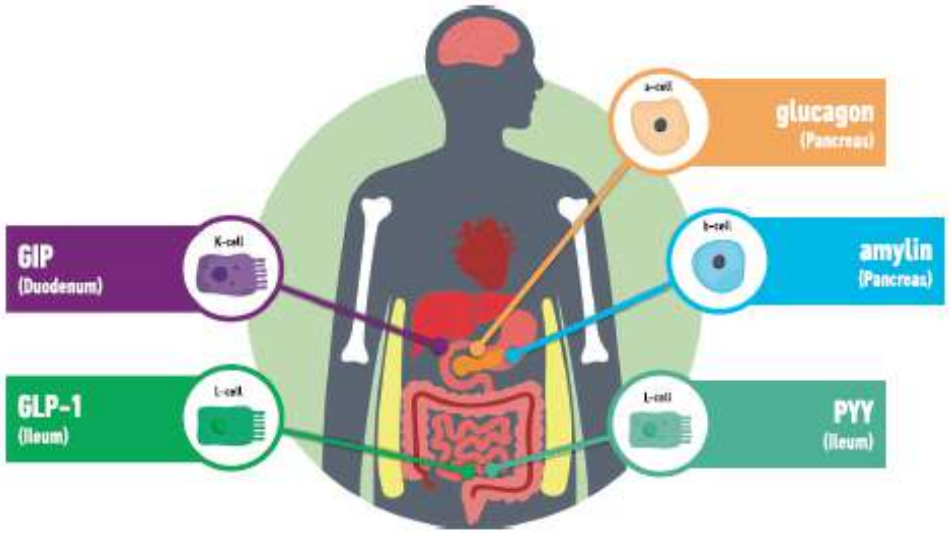
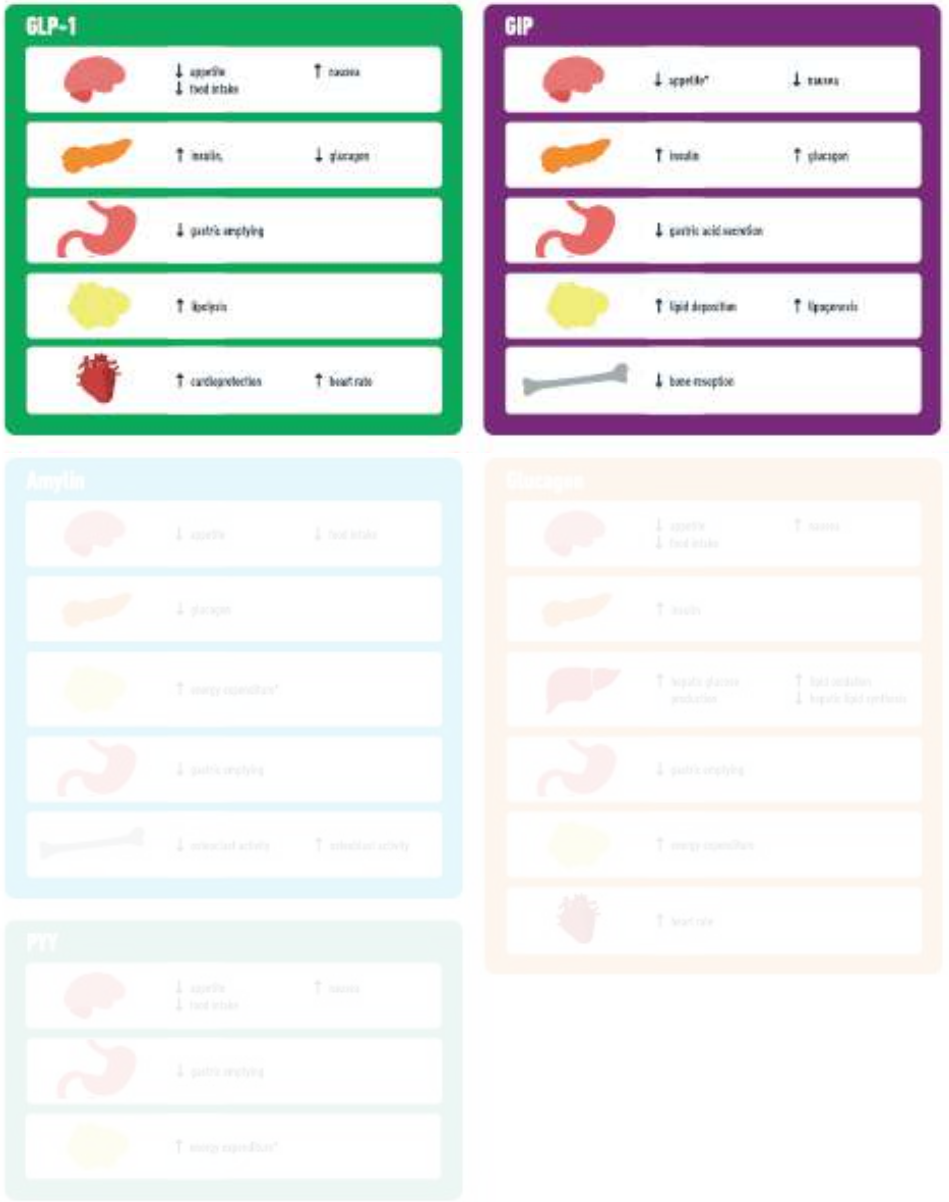
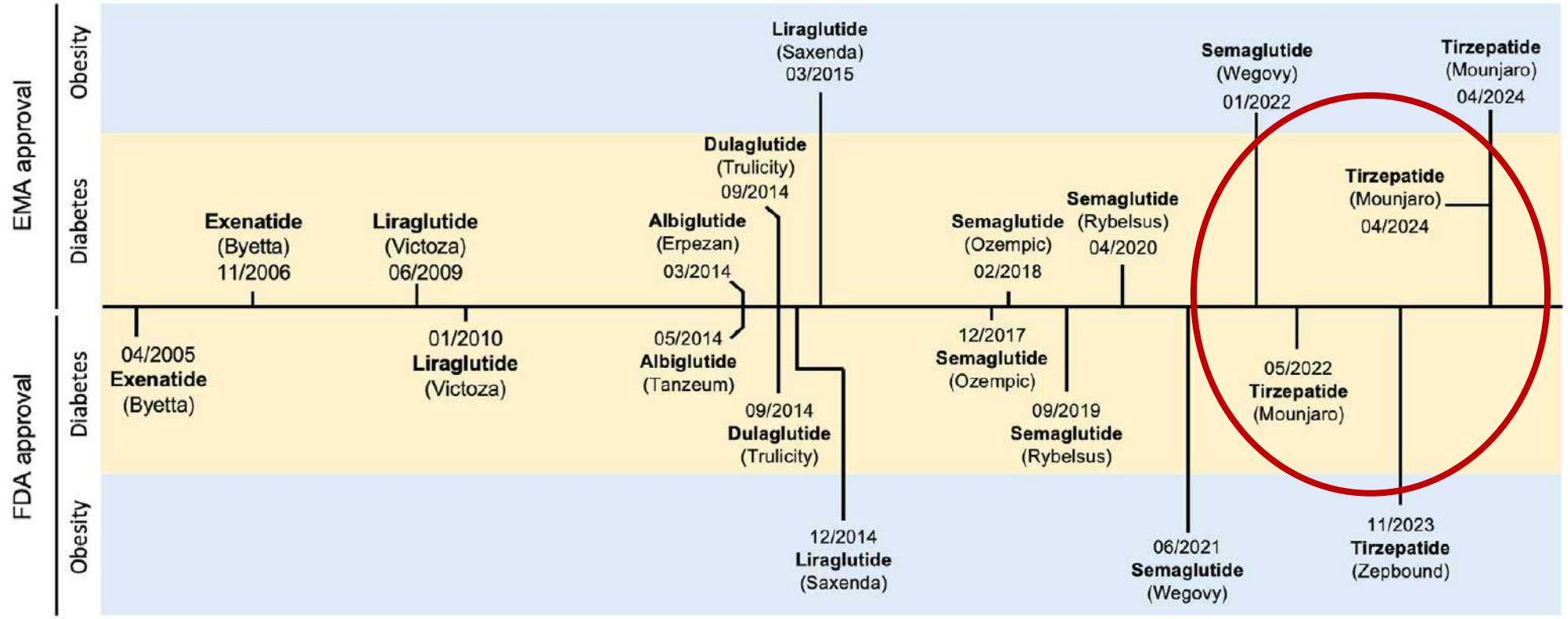
Gut hormones used in the pipeline obesity and type 2 diabetes (T2D) treatments





Melson E at al. International Journal of Obesity 2024

Schematic time-line on the approval of incretin-based drugs for treatment of T2D and obesity



The Lancet Regional Health – Europe 2024;47: 101100

Structures of GLP-1, GIP and tirzepatide

GLP1

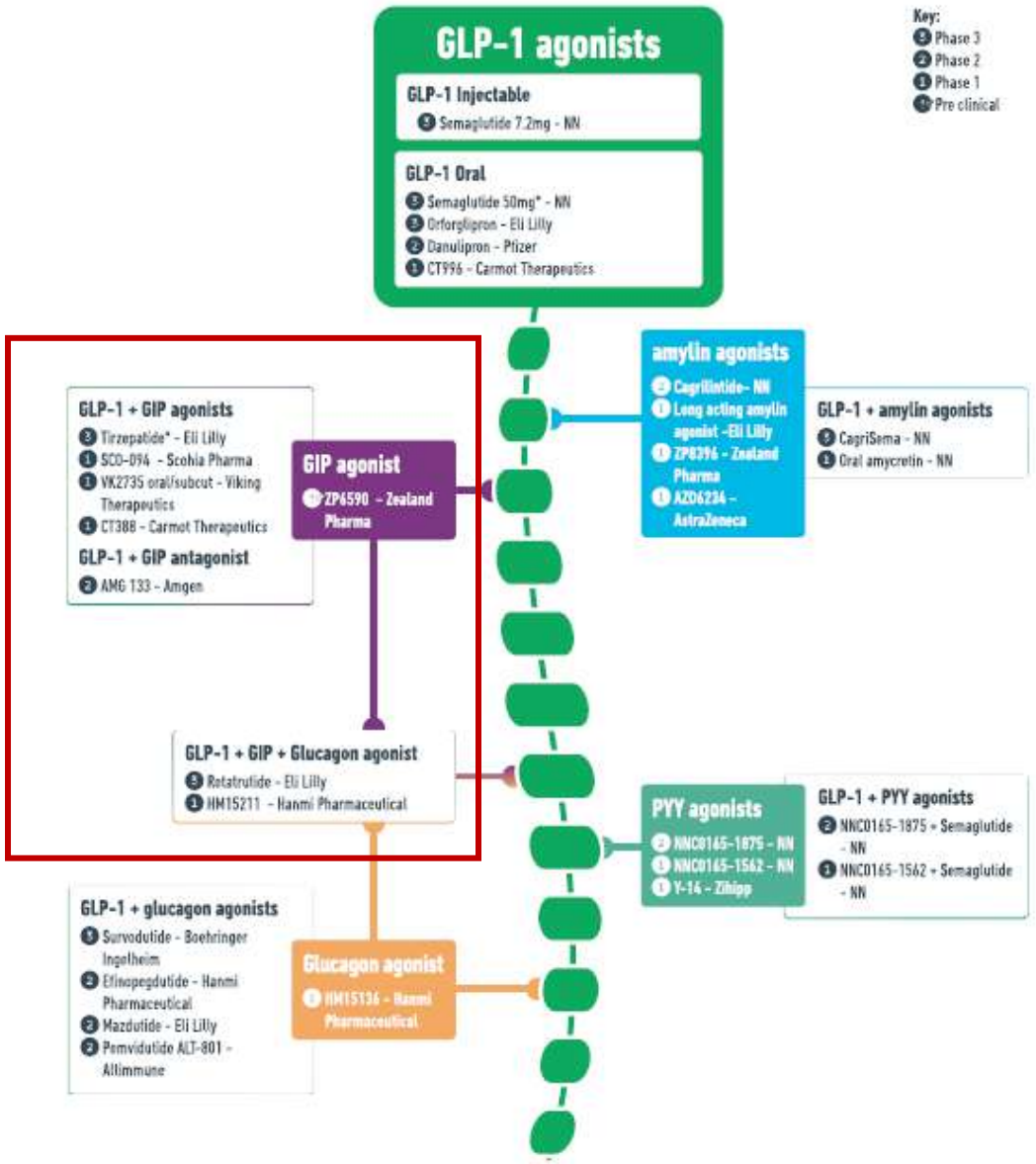
GIP

TIRZEPATIDE

Blue circles show amino acids that are identical to those in GLP-1; black circles show amino acids that are present in GIP and tirzepatide but not in GLP-1; red circles show amino acids that are identical in tirzepatide and exenatide; Green circles show amino acids that are present in tirzepatide but not in GLP-1, GIP or exenatide. AiB, aminoisobutyric acid

Diabetologia (2023) 66:1796–1808

GLP-1 as the backbone of dual and triple incretin-based co-agonist therapies



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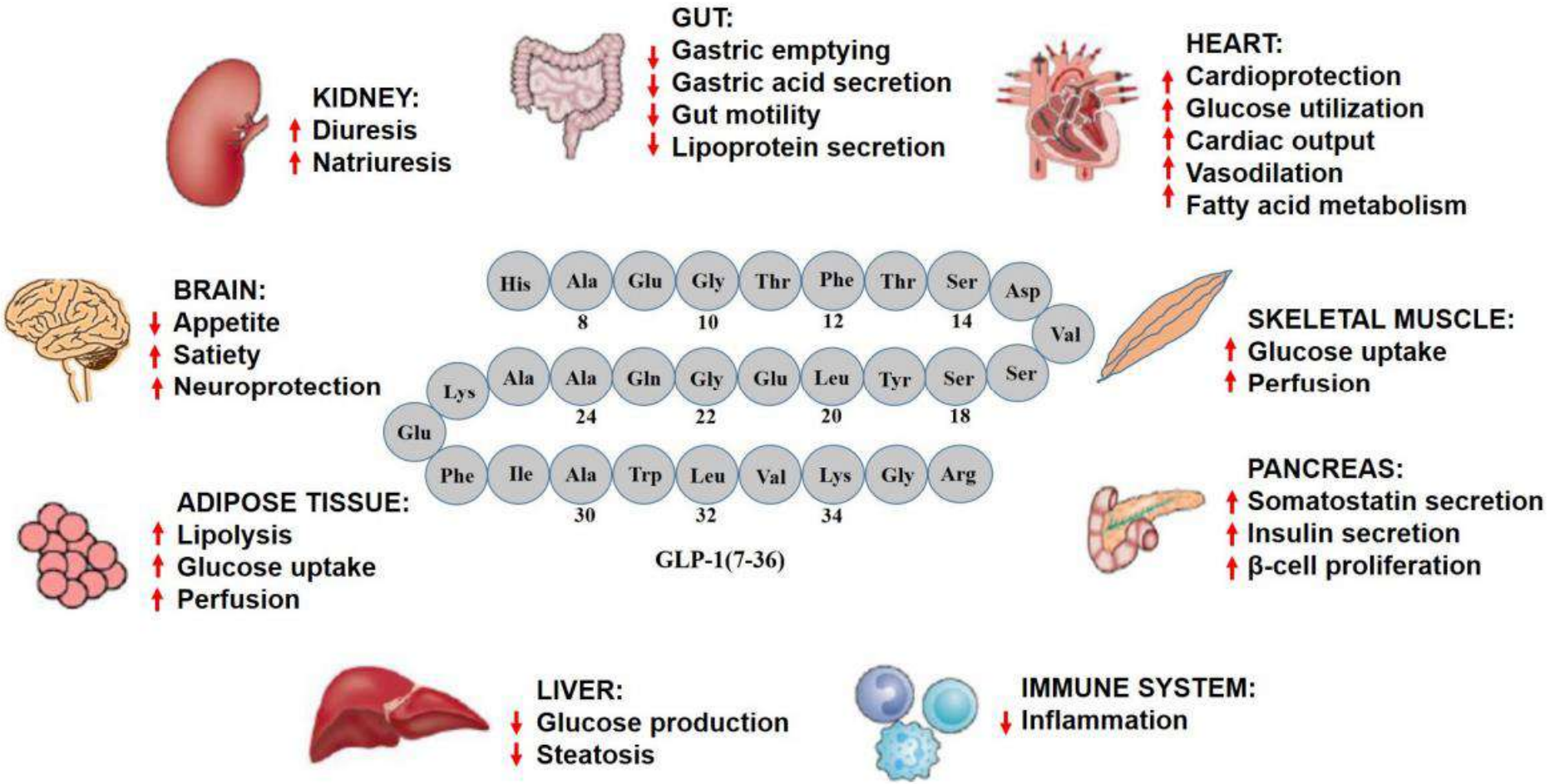
Pleiotropic effects of GLP-1 and analogs



Pharmaceuticals 2023, 16, 836

How may GIP enhance the therapeutic efficacy of GLP-1?

Glucagon-like Peptide-1 Receptor Agonism

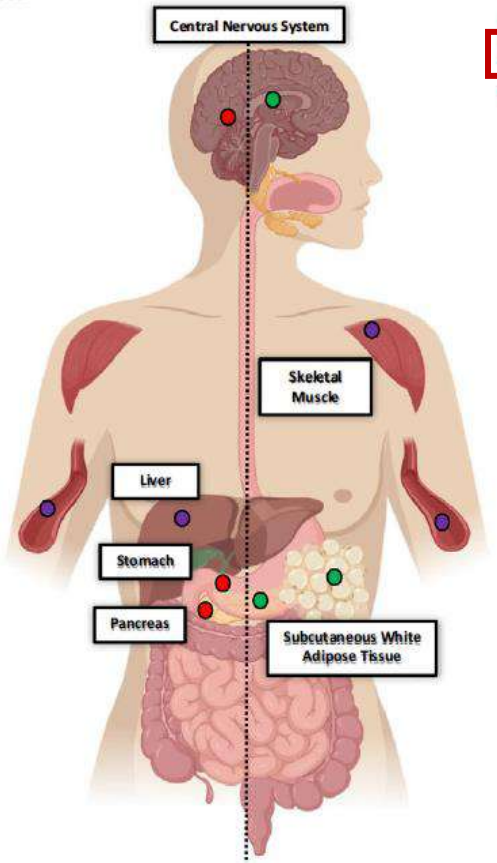
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

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



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

Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

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

Pancreas
- ↑ Insulin
- ↑ Glucagon

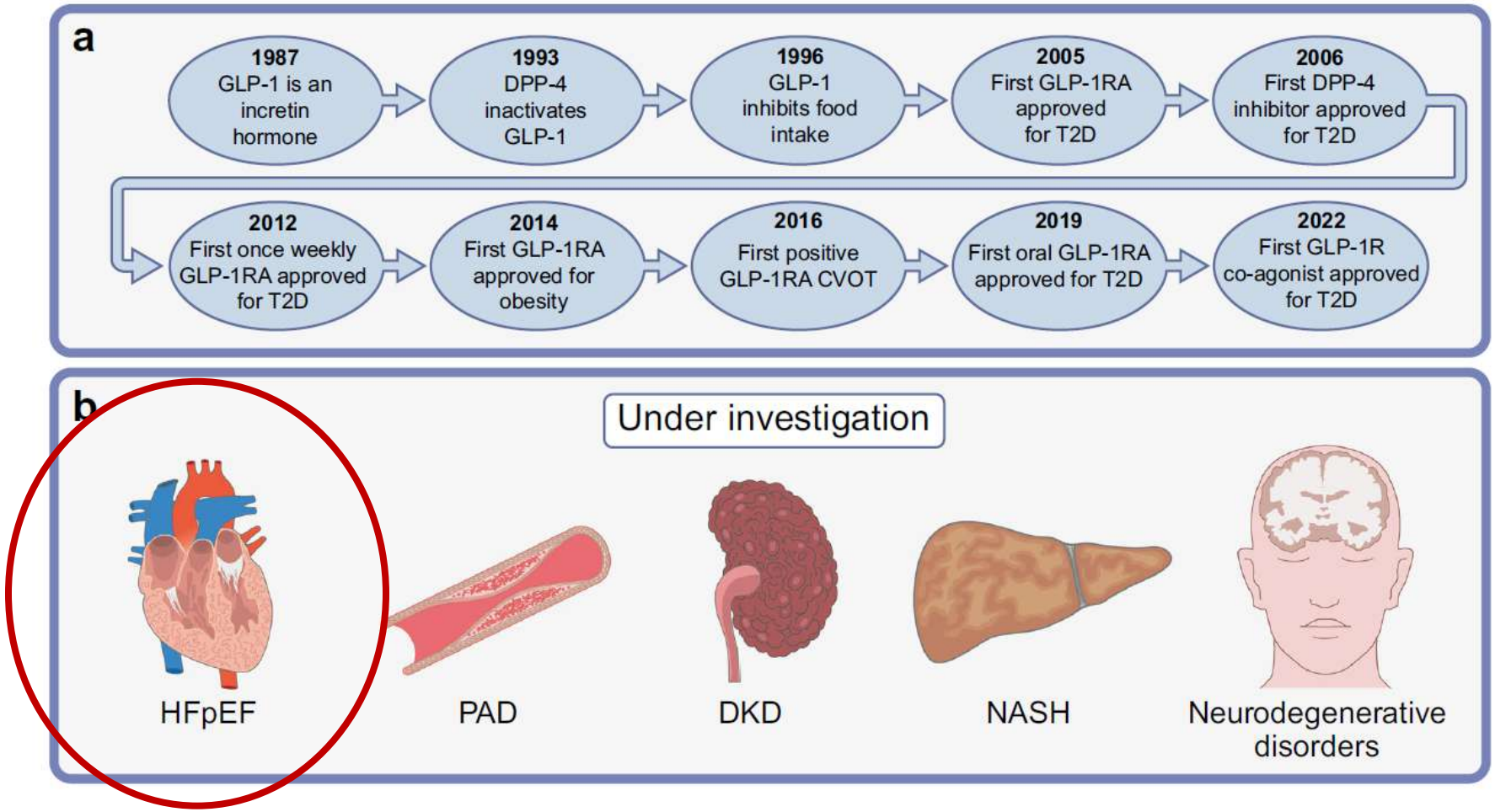
Subcutaneous White Adipose Tissue
- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

Systemic
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

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

Trends in Endocrinology & Metabolism, June 2020, Vol. 31, No. 6

Timeline of GLP-1 discovery and clinical development: beyond glycemia and weight loss



Diabetologia (2023) 66:1765–1779

Summary of composition and metabolic outcome of the SURPASS

	SURPASS-1 (40 weeks)				SURPASS-2 (40 weeks)			SURPASS-3 (52 weeks)			SURPASS-4 (52 weeks)				SURPASS-5 (40 weeks)				SURPASS-6 (52 weeks)		
Participants Background Med. Comparator	Obesity with T2D No OAMs Placebo				Obesity with T2D + Met Semaglutide 1 mg			Obesity with T2D + Met ± SGLT-2i Insulin Degludec			Obesity with T2D Met ± SGLT-2i ± SU Insulin Glargine				Obesity with T2D Ins. Glargine ± Met Placebo				Obesity with T2D Basal Ins. Insulin Lispro		
Participant race (%)	AS (35); AI/AN (25); White (36); Black or Afr. Am. (5)				AS (1); White (82); HS (70); Non-HS (30); Black or Afr. Am. (4)			AS (5); White (91); Black or Afr. Am. (3); Other (1)			AS (4); White (82); Black or Afr. Am. (4)				AS (18); Black or Afr. Am. (1); AI/AN (1); White (80)				AS (<1); Black or Afr. Am. (4); AI/AN (<1); Multiple (1); White (94)		
Trial locations	USA, IN, JPN, MX, PR				USA, ARG, AUS, BR, CA, ISRL, MX, UK, PR			AS (2); EU (8); NAM (2); SOAM (1)			AS (1); EU (6); ME (1); OC (1); NAR (4); SOAM (2)				AS (1); EU (5); NAR (2)				EU (11); NAR (3); SOAR (2)		
Main drug effects after study completion																					
Doses (mg QW)	5	10	15	Pl.	5	10	15 Sema	5	10 15	Ins	5	10	15	Ins	5	10	15	Pl.	5	10 15	Ins
HbA1c (Δ% unit)	−1.9	−1.9	−2.1	0.0	−2.0	−2.2	−2.3–1.9	−1.9	−2.2–2.4	−1.3	−2.2	−2.4	−2.6	−1.4	−2.1	−2.4	−2.3	−0.9	−1.9	−2.2–2.3	−1.1
BW (Δ%)	−8	−9.1	−8.3	−0.8	−8.2	−9.8	−11.9–6.1	−7.9	−11.3–13.6	2.4	−7.9	−11	−13	2.1	−5.6	−7.9	−9.2	1.7	−7.3	−10.3–12.1	3.5
SBP (Δ mmHg)	−4.7	−5.2	−4.7	−2	−4.8	−5.3	−6.5–3.6	−4.9	−6.6–5.5	0.5	−0.6	−6	−3.2	3.6	−6.1	−8.3	−12.6	−1.7	−7.4	−9–5.9	−0.4
DBP (Δ mmHg)	−2.9	−3.1	−3.4	−1.4	−1.9	−2.5	−2.9–1	−2	−2.5–1.9	0.4	−1	−1.4	−1.2	1	−2	−3.3	−4.5	−2.1	−2.3	−3.3–1	−0.4
Pulse rate (Δ bpm)	0.8	2.2	1.3	1.2	2.3	2.2	2.6 2.5	0.9	0.7 2.7	0.6	2.4	4	4.8	0.4	1.3	3.5	5.6	−0.8	2.6	1.4 1.4	1
BW ≥ 10% (%)	31	40	47	1	36	53	65 25	37	56 69	3	36	53	66	2	20.7	41.6	40.7	0.8	32	49 57	5
Adverse effects observed in ≥ 5% of subjects																					
Nausea (%)	12	13	18	6	17	19	22 18	12	23 24	2	12	16	23	2	13	18	18	3	14	21 26	1
Vomiting (%)	3	2	6	2	6	9	10 8	6	9 10	1	5	8	9	2	7	8	13	3	5	9 13	1
Diarrhea (%)	12	14	12	8	13	16	14 12	15	17 16	4	13	20	22	4	12	13	21	10	12	15 11	2
Dyspepsia (%)	9	7	6	3	7	6	9 7	4	9 5	0	6	8	8	1	7	8	5	2	11	11 6	1
Constipation (%)	6	5	7	1	7	5	5 6	n/a	n/a n/a	n/a	5	4	4	<1	6	7	7	2	3	3 6	1
Nasopharyngitis (%)	6	7	7	9	n/a	n/a	n/a n/a	3	4 4	6	3	5	5	7	16	7	13	19	n/a	n/a n/a	n/a
Abdominal pain (%)	n/a	n/a	n/a	n/a	3	5	5 5	2	5 6	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a n/a	n/a
Lipase Increase (%)	5	0	2	0	n/a	n/a	n/a n/a	6	4 6	2	3	4	6	2	3	2	8	2	n/a	n/a n/a	n/a

Treatment: OAM: Oral Anti-Diabetic Medication; Met: Metformin; SGLT-2i: SGLT-2 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinediones; Ins: Insulin; Exen: Exenatide ER; Dula: Dulaglutide; PL: Placebo. **Race:** Afr. Am.: African American; AS: Asian; AI/AN: American Indian and Alaska Native; EU: Europe(an); HS: Hispanic; NHPI: Native Hawaiian and Pacific Islander. **Geography:** AF: Africa; AS: Asia; EU: Europe; ME: Middle East; NAR: North American Region; OC: Oceania; SOAM: South America; ARG: Argentina; AUS: Australia. BR: Brazil; CA: Canada; CN: China; ES: Spain; DE: Germany; HK: Hong Kong; HU: Hungary; IN: India; ISRL: Isreal; ITLY: Italy; JPN: Japan; KOR: South Korea; MX: Mexico; PR: Puerto Rico; RS: Serbia; RUS: Russia; SA: South Africa; SK: Slovakia; USA: United States of America; UK: United Kingdom. **Endpoints:** WL: weight loss; Li: Lifestyle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure; BW: body weight; [E] Efficacy Estimand.

***Table 3*: Summary of composition and metabolic outcome of the SURPASS (A) trials.**

The Lancet Regional Health – Europe 2024;47: 101100

Summary of composition and metabolic outcome of the SURMOUNT

	SURMOUNT-1 (72 weeks)			SURMOUNT-2 (72 weeks)			SURMOUNT-3 (72 weeks)		SURMOUNT-4 (36 + 52 weeks)[E]		
Participants Background Med. Comparator	Obesity without T2D No OAMs Placebo			Obesity with T2D OAMs Placebo			Obesity with at least one comorbidity (excl. T2D) No OAMs Placebo after ≥5 WL after Li		Obesity without T2D No OAMs Placebo		
Participant race (%)	AS (11); Black or Afr. Am. (8); AI/AN (9); White (71)			AS (13); Black or Afr. Am. (8); NHPI (<1); White (76)			AS (1); Black or Afr. Am. (11); NHPI (1); White (86)		AS (7); Black or Afr. Am. (11); NHPI (<1); White (82)		
Trial Locations	AS (4); EU (1); NAR (3); SOAM (2)			AS (3); EU (1); NAR (2); SOAM (2)			NAR (2); SOAM (2)		AS (1); NAR (2); SOAM (2)		
Main drug effects after study completion											
Doses (mg QW)	10	15	Pl.	10	15	Pl.	10 or 15	PL	for 36 weeks	10 or 15 (Δ week 36 to 88)	Pl. (Δ week 36 to 88)
HbA1c (Δ% unit)	−0.5	−0.5	−0.1	−2.1	−2.1	−0.5	−0.5	0	−0.5	−0.1	0.3
BW (Δ%)	−19.5	−20.9	−3.1	−12.8	−14.7	−3.2	−18.4	2.5	−20.9	−6.7	14.8
SBP (Δ mmHg)	−7.2	−7.2	−1	−5.9	−7.7	−1.2	−5.1	4.1	−5.1	−0.4	3.2
DBP (Δ mmHg)	−4.8	−4.8	−0.8	−2.1	−2.9	−0.3	−3.2	2.3	n/a	n/a	n/a
Pulse rate (Δ bpm)	2.3	2.6	0.1	0.6	1	−0.5	2.7	0.9	n/a	n/a	n/a
BW ≥ 10% (%)	78.1	83.5	18.8	61	65	9	76.7	8.9	n/a	n/a	n/a
Adverse effects observed in ≥ 5% of subjects											
Nausea (%)	33	31	10	20	22	6	40	14	n/a	8,1	2,7
Vomiting (%)	11	12	2	11	13	3	18	1	n/a	5,7	1,2
Diarrhea (%)	21	23	7	20	22	9	31	9	n/a	10,7	4,8
Dyspepsia (%)	10	11	4	7	7	3	9	3	n/a	n/a	n/a
Headache (%)	7	7	7	5	5	3	9	8	n/a	n/a	n/a
Constipation (%)	17	12	6	8	9	4	23	7	n/a	n/a	n/a
Nasopharyngitis (%)	n/a	n/a	n/a	3	5	5	2	6	n/a	n/a	n/a
Abdominal pain (%)	5	5	3	4	7	2	11	2	n/a	n/a	n/a

Treatment: OAM: Oral Anti-Diabetic Medication; Met: Metformin; SGLT-2i: SGLT-2 inhibitor; SU: Sulfonylurea; TZD: Thiazolidinediones; Ins: Insulin; Exen: Exenatide ER; Dula: Dulaglutide; PL: Placebo. **Race:** Afr. Am.: African American; AS: Asian; AI/AN: American Indian and Alaska Native; EU: Europe(an); HS: Hispanic; NHPI: Native Hawaiian and Pacific Islander. **Geography:** AF: Africa; AS: Asia; EU: Europe; ME: Middle East; NAR: North American Region; OC: Oceania; SOAM: South America; ARG: Argentina; AUS: Australia. BR: Brazil; CA: Canada; CN: China; ES: Spain; DE: Germany; HK: Hong Kong; HU: Hungary; IN: India; ISRL: Isreal; ITLY: Italy; JPN: Japan; KOR: South Korea; MX: Mexico; PR: Puerto Rico; RS: Serbia; RUS: Russia; SA: South Africa; SK: Slovakia; USA: United States of America; UK: United Kingdom. **Endpoints:** WL: weight loss; Li: Lifestyle intervention; SBP: systolic blood pressure; DBP: diastolic blood pressure; BW: body weight; [E] Efficacy Estimand.

Table 4: **Summary of composition and metabolic outcome of the SURMOUNT (B) trials.**

The Lancet Regional Health – Europe 2024;47: 101100

Clinical outcomes of tirzepatide in type 2 diabetes

Table 1. Baseline Characteristics of the Tirzepatide and GLP-1 RA Groups Before and After Propensity Score Matching

Characteristic	Before matching, No. (%)			After matching, No. (%)		
	Tirzepatide (n = 14 834)	GLP-1 RA (n = 125 474)	Standardized difference	Tirzepatide (n = 14 832)	GLP-1 RA (n = 14 832)	Standardized difference
Age, mean (SD), y	55.4 (11.8)	58.1 (13.3)	0.213	55.4 (11.8)	55.5 (13.3)	0.004
Sex						
Female	8444 (56.9)	67 474 (53.8)	0.064	8444 (56.9)	8436 (56.9)	0.001
Male	5563 (37.5)	53 326 (42.5)	0.106	5563 (37.5)	5577 (37.6)	0.008
Race and ethnicity						
African American or Black	2517 (17.0)	25 212 (20.1)	0.088	2517 (17.0)	2469 (16.6)	0.009
Asian	337 (2.3)	4558 (3.6)	0.080	337 (2.3)	355 (2.4)	0.008
Hispanic or Latinx	957 (6.5)	11 676 (9.3)	0.106	957 (6.5)	906 (6.1)	0.014
White	9978 (67.3)	75 762 (60.4)	0.144	9978 (67.3)	10 052 (67.8)	0.011
Other*	466 (3.1)	3137 (2.5)	0.092	466 (3.1)	451 (3.0)	0.003
Unknown	579 (3.9)	5129 (4.1)	0.026	579 (3.9)	599 (4.0)	0.002
Comorbidities						
Hypertension	8265 (55.7)	72 438 (57.7)	0.041	8265 (55.7)	8149 (54.9)	0.016
Ischemic heart disease	1623 (10.9)	16 814 (13.4)	0.075	1623 (10.9)	1588 (10.7)	0.008
Heart failure	821 (5.5)	9447 (7.5)	0.081	821 (5.5)	736 (5.0)	0.026
Atrial fibrillation or flutter	670 (4.5)	7334 (5.8)	0.060	670 (4.5)	685 (4.6)	0.005
Cerebrovascular disease	437 (2.9)	5579 (4.4)	0.080	437 (2.9)	441 (3.0)	0.002
Peripheral vascular disease	320 (2.2)	4150 (3.3)	0.071	320 (2.2)	288 (1.9)	0.015
Chronic lower-respiratory disease	1789 (12.1)	17 673 (14.1)	0.060	1789 (12.1)	1760 (11.9)	0.006
Chronic kidney disease	1261 (8.5)	14 841 (11.8)	0.110	1261 (8.5)	1207 (8.1)	0.013
Anemia	822 (5.5)	10 552 (8.4)	0.113	822 (5.5)	801 (5.4)	0.006
Inflammatory liver disease	308 (2.1)	2064 (1.6)	0.032	308 (2.1)	277 (1.9)	0.015
Liver cirrhosis	259 (1.7)	2241 (1.8)	0.003	259 (1.7)	286 (1.9)	0.014
Neoplasm	2166 (14.6)	19 460 (15.5)	0.025	2166 (14.6)	2209 (14.9)	0.008
Systemic connective tissue disorder	248 (1.7)	2124 (1.7)	0.002	248 (1.7)	244 (1.6)	0.002
Rheumatoid arthritis	74 (0.5)	632 (0.5)	0.001	74 (0.5)	81 (0.5)	0.007
HIV	53 (0.4)	895 (0.7)	0.049	53 (0.4)	45 (0.3)	0.009
Dementia	36 (0.2)	614 (0.5)	0.041	36 (0.2)	32 (0.2)	0.006
Diabetic complications						
Kidney	1281 (8.6)	13700 (10.8)	0.069	1281 (8.6)	1226 (8.3)	0.013
Ophthalmic	699 (4.7)	6015 (4.8)	0.002	698 (4.7)	663 (4.5)	0.011
Neurologic	1610 (10.9)	14143 (11.2)	0.004	1609 (10.8)	1555 (10.5)	0.012
Circulatory	850 (5.7)	7503 (5.9)	0.004	850 (5.7)	812 (5.5)	0.011

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used US Collaborative Network of TriNetX data collected on individuals with type 2 diabetes aged 18 years or older initiating tirzepatide or GLP-1 RA between June 1, 2022, and June 30, 2023; without stage 5 chronic kidney disease or kidney failure at baseline; and without myocardial infarction or ischemic or hemorrhagic stroke within 60 days of drug initiation.

EXPOSURES Treatment with tirzepatide compared with GLP-1 RA.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality, and secondary outcomes included major adverse cardiovascular events (MACEs), the composite of MACEs and all-cause mortality, kidney events, acute kidney injury, and major adverse kidney events. All outcomes were analyzed using Cox proportional hazards regression models.

Table 1. Baseline Characteristics of the Tirzepatide and GLP-1 RA Groups Before and After Propensity Score Matching (continued)

Characteristic	Before matching, No. (%)			After matching, No. (%)		
	Tirzepatide (n = 14 834)	GLP-1 RA (n = 125 474)	Standardized difference	Tirzepatide (n = 14 832)	GLP-1 RA (n = 14 832)	Standardized difference
Laboratory tests and examinations						
HbA_{1c}, mean (SD), %	7.66 (1.82)	8.01 (1.95)	0.185	7.66 (1.82)	7.69 (1.94)	0.016
≥7%	6391 (43.1)	57 672 (46.0)	0.058	6391 (43.1)	6230 (42.0)	0.022
Hemoglobin, mean (SD), g/dL	13.7 (1.8)	13.4 (1.9)	0.165	13.7 (1.8)	13.6 (1.9)	0.071
≥12 g/dL	7514 (50.7)	62 308 (49.7)	0.020	7514 (50.7)	7451 (50.2)	0.008
eGFR, mean (SD), mL/min/1.73 m^2	81.4 (24.9)	80.3 (27.7)	0.042	81.4 (24.9)	82.6 (27.4)	0.044
≥45 mL/min/1.73 m^2	9527 (64.2)	79 769 (63.6)	0.014	9527 (64.2)	9330 (62.9)	0.028
SBP, mean (SD), mm Hg	131.4 (17.1)	131.8 (17.9)	0.023	131.4 (17.1)	131.5 (17.7)	0.009
≥130 mm Hg	7591 (51.2)	65 805 (52.4)	0.025	7591 (51.2)	7609 (51.3)	0.002
LDL cholesterol, mean (SD), mg/dL	92.9 (37.3)	92.3 (38.6)	0.016	92.9 (37.3)	93.2 (37.8)	0.008
≥160 mg/dL	563 (3.8)	4833 (3.9)	0.003	563 (3.8)	552 (3.7)	0.004
100-160 mg/dL	3082 (20.8)	24 892 (19.8)	0.023	3082 (20.8)	2984 (20.1)	0.016
Total cholesterol, mean (SD), mg/dL	169.0 (50.8)	169.3 (49.2)	0.006	169.0 (50.8)	169.6 (48.3)	0.014
≥240 mg/dL	697 (4.7)	6617 (5.3)	0.026	697 (4.7)	677 (4.6)	0.006
200-240 mg/dL	1412 (9.5)	13 071 (10.4)	0.030	1412 (9.5)	1394 (9.4)	0.004
BMI, mean (SD)	36.7 (6.2)	34.8 (6.7)	0.285	36.7 (6.2)	36.5 (6.3)	0.026
≥30	8055 (54.3)	58 981 (47.0)	0.146	8055 (54.3)	7980 (53.8)	0.010
25-30	1495 (10.1)	18 674 (14.9)	0.146	1495 (10.1)	1461 (9.9)	0.008

JAMA Network Open. 2024;7(8):e2427258.

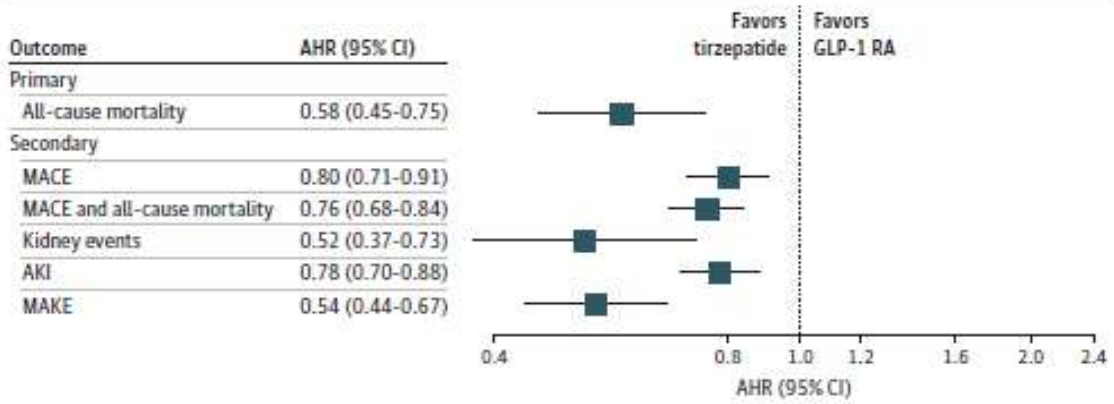
Clinical outcomes of tirzepatide in type 2 diabetes

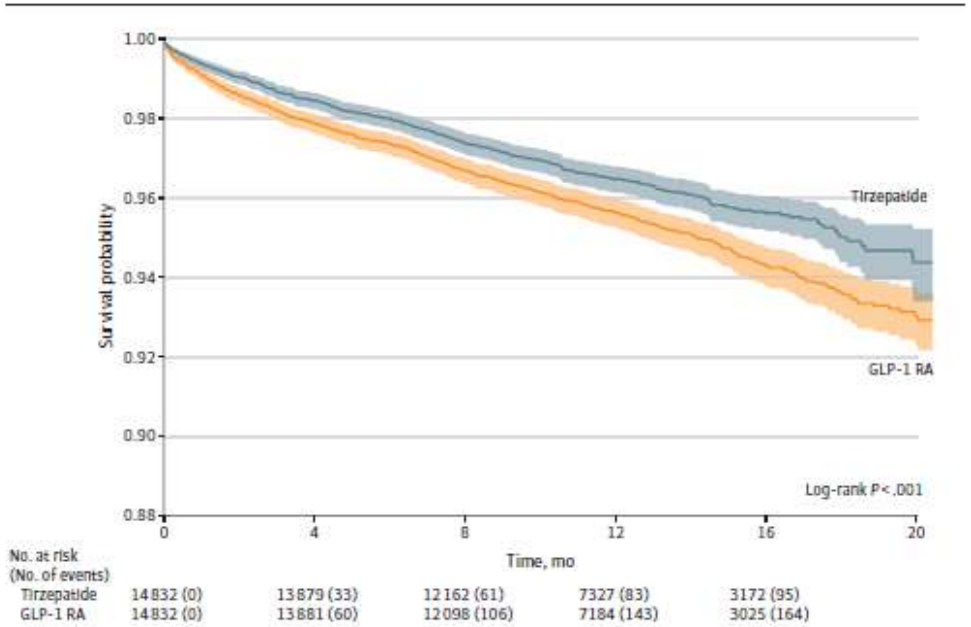
Table 2. Comparison of Tirzepatide vs GLP-1 RA for Primary and Secondary Outcomes

Outcome	No. of patients with outcome: Tirzepatide (n = 14 832)	No. of patients with outcome: GLP-1 RA (n = 14 832)	AHR (95% CI)	*P* value	E-value (E-value for the upper limit of CI)
Primary outcome					
All-cause mortality	95	166	0.58 (0.45-0.75)[a]	<.001[b]	2.82 (1.99)
Secondary outcomes					
MACEs	472	589	0.80 (0.71-0.91)[a]	<.001[b]	1.79 (1.44)
MACE and all-cause mortality	543	721	0.76 (0.68-0.84)[a]	<.001[b]	1.98 (1.65)
Kidney events	53	102	0.52 (0.37-0.73)[a]	<.001[b]	3.24 (2.09)
Acute kidney injury	506	652	0.78 (0.70-0.88)[a]	<.001[b]	1.87 (1.53)
MAKEs	129	241	0.54 (0.44-0.67)[a]	<.001[b]	3.11 (2.35)

↓42%

Figure 2. Forest Plot of Primary and Secondary Outcomes

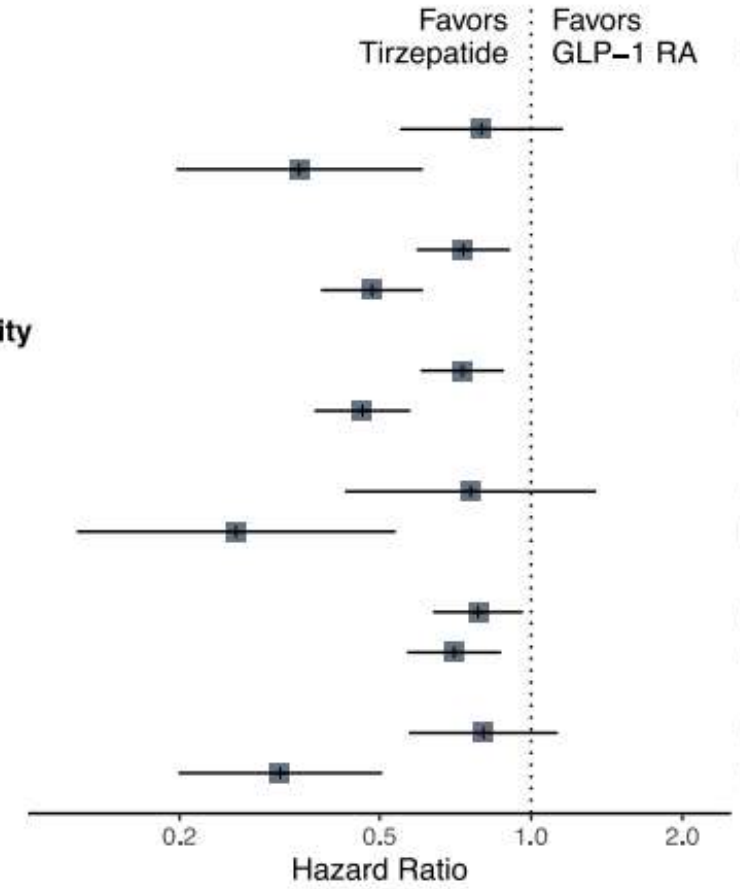




JAMA Network Open. 2024;7(8):e2427258.

Low-dose (maximum ≤7.5 mg) or high-dose (maximum ≥10 mg) tirzepatide vs all GLP-RA

2B. Low-dose (maximum ≤7.5 mg) or high-dose (maximum ≥10 mg) tirzepatide compared to all GLP-RA



Outcomes	aHR (95% CI)	P for interaction
All–cause mortality		0.02
TZP ≤7.5	0.80 (0.55–1.16)	
TZP ≥10	0.35 (0.20–0.61)	
MACE		0.01
TZP ≤7.5	0.73 (0.59–0.91)	
TZP ≥10	0.48 (0.38–0.61)	
MACE and all–cause mortality		0.002
TZP ≤7.5	0.73 (0.60–0.88)	
TZP ≥10	0.46 (0.37–0.58)	
Kidney events		0.02
TZP ≤7.5	0.76 (0.43–1.35)	
TZP ≥10	0.26 (0.13–0.54)	
AKI		0.47
TZP ≤7.5	0.78 (0.64–0.96)	
TZP ≥10	0.70 (0.57–0.87)	
MAKE		0.002
TZP ≤7.5	0.80 (0.57–1.13)	
TZP ≥10	0.32 (0.20–0.51)	

JAMA Network Open. 2024;7(8):e2427258.

Tirzepatide for heart failure with preserved ejection fraction and obesity

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Tirzepatide (N=364)	Placebo (N=367)
Age — yr	65.5±10.5	65.0±10.9
Female sex — no. (%)	200 (54.9)	193 (52.6)
Race or ethnic group — no. (%)†		
Native American, Alaska Native, or Pacific Islander	26 (7.1)	24 (6.5)
Asian	58 (15.9)	73 (19.9)
Black	22 (6.0)	14 (3.8)
White	256 (70.3)	256 (69.8)
Other or multiple	2 (0.5)	0 (0.0)
Region — no. (%)		
United States	83 (22.8)	68 (18.5)
Latin America	193 (53.0)	197 (53.7)
Asia	58 (15.9)	73 (19.9)
Other	30 (8.2)	29 (7.9)
New York Heart Association functional classification — no. (%)		
Class II	262 (72.0)	268 (73.0)
Class III or IV	102 (28.0)	99 (27.0)
Measures of adiposity		
Body weight — kg	102.9±21.7	103.1±22.7
Body-mass index‡	38.3±6.4	38.2±7.0
Waist-to-height ratio	0.73±0.09	0.73±0.09
Left ventricular ejection fraction — %	61.0±6.5	60.6±6.2
HFpEF-ABA score§	0.82±0.16	0.81±0.17
Coronary artery disease — no./total no. (%)	111/359 (30.9)	106/364 (29.1)
Median NT-proBNP level (IQR) — pg/ml	196 (56–488)	169 (64–476)
Estimated glomerular filtration rate — ml/min/1.73 m²	64.5±23.7	64.3±23.5
KCCQ-CSS score¶	53.9±17.9	53.2±19.0
6-Minute walk distance — m	305.0±80.0	300.6±83.5
High-sensitivity C-reactive protein level — mg/liter	5.8±8.5	5.8±8.4
Systolic blood pressure — mm Hg	127.9±13.1	128.2±13.7
Heart rate — beats/min	71.0±11.2	71.2±10.7
Hospitalization or urgent care visit for worsening heart failure within 12 months before enrollment — no. (%)	171 (47.0)	172 (46.9)
Atrial fibrillation — no. (%)	95 (26.1)	91 (24.8)
Type 2 diabetes — no. (%)	174 (47.8)	178 (48.5)

METHODS

In this international, double-blind, randomized, placebo-controlled trial, we randomly assigned, in a 1:1 ratio, 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo for at least 52 weeks. The two primary end points were a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better quality of life).

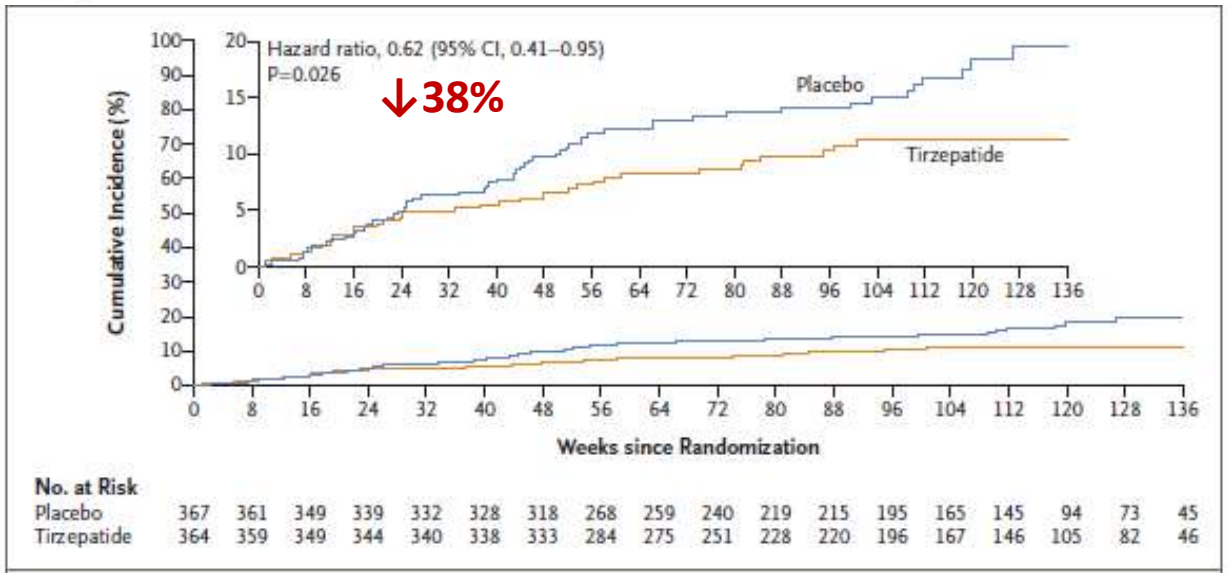


Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.
Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.

Packer M et al. NEJM November 16, 2024

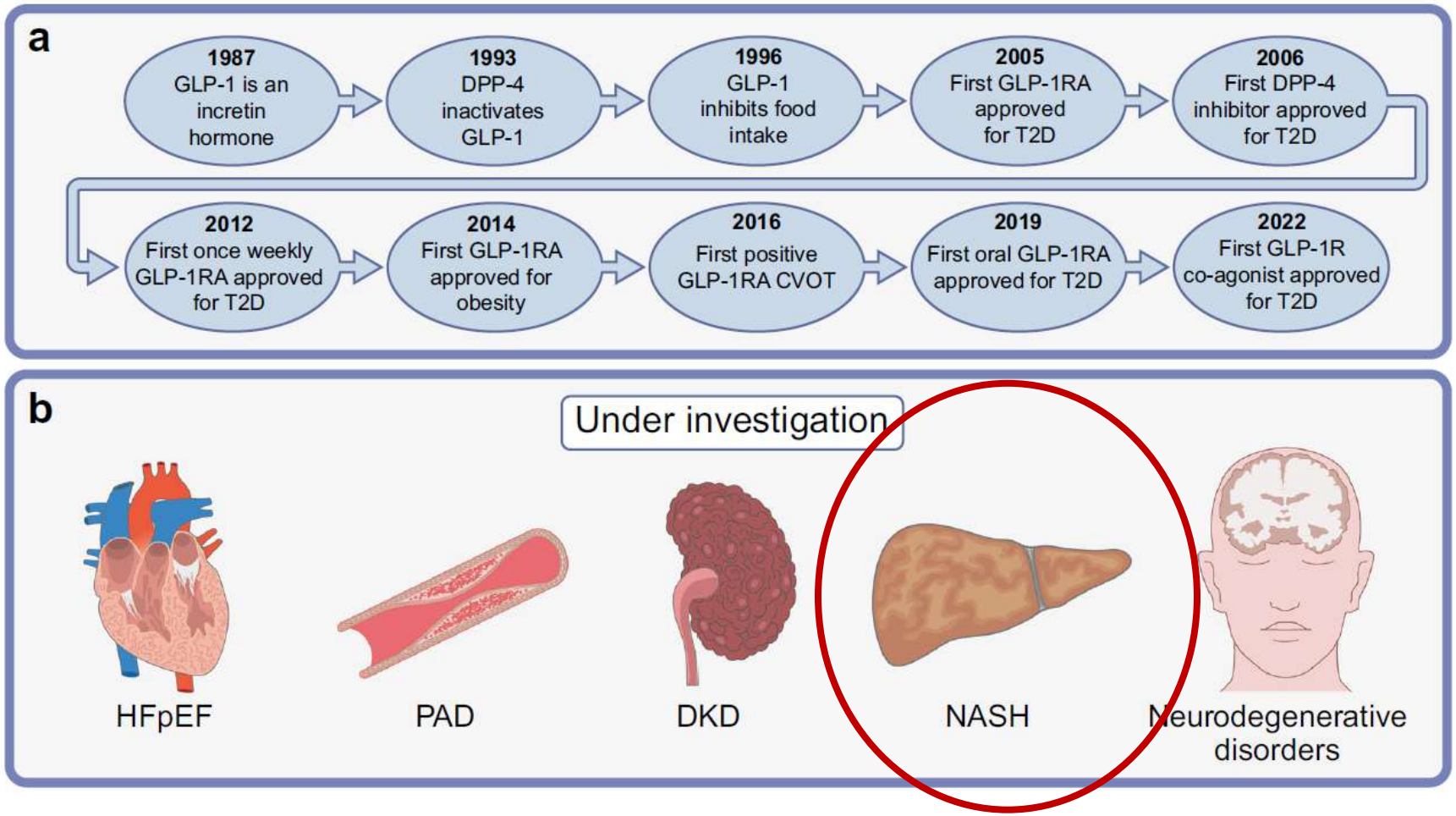
Tirzepatide for heart failure with preserved ejection fraction and obesity

Table 2. Primary and Secondary End Points.*

End Point	Tirzepatide (N=364) Value	Tirzepatide (N=364) Events/100 patient-yr	Placebo (N=367) Value	Placebo (N=367) Events/100 patient-yr	Hazard Ratio or Difference (95% CI)†	P Value
Primary end points and components						
Adjudicated death from cardiovascular causes or a worsening heart-failure event resulting in hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy — no. (%)	36 (9.9)	5.5	56 (15.3)	8.8	0.62 (0.41 to 0.95)	0.026
Adjudicated death from cardiovascular causes — no. (%)	8 (2.2)	1.2	5 (1.4)	0.7	1.58 (0.52 to 4.83)	
Adjudicated death from undetermined cause — no. (%)	2 (0.5)	0.3	0	0	—	
Adjudicated worsening heart-failure event resulting in hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy — no. (%)	29 (8.0)	4.5	52 (14.2)	8.2	0.54 (0.34 to 0.85)	
Adjudicated worsening heart-failure event resulting in hospitalization — no. (%)	12 (3.3)	1.8	26 (7.1)	3.9	0.44 (0.22 to 0.87)	
Adjudicated worsening heart-failure event resulting in intravenous diuretic therapy in an urgent care setting — no. (%)	5 (1.4)	0.7	12 (3.3)	1.8	0.41 (0.14 to 1.16)	
Adjudicated worsening heart-failure event resulting in intensification of oral diuretic therapy in an outpatient setting — no. (%)	17 (4.7)	2.6	21 (5.7)	3.2	0.80 (0.42 to 1.52)	
Death from any cause — no. (%)	19 (5.2)	2.8	15 (4.1)	2.2	1.25 (0.63 to 2.45)	
Change at 52 weeks in KCCQ-CSS	19.5±1.2	—	12.7±1.3	—	6.9 (3.3 to 10.6)‡	<0.001¶
Key secondary end points						
Change at 52 weeks in 6-minute walk distance — m	26.0±3.8	—	10.1±3.9	—	18.3 (9.9 to 26.7)‡	<0.001¶
Percent change at 52 weeks in body weight — %	−13.9±0.4	—	−2.2±0.5	—	−11.6 (−12.9 to −10.4)	<0.001
Percent change at 52 weeks in high-sensitivity C-reactive protein level — %	−38.8±4.5	—	−5.9±5.3	—	−34.9 (−45.6 to −22.2)¶	<0.001
Adjusted change at 52 weeks in physiological and laboratory measurements						
NT-proBNP — ratio of geometric means‖	0.93±0.04	—	1.04±0.04	—	0.90 (0.79 to 1.01)¶	
Systolic blood pressure — mm Hg	−4.6±0.8	—	0.1±0.8	—	−4.7 (−6.8 to −2.5)	
Heart rate — beats/min	3.0±0.5	—	0.3±0.5	—	2.8 (1.3 to 4.3)	

Packer M et al. NEJM November 16, 2024

Timeline of GLP-1 discovery and clinical development: beyond glycemia and weight loss



Diabetologia (2023) 66:1765–1779

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with liver fibrosis

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

Characteristic	Tirzepatide, 5 mg (N=47)	Tirzepatide, 10 mg (N=47)	Tirzepatide, 15 mg (N=48)	Placebo (N=48)	Total (N=190)
Age — yr	55.0±11.6	54.3±12.1	54.9±10.0	53.5±11.6	54.4±11.3
Female sex — no. (%)	27 (57)	26 (55)	29 (60)	27 (56)	109 (57)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	1 (2)	1 (2)	1 (2)	0	3 (2)
Asian	5 (11)	6 (13)	6 (12)	5 (10)	22 (12)
Black	0	1 (2)	0	0	1 (<1)
White	41 (87)	39 (83)	41 (85)	43 (90)	164 (86)
Hispanic or Latino ethnic group — no. (%)†	19 (40)	15 (32)	17 (35)	18 (38)	69 (36)
Body weight — kg	100.7±22.2	102.6±23.8	100.0±18.1	96.0±21.6	99.8±21.5
Body-mass index‡	36.1±6.0	36.6±6.3	35.9±5.7	36.0±6.7	36.1±6.1
Type 2 diabetes — no. (%)	26 (55)	27 (57)	29 (60)	29 (60)	111 (58)
Liver fibrosis stage — no. (%)§					
F2	17 (36)	25 (53)	22 (46)	17 (35)	81 (43)
F3	30 (64)	22 (47)	26 (54)	31 (65)	109 (57)
NAFLD activity score¶	5.4±1.0	5.3±0.9	5.0±0.9	5.3±1.0	5.3±0.9
Alanine aminotransferase (U/liter)	67.9±39.9	61.2±35.9	58.7±25.4	59.7±30.3	61.8±33.2
Aspartate aminotransferase (U/liter)	55.5±28.2	47.0±23.8	47.5±20.7	52.3±21.3	50.6±23.7
Glycated hemoglobin — %	6.6±1.3	6.4±1.1	6.4±0.9	6.8±1.2	6.5±1.1
Liver fat content — %‖	19.0±6.9	17.6±7.5	18.8±8.3	18.2±6.8	18.4±7.3
Extracellular hepatic water content — msec**	920.5±120.5	894.1±88.5	923.3±88.1	917.7±92.0	913.0±97.5
Liver stiffness — kPa††	12.6±5.9	11.1±4.3	11.4±5.7	12.0±5.1	11.8±5.3
Fibrosis-4 index score‡‡	1.8±1.1	1.5±0.7	1.5±0.6	1.6±0.7	1.6±0.8
NIS4 test score§§	0.8±0.2	0.7±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Enhanced Liver Fibrosis test score¶¶	9.9±1.0	9.8±0.8	9.7±0.6	9.9±0.8	9.8±0.8
Pro-C3 — μg/liter‖‖	145.3±103.2	127.9±76.8	115.6±49.7	127.4±57.9	128.9±74.6

METHODS

We conducted a phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis. Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at 52 weeks. A key secondary end point was an improvement (decrease) of at least one fibrosis stage without worsening of MASH.

Loomba R. et al. NEJM June 8, 2024

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with liver fibrosis

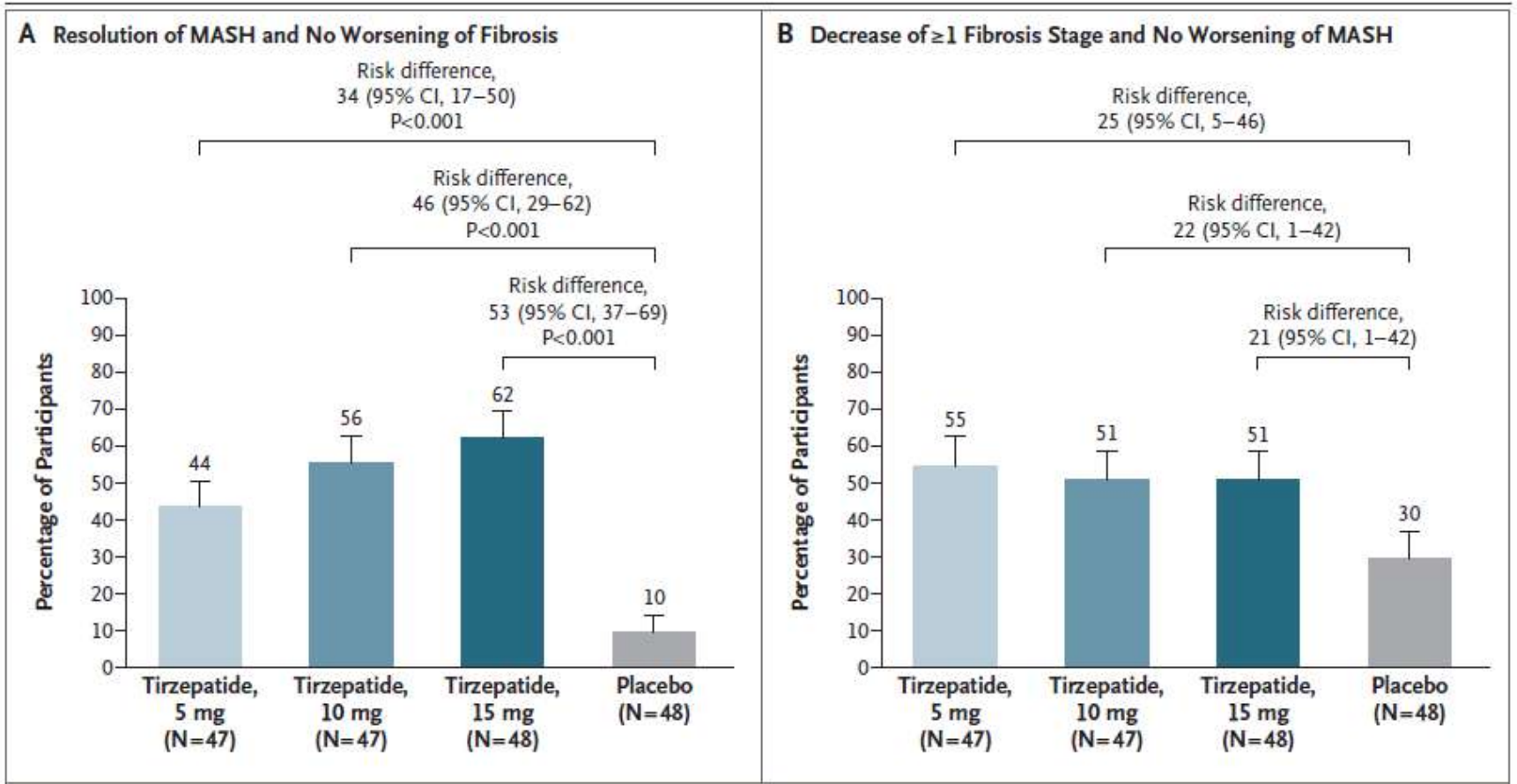


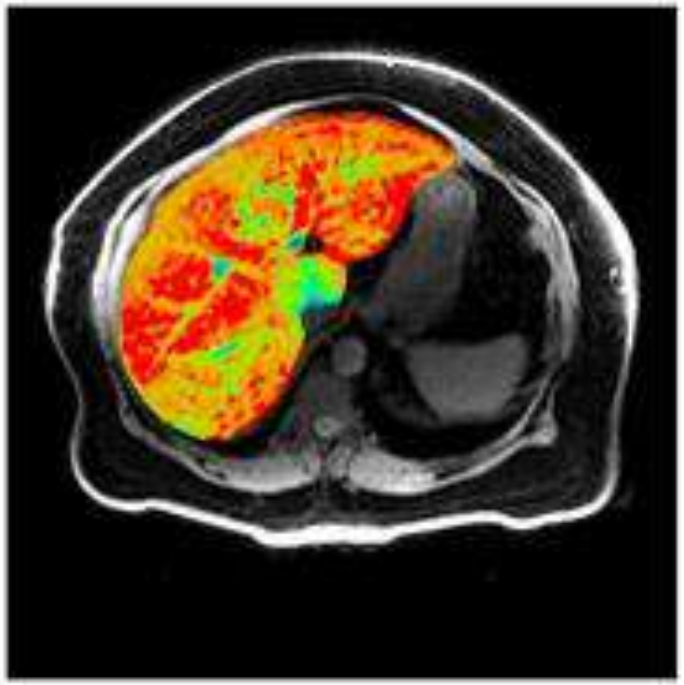
Figure 1. Primary and Key Secondary End Points.

Loomba R. et al. NEJM June 8, 2024

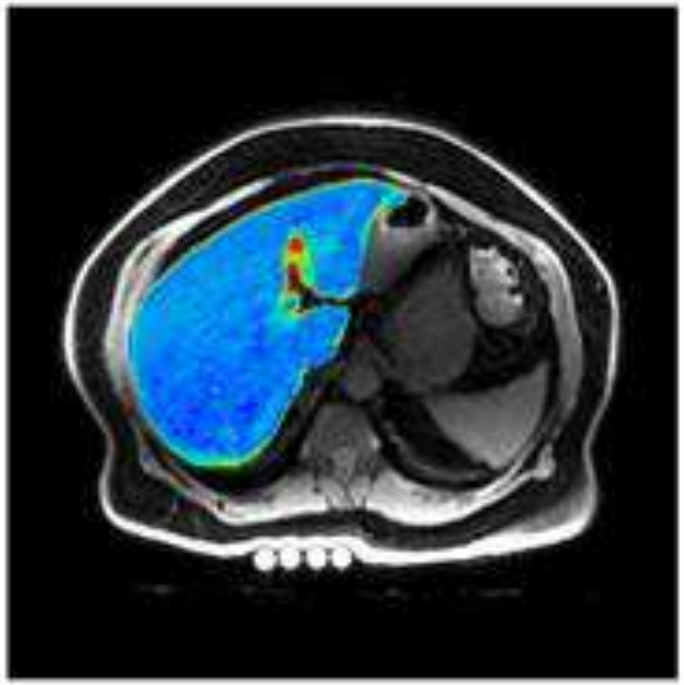
Effect of Tirzepatide on Liver Fat Content (LFC)

MRI Scans showing LFC (%) at baseline and at weeks 52[a]

SURPASS-3 MRI



LFC at Baseline: 27.3%



LFC at 52 Weeks: 2.6%

A MRI scans from one participant randomized to tirzepatide 5 mg; 59 year old male on metfromin with SGLT2i

Gastaldelli A et al. Lancet Diabetes Endocrinol 2022; 10(6):393-406

Dual and Triple Incretin-Based Co-agonists for in MASLD

nature medicine

Article

https://doi.org/10.1038/s41591-024-03018-2

Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial

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A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

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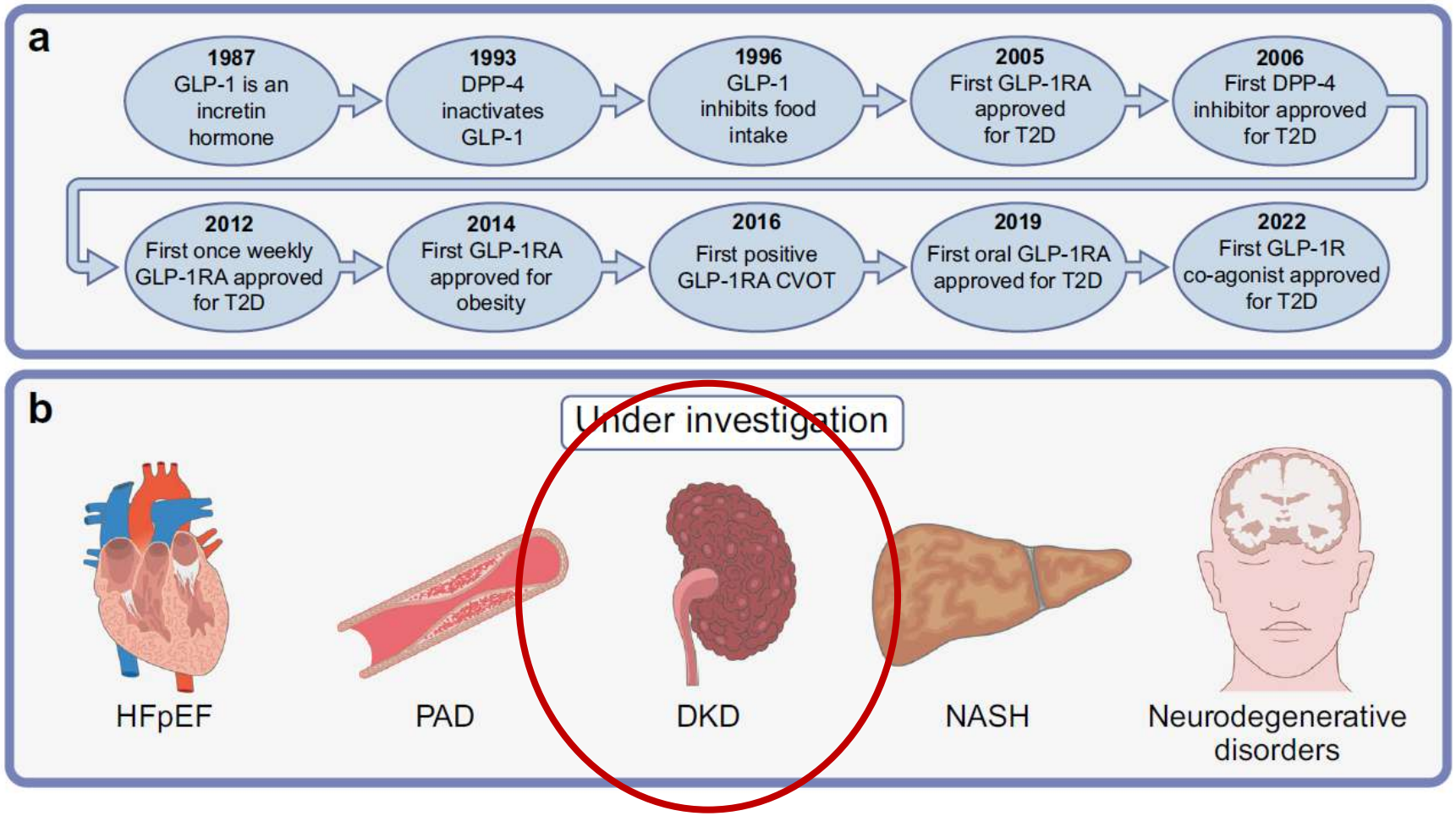
Timeline of GLP-1 discovery and clinical development: beyond glycemia and weight loss



Diabetologia (2023) 66:1765–1779

Renal effects of tirzepatide in individuals with type 2 diabetes

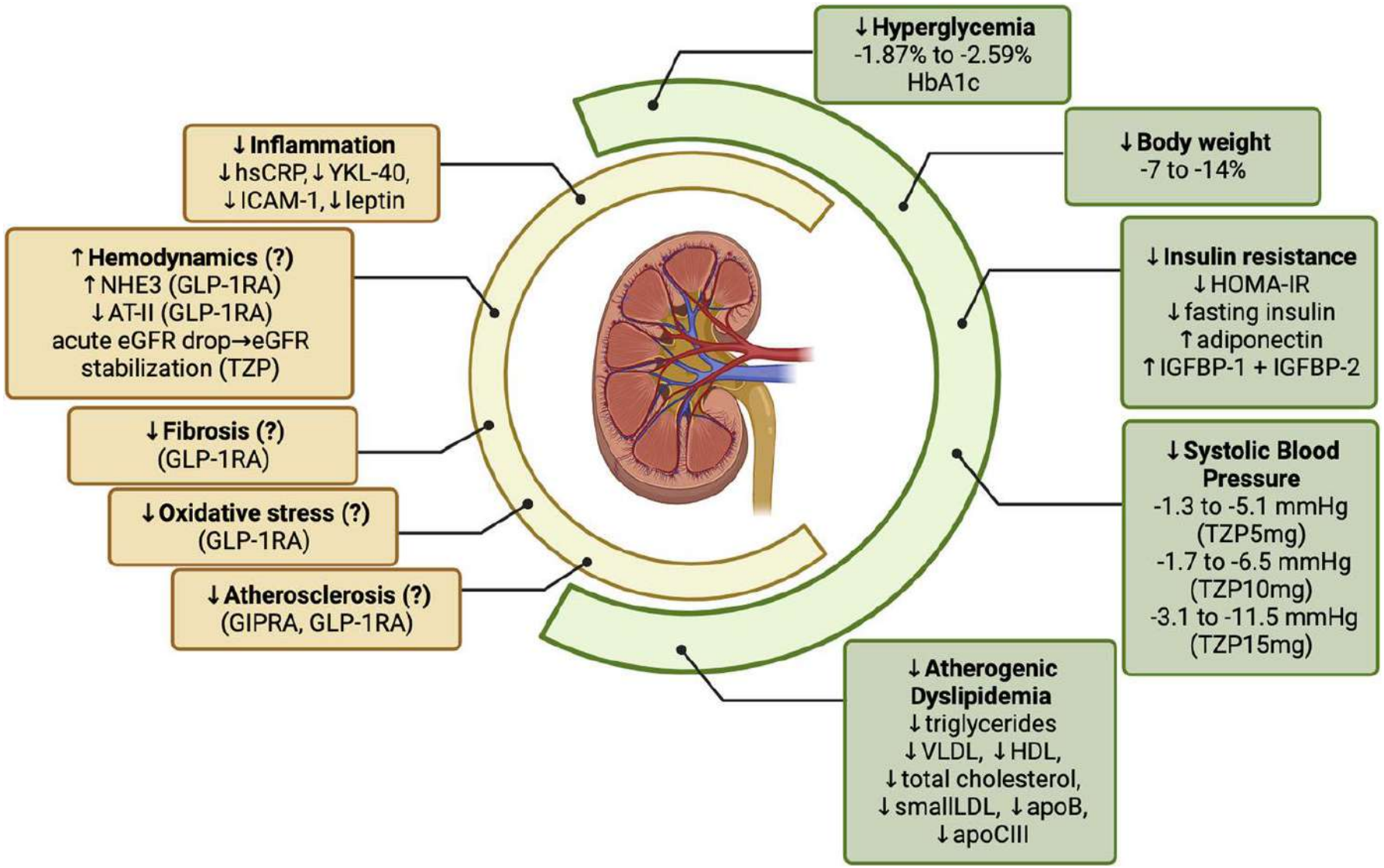
Table 4 Effects of tirzepatide on UACR across the SURPASS program

	UACR change from baseline			Comparator	UACR difference TZP vs. comparator		
	TZP 5 mg	TZP 10 mg	TZP 15 mg		TZP 5 mg	TZP 10 mg	TZP 15 mg
SURPASS-1 (vs. placebo)	−13.7 (6.9)	−8.5 (7.5)	4.8 (9.2)	52.5 (15.4)	−43.4 (−56.1, −27.0)	−43.0 (−53.6, −22.5)	−31.3 (−47.2, −10.5)
SURPASS-2 (vs. semaglutide 1 mg)	−11.0 (3.9)	−3.9 (4.2)	−16.9 (3.7)	−6.5 (4.1)	−4.8 (−15.6, 7.3)	2.8 (−8.9 to 16.1)	−11.1 (−21.3, 0.4)
SURPASS-3 (vs. insulin degludec)	−17.3 (4.3)	−19.4 (4.3)	−27.5 (3.9)	−5.3 (5.0)	−12.7 (−24.4, 1.0)	−14.9 (−26.6, −1.5)	−23.4 (−33.9, −11.4)
SURPASS-4 (vs. insulin glargine)	−11.4 (5.7)	−21.9 (5.1)	−25.2 (4.8)	15.5 (4.3)	−23.3 (−33.7, −11.2)	−32.3 (−41.6, −21.6)	−35.2 (−43.9, −25.2)
SURPASS-5 (vs. placebo)	4.7 (9.7)	−22.4 (7.3)	−17.3 (8.0)	17.2 (10.7)	−10.7 (−30.8, 15.3)	−33.8 (−48.8, −14.3)	−29.4 (−45.6, −8.3)

UACR change from baseline is indicated as % (SE), UACR difference of TZP vs. comparator is indicated as % (95% CI). UACR, urinary albumin-to-creatinine ratio

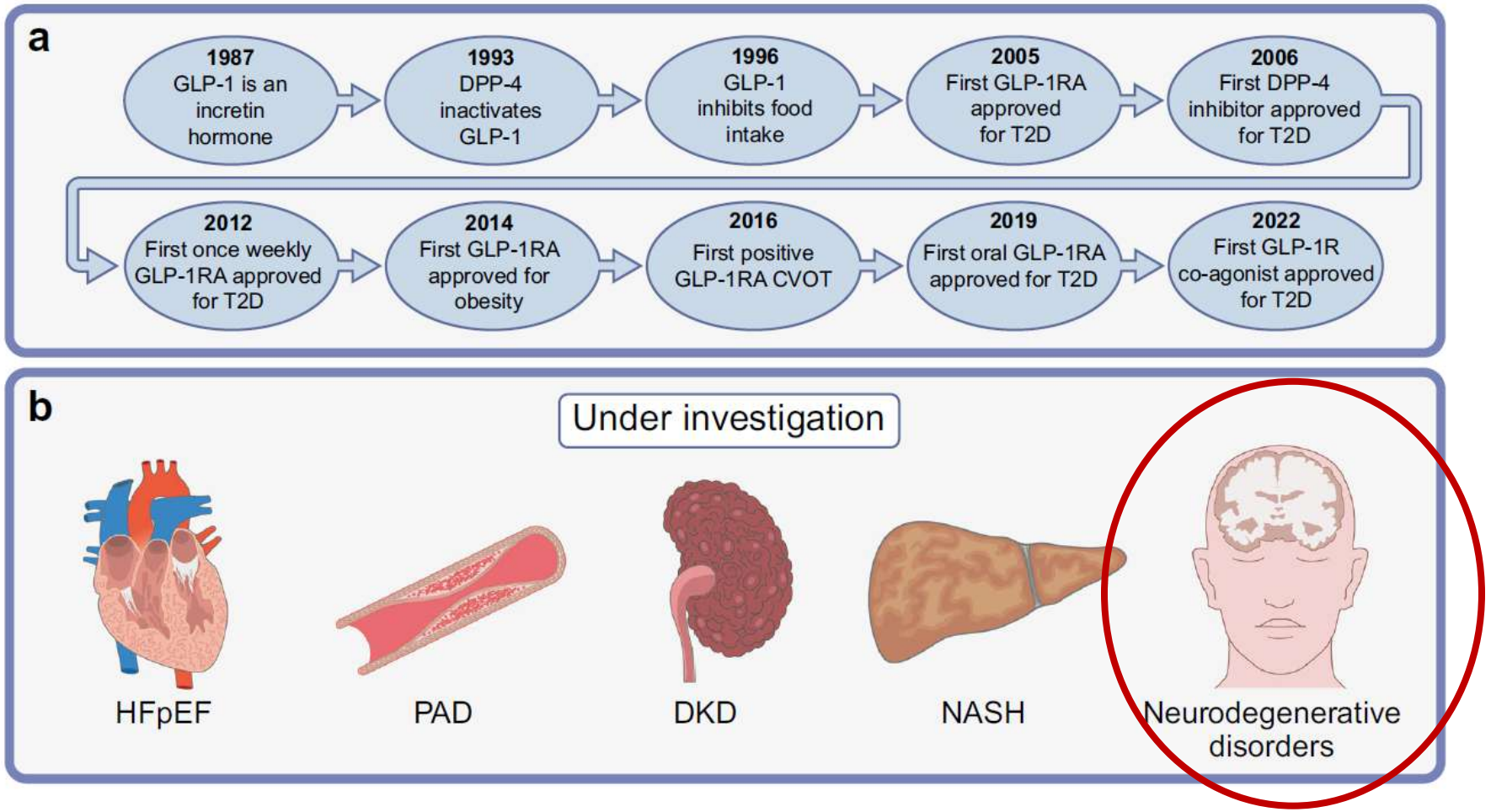
Caruso I et al. Endocrine (2024) 84:822–835

Putative mechanisms underlying the renal benefits of tirzepatide



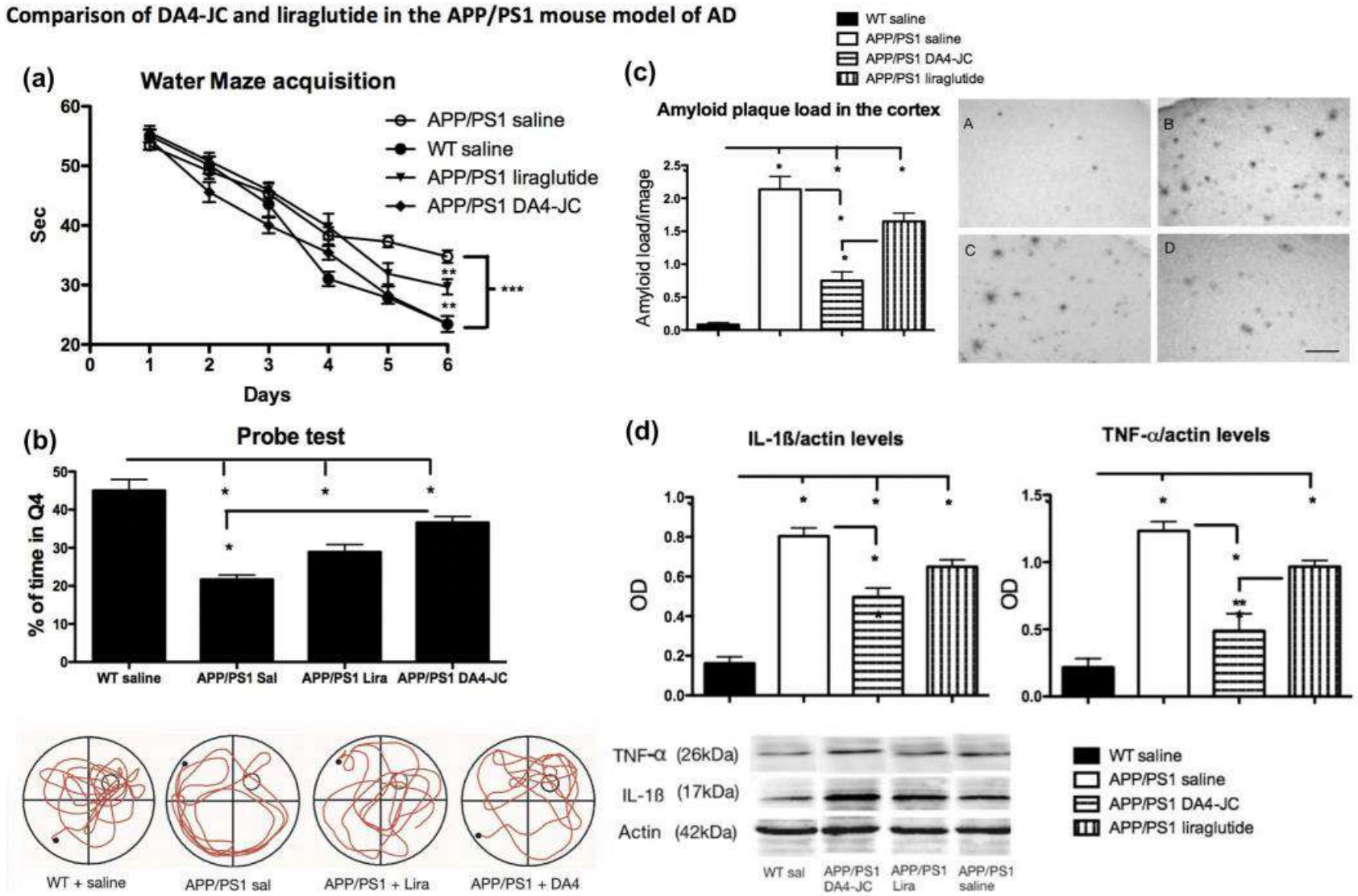
Caruso I et al. Endocrine (2024) 84:822–835

Timeline of GLP-1 discovery and clinical development: beyond glycemia and weight loss



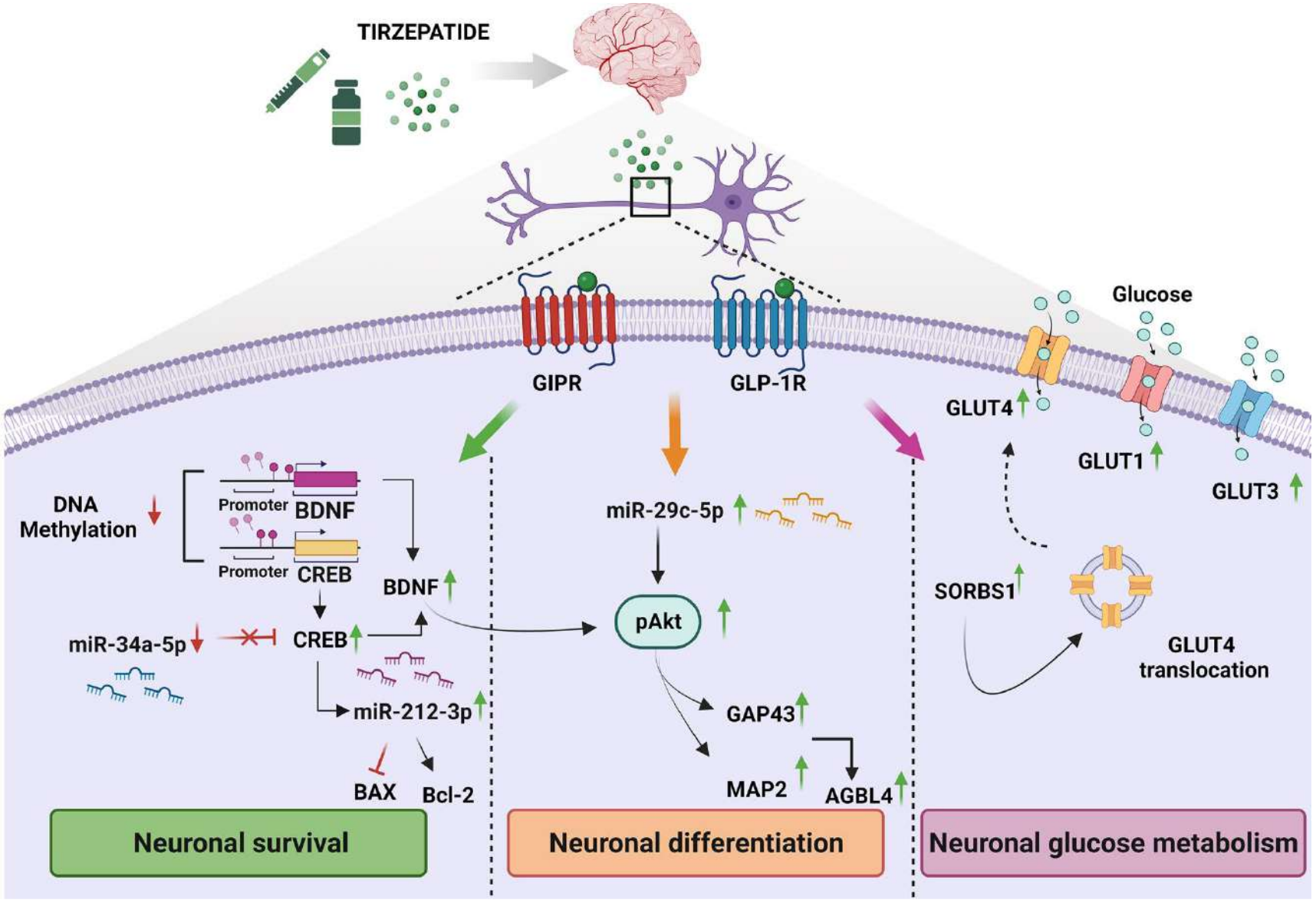
Diabetologia (2023) 66:1765–1779

GIP/GLP1 dual agonist in Alzheimer's Disease



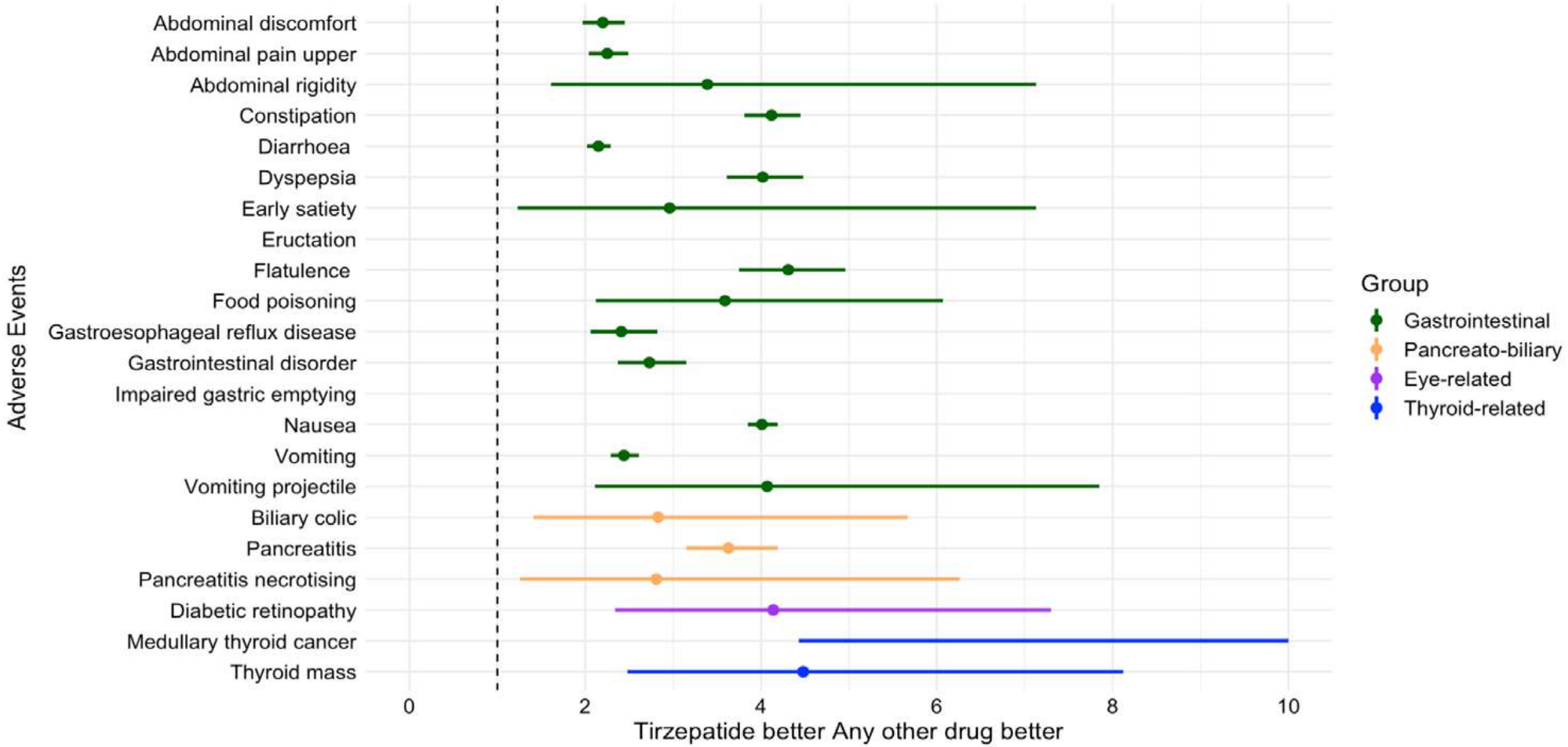
Br J Pharmacol. 2022 Feb;179(4):695-714

Tirzepatide prevents neurodegeneration through multiple molecular pathways



Fontanella et al. Journal of Translational Medicine (2024) 22:114

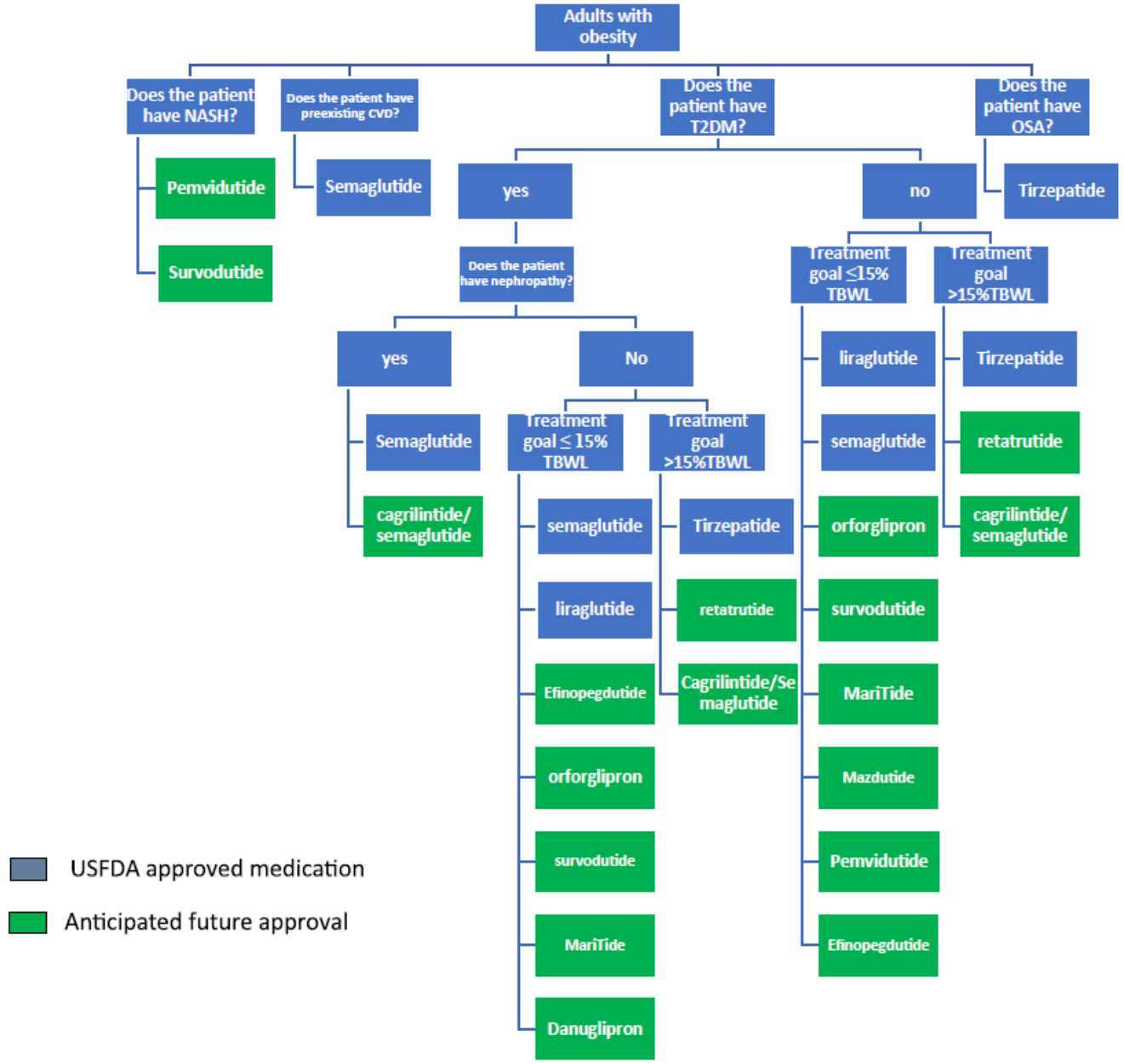
The real-world safety profile of tirzepatide



Caruso I et al. Journal of Endocrinological Investigation (2024) 47:2671–2678


What's
NEXT

GLP-1 single, dual, and triple receptor agonists for treating type 2 diabetes and obesity

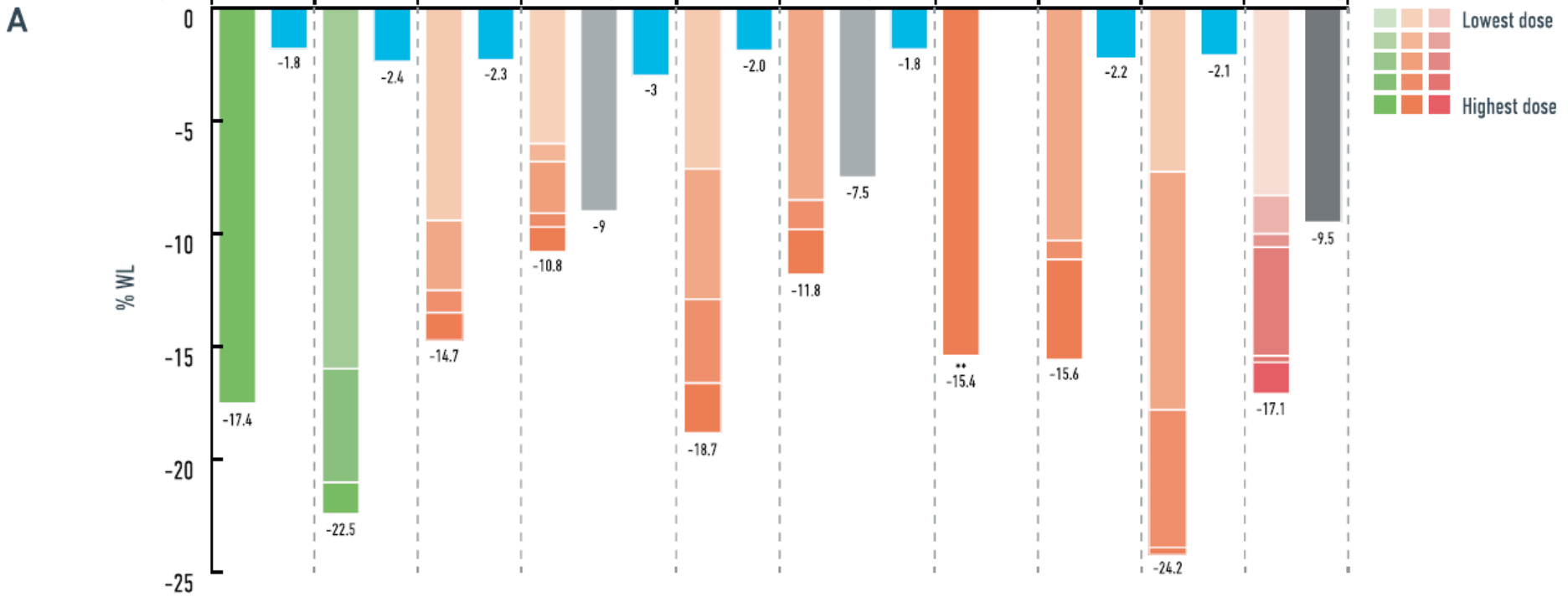


eClinicalMedicine 2024;75: 102782


Grazie

Weight loss with the gut hormone-based therapies in people without diabetes

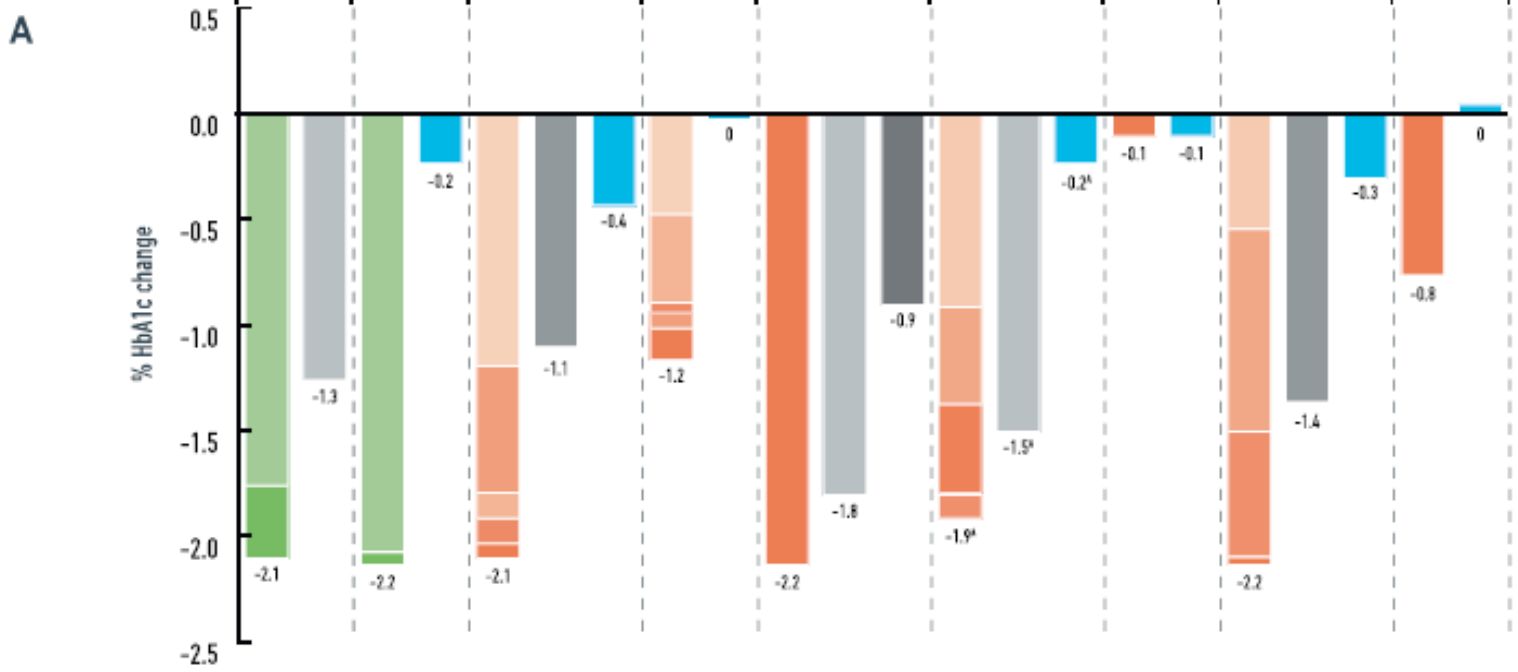
	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C**]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Number of participants	667	2539	272	706	387	474	80	391	338	95
Timepoint (weeks)	68	72	36	26	46	26	24	48	48	20
Baseline weight (kg)	105.4	104.8	108.7	107.4	105.7	113.3	96.9	104	107.7	95.7 - 99.6
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



Melson E at al. International Journal of Obesity 2024

HbA1c reduction with the gut hormone-based in people with type 2 diabetes

	Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Danuglipron[A]	CagriSema[A]	Survodutide[A,B*]	Efinopegdutide[B]	Retatrutide[A]	Bimagrumab[B]
Dose and frequency	25/50mg OD	10/15mg OW	3/12/24/36/45mg OD	1.5/10/40/ 80/120mg BD	2.4mg OW	0.3/0.9/1.8/2.7mg OW 1.2/1.8mg BW	25/50mg OW	0.5/4/8/12mg OW	10mg/kg every 4 wks
Route	PO	SC	PO	PO	SC	SC	SC	SC	IV
Mechanism of action	GLP-1	GLP-1+GIP	GLP-1	GLP-1	GLP-1+amylin	GLP-1 + GCG	GLP-1+GCG	GLP-1+GIP+GCG	ACVR2B antagonist
Number of participants	1606	938	383	411	92	413	195	281	75
Baseline HbA1c (%)	9	8	8-8.2	8.1	8.7	8.1	7.6	8.3	7.8
Duration of T2DM (years)	9.3	8.5	5-7.9	8.8	8.7	7.6	7.7	6-10.5	NA
Baseline weight (kg)	96.4 - 100.7	100.7	98.4-104.8	91.3	105.7	97	113	93.1-108.3	93.6
Timepoint (weeks)	68	72	26	16	32	16	12	36	48
Comparator	SEMA 14mg	PBO	DULA 1.5mg / PBO	PBO	SEMA 2.4mg / CAGR 2.4mg	SEMA 1.0mg / PBO	PBO	DULA 1.5mg / PBO	PBO



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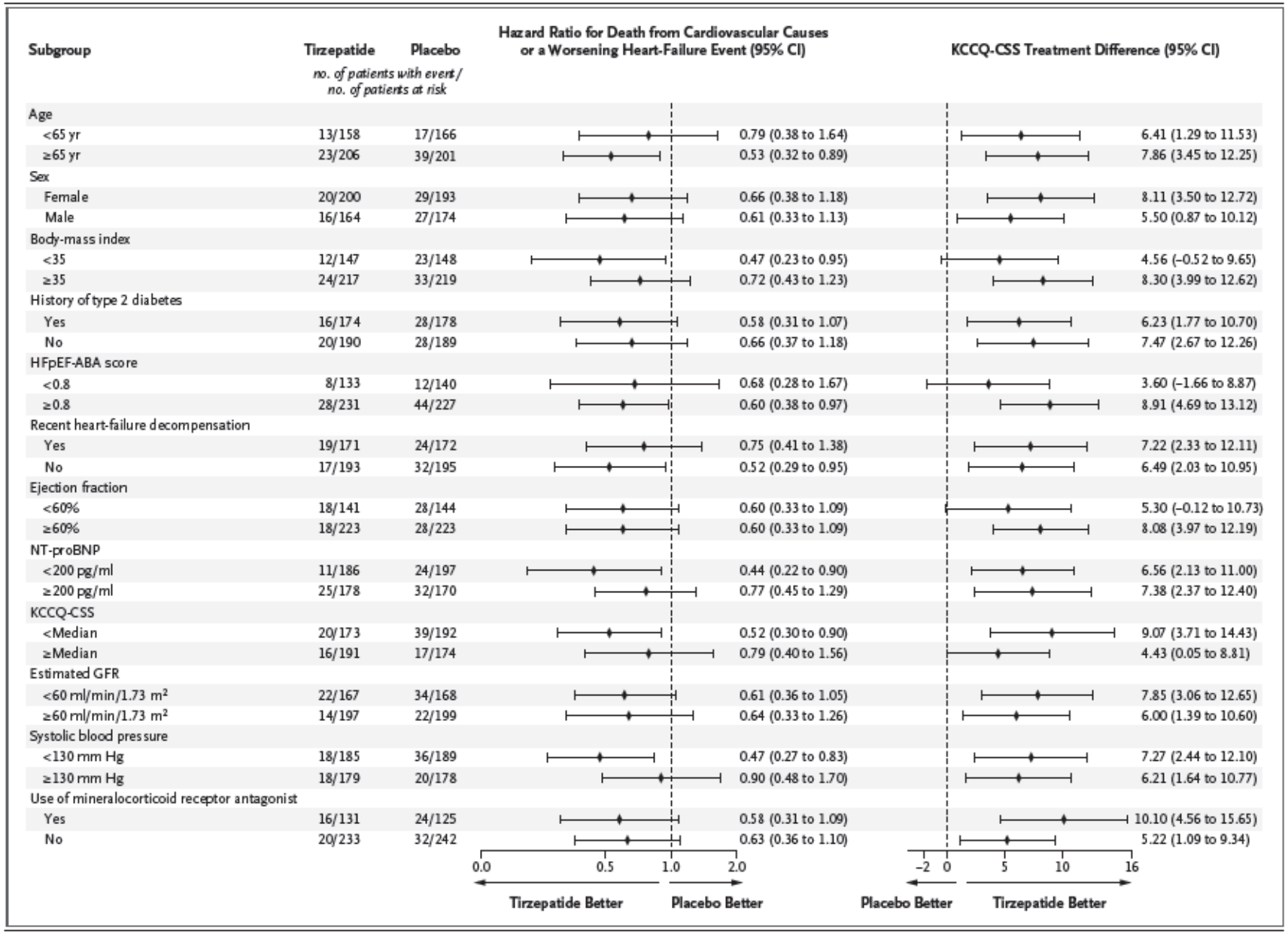
Tirzepatide for heart failure with preserved ejection fraction and obesity



Subgroup	Tirzepatide	Placebo	Hazard Ratio for Death from Cardiovascular Causes or a Worsening Heart-Failure Event (95% CI)	KCCQ-CSS Treatment Difference (95% CI)
	no. of patients with event / no. of patients at risk			
Age				
<65 yr	13/158	17/166	0.79 (0.38 to 1.64)	6.41 (1.29 to 11.53)
≥65 yr	23/206	39/201	0.53 (0.32 to 0.89)	7.86 (3.45 to 12.25)
Sex				
Female	20/200	29/193	0.66 (0.38 to 1.18)	8.11 (3.50 to 12.72)
Male	16/164	27/174	0.61 (0.33 to 1.13)	5.50 (0.87 to 10.12)
Body-mass index				
<35	12/147	23/148	0.47 (0.23 to 0.95)	4.56 (−0.52 to 9.65)
≥35	24/217	33/219	0.72 (0.43 to 1.23)	8.30 (3.99 to 12.62)
History of type 2 diabetes				
Yes	16/174	28/178	0.58 (0.31 to 1.07)	6.23 (1.77 to 10.70)
No	20/190	28/189	0.66 (0.37 to 1.18)	7.47 (2.67 to 12.26)
HFpEF-ABA score				
<0.8	8/133	12/140	0.68 (0.28 to 1.67)	3.60 (−1.66 to 8.87)
≥0.8	28/231	44/227	0.60 (0.38 to 0.97)	8.91 (4.69 to 13.12)
Recent heart-failure decompensation				
Yes	19/171	24/172	0.75 (0.41 to 1.38)	7.22 (2.33 to 12.11)
No	17/193	32/195	0.52 (0.29 to 0.95)	6.49 (2.03 to 10.95)
Ejection fraction				
<60%	18/141	28/144	0.60 (0.33 to 1.09)	5.30 (−0.12 to 10.73)
≥60%	18/223	28/223	0.60 (0.33 to 1.09)	8.08 (3.97 to 12.19)
NT-proBNP				
<200 pg/ml	11/186	24/197	0.44 (0.22 to 0.90)	6.56 (2.13 to 11.00)
≥200 pg/ml	25/178	32/170	0.77 (0.45 to 1.29)	7.38 (2.37 to 12.40)
KCCQ-CSS				
<Median	20/173	39/192	0.52 (0.30 to 0.90)	9.07 (3.71 to 14.43)
≥Median	16/191	17/174	0.79 (0.40 to 1.56)	4.43 (0.05 to 8.81)
Estimated GFR				
<60 ml/min/1.73 m²	22/167	34/168	0.61 (0.36 to 1.05)	7.85 (3.06 to 12.65)
≥60 ml/min/1.73 m²	14/197	22/199	0.64 (0.33 to 1.26)	6.00 (1.39 to 10.60)
Systolic blood pressure				
<130 mm Hg	18/185	36/189	0.47 (0.27 to 0.83)	7.27 (2.44 to 12.10)
≥130 mm Hg	18/179	20/178	0.90 (0.48 to 1.70)	6.21 (1.64 to 10.77)
Use of mineralocorticoid receptor antagonist				
Yes	16/131	24/125	0.58 (0.31 to 1.09)	10.10 (4.56 to 15.65)
No	20/233	32/242	0.63 (0.36 to 1.10)	5.22 (1.09 to 9.34)

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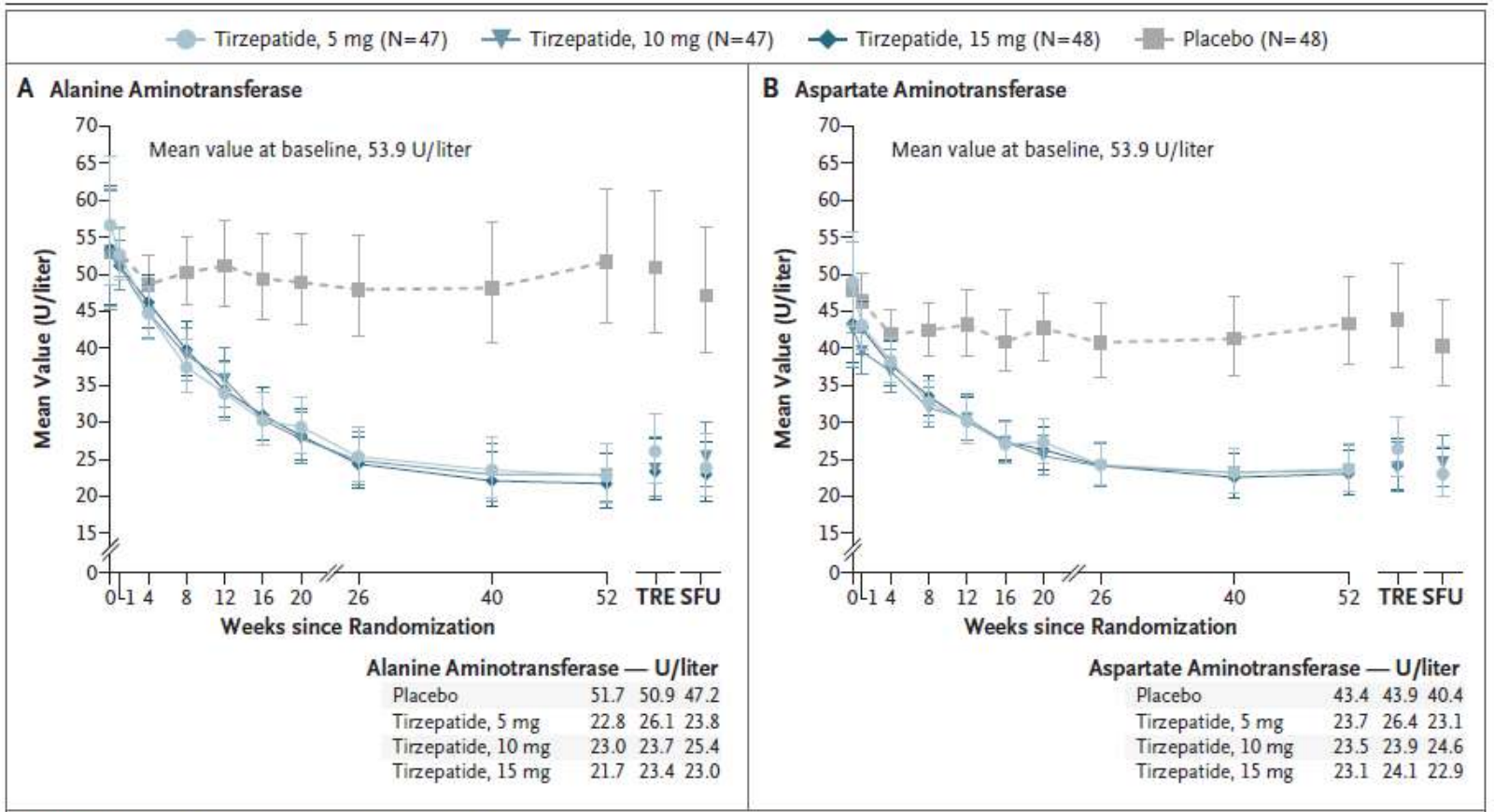
Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with liver fibrosis



Alanine Aminotransferase — U/liter			
Placebo	51.7	50.9	47.2
Tirzepatide, 5 mg	22.8	26.1	23.8
Tirzepatide, 10 mg	23.0	23.7	25.4
Tirzepatide, 15 mg	21.7	23.4	23.0

Aspartate Aminotransferase — U/liter			
Placebo	43.4	43.9	40.4
Tirzepatide, 5 mg	23.7	26.4	23.1
Tirzepatide, 10 mg	23.5	23.9	24.6
Tirzepatide, 15 mg	23.1	24.1	22.9

Figure 2. Mean Liver-Enzyme Levels over Time.

Loomba R. et al. NEJM June 8, 2024