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Terapia incretinica multirecettoriale: oltre il controllo glicemico e il peso

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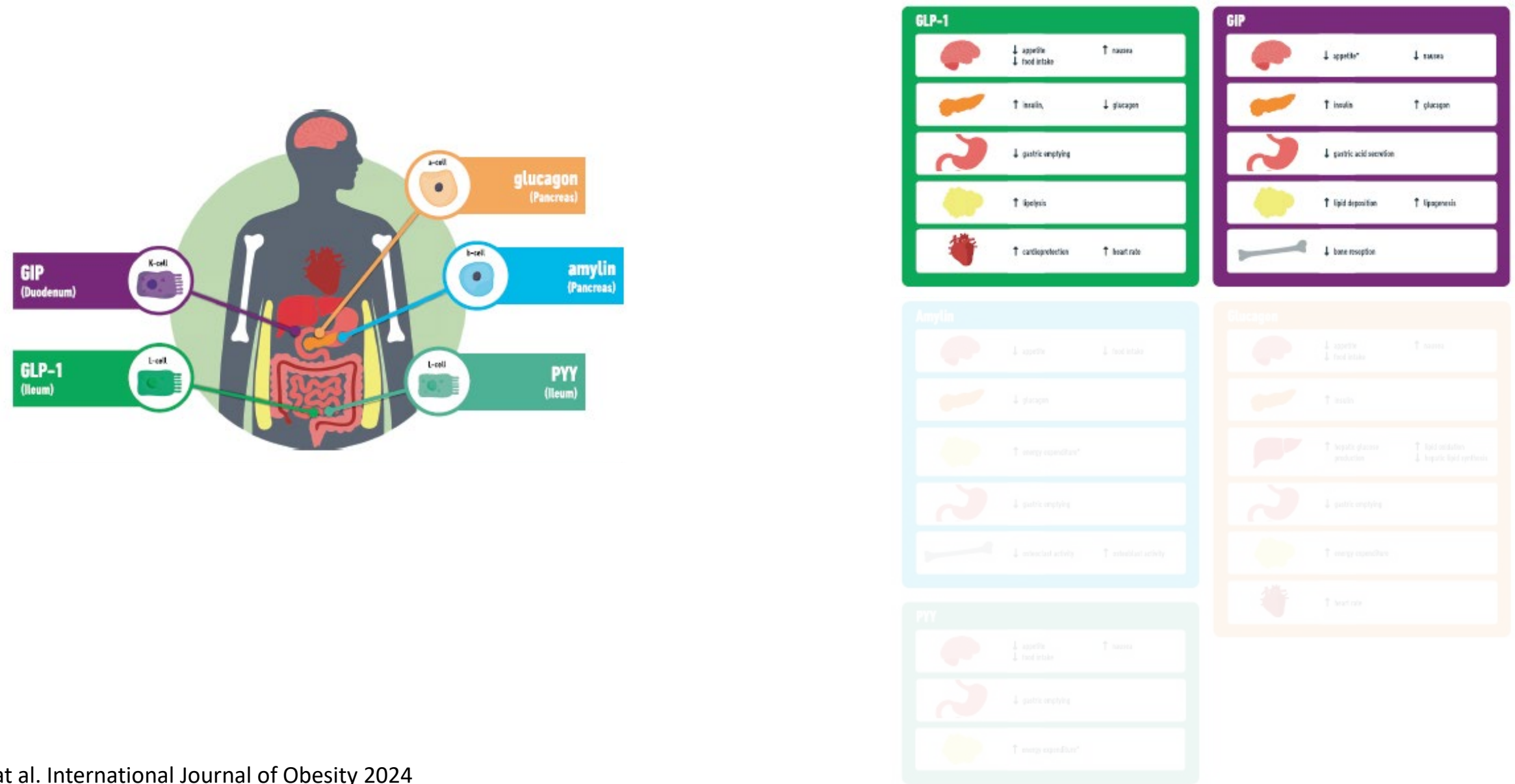
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Disclosure

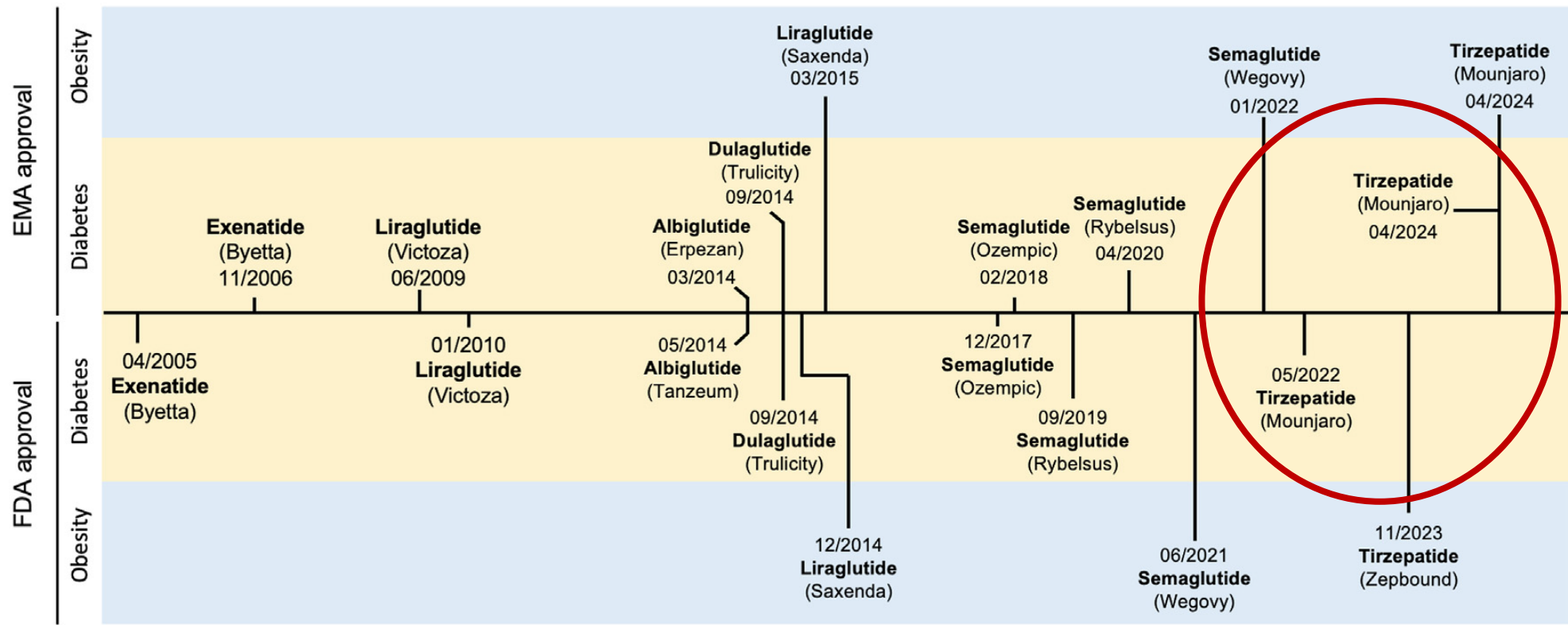
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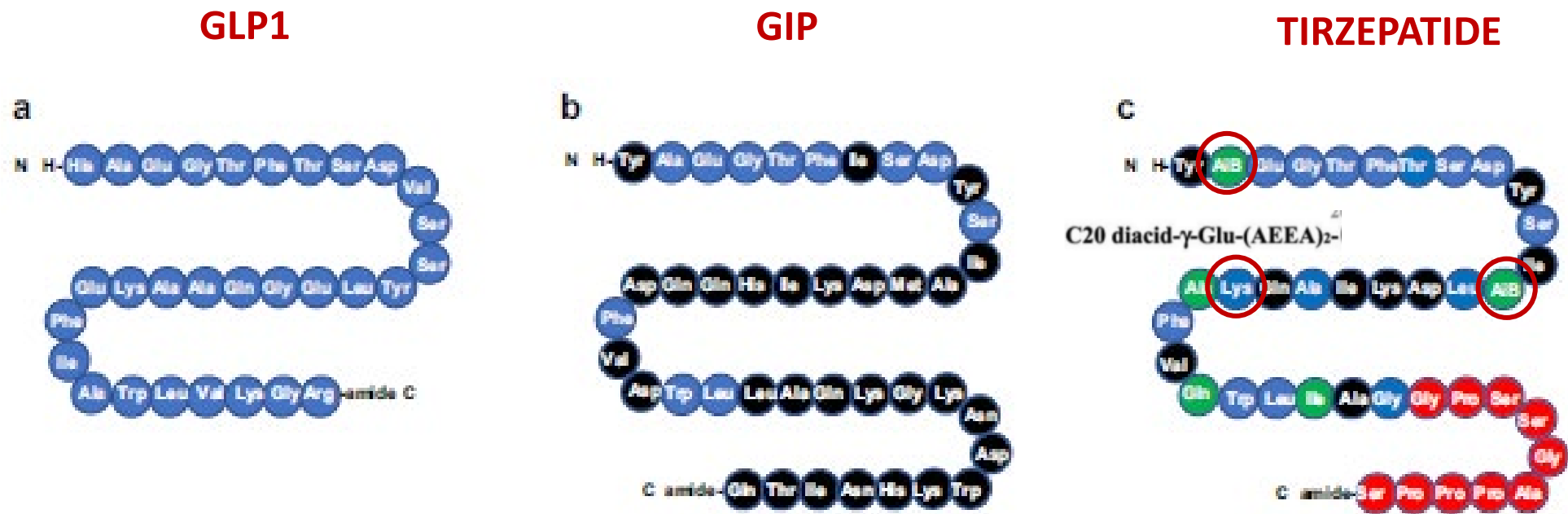
Gut hormones used in the pipeline obesity and type 2 diabetes (T2D) treatments



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

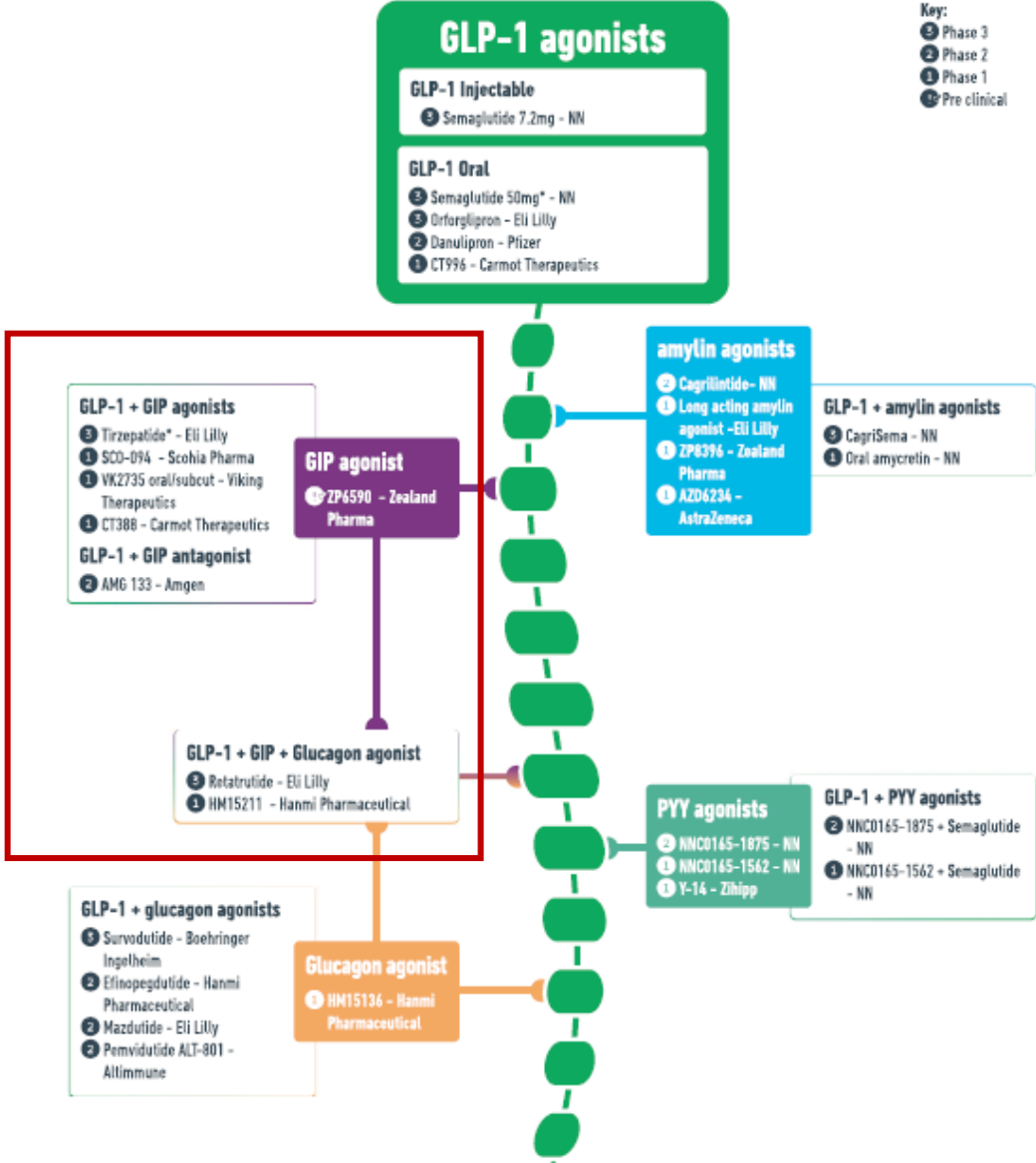


Structures of GLP-1, GIP and tirzepatide

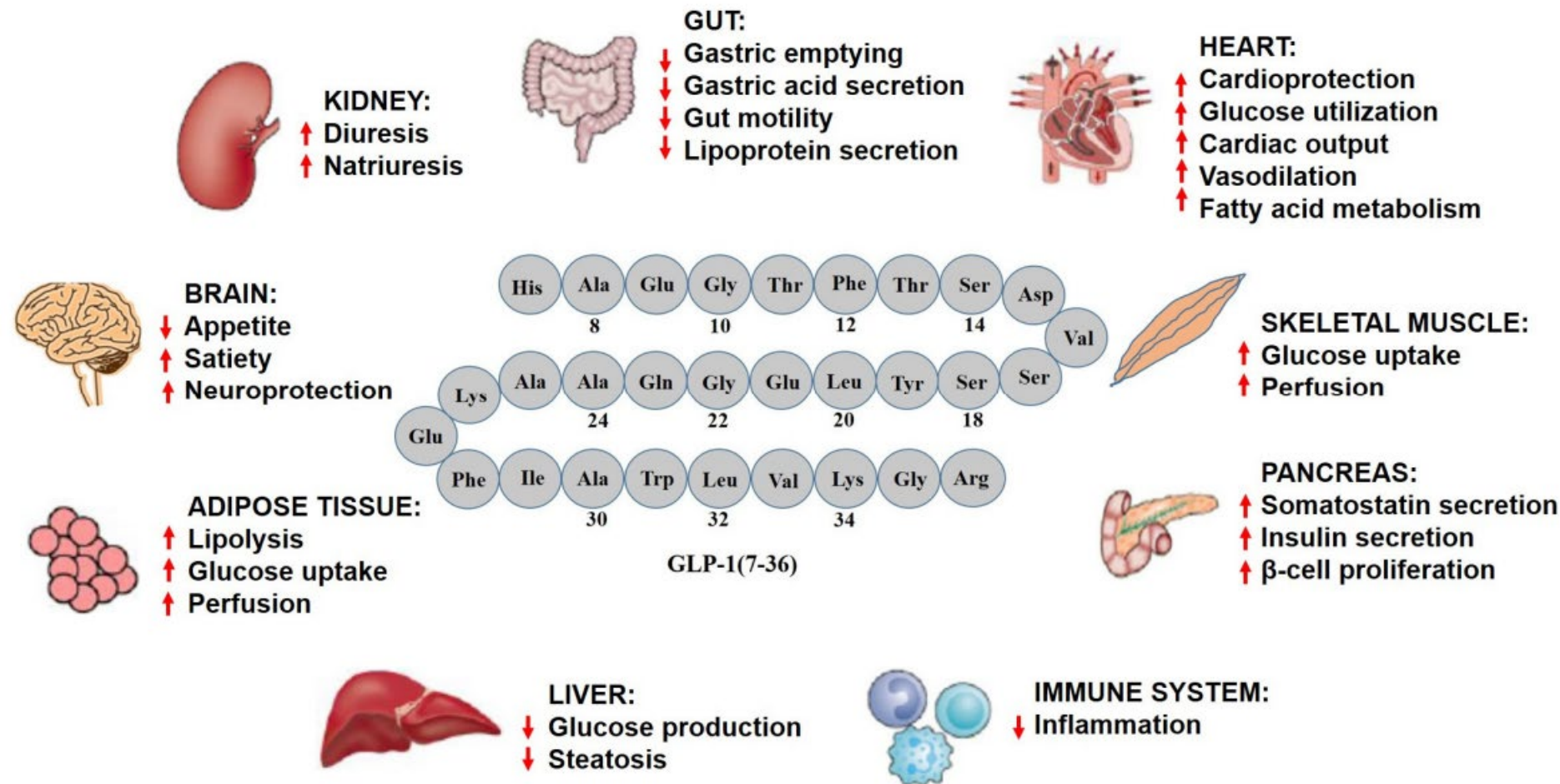


Blue circles show amino acids that are identical to those in GLP-1; black circles show amino acids that are present in GIP and tirzepatide but not in GLP-1; red circles show amino acids that are identical in tirzepatide and exenatide; Green circles show amino acids that are present in tirzepatide but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

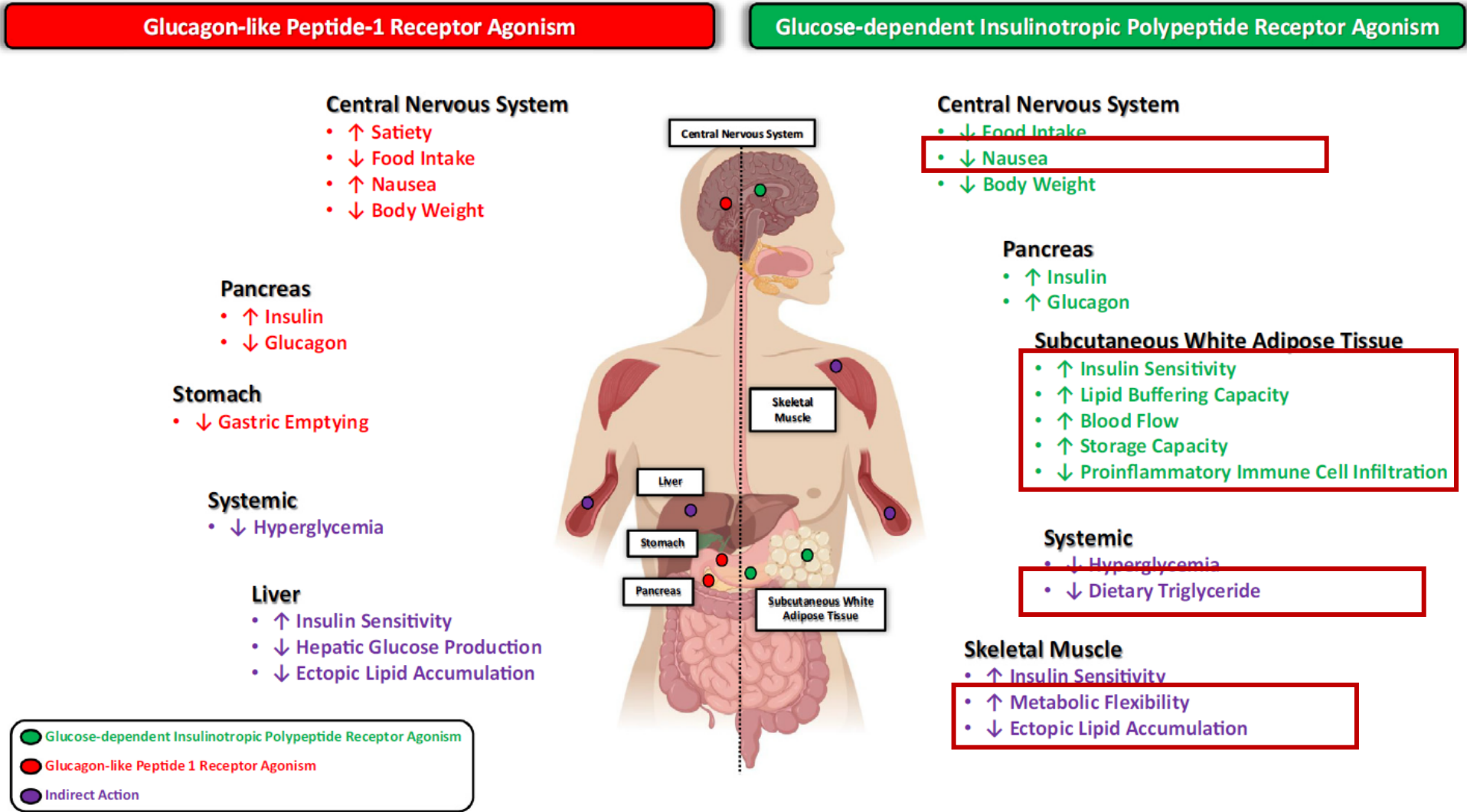
GLP-1 as the backbone of dual and triple incretin-based co-agonist therapies



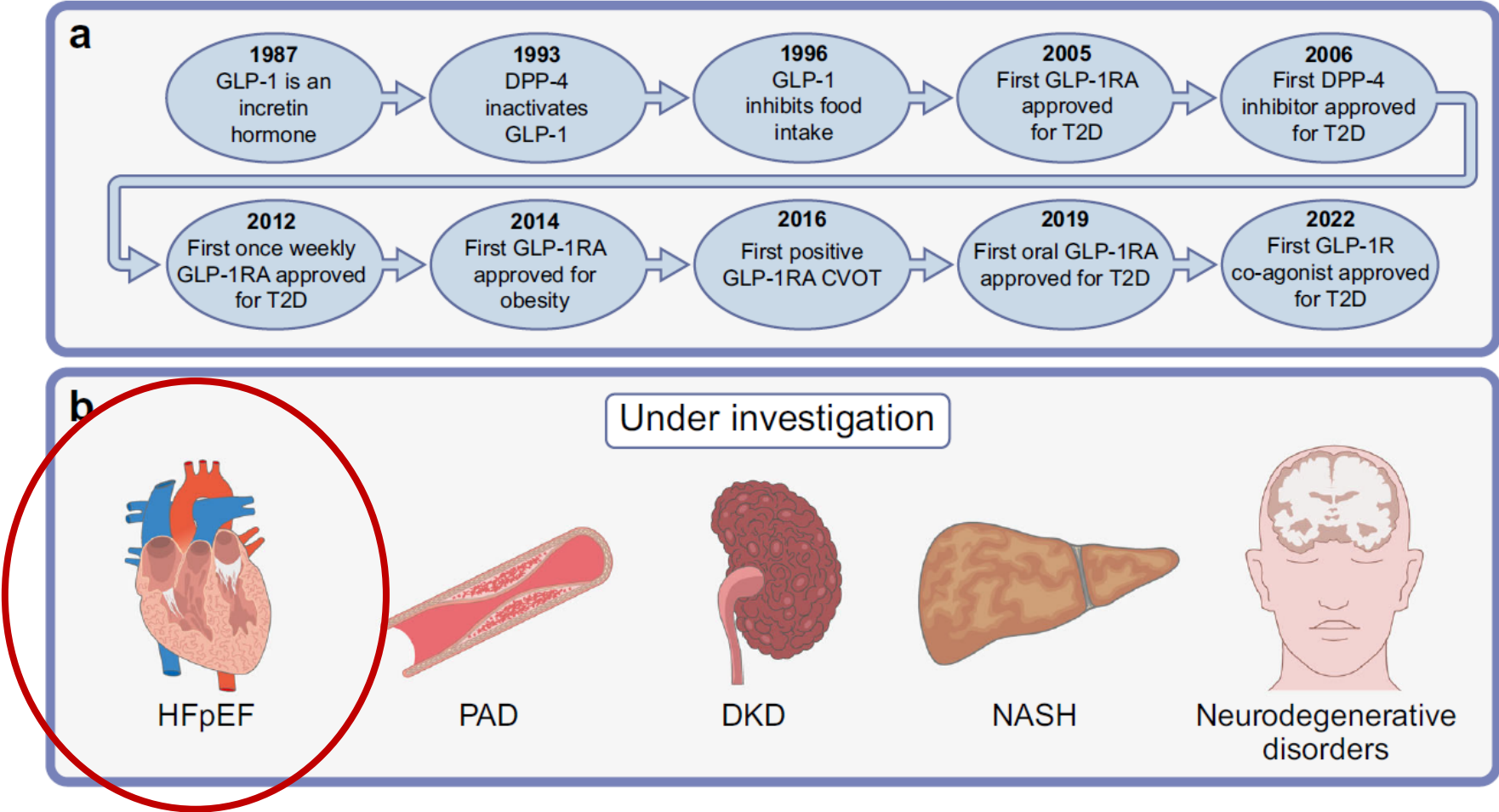
Pleiotropic effects of GLP-1 and analogs



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



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



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	Obesity with T2D				Obesity with T2D				Obesity with T2D				Obesity with T2D				Obesity with T2D Ins.				Obesity with T2D			
Background Med.	No OAMs Placebo				+ Met Semaglutide 1 mg				+ Met ± SGLT-2i Insulin				Met ± SGLT-2i ± SU Insulin				Glargine ± Met Placebo				Basal Ins. Insulin Lispro			
Comparator									Degludec				Glargine											
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 OW)	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.																								

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	Obesity without T2D			Obesity with T2D			Obesity with at least		Obesity without T2D			
Background Med.	No OAMs Placebo			OAMs Placebo			one comorbidity (excl. T2D)		No OAMs Placebo			
Comparator							No OAMs Placebo after ≥5 WL after Li					
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.												

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/1.73m 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
RMI, 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

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		AHR (95% CI)	P value	E-value (E-value for the upper limit of CI)
	Tirzepatide (n = 14 832)	GLP-1 RA (n = 14 832)			
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%

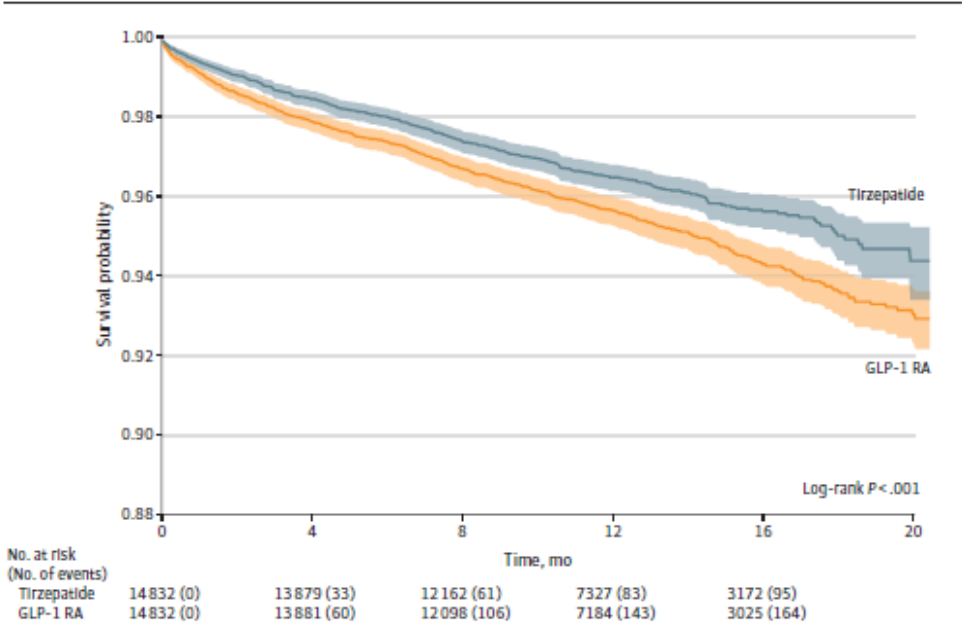
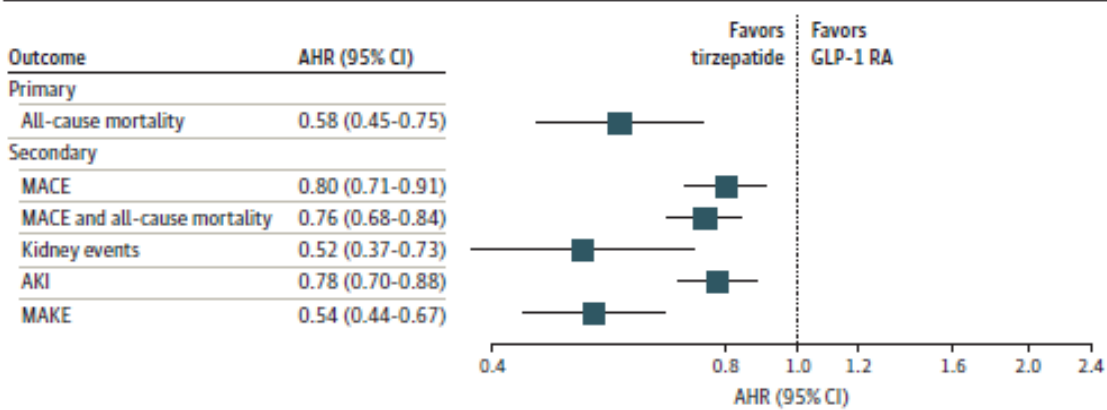
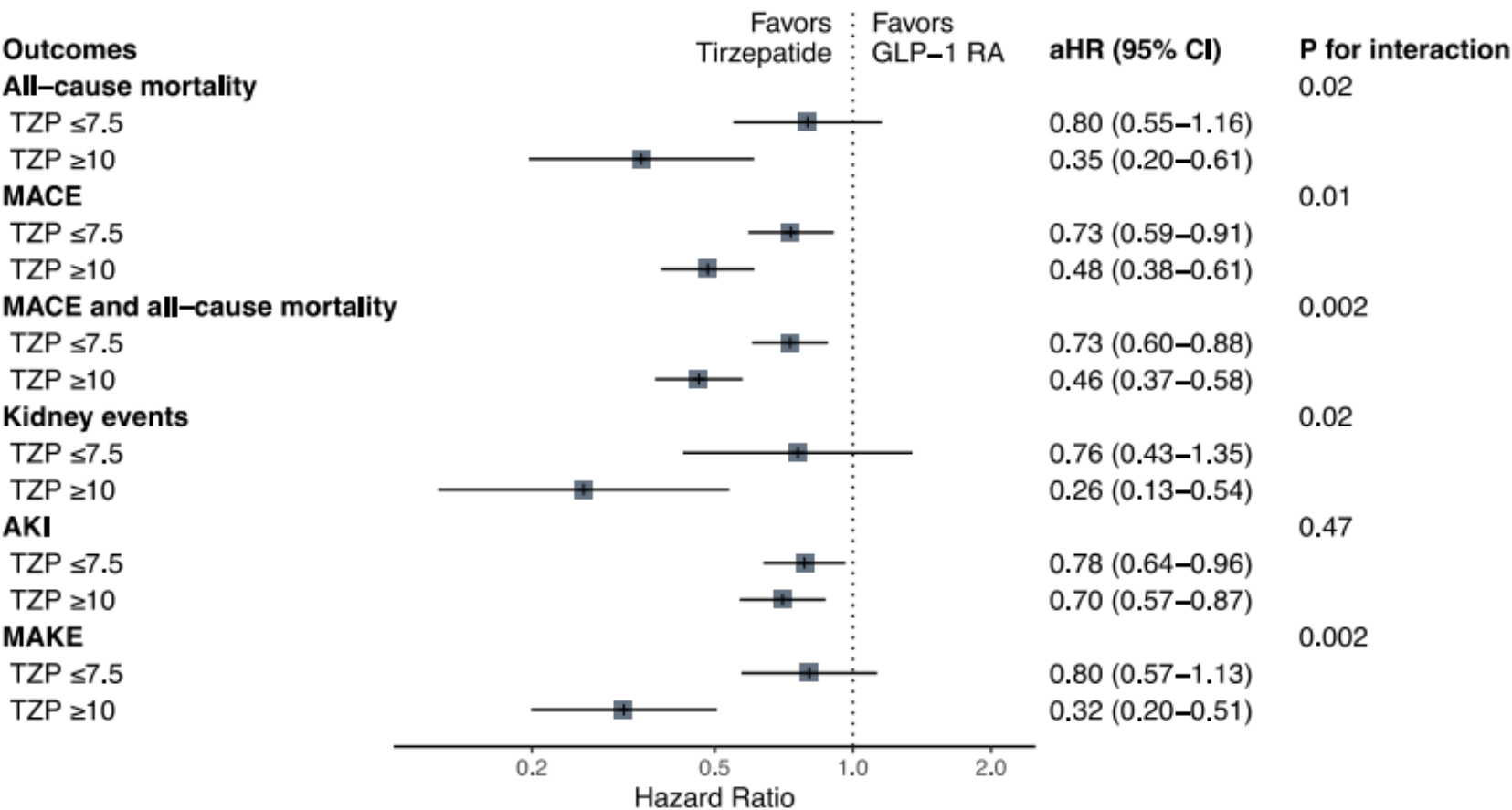


Figure 2. Forest Plot of Primary and Secondary Outcomes



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

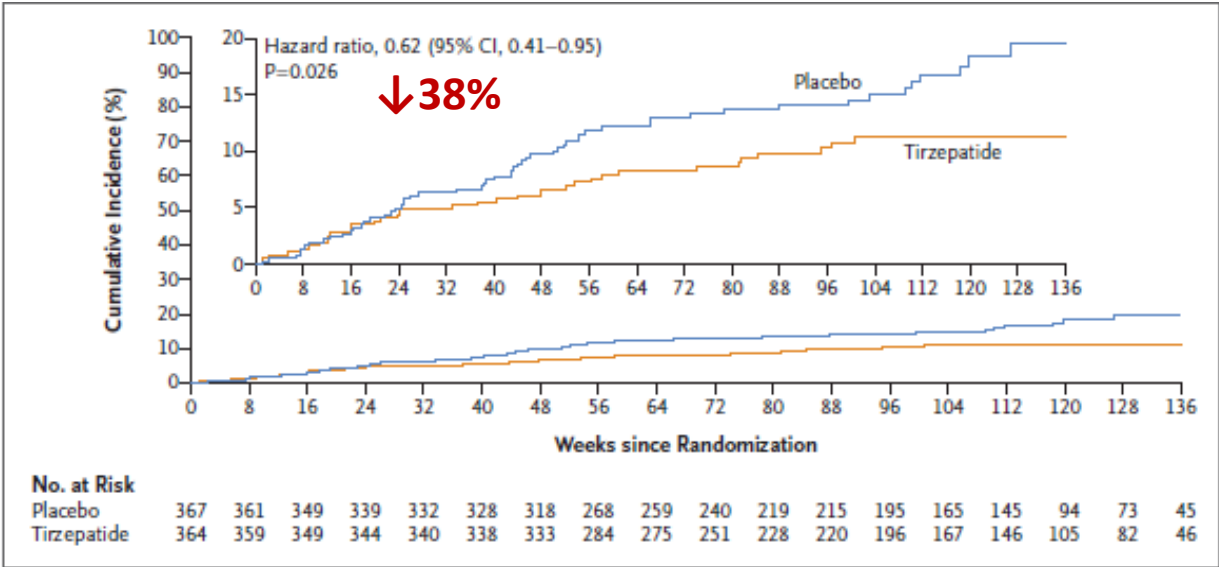


Tirzepatide for heart failure with preserved ejection fraction and obesity

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

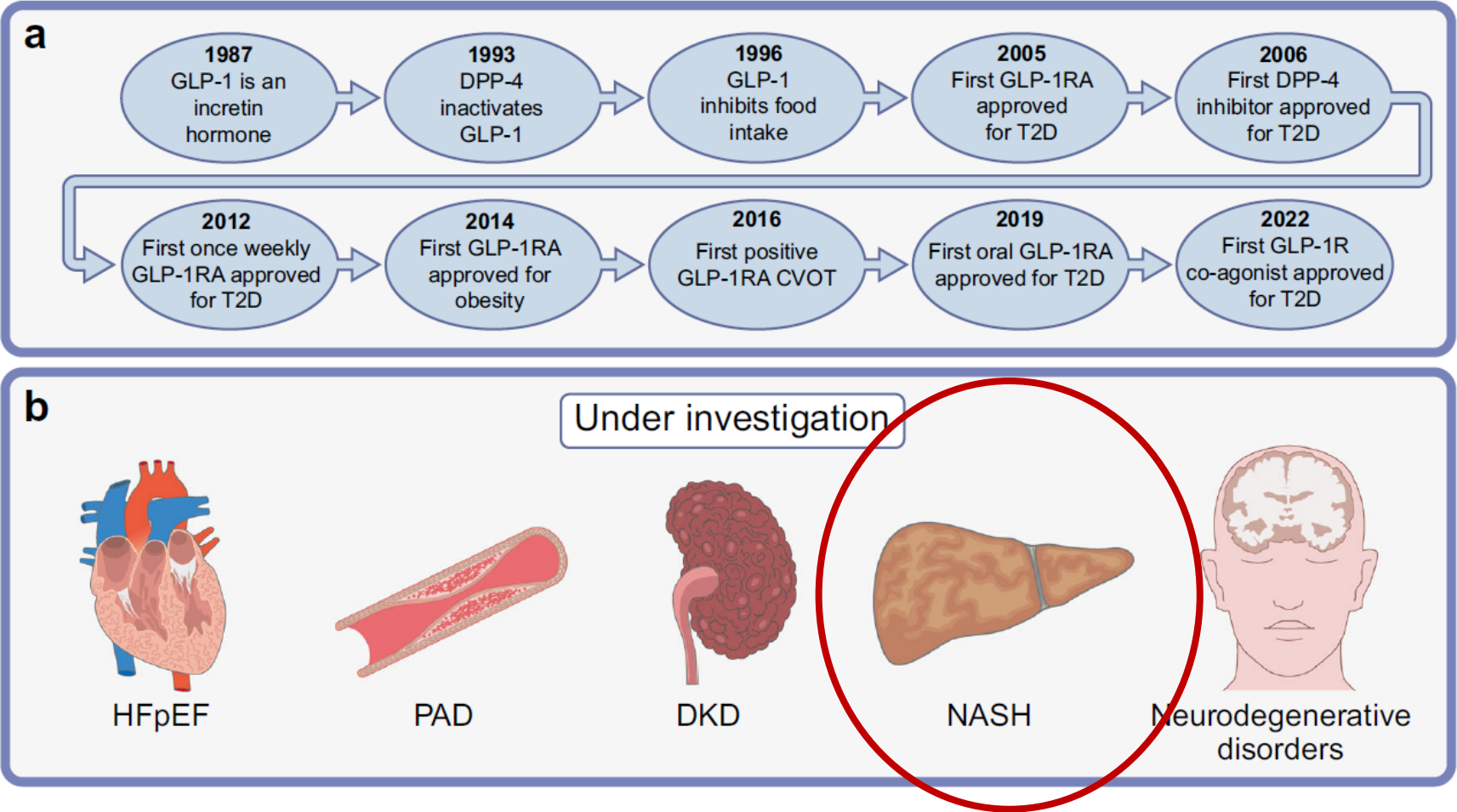
In this international, double-blind, randomized, placebo-controlled trial, we randomly assigned, in a 1:1 ratio, 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30 to receive 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).



Tirzepatide for heart failure with preserved ejection fraction and obesity

Table 2. Primary and Secondary End Points.*						
End Point	Tirzepatide (N= 364)		Placebo (N= 367)		Hazard Ratio or Difference (95% CI)†	P Value
	Value	Events/100 patient-yr	Value	Events/100 patient-yr		
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)	

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



Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with liver fibrosis

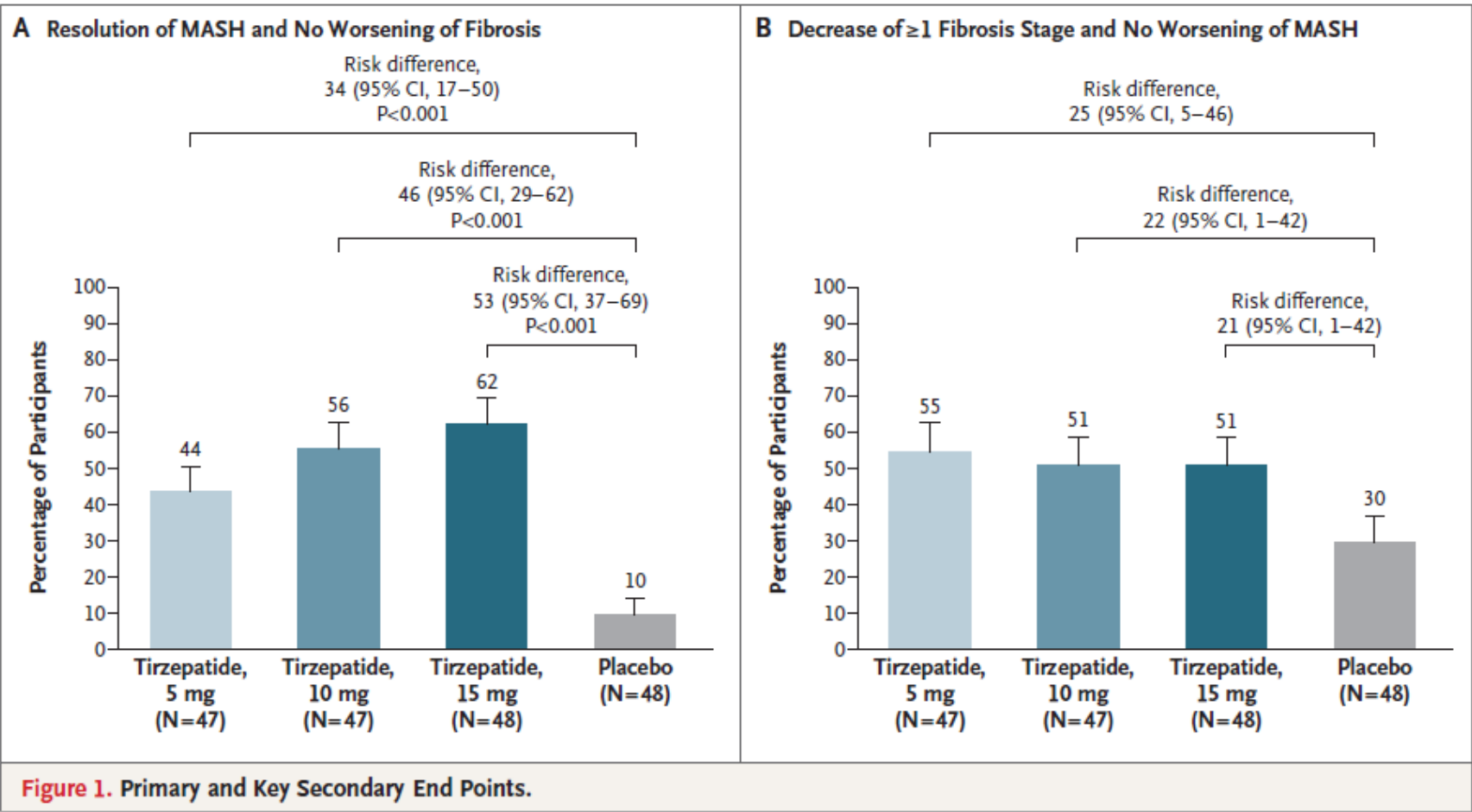
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

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

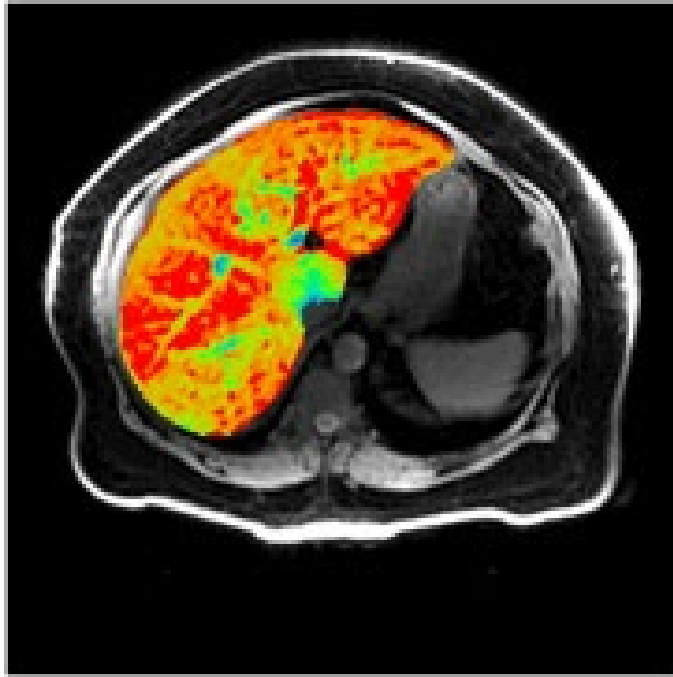
We conducted a phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis. Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 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.

Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with liver fibrosis

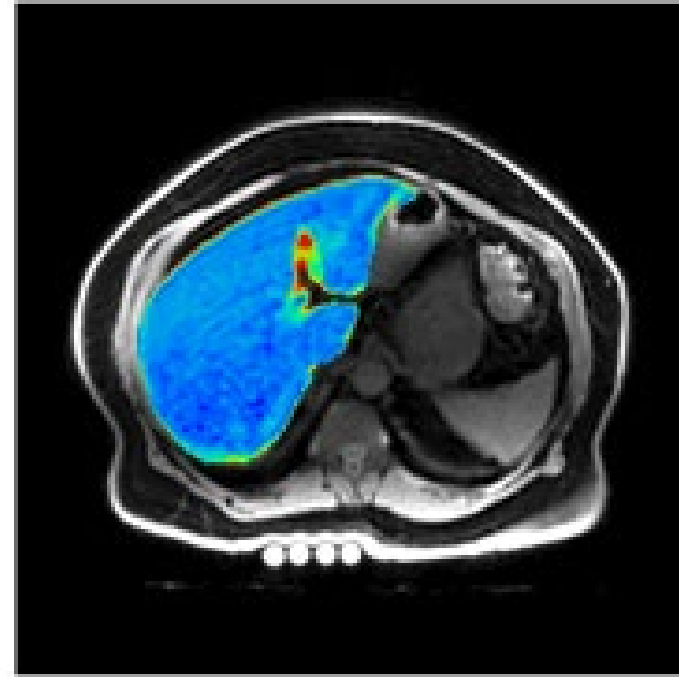


Effect of Tirzepatide on Liver Fat Content (LFC)

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 metformin with SGLT2i

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

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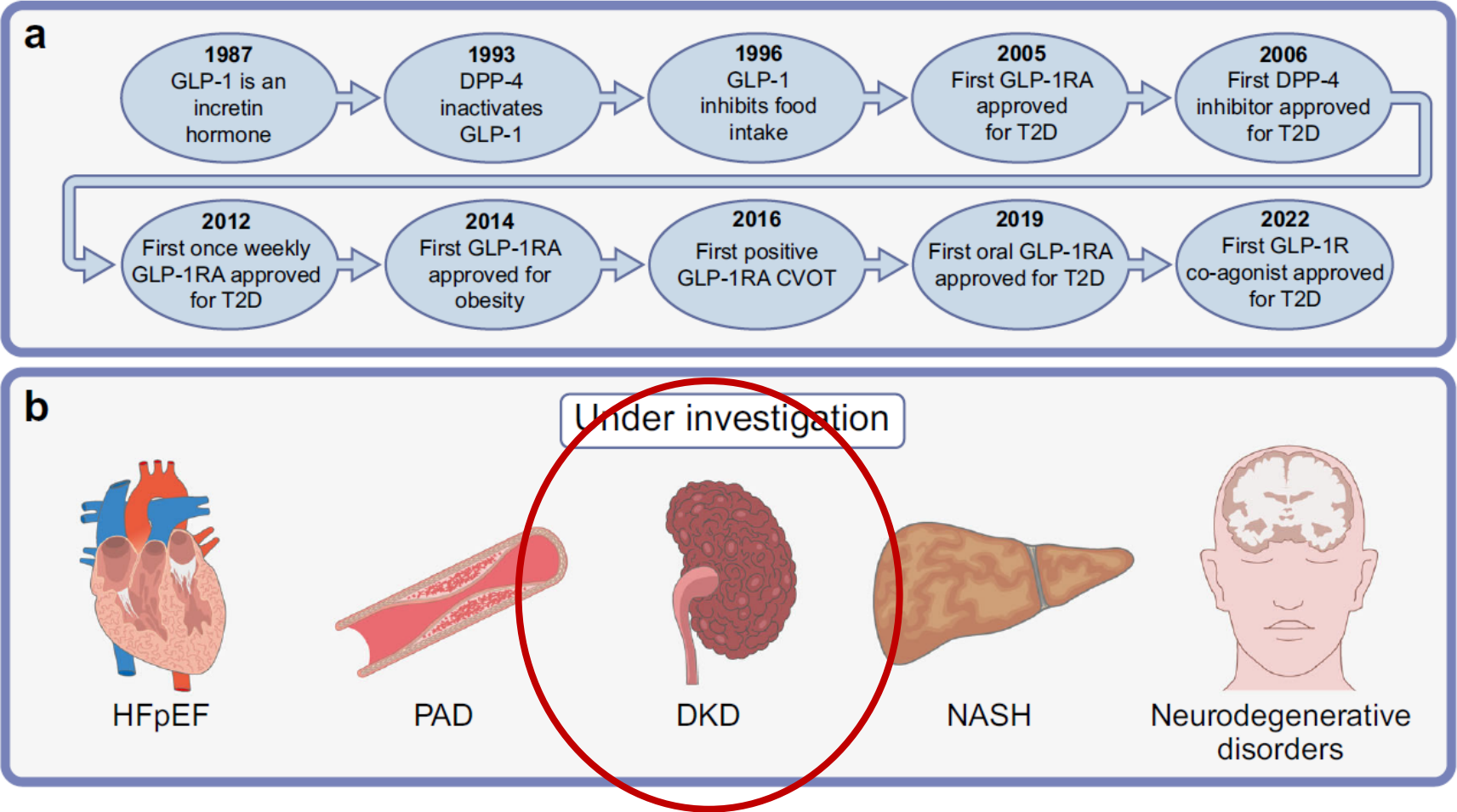
Arun J. Sanyal¹✉, Lee M. Kaplan², Juan P. Frias³, Bram Brouwers⁴, Qiwei Wu⁴,
Melissa K. Thomas⁴, Charles Harris⁴, Nanette C. Schloot⁵, Yu Du⁴,
Kieren J. Mather⁴, Axel Haupt⁴ & Mark L. Hartman⁴

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Authors: Arun J. Sanyal, M.D., Pierre Bedossa, M.D., Ph.D., Mandy Fraessdorf, Ph.D., Guy W. Neff, M.D., Eric Lawitz, M.D., Elisabetta Bugianesi, M.D., Quentin M. Anstee, Ph.D., F.R.C.P., , for the 1404-0043 Trial Investigators* [Author Info & Affiliations](#)

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



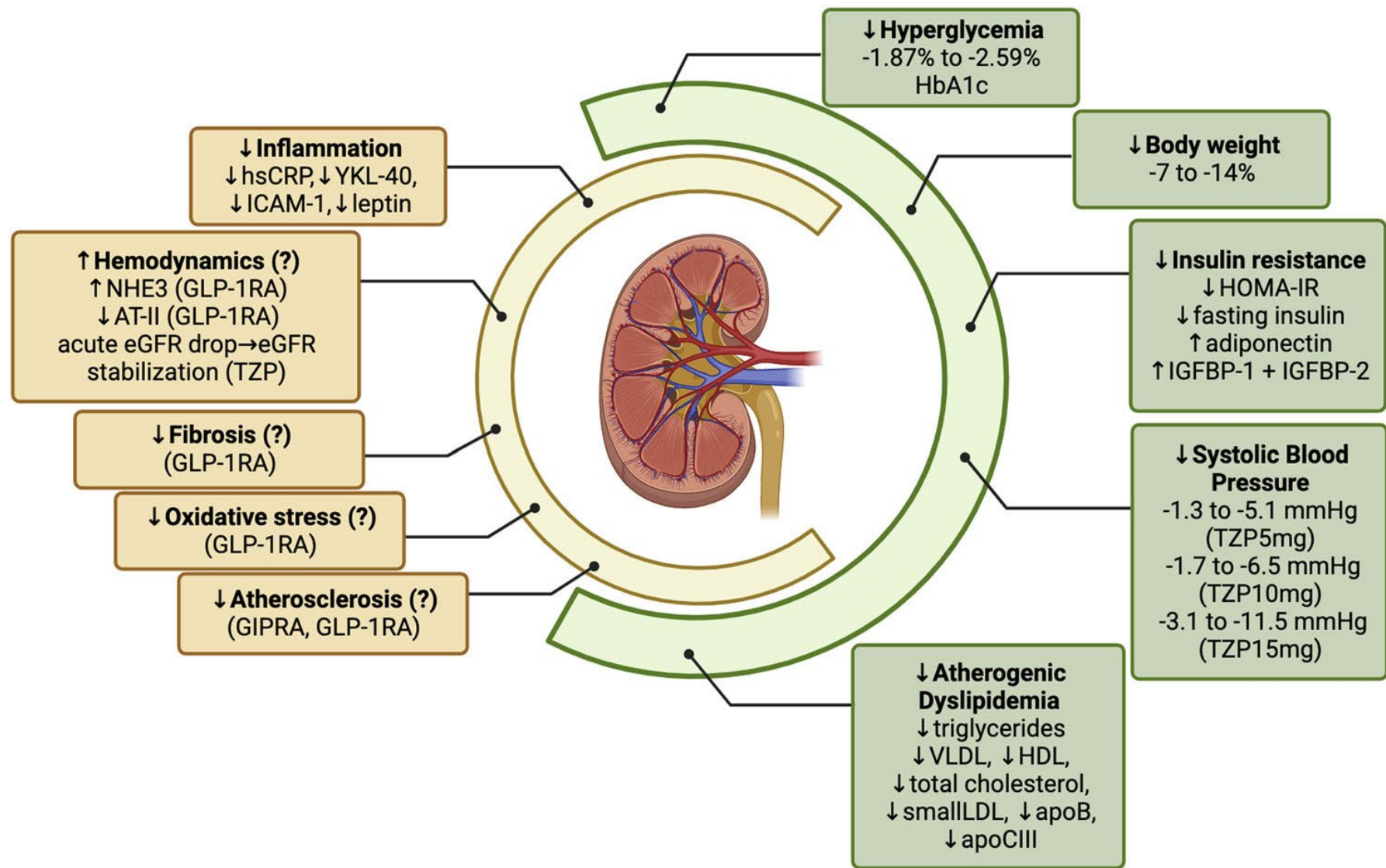
Renal effects of tirzepatide in individuals with type 2 diabetes

Table 4 Effects of tirzepatide on UACR across the SURPASS program

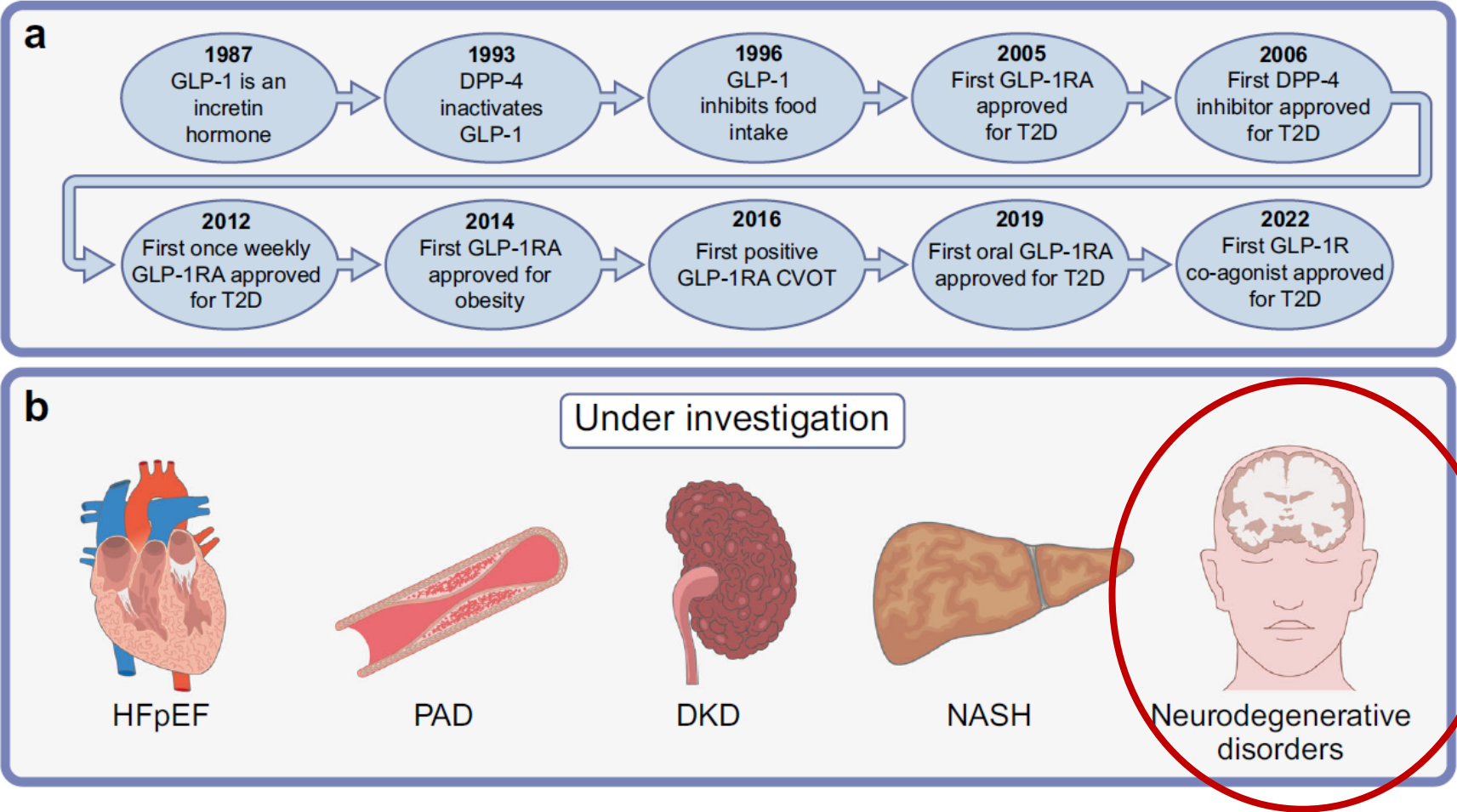
	UACR change from baseline			Comparator	UACR difference TZP vs. comparator		
	TZP 5 mg	TZP 10 mg	TZP 15 mg		TZP 5 mg	TZP 10 mg	TZP 15 mg
SURPASS-1 (vs. placebo)	−13.7 (6.9)	−8.5 (7.5)	4.8 (9.2)	52.5 (15.4)	−43.4 (−56.1, −27.0)	−43.0 (−53.6, −22.5)	−31.3 (−47.2, −10.5)
SURPASS-2 (vs. semaglutide 1 mg)	−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

Putative mechanisms underlying the renal benefits of tirzepatide

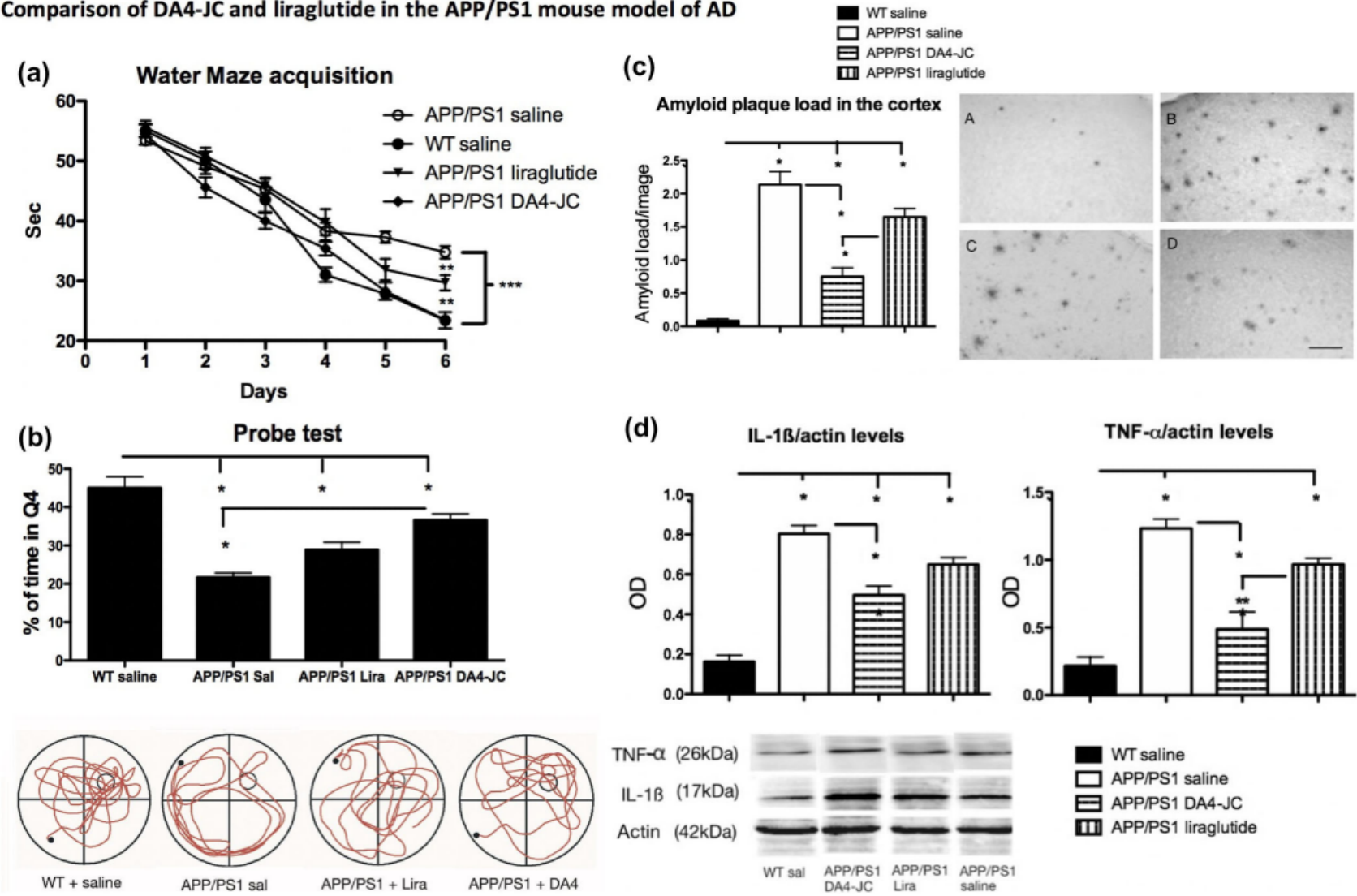


Timeline of GLP-1 discovery and clinical development: beyond glycemia and weight loss

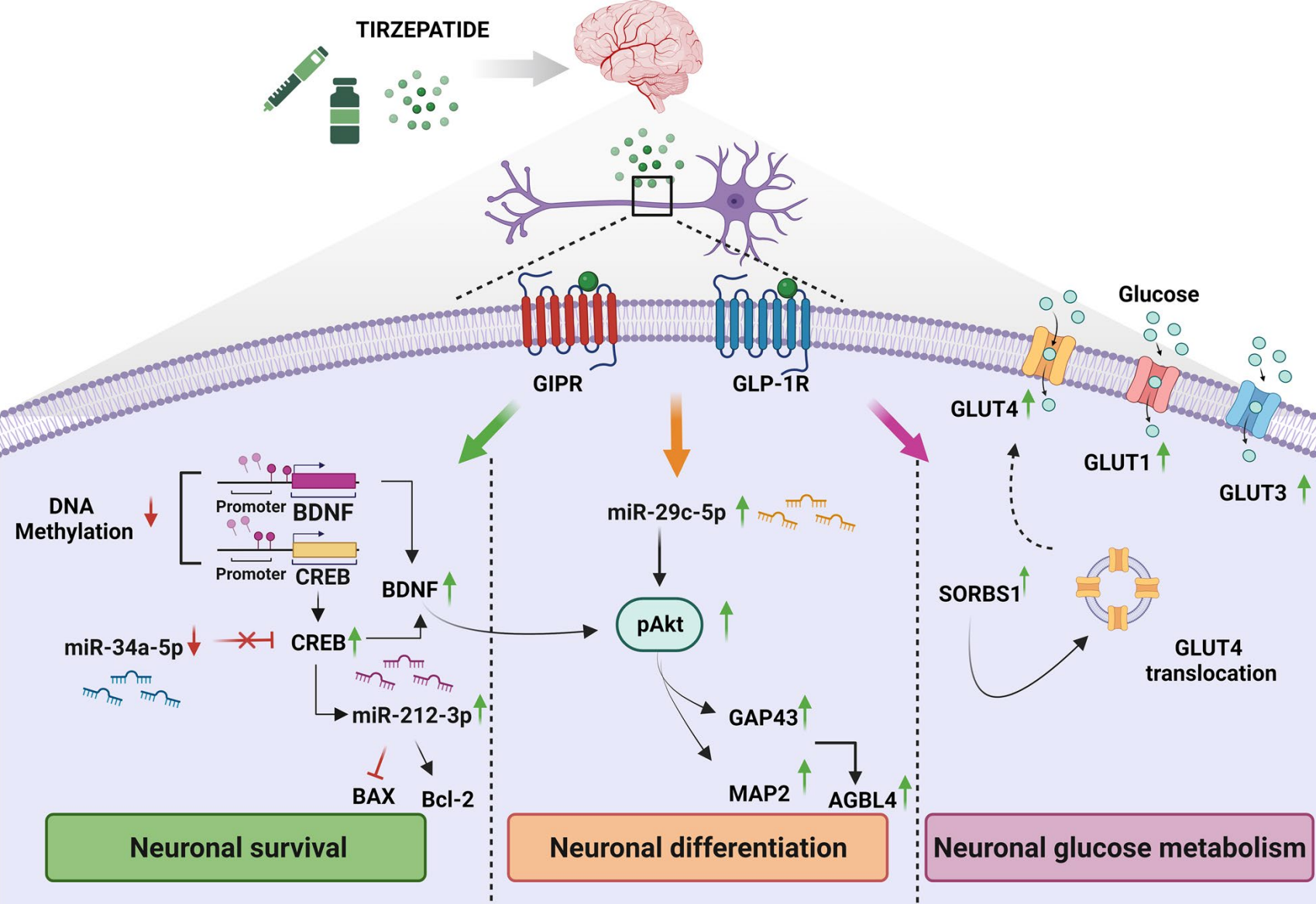


GIP/GLP1 dual agonist in Alzheimer's Disease

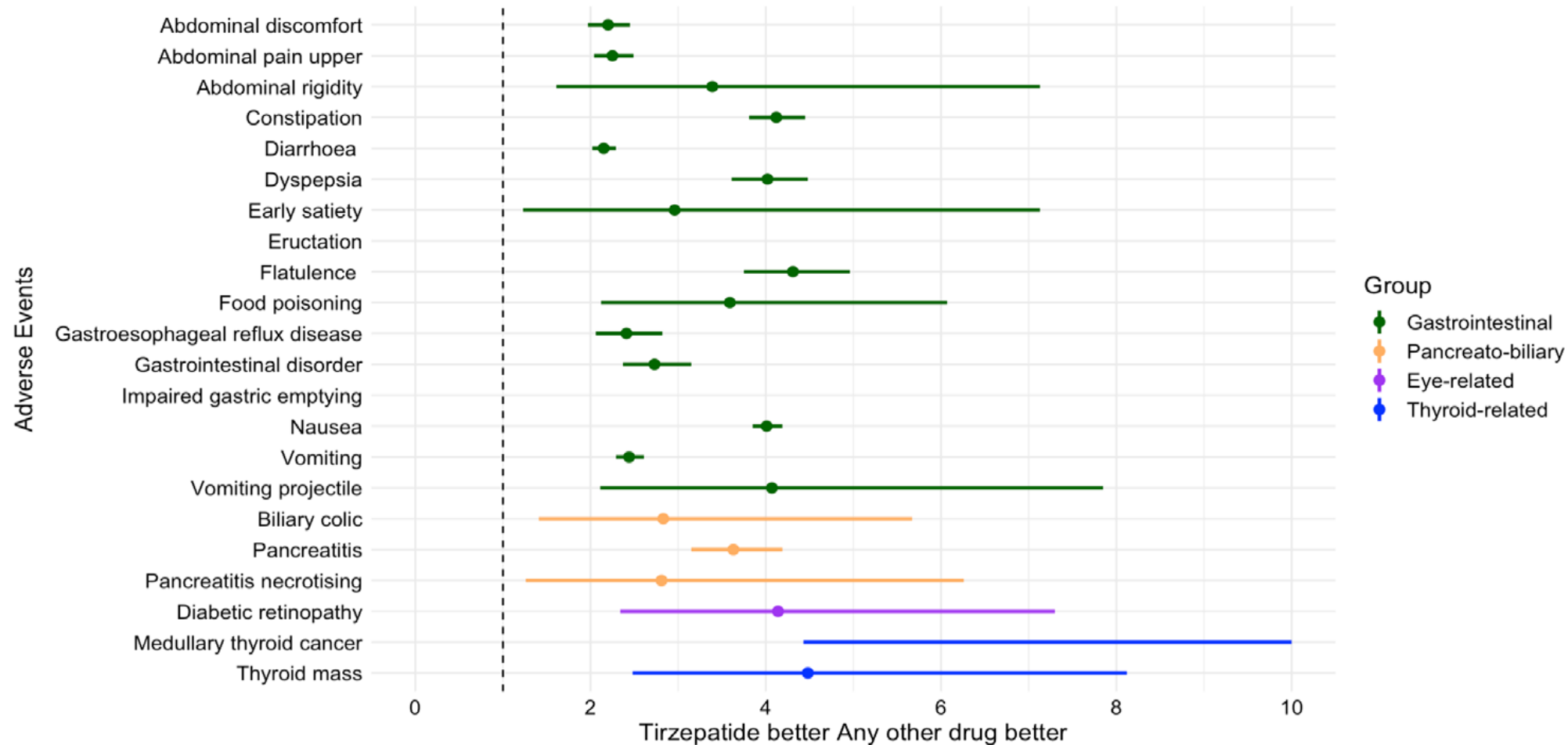
Comparison of DA4-JC and liraglutide in the APP/PS1 mouse model of AD



Tirzepatide prevents neurodegeneration through multiple molecular pathways



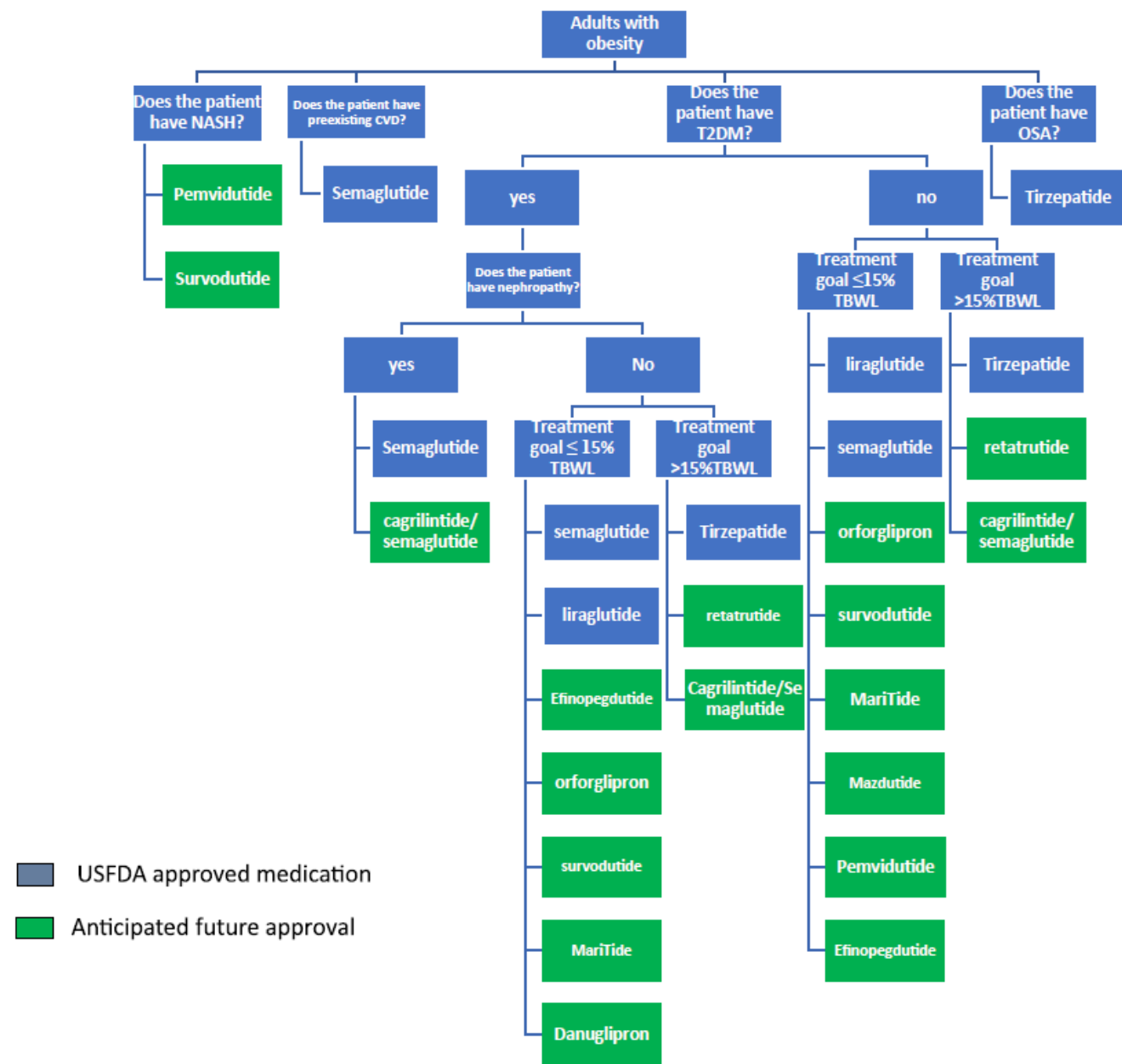
The real-world safety profile of tirzepatide



What's

NEXT

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



An aerial photograph of a large, multi-story university building with a terracotta roof and many windows. In front of the building is a large, circular courtyard with a green lawn and several palm trees. The courtyard is surrounded by a low wall and has a paved path. In the foreground, there are four stone pillars with decorative tops, likely part of a gate or entrance. The background shows a cityscape with various buildings and a clear sky.

Grazie

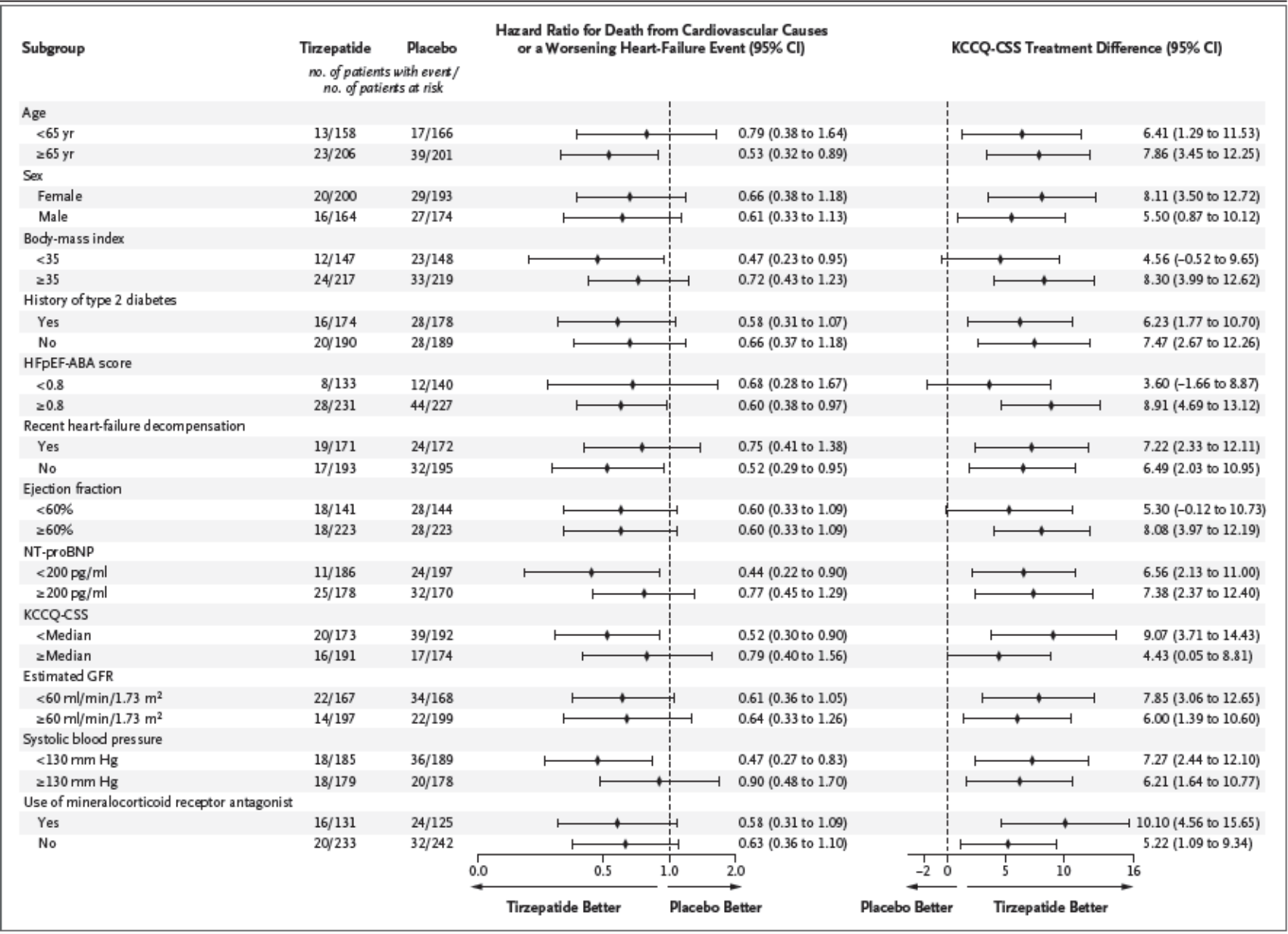
Weight loss with the gut hormone-based therapies in people without diabetes



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



Tirzepatide for heart failure with preserved ejection fraction and obesity



Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with liver fibrosis

