THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Nauck MA, Tuttle KR, Tschöp MH, Blüher M. Glucagon-like receptor agonists and next-generation incretin-based medications: metabolic, cardiovascular, and renal benefits. *Lancet* 2026; published online Jan 14. https://doi.org/10.1016/S0140-6736(25)02105-1.

Online Supplementary Material

to

Therapeutics Review:

Glucagon-Like Receptor Agonists and Next-Generation Incretin-Based Medications: Metabolic, Cardiovascular, and Renal Benefits

Professor Michael A. Nauck, MD [1,2], Professor Katherine R. Tuttle, MD [3], Professor Matthias H. Tschöp, MD[4], Professor Matthias Blüher, MD [5]

[1] Diabetes, Endocrinology, Metabolism Section, Medical Department I, St. Josef-Hospital, Katholisches Klinikum Bochum gGmbH, Ruhr-University Bochum, Bochum, Germany,
[2] Institute for Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany
michael.nauck@rub.de
https://orcid.org/0000-0002-5749-6954

[3] Executive Director for Research, Providence Inland Northwest Health,
Division of Nephrology and Kidney Research Institute
University of Washington School of Medicine
Spokane, Washington,
katherine.tuttle@providence.com
https://orcid.org/0000-0002-2235-0103

[4] Division of Metabolic Diseases, Technische Universität München, Helmholtz Diabetes Center, Helmholtz Zentrum München.
matthias.tschoep@helmholtz-munich.de
https://orcid.org/0000-0002-4744-371X

[5] Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum Munchen, University of Leipzig and University Hospital Leipzig, Leipzig, Germany.
matthias.blueher@medizin.uni-leipzig.de
https://orcid.org/0000-0003-0208-2065

Development of GLP-1 receptor agonists (GLP-1 RAs) for the treatment of type 2 diabetes.
Based on previous experience with the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), the question arose, whether a stimulation of insulin secretion would also be observed in subjects with type 2 diabetes. Under hyperglycaemic clamp conditions, a severely impaired insulinotropic response to GIP was confirmed, but GLP-1 elicited insulin secretory responses almost like in healthy individuals (1). In addition, exogenous GLP-1 was able to substantially reduce, if not normalize, fasting plasma glucose concentrations in previously hyperglycaemic T2D patients (2). The early development of GLP-1 receptor agonists has been summarized by Drucker & Nauck 2006 (3). In 1992, first reports were published on the potential of GLP-1 injected into the cerebrospinal fluid to dramatically reduce food intake in rats (4). This was later confirmed by other studies (5) that laid the foundation for clinical studies of body weight reduction with exogenous GLP-1 (6), and GLP-1 RAs used to treat T2D (7, 8) and obesity (*vide infra*).

GLP-1 is characterized by a rapid proteolytic degradation and inactivation (by dipeptidyl peptidase-4; DPP-4) and, in addition, by rapid elimination from the circulation via the kidney (with an elimination half-time of 1-2 min) (1). To be clinically useful, candidate peptide molecules needed to be protected from DPP-4-mediated proteolytic degradation, and needed a long elimination half-life (7, 8). The first GLP-1 receptor agonist approved for the treatment of T2D was based on the serendipitous identification of the GLP-1 paralog exendin-4, isolated from the venomous saliva of a lizard living in Arizona (*Heloderma suspectum*). It had to be injected twice daily because of its half-life of 2-3 h (9). Various strategies led to a longer duration of action: (a) “Microencapsulation” (exenatide once weekly); (b) attaching free fatty acids to modified GLP-1 peptides, which bind to albumin); (c) to attach modified GLP-1 to large proteins, taking advantage of the fact than large proteins are typically slowly eliminated from the circulation. Most recently developed GLP-1 RAs and preparations are characterized by an elimination half-life of 5-7 days and can be administered once weekly (7, 8). As peptides, they need to be administered by the subcutaneous route. A notable exception among approved therapies is semaglutide for oral administration, which leads to an acceptable bioavailability (still low at approximately 1 %) due to an absorption enhancer (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate or “SNAC”). However, it is mandatory to take oral semaglutide after fasting overnight, taking the pill with a small amount of water, and then to abstain from oral fluid and food intake for another 30 minutes.

Supplementary Table 1. Literature supporting discoveries, findings, and insights displayed in Figure 1

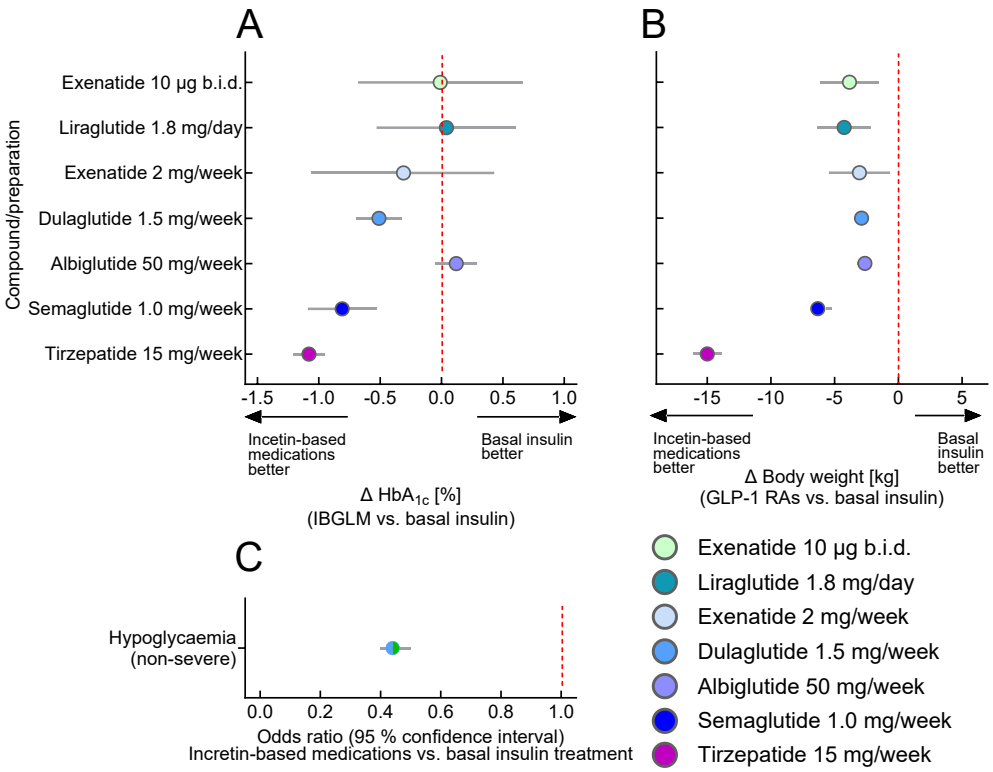
1964-67	Elrick et al. 1964 (10); McIntyre et al. 1965 (11); Perley & Kipnis 1967 (12)
1970-73	Brown & Dryburgh 1971 (13); Dupré et al. 1973 (14); Pederson et al. 1975 (15);Brown 1982 (16); Moody et al. 1984 (17)
1985-87	Amland et al. 1985 (18); Krarup et al. 1987 (19); Nauck et al. 1993 a (1)
1987	Holst et al. 1987 (20); Mojsov et al. 1987 (21); Kreymann et al. 1987 (22)
1992-93	Nathan et al. 1992 (23); Nauck et al. 1993 (1); Nauck et al. 1993 b (2); Zander et al. 2002 (6)
1992-98	Flint et al. 1998 (24); Verdich et al. 2001 (25); Secher et al. 2014 (26)
2003-today	Drucker & Nauck 2006 (3); Nauck et al. 2019 (7); Nauck et al. 2021 (8)
2007-today	Pi-Sunyer et al. 2007 (27); Davies et al. 2021 (28); Jastreboff et al. 2022 (29)
2016-today	Marso et al. 2016 (30); Sattar et al. 2021 (31); Badve et al. 2025 (32); Lee, Sattar et al. 2025 (33)
2013-near future	Finan et al. 2013 (34); Tschöp et al. 2016 (35); Sanchez-Garrido et al. 2017 (36); Kusminski et al. 2024 (37);
2022-24	Coskun et al. 2018 (38); Rosenstock et al. 2021 (39); Frias et al. 2021 (40); Jastreboff et al. 2022 (29); Nauck & D'Alessio 2022 (41)
2022-27 (projected)	Rosenstock et al. 2025 (42)
2024-30 (projected)	Blüher et al. 2024 (43); LeRoux et al. 2024 (44); Ji et al. 2025 (45); Davies et al. 2025 (46); Garvey et al. 2025 (47); Dahl et al. 2025 (48); Gasiorek et al. 2025 (49); Rosenstock et al. 2023 (50); Jastreboff et al. 2023 (51); Sanyal et al. 2024 (52)

References supplement information provided in Figure 1

GLP-1 receptor agonist treatment in T2D patients leads to reductions in HbA_{1c}, body weight, systolic blood pressure and LDL cholesterol, but also reduces fasting plasma glucose and additional cardiovascular risk factors (53). Reductions in plasma glucose are mediated by (glucose-dependent) stimulation of insulin secretion (1), suppression of glucagon (1), and, in the post-prandial state, by slowing gastric emptying (54). While for short-acting GLP-1 RAs (exenatide b.i.d. and lixisenatide), the deceleration of gastric emptying appears to persists with longer treatment durations, for long-acting GLP-1 RAs, it wanes over time (a phenomenon called tachyphylaxis) (55). At glucose concentrations below 66 mg/dl (3.7 mmol/l), the stimulation of GLP-1 receptors ceases to stimulate insulin secretion (56), and this explains, why lowering glucose with GLP-1 RAs (in the absence of treatment with sulfonylureas or insulin) rarely leads to hypoglycaemic episodes, and certainly not to severe ones.

Incretin-based medications for the treatment of type 2 diabetes mellitus. The efficacy for reducing plasma glucose, HbA_{1c}, and body weight vary between different compounds and preparations. Compared to the first approved GLP-1 receptor agonist, exenatide b.i.d., introduced 2006 (USA)/2007(Europe), or the other short-acting GLP-1 RA, lixisenatide, effect sizes for controlling glycaemia have approximately doubled, and for body weight reduction, more than tripled for the most efficacious agents (e.g., semaglutide s.c) (57). In meta-analyses of clinical trials studying head-to-head comparisons of various GLP-1 RAs and basal insulins in people with T2DM needing injectable glucose-lowering therapy, the effect sizes for reducing HbA_{1c} were at least equal (exenatide b.i.d., liraglutide, albiglutide) or greater for GLP-1 RA than for insulin, with significant differences in favour of GLP-1 RAs for exenatide once-weekly, dulaglutide, semaglutide s.c. (Supplementary Figure 1 A) (58). In addition, GLP-1 RAs lead to

weight loss, while basal insulin treatment is associated with weight gain. Therefore, initiating GLP-1 RA therapy vs. basal insulin therapy leads to differential effects on body weight (Supplementary Figure 1 B). Also, a combination of GLP-1 RAs with oral glucose-lowering medications is associated with a much lower risk for hypoglycaemia as compared to basal insulin combined with the same oral agents (Supplementary Figure 1 C) (58).. The incidence of severe hypoglycaemia was also found significantly reduced with incretin-based medications vs. insulin treatment (58). Albiglutide has been approved for the therapy of T2D, yet is currently not marketed, and efpeglenatide has undergone a phase 3 development program and a cardiovascular outcomes study, but has not been marketed so far.



Supplementary Figure 1. Results of head-to-head comparisons of GLP-1 receptor agonists and the dual GIP/GLP-1 receptor agonists tirzepatide with basal insulin treatment in type 2 diabetes mellitus. (A) Weighted differences for HbA_{1c} (representing glycaemic control) and (B) body weight, and (C) odds ratio for the proportions of patients reporting hypoglycaemic episodes (≥ 1) with incretin-based medications as compared to basal insulin. Panel (C) displays a pooled analysis across all compounds/studies studied. Data have been recalculated and redrawn from Nauck et al. 2023 (58). For each compound/preparation studied, weighted means and pooled standard deviations were calculated and expressed as 95 % confidence intervals (bars).

GLP-1 receptor agonists for the treatment of obesity. The observation that GLP-1 RA treatment leads to body weight reductions in patients with T2D (Supplementary Figure 1 B) led to the concept that such agents might be useful for treating people with obesity, but without diabetes. Liraglutide (for once-daily injection) led to greater body weight reduction compared to short-acting GLP-1 RAs and was the first agent/preparation to be studied in populations characterized

by obesity and related complications. Since in patients with T2D, liraglutide 1.8 mg/day (vs. 1.2 mg/day) did not further reduce HbA_{1c}, but led to greater weight loss, indicating different dose-response relationships for improving glycaemic control and for reducing weight, higher doses than customarily used for the treatment of T2D were tested. This was also based on the insight, that starting GLP-1 RA at a low initial dose, and increasing the dose at, e.g., 4-week intervals, led to the development of tolerance regarding nausea, vomiting, and other "gastrointestinal" adverse events, thus allowing the use of higher, more effective doses. Like liraglutide, semaglutide (s.c.) is used at higher doses (2.4 mg/week) (28, 59-68) compared to T2D for the treatment of obesity, although higher doses, likely to mediate greater weight reduction, are now also explored in clinical trials in people with T2D (oral semaglutide, 25 or 50 mg/day (69); s.c. semaglutide up to 16 mg per week (70)). Oral semaglutide (25 mg/day) has also been explored in subjects with obesity/overweight (71).

Supplementary Table 2. Potential mechanisms, how gastro-entero-pancreatic hormones with therapeutic potential may improve metabolic control and lower body weight

	Biological effect(s) contributing to improved glycaemic/metabolic control				Biological effect(s) contributing to body weight reduction			Commentary
Gastro-entero-pancreatic peptide hormone with therapeutic potential	Insulin sensitivity	Insulin secretion	Glucagon secretion	Gastric emptying	Weight loss/ adipose tissue distribution	Appetite/ energy intake	Energy expenditure	Details
Glucagon-like peptide-1 (GLP-1)	~ No evidence	↑↑ (1)	↓↓ (1)	↓↓ (72)	↓↓ (73)	↓↓ (24)	~ (74)	Insulin sensitivity can be improved by body weight reduction
Glucose-dependent insulinotropic polypeptide (GIP)	↑ (75)	↑↑ (1) (T2D ?) (1)	(↑) (76)	- (77)	Prevention of ectopic fat deposition? (78)	↓ (rodents)(79); humans: ? (80, 81)	~	Accentuated storage of triglycerides in subcutaneous adipose tissue may prevent ectopic fat deposition (liver, pancreas)
Glucagon	~ No evidence	↑ (82, 83)	↓ Feedback regulation	(↓) (84)	?	(↓) (85)	↑↑ (85)	Glucagon may stimulate insulin secretion and, thus even lower plasma glucose
Amylin	~ No evidence	- No evidence	↓ (86)	↓↓ (86, 87)	? (87)	↓↓ (87)	~	Insulin sensitivity can be improved by body weight reduction
Peptide Tyrosine Tyrosine (PYY)	~	~	-	-	?	↓↓ (88)	~	Insulin sensitivity can be improved by body weight reduction; maintenance of healthy islet structure (89)

~: Not changed; ↑, ↑↑, ↑↑↑: Increased (small, intermediate, large effect); ↓,↓↓, ↓↓↓: decreased/slowed (small, intermediate, large effect); ?: unproven; brackets: possible effect (small effect size, questionable)

Open questions regarding the role of GIP receptor agonism as part of the mechanism of action of the dual GIP/GLP-1 receptor agonist tirzepatide. In a mechanism-of-action study with similar design, tirzepatide therapy improved insulin sensitivity more than did semaglutide. When relating improvements in insulin sensitivity to the degree of weight loss, the regression lines had a steeper slope for tirzepatide than for semaglutide, indicating effects of tirzepatide on insulin sensitivity, which are not entirely explained by reducing adiposity (90). This may be related to the promotion of triglyceride storage in subcutaneous adipose tissue (increased blood flow to adipose tissue, induction of lipoprotein lipase, etc.) (91), which may prevent ectopic fat deposition e.g., in the liver (steatotic liver disease, strongly associated with insulin resistance) (92) and pancreas (associated with impaired insulin secretory function) (93). In hyperglycaemic clamp experiments, first and second phase insulin secretion were stimulated more with tirzepatide than with semaglutide, however, when T2D patients were fully exposed to tirzepatide and semaglutide (94). This contrasts with acute infusion experiments in T2D patients, where GIP hardly stimulated insulin secretion, and a combination was not more effective than GLP-1 alone in stimulating insulin secretion and in reducing fasting plasma glucose (95). While in rodents, a role for GIP interacting with GIP receptors in the brain, leading to reduced food intake and weight loss, has been well established (79), exogenous GIP has not been found to reduce *ad libitum* food intake in humans (81). In line with these findings, greater reduction in body weight was observed with tirzepatide than with semaglutide in the absence of differences regarding appetite, satiety, and *ad libitum* energy intake in subjects with T2D (96). Thus, open questions remain regarding which contribution GIP receptor agonism makes to improved glycaemic control and body weight reduction in the treatment of T2D (97).

Supplementary Table 3 A. Characteristics of cardiovascular outcomes studies with GLP-1 receptor agonists in people with type 2 diabetes and obesity (with established atherosclerotic cardiovascular disease or high risk as indicated by risk factors

			Study population		Patients completing study (proportion [%])		Vital status known (proportion [%])		Patients discontinuing study medication (proportion [%])	
Study acronym	Compound/ preparation	Duration [years]	Placebo treatment [n]	Active drug treatment [n]	Placebo treatment	Active drug treatment	Placebo treatment	Active drug treatment	Placebo treatment	Active drug treatment
ELIXA (98)	Lixisenatide	2.1	3034	3034	96.4	96.5	98.6	99.0	27.5	24.0
LEADER (30)	Liraglutide	3.5	4672	4668	96.6	97.0	99.6	99.7	n.r.	n.r
SUSTAIN-6 (99)	Semaglutide s.c.	2.1	1649	1648	97.6	98.5	99.6	99.6	n.r.	n.r.
EXSCEL (100)	Exenatide q.w.	3.2	7396	7356	95.9	96.4	98.1	98.3	45.2	43.0
HARMONY OUTCOMES (101)	Albiglutide	1.6	4732	4731	96.7	97.6	99.3	99.4	27.9	24.5
REWIND (102)	Dulaglutide	5.4	4952	4949	96.8	97.3	99.7	99.7	6.3	9.1
PIONEER 6 (103)	Oral semaglutide	1.3	1592	1591	99.6	99.7	100.0	100.0	9.7	15.3
AMPLITUDE-O (104)	Efpeglenatide	1.3	1359	2717	96.1	97.0	99.9	99.9	n.r.	n.r.
FREEDOM CVOT (105)	Exenatide (osmotic minipump)	1.3	2081	2075	96.7	96.4	99.4	99.5	13.4	17.6
FLOW (106)	Semaglutide s.c.	3.4	1767	1766	97.6	96.7	99.5	99.2	24.8	27.2
SOUL (107)	Semaglutide s.c.	4.0	4825	4825	98.5	98.2	98.8	98.6	21.7	28.5
SELECT* (108)	Semaglutide s.c.	2.9	8803	8801	97.1	96.8	99.6	99.7	26.7	23.6

n.r.: not reported; *: Study in obese subjects with established ASCVD

Supplementary Table 3 B Baseline patient characteristics

Study acronym	Age [years]	Female sex (proportion [%])	Body mass index [kg/m²]	Duration of diabetes [years]	HbA_{1c} [%]	Blood pressure systolic/ diastolic) [mmHg]	LDL cholesterol [mg/dl]	Patients with established cardiovascular disease [n] (proportion [%])	Patients with established heart failure [n] (proportion [%])
ELIXA	60.3±9.7	30.7	30.2±5.7	9.3±8.3	7.7±1.3	130/n.r.	78.5±35.3	100.0	22.4
LEADER	64.3±7.2	35.7	32.5±6.3	12.8±8.0	8.7±1.5	136/77	89.5±35.5	81.)	14.0
SUSTAIN-6	64.6±7.4	39.3	32.8±6.2	13.9±8.1	8.7±1.5	136/77	82.3±45.6	72.2 ¶	23.6
EXSCEL	61.9±9.4	38.0	31.8±5.9	12 *	8.0±1.2	135/80 *	88 *	73.4	16.2
HARMONY OUTCOMES	64.1±8.7	30.6	32.3±5.9	14.2±8.8	8.7±1.5	135/77	81.7 †	100.0	20.3
REWIND	66.2±6.5	46.3	32.3±5.7	10.6±7.3	7.3±1.1	137/79	98.5±37.7	31.5	8.6
PIONEER 6	66.0±7.0	31.6	32.3±6.5	14.9±8.5	8.2±1.6	136/76	78.0⁺	84.7	12.2
AMPLITUDE-O	64.5±8.2	33.0	32.7±6.2	15.4±8.8	8.9±1.5	135/77	79.6±37.7	89.6	18.1
FREEDOM CVOT	63 *	36.7	32.2 *	10.3 *	8.0 *	138/80 *	n.r.	76	16.1
FLOW	66,6±9.0	30.3	32.0±6.3	> 15	7.8±1.3	139/16	n.r.	22.9	19.2
SOUL	66.1±7.6	28.9	31.1±5.8	14.7	8.0±1.2	135/77	73.5	83.8	23.1
SELECT	61.6±8.9	27.7	33.3±5.0	n.a.	5.8±0.3	131/79	78*	100.0	24.4

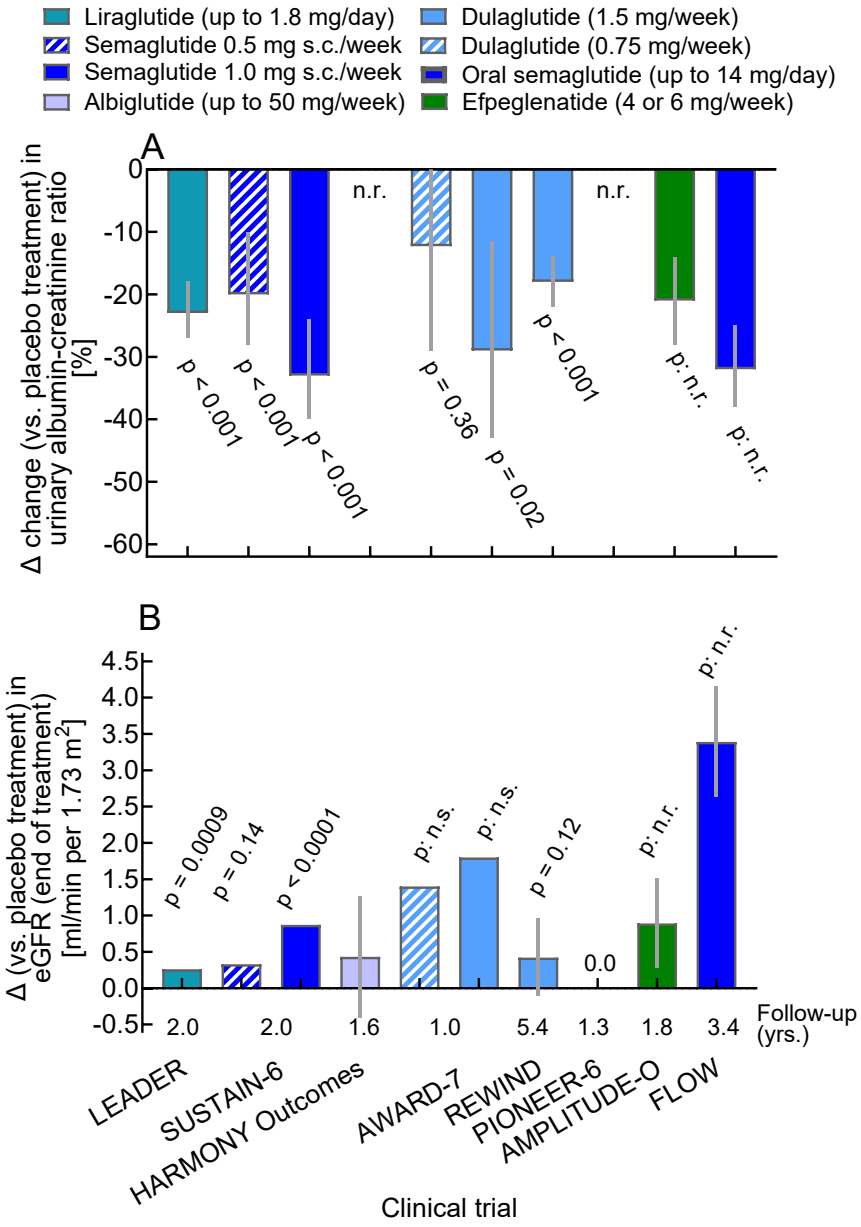
Mean ± SD or [n] (proportion [%]); * only median reported; † only mean without SD reported; ¶ from *post hoc* analysis (Leiter et al. (109)); n.r.: not reported

GLP-1 receptor agonists in real-world studies. With respect to glucose- and body weight-lowering effects, results from clinical trials have been confirmed in treatments real-world studies. Some studies have added insights regarding the inter-individual heterogeneity in clinical responses (110, 111) and regarding adherence to and persistence of GLP-1 RA therapy (112). Cardiovascular benefits regarding ischaemic events as well as heart-failure outcomes have been confirmed in large real-world databases (113, 114). Likewise, renal benefits were also described in real-world studies (115).

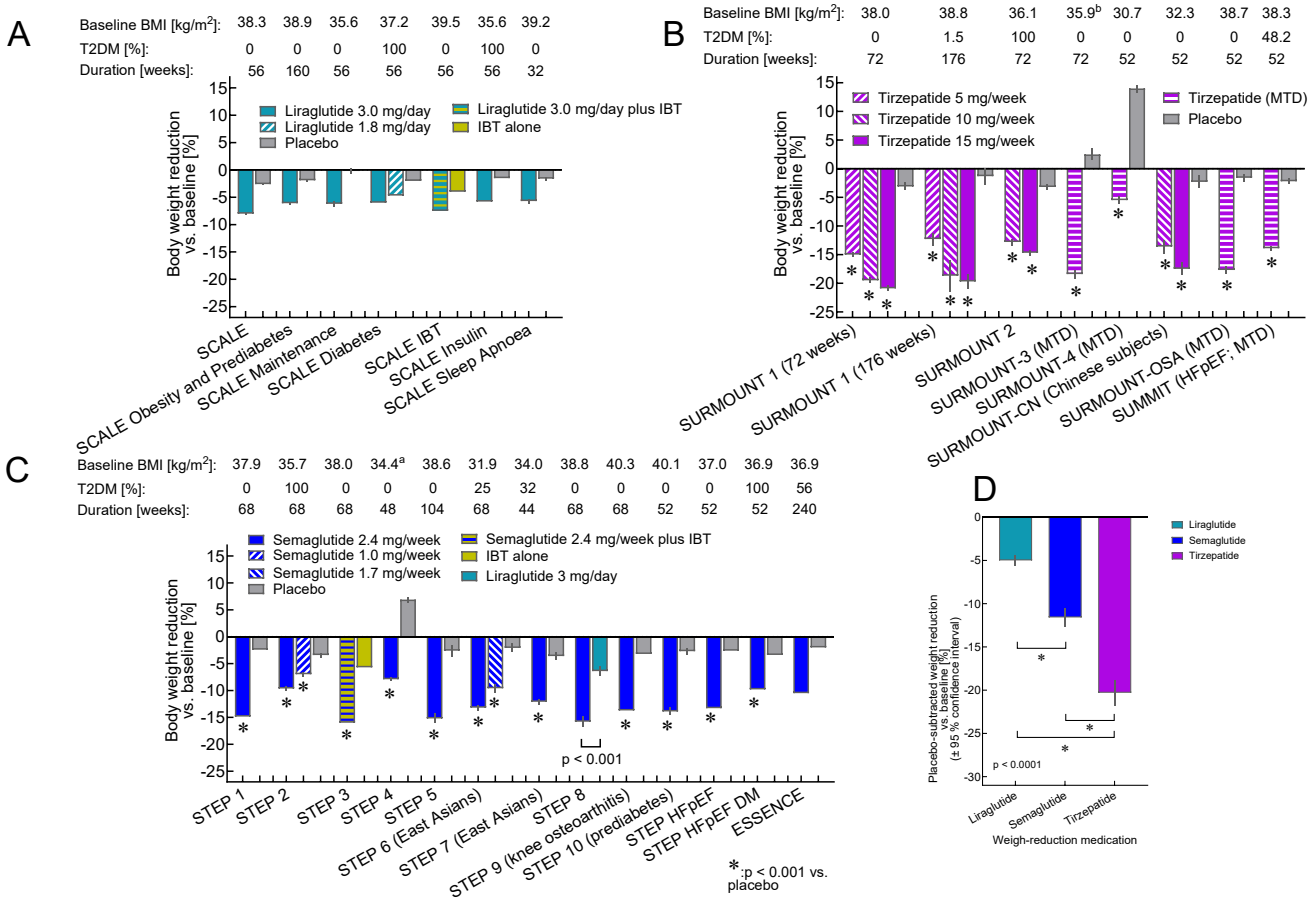
Supplementary Table 4. Effects of GLP-1 receptor agonists or the dual GIP/GLP-1 receptor co-agonist tirzepatide on composite kidney outcomes indicating the potential to prevent kidney failure in people with type 2 diabetes

Treatment/ duration	Population characteristics		Individual outcome(s) as component of composite outcomes					Results		Literature
GLP-1 RA or dual GIP/GLP-1 RA	Proportion with baseline eGFR < 60 ml/min per 1.73 m^2 [%]	Proportion with micro- or macro-albuminuria at baseline [%]	Albuminuria-related outcome	eGFR decline outcome	Persistent eGFR < 15 ml/min per 1.73 m^2	Need for kidr replacement therapy	Death from kidney-related causes	Composite outcome (hazard ratio; 95 % confidence interval)	Other important findings/ comments	References
Liraglutide up to 1.8 mg/day (vs. placebo) for 3.84 years	23.1	11.3	New-onset persistent macroalbuminuria	Persistent doubling of serum creatinine level	no	yes	yes	0.78 (0.67-0.92); p = 0.003	Driven by effects on macroalbuminuria; improved eGFR trajectories (mainly in those with baseline eGFR < 60 ml/min per 1.73 m^2)	Mann et al. 2017 (116)
Semaglutide 0.5 and 1.0 mg/week (vs. placebo) over 2.1 years	28.5	n.r.	Persistent macroalbuminuria	Persistent doubling of serum creatinine and an eGFR < 45 ml/min per 1.73 m^2 (MDRD)	no	yes	No	0.64 (0.46-0.88); p = 0.005	Driven by effects on macroalbuminuria; trajectories for eGFR and urinary albumin-creatinine ratio reported separately.	Marso et al. 2016 (117); Shaman et al. 2022 (118)
Dulaglutide up to 1.5 mg/ week over 5.4 years	22.2	35.0	Development of macroalbuminuria (UACR > 33.9 mg/mmol) in people with lower baseline concentrations	A sustained ≥ 30 % declined in eGFR	no	yes	no	0.85 (0.77-0.93); p = 0.0004	Driven by effects on macroalbuminuria; improved eGFR trajectories; Effect on macroalbuminuria mainly in those with baseline eGFR > 60 ml/min per 1.73 m^2)	Gerstein et al. 2019 (119)
Dulaglutide 0.75 or 1.5 mg/ week (vs. insulin glargine) over 52 weeks	94.8	44.8	no	eGFR at 52 weeks; A ≥ 40 % decline in eGFR	yes	yes	yes	0.45 (0.20-0.97) p=0.042 for dulaglutide 1.5 mg versus insulin glargine	eGFR decline as LSM (95% CI) at 52 weeks was less in dulaglutide 1.5 mg and 0.75 mg treatment groups -0.7 (-2.5, 1·0) and -0.7 (-2.4, 1.1) mL/min/1.73m^2, respectively, versus -3.3 mL/min/1.73m^2 (-5.1, -1.6) with insulin glargine	Tuttle et al. 2018 (120) Tuttle et al. 2020 (121)
Efpeglenatide 4 or 6 mg/ week over 1.81 years	31.6	n.r.	Incident macroalbuminuria plus rise in albumin-to-creatinine ratio by ≥ 30 %	A sustained ≥ 40 % decline in eGFR for ≥ 30 days	yes (for ≥ 30 days)	yes (for ≥ 90 days	no	0.68 (0.57-0.79); p < 0.001	Improved eGFR trajectories (higher by 0.9 ml/min per 1.73 m^2 [95 CI 0.3-1.5]) and reduced albuminuria (- 21% [95 % CI 14-28]; results not broken down into categories of baseline eGFR or albuminuria categories	Gerstein et al. 2021 (104)
Tirzepatide (5, 10, or 15 mg/week) over up to 104 weeks	17.1	35.4	New-onset macroalbuminuria; sustained UACR progression (change in category[a])	A ≥ 40 % decline in eGFR	yes	Chronic dialysis or kidney trans-plantation	yes	0.58 (0.43-0.80); p = 0.0008	All tirzepatide doses were pooled; comparator: Insulin glargine; No significant effect for a second composite endpoint calculated without new-onset macroalbuminuria.	Heerspink et al. 2022 (122)
Semaglutide s.c. 1 mg/week over 3.4 years	79.6	96.9	no	A sustained ≥ 50 % decline in eGFR for ≥ 28 days	yes (for ≥ 28 days)	Long-term dialysis, kidney trans-plantation	yes (death from kidney-related or CV causes)	0.79 (0.56-0.89; p = 0.0003;	Confirmed for extended composite outcome (inc. CV death): 0.76 (0.66-0.88) (Improved eGFR trajectories (annual slope different by 1.16 ml/min per 1.73 m^2 [95 CI 0.86-1.47])	Perkovic et al. 2024 (106)
Semaglutide, oral, 14 mg/day	29.2	n.r.	no	A persistent ≥ 50 % decline in eGFR	yes	Long-term kidney re-placement therapy	yes	0.86 (0.66-1.10); p-value n.r.	Qulitatively confirmed for extended composite outcome (inc. CV death): 0.91 (0.80-1,05), p = 0.19	McGuire et al. 2025 (123)

CI: Confidence interval; CV: Cardiovascular; eGFR: estimated glomerular filtration rate; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; n.r.: Not reported; UACR: Urinary albumin-creatinine ratio; [a]: normoalbuminuria (UACR < 30 mg/g creatinine; microalbuminuria (UACR 30-300 mg/g creatinine); macroalbuminuria (UACR > 300 mg/g creatinine)



Supplementary Figure 2. Effect of GLP-1 receptor agonists on albuminuria (A) and eGFR changes in cardiovascular and kidney outcome trials in populations with type 2 diabetes. In the upper panel (A), the differential (△) of reductions (vs. baseline values) in urinary albumin excretion (expressed as urinary albumin-creatinine ratio; UACR) between active and placebo treatment is shown. Lower values indicate a greater reduction in UACR. In the lower panel (B), the differential (△) of reductions (vs. baseline values) in estimated glomerular filtration rates (eGFR) between active and placebo treatment is shown. Higher values indicate a greater preservation in eGFR over time. For all these estimates, when available, 95 % confidence intervals are shown as bars. Original results were taken from the primary publications: LEADER (30); SUSTAIN-6 (117); HARMONY-Outcomes (101); AWARD-7 (120, 121); REWIND (102); PIONEER-6 (103); AMPLITUDE-O (104); FLOW (106). In LEADER, SUSTAIN-6, and PIONEER-6, CKD with an eGFR < 60 ml/min per 1.73 m^2 body surface was taken as an equivalent of established cardiovascular disease. In LEADER, the decline in eGFR was slower with liraglutide than with placebo treatment (estimated trial group ratio 1.02 (95% CI 1.00;1.03, p = 0.01); In HARMONY Outcomes, eGFR showed a significant difference at an earlier time point (8 months): 1.11 (95 % confidence interval 0.39;1.84). In ELIXA (98), UACR increased over time, less so with active treatment (lixisenatide). EXSCEL (100) , SELECT (108), and SOUL(123) did not report these outcomes.



Supplementary Figure 3. Body weight reduction with the selective GLP-1 receptor agonists liraglutide (A) and semaglutide (B), and with the dual GIP/GLP-1 receptor agonist tirzepatide (C), in populations with overweight/obesity, with and without type 2 diabetes. Body weight reduction is expressed relative to baseline body weight (% reduction) and displayed for various doses (see colour code) and placebo treatment (grey). Bars indicate the standard error of the mean. On top of each panel, the mean baseline body-mass-index (BMI), the proportion of each cohort with type 2 diabetes (T2DM), and the study duration is presented for all studies. Whenever possible, results based on the treatment policy estimand are depicted in the present figure. Asterisks indicate a significant difference ($p < 0.05$) from results of placebo treatment in the same study. Significances of differences to results from treatment with active comparators are indicated by p-values associated with brackets connecting the bars of interest. Panel (D) shows a comparison of weighted mean values and pooled standard errors of the mean of all studies with liraglutide (3 mg/day), semaglutide (2.4 mg/week) and tirzepatide (15 mg/week) by analysis of variance. Data depicted in this figure have been taken from the original publications (liraglutide: SCALE obesity and prediabetes (27, 124); SCALE Maintenance (125); SCALE diabetes (126); SCALE IBT (127); SCALE Insulin (128); SCALE Sleep Apnea (129); semaglutide: STEP 1 (73); STEP 2 (28); STEP 3 (68); STEP 4 (66); STEP 5 (61); STEP 6 (62); STEP 7 (65); STEP 8 (67); STEP 10 (64); ESSENCE (130); tirzepatide: SURMOUNT-1 (29, 131); SURMOUNT-2 (132); SURMOUNT-3 (133); SURMOUNT 4 (134); SURMOUNT-CN (135); SURMOUNT OSA (136); SUMMIT (137)).

Supplementary Table 5. Therapeutic effects of GLP-1 receptor agonists or the dual GIP/GLP-1 receptor co-agonist tirzepatide on clinically relevant endpoints representing specific obesity-associated conditions in people with overweight/obesity

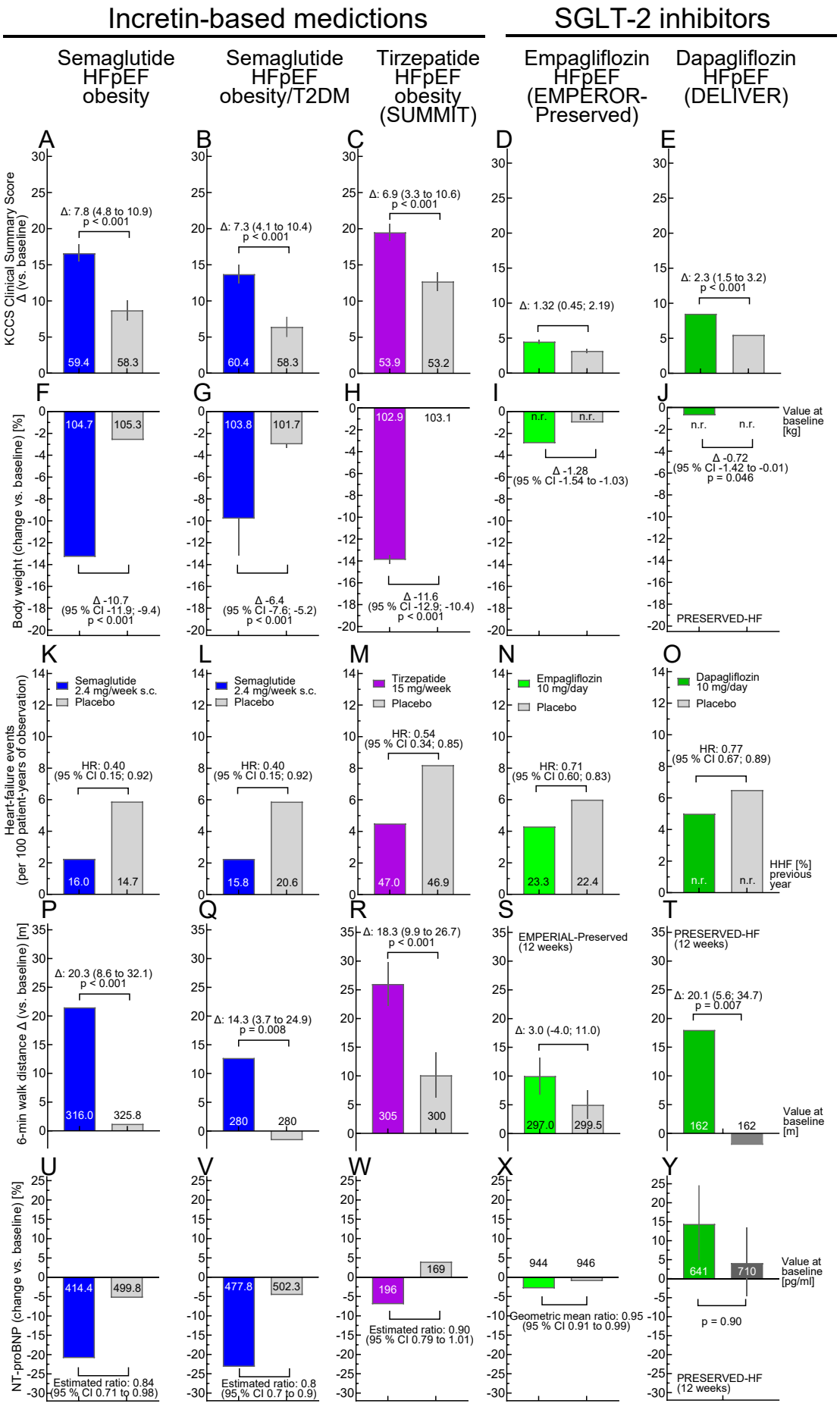
Obesity-associated condition	Therapeutic agent	Population studied	(Co-) primary endpoint(s)	Results	Other important findings (secondary or exploratory endpoints)	Commentary	References
Prediabetes	• Liraglutide 3 mg/day	• Obese subjects with pre-diabetes (IFG, IGT, or HbA_{1c} > 5.7 to < 6.5 %)	• Time to T2DM over 160 weeks	• Reduction by 79 % (HR 0.21 (95 % CI 0.14-0.34)	• Reversion to normoglycaemia (OR 2.6 [3.0 -4.4])	• Effect partially maintained after 12 weeks off treatment	• LeRoux et al. 2017 (124)
	• Semaglutide 2.4 mg/week	• Obese subjects with FPG 5.5-5.9 mmol/l or HbA_{1c} 6.0-6.4 %	• Patients reverting to normoglycaemia over 52 weeks	• Increase (81 vs. 14 %, OR 19.8 (95 % CI 8.7-45.2	• Progression to T2DM 1 vs. 3 %	• Effects partially maintained after 28 weeks off treatment	• McGowan et al. 2024 (64)
	• Tirzepatide 5, 10, or 15 mg/week	• Obese subjects with prediabetes (based on ≥ 2 measures of FPG, OGTT 2 h PG, HbA_{1c})	• Time to T2DM over 176 weeks	• Reduction by 93 %, HR 0.07 (95 % CI 0.00-0.10)	• Progression to T2DM 2.4 vs. 13.7 %, HR 0.12 (95 % CI 0.10-0.20)	• Effects partially maintained after 17 weeks off treatment	• Jastreboff et al. 2024 (138)
Atherosclerotic cardiovascular disease	• Semaglutide 2.4 mg/week	• Obese subjects with ASCVD at baseline (85.4 % with previous AMI or stroke)	• Time to MACE over 3.3 years	• Reduction by 20 % (HR 0.80 [95 % CI 0.72-0.90]	• Reduction in death from any cause • Reduction in coronary revascularization • Reduction in nephropathy composite endpoint	• Secondary endpoints were nominally significant (upper bound or 95% CI < 1.00), but cannot be considered confirmed significant (hierarchical testing)	• Lincoff et al. 2023 (108)
Heart failure with preserved ejection fraction (HFpEF)	• Semaglutide 2.4 mg/week	• Patients with obesity and heart failure with preserved ejection fraction (HFpEF) without T2DM	• (a) Change in Kansas City Clinical Cardiomyopathy Questionnaire Summary Score and (b) in body weight over 52 weeks	• (a) Increase (16.6 vs. 8.7 points [△ 7.8, 95 % CI interval 4.8-10.9, p < 0.001]); (b) reduction by 13.3 vs. 2.6 % (△ 10.7 [95 % CI 11.9-9.4])	• Improved 6-min walk distance • A combined analysis of the two studies (in patients without and with T2DM) demonstrated a reduction in first heart failure events (1 vs. 5 %, HR 0.27 [95 % CI 0.12-0.56])	• Similar effects on cardiovascular endpoints, but less weight reduction in T2DM patients vs. non-diabetic obese subjects	• Kosiborod et al. 2023 (139)
		• Patients with obesity and heart failure with preserved ejection fraction (HFpEF) with T2DM		• (a) Increase (13.7 vs. 6.4 points [△ 7.3, 95 % CI interval 4.1-10.4, p < 0.001); (b) reduction by 9.8 vs. 3.4 % (△ 6.4 [95 % CI 7.6-5.2])	• Improved 6-min walk distance		• Kosiborod et al. 2024(140) • Butler et al. 2024 (60)
		• Patients with obesity and heart failure with preserved ejection fraction (HFpEF) without T2DM	• a) Time to CV death or worsening heart failure event over 104 weeks; (b) change in Kansas City Clinical Cardiomyopathy Questionnaire Summary Score at week 52	• a) Reduction in events (9.9 vs. 15.3 %; HR 0.62 [95 % CI 0.41-0.95; p = 0.026]; (b) Increase (19.5 vs. 12.7 points [△ 6.9, 95 % CI interval 3.3-10.6, p < 0.001	• Improved 6-min walk distance		• Packer et al. 2024 (137)
	• Tirzepatide, up to 15 mg/week (highest tolerated dose)	• Patients with obesity and heart failure with preserved ejection fraction (HFpEF) without T2DM	• a) Time to CV death or worsening heart failure event over 104 weeks; (b) change in Kansas City Clinical Cardiomyopathy Questionnaire Summary Score at week 52	• a) Reduction in events (9.9 vs. 15.3 %; HR 0.62 [95 % CI 0.41-0.95; p = 0.026]; (b) Increase (19.5 vs. 12.7 points [△ 6.9, 95 % CI interval 3.3-10.6, p < 0.001	• Improved 6-min walk distance		• Packer et al. 2024 (137)

Table continued on next page

Table continued from previous page

Metabolic-dysfunction-associated steatotic liver disease (MASLD*)	• Liraglutide 1.8 mg/day	• Subjects with biopsy-proven NASH (fibrosis stage F1-F4)	• Resolution of NASH with no worsening of fibrosis	• Increase (39 vs. 9 %, RR 4.3 (95 % CI 1.0-17.7, p = 0.019	• Fewer subjects with worsening of fibrosis stage (9 vs. 36 %, RR 0.2 (95 % CI 0.1-1.0)	• Liraglutide dose lower than now recommended for the treatment of obesity	• Armstrong et al. 2015 (141)
	• Semaglutide 0.1, 0.2, or 0.4 mg/day	• Overweigh/obese subjects with biopsy-proven NASH (fibrosis stage F1-F3)	• Resolution of NASH with no worsening of fibrosis	• 59 vs. 17 %, OR 6.9 (95 % CI 2.6-17.6)	• Improvement by ≥ 1 stage of fibrosis with no worsening of NASH (n.s.)	• Small study, no clear dose-response relationship, daily injections of s.c. semaglutide	• Newsome et al. 2021 (142)
	• Semaglutide 2.4 mg/week	• Patients with biopsy-defined MASH and fibrosis stage 2 or 3	• Resolution of steatohepatitis without worsening of liver fibrosis and • Reduction in liver fibrosis without worsening of steatohepatitis	• 63 vs. 34 % (△29 (95% CI 21-36) % • 37 vs. 22 % (△14 (95 % CI 8-21) %	• Body weight reduction -10.5 vs. -2.0 % (△ -8.5 (95 % CI -9.6—7.4 %)	• Both co-primary endpoints show significant effects. The first study showing significant reduction in fibrosis after 240 weeks	• Sanyal et al. 2025 (143) (ESSENCE)
	• Tirzepatide 5, 10, or 15 mg/week	• Subjects with biopsy-proven MASLD (fibrosis stage F2 or F3)	• Resolution of MASLD with no worsening of fibrosis	• 44, 56, and 62 % with 5, 10, and 15 mg/week, vs. 10 % with placebo (all p < 0.0001)	• Increased proportion reaching an improvement in fibrosis by ≥ 1 stage without worsening of MASH	• Consistent effects on reduction in fibrosis stage	• Loomba et al. 2024 (144)
Obstructive sleep apnoea syndrome	• Liraglutide 3 mg/day (vs. placebo) as an adjunct to calorie restriction (by 500 kCal/day)	• Non-diabetic subjects with moderate (AHI 15-29.9 events/hour) or severe (AHI ≥ 30 events/h) obstructive sleep apnoea, unwilling/unable to use continuous positive airway pressure	• Change in AHI from baseline (vs. placebo) after 32 weeks	• Reduction in AHI events (by 6.1 events/h [95 % CI 1.2-11.0]; p = 0.015	• Reduction in body weight and related parameters (e.g. waist circumference)	• Change in AHI related to degree of body weight reduction	• Blackman et al. 2016 (129)
	• Tirzepatide 10 or 15 mg/week (maximum tolerated dose)	• Adults with moderate-to-severe obstructive apnoea not receiving (a; trial 1) or receiving positive airway pressure therapy (b; trial 2)	• Change in AHI from baseline (vs. placebo) after 52 weeks	• (a) - 20 events/h (95 % CI -29.3 - 21.1); • (b) -23.8 events/h 95 % CI -29.6 – 17.9)	• Reduction of AHI events into the range, where continuous positive airway pressure therapy may no longer be necessary in 42.2 (a) and 50.2 (b) % of participants	• Relationship of AHI improvements to degree of body weight reduction not reported	• Malhotra et al. 2024 (145)
Knee osteoarthritis	• Semaglutide 2.4 mg/week	• Obese adults with a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain	• Change in (a) body weight and (b) change in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index after 68 weeks	• (a) Reduction by 10.5 % (95 % CI 8.6-12.3); (b) Reduction by 14.1 points (95 % CI 8.3-20; p < 0.001)	• Reduction in pain medications (acetaminophen, non-steroidal anti-inflammatory drugs; opioids)	• Relationship of symptomatic improvement to degree of weight reduction achieved not reported	• Blidda l et al. 2024 (146)

AHI: Apnoea/hypopnoea index; CI: Confidence interval; FPG: Fasting plasma glucose; HR: Hazard ratio; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; MASH: Metabolic dysfunction-associated steatohepatitis; MASLD: Metabolic dysfunction-associated steatotic liver disease; NASH: Non-alcoholic steato-hepatitis; OGTT: Oral glucose tolerance test; OR: Odds ratio; RR: Relative risk; T2DM: Type 2 diabetes mellitus;



Legend on next page

Supplementary Figure 4. Clinical results of treating obesity-associated heart failure with preserved ejection fraction (HFpEF) with GLP-1 receptor agonists (semaglutide) and the dual GIP/GLP-1 receptor agonist tirzepatide compared to placebo treatment. For comparison, results obtained with SGLT-2 inhibitors (empagliflozin, dapagliflozin) are also shown. Improvements in the Kansas City Cardiomyopathy Score Clinical Summary Score (KCCQ-CCS; panels A-E), body weight reduction [% of baseline body weight] (F-J), incidence and reductions in heart failure events (hospitalization or urgent emergency room visits) (K-O), improvements in the 6-min walk-distance [m] (P-T), and reductions in N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations vs. baseline values [%] U-Y). Data are from the original publication of clinical trials (semaglutide 2.4 mg/week : HFpEF obesity (60, 147); HFpEF obesity/diabetes (60, 140); tirzepatide 15 mg/week : SUMMIT (137); empagliflozin 10 mg/day : EMPEROR-Preserved (148); dapagliflozin 10 mg/day : DELIVER (149); information on effects of empagliflozin treatment on 6-min walk distance has been taken from the EMPIRIAL-Preserved trial (150); for dapagliflozin, results regarding body weight reduction, 6-min walk distance and NT-proBNP have been taken from the PRESERVED-HF trial (151). In the latter clinical studies, the duration of treatment was 12 weeks. Where available, baseline values for KCCQ-CSS, body weight, proportion with hospitalization because of heart failure in the previous year, 6-min walk distance, and NT-proBNP concentrations are presented for better comparability. Results for statistical comparisons are presented in the original format (e.g., differences or ratios with 95 % confidence intervals) and, therefore, are not using a uniform format.

Supplementary Table 6. Summary of pre-clinical (proof-of-principle) studies and clinical trials of GLP-1 receptor agonists in healthy brain function, neurodegenerative disease, and substance abuse disorders

Indication	Specific disease/ condition	Pre-clinical proof-of-principle study/review		Clinical trial(s)		
		Animal model studied/review	Results/ commentary/ references	Population studied/ intervention (study drug/ comparator/ duration)	Results/ commentary/ references	Ongoing studies (ClinicalTrials.gov)
General brain function	Healthy physiology	Mice, hippocampal GLP-1 $R^{-/-}$ overexpression; treatment with GLP-1 analogue	Learning, memory improved; prevention of kainate-induced hippocampal apoptosis(152)	Patients with T2DM; liraglutide (12 weeks) vs. standard of care	Cognitive decline reduced (153)	n.a.
Neuro-degenerative disease	Alzheimer's dementia	Senescence-accelerated prone 8 (SAMP8) mice, treatment with liraglutide	Decline in memory function prevented, preservation of hippocampal CA1 pyramidal neuron numbers (154)	Patients with Alzheimers's disease; liraglutide (26 weeks)	Prevention of decline in brain glucose metabolism. No effect on accumulation of Aß or cognitive measures (155)	• NCT05891496 (semaglutide); phase 3 • NCT 04777396 (semaglutide: EVOKE); phase 3 • NCT04777409 (semaglutide: EVOKE plus); phase 3
	Parkinson's disease	Rat models of Parkinson's disease (6-hydroxydopamine- or lipopolysaccharide-induced)	Less "circling" after apomorphine challenge; higher striatal dopamine concentrations and nigral tyrosine hydroxylase staining (156)	Patients with (early) Parkinson's disease • Exenatide b.i.d., maintenance dose 10 µg (12 months; "proof-of-principle") • Exenatide once-weekly 2 mg per week (60 weeks) • Lixisenatide 20 µg (12 months; phase 2) • Exenatide 2 mg per week (96 weeks; phase 3) • NLY01 (brain-penetrant, pegylated, long-lasting exenatide (36 weeks; phase 3)	• Improved motor function (157) • Improved motor function (158) • Improved motor function (159) • No evidence of disease modification (160) • No significant improvement(161)	• NCT04232969 (exenatide once-weekly); phase 2
Substance abuse disorders	Nicotin (smoking) dependence	Mice (wild type and GLP-$1R^{-/-}$), treatment with exenatide (GLP-1 RA) or sitagliptin (DPP-4 inhibitor)	Exenatide treatment were associated with decreased, GLP-1 R k.o. with increased nicotine intake (162)	• Adult dependent smokers wanting to quit; dulaglutide (12 weeks) • Pre-diabetic or overweight smokers; exenatide once-weekly (6 weeks; "early-phase pilot study")	• No effect on abstinence (163) • Abstinence increased by 70 % (164)	n.a.
	Alcohol abuse	Rodents	Reduction in alcohol intake, promotion (by alcohol) of hyperlocomotion, dopamine release (*nucleus accumbens*) and reward suppressed (165)	• Subjects with alcohol use disorder; exenatide once-weekly • People undergoing a smoking cessation program; dulaglutide • People with T2DM and/or obesity treated with GLP-1 RAs vs. other medications	• No overall effect on heavy drinking days except for subgroup with BMI > 30 kg/m^2 (166) • Reduction in alcohol consumption (by 29 %) (167) • Lower rate of alcohol intoxication (168)	• NCT05895643 (semaglutide: SEMALCO); phase 2
	Opioid use disorder	• Mice (male) • Rats • Rats	• Exendin-4: No effect on morphine-induced conditioned place preference, withdrawal, or hyperlocomotion (169) • Exendin-4: Reduction in oxycodone self-administration (170). • Liraglutide: Reduction in heroin self-administration (171)	Patients with T2DM and opioid use disorder (observational study based on electronic health records) treated with semaglutide vs. other approved GLP-1 RAs or other classes of glucose-lowering medications	Reduction in the risk for opioid overdose by 42-68 % vs. other glucose-lowering medication classes (172) (even vs. other GLP-1 RAs (- 44 %).	• NCT06548490 (semaglutide); phase 2

Table continued on next page

Table continued from previous page

	Cocain use disorder	Mice	Exendin-4 (i.p.) reduced acute and chronic cocaine self-administration and reduced cocaine-induced striatal dopamine levels and c-*fos* expression (173)	Patients with cocaine use disorder; exenatide, 5 μg s.c.	No change in cocaine infusions, self-reported euphoria, or the subjective effect of cocaine (174)	• NCT06252623 (exenatide once-weekly); phase 1

GLP-1 R: Glucagon-like peptide-1 receptor; GLP-1 RAs: GLP-1 receptor agonists; DPP-4: Dipeptidyl peptidase-4;

Safety and Tolerability of Incretin-Based Medications. All approved GLP-1 RAs share typical adverse events associated with their use in patients with type 2 diabetes and in people with obesity. In a significant proportion of people exposed to GLP-1 RAs, nausea, vomiting, diarrhoea and other "gastrointestinal" symptoms occur early after initiating treatment, or when the dose is increased. Usually, these episodes are few, of short duration, and cease over time. This time course may mainly apply to the most prevalent adverse events (nausea and vomiting). Less is known regarding the less prominent side effects diarrhoea and constipation. However, they may be too severe to be tolerated or persist for too long, so that patients discontinue treatment. In clinical trials, the proportion discontinuing active treatment with GLP-1 RAs because of adverse events typically has been 5-10 %, with an odds ratio (vs. placebo treatment) of 2-5 and dose-dependence.
The co-stimulation of GIP receptors has, both in animal experiments (in shrews, a species able to vomit) (175) and in clinical studies in human subjects (176), been able to reduce "gastrointestinal" adverse events, which are mediated by an interaction of the respective incretin-based compound with the central nervous system (177), and not necessarily related to the gastrointestinal tract (motility, etc.).
Dose-escalation regimens starting with low doses, increasing doses in several steps, and allowing time to adapt at each dose level, have been successful to limit these side effects. Clinical observations suggest that slow titration in susceptible patients may prevent unnecessary discontinuations. Transient symptomatic treatment with antiemetics appear may alleviate symptoms after commencing GLP-1 RA treatment.

Based on case reports and adverse event reporting to pharmacovigilance databases (178), it had been speculated that GLP-1 RAs may cause acute pancreatitis based on: (a) abdominal pain; (b) elevations in serum amylase or lipase, and (c) imaging tests. Pancreatic enzyme activities in serum are commonly elevated to a mild degree in people treated with GLP-1 RAs. Carefully adjudicating suspected events of acute pancreatitis (e.g., severity, location, and characteristics of abdominal pain); imaging procedures) in the CVOTs, summarized in meta-analyses have not observed an elevated risk for acute pancreatitis (179).
An important concern is risk for medullary thyroid carcinomas in individuals with a personal or family history of multiple endocrine neoplasia [MEN] 2). While healthy human C-cells do not express GLP-1 receptors (180) and do not respond by secreting calcitonin or by proliferating, like in some rodent species (181). However, hyperplastic C-cells, C-cell adenomas, and medullary thyroid carcinomas express GLP-1 and GIP receptors, which mediate growth responses in rodents. Therefore, patients at risk for medullary thyroid carcinoma have been excluded from clinical trials with GLP-1 RA and therapy with medications activating GLP-1 receptors is generally contraindicated.

Due to their ability to precipitate rapid reductions in plasma glucose and HbA_{1c}, initiation of GLP-1 RA therapy may be associated with a risk to worsen pre-existing advanced retinopathy (99, 182), a phenomenon described as "initial worsening", because in type 1 diabetes this is followed by improvements in the retinopathy status later on (after > 2 years of treatment). Therefore, T2D patients should be monitored for their retinopathy status and appropriately treated by ophtalmologists before therapy with highly effective incretin mimetic medications is started.

GLP-1 RAs raise heart rate, usually by 2-5 beats per minute, mainly be interacting with GLP-1 receptors in the sinus node (183).

Recently, an analysis based on spontaneous reports to the European Medicines Agency suggested an increased risk for “suicidal ideation” in liraglutide-, dulaglutide-, and semaglutide-treated people (184). In studies employing a more systematic, population-based approach, this was not confirmed for Spanish (185) and US (186) cohorts.

Limitations to the prescription of and adherence to GLP-1 RAs. The main subpopulations within type 2 diabetes with substantial expected benefits are those in need of highly effective glucose-lowering therapy, which can otherwise only be provided by insulin therapy, and those with prevalent atherosclerotic cardiovascular disease, as mainly studied in cardiovascular outcomes trials. While insulin therapy is used in approximately 20-35 % of all patients with type 2 diabetes (187, 188), GLP-1 RAs are used in a lower proportion, which, however, keeps rising in recent years (189). Guidelines recommend GLP-1 RAs for the majority of type 2-diabetic patients needing injectable therapy (190), because recently developed compounds/preparations reduce HbA_{1c} more than does basal insulin treatment, with added benefits of reducing body weight (rather than increasing it) and avoiding a risk for hypoglycaemic episodes (58).

Atherosclerotic cardiovascular disease is present in approximately 35 % of the total type 2 diabetes population (191, 192). In such patients, 8-10 % received GLP-1 RAs in the year 2022 (and much less frequently earlier), with similar figures relating to the prescription of SGLT-2 Is (a therapy expected to be of similar benefit) (193). The underuse of cardiorenal-protective glucose-lowering drugs like GLP-1 RAs or SGLT-2 Is has been interpreted as “clinical inertia”, which deprives patients with a treatable condition of a clearly recommended treatment (194).

Along similar lines, patients starting treatment with GLP-1 RAs often discontinue this treatment within the first year (195), more frequently, if the indication was obesity (50 %) rather than type 2 diabetes (36 %) (195). There is no robust knowledge, why GLP-1 RAs are prescribed less frequently that suggested by guideline recommendations, and why their use is discontinued rather early, even though they are designed for long-term treatment (with benefits waning after discontinuation). Among the potential reasons may be adverse events limiting the tolerability, the relatively high costs, and lack of reimbursement by health insurance plans, which particularly is true for GLP-1 RAs prescribed for weight loss in obese subjects without type 2 diabetes (196).

References quoted in Online Supplementary Material

1. Nauck MA, Heimesaat MM, Ørskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 1993;91(1):301-7.
2. Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36:741-4.
3. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696-705.
4. Schick RR, Zimmermann JP, vorm Walde T, Schusdziarra V, Classen M. Glucagon-like Peptide (GLP)-1(7-36)-amide: A central suppressor of food intake in rats (abstract). Gastroenterol. 1992;102:A 756.
5. Turton MD, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. Nature. 1996;379:69-72.

6. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. Lancet. 2002;359:824-30.
7. Nauck MA, Meier JJ. MANAGEMENT OF ENDOCRINE DISEASE: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? Eur J Endocrinol. 2019;181:R 211-R 34.
8. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021;46:101102.
9. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28:1092-100.
10. Elrick H, Stimmler L, Hlad CJ, Arai Y. Plasma insulin response to oral and intravenous glucose administration. J Clin Endocrinol Metab. 1964;24:1076-82.
11. McIntyre N, Holdsworth CD, Turner DS. Intestinal factors in the control of insulin secretion. J Clin Endocrinol. 1965;25:1317-24.
12. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. J Clin Invest. 1967;46:1954-62.
13. Brown JC, Dryburgh JR. A gastric inhibitory polypeptide II. The complete amino acid sequence. Can J Biochem. 1971;49:867-72.
14. Dupré J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab. 1973;37:826-8.
15. Pederson RA, Schubert HE, Brown JC. Gastric inhibitory polypeptide. Its physiologic release and insulinotropic action in the dog. Diabetes. 1975;24:1050-6.
16. Brown JC. Gastric Inhibitory Polypeptide. Heidelberg: Springer-Verlag; 1982.
17. Moody AJ, Thim L, Valverde I. The isolation and sequencing of human gastric inhibitory peptide (GIP). FEBS Lett. 1984;172:142-8.
18. Amland PF, Jorde R, Aanderud S, Burhol PG, Giercksky KE. Effects of intravenously infused porcine GIP on serum insulin, plasma C-peptide, and pancreatic polypeptide in non-insulin-dependent diabetes in the fasting state. Scand J Gastroenterol. 1985;20:315-20.
19. Krarup T, Saurbrey N, Moody AJ, Kuhl C, Madsbad S. Effect of porcine gastric inhibitory polypeptide on beta-cell function in type I and type II diabetes mellitus. Metabolism. 1987;36:677-82.
20. Holst JJ, Ørskov C, Nielsen OV, Schwartz TW. Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut. FEBS Lett. 1987;211:169-74.
21. Mojsov S, Weir GC, Habener JF. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. J Clin Invest. 1987;79:616-9.
22. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 [7-36]: a physiological incretin in man. Lancet. 1987;2:1300-4.
23. Nathan DM, Schreiber E, Fogel H, Mojsov S, Habener JF. Insulinotropic action of glucagonlike peptide-I-(7-37) in diabetic and nondiabetic subjects. Diabetes Care. 1992;15:270-6.
24. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101:515-20.
25. Verdich C, Flint A, Gutzwiller JP, Näslund E, Beglinger C, Hellström PM, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. J Clin Endocrinol Metab. 2001;86:4382-9.
26. Secher A, Jelsing J, Baquero AF, Hecksher-Sorensen J, Cowley MA, Dalboge LS, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest. 2014;124:4473-88.

27. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373:11-22.
28. Davies M, Faerch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971-84.
29. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387:205-16.
30. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-22.
31. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9(10):653-62.
32. Badve SV, Bilal A, Lee MMY, Sattar N, Gerstein HC, Ruff CT, et al. Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol. 2025;13:15-28.
33. Lee MMY, Sattar N, Pop-Busui R, Deanfield J, Emerson SS, Inzucchi SE, et al. Cardiovascular and kidney outcomes and mortality with long-acting injectable and oral glucagon-like peptide 1 receptor agonists in individuals with type 2 diabetes: A systematic review and meta-analysis of randomized trials. Diabetes Care. 2025:published online March 29, 2025.
34. Finan B, Ma T, Ottaway N, Müller TD, Habegger KM, Heppner KM, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Sci Transl Med. 2013;5:209ra151.
35. Tschöp MH, Finan B, Clemmensen C, Gelfanov V, Perez-Tilve D, Müller TD, et al. Unimolecular polypharmacy for treatment of diabetes and obesity. Cell Metab. 2016;24:51-62.
36. Sanchez-Garrido MA, Brandt SJ, Clemmensen C, Müller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor co-agonism for treatment of obesity. Diabetologia. 2017;60:1851-61.
37. Kusminski CM, Perez-Tilve D, Müller TD, DiMarchi RD, Tschöp MH, Scherer PE. Transforming obesity: The advancement of multi-receptor drugs. Cell. 2024;187:3829-53.
38. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Mol Metab. 2018;18:3-14.
39. Rosenstock J, Wysham C, Frias JP, Kaneko S, Lee CJ, Fernandez Lando L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398:143-55.
40. Frias JP, Davies MJ, Rosenstock J, Perez Manghi FC, Fernandez Lando L, Bergman BK, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385:503-15.
41. Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regarding glycaemic control and body weight reduction. Cardiovasc Diabetol. 2022;21:169.
42. Rosenstock J, Hsia S, Nevarez Ruiz L, Eyde S, Cox D, Wu WS, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes. N Engl J Med. 2025:published online 21 June 2025.

43. Blüher M, Rosenstock J, Hoefler J, Manuel R, Hennige AM. Dose-response effects on HbA(1c) and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomised clinical trial. Diabetologia. 2024;67:470-82.
44. Le Roux CW, Steen O, Lucas KJ, Startseva E, Unseld A, Hennige AM. Glucagon and GLP-1 receptor dual agonist survodutide for obesity: a randomised, double-blind, placebo-controlled, dose-finding phase 2 trial. Lancet Diabetes Endocrinol. 2024;12:162-73.
45. Ji L, Jiang H, Bi Y, Li H, Tian J, Liu D, et al. Once-weekly mazdutide in Chinese adults with obesity or overweight. N Engl J Med. 2025:published online May 25, 2025.
46. Davies MJ, Bajaj HS, Broholm C, Eliasen A, Garvey WT, le Roux CW, et al. Cagrilintide-semaglutide in adults with overweight or obesity and type 2 diabetes. N Engl J Med. 2025:published online June 22, 2025.
47. Garvey WT, Blüher M, Osorto Contreras CK, Davies MJ, Winning Lehmann E, Pietilainen KH, et al. Coadministered cagrilintide and semaglutide in adults with overweight or obesity. N Engl J Med. 2025:published online June 22, 2025.
48. Dahl K, Toubro S, Dey S, Duque do Vale R, Flint A, Gasiorek A, et al. Amycretin, a novel, unimolecular GLP-1 and amylin receptor agonist administered subcutaneously: results from a phase 1b/2a randomised controlled study. Lancet. 2025;406:149-62.
49. Gasiorek A, Heydorn A, Gabery S, Hjerpsted JB, Kirkeby K, Kruse T, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the first-in-class GLP-1 and amylin receptor agonist, amycretin: a first-in-human, phase 1, double-blind, randomised, placebo-controlled trial. Lancet. 2025;406:135-48.
50. Rosenstock J, Frias J, Jastreboff AM, Du Y, Lou J, Gurbuz S, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet. 2023;402:529-44.
51. Jastreboff AM, Kaplan LM, Frias JP, Wu Q, Du Y, Gurbuz S, et al. Triple-hormone-receptor agonist retatrutide for obesity - A phase 2 trial. N Engl J Med. 2023;389:514-26.
52. Sanyal AJ, Kaplan LM, Frias JP, Brouwers B, Wu Q, Thomas MK, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nat Med. 2024;30:2037-48.
53. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation. 2017;136:849-70.
54. Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. J Clin Endocrinol Metab. 1996;81:327-32.
55. Jalleh RJ, Plummer MP, Marathe CS, Umapathysivam MM, Quast DR, Rayner CK, et al. Clinical consequences of delayed gastric emptying with GLP-1 receptor agonists and tirzepatide. J Clin Endocrinol Metab. 2024;110:1-15.
56. Nauck MA, Heimesaat MM, Behle K, Holst JJ, Nauck MS, Ritzel R, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab. 2002;87:1239-46.
57. Kang YM, Punov V, Lim S, Nauck MA. Comparative efficacy and tolerability of currently approved incretin mimetics: A systematic analysis of placebo-controlled clinical trials. Diabetes Obes Metab. 2025:published online April 11, 2025.
58. Nauck MA, Abd El Aziz M, Quast DR. Meta-analysis of head-to-head clinical trials comparing incretin-based glucose-lowering medications and basal insulin: An update including recently developed glucagon-like peptide-1 (GLP-1) receptor agonists and the

glucose-dependent insulinotropic polypeptide/GLP-1 receptor co-agonist tirzepatide. Diabetes Obes Metab. 2023;25:1361-71.
59. Borlaug BA, Kitzman DW, Davies MJ, Rasmussen S, Barros E, Butler J, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. Nat Med. 2023;29(9):2358-65.
60. Butler J, Shah SJ, Petrie MC, Borlaug BA, Abildstrom SZ, Davies MJ, et al. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. Lancet. 2024;403:1635-48.
61. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28:2083-91.
62. Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2022;10(3):193-206.
63. Kosiborod MN, Deanfield J, Pratley R, Borlaug BA, Butler J, Davies MJ, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet. 2024;404(10456):949-61.
64. McGowan BM, Bruun JM, Capehorn M, Pedersen SD, Pietilainen KH, Muniraju HAK, et al. Efficacy and safety of once-weekly semaglutide 2.4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. Lancet Diabetes Endocrinol. 2024;12:631-42.
65. Mu Y, Bao X, Eliaschewitz FG, Hansen MR, Kim BT, Koroleva A, et al. Efficacy and safety of once weekly semaglutide 2.4 mg for weight management in a predominantly east Asian population with overweight or obesity (STEP 7): a double-blind, multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2024;12:184-95.
66. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 randomized clinical trial. JAMA. 2021;325:1414-25.
67. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sorrig R, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The STEP 8 Randomized Clinical Trial. J Am Med Ass. 2022;327:138-50.
68. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. JAMA. 2021;325:1403-13.
69. Aroda VR, Aberle J, Bardtrum L, Christiansen E, Knop FK, Gabery S, et al. Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in adults with type 2 diabetes (PIONEER PLUS): a multicentre, randomised, phase 3b trial. Lancet. 2023;402:693-704.
70. Aroda VR, Jorgensen NB, Kumar B, Lingvay I, Laulund AS, Buse JB, et al. High-dose semaglutide (up to 16 mg) in people with type 2 diabetes and overweight or obesity: A randomized, placebo-controlled, phase 2 trial. Diabetes Care. 2025;48:905-13.
71. Wharton S, Lingvay I, Bogdanski P, Duque do Vale R, Jacob S, Karlsson T, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. N Engl J Med. 2025;393:1077-87.

72. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. Dig Dis Sci. 1993;38:665-73.
73. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384:989-1002.
74. Harder H, Nielsen L, Tu DT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care. 2004;27:1915-21.
75. Samms RJ, Christe ME, Collins KA, Pirro V, Droz BA, Holland AK, et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. J Clin Invest. 2021;131.
76. Meier JJ, Gallwitz B, Siepmann N, Holst JJ, Deacon CF, Schmidt WE, et al. Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia. Diabetologia. 2003;46:798-801.
77. Meier JJ, Goetze O, Anstipp J, Hagemann D, Holst JJ, Schmidt WE, et al. Gastric inhibitory polypeptide does not inhibit gastric emptying in humans. Am J Physiol (Endocrinol Metab). 2004;286:E 621-5.
78. Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? Trends Endocrinol Metab. 2020;31:410-21.
79. Zhang Q, Delessa CT, Augustin R, Bakhti M, Collden G, Drucker DJ, et al. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. Cell Metab. 2021;33:833-44 e5.
80. Bergmann NC, Lund A, Gasbjerg LS, Meessen ECE, Andersen MM, Bergmann S, et al. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. Diabetologia. 2019;62:665-75.
81. Bergmann NC, Gasbjerg LS, Heimburger SM, Krogh LSL, Dela F, Hartmann B, et al. No acute effects of exogenous glucose-dependent insulinotropic polypeptide on energy intake, appetite, or energy expenditure when added to treatment with a long-acting glucagon-like peptide 1 receptor agonist in men with type 2 diabetes. Diabetes Care. 2020;43:588-96.
82. Svendsen B, Larsen O, Gabe MBN, Christiansen CB, Rosenkilde MM, Drucker DJ, et al. Insulin secretion depends on intra-islet glucagon signaling. Cell Rep. 2018;25:1127-34 e2.
83. Capozzi ME, Wait JB, Koech J, Gordon AN, Coch RW, Svendsen B, et al. Glucagon lowers glycemia when beta-cells are active. JCI Insight. 2019(16).
84. Jonderko G, Golab T, Jonderko K. A pharmacological dose of glucagon suppresses gastric emptying of a radiolabelled solid meal in humans. Scand J Clin Lab Invest. 1988;48(8):743-6.
85. Al-Massadi O, Ferno J, Dieguez C, Nogueiras R, Quinones M. Glucagon control on food intake and energy balance. Int J Mol Sci. 2019;20.
86. Gedulin BR, Jodka CM, Herrmann K, Young AA. Role of endogenous amylin in glucagon secretion and gastric emptying in rats demonstrated with the selective antagonist, AC187. Regul Pept. 2006;137(3):121-7.
87. Lutz TA. Creating the amylin story. Appetite. 2022;172:105965.
88. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med. 2003;349:941-8.
89. Ramracheya RD, McCulloch LJ, Clark A, Wiggins D, Johannessen H, Olsen MK, et al. PYY-dependent restoration of impaired insulin and glucagon secretion in type 2 diabetes following Roux-en-Y gastric bypass surgery. Cell Rep. 2016;15:944-50.

90. Mather KJ, Mari A, Weerakkody G, Heise T, DeVries JH, Urva S, et al. Greater improvement in insulin sensitivity per unit weight loss associated with tirzepatide versus semaglutide: An exploratory analysis. Diabetes Obes Metab. 2025;27:1507-14.
91. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. Diabetes Obes Metab. 2021;23 (Suppl. 3):5-29.
92. Agarwal N, Sharma BC. Insulin resistance and clinical aspects of non-alcoholic steatohepatitis (NASH). Hepatology research : the official journal of the Japan Society of Hepatology. 2005;33:92-6.
93. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54:2506-14.
94. Heise T, Mari A, DeVries JH, Urva S, Li J, Pratt EJ, et al. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. Lancet Diabetes Endocrinol. 2022;10:418-29.
95. Mentis N, Vardarli I, Köthe LD, Holst JJ, Deacon CF, Theodorakis M, et al. GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes. Diabetes. 2011;60:1270-6.
96. Heise T, DeVries JH, Urva S, Li J, Pratt EJ, Thomas MK, et al. Tirzepatide reduces appetite, energy intake, and fat mass in people with type 2 diabetes. Diabetes Care. 2023;46:998-1004.
97. Gasbjerg LS, Rosenkilde MM, Meier JJ, Holst JJ, Knop FK. The importance of glucose-dependent insulinotropic polypeptide receptor activation for the effects of tirzepatide. Diabetes Obes Metab. 2023;25(11):3079-92.
98. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247-57.
99. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834-44.
100. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377:1228-39.
101. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392:1519-29.
102. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121-30.
103. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019.
104. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med. 2021;385:896-907.
105. Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. Nat Med. 2022;28:89-95.

106. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391:109-21.
107. McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med. 2025;392:2001-12.
108. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389:2221-32.
109. Leiter LA, Bain SC, Hramiak I, Jodar E, Madsbad S, Gondolf T, et al. Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial. Cardiovasc Diabetol. 2019;18:73.
110. Heni M, Frühwald L, Karges W, Naudorf M, Niemoller K, Pagnia F, et al. Heterogeneity in response to GLP-1 receptor agonists in type 2 diabetes in real-world clinical practice: insights from the DPV register - an IMI-SOPHIA study. Diabetologia. 2025.
111. Zhu X, Fowler MJ, Wells QS, Stafford JM, Gannon M. Predicting responsiveness to GLP-1 pathway drugs using real-world data. BMC Endocr Disord. 2024;24(1):269.
112. Palanca A, Ampudia-Blasco FJ, Calderon JM, Sauri I, Martinez-Hervas S, Trillo JL, et al. Real-world evaluation of GLP-1 receptor agonist therapy persistence, adherence and therapeutic inertia among obese adults with type 2 diabetes. Diabetes Ther. 2023;14:723-36.
113. Palanca A, Ampudia-Blasco FJ, Calderon JM, Sauri I, Martinez-Hervas S, Trillo JL, et al. Comparison of GLP-1 receptor agonists and other glucose-lowering agents on cardiovascular outcomes in individuals with type 2 diabetes and obesity: A Spanish real-world population-based study. Diabetes Res Clin Pract. 2024;207:111071.
114. Wallia A, O'Brien M, Hakimian S, Kang R, Cooper A, Lancki N, et al. Comparative cardiovascular effects of GLP-1 agonists using real-world data. Endocrinol Diabetes Metab. 2023;6(3):e339.
115. Schechter M, Melzer Cohen C, Fishkin A, Rozenberg A, Yanuv I, Sehtman-Shachar DR, et al. Kidney function loss and albuminuria progression with GLP-1 receptor agonists versus basal insulin in patients with type 2 diabetes: real-world evidence. Cardiovasc Diabetol. 2023;22(1):126.
116. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017;377:839-48.
117. Marso SP, Holst AG, Vilsboll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2017;376:891-2.
118. Shaman AM, Bain SC, Bakris GL, Buse JB, Idorn T, Mahaffey KW, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. Circulation. 2022;145:575-85.
119. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019;394:131-8.
120. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6:605-17.
121. Tuttle KR, Rayner B, Lakshmanan MC, Kwan AYM, Konig M, Shurzinske L, et al. Clinical outcomes by albuminuria status with dulaglutide versus insulin glargine in participants with diabetes and CKD: AWARD-7 exploratory analysis. Kidney360. 2021;2:254-62.

122. Heerspink HJL, Sattar N, Pavo I, Haupt A, Duffin KL, Yang Z, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2022.
123. McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med. 2025:published online 29 March 2025.
124. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017;389:1399-409.
125. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013;37:1443-14451.
126. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE diabetes randomized clinical trial. JAMA. 2015;314:687-99.
127. Wadden TA, Tronieri JS, Sugimoto D, Lund MT, Auerbach P, Jensen C, et al. Liraglutide 3.0 mg and intensive behavioral therapy (IBT) for obesity in primary care: The SCALE IBT randomized controlled trial. Obesity (Silver Spring). 2020;28:529-36.
128. Garvey WT, Birkenfeld AL, Dicker D, Mingrone G, Pedersen SD, Satylganova A, et al. Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: The SCALE insulin randomized controlled trial. Diabetes Care. 2020;43:1085-93.
129. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond). 2016;40:1310-9.
130. Sanyal AJ, Newsome PN, Kliers I, Ostergaard LH, Long MT, Kjaer MS, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med. 2025:published online April 30, 2025.
131. Jastreboff AM, le Roux CW, Stefanski A, Aronne LJ, Halpern B, Wharton S, et al. Tirzepatide for obesity treatment and diabetes prevention. N Engl J Med. 2024:published online Nov 13, 2024.
132. Garvey WT, Frias JP, Jastreboff AM, le Roux CW, Sattar N, Aizenberg D, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402:613-26.
133. Wadden TA, Chao AM, Machineni S, Kushner R, Ard J, Srivastava G, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nat Med. 2023.
134. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: The SURMOUNT-4 randomized clinical trial. JAMA. 2024;331:38-48.
135. Zhao L, Cheng Z, Lu Y, Liu M, Chen H, Zhang M, et al. Tirzepatide for weight reduction in Chinese adults with obesity: the SURMOUNT-CN randomized clinical trial. JAMA. 2024;332:551-60.
136. Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024;391:1193-205.

137. Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med. 2024:published online on November 16, 2024.
138. Jastreboff AM, le Roux CW, Stefanski A, Aronne LJ, Halpern B, Wharton S, et al. Tirzepatide for obesity treatment and diabetes prevention. N Engl J Med. 2024.
139. Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389:1069-84.
140. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024;390:1394-407.
141. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387:679-90.
142. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021;384(12):1113-24.
143. Sanyal AJ, Newsome PN, Kliers I, Ostergaard LH, Long MT, Kjaer MS, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med. 2025;392:2089-99.
144. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med. 2024;391:299-310.
145. Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024.
146. Bliddal H, Bays H, Czernichow S, Udden Hemmingsson J, Hjelmesaeth J, Hoffmann Morville T, et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med. 2024;391:1573-83.
147. Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide and heart failure with preserved ejection fraction and obesity. . N Engl J Med. 2023;389:1069-84.
148. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385:1451-61.
149. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089-98.
150. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. Eur Heart J. 2021;42:700-10.
151. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021;27:1954-60.
152. During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med. 2003;9(9):1173-9.
153. Li Q, Jia M, Yan Z, Li Q, Sun F, He C, et al. Activation of glucagon-like peptide-1 receptor ameliorates cognitive decline in type 2 diabetes mellitus through a metabolism-independent pathway. J Am Heart Assoc. 2021;10:e020734.
154. Hansen HH, Fabricius K, Barkholt P, Niehoff ML, Morley JE, Jelsing J, et al. The GLP-1 receptor agonist liraglutide improves memory function and increases hippocampal CA1

neuronal numbers in a senescence-accelerated mouse model of Alzheimer's Disease. J Alzheimers Dis. 2015;46:877-88.
155. Gejl M, Gjedde A, Egefjord L, Moller A, Hansen SB, Vang K, et al. In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Front Aging Neurosci. 2016;8:108.
156. Harkavyi A, Abuirmeileh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. J Neuroinflammation. 2008;5:19.
157. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, et al. Exenatide and the treatment of patients with Parkinson's disease. J Clin Invest. 2013;123:2730-6.
158. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390:1664-75.
159. Meissner WG, Remy P, Giordana C, Maltete D, Derkinderen P, Houeto JL, et al. Trial of lixisenatide in early Parkinson's disease. N Engl J Med. 2024;390:1176-85.
160. Vijiaratnam N, Girges C, Auld G, McComish R, King A, Skene SS, et al. Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial. Lancet. 2025;405:627-36.
161. McGarry A, Rosanbalm S, Leinonen M, Olanow CW, To D, Bell A, et al. Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2024;23:37-45.
162. Tuesta LM, Chen Z, Duncan A, Fowler CD, Ishikawa M, Lee BR, et al. GLP-1 acts on habenular avoidance circuits to control nicotine intake. Nat Neurosci. 2017;20:708-16.
163. Lengsfeld S, Burkard T, Meienberg A, Jeanloz N, Vukajlovic T, Bologna K, et al. Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial. EClinicalMedicine. 2023;57:101865.
164. Yammine L, Green CE, Kosten TR, de Dios C, Suchting R, Lane SD, et al. Exenatide adjunct to nicotine patch facilitates smoking cessation and may reduce post-cessation weight gain: A pilot randomized controlled trial. Nicotine Tob Res. 2021;23:1682-90.
165. Jerlhag E. The therapeutic potential of glucagon-like peptide-1 for persons with addictions based on findings from preclinical and clinical studies. Front Pharmacol. 2023;14:1063033.
166. Klausen MK, Jensen ME, Moller M, Le Dous N, Jensen AO, Zeeman VA, et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI Insight. 2022;7:e159863.
167. Probst L, Monnerat S, Vogt DR, Lengsfeld S, Burkard T, Meienberg A, et al. Effects of dulaglutide on alcohol consumption during smoking cessation. JCI Insight. 2023;8(22):e170419.
168. Qeadan F, McCunn A, Tingey B. The association between glucose-dependent insulinotropic polypeptide and/or glucagon-like peptide-1 receptor agonist prescriptions and substance-related outcomes in patients with opioid and alcohol use disorders: A real-world data analysis. Addiction. 2024.
169. Bornebusch AB, Fink-Jensen A, Wortwein G, Seeley RJ, Thomsen M. Glucagon-like peptide-1 receptor agonist treatment does not reduce abuse-related effects of opioid drugs. eNeuro. 2019;6:0443-18.2019.
170. Zhang Y, Kahng MW, Elkind JA, Weir VR, Hernandez NS, Stein LM, et al. Activation of GLP-1 receptors attenuates oxycodone taking and seeking without compromising the

antinociceptive effects of oxycodone in rats. Neuropsychopharmacology. 2020;45:451-61.
171. Douton JE, Horvath N, Mills-Huffnagle S, Nyland JE, Hajnal A, Grigson PS. Glucagon-like peptide-1 receptor agonist, liraglutide, reduces heroin self-administration and drug-induced reinstatement of heroin-seeking behaviour in rats. Addict Biol. 2022;27:e13117.
172. Wang W, Volkow ND, Wang Q, Berger NA, Davis PB, Kaelber DC, et al. Semaglutide and opioid overdose risk in patients with type 2 diabetes and opioid use disorder. JAMA Netw Open. 2024;7:e2435247.
173. Sørensen G, Reddy IA, Weikop P, Graham DL, Stanwood GD, Wortwein G, et al. The glucagon-like peptide 1 (GLP-1) receptor agonist exendin-4 reduces cocaine self-administration in mice. Physiol Behav. 2015;149:262-8.
174. Angarita GA, Matuskey D, Pittman B, Costeines JL, Potenza MN, Jastreboff AM, et al. Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder. Drug Alcohol Depend. 2021;221:108614.
175. Borner T, Geisler CE, Fortin SM, Cosgrove R, Alsina-Fernandez J, Dogra M, et al. GIP receptor agonism attenuates GLP-1 receptor agonist-induced nausea and emesis in preclinical models. Diabetes. 2021;70:2545-53.
176. Knop FK, Urva S, Rettiganti M, Benson CT, Roell WC, Mather KJ, et al. A long-acting glucose-dependent insulinotropic polypeptide receptor agonist improves the gastrointestinal tolerability of glucagon-like peptide-1 receptor agonist therapy. Diabetes Obes Metab. 2024;26:5474-8.
177. Borner T, Tinsley IC, Doyle RP, Hayes MR, De Jonghe BC. Glucagon-like peptide-1 in diabetes care: Can glycaemic control be achieved without nausea and vomiting? Br J Pharmacol. 2022;179:542-56.
178. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 2011;141:150-6.
179. Abd El Aziz M, Cahyadi O, Meier JJ, Schmidt WE, Nauck MA. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials. Diabetes Obes Metab. 2020;22:699-704.
180. Waser B, Beetschen K, Pellegata NS, Reubi JC. Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: relevance for incretin-based diabetes therapy. Neuroendocrinology. 2011;94:291-301.
181. Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151:1473-86.
182. Vilsbøll T, Bain SC, Leiter LA, Lingvay I, Matthews D, Simo R, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab. 2018;20:889-97.
183. Lubberding AF, Veedfald S, Achter JS, Nissen SD, Soattin L, Sorrentino A, et al. Glucagon-like peptide-1 increases heart rate by a direct action on the sinus node. Cardiovascular research. 2024;120:1427-41.
184. Ruggiero R, Mascolo A, Spezzaferri A, Carpentieri C, Torella D, Sportiello L, et al. Glucagon-like peptide-1 receptor agonists and suicidal ideation: Analysis of real-world data collected in the European Pharmacovigilance Database. Pharmaceuticals (Basel). 2024;17:published online Jan. 23, 2024.
185. Hurtado I, Robles C, Peiro S, Garcia-Sempere A, Sanfelix-Gimeno G. Association of glucagon-like peptide-1 receptor agonists with suicidal ideation and self-injury in individuals with diabetes and obesity: a propensity-weighted, population-based cohort study. Diabetologia. 2024;67:2471-80.

186. Tang H, Lu Y, Donahoo WT, Shao H, Shi L, Fonseca VA, et al. Glucagon-like peptide-1 receptor agonists and risk for suicidal ideation and behaviors in U.S. older adults with type 2 diabetes : A target trial emulation study. Ann Intern Med. 2024;177:1004-15.
187. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. Ann Intern Med. 2014;160:517-25.
188. Basu S, Yudkin JS, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ, et al. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabetes Endocrinol. 2019;7(1):25-33.
189. Watanabe JH, Kwon J, Nan B, Reikes A. Trends in glucagon-like peptide 1 receptor agonist use, 2014 to 2022. J Am Pharm Assoc (2003). 2024;64:133-8.
190. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65:1925-66.
191. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17:83.
192. Lautsch D, Wang T, Yang L, Rajpathak SN. Prevalence of established cardiovascular disease in patients with type 2 diabetes mellitus in the UK. Diabetes Ther. 2019;10:2131-7.
193. King A, Tan X, Dhopeshwarkar N, Bohn R, Dea K, Leonard CE, et al. Recent trends in GLP-1 RA and SGLT2i use among people with type 2 diabetes and atherosclerotic cardiovascular disease in the USA. BMJ Open Diabetes Res Care. 2024;12:e004431.
194. Schernthaner G, Shehadeh N, Ametov AS, Bazarova AV, Ebrahimi F, Fasching P, et al. Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. Cardiovasc Diabetol. 2020;19(1):185.
195. Do D, Lee T, Peasah SK, Good CB, Inneh A, Patel U. GLP-1 receptor agonist discontinuation among patients with obesity and/or type 2 diabetes. JAMA Netw Open. 2024;7:e2413172.
196. Dellgren JL, Persad G, Emanuel EJ. International coverage of GLP-1 receptor agonists: a review and ethical analysis of discordant approaches. Lancet. 2024;404:902-6.