GLP-1 receptor Analogs

Cardiovascular & Renal

Benefits

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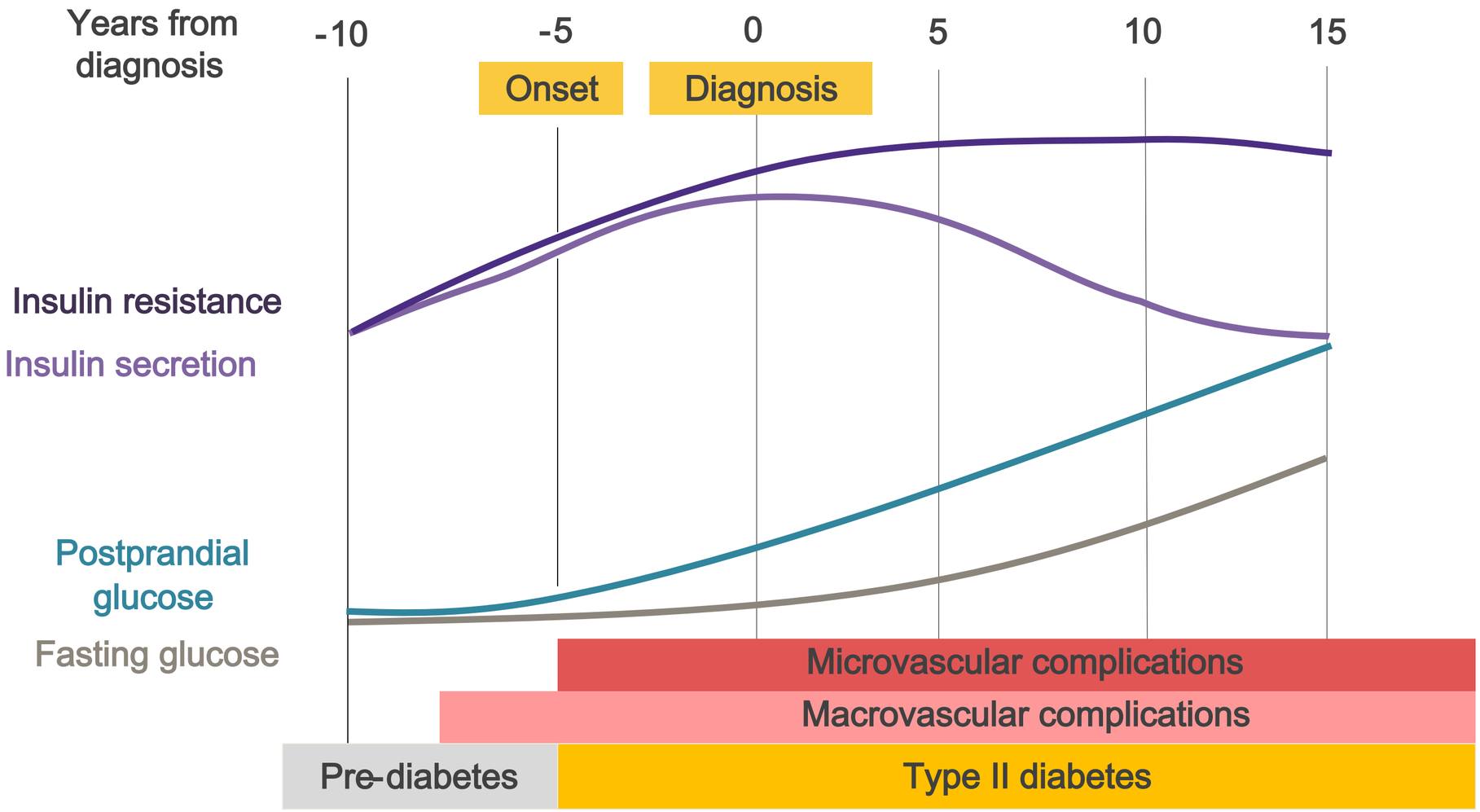
Objectives

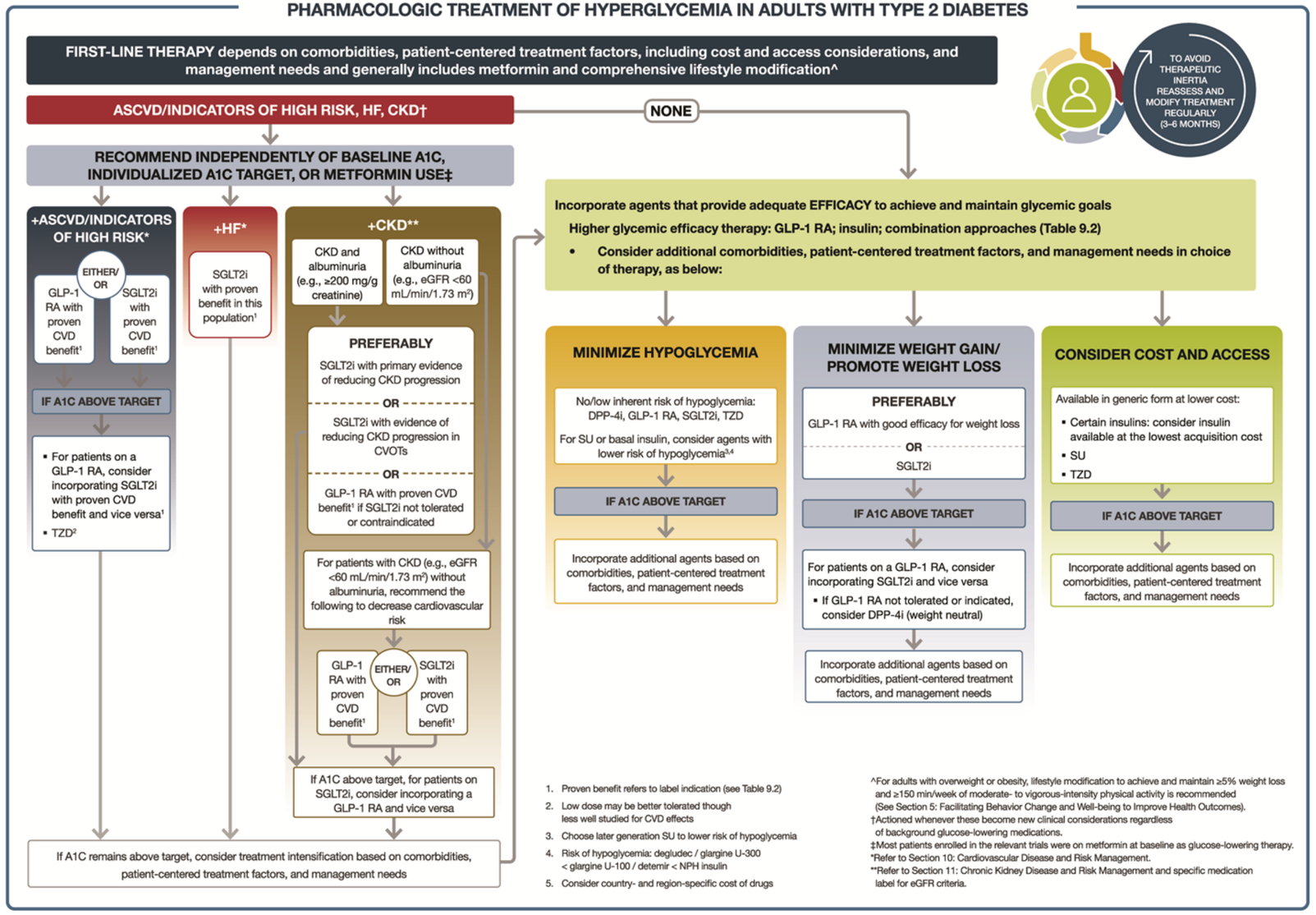
- Understand the mechanism of action of incretin-based treatment with, glucagon-like peptide- 1 receptor agonist (GLP-1 RA)
- Understand efficacy, benefits on the cardiovascular and renal system, and potential adverse effects of various drugs belonging to the class of GLP- 1 RA

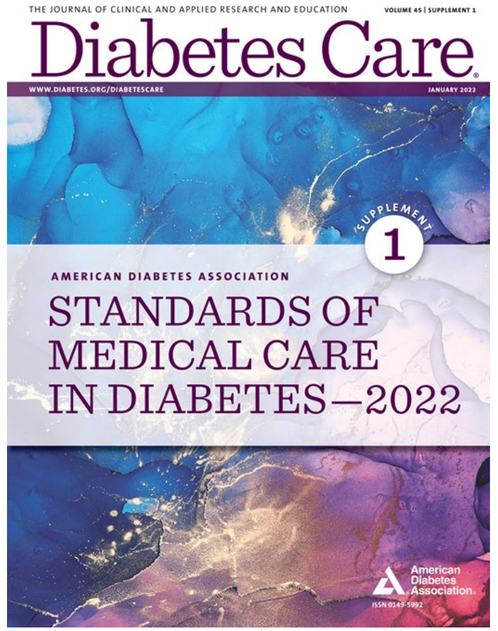
Natural History of Type II Diabetes Mellitus



Sources:
Ramlo-Halsted BA et al. *Prim Care.* 1999;26:771 -789
Nathan DM et al. *NEJM* 2002;347:1342 -1349

Type 2 Diabetes Treatment Algorithm 2022



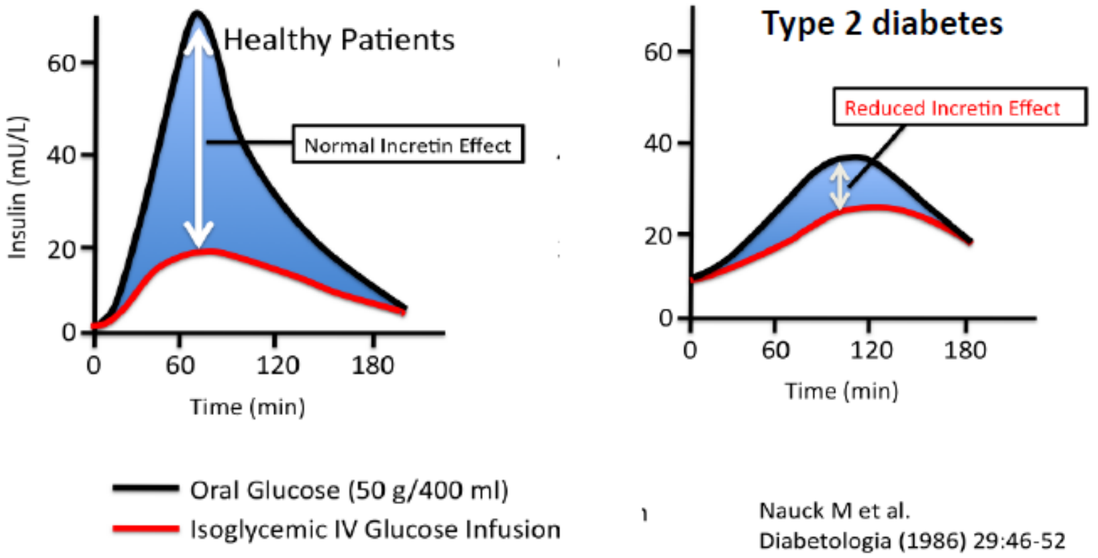


Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2022. Diabetes Care 45: S125-143*

GLP-1 receptor agonist

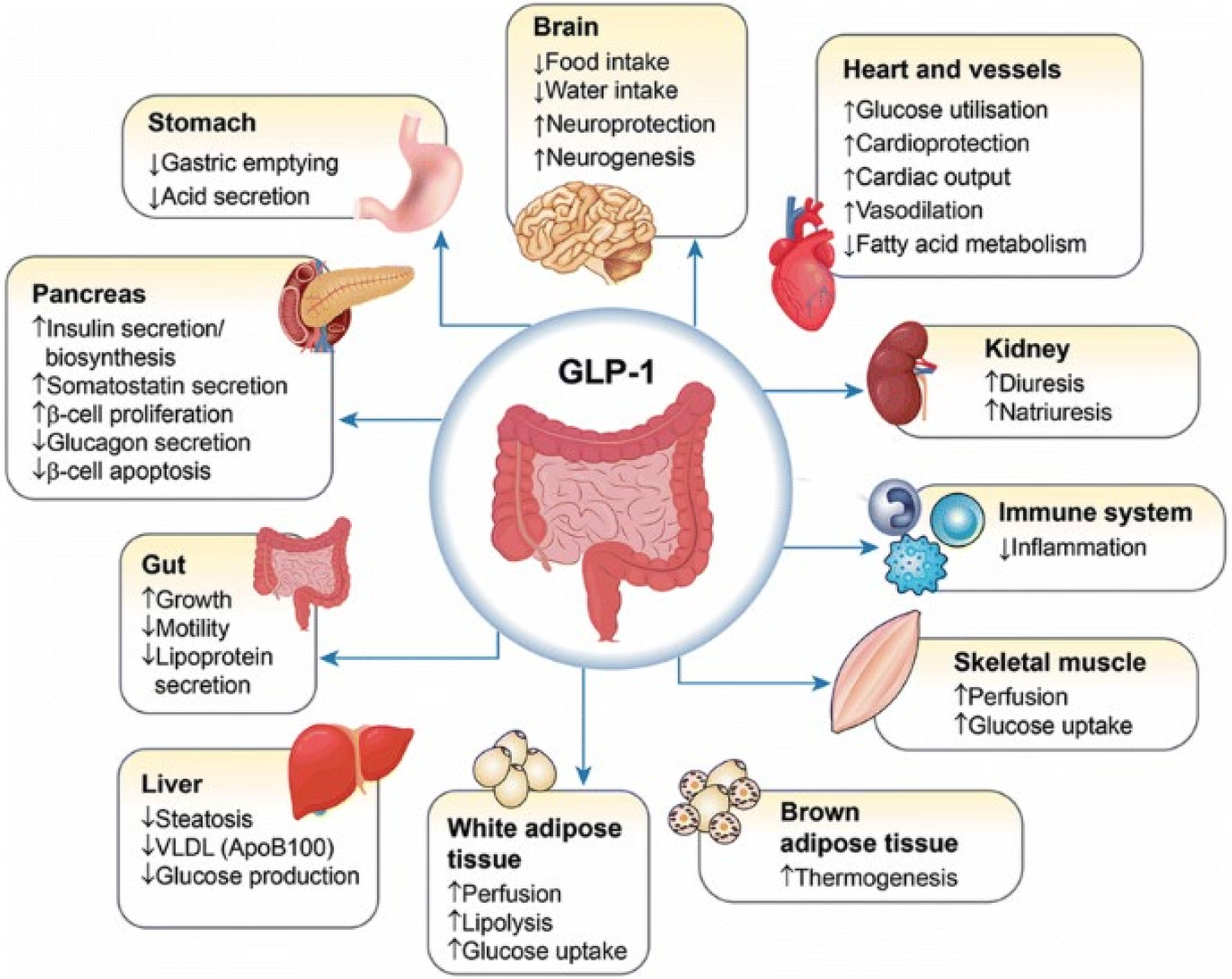
- Belong to the family of Incretin hormones
  - Glucagon like peptide 1 (GLP- 1) - from L cells and colon
  - Glucose Dependent Insulinotropic Peptide (GIP) from K cells in the small intestines
- They have the ability to glucose dependently augment insulin secretory response during periods of hyperglycemia

Incretin Effect: This is the phenomenon whereby in healthy individuals, oral glucose elicits higher insulin secretory responses than intravenous glucose despite inducing similar levels of glycemia



Nauck M et al. Diabetologia (1986) 29:46-52

Action of GLP-1



GLP-1 RA approved as of 2020 to treat type 2 DM

GLP-1 RA	First approved (date)	Molecular weight (Da)[c]	Reference amino acid sequence	Other important components	Elimination half-life	Administration schedule	Pharmaceutical company
For subcutaneous injection							
Short-acting compounds							
Exenatide b.i.d.	2005 (USA); 2006 (Europe); Byetta	4186.6	Exendin-4	None	3.3–4.0 h	Twice daily	AstraZeneca[i]
Lixisenatide	2013 (Europe); Lyxumia; 2016 (USA); Adlyxin	4858.5	Exendin-4	Poly-lysine tail	2.6 h	Once daily	Sanofi
Long-acting compounds/preparations							
Liraglutide	2009 (Europe); 2010 (USA); Victoza	3751.2	Mammalian GLP-1	Free fatty acid[e]	12.6–14.3 h	Once daily	Novo Nordisk
Once-weekly exenatide	2012; BYDUREON[a]	4186.6	Exendin-4	Active ingredient encapsulated in microspheres of poly-(D,L-lactide-co-glycolide)	3.3–4.0 h[f]	Once weekly	AstraZeneca[i]
Dulaglutide	2014; Trulicity	59670.6	Mammalian GLP-1	Immunoglobulin Fc fragment	4.7–5.5 d	Once weekly	Eli Lilly and Company
Albiglutide	2014 (Europe); Eperzan Tanzeum (USA)[b]	72971.3	Mammalian GLP-1	Albumin	5.7–6.8 d	Once weekly	GlaxoSmithKline
Semaglutide	2017 (USA); 2019 (Europe); Ozempic	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7–6.7 d	Once weekly	Novo Nordisk
For oral administration							
Semaglutide (long-acting)	2020; Rybelsus	4113.6	Mammalian GLP-1	Free fatty acid[e]	5.7–6.7 d	Once daily	Novo Nordisk
Fixed-dose combinations							
With basal insulin (for subcutaneous injection)							
Liraglutide/ insulin degludec (iDegLira)	2014 (Europe); 2016 (USA); Xultophy	3751.2[d]	Mammalian GLP-1	Basal insulin	12.6–14.3 h	Once daily (anytime[g])	Novo Nordisk
Lixisenatide/ insulin glargine (iGlarLixi)	2016 (USA); Soliqua 100/33; 2017 (Europe); Suliqua	4858.5[d]	Exendin-4	Basal Insulin	2.6 h	Once daily[h]	Sanofi

[a] Improved once-weekly auto-injector BYDUREON BCise was approved in 2018.
[b] Marketing was discontinued in 2018.
[c] Mammalian GLP-1: 3297.7.
[d] For the GLP-1 RA component only.
[e] Promoting binding to albumin.
[f] Identical to the short-acting preparation.
[g] Approximately the same time every day.
[h] Before meals with the highest expected glycemic excursion.
[i] Previously Amylin Pharmaceuticals, Eli Lilly and Company, and Bristol Myers Squibb.

Nauck MA et al Mol Metab 2021 April ; 46:101102

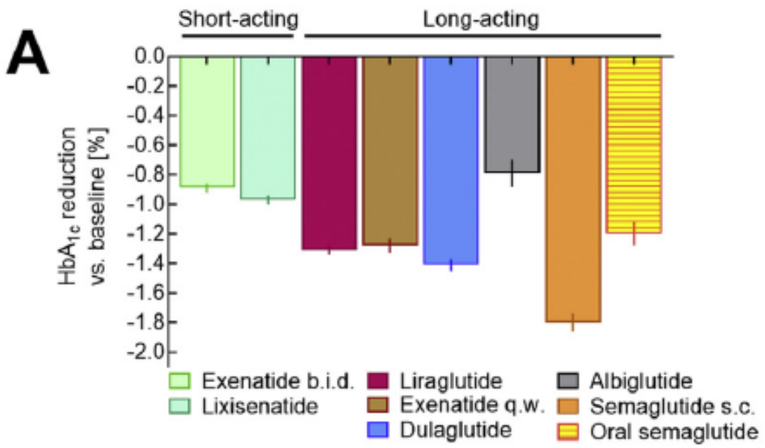
GLP-1 Receptor Agonist in the treatment of T2 DM

	GLP-1 receptor agonists								Fixed-dose combinations (GLP-1 RA/basal insulin)	
Pen devices for injection										
Drug: Generic/ commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon®	Bydureon® BCise	Dulalgutide Trulicity®	Albiglutide Eperzan®/ Tanzeum®	Semaglutide Ozempic®	iDegLira Xultophy®	iGlarLixi Soliqua®/ Suliqua®
Single (1) or multiple (x) use?	x	x	x	1	1	1	1	x	x	x
Predefined (p) or variable (v) dosing	p	p	v	p	p	p	p	p	v (for titration)	v (for titration)
Pens available (maximum dose)	a. 5 µg b. 10 µg	a. 10 µg b. 20 µg	a. 0.6 mg b. 1.2 mg c. 1.8 mg	2 mg	2 mg	a. 0.75 mg b. 1.5 mg	a. 30 mg b. 50 mg	a. 0.25 mg b. 0.5 mg c. 1.0 mg	1.8 mg/ iDeg 50 IU per dose	a. 20 µg/iGlar 40 IU per dose or b. 20 µg/iGlar 60 IU per dose
Resuspension necessary?	no	no	no	yes	no*	no	yes	no	no	no
Ease of use	+	+	+	-	(-)	+++	(-)	+	+	+

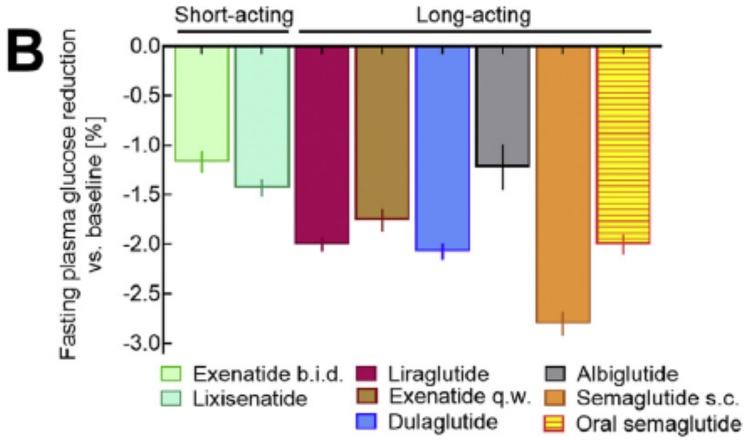
Nauck MA et al Mol Metab 2021 April ; 46:101102

Efficacy of GLP-1 RA

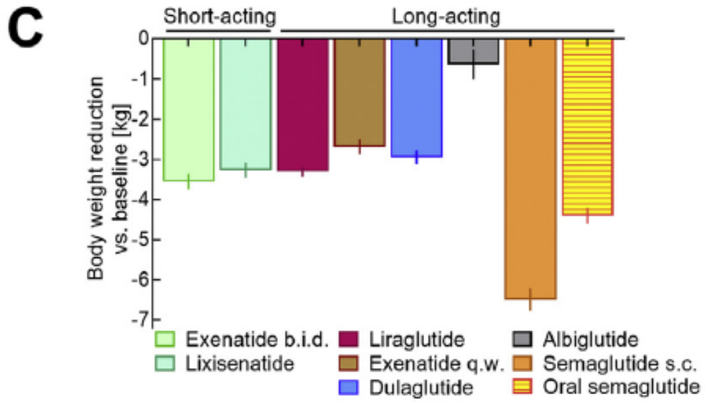
Hemoglobin A1c



Glucose



Weight



Nauck MA et al Mol Metab 2021 April ; 46:101102

Higher dose GLP-1 RA:

Dulaglutide:
The 4.5 mg dose reduced A1C by 1.9% with weight loss of10.4 pounds

Semaglutide:
 The 2mg dose reduce A1C by 2.1% with weight loss of 14.1 pounds

*****Not a direct comparison

Bornora et al (Award-11). Diabetes Obes Metab. 2021 Oct;23(10):2242-2250.
Frias P et al (SUSTAIN FORTE):*Lancet Diabetes Endocrinol*. 2021;9:563-574

GLP-1 receptor agonist: Safety consideration

- Nausea/vomiting/diarrhea – most common side effect
- No signal for pancreatitis or pancreatic cancer
- C cells of the thyroid contain receptors for GLP -1 avoid use in patients at risk of MTC
- ?risk of retinopathy: SQ semaglutide

Cardiovascular outcome trials for GLP-1 RA

Trial/year of Publication	Study drug/ mean follow up (years)	Participants (n)	Age mean (years)	Male sex (n, %)	Participants with established CV disease (n, %)	History of heart failure (n, %)	eGFR <60 ml/min per 1.73 m^2 (n, %)
ELIXA	Lixisenatide	6068	60.3	3174 (69.3%)	6068 (100%)	1922 (20.3%)	1407 (23.2%)
2015	2.1 year						
LEADER	Liraglutide	9340	64.3	6003 (64.3%)	6764 (72.4%)	1667 (17.8%)	2158 (23.1%)
2016	3.8 year						
SUSTAIN-6	Semaglutide	3297	64.6	2002 (60.7%)	2735 (83%)	777 (23.6%)	939 (28.5%)
2016	3.1 year						
EXSCEL	Eenatide OW	14,752	62.0	9149 (62%)	10,792 (73.1%)	2389 (16.2%)	3191 (21.6%)
2017	3.2 year						
HARMONY	Albiglutide	9463	64.1	6569 (69.4%)	9463 (100%)	1922 (20.3%)	NR
2018	1.6 year						
REWIND	Dulaglutide	9901	66.2	5312 (53.7%)	3109 (31.4%)	853 (8.6%)	2199 (22.2%)
2019	5.4 year						
PIONEER 6	Semaglutide	3183	66.0	2176 (68.4%)	2695 (84.7%)	388 (12.2%)	856 (26.8%)
2019	1.3 year						
AMPLITUDE-O	Efpeglenatide	4076	64.5	2732 (67%)	3650 (89.6%)	737 (18.1%)	1287 (31.6%)
2021	1.8 year						

Giugliano et al. *Cardiovasc Diabetol* (2021)20:189

LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)

Study Design

- N=9340 patients with T2D and high CV risk
- Randomization
  - Liraglutide: n=4672
  - Placebo: n=4668
- Noninferiority study: prespecified margin <1.3 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

Key Results

- Median follow-up: 3.5 years
- Difference from placebo at 36 months
  - A1C: −0.40% (95% CI, −0.45% to −0.34%)
  - Weight: −2.3 kg (95% CI, −2.0 to −2.5 kg)
  - SBP: −1.2 mm Hg (95% CI, −0.5 to −1.9 mm Hg)
- CV outcomes
  - Primary: HR 0.87 (95% CI 0.78 to 0.97); *P*=0.01 for superiority
  - Secondary HR: 0.88 (95% CI 0.81 to 0.96); *P*=0.005 for superiority
- Significantly lower rates of all-cause death and CV death with liraglutide
- Increased rates of gastrointestinal events in liraglutide-treated patients
- Lower numerical incidence of pancreatitis in liraglutide group (not statistically significant)

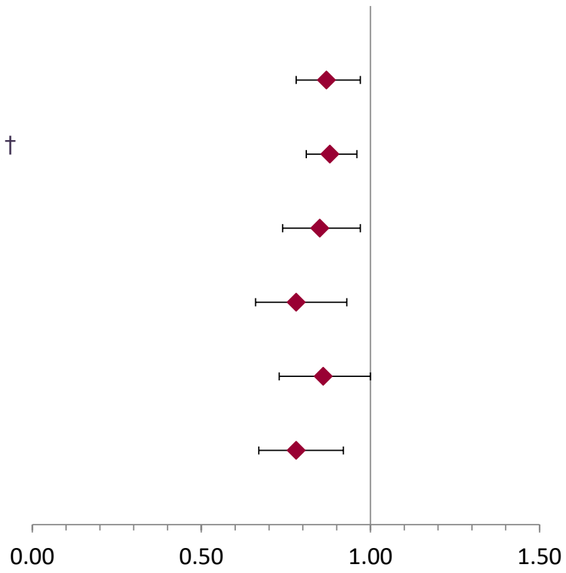
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med* 2016:375:311-322.

Clinical Outcomes with Liraglutide

LEADER (N=9340)

Median follow-up: 3.5 years



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.87 (0.78-0.97)	0.01
Expanded composite endpoint†	0.88 (0.81-0.96)	0.005
Death from any cause	0.85 (0.74 -0.97)	0.02
CV death	0.78 (0.66 -0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73 -1.00)	0.046
Nephropathy	0.78 (0.67 -0.92)	0.003

Favors liraglutide

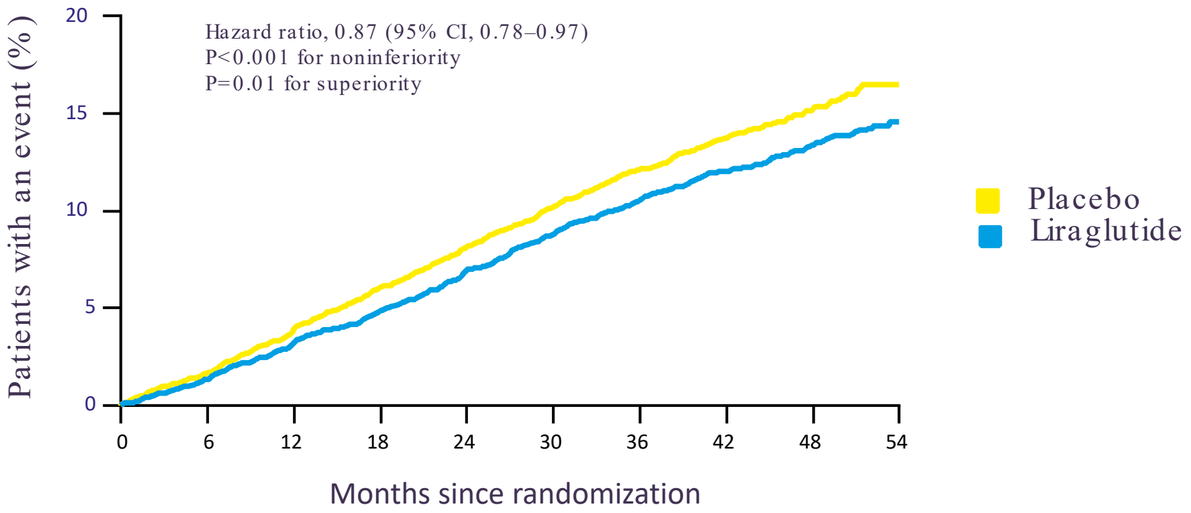
*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

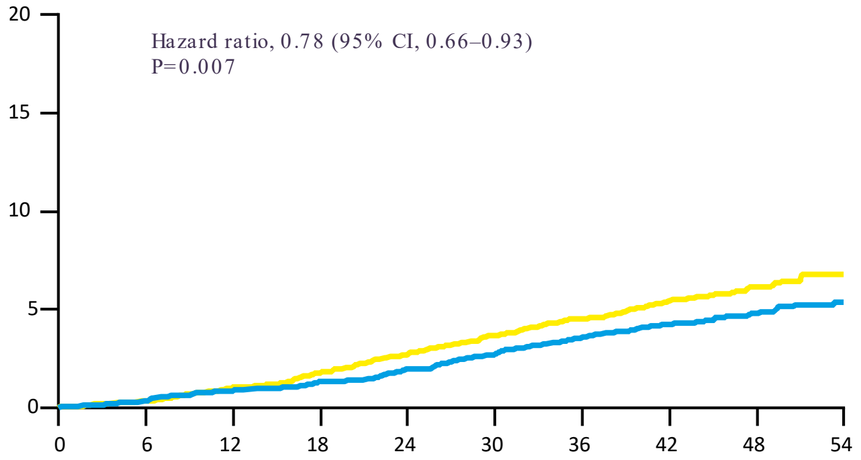
Marso SP, et al. *N Engl J Med* 2016:375:311-322.

LEADER Trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time -to-event analysis in patients with type 2 diabetes and high CV risk.



Death from Cardiovascular Causes



Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP *et al.,* NEJM 2016

Clinical Outcomes with Semaglutide

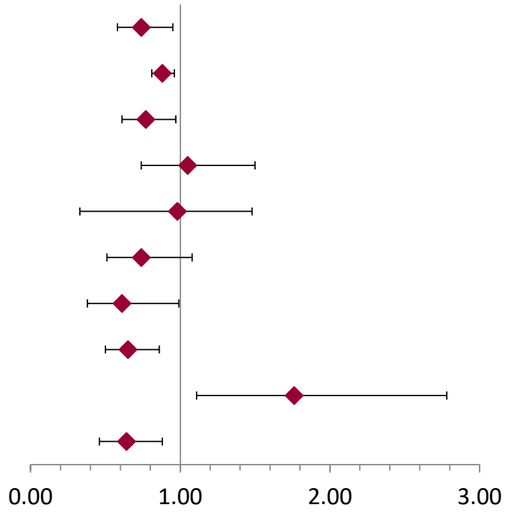
- N=3297 patients with T2D with CVD, CHF, CKD, or age ≥60 with ≥1 CV risk factor
- Randomization
  - Semaglutide: n=1648
  - Placebo: n=1649
- Noninferiority study: prespecified margin <1.8 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Key secondary endpoints
    - Composite of CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF
    - Composite of all-cause death, nonfatal MI, nonfatal stroke
    - Retinopathy complications
    - New or worsening nephropathy

CI, confidence interval; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

Marso SP, et al. *N Engl J Med* 2016:375:1834-1844.

Clinical Outcomes with Semaglutide

SUSTAIN 6
Results
(N=3297)
Median follow-up: 2.1 years



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.74 (0.58-0.95)	0.02
Expanded composite endpoint†	0.88 (0.81-0.96)	0.002
All-cause death, nonfatal MI, nonfatal stroke	0.77 (0.61 -0.97)	0.03
Death from any cause	1.05 (0.74 -1.50)	0.79
CV death	0.98 (0.65 -1.48)	0.92
Nonfatal MI	0.74 (0.51 -1.08)	0.12
Nonfatal stroke	0.61 (0.38 -0.99)	0.04
Revascularization	0.65 (0.50 -0.86)	0.003
Retinopathy complications	1.76 (1.11 -2.78)	0.02
New or worsening nephropathy	0.64 (0.46 -0.88)	0.005

Favors semaglutide

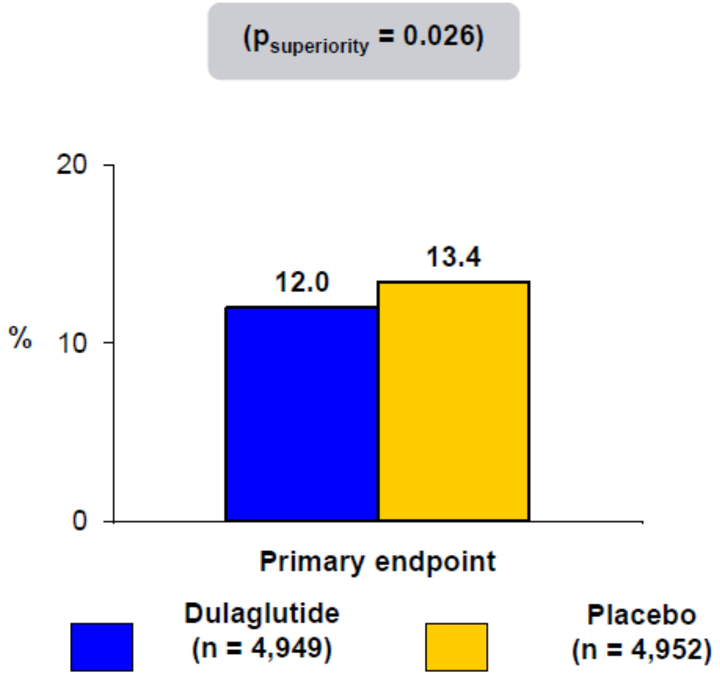
*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med*. 2016:375:1834-1844.

Rewind

Trial Description: Patients with type 2 diabetes mellitus (DM2) and higher cardiovascular (CV) risk were randomized in a 1:1 fashion to either subcutaneous dulaglutide 1.5 mg once weekly or matching placebo. They were followed for 5.4 years.



RESULTS

- Primary endpoint, CV death, MI, or stroke, for dulaglutide vs. placebo: 12.0% vs. 13.4%, $p_{superiority}$ = 0.026; CV death: 6.4% vs. 7.0% (p = 0.21); nonfatal MI: 4.1% vs. 4.3% (p = 0.65); nonfatal stroke: 2.7% vs. 3.5% (p = 0.017)
- CHF hospitalization/urgent visit: 4.3% vs. 4.6% (p = 0.46); composite microvascular outcome (eye or kidney): 18.4% vs. 20.6% (p = 0.002)
- Composite renal outcome: 17.1% vs. 19.6% (p = 0.0004)

CONCLUSIONS

- Dulaglutide (GLP-1 agonist) is superior to placebo in improving glycemic control and ↓ CV events (particularly stroke) in patients with DM2 and higher CV risk
- These are really important findings and suggest that dulaglutide may need to be considered for the management of DM2 in similar high-risk patients going forward

Gerstein HC, et al. Lancet 2019;Jun 9:[Epub]

Pioneer 6: Oral Semaglutide

- Participants: 50 years or older with CVD or CKD or 60 years or older with risk factors
- Randomization: 1:1 14 mg of drug or placebo
- Total number of participants: 3183
- Duration of study 15.9 months
- Baseline A1c 8.2%
- Primary outcome: time from randomization to the first occurrence of death from CV causes, nonfatal MI or non-fatal stroke

N Engl J Med 2019;381:841-51.

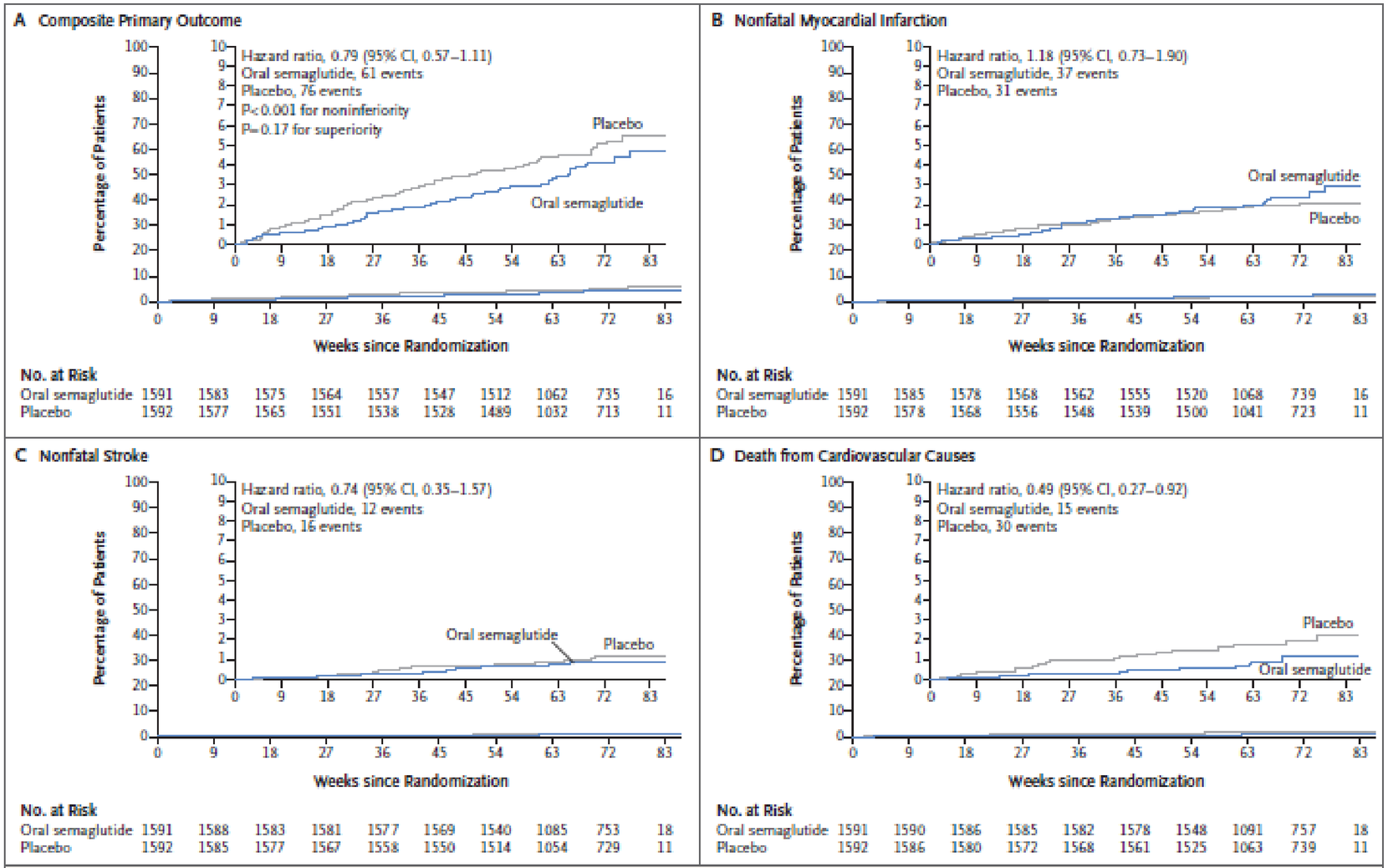


Figure 1. Cardiovascular Outcomes.

Shown are cumulative-incidence plots for the primary outcome (first major adverse cardiovascular events, representing a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). Cumulative-incidence estimates are based on time from randomization to first event confirmed by the event-adjudication committee, with death from noncardiovascular causes (Panels A and D) or death from any cause modeled as competing risks. Data for patients were censored at the end of the in-trial observation period (from randomization to the final follow-up visit). Deaths from cardiovascular causes included deaths for which the cause was undetermined. The analysis for confirmation of noninferiority was controlled for multiple comparisons; P values and confidence intervals for other analyses have not been adjusted for multiple comparisons. The insets show the same data on an expanded y axis. CI denotes confidence interval.

3.8 vs 4.8 in placebo vs primary outcome (p=0.17)

Meta-analysis of CVOT with GLP-1 RA on MACE

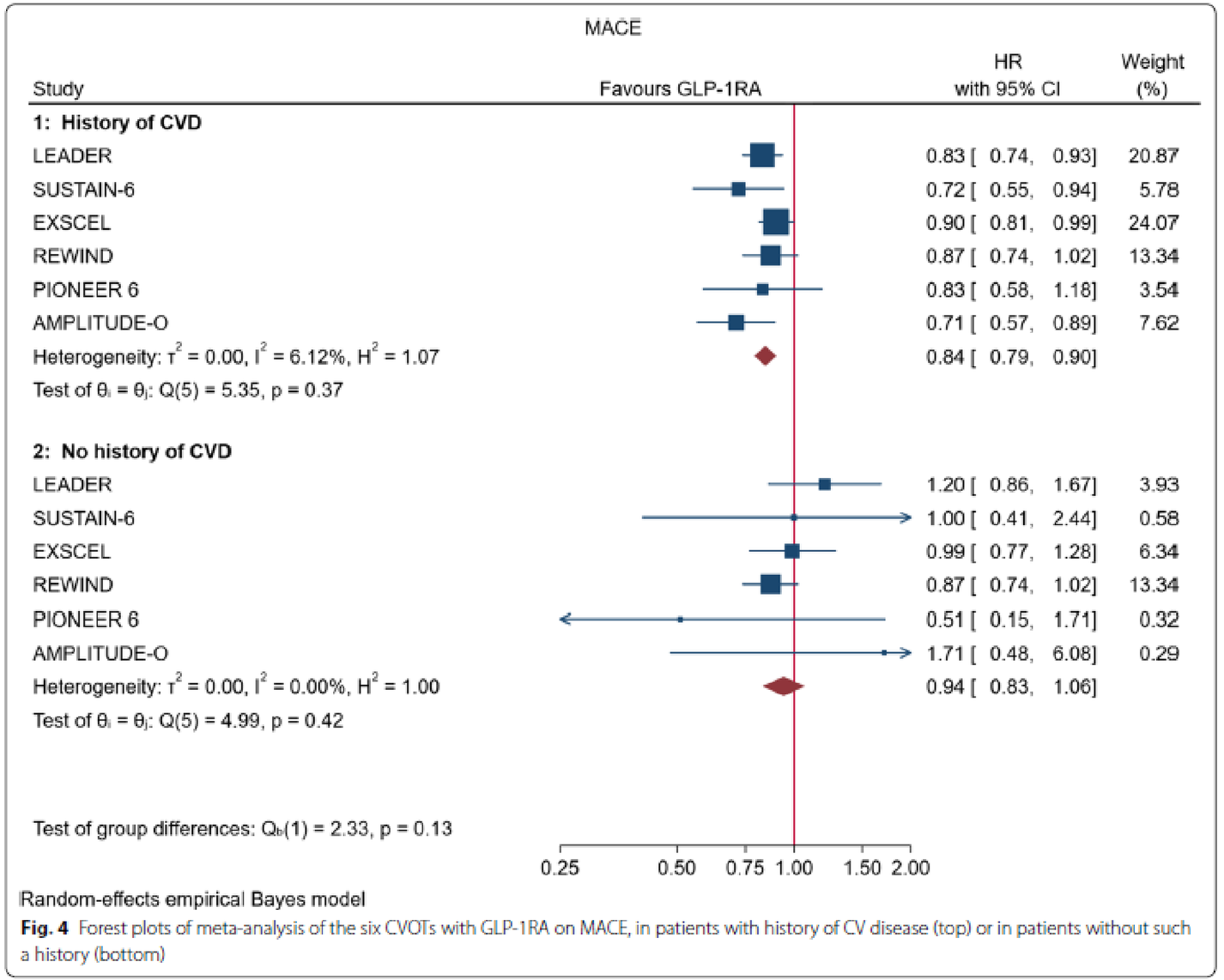


Fig. 4 Forest plots of meta-analysis of the six CVOTs with GLP-1RA on MACE, in patients with history of CV disease (top) or in patients without such a history (bottom)

Meta-analysis of CVOT with GLP-1 RA on renal endpoint

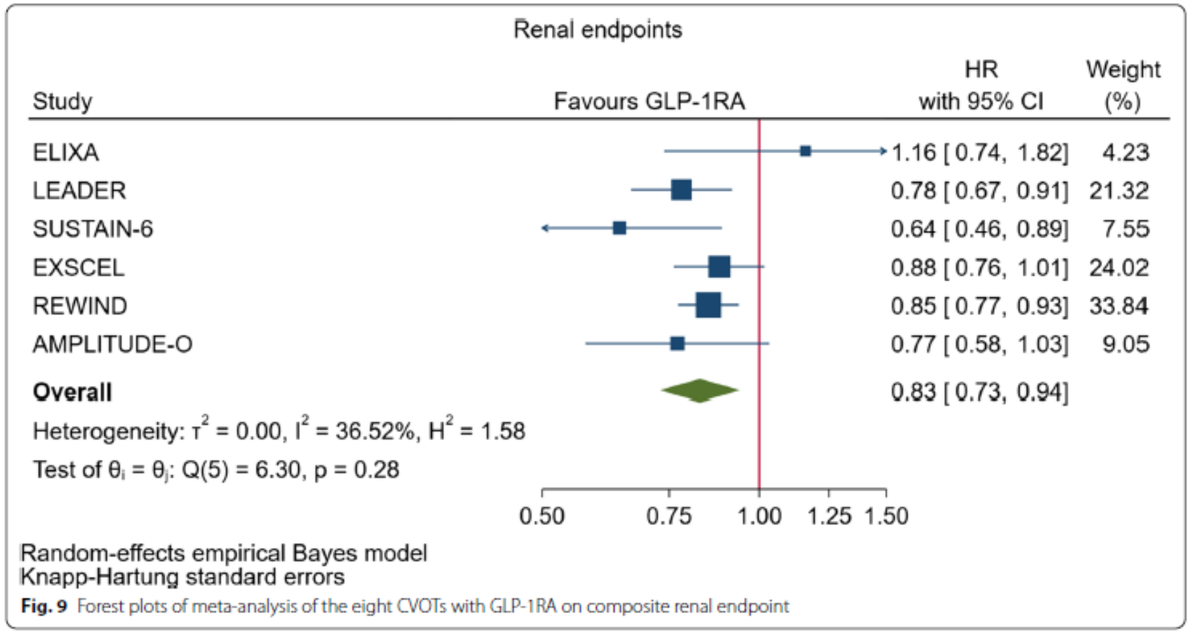


Fig. 9 Forest plots of meta-analysis of the eight CVOTs with GLP-1RA on composite renal endpoint

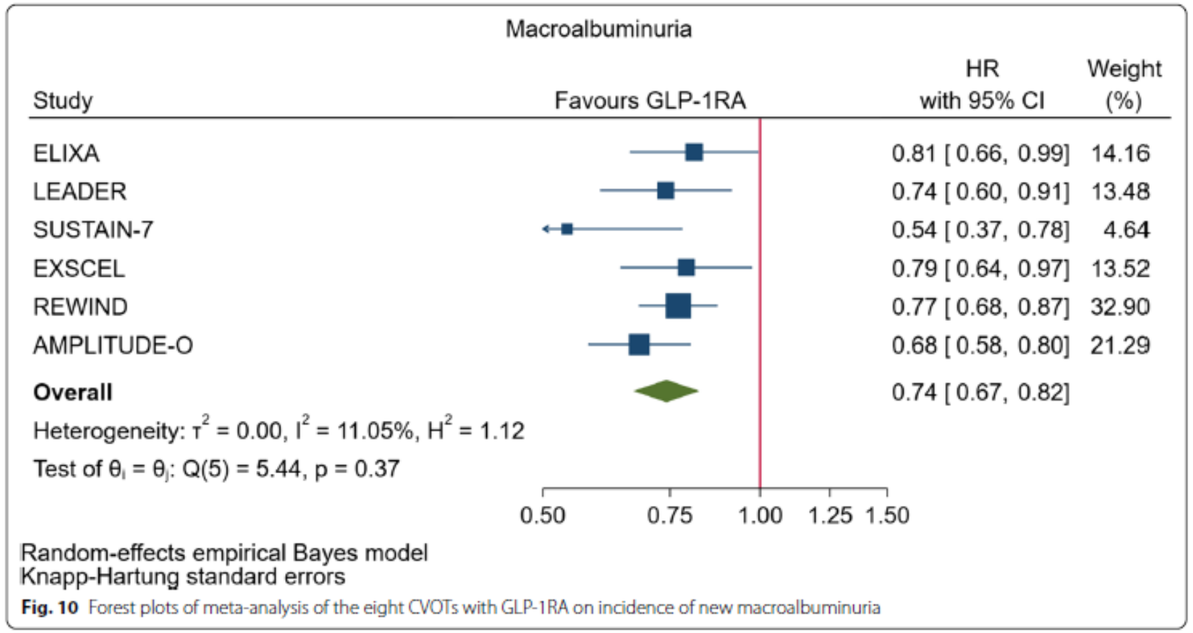


Fig. 10 Forest plots of meta-analysis of the eight CVOTs with GLP-1RA on incidence of new macroalbuminuria

Kidney effect from CVOT

- LEADER: (Liraglutide)
  - Fewer nephropathy events for liraglutide compared to placebo
- SUSTAIN – 6 (Semaglutide)
  - Fewer new or worsening nephropathy
- REWIND (Dulaglutide)
  - Significantly fewer adverse renal outcomes
- ELIXA (Lixisenatide)
  - Non significant reduction in percentage change to urninary albumin to creatinine ratio
- HARMONY (Albuglutide) , EXCEL (Exenatide QW) and PIONEER 6 (Semaglutide oral) did not assess for renal outcomes

Giugliano et al. Cardiovasc Diabetol (2021) 20:189

SURPASS TRIALS-TIRZAPATIDE

- Tirzepatide – Dual glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 receptor (GLP -1) agonist (aka twincretin)
- Tirzepatide showed mean A1c reduction of up to 2.6% and dose dependent body weight loss between 8 and 14 %
- Tirzepatide was superior to semaglutide in head- to- head comparisons in reducing hemoglobin A1c and body weight, with a similar incidence of GI adverse effects
- Tirzepatide was also superior to insulin degludec in reducing A1c an body weight with a lower risk of hypoglycemia

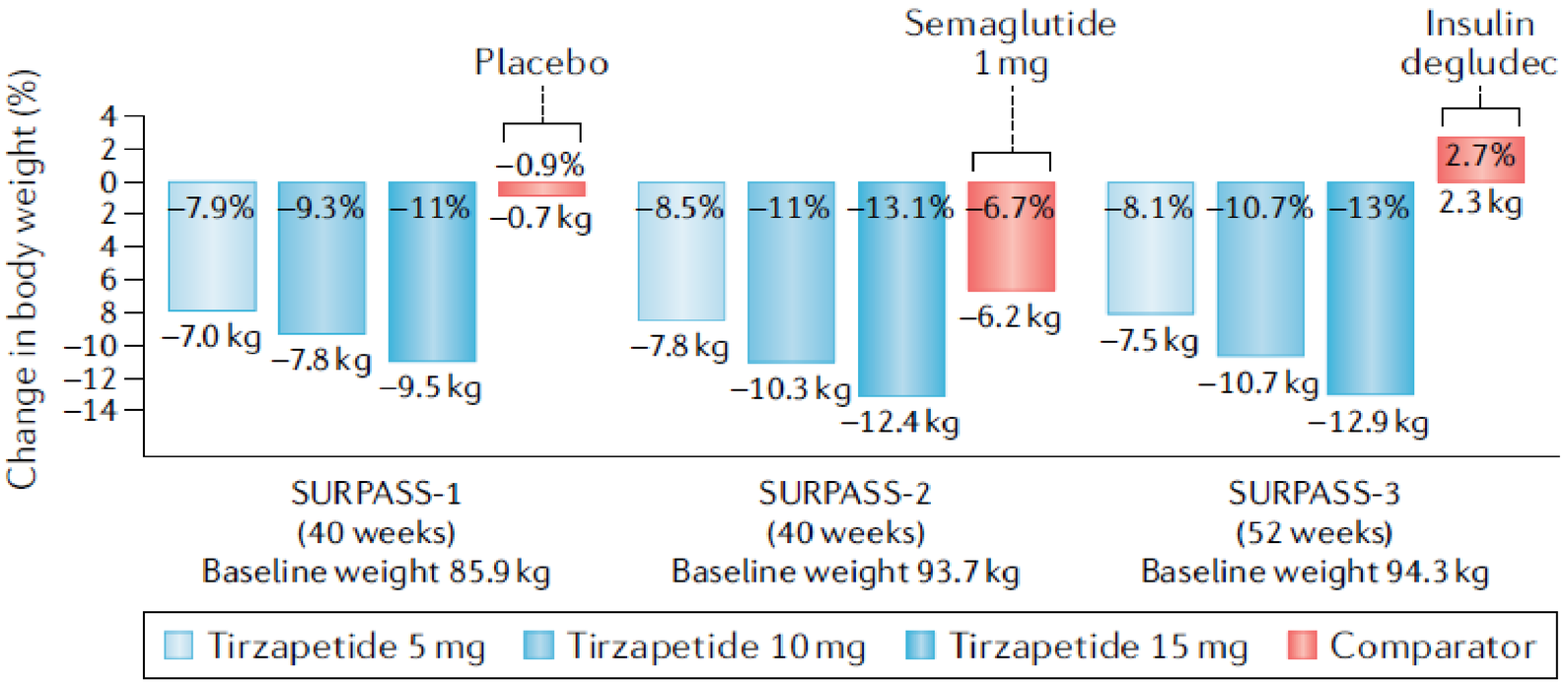


Fig. 1 | **Weight loss with tirzepatide in phase III trials in patients with T2DM.** Percentage change in body weight and absolute weight loss (in kg) in individuals treated with tirzepatide versus comparators: SURPASS-1 (placebo); SURPASS-2 (semaglutide, on background metformin); SURPASS-3 (insulin degludec, on background metformin with or without sodium glucose co-transporter 2 inhibitors). The differences between all tirzepatide groups and their comparators were statistically significant ($P < 0.05$).

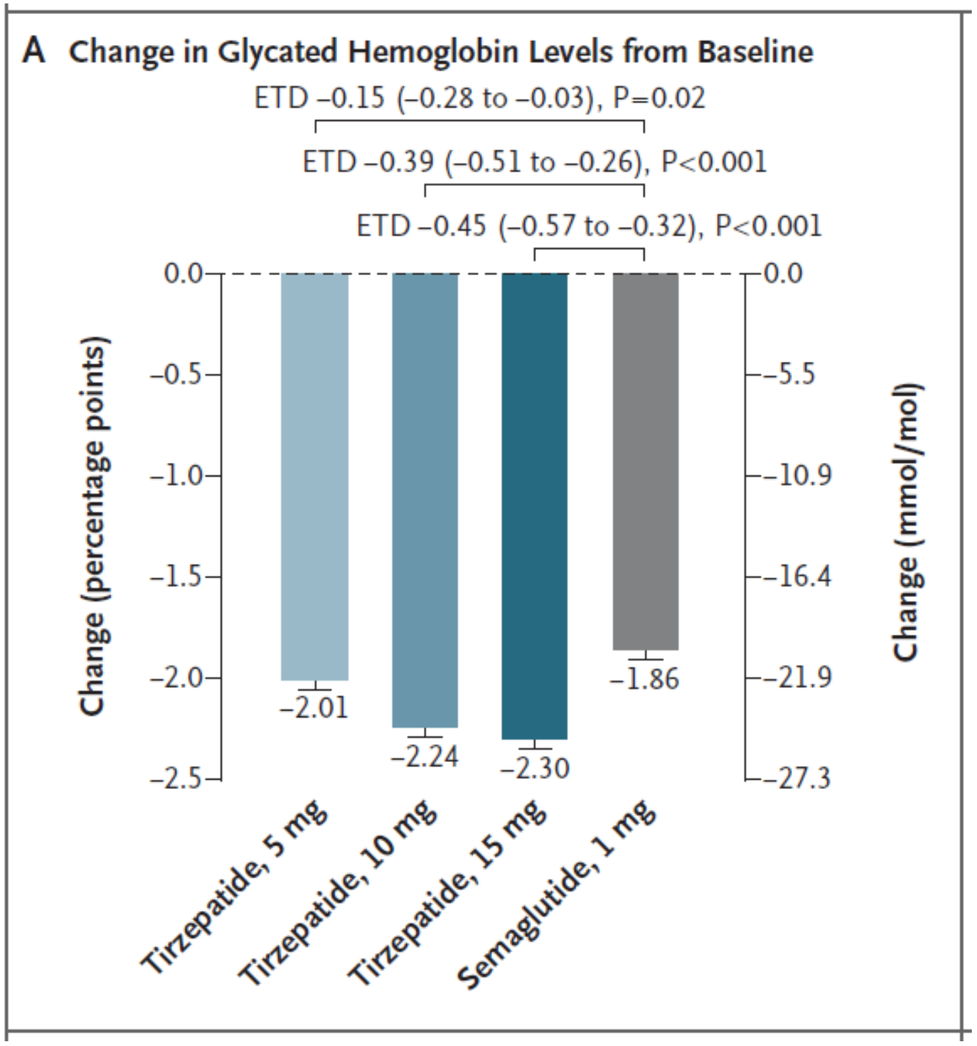
The NEW ENGLAND JOURNAL of MEDICINE

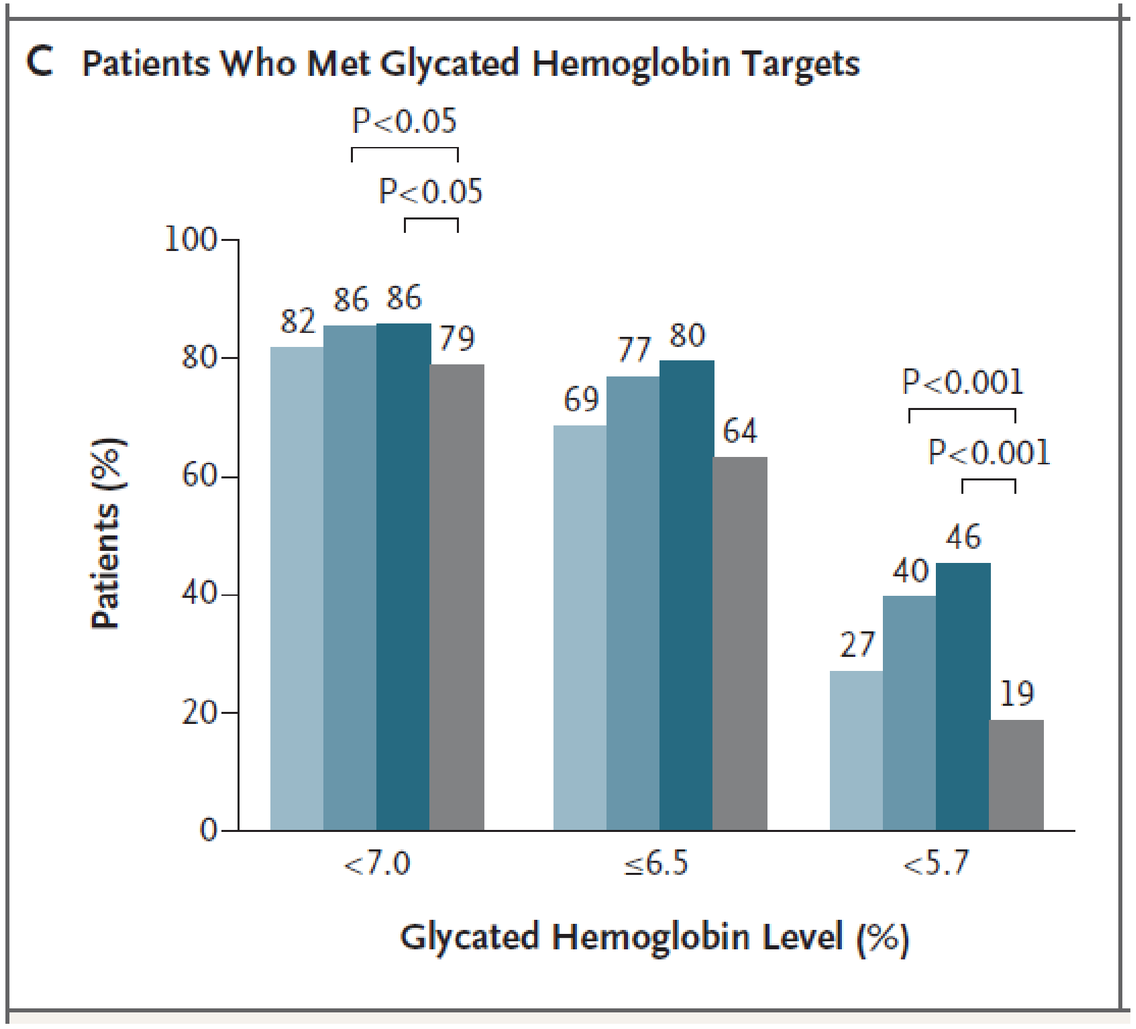
ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

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

Tirzepartide: dual glucose-dependent insulinotropic polypeptide GIP–GLP-1 receptor agonist





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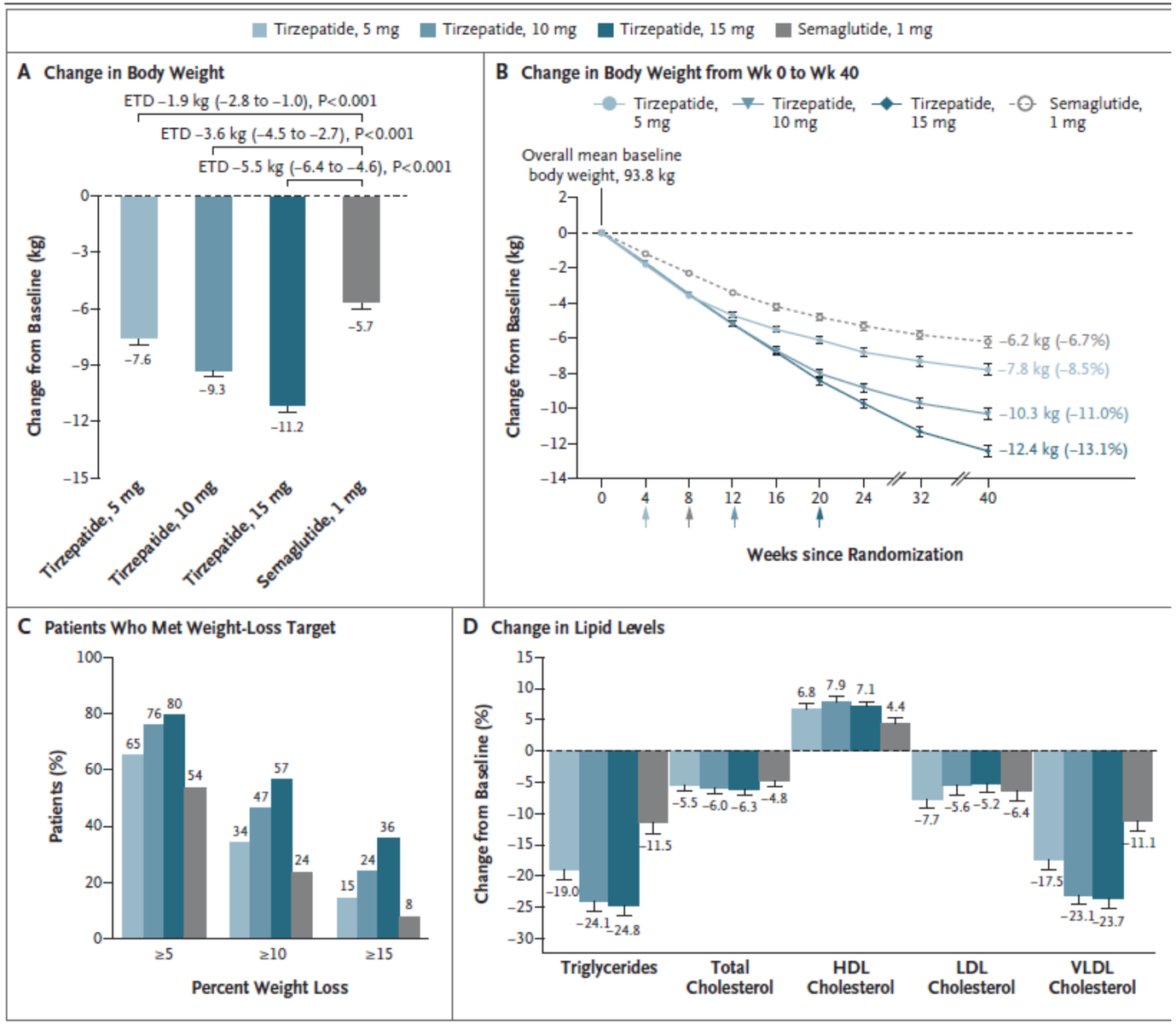

FDA approves Lilly's Mounjaro™(tirzepatide) injection, the first and only GIP and GLP-1 receptor agonist for the treatment of adults with type 2 diabetes

May 13, 2022

Take home points

- GLP-1 RA is generally effective and well-tolerated
- Reduces the risk of MACE in persons with diabetes, with the highest effect in persons with known risk of CVD compared with those without
- GLP1 –RA reduced the risk of kidney disease by causing a reduction in macro albuminuria
- Cardio renal benefits may be mediated by their effect on A1c, BP, and other CV risk factors
- Most common side effect - gastrointestinal
- New GIP/GLP-1 RA agonist - even more A1c lowering , weight loss improvement in metabolic profile

Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

Presentation Date: June 1st, 2022 **Presenter name:** Grant Bludorn, DO
Presenter Facility: Sea Mar Community Health Clinic

Case Report Recap: Pt is a 58 y/o female with history of type 2 diabetes, BMI 37 (wt 209) hypercholesterolemia, hypothyroidism, PTSD, Asthma, and previously well controlled A1c (5.5-6.4%) that is now 9.3%, presented to establish care. Previously had been on Bydureon up until 6 months ago.

Current Medication(s) (including dose frequency):

Medication	Dose	Frequency
Glipizide XL	10mg	Once daily
Rosuvastatin	20mg	Once daily
Levothyroxine	125mcg	Once daily
Quetiapine	300mg	QHS
Advair Discus	250-50 mcg/act	One puff BID
Albuterol	90mcg/act	PRN(has not used in over 1 year)
Citalopram	40mg	daily

Case Recommendations:

1. Continue to work on portion control. If there are no concerns for disordered eating, consider having patient track foods in a journal or app like My fitness pal. The goal would be to reduce total daily calories by about 500 calories. Consider referral to a nutritionist.
2. Monitor steps to increase activity. Obesity Medicine Association guidelines recommends at least 5,000 steps per day.
3. Consider replacing quetiapine with alternative sleep aid such as trazadone in partnership with mental health provider. If pt must stay on quetiapine consider adding topiramate in partnership with mental health provider.
4. Start liraglutide 0.6mg with increase over 3-4 weeks to goal 1.8mg daily and monitor. If not at A1c goal <7.0 in 3 months, convert to exenatide 10 mcg bid and monitor for ability to take. If barrier given timing, place pre-authorization for weekly GLP-1 RA. Once on Liraglutide at 1.8 mg, stop glipizide (since this causes weight gain) and replace with low dose metformin 500 mg XR daily with increase every 10 days if no loose stools/GI issues.
5. Maximize Rosuvastatin 40 mg, but likely need to add ezetimibe for optimal <70 LDL goal.
6. Consider Ace or arb if blood pressure remains about 120/80 after weight loss.
7. Monitor triglycerides. No indication for therapy at this time.
8. No indication for ASA therapy.
9. Evaluate pt with STOP BANG questionnaire to screen for sleep apnea. Refer for sleep study if positive screen.
10. Since this pt has type 2 diabetes, consider early referral for bariatric/metabolic surgery since this surgery is also a treatment for type 2 diabetes. Do not refer if pt is smoking. You will need to do a prior authorization with insurance.

Nicole Ehrhardt, MD

_____*Nicole Ehrhardt* ____

Physician Signature Nicole Ehrhardt
Represent case July 2022