GLP-1 Agonists /DPP-4 Inhibitors

Their Place in Type 2 Diabetes Treatment

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Disclosure

I have no actual or potential conflict of interest in relation to this program

Agenda

- Case presentation
- Incretin Effect
- GLP1 Agonists
- CVOTS Trials
- DPP4Is
- ADA 2023 Guidelines
- Conclusion

Case presentation

- A 58-year-old woman with 12-year history of type 2 diabetes is referred to you. She takes metformin 2000 mg and gliclazide MR 60 mg daily. She respects the diet recommended by the nutritionist.

- She has a history of acute MI during a couple of months ago.

- She claims that in the past, with increasing gliclazide dose, several hypoglycemic episodes had occurred. She fears hypoglycemia because she lives alone.

- BMI: 35.5 kg/m^2

Case presentation

- Laboratory tests:
  - FBS: 146 mg/dl
  - HbA1c: 8.5%
  - Cr: 1.3 mg/dl (eGFR ~ 50 ml/min)

- **Which therapeutic approach would you recommend to her?**

A) Add basal insulin
B) Add Liraglutide
C) Add pioglitazone
D) Add sitagliptin

Case 2

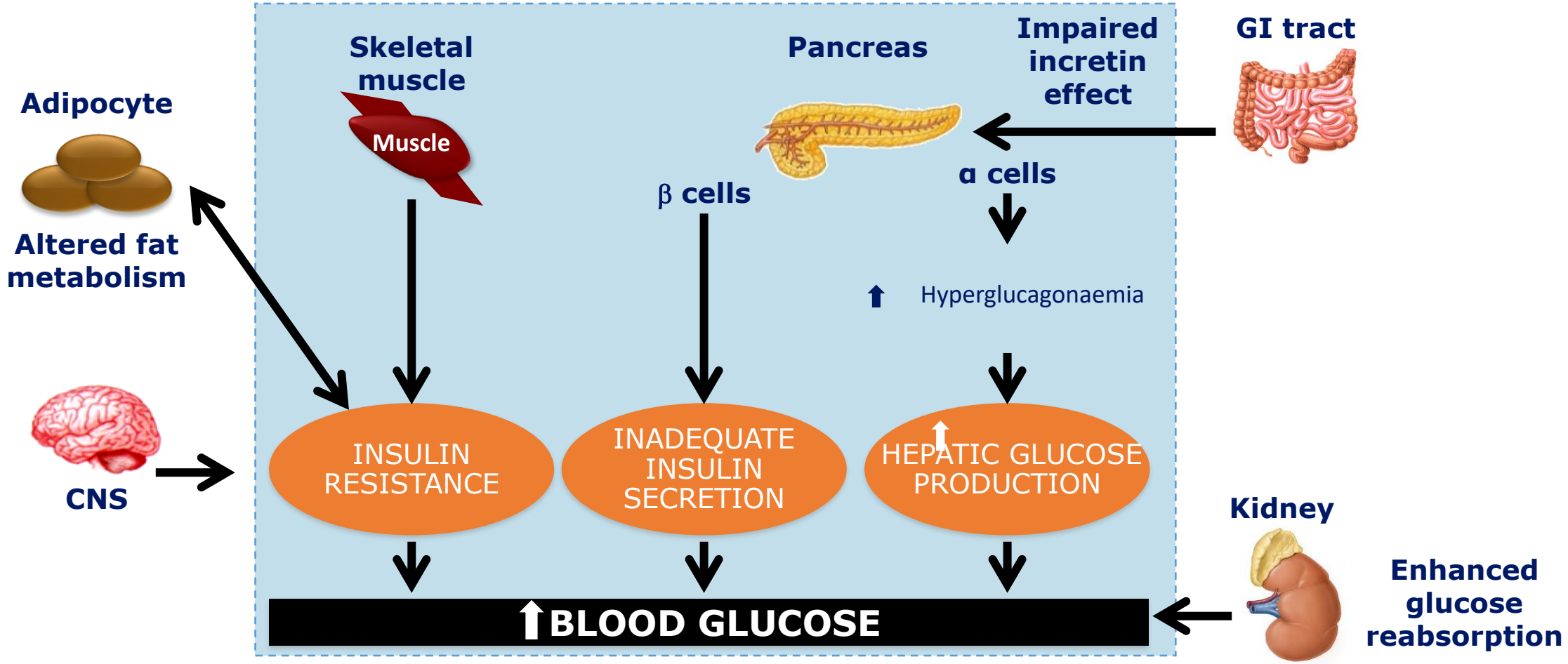
- A 56 years old patients with T2DM and CKD due to APKD is referred to use due to uncontroll DM. 1+ pitting edema is seen in pretibial. He is taking metformin 1000 mg/d
- Lab test results:
- GFR 20
- FBS 130, HBA1C 8.5%
  which is the best medication to control his diabetes?
- Liraglutide
- Sitagliptin 100
- Pioglitazone 15
- Linagliptin 5

Unmet Needs With Conventional Antihyperglycemic Therapies

- Many therapies are associated with weight gain
- Insulin and more conventional oral insulin secretagogue therapies are associated with significant risk for hypoglycemia
- Other adverse effects with some therapies include GI side effects and edema
- Many therapies fail to adequately control postprandial hyperglycemia
- Therapies often fail to maintain long-term glycemic control

Blonde L. *Am J Manag Care*. 2007;13:S36-S40.
Blonde L, et al. *J Manag Care Pharm*. 2006;12(suppl):S2-S12.

Pathophysiology of T2DM



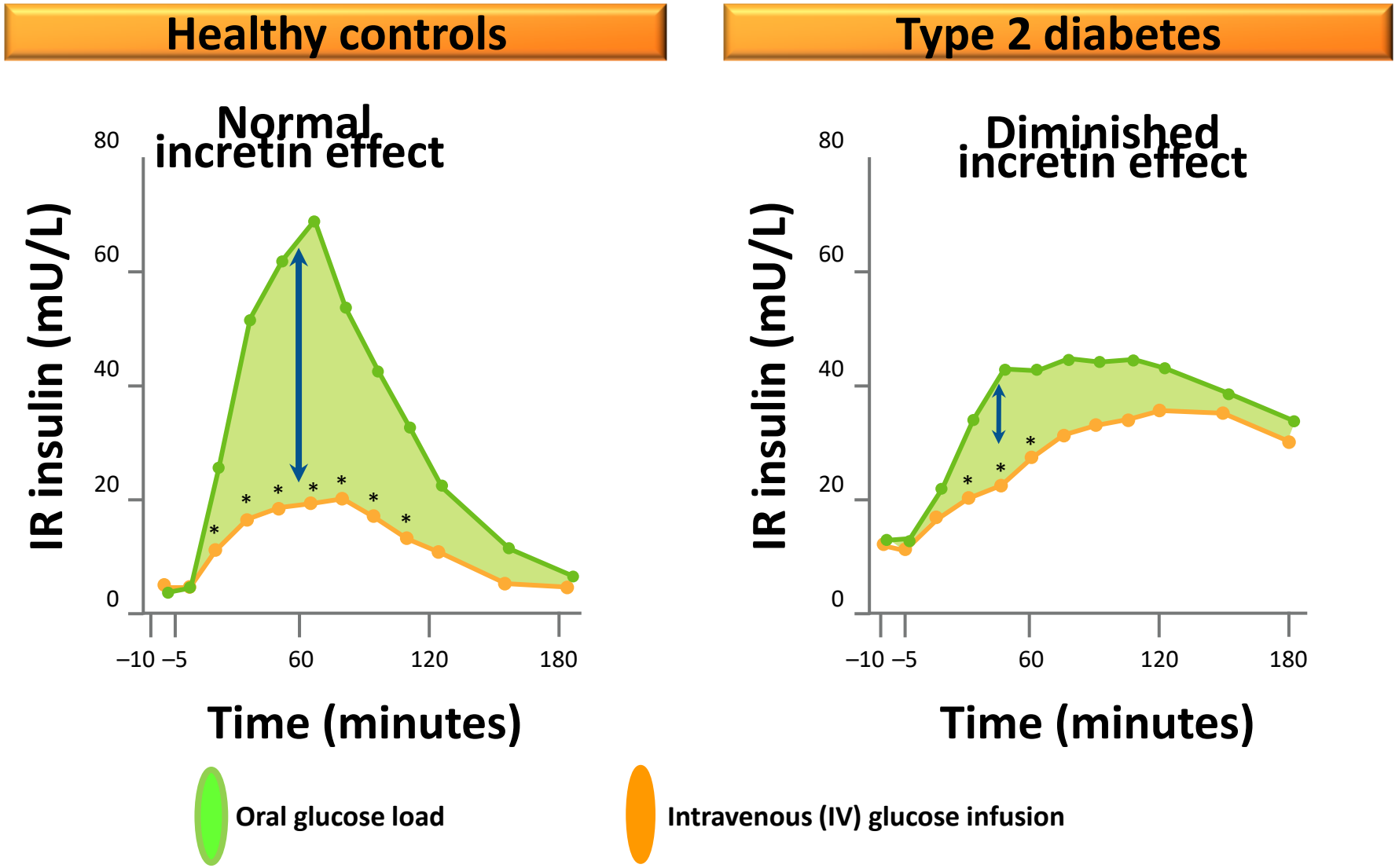
CNS, central nervous system; GI, gastrointestinal; T2DM, type 2 diabetes mellitus

Cernea S & Raz I. *Diabetes Care* 2011;34(suppl 2):S264–S271

INCRETIN Story

INCRETIN= INtestinal+seCRETion of INsulin

The Effect of Incretins in Type 2 Diabetes and Non-Diabetes[1]



1-Diabetologia. 1986 ;29(1):46-52.
IR: Immunoreactive

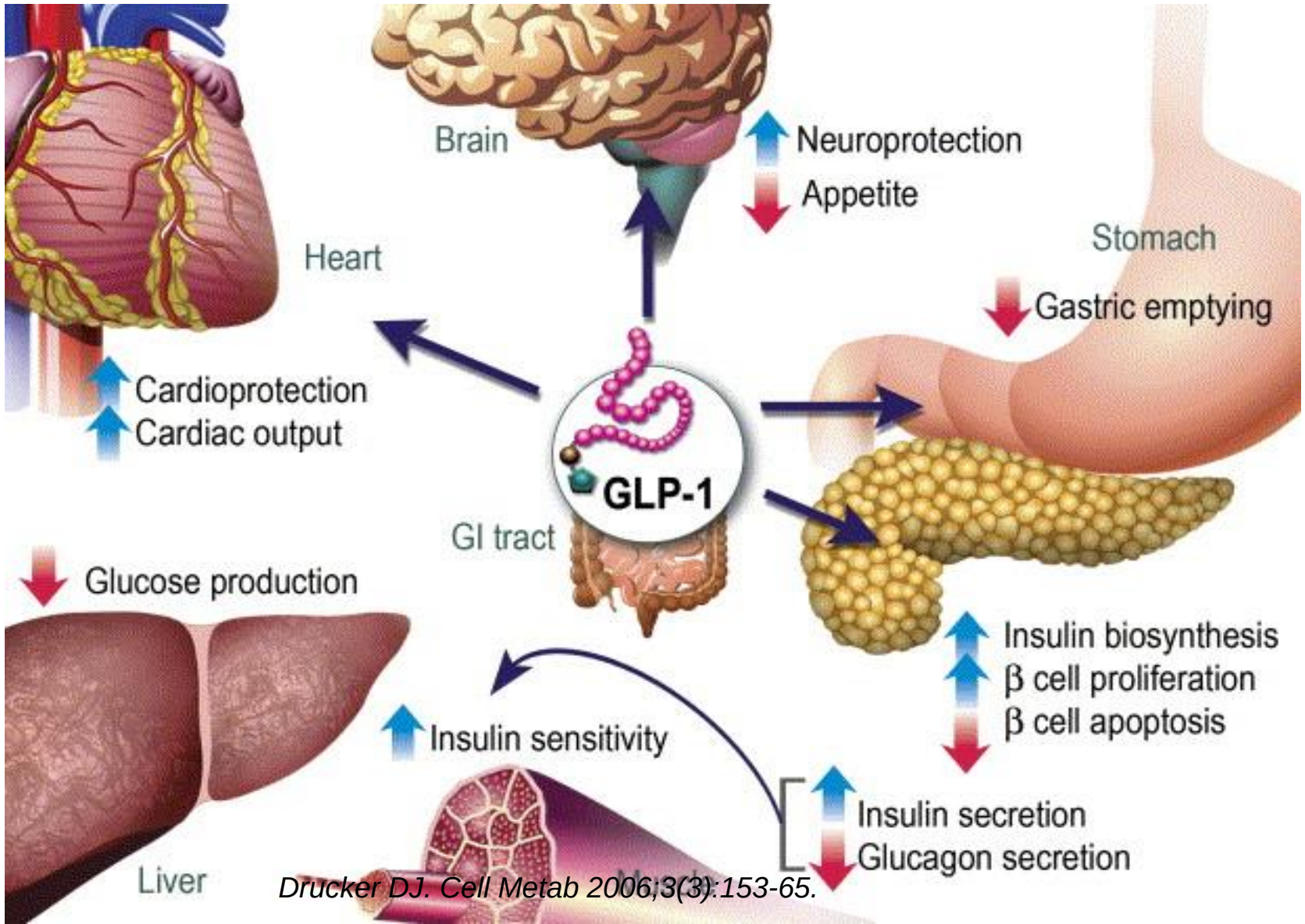
Incretins and DPP-4:

- Incretins: **GLP1** (Glucagon-Like Peptide-1)
  GIP (Glucose-dependent Insulinotropic Polypeptide)

- GLP1 is produced from the proglucagon gene in intestinal L cells and is secreted in response to nutrients.
- **Glucose-dependent mode of action of incretin hormones**

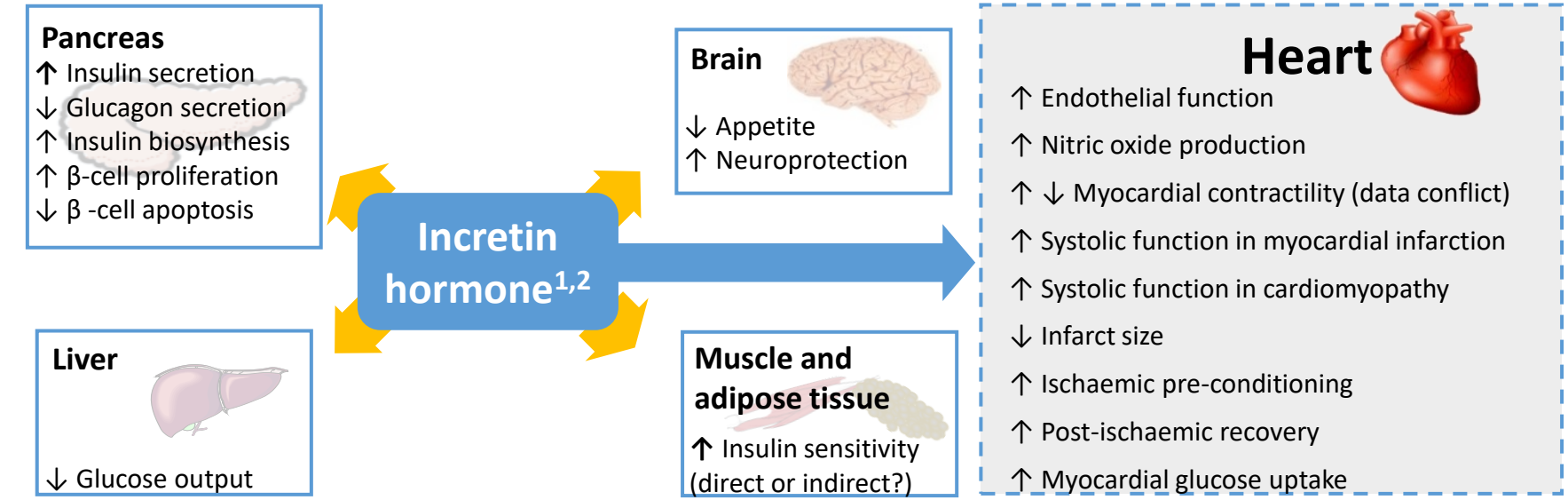
- GLP1 has a very short half-life in plasma (1 to 2 minutes) due to aminoterminal degradation by the enzyme dipeptidyl peptidase IV (DPP4). As a result of DPP-4 activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1.

GLP-1 Actions on Different Target Tissues



Drucker DJ. Cell Metab 2006;3(3):153-65.

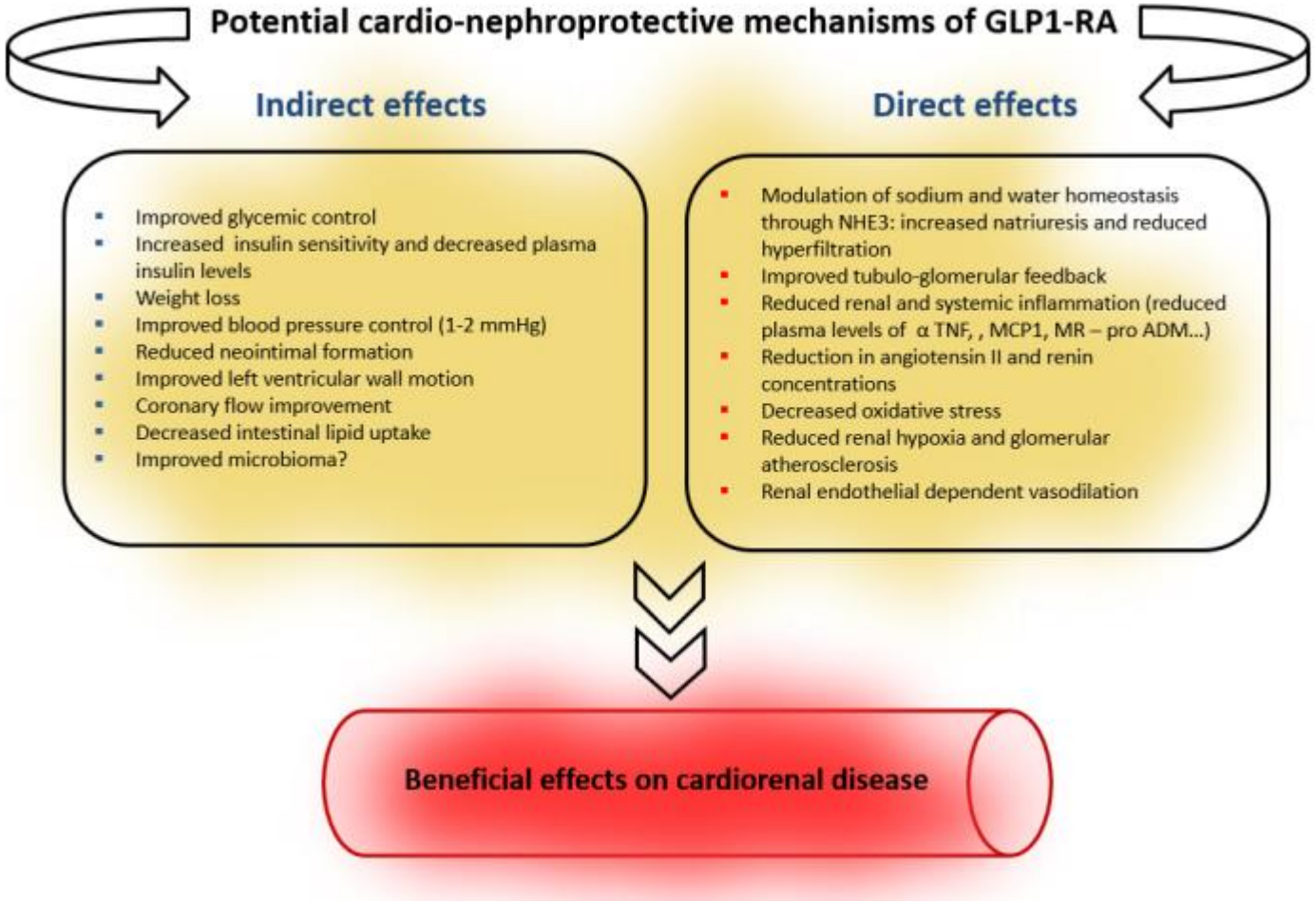
GLP1 has various potential effects on the CV system



Clinical trial data show that GLP1 receptor agonists are associated with small increases in heart rate and modest reductions in body weight and blood pressure[3]

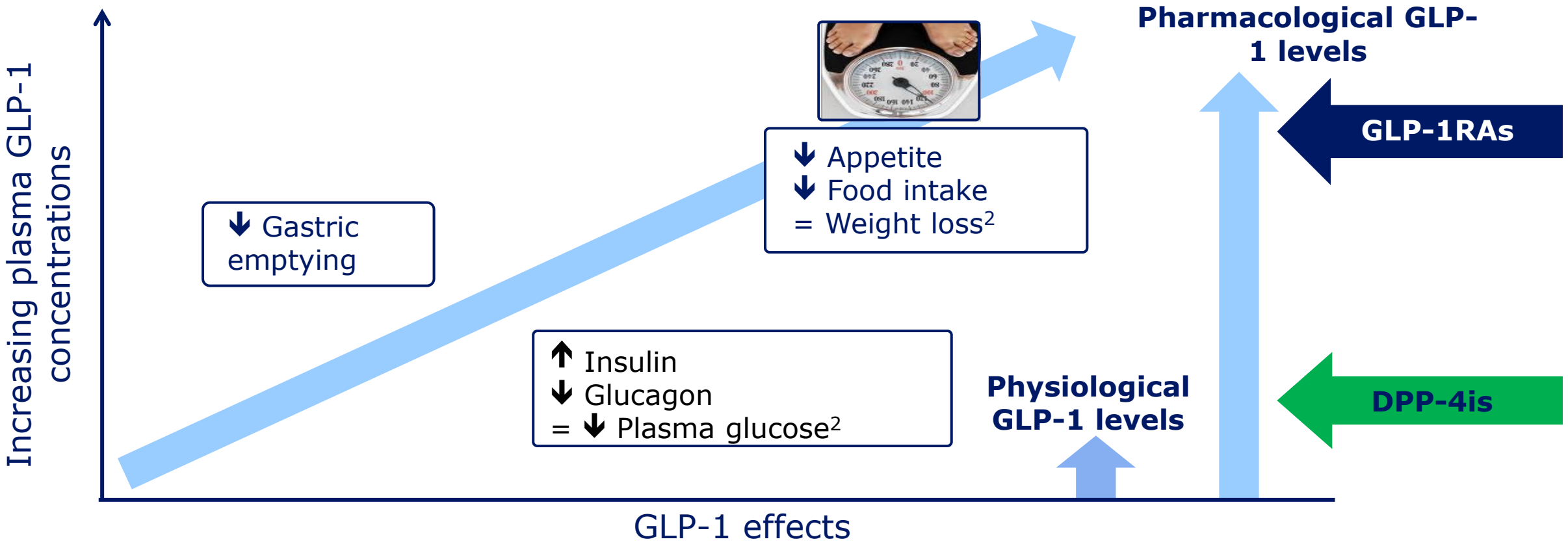
1. Jax. Clin Res Cardiol 2009;98:75–9. 2. Grieve. Br J Pharmacol 2009;157:1340–51 (modified).
3. Robinson et al. BMJ Open 2013;3:pii e001986.

Potential mechanisms for the cardio-nephroprotective effect of GLP-1RA



1. J. Clin. Med. 2020, 9, 947

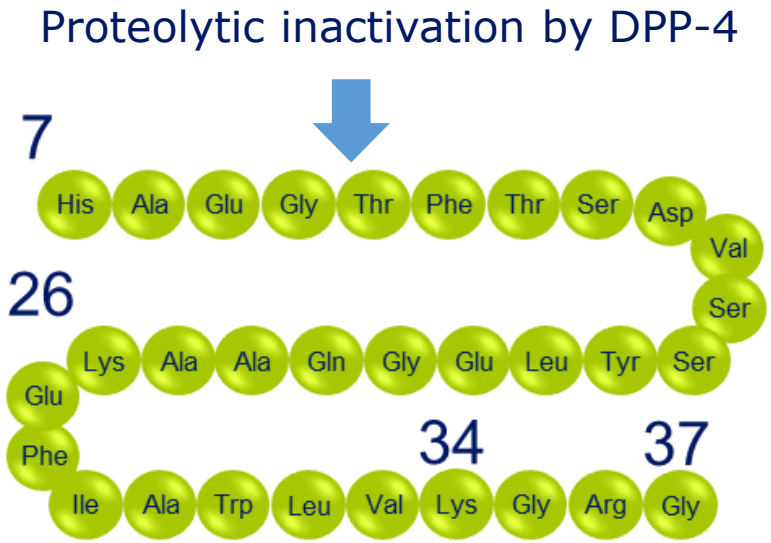
Additional physiological benefits are observed at pharmacological levels of GLP-1



DPP-4is, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1; GLP-1RAs, glucagon-like peptide 1 receptor agonists
Adapted from Holst et al.[1]

1. Holst JJ et al. *Trends Mol Med* 2008;14:161–168; 2. Flint A et al. *Adv Ther* 2011;28:213–226

Native GLP-1 has limited clinical value because of its short half-life



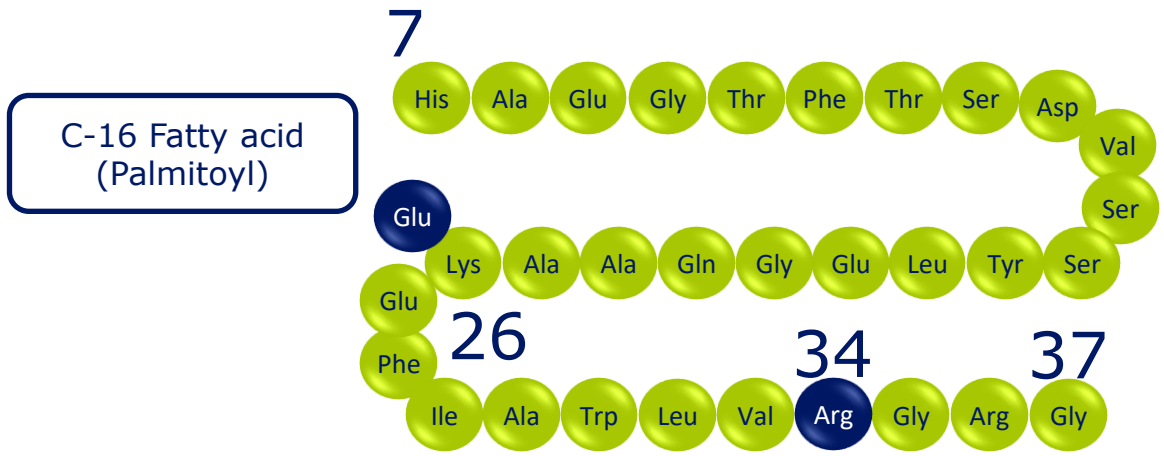
Enzymatic cleavage

High clearance (4–9 L/min)

→ $t_{1/2}$ = 1.5–2.1 minutes

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1
Adapted from Bjerre Knudsen. *J Med Chem* 2004;47:4128–34; Vilsbøll *et al*. J Clin *Endocrinol Metab* 2003;88:220–24

Liraglutide is a once-daily analogue of human GLP-1



97% homology to native human GLP-1

Improves pharmacokinetics:

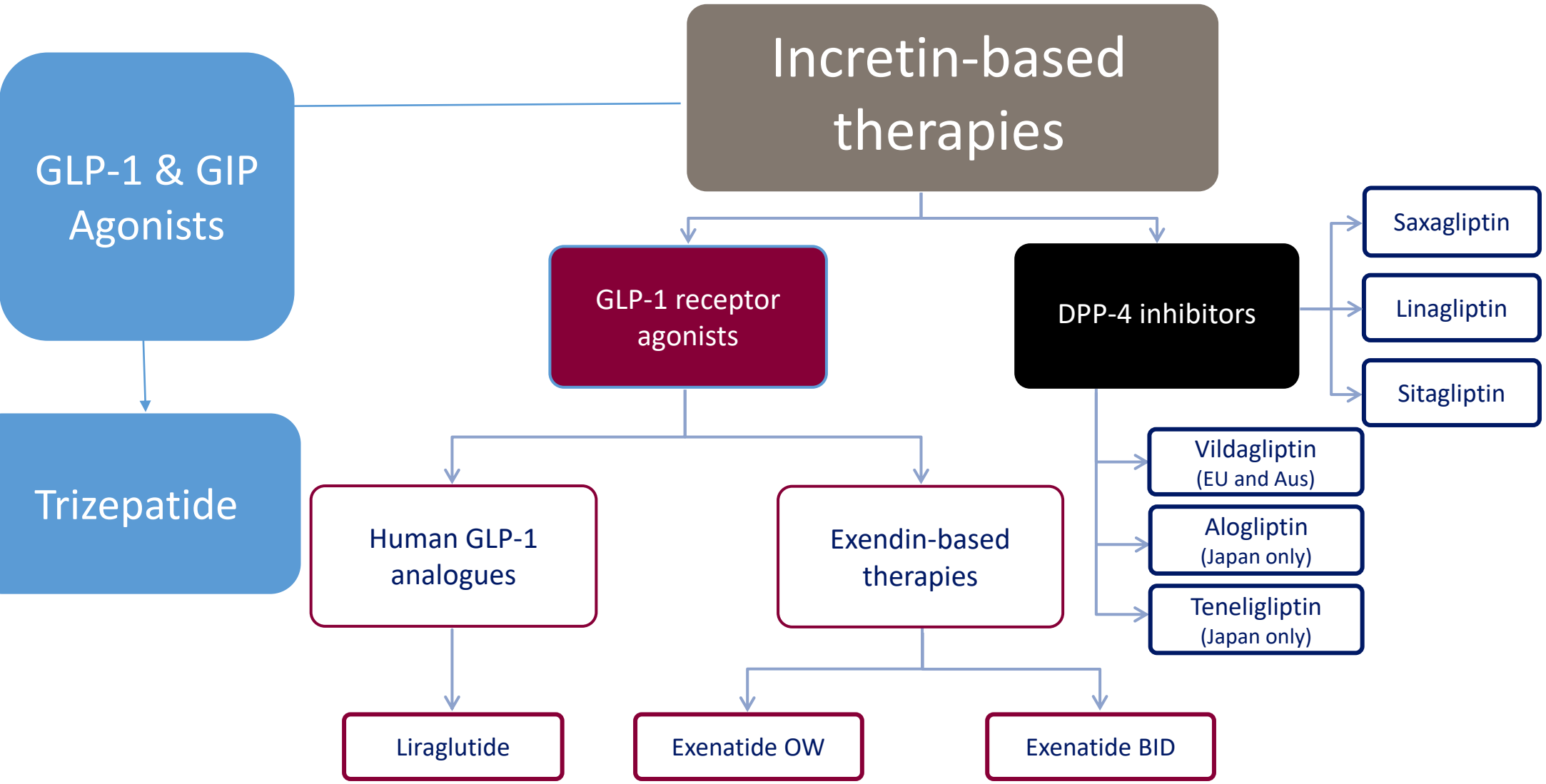
- Albumin binding
- Self-association

→

- Slow absorption from subcutis
- Stable against DPP-4
- Long plasma half-life ($t_{½} \approx$ 13 hrs)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1
Knudsen *et al*. *J Med Chem* 2000;43:1664–9

Incretin-Based Therapies

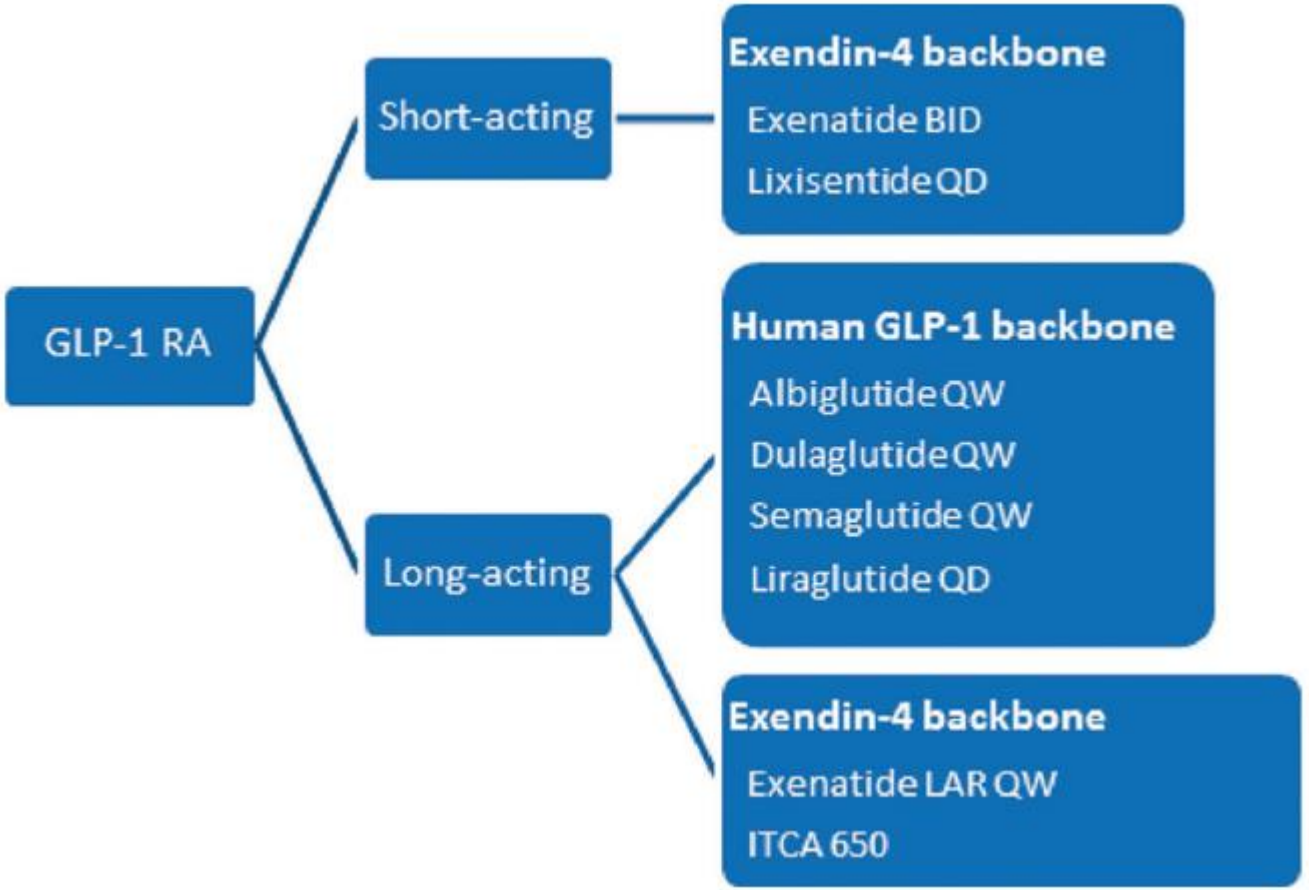


Aus, Australia; EU, Europe

Incretin mimetics
Exenatide

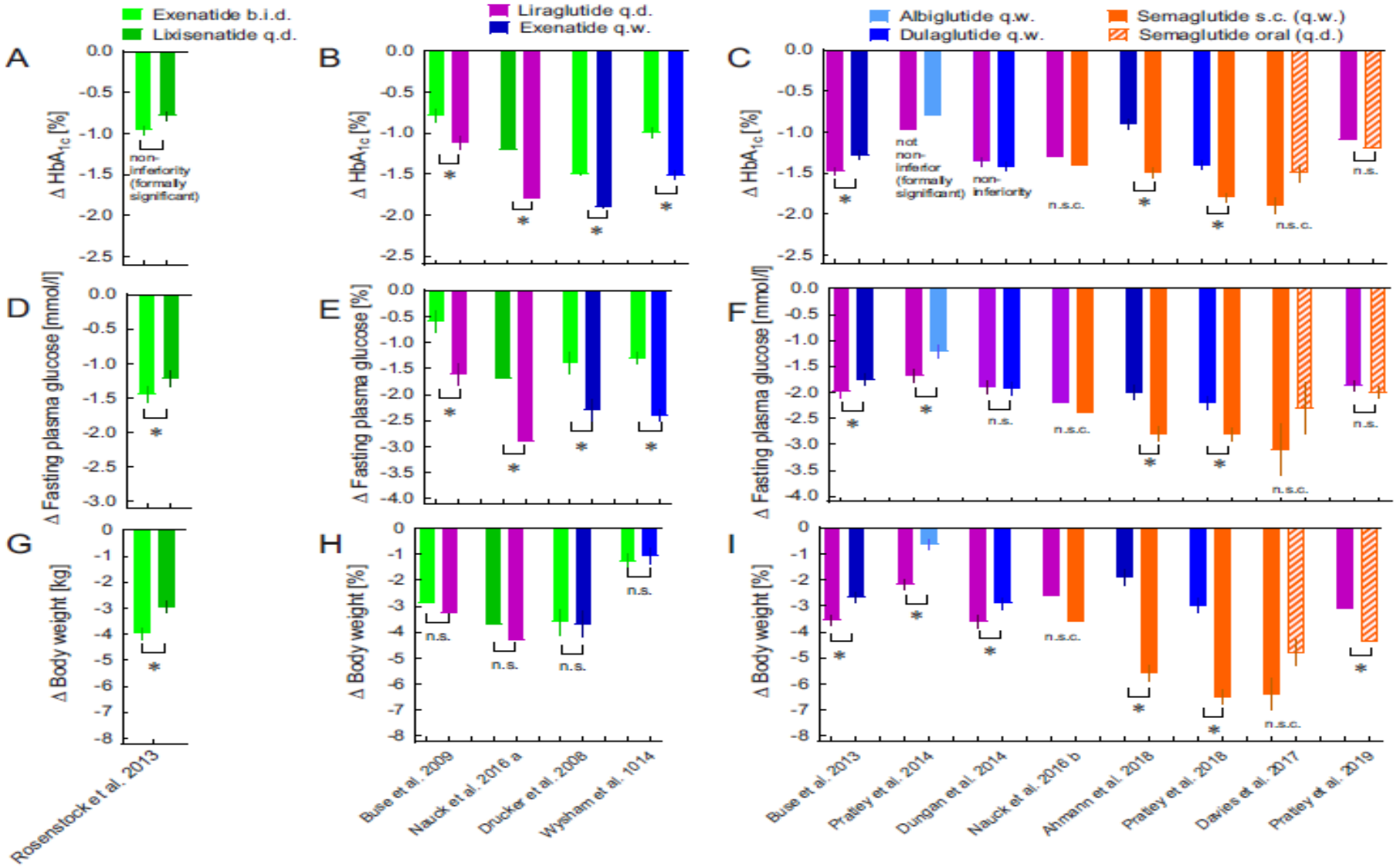
- The first incretin-related therapy available for patients with type 2 diabetes.
- Naturally occurring peptide from the saliva of the Gila Monster.
- Has an approximate 50% amino acid homology with GLP-1.
- Binds to GLP-1 receptors and behaves as GLP-1.

Classification of glucagon-like peptide-1 receptor agonists

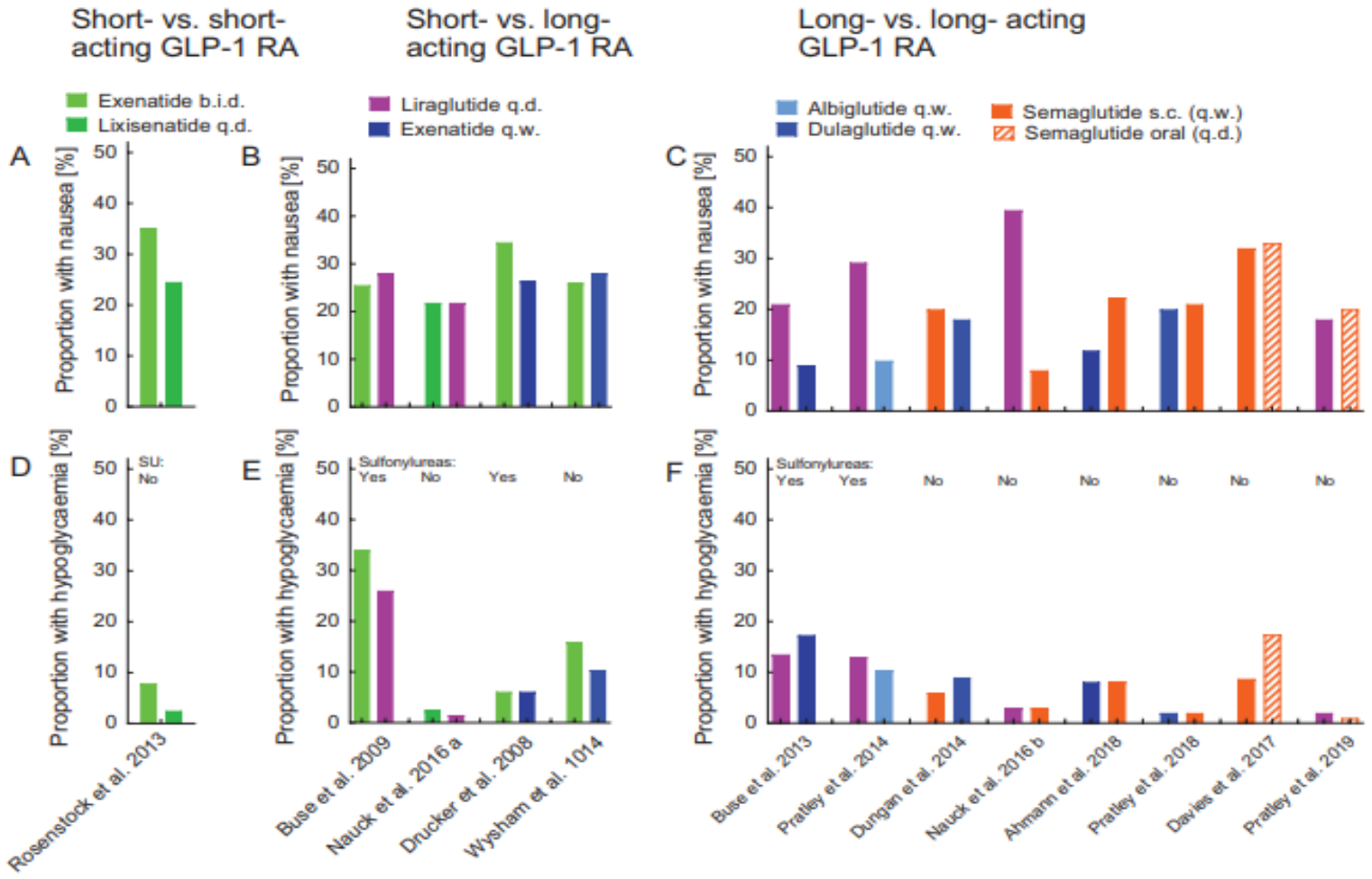


Diabetes Obes Metab 2011;13:394-407

Clinical efficacy results from clinical trials comparing different GLP-1 receptor agonists head-to-head. Reductions in HbA^{1c}, fasting plasma glucose and body weight



Safety and tolerability results from clinical trials comparing different GLP-1 receptor agonists head-to-head



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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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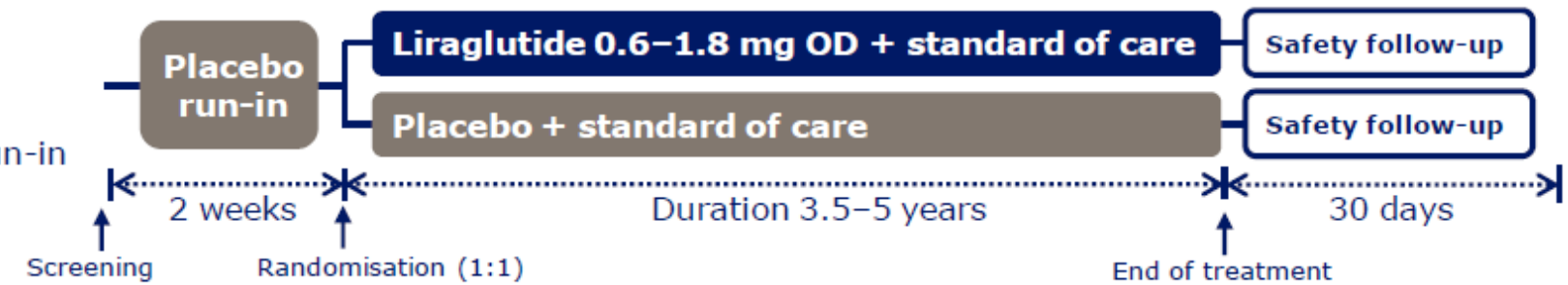
LEADER: Study design

9340 patients

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.

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

Primary and key secondary outcomes

Primary outcome	**Time to first MACE composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	**Time to first occurrence of** • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure) • All-cause death • Each individual component of expanded composite CV outcome

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

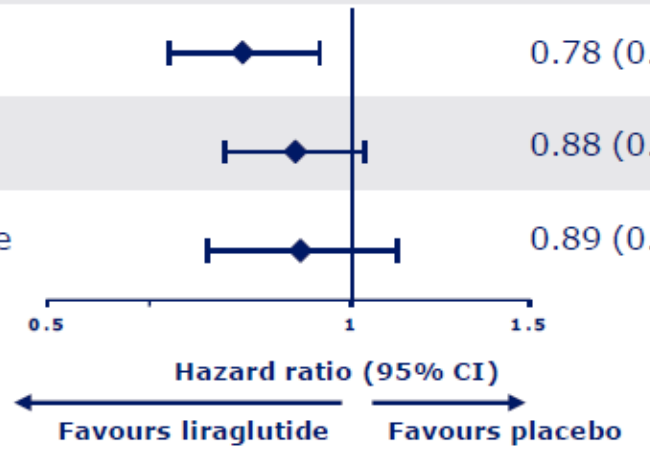
Results Of LEADER Trial

- Reduced the rate of the first occurrence of death from CV causes, nonfatal MI or nonfatal stroke by 13%
- Reduced all cause mortality by 15%
- Reduced cardiovascular death by 22%

NEJM 2016

Individual components of the primary endpoint

	Hazard ratio (95% CI)	p-value	Liraglutide N	Liraglutide %	Liraglutide R	Placebo N	Placebo %	Placebo R
Number of patients			**4668**	**100.0**		**4672**	**100.0**	
CV death	0.78 (0.66 ; 0.93)	0.007	219	4.7	1.2	278	6.0	1.6
Non-fatal MI	0.88 (0.75 ; 1.03)	0.11	281	6.0	1.6	317	6.8	1.8
Non-fatal stroke	0.89 (0.72 ; 1.11)	0.30	159	3.4	0.9	177	3.8	1.0



Hazard ratios and p-values were estimated with the use of a Cox-proportional hazards model with treatment as a covariate.
%, percentage of group; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; N, number of patients; R, incidence rate per 100 patient-years of observation.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

Liraglutide dosing

- To improve gastrointestinal tolerability, the starting posology is 0.6 mg liraglutide daily

*Some patients are expected to benefit from an increase in dose from 1.2 to 1.8 mg and, based on clinical response, after at least 1 week, the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended

1. Novo Nordisk. Liraglutide SPC. July 2011

Summary of baseline characteristics and primary composite cardiovascular outcomes of the completed CVOTs for GLP-1 RA

GLP-1 RA: Study name	No. of patients	Median follow-up (years)	% with CV disease*	% of statin use	Baseline age	Baseline HgA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	60.3	7.7%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	64.3	8.7%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	64.6	8.7%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.1%	74%	62.0	8.0%	31.8	0.91 (0.83 to 1.00)	0.06
Albiglutide: Harmony	9463	1.6	100%	84%	64.1	8.7%	32.3	0.78 (0.68 to 0.90)	0.0006
Dulaglutide: REWIND	9901	5.4	31.5%	66%	66.2	7.2%	32.3	0.88 (0.79 to 0.99)	0.026
Oral semaglutide: PIONEER 6	3183	1.3	84.7%	85%	66.0	8.2%	32.3	0.79 (0.57 to 1.11)	0.17

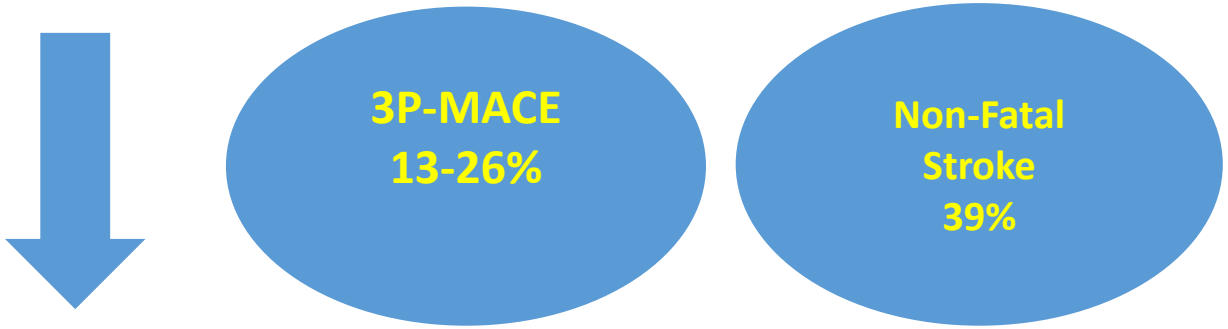
*Remaining participants with cardiovascular risk factors.
BMI, body mass index;CV, cardiovascular; HgA1c, glycated haemoglobin.

1. Postgrad Med J 2020;96:156–161

Key GLP-1RA RCTs with cardiovascular endpoint

Drug (Ref)	Trial	*n*	Studied Population	Mean Duration	Composite Primary CV Endpoint	Result HR (95% CI; *p*)	Individual Primary CV Endpoint	Result HR (95% CI; *p*)
Lixisenatide [45]	ELIXA	6068	T2D and acute coronary syndrome	25 m	3P-MACE	Neutral	None	Neutral
Exenatide [46]	EXSCEL	14,752	T2D with or without CVD	3.2 y	3P-MACE	Neutral	None	Neutral
Liraglutide [19,47]	LEADER	9340	T2D and high CV risk	3.8 y	3P-MACE	0.87 (0.78–0.97; $p < 0.001$)	Death from any cause	0.85 (0.74–0.97; $p = 0.02$)
Semaglutide [20] (sc)	SUSTAIN-6	3297	T2D 50 y or more with established CVD, CHF or CKD G3 or higher or >60 y w/CV risk factor	2.1 y	3P-MACE	0.74 (0.58–0.95; $p = 0.02$)	Nonfatal stroke	0.61 (0.38–0.99; $p = 0.04$)
Albiglutide [48]	HARMONY	9469	T2D and CVD or CV risk factors	3.8 y	3P-MACE	0.78 (0.68–0.90; $p = 0.0006$)	Fatal or nonfatal myocardial infarction	0.75 (0.61–0.90, $p = 0.003$)
Dulaglutide [28]	REWIND	9901	T2D and CVD or CV risk factors	5.4 y	3P-MACE	0.88 (0.79–0.99; $p = 0.026$)	Nonfatal Stroke	0.76 (0.61–0.95; $p = 0.017$)
Semaglutide [49] (oral)	PIONEER-6	3183	T2D and CVD or CV risk factors	15.9 m	3P-MACE	Neutral	None	Neutral
Exenatide [22]	FREEDOM-CVO	4000	T2D and CV disease	UK	UK	UK	UK	UK

T2D, type 2 diabetes mellitus; CVD, Cardiovascular disease; 3P-MACE, 3-point MACE (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke); SC; subcutaneous, UK, unknown; y, years; m, Month; RCTs: randomized clinical trial.



1. J. Clin. Med. 2020, 9, 947

Key GLP-1RA RCTs with kidney endpoints

Drugs	Trials	% *n* eGFR < 60	Composite Kidney Endpoint	Results	Individual Kidney Endpoint	Result HR (95% CI; *p*)
Lixisenatide [45]	ELIXA	23	NA	NA	New onset macroalbuminuria	0.808 (0.660–0.991; $p = 0.0404$)
Exenatide [46]	EXSCEL	17	40% reduction in eGFR loss, onset of dialysis or transplantation, renal death and onset of macroalbuminuria	0.85 (0.73–0.98; $p = 0.027$)	None	Neutral
Liraglutide [19,47]	LEADER	23	New onset macroalbuminuria, sustained serum creatinine duplication, initiation of renal replacement therapy or renal death	0.78 (0.67–0.92; $p = 0.003$)	New onset macroalbuminuria	0.74 (0.37–0.77; $p = 0.001$)
Semaglutide [20] (sc)	SUSTAIN-6	28.5	New onset macroalbuminuria, doubling serum creatinine reaching an eGFR <45 mL/min/1.73 m^2, initiation of renal replacement therapy or renal death	0.64 (0.46–0.88; $p = 0.005$)	Persistent macroalbuminuria	0.54 (0.60–0.91; $p = 0.0$
Albiglutide [48]	HARMONY	11	UK	UK	UK	UK
Dulaglutide [28]	REWIND	22	New onset macroalbuminuria, sustained decreased of eGFR <30% or the initiation of renal replacement therapy	0.85 (0.77–0.93, $p = 0.0004$)	New onset macroalbuminuria; Sustained decline in eGFR of ≥40%; Sustained decline in eGFR of ≥50%	0.77 (0.68–0.87; $p < 0.0001$); 0.70 (0.57–0.85; $p = 0.0004$); 0.74 (0.66–0.84; $p < 0.0001$)
Semaglutide [49] (oral)	PIONEER-6	27	UK	UK	UK	UK
Exenatide [22]	FREEDOM-CVO	UK	UK	UK	UK	UK

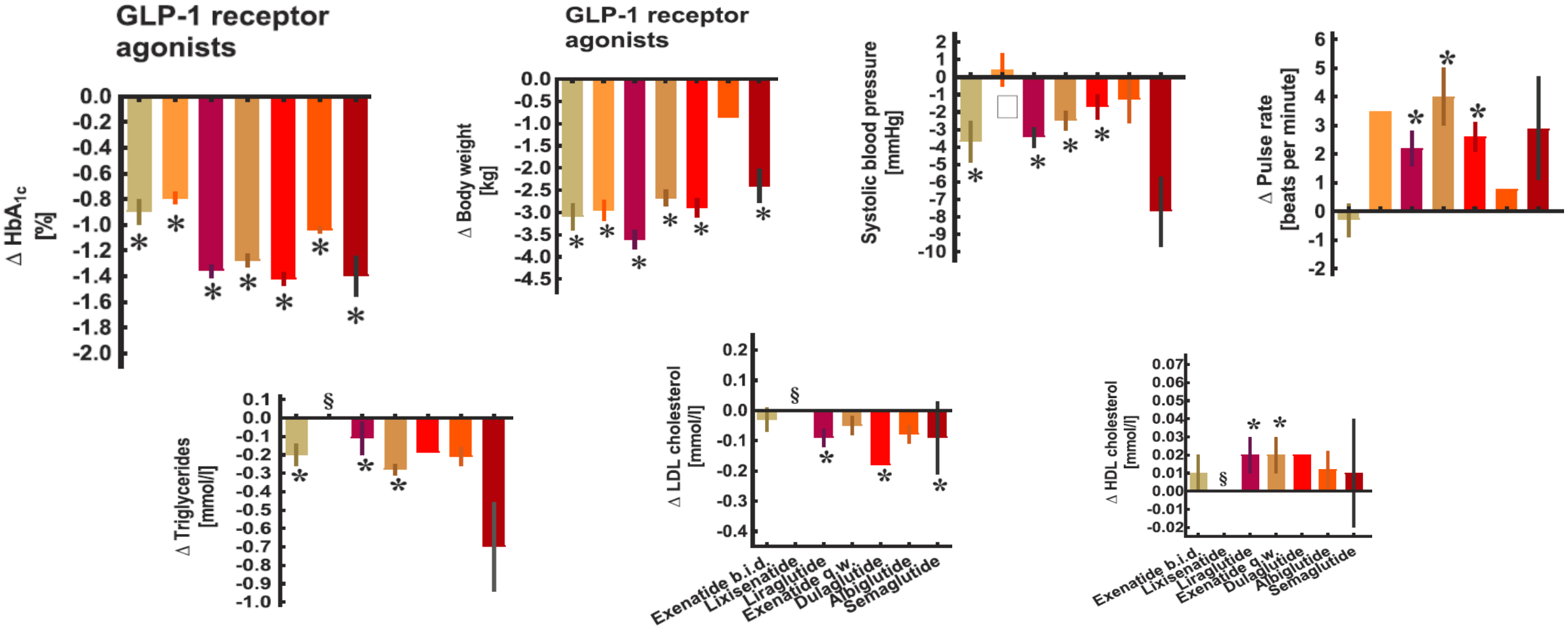
NA, not apply; SC; subcutaneous; UK, unknown; RCTs: randomized clinical trial.

22%
26%

36%
46%

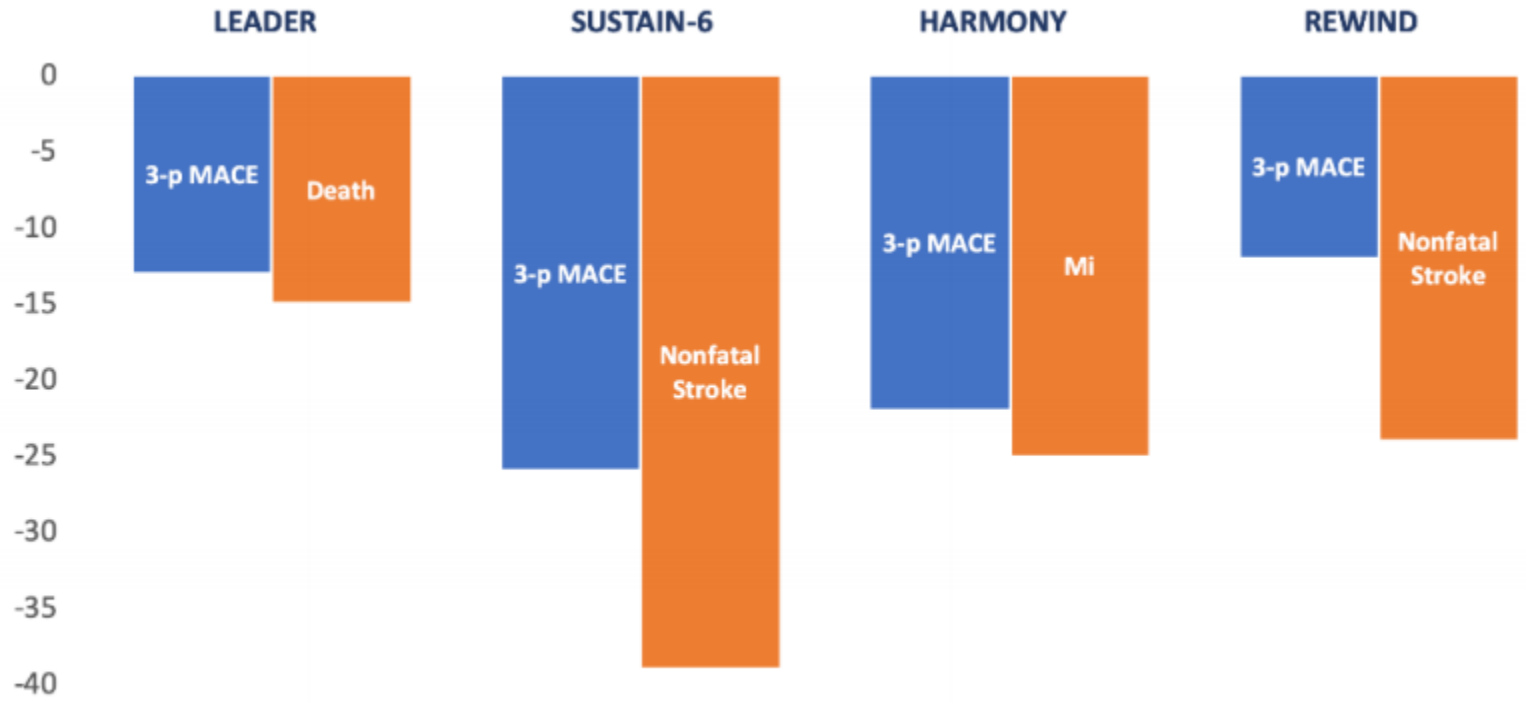
1. J. Clin. Med. 2020, 9, 947

Effects of Treatment with GLP-1R agonists on CV Risk Factors



1. Circulation. 2017;136:849–870

GLP-1RA RCT studies with known beneficial cardiovascular endpoints



Liraglutide, Semaglutide SC, Albiglutide, Dulaglutide

1. J. Clin. Med. 2020, 9, 947

Pen injection devices for GLP-1 receptor agonists and fixed-dose combinations of GLP-1 receptor agonists with basal insulin preparations

	GLP-1 receptor agonists								GLP-1 receptor agonist/ basal insulin fixed-dose combinations	
Pen devices for injection										
Drug name: Generic Commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon® (original)	Bydureon® BCise (improved)	Dulalgutide Trulicity®	Albiglutide Eperzan®, Tanzeum®	Semaglutide Ozempic®	IdegLira Xultophy®	iGlarLixi Soliqua®
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

European Journal of Endocrinology (2019) 181, R211–R234

GLP1-Agonists Precautions & Side Effects

- Should not be used in patients with a HX of pancreatitis
- Not approved in T1DM
- Not be used in pateints with a personal or familial HX of Medullary thyroid cancer or MEN 2A or 2B (multiple endocrine neoplasia)

- GI side effects: nausea, vomiting, diarrhea,
- Pancreatic adverse effects (pancreatic inflammation, pancreatic CA??)
- Gallbladder disease HR 1.79 95% CI, 1.21-2.67, JAMA 2022
- Injection site reactions , a bit 1-5% more common than insulin injection
- immunogenity

DPP4-Inhibitors

Native GLP-1 has limited clinical value because of its short half-life

Proteolytic inactivation by DPP-4

Enzymatic cleavage

High clearance (4–9 L/min)

→ $t_{½}$ = 1.5–2.1 minutes

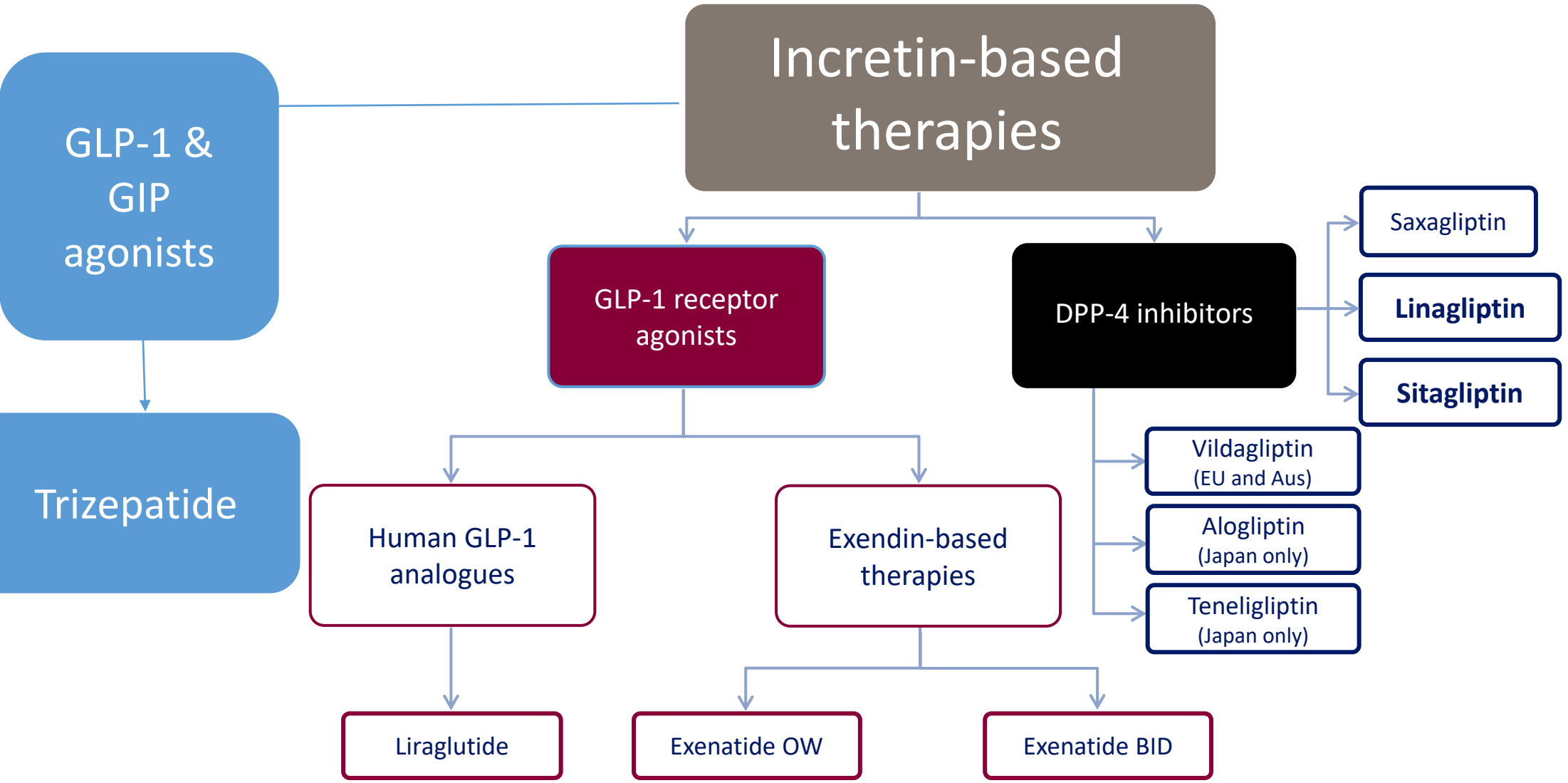
DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1
Adapted from Bjerre Knudsen. *J Med Chem* 2004;47:4128–34; Vilsbøll *et al*. J Clin *Endocrinol Metab* 2003;88:220–24

Differences Between GLP-1R Agonists and DPP-4 Inhibitors

Property/Effect	GLP-1R Agonists	DPP-4 Inhibitors
Effect on GLP-1 receptor	Direct	Indirect
Active GLP-1 level	~ 60 pmol/L	~ 10 pmol/L
A1C lowering	0.5%-2.0%	0.5%-0.9%
Slows gastric emptying	Yes	No
Promotes satiety	Yes	No

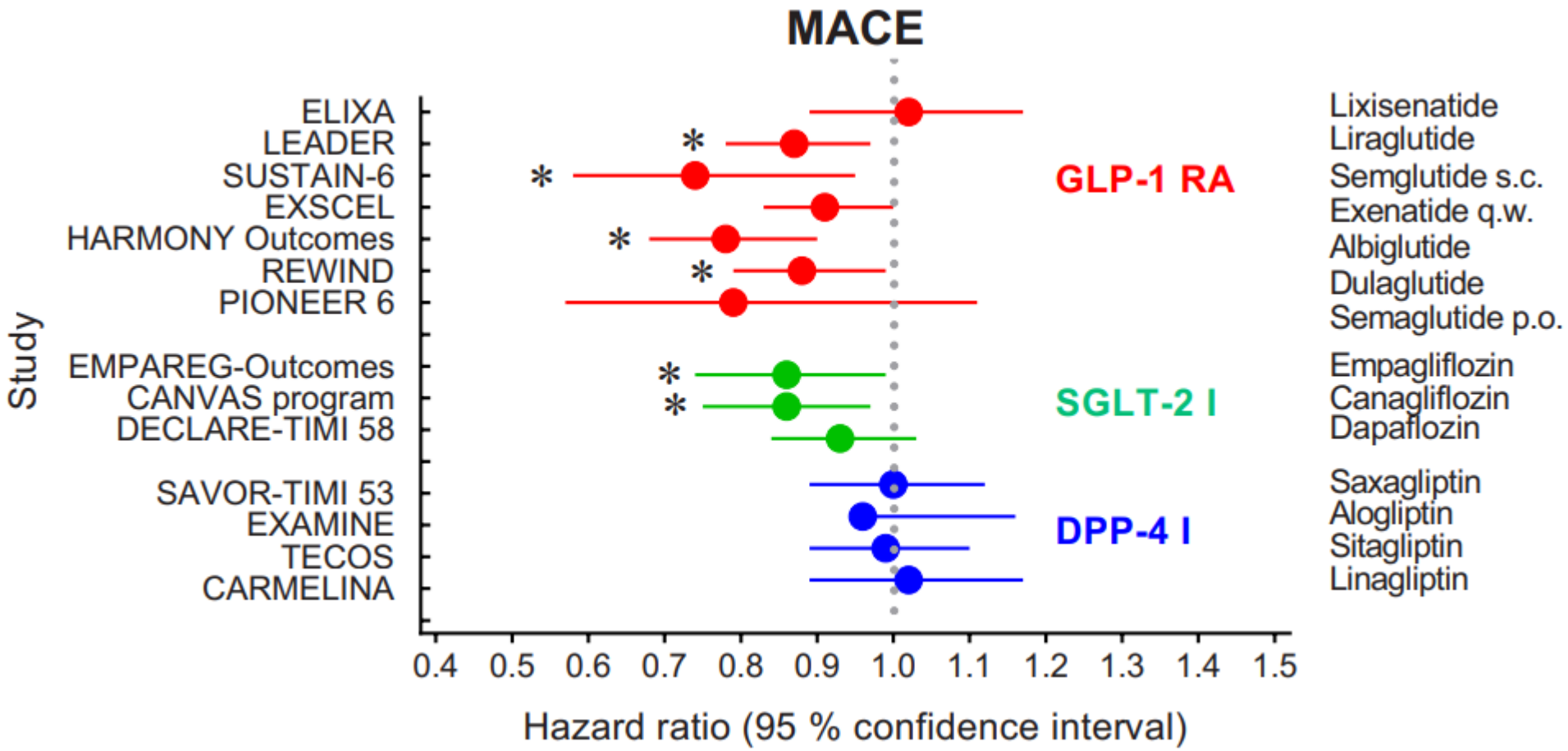
Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635; Blonde L, et al. *Diabetes Obes Metab*. 2006;8:436-447; Vilsboll T, et al. *Diabetes Care*. 2007;30:1608-1610; Garber A, et al. *Lancet*. 2009;373:473-481; Marre M, et al. *Diabet Med*. 2009;26:268-278; Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643; Scott R, et al. *Int J Clin Pract*. 2007;61:171-180; Rosenstock J, et al. *Diabetes Obes Metab*. 2008;10:376-386; Holst JJ, et al. *Diabetologia*. 2005;48(4):612-615; Herman GA, et al. *J Clin Endocrinol Metab*. 2006;91(11):4612-4619.

Incretin-Based Therapies



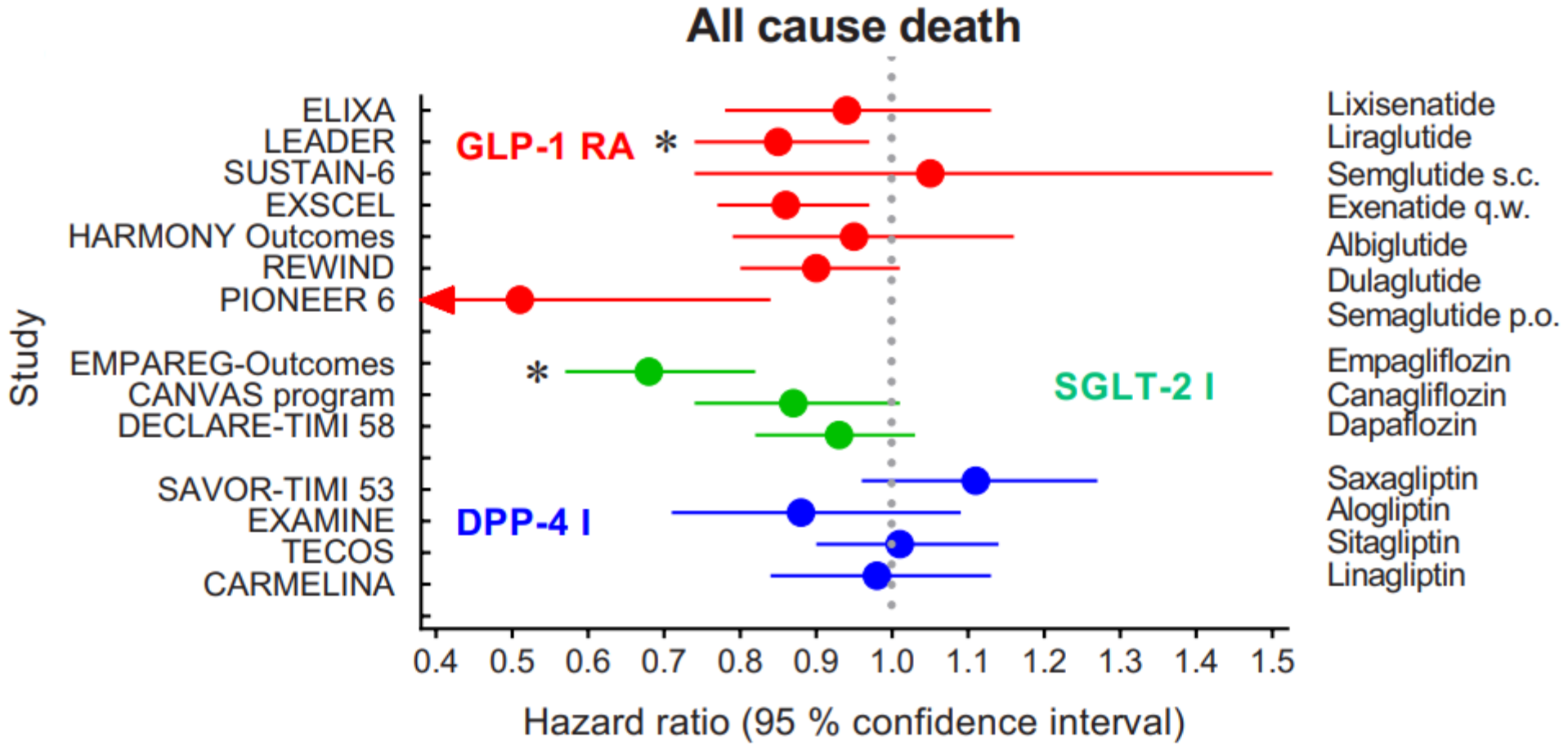
Aus, Australia; EU, Europe

Results of cardiovascular outcomes trials comparing GLP-1 receptor agonists and placebo on a background of standard of care



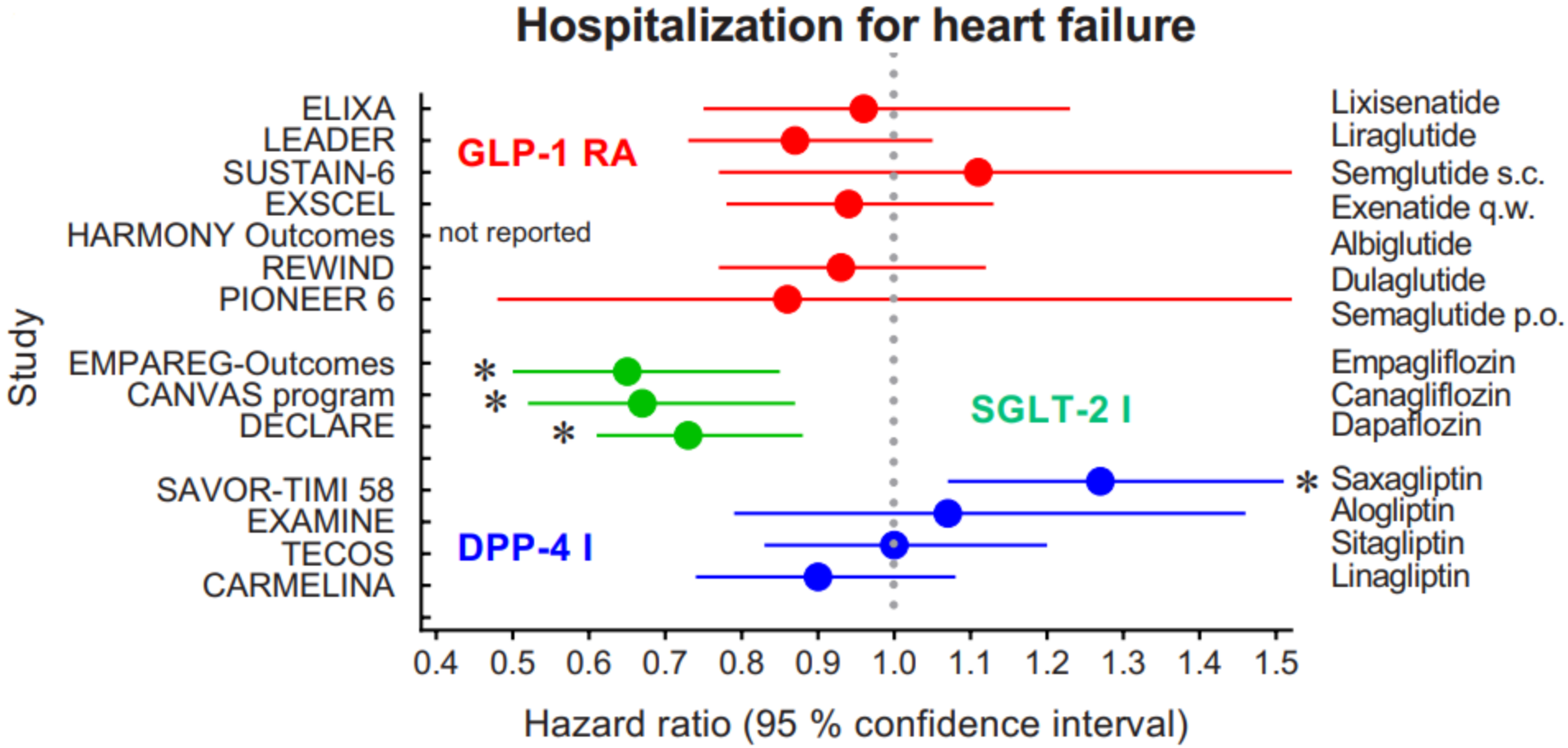
1. European Journal of Endocrinology (2019) 181, R211–R234

Results of cardiovascular outcomes trials comparing GLP-1 receptor agonists and placebo on a background of standard of care



1. European Journal of Endocrinology (2019) 181, R211–R234

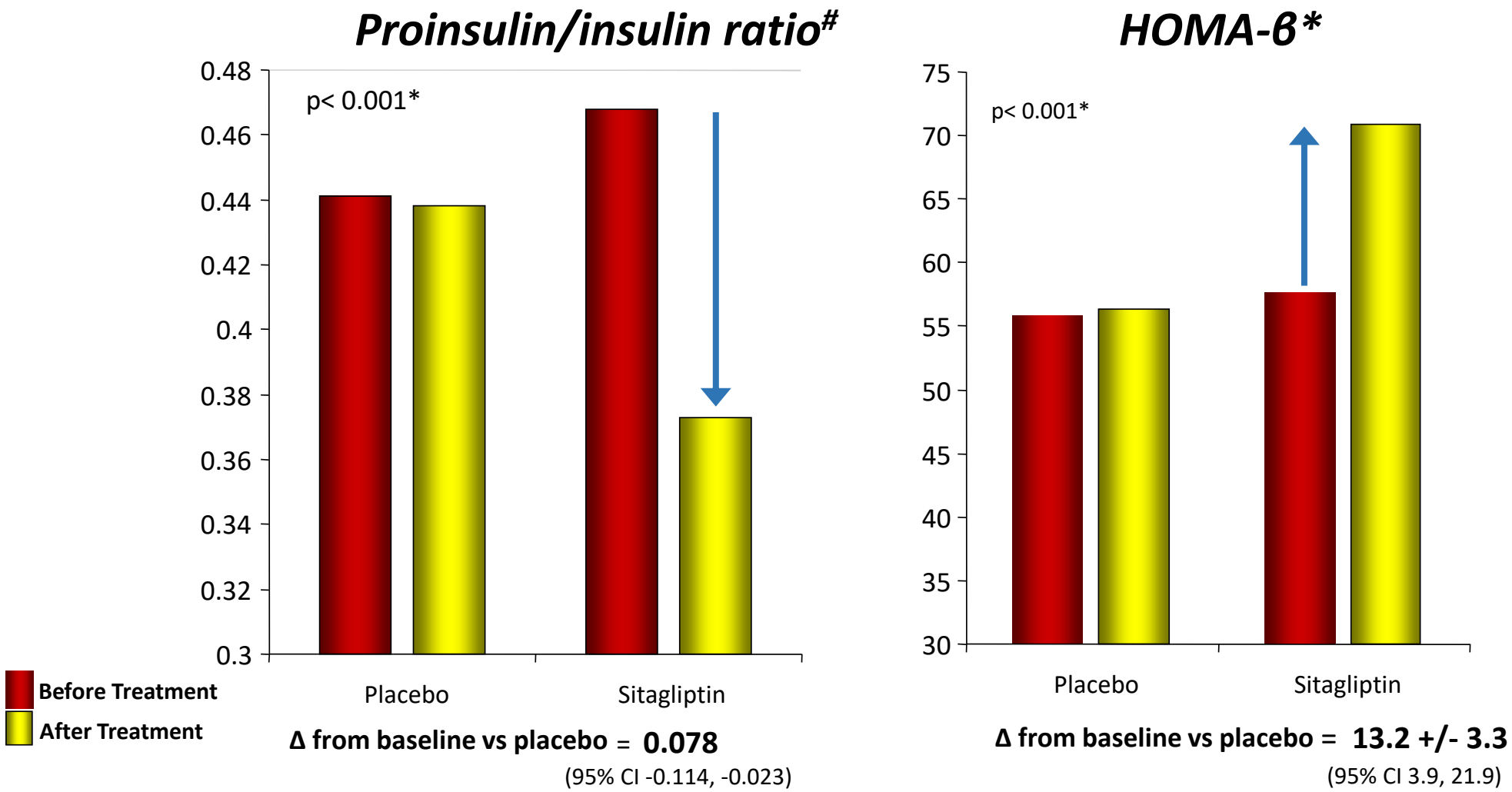
Results of cardiovascular outcomes trials comparing GLP-1 receptor agonists and placebo on a background of standard of care



1. European Journal of Endocrinology (2019) 181, R211–R234

- **Sitagliptin Efficacy**

Beta-Cell Function Improvement With Sitagliptin 24-Week Monotherapy Study[1]



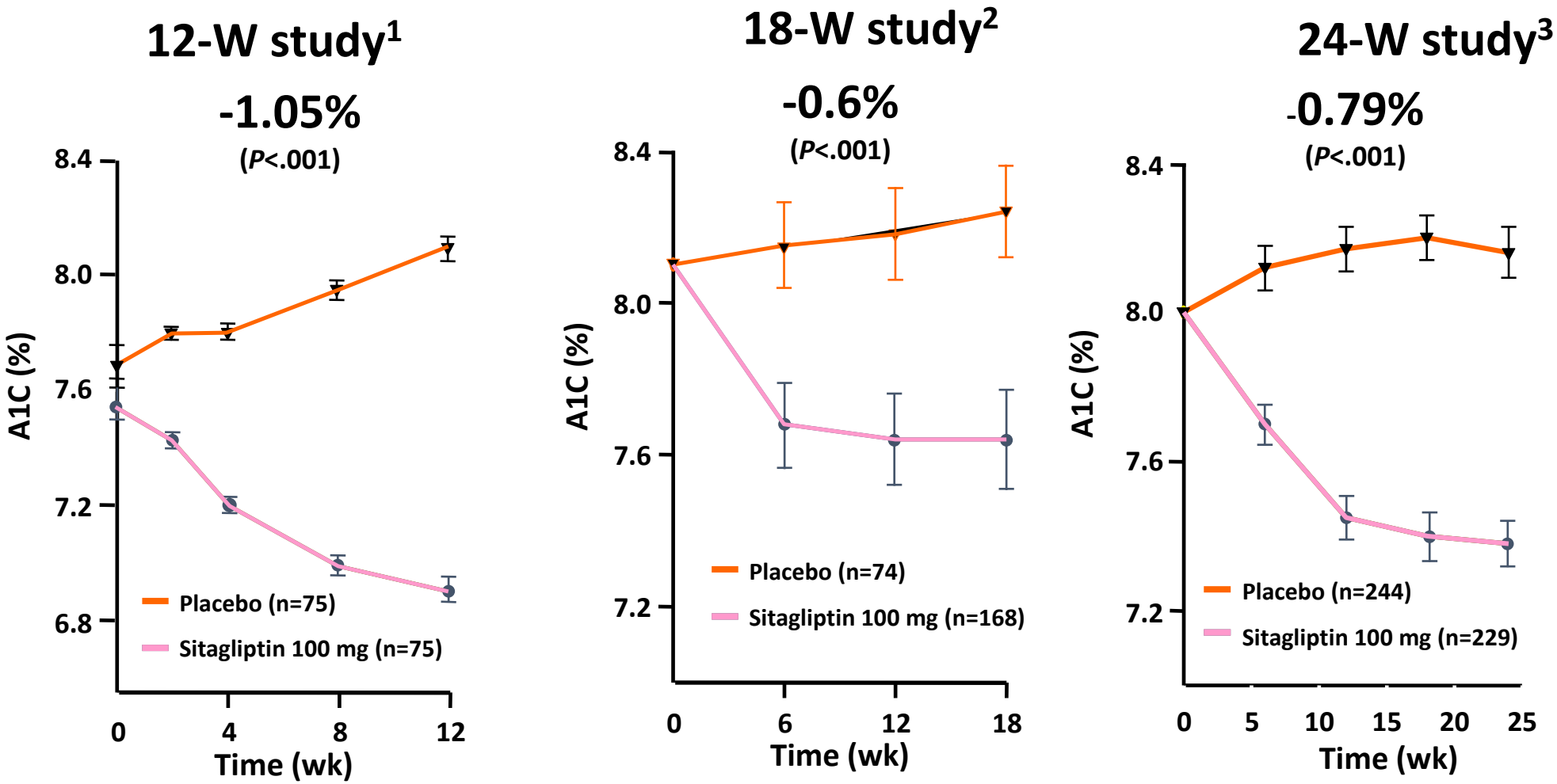
P value for change from baseline compared to placebo

1-Diabetes Care. 2006 ;29(12):2632-7.

*Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations

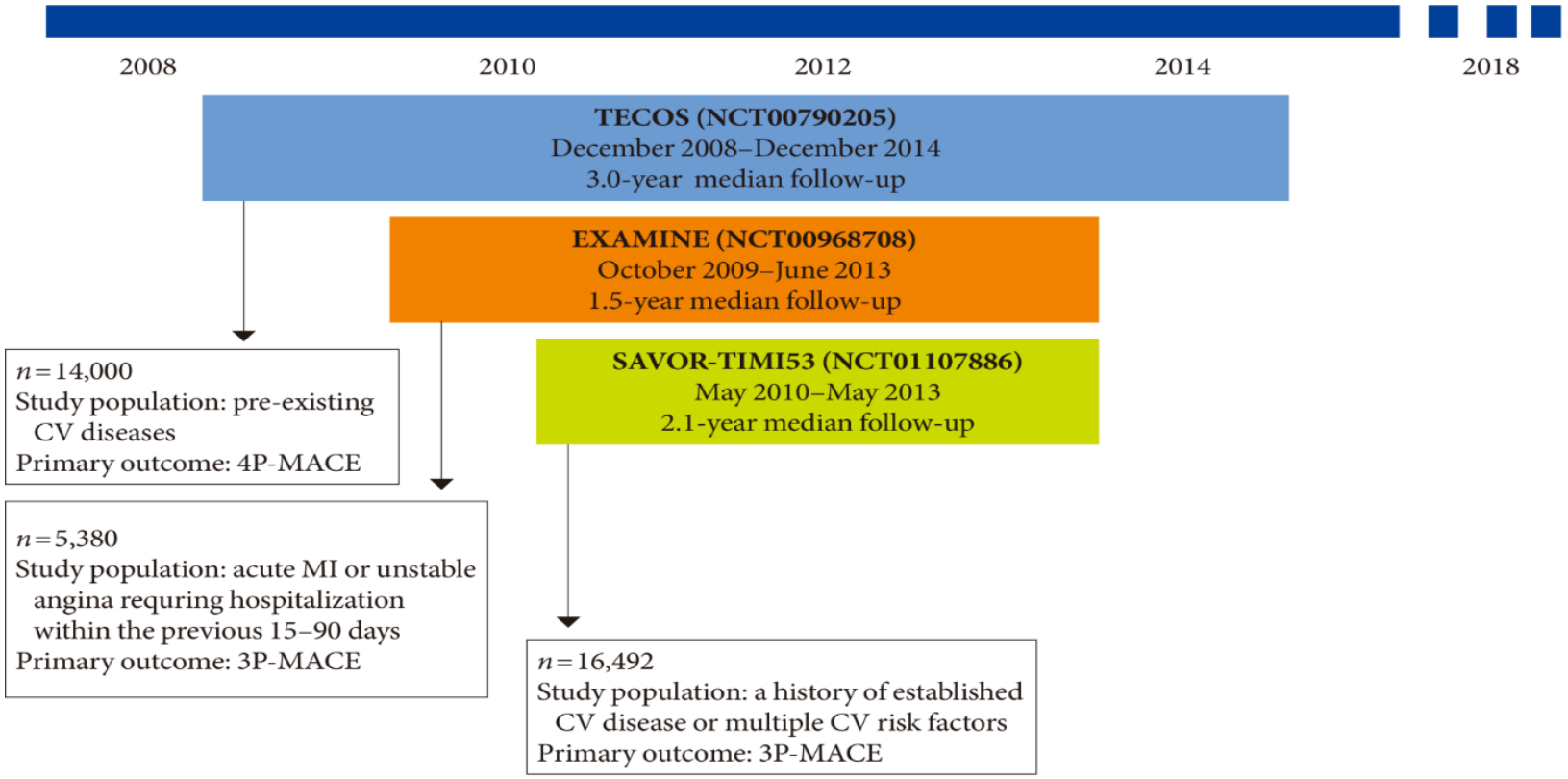
#Elevated proinsulin and proinsulin/insulin ratios are features of abnormal β-cell function in type 2 diabetes.

Sitagliptin Consistently and Significantly Lowers A1C With Once-Daily Dosing in Monotherapy



1. Diabetes Care. 2006;29(12):2632-7. 2- Diabetes Res Clin Pract. 2008 ;79(2):291-8 . 3. Diabetologia. 2006 ;49(11):2564-71.

DPP-4 inhibitors cardiovascular outcome trials (CVOTs)



TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

EXAMINE, EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE.

SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction.

Modified from Diabetes Metab J. 2015 Oct;39(5):373-383.

Sitagliptin Cardiovascular Outcomes Study (TECOS) Study Design[1]

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Main inclusion criteria

1. Patients aged ≥ 50 years with T2D
2. HbA_{1c} 6.5–8.0% receiving stable oral glucose-lowering therapy and/or insulin*
3. Pre-existing vascular disease

+ Usual care for T2D

Sitagliptin 100 mg daily* vs Placebo

N = 14,671; median follow-up 3.0 years

Primary endpoint: time to first occurrence of:

- CV-related death
- Unstable angina requiring hospitalisation
- Non-fatal stroke
- Non-fatal MI

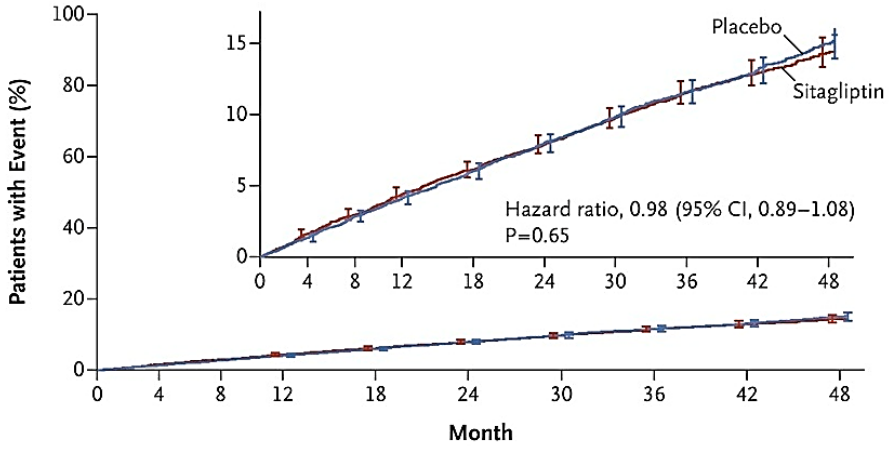
*50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL per minute per 1.73 m^2.

1-N Engl J Med. 2015.16;373(3):232-42

Results[1]

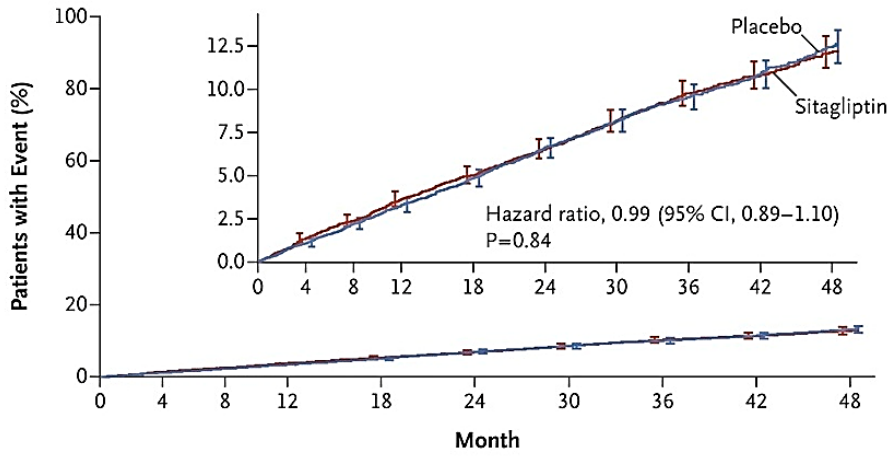
TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Primary Composite Cardiovascular Outcome#



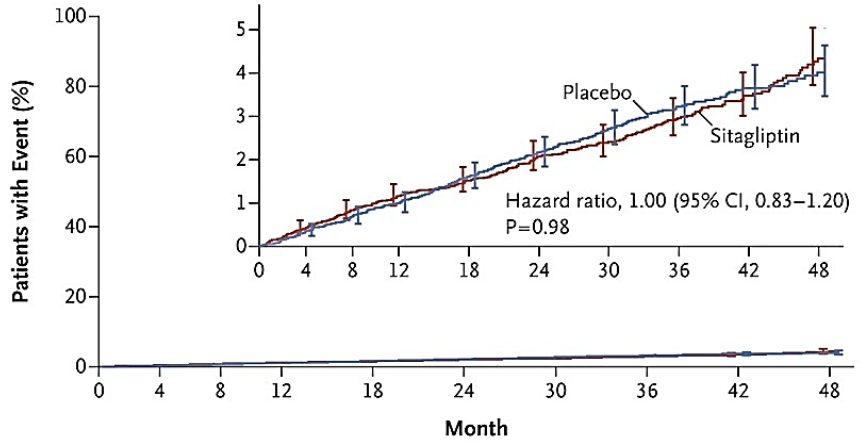
No. at Risk										
Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

Secondary Composite Cardiovascular Outcome*



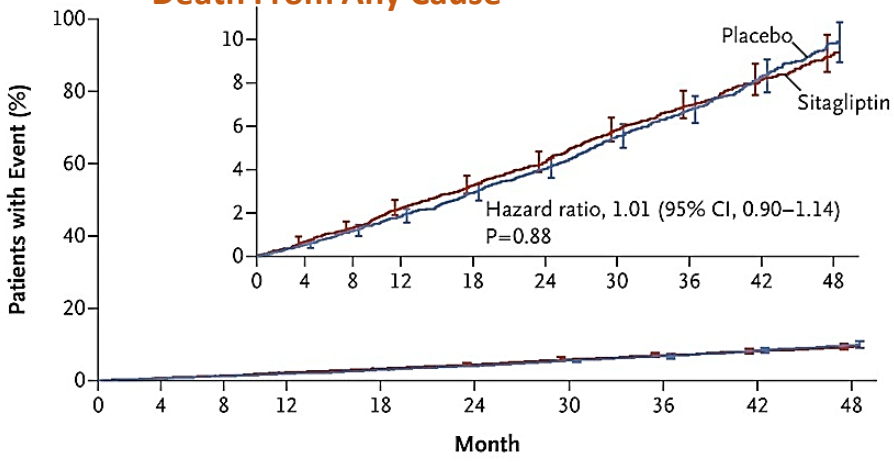
No. at Risk										
Sitagliptin	7332	7145	6969	6817	6638	6457	4584	3396	2097	1270
Placebo	7339	7161	6939	6796	6573	6359	4472	3332	2070	1260

Hospitalization for Heart Failure



No. at Risk										
Sitagliptin	7332	7189	7036	6917	6780	6619	4728	3515	2175	1324
Placebo	7339	7204	7025	6903	6712	6549	4599	3443	2131	1315

Death From Any Cause



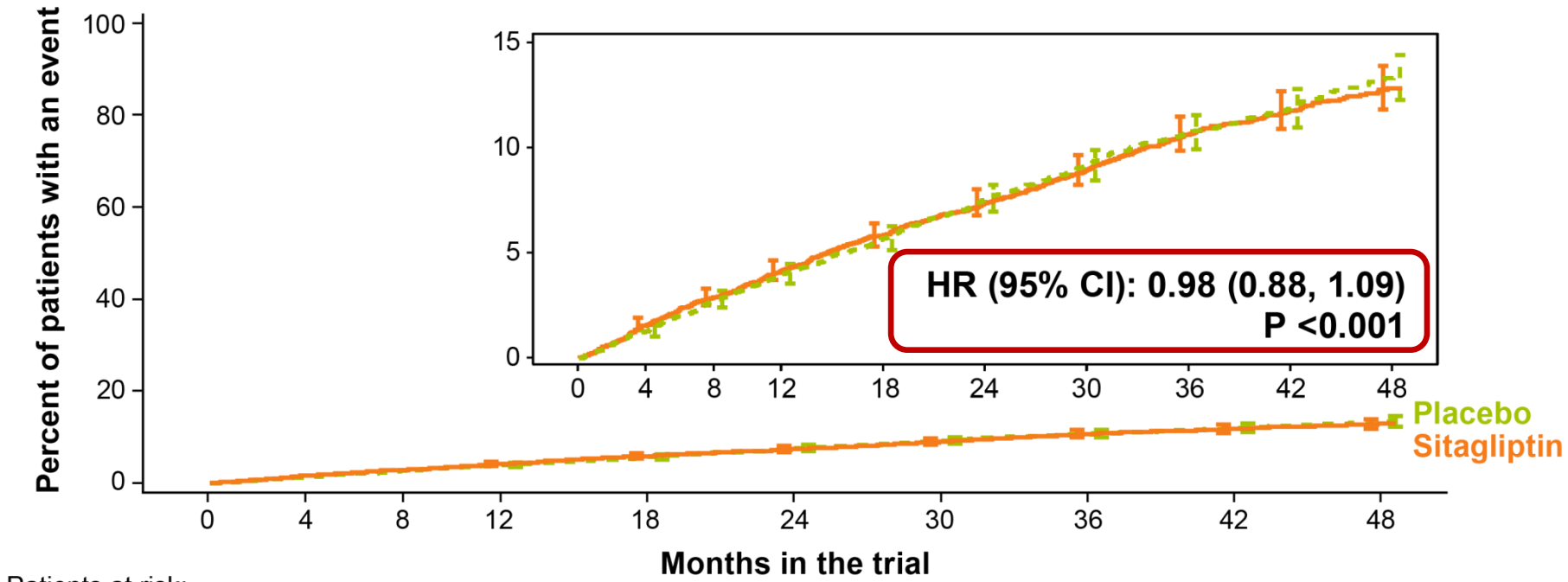
No. at Risk										
Sitagliptin	7332	7262	7180	7103	7010	6904	4964	3739	2321	1435
Placebo	7339	7271	7176	7098	6982	6864	4891	3673	2293	1412

#The primary composite cardiovascular outcome was defined as the first confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. *The secondary composite cardiovascular outcome was the first confirmed event of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

1-N Engl J Med. 2015. 16;373(3):232-42

Primary Composite Cardiovascular Outcome*

(PP Analysis for Non-inferiority)



Patients at risk:

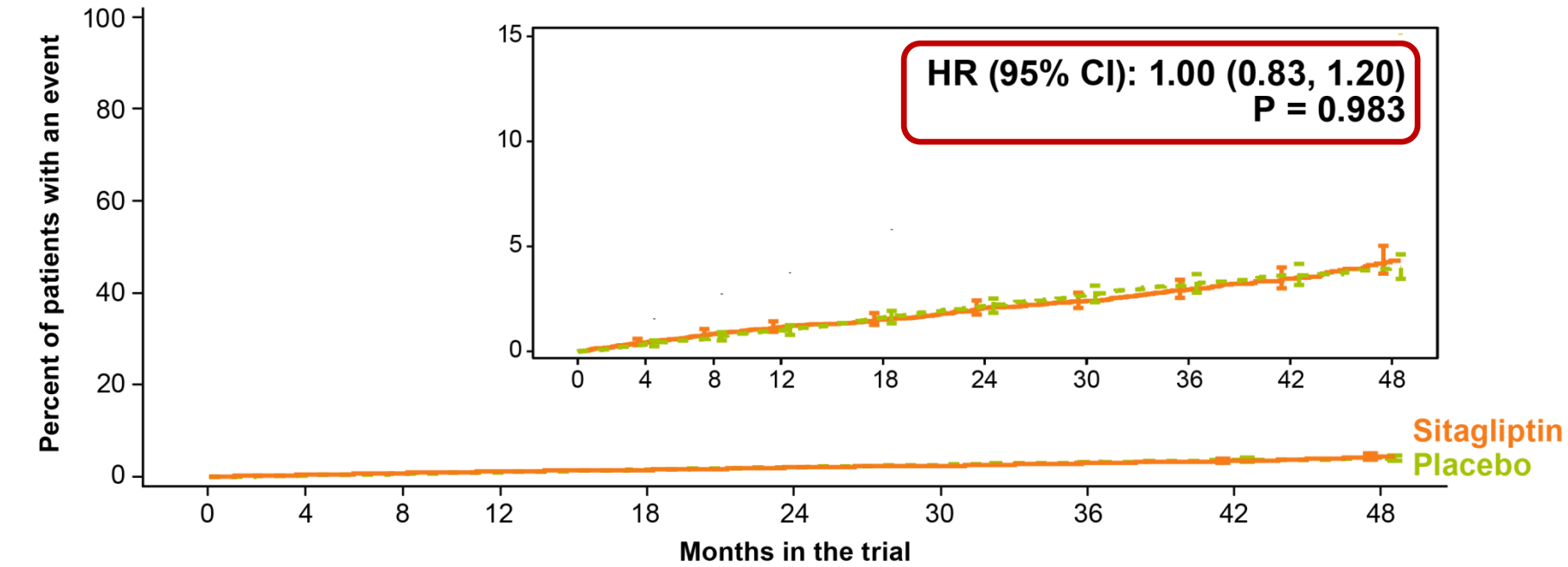
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina.*

Green JB, et al. TECOS Study Group NEJM 2015; 373: 232-42.

Hospitalization for Heart Failure*

(ITT Analysis)



Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

* Adjusted for history of heart failure at baseline.

Green JB, et al. TECOS Study Group NEJM 2015; 373: 232-42.

Conclusions

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

- Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did **not** appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

Dosage and Administration

Sitagliptin: Once-Daily Dosing Administration[1]

Usual Dosing for Sitagliptin*

The recommended dose of Sitagliptin is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPARγ agonist.

Patients With Renal Insufficiency*,†

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis.

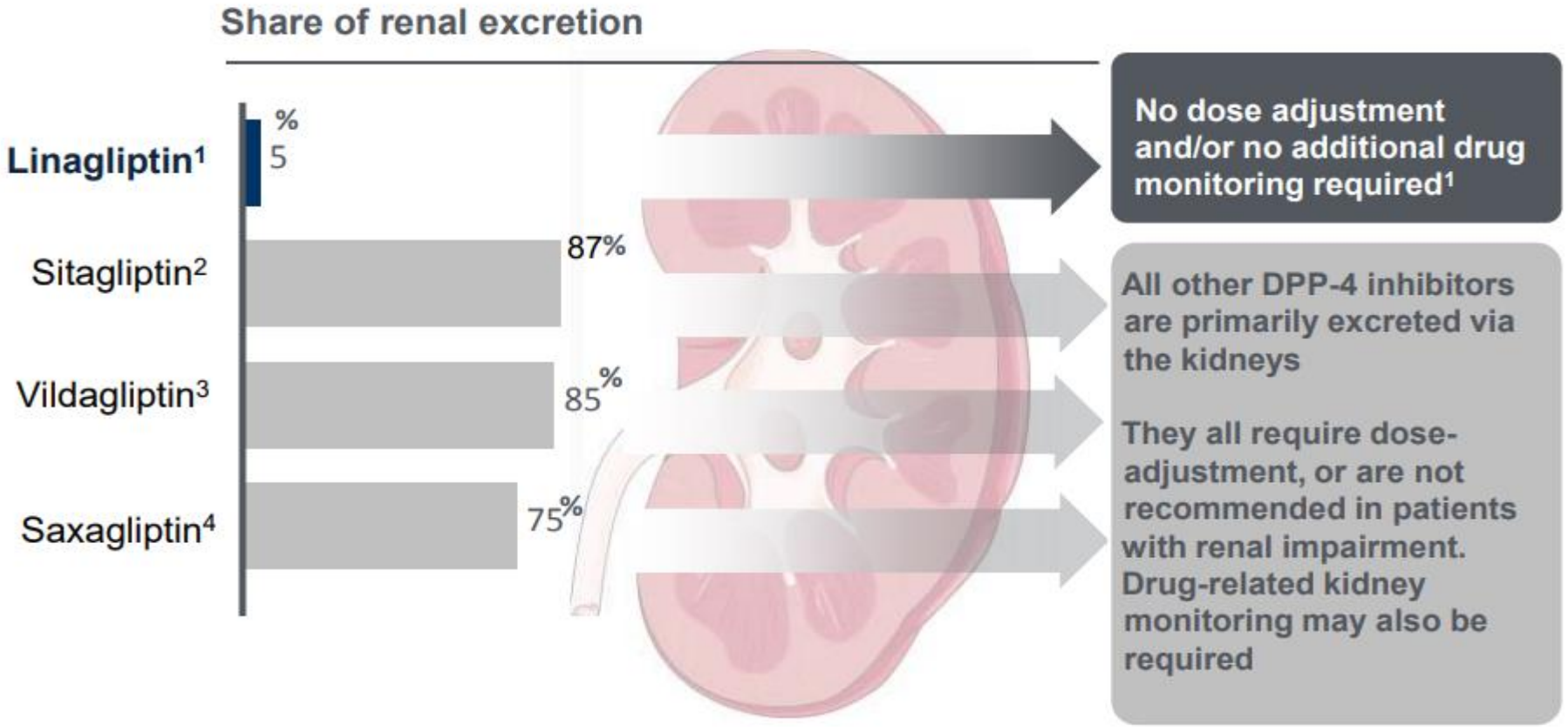
50 mg once daily	25 mg once daily
Moderate	**Severe and ESRD‡**
eGFR greater than or equal to 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2	**eGFR less than 30 mL/min/1.73 m^2 (including patients with end stage renal disease [ESRD] on dialysis)**

Assessment of renal function is recommended prior to Sitagliptin initiation and periodically thereafter.

*Sitagliptin can be taken with or without food. †Patients with mild renal insufficiency—100 mg once daily.
‡ESRD=end-stage renal disease requiring hemodialysis or peritoneal dialysis.
1-Sitagliptin FDA Label, 2018, Reference ID: 4219849.
PPAR agonist= Thiazolidinedione class.

- **Linagliptin Efficacy**

Linagliptin is the only DPP-4 inhibitor which is primarily excreted by gut

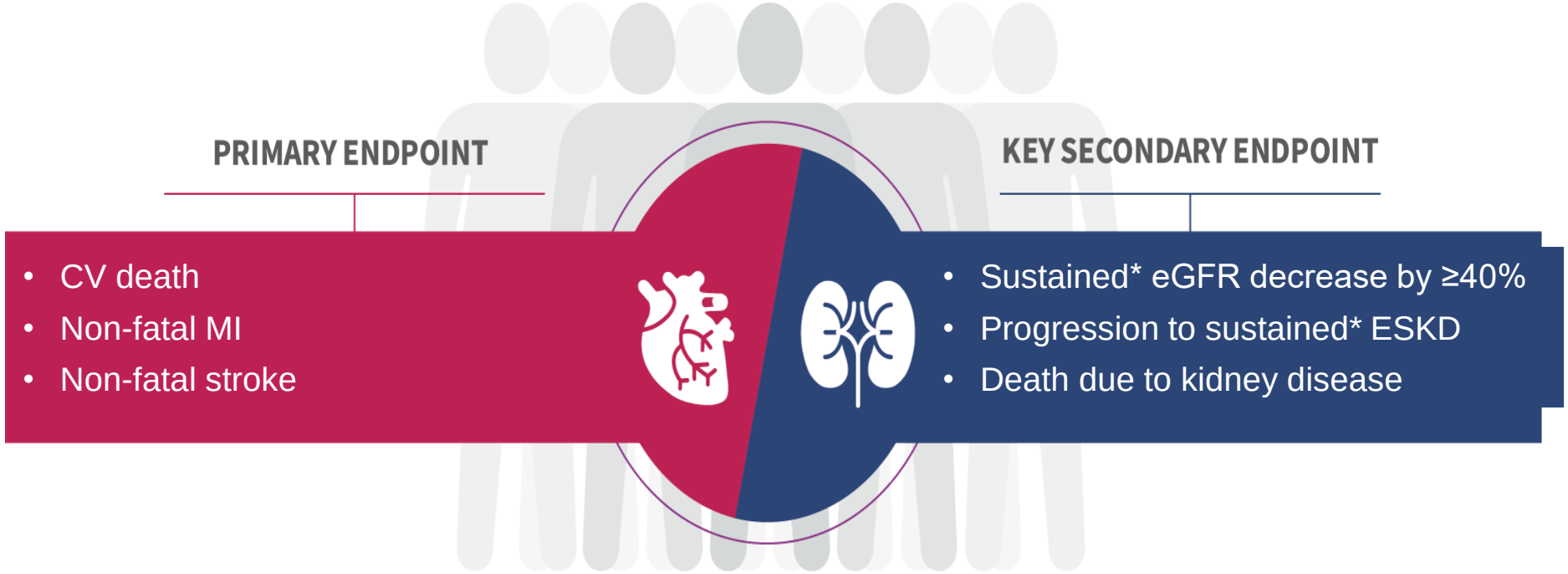


1. Linagliptin US prescribing information , 2. Vincent SH et al. Drug Metab Dispos. 2007;35(4): 533–538 , 3. He H, et al. Drug Metab. Dispos.2009 37(3):536–544 ,
4. Saxagliptin US prescribing information

Aim: **CARMELINA** is a large, long-term cardiovascular (CV) outcomes trial testing the impact of linagliptin vs. placebo on top of standard care on CV and renal outcomes.

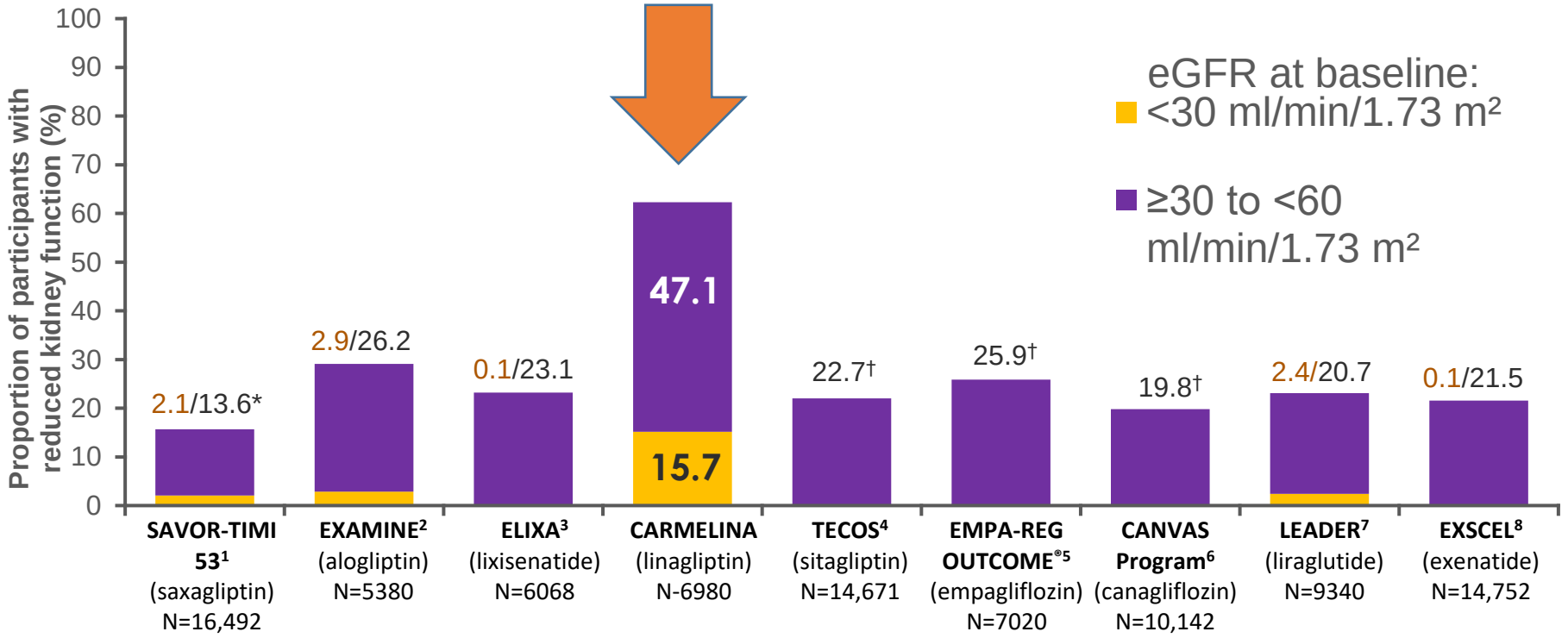
1. Cardiovasc Diabetol 2018;17:39

CARMELINA® was designed to evaluate the CV and kidney safety of linagliptin in patients with T2D[1]



1. Cardiovasc Diabetol 2018;17:39

Higher prevalence of renal impairment CARMELINA than recent CVOTs

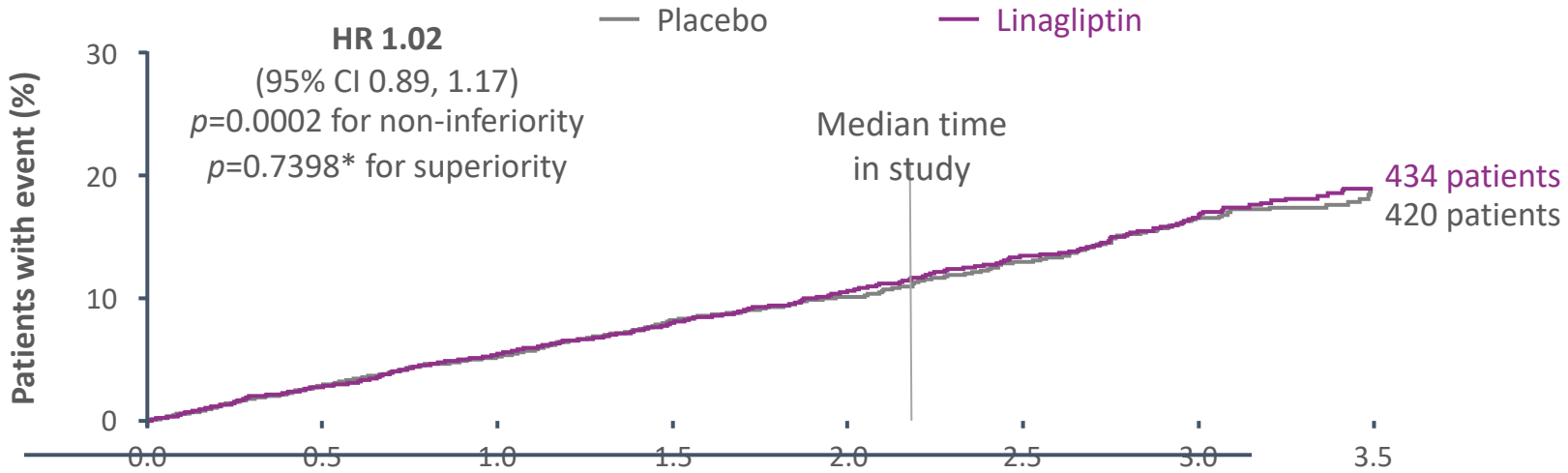


*eGFR ≥30 to <50 ml/min/1.73 m2; †Trial excluded patients with eGFR <30 ml/min/1.73 m^2 CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327 (supplementary appendix); 3. Pfeffer MA *et al. N Engl J Med* 2015;373:2247 (supplementary appendix); 4. Green JB *et al. N Engl J Med* 2015;373:232 (supplementary appendix); 5. Zinman B *et al. N Engl J Med* 2015;373:2117 6. Neal B *et al. Diabetes Obes Metabol* 2017;19:926; 7. Marso SP *et al. N Engl J Med* 2016;375:311; 8. Holman RR *et al. N Engl J Med* 2017;377:1228

The long-term CV safety profile of linagliptin was confirmed

Time to first occurrence of 3P-MACE

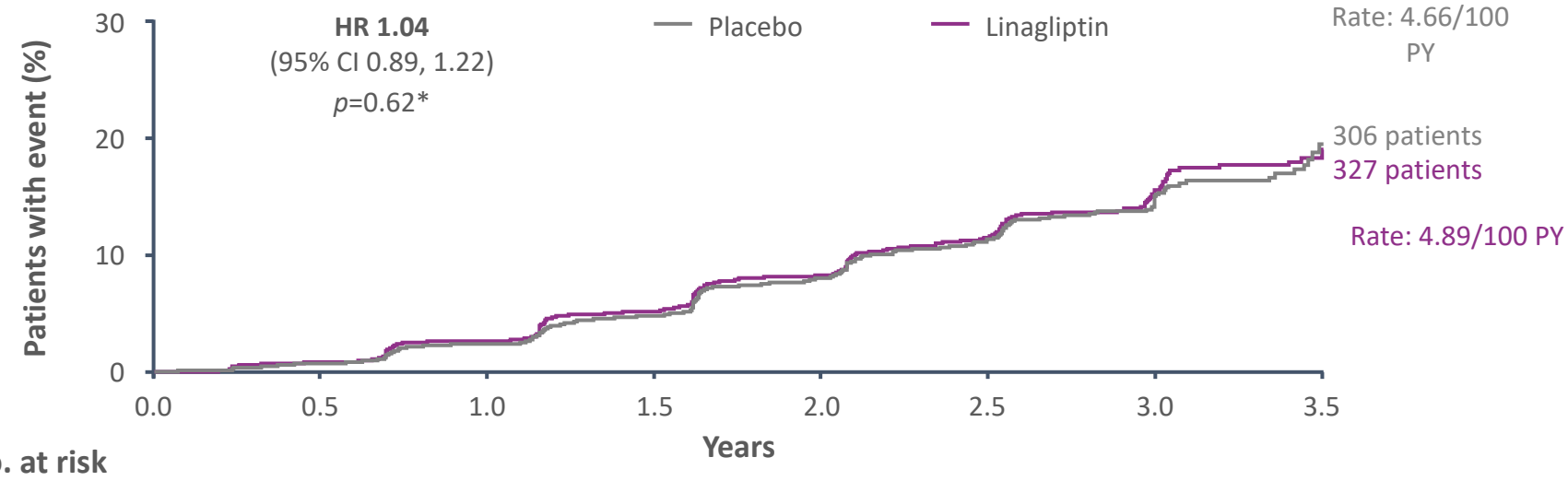


No. of patients								
Placebo (n)	3,485	3,353	3,243	2,625	1,931	1,285	758	251
Linagliptin (n)	3,494	3,373	3,254	2,634	1,972	1,306	778	269

Linagliptin event rate 5.77/100 PY Placebo event rate 5.63/100 PY
Treated set, Kaplan-Meier estimate. Hazard ratio and 95% CI based on Cox regression model with terms for treatment group (p=0.7398) and region (p=0.7878); *Two-sided
3P-MACE, 3-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)
Rosenstock J, et al. JAMA. 2018 Nov 9. doi: 10.1001/jama.2018.18269

Time to first occurrence of key secondary outcome: sustained ESKD, sustained decrease of ≥40% in eGFR from baseline, or death due to kidney disease

The kidney safety profile of linagliptin was confirmed

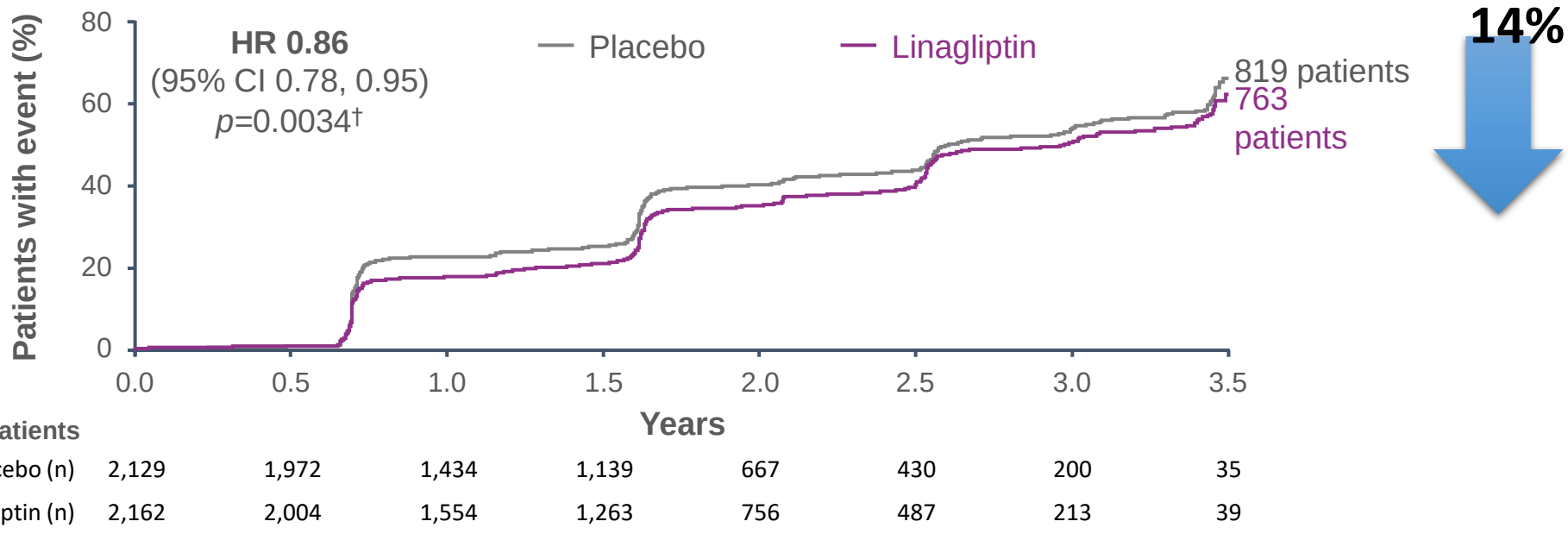


No. at risk								
Placebo	3485	3213	2995	2298	1608	1005	496	103
Linagliptin	3494	3227	3018	2345	1675	1040	518	109

1. Cardiovasc Diabetol 2018;17:39

Linagliptin was associated with a significant reduction in albuminuria progression

Time to first occurrence of albuminuria progression*

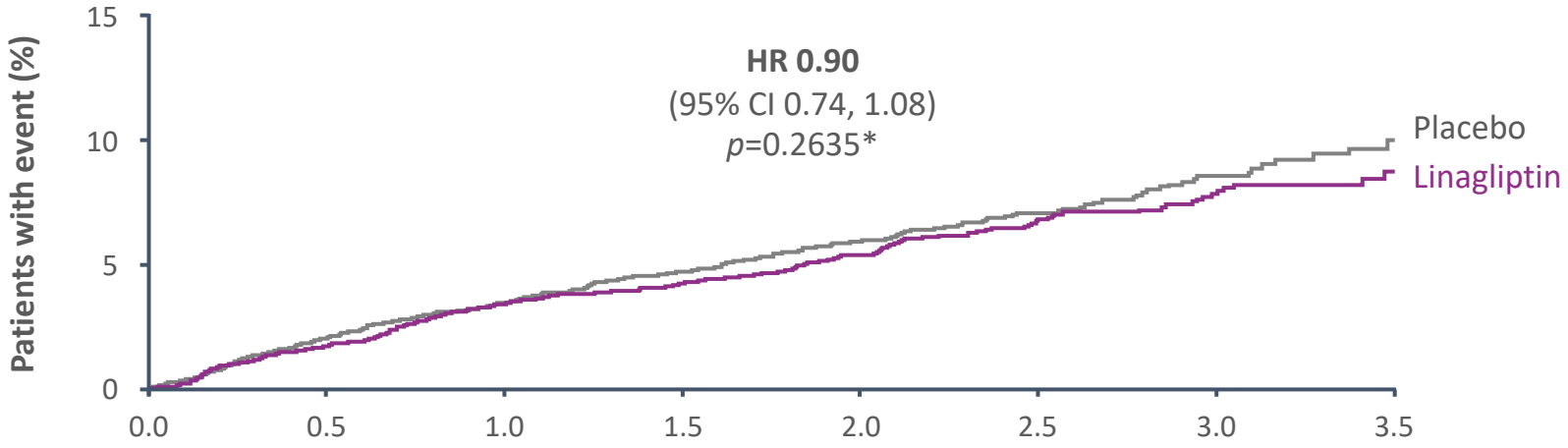


No. of patients								
Placebo (n)	2,129	1,972	1,434	1,139	667	430	200	35
Linagliptin (n)	2,162	2,004	1,554	1,263	756	487	213	39

1. Cardiovasc Diabetol 2018;17:39

There was no increased risk of hospitalization for HF with Linagliptin

Time to first occurrence of adjudication-confirmed hospitalization for HF

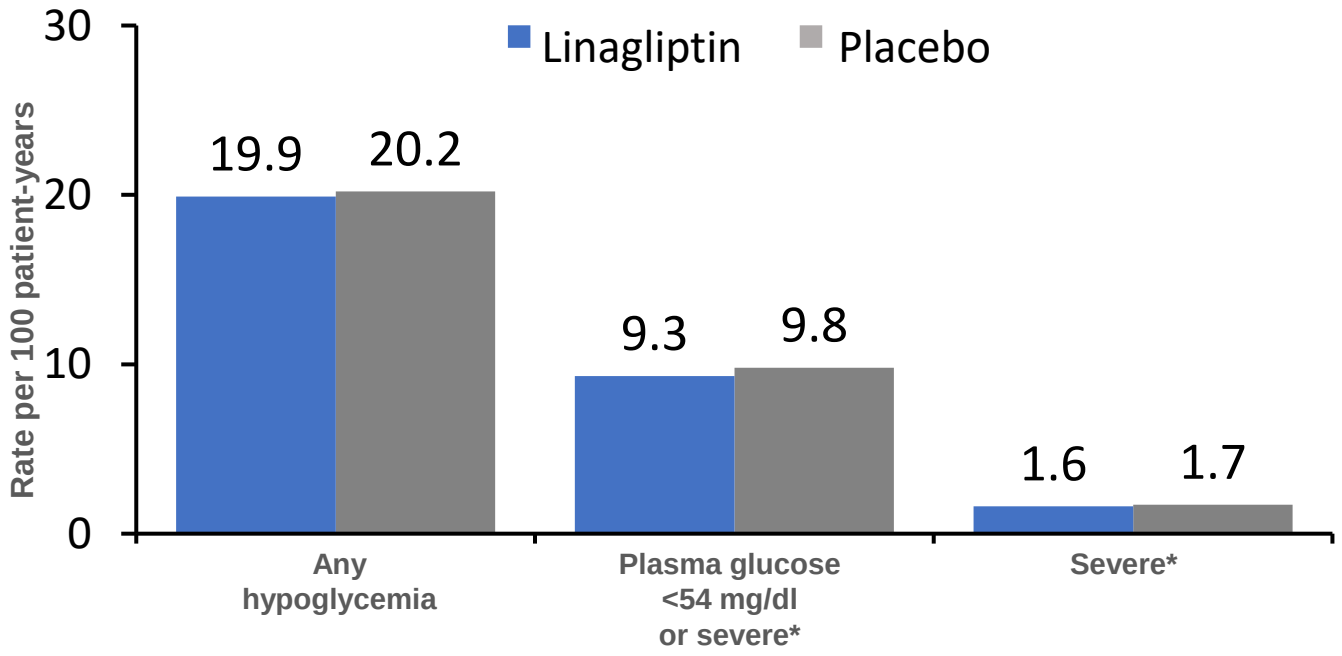


No. of patients								
Placebo (n)	3,485	3,336	3,222	2,621	1,923	1,285	767	258
Linagliptin (n)	3,494	3,361	3,243	2,647	1,979	1,317	787	280

1. Cardiovasc Diabetol 2018;17:39

Overall linagliptin did not increase the risk of hypoglycemia

Hypoglycemia: rates per 100 patient-years overall



1. Cardiovasc Diabetol 2018;17:39

Dosage And Administration [1]

Recommend dosing:

The recommended dose of Linagliptin is 5 mg once daily.

Linagliptin tablets can be taken with or without food.

1. Tradjenta (linagliptin) tablets Label – FDA 2019

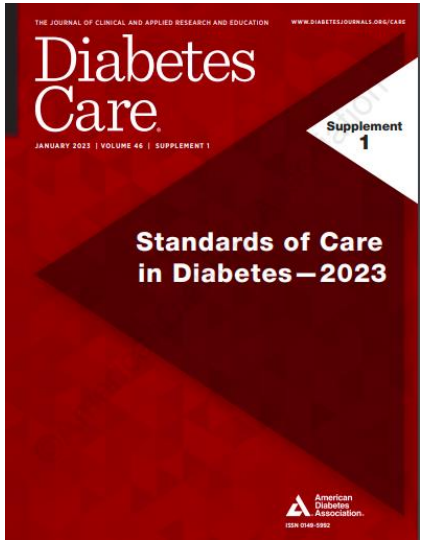
DPP-4 inhibitors as one available incretin-based therapy

Advantages	▪ No hypoglycemia ▪ Weight "neutrality" ▪ Well tolerated ▪ Once-daily dosage ▪ Evidence for cardiovascular safety
Disadvantages	▪ Intermediate efficacy for glycemic control ▪ Occasional reports of urticaria/angioedema ▪ Cases of pancreatitis observed ▪ Some concern regarding increased rate of hospitalization for heart failure (Saxagliptin) ▪ Long-term safety unknown
Cost	High

Modified from Inzucchi SE, et al. Diabetes Care 2015;38:140–19.

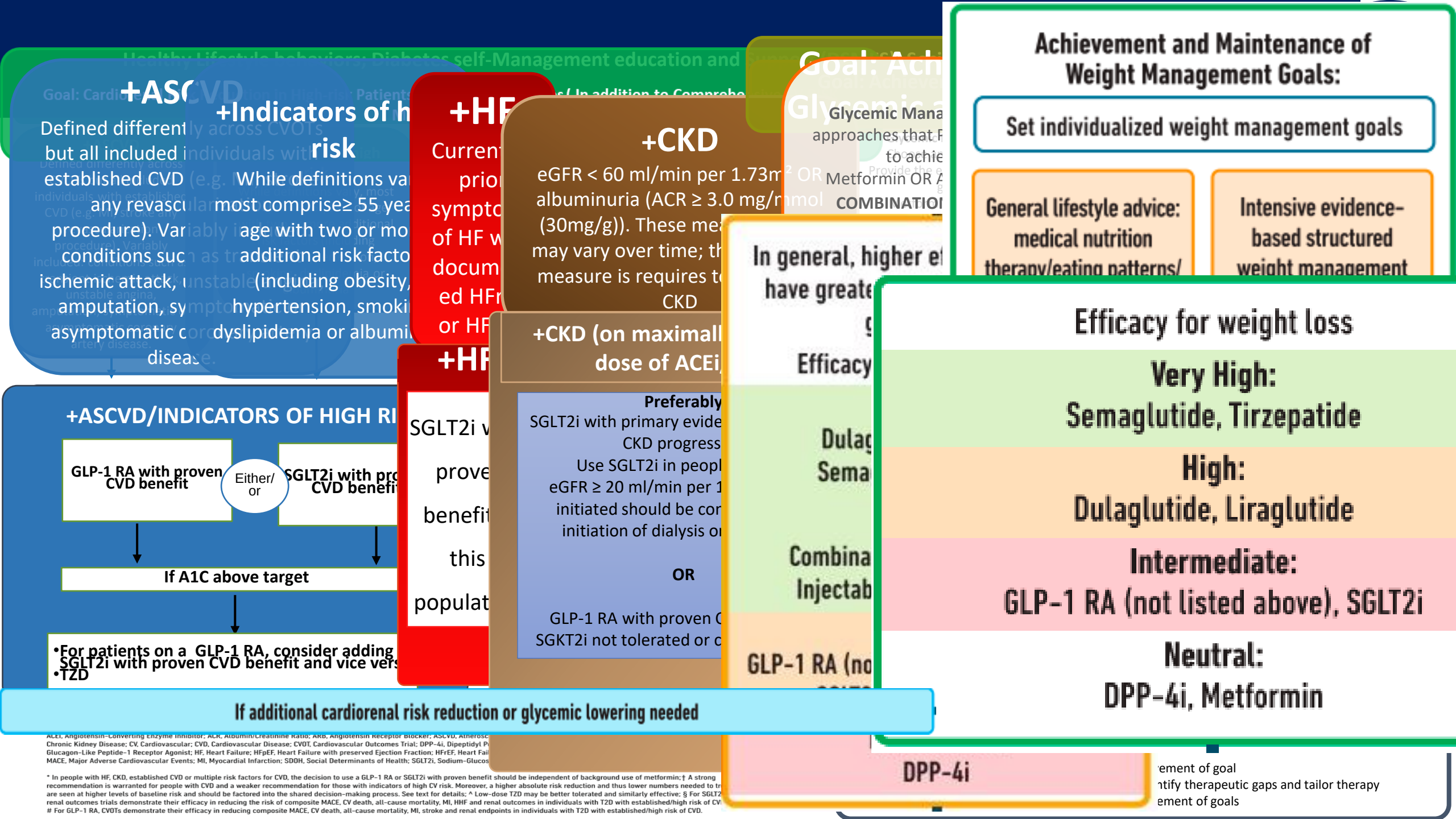
DPP4 Inhibitors Side Effects

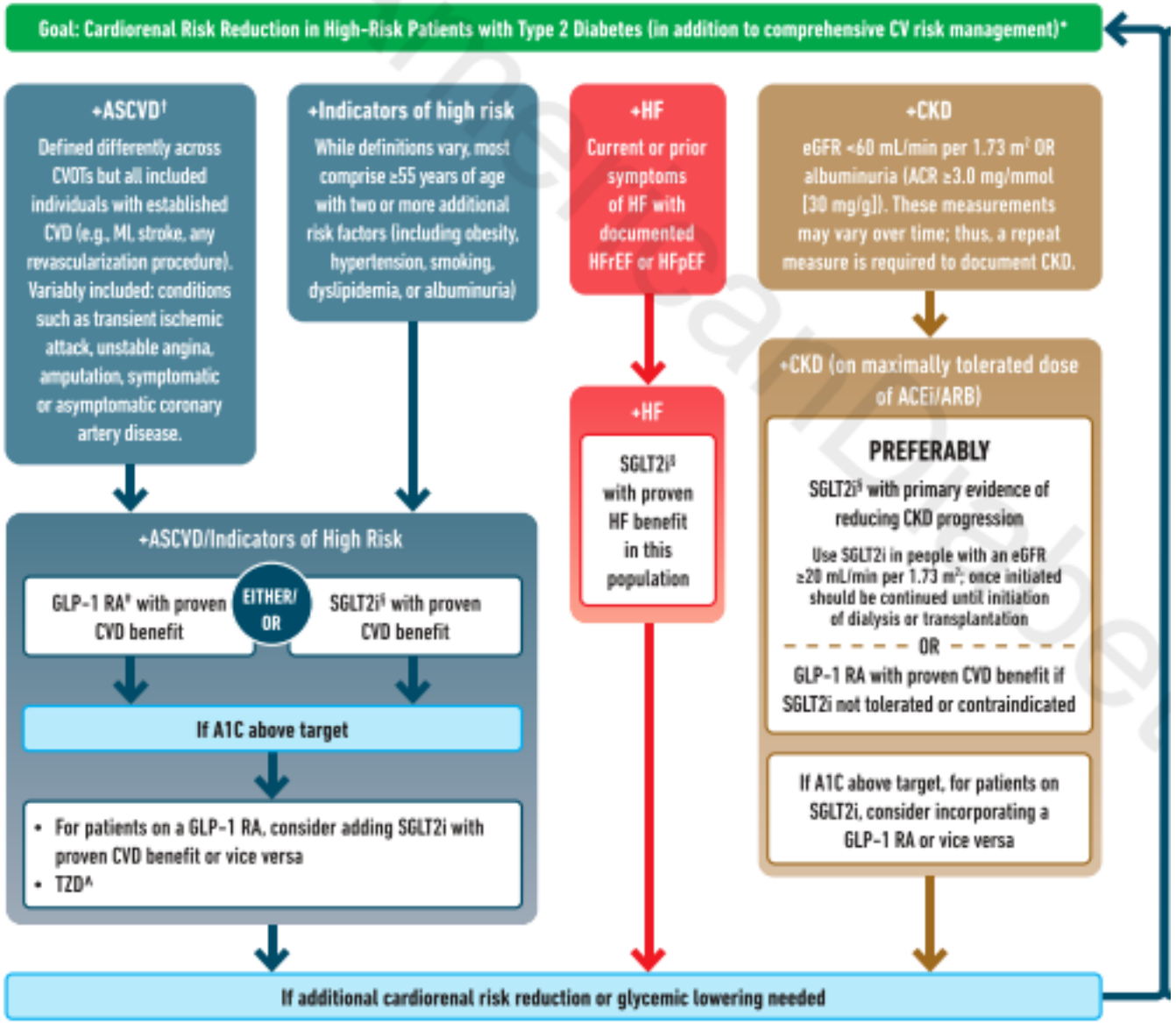
- Headache
- Nasopharyngitis (RR 1.13, 95% CI 0.99-1.29)Compared with placebo, and another class of anti-diabetic agents
- Acute pancreatitis has been reported but insufficient data to know if there is a causal relationship
- Should not be used in a patient with a hx of pancreatitis
- Increased risk of IBD??
- Skin reactions
- Muskuloskeletal ; joint pain

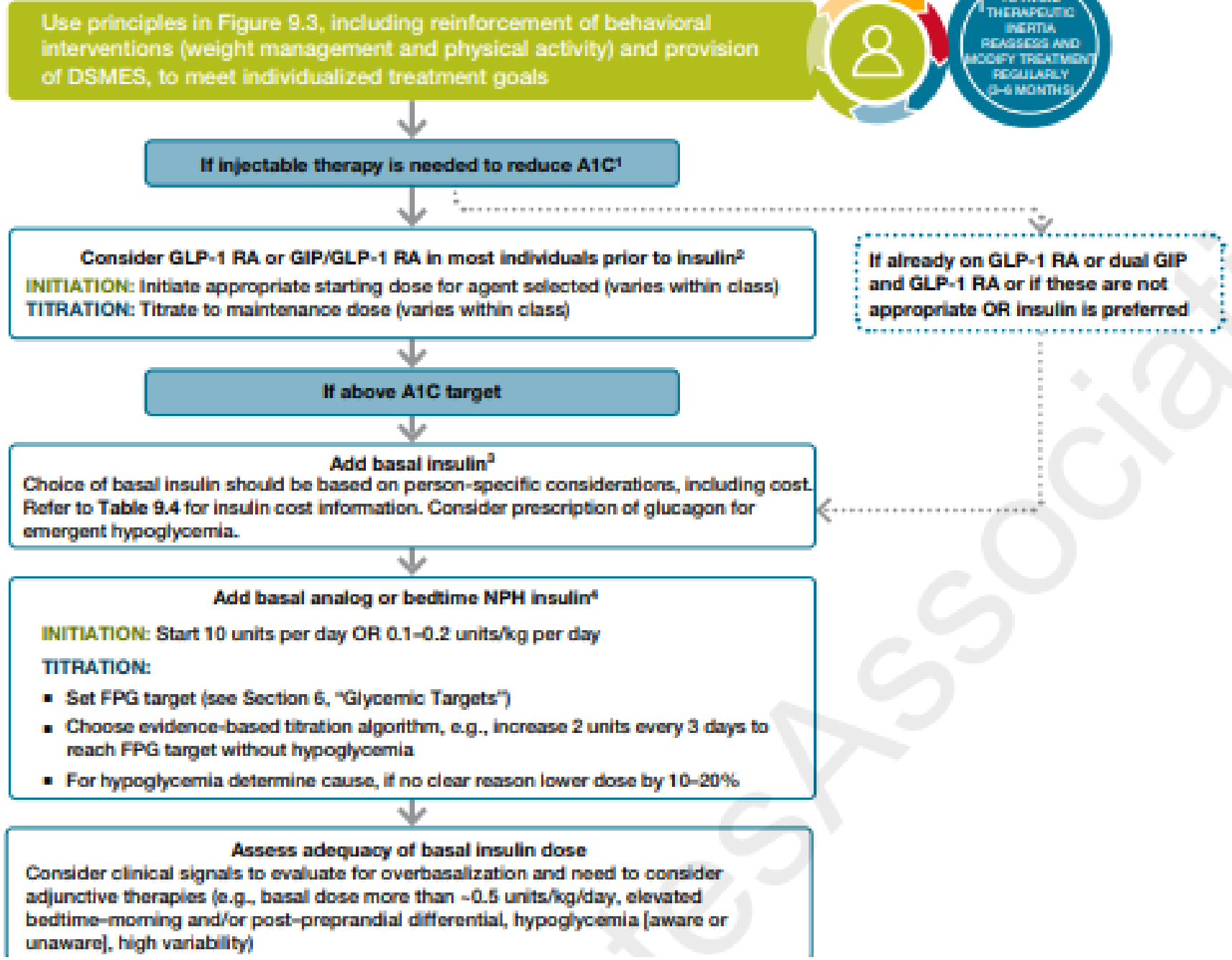


Recommendations of ADA 2023 Guideline

Standard of Medical Care in Diabetes-2023/The American Diabetes Association Guideline


+ASCVD
Defined different
but all included i
established CVD
any revasc
procedure). Var
conditions suc
ischemic attack,
amputation, sy
asymptomatic c
+Indicators of h
risk
While definitions va
most comprise≥ 55 yea
age with two or mo
additional risk facto
(including obesity,
hypertension, smoki
dyslipidemia or albumi
+HF
Current
prio
sympto
of HF w
docum
ed HFr
or HF
+CKD
eGFR < 60 ml/min per 1.73m² OR
albuminuria (ACR ≥ 3.0 mg/mmol
(30mg/g)). These mea
may vary over time; th
measure is requires t
CKD
+CKD (on maximall
dose of ACEi
+HF
SGLT2i v
prove
benefit
this
populat
Preferably
SGLT2i with primary evide
CKD progress
Use SGLT2i in peopl
eGFR ≥ 20 ml/min per 1
initiated should be cor
initiation of dialysis or
OR
GLP-1 RA with proven C
SGKT2i not tolerated or c
Goal: Achi
Glycemic Mana
approaches that F
to achie
Metformin OR A
COMBINATIO
In general, higher ef
have greate
Efficacy
Dulag
Sema
Combina
Injectab
GLP-1 RA (no
DPP-4i
+ASCVD/INDICATORS OF HIGH RI
GLP-1 RA with proven CVD benefit
Either/ or
SGLT2i with pro CVD benefi
If A1C above target
•For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice vers
•TZD
If additional cardiorenal risk reduction or glycemic lowering needed
Achievement and Maintenance of Weight Management Goals:
Set individualized weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/
Intensive evidence-based structured weight management
Efficacy for weight loss
Very High:
Semaglutide, Tirzepatide
High:
Dulaglutide, Liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
DPP-4i, Metformin
ement of goal
ntify therapeutic gaps and tailor therapy
ement of goals
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosc
Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl P
Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Fai
MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucos
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to tr
are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2
renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CV
For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.


Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*
+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.
+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.
+ASCVD/Indicators of High Risk
GLP-1 RA‡ with proven CVD benefit
EITHER/ OR
SGLT2i§ with proven CVD benefit
If A1C above target
• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
• TZD^
+HF
SGLT2i§ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiorenal risk reduction or glycemic lowering needed


Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
THERAPEUTIC INERTIA
REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.
Add basal analog or bedtime NPH insulin[4]
INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day
TITRATION:
Set FPG target (see Section 6, "Glycemic Targets")
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime–morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)

Case presentation

- A 58-year-old woman with 12-year history of type 2 diabetes is referred to you. She takes metformin 2000 mg and gliclazide MR 60 mg daily. She respects the diet recommended by the nutritionist.
- She has peripheral neuropathy.
- She has a history of acute MI during a couple of months ago.
- She claims that in the past, with increasing gliclazide dose, several hypoglycemic episodes had occurred. She fears hypoglycemia because she lives alone.
- BMI: 35.5 kg/m^2

Case presentation

- Laboratory tests:
  - FBS: 146 mg/dl
  - HbA1c: 8.5%
  - Cr: 1.3 mg/dl (eGFR ~ 50 ml/min)

- **Which therapeutic approach would you recommend to her?**

A) Add basal insulin
B) Add Liraglutide
C) Add pioglitazone
D) Add sitagliptin

Case 2

- A 56 years old patients with T2DM and CKD due to APKD is referred to use due to uncontroll DM. 1+ pitting edema is seen in pretibial. He is taking metformin 1000 mg/d
- Lab test results:
- GFR 20
- FBS 130, HBA1C 8.5%
  which is the best medication to control his diabetes?
- Liraglutide
- Sitagliptin 100
- Pioglitazone 15
- Linagliptin 5

Conclusions

- Compared with DPP-4 inhibitors, GLP-1 receptor agonists are associated with:
  - greater HbA_{1c} reduction and greater weight loss
  - similar low risk of hypoglycaemia but an increased incidence of gastrointestinal events
  - greater overall treatment satisfaction
- Switching from a DPP-4 inhibitor to a GLP-1 receptor agonists was associated with:
  - significant additional HbA_{1c} reductions
  - significant weight loss
  - improved overall treatment satisfaction without a change in perceived treatment flexibility or convenience

➢ Patients with higher baseline HbA1C and BMI experience better results regarding to glycemic control and weight loss

Thank you for your patience