GLP-1 Analogues

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Actualités Néphrologiques Jean Hamburger

CONFLICT OF INTEREST

Gautier Jean-François

I have the following potential conflicts of interest to report:

Consulting honoraria and/or lecture fees:
AZ-BMS, Gilead, Lilly, MSD, Novartis, NovoNordisk, Sanofi-Aventis, Servier

Research supports:
Lilly, MSD, Novartis, NovoNordisk

Study investigator:
Lilly, MSD, Novo

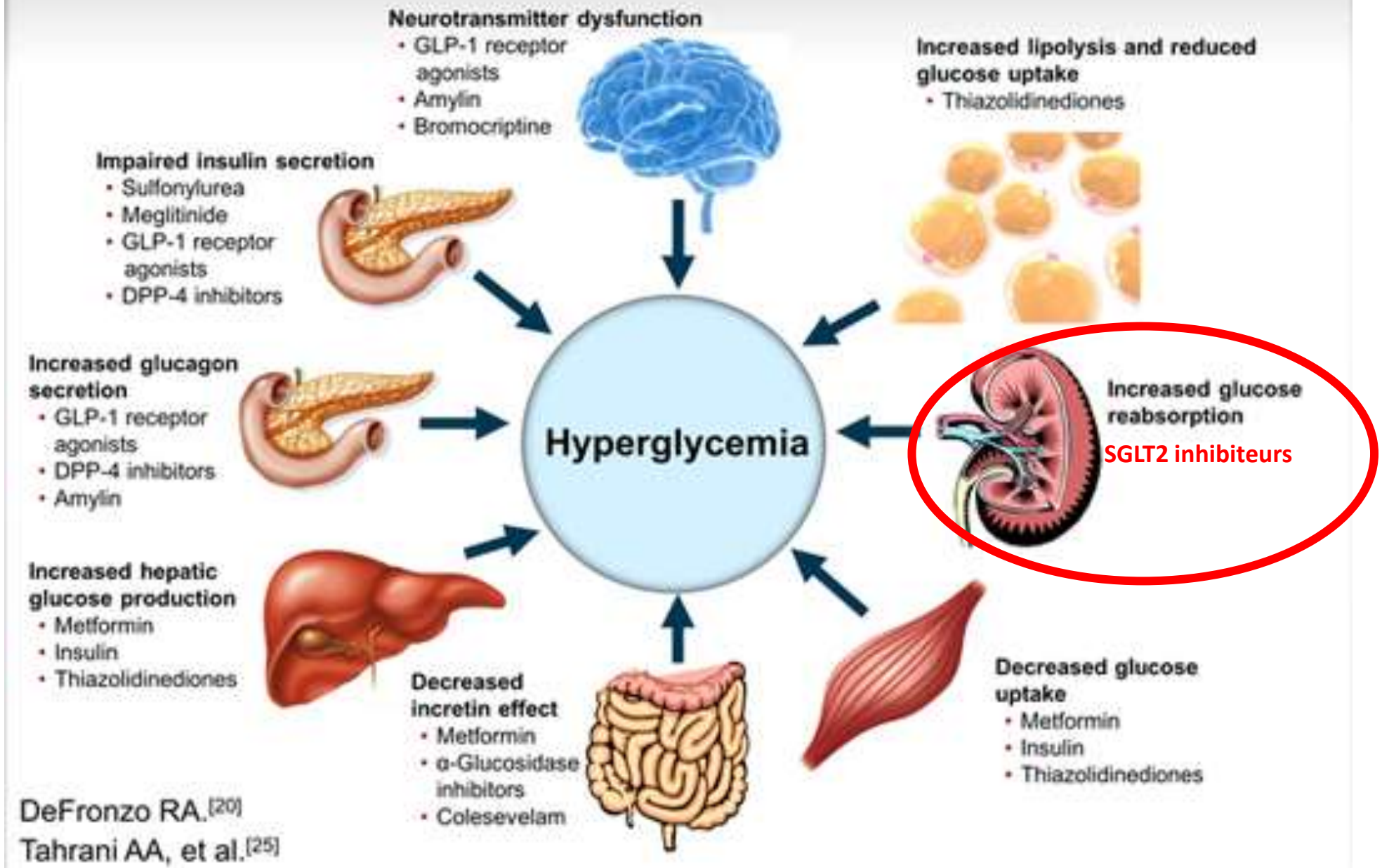
T2D in 2024…

- A highly prevalent disease worldwide (593 millions expected in 2035)
- A disease of the beta cells of Langerhans islet that are unable to cope with the occurrence or worsening of insulin resistance
- A multigenic, multifactorial and heterogeneous disease (gene-environment interaction)
- A diagnosis made by default because of the lack of positive diagnosis biomarker

T2D in 2024…

- Life style modifications remains the first line treatment
- Bariatric surgery is more and more used to treat diabetes and associated metabolic abnormalities
- Diabetes remission is possible (weight loss; ketosis prone type 2 diabetes..)
- Insulin therapy is frequently needed due to the lack of long term efficiency of oral hypoglycaemic drugs
- 2 new therapeutic classes with unexpected good effects

Hyperglycemia in Type 2 Diabetes



DeFronzo RA.[20]
Tahrani AA, et al.[25]

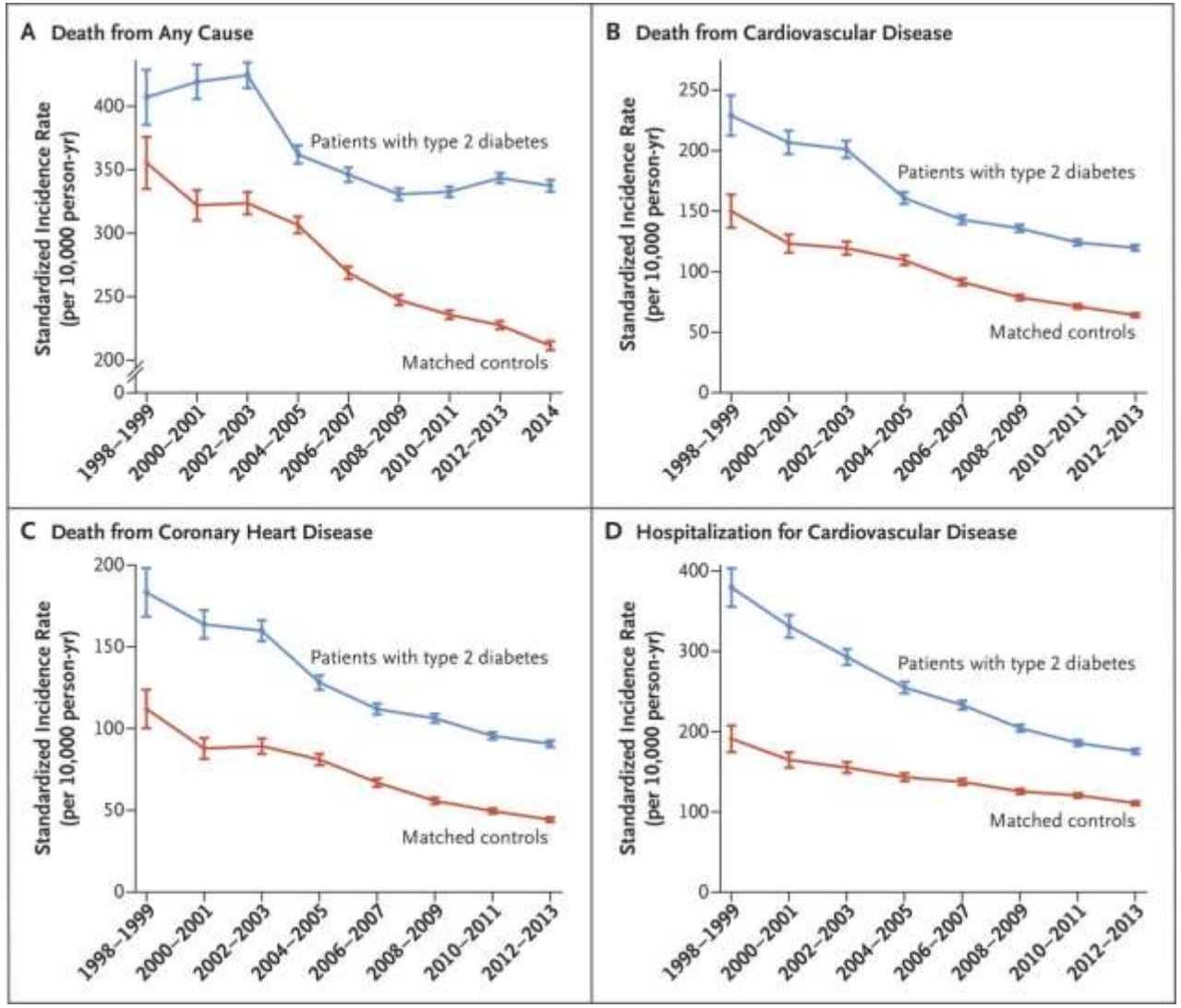
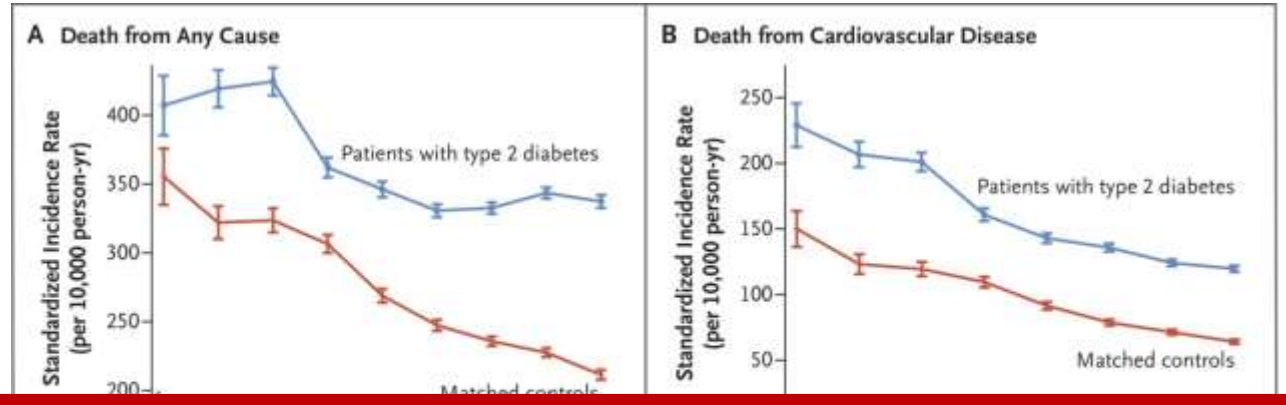


Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals

Rawshani A et al, NEJM 2017

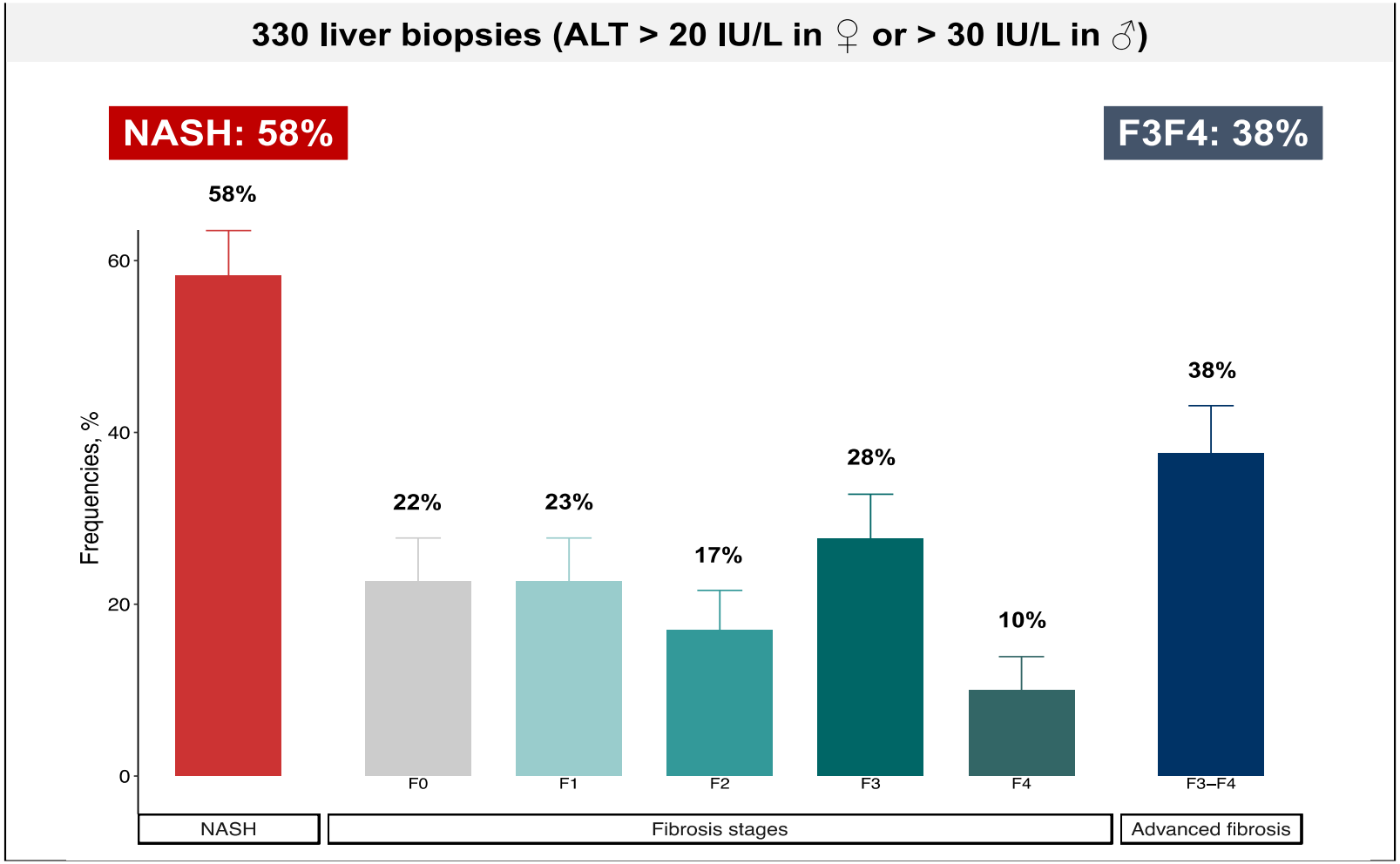


The better cardiovascular prognosis of T2D makes the occurrence at the "front stage" of:

- Diabetic foot ulcers: 20%
- Terminal kidney disease: 1st cause of dialysis
- Heart failure: 20%
- NAFLD: severe liver injuries > 30 %
- Cognitive impairment /dementia: risk X2
- Sleep Apnea Syndrome
- Cancer

Rawshani A et al, NEJM 2017

High prevalence of F3-F4 in patients with T2DM



Castera L et al. Diabetes Care 2023; doi: 10.2337/dc22-2048.

Table 1. characteristics of the 330 patients

Variables	Median (IQR)
Age (yrs)	59 [52 - 66]
Male gender (%)	63
WC (cm)	109 [101 - 120]
BMI (kg/m^2)	32 [28 - 35.75]
Obese (%)	66
Hypertension (%)	67
HDL-cholesterol (H <0.4g/L; F <0.5g/L) (%)	59
Triglycerides >1.5g/L (%)	51
Duration of diabetes (yrs)	9 [5 - 15]
At least one microvasc complication (%)	60
At least one macrovasc complication (%)	20
HbA1C (%)	7.5 [6.8-8.4]
AST (IU/L)	35 [27-46]
ALT (IU/L)	49 [34-70]
GGT (IU/L)	54 [35-86]
Platelet (G/L)	243 [197-292]
FIB-4	1.20 [0.90-1.69]
Liver stiffness (kPa)	8.3 [6.2-11.8]

Treatments of Type 2 diabetes

- Lifestyle modification
- Bariatric surgery

- Metformin
- Sulfonylureas: Hypos
- Peroxisome proliferator-activated receptor (PPAR) agonists
- ***Sodium glucose cotransporter* (SGLT)-2 inhibitors**
- ***GLP-1 receptor agonists***
- ***Bi-agonists GLP1-GIP***
- Insulin

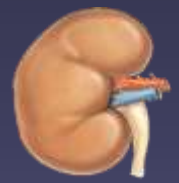
Sodium glucose cotransporter (SGLT)-2 inhibitors

- Beneficial effect on blood control, on body weight and on blood pressure (without increasing heart rate)
- No hypos
- Protection cardiovascular and/or renal in patients with high cardiovascular risk, chronic kidney disease or heart failure
- NAFLD?
- First class of hypoglycemic drug that does not favor glucose uptake by cells
- Side effects: genital infection; volemic depletion; “euglycemic” DKA

GLP-1 receptor agonists

- Superior anti-hyperglycemic efficacy than iSGLT2
- Beneficial effect on weight loss
- Increase insulin secretion (no effect on insulin action)
- No hypos
- NASH: biopsies proven
- Cognition?
- Cardiovascular protection and reduced risk of macroalbuminuria demonstrated in case of proven atheromatous disease with liraglutide, dulaglutide and semaglutide
- Side effects: digestive disorders - especially at initiation of treatment, cholelithiasis, rare cases of acute pancreatitis (causality not demonstrated)

GLP-1 RAs have multifactorial effects

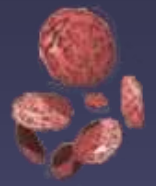


Kidneys
- ↑ Natriuresis
- ↑ Diuresis
- ↓ Inflammation
- ↓ Oxidative stress
- RAAS modulation

Blood vessels
- ↓ Blood pressure

Brain
- ↓ Body weight
- ↓ Appetite
- ↓ Satiety

Heart
- ↑ Cardioprotection



Platelets
- ↓ Coagulation

GLP-1

Intestine
- ↓ Postprandial lipids

Fat and liver
- ↓ Inflammation

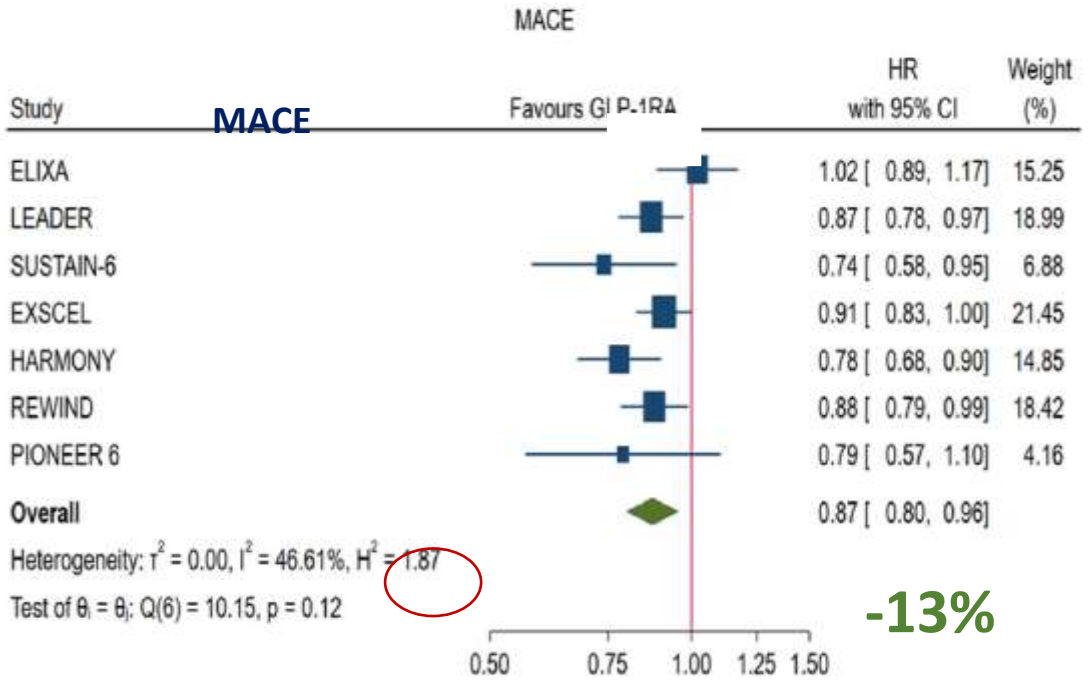
Pancreas
- ↓ Glucose and hypoglycaemia

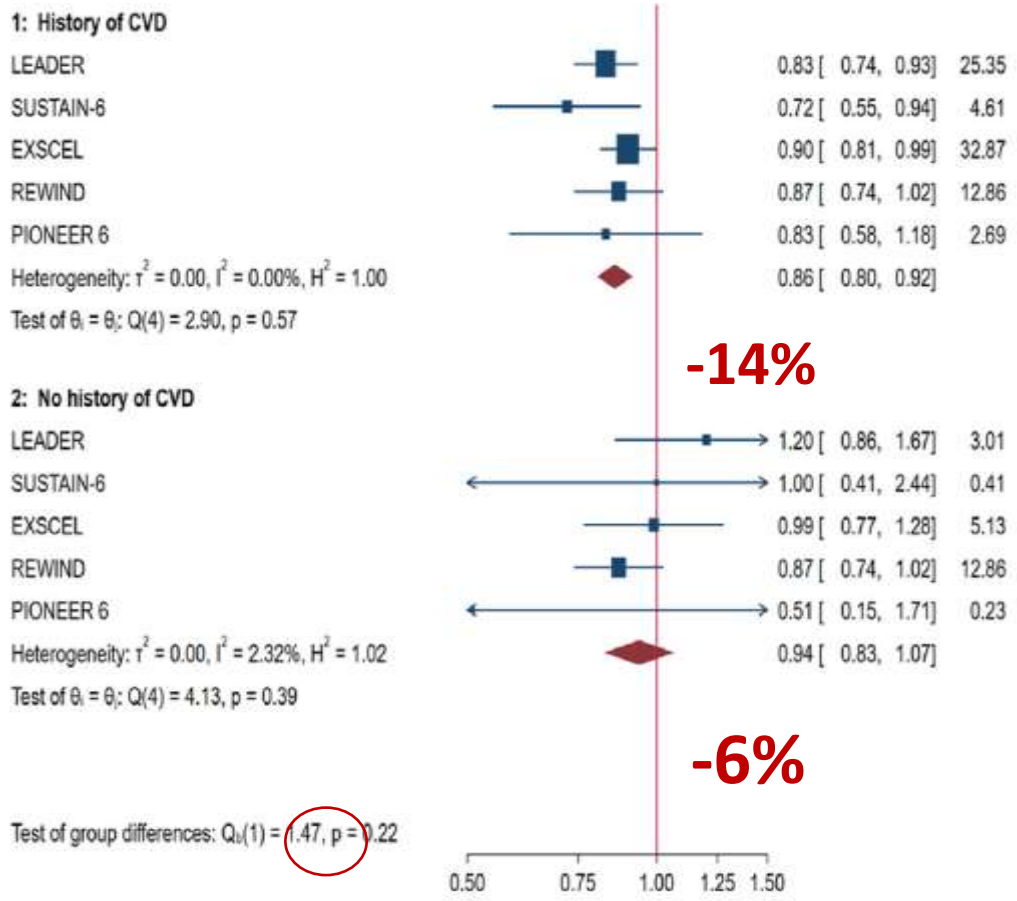
α-cells
- ↓ Glucagon secretion

β-cells
- ↑ Insulin secretion and biosynthesis
- ↓ Apoptosis

GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAAS, renin-angiotensin-aldosterone system
Adapted from Drucker. *Cell Metab* 2016;24:15–30; DeFronzo. *Diabetes Obes Metab* 2017;19:1353–62

GLP-1 RA : meta-analysis CVOTs



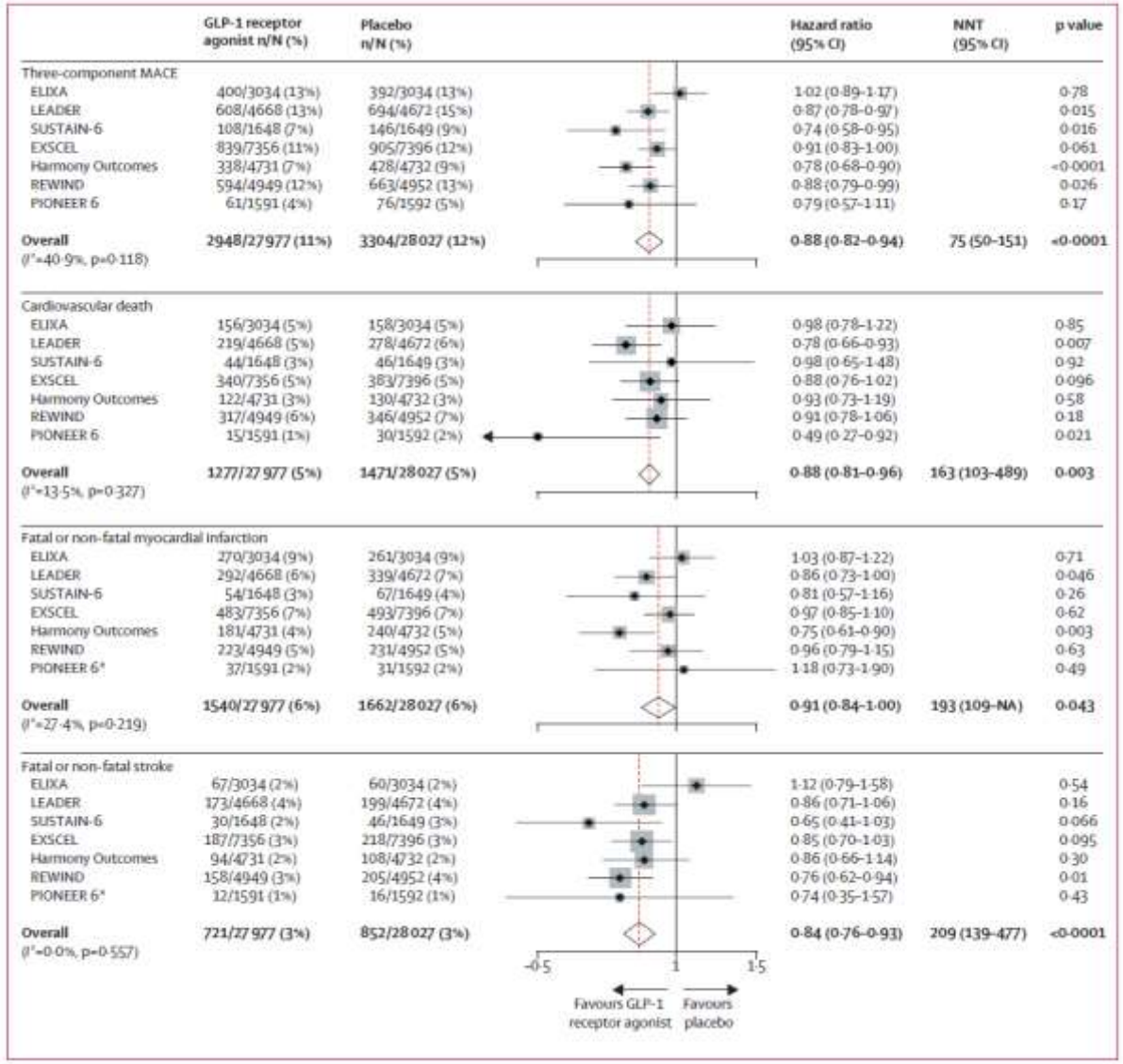


Excluding ELIXA

*HR = 0.86 (0.80-0.93); **I^2=2,7%***

Giugliano D et al. Diabetes Obes Metab 2019;21:2576-80

GLP-1 RA : meta-analysis CVOTs



MACE -12% (p< 0,0001)

I^2 = 40,9%

4 positive studies/ 7

Mortality CV -12% (p=0,003)

I^2 = 13,5%

2 positive studies/ 7

MI -9% (p=0,043)

I^2 = 27,4%

2 positive studies / 7

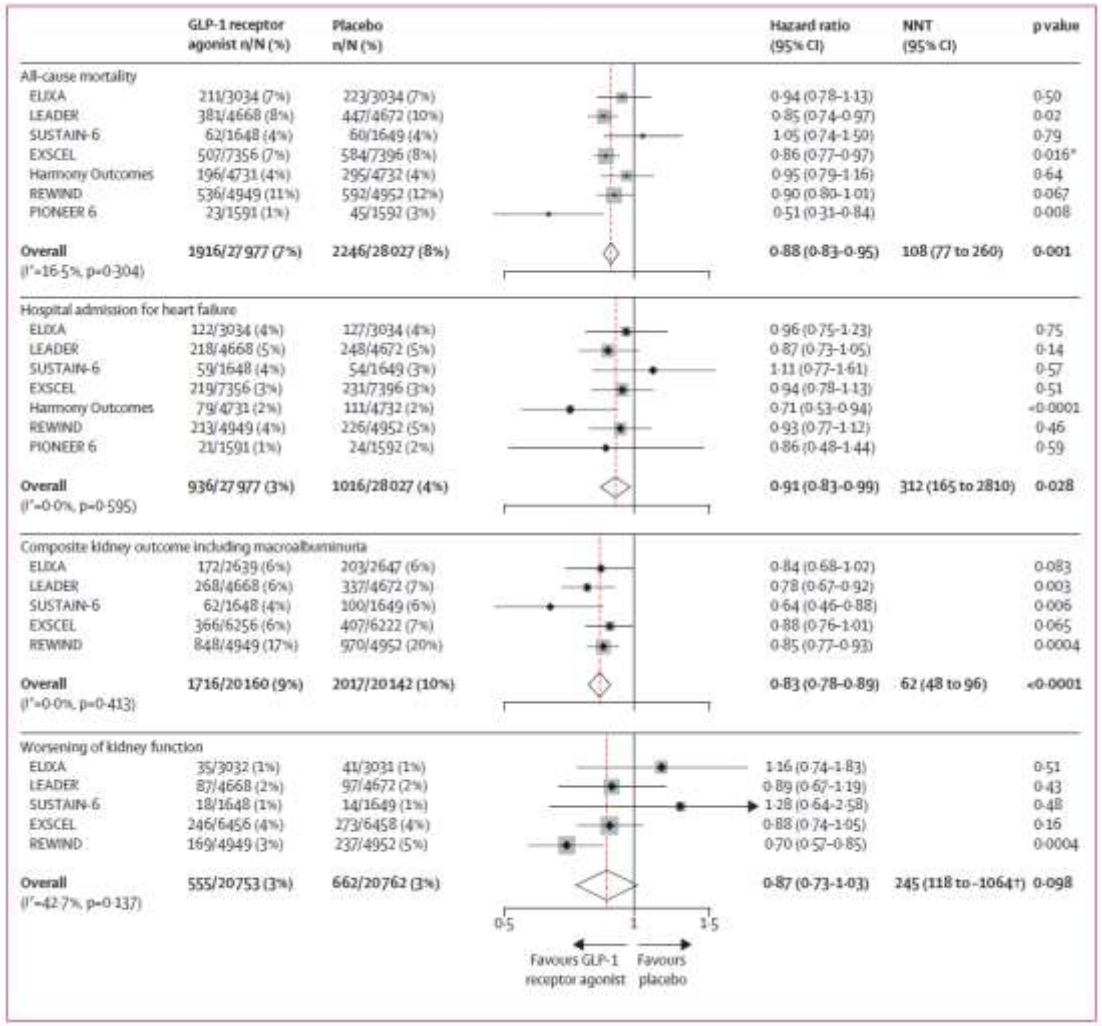
Stroke -16% (p<0,0001)

I^2 = 0%

1 positive study/ 7

Kristensen SL et al. Lancet Diabetes Endocrinol 2019

GLP-1 RA : meta-analysis CVOTs



	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)	0·95 (0·79–1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80–1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31–0·84)		0·008
Overall	**1916/27 977 (7%)**	**2246/28 027 (8%)**	**0·88 (0·83–0·95)**	**108 (77 to 260)**	**0·001**
(I²=16·5%, p=0·304)					
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall	**936/27 977 (3%)**	**1016/28 027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**
(I²=0·0%, p=0·595)					
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2639 (6%)	203/2647 (8%)	0·84 (0·68–1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67–0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46–0·88)		0·006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76–1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77–0·93)		0·0004
Overall	**1716/20 160 (9%)**	**2017/20 142 (10%)**	**0·83 (0·78–0·89)**	**62 (48 to 96)**	**<0·0001**
(I²=0·0%, p=0·413)					
Worsening of kidney function					
ELIXA	35/3032 (1%)	41/3031 (1%)	1·16 (0·74–1·83)		0·51
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67–1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64–2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74–1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57–0·85)		0·0004
Overall	**555/20 753 (3%)**	**662/20 762 (3%)**	**0·87 (0·73–1·03)**	**245 (118 to ∞)†**	**0·098**
(I²=42·7%, p=0·137)					

0·5 1 1·5

Favours GLP-1 receptor agonist — Favours placebo

All cause Mortality -12% (p=0,001)

I² = 16,5%

3 études positives / 7

Hosp. for Heart failure-9% (p=0,028)

I² = 0%

1 étude positive / 7

Critère composite rénal incluant macroalbU **-17% (p<0,0001)**

I² = 0%

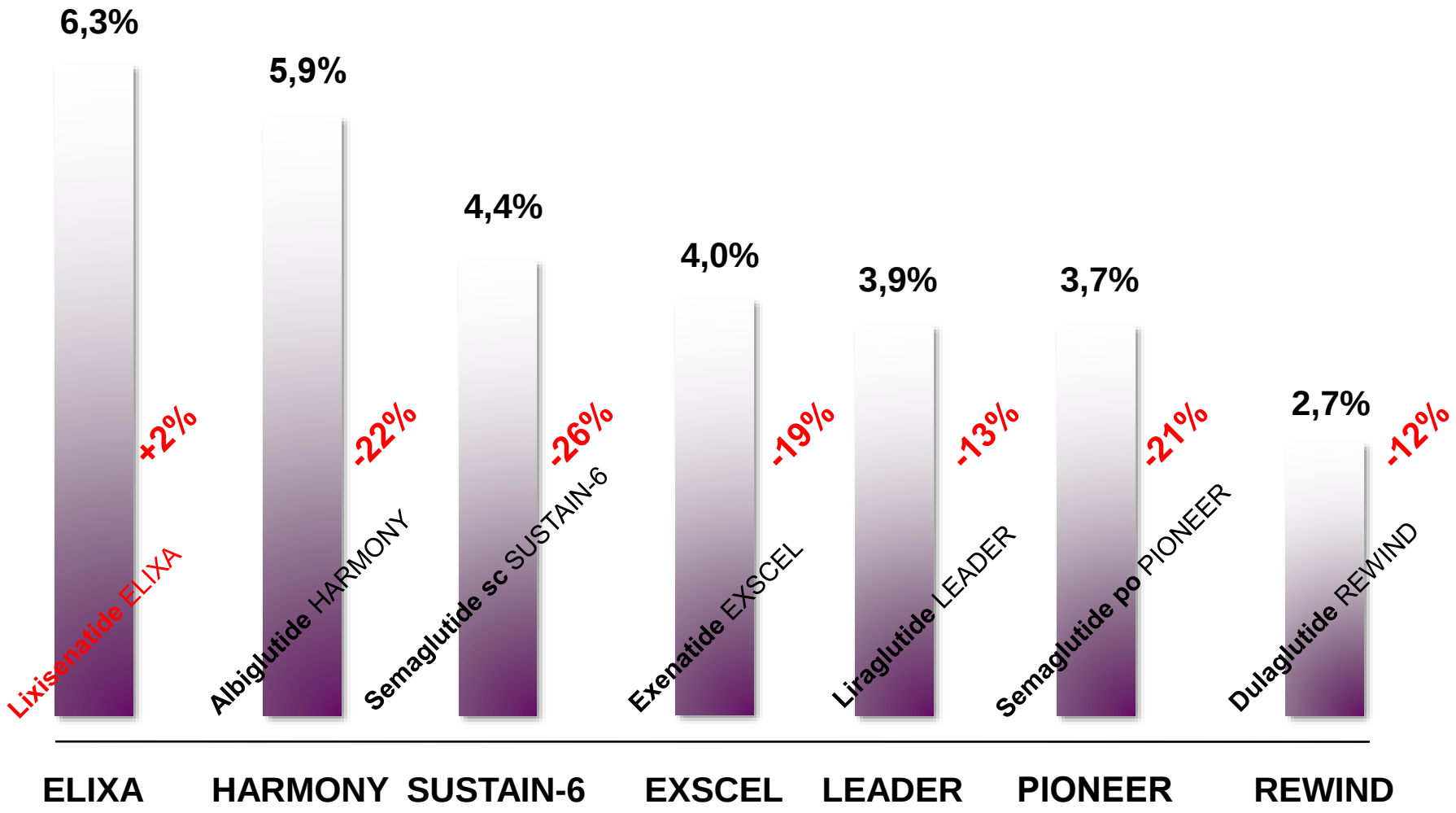
3 études positive / 5

Dégradation DFG ***ns***

Kristensen SL et al. Lancet Diabetes Endocrinol 2019

GLP-1 RAs and CVOTs

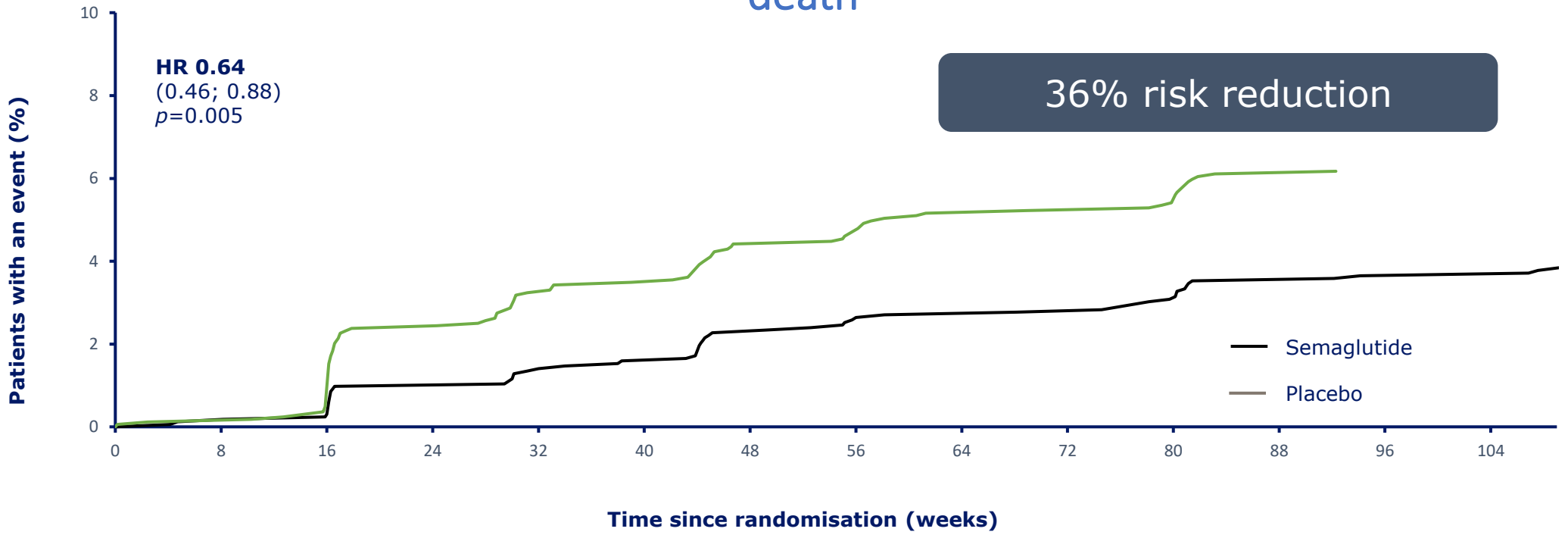
CV events/yr in the placebo group, RRR with GLP-1 RA



1. Gerstein HC et al. Diabetes Obes Metab 2018;20(1):42-9
2. Holman RR et al. N Engl J Med 2017;377(13):1228-39
3. Hernandez AF, Green JB, Janmohamed S et al. Lancet. 2018; (published online Oct 2.)
4. Eli Lilly and Company. 2018. Available at: https://investor.lilly.com/news-releases/news-release-details/trulicityr-dulaglutide-demonstrates-superiority-reduction. Accessed 5 Nov 2018
5. Marso SP, et al, *New Eng J of Med*. 2016;375(19):1834-1844.
6. Marso SP et al, *New Eng J of Med.* 2016;375(4):311-322.
7. Pfeffer MA et al, *New Eng J of Med.* 2015;373(23):2247-2257.
8. Husain M et al. N Engl J Med. 2019

SUSTAIN-6 indicating significant reno-protective effects

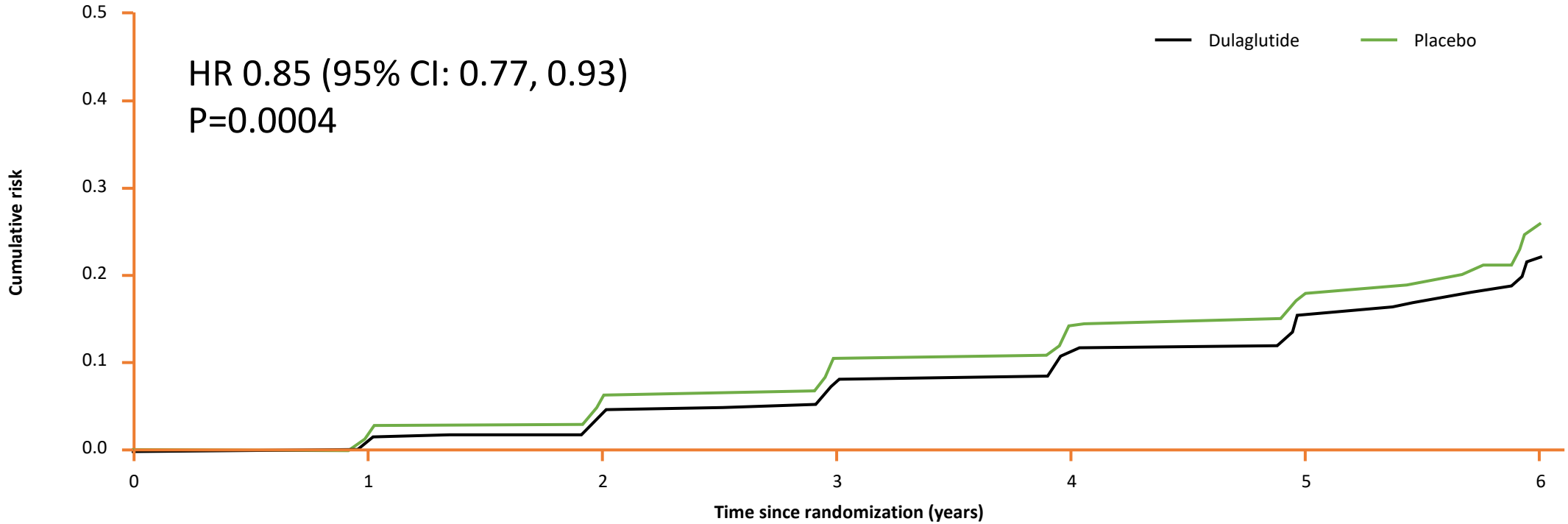
Secondary endpoint: Macroalbuminuria, doubling of serum creatinine, ESRD or renal death



Marso SP et al. N Engl J Med 2016;375:1834–44. ESRD, end-stage renal disease; HR, hazard ratio

REWIND: Renal composite outcome

New macroalbuminuria, 30% fall in eGFR, or renal replacement Rx



No. at risk							
Placebo	4952	4756	4475	4145	3887	3169	641
Dulaglutide	4949	4798	4571	4303	4045	3320	667

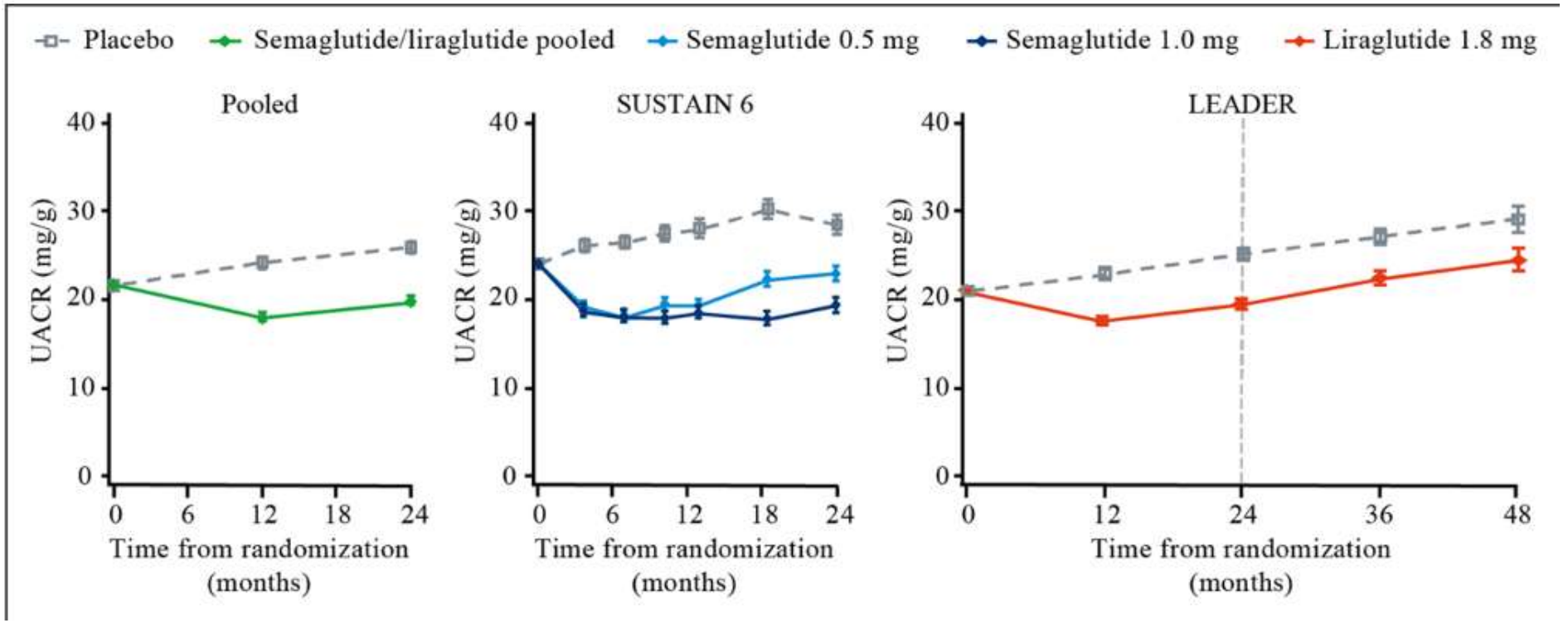
Gerstein HC et al. The Lancet. Published online June 10, 2019, https://doi.org/10.1016/S0140-6736(19)31150-X

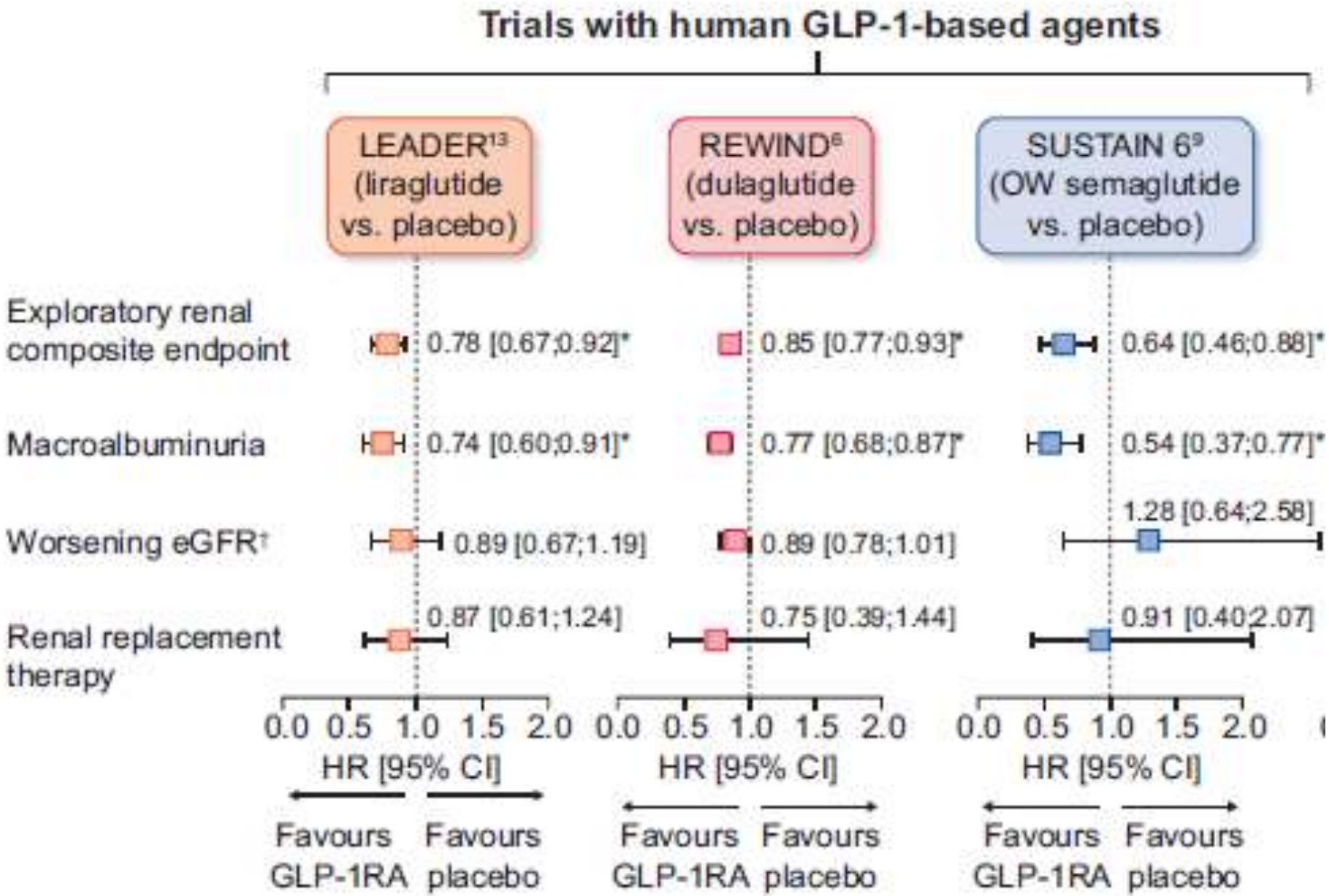
ORIGINAL RESEARCH ARTICLE

Circulation 2022

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

Ahmed M. Shaman, PhD; Stephen C. Bain, MD; George L. Bakris, MD; John B. Buse, MD; Thomas Idorn, MD; Kenneth W. Mahaffey, MD; Johannes F.E. Mann, MD; Michael A. Nauck, MD; Søren Rasmussen, PhD; Peter Rossing, MD; Benjamin Wolthers, MD; Bernard Zinman, MD; Vlado Perkovic, PhD





Rossing P Nephrol Dial Transplant (2023)

In conclusion

- Evidence has emerged of the potential kidney-protective effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in people with type 2 diabetes
- To date, data have mostly been derived from cardiovascular outcome or glycaemic control trials featuring populationsn not selected for chronic kidney disease (CKD) and/or with kidney disease events as secondary outcomes.
- Reduction of CKD progression by GLP-1RAs is yet to be confirmed and requires dedicated trials of kidney outcomes withGLP-1RAs.

Flow

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

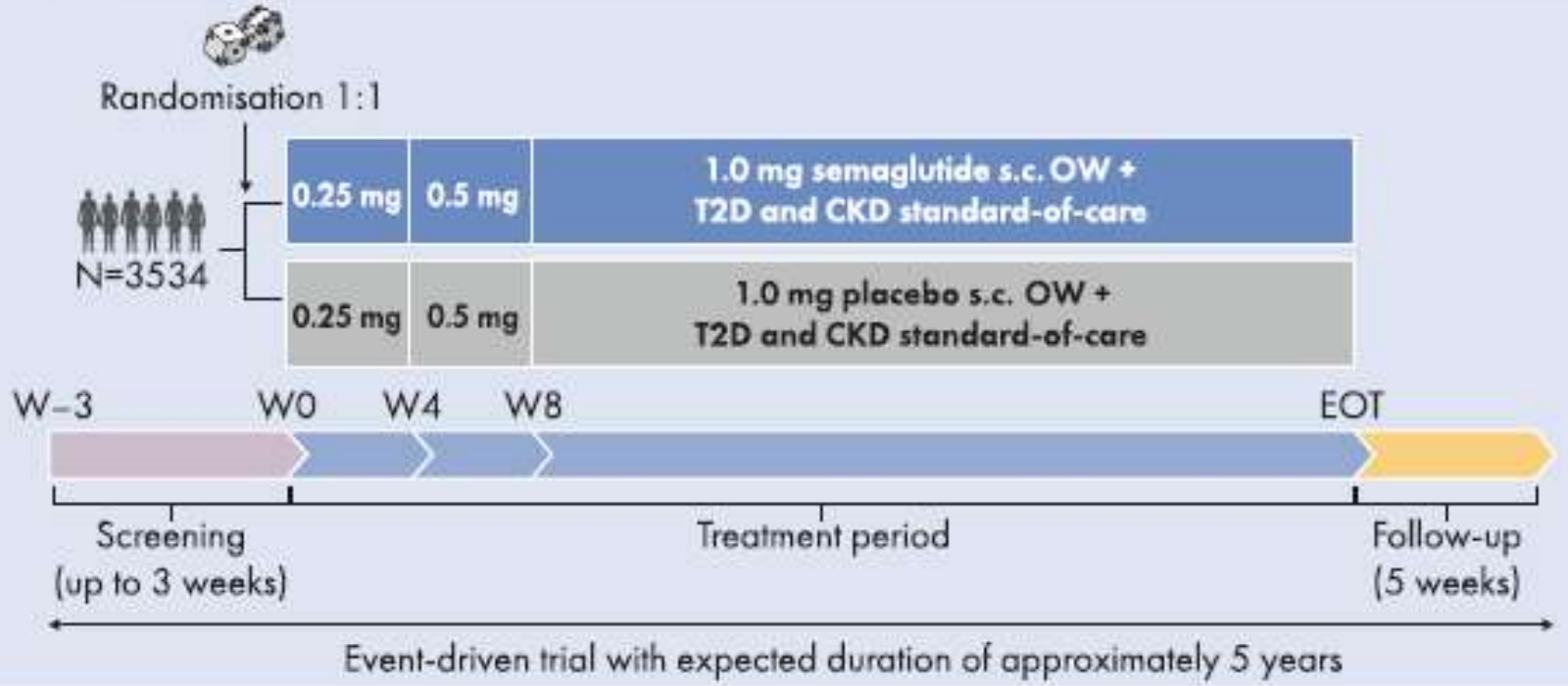
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

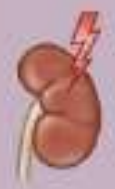
Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics



68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m^2; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

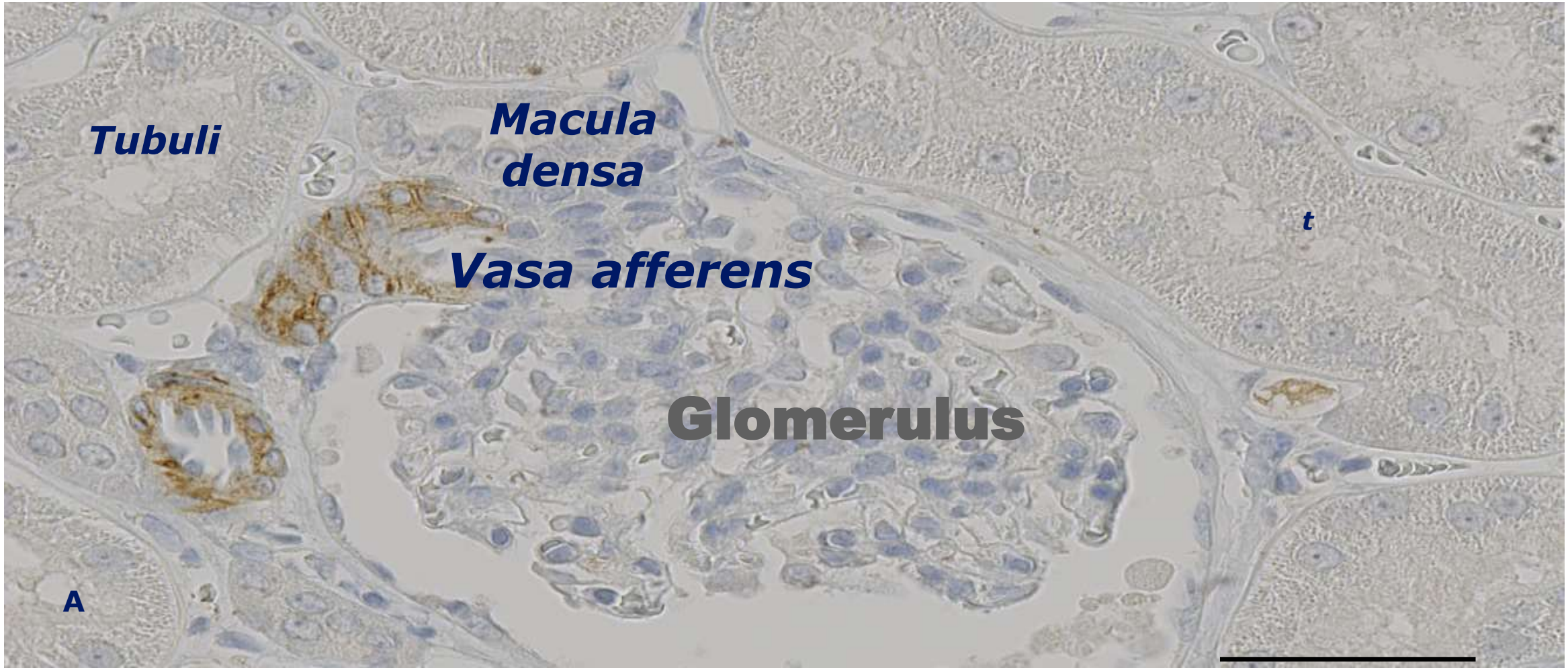
Rossing, P., et al. NDT (2023)
@NDTSocial

company announcement

Semaglutide 1.0 mg demonstrates 24% reduction in the risk of kidney disease-related events in people with type 2 diabetes and chronic kidney disease in the FLOW trial

Bagsværd, Denmark, 5 March 2024 – Novo Nordisk today announced the headline results from the kidney outcomes trial FLOW. The announcement today follows the decision to stop the trial early due to efficacy, which was announced on 10 October 2023, based on a recommendation from an Independent Data Monitoring Committee. The double-blind trial compared injectable semaglutide 1.0 mg with placebo as an adjunct to standard of care for prevention of progression of kidney impairment and risk of kidney and cardiovascular mortality in people with type 2 diabetes and chronic kidney disease (CKD). The trial enrolled 3,533 people with type 2 diabetes and CKD.

Renal GLP-1 R expression: vascular SMC in arterioles



SMC, smooth muscle cell

Pyke *et al. Endocrinology* 2014;155:1280–90

Direct and indirect renal MoA of GLP-1 Analogue

Direct effects:

- **Anti-inflammatory**
- Reduced oxidative stress
- Natriuresis
- Haemodynamic
- Inhibition of RAAS

Indirect effects:

- Improved glycaemic control
- Reduction in blood pressure
- Weight loss
- Improve lipid profile

Yu JH, Kidney Res Clin Pract. 2022

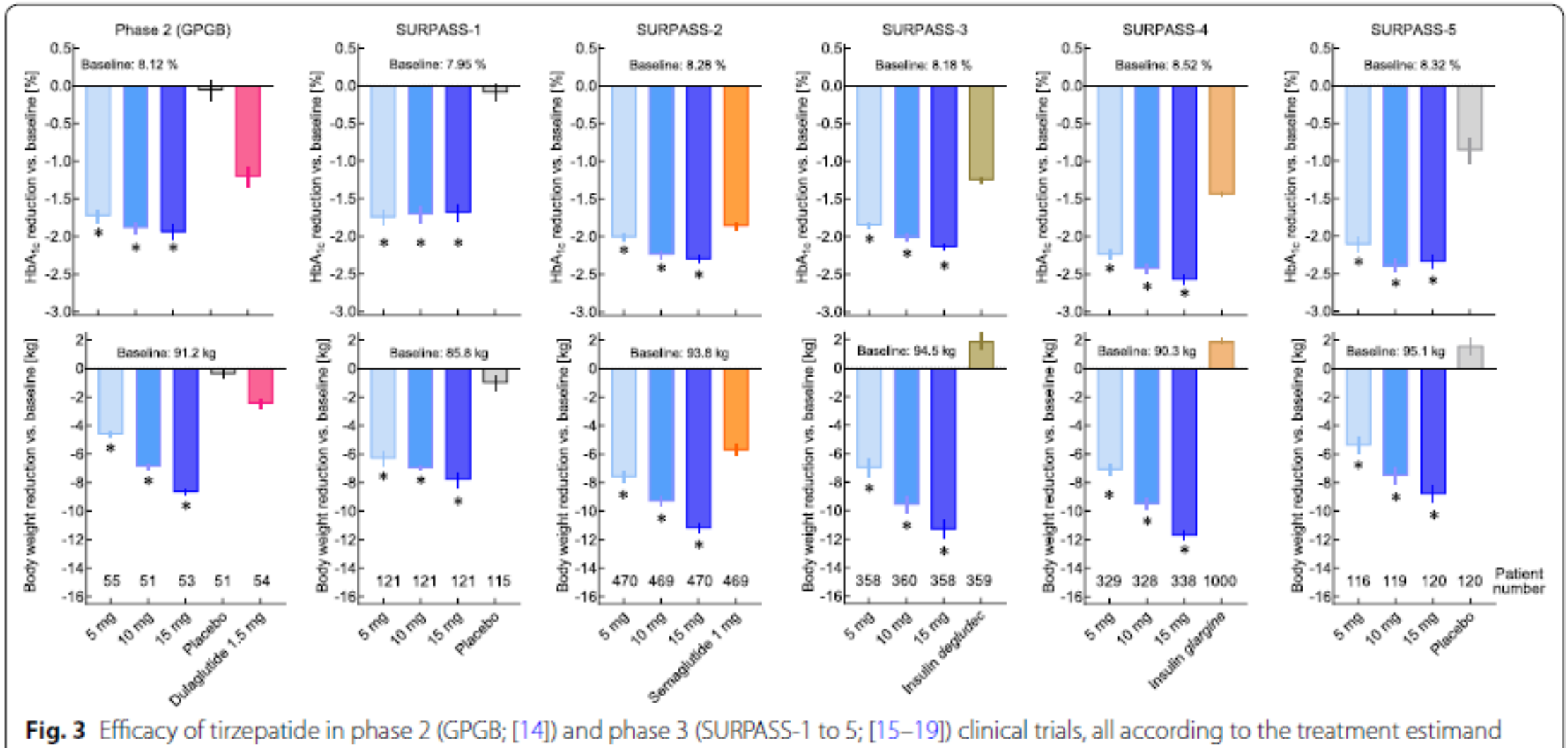


Fig. 3 Efficacy of tirzepatide in phase 2 (GPGB; [14]) and phase 3 (SURPASS-1 to 5; [15–19]) clinical trials, all according to the treatment estimand

Nauck M Cardiovascular Diabetology 2022

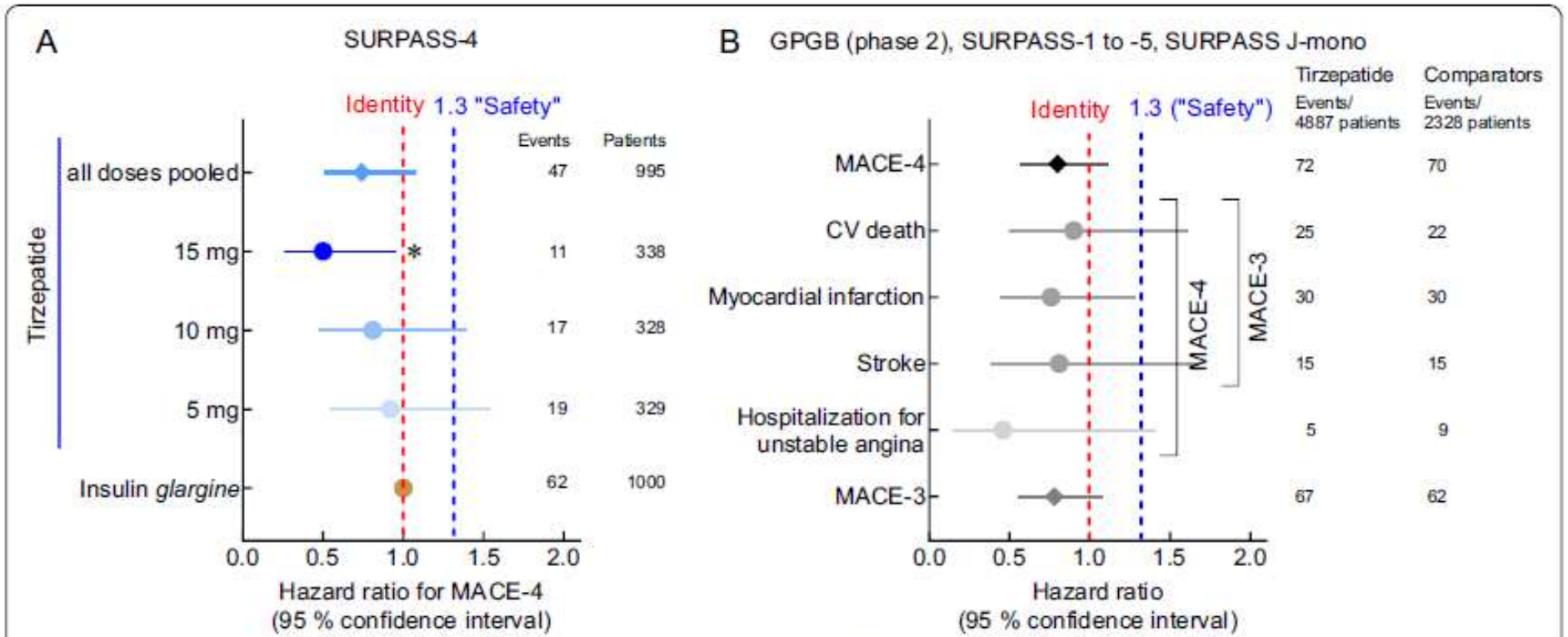


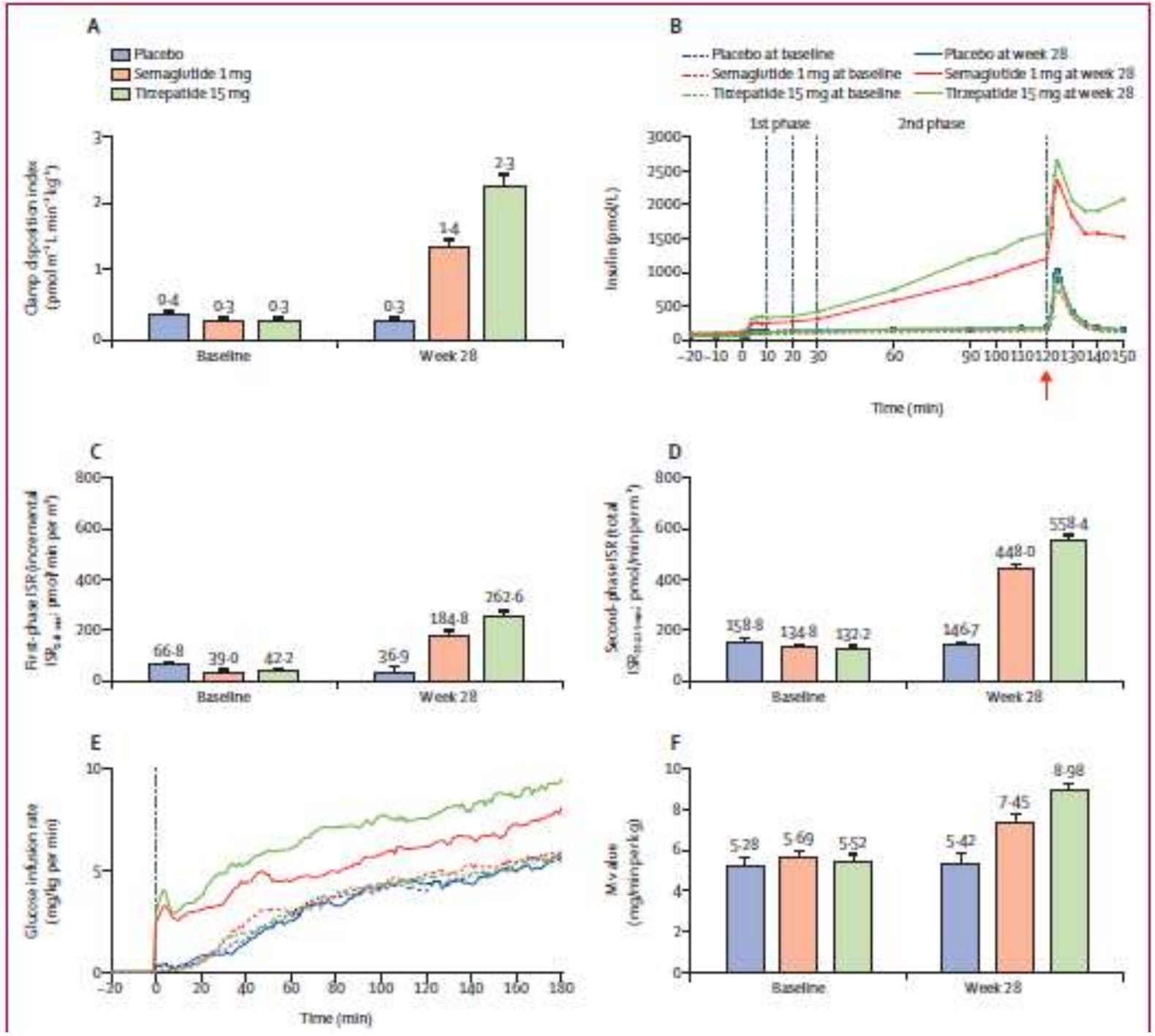
Fig. 4 Effects of tirzepatide on adjudicated cardiovascular events in SURPASS-4 [18] (**A**), a clinical trial recruiting subjects at high risk for cardiovascular events, and across the clinical trial program (phases 2 and 3) for tirzepatide [20] (**B**). MACE: Major adverse cardiovascular events. The line of identity (red, dashed) indicates an equal risk for CV events for tirzepatide and comparator(s). The blue, dashed line marks a hazard ratio of 1.3. An upper bound of the confidence interval for composite endpoints (MACE-3 and MACE-4, but not for individual endpoints) below 1.3 conventionally is interpreted as indicating a cardiovascular risk, which is not significantly elevated in comparison to the comparator(s). Comparators include placebo, insulin *degludec*, insulin *glargine*, dulaglutide 1.5 mg/week, and *semaglutide* 1.0 mg/week (GLP-1 receptor agonists). The numbers of patients at risk and the numbers of events observed are presented. The asterisk indicates a significant difference indirectly inferred from the 95% confidence interval completely being below the line of identity (= 1)

Nauck M Cardiovascular Diabetology 2022

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

Tim Heise, Andrea Mari, J Hans DeVries, Shweta Urva, Jing Li, Edward John Pratt, Tamer Coskun, Melissa K Thomas, Kieren J Mather, Axel Haupt, Zvonko Milicevic

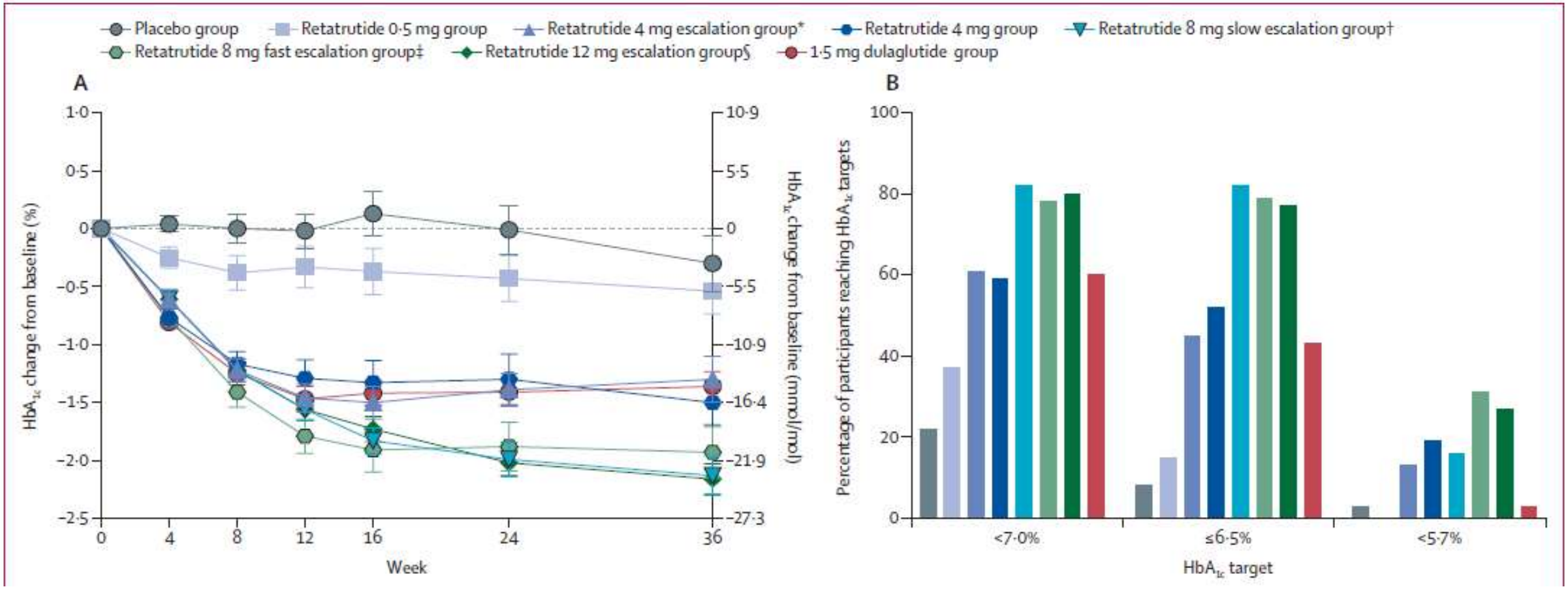
Lancet 2022

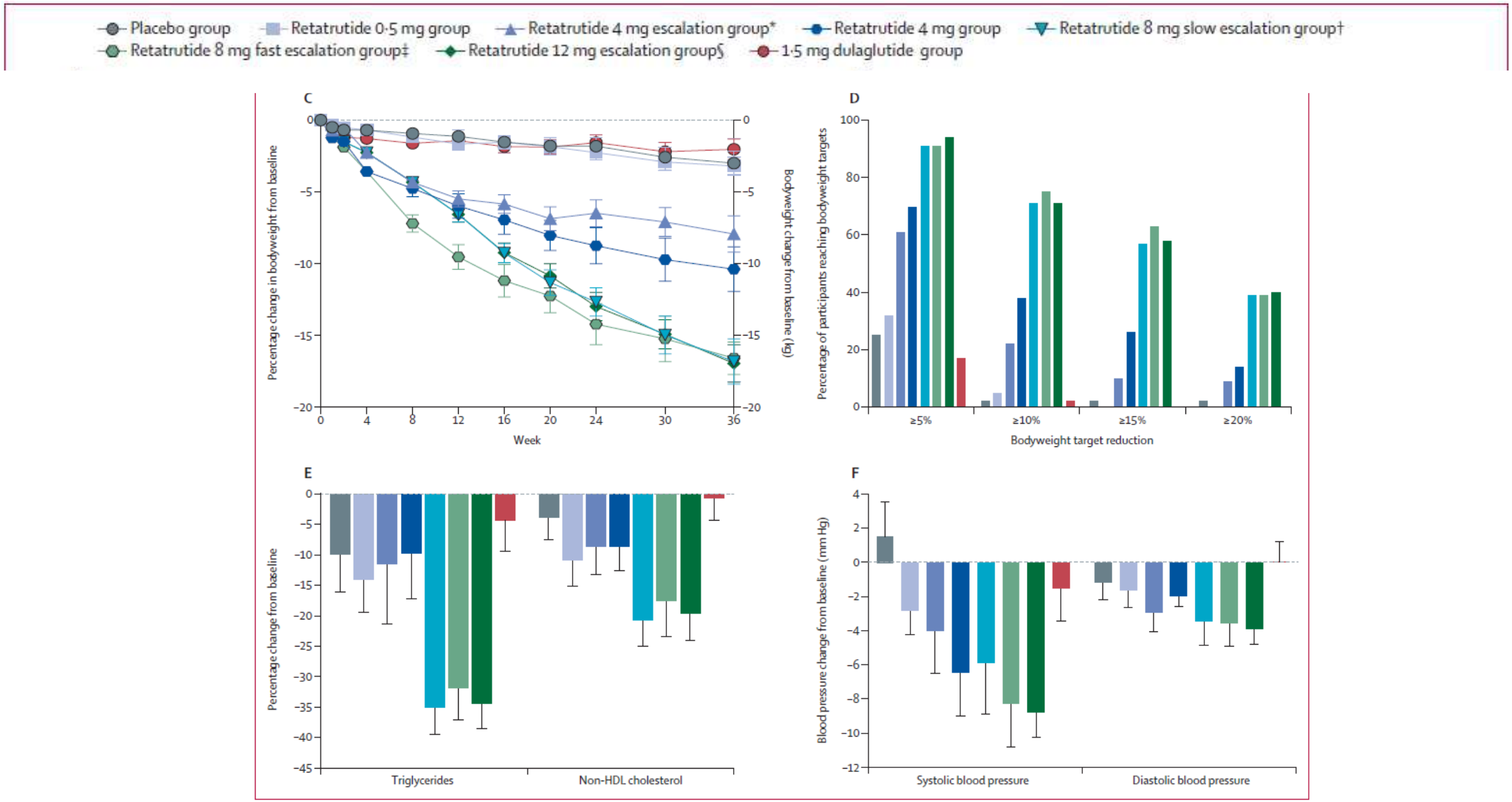

A
Placebo
Semaglutide 1 mg
Tirzepatide 15 mg
Clamp disposition index (pmol m⁻¹ L min⁻¹ kg⁻¹)
0·4
0·3
0·3
0·3
1·4
2·3
Baseline
Week 28
B
Placebo at baseline
Semaglutide 1 mg at baseline
Tirzepatide 15 mg at baseline
Placebo at week 28
Semaglutide 1 mg at week 28
Tirzepatide 15 mg at week 28
1st phase
2nd phase
Insulin (pmol/L)
Time (min)
C
First-phase ISR (incremental ISR0-10 min, pmol/min per m²)
66·8
39·0
42·2
36·9
184·8
262·6
Baseline
Week 28
D
Second-phase ISR (total ISR10-120 min, pmol/min per m²)
158·8
134·8
132·2
146·7
448·0
558·4
Baseline
Week 28
E
Glucose infusion rate (mg/kg per min)
Time (min)
F
M value (mg/min per kg)
5·28
5·69
5·52
5·42
7·45
8·98
Baseline
Week 28

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

Julio Rosenstock, Juan Frias, Ania M Jastreboff, Yu Du, Jitong Lou, Sirel Gurbuz, Melissa K Thomas, Mark L Hartman, Axel Haupt, Zvonko Milicevic, Tamer Coskun




Placebo group
Retatrutide 0·5 mg group
Retatrutide 4 mg escalation group*
Retatrutide 4 mg group
Retatrutide 8 mg slow escalation group†
Retatrutide 8 mg fast escalation group‡
Retatrutide 12 mg escalation group§
1·5 mg dulaglutide group
C
Percentage change in bodyweight from baseline
Bodyweight change from baseline (kg)
Week
D
Percentage of participants reaching bodyweight targets
≥5%
≥10%
≥15%
≥20%
Bodyweight target reduction
E
Percentage change from baseline
Triglycerides
Non-HDL cholesterol
F
Blood pressure change from baseline (mm Hg)
Systolic blood pressure
Diastolic blood pressure

We are waiting for the results of :

- SURPASS CVOT
- TREASURE CKD

DFG (ml/min/1,73m²)	60-89 (IRC légère)	30-44 et 45-59 (IRC modérée)	15-29 (IRC sévère)	< 15 ou dialyse (IRC terminale)
Metformine				
Répaglinide				
Glimépiride				
Gliclazide				
Acarbose				
Sitagliptine			***	***
Saxagliptine		**	***	
Vildagliptine				
Dapagliflozine			#	
Empagliflozine		##	##	
Canagliflozine				
Liraglutide				###
Dulaglutide				###
Sémaglutide				###
Tirzépatide*			####	####
Insuline				

Pas de réduction de la dose

Réduction de la dose

Non indiqué

* Produit non commercialisé en France à ce jour

** Forme commercialisée en France uniquement en combinaison avec 1 g de metformine

*** Forme non commercialisée en France

La dapagliflozine peut être instaurée à la dose de 10 mg jusqu'à un DFG de 25 mL/min/1,73 m² (diminution de l'effet anti-hyperglycémiant en dessous de 45 mL/min/1,73 m²)

L'empagliflozine peut être instaurée à la dose de 10 mg jusqu'à un DFG de 20 mL/min/1,73 m² (diminution de l'effet anti-hyperglycémiant en dessous de 45 mL/min/1,73 m²)

Expérience limitée, utilisation non recommandée

Expérience limitée, à utiliser avec prudence

RECO SFD 2023

diseases

MDPI

Systematic Review

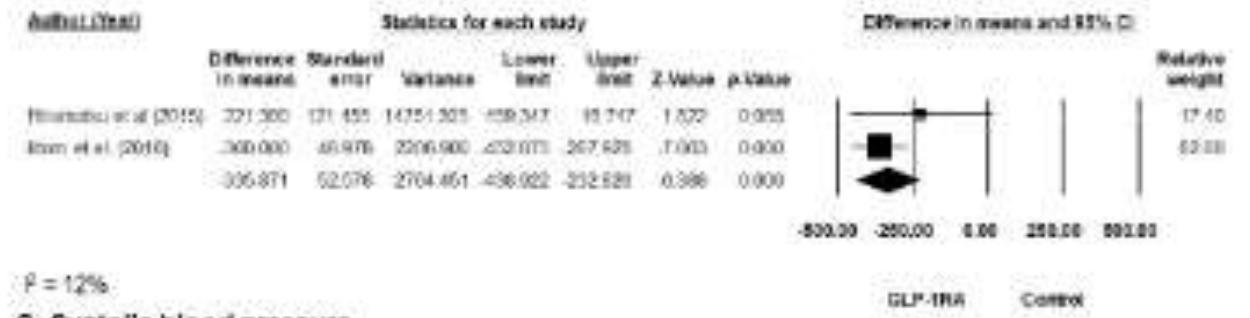
Safety and Efficacy of GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus with Advanced and End-Stage Kidney Disease: A Systematic Review and Meta-Analysis

Pajaree Krisanapan [1,2,3], Kanokporn Sanpawithayakul [4,5], Pattharawin Pattharanitima [2], Charat Thongprayoon [1], Jing Miao [1], Michael A. Mao [6], Supawadee Suppadungsuk [1,7], Supawit Tangpanithandee [7], Iasmina M. Craici [1] and Wisit Cheungpasitporn [1,*]

A. Cardiothoracic ratio

I² = 0%

B. Pro-BNP

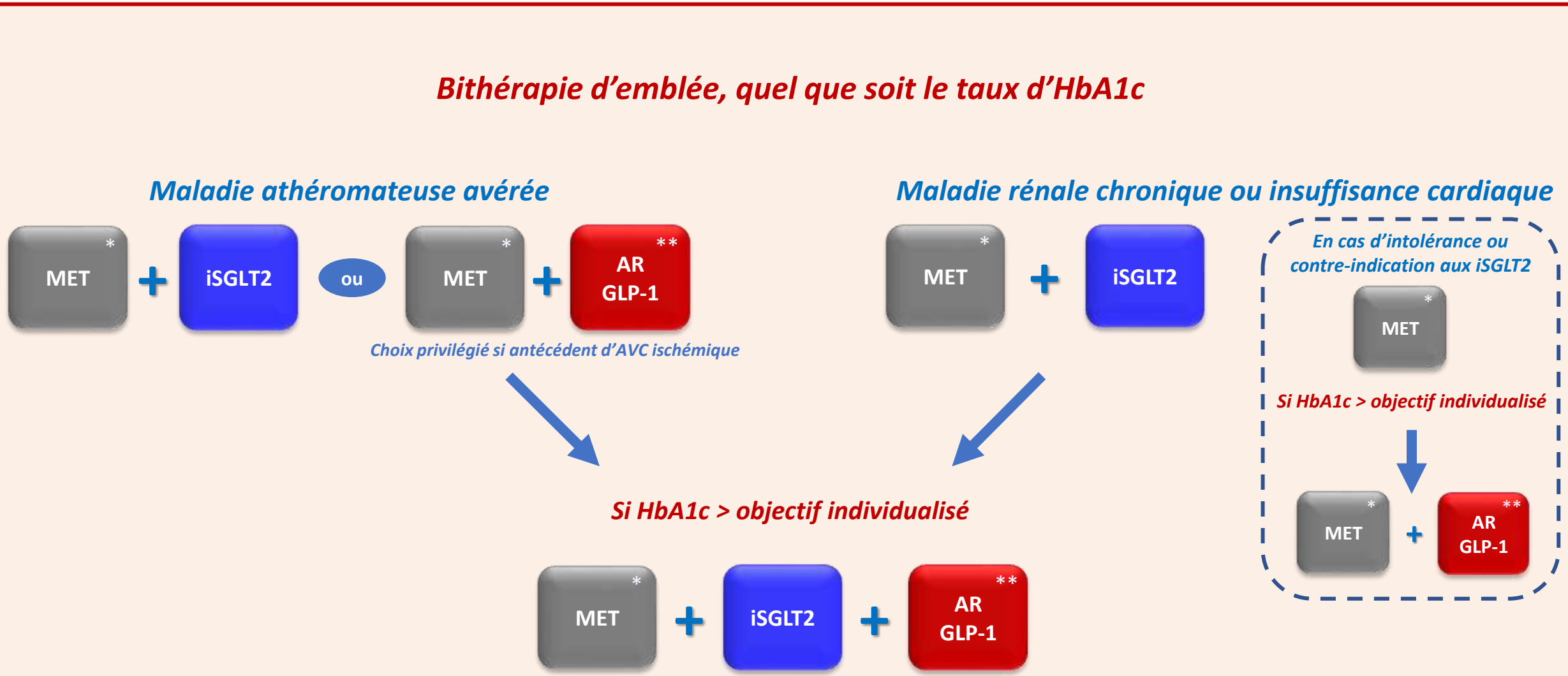


I² = 12%

C. Systolic blood pressure

I² = 87 %

Fig 8. Maladie athéromateuse avérée, maladie rénale chronique ou insuffisance cardiaque



** Ne pas utiliser la metformine en cas : d'insuffisance cardiaque décompensée (Stade IV NYHA), d'insuffisance rénale sévère (DFG < 30 ml/min/1.73 m²) et en phase aiguë d'IDM ou d'AVC*

*** Dans l'attente de nouvelles données, les AR GLP-1 devront être utilisés avec précaution en cas d'insuffisance cardiaque à fraction d'éjection diminuée (FEVG < 40%)*

Société francophone du diabète

Take home messages

- Secondary renal analyses from GLP-1 RA CVOTs suggest a renal benefit of GLP-1 RAs
- The effects of GLP-1 A in the kidney are not fully understood, although they may have an impact on oxidative stress and inflammation in diabetic kidney disease
- Increasing evidence suggests involvement of both direct and indirect pathways
- The combination of GLP-1 Analogue with SGLT2 inhibitors need to be tested

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