L'APPROCCIO CON GLP1-RA AL PAZIENTE CARDIO-METABOLICO AD ALTO RISCHIO

Michelangela Barbieri

Università degli Studi della Campania L. Vanvitelli-Napoli -

Relevant Financial Discloures :

As Speaker, Advisory Board or Consultant in the last 3 years

- AMARIN

European Heart Journal, Volume 44, Issue 39, 14 October 2023, Pages 4043–4140.

EASD European Association for the Study of Diabetes

ESC European Society of Cardiology

American Diabetes Association

High Cardiometabolic 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

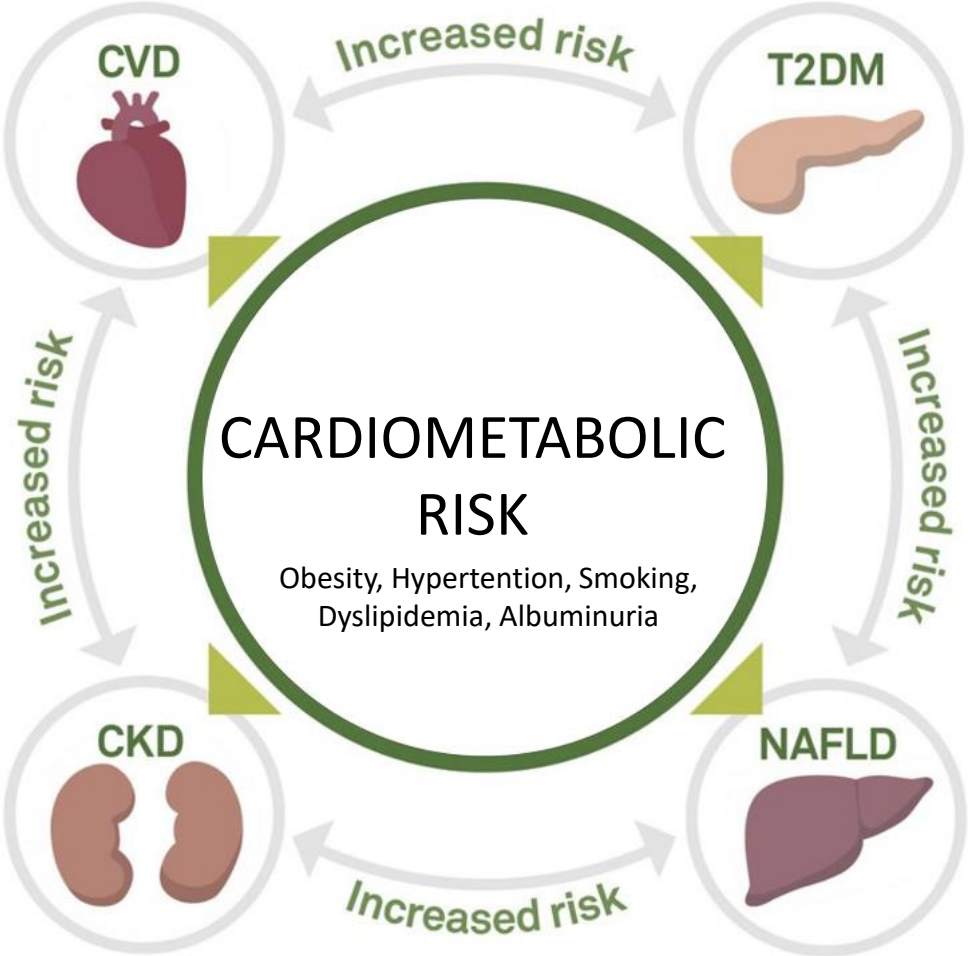
Patients with T2DM with:
- Clinically established ASCVD or
- Severe TOD or
- 10-year CVD risk ≥20% using SCORE2-Diabetes

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit

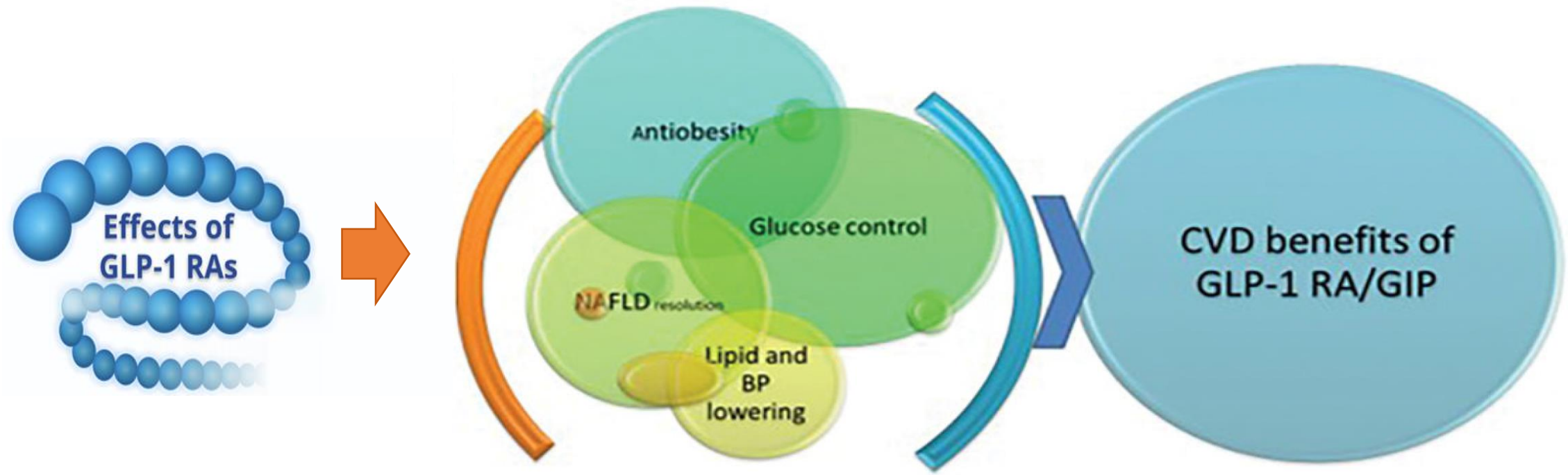
EITHER/ OR

SGLT2i§ with proven CVD benefit



SCORE 2 DIABETES Sex-specific competing risk-adjusted models were used including conventional risk factors (i.e. age, smoking, systolic blood pressure, total, and HDL-cholesterol), as well as diabetes-related variables (i.e. age at diabetes diagnosis, glycated haemoglobin [HbA1c] and creatinine-based estimated glomerular filtration rate [eGFR]).

GLP1 RA PROMOTE POSITIVE EFFECTS ON MOST COMPONENTS OF THE "*CARDIOMETABOLIC CONTINUUM*"

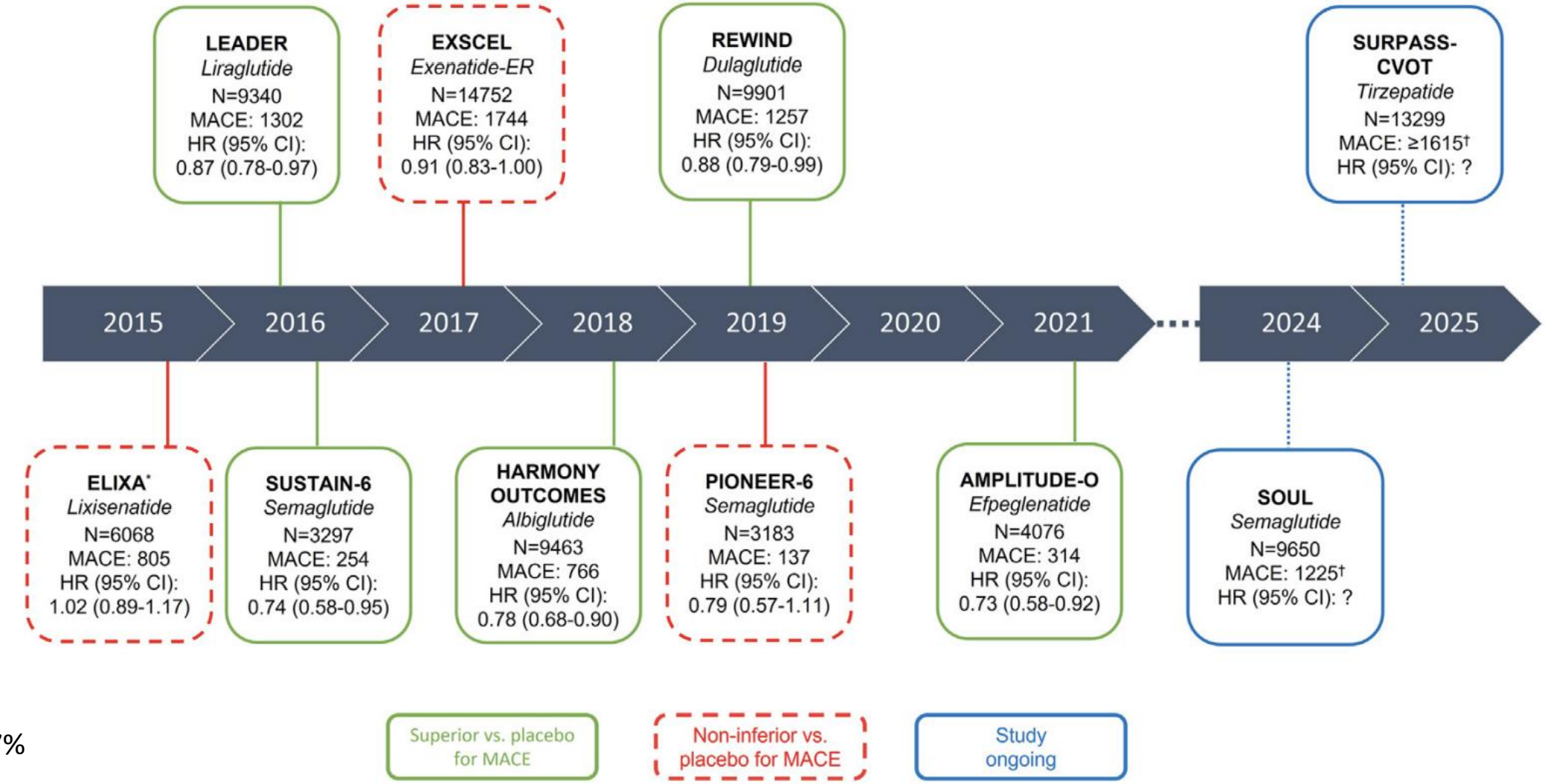


Journal of Cardiovascular Pharmacology and Therapeutics 2022, Vol. 27 1-22

Eur Heart J, Volume 44, Issue 39, 14 October 2023, Pages 4141–4156, https://doi.org/10.1093/eurheartj/ehad445

ESC
European Society of Cardiology

SUMMARIZES THE KEY RESULTS FROM EIGHT CVOT TRIALS



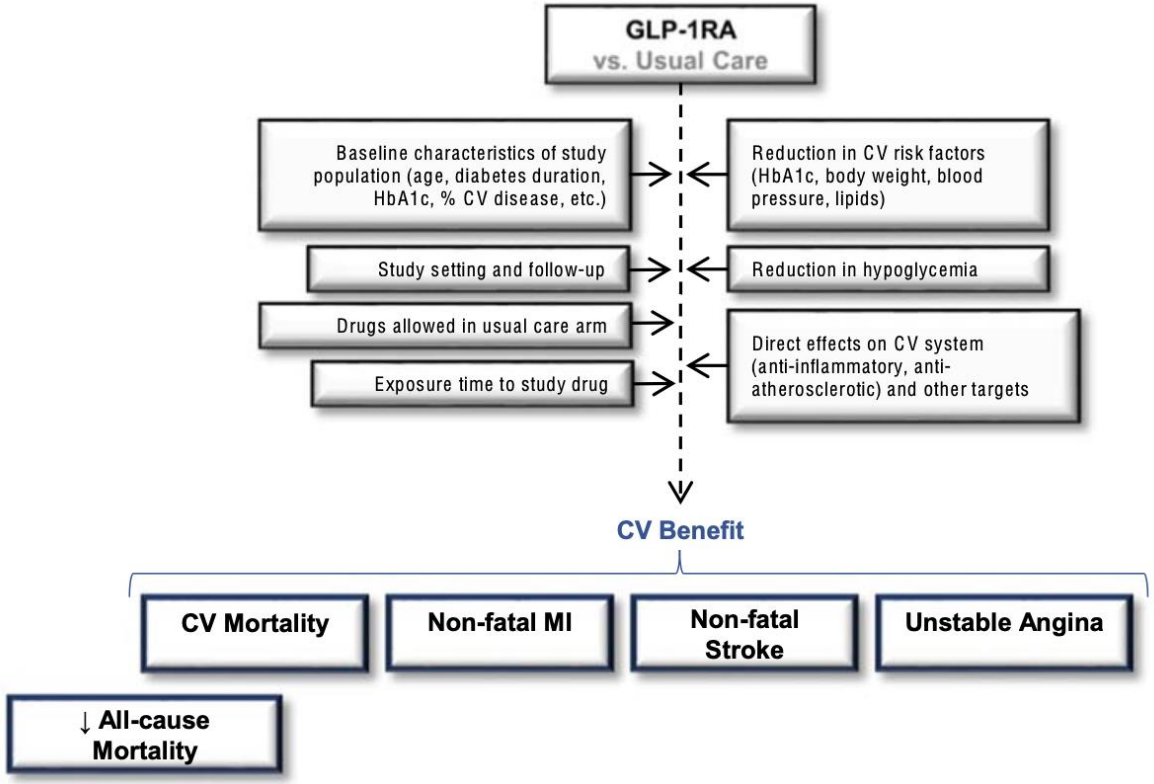
RR= ↓ 13-27%

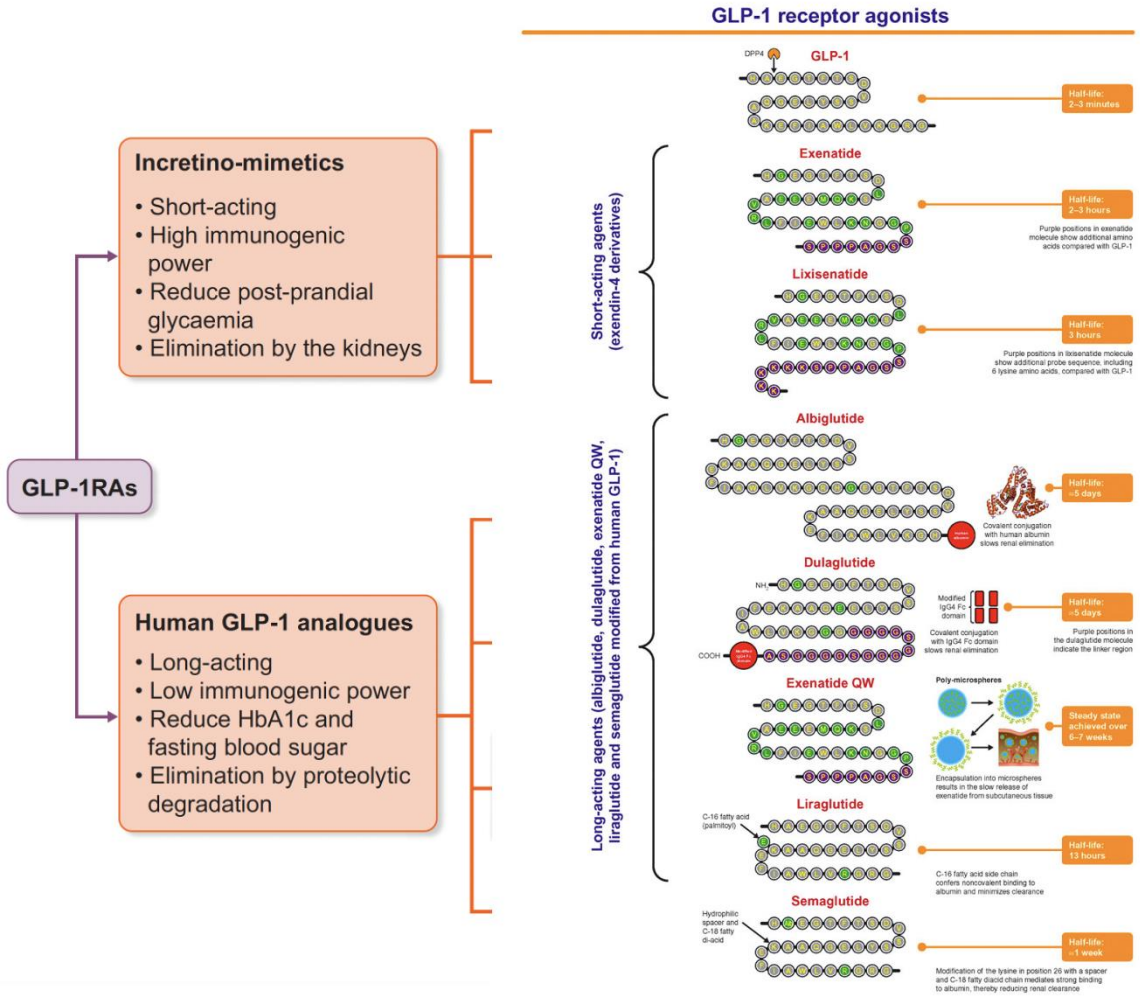
Summarizes the key results from eight CVOT trials

Trial	LEADER [36]	SUSTAIN-6 [37]	HARMONY [38]	REWIND [39]	AMPLITUDE-O [40]	PIONEER 6 [41]	EXSCEL [42]	ELIXA [43]	FREEDOM [44]
Intervention ** subcutaneous (if not specified otherwise)	Liraglutide 1.8 mg vs. placebo once daily	Semaglutide 0.5 mg vs. 1 mg vs. placebo once weekly	Albiglutide 30 mg vs. placebo once weekly	Dulaglutide 1.5 mg vs. placebo once weekly	Efpeglinatide 4 mg vs. 6 mg vs. placebo once weekly	Semaglutide 14 mg vs. placebo once daily per os	Exenatide 2 mg vs. placebo once weekly	Lixisenatide 20 µg vs. placebo once daily	Exenatide vs. placebo in a continuous subcutaneous infusion
Primary endpoint (95% CI)	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	4-point MACE	4-point MACE
	0.87; 0.78 to 0.97	0.74 (0.58–0.95)	0.78 (0.68–0.90)	0.88 (0.79–0.99)	0.73 (0.58–0.92)	0.79 (0.57–1.11)	0.91 (0.83–1.00)	1.02 (0.89–1.17)	1.21 (0.90–1.63)
Cardiovascular death; HR (95% CI)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.93 (0.73–1.19)	0.91 (0.78–1.06)	0.72 (0.50–1.03)	0.49 (0.27–0.92)	0.88 (0.76–0.97)	0.98 (0.78–1.22)	1.22 (0.70–2.12)
All-cause death; HR (95% CI)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.95 (0.79–1.16)	0.90 (0.80–1.01)	0.78 (0.58–1.06)	0.51 (0.31–0.84)	0.86 (0.77–0.97)	0.94 (0.78–1.13)	1.20 (0.79–1.81)
Hospitalization for heart failure; HR (95% CI)	0.87 (0.73–0.97)	1.11 (0.77–1.61)	-	0.93 (0.77–1.12)	0.61 (0.38–0.98)	0.86 (0.48–1.55)	0.94 (0.78–1.13)	0.96 (0.75–1.23)	0.95 (0.48–1.88)
Myocardial infarction; HR (95% CI)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.75 (0.61–0.90) *	0.96 (0.79–1.15)	0.75 (0.54–1.05)	1.18 (0.73–1.90) *	0.97 (0.85–1.10)	1.03 (0.87–1.22)	1.33 (0.82–2.17) *
Stroke; HR (95% CI)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.86 (0.66–1.14)	0·76 (0·62–0·94)	0.74 (0.47–1.17)	0.74 (0.35–1.57) *	0.85 (0.70–1.03)	1.12 (0.79–1.58)	1.00 (0.56–1.79)

Diabetes Obes Metab. 2023 Jun;25(6):1495-1502. doi: 10.1111/dom.14997

HETEROGENEITY AND SIMILARITIES IN GLP-1 RECEPTOR AGONIST CARDIOVASCULAR OUTCOMES TRIALS





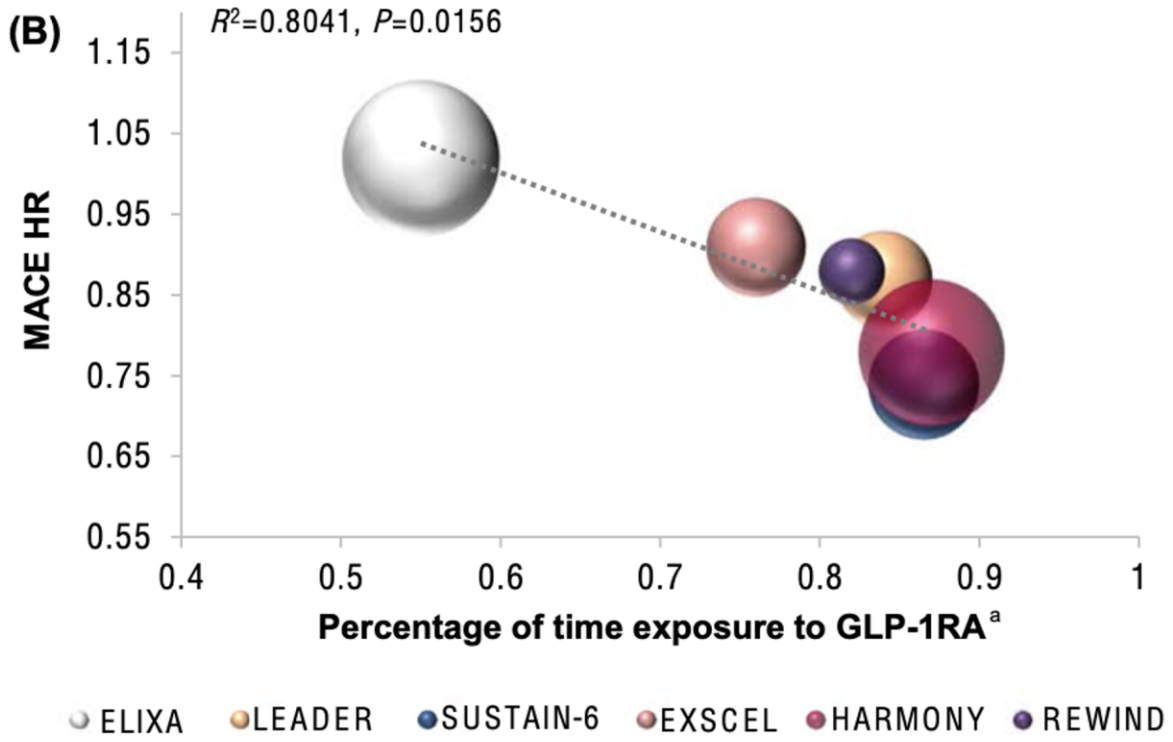
Diabetes Metab Res Rev. 2019;35:e3070.

European Journal of Internal Medicine 109 (2023) 79–88

Trends in Endocrinology & Metabolism

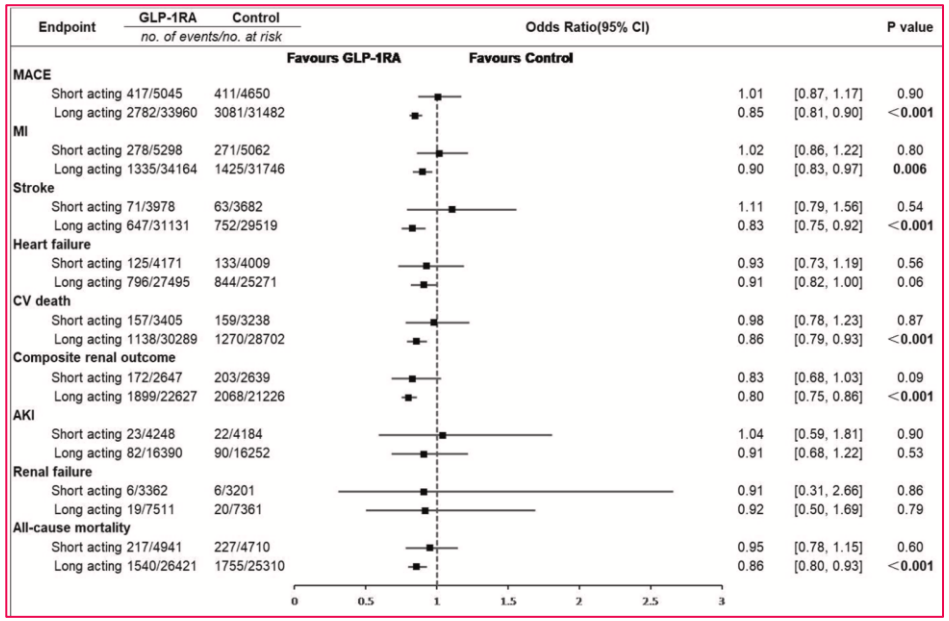
CellPress REVIEWS

ARE THE DURATION OF ACTION AND THE STEADY-STATE CONCENTRATION OF GLP-1RA ASSOCIATED WITH THE RISKS OF CARDIOVASCULAR OUTCOMES?



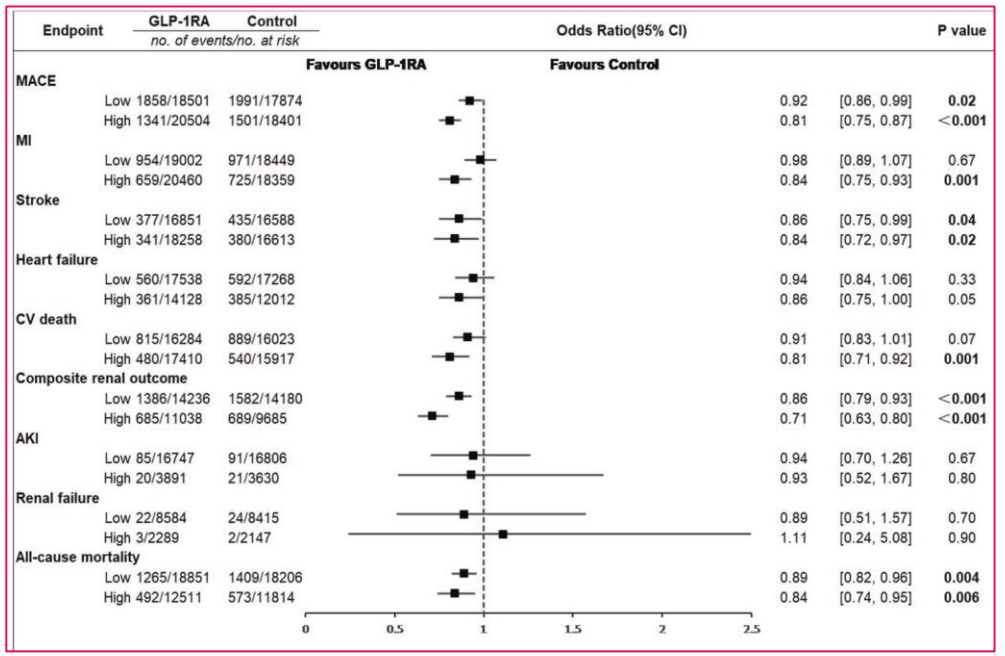
European Journal of Internal Medicine 109 (2023) 79–88

DURATION OF ACTION



Endpoint	GLP-1RA (no. of events/no. at risk)	Control (no. of events/no. at risk)	Odds Ratio(95% CI)		P value
	Favours GLP-1RA	Favours Control			
MACE					
Short acting	417/5045	411/4650	1.01	[0.87, 1.17]	0.90
Long acting	2782/33960	3081/31482	0.85	[0.81, 0.90]	**<0.001**
MI					
Short acting	278/5298	271/5062	1.02	[0.86, 1.22]	0.80
Long acting	1335/34164	1425/31746	0.90	[0.83, 0.97]	**0.006**
Stroke					
Short acting	71/3978	63/3682	1.11	[0.79, 1.56]	0.54
Long acting	647/31131	752/29519	0.83	[0.75, 0.92]	**<0.001**
Heart failure					
Short acting	125/4171	133/4009	0.93	[0.73, 1.19]	0.56
Long acting	796/27495	844/25271	0.91	[0.82, 1.00]	0.06
CV death					
Short acting	157/3405	159/3238	0.98	[0.78, 1.23]	0.87
Long acting	1138/30289	1270/28702	0.86	[0.79, 0.93]	**<0.001**
Composite renal outcome					
Short acting	172/2647	203/2639	0.83	[0.68, 1.03]	0.09
Long acting	1899/22627	2068/21226	0.80	[0.75, 0.86]	**<0.001**
AKI					
Short acting	23/4248	22/4184	1.04	[0.59, 1.81]	0.90
Long acting	82/16390	90/16252	0.91	[0.68, 1.22]	0.53
Renal failure					
Short acting	6/3362	6/3201	0.91	[0.31, 2.66]	0.86
Long acting	19/7511	20/7361	0.92	[0.50, 1.69]	0.79
All-cause mortality					
Short acting	217/4941	227/4710	0.95	[0.78, 1.15]	0.60
Long acting	1540/26421	1755/25310	0.86	[0.80, 0.93]	**<0.001**

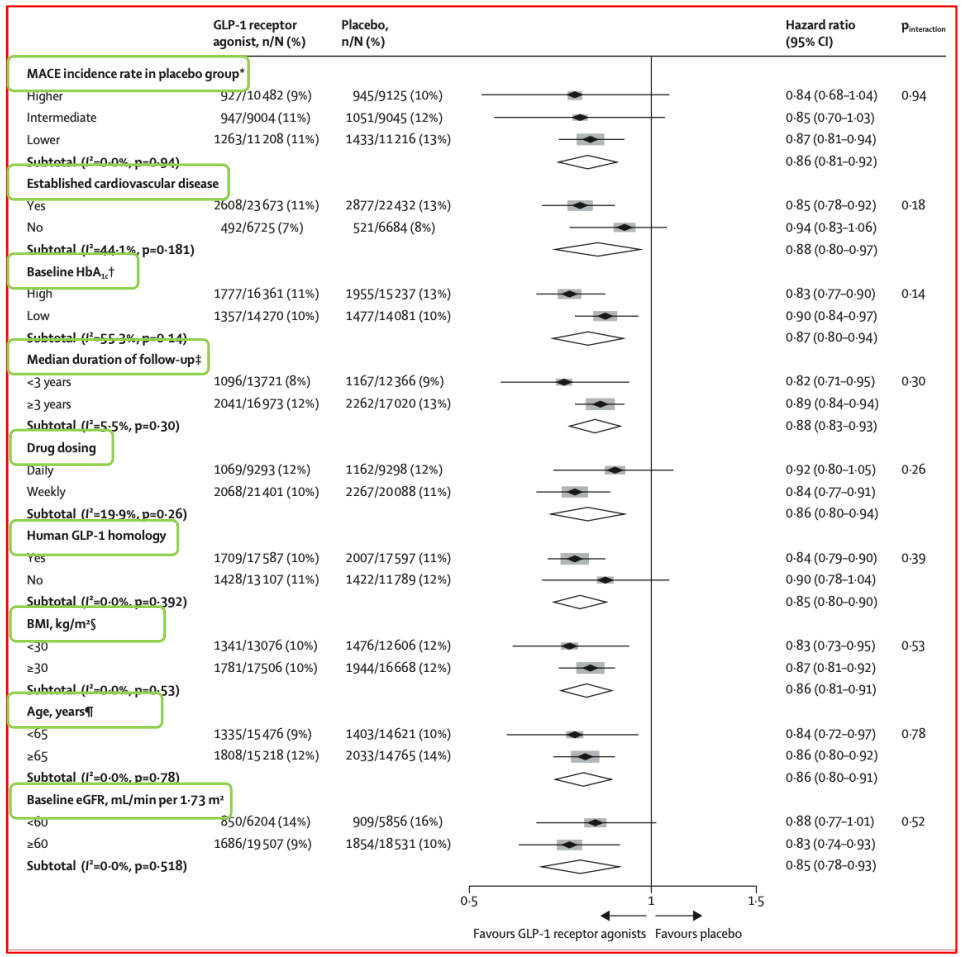
STEADY-STATE CONCENTRATION



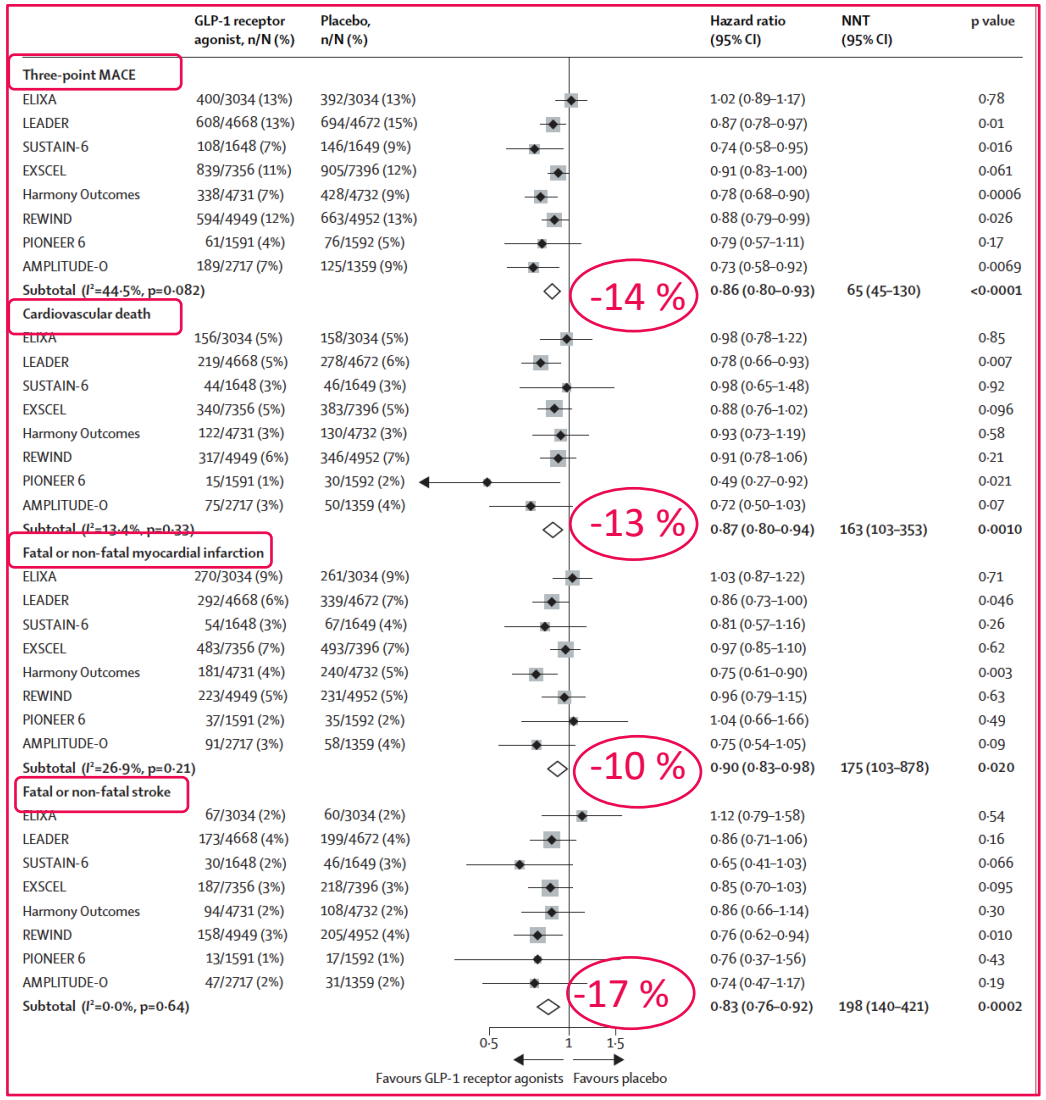
Endpoint	GLP-1RA (no. of events/no. at risk)	Control (no. of events/no. at risk)	Odds Ratio(95% CI)		P value
	Favours GLP-1RA	Favours Control			
MACE					
Low	1858/18501	1991/17874	0.92	[0.86, 0.99]	**0.02**
High	1341/20504	1501/18401	0.81	[0.75, 0.87]	**<0.001**
MI					
Low	954/19002	971/18449	0.98	[0.89, 1.07]	0.67
High	659/20460	725/18359	0.84	[0.75, 0.93]	**0.001**
Stroke					
Low	377/16851	435/16588	0.86	[0.75, 0.99]	**0.04**
High	341/18258	380/16613	0.84	[0.72, 0.97]	**0.02**
Heart failure					
Low	560/17538	592/17268	0.94	[0.84, 1.06]	0.33
High	361/14128	385/12012	0.86	[0.75, 1.00]	0.05
CV death					
Low	815/16284	889/16023	0.91	[0.83, 1.01]	0.07
High	480/17410	540/15917	0.81	[0.71, 0.92]	**0.001**
Composite renal outcome					
Low	1386/14236	1582/14180	0.86	[0.79, 0.93]	**<0.001**
High	685/11038	689/9685	0.71	[0.63, 0.80]	**<0.001**
AKI					
Low	85/16747	91/16806	0.94	[0.70, 1.26]	0.67
High	20/3891	21/3630	0.93	[0.52, 1.67]	0.80
Renal failure					
Low	22/8584	24/8415	0.89	[0.51, 1.57]	0.70
High	3/2289	2/2147	1.11	[0.24, 5.08]	0.90
All-cause mortality					
Low	1265/18851	1409/18206	0.89	[0.82, 0.96]	**0.004**
High	492/12511	573/11814	0.84	[0.74, 0.95]	**0.006**

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

Naveed Sattar, Matthew M Y Lee*, Søren L Kristensen*, Kelley R H Branch, Stefano Del Prato, Nardev S Khurmi, Carolyn S P Lam, Renato D Lopes, John J V McMurray, Richard E Pratley, Julio Rosenstock, Hertzel C Gerstein*



The analysis included 60,080 subjects



Lancet Diabetes Endocrinol. 2021 Oct;9(10):653-662. doi: 10.1016/S2213-8587(21)00203-5

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials

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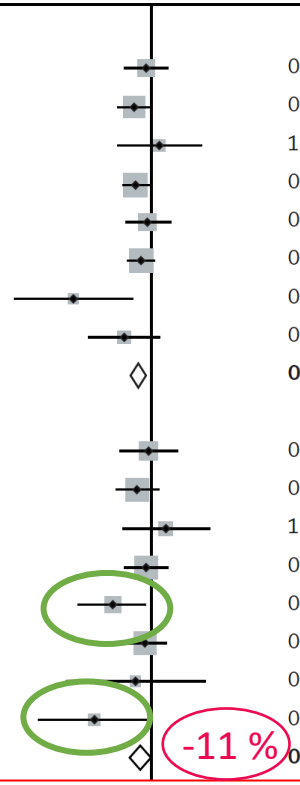
	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78 to 1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74 to 0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74 to 1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77 to 0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	205/4732 (4%)	0·95 (0·79 to 1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80 to 1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31 to 0·84)		0·008
AMPLITUDE-O	111/2717 (4%)	69/1359 (5%)	0·78 (0·58 to 1·06)		0·11
Subtotal (I^2=10·1%, p=0·35)			**0·88 (0·82 to 0·94)**	**114 (76 to 228)**	**0·0001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75 to 1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73 to 1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77 to 1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78 to 1·13)		0·49
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53 to 0·94)		0·019
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77 to 1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48 to 1·55)		0·59
AMPLITUDE-O	40/2717 (1%)	31/1359 (2%)	0·61 (0·38 to 0·98)		0·04
Subtotal (I^2=3·0%, p=0·41)			**0·89 (0·82 to 0·98)**	**258 (158 to 1422)**	**0·013**



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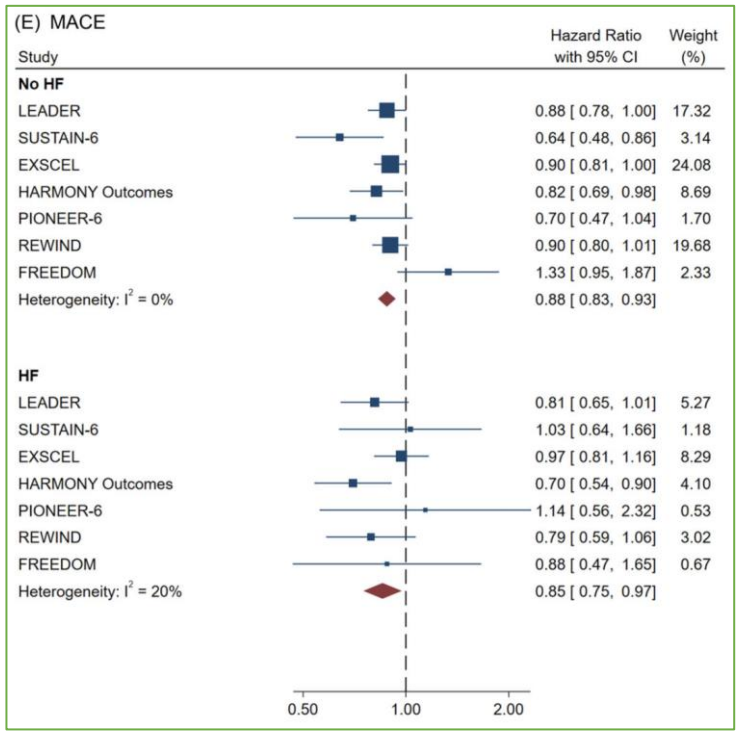
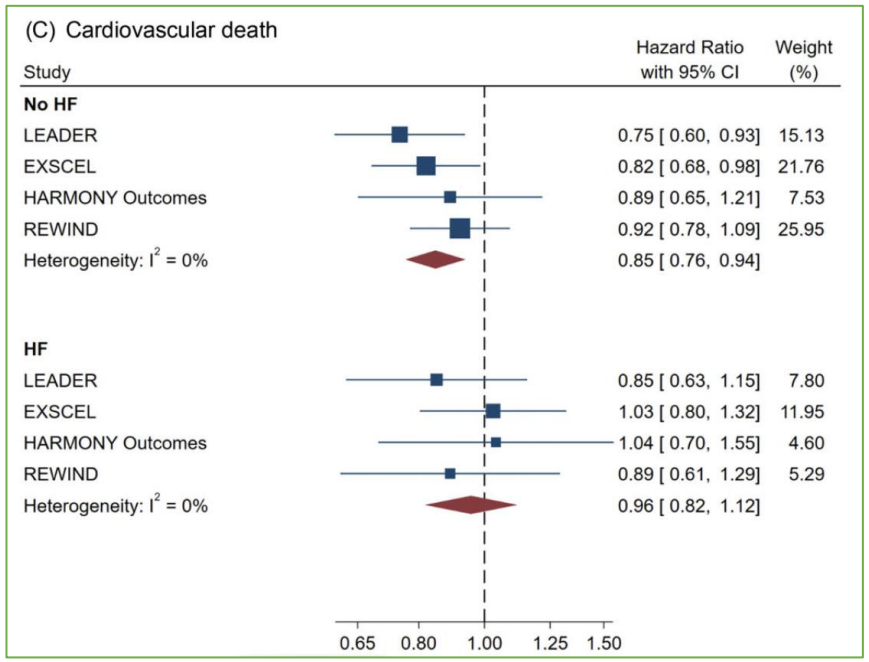
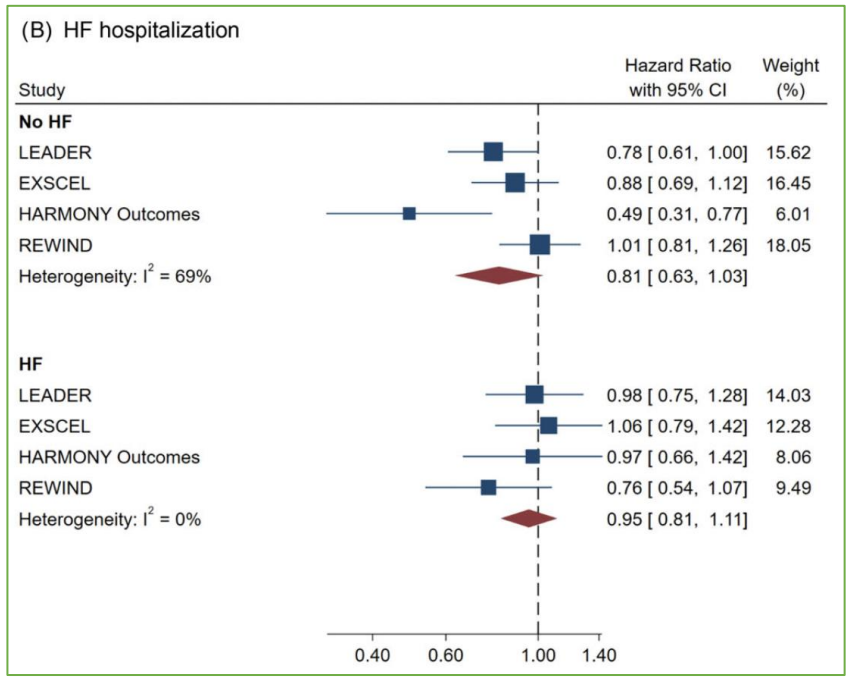
GLP-1 RA IN PATIENTS WITH TYPE 2 DIABETES WITH AND WITHOUT CHRONIC HEART FAILURE: A META-ANALYSIS OF RANDOMIZED PLACEBO-CONTROLLED OUTCOME TRIALS







Diabetes Obes Metab. 2023 Jun;25(6):1495-1502. doi: 10.1111/dom.14997

Risk of adverse events with liraglutide in heart failure with reduced ejection fraction: A post hoc analysis of the FIGHT trial

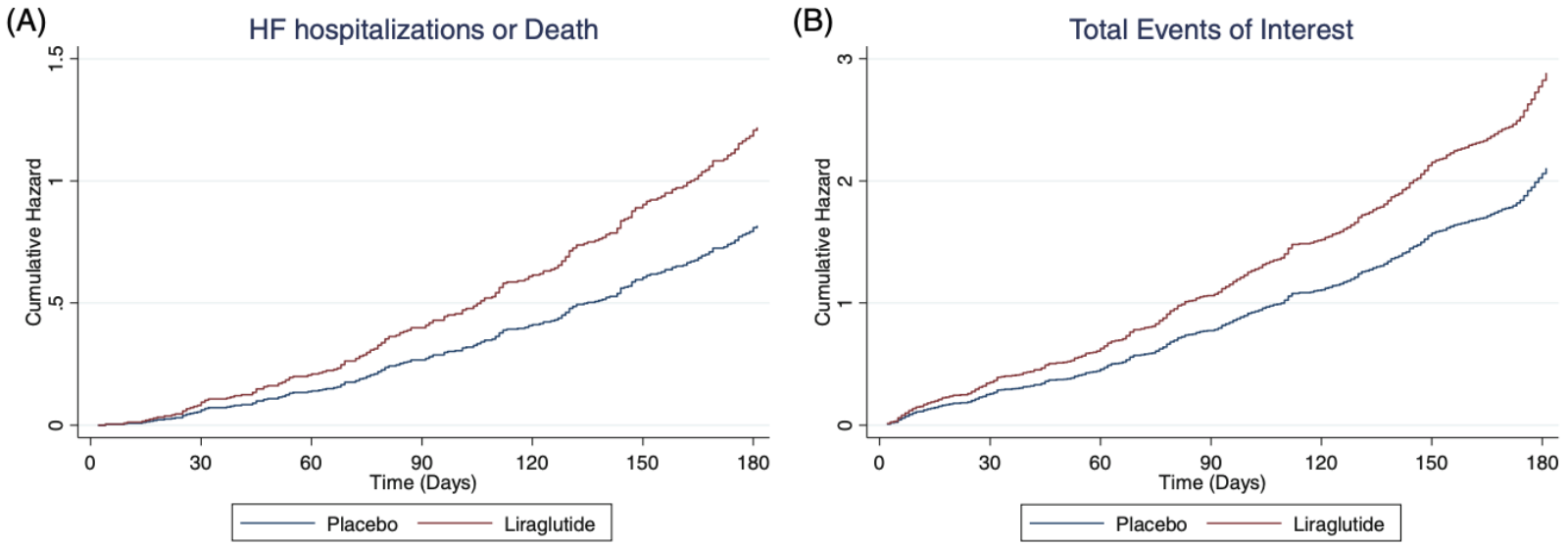
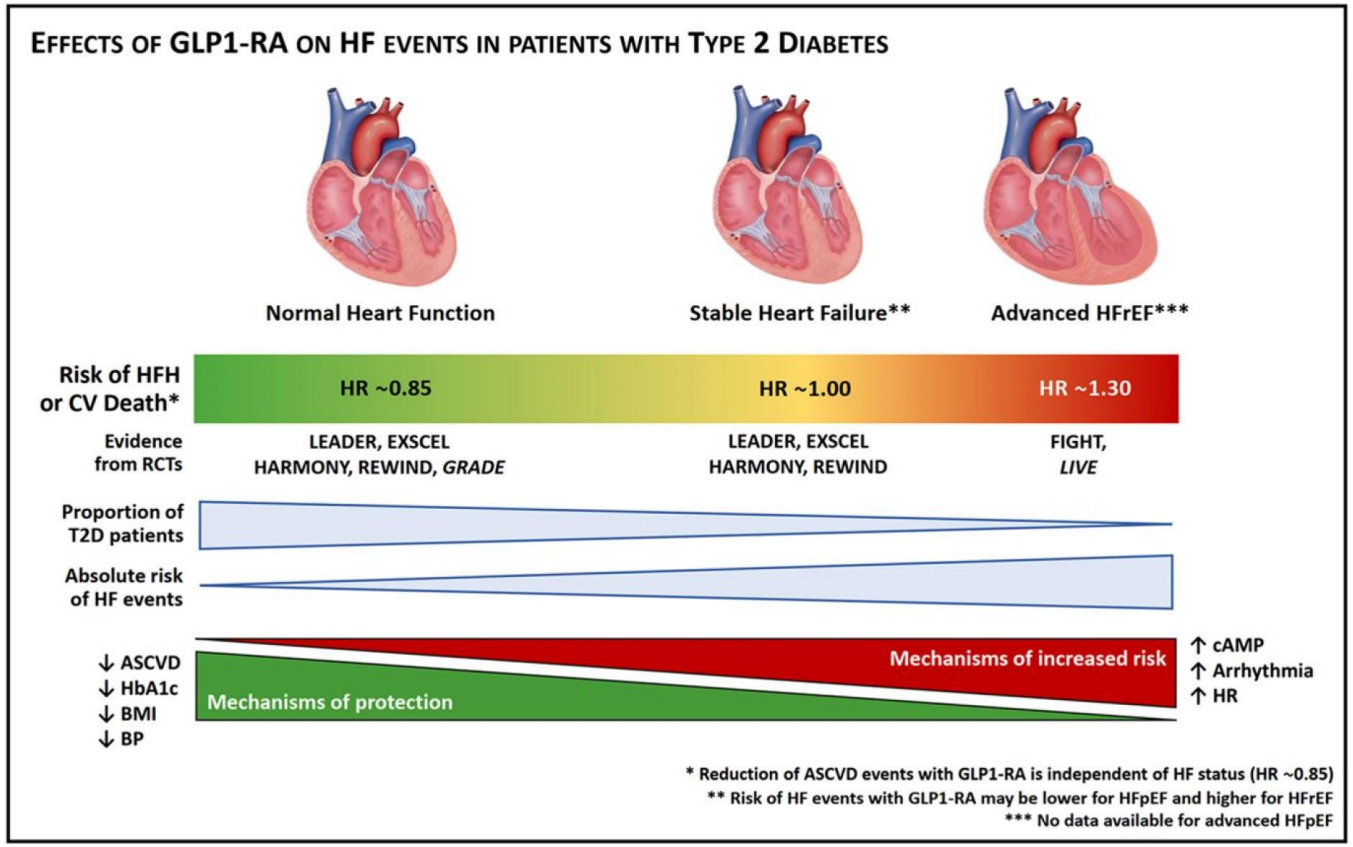


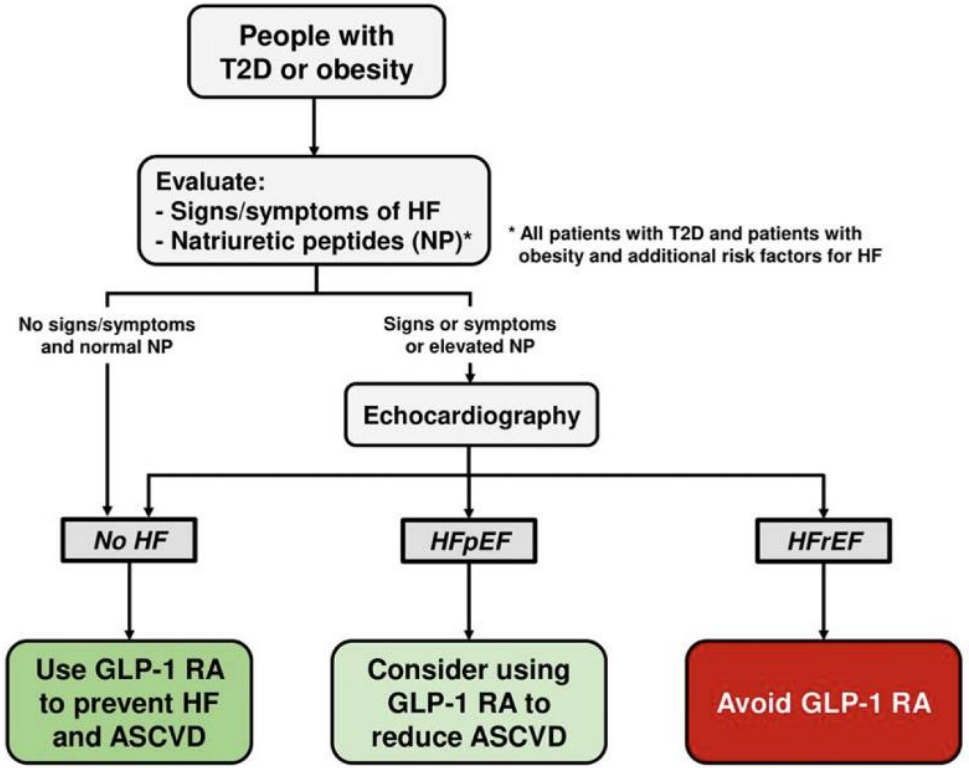
FIGURE 2 Cumulative hazard (Andersen-Gill model) of total events of heart failure (HF) hospitalization or all-cause mortality: hazard ratio [HR] 1.53, 95% confidence interval [CI] 1.02-2.31, $P = 0.040$ (A) and total events of interest: HR 1.41, 95% CI 1.01-1.97, $P = 0.043$ (B)

Drug dosage was uptitrated as tolerated every 14 days from 0.6 mg/d to 1.2 mg/d to 1.8 mg/d during the first 30 days

Diabetes Obes Metab. 2023;25:189–197.

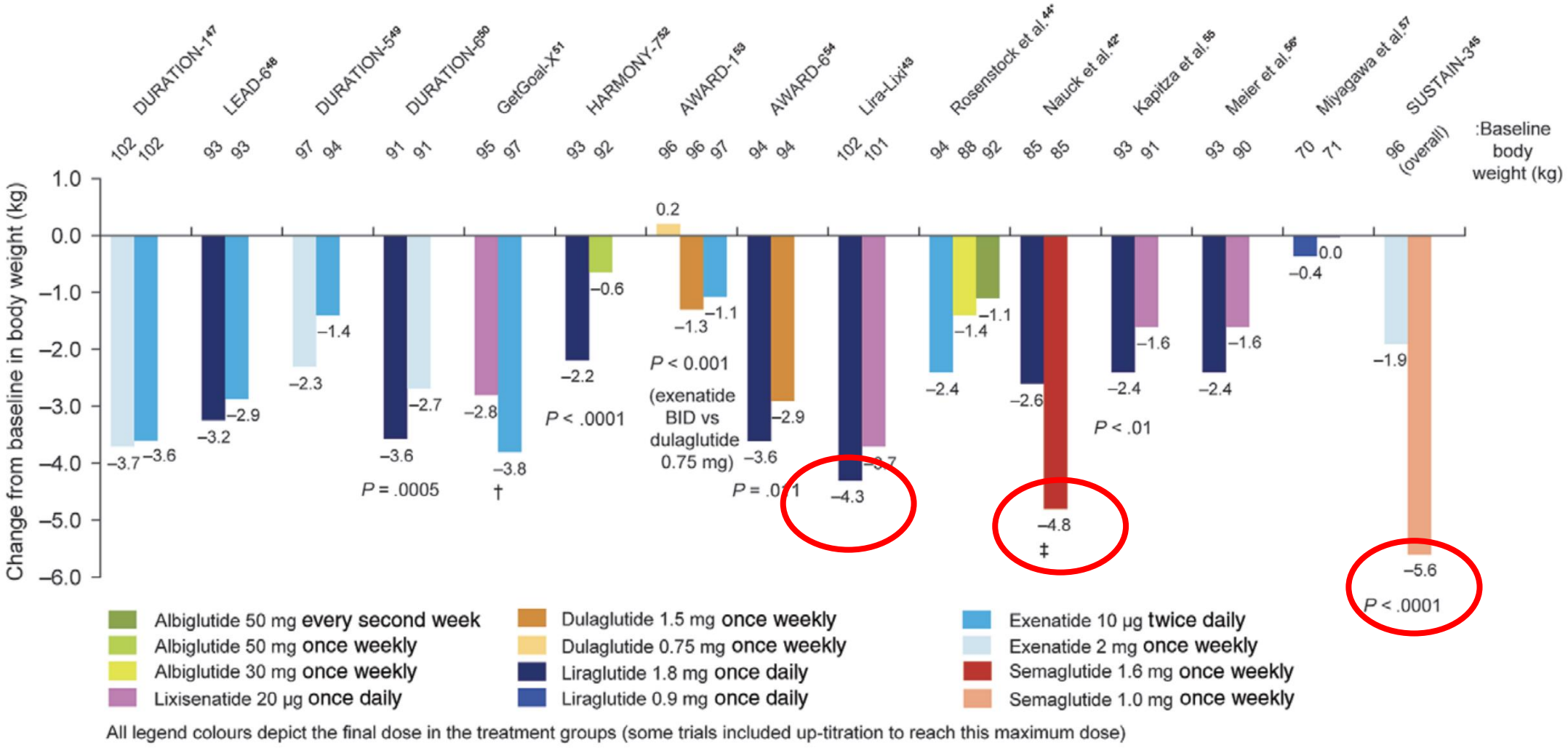
Glucagon-Like Peptide-1 Receptor Agonists Across the Spectrum of Heart Failure





TheJournal of Clinical Endocrinology &Metabolism, 2023, 00, 1-6

CHANGE IN BODY WEIGHT IN HEAD-TO-HEAD COMPARISON TRIALS OF GLP-1RAS

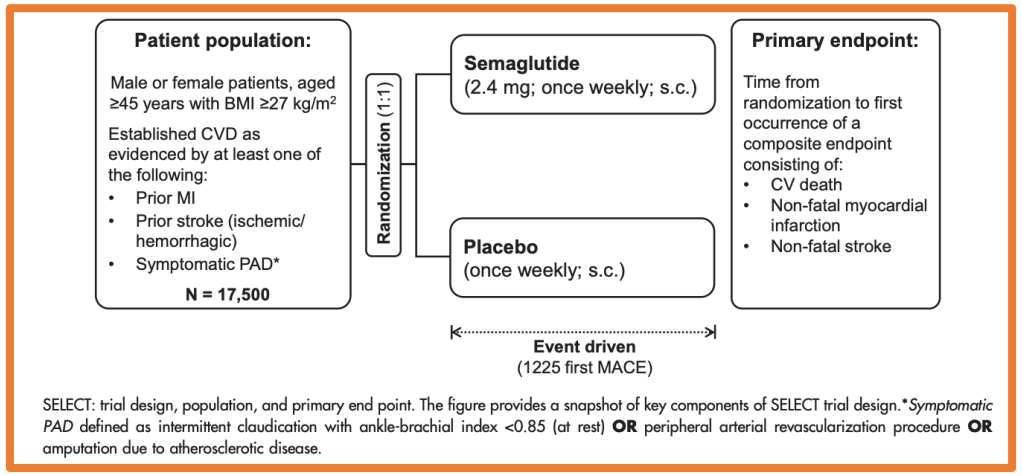


Obesity Reviews. 2022;23:e13435.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

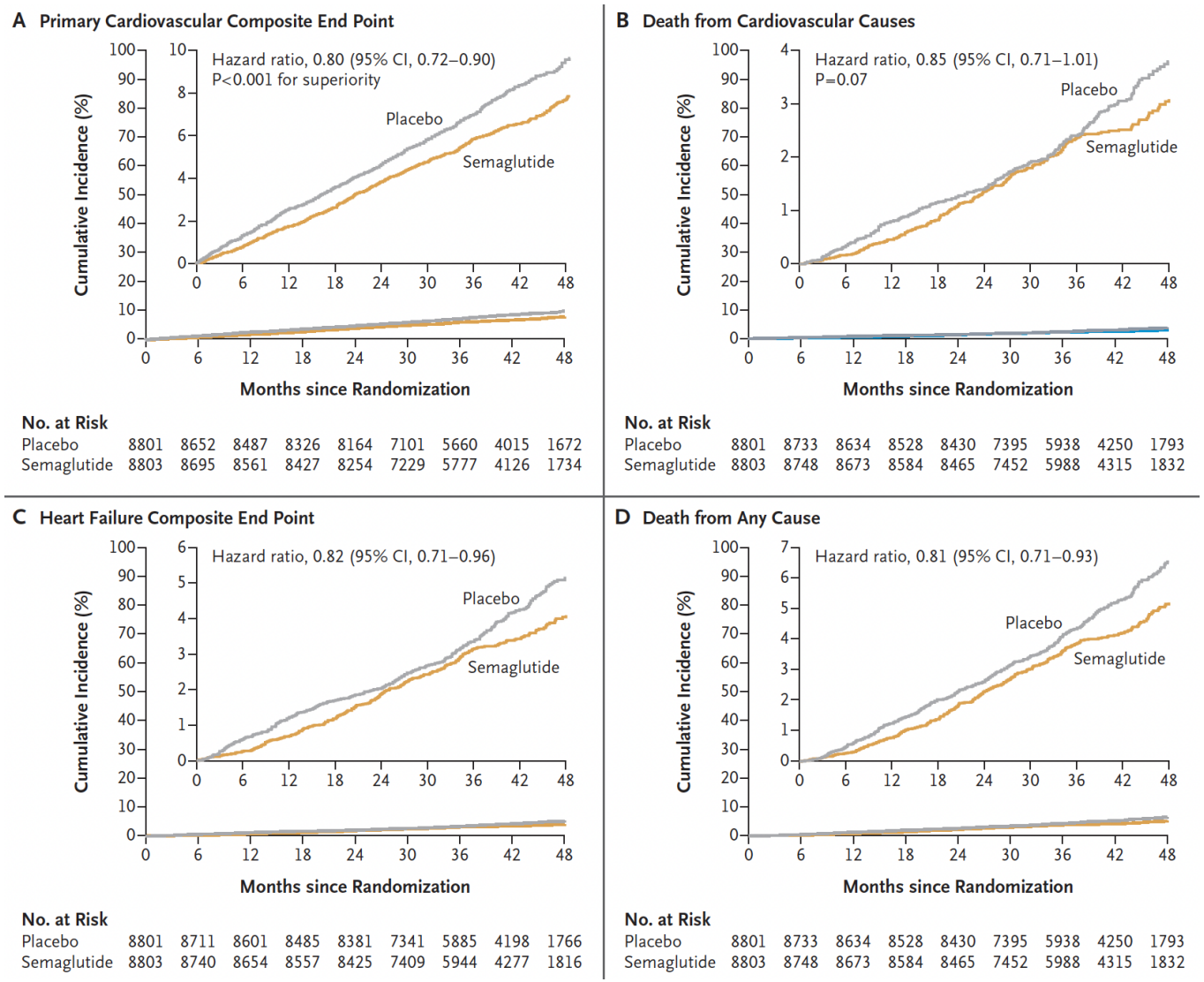
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes



SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design.*Symptomatic PAD defined as intermittent claudication with ankle-brachial index <0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

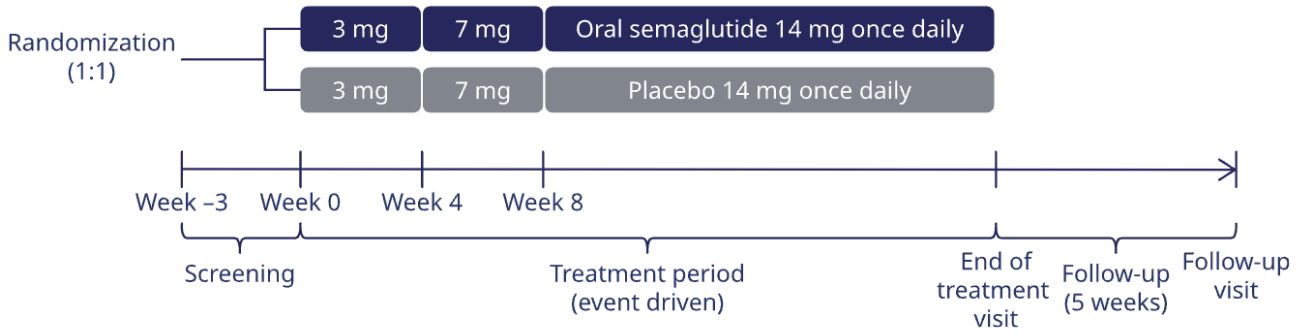
Mean duration of follow-up was 39.8±9.4 months.

November 11, 2023, DOI: 10.1056/NEJMoa2307563



Randomized Controlled Trial > Diabetes Obes Metab. 2023 Jul;25(7):1932-1941.
doi: 10.1111/dom.15058. Epub 2023 Apr 11.

Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial



SOUL (Semaglutide cardiOvascular oUtcomes triaL) in individuals with type 2 diabetes trial design

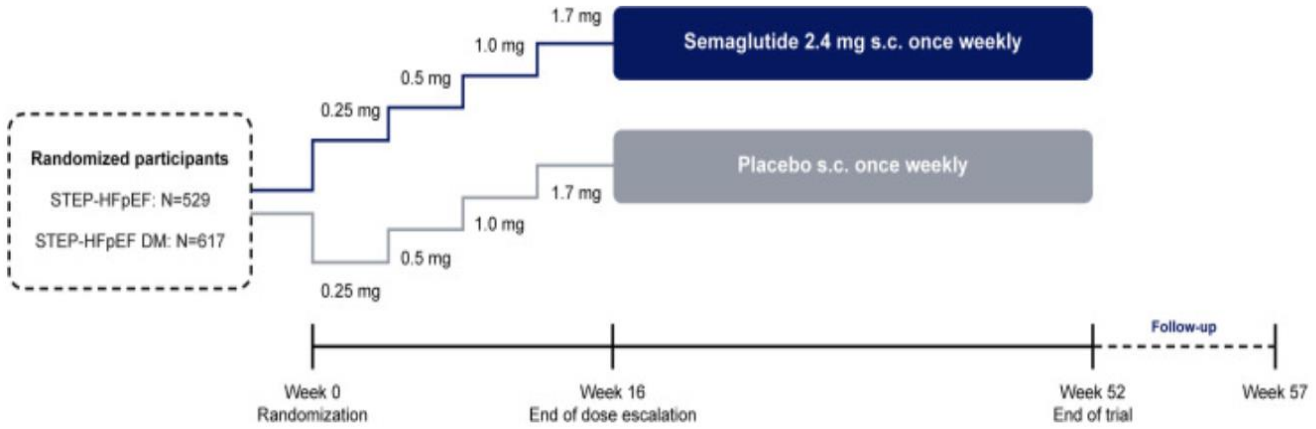
SOUL will provide evidence regarding the CV effects of oral semaglutide in individuals with type 2 diabetes and established ASCVD and/or CKD.

TABLE 1 Primary and confirmatory secondary outcomes

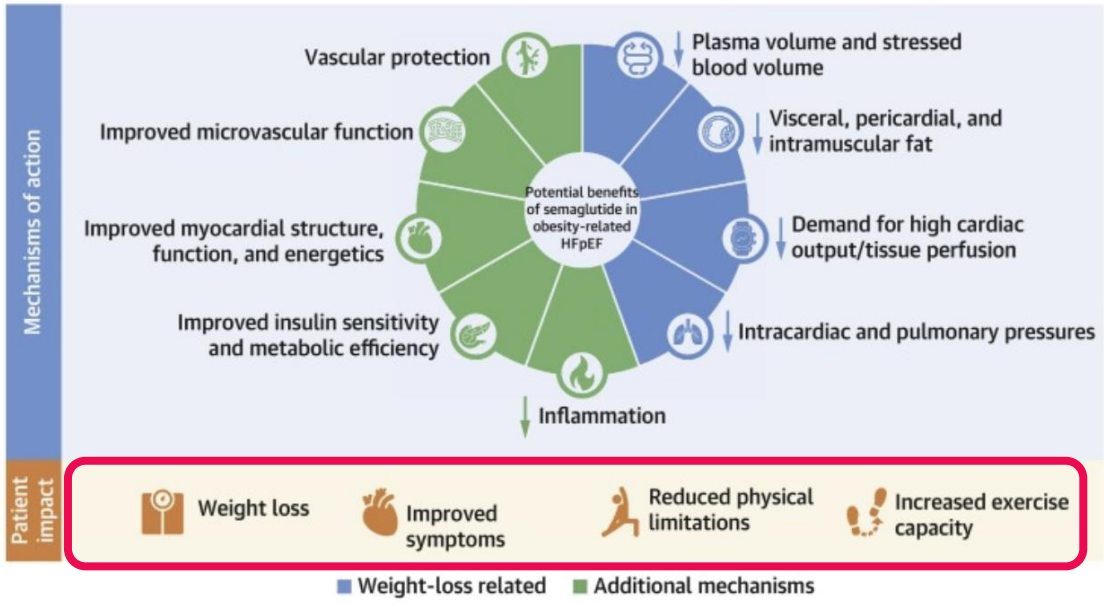
Outcome title	Timeframe
Primary outcome	
Time to first occurrence of MACE, a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• CV death	
• Nonfatal MI	
• Nonfatal stroke	
Confirmatory secondary outcomes	
Time to first occurrence of a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• CV death	
• Kidney-related death	
• Persistent ≥50% reduction in eGFR (CKD-EPI)[b]	
• Persistent eGFR (CKD-EPI) <15 mL/min/1.73 m^2	
• Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)	
Time to occurrence of CV death	From randomization (week 0) to end of trial (up to 61 months or more[a])
Time to first occurrence of major adverse limb events, a composite outcome consisting of:	From randomization (week 0) to end of trial (up to 61 months or more[a])
• Acute limb ischaemia hospitalization	
• Chronic limb ischaemia hospitalization	

Randomized Controlled Trial > JACC Heart Fail. 2023 Aug;11(8 Pt 1):1000-1010.
doi: 10.1016/j.jchf.2023.05.010. Epub 2023 May 21.

Design and Baseline Characteristics of STEP-HFpEF Program Evaluating Semaglutide in Patients With Obesity HFpEF Phenotype



CENTRAL ILLUSTRATION: Potential Mechanisms of Benefit for Semaglutide in Individuals With the Obesity Phenotype of HFpEF



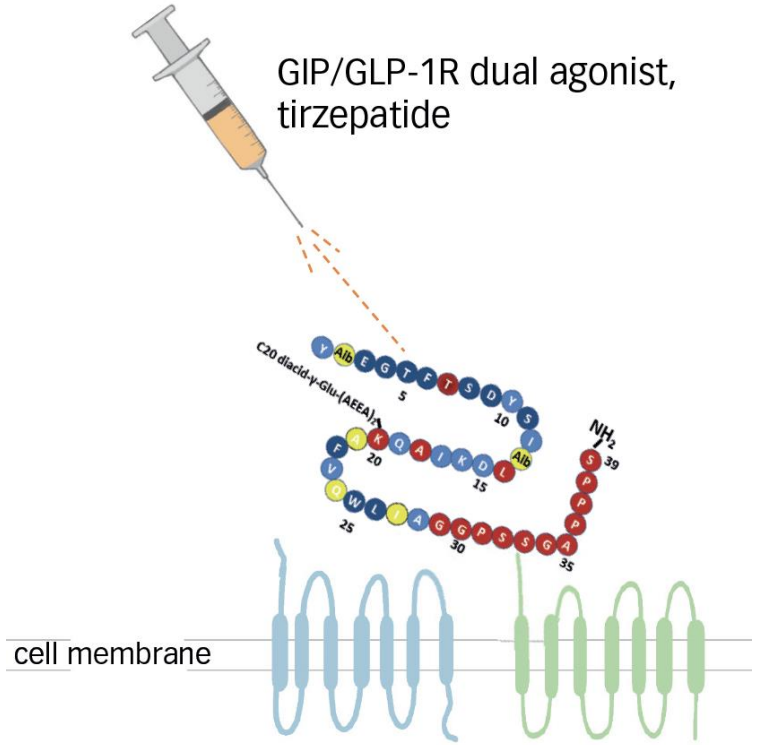
Kosiborod MN, et al. J Am Coll Cardiol HF. 2023;11(8P1):e009664.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

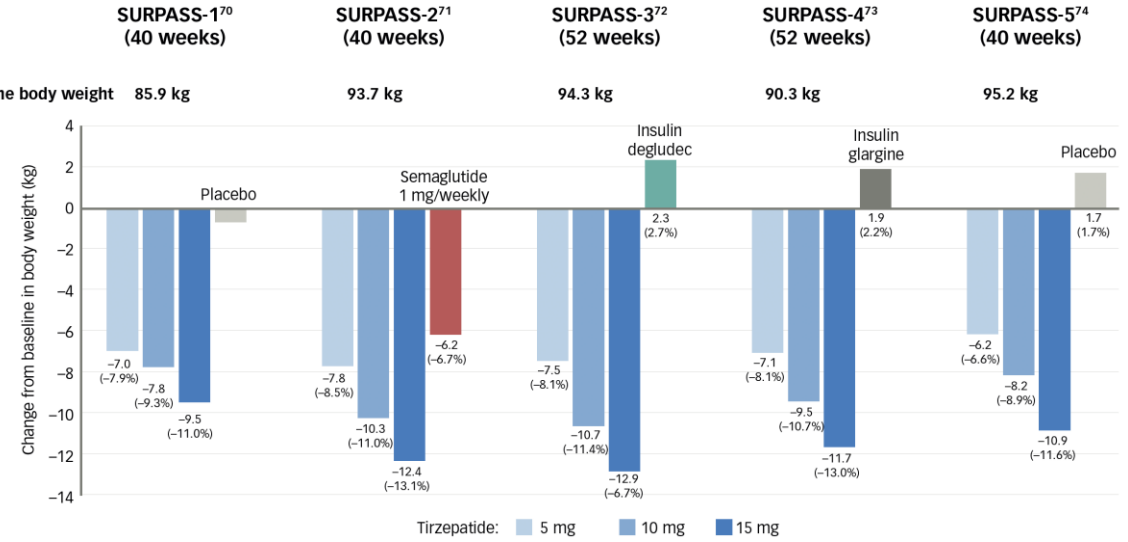
Tirzepatide Once Weekly for the Treatment of Obesity

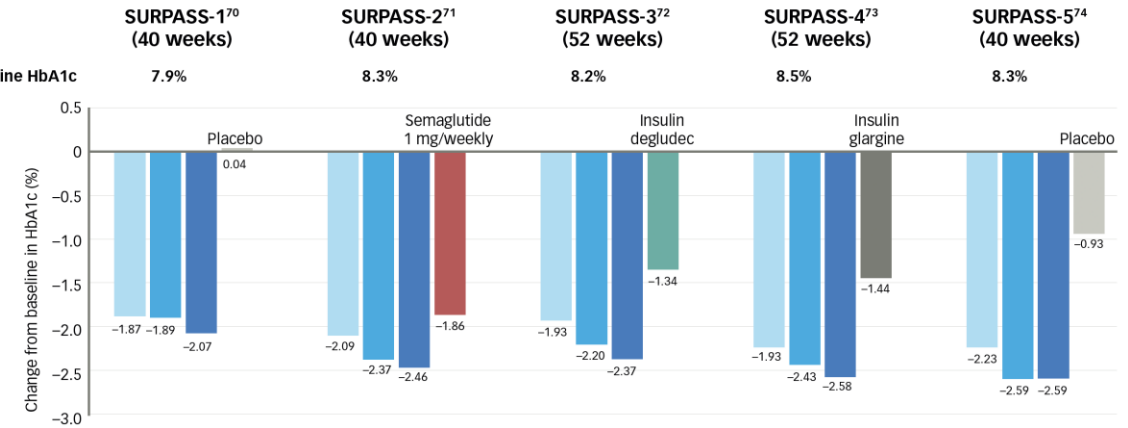
Jastreboff AM et al. DOI: 10.1056/NEJMoa2206038



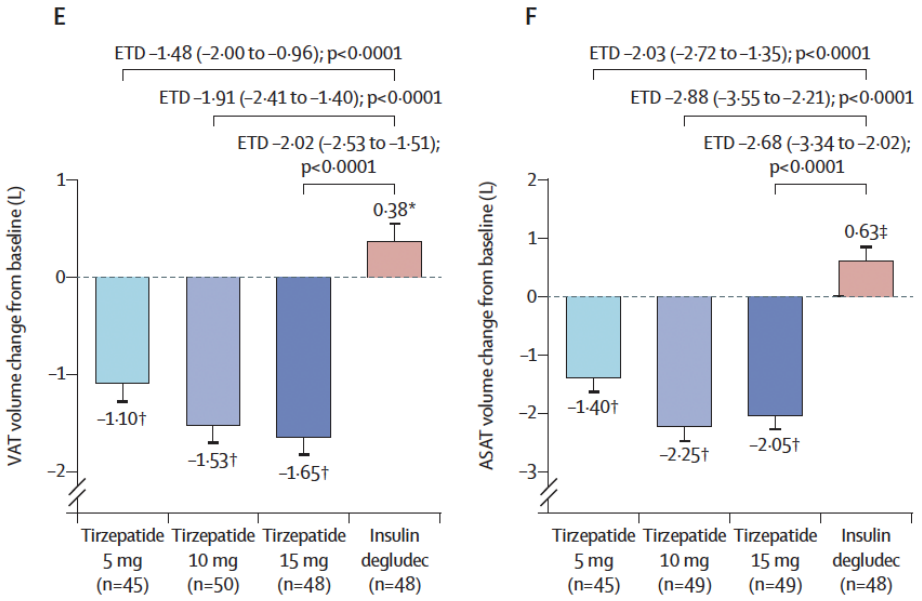
SURPASS CLINICAL PROGRAM

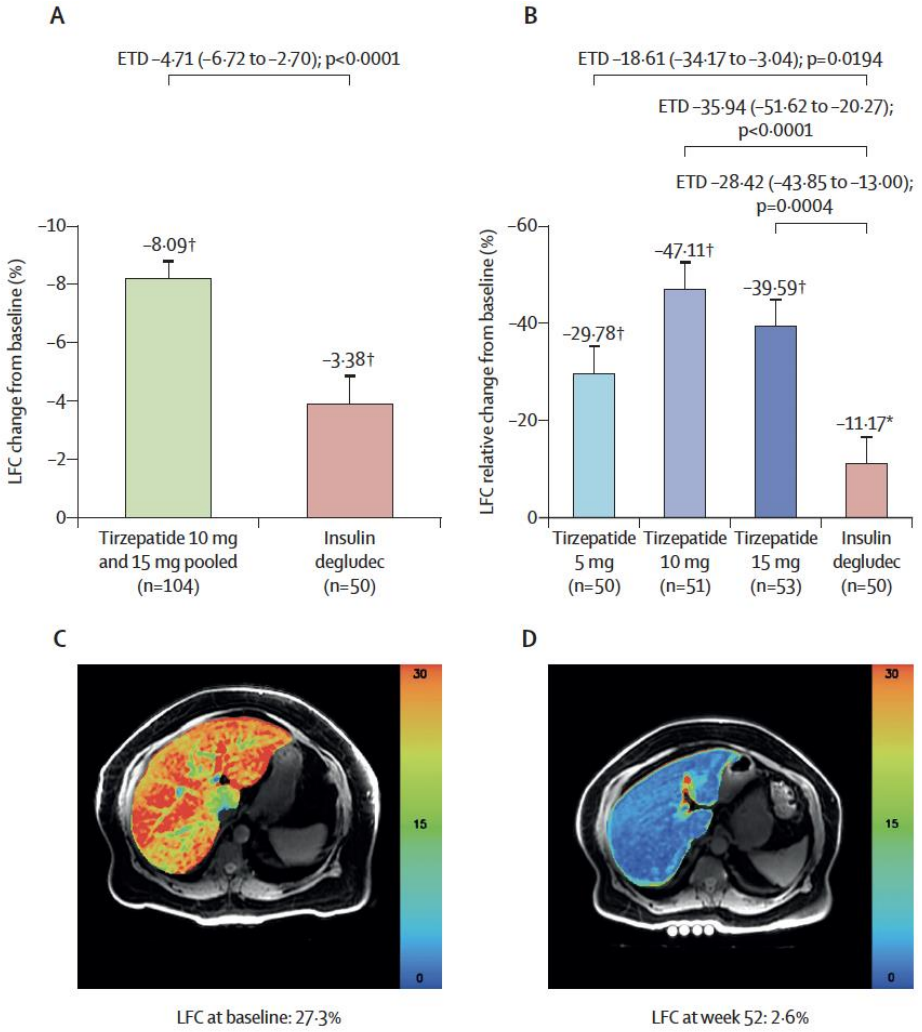
DESIGNED TO DELIVER ROBUST DATASET WITH MULTIPLE HEAD-TO-HEAD TRIALS





Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial



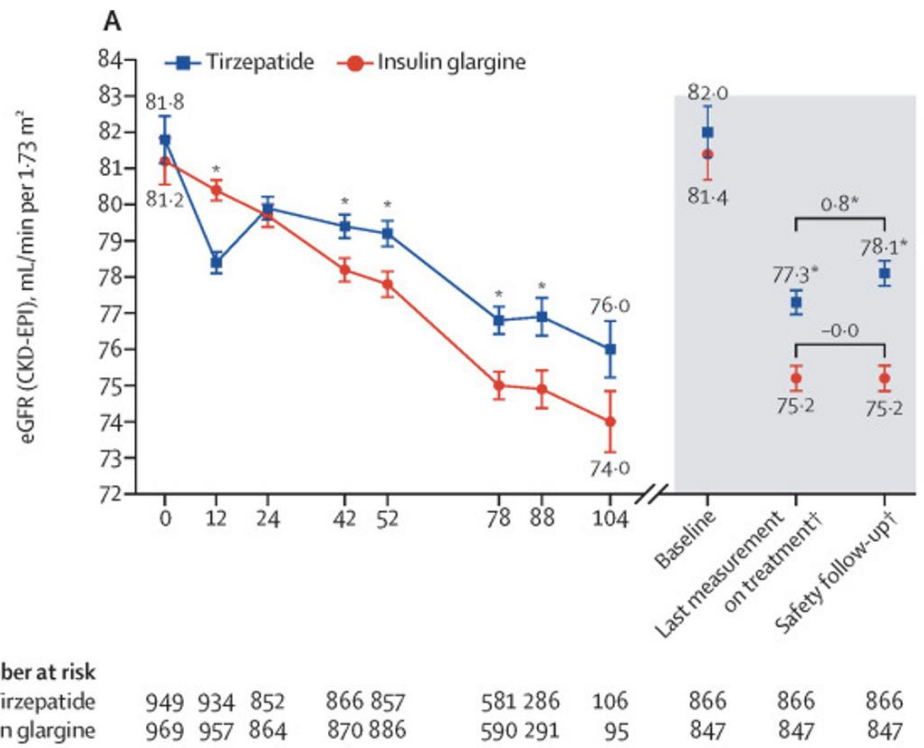


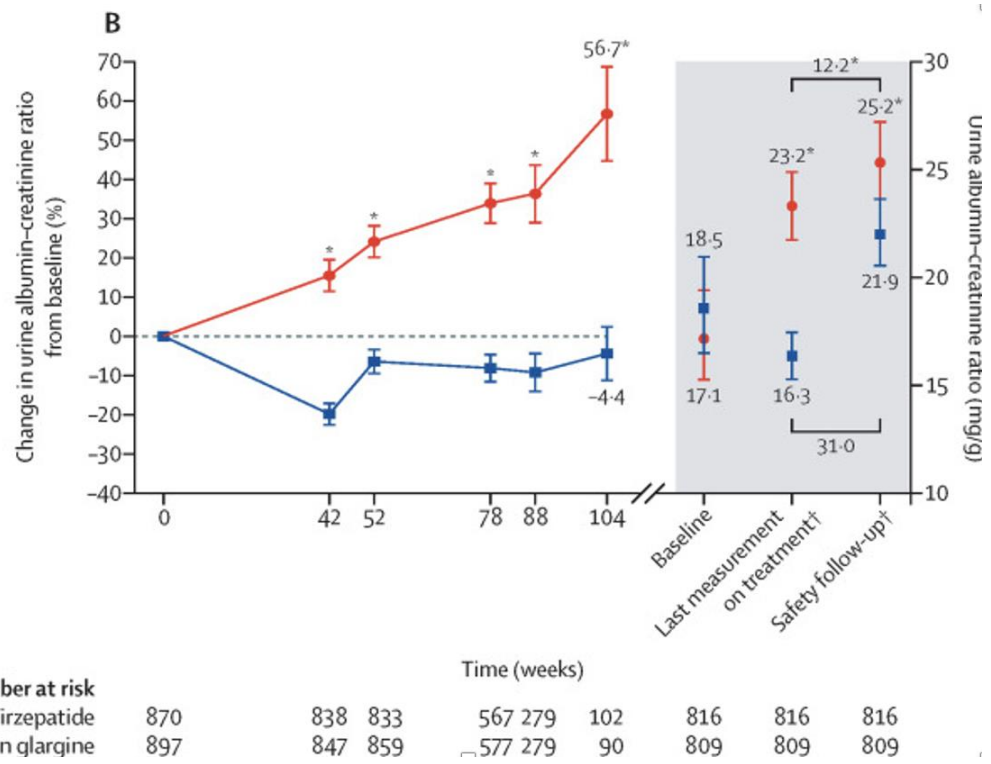
ASAT=abdominal subcutaneous adipose tissue

Lancet Diabetes Endocrinol 2022; 10: 393–406

Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial

Lancet Diabetes Endocrinol. 2022 Nov;10(11):774-785.





Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis

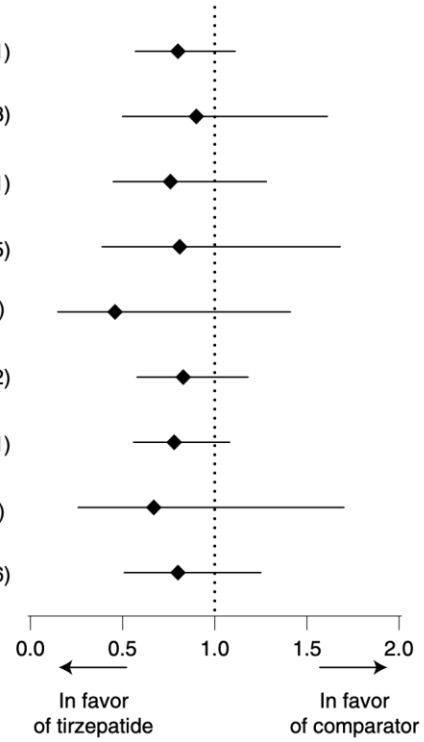
SURPASS-4

NATURE MEDICINE | VOL 28 | MARCH 2022 | 591–598 | www.nature.com/naturemedicine

ANALYSIS

NATURE MEDICINE

	All tirzepatide $N = 4,887$ n (n/100 person-years[a])	All comparator $N = 2,328$ n (n/100 person-years[a])	Hazard ratio with 95% CI	Hazard ratio (95% CI)	P value
Composite MACE-4	72 (1.35)	70 (1.61)		0.80 (0.57, 1.11)	0.183
Death due to cardiovascular cause[b]	25 (0.46)	22 (0.43)		0.90 (0.50, 1.61)	
Myocardial infarction	30 (0.56)	30 (0.71)		0.76 (0.45, 1.28)	
Stroke	15 (0.27)	15 (0.35)		0.81 (0.39, 1.68)	
Hospitalization for unstable angina	5 (0.09)	9 (0.20)		0.46 (0.15, 1.41)	
Composite MACE-3[c]	67 (1.25)	62 (1.42)		0.83 (0.58, 1.18)	0.306
Composite MACE-3 or hospitalization for heart failure	74 (1.39)	71 (1.71)		0.78 (0.56, 1.08)	0.137
Hospitalization for heart failure	10 (0.19)	9 (0.29)		0.67 (0.26, 1.70)	
All-cause death	41 (0.76)	39 (0.86)		0.80 (0.51, 1.25)	



This pre-specified cardiovascular meta-analysis included all seven randomized controlled trials from the tirzepatide T2D clinical development program, SURPASS.

ACTIVE, NOT RECRUITING

A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT)

ClinicalTrials.gov ID NCT04255433

Study Overview

Brief Summary

The purpose of the trial is to assess the efficacy and safety of tirzepatide to dulaglutide in participants with type 2 diabetes and increased cardiovascular risk.

Official Title

The Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes (SURPASS-CVOT)

Conditions

Type 2 Diabetes Mellitus

Intervention / Treatment

- Drug: Tirzepatide
- Drug: Dulaglutide

Other Study ID Numbers

- 17073
- I8F-MC-GPGN (Other Identifier) (OTHER: Eli Lilly and Company)
- 2019-002735-28 (EudraCT Number)

Study Start (Actual)

2020-05-29

Primary Completion (Estimated)

2024-10-17

Study Completion (Estimated)

2024-10-17

Enrollment (Actual)

13299

Study Type

Interventional

Phase

Phase 3

> Am Heart J. 2024 Jan:267:1-11. doi: 10.1016/j.ahj.2023.09.007. Epub 2023 Sep 25.

A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity (SUMMIT)

ClinicalTrials.gov ID NCT04847557

Study Overview

Brief Summary

The main purpose of this study is to assess the efficacy and safety of Tirzepatide (LY3298176) in participants with heart failure with preserved ejection fraction and obesity.

Detailed Description

The study will continue until approximately 52 weeks after the last participant is randomized. The maximum duration of an individual's participation is estimated to be 120 weeks and will depend on duration of study enrollment.

Official Title

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide Versus Placebo in Patients With Heart Failure With Preserved Ejection Fraction and Obesity (SUMMIT)

Conditions

Obesity | Heart Failure With Preserved Ejection Fraction

Intervention / Treatment

- Drug: Tirzepatide
- Other: Placebo

Study Start (Actual)
2021-04-20

Primary Completion (Estimated)
2024-06-30

Study Completion (Estimated)
2024-07-30

Enrollment (Estimated)
700

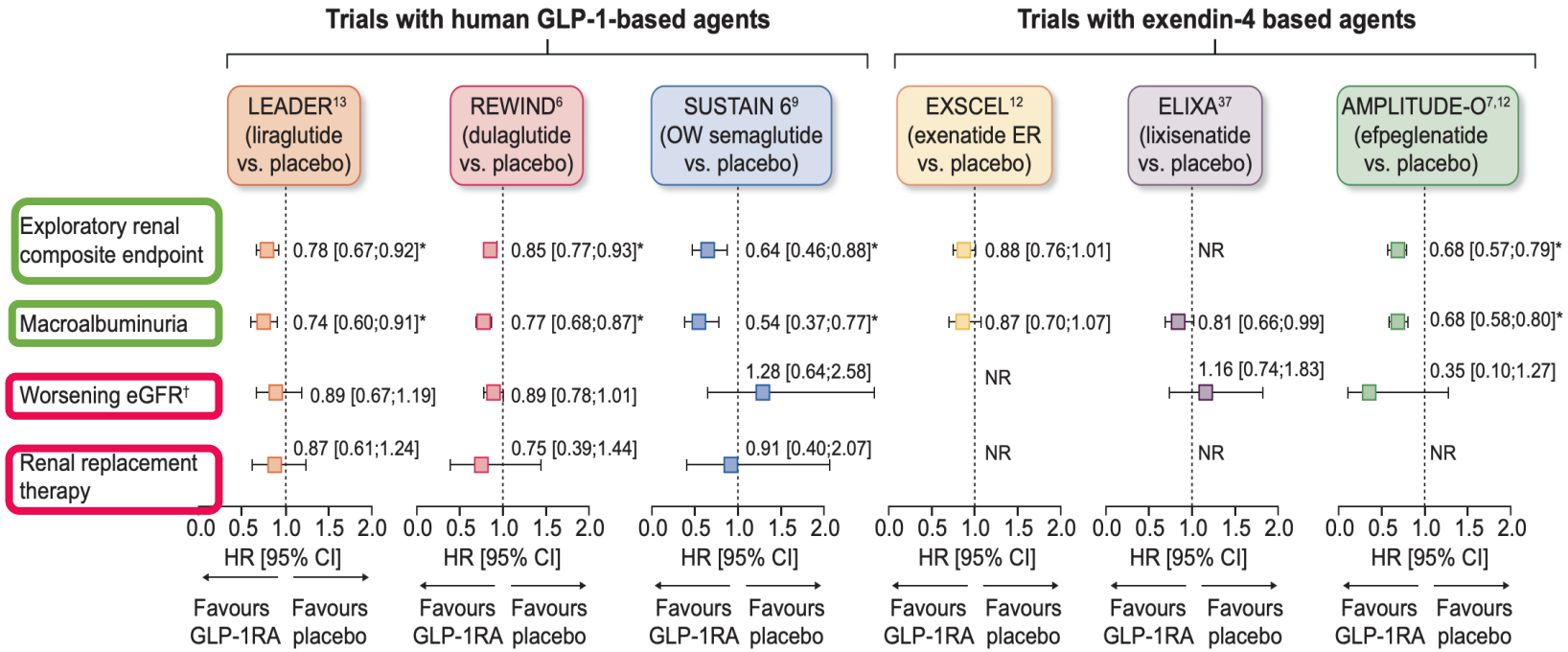
Study Type
Interventional

Phase
Phase 3

GLP-1 RECEPTOR AGONISTS AND RENAL OUTCOMES IN PATIENTS WITH DIABETES MELLITUS TYPE 2 AND DIABETIC KIDNEY DISEASE

RR= ↓ 15-36%

	Drug	Renal endpoint
LEADER	Liraglutide versus placebo	- Macroalbuminuria - Doubling of sCreat - eGFR <45 mL/min/1.73 m^2 - Need for dialysis - Death for renal causes
SCALE	Liraglutide versus placebo	- Changes in UACR
LIRA-RENAL	Liraglutide versus placebo	- Changes in eGFR - Changes in UACR
SUSTAIN–6	Semaglutide versus placebo	- Macroalbuminuria - Doubling of sCreat - eGFR <45 mL/min/1.73 m^2 - Need for dialysis
ELIXA	Lixisenatide versus placebo	- Changes in UACR
EXSCEL	Exenatide LAR versus placebo	- 40% eGFR decline - Need for dialysis - Death for renal causes - Macroalbuminuria *de novo*
AWARD-7	Dulaglutide versus glargine	- Changes in eGFR and UACR from baseline
REWIND	Dulaglutide versus Placebo	- Macroalbuminuria *de novo* - ≥30% eGFR decline from baseline - Need for dialysis



GLP-1RAs, showed a beneficial effect on albuminuria but not on hard kidney endpoints

Lancet Diabetes Endocrinol. 2021 Oct;9(10):653-662. doi: 10.1016/S2213-8587(21)00203-5

Clinical Trial > Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051.
doi: 10.1093/ndt/gfad009.

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

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

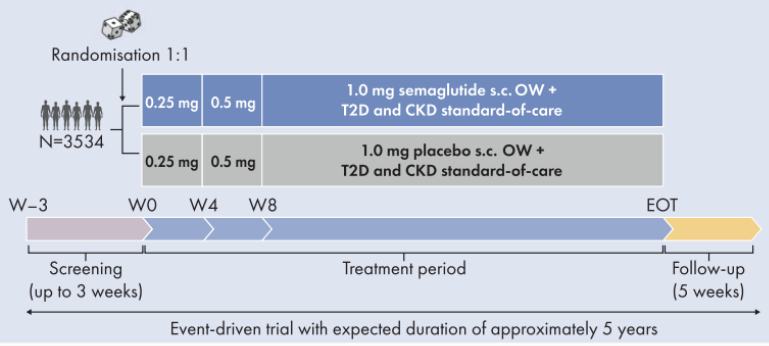
Participants:

- 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 m²; 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.

KEY LEARNING POINTS

What is already known about this subject?

- Evidence has emerged of the potential kidney-protective effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in people with type 2 diabetes (T2D).
- To date, data have mostly been derived from cardiovascular (CV) outcome or glycaemic control trials featuring populations 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 with GLP-1RAs.

What this study adds?

- FLOW (NCT03819153) is a dedicated kidney outcomes trial to assess semaglutide, a once-weekly GLP-1RA, in a population with CKD and T2D at high risk of kidney disease progression.
- The trial is designed to assess whether treatment with once-weekly subcutaneous semaglutide delays the progression of kidney disease and lowers the risk of kidney failure, as well as kidney and CV disease mortality, compared with placebo in people with CKD and T2D.
- Baseline data from the FLOW trial, which is ongoing, show that enrolled participants are nearly all classified as high or very high risk for CKD progression according to Kidney Disease: Improving Global Outcomes guidelines categorisation, which assesses risk based on estimated glomerular filtration rate and urine albumin:creatinine ratio.

What impact this may have on practice or policy?

- The FLOW trial will provide evidence on the effects of semaglutide on kidney outcomes, potentially expanding treatment options for patients with T2D to slow the progression of CKD and reduce kidney failure.

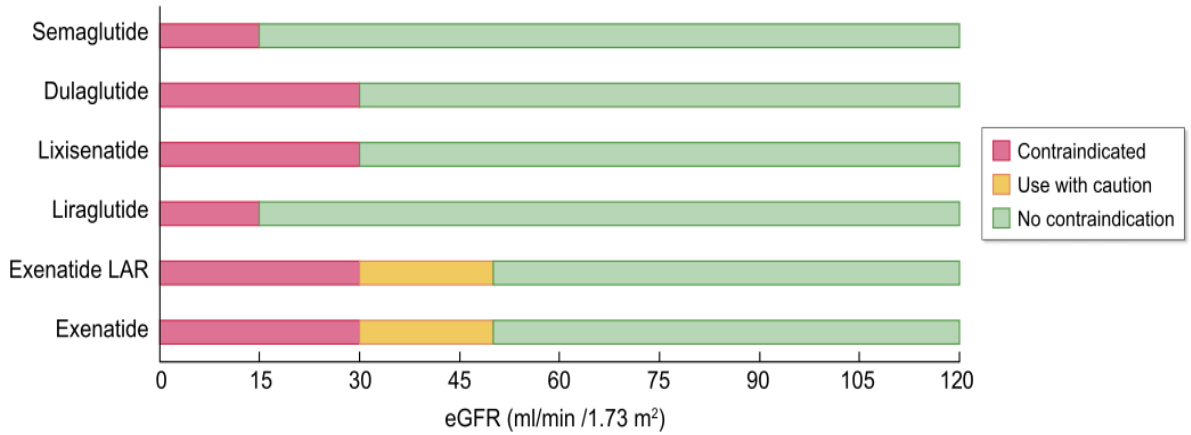
EASD European Association for the Study of Diabetes

KDIGO Kidney Disease Improving Global Outcomes

American Diabetes Association

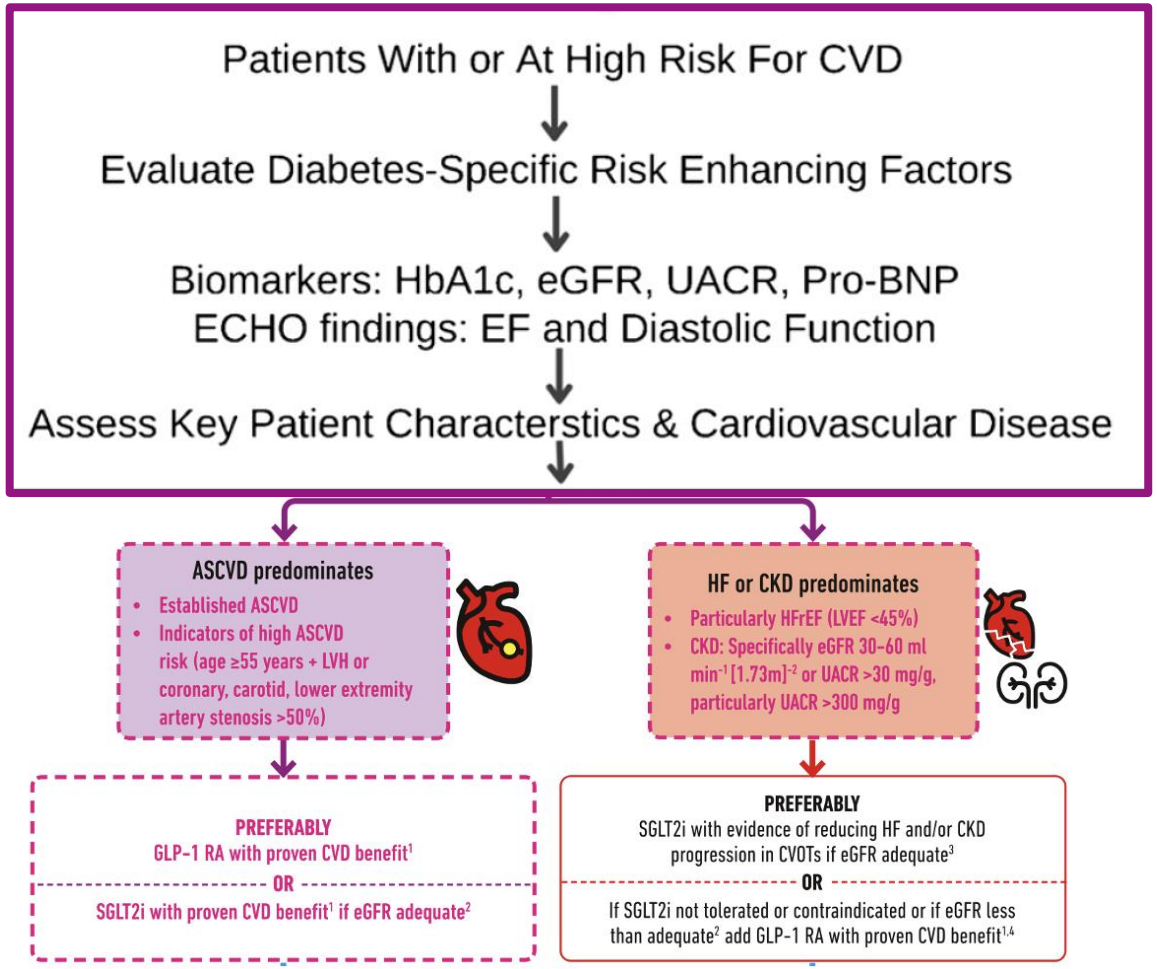
RECOMMENDATIONS FOR SGLT2I VERSUS GLP-1 RA ON THE BASIS OF KIDNEY FAILURE RISK STRATIFICATION

eGFR	UACR <30 mg/g	UACR 30–299 mg/g	UACR ≥300 mg/g
>60 ml/min per 1.73 m²	SGLT2i or GLP-1 RA[a]	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]	SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
30–60 ml/min per 1.73 m²	SGLT2i is preferred. GLP-1 RA as an alternative if SGLT2i is contraindicated or not tolerated, and as an add-on for uncontrolled metabolic risk[b]		SGLT2i should be initiated. GLP-1 RA as an add-on for uncontrolled metabolic risk[c]
15–29 ml/min per 1.73 m²	GLP-1 RA (dulaglutide) is preferred. Initiation of SGLT2i is currently contraindicated[d]		



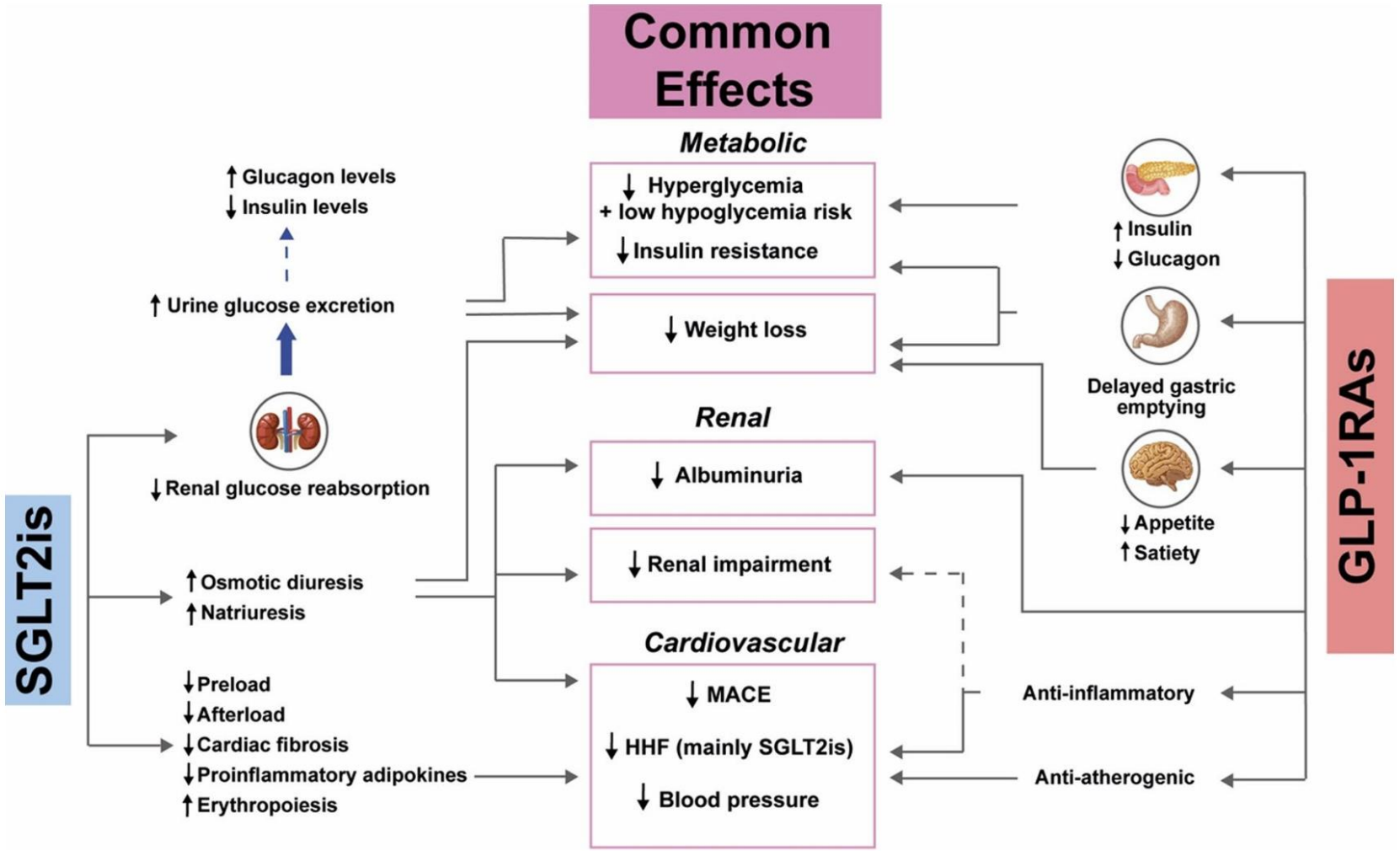
Clinical Kidney Journal, 2022, vol. 15, no. 9, 1657–1665

CONSIDERATIONS FOR SELECTING BETWEEN GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST AND SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR



GLP1-RA or SGLT2i ??

COMPLEMENTARY MECHANISMS OF ACTION OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2IS) AND GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1RAS)

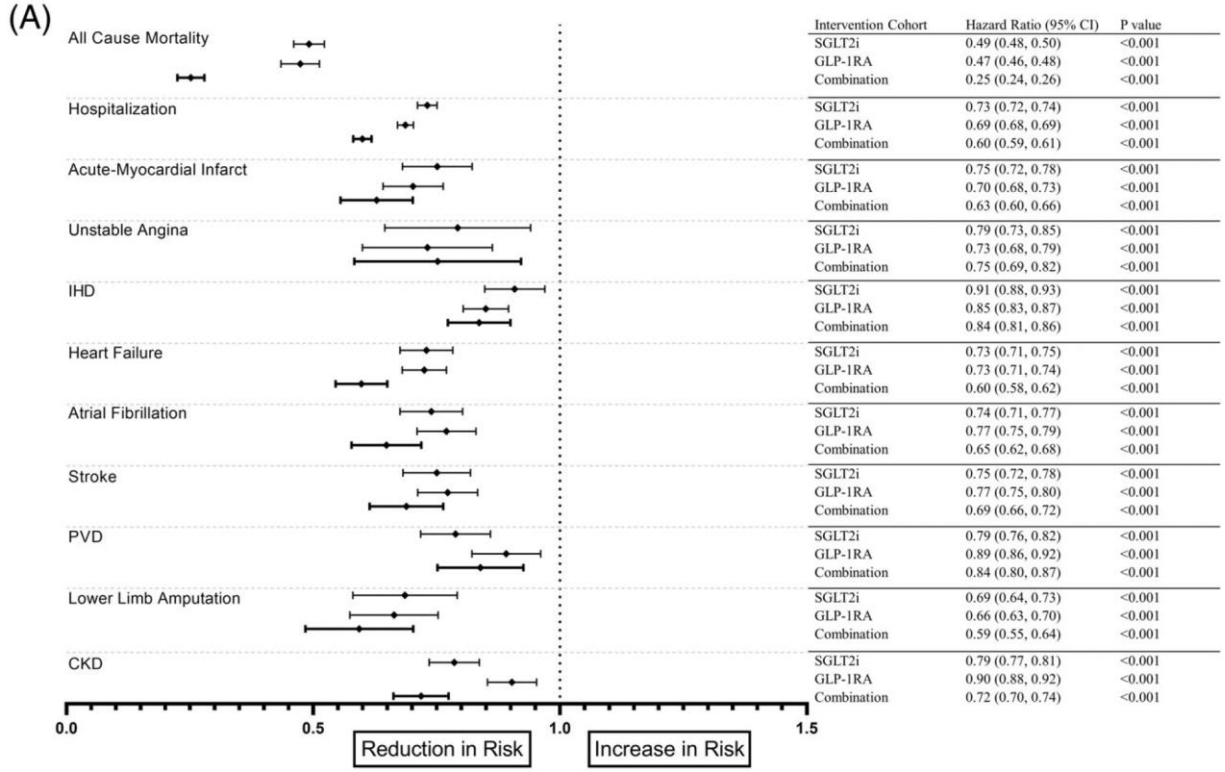


Gourdy *et al. Cardiovascular Diabetology (2023) 22:79*

BMC

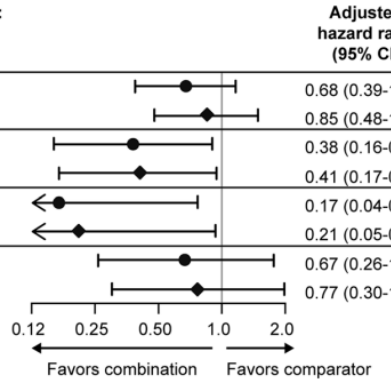
CARDIOVASCULAR OUTCOMES WITH SGLT2 i, GLP1 RA AND WITH COMBINATION THERAPY IN PEOPLE WITH T2DM

Outcome	SMD (95% CI) compared to GLP-1RAs alone and SGLT2is alone	p-value
Meta-analysis by Li et al. [59] of 8 RCTs including 1,895 adults with T2DM		
HbA1c reduction	−0.77% (−1.03% to −0.50%)	<0.001
Body weight loss	−0.36 kg (−0.50 to −0.21 kg)	<0.001
SBP reduction	−0.33 mmHg (−0.49 to −0.17 mmHg)	<0.001



Intervention Cohort	Hazard Ratio (95% CI)	P value
SGLT2i	0.49 (0.48, 0.50)	<0.001
GLP-1RA	0.47 (0.46, 0.48)	<0.001
Combination	0.25 (0.24, 0.26)	<0.001
SGLT2i	0.73 (0.72, 0.74)	<0.001
GLP-1RA	0.69 (0.68, 0.69)	<0.001
Combination	0.60 (0.59, 0.61)	<0.001
SGLT2i	0.75 (0.72, 0.78)	<0.001
GLP-1RA	0.70 (0.68, 0.73)	<0.001
Combination	0.63 (0.60, 0.66)	<0.001
SGLT2i	0.79 (0.73, 0.85)	<0.001
GLP-1RA	0.73 (0.68, 0.79)	<0.001
Combination	0.75 (0.69, 0.82)	<0.001
SGLT2i	0.91 (0.88, 0.93)	<0.001
GLP-1RA	0.85 (0.83, 0.87)	<0.001
Combination	0.84 (0.81, 0.86)	<0.001
SGLT2i	0.73 (0.71, 0.75)	<0.001
GLP-1RA	0.73 (0.71, 0.74)	<0.001
Combination	0.60 (0.58, 0.62)	<0.001
SGLT2i	0.74 (0.71, 0.77)	<0.001
GLP-1RA	0.77 (0.75, 0.79)	<0.001
Combination	0.65 (0.62, 0.68)	<0.001
SGLT2i	0.75 (0.72, 0.78)	<0.001
GLP-1RA	0.77 (0.75, 0.80)	<0.001
Combination	0.69 (0.66, 0.72)	<0.001
SGLT2i	0.79 (0.76, 0.82)	<0.001
GLP-1RA	0.89 (0.86, 0.92)	<0.001
Combination	0.84 (0.80, 0.87)	<0.001
SGLT2i	0.69 (0.64, 0.73)	<0.001
GLP-1RA	0.66 (0.63, 0.70)	<0.001
Combination	0.59 (0.55, 0.64)	<0.001
SGLT2i	0.79 (0.77, 0.81)	<0.001
GLP-1RA	0.90 (0.88, 0.92)	<0.001
Combination	0.72 (0.70, 0.74)	<0.001

Outcome		Number of events	Combination: Events per 100 pt-yrs	Comparator: Events per 100 pt-yrs	Adjusted hazard ratio (95% CI)
MACE	vs. placebo	57	3.29	4.81	0.68 (0.39-1.17)
	vs. exenatide	54	3.27	4.38	0.85 (0.48-1.49)
All-cause mortality	vs. placebo	30	1.00	2.71	0.38 (0.16-0.90)
	vs. exenatide	32	0.99	2.96	0.41 (0.17-0.95)
CV death	vs. placebo	16	0.28	1.65	0.17 (0.04-0.77)
	vs. exenatide	17	0.28	1.77	0.21 (0.05-0.93)
Serious hypoglycemia	vs. placebo	18	0.94	1.25	0.67 (0.26-1.76)
	vs. exenatide	18	0.93	1.25	0.77 (0.30-1.99)



Patient profile with anticipated benefit from GLP-1RA + SGLT2i combination

- Patients with ASCVD or MRF* for ASCVD without HFrEF**
- Patients not reaching treatment goals:
  - HbA1c above individualized target
  - Overweight/obesity
  - High blood pressure
- Patients with CKD in case of:
  - Persistent albuminuria with SGLT2is
  - Uncontrolled metabolic risks with SGLT2is

Diabetes Obes Metab. 2023;25:2897–2909.

Gourdy et al. Cardiovascular Diabetology (2023) 22:79

Cardiovasc Diabetol. 2019 Oct 22;18(1):138. doi: 10.1186/s12933-019-0942-x.

CONCLUSIONS

1. Nel paziente cardiometabolico ad alto rischio, gli GLP1-RA a lunga durata d'azione**,** indipendentemente dai loro effetto ipoglicemizzante, riducono l'incidenza degli eventi cardiovascolari maggiori (MACE), prevengono il ricovero per scompenso cardiaco di nuova insorgenza ed esercitano effetti nefroprotettivi prevenendo l'insorgenza della macroalbuminuria e rallentando il declino della funzionalità renale.

2. I risultati di trials clinici ancora in corso contribuiranno a definire meglio la capacità della semaglutide e della tirzepatide di implementare gli outcomes cardiovascolari e renali.

3. Prove crescenti supportano l'uso di GLP-1RA in combinazione con SGLT2i, nella prevenzione primaria e secondaria degli eventi cardiovascolari e renali nei pazienti diabetici e, più in generale, dei pazienti ad alto rischio cardiometabolico.