Reducing Cardiometabolic Risk with SGLT2i and GLP1-RA

– *How to Choose and in Who*

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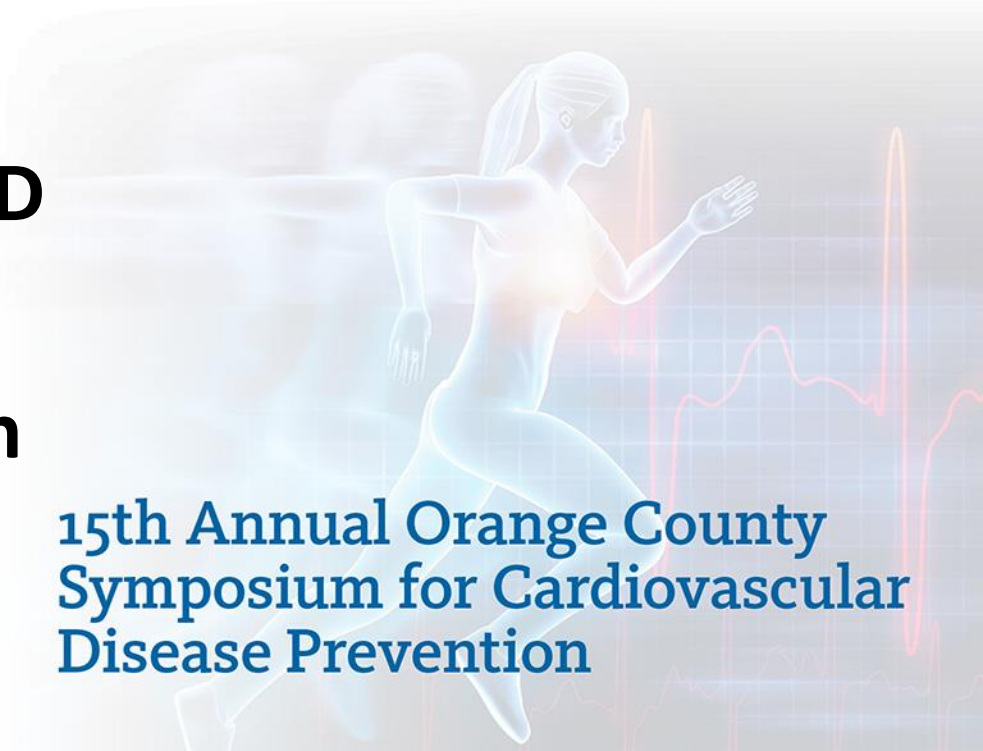
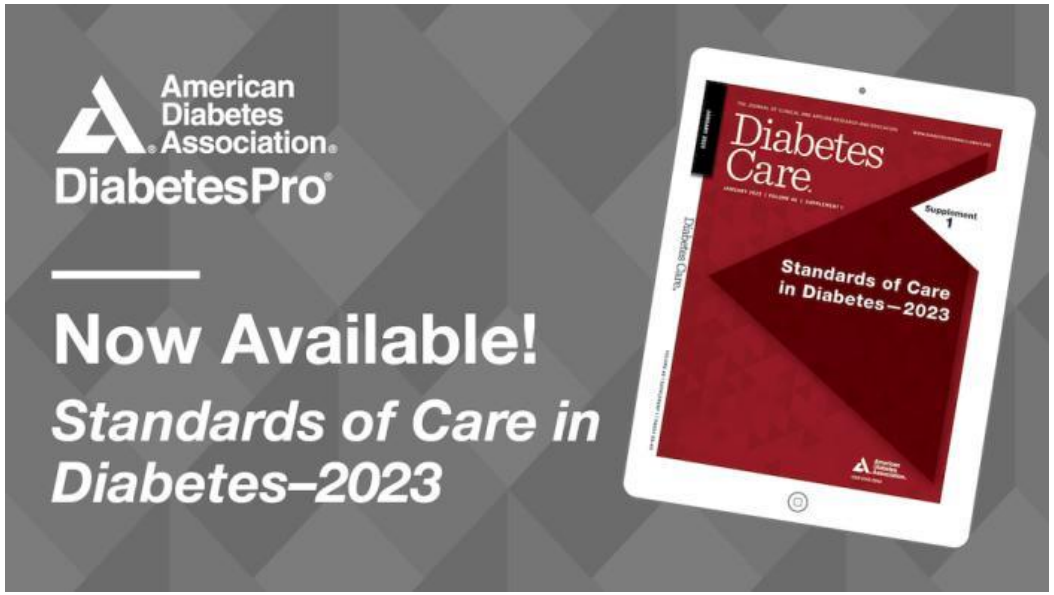
Endocrinology

UC Irvine Health



I have no relevant financial relationships to disclose

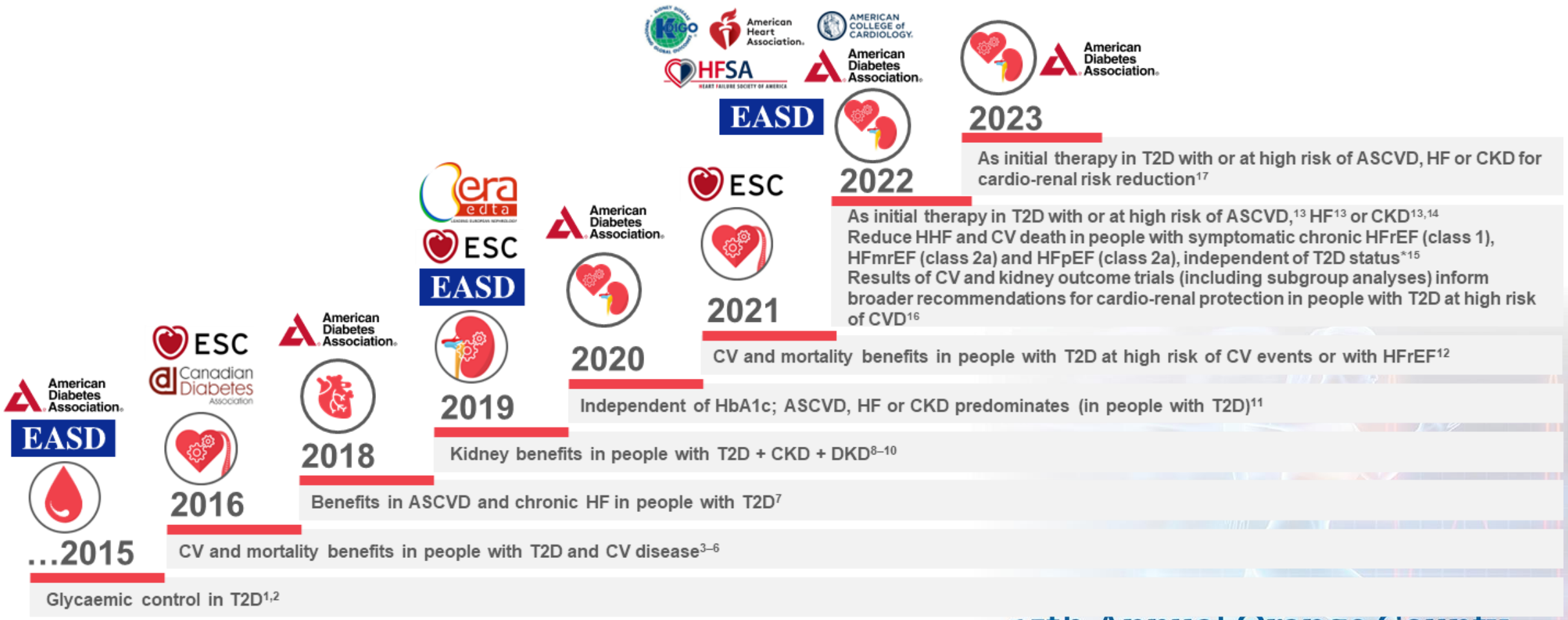
Notable updates to the Standards of Care in Diabetes—2023



- Emphasis on supporting **higher weight loss (up to 15%)** based on the efficacy of and access to newer medications when appropriate
- The **expanded role of SGLT2 inhibitor use** in preserved and reduced heart failure ejection fraction
- New recommendations related to **sleep health and physical activity** in people with diabetes
- Broad consideration of **social determinants of health** in guiding the design and delivery of care
- New **hypertension diagnosis cut-offs** (hypertension is now defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg)
- The **role of finerenone** in individuals with diabetes and chronic kidney disease with albuminuria
- New **lipid management recommendations** suggesting lower LDL goals for high-risk individuals

Symposium for Cardiovascular Disease Prevention

Guidelines and societies recommend the use of SGLT2 inhibitors and/or GLP-1 RAs for their metabolic, CV and kidney benefits



For full recommendations, please refer to the individual references and guidelines or the AT2D module 'Evolving evidence-based recommendations in T2D

*Class denotes strength of recommendation: class 1 = strong; class 2a = moderate[17]

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure

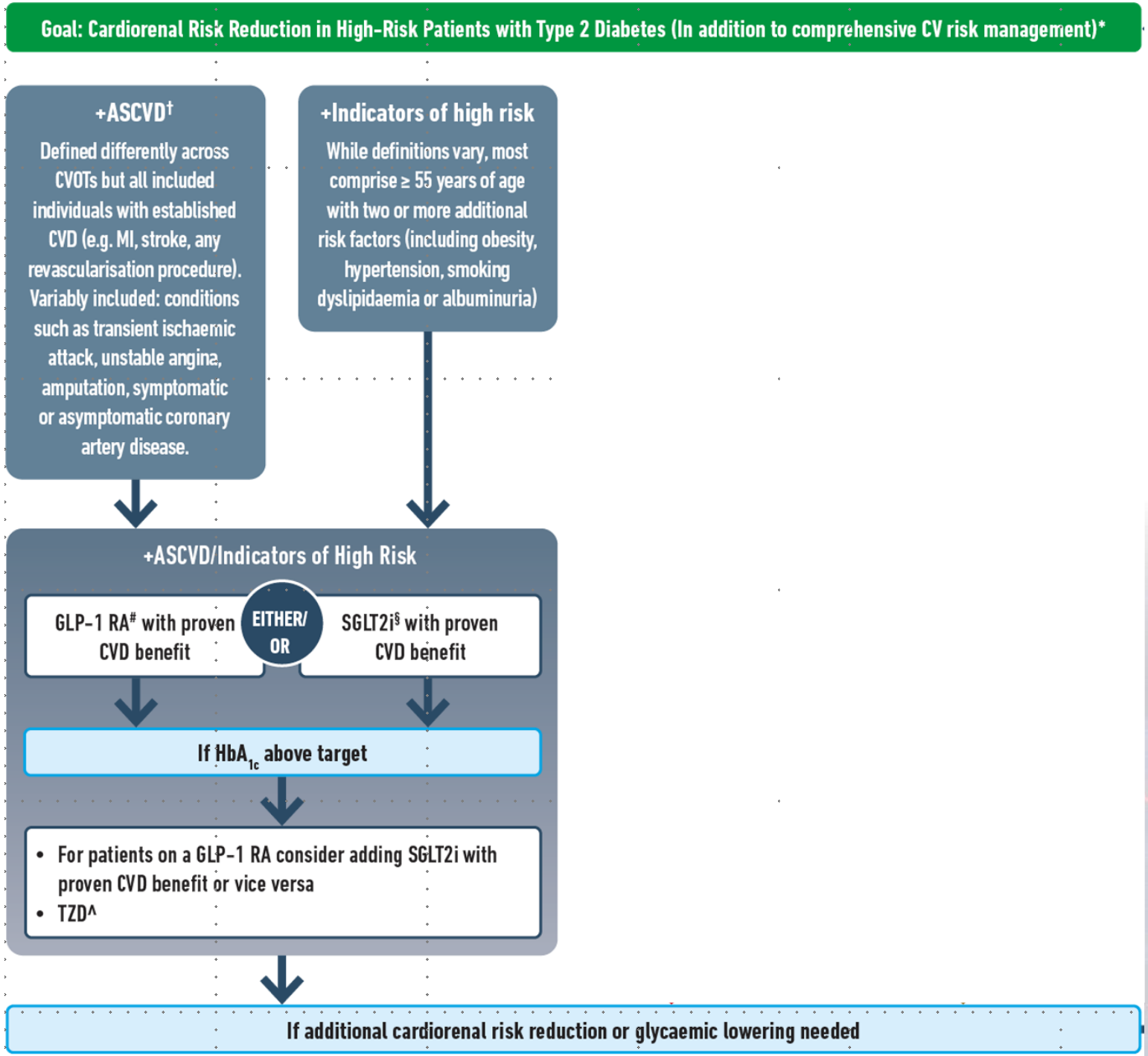
See slide notes for full list of references

Pharmacologic Therapy for Adults With Type 2 Diabetes

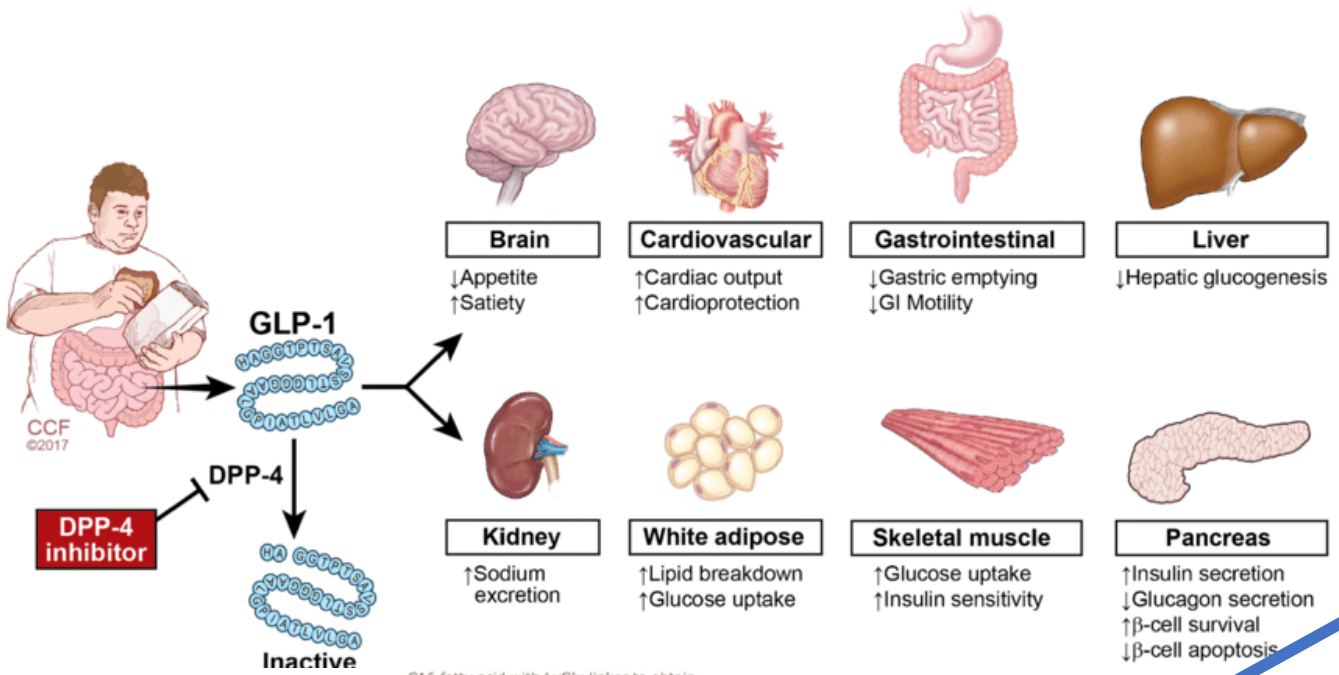
Among individuals with type 2 diabetes who have

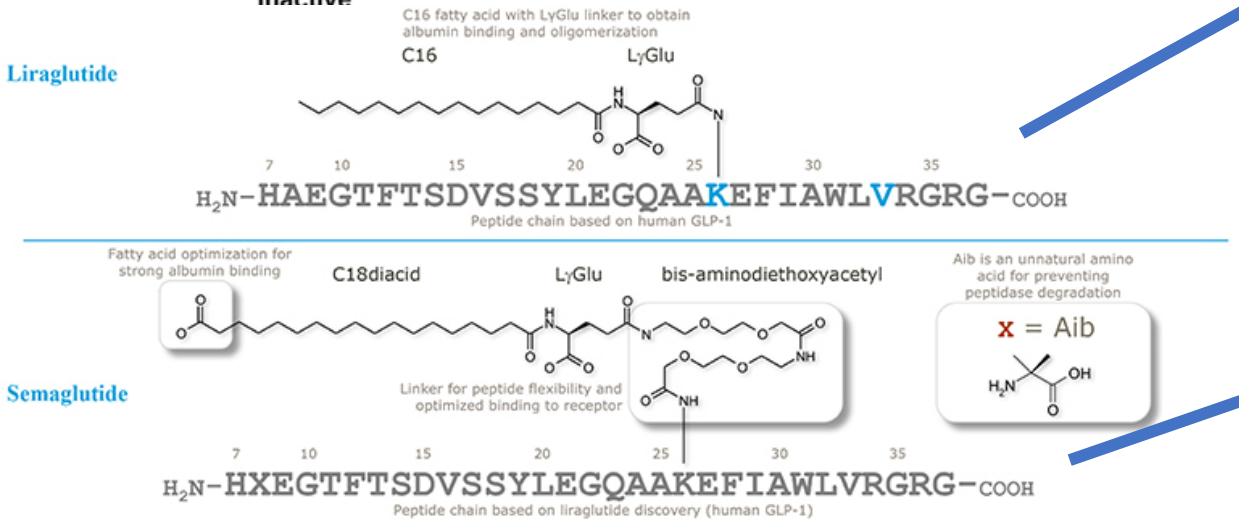
 # established ASCVD
 # indicators of high CV risk
 # established kidney disease
 # heart failure

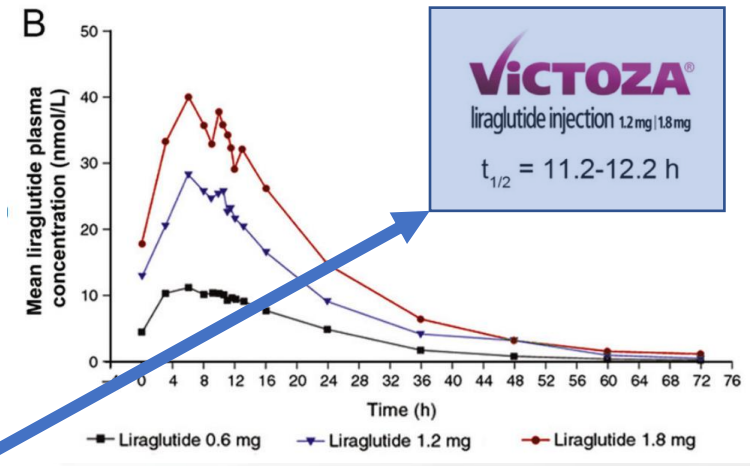
A sodium–glucose cotransporter 2 (SGLT2) inhibitor and/or glucagon-like peptide 1 (GLP-1) receptor agonist is recommended as part of the glucose-lowering regimen and comprehensive CV risk reduction, independent of A1C and in consideration of person-specific factors.

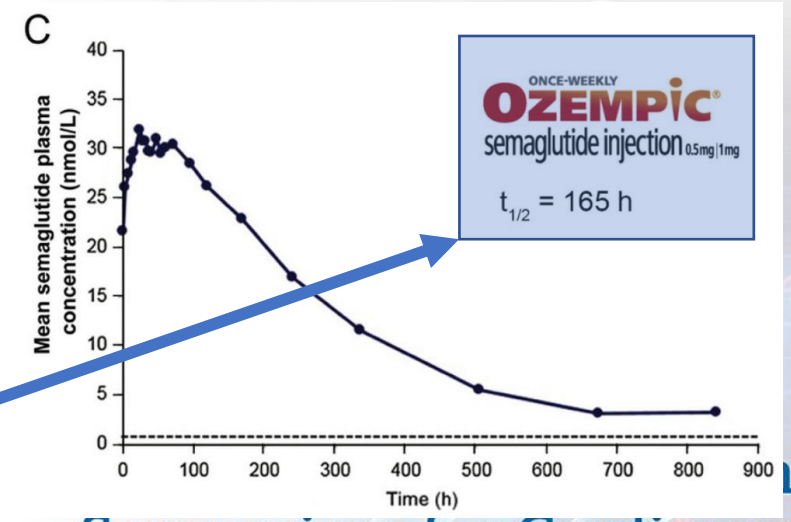


GLP1 and long-acting GLP1-RA





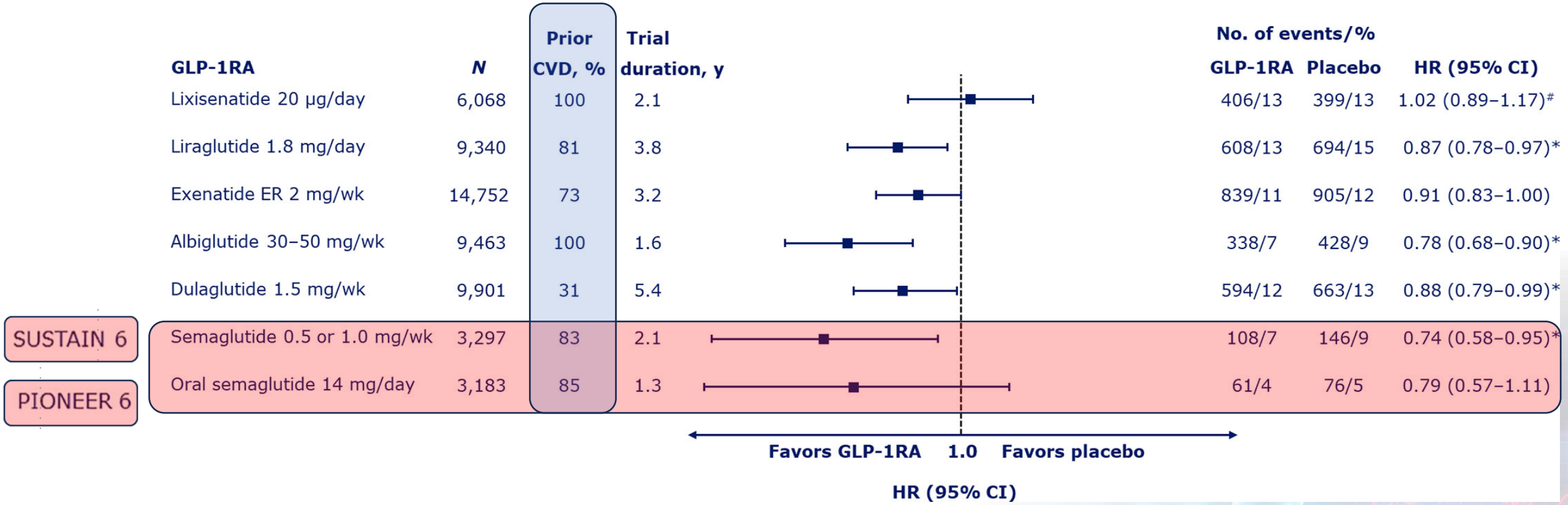




Lawrence L et al., Current Cardiology Reports 2018
Yu M et al., Advanced Drug Delivery Reviews 2018

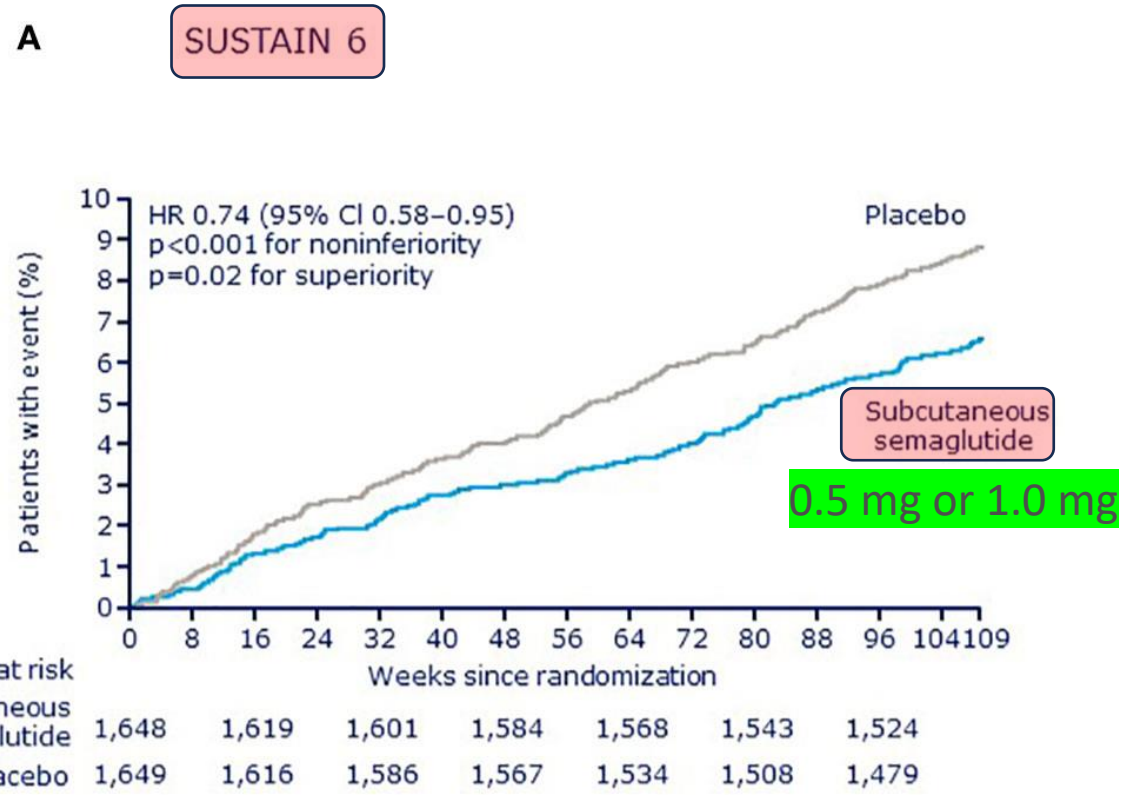
Symposium for Cardiovascular Disease Prevention

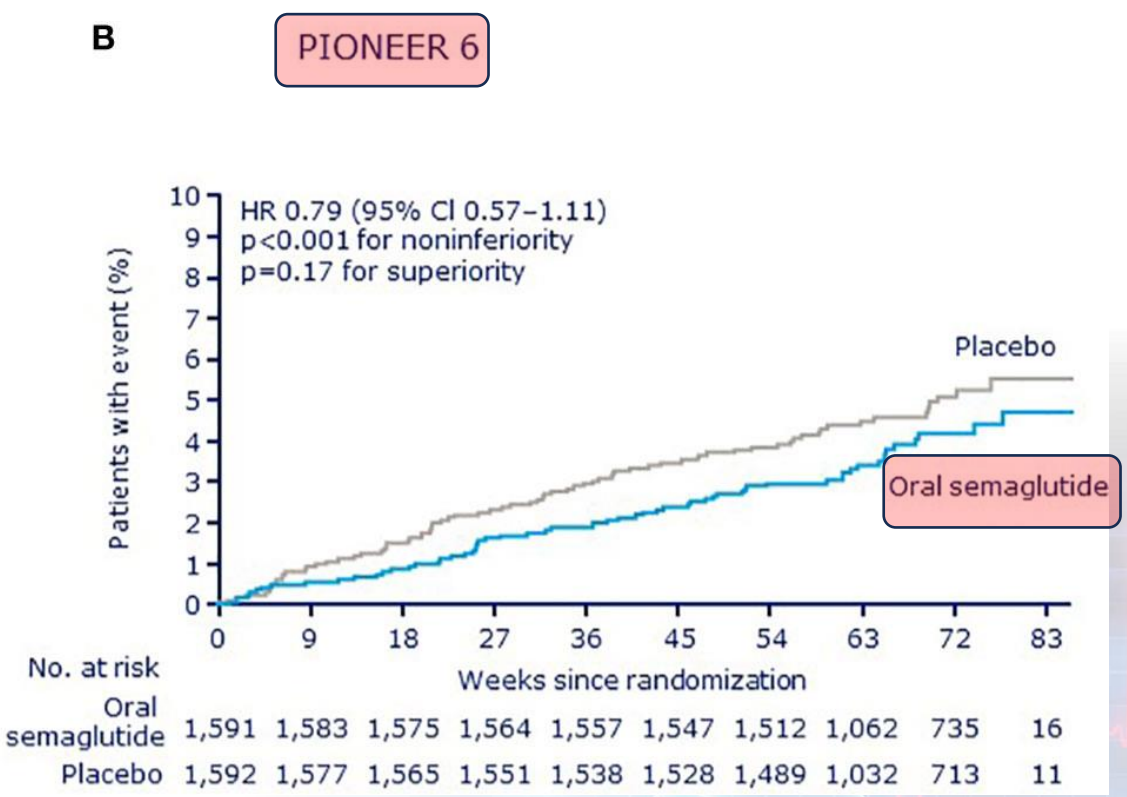
GLP1-RAs and cardiovascular outcomes



Nauck MA et al., Front in Endo 2021

Cardiovascular Safety and Benefits of Semaglutide in Patients With Type 2 Diabetes: Findings From SUSTAIN 6 and PIONEER 6

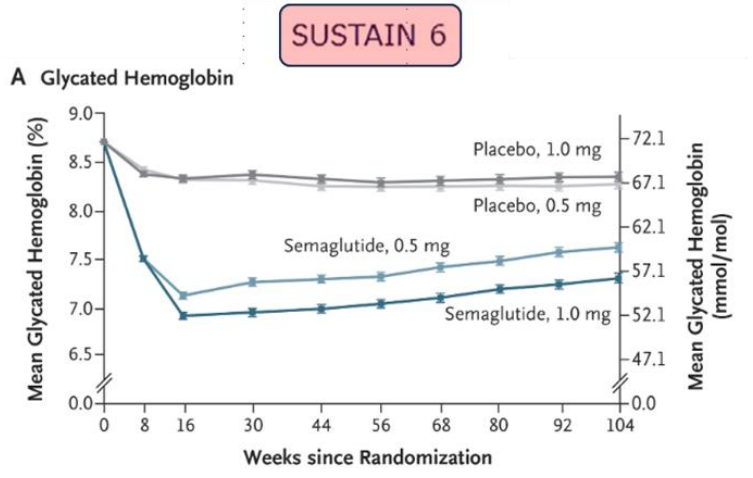


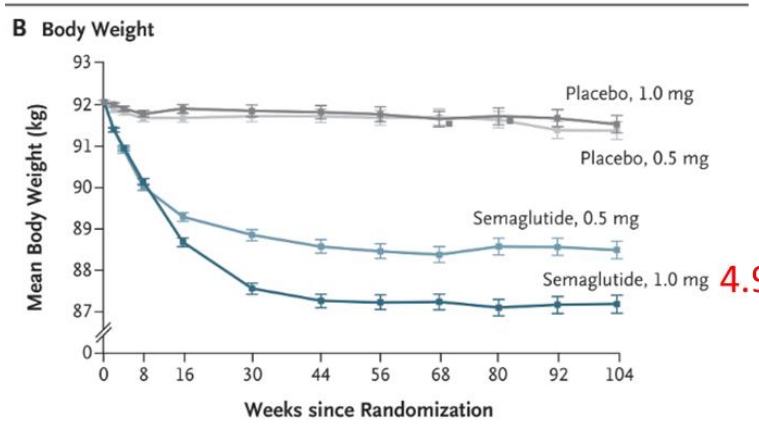


Marso SP et al., NEJM 2016
Husain M et al., NEJM 2019

Glycemic control and weight loss in the SUSTAIN 6 and PIONEER 6

SUSTAIN 6

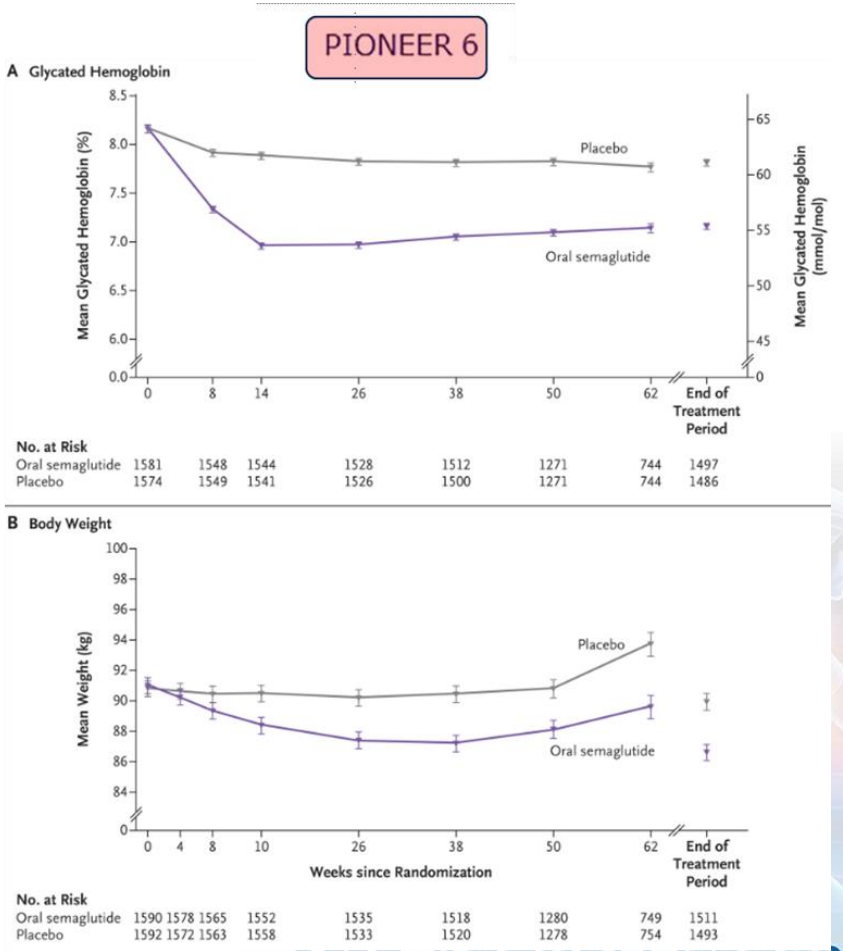




4.9kg, ~5%

How about a higher Semaglutide dose (Wegovy 2.4mg)?

PIONEER 6

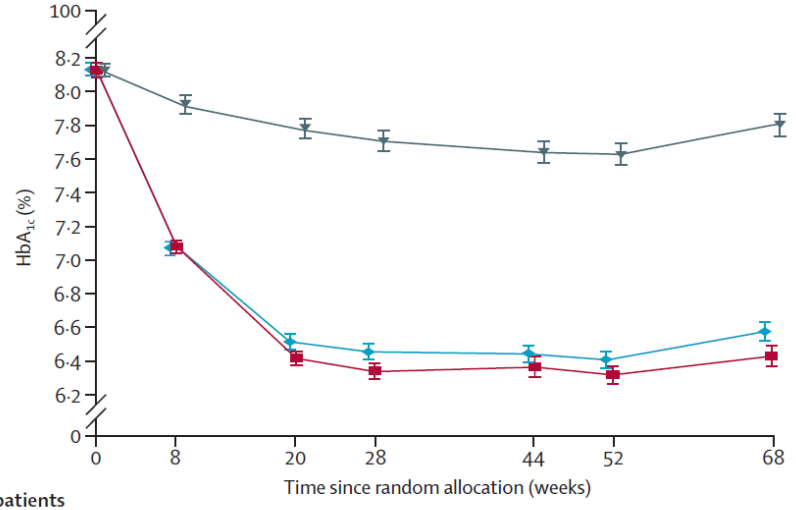


15th Annual Orange County Symposium for Cardiovascular Disease Prevention

Lancet 2021; 397: 971–84

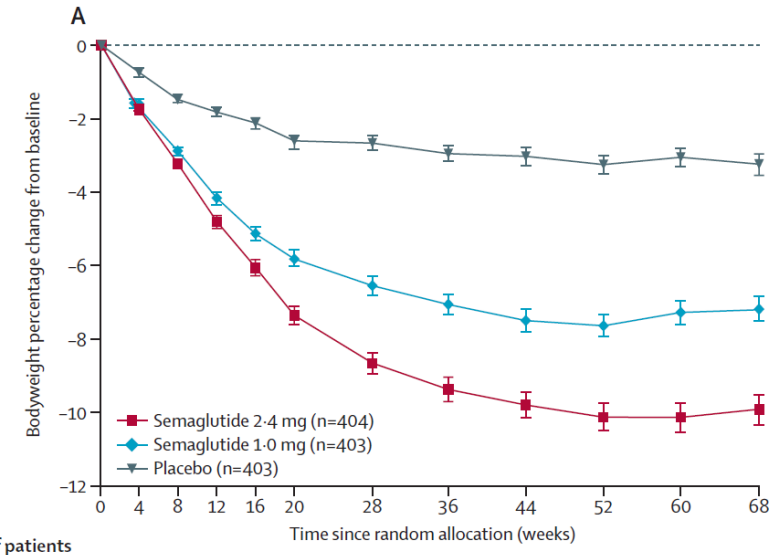
STEP 2 Trial A higher dose of Semaglutide at 2.4mg is more effective for weight loss

Sema 2.4mg – 1.0mg- Placebo
Age: 55-56-55
Female: 55-50-47
White 58-67-60%
Body weight (kg): 99.9-99-100.5
BMI: 35.9-35-35.9
HbA1c 8.1-8.1-8.1%



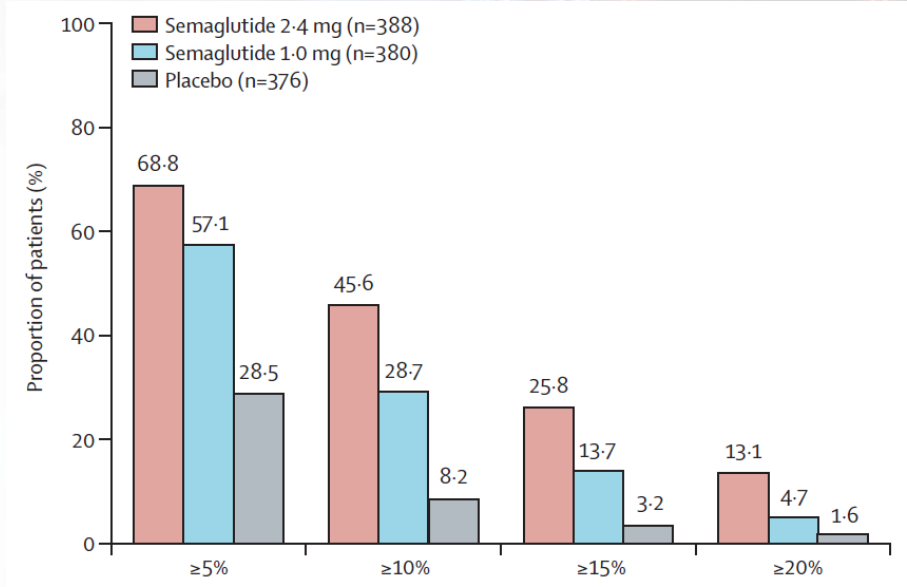
Number of patients

Semaglutide 2·4 mg	404	390	388	385	379	380	381
Semaglutide 1·0 mg	403	386	382	377	369	370	376
Placebo	403	391	381	379	371	366	374



Number of patients

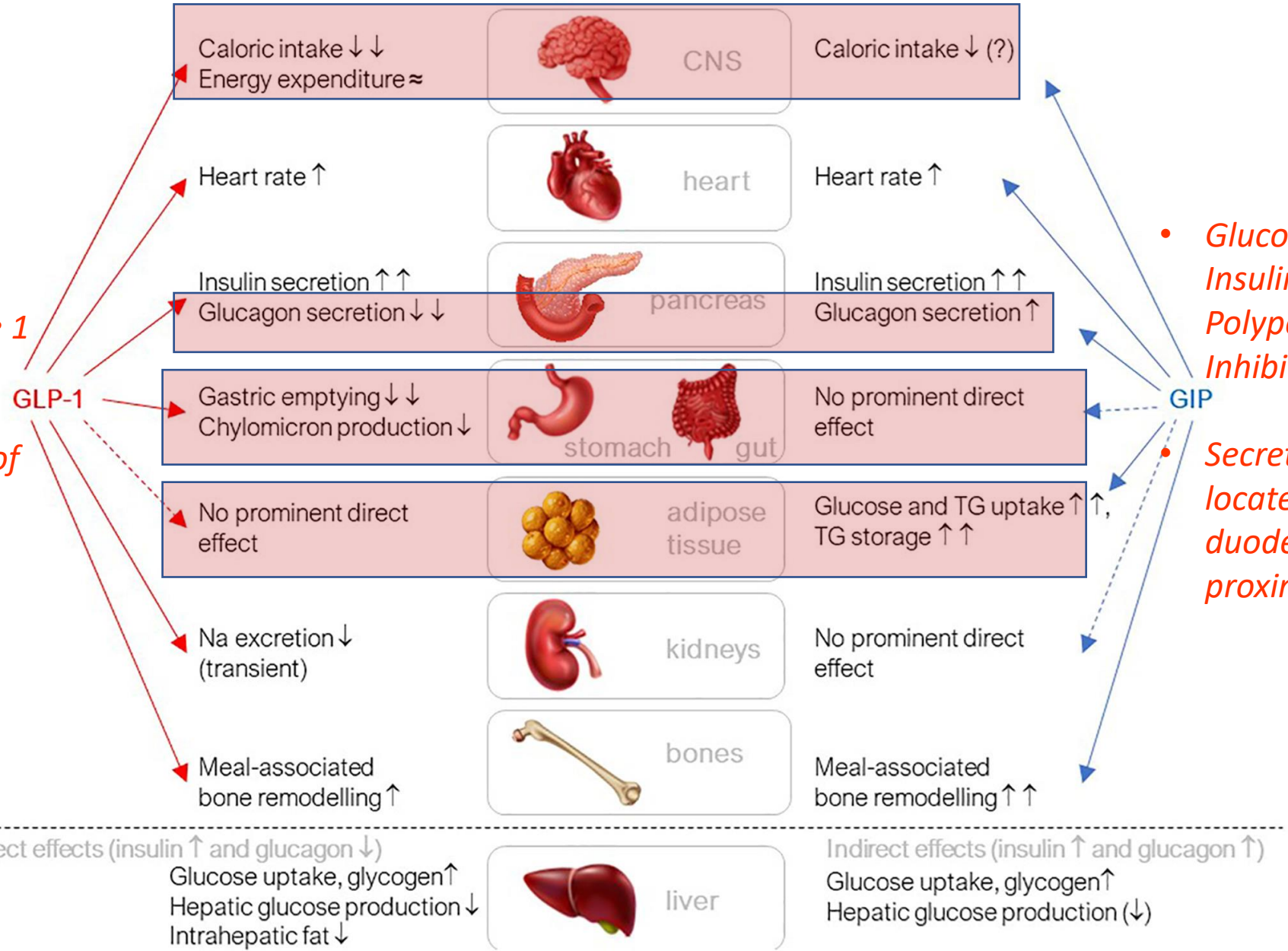
Semaglutide 2·4 mg	404	395	397	390	388	392	386	383	381	381	378	388
Semaglutide 1·0 mg	403	394	392	385	383	383	378	377	373	370	374	380
Placebo	403	398	394	389	387	383	381	377	371	367	366	376



Preliminary report: Subcutaneous once-weekly semaglutide 2.4 mg was associated with a statistically significant 20% reduction in major adverse cardiovascular events (MACE) compared with placebo.

Incretins – GLP1 and GIP

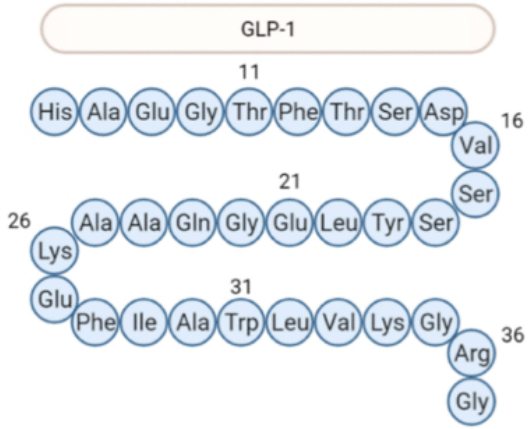
- *Glucagon-like peptide 1*
- *Secreted by L cells located in the L-cells of the distal ileum and colon*

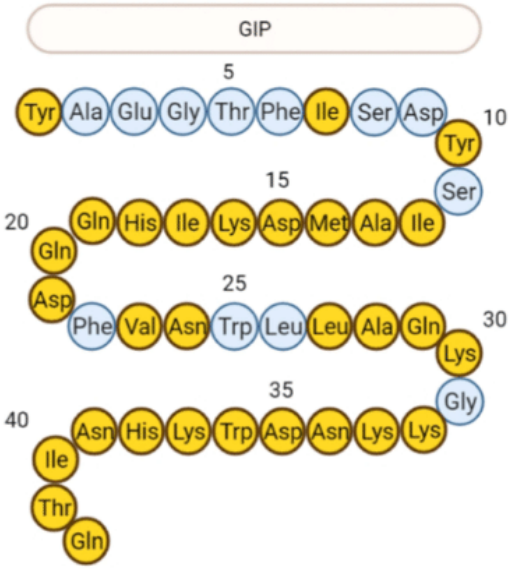


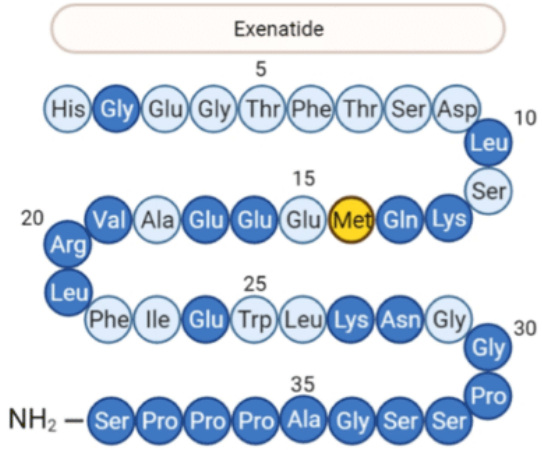
- *Glucose-Dependent Insulinotropic Polypeptide* or *Gastric Inhibitory Peptide*
- *Secreted by K cells located in the duodenum and proximal jejunum*

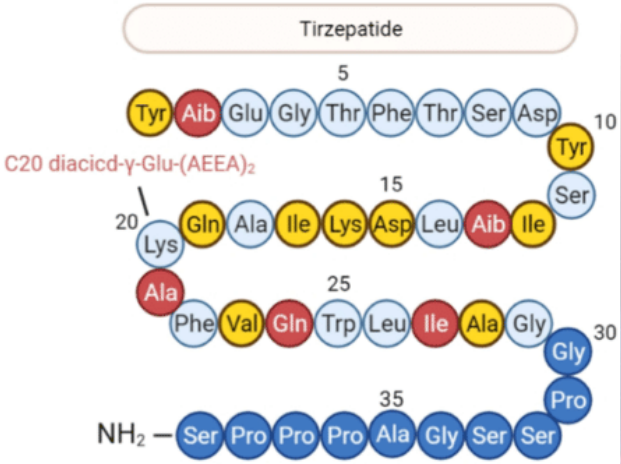
County
iovascular

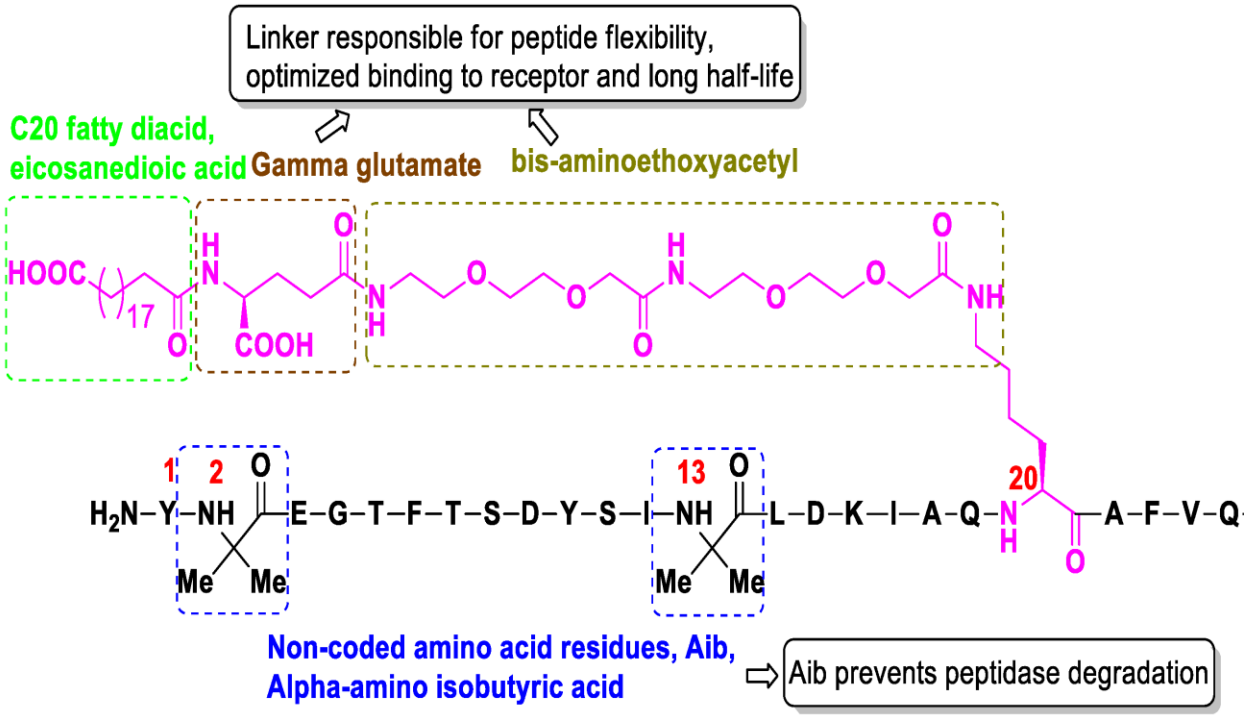
Tirzepatide – dual GLP1 and GIP receptor agonist











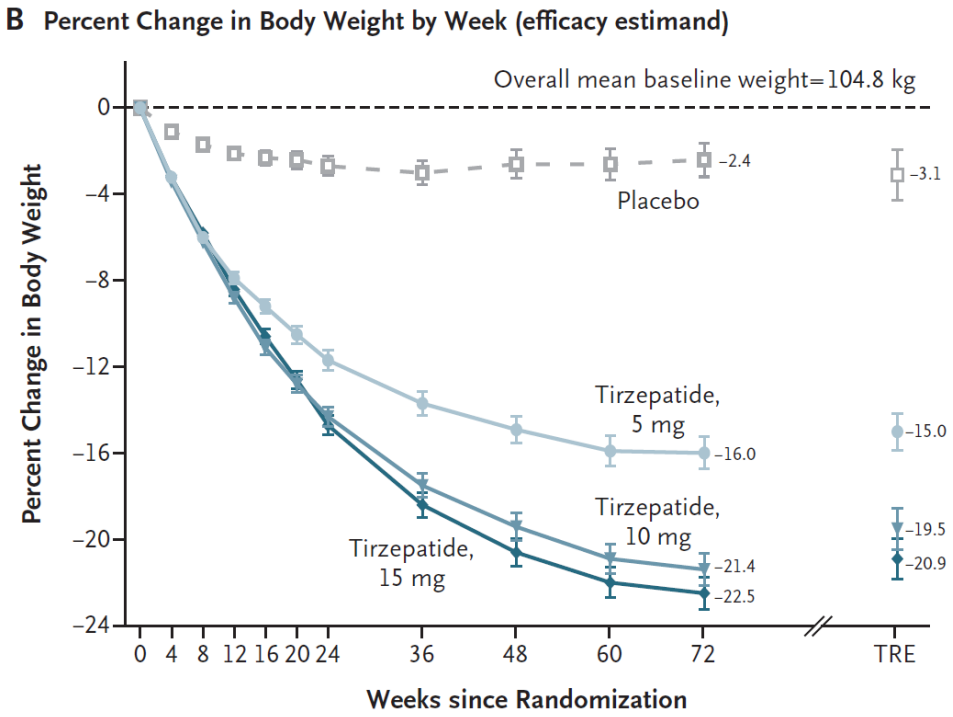
SURMOUNT (obesity) and SURPASS (T2D) TRIALS

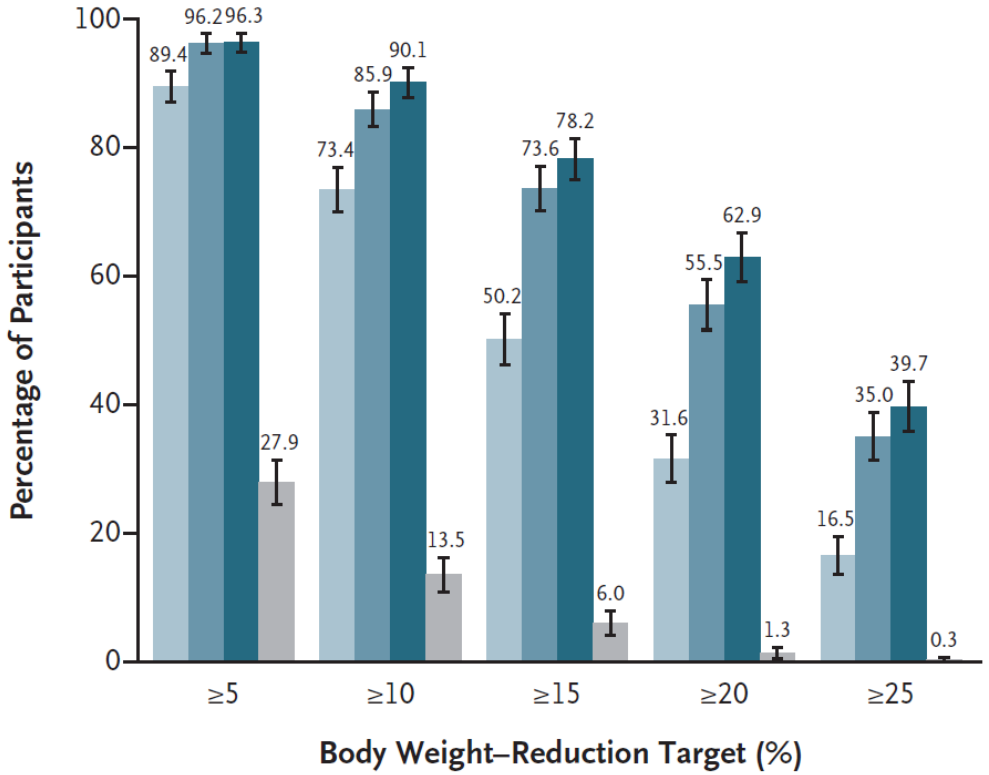
The NEW ENGLAND JOURNAL of MEDICINE JULY 21, 2022

SURMOUNT-1 Trial

Tirzepatide Once Weekly for the Treatment of Obesity

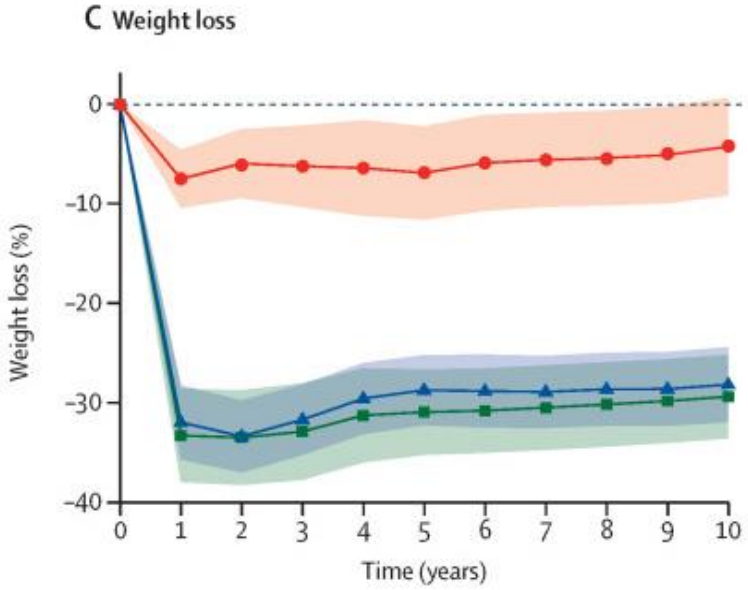
Characteristic	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Age — yr	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex — no. (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Body weight — kg	102.9±20.71	105.8±23.32	105.6±22.92	104.8±21.37	104.8±22.12
Mean body-mass index	37.4±6.63	38.2±7.01	38.1±6.69	38.2±6.89	38.0±6.81
Glycated hemoglobin — %	5.6±0.36	5.6±0.37	5.6±0.41	5.6±0.38	5.6±0.38

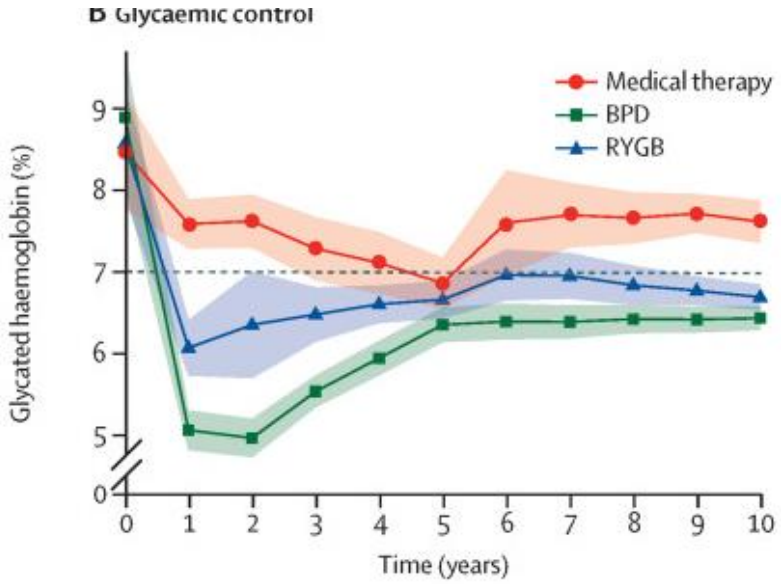




SURPASS-CVOT, the phase 3 cardiovascular outcomes trial for Tirzepatide, active.

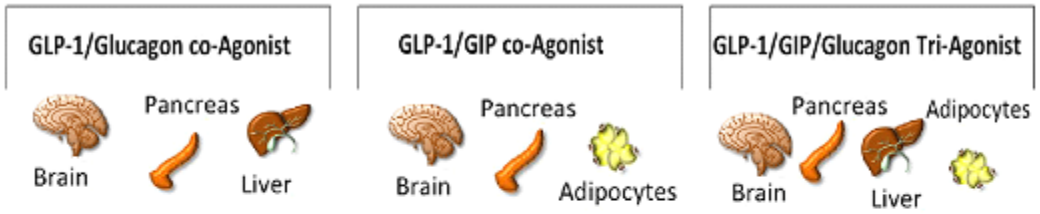
Weight Management: Metabolic Surgery





Mingrone et al. *The Lancet.* 2021 23;397:293-304

GLP1/GIP/Glucagon Tri-Agonist



Effects on:

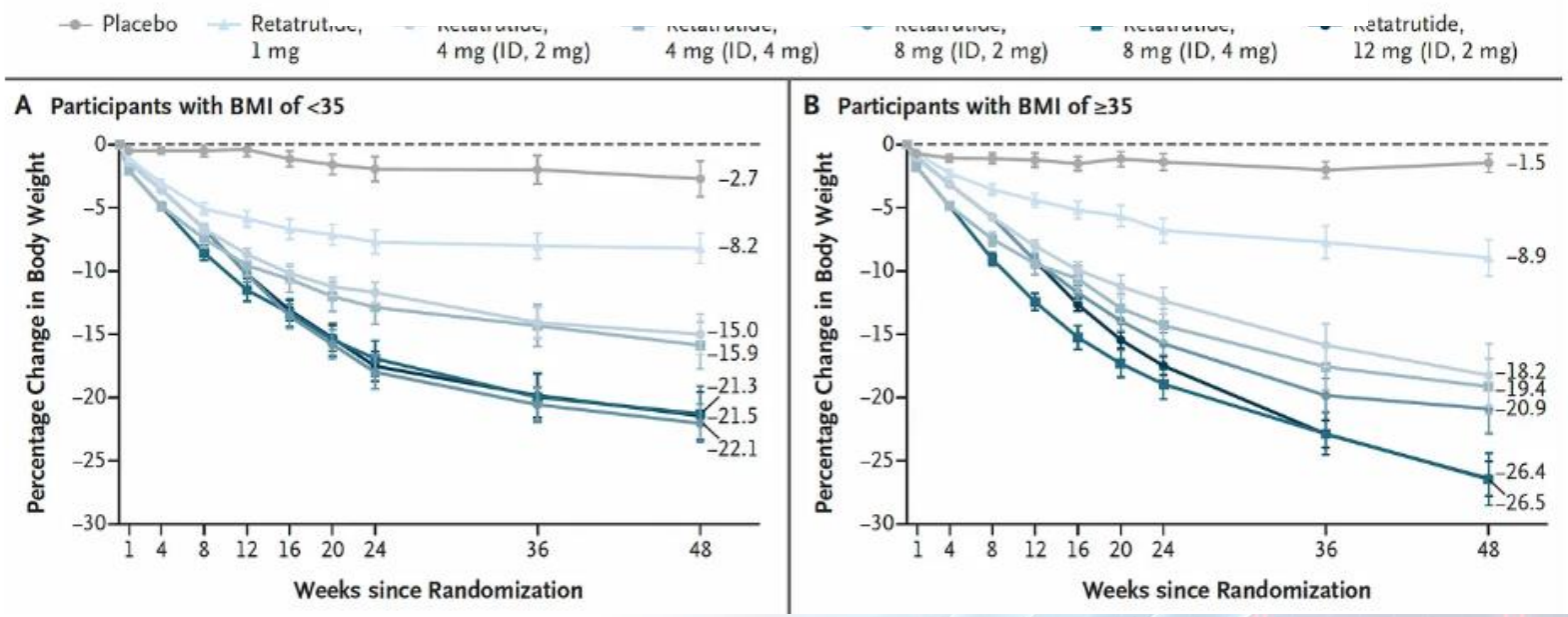
- **Body weight**
- Energy expenditure
- Glycaemic control
- Cholesterol

Effects on:

- **Glycaemic control**
- Body weight
- Lipolysis
- Cholesterol

Effects on:

- **Body weight**
- **Glycaemic control**
- **Hepatosteatosis**
- **Cholesterol**
- Energy expenditure
- Lipolysis



Jastreboff AM et al., NEJM 2023

TO BE CONTINUED…

GLP1-RAs, how to choose and in who

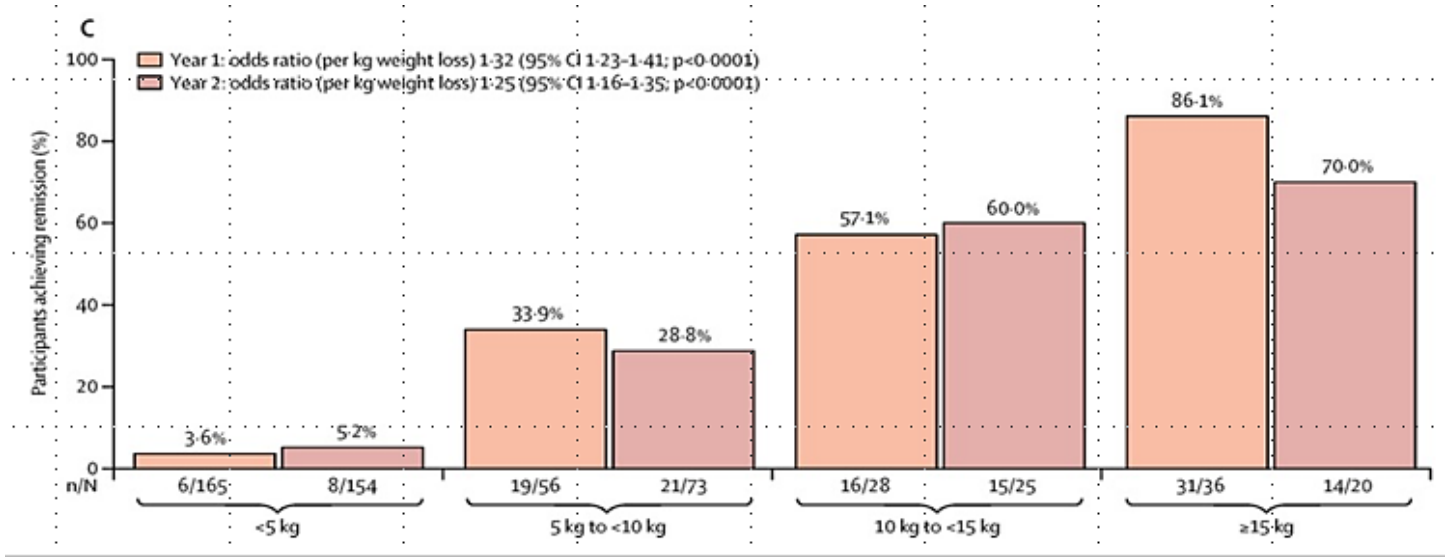
- **Theoretically, most of the obese patients**

- With clinical ASCVD or high risk – Liraglutide, Semaglutide, or Dulaglutide, Tirzepatide should work too, although perspective trial data available yet.

- If weight loss is the main goal, Tirzepatide and Semaglutide are stronger.

- **For obese patients with Type 2 diabetes, early treatment may be important.**

Intensive Structured Weight Management: the DiRect RCT



Lean et al. *The Lancet Diabetes & Endocrinology* 2019;7:344-355.

- 10 kg at 2 year follow-up = 64% diabetes remission

Table 4 Estimated Cardiovascular Events and Preventable Events, based on BMI parameters

From: US Population Eligibility and Estimated Impact of Semaglutide Treatment on Obesity Prevalence and Cardiovascular Disease Events

	n (M)	CVD Risk Pre-Treatment (%)	CVD Risk Post-Treatment (%)	Difference	CVD Events Pre	CVD Events Post	Difference
Overall	3493 (82.8M)	10.15%	8.34%	1.81%	355 (8.41 M)	291 (6.91 M)	63 (1.50 M)
Females	1915 (42.2M)	7.64%	6.24%	1.41%	146 (3.22 M)	119 (2.63 M)	27 (0.59 M)
Males	1578 (41.5M)	12.71%	10.51%	2.20%	201 (5.27 M)	166 (4.36 M)	35 (0.91 M)
Whites	1187 (50.1M)	11.60%	9.59%	2.01%	138 (5.81 M)	114 (4.80 M)	24 (1.01 M)
Asians	210 (2.1M)	7.07%	5.79%	1.28%	15 (0.15 M)	12 (0.12 M)	3 (0.03 M)
Blacks	833 (9.8M)	9.00%	7.39%	1.61%	75 (0.88 M)	62 (0.72 M)	13 (0.16 M)
Hispanic	1087 (14.8M)	6.95%	5.68%	1.27%	76 (1.03 M)	62 (0.84 M)	14 (0.19 M)
Other	176 (4.0M)	6.64%	5.43%	1.21%	12 (0.27 M)	10 (0.22 M)	2 (0.05 M)

Estimates combining strata may not total overall due to rounding error

Wong ND et al., Cardiovas Drigs Ther 2023

GLP1-RAs, risk considerations

Box 1. Who should not receive a GLP-1 receptor agonist?

- Type 1 diabetes.
- Pregnancy and breastfeeding.
- Severe gastrointestinal disease (e.g. inflammatory bowel disease).
- Diabetic gastroparesis.
- History of pancreatitis.
- Caution if high risk of pancreatitis (e.g. gallstones, alcohol excess, hypertriglyceridaemia).
- History of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2.
- Caution in renal impairment – see *Table 1*.

Make sure to ask your patient who is using a GLP1-RA to stop the treatment one week before procedures.

Table 2. Risks of Biliary Disease, Pancreatitis, Bowel Obstruction, and Gastroparesis Among Users of GLP-1 Agonists vs Bupropion-Naltrexone

Outcomes	GLP-1 agonists, HR (95% CI)[a] Crude	Adjusted[b]	Bupropion-naltrexone
Primary analysis			
Biliary disease	1.48 (0.88-2.47)	1.50 (0.89-2.53)	1 [Reference]
Pancreatitis	10.33 (1.44-74.40)	9.09 (1.25-66.00)	1 [Reference]
Bowel obstruction	5.16 (1.27-21.00)	4.22 (1.02-17.40)	1 [Reference]
Gastroparesis	3.31 (1.04-10.50)	3.67 (1.15-11.90)	1 [Reference]
Sensitivity analyses			
Exclusion of hyperlipidemia			
Biliary disease	1.50 (0.88-2.56)	1.46 (0.84-2.51)	1 [Reference]
Pancreatitis	9.80 (1.36-70.79)	7.99 (1.10-58.30)	1 [Reference]
Bowel obstruction	4.43 (1.08-18.20)	3.63 (0.87-15.10)	1 [Reference]
Gastroparesis	3.32 (1.04-10.60)	3.67 (1.14-11.80)	1 [Reference]
Analysis with less-restrictive obesity definition[c]			
Biliary disease	1.29 (0.92-1.80)	1.20 (0.85-1.69)	1 [Reference]
Pancreatitis	6.19 (1.99-19.30)	5.94 (1.90-18.60)	1 [Reference]
Bowel obstruction	3.11 (1.28-7.54)	2.44 (1.00-5.95)	1 [Reference]
Gastroparesis	2.11 (1.09-4.09)	2.35 (1.20-4.58)	1 [Reference]
E-values for adjusted HRs[d]			
Biliary disease	2.36		
Pancreatitis	17.67		
Bowel obstruction	7.91		
Gastroparesis	6.80		

Sodhi M et al., JAMA 2023

Is GLP1-RA treatment linked to thyroid cancer?

The use of GLP-1 receptor agonists is associated with an increased risk of thyroid cancer

GLP-1 receptor agonists and the risk of thyroid cancer

Bezin J., Gouverneur A., Pénichon M., Mathieu C., Garrel R., Hillaire-Buys D., Pariente A., Faillie J-L.

Nationwide population-based study on French SNDS database

3,746,672 individuals with type 2 diabetes treated with second-line antidiabetes drugs between 2006-2018

2,562 cases of thyroid cancers

45,184 matched control subjects

	Case subjects *n* = 2,572	Control subjects *n* = 45,184	Adjusted hazard ratio (95%CI)*
GLP-1 receptor agonists			
No use	2,255 (88.0)	40,836 (90.4)	Reference
Cumulative use ≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99 to 1.50)
Cumulative use 1-3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27 to 1.95)
Cumulative use >3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05 to 1.74)
DPP-4 inhibitors			
No use	1,522 (59.4)	27,406 (60.7)	Reference
Cumulative use ≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99 to 1.28)
Cumulative use 1-3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84 to 1.10)
Cumulative use >3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04 to 1.35)

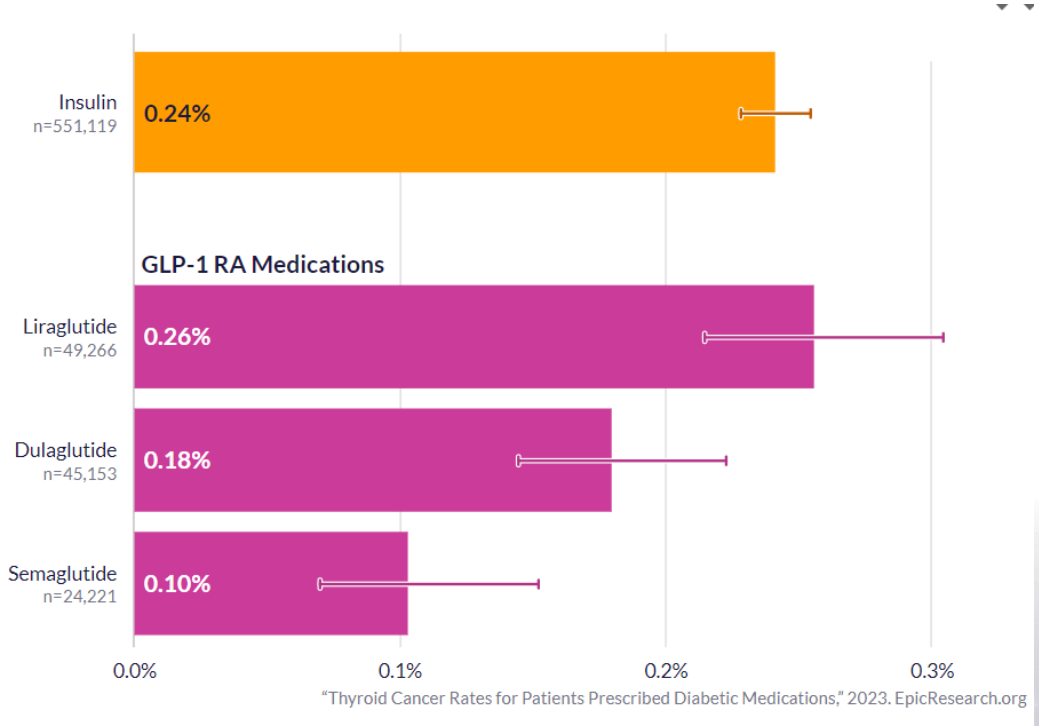
*Adjusted for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered in therapeutic class.

Diabetes Care

This study is part of the DRUGS-SAFER research program, funded by the French Medicines Agency. This publication represents the views of the authors and does not necessarily represent the opinion of the French Medicines Agency.

| 1

American Diabetes Association. Connected for Life

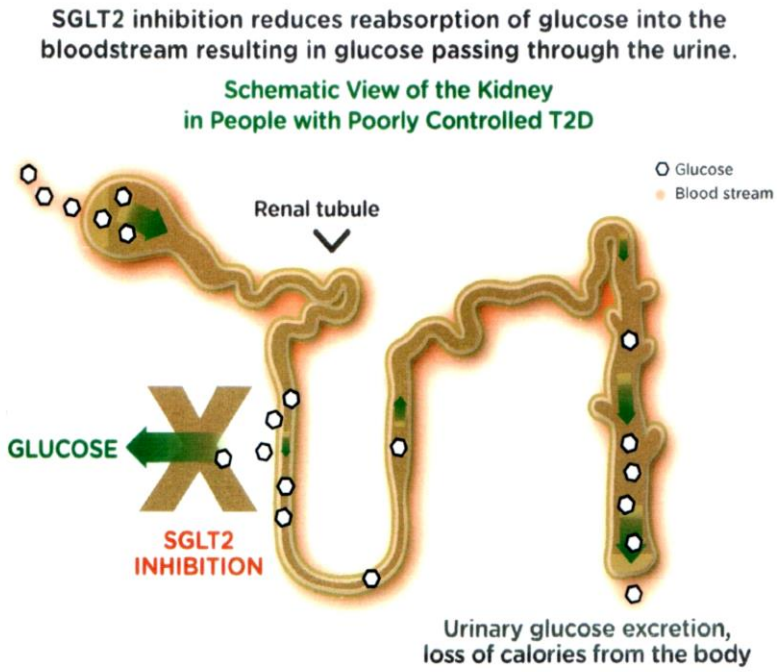


"Thyroid Cancer Rates for Patients Prescribed Diabetic Medications," 2023. EpicResearch.org

- The paper is widely published on social media, but the association between GLP1-RA treatment and thyroid cancer is unclear.
- Secondary analysis using the same data set found that other diabetes and hypertension medications are also associated with thyroid cancer.

A subsequent study found that GLP1-RA treatment did not increase thyroid risk compared with insulin treatment.

15th Annual Orange County Symposium for Cardiovascular Disease Prevention



SGLT2 inhibitors

Mechanism of action	• Inhibits SGLT2 (sodium/glucose cotransporter 2) in the proximal tubule, blocking reabsorption of filtered glucose (leading to osmotic diuresis)
Examples (_ gliflozin)	• Empagliflozin (Jardiance®) - Best risk/benefit ratio of the three • Dapagliflozin (Forxiga®) • Canagliflozin (Invokana®)
Major advantages	• Weight loss (~2-3kg) • Empagliflozin and canagliflozin ↓ CV mortality in high risk patients with T2D + atherosclerotic heart disease • All 3 ↓ heart failure hospitalizations and progression of nephropathy

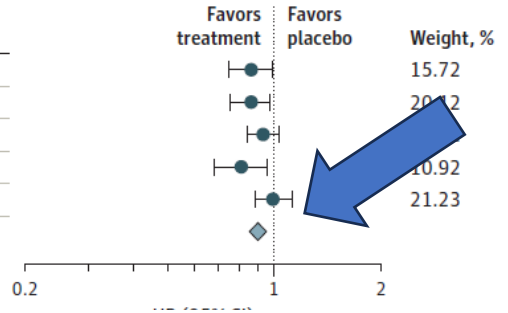
JAMA Cardiology | Original Investigation

Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes
A Meta-analysis

JAMA Cardiology February 2021 Volume 6, Number 2

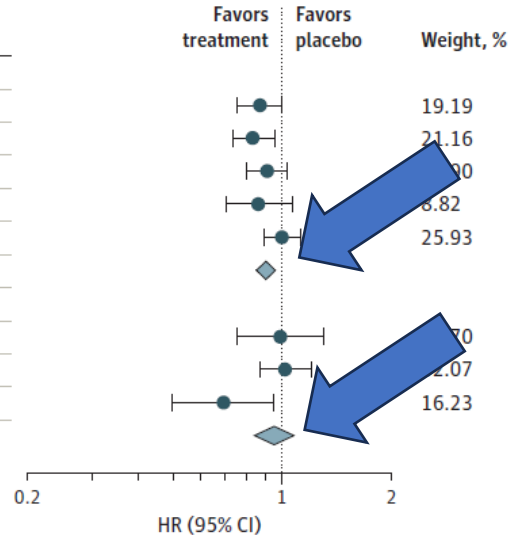
A Overall MACEs

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)



B MACEs by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/3756	34.1	NA/2900	41.3	0.82 (0.72-0.95)
DECLARE-TIMI 58	483/3474	36.8	537/3500	41.0	0.90 (0.79-1.02)
CREDENCE	155/1113	55.6	178/1107	65.0	0.85 (0.69-1.06)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model ($Q = 4.53$; $df = 4$; $P = .34$; $I^2 = 11.8\%$)					0.89 (0.84-0.95)
Patients without ASCVD					
CANVAS program	NA/2039	15.8	NA/1447	15.5	0.98 (0.74-1.30)
DECLARE-TIMI 58	273/5108	13.4	266/5078	13.3	1.01 (0.86-1.20)
CREDENCE	62/1089	22.0	91/1092	32.7	0.68 (0.49-0.94)
Fixed-effects model ($Q = 4.59$; $df = 2$; $P = .10$; $I^2 = 56.5\%$)					0.94 (0.83-1.07)

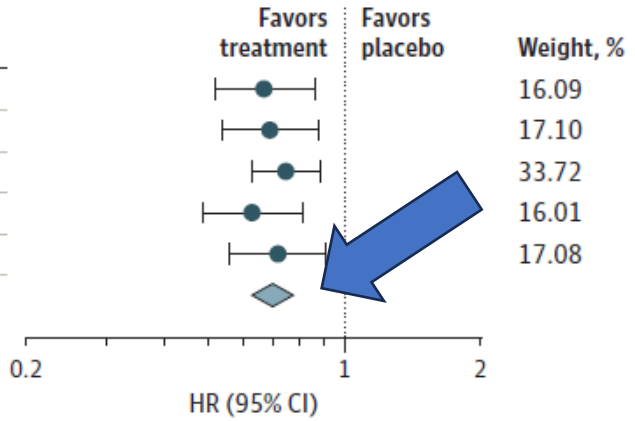


Similar results were observed in CV death (event reduction in patients with ASCVD, not in patients without ASCVD)

But HF is improved in patients with or without ASCVD

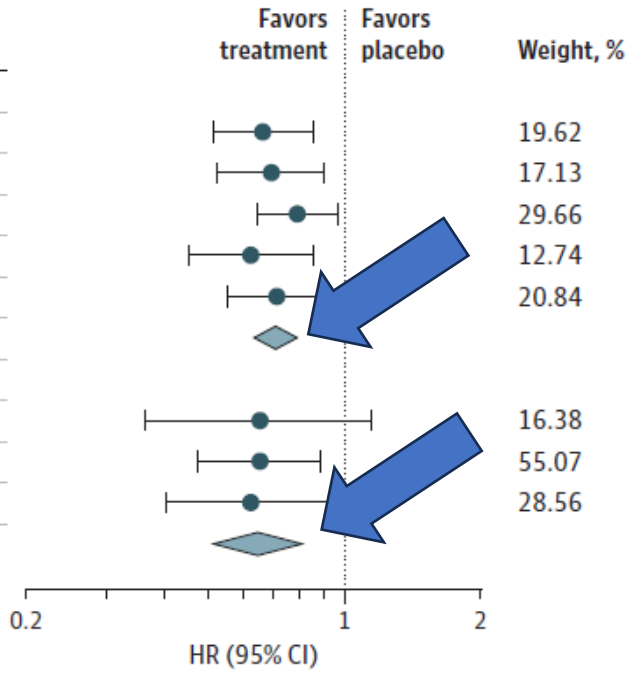
A Overall HHF

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)

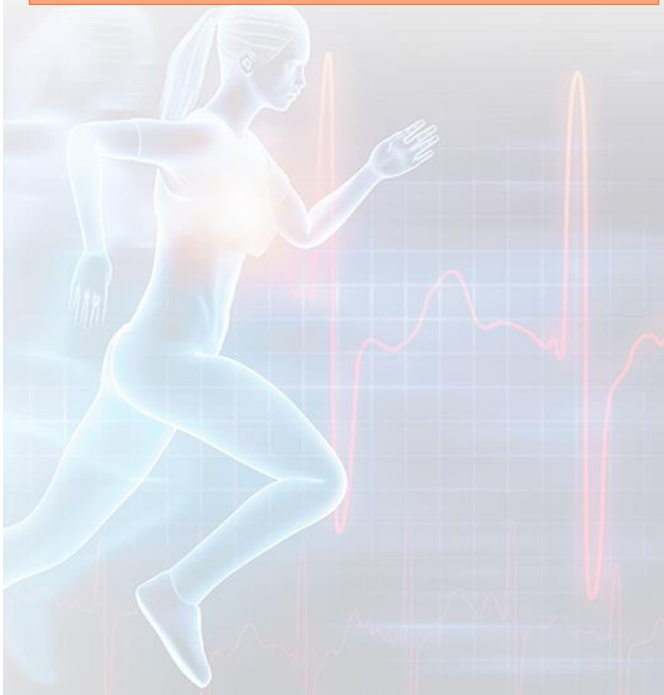


B HHF by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.97; *df* = 4; *P* = .74; I^2 = 0.0%)					0.70 (0.62-0.78)
Patients without ASCVD					
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)
Fixed-effects model (Q = 0.03; *df* = 2; *P* = .99; I^2 = 0.0%)					0.63 (0.50-0.80)



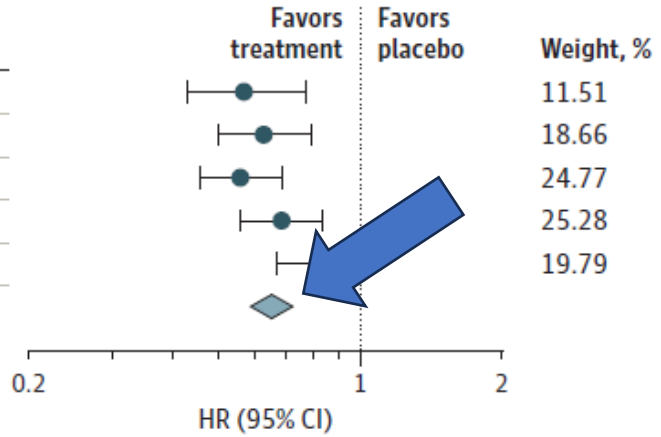
Effects of SGLT2 inhibitors on hospitalization for heart failure



Effects of SGLT2 inhibitors on kidney-related outcomes

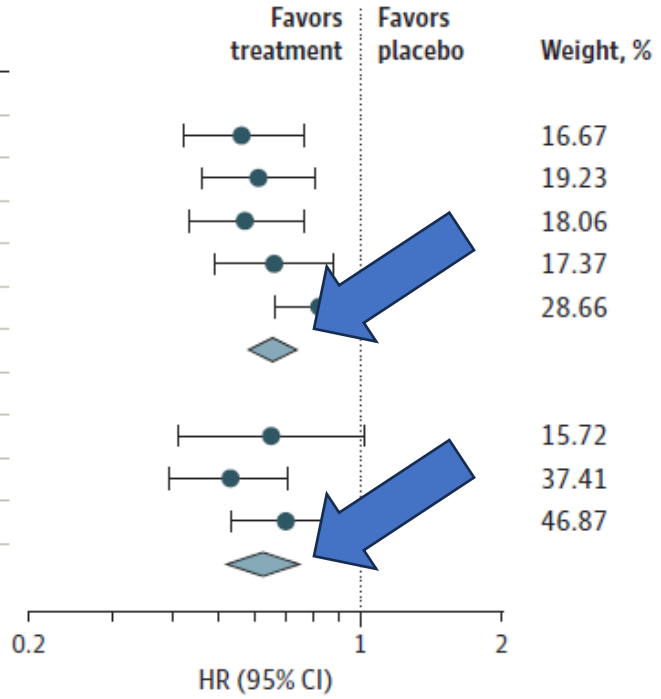
A Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)



B Kidney outcomes by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)



Effect of SGLT2 inhibitors in HHF or CV death, HHF alone and CV death alone

	EMPA-REG OUTCOME[1] (empagliflozin)	CANVAS Program[2,3] (canagliflozin)	DECLARE-TIMI 58[4] (dapagliflozin)	CREDENCE[5] (canagliflozin)	VERTIS CV[6] (ertugliflozin)
HHF or CV death	34% *p*<0.001	22% *p*-value not reported	17% *p*=0.005	31% *p*<0.001	12% *p*=0.11
HHF	35% *p*=0.002	33% *p*-value not reported	27% *p*-value not reported	39% *p*<0.001	30% *p*-value not reported
CV death	38% *p*<0.001	13% *p*-value not reported	2% *p*-value not reported	22% *p*=0.05	8% *p*-value not reported

Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

HHF, hospitalisation for heart failure

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Neal B *et al. N Engl J Med* 2017;377:644; 3. Rådholm K *et al. Circulation* 2018;138:458;
4. Wiviott S *et al. N Engl J Med* 2019;380:347; 5. Perkovic V *et al. N Engl J Med* 2019;380:2295; 6. Cannon C *et al. N Engl J Med* 2020;383:1425

SGLT2 inhibitors, contraindications and side effects

Contraindications and precautions

- Type 1 diabetes
- Type 2 diabetes and eGFR <45 mL/min/1.73 m2 (ertugliflozin), or <30 mL/min/1.73 m2 (empagliflozin, canagliflozin, dapagliflozin, bexagliflozin)
- Prior diabetic ketoacidosis (DKA)

Side effects.

- Genitourinary tract bacterial and yeast infections.
- Bone loss and fracture. SGLT2 inhibitors have been associated with fracture risk in some (Canagliflozin), but not all, studies.
- Mild volume loss.
- Lower extremity infection and amputation. SGLT2 inhibitors are associated with a small risk of lower extremity infection and amputation.
- DKA.

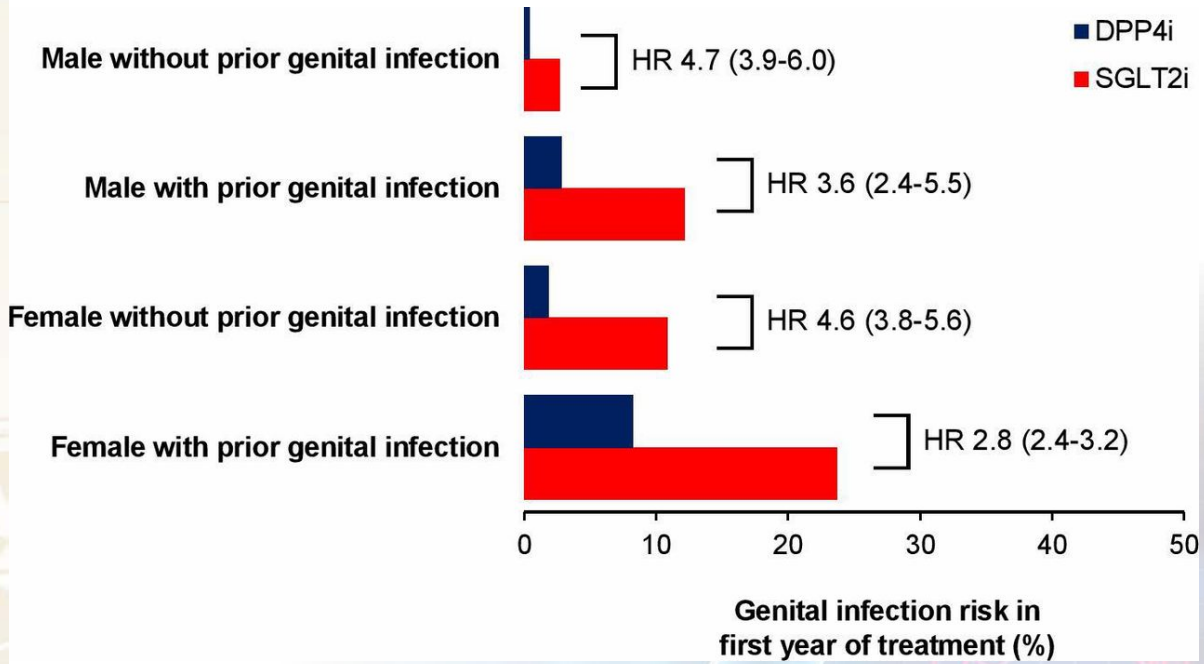
SGLT2 inhibitor and genital infection

EMPA-REG OUTCOME Safety Results

Event		Pooled Empagliflozin (%)	Placebo (%)
Any adverse event		90.2	91.7
Serious adverse event		38.2	42.3
Death		3.8	5.1
Any hypoglycemia		27.8	27.9
Severe hypoglycemia		1.3	1.5
Urinary tract infection	Male	10.5	9.4
	Female	36.4	40.6
Genital infection	Male	5.0	1.5
	Female	10.0	2.6
Volume depletion		5.1	4.9
Diabetic ketoacidosis		0.1	<0.1
Bone fracture		3.8	3.9

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

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.



McGovern AP et al., BMJ Open Diabetes 2020

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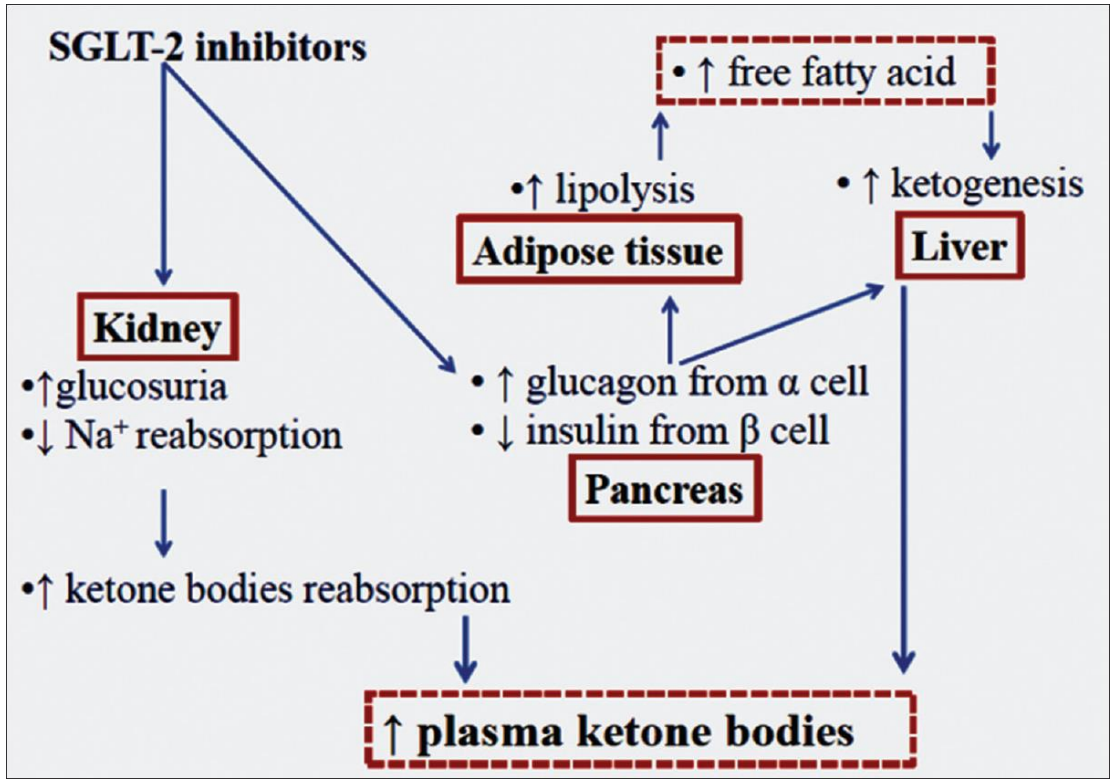
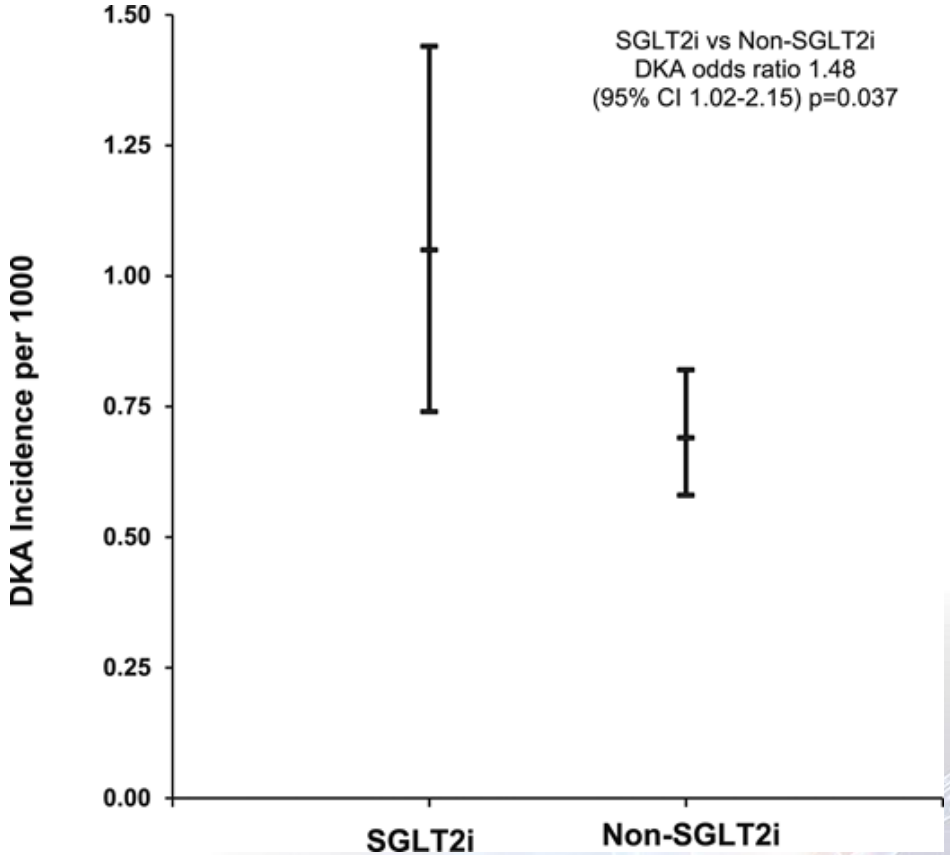
Euglycemic DKA Secondary to SGLT2 inhibitors





Incidence of DKA in confirmed type 2 diabetes in those exposed to dapagliflozin and empagliflozin and those unexposed (95% CI) during a 26-mo audit period. Confirmed type 2 diabetes cases were determined after reevaluation during the hospital admission.

Hamblin PS et al., JCEM 2019

ADA 2023 Standards of Medical Care and ADA–EASD Consensus Report[1,2]: Goal – cardio-renal risk reduction in high-risk people with T2D*†

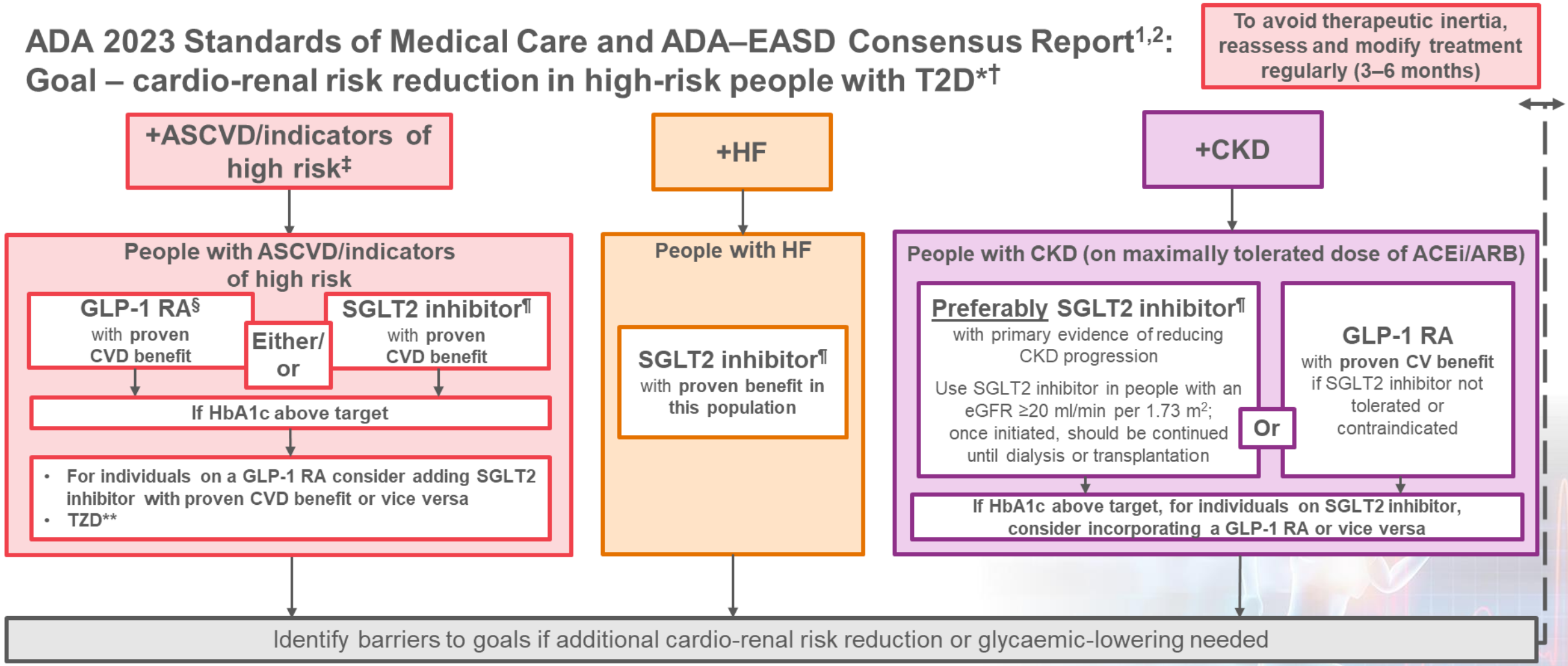


Figure adapted from ADA–EASD consensus report. Davies MJ *et al. Diabetes Care* 2022;45:2753. There are additional recommendations If HbA1c remains above target; for full recommendations, please refer to the reference.

1. American Diabetes Association. *Diabetes Care* 2023;46:S1; 2. Davies MJ *et al. Diabetes Care* 2022;45:2753

Please see speaker notes for footnotes and abbreviations

Patient question: Can I stop GLP1-RA treatment after weight loss?

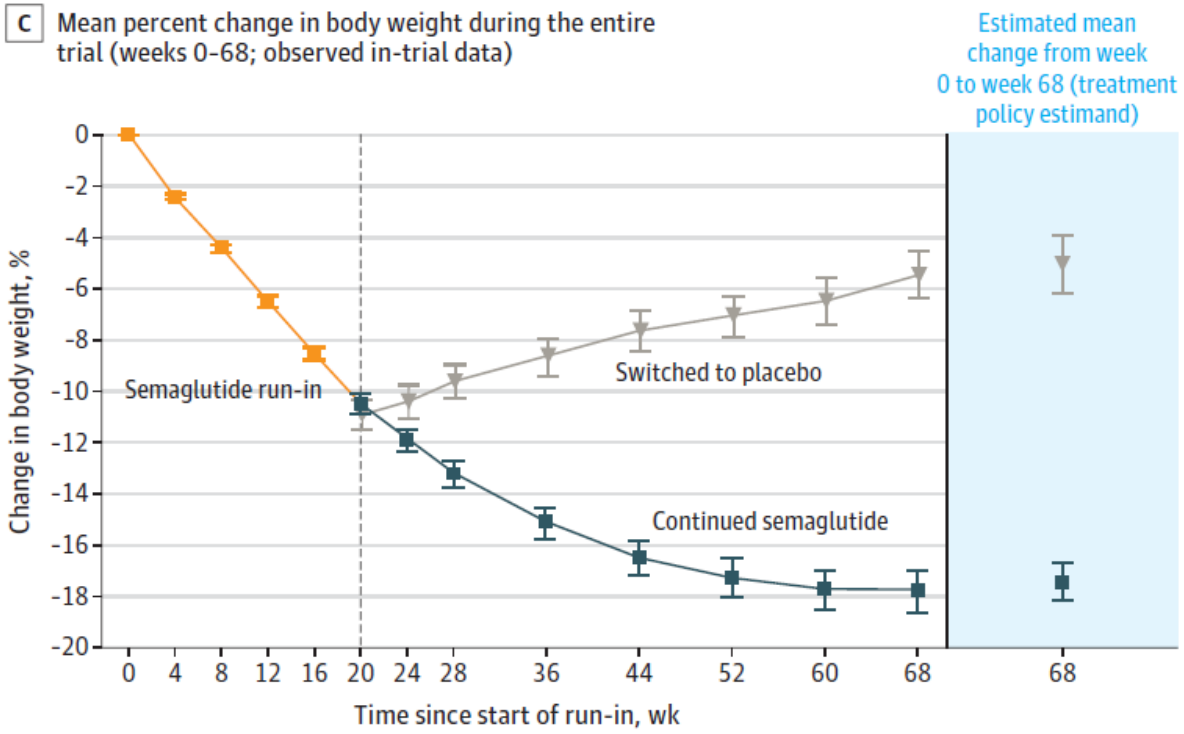
JAMA | Original Investigation JAMA. 2021;

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity

The STEP 4 Randomized Clinical Trial

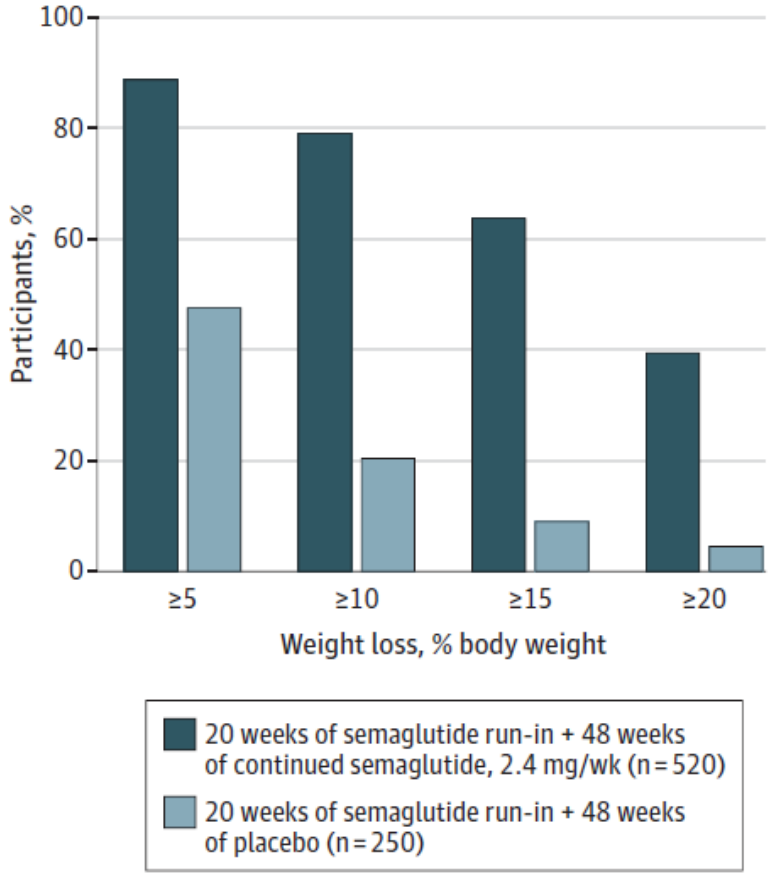
STEP 4 Trial

C Mean percent change in body weight during the entire trial (weeks 0-68; observed in-trial data)



No. of participants								
Semaglutide run-in	803	803	803	802	801			
Continued semaglutide	535	527	531	525	523	521	516	520	535
Switched to placebo	268	267	265	258	260	254	246	250	268

D Proportion of participants achieving thresholds of weight loss during the entire trial (weeks 0-68; observed in-trial data)



Thank you

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