SVM 2022: Updates in Vascular Disease

Real world benefits of GLP1 receptor agonists

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PRESENTER FINANCIAL DISCLOSURE

I do not have any relationships to report with ACCME defined ineligible companies.

I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals during this presentation.

Objectives

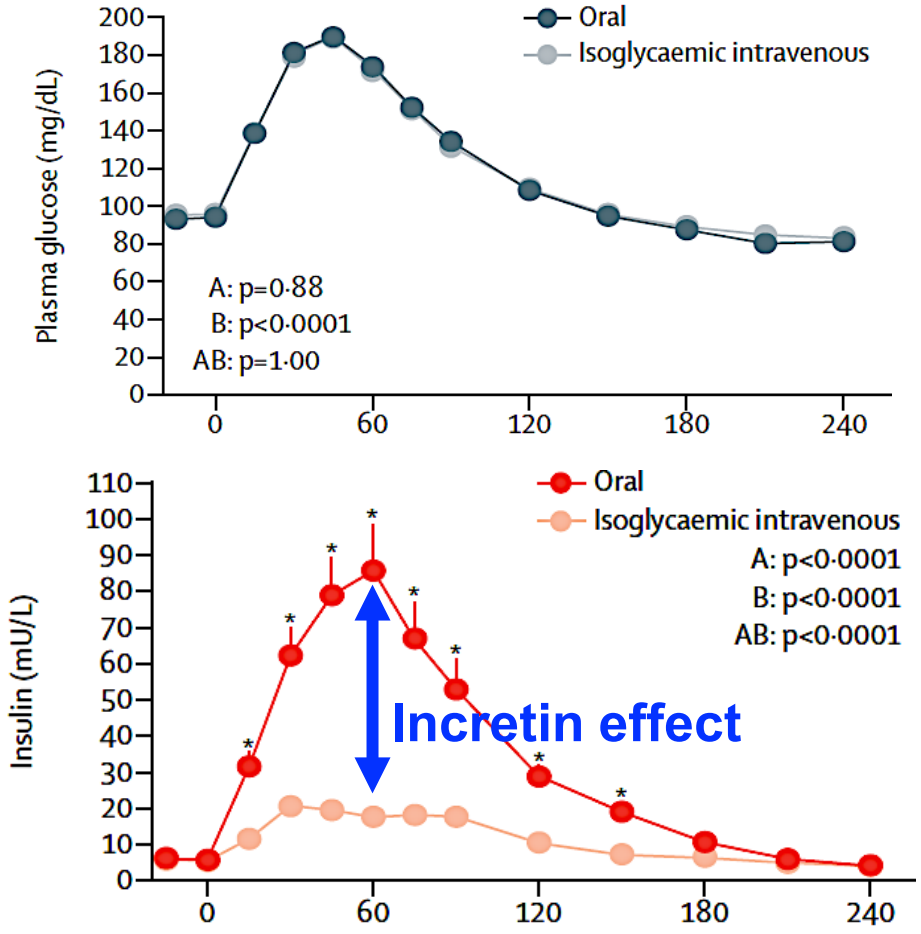
Background and overview of GLP-1 receptor agonists (GLP1RA)

Evidence for benefits of GLP1RA

Use of GLP1RA in the real world

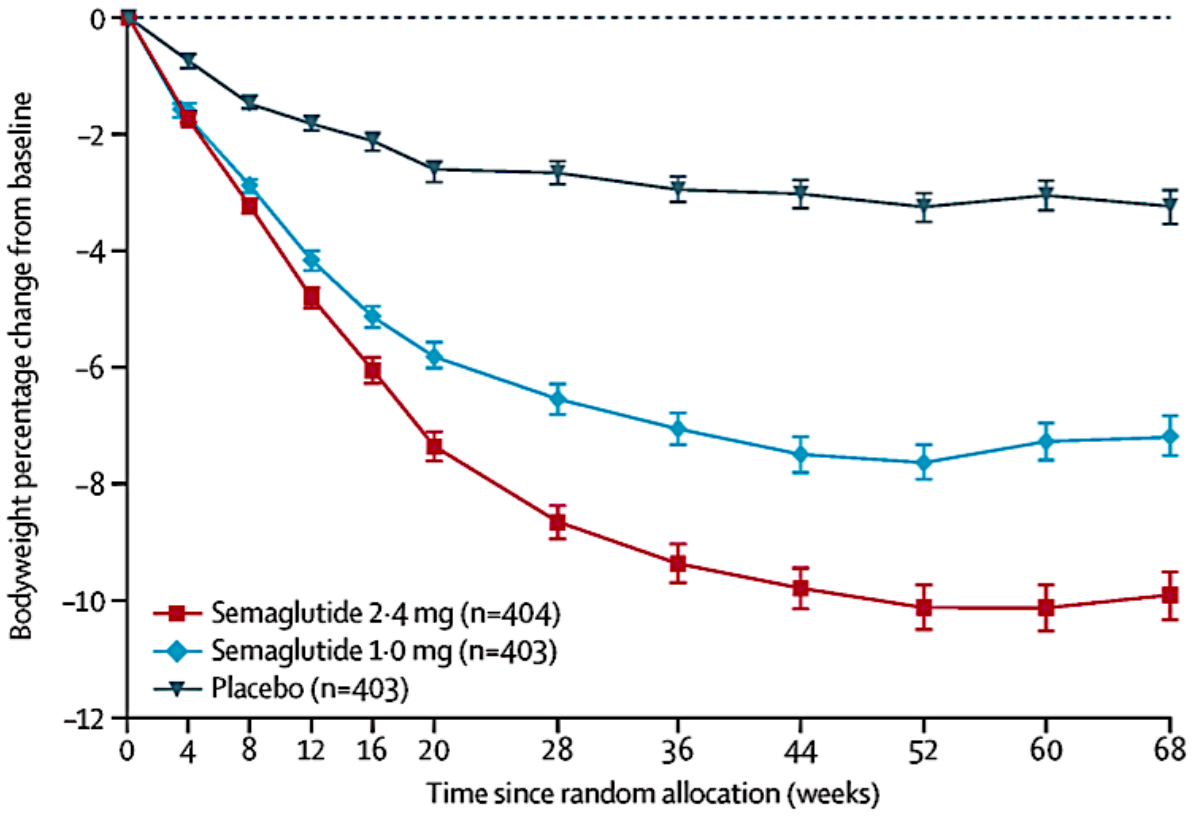
GLP-1 receptor agonists (GLP1RA) increase GLP1 action to pharmacologic levels

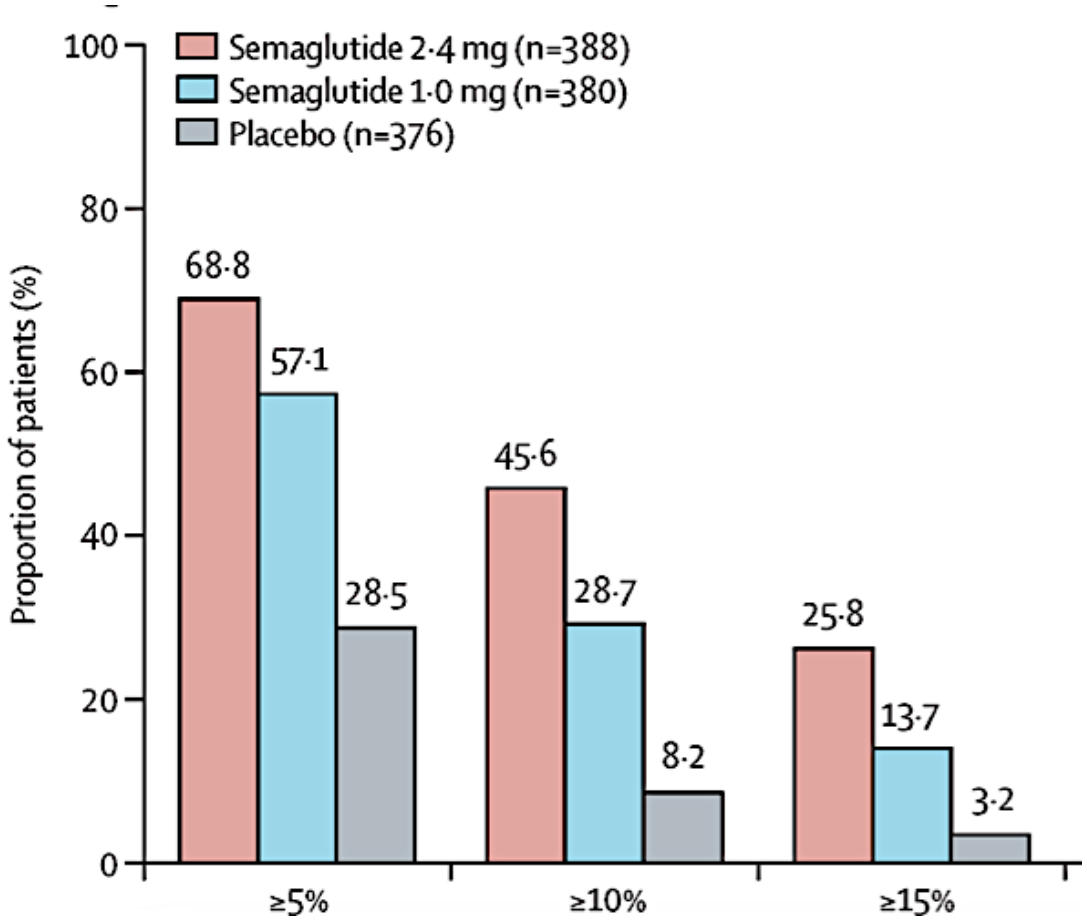
- **GLP1:**
  - **is an incretin hormone**
  - **is secreted by L-cells in the distal ileum and colon within minutes of nutrient ingestion**
  - **acts on GLP1 receptors in islet β-cells to secrete insulin and islet α-cells to suppress glucagon secretion**
  - **slows gastric emptying**
  - **promotes satiety**
- **The incretin effect is reduced or absent in type 2 diabetes (T2D)**



Shaefer CF, et al. User's guide to mechanism of action and clinical use of GLP-1 receptor agonists. *Postgrad Med* 2015;8:818-826.
Nauck M. The incretin effect in healthy individuals and those with type 2 diabetes. *Lancet Diab Endocrinol* 2016;4(6):525.

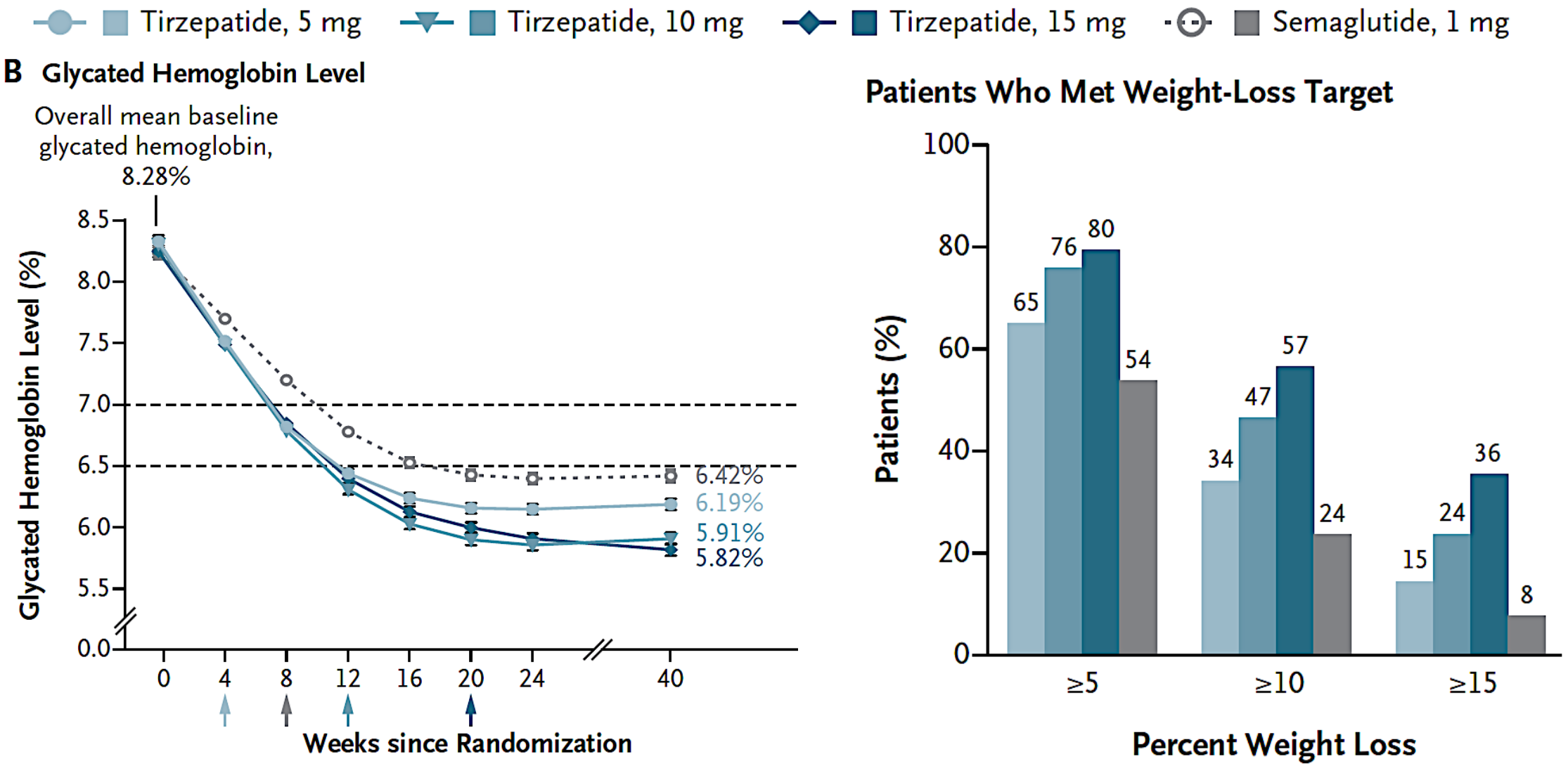
Besides marked lowering of A1c, GLP1RA have potent weight loss effects





Davies M, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomized, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397(10278):971-984.

Tirzepatide, a dual GIP/GLP1RA, vs semaglutide resulted in lower A1c and more weight loss in T2D



Frias JP, et al for SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503-515.

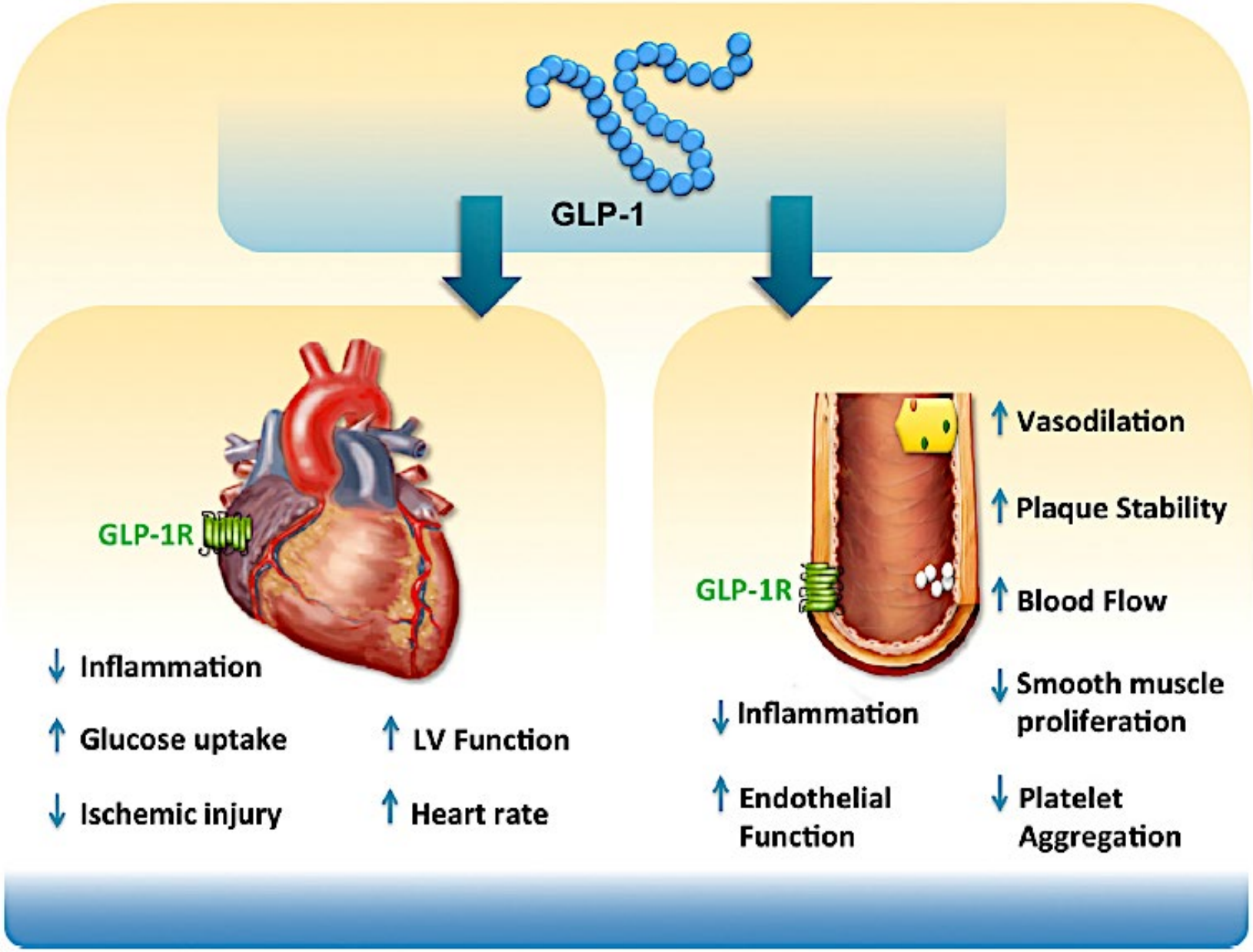
GLP1RA with cardiovascular (CV) benefit

	Dosing (mg)	CVOT*	CVOT: % with est. ASCVD	CVOT: duration (y)	MACE** reduction (%)	FDA indication for MACE?
Liraglutide	SQ QD 0.6, **1.2, 1.8**	LEADER	~81	3.8	13	T2D and established CVD
Semaglutide	SQ Qwk 0.25, **0.5, 1, 2**	SUSTAIN-6	83	2.1	26	T2D and established CVD
Dulaglutide	SQ Qwk **0.75, 1.5, 3, 4.5**	REWIND	31	5.4	12	T2D and est. CVD or multiple CV risk factors

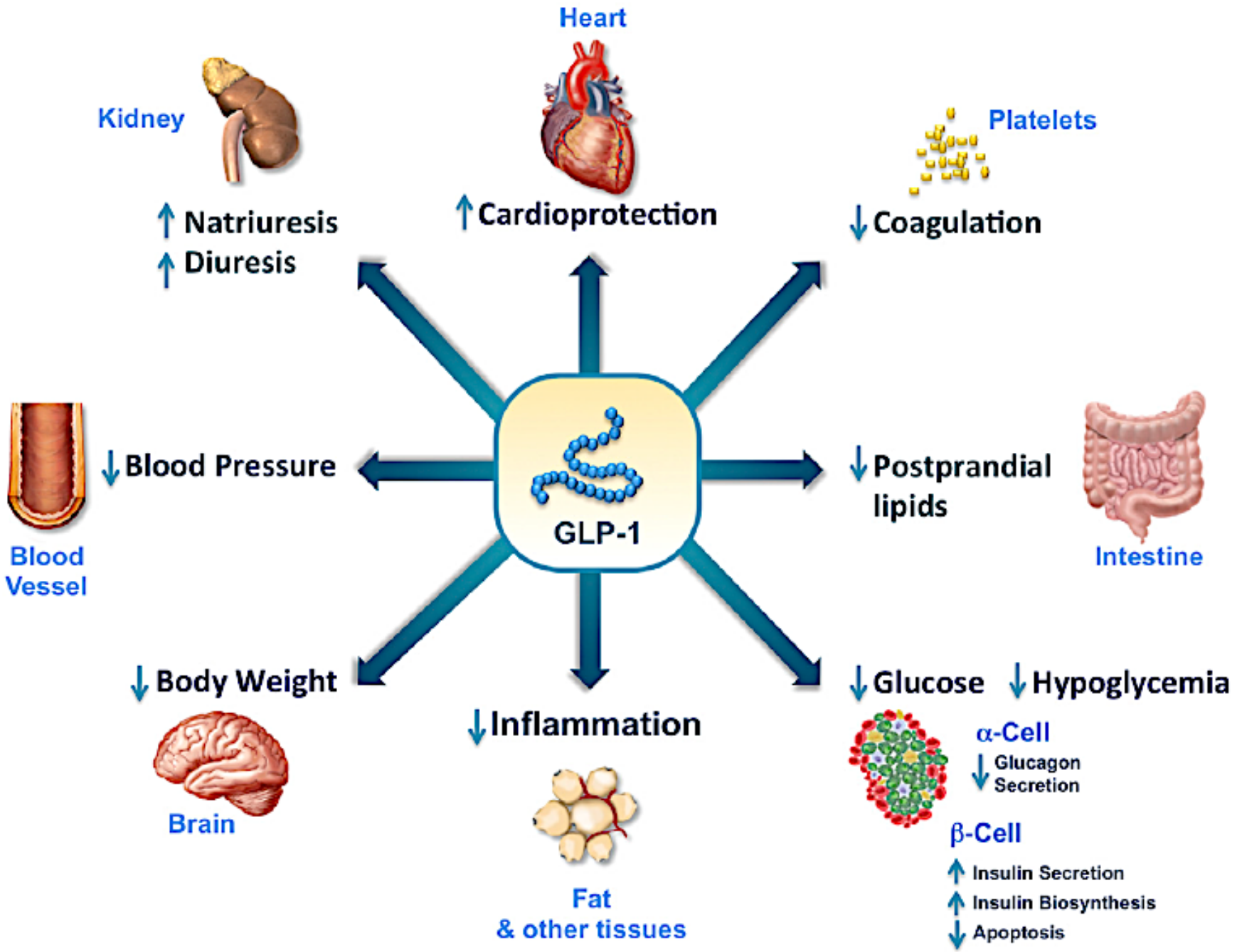
CVOT: cardiovascular outcome trial. MACE: major adverse cardiovascular event (nonfatal MI, nonfatal stroke, CV death)

McRae M, Low Wang CC. Macrovascular Complications. *Prim Care* 2022;49(2):255-273.

GLP1 has direct and indirect effects in the heart and blood vessels



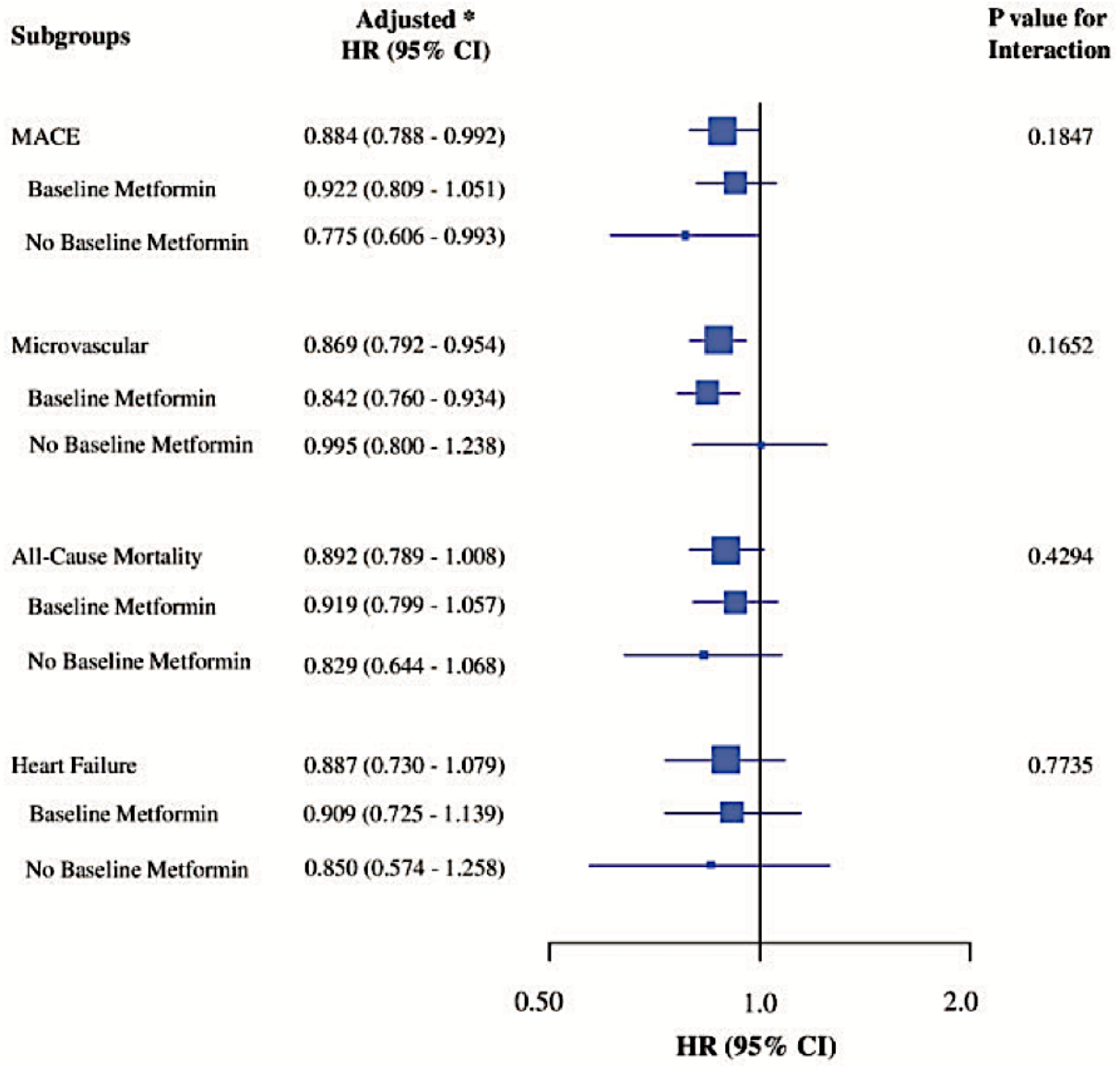
Drucker D. The Cardiovascular Biology of Glucagon-like Peptide-1. *Cell Metab* 2016;24:15-30.



GLP1 modifies CV risk through direct and indirect actions in multiple organs

Drucker D. The Cardiovascular Biology of Glucagon-like Peptide-1. *Cell Metab* 2016;24:15-30.

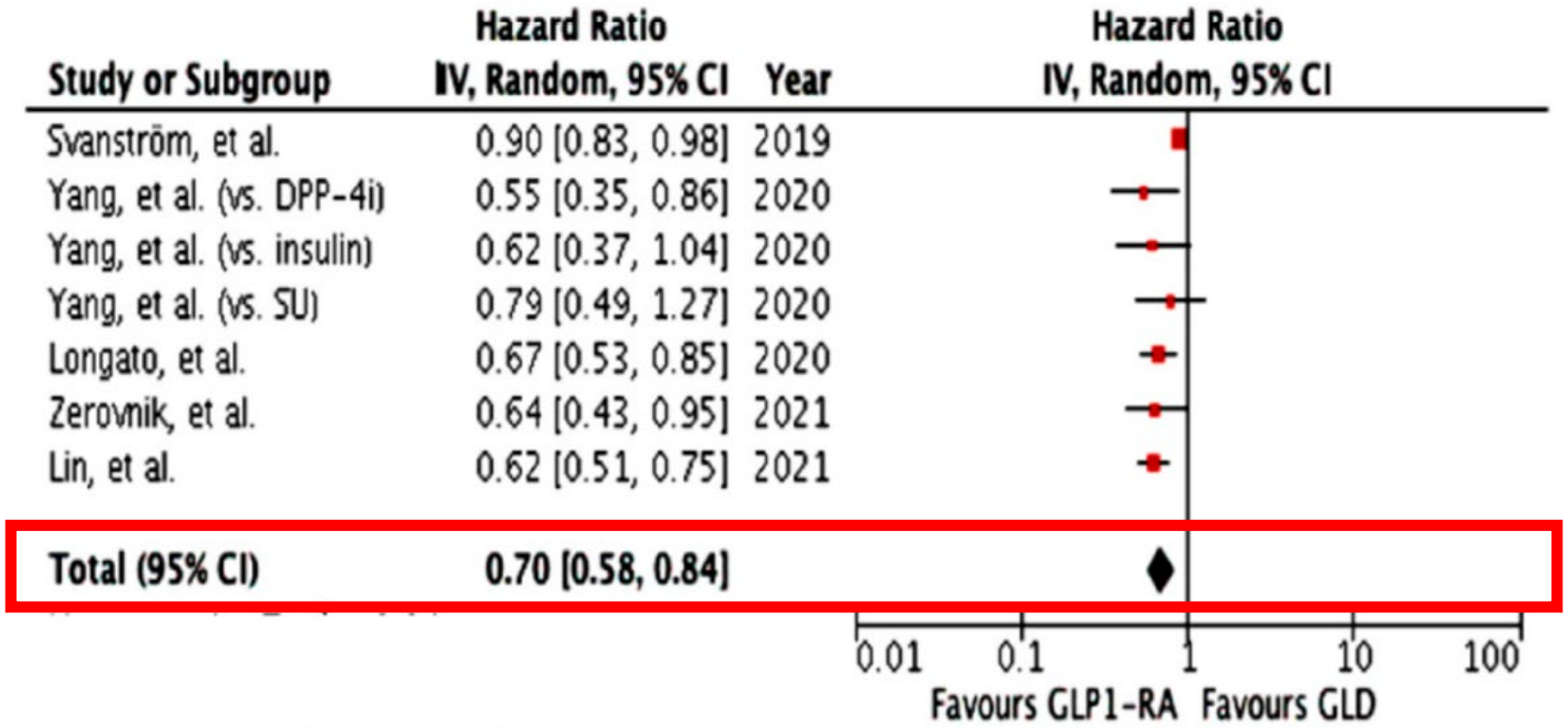
REWIND post-hoc analysis (dulaglutide) of T2D showed CV benefit w/ or w/o background metformin



Dulaglutide reduced the primary outcome whether patients were on metformin or not, at baseline

Ferrannini G, et al. Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. *Eur Heart J* 2021;42(26):2565-2673.

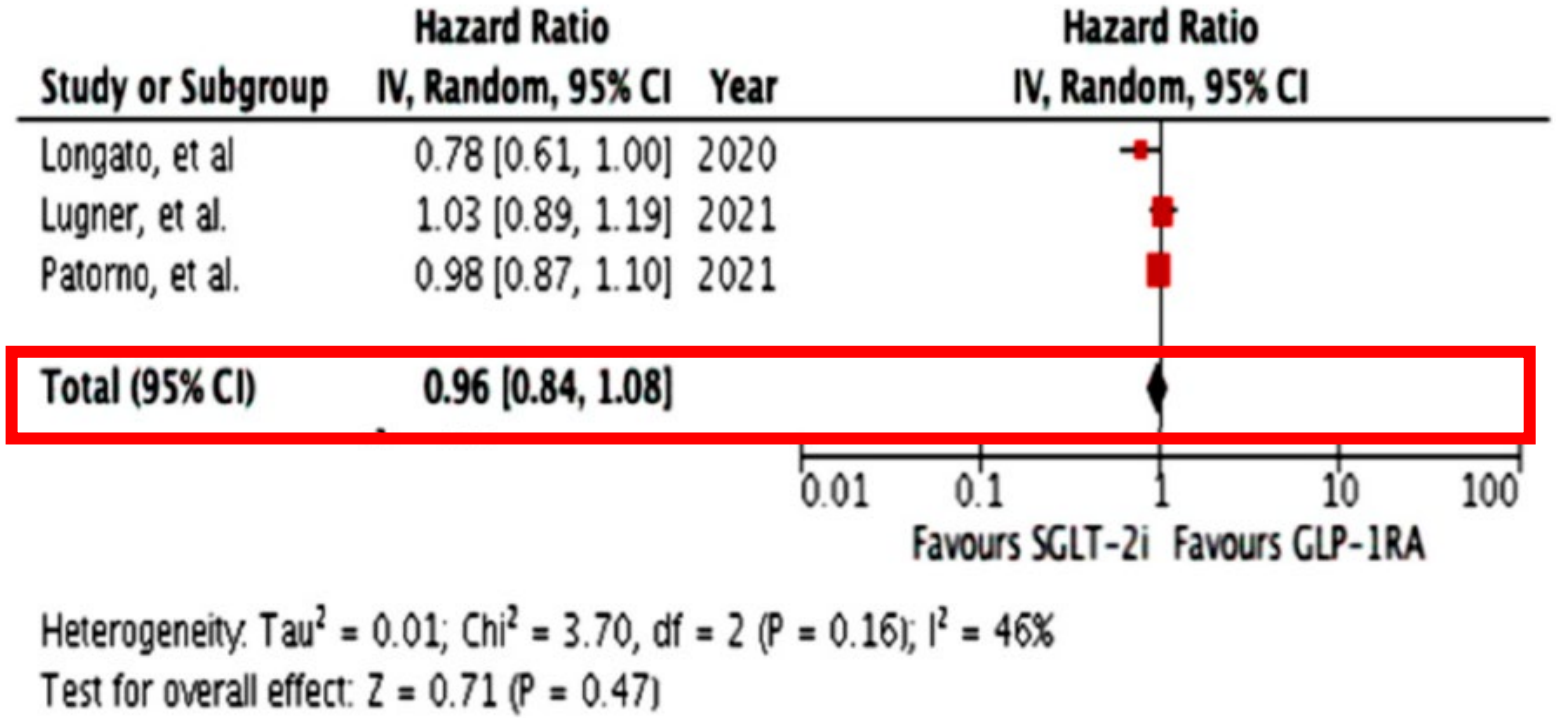
Real world evidence for effect of GLP1RA vs other glucose-lowering agents* on MACE



*except for SGLT2i

Caruso I, et al. Cardiovascular and Renal Effectiveness of GLP-1 Receptor Agonists vs. Other Glucose-Lowering Drugs in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Real-World Studies. *Metabolites* 2022;12:183.

Real world evidence for effect of GLP1RA vs SGLT2i on MACE



Real world studies tend to include patients at lower CV risk

Caveats:

- Most real-world studies do not have information about diabetes duration or A1c, or other metabolic features
- Short duration of follow-up. SGLT2i exert benefits very early while benefits of GLP1RA take longer especially with lower CV risk
- Real-world studies to date do not include semaglutide or ertugliflozin use

Caruso I, et al. Cardiovascular and Renal Effectiveness of GLP-1 Receptor Agonists vs. Other Glucose-Lowering Drugs in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Real-World Studies. *Metabolites* 2022;12:183.

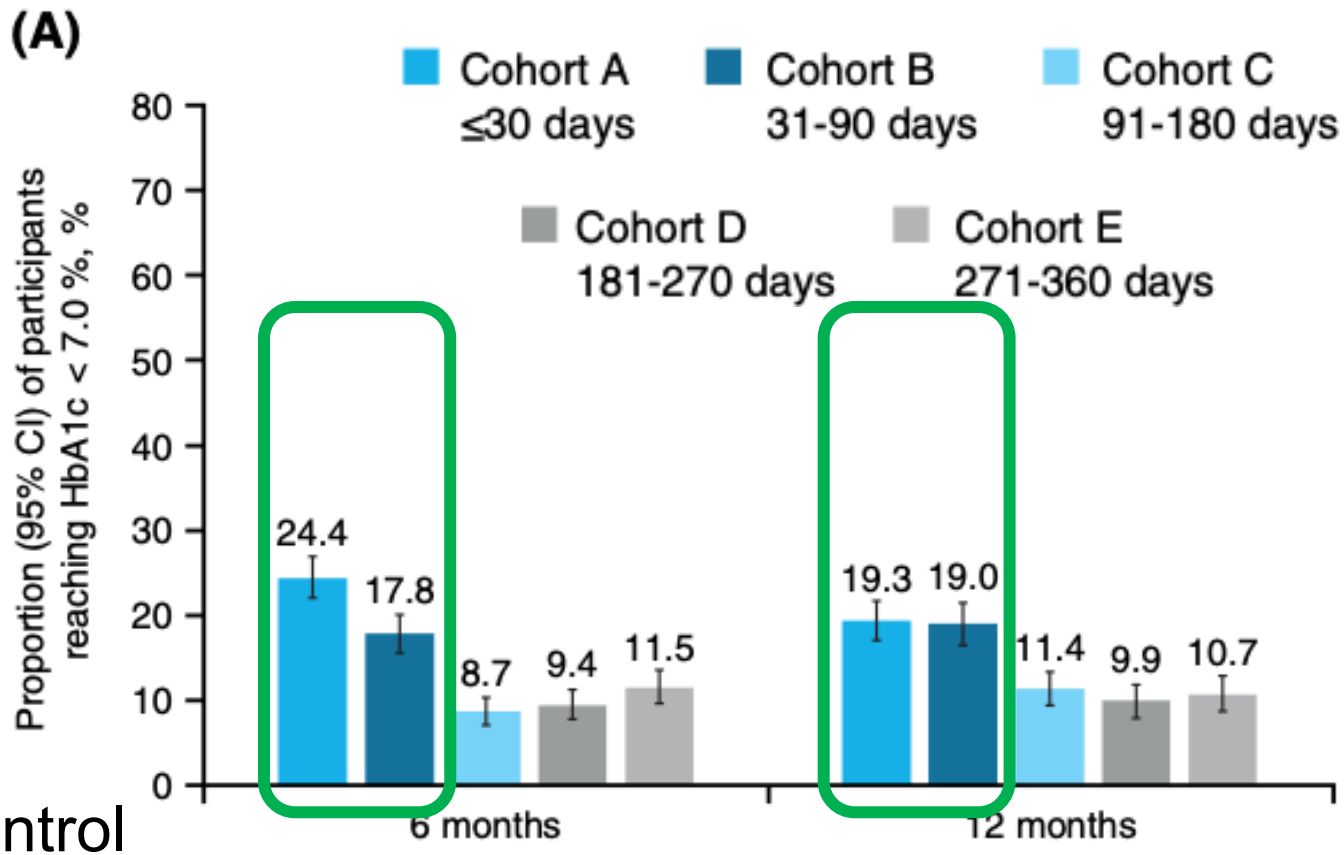
Using GLP1RA in the real world

- Start with a GLP1RA or SGLT2i first-line in ASCVD, CKD, HF
  - Select based on individual patient characteristics and preferences
- All weekly GLP1RA can be used without dose adjustment in patients with renal impairment
- Dulaglutide and semaglutide can be used in patients with severe renal impairment
- Start with the lowest dose and uptitrate every 4 weeks as tolerated to goal dose
  - Liraglutide: 0.6 mg/day titrated Q4wk to maximum 1.8 mg QD
  - Semaglutide: 0.25 mg/wk per week titrated Q4wk to maximum 2 mg/wk
  - Dulaglutide: 0.75 mg/wk or 1.5 mg/wk titrated Q4wk to maximum 4.5 mg/wk

American Diabetes Association. Standards of Medical Care in Diabetes: 9. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2022:45(Suppl_1):S125-S143.
ADA.. Standards of Medical Care in Diabetes: 2022 Abridged for Primary Care Providers. *Clin Diabetes* 2022:40(1):10-38.

If starting insulin too (for symptomatic hyperglycemia) start GLP1RA as soon after basal insulin as possible

Retrospective cohort study
Uncontrolled hyperglycemia
n=6339
47% male
Mean age 54 ± 11 (SD)
Weight 108 ± 26 kg
Baseline A1c 10.7% ± 1.5%
Dyslipidemia 82%
HTN 80%
CKD 26%
Neuropathy 23%
Cohorts A and B achieved control



Rosenstock J, et al. Real-world evidence of the effectiveness on glycaemic control of early simultaneous versus later sequential initiation of basal insulin and glucagon-like peptide-1 receptor agonists. *Diab Obes Metab* 2020;22:2295.

Take-home points and conclusions

- GLP1RAs are an important class of glucose-lowering drugs with benefits for potent A1c-lowering and weight loss, and are first-line in pts w/ estab/high risk for ASCVD

- Liraglutide, semaglutide and dulaglutide lower risk of MACE by 12-26%

- Real world evidence: GLP1RAs lower risk of MACE compared with other glucose-lowering drugs.
  - SGLT2i are the exception, but this may be due to limitations of available real world data

- Tirzepatide has weight reduction effects on par with bariatric procedures but CV data will not be available until 2024