GLP-1 Agonists: New Drug Cardio-Metabolic Therapies Impact on the CV Patient

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Objectives

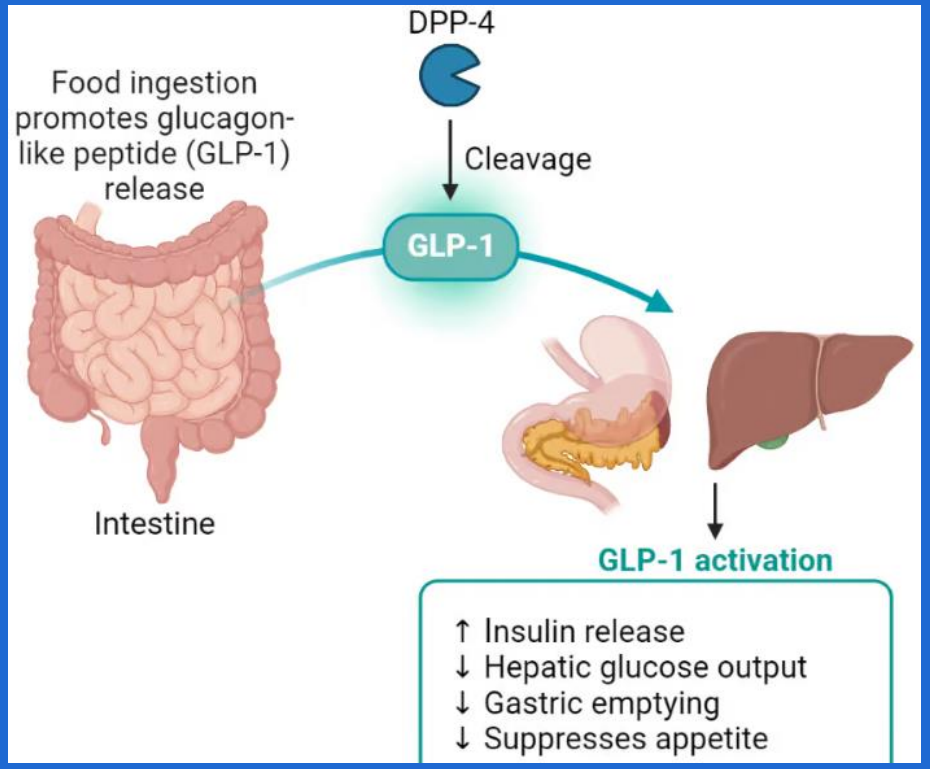
- Discuss the proposed mechanisms and clinical evidence demonstrating the cardiovascular benefits of glucagon-like peptide 1 receptor agonists (GLP-1RA)

- Identify the role of GLP-1RA in reducing CV risk as well as individual patient considerations for use in clinical practice

Mechanism of Action

- GLP-1 is a peptide hormone released after oral nutrient intake

- GLP-1RA administration results in supraphysiologic concentrations of GLP-1
  1)↑ glucose-dependent insulin secretion
  2)↓ glucagon secretion
  3)Delays gastric emptying
  4)Stimulates hypothalamic neurons = ↑ satiety



https://myendoconsult.com/learn/mechanism-of-action-of-glp-1-agonists/

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Das SR et al. *J Am Coll Cardiol* 2020.

Mechanism of Action

Effects on Cardiovascular Risk Factors:

- Modest SBP reduction
  - 2 - 6 mmHg
- Modest reductions in TC, LDL, TG
- HbA1c reduction
  - 0.8 - 1.5%
- Weight loss
  - 2.5 - 4 kg
  - Semaglutide/tirzepatide: 10-20% mean weight loss

Marx N et al. *Circulation* 2022.

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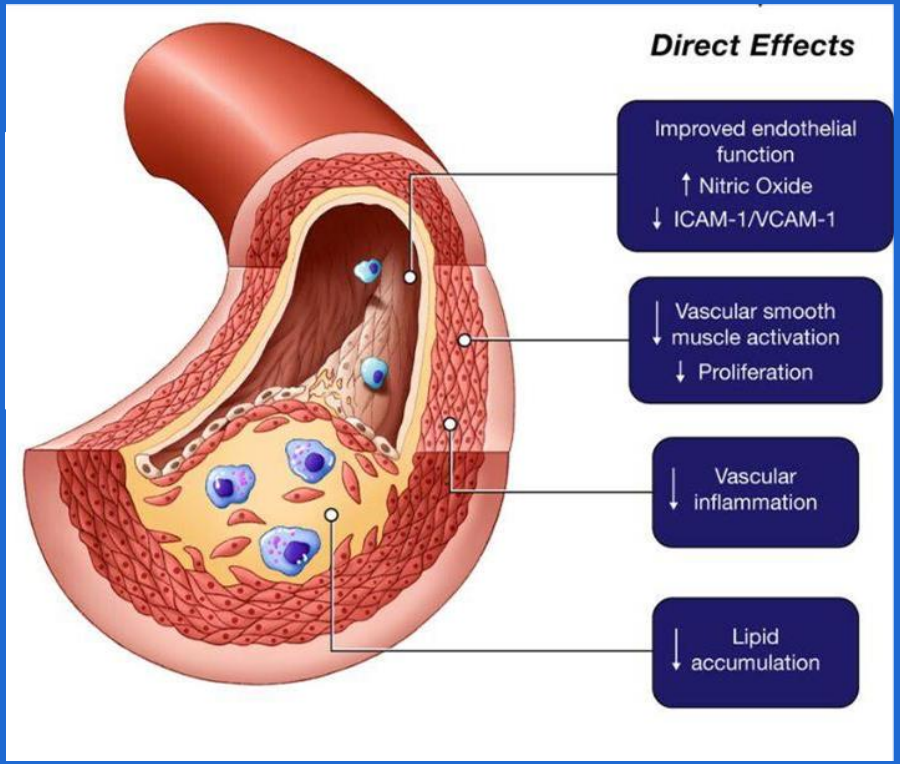
Marx N et al. *Circulation* 2022.

Atherosclerosis

- Reduce atherosclerotic lesion development & progression
- More stabilized, less vulnerable plaques
- Antiatherogenic effects in endothelial cells, monocytes, macrophages, vascular smooth muscle



Goldenberg RM et al. *STROKEAHA* 2022.

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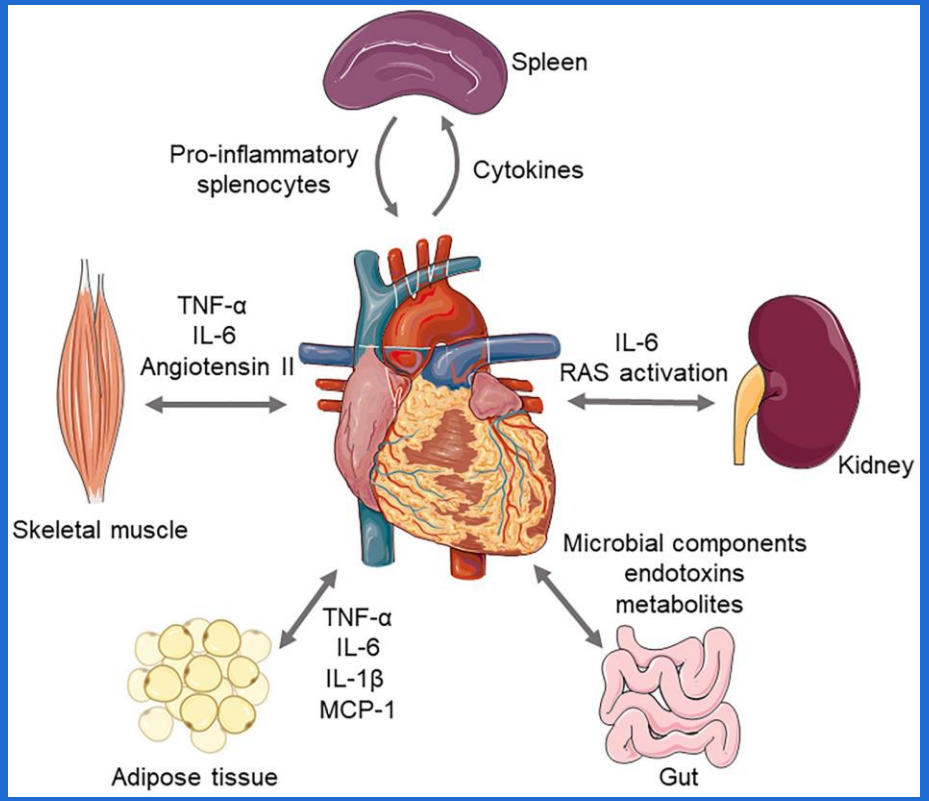
Marx N et al. *Circulation* 2022.

Anti-Inflammatory

- Data demonstrating decreased TNF-α and interleukin-1 production
- GLP-1RA have been shown to reduce systemic inflammation as measured by levels of CRP



Li H et al. *Front. Physiol.* 2021.

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Marx N et al. *Circulation* 2022.

Cardiovascular Benefits

Summary of GLP-1RA CV Outcome Trials

Trial	LEADER (2016)	SUSTAIN-6 (2016)	EXSCEL (2017)	REWIND (2019)	PIONEER-6 (2019)
Drug	Liraglutide	Semaglutide	Exenatide	Dulaglutide	Semaglutide (PO)
Composite 3-point MACE, HR (95% CI)	**0.87 (0.78–0.97)**	**0.74 (0.58–0.95)**	0.91 (0.83–1.00)	**0.88 (0.79-0.99)**	0.79 (0.57-1.11)
CV Death, HR (95% CI)	**0.78 (0.66–0.93)**	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78-1.06)	**0.49 (0.27-0.92)**
Fatal / Nonfatal MI, HR (95% CI)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79-1.15)	1.18 (0.73-1.90)
Fatal / Nonfatal Stroke, HR (95% CI)	0.86 (0.71-1.06)	**0.61 (0.38–0.99)**	0.85 (0.70–1.03)	**0.76 (0.62-0.94)**	0.74 (0.35-1.57)

Das SR et al. *J Am Coll Cardiol* 2020.

Guideline Recommendations

- 2022 American Diabetes Association "Standards of Medical Care in Diabetes"
  - Recommend GLP-1RA or SGLT2i in T2DM with ASCVD or high risk independent of baseline HbA1c, HbA1c target, or metformin use
- 2020 ACC Expert Consensus for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes
  - Recommend SGLT2i and/or GLP-1RA for patients with T2DM who have or who are at very high risk for clinical ASCVD, HF, and/or diabetic kidney disease
- 2019 European Society of Cardiology Guidelines on Diabetes, Prediabetes, CVD
  - Recommend GLP-1RA (or SGLT2i) in patients with T2DM and ASCVD or high/very high risk

10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care* 2022.
Das SR et al. *J Am Coll Cardiol* 2020.
Cosentino F et al. *European Heart Journal* 2020.

Medication Selection

	GLP-1RA	SGLT2i
HbA1c reduction	0.8 - 1.5%	0.5 - 0.8%
Weight reduction	2.5 - 4 kg*	2.2 - 3.2 kg
Systolic BP reduction	2 - 6 mmHg	2 - 4 mmHg
Patients who may benefit the most	ASCVD High Risk MACE	Heart Failure Kidney Disease
Contraindications	History thyroid cancer History of pancreatitis Pregnancy / Breastfeeding	Dialysis Pregnancy / Breastfeeding

*Semaglutide/tirzepatide: 10-20% weight loss

Marx N et al. *Circulation* 2022.
Giugliano D et al. *Cardiovasc Diabetol* 2021.
Pradhan A et al. *J Family Med Prim Care* 2019.

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