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TEACHING HOSPITAL

Impact of GLP-1 Agonists on Cardiovascular Disease Outcomes

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Disclosures: Research grant from Anumana; Abbott, Voiant, Medtronic

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Objectives

1) **Identify the mechanism of action of GLP-1 agonists.**

2) **Describe the indications for GLP-1 agonist use and the identified benefits.**

3) **Describe the adverse effects of GLP-1 agonist use.**

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Clinical Vignette 1

57F with BMI of 46 with HTN and HbA1C of 6.7. BP remains ~140mmHg despite a three-drug regimen and HbA1c has not declined despite use of oral hypoglycemics. Patient is not willing to consider insulin.

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Clinical Vignette 2

66M with BMI 36, severe OSA, HTN, and borderline diabetes. He is struggling to use CPAP despite multiple rounds of adjustment.

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Clinical Vignette 3

61F with known CAD, HTN, and hyperlipidemia. BMI is 35 and has not reduced despite multiple attempts to implement diet and exercise changes. BP, lipids, and HbA1c all within accepted range with medical therapy.

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Question 1

Which tissues are affected by GLP-1 agonists?

A. Pancreas
B. Brain
C. Stomach
D. Intestine
E. Vascular system
F. All of the above

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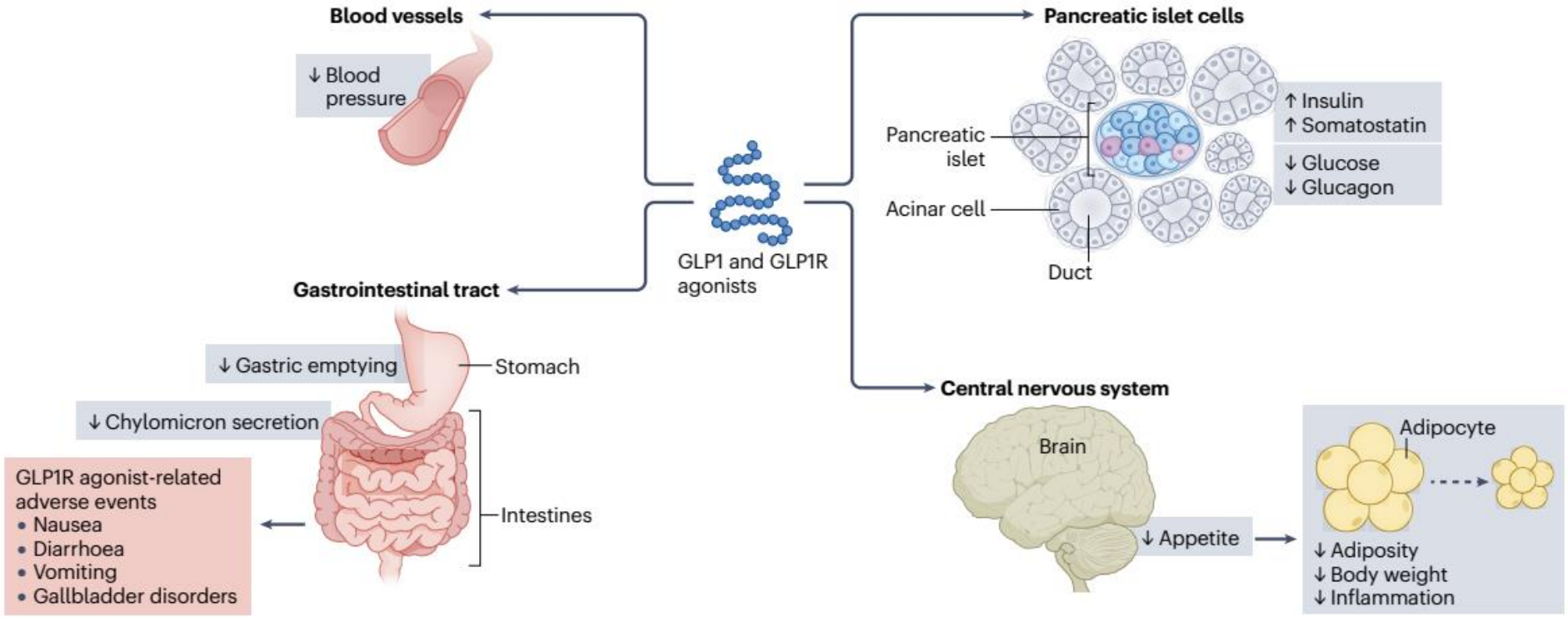
GLP-1 Agonists: Physiologic Effects



Ussher JR and Drucker DJ Nat Rev Card 2023;20:463-474.

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GLP-1 Agonists: Clinical Trials

	On the market	Clinical trial status	Route of administration	Receptor target
Exenatide	Yes	Finished	Injection	GLP-1
Liraglutide	Yes	Finished	Injection	GLP-1
Semaglutide	Yes	Finished	Injection or oral	GLP-1
Tirzepatide	Yes	Finished	Injection	GLP-1, GIP
Dulaglutide	Yes	Finished	Injection	GLP-1
Albiglutide	Yes	Finished	Injection	GLP-1
Lixisenatide	Yes	Finished	Injection	GLP-1
Cagrisema	No	Phase 3	Injection	GLP1, amylin
Survodutide	No	Phase 3	Injection	GLP-1, glucagon
Retatrutide	No	Phase 2	Injection	GLP-1, GIP, and glucagon
NNC0165–1875 + semaglutide	No	Phase 2	Injection	GLP-1, PPY
Efinopegdutide	No	Phase 2	Injection	GLP-1, glucagon
Danuglipron	No	Phase 2b	Oral	GLP-1
Orforglipron	No	Phase 1b	Oral	GLP-1
Amycretin	No	Phase 1	Oral	GLP-1, amylin

GIP=glucose-dependent insulinotropic polypeptide. PPY=pancreatic polypeptide.

Table: **List of selected currently available and future GLP-1 receptor agonists and their targets**

Zushin PH and Wu JC. Lancet 2025;405:181-183.

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GLP-1 Agonists: Baseline Characteristics of Patients in Clinical Trials

	ELIXA (n=6068)	LEADER (n=9340)	SUSTAIN 6 (n=3297)	EXSCEL (n=14 752)	HARMONY OUTCOMES (n=9463)	REWIND (n=9903)	PIONEER-6 (n=3183)	AMPLITUDE-O (n=4076)
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide	Efpeglenatide
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Subcutaneous
Target dose	10 µg/d or 20 µg/d	1.8 mg/d	0.5 mg/wk or 1 mg/wk	2 mg/wk	30 mg/wk or 50 mg/wk	1.5 mg/wk	14 mg/d	4 mg/wk or 6 mg/d
Age, y	60±10	64±7	65±7	62±9	64±7	66±7	66±7	65±8
Sex								
Female	31%	36%	39%	38%	31%	46%	32%	33%
Male	69%	64%	61%	62%	69%	54%	68%	67%
BMI kg/m^2	30.1±5.6	32.5±6.3	32.8±6.2	32.7±6.4	32.3±5.9	32.3±5.7	32.3±6.5	32.7±6.2
Diabetes duration, y	9.2±8.2	12.8±8.0	13.9±8.1	13.1±8.3	14.2±8.8	10.5±7.2	14.9±8.5	15.4±8.8
HbA1c %	7.7±1.3	8.7±1.6	8.7±1.5	8.1±1.0	8.7±1.5	7.3±1.1	8.2±1.6	8.9±1.5
Established cardiovascular disease	100%	81%	83%	73%	100%	31%	85%	90%
History of heart failure	22%	18%	24%	16%	20%	9%	12%	18%
Systolic blood pressure (mm Hg)	129±17	136±18	136±17	135±17	135±17	137±17	136±18	135±16
eGFR, mL/min per 1.73 m^2*	78±21	80 (NR)	80 (61–92)	77 (61–92)	79±25	77±23	74±21	72±22

Marx N et al. 2022 Circulation 2022;146:18821894

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Question 2

What is the measured impact of GLP-1 agonist use on HbA1c levels?

A. 0-1% reduction
B. 1-2% reduction
C. 2-3% reduction
D. 3-4% reduction

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Question 3

What is the measured impact of GLP-1 agonist use on weight?

A. 1% reduction
B. 2% reduction
C. 5% reduction
D. 7% reduction

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Question 4

What is the measured impact of GLP-1 use on reduction of major adverse clinical events (cardiovascular death, MI, stroke, hospitalization for unstable angina)?

A. Hazard ratio 0.6
B. Hazard ratio 0.7
C. Hazard ratio 0.8
D. Hazard ratio 0.9

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Question 4

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Question 5

Which of the following patients is not an optimal candidate for GLP-1 agonist use?

A. 60F with BMI 40, DM2, OSA (HbA1c 6.8%, GFR 66)
B. 60F with BMI 40, DM2, OSA (HbA1c 9.8%, GFR 66)
C. 60F with BMI 40, DM2, OSA (HbA1c 6.8%, GFR 20)
D. B
E. B and C
F. All of the above

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B. 60F with BMI 40, DM2, OSA (HbA1c 9.8%, GFR 66)

C. 60F with BMI 40, DM2, OSA (HbA1c 6.8%, GFR 20)

D. B

E. B and C

F. All of the above

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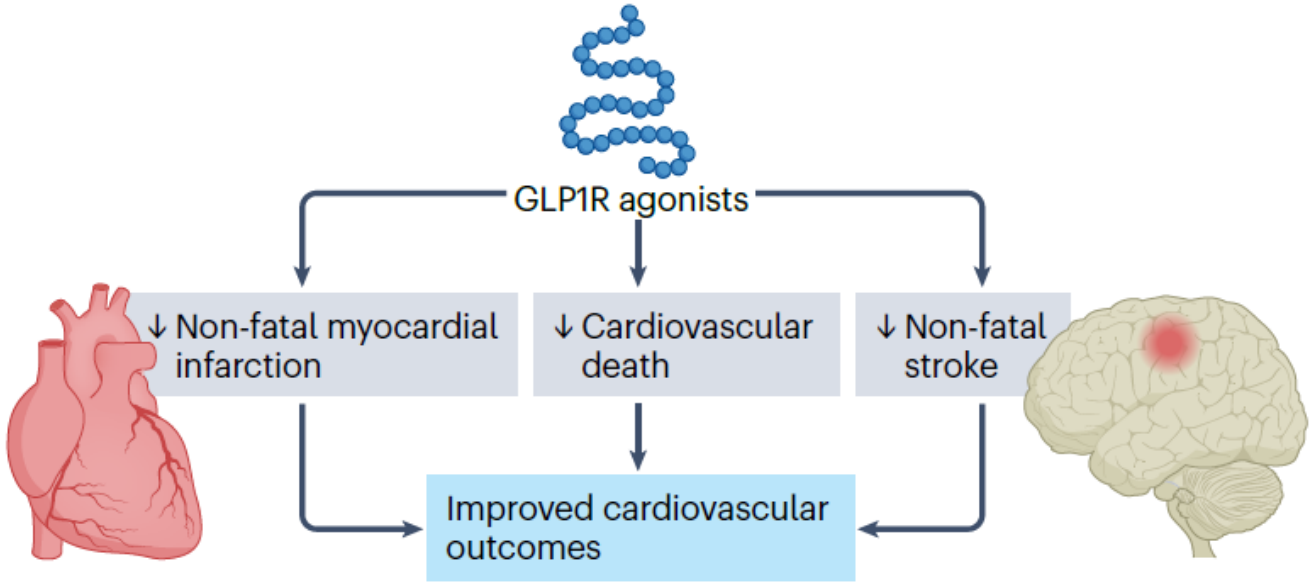
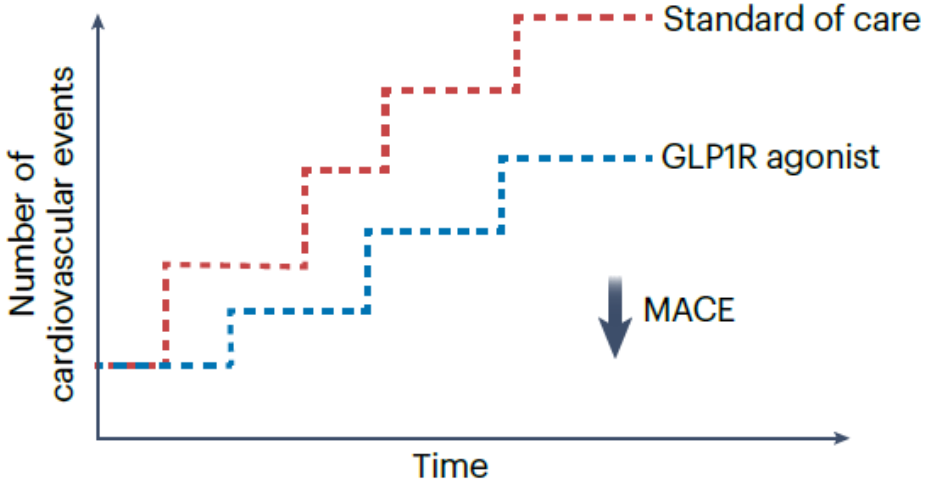
GLP-1: Reduction in MACE





Ussher and Drucker
Nat Rev Cardiol 2023;30:463-474

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GLP-1 Agonists: Clinical Trial Outcomes

	Main analysis with all 8 CVOTs (HR; I^2)	Sensitivity analyses minus ELIXA (HR; I^2)
MACE	0.86 (0.80 to 0.93) 45%	0.85 (0.80 to 0.90) 15%
CV death	0.87 (0.80 to 0.94) 13%	0.85 (0.78 to 0.93) 12%
MI	0.90 (0.83 to 0.98) 27%	0.88 (0.81 to 0.96) 16%
All-cause mortality	0.88 (0.82 to 0.94) 10%	0.87 (0.81 to 0.94) 17%
Incident HHF	0.89 (0.82 to 0.98) 3%	0.88 (0.79 to 0.98) 12%
Kidney composite (+ albuminuria)	0.79 (0.73 to 0.87) 48%	0.78 (0.71 to 0.87) 57%
Worsening kidney function (eGFR)	0.86 (0.72 to 1.02) 43%	0.82 (0.69 to 0.98) 40%

Marx N et al. 2022 Circulation 2022;146:18821894

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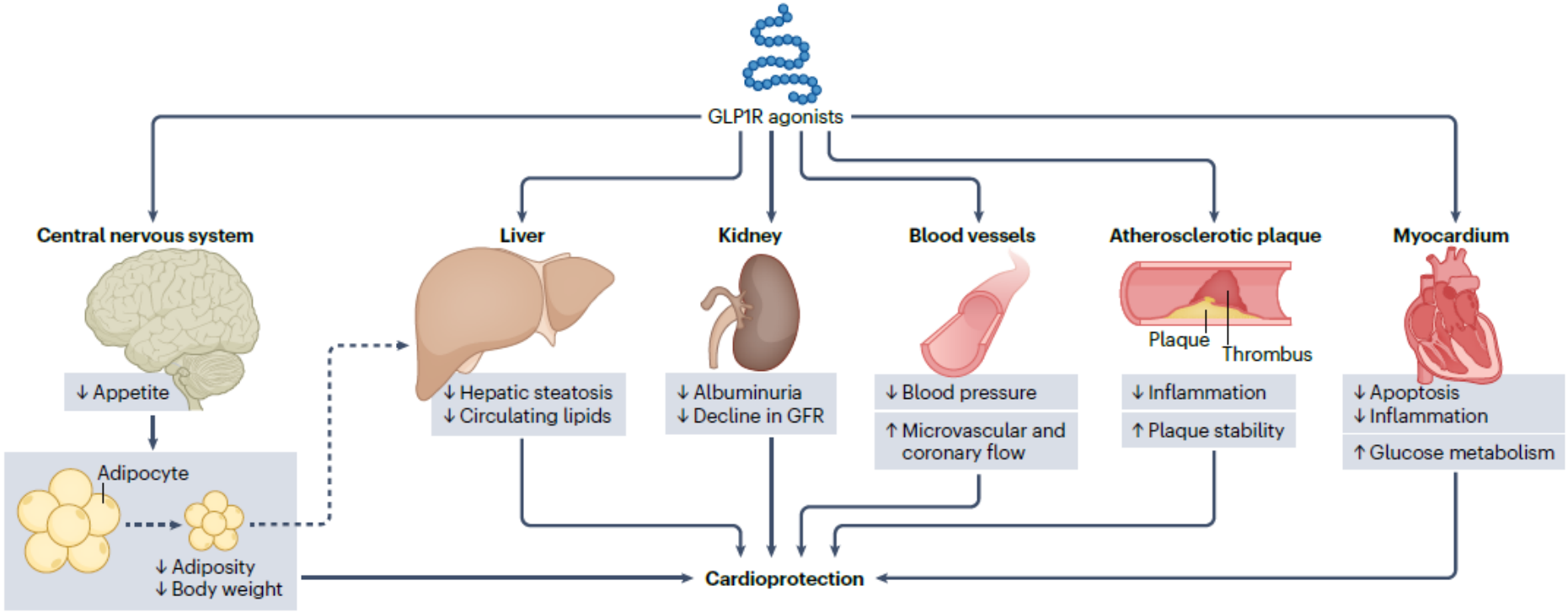
GLP-1 Agonists: Mechanisms for Cardiac Protection



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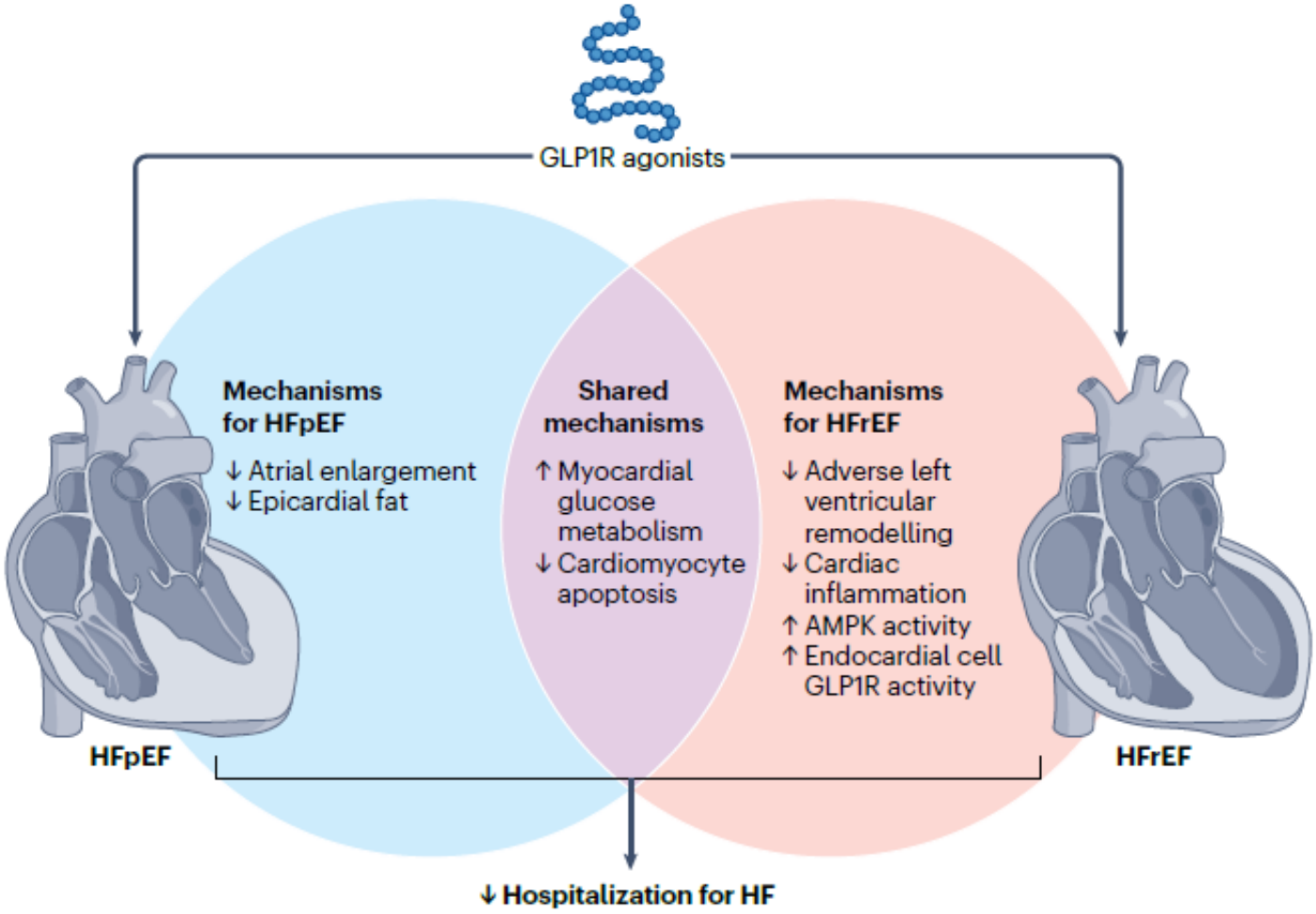
GLP-1 Agonists: Mechanisms for Cardiac Protection



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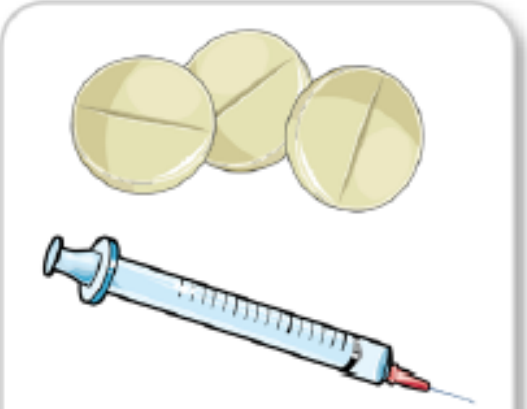
GLP-1 Agonists: Utilization and Early Outcomes

GLP-1 receptor agonists

Effects on CV outcomes

(HR; 95%CI)

- MACE 0.86 (0.80 to 0.93)
- MI 0.90 (0.83 to 0.98)
- Stroke 0.83 (0.76 to 0.92)
- CV death 0.87 (0.80 to 0.94)



Effects on risk factors

glucose	weight	blood pressure
HbA1 ~ 1.5 %	~ 4%	~ 3 mmHg

Side effects

- GI side effect
- Local reaction at injection side
- Use with caution in patients with history of pancreatitis

Patient profile

- ASCVD
- Overweight / obese
- High risk of stroke

Treatments aspects

- Start with low dose
- Increase dose slowly
- Use ≤ 32 gauge needle
- Adjust insulin / SU dose
- Recommend small meals

Marx N et al., Circulation 2022;146:1882-1894

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GLP-1 Agonists: Clinical Trials

- Originally developed to improve glycemic control in patients with type 2 diabetes.
- Emerged as promising agents for weight management.
- Multiple clinical trials (LEADER,[1] SELECT,[2] SURPASS[3]) have demonstrated cardiovascular benefits with GLP-1 agonist use.
- Other clinical trials (STEP 1[4]) focus on use of GLP-1 agonists for weight loss.

1. Alvarez-Villalobos NA et al. N Engl J Med 2016;375:1797-1798.
2. Gajos G Cardiol J 2024. Cardiol J 2024;31:782-783.
3. Nicholls SJ et al. Am Heart J 2024;267:1-11.
4. Stumpf MAM et al. Eur J Prev Cardiol 2023;30:1895-1905.

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GLP-1 Agonists: Clinical Indications

Proven cardiovascular benefit for patients with:

- Diabetes mellitus (type 2)
- Atherosclerotic cardiovascular disease
- High risk for cardiovascular events
- Elevated BMI
- Chronic kidney disease

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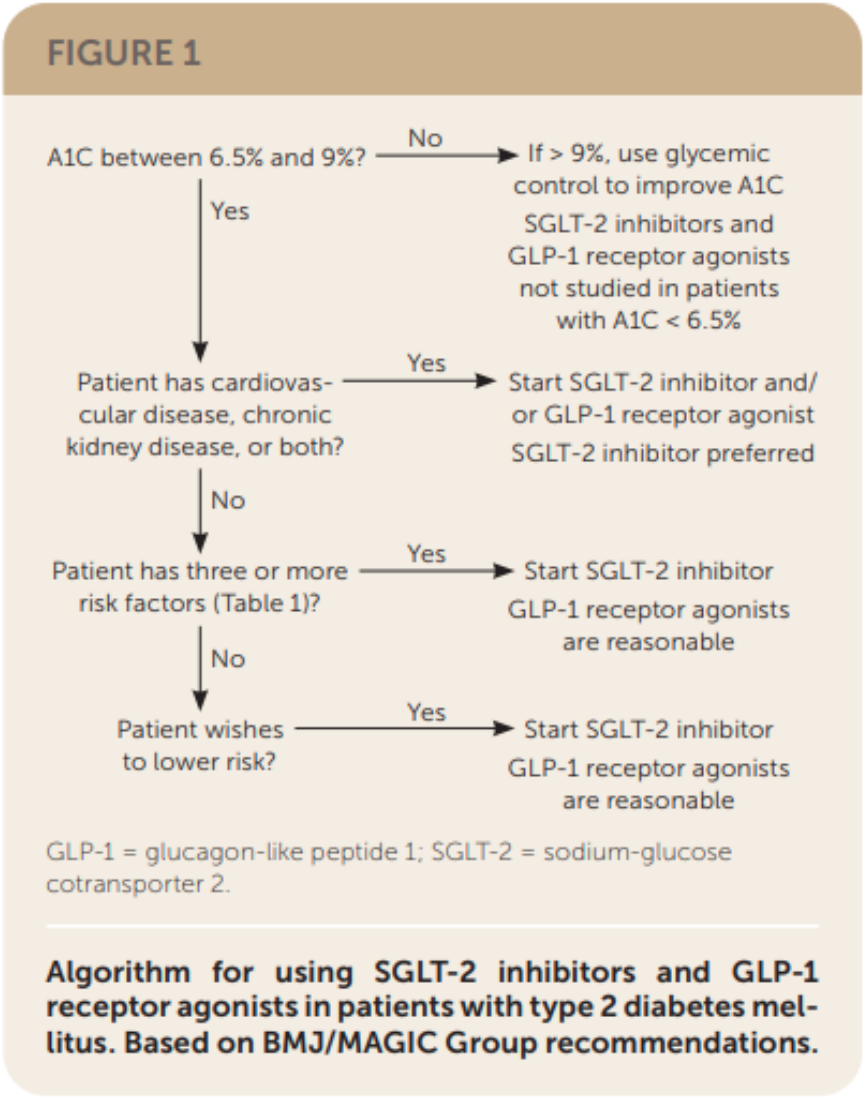
GLP-1 Agonists: Clinical Indications



(Accessed at: www.aafp.org 1/23/2025)

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GLP-1 Agonists: Different Formulations

GLP-1 receptor agonists	General aspects		Pharmacokinetics	
	Doses*	Administration	TTP	Elimination half-life
Exenatide BID	5 µg 10 µg	Twice daily	2.1–2.2 h	3.3–4.0 h
Liraglutide QD	0.6 mg 1.2 mg 1.8 mg	Once daily	11.0–13.8 h	12.6–14.3 h
Lixisenatide QD	10 µg 20 µg	Once daily	About 2 h	2.6 h
Dulaglutide QW	0.75 mg 1.5 mg 4.5 mg	Once weekly	48 h	4.7–5.5 h
Exenatide ER	2 mg	Once weekly	Not formally assessed†	3.3–4.0 h
Semaglutide SC	0.25 mg 0.5 mg 1.0 mg (2.4 mg)‡	Once weekly	24 h	5.7–6.7 d
Semaglutide oral	3 mg 7 mg 14 mg	Once daily	About 1–4 h	5.7–6.7 d

ER indicates extended release; and TTP, time to peak.
*For the initiation and up-titration, see Table 2.
†The onset of exenatide ER does not quickly lead to measurable concentrations; therefore, this has not been formally evaluated.
‡Semaglutide (2.4 mg once weekly) was approved by the Food and Drug Administration for obesity in patients without diabetes.

Marx N et al. 2022 Circulation 2022;146:188 21894

GLP-1 Agonists: The Down Side

- **Side effects:** GERD
- **Costs:** $1000/month
- **Weight re-gain:** two-thirds of weight regained 1 year after cessation
- **Contraindications:** not to be used in pregnancy or breastfeeding, use in combination with SGLT2i not well-understood, use in patients with ESRD not yet validated

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GLP-1 Agonists: Practical Considerations

Potential concerns	Practical recommendation
Concomitant glucose-lowering medication	Stop DPP4 inhibitors Depending on HbA1C: stop or reduce dose insulin dose (~25%) or sulfonylurea to reduce risk of hypoglycemia
GI side effects (nausea, vomiting, etc)	Start with low dose and up-titrate slowly Consider symptomatic therapy (eg, proton pump inhibitor) Counsel patients on: – side effects only transient – small meals – eat slowly – stop before feeling full – avoid fatty, spicy, and strong-flavored foods
Injectable therapy	Use small needle (≤32 gauge) Fear of injection: consider oral available GLP-1 RA (semaglutide)
Laboratory controls	Kidney function: not necessary Pancreatic enzymes: – only if patient is symptomatic – levels increase on average by ~20% (no increased risk of acute pancreatitis in studies) Liver enzymes: not necessary

Marx N et al. 2022 Circulation 2022;146:18821894

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GLP-1 Agonists: Upcoming Trials

Trial Name	Agent	Disease State
SYNERGY-NASH	tirzepatide	Metabolic dysfunction–associated steatohepatitis
STRIDE	semaglutide	PAD
SURMOUNT-OSA	tirzepatide	OSA
SUMMIT	tirzepatide	HFpEF
SURMOUNT-MMO	tirzepatide	CV outcomes (includes a high-risk, primary-prevention cohort)
EVOKE	semaglutide	Alzheimer disease

Pillar P and Modarressi T, Expert Analysis 15 Apr 2024 (acc.org)

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Summary

1) **Identify the mechanism of action of GLP-1 agonists.**

   Decrease gastric emptying and adiposity, increase in insulin secretion

2) **Describe the indications for GLP-1 agonist use and the identified benefits.**

   DM, High BMI with OSA and/or CV risk factors

3) **Describe the noted side effects associated with GLP-1 agonist use.**

   GI symptoms, rebound adiposity

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