
بسم الله الرحمن الرحيم

Incretin Therapies for Patients with Diabetes (DDP4I/GLP1RA)

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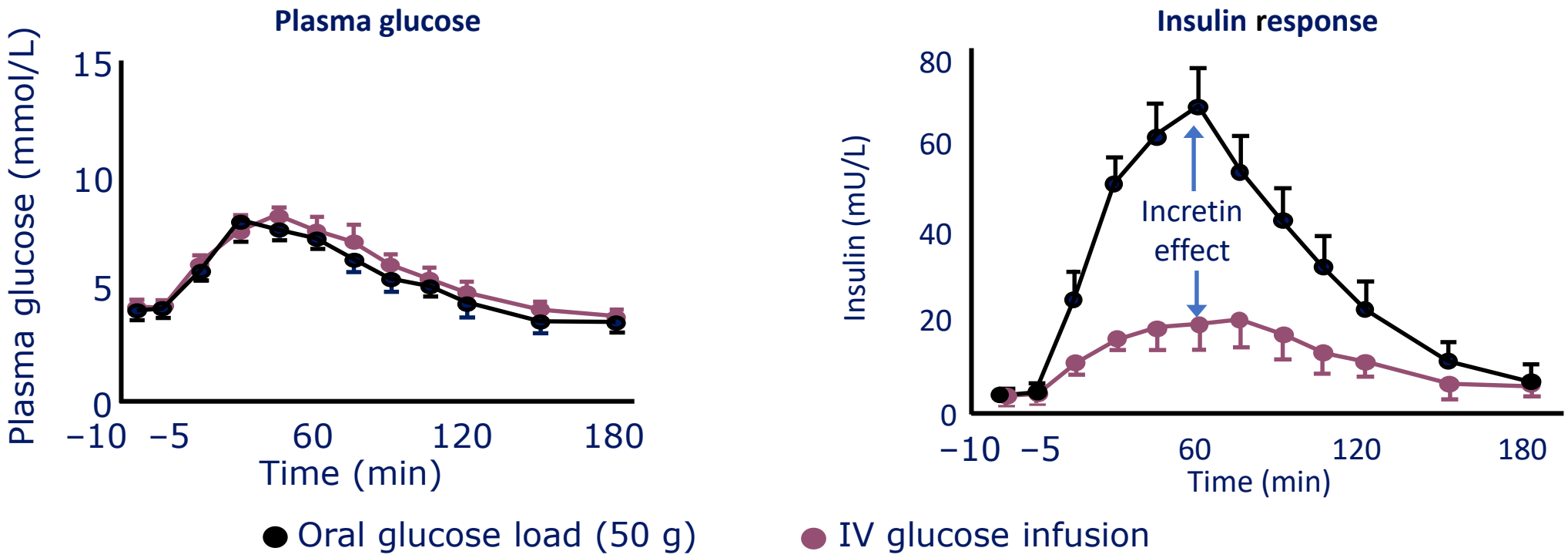
AGENDA

- ***Introduction***
- ***DPP4 Inhibitors***
- ***GLP1 Receptor Agonists***
- ***ADA guideline***

Introduction :Physiology of the incretin system

- The gut secretes several hormones in response to food intake, of which GLP-1 and GIP are the most important in terms of glucose regulation
- Under normal physiological conditions, the actions of these hormones serve to limit rises in postprandial blood glucose, and in their absence, the pancreatic response to glucose is diminished.
- This phenomenon, termed the “incretin effect,” was first illustrated in the 1960s after observations that equivalent plasma glucose concentrations elicited greater insulin release when ingested than when delivered through direct intravenous infusion.
- The incretin effect is compromised in type 2 diabetes
- *J Clin Endocrinol Metab* 24:1076–1082, 1964 /*Diabetologia* 29:46–52, 1986

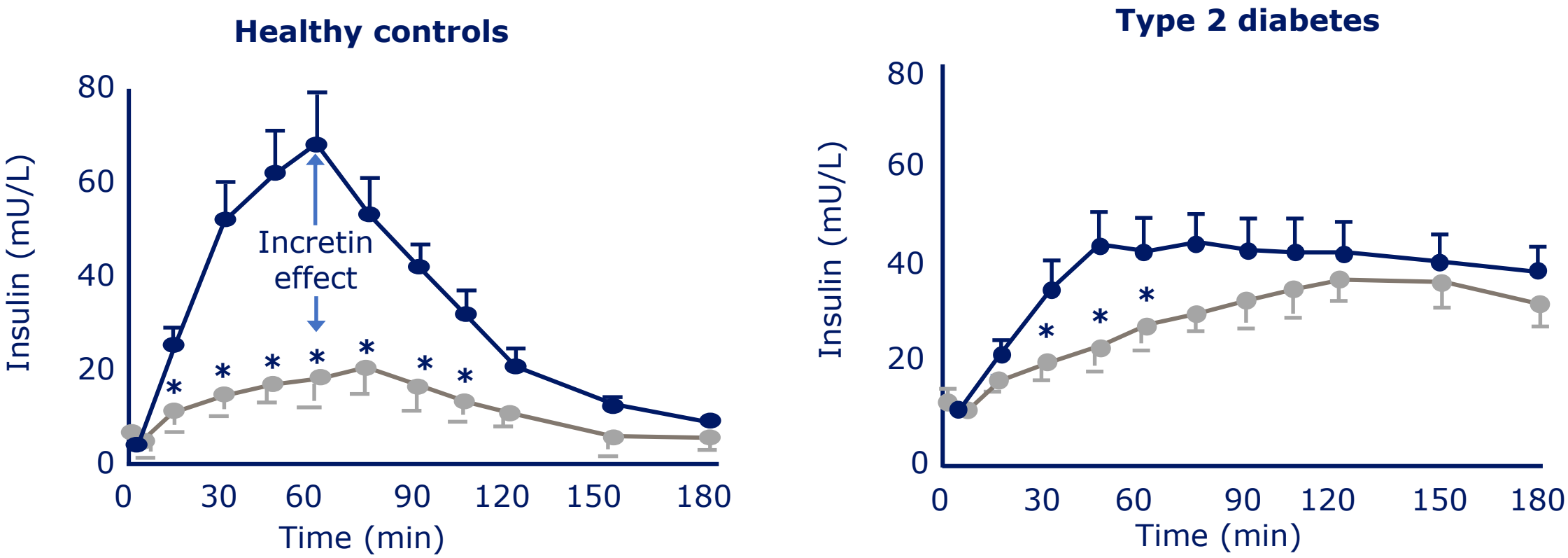
Role of incretin effect in healthy insulin response



- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

IV, intravenous
Nauck M et al. *Diabetologia* 1986;29:46–52

The incretin effect is diminished in patients with type 2 diabetes

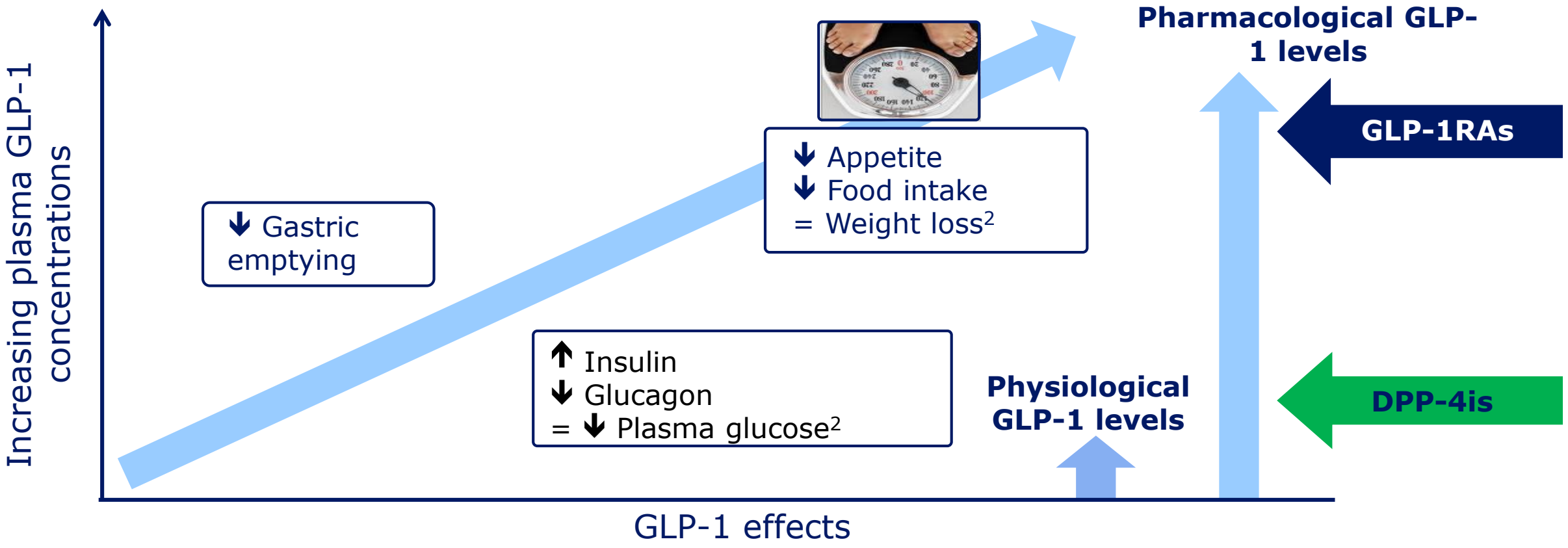


*$p<0.05$, healthy volunteers (n=8)
Nauck M et al. *Diabetologia* 1986;29:46–52

Introduction :Physiology of the incretin system

- Native GLP-1 is rapidly degraded by the enzyme DPP-4. This enzyme, expressed in many tissues, rapidly cleaves peptides, including the incretins.
- As a result, native GLP-1 persists in the circulation for < 2 minutes. This means that human GLP-1 cannot be readily adapted for clinical use because it would need to be given by continuous infusion.
- Therapeutic exploitation of GLP-1 physiology therefore required GLP-1 analogs that were resistant to DPP-4 or drugs that could maximize the effects of endogenous GLP-1 by inhibiting DPP-4.
- Using this approach, DPP-4 inhibitors and DPP-4–resistant GLP-1 receptor agonists were developed.
- *Lancet* 368:1696–1705, 2006

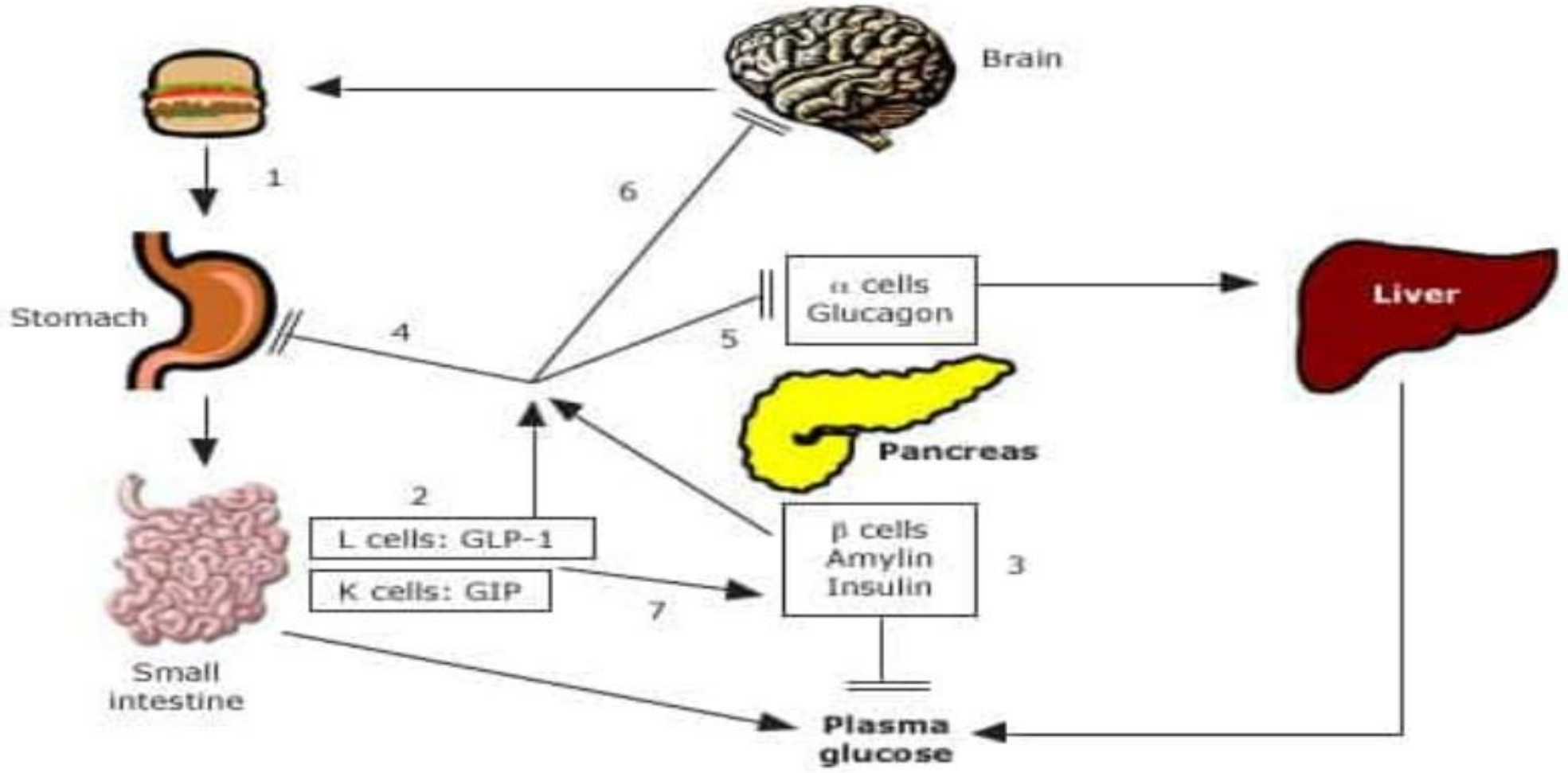
Additional physiological benefits are observed at pharmacological levels of GLP-1



DPP-4is, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1; GLP-1RAs, glucagon-like peptide 1 receptor agonists
Adapted from Holst et al.[1]

1. Holst JJ et al. *Trends Mol Med* 2008;14:161–168; 2. Flint A et al. *Adv Ther* 2011;28:213–226

Multihormonal regulation of glucose



DPP4 Inhibitors

- Five DPP4 inhibitors—sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin—are approved for clinical use
- These agents increase fasting and postprandial levels of GLP1 about twofold. This elevation of GLP1 potentiates glucose-dependent insulin secretion and suppresses basal and postprandial glucagon
- However, neither satiety nor the rate of gastric emptying is affected.
- They have no consistent effect on weight and no tendency to cause hypoglycemia
- The main clinical effect of DPP4 inhibitors is on fasting glucose levels, leading to HbA1c reductions of 0.5% to 1.0%

- *Diabetes Care*. 2011;34(suppl 2):S276–S278./*Diabetes Metab*. 2012;38:89–101.

DPP4 Inhibitors

- All agents in this class are remarkably well tolerated, with an adverse effect profile similar to that of placebo
- Postmarketing cases of pancreatitis have been reported, and DPP4 inhibitors are contraindicated for use by patients with a prior history
- In cardiovascular outcome trials, there was an increased risk for heart failure hospitalization with saxagliptin but no increased risk was demonstrated for sitagliptin or lingliptin
- Serious hypersensitivity reactions have been reported, but causality has not been substantiated because of the rarity of events.
- *Clin Ther*. 2014;36:2072–2079./*Am Heart J*. 2011;162:620–626

DPP4 Inhibitors (Patient selection)

- DPP-4 inhibitors may be used as add-on therapy for patients with type 2 diabetes who need modest, additional glucose lowering.
- They are not the preferred agents for patients with cardiovascular or kidney disease, because they do not impart protective effects on cardiovascular and kidney outcomes
- DPP-4 inhibitors may be a good option for glucose-lowering therapy particularly in patients at high risk of hypoglycemia, including older patients and those with chronic kidney disease
- DPP-4 inhibitors are not used as initial therapy for most patients with type 2 diabetes.

- Diabetes Ther 2014; 5:1./Diabetes Obes Metab 2018; 20:1972.

DPP4 Inhibitors (Contraindications and precautions)

- DPP-4 inhibitors should not be initiated in patients with a history of pancreatitis
- Acute pancreatitis has been reported in association with DPP-4 inhibitors, but data are insufficient to determine a causal relationship
- Alogliptin and vildagliptin have been associated with liver toxicity and require additional monitoring during treatment. For patients with underlying liver disease, an alternative DPP-4 inhibitor should be selected
- Patients who develop a hypersensitivity reaction to any DPP-4 inhibitor should not be treated with another agent in this class
- Saxagliptin and alogliptin have been associated with an increased risk of hospitalization for HF.
- If circumstances require use of DPP-4 inhibitor therapy, sitagliptin or linagliptin should be selected.

DPP4 Inhibitors(Monitoring)

- Prior to initiation of any DPP-4 inhibitor, serum creatinine should be measured for calculation of eGFR. Thereafter, calculated eGFR should be monitored every three to six months in patients with eGFR ≤45 mL/min/1.73 m^2 and approximately every 6 to 12 months in those with eGFR >45 mL/min/1.73 m^2
- Liver (vildagliptin and alogliptin only) : liver biochemical tests should be evaluated prior to initiation of either agent and at three-month intervals during the first year of therapy

Classes of Agents	Route of Delivery	Mechanism of Effect on Glucose	Basal Glucose Control	Prandial Glucose Control	Weight	BP Control	CV Risk Reduction	CKD Protection
Biguanide	Oral	↓ hepatic glucose production	+++	+	↓	+	+	↔
Sulfonylurea	Oral	↑ insulin secretion	+++	++	↑	↔	↔	↔
Thiazolidinedione	Oral	↓ insulin resistance	+++	++	↑	+	±+	↔
DPP4 inhibitor	Oral	↑ insulin, decrease glucagon	++	+	↔	↔	↔	↔
α-Glucosidase inhibitor	Oral	Delay carbohydrate absorption	+	+++	↓	↔	+	↔
SGLT inhibitor	Oral	↑ renal clearance of glucose, sodium	++	+	↓↓	++	+++	+++
Bile-acid sequestrant	Oral	Delay carbohydrate absorption?	+	+	↔	↔	?	?
Dopamine agonist	Oral	↓ insulin resistance	+	+	↓	+	?	?
Basal insulin	SC	↑ insulin availability	+++	+	↑	↔	↔	↔
Rapid-acting insulin	SC	↑ insulin availability with meals	↔	+++	↑	↔	↔	↔
GLP1 receptor agonist	SC (1 oral)	↑ insulin, ↓ glucagon, slow gastric emptying	+++	+++	↓↓↓	++	++	++
GLP1/GIP dual receptor agonist	SC	↑ insulin, ↓ glucagon, ↑ insulin sensitivity, ↓ gastric emptying	+++	+++	↓↓↓↓	++	?	?
Amylin receptor agonist	SC	↓ glucagon, slow gastric emptying	+	+++	↓↓	↔	?	?

BP, blood pressure; *CKD,* chronic kidney disease; *CV,* cardiovascular; *GIP,* glucose-dependent insulinotropic polypeptide; *GLP1,* glucagon-like peptide-1; *SC,* subcutaneous; *SGLT,* sodium-glucose cotransporter.

pharmacokinetics and pharmacodynamics of five DPP-4 inhibitors

Drug	Half-Life (t½)	Metabolism	Excretion	Dosing Frequency	Renal Dose Adjustment	Use in Hepatic Impairment
Sitagliptin	~12 hours	Minimal (CYP3A4, CYP2C8)	Primarily renal (~80%)	Once daily	Yes	Use with caution; no adjustment in mild/moderate
Saxagliptin	~2.5 h (parent), 3 h (active)	Hepatic (CYP3A4/5)	Renal (~75%)	Once daily	Yes	Use with caution; avoid in severe impairment
Linagliptin	>100 hours	Minimal hepatic	Biliary (~80%)	Once daily	No	Safe; no adjustment needed even in hepatic failure
Alogliptin	~21 hours	Minimal	Primarily renal (~76%)	Once daily	Yes	Use with caution; no adjustment in mild/moderate
Vildagliptin	~1.5–3 hours	Hydrolysis (non-CYP)	Renal (~85%)	Once or twice daily	Yes	Not recommended in hepatic impairment

DPP-4 inhibitor dosing

DDPI	Normal kidney function	Impaired kidney function
Linagliptin	5 mg once daily	No dose adjustment needed
Sitagliptin	100 mg once daily	***eGFR 30 to <45 mL/min/1.73 m²:***50 mg once daily ***eGFR <30 mL/min/1.73 m² or dialysis:*** 25 mg once daily

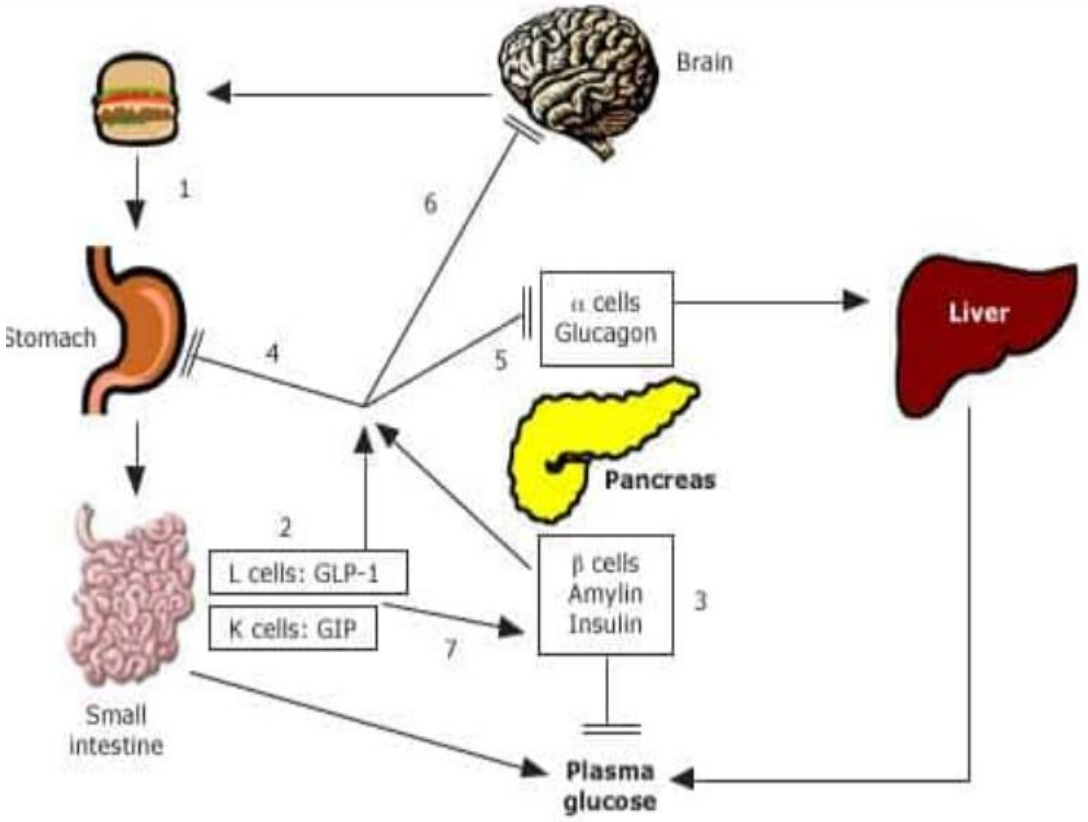
DPP4 Inhibitors(summary)

- The weight neutrality, lack of hypoglycemia, broad applicability, tolerability, and ease of use of DPP4 inhibitors are appealing properties

- Consequently, they have been widely used despite their relatively weak glucose-lowering power that is partly dependent on retained β-cell function

GLP1 Receptor Agonists

- **GASTROINTESTINALPEPTIDES:** GLP-1 and GIP are "incretin" hormones that link the absorption of nutrients from the gastrointestinal tract with pancreatic hormone secretion.
- They are released in the setting of a meal, after the ingestion and absorption of glucose, protein, and fat
- Metabolism 2014; 63:9./Obes Metab 2021; 23



GLP1 Receptor Agonists

	GLP-1	GIP
Site of synthesis	Small intestinal L cells	Small intestinal K cells
Glucose-dependent stimulation of insulin secretion	Yes	Yes
Reduction of gastric emptying	Yes	No effect
Reduction of inappropriate glucagon secretion	During euglycemia or hypoglycemia: No effect During hyperglycemia: Suppresses glucagon	During euglycemia or hypoglycemia: Stimulates glucagon During hyperglycemia: No effect
Weight loss	Yes	Yes

GLP1 Receptor Agonists(Patient selection)

- They are appropriate in certain clinical settings that include the following:

  - Presence of ASCVD

  - A1C above goal (≥1.5 percent above target)

  - Primary treatment goals of body weight loss or avoidance of hypoglycemia

  - Presence of chronic kidney disease –SGLT2 inhibitors are generally preferred, but a GLP-1 receptor agonist may be used , if SGLT2inhibitors are contraindicated or if additional glucose lowering is needed
  - Cost and gastrointestinal side effects may be barriers to use of GLP-1-based therapies

Diabetologia 2022; 65:1925./Diabetes Care 2024; 47:S158.

Definition of ASCVD

Clinical ASCVD Includes:

- Acute coronary syndromes (ACS) — unstable angina or myocardial infarction (STEMI/NSTEMI)
- History of myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization (PCI, CABG, carotid, peripheral)
- Stroke or transient ischemic attack (TIA) of atherosclerotic origin
- Peripheral arterial disease (PAD) presumed to be of atherosclerotic origin
- Aortic atherosclerotic disease (such as abdominal aortic aneurysm)

AHA/ACC

GLP1 Receptor Agonists(Contraindications and precautions)

- GLP-1 receptor agonist-based therapies should not be used in patients with:
- A history of pancreatitis.
- Type 1 diabetes. Some of the salutary effects of these agents are independent of islet cell function (eg, decreased glucagon, weight loss, cardiovascular and kidney protection) and might benefit specific individuals with type 1 diabetes
- All GLP-1-based therapies slow gastric emptying :short-acting should not be used in patients with gastrointestinal disease .Long-acting GLP-1 receptor agonists should be used with caution in those with gastroparesis.
- N Engl J Med 2023; 389:958./J Clin Endocrinol Metab 2023; 109:279.

GLP1 Receptor Agonists *(*Contraindications and precautions*)*

- Liraglutide, dulaglutide, exenatide once weekly, semaglutide (injectable or oral), and tirzepatid Should not be used in patients with a personal or family history of medullary thyroid cancer
- Exenatide (twice daily) should not be used in patients with creatinine clearance <30 mL/min.
- Exenatide (once-weekly formulation) should not be used in patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2.
- Lixisenatide should not be used in patients with eGFR <30 mL/min/1.73 m^2
- Liraglutide should be used with caution in patients with kidney impairment

GLP1 Receptor Agonists(Administration)

- Most GLP-1 receptor agonists are initiated at a low dose and then slowly advanced to avoid adverse gastrointestinal side effects, which are relatively common, usually affecting from 15 to 45 percent of patients. Gastrointestinal side effects may be attenuated somewhat with longer-acting agents, although high-quality comparative studies have not been performed.

Types and Generic Names (Brand Names)	Administration	Main Effects	Contraindications	Adverse Effects
Short-acting GLP1 agonist				
Exenatide (Byetta)	5–10 mcg bid before breakfast and dinner	Postprandial glucose control and weight loss	T1D DKA Pancreatitis History of medullary carcinoma	Nausea, diarrhea, abdominal pain Pancreatitis?
Lixisenatide (Adlyxin)	10–20 mcg qd before breakfast			
Long-acting GLP1 agonist				
Liraglutide (Victoza)	6.0–1.8 mcg daily	Basal glucose control and weight loss	T1D DKA Pancreatitis History of medullary carcinoma	Nausea, diarrhea, abdominal pain Pancreatitis?
Dulaglutide (Trulicity)	0.75–4.5 mg weekly			
Extended-release exenatide (Bydureon)	2 mg weekly			
Semaglutide (Ozempic)	0.5–2.0 mg weekly			
GIP/GLP1 dual agonist				
Tirzepatide (Mounjaro)	2.5–15 mg weekly	Basal glucose control and weight loss	T1D DKA Pancreatitis Medullary thyroid carcinoma	Nausea, diarrhea, abdominal pain Pancreatitis?
Fixed-dose GLP1/insulin combination				
Liraglutide/degludec (Xultophy)	Daily, titrated	Glucose and weight control	T1D DKA Pancreatitis History of medullary carcinoma	Hypoglycemia Nausea, diarrhea, abdominal pain Pancreatitis?
Lixisenatide/glargine (Soliqua)	Daily before breakfast, titrated			

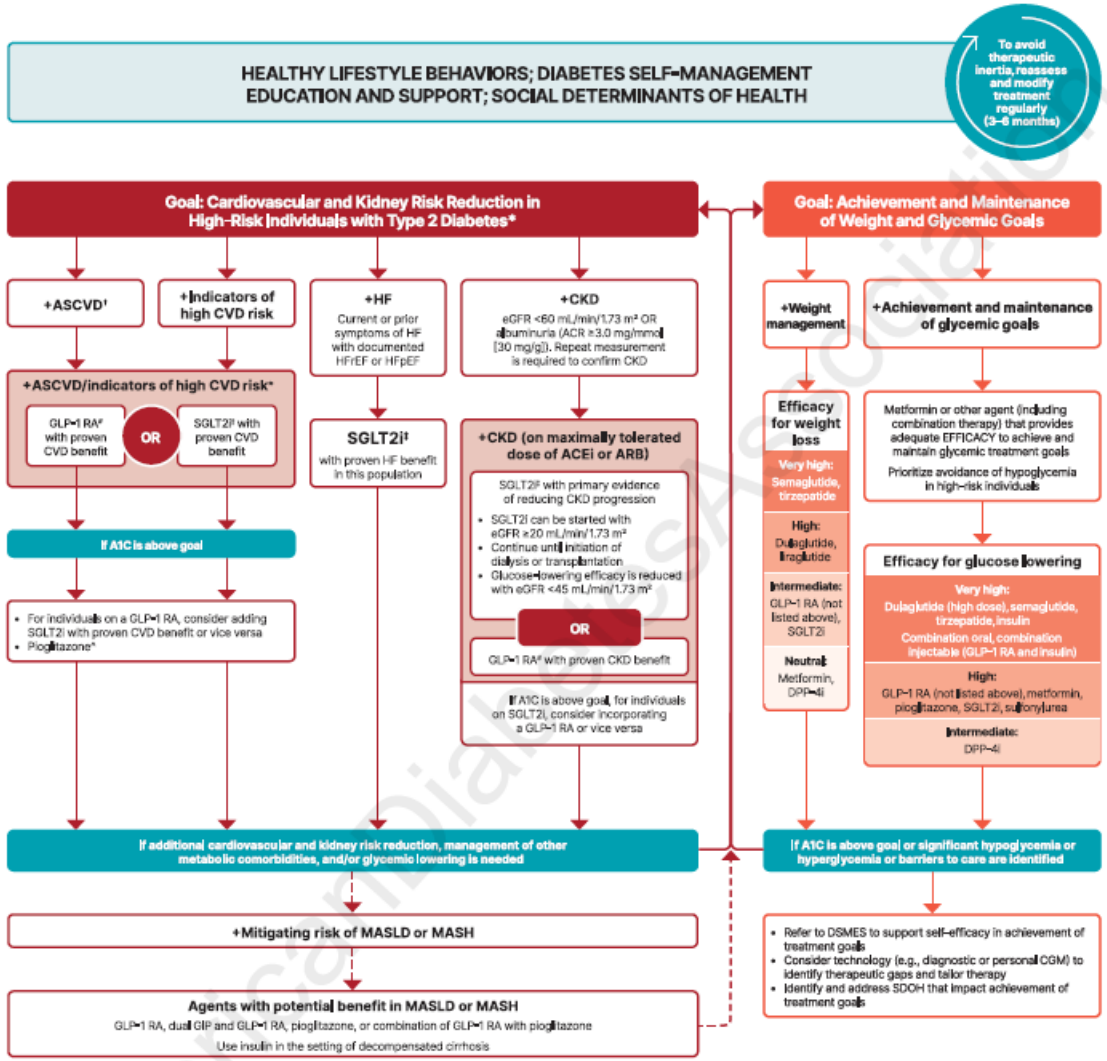
GLP-1 Receptor Agonists – Pharmacokinetic Comparison

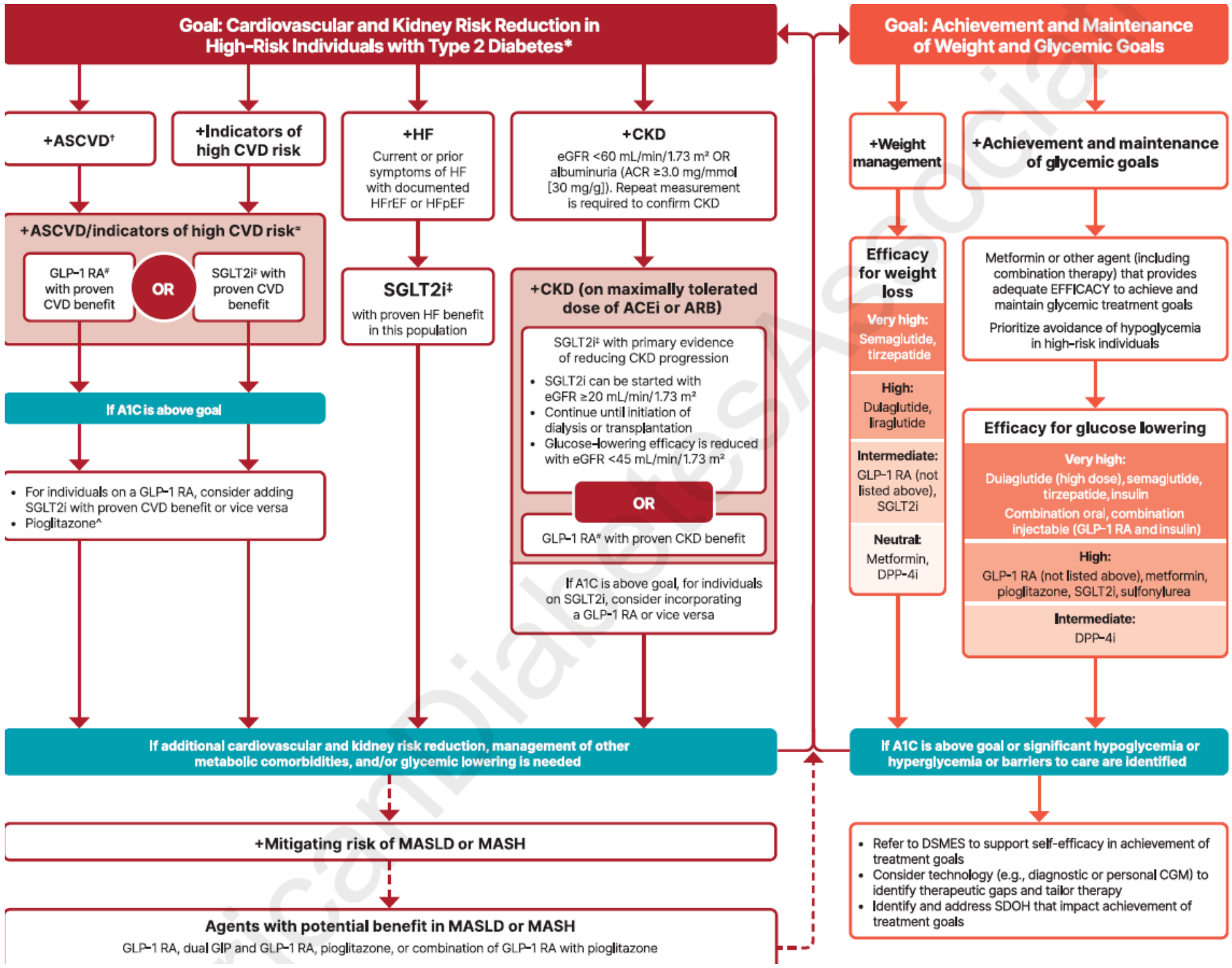
Drug	Half-Life (t½)	Dosing Frequency	Route	Renal Adjustment	Hepatic Impairment Use
Exenatide (BID)	~2.4 hours	Twice daily	Subcutaneous	Avoid if CrCl <30 mL/min	Limited data; caution advised
Liraglutide	~13 hours	Once daily	Subcutaneous	No adjustment needed	Can be used; monitor closely
Dulaglutide	~5 days	Once weekly	Subcutaneous	No adjustment needed	Can be used with caution
Semaglutide (inj.)	~1 week	Once weekly	Subcutaneous	No adjustment needed	Safe to use; no dose adjustment
Semaglutide (oral)	~1 week (absorption limited)	Once daily	Oral	No adjustment needed	Use with caution in hepatic disease
Mounjaro (tirzepatide)	~5 days	Once weekly	Subcutaneous	No adjustment needed	Limited data, use with caution

GLP-1 Receptor Agonist Available in Iran

Medication	Starting Dose	Titration Schedule	Total Pen Dose (Max Dose)	Pen Content (Formulation)	Pen Type / Notes
Mounjaro (Tirzepatide)	2.5 mg once weekly	Increase by 2.5 mg every 4 weeks as tolerated	Max: 15 mg once weekly	Single-dose prefilled pens (2.5, 5, 7.5, 10, 12.5, 15 mg)	Single-use pens (one dose per pen)
Soliqua 100/50 (Insulin glargine + Lixisenatide) – Peach pen	Usually start 10–15 units once daily (based on prior therapy)	Adjust by 2–4 units every 3–7 days per fasting glucose	Range: 10–40 units/day	100 units/mL insulin glargine + 50 µg/mL lixisenatide	Multi-dose 3 mL pen; delivers 10–40 U
Soliqua 100/33 (Insulin glargine + Lixisenatide) – Olive pen	Usually start 15–30 units once daily	Adjust by 2–4 units every 3–7 days per glucose	Range: 30–60 units/day (max 60 U)	100 units/mL insulin glargine + 33 µg/mL lixisenatide	Multi-dose 3 mL pen; delivers 30–60 U
Semaglutide (Ozempic)	0.25 mg once weekly × 4 weeks	Then 0.5 mg; may increase to 1 mg after ≥4 wk; may increase up to 2 mg weekly if needed	Max for T2DM: 2 mg once weekly	Multi-dose pens with 0.25, 0.5, 1.0, 2.0 mg dose options	Multi-dose pen with dial selector
Semaglutide (Wegovy)	0.25 mg once weekly × 4 weeks	0.25 → 0.5 → 1.0 → 1.7 → 2.4 mg (each step every 4 weeks)	Max for obesity: 2.4 mg once weekly	Prefilled pens for each dose step (0.25–2.4 mg)	Single-use pens for weekly titration
Liraglutide (Victoza)	0.6 mg once daily	Increase to 1.2 mg after 1 week; may increase to 1.8 mg daily	Max: 1.8 mg once daily	3 mL pen, 6 mg/mL (18 mg total)	Multi-dose pen (up to 6 doses)

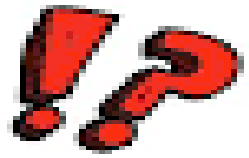
PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES




Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
Goal: Achievement and Maintenance of Weight and Glycemic Goals
+ASCVD†
+Indicators of high CVD risk
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD
+Weight management
+Achievement and maintenance of glycemic goals
+ASCVD/indicators of high CVD risk=
GLP-1 RA# with proven CVD benefit
OR
SGLT2i‡ with proven CVD benefit
SGLT2i‡ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi or ARB)
SGLT2i‡ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
Continue until initiation of dialysis or transplantation
Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m²
OR
GLP-1 RA# with proven CKD benefit
If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa
Efficacy for weight loss
Very high: Semaglutide, tirzepatide
High: Dulaglutide, liraglutide
Intermediate: GLP-1 RA (not listed above), SGLT2i
Neutral: Metformin, DPP-4i
Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals
Efficacy for glucose lowering
Very high: Dulaglutide (high dose), semaglutide, tirzepatide, insulin
Combination oral, combination injectable (GLP-1 RA and insulin)
High: GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
Intermediate: DPP-4i
If A1C is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone^
If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed
If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified
+Mitigating risk of MASLD or MASH
Refer to DSMES to support self-efficacy in achievement of treatment goals
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of treatment goals
Agents with potential benefit in MASLD or MASH
GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA with pioglitazone

Medication (route of administration)	Glucose-lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment for dulaglutide, liraglutide, or semaglutide • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	• Thyroid C-cell tumors identified in rodents; human relevance not determined. • Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. • Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. • Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]). • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). • GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	
DPP-4 Inhibitors (oral)	Intermediate	No	Neutral	Neutral	Neutral (potential risk: saxagliptin)	Neutral	• Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin) • No dose adjustment required for linagliptin	Unknown	• Pancreatitis has been reported, but causality has not been established. Discontinue if pancreatitis is suspected. • Postmarketing concerns about joint pain (consider discontinuing if debilitating and other treatment options are feasible) and bullous pemphigoid (discontinue if suspected).

Thank you

Any question? 

GLP-1 Receptor Agonist Available in Iran

Medication	Starting Dose	Titration Schedule	Total Pen Dose (Max Dose)	Pen Content	Pen Type
Mounjaro (Tirzepatide)	2.5 mg once weekly	Increases 2.5 mg every 4 weeks	15 mg once seekly	Single-dose prefilled pens	Single-dose pens (one dopen
Soliqua (iGiarLixi) (low-range pen (10-40')	Start commonly 10 units once daily (regionaily may be i5 U)	Adjust insulin by 2-4 U every 3-7 days based on glucose	10-40 U [illegible]	100 U/mL in-suiin glargine + 25 µg/ml. lixisenatide	Multi-dose pens (emL: [illegible]-100 U
Soliqua (iGlarLixi) (high-range pen (30-50')	Start commonly 15 units once daily (very common)	Adjust insulin by 2-4 U every 3-7 days based on glucose	30-60 U [illegible]	100 U/mL insulln glarh [illegible] 33 µg/ml. lixisenatide	Multi-dose pens (emL: [illegible]-40
Semaglutide (Ozempic)	0.25 mg once week-ly for 4 weeks (inifiation)	0.25 mg-0.5 mg after 4 weeks, increase a mg after ≧4 more w weeks	For [illegible] 0 mg weekly	Multi-dose pens formula ted for step-ped up titrati-on ([illegible]	Multi-dose pen [illegible] pen anom [illegible] doses
Semaglutide (Wegovy)	0.65 mg once wee-day [illegible]	0.25 → 0.5 → 1.0 → 1. 7 → 2.4 mg once we	Max dose [illegible] oncet weekly	Multi-dose pens dose-selector (fach pen provides several weekly doses	Multi-dose pen lup to 6 doses per p[illegible]
Liraglutide (Victoza)	0.6 mg once daily	1.8 mg once daily [illegible]	3 mL pen 6 mg total		

GLP-1 Receptor Agonist Available in Iran

Medication	Starting Dose	Titration Schedule	Total Pen Dose (Max Dose)	Pen Content (Formulation)	Pen Type / Notes
Mounjaro (Tirzepatide)	2.5 mg once weekly	Increase by 2.5 mg every 4 weeks as tolerated	Max: **15 mg once weekly**	Single-dose prefilled pens (2.5, 5, 7.5, 10, 12.5, 15 mg)	Single-use pens (one dose per pen)
Soliqua 100/25 (Insulin glargine + Lixisenatide) – *Olive pen*	Usually start **10–15 units once daily** (based on prior therapy)	Adjust by 2–4 units every 3–7 days per fasting glucose	Range: **10–40 units/day**	100 units/mL insulin glargine + **25 µg/mL lixisenatide**	Multi-dose 3 mL pen; delivers **10–40 U**
Soliqua 100/33 (Insulin glargine + Lixisenatide) – *Peach pen*	Usually start **15–30 units once daily**	Adjust by 2–4 units every 3–7 days per glucose	Range: **30–60 units/day** (max 60 U)	100 units/mL insulin glargine + **33 µg/mL lixisenatide**	Multi-dose 3 mL pen; delivers **30–60 U**
Semaglutide (Ozempic)	0.25 mg once weekly × 4 weeks	Then 0.5 mg; may increase to 1 mg after ≥4 wk; may increase up to **2 mg weekly** if needed	Max for T2DM: **2 mg once weekly**	Multi-dose pens with 0.25, 0.5, 1.0, 2.0 mg dose options	Multi-dose pen with dial selector
Semaglutide (Wegovy)	0.25 mg once weekly × 4 weeks	0.25 → 0.5 → 1.0 → 1.7 → **2.4 mg** (each step every 4 weeks)	Max for obesity: **2.4 mg once weekly**	Prefilled pens for each dose step (0.25–2.4 mg)	Single-use pens for weekly titration
Liraglutide (Victoza)	0.6 mg once daily	Increase to 1.2 mg after 1 week; may increase to **1.8 mg daily**	Max: **1.8 mg once daily**	3 mL pen, 6 mg/mL (18 mg total)	Multi-dose pen (up to 6 doses)

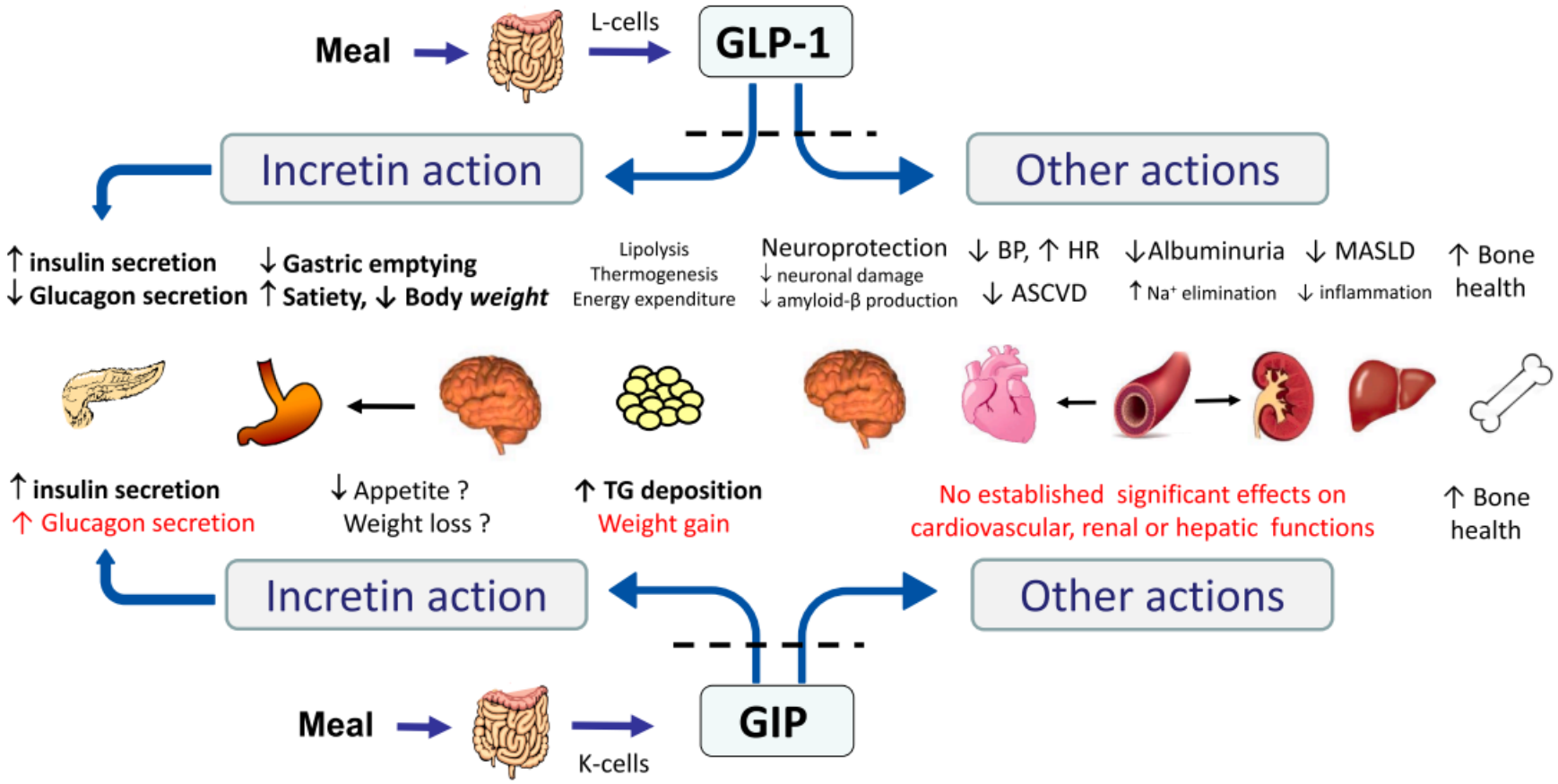
GLP-1 Receptor Agonist Available in Iran

Medication	Starting Dose	Titration Schedule	Total Pen Dose	Pen Content	Pen Type
Mounjaro (Tirzepatide)	2.5 mg weekly	Increase by 2.5 mg every 4 weeks up to 15 mg	2.5–15 mg per pen	0.5 mL (varies by dose)	Single-dose pen
Soliqua 10/40	15 units daily	Titrate by 2–4 units weekly based on FPG	300 units	3 mL	Multi-dose pen
Soliqua 30/60	30 units daily	Titrate by 2–4 units weekly based on FPG	300 units	3 mL	Multi-dose pen
Semaglutide (Ozempic)	0.25 mg weekly	0.25 mg × 4 weeks → 0.5 mg × 4 weeks → 1 mg	2 mg or 4 mg total	1.5 mL or 3 mL	Multi-dose pen
Semaglutide (Wegovy)	0.25 mg weekly	Increase every 4 weeks up to 2.4 mg weekly	0.25–2.4 mg per pen	0.5–2.4 mL	Single-dose pen
Liraglutide (Victoza)	0.6 mg daily	Increase to 1.2 mg after 1 week, then 1.8 mg	18 mg total	3 mL	Multi-dose pen

GLP1 Receptor Agonists

- GLP1 receptor agonists are homologs or analogues of human GLP1 that have substantially changed the landscape of T2D therapy
- Like GLP1 itself, these agents potentiate insulin secretion in response to rising glucose levels, suppress postprandial glucagon secretion, delay gastric emptying, and promote satiety.
- As with insulins, GLP1 agonists divide logically into two groups: those that are short acting and those with longer duration of effects.

Diverse actions of GLP-1 and GIP with therapeutic significance



Classes and Specific Agents (Brand Names)	Commonly Used Dosages	Contraindications	Adverse Effects	% HbA_{1c} Reduction as First- or Second-Line Therapy
DPP4 inhibitor[a]				
Sitagliptin (Januvia)	25–100 mg qd	T1D, DKA	Hypersensitivity	0.5–1.0
Vildagliptin (Galvus)	50 mg qd or bid		Pancreatitis	
Saxagliptin (Onglyza)	2.5–5 mg qd		Arthralgias	
Linagliptin (Tradjenta)	5 mg qd			
Alogliptin (Nesina)	6.25–25 mg qd			

GLP-1 Receptor Agonist Available in Iran

Medication	Starting Dose	Titration Schedule	Total Pen Dose (Max Dose)	Pen Content	Pen Type
Mounjaro (Tirzepatide)	2.5 mg once weekly	Increase by 2.5 mg every 4 weeks	Max dose: 15 mg once weekly	Single-dose prefilled pens: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Single-dose pens (one dose per pen)
Soliqua (Insulin Glargine / Lixisenatide)	Start 15 units insulin glargine + 5 mcg lixisenatide daily	Adjust insulin dose by 2-4 units every 3-7 days based on glucose	Max dose: 60 units insulin + 20 mcg lixisenatide daily	100 units insulin + 33 mcg lixisenatide per mL (3 mL pen)	Multi-dose (up to 60 units per day)
Semaglutide (Ozempic)	0.25 mg once weekly	Increase to 0.5 mg after 4 weeks; may increase to 1 mg after another 4 weeks	Max dose: 2 mg once weekly	0.25 mg, 0.5 mg, 1 mg, 2 mg per pen	Multi-dose (4 doses per pen)
Liraglutide (Victoza)	0.6 mg once daily	Increase to 1.2 mg after 1 week; may increase to 1.8 mg daily	Max dose: 1.8 mg once daily	3 mL pen with 6 mg/mL (18 mg total)	Multi-dose (up to 6 doses per pen)

At Risk of ASCVD

Common *Risk Factors* (AHA/ACC list):

- **Age:** ≥40 years in men or ≥50 years in women increases baseline risk
- **Dyslipidemia:** LDL-C ≥160 mg/dL or non-HDL ≥190 mg/dL
- **Hypertension**
- **Diabetes mellitus** (especially with duration ≥10 years for T2DM or ≥20 years for T1DM)
- **Cigarette smoking**
- **Chronic kidney disease (CKD)**
- **Family history of premature ASCVD** (men <55, women <65)
- **Inflammatory diseases** (e.g., rheumatoid arthritis, lupus, psoriasis, HIV)
- **South Asian ancestry** (as an ethnicity-based risk enhancer

Risk Stratification (AHA/ACC Pooled Cohort Equation)

Risk Category	10-Year Risk %	Meaning / Recommendation
Low risk	<5%	Lifestyle only
Borderline risk	5–7.4%	Consider moderate statin if risk enhancers present
Intermediate risk	7.5–19.9%	Moderate or high-intensity statin recommended
High risk	≥20%	High-intensity statin indicated

GLP-1 Receptor Agonist Available in Iran

Medication	Starting Dose	Titration Schedule	Total Pen Dose (Max Dose)	Pen Content (Formulation)	Pen Type / Notes
Mounjaro (Tirzepatide)	2.5 mg once weekly	Increase by 2.5 mg every 4 weeks as tolerated	Max: 15 mg once weekly	Single-dose prefilled pens (2.5, 5, 7.5, 10, 12.5, 15 mg)	Single-use pens (one dose per pen)
Soliqua 100/25 (Insulin glargine + Lixisenatide) – Olive pen	Usually start 10–15 units once daily	Adjust by 2–4 units every 3–7 days per fasting glucose	Range: 10–40 units/day	100 units/mL insulin glargine + 25 µg/mL lixisenatide	Multi-dose 3 mL pen; delivers 10–40 U
Soliqua 100/33 (Insulin glargine + Lixisenatide) – Peach pen	Usually start 15–30 units once daily	Adjust by 2–4 units every 3–7 days per glucose	Range: 30–60 units/day (max 60 U)	100 units/mL insulin glargine + 33 µg/mL lixisenatide	Multi-dose 3 mL pen; delivers 30–60 U
Semaglutide (Ozempic)	0.25 mg once weekly × 4 weeks	Then 0.5 mg; may increase to 1 mg after 4 wk; may increase up to 2 mg if needed	Max for T2DM: 2 mg once weekly	Multi-dose pens with 0.25, 0.5, 1.0, 2.0 mg dose options	Multi-dose pen with dial selector
Semaglutide (Wegovy)	0.25 mg once weekly × 4 weeks	0.25 → 0.5 → 1.0 → 1.7 → 2.4 mg (each step every 4 weeks)	Max for obesity: 2.4 mg once weekly	Prefilled pens for each dose step (0.25–2.4 mg)	Single-use pens for weekly titration
Liraglutide (Victoza)	0.6 mg once daily	Increase to 1.2 mg after 1 week; may increase to 1.8 mg daily	Max: 1.8 mg once daily	3 mL pen, 6 mg/mL (18 mg total)	Multi-dose pen (up to 6 doses)