The last, not the least…

In the era of growing number of diabetes medications and new data, we should consider the below factors to select the proper component for each individual patient:

- Effectiveness
- Safety profiles
- Side effects
- Extra-glycemic effects
- Cardiovascular effects
- Our experience in handling
- Availability
- Patient preference
- Cost

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Need for an Early and Intensive Approach to Type 2 Diabetes Management

- **At diagnosis of type 2 diabetes:**

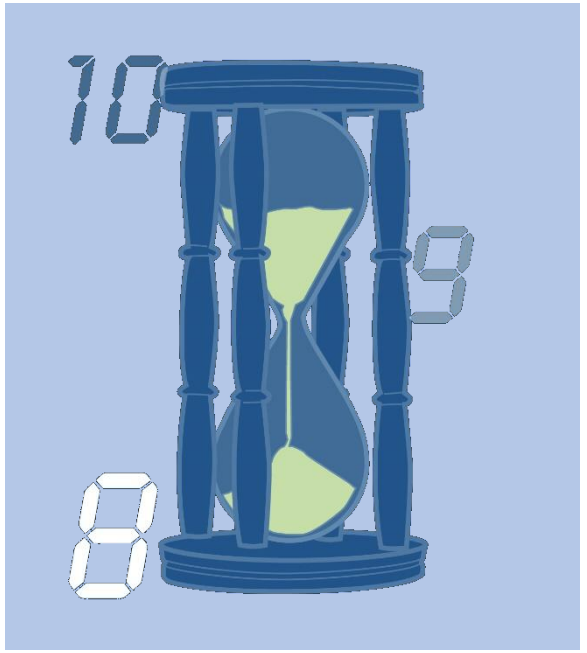
  Many of the patients already have diabetes complications. [1,2]

- **Current management:**

  One-thirds of patients do not achieve target HbA_1c [3]

  - In 2013–2016, 64% of adults with diagnosed diabetes met individualized A1C target levels in US.[3]

  Majority require polypharmacy to meet glycemic goals over time.[4]



1- JAMA. 2016;316(6). 2- J Diabetes Complications. 2018;32(1):34-40. 3-JAMA Intern Med. 2019. 4- Am J Manag Care. 2006;12(8):435-40.

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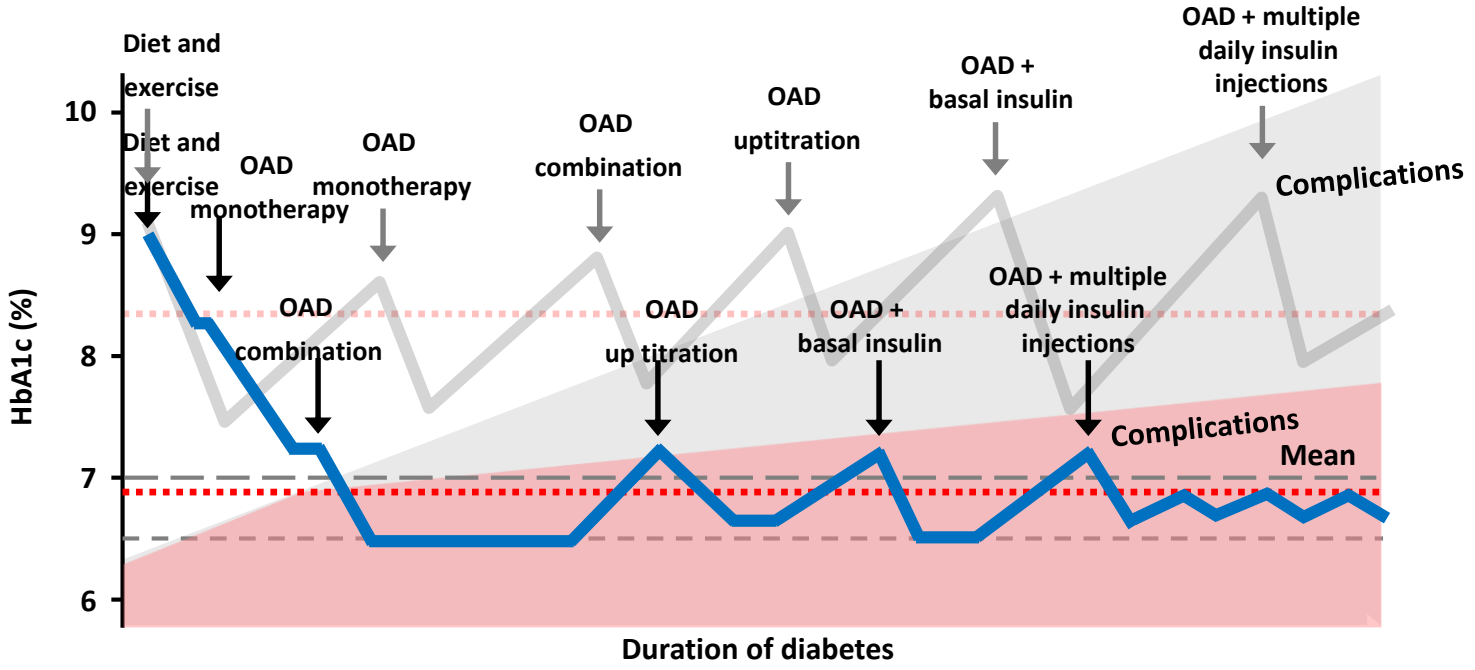
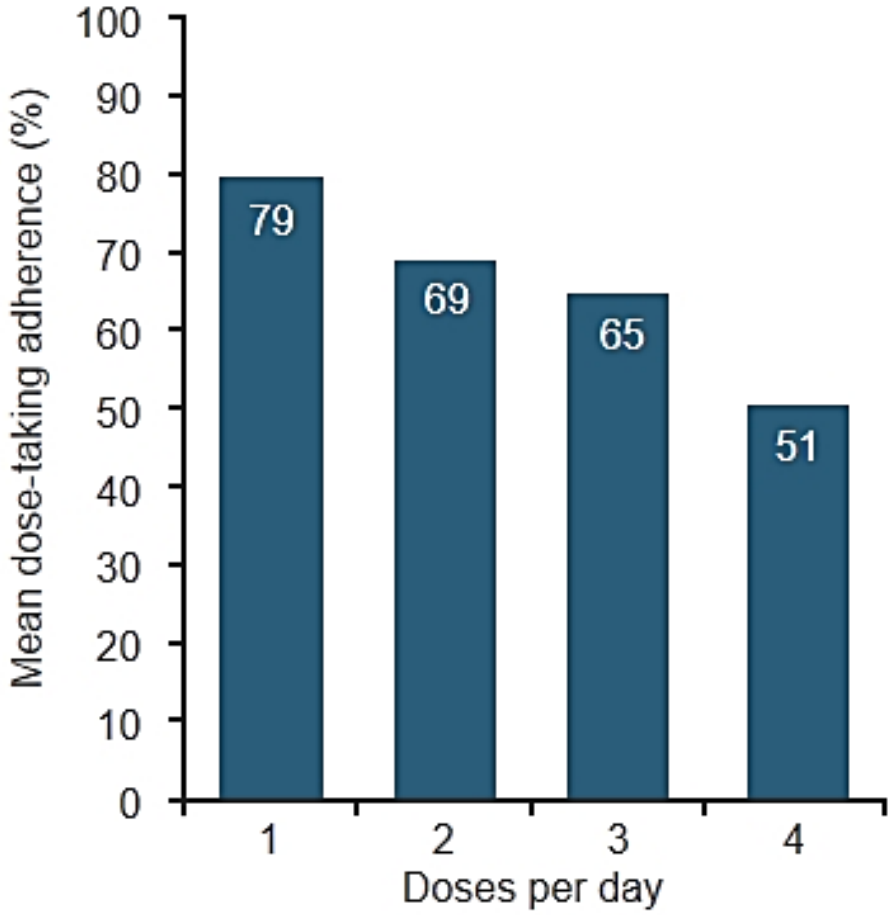
Improving Glycemic Control in T2DM Achieving Glycemic Goals Sooner May Reduce the Risk of Complications[1]



OAD = oral anti-diabetic

1. Int J Clin Pract 2005; 59:1345–1355. 2. BMJ 2000; 321:405–412.

Prescribed Number of Doses/Day Is Inversely Associated With Medication Adherence Across All Conditions[1]

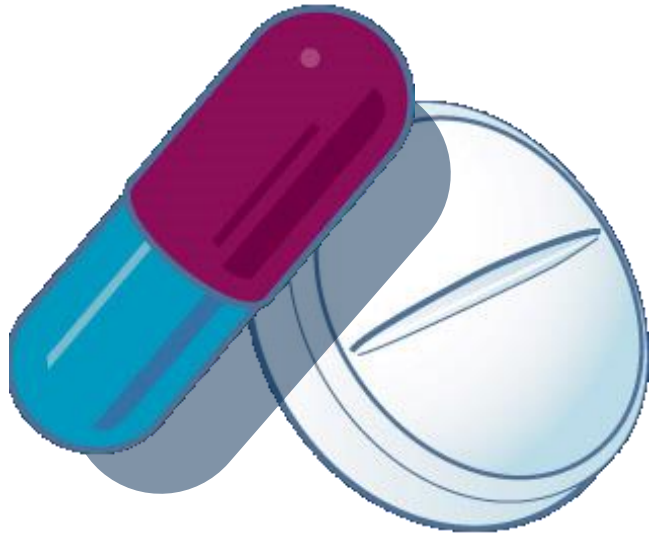


Dose-taking: taking the prescribed number of pills each day.

1- Clin Ther. 2001;23(8):1296-310.

Early Combination Therapy for T2DM Management[1]

- Ensure Prompter and Better Glycemic Control
- Improving patient's Adherence to Treatment
- Possibly Reducing Clinical Inertia
- More Opportunity to Address Individual Needs
- Reducing Risk of Diabetes Complications



1-Lancet. 2019;394(10208):1519-1529.

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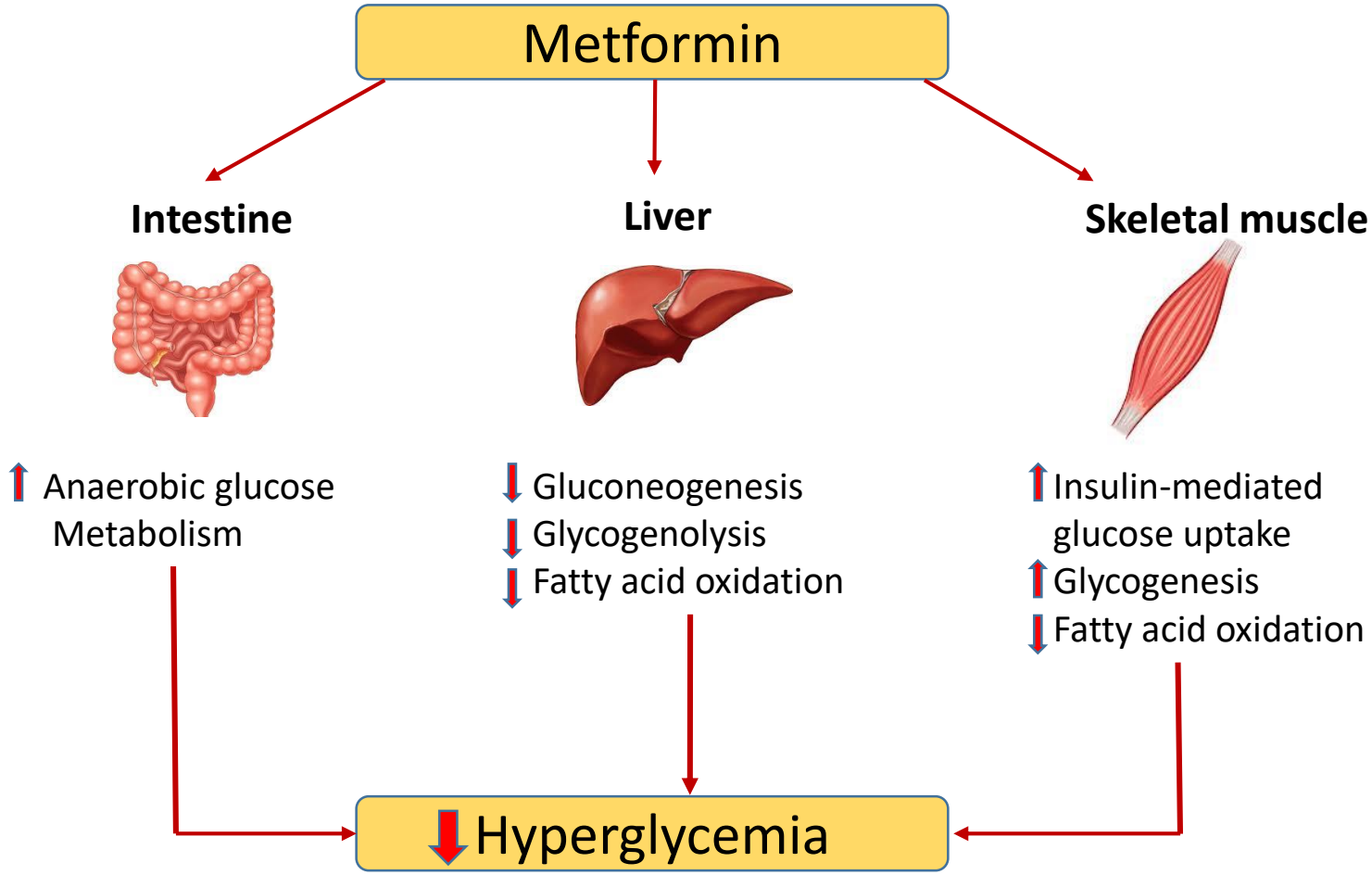
Metformin Targets the Pathophysiology of T2DM[1]



1-Diabetologia. 2017; 60(9): 1577–1585.

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DPP4-inhibitors Provide an Effective Pharmacological Approach in T2DM[1-4]

Ingestion of food

GI tract

Release of active incretins GLP-1 and GIP

Beta cells

Alpha cells

Glucose dependent ↑ Insulin

↑ Glucose uptake by peripheral tissue

↓ Blood glucose in fasting and postprandial states

Linagliptin (DPP-4 inhibitor)

DPP-4 enzyme

Glucose-dependent ↓ Glucagon

↓ Hepatic glucose production

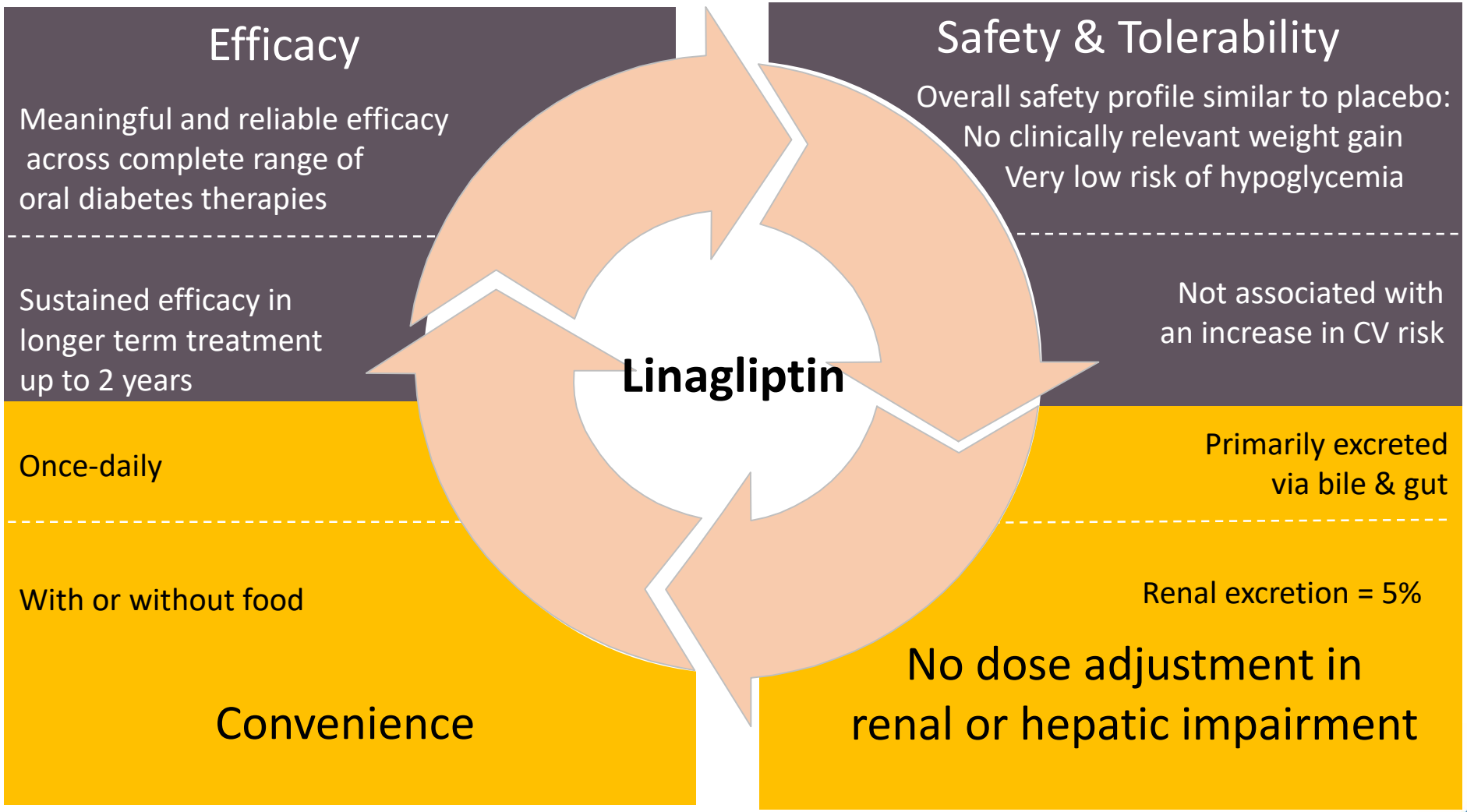
Inactive GLP-1

Inactive GIP

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.

1-Endocrinology. 2004 ;145(6):2653-9. 2- Lancet. 2002 ;359(9309):824-30. 3-Curr Diab Rep. 2003;3(5):365-72. 4-Buse JB et al. In Williams Textbook of Endocrinology. 10th ed., 2003:1427–1483.

Linagliptin clinical profile[1]



1- Linagliptin FDA Label; 2017, Reference ID: 4137622.

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Dosage Forms and Strengths[1]:

- 2.5 mg linagliptin/500 mg metformin HCl

- 2.5 mg linagliptin/1000 mg metformin HCl

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1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

Dosage and Administration[1]:

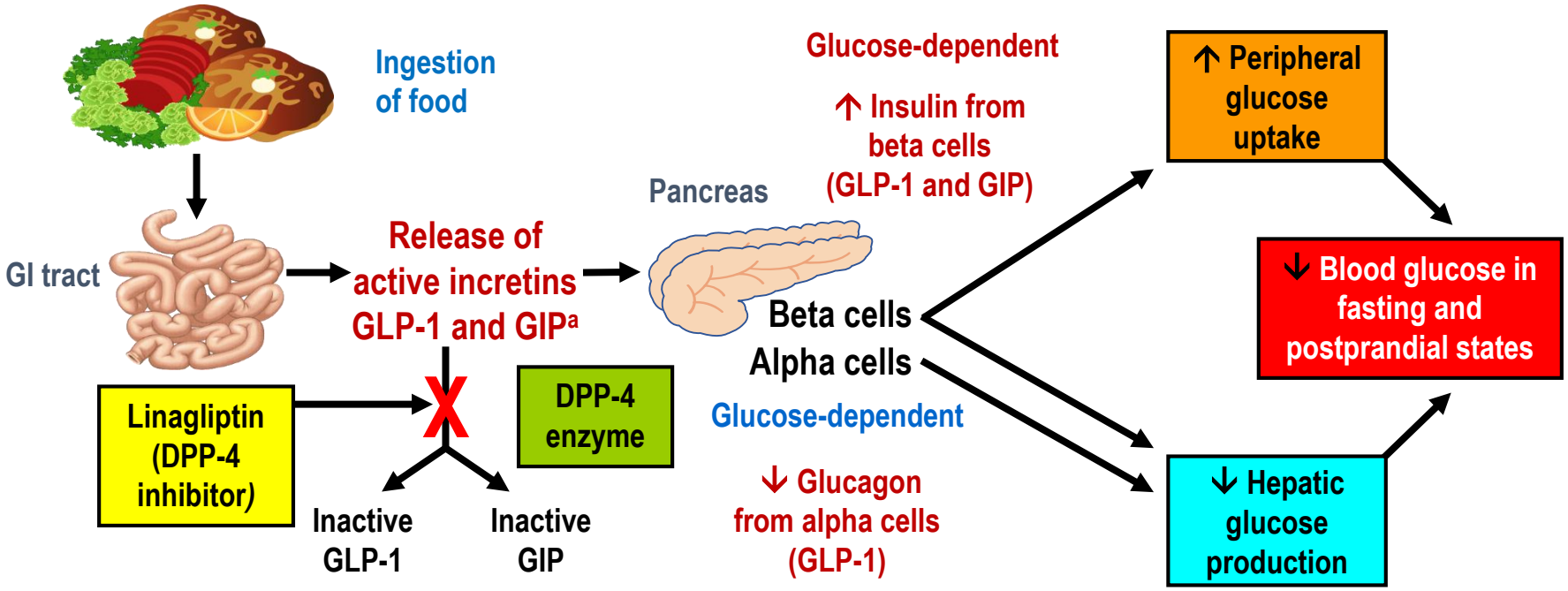
Individualize the starting dose of **LIROPRIM** based on the patient's current regimen.

Give **twice** daily **with meals**, with gradual dose escalation to reduce the gastrointestinal effects due to metformin.

The maximum recommended dose is **2.5 mg linagliptin/1000 mg metformin HCl** twice daily.

1- Linagliptin and Metformin FDA Label.;2019, Reference ID: 4457960.

DPP-4 inhibitors Provide an Effective Pharmacological Approach in T2DM [1-4]



By increasing and prolonging active incretin levels, Linagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

DPP-4=dipeptidyl peptidase 4; GI=gastrointestinal; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.
[a]Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

1. Kieffer TJ et al. Endocr Rev. 1999;20(6):876–913. 2. Ahrén B. Curr Diab Rep. 2003;3(5):365–372. 3. Drucker DJ. Diabetes Care. 2003;26(10):2929–2940, 4. Holst JJ. Diabetes Metab Res Rev. 2002;18(6):430–441.

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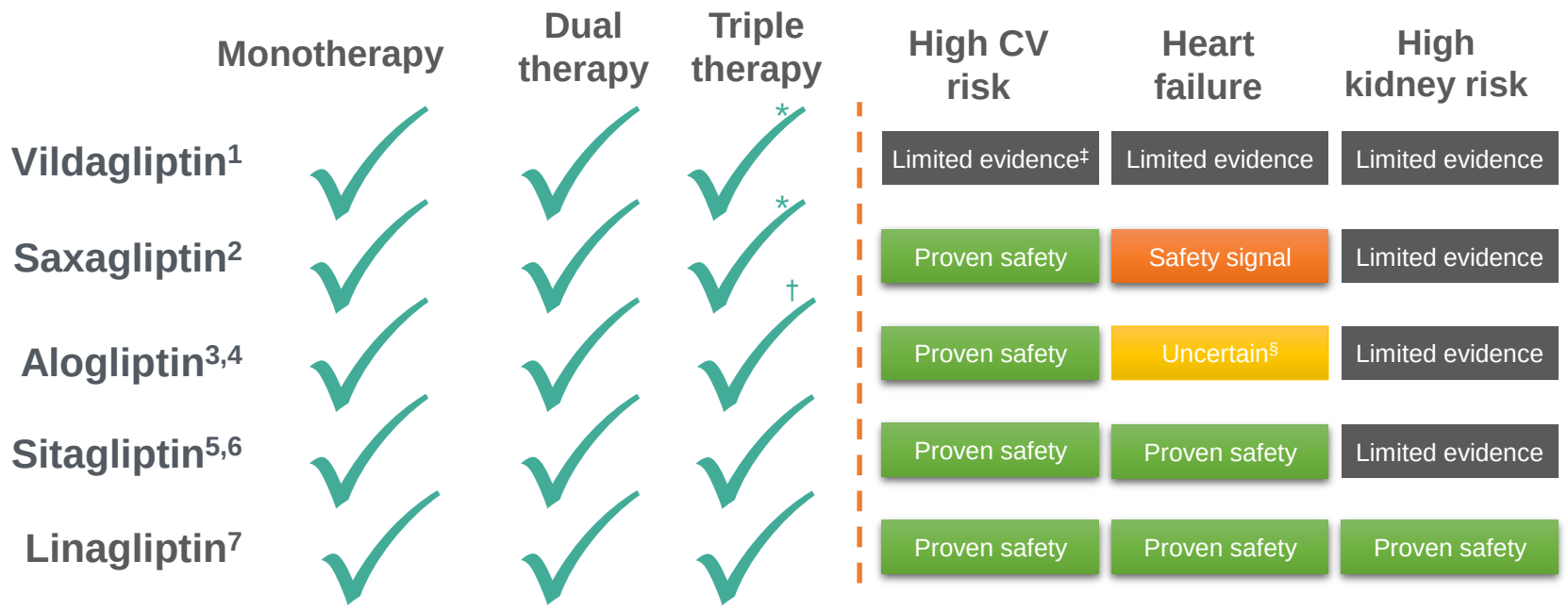
Linagliptin has the broadest clinical evidence in the DPP-4i class



*No CVOT of vildagliptin has been conducted; †Not studied in combination with metformin and thiazolidinedione(s); ‡Not studied in combination with metformin and sulphonylurea(s); §Numerical, non-significant increase in hospitalisation for heart failure, CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

1. Novartis Europharm Ltd. Galvus® (vildagliptin) summary of product characteristics; 2. Scirica B *et al. N Engl J Med* 2013;369:1317; 3. White W *et al. N Engl J Med* 2013;369:1327; 4. Takeda Pharma A/S. Vipidia® (alogliptin) summary of product characteristics; 5. Green J *et al. N Engl J Med* 2015;373:232; 6. Engel SE *et al. Diabetes Obes Metab* 2017;19:1587; 7. Rosenstock J, et al. JAMA. 2018 Nov 9. doi: 10.1001/jama.2018.18269

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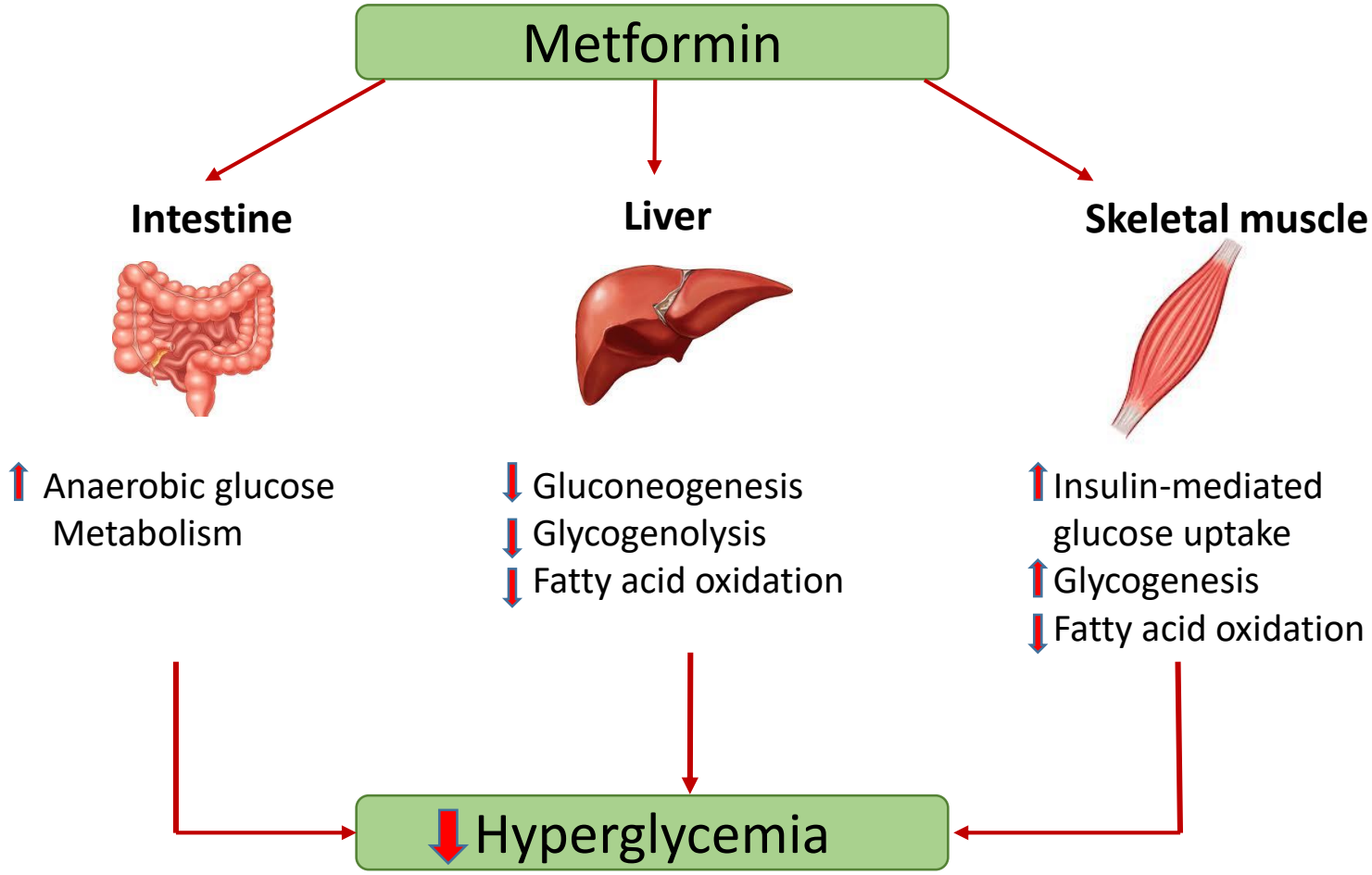
Metformin Targets the Pathophysiology of T2DM[1]



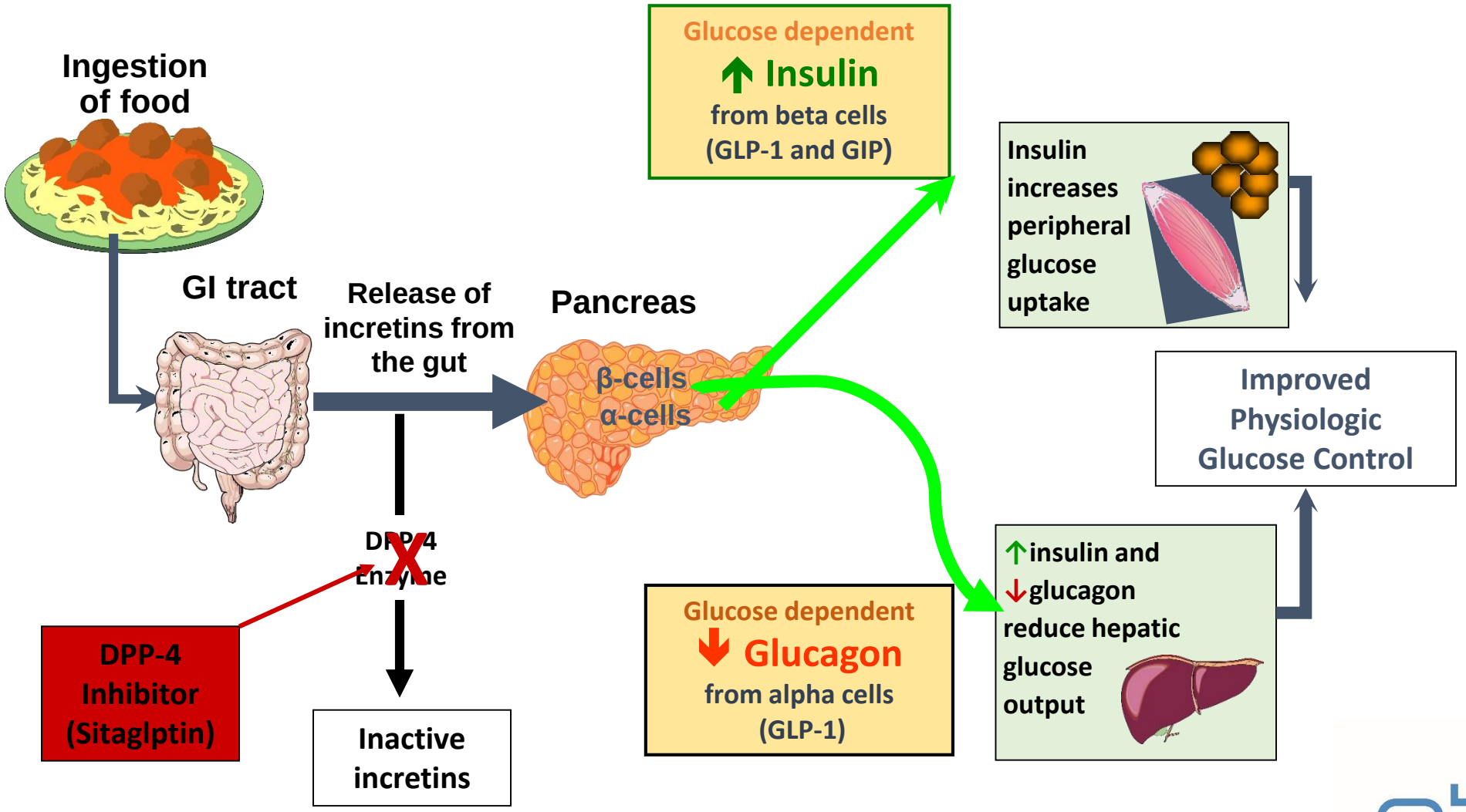
1-Diabetologia. 2017; 60(9): 1577–1585.

Gluconeogenesis: Gluconeogenesis is the metabolic process by which organisms produce sugars (namely glucose) for catabolic reactions from non-carbohydrate precursors.

Glycogenolysis is the breakdown of glycogen (n) to glucose-1-phosphate and glycogen (n-1). Glycogen branches are catabolized by the sequential removal of glucose monomers via phosphorolysis

Glycogenesis is the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage.

DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes[1-4]



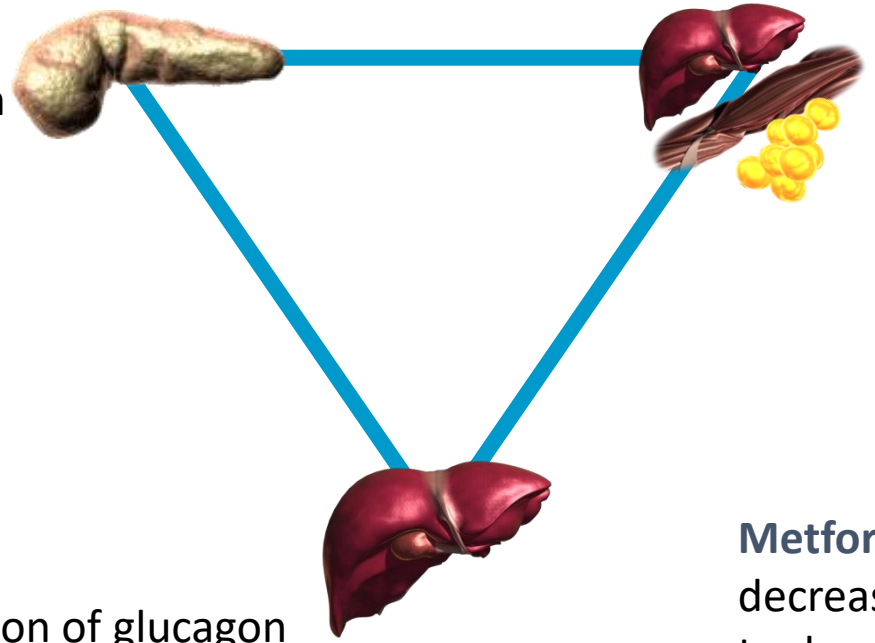
DPP-4 = dipeptidyl peptidase 4

1-Endocrinology. 2004 ;145(6):2653-9. 2- Lancet. 2002 ;359(9309):824-30; 3-Curr Diab Rep. 2003;3(5):365-72; 4-Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed., 2003:1427–1483.

Sitagliptin and Metformin Target the Core Metabolic Defects of Type 2 Diabetes

Beta-Cell Dysfunction

Sitagliptin
improves beta-cell function
increases insulin synthesis
and release.[1]



Insulin Resistance

Metformin
insulin- sensitizing [3–5]
(Liver, Muscle, Fat)

Sitagliptin
reduces HGO
through suppression of glucagon
from alpha cells.[2]

Hepatic Glucose Overproduction (HGO)

Metformin
decreases HGO by targeting the liver
to decrease gluconeogenesis and
glycogenolysis.[4]

1. Diabetes Care; 2006;29(12):2632–2637. 2- Curr Opin Endocrinol Diabetes Obes. 2007;14(2):98–107. 3- *Diabetes Care*. 1998;21(8):1301–1305.
4- *Ann Intern Med.* 2002;137(1):25–33. 5- *J Clin Invest.* 2001;108(8):1167–1174.

Gluconeogenesis: Gluconeogenesis is the metabolic process by which organisms produce sugars (namely glucose) for catabolic reactions from non-carbohydrate precursors.
Glycogenolysis is the breakdown of glycogen (n) to glucose-1-phosphate and glycogen (n-1). Glycogen branches are catabolized by the sequential removal of glucose monomers via phosphorolysis

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Sitagliptin: Once-Daily Dosing Administration[1]

Usual Dosing for Sitagliptin*

The recommended dose of Sitagliptin is 100 mg once daily as monotherapy or as combination therapy

Patients With Renal Insufficiency*,†

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis.

50 mg once daily	25 mg once daily
Moderate **eGFR greater than or equal to 30 mL/min/1.73 m2 to less than 45 mL/min/1.73 m2**	**Severe and ESRD‡** **eGFR less than 30 mL/min/1.73 m2 (including patients with end stage renal disease [ESRD] on dialysis)**

Assessment of renal function is recommended prior to Sitagliptin initiation and periodically thereafter.

*Sitagliptin can be taken with or without food. †Patients with mild renal insufficiency—100 mg once daily.
‡ESRD=end-stage renal disease requiring hemodialysis or peritoneal dialysis.
1-Sitagliptin FDA Label, 2018, Reference ID: 4219849.
PPAR agonist= Thiazolidinedione class.

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Sitagliptin + Metformin: Twice-Daily Dosing Administration[1]

- Individualize the starting dose of Sitagliptin +Metformin based on the patient's current regimen.

- Adjust the dosing based on effectiveness and tolerability;

➢not exceeding the maximum recommended daily dose:

(100 mg sitagliptin and 2000 mg metformin).

- Twice daily with meals, with gradual dose escalation:

➢ to reduce the gastrointestinal effects due to metformin.

- Not use in eGFR <30 mL/min/1.73 m^2.
- Not recommended in eGFR between 30 to <45 mL/min/1.73 m^2.

1-Sitagliptin+ Metformin FDA Label,2017,Reference ID: 4043185

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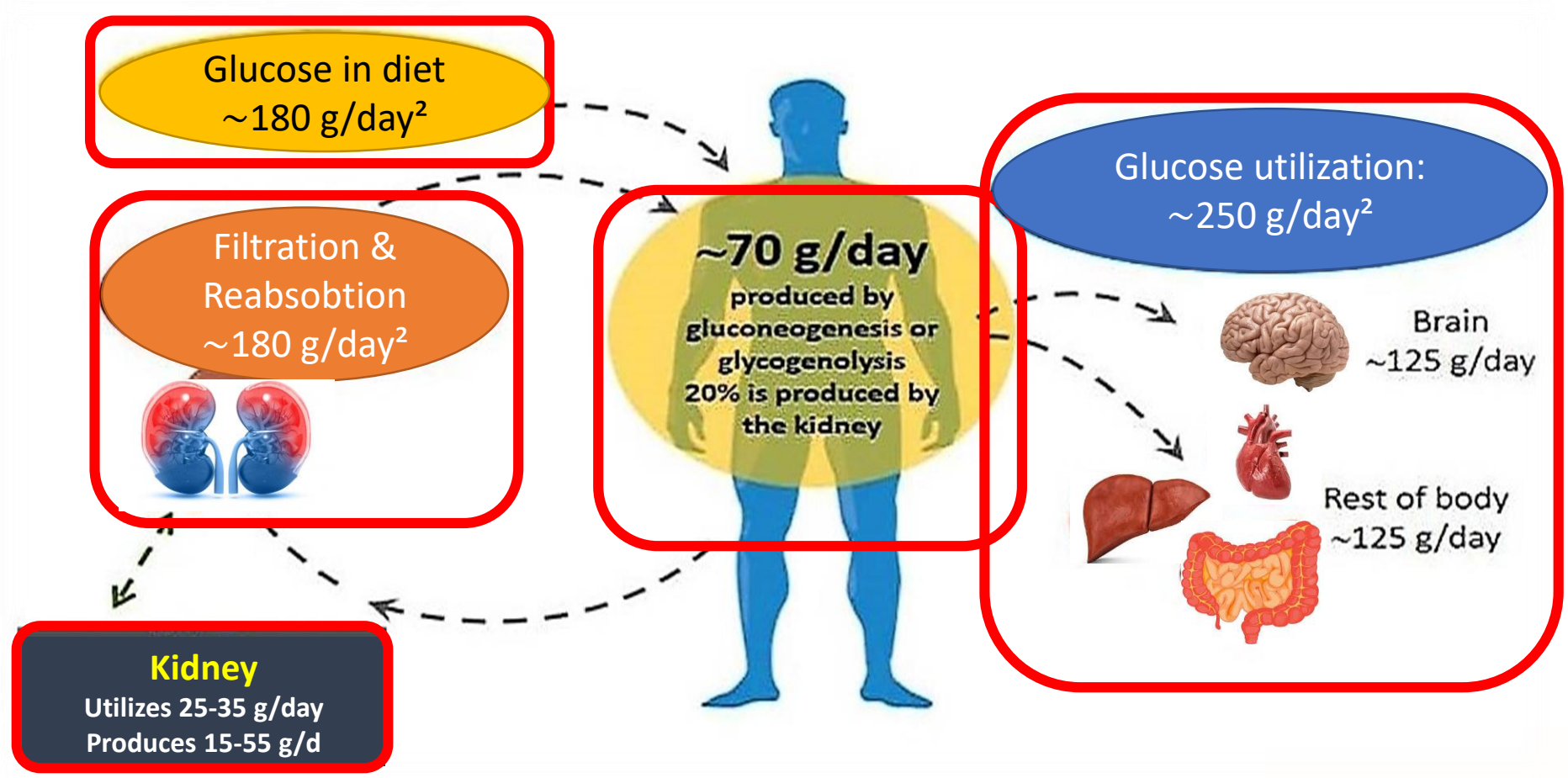
Kidney Plays a Significant Role in Glucose Balance

Reabsorption[1]

Production[1]
(Gluconeogenesis)

Utilization[1]



1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2):136-42.

2-Wright EM et al,. Active sugar transport in health and disease. Journal of internal medicine. 2007; 261(1):32-43.

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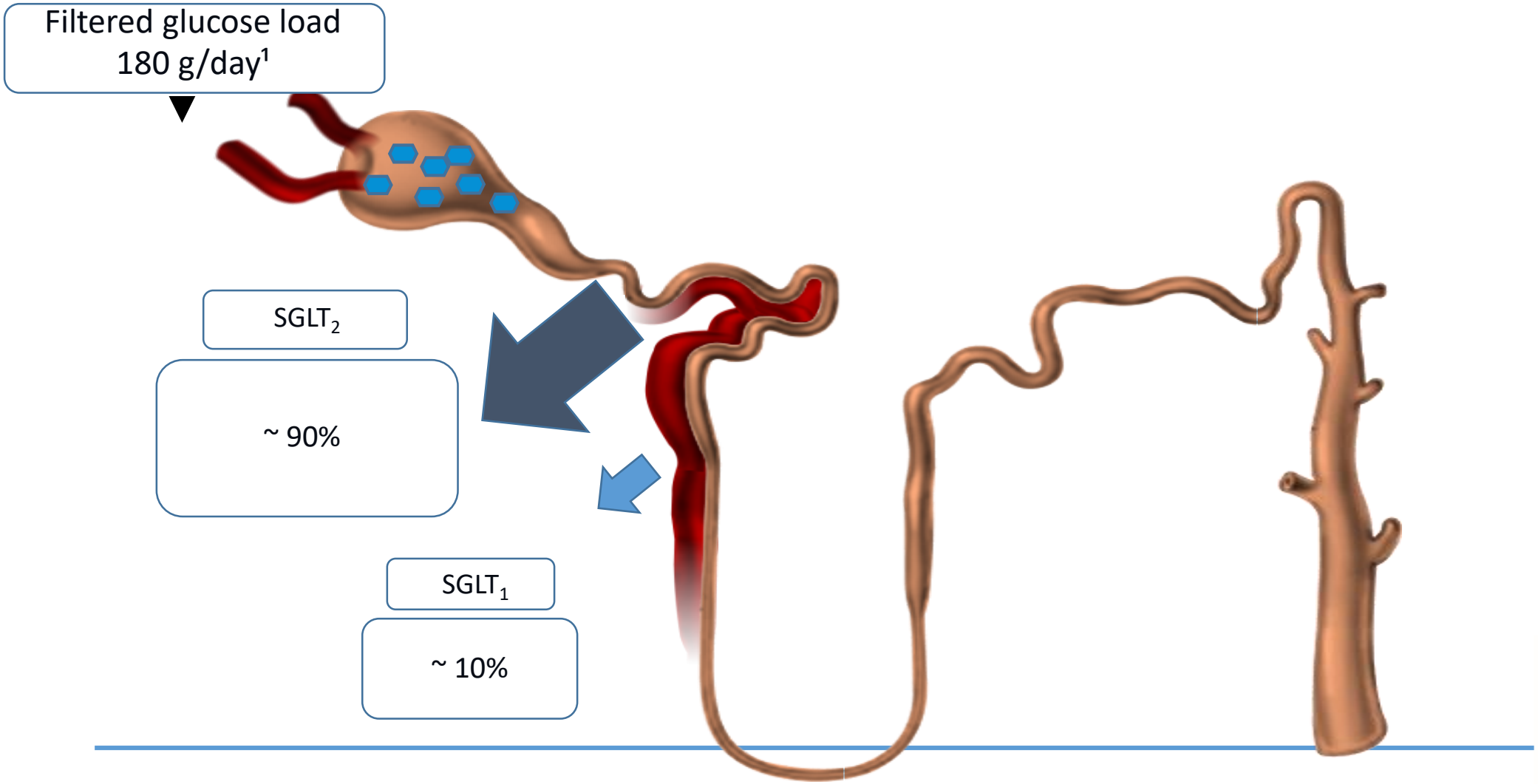
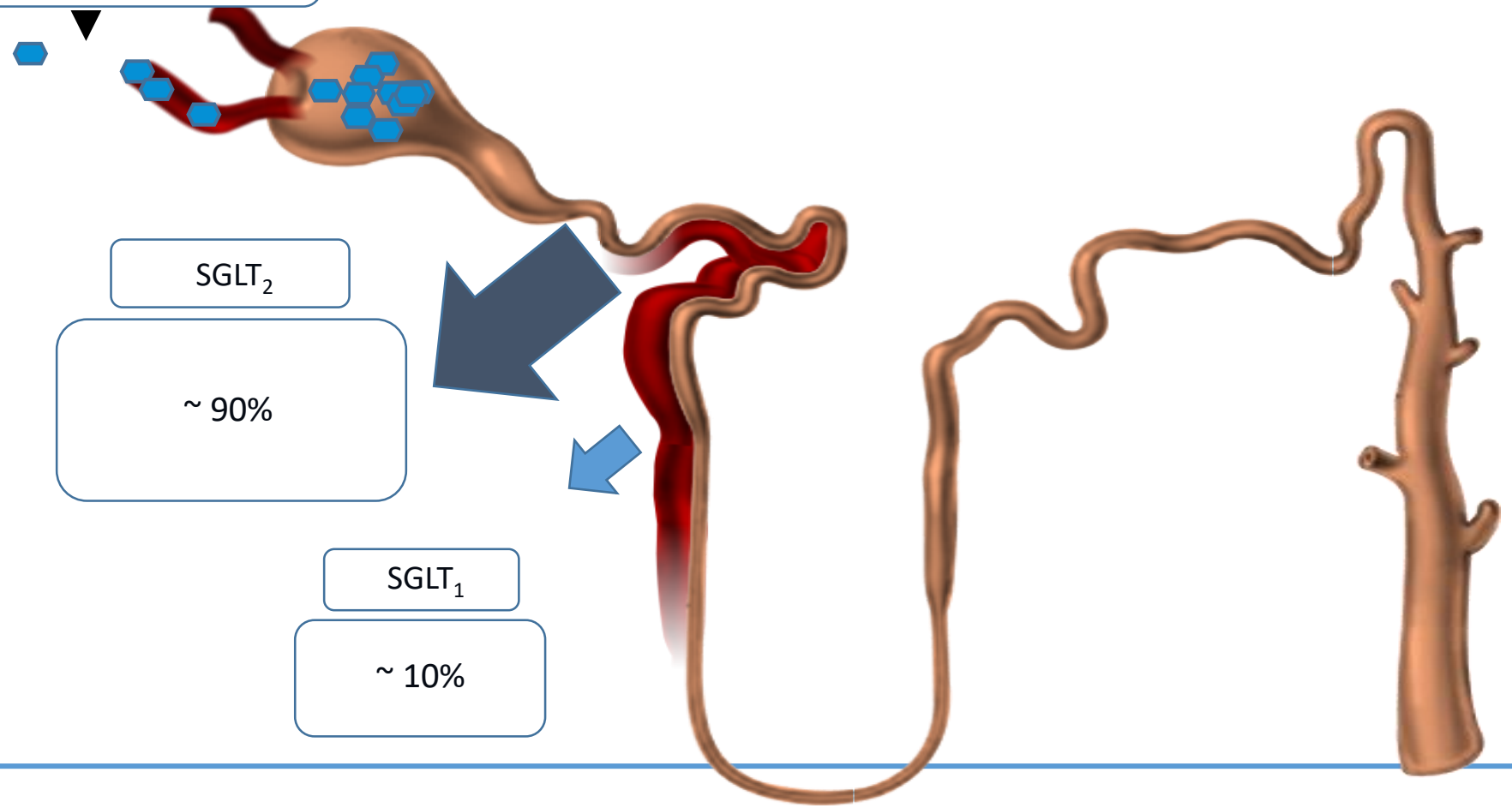
Renal glucose re-absorption in healthy individuals



1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

Renal glucose re-absorption in patients with diabetes

Filtered glucose load > 180[1] g/day



$SGLT_2$

~ 90%

$SGLT_1$

~ 10%

When blood glucose increases above the renal threshold *(~ 180 mg/dL),* the capacity of the transporters is exceeded, resulting in urinary glucose excretion[1]

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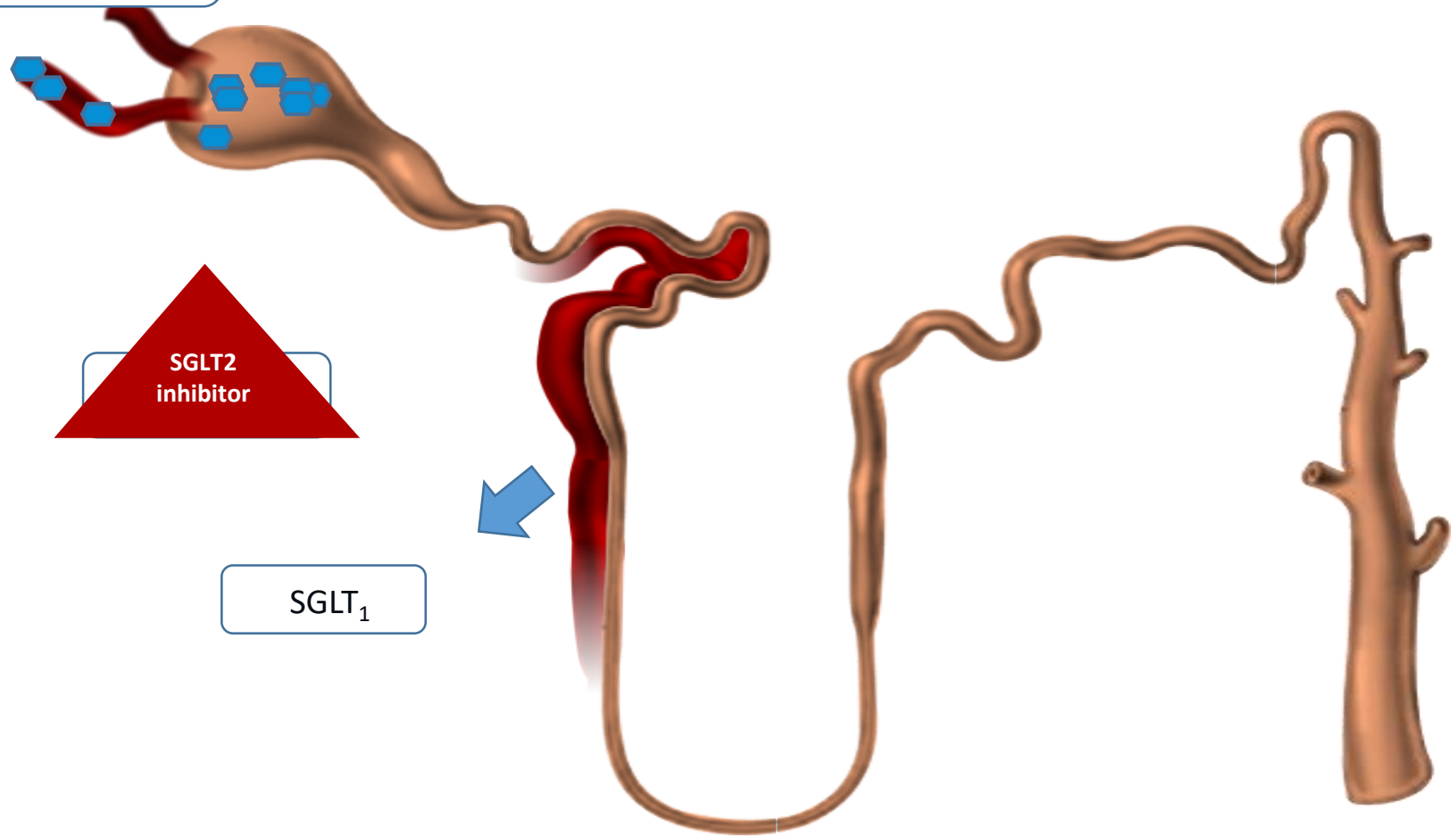
1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load
> 180 g/day



$SGLT_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

***Loss of ~ 80 g of glucose/day**

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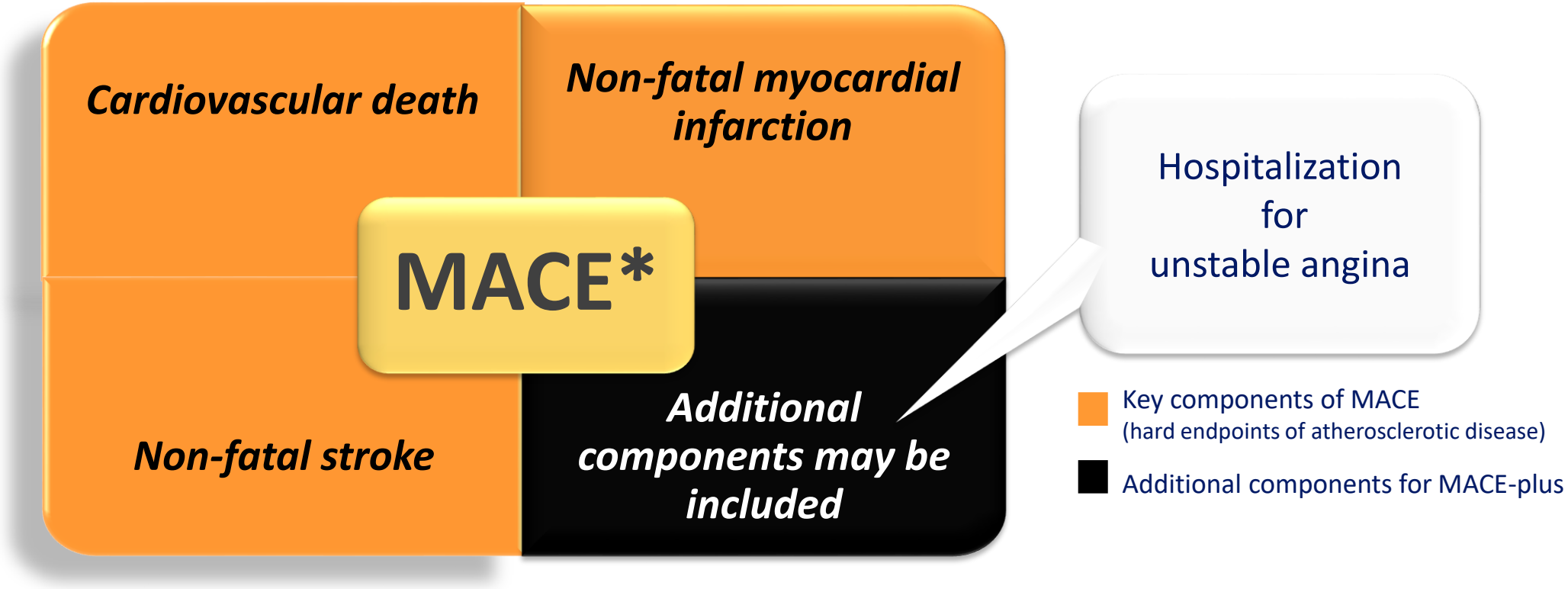
1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2):136-42.

Pre-specified primary and key secondary outcomes[1]

EMPA-REG OUTCOME



*Major Adverse Cardiovascular Events

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1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPA-REG OUTCOME®: summary

Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D at high CV risk[1]

14%

↓ 3P-MACE

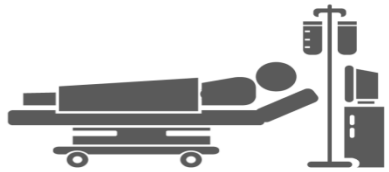
38%

↓ CV death

32%

↓ All-cause mortality

35%



↓ Heart failure hospitalisations

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information[1]

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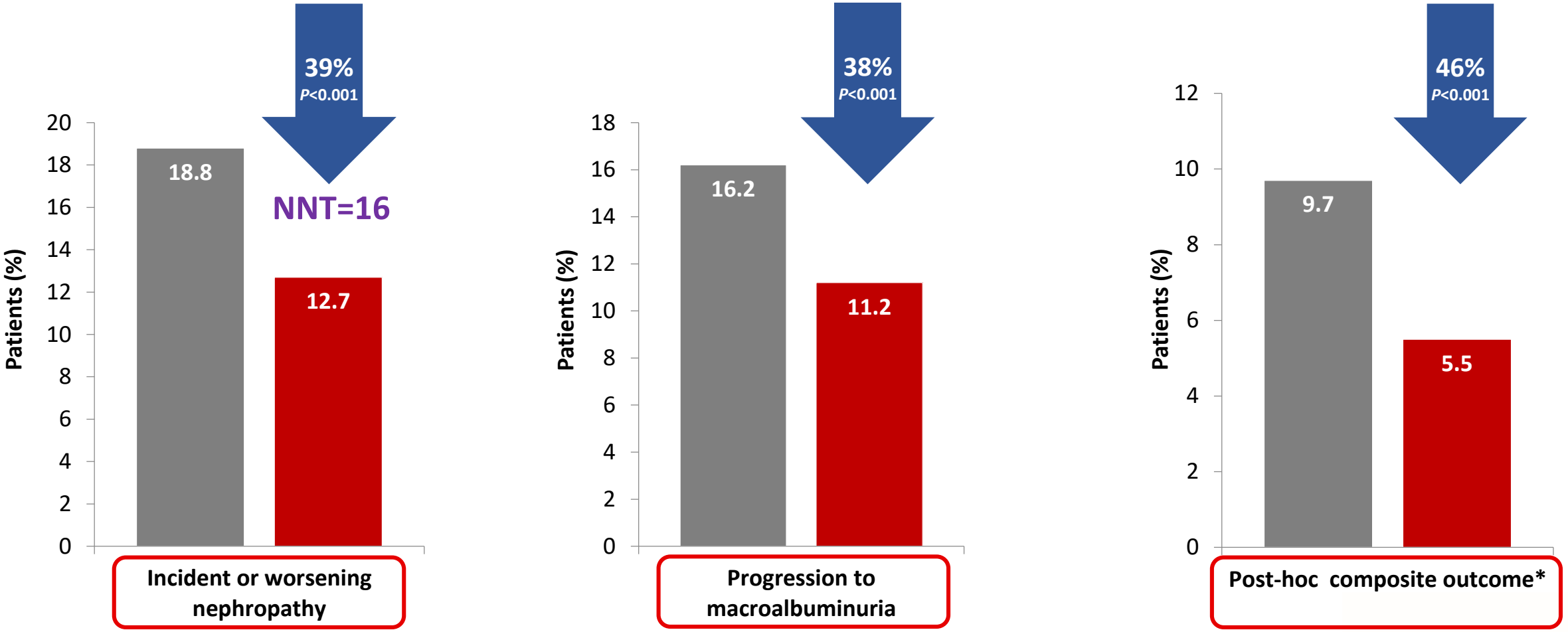
3P-MACE, 3-point major adverse cardiovascular events
Empagliflozin is not indicated for CV risk reduction. CV, cardiovascular; T2D, type 2 diabetes
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Renal Outcomes with Empagliflozin over 3.2 Years (EMPA-REG RENAL)[1]



Arrows = relative risk reduction

*Doubling of SCr + eGFR ≤45 *mL/min/1.73 m²*, initiation of renal replacement therapy, or death from renal disease.

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1-Wanner C et al,. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):323-34.

Gloripa®
Empagliflozin

Synoripa®
Empagliflozin / Metformin

abidi
Diabetes

Conclusions

Combination of empagliflozin/linagliptin:

- Significantly Reduced HbA1c compared with the individual components and were well tolerated.
- FPG was significantly reduced with empagliflozin 25 mg/linagliptin 5mg compared with individual components
- The combination of empagliflozin and linagliptin added on to metformin offered a sustained reduction in HbA1c, FPG, weight, and blood pressure, which persisted up to week 52.

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Dosage and Administration (Once Daily Tablet)[1]

- Recommended starting dose: 10/5mg (10mg Empagliflozin/ 5mg Linagliptin).
- Do not initiate GLORENTA if eGFR is below 45 mL/min/1.73 m².
- Discontinue GLORENTA if eGFR falls persistently below 45 mL/min/1.73 m²

1. GLYXAMBI® (empagliflozin and linagliptin) tablets label FDA 2018

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Pharmacologic Approaches to Glycemic Treatment

Pharmacologic Therapy for Type 1 Diabetes

1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. A

2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. A

3 Patients with type 1 diabetes should be trained to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. C

Pharmacologic Therapy for Type 2 Diabetes

4 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

5 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A

6 Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. A

7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. E

Pharmacologic Therapy for Type 2 Diabetes (continued)

8 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include cardiovascular comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (Table 9.2 and Figure 9.1). E

9 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit (Table 9.1, Table 10 .3B, Table 10.3C) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors (Figure 9.1). A

Pharmacologic Therapy for Type 2 Diabetes (continued)

10 In patients with type 2 diabetes who need greater glucose lowering than can be obtained with oral agents, glucagon-like peptide 1 receptor agonists are preferred to insulin when possible. B

11 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B

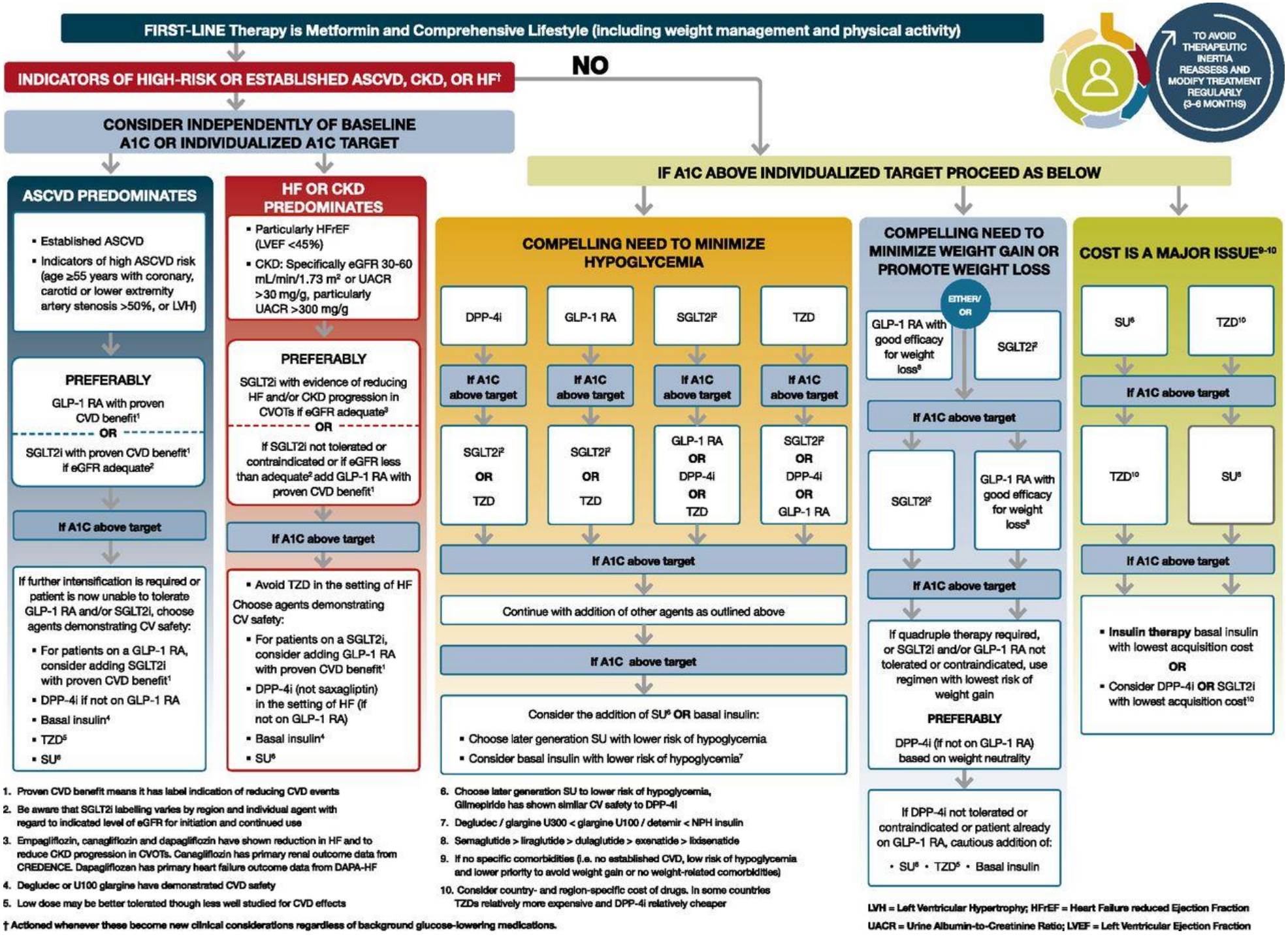
12 The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6months) and adjusted as needed to incorporate specific factors that impact choice of treatment (Fig. 4.1 and Table 9.1). E

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m²	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation **(canagliflozin)** • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors **(liraglutide, albiglutide, dulaglutide, exenatide extended release)** • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. ‡FDA-approved for heart failure indication; §FDA-approved for CKD indication. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020*. *Diabetes Care* 2020;43(Suppl. 1):S98-S110



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Glucose-lowering Medication in Type 2 Diabetes: Overall Approach

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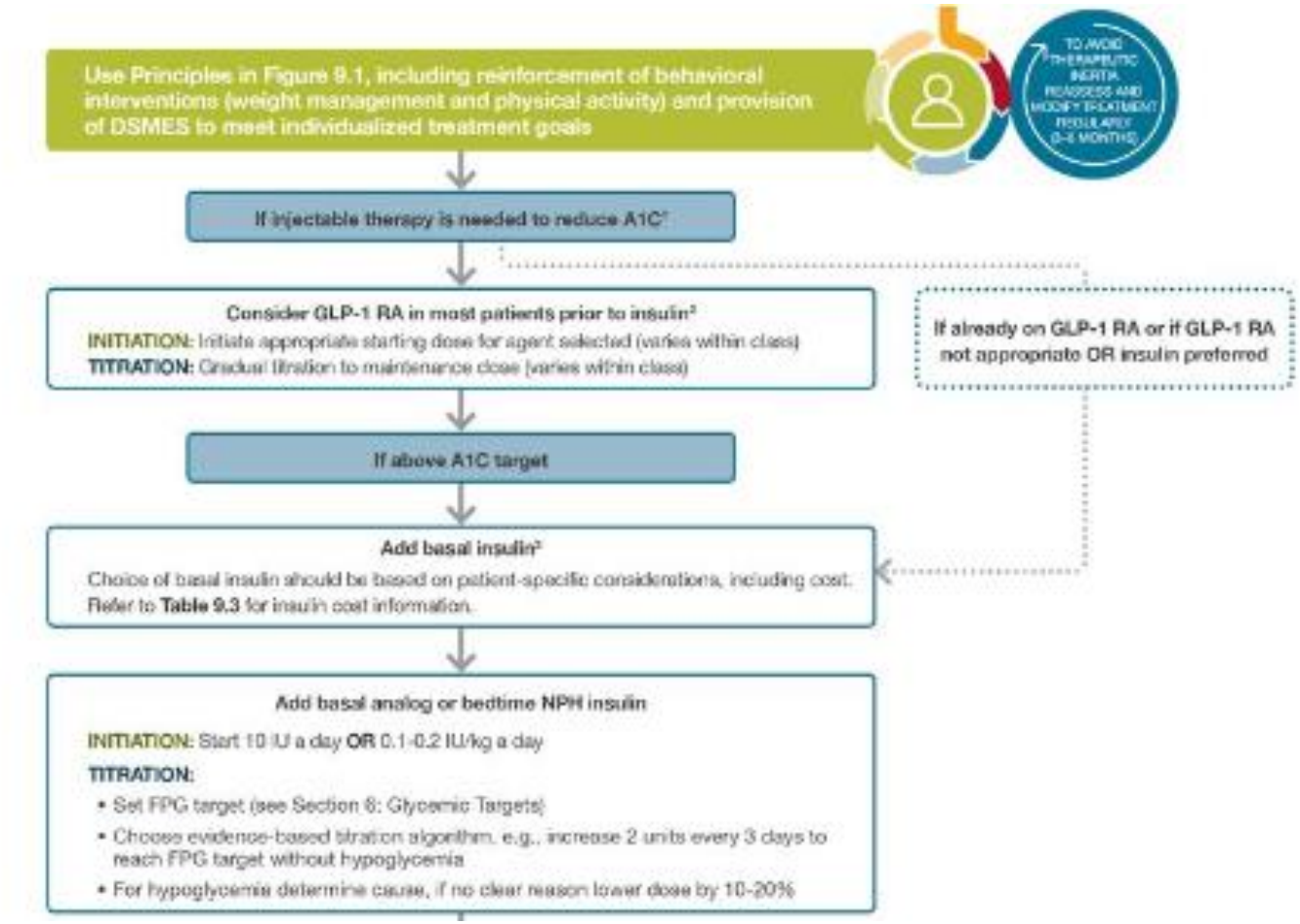
Intensifying to injectable therapies (1 of 2)



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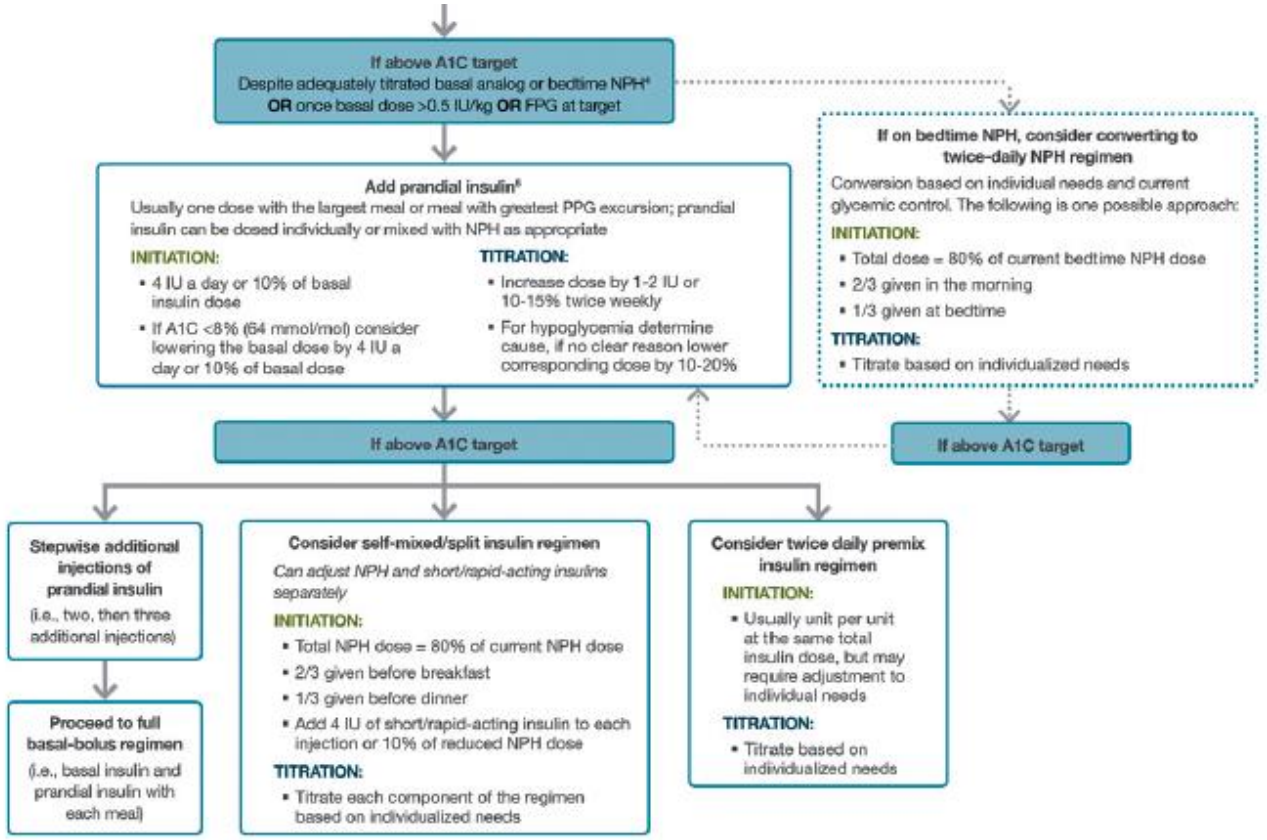
Intensifying to injectable therapies (2 of 2)



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

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Table 9.2—Median monthly (30-day) cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($4, $85)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($87, $7,412)	$5 ($5, $988)	2,000 mg
		750 mg (ER)	$74 ($65, $74)	$4	1,500 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$224 ($224, $910)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$4	8 mg
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$5	40 mg (IR)
		10 mg (XL)	$48	$15	20 mg (XL)
	• Glyburide	6 mg (micronized)	$50 ($48, $71)	$4	12 mg (micronized)
		5 mg	$93 ($63, $103)	$11	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$4	45 mg
	• Rosiglitazone	4 mg	$407	$330	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$23	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$39	360 mg
	• Repaglinide	2 mg	$878 ($162, $897)	$39	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$168	25 mg
	• Saxagliptin	5 mg	$505	$403	5 mg
	• Linagliptin	5 mg	$523	$419	5 mg
	• Sitagliptin	100 mg	$541	$433	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$338	$271	15 mg
	• Dapagliflozin	10 mg	$591	$473	10 mg
	• Empagliflozin	25 mg	$591	$473	25 mg
	• Canagliflozin	300 mg	$593	$475	300 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$840	$672	2 mg**
	• Exenatide	10 μg pen	$876	$730	20 μg
	• Dulaglutide	1.5/0.5 mL pen	$911	$730	1.5 mg**
	• Semaglutide	1 mg pen	$927	$745	1 mg**
		14 mg (tablet)	$927	N/A	14 mg
	• Liraglutide	18 mg/3 mL pen	$1,106	$886	1.8 mg
	• Lixisenatide	300 μg/3 mL pen	$744	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$712 ($674, $712)	$177	3.75 g
		3.75 g suspension	$675	$415	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$906	$729	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,623	$2,097	120 μg/injection†††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [54] or NADAC [55] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. †††AWP and NADAC calculated based on 120 μg three times daily.

Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

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Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (54) and NADAC (55) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$126
		U-100 prefilled pen	$202	$162
	• Lispro	U-100 vial	$330	$264
		U-100 3 mL cartridges	$408	$327
		U-100 prefilled pen; U-200 prefilled pen	$424	$340
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$353
	• Aspart	U-100 vial	$347†	$278†
		U-100 3 mL cartridges	$430	$345
		U-100 prefilled pen	$447†	$358†
	• Inhaled insulin	Inhalation cartridges	$924	$606
Short-acting	• human regular	U-100 vial	$165 ($165, $178)††	$134 ($134, $146)††
Intermediate-acting	• human NPH	U-100 vial	$165 ($165, $178)††	$135 ($135, $146)††
		U-100 prefilled pen	$377	$304
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$144
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$261	$210
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		U-300 prefilled pen	$346	$280
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165 ($165, $178)	$134 ($134, $145)
		U-100 prefilled pen	$377	$303
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial	$360	$289
		U-100 prefilled pen	$447	$358
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$565	$454
	• Degludec/Liraglutide	100/3.6 prefilled pen	$832	$668

AWP, average wholesale price; GLP-1, glucagon-like peptide 1; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**. †Inclusive of both the original and "faster-acting" products. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage

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