Oral Hypoglycemic Agents

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Objectives

1. อธิบายคุณสมบัติทางเภสัชวิทยา ทั้งทางเภสัชพลศาสตร์และเภสัชจลนศาสตร์ของยากลุ่มนี้ได้
2. สามารถบอกหลักการเลือกใช้ยาได้อย่างสมเหตุสมผล เหมาะสมกับโรคและสภาวะของผู้ป่วย
3. สามารถบอกฤทธิ์แทรกแซง ฤทธิ์ไม่พึงประสงค์ รวมทั้งปฏิกิริยาระหว่างยาที่เกิดกับยาในกลุ่มนี้
4. สามารถบอกหลักการและวางแผนการรักษาโรคเบาหวาน ทั้งการรักษาแบบใช้ยาชนิดเดียว ใช้ยาหลายชนิดร่วมกัน การใช้ยาฉีดอินซูลิน

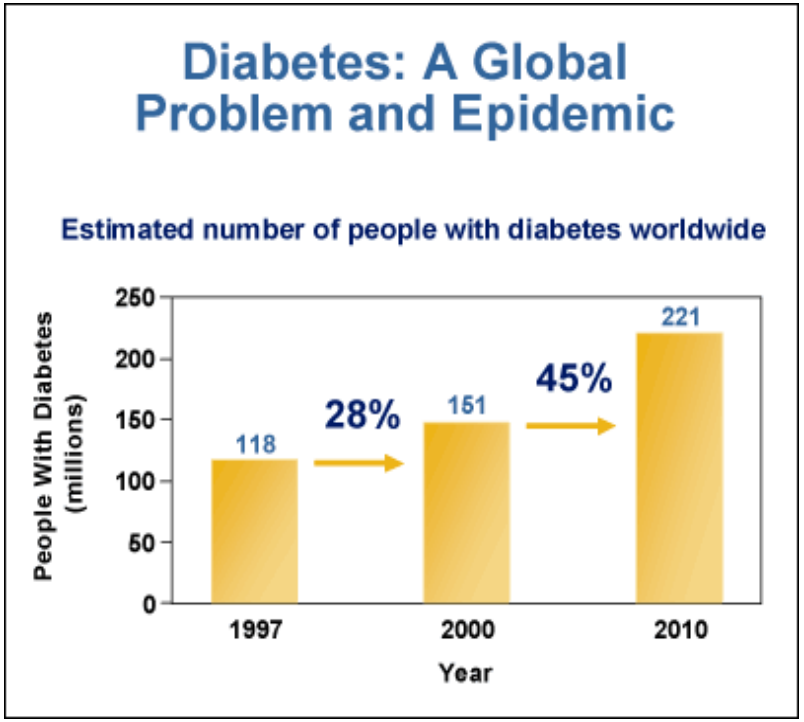
Contents

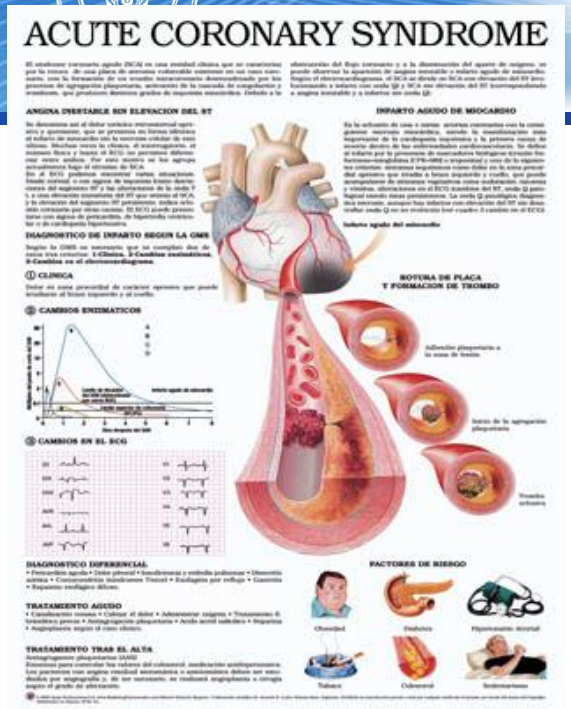
- Clinical important of diabetes mellitus
- **Oral hypoglycemic agents** and **Insulins**
  - Classification
  - Pharmacological aspect
  - Clinical used

Prevalence

- > 200 million people worldwide
- > 366 million by 2030
- In 2050: 33% of USA populations may have DM

N ENGL J MED 363;27 NEJM.ORG DECEMBER 30, 2010





Complications of DM

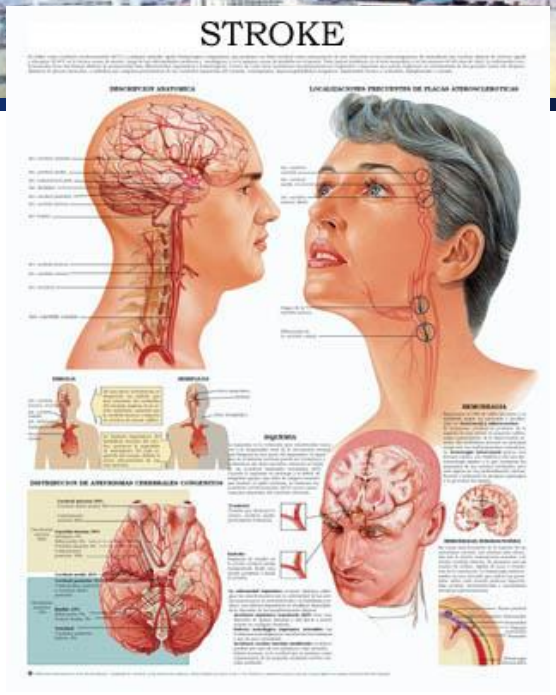
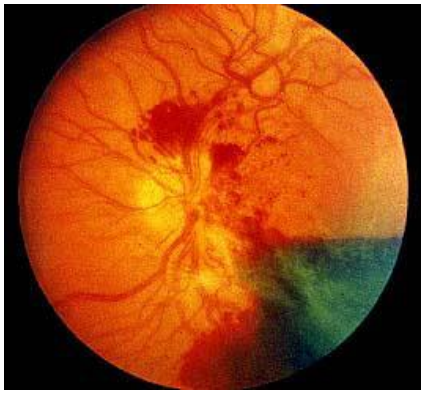
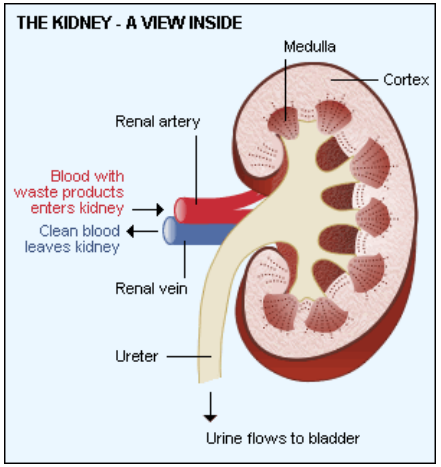


Figure 43-12 Neuropathic ulcers occur on pressure points in areas with diminished sensation in diabetic polyneuropathy. Pain is absent (and therefore the ulcer may go unnoticed). (Bates B.B. [1995]. *A guide to physical examination and history taking* [6th ed.]. Philadelphia: J.B. Lippincott)





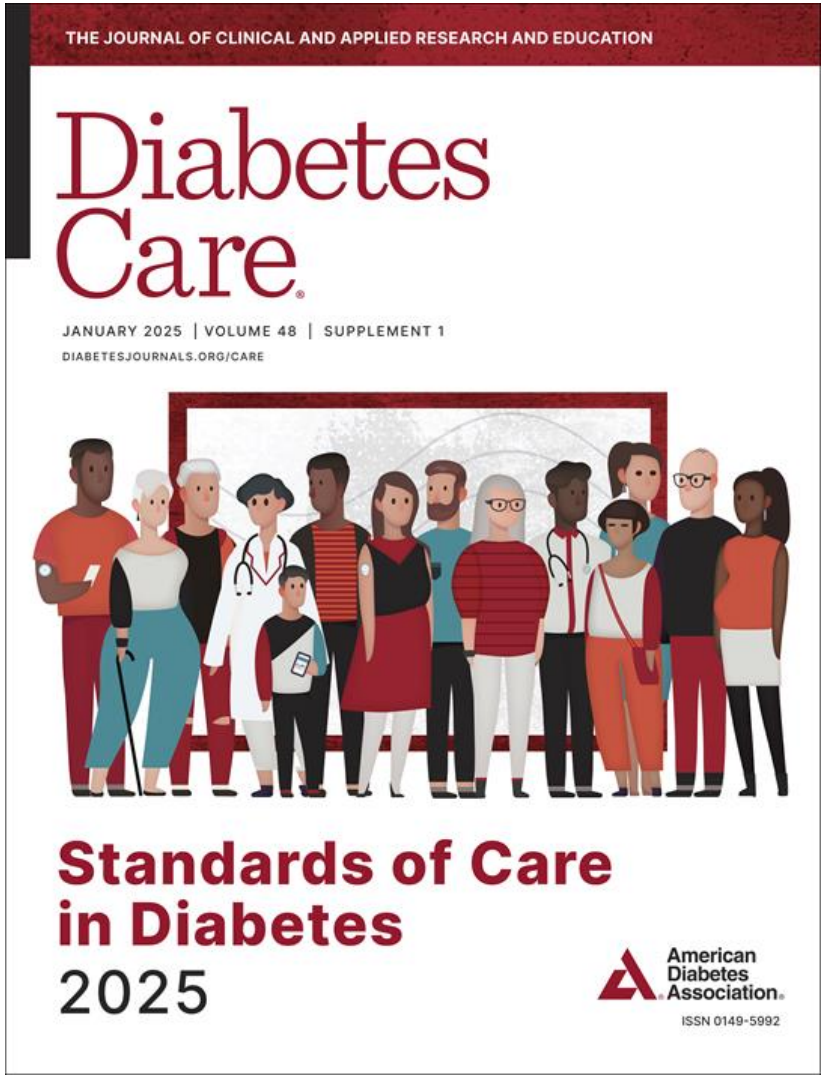
Pathogenic of DM

Insulin deficiency (inadequate insulin secretion)

And/Or

Resistance to insulin action

Guideline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Diabetes Care
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2025
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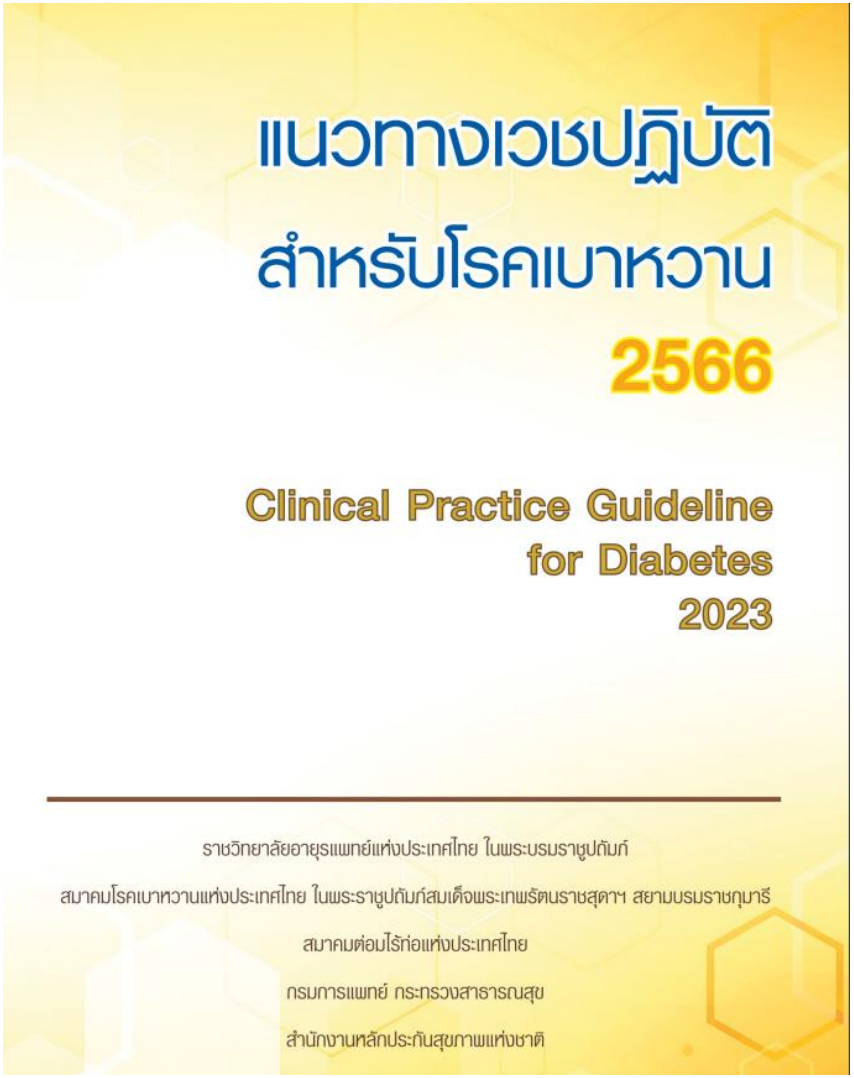

แนวทางเวชปฏิบัติ
สำหรับโรคเบาหวาน
2566
Clinical Practice Guideline
for Diabetes
2023
ราชวิทยาลัยอายุรแพทย์แห่งประเทศไทย ในพระบรมราชูปถัมภ์
สมาคมโรคเบาหวานแห่งประเทศไทย ในพระราชูปถัมภ์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี
สมาคมต่อมไร้ท่อแห่งประเทศไทย
กรมการแพทย์ กระทรวงสาธารณสุข
สำนักงานหลักประกันสุขภาพแห่งชาติ

Criterias diagnosis of Diabetes Mellitus

1. HbA1c ≥ 6.5 %

or

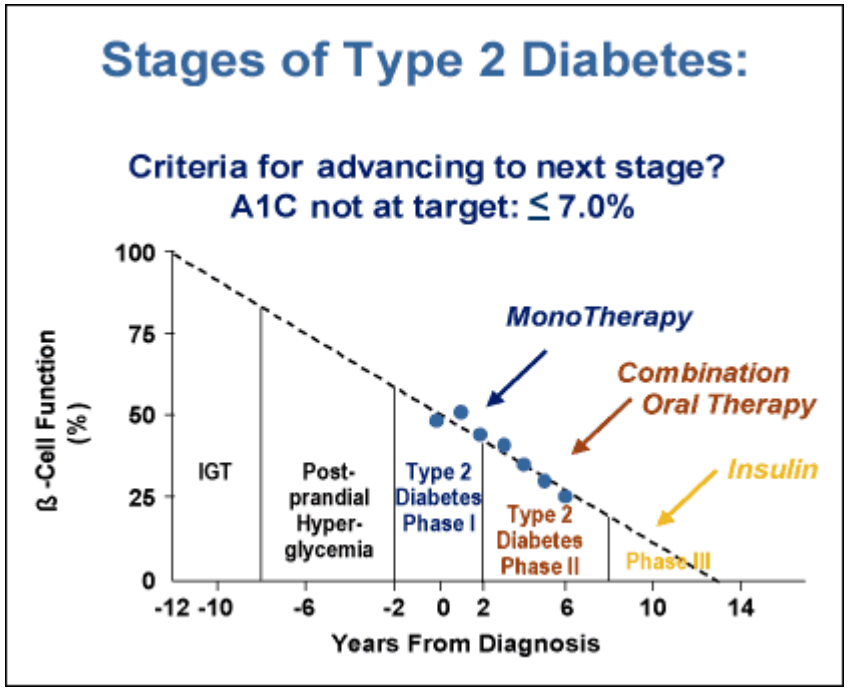
2. FPG ≥ 126 mg/dl

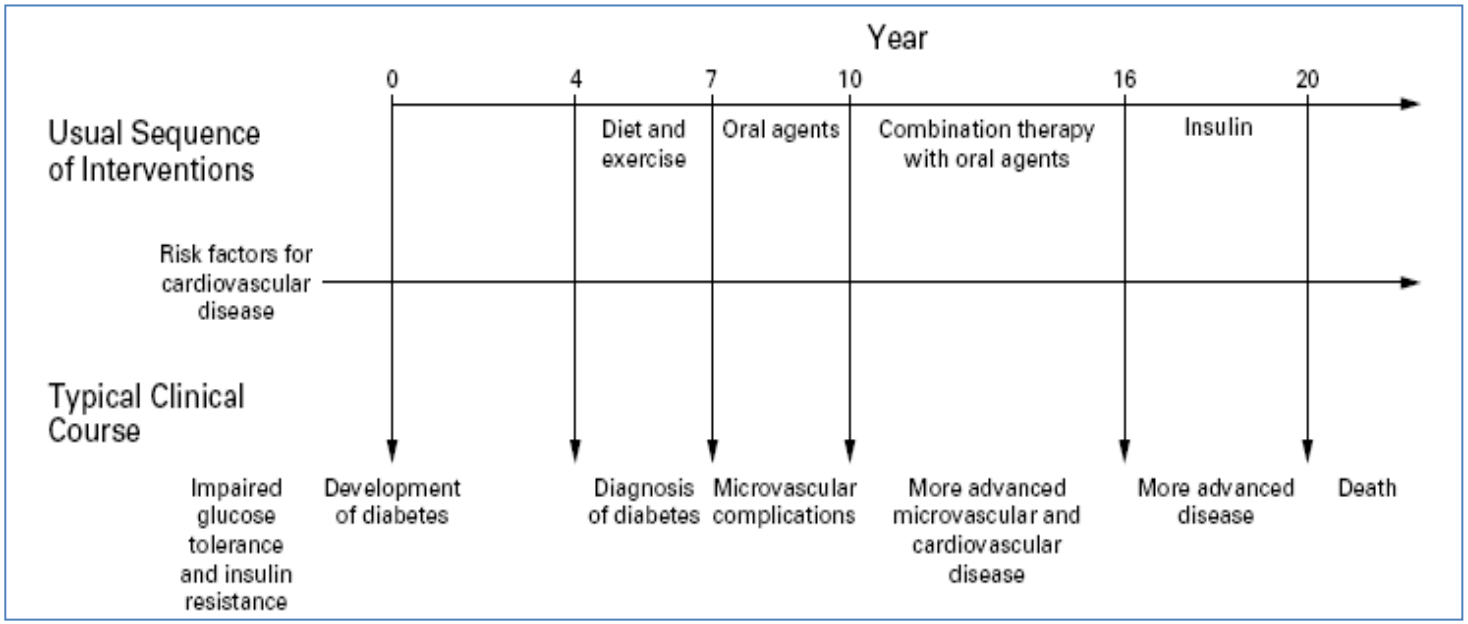
or

3. 2-h plasma glucose ≥ 200 mg/dl during an OGTT

or

4. A random plasma glucose ≥ 200 mg/dl with classic symptoms of hyperglycemia or hyperglycemic crisis


Stages of Type 2 Diabetes:
Criteria for advancing to next stage?
A1C not at target: ≤ 7.0%
β -Cell Function (%)
100
75
50
25
0
IGT
Post-prandial Hyper-glycemia
Type 2 Diabetes Phase I
Type 2 Diabetes Phase II
Phase III
MonoTherapy
Combination Oral Therapy
Insulin
-12 -10
-6
-2
0
2
6
10
14
Years From Diagnosis


Year
0
4
7
10
16
20
Usual Sequence of Interventions
Diet and exercise
Oral agents
Combination therapy with oral agents
Insulin
Risk factors for cardiovascular disease
Typical Clinical Course
Impaired glucose tolerance and insulin resistance
Development of diabetes
Diagnosis of diabetes
Microvascular complications
More advanced microvascular and cardiovascular disease
More advanced disease
Death

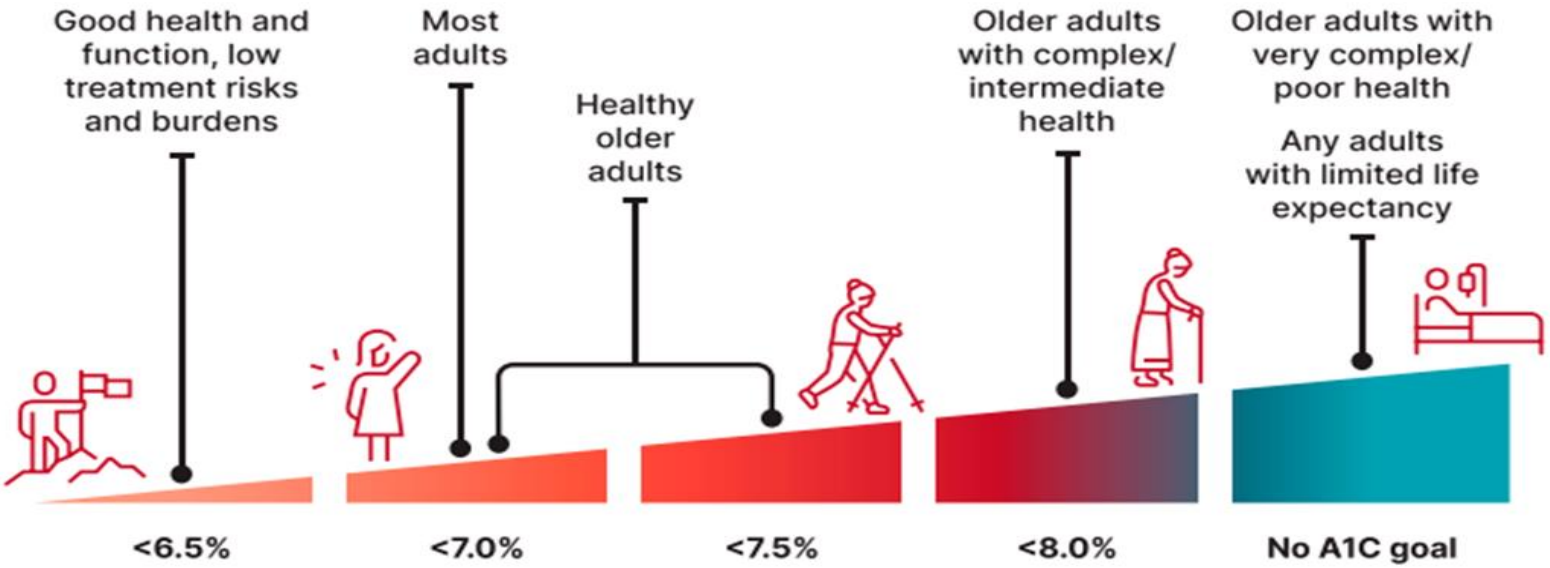
Glycemic Target

Table 6.3—Summary of glycemic goals for many nonpregnant adults with diabetes

A1C	<7.0% (<53 mmol/mol)*†
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose‡	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for certain individuals. †CGM may be used to assess glycemic status as noted in Recommendations 6.3b and 6.3c and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age and life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, impaired awareness of hypoglycemia, and individual considerations (per **Fig. 6.2**). ‡Postprandial glucose may warrant special attention if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, which is generally the timing for peak levels in people with diabetes.

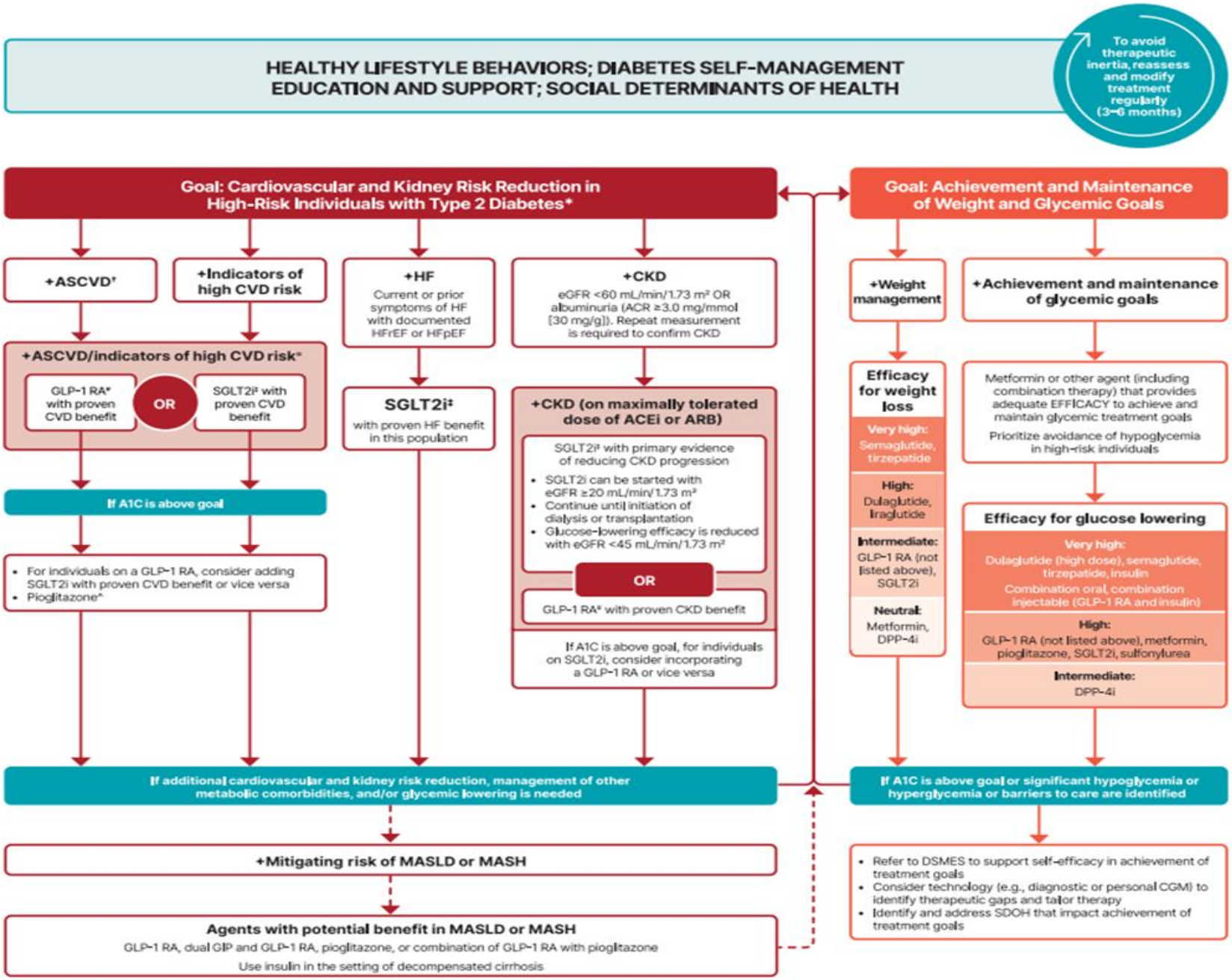
Glycemic Target



Modifying Factors

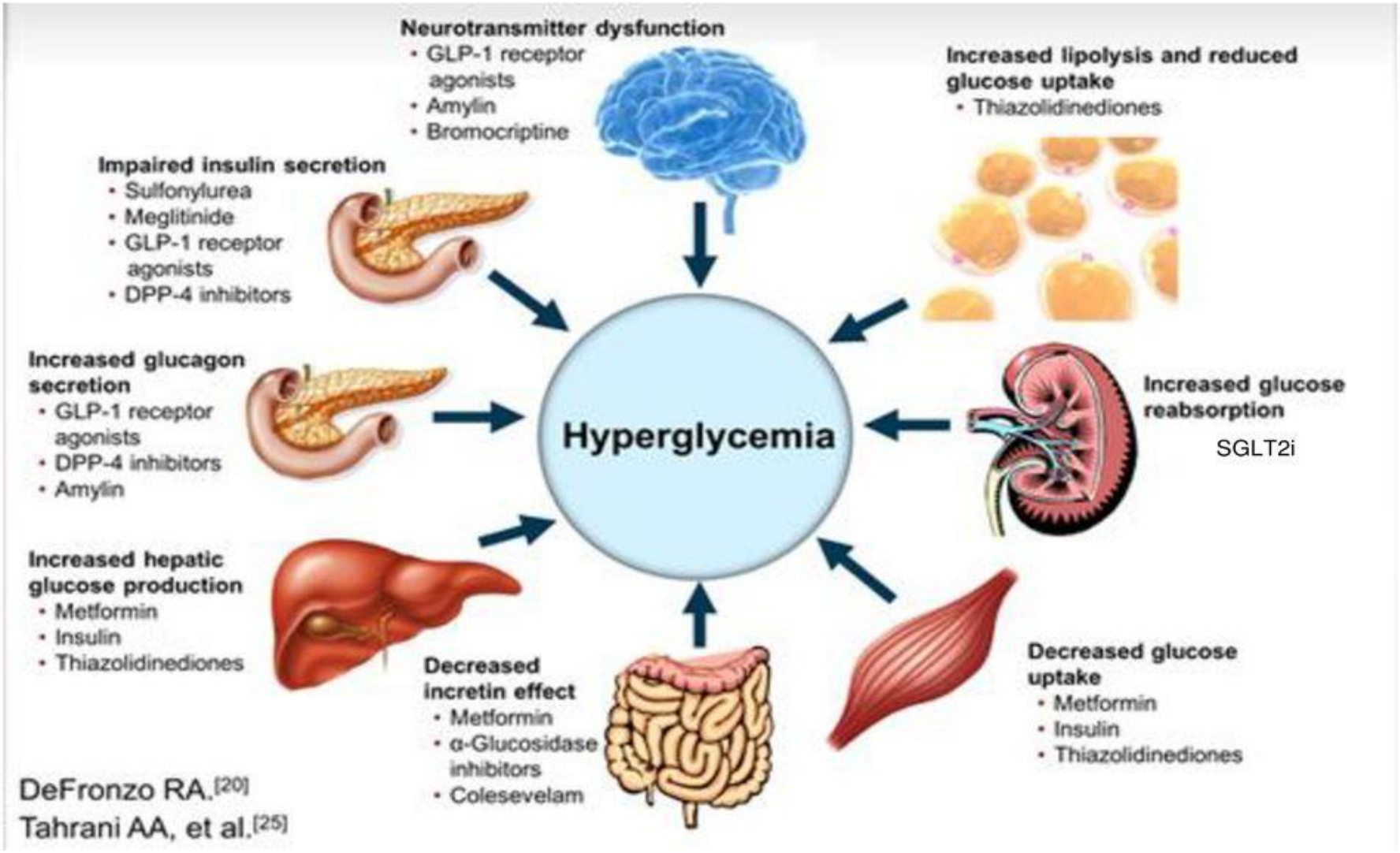
Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Oral Hypoglycemic Agents

Mechanism of Action: Oral Hypoglycemic Agents



DeFronzo RA.[20]
Tahrani AA, et al.[25]

Classification of Oral Hypoglycemic Agents

- **Insulin secretagogue**
  - Sulfonylurea
  - Non-sulfonylurea (Glinides or Meglitinides)
  - ยาที่มีผลต่อ GLP-1 (glucagon-like peptide-1) (incretin based therapy)
- **Insulin sensitizer**
  - Biguanide
  - Thiazolidinedione
- **Decrease carbohydrate absorption**
  - Alpha-glucosidase inhibitor
- **Decrease glucose reabsorption**
  - Sodium glucose co-transporter 2 inhibitor

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Insulin secretagogue

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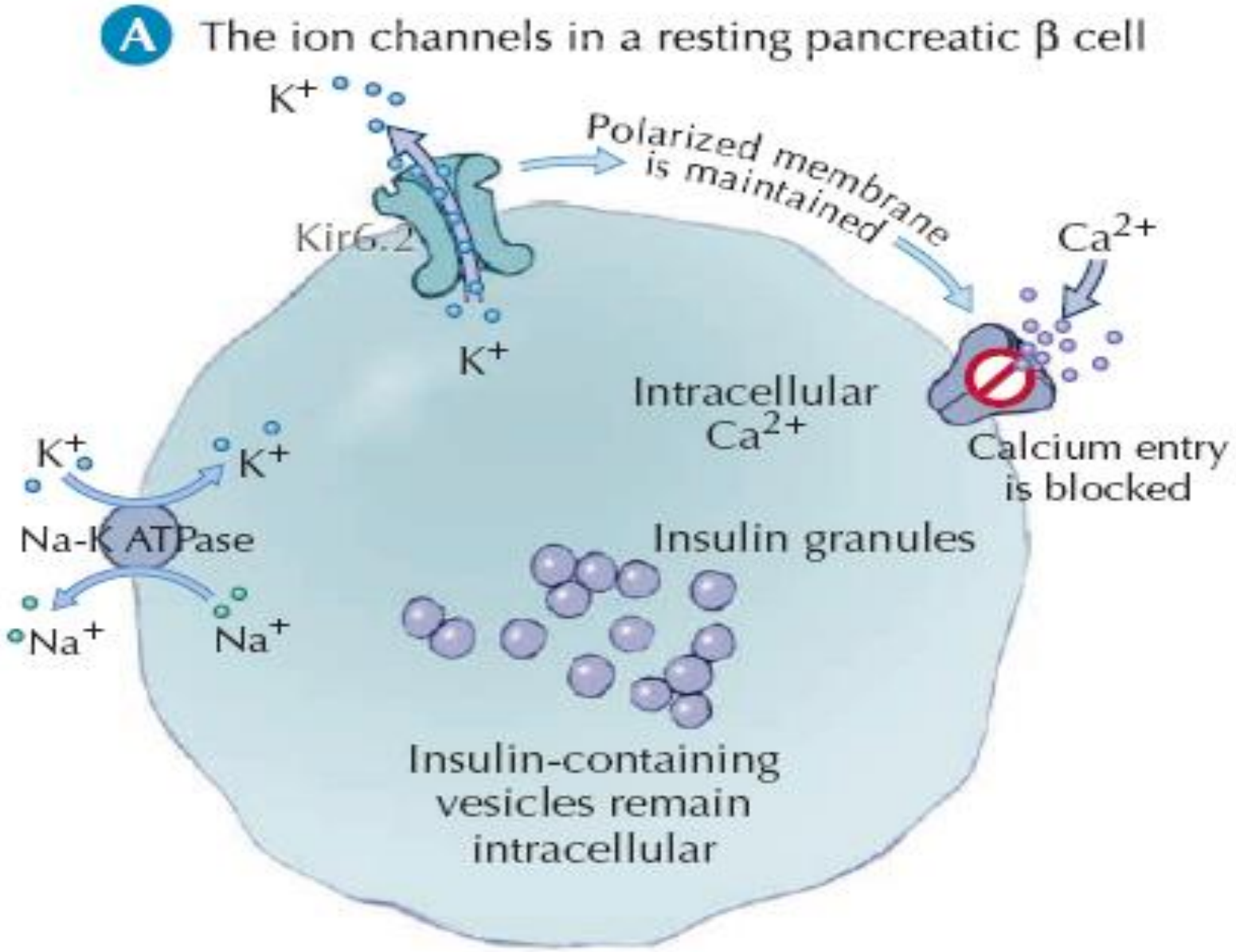
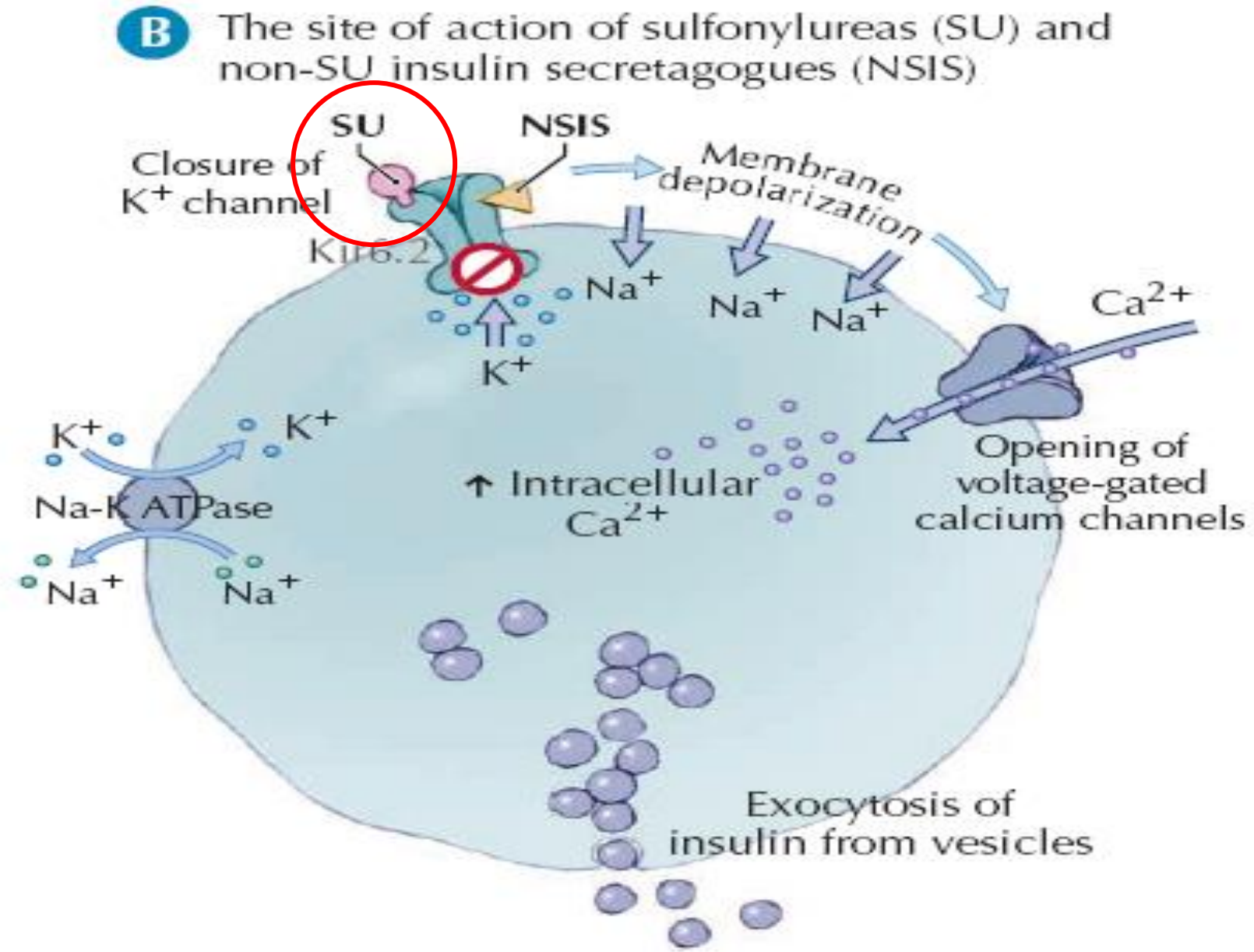
Sulfonylurea:Mechanism of Action

- Stimulating insulin release from pancreatic beta cells
- Sulfonylureas bind to the SUR1 subunits and block the ATP-sensitive K+ channel resemble physiological secretagogues
- Influx of Ca2+ through voltage-sensitive Ca2+ channels

Sulfonylurea:Mechanism of Action



Sulfonylurea:Mechanism of Action



Sulfonylurea:Classification

- First generation
  - ✓ **Chlopropamide**
  - ✓ Tolbutamide
  - ✓ Tolazamide
  - ✓ Acetohexamide

- Second generation
  - ✓ **Glibenclamide**
  - ✓ **Glipizide**
  - ✓ **Gliclazide**
  - ✓ **Glimepiride**
  - ✓ Gliquidone

Pharmacokinetic

- Effectively absorbed from the GI tract
- Largely (90% to 99%) bound to protein, especially albumin
- Metabolized by the liver
- Excreted in the urine
- Different in half-lives and duration of action

Pharmacokinetic properties of sulfonylurea

Sulphonylureas	Daily dosage (mg)	Duration of action[a]	Activity of metabolites	Main route of elimination
First generation				
Chlorpropamide[b]	100–500	Long	Active	Urine >90%
Tolbutamide[c]	500–2000	Short	Inactive	Urine ≈100%
Second generation				
Glibenclamide (glyburide)	2.5–15	Intermediate to long	Active	Bile ≈50%
Glimepiride	1–6	Intermediate	Active	Urine ≈80%
Glipizide	2.5–20	Short to intermediate	Inactive	Urine ≈70%
Gliquidone	15–180	Short to intermediate	Inactive	Bile ≈95%
Gliclazide	40–320[d]	Intermediate	Inactive	Urine ≈65%

a Long >24h; intermediate 12–24h; short <12h.

b No longer available in the UK.

c Should be taken immediately before meals.

d Modified (extended)-release preparation, Diamicron® MR dose range 30–120mg.

Sulfonylurea

- The oldest and most widely used medications for the treatment of T2DM
- Type 2 DM patients who cannot achieve appropriate control with non-pharmacological therapy
- Preferred for patients who are not overweight

Contraindications

- Type 1 DM
- Pregnancy
- Lactation
- Significant hepatic or renal insufficiency
- Severe stress: severe infection, trauma, major surgery
- Severe allergy to sulfonamides

Adverse Effects

- Hypoglycemia (most common) esp. in elderly, long acting, impaired hepatic and renal function
- Hypersensitivity reactions
- Nausea and vomiting
- Hyponatremia

Non-sulfonylurea (Glinides or Meglitinides)

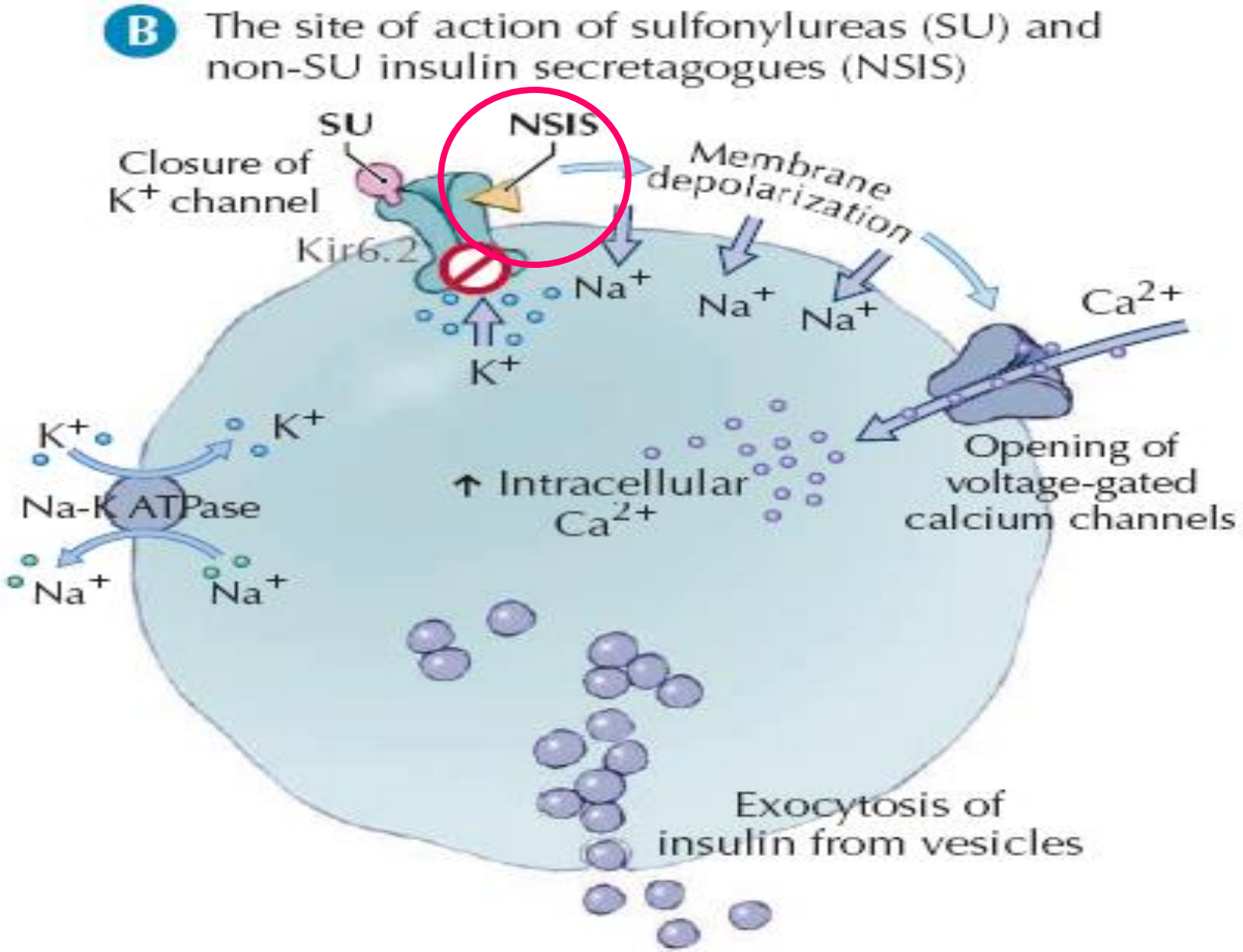
- Short-acting glucose-lowering drugs
- Oral insulin secretagogue
- Structures are unrelated to that of sulfonylureas

  - ✓**Repaglinide**
  - ✓**Nateglinide**

Mechanism of Action

- Like sulfonylureas
- Stimulates insulin secretion by blocking ATP-sensitive potassium channels in pancreatic beta cells
- Similar to sulfonylurea but effective in **reducing PPG**

Mechanism of Action



Repaglinide

- absorbed **rapidly** from the gastrointestinal tract
- peak blood levels are obtained within 1 hour
- the half-life of the drug is about 1 hour
- metabolized primarily by the liver to inactive derivatives
- mainly excreted in bile

Nateglinide

- more rapid but less sustained secretion of insulin than do other available oral antidiabetic agents
- major therapeutic effect is reducing **postprandial** glycemic elevations
- metabolized primarily by the liver
- excreted by the kidney

Indication

- Mono or combination therapy
- Irregular life-styles: meals are unpredictable or missed

One meal, one dose
No meal, no dose

Contraindication

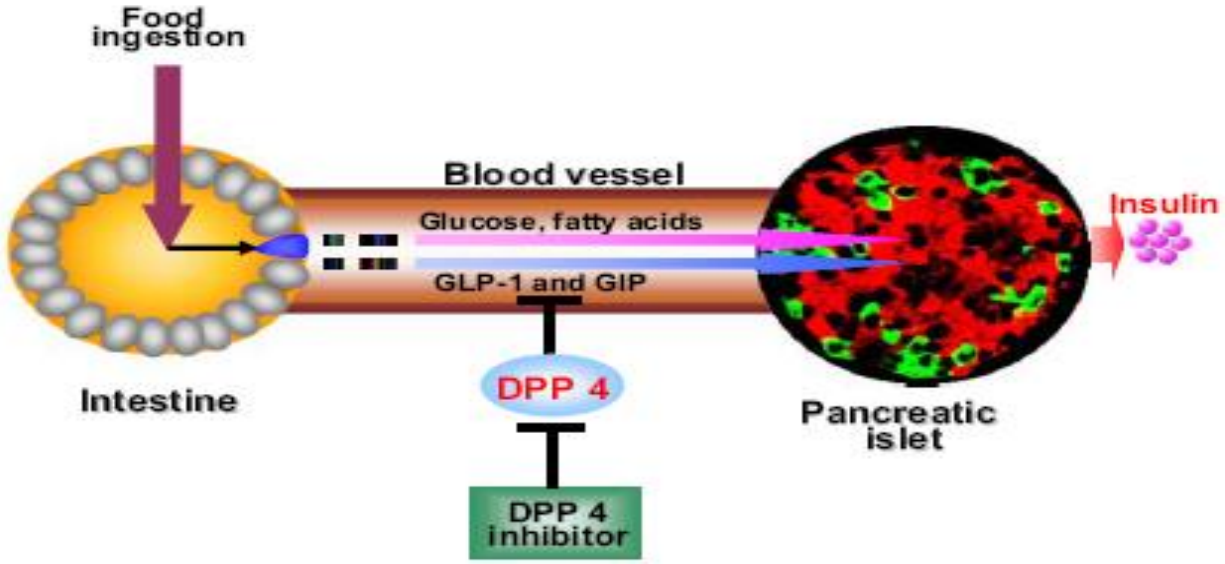
- Hepatic impairment
- Severe renal impairment

Adverse Effect

- Hypoglycemia (most common)
- Abdominal pain, Dyspepsia
- Weight gain

Incretin based therapy

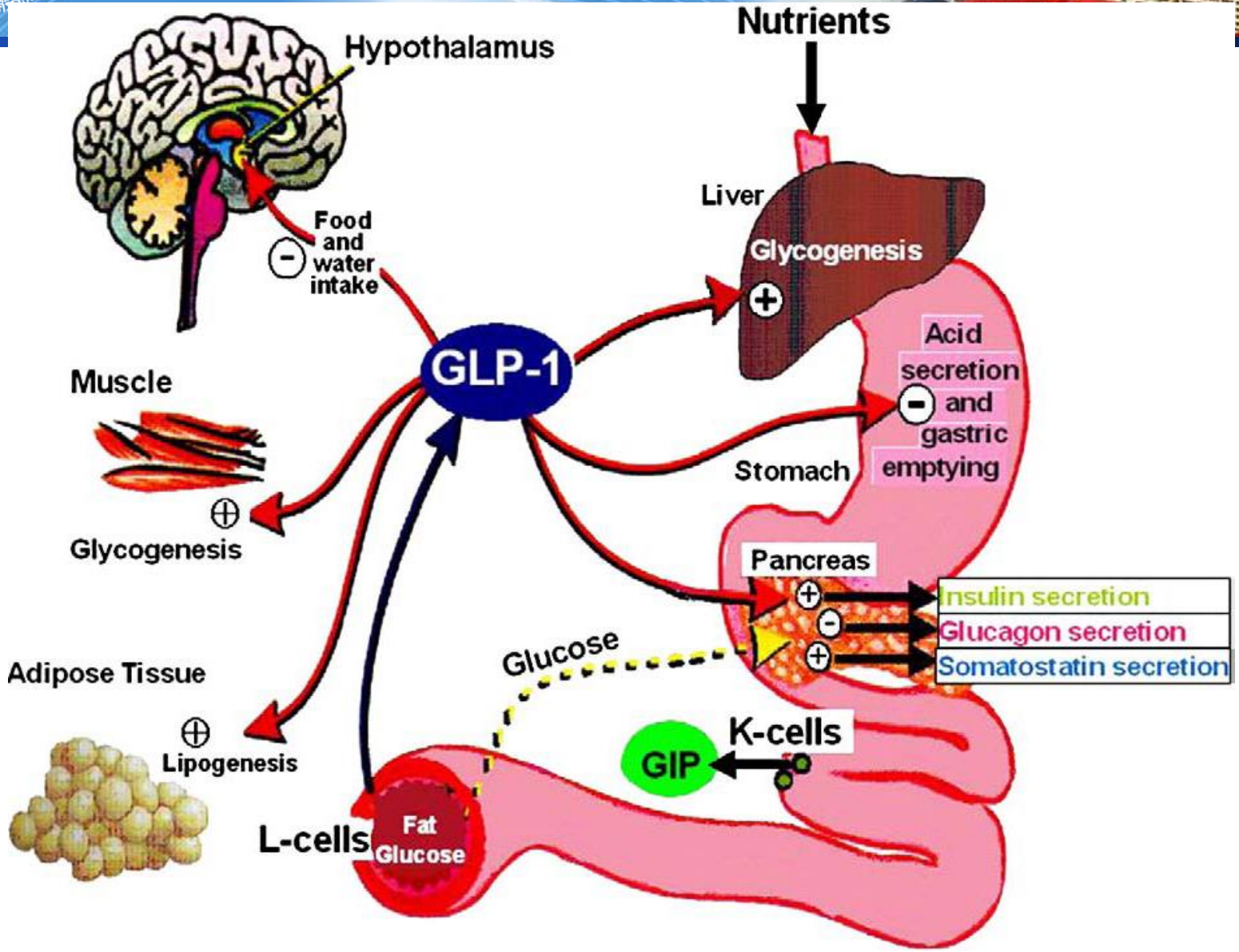
- **GLP-1 (glucagon-like peptide-1) receptor agonists**: Exenatide
- **DPP-IV(dipeptidylpeptidase-4) inhibitors**: Sitagliptin



Mechanisms of GLP-1-regulated glucose homeostasis

Site of action	Effect of GLP-1
Periphery	Increases glucose uptake
Pancreatic beta-cells	Enhances insulin secretion
Pancreatic alpha-cells	Decreases glucagon secretion
Stomach	Delays gastric emptying Reduces food intake
Central nervous system	Induces satiety

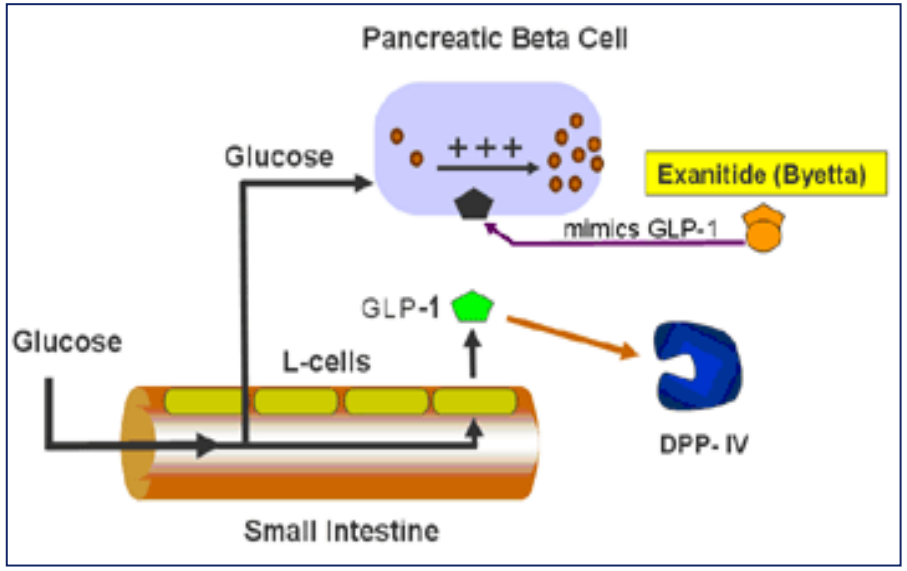
Physiology of GLP-1

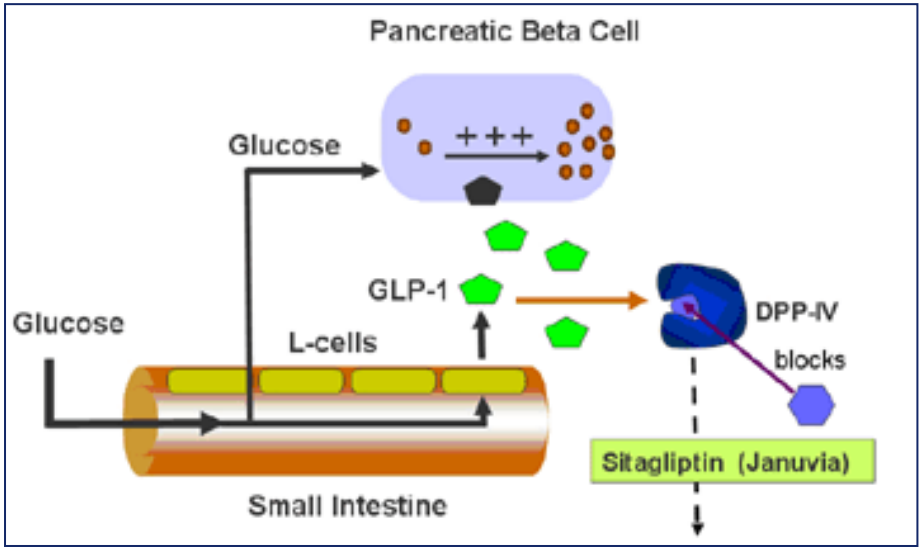


Mechanism of Action

Exenatide

Sitagliptin



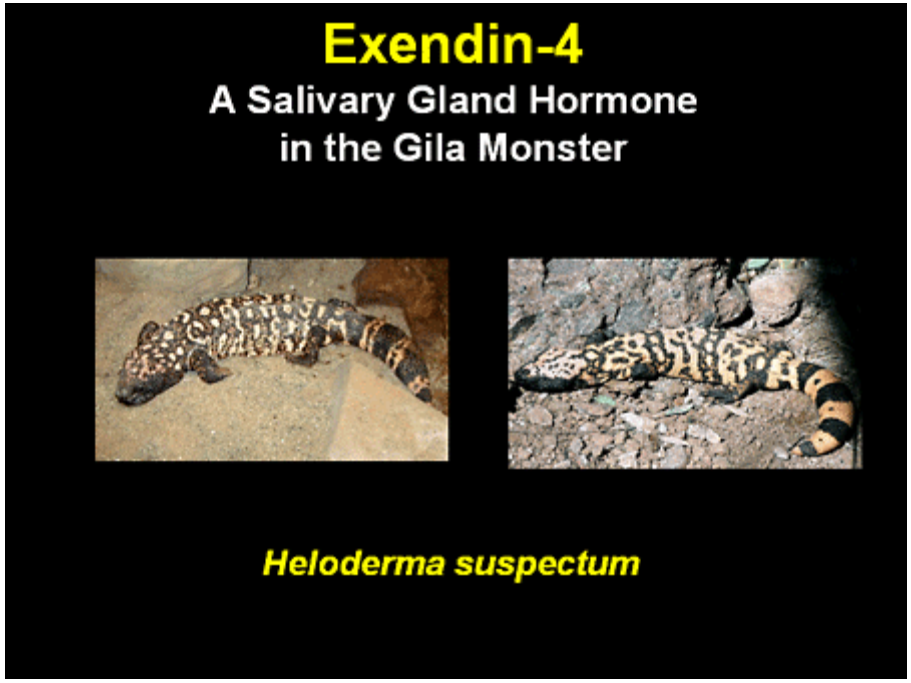


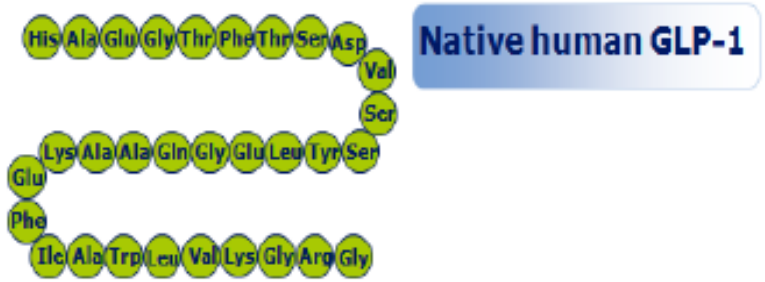
GLP-1 agonist

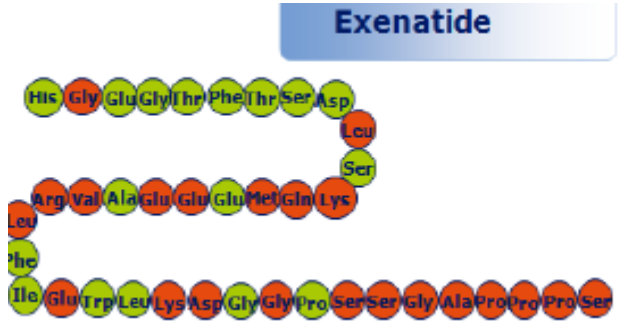
DPP-IV inhibitor

GLP-1 receptor agonists

- Exenatide
- GLP-1 analogs: Liraglutide







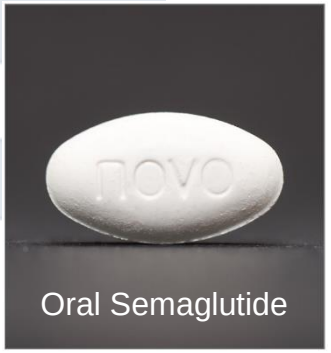
GLP-1 receptor agonists

- **Subcutaneous injection**
- DM type 2
- Adverse effect: nausea, vomiting, weight loss
- Not used in severe renal impairment
- Long acting GLP-1 agents: exenatide LAR, liraglutide

GLP-1 agonists can be effective for weight loss

GLP-1 receptor agonists

GLP-1R agonist generic name (trade name)	Dosing	Half-life	Administratio required before meals?
Short-acting			
Exenatide (Byetta)	Twice daily	2.4hours	Yes
Lixisenatide (Lyxumia)	Once daily	4hours	Yes
Intermediate-acting			
Liraglutide (Victoza)	Once daily	12hours	No
Long-acting			
Exenatide-LAR (Bydureon)	Once weekly	96hours	No
Albiglutide (Tanzeum)[a]	Once weekly	6–8 days	No
Dulaglutide (Trulicity)	Once weekly	90hours	No
Semaglutide (Ozempic)	Once weekly	165–184hours	No



Oral Semaglutide

GLP-1 receptor agonists

GLP-1 receptor agonist/ basal insulin fixed-dose combinations

Pen devices for injection

Drug name: Generic Commercial	Exenatide b.i.d. Byetta®	Lixisenatide Lyxumia®	Liraglutide Victoza®	Exenatide once weekly, Bydureon® (original)	Bydureon® BCise (improved)	Dulalgutide Trulicity®	Albiglutide Eperzan®, Tanzeum®	Semaglutide Ozempic®	IdegLira Xultophy®	iGlarLixi Soliqua®
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

DPP-IV(dipeptidylpeptidase-4) inhibitors

- Inhibit DPP-IV(dipeptidylpeptidase-4) enzyme
- Sitagliptin (FDA approval in October 2006),Vildagliptin, Saxagliptin, Linagliptin, Alogliptin
- Orally
- Monotherapy or combination with **metformin** or TZD

DPP-IV(dipeptidylpeptidase-4) inhibitors

- Well tolerated in short-term studies
- GI side effect, pancreatitis, drug rash
- Not associated with hypoglycemia and weight gain
- Precautions: DM type 1, Renal impairment

Table 2

Potential Risks and Benefits of DPP-4 Inhibitors

	Sitagliptin	Saxagliptin	Alogliptin	Linagliptin
Potential Benefits				
CV safety	Positive	Positive	Positive	NA
Blood pressure	Positive	Neutral	Neutral	Neutral
Weight gain	Neutral	Neutral	Neutral	Neutral
Renoprotective effects	Positive	Positive	Positive	Positive[a]
Hypoglycemia	Neutral	Neutral	Neutral	Neutral
Retinopathy	NA	Positive	NA	Positive
Wound healing	NA	Positive	NA	NA
Potential Risks				
HF hospitalization	Neutral	Increased risk	Potential risk[a]	NA
Acute pancreatitis	Potential risk[a]	Potential risk[a]	Potential risk[a]	Potential risk[a]
Arthralgia	Potential risk[b]	Potential risk[b]	Potential risk[b]	Potential risk[b]

[a] *Not significant.*
[b] *Postmarketing reports only.*
CV: cardiovascular; DPP-4: dipeptidyl peptidase-4; HF: heart failure; NA: not available.
Source: References 3, 11, 12, 17-38, 42.

Classification of Oral Hypoglycemic Agents

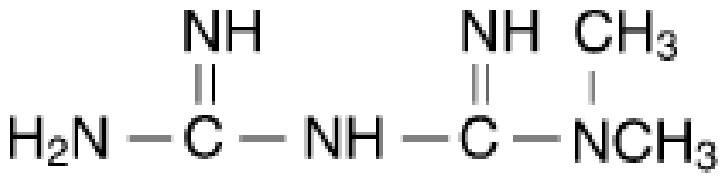
- **Insulin secretagogue**
  - Sulfonylurea
  - Non-sulfonylurea (Glinides or Meglitinides)
  - ยาที่มีผลต่อ GLP-1 (glucagon-like peptide-1) (incretin based therapy)
- **Insulin sensitizer**
  - Biguanide
  - Thiazolidinedione
- **Decrease carbohydrate absorption**
  - Alpha-glucosidase inhibitor
- **Decrease glucose reabsorption**
  - Sodium glucose co-transporter 2 inhibitor

Insulin sensitizers

- Biguanide
- Thiazolidinedione

Biguanides

- **Metformin**
- Phenformin
- Buformin

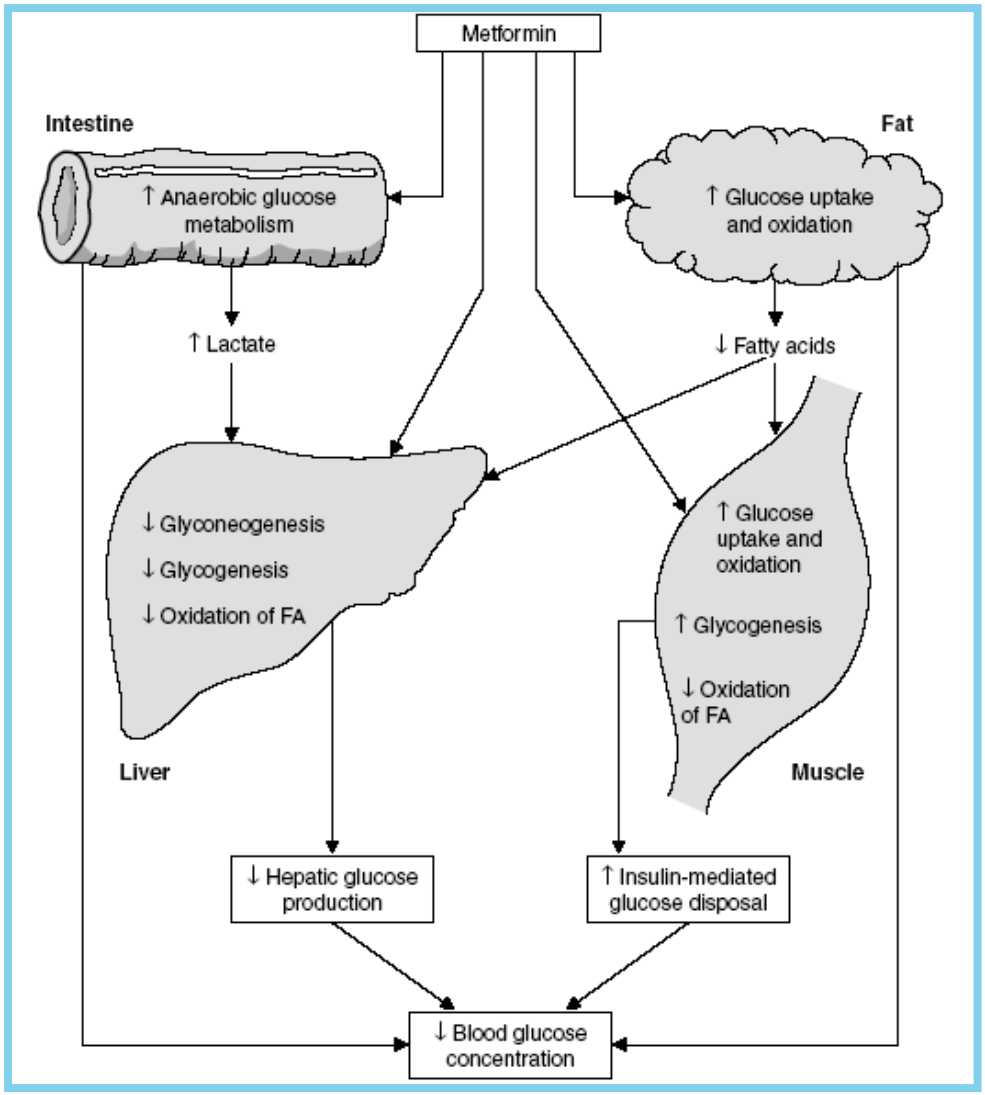


สูตรโครงสร้างของยา **Metformin**

Mechanism of Action

- Metformin is antihyperglycemic, not hypoglycemic
- Decreasing hepatic glucose production and by increasing insulin action in muscle and fat
- Activation of the cellular kinase AMP-activated protein kinase (AMPK)
- AMPK acts as a regulator of glucose and lipid metabolism and cellular energy regulation

Mechanism of Action



Metabolic and vascular effects of metformin

- Anti-hyperglycaemic action
- Weight stabilisation or reduction
- Improves lipid profile
- Counters insulin resistance
- No risk of serious hypoglycaemia
- Increased fibrinolysis
- Improved endothelial function

Pharmacokinetic

- absorbed mainly from the small intestine
- does not bind to plasma proteins
- not metabolised (not interfere with the metabolism of coadministered drugs)
- excreted unchanged in the urine
- half-life of about 2-5 hours

Indications

- The therapy of choice for **overweight** and **obese** patients with type 2 diabetes
- equally effective in normal weight patients

Contraindications

- Impaired renal function

  (GFR< 30mL/min/1.73m^2)
- Hepatic disease
- A past history of lactic acidosis (of any cause)
- Cardiac failure requiring pharmacological therapy
- Chronic hypoxic lung disease

Adverse Effect

- **Lactic acidosis** (most serious)
- Gastrointestinal side effect: abdominal dyscomfort, diarrhea, nausea
- Anorexia
- Metallic taste
- Minimized by increasing the dosage of the drug slowly and taking it with meals

Long-term use of metformin

- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency
- Periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy

Thiazolidinediones (TZD)

- Thiazolidinediones improve whole-body insulin sensitivity via multiple actions on gene regulation

  - ✓Rosiglitazone ✗
  - ✓Pioglitazone

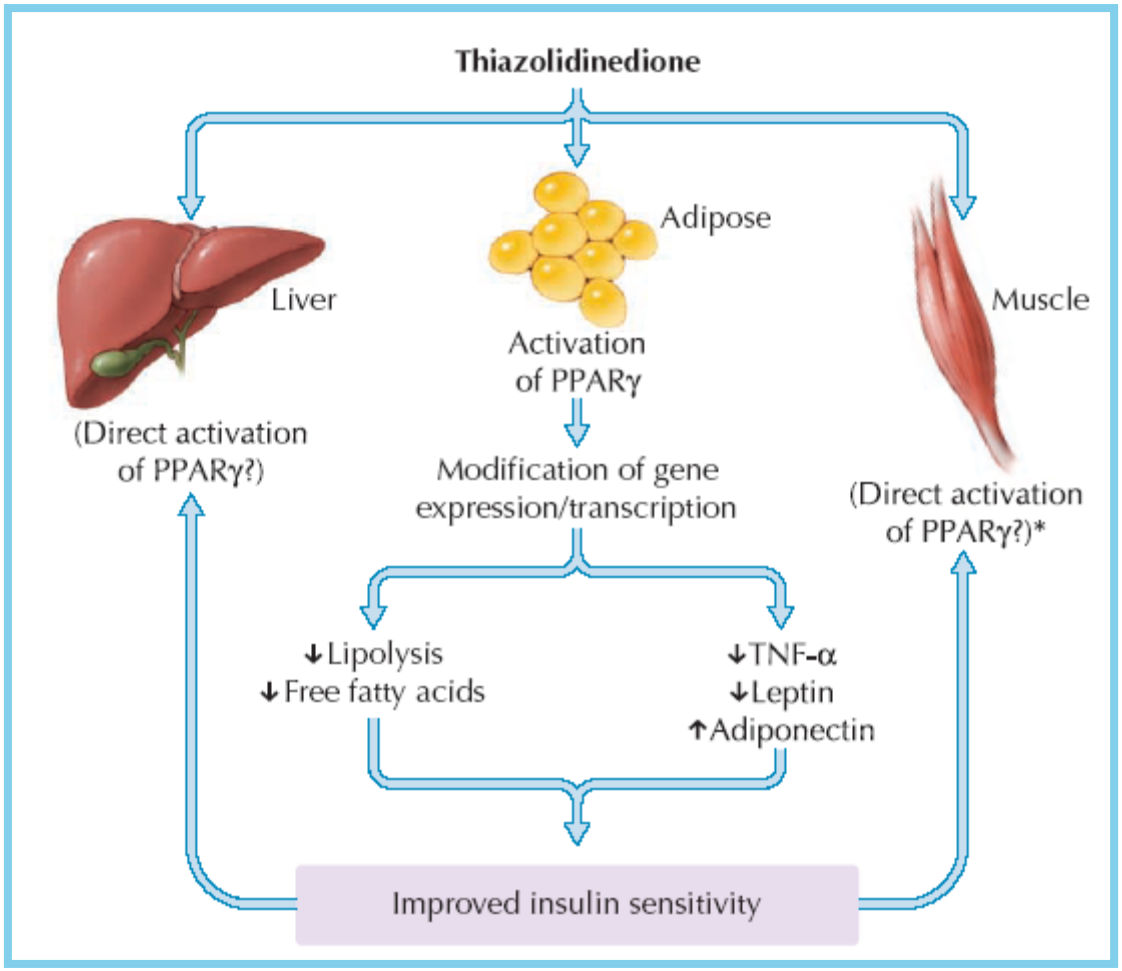
Mechanism of Action

- Selective agonists for nuclear peroxisome proliferator-activated receptor-γ (PPARγ)
- Activates insulin-responsive genes that regulate carbohydrate and lipid metabolism
- Increasing insulin sensitivity in peripheral tissue

Mechanism of Action

- Lower glucose production by the liver
- Increase glucose transport into muscle and adipose tissue
- Activate genes that regulate fatty acid metabolism in peripheral tissue

Mechanism of Action



Pharmacokinetic

- Rapidly, and nearly completely absorbed
- Extensively metabolised by the liver
- Rosiglitazone is metabolized by hepatic cytochrome P450 (CYP) 2C8
- Pioglitazone is metabolized by CYP3A4 and CYP2C8
- Almost completely bound to plasma proteins

Thiazolidinediones

- a slowly generated anti-hyperglycaemic effect that usually requires 2-3 months to reach maximum effect

Indication

- Mono or combination therapy
- non-obese and obese patients with type 2 diabetes
- Contraindicated for or intolerant of metformin

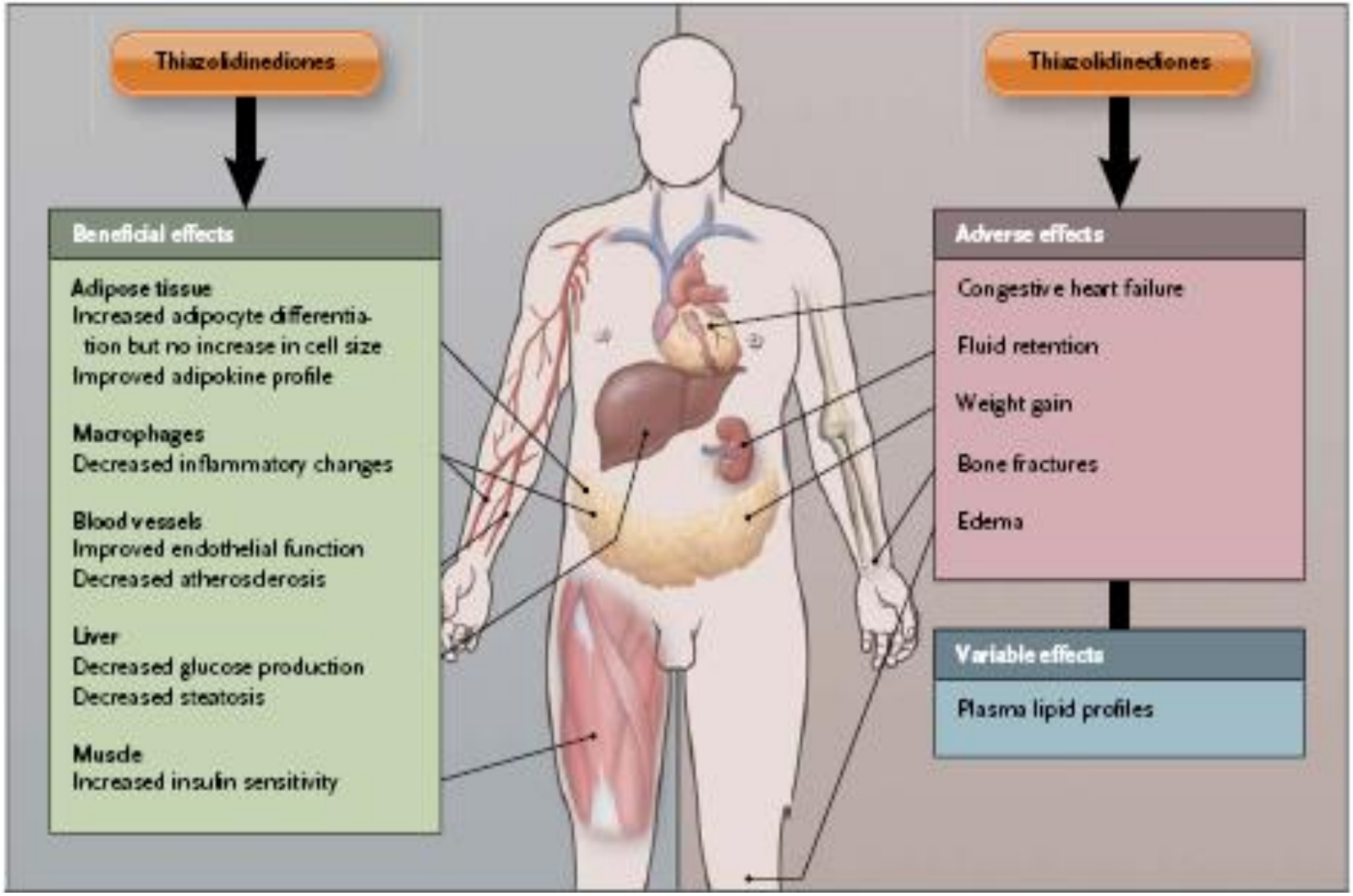
Contraindication

- Active liver disease
- **Heart failure** (NYHA class III,IV)
- Pregnancy and breast feeding (category C)
- Type 1 DM

Adverse Effects

- Hepatotoxicity (monitor liver function)
- **Fluid retention with increased plasma volume !!!**
- Reduced haematocrit and a decrease in haemoglobin concentration
- Weight gain
- Hypoglycemia

Effects of TZDs



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  - Alpha-glucosidase inhibitor
- **Decrease glucose reabsorption**
  - Sodium glucose co-transporter 2 inhibitor

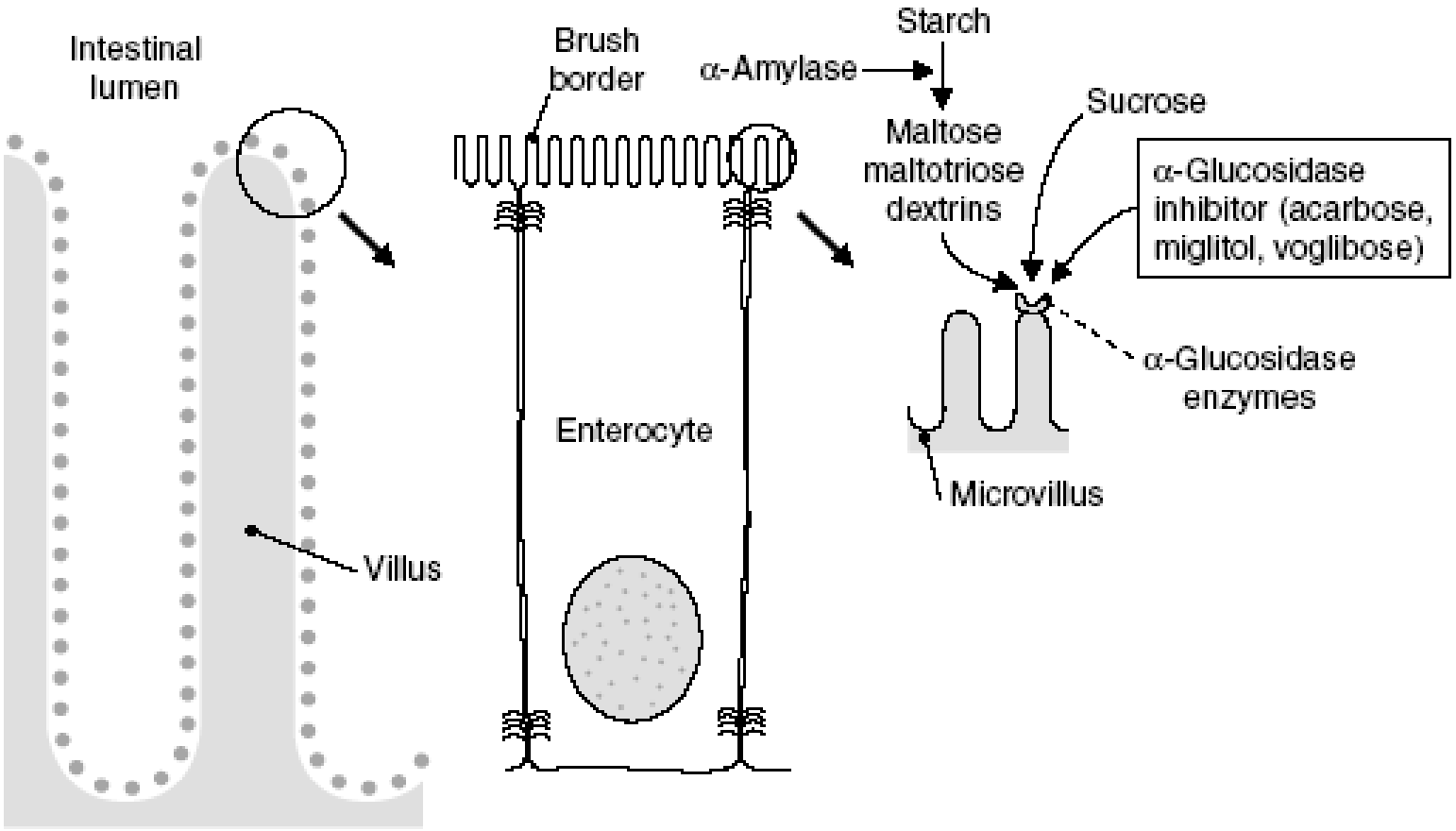
Alpha-glucosidase inhibitors

- Acarbose
- Voglibose

Mechanism of Action

- Inhibiting the action of alpha-glucosidase in the intestinal brush border
- Competitive and reversible inhibitors
- Reduce intestinal absorption of starch, dextrin, and disaccharides
- Slows the absorption of carbohydrates

Mechanism of Action

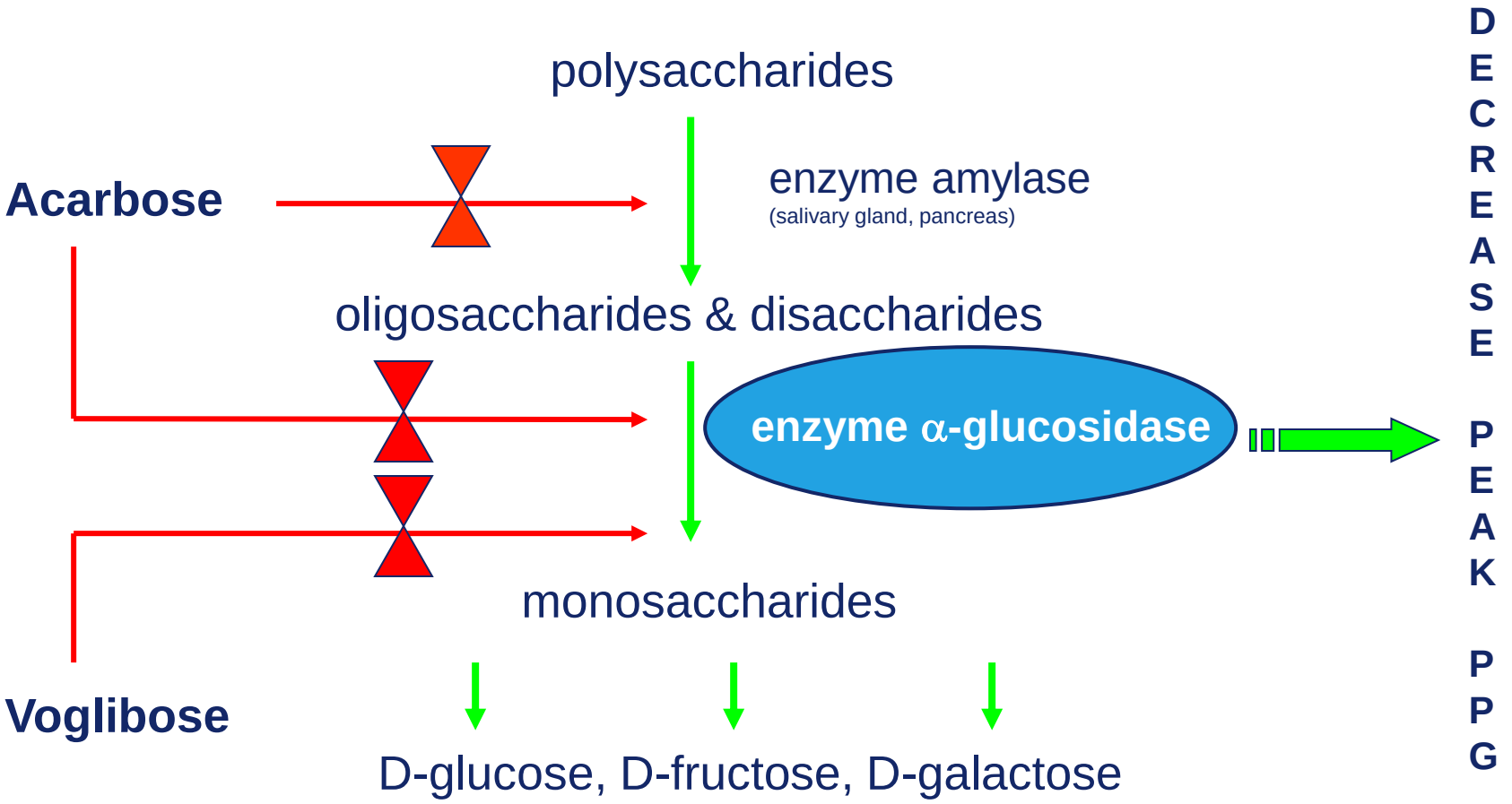


Alpha - Glucosidase Inhibitors

Acarbose

Voglibose

mechanism of action



Pharmacokinetic

- absorbed only to a trivial degree (<2%)
- degraded by amylases in the small intestine and by intestinal bacteria
- some of these degradation products are systemically absorbed
- eliminated in the urine
- for maximum effect, the drug must be taken with meal

Indication

- Mono or combination therapy
- α-glucosidase inhibitors target **postprandial** hyperglycaemia
- first- line treatment in patients who have raised basal glucose concentrations and more marked postprandial hyperglycaemia
- combine with insulin in treatment of Type 1 diabetes

Contraindications

- GI tract diseases that alter digestion and absorption
- Pregnancy and breast feeding
- Severe impairment of hepatic and renal function

Adverse Effects

- Gastrointestinal adverse effects: malabsorption, flatulence, diarrhea, and abdominal bloating
- Elevated liver enzymes
- Hypoglycemia (combination therapy)

Table 1. Side effects of select oral antidiabetic agents

	Hypoglycemia	Weight gain	Edema	GI effects	Lactic acidosis	Liver toxicity
Glipizide XL	1+	1+	0	±	0	±
Glyburide	4+	2+	0	±	0	±
Glimepiride	2+	1+	0	±	0	±
Repaglinide	1+	1+	0	0	0	0
Nateglinide	1+	?	0	0	0	0
Metformin	0	↓	0	2+	1+	0
Acarbose	0	0	0	3+	0	±
Miglitol	0	0	0	3+	0	0
Rosiglitazone	0	3+	2+	0	0	0*
Pioglitazone	0	3+	2+	0	0	0*

0 = none, ± = very infrequent, 1+ = infrequent, 2+ = occasional, 3+ = moderate, 4+ = significant, ↓ = decrease, ? = unknown

*Liver function monitoring is recommended

Table 1 Summary of glucose-lowering interventions as monotherapy

Interventions	Expected decrease in HbA_{1c} (%)	Advantages	Disadvantages
Step 1: initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in first year
Metformin	1–2	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: additional therapy			
Insulin	1.5–3.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycaemia, weight gain
Sulfonylureas	1–2	Inexpensive	Weight gain, hypoglycaemia[a]
Thiazolidinediones (glitazones)	0.5–1.4	Improved lipid profile[b]	Fluid retention, twofold increased risk of CHF, potential increase MI[c], potential decrease MI[b], atherogenic lipid profile[c], weight gain, expensive
Other drugs			
α-Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5[d]	Short duration	Three times/day dosing, expensive, hypoglycaemia
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience
Sitagliptin	0.5–0.8	Weight neutral	Little experience, expensive

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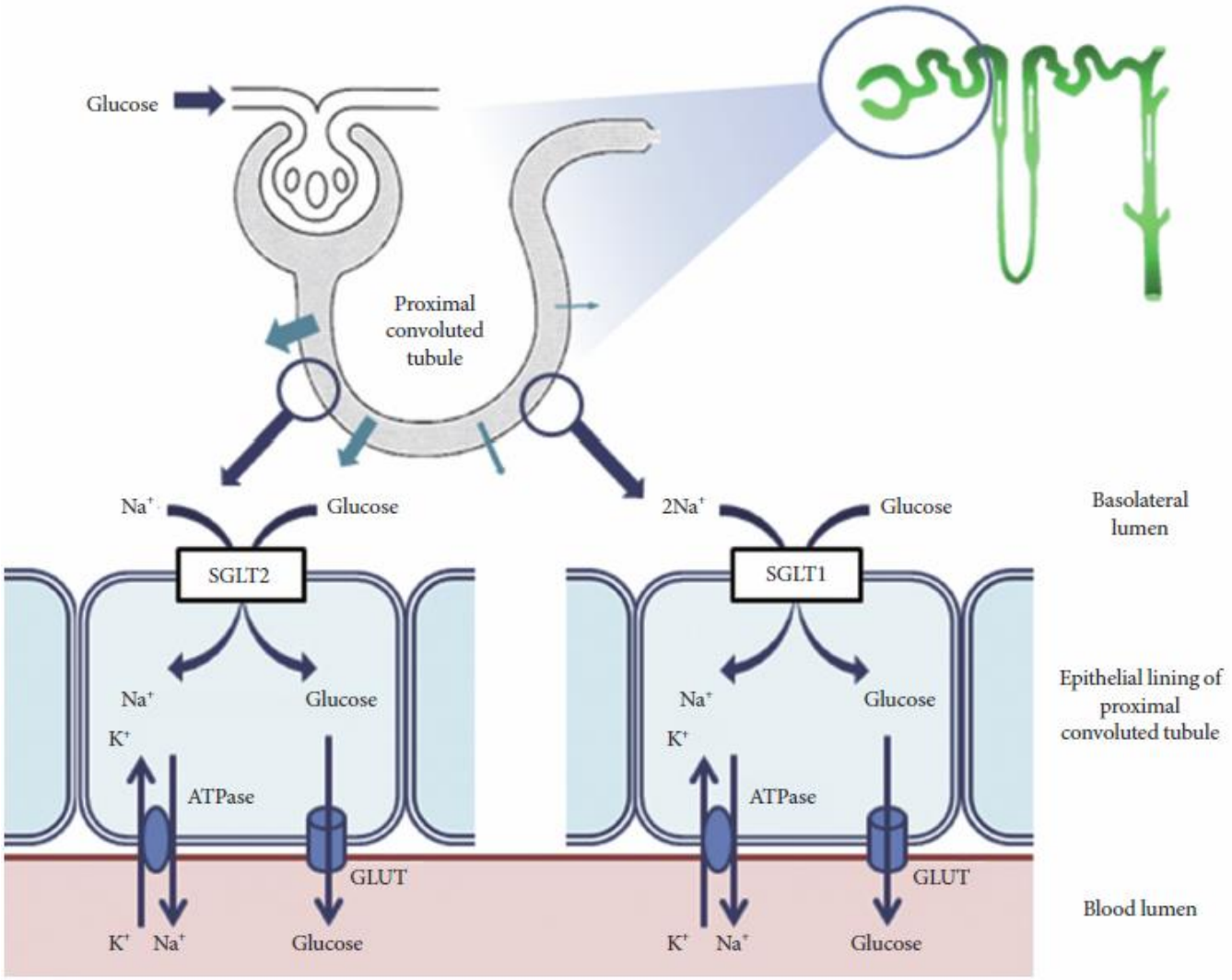
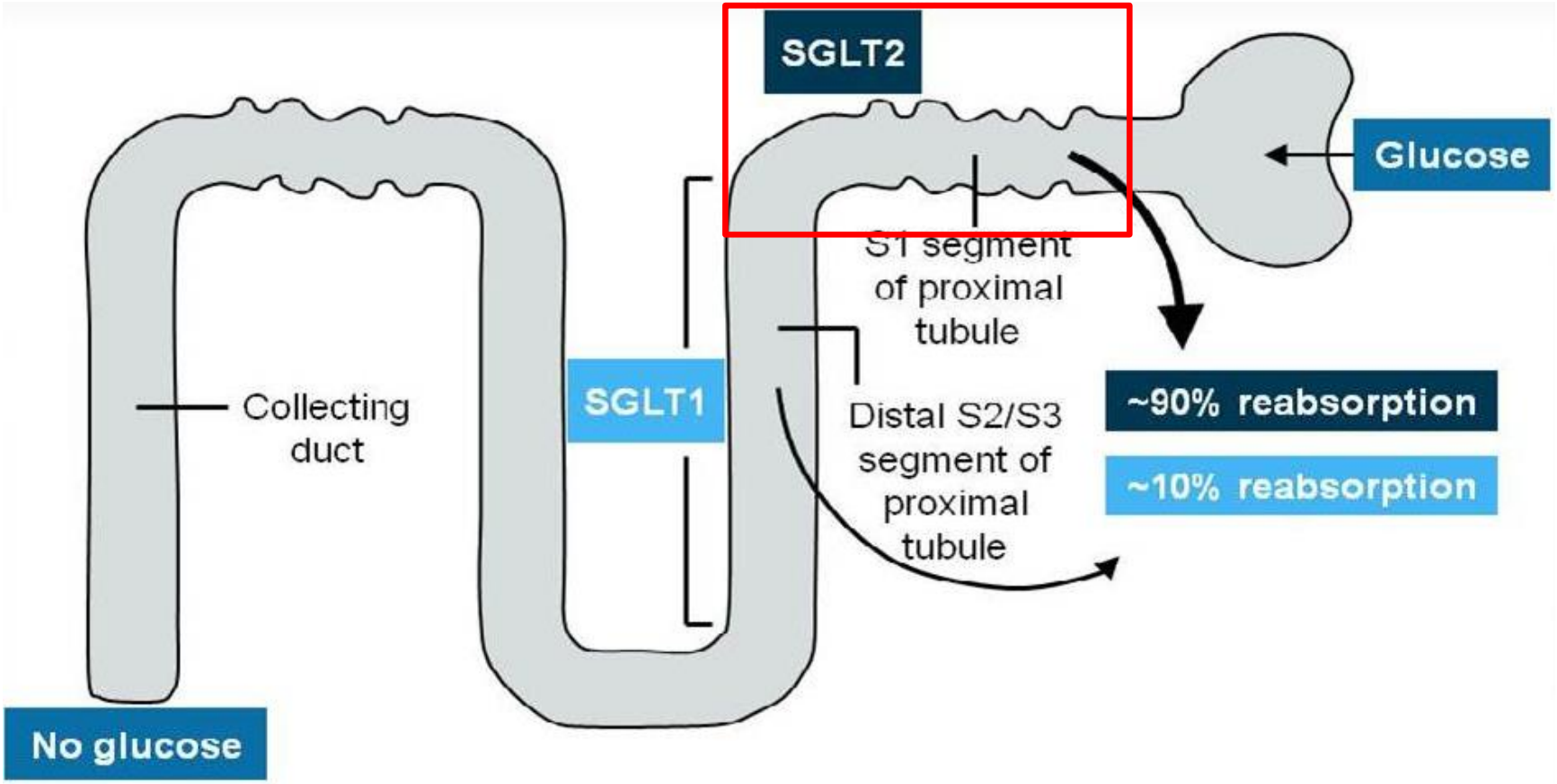
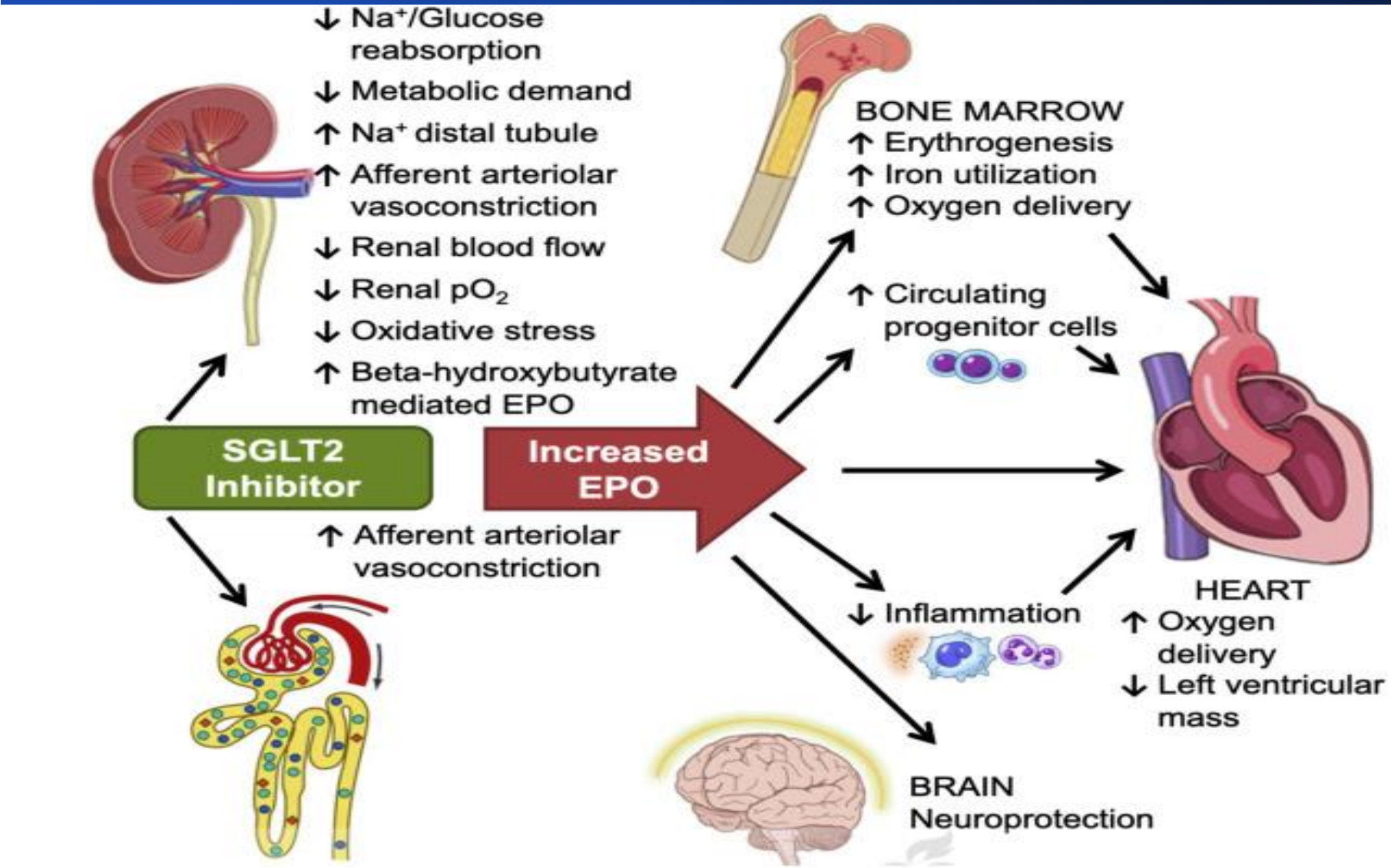
sodium-glucose co-transporter 2 (SGLT2) inhibitors

- The SGLT2 is expressed in the proximal tubule
- Reabsorption of approximately 90 percent of the filtered glucose load
- SGLT2 inhibitors promote the renal excretion of glucose
- Dapaglifozin,canaglifozin,empaglifozin

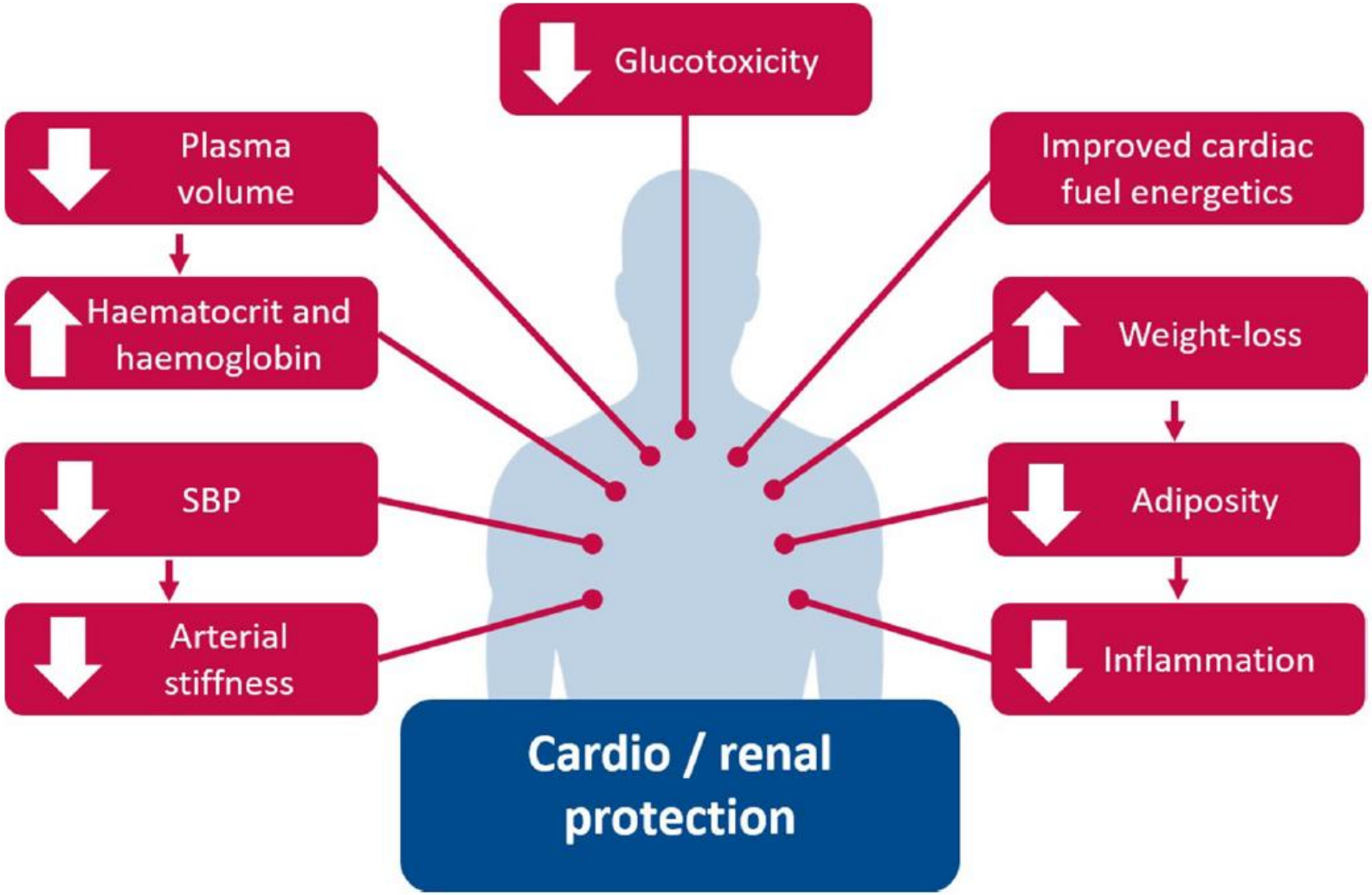

Glucose
Proximal convoluted tubule
Na+
Glucose
SGLT2
2Na+
Glucose
SGLT1
Basolateral lumen
Na+
Glucose
K+
ATPase
GLUT
Epithelial lining of proximal convoluted tubule
K+
Na+
Glucose
Blood lumen

sodium-glucose co-transporter 2 (SGLT2) inhibitors




↓ Na+/Glucose reabsorption
↓ Metabolic demand
↑ Na+ distal tubule
↑ Afferent arteriolar vasoconstriction
↓ Renal blood flow
↓ Renal pO2
↓ Oxidative stress
↑ Beta-hydroxybutyrate mediated EPO
SGLT2 Inhibitor
Increased EPO
↑ Afferent arteriolar vasoconstriction
BONE MARROW
↑ Erythrogenesis
↑ Iron utilization
↑ Oxygen delivery
↑ Circulating progenitor cells
↓ Inflammation
HEART
↑ Oxygen delivery
↓ Left ventricular mass
BRAIN
Neuroprotection

Benefit of SGLT 2 inhibitors



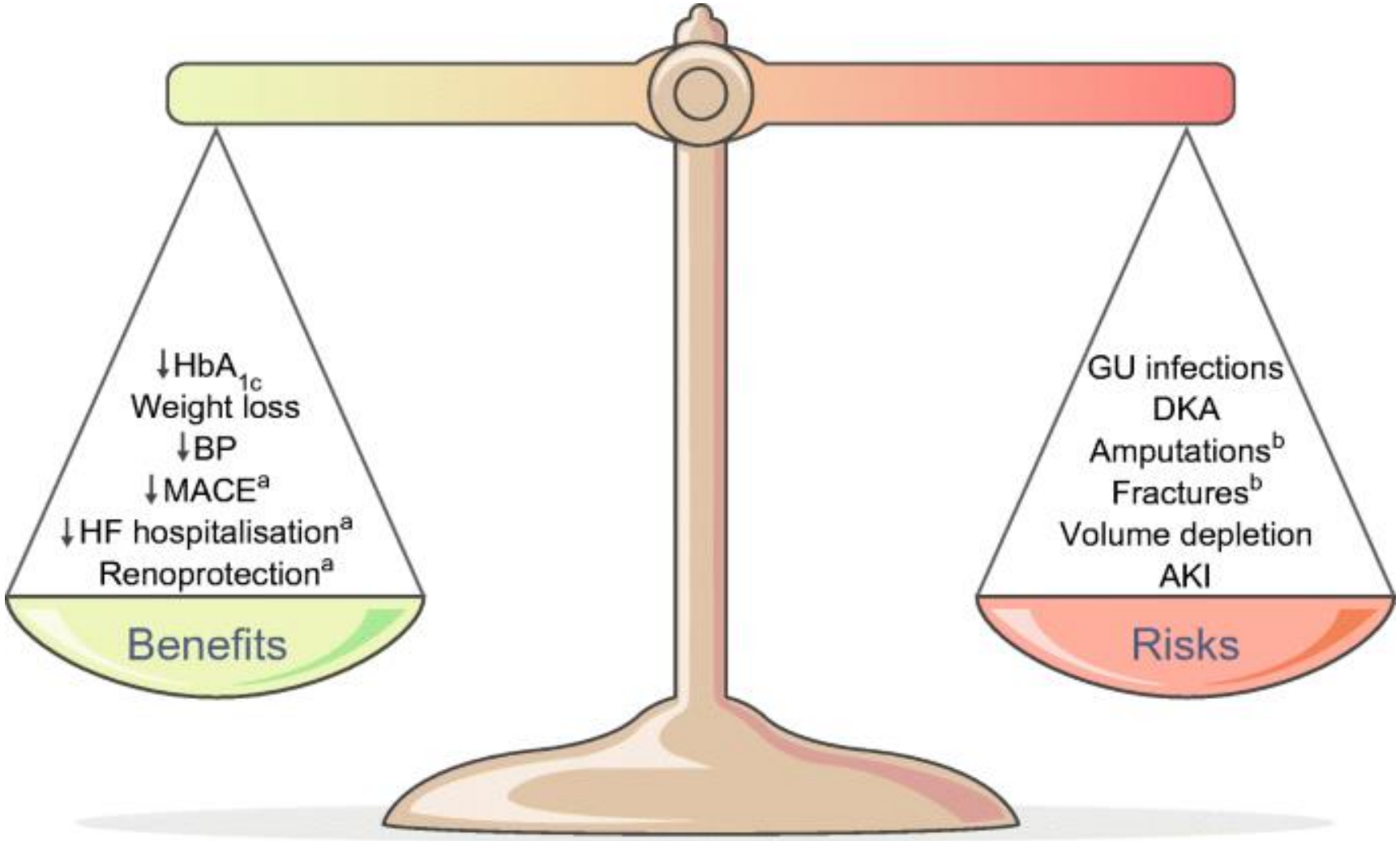
Side effects of SGLT2 inhibitors

- increased incidence of vulvovaginal candidiasis
- increase in the rate of urinary tract infections
- Do not use in severe renal impairment
- no long-term safety data with regard to the effects of chronic glucosuria on the urinary tract

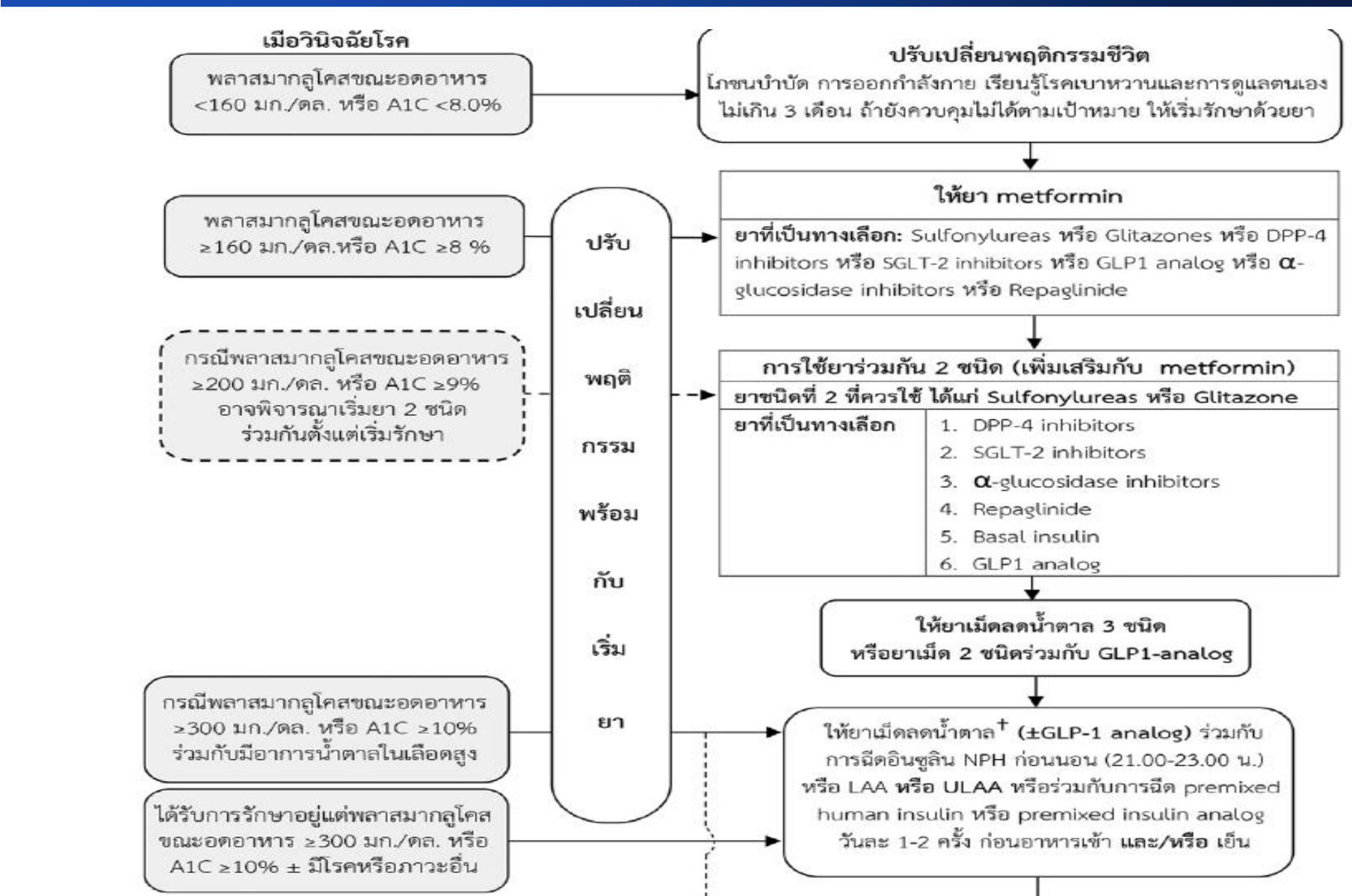
Side effects of SGLT2 inhibitors

- In May 2015, the FDA issued a warning that gliflozins can increase risk of diabetic ketoacidosis (DKA)
- Decreased bone mineral density, increased risk of bone fractures.

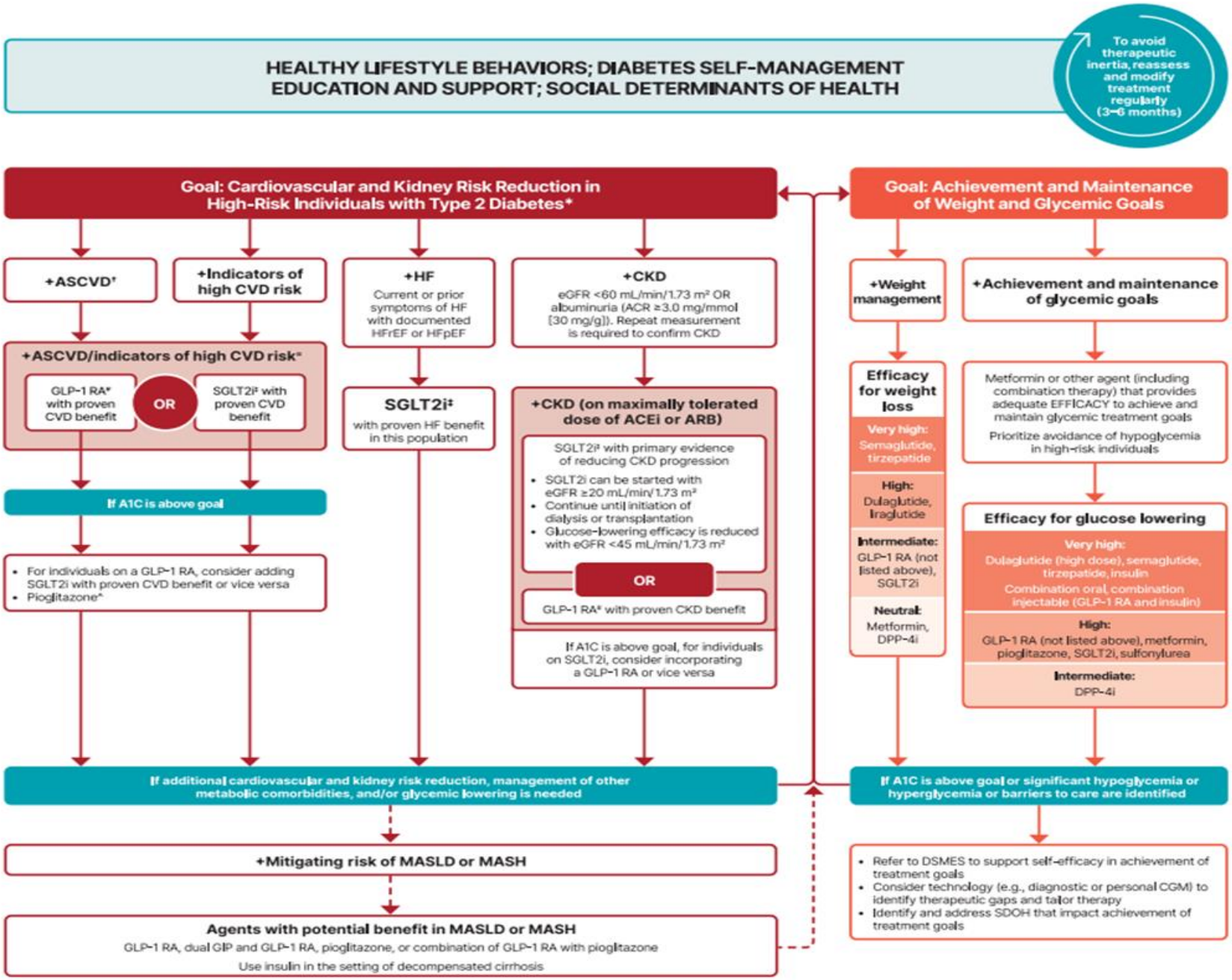
Benefit and Risk SGLT 2 inhibitors

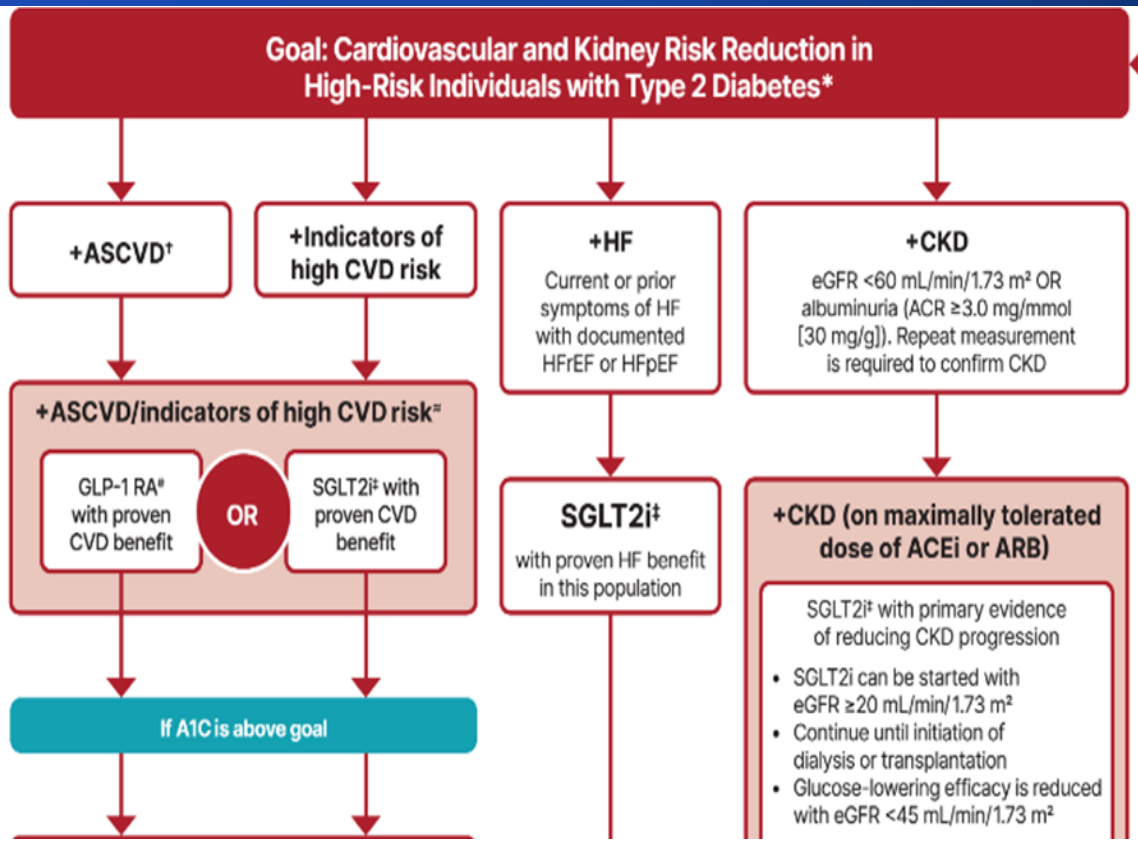


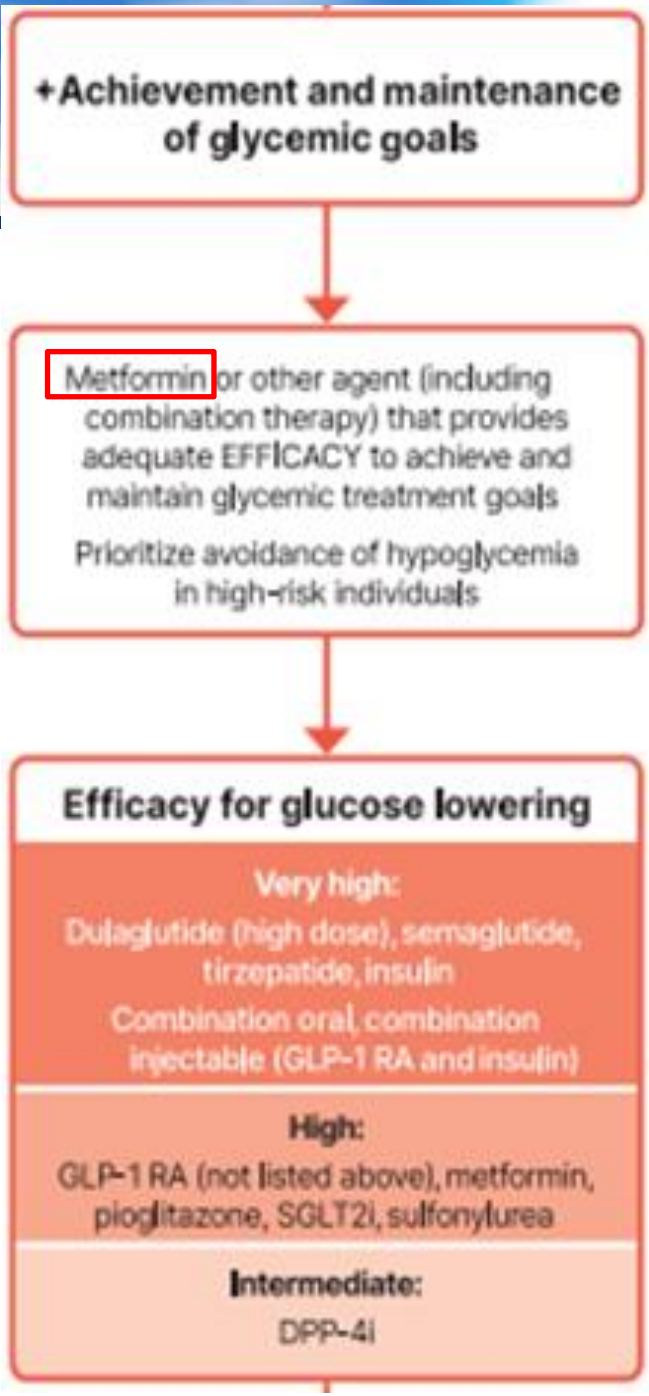
แนวทางการให้ยาควบคุมระดับน้ำตาล



Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes




Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
+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
+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
If A1C is above goal


+Achievement and maintenance of glycemic goals
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

Questions???