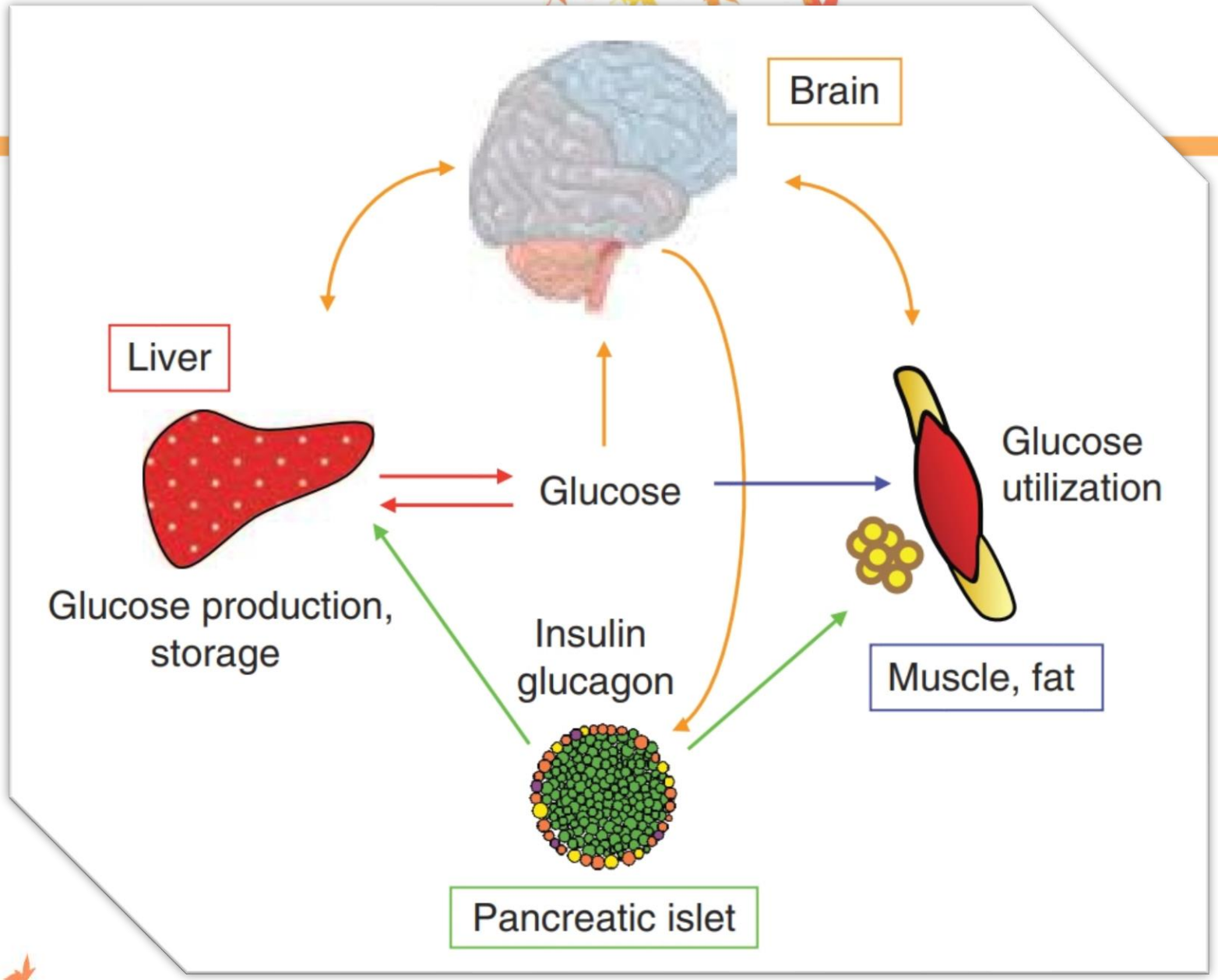
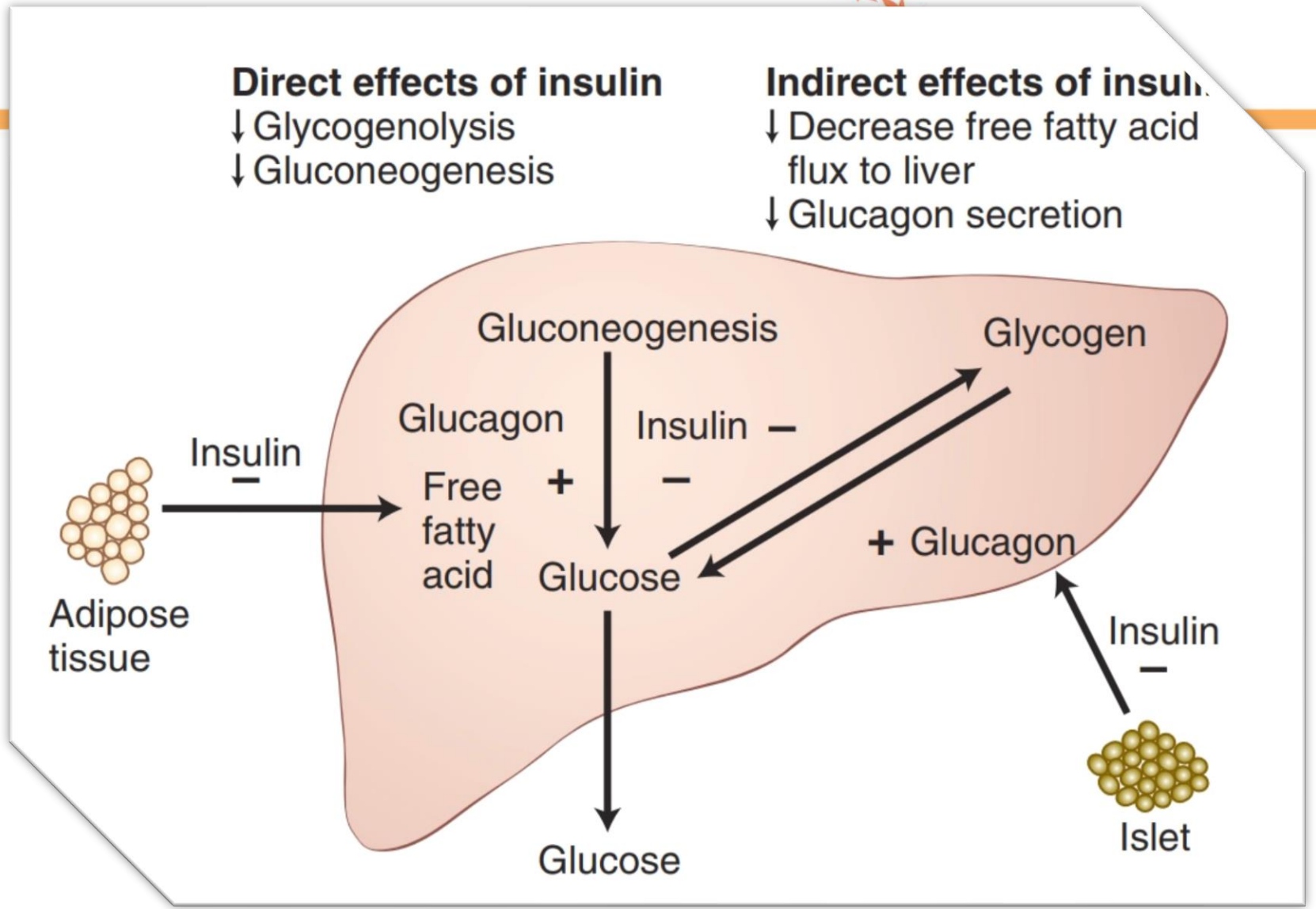

بسم الله الرحمن الرحيم

Pharmacologic Treatment Of

Diabetes mellitus

Dr. Abolfazl Heidari


Brain
Liver
Glucose
Glucose utilization
Glucose production, storage
Insulin glucagon
Muscle, fat
Pancreatic islet


Direct effects of insulin
↓ Glycogenolysis
↓ Gluconeogenesis
Indirect effects of insul
↓ Decrease free fatty acid flux to liver
↓ Glucagon secretion
Gluconeogenesis
Glycogen
Glucagon
Insulin −
Insulin
−
Free fatty acid
+
−
+ Glucagon
Glucose
Adipose tissue
Insulin
−
Glucose
Islet

Etiology of Type 2 Diabetes Mellitus

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of:

- insulin resistance
- impaired insulin secretion
- excessive hepatic glucose production
- abnormal fat metabolism

Criteria for the diagnosis of **diabetes**

Table 2.2—Criteria for the diagnosis of diabetes
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Criteria defining **prediabetes**

Table 2.5—Criteria defining prediabetes*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Screening for prediabetes and type 2 diabetes

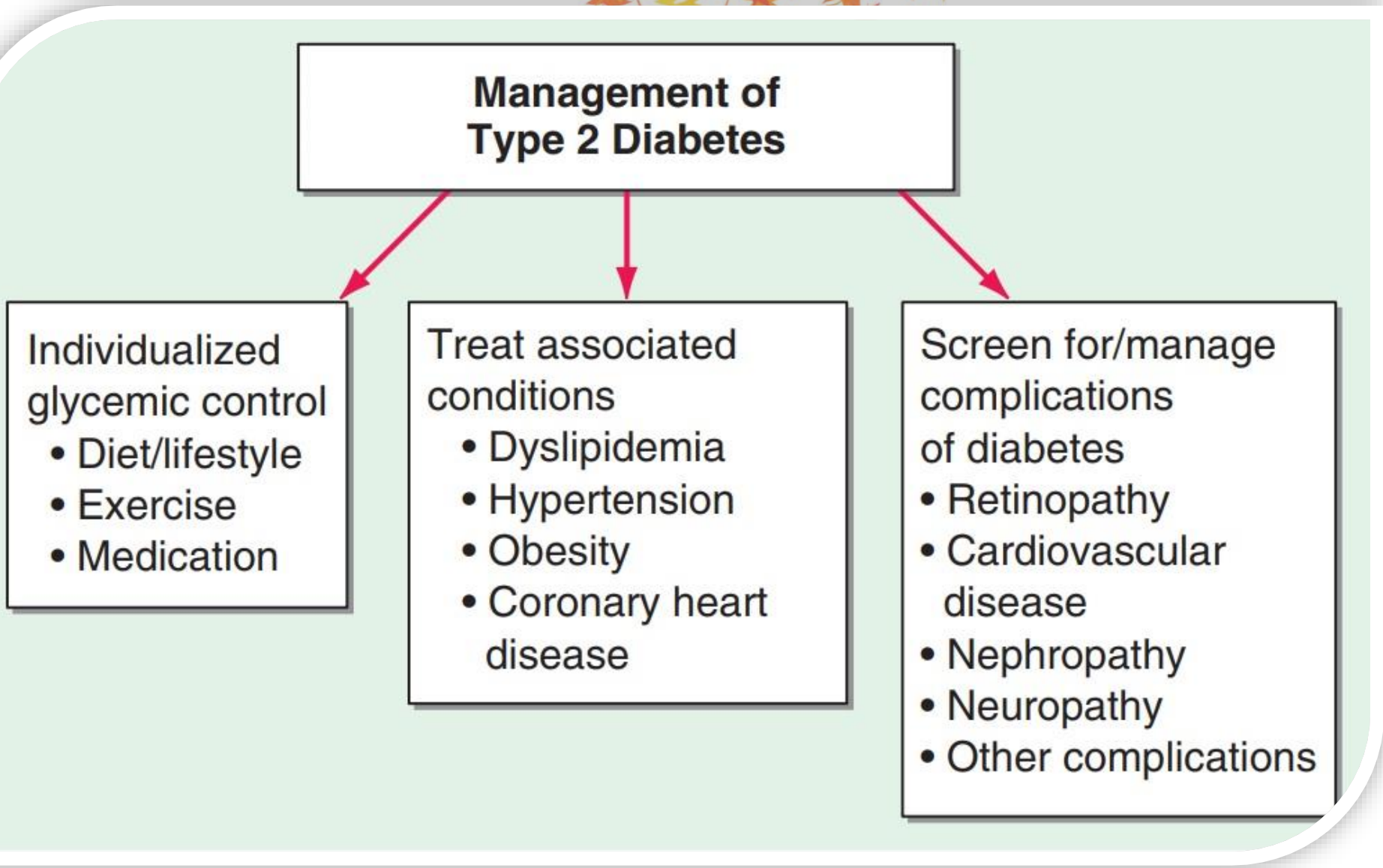
Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

CVD, cardiovascular disease; GDM, gestational diabetes mellitus.

Pharmacologic Treatment Of Diabetes

TYPE 2 DIABETES MELLITUS


Management of Type 2 Diabetes
Individualized glycemic control
• Diet/lifestyle
• Exercise
• Medication
Treat associated conditions
• Dyslipidemia
• Hypertension
• Obesity
• Coronary heart disease
Screen for/manage complications of diabetes
• Retinopathy
• Cardiovascular disease
• Nephropathy
• Neuropathy
• Other complications

Glucose-Lowering Agents

↓ Hepatic glucose production → **Metformin** (Glucophage)

↑ Insulin secretion → **Gliclazide**, **Glibenclamide**, **Repaglinide**

↓ Insulin resistance,↑ glucose utilization → **pioglitazone**

GLP1 receptor agonist → **Liraglutide** (Victoza)

DPP4 inhibitor → **Sitagliptin** (Ziptin), **Linagliptin** (Lirenta)

↑ Urinary glucose excretion → **empagliflozin** (Gloripa)

↓ GI glucose absorption → **Acarbose**

Insulin

Biguanides

Metformin (Glucophage) → 500, 1000

Action ⇨ ↓ Hepatic glucose production

HBA1C Reduction (%) ⇨ 1–2

Fasting/Prandial Effect ⇨ Fasting

Advantages

- Weight neutral
- No **hypoglycemia**
- Inexpensive
- Extensive experience
- ↓ CV events

Disadvantages

- Diarrhea, nausea
- **lactic acidosis**
- vitamin B12 deficiency

Contraindications

- Renal insufficiency (GFR<30 mL/min)
- CHF
- Radiographic contrast studies
- Hospitalized patients
- Acidosis

Sulfonylureas

Gliclazide (Diabezide)→80, 30, 60mg

Glibenclamide (Glyburide) →5mg

Action ⇨ **Insulin secretagogue**

(↑ Insulin secretion)

HBA1C Reduction (%) ⇨ 1–2

Fasting/Prandial Effect ⇨ Fasting

Advantages

- Short onset of action
- lower postprandial glucose
- inexpensive

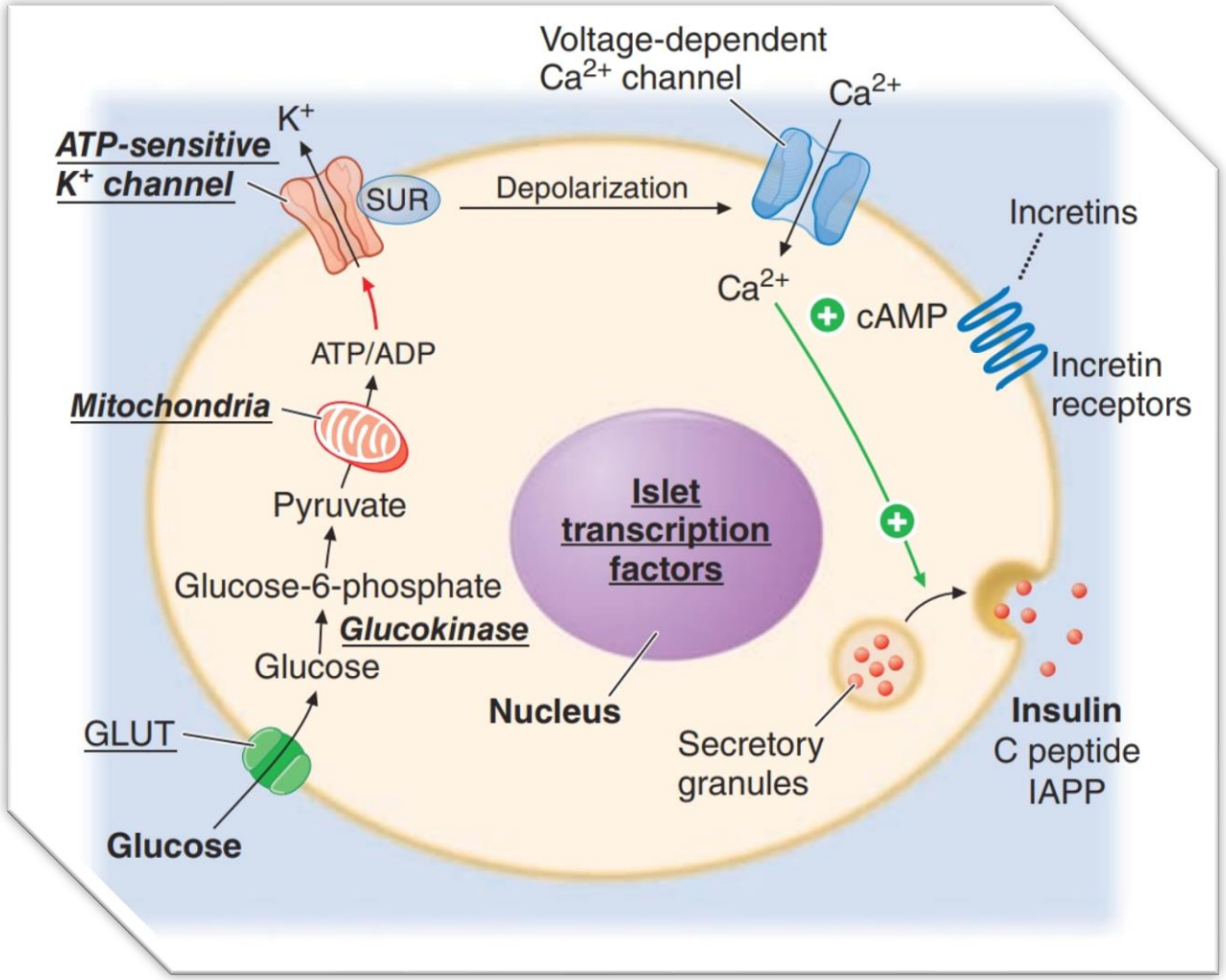
Disadvantages

- Hypoglycemia
- Weight gain

Contraindications

- Renal/liver disease

Sulfonylureas



Meglitinide

Repaglinide (Newbet) →0.5, 1, 2mg

Action ⇨ **Insulin secretagogue**

(↑ Insulin secretion)

HBA1C Reduction (%) ⇨ 0.5–1.0

Fasting/Prandial Effect ⇨ Prandial

Advantages

Short onset of action

lower postprandial glucose

Disadvantages

Hypoglycemia

Weight gain

Contraindications

Renal/liver disease

Thiazolidinediones (TZDs)

Pioglitazone → 15, 30, 45mg

Action ⇨

↓ Insulin resistance

↑ glucose utilization

HBA1C Reduction (%) ⇨ 0.5–1.4

Fasting/Prandial Effect ⇨ Fasting

Advantages

Lower insulin requirements

Disadvantages

Fluid retention (Peripheral edema)

CHF

weight gain

Contraindications

CHF (class III or IV)

liver disease

GLP-1 receptor agonists

Liraglutide (Victoza, Saxenda)

Action ⇨

- ↑ glucose-stimulated insulin secretion
- ↓ glucagon
- Slow gastric emptying
- Satiety

HBA1C Reduction (%) ⇨ 0.5–1.0

Fasting/Prandial Effect ⇨ Both

Advantages

- **Weight loss**
- No **hypoglycemia**
- decrease **CVD** events

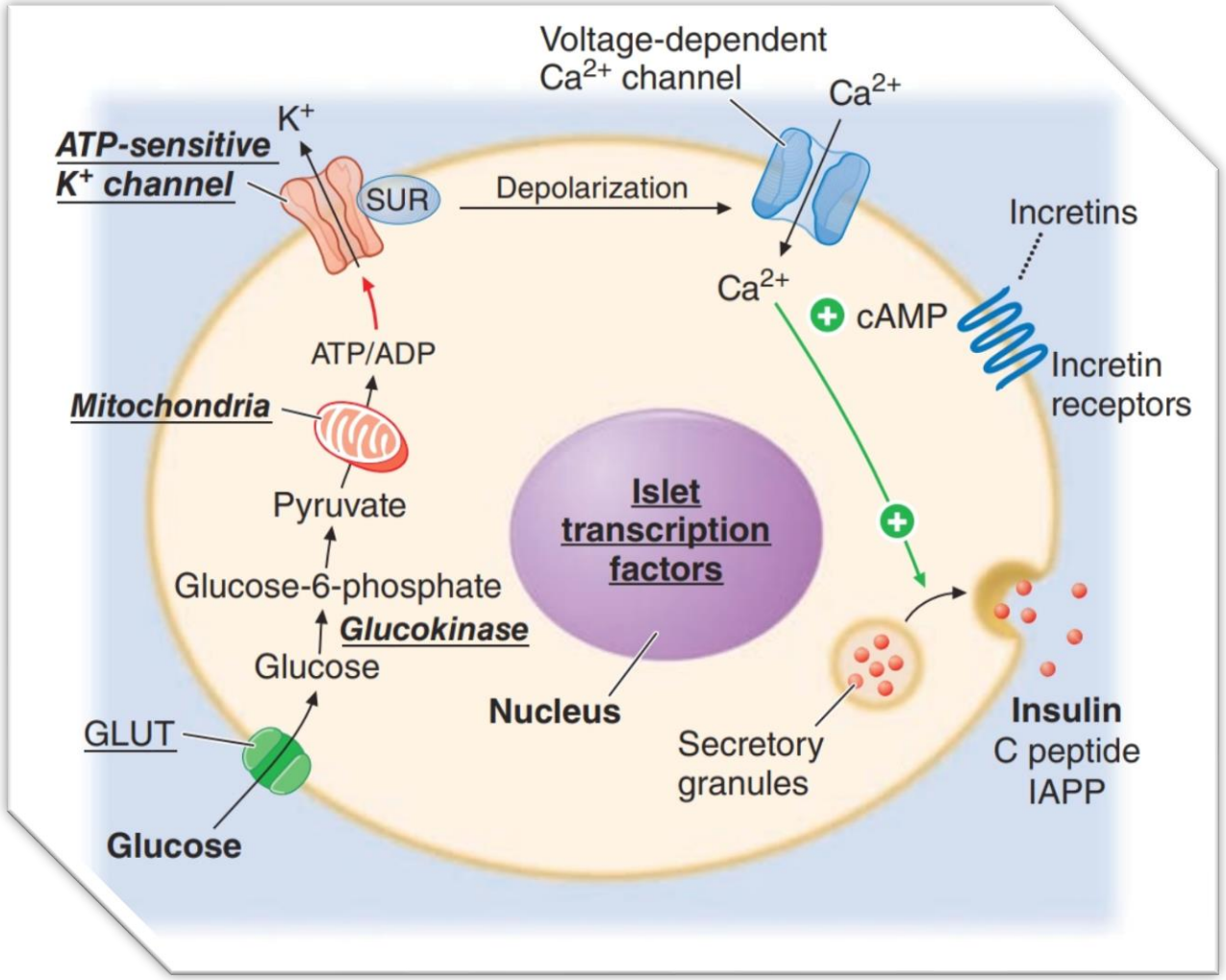
Disadvantages

- **Injection**, nausea, vomiting, diarrhea
- expensive

Contraindications

- Renal disease
- Agents that also slow GI motility
- History of Medullary thyroid carcinoma (MTC)
- pancreatic disease

GLP-1 receptor agonists



Dipeptidyl peptidase IV inhibitors

Sitagliptin (Ziptin) → 50, 100mg

Linagliptin (Lirenta) → 5mg

Action ⇨

Prolong endogenous GLP-1 action

↑ Insulin

↓ glucagon

HBA1C Reduction (%) ⇨ 0.5–0.8

Fasting/Prandial Effect ⇨ Both

Advantages

Well tolerated

do not cause hypoglycemia

Disadvantages

Angioedema/urticarial

Contraindications

Renal disease

Pancreatitis

Sodium-glucose cotransporter 2 (SGLT2)inhibitors

Empagliflozin (Gloripa) →10, 25mg

Action ⇨ ↑ renal glucose Excretion

HBA1C Reduction (%) ⇨ 0.5–1.0

Fasting/Prandial Effect ⇨ Both

Advantages

No hypoglycemia

↓ weight and BP

decrease CVD events

Disadvantages

Urinary and genital infections

Polyuria (diuretic effect)

Dehydration

Euglycemic DKA

Contraindications

Renal disease

Type 1 DM

α-Glucosidase inhibitors

Acarbose → 50, 100mg

Action ⇨ ↓ GI glucose Absorption

HBA1C Reduction (%) ⇨ 0.5–0.8

Fasting/Prandial Effect ⇨ Prandial

Advantages

Reduce postprandial Glycemia

Disadvantages

Diarrhea

GI flatulence

abdominal distention

Liver function tests

Contraindications

Renal/liver disease

inflammatory bowel disease

gastroparesis

Combination Pills

Zipmet (Sitagliptin + Metformin) → 50/500, 50/1000

Melijent-M (Linagliptin + Metformin) → 2.5/500, 2.5/1000

Synoripa (Empagliflozin + Metformin) → 5/500, 5/1000, 12.5/500, 12.5/1000

Glorenta (Empagliflozin + Linagliptin) → 10/5

Initiation of medication

Metformin is the preferred initial pharmacologic agent.

- Weight neutral
- No **hypoglycemia**
- Inexpensive
- Extensive experience
- ↓ CV events

Consider initiating dual therapy in patients with:

- A1C ≥1.5% above their glycemic target

patients who have **CVD** or **CKD**, SGLT2 inhibitors, or GLP1 receptor agonists are recommended as **second choice**.

patients with CVD with heart failure or at high risk of HF SGLT2 inhibitors are preferred.

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

NO

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ASCVD PREDOMINATES

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY

GLP-1 RA with proven CVD benefit[1]

OR

SGLT2i with proven CVD benefit[1] if eGFR adequate[2]

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m^2 or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If A1C above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If A1C above target			
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[7]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[8] — EITHER/OR — SGLT2i[2]

If A1C above target

SGLT2i[2] | GLP-1 RA with good efficacy for weight loss[8]

If A1C above target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU[6] • TZD[5] • Basal insulin

COST IS A MAJOR ISSUE[9-10]

SU[6] | TZD[10]

If A1C above target

TZD[10] | SU[6]

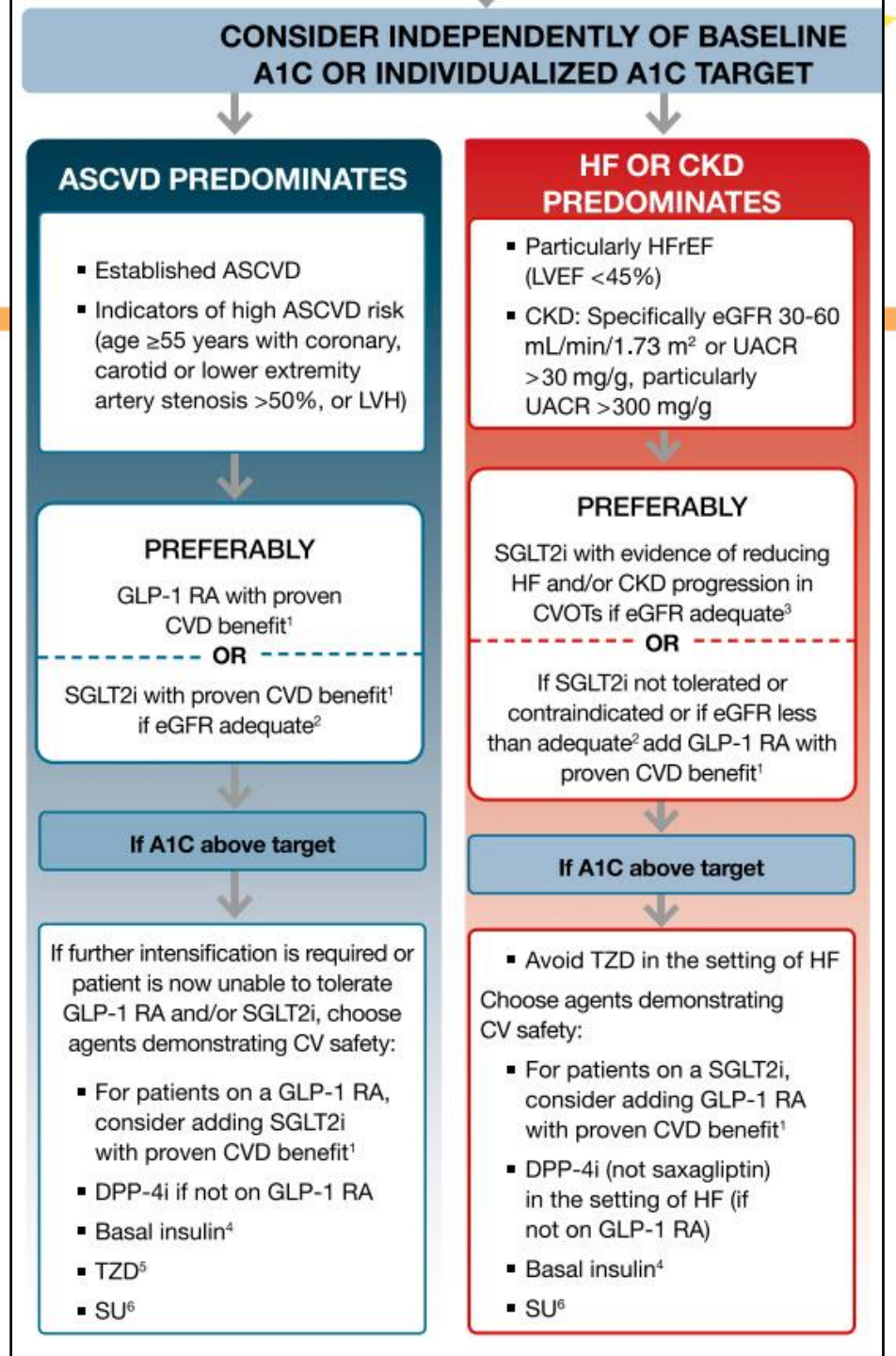
If A1C above target

- **Insulin therapy** basal insulin with lowest acquisition cost

OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

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
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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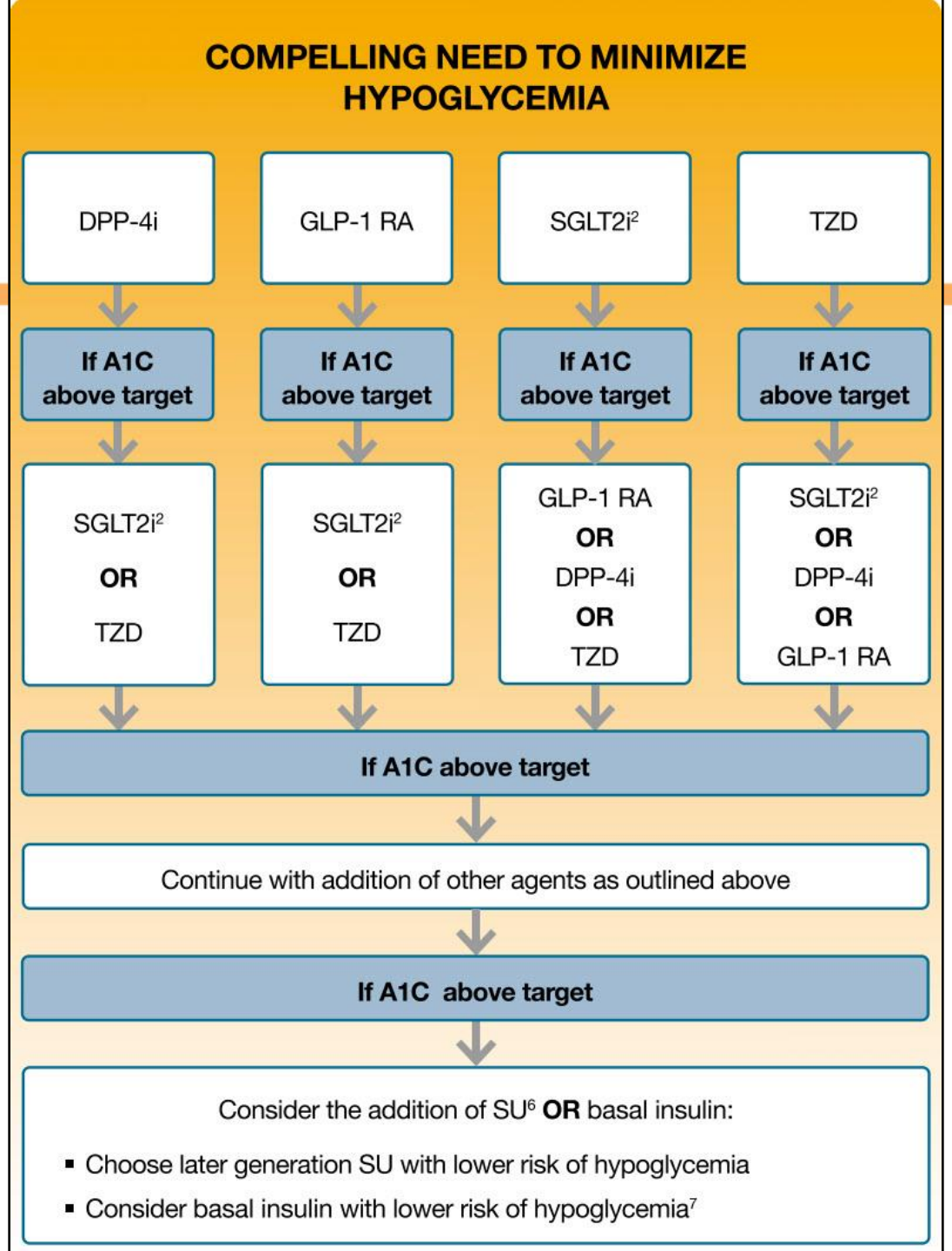
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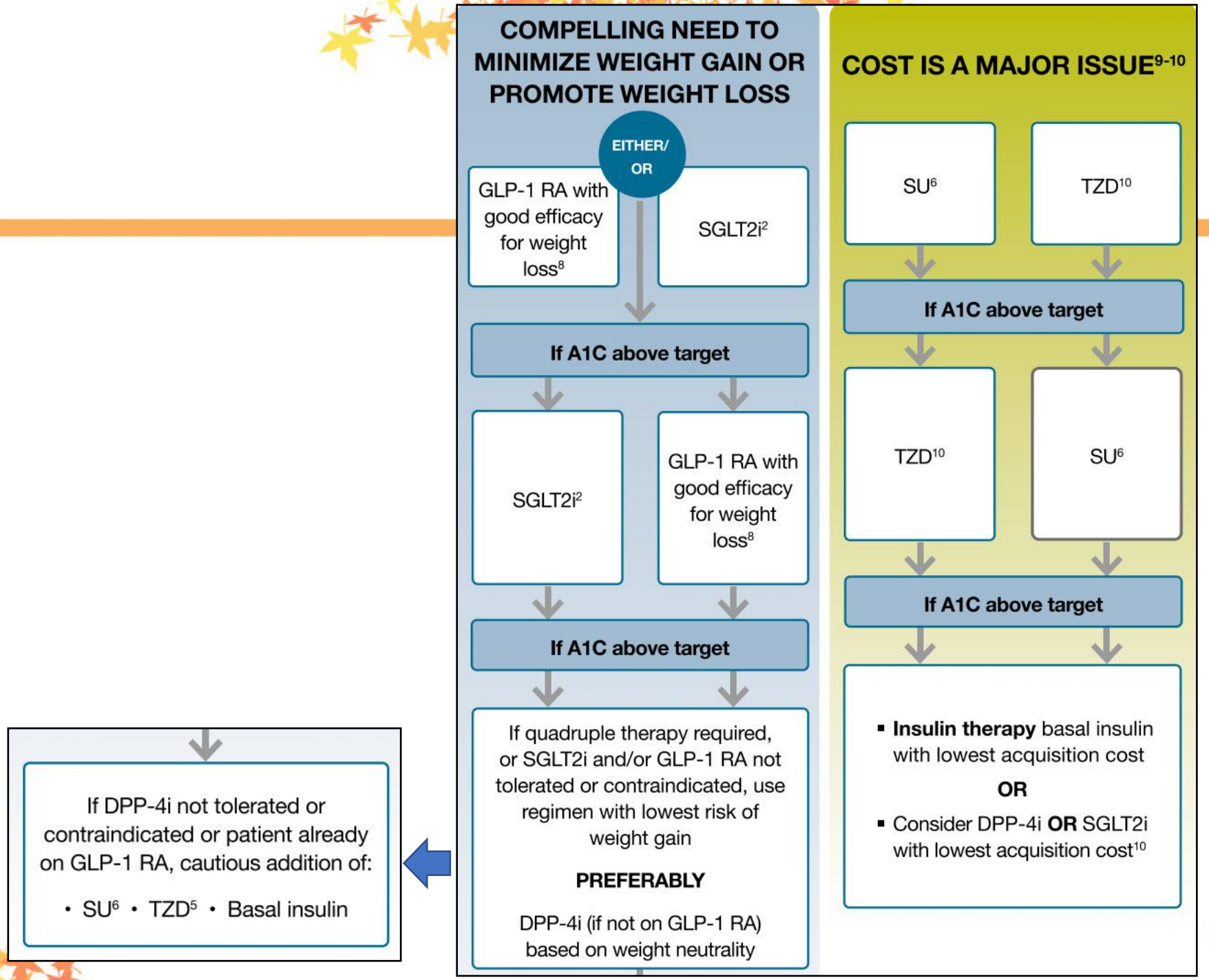
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SU[6]
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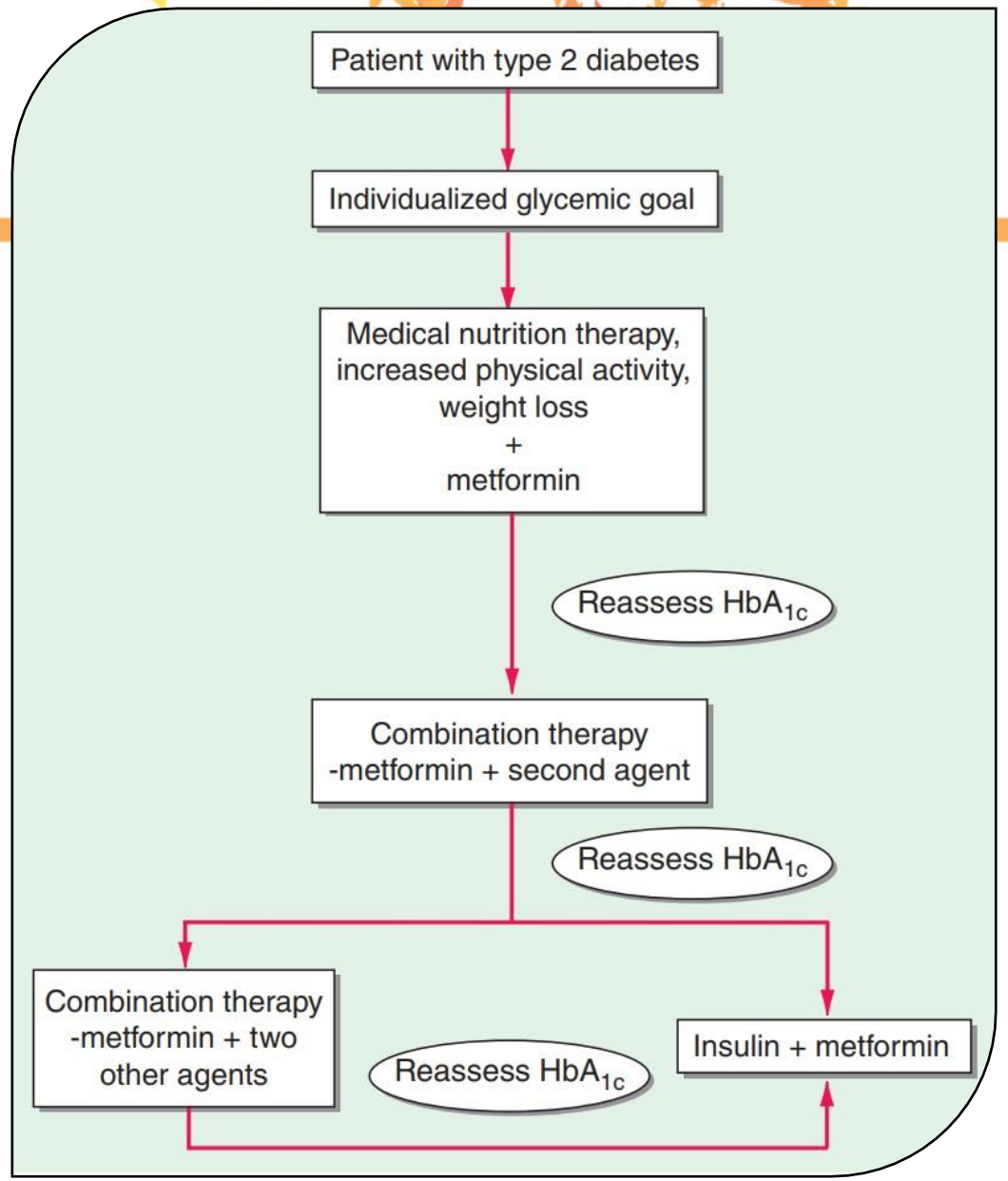
If A1C above target
TZD[10]
SU[6]
If A1C above target
▪ Insulin therapy basal insulin with lowest acquisition cost
OR
▪ Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]


Patient with type 2 diabetes
Individualized glycemic goal
Medical nutrition therapy, increased physical activity, weight loss + metformin
Reassess HbA_{1c}
Combination therapy -metformin + second agent
Reassess HbA_{1c}
Combination therapy -metformin + two other agents
Reassess HbA_{1c}
Insulin + metformin

A1C Level

Perform the A1C test at least two times a year in patients:

- who are meeting treatment goals and
- who have stable glycemic control

Perform the A1C test quarterly in patients

- whose therapy has changed or
- who are not meeting glycemic goals

Conditions that affect red blood cell **turnover**

- hemolytic and other anemias
- G6PD deficiency
- recent blood transfusion
- use of drugs that stimulate erythropoesis
- end-stage kidney disease
- **pregnancy**

A1C Level

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (6,7). Adapted from Nathan et al. (6).

Treatment goal

Table 6.3—Summary of glycemic recommendations 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 individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted 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, generally peak levels in patients with diabetes.

A1C goals

< 7% ⇨ for many **nonpregnant adults**

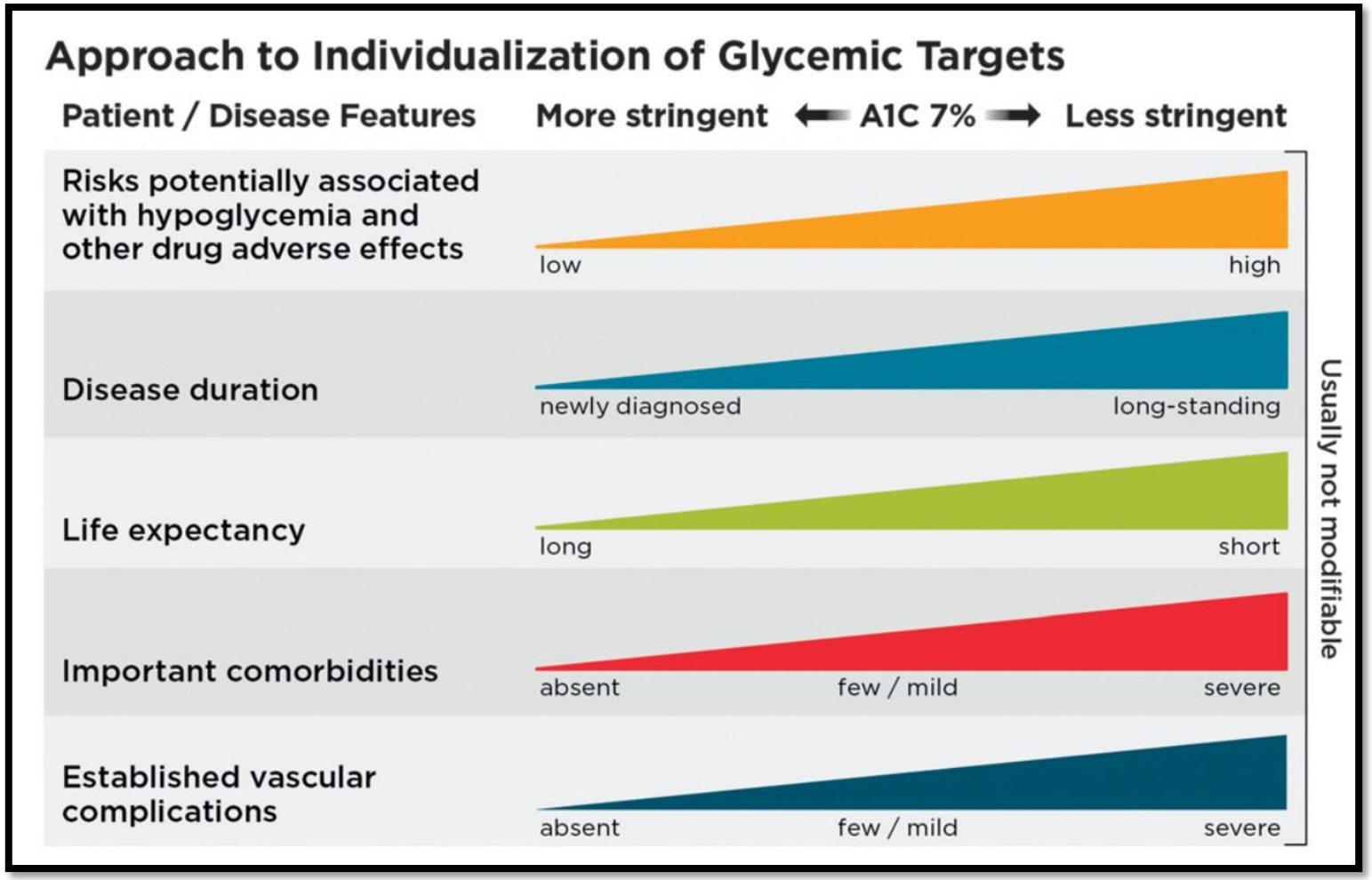
< 6.5% ⇨ those with:

- **short duration** of diabetes
- type 2 diabetes treated with **lifestyle** or **metformin only**
- **long** life expectancy
- no significant cardiovascular disease
- **Pregnancy**

< 8% ⇨ those with:

- history of **severe hypoglycemia**
- **long-standing diabetes** in whom the goal is difficult to achieve
- **limited** life expectancy
- advanced microvascular or macrovascular complications
- extensive comorbid conditions

A1C goals


Approach to Individualization of Glycemic Targets
Patient / Disease Features
More stringent
A1C 7%
Less stringent
Risks potentially associated with hypoglycemia and other drug adverse effects
low
high
Disease duration
newly diagnosed
long-standing
Life expectancy
long
short
Important comorbidities
absent
few / mild
severe
Established vascular complications
absent
few / mild
severe
Usually not modifiable

Thank you

for your attention