Universitatea de Stat de Medicină și Farmacie ”Nicolae Testemițanu”

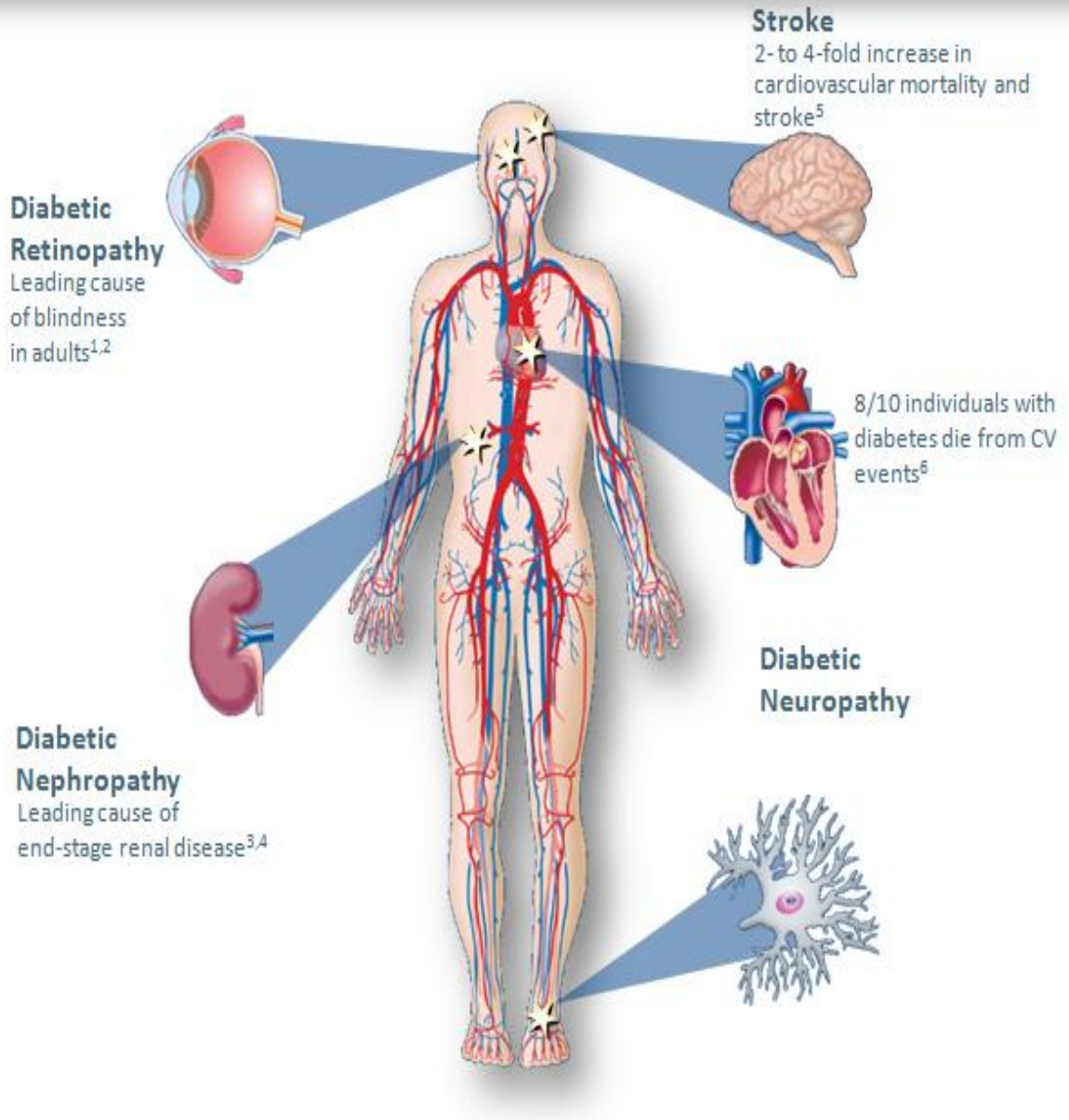
Endocrinology Department

Treatment of diabetes mellitus

Harea Dumitru

asistent universitar, dr.șt.med.

Why do we need to treat diabetes mellitus?



- **To suppress** the negative **effects of** excessive **hyperglycemia**
- **To prevent chronic complications**
- **To prevent premature death** and **to enable** the patients **good quality of life**

Overview

- Treatment targets for managing patients with DM
- Lifestyle modification
- Pharmacologic therapy for type 2 diabetes

Treatment targets for managing patients with DM

Treatment targets for managing patients with DM

- **Glycemic control**
- **Blood pressure control**
- **Lipid profile control**
- **Lifestyle changes (body weight control)**

Glycemic control

Glycemic control is assessed by:

- HbA1C measurement
- continuous glucose monitoring(CGM)
- and self-monitoring of blood glucose (SMBG)

Glycemic control - HbA1c level

- **HbA1c** - **is the major tool for assessing glycemic control** and has strong predictive value for diabetes complications.

- reflects **average glycemia** over approximately **3 months**.

- should be performed routinely in all patients:
  - at initial assessment and
  - as part of continuing care.

- Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained.

HbA1c - recomendation

- The frequency of A1C testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment.

HOW OFTEN?

- at **least 2 times** a year in patients who are **meeting treatment goals** (and who have stable glycemic control).

- **test quarterly** in patients whose therapy has changed or **who are not meeting glycemic goals**.

Glycemic recommendation for adults with diabetes

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.
#CGM may be used to assess glycemic target
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.

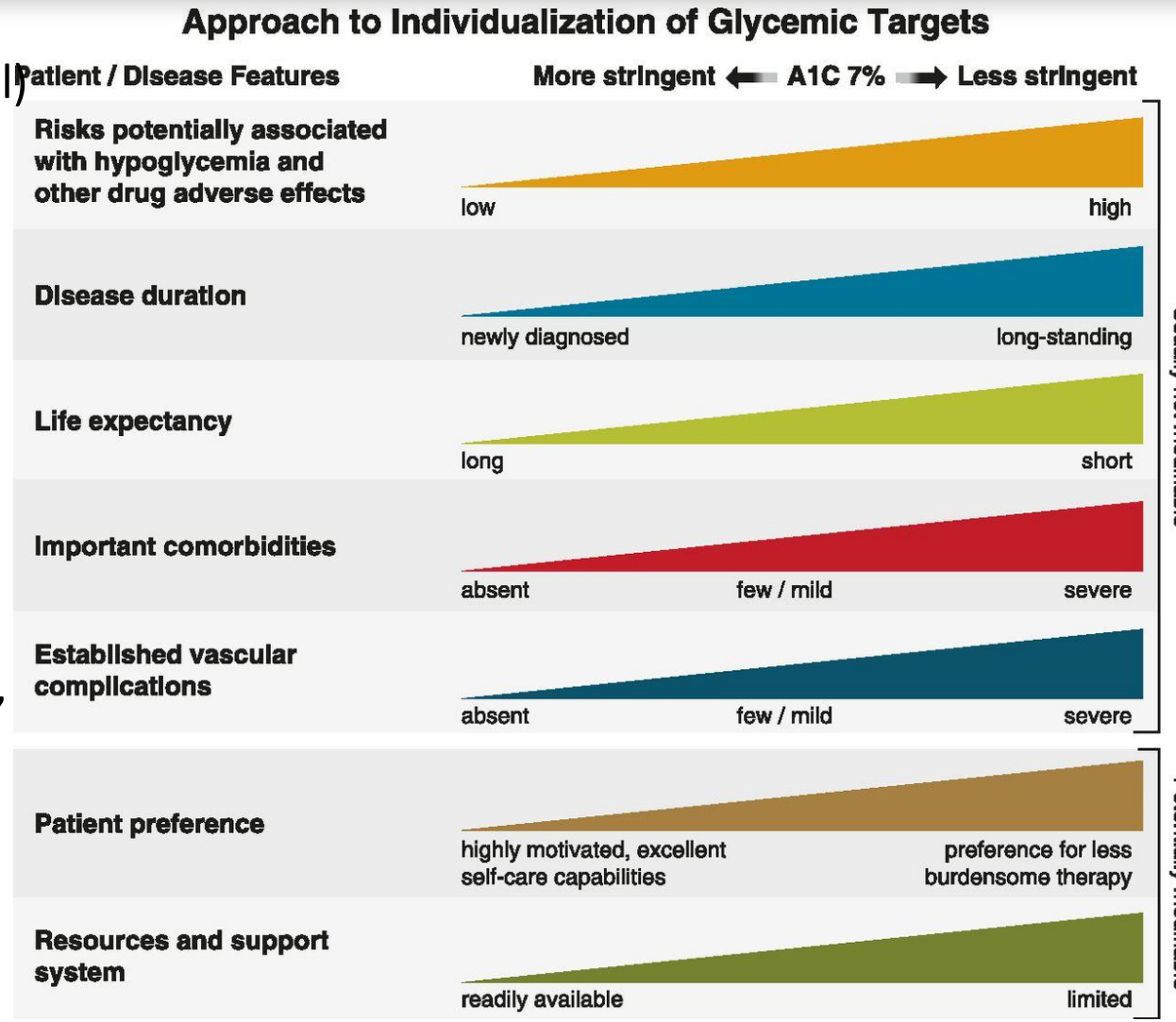
Approach to individualization of glycemic targets

A1C goal for many nonpregnant adults of **<7%** (53mmol/mol)

lower A1C levels (such as <6.5%) may be acceptable if this can be achieved safely without significant hypoglycemia or other adverse effects of treatment.

Less stringent A1C goals < 8% [64 mmol/mol]) may be appropriate for patients with:

- a history of severe hypoglycemia,
- limited life expectancy,
- advanced microvascular or macrovascular complications,
- extensive comorbid conditions,
- or long-standing diabetes,
- appropriate glucose monitoring, and
- effective doses of multiple glucose lowering agents including insulin.



ADA 2021

Approach to individualization of glycemic targets

	< 45 years-old	45-65 years-old	> 65 years-old
*patients **without** risk hypoglycemic*	HbA1c <6.5% GBM <6.5 mmol/l (<110 mg/dl) GAM < 8.0 mmol/l (140 mg/dl)	HbA1c <7.0% GBM <7.0 mmol/l (<126 mg/dl) GAM < 9.0 mmol/l (162 mg/dl)	HbA1c <7.5% GBM <7.5 mmol/l (<135 mg/dl) GAM < 9.5 mmol/l (170 mg/dl)
Patients **with** risk of hypoglycemia	HbA1c <7.0% GBM <7.0 mmol/l (<126 mg/dl) GAM < 9.0 mmol/l (162 mg/dl)	HbA1c <7.5% GBM <7.5 mmol/l (<135 mg/dl) GAM < 9.5 mmol/l (170 mg/dl)	HbA1c <8.0% GBM <8.0 mmol/l (<144 mg/dl) GAM < 10.0 mmol/l (180 mg/dl)

GBM – level of *blood sugar* befor meal
GAF – level of *blood sugar 2 hours after meal*s (eating)
Patients with risk of hypoglycemia:
Severe cardiovascular disease: sever arrhythmia (flutter or *fibrillation*), myocardial infarction, stroke, pectoral angina

A *severe decrease* in *kidney function (*end-*stage* renal failure*)*
severe liver disease (liver failure)
proliferative retinopathy
Severe mental illness
Severe syndrome of malabsorption0

CGM may be used to assess glycemic target

GLUCOSE STATISTICS AND TARGETS

14 days
% Sensor Time

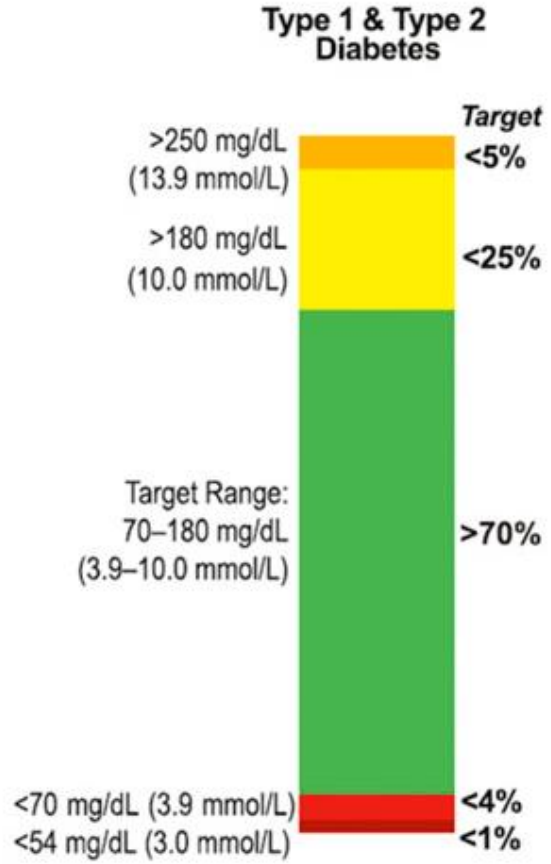
Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose
Glucose Management Indicator (GMI)
Glucose Variability

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES



ADA 2021

Recommendations for the management of blood pressure in patients with diabetes and pre-diabetes

Treatment targets
Antihypertensive drug treatment is recommended for people with DM when office BP is >140/90 mmHg.[155,178–180]
It is recommended that patients with hypertension and DM are treated in an individualized manner. The BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 - 139 mmHg.[155,159,160,181–183]
It is recommended that target DBP is targeted to <80 mmHg, but not <70 mmHg.[160]
An on-treatment SBP of <130 mmHg may be considered in patients at particularly high risk of a cerebrovascular event, such as those with a history of stroke.[154–157,173]

ESC-EASD 2019

Recommendations for the management of dyslipidaemia with lipid-lowering drugs

Cardiovascular risk categories in patients with diabetes

		Targets
Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)	**LDL-c < 1,4 mmol/l (55 mg/dl)** (or reduction with 50%)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor	**LDL-c < 1,8 mmol/l (70 mg/dl)** (or reduction with 50%)
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors	**LDL-c < 2,6 mmol/l (100 mg/dl)**

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

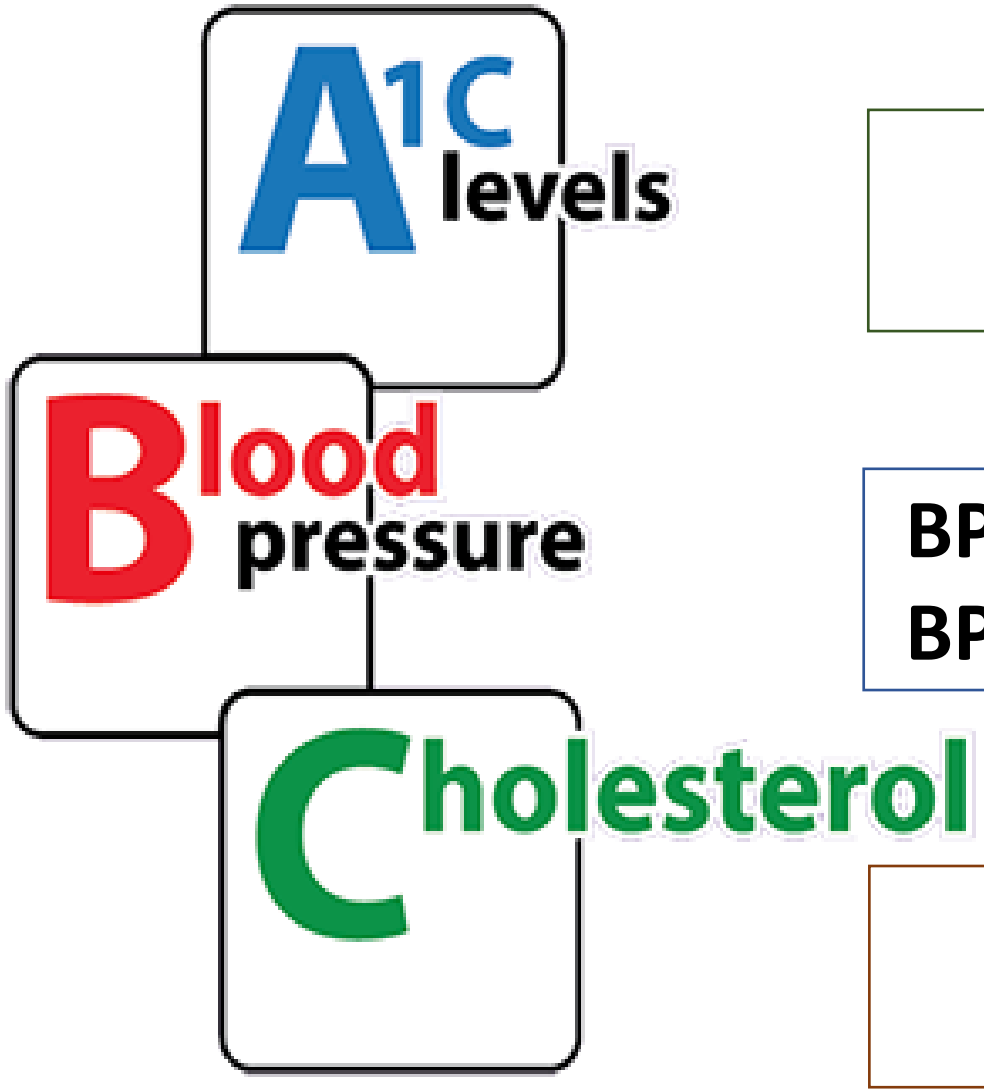
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

↓LDL-cholesterol 1 mmol/l - ↓ CV risk with 22%

Conclusion - Treatment targets for managing patients with DM



HbA1c < 7.0% (<6.5%; <8.0%)

BP 120-130/70-80mmHg (aged < 65 years)
BP 130-140/70-80 mmHg (aged > 65 years)

LDL-colesterol < 2,6 - 1,8 - 1,4 mmol/l
< 100 – 70 – 55 mg/dl

Management of diabetes mellitus

TYPE 1 DM

- Education
- Lifestyle modification + Insulin

- **TYPE 2 DM**

- Education
- Lifestyle modification + Noninsulinic agents
- Lifestyle modification + Noninsulinic agents + Insulin
- Lifestyle modification + Insulin

Patient education

- all people with diabetes should participate in diabetes self-management education and receive the support needed to facilitate the knowledge, decision-making, and skills mastery necessary for diabetes self-care

- It is essential that people with diabetes understand their disorder and learn to handle all aspects of their management & educating patients about diabetes complications.

- Diabetes self-management education and support should be patient centered, may be given in group or individual settings and/ or use technology, and should be communicated with the entire diabetes care team.

Patient education

There are four critical times to evaluate the need for diabetes self-management education to promote skills acquisition in support of regimen implementation, medical nutrition therapy, and well-being:

- at diagnosis,
- annually and/or when not meeting treatment targets,
- when complicating factors develop (medical, physical, psychosocial),
- when transitions in life and care occur

Lifestyle modification

Lifestyle modification

- Nutrition therapy
- Physical activity
- Non-smoking condition (smoking cessation)
- Sleep
- Stress prevention (behavirol support)

Goals of nutrition therapy for adults with diabetes

1. To promote and support **healthful eating patterns**, emphasizing a **variety of nutrient-dense foods** in **appropriate portion sizes**, to improve overall health and:
   - achieve and maintain body weight goals
   - attain individualized glycemic, blood pressure, and lipid goals
   - delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and existing barriers to change.
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices while limiting food choices only when indicated by scientific evidence
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods.

Eating Patterns and Meal Planning

- There **is not an ideal percentage of calories from carbohydrate, protein, and fat** for people with diabetes.

- **Macronutrient distribution** should be based on
  - an individualized assessment of current eating patterns,
  - preferences,
  - metabolic goals.

- Consider personal preferences (e.g., tradition, culture, religion, health beliefs and goals, economics) as well as metabolic goals to determine the best eating pattern for people with diabetes.

- An individualized medical **nutrition therapy program** as needed to achieve treatment goals, provided by a **registered dietitian nutritionist.**

Eating Patterns and Meal Planning

- **meal plans should be individualized** while keeping total calorie and metabolic goals in mind.

- An individualized eating pattern also considers the individual's
  - health status
  - Skills
  - resources
  - food preferences
  - health goals
  - physical activity
  - medication use.

Eating Patterns and Meal Planning

- **A variety of eating patterns are acceptable** for the management of type 2 diabetes and prediabetes.

- **Eating patterns should focus on the key factors :**
  - emphasize non-starchy vegetables,
  - minimize added sugars and refined grains
  - choose whole foods over highly processed foods to the extent possible

Eating Patterns and Meal Planning

- The Mediterranean-style, low-carbohydrate, and vegetarian or plant-based eating patterns are all examples of healthful eating patterns that have shown positive results in research, but individualized meal planning should focus on personal preferences, needs, and goals.

Nutrition therapy - *carbohydrates*

- Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber and minimally processed. Eating plans should emphasize
  - non-starchy vegetables,
  - minimal added sugars,
  - fruits,
  - whole grains,
  - dairy products.

- **Reducing overall carbohydrate intake** - demonstrated improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences.

Nutrition therapy - *carbohydrates*

- People with diabetes and those at risk are advised to replace sugar-sweetened beverages (including fruit juices) with water as much as possible in order to control glycemia and weight and reduce their risk for cardiovascular disease and fatty liver disease and should minimize the consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choice.

Protein and fat intake

- **Ingested protein** - increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should be avoided when trying to treat or prevent hypoglycemia.

- Mediterranean-style eating pattern rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk.

- Eating foods rich in long-chain ω-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat cardiovascular disease; however, evidence does not support a beneficial role for the routine use of ω-3 dietary supplements.

Nutrition therapy – alcohol

- Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men).

- Educating people with diabetes about the signs, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially when using insulin or insulin secretagogues, is recommended. The importance of glucose monitoring after drinking alcoholic beverages to reduce hypoglycemia risk should be emphasized.

Nutrition therapy

Sodium:

- As for the general population, people with diabetes and prediabetes should limit sodium consumption to <2,300 mg/day.

Nonnutritive sweeteners:

- The use of nonnutritive sweeteners **may have the potential to reduce overall calorie and carbohydrate intake** if substituted for caloric (sugar) sweeteners and without compensation by intake of additional calories from other food sources.
- For those who consume sugar sweetened beverages regularly, a low-calorie or nonnutritive-sweetened beverage may serve as a short-term replacement strategy, but overall, people are encouraged to decrease both sweetened and nonnutritive-sweetened beverages and use other alternatives, with an emphasis on water intake.

Weight Management

Management and reduction of weight is important for people with type 1 diabetes, type 2 diabetes, or prediabetes and overweight or obesity.

There is strong and consistent evidence that modest persistent **weight loss can delay the progression from prediabetes to type 2 diabetes** and is beneficial to the management of type 2 diabetes

For all patients with overweight or obesity, lifestyle modification to achieve and maintain a minimum weight loss of 5% is recommended for all patients with diabetes and prediabetes.

In prediabetes, the weight loss goal is 7–10% for preventing progression to type 2 diabetes

the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety

Physical activity

- **Physical activity is a general term** that includes **all movement that increases energy use** and is an important part of the diabetes management plan.

- **Exercise** is a **more specific form** of physical activity that **is structured and designed to improve physical fitness.**

- Both physical activity and exercise are important.

- **Exercise has been shown to**
  - improve blood glucose control,
  - reduce cardiovascular risk factors,
  - contribute to weight loss,
  - improve well-being

Physical activity - recomendation

- **Most adults** - should engage in **150 min/week** or more of moderate to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous intensity or interval training may be sufficient for younger and more physically fit individuals.

- **Adults** should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

- All adults - **should decrease the amount of time spent in daily sedentary** behavior. Prolonged sitting should be **interrupted every 30 min** for blood glucose benefits.

- Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes.

Pre-exercise evaluation

- Providers should assess cardiovascular risk factors in patients with diabetes and assess patients for conditions that might contraindicate certain types of exercise or predispose to injury:
  - uncontrolled hypertension,
  - untreated proliferative retinopathy,
  - autonomic neuropathy,
  - peripheral neuropathy,
  - a history of foot ulcers or Charcot foot.

- Certainly, high risk patients should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration as tolerated.

- The provider should customize the exercise regimen to the individual's needs.

Pre-exercise evaluation

Hypoglycemia

- insulin and/or insulin secretagogues,
- if the medication dose or carbohydrate consumption is not altered.
- need to ingest some added carbohydrate if pre-exercise glucose levels are < 90 mg/dL (5.0 mmol/L),
- **hypoglycemia after exercise** may occur and last for several hours due to increased insulin sensitivity.
- Patients need to be educated to check blood glucose levels before and after periods of exercise

Retinopathy

- Proliferative or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment.
- Consultation with an ophthalmologist prior to engaging in an intense exercise regimen may be appropriate.

Diabetic Kidney Disease

Physical activity can acutely increase urinary albumin excretion.

Pre-exercise evaluation

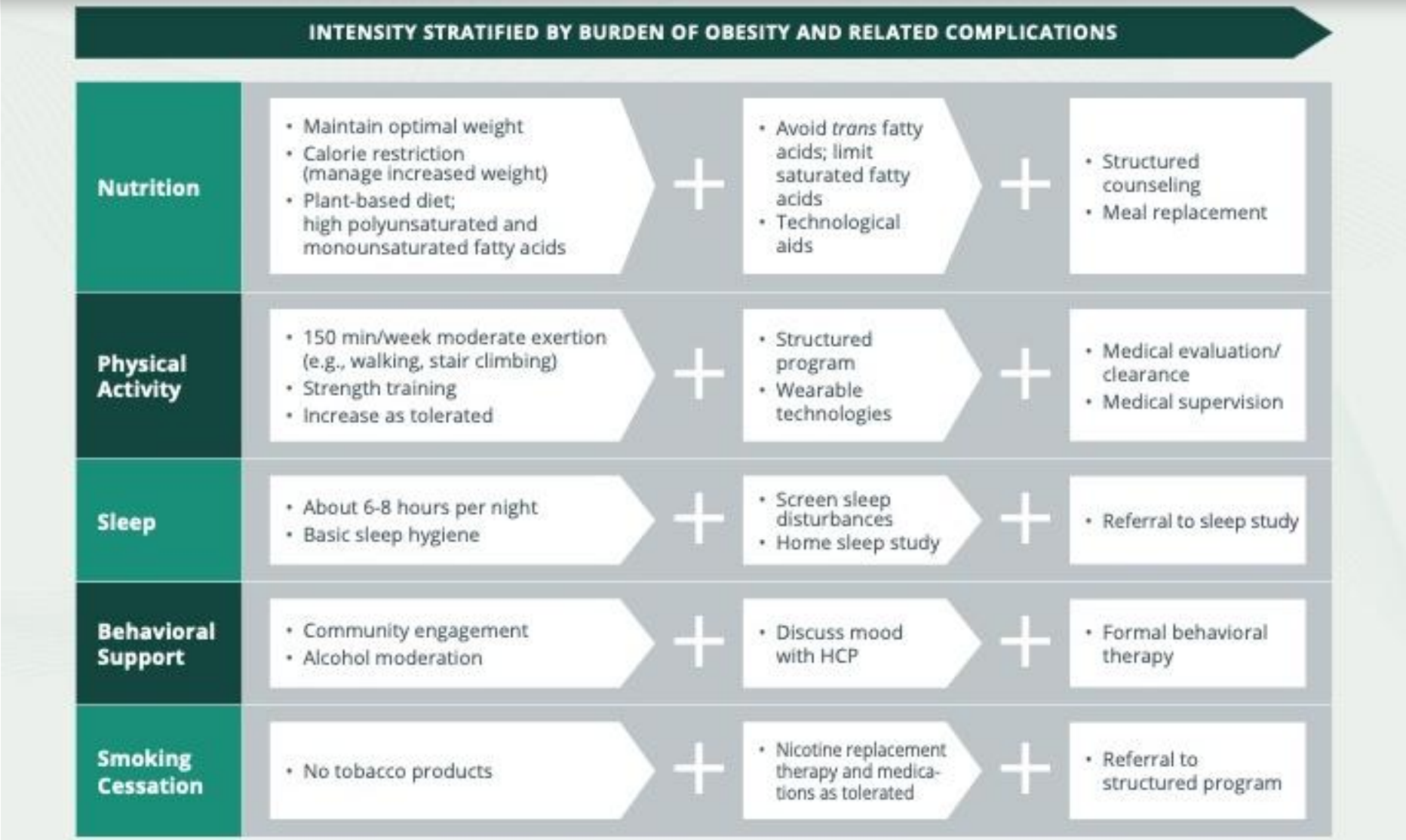
Peripheral Neuropathy

- Decreased pain sensation and a higher pain threshold - increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise.
- assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy.
- moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear .
- 150min/week of moderate exercise was reported to improve outcomes in patients with prediabetic neuropathy
- All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early.

Autonomic Neuropathy

- can increase the risk of exercise-induced injury or adverse events:
  - decreased cardiac responsiveness to exercise,
  - postural hypotension,
  - impaired thermoregulation,
  - impaired night vision due to impaired papillary reaction,
  - and greater susceptibility to hypoglycemia.
- Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia .
- Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Lifestyle therapy

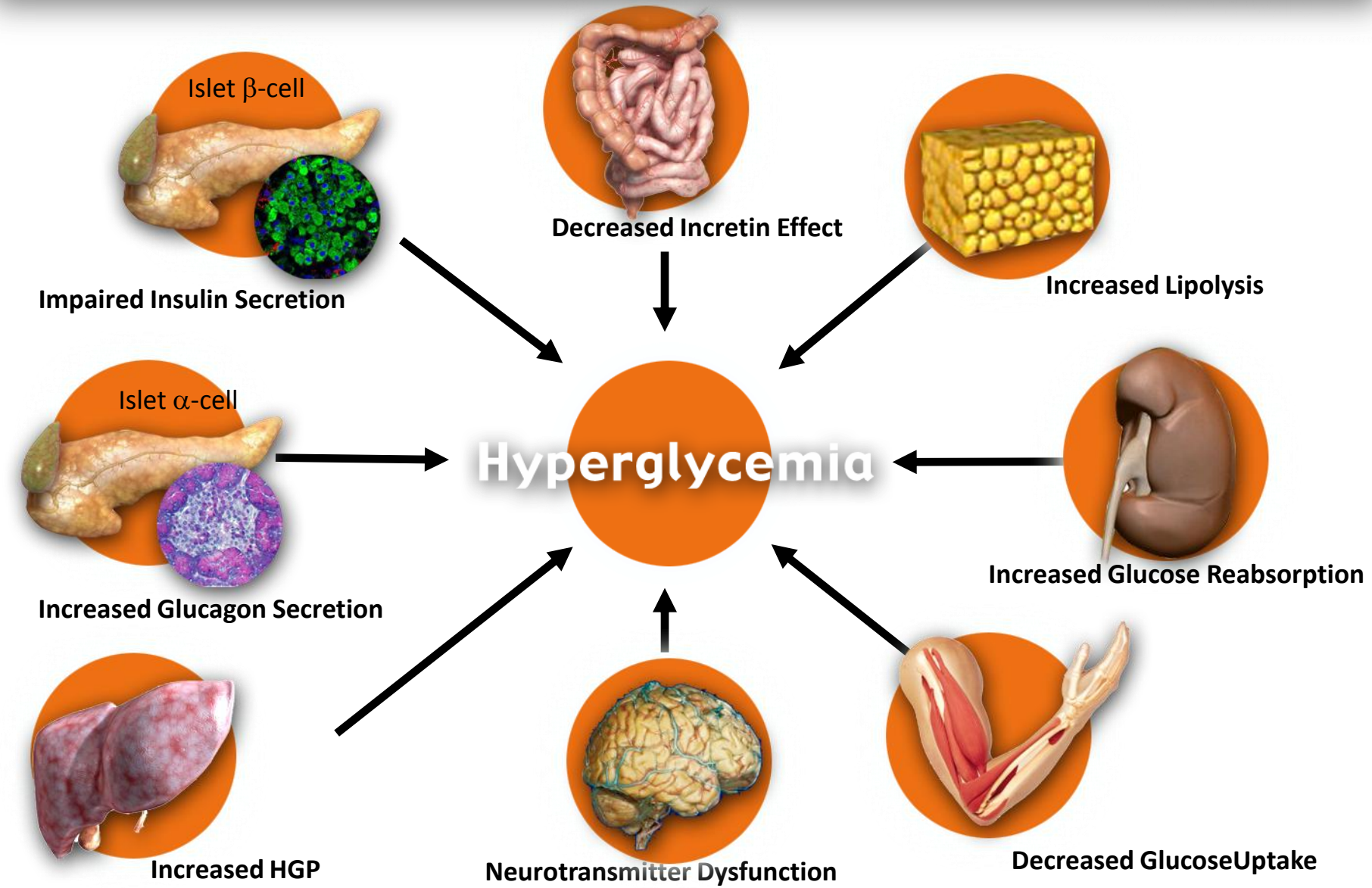


Pharmacologic therapy for type 2 diabetes

- Ominous octet
- Classification of anti-hyperglycemic drugs
- Mechanism of action, Indications, contraindications and side effects of antihyperglycemic drugs
- Recommendation for treatment

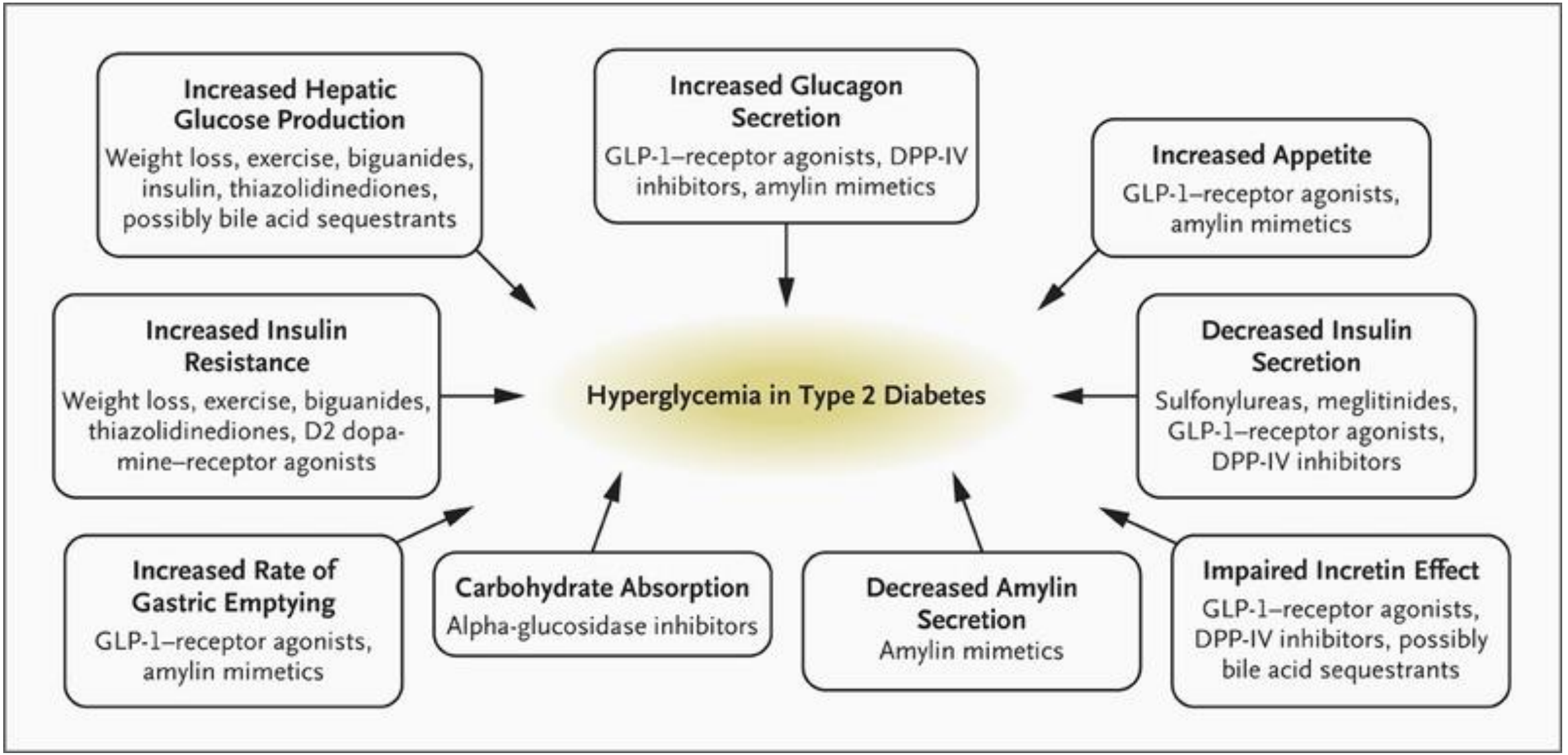
From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

Ralph A. DeFronzo



DeFronzo RA. Lilly Lecture: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 1988; 37: 667–687, De FronzoRA. Diabetes 2009

Key classes of glucose lowering drugs

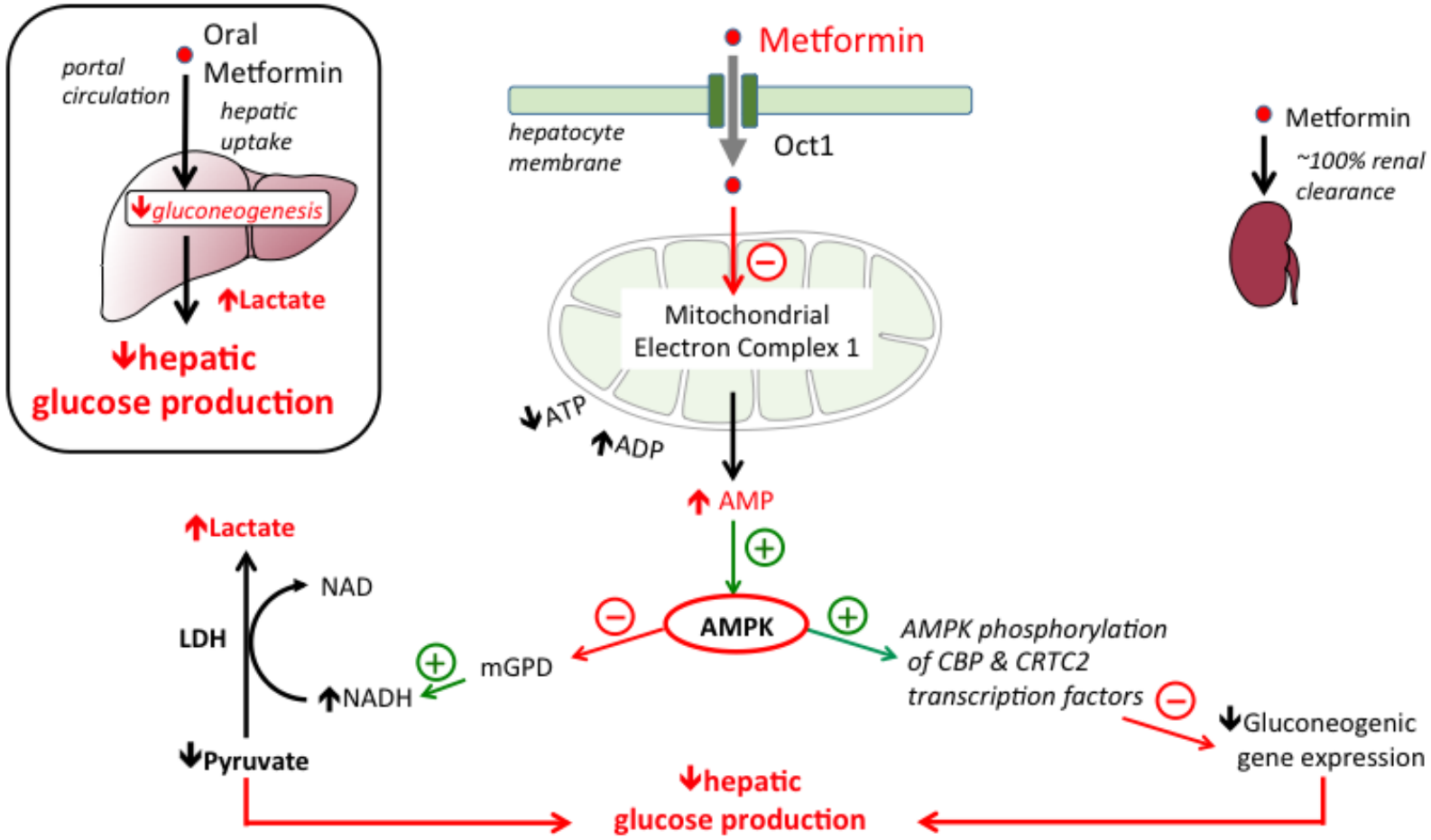


Non-insulin glucose lowering therapies in type 2 diabetes

Class	Drugs
Biguanides	**Metformin**
SU	**Gliburide, Gliclazide,** Glipizide, **Glimepiride**
Glinides	**Repaglinide,** Nateglinide
TZD	Pioglitason, Rosiglitason
DPP-4 inhibitors	**Sitagliptin, Vildagliptin**, Saxagliptin, Linagliptin, Alogliptin
GLP-1 receptor agonists	Exenatid, Liraglutid, Lixisenatid, Albiglutide, Dulaglutide
α- glucozidase inhibitors	Acarboza, Miglitol
Amilin mimetics	Pramlintid
SGLT2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
D2 agonists	Bromcriptin
Bile acids sequestrants	Colesteramin

Biguanides - Metformin

- **Metformin –** 500, 850, 1000mg
- **Cellular mechanism** - activate AMP-kinase
- **Primary physiological action** – reduce hepatic glucose production



Biguanides - Metformin

Indication	Contraindications	Advantages	Side effects
Prediabetes DM type 2 the first line therapy	• ALT, AST ↑x 3N value • eGFR<30ml/min/1,73m^2 • Acidosis • Hypoxia • Dehydration	• Extensive experience • Rare hypoglycemia • ↓CVD events • Higher HbA1c efficacy	• Gastrointestinal side effects • Vitamin B12 deficiency • Lactic acidosis (rare)

Sulfonylureas - 2nd generation

Cellular mechanism - closes K_{ATP} channels

Primary physiological action – increase insulin secretion

Other effects

Sensitize β-cells to glucose

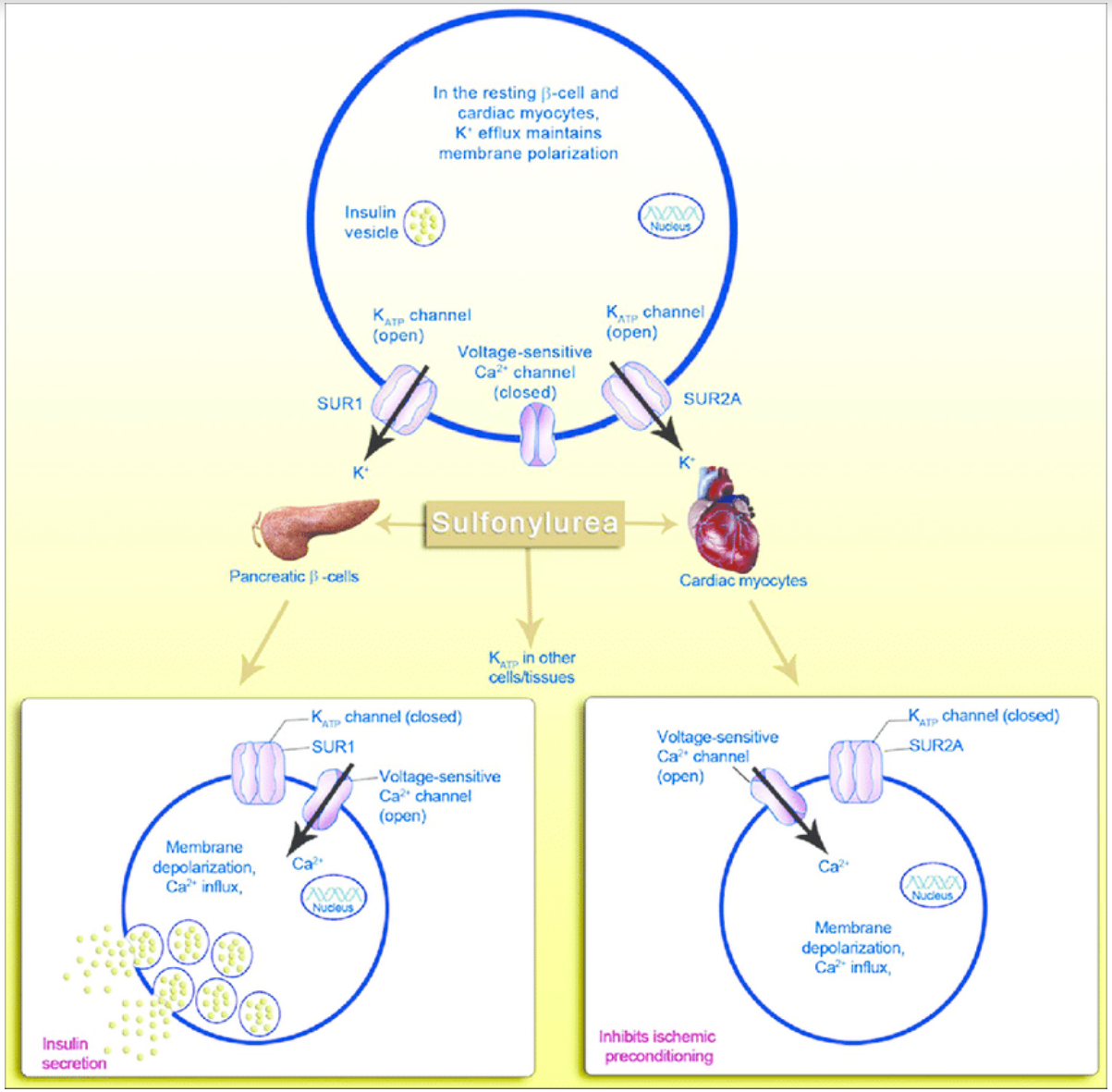
Limit glucose production in the liver

Decrease lipolysis

Decrease cleareance of insulin by liver

Anti-oxidative

Angiogenesis



Sulfonylureas

PK/PD properties	Glibenclamide	Gliclazide	Glipizide	Glimepiride	Glipizide XL	Gliclazide MR
Duration of action	16-24 h	10-24 h	12-24 h	24 h	>24 h	>24 h
Volume of distribution	9-10 L	13-24 L	10-11 L	19.8-37.1 L	10 L	19 L
Protein binding (%)	99	85-99	98-99	99	98-99	>90
Metabolism	Hepatic	Hepatic (no active metabolites)	Hepatic (no active metabolites)	Hepatic (active metabolites)	Hepatic (no active metabolites)	Hepatic, (no active metabolites)
Bioavailability (%)	99	80	100	100	100	97
Half-life	10 h	8-12 h	2-5 h	5±4.1 h	2-5 h	16 h
Time to peak	2-4 h	2-4 h	1-3 h	2-3 h	6-12 h	6-7 h
Excretion	50% renal	80% renal	80% renal	60% renal	80% renal, 10% feces	<60-70% renal 10-20% in feces
Drug-drug interaction	May interact with CYP2C9 inducers or inhibitors					
PK changes in elderly	Slow elimination; higher volume of distribution	Likely increase half-life and slower elimination	No significant differences in PK properties			
PK changes in renal and hepatic impairment	May be altered increasing the risk of toxic reactions to drug	May affect the distribution and may also reduce the capacity for neoglucogenesis	Metabolism and excretion may be slowed	No significant differences in PK properties in renal impairment while it is not evaluated in hepatic impairment	May affect the disposition of drug and also diminish gluconeogenic capacity	May affect the distribution and may also reduce the capacity for neoglucogenesis increasing the risk of hypoglycemia

MR: Modified release, XL: Extended release, PK/PD: Pharmacodynamic/pharmacokinetic, SUs: Sulfonylureas

Sulfanylureas - 2nd generation

2nd generation: Gliclazide, Glipizide, Glimepiride

Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd line therapy when cost is a major issue • MODY	• Hepatic failure • eGFR<30ml/min/1,73m^2 • Pregnancy and lactation	• Extensive experience • ↓microvascular complications • Higher HbA1c efficacy	• Hypoglycemia • Weight gain • β-cell failure (apoptosis)

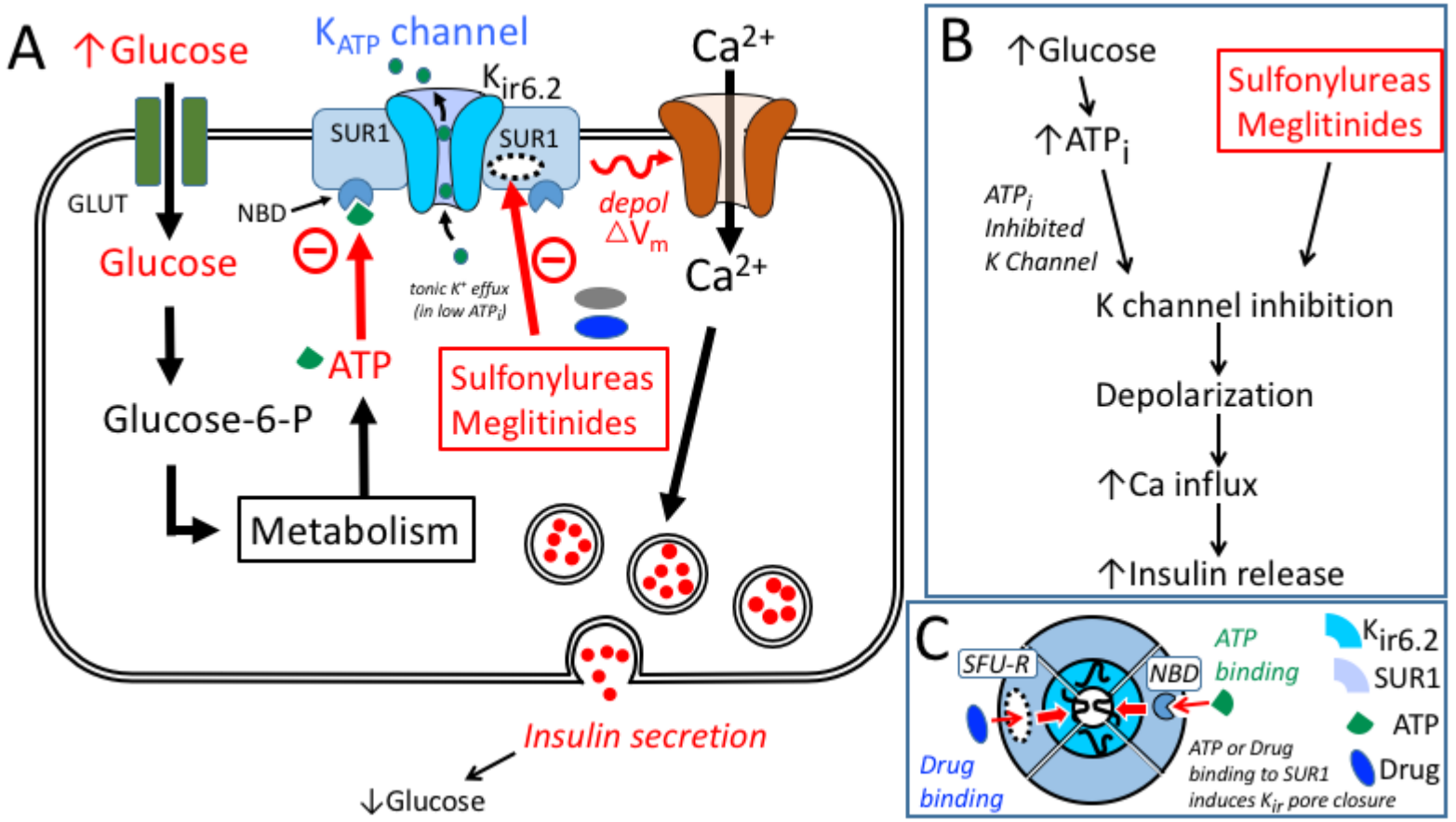
Meglitinides

Cellular mechanism - closes K_{ATP} channels

Primary physiological action –

increase insulin secretion

Faster onset (less than 30 min)**, slower duration** (4 hours) than SU



Meglitinedes

Repaglinide – 0,5, 1, 2mg, Nateglinide

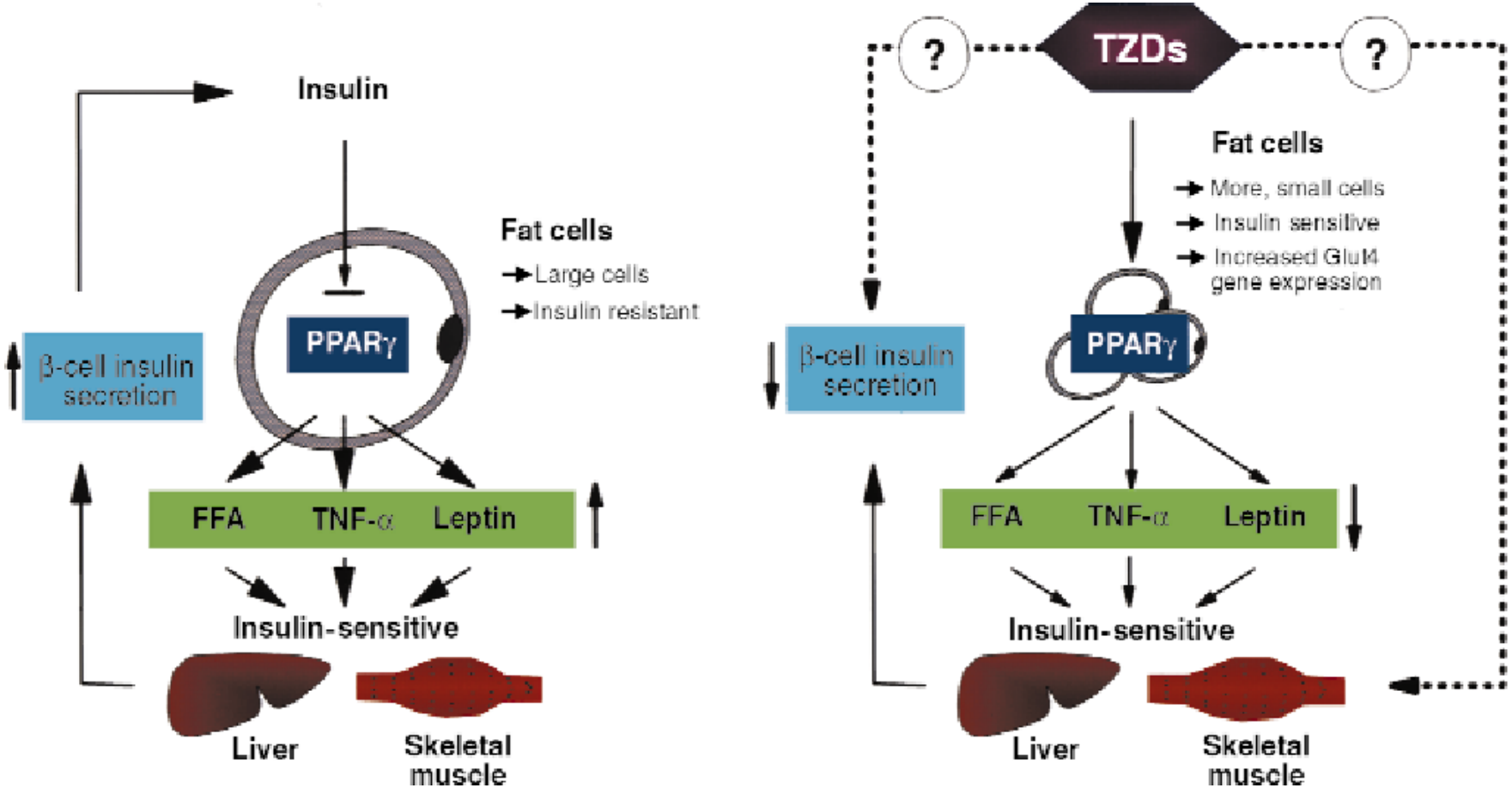
Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd line therapy when cost is a major issue	• Hepatic failure • eGFR<30ml/min/1,73m^2 • Pregnancy and lactation	• ↓postprandial glucose • Dosing flexibility	• Hypoglycemia • Weight gain • Frequent dosing shedule

Thiazolidindiones

Cellular mechanism - activates the nuclear transcription factor PPARγ

Primary physiological action –

increase insulin-sensitivity



Thiazolidindiones

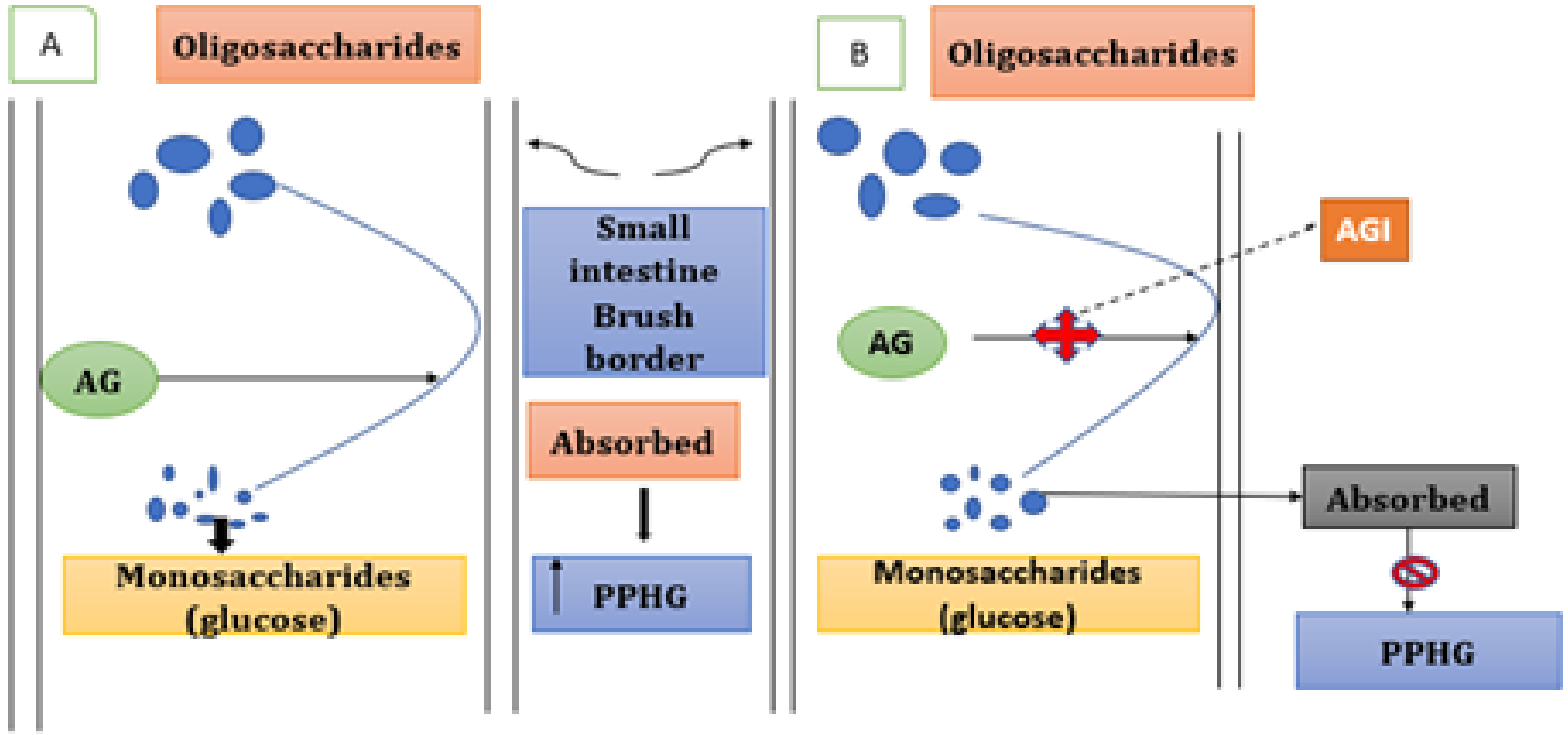
Pioglitasone 10, 20 mg

Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd line therapy when cost is a major issue • DM2 + obesity	• Heart failure • Pregnancy and lactation	• Durability • Rare hypoglycemia • ↓ risk of stoke	• Edema, heart failure • Weight gain • Bone fractures

α-glucosidase inhibitors

Cellular mechanism – inhibits intestinal α-glucosidase and pancreatic α-amylase

Primary physiological action – slows intestinal carbohydrates digestion and absobtion



α-glucosidase inhibitors

Acarbose, Miglitol

Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd line therapy when cost is a major issue • DM2 + obesity	• Pregnancy and lactation	• Rare hypoglycemia • ↓ postprandial glucose excursions	• Modest HbA1c efficacy • Gastrointestinal effects (flatulence, diarrhea) • Frequent dosing shedule

INCRETINS – INtestine SeCRETion INSulin

Effects of GLP and GIP

GLP1 receptor agonist

Intestinal secretion of GLP-1, GIP

GLP 1

- **Produced by L-cells** – distal gut (ileum and colon)
- **Stimulated** glucose-dependent **insulin release**
- Suppresses hepatic glucose output by **inhibiting glucagon secretion**
- **Inhibition of gastric emptying,**
- **Reduction of food intake** and body weight
- **Enhances β-cell proliferation**

GLP-1 (7-36)
GIP (1-42)

$T_{1/2}$
GLP-1 1-2 min
GIP 5 min

DPP-4

DPP4 inhibitors

GLP-1 (9-36)
GIP (3-42)

GIP

- Produced by K-cells – proximal gut
- Stimulated glucose-dependent insulin release
- Minimal effects on gastric emptying,
- Potentially enhances β-cell proliferation
- Stimulates glucagon secretion

Rothenberg P. Diabetes 2000, 49 (suppl 1), A 39,

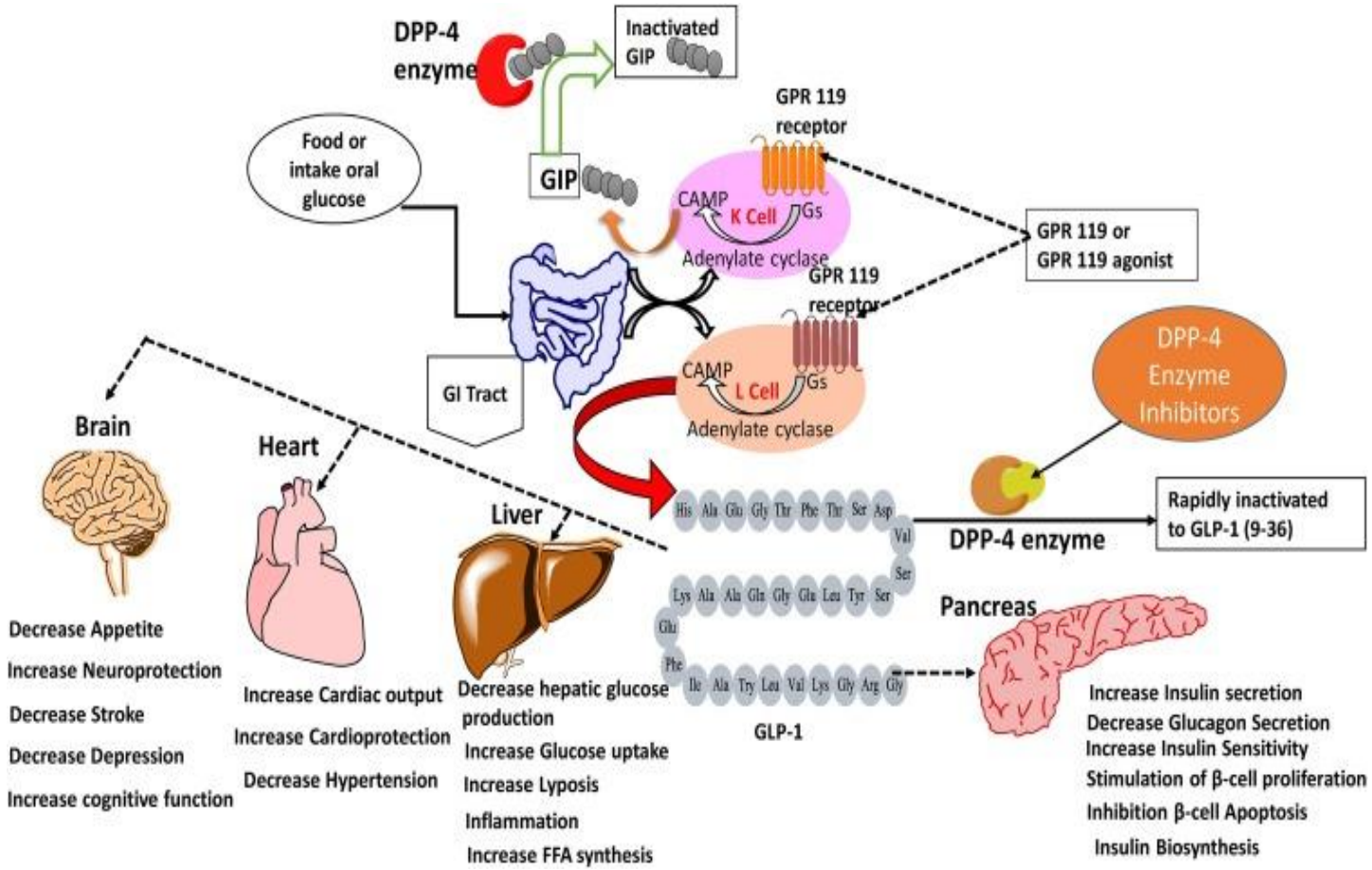
Deacon C. Diabetes 1995, 44, 1126-1131, Meier J. Diabetes 2004, 53,654-662

DPP-4 inhibitors

Cellular mechanism – inhibits DPP-4 activity, increasing postprandial incretins (GLP1, GIP) concentration

Primary physiological action – ↑insulin secretion (glucose dependent),

↓ glucagon secretion (glucose dependent)



DPP 4 inhibitors

Generic name	Trend name	Doses
Sitagliptin	Januvia	*100 mg*
Vildagliptin	Galvus	*50 mg BID*
Saxagliptin	Onglyza	*5 mg*
Linagliptin	Tradjenta	*5 mg*
Alogliptin	Nesina	
Dutogliptin		
Gemigliptin		

DPP-4 inhibitors

Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd compelling need to minimize hypoglycemia	• Pregnancy and lactation	• Rare hypoglycemia • Well tolerated	• Angioedema/urticarial and other immune-mediated effects • Acute pancreatitis • ↑heart failure hospitalization (saxagliptin)

GLP-1 receptors agonists

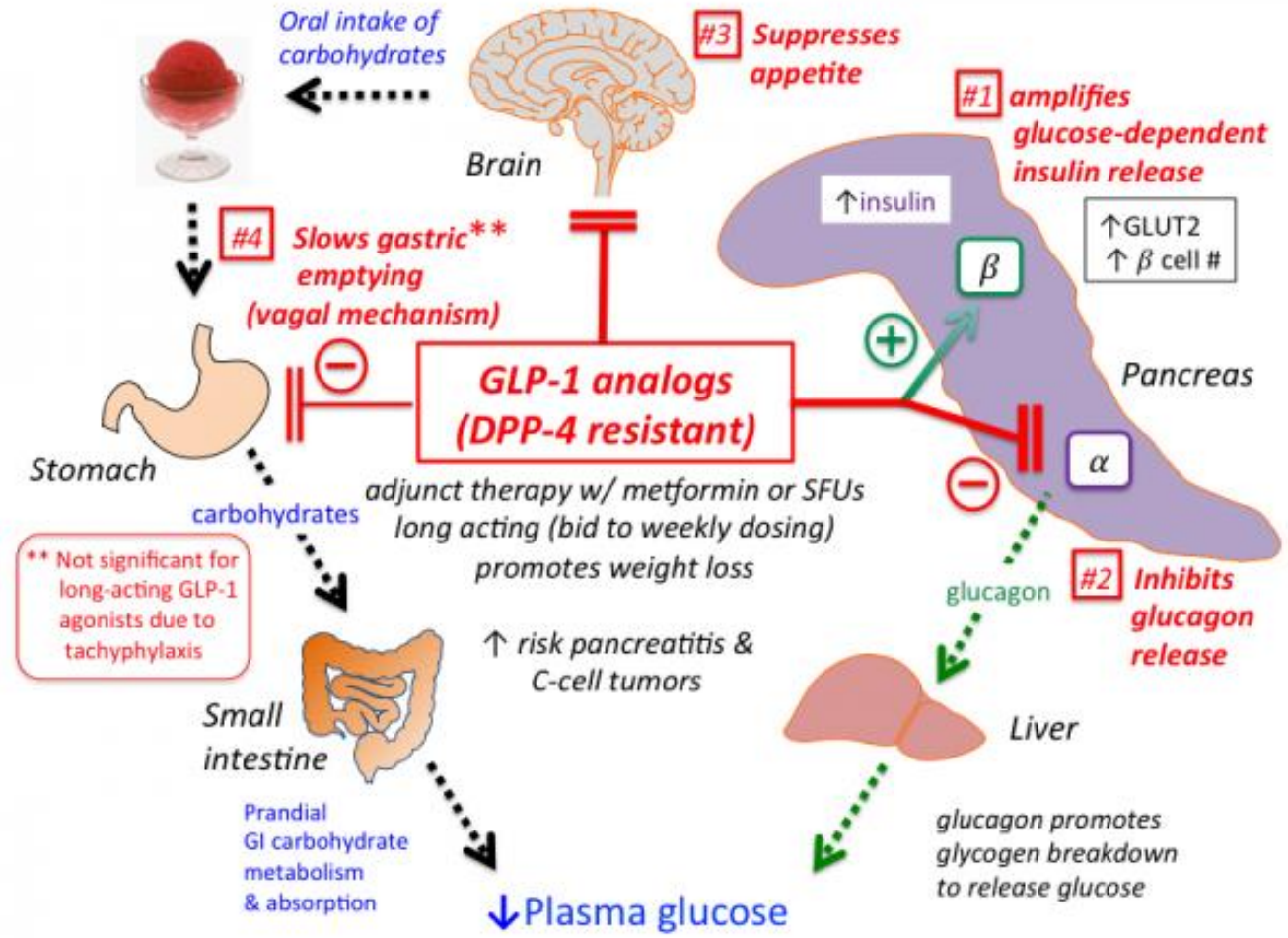
Cellular mechanism – activates GLP1 receptors

Primary physiological action – ↑insulin secretion (glucose dependent),

↓ glucagon secretion (glucose dependent)

Slows gastric empting

↑satiety



GLP – 1 receptor agonists - injections

Generic or proper name	Brand	Recomended dose
Exenatide (twice-daily)	**Byetta**	**Initiate**: with 5 mcg per dose, **increase** to 10 mcg BID
Exenatide LAR (once-weekly)	**Bydureon**	**Initiate:** 2 mg s/c weekly
Liraglutide (once-daily)	**Victoza**	**Initiate:** at 0,6 mg for 1 week, after 1 week **increase** dose to 1,2 mg
Lixisenatide (once-daily)	**Lixumia***	10 mcg
Dulaglutide (once-weekly)	**Trulicity**	

GLP-1 receptors agonists

Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd line therapy • The first line therapy ASCVD	• Pregnancy and lactation	• Rare hypoglycemia • ↓ weight • ↓postprandial excursion • ↓ CV risk	• Gastrointestinal side effects (nausea, vomiting) • ↑heart rate • C-cell hyperplasia, medullary thyroid tumors? • Acute pancreatitis • Injectable • Training requirements

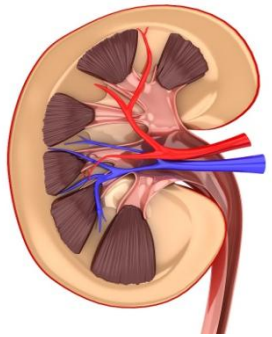
GLP-1 receptor agonist recommendations

- For patients with type 2 diabetes and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischaemic stroke, unstable angina with ECG changes, myocardial ischaemia on imaging or stress test, or revascularisation of coronary, carotid or peripheral arteries) where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 ml min^{-1} [1.73 $m]^{-2}$ or albuminuria.

MACE - Major adverse cardiovascular event

ADA/EASD 2019

The kidney and glucose



- **The kidney**
  - **Plays a significant** role in glucose homeostasis under both physiological and pathological conditions
  - Contributes to, and regulates blood glucose leves via three mechanisms:
    - Glucose utilisation
    - Gluconeogenesis
    - Glucose reabsorption following glomerular filtration

Marsenic G 2009 Am J Kidney,

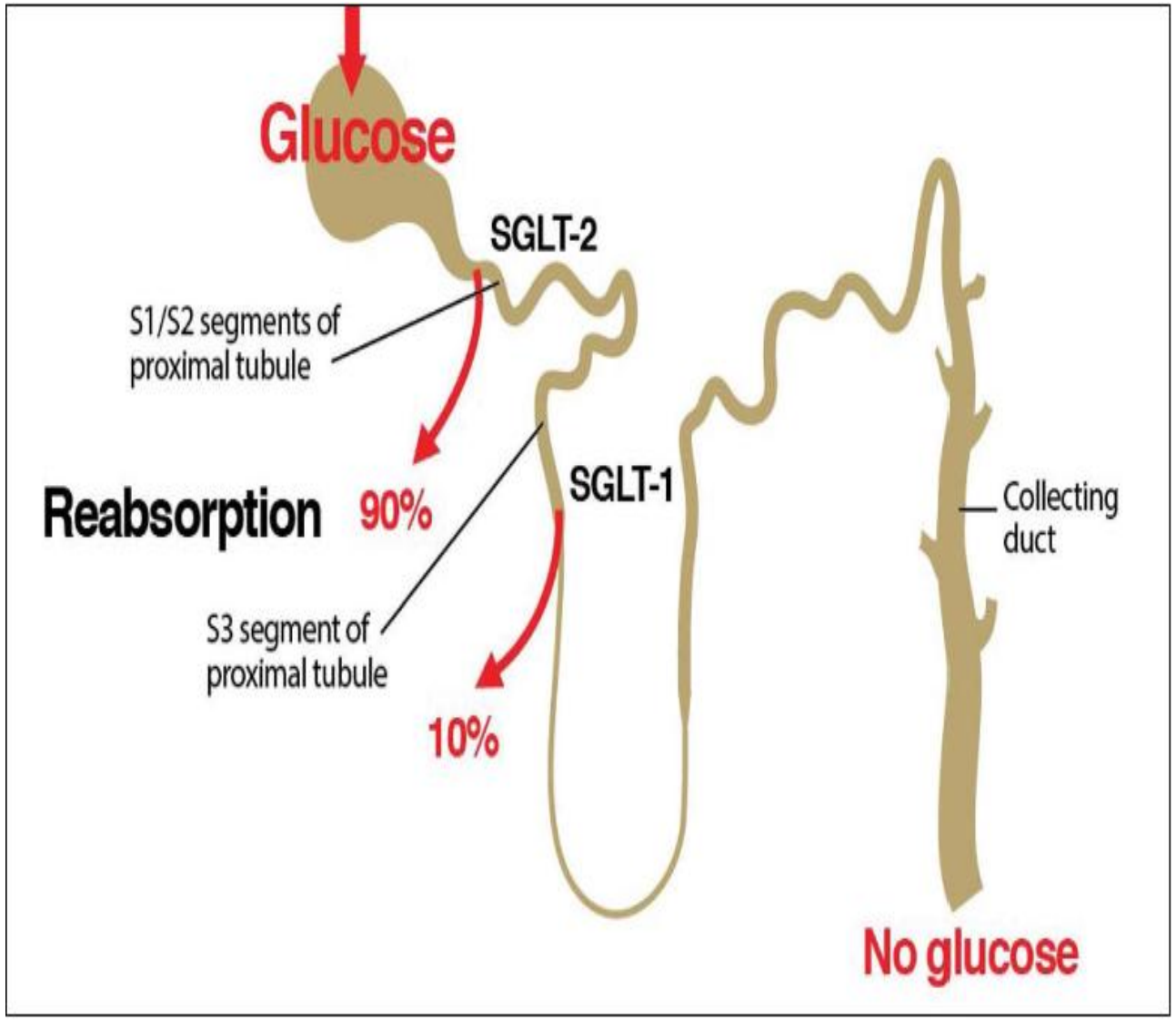
Glomerular filtration and glucose reabsorption

SGLT 2

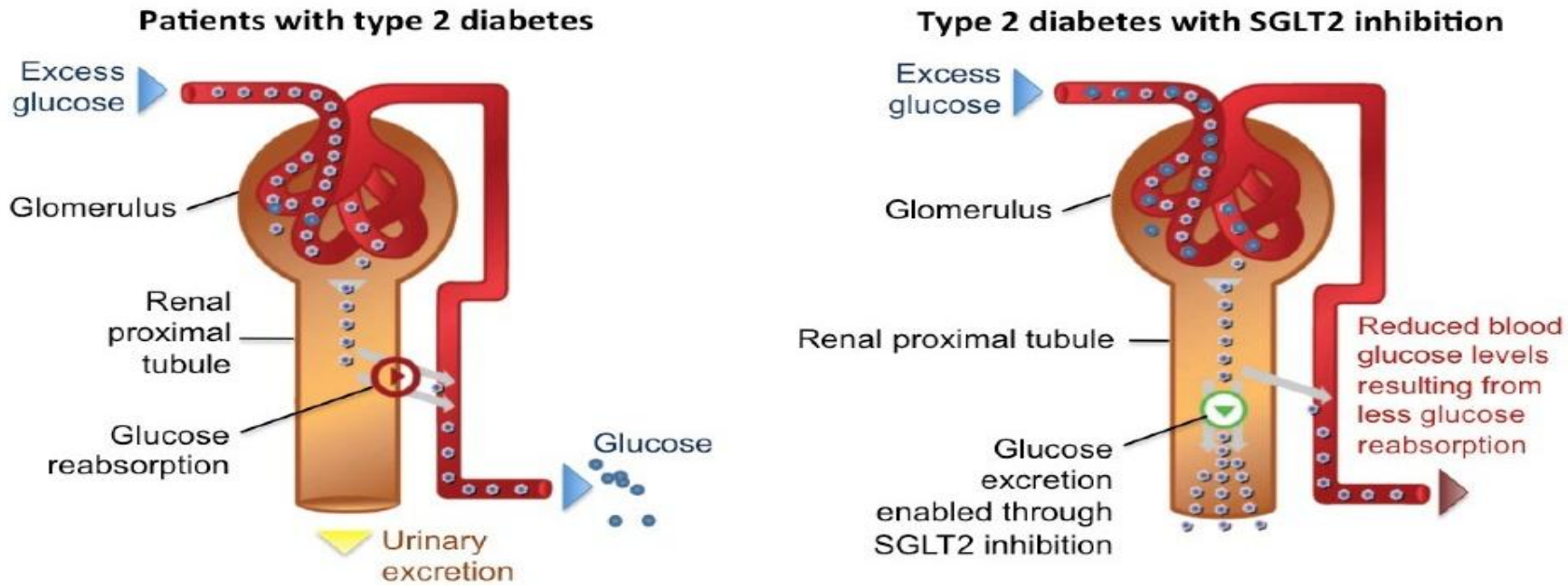
- Primarlly **expressed in kidney**
- Responsible for **majority of renal glucose reabsorption**

SGLT 1

- Responsible for **small portion** of renal glucose reabsorption
- Prominent role in **intestinal glucose absorption**



Renal SGLT2 inhibition



SGLT2 inhibitors		Dose
Dapagliflozin	Forxiga	5, 10 mg
Empagliflozin	Jardiance	10, 25 mg
Canagliflozin		100, 300 mg
Ipragliflozin		25, 50 mg
Luseogliflozin		2,5 5 mg

Chau E, Henry S Nature Reviews Drug Discovery 2010; DeFronzo R Diab Obes Metab 2012; Washburn W. J Med Chem 2009

SGLT-2 inhibitors

Indication	Contraindications	Advantages	Side effects
• DM type 2 the 2nd line therapy • The first line CKD, HF	• Pregnancy and lactation	• Rare hypoglycemia • ↓ weight • ↓Blood pressure • ↓ CVD events	• Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • DKA

SGLT2 inhibitor recommendations

- For patients with or without established atherosclerotic CVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to ≤60 ml min^{-1} [1.73 $m]^{-2}$ or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors.
- SGLT2 inhibitors are recommended in patients with type 2 diabetes and HF, particularly those with HFrEF, to reduce hHF, MACE and CV death.
- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, MACE and CV death in patients with type 2 diabetes with CKD.
- Patients with foot ulcers or at high risk for amputation should only be treated with SGLT2 inhibitors after careful shared decision making around risks and benefits with comprehensive education on foot care and amputation prevention.

HFrEF - Heart failure with reduced ejection fraction
CKD - Chronic kidney disease
UACR - Urinary albumin-to-creatinine ratio
HF - Heart failure
MACE - Major adverse cardiovascular event

ADA/EASD 2019

Key classes of glucose lowering drugs for type 2 diabetic patients: predominant effect on fasting vs postprandial glucose

Drugs lowering fasting BG

- Metformin
- Sulphonylureas
- TZD
- Basal insulin
- Long acting GLP1 agonists

Drug lowering PPBG

- α-glucosidase inhibitors
- DPP4 inhibitors
- Glinides
- Prandial insulin
- SGLT2 inhibitors
- Short acting GLP1 agonists

What should an optimal antidiabetic drug do to help us?

Good drug

- Effectively ↓ HbA1c
- Optimally oral treatment once daily
- Protect beta cells
- Decreased body weight
- Cardioprotection
- Decreased blood pressure
- Safety (no hypoglycemia, no weight gain)

PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

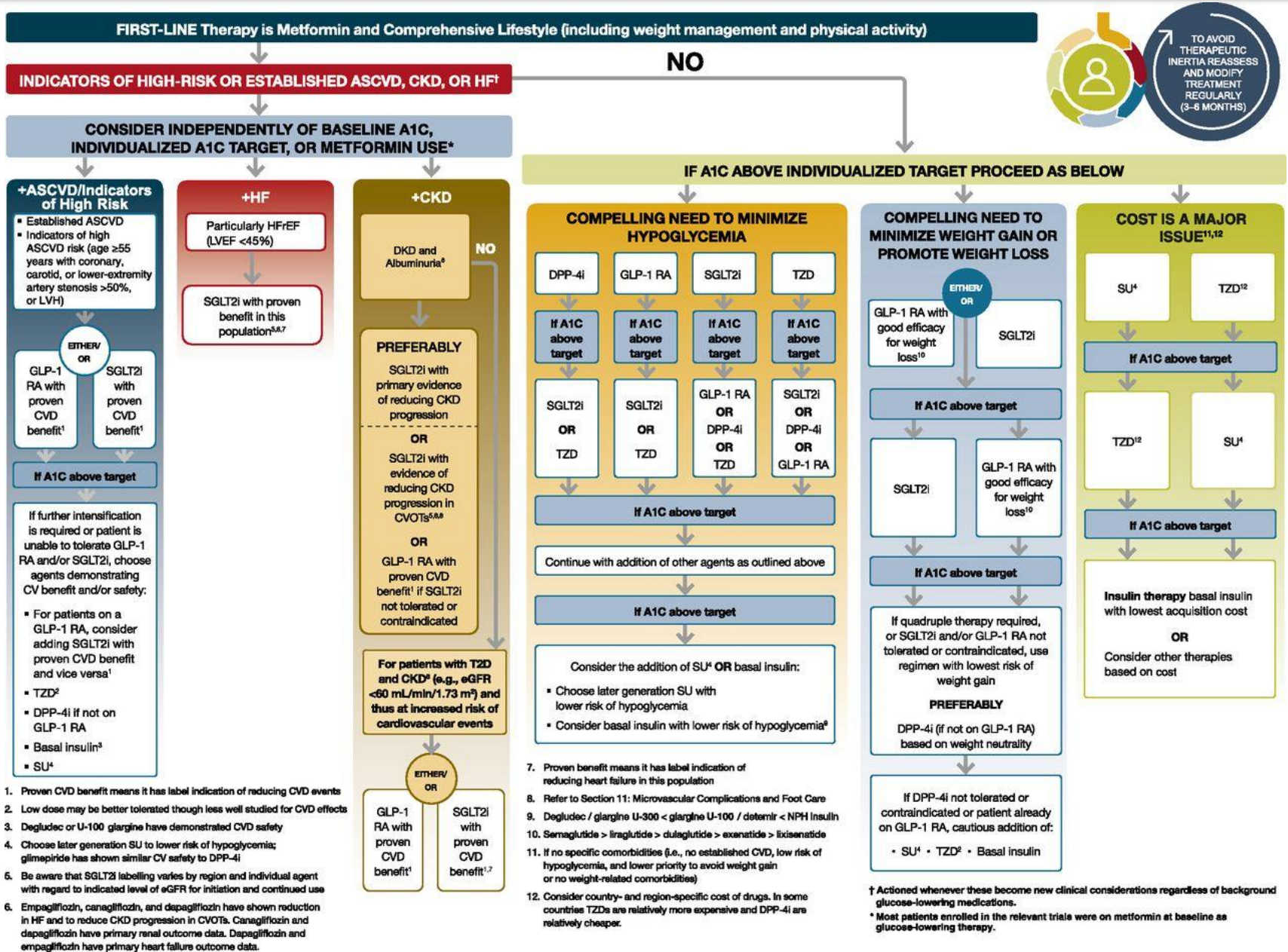
	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m²	Exenatide Not Indicated CrCl <30 Potential Benefit of LA GLP1-RA	Not Indicated for eGFR <45 mL/min/1.73 m² See #1 Genital Mycotic Infections Potential CKD Benefit; See #1	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Prevent HF Hospitalization Manage HFrEF; See #2	See #4	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC / ASCVD		Potential Benefit of LA GLP1-RA	See #3			May Reduce Stroke Risk	Possible ASCVD Risk	Lowers LDL-C	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects

1. Canagliflozin indicated for eGFR ≥30 mL/min/1.73 m² in patients with CKD 3 + albuminuria.
2. Dapagliflozin—potential primary prevention of HF hospitalization & demonstrated efficacy in HFrEF.
3. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
4. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

DOI 10.4158/CS-2019-0472

Glucose-lowering medication in type 2 diabetes: Overall approach

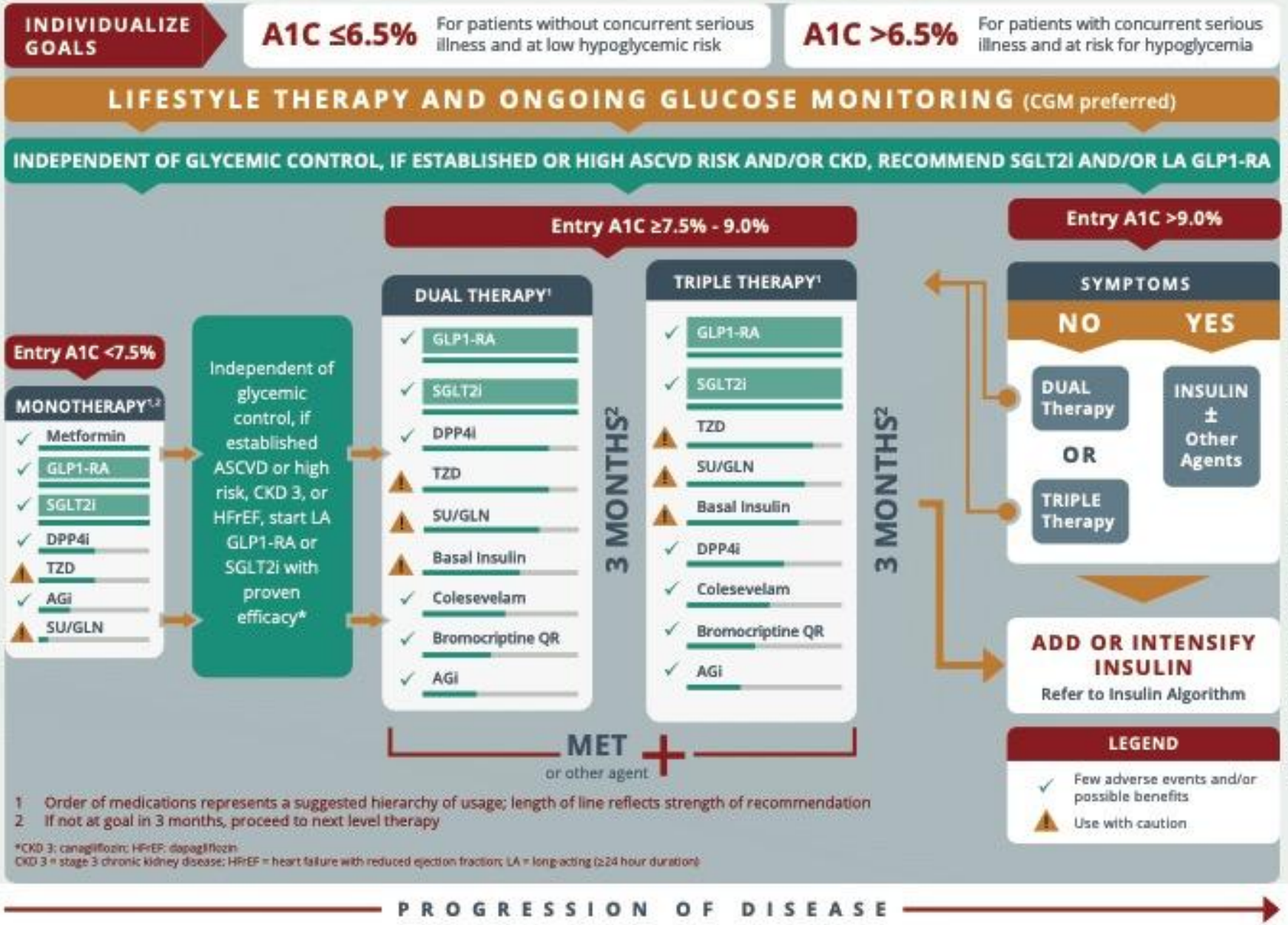


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. 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)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

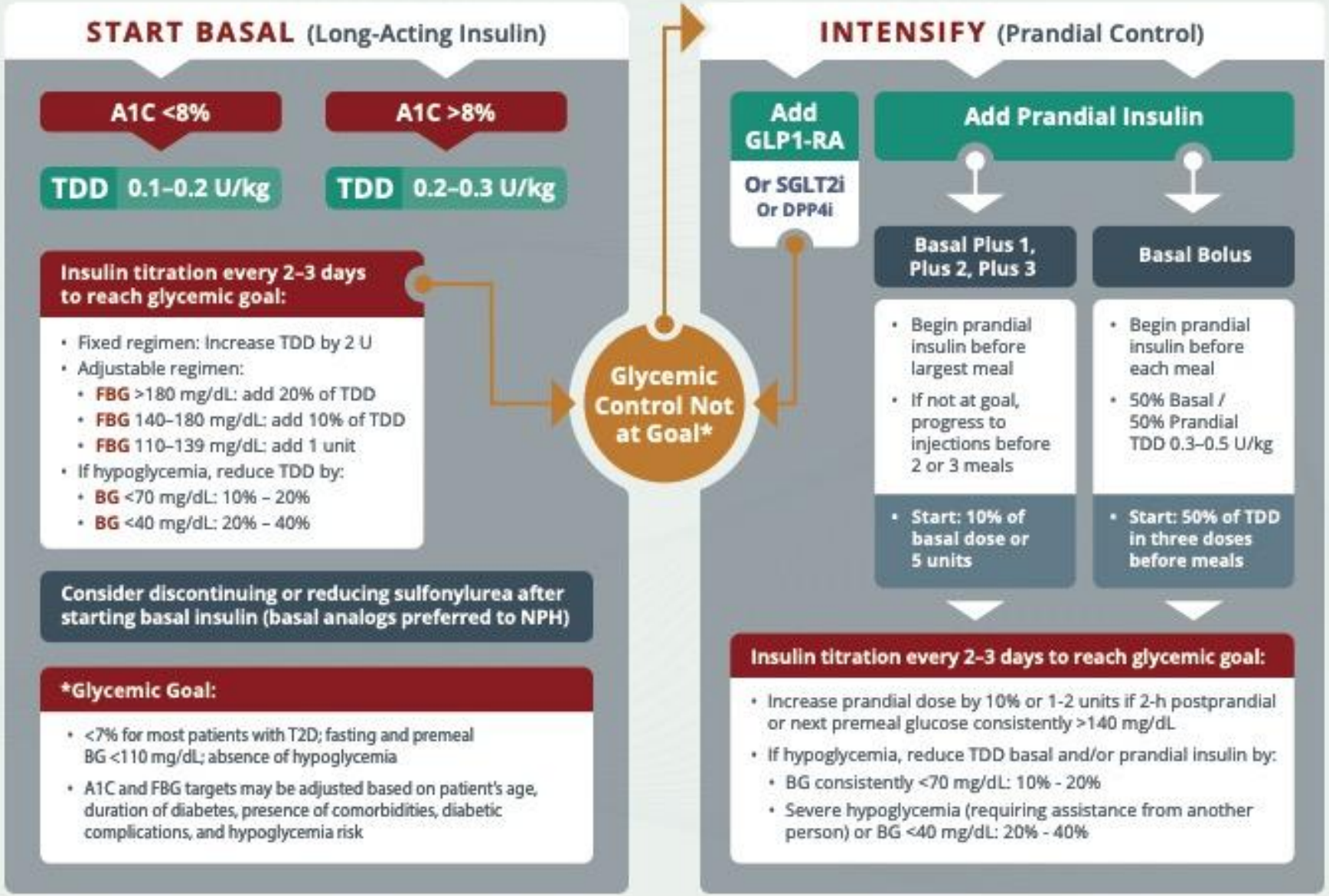
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

GLYCEMIC CONTROL ALGORITHM



ALGORITHM FOR ADDING/INTENSIFYING INSULIN



Conclusions – pharmacotherapy for DM type 2

- Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.
- Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin.
- Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure.
- 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 (>300mg/dL [16.7 mmol/L]) are very high.
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences

Conclusions – pharmacotherapy for DM type 2

- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors
- In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible.
- Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed.
- 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