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Treatment of diabetes mellitus type 2

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Conferențiar universitar, dr.șt.med.

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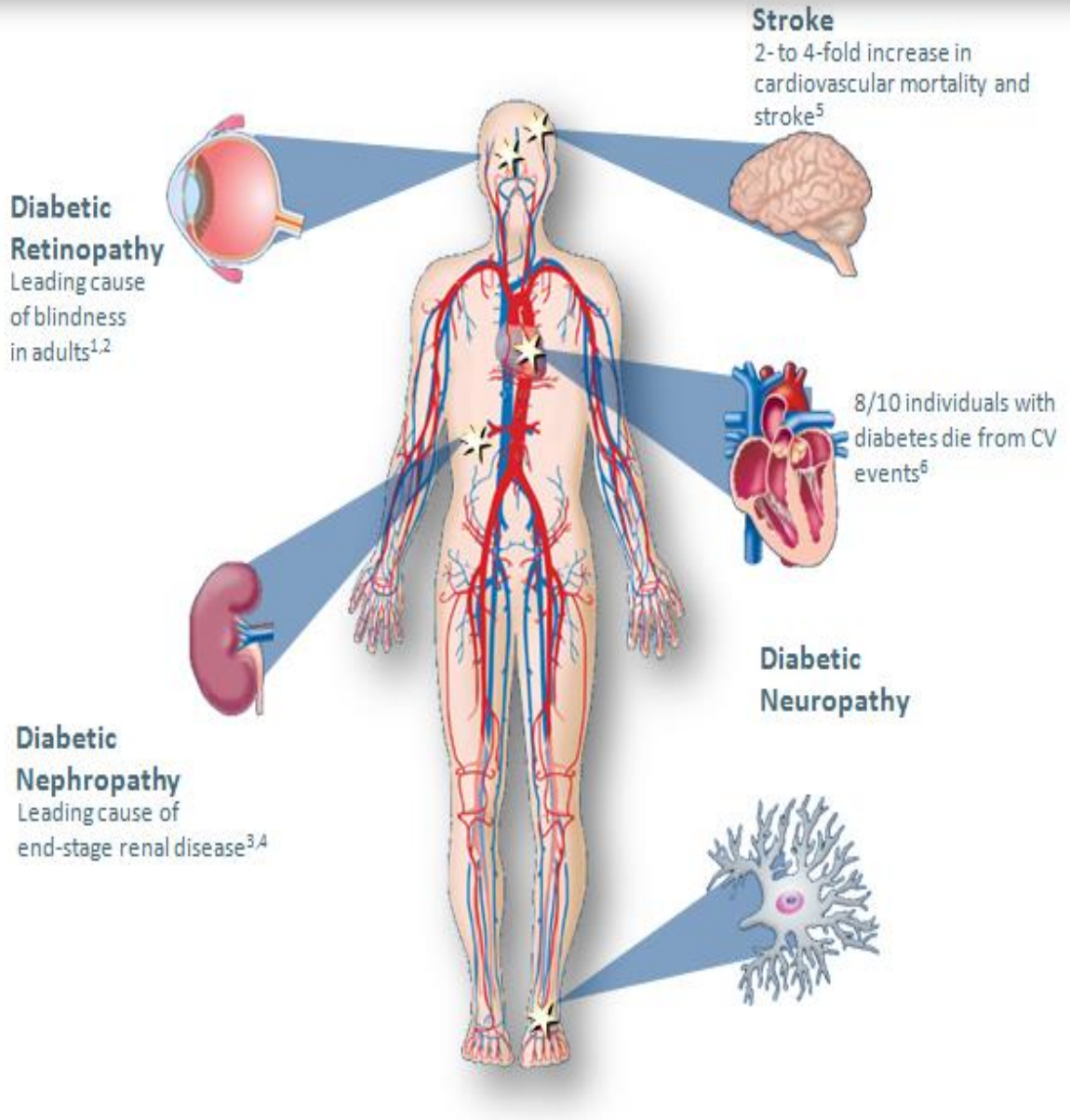
Overview

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

Why do we need to treat diabetes mellitus?



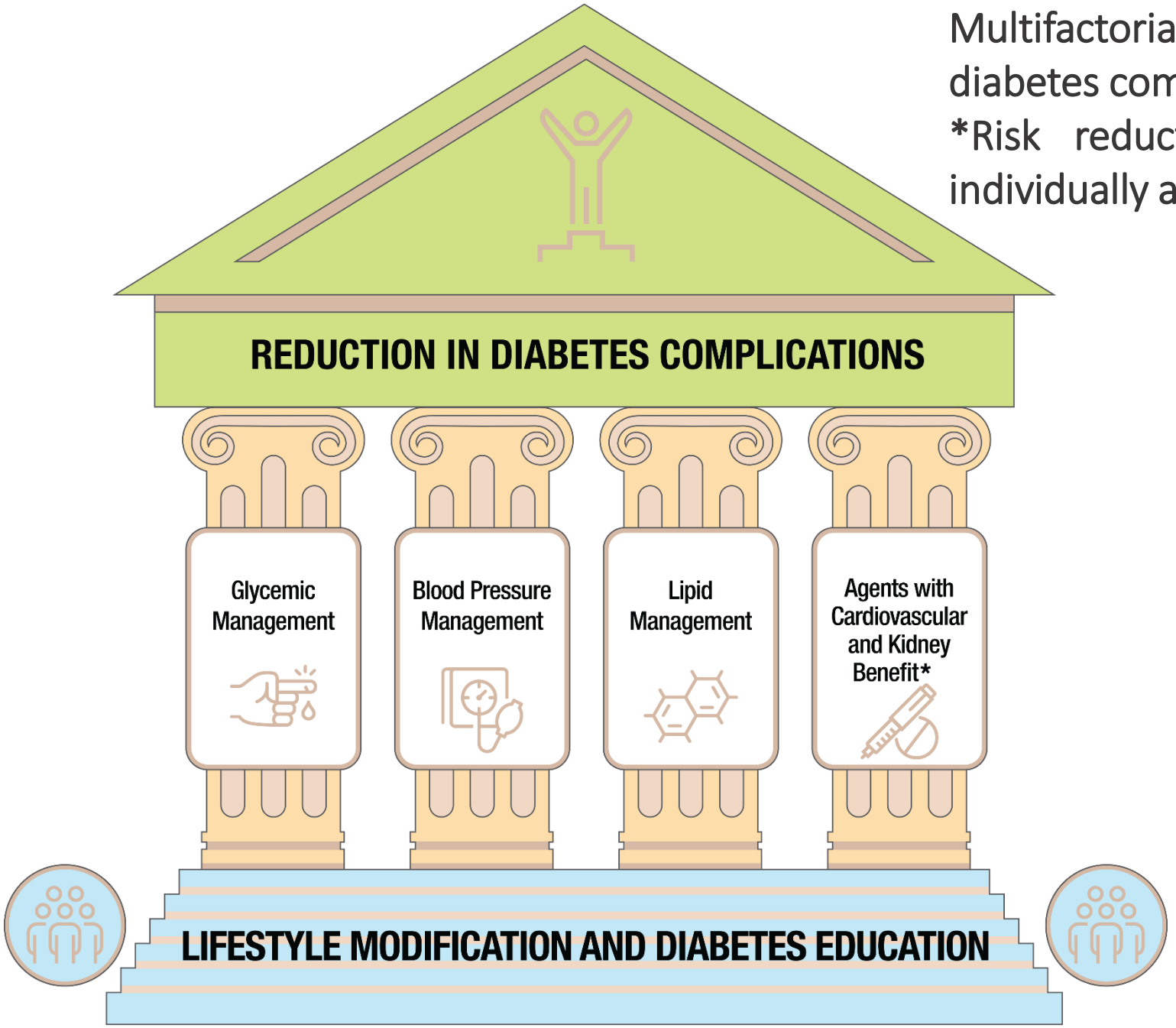
- **To suppress** the negative **effects of** excessive **hyperglycemia**
- **To prevent chronic complications**
- **To prevent premature death** and **to enable** the patients **good quality of life**

Risk factors for chronic microvascular complications

Controllable	Uncontrollable
Hyperglycaemia Hypertension Dyslipidemia Smoking Body weigh	Duration of DM DM type (T1DM) Insulin therapy Nephropathy Genetic factors Puberty Pregnancy

Multifactorial approach to reduction in risk of diabetes complications.

*Risk reduction interventions to be applied as individually appropriate.



Treatment targets for managing patients with DM

Treatment targets for managing patients with DM

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

Glycemic control (Glycemic goals/targets)

Glycemic control is assessed by:

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

Glycemic targets - 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.

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)

Glycemic targets - HbA1c level

HOW OFTEN?

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

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

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

Glycemic targets - HbA1c level, (SMBG)

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.

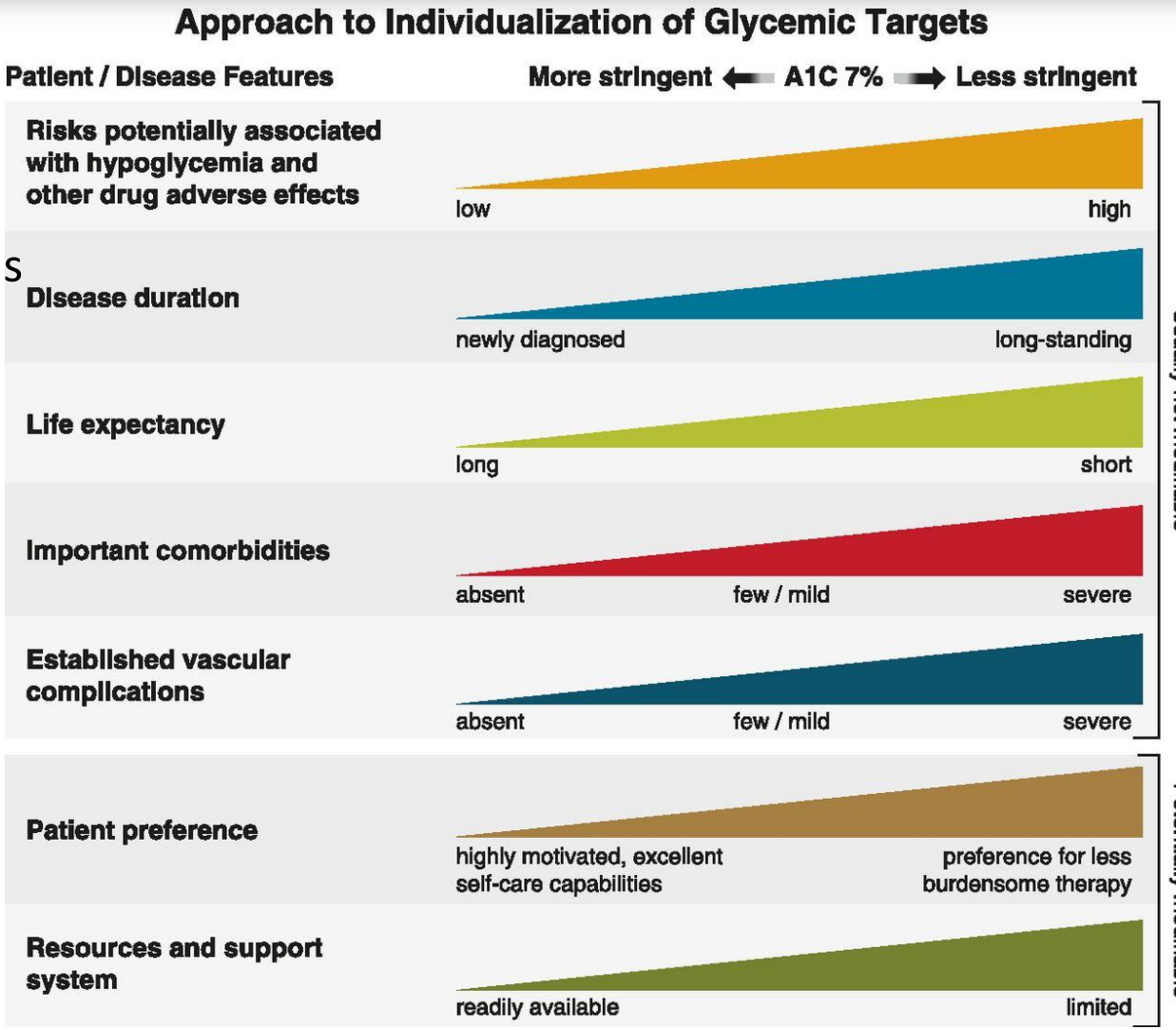
Glycemic targets - HbA1c level

HbA1C goal for many nonpregnant adults of **<7%** (53mmol/mol)

lower HbA1C levels (such as <6.5%) may be acceptable if this can be achieved safely without significant hypoglycemia or other adverse effects of treatment.

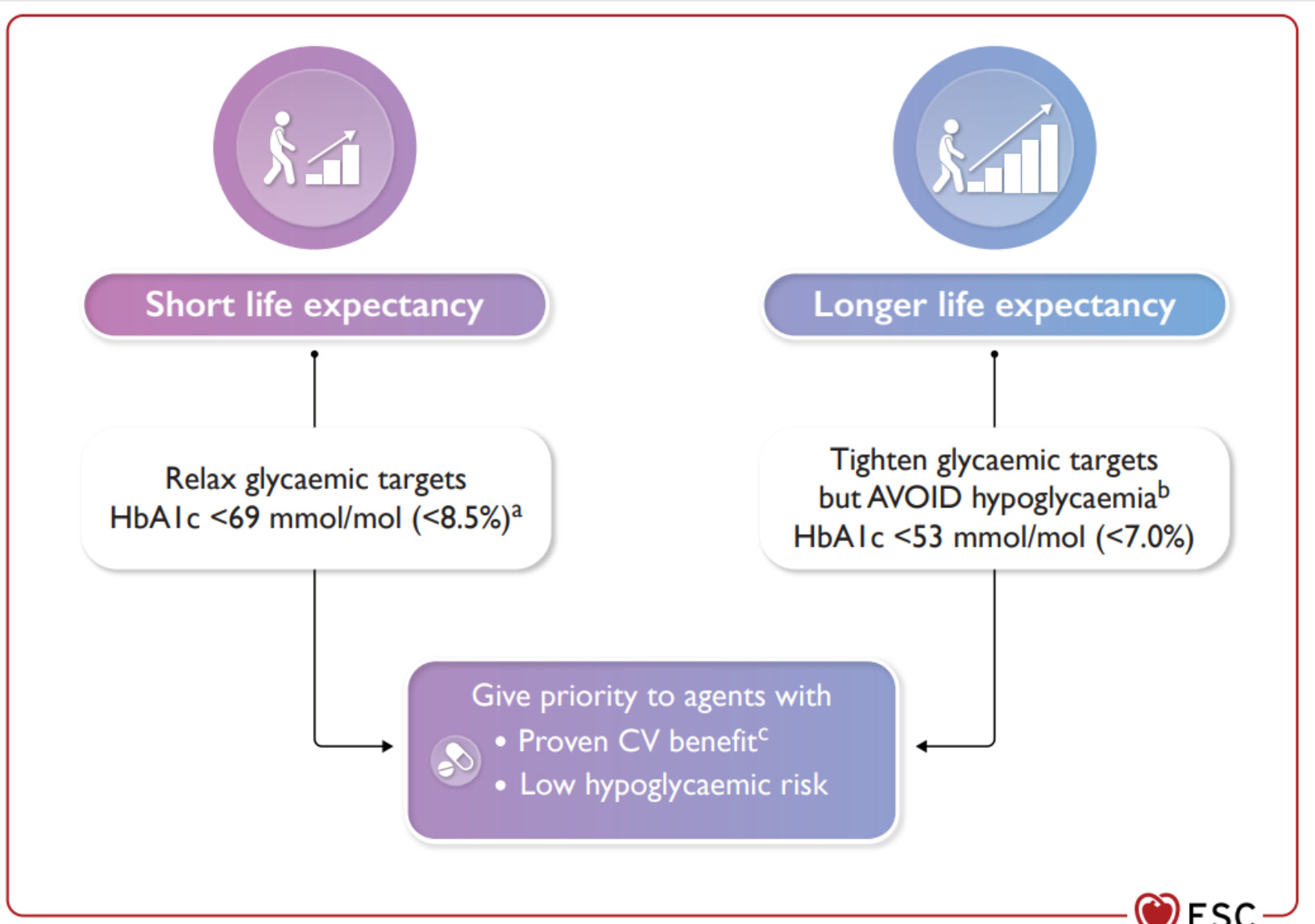
Less stringent HbA1C goals < 8% [64 mmol/mol]) may be appropriate for patients with:

- 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

Glycemic targets - HbA1c level



Glycemic targets - SMBG

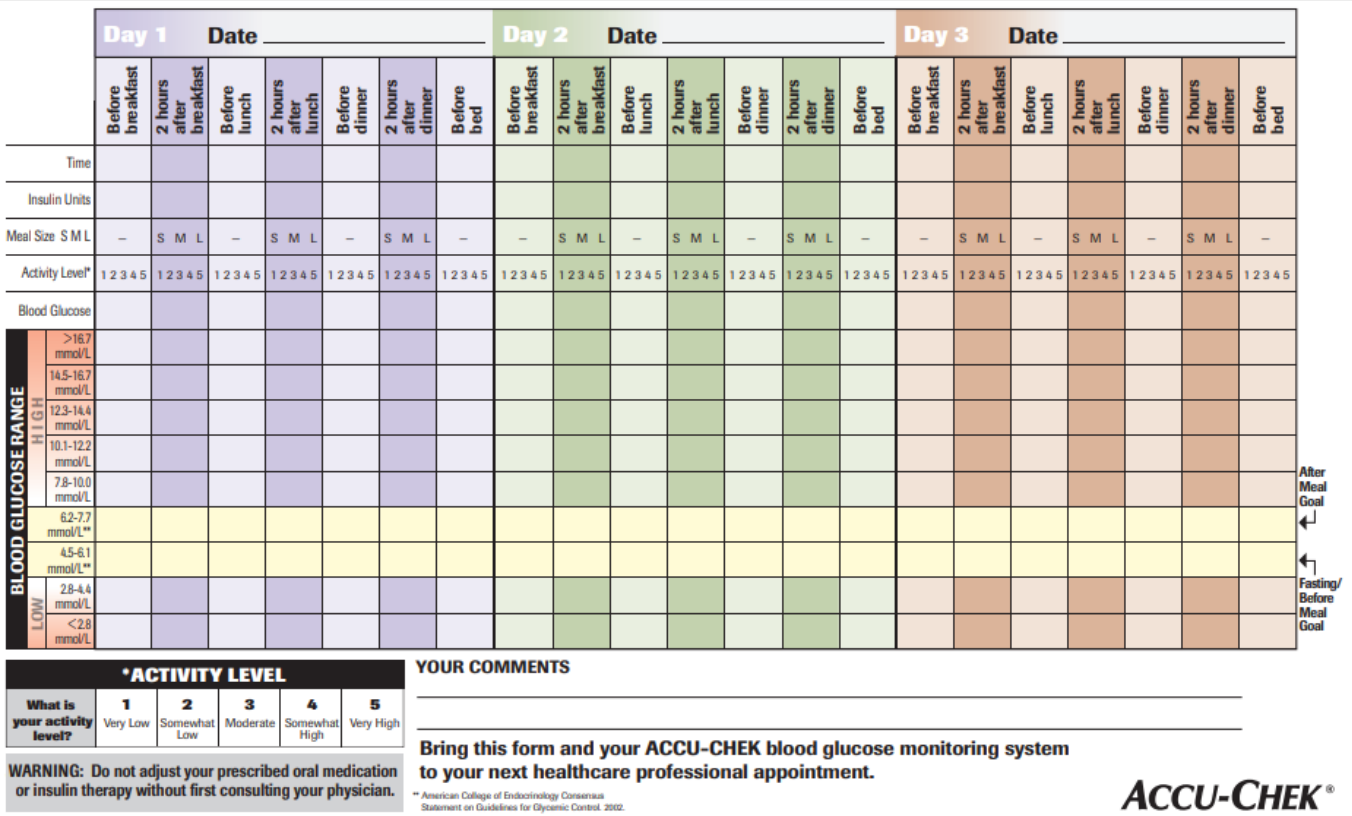
Diabetes: Daily Self-Care

Self-Monitoring Blood Glucose testing ○ ○ ○

Recommendations for the best time of day to test your medicine, meal times and sugar control. Use the chart below to note your doctor's recommendation for checking. Your doctor may also suggest different goals, depending on your situation. You may want to make a copy of this chart to use on a weekly basis.

Time to Test:	Fasting, Before Breakfast	1-2 Hours After Breakfast	Before Lunch	1-2 Hours After Lunch	Before Dinner	1-2 Hours After Dinner	Bedtime	3 a.m.
Target Goal Ranges*	80 - 120	< 180	80 - 120	< 180	80 - 120	< 180	100 - 140	70 - 110
Doctor's Recommendation								
Monday								
Tuesday								
Wednesday								
Thursday								
Friday								
Saturday								
Sunday								

*Blood glucose values are measured from blood samples obtained from the finger or other sites, as read on your blood glucose monitor. The target goals are based on recommendations from a panel of medical experts. Talk to your doctor about what changes to make if your blood sugar levels are not within this range.



EXAMPLE 1

	BREAKFAST		LUNCH		DINNER		BEDTIME
	Before	2h after	Before	2h after	Before	2h after	3h after dinner
Finger-prick test	✓		✓		✓		✓

EXAMPLE 2

	BREAKFAST		LUNCH		DINNER		BEDTIME
	Before	2h after	Before	2h after	Before	2h after	3h after dinner
Finger-prick test	✓	✓		✓		✓	

DURING PREGNANCY

	BREAKFAST		LUNCH		DINNER		BEDTIME
	Before	2h after	Before	2h after	Before	2h after	3h after dinner
Finger-prick test	✓	✓	✓	✓	✓	✓	✓

Glycemic targets - HbA1c level, (SMBG)

	< 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

Glycemic targets - CGM

GLUCOSE STATISTICS AND TARGETS

14 days
% Sensor Time

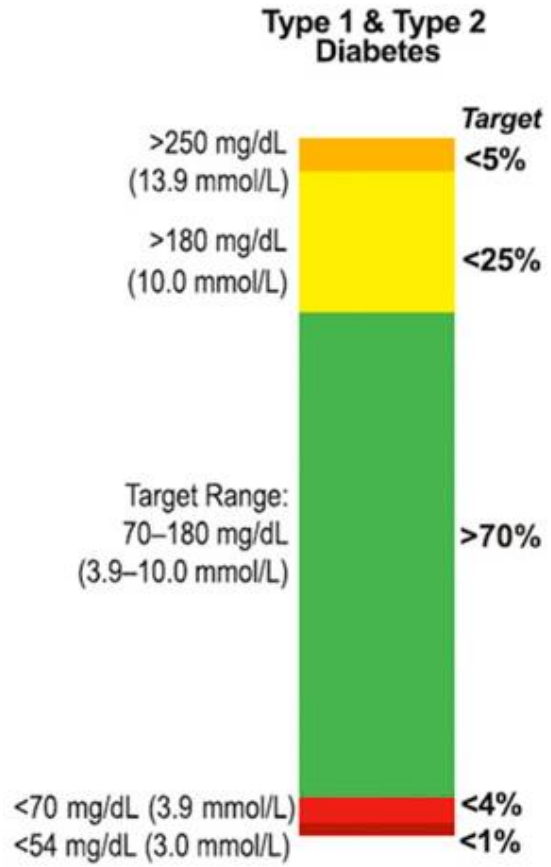
Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

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%

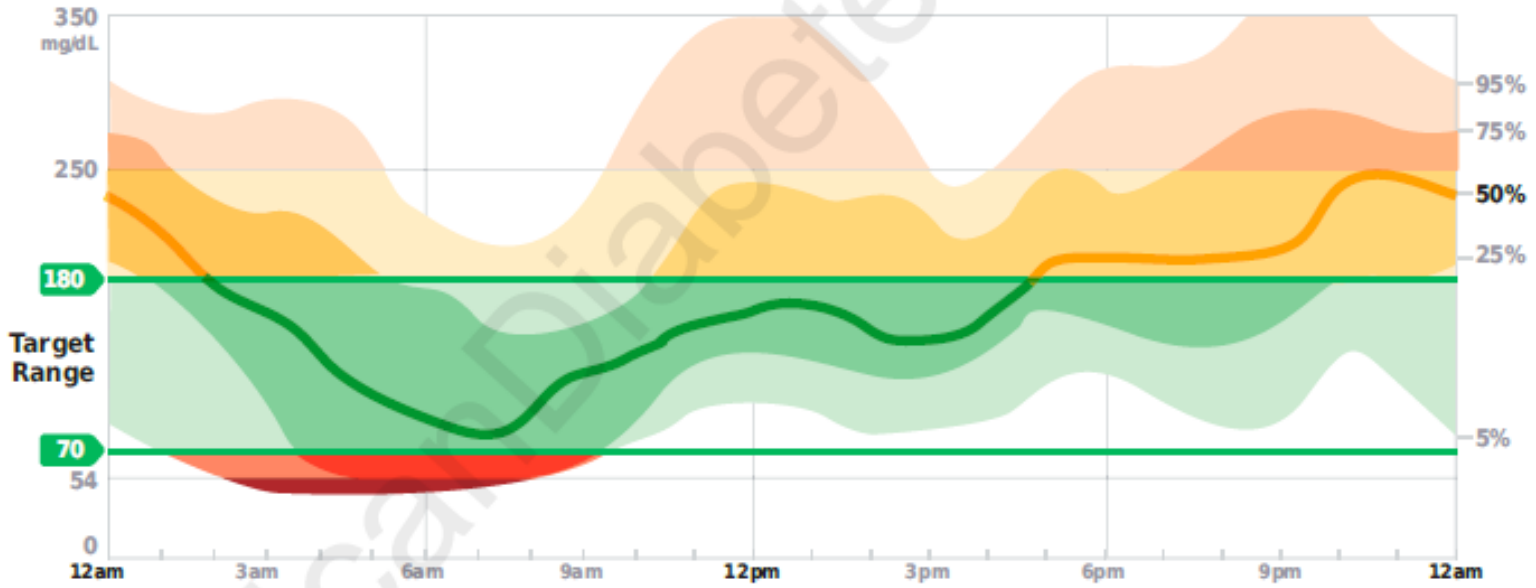
TIME IN RANGES



ADA 2021-2023

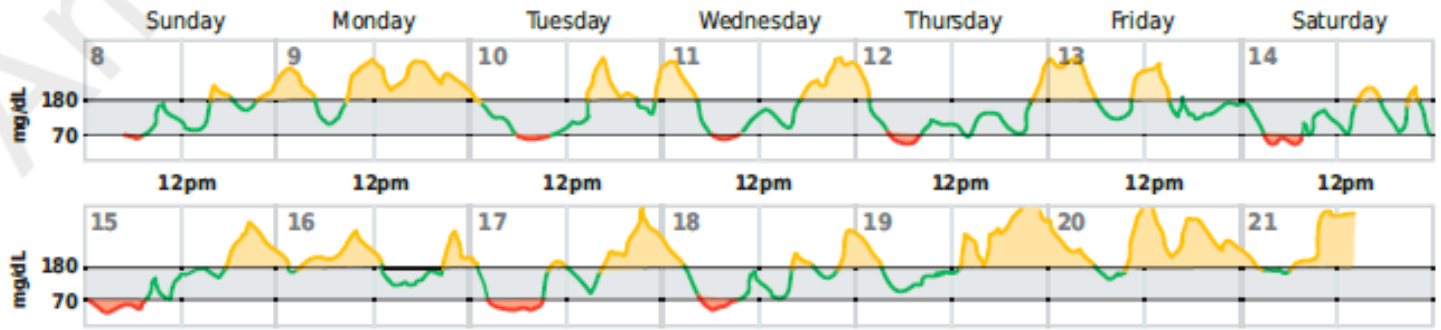
Ambulatory Glucose Profile (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if they occurred in a single day.



Daily Glucose Profiles

Each daily profile represents a midnight-to-midnight period.



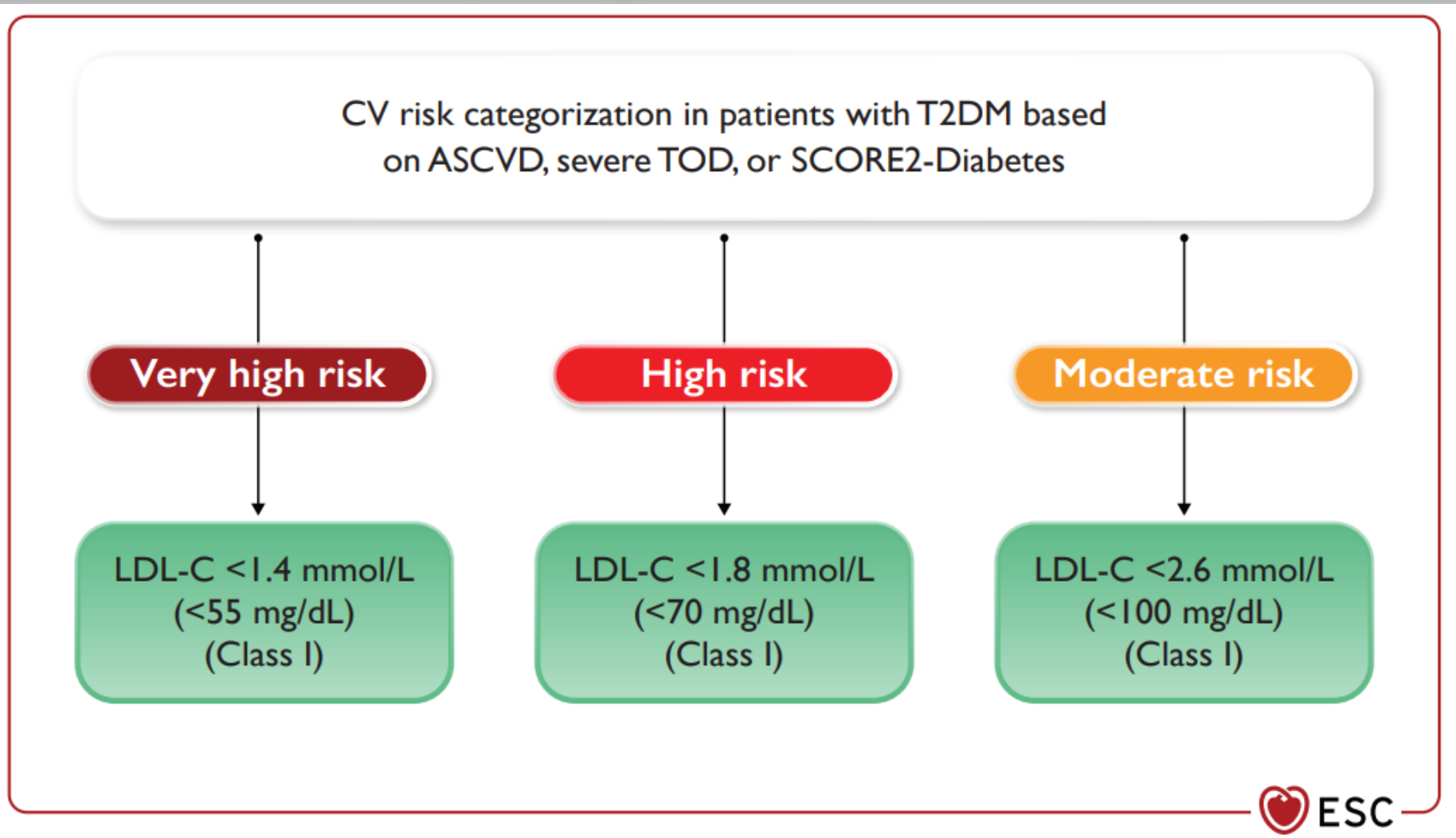
ADA 2023

Blood pressure targets

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 2023-2021

Lipid profile control / target

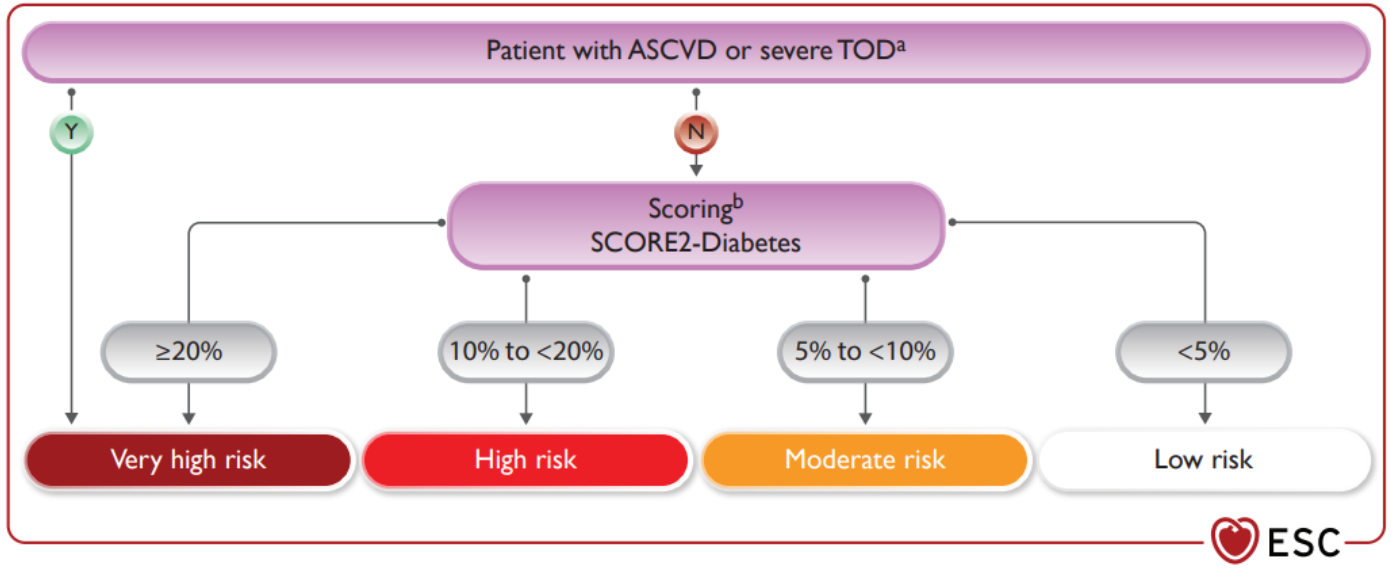


↓LDL-cholesterol 1 mmol/l - ↓ CV risk with 22%

Lipid profile control / target

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].[43–45]

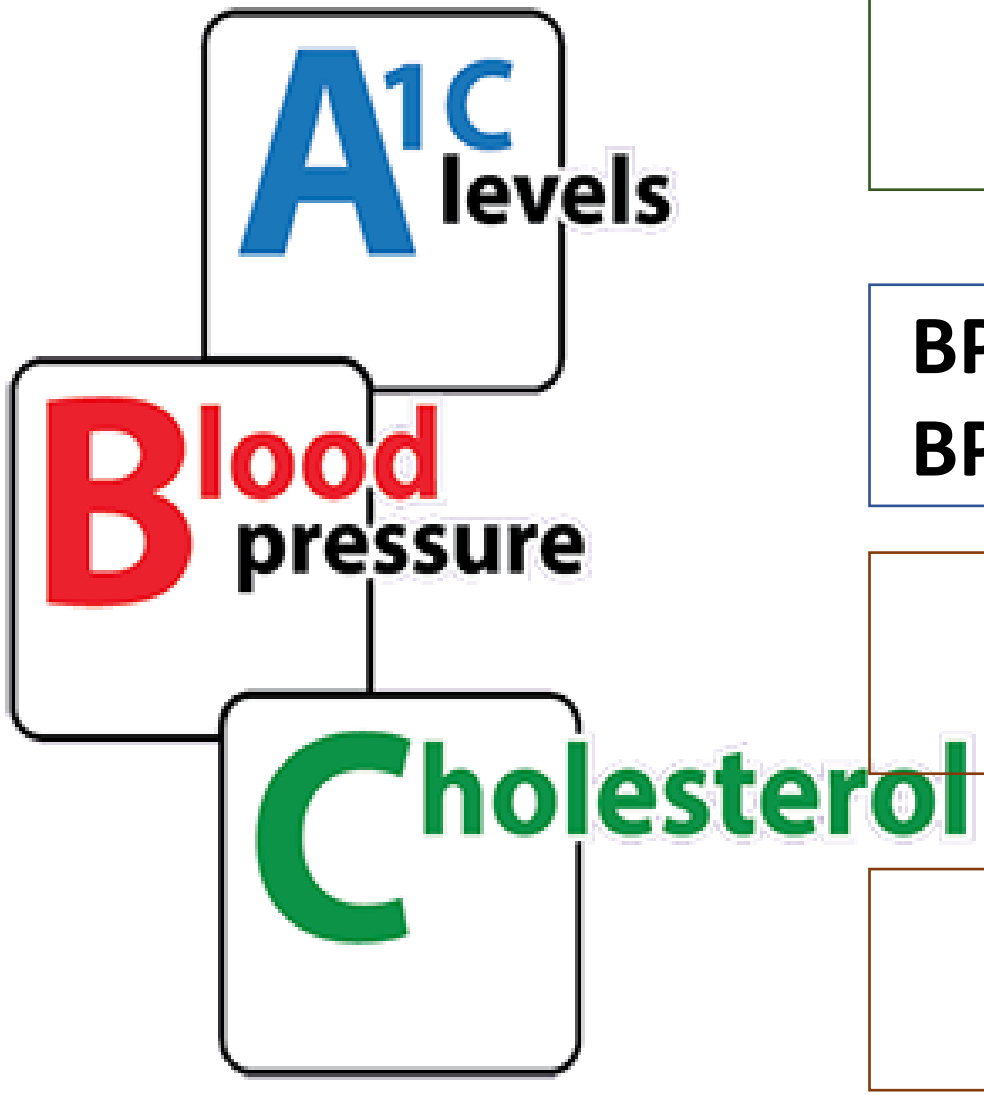


Weight reduction targets.

In patients with obesity and DM type 2, reducing weight is one of the cornerstones of treatment.

Weight loss of 5-15% improves glycaemic control, lipid levels, and BP in overweight and obese adults with DM type 2.

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

Weight loss 5-15%

Management of diabetes mellitus

TYPE 1 DM

- Education + Lifestyle modification +
- Insulin

- **TYPE 2 DM**

- Education + Lifestyle modification +
- Noninsulinic agents

OR

- Noninsulinic agents + Insulin

OR

- 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)

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.

Macronutrient distribution

- 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.

carbohydrates

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

- **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.

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

- **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.

- protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety

Fat intake

- The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and **it is recommended that the percentage of total calories from saturated fats should be limited.**

- **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.

- **An eating plan emphasizing** elements of a Mediterranean-style eating **pattern rich in monounsaturated and polyunsaturated fats** may be considered to improve glucose metabolism and lower cardiovascular disease risk.

Eating Patterns and Meal Planning

- **A variety of eating patterns are acceptable** for the management of type 2 diabetes and prediabetes. **The Mediterranean-style, low-carbohydrate, 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

- **meal plans should be individualized,** focus on:
  - personal preferences (e.g., tradition, culture, religion),
  - needs (physical activity, medication use, skills, resources)
  - metabolic goals (health goals)

- **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

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.

Lifestyle modification

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

Physical activity

Exercise has been shown to

- improve blood glucose control
- reduce cardiovascular risk factors
- contribute to weight loss
- improve well-being

	Glucose/insulin	Blood pressure	HbA_{1c}	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIOURS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ Higher levels/improvement (physical function, quality of life); ↓ Lower levels/improvement (glucose/insulin, blood pressure, HbA_{1c}, lipids, depression); ? no data available;
↑ Green arrows = strong evidence; ↑ Yellow arrows = medium strength evidence; ↑ Red arrows = limited evidence.

IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIOURS FOR TYPE 2 DIABETES

SITTING/BREAKING UP PROLONGED SITTING

Limit sitting. Breaking up prolonged sitting (every 30 min) with short regular bouts of slow walking/simple resistance exercises can improve glucose metabolism.

STEPPING

- An increase of only 500 steps/day is associated with 2-9% decreased risk of cardiovascular morbidity and all-cause mortality.
- A 5 to 6 min brisk intensity walk per day equates to ~4 years' greater life expectancy.

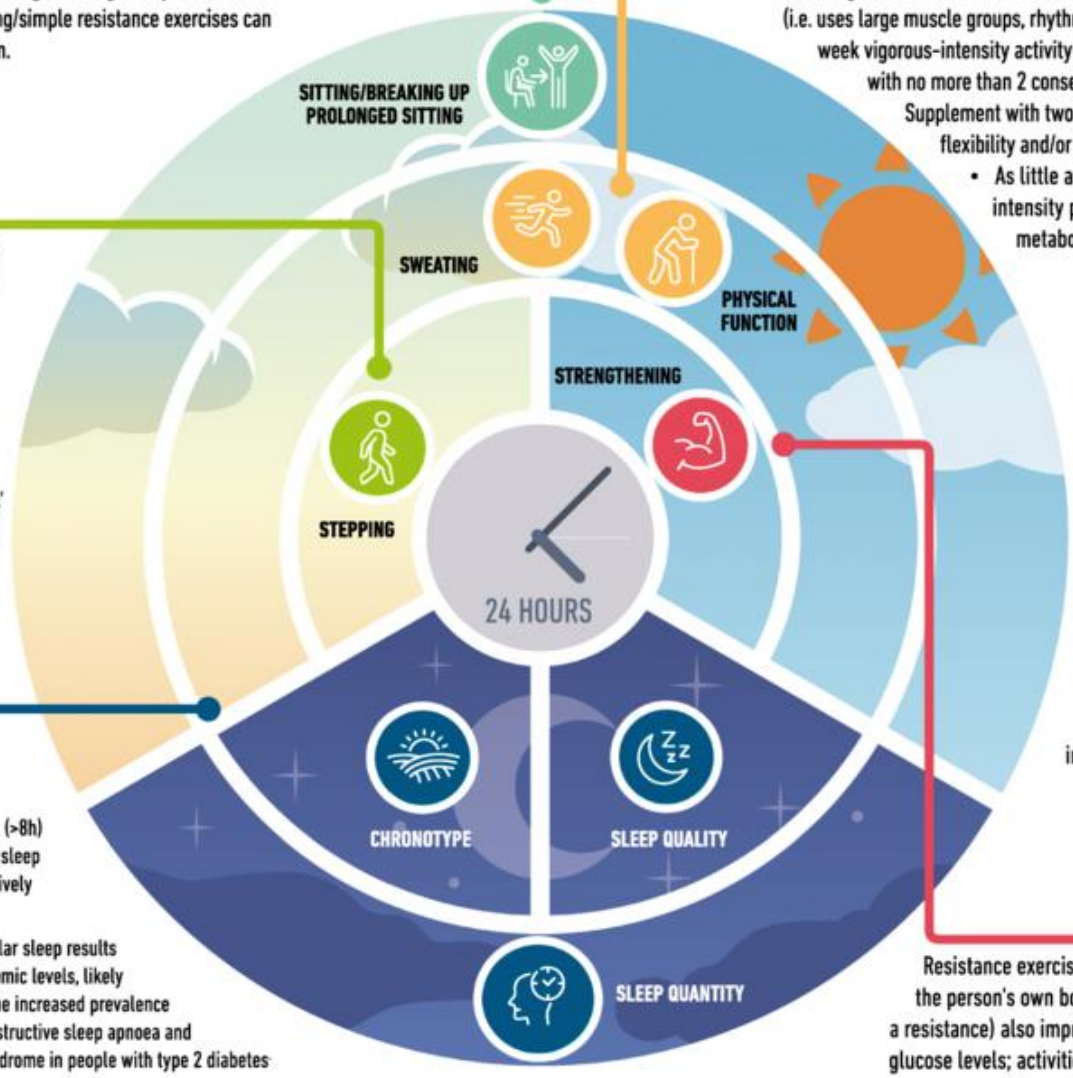
SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.

Quantity – Long (>8h) and short (<6h) sleep durations negatively impact HbA_{1c}.

Quality – Irregular sleep results in poorer glycaemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnoea and restless leg syndrome in people with type 2 diabetes

Chronotype – Evening chronotypes (i.e. night owl: go to bed late and get up late) may be more susceptible to inactivity and poorer glycaemic levels vs morning chronotypes (i.e. early bird: go to bed early and get up early).



SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)

- Encourage ≥150 min/week of moderate-intensity physical activity (i.e. uses large muscle groups, rhythmic in nature) OR ≥75 min/week vigorous-intensity activity spread over ≥3 days/week, with no more than 2 consecutive days of inactivity. Supplement with two to three resistance, flexibility and/or balance sessions.
- As little as 30 min/week of moderate-intensity physical activity improves metabolic profiles.

Physical function/frailty/ sarcopenia

- The frailty phenotype in type 2 diabetes is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with type 2 diabetes to undertake simple functional exercises in middle-age is similar to that in those over a decade older.

STRENGTHENING

Resistance exercise (i.e. any activity that uses the person's own body weight or works against a resistance) also improves insulin sensitivity and glucose levels; activities like tai chi and yoga also encompass elements of flexibility and balance.

Lifestyle modification

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

Smoking cessation: tobacco and e-cigarettes

Recommendations
It is recommended to stop smoking to reduce cardiovascular risk.[118–120]
Nicotine replacement therapy, varenicline, and bupropion, as well as individual or telephone counselling, should be considered to improve smoking cessation success rate.[121]

CV risk

Recommendations

5.34 Advise all individuals not to use cigarettes and other tobacco products or e-cigarettes. **A**

5.35 After identification of tobacco or e-cigarette use, include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **A**

5.36 Address smoking cessation as part of diabetes education programs for those in need. **B**

Smoking cessation - **↓ with 36% mortality**

Pharmacologic therapy for type 2 diabetes

Pharmacologic therapy for adults with type 2 diabetes

- Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals:
  - effects on cardiovascular and renal comorbidities,
  - efficacy,
  - hypoglycemia risk,
  - impact on weight,
  - cost and access,
  - risk for side effects,
  - and individual preferences

- In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk.

- Weight management is an impactful component of glucoselowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals

Pharmacologic therapy for adults with type 2 diabetes

- Early combination therapy can be considered in some individuals 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%) or blood glucose levels (>300mg/dL) are very high.

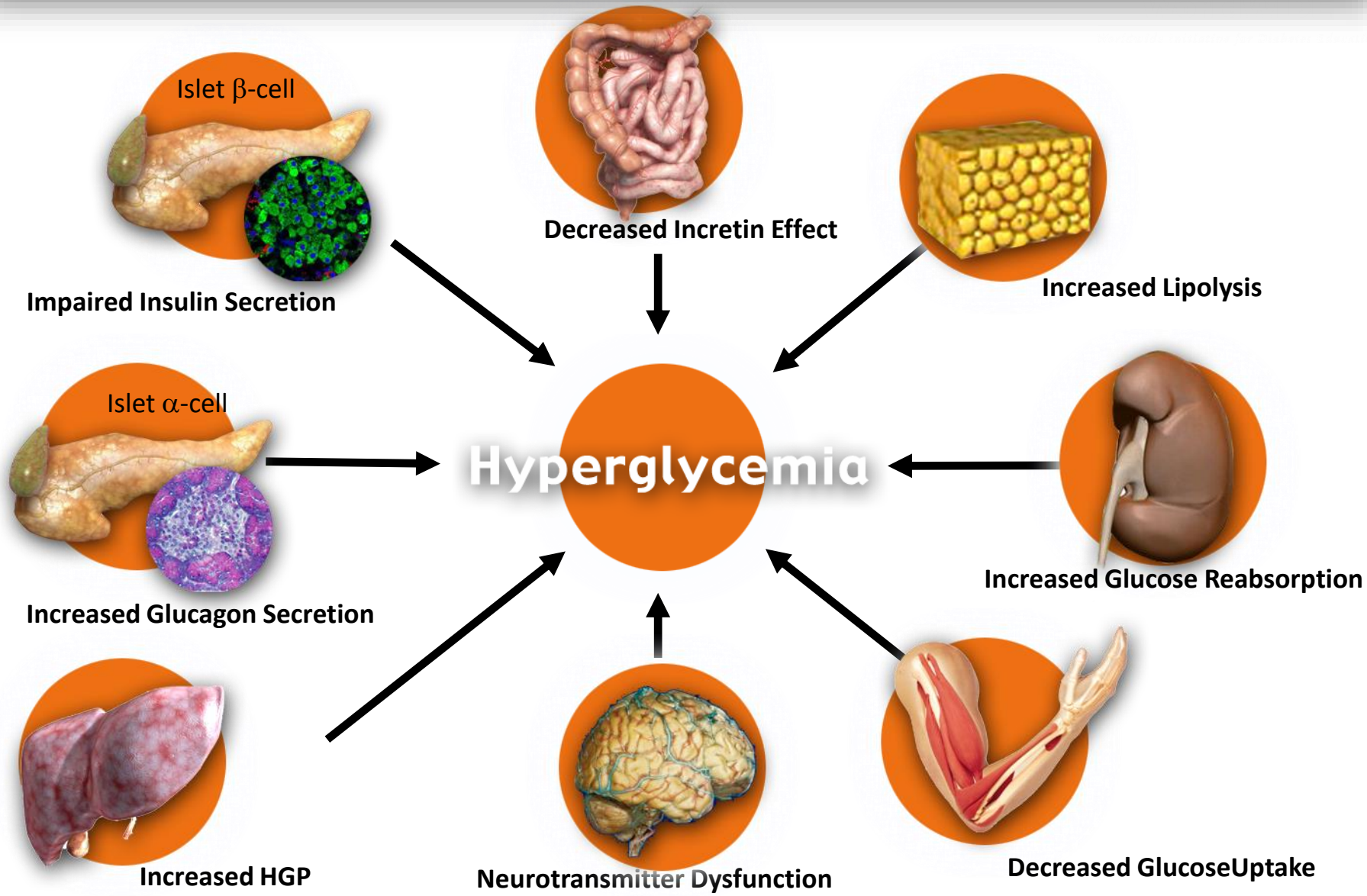
- Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease Benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors for details on cardiovascular risk reduction recommendations).

Class	Drugs
Biguanides	Metformin
SU 2nd generation	Gliclazide, Glimepiride, Gliburide, Glipizide,
Thiazolidinediones (TZDs)	Pioglitason
Alpha-glucosidase inhibitors	Acarboza, Miglitol
Meglitinides	Repaglinide, Nateglinide
Dipeptidyl peptidase-IV (DPP-4) inhibitors	Alogliptin, Saxagliptin, Sitagliptin, Linagliptin, Vildagliptin
GLP-1 receptor agonists	Exenatide, Dulaglutide, Semaglutide, Liraglutid, Lixisenatid, Albiglutide
Dual GLP-1 Receptor/GIP Receptor Agonists	Tirzepatide
SGLT2 inhibitors	Ertugliflozin, Canagliflozin, Dapagliflozin, Empagliflozin
Amilin mimetics	Pramlintid
Dopamine-2 agonists	Bromcriptin
Bile acids sequestrants	Colesevelam

Class	Drugs
Biguanides + iDPP4	Janumet (Metformin and Sitagliptin) Daltex (Metformin and vildagliptin)
Biguanides + iSGLT2	Xigduo (Metformin and dapagliflozin)
Insulin	Basal
	Prandial
Insulin + GLP-1 receptor agonists	Xultophy (insulin degludec and liraglutide)
	Suliqua (insulin glargine and lixisenadite)

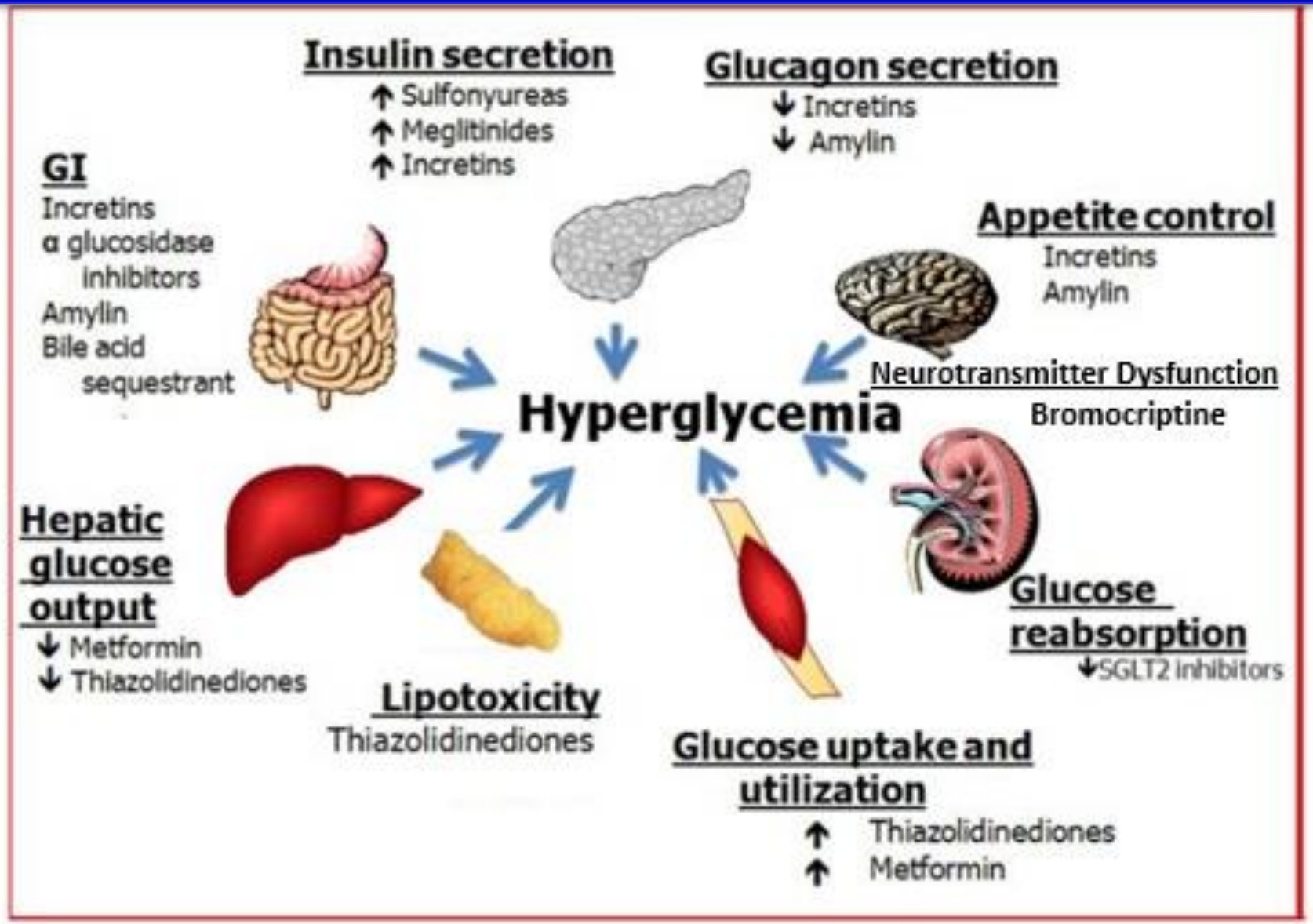
From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

Ralph A. DeFronzo

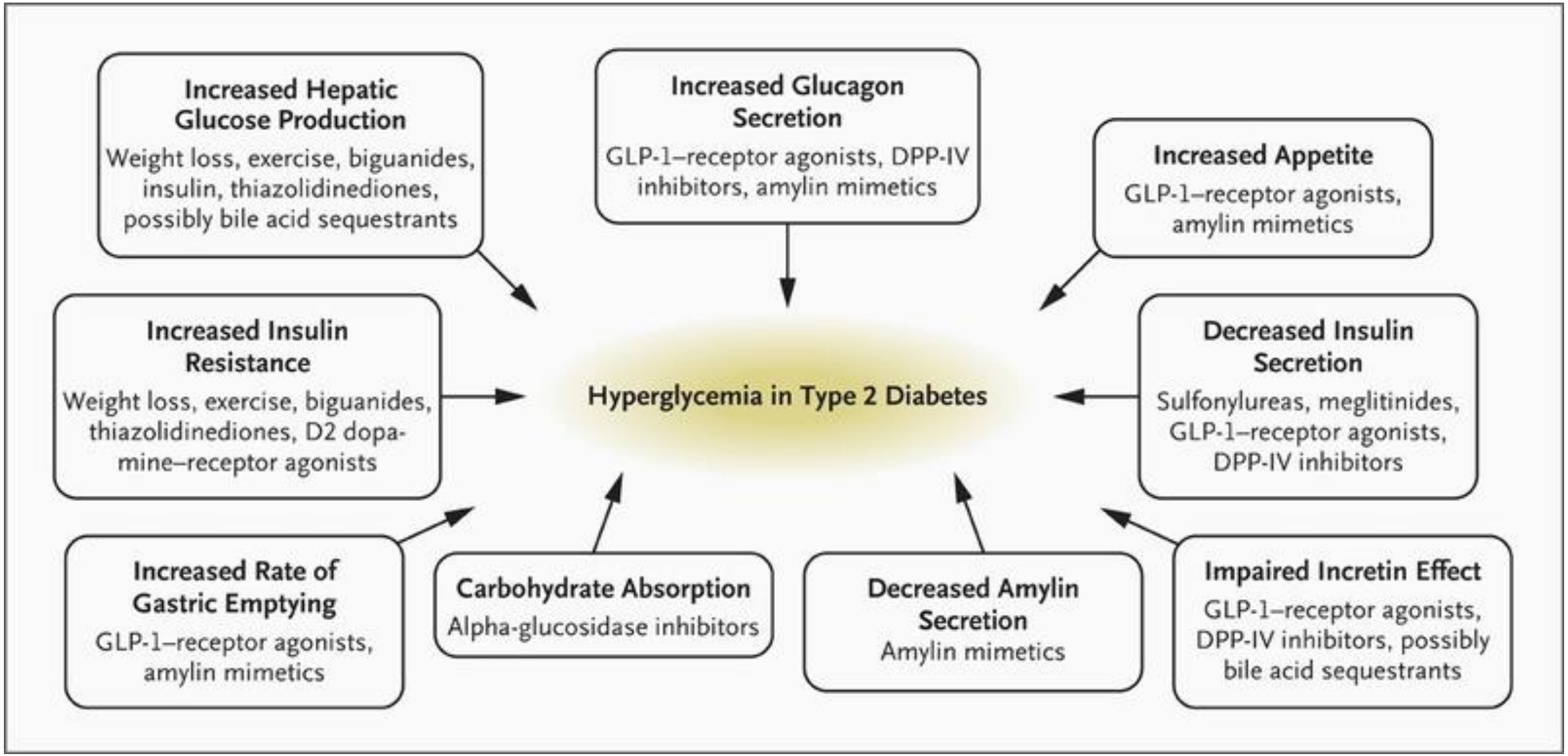


DeFronzo RA. Lilly Lecture: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 1988; 37: 667–687, De FronzoRA. Diabetes 2009

Key classes of glucose lowering drugs



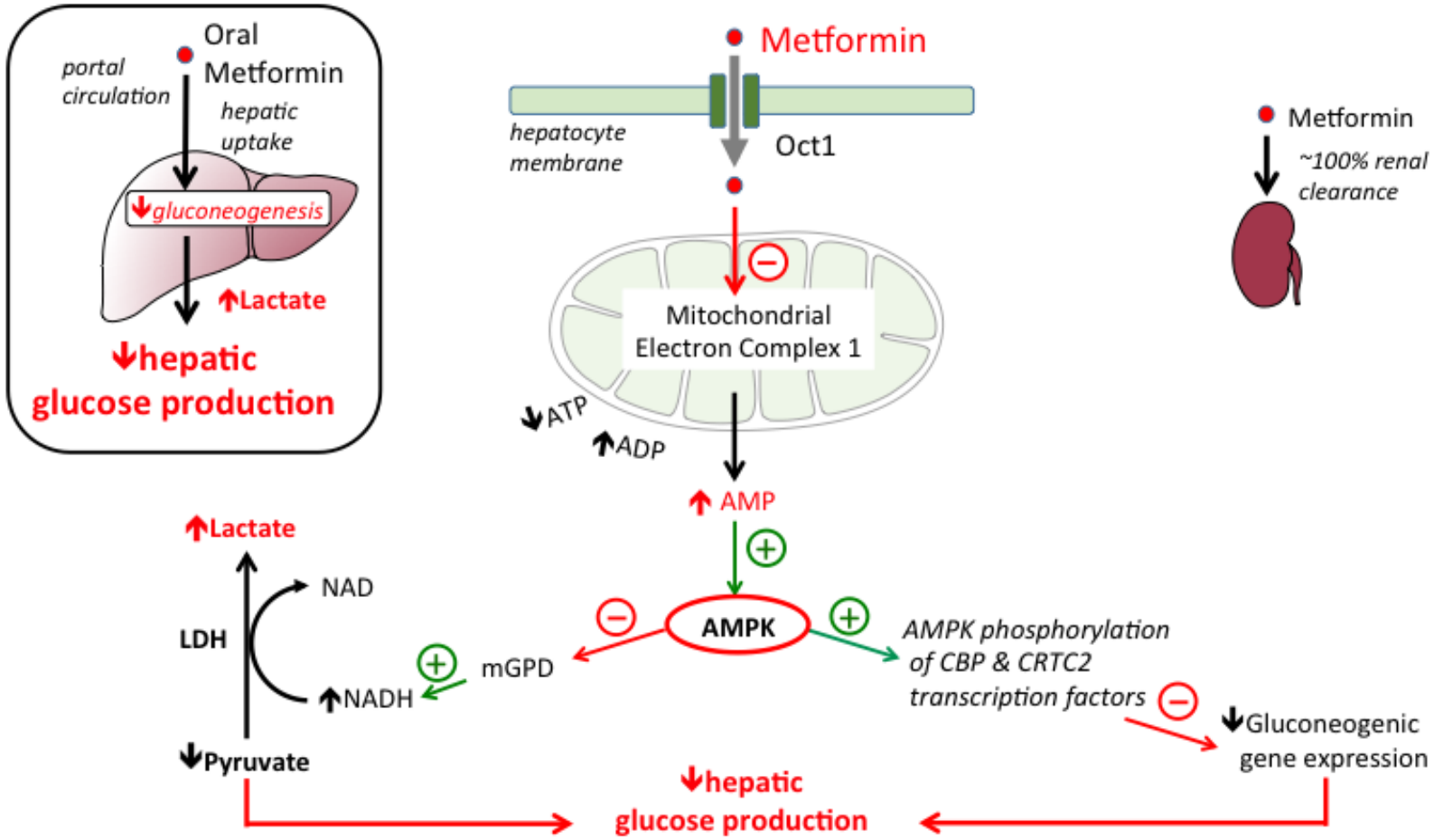
Key classes of glucose lowering drugs



Biguanides - Metformin

- **Cellular mechanism** - activate AMP-kinase

- decreases hepatic glucose production
- improves hepatic insulin sensitivity but has only a modest impact on peripheral insulin-mediated glucose uptake (i.e., insulin resistance)



Biguanides - Metformin

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 ml/min per 1.73 m^2

Oral/SQ	Cost	Clinical considerations
Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations and administration with food • Potential for vitamin B_{12} deficiency; monitor at regular intervals

Advantages	Disadvantages
Inexpensive	GI side effects
No hypoglycemia	B12 deficiency
Once a day administration possible	Lactic acidosis (very rare)
Long history of use	Need to monitor renal function
No weight gain and maybe weight loss	
May decrease cardiovascular disease	

Sulfonylureas - 2nd generation

Cellular mechanism - closes K_{ATP} channels

Primary physiological action – increase insulin secretion

Other effects

Sensitize β-cells to glucose

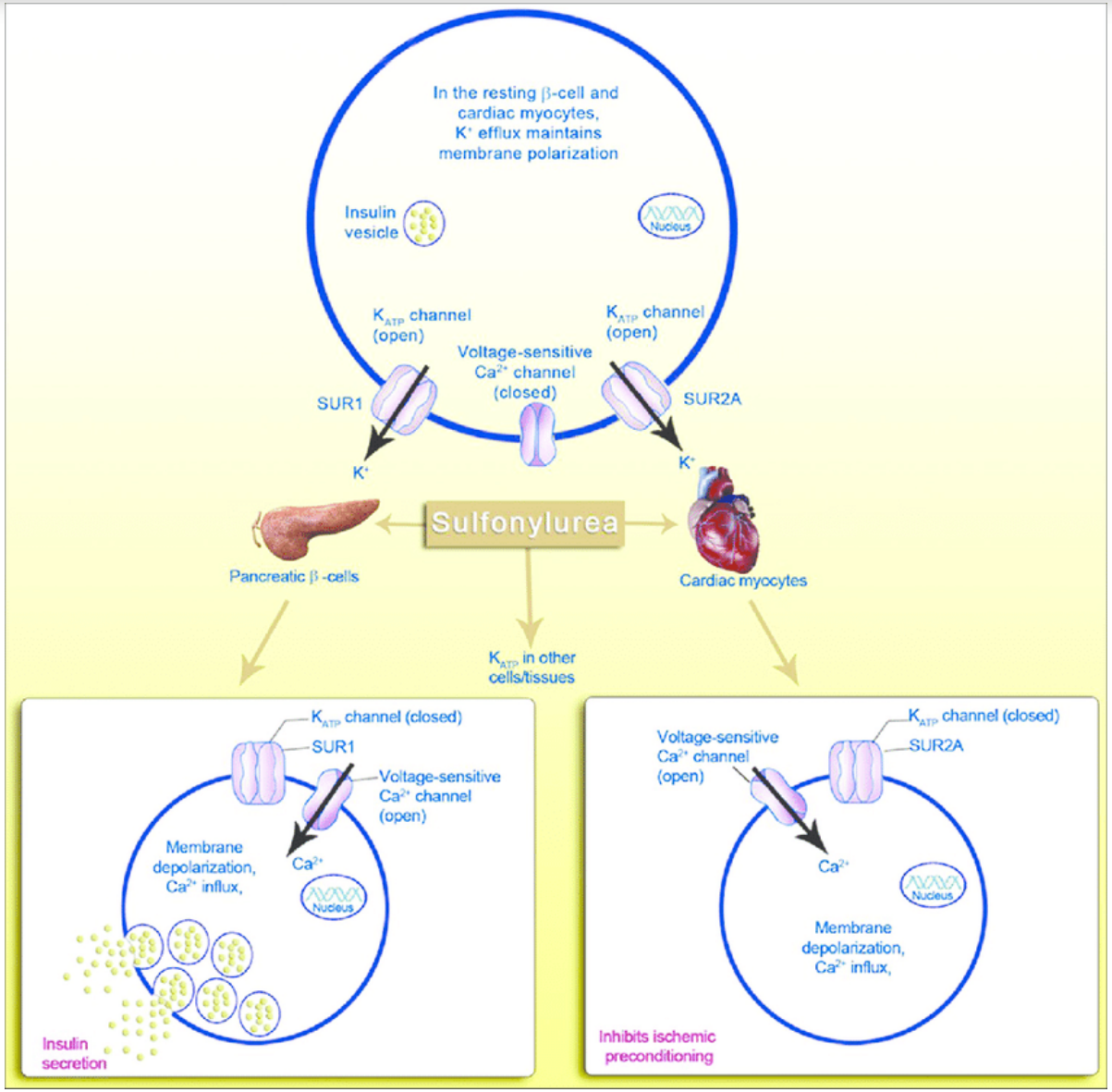
Limit glucose production in the liver

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

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycaemia

Oral/SQ	Cost	Clinical considerations
Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycaemia

Advantages	Disadvantages
Inexpensive	Hypoglycemia
Rapid acting	Weight gain
Once a day administration possible	Limited durability
Long history of use	Need to titrate dose

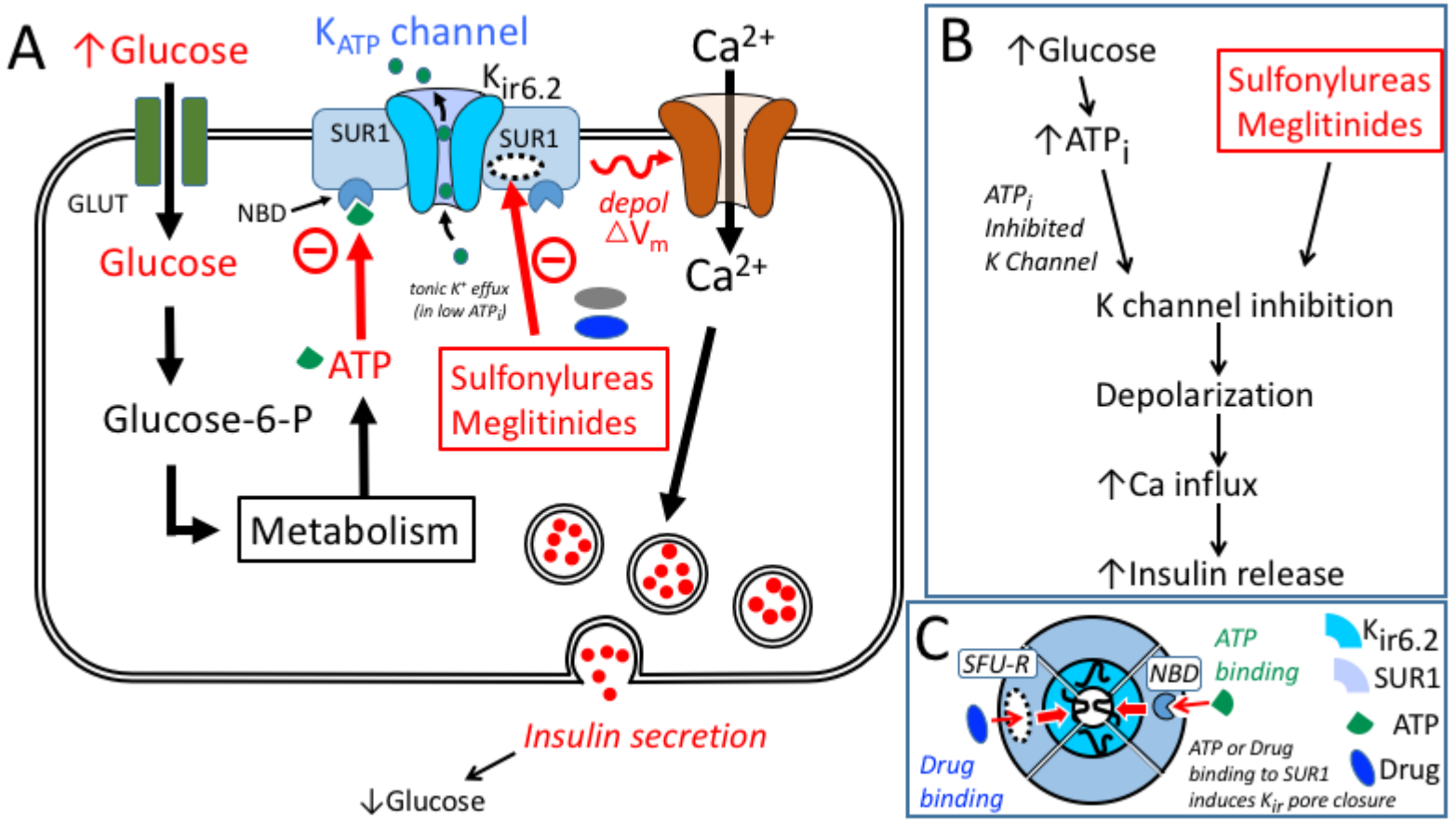
Meglitinides

Cellular mechanism - closes K_{ATP} channels

Primary physiological action –

increase insulin secretion

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



Meglitinides

Indication	• can be useful when there is a need to specifically lower postprandial glucose levels (i.e., patients with fasting glucose in desired range but elevated post meal glucose levels).
Contraindications	• Hepatic failure
Side effects	• Hypoglycemia but the risk of severe hypoglycemia is less sulfonylureas • Weight gain

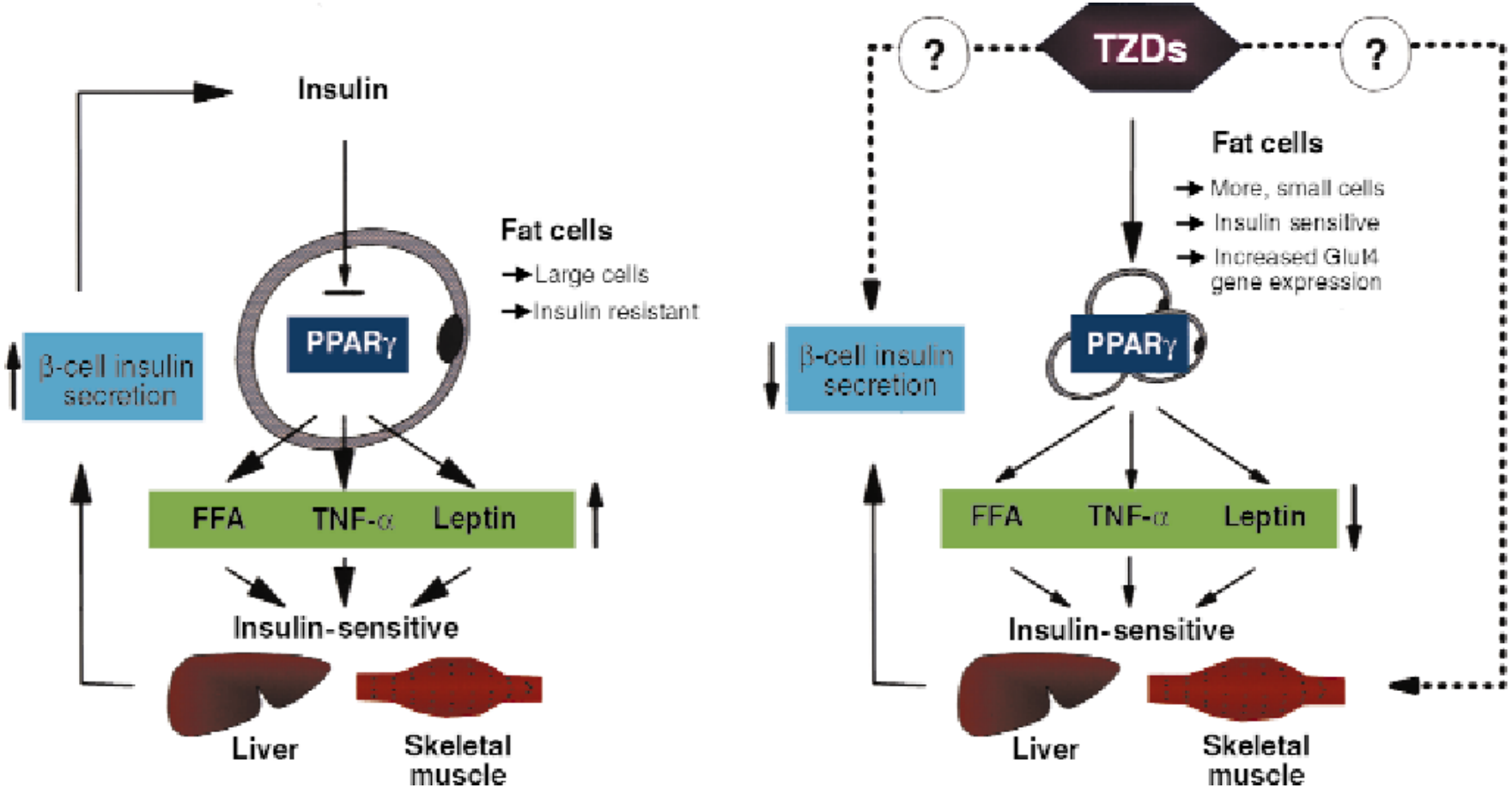
Advantages	**Disadvantages**
Decrease postprandial glucose	Hypoglycemia
Flexible dosing	Weight gain
Relatively inexpensive	Frequent dosing
Short action allowing for missing meals	Need to titrate dose

Thiazolidindiones

Cellular mechanism - activates the nuclear transcription factor PPARγ

Primary physiological action –

increase insulin-sensitivity



Thiazolidindiones

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention

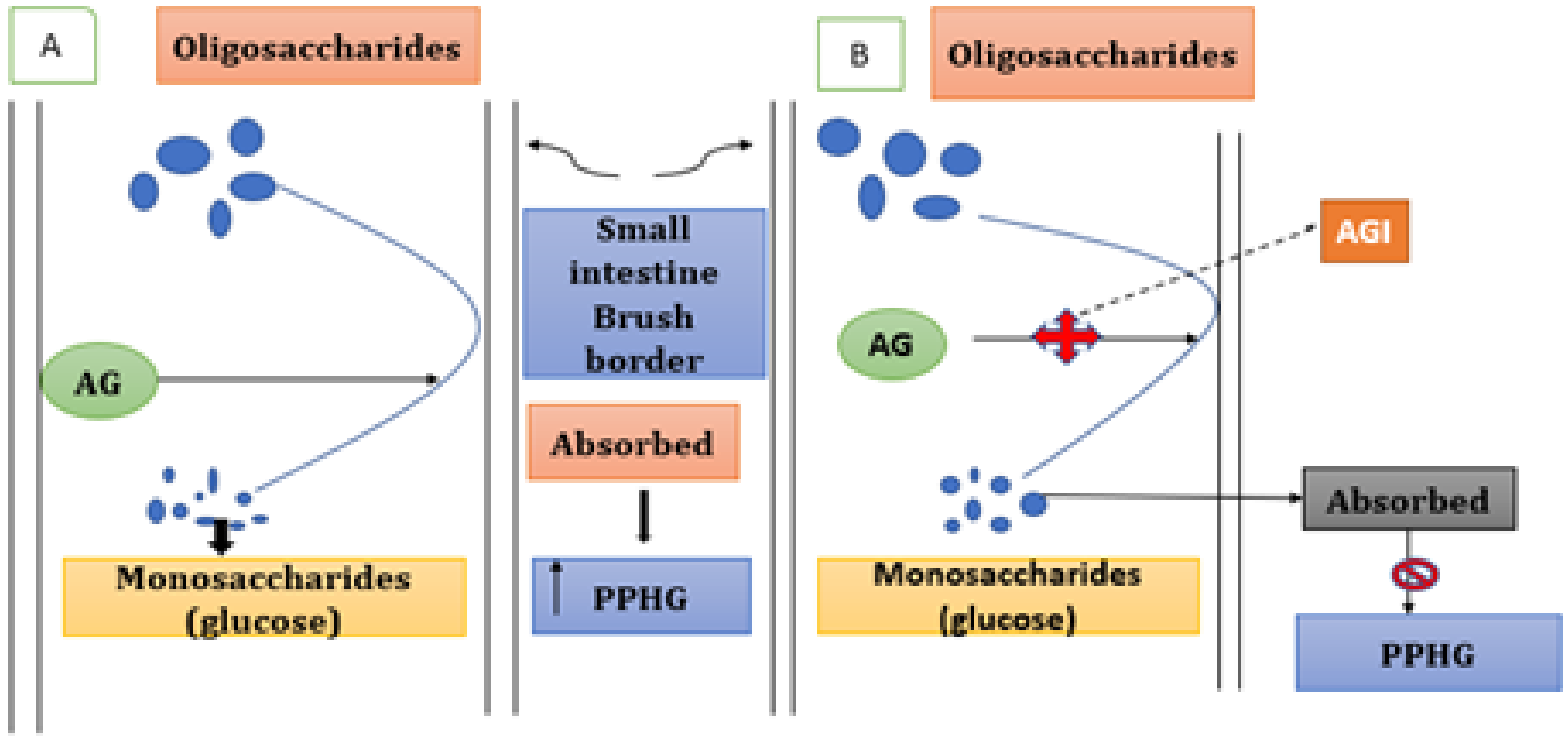
Oral/SQ	Cost	Clinical considerations
Oral	Low	• Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (oedema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain

Advantages	Disadvantages
Once a day administration	Edema
Reduces CVD (pioglitazone)	CHF
Durable Effect	Weight gain
Reduces NASH	Osteoporosis
No hypoglycemia	Bladder cancer (pioglitazone)?
Relatively inexpensive	Macula edema?
No dose adjustment for renal disease	Small increase in LDLc
Increase HDL-C and decrease triglycerides	

α-glucosidase inhibitors

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

Primary physiological action – slows intestinal carbohydrates digestion and absobtion



alpha-glucosidase inhibitors

Indication	• are excellent drugs for lowering postprandial glucose levels.
Contraindications	• in patients with inflammatory bowel disease, colonic ulceration, intestinal obstruction or those predisposed to intestinal obstruction, patients with chronic intestinal disease, or conditions that will be worsened by the increased gas formation in the intestine • in patients with cirrhosis • should not be used in patients with a creatinine > 2 mg/dl
Side effects	• may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. • Gastrointestinal side effects include flatulence, abdominal discomfort, and diarrhea and are very commonly encountered

Advantages	Disadvantages
No hypoglycemia	GI side effects
Weight neutral	Frequent dosing schedule
Decreases postprandial glucose	Avoid if renal disease (creatinine> 2mg/dL
Relatively inexpensive	

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

GIP and GLP1 RA

Characteristics of GLP-1 and GIP

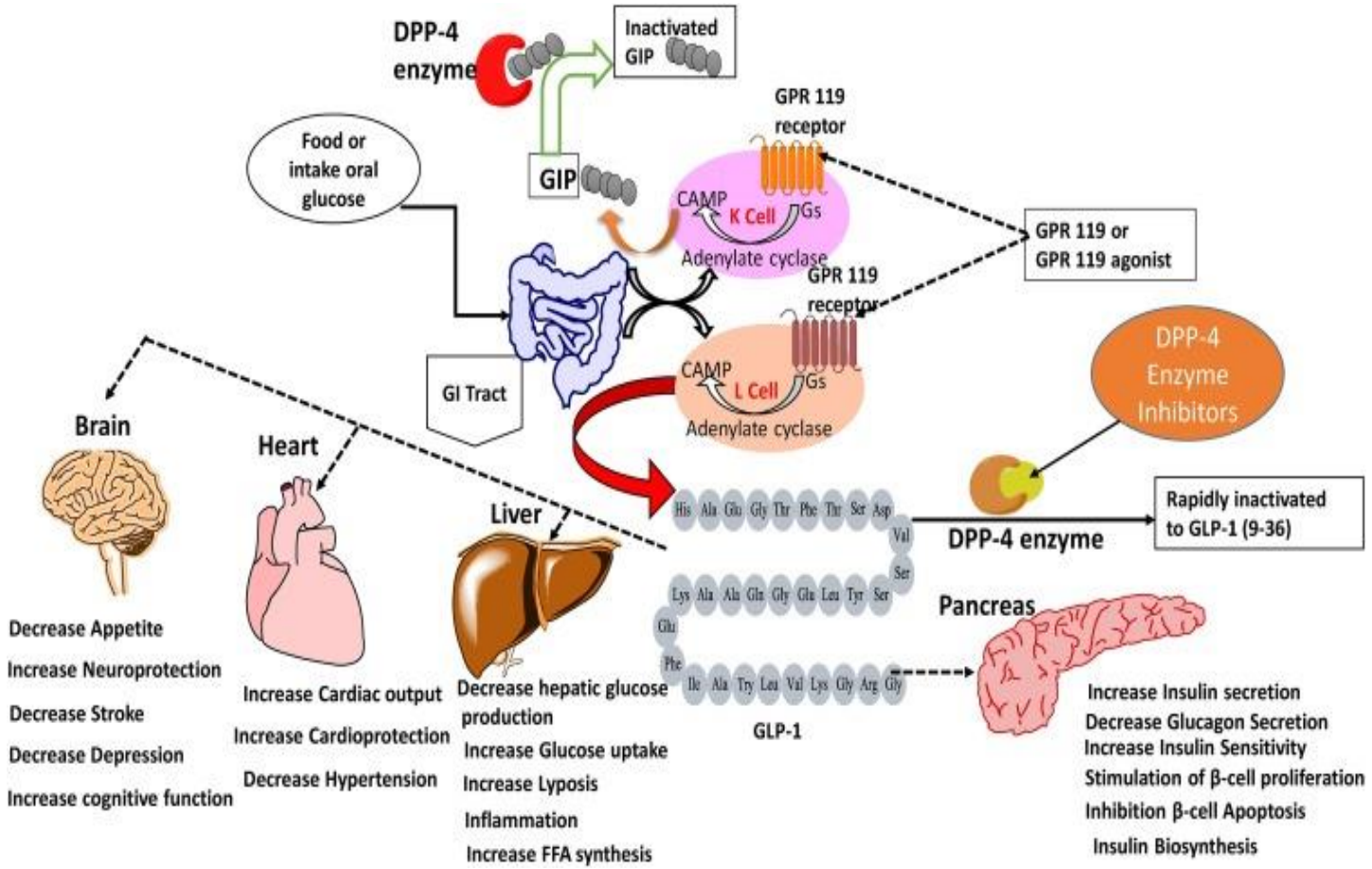
	GLP-1	**GIP**
Post meal levels in patients with diabetes	Normal	Normal
Effect on insulin secretion	Stimulates	Stimulates
Effect on glucagon secretion	Inhibits	No effect or stimulates
Gastric emptying	Delays	No effect
Satiety	Induces	No effect
Degradation by DPP-4	Yes	Yes

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

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin

Oral/SQ	Cost	Clinical considerations
Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected

Advantages	Disadvantages
No hypoglycemia	Pancreatic disease
Weight neutral	Heart failure (saxagliptin/alogliptin)?
Decreases postprandial glucose	Arthritis
Once a day	Bullous pemphigoid
Well tolerated	Relatively expensive
Decreases BP	Modest glycemic lowering

GLP-1 receptors agonists

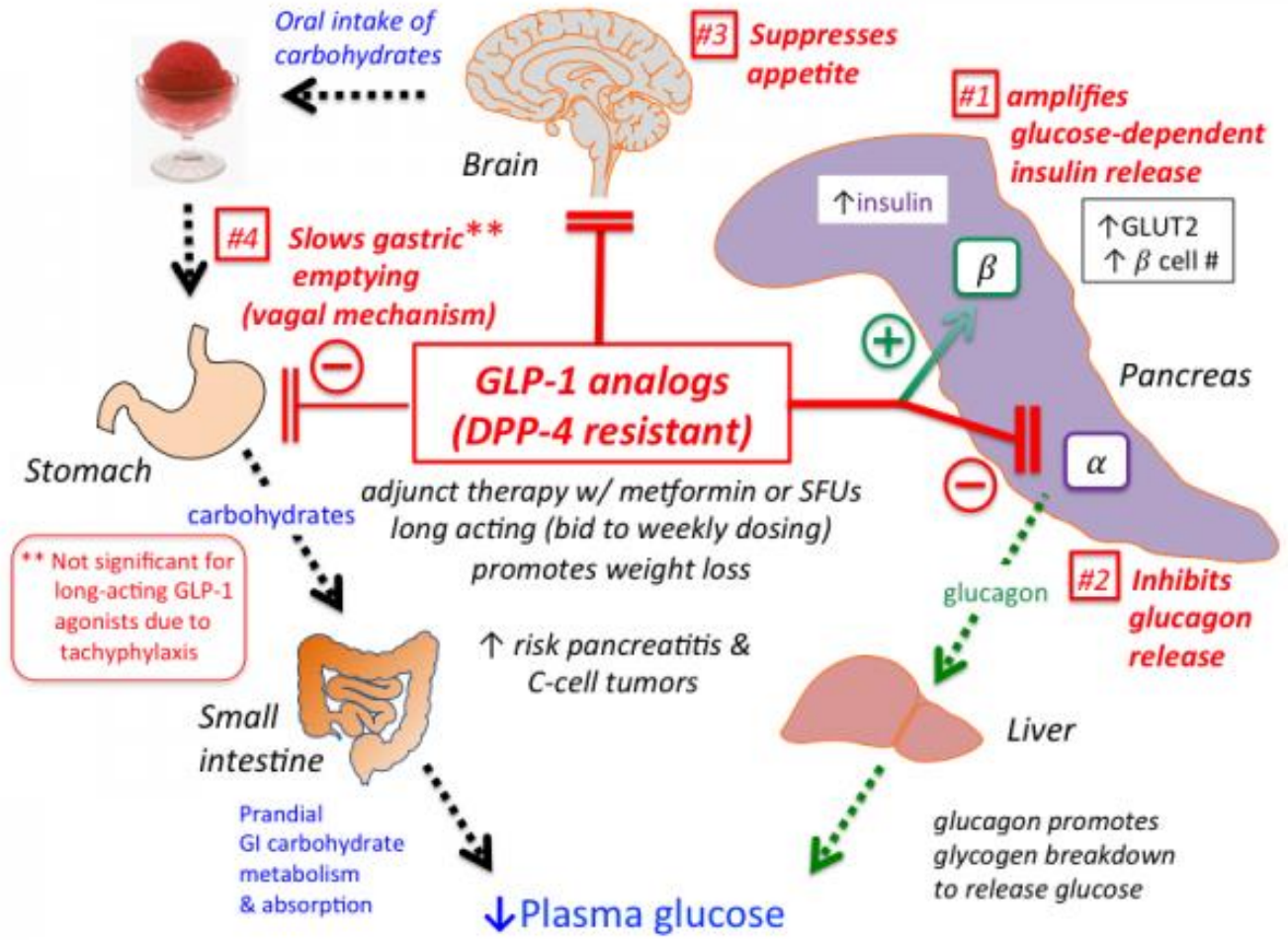
Cellular mechanism – activates GLP1 receptors

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

↓ glucagon secretion (glucose dependent)

Slows gastric empting

↑satiety



GLP-1 receptors agonists

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions

Oral/SQ	Cost	Clinical considerations
SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumours in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects [reduction in meal size, mindful eating practices (e.g. stop eating once full), decreasing intake of high-fat or spicy food]; consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis are suspected

GLP-1 receptor agonist recommendations

- In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.
- In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidaemia or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes.

9.10 In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**

MACE - Major adverse cardiovascular event

ADA/EASD 2022

GLP-1 receptors agonists

Advantages	Disadvantages
Weight Loss	GI side effects
No Hypoglycemia	Requires Injection
Reduce CVD (liraglutide, semaglutide, dulaglutide)	Pancreatitis?
Improve NAFLD	Thyroid cancer?
Once a week therapy possible	Gall bladder disease
Decrease albuminuria	Expensive
Decrease postprandial glucose	

GIP and GLP1 RA

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions

Oral/SQ	Cost	Clinical considerations
SQ	High	• Risk of thyroid C-cell tumours in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects [reduction in meal size, mindful eating practices (e.g. stop eating once full), decreasing intake of high-fat or spicy food]; consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis are suspected

GIP and GLP1 RA

Advantage	• compared to GLP-1 receptor agonists is the greater decrease in weight and A1c levels. • Significant weight loss
Contraindications	• in patients with a personal or family history of medullary thyroid carcinoma or in patients with MEN2.
Side effects	• As with other GLP-1 receptor agonists nausea, diarrhea, vomiting, dyspepsia, constipation, and decreased appetite are common side effects.

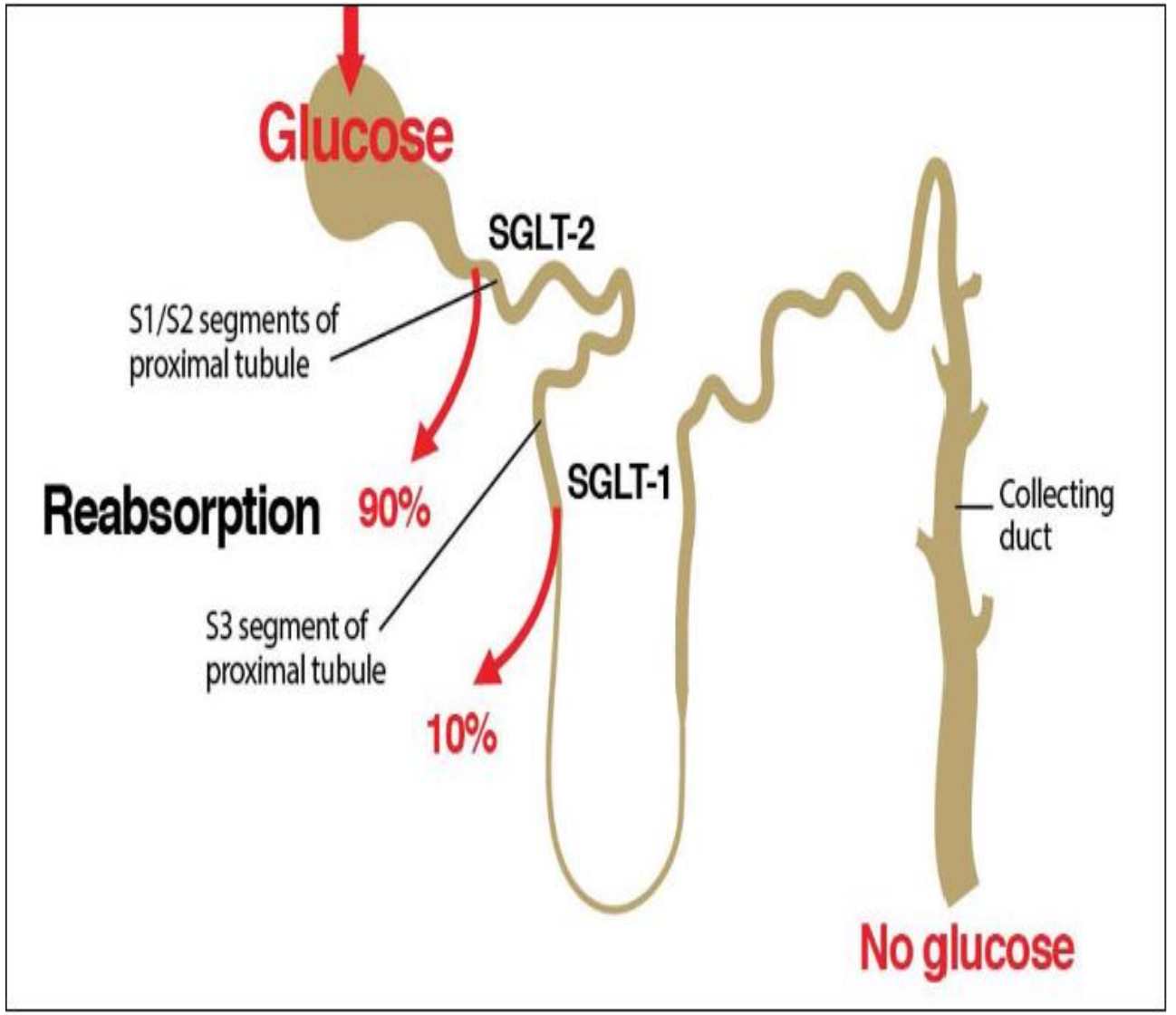
Glomerular filtration and glucose reabsorption

SGLT 2

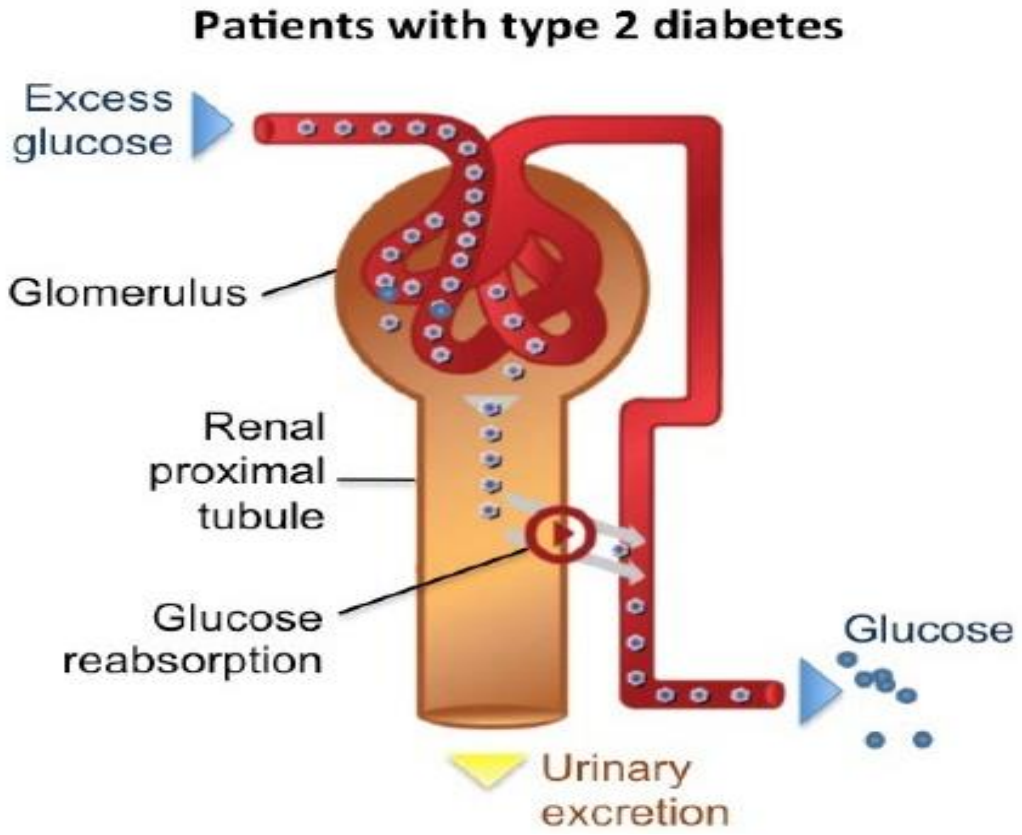
- Primarlly **expressed in kidney**
- Responsible for **majority of renal glucose reabsorption**

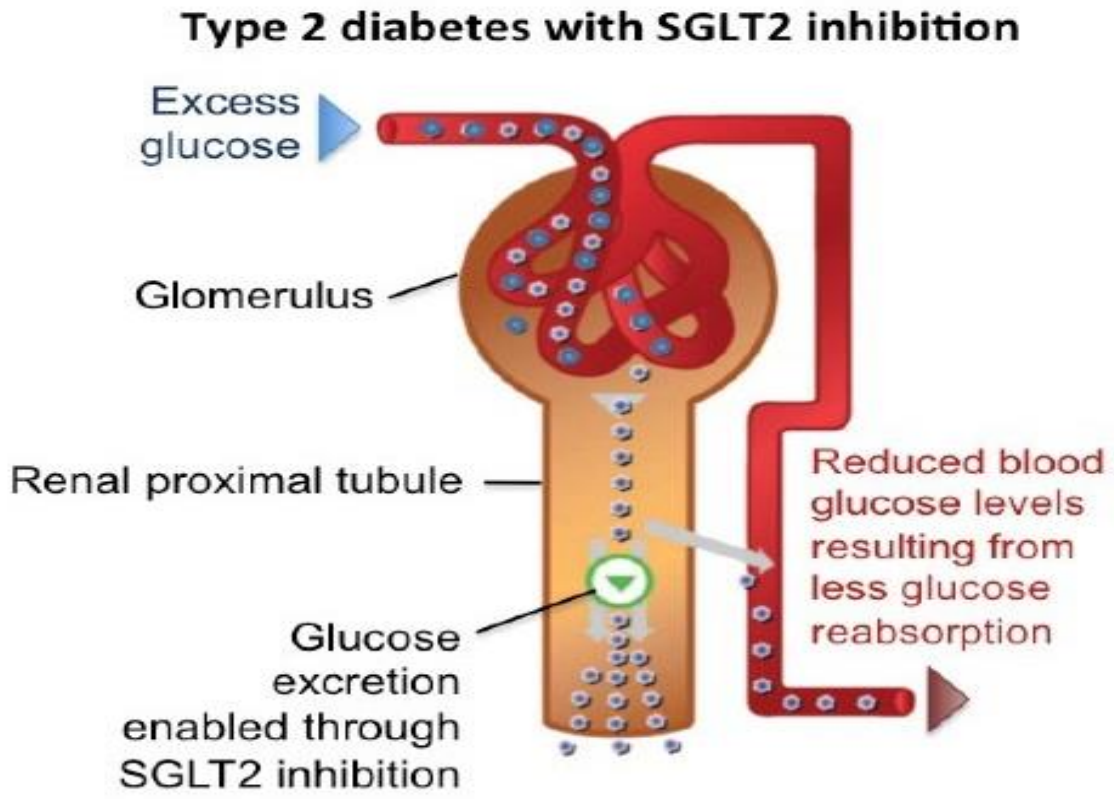
SGLT 1

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



SODIUM-GLUCOSE TRANSPORT PROTEIN 2 (SGLT2) INHIBITORS





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

SGLT2 Inhibitors

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
SGLT2 Inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR

Oral/SQ	Cost	Clinical considerations
Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycaemic DKA); discontinue before scheduled surgery (e.g. 3-4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotising fasciitis of the perineum (Fournier's gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable

SGLT2 inhibitor recommendations

- In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a UACR >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcomes benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated.
- In people with HF, SGLT2i should be used because they improve HF and kidney outcomes.

ADA/EASD 2019

SGLT2 Inhibitors

Advantages	Disadvantages
Weight loss	Urinary Tract Infections?
No hypoglycemia	Genital Mycotic Infections
Decrease heart failure	Increased LDL (small increase)
Decreases renal dysfunction	Increased risk of DKA
Once a day administration	Postural hypotension/volume depletion
Decrease BP	Fractures/ Osteoporosis?
	Increased risk amputations (canagliflozin)?
	Fournier's gangrene (rare)
	Expensive

Insulin

Advantages	• it lowers glucose in a dose-dependent manner and thus can address almost any level of blood glucose. • being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present.
Disadvantages (Challenges)	• weight gain, the need for education and titration for optimal efficacy, risk of hypoglycaemia, the need for regular glucose monitoring.
Indications	initiate insulin therapy for people who present with: • blood glucose levels >300 mg/dL (16.7mmol/L) or HbA1C > 10% (86mmol/mol) or • individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss). • ketosis

Insulin

		Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects	
					Effect on MACE	HF	Progression of DKD	Dosing/use considerations*
Insulin	**Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response
	Analogues							

Oral/SQ	Cost	Clinical considerations
SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycaemia with human insulin (NPH or premixed formulations) vs analogues
SQ	High	

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

PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

		MET	GLP-1 RA	DUAL GIP/ GLP-1 RA	SGLT2i	TZD	INSULIN (basal & basal bolus)	DPP-4i	SU	GLN	AGi	COLSVL	BRC	PRAML
EFFICACY FOR GLUCOSE LOWERING		++	+++	+++	++	++	+++/++++	+	++	+	+	+	+	+
ASCVD	MACE	Neutral	Benefit[1,3]	Safe	Benefit[2]	Neutral[3]	Neutral	Neutral	Possible Increased Risk	Neutral	Insufficient Evidence	Neutral[3]	Safe	Insufficient Evidence
	CHF		Unclear		Reduced Risk	Moderate to Severe[4]	Moderate	Moderate[4]						
	STROKE		Benefit[5]		Possible Benefit[2]	Benefit	Neutral	Neutral						
CKD		CKD3a/3b[6]	Benefit[7]	Insufficient Evidence	Benefit	Neutral	Increased hypoglycemia risk with impaired renal function	Neutral	Increased hypoglycemia risk with impaired renal function		Not recommended SCR >2 mg/dL or CrCl <25	Neutral	Neutral	Neutral
RENAL ADJUSTMENT		Not with CKD4 eGFR <30[6]	Exenatide not recommended eGFR <45		Check medication-specific eGFR thresholds[8]			Adjust Dose[9]						
HYPOGLYCEMIA RISK[14]		Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to Severe	Neutral	Moderate to Severe	Mild	Neutral	Neutral	Neutral	Neutral
WEIGHT		Slight loss	Loss	Loss	Loss	Gain[4]	Gain	Neutral	Gain	Neutral	Neutral	Neutral	Neutral	Loss
NAFLD		Neutral	Benefit	Benefit	Potential Benefit	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit
GI ADVERSE SYMPTOMS		Mild to Moderate	Moderate[10]	Moderate[10]	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Mild	Moderate	Moderate
OTHER CONSIDERATIONS			Medullary Thyroid Carcinoma/ MEN2	Medullary Thyroid Carcinoma/ MEN2	GU infections DKA[11] Fracture Risk[12]	Fracture Risk		Rare Arthralgias/ Myalgias						
ACCESS/COST		$	$$$	$$$	$$$	$	$ - $$$[13]	$-$$	$	$-$$	$-$$	$$$	$$$	$$$

key components of the comprehensive diabetes medical evaluation at initial and follow-up visits

Assessing risk of diabetes complications:

- ASCVD and heart failure history
- ASCVD risk factors and 10-year ASCVD risk assessment
- Staging of chronic kidney disease
- Hypoglycemia risk
- Assessment for retinopathy
- Assessment for neuropathy

Goal setting

- Set A1C/blood glucose/time-in-range target
- Diabetes self-management goals
- If hypertension/dyslipidemia/obesity is present, establish blood pressure/ lipid / body weight target

Therapeutic treatment plans

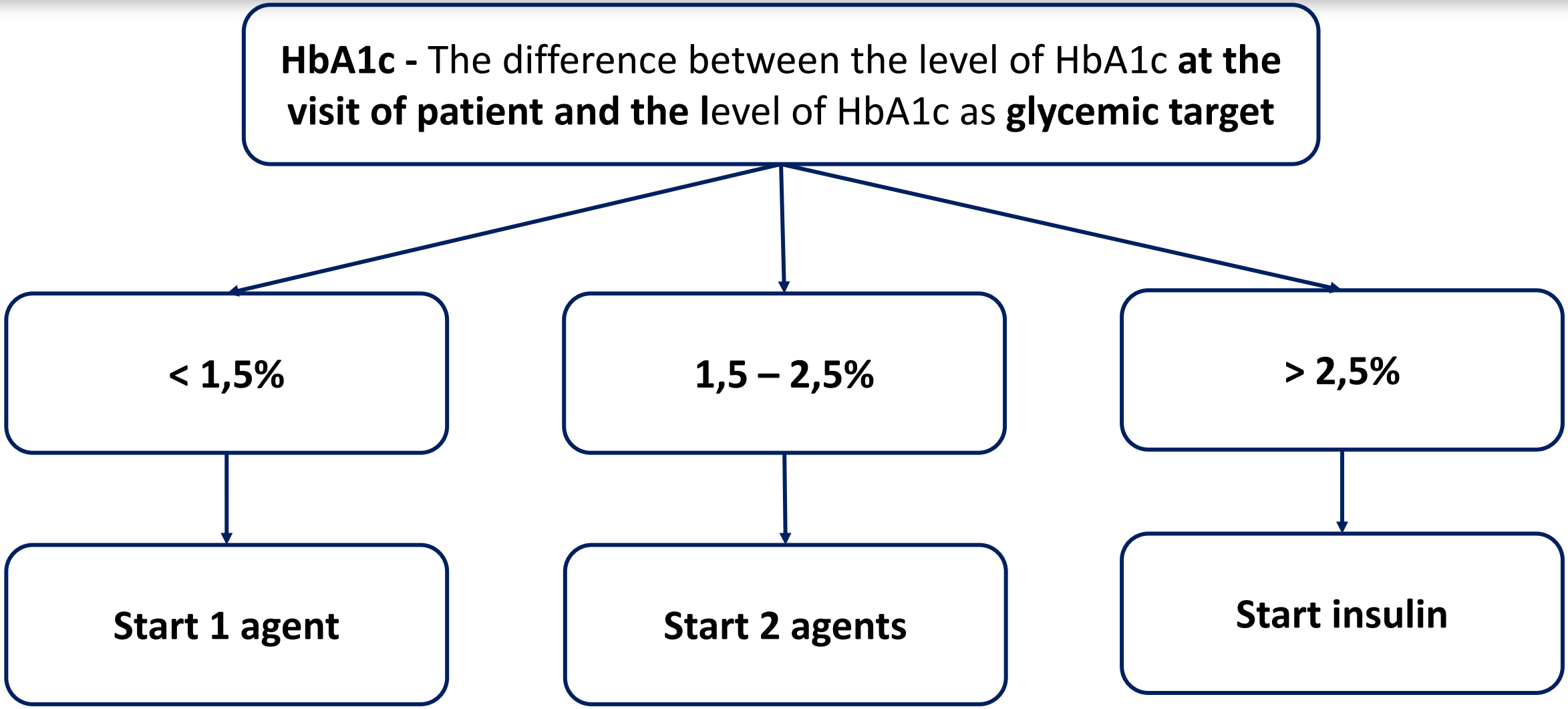
- Lifestyle management
- Pharmacologic therapy: glucose lowering
- Pharmacologic therapy: cardiovascular and renal disease risk factors
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

Treatment initiation

1. HbA1c
• Level of HbA1c - **at the visit of patient** • Level of HbA1c - **glycemic target** • **The difference** between the level of HbA1c **at the visit of patient and the l**evel of HbA1c as **glycemic target**

2. Diabetes complications/A concomitant illness (comorbidites)		
• ASCVD • CKD • HF	• Hypoglycemia risk • BMI	

Treatment initiation – HbA1c



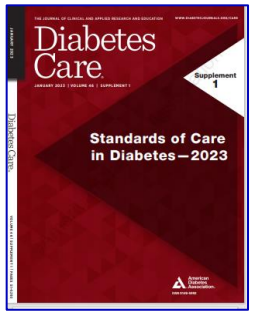
Strategia inițierii terapiei în diabet zaharat de tip 2 – HbA1c

A1C >7.5% start 2 agents, A1C >9.0% or >1.5% above goal start 2-3 agents

If A1C >10% and/or glucose >300 mg/dL with symptomatic hyperglycemia, use basal insulin +/- GLP-1 RA

Consider initial combination therapy with glucose-lowering agents, especially in those with high HbA_{1c} at diagnosis (i.e. >70 mmol/mol [>8.5%]), in younger people with type 2 diabetes (regardless of HbA_{1c}) and in those in whom a stepwise approach would delay access to agents that provide cardiorenal protection beyond their glucose-lowering effects.

In specific circumstances, insulin may be the preferred agent for glucose lowering, specifically in the setting of severe hyperglycaemia (HbA_{1c} >86 mmol/mol [>10%]), particularly when associated with weight loss or ketonuria/ketosis and with acute glycaemic dysregulation (e.g. during hospitalisation, surgery or acute illness), in underweight people or when the diagnosis of type 1 diabetes is suspected.



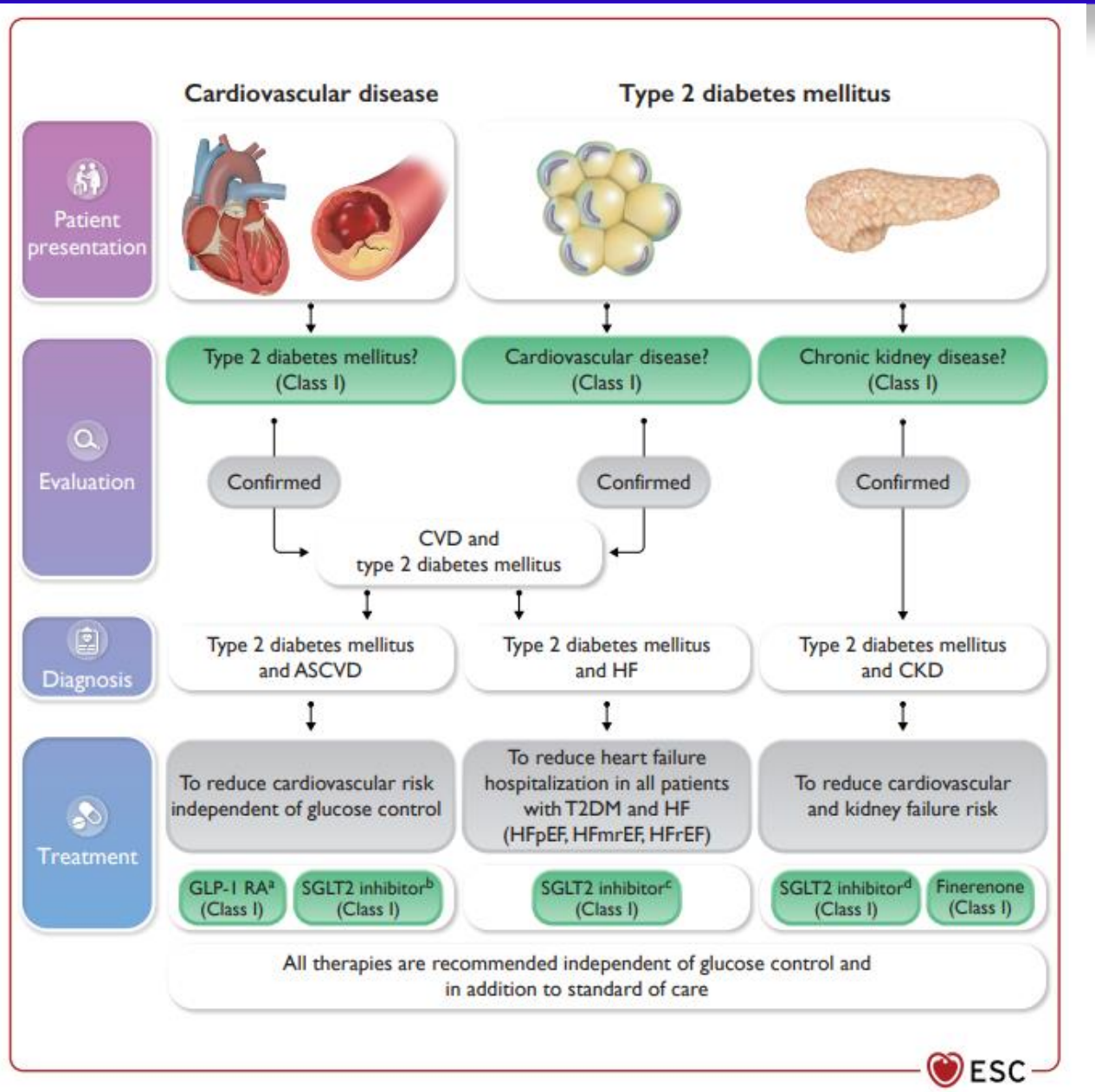
making process, as appropriate. Initial combination therapy should be considered in people presenting with A1C levels 1.5–2.0% above target. Finally, incorpora-

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

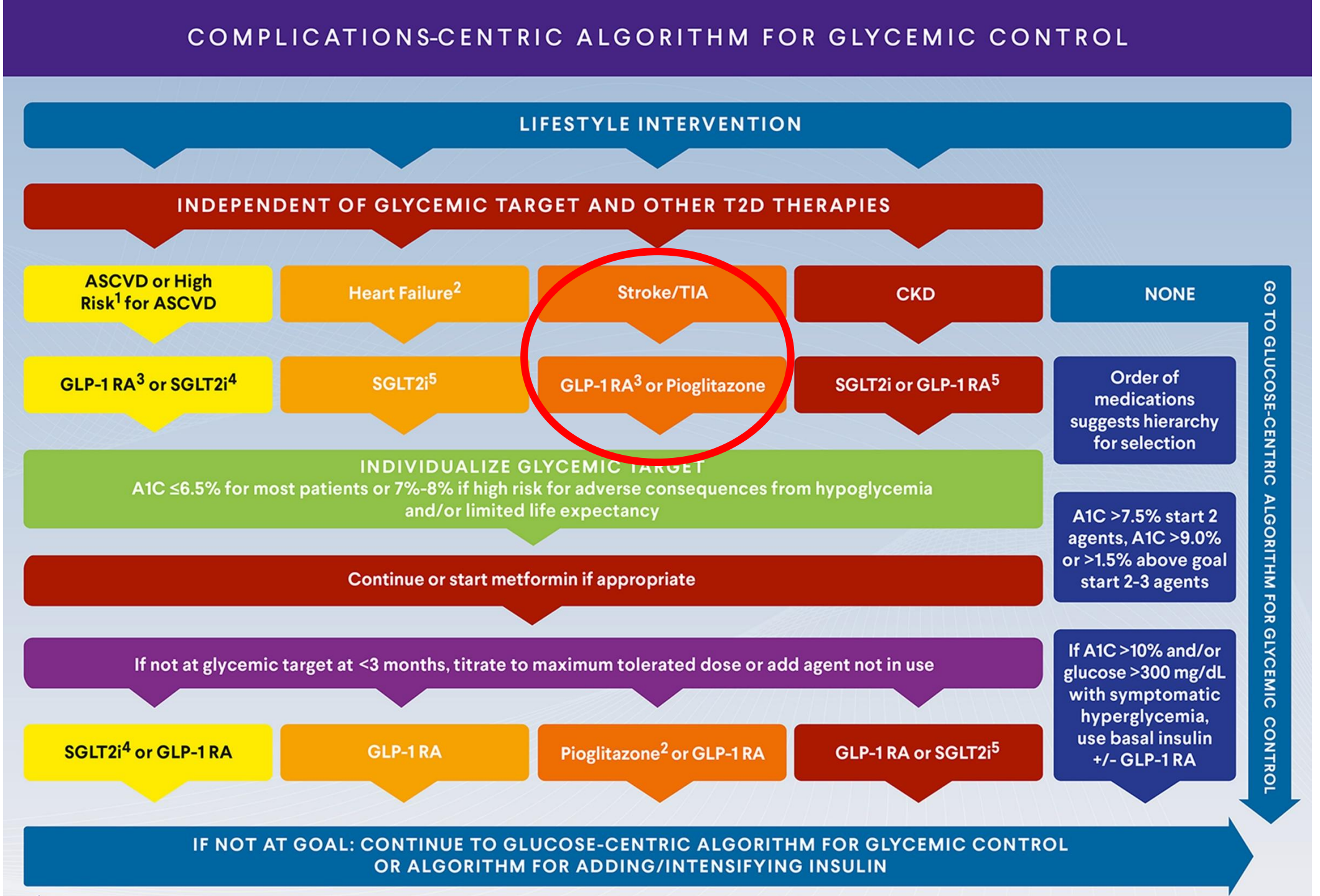
Treatment initiation

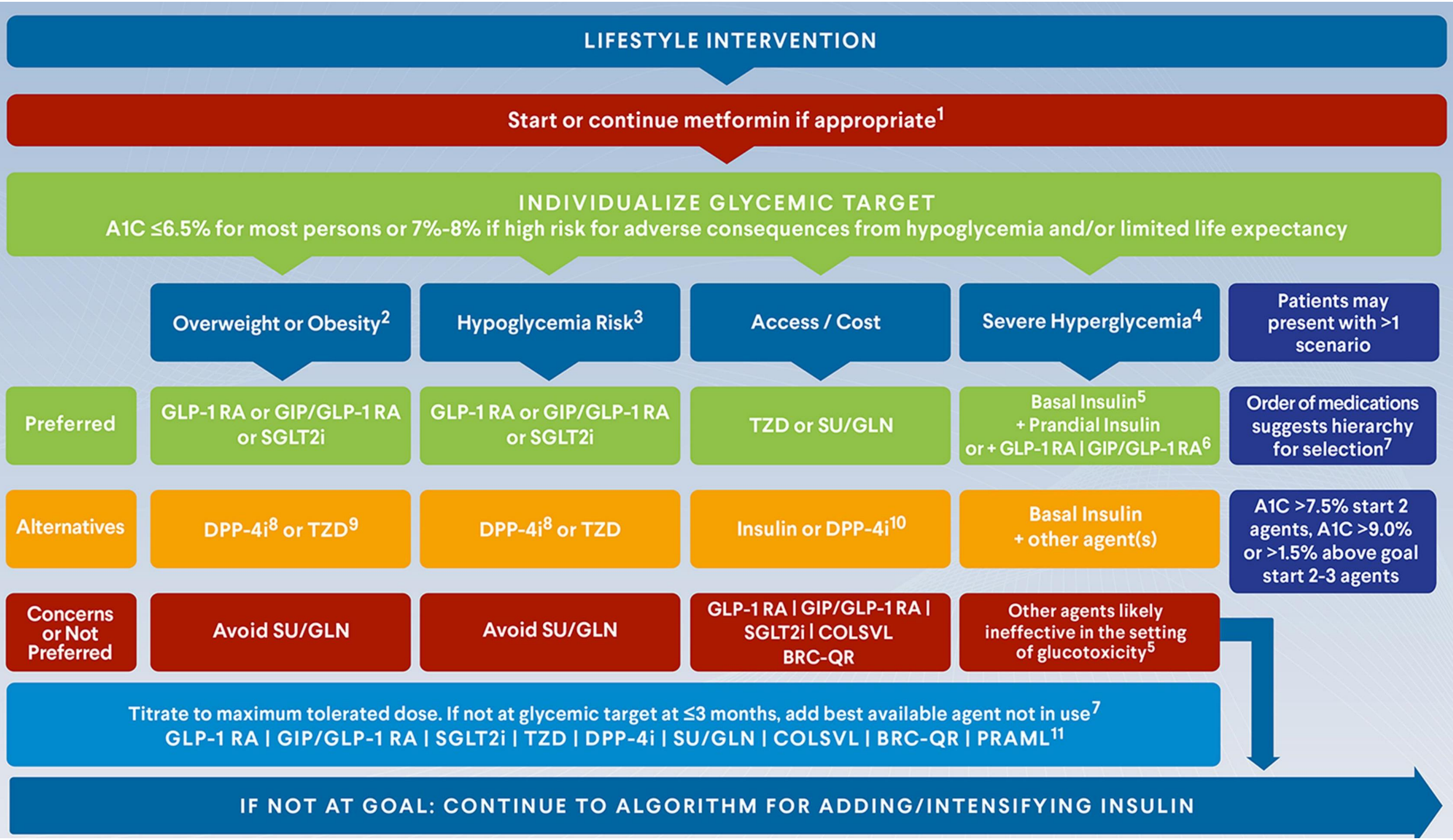
2. Diabetes complications/A concomitant illness (comorbidites)		
• ASCVD • CKD • HF	• Hypoglycemia risk • BMI	

Treatment initiation – ASCVD/HF/CKD



COMPLICATIONS-CENTRIC ALGORITHM FOR GLYCEMIC CONTROL




LIFESTYLE INTERVENTION
Start or continue metformin if appropriate[1]
INDIVIDUALIZE GLYCEMIC TARGET
A1C ≤6.5% for most persons or 7%-8% if high risk for adverse consequences from hypoglycemia and/or limited life expectancy
Overweight or Obesity[2]
Hypoglycemia Risk[3]
Access / Cost
Severe Hyperglycemia[4]
Patients may present with >1 scenario
Preferred
GLP-1 RA or GIP/GLP-1 RA or SGLT2i
GLP-1 RA or GIP/GLP-1 RA or SGLT2i
TZD or SU/GLN
Basal Insulin[5] + Prandial Insulin or + GLP-1 RA | GIP/GLP-1 RA[6]
Order of medications suggests hierarchy for selection[7]
Alternatives
DPP-4i[8] or TZD[9]
DPP-4i[8] or TZD
Insulin or DPP-4i[10]
Basal Insulin + other agent(s)
A1C >7.5% start 2 agents, A1C >9.0% or >1.5% above goal start 2-3 agents
Concerns or Not Preferred
Avoid SU/GLN
Avoid SU/GLN
GLP-1 RA | GIP/GLP-1 RA | SGLT2i | COLSVL BRC-QR
Other agents likely ineffective in the setting of glucotoxicity[5]
Titrate to maximum tolerated dose. If not at glycemic target at ≤3 months, add best available agent not in use[7]
GLP-1 RA | GIP/GLP-1 RA | SGLT2i | TZD | DPP-4i | SU/GLN | COLSVL | BRC-QR | PRAML[11]
IF NOT AT GOAL: CONTINUE TO ALGORITHM FOR ADDING/INTENSIFYING INSULIN

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

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

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/ OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m^2 OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

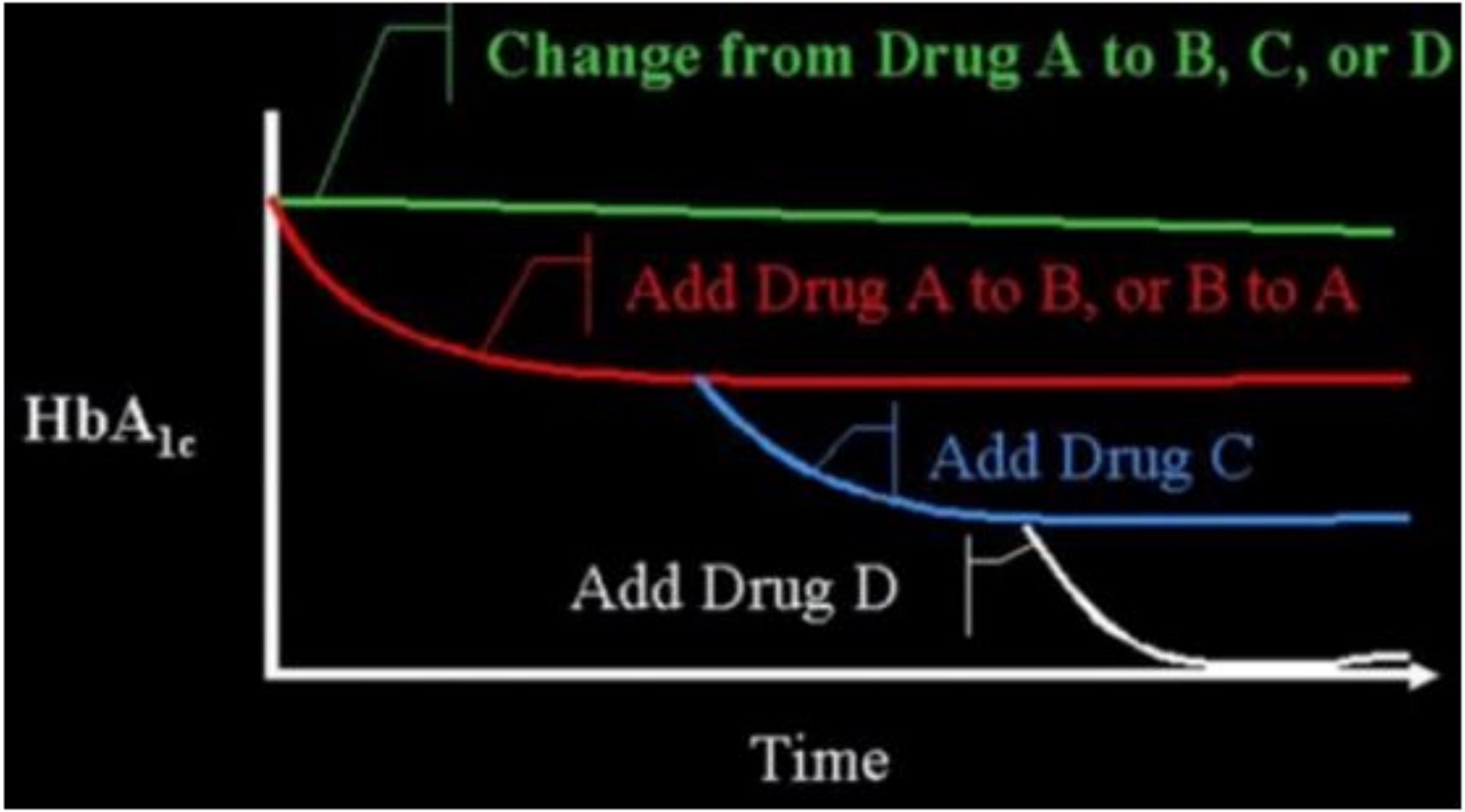
Neutral:
DPP-4i, Metformin

If A1C above target

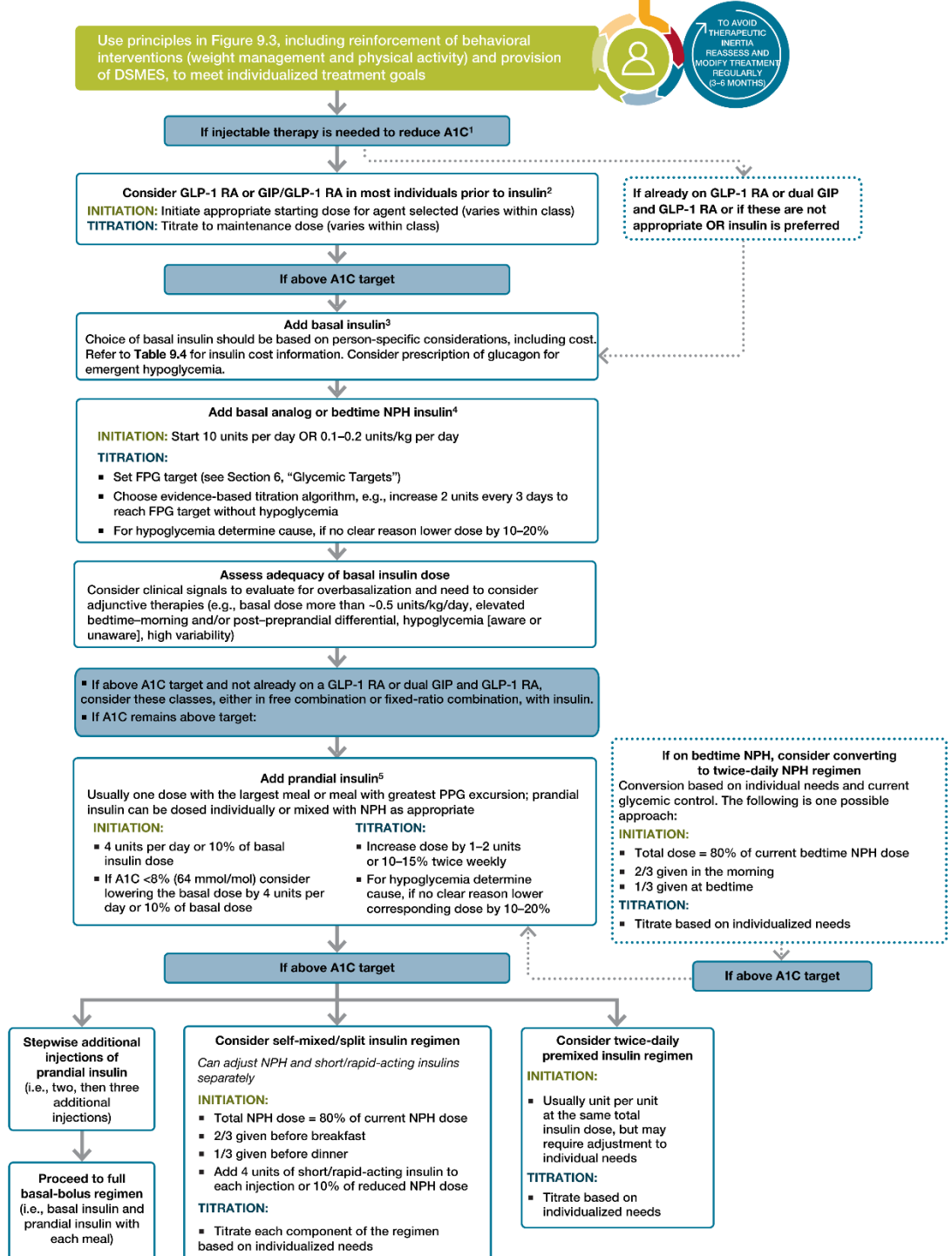
Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.


Change from Drug A to B, C, or D
Add Drug A to B, or B to A
Add Drug C
Add Drug D
HbA1c
Time

Insulin


Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.
Add basal analog or bedtime NPH insulin[4]
INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day
TITRATION:
Set FPG target (see Section 6, "Glycemic Targets")
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime–morning and/or post–preprandial differential, hypoglycemia [aware or unaware], high variability)
If above A1C target and not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes, either in free combination or fixed-ratio combination, with insulin.
If A1C remains above target:
Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
4 units per day or 10% of basal insulin dose
If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
Increase dose by 1–2 units or 10–15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
Total dose = 80% of current bedtime NPH dose
2/3 given in the morning
1/3 given at bedtime
TITRATION:
Titrate based on individualized needs
If above A1C target
If above A1C target
Stepwise additional injections of prandial insulin (i.e., two, then three additional injections)
Proceed to full basal-bolus regimen (i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
Total NPH dose = 80% of current NPH dose
2/3 given before breakfast
1/3 given before dinner
Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
Titrate each component of the regimen based on individualized needs
Consider twice-daily premixed insulin regimen
INITIATION:
Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
Titrate based on individualized needs

Insulin

PLACE OF INSULIN[1]

Consider immediate start of insulin

- Severe hyperglycemia
- Acute glycemic dysregulation
- When T1D is suspected

If not already on GLP-1 RA, consider use of GLP-1 RA

When not familiar with insulin use or when targets not reached, consider shared care with specialist team

Consider adding insulin when personalized HbA_{1c} targets are not met with strategies described in Fig. 4

- Maintain cardiorenal protective agents
- Maintain metformin, SGLT2i, and GLP-1 RA to avoid weight gain and limit insulin dose and hypoglycemia risk
- Consider using combination products of basal insulin/GLP-1 RA

Start using basal insulin*
(10 units or 0.1–0.2 units/kg per day) at bedtime or more flexibility with timing for longer-acting analogs

Titrate to FPG target but avoid overbasalization of insulin
(consider introduction of CGM)

When FPG is on target but HbA_{1c} or TIR is not

If not already on GLP-1 RA, consider use of GLP-1 RA

Intensify along the way and preferentially at each step

- Healthy behavior
- Nutritional therapy
- DSMES: with additional focus on injection technique, hypoglycemia, weight

ADD MEALTIME INSULIN UNDER FORM OF:

- Basal plus (progressive addition of boluses)
- Premixed insulins
- MDI (multiple daily injections)