Agenda

- Treatment goals.
- Guidelines: ADA 2022
- Different anti-diabetic drugs (Advantages-Disadvantages)
- Drug selection (First- Second and Third choices)
- Conclusion.

Treatment goals

Summary of glycemic recommendations for non-pregnant adults with diabetes.

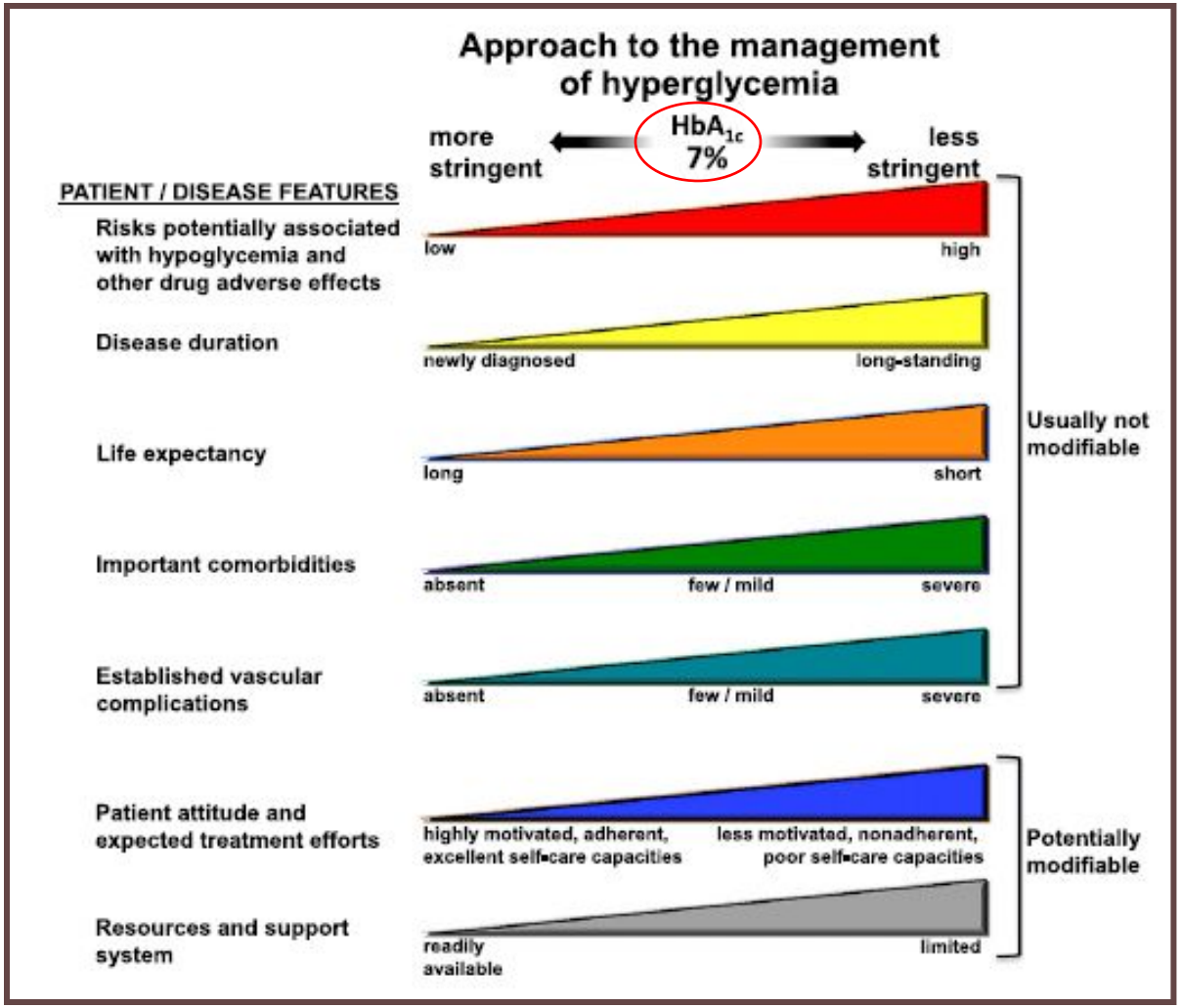
A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

American Diabetes Association

Diabetes Care Volume 40, Supplement 1, January 2022

Approach to the management of hyperglycemia



American Diabetes Association

Diabetes Care Volume 40, Supplement 1, January 2017

Inzucchi *et al. Diabetes Care* 2012;35:1364–79

More Stringent HbA1c Targets <6.5%

- Short disease duration.
- Long life expectancy.
- No significant CVD .
- Type 2 diabetes treated with lifestyle or metformin only.

If this can be achieved without significant hypoglycemia or other adverse effects of treatment.

American Diabetes Association

Diabetes Care Volume 40, Supplement 1, January 2017

Less Stringent HbA1c Targets < 8.0

- History of severe hypoglycemia.
- Limited life expectancy.
- Advanced complications.
- Extensive comorbid conditions.
- In whom the target is difficult to attain despite intensive self-management education, repeated counseling, and effective doses of multiple glucose-lowering agents, including insulin.

American Diabetes Association

Start with insulin terapy

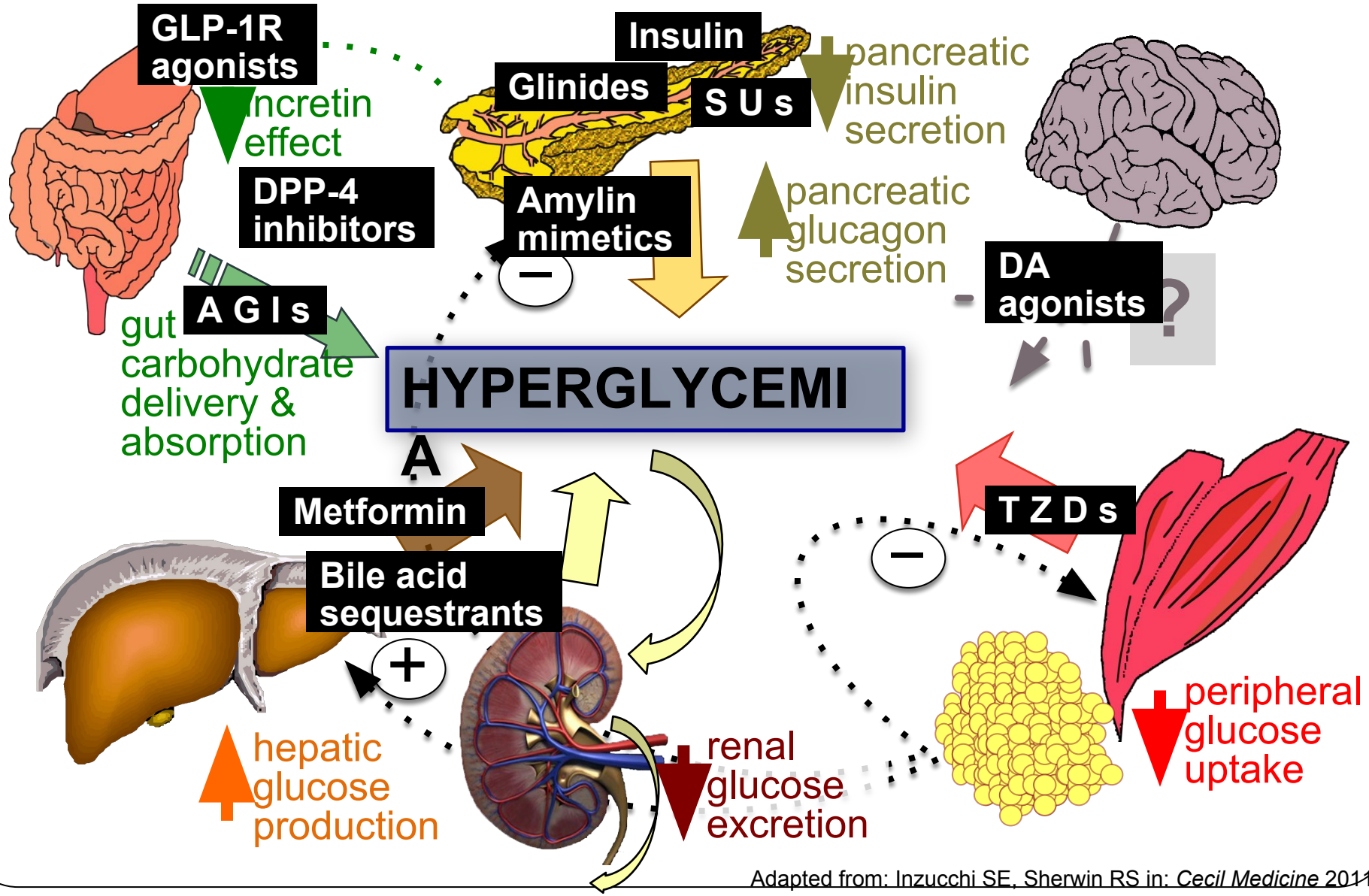
- The early introduction of insulin should be considered if there is :
- evidence of ongoing catabolism (weight loss),
- if symptoms of hyperglycemia are present
- when A1C levels (>10% [86 mol/mol]) or blood glucose levels ($300 mg/dL [16.7 mmol/L])are very high. E

Table 9.2—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Renal effects		Additional consideration
					ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin		High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects co (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT2 inhibitors		Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin‡, canagliflozin, dapagliflozin‡, ertugliflozin	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin§	▪ See labels for renal dose considerations of individual agents ▪ Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	▪ Should be discontinued before scheduled surgery to avoid po risk for DKA ▪ DKA risk (all agents, rare in T2 ▪ Risk of bone fractures (canagli ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs		High	No	Loss	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	▪ See labels for renal dose considerations of individual agents ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroi tumors in rodents; human relev not determined **(liraglutide, dulaglutide, exenatide extended release, semaglut** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported trials but causality has not bee established. Discontinue if pan is suspected.
DPP-4 inhibitors		Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported trials but causality has not bee established. Discontinue if pan is suspected. ▪ Joint pain
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive h failure **(pioglitazone, rosiglita** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: generally not recommended in chronic kidney disease ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on incre risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	**Human insulin**	High	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia wi human insulin (NPH or premix formulations) vs. analogs
	Analogs						High	SQ			

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glo filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type tes. *For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for cardiovascular disease benefit. ‡FDA-approved for heart failure indication. §FDA-a for chronic kidney disease indication.

Multiple, Complex Pathophysiological Abnormalities in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Oral Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase (?other) • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications	Low
Sulfonylurea	• Closes K_{ATP} channels • ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk	• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning	Low
Meglitinides	• Closes K_{ATP} channels • ↑ Insulin secretion	• ↓ Postprandial glucose • Dosing flexibility	• Hypoglycemia • ↑ Weight • ? Blunts ischemic preconditioning • Dosing frequency	Mod.
TZDs	• PPAR-g activator • ↑ Insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ? ↓ CVD events (pio)	• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)	Low

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442

Oral Class	Mechanism	Advantages	Disadvantages	Cost
a-Glucosidase inhibitors	• **Inhibits a-glucosidase** • **Slows carbohydrate digestion / absorption**	• **No hypoglycemia** • **Nonsystemic** • **↓ Postprandial glucose** • **? ↓ CVD events**	• **Gastrointestinal** • **Dosing frequency** • **Modest ↓ A1c**	**Mod.**
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated • Weight neutral	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
Bile acid sequestrants	• Bind bile acids • ? ↓ Hepatic glucose production	• No hypoglycemia • ↓ LDL-C	• Gastrointestinal • Modest ↓ A1c • Dosing frequency	High
Dopamine-2 agonists	• Activates DA receptor • Alters hypothalamic control of metabolism • ↑ insulin sensitivity	• No hypoglyemia • **?** ↓ CVD events	• Modest ↓ A1c • Dizziness, fatigue • Nausea • Rhinitis	High
SGLT2 inhibitors	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	•↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C • ↑Cr (transient)	High

Table 1. Properties of anti-hyperglycemic agents

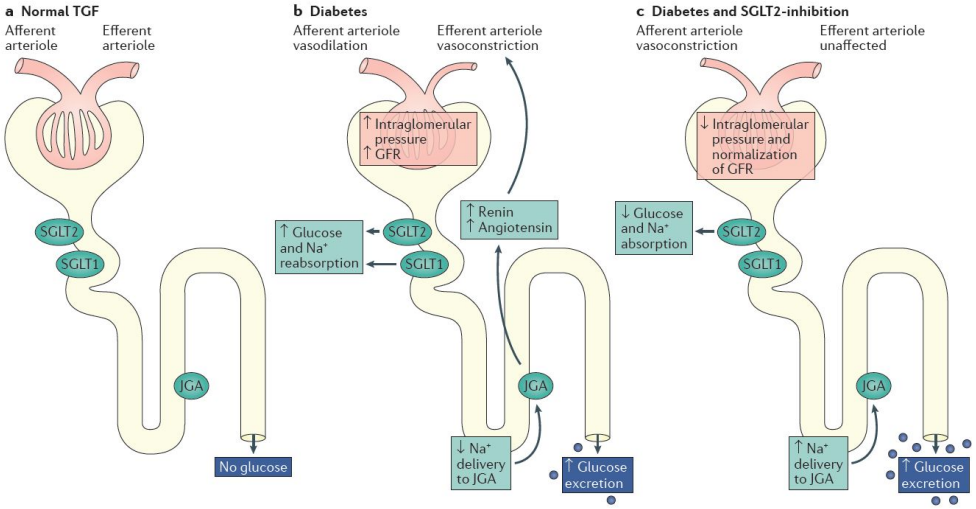
Diabetes Care 2015;38:140-149
Diabetologia 2022;58:429-442

Injectable Class	Mechanism	Advantages	Disadvantages	Cost
Amylin mimetics	• Activates amylin receptor • ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • ↓ Postprandial glucose	• Gastrointestinal • Modest ↓ A1c • Injectable • Hypo if insulin dose not reduced • Dosing frequency • Training requirements	High
GLP-1 receptor agonists	• Activates GLP-1 R • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • No hypoglycemia • ↓ Postprandial glucose • ↓ Some CV risk factors	• Gastrointestinal • ? Pancreatitis • ↑ Heart rate • Medullary ca (rodents) • Injectable • Training requirements	High
Insulin	• Activates insulin receptor • Myriad	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Patient reluctance • Training requirements	Variable

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

SGLT2 Inhibitors



- Endocrine Rev. 32, 515–531 (2011); permission conveyed through Copyright Clearance Center, Inc.

Mechanism of action of SGLT2is

- Decrease intraglomerular pressure
- Decrease arterial stiffness
- Decrease vascular resistance
- Lower rate of hyperglycemia
- Decreased body weight
- Decrease in SBP and DBP

Side effects

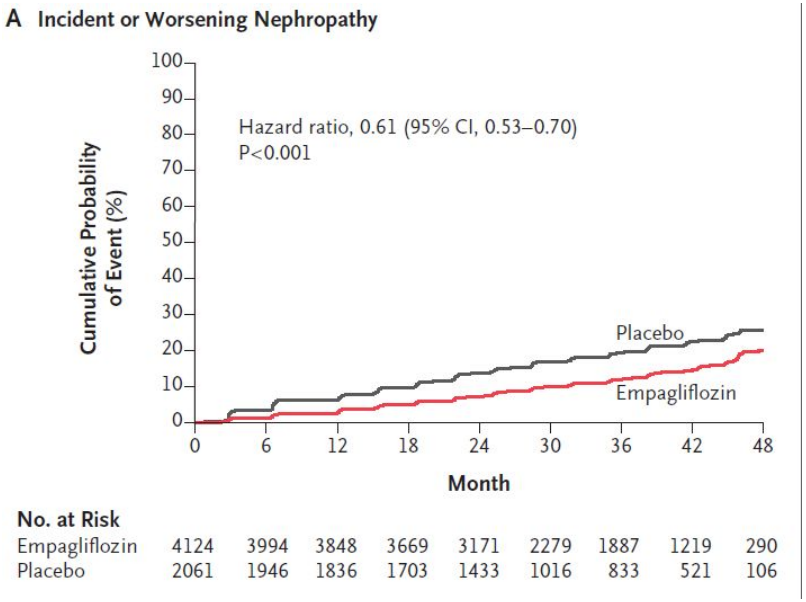
1. FDA black list risk of amputation (canagliflosen)
2. Risk of bone fracture (canagliflosen)
3. Risk of DKA
4. Genitourinary infection
5. Volume depletion & hypotension
6. Increase LDL cholestrole

Table 1. Kidney Outcomes in Clinical Trials of SGLT2 Inhibitors

Study	Intervention	Study Population	Outcomes
EMPA-REG OUTCOME (NCT01131676)[56,84]	Empagliflozin	T2DM, eGFR ≥ 30; high CV risk	• 44% RR reduction of Scr doubling (1.5% vs 2.6%) • 38% RR of progression to UACR > 300 (11.2% vs 16.2%) • 55% RR reduction of initiation of KRT (0.3% vs 0.6%) • Slowing of decline in GFR (annual decrease of 0.19 ± 0.11 vs 1.67 ± 0.13; $P < 0.001$)
CREDENCE (NCT02065791)[86]	Canagliflozin	T2DM; HbA_{1c} [6.5%, 12%]; high CV risk; UACR [300, 5,000]; eGFR [30, 90]	• Trial in progress; estimated completion in June 2019 • Primary outcome: time to the 1st occurrence of an event in the primary composite end point (ESRD, Scr doubling, kidney or CV death)
CANVAS, CANVAS R (NCT01032629, NCT01989754)[85]	Canagliflozin	T2DM; HbA_{1c} [7%, 10.5%], high CV risk; median UACR 12.3; mean eGFR 76.5	• ↓ progression of albuminuria (HR, 0.73; 95% CI, 0.67-0.79) • ↓ composite outcome of 40% reduction in eGFR, KRT, or kidney death (HR, 0.60; 95% CI, 0.47-0.77)
Dapa-CKD (NCT03036150)[87]	Dapagliflozin	T2DM; eGFR [25, 75]; UACR [200, 5,000]	• Trial in progress; estimated completion in November 2020 • Primary outcome: time to 1st occurrence of any of the components of the primary composite end point (ESRD, ≥50% sustained decline in eGFR, kidney or CV death)
DECLARE-TIMI-58 (NCT01730534)[93]	Dapagliflozin	T2DM; high CV risk	• Trial in progress; estimated completion in April 2019 • Secondary outcome measures: time to 1st event of kidney composite end point (confirmed sustained ≥ 40% decrease in eGFR to eGFR < 60 and/or ESRD and/or kidney or CV death [time frame: up to 6 y])

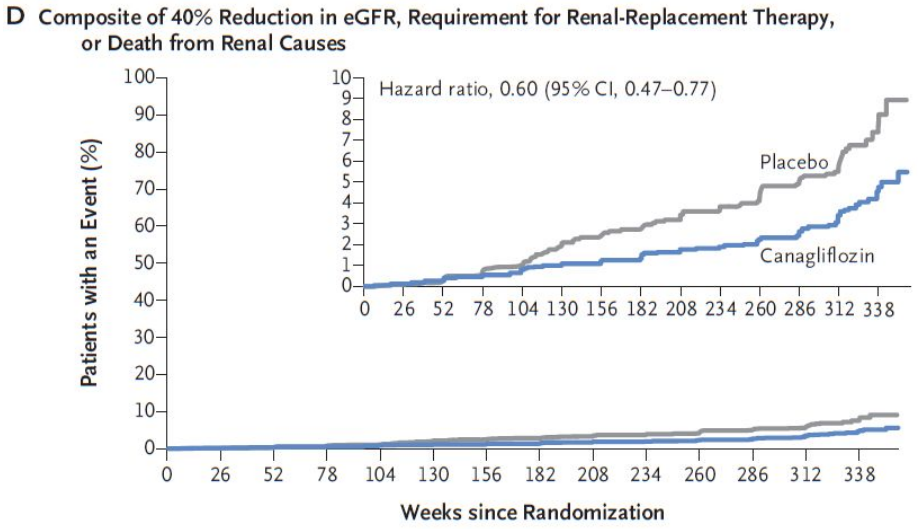
- CANVAS R:The primary end point was
- Development of microalbuminuria or macroalbuminuria in participants with baseline normoalbuminuria
- Development of macroalbuminuria in participants with baseline microalbuminuria, accompanied by an increase in the urinary Alb /Cr ratio of ≥30% from baseline

Renal outcome of nephropathy of Empagliflozin



N Engl J Med. 2016 Jul 28;375(4):323-34

CANVAS Trial

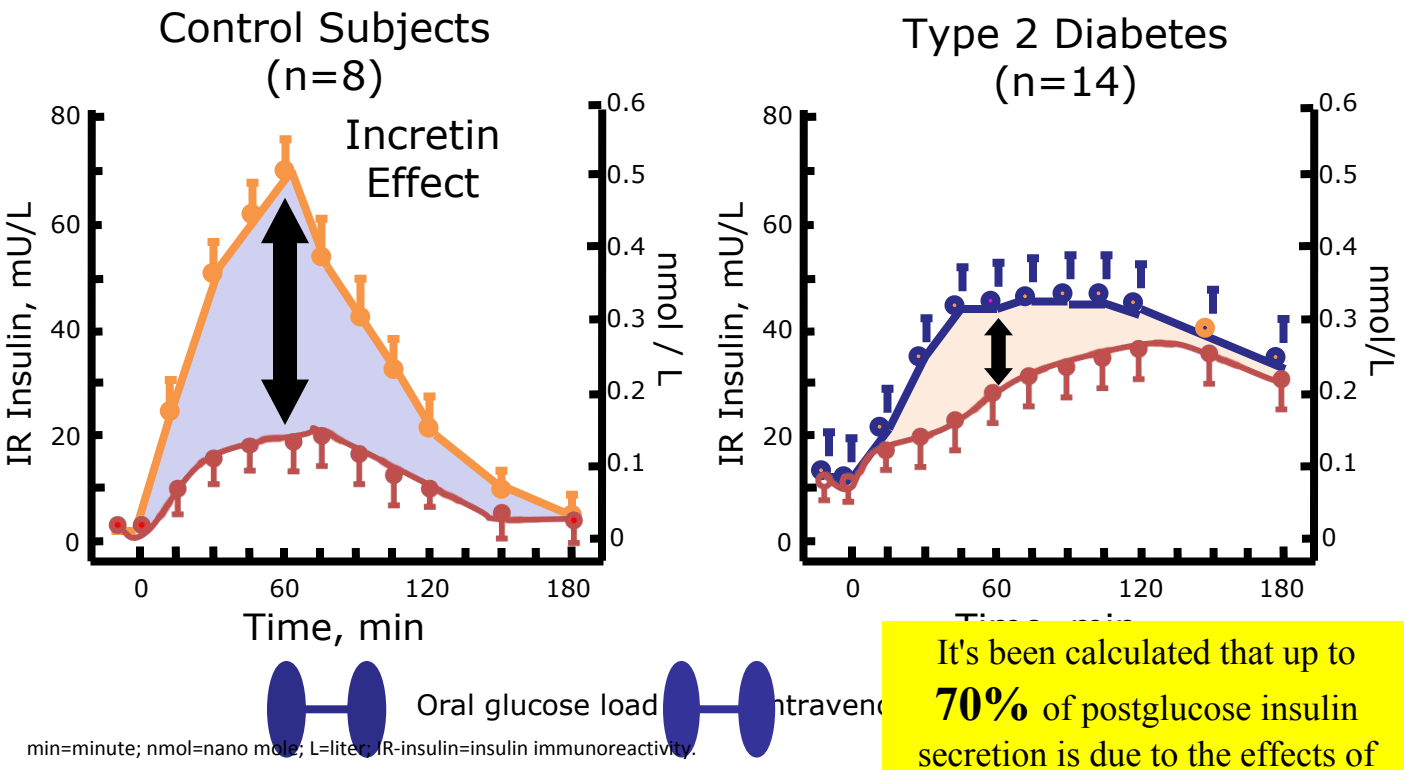


N Engl J Med. 2017 Aug 17;377(7):644-657

Kidney Function Dose Adjustments for Approved SGLT2 Inhibitors

SGLT2 Inhibitor	Dose	Kidney Dose Adjustment
Dapagliflozin	5-10 mg	Avoid initiating if eGFR < 60 Not recommended with eGFR 30-60 Contraindicated with eGFR < 30
Empagliflozin	10-25 mg	No dose adjustment if eGFR ≥ 45 Avoid use, discontinue with eGFR persistently <45
Canagliflozin	100-300 mg	No dose adjustment if eGFR > 60 100 mg daily if eGFR 45-59 Avoid use, discontinue with eGFR persistently <45
Ertugliflozin	5-15 mg	Avoid initiating if eGFR 30-60 Continued use is not recommended with persistent eGFR 30-60 Contraindicated with eGFR < 30

The Incretin Effect



min=minute; nmol=nano mole; L=liter; IR-insulin=insulin immunoreactivity.

1. Nauck M et al. *Diabetologia*. 1986;29:46–52. Copyright © 1986 Spr

It's been calculated that up to **70%** of postglucose insulin secretion is due to the effects of these incretin hormones

ROLE OF INCRETIN IN GLUCOSE HOMEOSTASIS

IN-CRET-IN

INtestine seCRETion INsulin

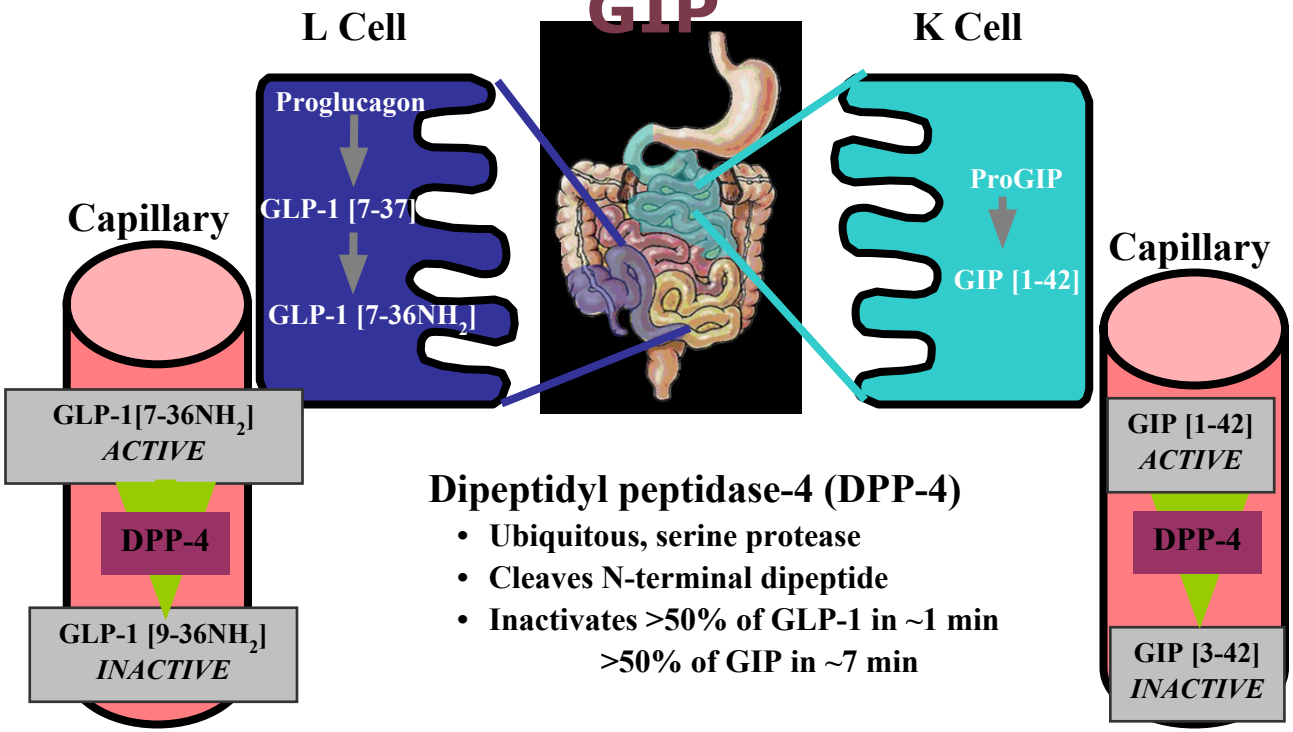
Definition: Hormones produced by the gastrointestinal tract in response to incoming nutrients, and increase glucose stimulated insulin secretion

Two hormones: (1) glucagon-like peptide-1 (GLP-1)

(2) glucose-dependent insulinotropic polypeptide (GIP)

Diabetologia 1985; 28: 5645.

Synthesis, Secretion, and Metabolism of the Incretin Hormones GLP-1 and GIP



Dipeptidyl peptidase-4 (DPP-4)

- Ubiquitous, serine protease
- Cleaves N-terminal dipeptide
- Inactivates >50% of GLP-1 in ~1 min
  >50% of GIP in ~7 min

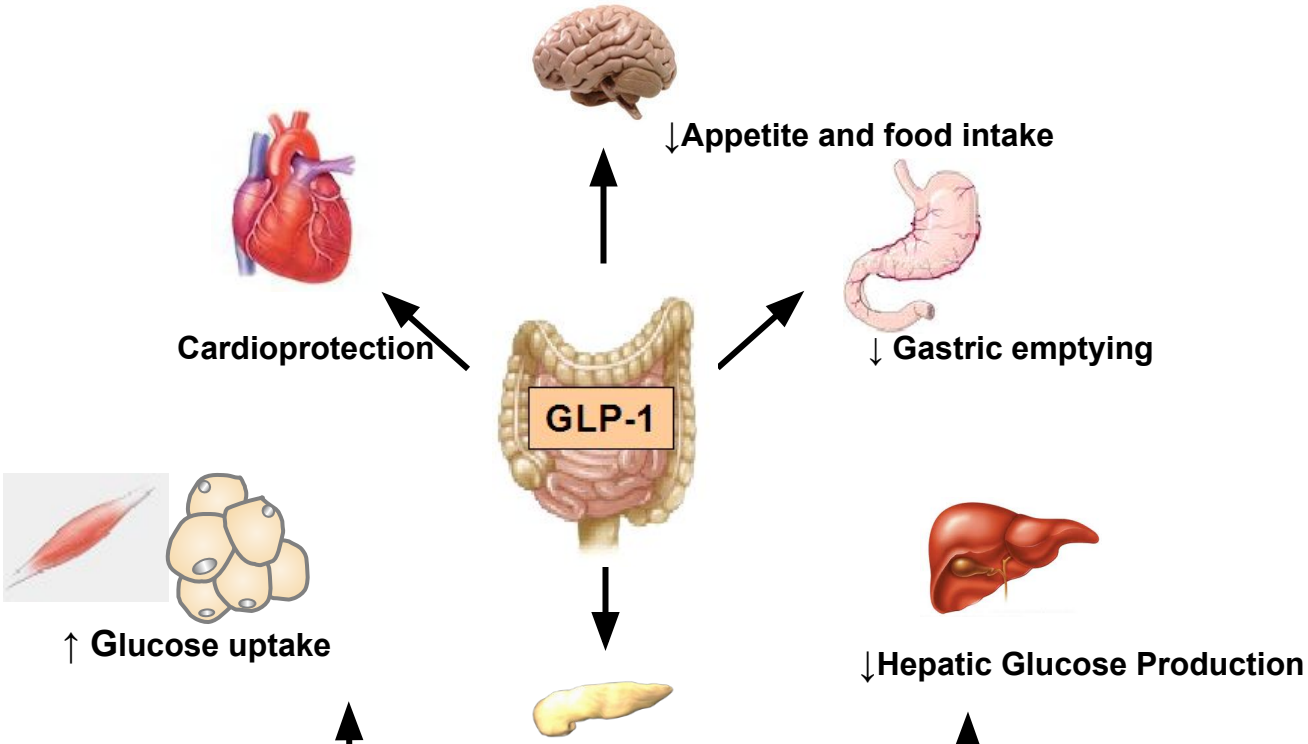
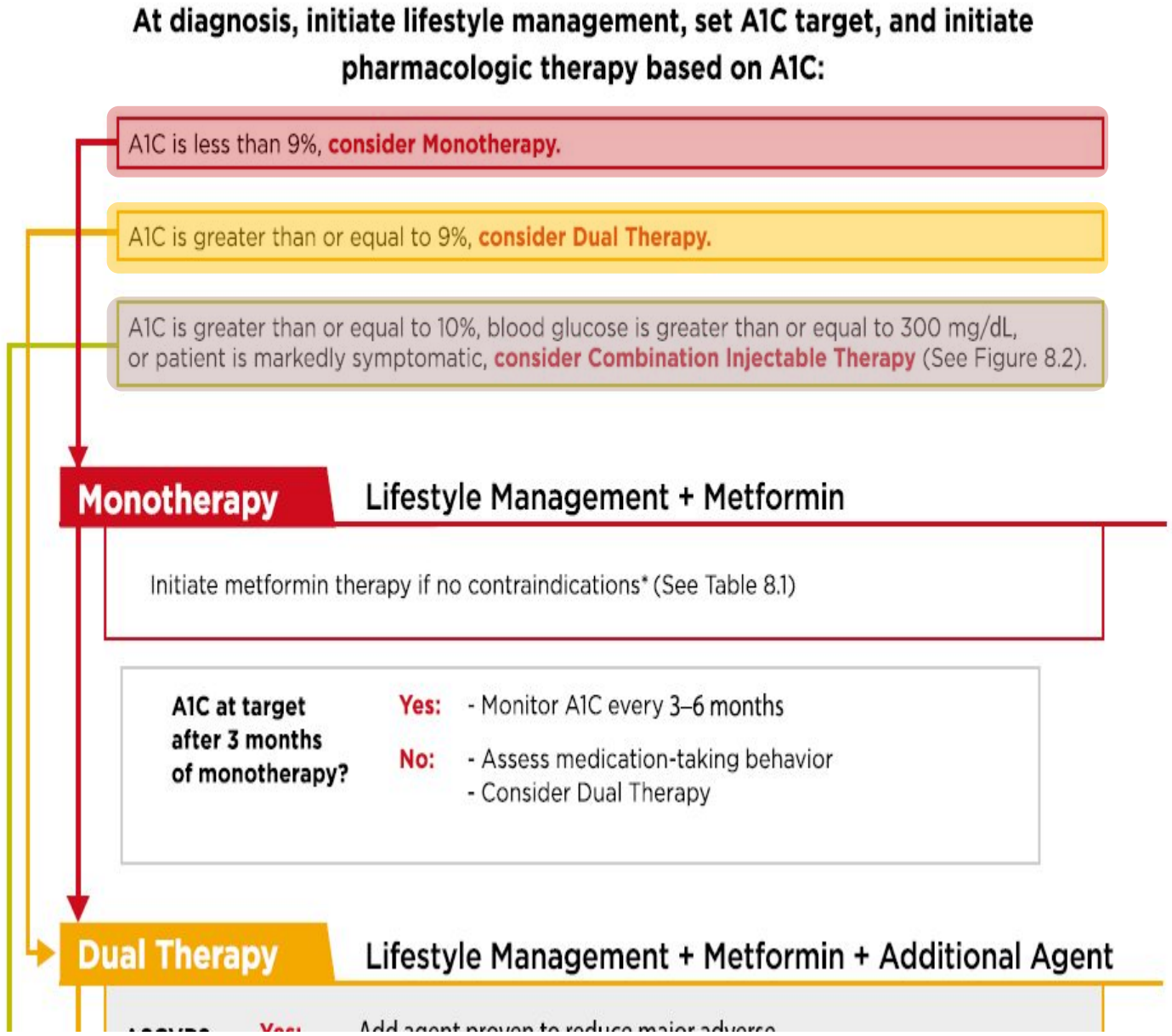

↓Appetite and food intake
Cardioprotection
↓ Gastric emptying
GLP-1
↑ Glucose uptake
↓Hepatic Glucose Production
↑Insulin synthesis and secretion
↓Glucagon production
↑ β-cell growth, proliferation and survival
↓ β-cell apoptosis

Figure 1

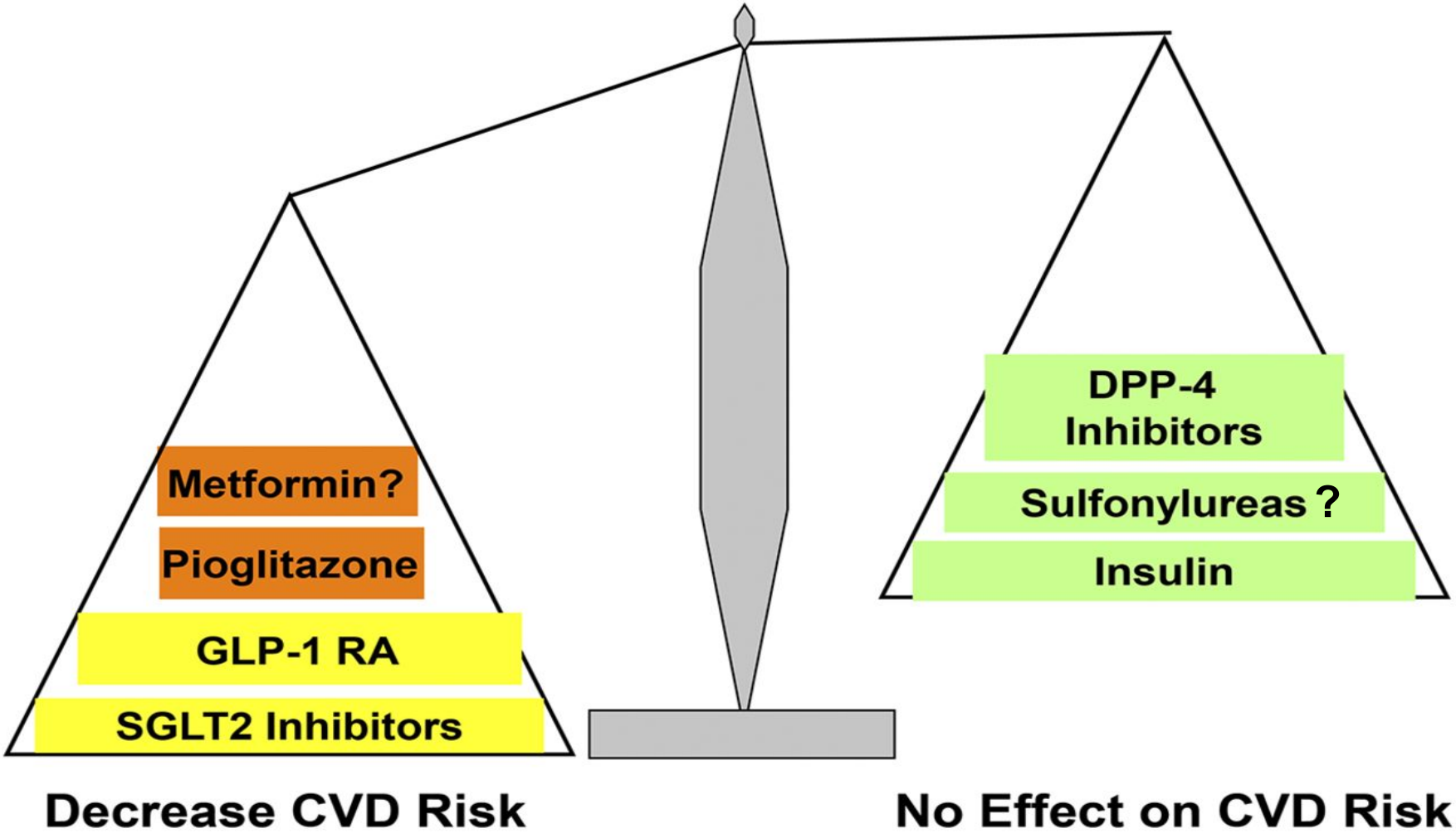
Antihyperglycemic Therapy in Adults with Type 2 Diabetes



American Diabetes Association recommendation-2022

- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors. (A)

Cardiovascular risk profile of antidiabetes medications



Abdul-Ghani M, et al. Diabetes Care 2017;40:813-820.

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

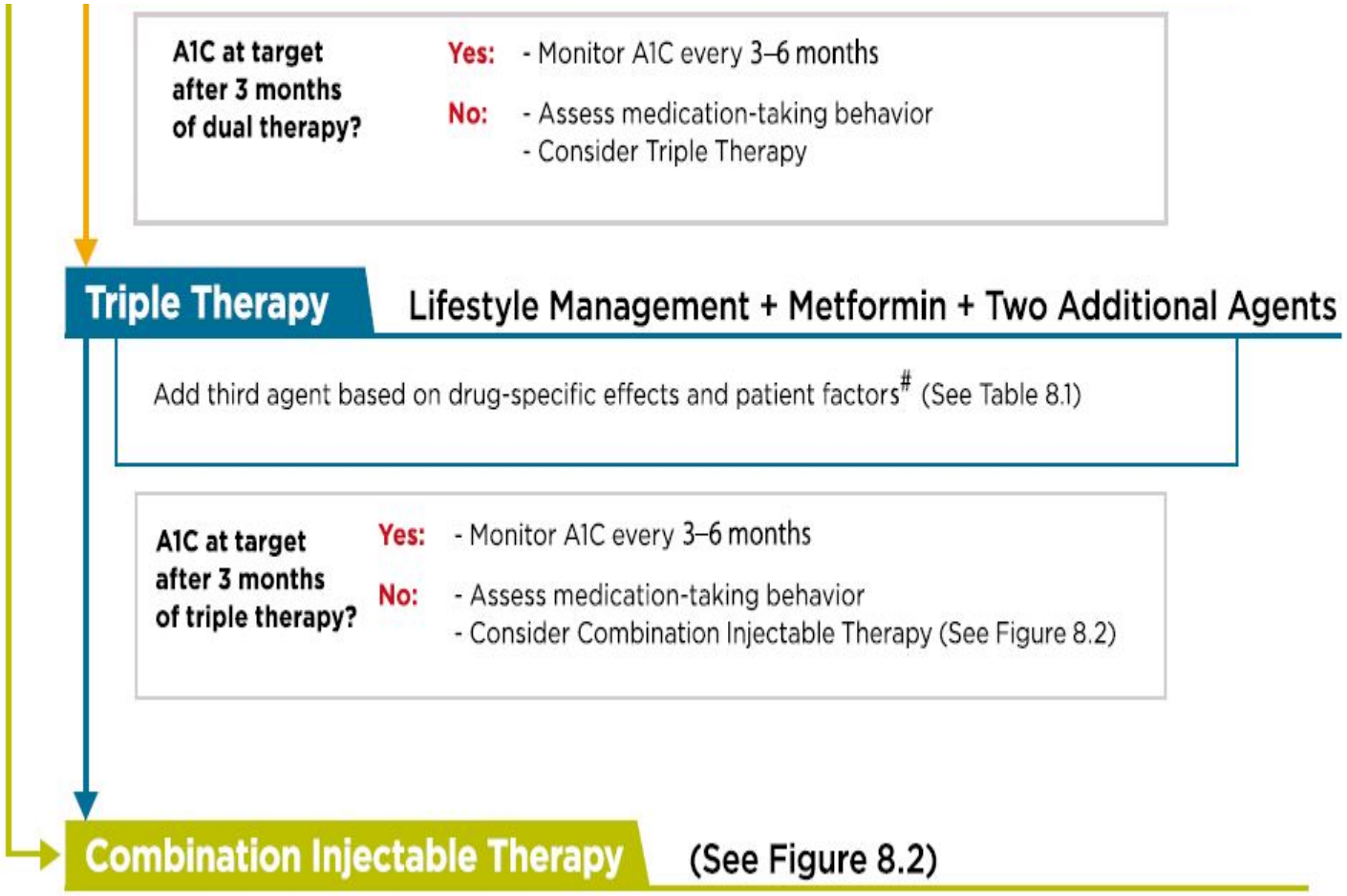


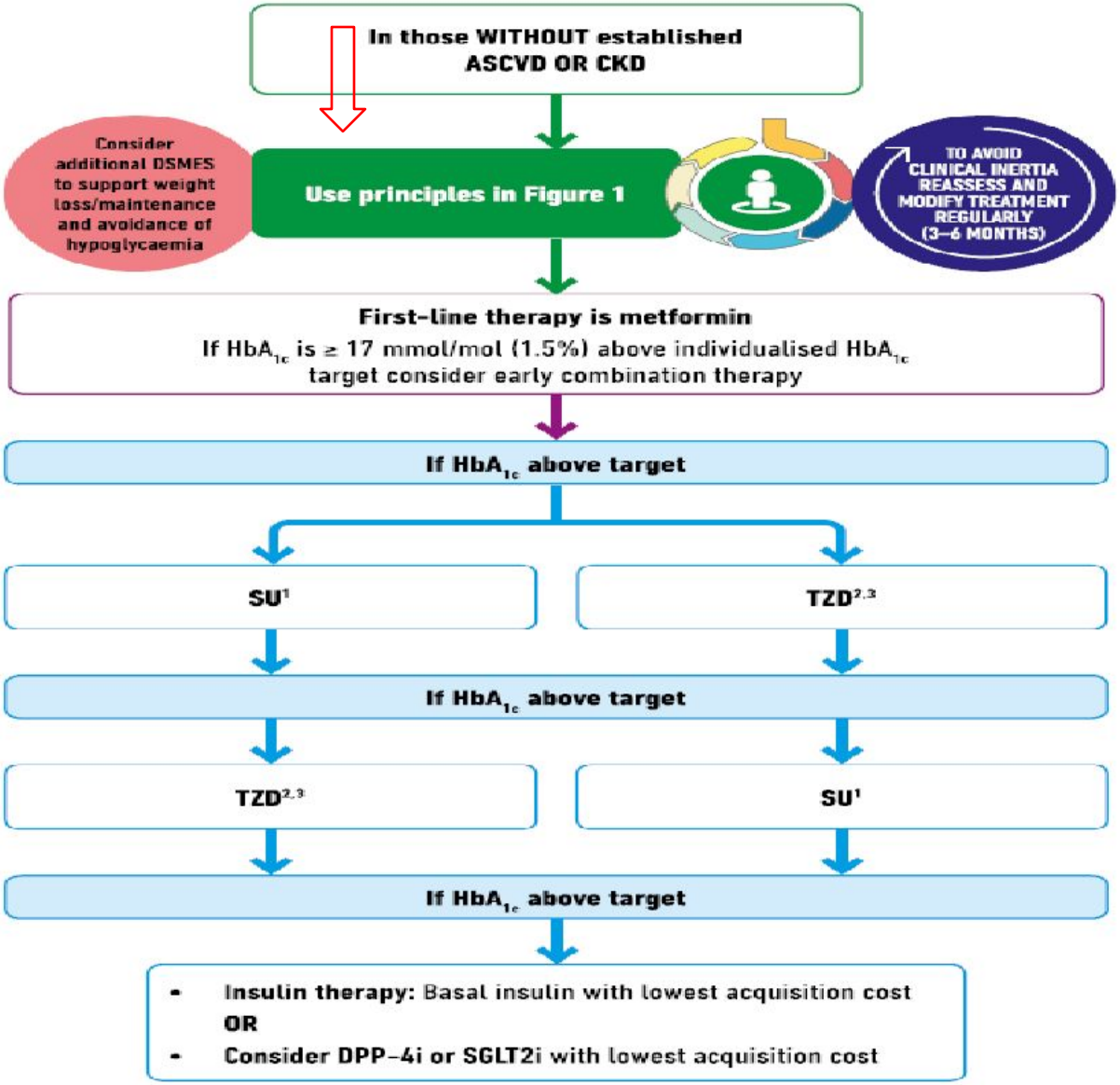
Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations. *If patient does not tolerate or has contraindications to metformin, consider agents from another class in Table 8.1. #GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination. If a patient with ASCVD is not yet on an agent with evidence of cardiovascular risk reduction, consider adding.

Expected HbA_{1c} reduction according to intervention

Intervention	Expected ↓ in HbA_{1c} (%)
Lifestyle interventions	1 to 2%
Metformin	1 to 2%
Sulfonylureas	1 to 2%
Insulin	1.5 to 3.5%
Glinides	1 to 1.5%[1]
Thiazolidinediones	0.5 to 1.4%
α-Glucosidase inhibitors	0.5 to 0.8%
GLP-1 agonist	0.5 to 1.0%
Pramlintide	0.5 to 1.0%
DPP-IV inhibitors	0.5 to 0.8%

Nathan DM, et al. Diabetes Care 2009;32:193-203.

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



نام دارو	تعداد	قیمت (تومان)	پوشش بیمه
متفورمین	100	11000 (25150)	√
Gly-Once 500-750	100	24.000-30.000	●
گلی بن کلامید	100	5200	√
گلی کلازید 80	100	13000 (19000)	√
Empagliflozin 10	30	82.500	●
ریپگلیناید (05-1-2)	100	8500-14.400-20.000	√
گلوتازون (15-30-45)	100	35-42-50000	●
آکاربوز (50-100)	100	27.000-50.000	●
سیتاگلیپتین 50-100	30	39.750-79500	●
NPH	1 ویال	18.840	√
Regular	1 ویال	18.840	√
سرنگ	100 عدد	20000	●

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

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

Implement strategies for maximising weight loss

First-line therapy is metformin

If HbA_{1c} is ≥ 17 mmol/mol (1.5%) above individualised HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

EITHER/ OR

GLP-1 RA with good efficacy for weight loss[1]

SGLT2i if eGFR adequate[2]

If HbA_{1c} above target

SGLT2i if eGFR adequate[2]

GLP-1 RA with good efficacy for weight loss[1]

If HbA_{1c} above target

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

PREFERABLY

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

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

• SU[3] • TZD[4] • Basal insulin

General lifestyle advice

- Medical nutritional therapy
- Eating patterns
- Physical activity

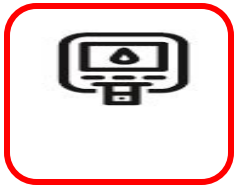
Non-surgical energy restriction for weight loss

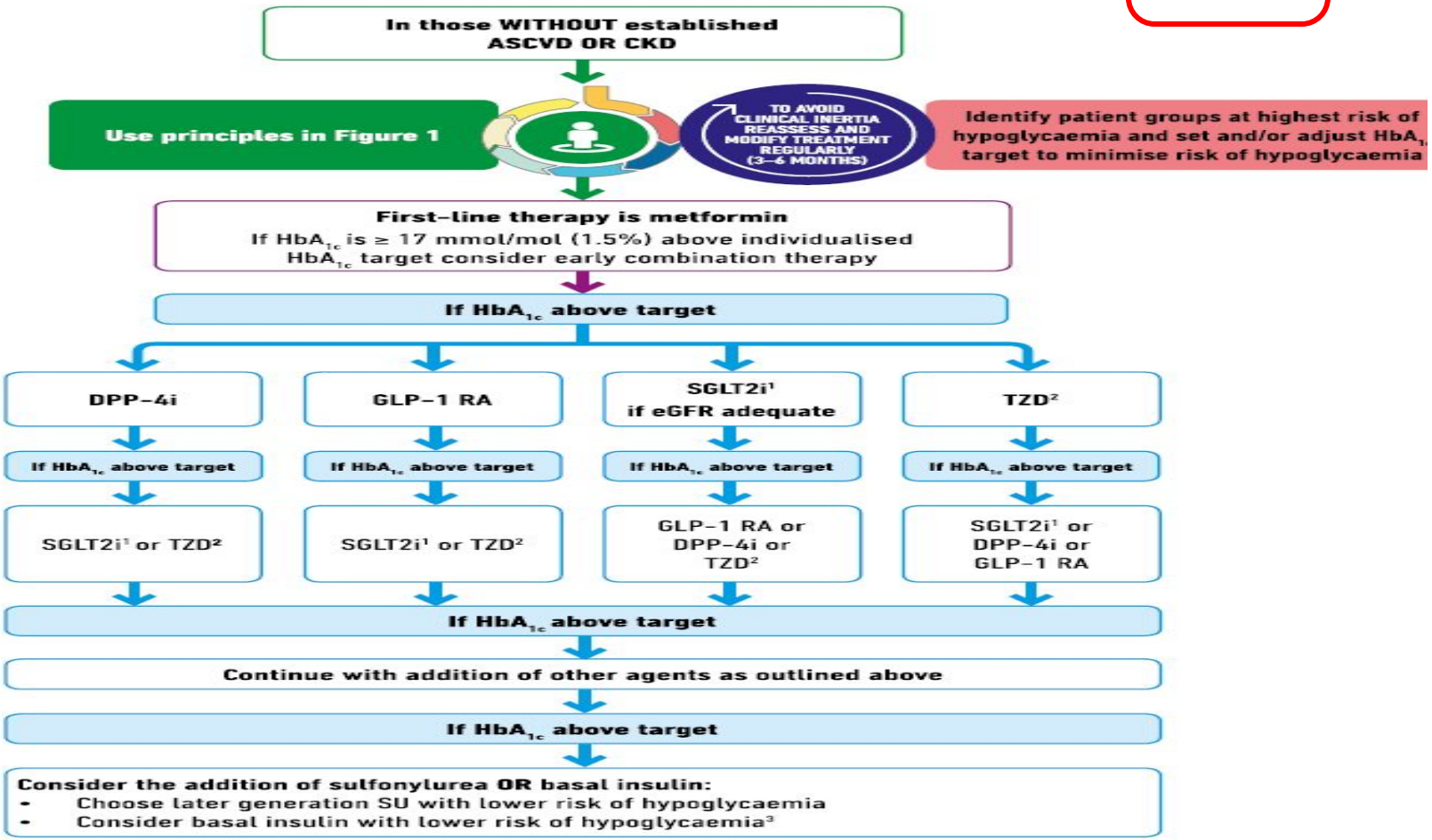
Weight loss of 15kg can lead to remission of T2DM in patient <6 years' duration, **consider evidence-based weight loss programmes**

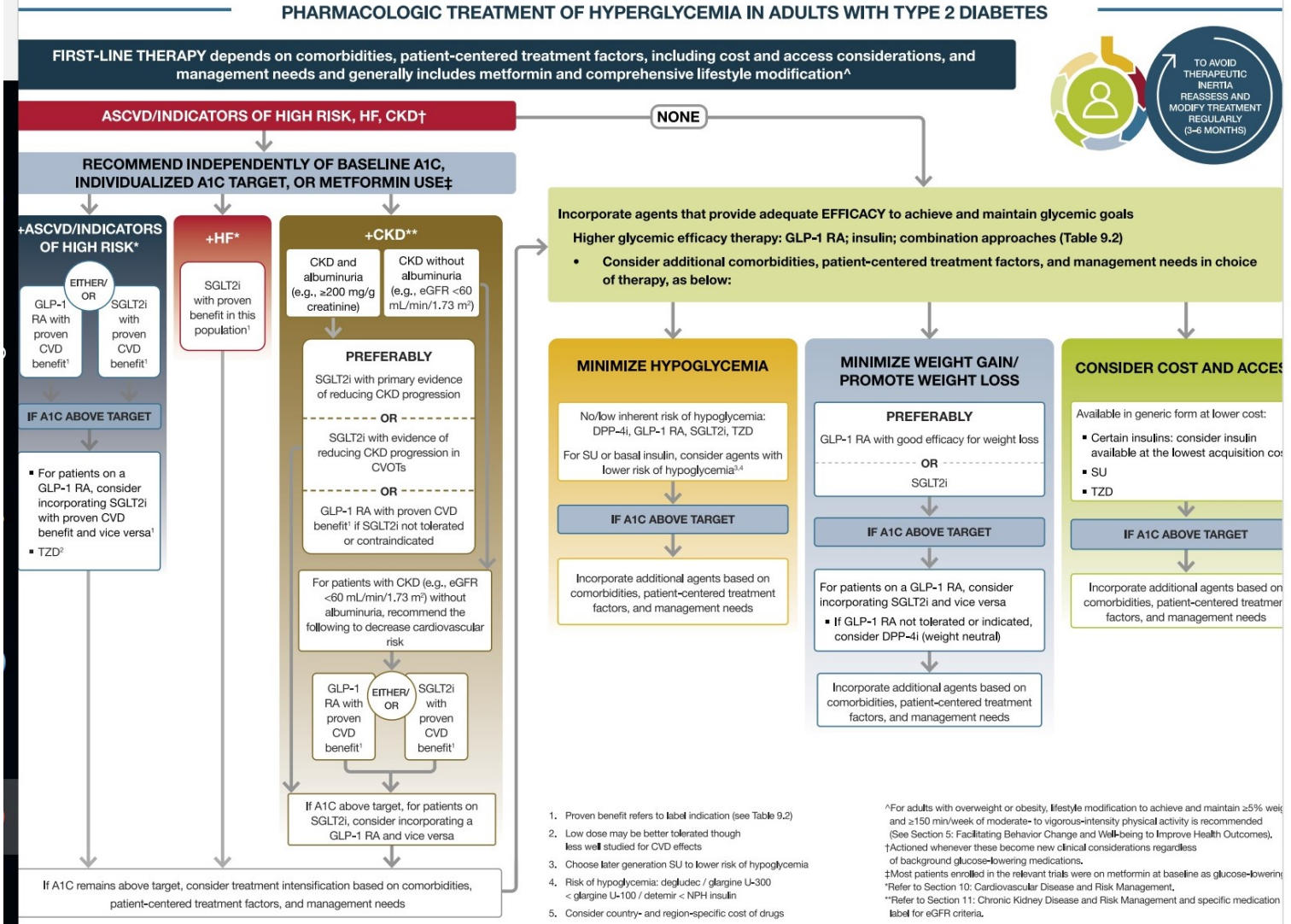
Consider medication for weight loss

Consider metabolic surgery

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA







igure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (43) and Buse et al. (44). For ap te context, see **Fig. 4.1**. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic r hould be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular d CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; odium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.