diabetes

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Classification and Diagnosis of Diabetes

- ***Diabetes can be classified into the following general categories***:

- 1. ***Type 1 diabetes*** (due to ***autoimmune b-cell destruction***, usually leading to absolute insulin deficiency, including ***latent autoimmune diabetes of adulthood***)

- 2. ***Type 2 diabetes*** (due to a ***non-autoimmune progressive loss of adequate b-cell insulin secretion*** frequently on the ***background of insulin resistance and metabolic syndrome***)

- 3. ***Specific types of diabetes*** due to other causes, e.g., ***monogenic diabetes syndromes*** (such as neonatal diabetes and maturity-onset diabetes of the young), ***diseases of the exocrine pancreas*** (such as cystic fibrosis and pancreatitis), and ***drug- or chemical-induced diabetes*** (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
- 4***. Gestational diabetes mellitus*** (diabetes diagnosed in the ***second or third trimester of pregnancy*** that was not clearly overt diabetes prior to gestation)

Table 2.1–Staging of type 1 diabetes (12,16)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

DIAGNOSTIC TESTS FOR DIABETES

- Diabetes may be diagnosed based on plasma glucose criteria, either the ***fasting plasma glucose*** (FPG) value or the ***2-h plasma glucose*** (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) or ***A1C criteria .***
- Generally, ***FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening.***
- It should be noted that detection rates of different creening tests vary in both populations and individuals.

Table 2.2—Criteria for the diagnosis of diabetes

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

- In conditions associated with an ***altered relationship between A1C and glycemia,*** such as ***hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes.***

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

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

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

▶GESTATIONAL DIABETES MELLITUS

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [251]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

- In individuals ***who are planning pregnancy***, screen those ***with risk factors*** and consider ***testing all individuals of childbearing potential for undiagnosed diabetes.***

- ***Before 15 weeks of gestation***, test ***individuals with risk factors*** and consider testing ***all individuals for undiagnosed diabetes at the first prenatal visit*** using standard diagnostic criteria if not screened preconception .

- Individuals with a ***history of gestational diabetes mellitus*** should have ***lifelong screening*** for the development of diabetes or prediabetes ***at least every 3 years.***

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

- Most individuals with ***type 1 diabetes*** should be ***treated with multiple daily injections*** of ***prandial and basal insulin***, or ***continuous subcutaneous insulin infusion.***

- Most individuals with type 1 diabetes should use ***rapid-acting insulin analogs to reduce hypoglycemia risk.***

- ***Typical multidose regimens*** for individuals with type 1 diabetes combine ***premeal use of shorter-acting insulins with a longer-acting formulation.***
- The ***long-acting basal dose*** is titrated to regulate ***overnight and fasting glucose.***
- ***Postprandial glucose*** excursions are best controlled by a well-timed ***injection of prandial insulin***. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled), the premeal blood glucose level, and carbohydrate consumption .

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. ***Pramlintide is based on the naturally occurring b-cell peptide amylin and is approved for use in adults with type 1 diabetes***

- The ***addition of metformin*** in adults with type 1 diabetes caused ***small reductions in body weight and lipid levels but did not improve A1C .***

- The largest clinical trials of glucagon-like peptide 1 receptor agonists ***(GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, showing modest A1C reductions (0.4%), decreases in weight (5 kg), and reductions in insulin doses .***

sodium–glucose cotransporter 2 (SGLT2) inhibitors have been
studied in clinical trials in people with type 1 diabetes, showing ***improvements in A1C, reduced body weight, and improved blood pressure*** ; however, SGLT2 inhibitor use in type 1 diabetes is associated with an ***increased rate of diabetic ketoacidosis.***

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
Less-preferred, alternative injected insulin regimens			
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	+

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

- Healthy ***lifestyle behaviors***, diabetes ***self-management education and support***, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. ***Pharmacologic therapy*** should be guided by person-centered treatment factors, including ***comorbidities and treatment goals.***
- 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*** .

- Pharmacologic approaches that provide adequate efficacy to
  achieve and maintain treatment goals should be considered, ***such as metformin or other agents, including combination therapy .***

- ***Weight management is an impactful component*** of glucoselowering management in type 2 diabetes.

- ***Metformin should be continued upon initiation of insulin*** therapy (unless contraindicated or not tolerated) for ongoing ***glycemic and metabolic benefits.***
- 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 [16.7mmol/L]) are very high.

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

- ***If insulin is used, combination therapy*** with a glucagon-like peptide 1 receptor agonist is recommended for ***greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit.***

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)

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

+ASCVD[1]

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 m² 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 m²; 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

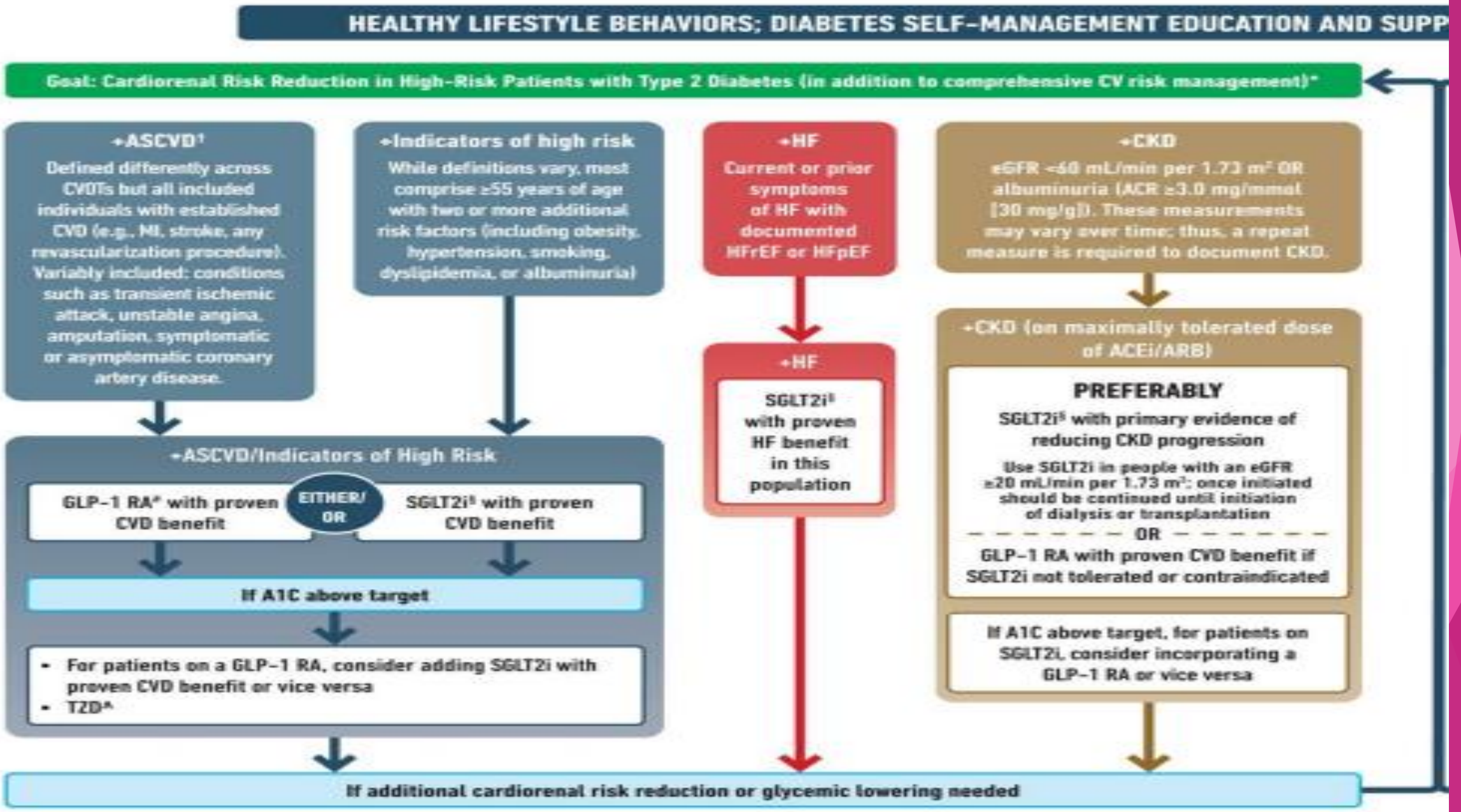
If A1C above target

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.

USE OF GLUCOSE–LOWERING MEDICATIONS IN THE M



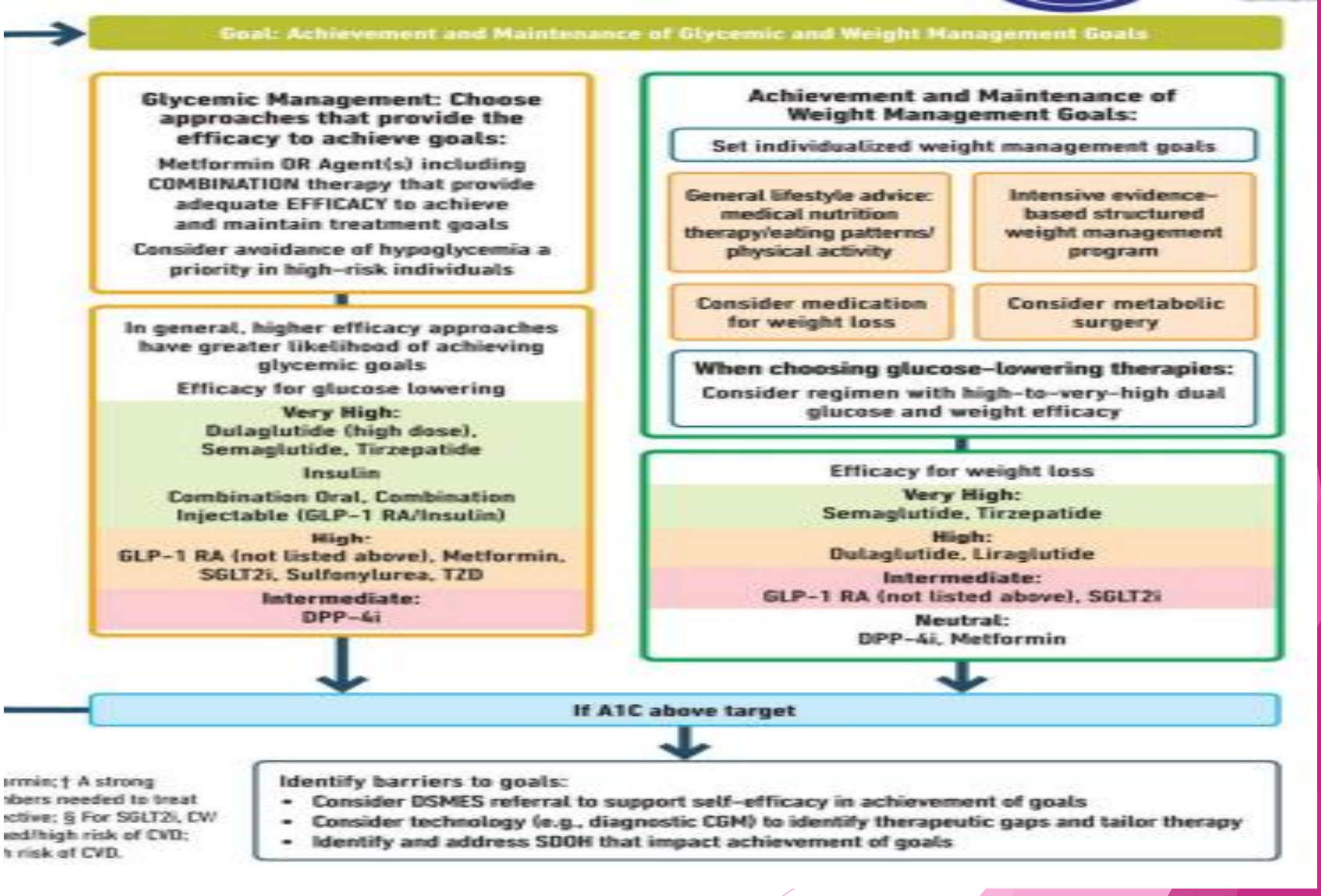
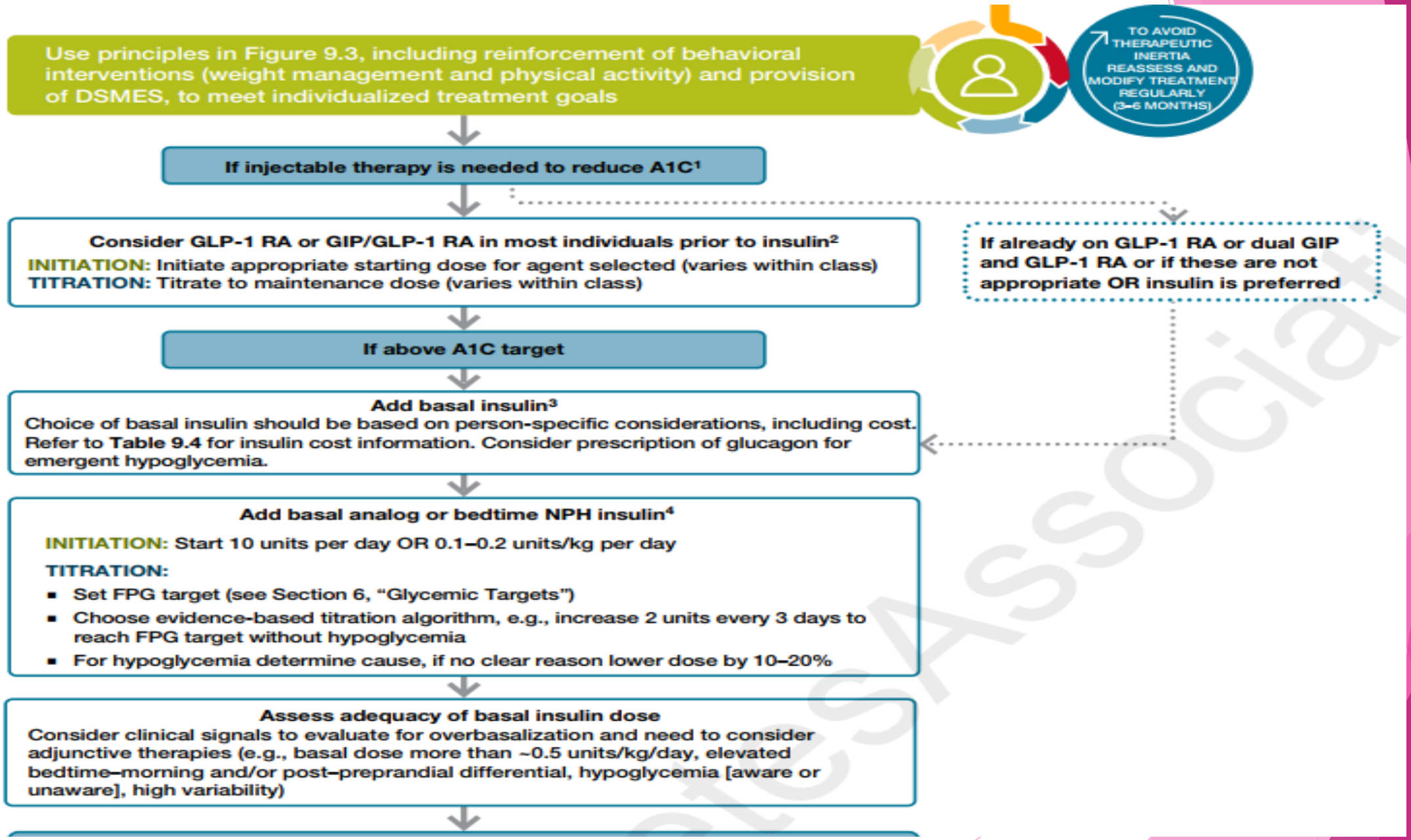
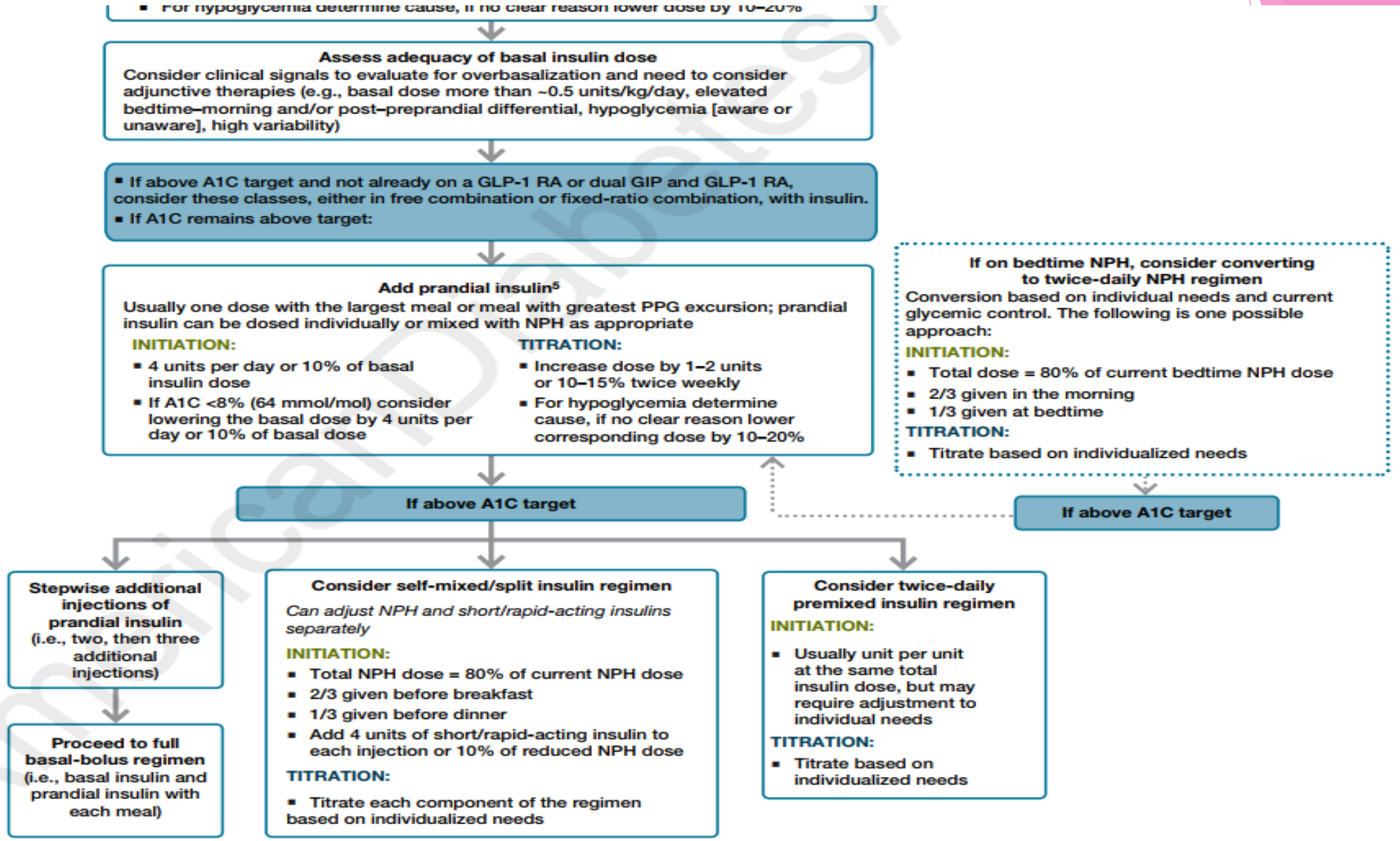

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals
Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of 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

Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
				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	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
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	High	• DKA risk, rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic 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 • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
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	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors 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 is suspected
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	SQ	High	• Risk of thyroid C-cell tumors 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 is suspected
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	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
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	Low	• Congestive HF (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	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 hypoglycemia
Insulin — **Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — **Analogs**								SQ	High	


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)


▪ 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

- ***Basal insulin alone is the most convenient initial insulin treatment and can be added t***o metformin and other noninsulin injectables.
- ***Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia***, with individualized titration over days to weeks as needed. The principal ***action of basal insulin*** is to ***restrain hepatic glucose production and limit hyperglycemia overnight and between meals*** . Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog.

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	$118 ($118, $157)	$94
		U-100 prefilled pen	$151	$121
	• Lispro	U-100 vial	$99†	$79†
		U-100 cartridge	$408	$326
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$261
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	NA
	• Glulisine	U-100 vial	$341	$272
		U-100 prefilled pen	$439	$351
	• Aspart	U-100 vial	$174†	$140†
		U-100 cartridge	$215†	$172†
		U-100 prefilled pen	$224†	$180†
	• Aspart ("faster acting product")	U-100 vial	$347	$277
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Inhaled insulin	Inhalation cartridges	$1,418	NA
Short-acting	• Human regular	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$166
Intermediate-acting	• Human NPH	U-100 vial	$165††	$132††
		U-100 prefilled pen	$208	$168
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on products	U-100 prefilled pen	$261 ($118, $323)	$209 ($209, $258
		U-100 vial	$118 ($118, $323)	$95
	• Glargine	U-100 vial; U-100 prefilled pen	$136†	$109†
		U-300 prefilled pen	$346	$277
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$296
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$339
	• Lispro 75/25	U-100 vial	$342	$273
		U-100 prefilled pen	$127†	$103†
	• Aspart 70/30	U-100 vial	$180†	$146†
		U-100 prefilled pen	$224†	$178†
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 µg prefilled pen	$646	$517
	• Degludec/Liraglutide	100/3.6 µg prefilled pen	$944	$760

- If basal insulin has been titrated to an acceptable fasting blood glucose level (or if ***the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above target***, consider advancing to ***combination injectable therapy*** .

- This approach can use a ***GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of insulin.*** The combination of ***basal insulin and GLP-1 RA*** has potent glucoselowering actions and ***less weight gain and hypoglycemia compared with intensified insulin regimens .***

Thank you