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Ohio Cardiovascular and Diabetes Health Collaborative

Outpatient Diabetes Management for Primary Care Providers:

Medications Intensification and Algorithm

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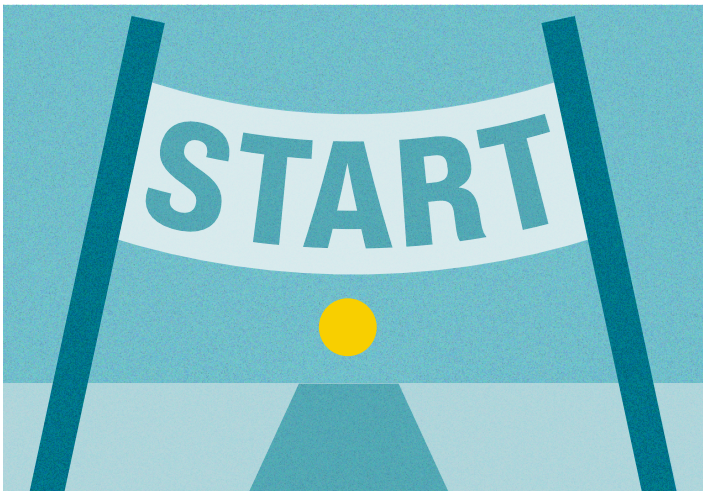
Primary care providers are integral health care team members in diabetes management and treatment, both of which should be individualized based on a variety of considerations.

This document highlights evidence-based strategies for pharmacologic management of type 2 diabetes (T2D) in outpatient settings focusing on newer therapies and treatment intensification strategies. It is important to emphasize that pharmacologic therapy should be implemented in conjunction with healthy lifestyle behaviors, Diabetes Self-Management Education and Support (DSMES), avoidance of clinical inertia, and attention to psychosocial care and social determinants of health (see links to other resources below).

When choosing pharmacological treatment for T2D, consider (Figure 1):[1-3]

- Associated comorbidities (especially cardiovascular or renal disease)
- Approaches with adequate efficacy to achieve and maintain glycemic and weight loss goals
- Other factors: risk of hypoglycemia, cost, side effects/tolerability

Treatment goals are discussed in detail elsewhere (see Expanded Resources, below). Generally an HbA1c goal of < 7% is reasonable for most individuals but should be personalized based upon hypoglycemia risk, life expectancy, treatment burden, patient preference, and other factors. Current data do not warrant differential treatment strategies based upon race/ethnicity.[1] Advances in precision medicine may one day help to inform individualized treatment strategies beyond the strategies discussed here.[4] The choice of therapy is complex (see Ohio Medicaid unified formulary in Table 1); thus, medical decision making is enhanced by decision support tools, including smart order sets, which are integrated into existing clinical workflows. Recommendations in this document reflect that of the American Diabetes Association 2025 Standards of Care. References to other pharmacologic management guidelines for T2D are provided below.



Initial Therapy for Type 2 Diabetes

Treatment for new-onset T2D should include lifestyle modifications and be tailored to the patient's comorbidities as well as glycemic and weight loss goals (Figure 1). As a result, metformin may not necessarily be the first drug of choice. Additional considerations include cost, complexity, and patient preference. Patients with specific comorbidities including atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD, heart failure (HF), chronic kidney disease (CKD), or metabolic dysfunction–associated steatotic liver disease (MASLD) should receive therapies with known benefit. Typically, therapy includes sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1 RA), depending on the specific comorbidites. Where used, metformin should be started at the lowest dose and titrated gradually to minimize side effects. Extended release formulations may decrease gastrointestinal side effects.

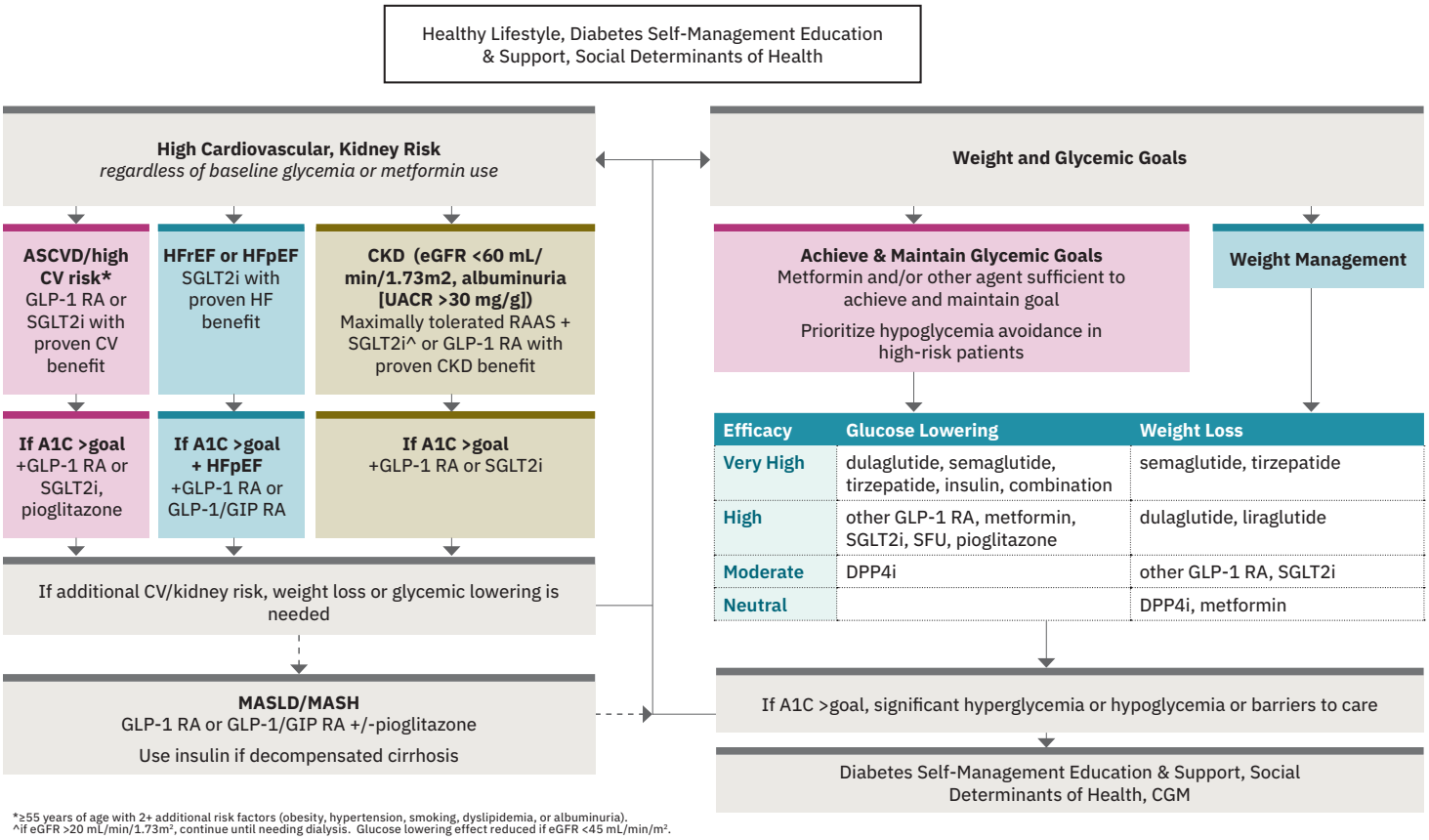
Metformin may reduce the risk of ASCVD and death.[5] Avoid starting it if glomerular filtration rate (GFR) is < 45 mL/min/1.73m^2. Reconsider existing use if the GFR drops below 45 and do not use if GFR < 30. Annual testing of vitamin B12 starting 4 years after initiation is recommended.[1]

Combination Therapy

Initial combination therapy is indicated in patients with an A1C level 1.5% above goal in order to reduce clinical inertia and extend the time to treatment failure.[1-3,6] Additional stepwise therapy should also be considered for those who are not meeting goals after three months. In particular, consider need for treatment adjustment during transitions of care (e.g., adolescent/young adult, pregnancy, hospitalization). The decision is based on the same factors as initial therapy while considering complementary mechanisms of action (Table 2). The MedTAPP Diabetes Quality Improvement Project Toolkit includes valuable information about dosing of individual agents.

When cost is a major concern, consider pharmaceutical discount programs, formulary alternatives, social work/ pharmacy referrals, and less expensive options where appropriate. Engage patients in shared decision-making discussions about the limitations of these therapies, including potential for weight gain, hypoglycemia, and durability of effect. Emphasize the value of glycemic control for reducing microvascular complications.

Figure 1. Modified ADA Diabetes Algorithm: Pharmacologic Treatment



*≥55 years of age with 2+ additional risk factors (obesity, hypertension, smoking, dyslipidemia, or albuminuria).
^if eGFR >20 mL/min/1.73m², continue until needing dialysis. Glucose lowering effect reduced if eGFR <45 mL/min/m².

ASCVD = atherosclerotic cardiovascular disease; CGM = continuous glucose monitoring; CKD = chronic kidney disease; CV = cardiovascular; DPP4i = dipeptidyl peptidase-4 inhibitor; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GIP = gastric inhibitory peptide; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; MASH = metabolic dysfunction associated steatohepatitis; MASLD = metabolic dysfunction associated steatotic liver disease; RAAS = renin angiotensin aldosterone system; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SFU = sulfonylurea; UACR = urine albumin/creatinine.

Adapted from *9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2025. Diabetes Care.*[1]

Table 1. 2025 Ohio Medicaid Preferred Diabetes Formulary *As of January 1, 2025*

Drug Class	Preferred
Non-Insulin	
Metformin and combination	Actoplus Met XR (pioglitazone/metformin), glipizide/metformin, glyburide/metformin, Jentadueto (linagliptin/metformin), Janumet (sitagliptin/metformin), Janumet XR, Jentadueto (linagliptin/metformin), metformin, metformin ER (generic of Glucophage XR), pioglitazone/metformin, Synjardy (empagliflozin/metformin), Xigduo XR (dapagliflozin/metformin)
Sulphonylurea SFU	glimepiride, glipizide, glyburide
Glucagon-like peptide-1 receptor agonist GLP-1 RA	Byetta (exenatide), Trulicity (dulaglutide), Victoza (liraglutide)
Sodium-glucose cotransporter-2 inhibitor SGLT2i	Farxiga (dapagliflozin), Jardiance (empagliflozin)
Dipeptidyl peptidase-4 inhibitor DPP-4i	Januvia (sitagliptin), Tradjenta (linagliptin)
Thiazolidinedione TZD	pioglitazone
Alpha glucosidase inhibitor AGI	acarbose, miglitol
Glinide	nateglinide, repaglinide
Insulin	
Basal	Lantus (glargine), Levemir (detemir), Toujeo (glargine U-300), Tresiba (degludec)
Bolus	Apidra (glulisine), Humalog (lispro) U-100, Humulin R (regular insulin) U-500, lispro, Novolog (aspart) U100
Premix	Humalog 50/50 (lispro protamine/lispro), Humalog 75/25 (lispro protamine/lispro), Humulin 70/30 (insulin isophane/regular insulin), aspart protamine/aspart

[S] Step therapy

Table 2. Characteristics and Side Effects of Common Diabetes Therapies[1]

	Metformin	SFU	TZD	DPP-4i	SGLT2i	GLP-1 RA	Insulin
Efficacy	++	++	++	+	++	+++	+++
Hypoglycemia	-	+	-	-	-	-	+
Weight	-	↑	↑	-	↓	↓↓	↑
Side effect	GI, lactic acidosis	Hypoglycemia	Edema, fracture	Arthralgia	GU, dehydration, DKA, fracture	GI	Hypoglycemia
MACE benefit[1]	+/-	-	+/-	-	+	+	-
Heart failure benefit	-	-	[2]	[2]	+	+/-[3]	-
Renal benefit[1]	-	-	+/-	+/-	++	+	-
Cost	↓	↓	↓	↑	↑	↑	↑

[1]Benefits for overall MACE, MACE components, and renal outcomes vary by glucose lowering agent within class Pioglitazone reduces risk of stroke in persons with insulin resistance.

[2]increased risk of heart failure with TZDs, saxagliptin, possibly alloglitpin

[3]HFpEF only

SFU=sulfonylurea, TZD=thiazolidinedione, DPP-4i=dipeptidyl peptidase inhibitor, SGLT2i=sodium glucose cotransporter-2, GLP-1 RA=glucagon-like peptide-1 receptor agonist, GI=gastrointestinal, HF=heart failure, GU=genitourinary, DKA=diabetic ketoacidosis (may be euglycemic DKA), MACE=major adverse cardiovascular event (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death +/- other endpoints). +=Yes, -=No, +/-=weak evidence, ↑=increased/high, ↓=decreased/low

Table 3. Cardiovascular and Renal Benefits of Medications for Treatment of Type 2 Diabetes

Drug	ASCVD	Heart Failure	Chronic Kidney Disease	MASH
Sodium glucose cotransporter-2 inhibitor SGLT-2i	Canagliflozin **Empagliflozin**	Canagliflozin **Empagliflozin** **Dapagliflozin** Ertugliflozin	Canagliflozin* **Dapagliflozin*** **Empagliflozin***	Possible benefit
Glucagon-like peptide-1 receptor agonist GLP-1 RA	**Dulaglutide** Liraglutide Semaglutide (SQ)	Semaglutide* Tirzepatide*	**Dulaglutide^** Liraglutide^ Semaglutide (SQ)^	Potential benefit
Thiazolidinedione TZD	**Pioglitazone** (Secondary prevention)	Avoid	N/A	Potential benefit

*Items in bold are preferred on the Ohio Medicaid Unified Formulary

#Benefit in HFpEF only: semaglutide reduced symptoms and tirzepatide reduced a composite of cardiovascular death or worsening heart failure.

^semaglutide demonstrated reduction in progression of chronic kidney disease in a dedicated renal study. Dulaglutide and liraglutide demonstrated reduction in albuminuria

ASCVD=atherosclerotic cardiovascular disease, MASH=metabolic dysfunction associated steatohepatitis

GLP-1 RA and GLP-1/Glucose-Dependent Insulinotropic Polypeptide (GIP) Dual Agonist

Consider GLP-1 RA or GLP-1/GIP as monotherapy or combination therapy, with or without insulin, and particularly in patients needing high glucose lowering or weight loss efficacy, or those with established ASCVD, or who have high cardiovascular risk (Table 3). GLP-1 RA and GLP-1/GIP therapies should not be combined with dipeptidtyl peptidase inhibitors as there is no additive glucose lowering benefit. Glucose lowering and weight loss vary across therapies within this class (Figure 1). It is important to weigh the following risks and benefits to determine the best fit for the patient.

Benefits:

- High to very high efficacy.
- Greater durability vs. sulfonylurea or DPP-4i.[7]
- Low risk of hypoglycemia.
- High to very high weight loss.
- No renal adjustment (except exenatide, lixisenatide).
- Option for once weekly dosing after weight loss.
- Preferred for patients with a history of stroke.
- Agents with proven ASCVD benefits (liraglutide, dulaglutide, SQ semaglutide) are preferred in persons with known ASCVD or at highest cardiovascular risk.
- Preferred for metabolic dysfunction associated steatatotic liver disease (MASLD) or metabolic dysfunction associated steatohepatitis (MASH).
- HF with preserved ejection fraction (HFpEF) benefit: Semaglutide reduces physical limitations, exercise capacity, and HF symptoms, while tirzepatide reduces a composite of death from cardiovascular causes or worsening HF.
- Recommend before starting basal insulin: similar or better efficacy and lower risk of hypoglycemia or weight gain.

Risks:

- Common side effects are nausea, vomiting, diarrhea, and constipation; titrate gradually to minimize.
- Contraindicated if personal or family history of medullary thyroid cancer (observed in rodent studies only, relevance in humans is unknown).
- Increased risk of gallbladder disease (related to weight loss).
- Possible increased risk for acute pancreatitis (mechanism unclear).
- High cost.

SLGT-2i

Consider SLGT-2i as monotherapy or combination therapy, and particularly in patients with heart failure, ASCVD, or CKD (Table 3). It is important to weigh the following risks and benefits to determine the best fit for the patient.

Benefits:

- High efficacy but less than that for some GLP-1-based therapies.
- Modest weight loss.
- Renal dose adjustment may be required. Glucose lowering effects are reduced in CKD, and are negligible below eGFR < 45 mL/min/1.73m^2.
- Proven cardiovascular benefits (reduction in major adverse cardiovascular events, HF [both reduced and preserved ejection fraction]), even at reduced eGFR.
- Slows progression of nephropathy and CKD, even at reduced eGFR and in combination with angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEi/ARB).

Risks:

- Increased risk of genital mycotic infections.
- Risk of polyuria, volume dehydration, consider need to adjust diuretics.
- Some SGLT2is are associated with increased risk of amputation. Use with caution in patients with severe neuropathy, vascular disease or prior foot ulcer.[9-11]
- Post-marketing cases of Fournier's gangrene have been reported but increased risk has not been observed in clinical trials or epidemiologic studies.[12-15]
- Diabetic ketoacidosis (DKA)/euglycemic DKA.
- High cost.

DPP-4i

Consider DPP-4i as a combination therapy to metformin and/or other agents if additional glucose lowering is needed. It is important to weigh the following risks and benefits to determine the best fit for the patient. DPP-4i should not be combined with GLP-1 RA as there is no additive glucose lowering benefit.

Benefits:

- Moderate efficacy and no impact on weight.
- Renal adjustment is required except for linagliptin.
- Well tolerated; consider with older patients.

Risks:

- No cardiovascular benefits; potential risk for HF with saxagliptin and possibly alogliptin.
- No significant renal benefit.
- Shorter durability versus GLP-1 RA or insulin.[7]
- Possible increased risk of acute pancreatitis and arthralgia (mechanism is not clear).[15,16]
- High cost.

Advancing to Insulin Therapies (Figure 2)[1]

Basal Insulin

Consider starting basal insulin in the following situations:

- A1C above goal with combination therapy of three non-insulin agents.
- A1C is 10% or more and/or fasting glucose is ≥ 300 mg/dL, especially if the patient has symptoms of hyperglycemia or catabolic features.
  - Start 10 units/day or 0.1-0.2 unit/kg/day.
  - Should be adjusted every three days until reaching a fasting glucose goal of 80 to 130 mg/dL (goals should be individualized)
  - Avoid overbasalization (suggested when there is elevated bedtime-to-morning and/or postprandial differentials, hypoglycemia, or high glucose variability).
  - Associated with risk of weight gain and hypoglycemia.
  - Refer for education focusing on glucose monitoring and prevention/treatment of hypoglycemia.
  - Consider prescription for glucagon with education for care givers on use.
- Continue metformin, GLP-1 based therapy, and/or SGLT-2i.

Consider initiation of continuous glucose monitoring (CGM) in all patients who require insulin therapy to guide their treatment. Additionally, consider using CGM in other patients as a tool to support therapeutic lifestyle changes and medication-taking behaviors.

Prandial Insulin

Basal Plus Regimen

Consider prandial insulin if A1C above target despite:

- Adequate titration of basal insulin with fasting blood glucose at goal **OR**
- High variability, high bedtime—morning glucose differential, or hypoglycemia **AND**
- Patient is already taking GLP-1 RA or not a candidate for therapy
  - Start with the largest meal of the day or the meal with greatest post-meal glucose.
  - Starting dose is 10% of the total basal dose or 4 units a day.
  - Rapid acting agents should be taken 10-15 minutes before starting (preferred) the meal. Ultra-rapid insulins may be taken at the start of the meal.
  - Titrate by 1-2 units or 10-15% every three days.
  - Decrease by 10-15% if hypoglycemia occurs with no alternative reason.

Premix Insulin

- An alternative to basal plus insulin regimen is premix insulin, typically dosed 2/3 of daily dose before breakfast and 1/3 of dose before dinner. May be preferred to more complex regimens in patients with consistent meals.

Basal Prandial Regimen

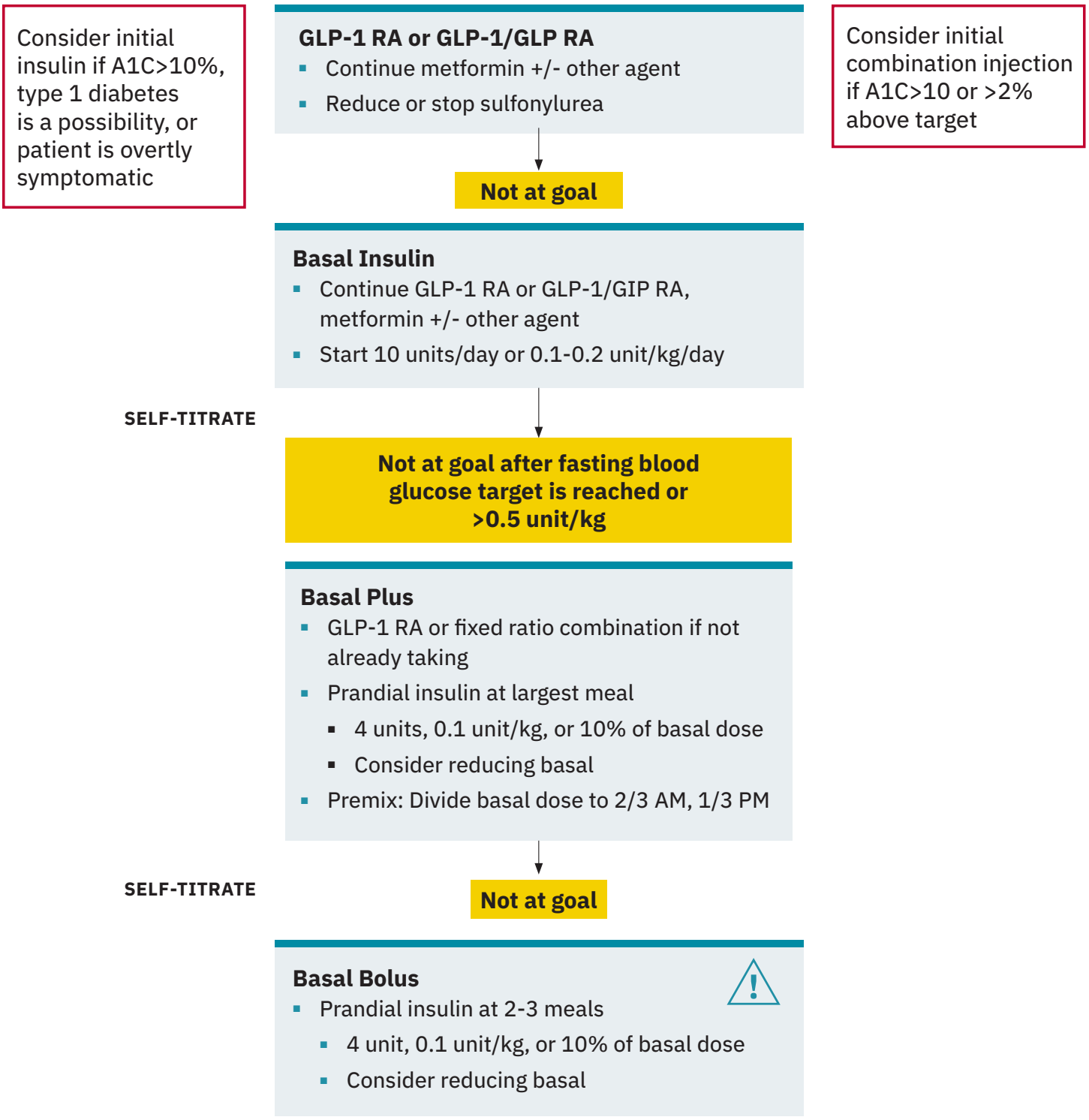
- If A1C is still elevated on a basal plus regimen, add prandial insulin to 2-3 meals per day.
- Total daily prandial insulin dose should be 40-60% of the total daily dose of insulin.
- Counsel the patient to maintain a consistent carbohydrate diet.

Flexible Meal Dosing

Consider flexible meal dosing for patients who have received education and can demonstrate competency. Below are options, based on the A1C and predicted insulin sensitivity:

- Big meal/small meal (e.g., six units for a big meal [60 grams carbs], three units for small meal [30 grams carbs]).
- Insulin to carbohydrate ratio (e.g., one unit per 10 grams carbs).
- Correction scale: with or without skipped meals if glucose before meal is above target (often set at 150 mg/dL) based on the A1C and predicted insulin sensitivity.

Figure 2. Initiation and Intensification of Insulin



Access Cardi-OH's Expanded Resources

- **Beyond the A1C: Targets for Blood Glucose and Methods of Measurement**
  cardi-oh.org/resources/beyond-the-a1c-targets-for-blood-glucose-and-methods-of-measurement
- **Minimizing Hypoglycemia Risk to Improve Cardiovascular Health**
  cardi-oh.org/resources/minimizing-hypoglycemia-risk-to-improve-cardiovascular-health
- **Managing Diabetes in Older Populations: Targets, Challenges, and Medications**
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- **Talking With Your Patients About Diabetes Pharmacotherapy: Side Effects and Adverse Events**
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- **Navigating Barriers to Medication Access**
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- **Addressing Common Barriers to Insulin Initiation and Use**
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- **Implementing Shared Decision Making in Clinical Practice**
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- **Shared Decision Making and Diabetes Care**
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- **Addressing Clinical Inertia in Diabetes Care**
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- **Diabetes Self-Management Education and Support: Provider Use and Patient Benefits**
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- **Interpretation of Continuous Glucose Monitoring in Primary Care: A Case-Based Approach**
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- **Youth-Onset Type 2 Diabetes: How to Identify, Screen, and Treat**
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- **Building Your Person-Centered Diabetes Care Team**
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- **Optimizing the Telehealth Diabetes Visit: Glucose Monitoring Data**
  cardi-oh.org/resources/optimizing-the-telehealth-diabetes-visit-glucose-monitoring-data
- **Diabetes Distress: Screening Tools and Intervention Strategies**
  cardi-oh.org/resources/diabetes-distress-screening-tools-and-intervention-strategies
- **Ohio Pathways Community HUBs: Understanding the Benefits for Patients with Diabetes**
  cardi-oh.org/resources/ohio-pathways-community-hubs-understanding-the-benefits-for-patients-with-diabetes

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