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Outpatient Diabetes Management for Primary Care Providers:

Medications Intensification and Algorithm

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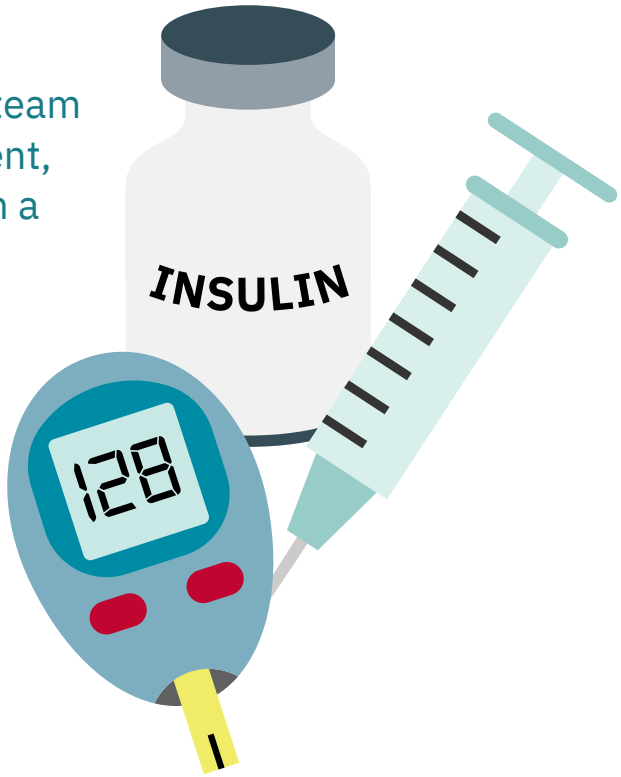


Primary care providers are integral health care team members in diabetes management and treatment, both of which should be individualized based on a variety of considerations.

This document highlights a successful model for diabetes management in outpatient settings while focusing on newer therapies and treatment intensification strategies.

It is important to consider the following when choosing pharmacological treatment for type 2 diabetes mellitus: (Figure 1)[1,2,3]

- Associated comorbidities
- Risk of hypoglycemia
- Side effects
- Effects on body weight
- Cost

While the phenotype of diabetes, as well as responses to therapy, vary somewhat by race/ethnicity, current data do not warrant differential treatment strategies.[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 and the number of individual agents is extensive. Thus, medical decision-making is enhanced by decision support tools, including smart order sets, that are integrated into existing clinical workflows.

Initial Therapy for Type 2 Diabetes

Metformin is the drug of choice, along with lifestyle modifications, for the treatment of new onset type 2 diabetes in most patients, and is available in immediate release (twice daily) or extended release (once daily).

Metformin should be titrated gradually to avoid or minimize side effects. It may reduce the risk of atherosclerotic cardiovascular disease (ASCVD) and death.[5] Avoid using it if glomerular filtration rate (GFR) is <30 m//min/1.73m^2. Periodic testing of vitamin B12 every 3-5 years is suggested for patients using metformin therapy.

Combination Therapy with Metformin

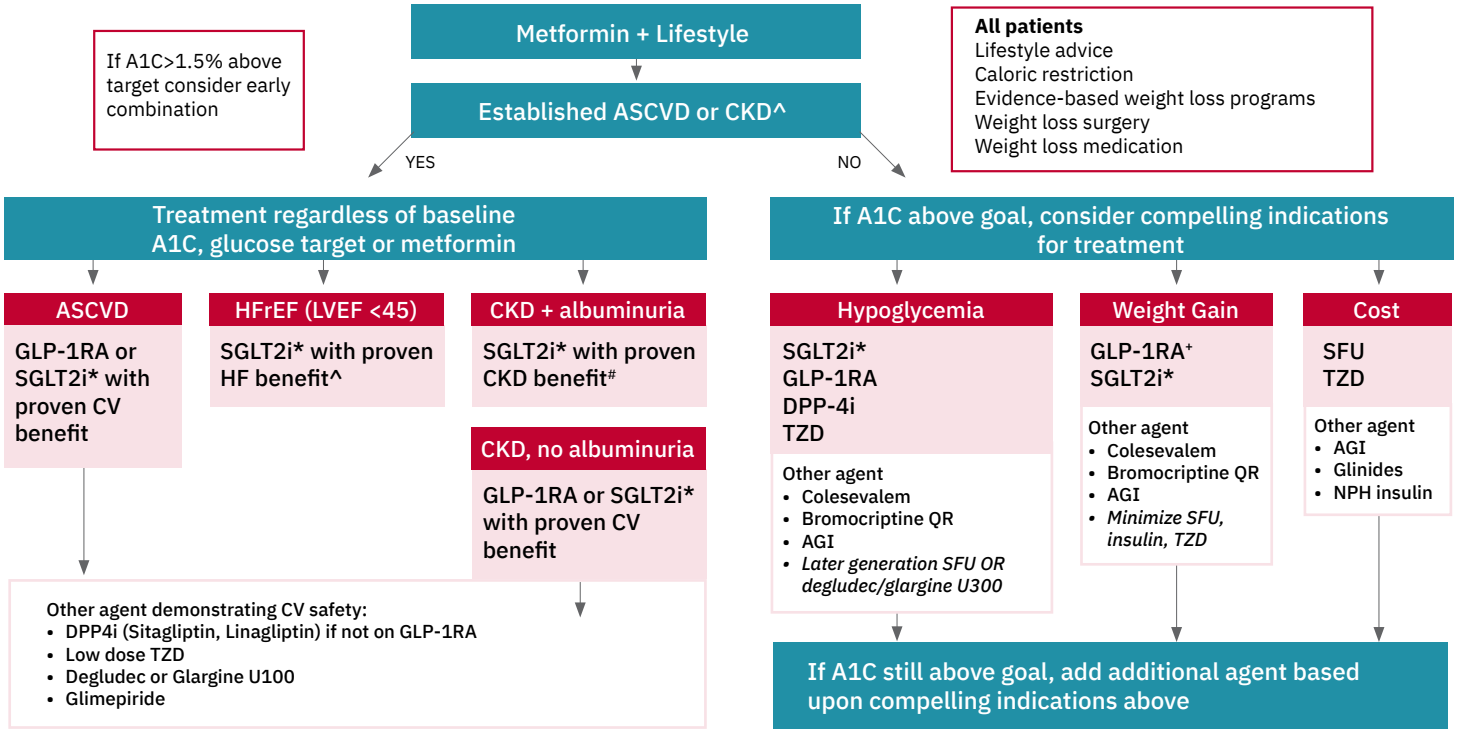
Initial combination therapy is indicated in patients with an A1C level 1.5% above target or who are not meeting targets after three months of using metformin and lifestyle modifications. The decision is based on several factors: associated ASCVD, cost, side effects, other comorbidities, and consideration of complementary mechanisms of action (Table 1). Other combination therapies with metformin include:

- SGLT2-inhibitor
- GLP-1RA
- Dipeptidyl peptidase-4 (DPP-4) inhibitor
- Sulfonylureas
- Thiazolidinedione
- Basal insulin

Patients should continue metformin even after starting insulin therapy since it decreases the risk of hypoglycemia and weight gain, and lowers daily insulin requirements. Oral anti-hyperglycemic agents should not be discontinued abruptly to avoid the risk of rebound hyperglycemia and worsening A1C levels. 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 (sulfonylureas, pioglitazone, human insulins) in combination with metformin where appropriate. Engage patients in shared decision-making discussions about the limitations of these therapies, including potential for weight gain, hypoglycemia, and in the case of sulfonylureas, shorter durability. Emphasize the role of therapeutic lifestyle changes and value of glycemic control for reducing microvascular complications.

Figure 1. American Diabetes Association (ADA) Standards of Care 2021[1]



*If adequate eGFR, ^Empagliflozin and dapagliflozin have shown benefit in dedicated HF studies. Canagliflozin has demonstrated reduction in hospitalization for HF in CV outcomes trials. #Dapagliflozin and canagliflozin have demonstrated benefit in dedicated renal outcomes studies. Empagliflozin has demonstrated reduction in CKD progression in CV outcomes trials. +Weight loss is greatest with semaglutide > liraglutide >dulaglutide >exenatide >lixisenatide

ASCVD=atherosclerotic cardiovascular disease, CKD=chronic kidney disease, GLP-1RA=glucagon-like peptide-1 receptor agonist, SGLT28i=sodium-glucose cotransporter-2 inhibitor, AGI=alpha-glucosidase inhibitor, SFU=sulfonylurea, TZD=thiazolidinedione

Ohio Medicaid Formulary

	Preferred	Step Therapy*
Basal insulin	Lantus or Levemir	Tresiba
Bolus insulin	Humalog, Novolog Humulin R, U500	
Premix	Lispro or Aspart Premix	
Sulfonylurea	Glimepiride, glipizide, glyburide	
Glinide	Repaglinide, nateglinide	
DPP4i		Sitagliptin, Linagliptin
SGLT2i		Empagliflozin
GLP-1RA		Liraglutide, Dulaglutide
Amylin analog		Pramlintide
Thiazolidinedione	Pioglitazone	
Alpha glucosidase inhibitor	Acarbose	Miglitol

Colesevalem is first-line for hyperlipidemia in setting of DM
Cycloset is not listed
*Inadequate response to metformin or failure of preferred agent

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

	Metformin	SFU	TZD	DPP4i	SGLT2i	GLP-1RA	Insulin
Efficacy	++	++	++	+	++	+++	+++
Hypoglycemia	-	+	-	-	-	-	+
Weight	-	↑	↑	-	↓	↓↓	↑
Side Effect	GI, lactic acidosis	Hypoglycemia	Edema, Fracture	Arthralgia	GU, dehydration, DKA, fracture	GI	Hypoglycemia
MACE benefit*	+/-	-	+/-	-	+	+	-
Heart Failure benefit	-	-	^	^	+	+/-	-
Renal benefit*	-	-	+/-	+/-	++	+	-
Cost	↓	↓	↓	↑	↑	↑	↑

SFU=sulfonylurea, TZD=thiazolidinedione, DPP4i=dipeptidyl peptidase inhibitor, SGLT2i=sodium glucose cotransporter-2, GLP-1RA=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). *Benefits for overall MACE, MACE components, and renal outcomes vary by glucose lowering agent within class. GLP-1RA but not SGLT2i demonstrate reductions in stroke and pioglitazone reduces risk of stroke in persons with insulin resistance. While all SGLT2i have shown reductions in hospitalizations for heart failure in cardiovascular outcomes trials, empagliflozin and dapagliflozin have shown benefit in dedicated HF studies. Likewise, while empagliflozin has demonstrated reduction in chronic kidney disease progression in cardiovascular outcomes trials, dapagliflozin and canagliflozin have demonstrated benefit in dedicated renal outcomes studies. +=Yes, -=No, +/-=weak evidence, ↑=increased/high, ↓=decreased/low, ^increased risk of heart failure with TZDs, saxagliptin, possibly alloglipti

GLP-1 Receptor Agonists (GLP-1RA)

Consider GLP-1RA as combination therapy with metformin, and particularly in patients with established ASCVD or who have high cardiovascular risk. It is important to weigh the following risks and benefits to determine the best fit for the patient.

Benefits:

- Very high efficacy with low risk of hypoglycemia.
- Proven to reduce weight.
- No renal adjustment (only with exenatide and lixisenatide).
- GLP-1RA with proven ASCVD benefits are preferred (liraglutide, dulaglutide, semaglutide). Cardiovascular outcomes trials demonstrate reductions in major adverse cardiovascular events, preferred for patients with history of stroke.
- Recommend before starting basal insulin: similar efficacy and lower risk of hypoglycemia or weight gain.

Risks:

- Should be titrated gradually to minimize GI side effects.
- Possible risk of thyroid C-cell tumors (rodent studies only) and acute pancreatitis.
- Common side effects are nausea, vomiting, and diarrhea.
- High cost.

SGLT-2 Inhibitors

Consider SGLT-2 inhibitors in combination therapy with metformin if A1C is still above target in patients with heart failure or chronic kidney disease (eGFR 30-60 ml/min/1.73m^2). 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 semaglutide[8] (estimated treatment difference 0.4% at 26 weeks and 0.5% at 52 weeks and a significantly greater proportion achieved A1C <7.0% at 26 weeks (67 vs. 40%) and 52 weeks (66 vs. 43%).
- Proven to reduce weight.
- Renal dose adjustment is required. Glucose lowering effects are reduced in chronic kidney disease (CKD), and are negligible below eGFR <45 ml/min/1.73m^2
- SGLT-2 inhibitors, which are proven to reduce heart failure (HF) (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) and/or CKD (dapagliflozin, empagliflozin, canagliflozin), are preferred.
- Have proven cardiovascular benefits (reduction in major adverse cardiovascular events, HF [in patients with known HF with reduced ejection fraction[9,10] as well as patients without known HF[11]]), even at reduced eGFR.
- Slows progression of nephropathy and CKD, even at reduced eGFR and in combination with ACEi/ARB.

Risks:

- Canagliflozin is associated with possible increased risk of amputation (6.3 vs. 3.4 participants per 1,000 patient-years in the CANVAS trial[12], though no increase in risk was observed in CREDENCE[13]).
- Have increased risk of genital mycotic infections, polyuria, volume depletion, hypotension, and elevated LDL.
- Post-marketing cases of Fournier's gangrene have been reported[14] but increased risk has not been observed in clinical trials or epidemiologic studies.[15-17]
- High cost.

DPP-4 Inhibitors

Consider DPP-4 Inhibitors as a combination therapy to metformin and/or insulin. It is important to weigh the following risks and benefits to determine the best fit for the patient.

Benefits:

- DPP-4 Inhibitors are indicated in
  - » patients with established ASCVD, HF and or CKD (not saxagliptin or alogliptin) if GLP-1RA or SGLT2i can't be used.
  - » patients without established ASCVD, HF or CKD with A1C above target.
- Intermediate efficacy and no impact on weight.
- Renal adjustment is required except for Linagliptin.
- Consider with elderly patients.

Risks:

- No cardiovascular benefits, potential risk for HF with saxagliptin and possibly alogliptin.
- No benefits with progression of CKD.
- Possible increased risk of acute pancreatitis[18] and arthralgia (mechanism is not clear).[19]
- High cost.

Advancing to Insulin Therapies (Figure 2)[1]

Basal Insulin

Consider starting basal insulin in the following situations:

- A1C above target 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 unit/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 per dL (goals should be individualized) or up to 0.5 unit/kg/day.
  - » Associated with risk of weight gain and hypoglycemia.
  - » Refer for education focusing on glucose self-monitoring and prevention/treatment of hypoglycemia.

Prandial Insulin

Basal Plus Regimen

Consider prandial insulin if A1C or postprandial glucose readings are above target despite:

- Accurate titration of basal insulin with fasting blood glucose (FBG) at goal **OR**
- Total dose of basal insulin exceeds 0.5 unit/kg/day **AND**
- Patient is already taking GLP-1RA 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.
  - » Should be taken 10-15 minutes before starting (preferred) or within 10 minutes of finishing 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, 1/3 of dose before dinner.

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.

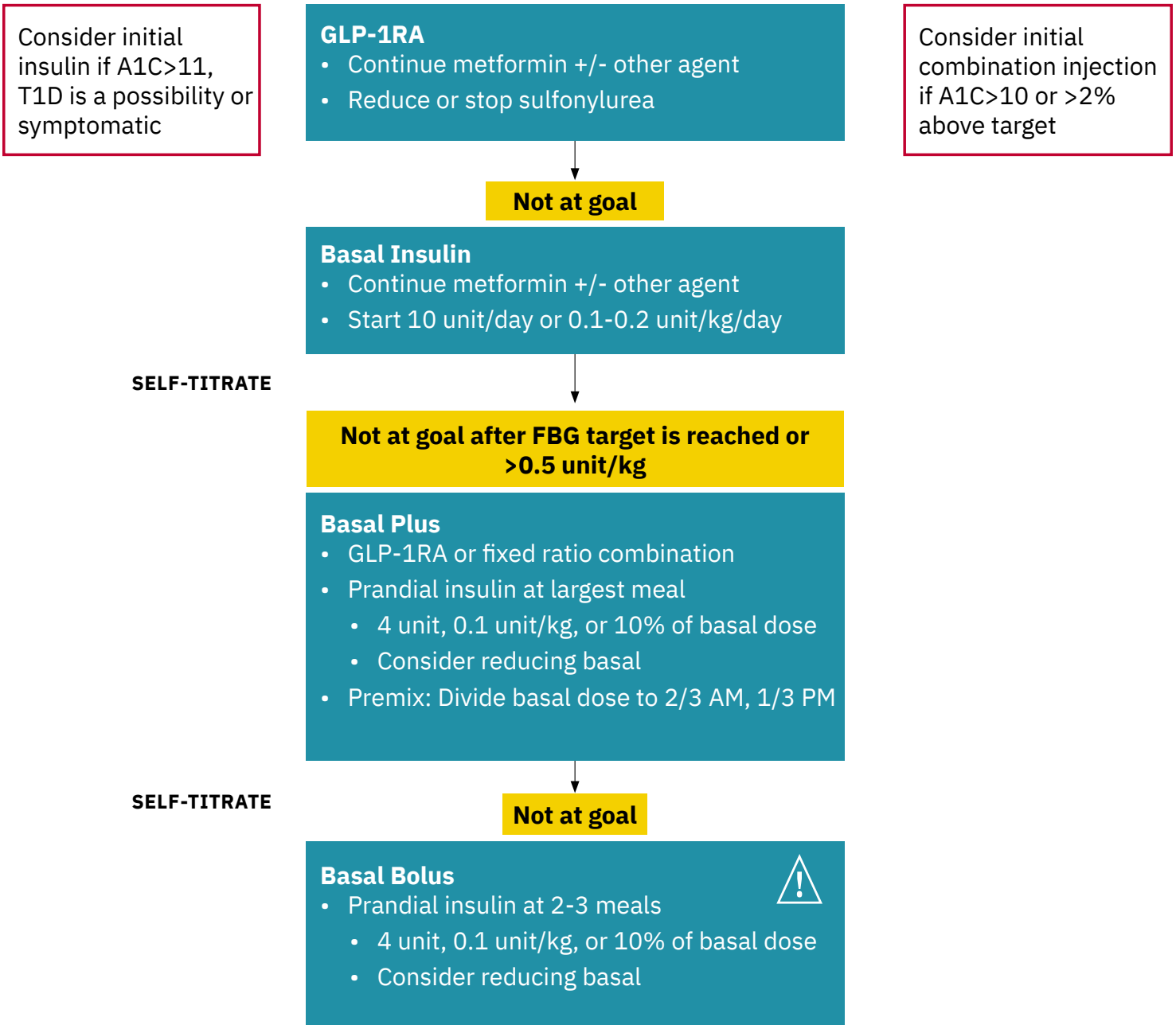
Flexible Meal Dosing

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 unit for a big meal [60 grams carbs], three unit 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



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