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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 while 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 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* treatment goals
- Weight loss potential
- Other factors: risk of hypoglycemia, cost, side effects/tolerability

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 and the number of individual agents is extensive (Table 1). 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 often the drug of choice, along with lifestyle modifications, for initial treatment of new onset T2D. However, other medications (such as sodium-glucose cotransporter-2 inhibitors [SGLT2i] or glucagon-like peptide-1 receptor agonists [GLP-1 RA]), with or without metformin (based upon the need for additional glucose-lowering) may be appropriate as initial therapy, particularly for individuals who are at high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure, and/or kidney disease.

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

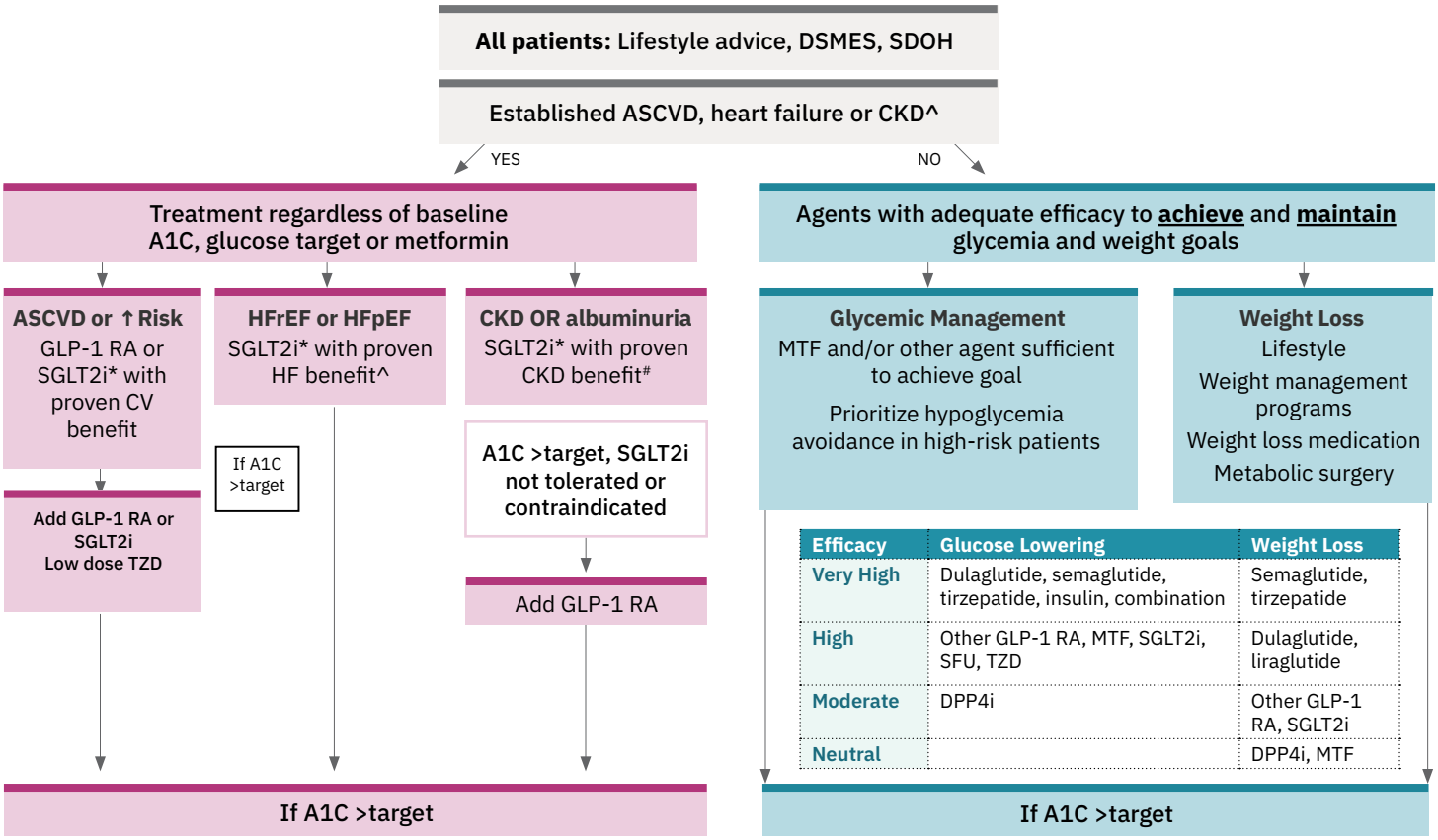
Combination Therapy

Initial combination therapy is indicated in patients with an A1C level 1.5% above target 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 targets after three months of monotherapy or dual therapy. 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 (sulfonylurea, pioglitazone, human insulin) 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. 2022 Guidelines: Pharmacologic Management Algorithm *As of November 2022*

American Diabetes Association/European Association for the Study of Diabetes recommendations for the treatment of hyperglycemia in people with diabetes[3]



*If adequate eGFR, ^Empagliflozin/dapagliflozin have shown benefit in dedicated HF studies. Canagliflozin/ertugliflozin demonstrated reduction in hospitalization for HF in cardiovascular outcomes trials. #Dapagliflozin/canagliflozin/empagliflozin demonstrated benefit in dedicated renal studies.
*start if eGFR >20 mL/min/1.73 m^2, continue until HD or transplant.

DSMES=diabetes self-management education and support, SDOH=social determinants of health, ASCVD=atherosclerotic cardiovascular disease, HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, CV=cardiovascular, CKD=chronic kidney disease, GLP-1 RA=glucagon-like peptide-1 receptor agonist, SGLT2i=sodium-glucose cotransporter-2 inhibitor, TZD=thiazolidinedione, SFU=sulfonylurea, MTF=metformin.

Table 1. 2022 Ohio Medicaid Preferred Diabetes Formulary *As of July 2022*

Drug Class	Preferred
Non-Insulin	
Metformin and combination	Actoplus Met XR (pioglitazone/metformin), glipizide/metformin, glyburide/metformin, Invokamet (canagliflozin/metformin), Janumet (sitagliptin/metformin), Janumet XR, Jentadueto (linagliptin/metformin), metformin, metformin ER (generic of Glucophage XR), pioglitazone/metformin, repaglinide/metformin, Synjardy (empagliflozin/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), Invokana (canagliflozin), 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, Novolog 70/30 (aspart protamine/aspart)

[5] 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*	+/-	-	+/-	-	+	+	-
Heart failure benefit	-	-	^	^	+	+/-	-
Renal benefit*	-	-	+/-	+/-	++	+	-
Cost	↓	↓	↓	↑	↑	↑	↑

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). *Benefits for overall MACE, MACE components, and renal outcomes vary by glucose lowering agent within class. GLP-1 RA 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 alloglitpin

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

Drug	ASCVD	Heart Failure	Chronic Kidney Disease
SGLT-2i	Canagliflozin Empagliflozin	Canagliflozin Empagliflozin Dapagliflozin Ertugliflozin	Canagliflozin* Dapagliflozin* Empagliflozin*
GLP-1 RA	Dulaglutide Liraglutide Semaglutide (SQ)		

* benefit driven by reduction in proteinuria

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

Consider GLP-1 RA as monotherapy or combination therapy, particularly in patients needing high glucose lowering or weight loss efficacy, or those with established ASCVD, or who have high cardiovascular risk (Table 3). 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).
- Preferred for patients with history of stroke.
- Agents with proven ASCVD benefits (liraglutide, dulaglutide, SQ semaglutide) are preferred in persons with known ASCVD or at highest cardiovascular risk.
- Recommend before starting basal insulin: similar efficacy and lower risk of hypoglycemia or weight gain.

Risks:

- Common side effects are nausea, vomiting, and diarrhea; titrate gradually to minimize.
- Possible risk of thyroid C-cell tumors (rodent studies only) and acute pancreatitis.
- Gallbladder disease (related to weight loss)
- High cost.

SLGT-2i

Consider SLGT-2i as monotherapy or combination therapy, and particularly in patients with heart failure, ASCVD, or chronic kidney disease (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 semaglutide.[8]
- 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.
- 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 blocker (ACEi/ARB).

Risks:

- Increased risk of genital mycotic infections, polyuria, volume depletion.
- Canagliflozin is associated with possible increased risk of amputation in the CANVAS trial, though no increase in risk was observed in CREDENCE or with other SGLT2i.[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 elderly patients.

Risks:

- No cardiovascular benefits; potential risk for HF with saxagliptin and possibly alogliptin.
- No renal benefits.
- 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 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 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) or up to 0.5 unit/kg/day.
  - » Associated with risk of weight gain and hypoglycemia.
  - » Refer for education focusing on glucose monitoring and prevention/treatment of hypoglycemia
- Continue metformin, GLP-1 RA, and/or SGLT-2i.

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**
- Total dose of basal insulin exceeds 0.5 unit/kg/day **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.
  - » 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

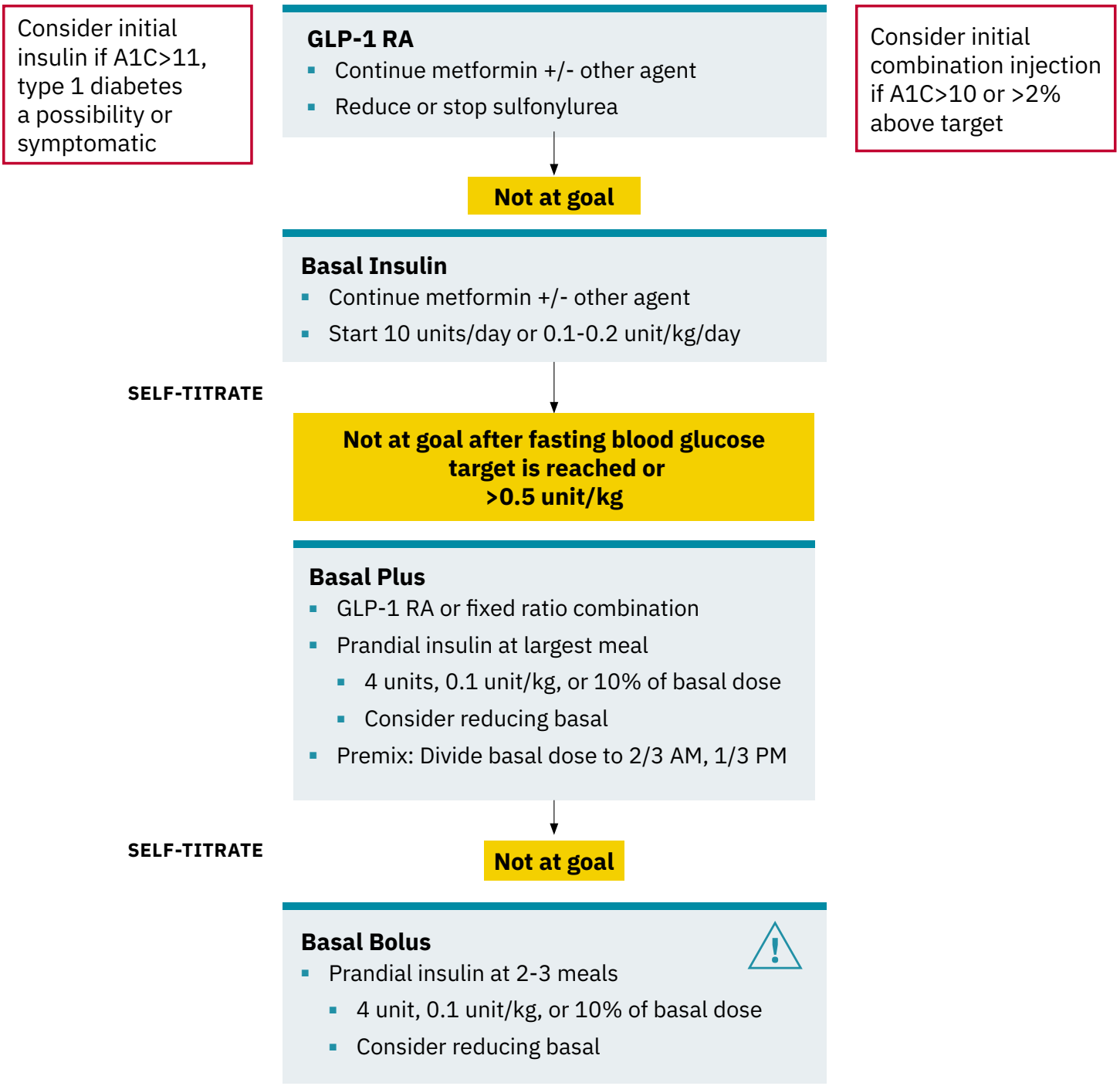
- If A1C is still elevated on a basal plus regimen, add prandial insulin to 2-3 meals per day.
- Total daily prandial insulin dose should be 40-60% of the total daily dose of insulin.
- Counsel the patient to maintain a consistent carbohydrate diet.

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 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/best-practices/diabetes-management/beyond-the-a1c-targets-for-blood-glucose-and-methods-of-measurement
- **Minimizing Hypoglycemia Risk to Improve Cardiovascular Health**
  cardi-oh.org/best-practices/diabetes-management/minimizing-hypoglycemia-risk-to-improve-cardiovascular-health
- **Managing Diabetes in Older Populations: Targets, Challenges, and Medications**
  cardi-oh.org/best-practices/diabetes-management/managing-diabetes-in-older-populations-targets-challenges-and-medications
- **Talking With Your Patients About Diabetes Pharmacotherapy: Side Effects and Adverse Events**
  cardi-oh.org/best-practices/patient-adherence/talking-with-your-patients-about-diabetes-pharmacotherapy-side-effects-and-adverse-events
- **Navigating Barriers to Medication Access**
  cardi-oh.org/best-practices/patient-adherence/navigating-barriers-to-medication-access
- **Addressing Common Barriers to Insulin Initiation and Use**
  cardi-oh.org/best-practices/patient-adherence/addressing-common-barriers-to-insulin-initiation-and-use
- **Implementing Shared Decision Making in Clinical Practice**
  cardi-oh.org/best-practices/patient-adherence/implementing-shared-decision-making-in-clinical-practice
- **Shared Decision Making and Diabetes Care**
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- **Addressing Clinical Inertia in Diabetes Care**
  cardi-oh.org/best-practices/patient-adherence/addressing-clinical-inertia-in-diabetes-care
- **Diabetes Self-Management Education and Support: Provider Use and Patient Benefits**
  cardi-oh.org/best-practices/lifestyle/diabetes-self-management-education-and-support-provider-use-and-patient-benefits
- **Social Determinants of Health**
  cardi-oh.org/best-practices/social-determinants-of-health

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