

Type 2 Diabetes Step-Wise Therapy

All patients at diagnosis: Start lifestyle interventions, add metformin & titrate to max dose (if not contraindicated), refer to DM education for lifestyle change education, and complete DM health maintenance. Reassess in 3 months.

ASCVD risk predominates?

HF/CKD risk predominates?

A1C ≥ 9% or Symptomatic Hyperglycemia

GLP-1 agonists: Liraglutide; Semaglutide; Dulaglutide
OR
SGLT2 inhibitors: Empagliflozin > Canagliflozin > Dapagliflozin

Start with agent with evidence of reducing HF and/or CKD progression
1st - SGLT2 inhibitors: Empagliflozin > Canagliflozin
2nd - GLP-1 agonist: Liraglutide; Semaglutide; Dulaglutide

At diagnosis: Strongly consider insulin, especially if BMI < 25 or symptomatic; OR consider 2nd agent to metformin

Add additional agent by prioritizing individual patient characteristics

PATIENT CHARACTERISTIC	CHOICE OF AGENT
<ul style="list-style-type: none"> Degree of hyperglycemia Risk of hypoglycemia Overweight or obesity Renal dosing Preferences & medication access NASH 	<ul style="list-style-type: none"> Consider A1c lowering potential Rare hypoglycemia Weight loss or weight neutral See below therapeutic considerations, consider eGFR See cost column and consider access Consider pioglitazone or liraglutide

Class*	Expected A1c ↓ (%)	Hypo-glycemia	Effect on Wt	Effect on CVD Outcomes	Other Considerations	Cost
Insulin	Greatest ↓	Yes	↑	Neutral: glargine (Lantus, Basaglar), detemir (Levemir), degludec (Tresiba)	Lowest cash price is ReliOn brand at Sam's Club or Wal-Mart (R, NPH, and 70/30)	Moderate to high
Sulfonylureas	1-1.5	Yes	↑	Unknown: glipizide, glimepiride, glyburide	↑ hypoglycemia risk: glyburide & glimepiride	Low (generic)
Thiazolidinediones	1-1.5	None as monotherapy	↑	Improves: * pioglitazone (Actos) Neutral: * rosiglitazone (Avandia) <small>*Based on CV morbidity/mortality outcomes, but does ↑ HF risk</small>	Edema, ↑HF risk; Pioglitazone: ↓TG, debate if ↑ bladder cancer risk; ↑ fracture risk Rosiglitazone: ↑ LDL	Low (generic)
GLP-1R agonists	1-1.5	None as monotherapy	↓	Improves: liraglutide (Victoza), semaglutide (Ozempic), dulaglutide (Trulicity), exenatide ER (Bydureon) Neutral: lixisenatide (Adlyxin) Unknown: exenatide (Byetta)	GI side effects, ↓ PP BG, Exenatide not recommended CrCl < 30 and lixisenatide not recommended CrCl < 15 Weekly options: semaglutide, dulaglutide, exenatide ER	High
SGLT2 inhibitors	0.5-1	None as monotherapy	↓	Improves: empagliflozin (Jardiance), canagliflozin (Invokana), dapagliflozin (Farxiga)	↓ BP, Do not initiate with eGFR < 45, Contraindicated with eGFR < 30, volume depletion, GU infections, DKA, ↓ progression of renal disease Canagliflozin: ↑ risk of amputations and bone fractures	High
DPP-4 inhibitors	0.5-1 (actual effect may be ≤ 0.7)	None as monotherapy	Neutral	Neutral: sitagliptin (Januvia), saxagliptin (Onglyza), alogliptin (Nesina) Unknown: linagliptin (Tradjenta)	Saxagliptin and alogliptin associated with increased HF admissions. Initiate at max dose unless renal dose adjustment indicated. Linagliptin: no renal adjustment.	High
Meglitinides	0.5-1	Yes	↑	Unknown: nateglinide (Starlix), repaglinide (Prandin)	↓ PP BG, can replace sulfonylurea if hypoglycemic or irregular meal schedule	Moderate (generic)
Bile acid sequestrant (colesevelam)	0.5-1	None as monotherapy	Neutral	Unknown: colesevelam (Welchol)	↓ LDL, ↑TG, May ↓ other med absorption, constipation	Moderate (generic)
Alpha-glucosidase inhibitors	0.5-1	None as monotherapy	Neutral	Unknown: acarbose (Precose), miglitol (Glyset)	GI side effects, ↓ PP BG	Low to moderate (generic)

*Hierarchal order based on A1c impact. When A1c effect is similar, cost and CV benefits considered. Updated 07.19: Patrick Gregory, PharmD, Ben Smith, PharmD, Susan Spratt, MD, Lee Jackson, PharmD

References: 1. 2019 ADA Standards of Medical Care in Diabetes. Diabetes Care 2019 Jan; 42(Suppl. 1): S1-S2. 2. Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update. Canadian Diabetes Association. Can J Diabetes. 2016 Jun;40(3):193-5. 3. AACE and ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm: 2019 Executive Summary. Endocr Pract 2019 Jan;25(1):69-100. 4. PL Detail-Document, Drugs for Type 2 Diabetes. Pharmacist's Letter/Prescriber's Letter. June 2015. 5. Professional Resource, Diabetes Medications and Cardiovascular Impact. Pharmacist's Letter/Prescriber's Letter. August 2016.