MOUNT CARMEL Health Partners

Diabetes Type 2 Clinical Guideline

Definition: Diabetes is a multifactorial metabolic disease that is influenced by environmental and genetic factors characterized by impairment of insulin secretion from pancreatic B-cells and insulin resistance in peripheral tissues.
Causes: Diabetes Type 2 is due mostly to lifestyle factors and genetics.

Screening Recommendations

Population	Method	Frequency
Patients age 45 and older	FPG or two-hour OGTT, HbA1c	If normal, every 3 years at minimum, annually if prediabetes.
Adults any age with BMI greater than 25 AND one or more risk factors.	FPG or two-hour OGTT, HbA1c	If normal, every 3 years at minimum, annually if prediabetes.
Overweight children (BMI greater than 85th percentile) with ANY 2 risk factors	FPG preferred for children	Initiate screening at age 10 or at onset of puberty, whichever comes first. If normal, every 3 years at minimum

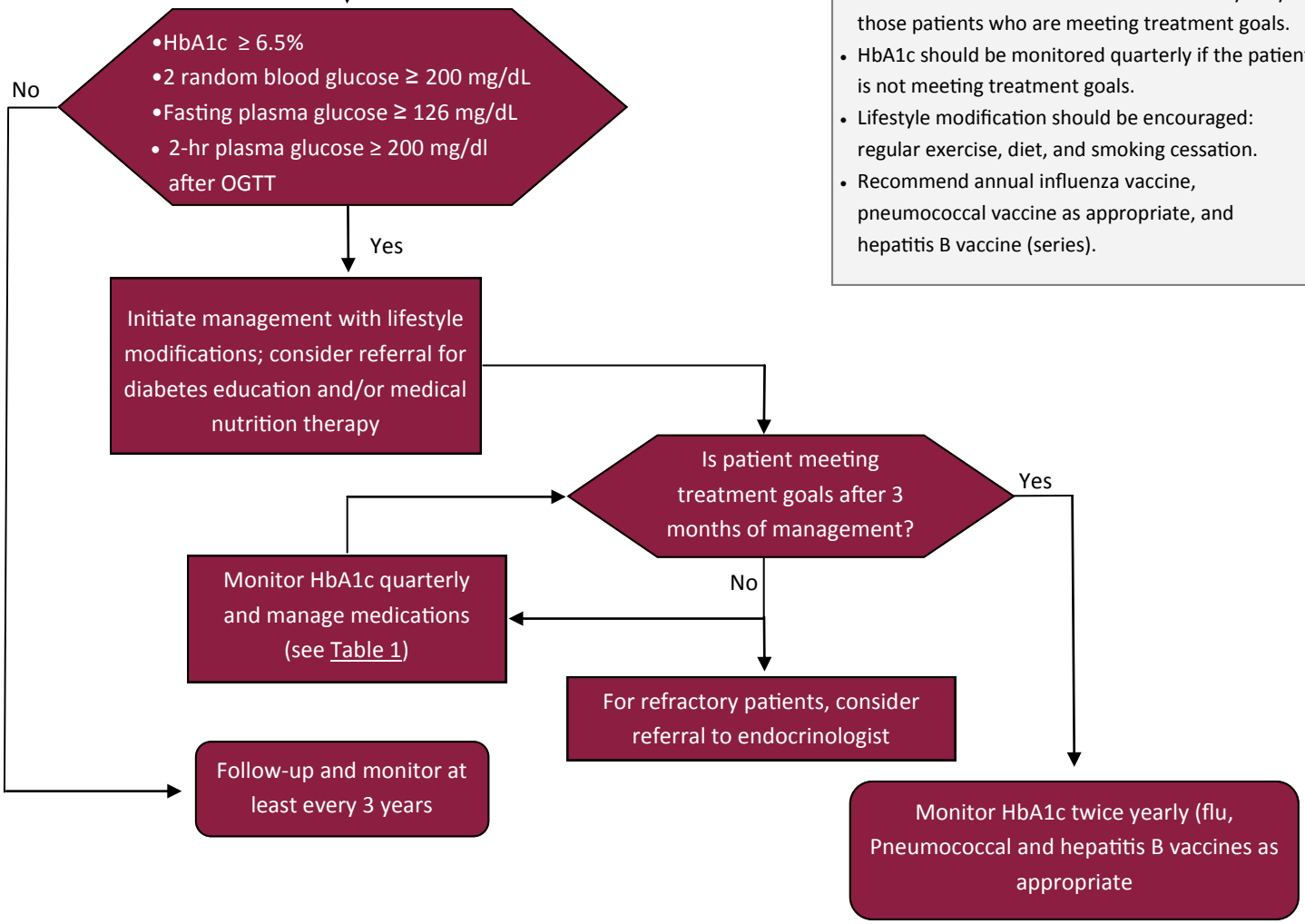
Quick Guide to Diabetes Care

Diagnostic criteria:

- HbA1c greater than or equal to 6.5%
- Fasting glucose greater than or equal to 126 mg/dL
- 2-hr oral glucose tolerance test greater than or equal to 200 mg/dL.
- 2 random plasma glucose ≥200 (or 1 random plasma glucose ≥200 + signs/symptoms of hyperglycemia)

Goals and Monitoring:

- A reasonable treatment goal for most non-pregnant adults is HbA1c < 7.0%[1]
- HbA1c should be monitored at least twice yearly in those patients who are meeting treatment goals.
- HbA1c should be monitored quarterly if the patient is not meeting treatment goals.
- Lifestyle modification should be encouraged: regular exercise, diet, and smoking cessation.
- Recommend annual influenza vaccine, pneumococcal vaccine as appropriate, and hepatitis B vaccine (series).



[1] Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children or older adults, and individuals with comorbid conditions. More stringent goals may be appropriate for certain populations.

Diagnosis

- HbA1c greater than or equal to 6.5%
  OR
- Fasting plasma glucose (FPG) greater than or equal to 126 mg/dL
  OR
- 2-hour glucose tolerance test (GTT) greater than or equal to 200 mg/dL
  OR
- Two random blood glucose measurements 200mg/dL greater than 200 mg/dL (second test for confirmation)

Risk Factors

Intrinsic

- Age greater than 45
- Ethnic origin/race
- History of hypertension or cardiovascular disease
- Polycystic ovary syndrome
- History of gestational diabetes; baby over 9 lbs.
- Family history of diabetes
- Metabolic syndrome

Extrinsic

- Excess body weight (BMI greater than 25)
- Pre-diabetes diagnosis
- Diet (saturated fats and refined sugars)
- Physical inactivity
- Heavy alcohol use (more than two drinks/day)
- Tobacco use

Treatment

- Appropriate history and physical exam upon diagnosis.
- Monitor HbA1c twice yearly for those meeting treatment goals.
- Monitor HbA1c quarterly for those not meeting treatment goals.
- Treat to desired goal of HbA1c less than 7 percent [1]
- Emphasis on lifestyle modification as the foundation, with medication added when treatment goal otherwise not met.
- Review self-management of finger-stick blood sugar monitoring.
- Reinforce lifestyle modification (such as diet, exercise, and smoking cessation).
- Assess compliance to therapy.
- Positive microalbuminuria screen is treated with ACE/ARB pharmacological therapy.
- American Diabetes Association recommends a blood pressure goal of 140/80.
- Moderate-high intensity statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for patients with diabetes:
  - with overt ASCVD
  - without ASCVD and have one or more other ASCVD risk factors (family history of ASCVD, hypertension, smoking, dyslipidemia, or albuminuria).
- For low-risk patients who are over the age of 40 years, moderate-intensity statin therapy should be considered in addition to lifestyle therapy.
- Daily low-dose aspirin therapy is recommended as a primary prevention in men and women ≥50 years old with at least one ASCV risk factor and as secondary prevention in all patients with diabetes and history of ASCVD. If contraindicated, clopidogrel or ticlopidine are suitable alternative for patients at high risk for cardiovascular disease.

Treatment *(continue…)*

- If patients with inadequate diabetic controlled and are overweight consider metabolic Surgery.
  - BMI (body mass index) ≥40 kg/m² (BMI ≥37.5 kg/m² in Asian Americans)
  - BMI 35 to 39 kg/m² (BMI 32.5 to 37.4 kg/m² in Asian Americans) when hyperglycemia is inadequately controlled by lifestyle measures and optimal medical therapy

Evaluation

- Assess risk factors, comorbidities, and identifiable causes of hyperglycemia
- Conduct a comprehensive history and physical
- Obtain tests: urinalysis, fasting blood glucose, HbA1c, and renal function panel with GFR, microalbuminuria
- Identify and treat appropriate additional comorbid conditions:
  - Hypertension
  - Dyslipidemia
  - Cardiovascular disease
  - Depression
  - Disordered eating behaviors
- Assess for metabolic syndrome

Annual Tests

- Dilated retinal examinations
- Diabetic foot exam
- Lipid profile
- Renal panel with GFR
- Microalbuminuria
- Consider ECG

Follow-up

Assess treatment and update plan of care quarterly until stable, and twice more annually depending on classification and patient comorbidities. Reinforce lifestyle modification every 12 months or more frequently if needed.

- Nutrition: reduce calories, reduce intake of dietary fat, 14 g fiber daily, increase whole grain foods, monitor carbohydrate intake, weight reduction as appropriate with goal of normal BMI range (18.5 - 24.9)
- Exercise: Regular aerobic activity, e.g., walk 150 minutes per week, resistance training 3 times per week, adapt per patient's ability
- Counseling:
  -- Limit alcohol consumption to less than 2 drinks per day
  -- Smoking cessation counseling, offer additional resources to quit and advise impact of smoking
  -- Adherence to medication regimen and self-monitoring of blood glucose levels
  -- Psychological counseling for emotional well-being
- Effective self-management and quality of life are the key out comes of diabetes self-management education
- Stress importance of annual administration of influenza vaccine
- Pneumococcal vaccine if not already vaccinated
- Hepatitis B vaccine ages 19 - 59, after 59 at the discretion of the physician

[1] Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children or older adults, and individuals with comorbid conditions. More stringent goals may be appropriate for certain populations.

Diabetes Type 2 Clinical Guideline: Treatment should begin by making therapeutic lifestyle changes to include weight reduction, diet modification (reduce saturated fats and simple carbohydrates, and increase fiber and complex carbohydrates), reduction in alcohol consumption, cessation of tobacco use, and increased physical activity levels.

Table 1 -- Medication Management

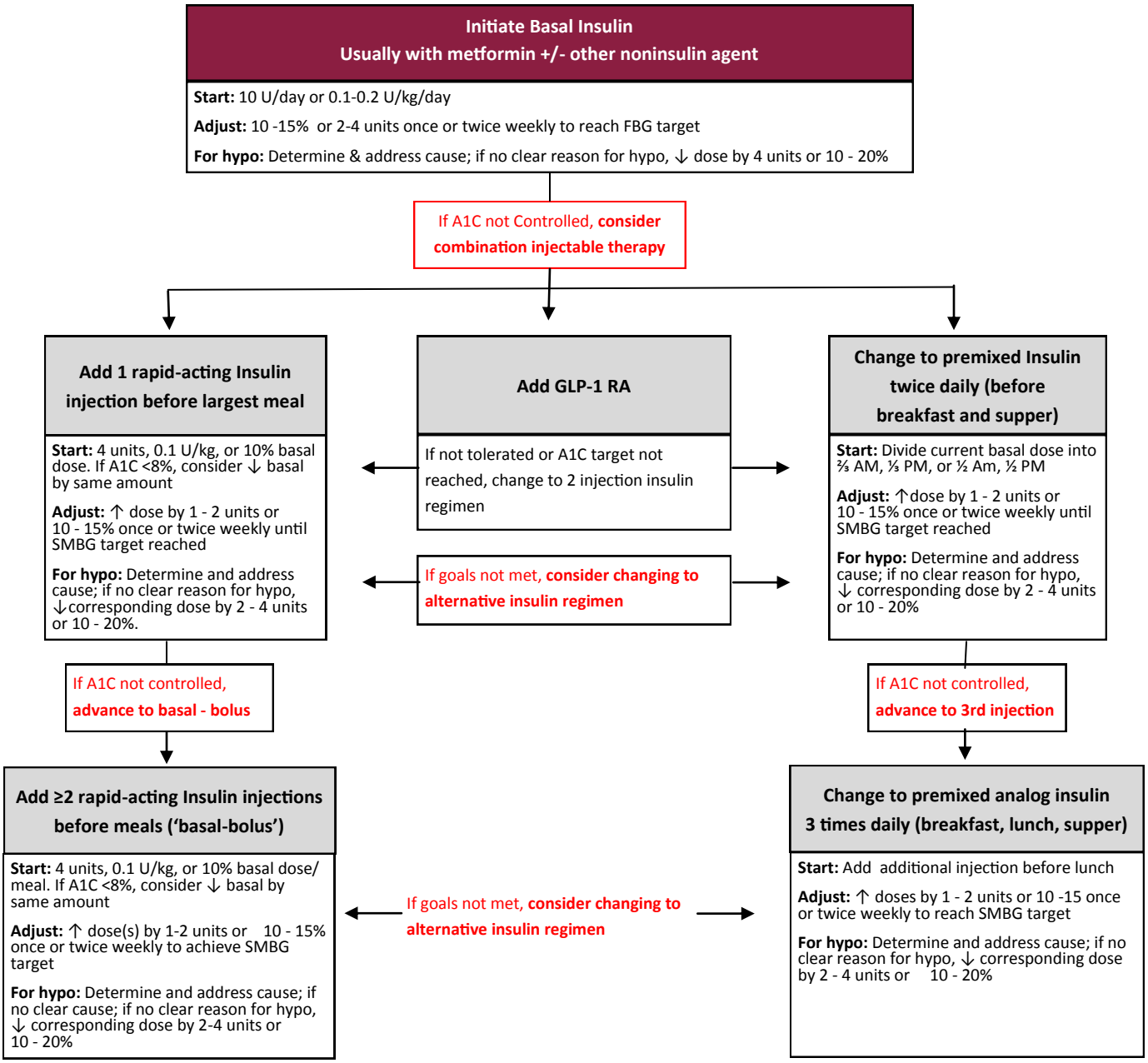
Healthy eating, weight control, increased physical activity, and diabetes education						
Monotherapy	**Metformin**	Metformin is contraindicated in patients with a estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73m². (See Table 2)				
Efficacy	High					
Hypo risk	Low risk					
Weight	Neutral/loss					
Side effects	GI/lactic acidosis					
Costs	Low					
If A1C target is not achieved after ~3 months of monotherapy, proceed to 2-drug combination. (Order is not meant to denote any specific preference; choice is dependent upon a variety of patient– and disease– specific factors.)						
Dual Therapy†	**Metformin +**	**Metformin +**	**Metformin +**	**Metformin +**	**Metformin +**	**Metformin +**
	Sulfonylurea	**Thiazolidinedione**	**DPP-4 inhibitor**	**SGLT2 inhibitor**	**GLP-1 receptor agonist**	**Insulin (basal)**
Efficacy	High	High	Intermediate	Intermediate	High	Highest
Hypo risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Loss	Gain
Side effects	Hypoglycemia	Edema, HF, Fxs	Rare	GU, dehydration	GI	Hypoglycemia
Costs	Low	Low	High	High	High	Variable
If A1C target is not achieved after ~3 months of dual therapy, proceed to 3-drug combination. (Order is not meant to denote any specific preference; choice is dependent upon a variety of patient– and disease– specific factors.)						
Triple Therapy	**Metformin +**	**Metformin +**	**Metformin +**	**Metformin +**	**Metformin +**	**Metformin +**
	Sulfonylurea +	**Thiazolidinedione +**	**DPP-4 inhibitor +**	**SGLT2 inhibitor +**	**GLP-1 receptor agonist +**	**Insulin (basal) +**
	TZD	SU	SU	SU	SU	TZD
	or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
	or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or Insulin§	or SGLT2-i
	or GLP-1-RA	or GLP-1-RA	or Insulin§	or Insulin§		or GLP-1-RA
	or Insulin§	or Insulin§				
If A1C target is not achieved after ~3 months of triple therapy and patient: 1) is on oral combination, move to injectables; 2) is on GLP-1-RA, add basal insulin; or 3) is on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients, consider adding TZD or SGLT2-i.						
Combination Injectable Therapy‡	**Metformin + Basal insulin + Mealtime Insulin or GLP-1-RA**					

Antihyperglycemic therapy in type 2 diabetes: general recommendations. The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i: DPP-4; fxs: fractures; GI: gastrointestinal; GLP-1-RA: GLP-1 receptor agonist; GU: genito-urinary; HF: heart failure; hypo: hypoglycemia; SGLT2-i: SGLT2 inhibitor; SU: sulfonylurea; TZD: thiazolidinedione. †Consider starting at this stage when A1C is ≥ 9%. ‡Consider starting at this stage when blood glucose is ≥ 300-350 mg/dL (16.7-19.4 mmol/L) and/or A1c is ≥ 10-12%, especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec).
Source: "Diabetes Care." The Journal of Clinical and Applied Research and Education, January 2015.

Table 2: Proposed recommendations for use of metformin based on eGFR

eGFR level (mL/min per 1.73 m^2)	Action
≥ 60	No renal contraindication to metformin Monitor renal function annually No dosage adjustment necessary
< 60 and ≥ 45	Continue use. Increase monitoring of renal function (every 3-6 months) No Dosage adjustment necessary
< 45 and ≥ 30	Prescribe metformin with caution. Use lower dose (e.g., 50% or half-maximal dose). Closely monitor renal function (every 3 months). Do not start new patients on metformin.
< 30	Stop metformin.

Figure 1: Combination injectable therapy algorithm for type 2 diabetes



Source: American Diabetes Association Dia Care 2017;40:S64-S74

Table 4: Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes.

Class	Compounds *(Brand Names)*	Cellular Mechanisms	Primary Physiological Action(s)	Advantages	Disadvantages	Cost
Biguanides	Metformin *(Fortamet, Glucophage, Glucohage XT, Glumetza, Riomet)*	Activates AMP-kinase	↓Hepatic glucose production	• Extensive experience • No hypoglycemia • ↓ASCVD events (UKPDS) • Weight neutral	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.	Low
Sulfonylureas	2nd Generation • Glyburide *(DiaBeta, Micronase, Glyron, Glynase PresTab)* • Glipizide *(Glucotrol)* • Glimepiride *(Amaryl)*	Closes K ATP channels on ß-cell plasma membranes	↑Insulin secretion	• Extensive experience • ↓Microvascular risk (UKPDS)	• Hypoglycemia • ↑Weight • ?Blunts myocardial ischemic preconditioning • Low durability	Low
Meglitinides (glinides)	• Repaglinide (*Prandin)* • Nateglinide *(Starlix)*	Closes K ATP channels on ß-cell plasma membranes	↑Insulin secretion	• ↓Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑Weight • ?Blunts myocardial ischemic preconditioning • Frequent dosing schedule	Moderate
TZDs	• Pioglitazone‡ *(Actos)* • Rosiglitazone§ *(Avandia)*	Activates the nuclear transcription factor PPAR-y	↑Insulin sensitivity	• No hypoglycemia • Durability • ↑HDL-C • ↓Triglycerides • ↓ASCVD events (PROactive, pioglitazone)	• ↑Weight • Edema/heart failure • Bone fractures • ↑LDL-C (rosiglitazone) • ? ↑MI (meta-analyses, rosiglitazone)	Low
α-Glucosidase inhibitors	• Acarbose *(Precose)* • Miglitol *(Glyset)*	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/ absorption	• No hypoglycemia • ↓Postprandia glucose excursions • ↓ASCVD events (STOP-NIDDM) • Nonsystemic	• Generally modest A1C efficacy • Gastrointestinal side effects (flatulence, diarrhea) • Frequent dosing schedule	Moderate
DPP-4 inhibitors	• Sitagliptin *(Januvia)* • Saxagliptin *(Onglyza)* • Linagliptin *(Tradjenta)* • Alogliptin *(Nesina)*	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	• ↑Insulin secretion (glucose-dependent) • ↓Glucagon secretion (glucose-dependent)	• No hypoglycemia • Well tolerated • Weight neutral	• Angioedema/urticarial and other immune-mediated dermatological effects • ?Acute pancreatitis • ? ↑Heart failure hospitalizations	High
Bile acid sequestrants	Colesevelam *(WelChol)*	Binds bile acids in intestinal tract, increasing hepatic bile acid production	• ? ↓Hepatic glucose production • ? ↑Incretin levels	• No hypoglycemia • ↓LDL-C	• Generally modest A1C efficacy • Constipation • ↑Triglycerides • May ↓absorption of other medications	High
Dopamine-2 agonists	Bromocriptine (quick release)§ *(Cycloset, Parlodel)*	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑Insulin sensitivity	• No hypoglycemia • ? ↓CVD events (Cycloset Safety Trial)	• Generally modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	High
SGLT2 inhibitors	• Canagliflozin *(Invokana)* • Dapagliflozin‡ *(Farxiga)* • Empagliflozin *(Jardiance)*	Inhibits SGLT2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glucosuria	• No hypoglycemia • ↓Weight • ↓Blood pressure • Effective at all stages of T2DM • Reduce mortality in patients with CVD (empagliflozin)	• Genitourinary infections • Polyuria • Volume depletion/ hypotension/dizziness • ↑LDL-C • ↑Creatinine (transient) • DKA	High
GLP-1 receptor agonists	• Exenatide *(Bydureon, Byetta)* • Exenatide Extended release • Liraglutide *(Victoza)* • Albiglutide *(Tanzeum)* • Lixisenatide *(Adlyxin)* • Dulaglutide *(Trulicity)*	Activates GLP-1 receptors	• ↑Insulin secretion (glucose-dependent) • ↓Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑Satiety	• No hypoglycemia • ↓Weight • ↓Postprandial glucose excursions • ↓Some cardiovascular risk factors • Reduce mortality in patients with CVD (liraglutide)	• Gastrointestinal side effects (nausea, vomiting, diarrhea) • ↑Heart rate • ?Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements	High

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Table 4: Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes. *(continued)*

Class	Compounds *(Brand Names)*	Cellular Mechanisms	Primary Physiological Action(s)	Advantages	Disadvantages	Cost
Amylin mimetics	Pramlintide§ *(Symlin)*	Activates amylin receptors	• ↓Glucagon secretion • Slows gastric emptying • ↑Satiety	• ↓Postprandial glucose excursions • ↓Weight	• Generally modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	High
Insulins	• Rapid-acting analogs - Lispro *(HumaLog)* -Aspart *(NovoLog)* -Glulisine *(Apidra, Apidra SoloStar)* • Short-acting -Human Regular • Intermediate-acting -Human NPH • Basal insulin Analogs -Glargine *(BASAGLAR, Lantus, Lantus SoloStar, Toujeo SoloStar)* -Detemir *(Levemir)* -Degludec *(Tresiba)* • Premixed (several types)	Activates insulin receptors	• ↑Glucose disposal • ↓Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓Microvascular risk (UKPDS)	• Hypoglycemia • Weight gain • ?Mitogenic effects • Injectable • Patient reluctance • Training requirements	Variable#

CKD: chronic kidney disease; ASCVD: atherosclerotic cardiovascular disease; GIP: glucose-dependent insulinotropic peptide; HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; MI: myocardial infarction; PPAR-g: peroxisome proliferator–activated receptor g; PROactive: Prospective Pioglitazone Clinical Trial in Macrovascular Events (30); STOP-NIDDM: Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (31); TZD: thiazolidinedione; T2DM,: type 2 diabetes mellitus; UKPDS: UK Prospective Diabetes Study (32,33). Cycloset trial of quick-release bromocriptine (34). *Cost is based on lowest-priced member of the class. ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analogs > human insulins) and dosage.

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