MI-CCSI

Center for Clinical Systems Improvement

DIABETES LEARNING SERIES

Module 1: Building the foundation to support patients with Type II Diabetes

Today's Presenter

Claire Nolan, PharmD

Content expert, faculty member, and participant in practice transformation initiatives. Dr. Nolan has experience in community, specialty, and ambulatory pharmacy.

Disclosure to Participants

Criteria for Successful Completion:

- Attendance of the entire session and submission of an evaluation form.

Conflict of Interest:

- There is no conflict of interest for anyone with the ability to control content for this activity.
- This nursing continuing professional development activity was approved by the Ohio Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. (OBN-001-91)
- *Expiration Date for enduring materials is X-X-2024 for the recorded 2- part taped webinar series).*
-
- Susan J. Vos RN BSN

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Disclosure

MI-CCSI, or the presenter, does not have any financial interest, relationships, or other potential conflicts, with respect to the material which will be covered in this presentation.

OBJECTIVES

At the conclusion of this presentation, the participant will be able to:

- Describe the epidemiology, pathophysiology, clinical manifestations, and risk factors for type 2 diabetes mellitus.
- Define updated treatment targets and treatment strategies for type 2 diabetes mellitus based on the American Diabetes Association 2022 Standards of Medical Care in Diabetes.
- Recognize the relative place in therapy and adverse events of medications available for the treatment of type 2 diabetes mellitus.
- List medications that may induce hyperglycemia.

Epidemiology, Pathophysiology, Clinical Manifestations, and Risk Factors

Diabetes: Module 1

Epidemiology

- Worldwide: 537 million people
- United States:
  - 37.3 million people (2019)
    - 11.3% of population
    - Type 1: 1.9 million (~ 5%), Type 2: 35.4 million (~ 95%)
    - > 20% undiagnosed
    - 1.4 million diagnosed per year
  - 96 million > 18 years of age have prediabetes (2019)
  - Seventh leading cause of death (2019)

Robertson RP. Type 2 diabetes mellitus: Prevalence and risk factors. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Statistics About Diabetes. American Diabetes Association. Available from: https://www.diabetes.org/resources/statistics/statistics-about-diabetes. Accessed May 14, 2022.

Diabetes: Module 1

Epidemiology

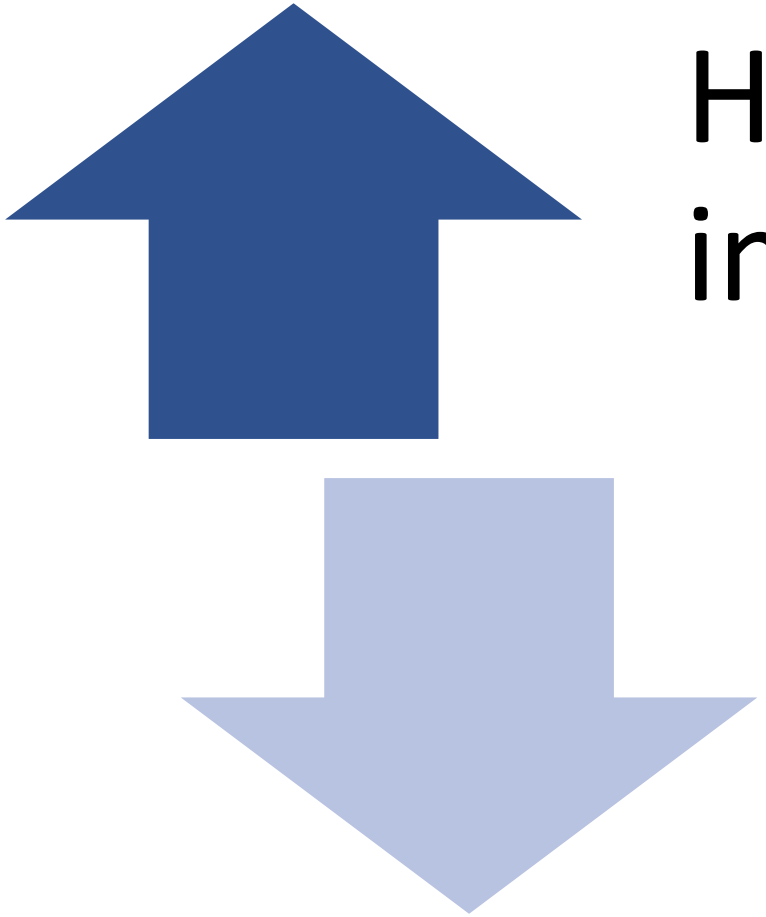
- 29.2% of Americans ≥ 65 years of age
- Variation by race/ethnicity

Race/Ethnicity	Prevalence
American Indian/Alaskan Native	14.5%
Non-Hispanic Black	12.1%
Hispanic	11.8%
Asian American	9.5%
Non-Hispanic White	7.4%

Statistics About Diabetes. American Diabetes Association. Available from: https://www.diabetes.org/resources/statistics/statistics-about-diabetes. Accessed May 14, 2022.

Diabetes: Module 1

Pathophysiology



Hyperglycemia and insulin resistance

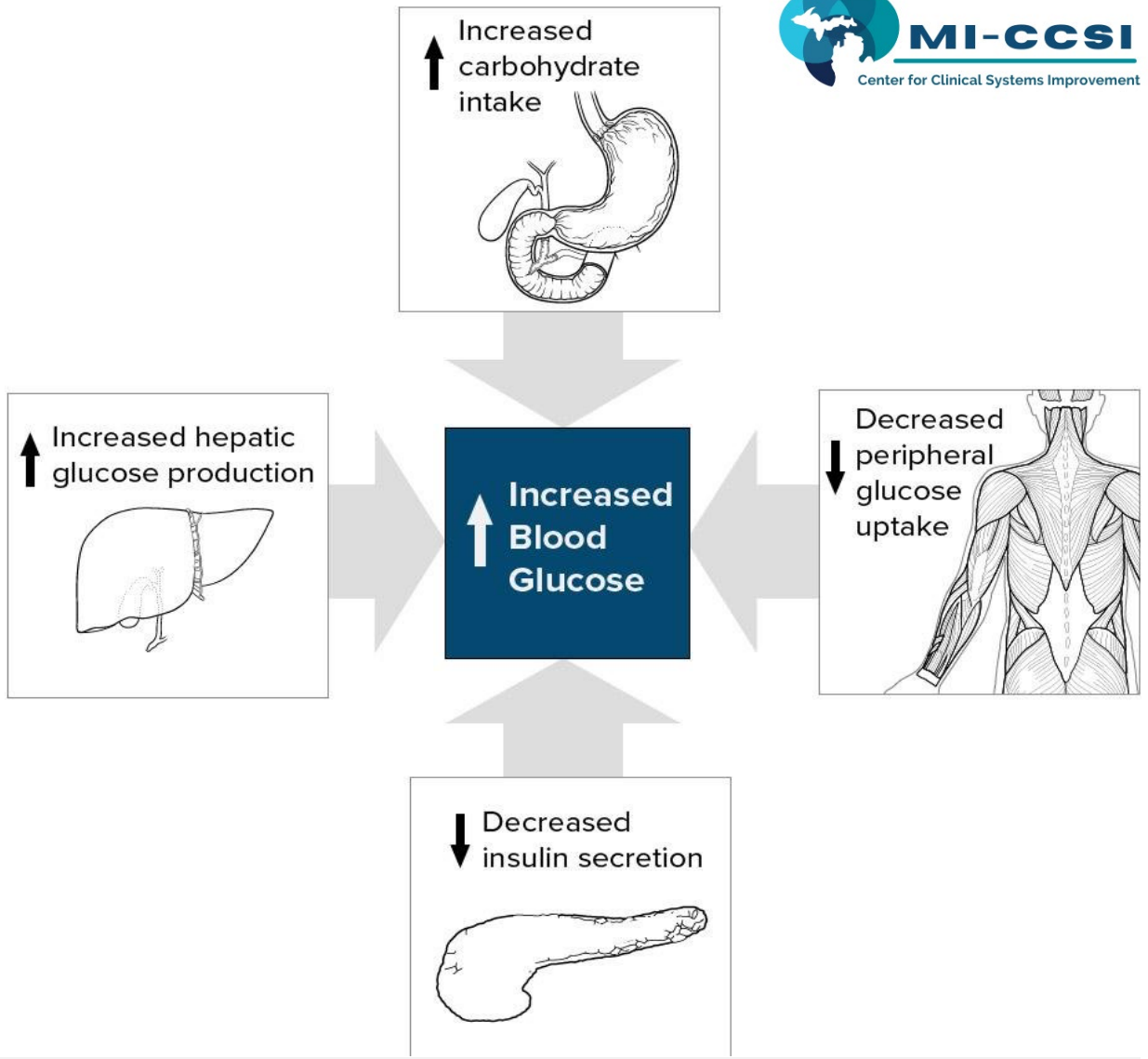
Insulin secretion

Khardori R. Type 2 Diabetes Mellitus. Available from: https://emedicine.medscape.com/article/117853-overview. Last updated April 25, 2022. Accessed May 14, 2022.
Robertson RP and Udler MS. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

Diabetes: Module 1

Pathogenesis

- Heterogeneous and multifactorial disease
- The exact cause can be difficult to identify for a given patient



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Diabetes: Module 1

Clinical Manifestations

- Majority of patients
  - Asymptomatic at presentation
  - Diagnosed upon routine screening
- Classic symptoms of hyperglycemia
  - Frequent urination
  - Nighttime urination
  - Excessive thirst
  - Blurred vision
  - Weight loss
  - (often noted in retrospect)

Inzucchi SE and Lupsa B. Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022..

Diabetes: Module 1

Complications

- Patients diagnosed later in their disease course may present with complications:
  - Macrovascular disease (atherosclerosis)
  - Microvascular disease (retinopathy, nephropathy, neuropathy)
- Onset and progression can be delayed with
  - Glycemic control
  - Appropriate management of comorbidities (e.g., hypertension, dyslipidemia, etc.)

Wexler DJ. Overview of general medical care in nonpregnant adults with diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020..

Clinical Risk Factors

Family history

- Two- to three-fold increased risk for Individuals with a family history in any first-degree relative
- Five- to six-fold increase in risk for those with both a maternal and paternal history

Ethnicity

- Elevated risk for Asian, Hispanic, and Black Americas
- Disparities may be related, in part, to modifiable risk factors along with neighborhood, psychosocial, socioeconomic, and behavioral factors during young adulthood

Obesity

- More highly correlated to the risk of developing diabetes than age or race/ethnicity
- 100-fold increased risk for BMI > 35 kg/m^2 compared to < 22 kg/m2

Fat distribution

- Degree of insulin resistance highest in those with “central”/abdominal/”male type” obesity

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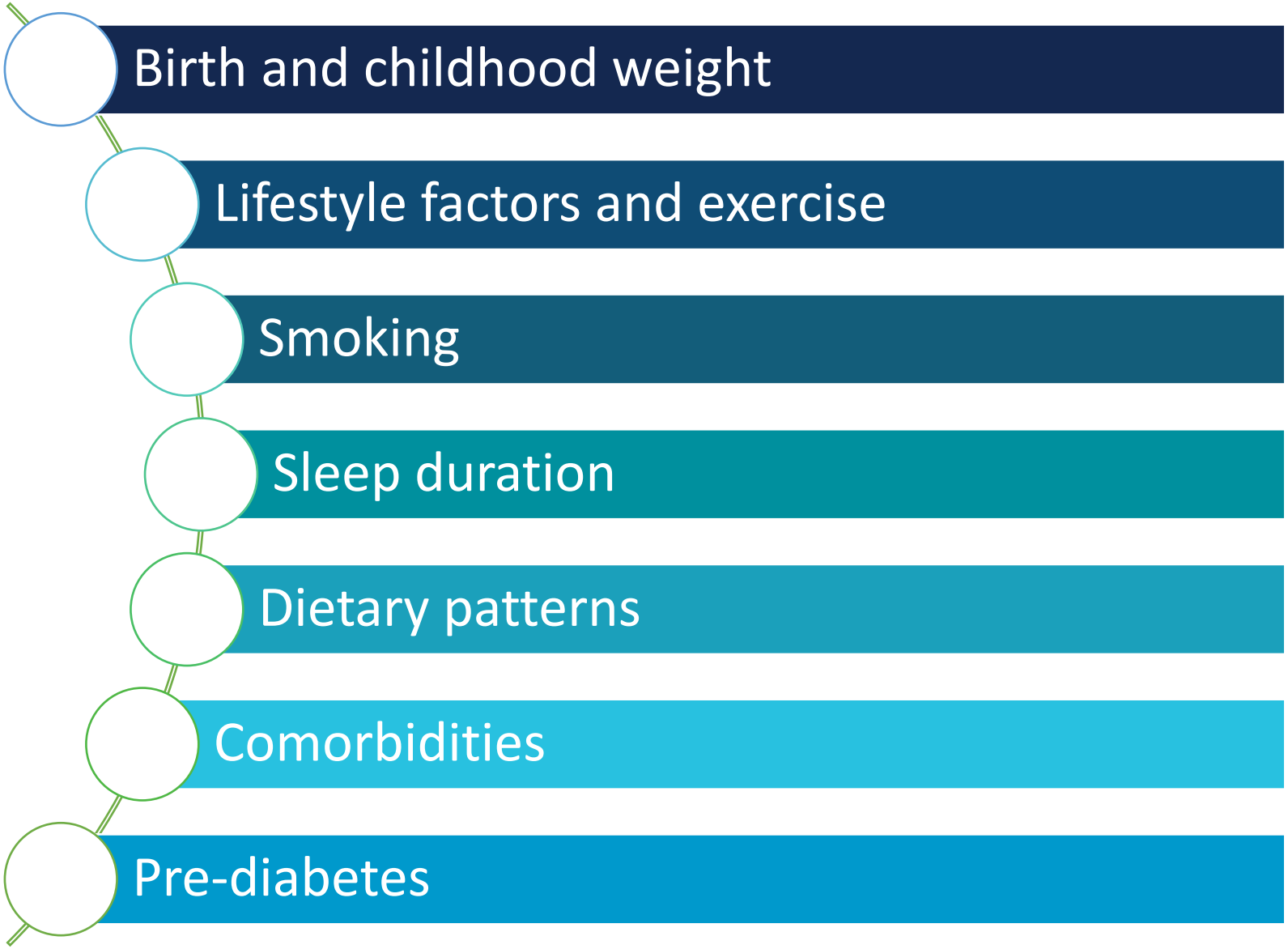
Clinical Risk Factors



Robertson RP. Type 2 diabetes mellitus: Prevalence and risk factors.. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Diagnostic Criteria and Treatment Targets

ADA Screening Recommendations

TABLE 2.3 Criteria for Screening for Diabetes or Prediabetes in Asymptomatic Adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], impaired glucose tolerance, or impaired fasting glucose]) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022...

ADA Criteria for Diagnosis

TABLE 2.2/2.5 Criteria for the Screening and Diagnosis of Prediabetes and Diabetes

	Prediabetes	Diabetes
A1C	5.7–6.4% (39–47 mmol/mol)*	≥6.5% (48 mmol/mol)†
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L)*	≥126 mg/dL (7.0 mmol/L)†
2-hour plasma glucose during 75-g OGTT	140–199 mg/dL (7.8–11.0 mmol/L)*	≥200 mg/dL (11.1 mmol/L)†
Random plasma glucose	–	≥200 mg/dL (11.1 mmol/L)‡

Adapted from Tables 2.2 and 2.5 in the complete 2022 Standards of Care. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. †In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate samples ‡Only diagnostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022...

Diagnostic Criteria and Treatment Targets

Monitoring

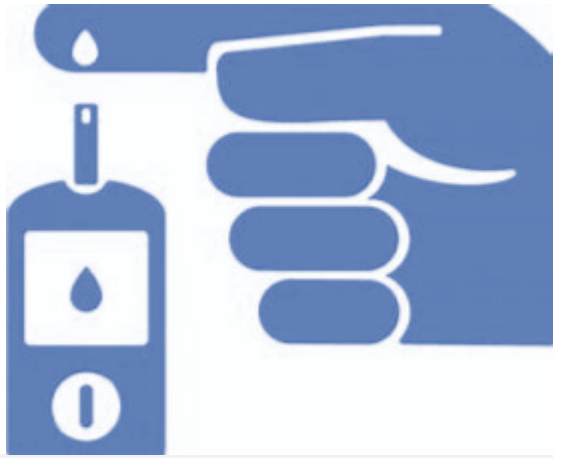
- Once a diagnosis has been confirmed, assess glycemic status (e.g., A1C, time in range [TIR])
  - Twice yearly in patients meeting treatment goals with stable glycemic control
  - At least quarterly in patients who have had a change in therapy and/or who are not meeting glycemic goals

Wexler DJ. Initial management of blood glucose in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022...

Diagnostic Criteria and Treatment Targets

Self-Monitoring of Blood Glucose (SMBG)

- Recommended for patients who take insulin and in some patients who take other glucose-lowering medications that can cause hypoglycemia
- Generally, not necessary for patients who are on a stable regimen of diet or oral agents that are unlikely to cause hypoglycemia
- Options include
  - Blood glucose meters
  - Continuous glucose monitoring (CGM) systems
- Covered in more detail in module 2



Weinsock RS. Glucose monitoring in the management of nonpregnant adults with diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
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Treatment Targets

Patient-Centered Care

- Clinical trials primarily use A1C to assess glycemic control
- CGM serving an increasingly important role
- Not a one size fits all approach
- A1C ≤ 7% and/or TIR > 70% is a reasonable goal for most patients
- Targets are generally set higher (e.g., ≤ 8%) for older patients and those with comorbidities or limited life expectancy

Wexler DJ. Overview of general medical care in nonpregnant adults with diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
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Average glucose levels before and after meals for specified A1C levels

	A1C percentage (mmol/mol)				
	5.5–6.49 (37–47)	6.5–6.99 (48–52)	7.0–7.49 (52–58)	7.5–7.99 (58–64)	8.0–8.5 (64–69)
	Estimated average glucose as mg/dL (95% CI)				
	111–139	140–153	154–168	169–182	183–197
Pre-breakfast	122 (117–127)	142 (135–150)	152 (143–162)	167 (157–177)	178 (164–192)
Pre-lunch	113 (108–117) *	127 (121–133) *	147 (139–155)	140 (132–149) *	167 (151–182)
Pre-supper	119 (115–123)	145 (138–152)	155 (148–162)	163 (153–173)	186 (168–205)
Post-breakfast	150 (144–157) ¶	177 (170–184) ¶	192 (181–203) ¶	206 (193–219) ¶	219 (204–234) Δ
Post-lunch	140 (135–145)	158 (151–164)	172 (164–180)	181 (170–191)	194 (178–209)
Post-supper	142 (136–146)	159 (152–166)	169 (162–177)	182 (171–193)	211 (195–227)

Wexler DJ. Overview of general medical care in nonpregnant adults with diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Blood Glucose and A1C Levels

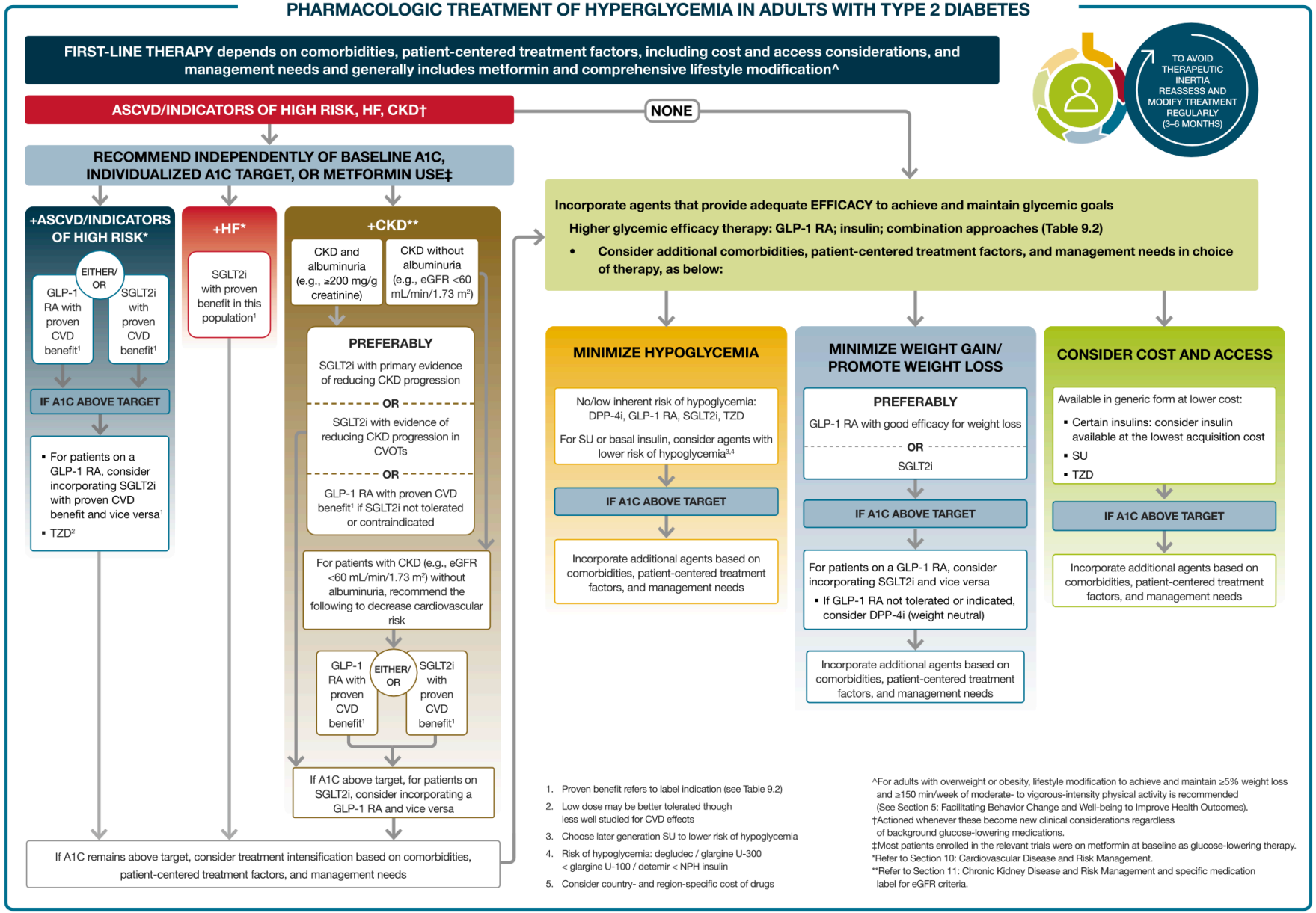
Pharmacologic Treatment

A Note on Prevention/Treatment of Pre-Diabetes

- Recommended first-line preventive therapy involves lifestyle changes
- Metformin is the pharmacologic intervention of choice:
  - Consider for adults aged 25-59 years with BMI ≥ 35 kg/m2, fasting plasma glucose ≥ 110 mg/dL, A1C ≥ 6.0%, and in women with prior gestational diabetes
  - Off-label (not currently approved for this use in the U.S.)
  - Impact on micro- and macrovascular outcomes and mortality are currently unclear

Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022.
Robertson RP. Prevention of type 2 diabetes mellitus.. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

Consensus Guidelines for Treatment



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Approach to INITIAL Therapy

When to initiate therapy

- The earlier, the better
- Preferably at the time of diagnosis for most patients presenting with A1C at or above target levels
- A 3-month trial of lifestyle modification prior to initiation may be warranted for select patients

Considerations

- Patient presentation – symptoms, comorbidities, baseline A1C
- Treatment goals
- Patient preferences
- Medication efficacy, tolerability, and cost

Wexler DJ. Initial management of hyperglycemia in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022..

Pharmacologic Treatment

Approach to INITIAL Pharmacotherapy

- **Metformin** is the initial pharmacotherapy of choice for asymptomatic patients
- Regardless of baseline A1C, A1C target, or metformin use, specific therapies are recommended for patients with comorbid:
  - Atherosclerotic cardiovascular disease (ASCVD) or indicators of high risk
  - Heart failure
  - Chronic kidney disease
- Insulin may be necessary in cases where the patient presents with symptomatic or severe hyperglycemia at diagnosis

Wexler DJ. Initial management of blood glucose in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.
Davies MJ. Management of Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41:2669-2701.

METFORMIN

- Can expect a 1-2% decrease in A1C with monotherapy
- Weight neutral (i.e., not known to cause weight gain or loss)
- GI side effects (e.g., diarrhea, gas, nausea, and vomiting) can be mitigated through slow dose titration and taking each dose with food
- Contraindicated with GFR < 30 mL/min
- Patients who are not able to tolerate metformin or who have a contraindication should be prescribed alternative therapy using shared decision making

How It Works

Increases glucose uptake and utilization in the tissues (e.g., improves insulin sensitivity)	Decreases glucose production in the liver and intestinal absorption of glucose

Metformin: Drug Information. In: Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2020. Available from: http://online.lexi.com. Accessed May 26, 2022.

Pharmacologic Treatment

Metformin Dosing

- Immediate release
  - Initial: 500 mg once or twice daily OR 850 mg once daily
  - Increase the dose gradually (500 mg or 850 mg incremental increase every 7 days)
  - Target maintenance dose: 1 g twice daily OR 850 mg twice daily
- Extended release
  - Initial: 500 mg to 1 g once daily
  - Increase the dose gradually (500 mg incremental increase every 7 days)
  - Target maintenance dose: 2 g once daily

Metformin: Drug Information. In: Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2020. Available from: http://online.lexi.com. Accessed June 10, 2022

Pharmacologic Treatment

Approach to Therapy Beyond Initiation

- Considerations
  - Comorbid ASCVD or indicators of high risk, HF, or CKD?
  - Compelling need to minimize hypoglycemia?
  - Cost and access considerations?
  - Compelling need to minimize weight gain or promote weight loss?
  - Current A1C level and relative potential impact of available therapies?
  - Patient-centered treatment factors?

Wexler DJ. Initial management of hyperglycemia in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
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Combination Therapy

- When metformin alone or in combination with lifestyle modification is not sufficient, combination therapy is necessary
  - Should be considered when the glycemic target is not achieved within three months of initiation of metformin plus lifestyle intervention
- Need for combination therapy is not uncommon
  - One study found that 50% and 75% of patients originally controlled with a single agent required a second medication after three and nine years, respectively

Wexler DJ. Initial management of hyperglycemia in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

Summary of Common Glucose Lowering Interventions

Class	Example(s)	Expected A1C Decrease *(Monotherapy)*
Insulin (once daily, intermediate- or long-acting insulin)	Insulin glargine, insulin detemir, insulin degludec	1.5-3.5%
Sulfonylureas	Short-acting: glipizide, glimepiride Long-acting: glyburide	1-2%
GLP-1 Receptor Agonists	Short-acting: exenatide twice daily, lixisenatide Long-acting: liraglutide, exenatide once weekly, dulaglutide, semaglutide	0.5-1.5%
Thiazolidinediones	Rosiglitazone, pioglitazone	0.5-1.4%
SGLT2 Inhibitors	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5-0.7%
DPP-4 Inhibitors	Sitagliptin, saxagliptin, linagliptin, alogliptin	0.5-0.8%

Wexler DJ. Initial management of hyperglycemia in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Insulin Therapy

- Place in therapy
  - Consider early introduction for patients with evidence of ongoing catabolism (weight loss), symptoms of hyperglycemia, or high A1C (>10%) or blood glucose (≥ 300 mg/dL)
  - Likelihood of necessity increases as beta-cell function declines over time

Insulin Type	Approximate Onset	Peak Effect	Approximate Duration
Lispro, Aspart	15-30 min	1-3 hrs	4-6 hrs
Regular	30 min	1.5-3.5 hrs	8 hrs

Insulin Type	Half-Life	Peak Effect	Approximate Duration
NPH	4.4 hrs	4-6 hrs	12 hrs
Insulin glargine	12-19 hrs	No peak	20 to > 24 hrs
Insulin detemir	5-7 hrs	3-9 hrs	6-24 hrs
Insulin degludec	25 hrs	No peak	> 24 hrs

Weinstock RS. General principles of insulin therapy in diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022.

Pharmacologic Treatment

Sulfonylureas

- Directly stimulate pancreatic beta cells to release insulin
- Clinical pearls:
  - Glyburide has a longer duration or action – higher potential for hypoglycemia – than glipizide or glimepiride
  - Onset of action is quick
  - Modest weight gain is a common side effect
  - Short-acting sulfonylureas may be used as initial therapy in select circumstances:
    - Contraindication to metformin and NO cardiovascular disease
    - Severe hyperglycemia without ketonuria or unintentional weight loss when the patient is injection averse or unable to afford insulin or GLP-1 therapy
  - Generally, NOT used in combination with insulin

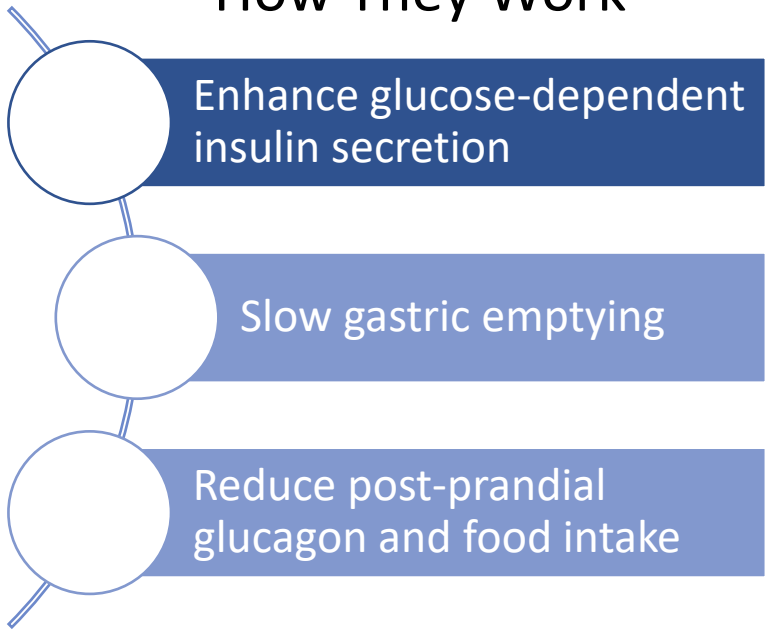
Wexler DJ. Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Pharmacologic Treatment

GLP-1 Receptor Agonists

- Injectable products, except for oral semaglutide
- Do not usually cause hypoglycemia
- Use is associated with modest weight loss (4.5-6.5 lb)
- Side effects primarily involve gastrointestinal upset (nausea, vomiting, diarrhea), which can occur in up to 50% of patients
- Cost and payer coverage are important considerations for this drug class

How They Work



Dungan K and DeSantis A. Glucagon-like peptide 1 receptor agonists for the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
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Pharmacologic Treatment

GLP-1 Receptor Agonists

- Appropriate for use in combination with metformin and/or another oral agent:
  - Atherosclerotic cardiovascular disease (ASCVD)
  - Weight loss and/or avoidance of hypoglycemia are primary concerns
  - When cost or injection therapy are not major barriers
- Should not be used in combination with DPP-4 inhibitors due to lack of additive benefit
- A note on GLP-1 receptor agonists and insulin combination
  - Basal insulin – glycemic targets achieved at lower insulin doses with less hypoglycemia or weight gain, but more GI side effects
  - Combination products available

Dungan K and DeSantis A. Glucagon-like peptide 1 receptor agonists for the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Pharmacologic Treatment

Thiazolidinediones

- How they work:
  - ↑ insulin sensitivity in the adipose tissue and muscle → ↑ glucose utilization
  - To a lesser extent, they also ↓ glucose production by the liver
- Limited utility as an initial therapy option
  - Pioglitozone for patients who have a contraindication to other oral agents, decline injectable therapies, and cannot afford DPP-4 inhibitors or SGLT-2 inhibitor therapy
- More commonly used second- or third-line, as combination therapy, especially when cost is of concern
- Risks (weight gain, heart failure, fractures, bladder cancer) require careful consideration
- Contraindicated in patients with heart failure or any evidence of fluid overload, history or high risk of fracture, active liver disease, active or historical bladder cancer, and pregnancy
- Should not be used in combination with insulin due to increased risk of heart failure and edema

Inzucchi SE and Lupsa B. Thiazolidinediones in the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

Pharmacologic Treatment

SGLT2 Inhibitors

- Administered orally, with or without food, first thing in the morning
- Patients should be routinely monitored for renal function and foot ulceration
- Most common side effects include vulvovaginal candida infections and hypotension

Promote the renal excretion of glucose, thereby impacting blood glucose levels

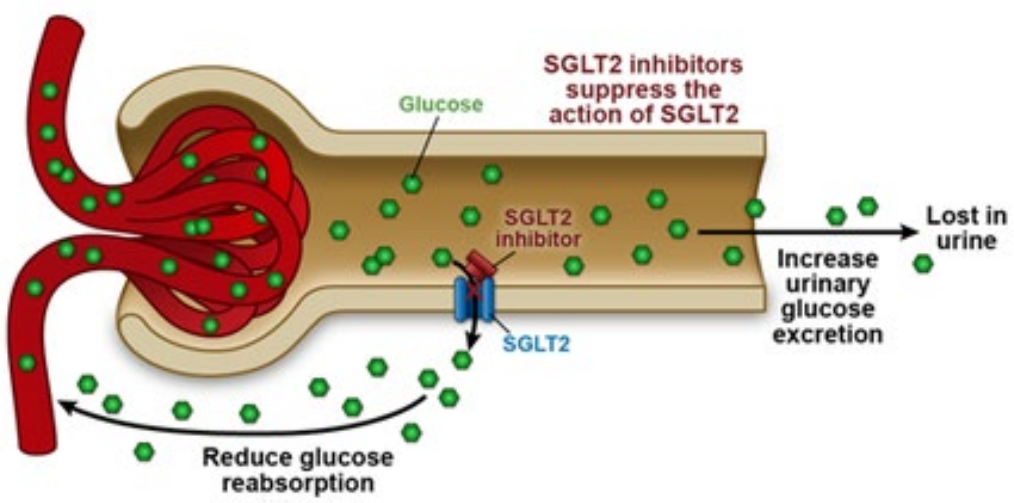

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Image available from: https://www.medscape.org/viewarticle/869716_2. Accessed June 11, 2020.

Pharmacologic Treatment

DPP-4 Inhibitors

- DPP-4 is an enzyme that is found throughout the body which deactivates a variety of other bioactive peptides, including GLP-1
  - Inhibition of DPP-4 has the potential to affect glucose regulation through a variety of mechanisms
  - DPP-4 inhibitors have a modest impact on GLP-1 levels and activity compared to GLP-1 receptor agonists themselves
- All oral products
- Linagliptin is the preferred product for patients with chronic kidney disease because it is eliminated through the enterohepatic system

Dungan K and DeSantis A. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

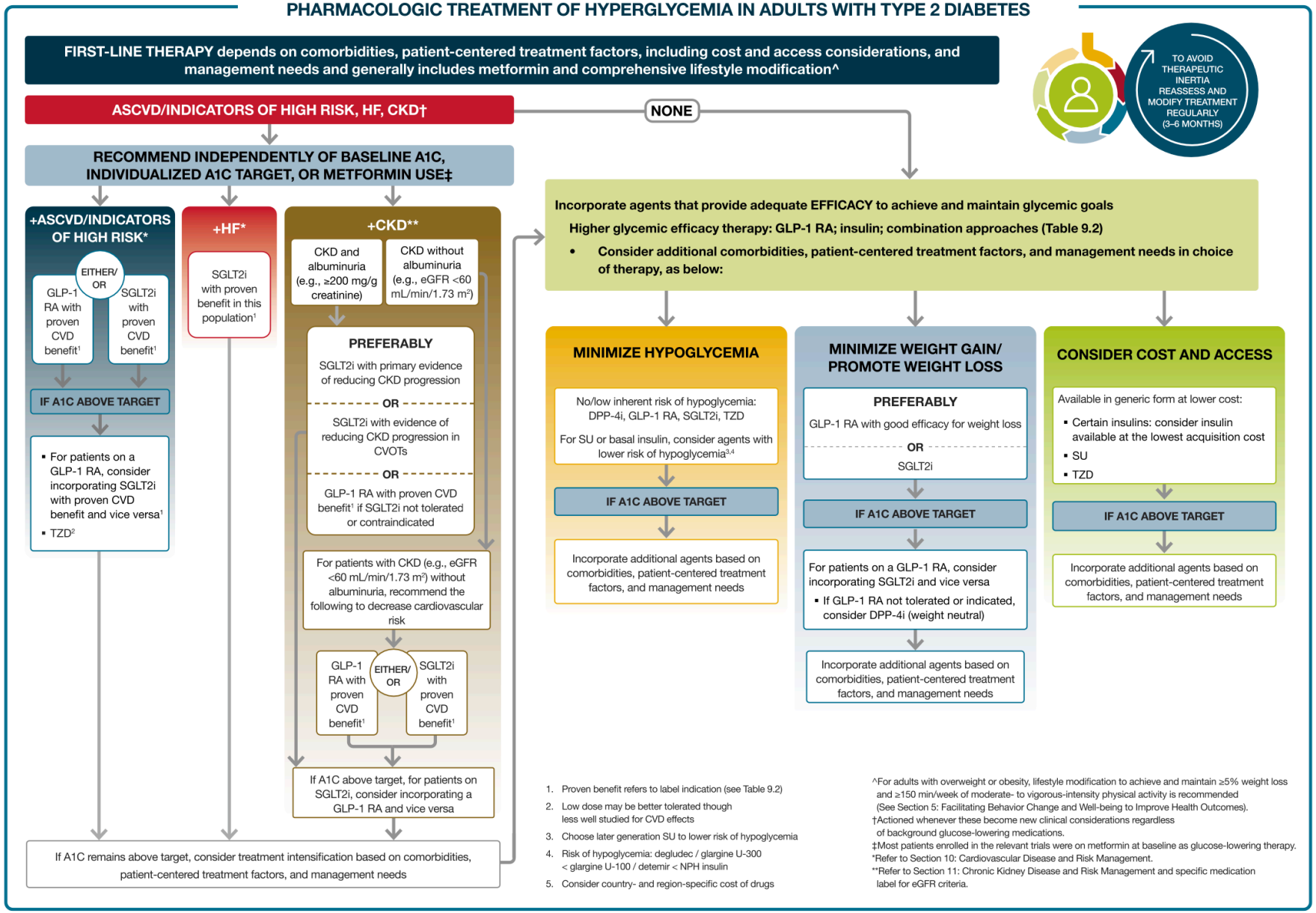
Pharmacologic Treatment

DPP-4 Inhibitors

- Not associated with an impact on body weight or a risk of hypoglycemia
- Side effects may include headache, nasopharyngitis, and upper respiratory tract infections
- No known impact (positive or negative) on the risk of cardiovascular events
- Product labeling includes a warning regarding use in patients at high risk for heart failure

Dungan K and DeSantis A. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

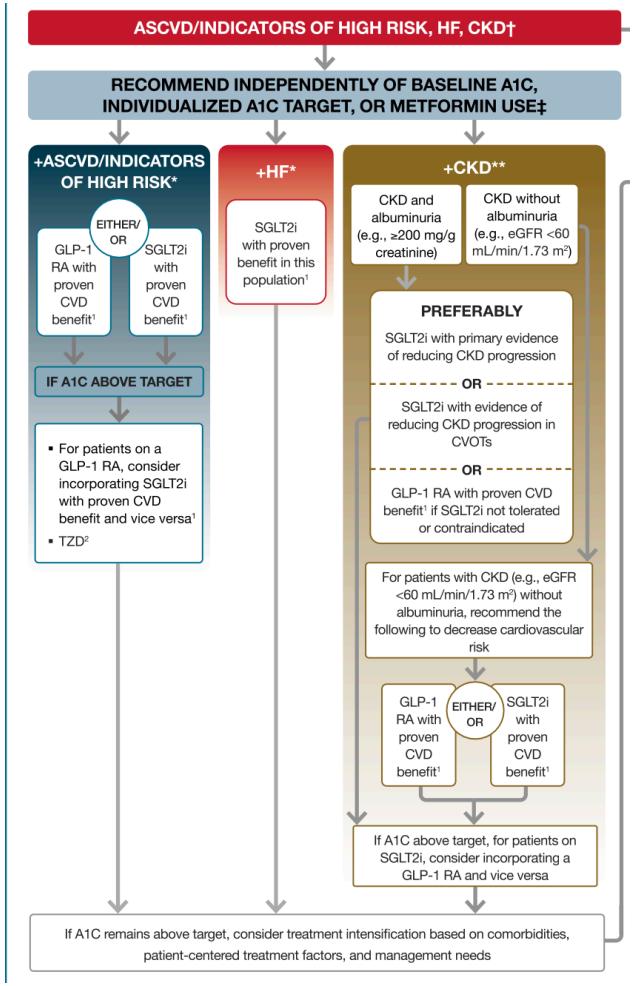
Consensus Guidelines for Treatment



Standards of Medical Care in Diabetes – 2022 Abridged for Primary Care Providers. American Diabetes Association. Available from: https://diabetesjournals.org/clinical/article/40/1/10/139035/Standards-of-Medical-Care-in-Diabetes-2022. Accessed May 14, 2022.

Consensus Guidelines for Treatment

- Initial therapy for patients at high-risk of or with established ASCVD, CKD, or HF requires therapy beyond metformin, regardless of baseline or target A1C
- The choice of therapy depends on whether ASCVD, HF, or CKD predominates



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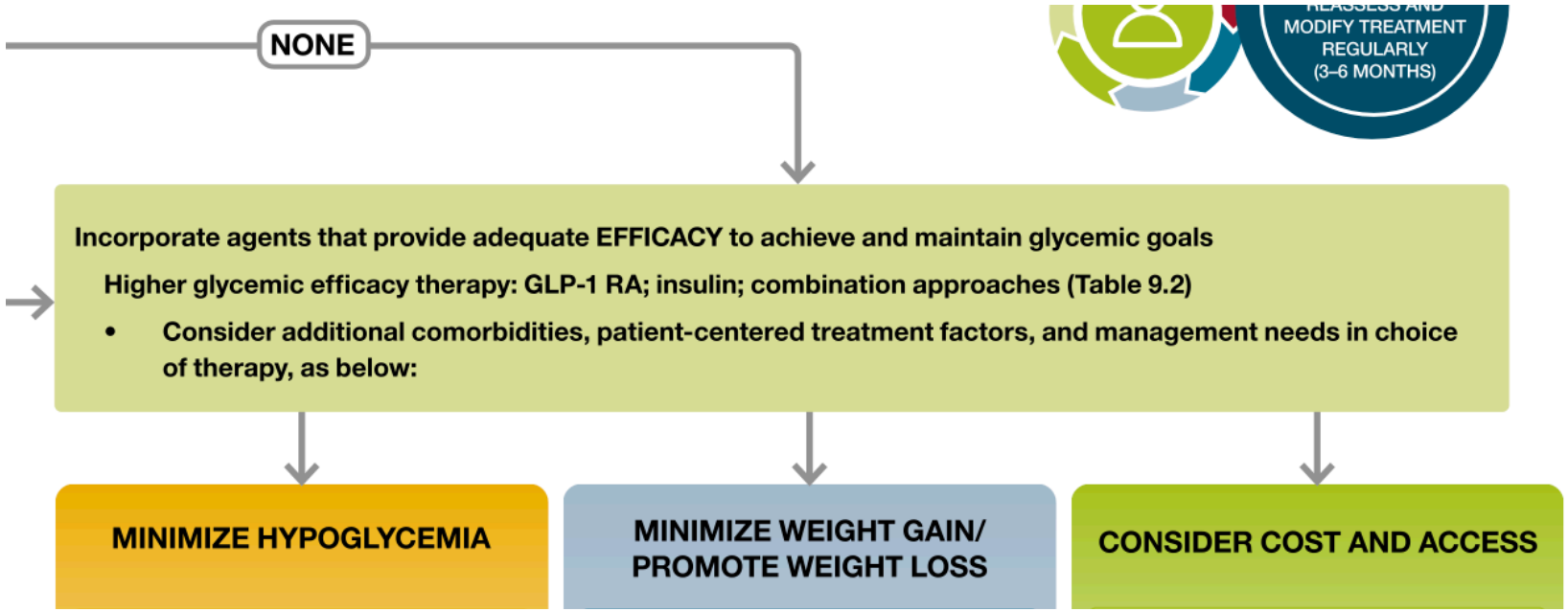
Consensus Guidelines for Treatment

For patients **not** at high-risk or **without** established ASCVD, CKD, or HF the choice of therapy beyond metformin is based on an evaluation of the following patient-specific factors:



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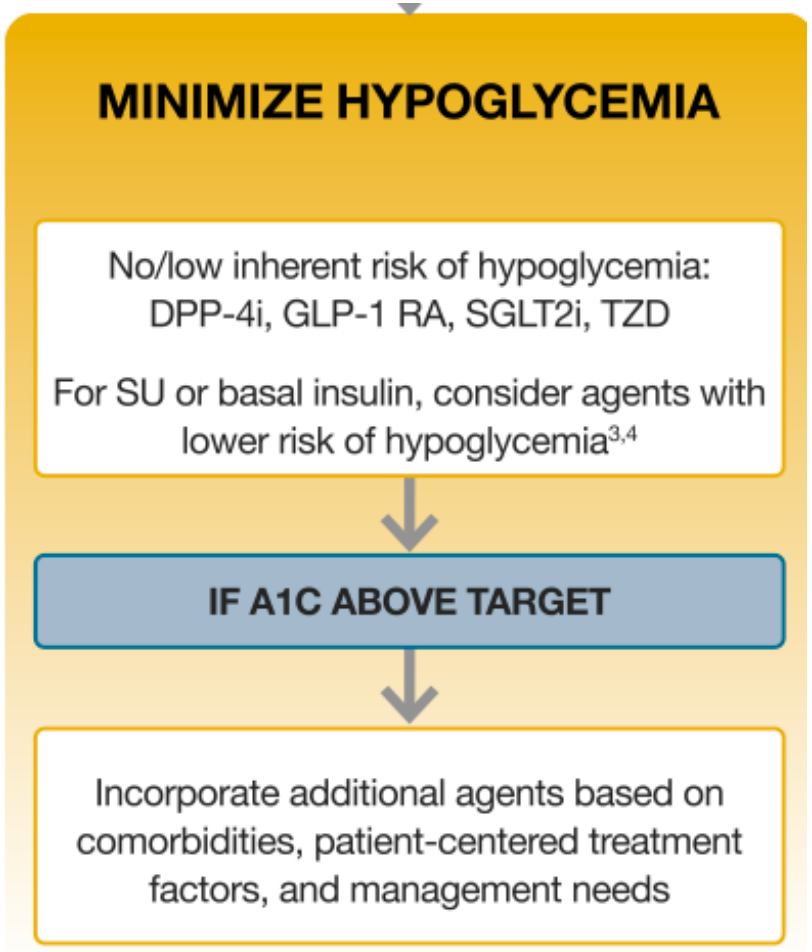
Consensus Guidelines for Treatment



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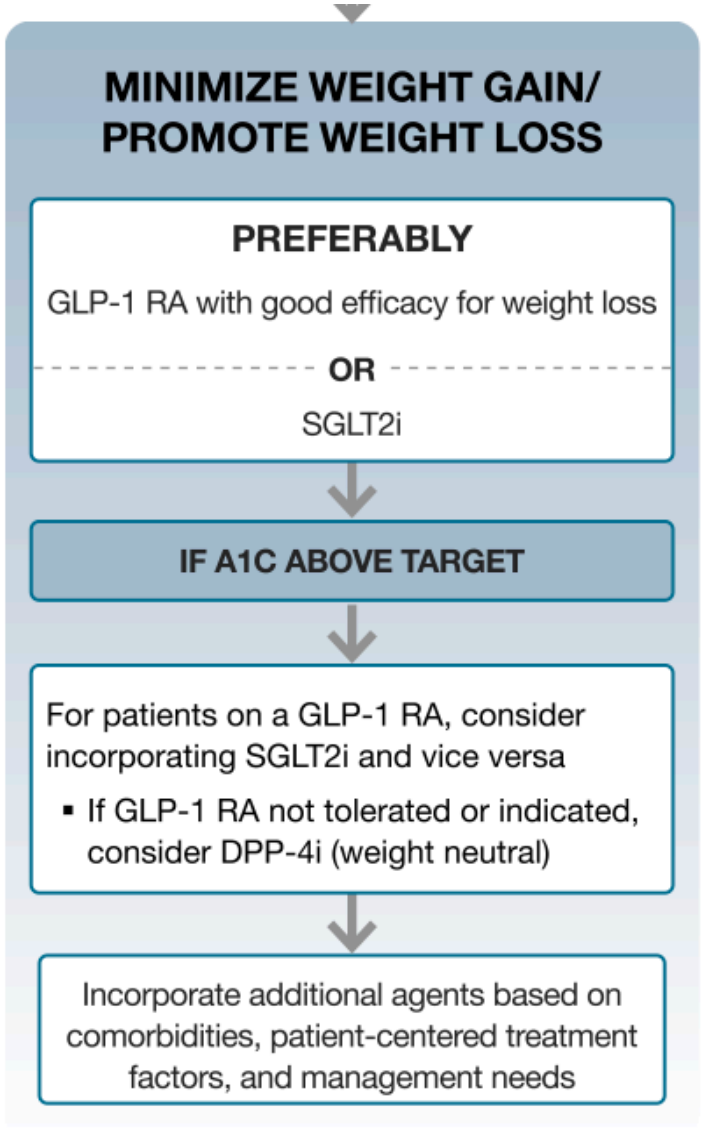
Consensus Guidelines for Treatment



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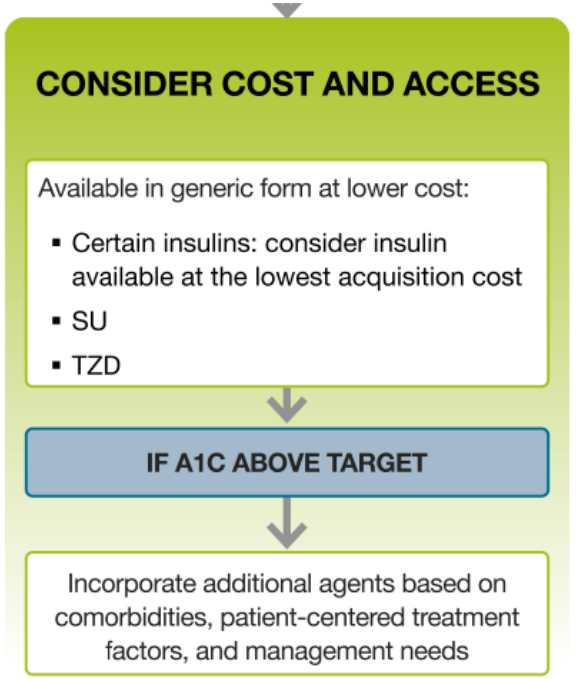
Consensus Guidelines for Treatment

When cost is a barrier

- Oral therapies with generic equivalents available should be prioritized
- Injectable therapies should be deferred
- Seek support through manufacturers



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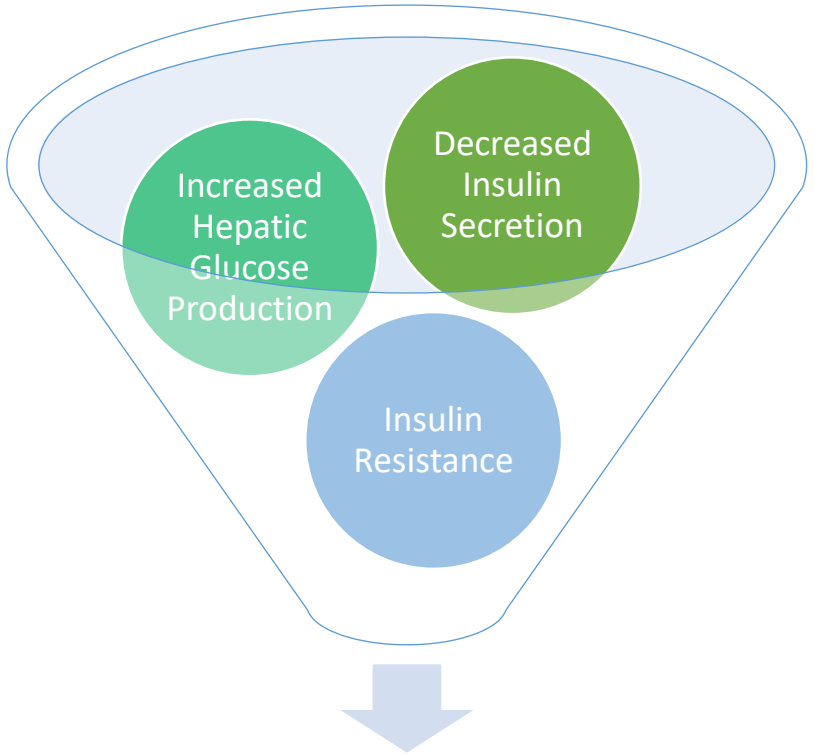
Medication-Induced Hyperglycemia



Drug-Induced Hyperglycemia

Robertson RP and Udler MS. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Medication-Induced Hyperglycemia

Thiazide Diuretics

- Hydrochlorothiazide (HCTZ), chlorthalidone, chlorothiazide, and indapamide
- Small increase in fasting plasma glucose
  - Substantial increases are unusual at recommended doses
- ↓ potassium (due to loss in via urine) → hypokalemia (e.g., low potassium levels)
  - Hypokalemia is associated with ↑ risk of type 2 DM
  - Due to decreased insulin secretion and increased insulin resistance
  - Can be mitigated with potassium replacement therapy

Robertson RP and Udler MS. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

Medication-Induced Hyperglycemia

Antipsychotics

- Hyperglycemia may worsen in patients with established diabetes that begin an antipsychotic (mechanism not defined)
- Atypical antipsychotics clozapine and olanzapine:
  - Weight gain, obesity, hypertriglyceridemia, and development of diabetes mellitus
- Risperidone and quetiapine:
  - Increased risk of weight gain
  - Conflicting data regarding diabetes and dyslipidemia risk
- Ziprasidone and aripiprazole do not increase the risk for diabetes or dyslipidemia

Robertson RP and Udler MS. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.

Drug-Induced Hyperglycemia

Glucocorticoids	• Example: prednisone • Dose- and duration-dependent impact • Multi-factorial mechanism: augmented hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue, and alteration of receptor and post-receptor functions
Anti-Infectives	• HIV therapy, specifically protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs,) increase peripheral insulin resistance, thereby contributing to antiretroviral-associated metabolic syndrome
Immunosuppressants	• Cyclosporine, sirolimus, and tacrolimus • Use results in decreased insulin production and release

Saag KG and Furst DE. Major side effects of systemic glucocorticoids. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Robertson RP and Udler MS. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

Drug-Induced Hyperglycemia

Select Beta Blockers	• Atenolol, metoprolol, propranolol: moderately decrease insulin sensitivity • Carvedilol: effect not evident
Niacin	• Alters hepatic glucose metabolism • Effect likely greater with extended-release formulation
Statins	• Conflicting evidence - may have a low risk of impaired glucose tolerance
Immune Checkpoint Inhibitors	• PD-1 (nivolumab), PD-L1 (atezolizumab), and CTLA-4 (ipilimumab) inhibitors • Promote activation of cytotoxic T cells that act "off target" to attack and destroy islet cells.

Saag KG and Furst DE. Major side effects of systemic glucocorticoids. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022.
Robertson RP and Udler MS. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2022

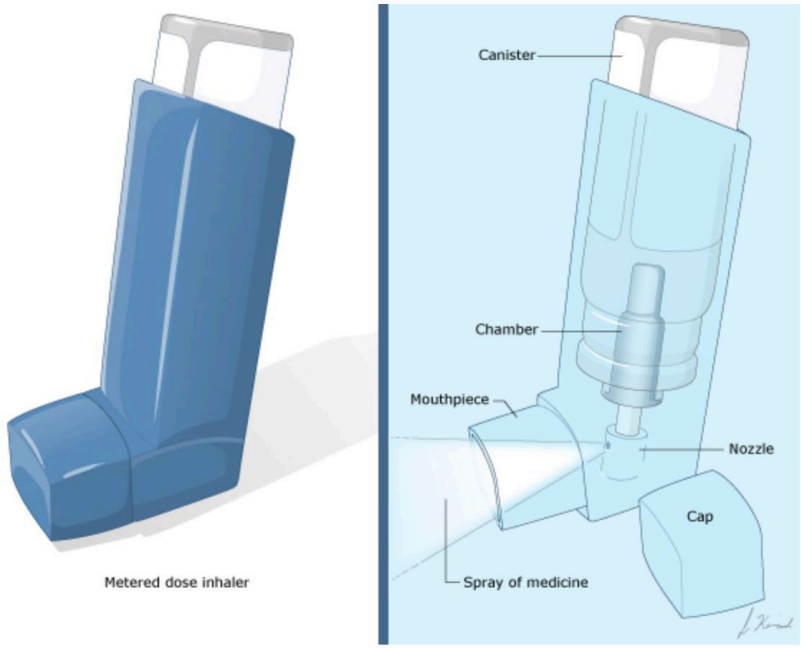
SUMMARY

- Over one-quarter of Americans ≥ 65 years of age have either diagnosed or undiagnosed diabetes
- A1C ≤ 7% is a reasonable goal for most patients
- Metformin (in combination with comprehensive lifestyle change) is the initial therapy of choice for asymptomatic patients
- Drug-induced hyperglycemia can be recognized and addressed by ensuring that a thorough review of the patient's list of medications occurs at every encounter

Metered Dose Inhalers (MDIs)

Tips and Clinical Pearls

- Priming necessary prior to first use
- Shake vigorously for 5 seconds before each use
- Slow, deep breath at the same time as the canister is pressed down
- Hold breath for 5-10 second prior to exhalation
- Clean mouthpiece at least weekly
- If no dose counter, counsel to refill at set intervals



Medicine is stored in the canister. When you press down on the top of the canister, the medicine travels through the dosing chamber and sprays out of the mouthpiece.

Graphic 61575 Version 6.0

Gerald LB and Chand R. Patient education: Inhaler techniques in adults (Beyond the Basics). In: UpToDate, Dieffenbach P (Ed), UpToDate, Waltham, MA, 2022.

Spacers

- **Spacer devices** — Spacers and chambers are devices that some people use with MDIs to help them inhale the aerosol. While MDI inhalers do not usually require a spacer, it may be helpful to use a spacer if you have difficulty timing the spray with inhalation.
- As the aerosol travels through a spacer, the propellant evaporates and the particle size and velocity of the particles is reduced. Even with a spacer, it's important to coordinate the timing between releasing the medication (also called "actuation") and breathing it in.
- Spacers reduce deposition of medication in the mouth and throat and decrease the amount of swallowed drug that is absorbed through the stomach. As a result, spacers can lower your risk of certain adverse effects, such as thrush (a fungal infection of the mouth and throat).
- Some spacers include a low resistance, one-way valve that allows airflow only during inhalation. These valved holding chambers hold the medicine in the chamber after you press the canister, allowing you to inhale slowly and deeply once or twice (picture 2).
- There are many different designs of spacers available. In general, larger spacers appear to be more effective than smaller ones but choosing one depends on your preference. For example, one spacer has a pop-up design that allows it to be stored flat so that it can easily be placed in a purse or backpack. It is also available at a fraction of the cost of other spacers (picture 3). However, its cardboard design means that it cannot be cleaned, so it needs to be replaced if it gets torn or after significant use.
- Proper technique is important to ensure optimal drug delivery. It is better to use one spray in the spacer at a time, rather than two or more sprays. It is also preferable to inhale as soon as possible after the medication is released into the spacer.
- Be sure to read the package insert that comes with your spacer for specific directions about cleaning and use.
- **Cleaning the spacer** — Non-cardboard spacers should be cleaned periodically, approximately every one to two weeks. The powder residue deposited in the spacer is not harmful. Nevertheless, you should wash the spacer with a dilute solution of warm water and dishwashing detergent to remove the electrostatic charge that can develop on the inside of the spacer. Otherwise, the electrostatic charge can reduce the effectiveness of the spacer. Spacer parts can be washed in a dishwasher, but should be placed on the top shelf.
- After washing, air-dry the spacer before the next use. The spacer should **not** be wiped dry with a towel.