Type 2 Diabetes Mellitus

Module 1

Michigan Center for Clinical Systems Improvement
(Mi-CCSI)

Content Last Updated: June 2020

Objectives

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

1. Describe the epidemiology, pathophysiology, clinical manifestations, and risk factors for type 2 diabetes mellitus.
2. Define diagnostic criteria and blood glucose treatment targets for various subgroups of patients with type 2 diabetes mellitus.
3. Recognize the relative place in therapy and adverse events of medications available for the treatment of type 2 diabetes mellitus.
4. List medications that may induce hyperglycemia.

Epidemiology, Pathophysiology, Clinical Manifestations, and Risk Factors

Epidemiology

- Estimated to affect approximately 425 million people worldwide
- In 2018, 34.2 million Americans (10.5% of the U.S. population) had diabetes
  - Type 1: 1.6 million (< 5%), Type 2: 32.6 million (> 95%)
  - > 20% undiagnosed
- In 2015, an additional 88 million Americans > 18 years of age had prediabetes
- 1.5 million Americans are diagnosed with diabetes every year
- Reported as the seventh leading cause of death in the U.S. in 2017

Robertson RP. Risk factors for type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.
Statistics About Diabetes. American Diabetes Association. Available from: https://www.diabetes.org/resources/statistics/statistics-about-diabetes. Accessed June 3, 2020.

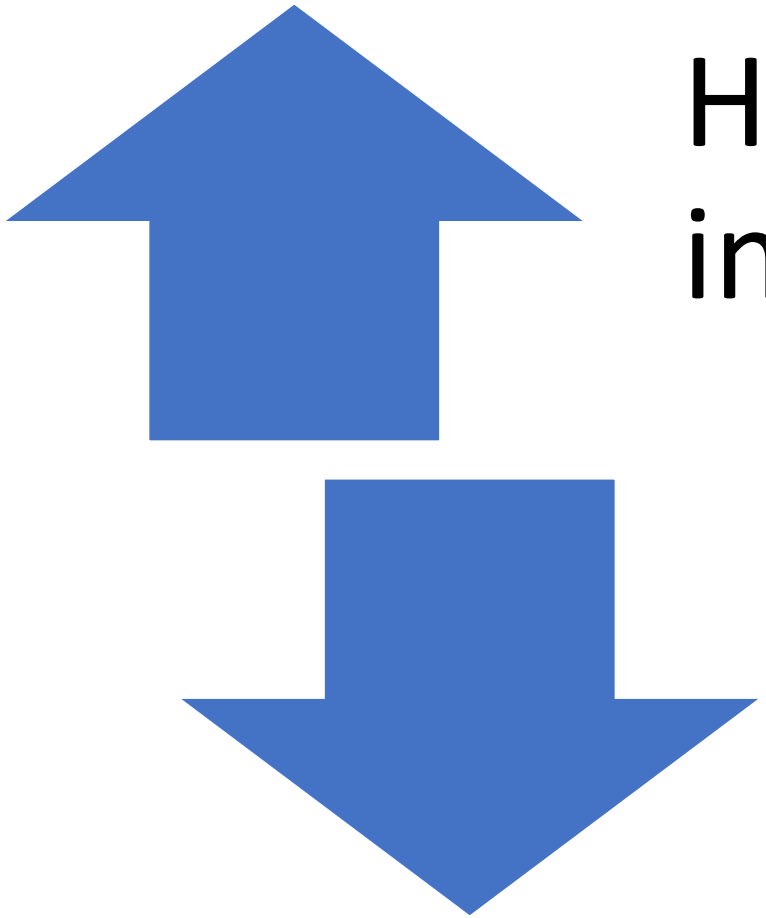
Epidemiology

- Over one-quarter of Americans ≥ 65 years of age have either diagnosed or undiagnosed diabetes
- Variation by race/ethnicity

Race/Ethnicity	Prevalence
American Indian/Alaskan Native	14.7%
Hispanic	12.5%
Non-Hispanic Black	11.7%
Asian American	9.2%
Non-Hispanic White	7.5%

Statistics About Diabetes. American Diabetes Association. Available from: https://www.diabetes.org/resources/statistics/statistics-about-diabetes. Accessed June 3, 2020.

Pathophysiology



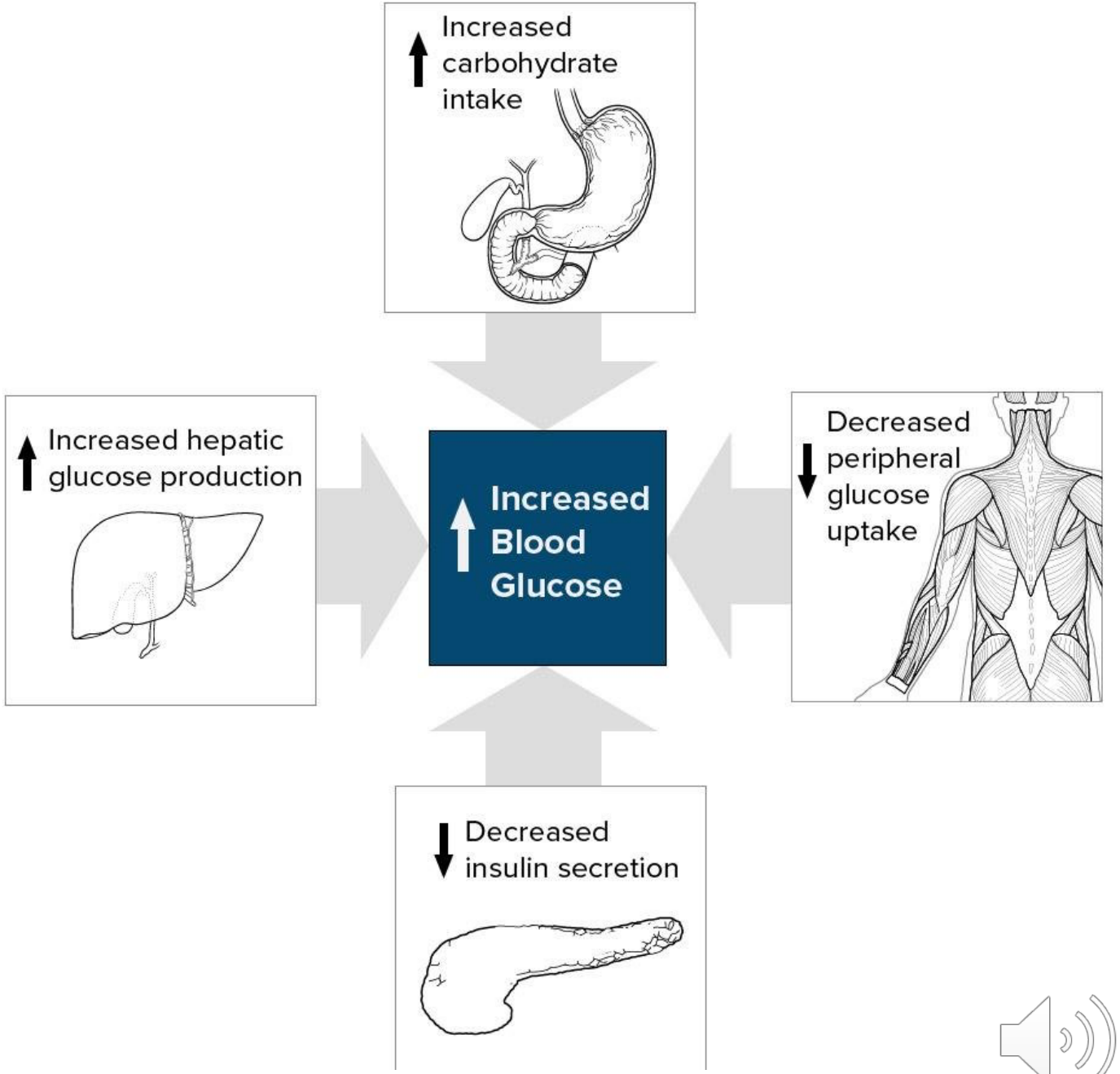
Hyperglycemia and insulin resistance

Insulin secretion

Khardori R. Type 2 Diabetes Mellitus. Available from: https://emedicine.medscape.com/article/117853-overview. Last updated June 2, 2020. Accessed June 3, 2020.
McCulloch DK and Robertson RP. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Pathogenesis

- Multifactorial impairments that can lead to a vicious cycle
- The exact cause can be difficult to identify in an individual patient



Khardori R. Type 2 Diabetes Mellitus. Available from: https://emedicine.medscape.com/article/117853-overview. Last updated June 2, 2020. Accessed June 3, 2020.
McCulloch DK and Robertson RP. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Clinical Manifestations

- The majority of patients are asymptomatic at presentation
  - Most commonly noted on routine lab evaluation
  - The incidence of symptomatic diabetes has declined as routine screening efforts have increased
- Classic symptoms of hyperglycemia
  - Include frequent urination, excessive thirst, nighttime urination, blurred vision and weight loss
  - Are often only 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, 2020.

Complications

- Not all patients are diagnosed with diabetes early in their disease course
- Patients diagnosed later in their disease course may present with complications:
  - Macrovascular disease (atherosclerosis)
  - Microvascular disease (retinopathy, nephropathy, neuropathy)
- Onset and progression of complications can be delayed with glycemic control in addition to 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

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

Demographics

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

Obesity

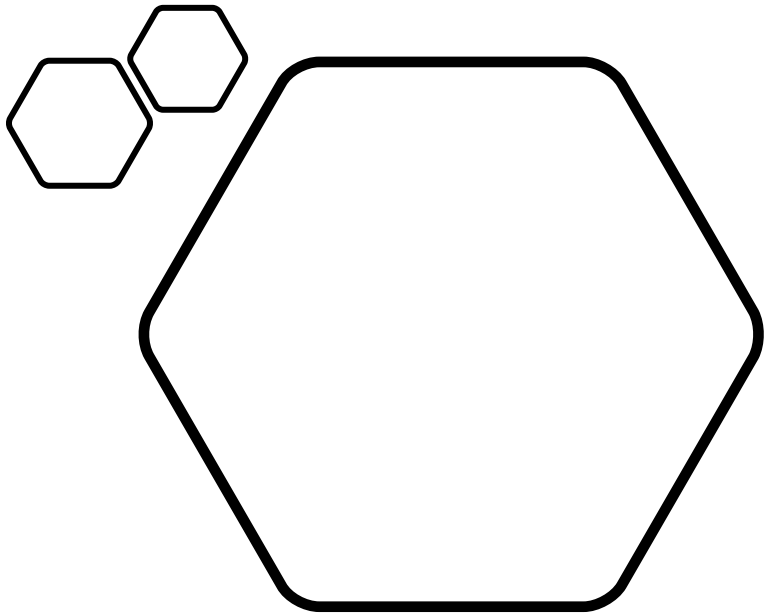
- Leads to reduced glucose uptake in the peripheral tissues (e.g., insulin resistance)
  - More pronounced in those with central or abdominal obesity (e.g., “male-type” obesity)
- More highly correlated to the risk of developing DM than age or race/ethnicity

Lifestyle

- Even without weight gain, physical inactivity increases risk
- Risk increases with longer duration and frequency of cigarette smoking
- There is some evidence to suggest that too little or too much sleep may increase risk.

Robertson RP. Risk factors for type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Abnormal Glucose Metabolism and Risk



- Categories of increased risk for diabetes (e.g., pre-diabetes)
  - Fasting plasma glucose: 100-125 mg/dL
  - 2-hour post-load glucose on 75 g oral glucose tolerance test: 140-199 mg/dL
  - A1C: 5.7-6.4%

Robertson RP. Risk factors for type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Diagnostic Criteria and Treatment Targets

Screening Recommendations

American Diabetes Association (ADA)	• Test at three-year intervals beginning at age 45 for anyone without risk factors or prior to age 45 in all adults with a BMI ≥25 kg/m^2 (or ≥23 kg/m^2 in Asian Americans) and one or more additional risk factors for diabetes • Positive results should be confirmed, per ADA diagnostic criteria
US Preventative Task Force (USPTF)	• Screen for abnormal glucose as part of cardiovascular risk assessment in adults ages 40 to 70 years who are overweight or obese • Suggested screening interval of every three years, based on limited evidence
Centers for Disease Control and Prevention (CDC)	• Screen individuals age 45 years and older and for those with risk factors • No screening interval specified

McCulloch DK and Hayward RA. Screening for type 2 diabetes mellitus. In: UpToDate, Givens J (Ed), UpToDate, Waltham, MA, 2020.

ADA Criteria for Diagnosis

A1C ≥ 6.5%*

OR

Fasting (x 8 hours) plasma glucose ≥ 126 mg/dL*

OR

2-hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test*

OR

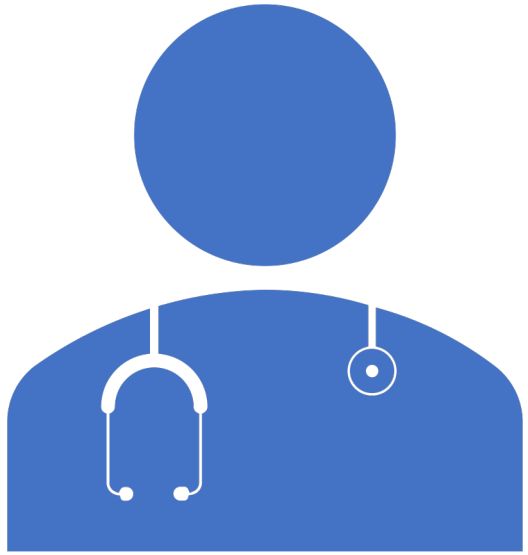
Random plasma glucose ≥ 200 in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

**** Diagnosis is confirmed if (1) two different tests (e.g., A1C and fasting plasma glucose) run on the same sample are both concordant; OR (2) the same diagnostic test result is confirmed on a subsequent day by repeat measurement***

McCulloch DK and Hayward RA. Screening for type 2 diabetes mellitus. In: UpToDate, Givens J (Ed), UpToDate, Waltham, MA, 2020.
Inzucchi SE and Lupsa B. Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Monitoring

- Once a diagnosis has been confirmed, A1C should be monitored:
  - Twice yearly in patients meeting glycemic goals
  - Quarterly in patients who have had a change in therapy or who are not meeting glycemic goals
- A note on 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
  - Covered in more detail in module 2



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Weinsock RS. Self-monitoring of glucose in management of non-pregnant adults with diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Treatment Targets

- Not a one size fits all approach
  - Balance potential for improvement with risk for adverse effects
  - Keep in mind that most patients with type 2 DM do not achieve recommended goals for A1C reduction
  - It's ok to set an initial goal and modify that goal over time in order to set achievable targets
- A1C ≤ 7% 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. Initial management of blood glucose in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.
Wexler DJ. Overview of general medical care in nonpregnant adults with diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Blood Glucose and A1C Levels

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, 2020.

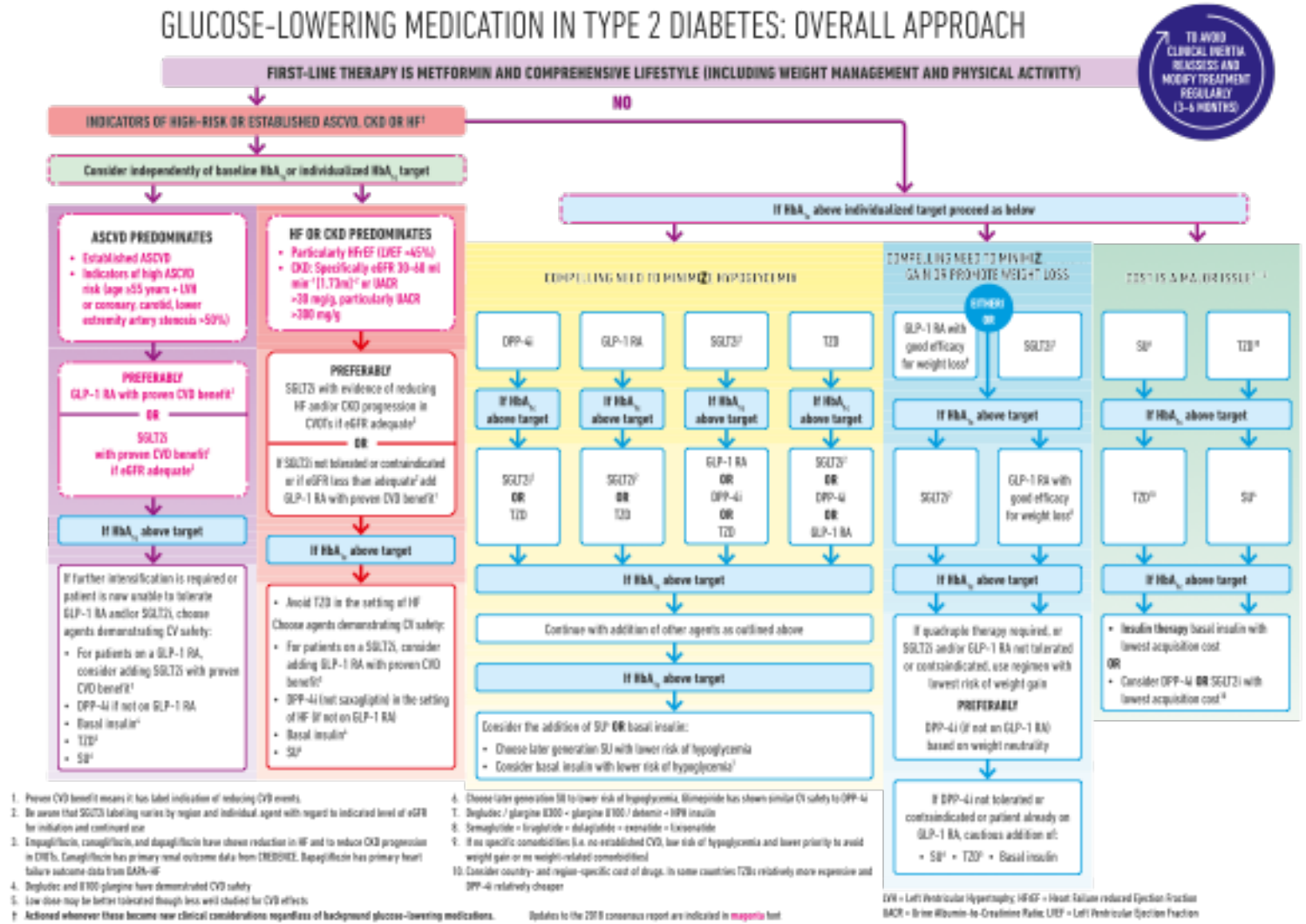
Pharmacologic Treatment

A Note on Prevention/Treatment of Pre-Diabetes

- Recommended first-line preventive therapy involved lifestyle changes
  - At least as effective as most pharmacological therapy at less cost and lower risk of adverse effects
- If pharmacologic therapy is preferred, metformin is recommended for select patient populations
  - Off-label (not currently approved for this use in the U.S.)
  - < 60 years of age, BMI ≥ 35 with impaired glucose tolerance, impaired fasting glucose, or A1C between 5.7% and 6.4% in whom lifestyle intervention has not improved glycemic control
  - Impact on micro- and macrovascular outcomes and mortality are currently unclear
  - Most effective in reducing the risk of diabetes in younger, obese patients or in women with a history of gestational diabetes
- A few other medications medications have shown efficacy for prevention, but are not currently recommended due to the potential for side effects

Robertson RP. Prevention of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Consensus Guidelines for Treatment



Buse JB, et al. 2019 Update to: Management of Hyperglycemia in 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. 2020;43:487-93.

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

Considerations

- Baseline A1C
- Treatment goals
- Existing comorbidities
- Signs and symptoms
- Patient preferences
- Medication efficacy, tolerability, and cost

Wexler DJ. Initial management of blood glucose in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Approach to INITIAL Therapy

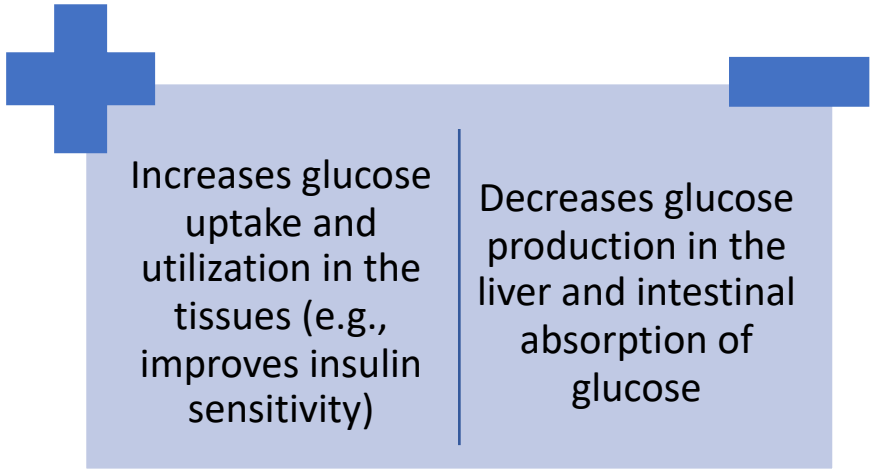
- A trial of lifestyle modification may be considered prior to initiation of pharmacologic therapy when the patient has clear and modifiable risk factors
- **Metformin** (in combination with comprehensive lifestyle change) is the initial therapy of choice for asymptomatic patients
- For patients who cannot tolerate or have a contraindication to metformin, an alternative agent should be selected based on comorbidities
- Regardless of baseline A1C or A1C target, patients with established cardiovascular disease should receive
  - GLP-1 receptor agonist with proven cardiovascular benefit when ASCVD predominates
  - SGLT-2 inhibitor shown to reduce HF and/or CKD progression when HF or CKD predominates
- 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



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

Metformin Dosing

- Immediate release
  - 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 a maintenance dose of 1 g twice daily OR 850 mg twice daily
- Extended release
  - 500 mg to 1 g once daily
  - Increase the dose gradually (500 mg incremental increase every 7 days)
  - Target a maintenance dose of 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, 2020.

Approach to Therapy Beyond Initiation

- Considerations
  - High risk for or established ASCVD, CKD, or HF?
  - Compelling need to minimize hypoglycemia?
  - Cost a major issue?
  - Compelling need to minimize weight gain or promote weight loss?
  - Current A1C level and relative potential impact of available therapies?

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Buse JB, et al. 2019 Update to: Management of Hyperglycemia in 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. 2020;43:487-93.

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
- Patients who initially respond well to monotherapy may later require combination therapy
  - 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
  - May be precipitated by patient compliance, weight gain, illness, disease progression, or use of medications that can induce hyperglycemia through a variety of mechanisms

Wexler DJ. Initial management of blood glucose in adults with type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.
Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Summary of Common Glucose Lowering Interventions

Class	Examples	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, depagliflozin, empagliflozin, ertugliflozin	0.5-0.7%
DPP-4 Inhibitors	Sitagliptin, saxagliptin, linagliptin, alogliptin	0.5-0.8%

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Insulin Therapy

- Place in therapy
  - Can be considered at diagnosis for patients well above A1C target
  - Likelihood of necessity increases as beta-cell function declines over time

Insulin Type	Approximate Onset	Peak Effect	Approximate Duration
Lispro, Aspart, Glulisine	3-15 min	45-75 min	2-4 hrs
Regular	30 min	2-4 hrs	5-8 hrs
NPH	2 hrs	4-8 hrs	8-18 hrs
Insulin glargine	2 hrs	No peak	20 to> 24 hrs
Insulin detemir	2 hrs	3-9 hrs	6-24 hrs
Neutral protamine lispro	2 hrs	6 hrs	15 hrs
Insulin degludec	2 hrs	No peak	> 40 hrs

Weinstock RS. General principles of insulin therapy in diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Sulfonylureas

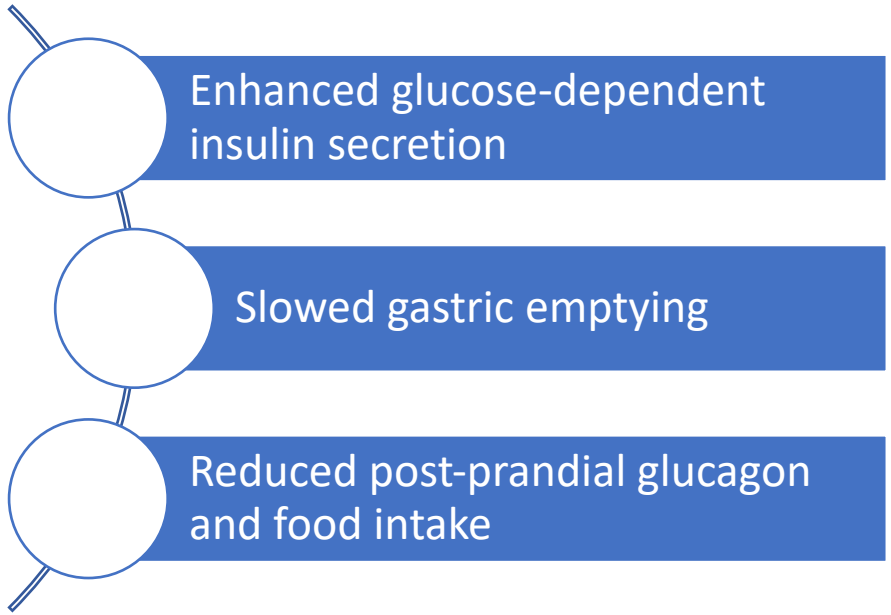
- Directly stimulate pancreatic beta cells to release insulin
- Clinical pearls:
  - Onset of action is quick
  - Modest weight gain is a common side effect
  - Potential for hypoglycemia
    - Glipizide and glimepiride are preferred over glyburide owing to their shorter duration of action and subsequent reduced risk for hypoglycemia
  - Short-acting sulfonylureas may be used as initial therapy in the following situations:
    - There is a contraindication to metformin
    - 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, 2020.

GLP-1 Receptor Agonists

- Injectable products, with the exception of 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



GLP-1 Receptor Agonists

- Most often used
  - For patients at high risk of or with established CVD when ASCVD predominates
  - In combination with metformin and/or another oral agent
  - After a failed trial of initial therapy with one or more oral agents
  - When weight loss and/or avoidance of hypoglycemia are primary concerns
  - When cost/coverage is not a major barrier
  - In patients without an aversion to injection therapy
- Should not be used in combination with DPP-4 inhibitors due to lack of additive benefit

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, 2020.

GLP-1 Receptor Agonists

- In clinical trials, longer-acting products have a significantly greater impact on A1C reduction than shorter-acting products
- Liraglutide, semaglutide, and dulaglutide are the preferred agents for patients with a history of myocardial infarction or stroke
- Longer-acting agents (liraglutide, once-weekly exenatide, dulaglutide, semaglutide) are preferred for patients without a history of ASCVD due to patient convenience
- A note on GLP-1 and insulin combinations
  - Two products available
  - Very modest (< 0.5% reduction in A1C) is seen when GLP-1 receptor agonist products are used in combination with basal insulin

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, 2020.
Insulin glargine and lixisenatide: Drug Information. In: Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2020. Available from: http://online.lexi.com. Accessed June 10, 2020.
Insulin degludec and liraglutide: Drug Information. In: Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2020. Available from: http://online.lexi.com. Accessed June 10, 2020.

Thiazolidinediones

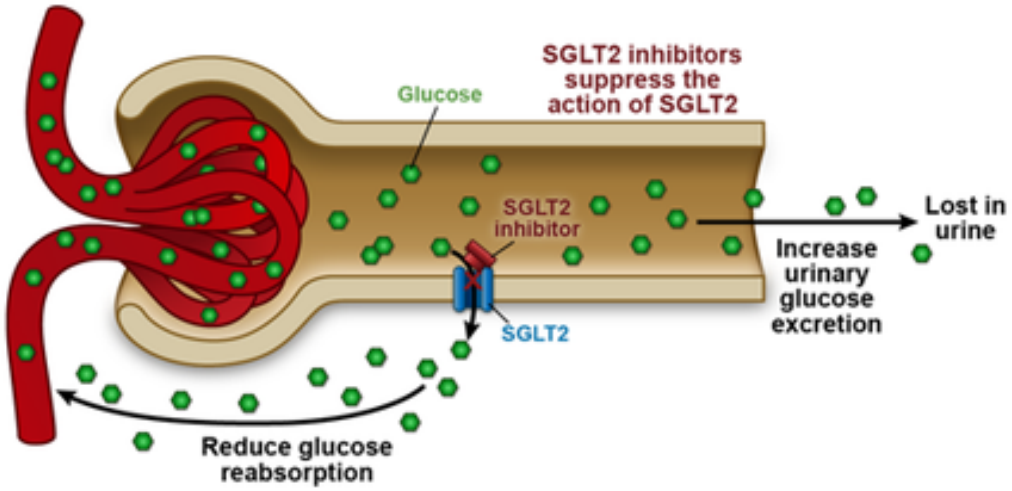
- Increase insulin sensitivity in the adipose tissue and muscle, increasing glucose utilization; to a lesser extent, they also decrease glucose production by the liver
- Limited utility as an initial therapy option
    - Pioglitozone for patients who have a contraindication to other oral agents, decline 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, 2020.

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



DeSantis A. Sodium-glucose co-transporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.
Image available from: https://www.medscape.org/viewarticle/869716_2. Accessed June 11, 2020.

SGLT2 Inhibitors

- Potential role:
  - Empagliflozin or canagliflozin for patients with atherosclerotic CVD not reaching their glycemic target with metformin plus lifestyle modification
  - Empagliflozin, canagliflozin, or dapagliflozin in patients with heart failure not achieving glycemic goals with metformin plus lifestyle modification
  - As a third agent in patients taking full dose metformin and sulfonylurea who cannot or will not take insulin
  - When the risk of hypoglycemia is high or when avoidance of weight gain is a priority

DeSantis A. Sodium-glucose co-transporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

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
- 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

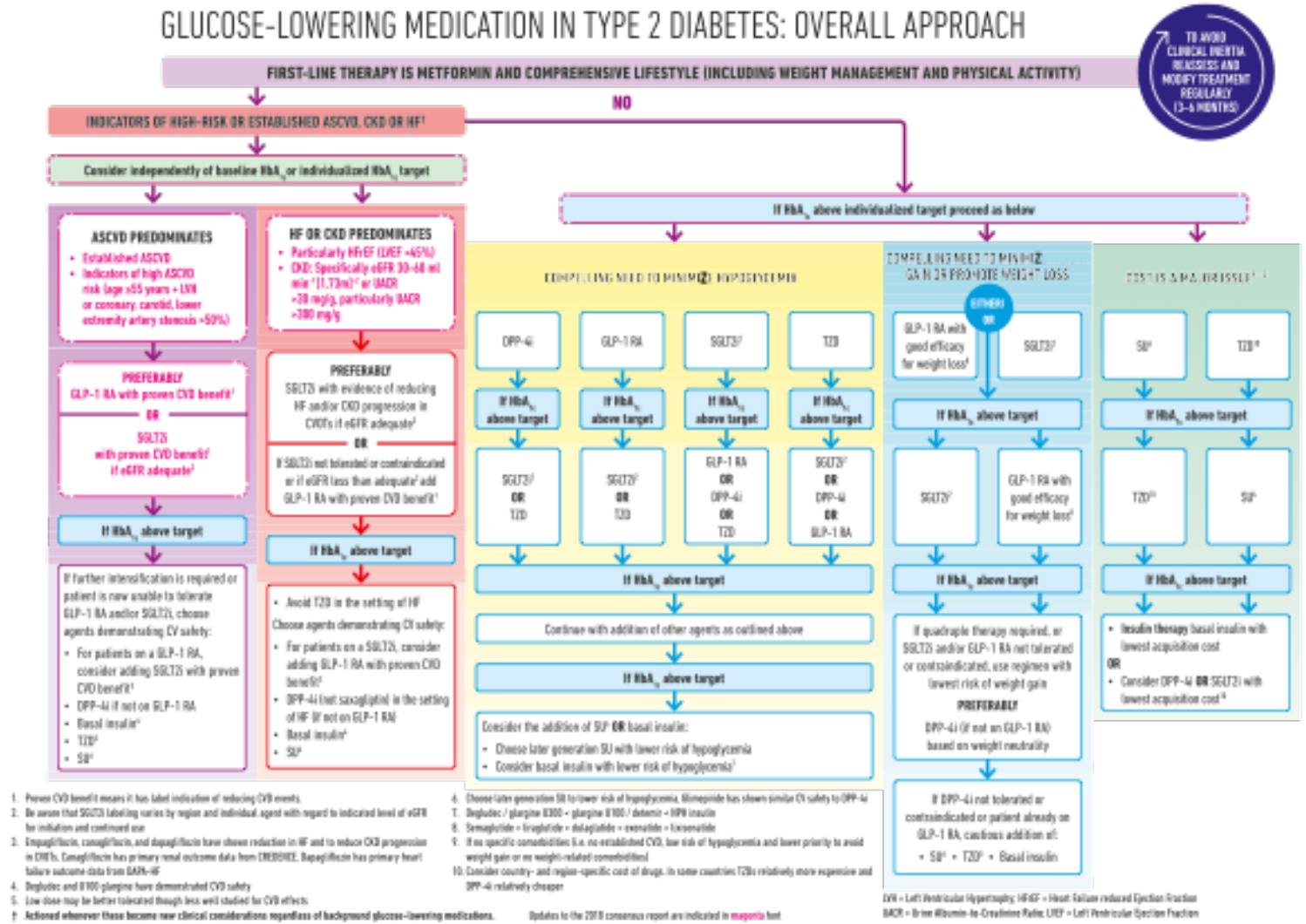
Dungan K and DeSantis A. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

DPP-4 Inhibitors

- Limited role as initial monotherapy
  - Example – linagliptin may be a good choice for a patient with chronic kidney disease who is unable to take metformin or other agents
- Can be considered as add-on therapy for patients not achieving glycemic control using metformin, thiazolidinediones, SGLT-2 inhibitors, or a sulfonylurea
- Incomplete information regarding long-term efficacy and safety, cost concerns, and modest efficacy impact the utility for this drug class
- Should not be used in combination with GLP-1 receptor agonists due to lack of additive benefit

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



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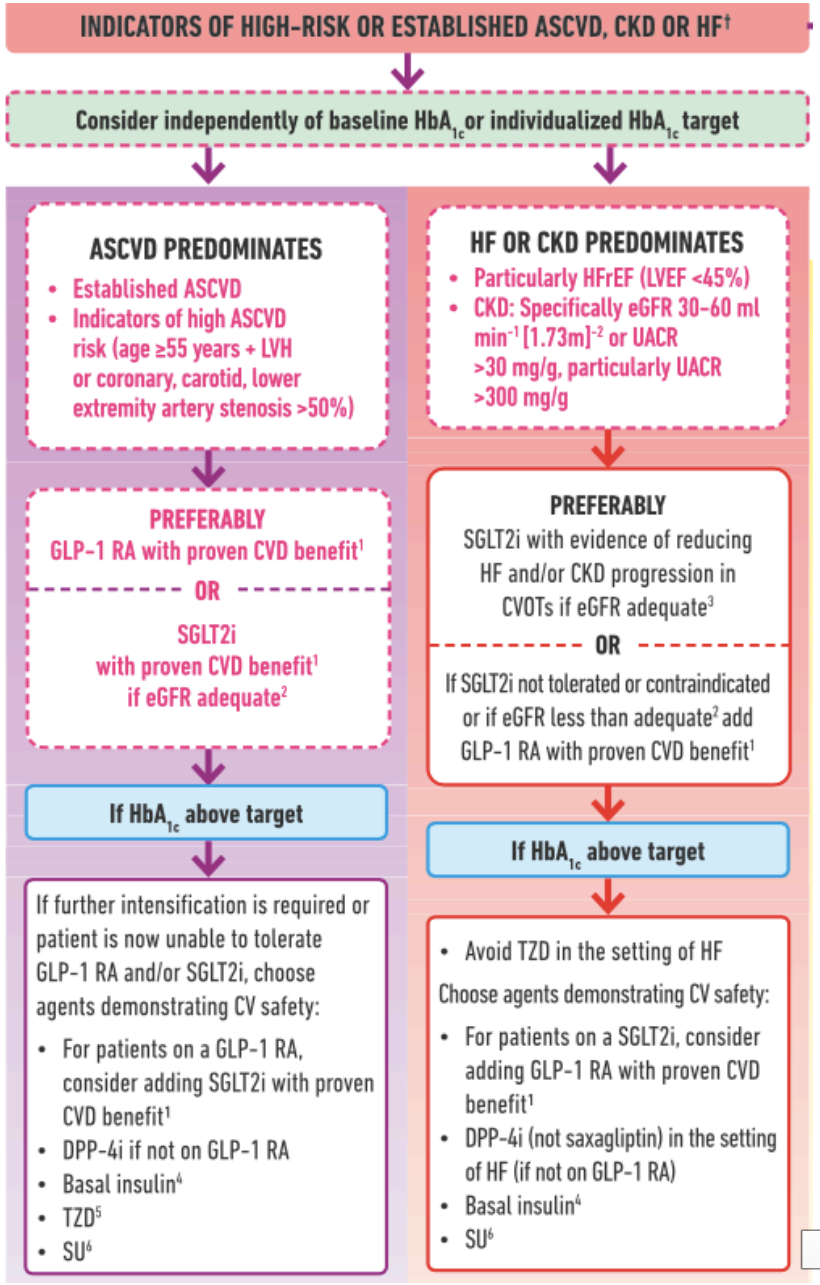
Consensus Guidelines for Treatment

- 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 or HF/CKD predominates



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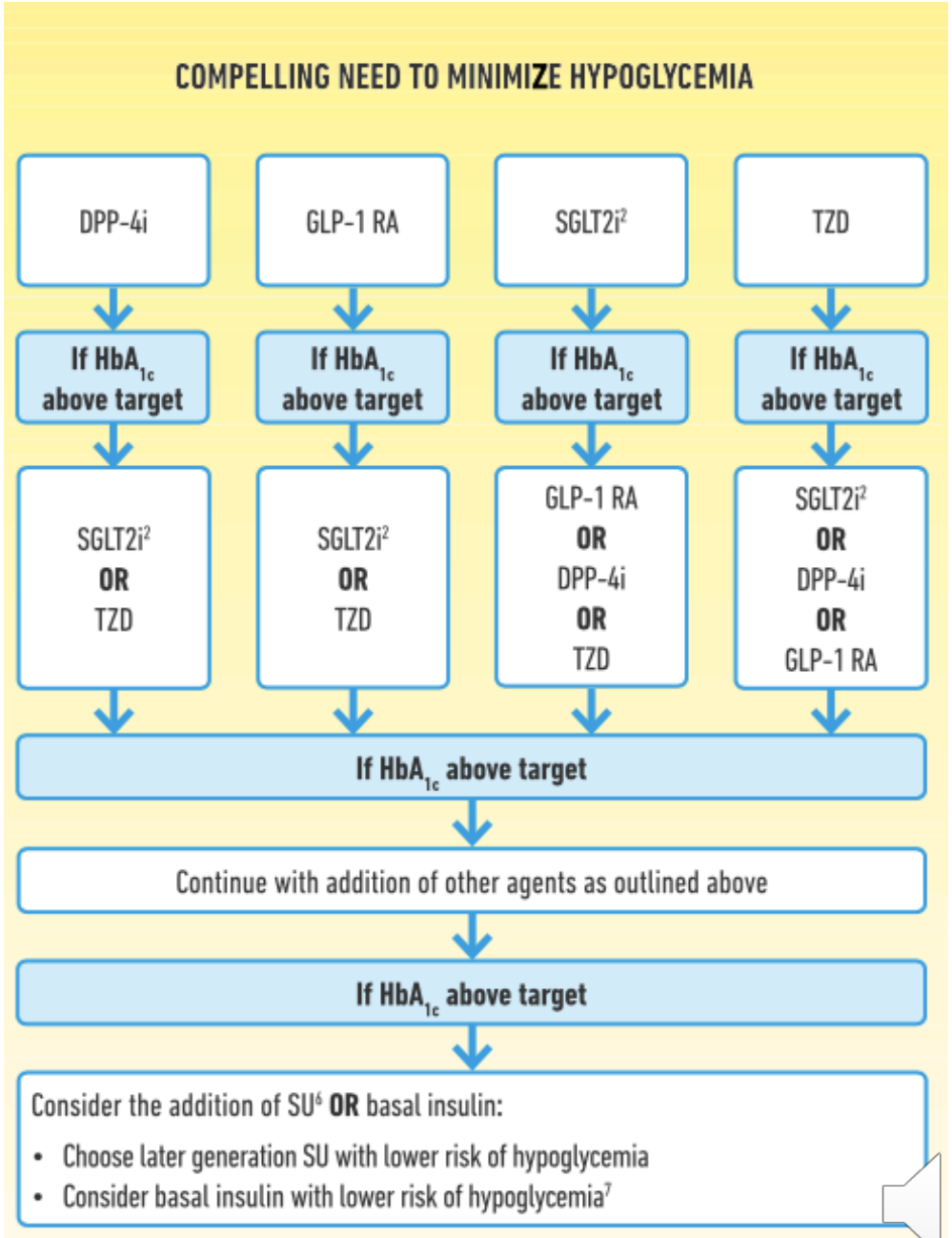
Consensus Guidelines for Treatment

- 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:

Buse JB, et al. 2019 Update to: Management of Hyperglycemia in 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. 2020;43:487-93.

Consensus Guidelines for Treatment

- When there is a compelling need to minimize hypoglycemia
  - Long-acting sulfonylurea agents (e.g., glyburide) should be avoided



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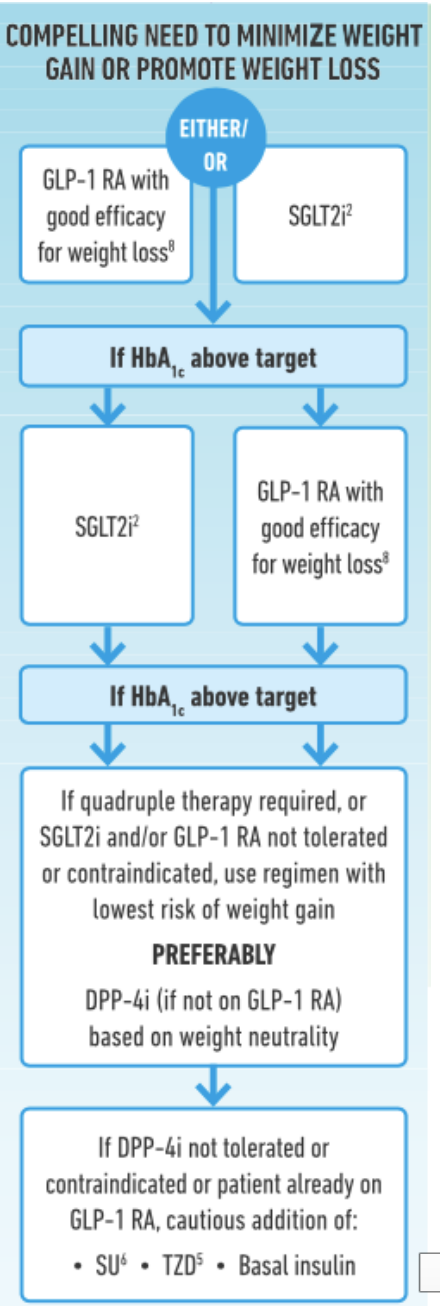
Consensus Guidelines for Treatment

- When there is a compelling need to minimize weight gain or promote weight loss
  - Weight neutral products or products associated with weight loss should be prioritized
  - Sulfonylurea and thiazolidinediones should be avoided, if possible



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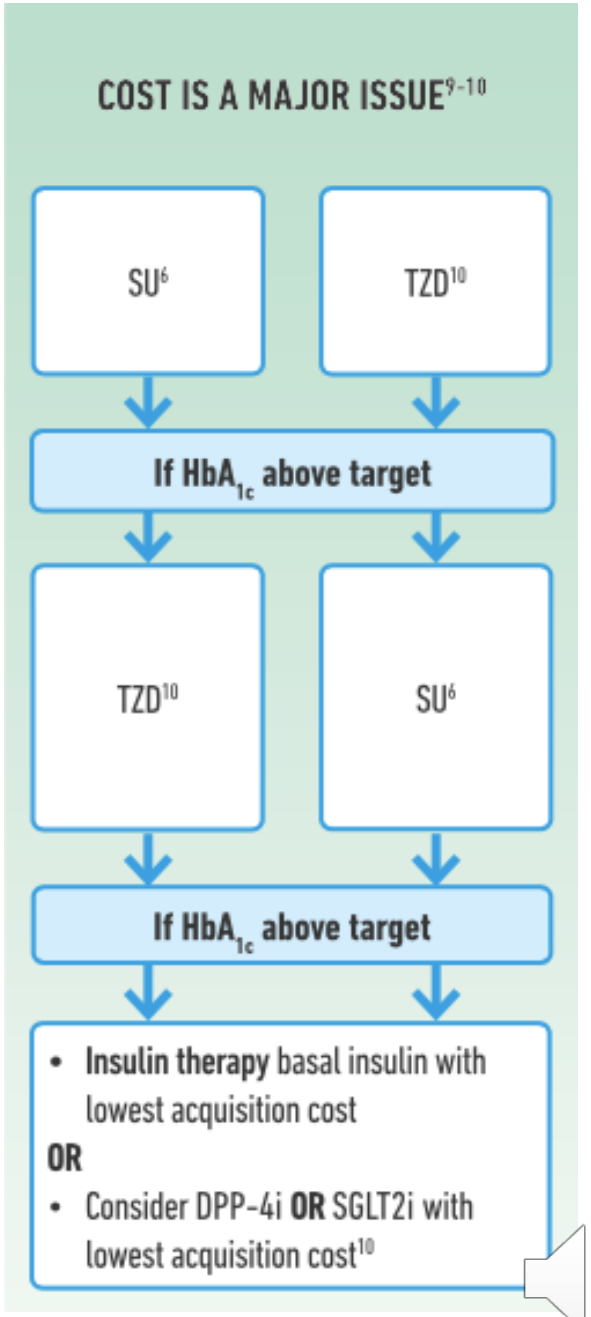
Consensus Guidelines for Treatment

- 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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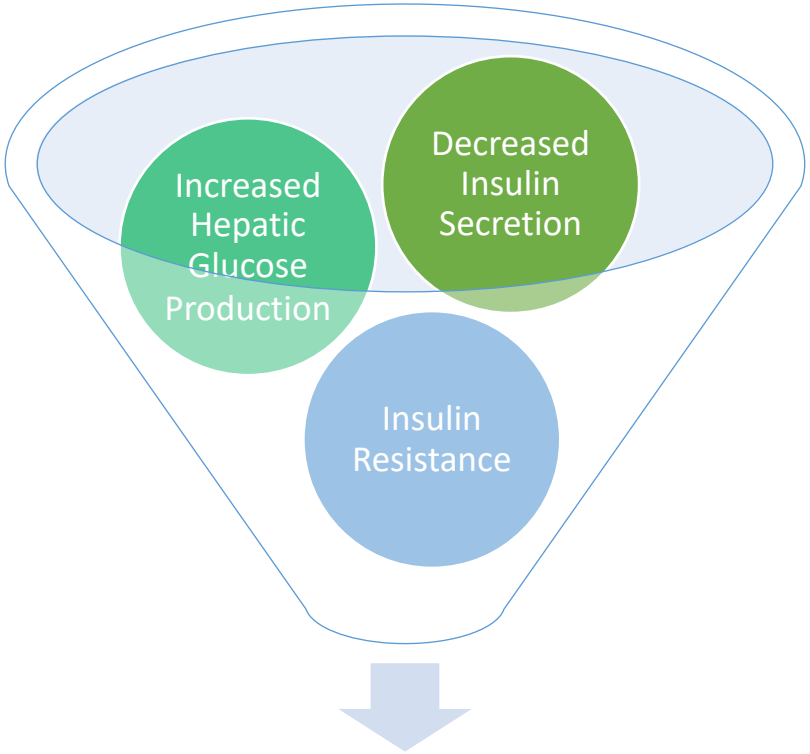
Medication-Induced Hyperglycemia

Drug-Induced Hyperglycemia



Drug-Induced Hyperglycemia

McCulloch DK and Robertson RP. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Thiazide Diuretics

- Examples include hydrochlorothiazide (HCTZ), chlorthalidone, chlorothiazide, and indapamide
- Use is associated with an increase in fasting plasma glucose
  - A substantial increase is unusual at currently recommended doses
- Loss of potassium in the urine leads to hypokalemia (e.g., low potassium levels), which is associated with a higher risk of developing type 2 DM
  - Due to decreased insulin secretion and increased insulin resistance
  - Can be mitigated with potassium replacement therapy

McCulloch DK and Robertson RP. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Antipsychotics

- Hyperglycemia may worsen in patients with established diabetes that are started on an antipsychotic agent
- The atypical antipsycotics clozapine and olanzapine, in particular, have been associated with weight gain, obesity, hypertriglyceridemia, and development of diabetes mellitus
- Risperidone and quetiapine increase the risk of weight gain, but there is conflicting data regarding diabetes and dyslipidemia risk
- Ziprasidone and aripiprazole do not increase the risk for diabetes or dyslipidemia

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Drug-Induced Hyperglycemia

- Some beta blockers (e.g., atenolol, metoprolol, propranolol) moderately decrease insulin sensitivity
  - Carvedilol does not appear to have this effect
- Niacin alters hepatic glucose metabolism
  - The effect is likely greater with the extended release formulation
- Statins may (evidence is conflicting) have a low risk of impaired glucose tolerance
- Combination estrogen-progestin oral contraceptives (OCs) and progestin-only contraceptives may cause altered hepatic glucose metabolism as well as peripheral insulin resistance
  - OCs with low doses of ethinyl estradiol (≤ 35 mcg) have little effect on carbohydrate metabolism in most women

McCulloch DK and Robertson RP. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Drug-Induced Hyperglycemia

Anti-Infectives

- HIV therapy, specifically protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs) increase peripheral insulin resistance, thereby contributing to antiretroviral-associated metabolic syndrome
- Rare reports of moxifloxacin altering insulin secretion
- Pentamidine alters pancreatic beta cell function

Glucocorticoids

- An example is prednisone
- Use can result in clinically significant drug-induced hyperglycemia as a result of a multifactorial impact on hepatic glucose production, increased insulin resistance, etc.

Immunosuppressants

- Examples include cyclosporine, sirolimus, and tacrolimus
- Use results in decreased insulin production and release

McCulloch DK and Robertson RP. Pathogenesis of type 2 diabetes mellitus. In: UpToDate, Mulder JE (Ed), UpToDate, Waltham, MA, 2020.

Summary

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

Thank you!