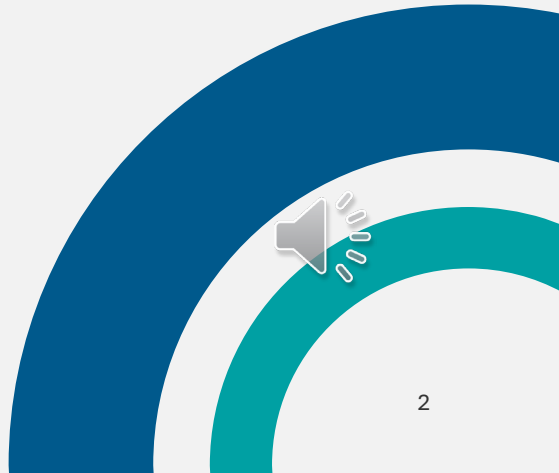
Type 2 Diabetes: Glucagon-Like Peptide 1 (GLP-1) Agonist & Dipeptidyl Peptidase 4 (DPP-4) Inhibitor Concurrent Use

Veronica Trinidad, University of Florida
Vimalpreet Khinda, University of the Pacific
PharmD Candidates 2026
Managed Care APPE Rotation

Objectives

1. Define Type 2 Diabetes Mellitus (T2DM), including Epidemiology, and Prevalence
2. Explain Pathophysiology, Risk Factors, and Diagnosis Criteria for T2DM
3. Review Treatment Standards of Care (Guidelines and Medications)
4. Compare GLP-1 Receptor Agonists vs. DPP-4 inhibitors
5. Discuss Therapy Considerations and Medications to Avoid

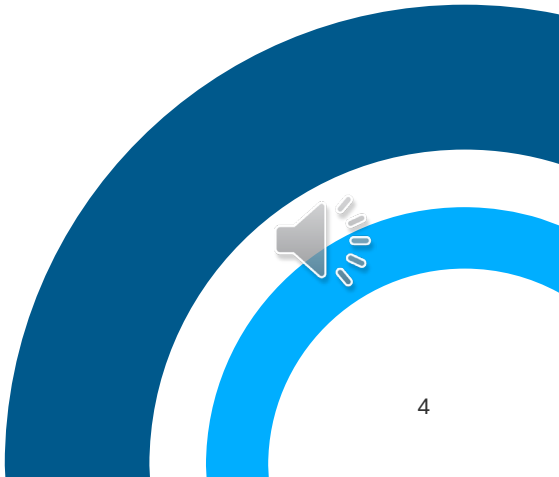


Background

Type 2 Diabetes Mellitus (T2DM)

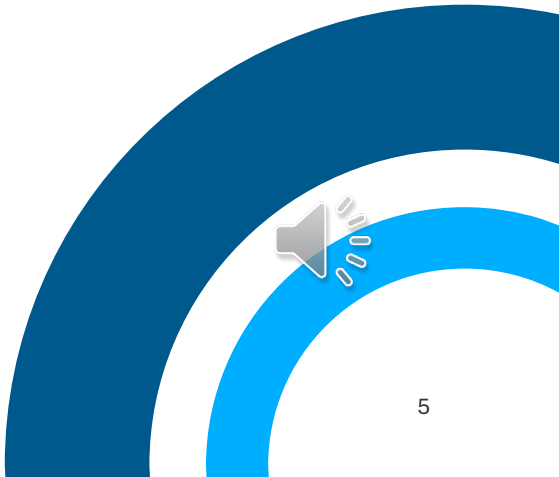
- A heterogeneous metabolic disorder characterized by hyperglycemia, a progressive loss of adequate B-cell insulin secretion, relative insulin deficiency and insulin resistance

- Associated with risk of microvascular and macrovascular complications



Epidemiology and Prevalence

- More common in adults; youth increased over the past 2 decades
- Strongly associated with obesity and physical inactivity
- More common among African American, Hispanic/Latino, American Indian, Alaska Native, and Asian American groups
- 462 million people worldwide are living with T2D, affecting 6.28% of the global population
- Prevalence is highest in rapidly developing regions (e.g., Pacific Island)
- Forecasts are projecting over 700 million cases by 2030-2040

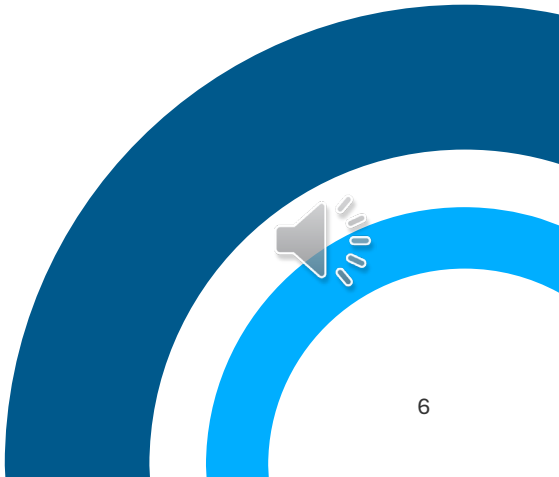


Pathophysiology

- Type 2 Diabetes Mellitus is a condition characterized by
  - Insulin resistance
  - Impaired insulin secretion by pancreatic β-cells
  - Inadequate compensatory insulin response

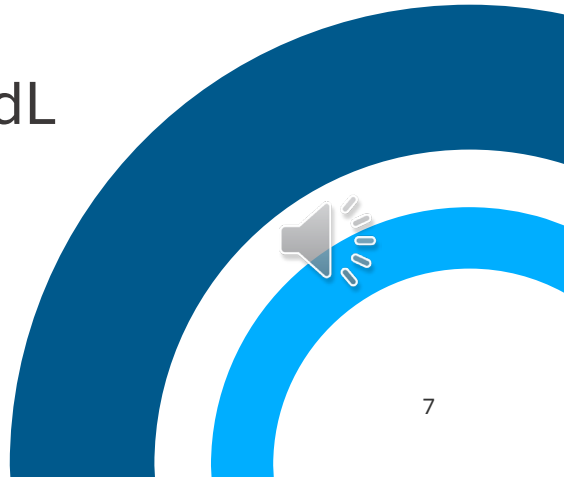
- Decreased insulin secretion during β-cell dysfunction can limit the body's ability to maintain glucose levels while insulin resistance can lead to increased glucose production.

- Organs involved in T2DM include the liver, kidneys, pancreas, brain, small intestine, adipose tissue, and skeletal muscle.



Risk Factors

- Having a first-degree relative with diabetes
- History of cardiovascular disease
- High-risk race, ethnicity and ancestry
- Hypertension
- Individuals with Polycystic Ovary Syndrome (PCOS)
- Gestational diabetes
- Physical inactivity
- Overweight or obesity
- HDL cholesterol level < 35 mg/dL and/or triglyceride level > 250 mg/dL

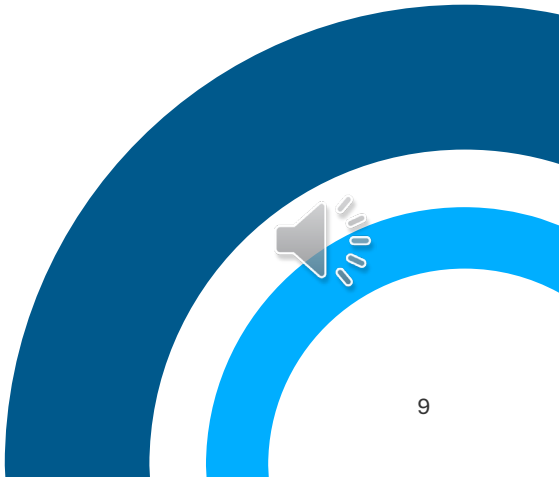


Diagnosis of Type 2 Diabetes (ADA Criteria)

- A1c ≥ 6.5%
- Fasting Plasma Glucose ≥ 126 mg/dL
- 2-Hour Plasma Glucose ≥ 200 mg/dL OGTT
- Random Plasma Glucose ≥ 200 mg/dL (in individuals with classic symptoms of hyperglycemia or hyperglycemic crisis)

Symptoms

- Polyuria
- Polydipsia
- Polyphagia
- Extreme fatigue
- Blurry vision
- Slow-healing cuts or bruises
- Tingling, pain, or numbness in the hands and feet
- Unexplained weight loss



Complications of T2D

Microvascular Complications

- **Retinopathy**
  - Most common cause of vision loss in adults
  - Associated with long term hyperglycemia, hypertension, and dyslipidemia
- **Neuropathy**
  - Includes peripheral and autonomic neuropathy
  - Loss of protective sensation, pain, gait abnormalities, and higher risk of foot ulcers and amputations
- **Foot Complications**
  - Caused by peripheral artery disease, neuropathy, and structural deformity
  - Increase risk of amputations, ulcerations and infections

Complications of T2D

Macrovascular Complications

- **Cardiovascular Disease (CVD)**
  - Leading cause of death
  - T2D is associated with an elevated risk of CVD
- **Cerebrovascular Disease (CVA)**
  - Leading cause of mortality and severe morbidity
  - T2D is associated with an elevated risk of stroke
- **Peripheral Artery Disease (PAD)**
  - Higher risk of lower-extremity complications and amputations
  - Greater rates of cardiovascular events and mortality

Treatment/Standard of Care

General Approach

- Lifestyle
  - Lifestyle/behavioral intervention with individualized calorie meal plan is highly effective to prevent and/or delay T2D
  - Healthy eating pattern: nutrient-rich foods, high fiber, less ultra processed foods
  - Physical activity: aerobic exercise and resistant training
  - Weight management: 3-7% loss for metabolic benefit
  - Avoid alcohol and tobacco products

- Blood glucose targets
  - Fasting/pre-prandial: 80-130 mg/dL
  - Post-prandial: < 180 mg/dL
  - A1c: < 7% for most adults

Hypoglycemia: Symptoms

- ADA classifies hypoglycemia into
  - Level 1 (< 70 mg/dL)
  - Level 2 (< 54 mg/dL)
  - Level 3 (severe event requiring assistance)

- Symptoms
  - Shakiness
  - Irritability
  - Confusion
  - Hunger
  - Sweating
  - Tachycardia

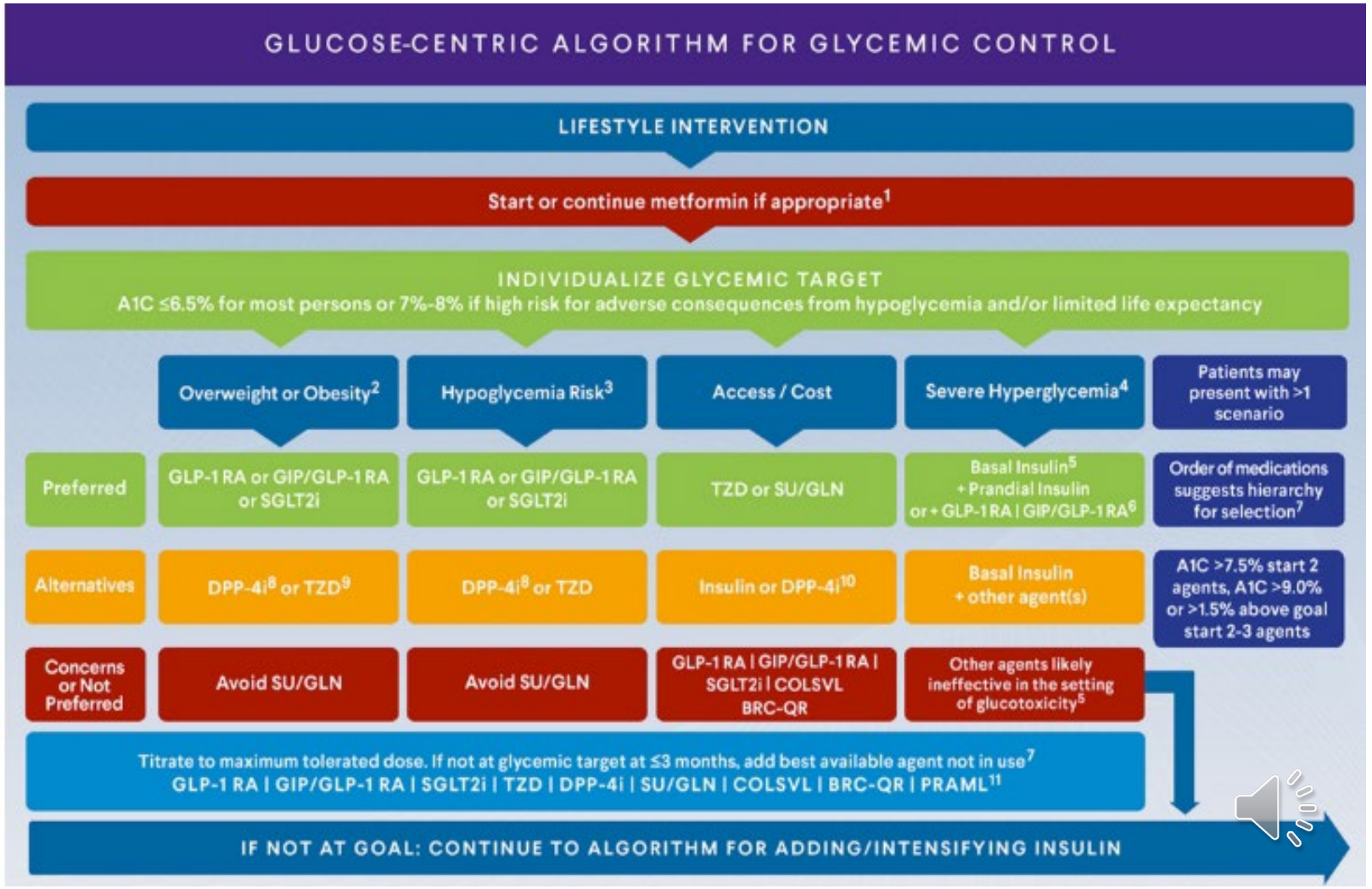
Hypoglycemia: Risk Factors and Treatment

- Risk factors include
  - Recent episodes of level 2 or 3 hypoglycemia
  - Intensive insulin therapy
  - Impaired hypoglycemia awareness
  - End-Stage Kidney Disease (ESKD)
  - Cognitive impairment

- Treatment:
  - 15-15 rule
    - 15 g fast-acting carbohydrates
    - Recheck blood glucose after 15 minutes
    - Repeat treatment if blood glucose is < 70 mg/dL

Treatment Algorithm

- Pharmacotherapy is typically started at the time of diagnosis
- The plan should be individualized to the patient's goals with respect to glucose lowering, cardiovascular and kidney disease risk, weight, treatment burden, and other health conditions



2023 AACE Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm | American Association of Clinical Endocrinology

Medications

- Biguanides:
  - Metformin
- Sulfonylureas:
  - Glipizide (Glucotrol XL)
  - Glimepiride (Amaryl)
  - Glyburide (Glynase)
- Insulin:
  - Rapid Acting: Aspart (Novolog), Lispro (Humalog)
  - Short Acting: Regular (Humulin R, Novolin R)
  - Intermediate Acting: NPH (Humulin N, Novolin N)
  - Long Acting: Glargine (Lantus, Toujeo, Basaglar)
  - Ultra Long Acting: Degludec (Tresiba)
- Meglitinides:
  - Repaglinide
  - Nateglinide
- Thiazolidinediones (TZDs):
  - Pioglitazone (Actos)
- Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors:
  - Empagliflozin (Jardiance)
  - Dapagliflozin (Farxiga)
  - Canagliflozin (Invokana)
  - Bexagliflozin (Brenzavvy)
  - Ertugliflozin (Steglatro)

GLP-1 Receptor Agonists vs. DPP-4 Inhibitors

GLP-1 Receptor Agonists

MOA

- Analogs of the incretin hormone GLP-1
- Increase insulin secretion
- Decrease glucagon secretion
- Slows gastric emptying → promotes weight loss

Choice of Therapy

- ASCVD or cardiovascular protection
- A1C and glycemic control
- Obesity
- CKD or kidney benefit
- Avoidance of hypoglycemia

Contraindications

- Personal or family history of medullary thyroid carcinoma (MTC)
- History of Multiple Endocrine neoplasia syndrome type 2 (MEN2)
- Serious hypersensitivity

Boxed Warning

- Risk of Thyroid C-cell tumors
- Gallbladder disease
- GI effects
- Acute kidney injury
- Diabetic retinopathy risk

Side Effects

- Weight loss
- Nausea
- Vomiting
- Diarrhea
- Injection site reactions

GLP-1 Receptor Agonists

- Liraglutide (Victoza)
  - Dosing: 0.6 mg SC daily x 1 week → 1.2 mg SC daily
- Dulaglutide (Trulicity)
  - Dosing: 0.75 mg SC weekly
- Semaglutide (Ozempic)
  - Dosing: 0.25 mg SC weekly x 4 weeks → 0.5 mg weekly
- Exenatide (Byetta)
  - Dosing: 5 mcg SC BID x 1 month → 10 mcg BID
- Exenatide ER (Bydureon BCise)
  - Dosing: 2 mg SC weekly
  - Discontinued in the U.S.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes- SUSTAIN-6

- Study Design: Randomized, double-blind, placebo-controlled trial in 3,297 patients with type 2 diabetes and high cardiovascular risk
  - Semaglutide 0.5 mg or 1.0 mg weekly vs placebo for 104 weeks

Primary Outcome: Composite of **cardiovascular death**, non-fatal Myocardial Infarction (MI), **or** non-fatal **stroke**

- Semaglutide reduced MACE from 8.9% to 6.6% -HR 0.74 (95% CI 0.58-0.9)
- 26% relative risk reduction; significant for non-inferiority and superiority (p=0.02)

Key Secondary Findings:

- Non-fatal stroke HR 0.61 (p= 0.04)
- Non-fatal MI HR 0.74 (p=0.12)
- Reduction in new or worsening nephropathy HR 0.64 (p=0.005)
- Retinopathy complications HR 1.76 (p=0.02)

Conclusion:

- Semaglutide reduces MACE, particularly the risk of non-fatal stroke.

DPP-4 Inhibitors

MOA

- DPP-4 inhibitors work by preventing DPP-4 from breaking down incretin (including GLP-1 and Gastric inhibitory polypeptide (GIP)). These hormones increase glucose-dependent insulin secretion and decrease glucagon secretion which helps to regulate blood glucose levels.

Choice of Therapy

- Weight neutral
- Blood glucose reduction

Warnings

- Pancreatitis
- Arthralgia
- Renal failure
- Risk of HF (Saxagliptin and Alogliptin)
- Hepatotoxicity (Alogliptin)

Side Effects

- Upper Respiratory Tract Infections
- Headache
- Rash
- Nasopharyngitis

Interactions

- Saxagliptin and linagliptin are substrates of CYP450 3A4 and P-gp
- Use caution with inducers and inhibitors

DPP-4 Inhibitors

- Sitagliptin (Januvia)
  - Dosing: 100mg PO daily
  - Renal Dosing: eGFR 30 - <45: 50mg PO daily, eGFR <30: 25mg PO daily
- Linagliptin (Tradjenta)
  - Dosing: 5mg PO daily
  - No renal dose adjustments
- Saxagliptin (Onglyza)
  - Dosing: 2.5-5mg PO daily
  - Renal Dosing: eGFR <45: 2.5mg PO daily
- Alogliptin
  - Dosing: 25mg daily
  - Renal Dosing: CrCl 30 - <60: 12.5mg PO daily, CrCl <30: 6.25mg PO daily

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk (CARMELINA)

- Study design: Randomized, double-blind, placebo-controlled trial

Primary Outcome: Time to first cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke

- Results:
  - Linagliptin group: occurred in 434 participants
  - Placebo group: occurred in 420 participants

Secondary Outcome: Time to first occurrence of a composite of adjudication-confirmed ESRD, death due to renal failure, or a sustained decrease of at least 40% in eGFR from baseline

- Result:
  - Linagliptin group: occurred in 327 participants
  - Placebo group: occurred in 306 participants

Conclusion:

- The study results did not demonstrate any significant benefit of linagliptin for CV benefit or kidney benefit. Linagliptin was non-inferior compared to placebo for both outcomes. There were no significant changes in weight

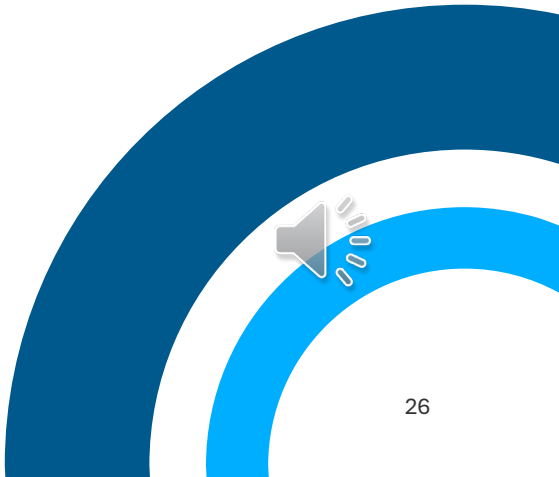
Therapy Considerations and When to Avoid Use

Therapy Considerations

- GLP-1 agonists and DPP-4 inhibitors are not concurrently used due to overlapping mechanism of action

- GLP-1 RAs are preferred for:
  - Weight Loss
  - Cardiovascular Protection (ASCVD or high risk, heart failure)
  - Chronic Kidney Disease (to slow progression)
  - Need for a greater blood glucose reduction

- DPP-4 inhibitors are preferred for:
  - Mild to moderate blood glucose reduction
  - Neutral weight loss



Avoid

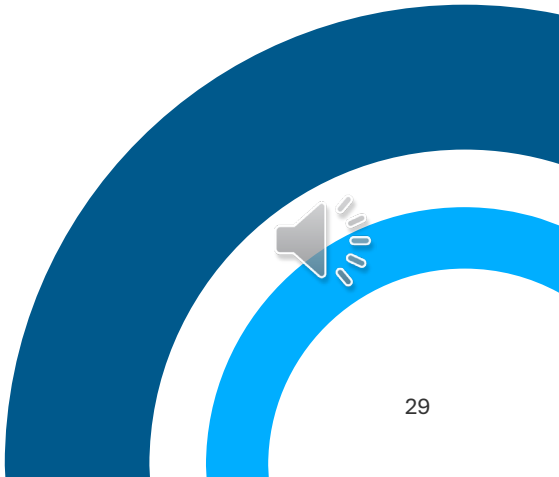
- **GLP-1 RAs + DPP-4 inhibitors**
  - Provides only modest improvement in glycemic control with minimal weight loss benefit
  - Same incretin pathway
- **Insulin + sulfonylureas**
  - Increase the risk of hypoglycemia and weight gain
  - No clinical benefit
- **Heart Failure + TZDs**
  - Can cause fluid retention
  - Have a strong relationship with increased risk of HF
- **UTIs + SGLT2 inhibitors**
  - Lead to elevated glucose levels in the urine, which can cause mycotic or bacterial infections
  - Higher risk with recurrent UTIs

Avoid

- Alcohol Use + Metformin
  - Alcohol impairs the liver's ability to clear lactate
  - When combined with metformin the risk of lactic acidosis increases especially with kidney dysfunction or heavy alcohol intake

Summary of Key Points

- T2DM is a leading cause of health complications and death affecting hundreds of millions of people.
- Early detection and treatment improve outcomes and reduce risks.
- Multiple therapy options are available.
- The latest development includes GLP-1 agonists and DPP-4 inhibitors.
- Certain disease states and conditions favor and limit the use of certain medication classes.



References

- American Association of Clinical Endocrinology. Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update. Endocrine Practice. 2023;29(5):305–340. https://doi.org/10.1016/j.eprac.2023.02.001
- “Understanding Type 2 Diabetes.” Diabetes.org, American Diabetes Association, 2024, diabetes.org/about-diabetes/type-2.
- Lu, Y., Wang, W., Liu, J., Xie, M., Liu, Q., & Li, S. (2023). Vascular complications of diabetes: A narrative review. Medicine, 102(40), e35285–e35285. https://doi.org/10.1097/md.0000000000035285
- Khan MA, Hashim MJ, King J, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. *Journal of Epidemiology and Global Health*. 2020;10(1):107-111. https://doi.org/10.2991/jegh.k.191028.001.
- Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci*. 2020;21(17):6275. Published 2020 Aug 30. doi:10.3390/ijms21176275.
- Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA*. 2019;321(1):69-79. doi:10.1001/jama.2018.18269.
- Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other?. *Int J Clin Pract*. 2014;68(5):557-567. doi:10.1111/ijcp.12361.

References

- Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *NEJM*. 2016;375(19):1834-1844. doi:10.1056/nejmoa1607141.
- Kittipibul, V, Cox, Z, Chesdachai, S. et al. Genitourinary Tract Infections in Patients Taking SGLT2 Inhibitors: JACC Review Topic of the Week. JACC. 2024 Apr, 83 (16) 1568–1578. https://doi.org/10.1016/j.jacc.2024.01.040
- Laffel L, Svoren B. Epidemiology, presentation, and diagnosis of type 2 diabetes mellitus in children and adolescents. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on December 05, 2025.)
- U.S. Food and Drug Administration. [Drug Label for Glucophage (metformin hydrochloride)]. Silver Spring, MD: FDA; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020357s037s039,021202s021s023lbl.pdf
- Elsevier. Clinical Pharmacology [database]. ClinicalKeyClinicalKeyClinicalKey. Accessed December 16, 2025. Available from: https://www.clinicalkey.com/pharmacology/
- American Diabetes Association: Standards of Care in Diabetes – 2026. Diabetes Care Vol 49(Supplement 1): S132–S149. January 2026. https://doi.org/10.2337/dc26-S006.
- American Diabetes Association: Standards of Care in Diabetes – 2026. Diabetes Care Vol 49(Supplement 1): S89–S131 https://doi.org/10.2337/dc26-S005.
- Wexler DJ. Initial management of hyperglycemia in adults with type 2 diabetes mellitus. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on December 16, 2025)

References

- American Diabetes Association: Standards of Care in Diabetes – 2026. Diabetes Care Vol 49(Supplement 1): S27-S49. January 2026. https://doi.org/10.2337/dc26-S002.
- American Diabetes Association: Standards of Care in Diabetes – 2026. Diabetes Care Vol 49(Supplement 1): S183–S215. January 2026. https://doi.org/10.2337/dc26-S009.
- American Diabetes Association: Standards of Care in Diabetes – 2025. Diabetes Care Vol 48(Supplement 1): S27-S49. January 2025. https://doi.org/10.2337/dc25-S002
- American Diabetes Association: Standards of Care in Diabetes – 2025. Diabetes Care Vol 48(Supplement 1): S181-S206. January 2025. https://doi.org/10.2337/dc25-S009
- Dungan K, DeSantis A. Glucagon-like peptide-1 based therapies for the treatment of type 2 diabetes mellitus. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on December 16, 2025.)
- Dungan K, DeSantis A. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. In: UpToDate, Connor RF (Ed). Wolters Kluwer. (Accessed on December 16, 2025)
- Saxagliptin. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://uptodate.com. Accessed December 16, 2025.
- Alogliptin. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://uptodate.com. Accessed December 16, 2025.
- Linagliptin. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://uptodate.com. Accessed December 16, 2025.
- Sitagliptin. Lexi-Drugs. UpToDate Lexidrug. UpToDate Inc. https://uptodate.com. Accessed December 16, 2025.

Thank you!