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

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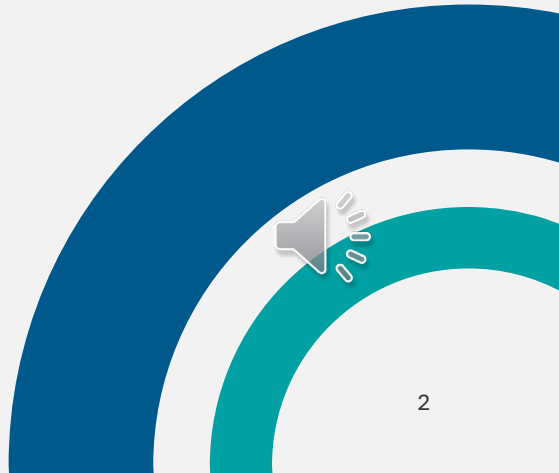
Managed Care APPE Rotation

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

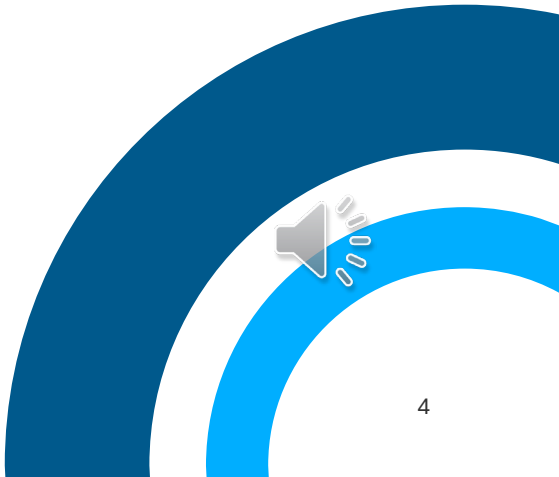


Background

Type 2 Diabetes Mellitus (T2DM)

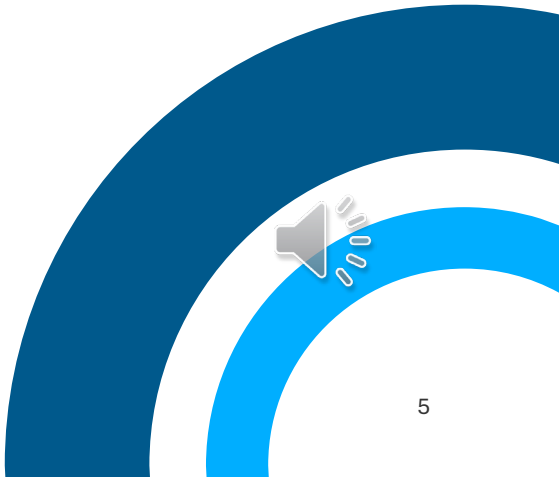
- A heterogeneous metabolic disorder characterized by hyperglycemia, a progressive loss of adequate B-cell insulin secretion, relative insulin deficiency and insulin resistance

- 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

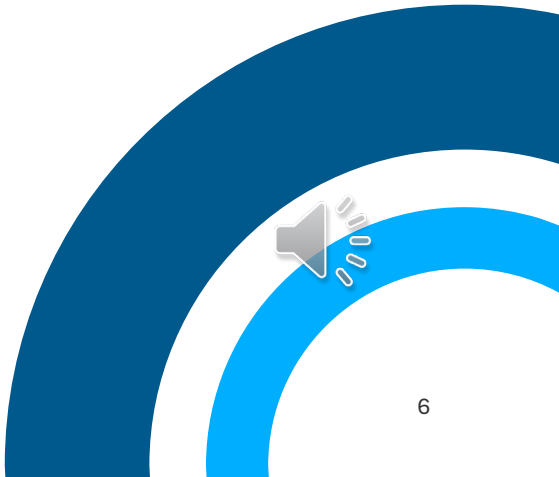


Pathophysiology

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

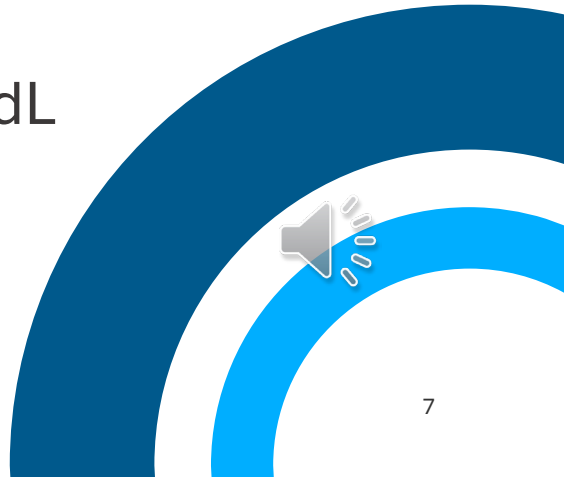
- Decreased insulin secretion during β-cell dysfunction can limit the body's ability to maintain glucose levels while insulin resistance can lead to increased glucose production.

- 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

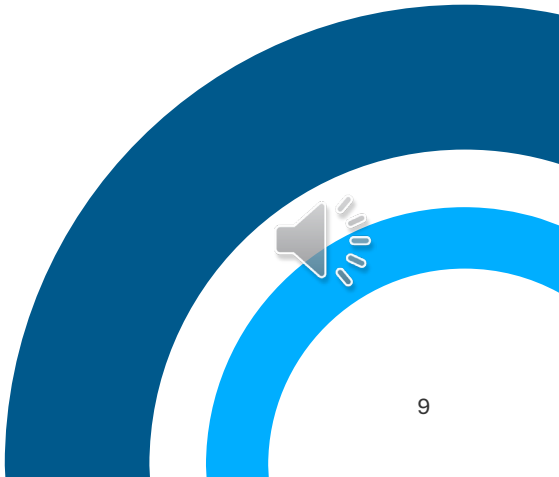


Diagnosis of Type 2 Diabetes (ADA Criteria)

- 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

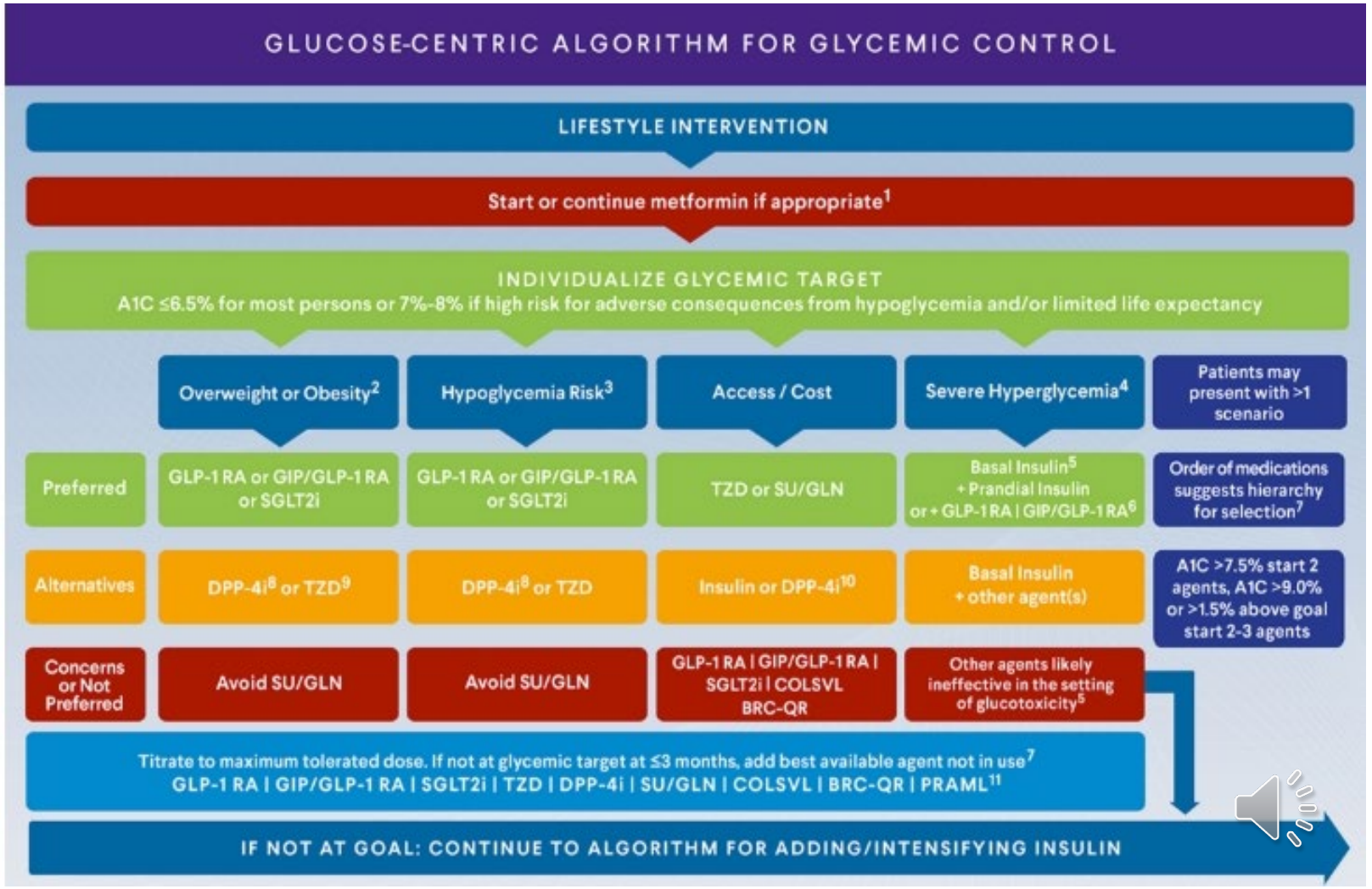
Hypoglycemia: Risk Factors and Treatment

- 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

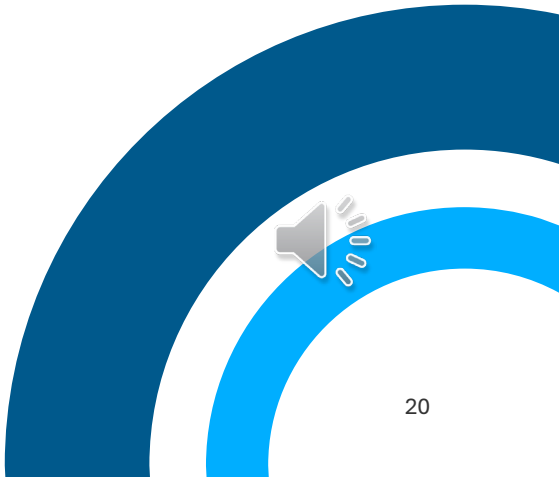
- Risk of Thyroid C-cell tumors
- Gallbladder disease
- GI effects
- Acute kidney injury
- Diabetic retinopathy risk

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

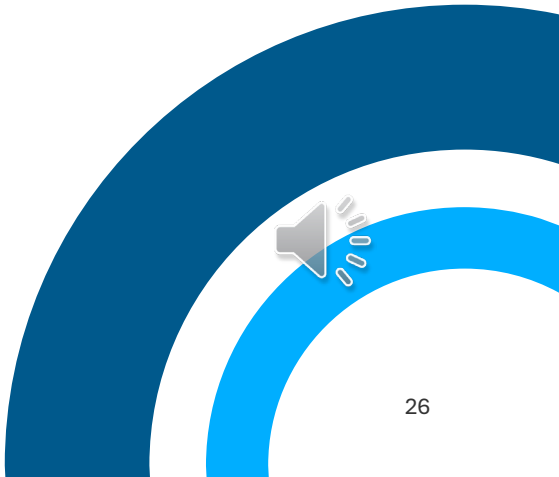
Therapy Considerations and When to Avoid Use

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

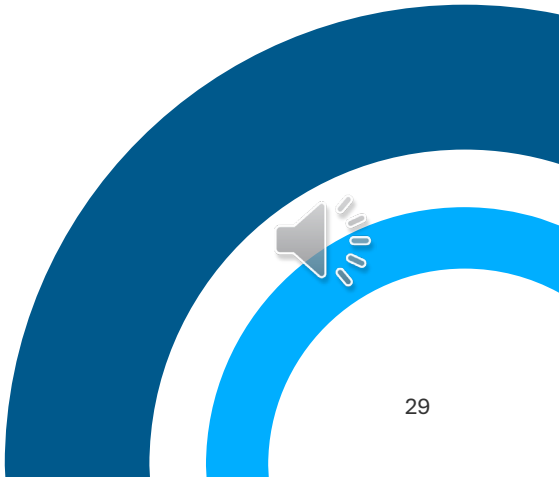
- **GLP-1 RAs + DPP-4 inhibitors**
  - Provides only modest improvement in glycemic control with minimal weight loss benefit
  - Same incretin pathway
- **Insulin + sulfonylureas**
  - Increase the risk of hypoglycemia and weight gain
  - No clinical benefit
- **Heart Failure + TZDs**
  - Can cause fluid 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.



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