AETC AIDS Education & Training Center Program
Southeast

Webcast Wednesday: Updates in Diabetes Treatment in Persons with HIV

Andrea Levin, PharmD, BCACP
Faculty, South Florida Southeast AETC
Assistant Professor,
Nova Southeastern University College of Pharmacy
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Disclosures

- The activity planners and speakers do not have any financial relationships with commercial entities to disclose.
- The speakers will not discuss any off-label use or investigational product during the program.
- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation

Objectives

- Discuss updates in the management of diabetes in persons with HIV
- Apply evidence-based recommendations to non-pharmacologic and pharmacologic treatment
- Identify counseling pearls for pharmacologic and non-pharmacologic therapies

Abbreviations

- Type 1 diabetes (T1DM)
- Type 2 diabetes (T2DM)
- Hemoglobin A1c (HbA1c)
- Blood glucose (BG)
- Fasting plasma glucose (FPG)
- Fasting blood glucose (FBG)
- Postprandial blood glucose (PPG)
- Total daily dose (TDD)
- Contraindication (CI)
- Black box warning (BBW)
- Glucagon-like peptide 1 receptor agonists (GLP1 RA)
- Sodium glucose cotransporter 2 inhibitors (SGLT2i)
- Dipeptidyl peptidase 4 inhibitors (DPP4-i)

Abbreviations

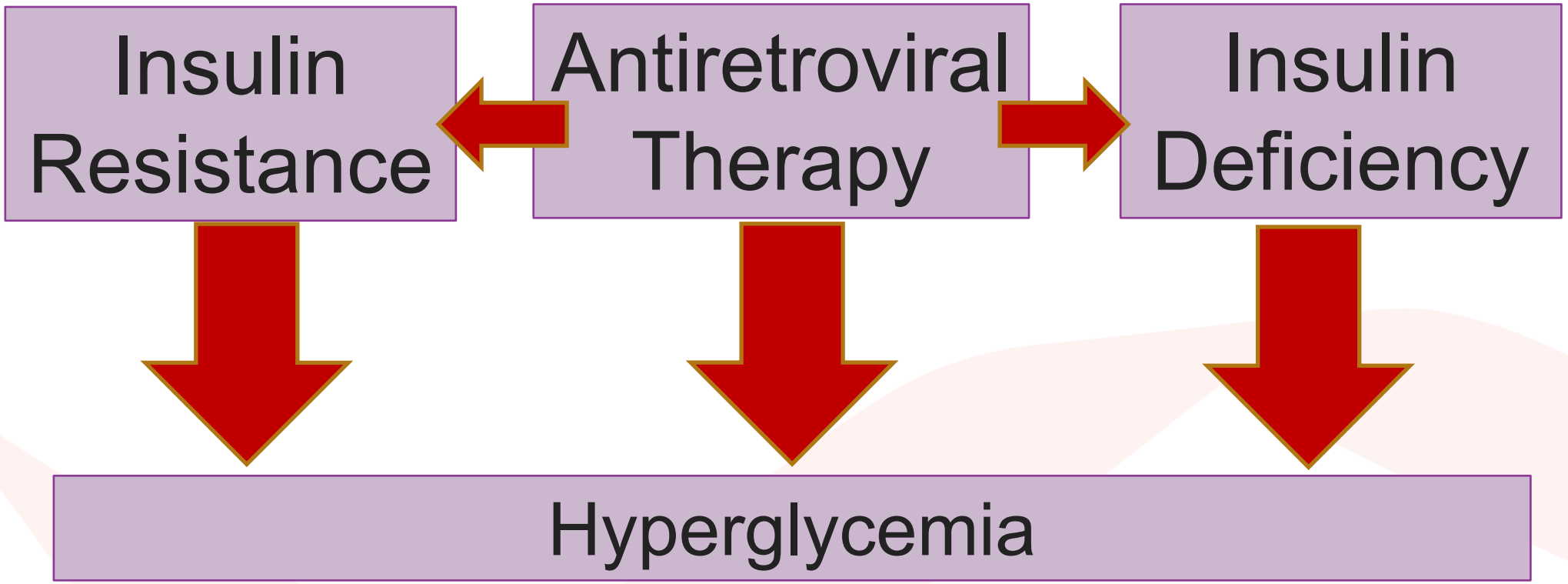
- Sulfonylureas (SU)
- Thiazolidinediones (TZDs)
- Meglitinides (Glinides)
- Alpha glucosidase inhibitors (AGi)
- Self monitoring blood glucose (SMBG)
- Atherosclerotic cardiovascular disease (ASCVD)
- Heart failure (HF)
- Chronic kidney disease (CKD)

Statistics

- 30.3 million individuals have diabetes (9.4% of the population)
- 84.1 million Americans have prediabetes
- New-onset T2DM occurs in approximately > 5% of patients with HIV on PIs with
  - 15% develop prediabetes

American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care 2021; 44 Suppl 1.

T2DM Pathophysiology



American Diabetes Association. Standards of medical care in diabetes-2021. Diabetes Care 2021; 44 Suppl 1.

ADA Testing Criteria

- Consider testing in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) with one or more additional risk factors:
  - Physical inactivity
  - First-degree relative with diabetes
  - High-risk race/ethnicity (African American, Latino, Native American, Asian American, Pacific Islander)
  - Hypertension (≥140/90 mmHg or on antihypertensive medication)
  - HDL cholesterol level <35 mg/dL and/or a triglyceride level > 250 mg/dL
  - Women with polycystic ovary syndrome
  - HbA1c ≥5.7% , impaired glucose tolerance or impaired FBG on previous laboratory test
  - Other manifestation associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
  - History of CVD
- Women delivering a baby >9 lbs or diagnosed with gestational diabetes
- HIV
- For all patients, testing should begin at 45 years of age.
  - If results are normal, repeat at a minimum of 3-year intervals
  - Perform yearly testing if results indicate prediabetes

Considerations in HIV

- Be aware of HbA1c limitations
- Consideration can be made for using FBG instead of HbA1c
- Testing for T2DM and prediabetes should occur prior to starting ART, at the time of switching ART, and 3-6 months after changing ART therapy
  - If BG is within range, follow up annually
- Concern in switching ART therapy if impaired glucose tolerance develops
- Be mindful of potential drug interactions

ADA Prediabetes vs. T2DM

Prediabetes Classification

- FPG: 100-125 mg/dL

OR

- **HbA1c: 5.7-6.4%**

OR

- 2hr postprandial 75 gram oral glucose tolerance test: 140-199 mg/dL

T2DM Diagnosis*

- FPG: ≥126 mg/dL

OR

- **HbA1c: ≥6.5%**

OR

- Random BG: ≥200 mg/dL with symptoms of hyperglycemia

OR

- 2hr postprandial 75 gram oral glucose tolerance test: ≥200 mg/dL

***Consider limitations of HbA1c**

***Two abnormal readings from the same sample to confirm diagnosis**

American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care 2021; 44 Suppl 1.

Diabetes Goals*: ADA vs. AACE

ADA

- ***HbA1c goal: <7%***
- FBG goal:
  - 80-130 mg/dL
- Pre meal goal:
  - 80-130 mg/dL
- 2 hr PPG:
  - <180 mg/dL

AACE

- ***HbA1c goal: ≤6.5%***
- FBG goal:
  <110 mg/dL
- 2 hr PPG goal:
  - <140 mg/dL

*Patient specific goals may vary

American Diabetes Association. Standards of medical care in diabetes-2021. Diabetes Care 2021; 44 Suppl 1.

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2020. Endocr Pract. 2020;26(1):91-120.

Therapeutic Lifestyle Changes

Physical Activity

- Aerobic physical activity for overall CV health
  - 150 min moderate-intensity
    - At least 3 days/week (there should not be 2 consecutive days without exercise)
  - Muscle-strengthening activity at least 2 days/week

Physical Activity

- Positive effects on blood glucose and HbA1c
  - Consider counseling regarding decrease in blood glucose
    - May predispose patient to hypoglycemia
- Reduces cardiovascular risk
- Contributes to weight loss
- Improves insulin sensitivity

Physical Activity Considerations

- Consider age and exercise history
- Consider initiating low intensity exercise in those with multiple risk factors for CAD with the goal of slow intensification
- Assess patient for contraindications to certain types of exercise
  - Uncontrolled HTN
  - Severe autonomic neuropathy
  - Foot lesions
  - Proliferative retinopathy

Plate Method

Nutrition Facts

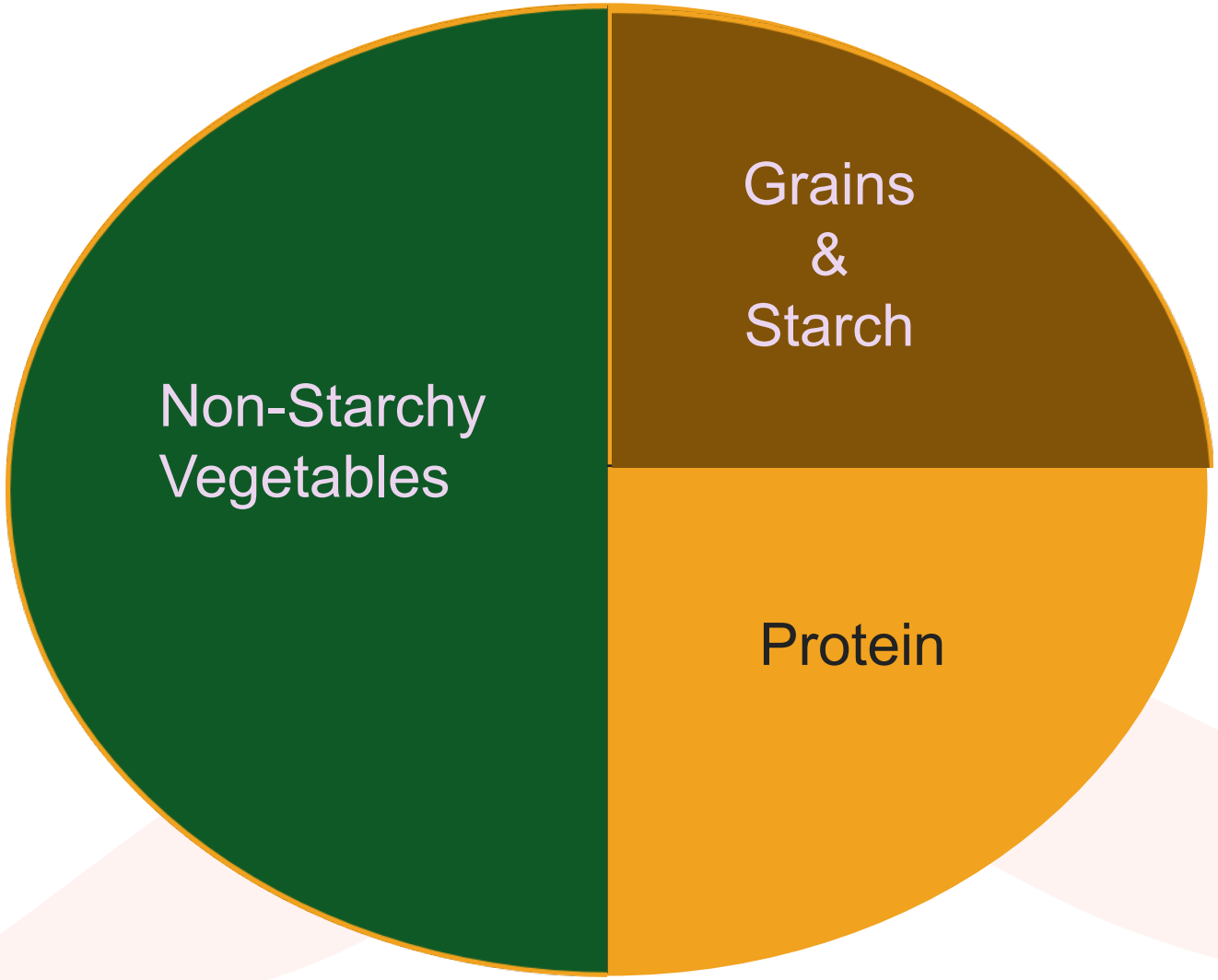
Serving Size ½ cup (30g)
Servings Per Container about 3

Amount Per Serving

Calories 110	Calories from Fat 0
	% Daily Value*
Total Fat 0g	0%
Saturated Fat 0g	0%
Trans Fat 0g	
Cholesterol 0mg	0%
Sodium 0mg	0%
Total Carbohydrate 27g	9%
Dietary Fiber 4g	15%
Sugars 21g	
Protein 0g	

Vitamin A 0%	•	Vitamin C 0%
Calcium 2%	•	Iron 2%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher



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Pharmacologic Management

ADA 2021 Treatment Algorithm

Initiation of Therapy

- Metformin monotherapy

Dual Therapy

- Consider if not at goal after 3 months of monotherapy or if HbA1c is ≥1.5% from their goal
- **Consider ASCVD, CKD, and HF benefits**
- **Cost/hypoglycemia/weight gain should be considered in those without ASCVD, CKD, or HF**

Triple Therapy

- Consider if not at goal after 3 months of dual therapy
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

Combination Injectable Therapy

- Consider if not at goal after 3 months of triple therapy
- Consider insulin if HbA1c is ≥10% or BG is >300 mg/dl at diagnosis
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

Adapted from *Diabetes Care* 2021; 44 Suppl 1

Metformin Considerations

- GI counseling points
- Heart failure and renal consideration
- Vitamin B12 deficiency-periodic monitoring
- May improve lipoaccumulation (mixed evidence) but may worsen lipoatrophy
- CI: Renal insufficiency
  - Lactic acidosis (SOB, weakness, dizziness, muscle pain)
    - Dolutegravir (Tivicay®) controversy
      - Consideration not to exceed 1000 mg daily of metformin?
    - Bictegravir, emtracitabine, tenofovir (Biktarvy®)
      - May increase serum concentrations of metformin
    - *Stavudine (d4t) and didanosine (ddi) interaction*

GLP 1 RA

- Exenatide extended release (Bydureon®)
  - 2 mg subq **once weekly**
- Liraglutide (Victoza®)
  - Initial: 0.6 mg subq **once daily** for 1 week
  - Titrate to 1.2 mg subq once daily for maintenance
  - Maximum 1.8 mg subq once daily
- Lixisenatide (Adlyxin®)
  - Initial: 10 mcg sub q **once daily** for 14 days
  - Titrate to 20 mcg subq once daily for maintenance

GLP 1 RA

- Albiglutide (Tanzeum®)
  - Initial: 30 mg subq **once weekly**
  - Titrate to 50 mg subq once weekly if needed
- Dulaglutide (Trulicity®)
  - 0.75 mg subq **once weekly**
  - May increase to 4.5 mg subq once weekly if needed
- Semaglutide (Ozempic®)
  - 0.25 mg **once weekly** subq for 4 weeks then increase to 0.5 mg once weekly maintenance
  - Increase to 1 mg if necessary

SGLT2-i

- Canagliflozin (Invokana®) 100-300 mg before first main meal
- Dapagliflozin (Farxiga®) 5-10 mg daily in AM
- Empagliflozin (Jardiance®) 10-25 mg daily in AM
- Ertugliflozin (Steglatro®) 5-15 mg daily in AM
- Monitor renal function

SGLT2-i ADEs

- GU infection, polyuria, dehydration, hypotension, dizziness, increased LDL, bone fractures (canagliflozin)
- Rare: DKA
- Ritonavir can increase clearance of canagliflozin
  - May need to increase canagliflozin dose to 300 mg

DPP4-i Medications

Medication	Dose	Renal Adjustment
Sitagliptin (Januvia®)	100 mg PO daily	CrCl 30-49 ml/min: 50 mg PO daily CrCl <30 ml/min or dialysis: 25 mg PO daily
Saxagliptin (Onglyza®)	2.5-5 mg PO daily	CrCl ≤50 ml/min or hemodialysis: 2.5 mg PO daily Do not exceed 2.5 mg daily if on strong CYP 3A4/5 inhibitors (such as ritonavir)
Linagliptin (Tradjenta®)	5 mg PO daily	No renal adjustment
Alogliptin (Nesina®)	25 mg PO daily	CrCl 30-59 ml/min: 12.5 mg PO daily CrCl <30 ml/min or hemodialysis: 6.25 mg PO daily

SU

Medication	Usual dosage
Glipizide (Glucotrol®)	5-40 mg (TDD) (above 15 mg, initiate BID dosing
Glipizide XL (Glucotrol XL®)	5-20 mg (TDD) once daily
Glyburide (Diabeta®)	1.25-20 mg (TDD) (above 10 mg, dose BID)
Glimepiride (Amaryl®)	1-8 mg (TDD) (indicated once daily; however, will sometimes be divided with larger doses)

TZDs

Drug	Initial Dose	Max
Pioglitazone (Actos®)	15-30 mg daily	30-45 mg/day
Rosiglitazone (Avandia®)	4 mg daily	8 mg/day (may be divided in two doses)

Other Non-insulin Therapy Considerations

Sulfonylureas

- Renal considerations
  - Glipizide preferred
- Adverse effects
  - Weight gain
  - Hypoglycemia

Thiazolidinediones

- Levels of TZDs can increase in combination with CYP2C8 inhibitors (many PIs)
- Hepatic considerations
- Adverse effects
  - Weight gain
  - Fluid retention (HF concern)

ADA 2021 Treatment Algorithm

Initiation of Therapy

- Metformin monotherapy

Dual Therapy

- Consider if not at goal after 3 months of monotherapy or if HbA1c is ≥1.5% from their goal
- **Consider ASCVD, CKD, and HF benefits**
- **Cost/hypoglycemia/weight gain should be considered in those without ASCVD, CKD, or HF**

Triple Therapy

- Consider if not at goal after 3 months of dual therapy
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

Combination Injectable Therapy

- Consider if not at goal after 3 months of triple therapy
- Consider insulin if HbA1c is ≥10% or BG is >300 mg/dl at diagnosis
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

Adapted from *Diabetes Care* 2021; 44 Suppl 1

ASCVD or CKD + metformin & lifestyle

ASCVD Predominates

---Established ASCVD

---High ASCVD risk (≥55 y/o with coronary, carotid, or lower extremity artery stenosis >50%)

---LVH

GLP1 RA
(liraglutide, semaglutide, or dulaglutide)
and/or
SGLT2i
(empagliflozin or canagliflozin)

If not at goal (utilize GLP 1 RA or SGLT2 i)

- DPP-4i**
- Basal Insulin (degludec)
- Low Dose TZD
- SU

HF or CKD Predominates

---**HFrEF**: LVEF < 45%

---**CKD**:

eGFR 30-60 ml/min/1.73m^2

OR

UACR >30 mg/g, especially >300 mg/g

SGLT2i First Line
(empagliflozin or canagliflozin, *dapagliflozin*)
or
GLP 1 RA (liraglutide, semaglutide, dulaglutide)

If not at goal (utilize GLP 1 RA)

- DPP4i** (avoid saxa/alo in HF)
- Basal Insulin (degludec)
- SU

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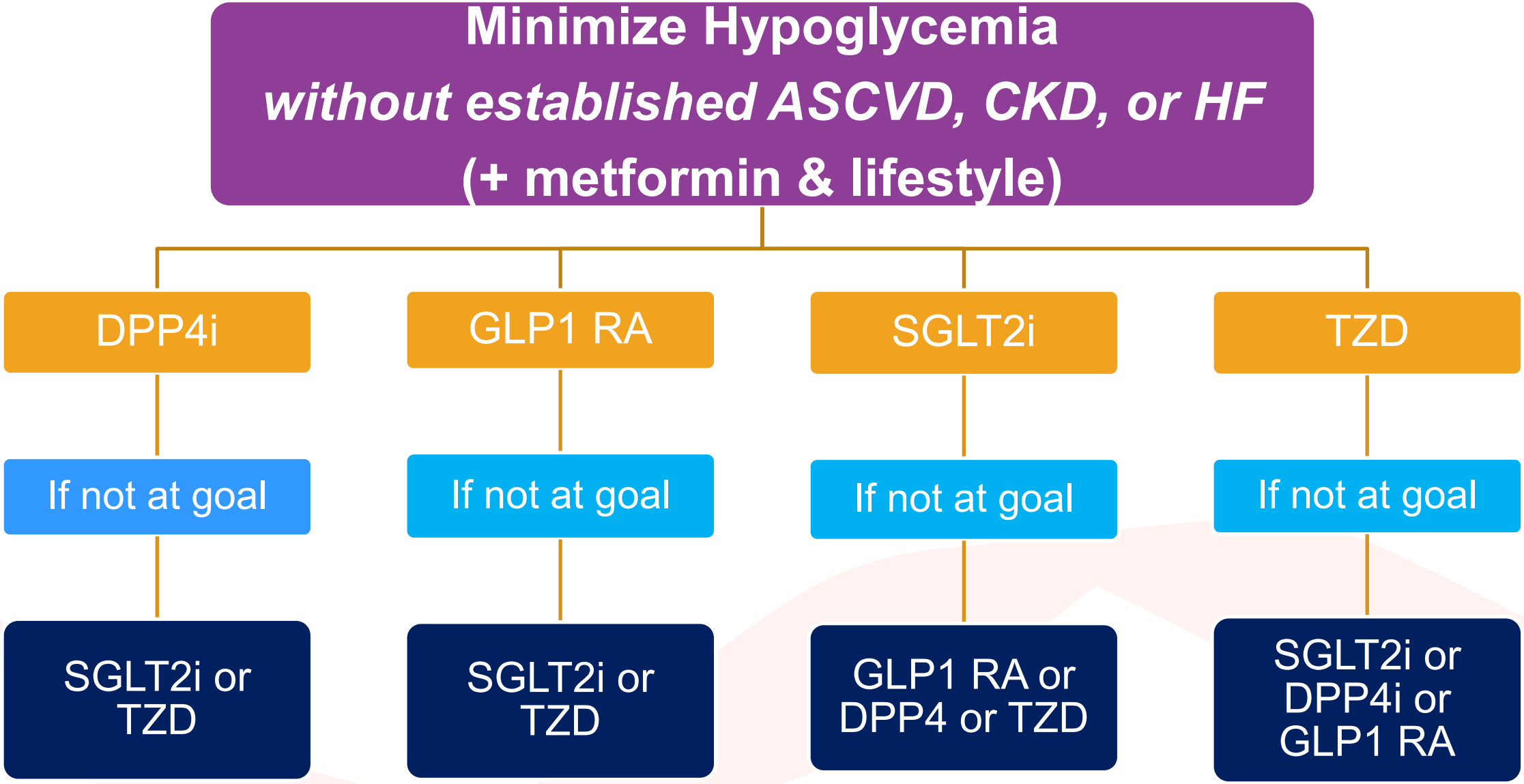
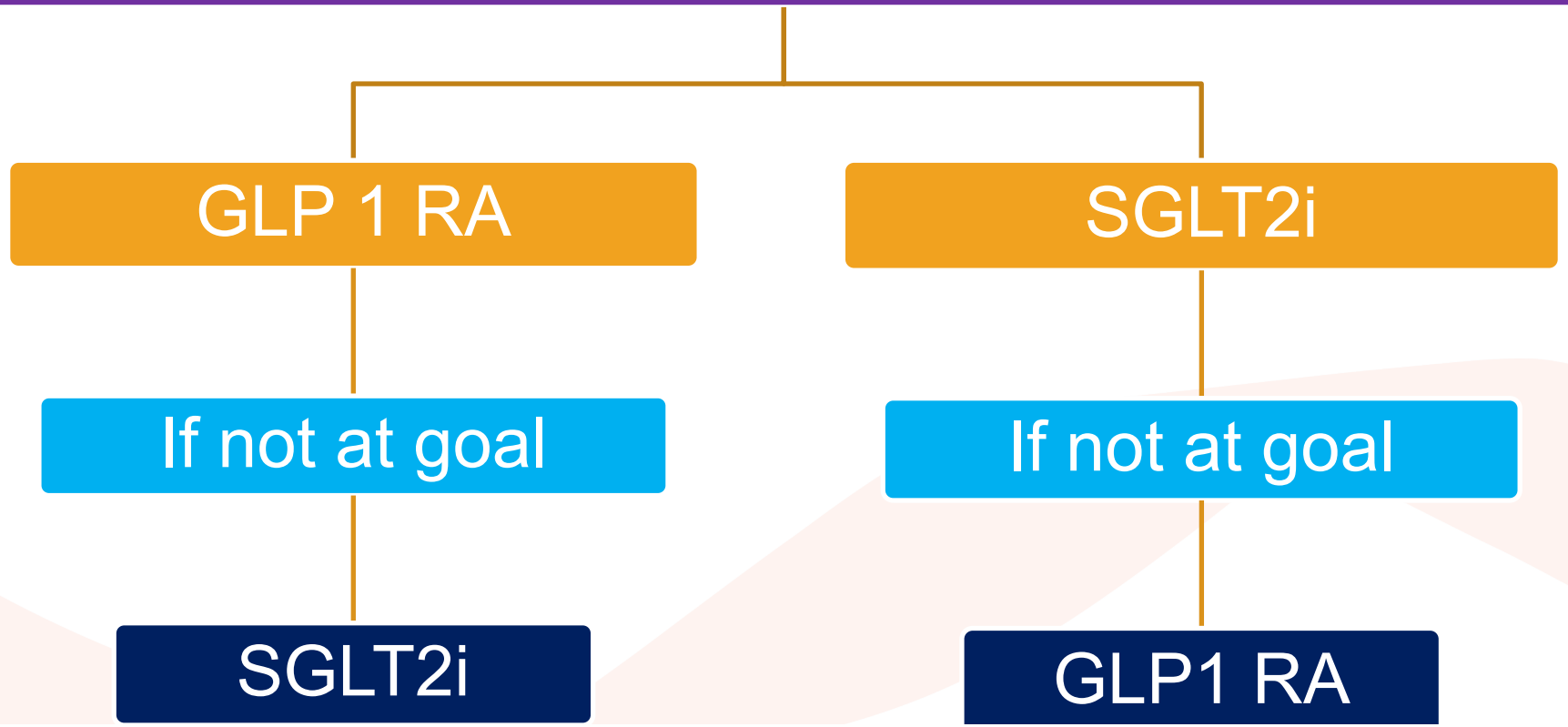
**Do not combine DPP4i and GLP1 RA

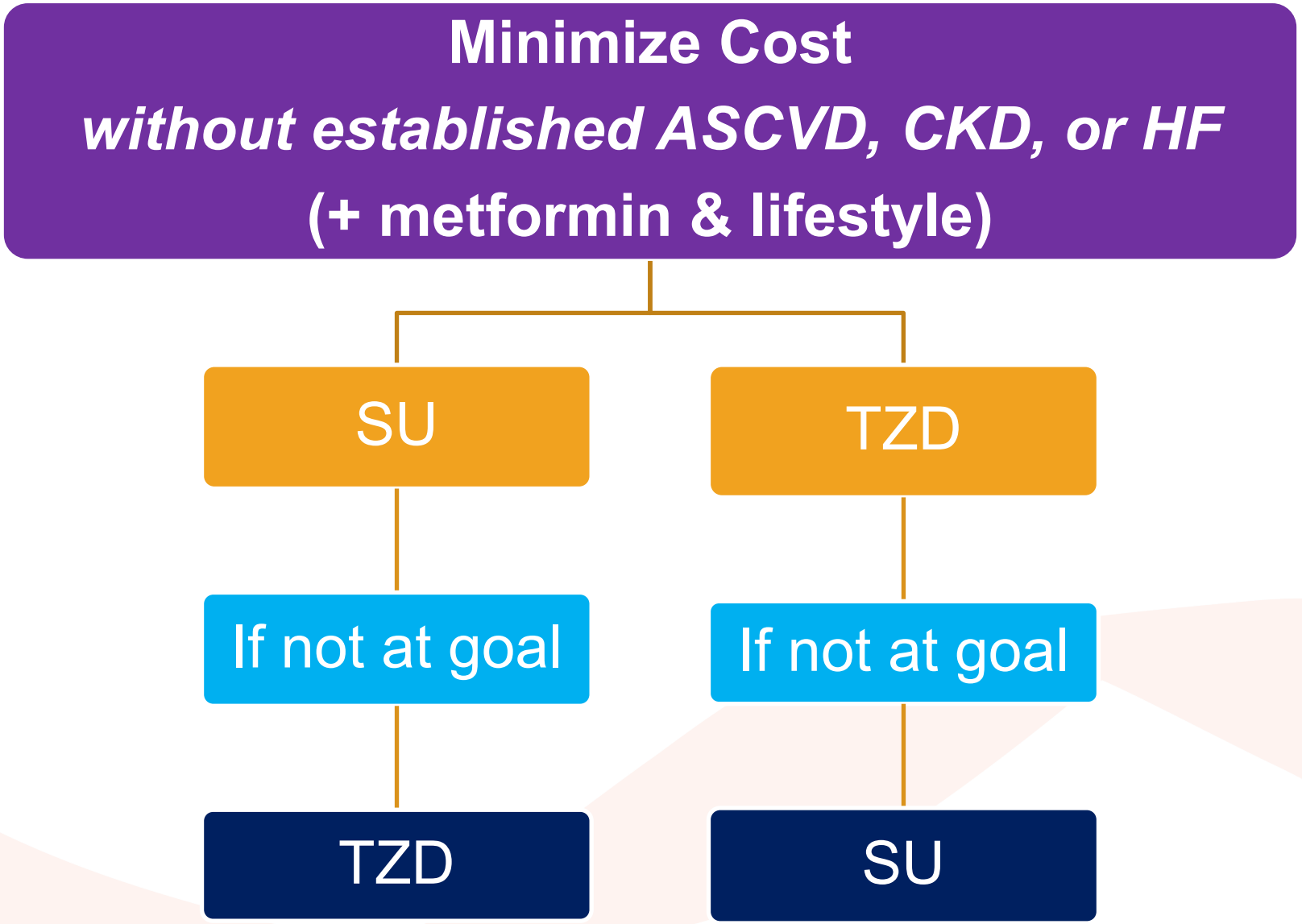


- **If not at goal, can continue with additional agents as shown above**
- **If above agents have been utilized, consider SU or basal insulin**
- ****Do not combine DPP4i and GLP1 RA**

Minimize Weight Gain/Promote Weight Loss *without established ASCVD, CKD, or HF* (+ metformin & lifestyle)



- **If not at goal, or cannot tolerate the above agents, consider a DPP4i if not currently on a GLP1 RA**
- **Use caution with SU, TZD, Basal insulin**



If above agents have been utilized, consider basal insulin, DPP4i OR SGLT2i with lowest cost

Combination Therapy Considerations

- Each additional agent added to initial therapy will lower HbA1c by approximately 0.7-1%
- ASCVD, CKD, and/or HF
- Cost
- Adverse effects

Insulin	Onset	Peak	Duration
Rapid Acting			
Lispro (Humalog®)	15-30 min	0.5-2.5 hr	3-6.5 hrs
Aspart (Novolog®)	10-20 min	40-50 min	3-5 hrs
Glulisine (Apidra®)	25 min	45-48 min	4-5 hrs
Afrezza®-inhaled insulin	15-30 min	53 min	160 min
Short Acting			
Humulin R ®, Novolin R ®	~30 min	1.5-3.5 hr	~8 hrs
Intermediate Acting			
Humulin N ®, Novolin N ®	1-2 hrs	4-12 hr	12+ hrs
Long Acting			
Glargine(Lantus®,Basaglar®,**Toujeo®**)	1/**6** hr	Not sig	Up to 24/**>24**hr
Detemir (Levemir®)	1-2 hrs	Not sig	7.6-24 hrs
Ultra Long-Acting			
Degludec (Tresiba®)	30-90 min	Not sig	42 hrs

Insulin Premix

Intermediate/Rapid	NPH/Regular	Ultra Long Acting/ Rapid
Novolog Mix 70/30® (aspart protamine/aspart)	Humulin 70/30® (NPH/Regular)	Ryzodeg 70/30® (degludec/aspart)
Humalog Mix 75/25® (lispro protamine/lispro)	Novolin 70/30® (NPH/Regular)	
Humalog Mix 50/50® (lispro protamine/lispro)		

Basal Insulin-GLP 1 RA Combination Pens

- Insulin glargine and lixisenatide (Soliqua 100/33®)
- Insulin degludec and liraglutide (Xultophy 100/3.6®)

Insulin Injection Options

- Insulin vials:
  - Available as **100 units/ml** or **500 units/ml**
  - Majority of U-100 vials contain 10 ml of insulin

- Insulin Pens
  - Available as **U-100, U-200, U-300, U-500**
  - Majority of pens contain 3 ml of insulin

Hypoglycemia Classification

Level	Glycemic Criteria (mg/dl)	Description
Hypoglycemia Alert Value (Level 1)	<70	Sufficiently low
Clinically Significant Hypoglycemia (Level 2)	<54	Clinically significant hypoglycemia
Severe Hypoglycemia (Level 3)	No Specific Value	Hypoglycemia associated with severe cognitive impairment requiring external assistance

Hypoglycemia

- Symptoms:
  - Shakiness
  - Rapid heartbeat
  - Sweating
  - Dizziness
  - Anxious
  - Hunger
  - Blurry vision
  - Weakness/fatigue
  - Headache
  - Irritable
- Hypoglycemia can occur after sudden increase in exercise

Hypoglycemia

- 7-15% of patients on insulin will experience hypoglycemia annually with 1-2 % experiencing severe hypoglycemia
- Treat with **ONE** of the following (**15**-20 grams of carbohydrates-simple sugars):
  - 3 to 4 glucose (dextrose) tablets
  - ½ cup or 4 ounces of fruit juice or soft drink (not diet)
  - 5 to 6 pieces of hard candy
  - 2 tablespoons of raisins
  - 1 tablespoon of honey or syrup
- Recheck blood glucose in **15** minutes, if still less than goal, retreat with **ONE** of the above
- Be sure to have a small meal once blood sugar is above goal
- **If a patient feels as though they are hypoglycemic and cannot check their blood glucose, they should still treat**

Summary

- Lifestyle modifications play a key role in the management of T2DM
- Consider the benefits of goal setting
- Consider patient related factors in decision making
- Utilize drug information resources to identify drug interactions
- Consider the patient in decision making

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