AETC AIDS Education & Training Center Program Southeast

Webcast Wednesday Metabolic Madness Part 3: Updates in Diabetes

Andrea Levin, PharmD, CPh, BCACP
Faculty, South Florida Southeast AETC
Assistant Professor,
Nova Southeastern University College of Pharmacy
March 20, 2024

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.

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

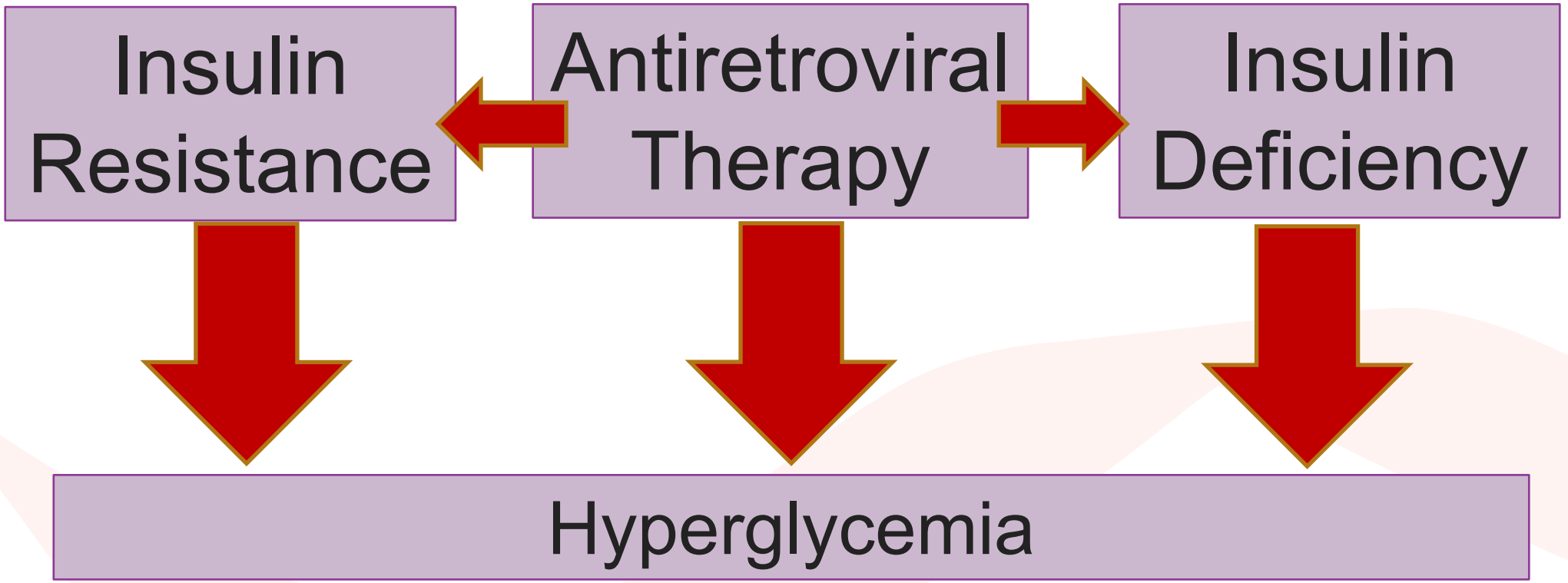
- Sulfonylureas (SU)
- Thiazolidinediones (TZDs)
- Meglitinides (Glinides)
- Alpha glucosidase inhibitors (AGi)
- Self monitoring blood glucose (SMBG)
- Atherosclerotic cardiovascular disease (ASCVD)
- Heart failure (HF)
- Chronic kidney disease (CKD)

US Statistics

- 38.4 million individuals have diabetes (11.6%)
  - Diagnosed: 29.7 million people, including 28.5 million adults
  - Undiagnosed: 8.7 million people
- 97.6 million adults have prediabetes (38% of US population)
  - 27.2 million people aged 65 years or older have prediabetes
- New-onset T2DM occurs in approximately > 5% of patients with HIV on PIs with
  - 15% develop prediabetes

CDC Data and https://www.cdc.gov/diabetes/health-equity/diabetes-by-the-numbers.html. Accessed January 19, 2024

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 35 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-2023. Diabetes Care 2024; 47 Suppl 1.

Goals*: ADA vs. AACE

	ADA	AACE
HbA1c	<7%	≤6.5%
FBG/Pre prandial	80-130 mg/dL	<110 mg/dL
2 hour PPG	<180 mg/dL	<140 mg/dL

*Patient specific goals may vary
*Gestational DM goals differ

- American Diabetes Association. Standards of medical care in diabetes-2023. Diabetes Care 2024; 47 Suppl 1.

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

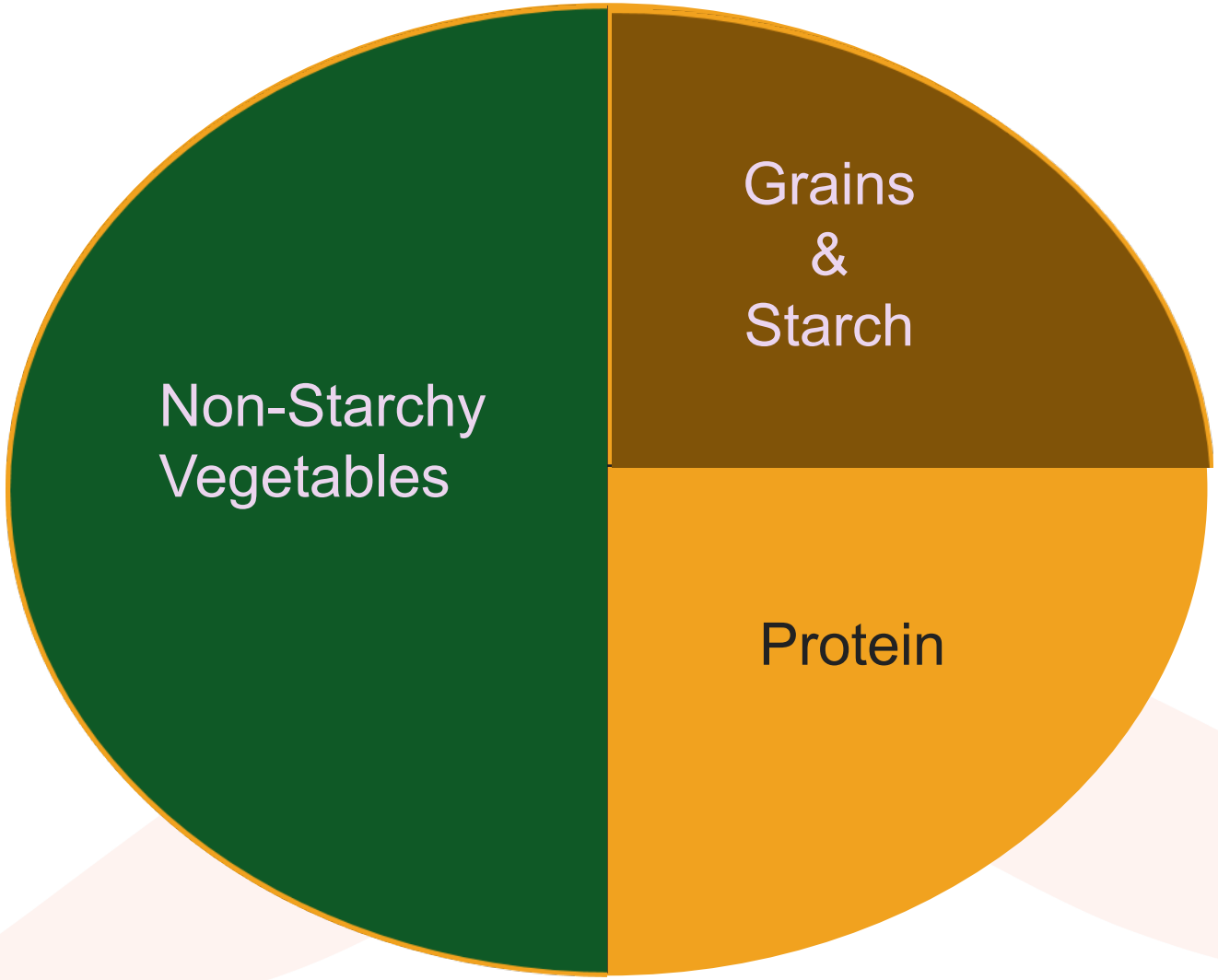
Physical Activity

- 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



http://www.choosemyplate.gov/sites/default/files/printablematerials/2013-EatTheMyPlateWay.pdf Accessed February 23, 2019.

http://www.diabetes.org/food-and-fitness/food/planning-meals/create-your-plate/. Accessed March 1, 2019

Pharmacologic Management

ADA 2024 Treatment Algorithm

Initiation of Therapy

- Individualized approach (comorbidities)/Metformin monotherapy

Dual Therapy

- Consider if not at goal after 3 months of monotherapy or if HbA1c is ≥1.5-2% 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* 2024; 47 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*

Case 1:

- LR is a 52 YOF with new onset DM and HIV
- Current medications include Biktarvy® once daily
- Pertinent labs include:
- HbA1c: 7.8%
- FBG: 150 mg/dl
- **How would you proceed with this patient?**

140	101	19	160
3.8	20	0.8	

GFR: 96 mL/min/1.73m^2

GLP 1 RA

- Decreases A1c by ~1-1.5% as monotherapy
- Dulaglutide (Trulicity®)
  - 0.75 mg subq weekly
  - May increase to 1.5 mg subq once weekly if needed (up to 4.5 mg)
- Semaglutide (Ozempic®)
  - 0.25 mg weekly subq for 4 weeks then increase to 0.5 mg weekly maintenance
  - Increase to 2 mg if necessary
- Tirzepatide (Mounjaro®)
  - 2.5 mg subq weekly x 4 weeks then increase to 5 mg subq weekly
  - Can increase by 2.5 mg every 4 weeks up to 15 mg subq weekly

Oral GLP1 RA

- First PO formulation: Semaglutide (Rybelsus)
  - 3 mg PO daily x 30 days and increase to 7 mg PO daily
  - Can increase to 14 mg PO daily after >30 days on 7 mg PO daily (if necessary)
- Counseling: take with no more than 4 oz of plain water, ≥ 30 min before the first food, beverage, or other oral medication.
  - 14 mg **PO** can be switched to 0.5 mg **SQ** q weekly, beginning the day following the last oral dose
  - 0.5 mg **SQ** can be switched to 7 mg OR 14 mg **PO**, beginning 7 days following the last SQ dose.

GLP1 RA and GIP/GLP RA Considerations

- Route
- Frequency of dose
- GI side effects
- Weight loss potential
- Drug shortages

SGLT2-i

- Decreases A1c by ~0.5-1% as monotherapy
- 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
- All SGLT2i have GFR considerations for maximum doses and for initiation
  - **Avoid when GFR <20-25 ml/min/1.73m^2**
- Initiate at starting doses and titrate as necessary

SGLT2-i ADEs

- **GU infection**, polyuria, dehydration, hypotension, dizziness, increased LDL, bone fractures (canagliflozin)
- Rare: DKA
- Newer SGLT2i (approved 2023)
  - Bexagliflozin (Brenzavvy®) 20 mg qAM
  - Not recommended if CrCl <30 ml/min
- 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)

*No Known Drug-Drug Interactions with ART

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)

*May increase limb fat in patients with HIV-associated lipodystrophy syndrome

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)

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**

ADA 2024 Treatment Algorithm

Initiation of Therapy

- Individualized approach (comorbidities)/Metformin monotherapy

Dual Therapy

- Consider if not at goal after 3 months of monotherapy or if HbA1c is ≥1.5-2%% 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**

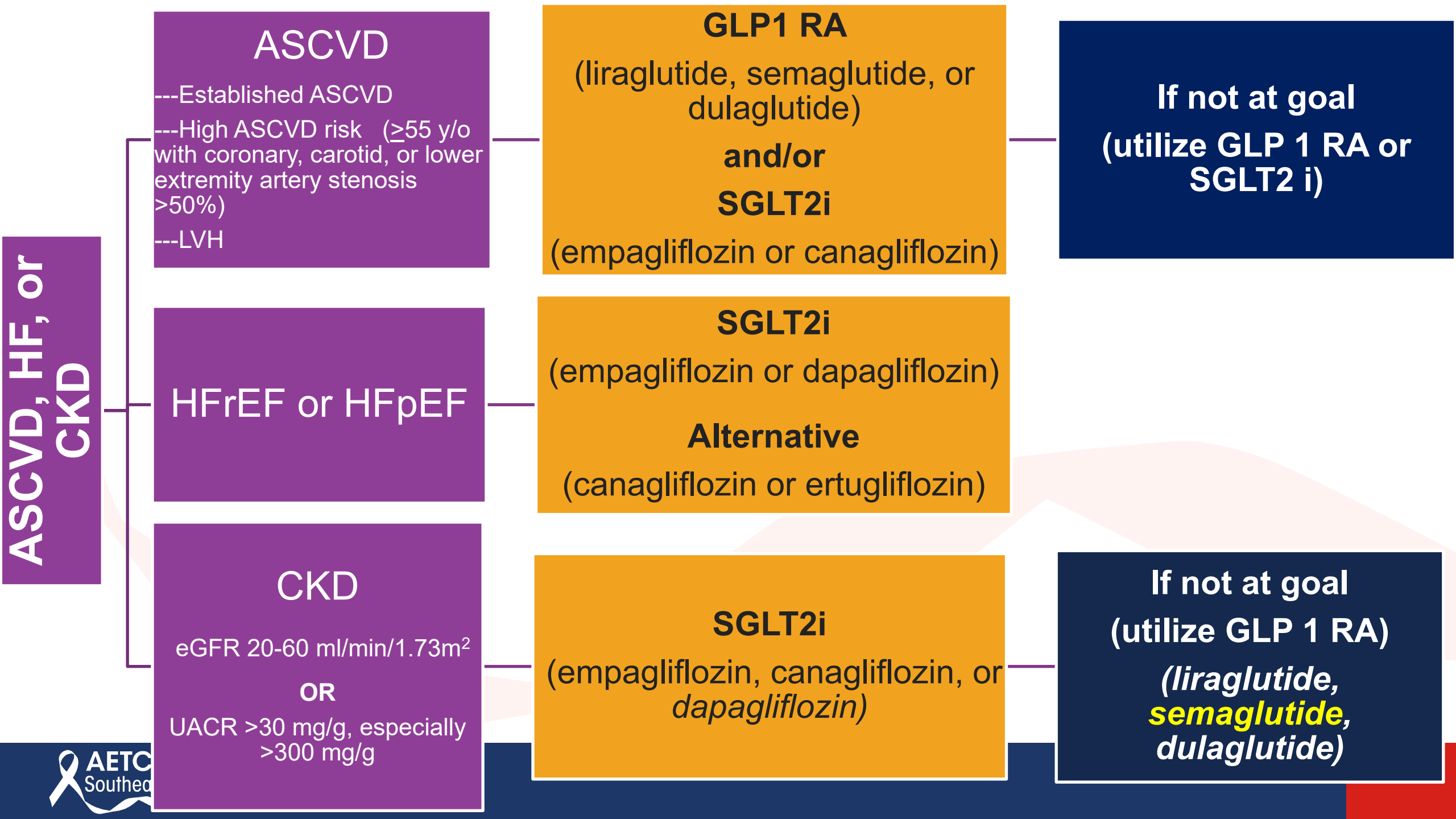
Combination Injectable Therapy

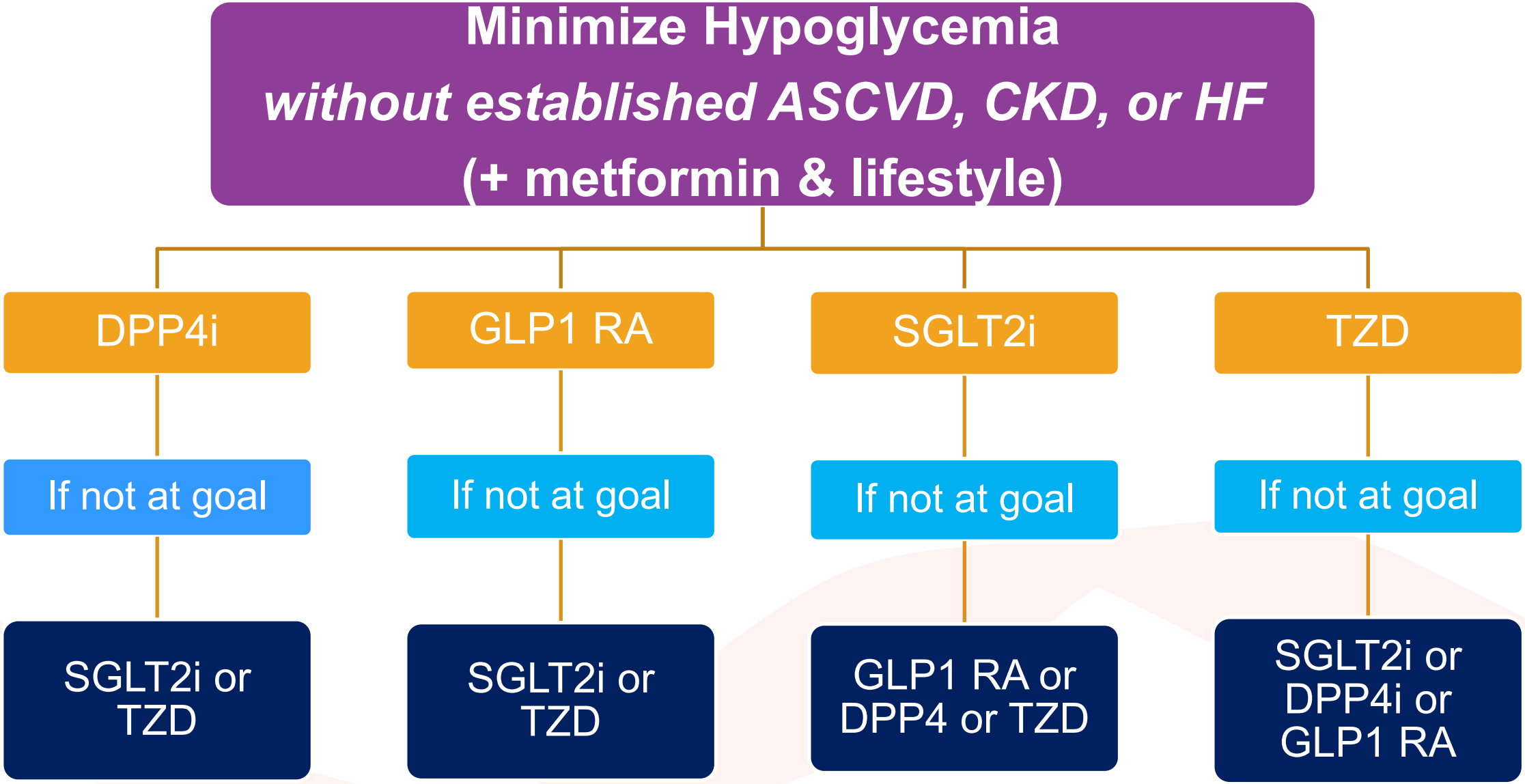
- Consider if not at goal after 3 months of triple therapy
- Consider insulin if HbA1c is ≥10% or BG is >300 mg/dl at diagnosis
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

Adapted from *Diabetes Care* 2024; 47 Suppl 1

Combination Therapy Considerations

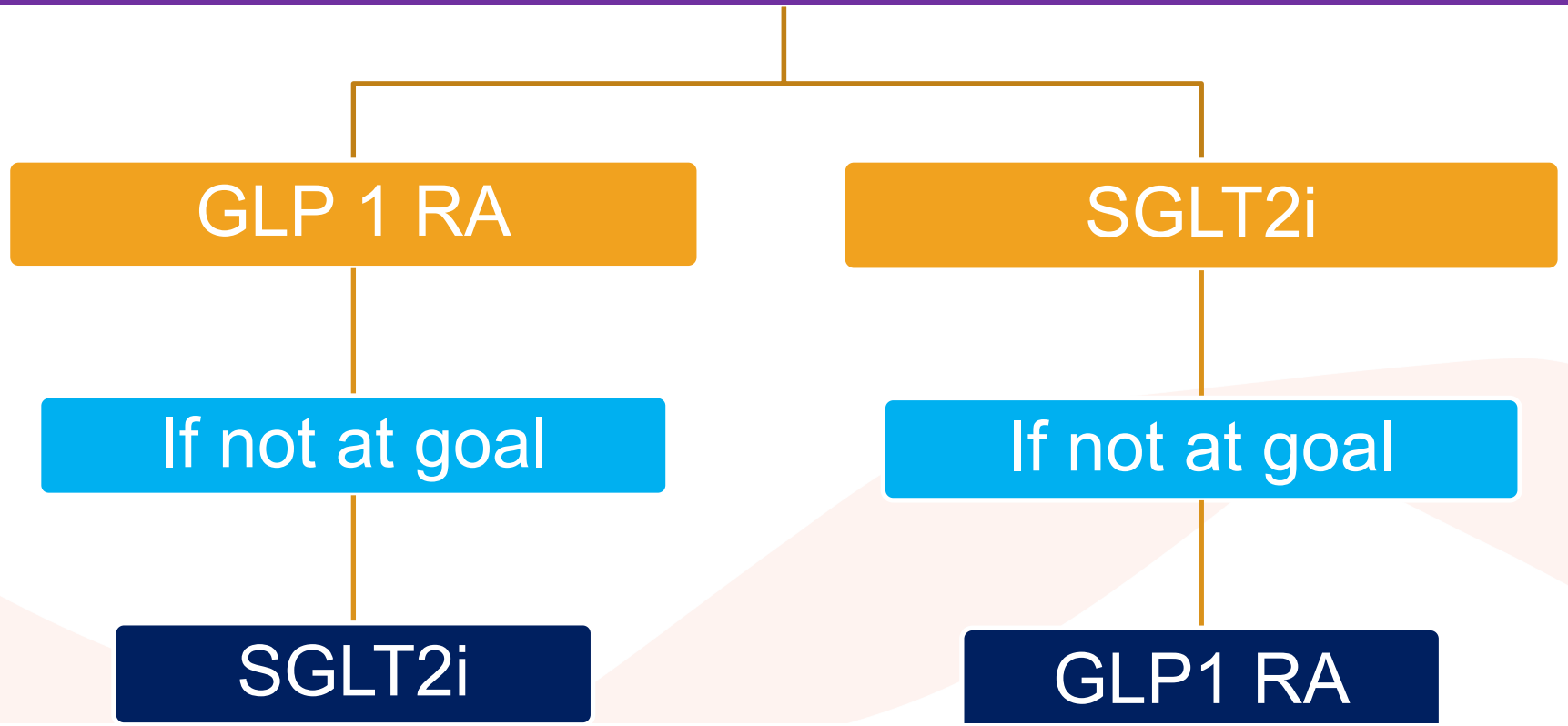
- Each additional agent added to initial therapy will lower HbA1c by approximately 0.7-1%
- ASCVD, CKD, and/or HF
- Cost
- Adverse effects


ASCVD, HF, or CKD
ASCVD
---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)
HFrEF or HFpEF
SGLT2i
(empagliflozin or dapagliflozin)
Alternative
(canagliflozin or ertugliflozin)
CKD
eGFR 20-60 ml/min/1.73m2
OR
UACR >30 mg/g, especially >300 mg/g
SGLT2i
(empagliflozin, canagliflozin, or dapagliflozin)
If not at goal
(utilize GLP 1 RA)
(liraglutide, semaglutide, dulaglutide)
AETC
Southea

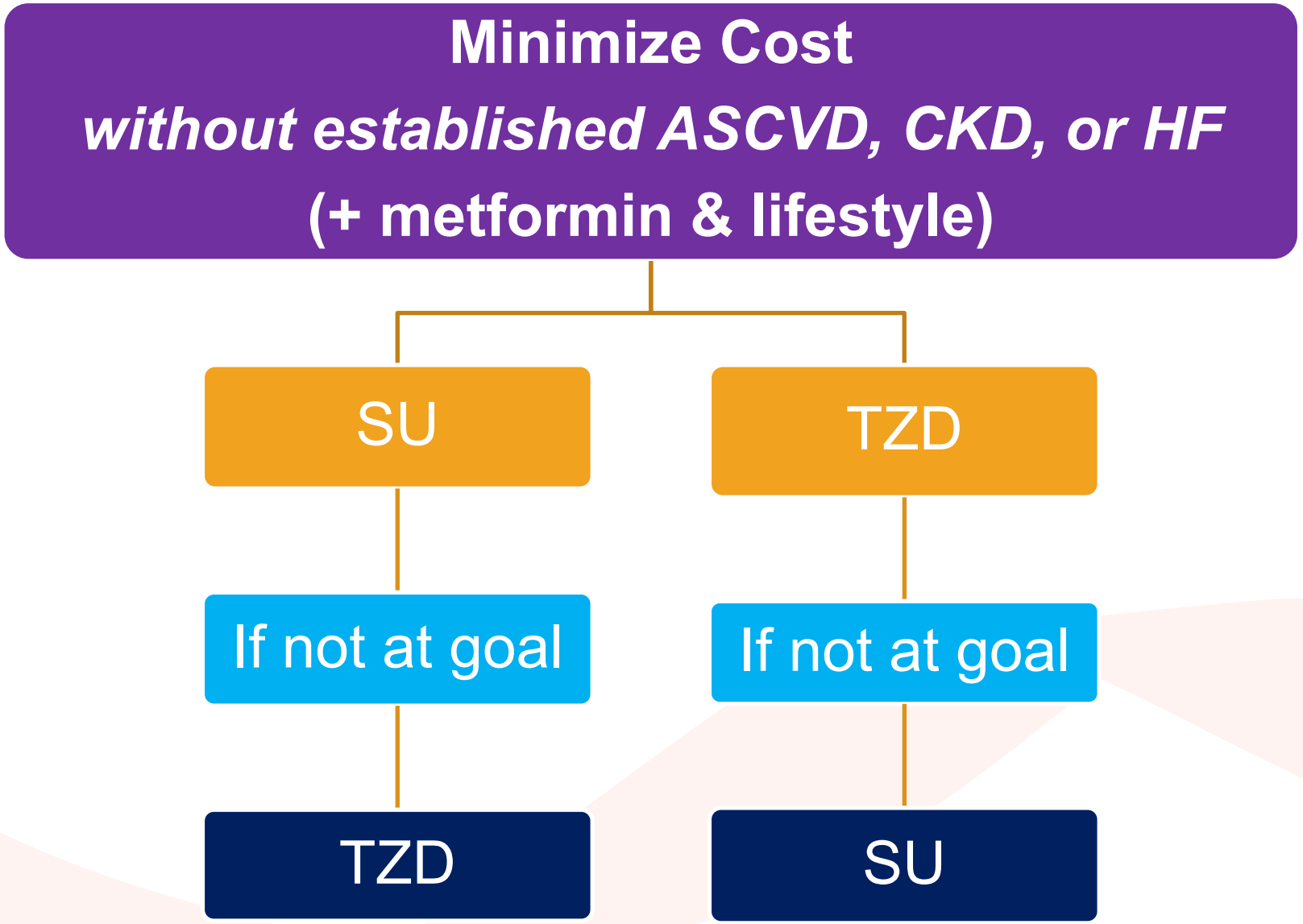


- **If not at goal, can continue with additional agents as shown above**
- **If above agents have been utilized, consider SU or basal insulin**
- ****Do not combine DPP4i and GLP1 RA**

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**



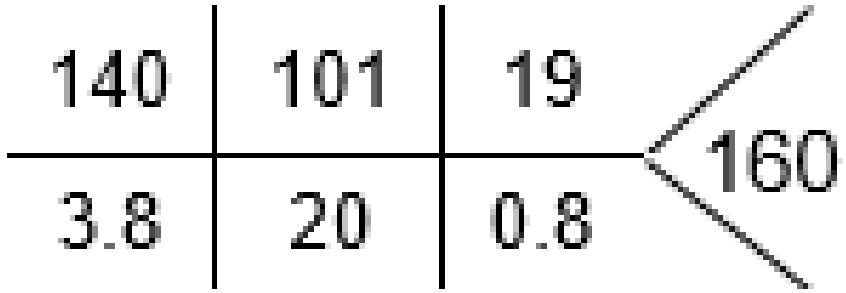
If above agents have been utilized, consider basal insulin, DPP4i OR SGLT2i with lowest cost

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

Case 1: Three Years Later…

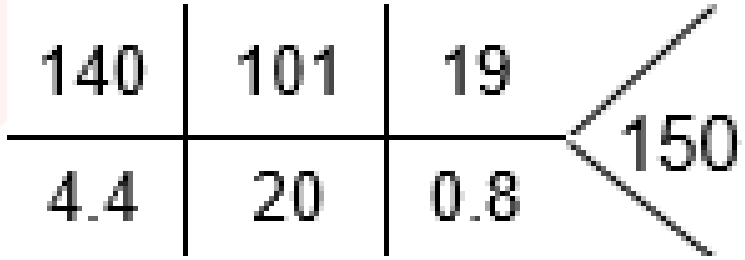
- LR is a 55 YOF returns for follow up three years later
  - Metformin 1000 mg BID and Biktarvy® once daily
- Pertinent labs include:
- HbA1c: 8%
- BMI: 32 kg/m2
- What would you recommend?
  - Treatment?
  - Follow up?



GFR: 88 mL/min/1.73m^2

Case 2

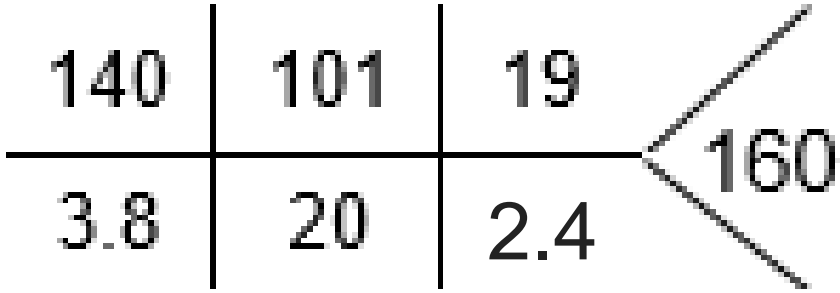
- BH is a 53 YOM who presents to clinic with a PMH of T2DM and HF
- His current medications include: metformin 1000 mg BID, Entresto 97-103 mg BID, Toprol XL 50 mg daily
- HbA1c: 7.8%
- What would you recommend?



GFR: 92 mL/min/1.73m^2

Case 3

- ML is a 65 YO Hispanic female with newly diagnosed T2DM
- PMH significant for HTN, CKD, MI, and dyslipidemia
- Current meds: amlodipine 10 mg qday, Toprol XL 50 mg qday, atorvastatin 20 mg qday
- HbA1c: 8.3%
- BMI: 33 kg/m2
- Insurance: BCBS PPO
  - Branded Products ($25 copay)



GFR: 34 mL/min/1.73m^2

ACR: 450 mg/g

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

References

- CDC Data and https://www.cdc.gov/diabetes/health-equity/diabetes-by-the-numbers.html. Accessed January 19, 2024.
- American Diabetes Association. Standards of medical care in diabetes-2024. Diabetes Care 2024; 47 Suppl 1.
- Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.
- AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2020. Endocr Pract. 2020;26(1):91-120
- Diabetes: Primary Care of Veterans with HIV. https://www.hiv.va.gov/provider/manual-primary-care/diabetes.asp. January 2019.
- Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/287/insti-drug-interactions. 2017.
- American Diabetes Association Food and Fitness. http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/food-tips/. Accessed March 16, 2023.
- Sarkar S, Brown TT. Diabetes in People with HIV. Curr Diab Rep. 2021 Mar 17;21(5):13. doi: 10.1007/s11892-021-01382-8. PMID: 33730223; PMCID: PMC8208107.

AETC AIDS Education & Training Center Program Southeast

Webcast Wednesday Metabolic Madness Part 3: Updates in Diabetes

Andrea Levin, PharmD, CPh, BCACP
Faculty, South Florida Southeast AETC
Assistant Professor,
Nova Southeastern University College of Pharmacy
March 20, 2024