



Webcast Wednesday

Metabolic March Madness Part 3: Updates in Diabetes

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Disclosures

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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

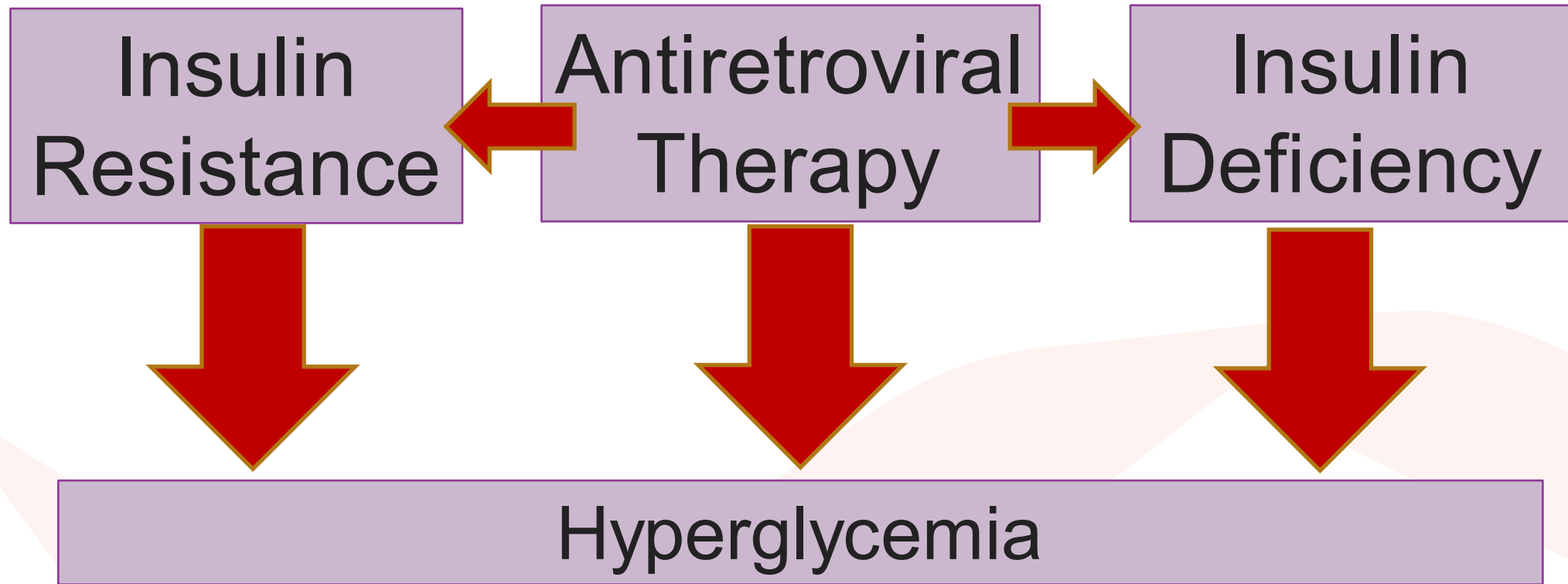
- Sulfonylureas (SU)
- Thiazolidinediones (TZDs)
- Meglitinides (Glinides)
- Alpha glucosidase inhibitors (AGi)
- Self monitoring blood glucose (SMBG)
- Atherosclerotic cardiovascular disease (ASCVD)
- Heart failure (HF)
- Chronic kidney disease (CKD)

US Statistics

- 37.3 million individuals have diabetes (11.3%)
 - Diagnosed: 28.7 million people, including 28.5 million adults
 - Undiagnosed: 8.5 million people
- 96 million adults have prediabetes (38% of US population)
 - 26.4 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 Statistics <https://www.cdc.gov/diabetes/data/statistics-report/index.html>.
Accessed February 22, 2023

T2DM Pathophysiology



ADA Testing Criteria

- Consider testing in all adults who are overweight (BMI ≥ 25 kg/m² or ≥ 23 kg/m² 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 ($\geq 140/90$ 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 $\geq 5.7\%$, 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: $\geq 6.5\%$**
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**

Goals*: ADA vs. AACE

	ADA	AACE
HbA1c	<7%	<u>≤</u> 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

Adapted from *Diabetes Care* 2023; 46 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

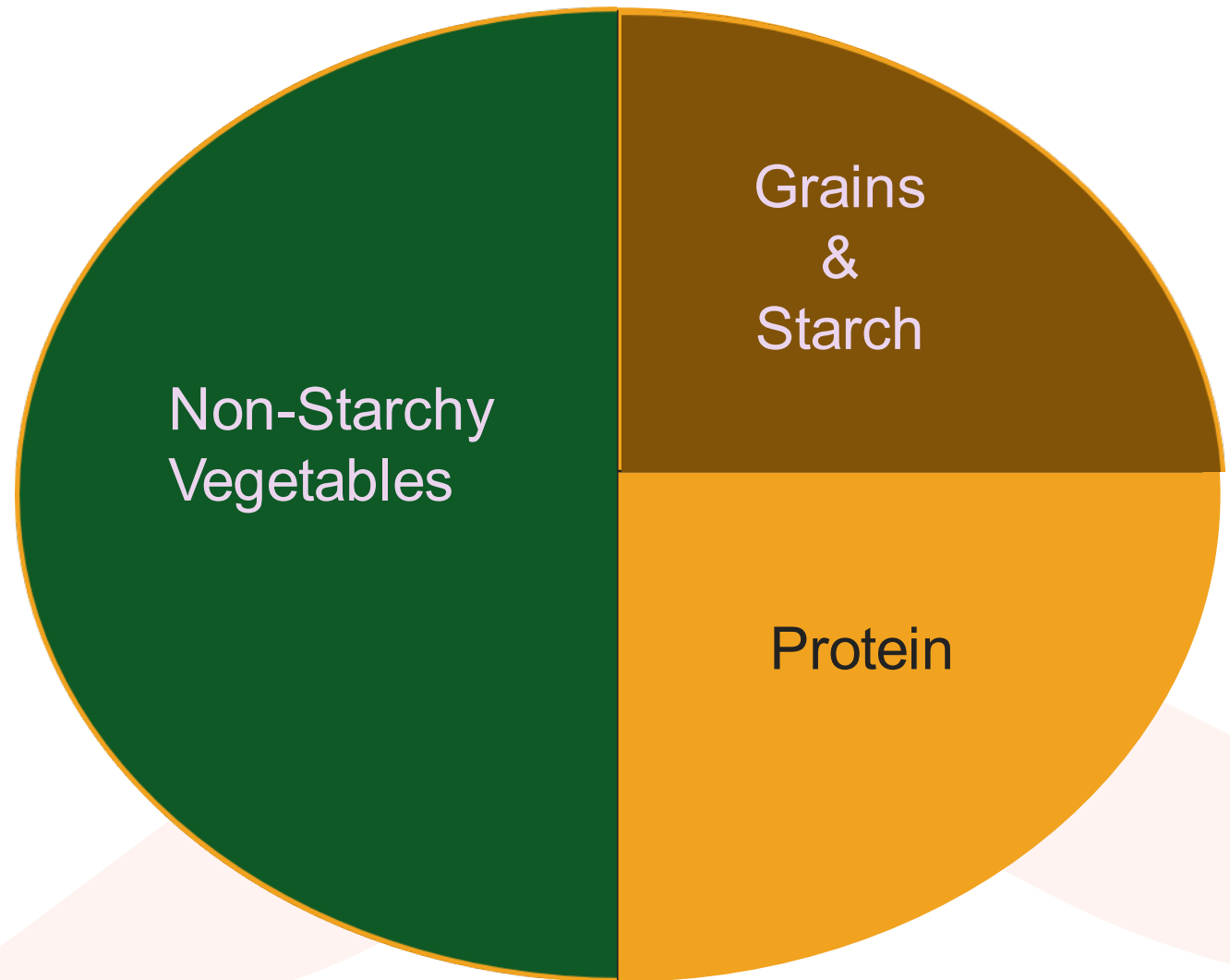
Physical Activity

- 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 2023 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 $\geq 1.5-2\%$ 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 $\geq 10\%$ or BG is >300 mg/dl at diagnosis
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

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/1.73m²

How would you proceed with LR?

Metformin 500 mg qday or BID and increase weekly if needed (NTE 2 grams daily)

Metformin 1000 mg BID and increase weekly if needed (NTE 2 grams daily)

Metformin 850 mg TID and increase weekly if needed (NTE 2.55 grams daily)

GLP 1 RA

- Decreases A1c by ~1-1.5% as monotherapy
- 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

- Dulaglutide (Trulicity®)
 - 0.75 mg subq **once weekly**
 - May increase to 1.5 mg subq once weekly if needed (up to 4.5 mg)
- Albiglutide (Tanzeum®)
 - Initial: 30 mg subq **once weekly**
 - Titrate to 50 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 2 mg if necessary

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.

Hot-ish off the Press: Tirzepatide (Mounjaro)

- 2.5 mg subq every 7 days x 4 weeks then increase to 5 mg subq every 7 days
- Can increase by 2.5 mg every 4 weeks up to 15 mg subq every 7 days
- Can reduce weight by $\geq 15-20\%$

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
 - **Contraindicated when GFR <20-25 ml/min/1.73m²**
- Initiate at starting doses and titrate as necessary

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 \leq 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)

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 2023 Treatment Algorithm

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Dual Therapy

- Consider if not at goal after 3 months of monotherapy or if HbA1c is $\geq 1.5-2\%$ 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 $\geq 10\%$ or BG is >300 mg/dl at diagnosis
- **Consider ASCVD, CKD, HF cost, hypoglycemia, and weight gain**

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

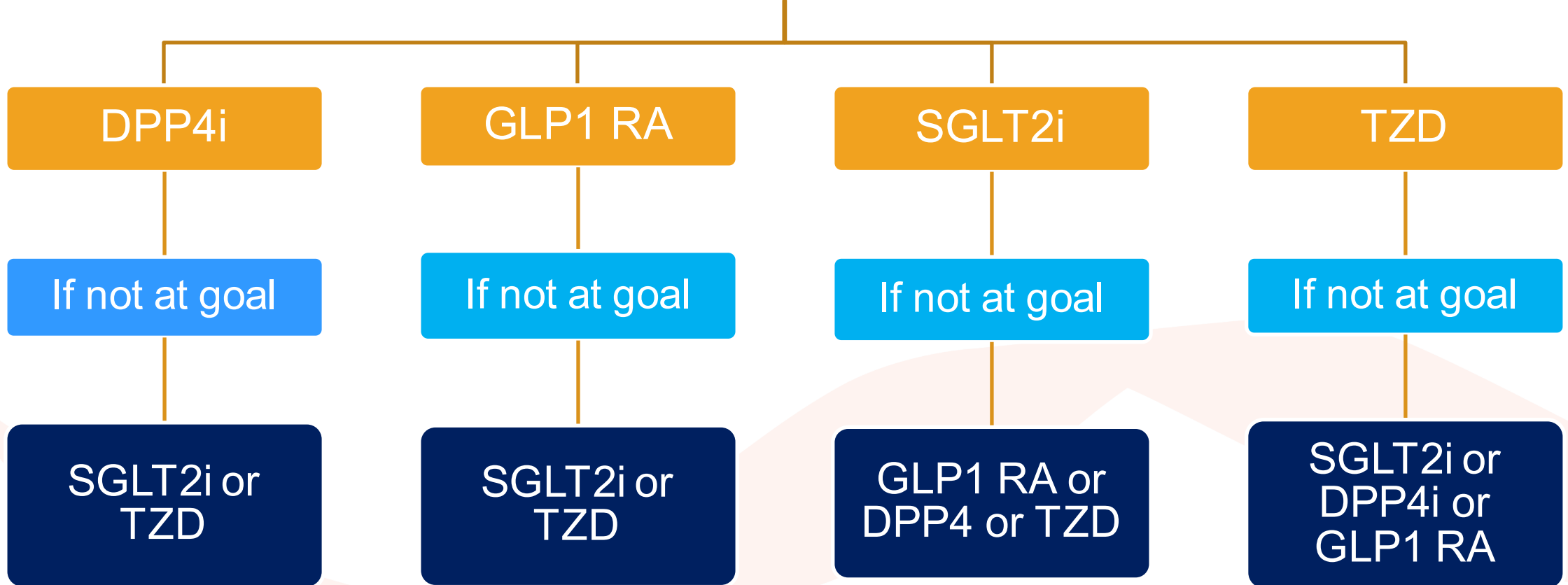
SGLT2i
(empagliflozin or dapagliflozin)
Alternative
(canagliflozin or ertugliflozin)

CKD
eGFR 20-60 ml/min/1.73m²
OR
UACR > 30 mg/g, especially > 300 mg/g

SGLT2i
(empagliflozin, canagliflozin, or dapagliflozin)

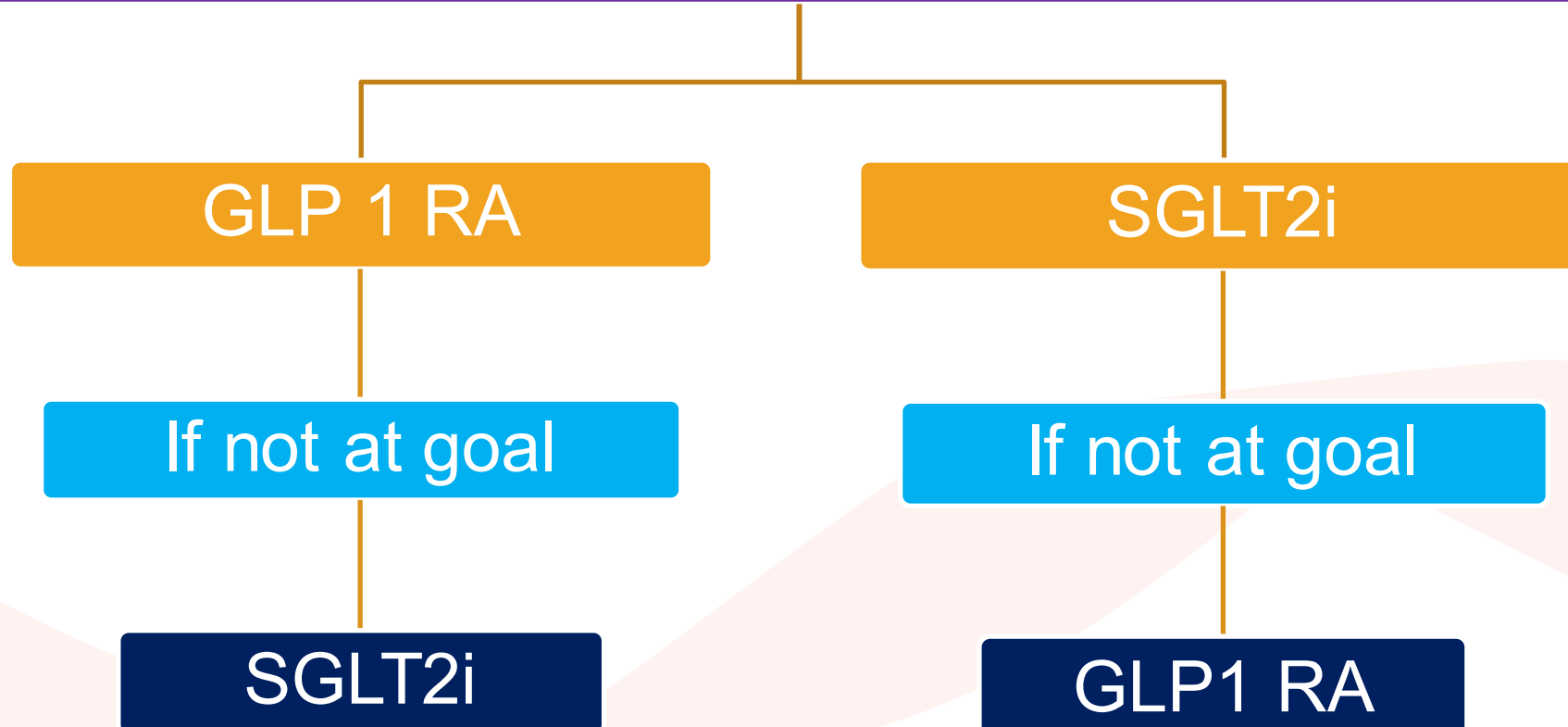
**If not at goal
(utilize GLP 1 RA)
(liraglutide,
semaglutide,
dulaglutide)**

Minimize Hypoglycemia
without established ASCVD, CKD, or HF
(+ metformin & lifestyle)



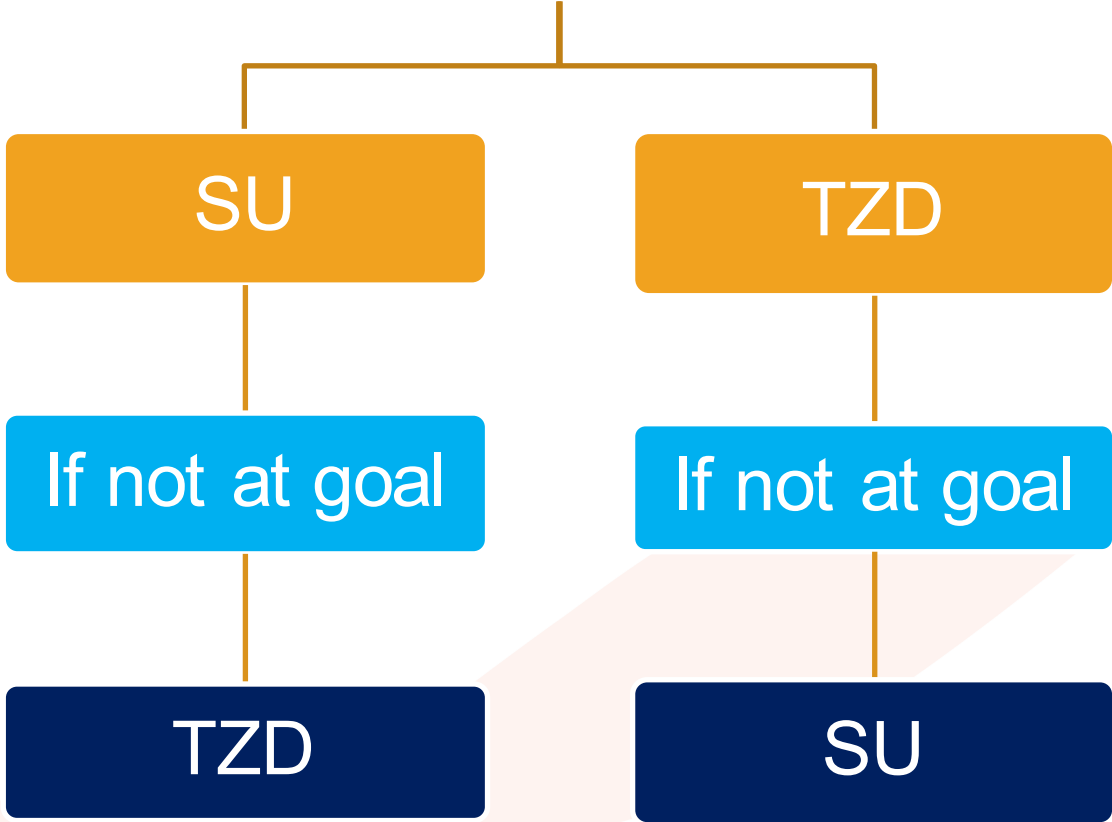
- If not at goal, can continue with additional agents as shown above
- If above agents have been utilized, consider SU or basal insulin
- ****Do not combine DPP4i and GLP1 RA**

**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**

Minimize Cost
without established ASCVD, CKD, or HF
(+ metformin & lifestyle)



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?

140	101	19	160
3.8	20	0.8	

GFR: 88 mL/min/1.73m²

What is the BEST OPTION to address LR's T2DM?

Increase metformin to 850 mg PO TID

Initiate glipizide 5 mg PO qday

Initiate dapagliflozin (Farxiga) 5 mg PO qday

Initiate exenatide (Bydureon) 2 mg SQ once daily

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?

140	101	19	150
4.4	20	0.8	

GFR: 92 mL/min/1.73m²

How would you proceed for BH if he reports being afraid of needles

Addition of semaglutide (Rybelsus) daily

Addition of glipizide qday

Addition of pioglitazone qday

Addition of saxagliptin qday

Addition of dapagliflozin qday

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)

140	101	19	160
3.8	20	2.4	

GFR: 34 mL/min/1.73m²
ACR: 450 mg/g

What is the BEST OPTION to initiate for ML's T2DM?

Glipizide 5 mg PO qday

Invokana 100 mg PO qday

Metformin 500 mg PO BID

Januvia 25 mg PO qday

Assuming that you titrated ML's initial medication accordingly....what would be a potential add-on option if needed?

Ozempic 0.25 mg SQ weekly **(A)**

Januvia 25 mg PO qday **(B)**

Bydureon 2 mg PO qweek **(C)**

Actos 15 mg PO qday **(D)**

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 Statistics. <http://www.cdc.gov/diabetes/data/index.html>. Accessed Mar 16, 2023.
- 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.
- American Diabetes Association. Standards of medical care in diabetes-2023. Diabetes Care 2023; 46 Suppl 1.
- 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.



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