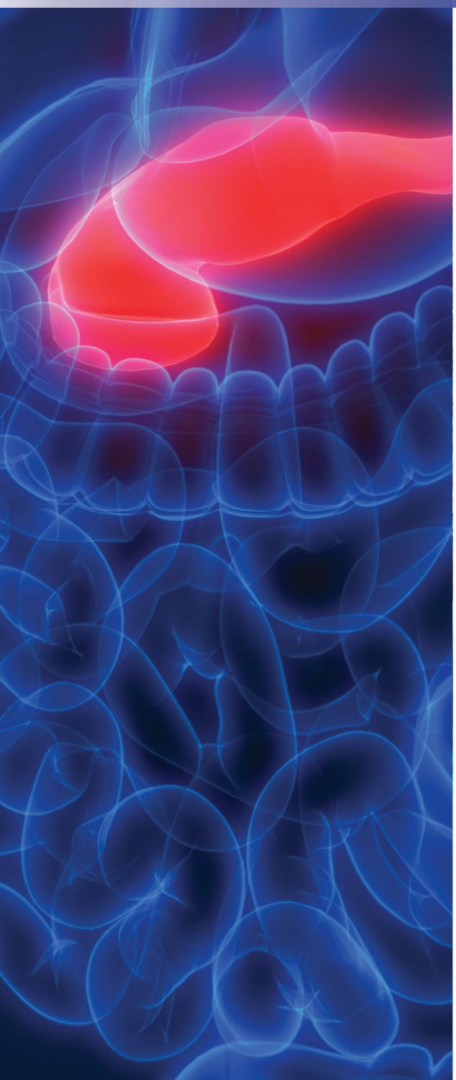


Diabetes Management with GLP-1 Receptor Agonists

Patient Perspectives and Pharmacist Insights

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is sponsored by Postgraduate Healthcare Education, LLC, and is supported by an educational grant from Novo Nordisk, Inc.

Faculty

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Dr Trujillo is a professor at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences in Aurora, CO. She received her Doctor of Pharmacy at the University of Arizona and completed her pharmacy practice residency at Boston Medical Center. Dr Trujillo currently practices as a clinical pharmacist and certified diabetes care and education specialist at the UCHealth Diabetes and Endocrinology Clinic on the University of Colorado Anschutz Medical Campus. She is an active member of the American Diabetes Association's Primary Care Advisory Group and "Diabetes Is Primary" program planning committee. She has published several book chapters and has authored more than 50 peer-reviewed journal articles in the field of diabetes.

Faculty

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Clinical Professor of Pharmacy Practice
Auburn University Harrison School of Pharmacy
Auburn, AL

Dr Whitley is a Clinical Professor of Pharmacy Practice at Auburn University Harrison School of Pharmacy. She completed her Doctor of Pharmacy degree from the Medical University of South Carolina, and ASHP-accredited residency programs in Pharmacy Practice and Primary Care. She is also a Board-Certified Pharmacotherapy Specialist (BCPS) and a Certified Diabetes Care and Education Specialist (CDCES). She has practiced in multiple locations in Alabama as a Clinical Pharmacy Diabetes Specialist, including family medicine practices in the rural Black Belt, FQHC facilities, and, since 2014, a family medicine residency program in Montgomery, AL. She has published nearly 40 manuscripts and presented at the national and international arena predominantly on her diabetes-related research.



Patient Faculty

- David Constantine
- Carrie Parker
- Terrence Salter

Disclosures

Dr Trujillo has disclosed that she has served as a consultant for Sanofi and Novo Nordisk, Inc.

Dr Whitley has disclosed that she has served as a consultant for the Medication Information Institute.

The patients participating in this program have no relevant financial relationships to disclose.

The clinical reviewer, Susan Cornell, BS, PharmD, CDCES, FAPhA, FADCES, has disclosed that she has received fees for consulting and non-CME services from Novo Nordisk, Inc.

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UAN: 0430-0000-21-073-H01-P

Credits: 1.5 hour (0.15 CEU)

Type of Activity: Application

Learning Objectives

- **Discuss** current clinical practice recommendations concerning use of glucagon-like peptide receptor agonists (GLP-1 RAs) in patients with type 2 diabetes (T2D) to improve glycemia and/or mitigate cardiovascular (CV) and kidney risk
- **Assess** patient-specific considerations when deciding between a GLP-1 RA or other treatment options in a patient with T2D
- **Apply** an understanding of the patient experience with GLP-1 RAs to inform shared decision-making thus leading to optimized patient-centered care

The GLP-1 RA Class

	Short-acting		Long-acting				
Agent	Exenatide (Byetta)	Lixisenatide (Adlyxin)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)	Oral Semaglutide (Rybelsus)
Glucose profile target	PPG		FPG and PPG				
Dosing duration	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly	Once daily
Phase 3 Clinical Program	AMIGO	GetGoal	LEAD	DURATION	AWARD	SUSTAIN	PIONEER
A1C lowering	-0.4 to -1.1	-0.46 to -0.99	-0.84 to -1.5	-1.48 to -1.9	-0.71 to -1.9	-1.1 to -2.2	-0.6 to -1.4
Weight lowering	-0.3 to -2.8	+0.3 to -2.96	+0.3 to -3.24	-2.0 to -4.0	+0.2 to -4.7	-1.4 to -6.5	-1.2 to -4.4

FPG, fasting plasma glucose; PPG, post-prandial glucose.

Trujillo JM. Glucagon-like peptide-1 receptor agonists. In: White JR, ed. *2019 Guide to Medications for the Treatment of Diabetes Mellitus*. Arlington, VA: American Diabetes Association; 2019:190-210.

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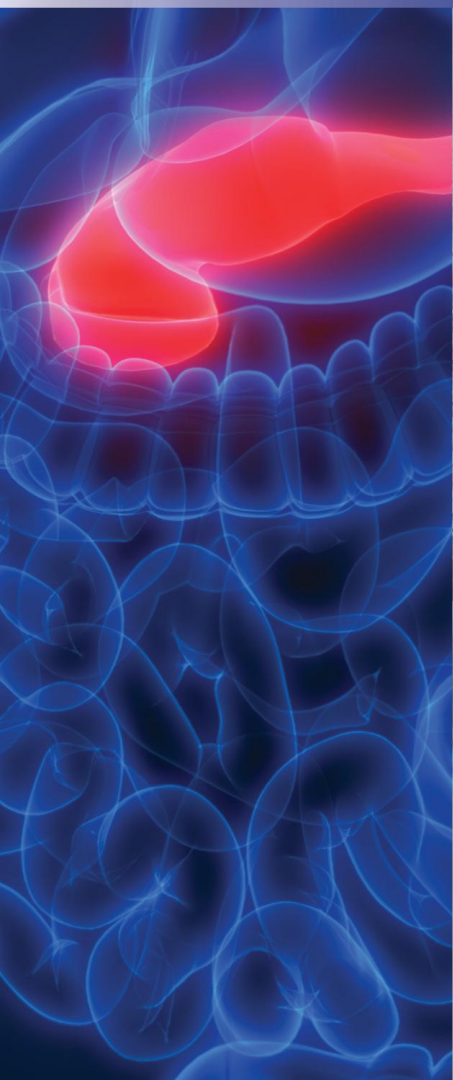
GLP-1 RA CV Outcome Trials (CVOTs)

	ELIXA (n = 6068)	LEADER (n = 9340)	SUSTAIN-6 (n = 3297)	EXSCEL (n = 14,752)	REWIND (n = 9901)	PIONEER-6 (n = 3183)
Agent	Lixisenatide	Liraglutide	Semaglutide	Exenatide XR	Dulaglutide	Oral Semaglutide
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Metformin use (%)	66	76	73	77	81	77
Prior CV disease (%)	100	81	60	73.1	32	84.7
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2
Primary outcome major adverse CV event (MACE)	4-point MACE 1.02 (0.89-1.17)	3-point MACE 0.87 (0.78-0.97)	3-point MACE 0.74 (0.58-0.95)	3-point MACE 0.91 (0.83-1.00)	3-point MACE 0.88 (0.79-0.99)	3-point MACE 0.79 (0.57-1.11)
Cardiovascular death	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
Myocardial infarction	1.03 (0.87-1.22)	0.86 (0.73-1.00)	0.74 (0.51-1.08)	0.97 (0.85-1.10)	0.96 (0.79-1.15)	1.18 (0.73-1.90)
Stroke	1.12 (0.79-1.58)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.85 (0.70-1.03)	0.76 (0.61-0.95)	0.74 (0.35-1.57)
Heart failure hospitalizations	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	0.93 (0.77-1.12)	0.86 (0.48-1.55)
All-cause mortality	0.94 (0.78-1.13)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
Worsening nephropathy	-	0.78 (0.67-0.92)	0.64 (0.46-0.88)	-	0.85 (0.77-0.93)	-

Expanded FDA-Approved Indications

Medication	Expanded CV FDA Indication
Liraglutide (Victoza)	“...reduce the risk of <u>major adverse CV events</u> in adults with T2D and <u>established CVD</u> ”
Semaglutide (Ozempic)	“...to reduce the risk of <u>major adverse CV events</u> in adults with T2D and <u>established CVD</u> ”
Semaglutide (Rybelsus)	None
Exenatide XR (Bydureon, Bydureon BCise)	None
Dulaglutide (Trulicity)	“...to reduce the risk of <u>major adverse CV events</u> in adults with T2D who have <u>established CVD</u> <u>or</u> <u>multiple CV risk factors.</u> ”

Select Ongoing GLP-1 RA Trials Examining Kidney Outcomes



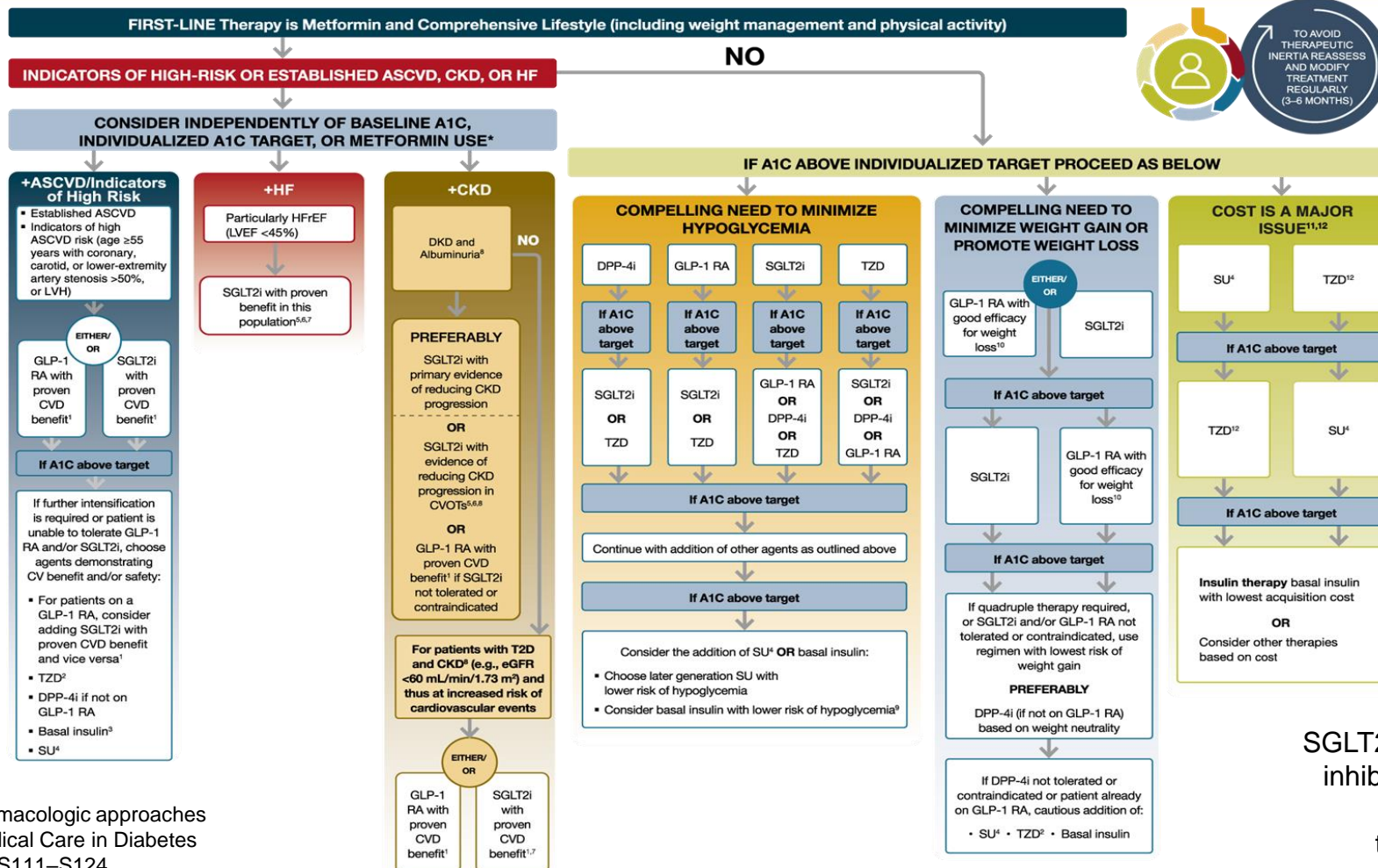
Drug Under Study	Trial	Key kidney-related outcomes
Semaglutide	FLOW	<ul style="list-style-type: none"> ○ Primary Outcome: <ul style="list-style-type: none"> ▪ Time to first occurrence of a composite of: eGFR decline of $\geq 50\%$ from baseline, ESRD, or death from kidney or cardiovascular disease ○ Secondary Outcome Measures: <ul style="list-style-type: none"> ▪ Annual rate of change in eGFR ▪ Time to occurrence of all-cause death ▪ Time to occurrence of each individual component of the primary composite outcome ▪ Relative change in UACR
Semaglutide (in combination with empagliflozin)	EmpaSema	<ul style="list-style-type: none"> ○ Primary Outcome: <ul style="list-style-type: none"> ▪ Change in albuminuria (from randomization to week 52) ○ Secondary Outcome Measures: <ul style="list-style-type: none"> ▪ Change in GFR (from randomization to week 52) ▪ Change in inflammatory and endothelial biomarkers

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; UACR, urinary albumin-to-creatinine ratio.

www.clinicaltrials.gov. Accessed October 26, 2020.

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Glucose Lowering Medications in Type 2 Diabetes: Overall Approach



SGLT2i, sodium glucose cotransporter-2 inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; MET, metformin.

American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care*. 2021;44(Suppl 1):S111–S124.

Indicators of High-Risk or Established ASCVD, CKD, or HF

Step 1: Does the patient have established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure (HF) or do they have indicators for these?

If the answer is “Yes”

FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity)

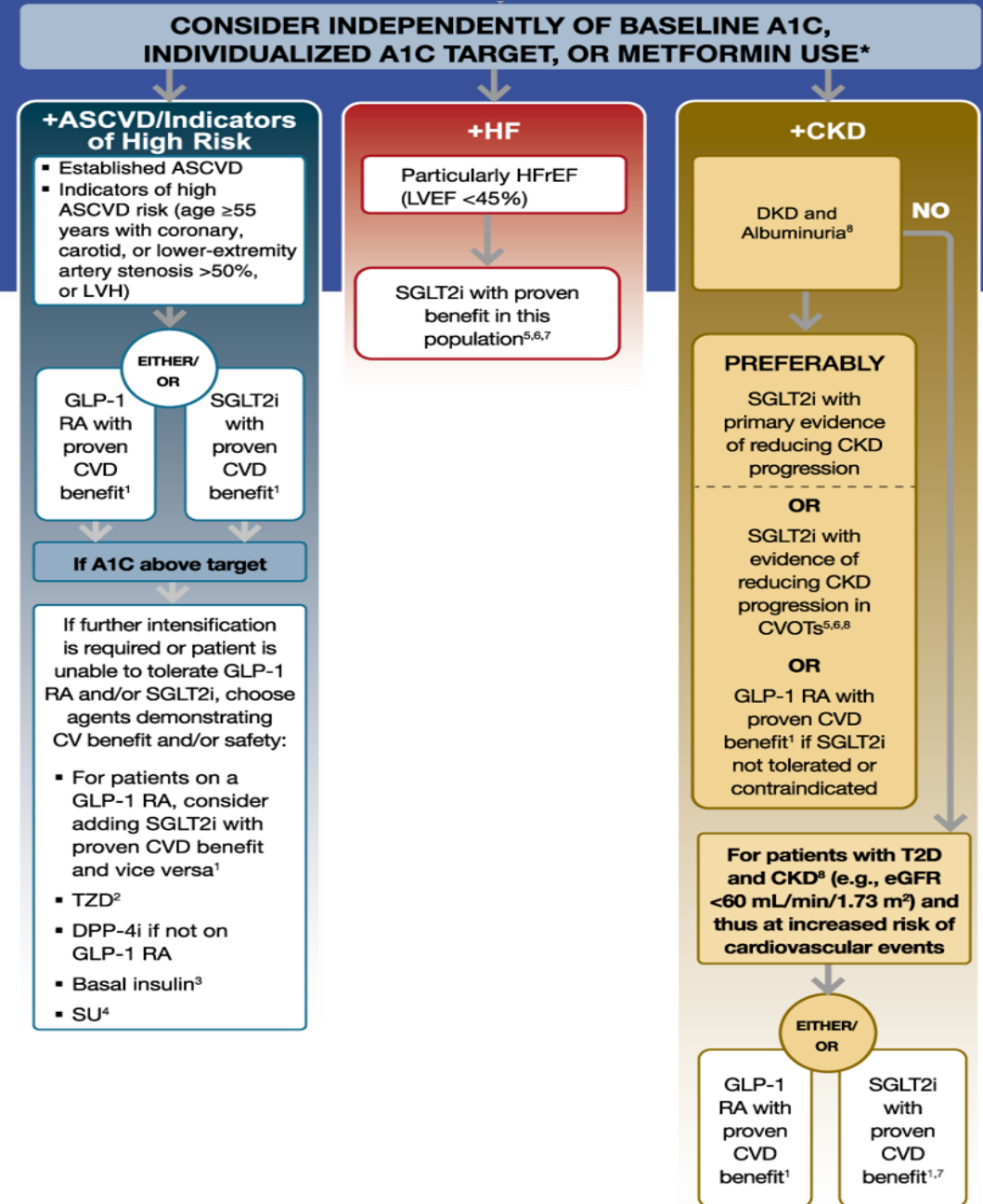
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF

No

Yes

Indicators of high-risk or established ASCVD, CKD, or HF

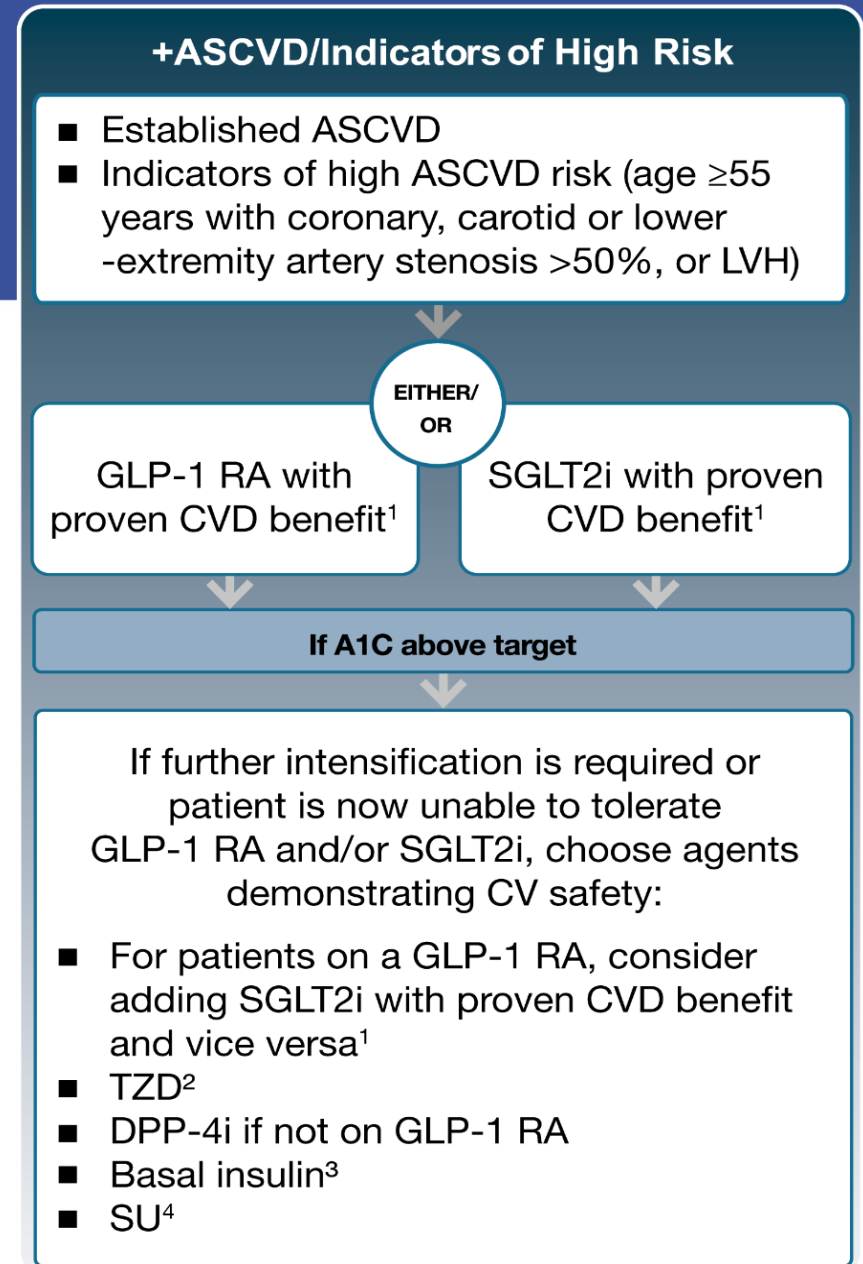
Consider independently of baseline A1C, individualized A1C target, or metformin use



American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care*. 2021;44(Suppl 1):S111–S124.

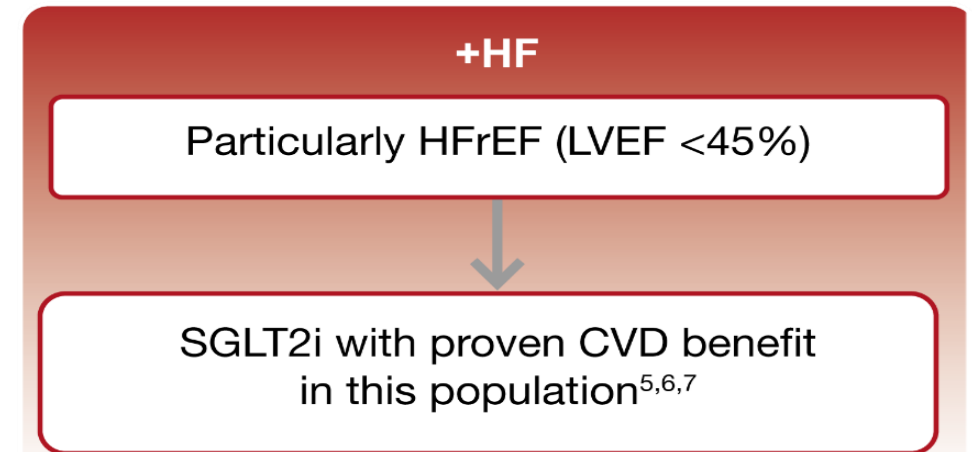
If ASCVD Predominates:

- GLP-1 RA with proven cardiovascular benefit
 - Liraglutide
 - Semaglutide
 - Dulaglutide
- SGLT2i with proven cardiovascular benefit
 - Empagliflozin
 - Canagliflozin



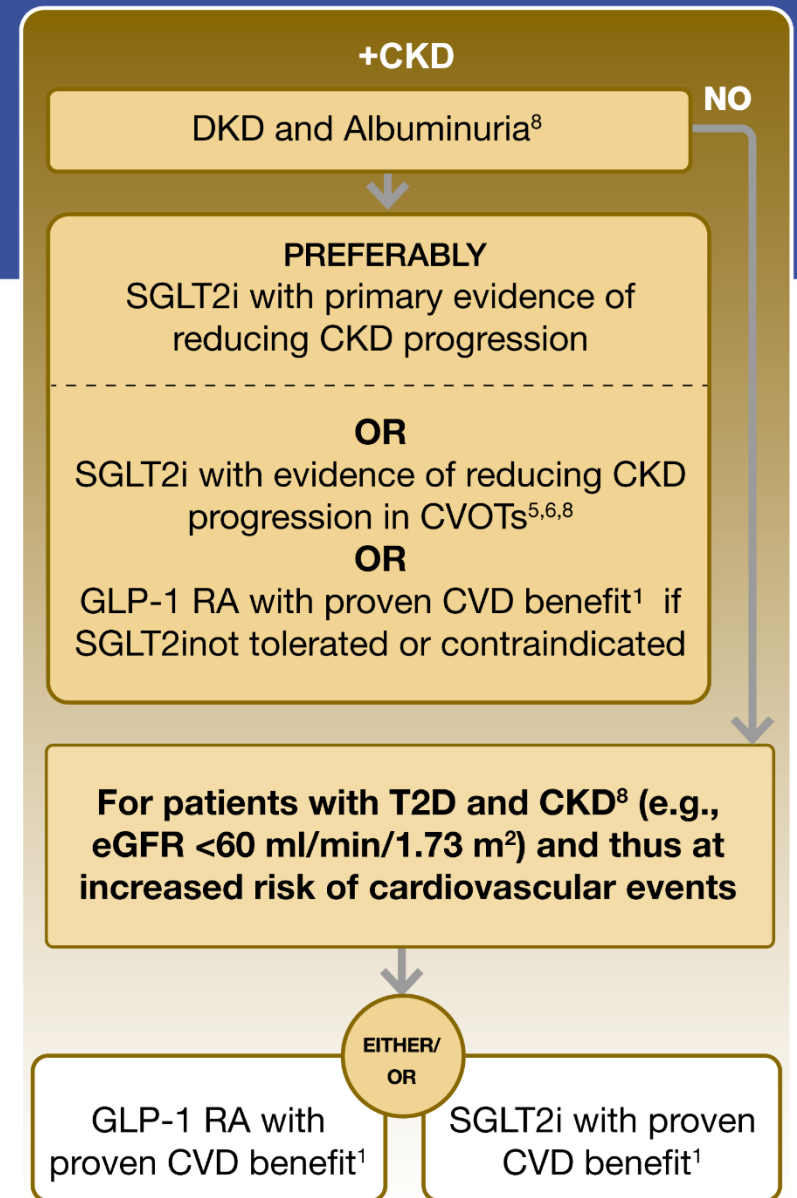
If HF Predominates:

- Empagliflozin
 - Canagliflozin
 - Dapagliflozin
 - Ertugliflozin
- Dapagliflozin and empagliflozin have primary and secondary benefit to reduce HF
 - Canagliflozin and ertugliflozin have secondary benefit to reduce HF
 - Dapagliflozin has specific HF FDA indication



If CKD Predominates:

- Canagliflozin
 - Dapagliflozin
 - Empagliflozin
-
- Benefit seen in CVOTs
 - FDA-approved for CKD indication- canagliflozin and dapagliflozin
 - Empagliflozin primary renal trial is ongoing

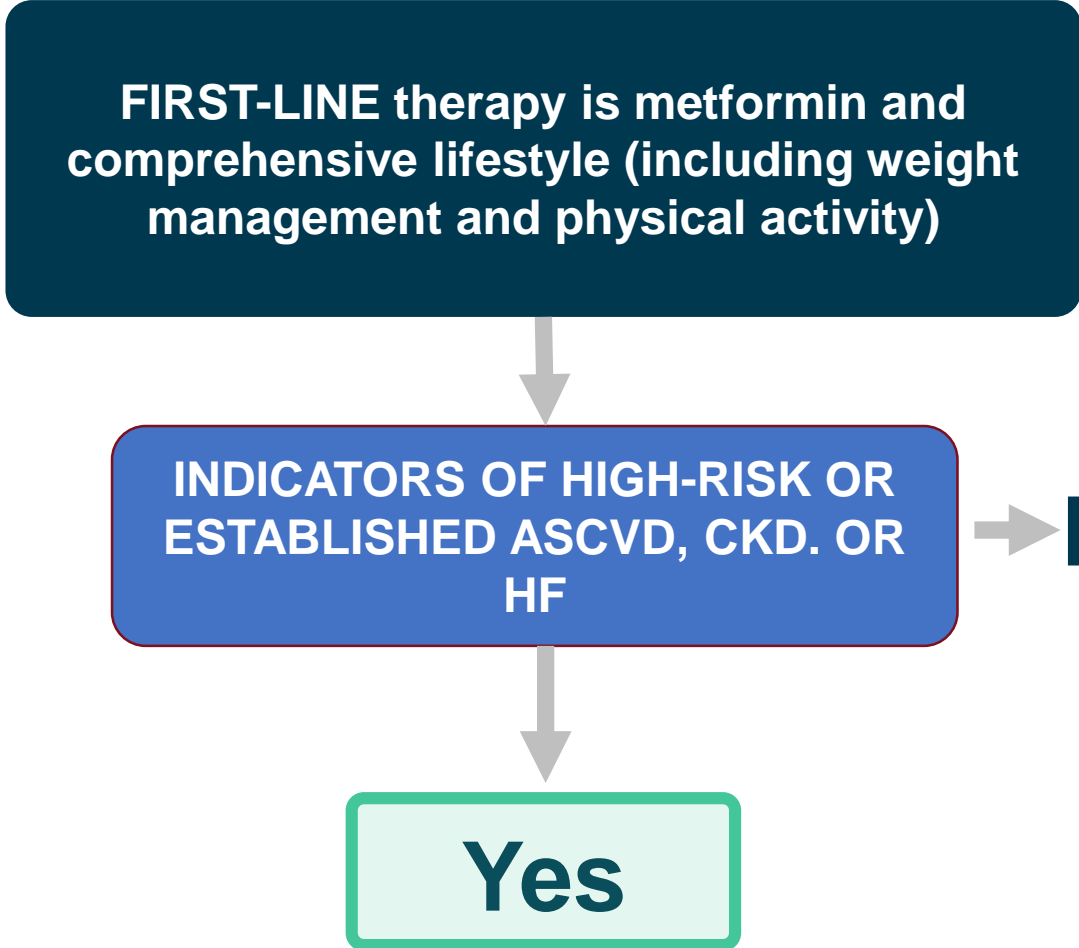


American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care*. 2021;44(Suppl 1):S111–S124.

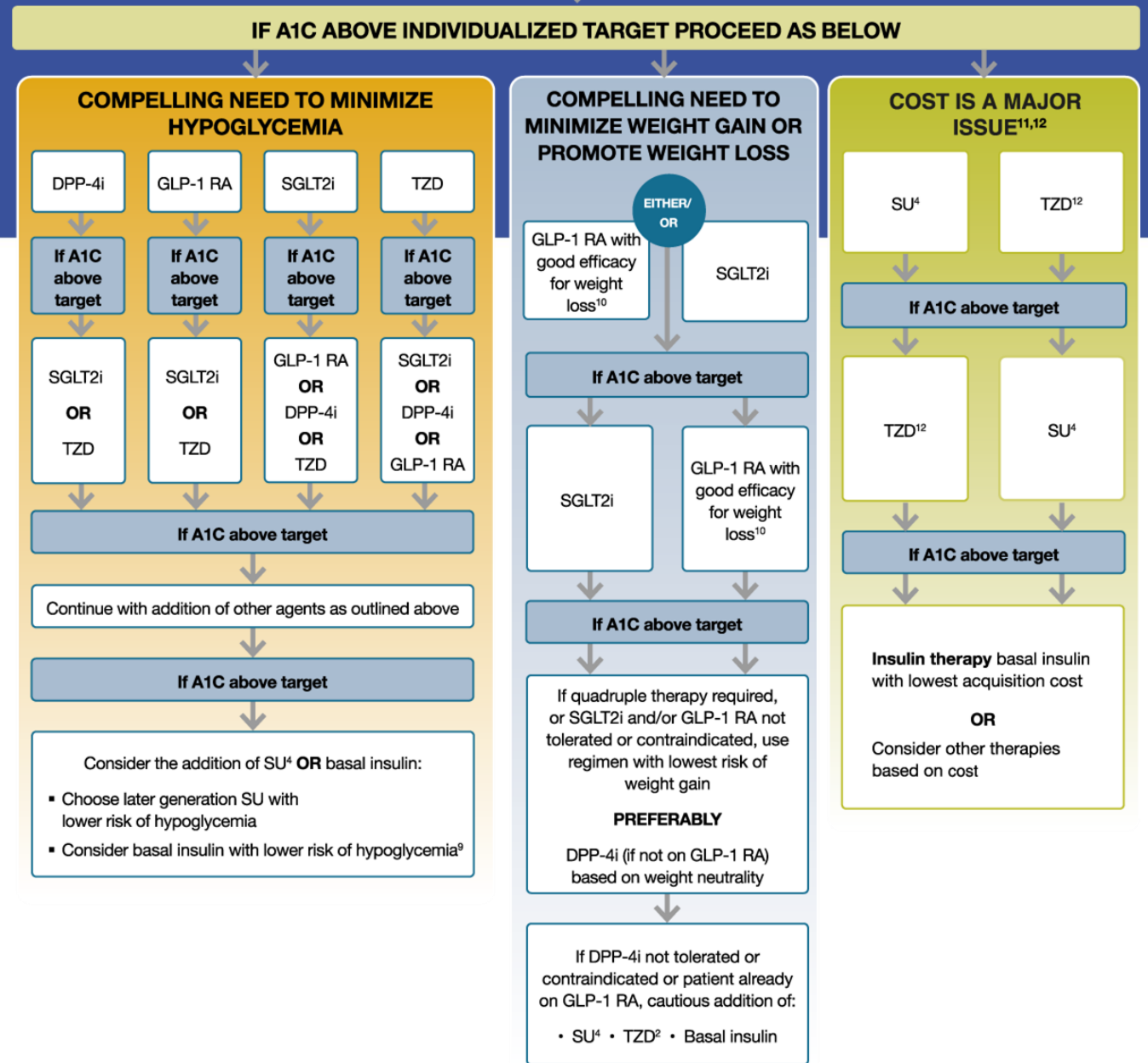
No Indicators of High-Risk or Established ASCVD, CKD, or HF

Step 1: Does the patient have established ASCVD, CKD, or HF or do they have indicators for these?

If the answer is “No”



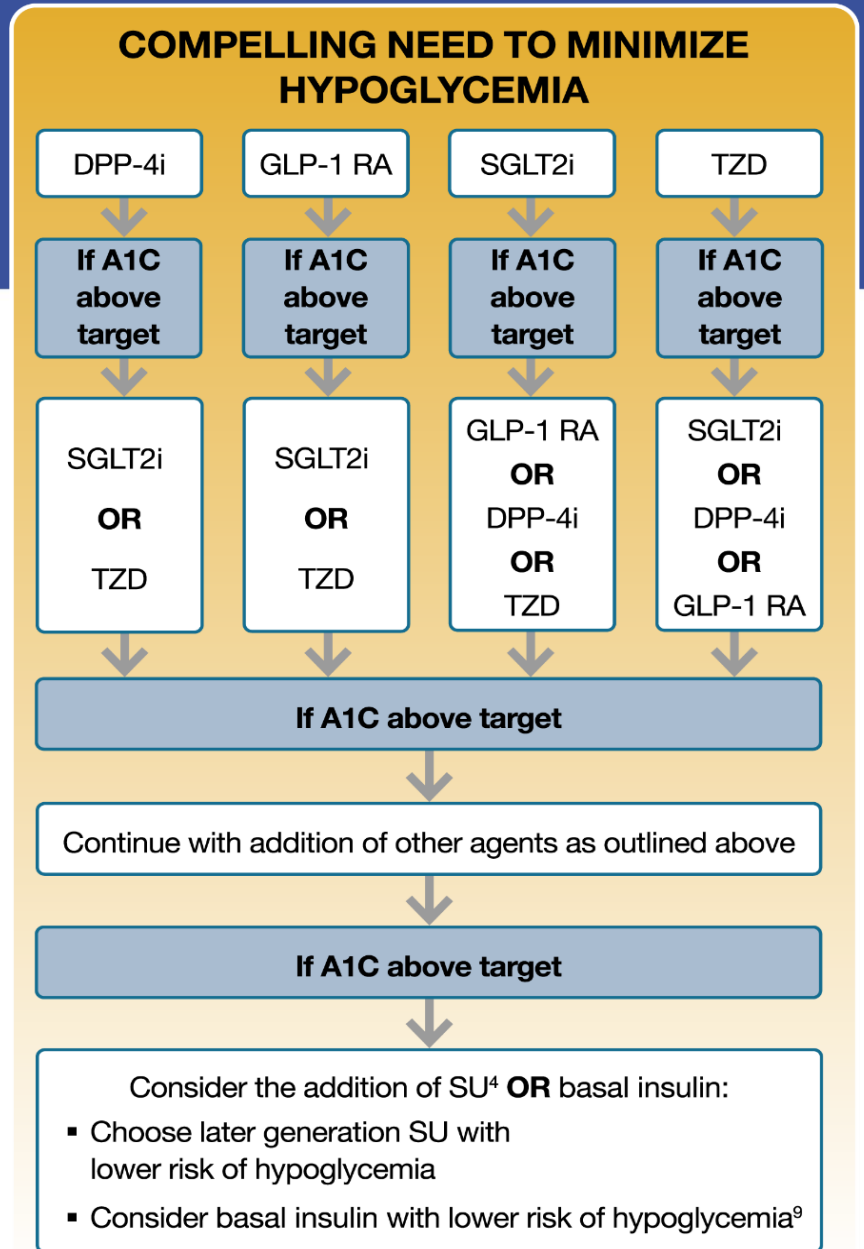
Step 2: If A1C is above the individualized target, consider patient-specific factors when selecting add-on medications.



American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care*. 2021;44(Suppl. 1):S111–S124.

Compelling Need to Minimize Hypoglycemia

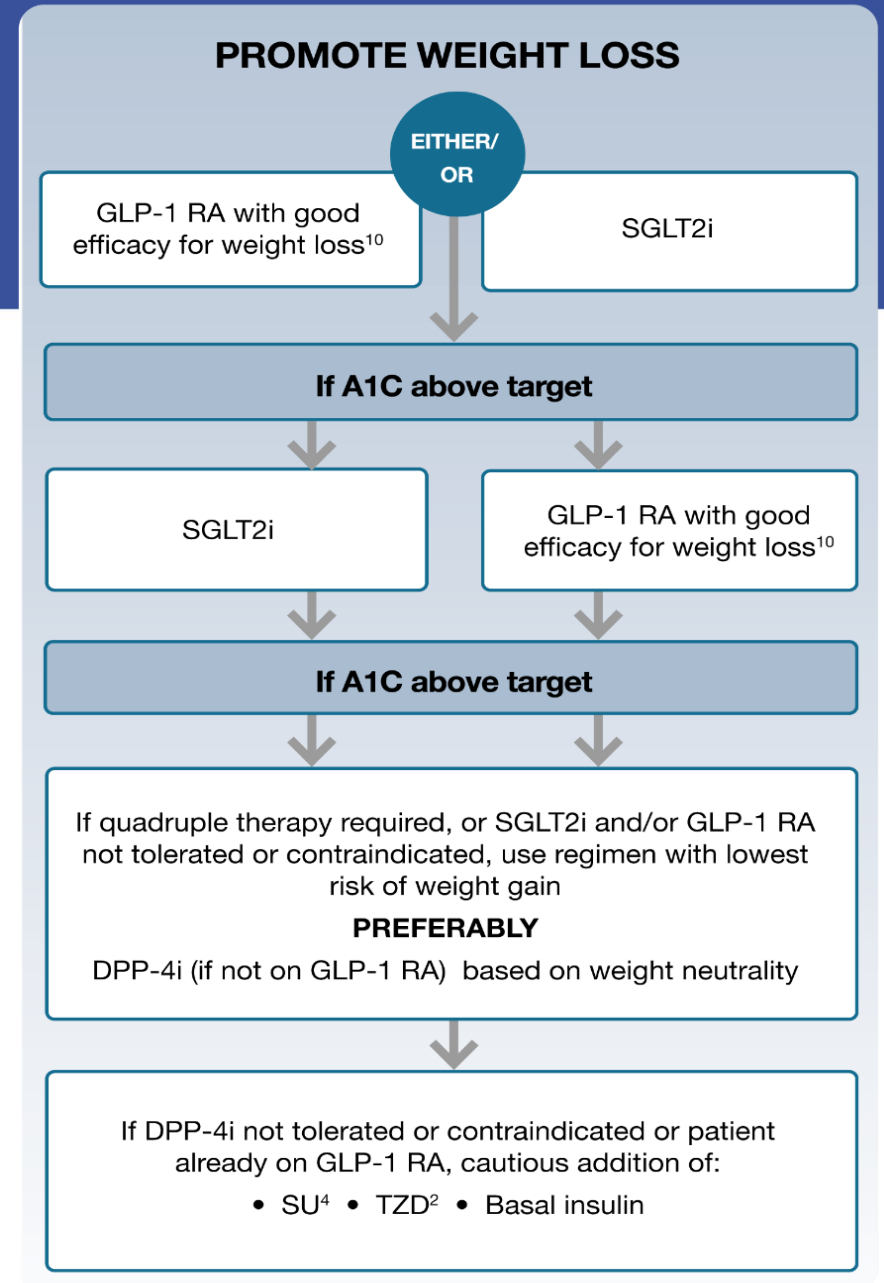
- DPP-4 inhibitors
- GLP-1 receptor agonists
- SGLT2 inhibitors
- Thiazolidinediones



Promote Weight Loss

If choosing a GLP-1 RA with good efficacy for weight loss:

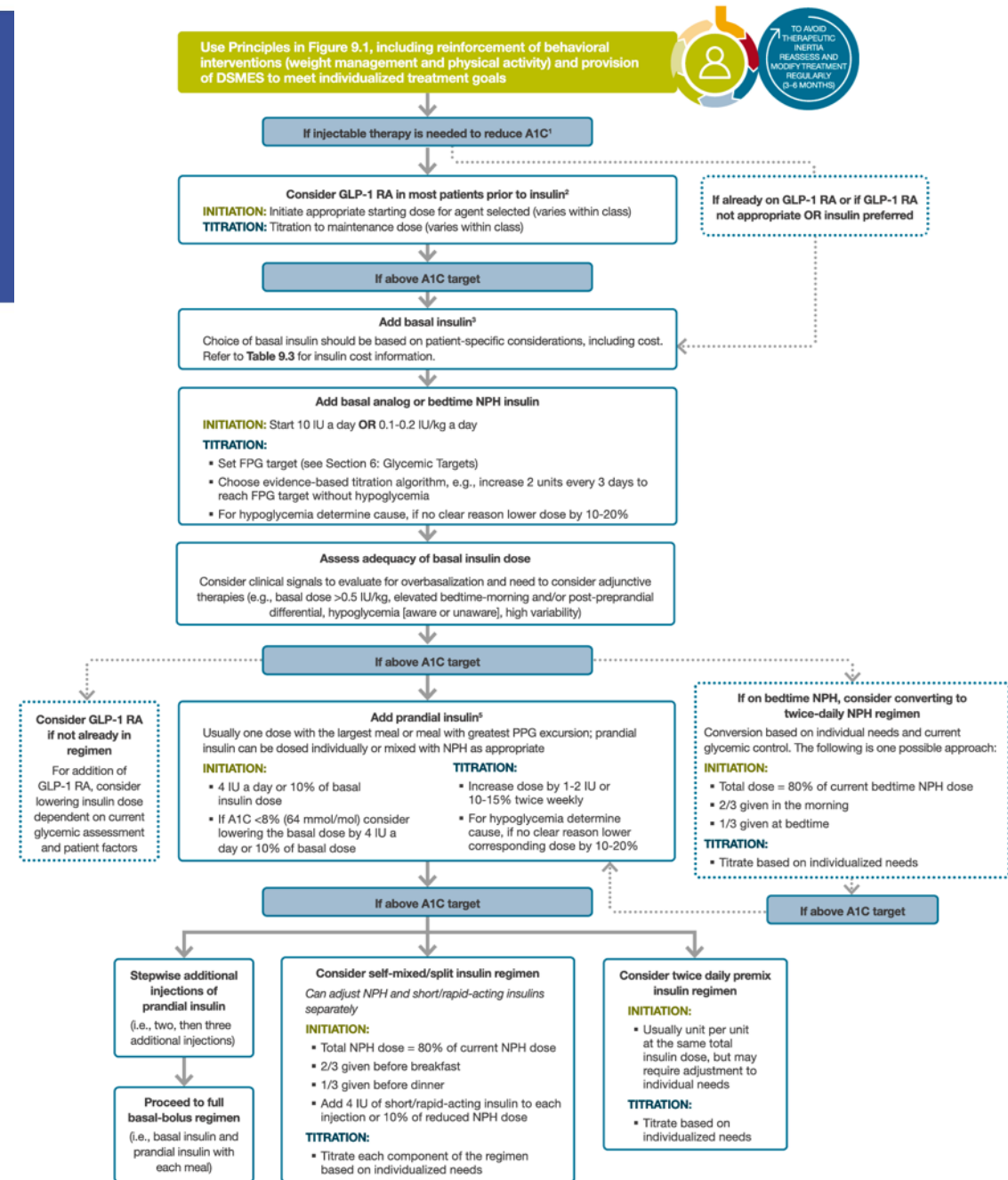
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide



American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care*. 2021;44(Suppl 1):S111–S124.

Intensifying to Injectable Therapies

- Injectable antihyperglycemic medications
 - GLP-1 RA
 - Basal insulin
 - Prandial coverage
 - Pre-mixed insulin
 - Intensive basal-bolus

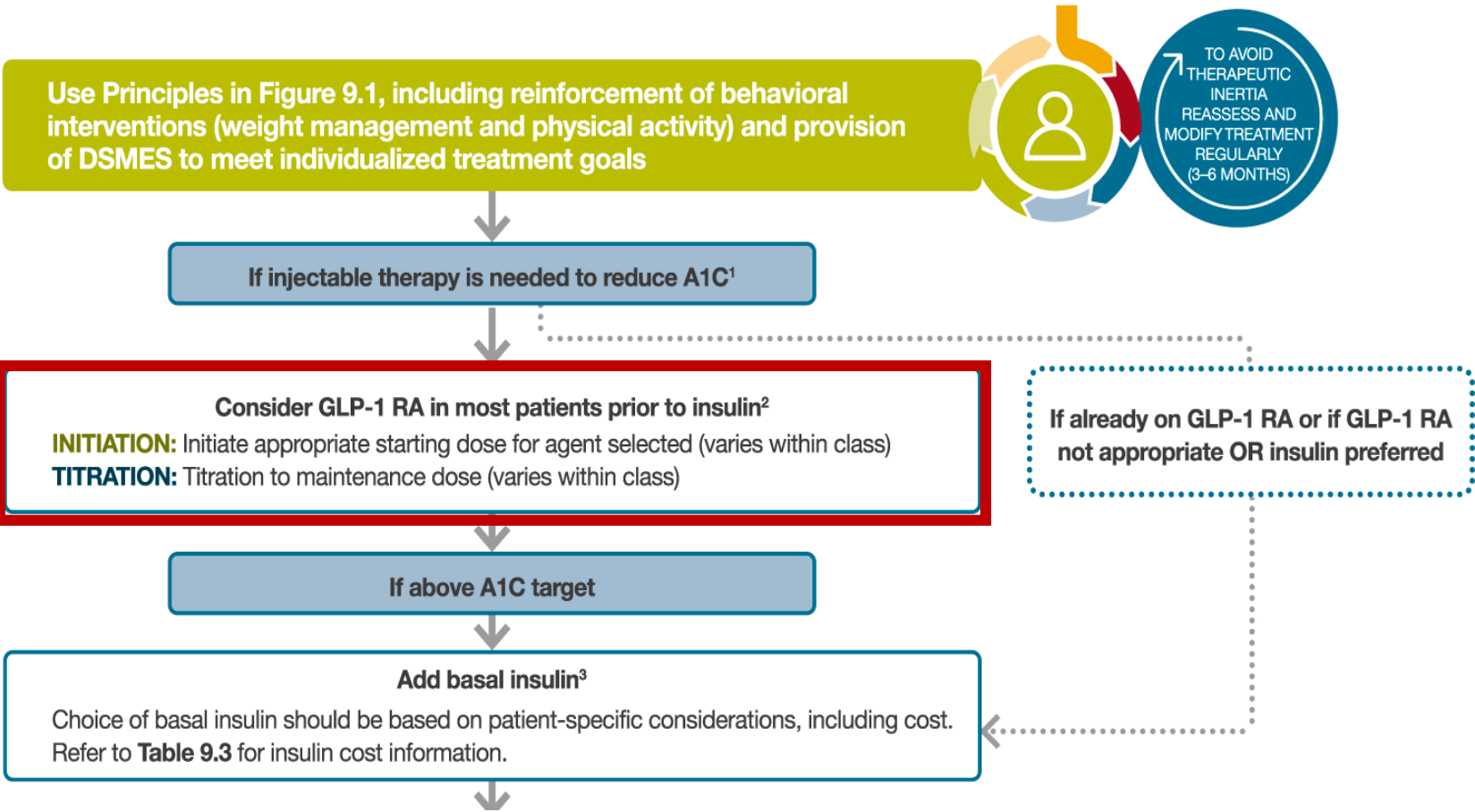


American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care*. 2021;44(Suppl. 1):S111-S124.

What Injectable Should I Use First?

Meta-analyses of GLP-1 RAs compared to insulin:

- ✓ Similar reductions in A1C
- ✓ Weight loss instead of weight gain
- ✓ Lower risk of hypoglycemia



Diabetes Care. 2021;44(Suppl 1):S111–S124.

Patient-specific Considerations

- Glycemic level
- Other disease states (ASCVD, HF, CKD)
- Weight
- Concern for hypoglycemia
- Risk of possible side effects
- Concern for side effects
- Contraindications
- Treatment burden / cost
- Ease of use / ability to adhere
- Cultural beliefs about medications
- What is most important to the patient?

Patient-specific Considerations

GLP-1 RA vs SGLT-2 inhibitor

	GLP-1 RA	SGLT-2i
Glucose lowering	High	Intermediate
Effect on weight	Loss	Loss
CV benefit	Benefit	Benefit
HF benefit	Neutral	Benefit
CKD benefit	Benefit (secondary outcomes)	Benefit (primary outcomes)
Other benefits	Nonalcoholic fatty liver disease (NAFLD)	
Side effects and precautions	<ul style="list-style-type: none"> Nausea, vomiting, diarrhea Injection site reaction Black box: thyroid c-cell tumor in rodents Potential risk of pancreatitis 	<ul style="list-style-type: none"> Genitourinary infections Risk of volume depletion, hypotension Risk of diabetic ketoacidosis (DKA) (discontinue before any scheduled surgery) Risk of bone fracture (canagliflozin) Risk of Fournier's gangrene
Use in renal disease	<ul style="list-style-type: none"> exenatide, lixisenatide – avoid if eGFR < 30 No dose adjustments for dulaglutide, liraglutide, semaglutide 	<ul style="list-style-type: none"> Renal dose adjustment required Avoid if eGFR is low (varies between agents < 25-45)
Administration	<ul style="list-style-type: none"> Injection, daily/weekly; (semaglutide – oral daily option) 	Oral, once daily

Diabetes Care. 2021;44(Suppl 1):S111–S124.

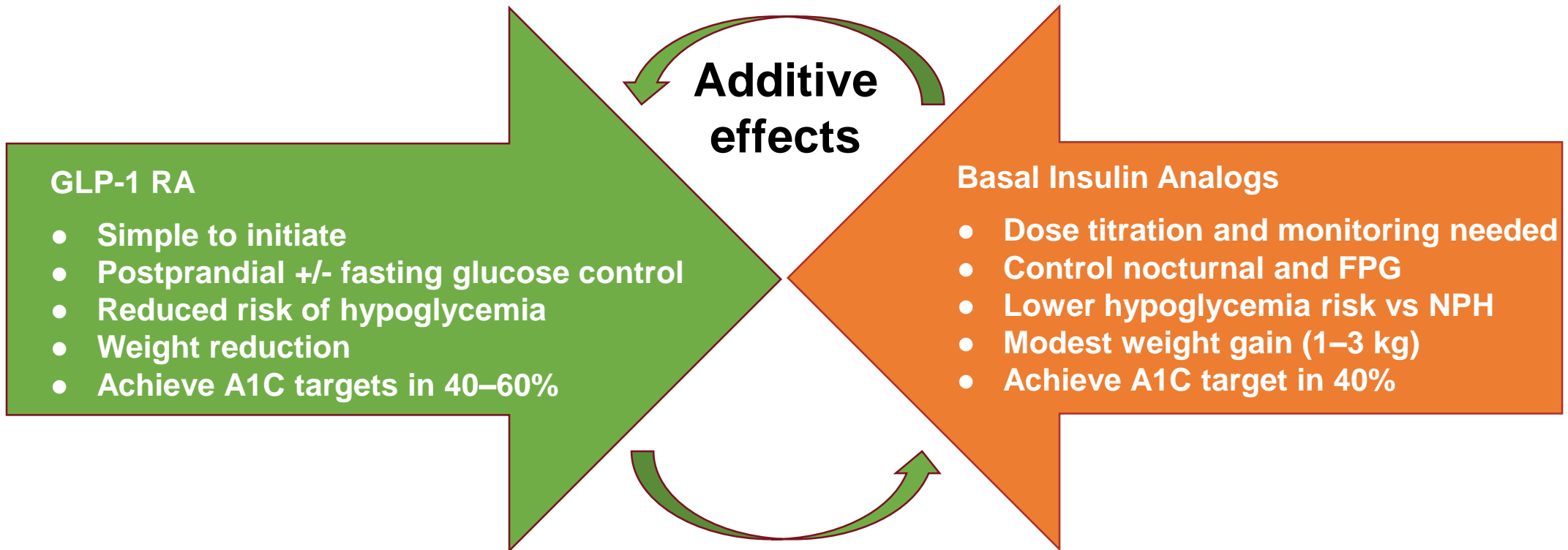
Patient-specific Considerations

GLP-1 RA vs Insulin

	GLP-1 RA	Insulin
Glucose lowering	High	High
Effect on weight	Loss	Gain
CV benefit	Benefit	Neutral
HF benefit	Neutral	Neutral
CKD benefit	Benefit (secondary outcomes)	Neutral
Side effects and precautions	<ul style="list-style-type: none"> • Nausea, vomiting, diarrhea • Injection site reaction • Black box: thyroid c-cell tumor in rodents • Potential risk of pancreatitis 	<ul style="list-style-type: none"> • Hypoglycemia (higher risk with NPH, premixed, or rapid compared to basal analogs) • Injection site reactions
Use in renal disease	<ul style="list-style-type: none"> • exenatide, lixisenatide – avoid if eGFR < 30 • No dose adjustments for dulaglutide, liraglutide, semaglutide 	<ul style="list-style-type: none"> • Renal dose adjustment required • Avoid if eGFR is low (varies between agents < 25-45)
Administration	<ul style="list-style-type: none"> • Injection, daily/weekly; (semaglutide – oral daily option) 	SC, schedule depends on insulin type/regimen Most require self-monitored blood glucose (SMBG) for dosing or titration

Diabetes Care. 2021;44(Suppl 1):S111–S124.

GLP-1 RA vs (or with) Basal Insulin



Considerations When Adding a GLP-1 RA

- Practical patient education on administration, storage, missed doses
- Anticipatory guidance to set expectations
 - Time to full effect
 - Dosing titration
 - Timing and side effects
 - How to mitigate side effects
- Adjusting background therapies
- Switching from one GLP-1 RA to another

Comparing Injection Devices

- Dosing
- Single-use vs multi-use
- Needles
- Preparation
- Accuracy
- Ease of use
- Storage requirements
- Patient preference
- Time required for training

Oral Semaglutide: Administration

- Take at least 30 minutes before the first food, beverage, or other oral medication of the day
- Take with no more than 4 oz of plain water only
- Swallow tablets whole: do not crush or chew
- Start with 3 mg once daily for 30 days (starting dose; not therapeutic); increase to 7 mg once daily for 30 days; increase to 14 mg once daily if needed
- Drug interactions
 - Levothyroxine
 - Oral bisphosphonates

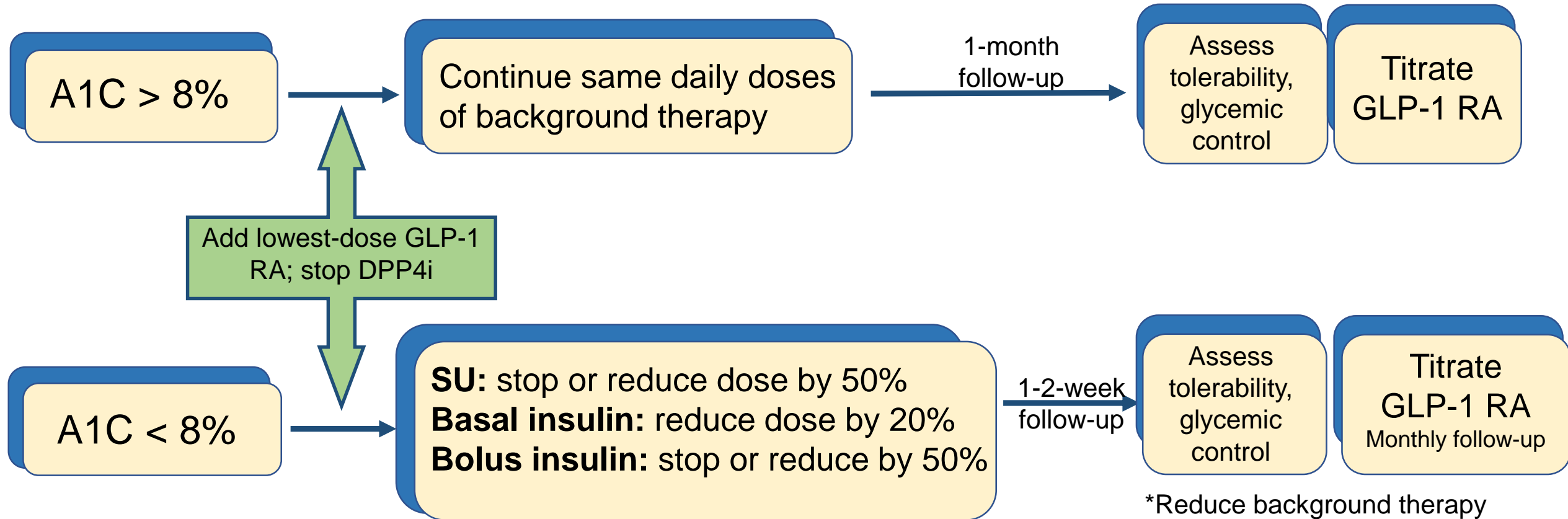
Mitigation of Gastrointestinal (GI) Adverse Effects

- Educate the patient that it is usually mild and usually transient
- Resolves in ~ 90% of cases
- Educate patients to decrease portions and eat slowly
- Start at a low dose
- Consider agent with lower rates of GI adverse effects
- Consider slower titration if possible
- Consider fixed-ratio combination

Considerations when Initiating GLP-1 RAs

- Background therapy
 - Continue, reduce, or discontinue
 - Redundant incretin therapies
- Current glycemic control
 - Risk of hypoglycemia
- Rationale for GLP1-RA addition
 - Efficacy: glucose control, weight reduction, cardioprotection

Adjusting Background Antihyperglycemic Therapy



*Reduce background therapy per SMBG to prevent hypoglycemia: bolus insulin/SU > basal insulin > TZD > MET

Rationale for Switching GLP-1 RA

- Enhanced efficacy
 - Glycemic control
 - Weight reduction
 - Added cardioprotection
- Improved safety or tolerability
 - GI
 - Injection site reactions
- Dosing and convenience
 - Alternative dosing frequency
 - Patient preferred delivery device
 - Alternative route of administration
 - Replace more cumbersome therapies
- Formulary restrictions and cost

Switching GLP-1 RAs

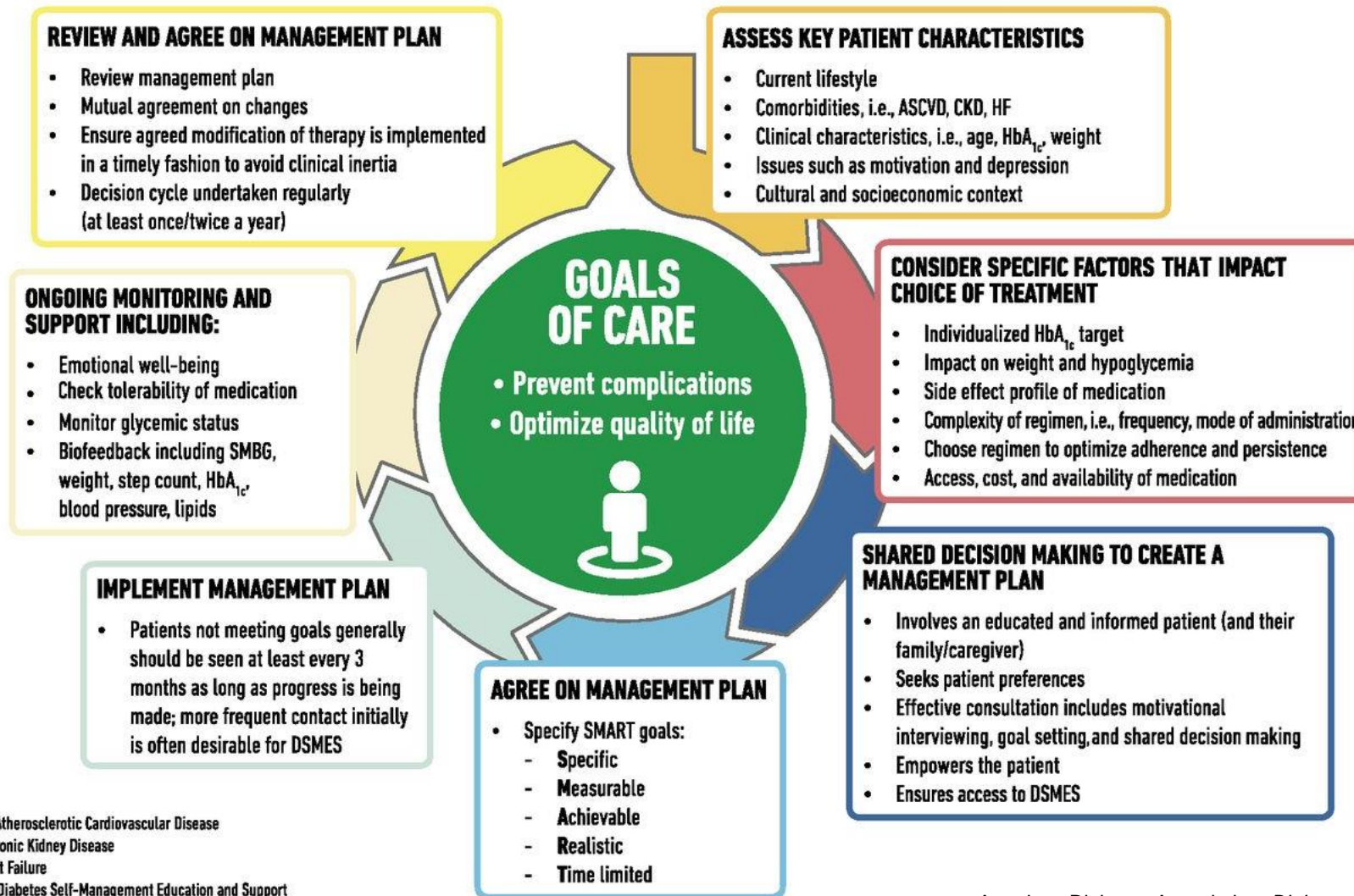
Prompted by GI Side Effects

- Discontinue first GLP-1 RA
- Wait for symptoms to resolve
- Select GLP-1 RA with lower rates of GI side effects
- Initiate new GLP-1 RA at lowest dose
- Consider slower dose titration

Prompted for Other Reasons

- Discontinue first GLP-1 RA
- Select GLP-1 RA with desired aspect
- Start with equivalent (or lower) dose
- Titrate accordingly

Patient-Centered Decision Cycle



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

American Diabetes Association. *Diabetes Care*. 2021;44(Suppl 1):S40–S52.

Use of Empowering Language

- Five key consensus recommendations for language use:
 - Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology;
 - Use language that is free from stigma;
 - Use language that is strength based, respectful, inclusive, and imparts hope;
 - Use language that fosters collaboration between patients and providers;
 - Use language that is person centered (eg, “person with diabetes” is preferred over “diabetic”).

Key Elements of Motivational Interviewing

- Open-ended questions
- Active listening
- Reflective empathetic responses
- Roll with resistance (resist the righting reflex)
- Ask for permission
- Ask rather than tell; listen rather than advise

PWD #1: David

- 61-year-old man with T2D, diagnosed at age 49 in 2009
- Complications of T2D: albuminuria
- Other medical problems: hypertension, dyslipidemia, NAFLD, prolactinoma
- Current medications for T2D
 - Semaglutide 1 mg SC once weekly
 - Metformin 1000 mg twice daily
- Past medications for T2D
 - Exenatide
 - Liraglutide
 - Exenatide XR
 - Dulaglutide
- A1C at last visit was 6.8%; prior 9.2% (past 5.8-6.8%)

Patient Perspectives: David

- What has been your general experience with the GLP-1 RA class?
 - Can you give us a summary of your diabetes journey?
 - What has been your general experience with self-managing your diabetes?
 - What has been your general experience with diabetes medications?

Patient Perspectives: David

- How would you compare the different devices in terms of effect, ease of use, side effects?
- Can you describe what those side effects were like?
- What are the logistical challenges of switching from one medication to another?

PWD #2: Terrence

- 44-year-old man with T2D, diagnosed at age 31 in 2008
- Complications of T2D: none
- Other medical problems: dyslipidemia, hypertension
- Current medications for T2D
 - Dulaglutide 1.5 mg SC once weekly
- Past medications for T2D
 - Metformin
 - Sitagliptin/metformin
 - Glipizide ER
 - Humalog 75/25: 12 U twice daily
 - Albiglutide 30 mg once weekly
 - Empagliflozin
- A1C at last visit was 7.1% (prior ranged 10.4 – 14.2%)

Patient Perspective: Terrence

- How would you compare your experience with Trulicity compared to your experience with insulin?
- When you are considering taking a new medication for diabetes, what is most important to you?

PWD #3: Carrie

- 74-year-old woman with T2D diagnosed in the 1990s
- Complications of T2D: CKD stage 4
- Other medical problems: dyslipidemia, hypertension, hypothyroid, gout, insomnia, carpal tunnel syndrome
- Current medications for T2D
 - NPH 46 U QAM and 30 U QPM
 - Dulaglutide 4.5 mg weekly
 - Kidney function has stabilized, improved slightly
- Past medications for T2D
 - Metformin, glipizide, pioglitazone, linagliptin, empagliflozin
 - Insulin glargine U-300, insulin lispro
 - Kidney function decline limited use of many medications
- A1C at last visit 6.2% (baseline 8.6%)

Patient Perspective: Carrie

- Who explained to you how to take your diabetes medications?
- Who explained the possible side effects? Particularly low blood sugars? How comfortable did you feel about how to take your diabetes medications and what to do if you had a side effect like hypoglycemia?

Patient Perspectives

- What are your thoughts about this idea of “shared-decision making”? Do you feel like you have a collaborative relationship with your diabetes provider?
- How have you interacted with pharmacists?
 - in your diabetes clinic?
 - In your community pharmacy?
- How would you describe the role of the pharmacist in helping people manage their diabetes?

Patient Perspectives

- Given that you are speaking with several hundred pharmacists today, what is the most important thing you want them to know about the role of the pharmacist in health care?
- What is the most important topic a pharmacist should share with a person with diabetes before they start a GLP-1 RA?

Patient Perspectives

- What is the most challenging aspects of having diabetes?
- What are the best things your health care providers/team can do to support you?



GLP-1 360
PHARMACISTS ↔ PATIENTS

Questions & Answers



GLP-1 360

PHARMACISTS ↔ PATIENTS

Thank You!