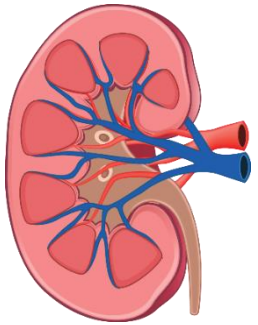

GUIDELINE DIRECTED CARE OF TYPE 2 DIABETES

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University of Washington, Seattle

UW ECHO 03-31-21

Case 1

- 53 year old male with 5 years of type 2 diabetes, no complications
- On metformin 1000mg twice daily
- Has gained 15 lbs early during pandemic working from home
- Commercially insured
- A1C 8.6% over recent 12 months

What is the next step?

Common questions

I don’t know which one to pick

OR

My patient can’t afford these new and expensive drugs, what can I use for diabetes management?

Several available guidelines

- American College of Physicians
- American Association of Clinical Endocrinologists
- American Diabetes Association

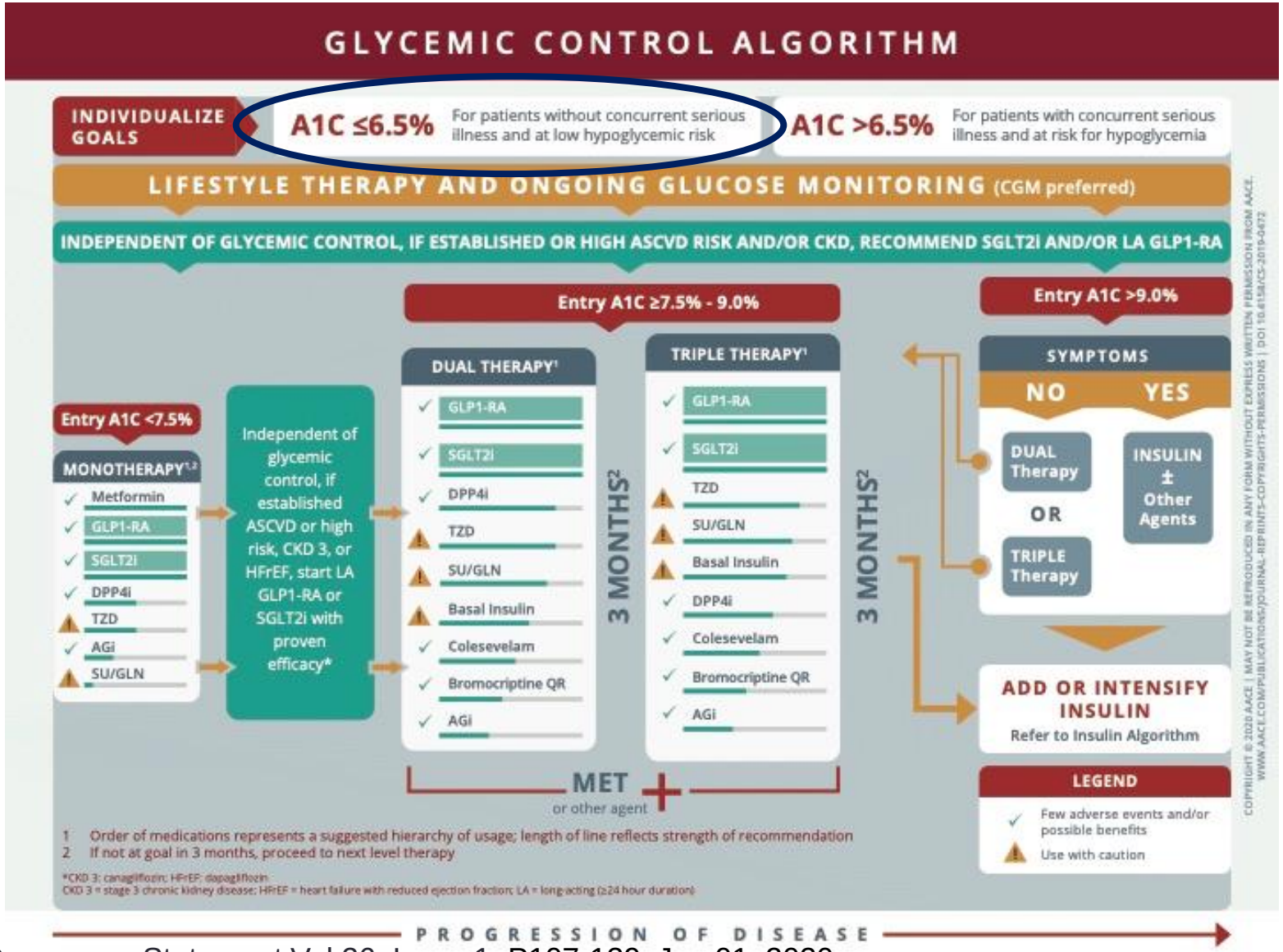
ACP recommendations for A1c targets for T2D

- Less intense approach

1. Personalize goals based on patient preference, discussion of benefits and harms of pharmacotherapy, general health and life expectancy, treatment burden and costs of care
2. A1C between 7-8% in most patients with T2D
3. De-intensify therapy with A1C <6.5%
4. Treat to minimize sx of hyperglycemia, no targets for older individuals with ↓ life expectancy, chronic conditions (COPD, CHF) as harms outweigh benefits

Qaseem A et al Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2018;168:569-576

AACE Diabetes management guidelines

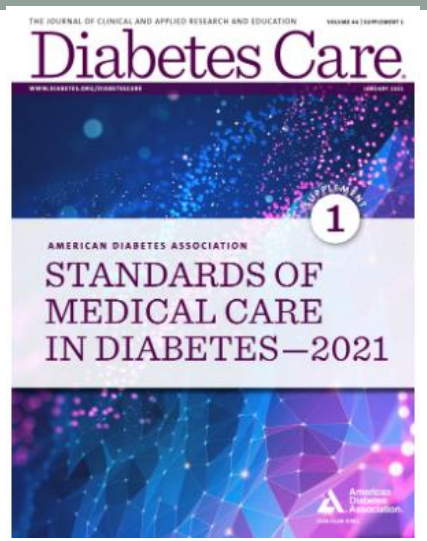


Garber AJ et al. AACE Consensus Statement Vol 26, Issue 1, P107-139, Jan 01, 2020

Several available guidelines

- American College of Physicians
- American Association of Clinical Endocrinologists
- American Diabetes Association

ADA Standards of Care (SOC)



- Reviewed and updated annually
- Evidence-based
  - Evidence grading system (A, B, C, E)
  - Search Medline for new evidence since January 2020
  - Print (January supplement of Diabetes Care)
  - Abridged for PCPs: Clinical Diabetes
- Online: professional.diabetes.org/SOC
  - Full and abridged PDF
  - SOC Slides
  - SOC App


Standards of Care

Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers

American Diabetes Association

Clinical Diabetes 2021 Jan; 39(1): 14-43.

https://clinical.diabetesjournals.org/content/39/1/14

Evidence grading

- **A**—Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
- **B**—Supportive evidence from well-conducted cohort studies
- **C**—Supportive evidence from poorly controlled or uncontrolled studies
- **E**—Expert consensus or clinical experience

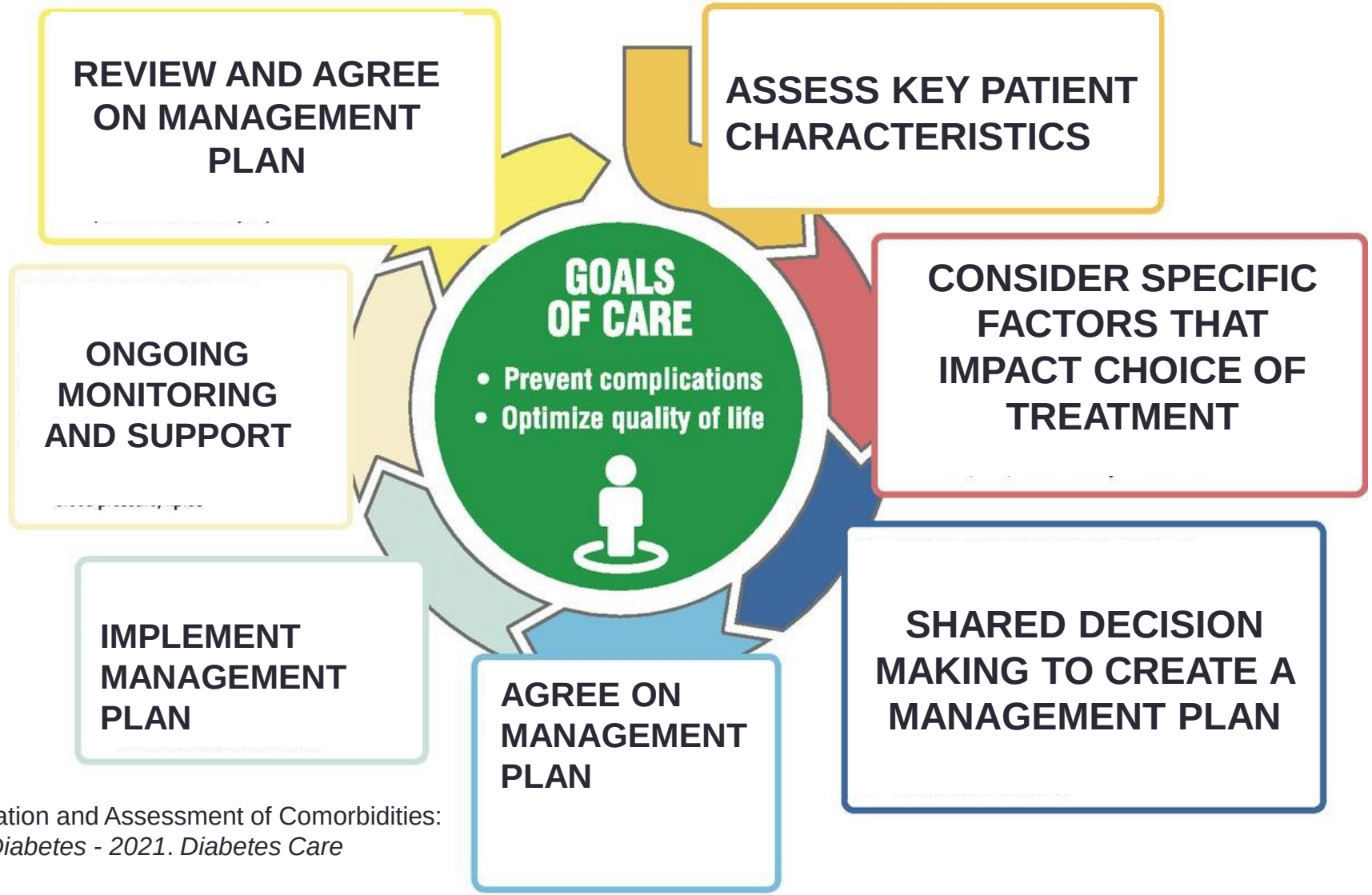
Two themes

1. How to individualize care

2. How to pick the appropriate diabetes therapy based on patient characteristics

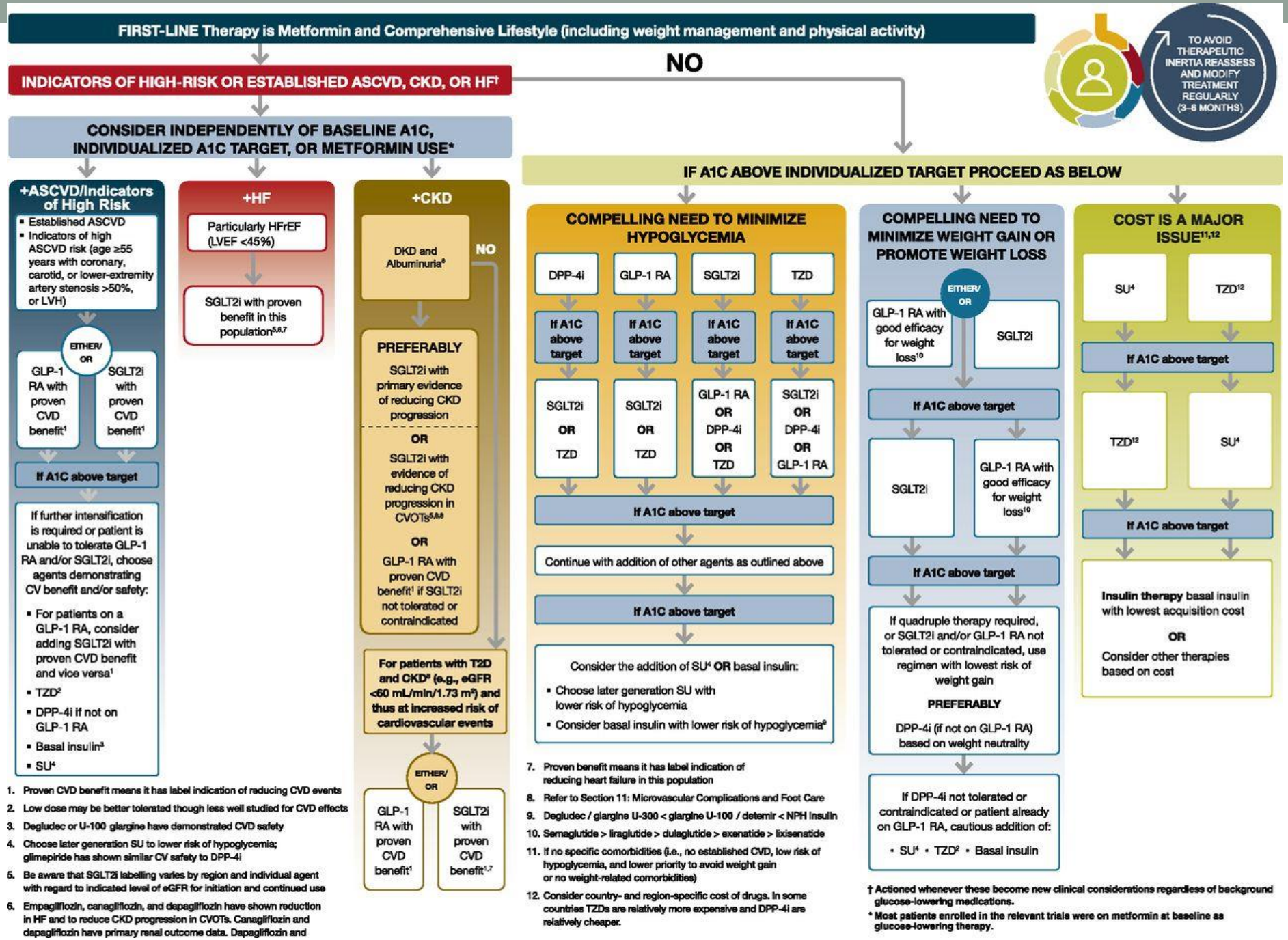
    - ✓Glycemic management
    - ✓CV risk reduction
    - ✓Kidney risk reduction

Decision cycle for patient-centered glycemic management in Type 2 diabetes



Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1):S40-S52

Medication selection sequence for type 2 diabetes treatment – v2021

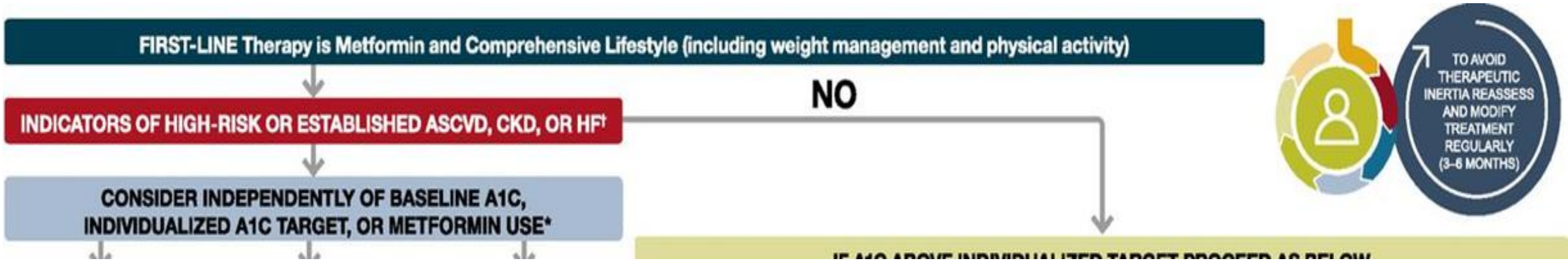


Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1) S111-S124

Appropriate Glucose-lowering Medication Selection in T2D

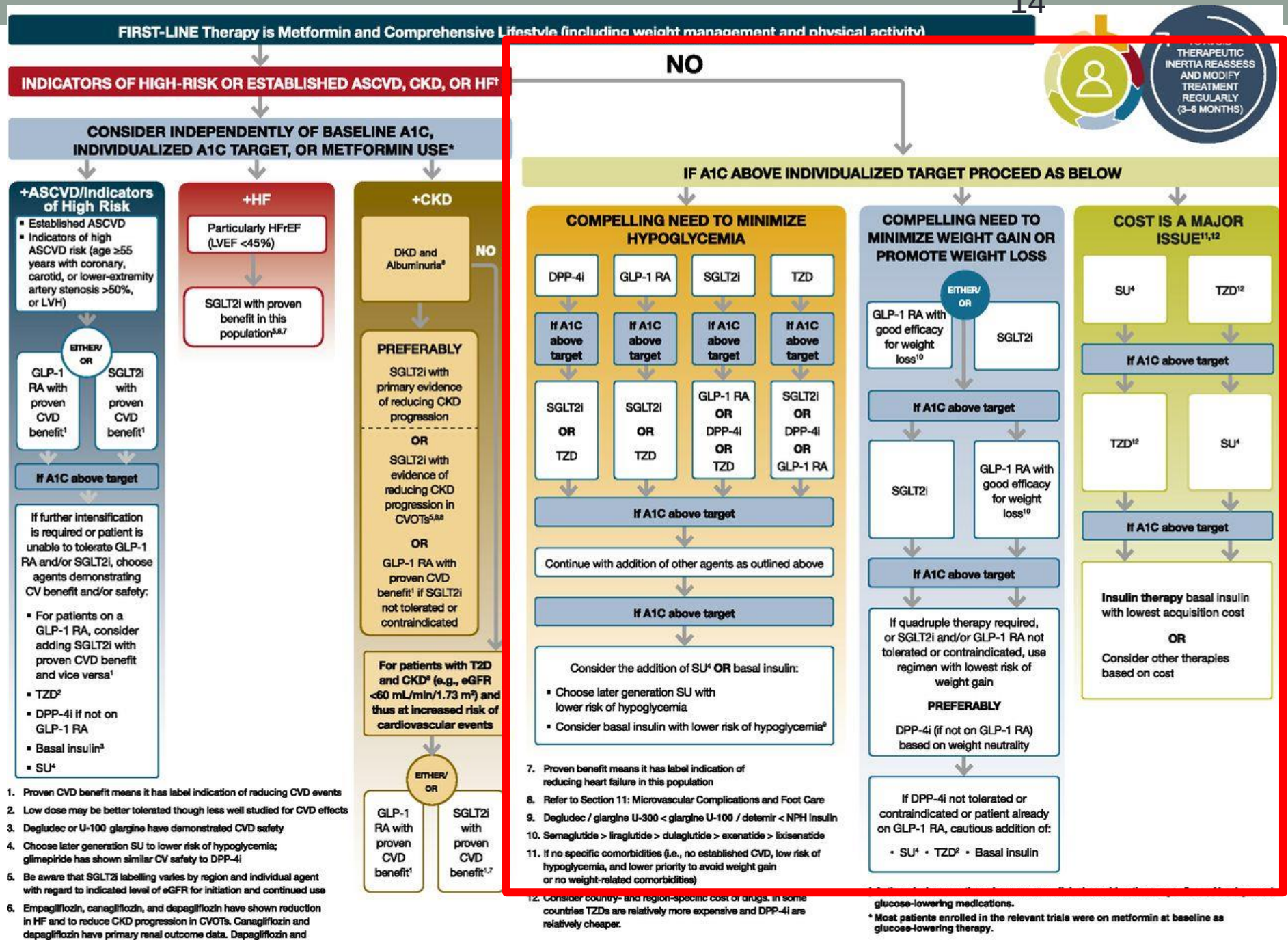
- ✓Glycemic management
- ✓CV and renal risk reduction

- Metformin at the time of diagnosis + lifestyle modification
- Additional or alternative agents can be considered in special circumstances



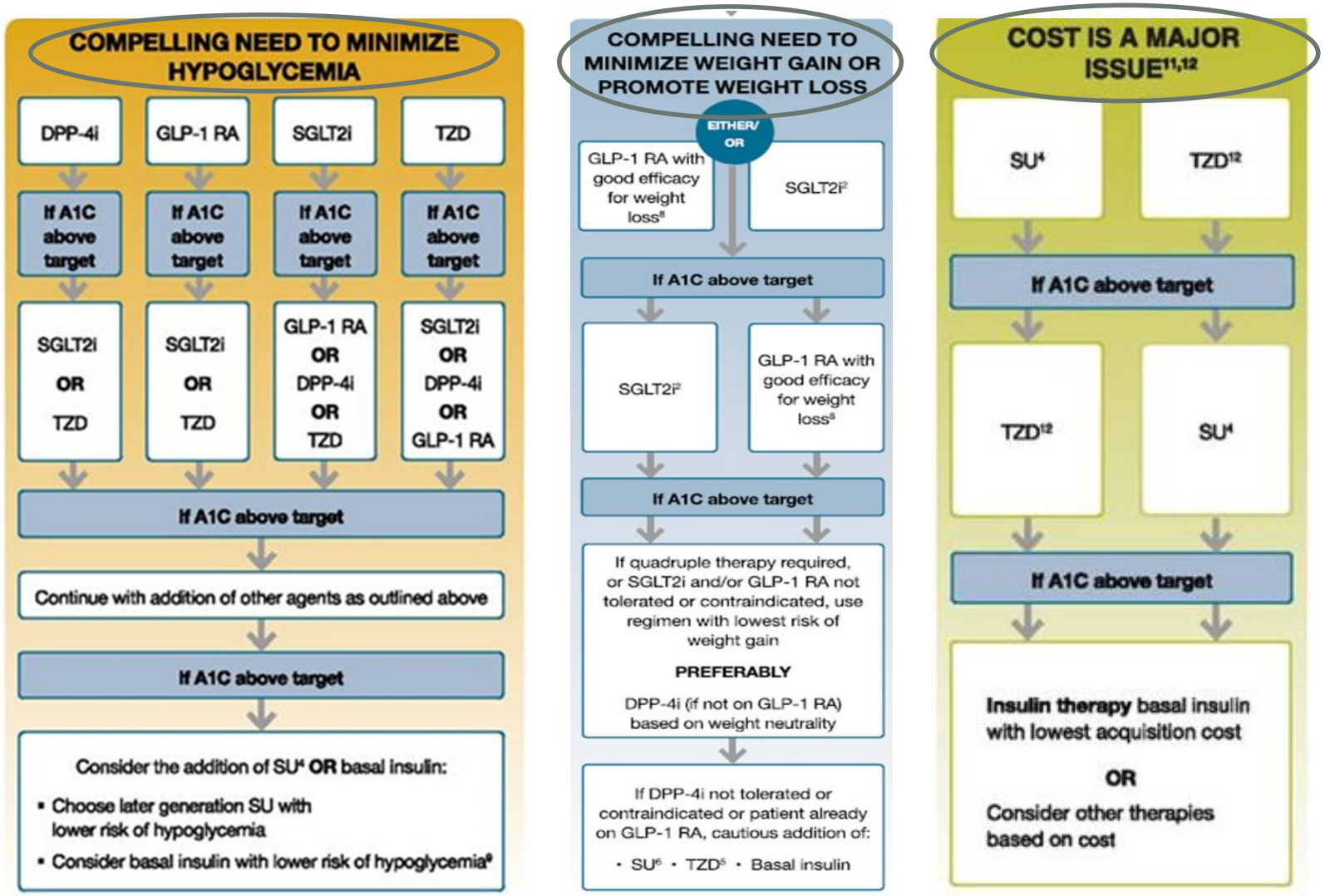
PICK BASED ON CARDIAC OR RENAL STATUS!

Medication selection sequence for type 2 diabetes treatment – v2021



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1) S111-S124

No ASCVD/HF/CKD: If A1C is above individualized target



1. Minimize hypoglycemia
2. Weight loss
3. Cost issues

53 y/o male on metformin
A1C 8.6%
15 lb weight gain

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*.

No ASCVD/HF/CKD: If A1C is above individualized target

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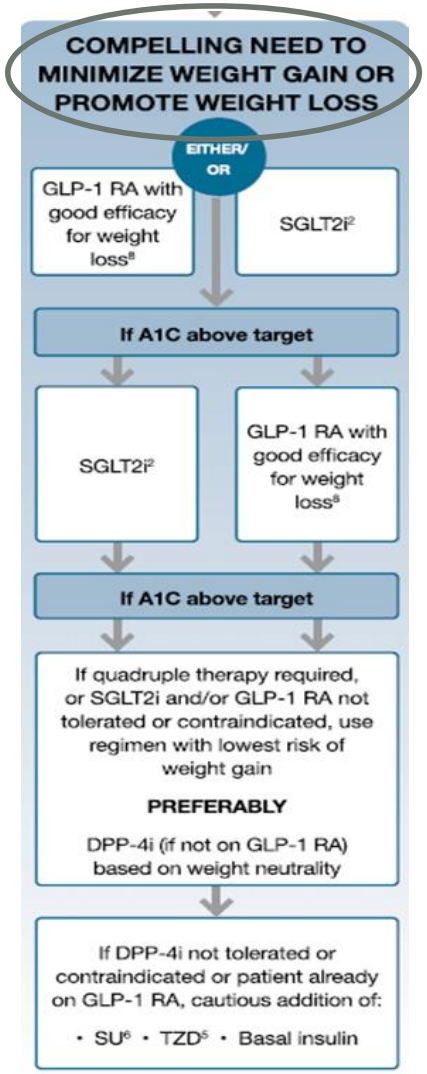
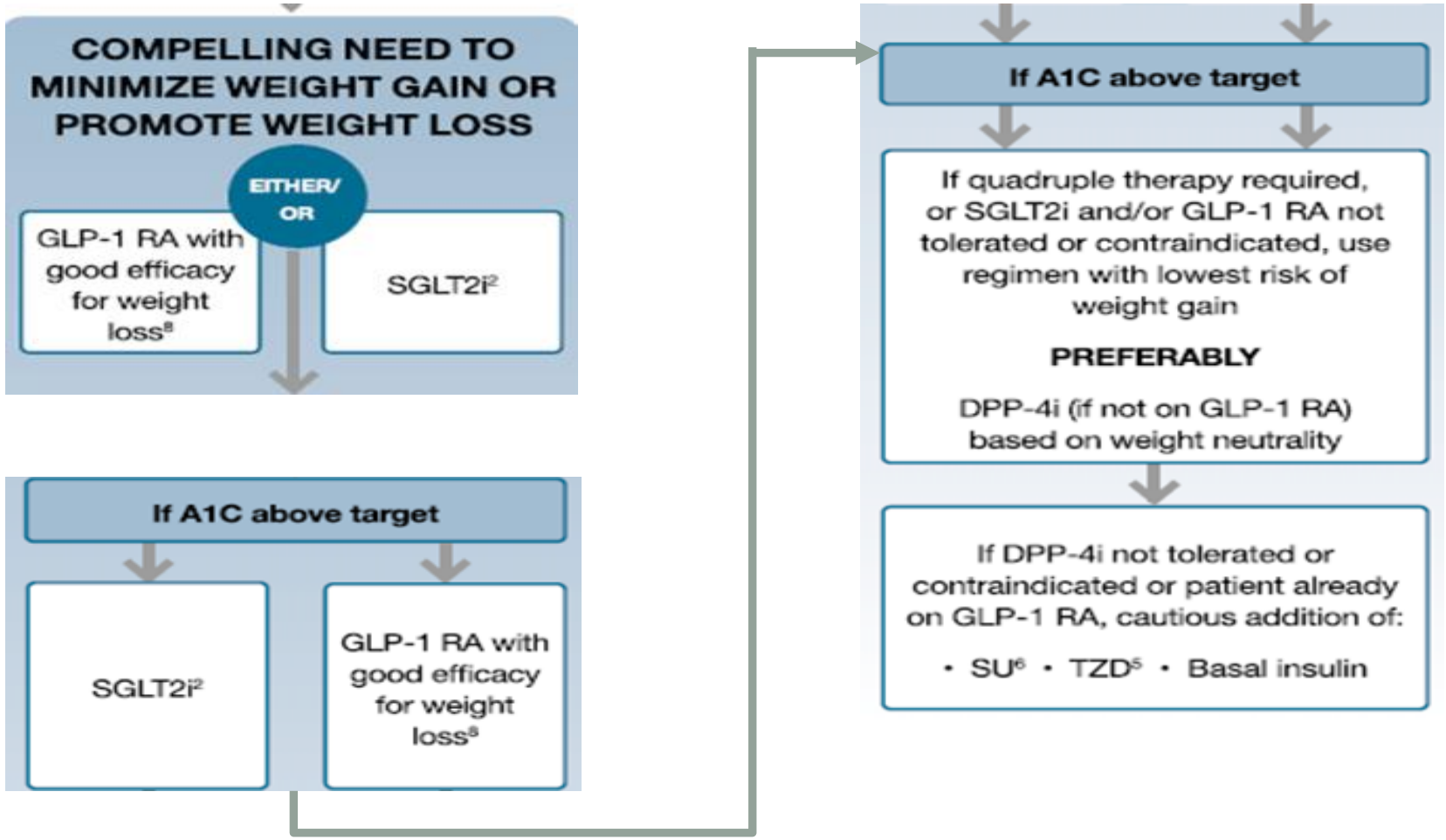
15 lb weight gain



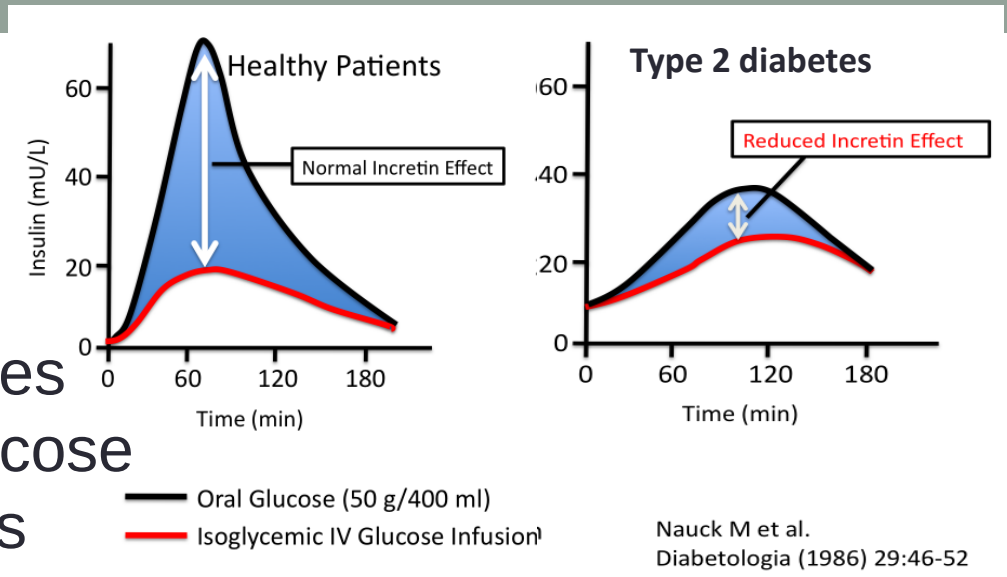
Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2020;43(Suppl. 1):S111-124

Choosing SGLT2i or GLP1RA for weight loss



GLP1 receptor analogs

- Incretin effect - greater insulin secretory responses after oral glucose load than after intravenous glucose infusion that lead to identical glycemic excursions
- Short-acting or long acting
- Daily or weekly injections; oral formulation also available
- Can be chosen before insulin therapy
- Semaglutide >liraglutide > dulaglutide > exenatide lixisenatide
- Mostly covered by state Medicaid plans and Medicare Part D



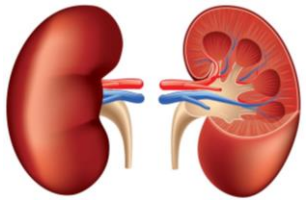
Liraglutide (Victoza)

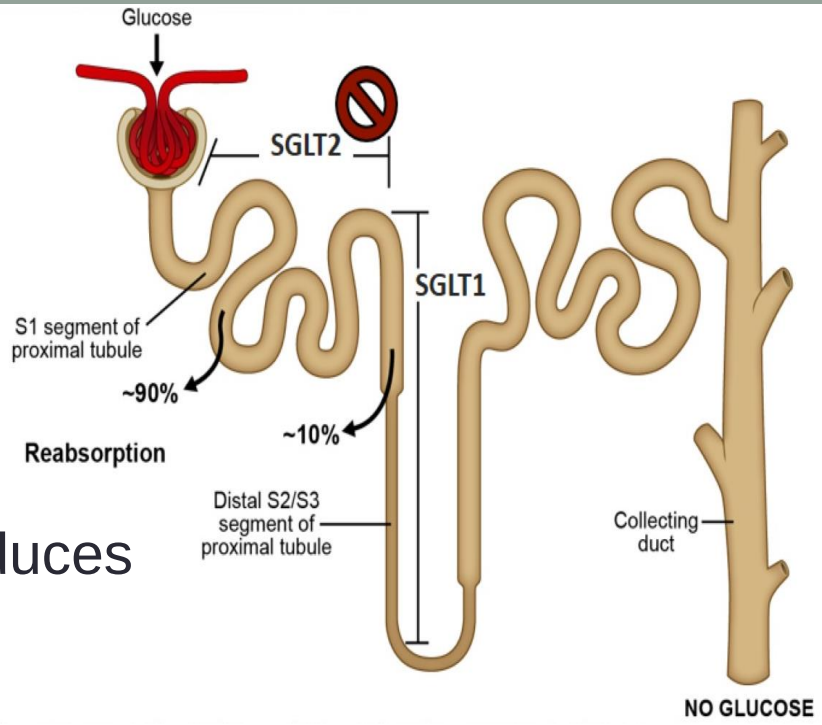
Dulaglutide (Trulicity)

Semaglatide (Ozempic)

Exenatide (Bydureon)

SGLT2 inhibitors





- SGLT2 mediates glucose reabsorption in the kidney
- Blockade of SGLT2
  - Inhibits glucose absorption at the proximal nephron → reduces glucose reabsorption
  - Self limited glucose lowering and weight loss

- Available drugs:
  - empagliflozin, canagliflozin, dapagliflozin, ertugliflozin (the “flozins”)
  - Come in 2 doses
  - Combinations with metformin or DPP4 inhibitors also available

Case 1

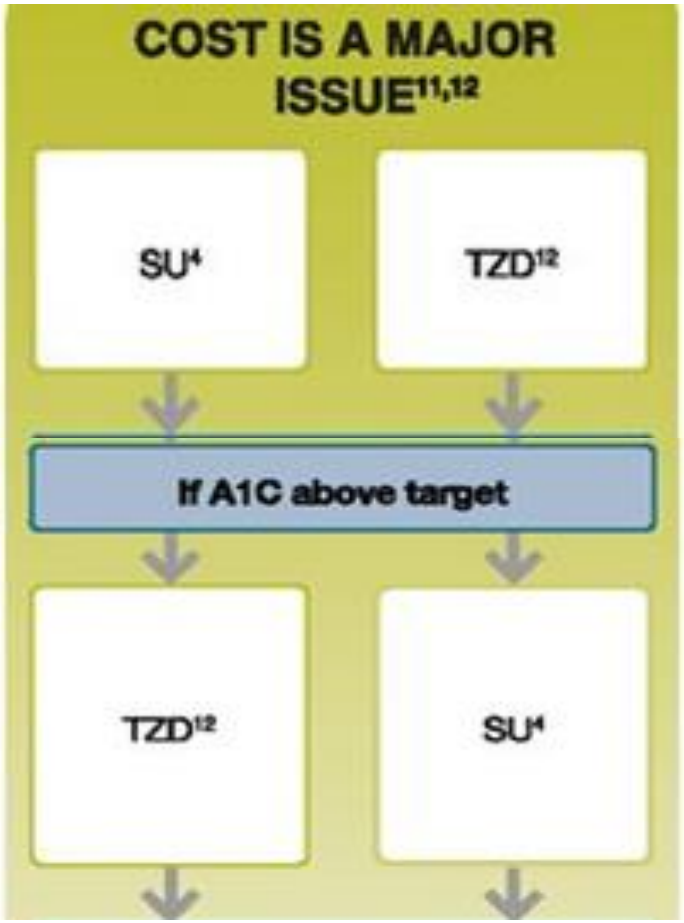
- Started on dulaglutide 0.75mg weekly and tolerated well
- Returned in 3 months and had lost 8 lbs
- A1C 7.1%

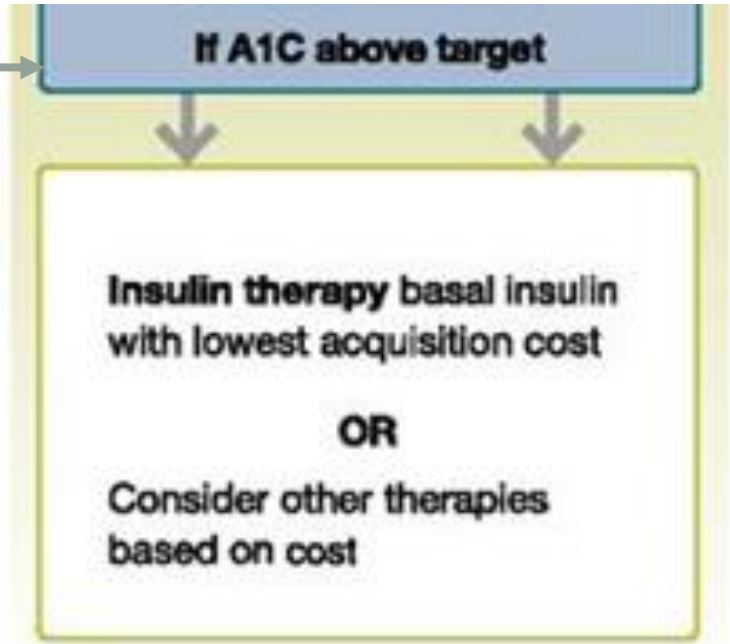
- Option to increase to 1.5mg weekly
- Continue metformin indefinitely

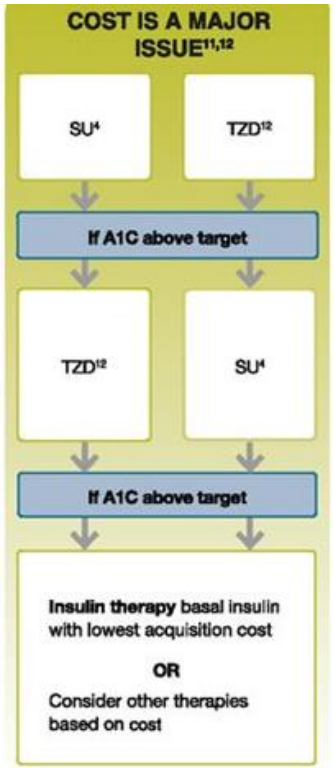
If newer agents not affordable what options do we have?

If cost is an issue

- Sulfonylurea; TZD; basal insulin with lowest cost
- Without specific comorbidities
- Country and region-specific choice- TZD, DPP4i

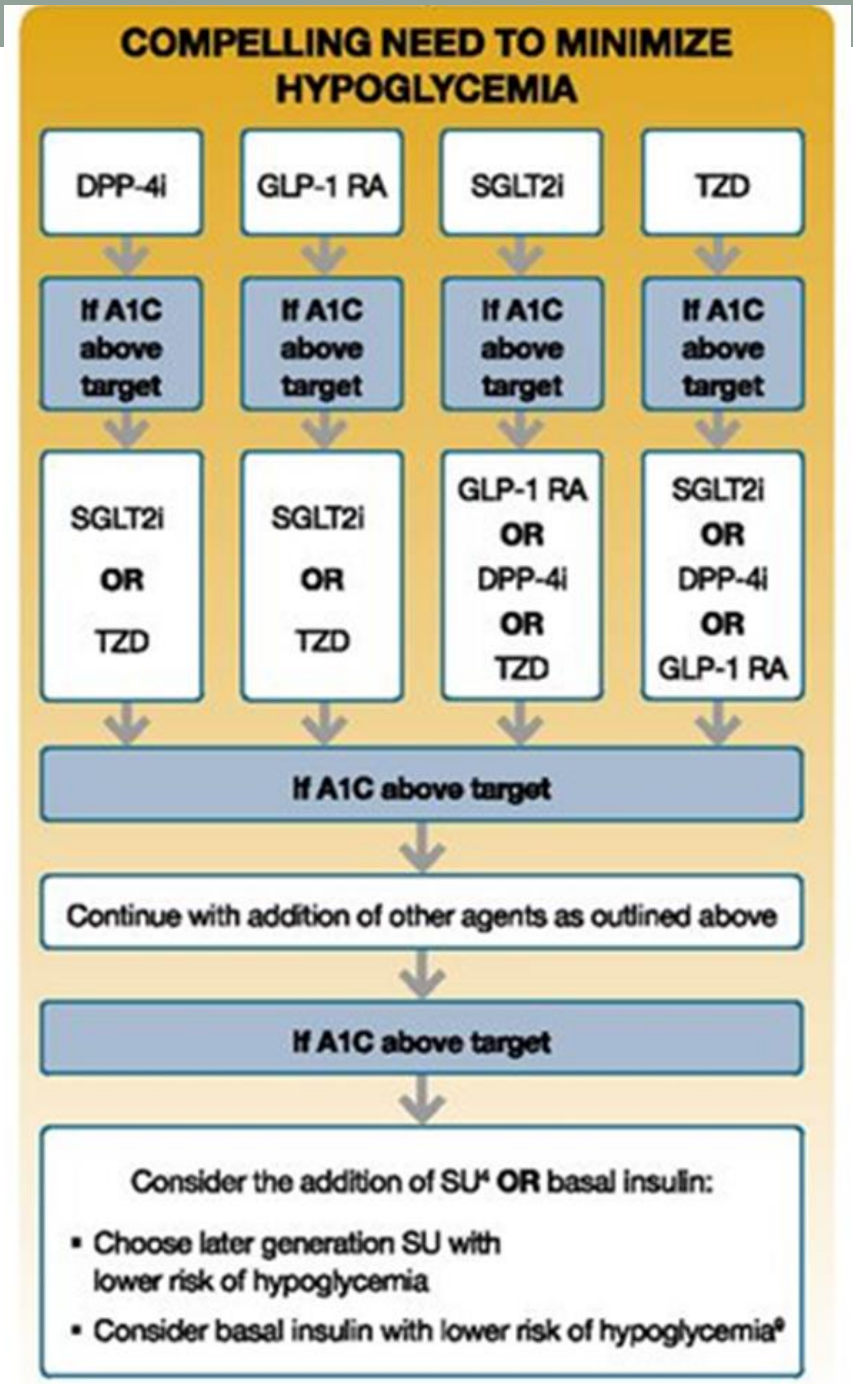






Need to reduce hypoglycemia

- Don’t use a sulfonylurea



Case 2

- 67 year old male with Type 2 diabetes for 8 years establishes care
- Diabetes regimen: metformin 1000mg twice daily, glipizide 10mg twice daily
- HTN, CAD, 2 stents placed 3 years ago; EF is 40%
- Other meds: aspirin, beta blocker, ACEI, statin
- BP 132/76 mmHg, BMI 33 kg/m^2; eGFR 57 $ml/m^2/min$
- A1C 8.1%
- UACR 210 mg/g (<30)

What is the next best medication?

Case 2

- 67 year old male with Type 2 diabetes for 8 years establishes care
- Diabetes regimen: metformin 1000mg twice daily, glipizide 10mg twice daily
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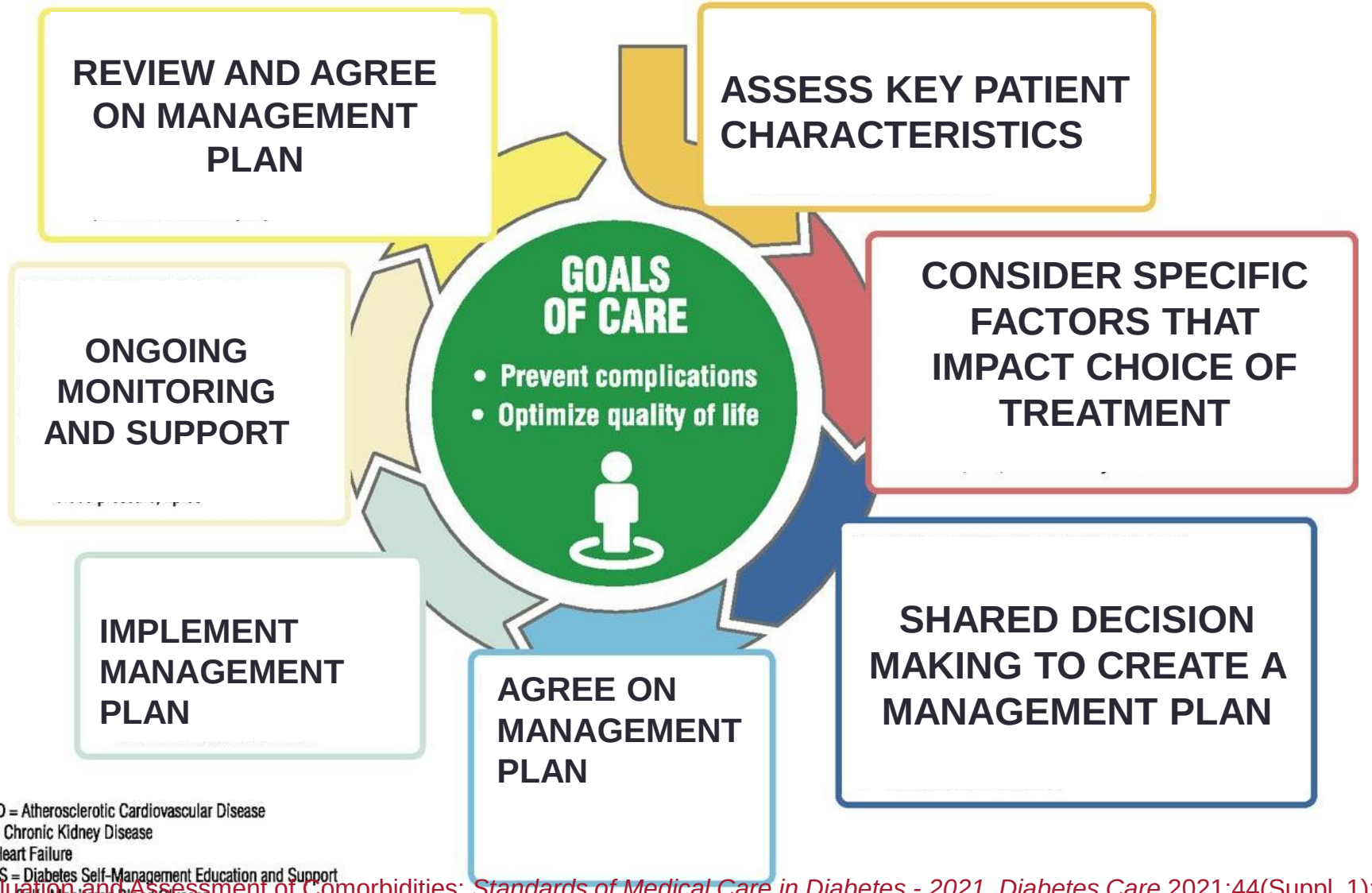
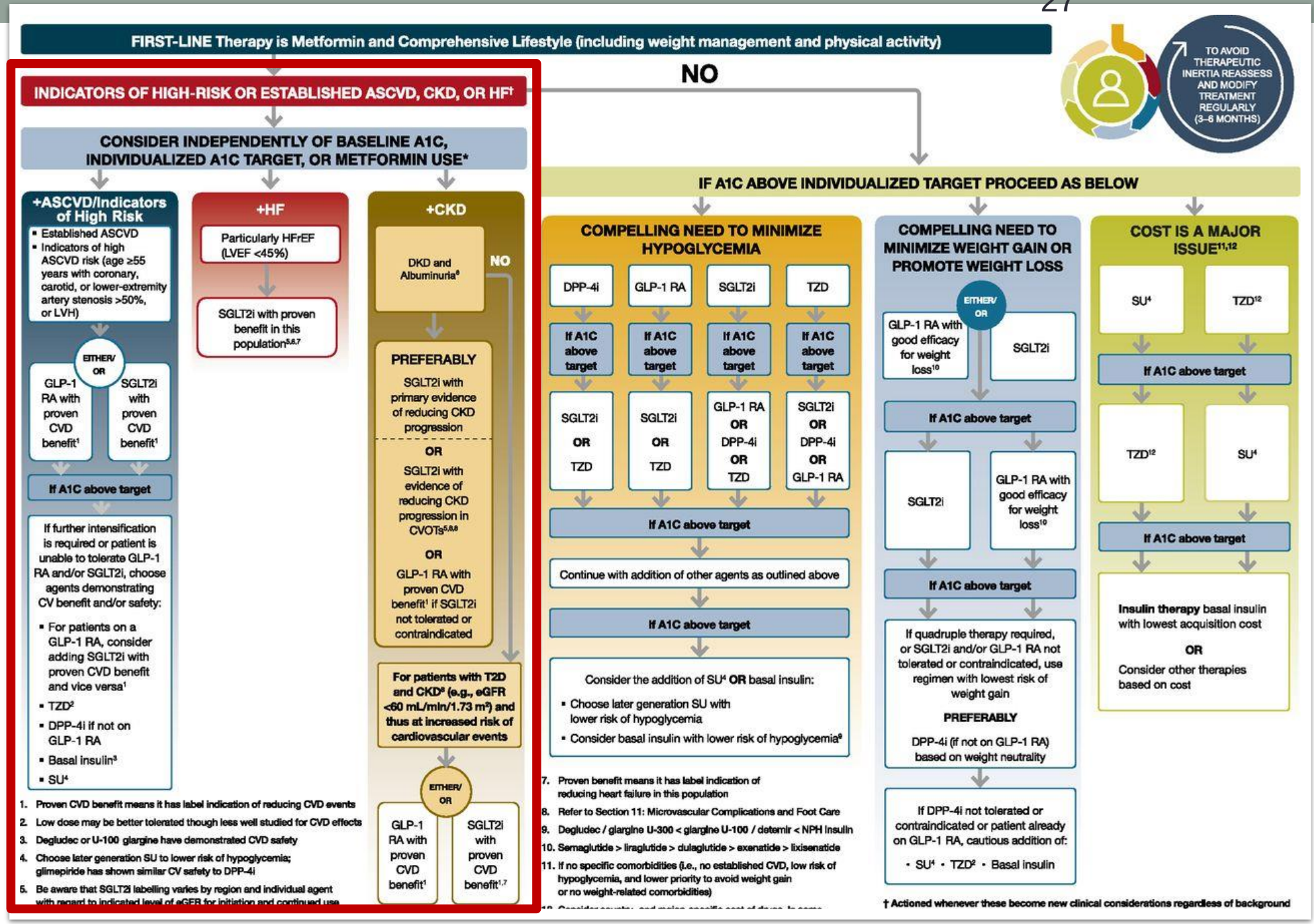
What is the next best medication?

Decision cycle for patient-centered glycemic management in Type 2 diabetes



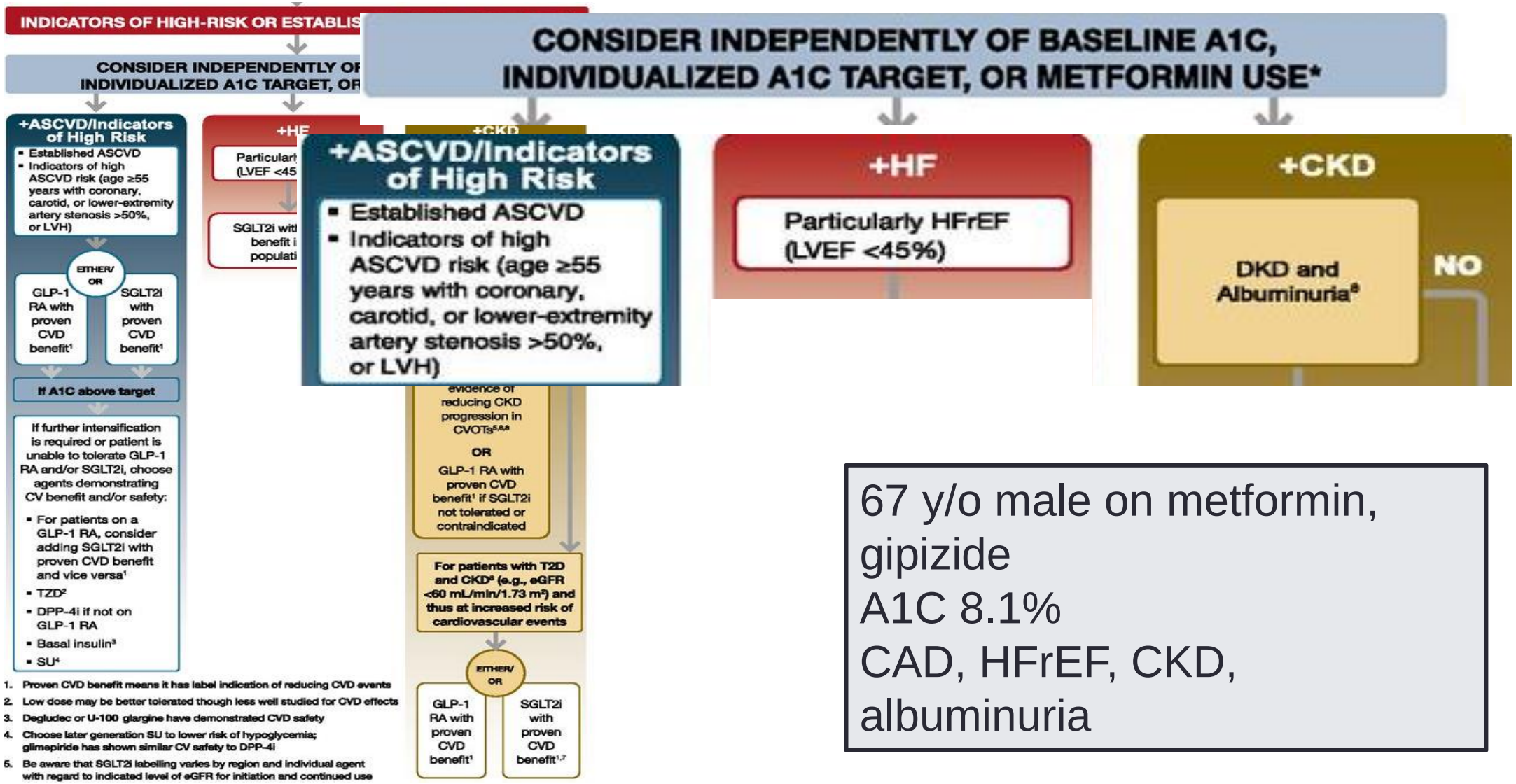
Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1):S40-S52

Medication selection sequence in type 2 diabetes



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1)

Medication selection in the presence of ASCVD, CHF or CKD



67 y/o male on metformin, gipizide
A1C 8.1%
CAD, HFrEF, CKD, albuminuria

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1)

Choosing Based on Cardiac and/or Renal status: Key Concepts

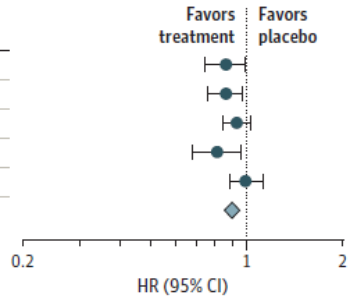
If patients have :

- ASCVD (established ASCVD or indicators of high risk)
  - Add GLP-1 RA with proven benefit
  - Add SGLT2i with proven benefit
- If HF or CKD predominates
  - Add SGLT2i with evidence of reducing HF and/or CKD progression
  - If patient can’t take an SGLT2i, use a GLP1 RA with proven benefit for CVD

SGLT2i improve CV & kidney outcomes in T2D

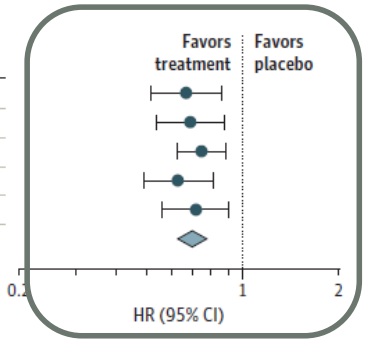
3 point MACE ↓ 10%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)



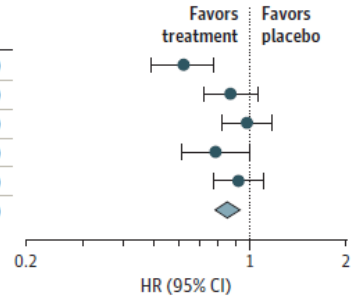
Hosp. heart failure ↓ 32%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)



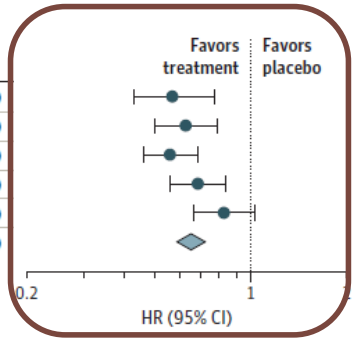
Cardiovascular death ↓ 15%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model (Q = 11.22; *df* = 4; *P* = .02; I^2 = 64.3%)					0.85 (0.78-0.93)



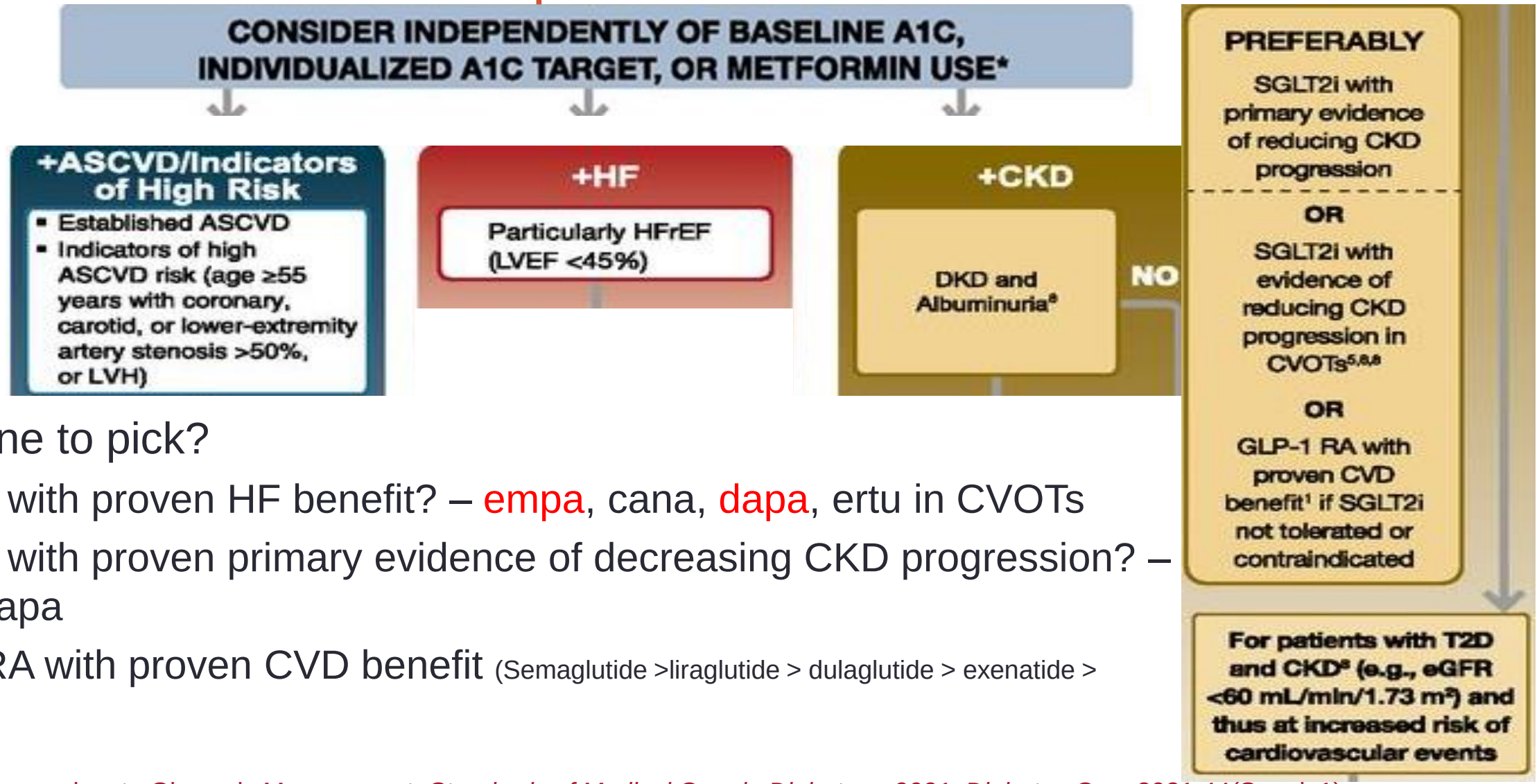
CKD progression ↓ 38%

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)



McGuire DK *et al*, *JAMA Cardiology* 2020

Medication selection in the presence of ASCVD, CHF or CKD



Which one to pick?

- SGLT2i with proven HF benefit? – empa, cana, dapa, ertu in CVOTs
- SGLT2i with proven primary evidence of decreasing CKD progression? – cana, dapa
- GLP-1RA with proven CVD benefit (Semaglutide >liraglutide > dulaglutide > exenatide > lixisenatide)

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021*. *Diabetes Care* 2021;44(Suppl. 1)

Case 2: Management of diabetes, CAD, EF 40% and early CKD

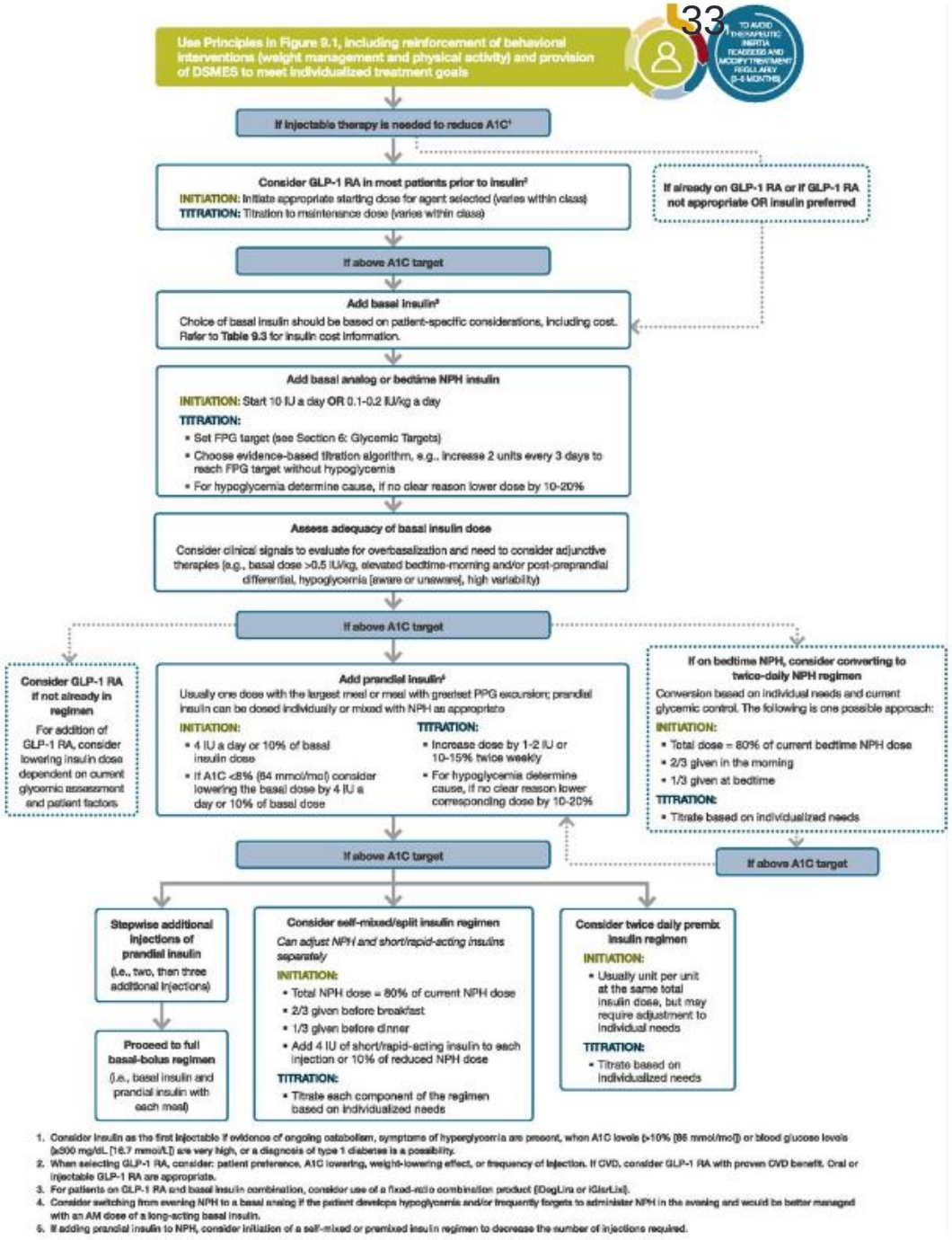
- Early initiation of SGLT2i is beneficial
- eGFR threshold is 30ml/min/1.73m^2; may change with reporting of new trials
- **Low dose** SGLT2i for albuminuric kidney disease
- If not tolerated, can consider GLP-1RA

- Patient started on empagliflozin 10mg
- eGFR dropped to 54ml/min/1.73m^2 and hovered

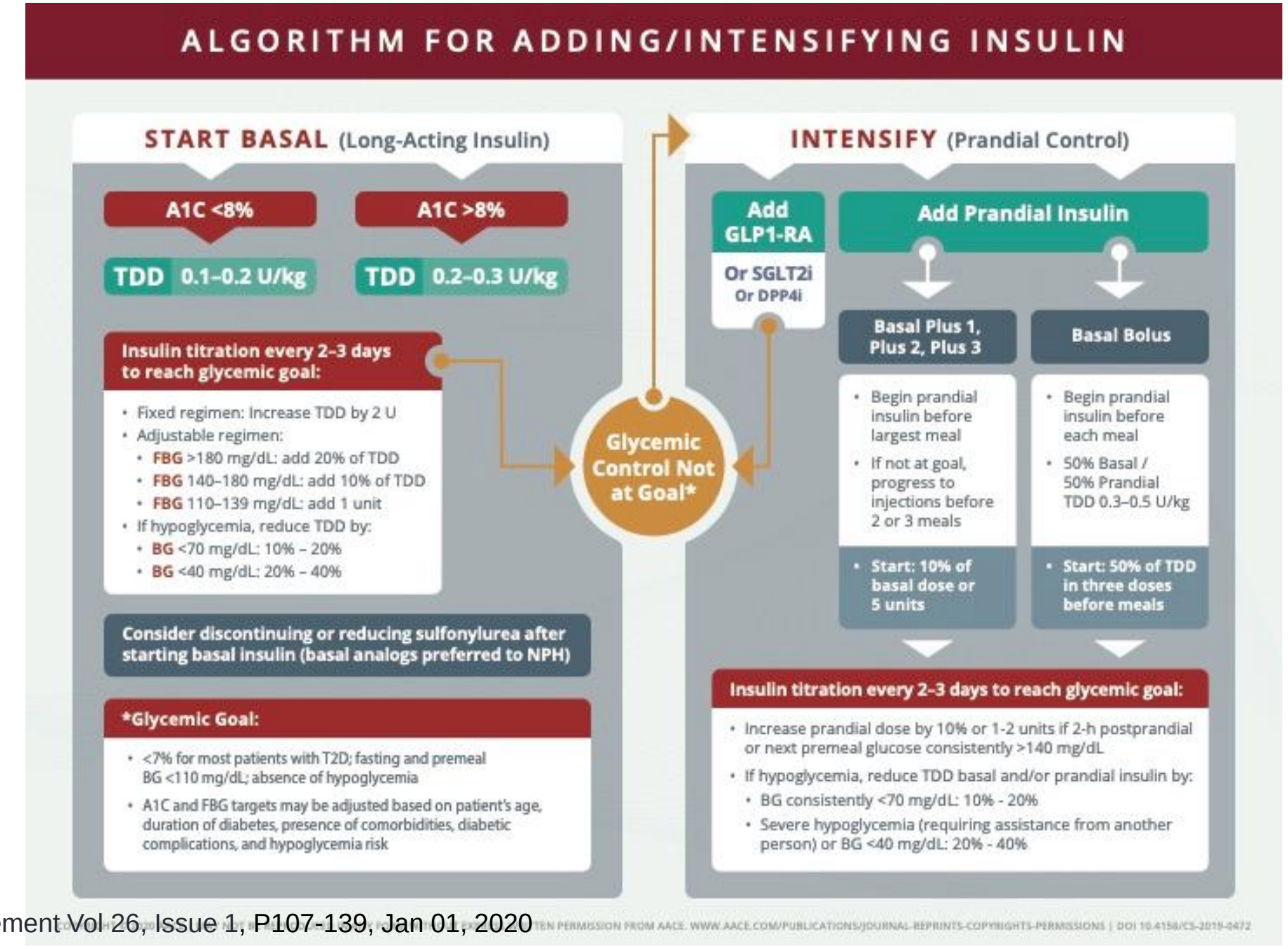
Injectable therapy algorithm

If injectable therapy needed

- Consider GLP1 RA prior to insulin
- If already on GLP1RA, add basal insulin



AACE Diabetes guidelines



Garber AJ et al. AACE Consensus Statement Vol 26, Issue 1, P107-139, Jan 01, 2020

Management of Type 2 diabetes in 2021

EFFICACY
A1C reduction

SAFETY
No hypoglycemia

CARDIOVASCULAR and RENAL
risk reduction

Cardiovascular Disease and Risk Management

Case 1 again – addressing CV risk

- 53 year old male with type 2 diabetes, no complications
- On metformin 1000mg twice daily and dulaglutide 0.75mg weekly
- BMI 32
- BP: 145-150mmHg systolics; diastolic 85-95mmHg
- Non-fasting lipid profile – Total cholesterol 237; Triglycerides 320; HDL-C 25; LDL-C 148 mg/dL

How do you address his CV risk?

Case 1 again – addressing CV risk

- 53 year old male with type 2 diabetes, no complications
- On metformin 1000mg twice daily and dulaglutide 0.75mg weekly
- BMI 32
- BP: 145-150mmHg systolics; diastolic 85-95mmHg
- Non-fasting lipid profile – Total cholesterol 237; Triglycerides 320; HDL-C 25; LDL-C 148 mg/dL

How do you address his CV risk?

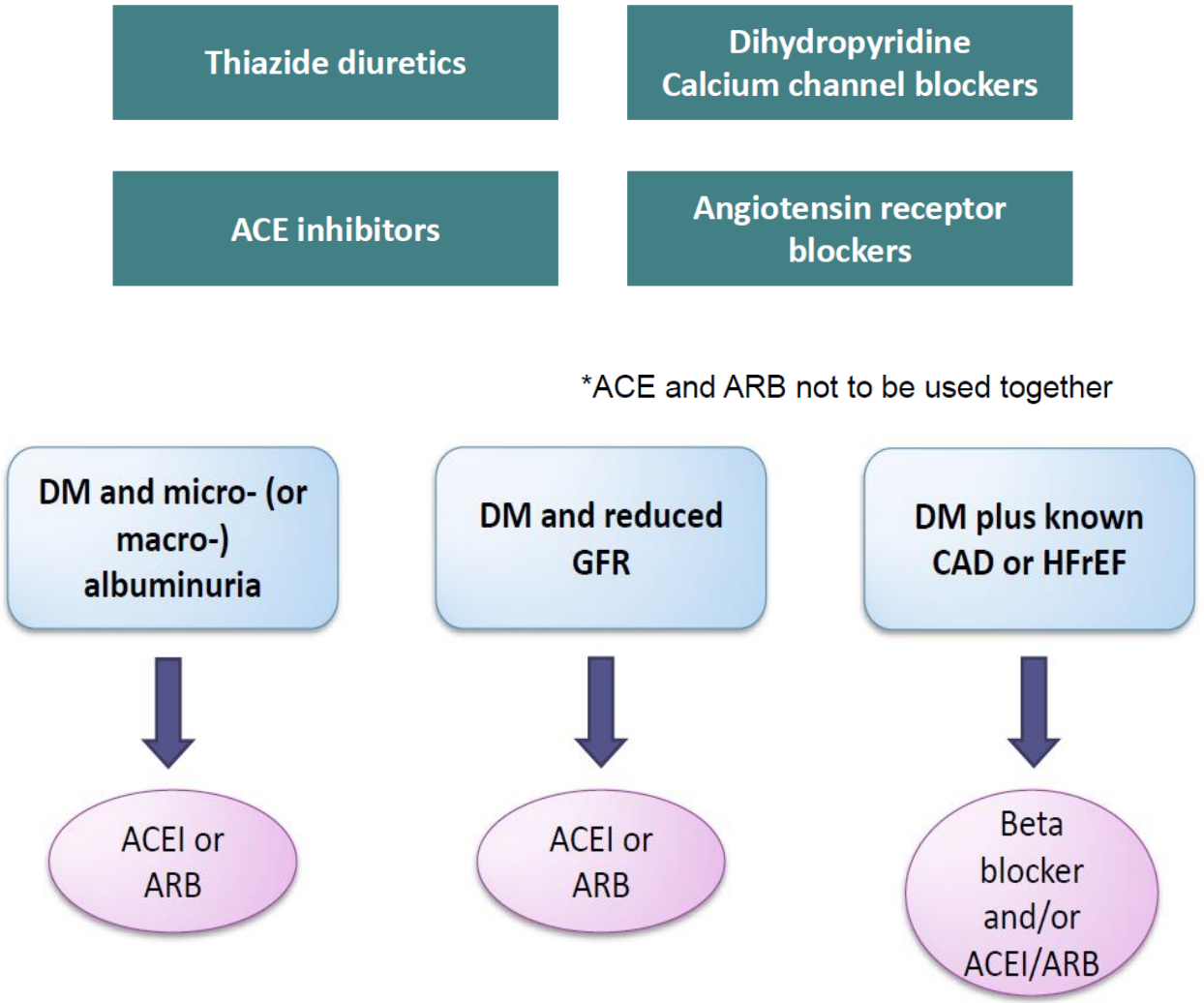
Hypertension: Screening and Diagnosis

- Blood pressure - measured at every routine clinical visit.
  - Patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension.

- All hypertensive patients with diabetes should monitor their blood pressure at home.

Treatment of hypertension in diabetes

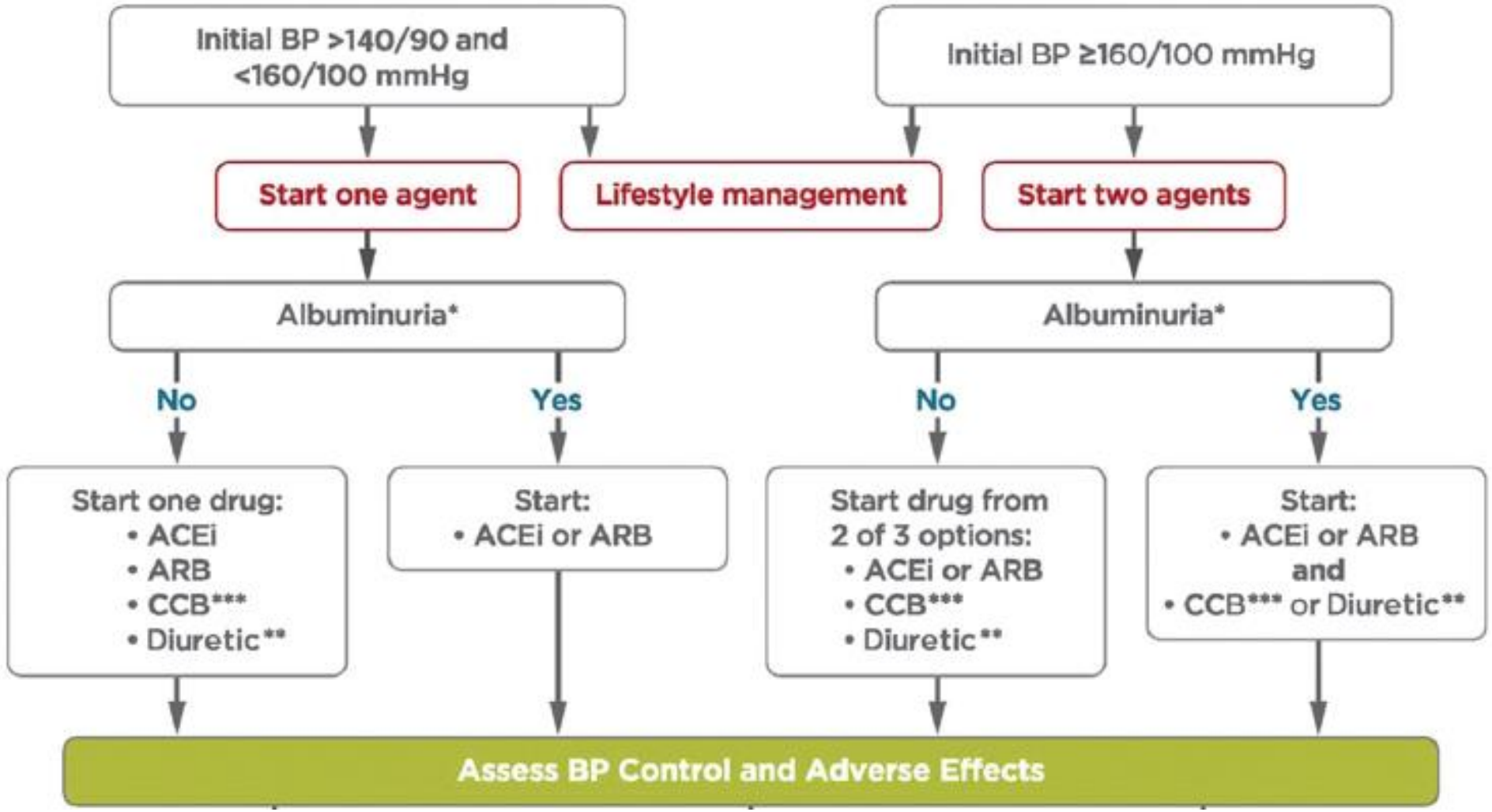
- Lifestyle management –
  - weight loss
  - physical activity 30-45min/d
  - ↓ Na intake (DASH diet)
- First line medications
  - ACEi, ARB, CCB, Thiazides
  - Thiazides should not be withheld
    - Impaired pancreatic insulin release in in observational studies
    - No adverse clinical outcomes data
- Compelling indications



Case 1 again – addressing hypertension

- 53 year old male with type 2 diabetes, no complications
- BMI 32
- BP: 145-150mmHg systolics; diastolic 85-95mmHg
- Started on single agent- lisinopril 10 mg, titrated to 20mg daily

Hypertension in diabetes: treatment



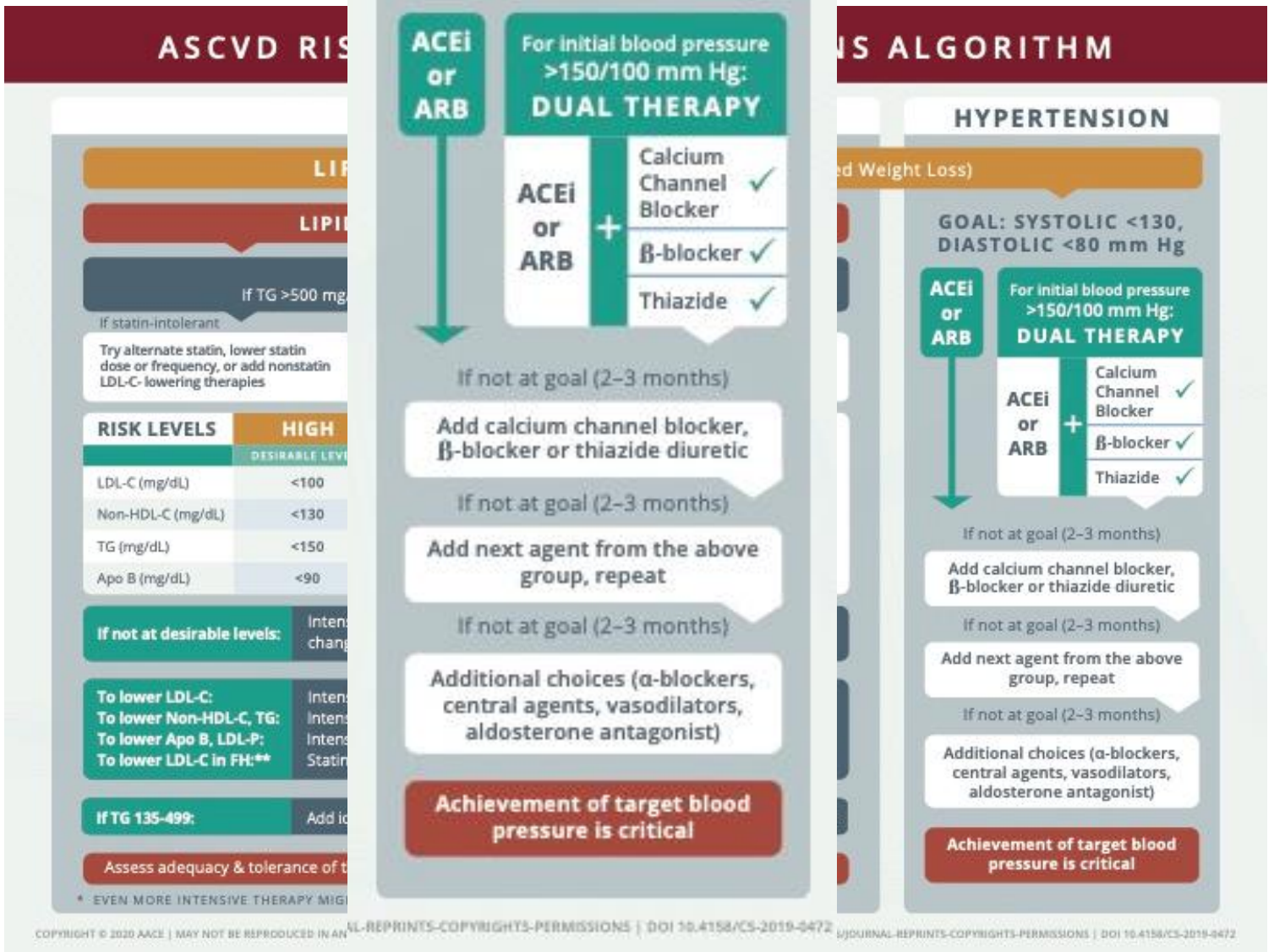
Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes - 2021*.

Resistant hypertension in diabetes: treatment

- If BP targets are not met, add medications in sequence
- If not controlled on ≥3 medications (incl diuretic) or controlled HTN on ≥4 medications- evaluate for secondary HTN
  - Renal artery stenosis
  - Primary hyperaldosteronism
- Use a mineralocorticoid receptor antagonist and refer to specialist

Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes - 2021*.

AACE Diabetes/ASCVD ification algorithm 2020



Case 1 again – addressing CV risk, lipids

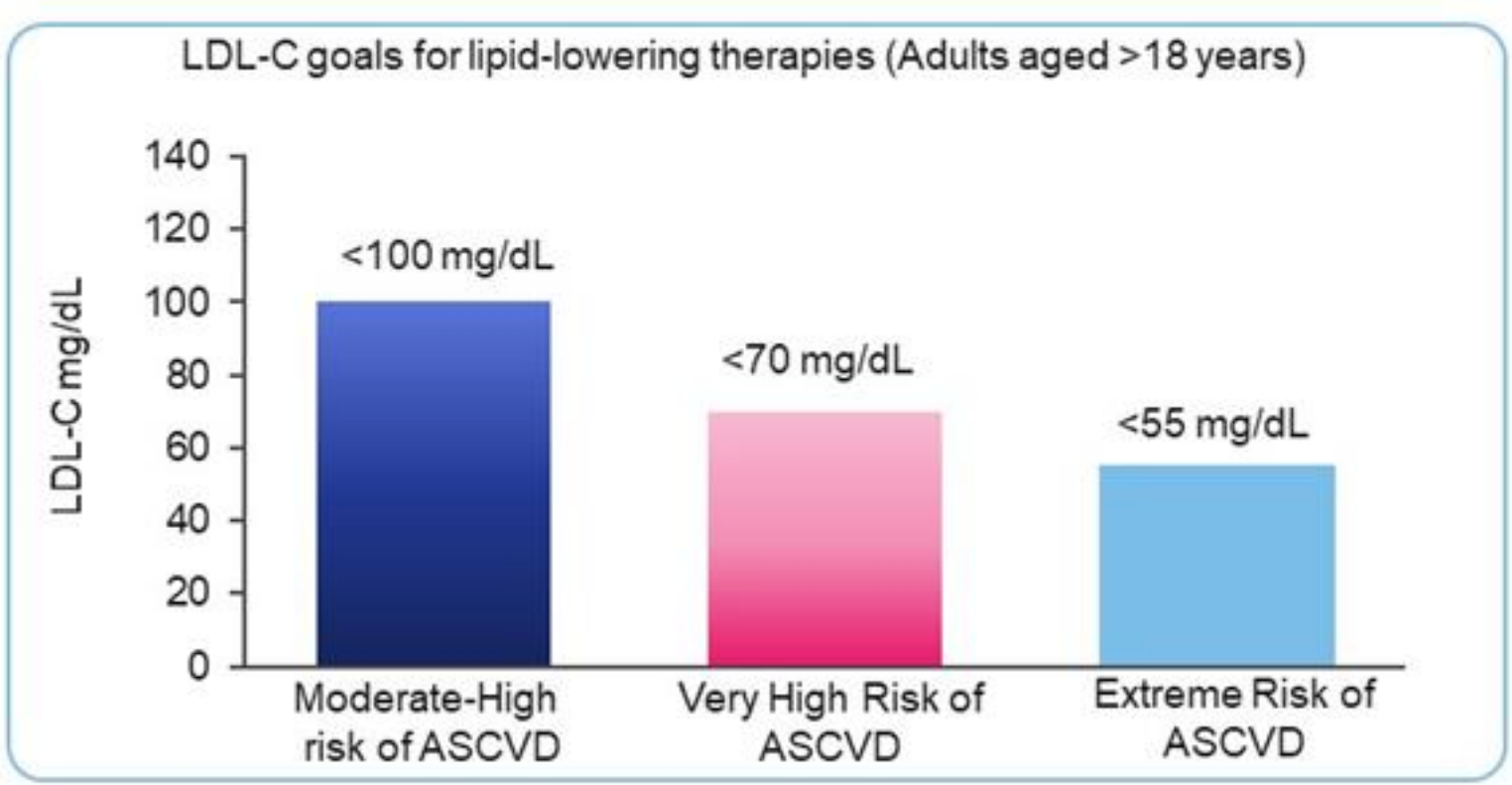
- 53 year old male with 5 years of type 2 diabetes, HTN, no complications
- On metformin 1000mg twice daily, dulaglutide 0.75mg weekly, lisinopril 20mg
- BMI 32
- Non-fasting lipid profile – Total cholesterol 237; Triglycerides 320; HDL-C 25; LDL-C 148 mg/dL

Lipid management in diabetes

- Drug of choice for CV risk reduction and LDL-C lowering are the statins
- Overall benefits of statin therapy across all risk levels and subgroups
- Two dose intensities- moderate and high
- CV risk enhancers- retinopathy, albuminuria, CKD
- Drugs besides statins for CV risk reduction-
  - Ezetimibe
  - PCSK9 inhibitors
  - Icosapent ethyl
- Triglycerides ≥ 500mg/dL increase pancreatitis risk
  - R/o secondary causes
  - Medical therapy to prevent pancreatitis

	High-Intensity	Moderate-Intensity
LDL-C Lowering†	≥50%	30% to 49%
Statins	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§
	–	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg

ASCVD risk categories and goals in diabetes



Lipid Management in Diabetes

Primary Prevention – without ASCVD
Age 40-75: Moderate intensity statin therapy
Patients at high risk: Multiple risk factors or age 50-75 it is reasonable to use high intensity statin therapy
Age > 75: Moderate intensity statin therapy is reasonable after discussion
Patients with 10-year risk > 20%: reasonable to add ezetimibe to maximally tolerated statin to reduce LDL by > 50%
Age <40 or Type 1 diabetes: With additional risk factors may be reasonable to initiate moderate intensity statin therapy

Secondary Prevention – known ASCVD
All ages < 75: High intensity statin therapy/maximally tolerated statin
Age >75: Reasonable to continue statin therapy or initiate statin therapy after discussion.
Very High Risk: If LDL > 70mg/dl on maximally tolerated statin consider adding ezetimibe or PCSK9 inhibitor

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- Primary ASCVD prevention
- Moderate intensity statin

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