WHAT TO DO AFTER METFORMIN? A REVIEW OF PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT IN TYPE 2 DIABETES

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DISCLOSURES

- Speakers bureaus: Novo Nordisk
- Advisory boards: Novo Nordisk, Xeris Pharmaceuticals

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AT THE CONCLUSION OF THIS SESSION, PARTICIPANTS SHOULD BE ABLE TO:

- Discuss the current glycemic target guidelines from the American Diabetes Association Standards of Medical Care
- Promote a patient-centered and shared-decision making approach to develop an individualized patient treatment plan
- Review 2020 ADA Standards of Care Pharmacologic Approach to treatment
- Discuss patient specific characteristics to drive treatment decisions after metformin

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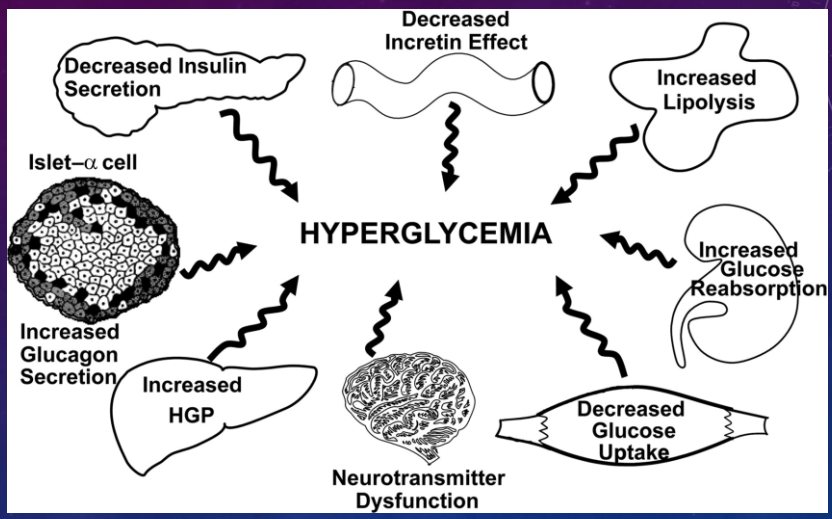
HOW I HAVE FELT SOME DAYS???

- How about you?
- How about your patient who lives this disease 24/7?
- Let's try to simplify together!!

4

The Ominous Octet.



Ralph A. DeFronzo Diabetes 2009;58:773-795

American Diabetes Association.

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Glycemic Recommendations for Many Non-Pregnant Adults with Diabetes

A1C	<7.0%* # (53 mmol/mol)
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients.
CGM may be used to assess glycemic target
† Postprandial glucose may be targeted if A1C goal is not met despite reaching preprandial glucose goals. Should be made 1–2 hours after the beginning of the meal, generally peak levels in patients with diabetes.

American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes 2021. Diabetes Care 2021;44(Suppl. 1):S73–S84

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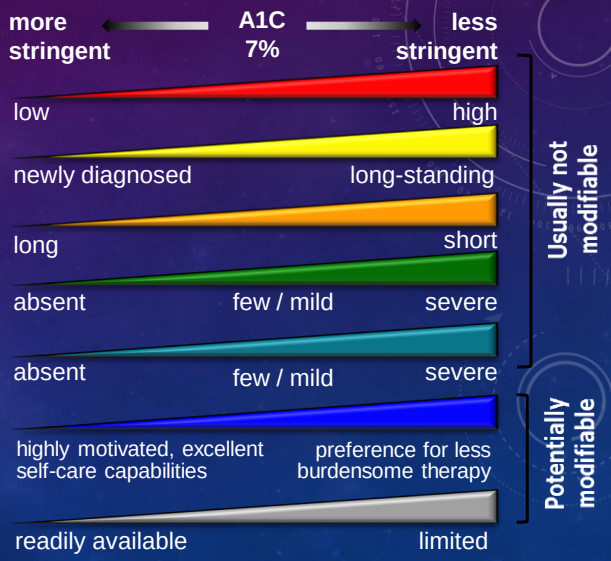
APPROACH TO INDIVIDUALIZATION OF GLYCEMIC TARGETS

Patient/Disease Features

- Risks potentially associated with hypoglycemia & other drug adverse effects
- Disease Duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient preference
- Resources & support system



American Diabetes Association. Diabetes Care 2021;44(Suppl. 1):S73–S84

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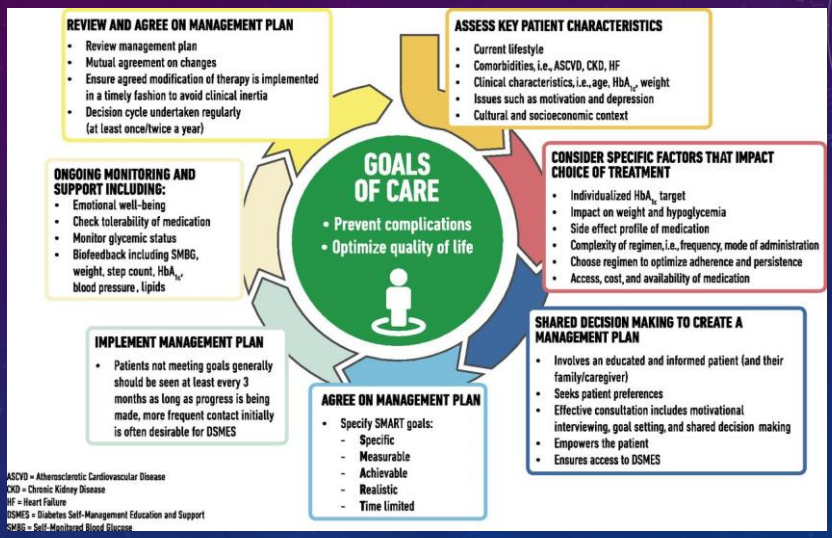
Decision Cycle for Patient-Centered Glycemic Management in Type 2 Diabetes



American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities Diabetes Care: Standards of Medical Care in Diabetes 2021;44(Suppl. 1):S40–S52

THERAPEUTIC INERTIA

Intensification of treatment for patients not meeting treatment goals should not be delayed

Medication regimen and medication-taking behavior should be reevaluated every 3 to 6 months and adjusted as needed to incorporate specific factors that impact treatment choice

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

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DIABETES IS PROGRESSIVE

- Monotherapy is often only possible for a few years
- Combination therapy will be required
- Duration of disease and decline in beta cell function will require the need for insulin in patients
- Important for health care professional to be comfortable with the use of agents in combination to achieve glycemic target

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Table 9.1 - Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m²	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk (all agents, rare in T2D) • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	• Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m² • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	• **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin — Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin — Analogs						High	SQ			

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

METFORMIN

- Efficacy- High
- Hypoglycemia- No
- Weight Change- Neutral (potential modest loss)
- CV effects- ASCVD- Potential benefit/ Heart Failure- Neutral
- Cost- Low
- Renal effects
  - Progression of DKD- Neutral
  - Dosing/use considerations- Contraindicated with eGFR < 30 mL/min/1.73 $m^{2;}$
  - GFR > 45 may use maximum tolerated dose
  - GFR <45 decrease dose in half to 500 mg twice daily
- Additional considerations- Gastrointestinal side effects common (diarrhea, nausea), Potential for B12 deficiency
- Primary target: decrease hepatic glucose release by the liver, insulin sensitivity at the muscle

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

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SGLT2 INHIBITORS

- Efficacy- Intermediate
- Hypoglycemia- No
- Weight Change- Loss
- CV effects- ASCVD- empagliflozin, canagliflozin/ Heart failure- empagliflozin, canagliflozin, dapagliflozin
- Cost- High
- Renal effects
  - Progression DKD- Benefit- canagliflozin, empagliflozin, dapagliflozin
  - Dosing/use considerations- Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)

- Additional considerations- DKA risk (rare in T2DM), bone fractures (canagliflozin), GU infections, volume depletion, hypotension, Increase LDL, Fournier's gangrene
- Temporarily discontinue all SGLT2 inhibitors prior to surgery to avoid risk of diabetic ketoacidosis
- Primary target: decrease glucose reabsorption at the kidney

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GLP-1 RECEPTOR AGONIST

- Efficacy- High
- Hypoglycemia- No
- Weight Change- Loss
- CV effects-
  - ASCVD: Benefit: dulaglutide, liraglutide, semaglutide; Neutral: exenatide once weekly, lixisenatide
  - Heart Failure: Neutral
  - Progression of DKD- benefit seen in trials with secondary endpoint- liraglutide, semaglutide, dulaglutide
  - Dosing/use considerations- Exenatide, lixisenatide avoid for GFR <30; No dose adjustment dulaglutide, liraglutide, semaglutide
- Additional considerations- FDA Black Box: Risk of thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide extended release), GI side effects, injection site reactions, discontinue if pancreatitis is suspected
- Recent first oral formulation: oral semaglutide
- Primary target: stimulates insulin release in glucose dependent manner, decrease glucagon at pancreas, decrease hepatic glucose production, increases incretin effect, helps with satiety at the brain, improves insulin sensitivity at muscle (due to weight loss)

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DPP-4 INHIBITORS

- Efficacy- Intermediate
- Hypoglycemia- No
- Weight Change- Neutral
- CV effects-
  - ASCVD- Neutral
  - Heart Failure- Potential risk: saxagliptin
- Cost- High
- Renal effects
  - Progression of DKD- Neutral
  - Dosing/use considerations- Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin) can be used in renal impairment. No dose adjustment for linagliptin
- Additional considerations- Discontinue if pancreatitis suspected, joint pain
- Primary target: release insulin in glucose dependent manner, suppress hepatic glucose production

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THIAZOLIDINEDIONES (TZD)

- Efficacy- High
- Hypoglycemia- No
- Weight Change- Gain
- CV effects-
  - ASCVD- Potential benefit: pioglitazone
  - Heart Failure- Increased risk
- Cost- Low
- Renal effects-
  - Progression of DKD- Neutral
  - Dosing/use considerations- No dose adjustment required. Generally not recommended in renal impairment due to potential for fluid retention
- Additional considerations- FDA Black Box: Congestive heart failure, fluid retention, benefit in NASH, Risk of bone fractures, Bladder cancer (pioglitazone), Increase LDL cholesterol (rosiglitazone)
- Primary target: insulin sensitizer. Target insulin resistance at the muscle

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SULFONYLUREAS (2ND GENERATION)

- Efficacy- High
- Hypoglycemia- Yes
- Weight Change- Gain
- CV effects-
  - ASCVD- Neutral
  - Heart Failure- Neutral
- Cost- Low
- Renal effects-
  - Progression of DKD- Neutral
  - Dosing/use considerations- Glyburide: not recommended, Glipizide and glimepiride: Initiate conservatively to avoid hypoglycemia
- Additional considerations- FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
- Primary target: release insulin from pancreas in a non glucose dependent manner

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INSULIN (HUMAN/ANALOGS)

- Efficacy- Human Insulin: Highest/ Analogs: Highest
- Hypoglycemia- Human Insulin: Yes/ Analogs: Yes
- Weight Change- Human Insulin: Weight gain/ Analogs: Gain
- CV effects-
  - ASCVD- Both neutral
  - Heart Failure- Both Neutral
- Cost- Human Insulin: Low/ Analogs: High
- Renal effects-
  - Progression of DKD- Both Neutral
  - Dosing/Use Considerations- Both Lower insulin doses required with a decrease in eGFR; titrate per clinical response
- Additional considerations- Injection site reactions, Higher risk of hypoglycemia with human insuin NPH (NPH or premixed formulations) vs. analogs

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METFORMIN

- Preferred Initial Pharmacologic agent
- Once initiated, it should be continued as long as it is tolerated and not contraindicated
- If A1C not to goal, other agents should be ADDED to Metformin

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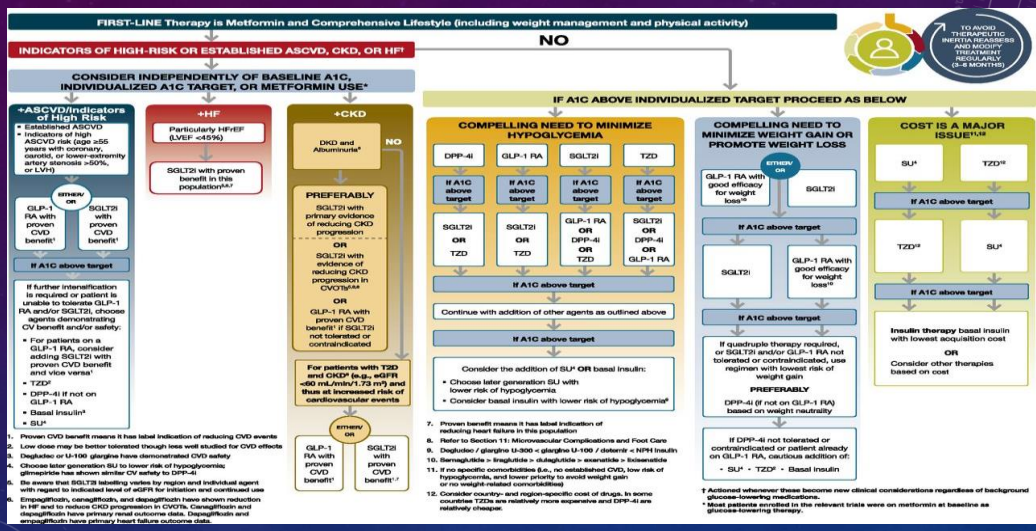
Glucose-lowering medication in type 2 diabetes



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DOES YOUR PATIENT HAVE ANY OF THE FOLLOWING?

- Established ASCVD or heart failure (HF) or indicators of high ASCVD (≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
- LVEF <45%
- DKD and Albuminuria

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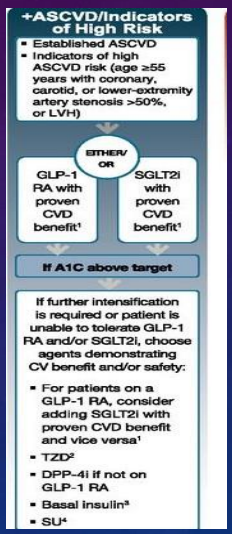
IF ASCVD PREDOMINATES:

- GLP-1 RA with proven cardiovascular benefit
  - Liraglutide
  - Semaglutide
  - Dulaglutide
- SGLT2 inhibitor with proven cardiovascular benefit
  - Empagliflozin
  - Canagliflozin
  - Dapagliflozin



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PATIENT SARAH

53 year old patient
Type 2 diabetes x 5 years
History of 2 cardiac stents
Fasting glucose range 120 to 140 mg/dl.
Hemoglobin A1C increased from 6.5% to 7.1%
Desire to lose weight
Commercial Insurance

Current diabetes medications:
Metformin 1000 mg twice daily

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PATIENT SARAH

Vitals:

Blood Pressure 128/82

Pulse 68 regular

BMI 32

Labs:

- A1C- 7.1%
- Cholesterol- 178
- Triglycerides- 227
- HDL 42
- LDL 78
- GFR- >60
- Urine microalbumin- 14

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WHAT SECOND LINE MEDICATION WOULD YOU CHOOSE FOR SARAH?

A. DPP IV Inhibitor
B. Basal insulin
C. GLP1 RA
D. TZD

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WHAT SECOND LINE MEDICATION WOULD YOU CHOOSE FOR SARAH?

The correct answer is: **C. GLP1 RA**

Patient has established ASCVD and is not to A1C less than 7%

Second line treatment is GLP1 RA or SGLT2 inhibitor with proven ASCVD benefit

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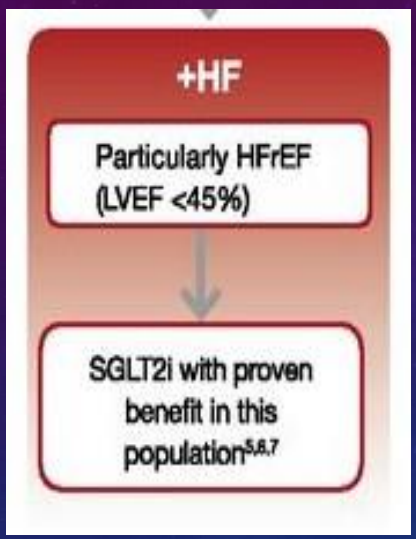

IF HEART FAILURE PREDOMINATES:

- Empagliflozin
- Canagliflozin
- Dapagliflozin

Benefit seen in CVOTs

*Dapagliflozin and empagliflozin have primary heart failure outcome data

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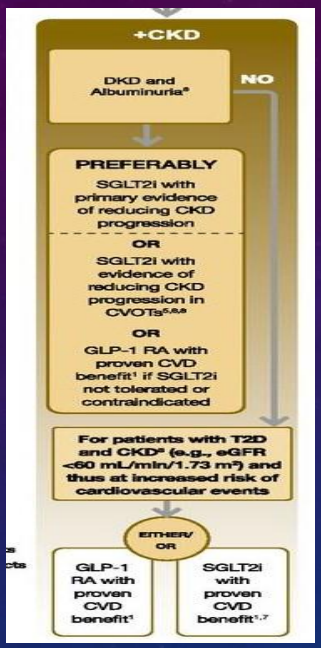

IF CHRONIC KIDNEY DISEASE PREDOMINATES:

- Empagliflozin
- Canagliflozin
- Dapagliflozin

Benefit seen in CVOTs

*Canagliflozin and Dapagliflozin have primary renal outcome data

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PATIENT JOE

68 year old patient

Type 2 diabetes x 12 years. His recent blood glucose logs reveal fasting glucose numbers between Fasting glucose 150 and 170 mg/dl and bedtime readings between 180 and 190 mg/dl.

Recent hospitalization for heart failure

Past history of 3 vessel CABG

Has commercial prescription coverage through his spouse

Medications:

Metformin 500 mg twice daily

Dulaglutide 1.5 mg sq daily

Glimepiride 4 mg twice daily

Other medications per standards of care

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PATIENT JOE

Vitals:

Blood Pressure 136/88

Pulse 72 regular

BMI 36

Labs:

- A1C- 8.2%
- Cholesterol- 133
- Triglycerides- 227
- HDL 32
- LDL 55
- GFR- 42
- Urine microalbumin- 332

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WHAT IS THE BEST MEDICATION CHANGE OR ADDITION FOR JOE?

A. DPP IV inhibitor
B. Increase Metformin to 1000 mg twice daily
C. TZD
D. SGLT2 inhibitor

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WHAT IS THE BEST MEDICATION CHANGE OR ADDITION FOR JOE?

The correct answer is **D. SGLT2 inhibitor**

- The patient has a recent history of hospitalization of heart failure and has DKD.
- SGLT2 inhibitor is recommended in both of these patients.
- He is already on a GLP1 RA for his established ASCVD.
- Caution increasing metformin to 1000 mg twice daily due to GFR 42
- TZD would worsen heart failure
- DPP IV not beneficial for heart failure or DKD

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WHAT SHOULD YOU DO IF YOUR PATIENT DOES NOT HAVE INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF?

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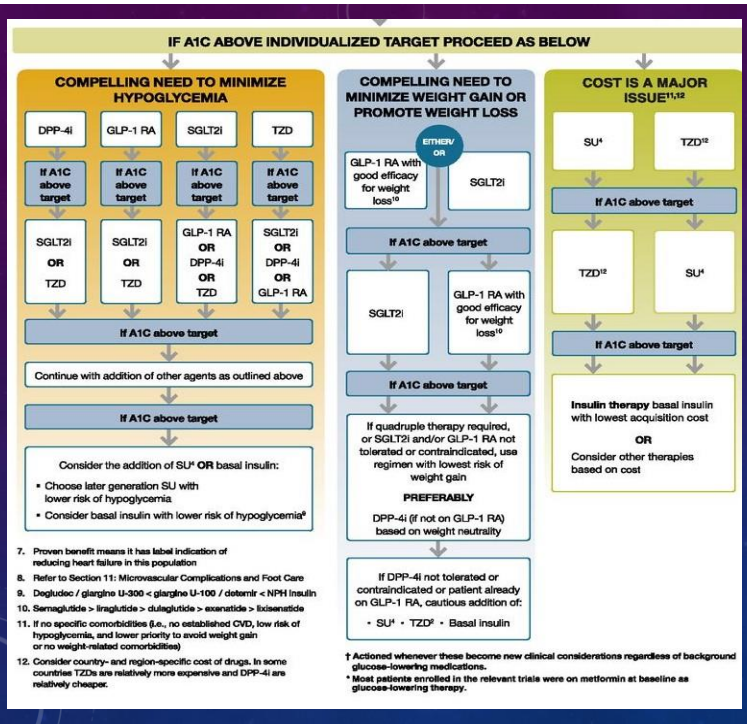

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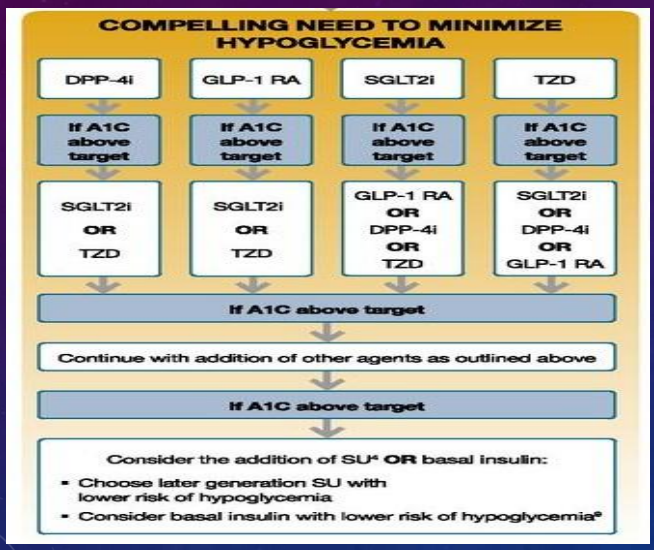

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HYPOGLYCEMIA

Yes

- Sulfonylureas
- Insulin

No

- Metformin
- SGLT-2 inhibitors
  - GLP-1RAs
- DPP-4 inhibitors
  - TZDs

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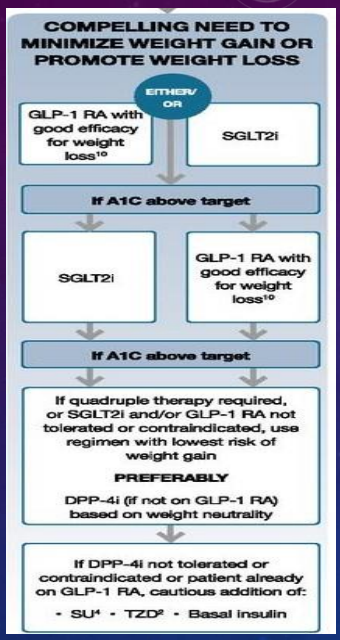

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WEIGHT CHANGE

Loss	Neutral	Gain
	Metformin (potential modest loss)	TZDs
SGLT-2 inhibitors	DPP-4 inhibitors	Sulfonylureas
GLP-1 RAs		Insulin

If choosing a GLP-1 receptor agonist with good efficacy for weight loss:
Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

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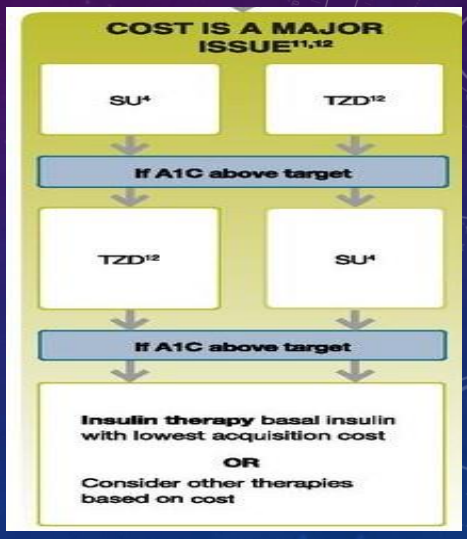
*If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)

*Consider country- and region-specific cot of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper



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COST

Low:

- Metformin
- TZDs
- Sulfonylureas
- Human Insulin (SQ)

High:

- SGLT-2 inhibitors
- GLP-1 RAs
- DPP-4 inhibitors
- Insulin Analogs

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RISING COST OF MEDICATION

- Dramatic increase in cost over the last two decades
- Significant portion of this cost is passed to patients and families
- Major source of stress for patients which leads to worse adherence
- Important to have an open conversation with patients
- Consider patient assistance programs (Increase access for medicare patients, loss of insurance due to COVID), $99 insulin offers for noninsured with certain pharm companies, GoodRx, Prescription Hope

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PATIENT ROBERT

44 year old male

Type 2 diabetes x 3 years

Fasting glucose readings 90 to 125 mg/dl

Refused considering taking injections due to fear of needles

Fearful of low blood glucose because he saw his grandfather have them as a child

No history of ASCVD or CHF.

Since his last visit he has lost his job and insurance

Diabetes Medications:

Metformin 1000 mg twice daily

Sitagliptin 100 mg one daily (ran out and discontinued 4 weeks ago)

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PATIENT ROBERT

Vitals:

Blood Pressure 128/74

Pulse 68 regular

BMI 26

Labs:

- A1C- 7.3%
- Cholesterol- 140
- Triglycerides- 215
- HDL 36
- LDL 62
- GFR- >60
- Urine microalbumin- 0

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WHAT IS THE BEST MEDICATION CHANGE FOR ROBERT ?

A. Sulfonylurea
B. TZD
C. SGLT2 inhibitor
D. NPH insulin

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WHAT IS THE BEST MEDICATION CHANGE FOR ROBERT ?

The correct answer is **B. TZD**

Patient is fearful of needles and hypoglycemia

Cost is an issue due to loss of insurance

Sulfonylurea and NPH insulin both increase hypoglycemia

SGLT2 inhibitor too expensive with loss of insurance

TZDs do not cause hypoglycemia and patient has no history of heart failure

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SUMMARY

- Establish individualized glycemic targets for all patients
- Shared-decision making should be utilized when establishing a treatment plan
- Pharmacologic decision-making should be patient-centered and established based off of patient's comorbid conditions

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RESOURCES:

- professional.diabetes.org
- American Diabetes Association. Standards of Medical Care in Diabetes 2021. Diabetes Care 2021;44(Suppl. 1)

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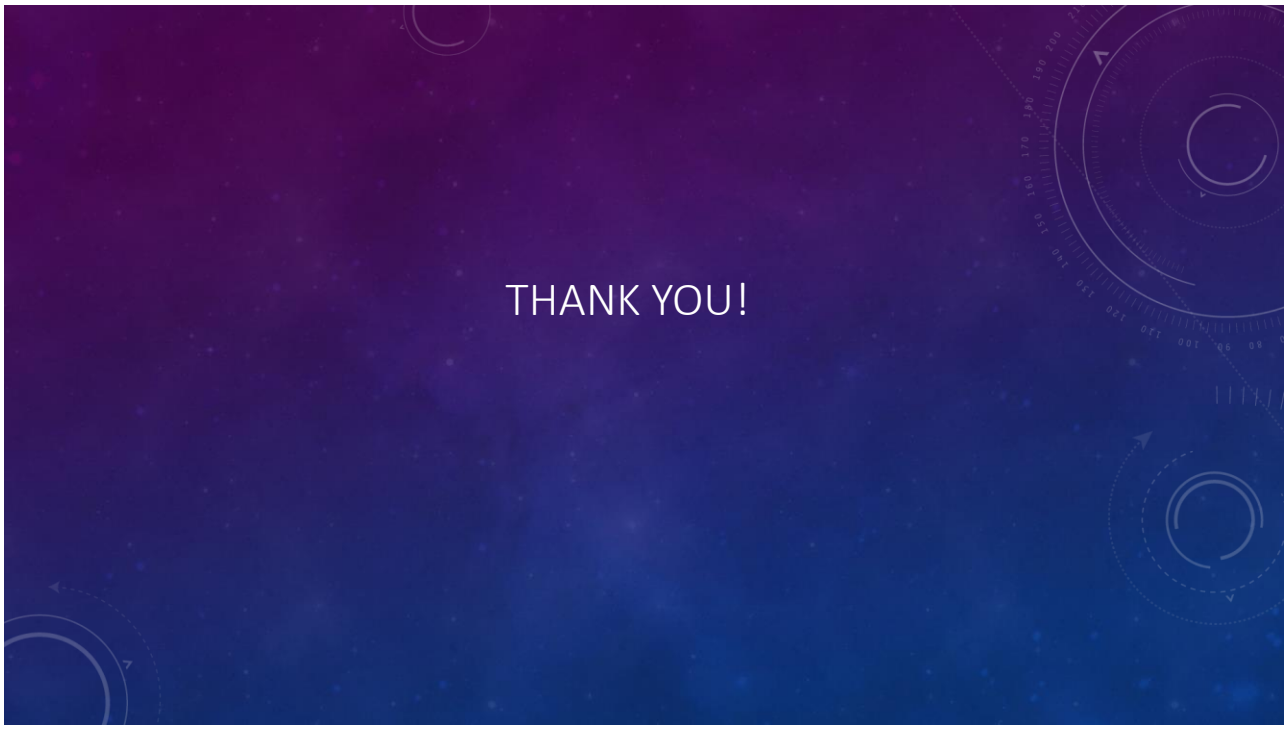

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