Seed
GLOBAL HEALTH

DIABETES MEDICATIONS

Registrar Education Series

Updated 10/2022

ADA
AACE
USPSTF
Choosing Wisely

For each medication class determine:

- Effect on A1c
- How to explain how it works to a patient
- Risk of hypoglycemia
- Common adverse effects
- Good POEMs/DOEs
- Bad POEMs/DOEs
- Pearls

METFORMIN (BIGUANIDE)



Mechanism: sensitizes
this means that 15u of insulin may have the same effect as 20u of insulin in someone who is not taking it

Hypoglycemia: none
people who do not have DM take 750mg bid for other conditions

Good:
decreases all cause mortality
decreases cardiovascular mortality
cheap - NHIMA
pill form
has extended-release form

A1C ↓: 1 - 2.5%

Weight: loss

Bad:
GI side effects if not titrated
BID dosing

Other:
CKD does not increase lactic acidosis
avoid GI side effects by titrating (i.e. 500mg x3 days then 500mg bid x3 days then 1g bid)
if it is not tolerated switch to ER version, 500mg x4 (can all be taken at the same time)

SULFONYLUREAS (GL----IDE)

Mechanism: secretagogue
squeezes insulin out of the pancreas

A1C ↓: 1 to 3%

Hypoglycemia: high risk
decrease in sugar and response is unpredictable

Weight: gain

Good:
decreases sugar
cheap - NHIMA
pill form

Bad:
hypoglycemia
Increases cardiovascular mortality
Not a smart medication

Other:
at 50% the max dose you will get 90% the efficacy
It is said that efficacy wanes after 3 years of use
both ADA and AACE discourage use due to the predictably unpredictable hypoglycemic effects
Glimepiride is the safest of its class

SGLT2 INHIBITOR(----FLOZIN)

Mechanism: excretes sugar through kidney
If the sugar raises to high these channels will remain in place excreting sugar until the threshold is met

Hypoglycemia: none
Only works when sugars are high

Good:
CV and CHF mortality benefit
Renal protective
Pill form
Can decrease blood pressure

Other:
Has caused normoglycemic DKA
Can be used in Type1 DM but is off label use

A1C ↓: 0.5-1.0%

Weight: loss

Bad:
Expensive
Can increase risk of UTI and yeast infections
Can decrease blood pressure

DPP4 INHIBITOR(----GLIPTIN)

Mechanism: InCretIn effect
When there is food in the gut it causes **IN**testinal se**CRET**ion of **IN**sulin, also decreases glucose production by the liver and slows gastric emptying

A1C ↓: 0.5-1.0%

Hypoglycemia: none
Only works when there is food in the gut

Weight: neutral

Good:
Pill form
Once daily
Can be used with renal failure

Bad:
Expensive
Caution with pancreatitis

Other:
Never use with a GLP1 since they do the same thing. DPP4 is the enzyme that breaks down GLP1 so this medication indirectly leads to higher GLP1 levels

GLP1(----TIDE)

Mechanism: InCretIn effect
when there is food in the gut it causes **IN**testinal seC**RET**ion of **IN**sulin, also decreases glucose production by the liver and slows gastric emptying

A1C ↓: 0.5-1.5%

Hypoglycemia: none
Is used in people without DM for weight loss

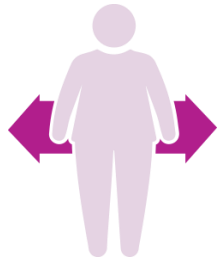
Weight: loss

Good:
CV mortality benefit
Can be used in renal failure, might be protective
Can be once weekly
Oral form is available (CVA benefit)

Bad:
Expensive
Daily or weekly injection (there is an oral form)
GI side effects (needs to be titrated)

Other:
Never use with a DPP_4 since they do the same thing.
Can be used in place of DPP_4 if you do not have the desired effect

Pioglitazone (TZDs)



Mechanism: sensitizes

A1C ↓: 0.5 to 1.5%

Weight: gain

Hypoglycemia: none

Good:
Cheap
NHIMA
pill

Bad:
Contraindicated in CHF

Other:
Not a substitute for metformin

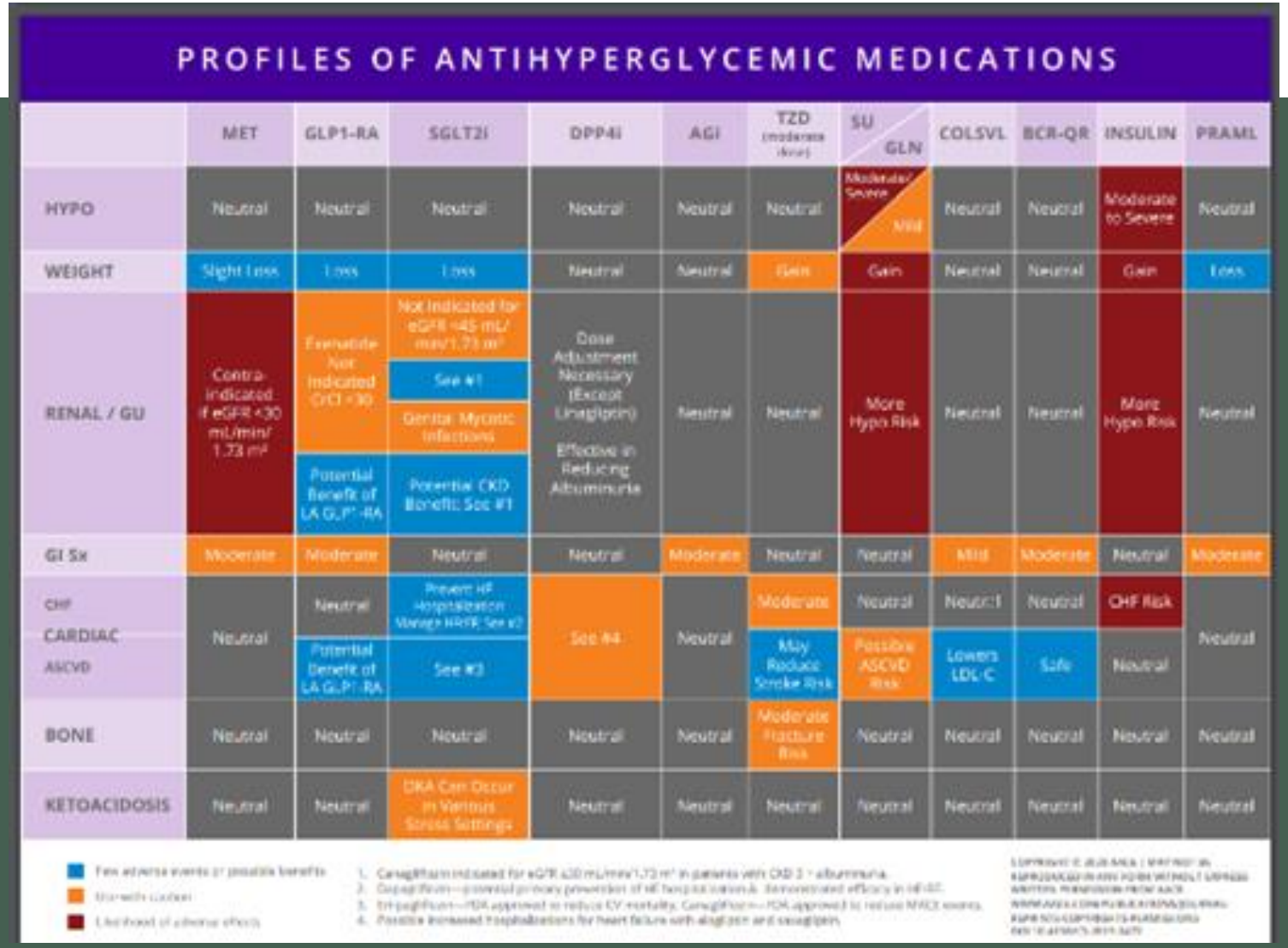
COMBOS

- Many medications come combined which can increase compliance and decrease cost
  - Metformin + DPP4
    - Also in extended release form
  - Metformin + SGLT2
    - Also in extended release form
  - DPP4 + SGLT2
  - GLP1 + Basal insulin

SUMMARY

Medication	Mechanism	A1c	Hypo	Weight	Good	Bad
Metformin	Sensitizes	1-2.5	No	Loss	All cause mortality NHIMA	Reputation
Sulfonylurea	Secretagogue	1-3.0	YES!!!!	Gain	Cost NHIMA	hypoglycemia
GLP1	InCretIn	0.5-1.0	No	Loss	CV/renal mortality	Injectable
DPP4	InCretIn	0.5-1.0	No	Neutral	Safe, renal failure NHIMA	Cost
SGLT2	Renal excretion	0.5-1.0	No	Loss	CV/CHF Renal benefit NHIMA?	UTI/yeast
TZD	Sensitizes	0.5-1.5	No	Gain	Cost NHIMA	Contraindicated in CCF

AACE Summary



PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP1-RA	SGLT2I	DPP4I	AGI	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m²	Exenatide Not Indicated CrCl <30	Not Indicated for eGFR <45 mL/min/1.73 m²	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
		Potential Benefit of LA GLP-1 RA	See #1 Genital Mycotic Infections Potential CKD Benefit: See #1								
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF CARDIAC ASCVD	Neutral	Neutral	Prevent HF Hospitalization Manage HHFR See #2	See #4	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
		Potential Benefit of LA GLP-1 RA	See #3			May Reduce Stroke Risk	Possible ASCVD Risk	Lowers LDL-C	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits

Uncertain outcomes

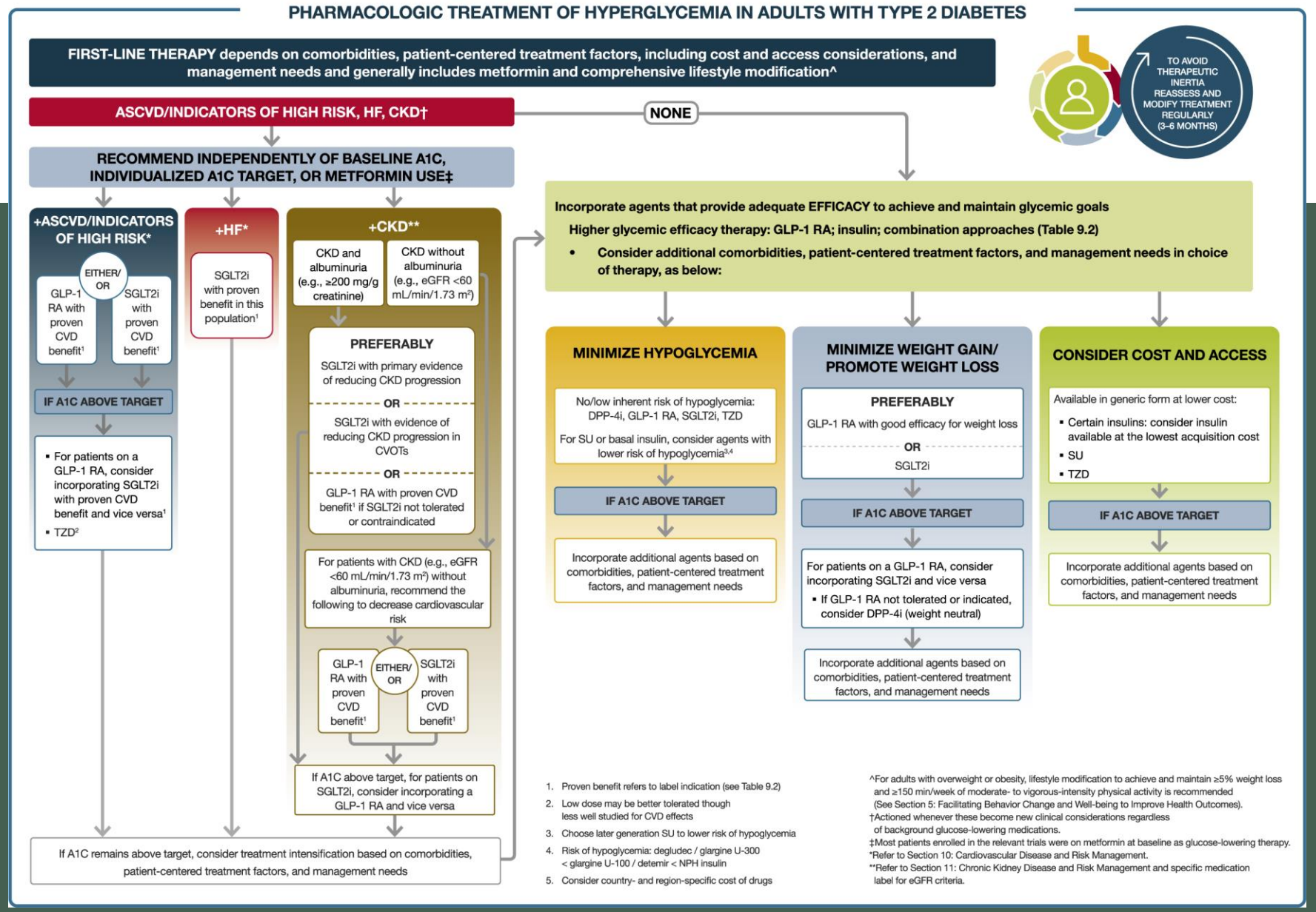
Likelihood of adverse effects

1. Canagliflozin indicated for eGFR ≥30 mL/min/1.73 m² in patients with CKD 3 + albuminuria.
2. Dapagliflozin—approved primary prevention of HF hospitalization. Demonstrated efficacy in HF-EF.
3. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
4. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

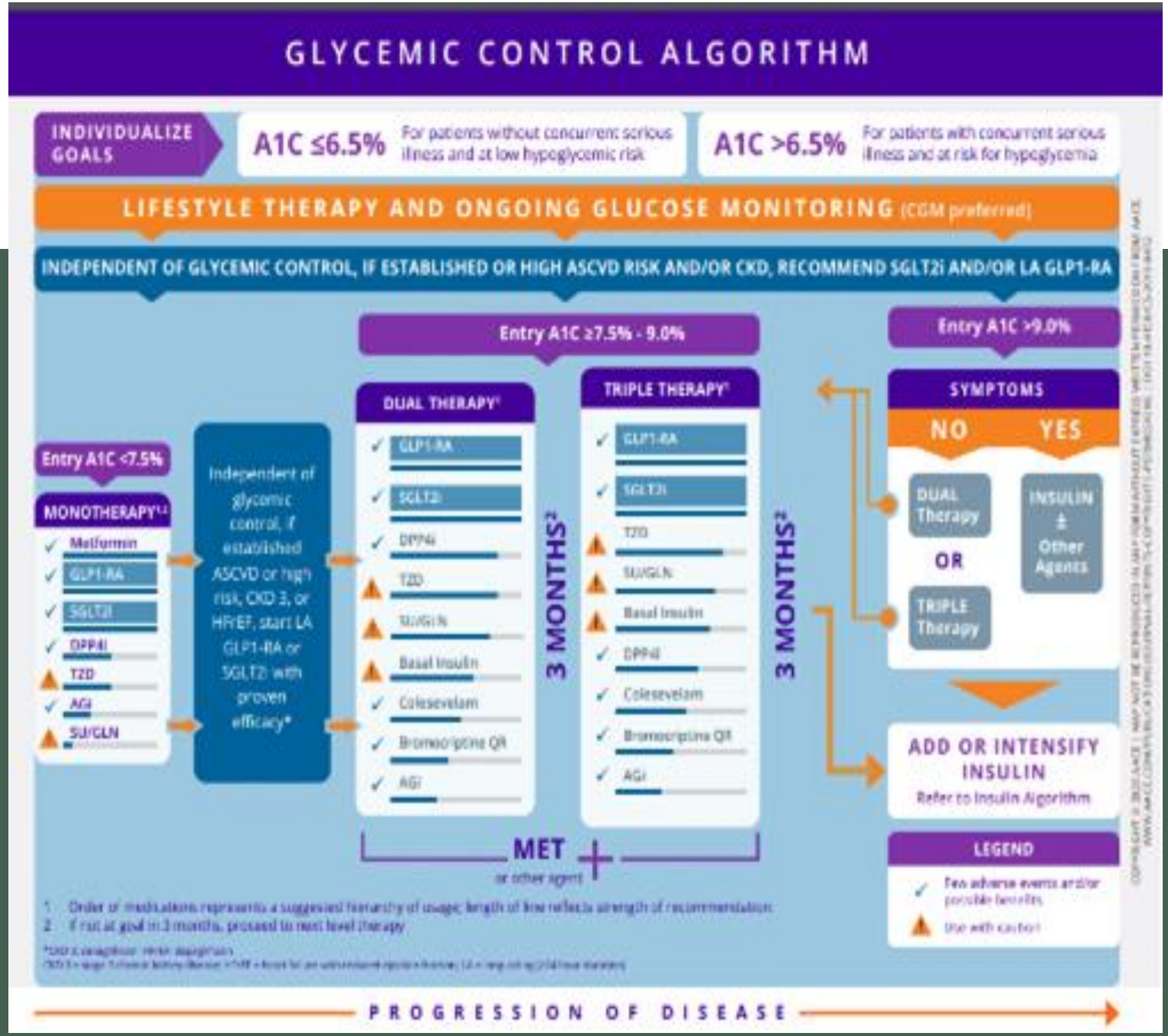
ADA Summary

	Efficacy (60)	Hypoglycemia	Weight change (109)	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 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin‡, canagliflozin, dapagliflozin‡, ertugliflozin	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin§	▪ See labels for renal dose considerations of individual agents ▪ Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	▪ 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	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	▪ See labels for renal dose considerations of individual agents ▪ 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, 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: generally not recommended in chronic kidney disease ▪ 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**	High	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			

ADA Algorithm



AACE Algorithm



The AACE makes specialty based recommendations. An A1c of 6.5% is not a typical goal for the average person with DM and waiting 3 months prior to addressing high sugars is not recommended

CASES

- 1. 56yo F with DM, HTN, HLD has been on metformin 2500mg and daonil 20mg for 3 years and A1c is 8.0.
- 2. 43yo M with DM on metformin 1g bid, NPH 20AM, 30PM and fastings are controlled but postprandials are still 0.5-2.0 points high.
- 3. 32yo M recently diagnosed with DM with an A1c of 9.0.
- 4. 68yo F recently hospitalized with a stroke and new diagnosis of DM with an A1c of 9.7.
- 5. 26yo F with a 4 year history of DM controlled on metformin and daonil with an A1c of 6.8 who cannot lose weight despite being at goal with diet and exercise.

POSSIBLE TREATMENT OPTIONS

- 1. Decrease metformin to 1g bid, stop daonil and start an SGLT2-DPP4 combo
- 2. Add GLP1 to basal insulin in combo injection or add an SGLT2 or DPP4
- 3. Start metformin + DPP4 or SGLT2
- 4. Start metformin-DPP4 combo and GLP1
- 5. Stop daonil and add a GLP1 or SGLT2