Helping Your Patients with Diabetes

An Update of Management Recommendations for T2D

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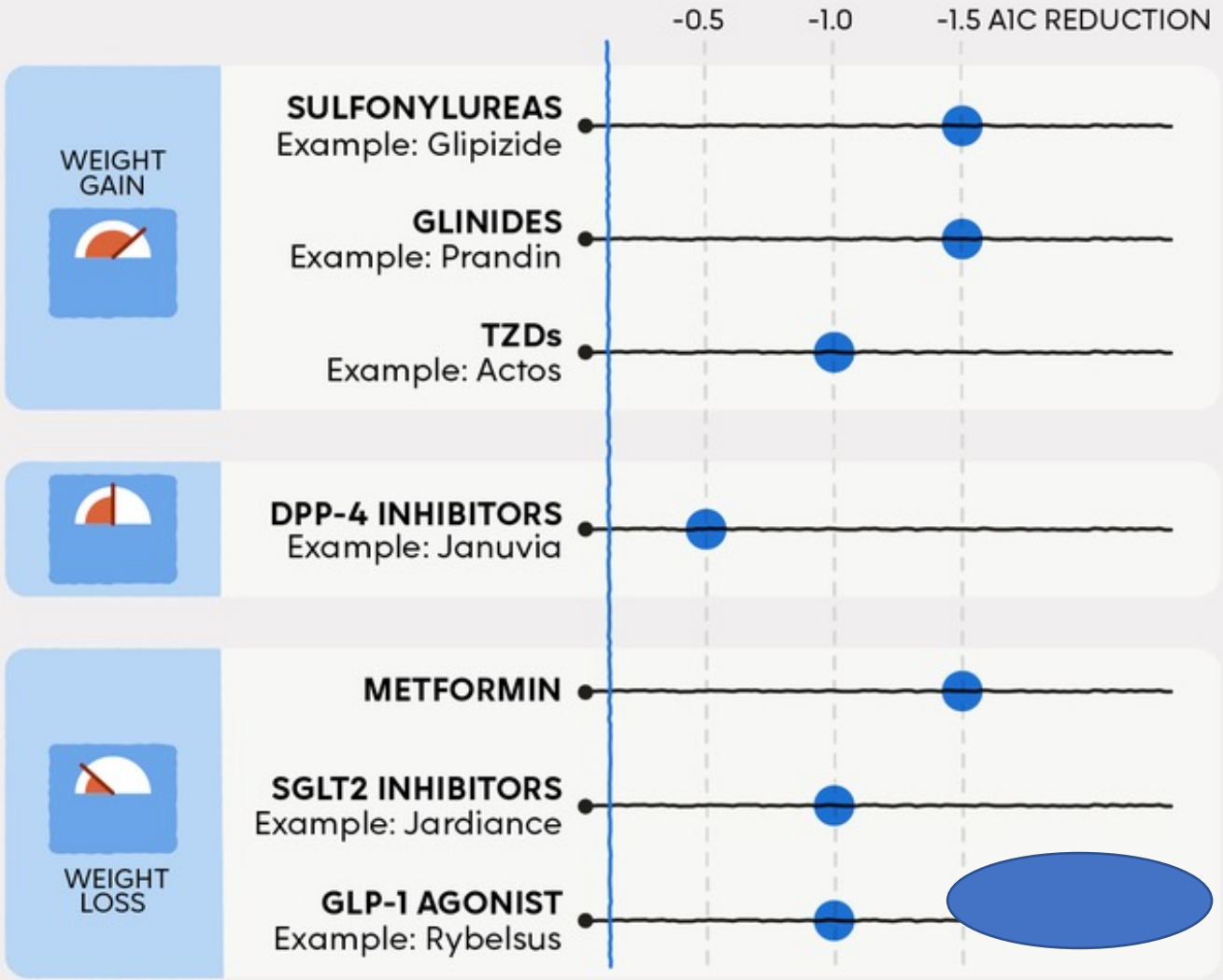
Background

- 2006 – Byetta – short acting GLP1 RA approved for type 2 diabetes
  - Injectable
  - Expensive
  - Long-acting GLP1 RA injectables entered market, along with an oral formulation

- 2013-2014 – SGLT2i medications approved for type 2 diabetes
  - Oral
  - Expensive
  - ? Acute Kidney Injury, etc.

Initial reservations / caution by many providers … cost for benefit, unknows, etc.

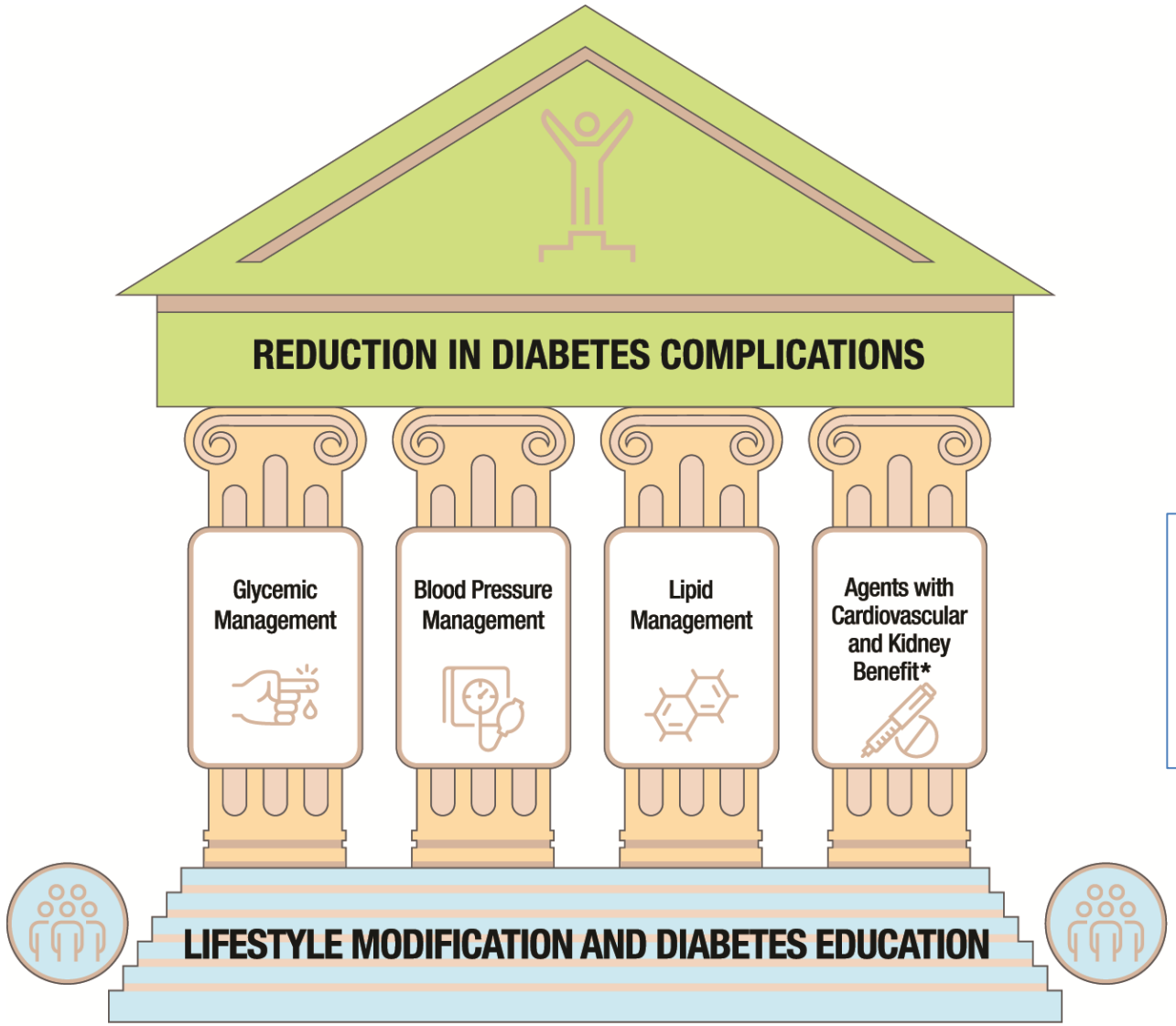
How Diabetes Pills Affect Body Weight and A1C



"Non-glycemic Benefits"

Injectable GLP1 RA meds lower A1c more than the Current oral GLP1 RA

Treatment to Reduce Diabetes Complications



When possible,
select meds
that do
"double (or more) duty"

Direct cardio-renal effects
not mediated through glycemia
→"**non-glycemic benefits**"
multiple mechanisms

American Diabetes Association.

Indian Health Service Formulary

- November 2019:
  - The NPTC voted to add **empagliflozin** to the IHS National Core Formulary.
  - The NPTC voted to add either subcutaneous (1) **dulaglutide**, (2) **liraglutide** or (3) **semaglutide** to the National Core Formulary (listed alphabetically only, no preference).

Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: November 2019

- American Indian/Alaska Native (AI/AN) adults are 2.4 times as likely as white adults to be diagnosed with diabetes with an estimated 30% of the AI/AN population having prediabetes.
- Death rates due to diabetes for AI/AN are 1.6 times higher than the general U.S. population
  - the incidence of kidney failure due to diabetes is 1.9 times higher.
  - The risk for cardiovascular (CV) disease in AI/AN adults is three to eight times higher than those without diabetes.
- With the CV and renal complications of diabetes disproportionately affecting the IHS patient population, **medications that improve outcomes in CV disease and renal disease could substantially improve the health of our patients.**

Objectives

- Overarching objective - Improve health outcomes for your patients with T2D - Prevent complications, improve outcomes & quality of life
  - Understand the CVOT (cardio-vascular outcome trial) results that led to the updated recommendations
  - Review the ADA 2023 standards of care for pharmacologic therapy of T2D for both glycemic and non-glycemic benefits
  - Develop confidence in using SGLT2i medications for your patients with ASCVD risk, diabetic kidney disease and/or heart failure
  - Gain confidence in using GLP1 RA and/or Dual GIP-GLP1 RA medications for your patients with ASCVD risk, obesity and/or diabetic kidney disease

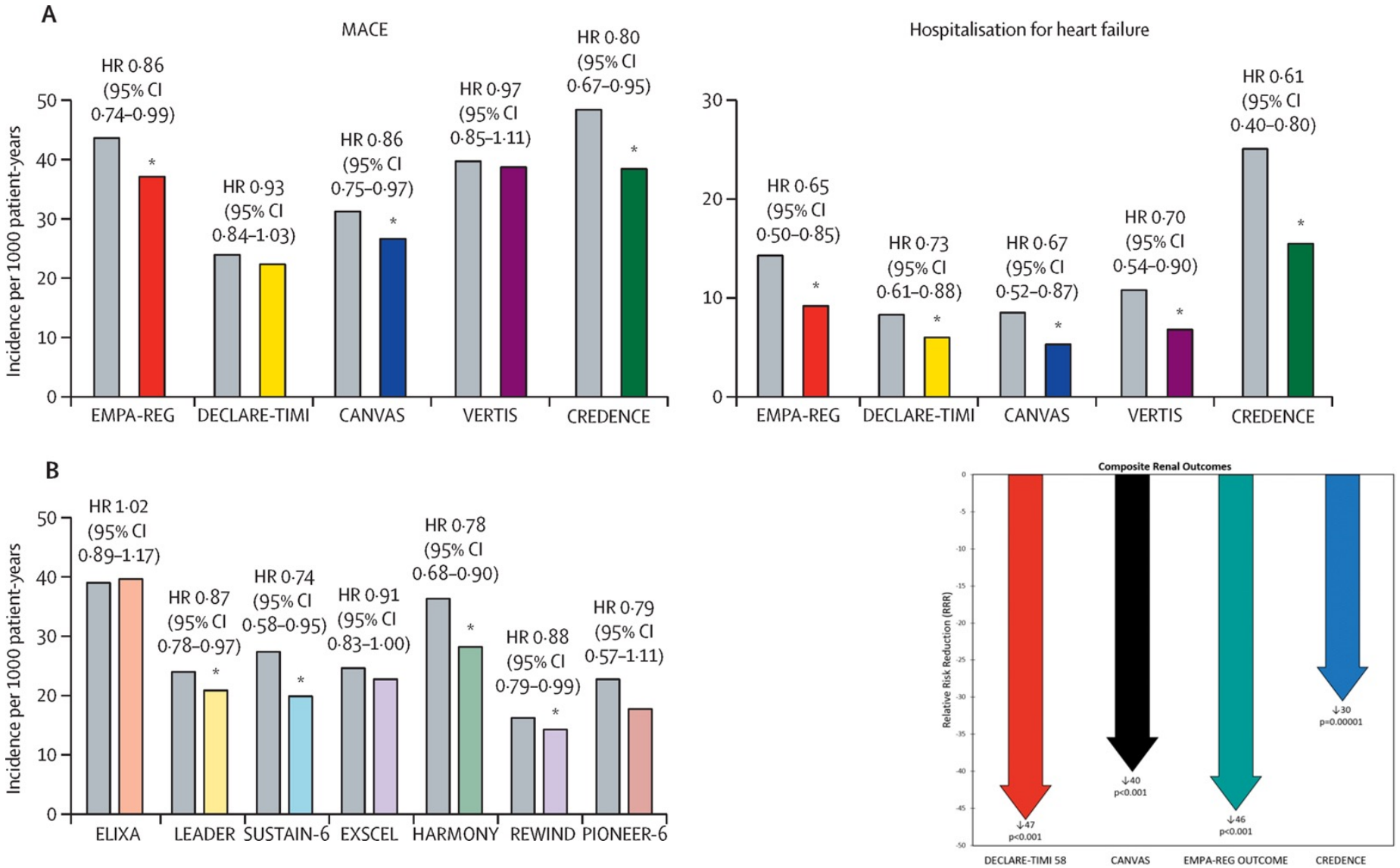
Learning from the Cardiovascular Outcome Trials (CVOTs)

- Mandated by FDA in 2008 to assess **CV safety** for *any new* diabetes medications (glucose lowering drugs [GLDs])(in addition to demonstrating improvements in glycemic control)
  - Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with type 2 diabetes (T2D).
    - Reducing CV risk is a key part of T2D disease management
    - Historical concerns about cardiovascular (CV) risks associated with certain glucose-lowering medications gave rise to the introduction of cardiovascular outcomes trials (CVOTs).
      - Larger exposure needed (in patient-years of exposure) than with glucose lowering trials
        - More patients, longer duration study (e.g., ~5000 vs 250 person-years)

Learning from the Cardiovascular Outcome Trials (CVOTs)

- Notably, some CVOTs have not only illustrated **CV safety**, but also reported **cardioprotective benefits**. for certain sodium–glucose transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs)
  - Reductions in 3-point major adverse CV events (3P-MACE) and CV death have been noted in some of these CVOTs
    - 3P-MACE = a composite of CV death, nonfatal MI and nonfatal stroke
  - Additional benefits include reduced risks of
    - hospitalization for heart failure (HHF)
    - progression of renal disease
    - all-cause mortality
  - These new data are leading to a ***paradigm shift in the current management of T2D***, with international guidelines now prioritizing SGLT2 inhibitors and/or GLP-1 RAs in certain patient populations.

Overview of Findings of CVOT Trials



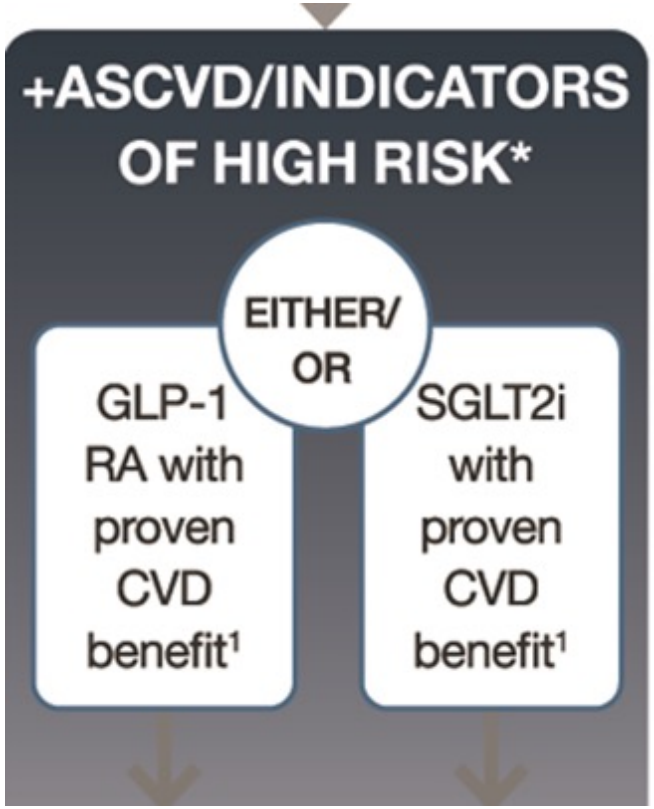
CVOT findings: *Cardioprotection* with some GLDs

- DPP-4 inhibitors: no evidence for cardioprotection
  - However, ***saxagliptin*** had a significantly elevated risk of **HHF** (HR [95% CI] 1.27 [1.07–1.51], $p < 0.01$) and there was a suggestion of increased risk of HHF with ***alogliptin*** (HR [95% CI] 1.19 [0.90–1.58])
  - Led to the FDA issuing a ***safety warning*** for both alogliptin and saxagliptin
- SGLT2 inhibitors: cardioprotection with empagliflozin & canagliflozin
  - findings suggest that significant improvements in CV outcomes (14%), which were observed in CVOTs of e***mpagliflozin*** and ***canagliflozin***, may not apply to all SGLT2 inhibitors (Dapagliflozin – trend for CV benefit/ Ertugliflozin – no benefit in trial)
    - Some experts think class effect for benefits / others think maybe individual compounds
- GLP-1 RAs: cardioprotection (13-27%) with subcutaneous and long acting GLP-1 RAs (dulaglutide, liraglutide or injectable semaglutide)
  - Inconclusive evidence for short-acting and oral long-acting medications - more research is needed
- Unlike DPP-4 inhibitors, ***SGLT2 inhibitors*** **and** ***some GLP-1 RAs*** are associated with significant **reductions in all-cause mortality**

International Guidelines

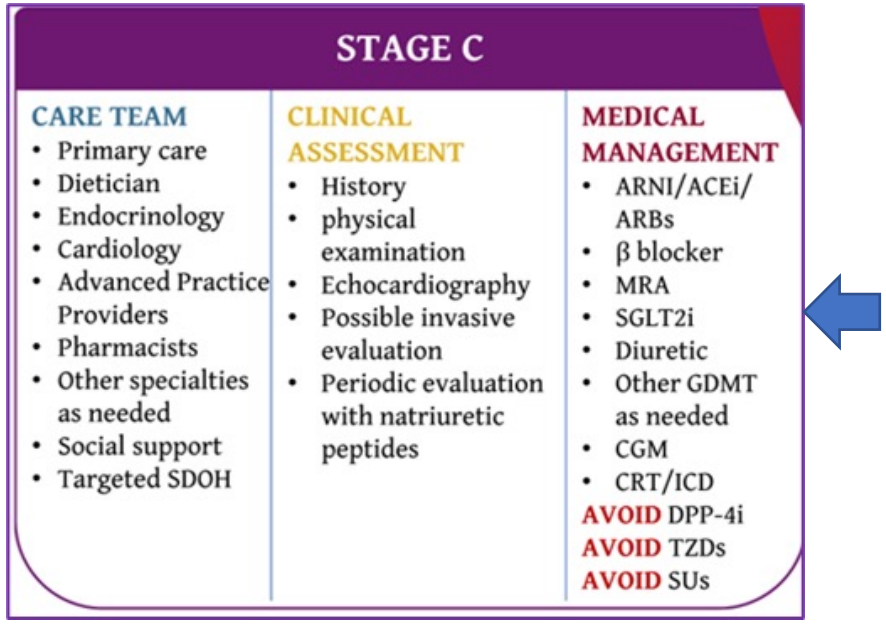
The general consensus between the guidelines is that patients diagnosed with T2D and CVD (or high risk of CVD) should be treated with an SGLT2 inhibitor or GLP-1 RA with proven CVD benefit, either as first add-on to metformin or as monotherapy.

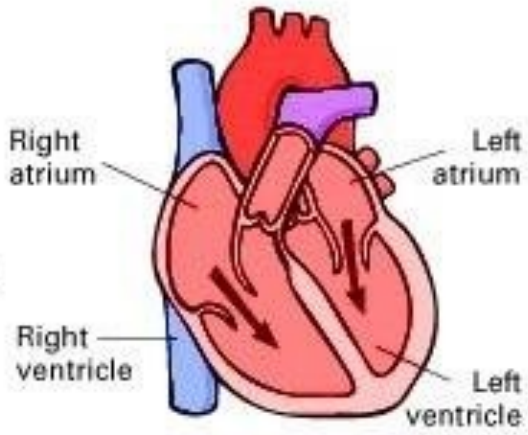
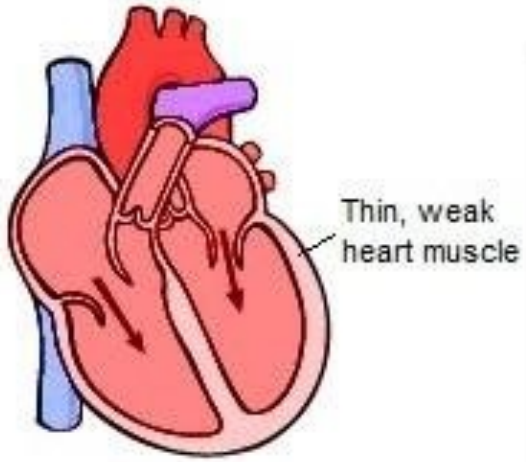
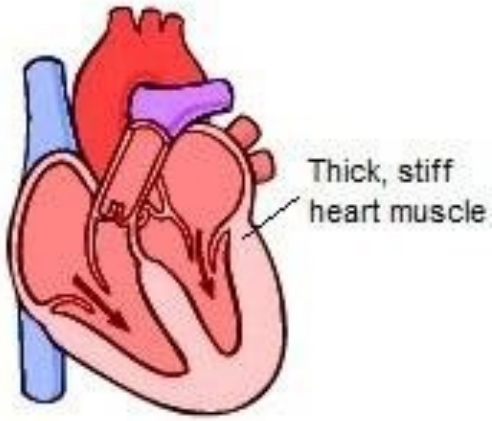
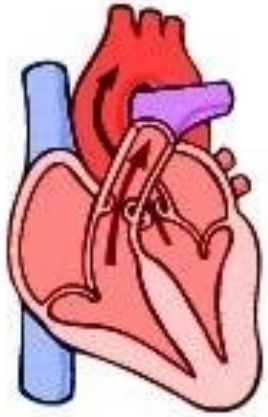
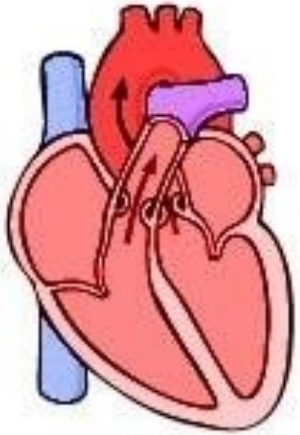
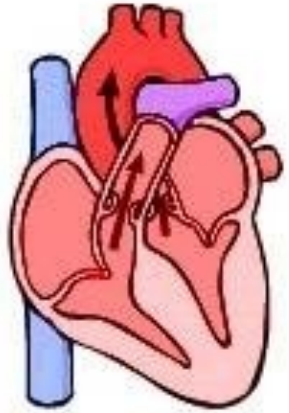
(regardless of A1c)



SGLT2 inhibitors: evidence for reduced risk of HHF

- CVOTs were not designed to look at HF - most patients did not have HF on enrollment
  - *A consistent pattern of **fewer HHF events**, with a large effect size, has been seen across the SGLT2 inhibitor class*
  - *Real-world studies have confirmed the pattern of **fewer HHF events** in the more diverse patients seen in routine clinical practice*
  - ***International guidelines*** for the treatment of patients with T2D now recommend SGLT2 inhibitors to *protect* patients from HF
  - Both dapagliflozin and empagliflozin are approved in Europe and the US for the treatment of patients with chronic **HFrEF (reduced EF)**
  - In 2022, empagliflozin received FDA and European Commission approval for the treatment of patients with **preserved EF (HFpEF)**



	Normal Heart	Systolic Heart Failure (HFrEF)	Diastolic Heart Failure (HFpEF)
Filling (Diastole)	 Ventricles relax and expand to fill with blood	 Enlarged ventricles fill with blood	 Thickened and stiff ventricles fill with blood less than normal
Pumping (Systole)	 Ventricles contract and pump out between 50% and 60% of the blood	 Stretched ventricles are weaker, pumping out less blood than normal	 Thickened ventricles contract normally, but have less blood to pump out

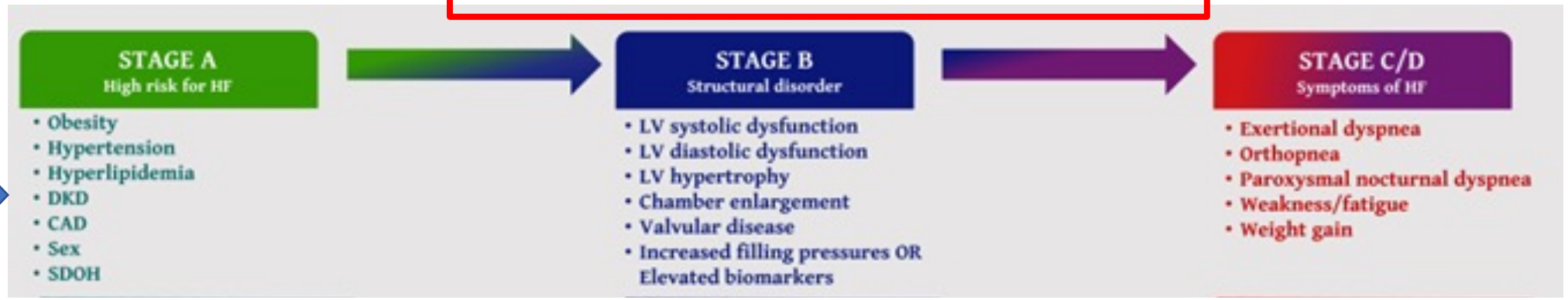
CVOTs increased awareness of Heart Failure (HF) in People with Diabetes

- HF is more common and higher risk (for poor outcomes) in people with diabetes – and diabetes is more common in people with HF
- HF is more common in women than men with diabetes
- HF can be an ***early*** complication of diabetes
- HF can occur without CAD or HTN – i.e., as a direct effect of diabetes on the heart muscle ("diabetic cardiomyopathy")
- Anyone with diabetes is at risk for HF – the more additional risk factors, the higher the risk
  - Patients with Stage B HF ("pre-HF") can progress rapidly to symptoms & death
- Early intervention can improve outcomes
  - Attention to how you manage the diabetes – preferred meds/ meds to avoid

Heart Failure - Clinical Stages & Medical Management

- HF represents a *continuum* of cardiac structural abnormality and dysfunction and associated cardiovascular risk

Many individuals with diabetes can be classified in stage B



The presence of established diabetes indicates that an individual is at risk for HF (stage A) In this stage, the achieved control of glycemia and other risk factors may modify (or amplify) risk for clinical HF.

MEDICAL MANAGEMENT
- ACEi/ARBs
- Optimize BP and lipid control
- Optimize glucose control (SGLT2i, GLP-1RA metformin preferred)

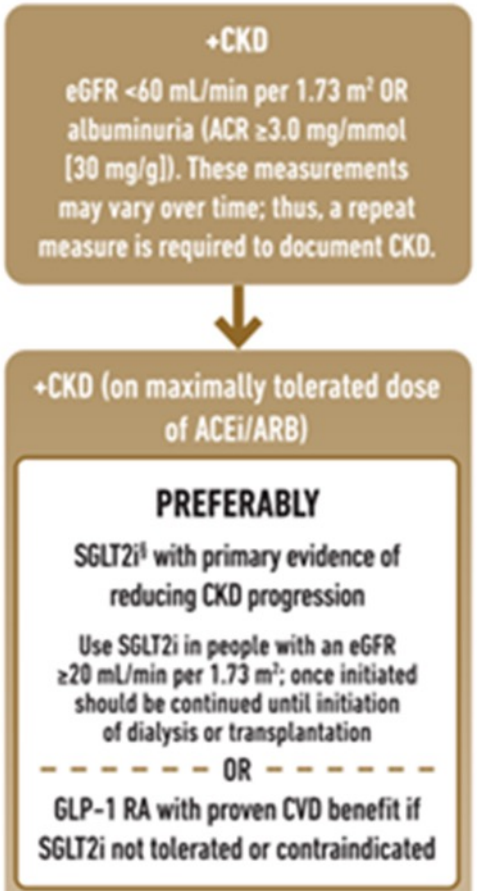
- Stage B includes *asymptomatic* individuals with at least one of the following:
  1) evidence of structural heart disease
  2) abnormal cardiac function
  3) elevated natriuretic peptide levels or elevated cardiac troponin levels
- Stage B HF is linked to
  - increased risks of cardiovascular and all-cause mortality
  - progression to more advanced stages of overt HF
  - may be referred to as ***"pre-HF."***
  - *can progress rapidly to symptoms & death*

MEDICAL MANAGEMENT
- ACEi/ARBs
- SGLT2i (± GLP-1RA, metformin preferred; insulin SU alternatives)
- BP and lipid control

AVOID DPP-4i
AVOID TZDs
AVOID SUs

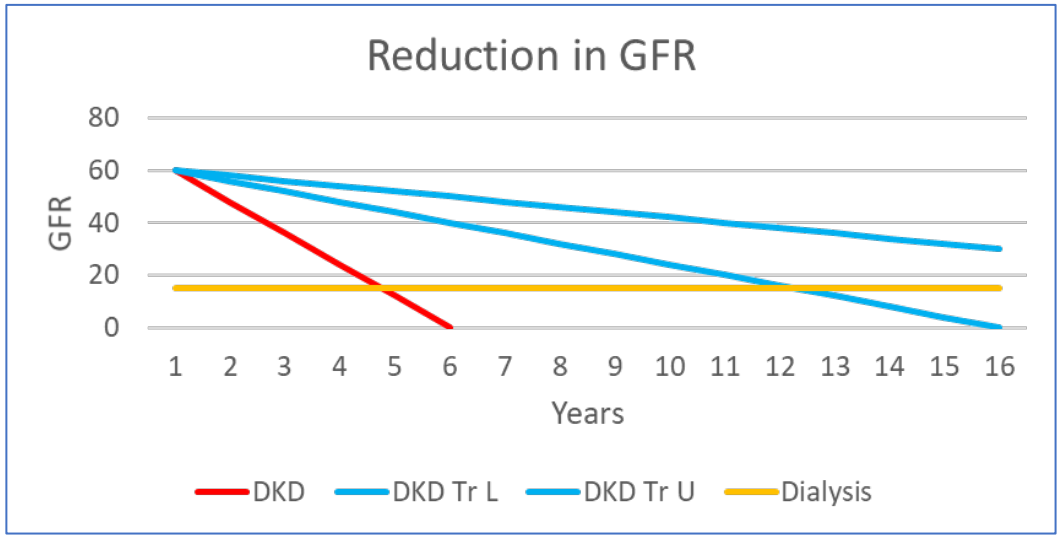
SGLT2 inhibitors: evidence for renal benefits

- Improved renal outcomes have been consistent across CVOTs for SGLT2 inhibitors, both in terms of renal function and albuminuria.
  - RRR in renal function outcomes were ≥ 35% across the class
    - sustained decline in the eGFR of ≥ 50%, end-stage kidney disease, or death from renal or CV causes
  - Progression of albuminuria was consistently slowed with SGLT2 inhibitors
- CVOTs and renal outcomes studies shows conclusively that patients with T2D experience *superior renal benefits* with SGLT2 inhibitors than with DPP-4 inhibitors and currently approved GLP-1 RAs
  - the evidence for HF and renal benefits with SGLT2 inhibitors was deemed sufficient by professional societies to update guidelines
  - SGLT2 inhibitors are recommended as either first add-on, concomitant to metformin, or as a monotherapy in patients with T2D and HF or CKD



Glomerular Filtration Rate ("renal function")

- Normal GFR >90 ml/min/1.73M2
  - Hyperfiltration >120
  - Chronic Kidney Disease (CKD) <60 for =/>3 months
- GFR declines with normal aging (>30) – average 0.75-0.8 ml/min/year (GFR 50-60 by age 80)
- Rate of decline of GFR in Diabetic Kidney Disease (DKD) – average 12 ml/min/year
- Decline in GFR associated with structural & functional changes in the kidney → complications of CKD (anemia, bone, electrolytes, hypoglycemia, etc.)
  - At GFR<15 – require renal replacement
- Treatment of DKD can slow decline in GFR from average of ***12 ml/min/year*** to an average of ***2-4 ml/min/year*** – thus delaying or avoiding ESRD (ESKD) – and at same time help reduce CVD/HF risk (markedly increased with CKD)



USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Recommendations for Reducing *ASCVD* events

ADA 2023 Standards of Care

- 10.41 Among people with type 2 diabetes who have **established atherosclerotic cardiovascular disease (ASCVD) or established kidney disease**, a ***SGLT2i*** or ***GLP1 RA*** with demonstrated cardiovascular disease benefit is recommended as part of the *comprehensive cardiovascular risk reduction and/or glucose-lowering regimens*. A
  - 10.41a In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, a **SGLT2i** with demonstrated cardiovascular benefit is recommended to ***reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization***. A
  - 10.41b In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a **GLP1 RA** with demonstrated cardiovascular benefit is recommended to ***reduce the risk of major adverse cardiovascular events.*** A
  - 10.41c In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, **combined therapy** with a SGLT2i with demonstrated cardiovascular benefit and a GLP1 RA with demonstrated cardiovascular benefit may be considered for ***additive reduction in the risk of adverse cardiovascular and kidney events***. A

Recommendations for Patients with *Heart Failure (HF)*

- 10.42a In people with type 2 diabetes and established **heart failure** with either *preserved or reduced ejection fraction*, a **SGLT2i** with proven benefit in this patient population is recommended ***to reduce risk of worsening heart failure and cardiovascular death***. A

- 10.42b In people with type 2 diabetes and established **heart failure** with either *preserved or reduced ejection fraction*, a **SGLT2i** with proven benefit in this patient population is recommended to ***improve symptoms, physical limitations, and quality of life.*** A

Updated ADA & EASD Guidelines

As ***first-line*** therapy
Can then add metformin
And/or GLP1 RA if needed

ADA & NKF recommend SGLT2i for *Non-glycemic* Benefits

- 11.3a For patients with type 2 diabetes and diabetic kidney disease, use of a **SGLT2i** in patients with an eGFR >/= 20 ml/min/1.73 m2 and urinary albumin >200 mg/g Cr is recommended to ***reduce Chronic Kidney Disease progression*** & ***Cardiovascular events***. B

- 11.3b For, patients with type 2 diabetes and chronic kidney disease, use of a **SGLT2i** is recommended to ***reduce CKD progression and CV events*** in patients with an eGFR >/= 20 *and* **urine albumin ranging from *normal to 200 mg/g***. B
  - Reduced eGFR with no or minimal albuminuria (UACR <200 mg/g)
  - Albuminuria with UACR <200 mg/g

- *"SGLT2i should be given to all patients with stage 3 CKD or higher* ***regardless of glycemic control****, as they* ***slow CKD progression and reduce heart failure risk*** *independent of glycemic control"* ADA Standards

CKD markedly increases risk for ASCVD & HF events & death in T2D

Both *albuminuria* & *eGFR* must be quantified to guide treatment decisions

- eGFR levels are essential to allow staging, monitor progression & modify drug dosages or restrictions of use
  - Risk for complications/management issues (CVD, low BG, anemia, bone disease, volume overload, AKI)
- At any eGFR, the degree of **albuminuria** is associated with risk of
  - Cardiovascular disease (CVD)
  - CKD progression
  - Mortality

At any eGFR, the Degree of Albuminuria is associated with Risk of Cardiovascular Disease (CVD)

Table 2. Risk Assessment for CVD in CKD

CKD Stages	GFR	10-29	30-299	>300
1	90+			
2	89-60			
3A	59-45			
3B	44-30			
4	29-15			
5	< 15			

CVD, cardiovascular disease; CKD, chronic kidney disease; GFR, glomerular filtration rate.
Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group[3]

Risk of CKD Progression, Morbidity & Mortality

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
Green: Low Risk (if no other markers of kidney disease, no CKD)
Yellow: Moderately Increased Risk
Orange: High Risk
Red: Very High Risk
Deep Red: Highest Risk

New ADA Standard regarding Treatment Goal for *Albuminuria*

- 11.6 In patients with chronic kidney disease who have =/>300 mg/g urinary albumin, a ***reduction of 30% or greater in mg/g urinary albumin*** is recommended to slow chronic kidney disease progression B
  - Monitor for reduction over 6-12 months

"In clinical trials of ACEI or ARB therapy in T2D, reducing albuminuria to levels <300 mg/g Cr or by >30% from their baseline has been associated with ***improved renal & cardiovascular outcomes****"*

- CKD increases risk of ASCVD events & HF

Clinical inertia to the use of SGLT2 inhibitors and GLP-1 RAs

- Many patients with CV risk still do not receive SGLT2 inhibitors or GLP-1 RAs as part of their GLD regimen, even though these medications are recommended for CVD prevention in the treatment guidelines.
- *DPP-4 inhibitors* are more widely used than SGLT2 inhibitors or GLP-1 RAs, despite *comparable costs* to SGLT2 inhibitors and the *lack of evidence that DPP-4 inhibitors improve cardiorenal outcomes.*

- Primary Care clinicians need to be comfortable using these medications
  - Treatment started early stages helps prevent worsening of ASCVD, HF and CKD
  - Most nephrologists not accepting patients for management unless eGFR <30 ml/min

What you need to know to help your patients with diabetes (T2D)….

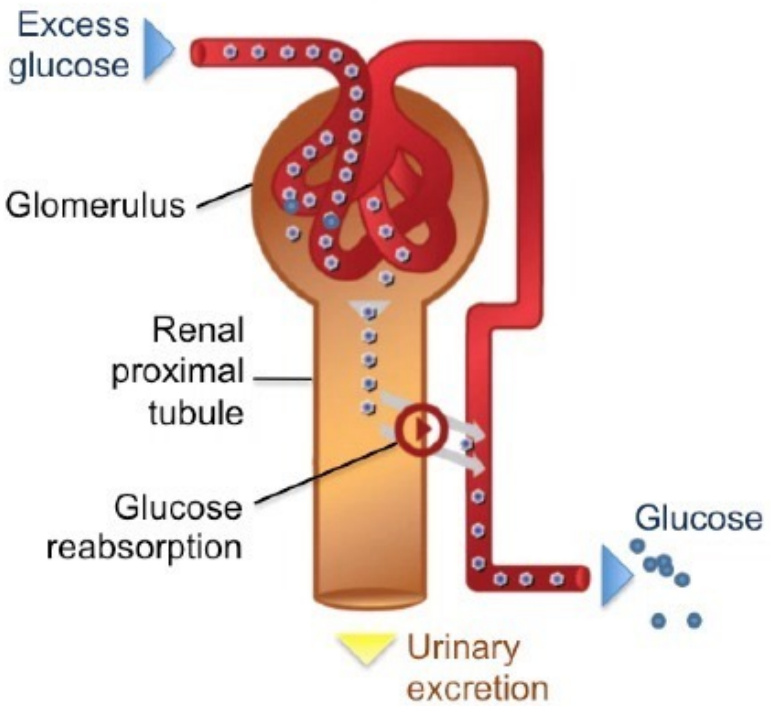
SGLT2i Medications

SGLT2 inhibitor	FDA approval	Indications	Dose
Invokana (canagliflozin)	2013	Type 2 diabetes	100 – 300 mg daily
Farxiga (dapagliflozin)	2014	Type 2 diabetes Heart failure	*Type 2 diabetes:* 5 – 10 mg daily *Heart failure:* 10 mg daily
Jardiance (empagliflozin)	2014	Type 2 diabetes	10 – 25 mg daily
Steglatro (ertugliflozin)	2017	Type 2 diabetes	5 – 15 mg daily

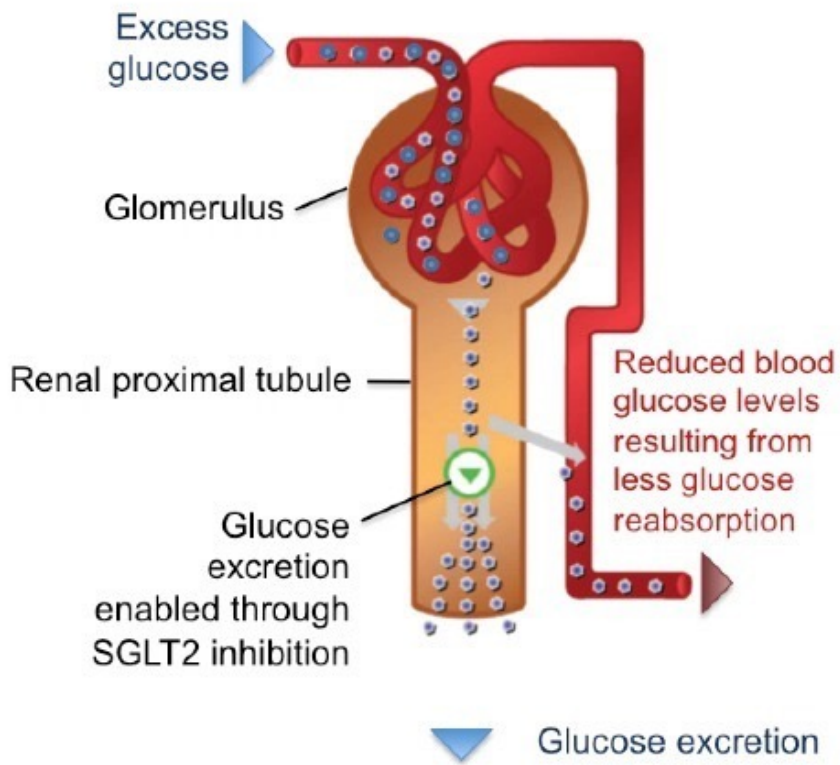
- Initiate SGLT2i therapy at the ***lowest recommended daily dose*** (10 mg empagliflozin, 100 mg canagliflozin, or 5 mg ertugliflozin) or 5 or 10 mg dapagliflozin.
  - SGLT2i titration to **a *higher dose is not necessary*** for maximal ***cardiorenal benefits*** *(10 mg dapagliflozin)*
  - A ***higher dose*** of SGLT2i can be used to *improve* ***glycemic control***
- SGLT2i therapy *can be continued until the patient initiates dialysis therapy* (currently not recommended to start at eGFR <20, but once started recommended to **continue until renal replacement started) (for cardio-renal benefits)**

Renal SGLT2 Inhibition
A Novel Approach to Type 2 Diabetes

Patients with type 2 diabetes



Type 2 diabetes with SGLT2 inhibition



Adapted from:
1. Chao EC & Henry RR. Nature Reviews Drug Discovery 2010;9:551-559.
2. DeFronzo RA, et al. Diab Obes Metab 2012;14:5-14.
3. Washburn WN. J Med Chem 2009;52:1785-1794.

SGLT2 inhibitors lower the renal threshold for glucose excretion and cause glucosuria – the amount of glucose excreted depends on the *level of hyperglycemia* and the glomerular filtration rate

SGLT2 inhibitor medications – Benefits & Risks

Benefits

- Glycemic benefits
  - reduced with eGFR <45
- Lower BP
- Weight loss (NAFLD benefit)
- Cardiac protection
  - Heart Failure reduction
  - Reduced MACE/ CVD events
- Renal protection
  - **Slow progression of CKD**
  - Diuresis without risk of AKI
    - Do not increase/ can decrease uric acid
    - Work with diuretics when needed (HF)
    - Potassium moderating

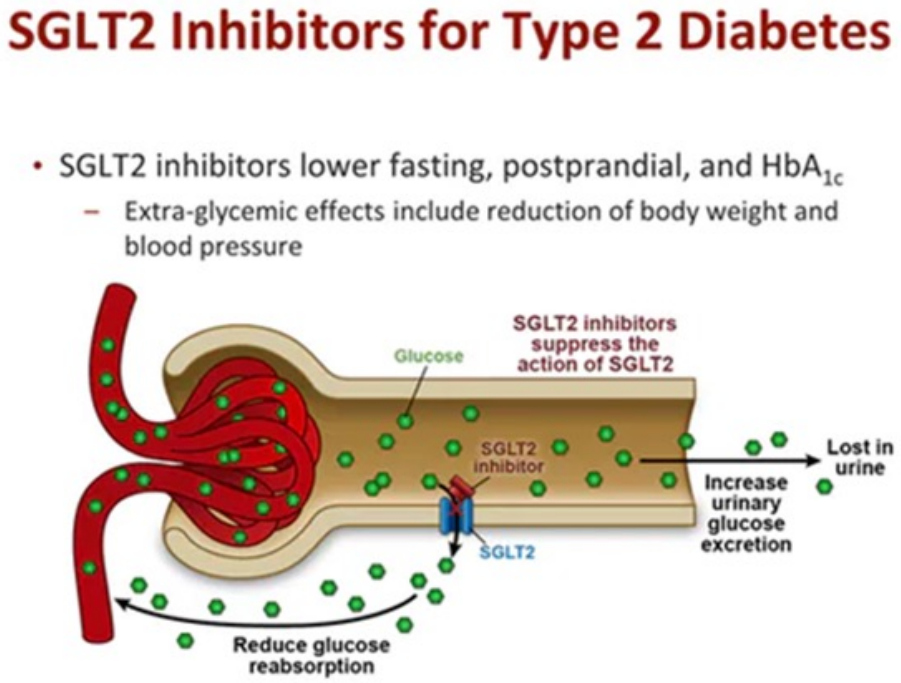
Risks

- Mycotic Genital Infections
- Fournier gangrene
- Euglycemic Diabetic Ketoacidosis (euDKA)
- Urinary Tract Infections (UTI)?
- Amputations ?
- Osteoporosis/fractures?

SGLT2i Glycemic Effectiveness

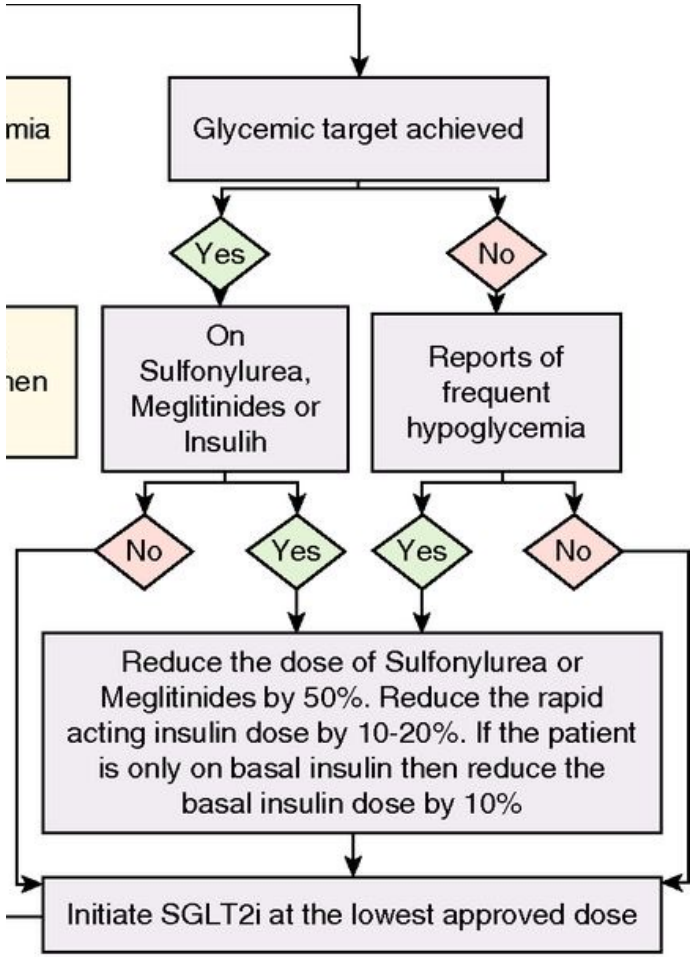
- ***Glycemic efficacy* of SGLT2 inhibitors is dependent on kidney function**.
  - SGLT2 inhibitors have been shown to be very effective in reducing glycated hemoglobin (HbA1c), with an ***average reduction of HbA1c by 0.6 - 1.2*** *(0.5-1.0)* depending on the baseline *level of glycemia* in people with preserved renal function

  - Higher BG results in larger drop
    - E.g., patients with higher baseline HbA1c (10.1%–12.0%) had greater reductions in HbA1c levels (−2.88%) - change in HbA1c is strongly associated with baseline HbA1c values
  - Can help "break" glucotoxicity
  - Help reduce *glucose variability*



Zaccardi F, et al. *Diabetes Obes Metab*. 2016;18:783-794.

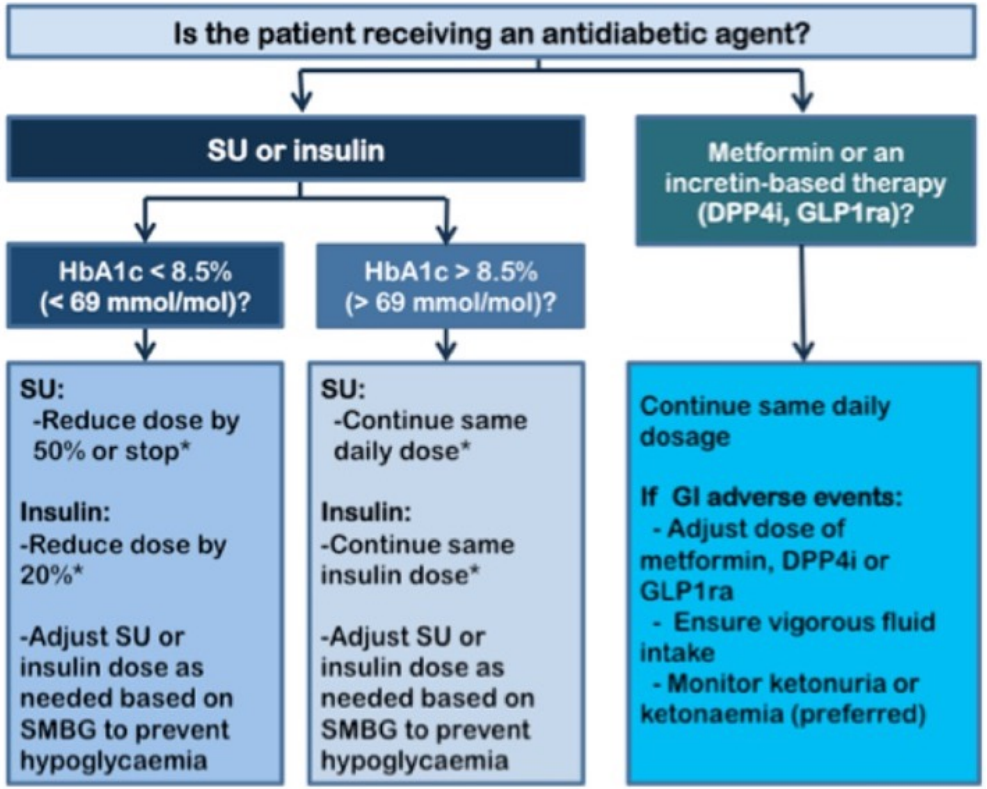
Algorithm to assess BP, volume status and glycemic control at the time of sodium-glucose cotransporter-2 inhibitor (SGLT2i) initiation.



Kidney360

David Lam, and Aisha Shaikh Kidney360 2021;2:742-746

Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes
Diabetes Ther. 2017 Oct; 8(5): 953–962.



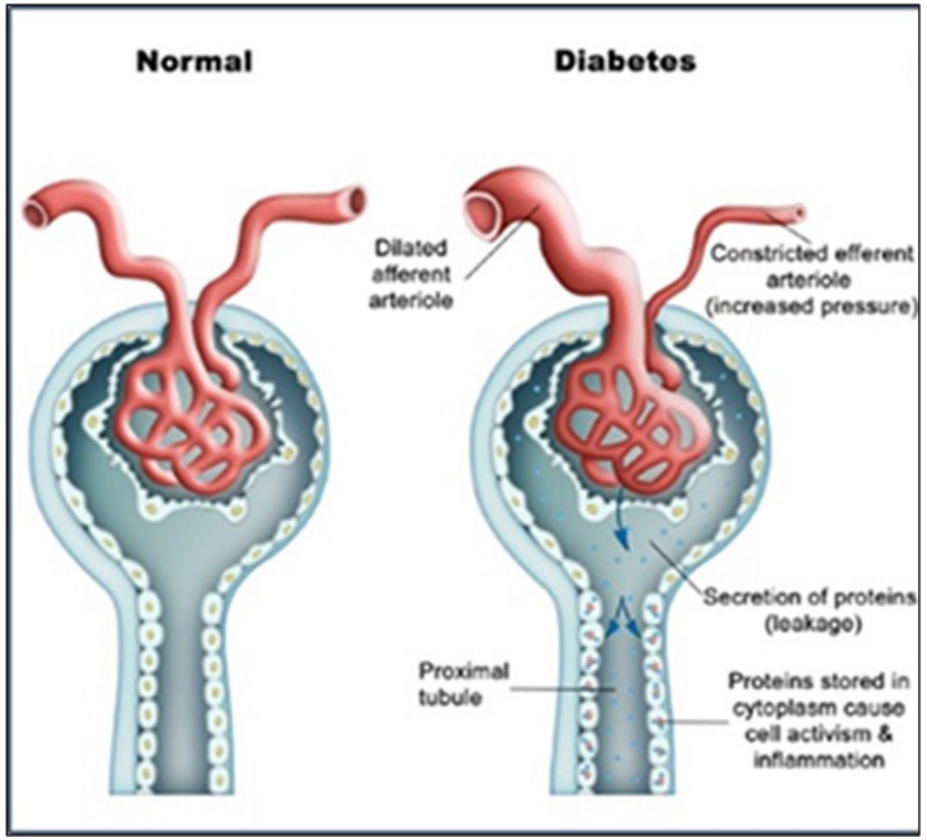
SGLT2i effectiveness in people with CKD

- ***Glycemic efficacy* of SGLT2 inhibitors is dependent on kidney function**.
  - The ***glucose-lowering efficacy*** of SGLT2i in the patients with an **eGFR <45 mL/min/1.73 m2 is *diminished*** because of their *reduced glucose filtration*
    - The glucose-lowering effect of SGLT2 inhibitors is attenuated in patients with eGFR <60 ml/min per 1.73 m2 and **minimal when eGFR is <30 ml/min** per 1.73 m2
    - Will need other agents for glycemic benefits (GLP1 RA preferred)

- ***Non-glycemic benefits*** are **not diminished**
  - In patients with T2D and CKD with low eGFR, despite only modest reductions in A1c, SGLT2 inhibitors **reduce the risk of cardiovascular and renal outcomes**, without clear evidence of additional safety concerns.
    - Higher risk patients – greater benefit

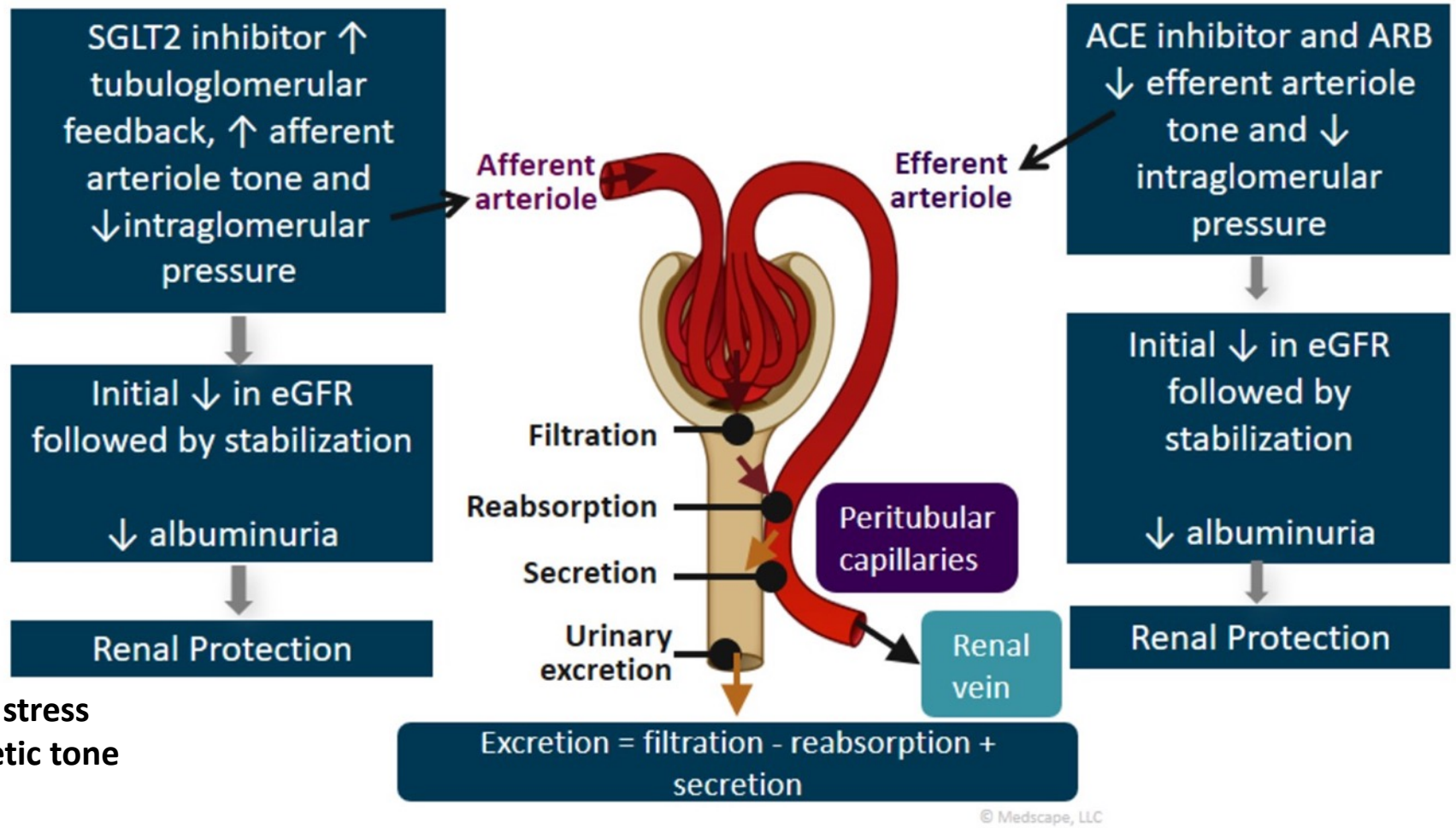
Renal Hemodynamic Derangements in DKD
glomerular hypertension and hyperfiltration

- Auto-regulation of renal blood flow is *impaired* (*faulty tubuloglomerular feedback & RAAS activation*) in CKD in diabetes:
  - abnormal dilation of afferent arteriole &
  - inappropriate constriction of efferent arteriole
  - leads to increased glomerular filtration & perfusion pressure (*glomerular hypertension)*
- This increase in filtration & glomerular hypertension can lead to *glomerular sclerosis* in long term
  - Perpetuated injury: After development of sclerosis blood flow in remaining intact glomeruli increases causing a rise in glomerular pressure and further sclerosis
- Leads to albuminuria & decline in GFR



SGLT2 Inhibition and ACE Inhibition/ARBs Reduce Intraglomerular Pressure

Newer data suggests only minimal effect on afferent arteriole & increased vasodilatation of efferent arteriole via TGF

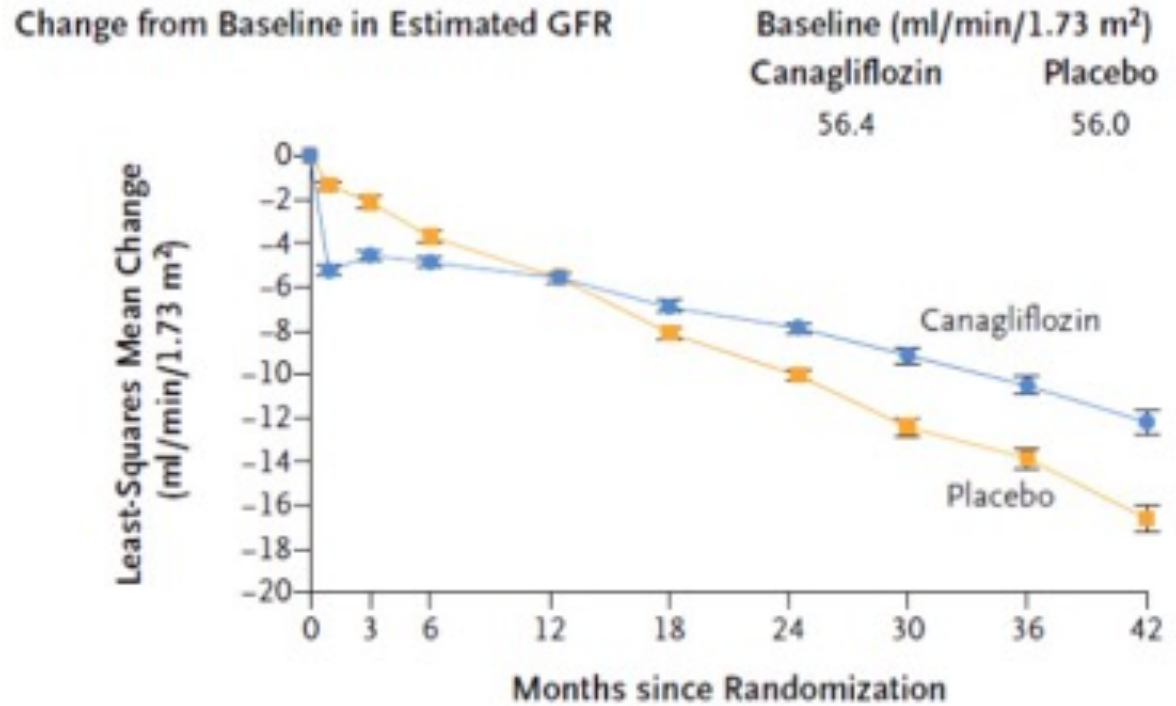


Multiple additional renal protective effects, including:

- **Reduced fibrosis**
- **Reduced oxidative stress**
- **Reduced sympathetic tone**
- **Diuretic sparing**

Cherney DZ, et al. *Circulation*. 2014;129:587-597; Perkovic V, et al. *Curr Med Res Opin*. 2015;31:2219-2231.

Effects of Canagliflozin on eGFR



No. of Patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

Acute eGFR slope (3 weeks)
Difference: –3.17 (95% CI: –3.87, –2.47)

Chronic eGFR slope
Difference: 2.74/year (95% CI: 2.37–3.11)

Small elevations of serum Cr (drop in eGFR) (***up to 30%*** from baseline) with RAAS blockers (ACEIs & ARBs) [also, SGLT2i & MRA meds] must ***not*** **be confused with AKI**

AKI usually 50% or more Increase in Cr

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

Additional Benefits – Reduction in Uric Acid & Gout

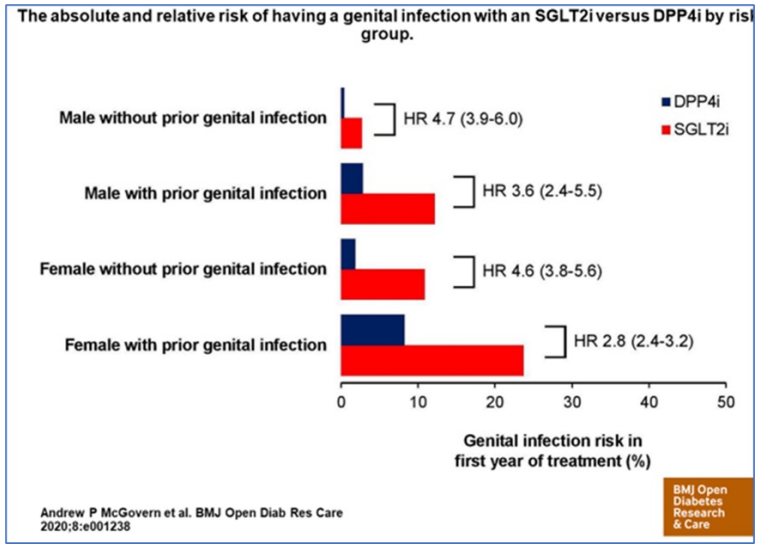
- Reduction in uric acid levels and in incidence of gout
  - In several studies, SGLT2 inhibitor medications consistently **lowered blood urate levels**
  - A 2020 study published in Annals of Internal Medicine found **~ 30% reduced incidence of gout with SGLT2i** therapy compared to *GLP1 RA* therapy in patients with T2D
  - A 2021 Taiwanese study found that use of SGLT2 inhibitors is associated with **~15% lower gout incidence** in patients with T2D compared with *DPP4 inhibitors* (DPP4i meds also reduce gout)

Additional Benefits – Edema, Hyperkalemia, AKI

- ***Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials*** Katherine R. Tuttle et al Diabetes Care 2022;45(6):1445–1452
  - **Edema** *was less common* in patients receiving empagliflozin versus placebo
  - *No increase* in **acute renal failure / AKI** or volume depletion
  - Studies show **additive or synergistic natriuretic effects** of SGLT1i with loop diuretics when needed
  - *Lower risks* were observed with empagliflozin for **hyperkalemia**
    - Patients with advanced CKD, especially those receiving renin-angiotensin system blockers, are prone to hyperkalemia.
    - This favorable effect of SGLT2 inhibitors on serum potassium in patients with type 2 diabetes and CKD **might permit the broader use of drugs** associated with hyperkalemia, such as mineralocorticoid receptor antagonists (spironolactone, finerenone)

Prevention and management of genital mycotic infections in the setting of sodium-glucose cotransporter 2 inhibitors Annals of Pharmacotherapy 2020

- The 3- to 4-fold increased incidence of GMIs is considered a class wide effect of SGLT2 inhibitors
  - female sex and a prior history of GMIs are factors associated with the highest risk, whereas
  - circumcised males are at the lowest risk of SGLT2 inhibitor–induced GMI
- Personal hygiene advice/education can reduce the infection risk in patients taking SGLT2 inhibitors
  - i.e., **rinse genital area with water after voiding and before bed**; wear cotton underwear
- When candidiasis occurs, it is often mild and responsive to treatment and often ***does not require discontinuation*** of the medication.
  - management strategies may include the use of
    - oral antifungals (i.e., single dose of oral fluconazole)
    - topical antifungal creams (i.e., miconazole or clotrimazole for 1-3 days)
    - over-the-counter topical antifungals in milder cases
- "Strong consideration should be given to avoid SGLT2 inhibitors in female patients with a history of severe, recurrent infections."



"If those at highest risk elect to start an SGLT2i, then practitioners should pay particular attention to counseling regarding genital hygiene and when to start antifungal treatments."

Annals of Internal Medicine |4 JUNE 2019

Fournier Gangrene Associated With Sodium–Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases

Susan J. Bersoff-Matcha, MD; et al

Results: The FDA identified 55 unique cases of FG in patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019 (***55 cases in ~6 years***)

- For comparison, the FDA identified 19 FG cases associated with other anti-glycemic agents between 1984 and 31 January 2019 ***(19 cases in 35 years)***

Fournier Gangrene = A type of necrotizing fasciitis or gangrene affecting the external genitalia or perineum (usually ***bacterial*** etiology)

- Symptoms
  - Fever
  - Pain and swelling in the genitals or anal area
  - Unpleasant odor coming from the affected skin tissue
  - Crackling sound when touching the affected area

Need for Education & Awareness

Causes of Fournier's Gangrene

Fournier's gangrene usually happens because of an **infection near the genitals** including:

- Urinary tract infections/ Bladder infections
- Hysterectomies
- Abscesses
- Piercings

- **Conditions and medications that make it more** likely to get this disease, include:
- Diabetes
- Alcohol abuse
- Trauma to the genital area
- Steroids
- Chemotherapy
- HIV
- Obesity
- Cirrhosis (liver disease)
- Sodium-glucose cotransporter-2 (SGLT2) inhibitor medication use

If patient has multiple risk factors need to be all that more aware of risk

Ketosis vs DKA - Defining

- **Ketosis** results from ***restriction of carbohydrate usage*** with increased reliance on fat oxidation for energy production
  - Fasting (urine ketones usually only 1+, no ketones in blood)
  - Low Carb intake ("ketogenic diet", the Atkins diet, etc.)
  - *SGLT2 inhibitors* (Urinary glucose loss (50-100 g/day) →lowered insulin levels, SGLT2 receptor inhibition alpha cells →raised glucagon level (stimulates ketones))

- **Diabetic Ketoacidosis (DKA)** results when ***absolute insulin deficiency*** occurs in both T1D and T2D,
  - **DKA presents with**
    - ***marked hyperglycemia* (>250 mg/dL, typically 350–800 mg/dL),**
    - ***profuse glycosuria***
    - elevated ***blood ketones*** as well urinary ketones

Euglycemic DKA (euDKA) with SGLT-2 inhibitors

- **<u>euDKA</u>** due to SGLT2i is DKA except—
  - SGLT2i-induced glycosuria *"artificially" lowers plasma glucose levels*
  - SGLT2i predisposes to ***increased ketogenesis***

DKA with glucose <250 mg%

- The risk of bona fide euDKA, vs simple ketosis, in T2D related to the use of SGLT2 inhibitors is generally low
  - keto-acidosis has not been observed in *patients without diabetes* in the large SGLT2i trials
- Risk may be increased in people with diabetes if
  - ***insulin deficiency*** is more profound—as can happen in
    - T1D patients
      - In the CANVAS study, 6 out of the 12 cases of euDKA had evidence of autoimmune diabetes (latent autoimmune diabetes in adults (LADA) or T1D or tested positive for GAD65 antibodies)
    - long-standing T2D patients with marked β-cell insufficiency
  - ***carbohydrate availability*** has been drastically ***restricted***
    - during prolonged starvation (carb restriction), keto diet, after surgery, alcohol excess, or during intercurrent illness (and colonoscopy prep) [recommend hold SGLT2i pre-procedure, not eating]

Annals of Internal Medicine 20 AUGUST 2019

Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study

Chintan V. Dave, PharmD, PhD et al

- Objective: To assess whether patients initiating use of SGLT-2 inhibitors were at increased risk for severe UTI events compared with those initiating use of dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor (GLP-1) agonists
  - SGLT-2 inhibitors **were not associated with increased risk for outpatient UTIs**
- Conclusion: In a large cohort of patients seen in routine clinical practice, **risk for severe and non-severe UTI events among those initiating SGLT-2 inhibitor therapy was similar to that among patients initiating treatment with other second-line antidiabetic medications.**

"SGLT2is do not increase the risk of UTIs; however, their use in patients at high risk for UTIs, such as those with an indwelling Foley catheter, recurrent UTIs, or neurogenic bladder, has not been studied." Kidney 360 April 2021

Safety of Empagliflozin in Patients With Type 2 Diabetes and Chronic Kidney Disease: Pooled Analysis of Placebo-Controlled Clinical Trials

Katherine R. Tuttle et al Diabetes Care 2022;45(6):1445–1452

- No significant increase in **ARF (AKI), volume depletion, bone fracture or lower limb amputations**

- Comment from combined **ADA – EASD consensus paper-** reassuring …. *"While early studies brought attention to several safety areas of interest (acute kidney injury, dehydration, orthostatic hypotension, amputation, and fractures),* ***longer-term studies*** *that have prospectively assessed and monitored these events* ***have not seen a significant imbalance in risks."***
    - Analyses of SGLT2i outcome trial data also suggest that people with **type 2 diabetes and peripheral arterial disease** derive **greater absolute outcome benefits** from SGLT2i therapy than those without peripheral arterial disease, ***without an increase in risk of major adverse limb events.*** (caution in patients with high-risk feet)
    - In post hoc analyses, SGLT2i use has been associated with ***reduced incidence of serious and nonserious kidney-related adverse events*** in people with type 2 diabetes and CKD and ***greater full recovery from acute kidney injury***.

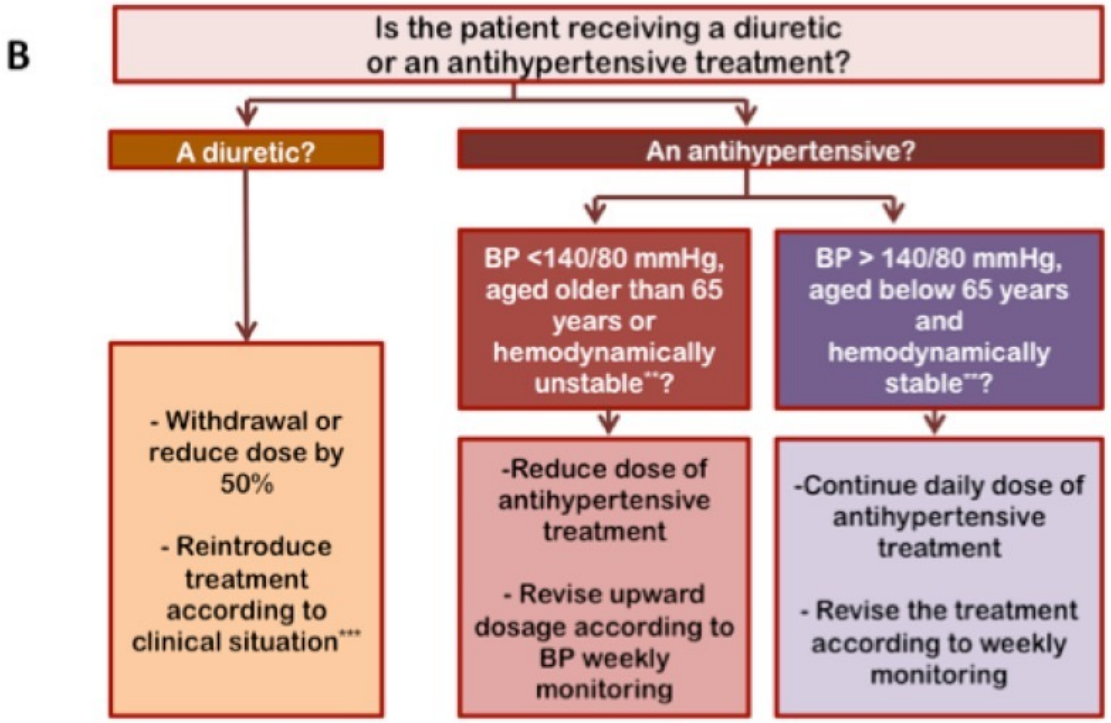
Consider the Patient's BP & Volume Status before Initiating SGLT2i

- Guide from Kidney 360 April 2021
  - If the patient is **hypotensive/hypovolemic**, then SGLT2is must not be initiated
    - In patients who are hypotensive, the antihypertensive medications, including diuretics, may need to be stopped or reduced to restore normotension.
  - If the patient is **hypervolemic/hypertensive**, then SGLT2i therapy can be initiated without adjusting the dose of other antihypertensive medications.
  - If the patient is **euvolemic/normotensive** then the *antihypertensive agents*, including *diuretics*, *may need to be reduced or stopped* if the BP decreases.

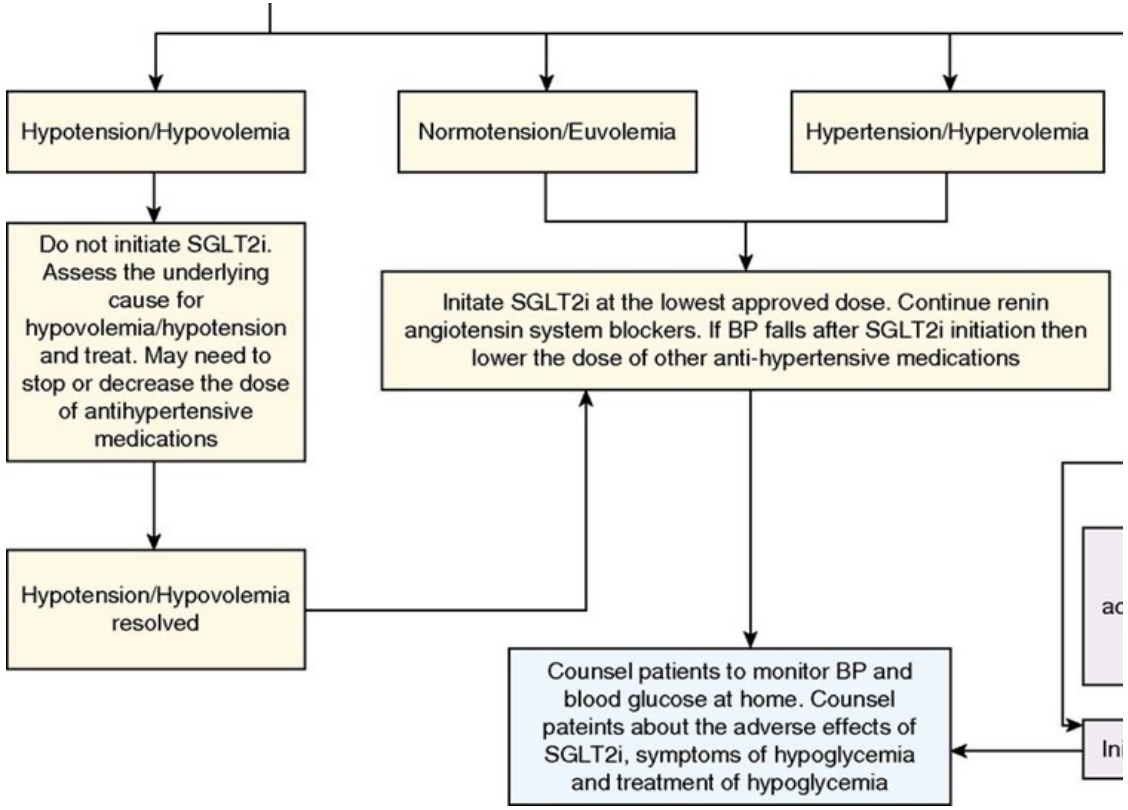
  - In the SGLT2i CV and kidney outcome trials, patients were required to be on the ***maximally tolerated dose of renin-angiotensin system (RAS) blockers*** **-** A similar strategy to continue RAS blockers must be adopted in clinical practice.

  - ***Monotherapy with SGLT2i*** is reasonable in patients who *are unable to tolerate RAS blockers.*

Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes
Diabetes Ther. 2017 Oct; 8(5): 953–962.



Kidney 360



Based on survey done by NKF

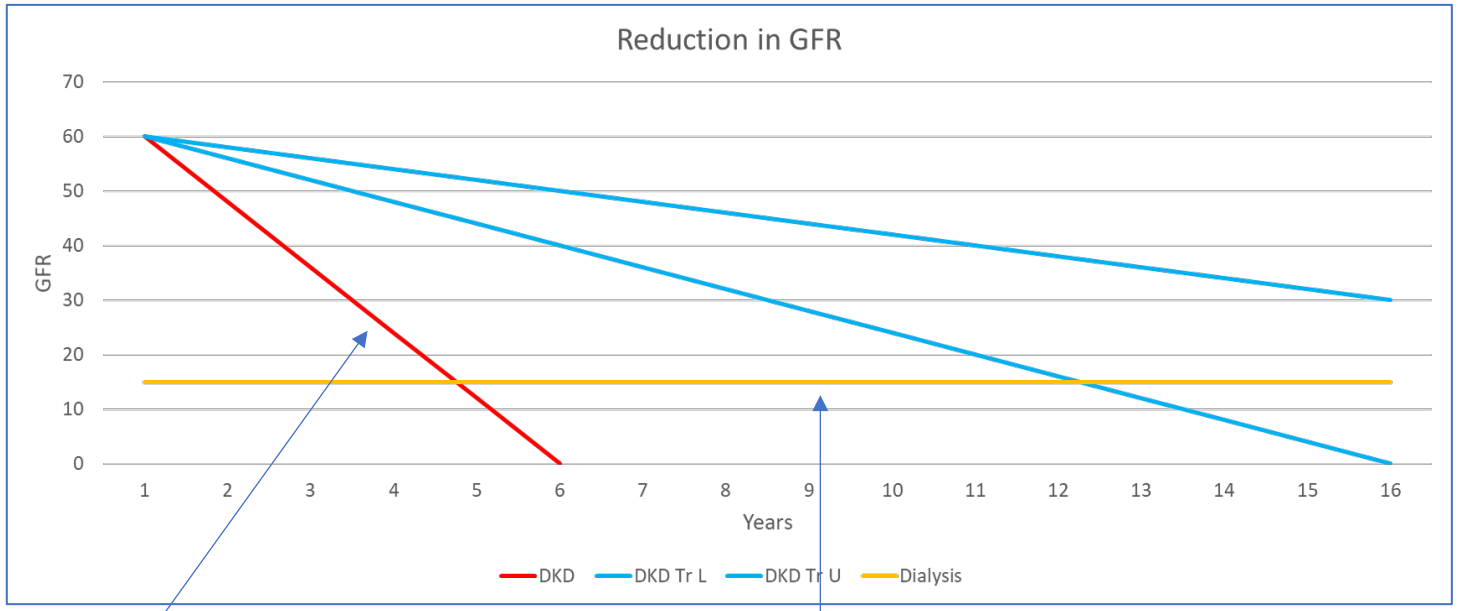
- Physicians/ HCPs might consider initiating **risk vs. benefit conversations with patients** when prescribing a new medication to slow disease progression.
  - In order of importance, patients considered the **most critical factors in the decision** of taking a new medication
    - the severity of known adverse events (60.6% very important),
    - the cost or insurance (57.9% very important)
    - **what their doctor recommends** (55.4% very important)
  - Patients were least concerned about how often they would have to take the medication.

Are you comfortable having that conversation?

Explaining the benefits along with precautions – answering questions

Utilize team-based care

Slowing Down the Loss of Kidney Function with Diabetes Kidney Disease



This is how quickly your kidneys will lose function without any treatment

The yellow line is the level where you need to start dialysis

The aqua lines show how much treatment can reduce the rate at which your kidneys lose function

Treatment includes

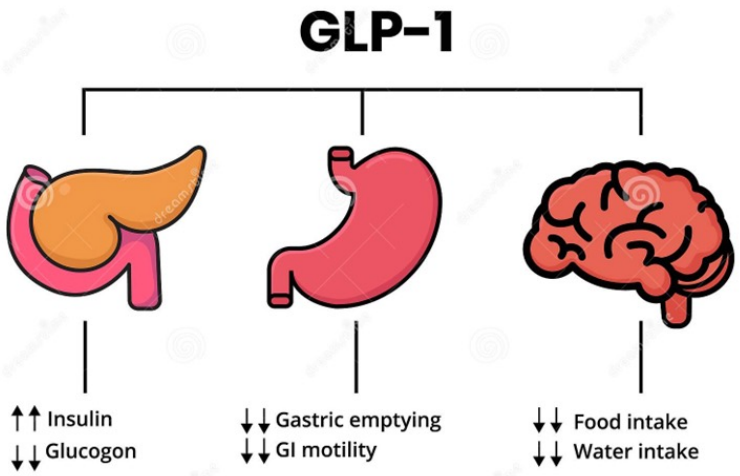
- Optimal blood pressure, using an ACEI or ARB medication along with other meds if needed
- An SGLT2 inhibitor medication (and/or a GLP1 RA or MRA)
- Blood glucose levels in individualized safe range
- Avoiding drugs that hurt your kidneys such as NSAIDs (ibuprofen, Advil, Motrin, etc.)
- Keeping your muscles strong, avoiding being too sedentary
- Healthy food choices – especially, avoid excess animal protein & fats

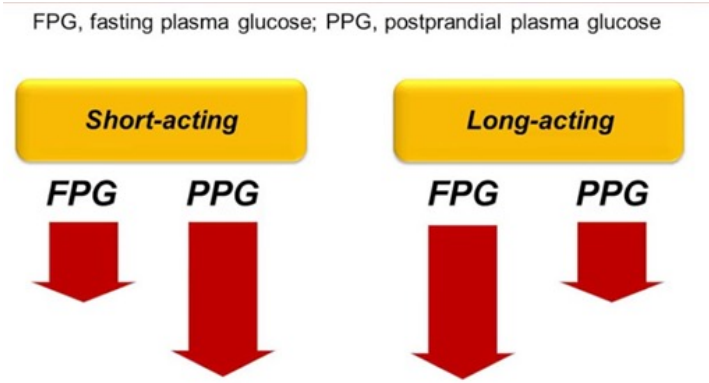
Handout for the Patients when initiating SGLT-2 Inhibitor Therapy

- Increase in Urine Output
  - You may notice an increase in your urine output after starting this medication
  - Monitor your weight at home
- Blood Pressure
  - Monitor your blood pressure at home as this medicine may lower blood pressure
  - Inform your doctor if your blood pressure is too low, or if you experience lightheadedness or dizziness
- Blood Glucose
  - Monitor your blood glucose level at home as this medicine may lower blood glucose
  - Inform your doctor if your blood glucose is low
- Redness or itching in the genital area, or foul smelling vaginal or penile discharge
  - Keep the genital area clean
  - If you notice redness or itching in the genital area, or foul-smelling vaginal or penile discharge, then inform your doctor. You may need a cream or oral medication to treat an underlying infection
- Follow the 'Sick Day Rule'
  - On days that you are unable to eat because you are feeling sick due to fever, infection, poor appetite, nausea, vomiting or diarrhea then hold this medicine.
  - You can resume the medicine once you are able to eat and drink.
  - If you continue to feel sick, then call your doctor as you may need to have blood tests to rule out Diabetic ketoacidosis
  - Stop the medication 3 to 4 days before a scheduled surgery that requires you to be NPO (meaning you are instructed to not eat or drink anything for several hours before your surgery) (including colonoscopy)
  - Avoid very low Carbohydrate diet and Keto diet as it may increase the risk of Diabetic Ketoacidosis
- Wound on your feet or legs
  - If you notice a wound, ulcer or skin breakdown on your feet or legs, then hold this medicine and inform your doctor
- Burning or pain during urination
  - If you experience pain or burning on urination, then inform your doctor as you may need further evaluation

GLP1 Receptor Agonists

- Dulaglutide (Trulicity) (weekly)
- Exenatide extended release (Bydureon) (weekly)
- Exenatide (Byetta) (twice daily) (not available)
- Semaglutide (Ozempic, Wegovy) (weekly)
- Liraglutide (Victoza, Saxenda) (daily)
- Lixisenatide (Adlyxin) (daily) (removed in US)
- Semaglutide (Rybelsus) (taken by mouth once daily)





ADA 2023 Standards of Care
Pharmacotherapy for Type 2 Diabetes

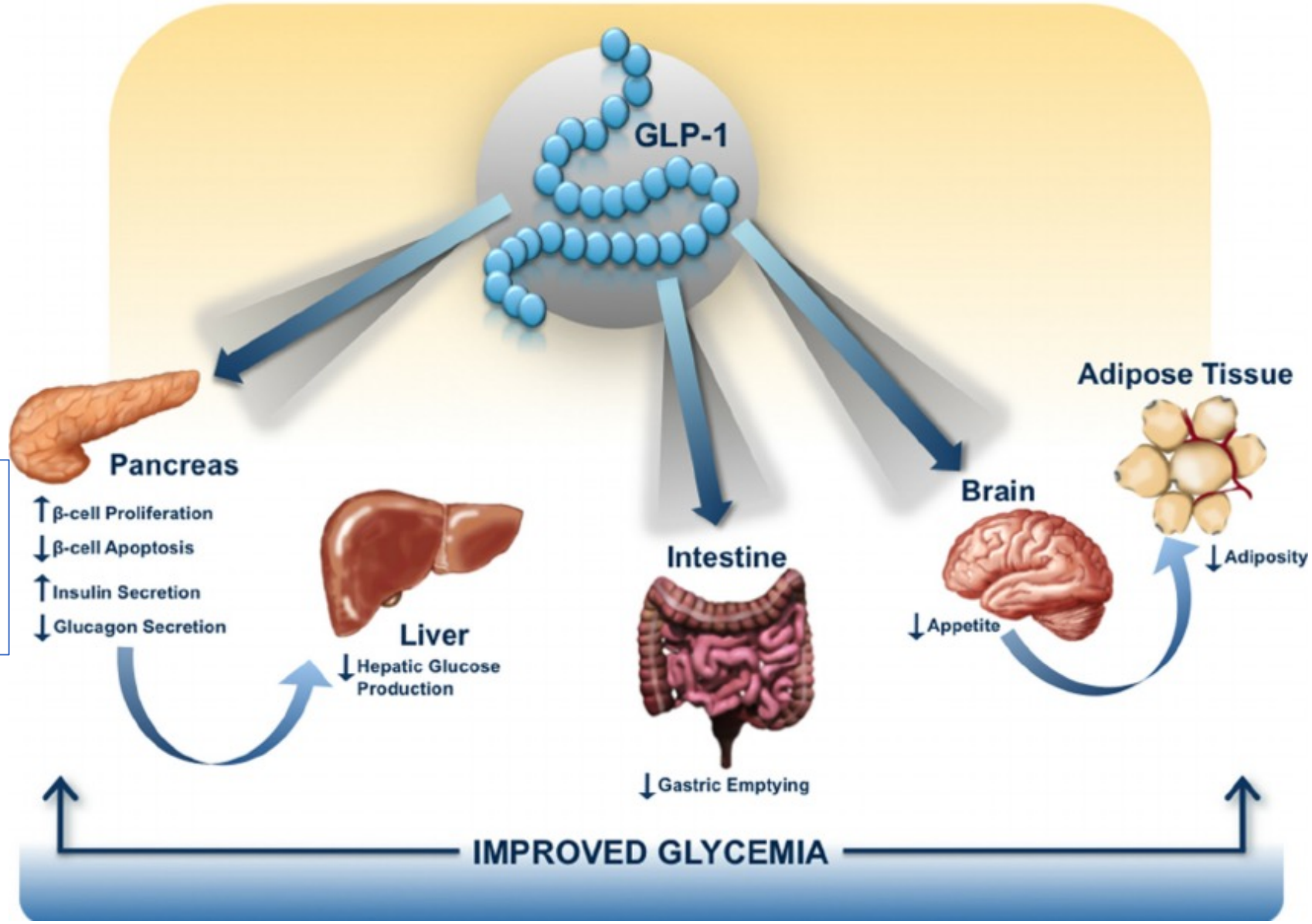
- 9.9 Among individuals with type 2 diabetes who have
  - established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk,
  - established kidney disease, or
  - heart failure,

a **SGLT2i** and/or **GLP1 RA** with *demonstrated cardiovascular disease benefit** is recommended as part of the ***glucose-lowering regimen*** and ***comprehensive cardiovascular risk reduction***, *independent* of A1C and in consideration of person-specific factors

- *liraglutide, semaglutide (SQ) & dulaglutide
- Demonstrated CVD benefit, some renal benefit (albuminuria) – trials ongoing
- No dose adjustment for renal impairment
- Glycemic benefit even at reduced GFR (unlike SGLT2i)
- Combination therapy with SLGT2i & GLP1 RA appears to have additive CVD protection
- Do not cause hypoglycemia (may result in lower requirements for insulin or SU meds)

GLP1 Receptor Agonists effect on Glycemia

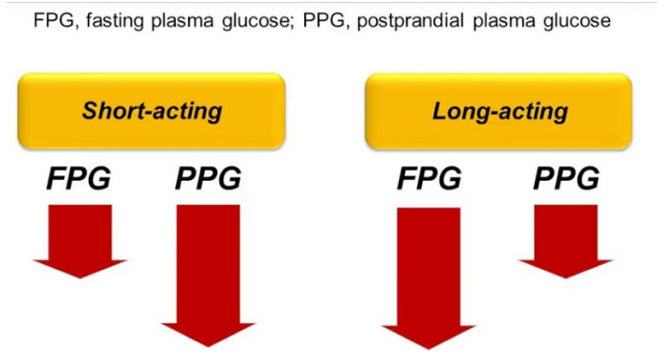
Glucose-dependent insulin secretion

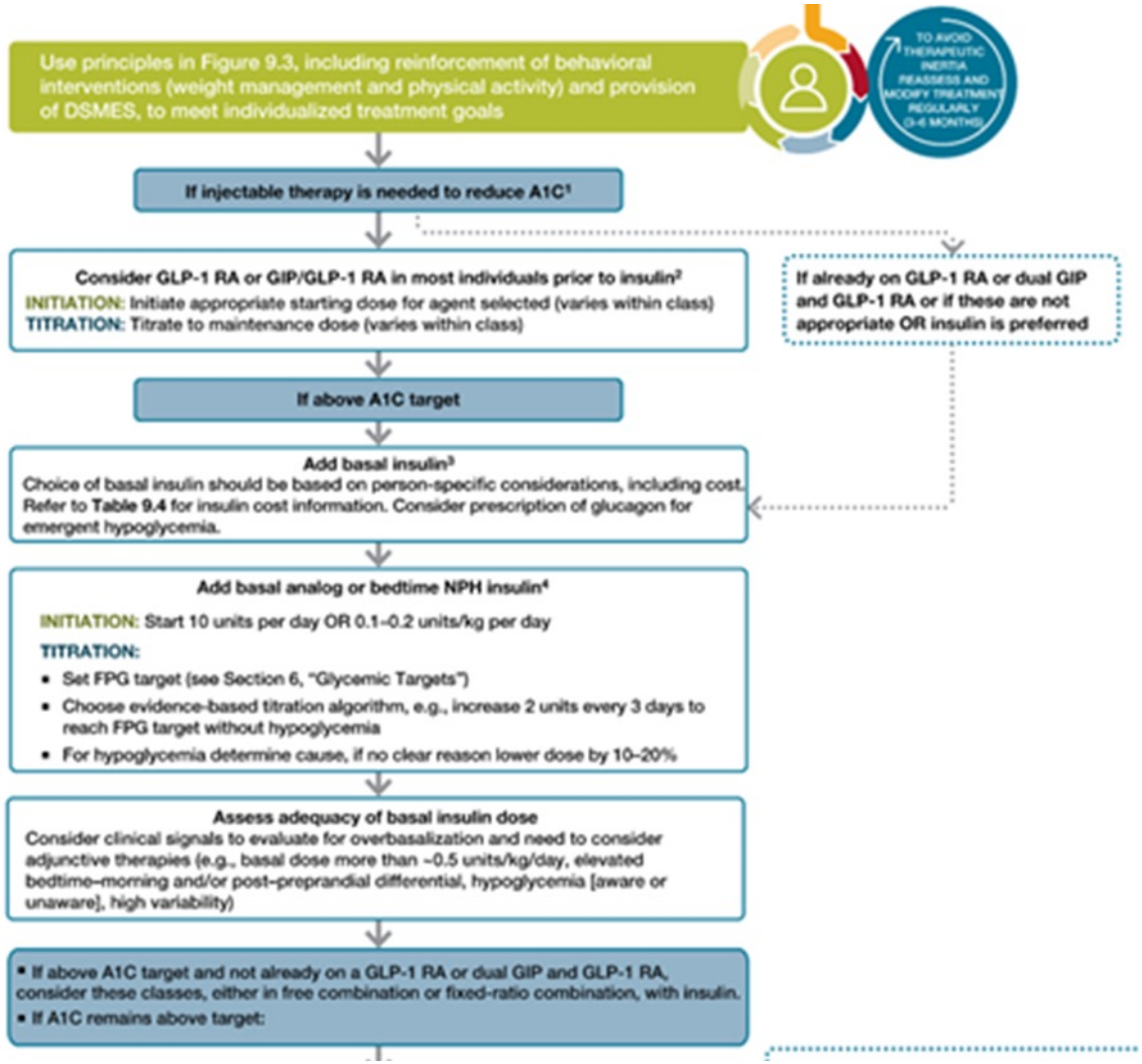


ADA 2023 Standards of Care
Pharmacologic Therapy for Adults with T2D

- 9.10 In patients with T2D, a **GLP1 RA is preferred to insulin** when possible. A

- 9.11 If insulin is used, ***combination with a GLP1 RA*** is recommended for greater efficacy and durability of treatment. A





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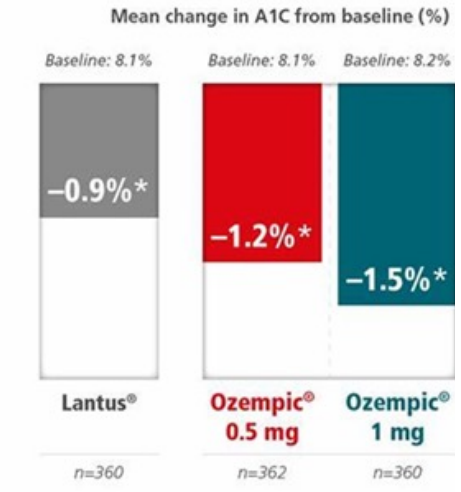
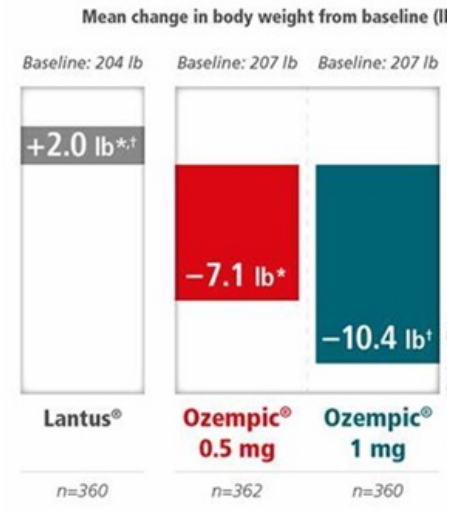
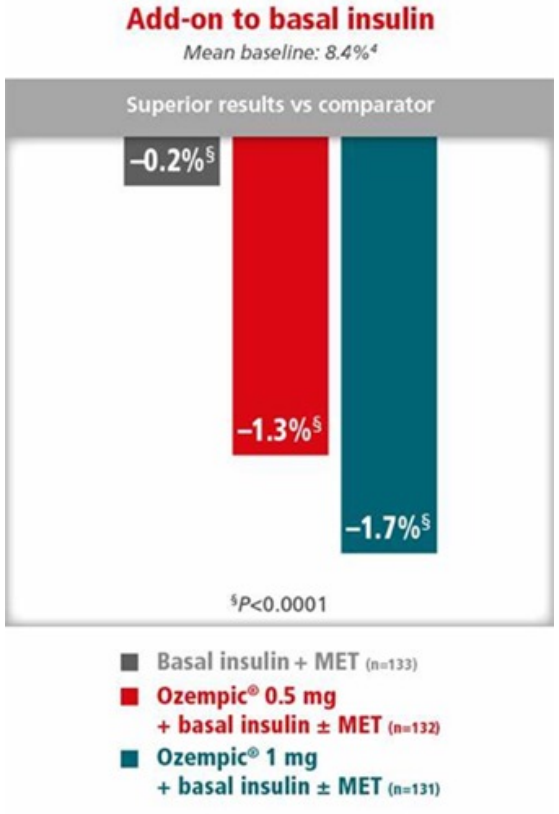






Insulin titrated to target - limited by hypoglycemia

GLP1 RA medications

- A1c reduction 0.8 to 1.6% (0.5-2.0%)
- Most are weekly SQ injections, one oral med
  - Long-acting GLP-1 analogues should be taken on or around the same day each week
    - Short acting GLP1 RA have been largely withdrawn from market (low market share)
  - No dose reduction in patients with mild, moderate, or severe renal impairment (estimated glomerular filtration rate 15–89 mL/min/1.73 m2)
    - Except for Exenatide (Bydureon) – should not be used with severe renal impairment (eGFR <30 mL/min) or ESRD and should be used with caution in patients with moderate renal impairment

GLP1 RA medications

- Most common side effects are GI (nausea, vomiting, diarrhea)
  - Initiate therapy with the lowest dose & titrate *slowly* to avoid GI side effects
    - Okay to back down on dose/remain on lower dose if tolerated (nausea is dose-dependent)
    - Most GI side effects diminish over time
    - Long-acting GLP-1 RAs linked to less nausea and vomiting but more diarrhea than the short-acting GLP-1 drugs
    - Down titrate doses of insulin , sulfonylureas to avoid hypoglycemia
    - Counsel patients to stop medication with severe nausea, vomiting and diarrhea to avoid dehydration & potential Acute Kidney Injury (AKI)
  - For a patient who does not tolerate one GLP-1 agonist, another might be tried.
  - Use of metformin is associated with more nausea and vomiting in those taking GLP-1 receptor agonists – consider reducing the dose of metformin
  - Counsel patients on how to adjust diet after initiation

Counselling on nausea & diet (foods & volume)

- What some patients describe as nausea is more accurately described as a bloated feeling or a sense of gastric *fullness* after eating, most likely related to delayed gastric emptying.
  - Also just not feeling hungry (satiety or anorexia) can be confused with nausea
- There appears to be an association between nausea during GLP-1 RA therapy and both the ***fat*** content and ***size of meals***;
  - limiting or avoiding greasy, fatty or fried foods and eating smaller portions at mealtimes may help to prevent the feeling of nausea.
  - also limit soda (fizzy beverages) and foods such as onions, peppers (select more bland foods)
  - patients should be encouraged to eat slowly while undistracted and to pay careful attention to the amount and the pace at which that they eat.
    - Patients might be told **to eat less and to eat slower than they ever have before.**
    - **STOP EATING when feel full (satiety).**
- Patients may obtain some relief from nausea by consuming ginger (e.g., fresh ginger, ginger tea), soda crackers, or rice crackers. Slowly sipping hot water or sucking on sugar-free mints also may ease nausea.
  - Pharmacologic options are rarely needed.

GLP1 RA medications – Precautions

- Do not use in patients with history of pancreatitis or known pancreatic dysfunction (some exceptions – e.g., consider resume following cholecystectomy)
  - Not clear if cause pancreatitis – caution
  - Not associated with pancreatic cancer
- Avoid in patients with gastroparesis and untreated gall bladder disease
- Do not use in personal or family history significant for multiple endocrine neoplasia 2A, multiple endocrine neoplasia 2B, or medullary thyroid cancer
  - Unlikely association with the more common non-medullary thyroid cancer (poorly done study)
- Monitor patients with severe retinopathy closely when on semaglutide and dulaglutide (rapid improvement in glycemia can accelerate DR)
- Do not use with DPP-4 inhibitors – no benefit just cost and burden
  - Stop the DPP-4i when start GLP1 RA

Persistence with GLP1 receptor agonist therapy

Continuers

- Perceived treatment efficacy
  - Glycemia
  - Weight loss
  - *"The knowledge of the cardiovascular benefit helped me stay on the GLP-1 [receptor agonist]."*
- Perceived treatment burden
  - Cost/insurance coverage
  - Ease of use
- Relevant information from healthcare team
  - explained that GLP-1 receptor agonist therapy would improve my blood glucose control [and other benefits]
  - explained the importance of **gradual dosage titration**
  - explained **how to manage food volume and fats**
    - [stop eating when feel full/ satiety – also bland foods, avoid carbonation & fatty or greasy foods]
  - my questions were answered by my health care team when I started on GLP-1 receptor agonist therapy.
  - I was provided information about GLP-1 receptor agonist medications.
  - my physician's office called to check on my progress and ask if I had any additional questions.

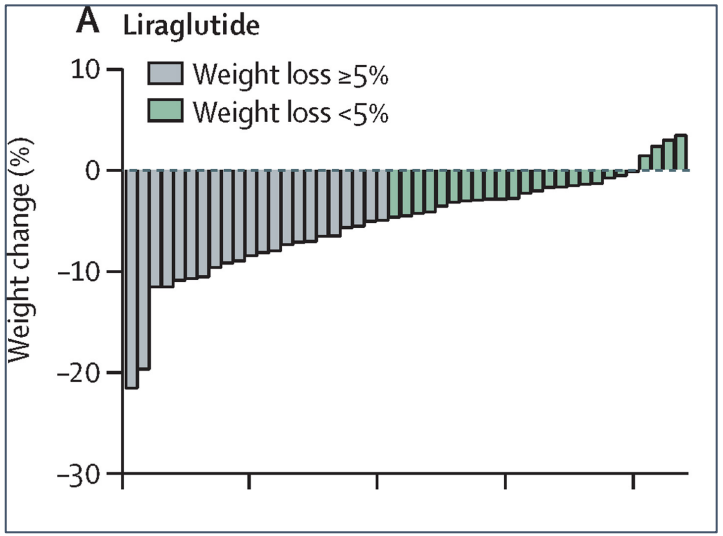
Discontinuers

- Side Effects (GI, injection site)
- Cost
- Lack of benefit
  - **therapeutic heterogeneity**: *"lack of glycemic improvement, lack of weight loss, and/or intolerability of side effects may simply be an unmodifiable class effect in some participants, which could explain why 25.0% of discontinuers reported 'numbers did not improve' as their primary reason for discontinuation"*
- Less likely to receive relevant information from healthcare team

Continuers were more likely than discontinuers to **receive clinically relevant information from their health care team**, including facts about GLP-1 receptor agonist medications, likely treatment benefits, the importance of gradual dose titration, and the need to adjust diet after initiation.

Therapeutic Heterogeneity
(not everyone responds the same)

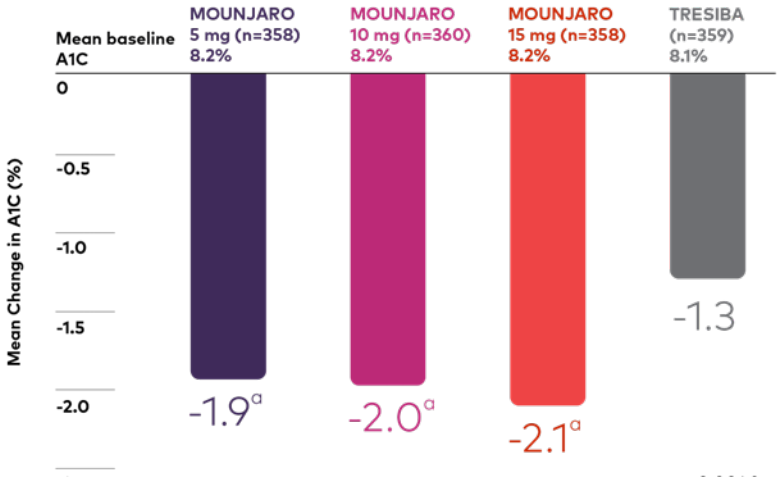
- Based on our individual make-up, some things work better or not as well for some of us- this includes:
  - Type of foods/meal plan (low fat, low carb, low glycemic index, intermittent fasting, etc.)
    - Glucose lowering
    - Weight loss
  - Exercise (aerobic, strength training)
    - Glucose lowering
    - Weight loss
    - Fitness
  - Medications
    - for example, the research reports the average A1c lowering or weight loss with a medication but in the test group of patients, some had a greater than average response and some had less than average or worsening



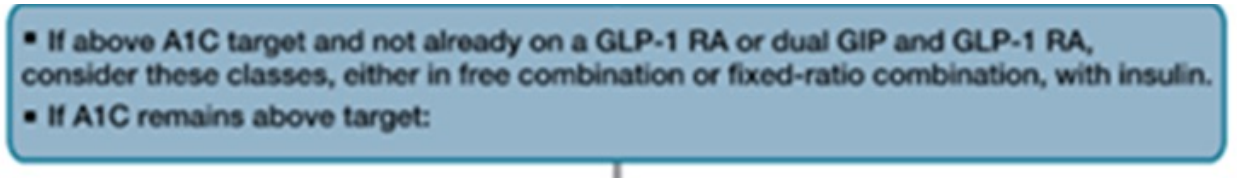
DUAL GLP1 and GIP RA - tirzepatide

GLP-1 & GIP Receptor Agonists

Class/Main Action	Name	Dose Range	Considerations
GLP-1 RA - Glucagon Like Peptide Receptor Agonist **"Incretin Mimetic"** • Increases insulin release with food • Slows gastric emptying • Promotes satiety • Suppresses glucagon	exenatide (Byetta)	5 and 10 mcg BID	**Side effects for all:** Nausea, vomiting, weight loss, injection site reaction. Report signs of acute pancreatitis (severe abdominal pain, vomiting), stop med. Increase dose monthly to acheive targets. **Black box warning:** Thyroid C-cell tumor warning (avoid if family history of medullary thyroid tumor). *Significantly reduces risk of CV death, heart attack, and stroke. †Approved for pediatrics 10-17 yrs Lowers A1c 0.5 – 1.6% Weight loss of 1.6 to 6.0 kgs
	exenatide XR† (Bydureon)	2 mg 1x a week Pen injector - Bydureon BCise	
	liraglutide (Victoza)*†	0.6, 1.2 and 1.8 mg daily	
	dulaglutide* (Trulicity)	0.75, 1.5, 3.0 and 4.5 mg 1x a week pen injector	
	lixisenatide (Adlyxin)	10 mcg 1x a day for 14 days 20 mcg 1x day starting day 15	
	semaglutide* (Ozempic)	0.25, 0.5, 1.0 and 2.0 mg 1x a week pen injector	
	(Rybelsus) Oral tablet	3, 7, and 14 mg daily in a.m. Take on empty stomach w/H2O sip	
GLP-1 & GIP Receptor Agonist Activates receptors for GLP-1 (see above) & Glucose-dependent Insulinotropic Polypeptide (GIP).	Tirzepatide (Mounjaro)	2.5, 5.0, 7.5, 10, 12.5 and 15 mg 1x a week prefilled single dose pen Increase dose by 2.5 mg once monthly to reach targets.	**Side effects include:** Nausea, diarrhea, injection site reactions. Avoid if family history medullary thyroid tumor. Report pancreatitis or acute gallbladder problems. Lowers A1C ~ 1.8 - 2.4% Weight loss of ~ 5.4 – 10 kgs



Adding GLP1 RA or Dual GIP & GLP1 RA if already on Basal or Basal-Bolus Insulin



- Studies show that the ***addition of a GLP-1 RA to basal insulin*** results in
  - *equal or slightly superior efficacy* compared to the addition of prandial insulin,
  - *weight loss*
  - *less hypoglycemia*

- If on ***Basal-Bolus insulin: introduction of a once-weekly GLP-1RA*** with ***planned cessation of prandial insulin*** can
  - *improve glucose control* to near normoglycemia with
  - *substantially less insulin*
  - *fewer injections*
  - *less hypoglycemia*
  - *reduced body weight*

How to transition dosing when adding a GLP1 RA or Dual RA to Basal-Bolus Insulin

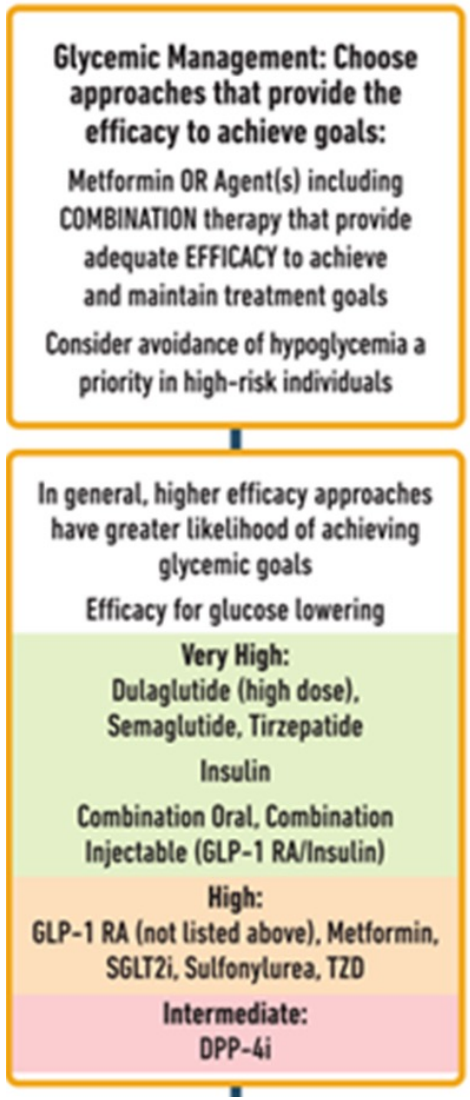
- Based on study with albiglutide (no longer on market)
- Start with the lowest (initial) dose of the weekly GLP1 RA and reduced lispro insulin (or other mealtime insulin) doses to ½ at same time
- At 4 weeks increased GLP1 RA to next higher weekly dose & discontinued lispro insulin injections
  - Continue to titrate up to the maximum tolerated weekly dose of GLP1 RA
  - Titrate (reduce or increase) basal insulin based on glucose monitoring results
- At 8 weeks or 4 weeks after final titration – add back in lispro/mealtime insulin if postprandial BGs were averaging >180
  - May only need with one meal

Selecting for Efficacy & Lower Risks

- Most of the earlier GLDs associated with the adverse effects of
  - weight gain
  - hypoglycemia

  } Additional adverse effects
  - Increased care needs
  - Increased costs

- More effective & safer treatments
  - Easier on the patient
  - Easier on the clinician
  - Easier on the system

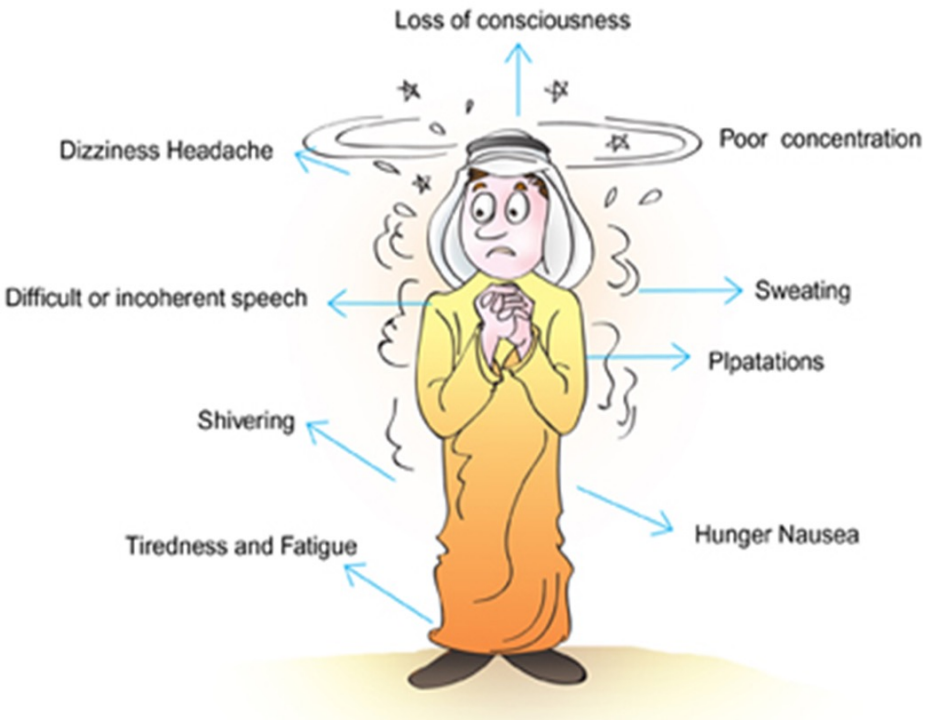


Hypoglycemia (Low Blood Sugar)

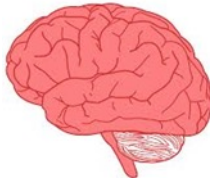
- **Level 1 hypoglycemia** is defined as a measurable glucose concentration <70 mg/dL but ≥54 mg/dL.
  - A blood glucose concentration of 70 mg/dL has been recognized as a threshold for ***neuroendocrine /neurogenic responses***
- **Level 2 hypoglycemia** (defined as a blood glucose concentration <54 mg/dL)
  - This is the threshold at which ***neuroglycopenic symptoms*** begin to occur and requires immediate action to resolve the hypoglycemic event.
- **Level 3 hypoglycemia** -A severe event characterized by altered mental and/or physical status ***requiring assistance*** for treatment of hypoglycemia
  - may be recognized or unrecognized and can progress to ***loss of consciousness, seizure, coma, or death***.

- In people without diabetes – hypoglycemia defined as BG <55 with signs & symptoms that resolve when BG increased by treatment (can be due to tumors, dumping syndrome, etc.)

Neurogenic response ➡ Neuroglycopenia

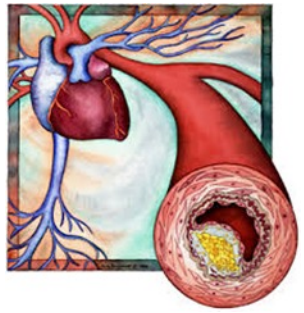


Hypoglycemic Effects

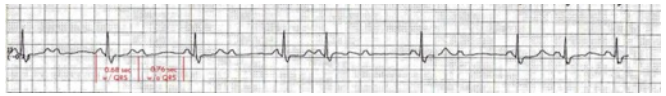


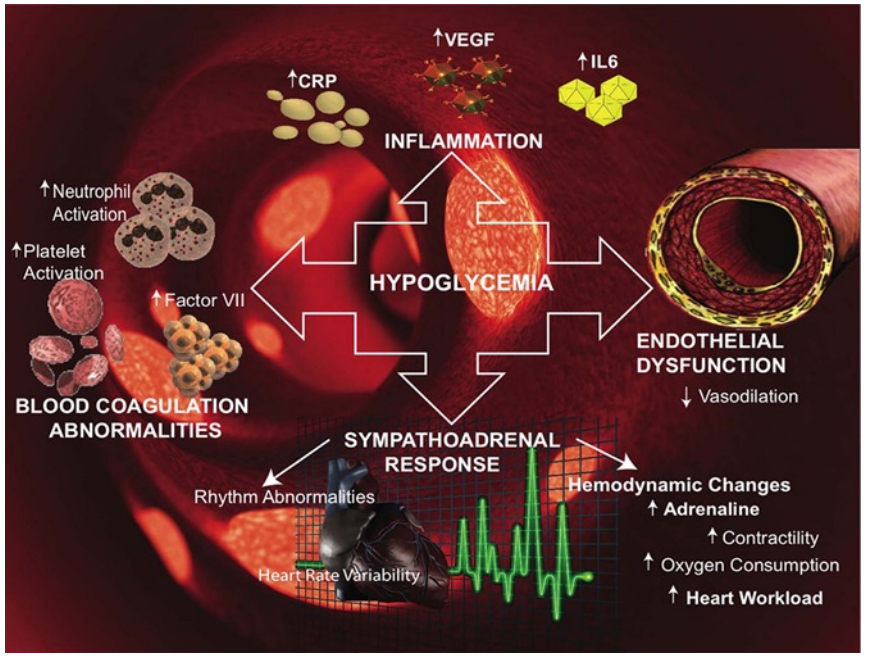
- Neurocognitive effects
  - cognitive effects & impairment, coma, brain dead, dementia

- Increased falls and trauma
  - Impaired driving/ accidents
  - Fractures, lacerations, Traumatic Brain Injury



- Increased CVD and Mortality
  - Acute Ischemia
  - Atherogenic effects
    - Pro-inflammatory/ Pro-coagulant
    - Greater at BG 50 than BG 200;
    - Elevated for >7-8 days after event
  - Arrhythmogenic effects
    - “ Dead in bed”





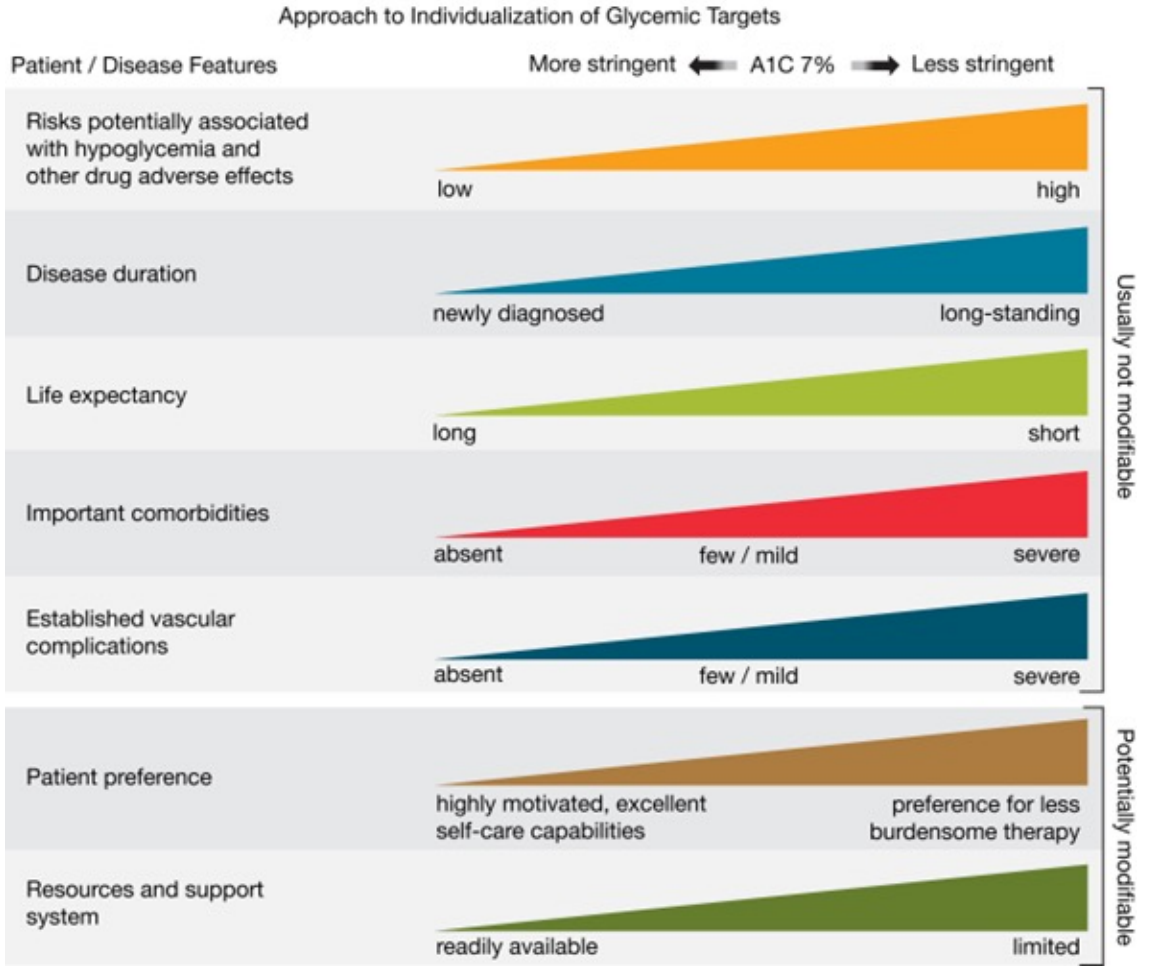
The goal of diabetes care is to help our patients with diabetes stay healthy

– Reduce complications & improve outcomes

Diabetes – Goal of Therapy

A1c Glucose sticking to RBC	Fasting Blood Glucose (not eat for 8 hrs)	Postprandial Blood Glucose (after eating a meal)
< 7 %	90 – 130 mg/dl	< 180 mg/dl

- Diet
- Exercise
- Medication



Med Costs – from ADA 2023 Standards of Care

			Median AWP	Median NADAC	
-4 inhibitors	• Alogliptin	25 mg	$234	$154	25 mg
	• Saxagliptin	5 mg	$565	$452	5 mg
	• Linagliptin	5 mg	$606	$485	5 mg
	• Sitagliptin	100 mg	$626	$500	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$390	$312	15 mg
	• Dapagliflozin	10 mg	$659	$527	10 mg
	• Canagliflozin	300 mg	$684	$548	300 mg
	• Empagliflozin	25 mg	$685	$547	25 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$936	$726	2 mg**
	• Exenatide	10 µg pen	$961	$770	20 µg
	• Dulaglutide	4.5 mg mL pen	$1,064	$852	4.5 mg**
	• Semaglutide	1 mg pen	$1,070	$858	2 mg**
		14 mg (tablet)	$1,070	$858	14 mg
	• Liraglutide	1.8 mg pen	$1,278	$1,022	1.8 mg

Summary – Key Points

- Since 2008, all new diabetes GLD have been subject to CVOTs
- Results of these trials have demonstrated **non-glycemic cardio-renal benefits** in addition to glycemic benefits for some of the **SGLT2i & GLP1 RA** medications
- New treatment guidelines now recommend taking advantage of these non-glycemic benefits to help ***reduce ASCVD risk, progression of renal disease and heart failure risk in patients with T2D***
  - For some patients this means selecting one of these medications when attempting to improve glycemia to provide both glycemic & non-glycemic benefits
  - For other patients, these meds are recommended to be added for the non-glycemic (risk reduction) benefit even if additional glycemic benefit is not needed or not possible (e.g., SGLT2i added when eGFR is <30)
- Medications that more effectively and safely lower blood glucose can ***reduce treatment burden*** for the patient, the clinical care team and the overall system.
  - If the medication also improves other factors, there is added benefit, less need for additional medications and improved outcomes.


Questions?
Comments?
Suggestions?

Extra Slides, Resources and References

Some references

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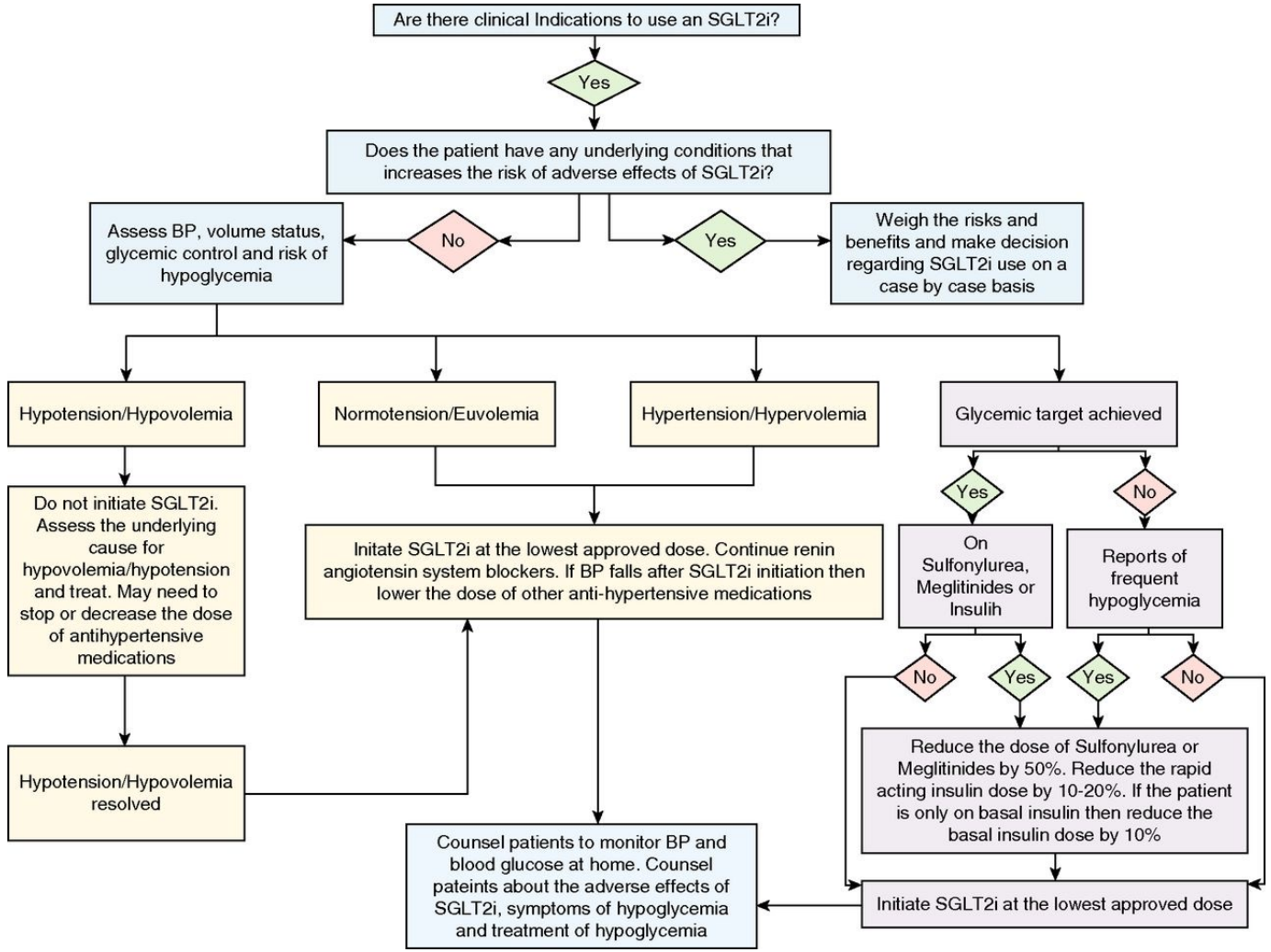
- Treatment Response to SGLT2 Inhibitors: From Clinical Characteristics to Genetic Variations - PMC (nih.gov)
- SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects - PMC (nih.gov)
- https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment
- Davies, M.J., Drexel, H., Jornayvaz, F.R. et al. Cardiovascular outcomes trials: a paradigm shift in the current management of type 2 diabetes. Cardiovasc Diabetol 21, 144 (2022). https://doi.org/10.1186/s12933-022-01575-9
- Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association | Diabetes Care | American Diabetes Association (diabetesjournals.org)
- Review Curr Med Res Opin 2018 Jan;34(1):1-10
  Adding Prandial GLP-1 Receptor Agonists to Basal Insulin: A Promising Option for Type 2 Diabetes Therapy Ronald M Goldenberg, Lori Berard

References

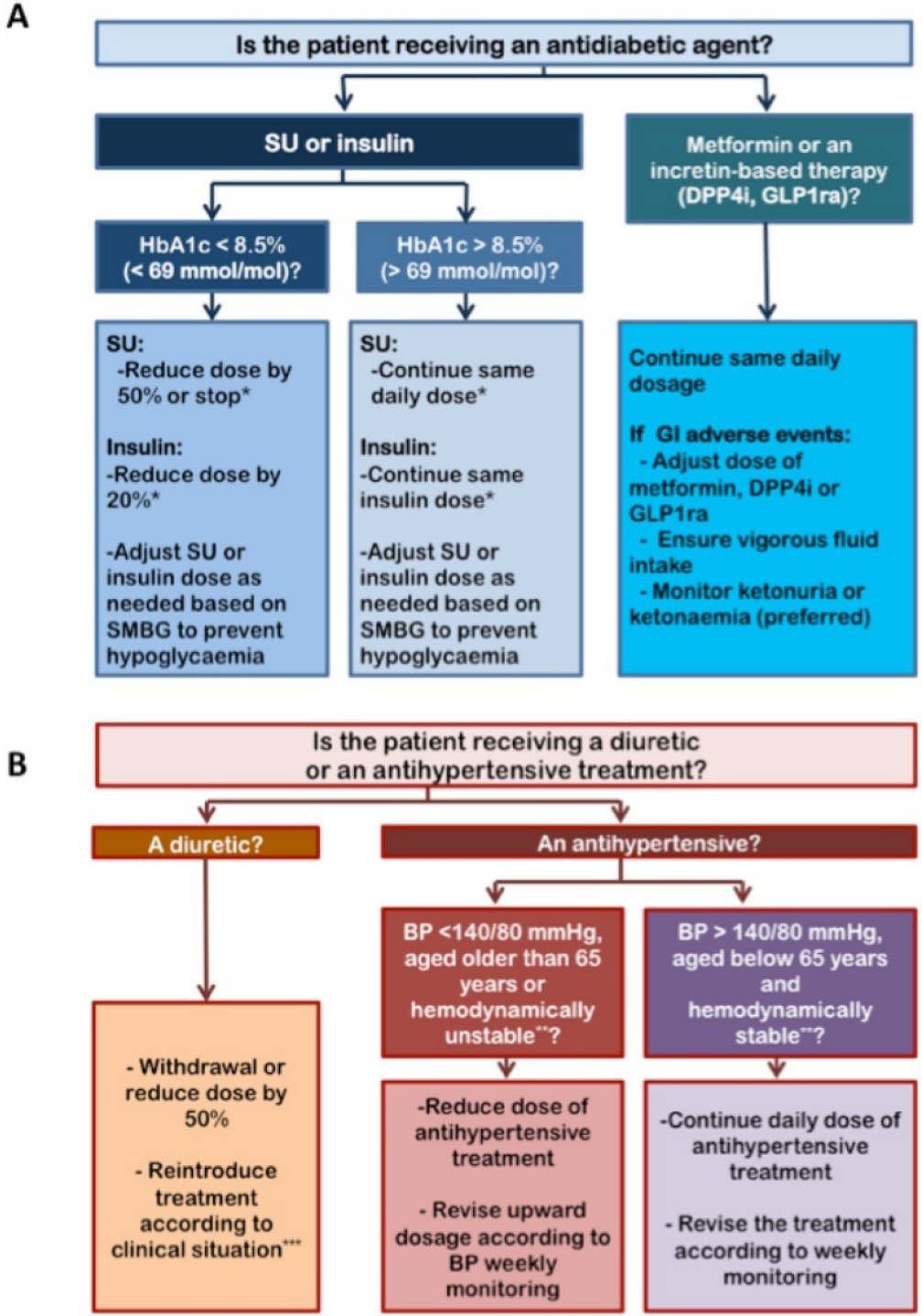
- https://kidney360.asnjournals.org/content/2/4/742 (very good review of SGLT2i meds & side effects)
- ADA Standards of Care 2023: https://diabetesjournals.org/care/article/46/Supplement_1/S191/148040/11-Chronic-Kidney-Disease-and-Risk-Management
- https://diabetesjournals.org/care/article/45/11/2753/147671/Management-of-Hyperglycemia-in-Type-2-Diabetes
- In Depth Article (also available as 2-hour Webinar) Expert Insights for Primary Care Physicians in Managing Chronic Kidney Disease in T2DM (medscape.org)
- Article on eGFR using Cr and/or cystatin https://www.aacc.org/cln/articles/2016/april/cystatin-c-and-creatinine-complementary-markers-of-gfr-expert-john-c-lieske-md
- Review Diabetes Obes Metab. 2019 Jun;21(6):1291-1298. doi: 10.1111/dom.13670. Epub 2019 Mar 15.Uric acid and the cardio-renal effects of SGLT2 inhibitors Clifford J Bailey PMID: 30762288 DOI: 10.1111/dom.13670
- K+ : https://academic.oup.com/ckj/article/14/5/1396/5900434
- https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf
- Serum Cystatin C for Estimation of GFR | Chronic Kidney Disease | JAMA | JAMA Network
- https://www.kidney.org/professionals/kdoqi/gfr_calculator

Algorithm to assess BP, volume status and glycemic control at the time of sodium-glucose cotransporter-2 inhibitor (SGLT2i) initiation.



David Lam, and Aisha Shaikh Kidney360 2021;2:742-746

Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes
Diabetes Ther. 2017 Oct; 8(5): 953–962.



From: **Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association**

Diabetes Care. 2022;45(7):1670-1690. doi:10.2337/dci22-0014

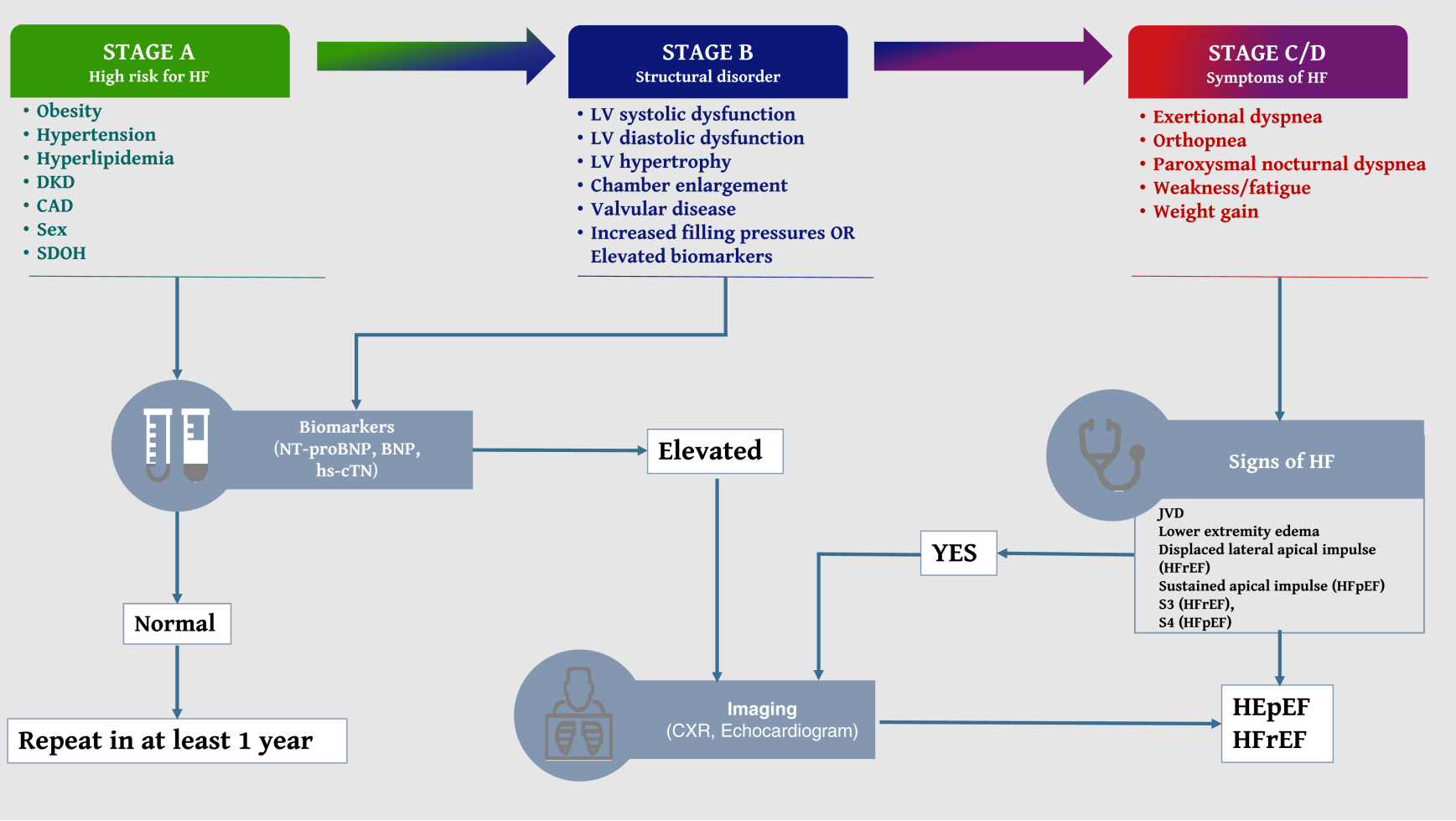


Figure Legend:

Stepwise approach for screening and diagnosis across HF stages. CXR, chest X-ray; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTN, high-sensitivity cardiac troponin; JVD, jugular vein distension; LV, left ventricle.

From: **Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association**

Diabetes Care. 2022;45(7):1670-1690. doi:10.2337/dci22-0014

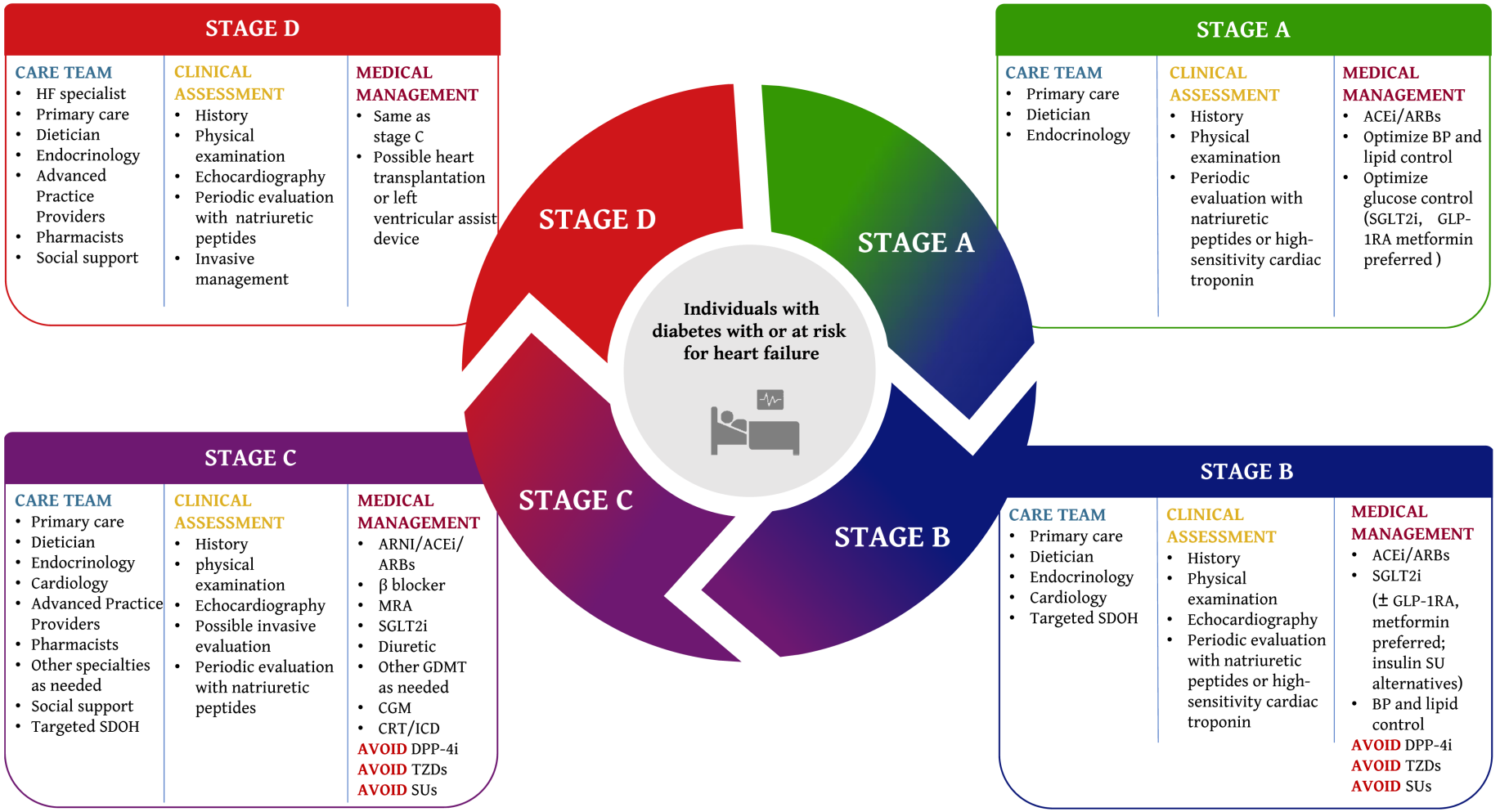


Figure Legend:

Multidisciplinary personalized care for in individuals with HF and diabetes. DPP-4i, DPP-4 inhibitors; SUs, sulfonylureas.

ADA: within the constraints of renal dosing *"metformin should be considered the first-line treatment for all patients with T2D, including those with CKD."* [survival benefit seen with metformin]

- The renal dosing recommendations from the FDA based on eGFR:
  - Patients with an **eGFR ≥60** require *no dose adjustments* and can safely use metformin with *annual* monitoring.
  - Patients with an **eGFR between 45 and 60** may continue treatment but require *more frequent renal function monitoring* every *3 to 6 months*.
  - Patients with *moderate chronic kidney disease* (**eGFR between 30 and 45**) aren't candidates for initiation of metformin, but patients currently maintained on the medication *may continue cautiously*.
    - The FDA suggests assessing the appropriateness of continuing metformin in this patient population and ***considering a 50% dose reduction*** with renal function monitoring every 3 months.
  - The FDA still recommends a **contraindication** in advanced kidney disease (eGFR <30 mL/min/1.73m^2).

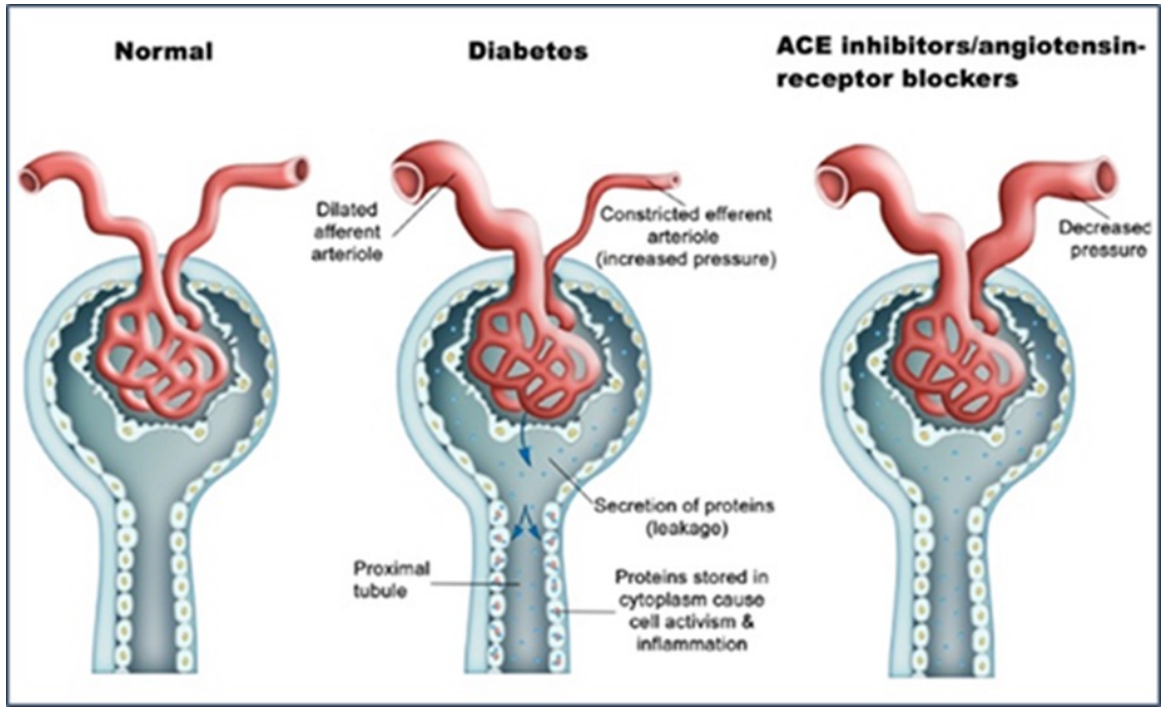
Metformin *should be* ***temporarily discontinued*** *at the time of or before* ***iodinated contrast imaging procedures*** *in patients with* ***eGFR 30-60 mL****/min/1.73 m2*

ADA Standards of Care – additional comments

- **Small elevations of serum Cr** (***up to 30%*** from baseline) with RAAS blockers (ACEIs & ARBs) must ***not*** **be confused with AKI** –
  - usually begins 3-5 days after start of ACEI or ARB therapy
  - Studies found a strong association between acute increases in serum creatinine of up to 30% that stabilize within the first two months of ACE-inhibitor therapy and ***long-term preservation*** of renal function (*reduce intraglomerular hypertension*)

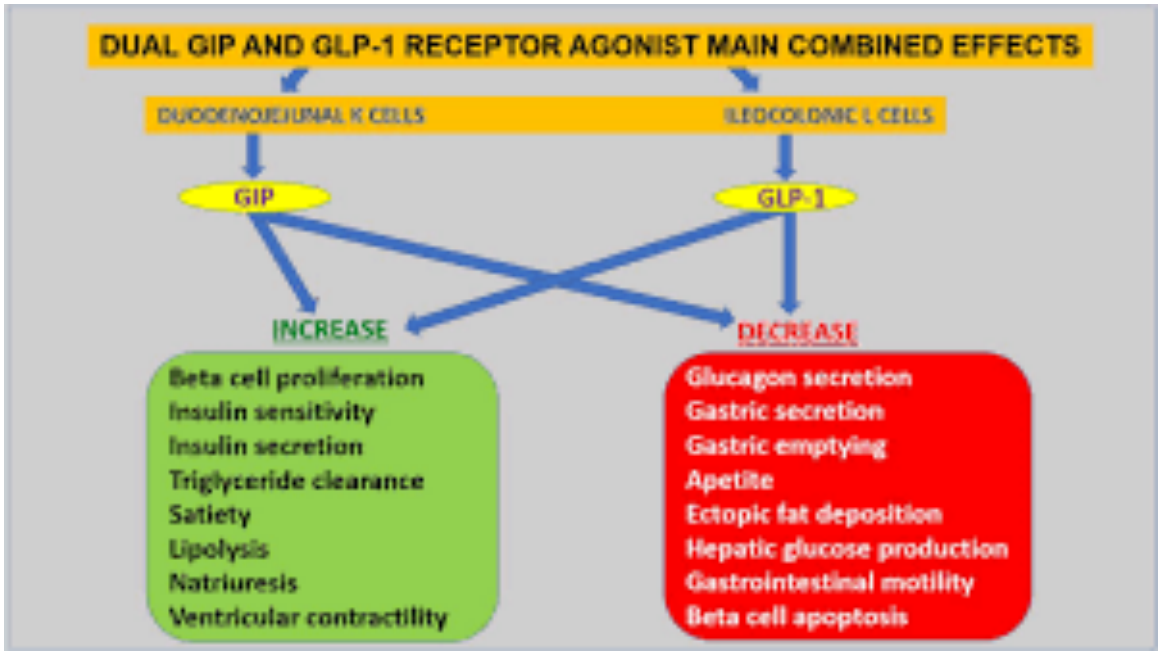
- **11.4d Do not discontinue renin-angiotensin system blockade for increases in serum creatinine (≤30%) in the absence of volume depletion. A**

Also applies with
- SGLT2i therapy
- MRA therapy



Prophylactic use of anti-emetic medications reduced nausea and vomiting associated with exenatide treatment: a retrospective analysis of an open-label, parallel-group, single-dose study in healthy subjects. Diabet Med. 2010; 27(10):1168-73 (ISSN: 1464-5491)
Ellero C; Han J; Bhavsar S; Cirincione BB; Deyoung MB; Gray AL; Yushmanova I; Anderson PW

- Another strategy to aid in the reduction of severe nausea and vomiting is the **temporary use of antiemetics**. Prophylactic use of antiemetics was explored in a retrospective analysis of a phase 1, open-label, parallel-group, single-dose study of healthy individuals who were given a dose of *exenatide 10 mcg immediate release.*
  - In that study, patients were randomly assigned to either premedication with **ondansetron 8 mg plus metoclopramide 10 mg** 30 minutes before exenatide injection or no pretreatment. Significantly less nausea (16.7% vs 61.7%) and vomiting (6.7% vs 38.3%) occurred in the premedication vs no pretreatment group ($P < .001$ for both nausea and vomiting).
- Although not a long-term solution, this strategy might be used when the potential benefit of GLP-1 agonist therapy is considered high and outweighs the potential risks and costs associated with short-term antiemetic use.


DUAL GIP AND GLP-1 RECEPTOR AGONIST MAIN COMBINED EFFECTS
DUODENOJEJUNAL K CELLS
ILEOCOLONIC L CELLS
GIP
GLP-1
INCREASE
DECREASE
Beta cell proliferation
Insulin sensitivity
Insulin secretion
Triglyceride clearance
Satiety
Lipolysis
Natriuresis
Ventricular contractility
Glucagon secretion
Gastric secretion
Gastric emptying
Apetite
Ectopic fat deposition
Hepatic glucose production
Gastrointestinal motility
Beta cell apoptosis

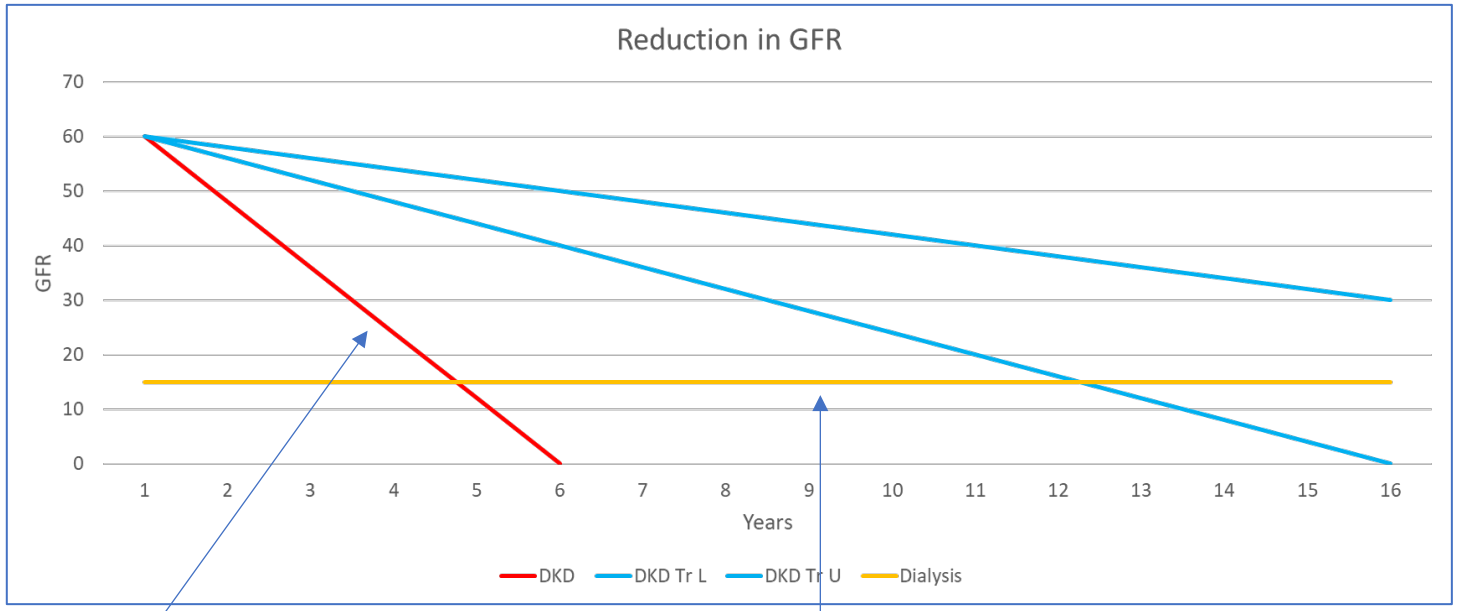
Diagnosis of DKD: National Kidney Foundation

KDIGO Recommended staging

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Increasingly see staging listing both G &A
e.g., G1/A3, G3b/A1, G3a/A2, etc.

Slowing Down the Loss of Kidney Function with Diabetes Kidney Disease



This is how quickly your kidneys will lose function without any treatment

The yellow line is the level where you need to start dialysis

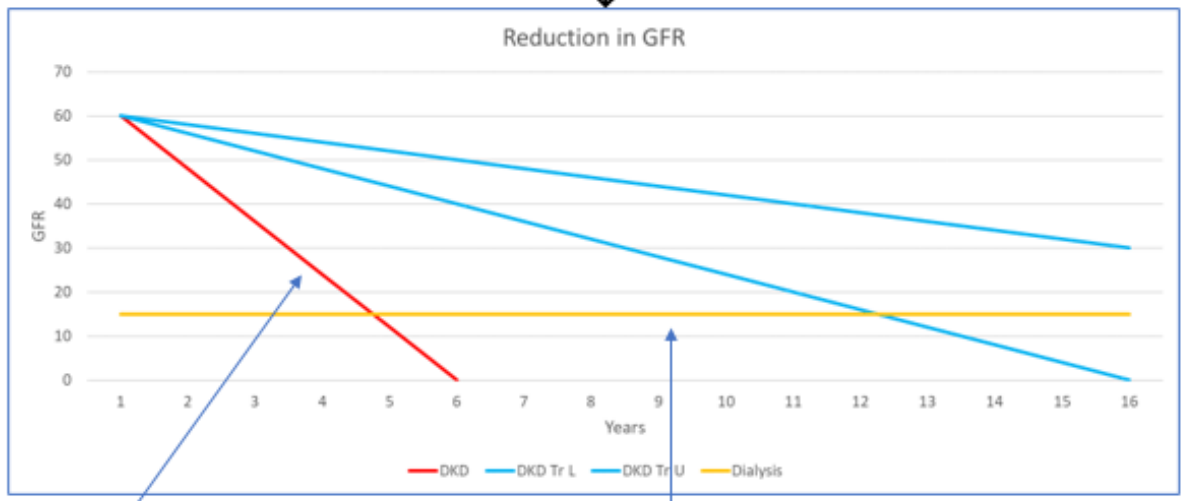
The aqua lines show how much treatment can reduce the rate at which your kidneys lose function

Treatment includes

- Optimal blood pressure, using an ACEI or ARB medication along with other meds if needed
- An SGLT2 inhibitor medication (and/or a GLP1 RA or MRA)
- Blood glucose levels in individualized safe range
- Avoiding drugs that hurt your kidneys such as NSAIDs (ibuprofen, Advil, Motrin, etc.)
- Keeping your muscles strong, avoiding being too sedentary
- Healthy food choices – especially, avoid excess animal protein & fats

Cómo retrasar la pérdida de la función de los riñones causada por la enfermedad renal diabética

Reducción de la GFR (o sea, tasa de filtración glomerular) es un marcador de la función de los riñones



Así de rápido perderán la función sus riñones si no toma ningún tratamiento

La línea amarilla representa el nivel donde ya necesita empezar a hacerse diálisis

Las líneas azules muestran cuánto ayuda un tratamiento a reducir la velocidad con la que los riñones pierden su función.

El tratamiento incluye:

- Controlar la presión a un nivel óptimo, usando un medicamento ACEI (inhibidor de la enzima convertidora de angiotensina, que es para la presión y protege los riñones) o un ARB (bloqueador de los receptores de angiotensina 2 , es para la presión y protege los riñones) junto con otras medicinas si es necesario.
- Un medicamento para diabetes SGLT2 (inhibidor del cotransportador de sodio y glucosa 2) y/o un GLP1 RA (agonista del receptor del péptido 1 similar al glucagón) o un MRA (antagonista de los receptores de mineralocorticoides).
- Tener niveles de azúcar en la sangre individualizados en un rango seguro.
- Evitar medicamentos que dañan los riñones, como los NSAIDs (antiinflamatorios que no contienen esteroides, como Ibuprofeno, Advil, Motrin, etc.).
- Mantener sus músculos fuertes, evitar llevar una vida sedentaria.
- Elegir alimentos saludables, especialmente evitar excederse con las proteínas y grasas de origen animal

For Patients & Families

- https://www.kidneyfund.org/kidney-disease/chronic-kidney-disease-ckd/stages-of-chronic-kidney-disease/

- 11-10-1813_abe_patbro_gfr_b.pdf (kidney.org)