UT Southwestern Medical Center

Treatment Updates of Diabetic Nephropathy based upon 2020 KDIGO Guidelines

Denise K Link, MPAS, PA-C, FNKF

The University of Texas Southwestern Medical Center

American Academy of Nephrology PAs

Denise.Link@utsouthwestern.edu

Nothing to Disclose

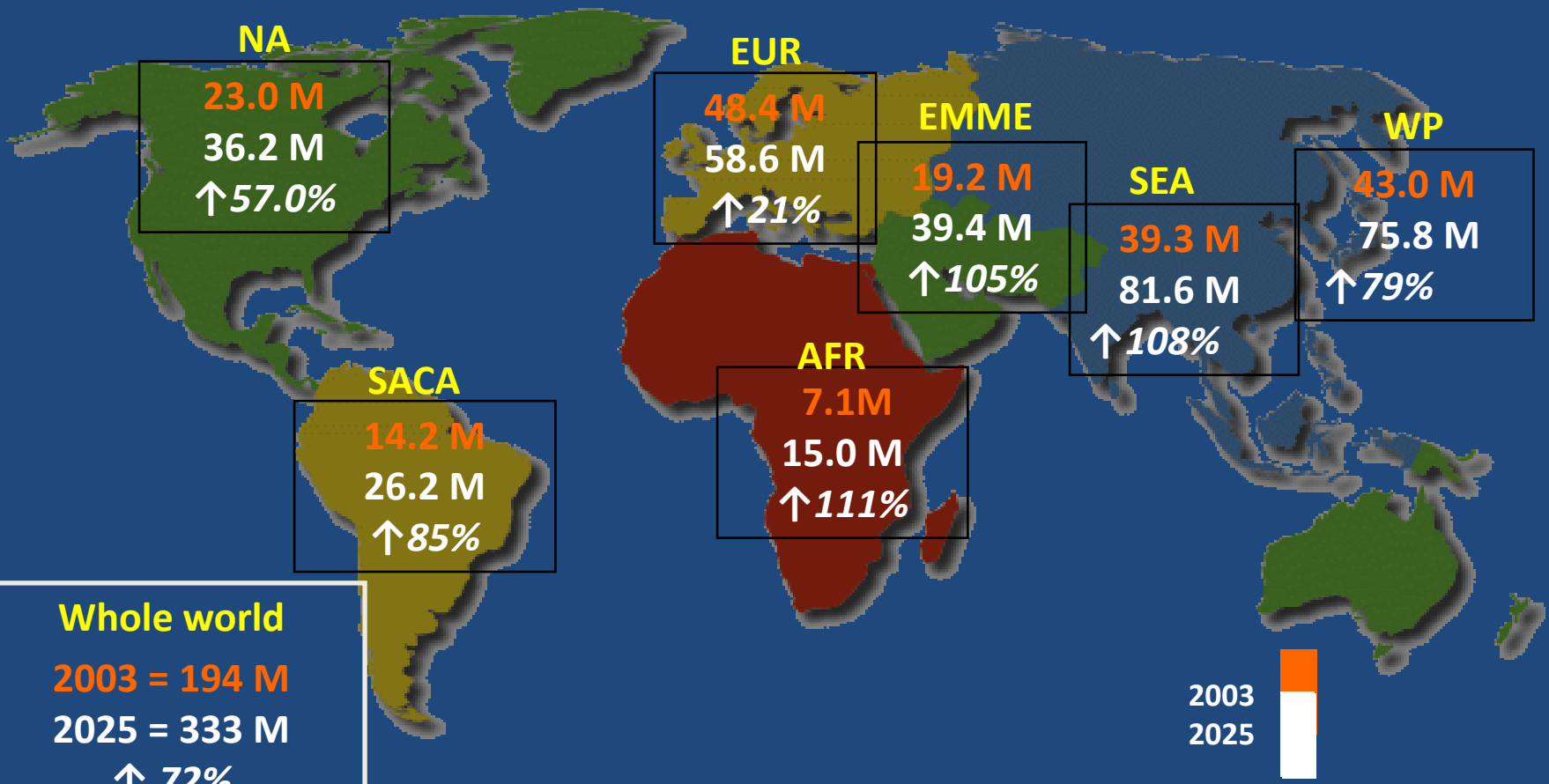
Objectives

- 1. To understand the parameters that define DM nephropathy
- 2. To illuminate the current recommendations for treatment of diabetic kidney disease based upon KDIGO 2021 guidelines
- 3. To recognize the factors that increase of death of DM nephropathy patients
- 4. To identify the multi-risk factor interventions for treating diabetic kidney disease and limiting cardiovascular death
- 5. To discuss new pharmacologic options for treatment of DM nephropathy

Disclosure

- I have nothing to disclose

Diabetes is a Global Epidemic



IDF World Atlas of Diabetes 2nd Edition 2003 (www.idf.org/diabetes atlas/)

Diabesity

- 90-95% of DM have type 2 (T2D)
- 86% of T2D are overweight or obese
- Although obesity has traditionally been considered to be a disease of energy imbalance, its etiology is highly complex and involves interplay between genetic, environmental, physiological, behavioral, social, and economic factors

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2579635/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4887150/

Alarming Obesity Projections for Children in US

- If current U.S. trends continue, more than 57 percent of today's youth will be obese at age 35, according to a new study from Harvard T.H. Chan School of Public Health.

- The research also found that excess weight in childhood is predictive of adult obesity, even among young children, and that healthy-weight children are the only ones with less than a 50 percent chance of adult obesity. The findings were based on a rigorous simulation model that provides the most accurate predictions to date of obesity prevalence at various ages

The Power of the Human Story

Empathy, Neurochemistry, and the Dramatic Arc: Paul Zak at the Future of StoryTelling 2012

https://www.youtube.com/watch?v=q1a7tiA1Qzo

What stories have we never heard?

- The Weight of the World. www.weightoftheworld.com
- https://www.weightoftheworld.com/library/

Obesity-Trauma-Shame

Obesity can't be tackled until we address the trauma that causes it

Eleanor Morgan

Burn fat to reduce your Covid-19 risk, we're told. But how to dispel the shame and distress that so often lie behind weight gain?

▲ 'Increasing the stress and shame that a person with obesity feels often leads to increased eating and decreased motivation to lose weight.' Photograph: Getty/iStockphoto

People with Covid-19 who are overweight or obese have an increased risk of serious complications and death. In the light of this evidence, the government has launched a plan to address obesity, framed as a way of preventing as many casualties in a second wave

- "Psychologists have been writing for years about how obesity is not caused by a lack of willpower…[t]his cycle of shame speaks to another body of evidence that is being willfully overlooked: the correlation between obesity and trauma

https://www.theguardian.com/commentisfree/2020/jul/30/obesity-trauma-fat-covid-19-shame-weight-gain

Blame/Shame: Makes obesity worse

The Harvard Gazette

HEALTH & MEDICINE

Expert advice for reducing obesity: Take the blame out of it

Fatima Cody Stanford, a leading expert on obesity, is exploring the impact of behavioral and environmental factors in the complex processes of weight regulation.

Rose Lincoln/Harvard Staff Photographer

"We don't blame people for developing cancer. But when they develop diabetes, high blood pressure, or any of a number of other health issues related to obesity, we tend to view the underlying cause — excess weight — as a moral failing. That approach, says Fatima Coy Stanford , an instructor in medicine and pediatrics at Harvard Medical School, is not only counterproductive, it can also aggravate weight issues and their associated health risks"

Who copes well? Obesity-related coping and its associations with shame, guilt and weight loss

- "Weight-related SHAME at baseline was a significant negative predictor for problem-focused engagement coping"

JOURNAL OF CLINICAL PSYCHOLOGY, Vol. 64(10), 1129--1144 (2008)

SHAME

Shame is the most powerful master emotion. It's the fear that we're not good enough.

Dr. Brene Brown

Shame is the intensely painful feeling that we are unworthy love and belonging.

Brene Brown, PHD, LMSW

SHAME IS THE VOICE OF "I'm not enough"

- KOREN MOTEKAITIS

What stories have I heard from my patients?

Shame: Never Good Enough

- Everyone has shame. I have shame
- Making space for our patients to share their shame about their weight
- To enable them to be vulnerable AND COURAGEOUS

What stories have I never told?

My *Shame: Never Good Enough*

- Never_____ enough?
- For me…….

- Now my “Vulnerability Hangover” begins.
- But my Courage is Contagious

What is your patient's story?

- We cannot treat and heal without knowing our patient
- How is shame part of my patient's story?
- How is my patient doing understanding their disease and how can I encourage and empower them?
- It takes time…to know about a person. To ask questions, to know this person in front of me

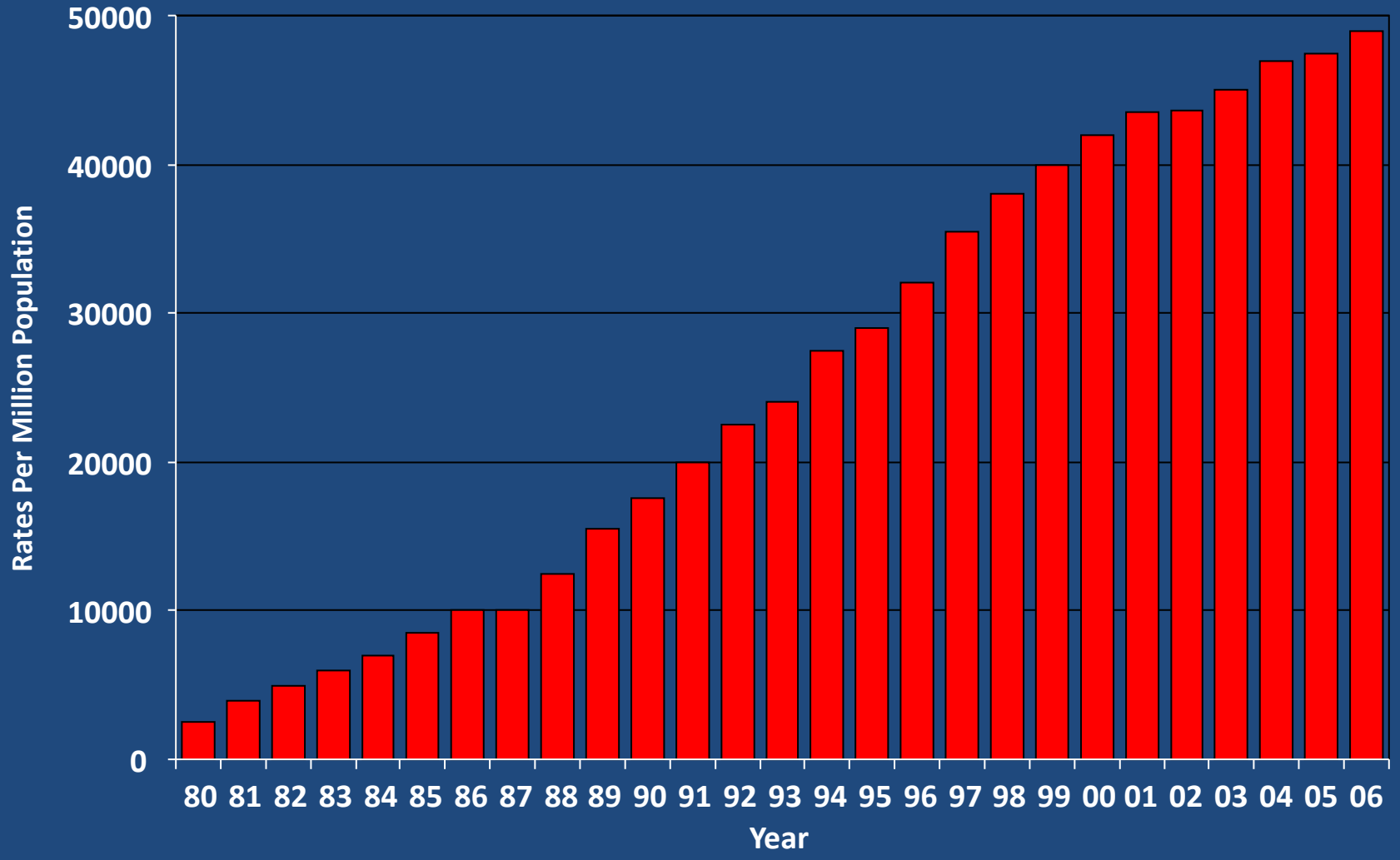
"Learning you have diabetes is one of those moments you never forget."

- Patients do not always know they can take an active role in their health care, because that was not common in the past
- [Providers] should not assume they know what patients want and need. They, too, must ask questions and get to know their patients so that they can develop a treatment plan that is not only in the best interest of the patient medically, but also fits the patient's lifestyle
- [Providers] must listen to their patients' voices. They should communicate often and clearly and take the time to explain things, because it is the sharing of information that allows patients to learn and help with their own care.
- [Providers] also have a responsibility to listen to their patients and learn about them: the best health care decisions are based not only on a [provider's] experience and knowledge, but also a patient's lifestyle and preferences. With close cooperation between patients and physicians, the work of the health care team will be enhanced, and the lives of patients will be better.
- In conclusion, we say to our fellow patients: speak up and let your voice be heard—your life may depend on it

https://cjasn.asnjournals.org/content/early/2021/03/12/CJN.18191120?&WT.MC_ID=ITL&utm_source=ITL

Changes in the numbers of ESKD cases due to Diabetes in the US over 25 years

Number of people initiating treatment for ESKD 1980-2006



U.S. Renal Data System, USRDS 2008 Annual Data Report

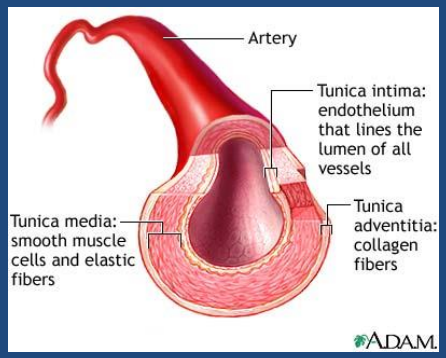
Nephropathy

MI, Cardiac failure

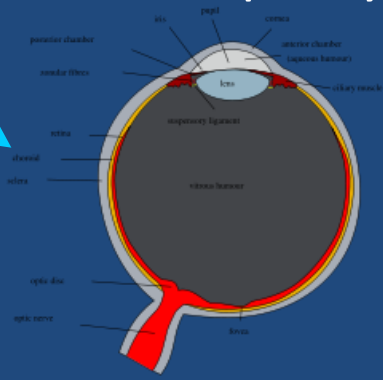
Neuropathy

Diabetic complications

Stroke, PVD

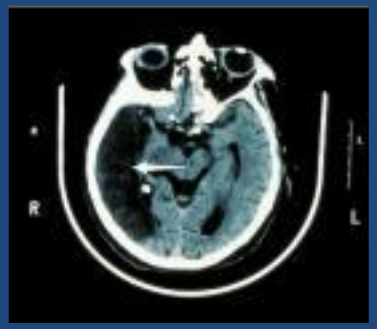


Retinopathy



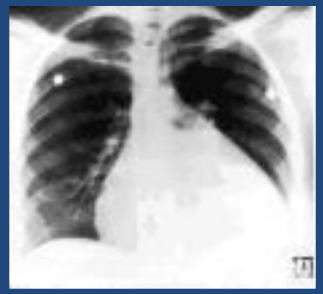
Big players of all-cause mortality of DKD? Its NOT ESRD

Stroke

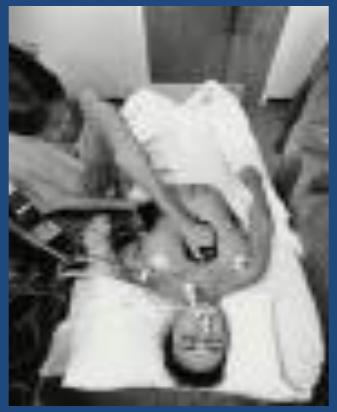


Myocardial Infarction

Heart Failure



Sudden Death



Diabetic Kidney Disease Risks

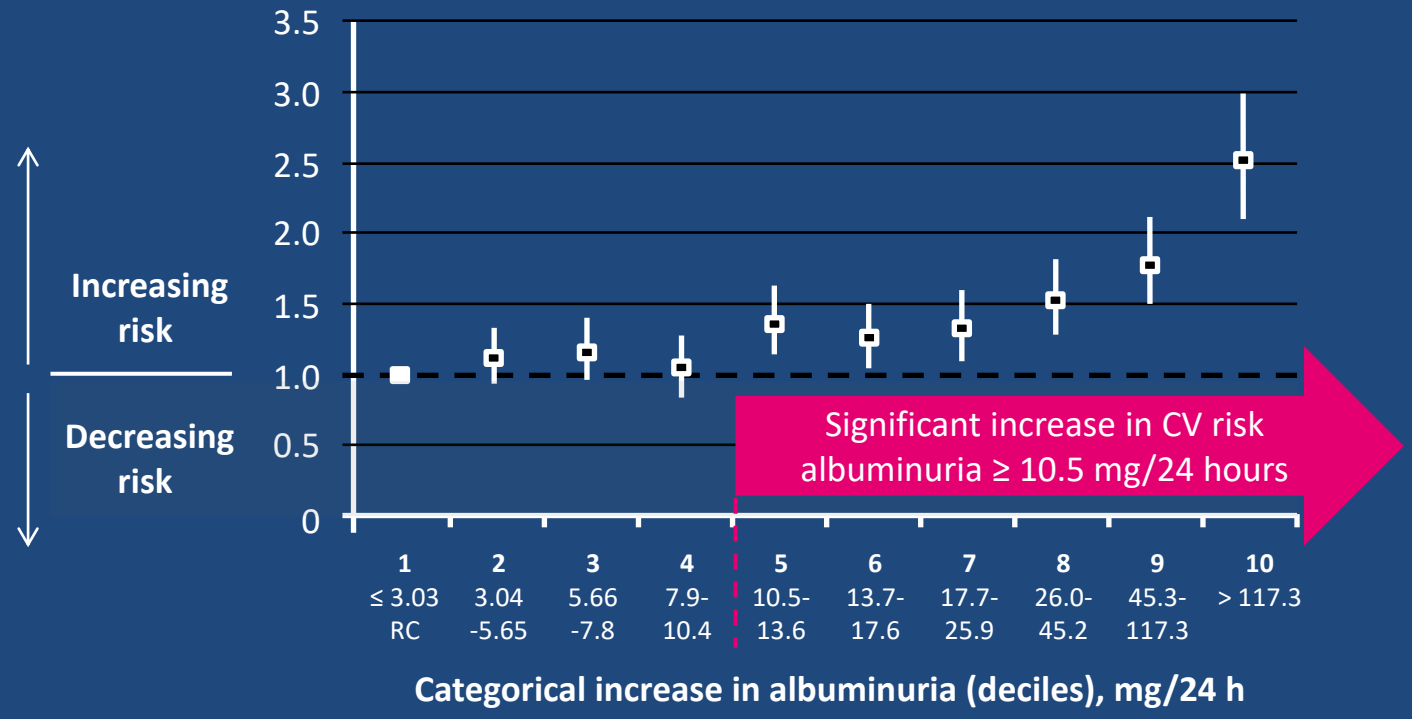
- Progress to end-stage-kidney disease (ESKD) (10 %).
  - Dialysis
  - Kidney transplant
- Die of other causes without reaching ESKD (90 %).
  - CVD 1/2
  - Infections 1/3

Alicic RZ, Rooney MT, Tuttle KR. *CJASN* 2017;12:2032-2045

Albuminuria: a risk factor for CVD

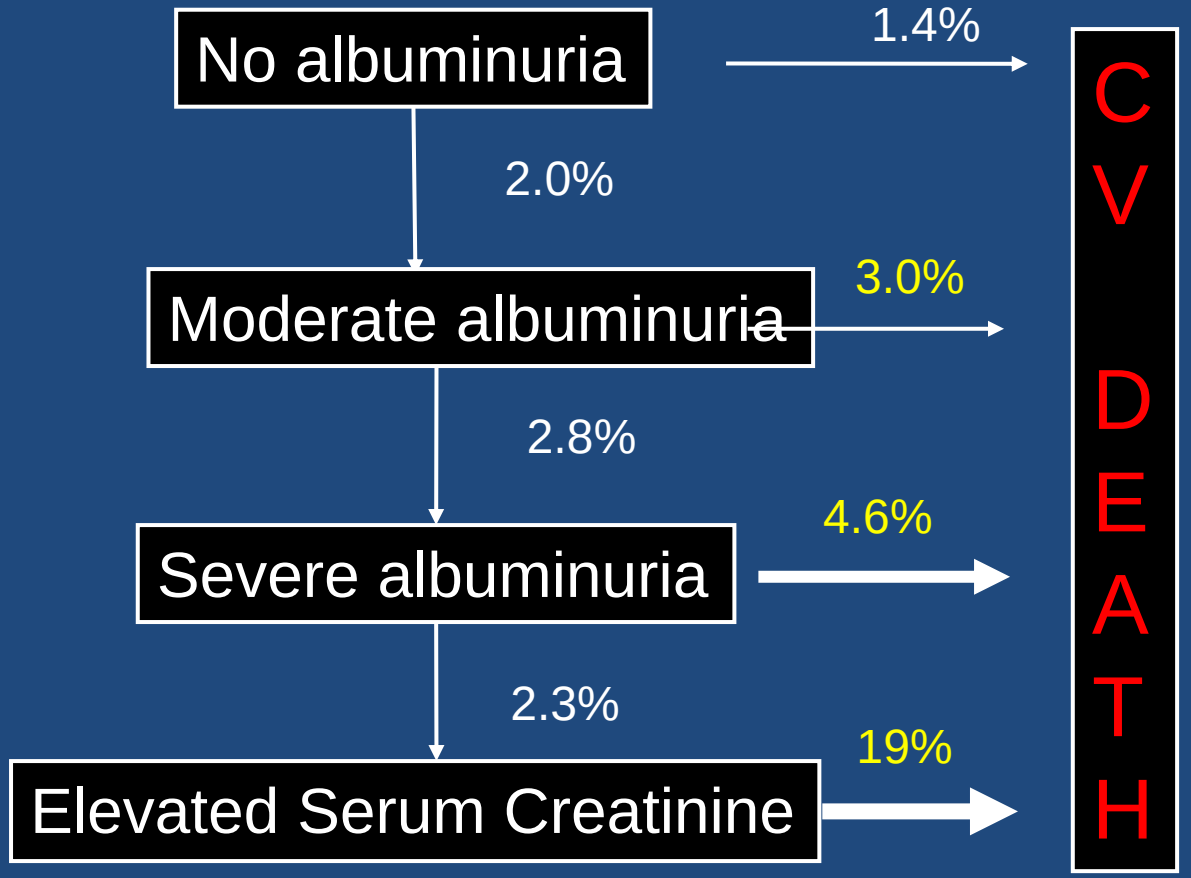
The risk of CV outcomes according to degree of albuminuria in patients with T2DM: The Renal Insufficiency and Cardiovascular Events Study, N = 15,773

Odds ratio (95% CI) for major acute CVD events



*Coronary events (including myocardial infarction and/or coronary revascularization); cerebrovascular events (including stroke and/or carotid revascularization; and peripheral events including ulcer/gangrene/amputation and/or lower limb revascularization). Solini et al. *Diabetes Care*. 2012:35:143–149.

T2 DM with Severe Albuminuria are More Likely to Die than Develop ESKD



The United Kingdom Prospective Diabetes Study (approx. 5000 T 2 DM)
Newly dx'd, predominantly white, medically treated. Adler et al. *Kid Int, 2003*

2020 Clinical practice guidelines for DM management in CKD

1. Comprehensive care

   -Control of risk factors including RAS blockade in those with albuminuria remains part of standard of care

2. Lifestyle intervention
3. Glycemic goals based upon A1C and BS
4. Anti-hyperglycemic treatment options

   -Initial use of BOTH metformin and SGLT2i is recommended

5. Approaches to management of patients

Amazing 32yo single mom of 3 boys

PMH: Type 2 DM x 15 yrs with retinopathy, obesity, CKD stage 2A3, smoker
Meds: metformin 500mg BID, carvedilol 6.25mg BID
LABS: SCr 1.3mg/dl, eGFR 63ml/min, sK+ 4.0mmol/L, A1C 9.2%, UACR 1500mg/g
PE: BP 145/90, P 80, weight 265lbs, BMI 33, +trace LE edema

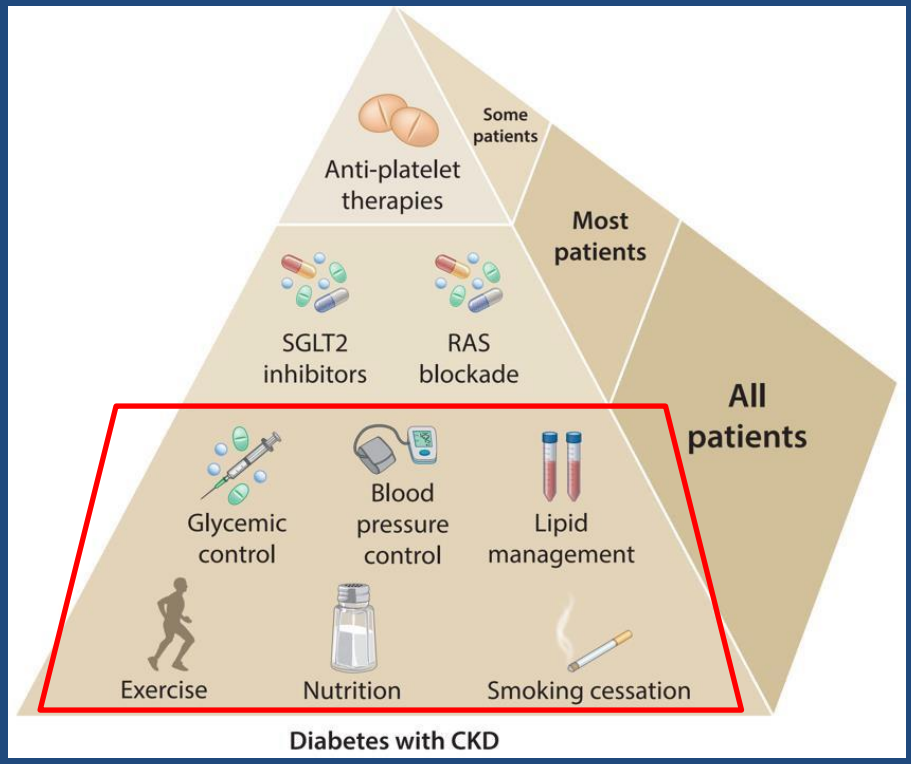
What treatment goals do you have for Amazing Mom of 3 boys

1. Improve diabetic control
2. Improve BP to goal of <120/70
3. Check cholesterol profile
4. Address smoking cessation
5. Communicate about environmental, physiological, behavioral, social, and economic factors that are contributing to her complex medical history

KDIGO 2020 Tx Updates : *Comprehensive Care in Patients with DM and CKD*

Practice Point 1.1.1:

Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.



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How do we know that she has CKD?

1. Serum creatinine is elevated at 1.3
2. eGFR is > 60
3. UACR (urine albumin/creatinine ratio) is > 30mg/g
4. She has type 2 DM and retinopathy

KDOQI Definition DKD

- In most patients with diabetes, CKD should be attributable to diabetes if:

  – Severe albuminuria (macroalbuminuria) ≥ 300 mg/g;

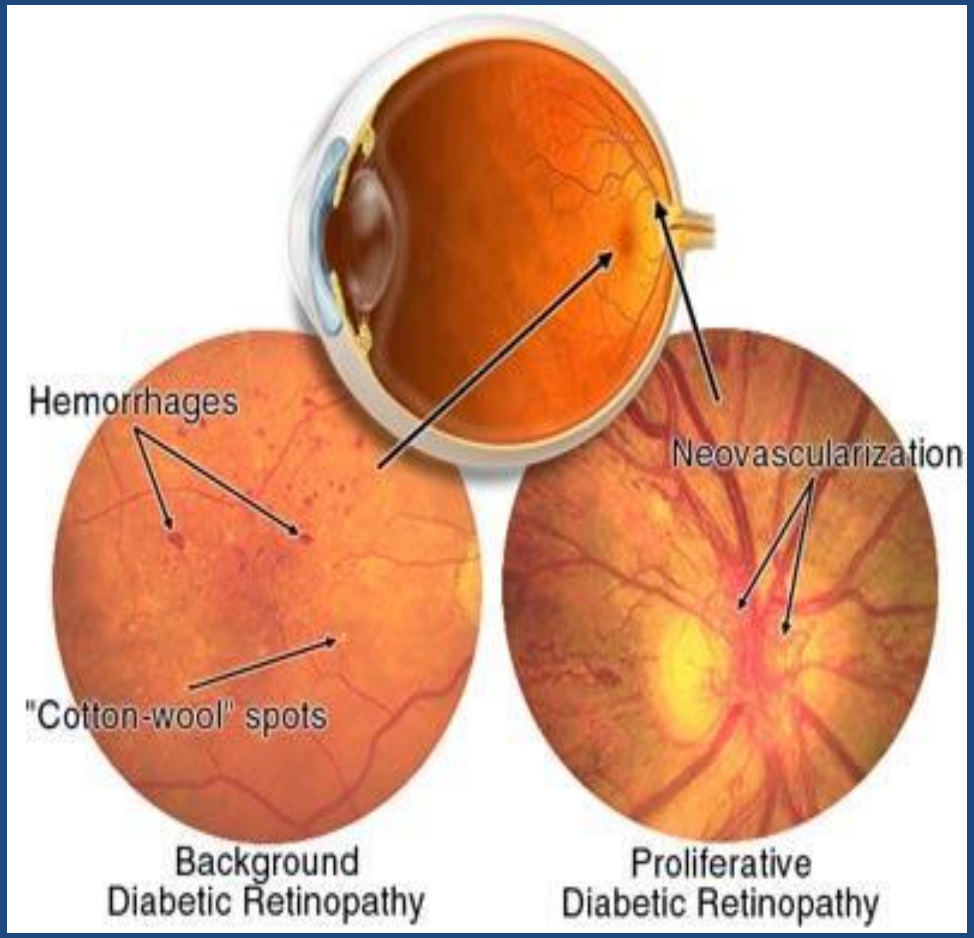
  OR

  – Moderate albuminuria (microalbuminuria) 30-299 mg/g in the presence of
    - diabetic retinopathy
    - type 1 diabetes of at least 10 years' duration.

Tuttle et al. Am. J. Kid. Dis. VOL 49, NO 2, SUPPL 2 FEBRUARY 2007

Relation between DM Nephropathy and Retinopathy

- DM retinopathy can differentiating diabetic nephropathy from non-diabetic kidney diseases in patients with type 2 diabetes and renal disease.
- Proliferative DM retinopathy may be highly specific indicator for DKD



He, ect al. DM retinopathy in predicting DM nephropathy in T2 DM and renal Dz: a meta-analysis. Diabetologia 2013. 457-66

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How do we know that she has CKD?

1. Serum creatinine is elevated at 1.3
2. eGFR is > 60
3. UACR (urine albumin/creatinine ratio) is > 30mg/g
4. **She has type 2 DM and retinopathy---microvascular dz**

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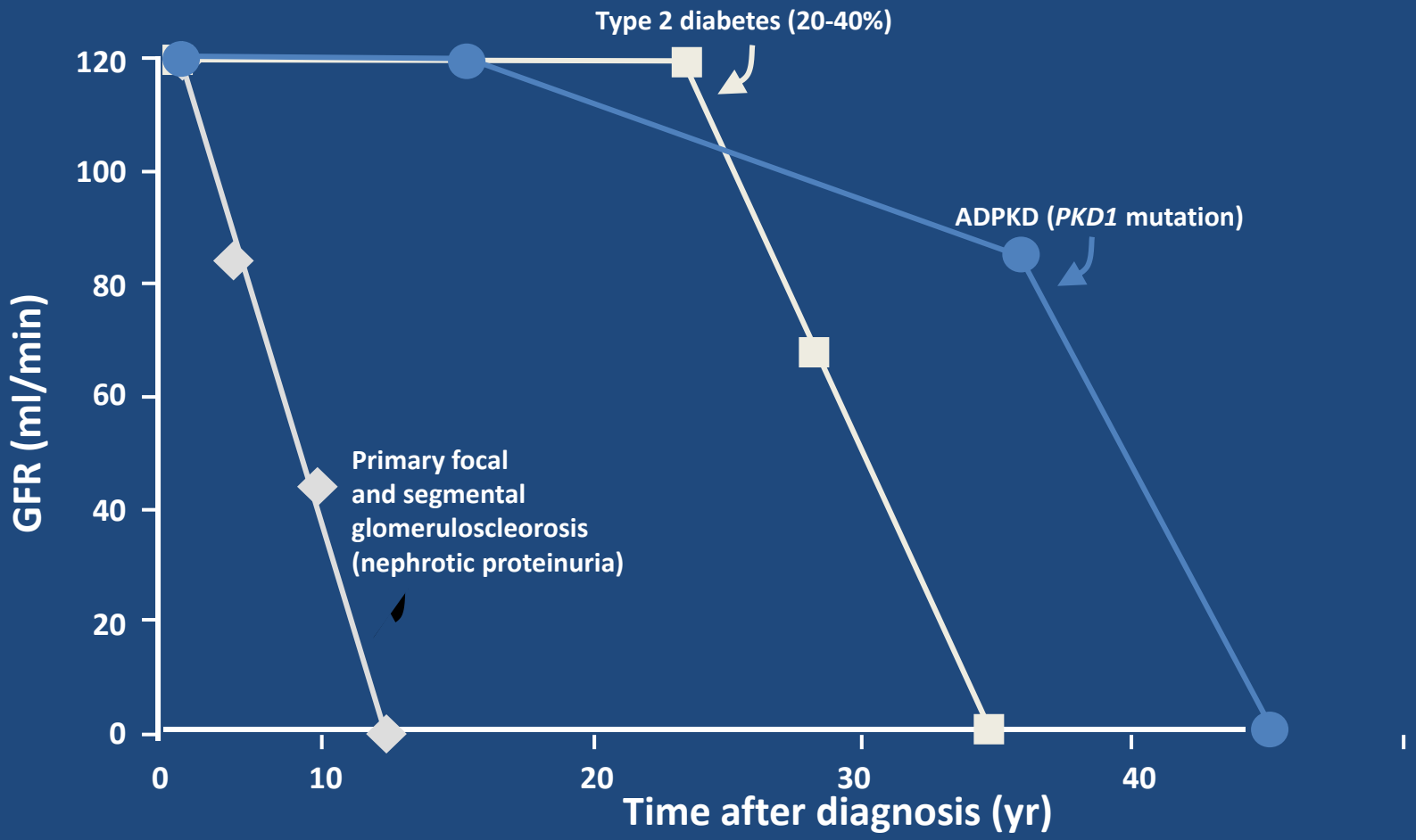
What change would you make for Tx of DKD

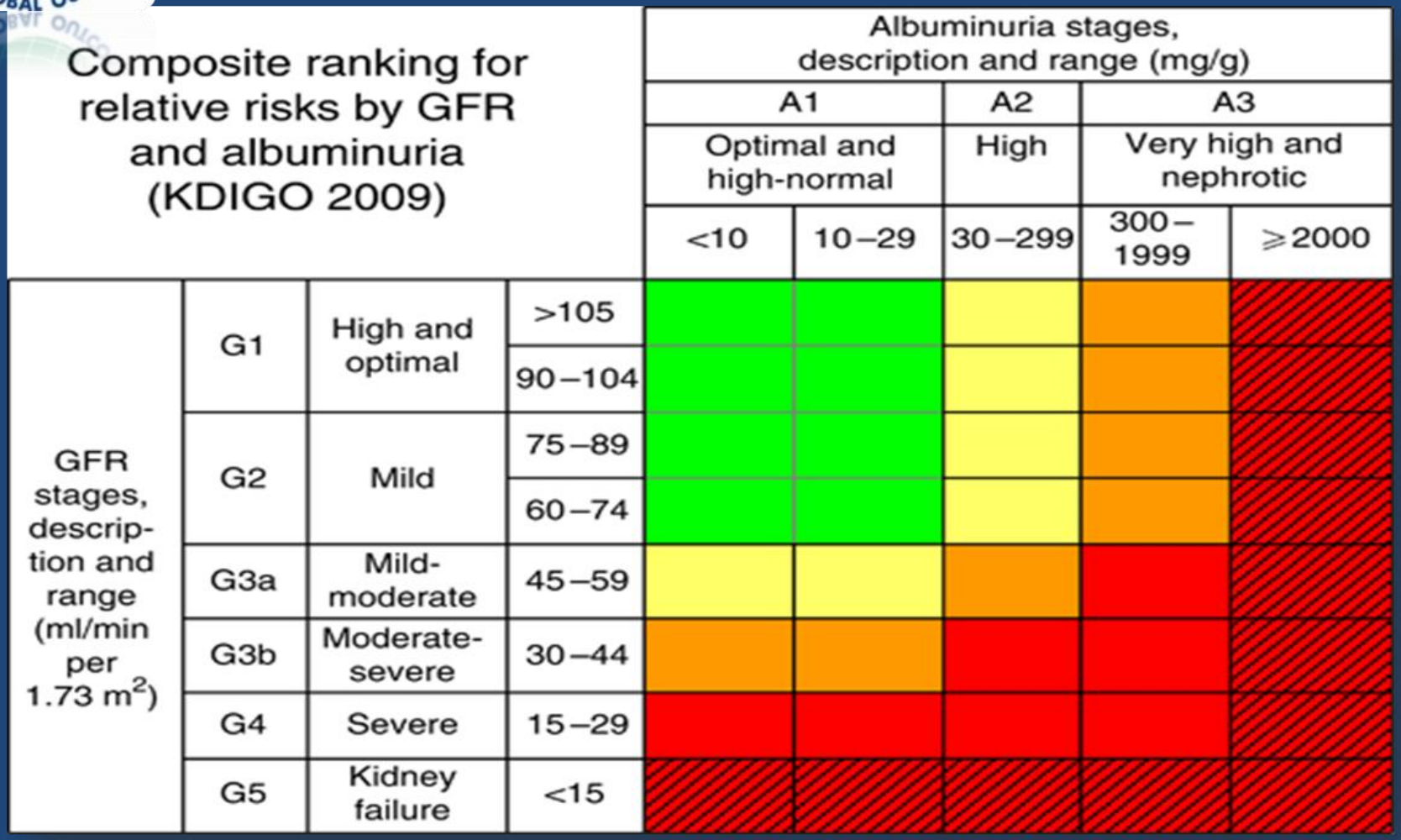
1. Increase metformin to 1000mg BID
2. Increase carvedilol 12.5mg BID
3. Start chlorthalidone 25mg every other day
4. Start losartan 25mg daily
5. A combination of multiple answers and if so which answers?

Decline in GFR varies by Disease State, From Patient to Patient and is Accelerated in those with Albuminuria



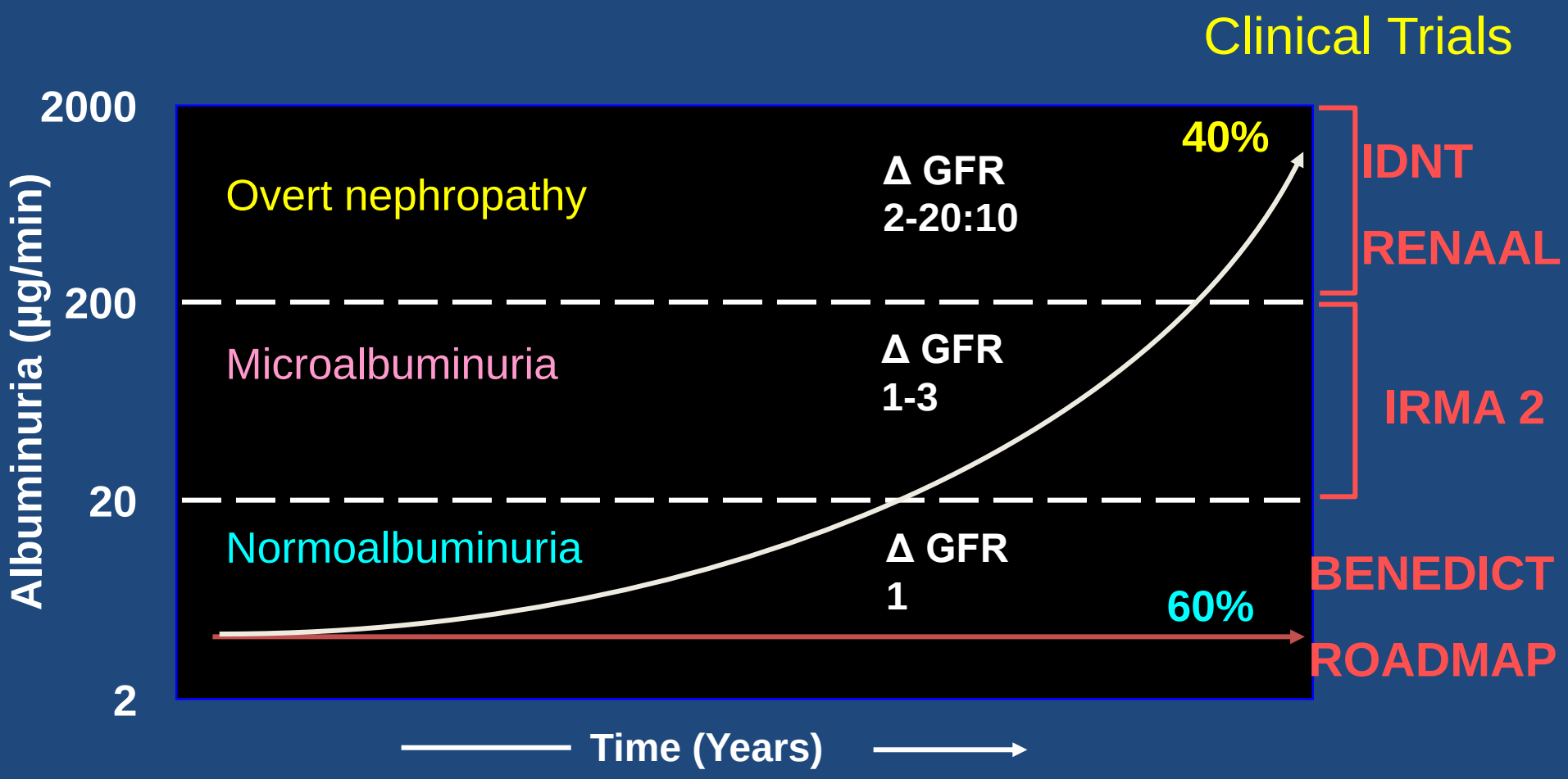
Remuzzi, G. et al. *J. Clin. Invest*. 116:288-296, 2006

CKD Stages with Prognosis



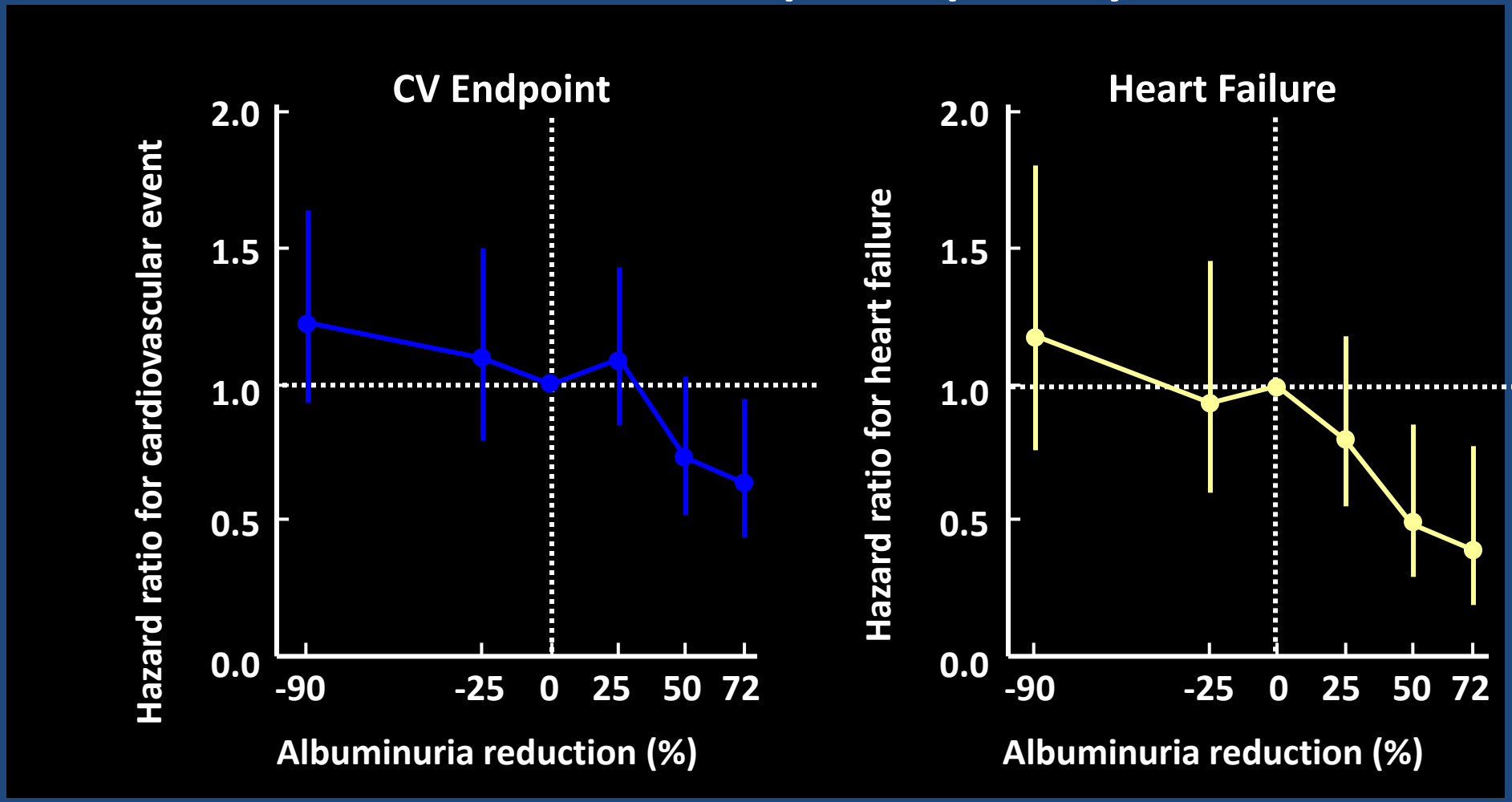
KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD, *Kidney International*, Jan 2013, Vol 3, Issue 1

ACEi and ARBs Slow Progression of DKD Hypertensive Type 2 Diabetics



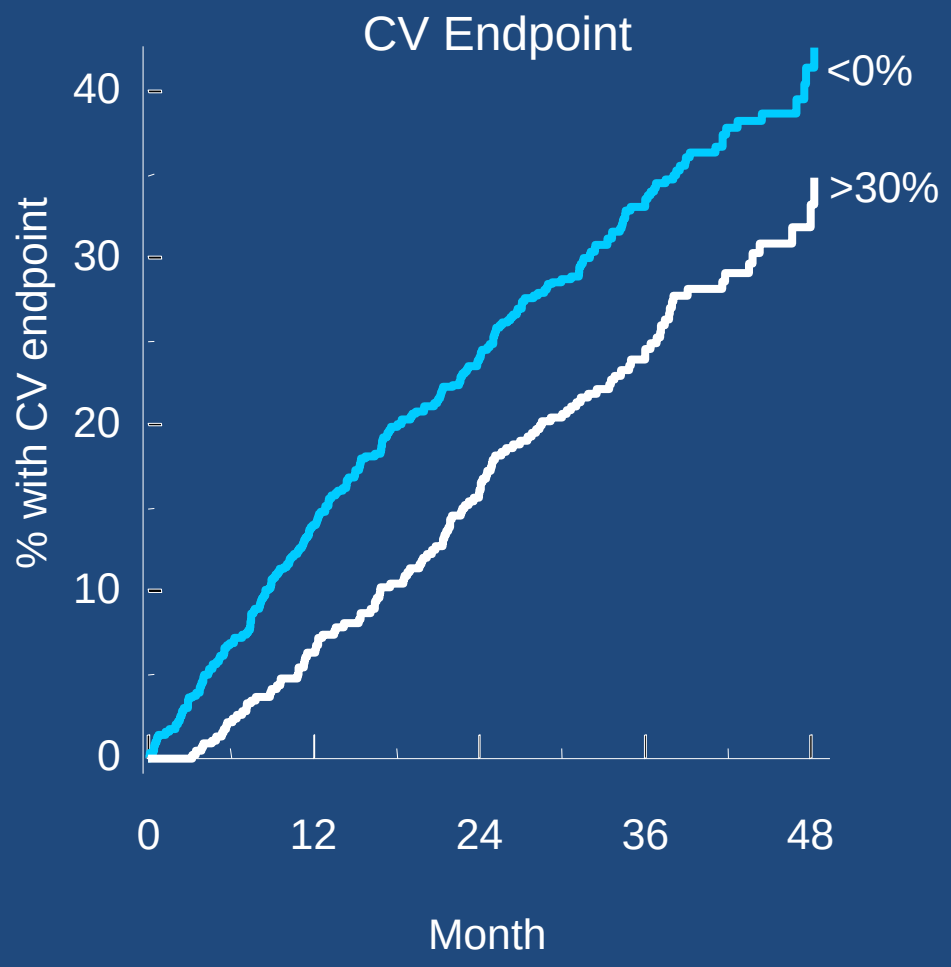
Brenner et al. New Engl J Med 2001 Sep 20;345(12):861-9, Lewis et al. N Engl J Med 2001; 345:851-860,
Parving et al. New Engl J Med 2001 Sep 20;345(12):870-8, Ruggenenti et al. N Engl J Med 2004; 351:1941-1951, Haller et al. N Engl J Med 364;1

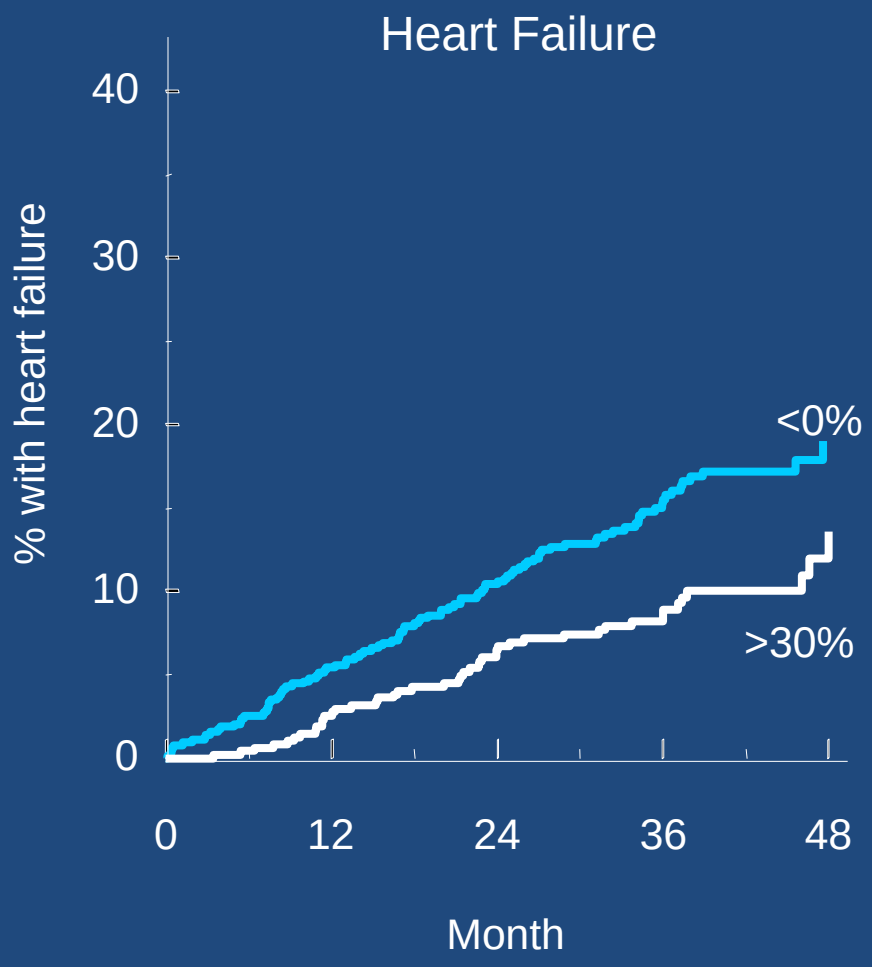
Change in Albuminuria Predicts CV Endpoint and Heart Failure in Type 2 DM with Nephropathy



de Zeeuw et al. Circulation 110:921-7, 2004

RENAAL: Proteinuria Reduction (<0% vs >30%) determines the CV outcome





de Zeeuw et al. Circulation 110:921-7, 2004

We have tried, but NO new therapy for ~20 years

Trial	Year Journal	Drug	DM Type	Outcome	Benefit	Potential Harm
CSG Group	1993 NEJM	Captopril	1	DScr, ESRD Death	Yes	No
RENAAL/IDNT	2001 NEJM	Losartan/ Irbesartan	2	DScr, ESRD Death	Yes	No
TREAT	2009	Darbepoetin	2	CV and ESRD	No	Yes
ASCEND	2010	Avosentan	2	DScr, ESRD	No	Yes
SUN trial	2011 JASN	Sulodexide	2	DScr, ESRD	No	No
ALTITUDE	2012 NEJM	Aliskerin	2	DScr ESRD Death	No	Yes
BEACON	2013 NEJM	Bardoxolone	2	ESRD and CV Death	No	Yes
VA NEPHRON D	2014 NEJM	Dual RAAS blockade	2	DScr, ESRD Death	No	Yes

2020 Clinical practice guidelines for DM management in CKD

1. Comprehensive care

   -Control of risk factors including RAS blockade in those with ALBUMINURA remains part of standard of care

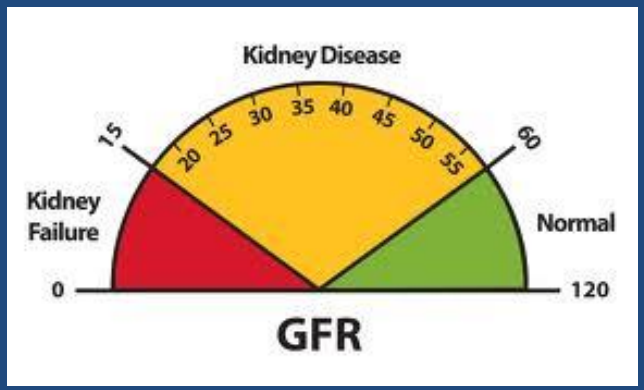
2. Lifestyle intervention
3. Glycemic goals based upon A1C and BS
4. Anti-hyperglycemic treatment options

   -Initial use of BOTH metformin and SGLT2i is recommended

5. Approaches to management of patients

NKDEP

National Kidney Disease Education Program



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What change would you make for Tx of DKD

1. Increase metformin to 1000mg BID
2. Increase carvedilol 12.5mg BID
3. Start chlorthalidone 25mg every other day
4. Start losartan 25mg daily
5. A combination of multiple answers and if so which answers?

Black Box Warnings for ACEi or ARBS

- Pregnancy: fetal/neonatal morbidity/mortality may occur when drugs that act directly on the renin-angiotensin system are used in pregnancy; D/C drug as soon as possible once pregnancy detected

Comprehensive Care

1. Comprehensive DM and CKD management

2. RAS blockade when albuminuria is present

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated *(1B)*. Why?

3. Smoking cessation

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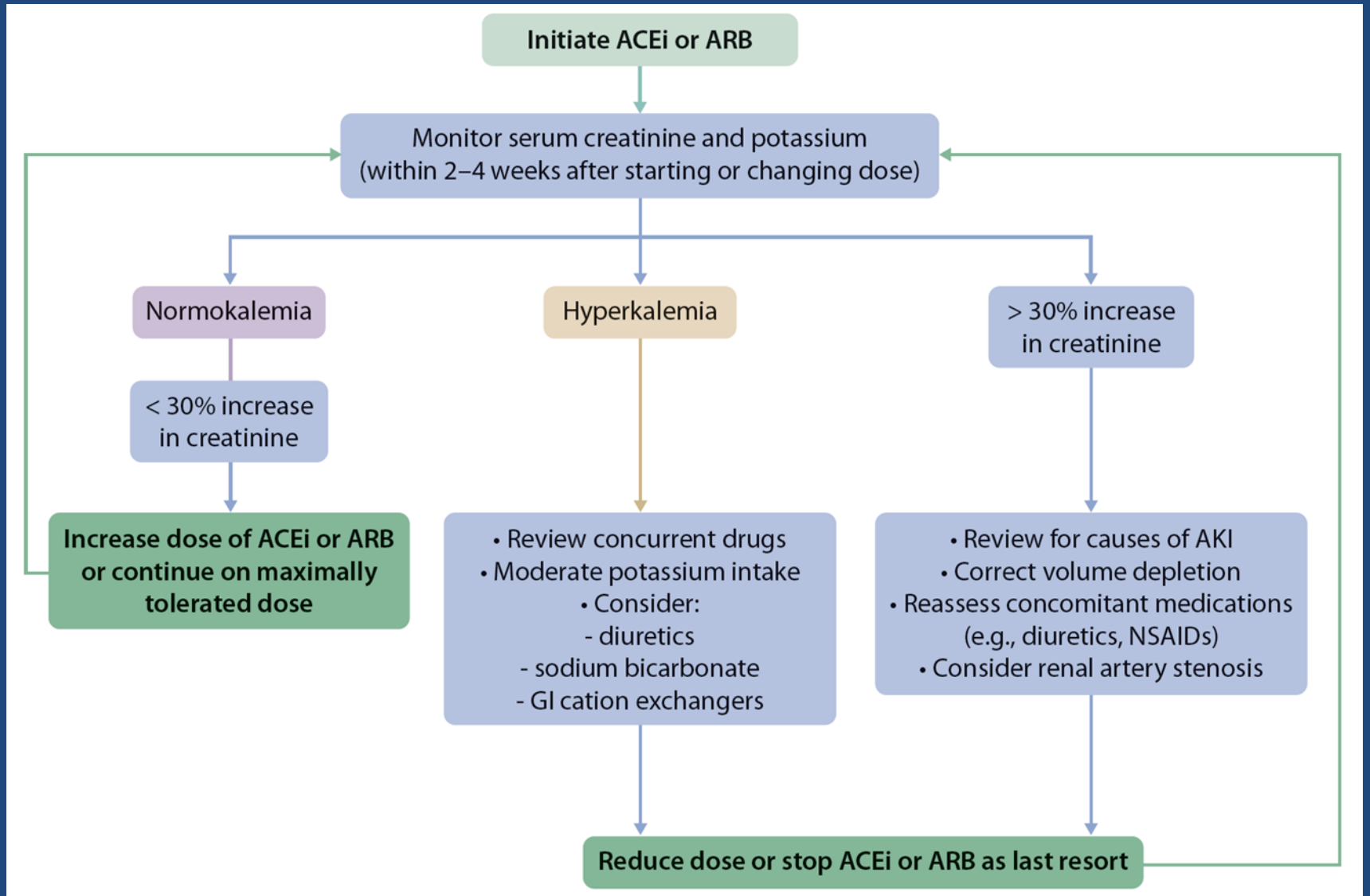
PMH: Type 2 DM x 15 yrs with retinopathy, obesity, CKD stage 2A3, smoker
Meds: losartan 25mg daily is started and metformin is increased to 1000mg BID, carvedilol 6.25mg BID
LABS: SCr 1.6mg/dl, eGFR 49ml/min, sK+ 5.0 mmol/L, A1C 8.2%, UACR 1000mg/g
PE: BP 138/85
Denies hypotension, usage of NSAIDs, vomiting/diarrhea

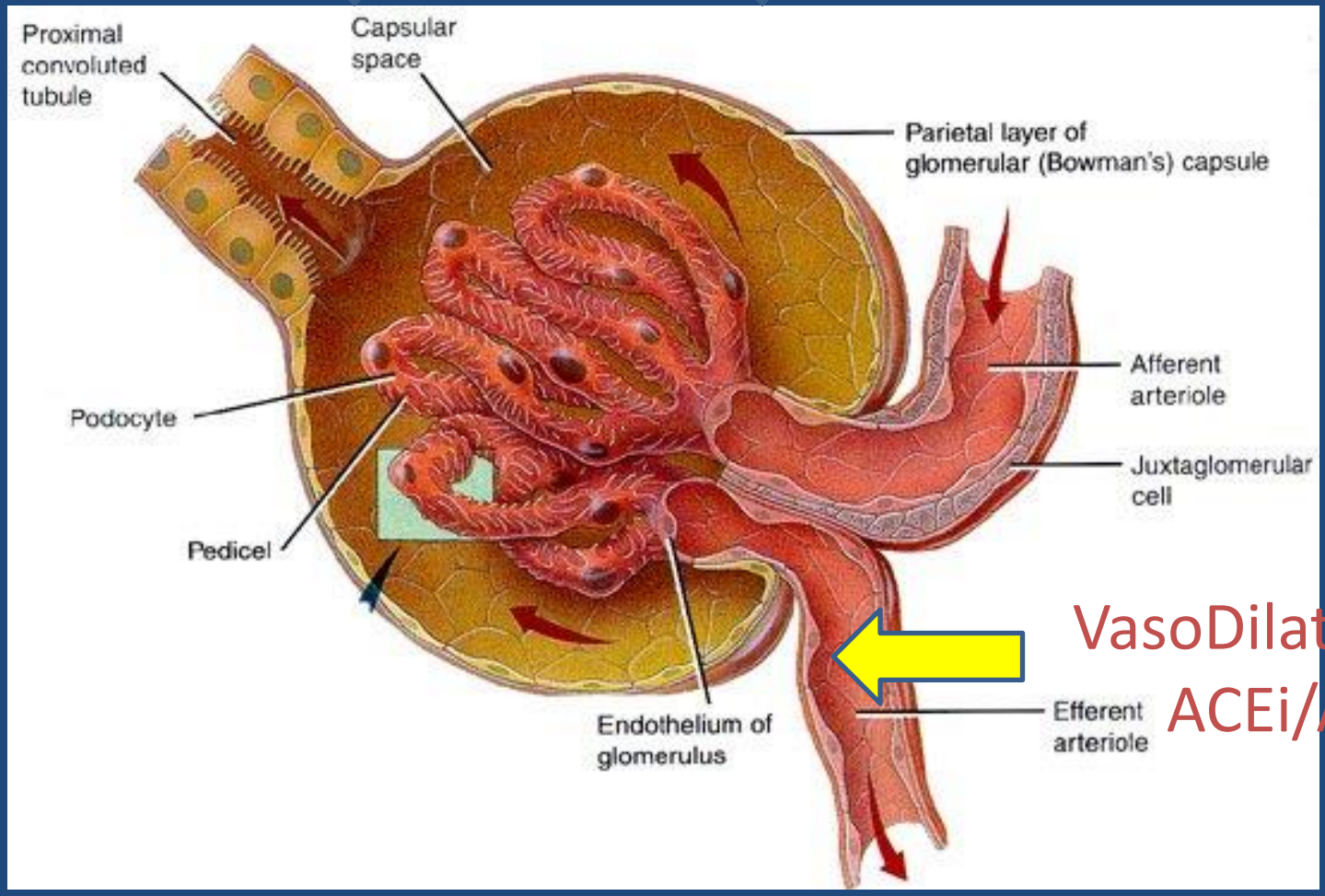
What change would you make to the above Tx for DKD?

1. Decrease losartan to 12.5mg daily
2. Increase losartan to 50mg daily
3. Order renal sonogram with dopplers to ensure no renal artery stenosis
4. Increase carvedilol 12.5mg BID

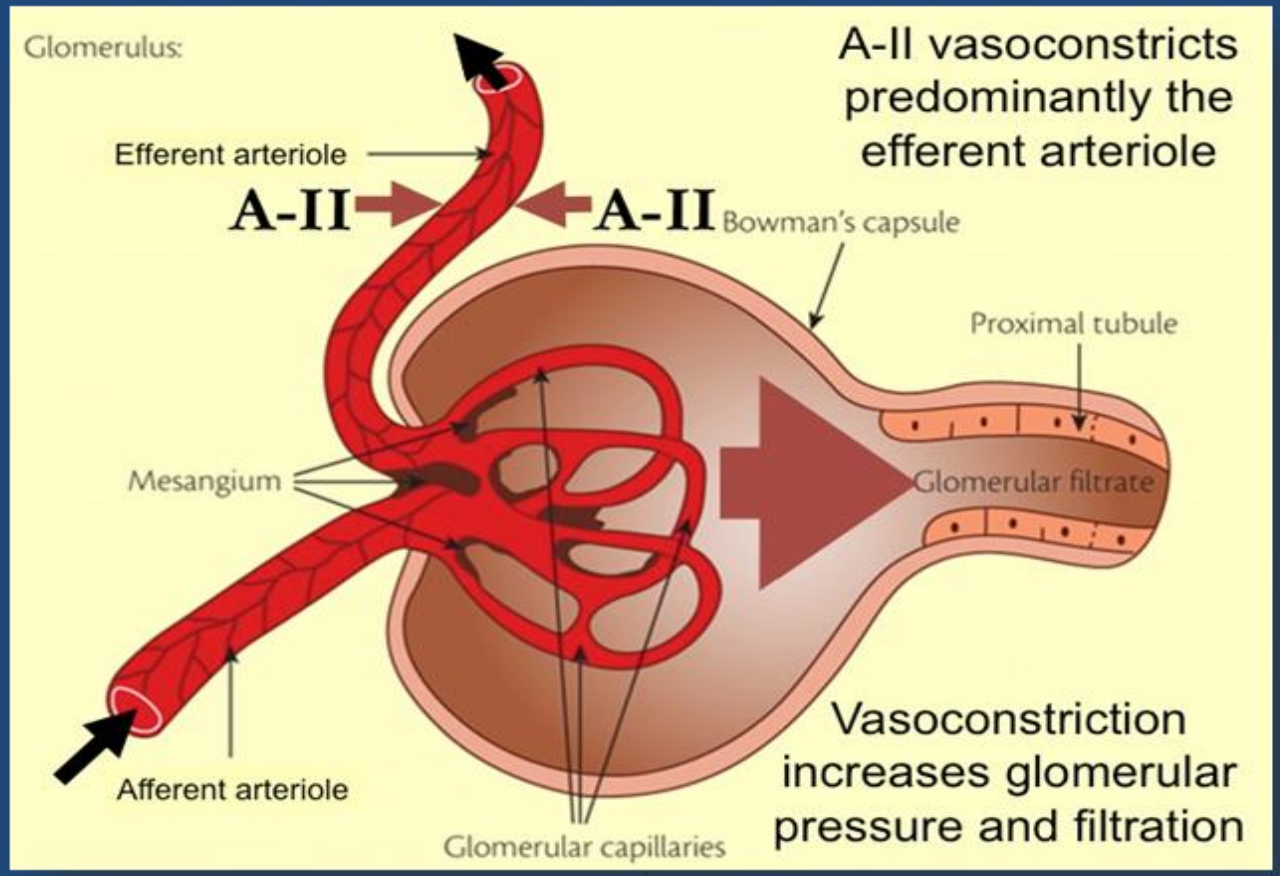
RAS Blockade with Albuminuria



Vaso-dilation Efferent Arteriole= ↓ GFR + ↓ albuminuria



ACEi or ARBs even with Advanced CKD



20-30% bump in SCr is normal. This should be expected. Repeat labs in 2 weeks

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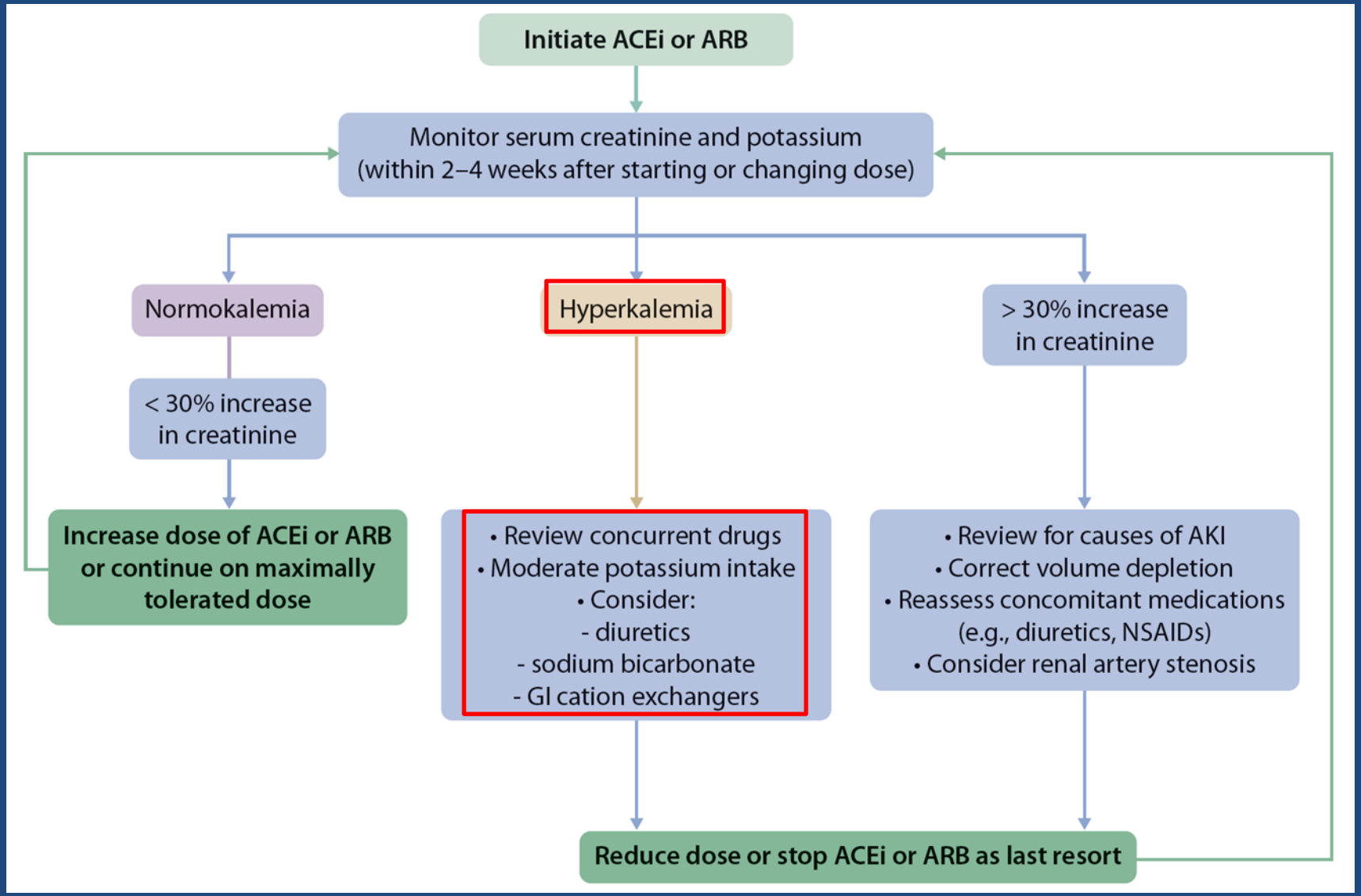
Meds: Increased losartan 50mg daily, metformin is increased to 1000mg BID, carvedilol 6.25mg BID
LABS: SCr 1.8mg/dl, eGFR 42ml/min, sK+ 5.8 mmol/L, A1C 8.2%, UACR 300mg/g
PE: BP 130/80, +trace LE edema
Denies hypotension, usage of NSAIDs, vomiting/diarrhea

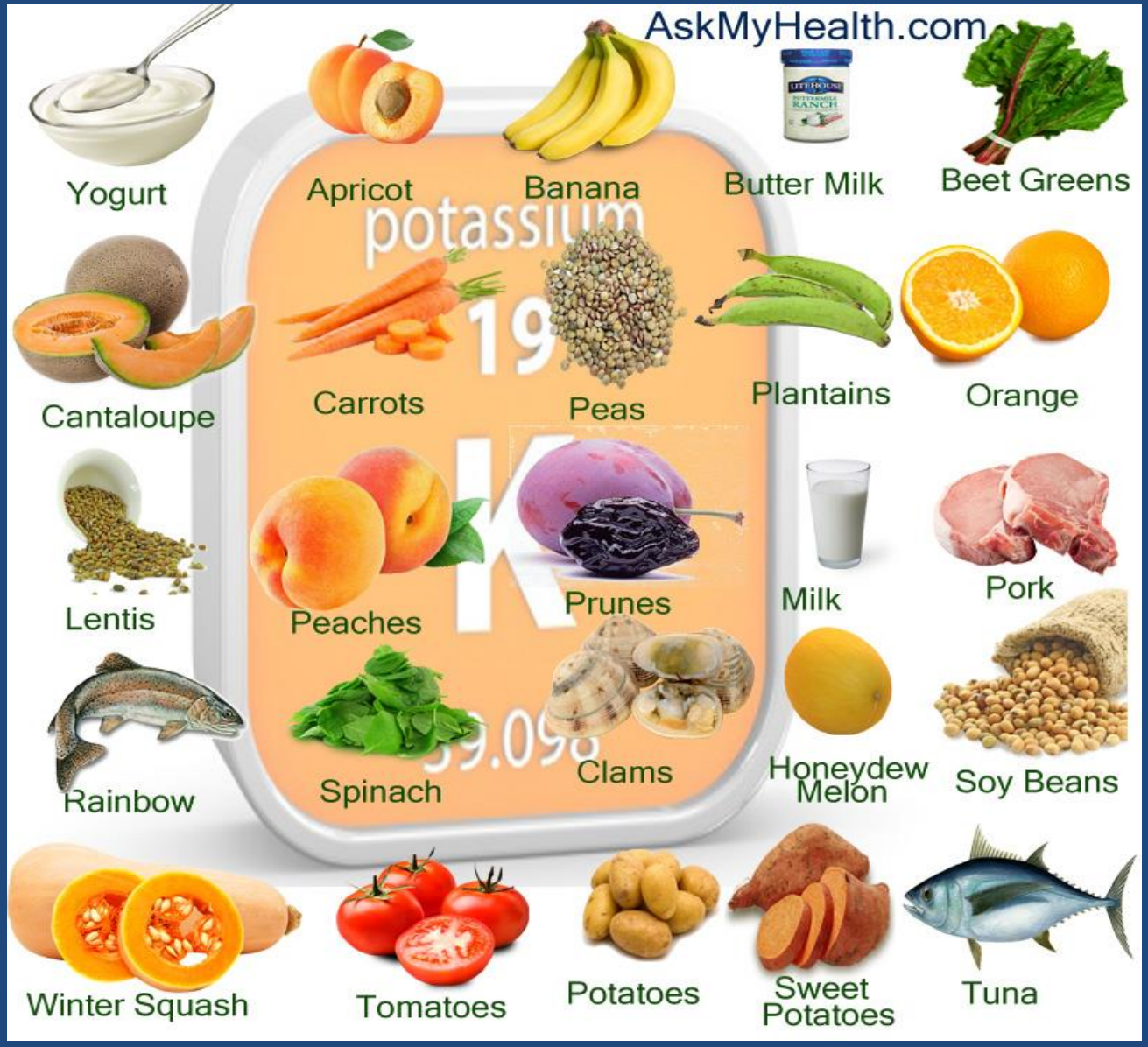
After discussing avoidance of orange juice and watermelon, what change would you make to the above Tx for DKD?

1. Decrease losartan to 25mg daily
2. Decrease losartan to 12.5mg daily
3. Discontinue losartan
4. Start chlorthalidone 25mg every other day

RAS Blockade with Albuminuria



High Potassium Diet



Amazing 32yo single mom of 3 boys

PMH: Type 2 DM x 15 yrs with retinopathy, obesity, CKD stage 2A3, smoker
Meds: Increased losartan 50mg daily, metformin is increased to 1000mg BID, carvedilol 6.25mg BID
LABS: SCr 1.8mg/dl, eGFR 42ml/min, sK+ 5.8 mmol/L, A1C 8.2%, UACR 300mg/g
PE: BP 130/80, +trace LE edema
Denies hypotension, usage of NSAIDs, vomiting/diarrhea

After discussing avoidance of orange juice and watermelon, what change would you make to the above Tx for DKD?

1. Decrease losartan to 25mg daily
2. Decrease losartan to 12.5mg daily
3. Discontinue losartan
4. Start chlorthalidone 25mg every other day

Chronic Management of Hyperkalemia

When starting ACEi or ARB

- Start w/ low dose
- Check serum K+ within 1-2 weeks of initiation or dose escalation

1. Low K+ diet

2. Thiazide or loop diuretics

- Select loop diuretics if eGFR <30 ml/min OR edematous

3. If acidotic, correct metabolic acidosis with oral bicarb repletion

4. Potassium binder : older generation: kayexalate

$$$$ newer generation: patiromer, sodium zirconium

Amazing 32yo single mom of 3 boys

PMH: Type 2 DM x 15 yrs with retinopathy, obesity, CKD stage 2A3, smoker

Meds: Continued losartan 50mg daily, started chlorthalidone 25mg every other day, metformin 1000mg BID, carvedilol 6.25mg BID

LABS: SCr 1.8mg/dl, eGFR 42ml/min, sK+ 5.0 mmol/L, A1C 8.2%, UACR 200mg/g

PE: BP 120/70, No LE edema

Denies hypotension, usage of NSAIDs, vomiting/diarrhea

After discussing avoidance of orange juice and watermelon, what change would you make to the above Tx for DKD?

Beautiful 44 yo Special Ed Teacher

PMH: HTN, morbid obesity, CKD stage 2A3, depression & recently diagnosed with T2DM

Meds: Lisinopril 40mg BID, sertraline 200mg daily & metformin 500mg daily

Labs: SCr 0.9mg/dl, eGFR 78ml/min, A1C 7.0%, UACR 400mg/g. Cholesterol is at goal

PE: BP 115/65, P 95, BMI 41. otherwise unremarkable

What is the most appropriate next steps for treatment of DKD?

1. Refer her to surgical weight loss clinic
2. Refer her to endocrinologist for management
3. Spend time assessing psychological health and need for referral to psychologist/psychiatrist
4. Assess her knowledge of necessary lifestyle interventions (diet, exercise, weight loss)

2020 Clinical practice guidelines for DM management in CKD

1. Comprehensive care

   -Control of risk factors including RAS blockade in those with albuminuria remains part of standard of care

2. Lifestyle intervention
3. Glycemic goals based upon A1C and BS
4. Anti-hyperglycemic treatment options

   -Initial use of BOTH metformin and SGLT2i is recommended

5. Approaches to management of patients

Lifestyle Modifications

1. Diet
2. Exercise
3. Weight loss

Diet

Animal proteins

Meat, poultry, fish, seafood, eggs:
28 g (1 oz) = 6–8 g protein
1 egg = 6–8 g protein

Dairy, milk, yogurt, cheese:
250 ml (8 oz) = 8–10 g protein
28 g (1 oz) cheese = 6–8 g protein

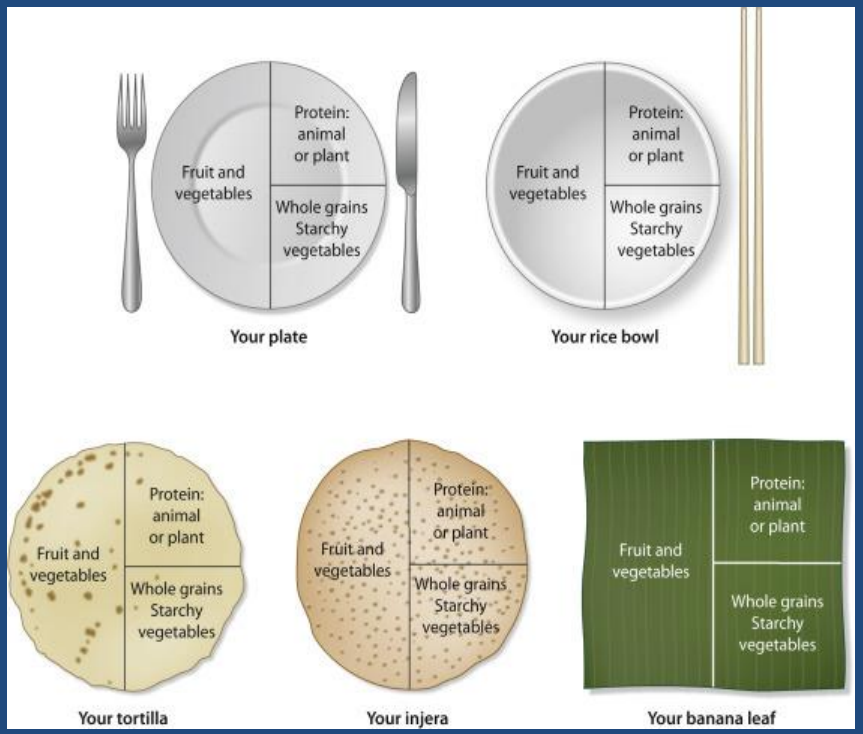
Plant proteins

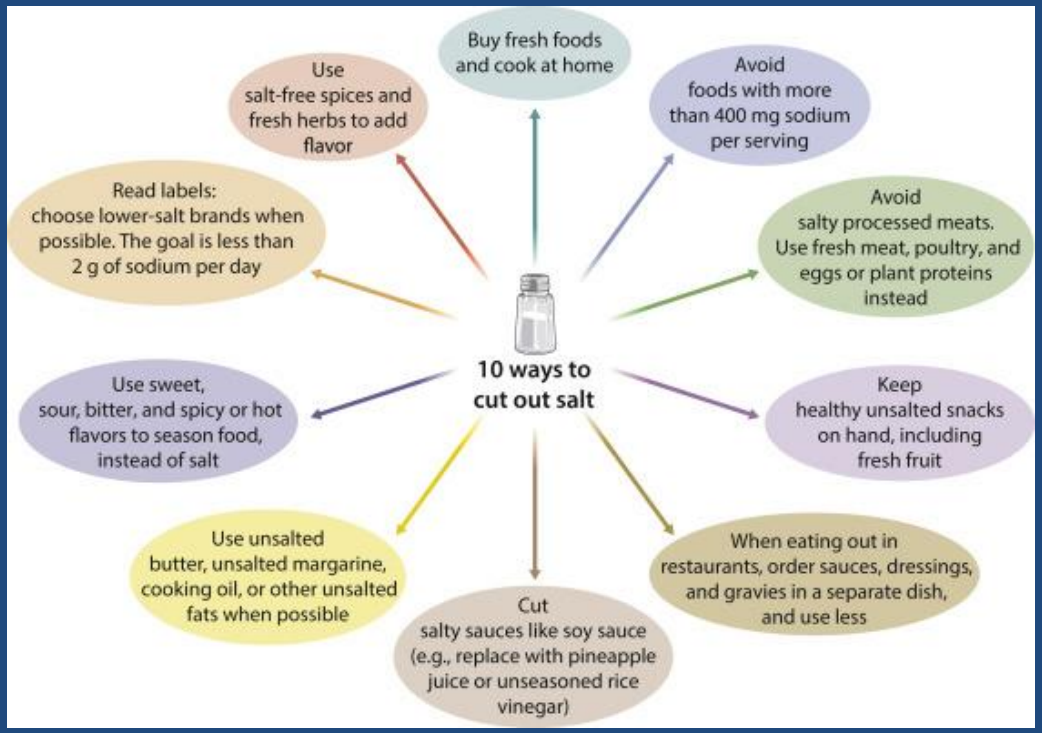
Legumes, dried beans, nuts, seeds:
100 g (0.5 cup) cooked = 7–10 g protein

Whole grains, cereals:
100 g (0.5 cup) cooked = 3–6 g protein

Starchy vegetables, breads:
2–4 g protein

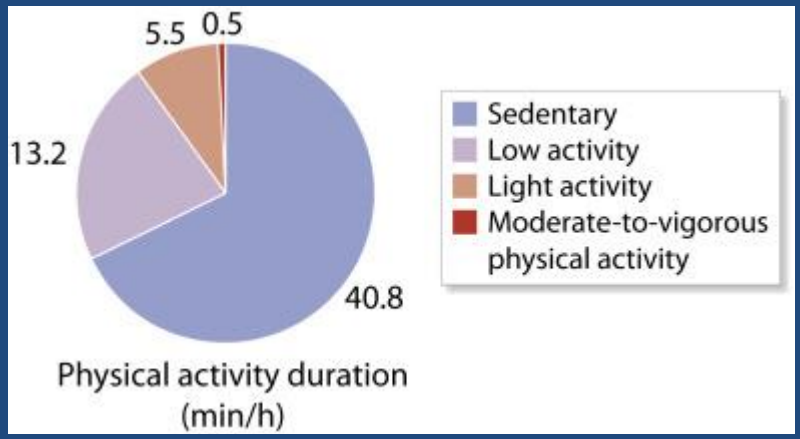
Weight (kg)	35	40	50	55	60	65	70	75	80	85	90	95	100
Grams of protein per day (wt × 0.8 g/kg)	28	32	40	44	48	52	56	60	64	68	72	76	80

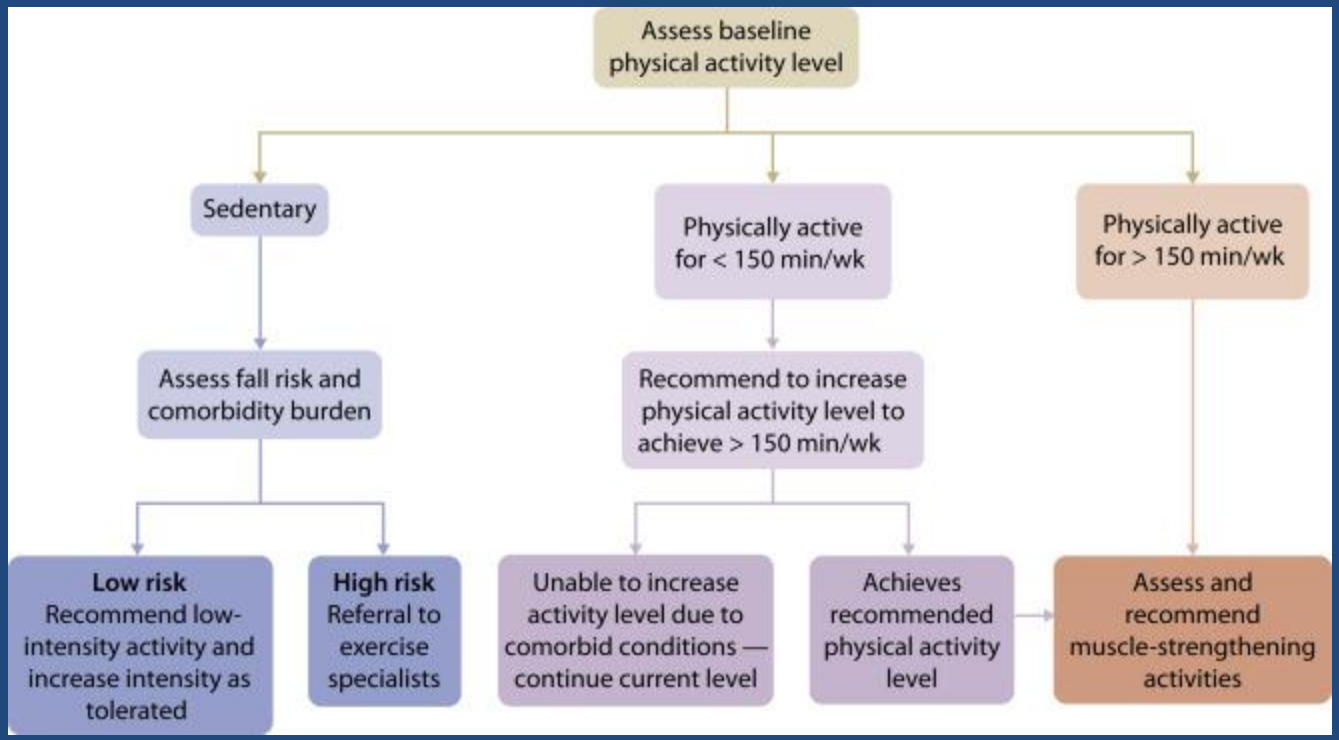




Exercise

Intensity of physical activity	METs	Examples
Sedentary	<1.5	Sitting, watching television, reclining
Light	1.6–2.9	Slow walking, household work such as cooking, cleaning
Moderate	3.0–5.9	Brisk walking, biking, yoga, swimming
Vigorous	>6	Running, biking, swimming, lifting heavy weights





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4. Assess her knowledge of necessary lifestyle interventions (diet, exercise, weight loss)

Beautiful 44 yo Special Ed Teacher

PMH: HTN, morbid obesity, CKD stage 2A3, depression & recently diagnosed with T2DM

You refer her Weight Wellness Clinic and dietician

She is a no show to 2 f/u visit.

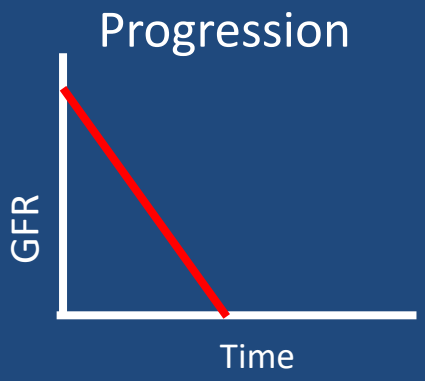
Returns 6 months later with further increase in weight by 20lbs, worsening A1C 8.5% and UACR 1000mg/g. You review notes from weight loss provider who suggested starting GLP 1RA + topiramate to aid with weight loss but current med list does not show these 2 meds

Which of the above is NOT the appropriate next next step for optimal treatment of DKD?

1. Add an ARB to ACEi for dual RAS blockade for further lowering of albuminuria
2. Order 24hr urine to assess total daily sodium intake
3. Spend time assessing how her visit went with Weight Wellness Clinic
4. Spend time assessing mental health

Proteinuria and Progression of Diabetic Nephropathy

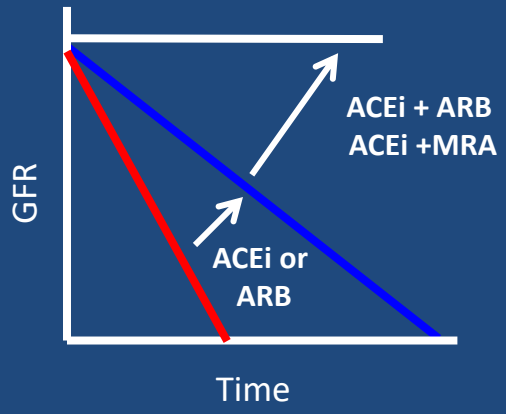
Proteinuria



ACEi + ARB
ACEi + MRA

Proteinuria

Progression slowed or halted ?



ACEi = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
MRA = mineralocorticoid receptor antagonist

Dual RAS Blockade

- Long-term outcome trials in T2D and CKD demonstrated NO kidney or cardiovascular benefit of RAS blockade with combined therapy to block the RAS versus the single use of RAS inhibitors. However, combination therapy was associated with a **higher rate of hyperkalemia and AKI**

Beautiful 44 yo Special Ed Teacher

PMH: HTN, morbid obesity, CKD stage 2A3, depression & recently diagnosed with T2DM

You refer her Weight Wellness Clinic and dietician

She is a no show to 2 f/u visit.

Returns 6 months later with further increase in weight by 20lbs, worsening A1C 8.5% and UACR 1000mg/g. You review notes from weight loss provider who suggested starting GLP 1RA + topiramate to aid with weight loss but current med list does not show these 2 meds

Which of the above is NOT the appropriate next next step for optimal treatment of DKD?

1. Add an ARB to ACEi for dual RAS blockade for further lowering of albuminuria

You discover she is eating a salt intake leading to increase in albuminuria and contributing to weight gain. After assess mental health, you learn that her depression is worse. She is struggling with shame and self harm as she continues to gain more weight.

Kindest, elderly 75yo male with CHF

PMH: HFpEF, HTN, T2M, CKD 3A3

Meds: torsemide 20mg BID, carvedilol 12.5mg BID, losartan 50mg BID, metformin 500mg BID

Labs: SCr 2.0, eGFR 37, A1C 7.5%, UACR 2000mg/g

PE: 130/65, 70, BMI 25

Chest: CTA B/L CVS: S4, no JVD

Ext: +1 LE edema

What is the best treatment option for treatment of T2D and CKD?

2020 Clinical practice guidelines for DM management in CKD

1. Comprehensive care

   -Control of risk factors including RAS blockade in those with albuminuria remains part of standard of care

2. Lifestyle intervention
3. Glycemic goals based upon A1C and BS
4. Anti-hyperglycemic treatment options

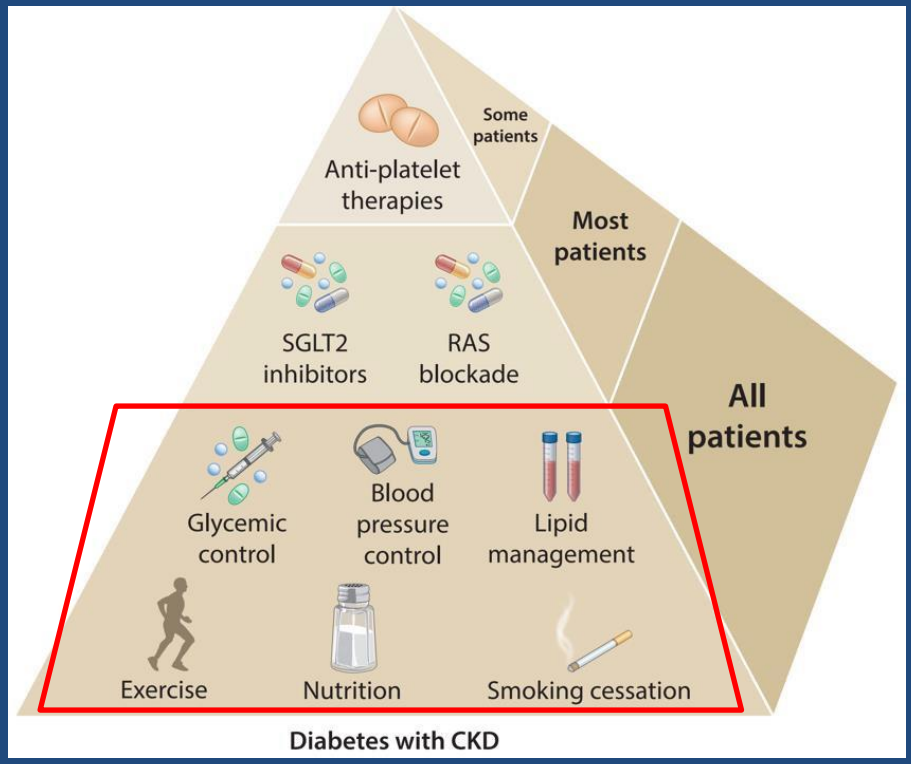
   -Initial use of BOTH metformin and SGLT2i is recommended

5. Approaches to management of patients

KDIGO 2020 Tx Updates : *Comprehensive Care in Patients with DM and CKD*

Practice Point 1.1.1:

Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease.



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PE: 130/65, 70, BMI 25

Chest: CTA B/L CVS: S4, no JVD

Ext: +1 LE edema

What is the best treatment option for treatment of T2D and CKD?

1. Comprehensive care—smoker? Highest tolerable dose of RAS blockade?
2. BP to goal
3. Lipid management
4. Lifestyle intervention
5. Mental health—guilt/shame

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

#NephJC

Comprehensive care

To reduce risks of CKD progression and CV disease

ACEi or ARB in pts with DM, HTN and albuminuria

Dietary changes

Individualized HbA1c Target (<6.5 - <8.0%)
(for non dialysis pt)

Lifestyle interventions

Protein intake 0.8 g /kg /day
(for non dialysis pt)

Tobacco cessation

Physical activity
Moderate-intensity for at least 150 min/wk

Nacl intake <5gm/day

Antihyperglycemic therapies

Metformin

eGFR :
<45 – Dose modification
< 30 or Dialysis – Discontinue

SGLT2inhibitors

eGFR :
<30 – Do not initiate
Dialysis – Discontinue

- ✓ Long-acting **GLP-1 RA** : if glycemic targets not achieved despite use of metformin and SGLT2i, or unable to use those medications
- ✓ Additional drug therapy as needed for glycemic control, Guided by patient preferences, comorbidities, eGFR, and cost

- ✓ **Structured self-management educational program as per local context, cultures, and availability of resources**
- ✓ **Team-based, integrated care focused on risk evaluation and patient empowerment**

Conclusion: New KDIGO guideline on DM management in CKD offers approaches for evidence-based care, supplemented with practice points to inform clinical management and implementation..

Reference: IH de Boer et al.: KDIGO guideline on diabetes in CKD; Kidney International (2020)

VA by Priti Meena, M.D @**Priti899**

2020 Clinical practice guidelines for DM management in CKD

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Kindest, elderly 75yo male with CHF

PMH: HFpEF, HTN, T2M, CKD 3A3

Meds: torsemide 20mg BID, carvedilol 12.5mg BID, losartan 50mg BID, metformin 500mg BID

Labs: SCr 2.0, eGFR 37, A1C 7.5%, UACR 2000mg/g

PE: 130/65, 70, BMI 25

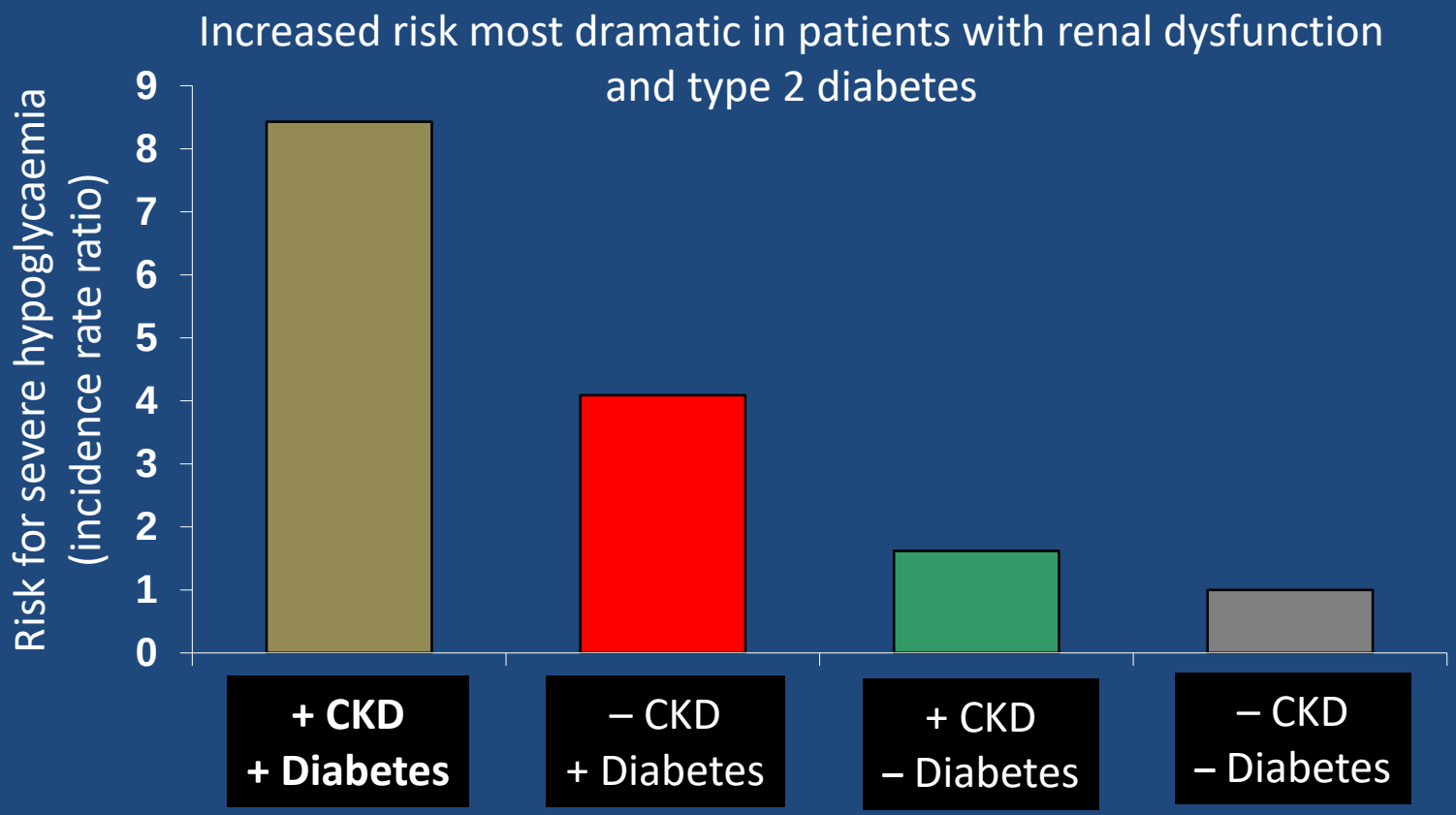
Chest: CTA B/L CVS: S4, no JVD

Ext: +1 LE edema

What is the recommended A1C goal for kindest, elderly 75yo male?

1. <6.5%
2. <7%
3. <7.5%
4. <8%

Declining renal function also increases risk of severe hypoglycemia



Around 74% of sulphonylurea-induced severe hypoglycaemic events (loss of consciousness) occurs in patients with reduced renal function

Moen et al. CJASN 2009;4:1121–27; Weir et al. Nephrol Dial Transplant 2011;26:1888–94

Glycemic goals based upon A1C & BS

- Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis *(1C)*.

< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

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What is the recommended A1C goal for kindest, elderly 75yo male?

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2. <7%
3. <7.5%
4. <8%

We need to assess hypoglycemic risk

2020 Clinical practice guidelines for DM management in CKD

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What is the best treatment option for treatment of T2D and CKD?

1. Increase metformin to 1000mg BID
2. Increase torsemide 40mg BID
3. Increase carvedilol 25mg BID
4. Start SGLT2i

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Meds: torsemide 20mg BID, carvedilol 12.5mg BID, losartan 50mg BID, metformin 500mg BID

Labs: SCr 2.0, eGFR 37, A1C 875%, UACR 2000mg/g

PE: 130/65, 70, BMI 25

Chest: CTA B/L CVS: S4, no JVD

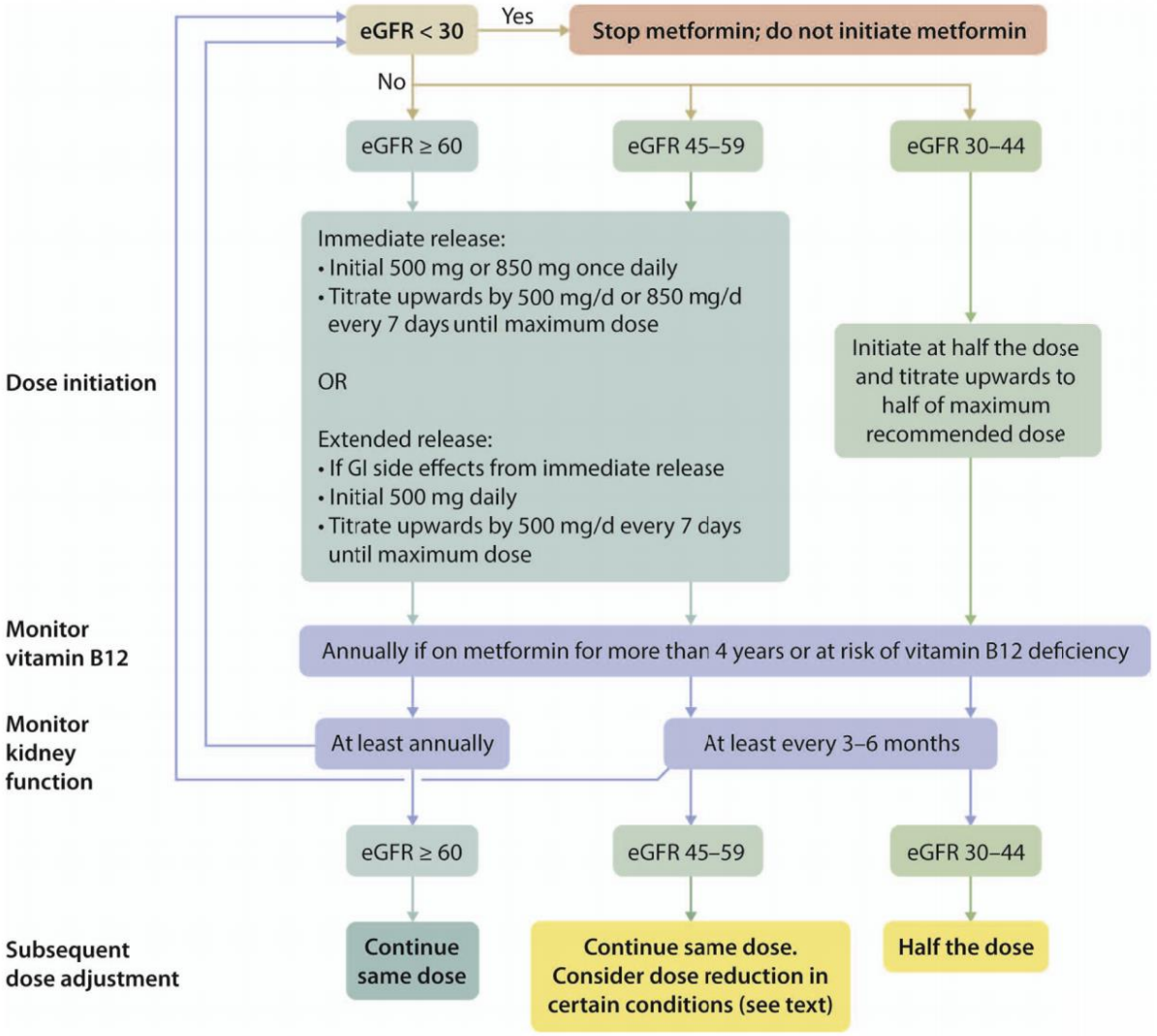
Ext: +1 LE edema

What is the potential side effect of increasing metformin to 1000mg BID with eGFR 37ml/min?

1. Worsening of kidney function
2. Increase risk of hyperkalemia
3. Development of lactic acidosis
4. Hypoglycemia

Metformin titration

Practice Point 2. Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is < 60 ml/min per 1.73 m²



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Labs: SCr 2.0, eGFR 37, A1C 7.5%, UACR 2000mg/g

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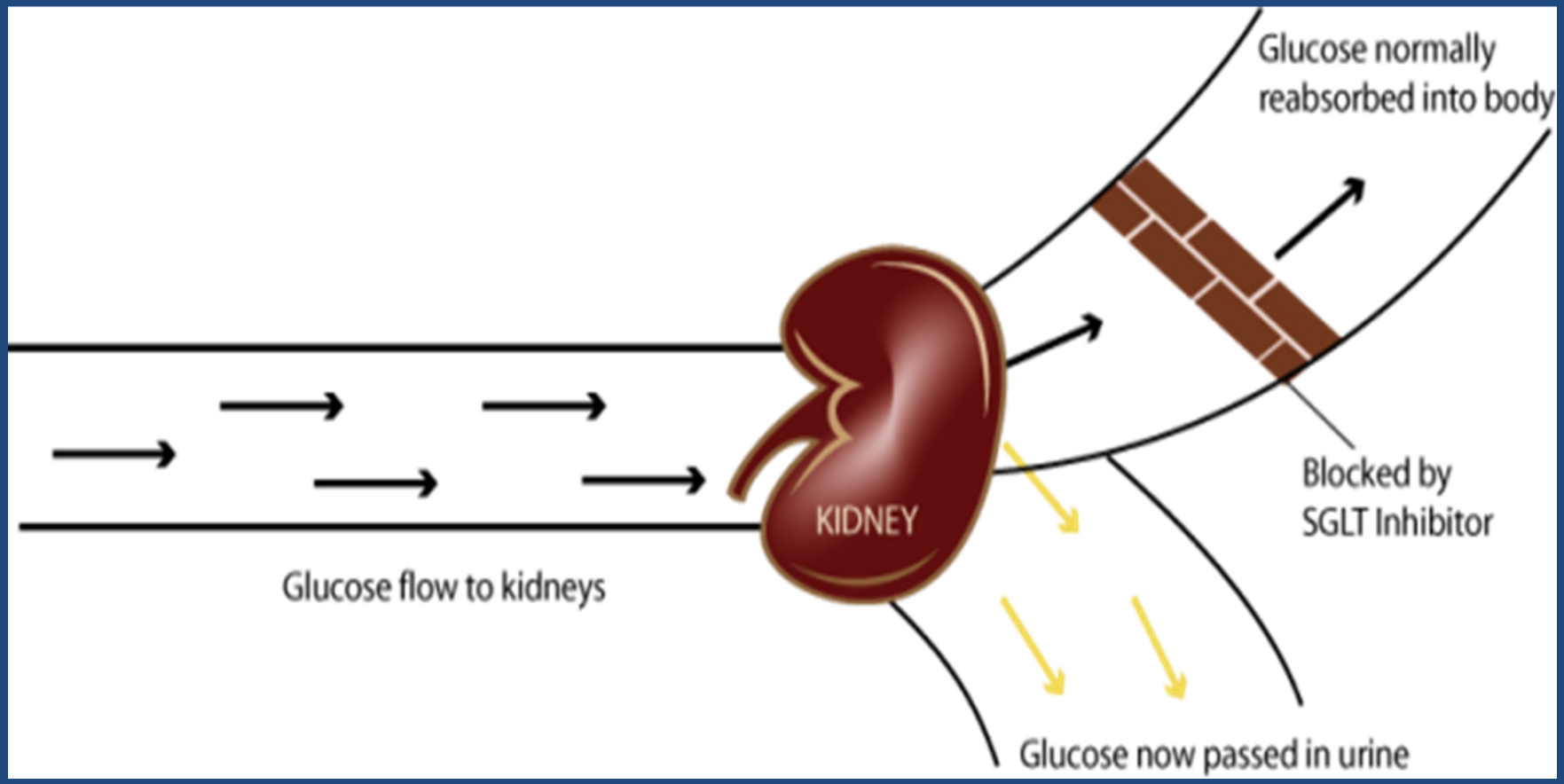
What is the best treatment option for treatment of T2D and CKD?

1. Increase metformin to 1000mg BID
2. Increase torsemide 40mg BID
3. Increase carvedilol 25mg BID
4. Start SGLT2i

SGLT 2 Inhibitors “gliflozins”

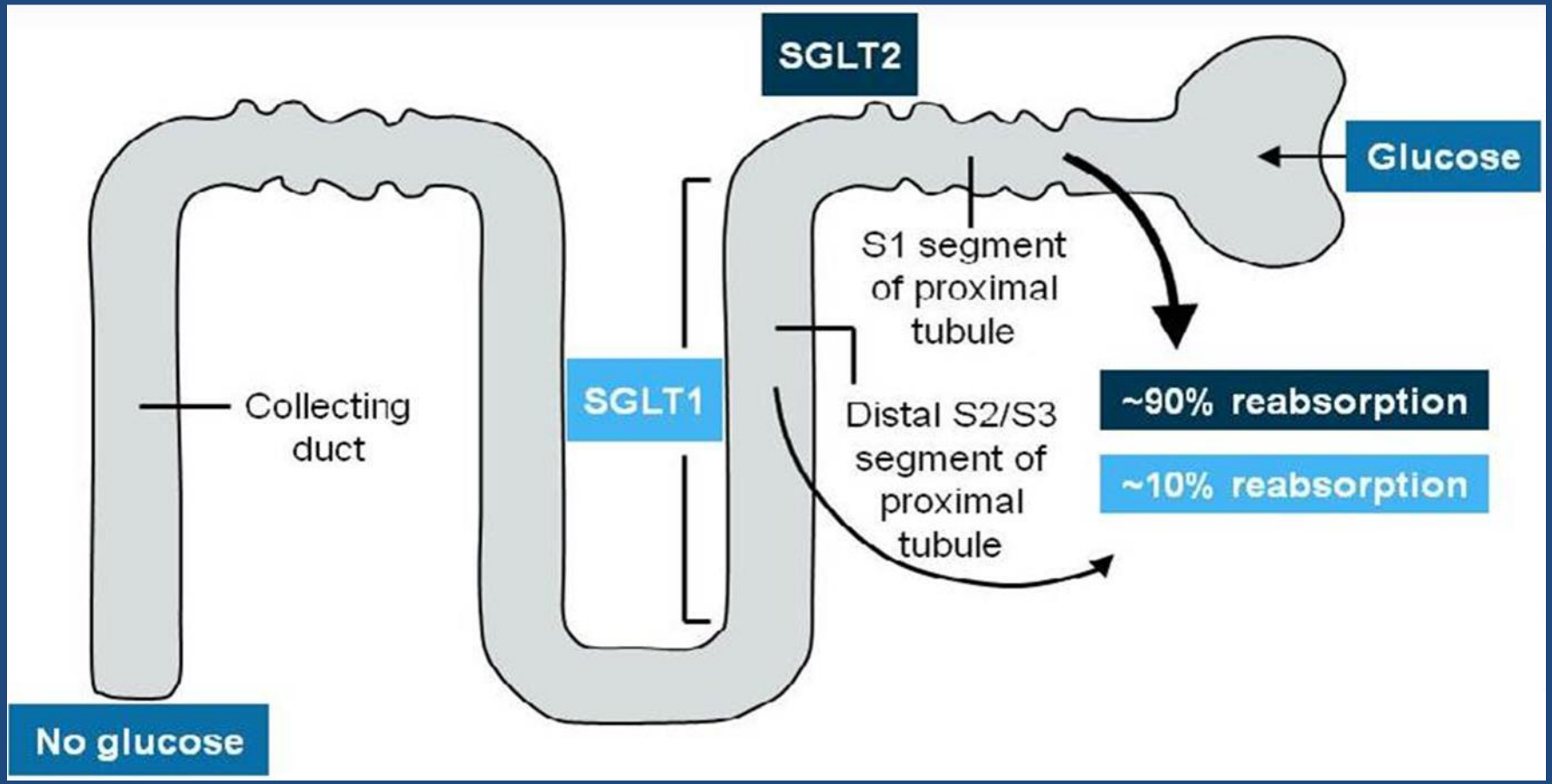
Block glucose resorption into body

Increasing urinary excretion of glucose



Sodium–glucose cotransporter 2 inhibitors (SGLT 2 Inhibitors)

SGLT 2 segment in proximal tubule reabsorbs 90% of glucose

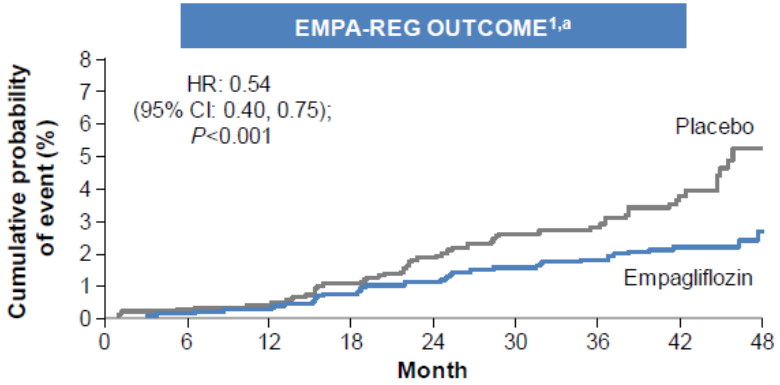


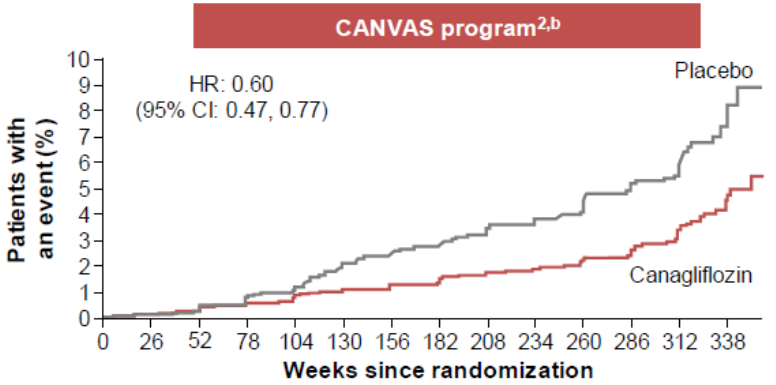
SGLT2 Inhibitors

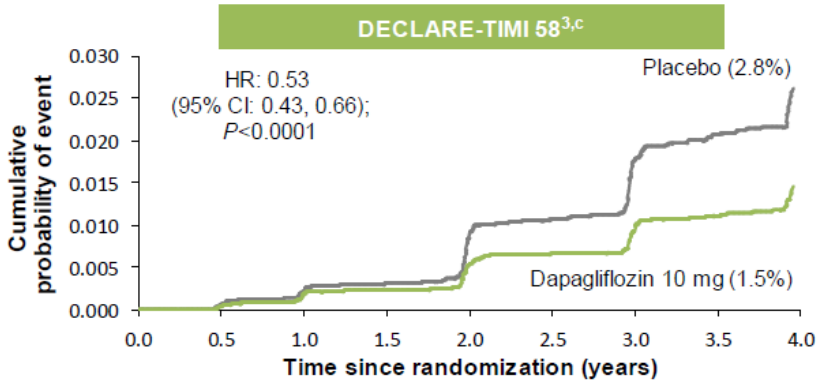
Cardiovascular and Renal Outcome Trials in T2D

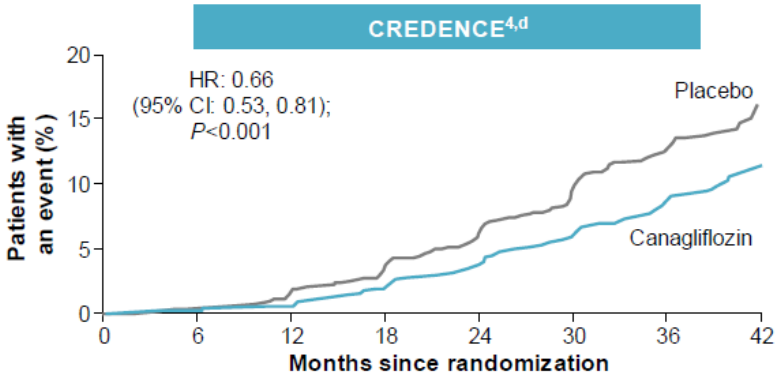
- Reduce risk of major adverse CVD Events
  - 3-point MACE (myocardial infarction, stroke, CVD death)
  - Heart failure (empagliflozin, canagliflozin, dapagliflozin)
  - CVD death (empagliflozin, dapagliflozin)
- Decrease severe albuminuria, decline in eGFR, and ESRD. SGLT2i enhance natriuresis, cause intravascular volume contraction and alter intra-renal hemodynamics, which probably contribute to beneficial effects on blood pressure, body weight and albuminuria
- CVD and CKD benefits are present in patients with pre-existing CKD

Class Effect of SGLT2 Inhibitors on CKD Outcomes







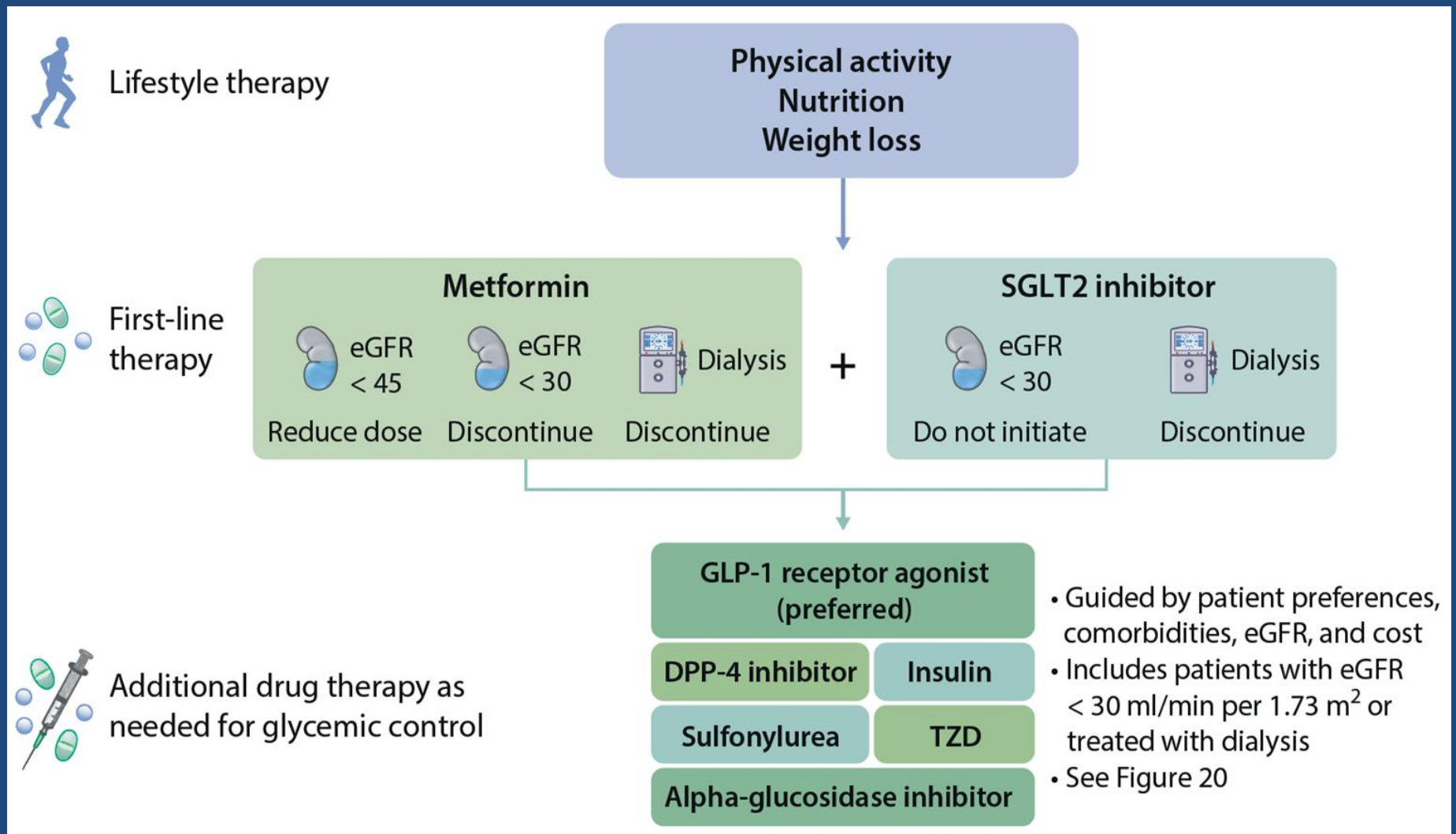


[a]Composite kidney disease endpoint was defined as: dSCr accompanied by eGFR ≤45 mL/min/1.73 m^2, RRT, or kidney death; [b]40% reduction in eGFR, RRT, or death from kidney causes; [c]eGFR decrease ≥40% to <60 mL/min/1.73 m^2, ESKD or kidney death; [d]ESRD, dSCr, or kidney death

CI, confidence interval; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; RRT, renal replacement therapy; SGLT2, sodium–glucose co-transporter 2

1. Wanner C, et al. *N Engl J Med* 2016;375:323–334; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657; 3. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 4. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306

Tx algorithm for selecting anti-hyperglycemic drugs for DM & CKD



Kindest, elderly 75yo male with CHF

PMH: HFpEF, HTN, T2M, CKD 3A3

Meds: started empaglifozin 10mg daily in addition to: torsemide 20mg BID, carvedilol 12.5mg BID, losartan 50mg BID, metformin 500mg BID

Labs: SCr 2.2, eGFR 33, A1C 7.4%, UACR 1500mg/g

PE: 125/60, 70, BMI 25

Chest: CTA B/L CVS: S4, no JVD

Ext: +trace LE edema

What should we do next due to increase in SCr and decline in eGFR?

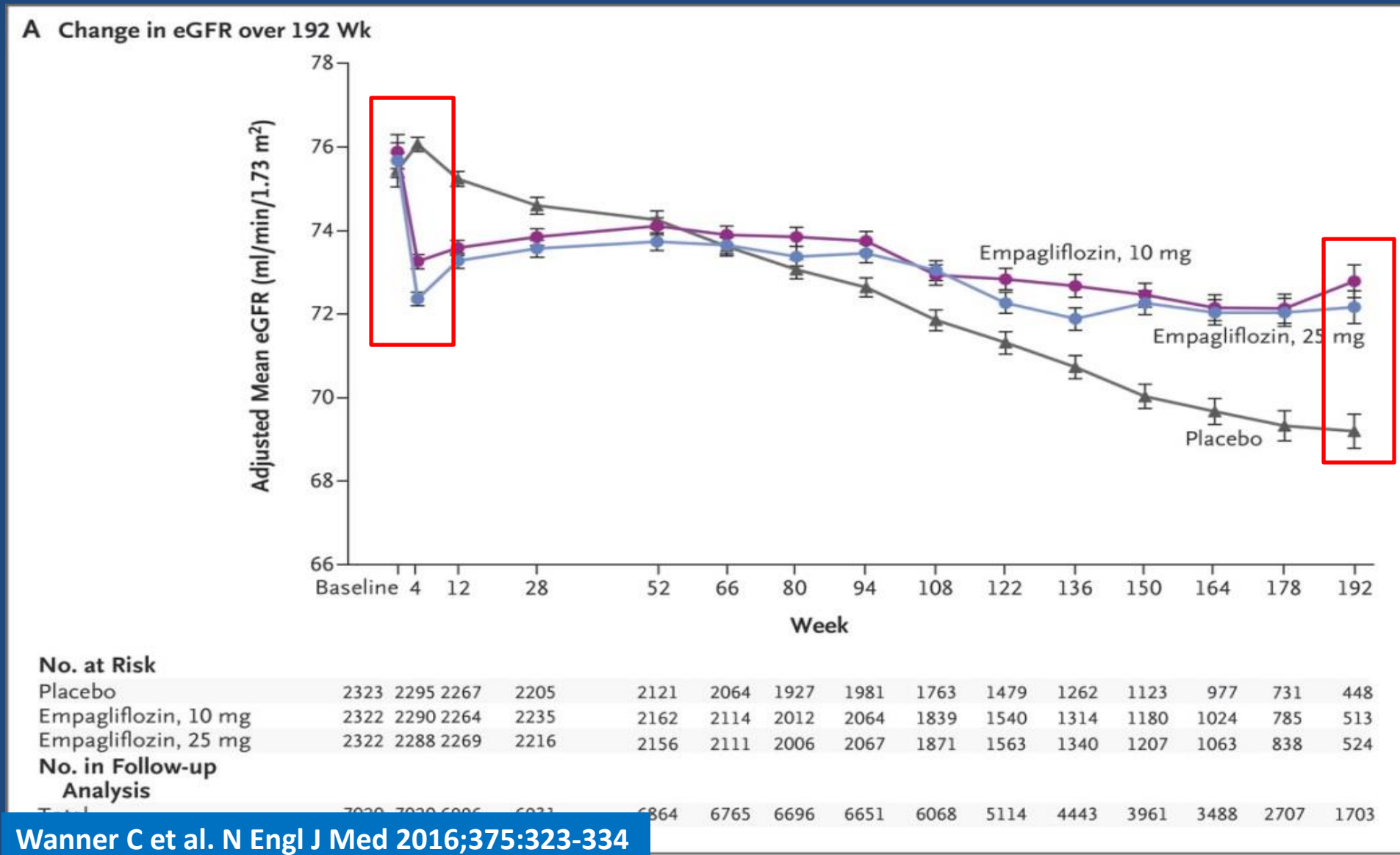
1. Discontinue empagliflozin
2. Decrease torsemide 10mg BID
3. Decrease losartan 25mg BID
4. Look for evidence of volume depletion/hypotension

SGLT2i Safety and Prescribing

1. AKI safety and the GFR “dip”
2. Volume depletion/hypotension
3. Concern about having to manage glucose, hypoglycemia
4. DKA risks
5. Genital tract infection

The NEW ENGLAND JOURNAL of MEDICINE

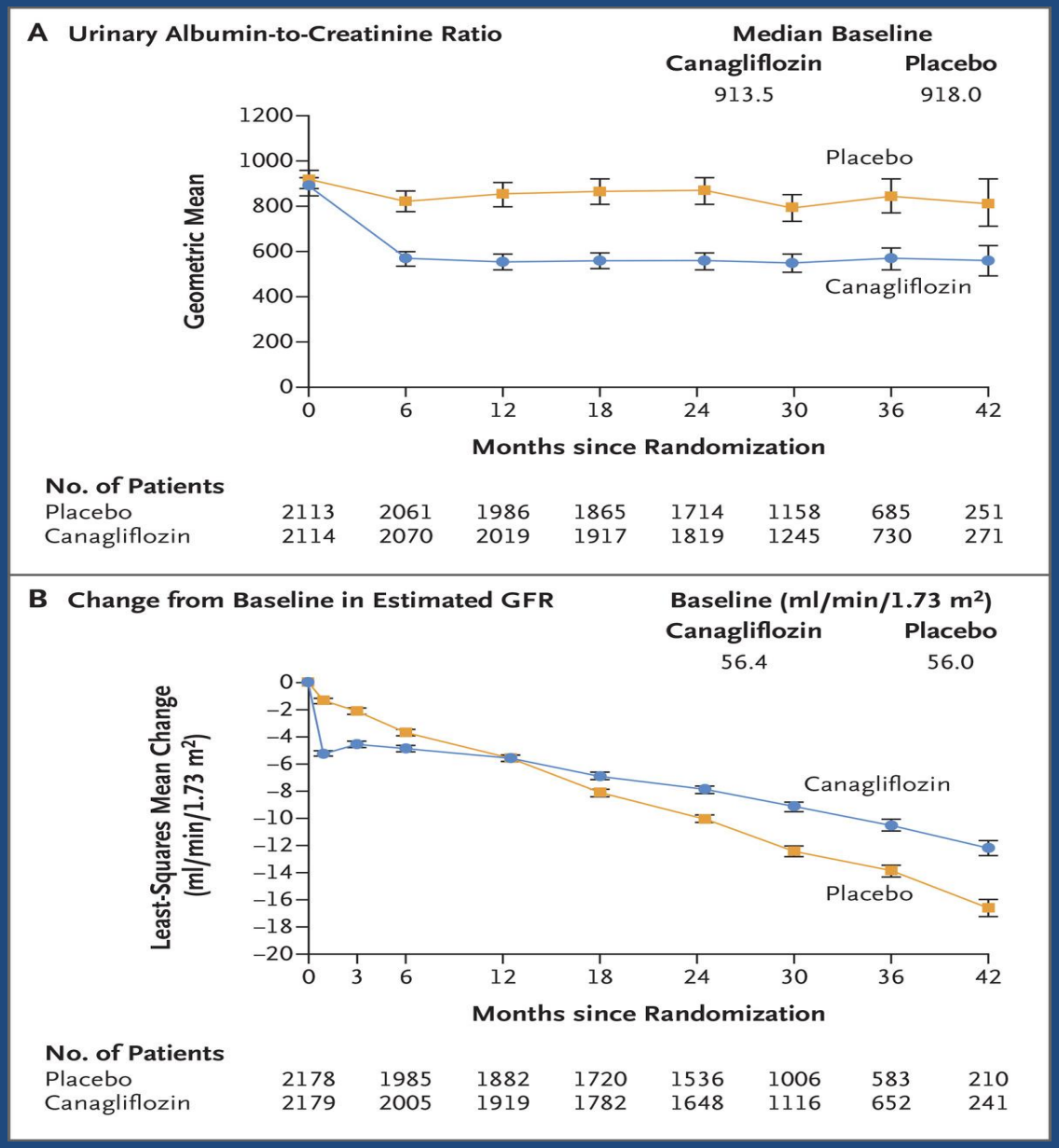
Renal Function over Time.



Wanner C et al. N Engl J Med 2016;375:323-334

CREDENCE

Effects on GFR and albuminuria



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

SGLT2i are associated with LOWER risk of AKI

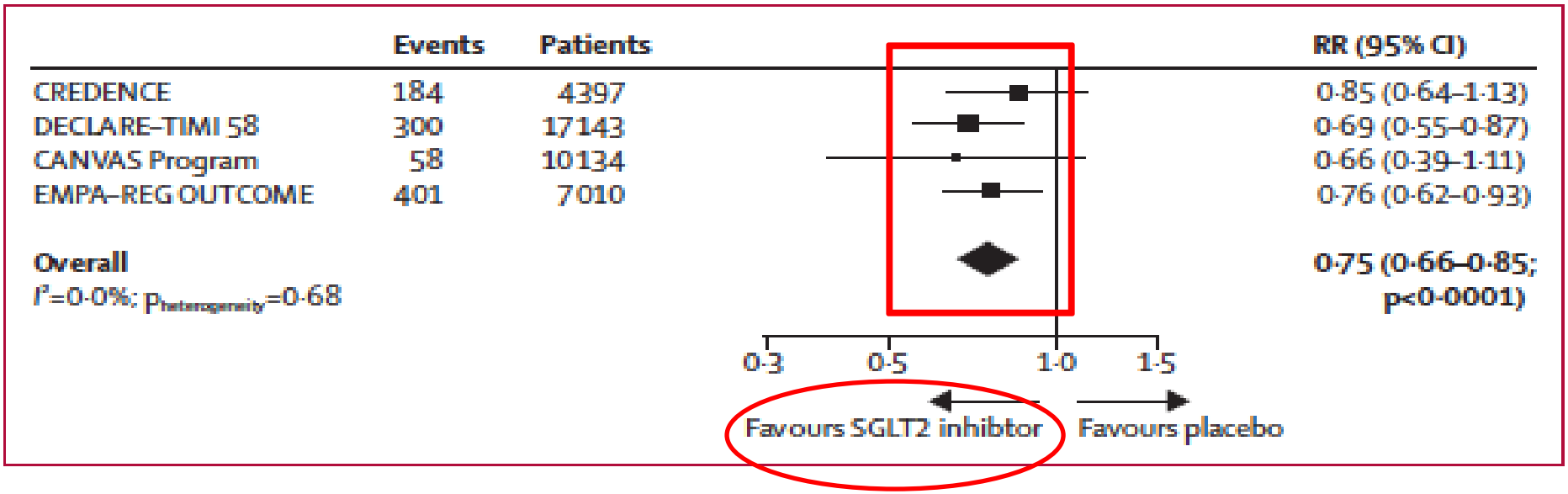


Figure 3: **Effect of SGLT2 inhibitors on acute kidney injury**
Weights were from random-effects meta-analysis. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

Neuen et al. Lancet DE 2019

SGLT2i Safety and Prescribing

1. AKI safety and the GFR “dip”
2. Volume depletion/hypotension
3. Concern about having to manage glucose, hypoglycemia
4. DKA risks
5. Genital tract infection

SGLT2 Inhibitors

Cardiovascular and Renal Outcome Trials in T2D

- Reduce risk of major adverse CVD Events
  - 3-point MACE (myocardial infarction, stroke, CVD death)
  - Heart failure (empagliflozin, canagliflozin, dapagliflozin)
  - CVD death (empagliflozin, dapagliflozin)
- Decrease severe albuminuria, decline in eGFR, and ESRD. **SGLT2i enhance natriuresis, cause intravascular volume contraction and alter intra-renal hemodynamics, which probably contribute to beneficial effects on blood pressure, body weight and albuminuria**
- CVD and CKD benefits are present in patients with pre-existing CKD

GFR “dip”

- The GFR dip is reversible and NOT a sign of injury—similar to ACEi/ARB GFR “dip” with altered blood hemodynamics
- SGLT2i may REDUCE AKI–Mechanism?
- Significant volume depletion/hypotension RARE
- BP lowering effect quite modest

Kindest, elderly 75yo male with CHF

PMH: HFpEF, HTN, T2M, CKD 3A3

Meds: started empaglifozin 10mg daily in addition to: torsemide 20mg BID, carvedilol 12.5mg BID, losartan 50mg BID, metformin 500mg BID

Labs: SCr 2.2, eGFR 33, A1C 7.4%, UACR 1500mg/g

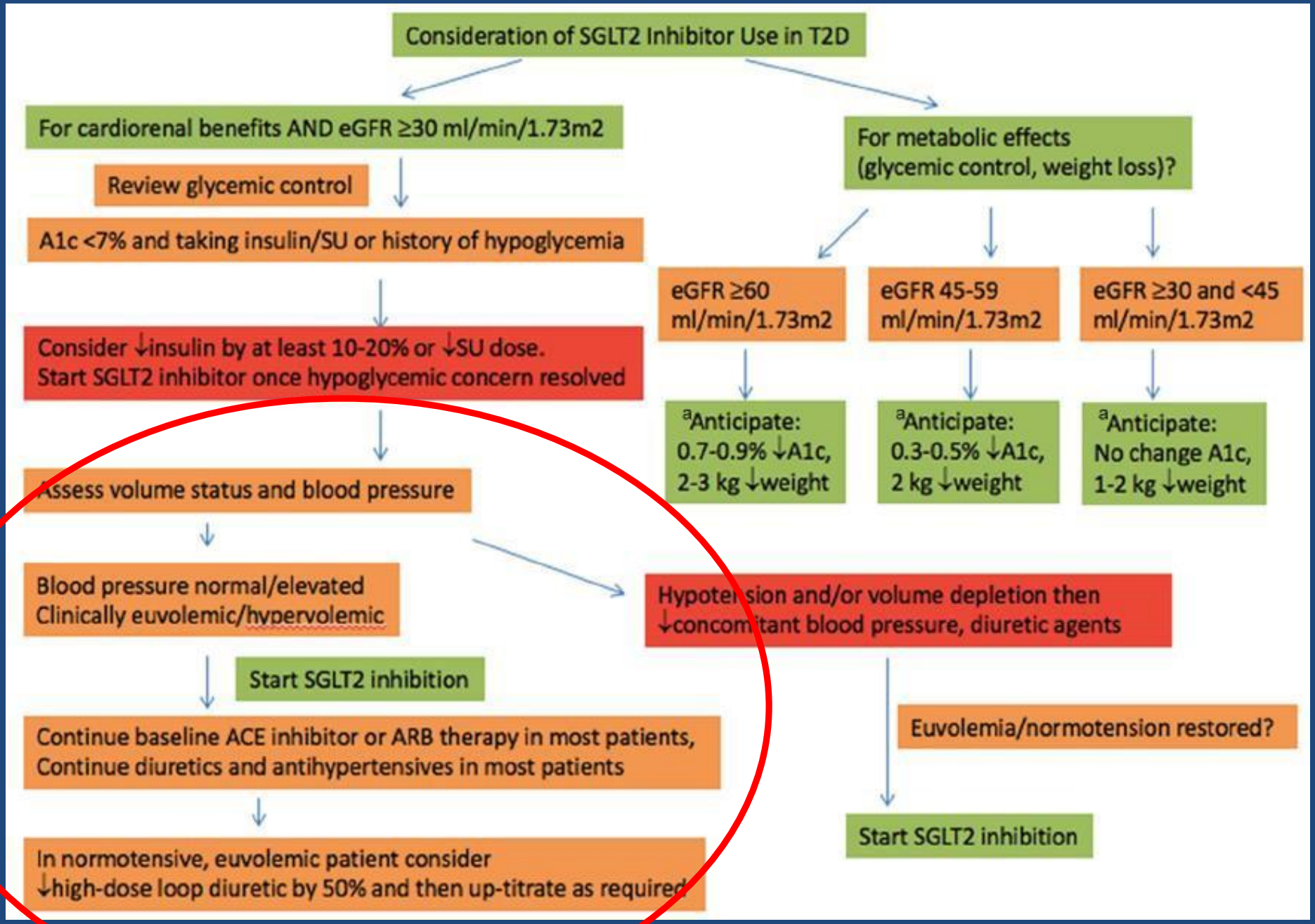
PE: 125/60, 70, BMI 25

Chest: CTA B/L CVS: S4, no JVD

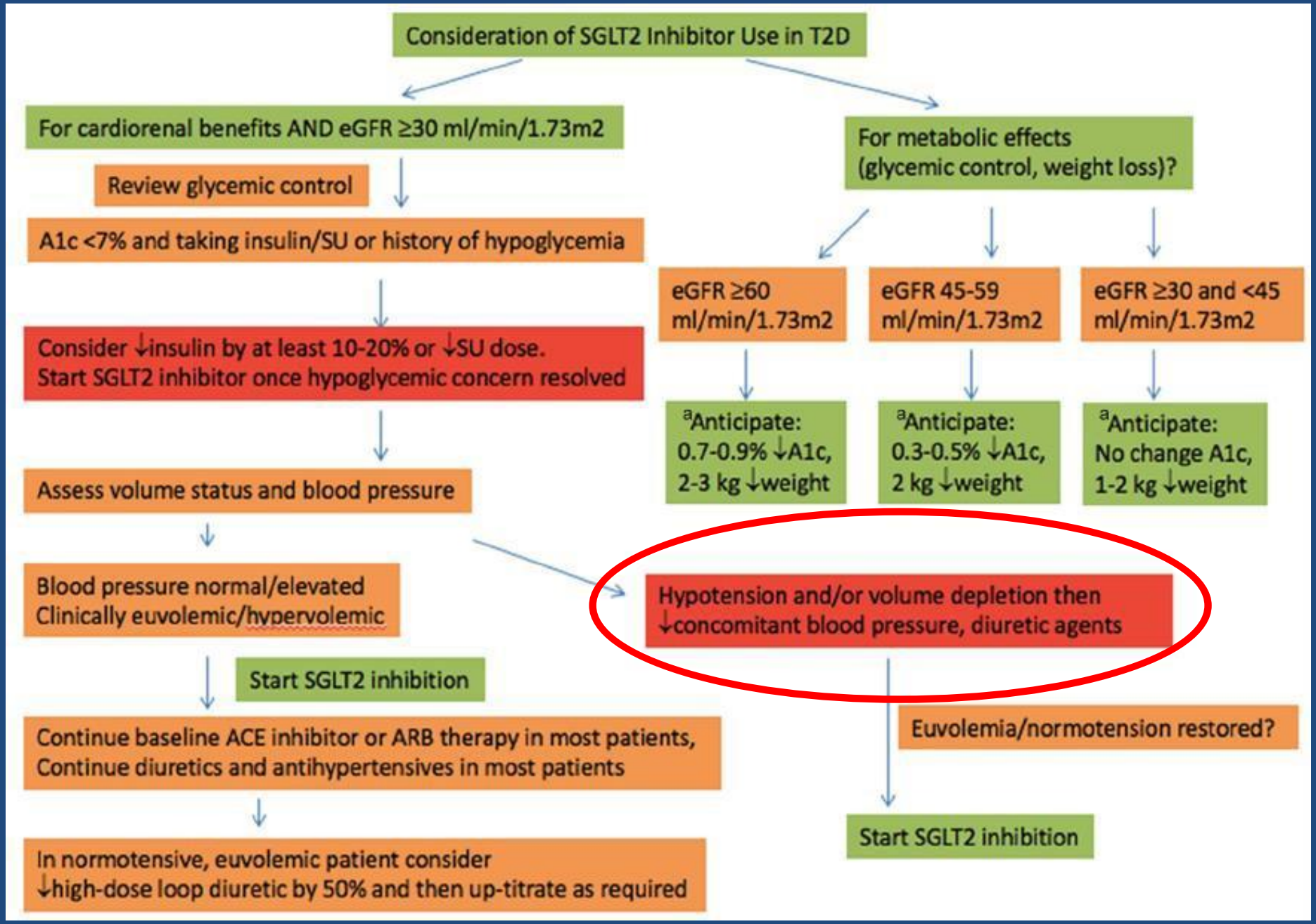
Ext: +trace LE edema

What should we do next due to increase in SCr and decline in eGFR?

1. Discontinue empagliflozin
2. Decrease torsemide 10mg BID
3. Decrease losartan 25mg BID
4. Look for evidence of volume depletion/hypotension→though RARE.



Dubrofsky//Cherney. CJKHD 2020



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Labs: SCr 2.2, eGFR 33, A1C 7.4%, UACR 1500mg/g

PE: 110/60, 70, orthostatic vitals with 90/60, 90 with standing

What should we do next due to increase in SCr and decline in eGFR?

1. Discontinue empagliflozin
2. Decrease torsemide 10mg BID
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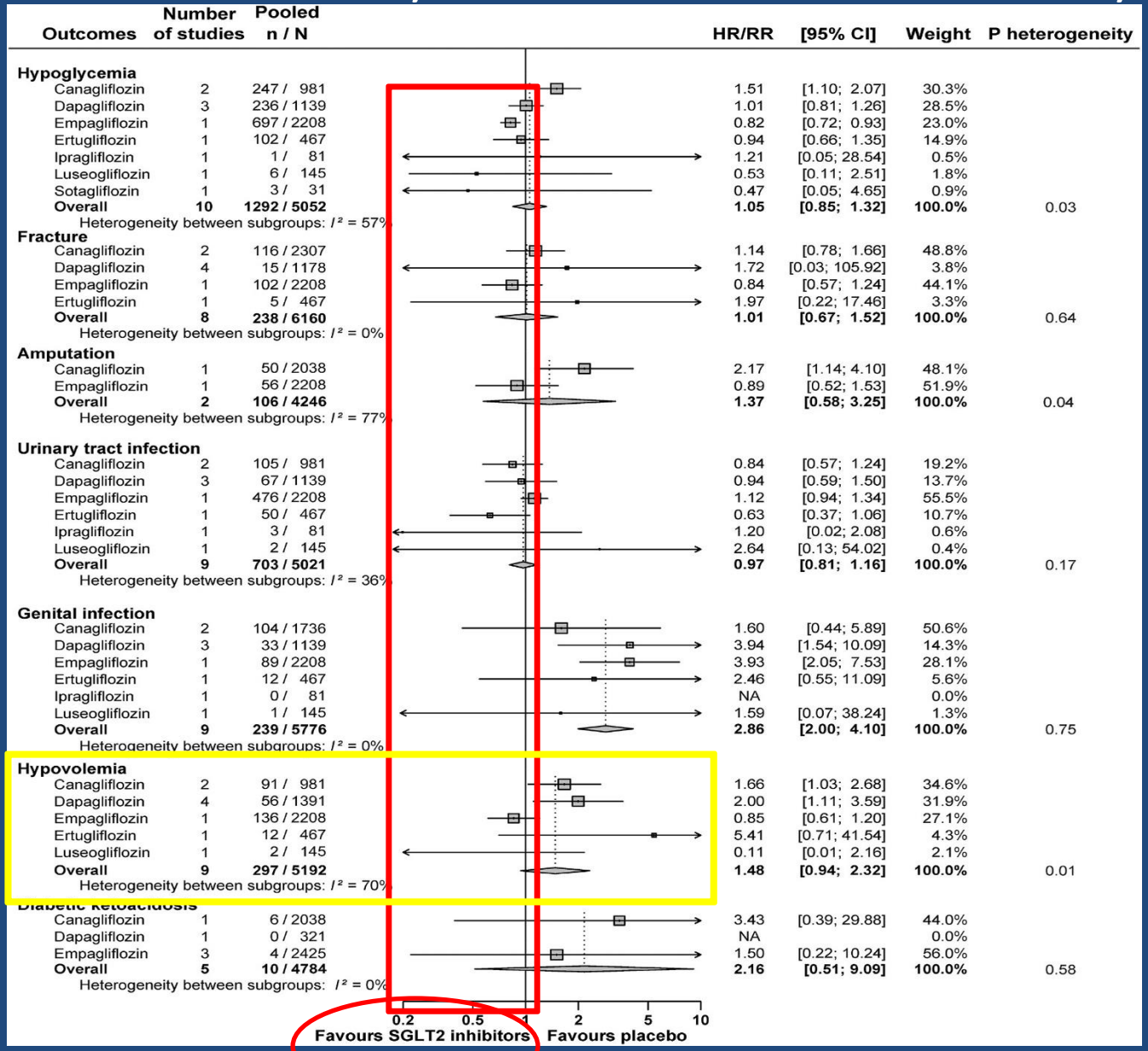
Effect of SGLT2i on cardiovascular, renal & safety outcomes in patients with Type 2 DM & CKD: A systematic review and meta-analysis



Diabetes, Obesity and Metabolism, Volume: 21, Issue: 5, Pages: 1237-1250, First published: 29 January 2019, DOI: (10.1111/dom.13648)

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Chest: CTA B/L CVS: S4, no JVD

Ext: +trace LE edema

Are you concerned about development of hypoglycemia?

1. Yes
2. No

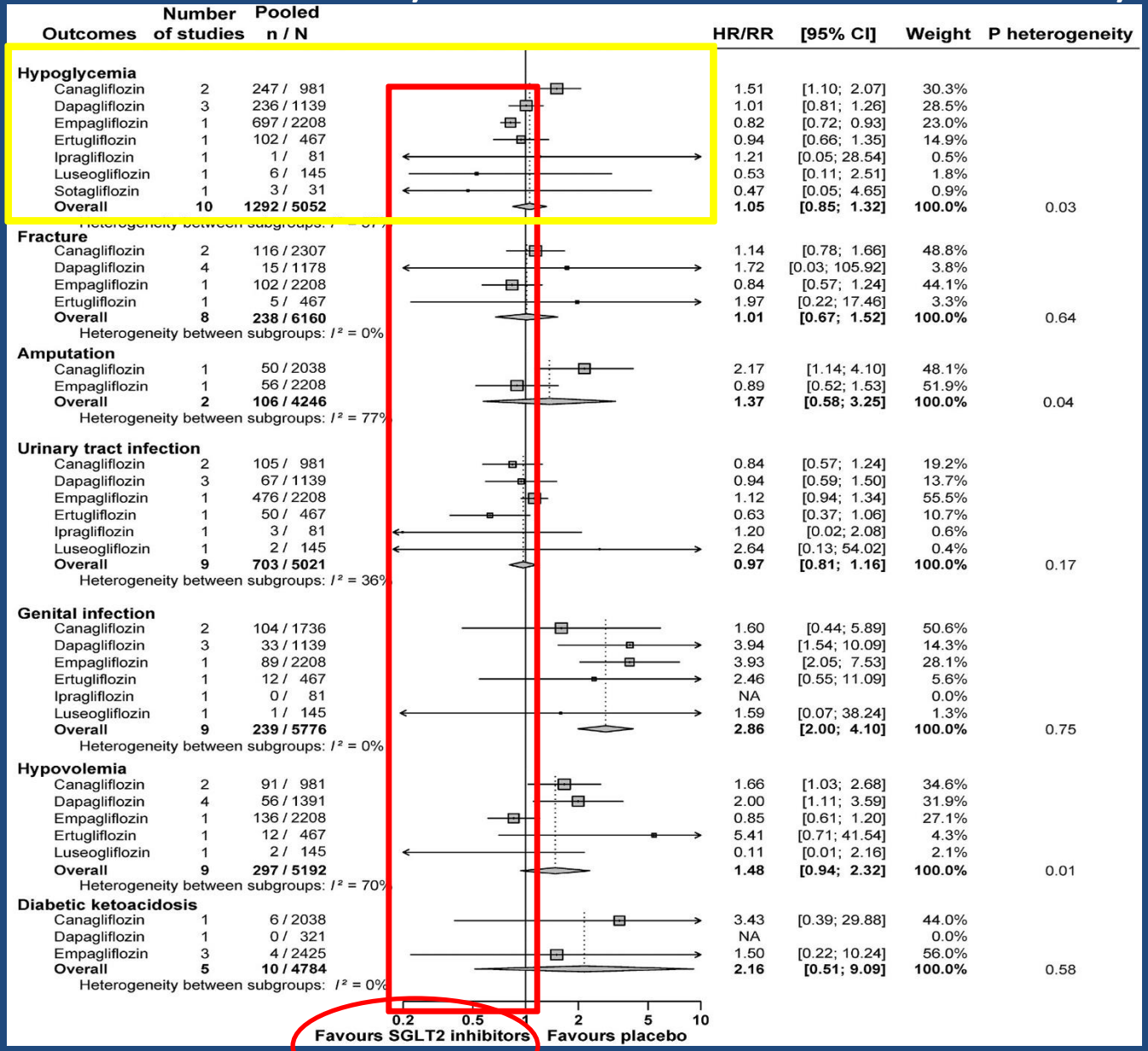
SGLT2i Safety and Prescribing

1. AKI safety and the GFR “dip”
2. Volume depletion/hypotension
3. Concern about having to manage glucose, hypoglycemia
4. DKA risks
5. Genital tract infection

Management of Glucose
Hypoglycemia

- Effects of SGLT2i on glycemia DECLINE as GFR DECLINE, however reductions in BP and albuminuria appear similar across different levels of GFR
- Rarely have to make adjustments, except in people with tight control on insulin/SU
- Benefits are independent of glucose (DAPA- CKD, DAPA-HF, EMPEROR-reduced)

Effect of SGLT2i on cardiovascular, renal & safety outcomes in patients with Type 2 DM & CKD: A systematic review and meta-analysis



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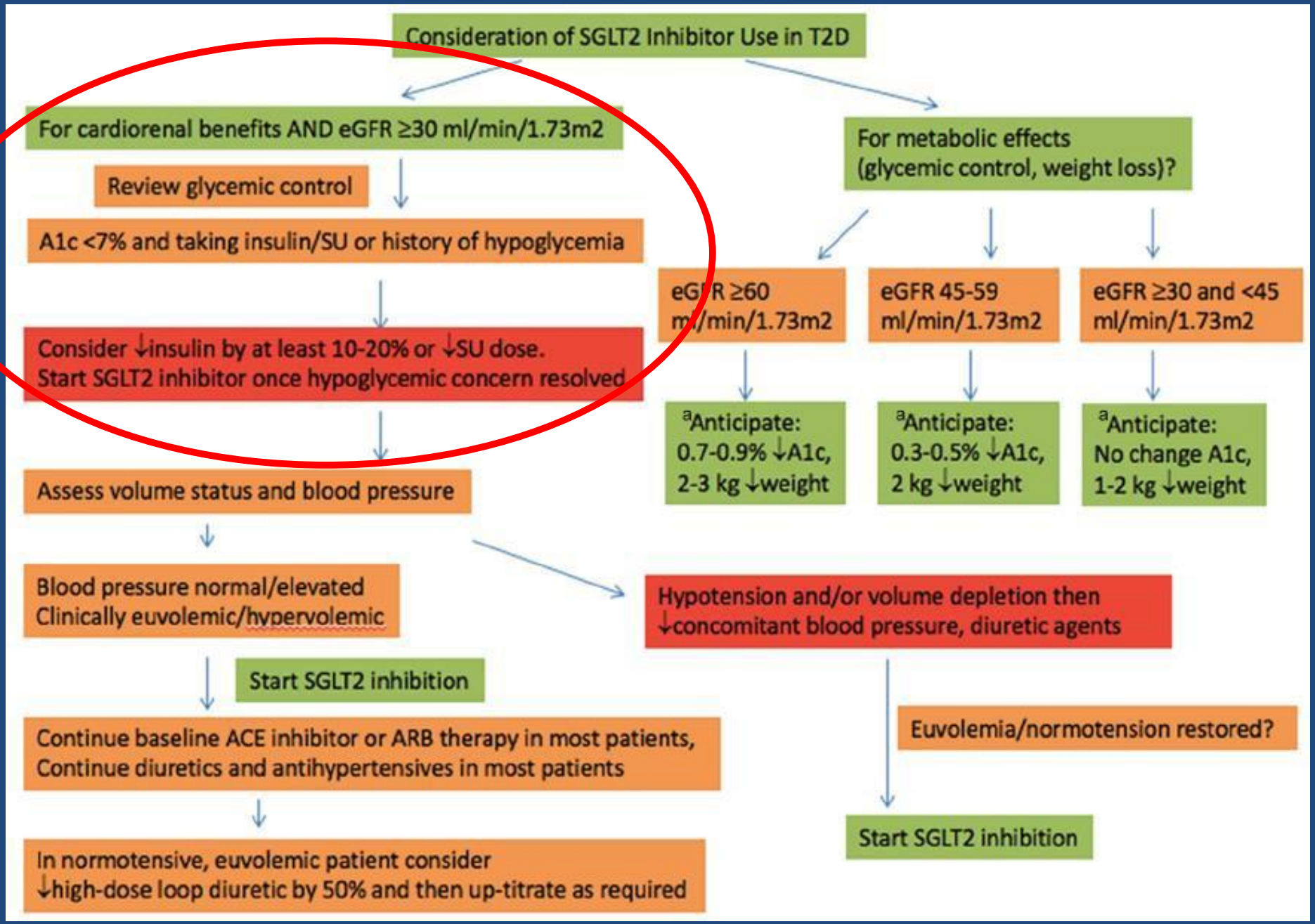
Are you concerned about development of hypoglycemia?

1. Yes—if on insulin or sulfonyurea
2. No



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SGLT2i Safety and Prescribing

1. AKI safety and the GFR “dip”
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Who should NOT receive SGLT2i

1. T2D with history of DKA---on insulin without pancreatic reserve—at increased risk of euglycemic DKA. Make sure to warn patients of symptoms of DKA (abdominal pain, nausea/vomiting) in the setting of NORMAL blood sugar (euglycemic)
2. Frequent genital tract infection
3. Catheterized patients
4. Dynamic volume status, significant concern volume depletion
5. Polycystic kidney disease, immunosuppression (until data available)

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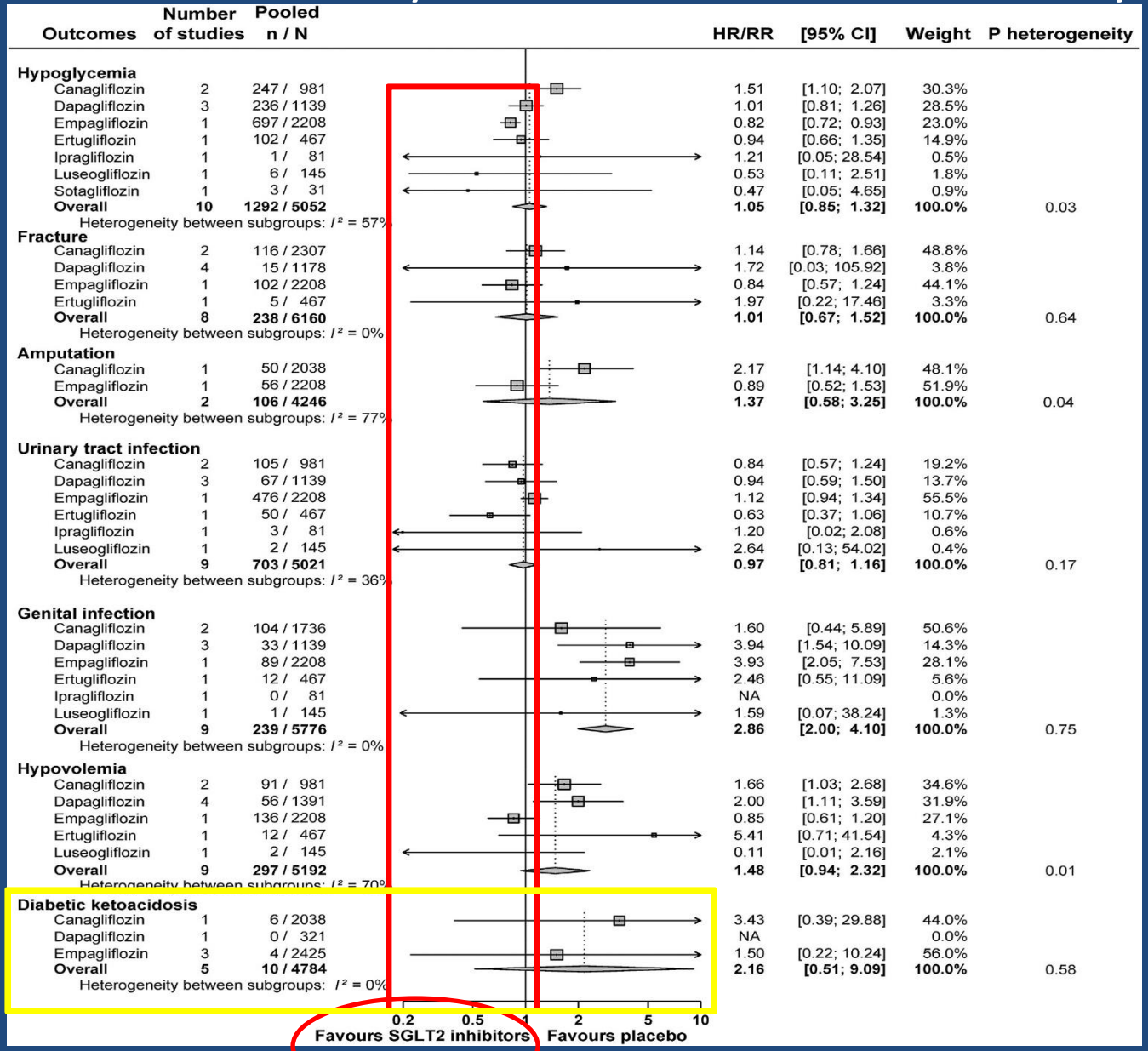

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Are you concerned about development of hypoglycemia?

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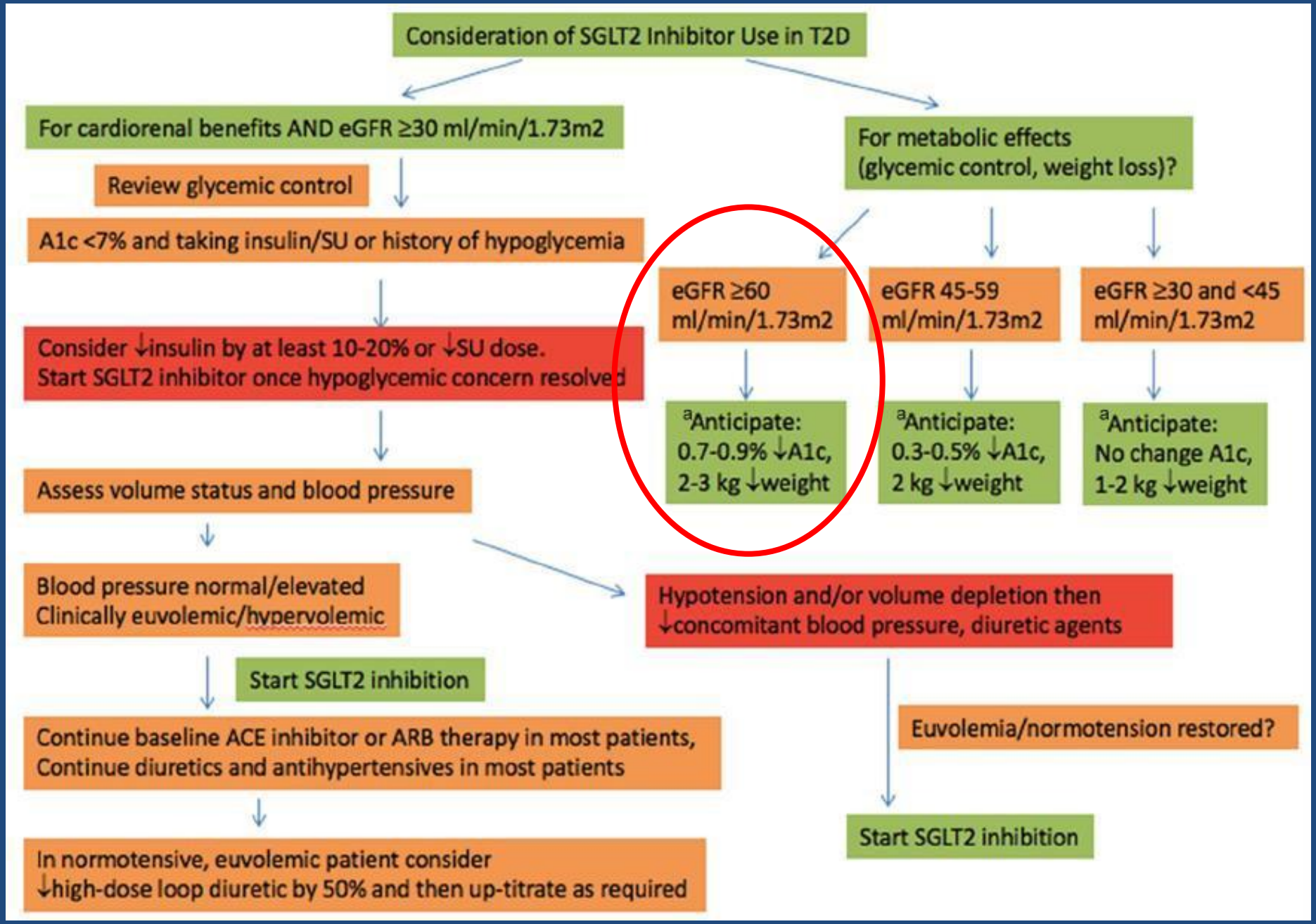
2. No---if eGFR was better at near >60, then this would be a different story



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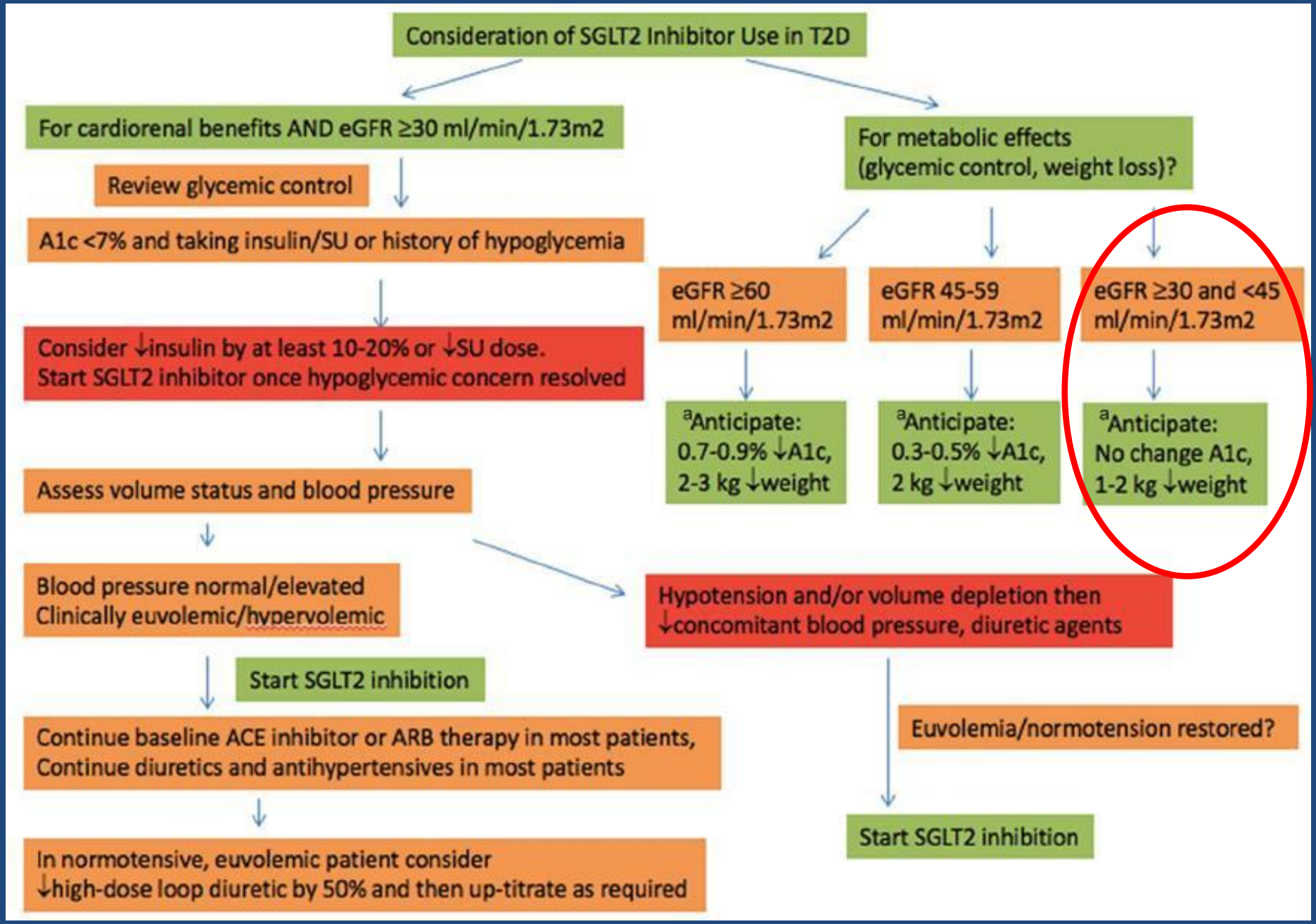
Are you concerned about development of hypoglycemia?

1. Yes—if on insulin or sulfonyurea
2. No. His eGFR is 33



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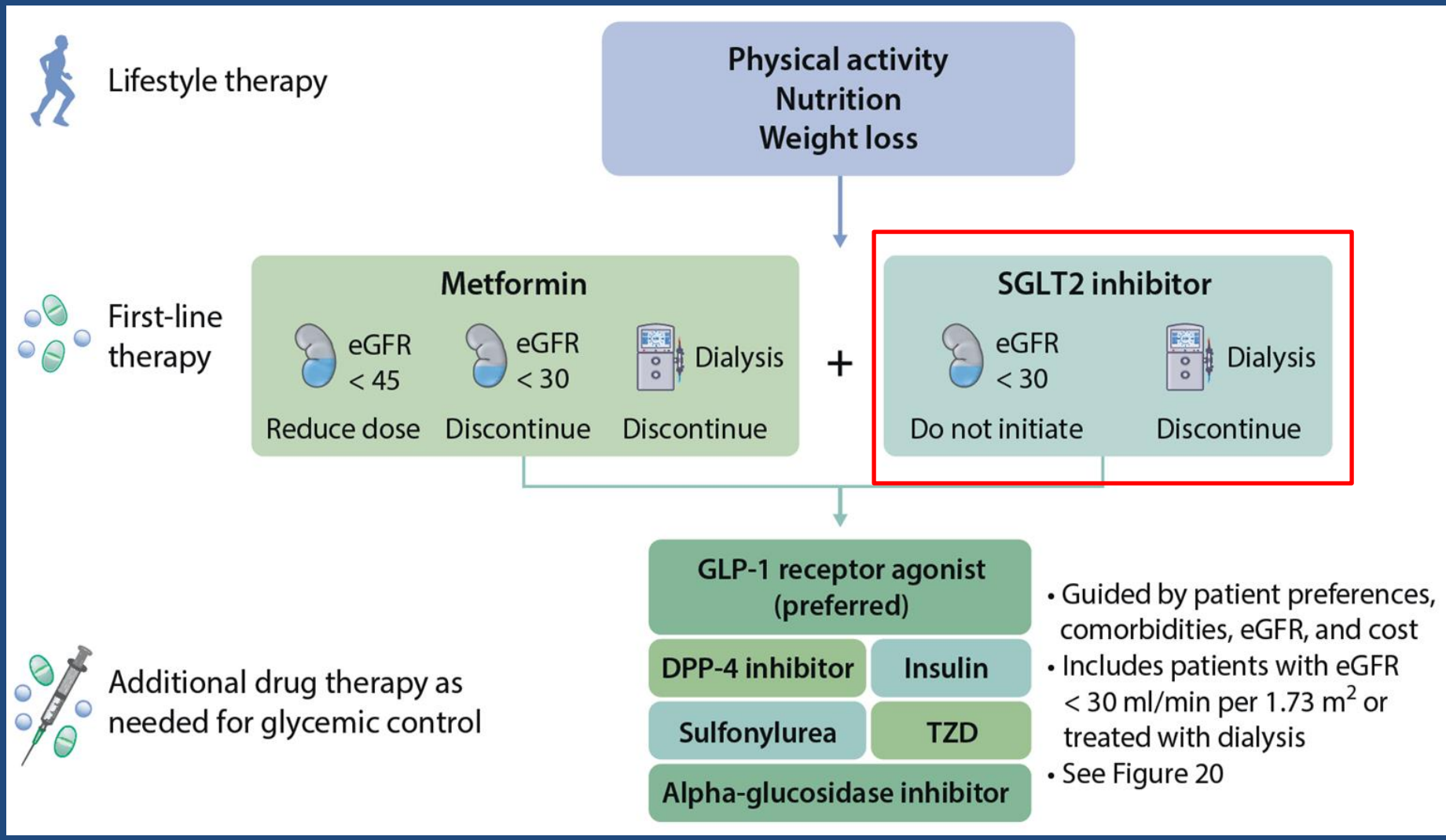
IS there too low of eGFR to initiation SGLT2i ?

1. eGFR <60
2. eGFR<45
3. eGFR <30
4. eGFR <25
5. eGFR <20

Tx algorithm for selecting anti-hyperglycemic drugs for DM & CKD



What GFR is too low for SGLT2i?

- DAPA-CKD included eGFR<25 & 1/3 of patients enrolled did NOT have DM
- eGFR ≥25 and ≤75 mL/min/1.73m2 (CKD-EPI Formula) at visit 1
- Evidence of increased albuminuria 3 months or more before visit 1 and UACR ≥200 and ≤5000 mg/g at visit 1

- EMPA KIDNEY-trial completion 2022 will enroll eGFR <20 & include those with and w/o DM
- CKD-EPI eGFR ≥20 to <45 mL/min/1.73m^2 or
- CKD-EPI eGFR ≥45 to <90 mL/min/1.73m^2 with urinary albumin:creatinine ratio ≥200 mg/g (or protein:creatinine ratio ≥300 mg/g)

Some advocate to continue SGLT2i despite decreasing GFR?

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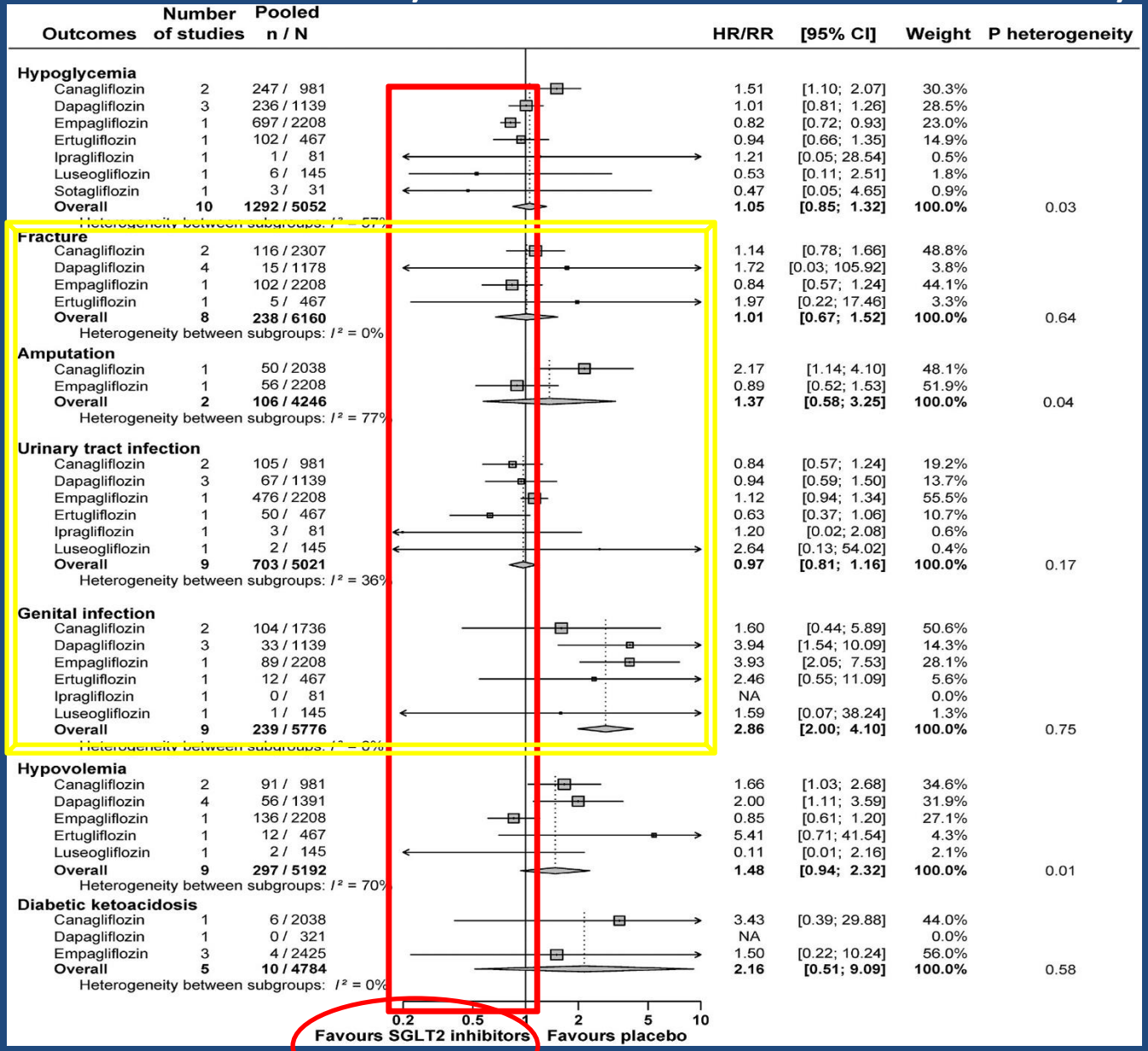
IS there too low of eGFR to initiation SGLT2i ?

1. eGFR <60
2. eGFR<45
3. eGFR <30
4. eGFR <25
5. eGFR <20????

Some advocate to continue SGLT2i despite decreasing GFR? However, we do NOT have data on continuation of SGLT2i as eGFR < 25

Effect of SGLT2i on cardiovascular, renal & safety outcomes in patients with Type 2 DM & CKD: A systematic review and meta-analysis



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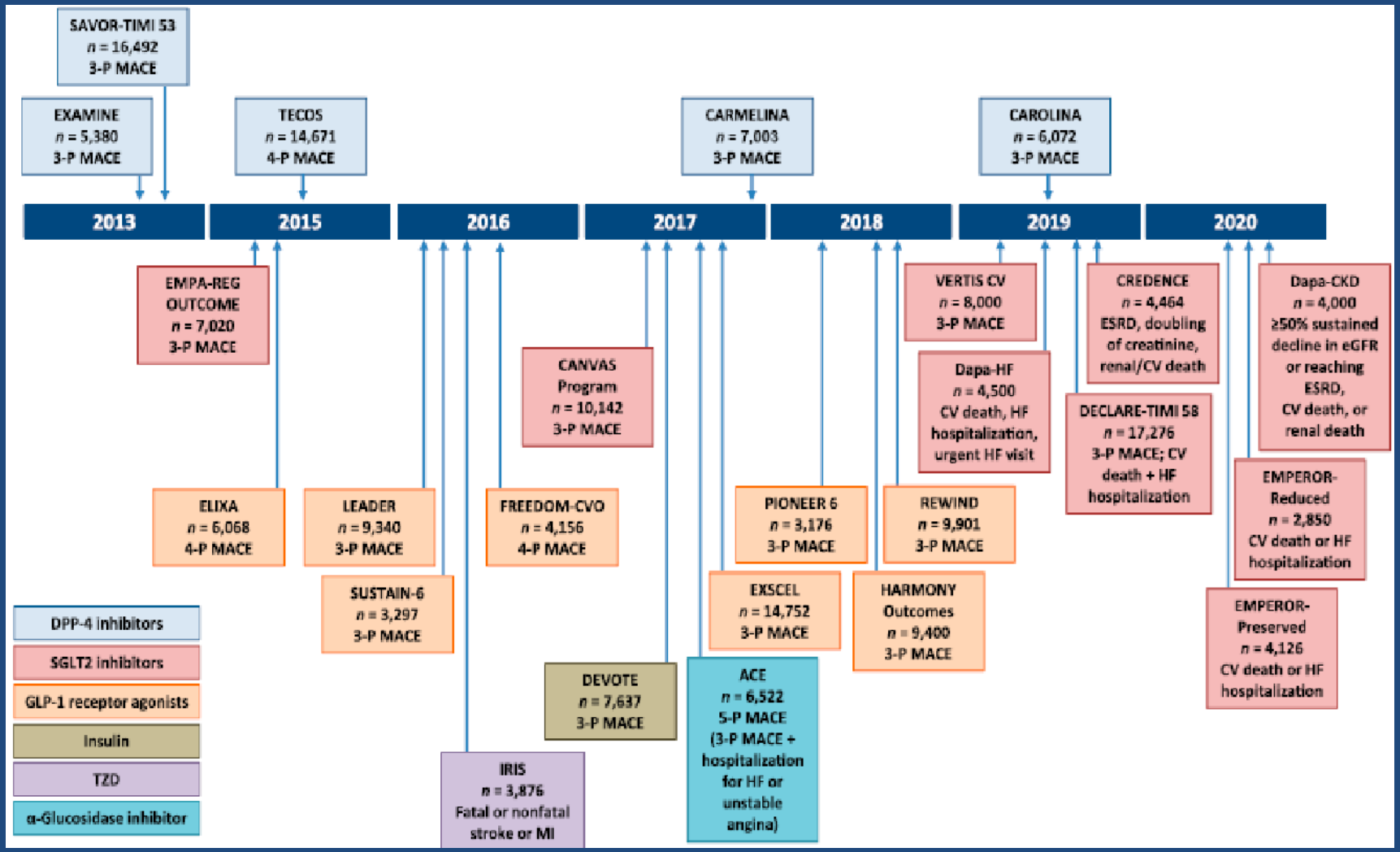
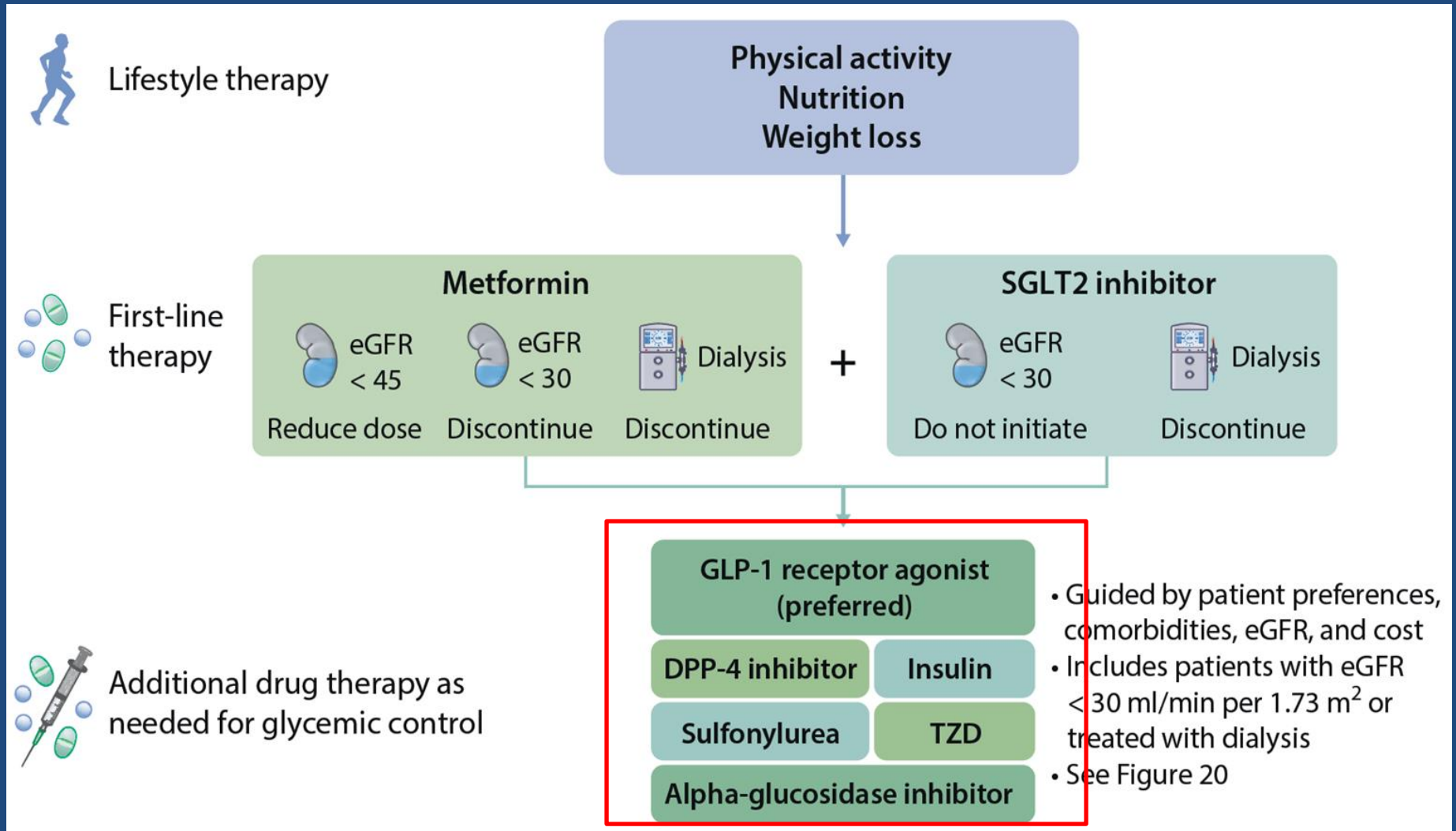
Clinical Trials of New Diabetes Drugs



Cefalu W *et al, Diabetes Care* 2018

Tx algorithm for selecting anti-hyperglycemic drugs for DM & CKD



Tx algorithm for selecting anti-hyperglycemic drugs for T2D & CKD

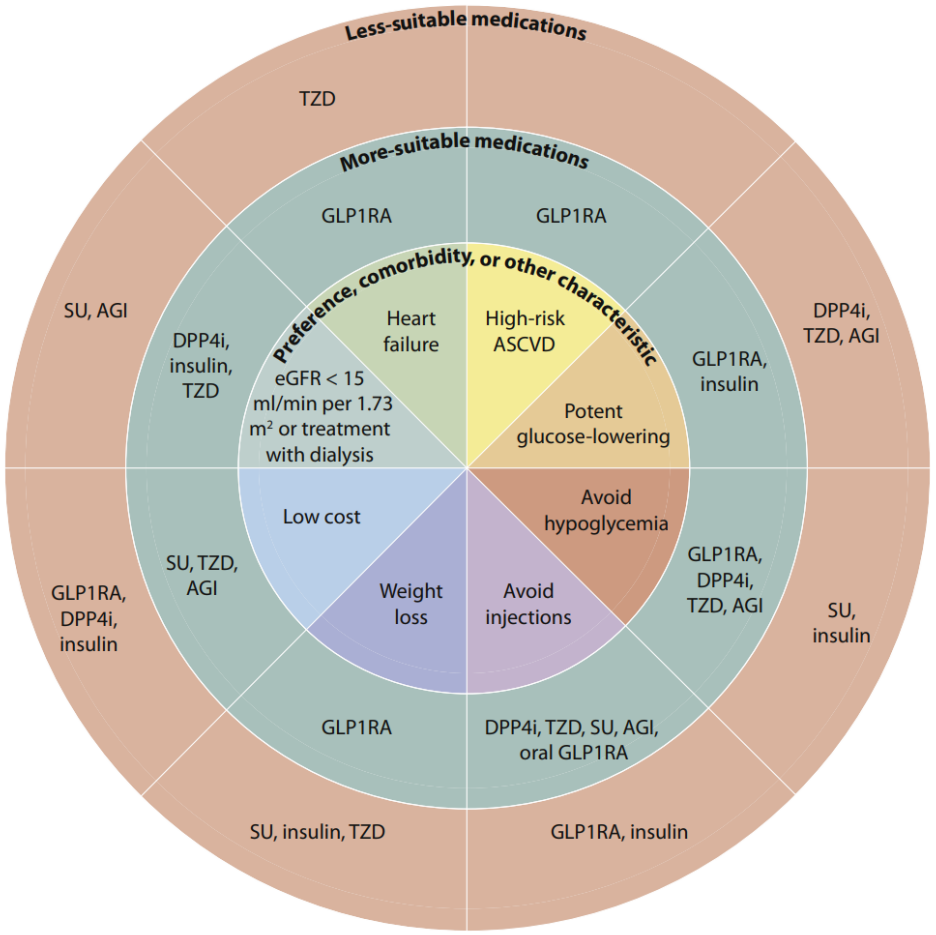


Figure 20| Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD. AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

2020 Clinical practice guidelines for DM management in CKD

1. Comprehensive care

   -Control of risk factors including RAS blockade in those with albuminuria remains part of standard of care

2. Lifestyle intervention
3. Glycemic goals based upon A1C and BS
4. Anti-hyperglycemic treatment options

   -Initial use of BOTH metformin and SGLT2i is recommended

5. Approaches to management of patients

Top 10 Takeaways for Clinicians from KDIGO 2020 Clinical Practice Guideline

1 Comprehensive care

Patients with diabetes and CKD have multisystem disease that requires treatment including a foundation of lifestyle intervention (healthy diet, exercise, no smoking) and pharmacologic risk factor management (glucose, lipids, blood pressure).

2 Nutrition intake

Patients should consume a balanced, healthy diet that is high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweet- ened beverages. Sodium (<2 g/day) and protein intake (0.8 g/kg/day) in accordance with recommendations for the general population.

3 Glycemic monitoring

It is advised to monitor glycemic control with HbA1c in patients with diabetes and CKD. For patients with advanced CKD (particularly those on dialysis), reliability of HbA1c decreases and results should be interpreted with caution. CGM or SMBG may also be useful, especially for treatment associated with risk of hypoglycemia.

4 Glycemic targets

Targets for glycemic control should be individualized ranging from <6.5% to <8.0%, taking into consideration risk factors for hypoglycemia, including advanced CKD and type of glucose-lowering therapy.

5 SGLT2i

SGLT2i should be initiated for patients with T2D and CKD when eGFR is ≥30 ml/min/1.73 m^2 and can be continued after initiation at lower levels of eGFR. SGLT2i markedly reduce risks of CKD progression, heart failure, and atherosclerotic cardiovascular diseases, even when blood glucose is already controlled.

6 Metformin

Metformin should be used for patients with T2D and CKD when eGFR is ≥30 ml/min/1.73 m^2. For such patients, metformin is a safe, effective, and inexpensive drug to control blood glucose and reduce diabetes compli- cations.

7 GLP-1 RA

In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications, a long-acting GLP-1 RA is recommend- ed as part of the treatment.

8 RAS blockade

Patients with T1D or T2D, hypertension, and albuminuria (persistent ACR >30 mg/g) should be treated with a RAS inhibitor (ACEi or ARB), titrated to the maximum approved or highest tolerated dose. Serum potassium and creatinine should be monitored.

9 Approaches to management

A team-based and integrated approach to manage these patients should focus on regular assessment, control of multiple risk factors, and structured education in self-management to protect kidney function and reduce risk of complications.

10 Research recommendations

There is a paucity of data on optimal management of diabetes in kidney failure, including dialysis and transplantation, which should be a focus for future studies.

Questions?

Denise.Link@utsouthwestern.edu

214-668-8080