

A top-down view of a desk with a white keyboard, a white mouse, a pair of black-rimmed glasses, and a blue stethoscope. A tablet is partially visible on the left side of the frame.

Approach to Managing Kidney Disease

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Pre-Lecture Question 1

Which of the following statements is correct?

1. A proper assessment of CKD staging should include the degree of albuminuria
2. Hypertension is the most common cause of CKD
3. Glyburide is a safe medication if the eGFR < 30 ml/min
4. In a 77-year-old patient with HFrEF, dialysis initiation increases survival compared to conservative management
5. A patient with CKD Stage 3B should use NSAIDs for arthritis

Pre-Lecture Question 2

Which of the following is TRUE regarding SGLT2 inhibitors?

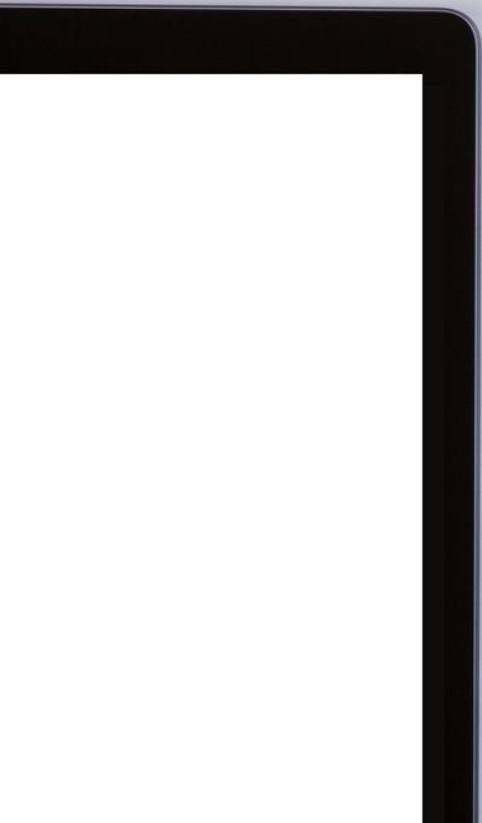
1. Glycemic efficacy is reduced when the eGFR < 30 ml/min
2. All SGLT2i are FDA-approved in patients with an eGFR 30-45 ml/min
3. The drug has a diuretic effect and can result in modest weight loss after initiation
4. The ADA recommends considering their use in patients with diabetic kidney disease and an eGFR ≥60
5. The drug can increase uric acid levels

Objectives

At the conclusion of this talk, you will be able to:

1. Diagnose kidney disease with cost-effective and appropriate testing
2. Recognize the national burden of diabetic kidney disease (DKD) and identify strategies to treat patients with DKD
3. Describe the principles of safe medication prescribing for patients with chronic kidney disease (CKD)

Case 1:
Ms. Nicole Kidney



Nicole Kidney

This is a 48-year-old female with hypertension for 15 years. Her serum creatinine is 1.9 mg/dl. It was 1.8 mg/dl one year earlier. Her estimated GFR is 35 ml/min. The urine dipstick shows only trace proteinuria. She has not yet seen a Nephrologist.

She is feeling well and otherwise healthy. Her mother had hypertension and CKD.

Ms. Kidney

BMI	32
Height	5'4"
Blood Pressure	152/89

PMHx: Hypertension

Social: Actress. Non-smoker. 2 drinks/week.

NAME _____
ADDRESS _____ DATE _____

R_x

- Amlodipine 10 mg daily
- Lisinopril 2.5 mg qhs
- HCTZ 12.5 mg daily
- Multivitamin

Case Question 1

Identify the correct pair of both test and result that you may expect to find in Ms. Nicole Kidney?

Choice	Test	Finding
A	Kidney Ultrasound	Small, echogenic kidneys (< 10 cm bilaterally)
B	Urinalysis	3+ protein, 3+ blood, granular casts
C	Metabolic Panel	Hyperkalemia: Potassium > 6.1 meq/L
D	Complete blood count	Normocytic Anemia: Hemoglobin < 8 g/L

Rationale

- **Kidney Ultrasound | Small, echogenic kidneys**
 - *Correct. Small, echogenic kidneys are typical of CKD secondary to hypertension*
- **Urinalysis | 3+ protein, 3+ blood, granular casts**
 - *Incorrect. This pattern suggests an active glomerulonephritis with tubular injury that requires urgent evaluation*
- **Metabolic Panel | Potassium > 6.1 meq/L**
 - *Incorrect. Hyperkalemia is typically a late finding in CKD (eGFR < 15 ml/min). In this patient, this finding warrants further evaluation. Diabetics may rarely manifest hyperkalemia at a higher eGFR.*
- **Complete Blood Count | Hemoglobin < 8 g/L**
 - *Incorrect. Anemia typically a late finding in CKD (eGFR < 30 ml/min)*

Prognosis of CKD by GFR and Albuminuria

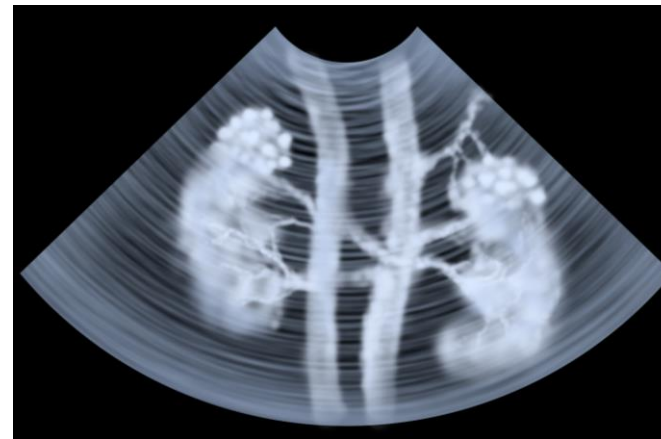
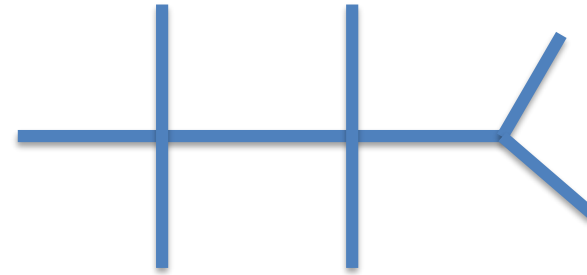
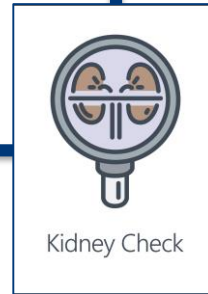
15% of the U.S. Population has Chronic Kidney Disease (CKD)

Most common causes of CKD

1. Diabetes Mellitus
2. Hypertension

	Glomerular Filtration Rate (mL/min/1.73m ²)	Normal to Mildly Increased Albuminuria	Moderately Increased Albuminuria	Severely Increased Albuminuria
1	Normal or High >90	Low risk	Moderately increased risk	High risk
2	Mildly decreased 60-89	Low risk	Moderately increased risk	High risk
3a	Mildly to moderately decreased 45-59	Moderately increased risk	High risk	Very high risk
3b	Moderately to severely decreased 30-44	High risk	Very high risk	Very high risk
4	Severely decreased 15-29	Very high risk	Very high risk	Very high risk
5	Kidney failure <15	Very high risk	Very high risk	Very high risk

Initial Diagnostic Testing to Detect Chronic Kidney Disease (CKD)



Clinical Pearls in Lab Assessment

Serum Creatinine

Developed and in use since 1950

Equations that *estimate* GFR (eGFR) speak the patient's language: MDRD, CKD-EPI



Order a 24 hour
urine for
creatinine
clearance

Proteinuria

Urine dipstick checks for albuminuria... but we want to quantify the amount

24-hour urine is **gold standard**

“Spot” Urine Albumin to Creatinine Ratio (UACR) is **equally effective and easy**

Albuminuria Definitions

- **normal to mildly increased:** ACR < 30 mg/g
- **moderately increased:** ACR 30-299 mg/g
- **severely increased:** ACR ≥ 300 mg/g

American College of Physicians Recommendations for Screening for CKD

	Population	Management
1	Healthy adults without risk factors for CKD	No screening for CKD
2	Hypertensive patients with CKD 1-3	Select therapy that includes RAASI
3	Elevated LDL in patients with CKD 1-3	Select therapy that includes a statin

RAASI includes: Angiotensin-converting enzyme inhibitor or an Angiotensin II– receptor blocker

Section 1: Clinical Pearls

- 30 million Americans have Chronic Kidney Disease and it is typically silent in Stages 1, 2 & 3
- Must include *degree* of albuminuria in CKD staging
- Four investigations to detect CKD include: accurate patient history, urinalysis, kidney ultrasound, & serum chemistries



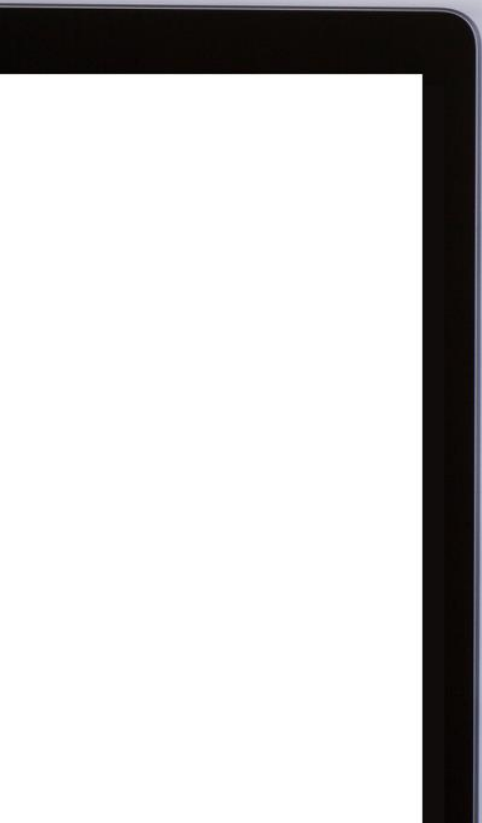
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Case 2:
Mr. Walt Kidney



Mr. Walt Kidney

This is a 56 year old male with Type 2 Diabetes Mellitus for 21 years. He feels well and is seeing you for a 4-month follow-up appointment.

His serum creatinine is 2.8 mg/dl, the eGFR is 28 ml/min, potassium is 4.5 meq/L, and the UACR* is 1200 mg/g.

*Normal UACR: < 30 mg/g

Mr. Walt Kidney

BMI	31
Height	5'9"
Blood Pressure	130/70

PMHx: Type 2 Diabetes Mellitus (A1c 7.5%),

Social: Bus driver. Non-smoker, non-drinker.

NAME _____
ADDRESS _____ DATE _____

R_x

Lisinopril 40 mg qhs
Metformin 1000 mg bid
Aspirin 81 mg daily



Case Question 2

Which statement below is the next best step in management of Mr. Walt Kidney?

Choice	Answer
A	Stop Lisinopril due to risk of hyperkalemia in CKD Stage 4
B	Intensive glucose lowering (Hgb A1c < 6%) will lower risk of progression to end-stage renal disease
C	Metformin should be discontinued due to risk of lactic acidosis
D	The ACE-inhibitor (Lisinopril) should be exchanged for an Angiotensin-Receptor Blocker

Rationale

- **Metformin should be discontinued due to risk of lactic acidosis**
 - *Correct. This drug should be discontinued if eGFR < 30 ml/min*
- **Stop Lisinopril due to risk of hyperkalemia in CKD Stage 4**
 - *Incorrect. This risk is primarily in patients with CKD stage 5 (eGFR < 15 ml/min).*
- **Intensive glucose lowering (Hgb A1c < 6.0%) will lower risk of progression to ESRD**
 - *Incorrect. Studies suggest both intensive and poor glycemic control (>9%) result in faster CKD progression*
- **The ACE-inhibitor should be exchanged for an Angiotensin-Receptor Blocker**
 - *Incorrect. Both classes of RAAS-inhibitors are equivalent to treat proteinuria*

Defining CKD and DKD

CKD is...

Reduced eGFR
($< 60 \text{ mL/min/1.73 m}^2$)

and/or

Increased urinary albumin excretion
($> 30 \text{ mg/g creatinine}$)

Persistently for ≥ 3 months

DKD is CKD

in the presence of diabetes
mellitus with exclusion of other
causes of CKD



Diabetic Kidney Disease (DKD)

WHY DOES IT MATTER?



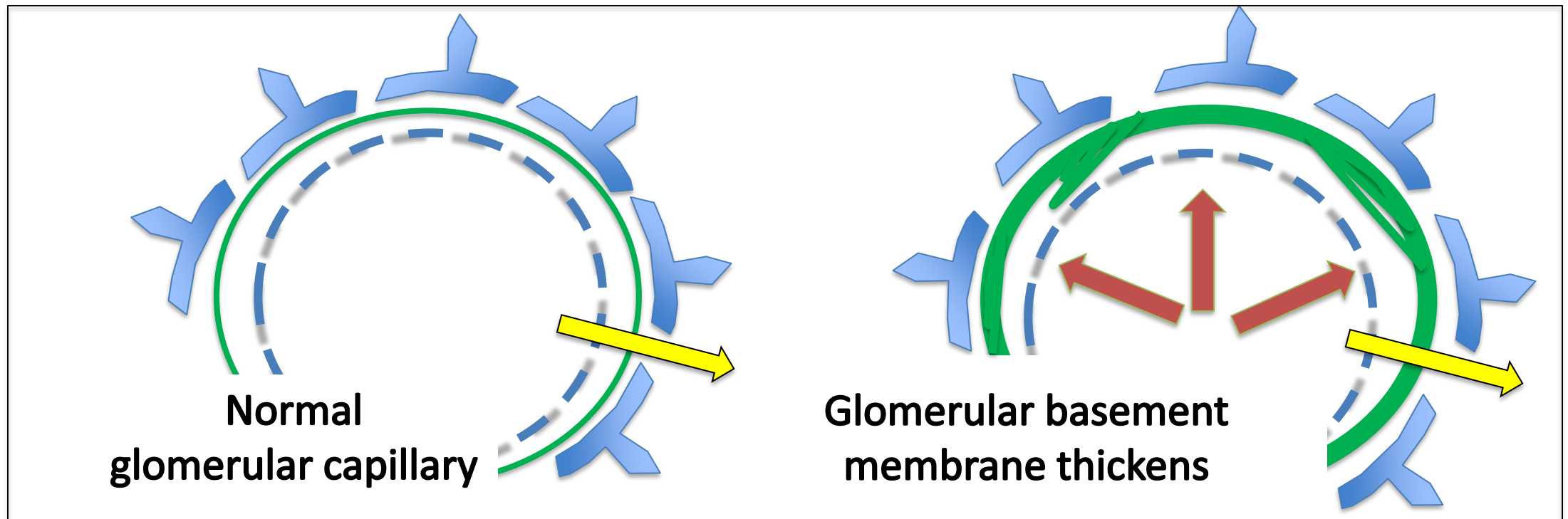
- U.S. prevalence of diabetes mellitus is **9-14%**¹ (2012 CDC estimate)
- **25%** of individuals with diabetes have DKD¹
- Prevalence of DKD in U.S. is likely to increase by 2030, given the projected **54% increase in prevalence of diabetes**¹
- DKD is associated with **higher cardiovascular** and **all-cause mortality** than people with diabetes and no kidney disease²

(1) Duru OK, et. Al. *Curr Diab Rep.* 2018;18(3):14.

(2) Afkarian M, et al. *J Am Soc Nephrol.* 2013;24(2):302-308.

Simplified Pathogenesis of Diabetic Nephropathy

- Deposition of glycosylation products thickens the basement membrane and requires a higher pressure in the capillary to achieve filtration, resulting in proteinuria.

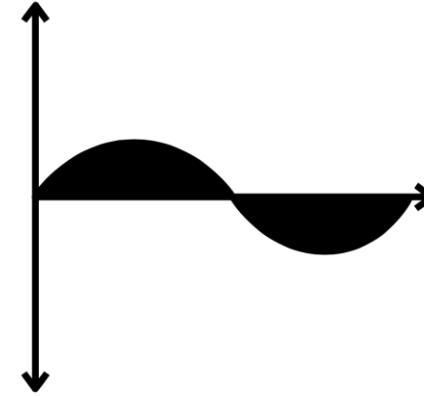


Eventually, nephron loss and steady decline in renal function occurs

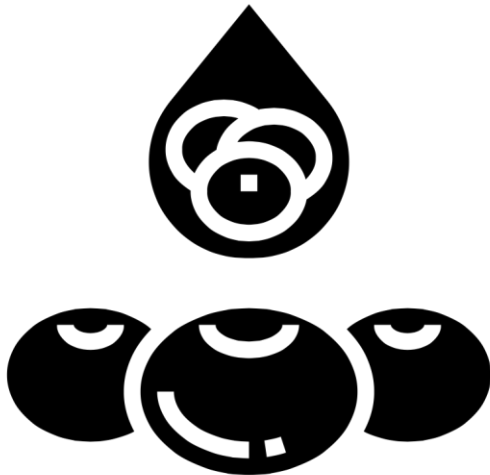
Limitations of the Hemoglobin A1c



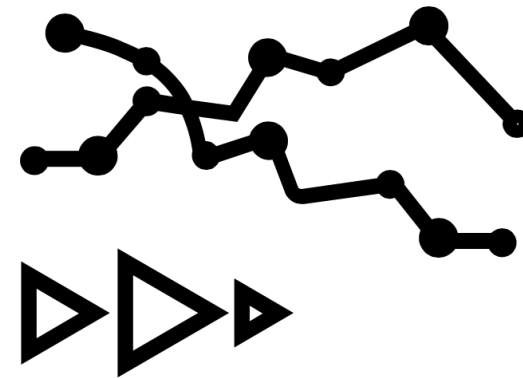
Averaged blood glucose over 3 months



Beware of the ^{high} highs, _{low} lows!



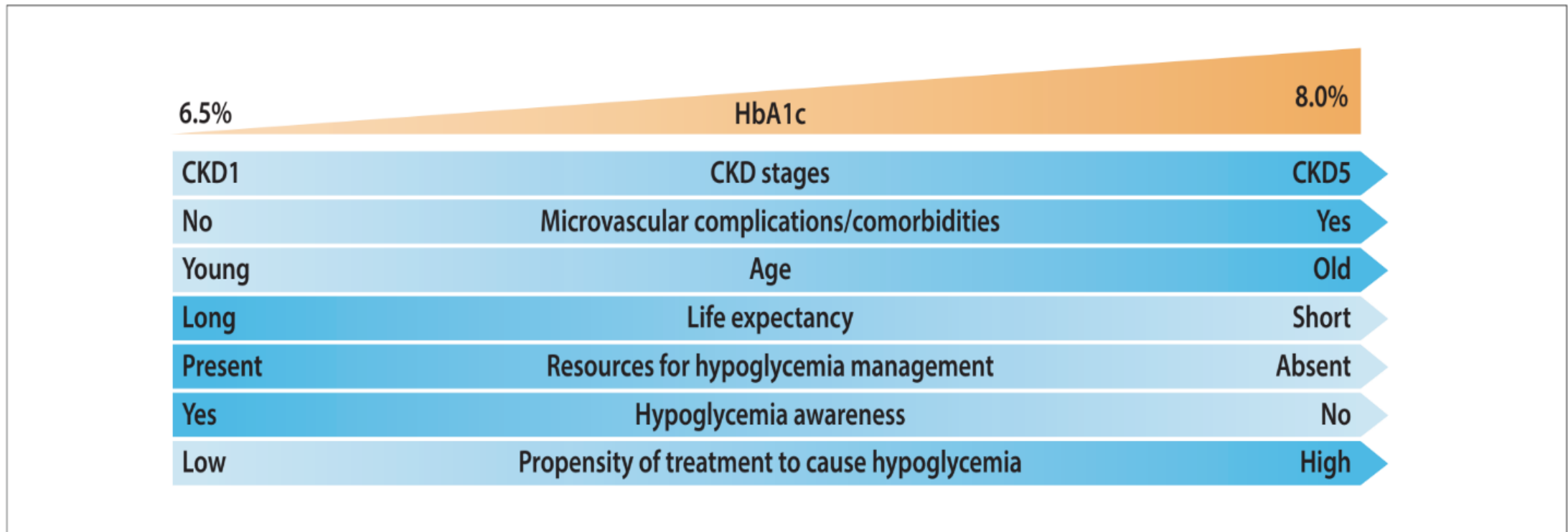
Affected by red blood cell turnover



Variability of 0.5%, SAME patient, SAME day!

HbA1C target in DKD

We recommend an individualized HbA1c target ranging from **6.5%** to **<8.0%** in patients with diabetes and non-dialysis dependent CKD (1C)

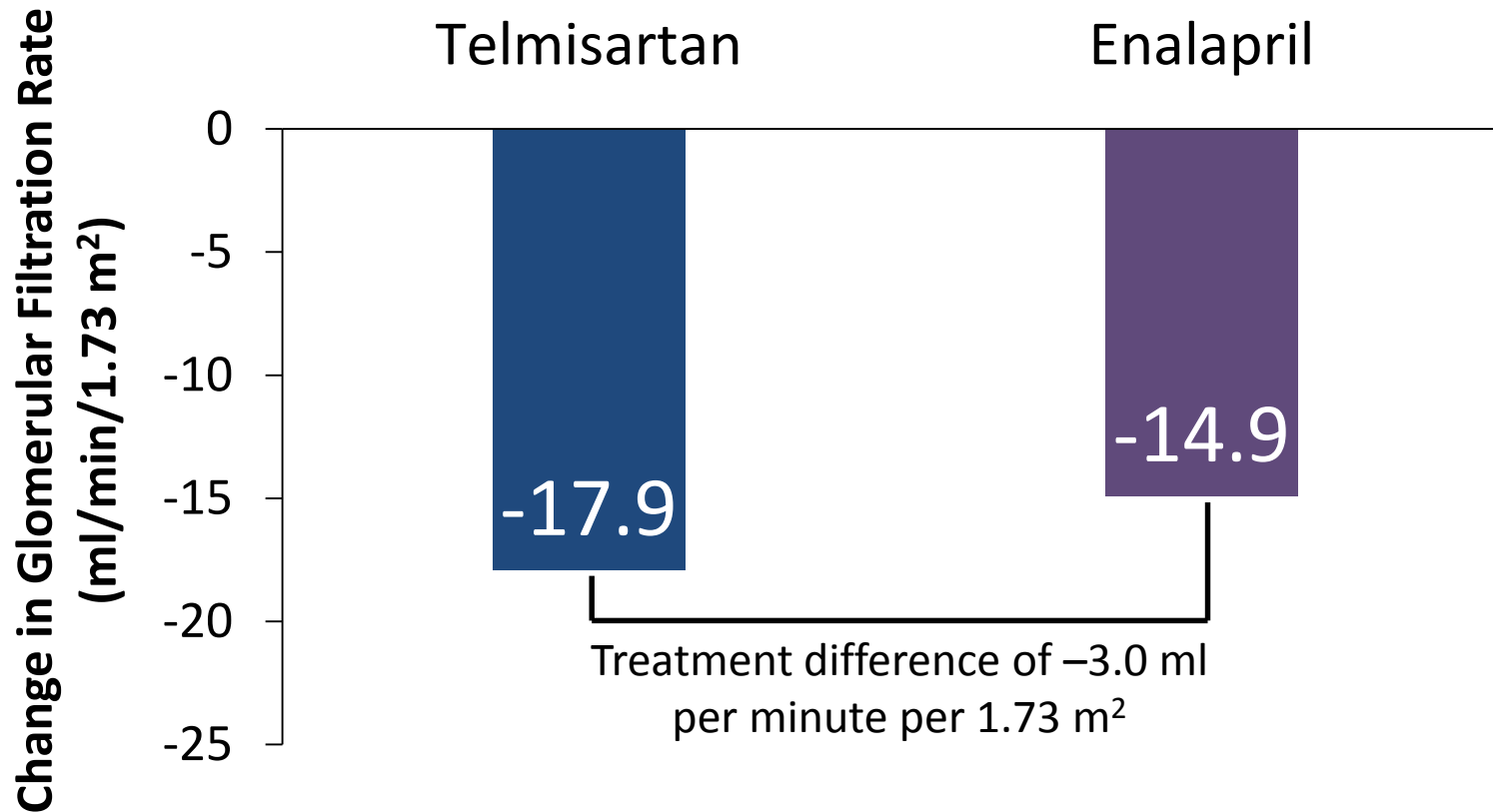


Intensive Glucose Lowering (<6%) Increases Mortality in Patients with CKD

- **Both** intensive (A1c < 6%) and poor (A1c > 9%) glycemic control increases risk of CV and all-cause mortality in this population
 - ACCORD (n=6165 patients) | Type 2 diabetes with eGFR 30-90 ml/min
 - Increased hypoglycemic episodes
- Poor concordance between Hgb A1c and fasting glucose in patients with CKD
- **Caution**: improved glycemic control may be worsening CKD

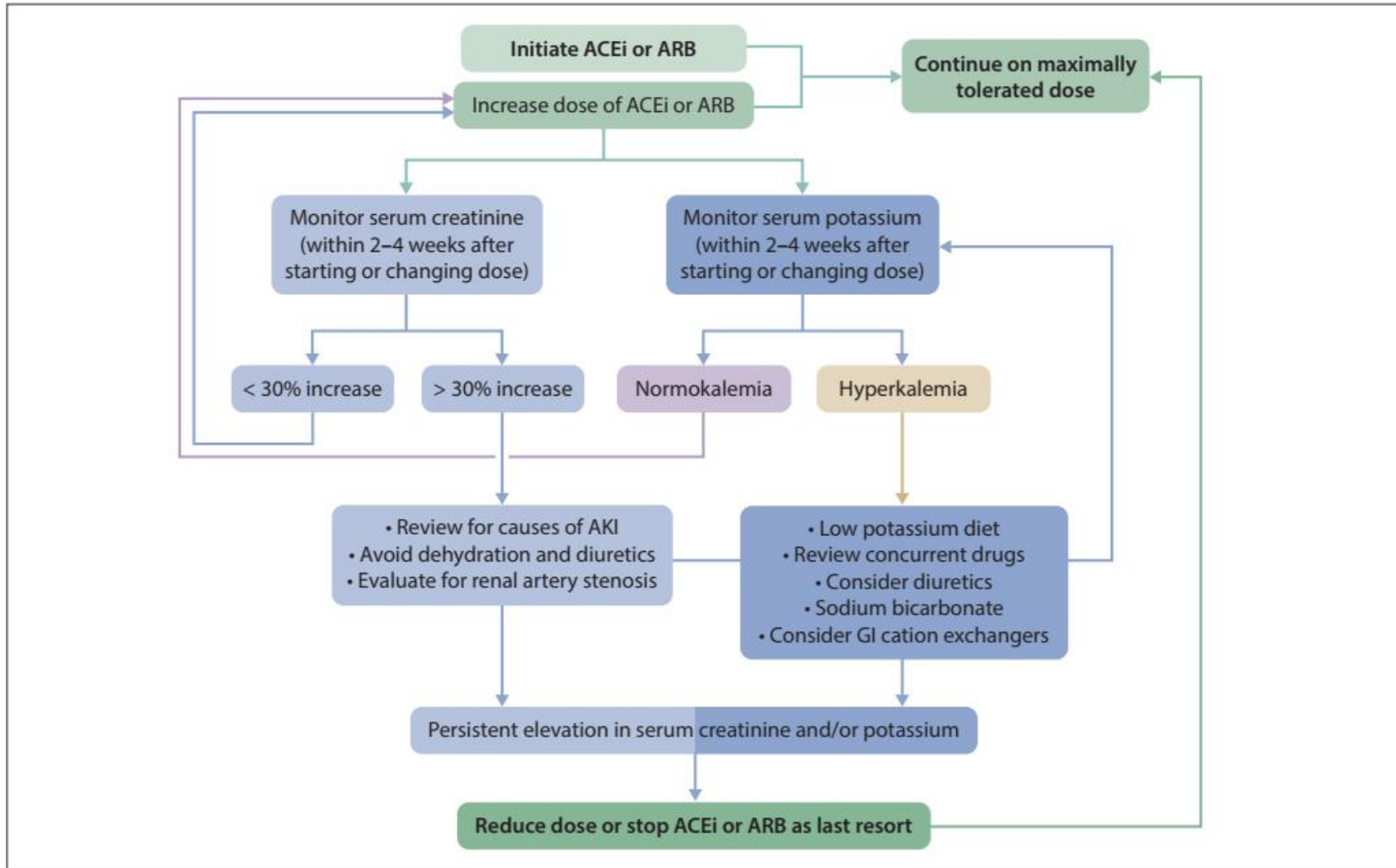
ACEi vs ARB: No Difference in GFR Decline

Change in Glomerular Filtration Rate After 5 Years

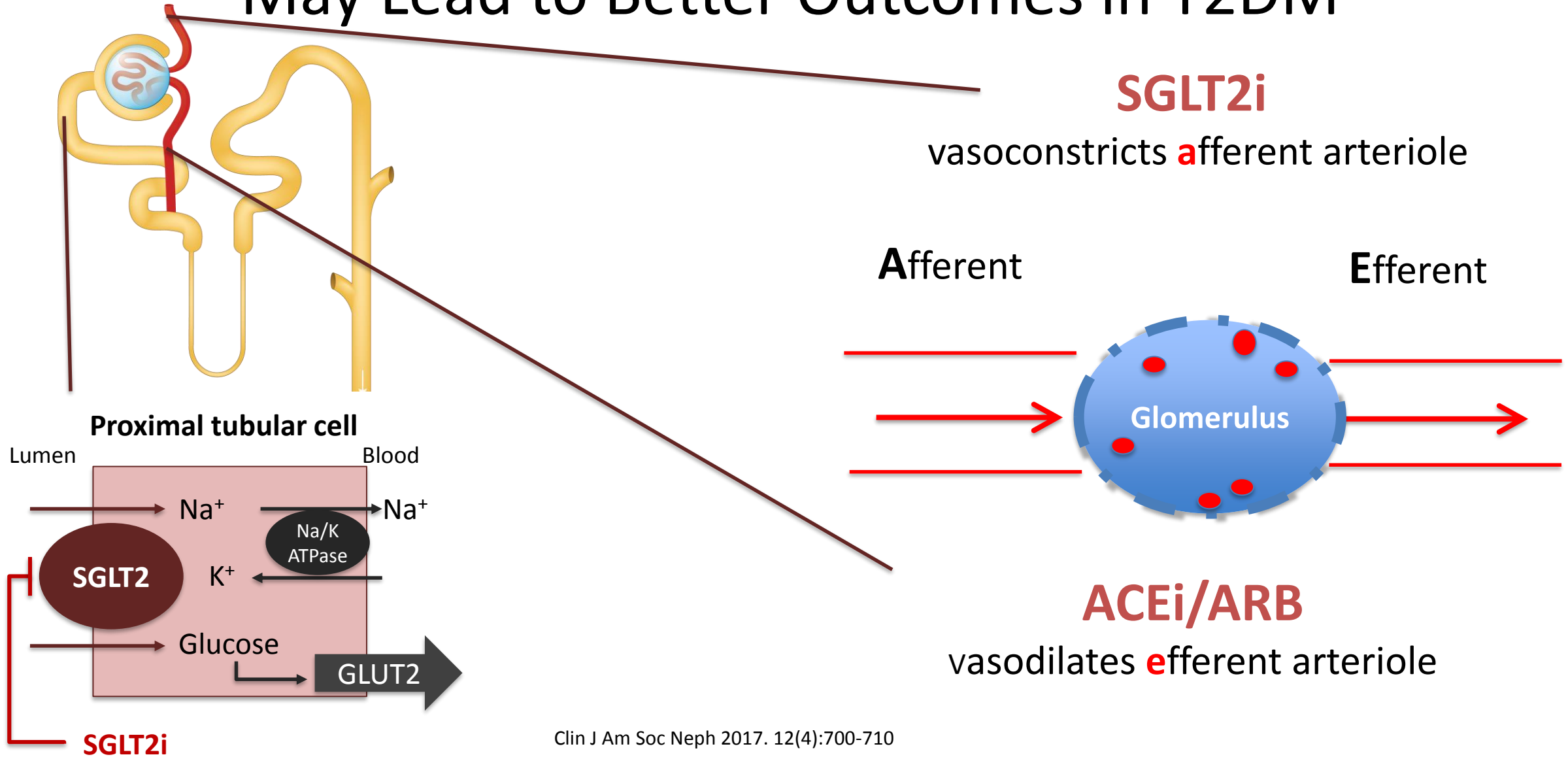


Telmisartan is noninferior to enalapril for long-term renoprotection in persons with T2DM

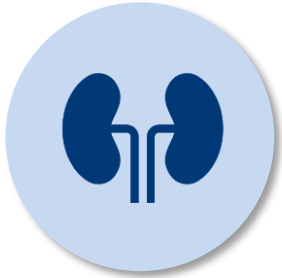
Suggested approach to manage adverse events with RAASi use



RAAS Inhibition plus SGLT2 inhibition May Lead to Better Outcomes in T2DM



Studies Demonstrate SGLT2 Inhibitors Reduce Risk of Renal Disease Progression



Empagliflozin (EMPA-REG) ¹	Canagliflozin (CANVAS) ²	Canagliflozin (CREDENCE) ³	Dapagliflozin (DECLARE-TIMI 58) ⁴	Ertugliflozin (VERTIS CV) ⁵
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**Composite
Endpoint***

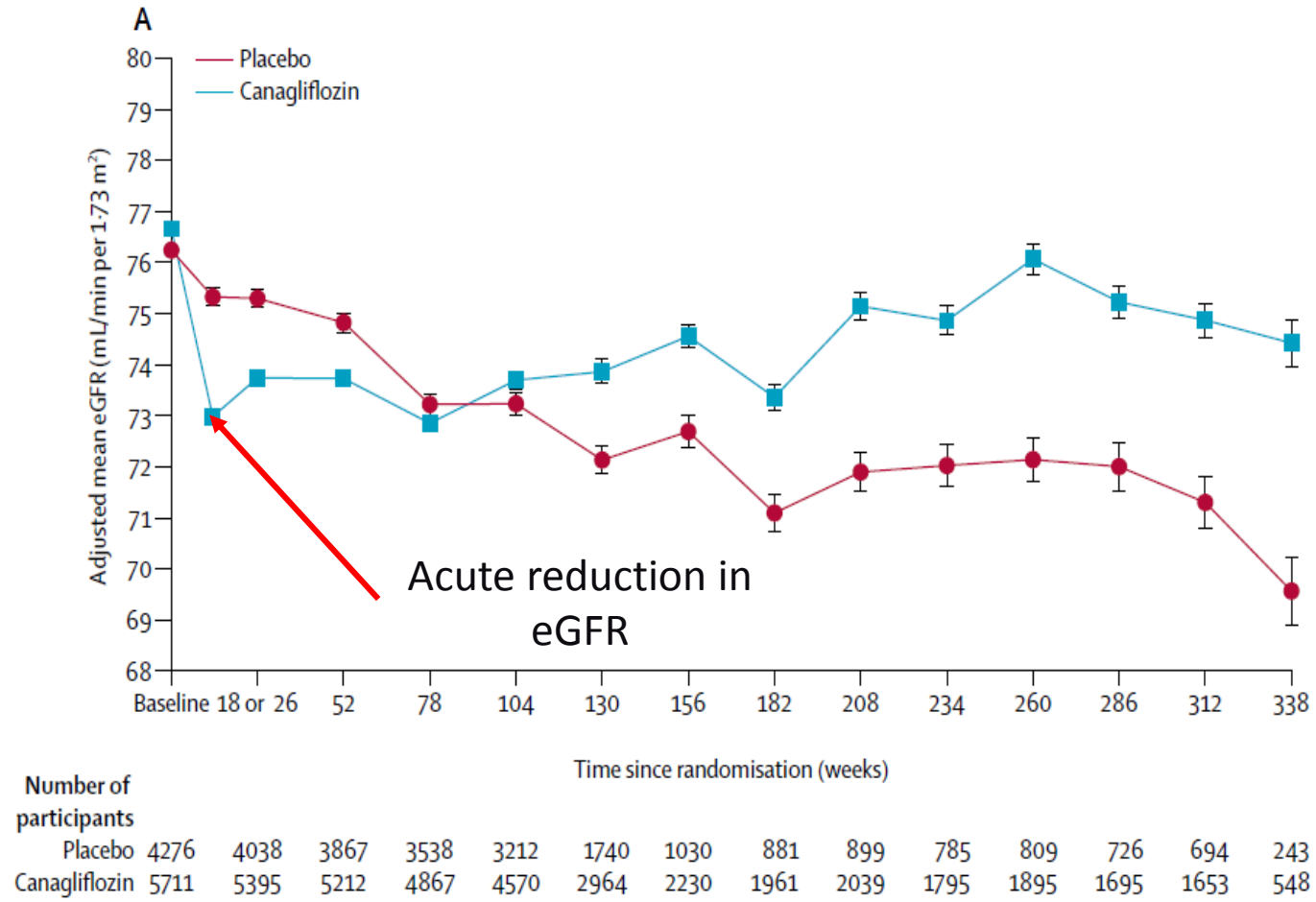


*Trial
ongoing*

*Endpoints vary by trial but share some components:

- New or worsening nephropathy
- Development of End Stage Kidney Disease
- Death from renal causes

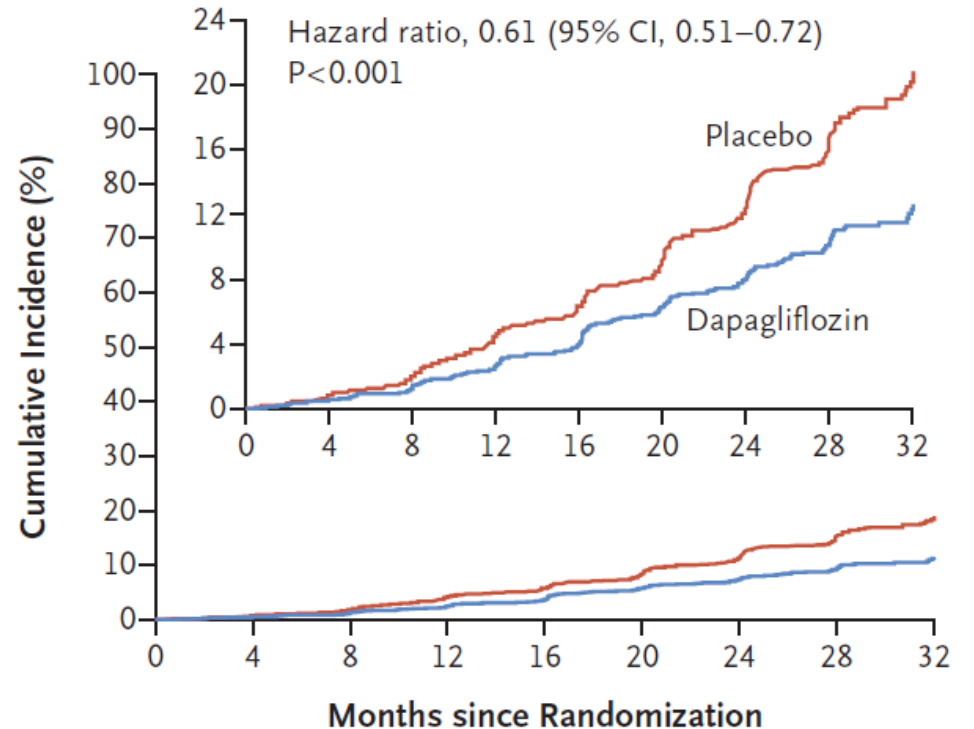
Acute decline in EGFR with SGLT2i initiation



SGLT2i for non diabetic CKD

- DAPA CKD trial: 4304 participants with EGFR 25-75 and 33% were non-diabetic
- Primary outcome measure: Sustained decline in EGFR of >50%, ESRD or death from renal or CV causes
- Results similar among diabetics and non-diabetics

A Primary Composite Outcome



No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

FDA Guidance on Metformin Use

- Do NOT start metformin in patients with an eGFR between 30-45
- Metformin should NOT be used in patients with an eGFR below 30
- Obtain an eGFR at least annually in all patients taking metformin
- In patients currently taking metformin whose eGFR falls below 45, assess the benefits and risks of continuing treatment

General Guidelines for Patients with T2DM and DKD

American Diabetes Association (ADA)



ACE inhibitor or ARB recommended if UACR is 30-299 mg/g and strongly recommended if UACR \geq 300 mg/g



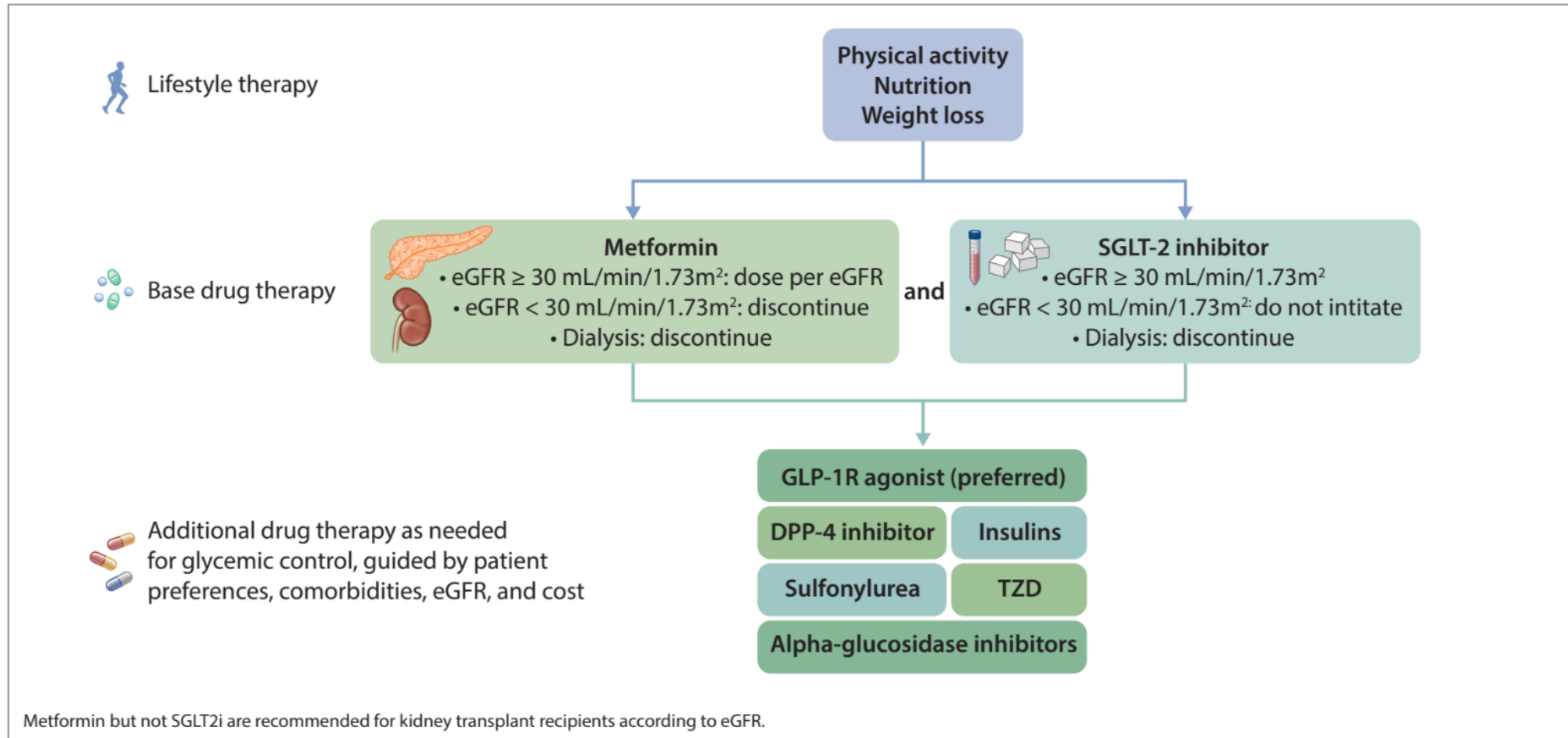
Assess urinary albumin and estimated GFR *annually* in patients with diabetes mellitus¹



Consider using SGLT2 inhibitors in patients with diabetic kidney disease and an eGFR \geq 30¹

(1) American Diabetes Association. 11. Microvascular complications and foot care: Standards of Medical Care in Diabetes—2019 [web annotation]. Diabetes Care 2019;42(Suppl. 1):S124–S138.

Suggested approach for those with DM and CKD



Recommended dosing in CKD

SGLT-2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials
Dapagliflozin	5–10 mg once daily	No dose adjustment if eGFR \geq 45 mL/min/1.73m ² Not recommended with eGFR < 45 mL/min/1.73m ² Contraindicated with eGFR < 30 mL/min/1.73m ²
Empagliflozin	10–25 mg once daily	No dose adjustment if eGFR \geq 45 mL/min/1.73m ² Avoid use, discontinue with eGFR persistently < 45 mL/min/1.73m ²
Canagliflozin	100–300 mg once daily	No dose adjustment if eGFR > 60 mL/min/1.73m ² 100 mg daily if eGFR 30–59 mL/min/1.73m ² Avoid use, discontinue with eGFR persistently < 30 mL/min/1.73m ²

Section 2: Clinical Pearls

- Diabetes mellitus is the leading risk factor for CKD
- Targeting moderate glycemic control is ideal
- Metformin should not be started in CKD stage 3b (eGFR 30-45 ml/min); Metformin should be discontinued in CKD stage 4 and 5
- Consider using newer anti-diabetic drugs
 - SGLT2 Inhibitors slow progression of CKD, but avoid if eGFR < 30 ml/min
 - GLP Receptor Agonists are tolerated if eGFR < 30 ml/min and delay ASCVD



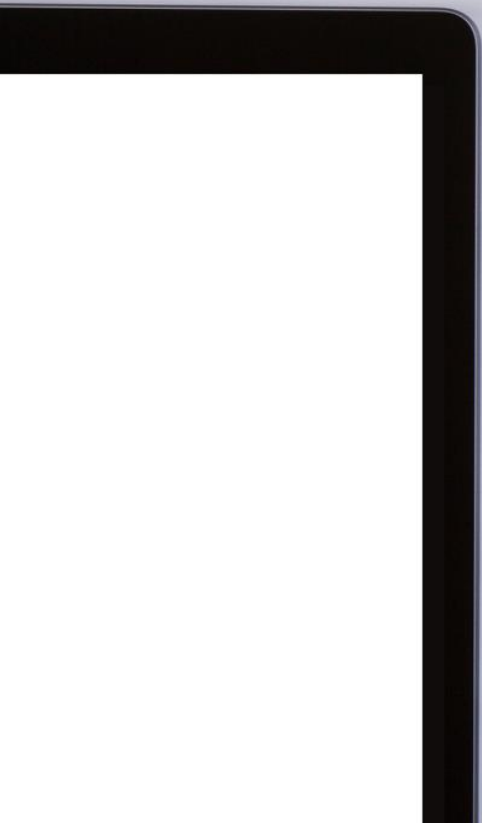
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Case 3: *Mr. Paul McKidney*



Paul McKidney

He is a 34-year-old male with IgA nephropathy, diagnosed 5 years ago. He is an avid weight lifter. He recently started to drink Noni Juice daily for the health benefits.

His serum creatinine is 1.4 mg/dl, the eGFR is 65 ml/min. The UACR is 0.8 g/g.

Mr. Paul McKidney

BMI	24
Height	5'8"
Blood Pressure	134/82

PMHx: Asthma (childhood)

Social: Guitar teacher. Non-smoker. Non-drinker. Marijuana twice weekly. Sexually active with 1 partner.

NAME _____ DATE _____
ADDRESS _____

R_x

Lisinopril 5 mg qhs
Ibuprofen 800 mg daily



Case Question 3

What electrolyte disturbance is Mr. McKidney at greatest risk of developing?

Choice	Answer
A	Hypernatremia
B	Hyperkalemia
C	Hypomagnesemia
D	Hypercalcemia

Rationale

- **Hyperkalemia**

- *Correct. RAASi reduce synthesis of aldosterone, a hormone that stimulates potassium loss; Noni juice has high potassium content*

- **Hypernatremia**

- *Incorrect.*

- **Hypomagnesemia**

- *Incorrect. This disturbance is seen with proton-pump inhibitors*

- **Hypercalcemia**

- *Incorrect. This disturbance is seen with thiazide diuretics*

Drug Induced Clinical Kidney Syndromes



Kidney Syndrome	Causative Agent(s)
Acute Kidney Injury	
Pre-renal	Iodinated contrast, RAASi, NSAID
Intra-Renal	
Vascular	Gemcitabine
Interstitial	Proton Pump Inhibitors, Check Point Inhibitors
Tubular Necrosis	Vancomycin, Cisplatin
Crystal	Acyclovir, Ciprofloxacin
Osmotic	Mannitol
Proteinuria	Bisphosphonates
Tubulopathies	Aminoglycosides
Nephrolithiasis	Sulfadiazine, Topiramate
Chronic Kidney Disease	Herbal Supplements

Alternative Medicine Products

Unlisted ingredients & Unregulated

- Ephedra, Datura, Cape Aloes, Dichromate, Cadmium, Gingko, Melamine, Phenylbutazone, Glycyrrhiza, Taxus Celebica, Aristolochic Acid



How NSAIDs affect the Kidney...

- Pre-renal Azotemia
- Acute Tubular Necrosis
- Hypertension / Edema
- Glomerular disease (minimal change)
- Acute Interstitial Nephritis
- Hyperkalemia / Hyponatremia
- Papillary Necrosis
- Chronic Interstitial Nephritis

NSAID + RAASI + Vol Depletion = *Triple Whammy*

'C' What's New in Nephrology: 2018-19

Contrast

- Contrast **Associated** Acute Kidney Injury (CA-AKI); risk may be *smaller* than previously thought
- Do not avoid critical procedures because a patient has CKD

Cystatin C and Cardiovascular Disease

- GFR calculated by cystatin C compared to creatinine better predicted future CV events

Contaminants

- Angiotensin Receptor Blockers
- Carcinogenic impurities ingested for >4 years... 1 cancer per 8000 patients
- Patients alerted if exposure occurred

Credence

- 4,401 patients with DKD randomized to Canagliflozin vs. placebo for median of 2.62 years
- Renal Specific Outcome (NNT 28)
 - End Stage Kidney Disease
 - Doubling of serum creatinine for ≥ 30 days



34%
RRR

Section 3: Clinical Pearls

- Drugs and their metabolites may accumulate with or without a reduced eGFR resulting in nephrotoxicity
- NSAIDs should be used sparingly in all patients with CKD
- The association of iodinated contrast and kidney injury requires further exploration, and clinicians should not withhold potentially life saving procedures



Post-Lecture Question 1

Which of the following statements is correct?

1. A proper assessment of CKD staging should include the degree of albuminuria
2. Hypertension is the most common cause of CKD
3. Glyburide is a safe medication if the eGFR < 30 ml/min
4. In a 77-year-old patient with HFrEF, dialysis initiation increases survival compared to conservative management
5. A patient with CKD Stage 3B can use NSAIDs for arthritis

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Which of the following is TRUE regarding SGLT2 inhibitors?

1. Glycemic efficacy is reduced when the eGFR < 30 ml/min
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