Chronic Kidney Disease Management 2022: Advancing the American Kidney Health Initiative

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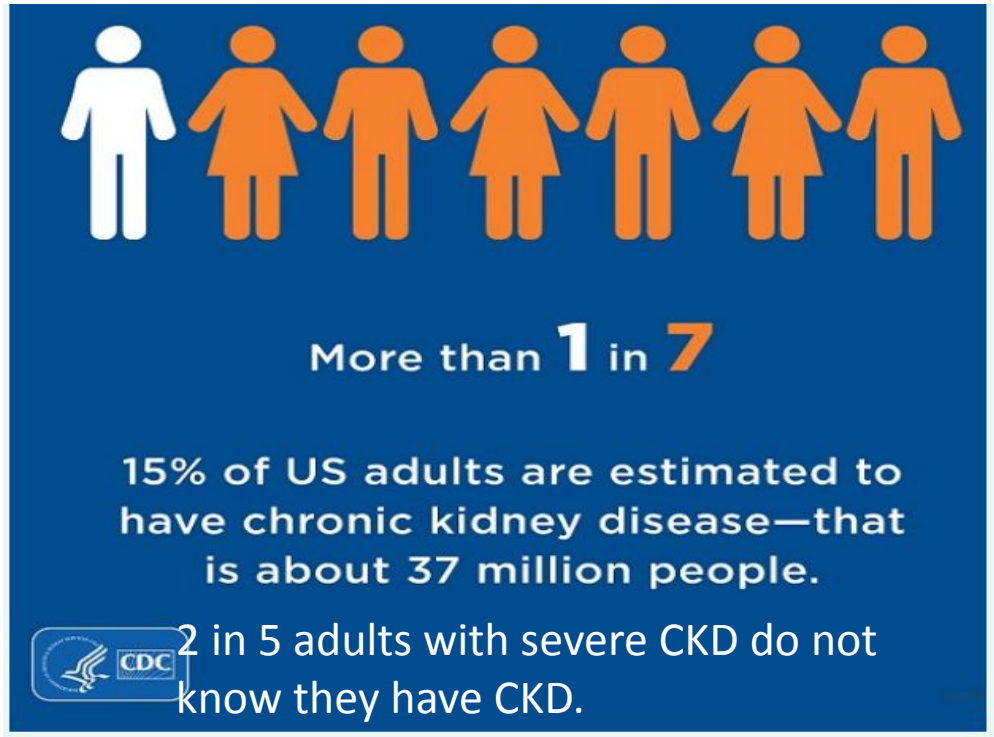
ASCENSION



37,000,000 Americans have kidney diseases

>726,000 Americans have kidney failure

>100,000 Americans begin dialysis each year and nearly 60% of those will die within the first 5 years of treatment

~100,000 Americans are on the kidney transplant waiting list

NIH Spending per Patient

HIV/AIDS

$3.1 B for 1.2 M patients

Cancer

$7.4 B for 23.3 M patients

Heart Disease

$1.6 B for 30.3 M patients

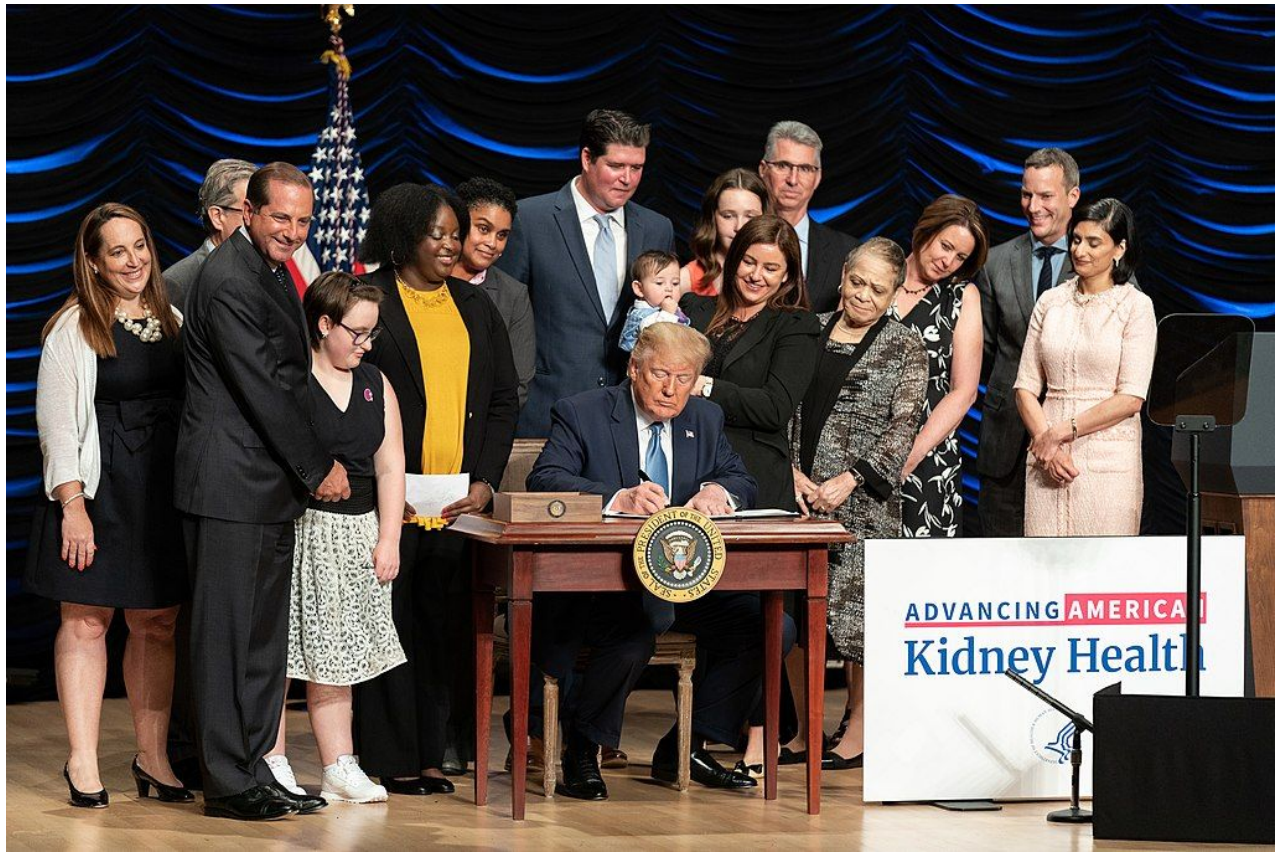
Kidney Disease

$0.72 B for 37 M patients

SOM22

NATIONAL KIDNEY FOUNDATION

Advancing American Kidney Health initiative



Goals:

- Reduce the Risk of Kidney Failure
- Improve Access to and Quality of Person-Centered Treatment Options
- Increase Access to Kidney Transplants

Executive Order on Advancing American Kidney Health

10 July 2019

whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health

Designed by: Tejas Desai, MD | @nephondemand

Goals

- 80% of incident ESRD patients receive either home dialysis therapy or transplantation by CY 2025
- Standardize organ procurement reduce percentage of discarded organs
- Remove financial barriers for living kidney donors
- Encourage development of the artificial kidney
- Restructure payment models to incentivize prevention, home therapy/transplantation

Payment Models

ETC | KCF
CKCC Graduated
CKCC Pro/Global

Randomized

based on Hospital Referral Region

CMS

ESRD Treatment Choices (ETC)

Mandatory randomization: no crossover/dropout allowed

- ↑ $ adjustment for patients receiving home therapy from 1/2020-12/2022
- ↑ or ↓ $ adjustment for patients receiving in-center or home dialysis

Conventional Payment Model

- Payment not affected

↑ MANDATORY

↓ OPTIONAL

Nephrologist-only

Kidney Care First (KCF)

- Receive capitated payments for CKD 4-5 and ESRD patients
- Receive bonus $ for patients transplanted (distributed over 3 year period if transplant remains "successful")

Kidney Care Organization + Nephrologist

Comprehensive Kidney Care Contracting (CKCC)

- Same as KCF
- Assume 50-100% risk as well as 50-100% of shared savings

A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease

Recommend immediate implementation of the *CKD-EPI creatinine equation refit without the race variable* in all laboratories in the U.S.

The equation refit excludes race in the calculation and reporting, includes diversity in its development, is immediately available to all labs in the U.S. and has acceptable performance characteristics and potential consequences that do not disproportionately affect any one group of individuals.

Recommend national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in clinical decision-making

Encourage and fund research on GFR estimation with new endogenous filtration markers and on interventions to eliminate racial and ethnic disparities

The Task Force gathered input from diverse stakeholders and carefully reviewed the evidence to create these recommendations

Cynthia Delgado, Mukta Baweja, Deidra C. Crews, et al. *A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease.* *AJKD DOI:* 10.1053/j.ajkd.2021.08.003, *JASN DOI: 10.1681/ASN.2021070988*

Visual Graphic by Edgar Lerma, MD, FASN

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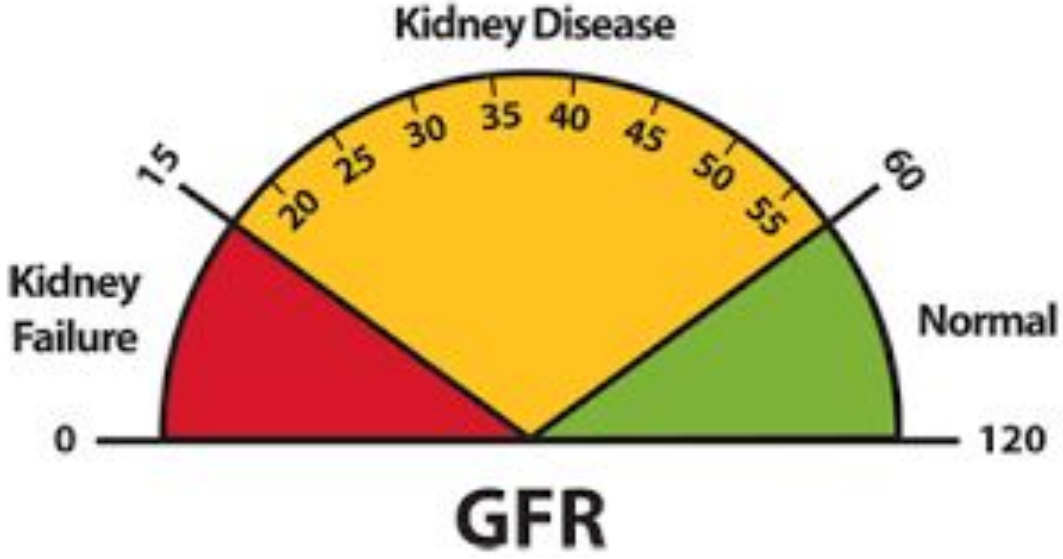
Eliminating Race Coefficient in CKD-EPI

Potential Benefits:

- Expand Access to Care
- Expanding Medicare coverage for medical nutrition therapy (0.47%) and kidney disease education (0.14%)
- Increase nephrology referrals
- Potentially earlier transplant referral



Potential Unintended Consequences

- Medication limitations (i.e., SGLT2i candidacy)
- Financial implications (higher insurance costs)
- Possible ineligibility for living donor (2.1% disqualified in Diao/NHANES study)
- Clinical trial enrollment eligibility

60-year-old man has a known diagnosis of type 2 diabetes (micro- and macrovascular disease). He has established chronic kidney disease, hyperlipidemia, hypertension, and proteinuria. Which of the following statements is true?

A. Intensive treatment of blood pressure in diabetics improves survival

B. Early start of dialysis is associated with improved survival

C. Intensive treatment of lipid level improves survival

D. The use of SGLT2 in moderate CKD is associated with improved renal outcomes

E. Intensive treatment of blood pressure in CKD preserves kidney function

Proteinuria Significance

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

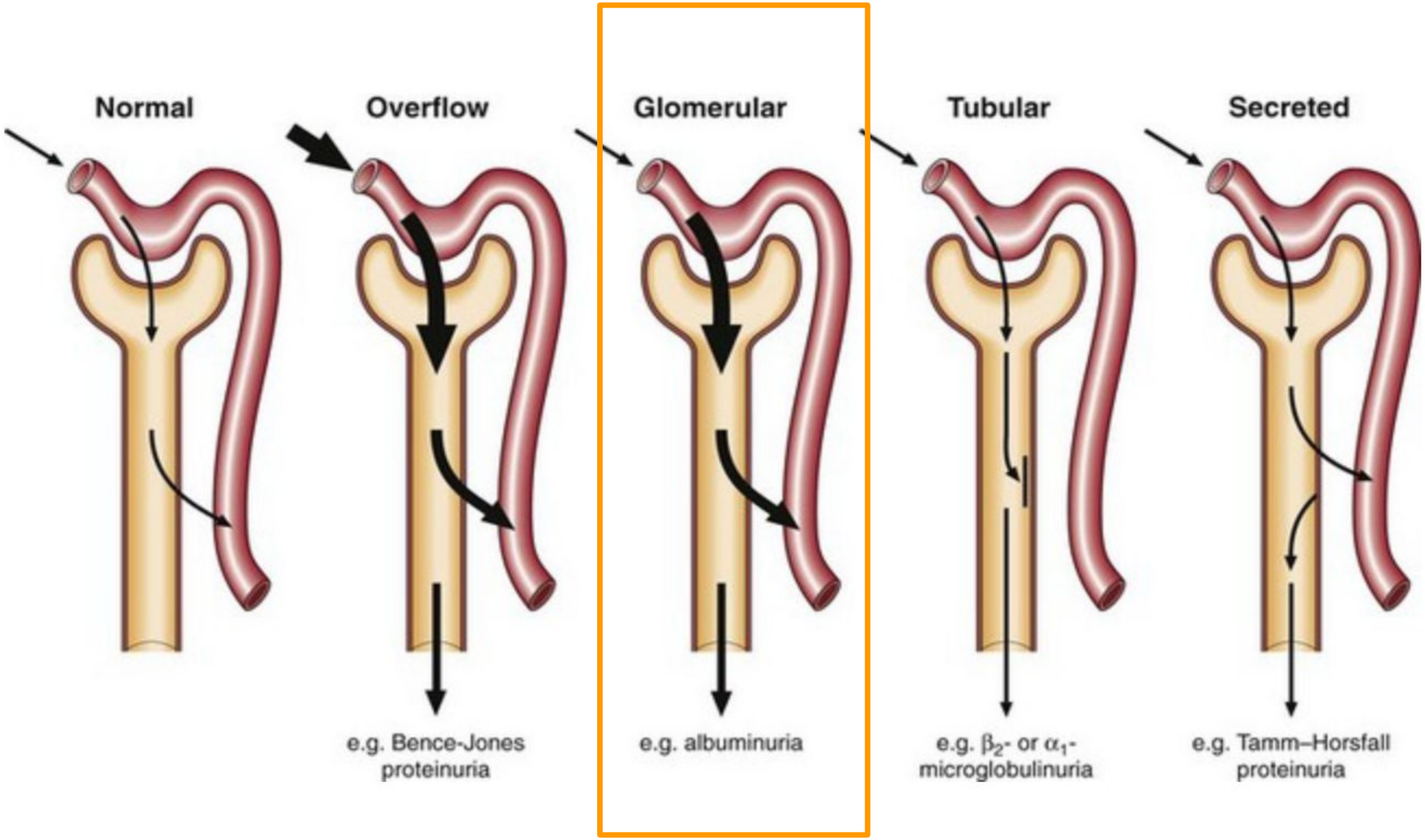
GFR categories (ml/min/ 1.73m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

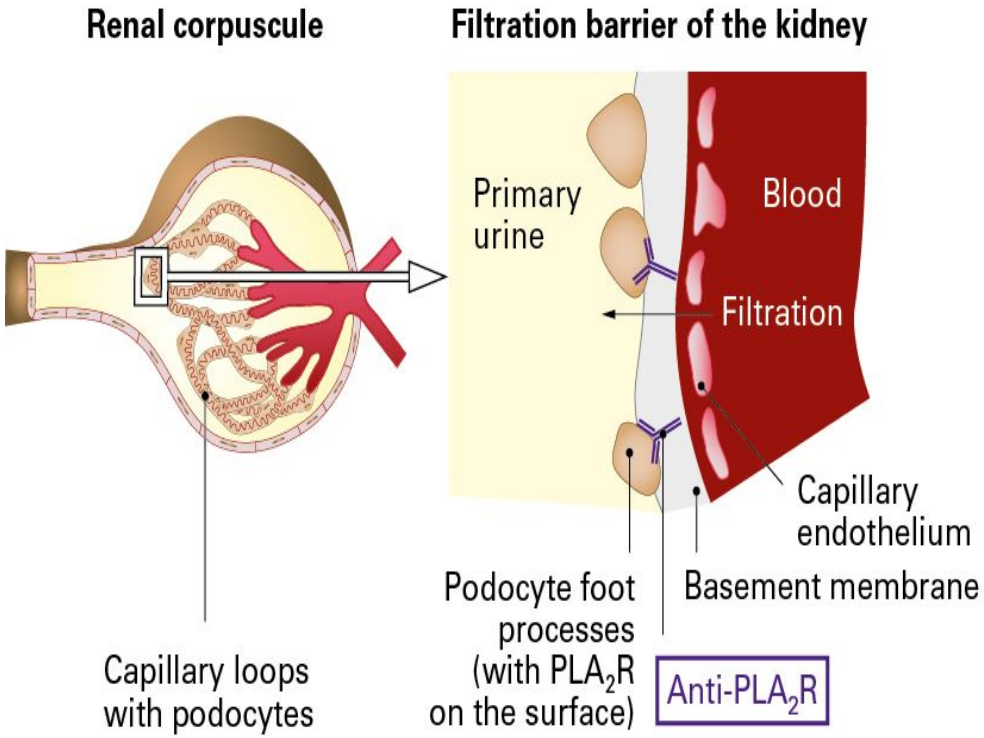
- Powerful predictor of progressive renal disease
- Even low level (1+ dipstick) is associated with twofold increased risk of ESRD
- Hallmark of diabetic and hypertensive nephropathy (accounts for the majority of patients with proteinuria)
- Significant (>1g/day) in absence of identifiable cause warrants further investigation

Urine Studies	Protein	Pointers
Dipstick		• **Albumin / negatively charged proteins** • Can miss microalbuminuria/+ proteins (Ig)

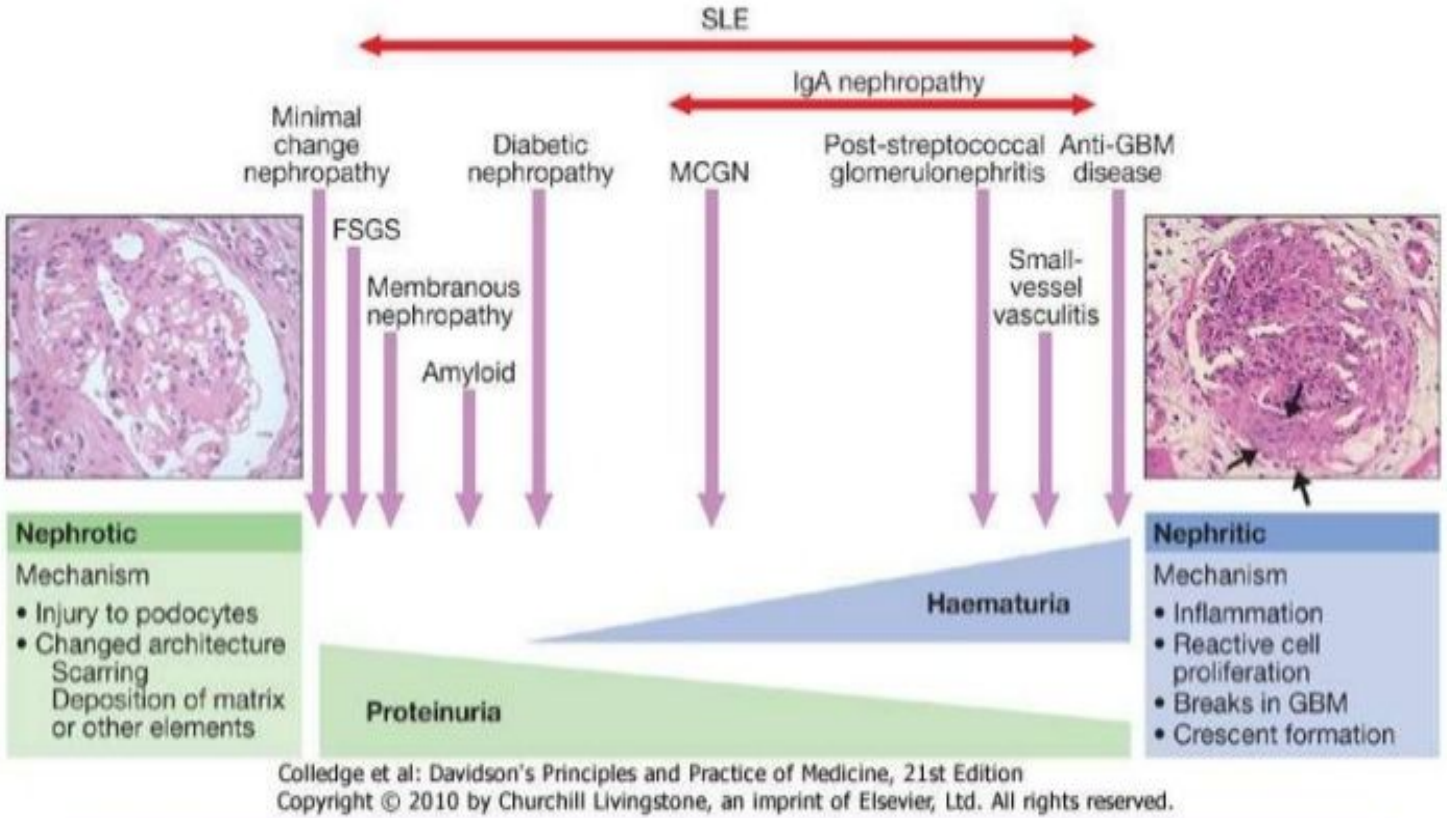
<u>Spot Urine</u>
 	
UACR
	<u>Albumin/creatinine ratio (UACR)</u>
	• **< 30 mg/g:** Normal
	• **30-300**: Microalbuminuria
	• **> 300:** Macroalbuminuria
	  ○ → Check UPCR
		• More precise at **lower concentrations**
		  ○ **Albumin only**
		• **Screening** increased risk of **CKD** (ie DM, HTN, glomerular disease)
		  ○ One of the first proteins to pass

UPCR	**<u>Protein-creatinine ratio (UPCR)</u>** • **< 0.15 g/g (150 mg/g)** : Normal • **0.15-3.0 (150-3000)**: Proteinuria • **> 3.5 mg/g:** Nephrotic range	• Check **UPCR if HIGH UACR** ○ **Checks non-albumin + albumin** • **Closely correlates to 24-hour** urine protein • Trend proteinuria
24-hour urine collection	**<u>Albumin</u>** • 30-300 mg/dL: microalbuminuria • > 300 mg/dL: macroalbuminuria **<u>Protein</u>** • > 150 mg/dL: proteinuria • > 3-3.5 g/dL: nephrotic	• Gold standard • Cumbersome • Significant collection errors (missed samples, timing)


Normal
Overflow
Glomerular
Tubular
Secreted
e.g. Bence-Jones proteinuria
e.g. albuminuria
e.g. β_2- or α_1-microglobulinuria
e.g. Tamm–Horsfall proteinuria



Differential diagnosis of glomerular diseases



Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition
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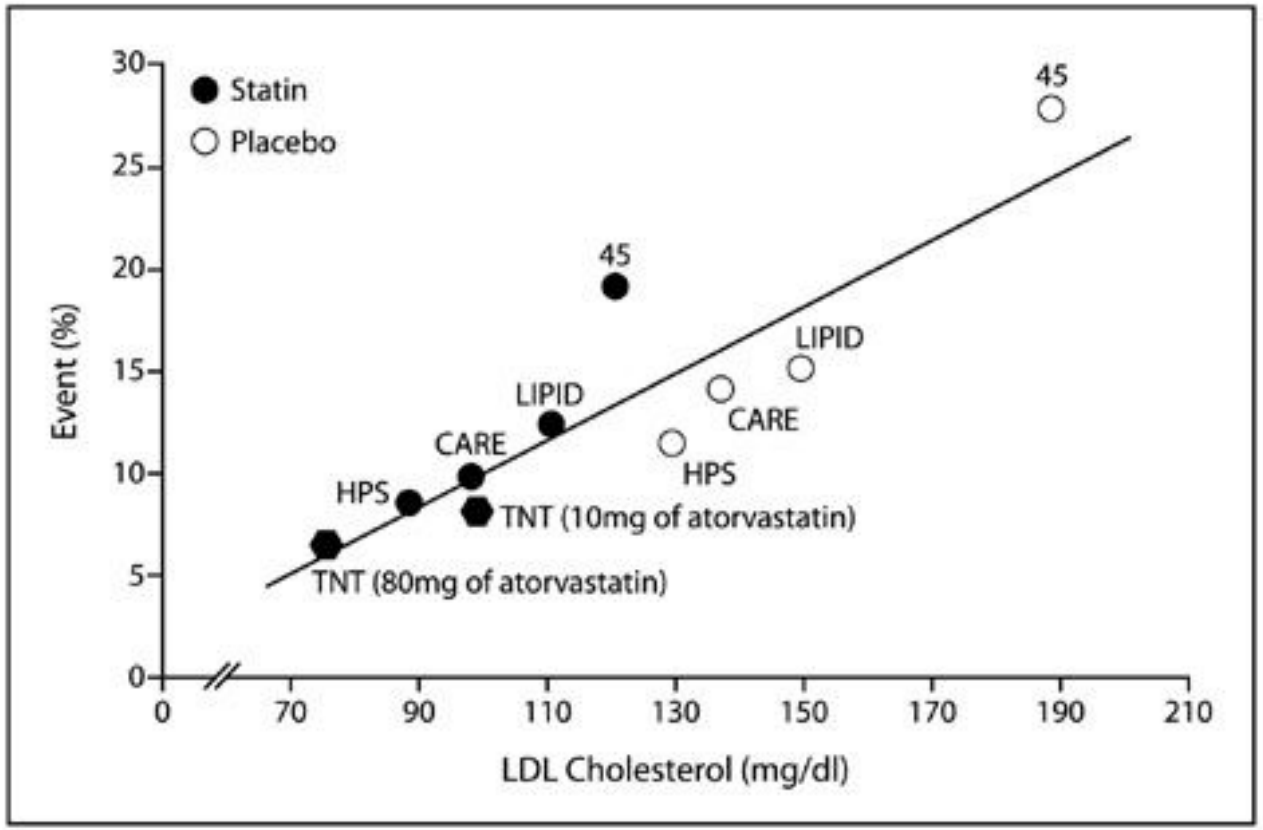
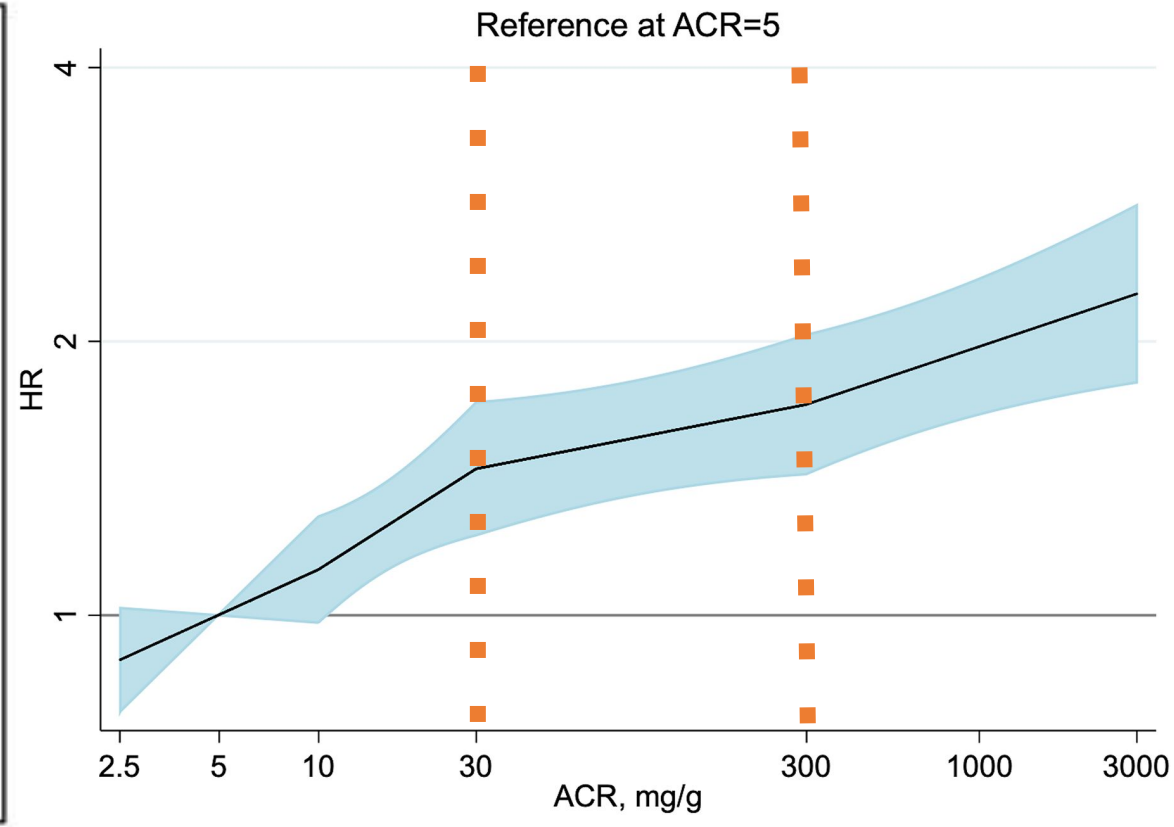
Diseases presented by either nephrotic and nephritic can be idiopathic or secondary to other causes.


Statin
Placebo
Event (%)
LDL Cholesterol (mg/dl)
0
5
10
15
20
25
30
0
70
90
110
130
150
170
190
210
45
45
LIPID
LIPID
CARE
CARE
HPS
HPS
TNT (10mg of atorvastatin)
TNT (80mg of atorvastatin)


Reference at ACR=5
HR
1
2
4
2.5
5
10
30
300
1000
3000
ACR, mg/g

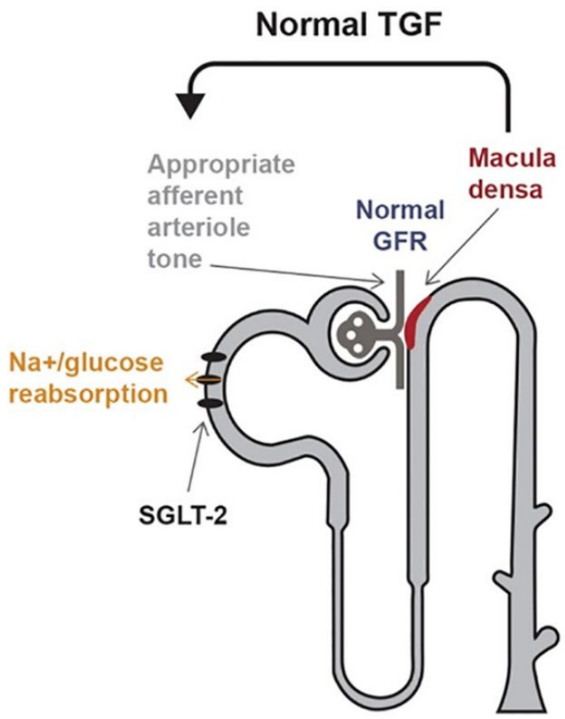
Strategies for Preventing Progressive Nephropathy in Type 2 Diabetes

- *Target glomerular hemodynamics*
  - Efferent vasodilation (RAASi)
  - Afferent vasoconstriction (SGLT2i)
  - BP control
- *CV risk reduction strategies*
- *Glucose control*
- *Future therapies*
  - Anti-inflammatory, anti-fibrotics

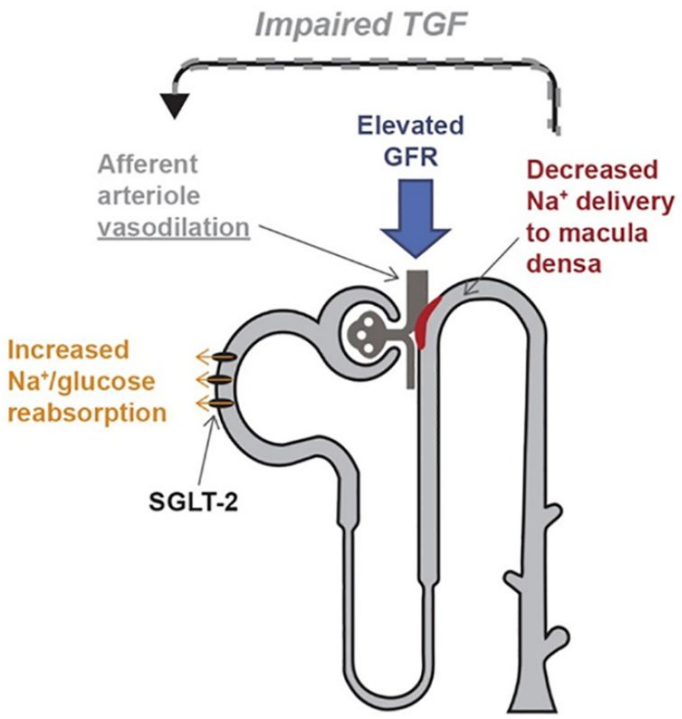
Renoprotection with RAAS Inhibition

Trial	Population	N	Intervention	Conclusions	Comments
ROADMAP	T2DM without microalbuminuria	4,449	Olmesartan vs placebo	Olmesartan delayed the onset of microalbuminuria	Olmesartan group had lower BPs and more CV deaths
IRMA-2	T2DM and microalbuminuria	590	Irbesartan 150 mg vs irbesartan 300 mg vs placebo	Irbesartan reduced the development of overt proteinuria	Subgroup analysis suggested a dose-dependent effect
Captopril Trial	T1DM with proteinuria	409	Captopril 25 mg 3×/d vs placebo	Captopril reduced the risk for doubling of SCr as a primary outcome and death, dialysis therapy, or transplantation as a secondary outcome	
IDNT	T2DM with proteinuria and reduced kidney function	1,715	Irbesartan vs amlodipine vs placebo	Irbesartan reduced the risk for doubling of SCr, ESRD, or death	
RENAAL	T2DM with proteinuria and reduced kidney function	1,513	Losartan vs placebo	Losartan reduced the risk for doubling of SCr, ESRD, or death	

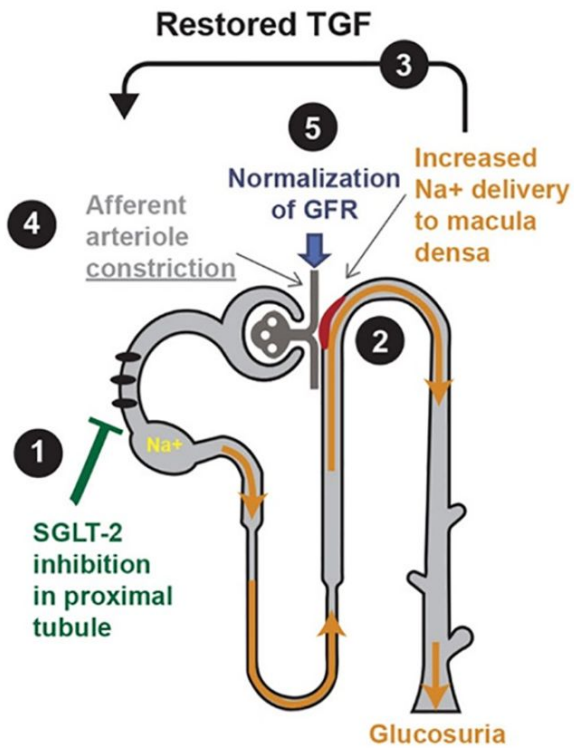
SGLT2 Inhibition



Normal physiology



Hyperfiltration in early stages of diabetic nephropathy



SGLT-2 inhibition reduces hyperfiltration via TGF

49-year-old man with type 2 DM and a recent hemoglobin A1c of 8.9%. He has recently started empagliflozin. Which is true regarding empagliflozin?

A. Empagliflozin is effective in patients with an eGFR <20 ml/min/per 1.73 m2

B. The risk of urinary tract infections is not increased with empaglifozin

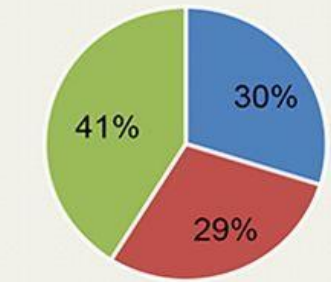
C. There is an increased risk of ketoacidosis with empaglifozin

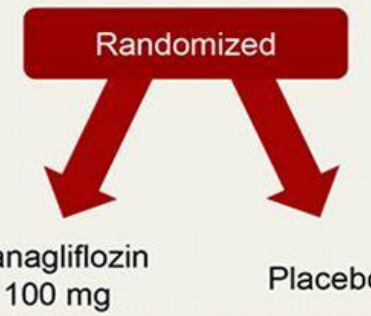
D. The risk of genital fungal infection is not increased with empaglifozin

Renal, Cardiovascular, and Safety Outcomes of Canagliflozin By Baseline Kidney Function: Post hoc Secondary Analysis of the CREDENCE Randomized Trial

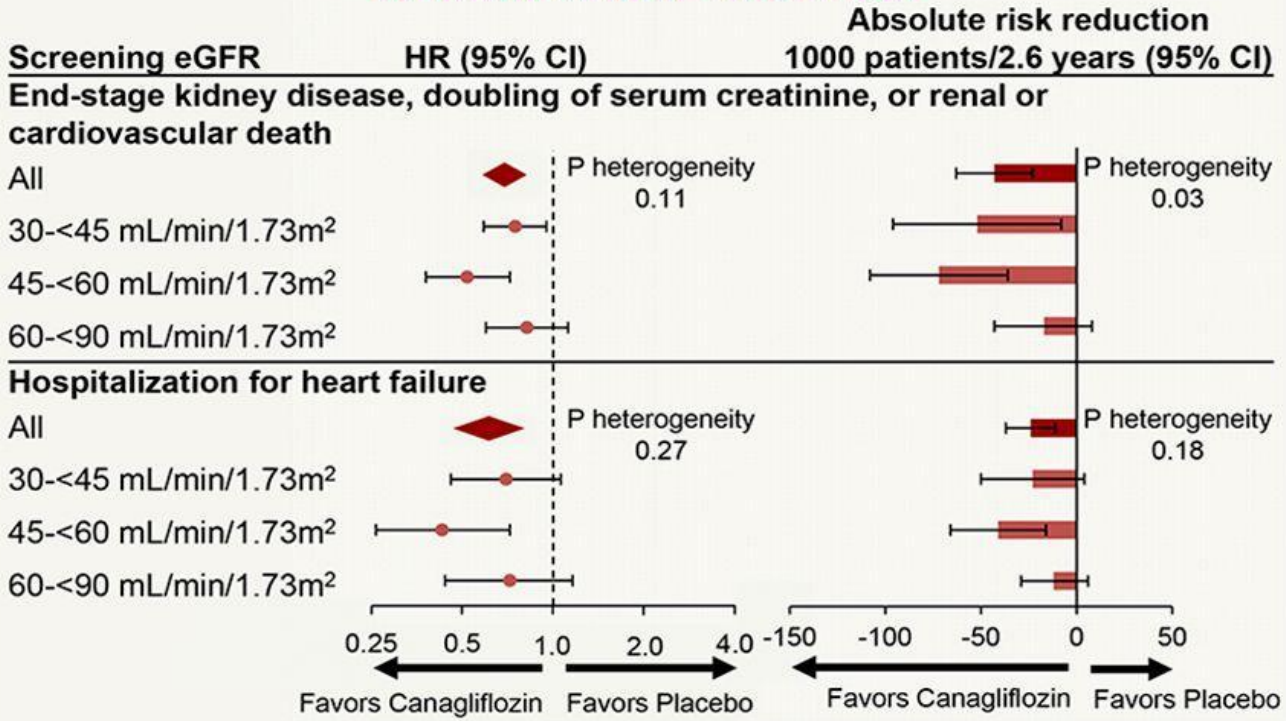
METHODS

4401 participants with T2DM and screening eGFR 30-<90 mL/min/1.73m²





Effect of Canagliflozin on Kidney and Cardiovascular Outcomes



CONCLUSION In CREDENCE, canagliflozin safely reduced the risk of renal and cardiovascular events with consistent results across eGFR subgroups, including those initiating treatment with eGFR 30-<45 mL/min/1.73m². Absolute benefits for renal outcomes were greatest in lower initial eGFR subgroups.

doi: 10.1681/ASN.2019111168

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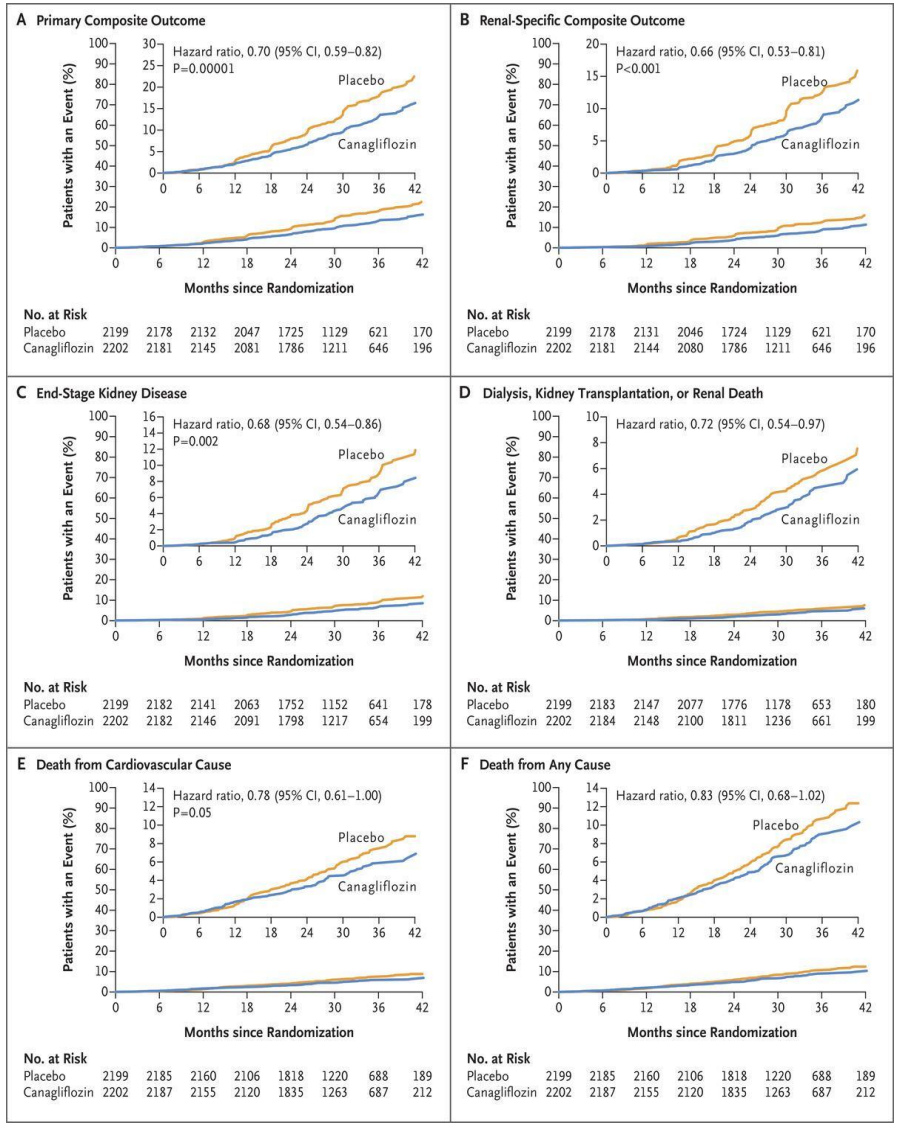
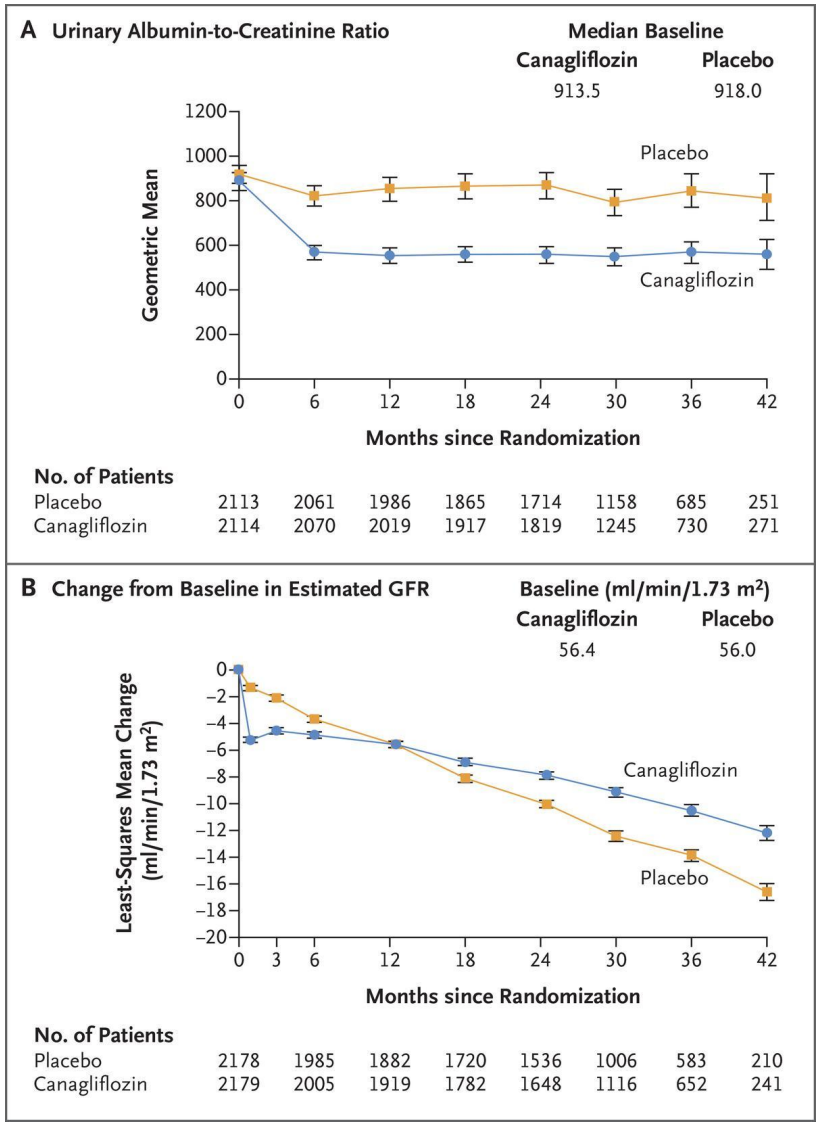
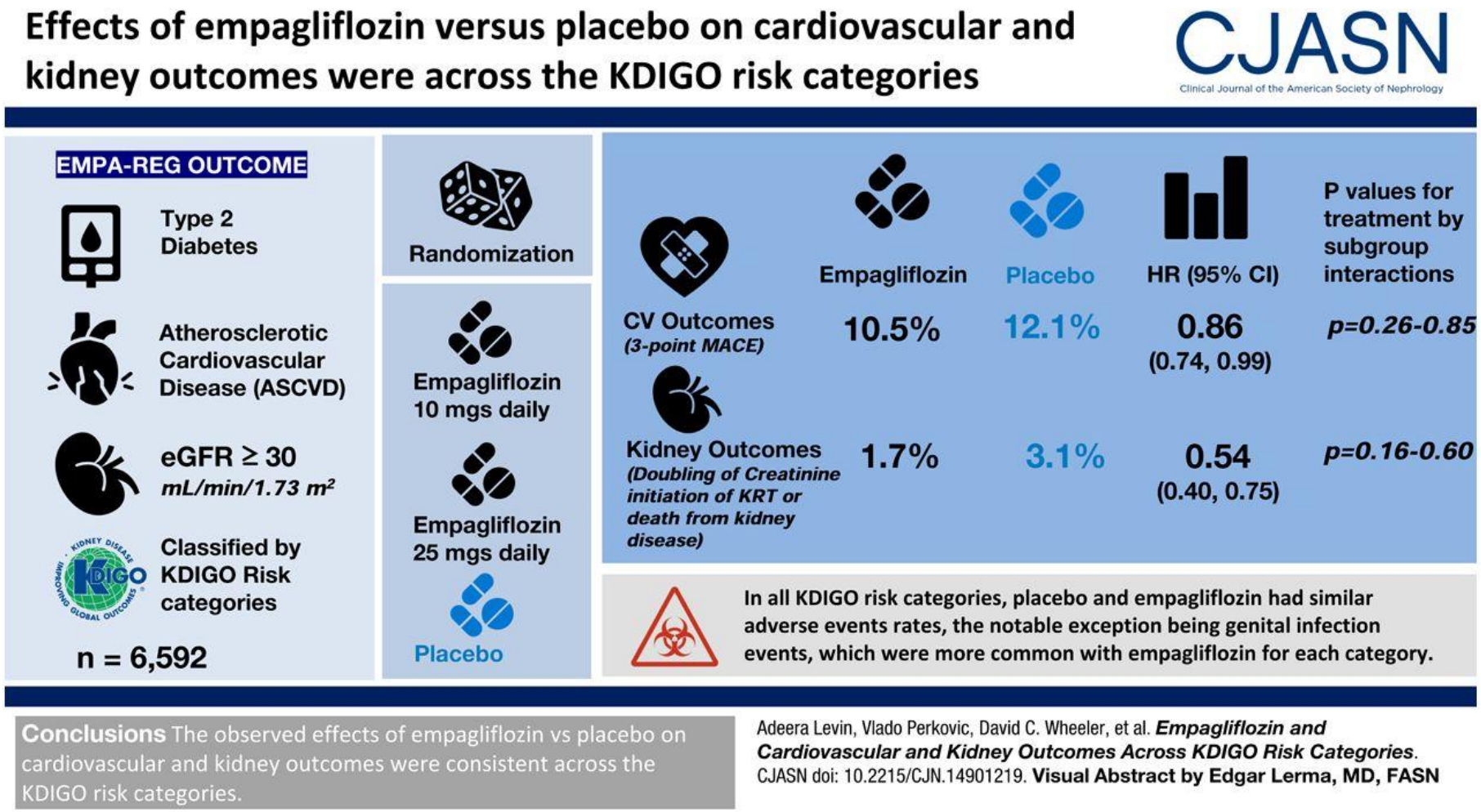
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy-**CREDENCE** Trial



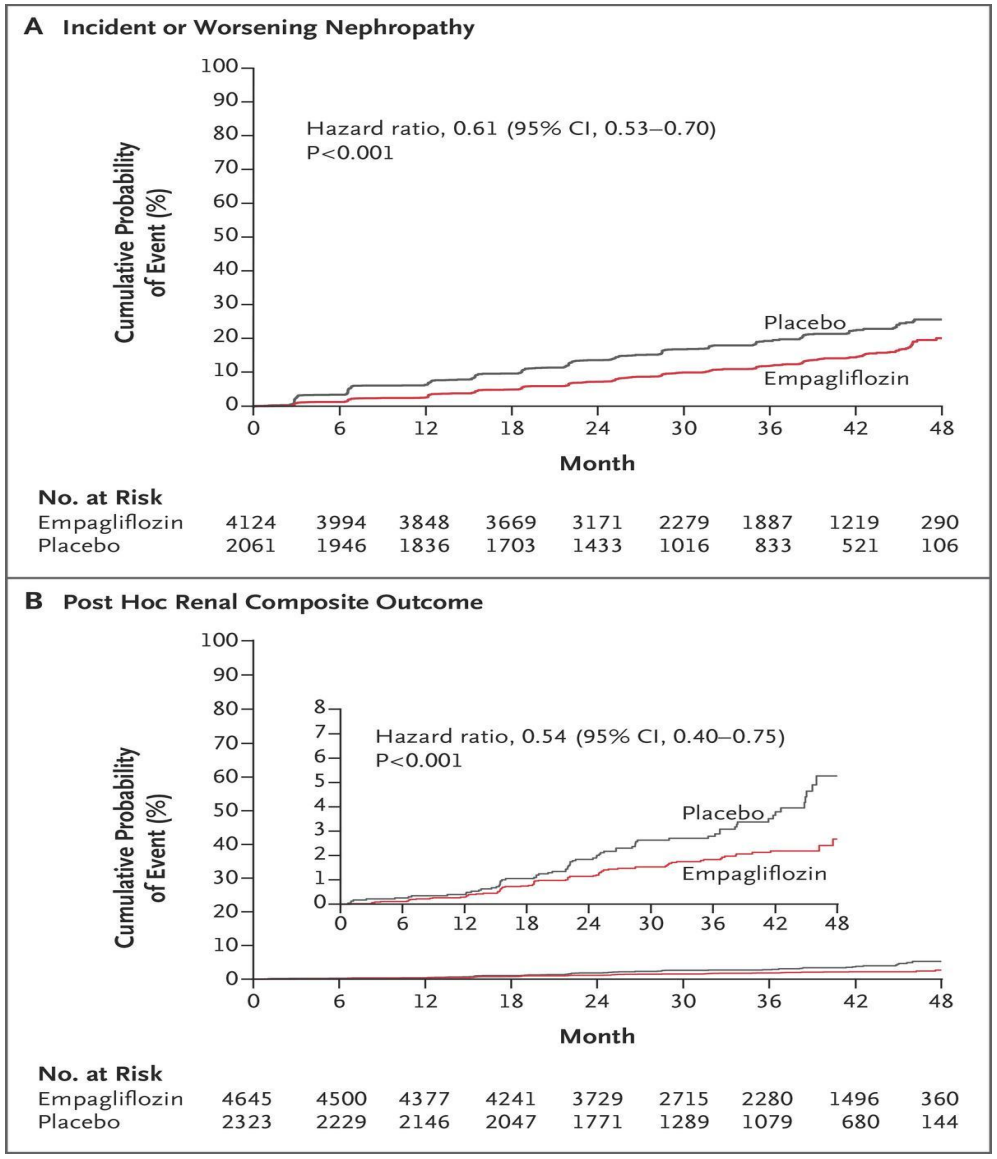


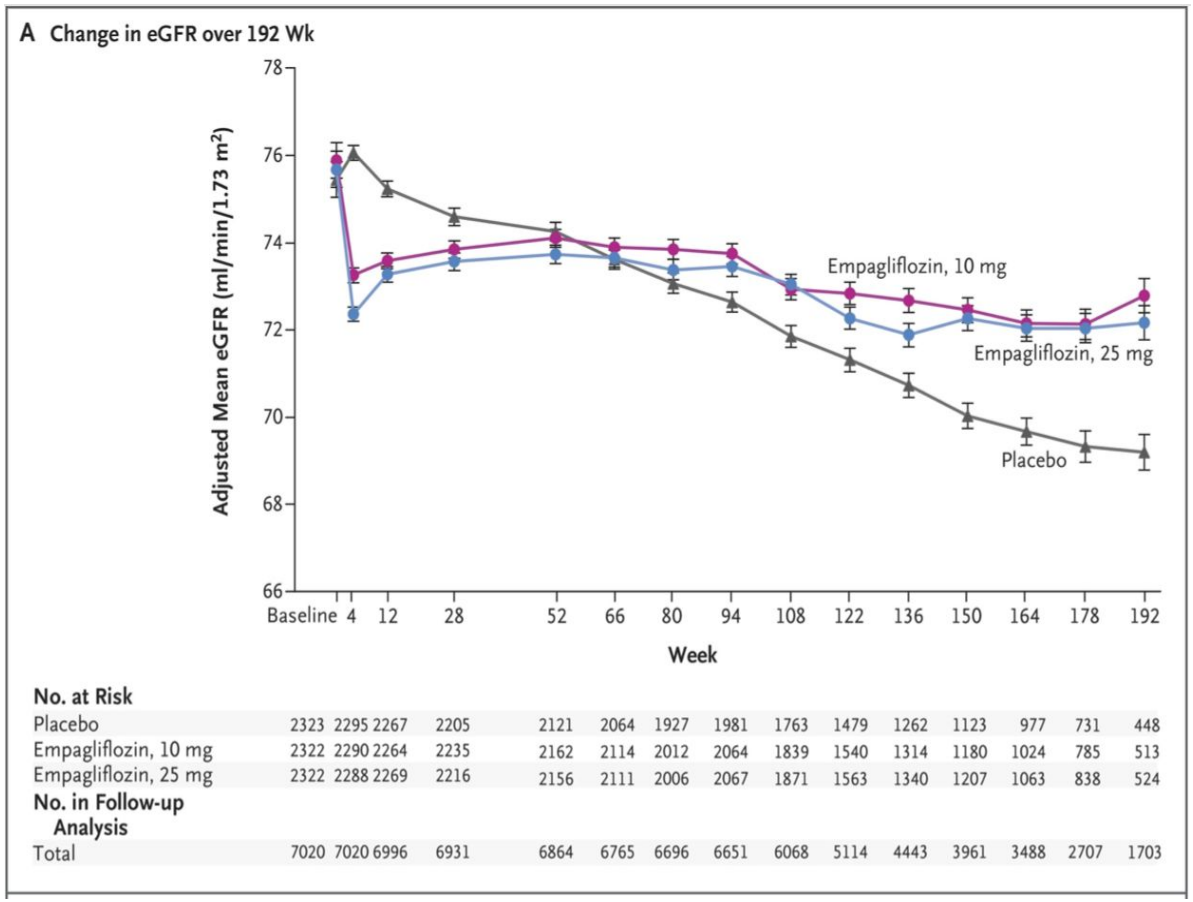
N Engl J Med 2019; 380:2295-2306

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes- EMPA-REG OUTCOME



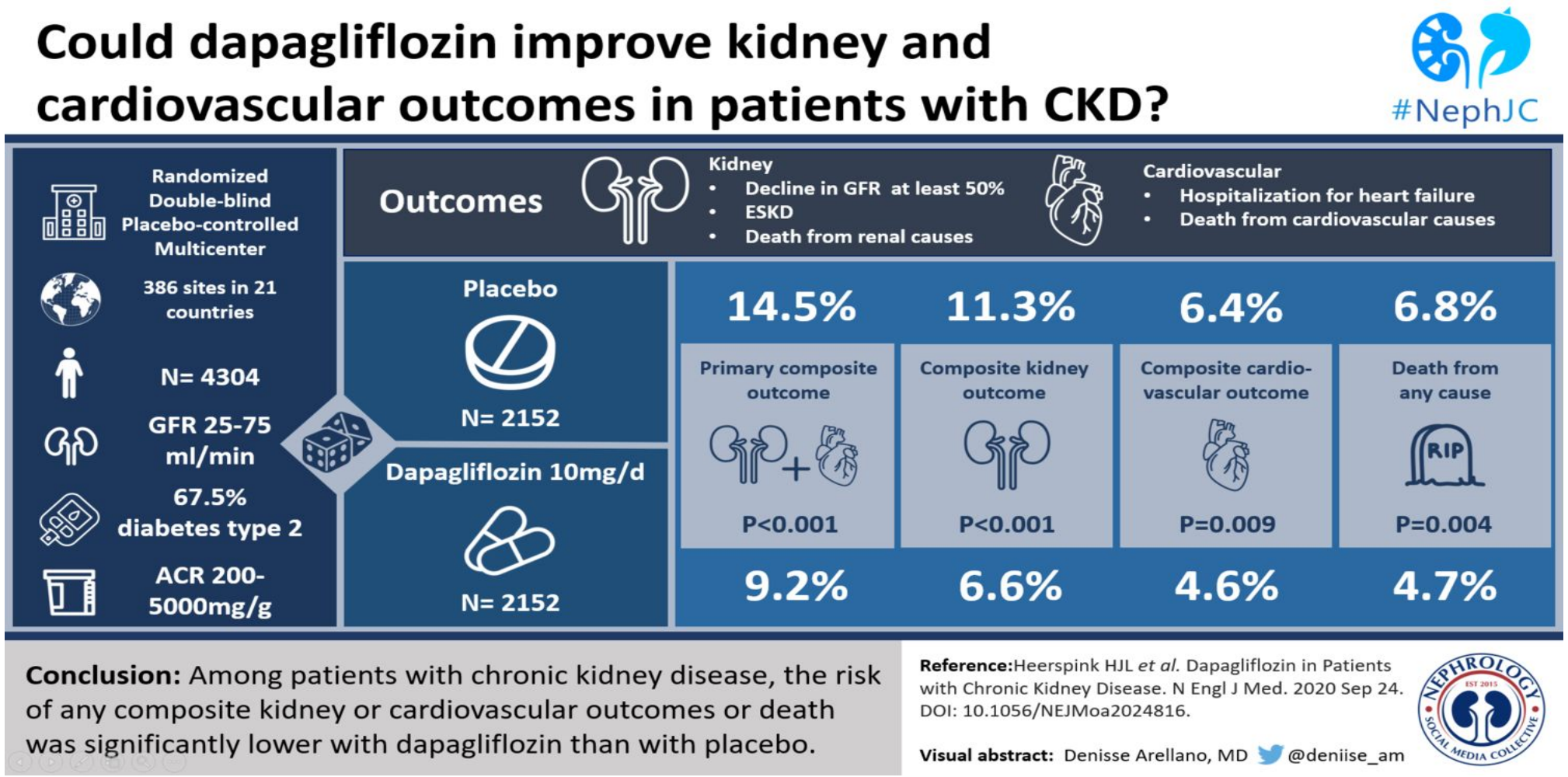
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes- **EMPA-REG OUTCOME**



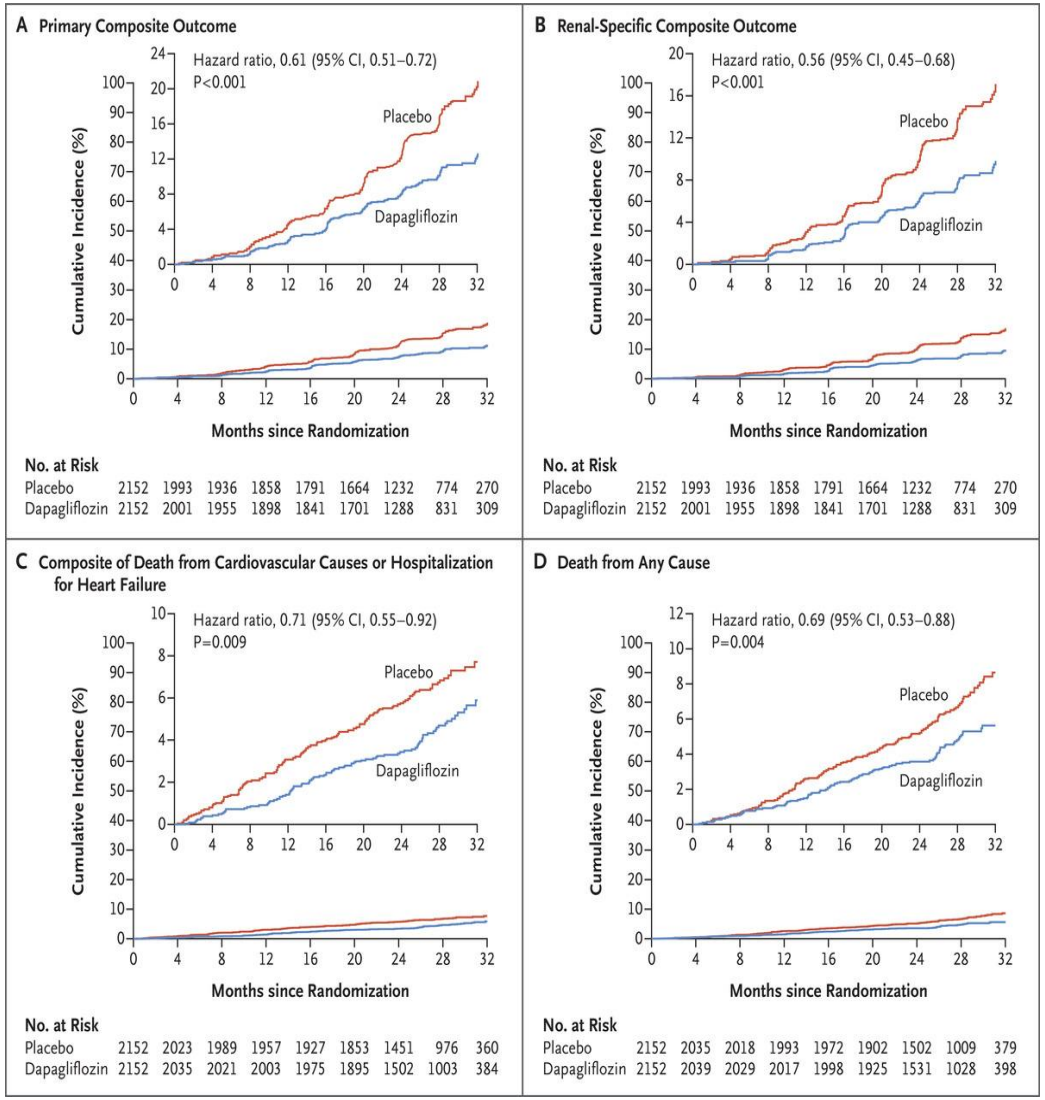


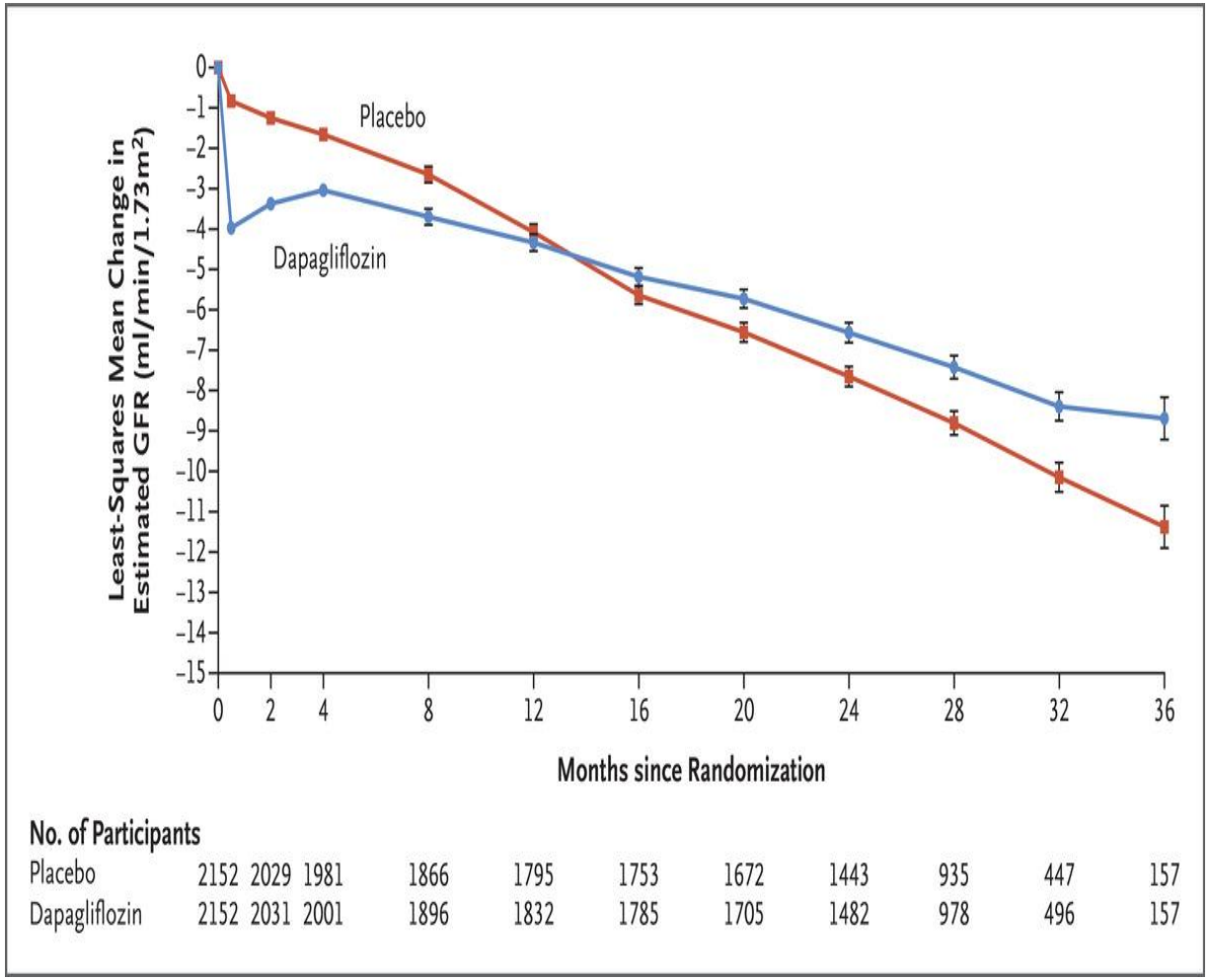
N Engl J Med 2016; 375:323-334

Dapagliflozin in Patients with Chronic Kidney Disease- **DAPA-CKD Trial**



Dapagliflozin in Patients with Chronic Kidney Disease- DAPA-CKD Trial





N Engl J Med 2020;

FDA-approved SGLT2 inhibitors[2]

Generic agent (brand)	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
Initial dose (maximum dose)	100 mg/d if eGFR is 45 to <60 and 300 mg/d if eGFR ≥60	5 mg/d (10 mg/d)	10 mg/d (25 mg/d)
Renal dosage adjustments	Discontinue if eGFR is persistently <45 (Contraindicated if eGFR <30)	Do not administer/discontinue with eGFR <60	Do not initiate/discontinue with eGFR persistently <45 (Contraindicated if eGFR <30)
Hepatic dosage adjustments	No adjustment for mild to moderate impairment; not recommended in severe impairment (has not been studied)		None to note
Drug interactions	If receiving concurrent UGT enzyme inducers and eGFR is 45 to <60, consider alternative antihyperglycemic therapy	None to note	
Administration	Administer prior to first meal	Administer in the morning without regard to food	
Common adverse effects	Genital mycotic infections, urinary tract infections, volume-related effects such as dizziness and hypotension		
Available combination products, generic (brand)	canagliflozin + metformin (Invokamet)	dapagliflozin + metformin ER (Xigduo)	empagliflozin + metformin (Synjardy) empagliflozin + linagliptan (Glyxambi)

Side effects

- Euglycemic DKA
- Genital Infections
- Peripheral vascular disease/amputations (Empagliflozin only, not Dapagliflozin)
- Possibly bladder Ca (Dapagliflozin only)
- Hypotension/AKI (diuretic)
- Increased LDL-C
- NOT hypoglycemia

Does finerenone slow progression of CKD and reduce cardiovascular mortality in patients with type 2 diabetes?

#NephJC

PHASE 3, DOUBLE-BLIND, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL

5674

Patients with type 2 diabetes and CKD

	Finerenone (10 mg or 20mg daily)		Placebo
	n = 2833		n = 2841
	2.6 year median follow up		
Primary Composite Outcome: Kidney Failure with >40% decrease in eGFR over 4-week period or death from renal causes	17.8% (504/2833)	HR 0.82 (0.73 – 0.93) p = 0.001	21.1% (600/2841)
Secondary Composite Outcome: Death from cardiovascular causes or hospitalization for any cause	13.0% (367/2833)	HR 0.86 (0.75 – 0.99) p = 0.03	14.8% (420/2841)

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risk of CKD progression and cardiovascular events than placebo.

N Engl J Med 2020;

FIGARO-DKD trial

RESEARCH SUMMARY

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

Pitt B et al. DOI: 10.1056/NEJMoa2110956

CLINICAL PROBLEM

Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, improves cardiorenal outcomes in patients with stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. Whether finerenone is beneficial in patients with diabetes and less-advanced CKD is unclear.

CLINICAL TRIAL

Design: A phase 3, multicenter, randomized, placebo-controlled trial examined the efficacy and safety of finerenone in adults with type 2 diabetes and a range of CKD stages.

Intervention: 7437 patients with diabetes and CKD treated with a maximum-dose renin–angiotensin system inhibitor were assigned to receive oral finerenone or placebo. Eligible patients had persistent, moderately elevated albuminuria plus an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 (stage 2 to 4 CKD) or persistent, severely elevated albuminuria plus an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

Efficacy: During a median 3.4 years of follow-up, the incidence of primary outcome events was lower with finerenone than with placebo, a difference driven mainly by a lower incidence of hospitalization with finerenone.

Safety: The incidence of serious adverse events was similar in the two groups. Hyperkalemia occurred more often with finerenone but did not result in any deaths and rarely resulted in treatment discontinuation.

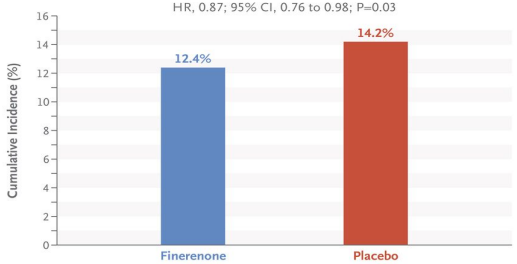
LIMITATIONS AND REMAINING QUESTIONS

- Few Black patients were included. Patients with symptomatic heart failure with a reduced ejection fraction were excluded.
- Current clinical guidance recommends sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes and CKD. Whether using finerenone with these agents offers additive cardiorenal benefits is unclear.

Links: Full Article | NEJM Quick Take

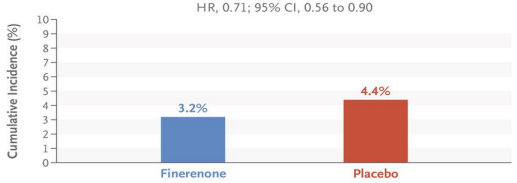
Death from Cardiovascular Causes, Nonfatal MI, Nonfatal Stroke, or Hospitalization for Heart Failure

HR, 0.87; 95% CI, 0.76 to 0.98; P=0.03



Hospitalization for Heart Failure

HR, 0.71; 95% CI, 0.56 to 0.90



Safety Outcomes

Adverse Event	Finerenone	Placebo
Serious adverse events	31.4%	33.2%
Hyperkalemia	10.8%	5.3%
Treatment discontinuation due to hyperkalemia	1.2%	0.4%

CONCLUSIONS

The mineralocorticoid receptor antagonist finerenone lowered the risk of major adverse cardiovascular events among patients with type 2 diabetes and a wide range of CKD stages.

Albuminuria Lowering Effect of Dapagliflozin, Eplerenone and Their Combination in Patients with Chronic Kidney Disease: A Randomized Cross-Over Clinical Trial

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METHODS

46 patients

- Age ≥18 years
- UACR 100-3500 mg/24-hour
- eGFR >30 - <90 mL/min/1.73m^2
- Stable (>4 weeks) dose of ACEi **or** ARB

Dapagliflozin 10 mg → **Eplerenone** 50 mg → **Eplerenone** 50 mg **Dapagliflozin** 10 mg

4-weeks treatment in random order with 4-weeks wash-out in between

OUTCOMES

UACR change (%) from baseline

combination vs. dapa: p<0.001

combination vs. eple: p=0.0127

Change from baseline in serum K (mmol/L)

combination vs. dapa: p<0.0018

combination vs. eple: p=0.0296

Conclusion

Dapagliflzoin in combination with eplerenone reduced albuminuria to a greater extent than either drug alone. Compared to eplerenone, dapagliflozin-eplerenone combined decreased serum potassium.

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Advancing American Kidney Health Initiative

- Appropriate identification of at risk population with appropriate screening tools
- Management of risk factor progression via proper therapeutic interventions
- Preparation for optimal decision making based on risk factors

ASCENSION