What's New in Management of Chronic Kidney Disease (CKD) ?

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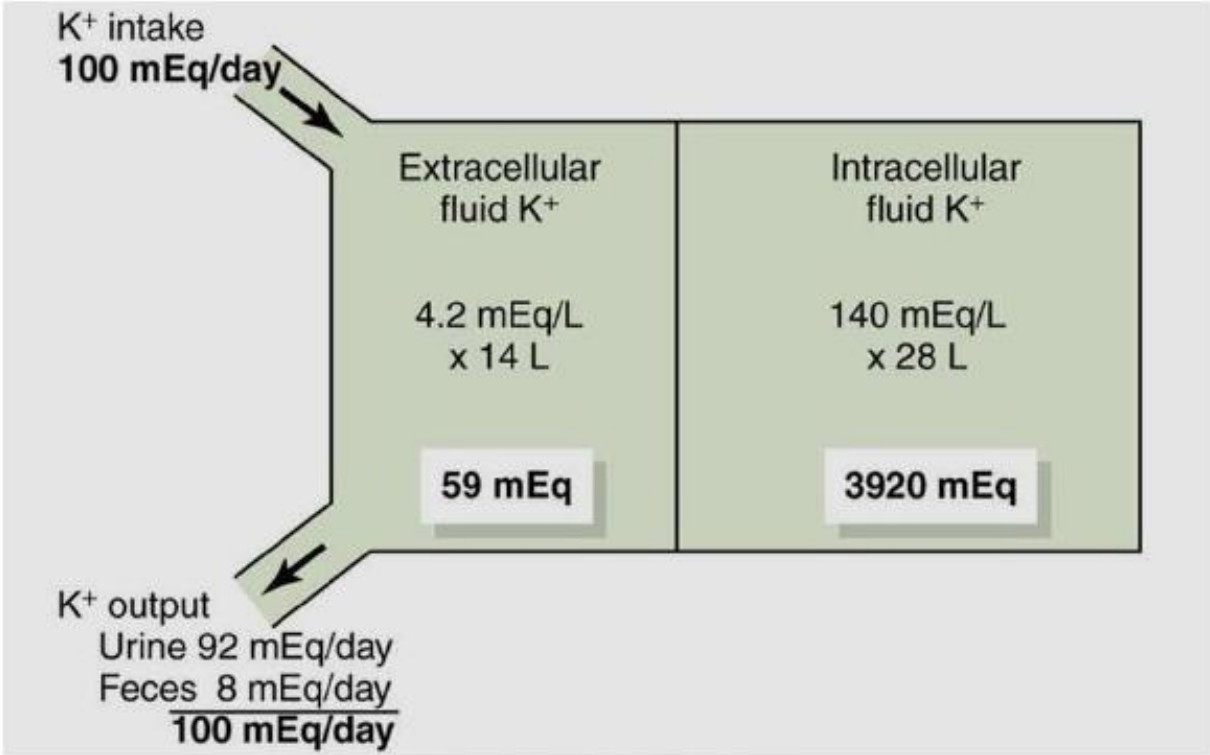
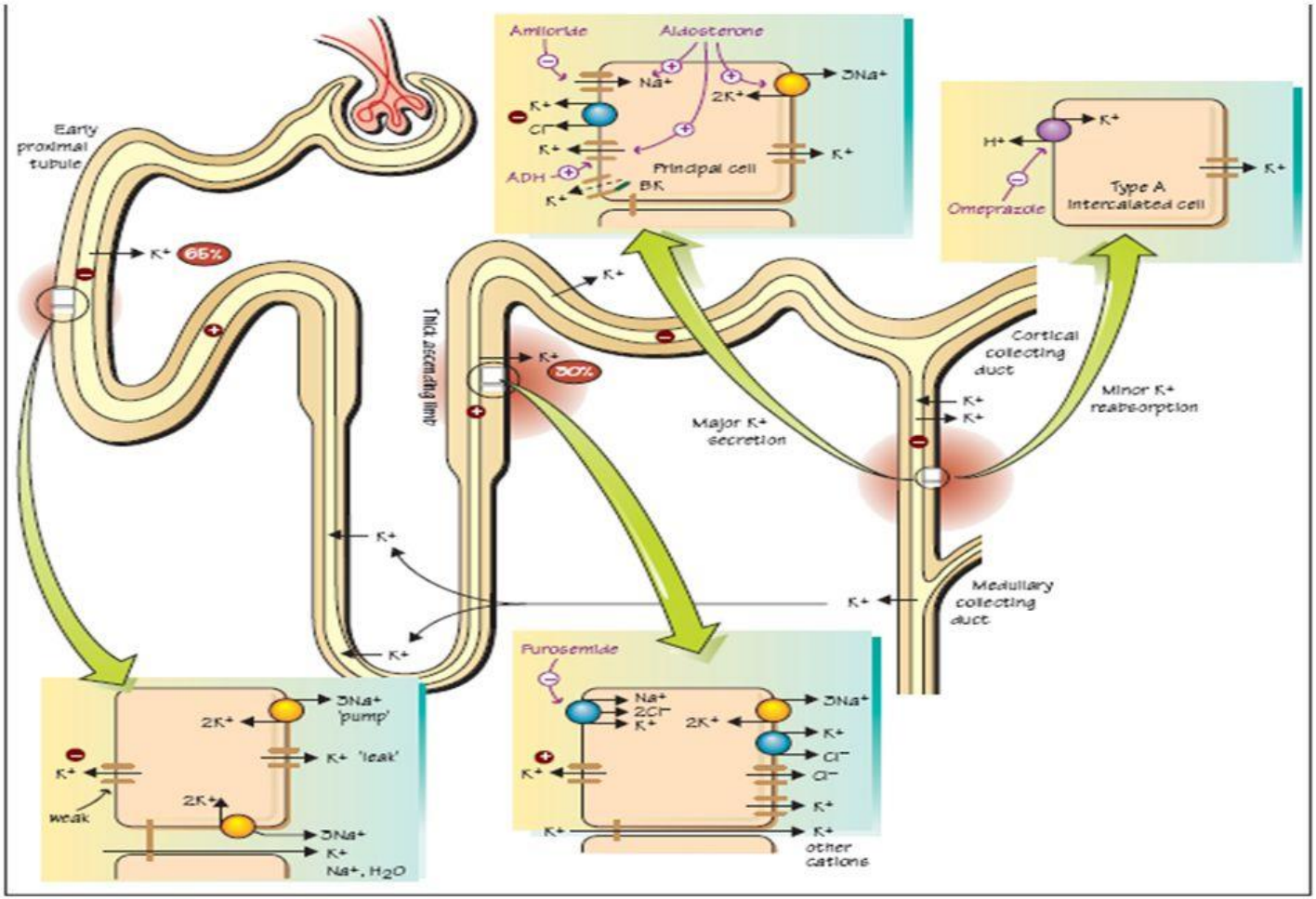
Objectives

1. Review potassium homeostasis and renal handling of potassium
2. Understand importance of managing hyperkalemia in setting of RAAS blockade
3. Explore new potassium binder options and review mechanisms of action
4. Review epidemiology of CKD
5. List new options for delaying progression of CKD
6. Review mechanism of action of SGLT-2 inhibitors

Potassium Homeostasis



Renal Potassium Handling



Epidemiology of Hyperkalemia

- Prevalence in hospitalized pts ranges from 1-10% depending on definition of hyperkalemia
- Prevalence in pts with CKD ranges from 5-50%, increasing as kidney fxn declines
- Hyperkalemia is more common in pts with reduced kidney fxn, multiple medications (especially RAAS inhibitors), older age, diabetes

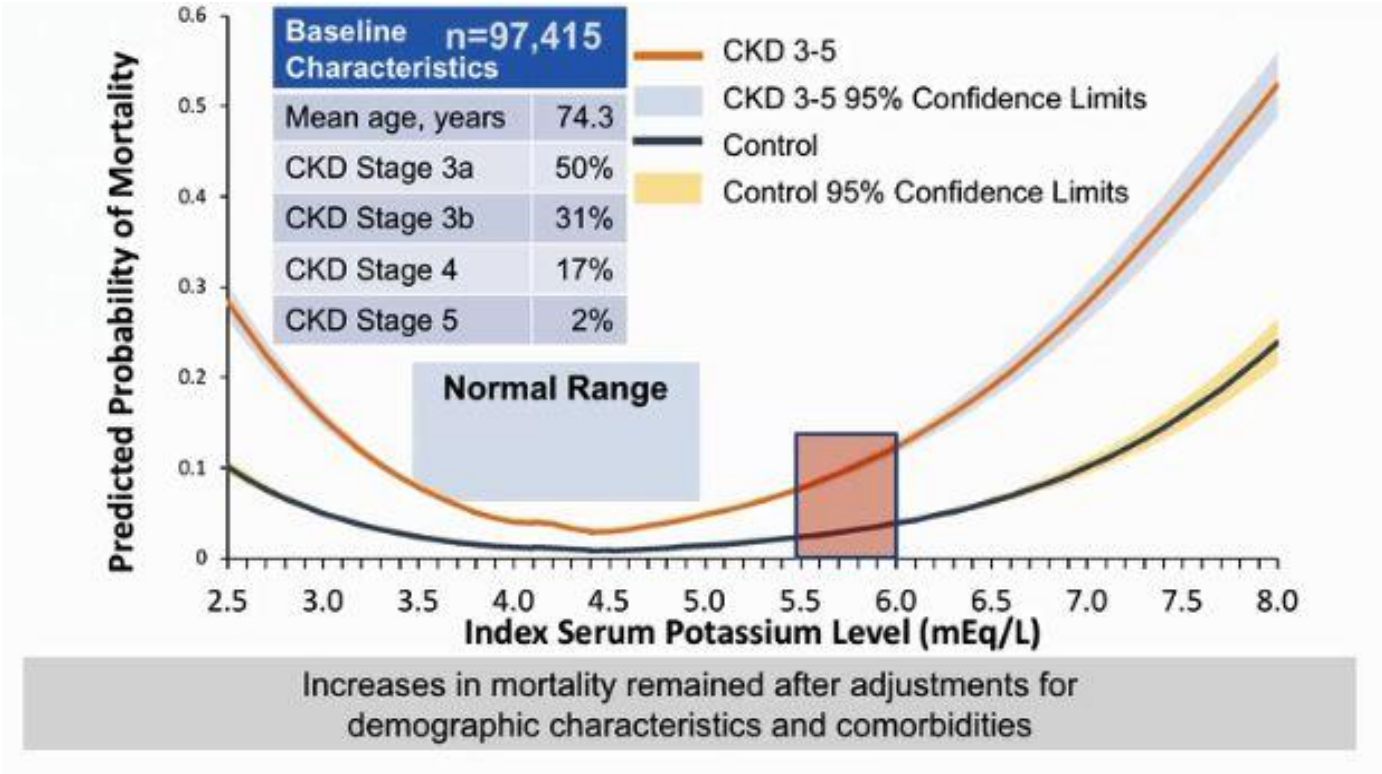
Hyperkalemia ≥5.5 mEq/L in CKD

Patient Population	Patients (n)	Rate (%)
Pre-dialysis CKD[1] • Mean eGFR 14.4 ± 4.6	238	31.5
VA Study[2] • No CKD • Stage 3 • Stage 4 • Stage 5	 174,935 57,798 8351 4724	 8.9 20.7 42.1 56.7
As kidney function declines, the risk of hyperkalemia increases		

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); VA: Veterans Affairs.

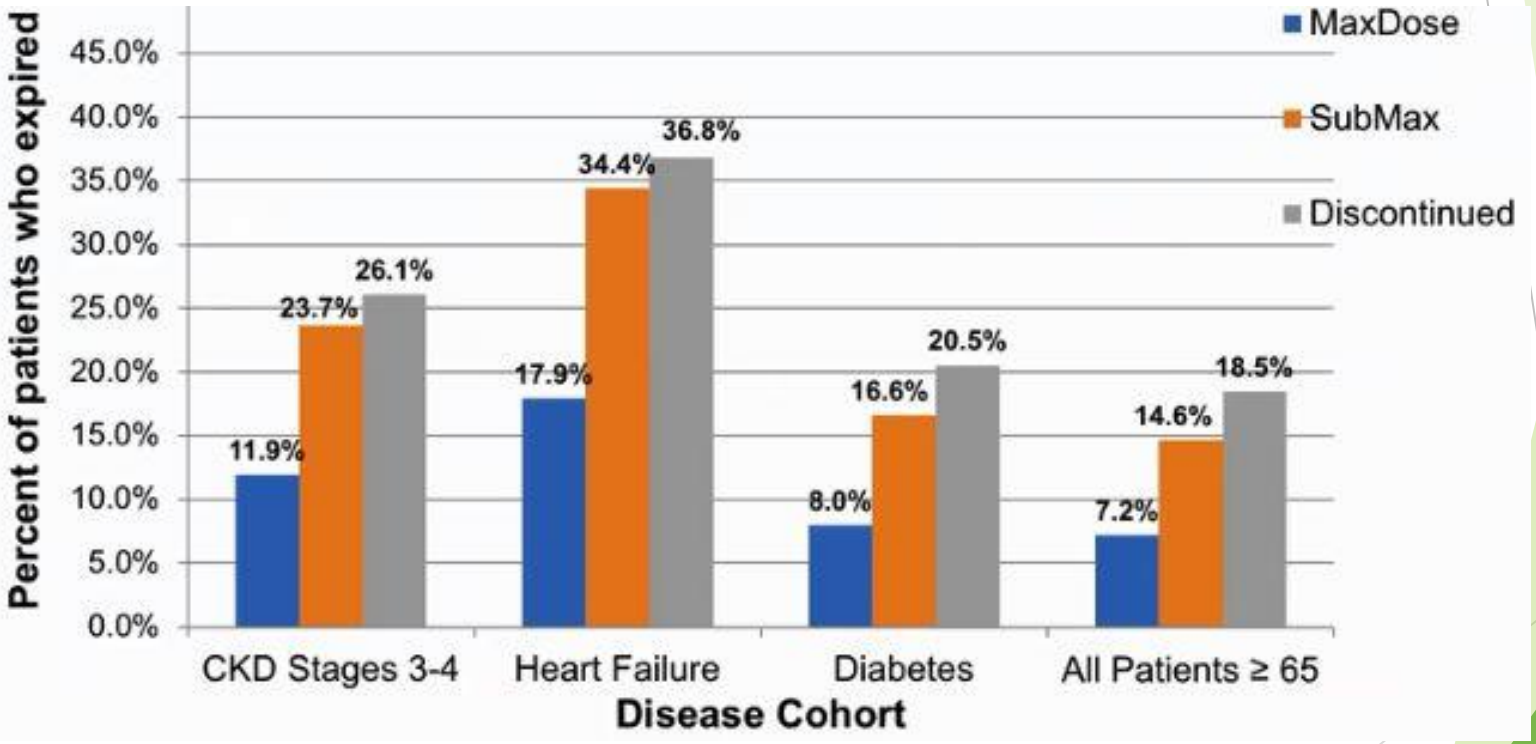
1. Sarafidis PA, et al. *Clin J Am Soc Nephrol*. 2012;7(8):1234-1241. 2. Binhorn LM, et al. *Arch Intern Med*. 2009;169(12):1156-1162.

C-V Mortality in Context of [K^+]



Collins, et al, Am J Nephrol, 2017:46:213-221

Mortality among pts where RAASi ↓ or D/C



Epstein M, et al, Am J Manag Care 2015;21(11 suppl):S212-220

Management of Hyperkalemia

- Review medications ~ eg, NSAIDs, βblockers, TMP-SMX, etc
- Low potassium diet
- Effective diuretic therapy: loop diuretics for CKD (eGFR<30 ml/min) in appropriate dose and frequency
- Sodium bicarbonate tabs ~ 650 mg is ~8 mEq $NaHCO_3$
- Decrease or discontinue RAAS inhibition
- K^+ binding agents

Available enteric potassium binders

- Sodium polystyrene sulfonate (SPS) ~ ion exchange resin binding potassium in exchange for sodium ~ may not be much more effective than laxatives ~ rare but deadly complication of colonic necrosis

- Patiromer (Veltassa) ~ a nonabsorbed spherical organic polymer that binds potassium in exchange for calcium in the colon ~ approved by the FDA in October 2015

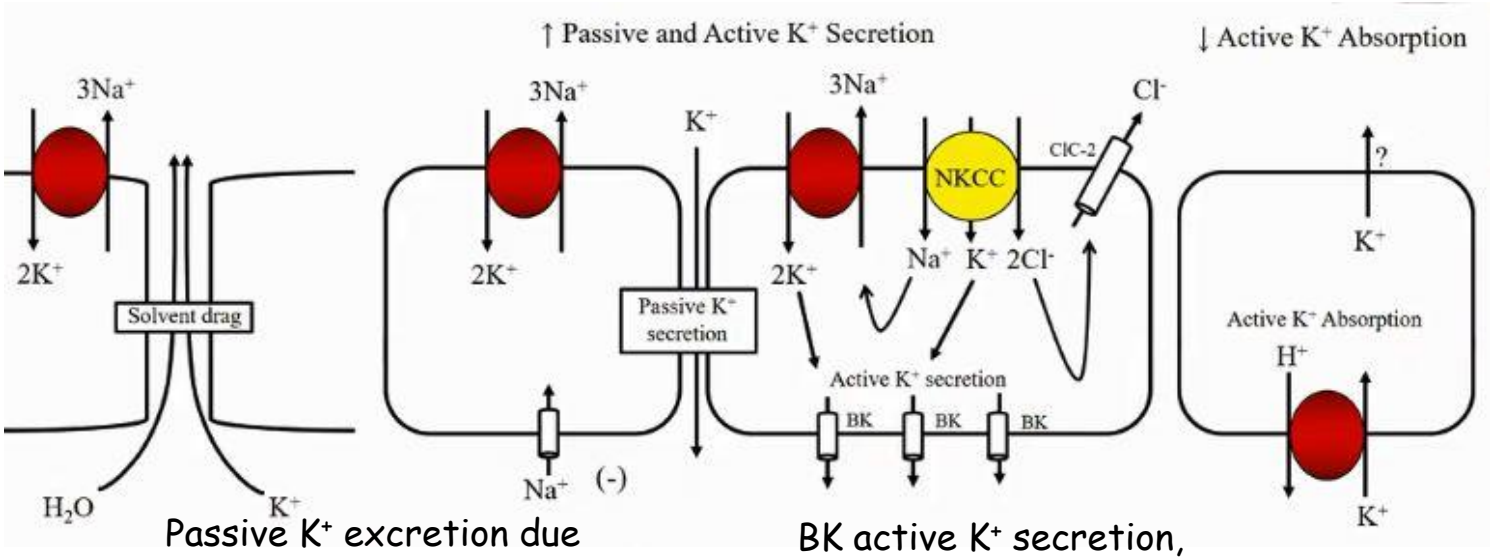
- Sodium zirconium cyclosilicate (Lokelma) ~ inorganic, nonabsorbable crystalline compound which serves as a highly selective cation exchanger binding potassium in exchange for sodium and hydrogen throughout the intestinal transit ~ approved by the FDA May 2018

Patiromer
(Veltassa)

Uniform, spherical patiromer beads

- Orally administered, non-absorbed Ca^{2+}-based K^+ binding polymer
- Indicated for the treatment of hyperkalemia
  - Not an emergency treatment for life-threatening hyperkalemia
- Mechanism of action: exchanges Ca^{2+} for K^+ in the colon
- Drug-drug interactions: take 3 hours apart from other oral medications
- Most common AEs (>2%): constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence
- Avoid use in patients with severe constipation, bowel obstruction, or impaction

Small intestine→ Prox colon→→→→ Distal colon



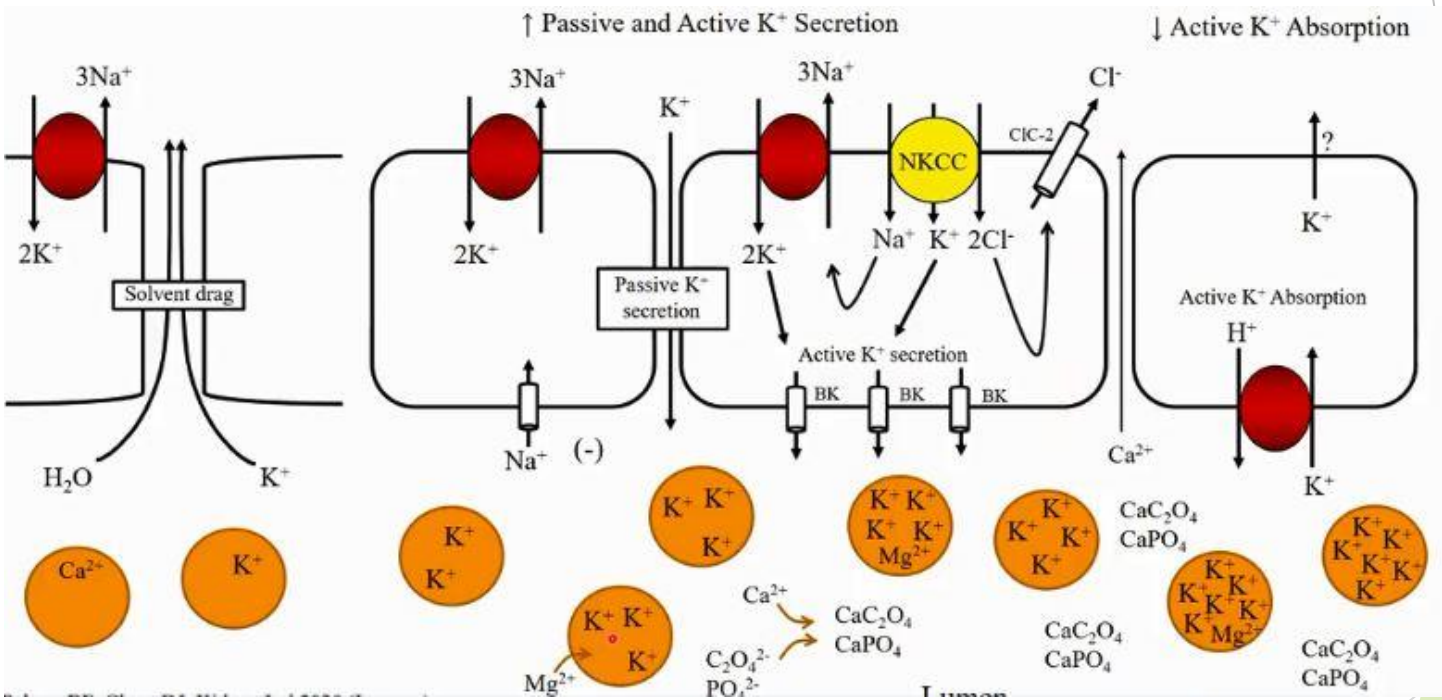
Passive K^+ excretion due to negative charge in lumen caused by active Na^+ reabsorption

BK active K^+ secretion, upregulated in CKD

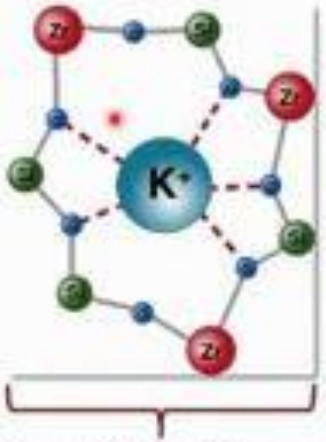
K^+ absorption in distal colon

Lumen

Small intestine→ Prox colon→→→→ Distal colon



Sodium Zirconium Cyclosilicate (Lokelma)



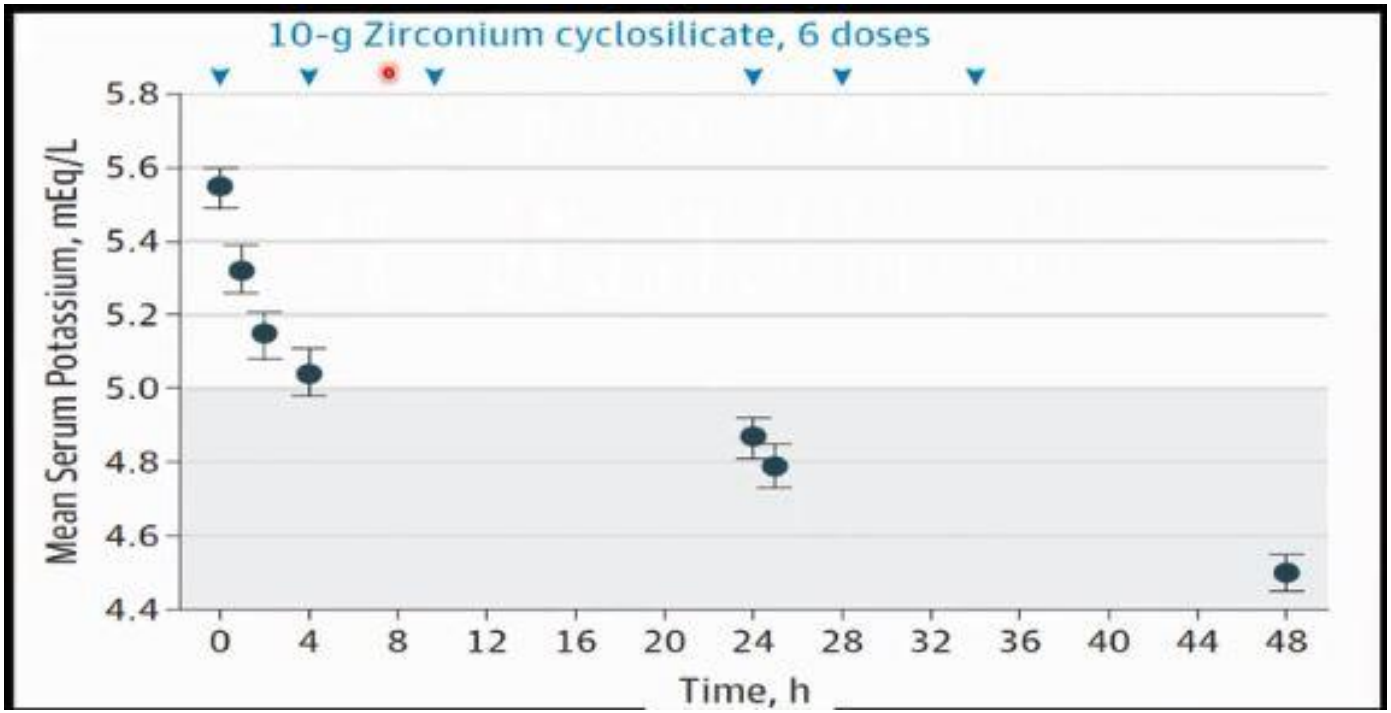
Average Width of Micropore Opening 3Å

- Indicated for the treatment of hyperkalemia in adults
- Should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action
- 2-hour dosing window is recommended when coadministered with medications with pH-dependent bioavailability
- Most common AE: mild-moderate edema
- Avoid use in patients with severe constipation, bowel instruction, or impaction

Sodium Zirconium Cyclosilicate Properties

- Microporous zirconium silicate compound
- Insoluble, highly stable
- 9.3x more K^+ binding capacity than sodium polystyrene sulfonate (Kayexalate®)
- >125x more selective for K^+ than sodium polystyrene sulfonate

[K^+] during open label Phase (48 hrs)



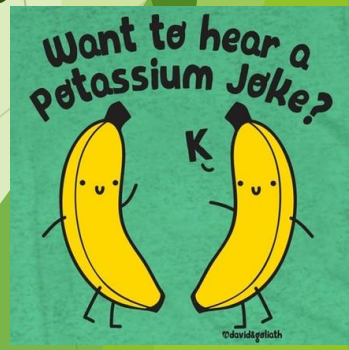
Comparison of Potassium Binders

	SPS	Patiromer	Sodium Zirconium Cyclosilicate
Approval date	1958	US: 2015; EU: 2017	US: 2018; EU: 2018
Mechanism	Nonspecific sodium cation-exchange resin; may also bind calcium and magnesium	Nonspecific cation binding in exchange for calcium	Highly selective; preferentially captures K^+ ions
Onset	1-2 hours (up to days)	4-7 hours	1 hour
Starting dose	15 g 3-4 times daily[5]	8.4 g once daily	10 g 3 times daily (starting) 5-10 g once daily (maintenance)
Location	Colon	Predominantly distal colon	Entire gastrointestinal tract
Drug interactions	Interaction with antacids, laxatives, sorbitol, digitalis, lithium, thyroxine	Administer at least 3 hours before or after other oral medications	2-hour dosing window is recommended when coadministered with medications with pH-dependent bioavailability

Palmer BF, Clegg DJ. Am J Kidney Ds 2019;74:682-695

Summary

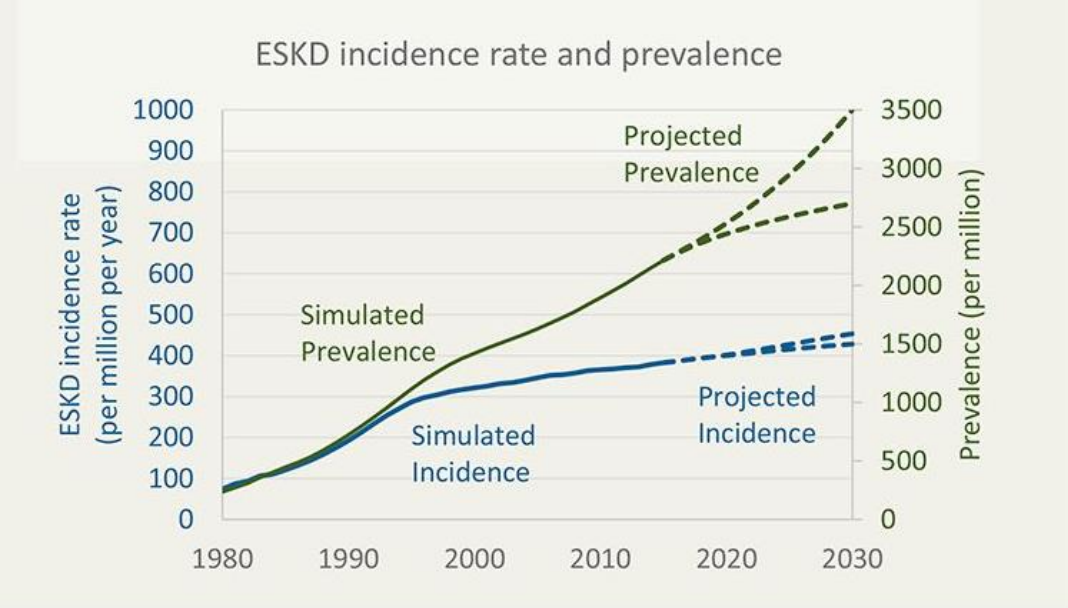
- Hyperkalemia is common in clinical practice and in real world CKD pts
- Elevated [K+] is associated with increased mortality in CKD pts (both dialysis and non-dialysis)
- Review and adjustment of medications, dietary restriction, effective use of diuretics and correction of metabolic acidosis are all reasonably effective strategies to manage hyperkalemia but have their limitations
- Down titration or discontinuation of RAAS blockade is frequently due to concern about hyperkalemia
- SPS is poorly tolerated and therefore less likely for patients to adhere to therapy
- Patiromer and sodium zirconium cyclosilicate are effective adjunctive therapies to correct hyperkalemia and allow ongoing use of RAAS blockers as well as liberalization of dietary restrictions



CKD ~
Why is it Important?

- 30 Million Americans affected
- 25 More Million Americans are at Risk
- Affects Quality of Life and Life Span

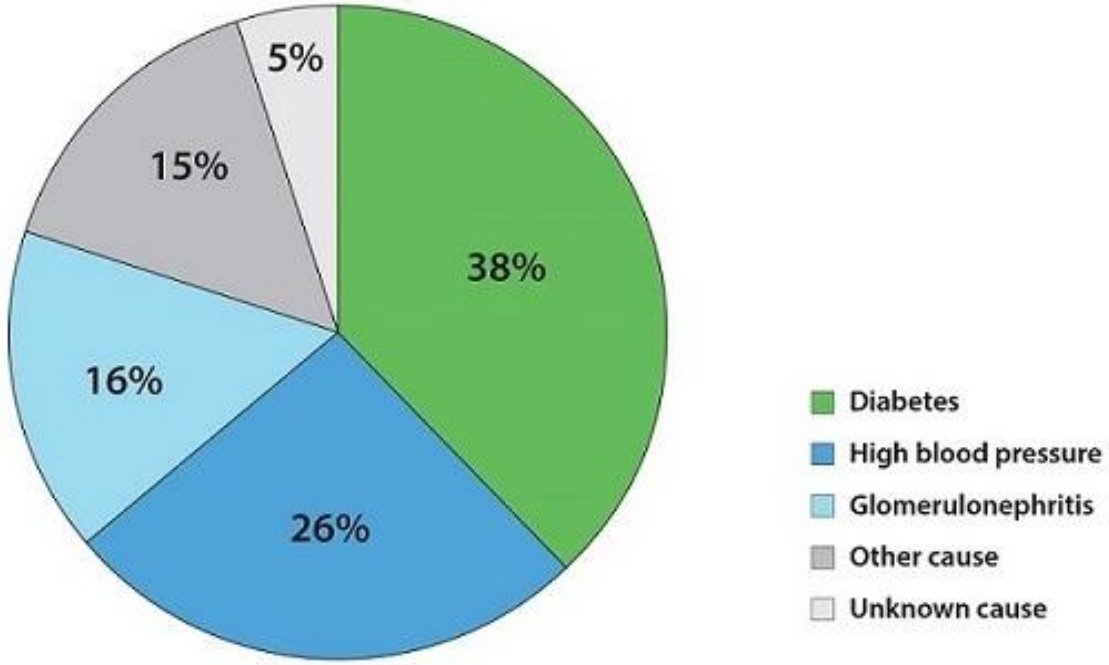
Incidence and Prevalence Projection



CONCLUSION The ESKD incidence rate is projected to rise between 11-18% between 2015 and 2030, and the number of prevalent patients is projected to rise from 690,000 to 971,000-1,259,000 patients over the same period.

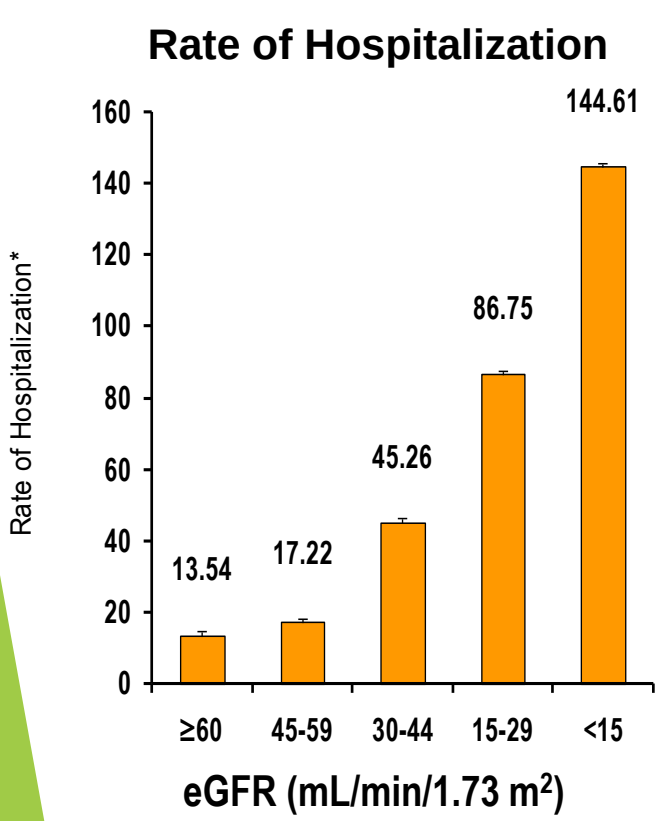
Keith P. McCullough et al. JASN 2019;30:127-135

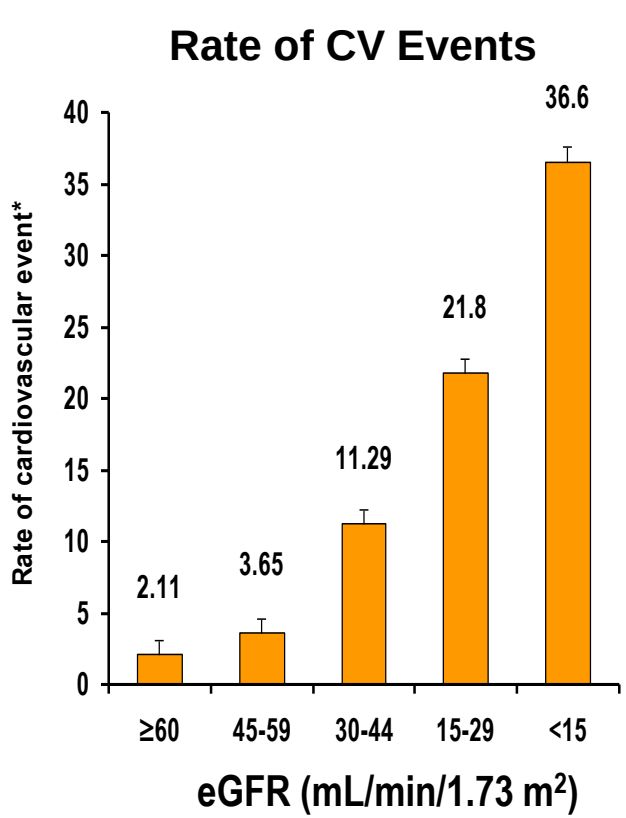
Causes of ESRD in United States

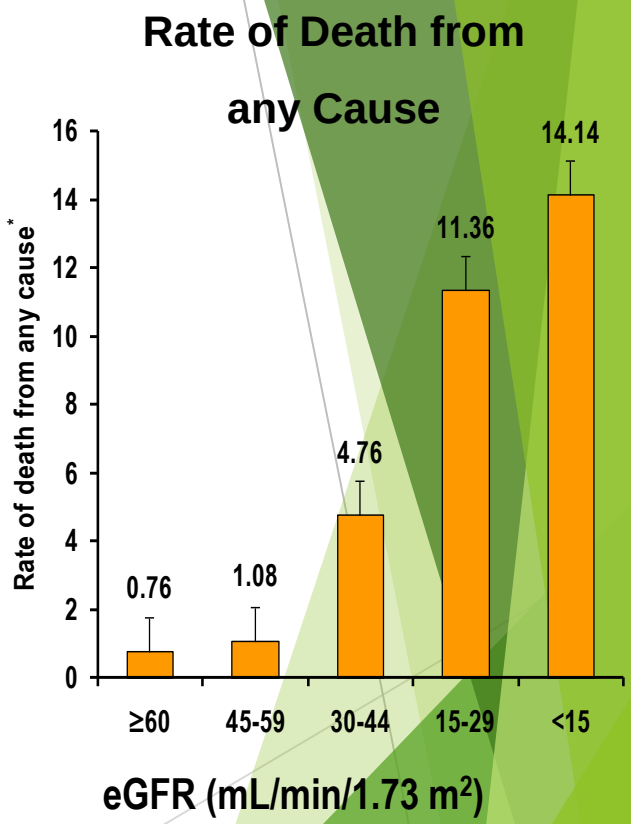


USRDS 2016 report

Consequences of CKD/ESRD







eGFR=estimated glomerular filtration rate

***Age-standardized rates per 100 person-years**
N=1,120,295 ambulatory adults

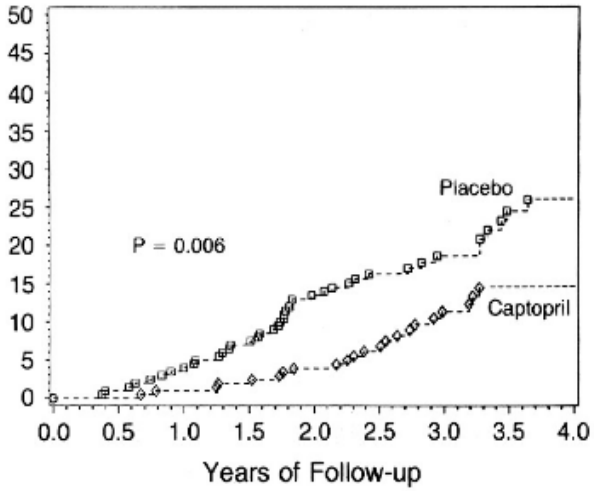
Go AS et al. *N Engl J Med.* 2004;351:1296-1305

Delaying the Progression of CKD

1) good control of primary etiologic process
2) good hypertension control
3) avoidance of nephrotoxins
4) "blunting" of the hyperfiltration compensatory mechanisms
    - protein restriction
    - RAAS blockade (ACE, ARB, DRI)

RAAS Blockade: The Only Proven Treatment for Renoprotection in DM

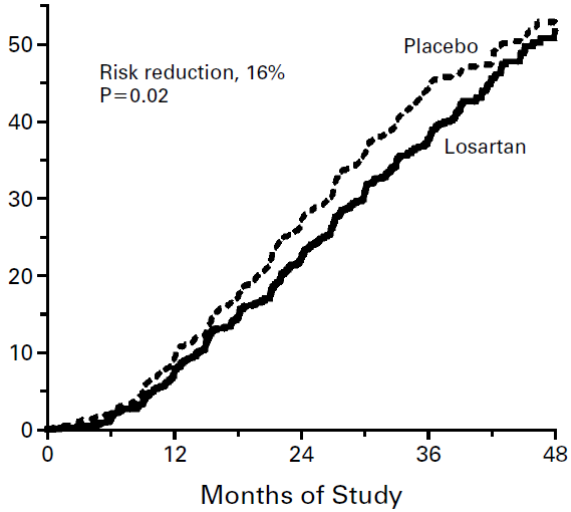
Doubling of serum creatinine, dialysis or transplant



Captopril vs placebo

Lewis EJ, et al. N Eng J Med 1993;330(2):152

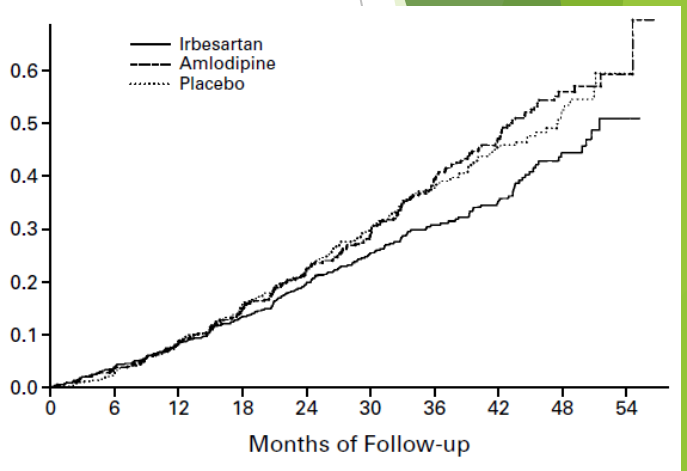
Doubling of serum creatinine, ESRD or death



RENAAL

Brenner B, et al. *N EnglJ Med*. 2001;345(12):861-869.

Doubling of serum creatinine, ESRD or death



IDNT

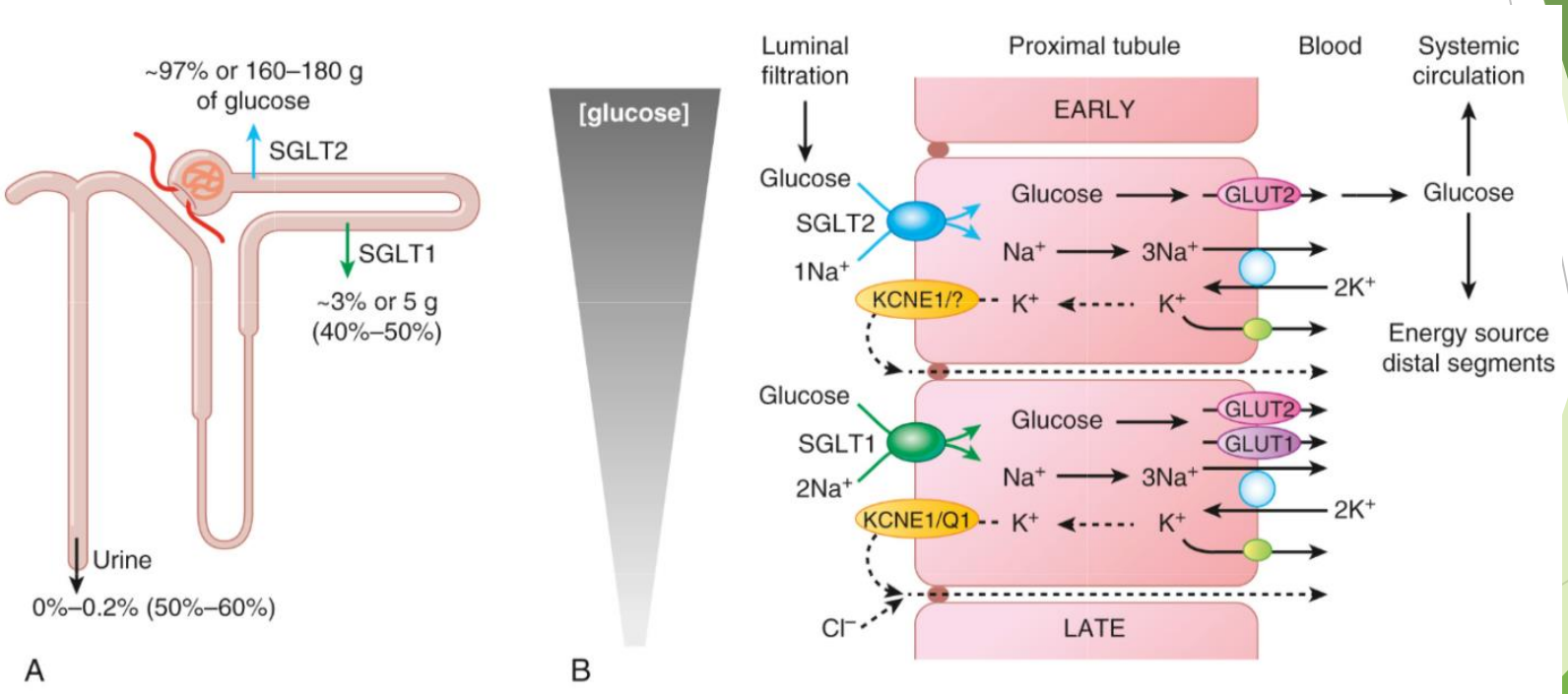
Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Until now…..
SGLT2 Inhibitors in CV Outcome Trials

	Trial	Drug	Study population	Outcome
1	**EMPAREG – 2015 (CV M&M)**	Empagliflozin	Established CV (99%) disease, T2DM	HR 0.86; 95% CI, 0.74 to 0.99; P=0.04
2	**CANVAS, CANVAS R 2017 (renal/CV M&M)**	Canagliflozin	High CV disease (65%), T2DM	HR 0.86; 95% CI, 0.75 to 0.97; P <0.001
3	**DECLARE TIMI 58 -2018 (renal/CV M&M)**	Dapagliflozin	40% CV disease, 60% with CV risk	HR 0.83; 95% CI, 0.73 – 0.95; P=0.005

1. N Engl J Med 2015; 373:2117-2128
2. N Engl J Med 2017; 377:644-657
3. N Engl J Med 2019; 380:347-357

Glucose Homeostasis



Brenner and Rector's The Kidney.
2019: 219

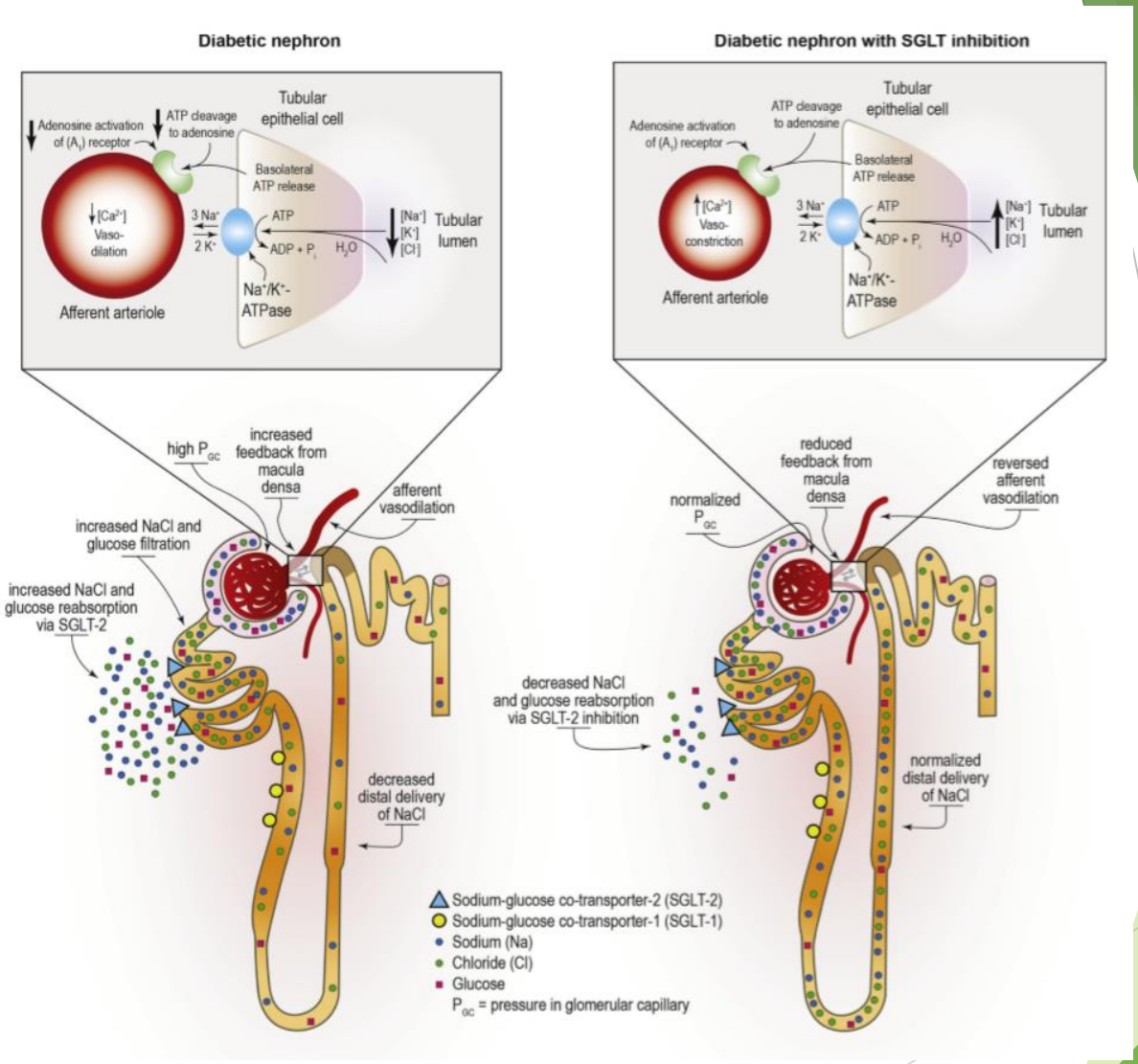
SGLT2 Inhibitors

Canagliflozin (Invokana)

Dapagliflozin (Farxiga)

Empagliflozin (Jardiance)

Ertugliflozin (Steglatro)



Radica Z, et al. AJKD 2018; 72 (2): 267

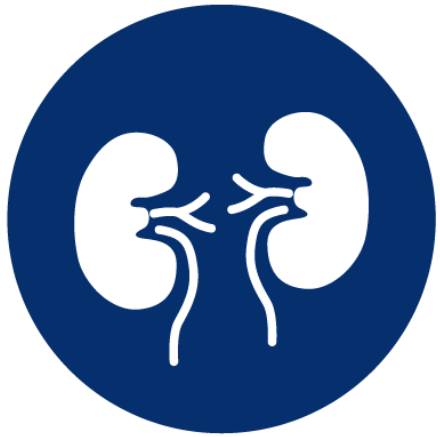
Renal Effects of SGLT2 Inhibition

↓ Intraglomerular pressure

↓ Glucose

↓ Systolic and diastolic blood pressure

↓ Volume



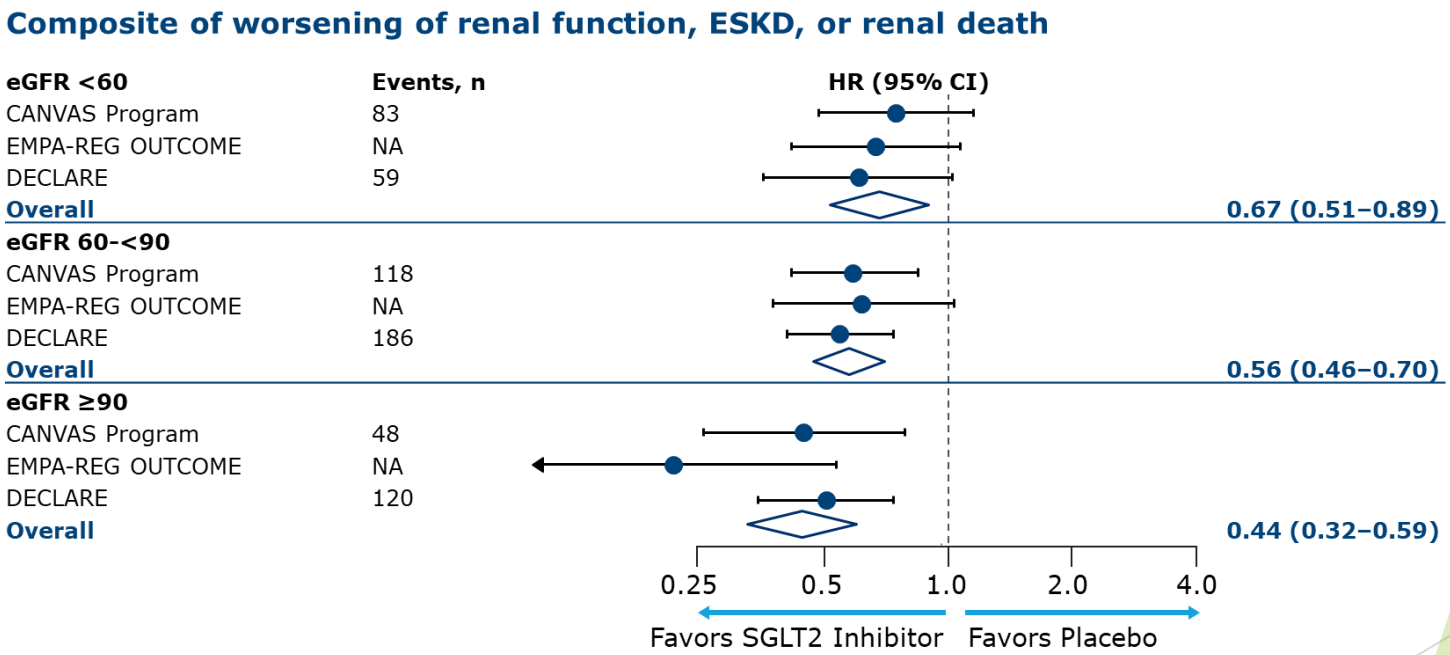
↓ Albuminuria

↓ Oxidative stress

↑ Weight loss

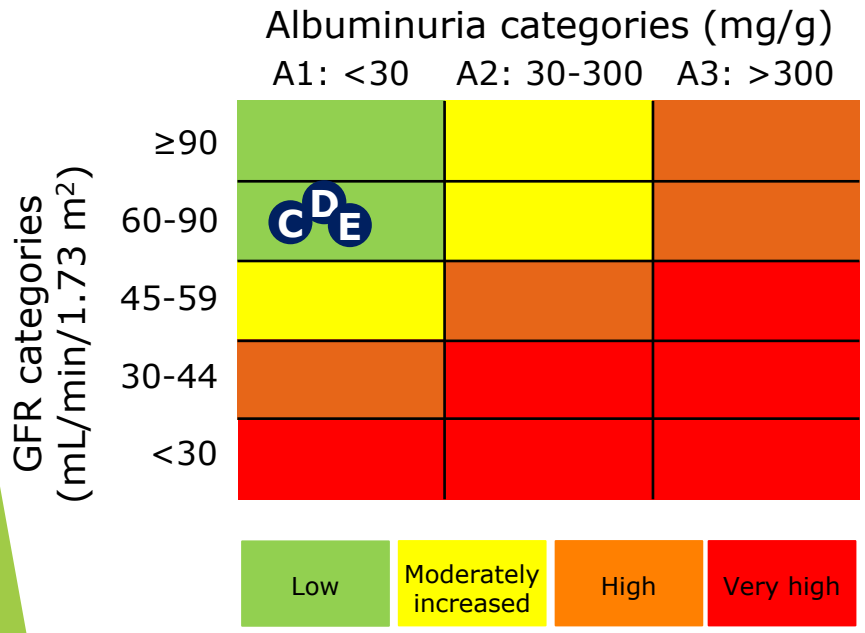
↓ Inflammation/fibrosis

SGLT 2 Inhibitor Trials: Meta-analysis



Zelniker TA, et al. Lancet. 2019;393(10166):31-39

Renal Population in SGLT 2 Trials



	Mean eGFR (mL/min/1.73 m^2)	Median U A:Cr (mg/g)
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG OUTCOME	74	18

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11

*Total of 29 sustained RRT events reported across trials

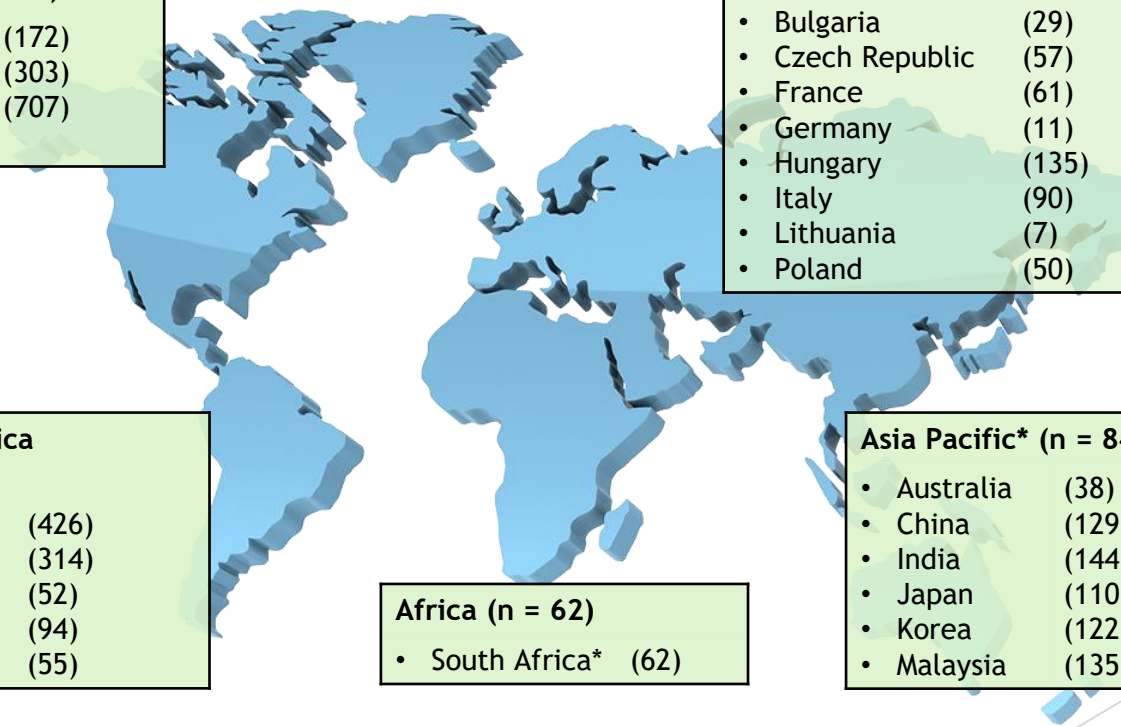
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Randomized double-blind placebo controlled study
34 Countries, 690 Sites, 4401 Participants



North America (n = 1182)

- Canada (172)
- Mexico (303)
- United States (707)

Europe (n = 1368)

- Bulgaria (29)
- Czech Republic (57)
- France (61)
- Germany (11)
- Hungary (135)
- Italy (90)
- Lithuania (7)
- Poland (50)
- Romania (59)
- Serbia (40)
- Slovakia (66)
- Spain (141)
- Russia (133)
- Ukraine (371)
- United Kingdom (118)

Central/South America (n = 941)

- Argentina (426)
- Brazil (314)
- Chile (52)
- Colombia (94)
- Guatemala (55)

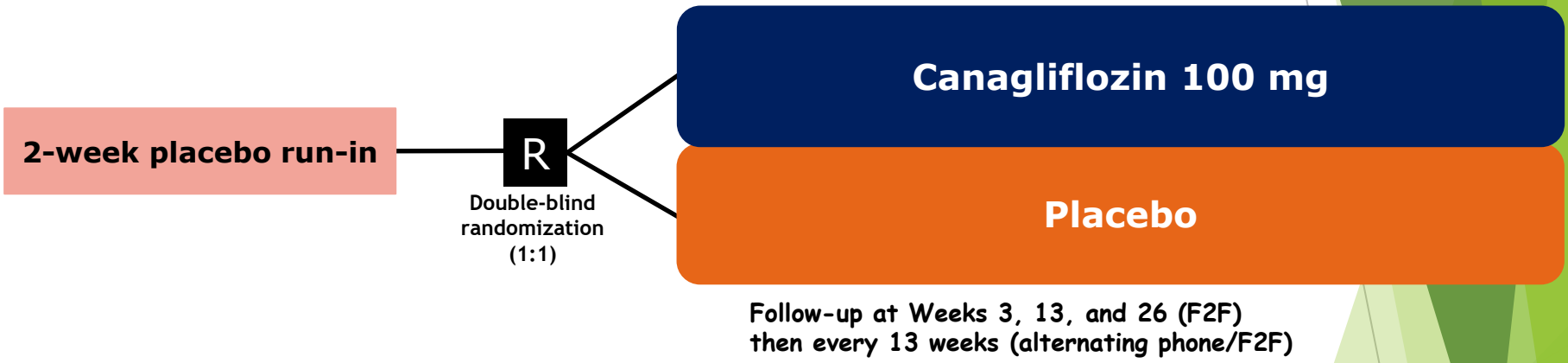
Africa (n = 62)

- South Africa* (62)

Asia Pacific* (n = 848)

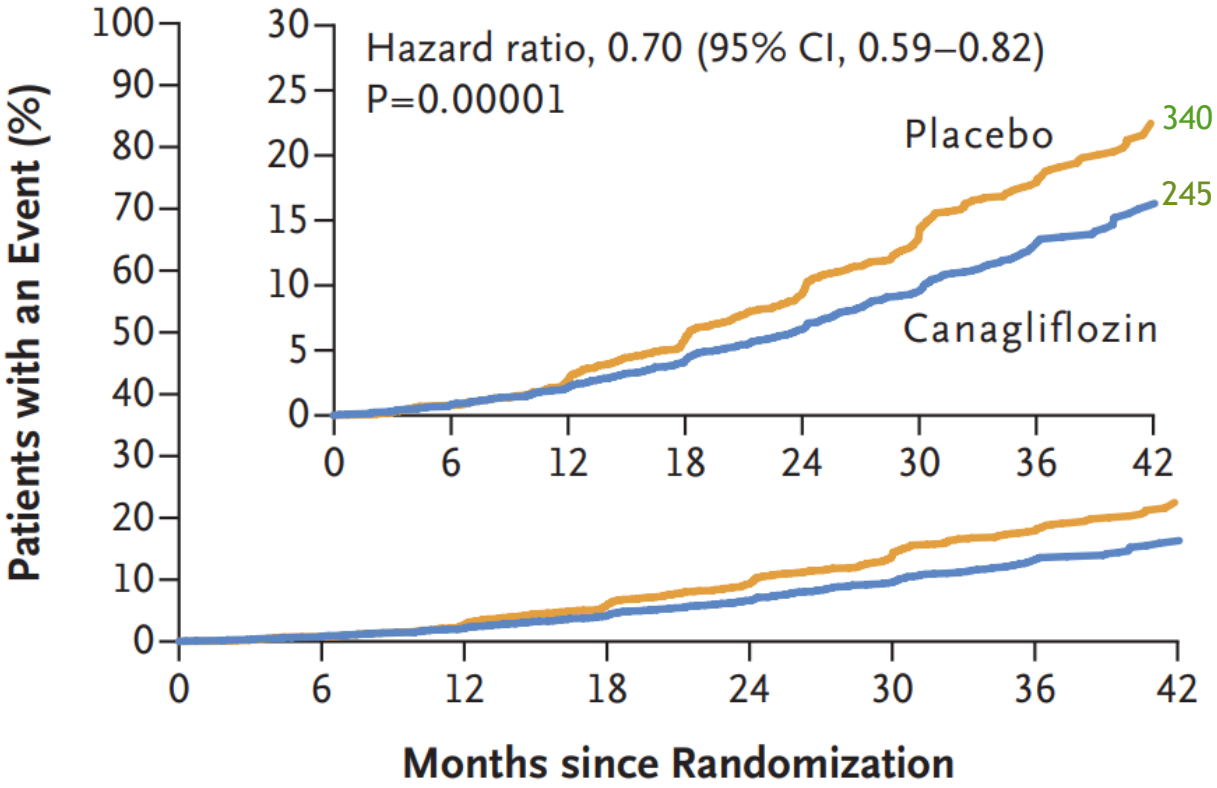
- Australia (38)
- China (129)
- India (144)
- Japan (110)
- Korea (122)
- Malaysia (135)
- New Zealand (61)
- Philippines (71)
- Taiwan (37)
- United Arab Emirates (1)

Study Design

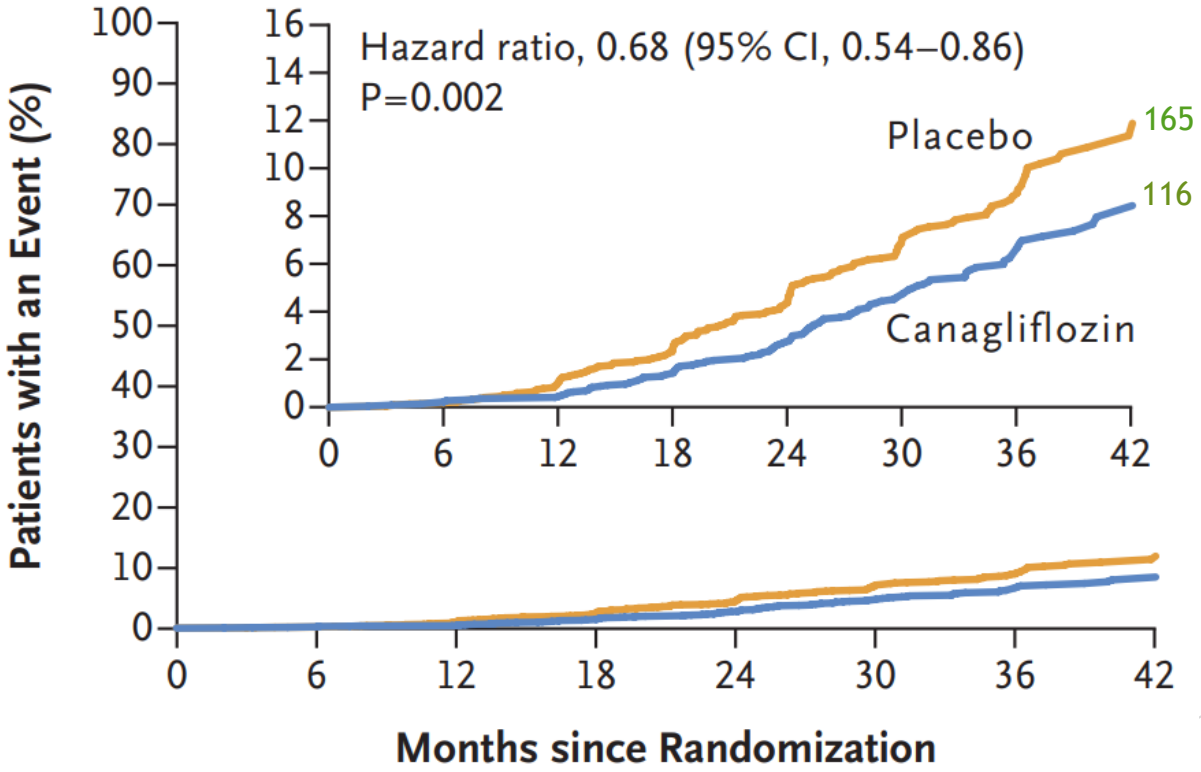


*Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

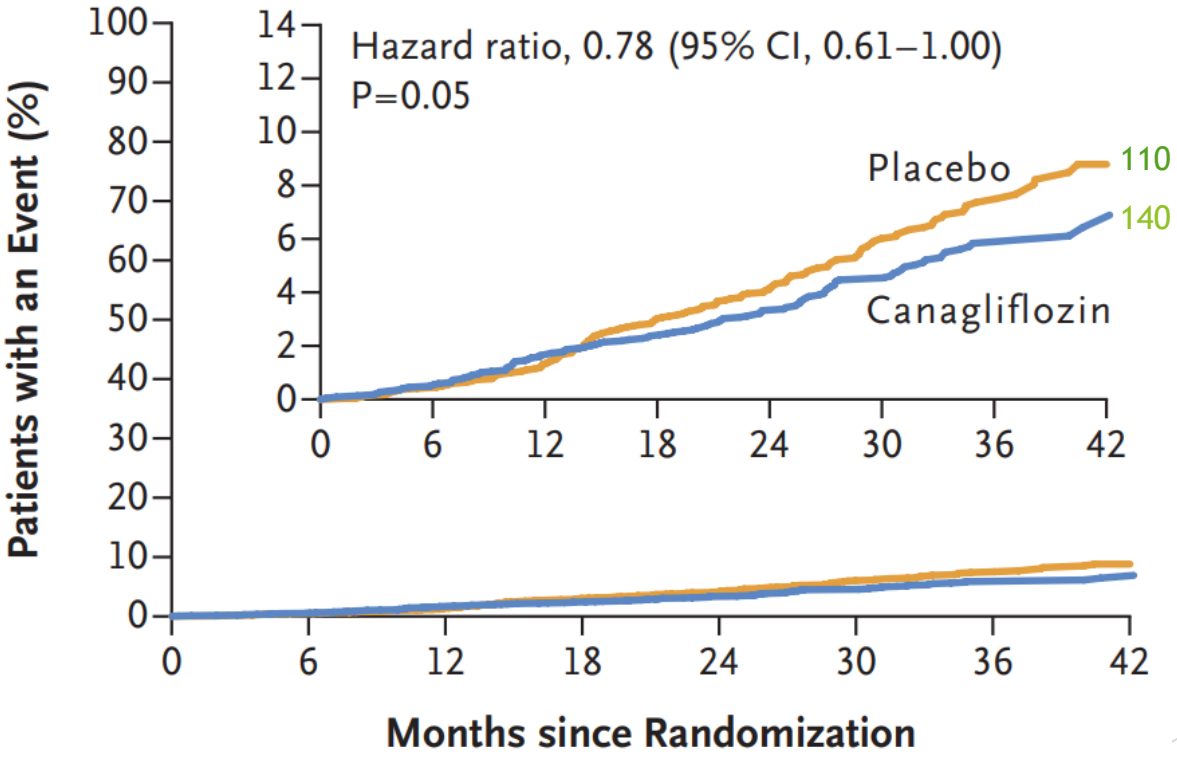
Primary Outcome: ESRD, doubling of creatinine, renal or CV death



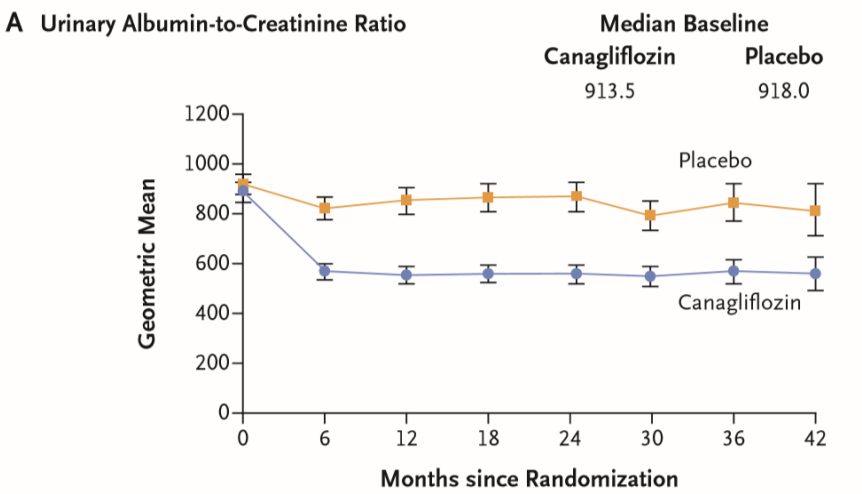
End Stage Renal Disease

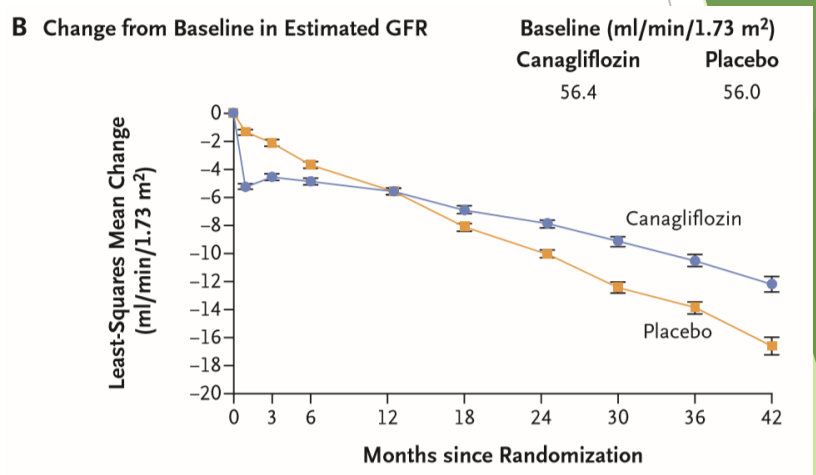


Death From Cardiovascular Cause



Effects on Intermediate Outcomes





Secondary Outcomes

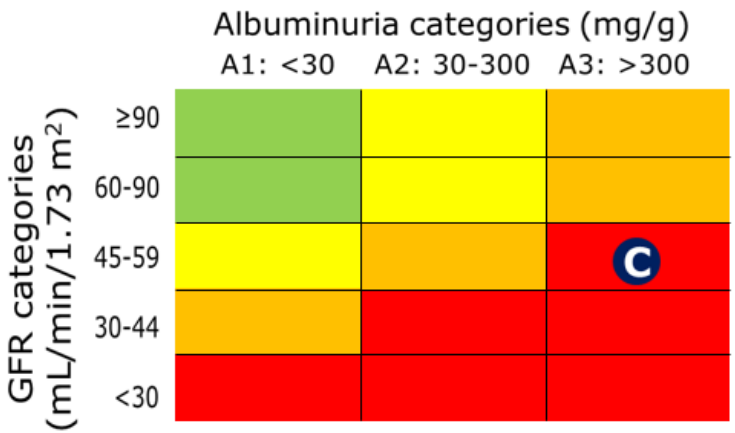
Outcomes	Hazard ratio (95% CI)	*P* value
1. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001
2. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01
3. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001
4. ESRD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001
5. CV death	0.78 (0.61–1.00)	0.0502
6. All-cause mortality	0.83 (0.68–1.02)	-
7. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	-

Analysis, Critique, Limitations

- Overall well designed, well conducted trial
- High risk renal population
- The trial was stopped early
- The initiation of the SGLT 2 inhibitor

was associated with initial decrease in eGFR

- All patients were on ACE
- NNT: 22 for primary composite outcome
- NNT: 28 for composite of renal outcome



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

September 24, 2020

Randomized, double blind, placebo controlled
21 Countries, 386 Sites, 4304 Participants

Primary Outcome

- Decline in at least 50% of eGFR Doubling of serum creatinine
- Onset of ESKD
- Death from renal or cardiovascular cause

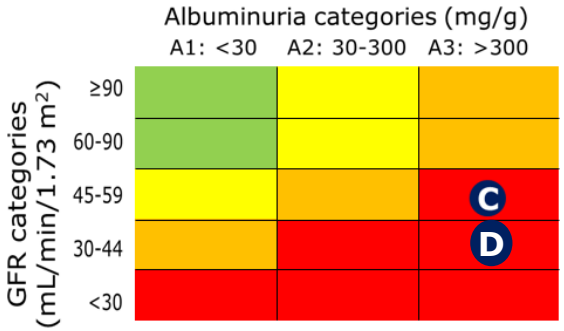
Secondary Outcomes

- Composite kidney outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes
- Composite cardiovascular outcome defined as hospitalization for heart failure or death from cardiovascular causes
- Death from any cause

Major Inclusion Criteria

1. Female or male aged ≥18 years > 30 years
2. eGFR ≥25 and ≤75 mL/min/1.73m2 > 30 and < 90 mL/min2
3. UACR ≥200 and ≤5000 mg/g > 300 and < 5000 mg/g
4. Stable maximum tolerated dose of ACE/ARB for at least 4 weeks but those unable to take ACE/ARB were included All patients were taking ACE/ARB
5. With or without diabetes With diabetes

Baseline Characteristics

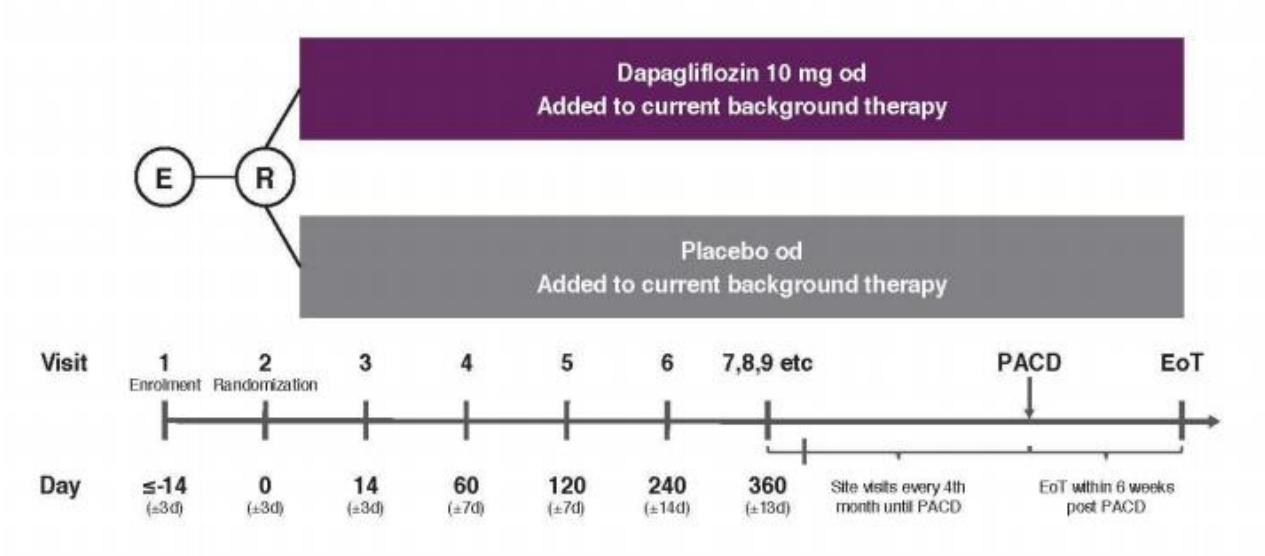


Exclusions

1. DM type 1, PKD, Lupus Nephritis, ANCA associated vasculitis
2. History of organ transplant or receiving immunosuppressive therapy for primary or secondary renal disease with 6 months prior to enrollment
3. NYHA class lV
4. MI, unstable angina, stroke or TIA within 12 weeks prior to enrolment
5. CABG or PCI within 12 weeks before enrollment
6. Active malignancy requiring treatment
7. Hepatic impairment

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Body-mass index‡	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure — mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean — ml/min/1.73 m²	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m²	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m²	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m²	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m²	293 (13.6)	331 (15.4)
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

Study Design

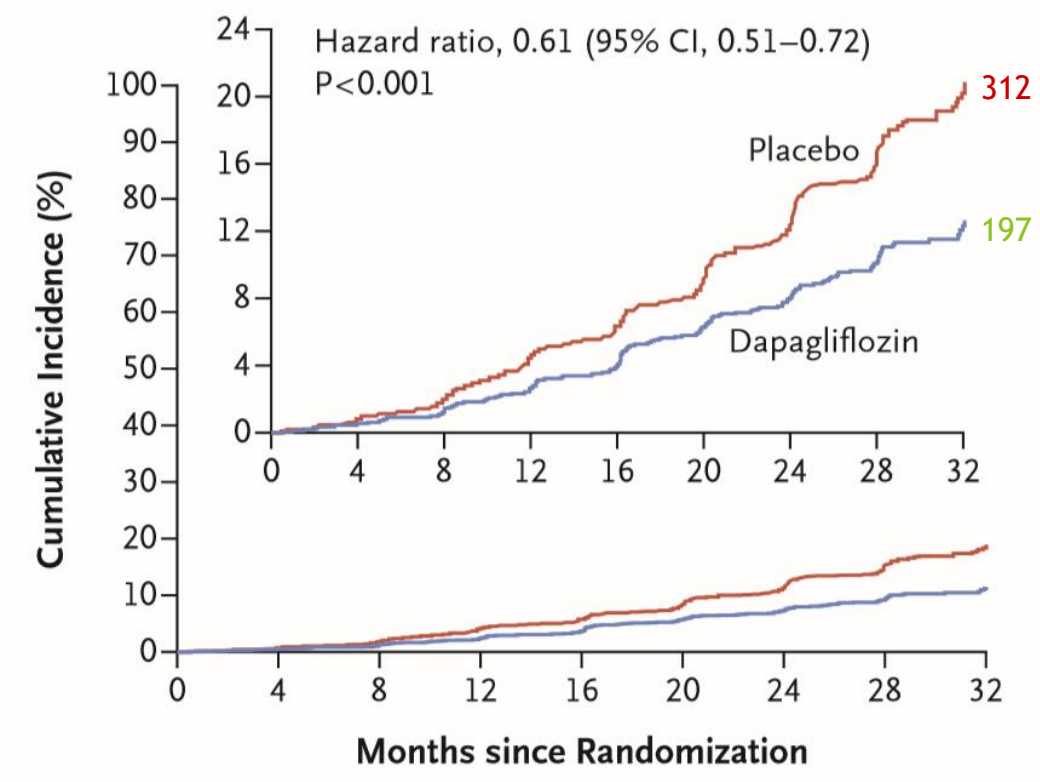


Trial Stopped Early !!

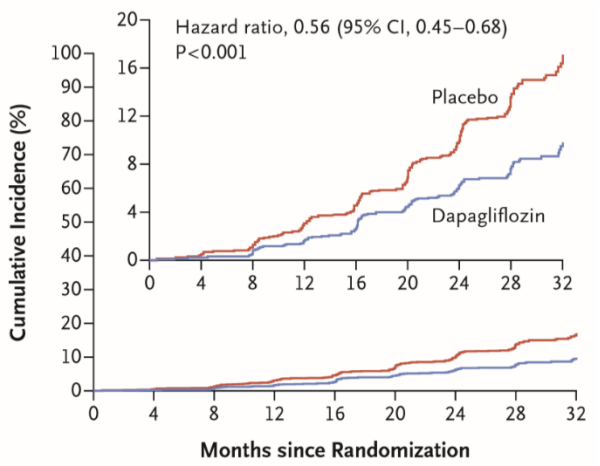
After 408 primary outcome events, the Independent Data Monitoring Committee detected clear efficacy and recommended that the trial be stopped

At the conclusion of the trial the median follow up was 2.4 years

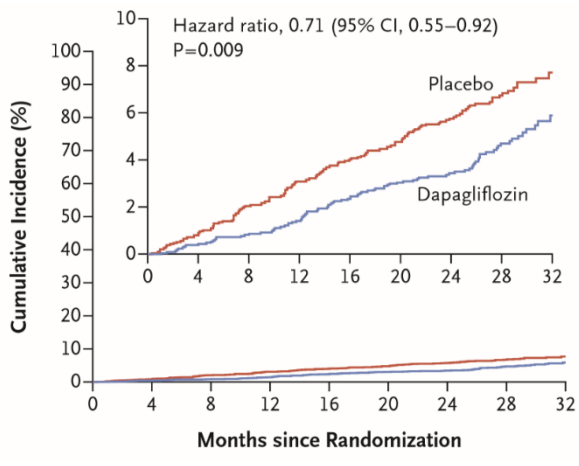
Primary Composite Outcome



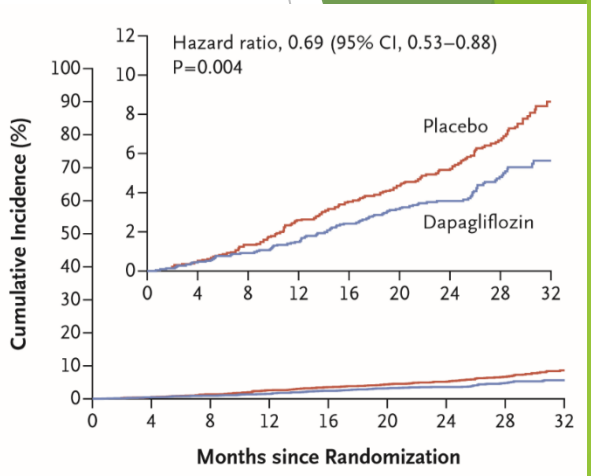
Secondary Outcomes



Renal Specific Composite Outcome



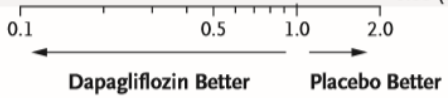
Composite of death from CV causes or Hospitalization for Heart Failure



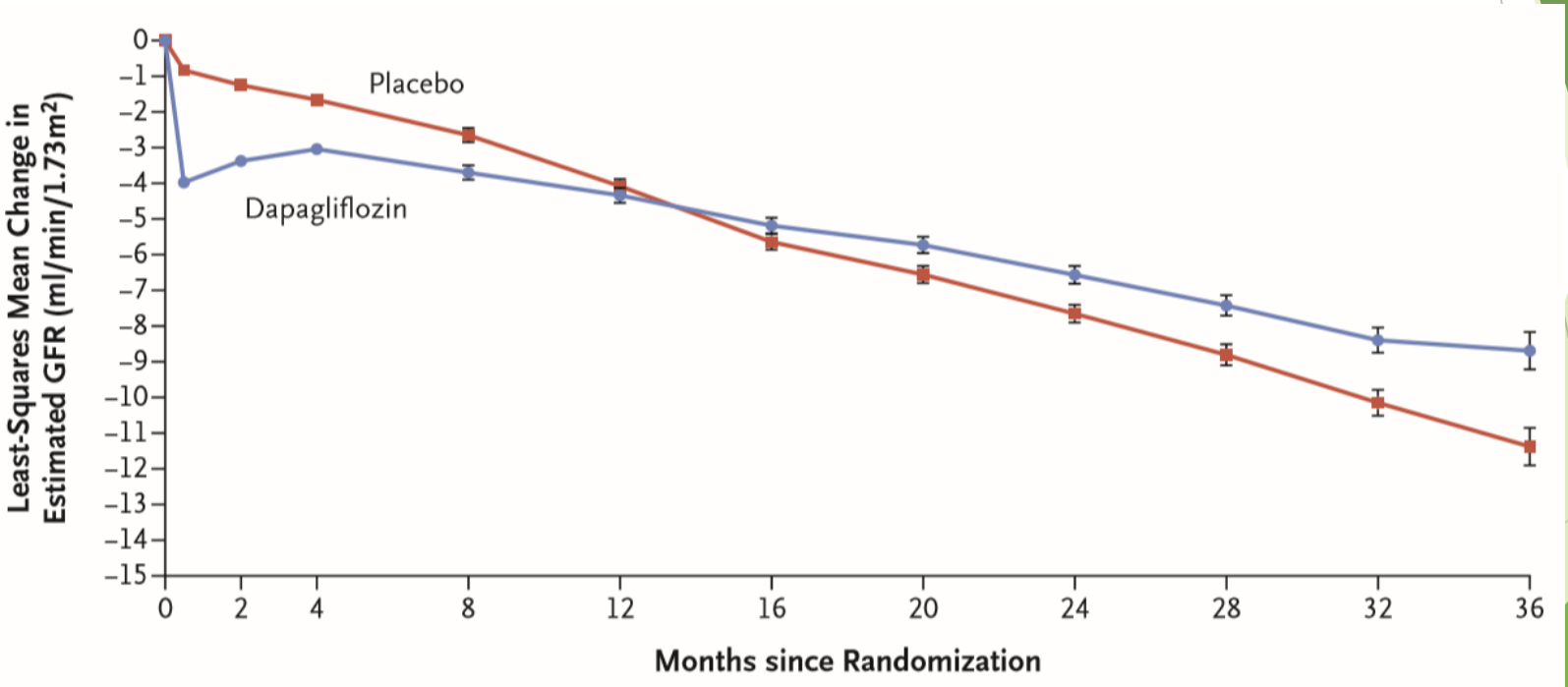
Death from any cause

Subgroup Analysis

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



Changes from Baseline eGFR



What did she say?

- SGLT2 inhibitors are multipurpose drugs

  Improve HbA1c
  Decrease Blood pressure
  Promote Weight loss
  Protect kidneys

- SGLT2 inhibitors improve cardiovascular outcomes

  CANVAS, CANVAS R
  EMPA REG
  DAPA HF
  DECLARE TIMI 58

- SGLT2 inhibitors improve renal outcomes

  CREDENCE
  DAPA CKD

- SGLT2 inhibitors have acceptable safety profile

Questions ?

A very special 'Thanks' to Dr. Abdullah Shahid for sharing his slides ~

ECU BRODY SCHOOL OF MEDICINE

Opportunities to Prevent CKD and Lower the Risk for Kidney Failure

- *Control* risk factors for CKD that can be modified.
  - High blood pressure.
  - High blood sugar levels.
- *Test* for kidney disease among people who are at high risk for developing CKD.
  - Testing people with diabetes or with high blood pressure has been shown to be a cost-effective way of identifying people with CKD.
- *Manage* CKD.
  - Make lifestyle changes (e.g., healthy eating) to prevent more kidney damage.
  - Use medications (e.g., drugs to lower blood pressure) to slow CKD progression.
  - Avoid conditions or exposures that can harm the kidneys or cause a sudden drop in kidney function (called acute kidney injury) and may quicken CKD progression.
    - Kidney infections.
    - Medications.
      - Over-the-counter pain medicines like ibuprofen and naproxen.
      - Certain antibiotics.
    - Herbal supplements.
    - Dyes that are used to make the blood vessels or organs visible on X-rays or other imaging tests.
- *Learn* about kidney disease from your health care team to make sure your treatment is optimal and also to help improve outcomes after beginning ESRD treatment.