Spokane County Medical Society

Update in Chronic Kidney Disease:
'An Apple Bark-a-Day, Keeps the CKD/CAD Away'

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Disclosures

I have no disclosures.

Goals

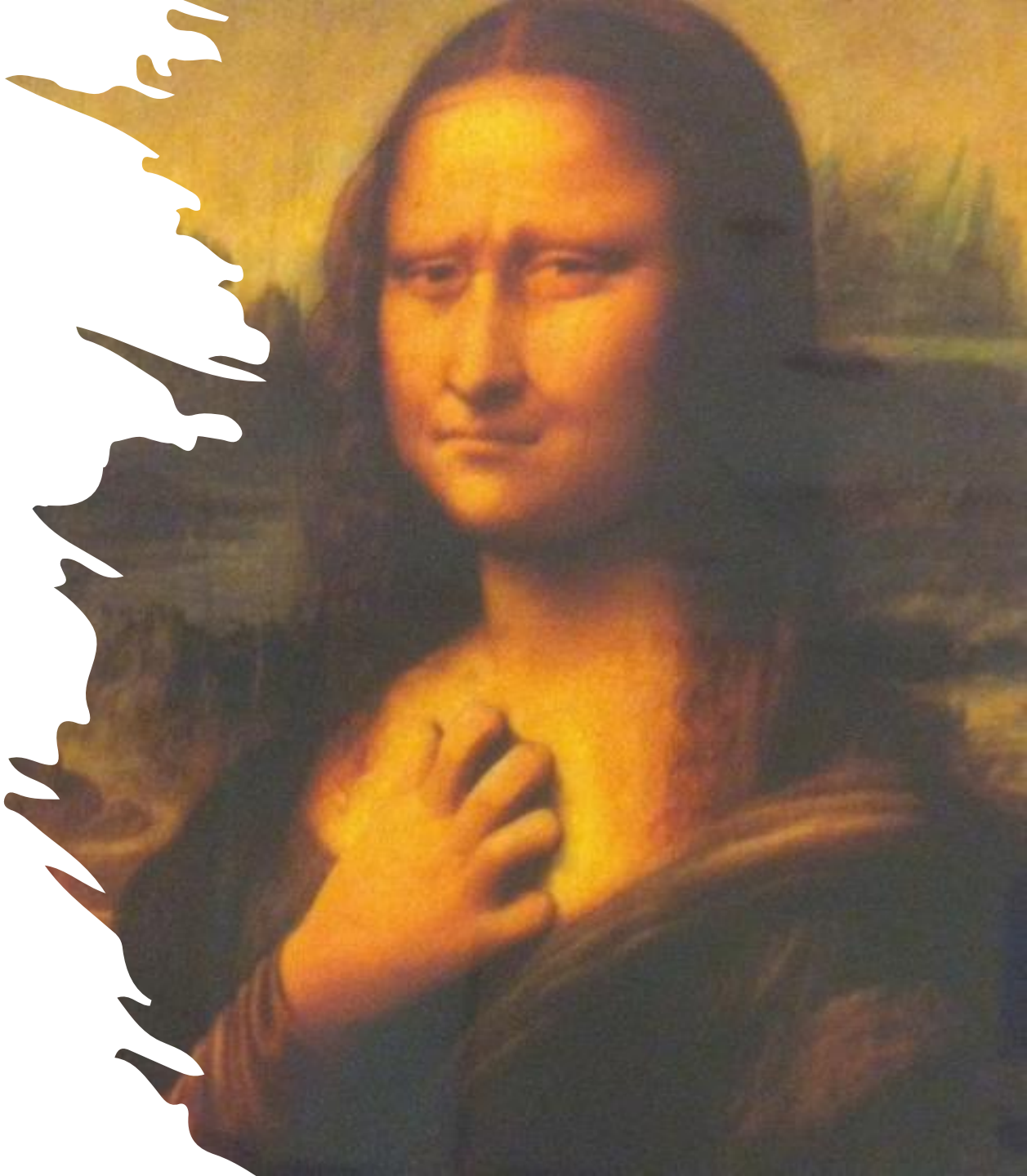
- Recognize the risks of diabetes and chronic kidney disease (CKD)
- Identify the roles of albuminuria and GFR *slope* in identifying at risk patients earlier in the course of CKD
- Raise awareness of CKD as a significant cardiovascular risk
- Recognize sodium glucose cotransporter-2 (SGLT2) inhibitors as a potential new standard-of-care in the treatment of CKD
- Discuss SGLT2 inhibitor side effects and implementation into clinical practice

Case

A 60 years old patient is concerned they might have CKD. $eGFR_{Cr}$, $eGFR_{Cys}$, and measured urine CrCl are all above 60 ml/minute.

There is no proteinuria by urinalysis.

Clutching their chest, they voice concern, "**I don't want to have…. *The Big One***".



What is the most common cause of death in patients eGFR > 60 ml/min?

A. Infection
B. Cancer
C. Cardiac disease
D. Stroke
E. GI bleeding

What is the most common cause of death in patients eGFR > 60 ml/min?

A. Infection
B. Cancer
C. Cardiac disease
D. Stroke
E. GI bleeding

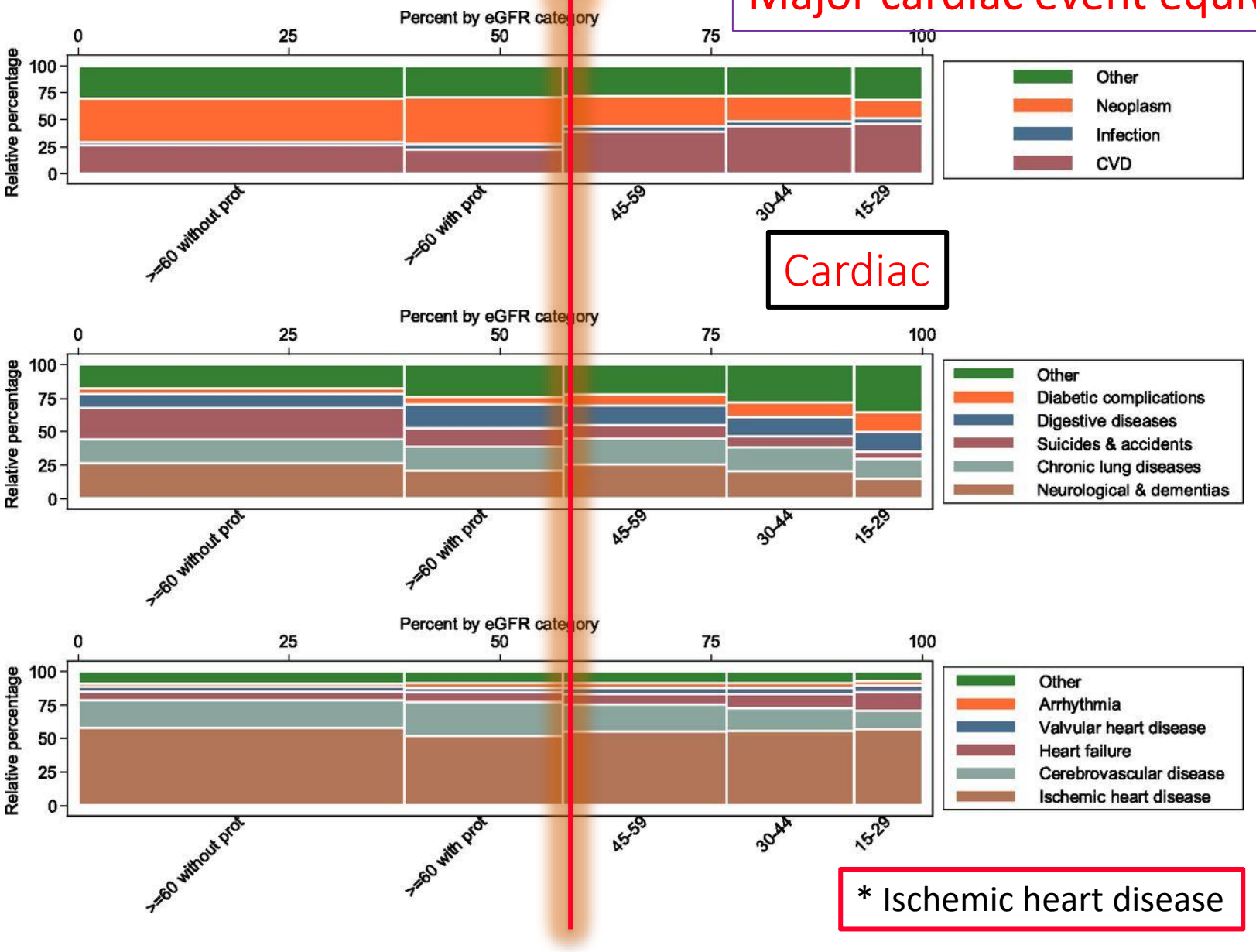
CKD is a cardiac risk factor

"CKD dies from CAD"
Major cardiac event equivalent

Cancer

Cardiac

Alberta, Canada
~85,000 deaths
2002-2009



* Ischemic heart disease

Thompson; *CJASN*; 8: 371– 381, Oct 2015

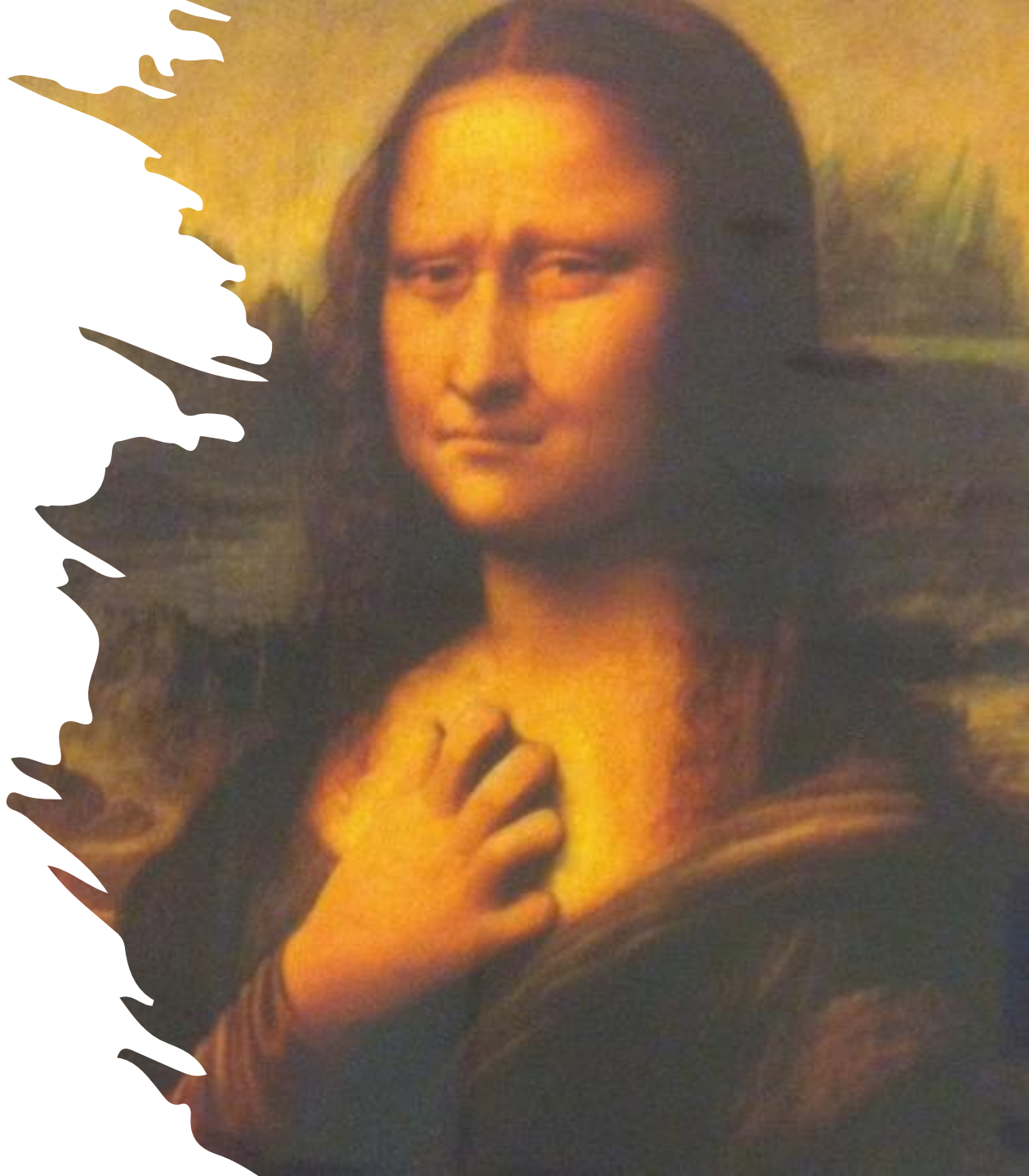
Case

A 60 years old patient is concerned they might have CKD. eGFR, $eGFR_{Cys}$, and urine CrCl are **35 ml/minute.**

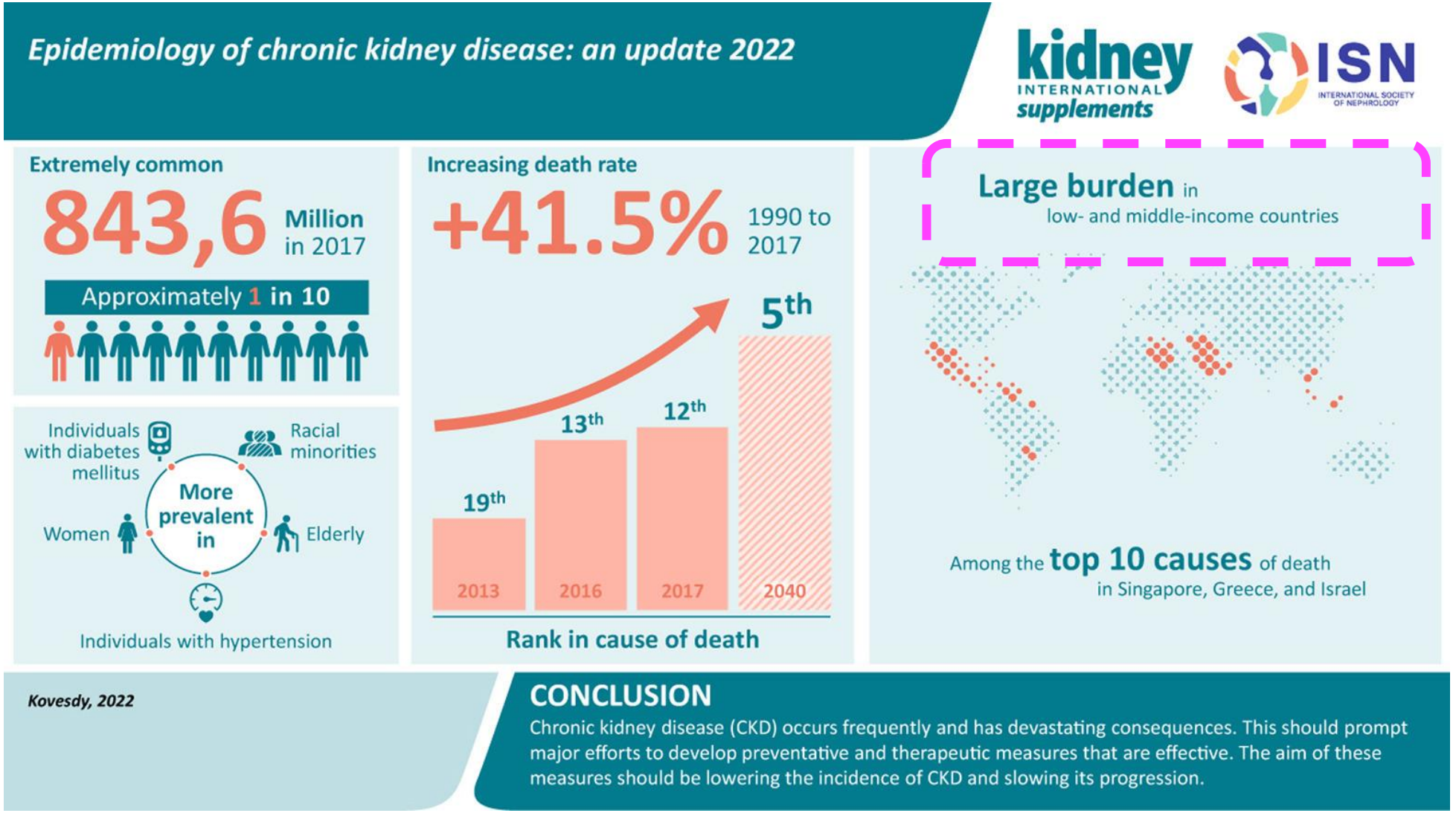
There **is proteinuria** by urinalysis.

Clutching their chest, they voice concern, "**I don't want to have…. *The Big One***".

Risk factors for The Big One are very high

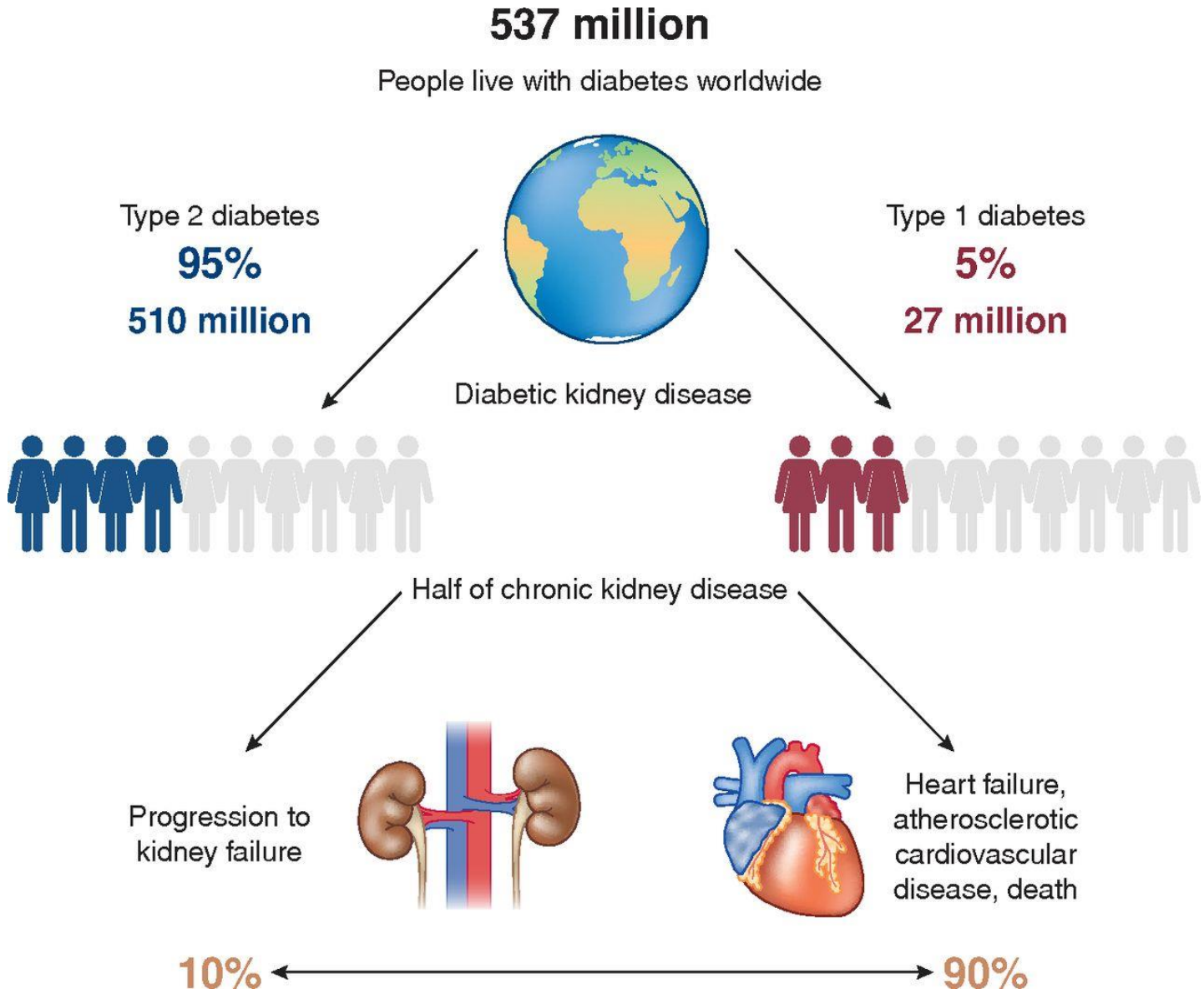


Chronic Kidney Disease Spans the Globe



Kidney Int Suppl 2022 127-11

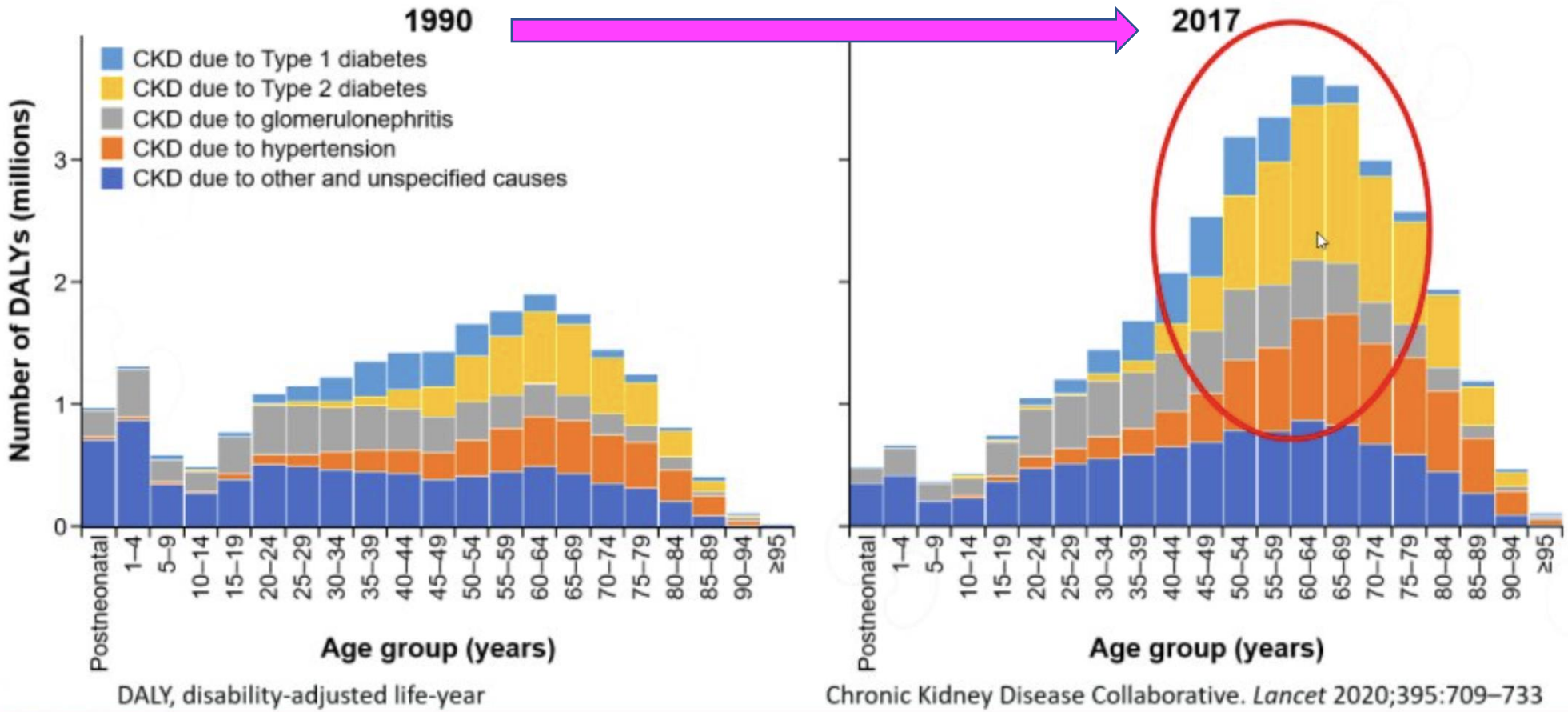
The Enormity of Diabetes and CKD



Tuttle KR *et al. CJASN* 2022;17:1092-1103

Productive Life Years Lost Due to Premature Death or Disability in CKD

Better care for CKD is urgently needed

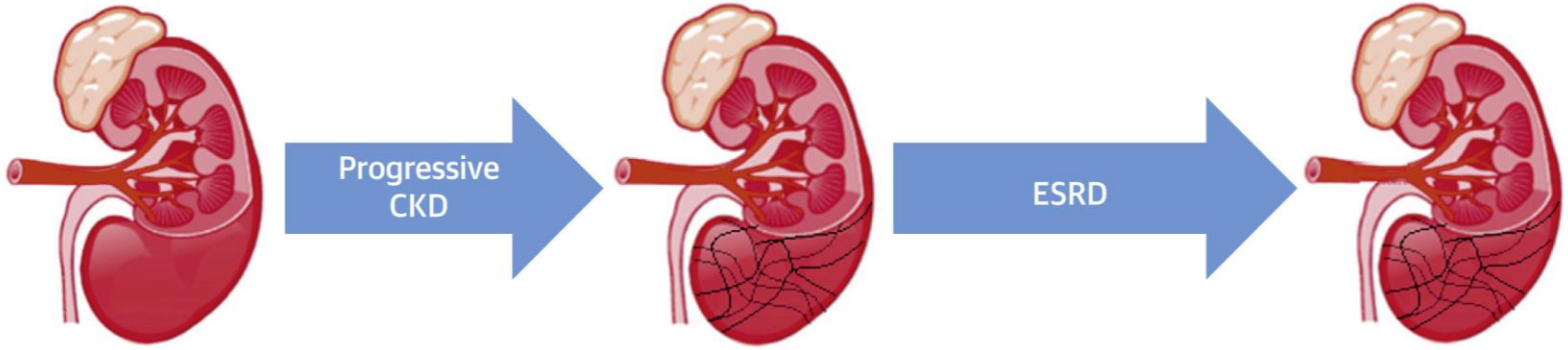


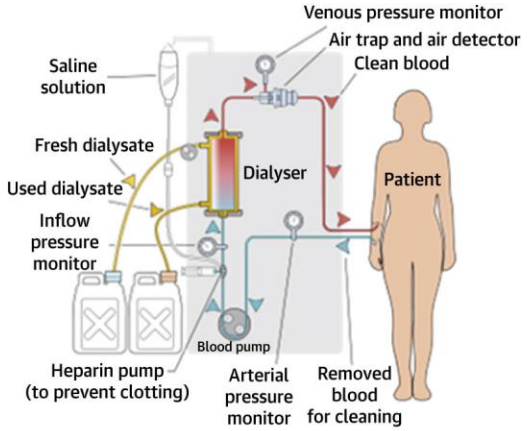
DALY, disability-adjusted life-year

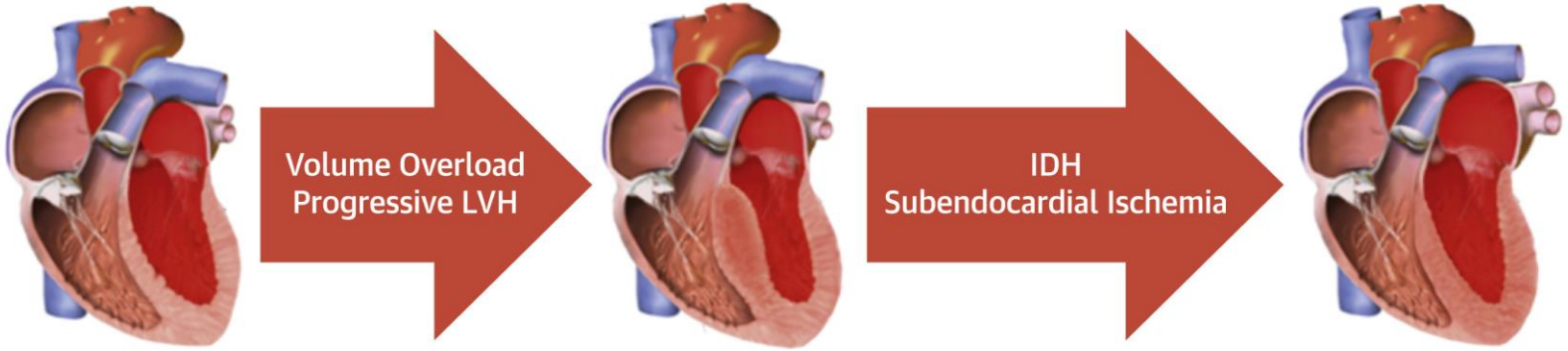
Chronic Kidney Disease Collaborative. *Lancet* 2020;395:709–733

CKD dies from CAD

ESRD = Small Survivor Cohort

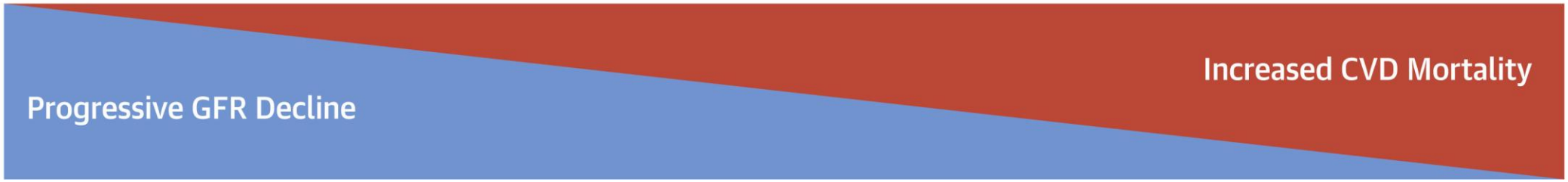






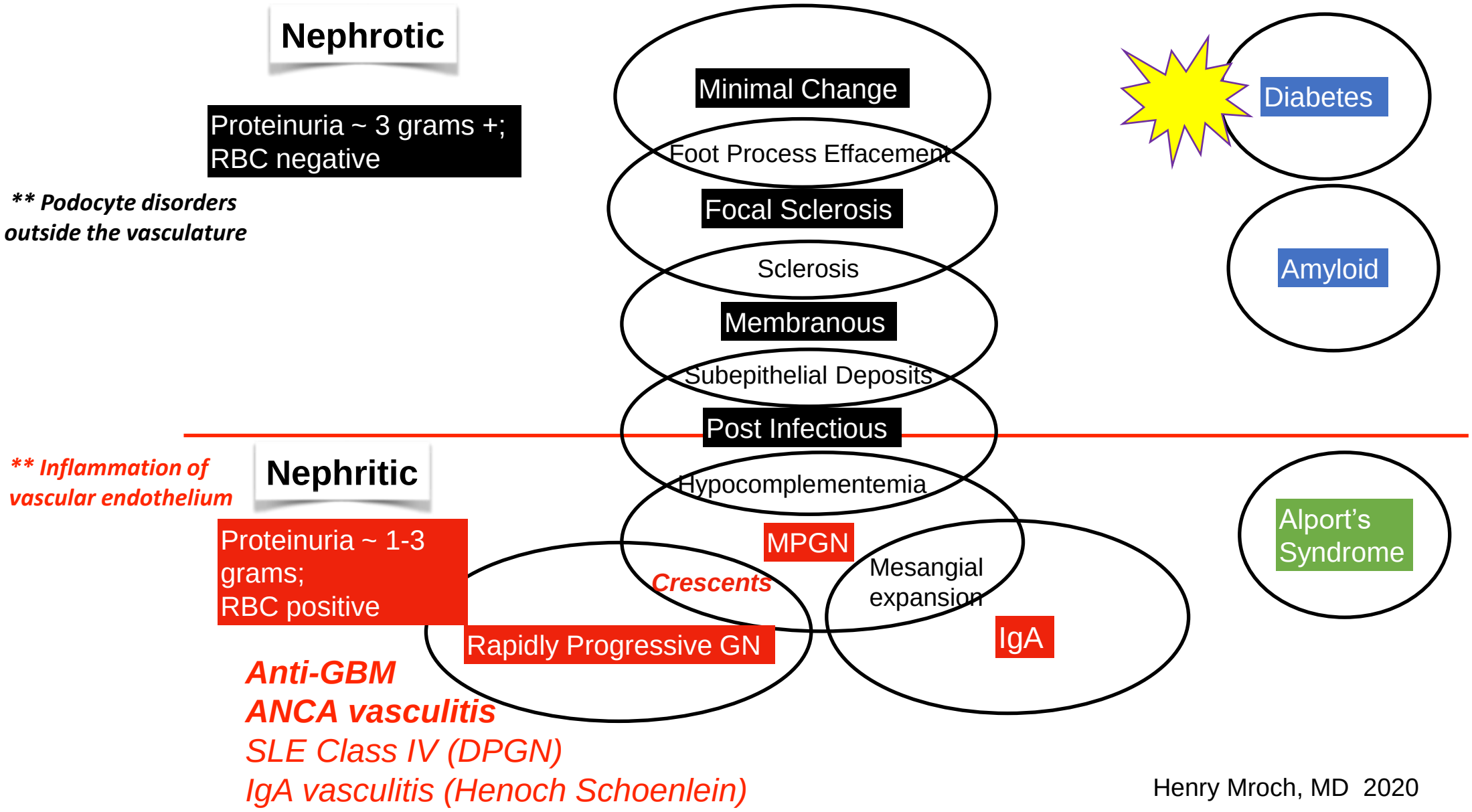
Myocardial fibrosis
Arrhythmias
Sudden Cardiac Death

IDH = Intradialytic hypotension



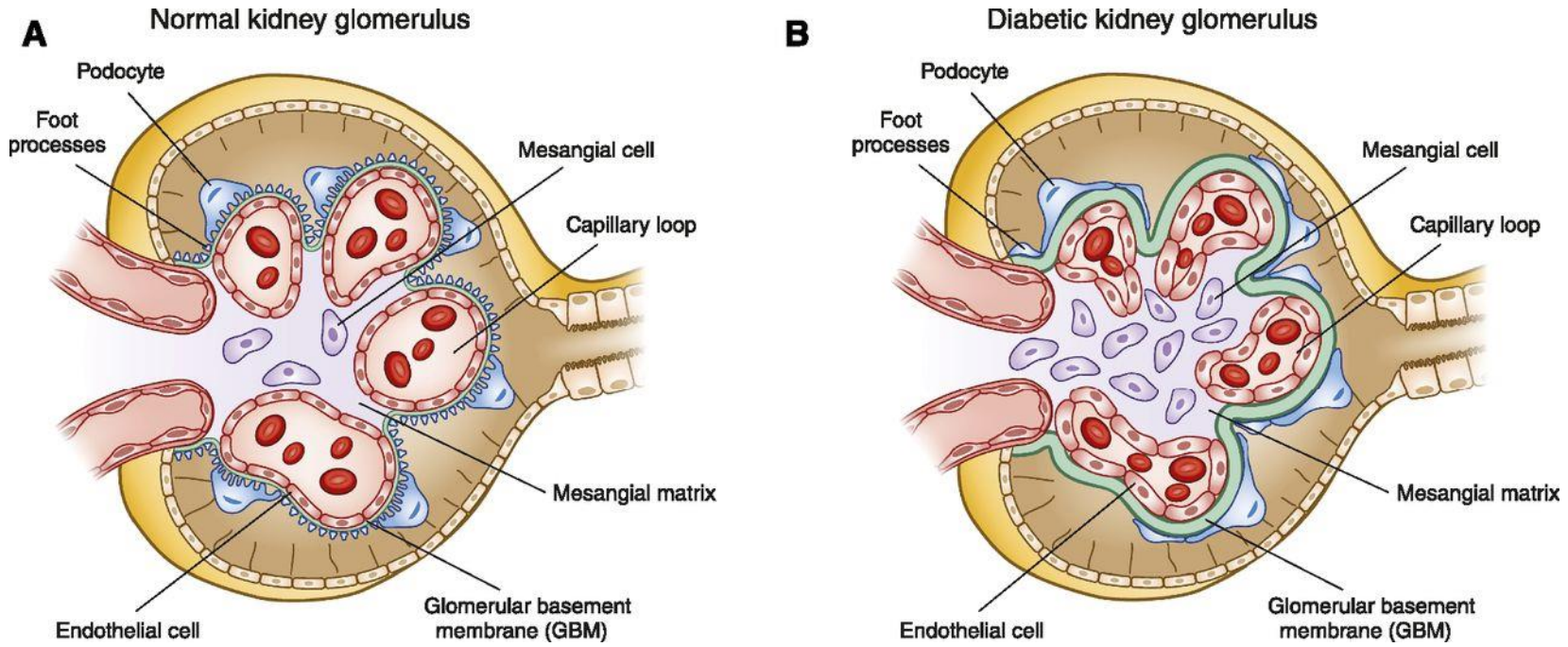
Lai, AC, et al, *JACC,* March 2021

Common Glomerular Disorders



Henry Mroch, MD 2020

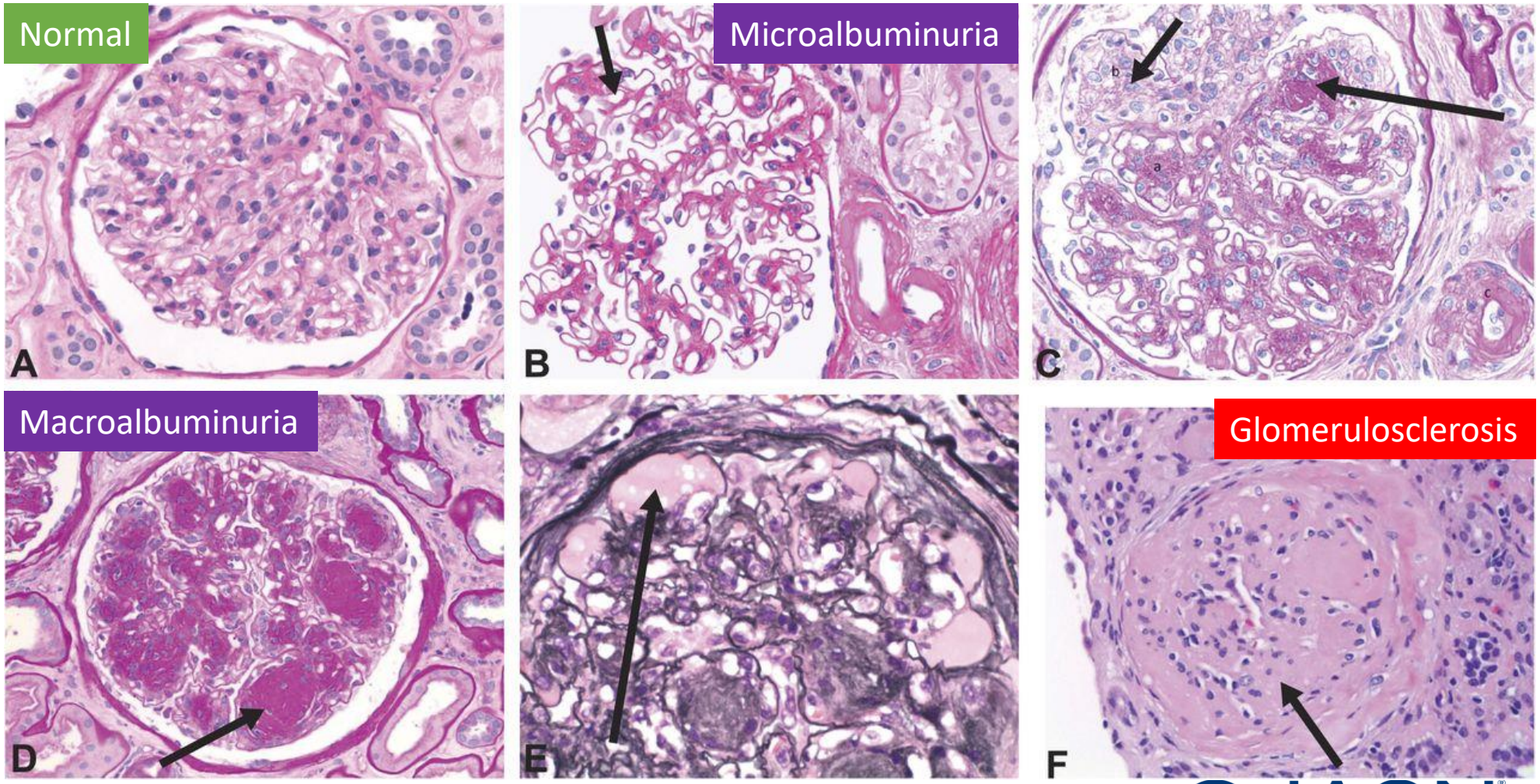
Normal kidney morphology and structural changes in diabetes mellitus



Radica Z. Alicic et al. CJASN

CJASN®
Clinical Journal of the American Society of Nephrology

The Faces of the Enemy:
Diabetic glomerulopathy



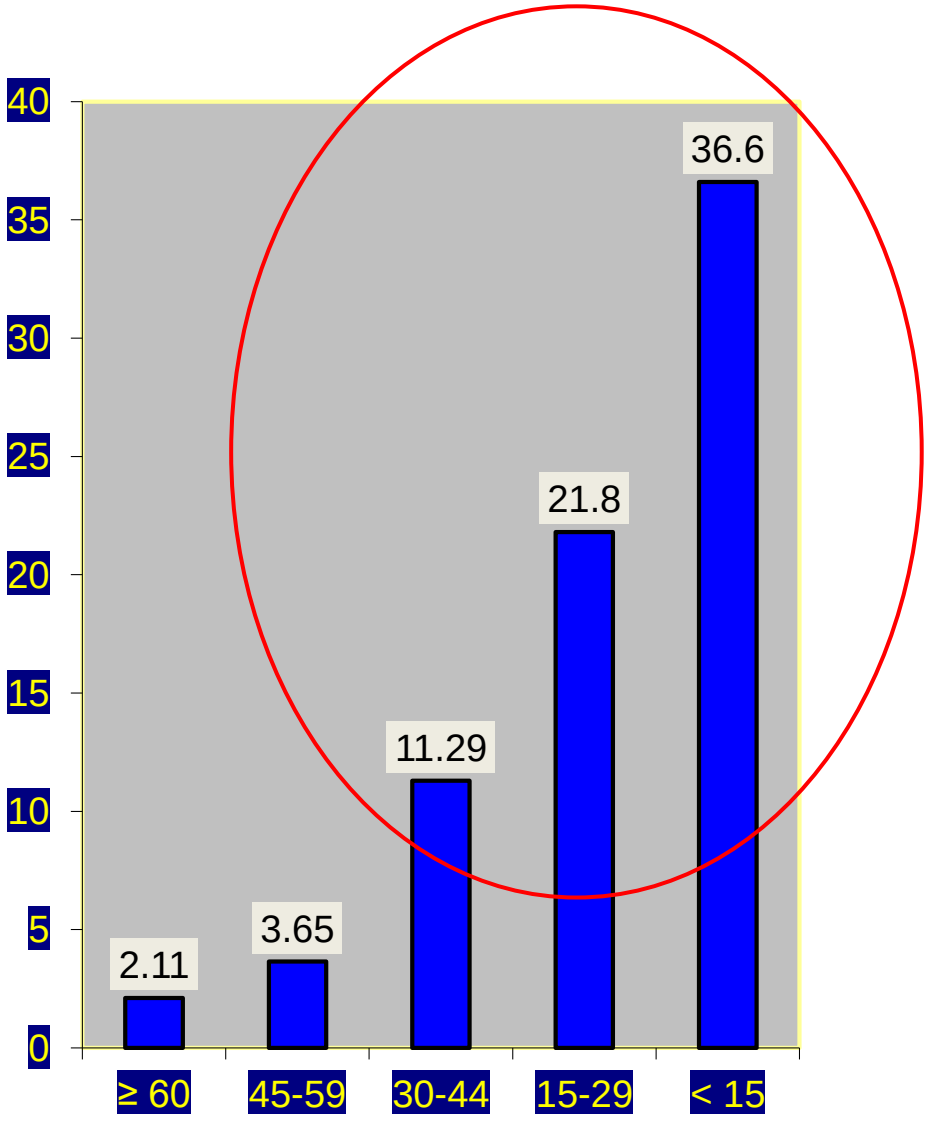
Radica Z. Alicic et al. CJASN

CJASN
Clinical Journal of the American Society of Nephrology

CKD predicts Cardiac Disease

"The luckier ones make it to dialysis..."

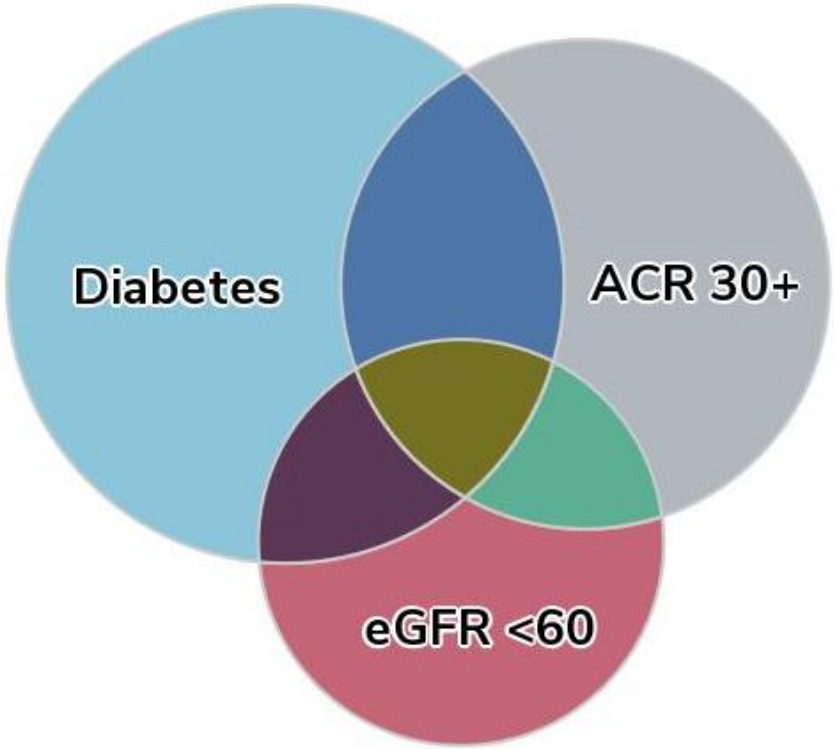
Age standardized rate of CV events per 100 person-yr



Go, et al
NEJM 2004, 351: 1296

Diabetic Kidney Disease Risks

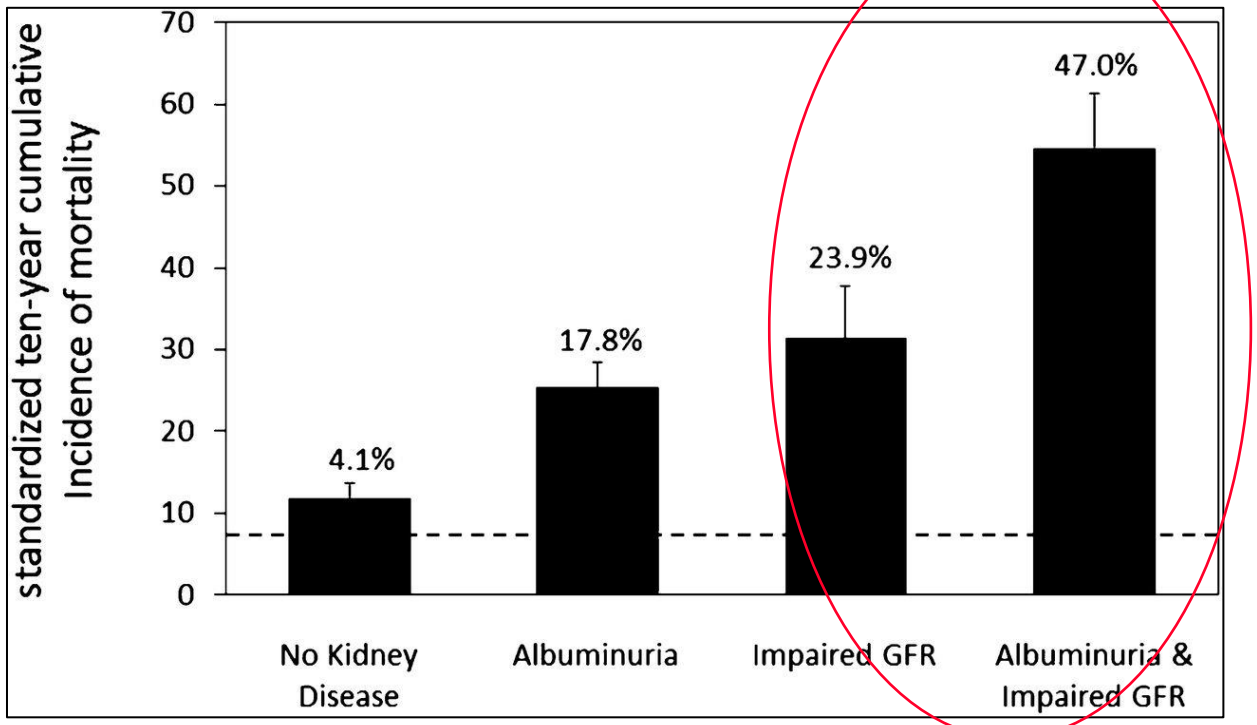
- Progress to ESRD (10 %).
  - Dialysis
  - Kidney transplant
- Die of other causes without reaching ESRD (90 %).
  - CVD 1/2
  - Infections 1/3



Alicic RZ, Rooney MT, Tuttle KR. *CJASN* 2017;12:2032-2045
2020 United States Renal Data System Annual Report

Development of CKD in Diabetes: A Serious Matter

- Diabetes prevalence in US patients with ESKD is 66-86%
- US prevalence of ESKD *>doubled to ~800,000 in 2000-2019*, primarily driven by diabetes
- Most of diabetes-related excess risk for all-cause and CVD mortality occurs in people with CKD



Burrows NR *et al. MMWR Morb Mortal Wkly Rep* 2022;71:412-415
Alicic RZ *et al*. *CJASN* 2017;12:2032-2045
Afkarian M *et al*. *JASN* 2013;24:302-308

Barriers to the Prevention of CKD

Before we can prevent, preserve, or treat, ***we need a diagnosis***.

How should we test?

- Serum **creatinine** for **kidney function**
- **Albuminuria** for **kidney damage**

Awareness and Detection of CKD

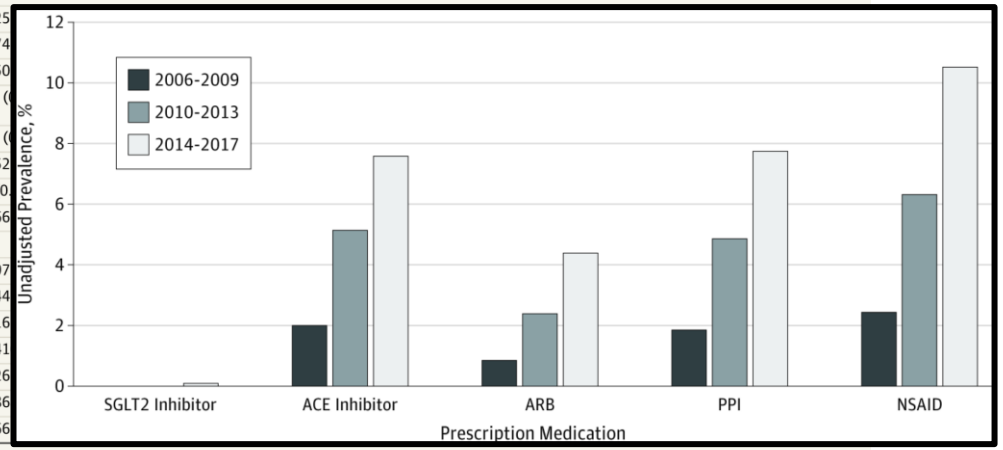
- Providence & UCLA Health Systems
- Electronic health records
- Jan 2006- Dec 2017
- 2.6 million adults and children
- **600,000 with CKD**

- Pressing need for improvement in CKD prevention, recognition, and treatment.
- Nephrotoxic medication use was widespread.

Tuttle, KR et al, *JAMA Online,* 2019

Table 1. Characteristics of Adults With CKD in the CURE-CKD Registry

Characteristic	No. (%) All CKD (N = 606 064)	CKD With Diabetes, Prediabetes, and Hypertension (n = 300 157)	CKD With Hypertension (n = 134 500)	CKD With Diabetes or Prediabetes (n = 81 266)	CKD Alone (n = 90 141)
Demographic					
Sex					
Men	267 285 (44.1)	142 197 (47.4)	53 703 (39.9)	38 600 (47.5)	32 785 (36.4)
Women	338 755 (55.9)	157 959 (52.6)	80 795 (60.1)	42 657 (52.5)	57 344 (63.6)
Race/ethnicity					
Non-Latino white	434 474 (71.7)	217 009 (72.3)	106 538 (79.2)	52 453 (64.5)	58 474 (64.9)
Latino	17 625				
Black	29 974				
Asian	32 850				
American Indian or Alaska Native	5461 (				
Hawaiian or Pacific Islander	3899 (				
Other	33 152				
Multiple races	163 (0.				
Not reported[a]	48 466				
Entry age, y					
18-39	49 097				
40-49	37 544				
50-59	74 616				
60-69	129 41				
70-79	144 26				
80-89	127 86				
≥90	43 266				
Clinical					
eGFR CKD category					
1-2	137 784 (22.7)	76 605 (25.5)	25 718 (19.1)	15 882 (19.5)	19 579 (21.7)
3a	226 693 (37.4)	112 931 (37.6)	58 757 (43.7)	27 773 (34.2)	27 232 (30.2)
3b	100 239 (16.5)	48 384 (16.1)	21 642 (16.1)	17 197 (21.2)	13 016 (14.4)
4	39 125 (6.5)	18 737 (6.2)	6083 (4.5)	8862 (10.9)	5443 (6.0)
5, Not dialyzed	20 328 (3.4)	10 181 (3.4)	2861 (2.1)	4652 (5.7)	2634 (2.9)
Not categorized[b]	81 895 (13.5)	33 319 (11.1)	19 439 (14.5)	6900 (8.5)	22 237 (24.7)
UACR, mg/g					
≤30	17 651 (2.9)	12 703 (4.2)	1776 (1.3)	2224 (2.7)	948 (1.1)
>30 to ≤300	27 227 (4.5)	21 435 (7.1)	1089 (0.8)	4066 (5.0)	637 (0.7)
>300	7673 (1.3)	5860 (2.0)	509 (0.4)	995 (1.2)	309 (0.3)
Not measured	553 513 (91.3)	260 159 (86.7)	131 126 (97.5)	73 981 (91.0)	88 247 (97.9)
UPCR, mg/g					
≤150	14 467 (2.4)	7823 (2.6)	2723 (2.0)	2076 (2.6)	1845 (2.0)
>150 to ≤500	5688 (0.9)	3087 (1.0)	1163 (0.9)	763 (0.9)	675 (0.7)
>500	4880 (0.8)	2978 (1.0)	785 (0.6)	696 (0.9)	421 (0.5)
Not measured	581 029 (95.9)	286 269 (95.4)	129 829 (96.5)	77 731 (95.7)	87 200 (96.7)
Age, median (IQR) [No.], y	70 (59-81) [606 064]	70 (60-79) [300 157]	72 (60-83) [134 500]	73 (63-83) [81 266]	64 (42-81) [90 141]
eGFR, median (IQR) [No.], mL/min/1.73 m^2	53 (41-61) [524 169]	54 (43-63) [266 838]	53 (44-59) [115 061]	49 (35-59) [74 366]	53 (41-66) [67 904]
SBP, mean (SD) [No.], mm Hg	129 (18) [365 561]	131 (18) [202 951]	132 (18) [92 051]	119 (17) [25 533]	119 (16) [45 026]
DBP, mean (SD) [No.], mm Hg	72 (11) [365 561]	72 (10) [202 951]	74 (11) [92 051]	67 (10) [25 533]	70 (10) [45 026]



Screen for CKD with GFR and Albuminuria

Adults with Diabetes, Hypertension, older than 60, or a family history of kidney disease → Request Kidney Profile (eGFR & ACR)

CKD is classified on the basis of:
- Cause (C)
- GFR (G)
- Albuminuria (A)

GFR categories (mL/min/1.73m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severly increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	1	1	2
	G2	Mildly decreased	60-89	1	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

KDIGO, 2021

A familiar case

64 years, male, IgA nephropathy on biopsy 10 years ago.
T2DM diagnosed 4 years ago
CKD/DKD G3aA3
eGFR 47 ml/min, UACR 1.6 g/g
BP 145/87 mmHg
BMI 32
HgbA1C 7.9%
Hgb 11.8
Non-smoker, struggles with lifestyle, takes 6 pills/day

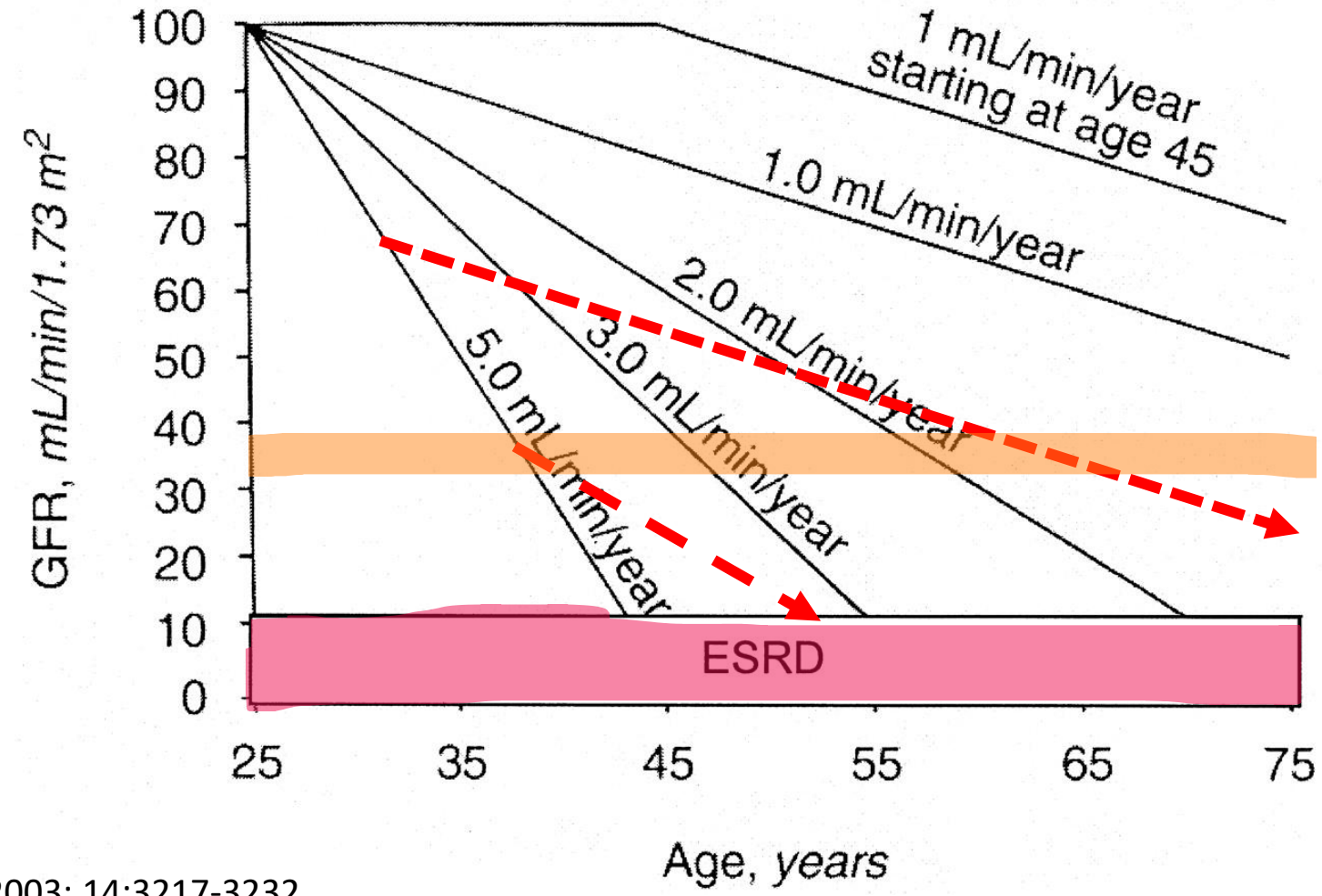
Current treatment with:

Losartan 100 mg/d
Amlodipine 5 mg/d
Atorvastatin 10 mg/d
Aspirin 81 mg/d
Metformin 2 g/d
DPP4 inhibitor

GOLD STANDARD: *Glucose control, RAAS inhibition, BP control*

Goal: Changing the Slope with Intervention

Buying patients time…

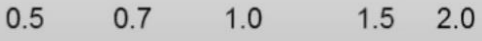


Wilmer, W *et al, JASN* 2003; 14:3217-3232

ACE/ARB Trials showed little or no CV benefit in T2DM + CKD

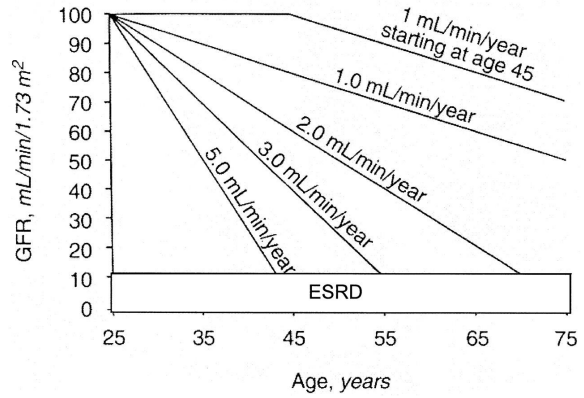
- Included IDNT, RENAAL, and ADVANCE

Outcome	Events ACEi/ARB	Control*	Hazard Ratio (95%CI)	P
All-cause mortality	362/2363	466/2946	0.97 (0.85-1.10)	0.61
CV mortality	118/1588	165/2160	1.03 (0.75-1.41)	0.85
Non-fatal CV events	284/1588	489/2160	0.90 (0.79-1.02)	0.10



1990's – 2000's

- ***RAAS inhibition***
- ***Sugar control***
- ***BP control***



2015 - the eGFR Narrative Changed

Kidney Function Decline in Type 2 Diabetes
Slope Analysis From the EMPA-REG OUTCOME® Trial

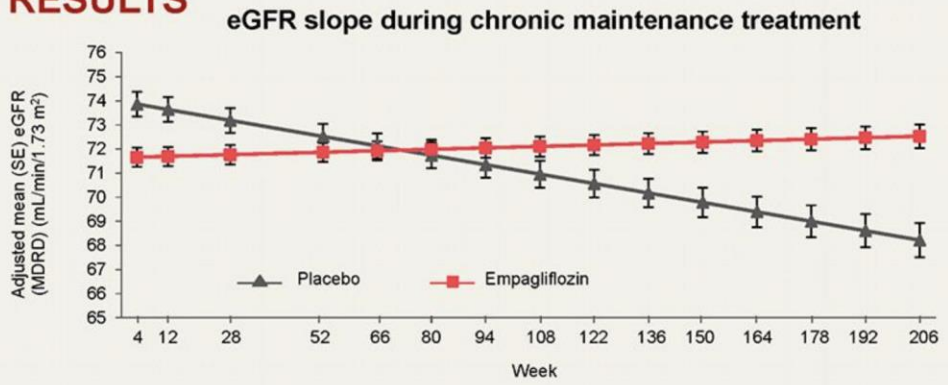
METHODS

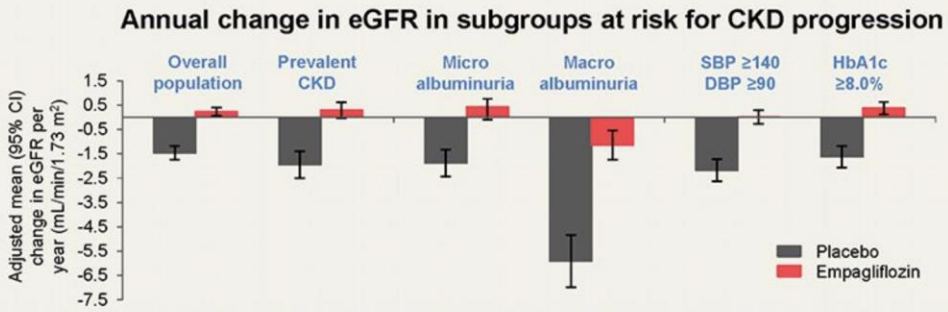
EMPA-REG OUTCOME® studied 7020 people with type 2 diabetes and established CVD over a median follow-up of 3.1 years. This manuscript reports a pre-specified 'eGFR slope' analysis from this trial, evaluating changes in kidney function over time.

eGFR slopes for pooled empagliflozin or placebo groups were calculated using a random intercept, random coefficient model.

CONCLUSION During long-term chronic treatment (from Week 4 to last value on treatment), empagliflozin significantly slowed kidney function loss, and this effect was consistent among individuals at high risk of progressive kidney disease. These data support the utility of slope analysis as an emerging surrogate endpoint of CKD progression.

RESULTS





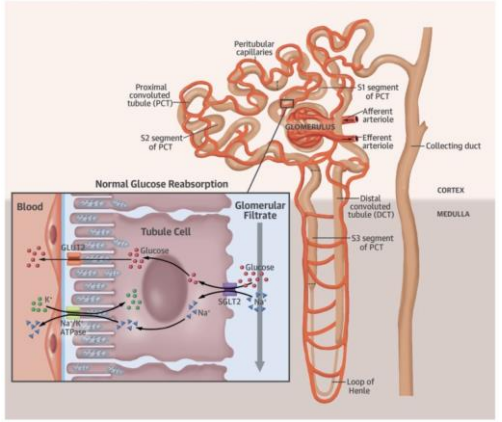
doi: 10.1681/ASN.2018010103

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

A simple drug for diabetes…

- 1835: Phlorizin isolated from bark of apple trees
- 1866: High doses of phorizin led to glucosuria in dogs
- 1960: Phlorizin inhibits renal glucose reabsorption
- 1997: Phlorizin in mice blocked increase in blood glucose
- 1999: Phlorizin analogues developed
- 2003: SGLT2 inhibitor first tested in humans
- 2012: First SGLT2 inhibitor approved for use in humans (*dapagliflozin*)

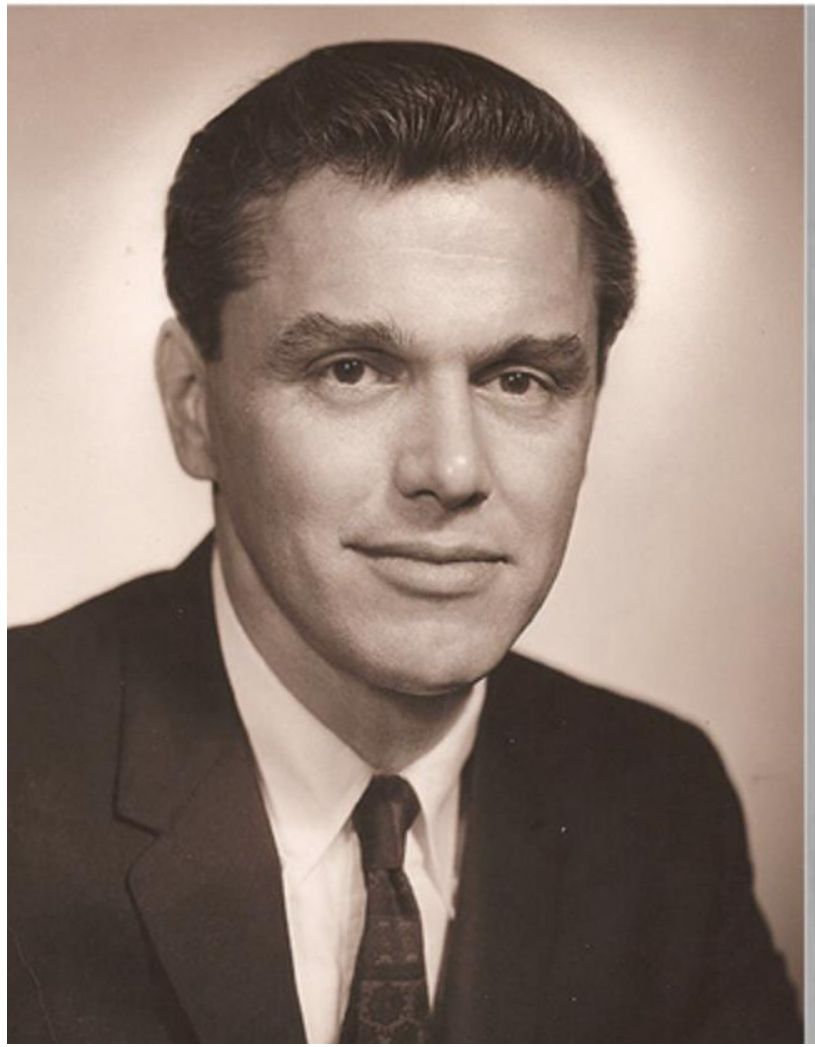
HgbA1C – 0.6%



Zelniker, T.A. et al. J Am Coll Cardiol. 2018;72(15):1845-55.

Robert Crane, 1960

A



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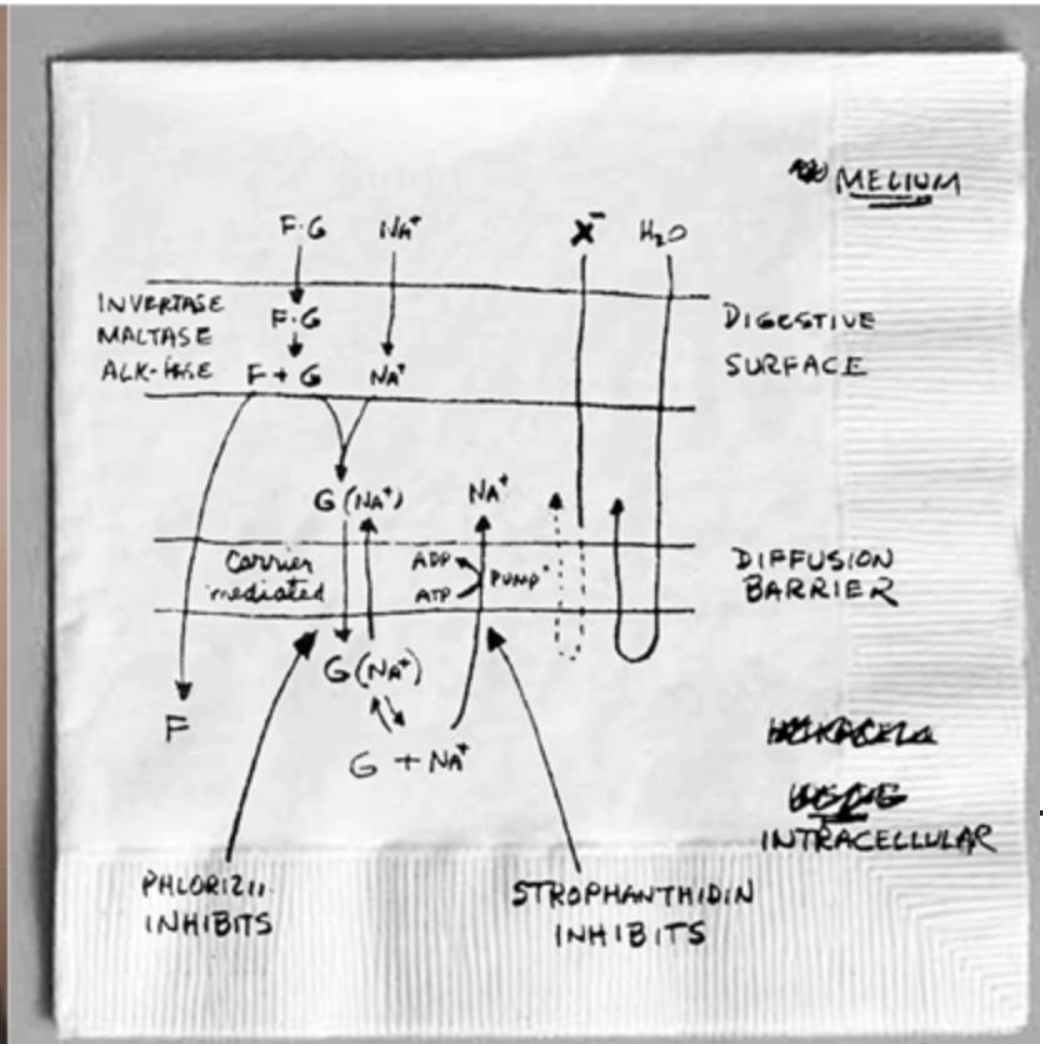
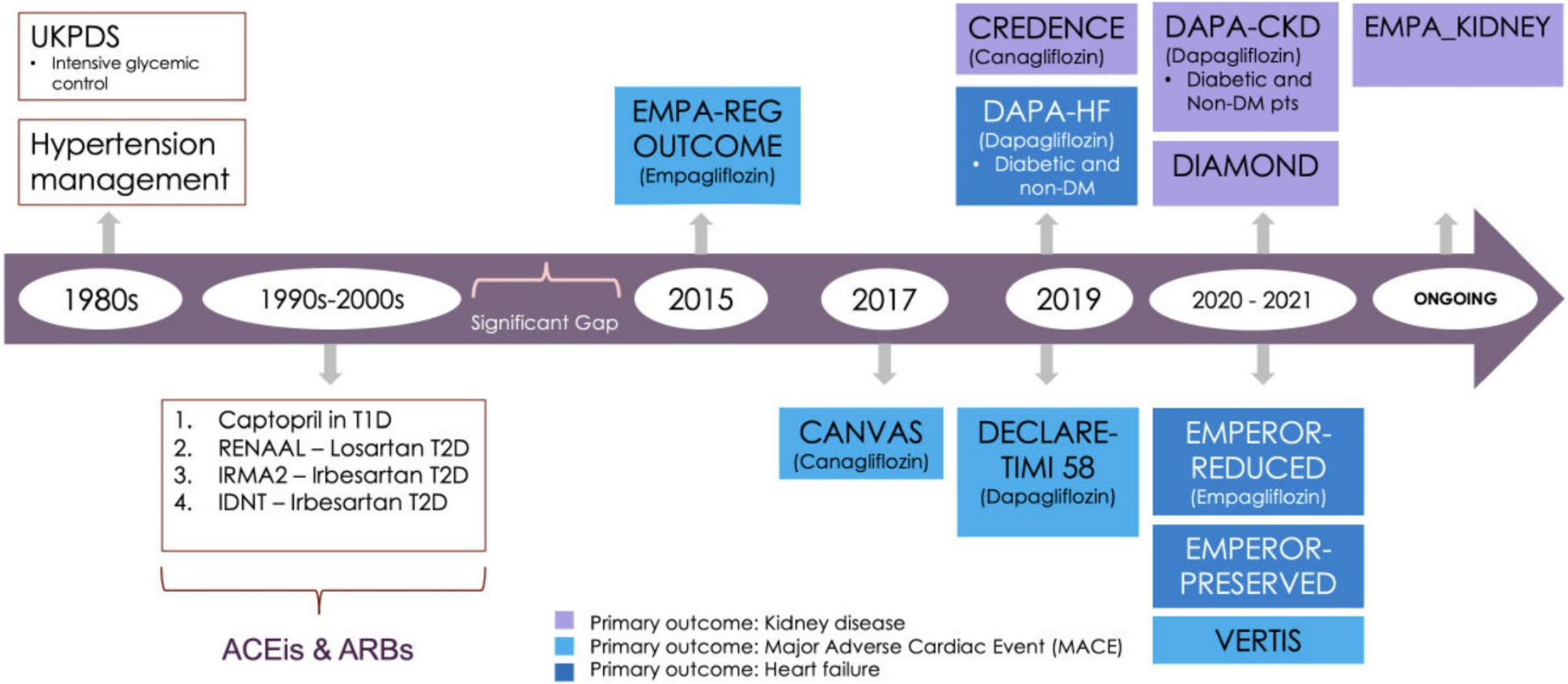
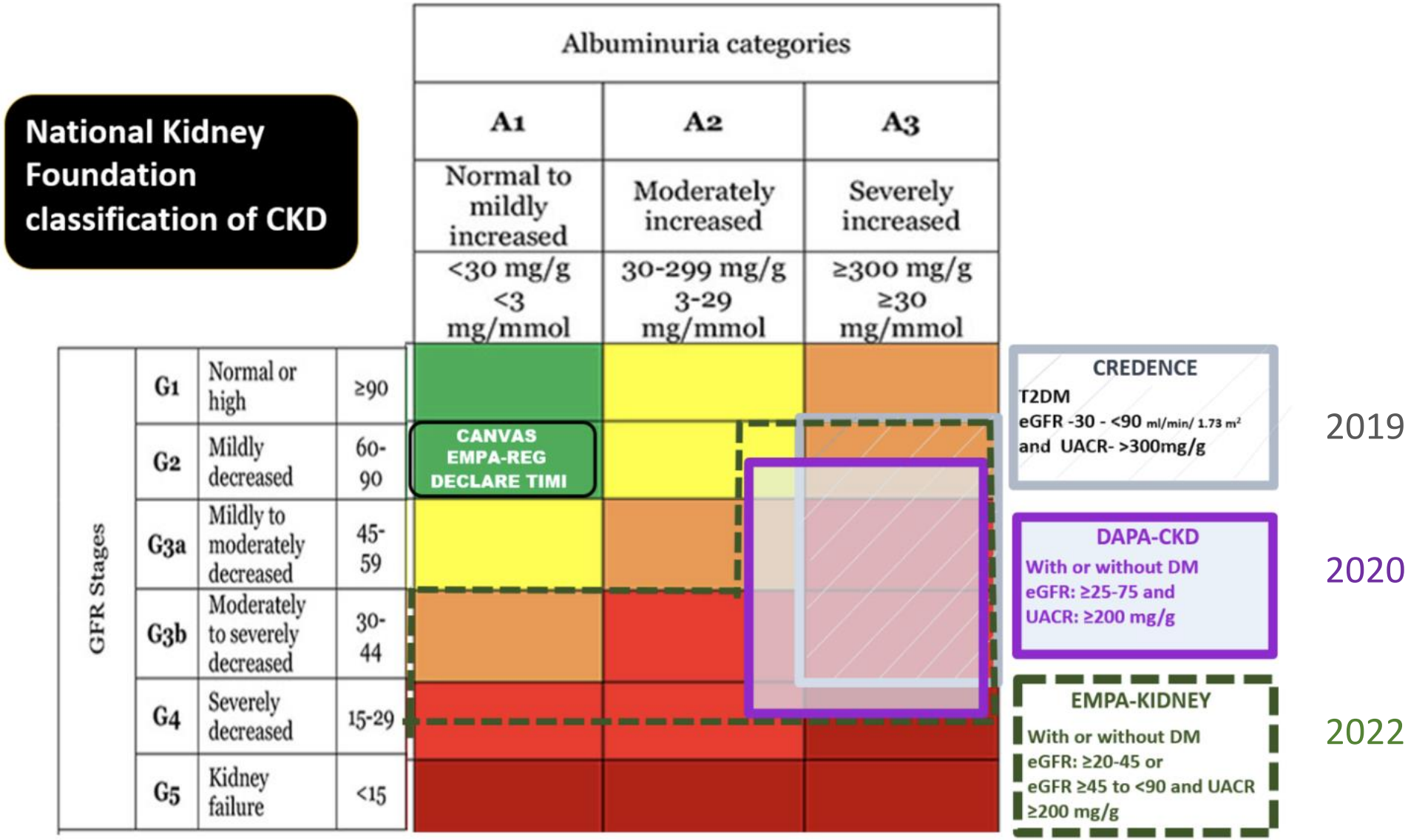


Frontiers in Physiology *website*

Timeline of the key treatment milestones for diabetic kidney disease over the past 40 years

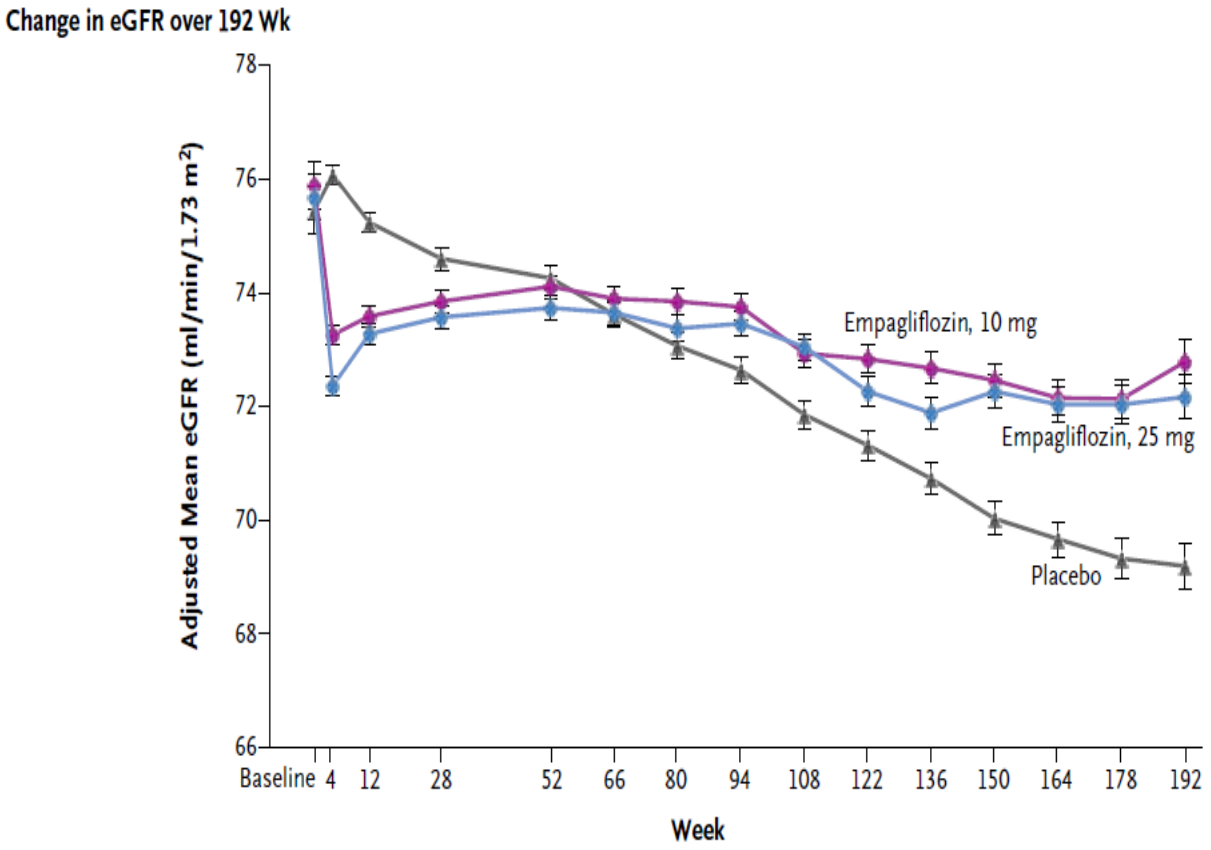


SGLT2 Trials in CKD

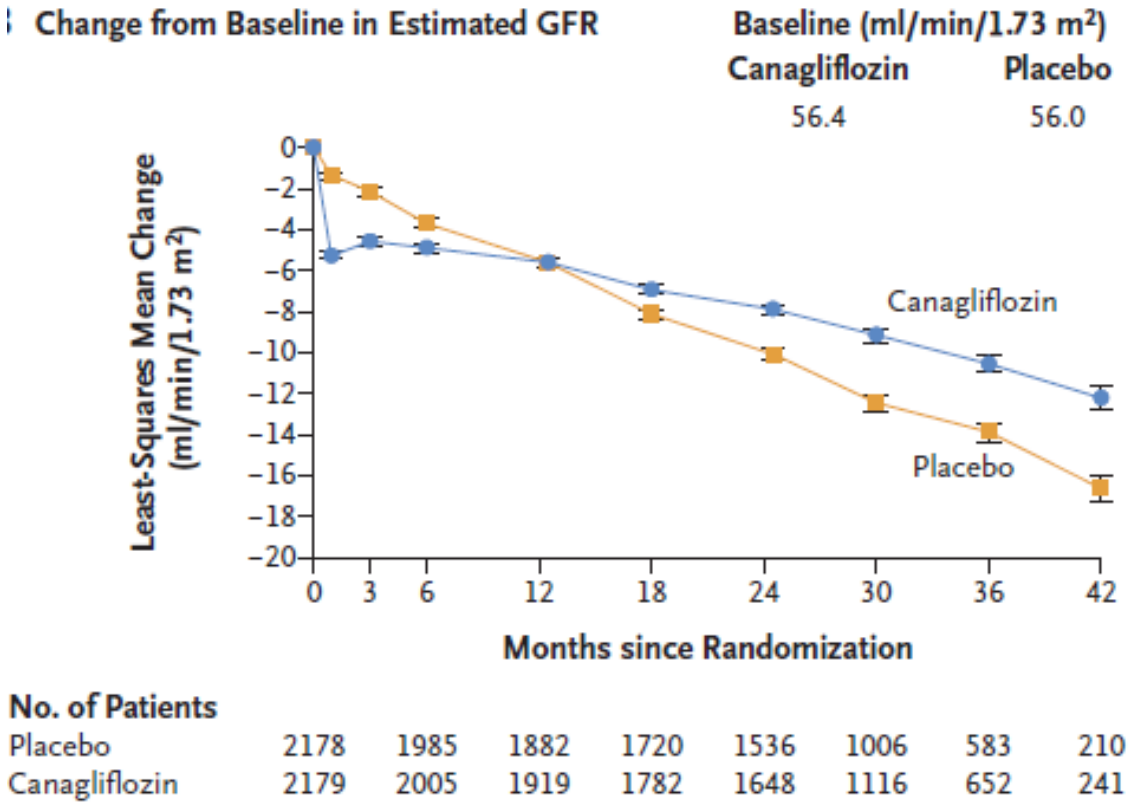


Heerspink et al, NDT, 2020

EMPA-REG and CREDENCE
eGFR over Time in Type 2 Diabetes

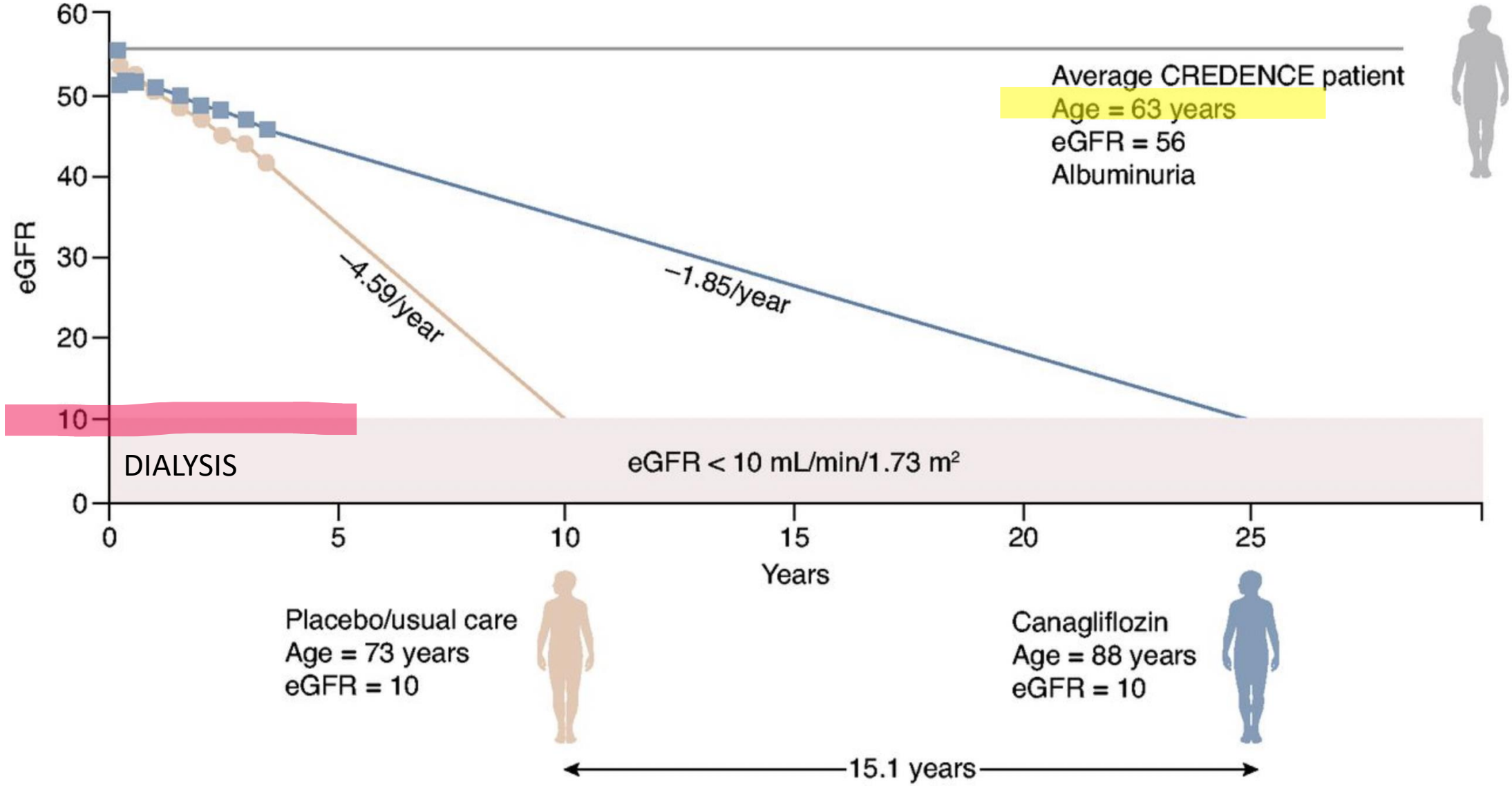


Wanner C *et al. N Engl J Med* 2016;375:323-334



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

2019 CREDENCE - Canagliflozin reduces loss of GFR



Dapagliflozin slows the loss of GFR in diabetic and non-diabetic CKD

DAPA-CKD

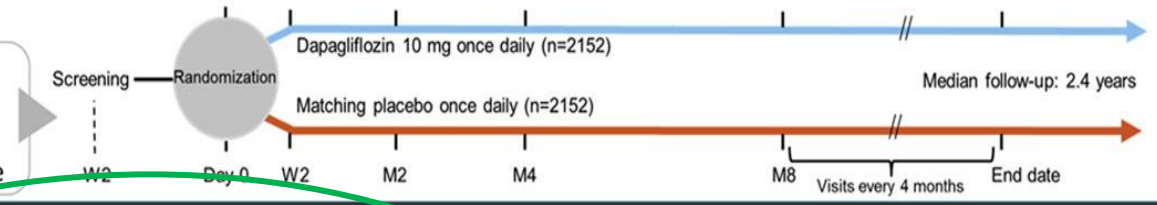
A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

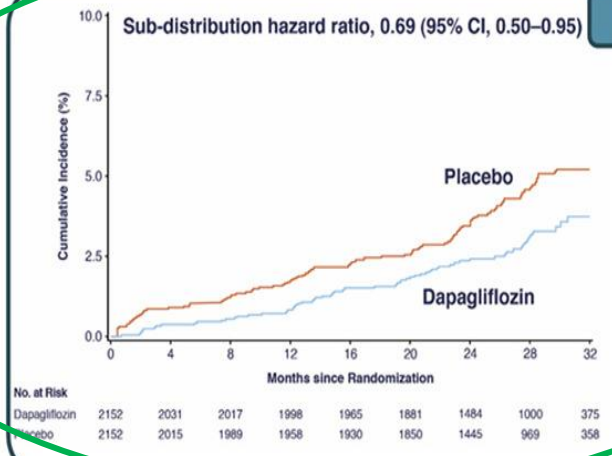
Study design

- eGFR 25–75 mL/min/1.73m^2
- UACR 200–5000 mg/g
- With/without type 2 diabetes
- Stable, maximally-tolerated ACEi/ARB dose



Outcomes

- Abrupt declines in kidney function, defined as a doubling of serum creatinine between two subsequent visits (median time-interval, 100 days)
- Investigator-reported SAEs of acute kidney injury (pre-defined list)



Results

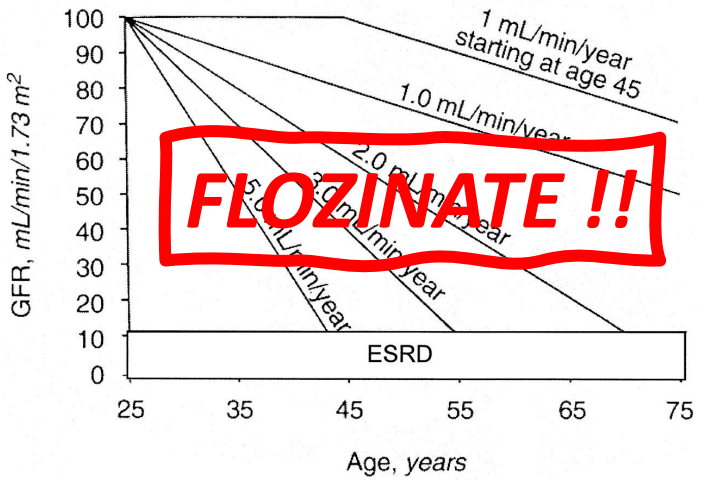
- **Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease with increased albuminuria (Figure)**
- **No heterogeneity in effect of dapagliflozin versus placebo across baseline subgroups**
- **SAEs of acute kidney injury occurred less frequently with dapagliflozin versus placebo**

Heerspink et al, 2021

eGFR=estimated glomerular filtration rate; SAE=serious adverse event; UACR=urinary albumin-to-creatinine ratio

CONCLUSION: *Dapagliflozin reduced the risk of abrupt declines in kidney function in patients with chronic kidney disease and substantial albuminuria, with and without type 2 diabetes*

A familiar case - **Goals**

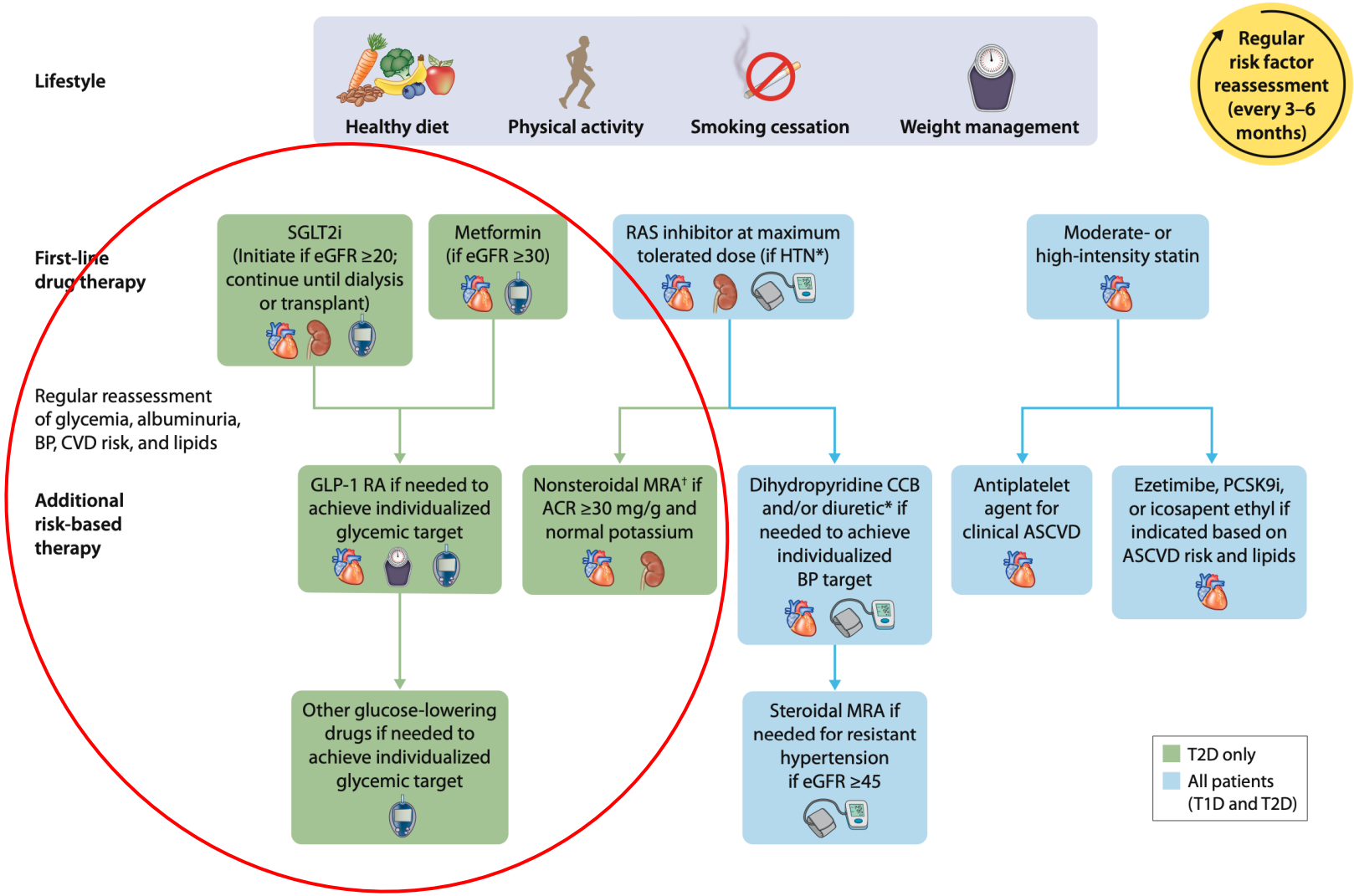


68 years, male, IgA nephropathy
T2DM diagnosed 4 years ago
CKD/DKD G3aA3
eGFR 49 ml/min, UACR 1.6 g/g
BP 145/87 mmHg
BMI 32
HgbA1C 7.9%
Hgb 11.8
Non-smoker, struggles with lifestyle, takes 6 pills/day

Current treatment with:

Losartan 100 mg/d
Amlodipine 5 mg/d
Atorvastatin 10 mg/d
Aspirin 81 mg/d
Metformin 2 g/d
SGLT2 inhibitor

Holistic approach for improving outcomes with diabetes and CKD



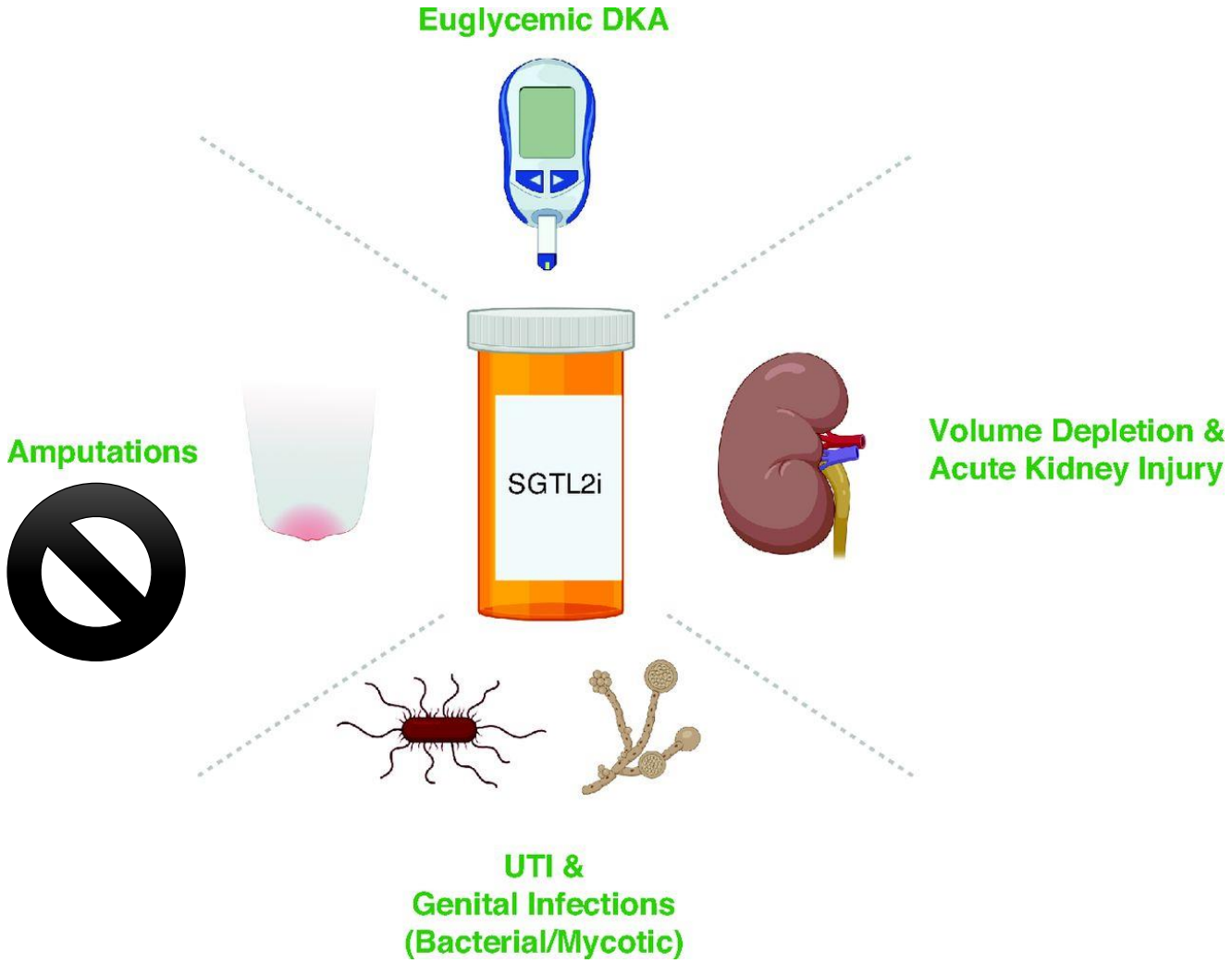
de Boer, et al, June 2022, *American Diabetes Association, KDIGO Consensus Report*

Risk Mitigation for Side Effects of SGLT2 inhibitors

Adverse Events	Potential Mitigating Strategies
	SGLT2 Inhibitors
Genital mycotic infections	○ Daily hygiene to keep genital area clean and dry
Volume depletion	○ Diuretic dose reduction in patients at risk for hypovolemia ○ Hold SGLT2 inhibitors during acute illness (nausea, vomiting, diarrhea) ○ Implement sick day protocol
DKA	○ Educate patients on early recognition ○ "STOP DKA" protocol (stop SGLT2 inhibitor, test for ketones, maintain fluid and carbohydrate intake, insulin)
Amputation	○ Encourage foot self-examinations ○ Examinations by healthcare professionals at each visit
Hypoglycemia	○ Dose adjustment of insulin and insulin secretagogues with maintenance of at least low dose insulin to avoid DKA

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD. *Kidney Int* 2020;98:S1-S115.

Reported adverse effects associated with sodium-glucose cotransporter 2 inhibitor (SGLT2i) use include euglycemic diabetic ketoacidosis, limb amputation, AKI, UTI, and genital infections.



Niralee Patel et al. Kidney360 2021;2:1174-1178

Risk Mitigation for Side Effects of SGLT2 inhibitors

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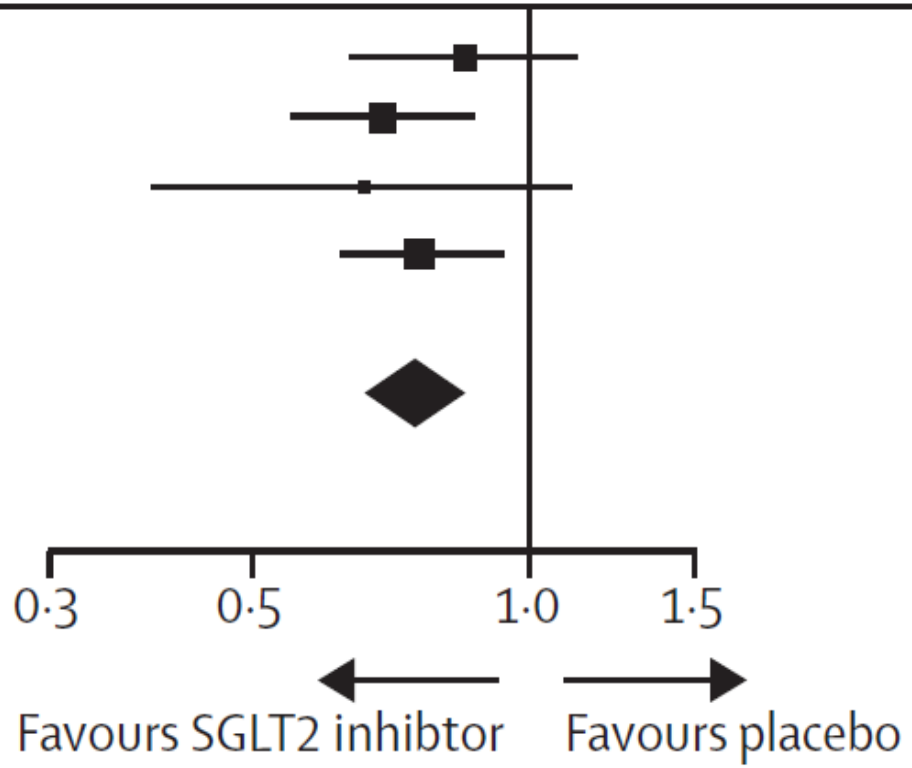
Amputation	○ **Encourage foot self-examinations** ○ **Examinations by healthcare professionals at each visit**
Hypoglycemia	○ **Dose adjustment of insulin and insulin secretagogues with maintenance of**

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD. *Kidney Int* 2020;98:S1-S115.
Li J, *et al. CJASN* 2020;15:1678-1688

SGLT2 Inhibitors Reduce Risk of Acute Kidney Injury

	Events	Patients	RR (95% CI)
CREDENCE	184	4397	0·85 (0·64–1·13)
DECLARE–TIMI 58	300	17143	0·69 (0·55–0·87)
CANVAS Program	58	10134	0·66 (0·39–1·11)
EMPA–REG OUTCOME	401	7010	0·76 (0·62–0·93)
Overall			**0·75 (0·66–0·85; p<0·0001)**

I^2=0·0%; $p_{heterogeneity}$=0·68



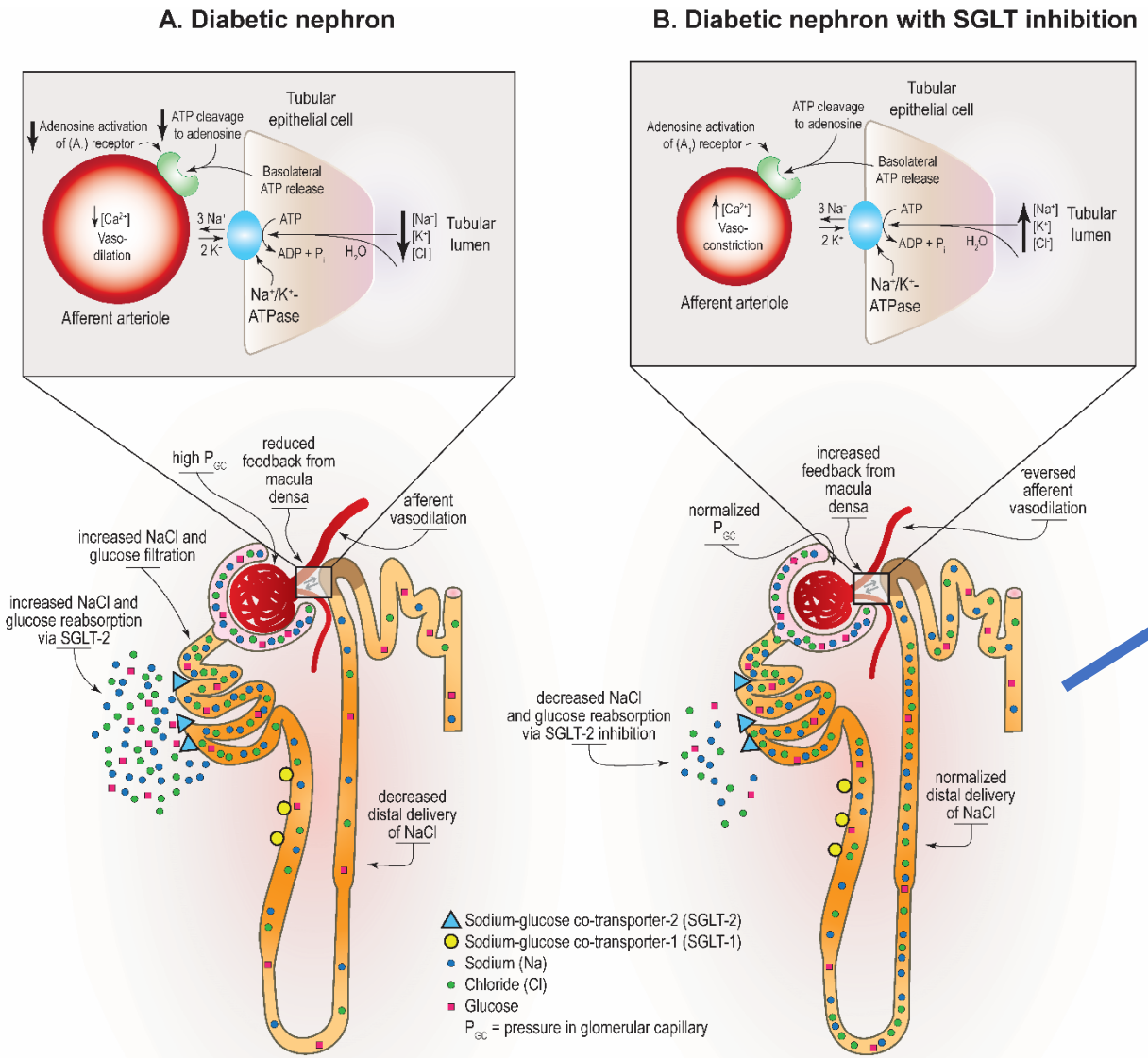
Neuen BL, *et al. Lancet Diabetes Endocrinol* 2019;7:845-854

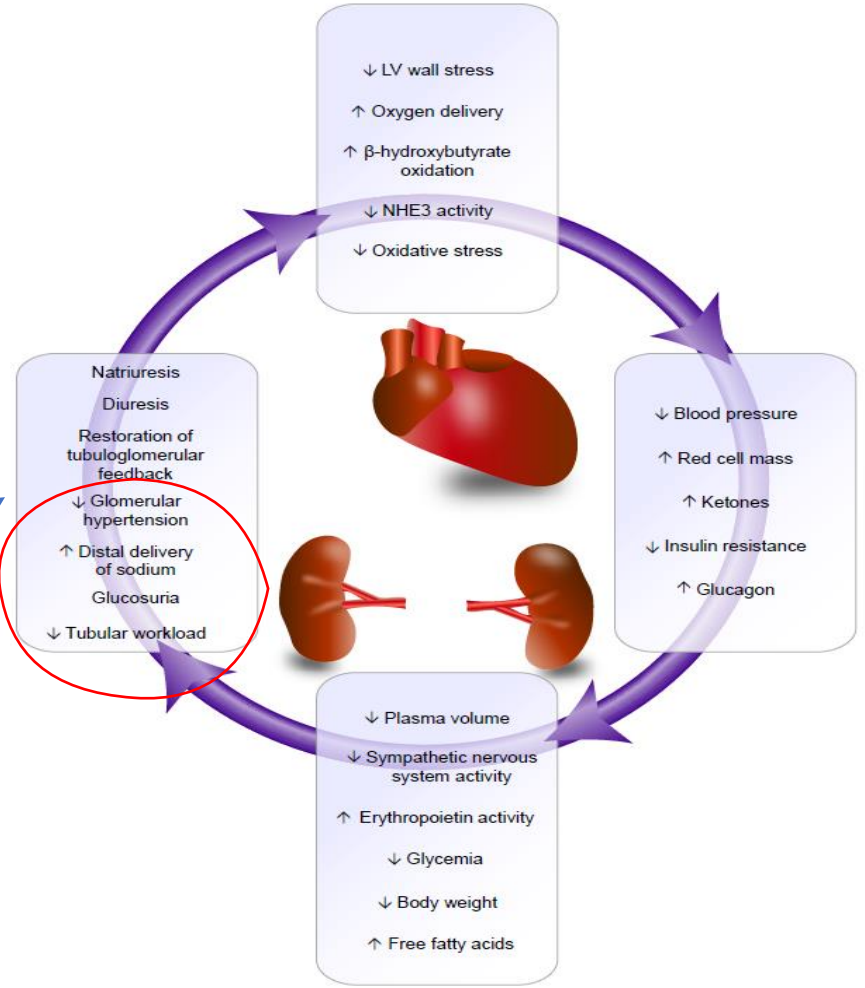
SGLT2 Inhibitors
Cardiovascular Trials in Type 2 Diabetes

- Reduce risk of major adverse CVD Events.
  - Heart failure (empagliflozin, canagliflozin, dapagliflozin)
  - Atherosclerotic CVD (3-point MACE: myocardial infarction, stroke, CVD death)
  - CVD death (empagliflozin, dapagliflozin)
- Decrease macroalbuminuria, eGFR decline, and kidney failure.
- CVD and CKD benefits are present in patients with CKD.

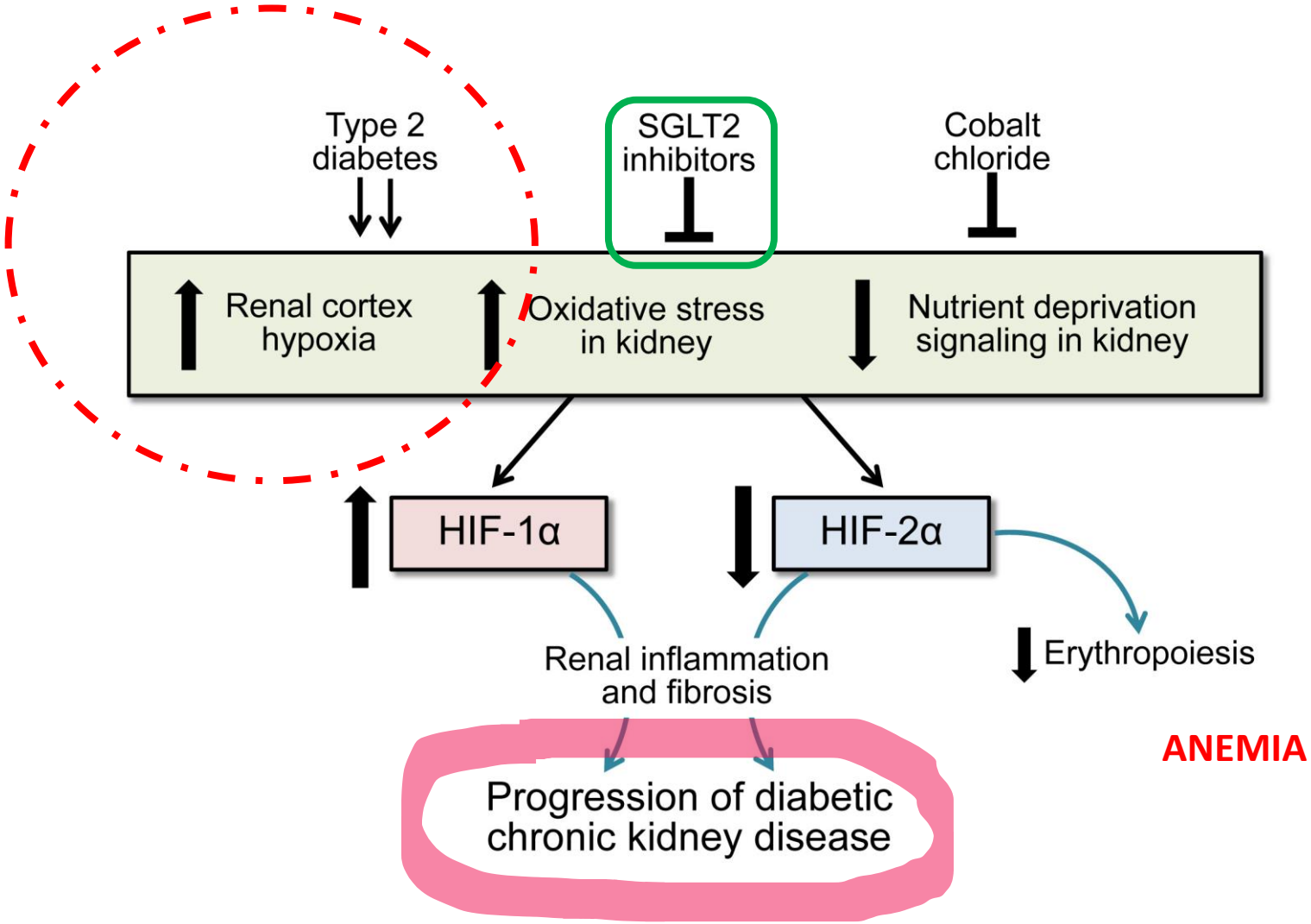
Cardio-Metabolic-Kidney Syndrome

Mechanisms of SGLT-2 Inhibition for Kidney and Heart Protection





Alicic RZ, Johnson EJ, Tuttle KR. *Am J Kidney Dis* 2018;72:267-277
Scheen AJ; *Circ Res* 2018;122:1439-1459
Tuttle KR *et al. Am J Kidney Dis.* 2021;77:94-109



The unfolding story for SGLT2 inhibitors in CKD, and not only for diabetics ...

Eur Heart J, Volume 42, Issue 48, 21 December 2021, Pages 4902–4904

ESC European Society of Cardiology

The Future (?): SGLT2 inhibitors in Cirrhosis

Gao Y. *et al*: SGLT2 inhibitors in cirrhotic ascites

Table 1. Characteristics and clinical outcomes of cirrhotic patients with fluid retention and receiving SGLT2 inhibitors

Patient	Age (y)	Sex	Signs and symptoms	SGLT2 inhibitors used	Serum Na/K (mmol/L)		Body weight (Kg)		Fasting glucose (mg/dL)		Outcomes
					Baseline	After treatment	Baseline	After treatment	Baseline	After treatment	
No. 1 [Ref. 8]	63	F	Ascites and peripheral edema; Discontinuation of diuretics for encephalopathy	Empagliflozin	139/4.2	140/4.2	63	58.1	86	90	Free of ascites, edema and encephalopathy
No. 2 [Ref. 8]	64	F	Ascites and poorly controlled diabetes; Discontinuation of diuretics for severe hyponatremia	Canagliflozin	120/4.1	141/4.7	57.6	51	140	121	Hyponatremia corrected; Free of ascites and edema (off diuretics)
No. 3 [Ref. 8]	53	M	Severe peripheral edema without ascites and diuretics-related acute kidney injury	Canagliflozin	135/4.9	145/4.4	81	69.9	187	151	Free of ascites and edema
No. 4 [Ref. 9]	54	F	Hepatic hydrothorax, peripheral edema, refractory ascites and deteriorating hyperglycemia	Empagliflozin	133/4.39	140/3.71	NS	NS	286	116	Hepatic hydrothorax improved dramatically; Free of ascites and edema (off diuretics); Hemodynamic index and renal function improved

NS, not specified.

The Future (?): SGLT2 inhibitors ESRD

RECRUITING

SGLT2 Inhibition in Hemodialysis (DAPA-HD)

ClinicalTrials.gov ID NCT05179668

Sponsor Medical University of Vienna

Information provided by Assoc. Prof. Dr. Manfred Hecking, MD PhD, Medical University of Vienna (Responsible Party)

Last Update Posted 2022-10-25

+ Expand all content | — Collapse all c

Study Details | Table View | No Results Posted | Record History

On this page

- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Publications
- Study Record Dates
- More Information

Study Overview

Brief Summary

The study is designed as a prospective randomized, controlled, double-blinded phase II trial to examine the effect of the SGLT2 inhibitor dapagliflozin, in comparison with placebo on cardiovascular outcome parameters in kidney failure patients undergoing replacement therapy with hemodialysis.

The primary endpoint is the change (Δ) in left ventricular mass indexed to body surface area (LVMi) from baseline to 6 months measured by cardiac magnetic resonance imaging.

Null and alternative hypotheses:

H0: There is no difference in the Δ Left Ventricular Mass indexed to BSA after six months of treatment,...

+ Show more

Study Start (Actual)
2022-10-01

Primary Completion (Estimated
2025-04-01

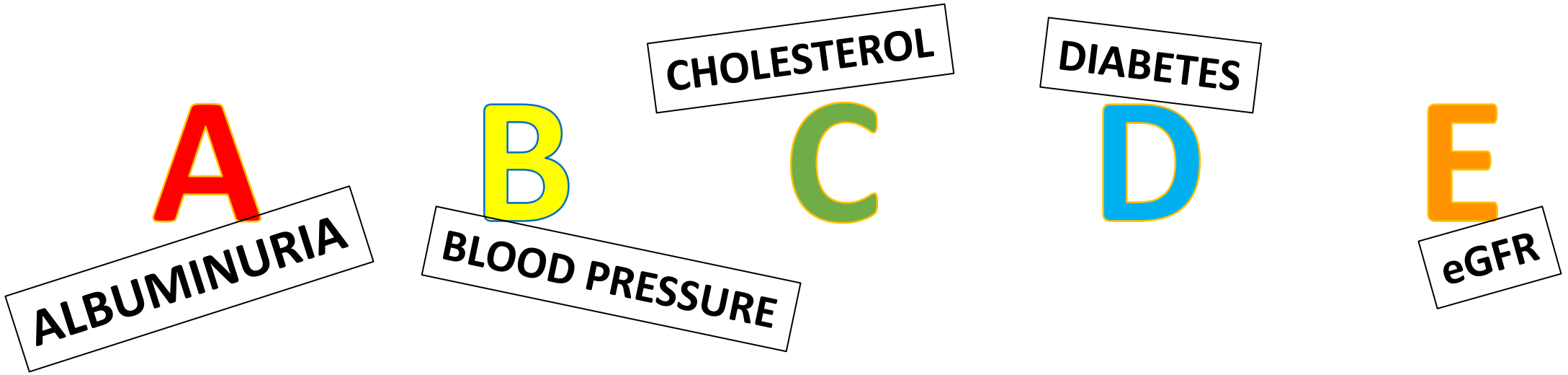
Study Completion (Estimated)
2025-09-30

Enrollment (Estimated)
108

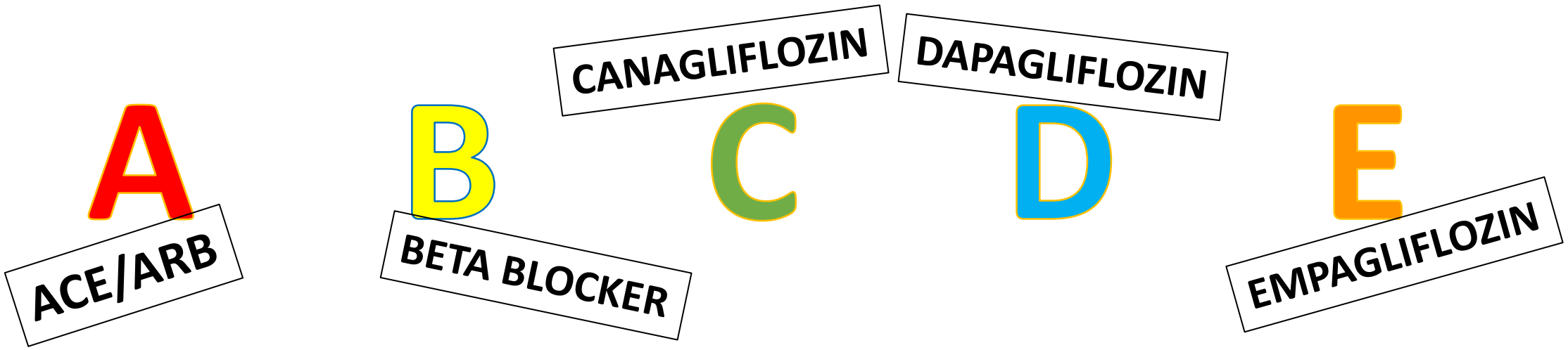
A truly remarkable journey

- In 2021, 4.4 papers on SGLT2 inhibitors were published per day
- *In less than 8 years:*
  - **Fringe hypoglycemic agent in type 2 DM**
  - **Major player in cardiac protection and HF treatment**
  - **Major player in both diabetic and non-diabetic CKD protection**
  - **Future uses…**

Screening and Monitoring CAD and CKD



Treatment of CAD and CKD



Take Home Points

- SGLT2 inhibitors along with a conventional ACE inhibitor or an ARB, are now guideline recommended therapies for CKD in type 2 diabetes.
- SGLT2 inhibitors should be implemented across a wide spectrum of patients with CKD (+/- DM2) and CAD
- CKD risk assessment and monitoring by both eGFR and albuminuria is necessary for delivering guideline-directed medical therapies.

THANK YOU!

GO FORTH,
AND BECOME A…

Are you a #Flozinator?