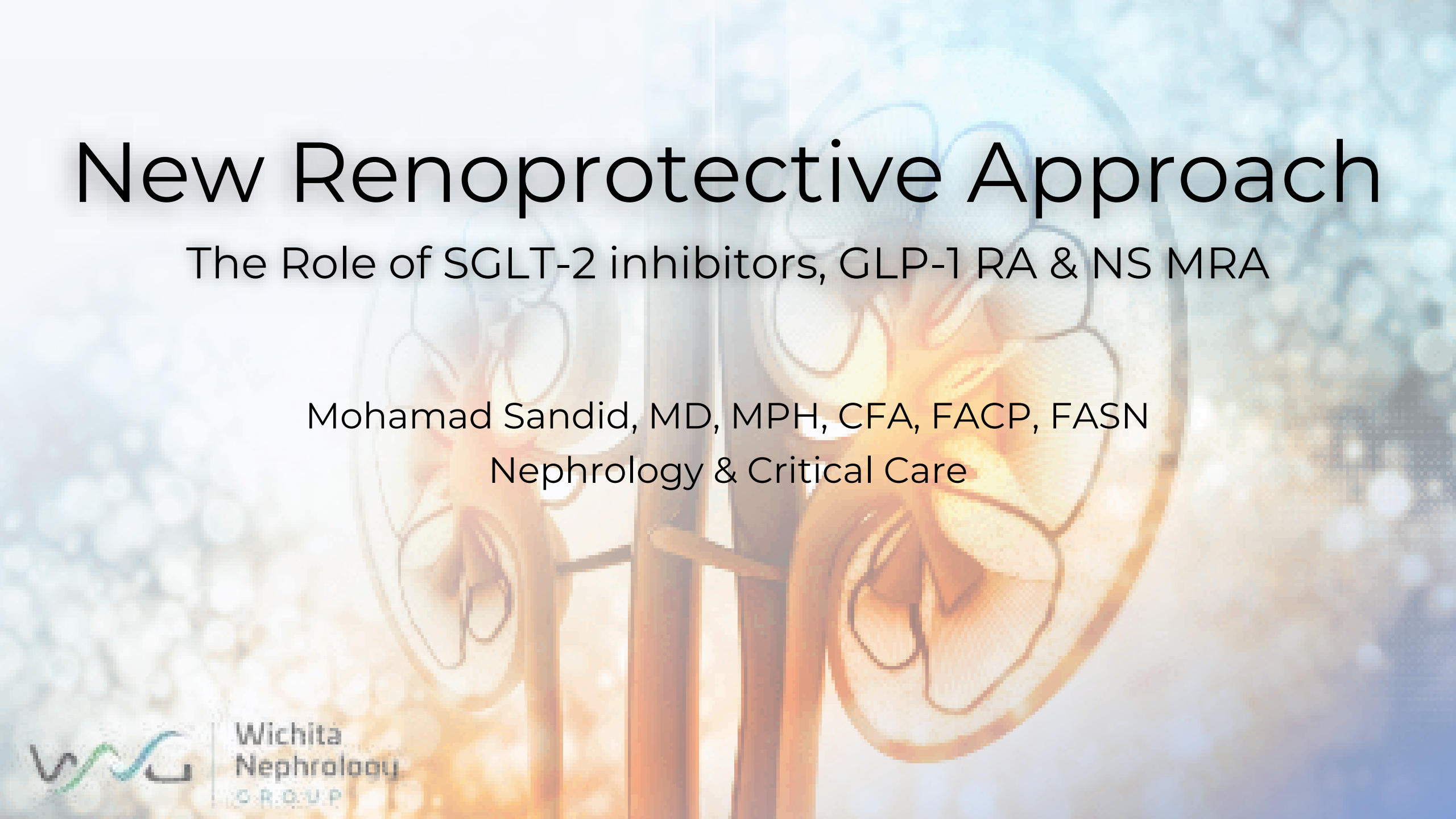
New Renoprotective Approach

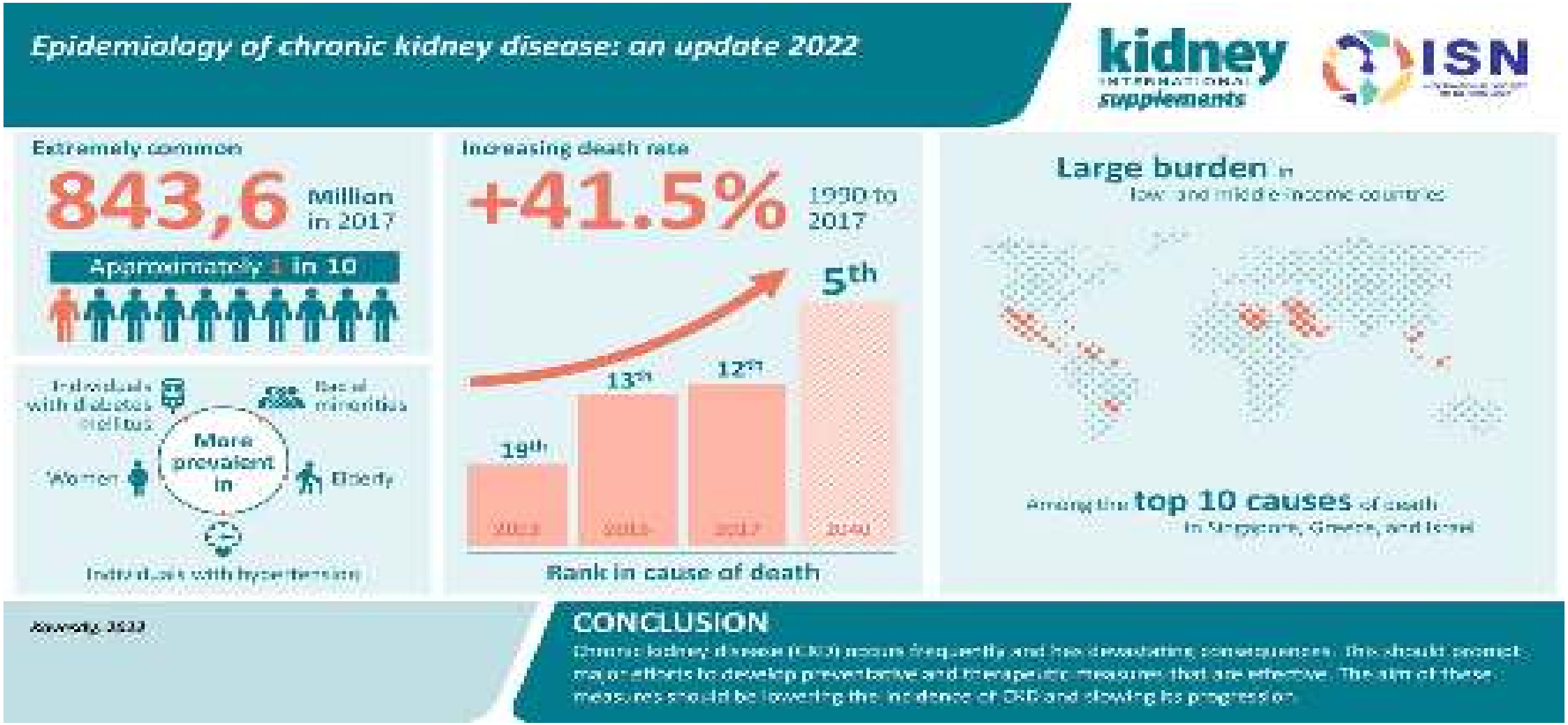
The Role of SGLT-2 inhibitors, GLP-1 RA & NS MRA

Mohamad Sandid, MD, MPH, CFA, FACP, FASN
Nephrology & Critical Care

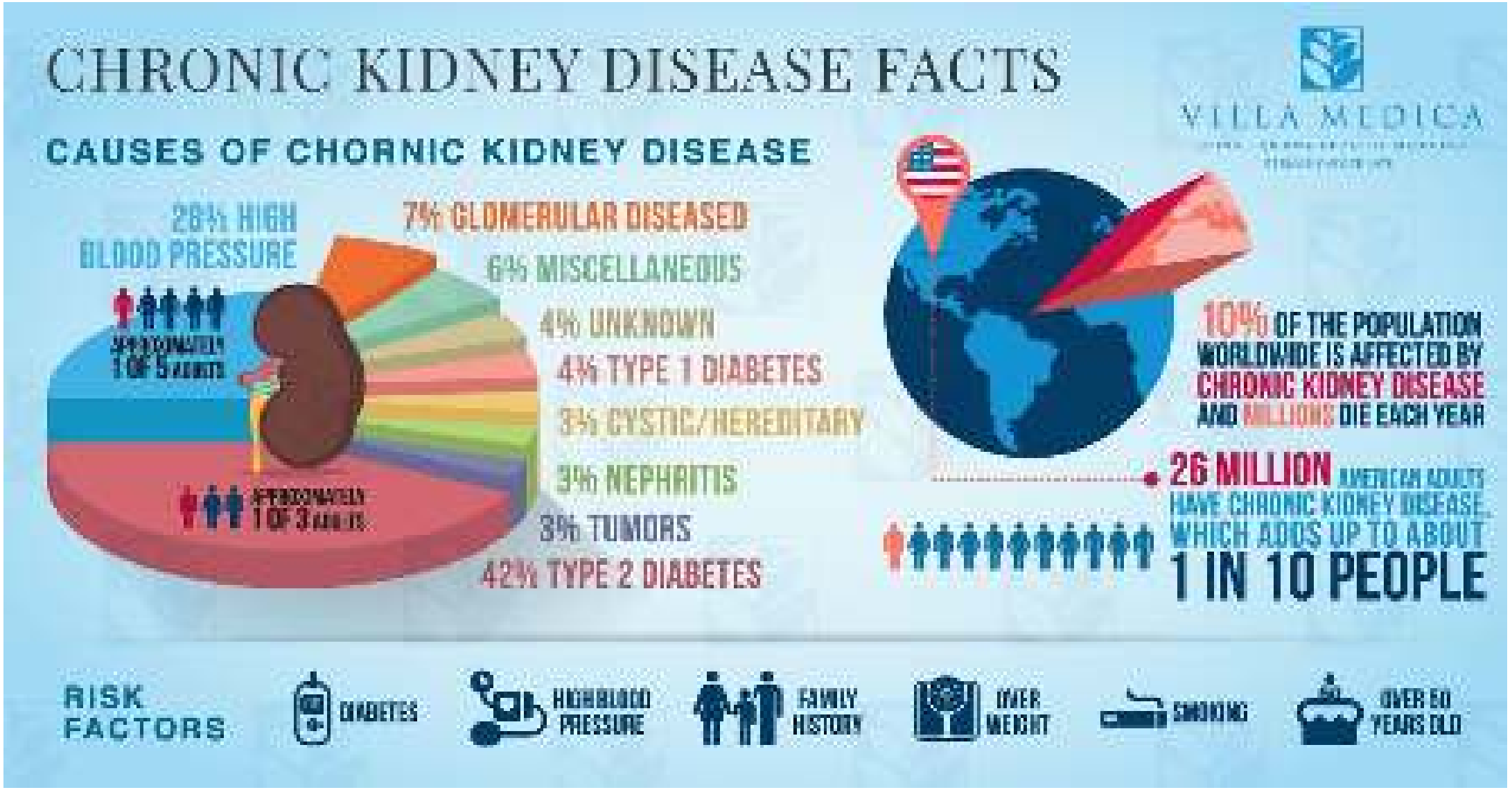


Wichita Nephrology GROUP

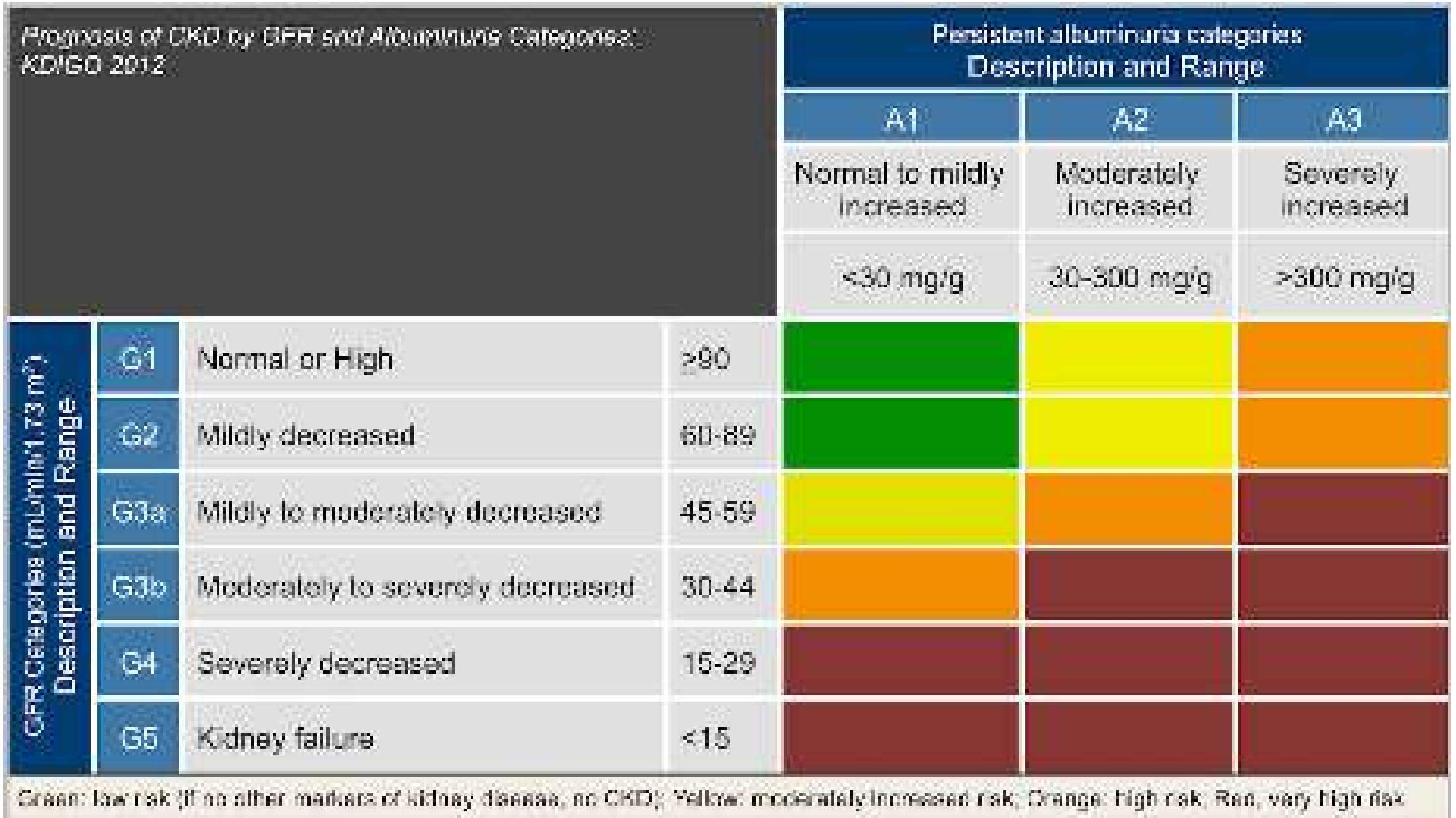
Burden of CKD



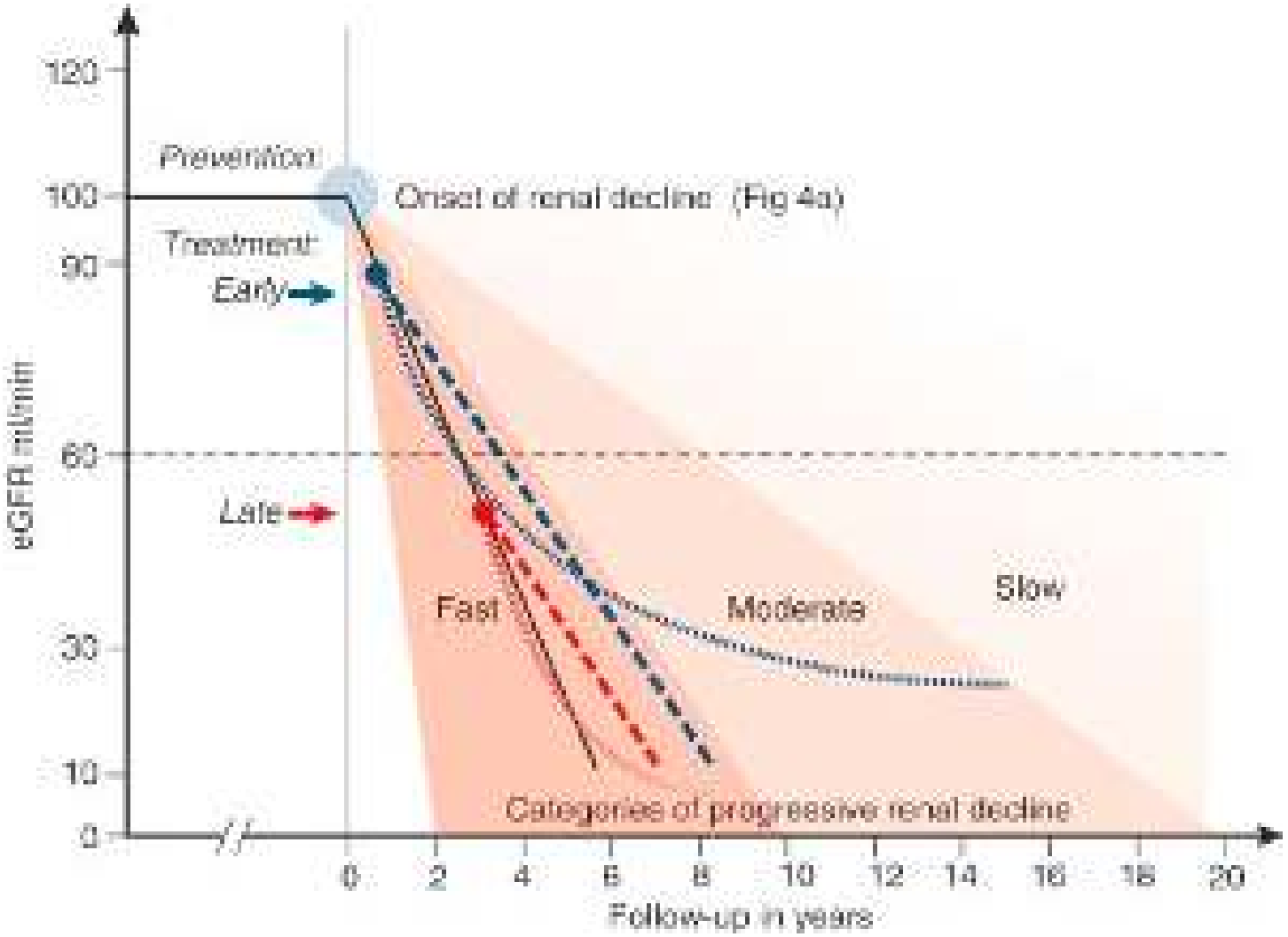
Caused of CKD

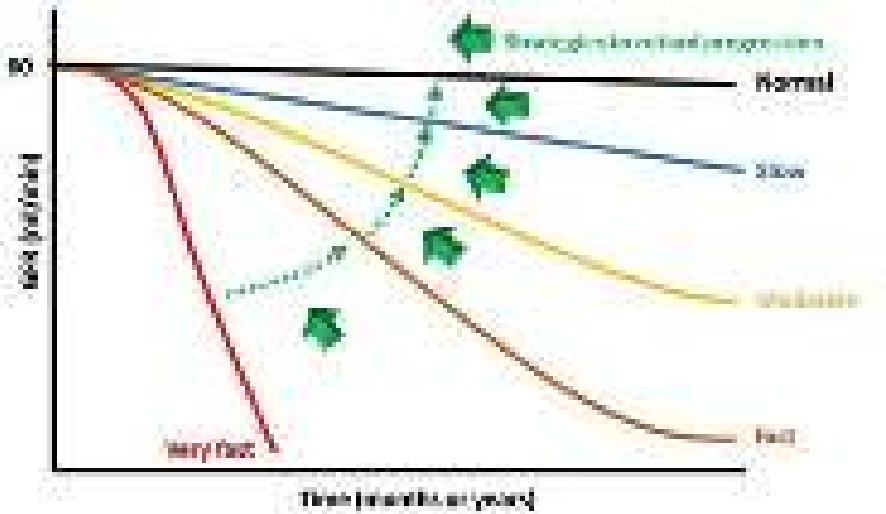


KDIGO Classification

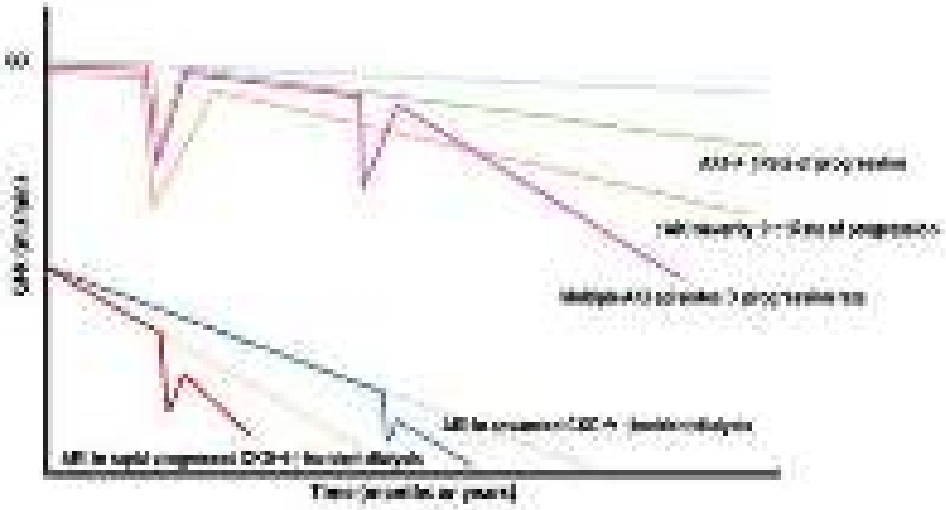


Goal of treatment



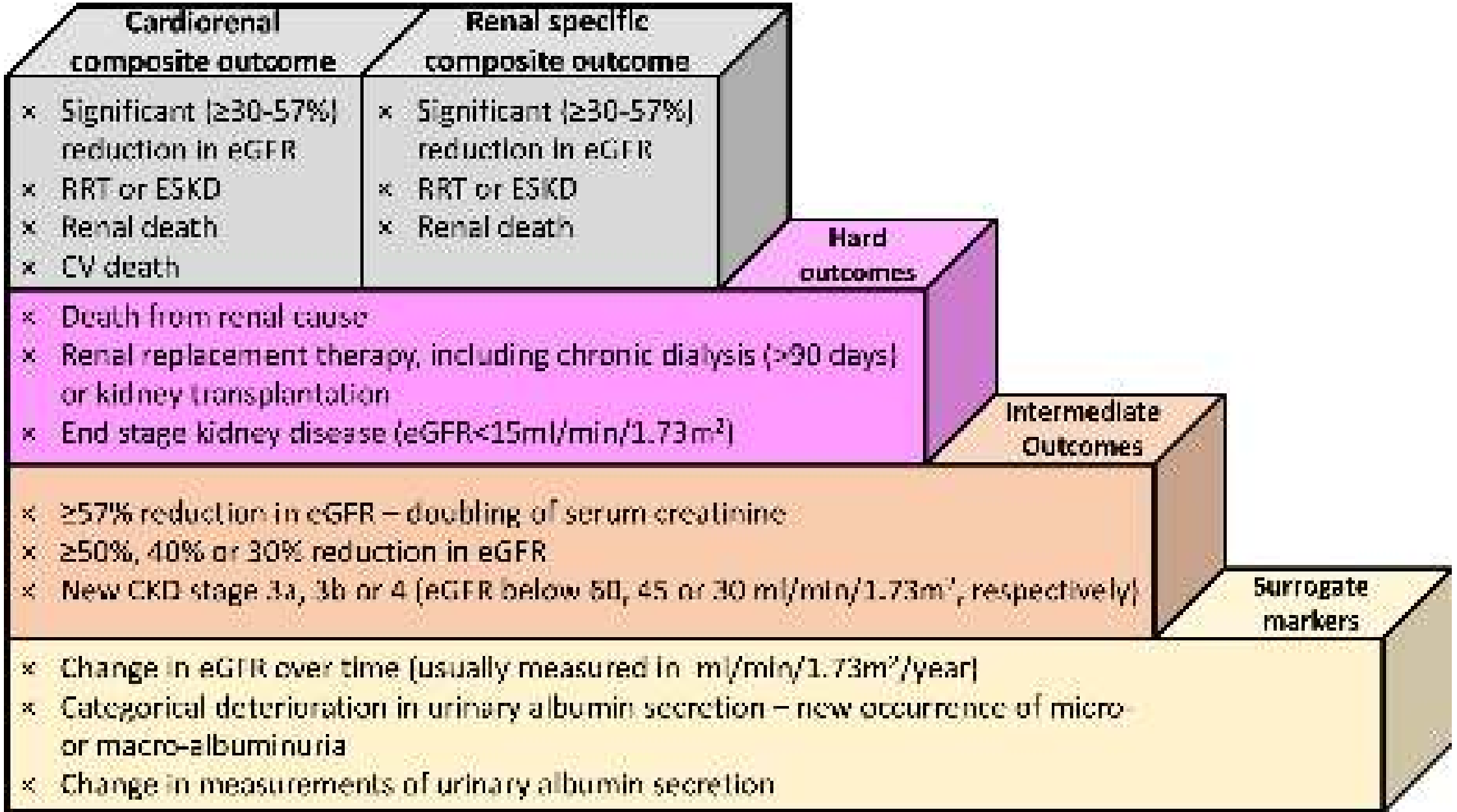


(A)

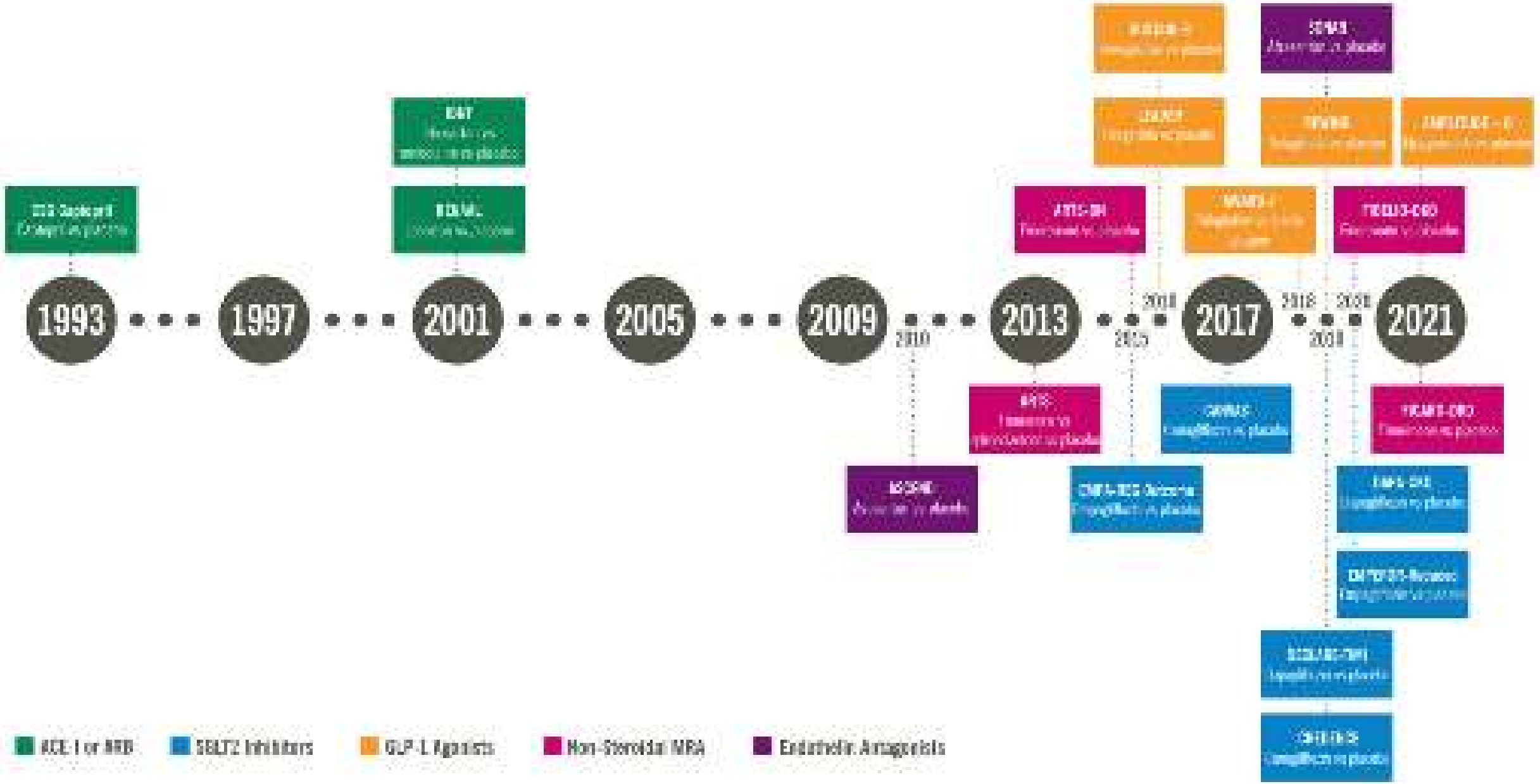


(B)

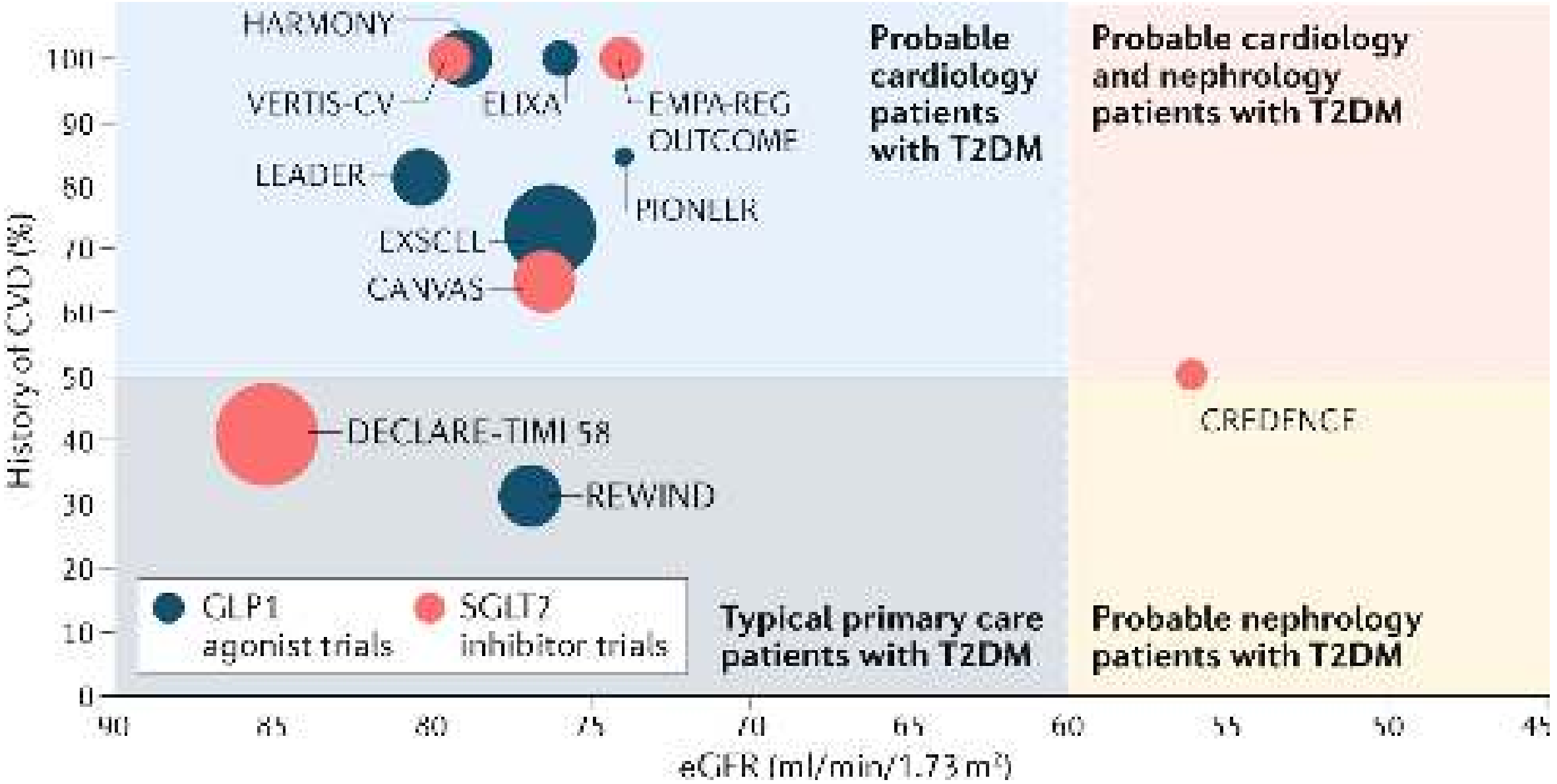
Definition of Outcomes



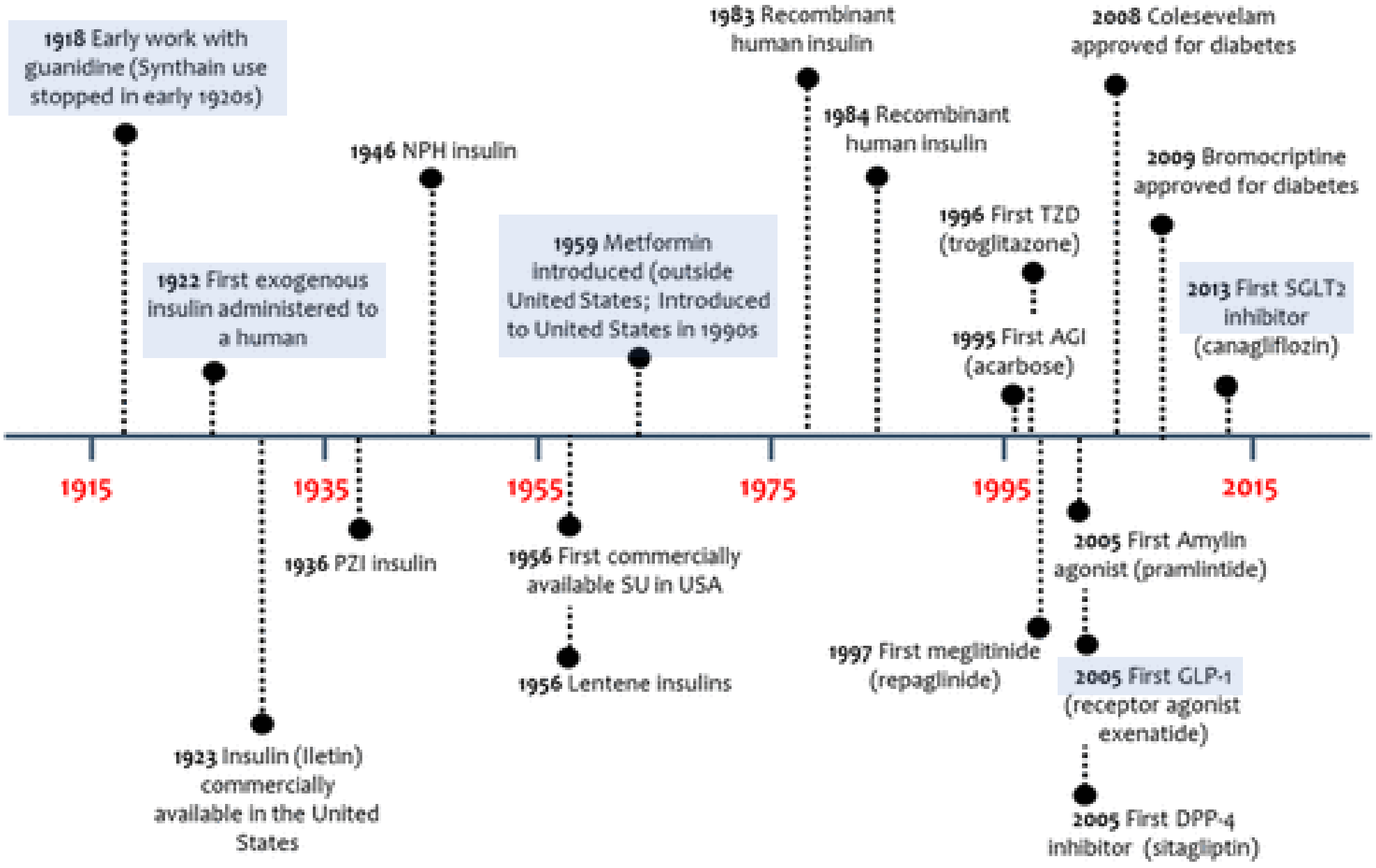
Plethora of studies



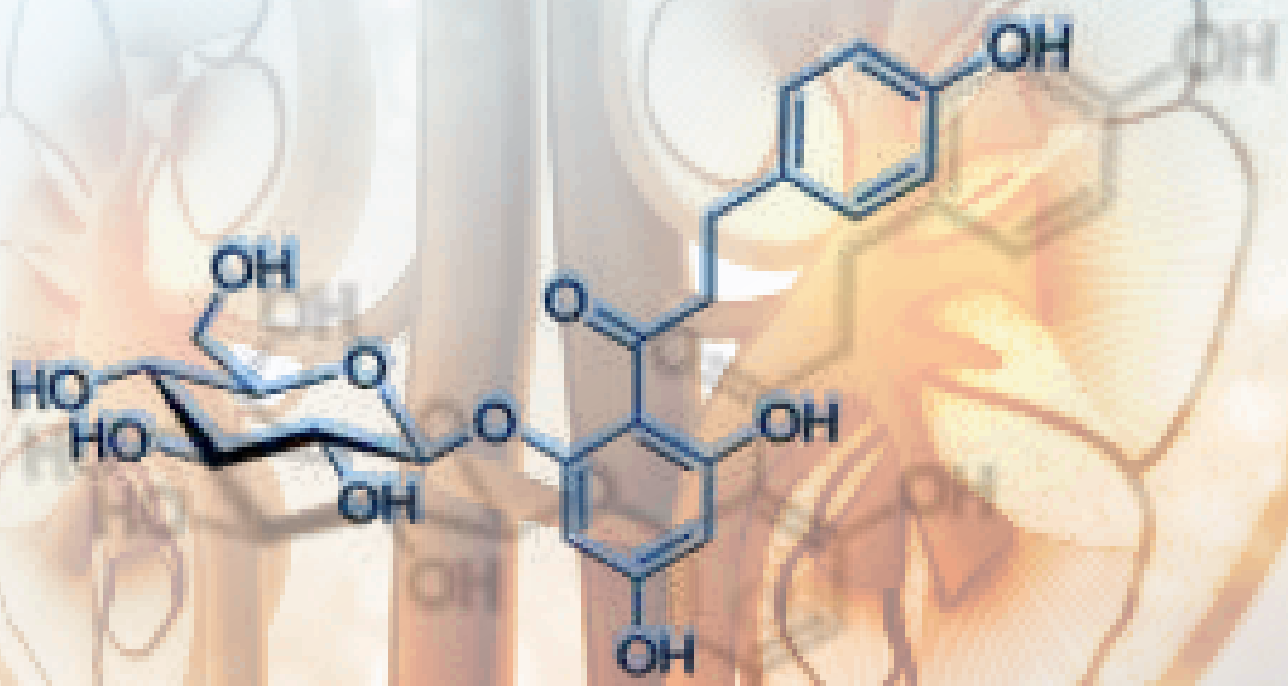
CKD vs CVD


HARMONY
VERTIS-CV
ELIXA
EMPA-REG OUTCOME
LEADER
PIONEER
EXSCEL
CANVAS
DECLARE-TIMI 58
REWIND
CREDENCE
Probable cardiology patients with T2DM
Probable cardiology and nephrology patients with T2DM
Typical primary care patients with T2DM
Probable nephrology patients with T2DM
GLP1 agonist trials
SGLT2 inhibitor trials
History of CVD (%)
100
90
80
70
60
50
40
30
20
10
0
90
85
80
75
70
65
60
55
50
45
eGFR (ml/min/1.73 m²)

Historic Invention



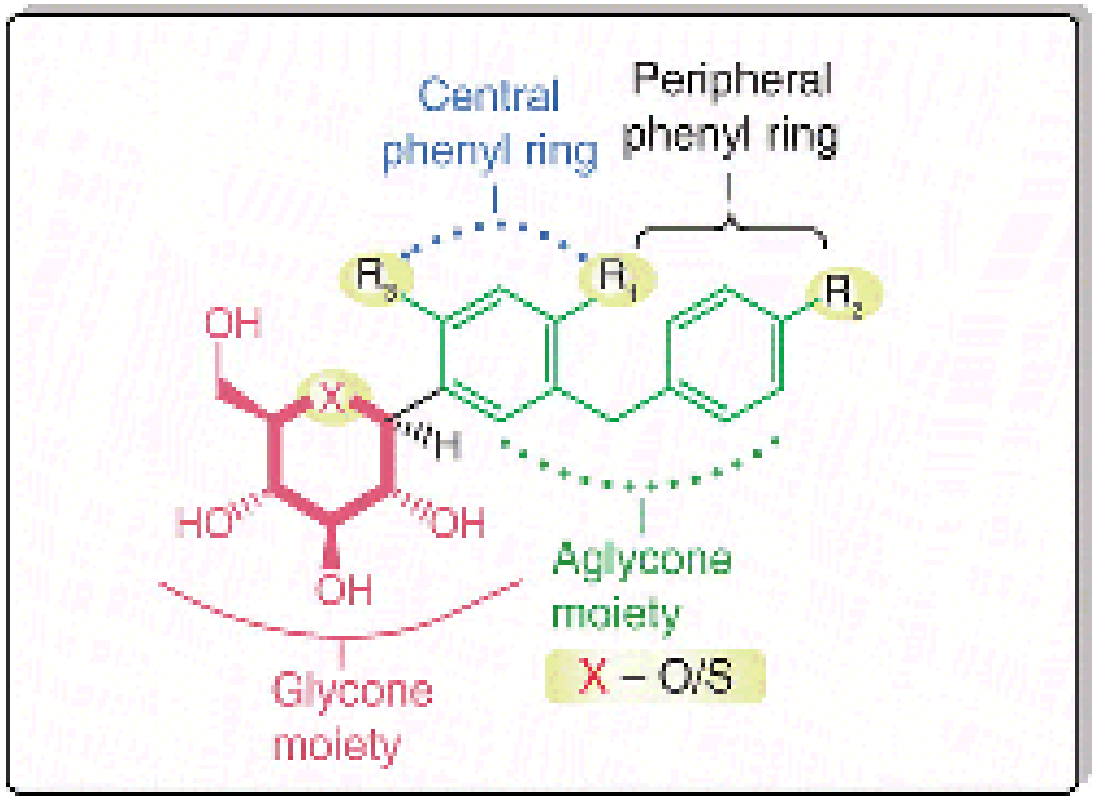
SGLT2 Inhibitors



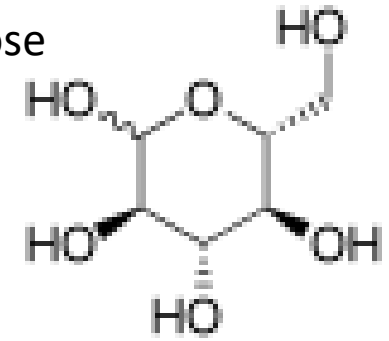
SGLT2 Inhibitors

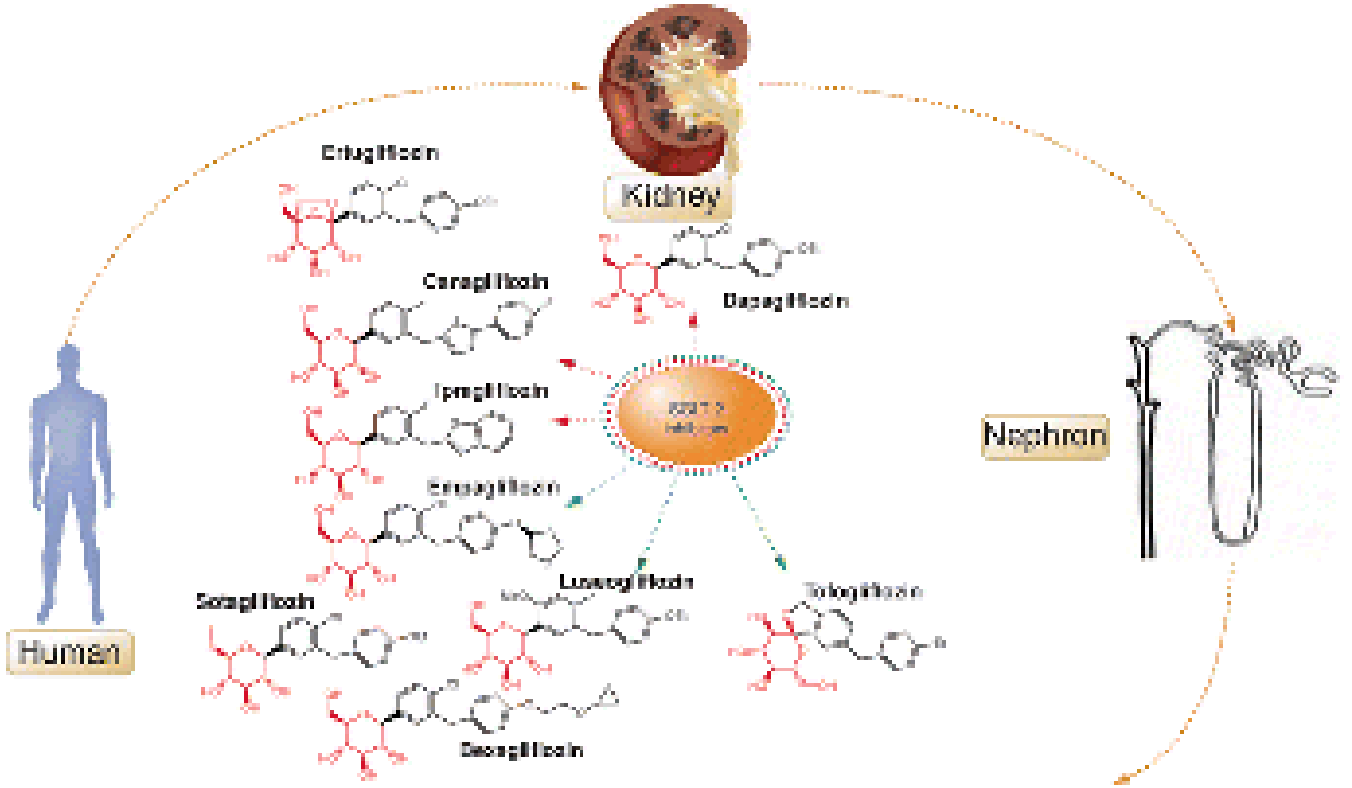
- Bexagliflozin (Brenzavvy)
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
- Sotagliflozin (Inpefa)

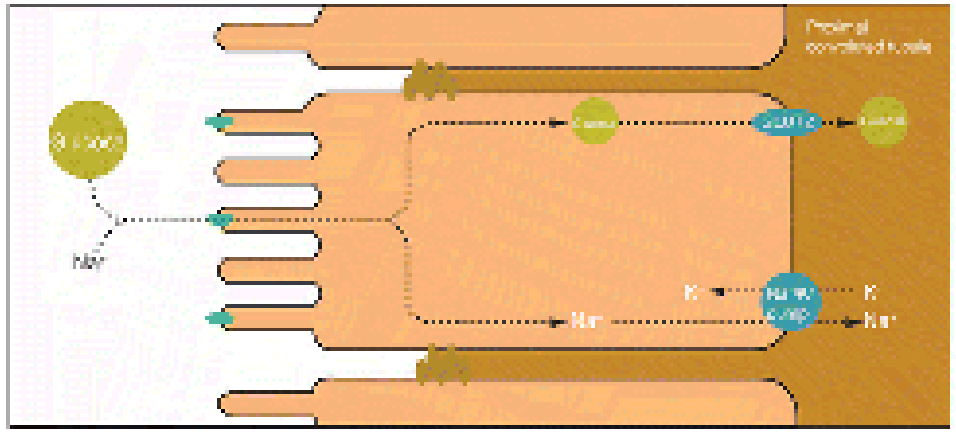
Gliflozin



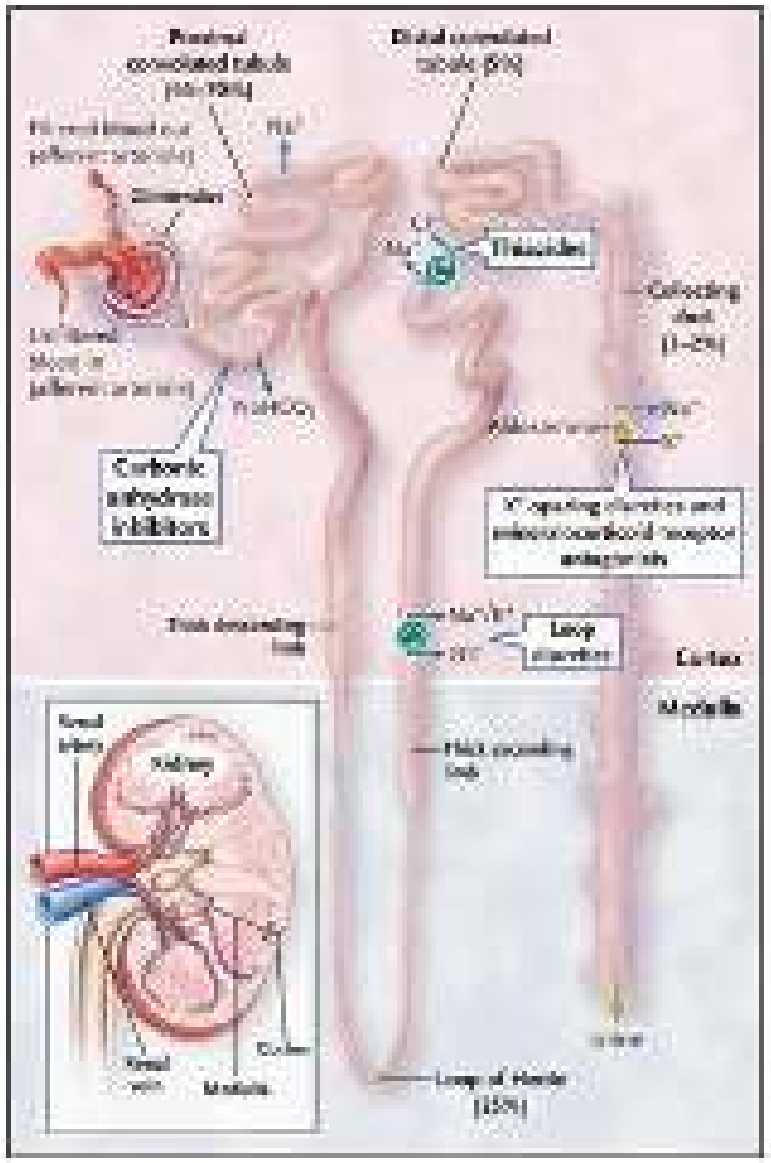
Glucose

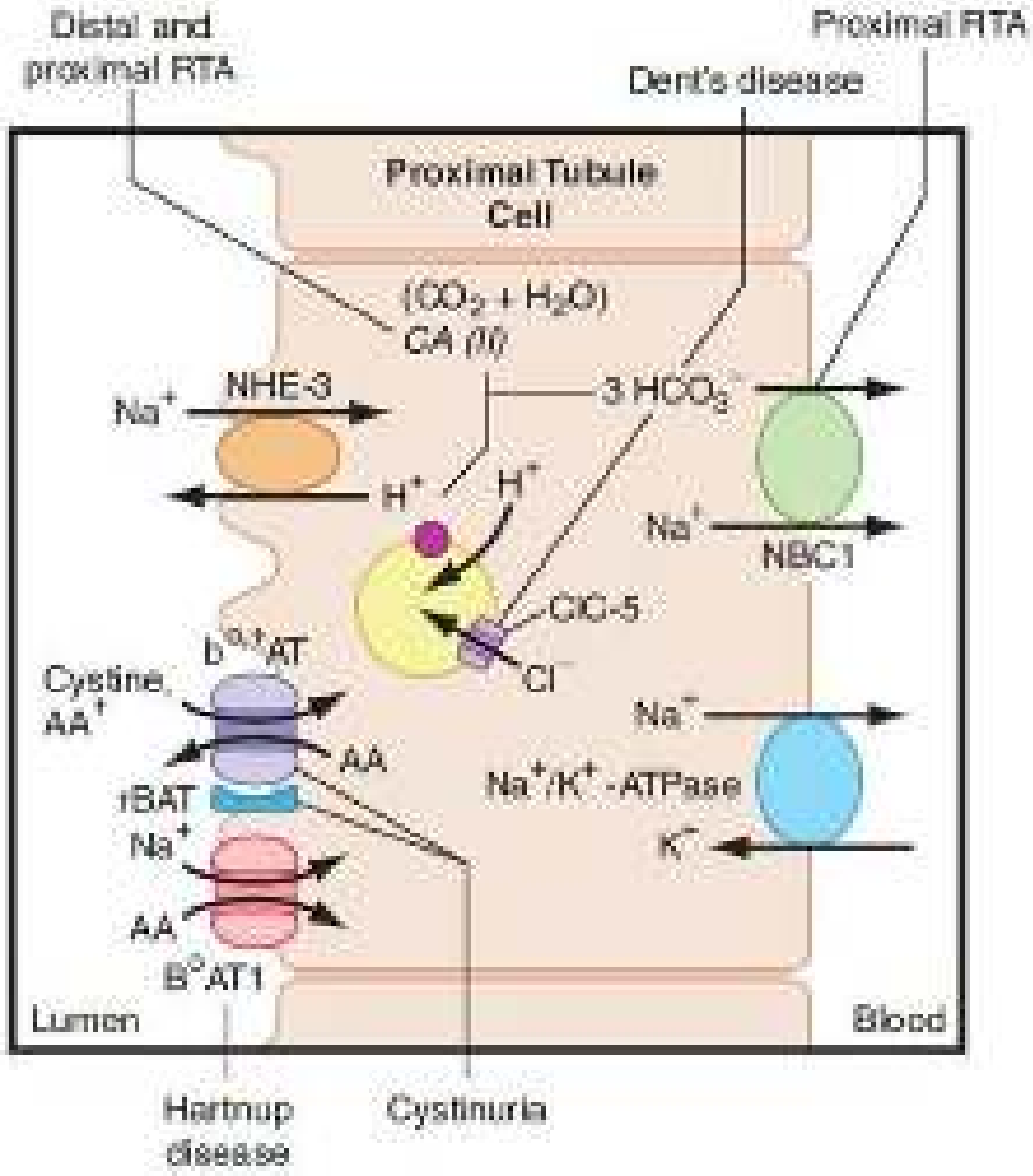




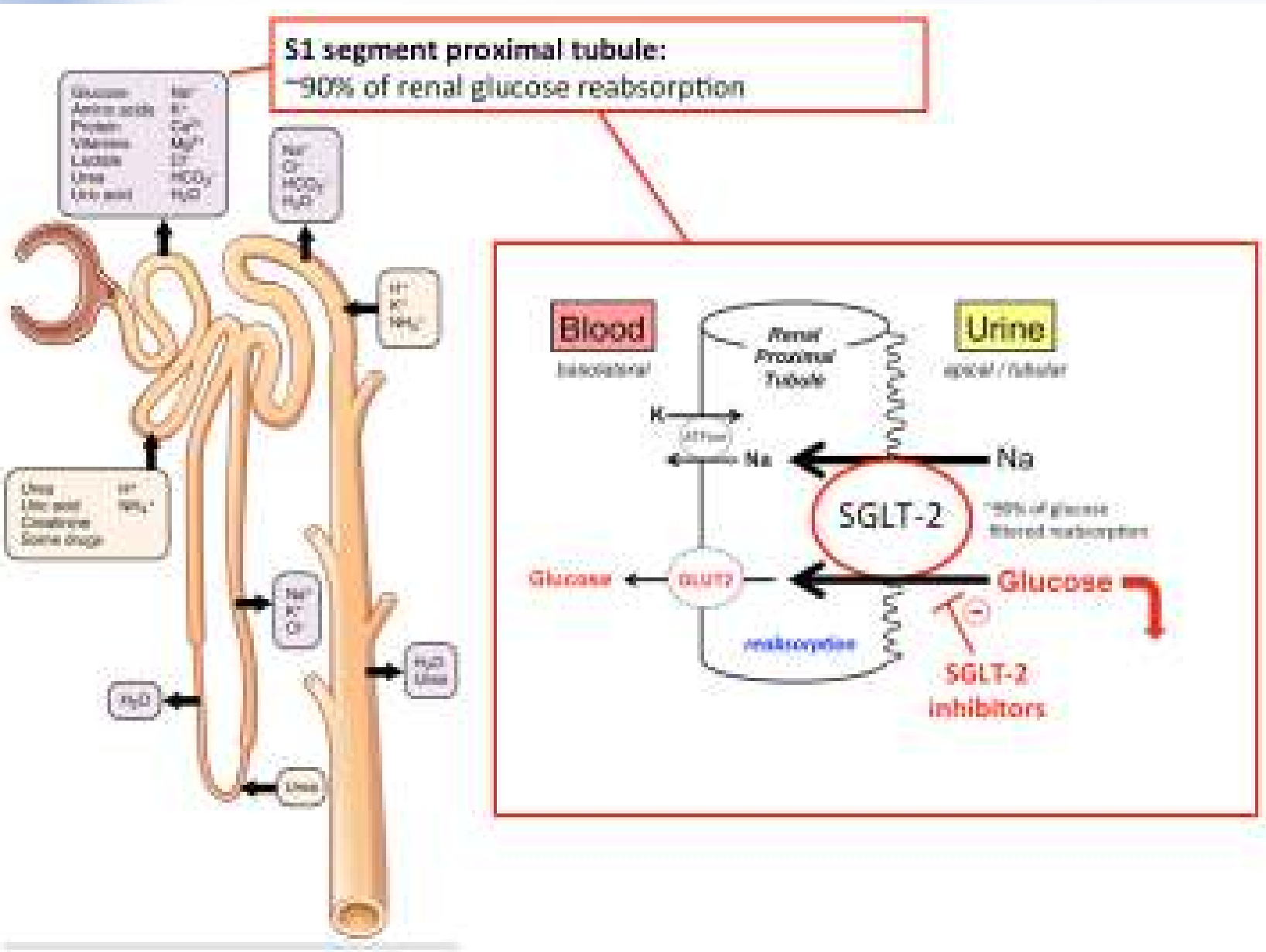


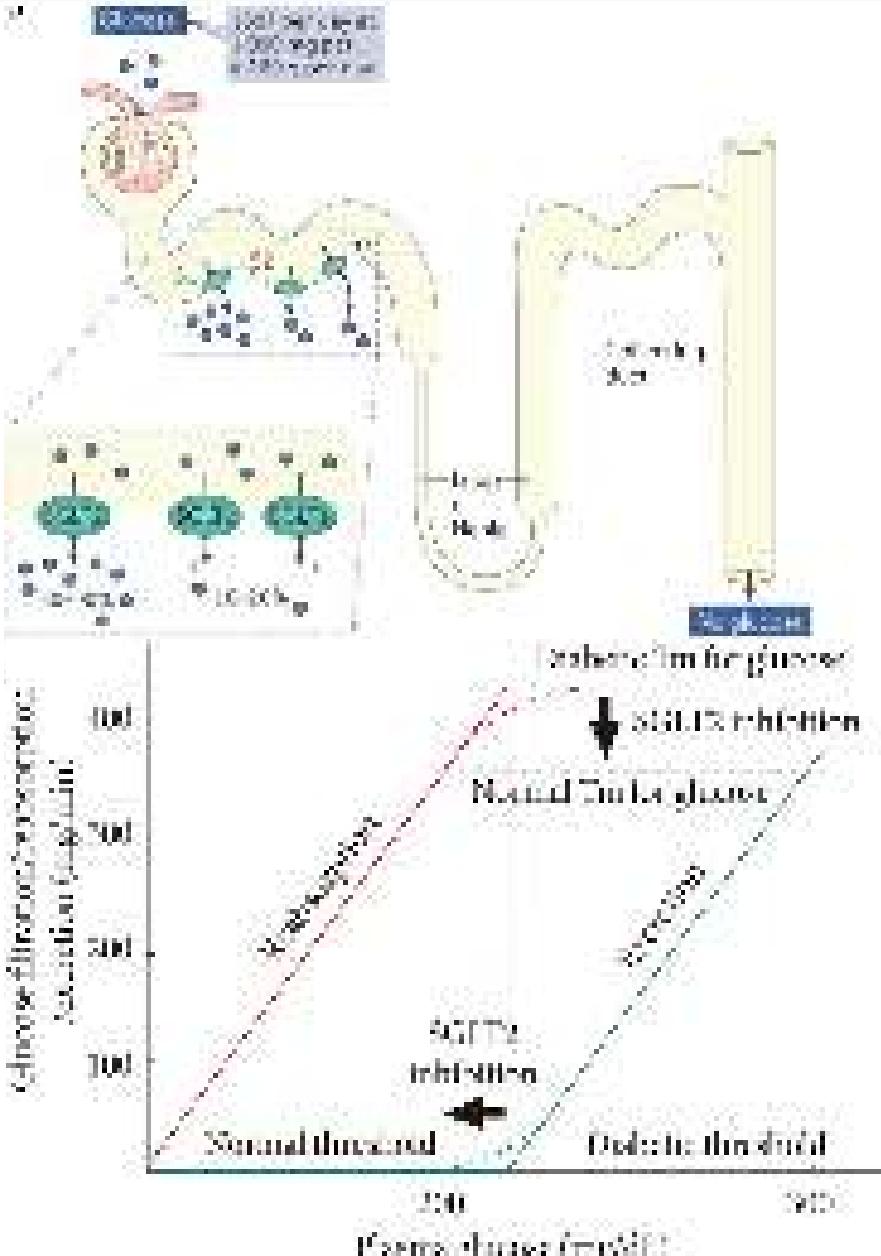
Diuretics mechanism of action





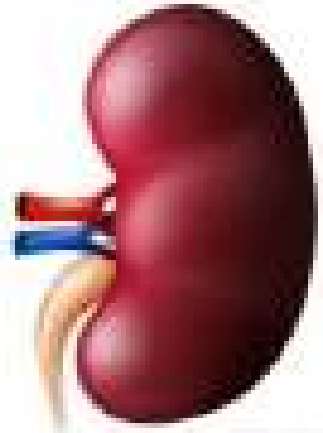
Mechanism of action



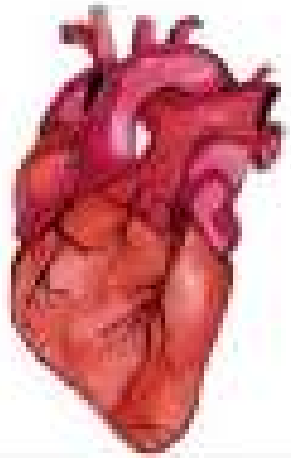


Systemic Effects

SGLT2 Inhibitors

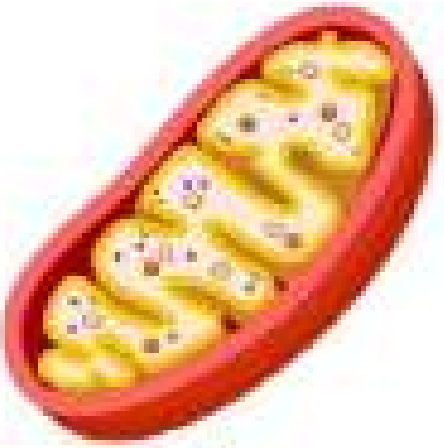


- Diuretic effect
- Glycosuria
- Nephroprotection
- Erythropoetin increase



- Decreased left ventricular mass
- Improved diastolic function

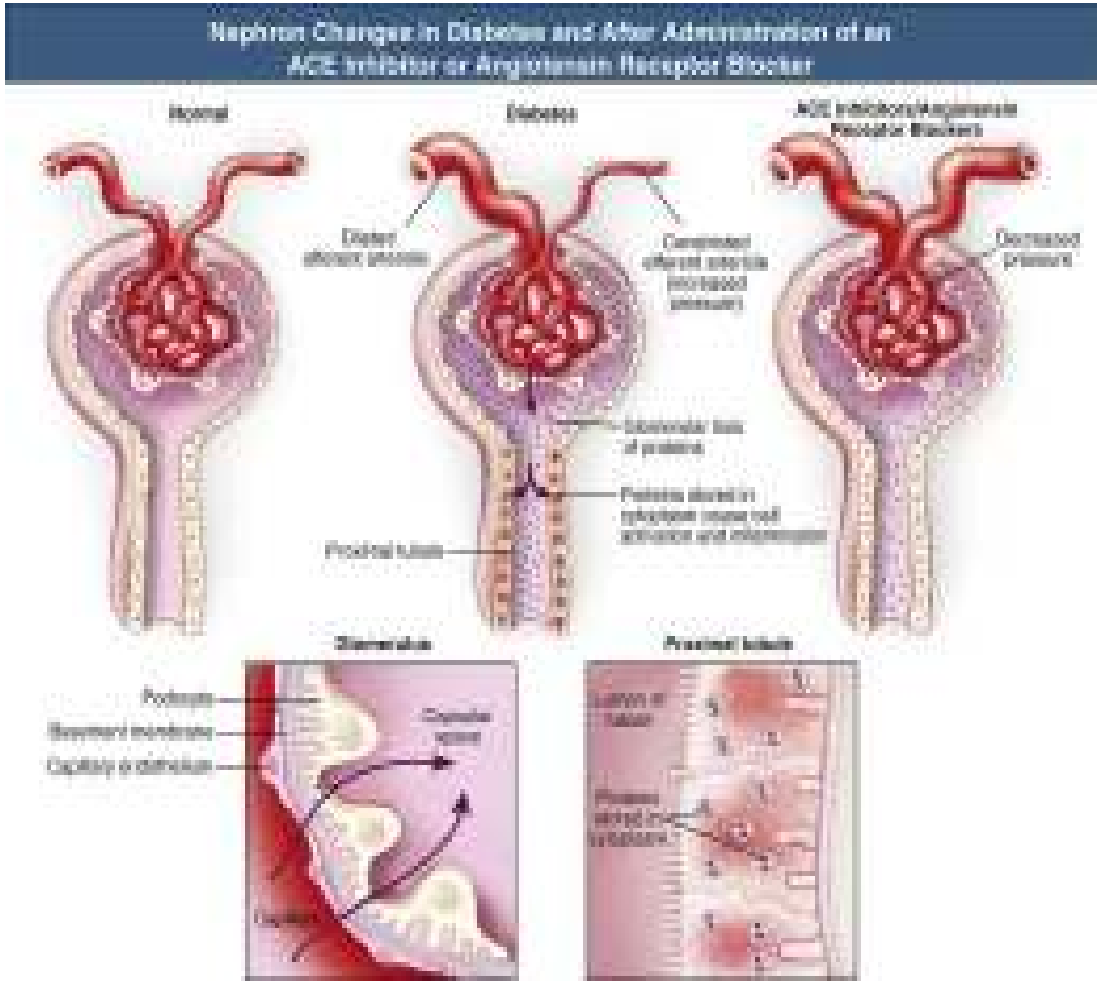
- Reduced vascular stiffness
- Improved endothelial function



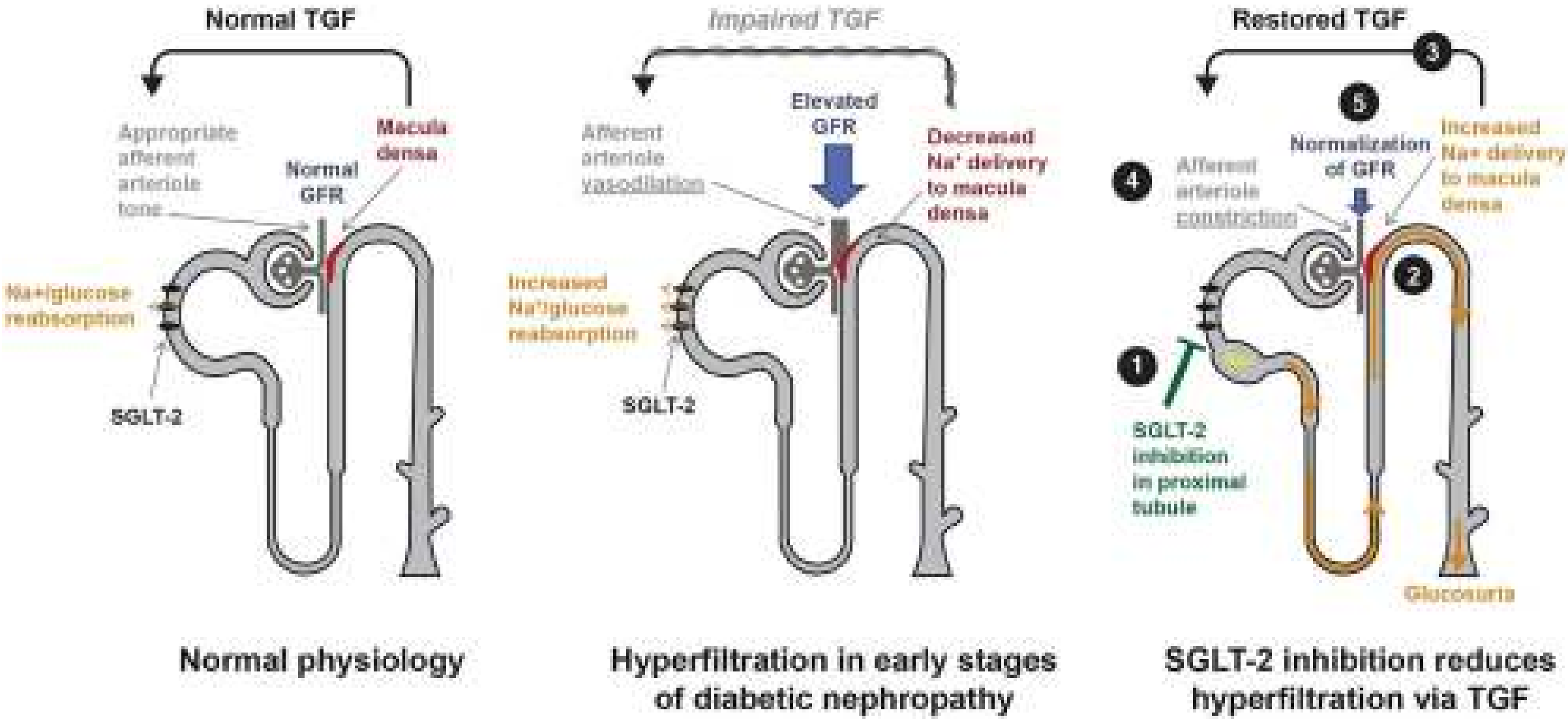
- Increased utilization of ketone bodies
- Improved energy processes

Diabetic kidney disease

- Increased tubular reabsorption of Na partly from SGLT2 upregulation
- Resulting in lowering of the [Na] at the macula densa
- Leading to decreased afferent arteriolar tone
- Eventually increased GFR
- Hyperfiltration eventually leads to fibrosis within the glomerulus and tubulointerstitium



Mechanism of renoprotection of SGLT-2

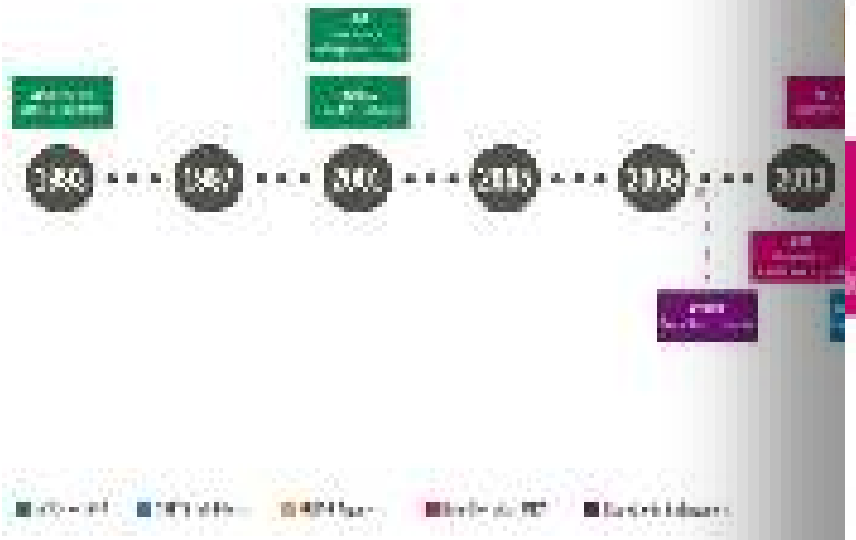


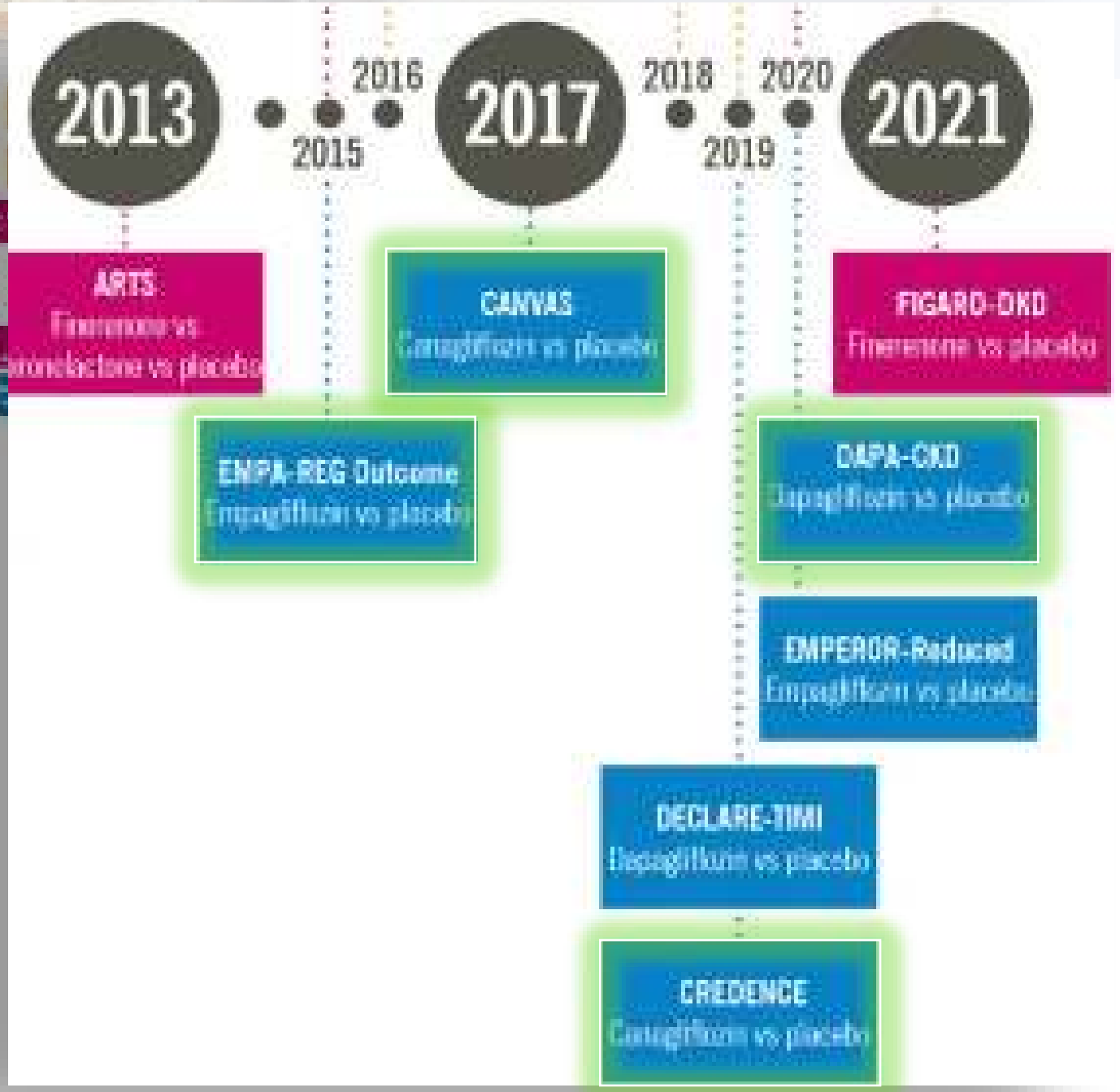
Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

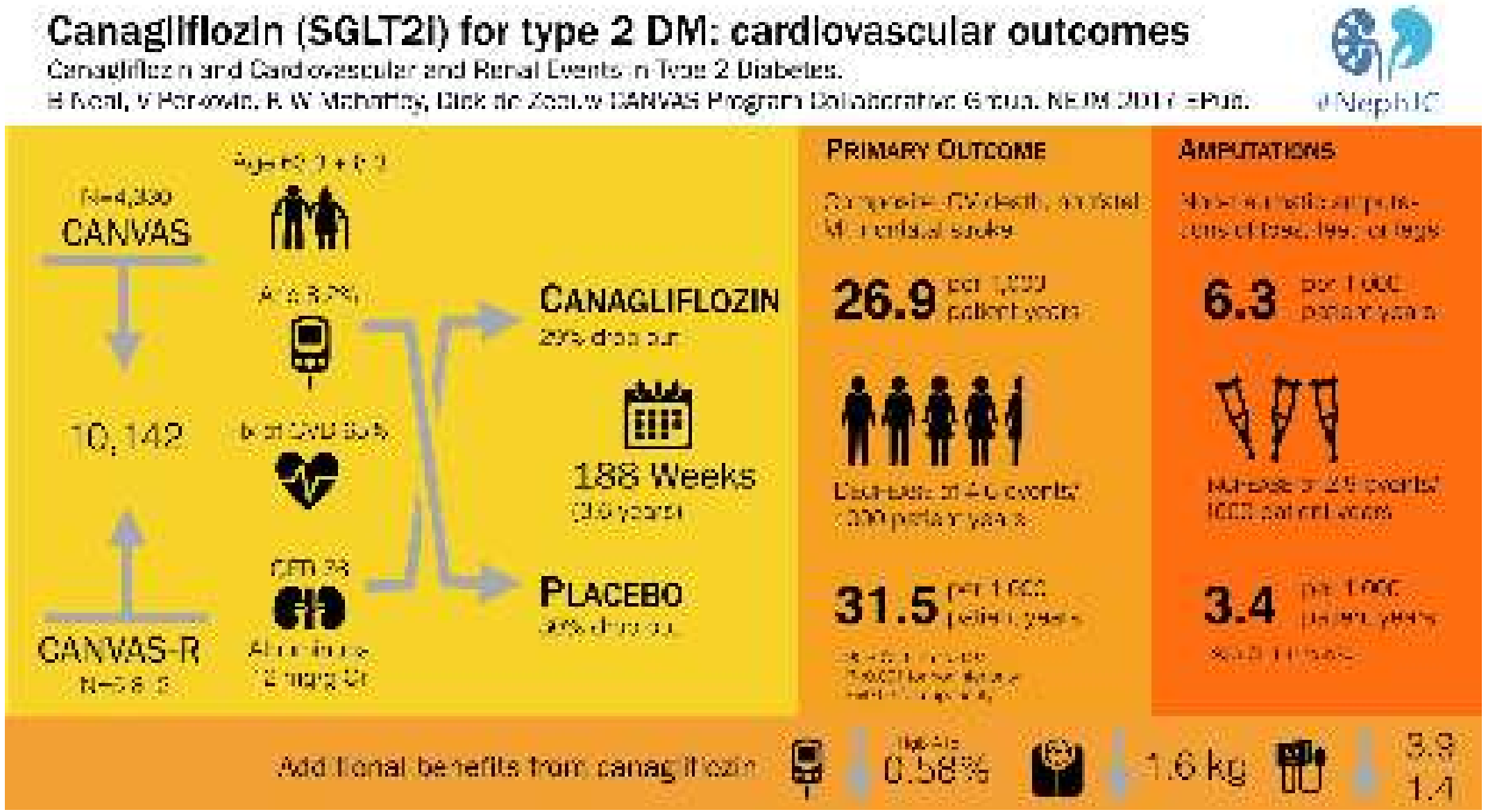
SGLT-2 inhibition reduces hyperfiltration via TGF

Outcome




2013
2015
2016
2017
2018
2019
2020
2021
ARTS
CANVAS
FIGARO-DKD
ENPA-REG Outcome
DAPA-CKD
EMPEROR-Reduced
DECLARE-TIMI
CREDENCE

CANVAS


Canagliflozin (SGLT2i) for type 2 DM: cardiovascular outcomes
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.
CANVAS
CANVAS-R
CANAGLIFLOZIN
PLACEBO
188 Weeks
PRIMARY OUTCOME
26.9
31.5
AMPUTATIONS
6.3
3.4
Additional benefits from canagliflozin
0.58%
1.6 kg

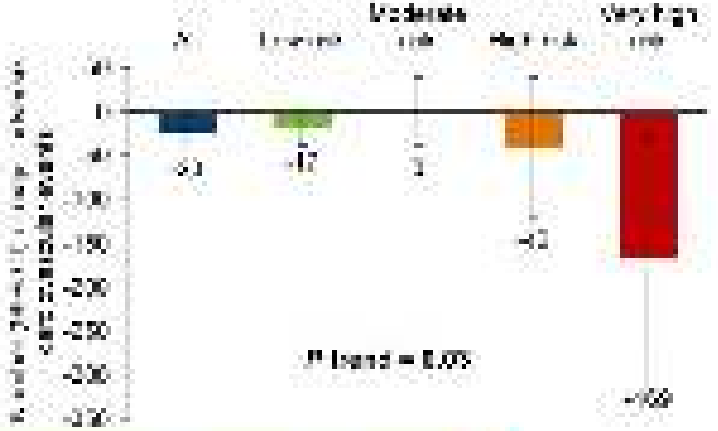
CANVAS

Risk Reductions in Cardiovascular and Kidney Outcomes With Canagliflozin Across KDIGO Risk Categories

Design	Population	Results
CANVAS Program Double-blind, placebo-controlled randomized trial	10,142 people with T2DM and eGFR ≥ 30 mL/min/1.73 m² at high cardiovascular risk	Major adverse cardiovascular events prevented per 1,000 patients treated over 5 years

667 centers
30 countries

KDIGO Risk Classification

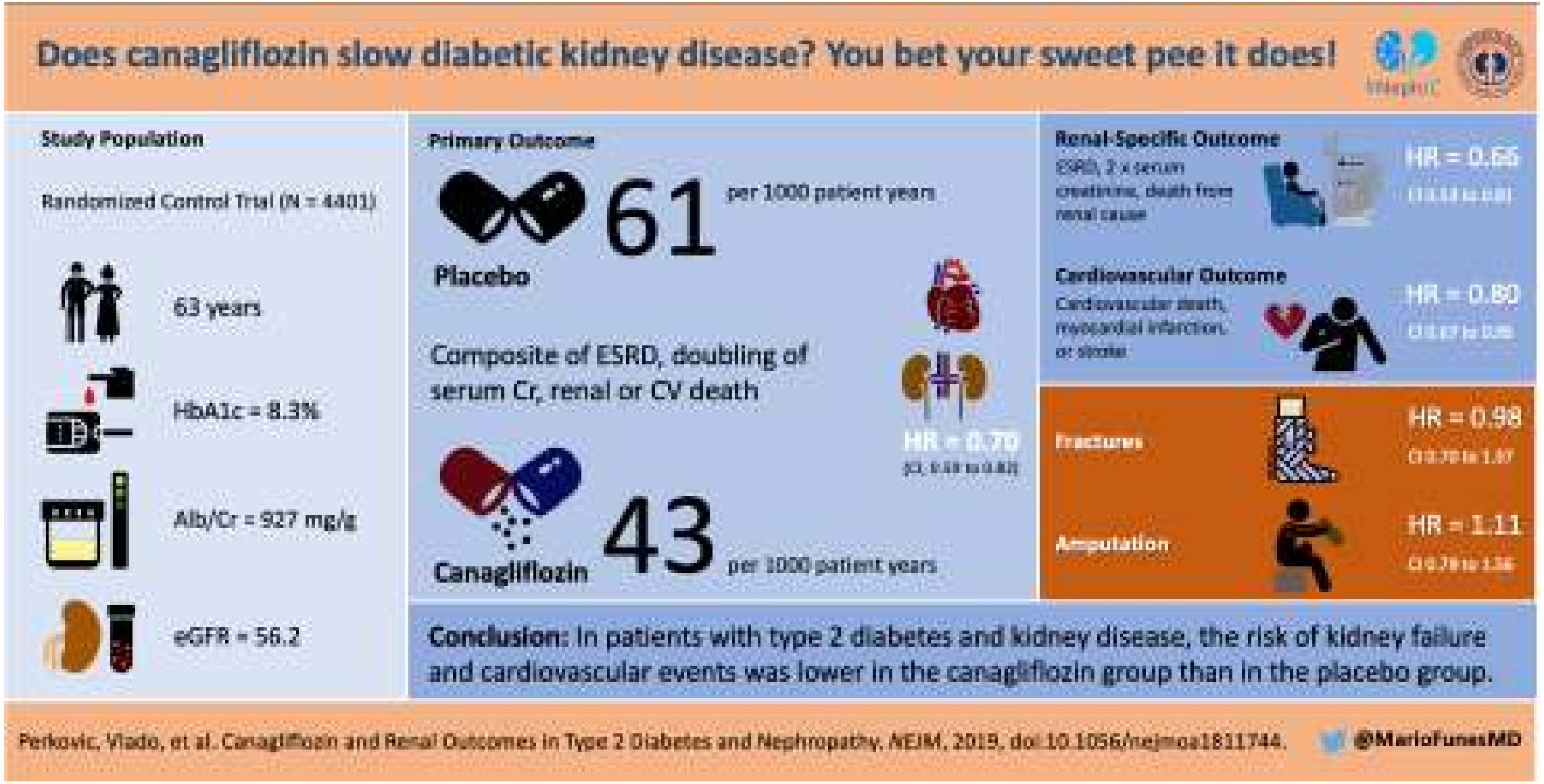


CONCLUSION: Absolute risk reductions for cardiovascular disease with canagliflozin are likely greater for individuals at higher KDIGO risk.

Brendon L. Neuen, Vlasios Chatzis, Bruce Neal et al. (2020)
AJKDonline | DOI: 10.1053/j.ajkd.2020.06.013

AJKD

CREDENCE

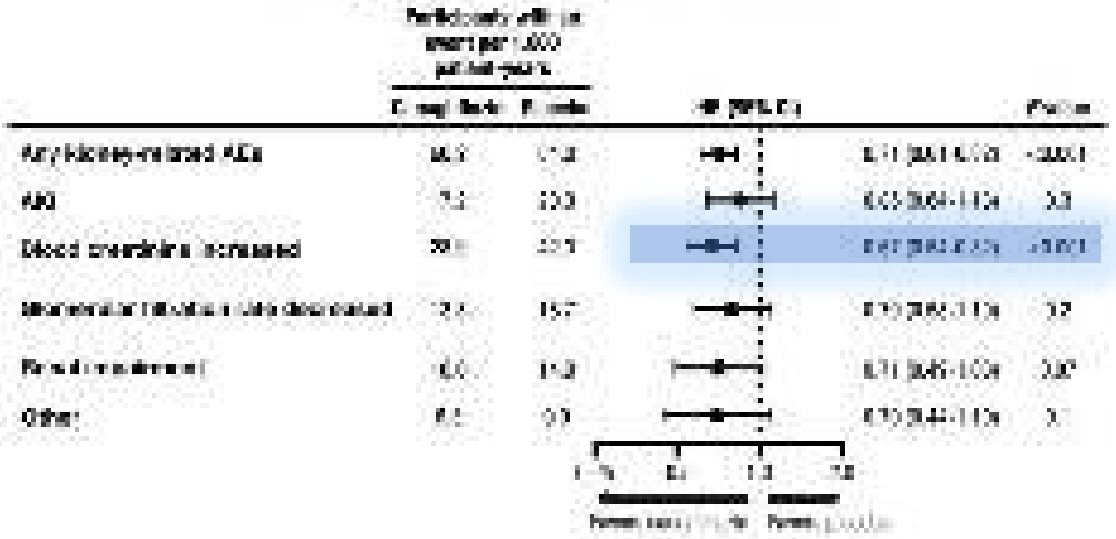

Does canagliflozin slow diabetic kidney disease? You bet your sweet pee it does!
Study Population
Randomized Control Trial (N = 4401)
63 years
HbA1c = 8.3%
Alb/Cr = 927 mg/g
eGFR = 56.2
Primary Outcome
61
per 1000 patient years
Placebo
Composite of ESRD, doubling of serum Cr, renal or CV death
HR = 0.70
Canagliflozin
43
per 1000 patient years
Renal-Specific Outcome
HR = 0.65
Cardiovascular Outcome
HR = 0.80
Fractures
HR = 0.98
Amputation
HR = 1.11
Conclusion: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group.
Perkovic, Vlado, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. NEJM. 2019. doi:10.1056/nejmoa1811744.
@MarioFunesMD

CREDENCE

Canagliflozin and Kidney-Related Adverse Events in Type 2 Diabetes and CKD: Findings From the Randomized CREDENCE Trial

Design	Population	Results
CREDENCE Multicenter, double-blind, placebo-controlled, randomized trial	4,401 people with type 2 diabetes, CKD, and UACR >300-5,000 mg/g	Canagliflozin reduces the risk of kidney-related adverse events

690 centers
34 countries

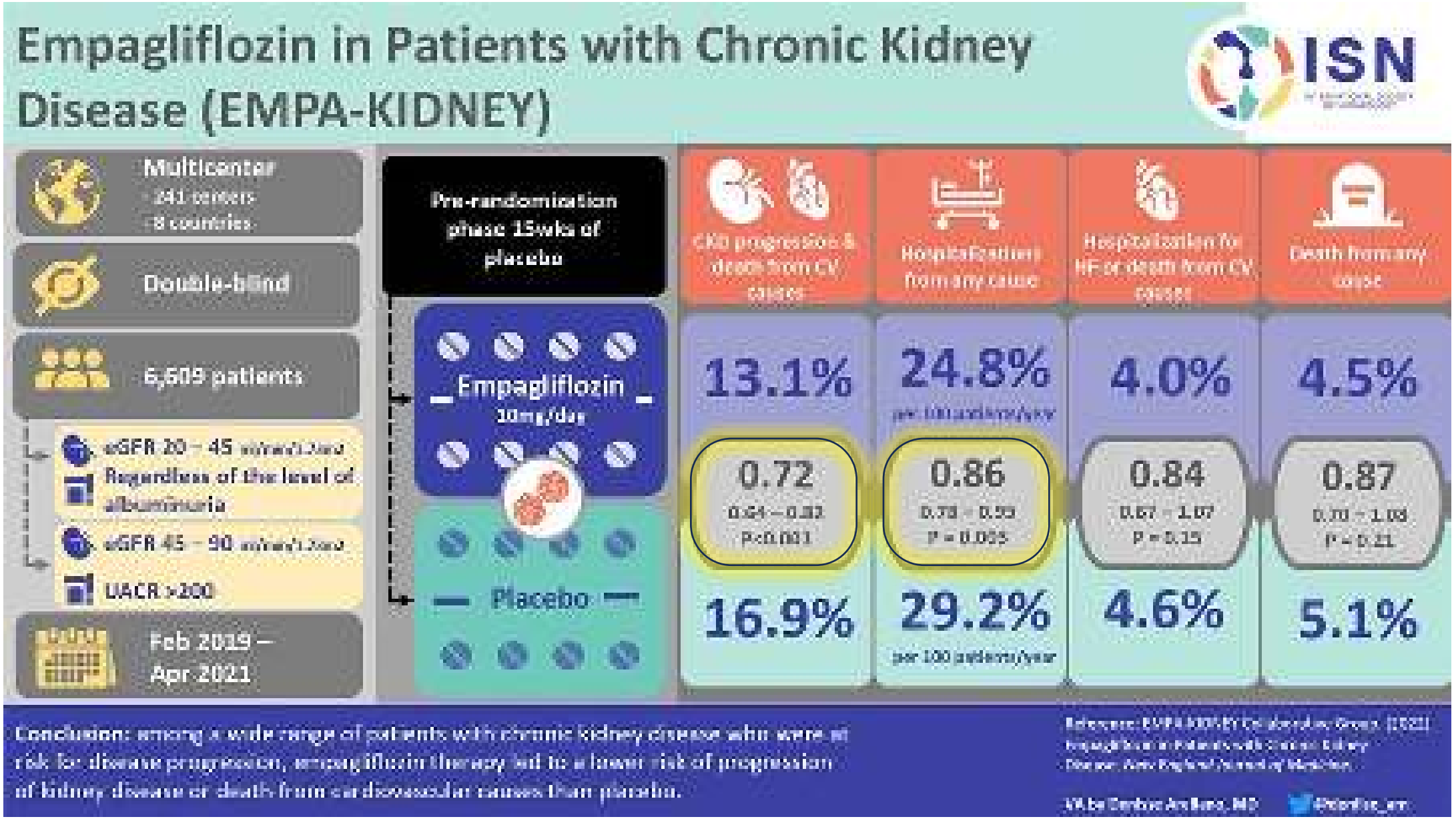


CONCLUSION: Canagliflozin decreased the incidence of kidney-related adverse events, highlighting the renal safety of canagliflozin in patients with type 2 diabetes and CKD.

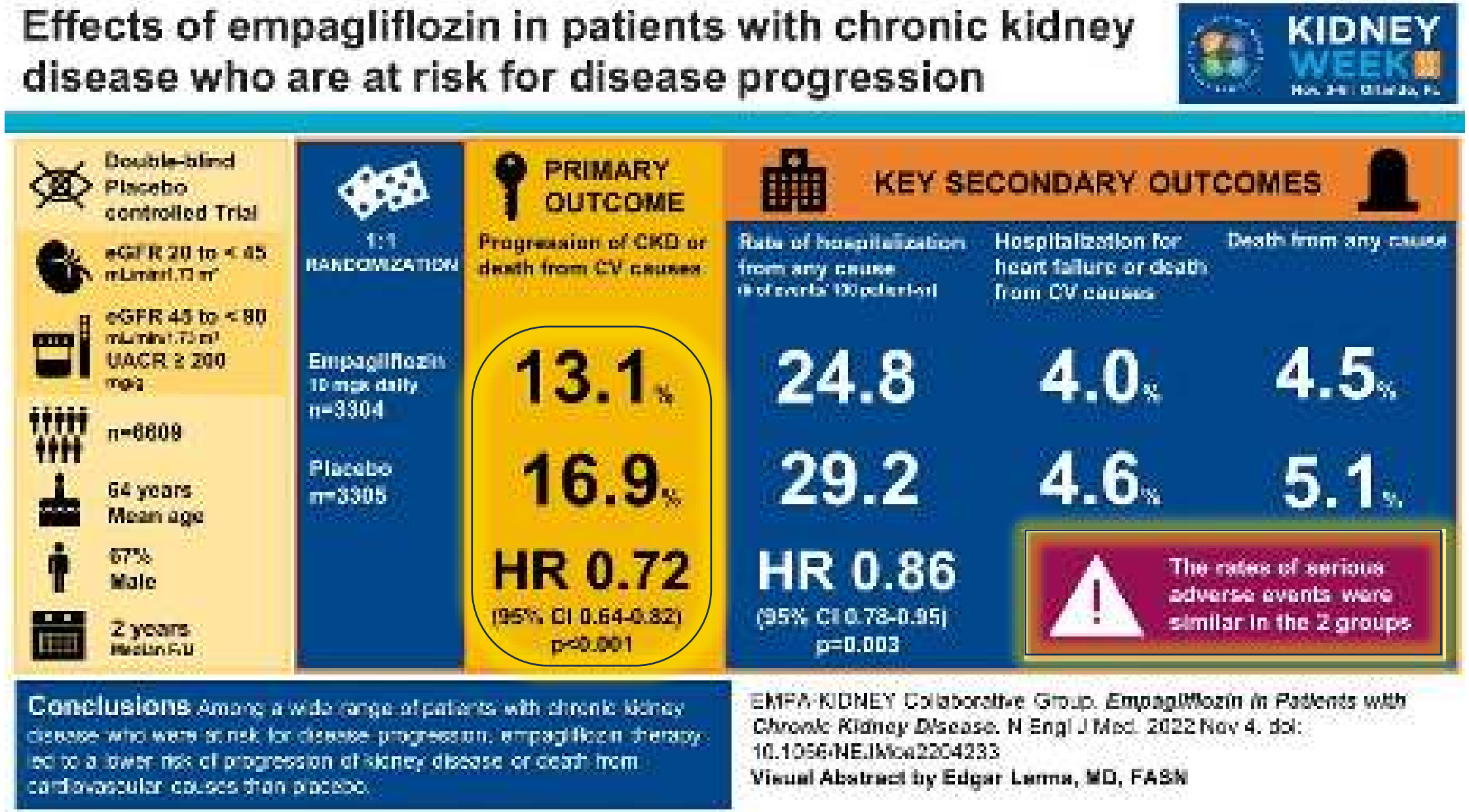
Hiddo JL Heerspink, Megumi Oshima, Hong Zhang et al. (2021)
@AJKDonline | DOI: 10.1053/j.ajkd.2021.05.005

AJKD

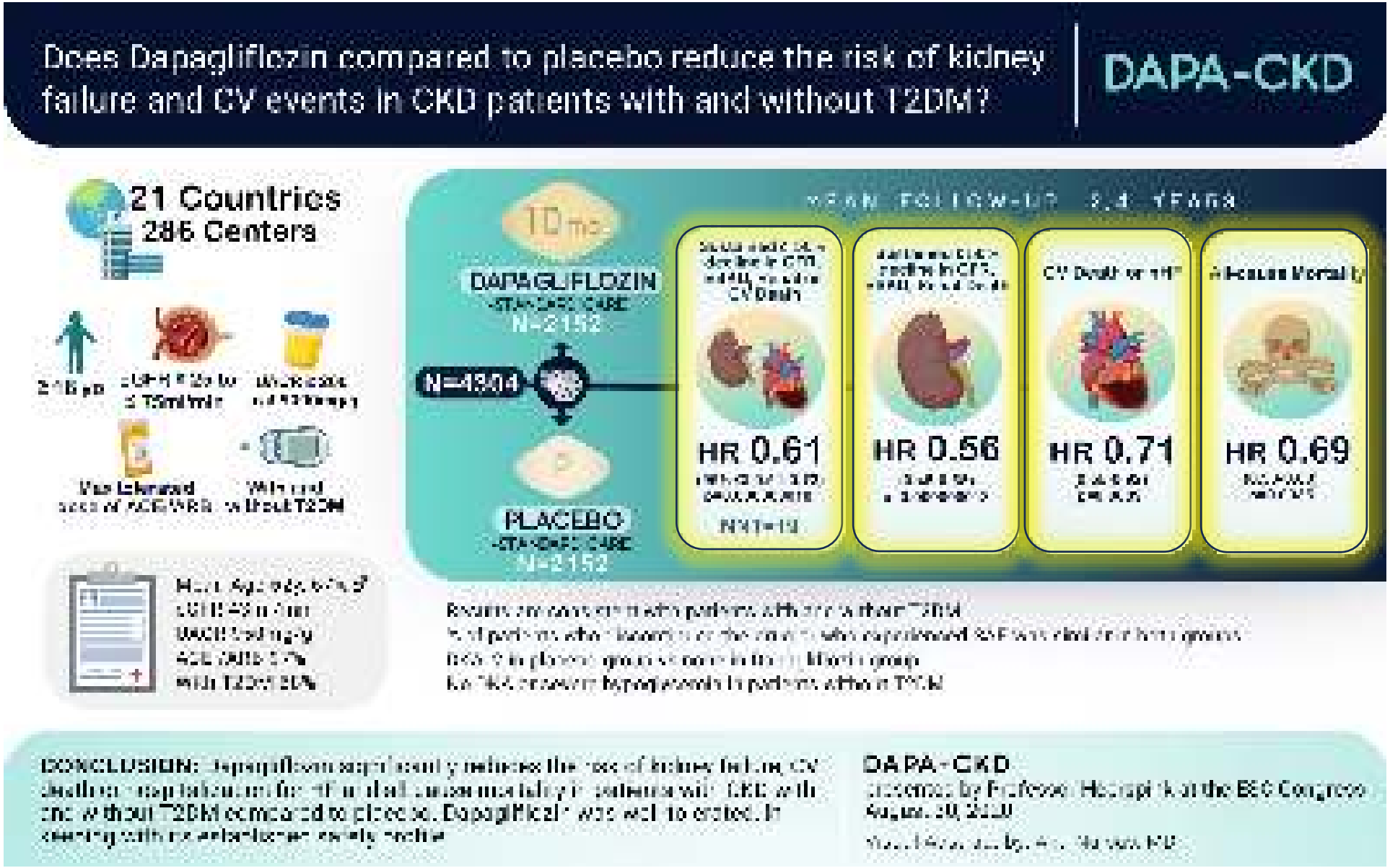
EMPA-KIDNEY


Empagliflozin in Patients with Chronic Kidney Disease (EMPA-KIDNEY)
ISN
Multicenter
241 centers
8 countries
Double-blind
6,609 patients
eGFR 20 – 45
Regardless of the level of albuminuria
eGFR 45 – 90
UACR >200
Feb 2019 – Apr 2021
Pre-randomization phase 15wks of placebo
Empagliflozin
10mg/day
Placebo
CKD progression & death from CV causes
Hospitalization from any cause
Hospitalization for HF or death from CV causes
Death from any cause
13.1%
24.8%
4.0%
4.5%
0.72
0.86
0.84
0.87
16.9%
29.2%
4.6%
5.1%
per 100 patients/year
Conclusion: among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo.

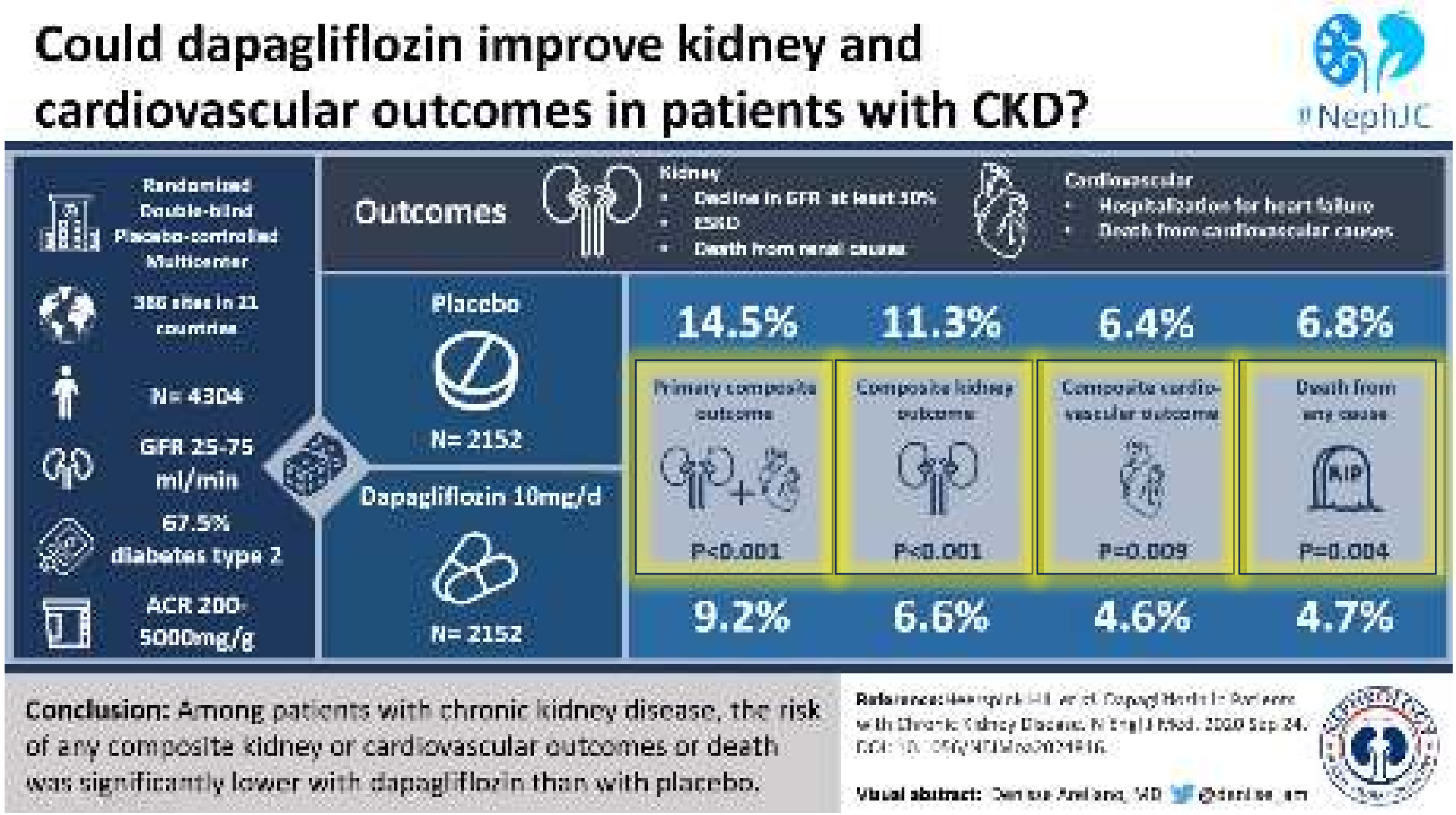
EMPA-KIDNEY


Effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression
KIDNEY WEEK
Double-blind Placebo controlled Trial
eGFR 20 to < 45 mL/min/1.73 m²
eGFR 45 to < 80 mL/min/1.73 m² UACR ≥ 200 mg/g
n=6609
64 years Mean age
67% Male
2 years Median FU
1:1 RANDOMIZATION
Empagliflozin 10 mg/d daily n=3304
Placebo n=3305
PRIMARY OUTCOME
Progression of CKD or death from CV causes
13.1%
16.9%
HR 0.72
(95% CI 0.64-0.82)
p<0.001
KEY SECONDARY OUTCOMES
Rate of hospitalization from any cause (# of events/100 patient-yrs)
Hospitalization for heart failure or death from CV causes
Death from any cause
24.8
29.2
HR 0.86
(95% CI 0.78-0.95)
p=0.003
4.0%
4.6%
4.5%
5.1%
The rates of serious adverse events were similar in the 2 groups
Conclusions Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo.
EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2022 Nov 4. doi: 10.1056/NEJMoa2204233
Visual Abstract by Edgar Lerma, MD, FASN

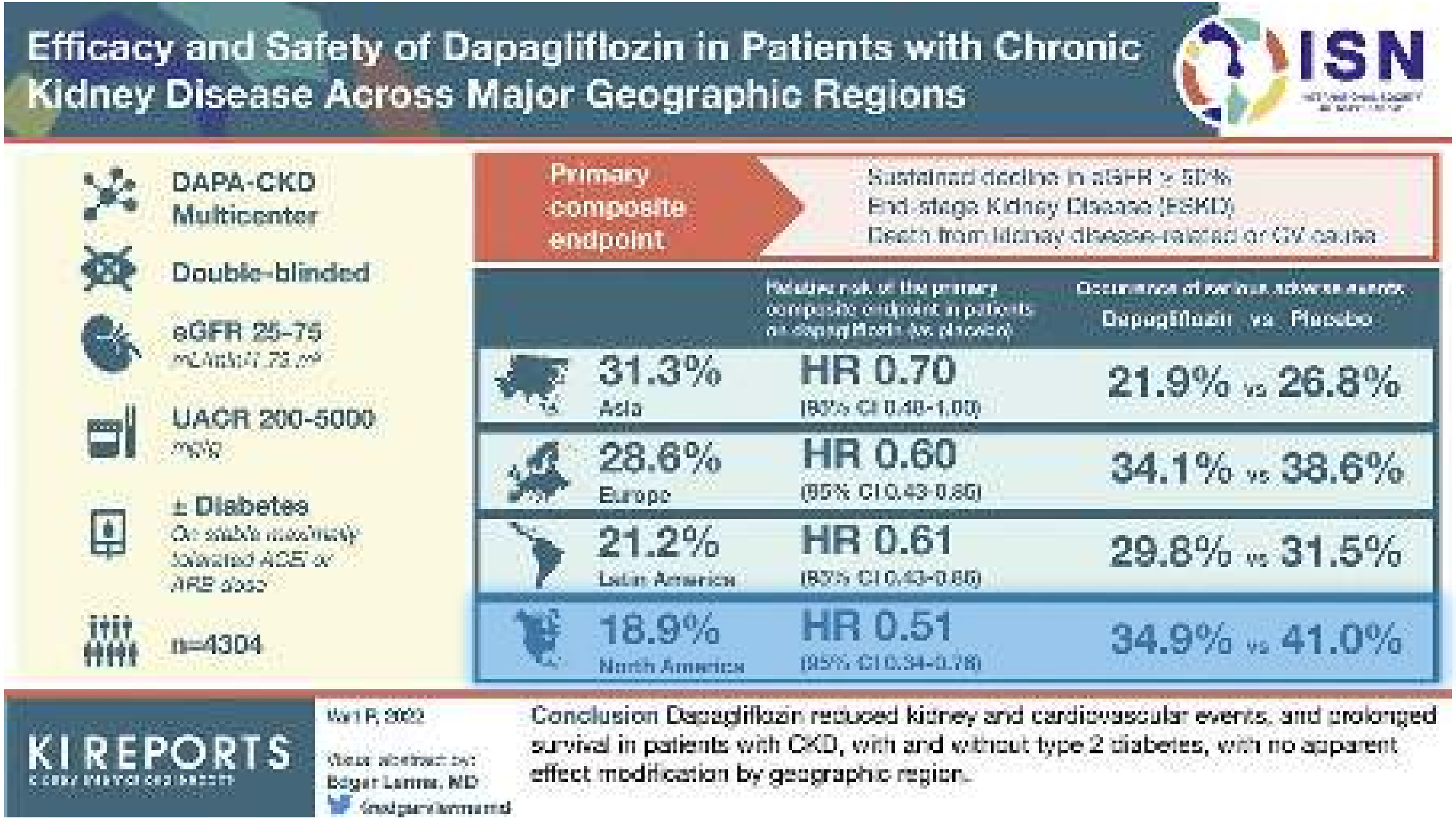
DAPA-CKD


Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?
DAPA-CKD
21 Countries
286 Centers
10 mg
DAPAGLIFLOZIN
N=2152
N=4304
PLACEBO
N=2152
HR 0.61
HR 0.56
HR 0.71
HR 0.69
CV Death or HF
DAPA-CKD

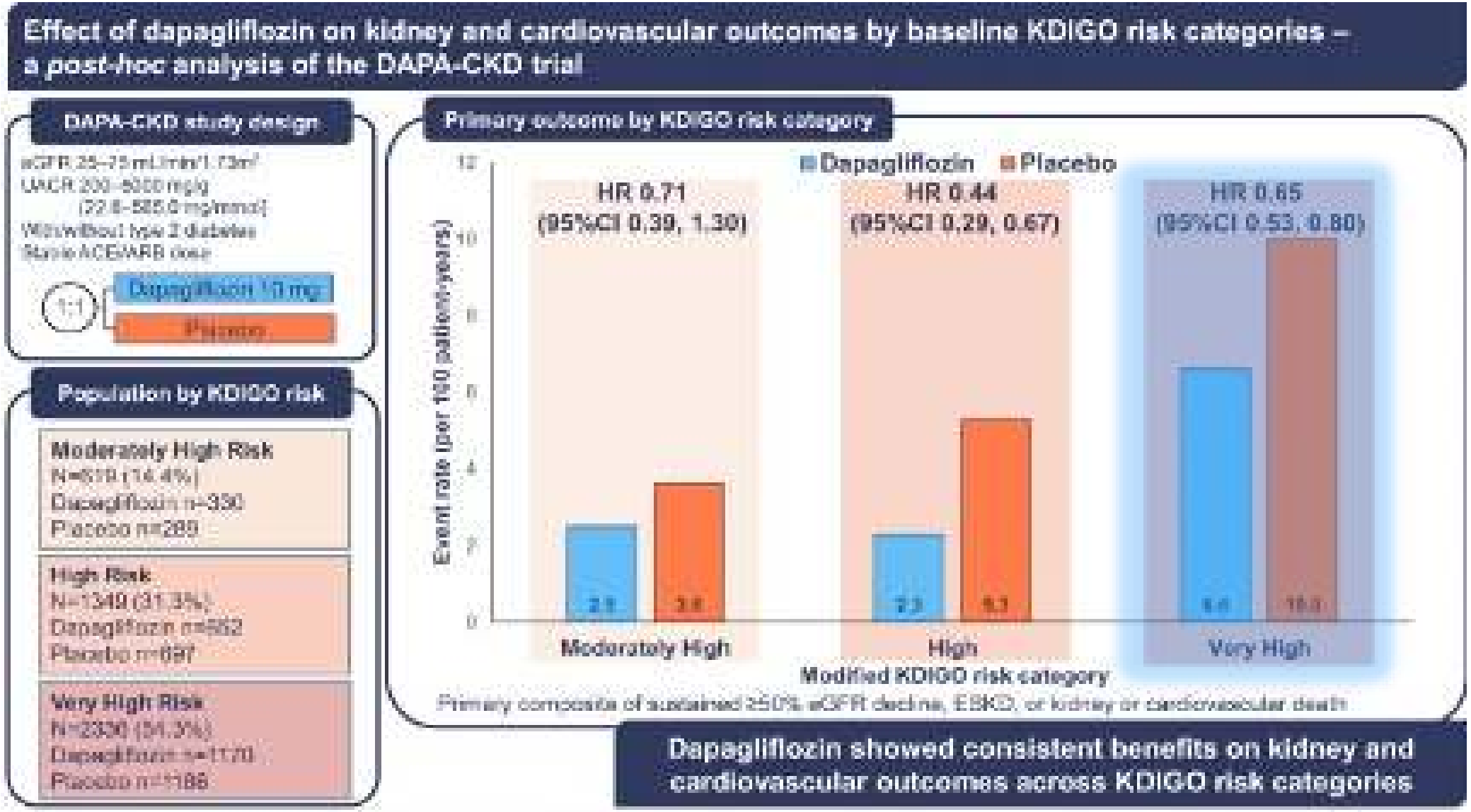
DAPA-CKD


Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?
NephJC
Randomized
Double-blind
Placebo-controlled
Multicenter
386 sites in 31 countries
N= 4304
GFR 25-75 ml/min
67.5% diabetes type 2
ACR 200-5000mg/g
Outcomes
Kidney
Decline in GFR at least 50%
ESKD
Death from renal causes
Cardiovascular
Hospitalization for heart failure
Death from cardiovascular causes
Placebo
N= 2152
Dapagliflozin 10mg/d
N= 2152
14.5%
11.3%
6.4%
6.8%
Primary composite outcome
Composite kidney outcome
Composite cardiovascular outcome
Death from any cause
P<0.001
P<0.001
P=0.009
P=0.004
9.2%
6.6%
4.6%
4.7%
Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.
Reference:
Visual abstract:

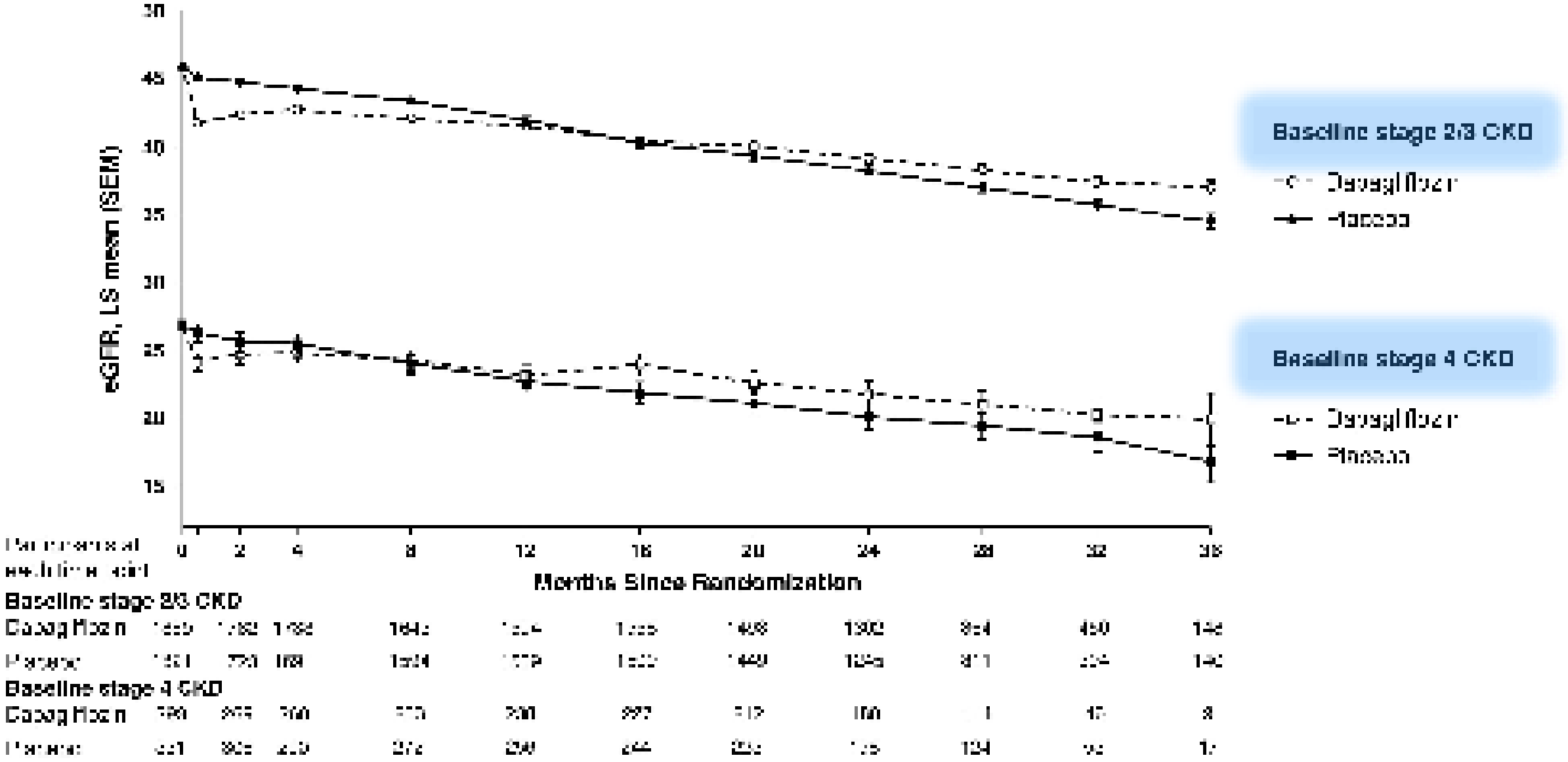
DAPA-CKD – by Geography



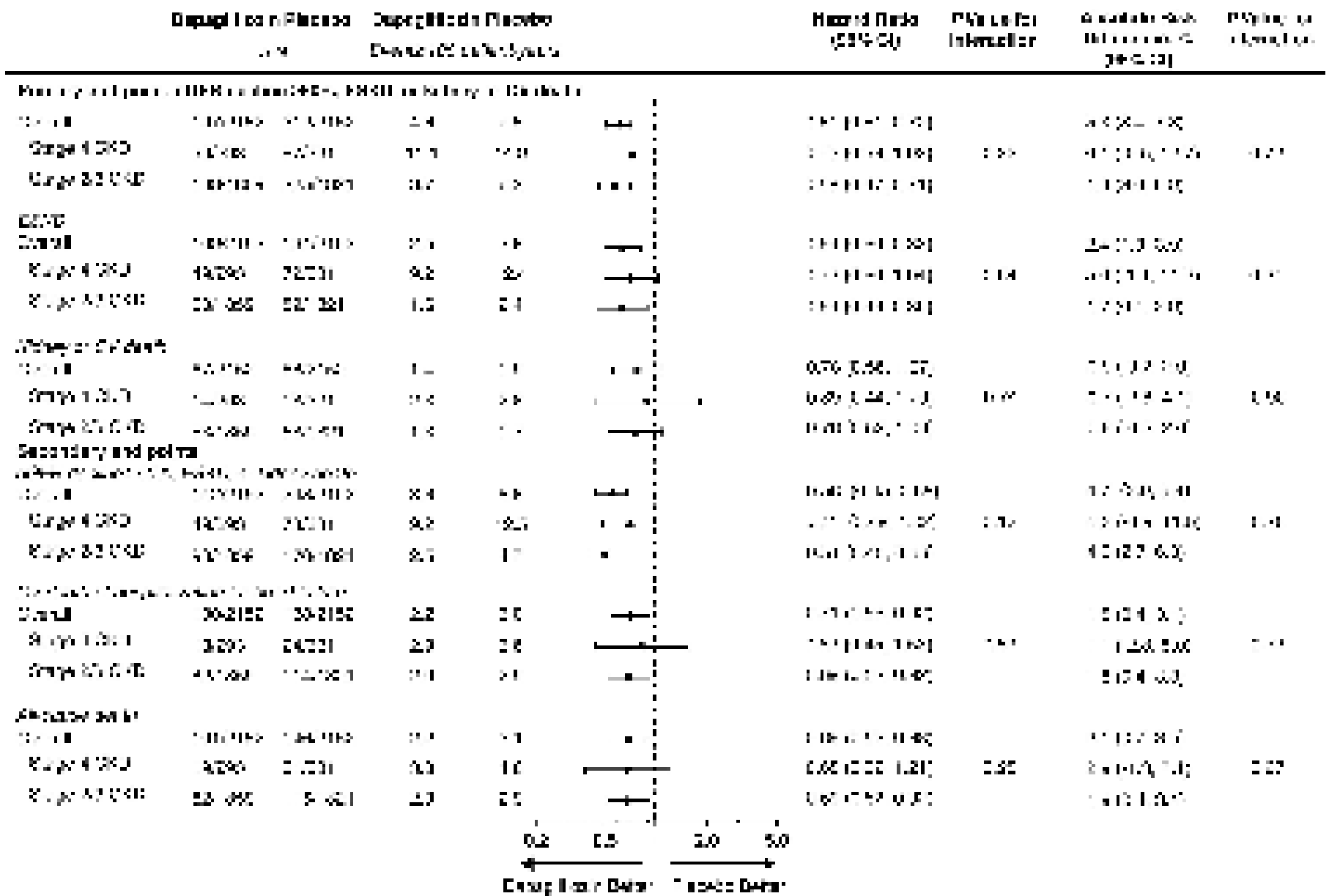
DAPA-CKD


Effect of dapagliflozin on kidney and cardiovascular outcomes by baseline KDIGO risk categories – a post-hoc analysis of the DAPA-CKD trial
DAPA-CKD study design
1:1
Population by KDIGO risk
Moderately High Risk
High Risk
Very High Risk
Primary outcome by KDIGO risk category
Dapagliflozin
Placebo
HR 0.71
(95%CI 0.39, 1.30)
HR 0.44
(95%CI 0.29, 0.67)
HR 0.65
(95%CI 0.53, 0.80)
Event rate (per 100 patient-years)
Moderately High
High
Very High
Modified KDIGO risk category
Dapagliflozin showed consistent benefits on kidney and cardiovascular outcomes across KDIGO risk categories

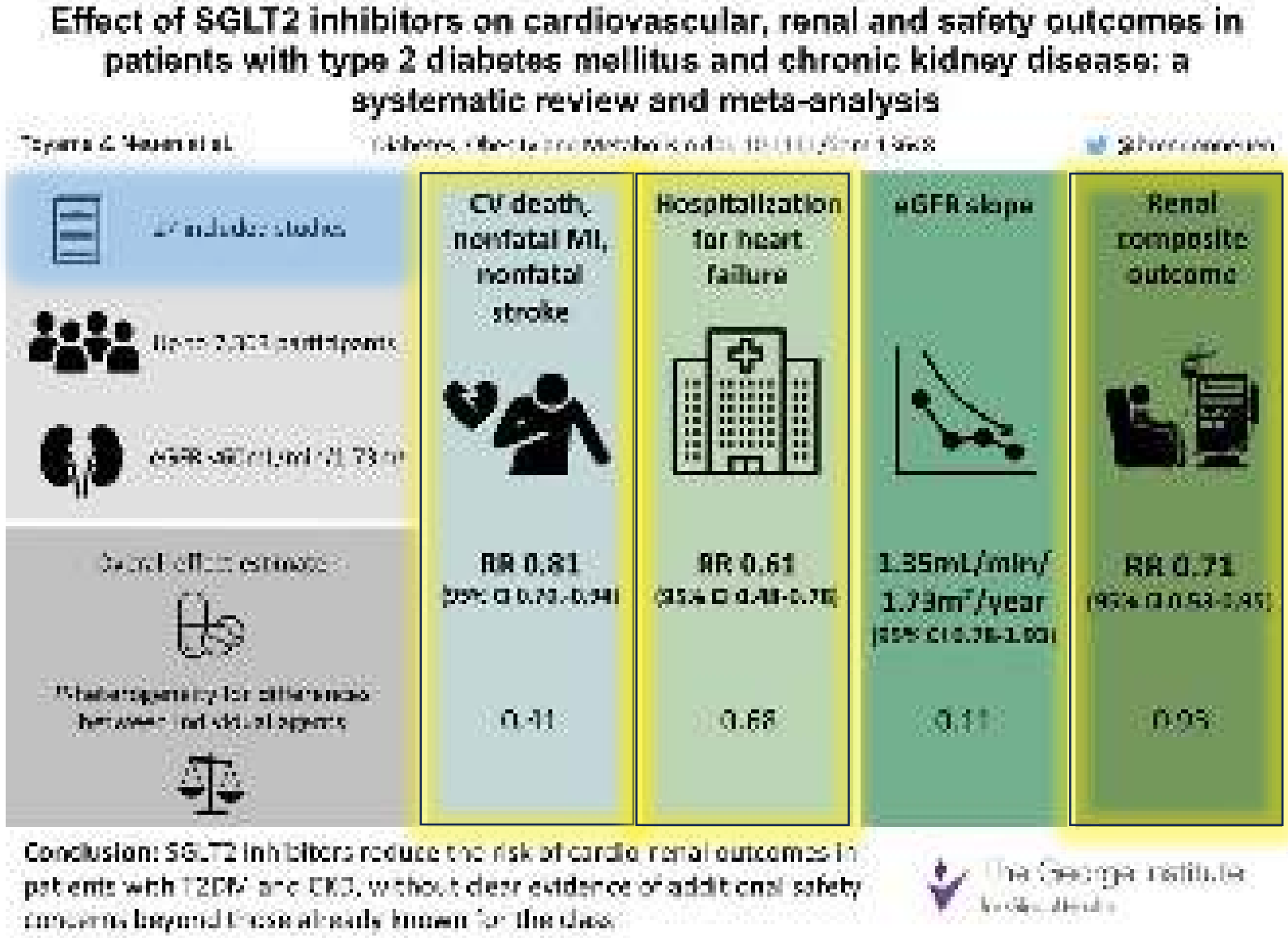
DAPA-CKD


eGFR, LS mean (SEM)
45
40
35
30
25
20
15
0
2
4
8
12
16
20
24
28
32
36
Months Since Randomization
Baseline stage 2/3 CKD
Dapagliflozin
Placebo
Baseline stage 4 CKD
Dapagliflozin
Placebo
Baseline stage 2/3 CKD
Dapagliflozin
Baseline stage 4 CKD
Dapagliflozin

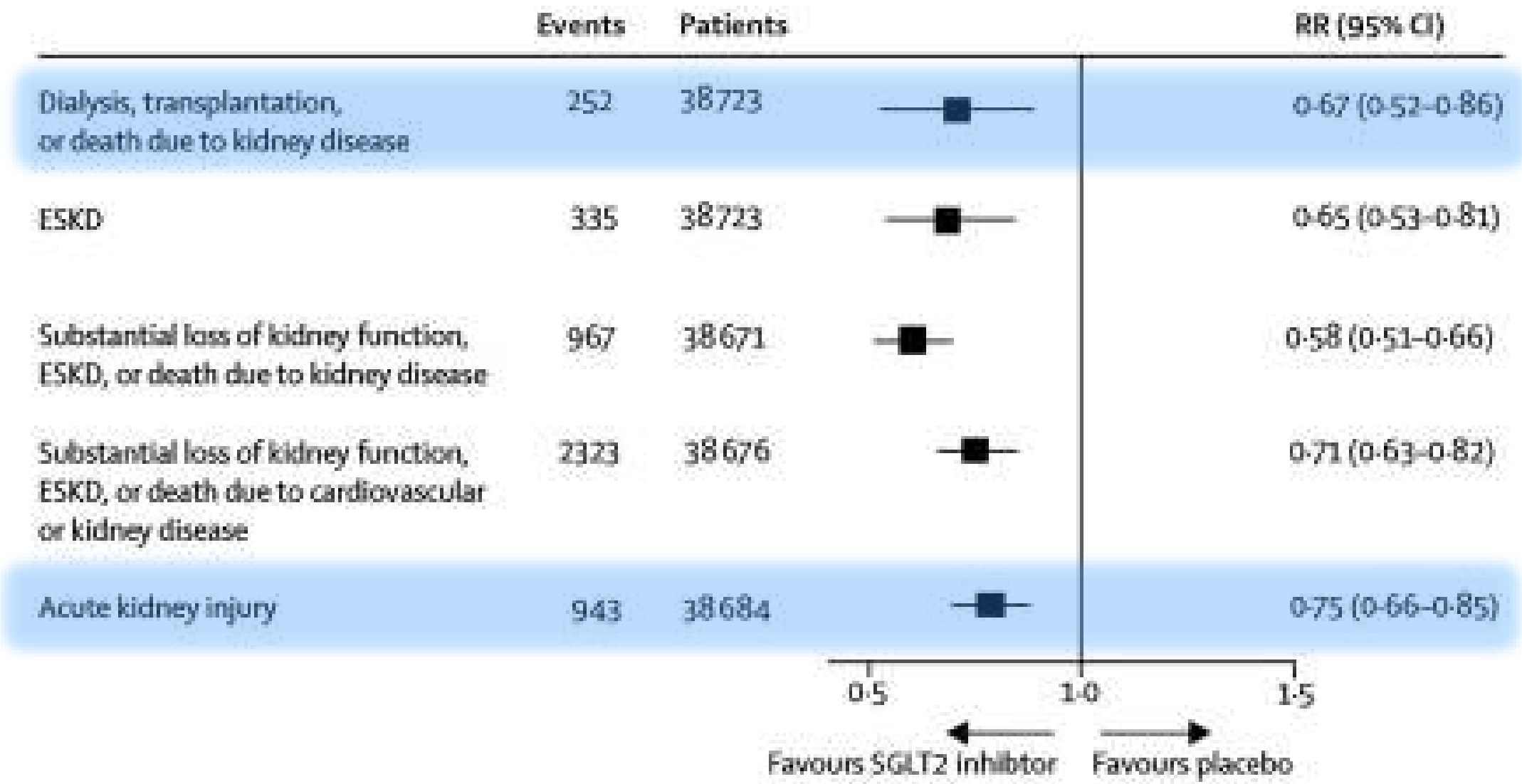
DAPA-CKD



Metanalysis

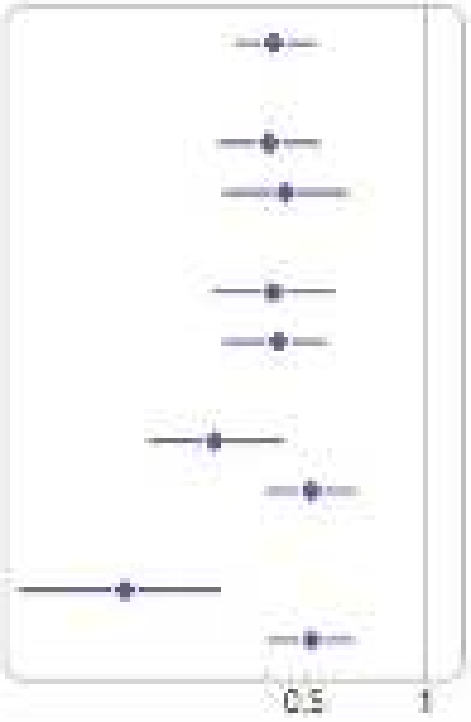


Another metanalysis

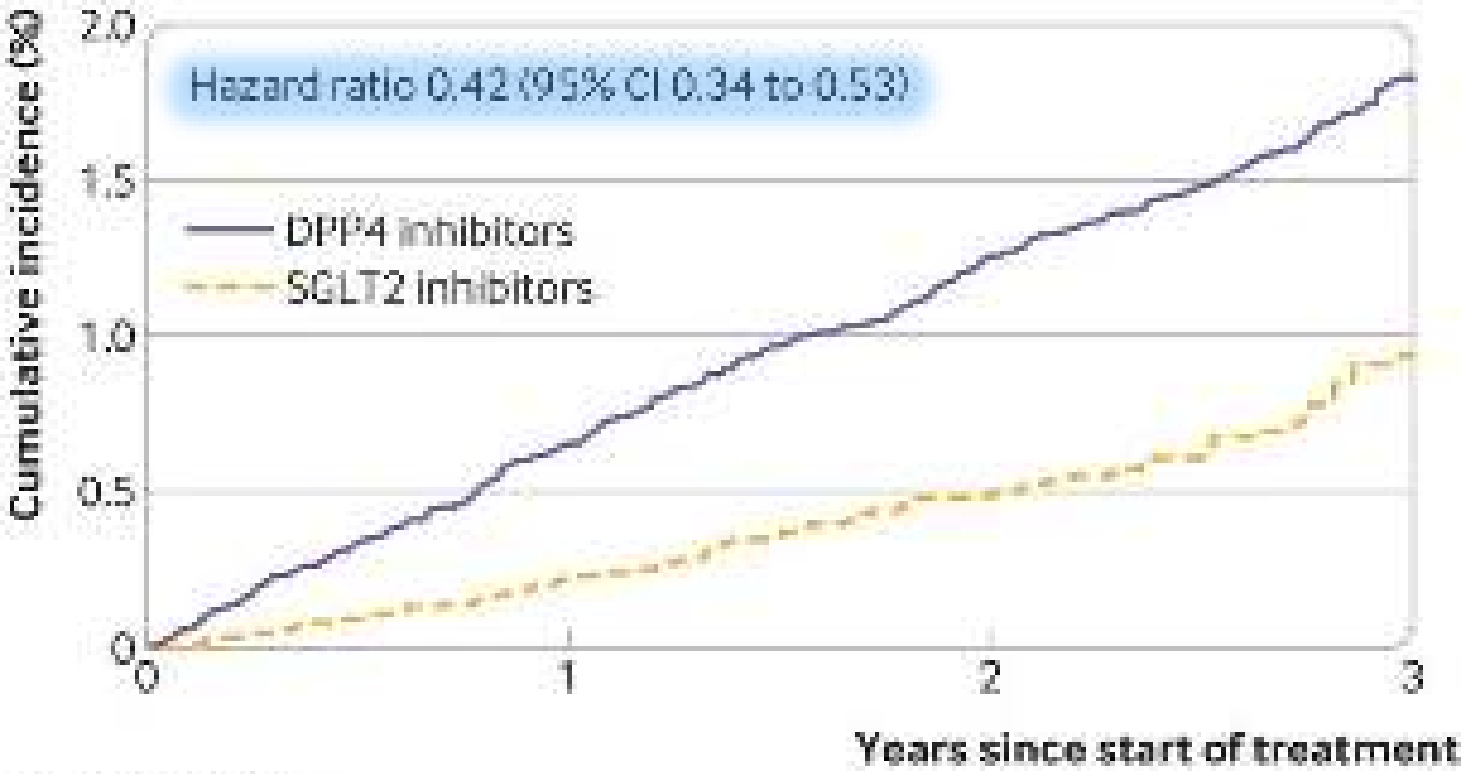


Outcome: Regardless of A1C control

	SGLT2 inhibitors			DPP4 inhibitors					
	Patients (%)	Events	Events per 1000 patient yrs	Patients (%)	Events	Events per 1000 patient yrs	Hazard ratio (95% CI)	P value for interaction	Hazard ratio (95% CI)
Total population	29 887 (100)	111	2.6	29 887 (100)	360	8.2			0.42 (0.34 to 0.53)
Sex								0.704	
Men	18 129 (61)	69	2.7	18 129 (61)	232	8.8			0.41 (0.31 to 0.54)
Women	11 758 (39)	42	2.4	11 758 (39)	128	5.8			0.43 (0.32 to 0.58)
Age								0.965	
35-64 years	17 984 (60)	45	1.7	17 984 (60)	145	4.2			0.42 (0.30 to 0.59)
65-84 years	11 903 (40)	66	4.0	11 903 (40)	212	9.4			0.43 (0.32 to 0.58)
Major cardiovascular disease								0.022	
Yes	5 650 (19)	36	4.6	5 449 (18)	155	14.8			0.30 (0.21 to 0.44)
No	24 238 (81)	75	2.2	24 438 (82)	205	4.3			0.52 (0.40 to 0.67)
Chronic kidney disease								<0.001	
Yes	987 (3)	14	9.2	987 (3)	97	51.3			0.18 (0.10 to 0.31)
No	28 900 (97)	97	2.4	28 900 (97)	263	4.7			0.52 (0.41 to 0.65)



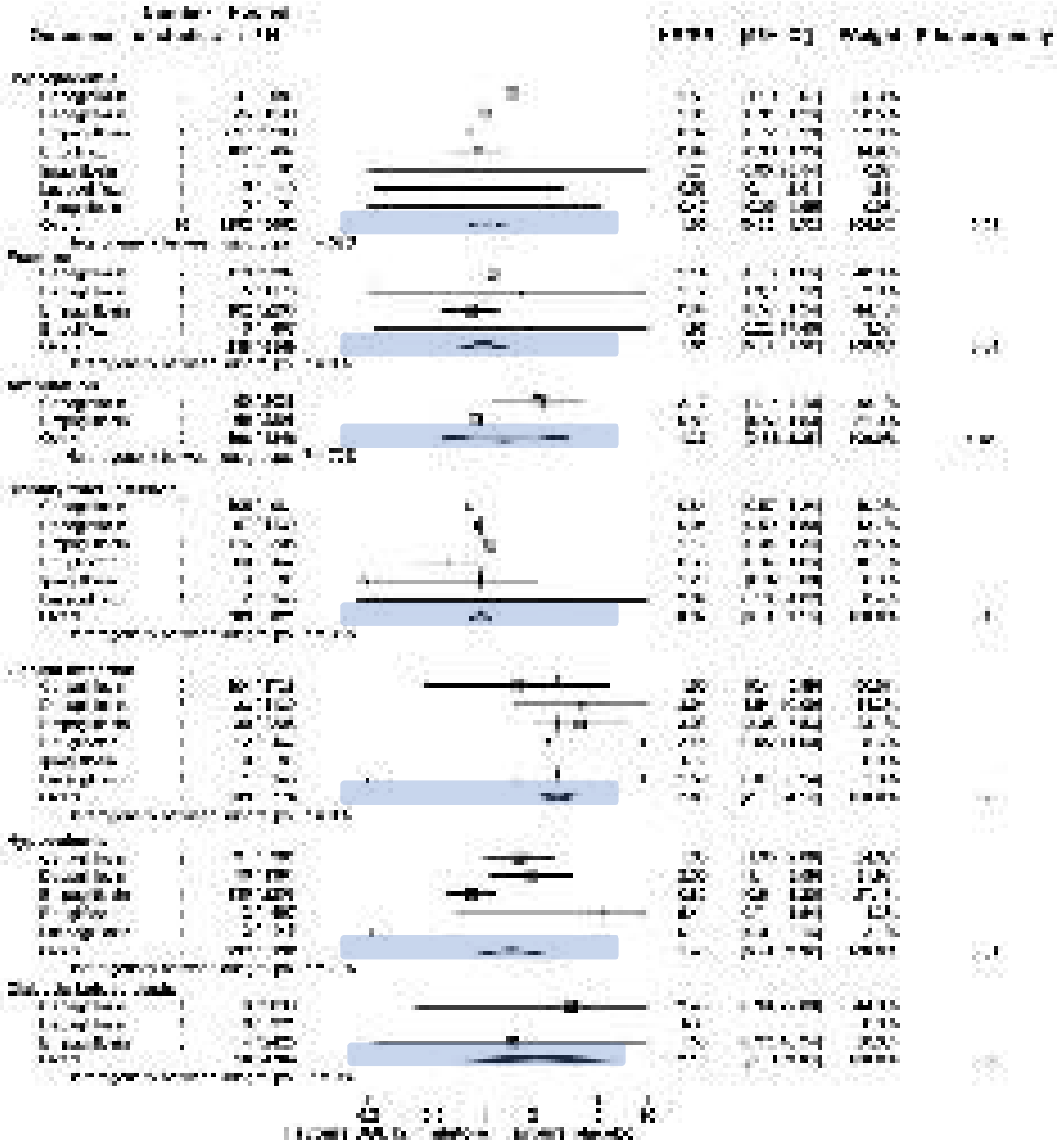
Outcome: Regardless of A1C control



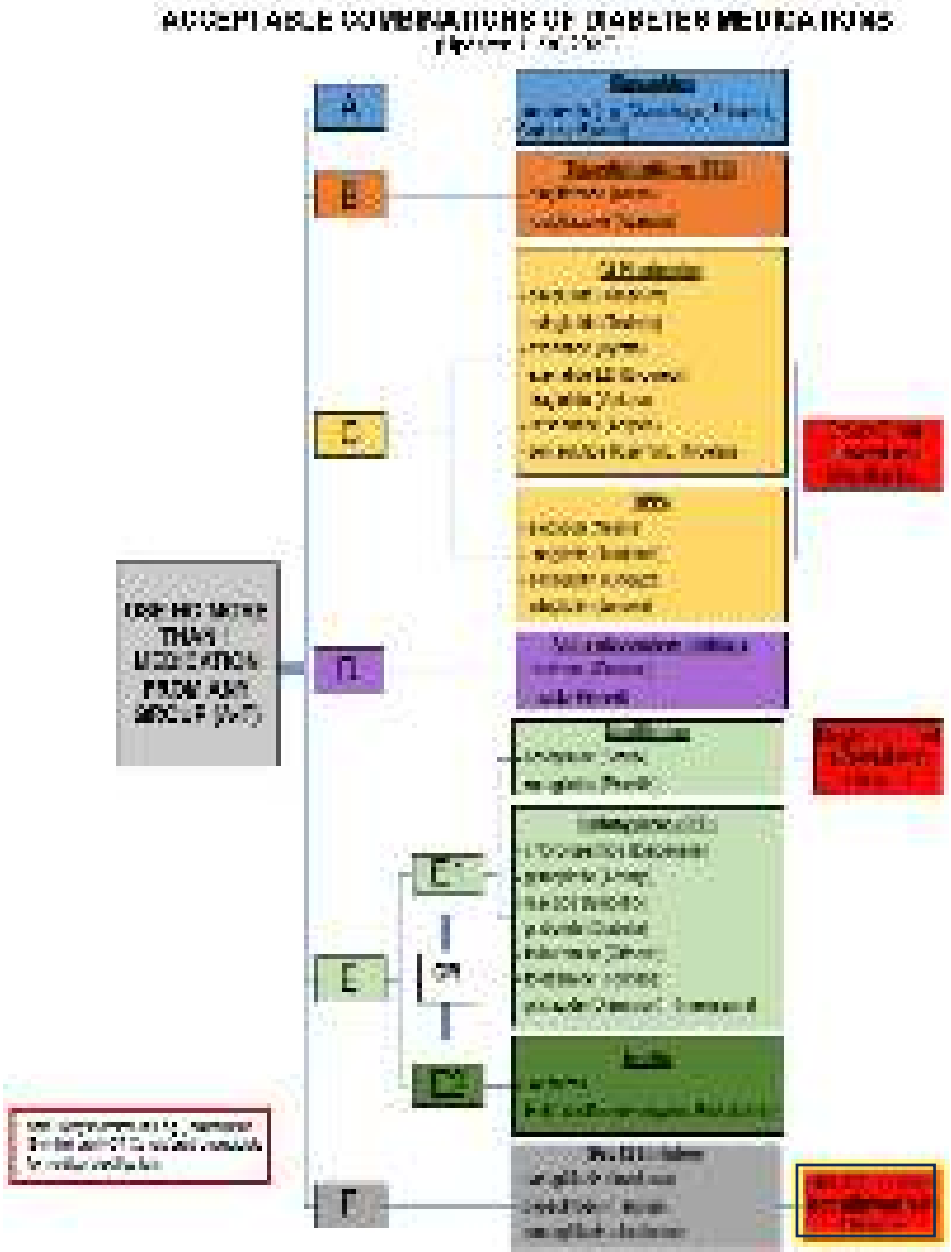
Number at risk

SGLT2 inhibitors				
	29 887	17 734	9109	3198
DPP4 inhibitors				
	29 887	22 689	15 720	9344

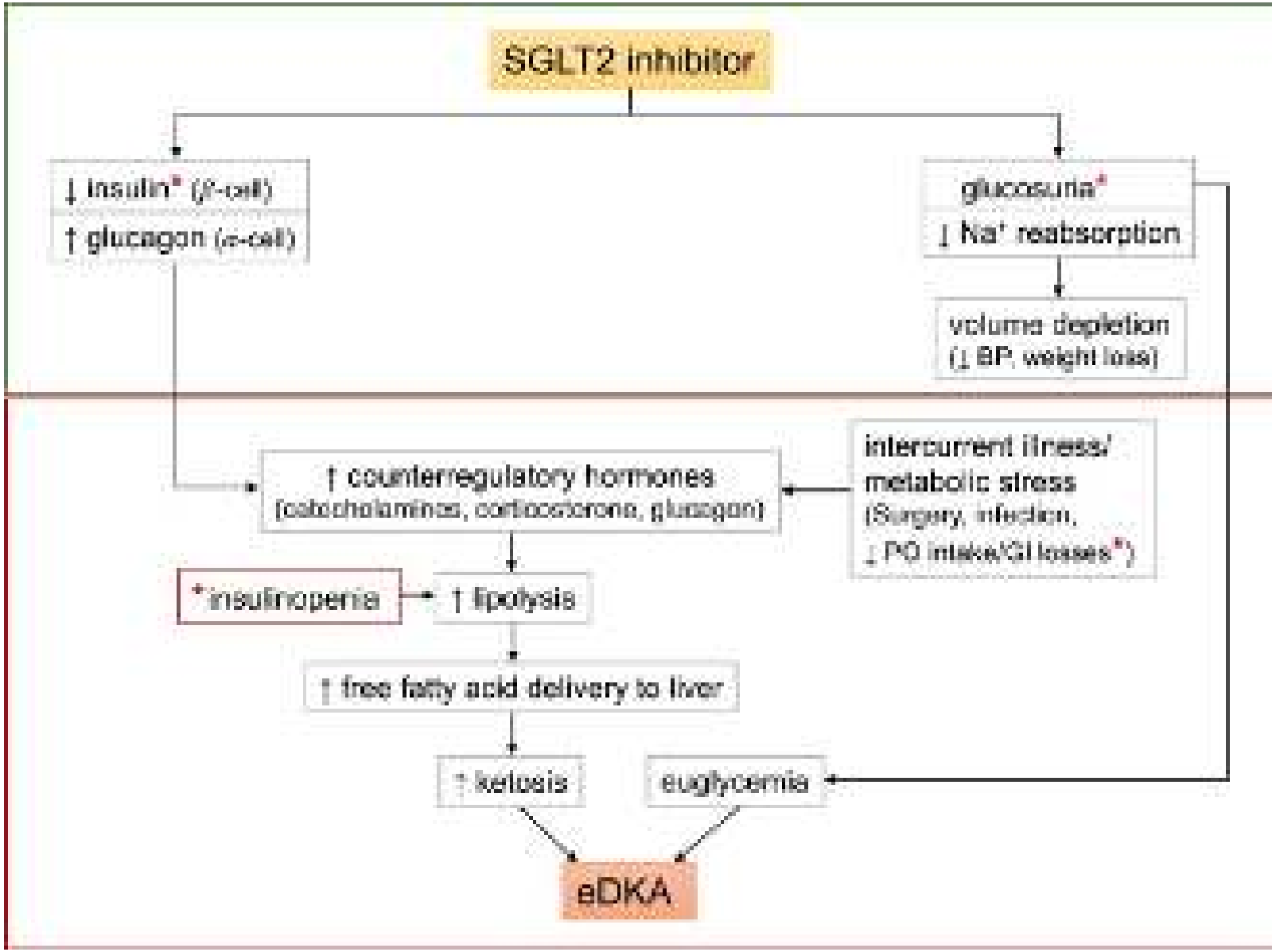
Safety: Overall summary



Safety: Severe hypoglycemia



Safety: EuDKA



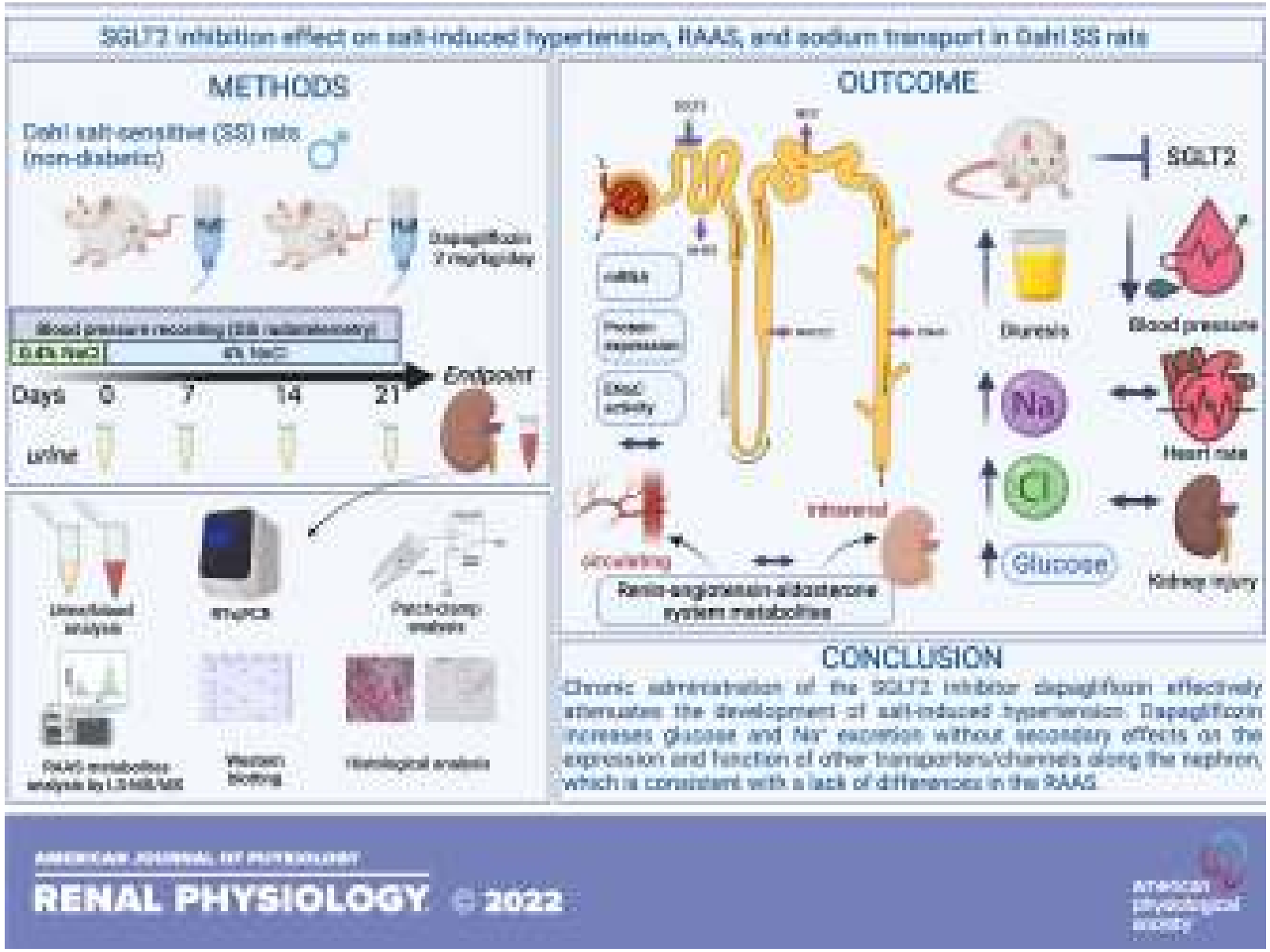
Safety: Hypotension

- FDA warning on all SGLT2 class relating to assessment of volume status prior to initiation of, and during, therapy:

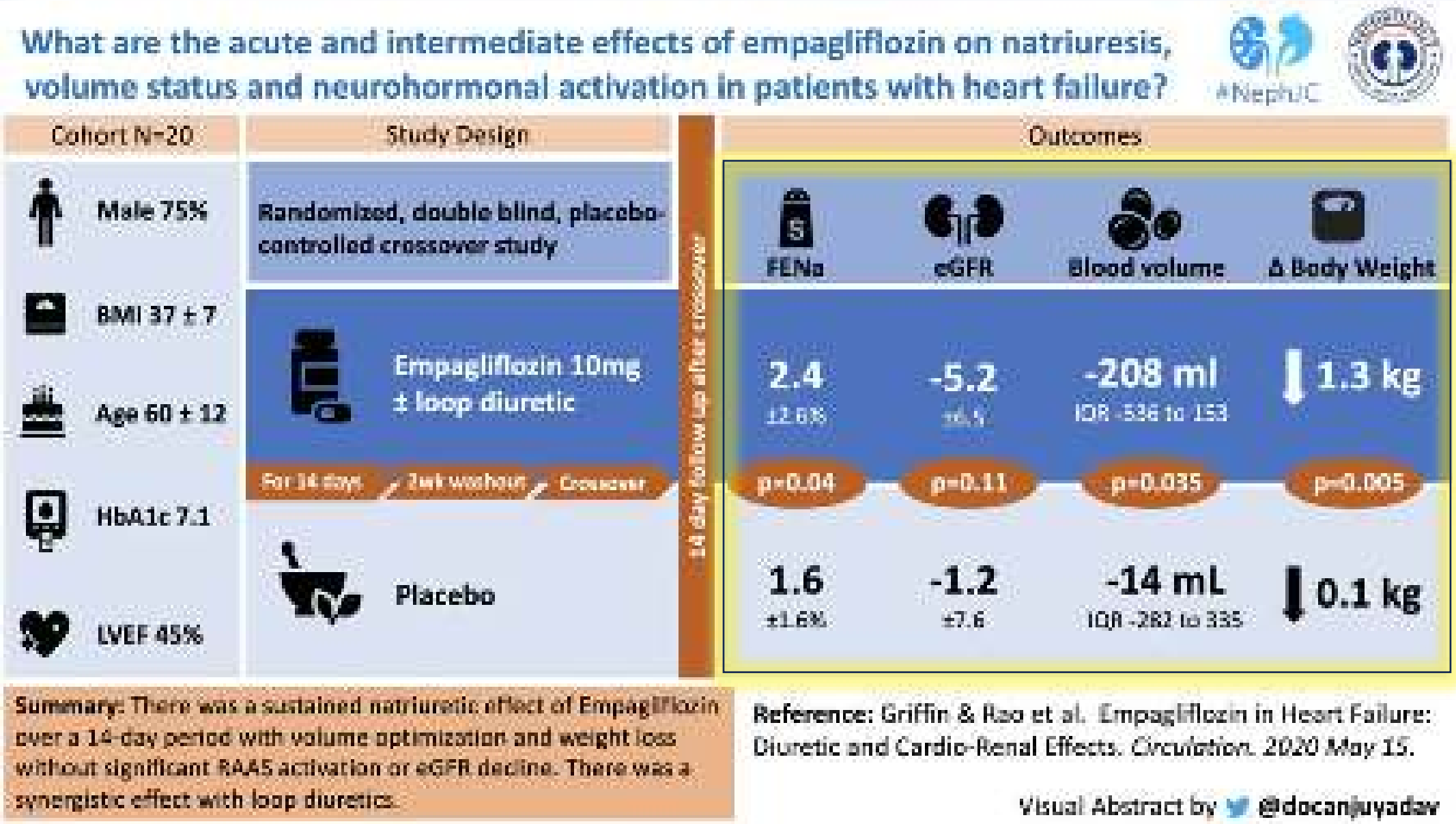
  - Meta-analysis of data from >5,000 individuals showing significantly lower SBP & DBP with SGLT2 inhibitor (RR, 1.48; 95% CI, 0.94–2.32)

  - Lower blood pressure may, however, be beneficial in many people with T2DM

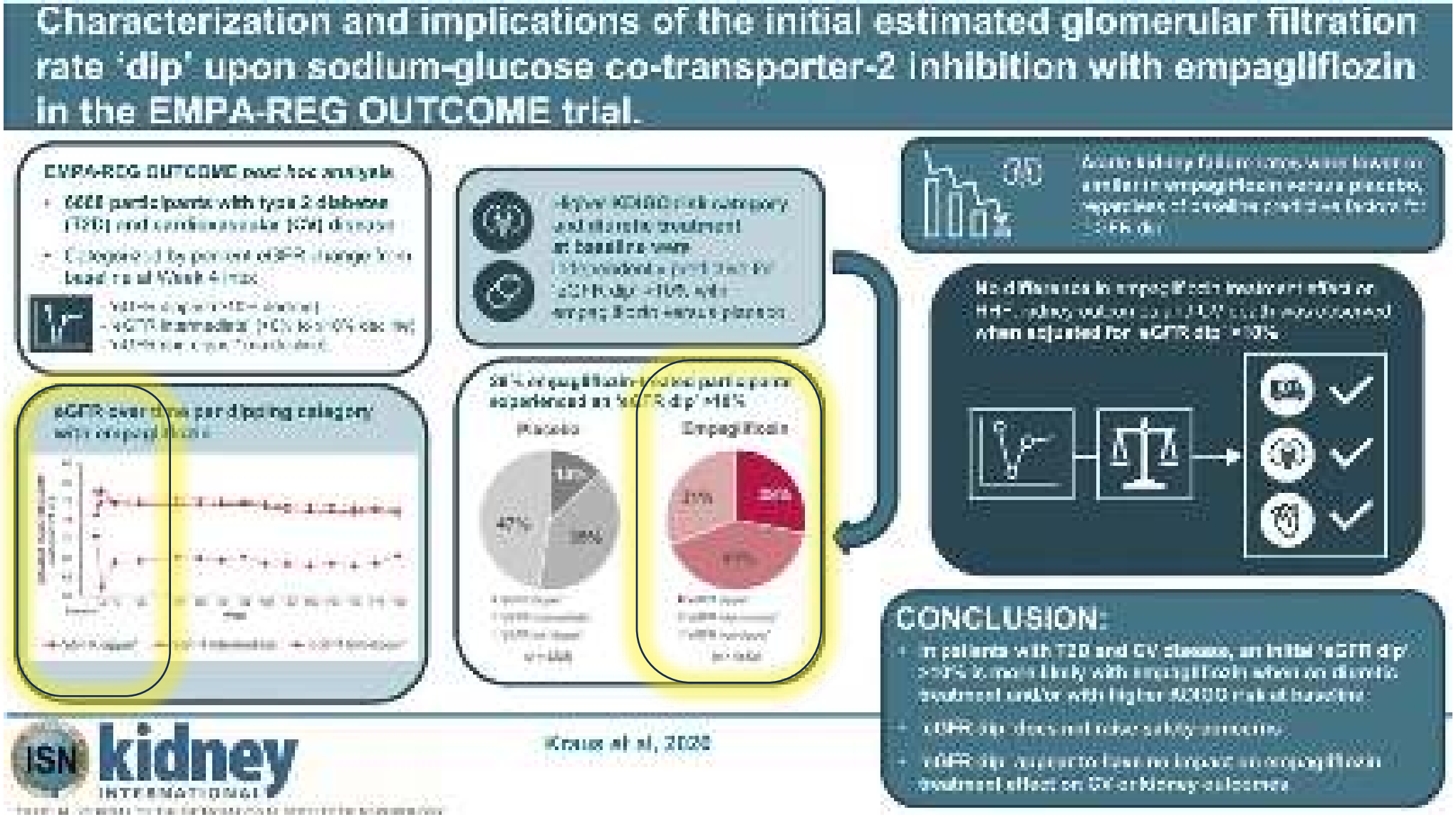
Decrease salt-induced hypertension



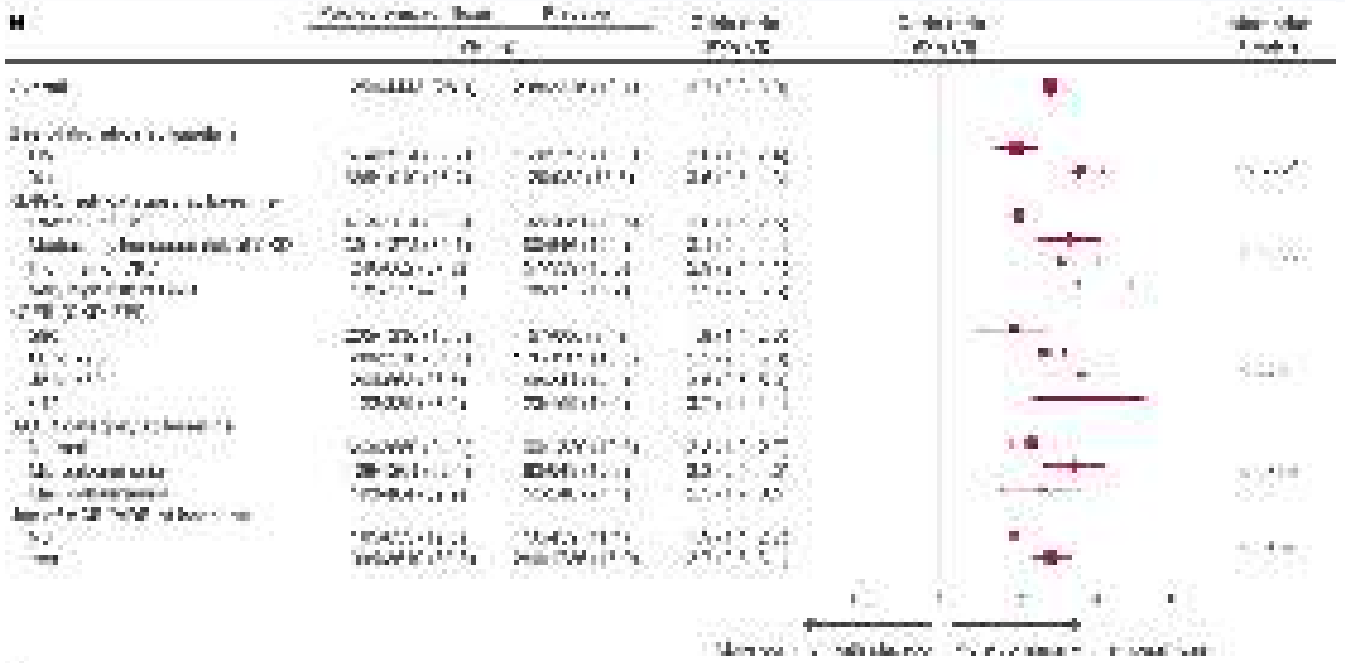
Safety: Diuretic Effect

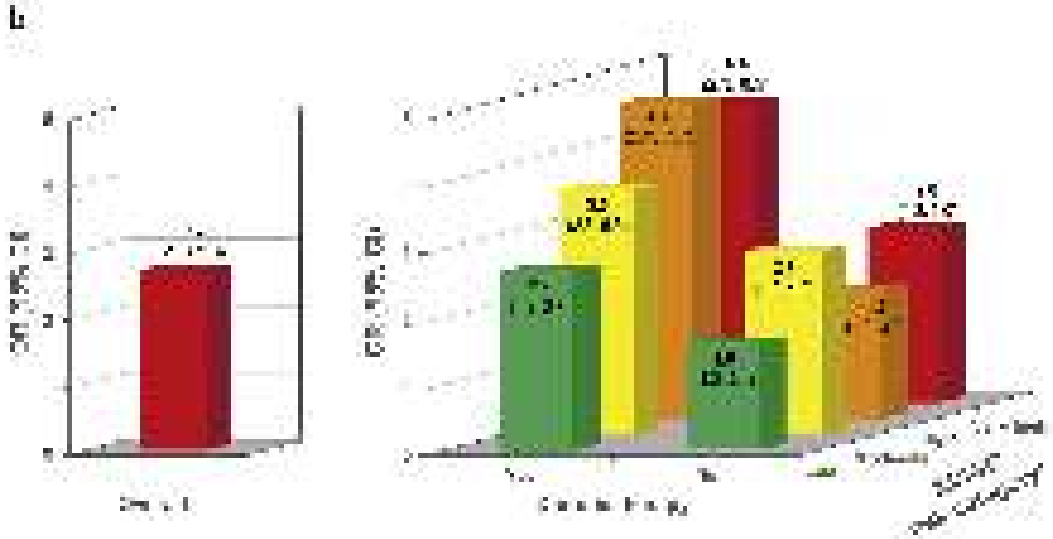


Safety: AKI

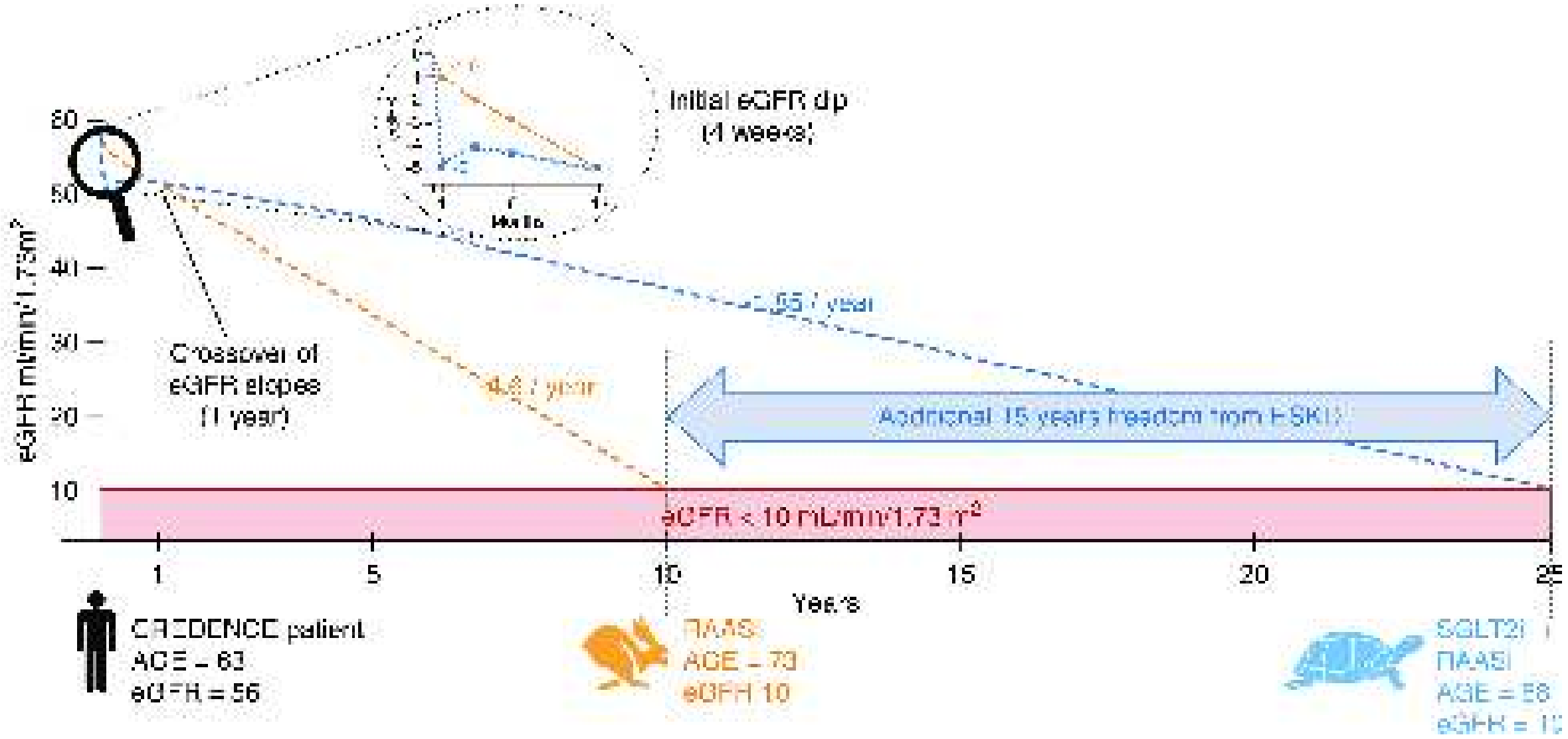

Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose co-transporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial.
EMPA-REG OUTCOME post hoc analysis
Placebo
Empagliflozin
CONCLUSION:
Kraus et al, 2020

Safety: AKI

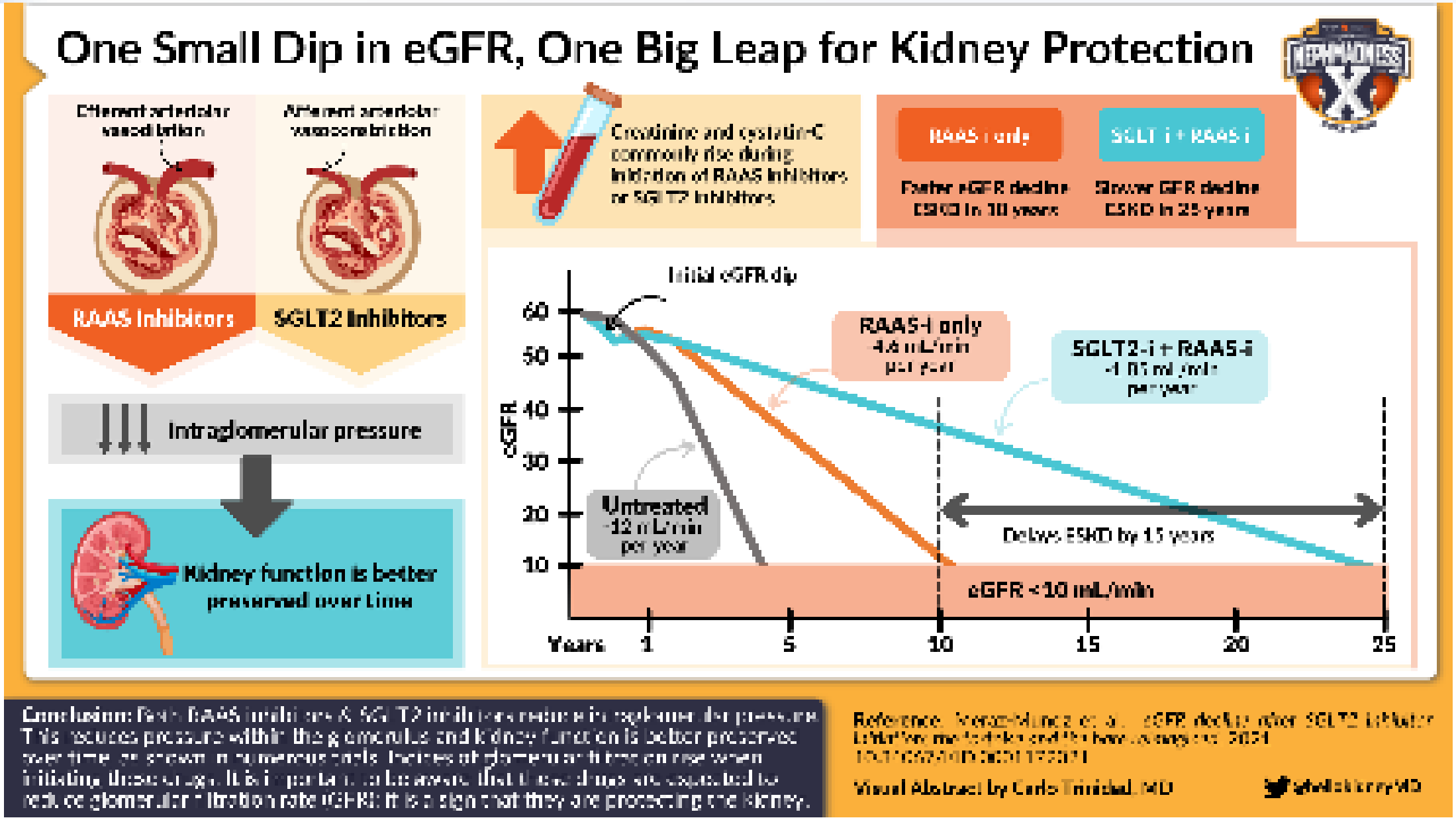




Safety: AKI


Initial eGFR dip
(4 weeks)
Crossover of
eGFR slopes
(1 year)
-5 / year
-4 / year
Additional 15 years freedom from ESKD
eGFR < 10 mL/min/1.73 m²
eGFR mL/min/1.73m²
60
50
40
30
20
10
1
5
10
15
20
Years
CREDENCE patient
AGE = 63
eGFH = 56
RAAS
AGE = 73
eGFH 10
SGLT2i
RAASi
AGE = 68
eGFH = 1

Combining RAAS Inhibitor & SGLT2 Inhibior



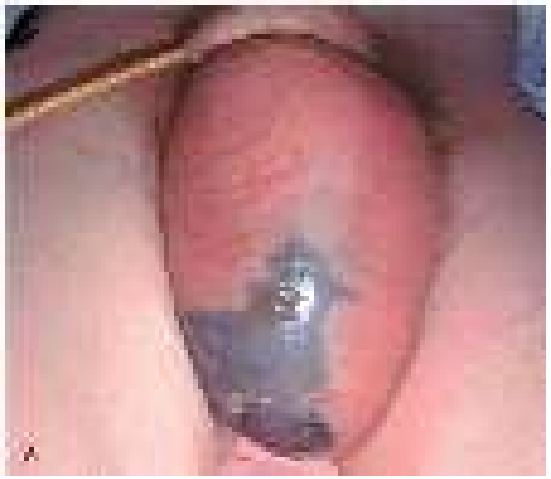
Safety: GU Infection

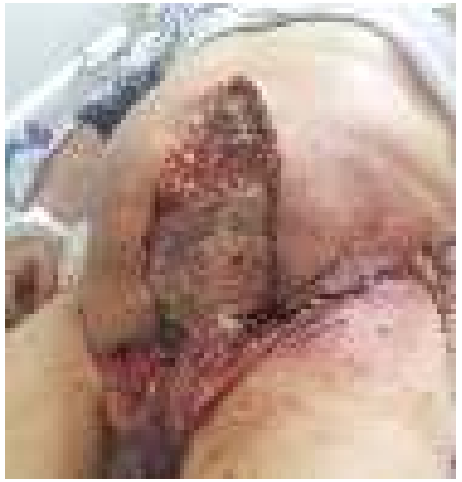
- GU infections were the most prevalent
  - *Candida* species was 3–4 x higher than in the control group
  - The risk factors include:
    - Female sex
    - Past GU infections
  - Higher A1C were not associated with a higher incidence of the infection
  - A high rate of treatment discontinuation in patients who had UTI
  - Adequate intimate hygiene is crucial as it allows a considerable reduction in infections:
    - 40.8% in the control group vs.
    - 4.8% in the group instructed about hygiene

Safety: GU Infection - Fournier's gangrene

Serious type of GU infection is Fournier's gangrene

- Extremely rare but potentially fatal condition characterized by necrotizing fasciitis of the perineal soft tissues
  - Historically affected ♂ / ♀ = **40 : 1**
  - SGLT2 & Fournier's gangrene was reported in 55 cases over 6-yr ♂ / ♀ = **2.4 : 1**
  - FDA included a warning about the risk of Fournier's gangrene





Safety: Limb amputation

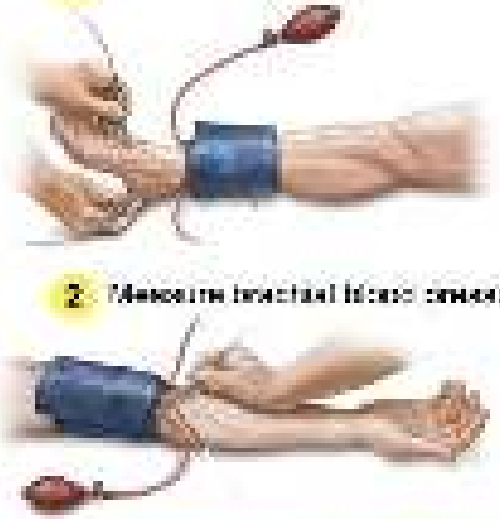
- CANVAS trial, a significantly higher incidence of limb amputations with canagliflozin compared to the placebo:

  - 6.3 vs. 3.37 per 1000 person-years. **[HR], 1.97** (95% CI, 1.41–2.75)
  - Pt w risk factors for limb ischemia were most at risk for amputation
  - Boxed warning was added by the FDA for canagliflozin in 2017
  - ADA guidelines recommend:
    - Feet of all patients with DM should be evaluated at least annually
    - Patients with evidence of claudication or who have a reduced or absent pedal pulses should be referred for assessment of ABI

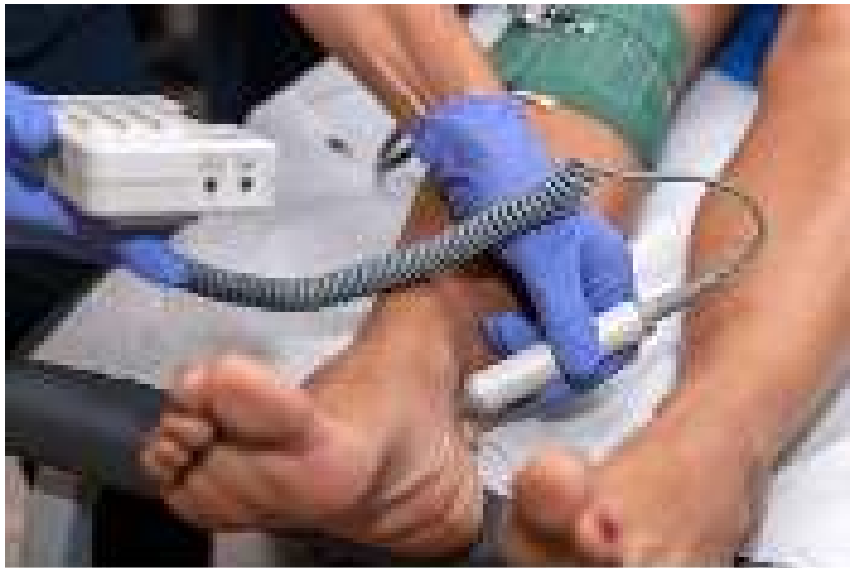
Safety: Limb amputation - ABI

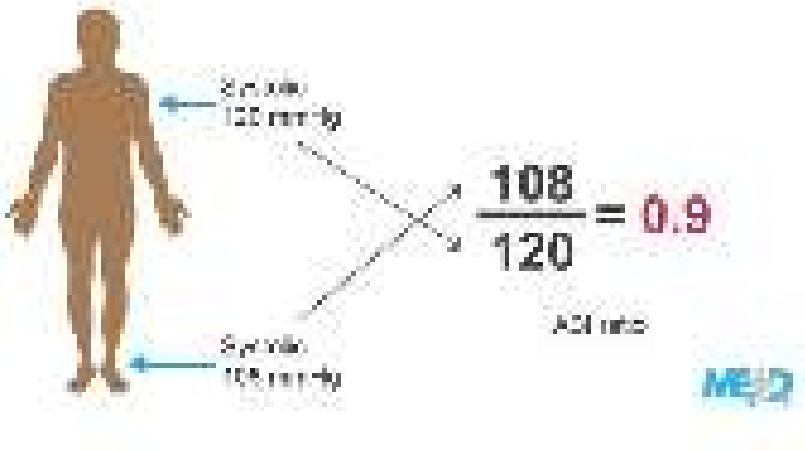
Ankle–Brachial Index

1. Measure ankle blood pressure
2. Measure brachial blood pressure



ABI Value	Interpretation	Recommendation
>1.4	Calcification	Refer to vascular specialist
1.0–1.4	Normal	None
0.8–1.0	Acceptable	None
0.6–0.8	Some arterial disease	Treat risk factors
0.5–0.8	Moderate arterial disease	Refer to vascular specialist
<0.5	Severe arterial disease	Refer to vascular specialist

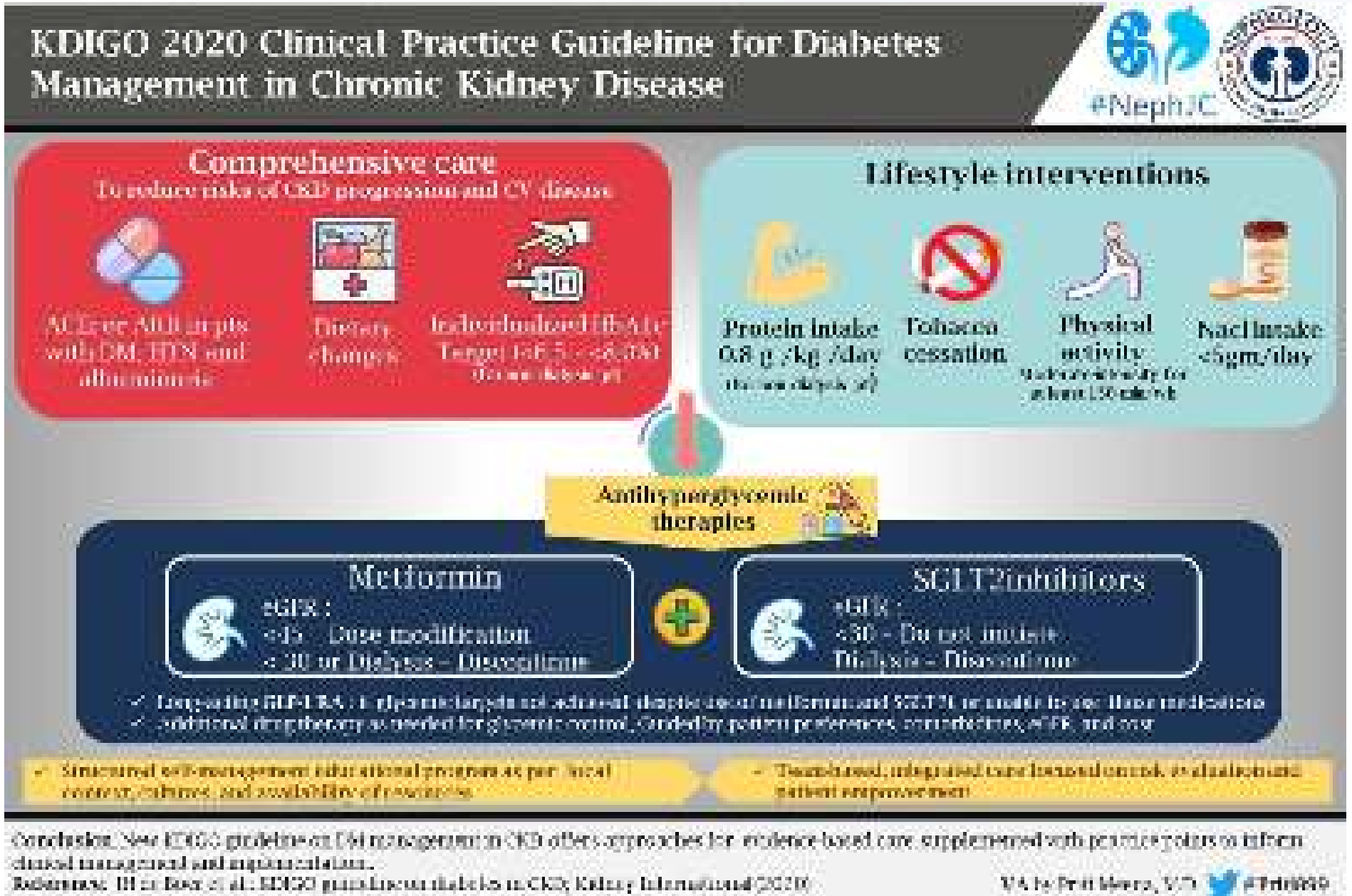




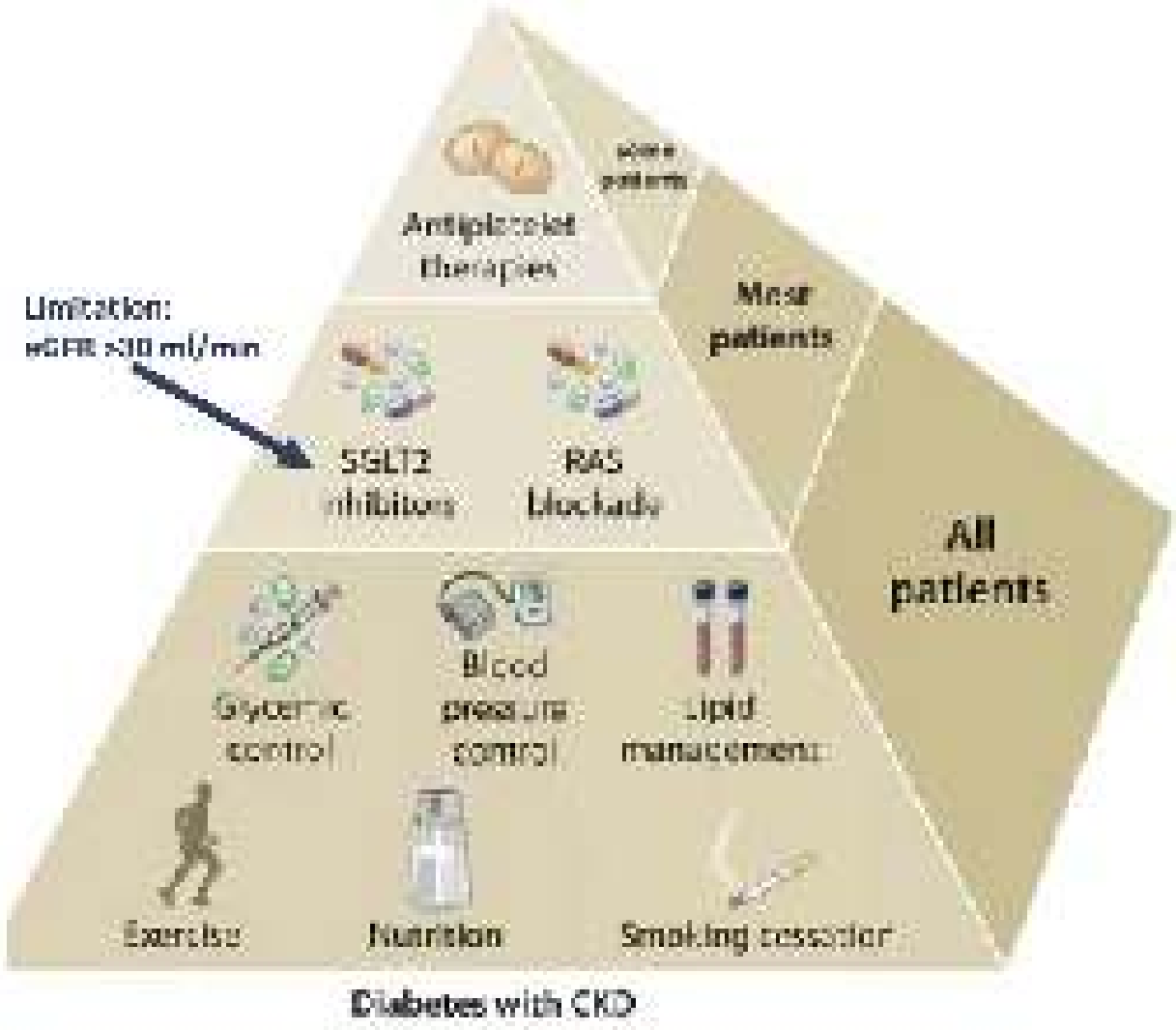
Contraindication of SGLT2

- Hypersensitivity reaction to SGLT2 inhibitors
- ESRD
- eGFR < 20 ml/min/m2
- Type 1 Diabetes

Diabetes management in CKD



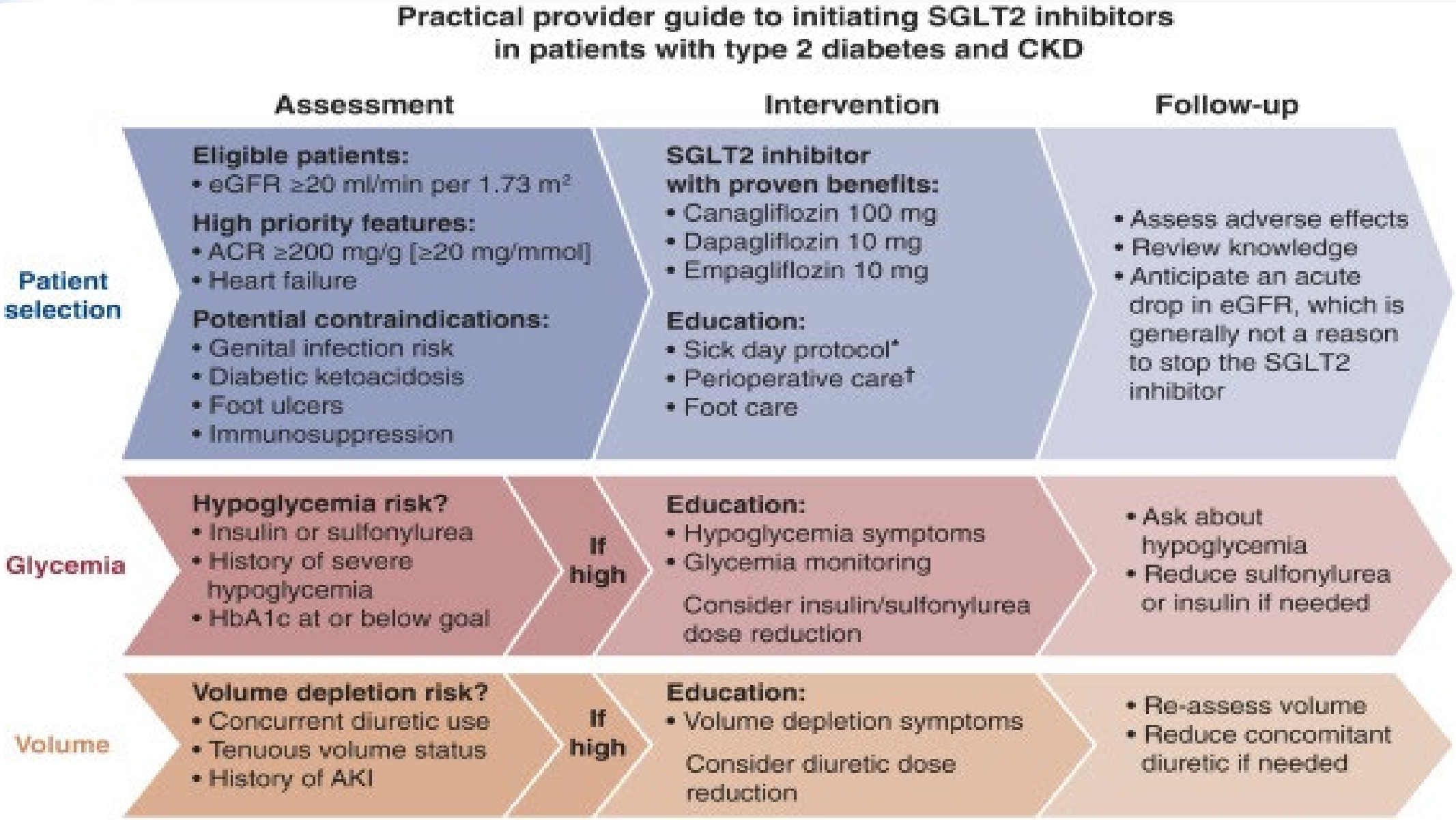
KDIGO Guidelines 2020



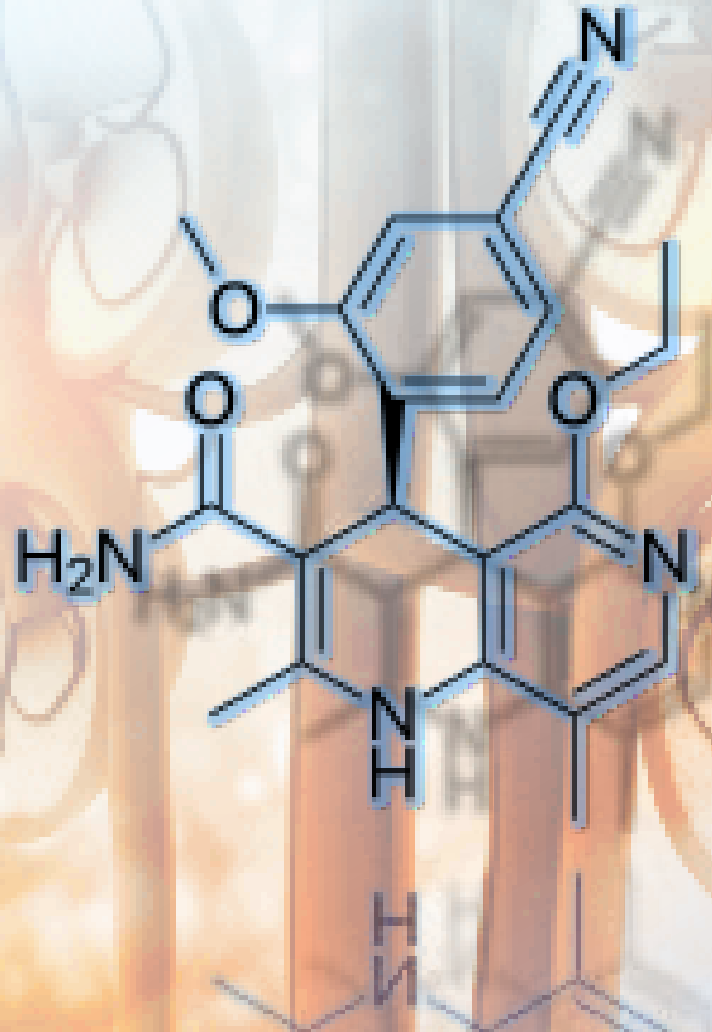
Case

- CC: 58 yo male presents for routine follow-up
- PMHx:
  - DM II x 20 yrs
  - HTN
  - CKD IIIb: Cr 1.5, eGFR 45 ml/min/1.73m2
- Med:
  - Atorvastatin 10 mg PO QD
  - Lisinopril 20 mg PO QD
  - Carvedilol 12.5 mg PO BID
  - HCTZ 12.5 mg PO QD
  - Metformin 1000 mg BID
- Pertinent PE:
  - VS: BMI 37, BP 155/94, HR 80
  - Decreased sensation in both feet without foot ulcers
- Labs: eGFR 49, A1C 8.9, K 5.1, urine albumin/Cr ratio 760 mg/g.

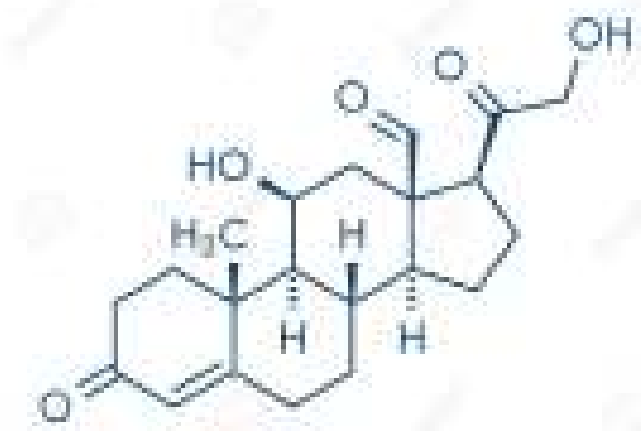
Initiation of SGLT2



Non-Steroidal Mineralocorticoid Antagonist



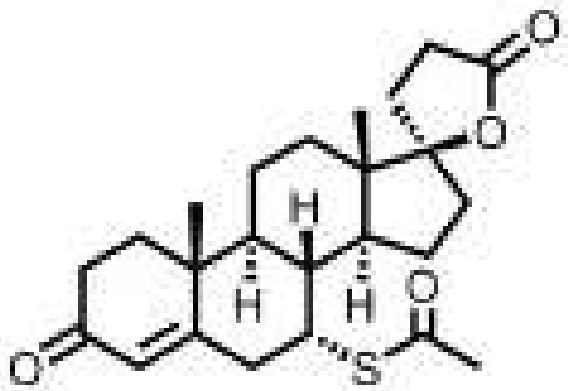
MRA structure



aldosterone

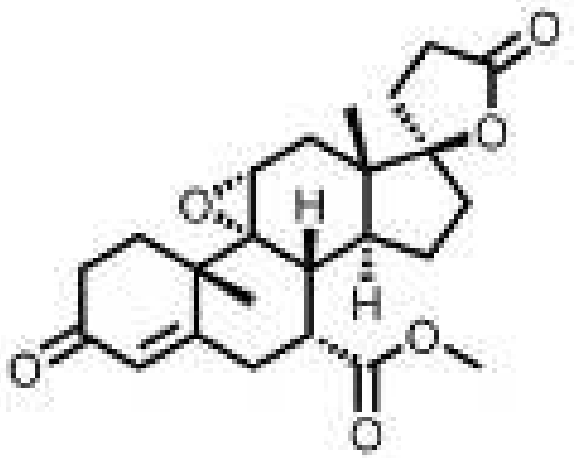
Mineralocorticoid Receptor Antagonists

1st generation



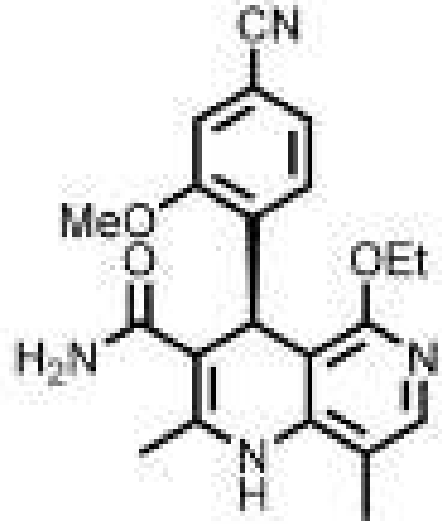
1
Spironolactone

2nd generation



2
Eplerenone

3rd generation



(–)-3
Finerenone

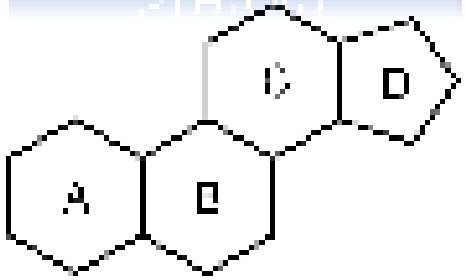
More NS-MRA to follow

Steroidal MRAs
(aldosterone antagonists)

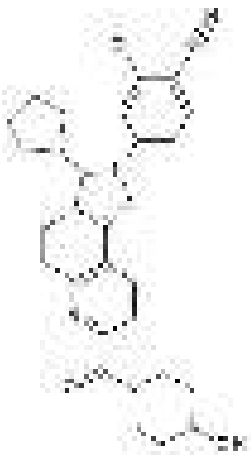
Spironolactone

Eplerenone

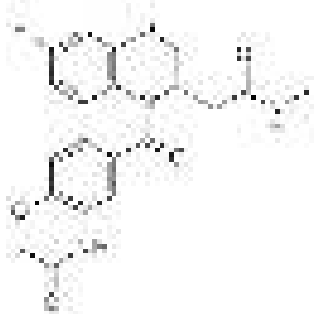
Steroid



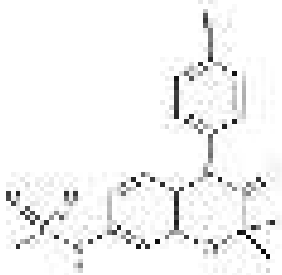
Non-steroidal MRAs



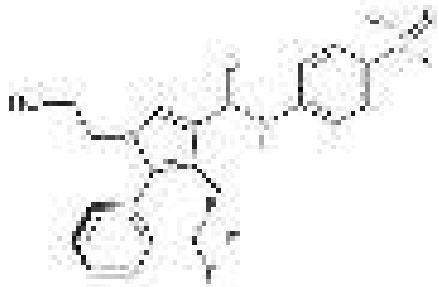
KBP-5074
(Phase II)



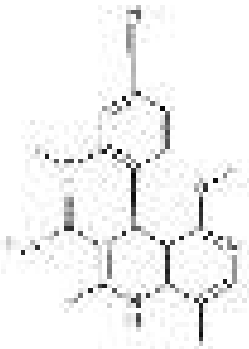
AZD9977
(Phase III)



Apararenone
MT-3995
(Phase II)

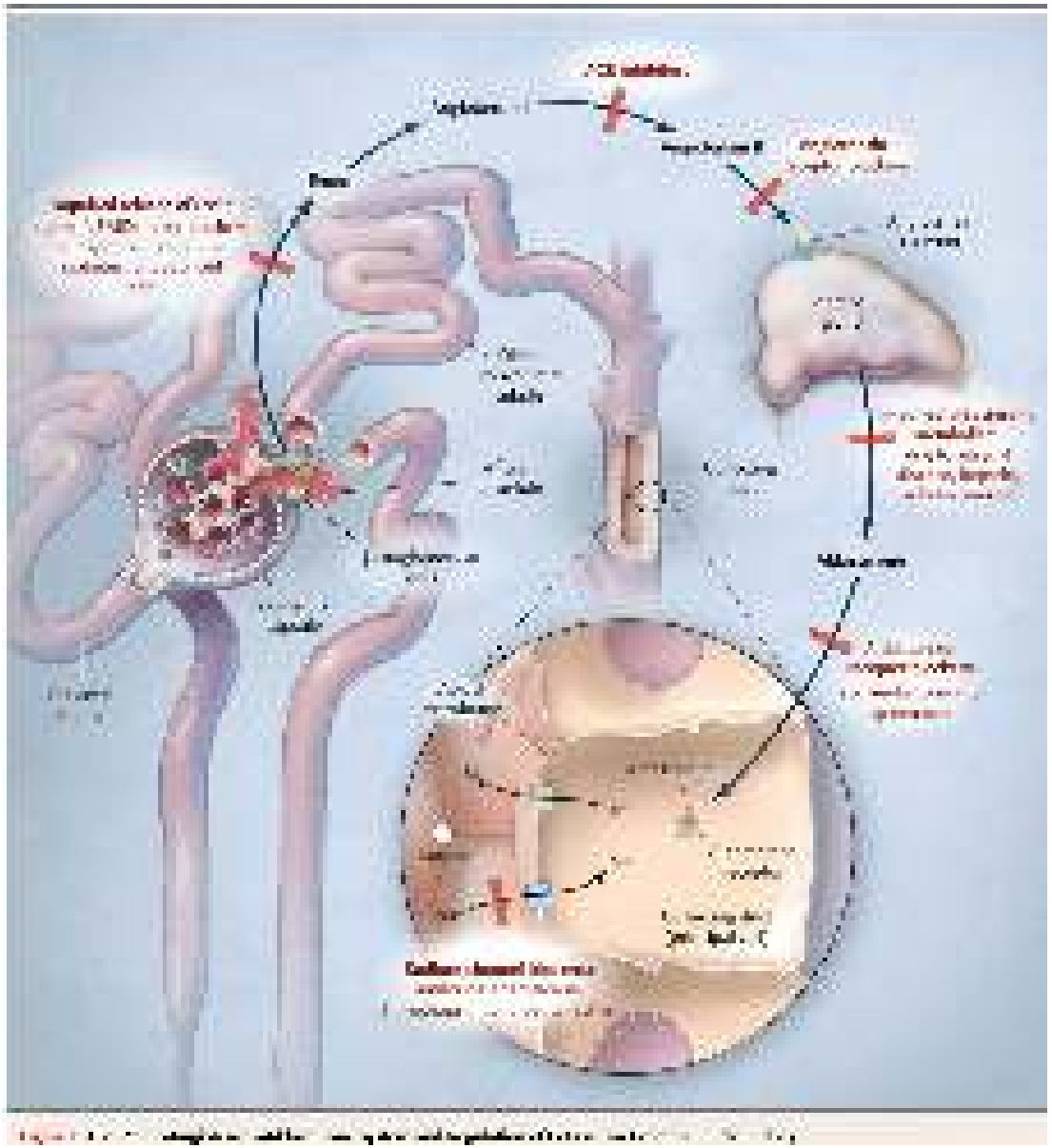


Esaxerenone
CS-3150
(launched in Japan)

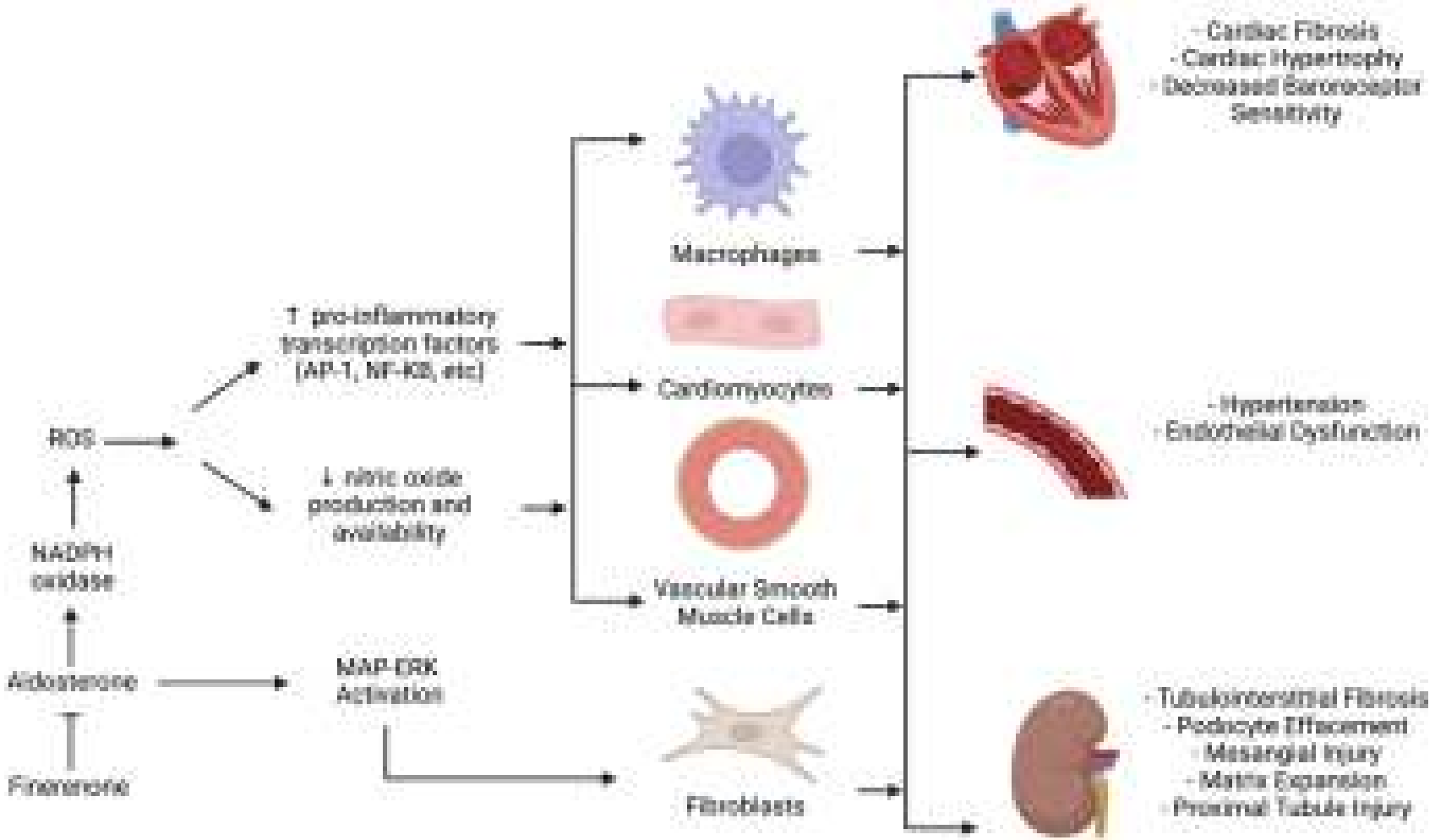


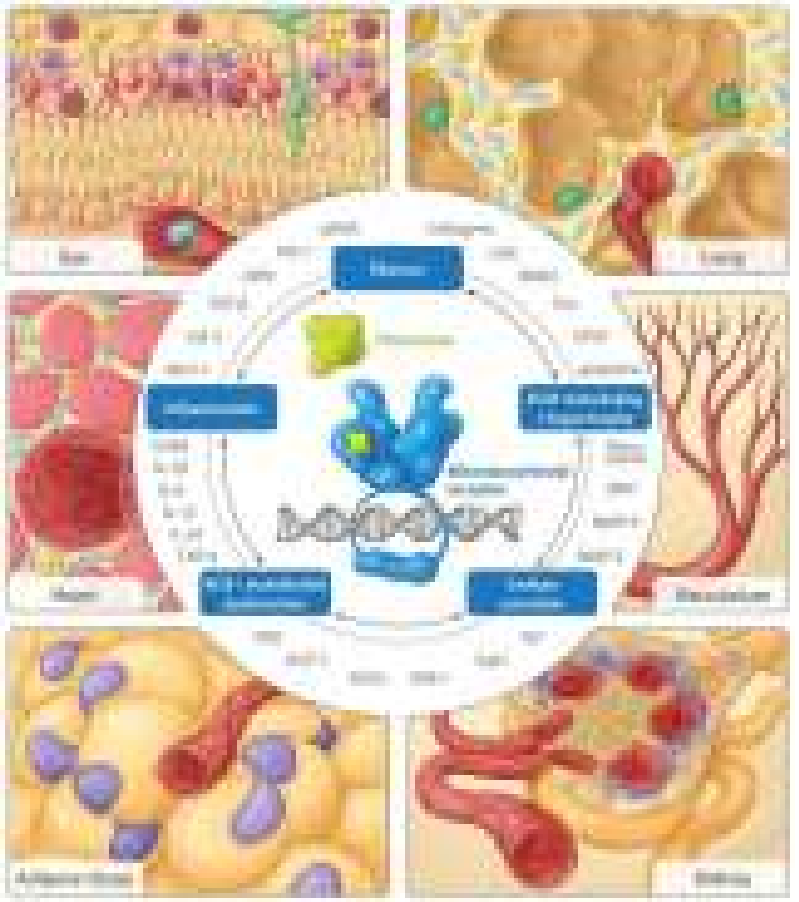
Finerenone
BAY 94-8862
(launched in the United States)

Steroidal MRA

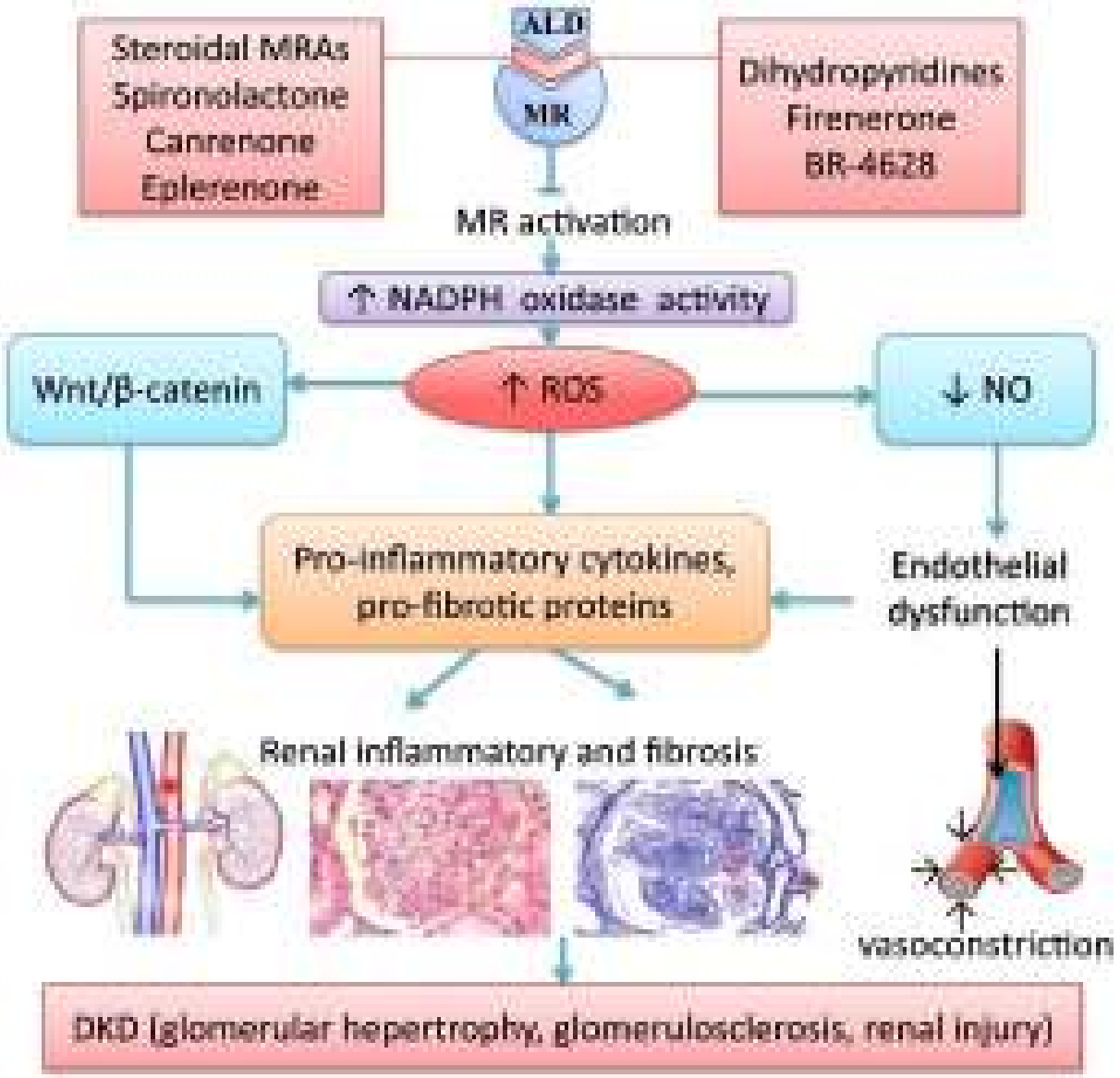


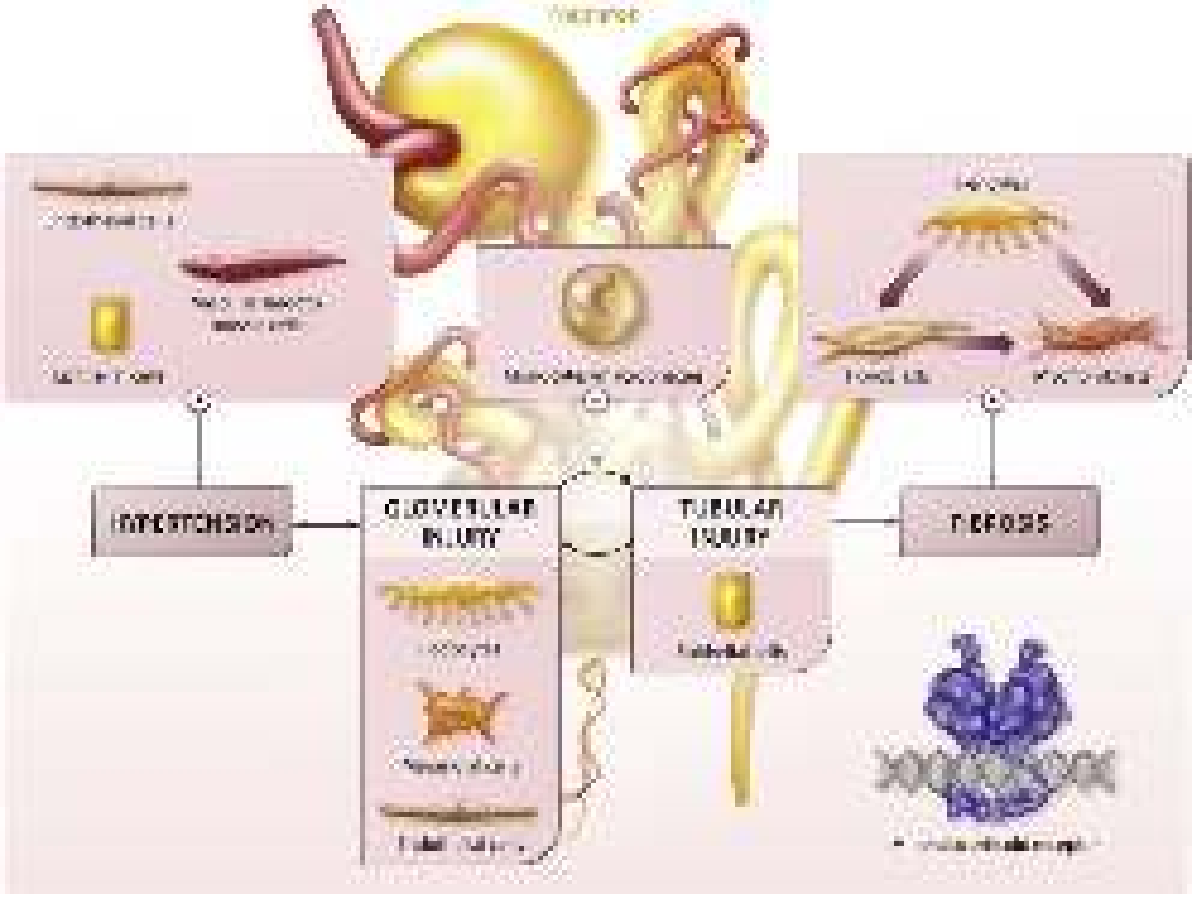
Mechanism of action of NS MRA



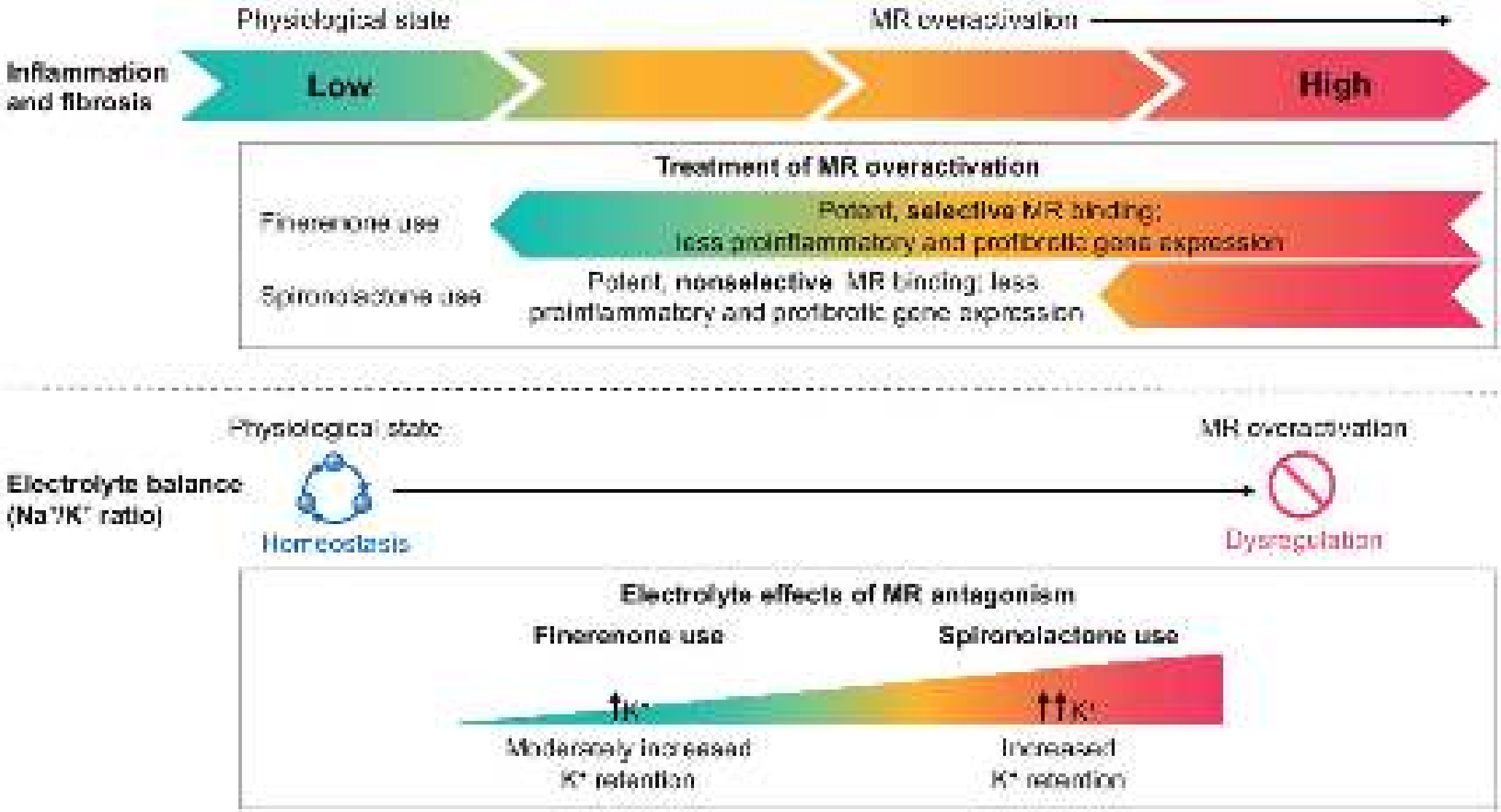


Mechanism of action

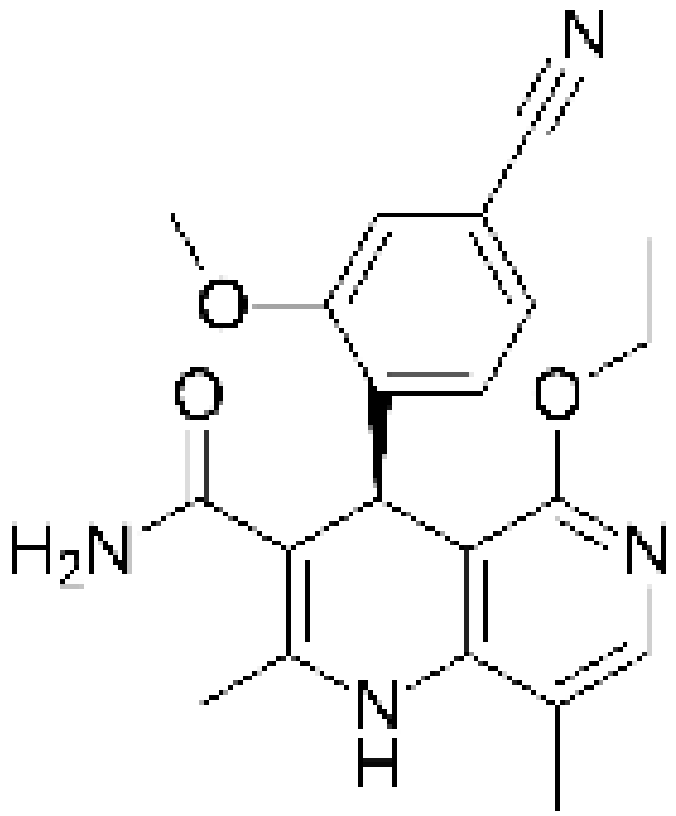




MRA: steroidal vs non steriodal



Finerenone

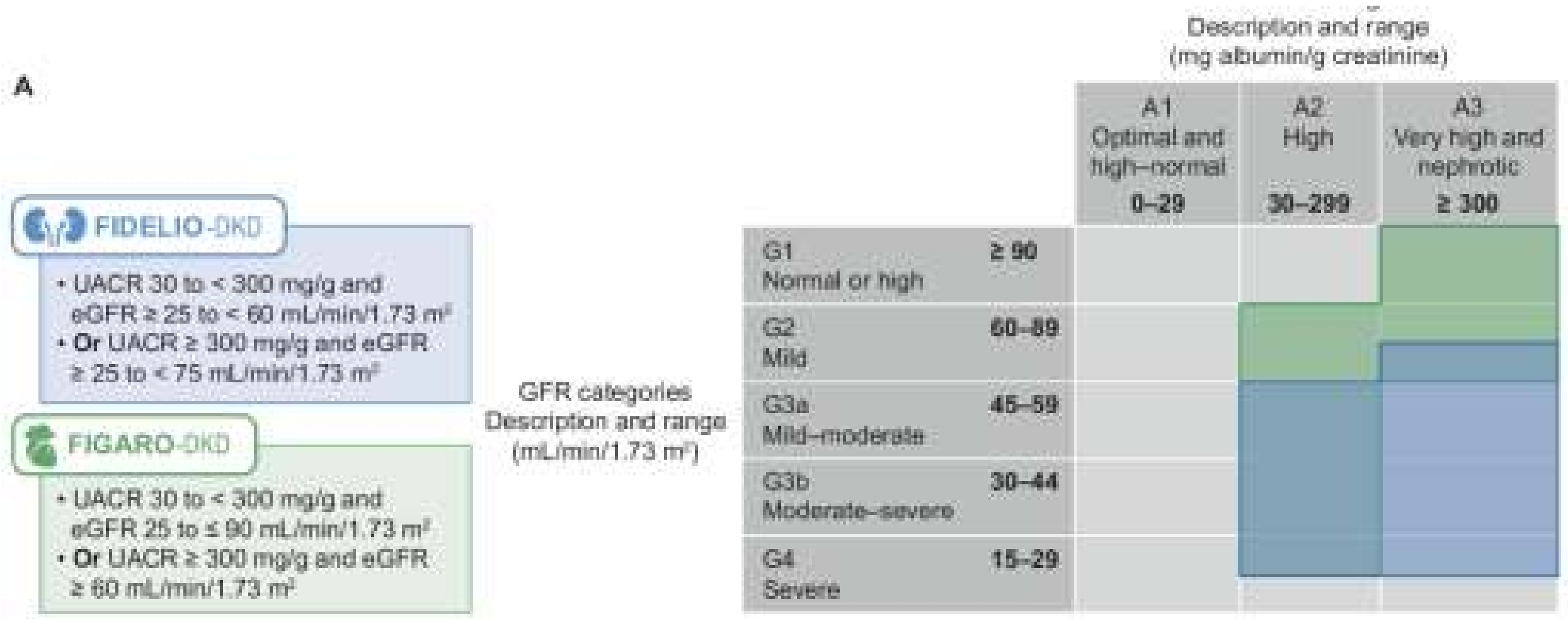

N
O
O
O
H2N
N
N
H


Kerendia
(finerenone) tablets
10
30
Kerendia
(finerenone) tablets
20
90

NS MRA Indications: 2 studies & 1 pooled analysis

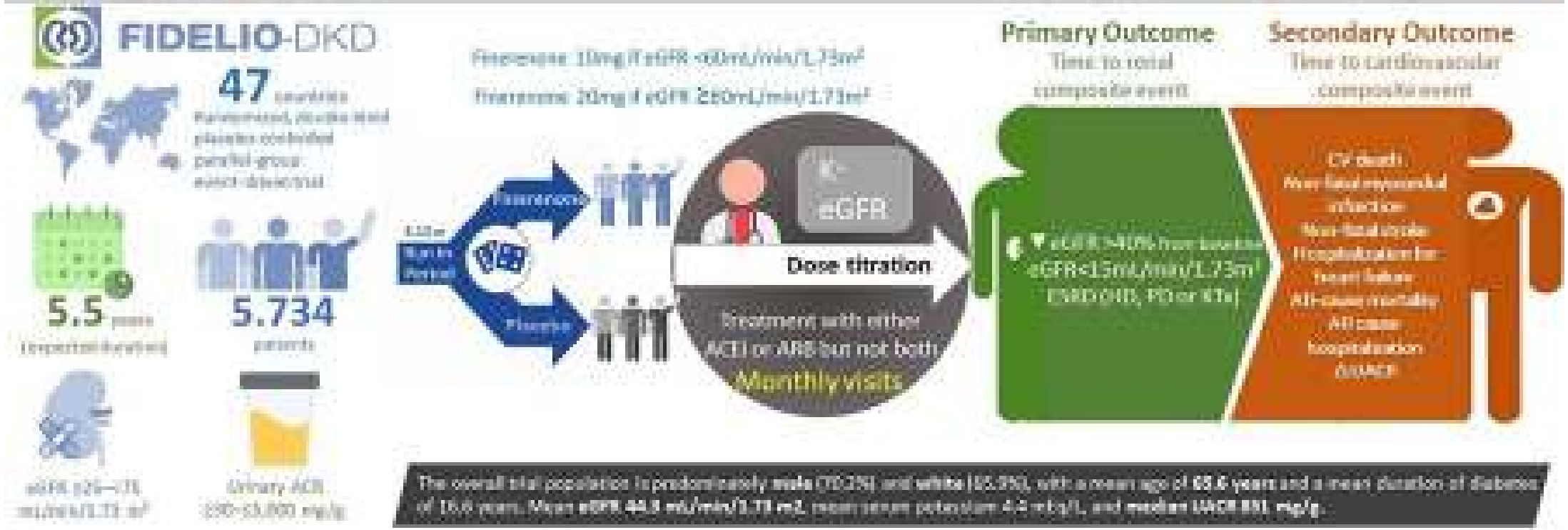
- **FIDELIO-DKD** investigated the efficacy & safety of finerenone in delaying CKD progression in advanced CKD
- **FIGARO-DKD** evaluated the efficacy & safety of finerenone in reducing CV morbidity & mortality in earlier stages of CKD
- **FIDELITY** prespecified individual patient analysis of both trials
- The primary outcomes were defined as:
  - CV endpoints
  - Renal endpoints including:
    - Doubling of serum creatinine
    - Time to ESKD

Indication for MRA



FIDELIO-DKD Prespecified

What's the Design of the "Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease" Trial (FIDELIO-DKD)?

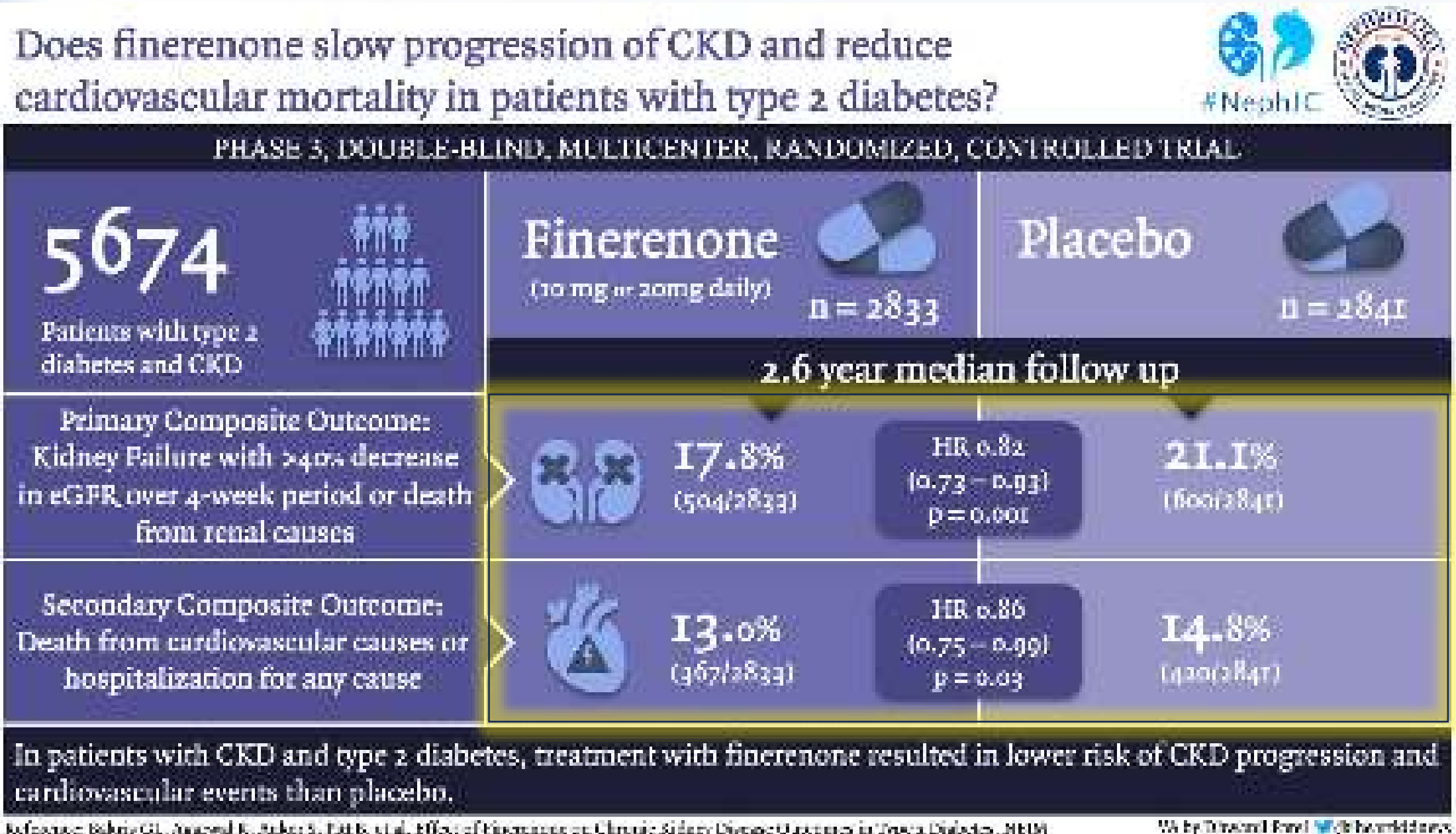


The overall trial population is predominantly male (70.3%) and white (65.3%), with a mean age of 65.6 years and a mean duration of diabetes of 16.6 years. Mean eGFR 44.8 mL/min/1.73 m2, mean serum potassium 4.6 mEq/L, and median UACR 851 mg/g.

Conclusion: The results of FIDELIO-DKD will determine whether an optimally treated cohort of T2D patients with CKD at high risk of progression of their renal disease and CV events will experience cardiorenal benefits with the addition of finerenone to their treatment regimen. Results are expected in 2020.

Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Nowack C, Kolkhof P, Ferreira AC, Schloemer P, Filippatos G. Design and Baseline Characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. Am J Nephrol DOI: 10.1159/000503713

FIDELIO-DKD


Does finerenone slow progression of CKD and reduce cardiovascular mortality in patients with type 2 diabetes?
#NephIC
PHASE 3, DOUBLE-BLIND, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL
5674
Patients with type 2 diabetes and CKD
Finerenone
(10 mg or 20mg daily)
n = 2833
Placebo
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.

FIGARO

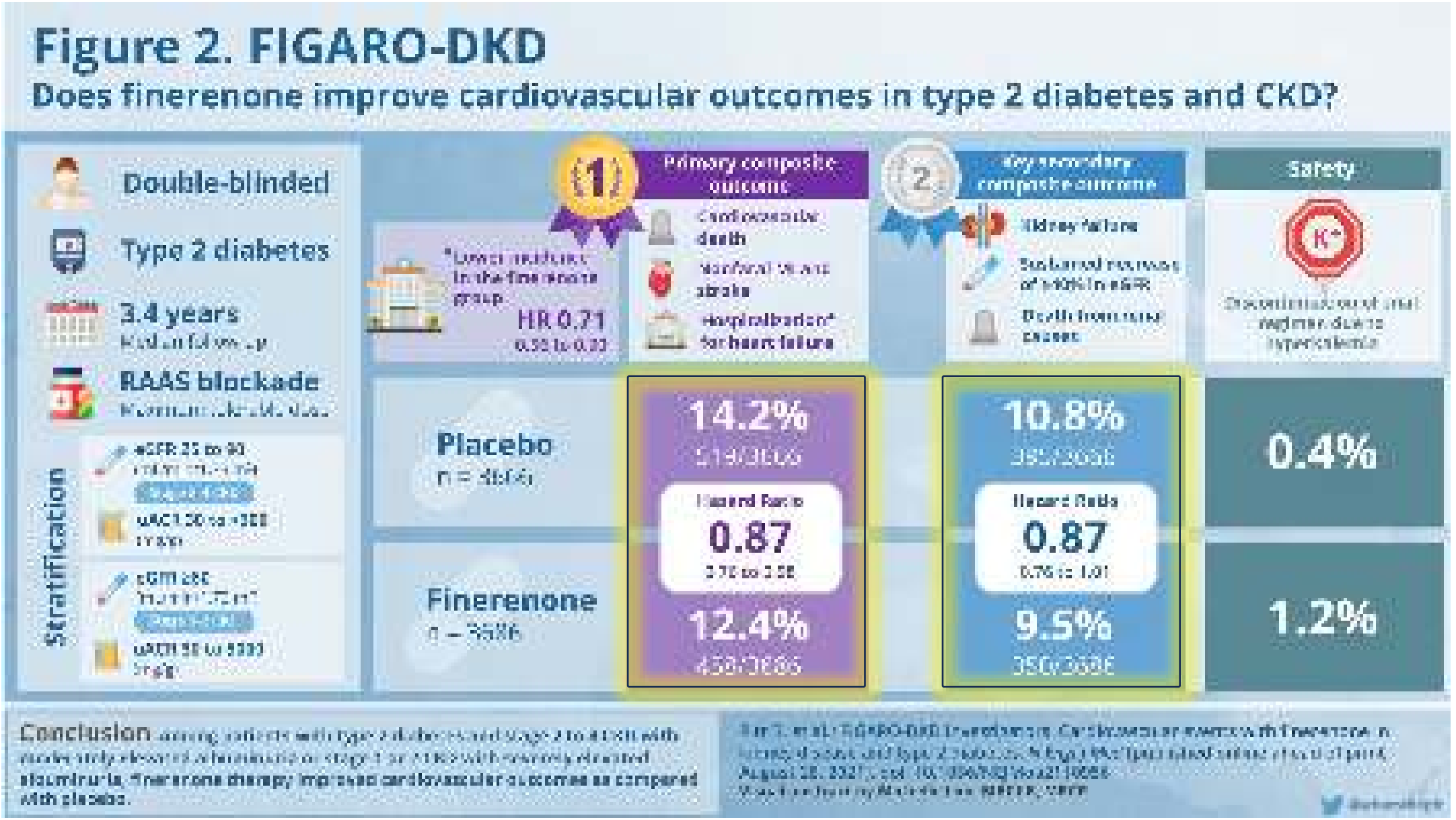
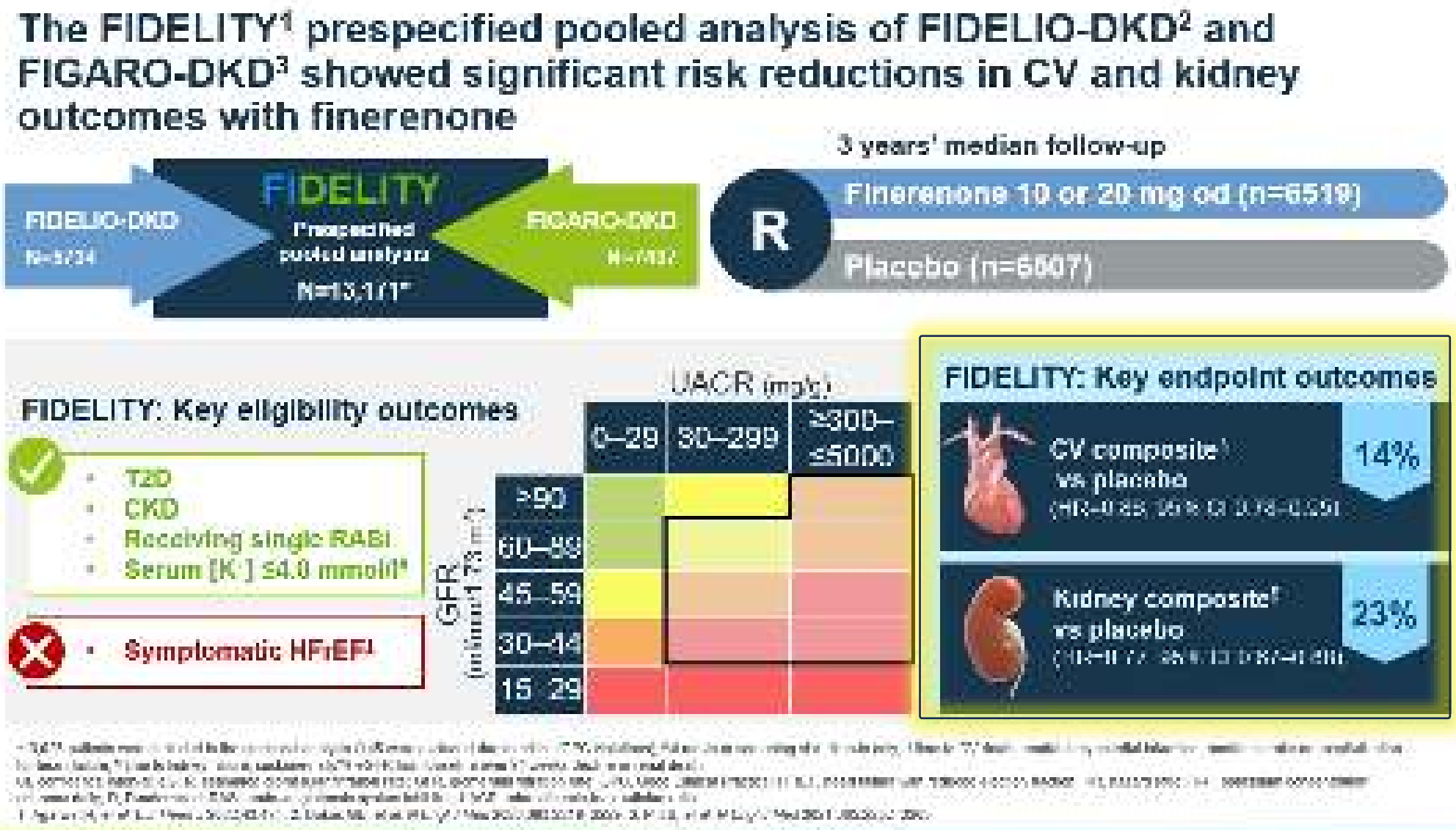


Figure 2. FIGARO-DKD
Does finerenone improve cardiovascular outcomes in type 2 diabetes and CKD?
Double-blinded
Type 2 diabetes
3.4 years
RAAS blockade
Stratification
1
Primary composite outcome
Cardiovascular death
Nonfatal MI and stroke
Hospitalization* for heart failure
*Lower incidence in the finerenone group
HR 0.71
2
Key secondary composite outcome
Kidney failure
Sustained decrease of ≥40% in eGFR
Death from renal causes
Safety
Discontinuation of trial regimen due to hyperkalemia
Placebo
Finerenone
14.2%
12.4%
Hazard Ratio
0.87
10.8%
9.5%
Hazard Ratio
0.87
0.4%
1.2%
Conclusion

FIDELITY pooled analysis



FIDELITY pooled analysis

Kidney Outcomes with Finerenone in Patients with Type 2 Diabetes and Chronic Kidney Disease: The FIDELITY Pre-Specified Pooled Analysis

Methods and Cohort

- Pre-specified pooled efficacy and safety analysis
- FIDELIO and FIGARO RCT cohorts (n= 13 026)
  - ✓ Age ≥18 years
  - ✓ Type 2 DM and CKD
    - mean eGFR 57.6mL/min/1.7m2
    - median UACR 515 mg/g
  - ✓ on maximum tolerated RASi
- Finerenone vs placebo

Key Outcomes

	Placebo	Finerenone	HR (95% CI)
Kidney composite efficacy outcome	7.1%	5.5%	0.77 (0.67–0.88) p= 0.0002
Sustained eGFR reduction ≥57%	5.5%	3.9%	0.70 (0.60-0.83) p<0.0001
Kidney failure*	4.6%	3.9%	0.84 (0.71-0.99) p=0.03
Renal death	<0.1%	0.1%	0.53 (0.10-2.91) p= 0.46
Safety			
SAE†	33.7%	31.6%	
Hyperkalemia	5.9%	12.0%	

*Kidney failure = end-stage kidney disease (ESKD) or a sustained decrease in eGFR to <15 mL/min/1.73 m2

†Serious adverse event

Conclusion: Finerenone reduced the risk of clinically important kidney outcomes vs. placebo across the spectrum of CKD in patients with type 2 diabetes.

supported by an unrestricted educational grant from Bayer AG

Agarwal et al., *European Heart Journal* (2022)

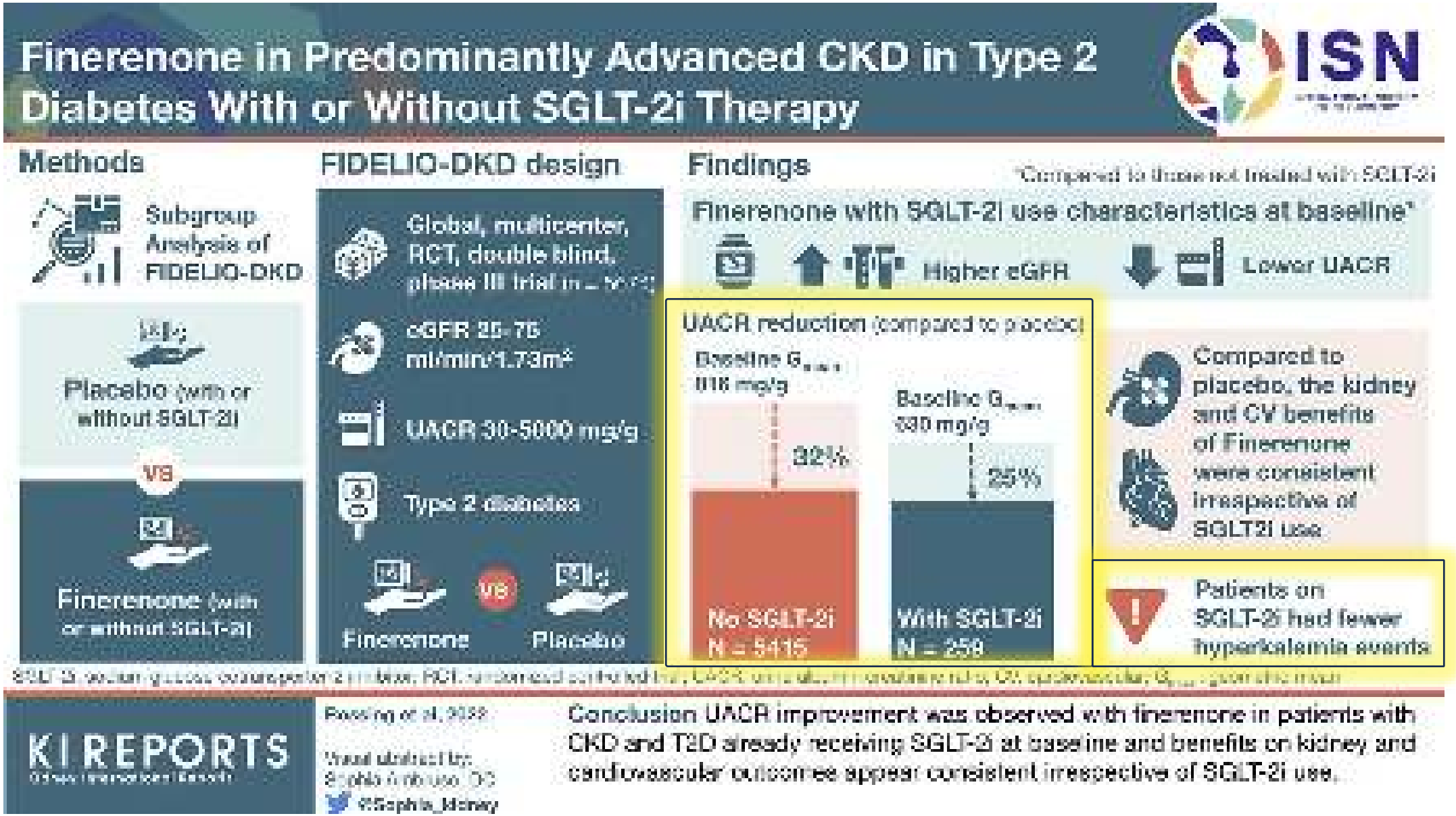
by Dilushi Wijayaratne MD MRCP
@Dilushiwijay

Finerenone in CKD: Meta-Analysis of RCT

- **Objective:** validate efficacy & safety of finerenone in CKD
- **Results:** 5 trials (n = 13,078) were included. Finerenone significantly:
  - Lower UACR from baseline [**MD -0.30** (95% CI -0.32, -0.28), $p < 0.00001$]
  - Decrease eGFR from baseline [**MD -2.44** (95% CI -2.82, -2.05), $p < 0.00001$]
  - Proportion of patients with decreased eGFR (≥40%) was lower [**RR 0.85** (95% CI 0.78, 0.93), $p = 0.0002$]
  - Lower ESKD [**RR 0.80** (95% CI 0.65, 0.99), $p = 0.04$]
  - Lower CVs [**RR 0.88** (95% CI 0.80, 0.95), $p < 0.003$]
- Safety:
  - Increase in the [K] [**MD 0.17** (95% CI 0.10, 0.24), $p < 0.00001$]
  - Higher incidence of hyperkalemia [**RR 2.03** (95% CI 1.83, 2.26), $p < 0.00001$]
- **Conclusion:** finerenone confers significant renal & CV benefits in patients with CKD. While higher risk of hyperkalemia

Front Pharmacol 2022 Feb

Combining NS MRA & SGLT2



Cochrane Central Register: Hyperkalemia & AKI

BMC Cardiovasc Disord 2016 Dec 1;16(1):246

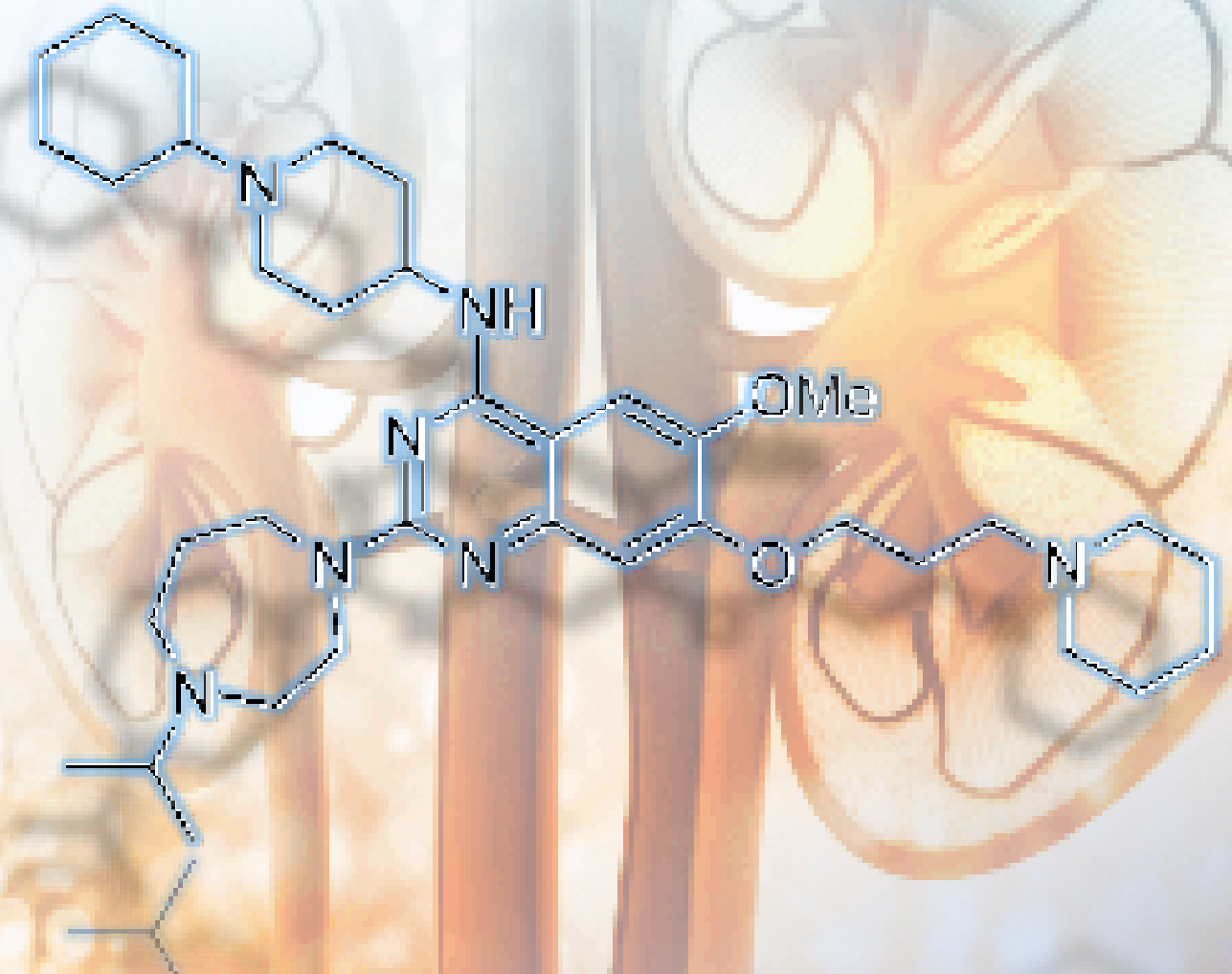
Aldosterone antagonist versus placebo or standard care for proteinuric CKD					
Patient or population: [illegible] Intervention: [illegible] Comparison: placebo or standard care					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or standard care	Risk with aldosterone antagonist			
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible] per 1,000	[illegible] per 1,000 [illegible]	RR [illegible] [illegible]	[illegible]	[illegible] MODERATE
[illegible]	[illegible] per 1,000	[illegible] per 1,000 [illegible]	RR [illegible] [illegible]	[illegible]	[illegible] LOW [illegible]
[illegible]	[illegible] per 1,000	[illegible] per 1,000 [illegible]	RR [illegible] [illegible]	[illegible]	[illegible] LOW [illegible]
[illegible]	[illegible]	[illegible] per 1,000 [illegible]	RR [illegible] [illegible]	[illegible]	[illegible] LOW [illegible]
AKI	[illegible] per 1,000	[illegible] per 1,000 [illegible]	RR [illegible] [illegible]	[illegible]	[illegible] MODERATE [illegible]
[illegible]	[illegible]		-	[illegible]	[illegible] VERY LOW [illegible]
[illegible]	[illegible]			[illegible]	[illegible] LOW [illegible]

Conclusion

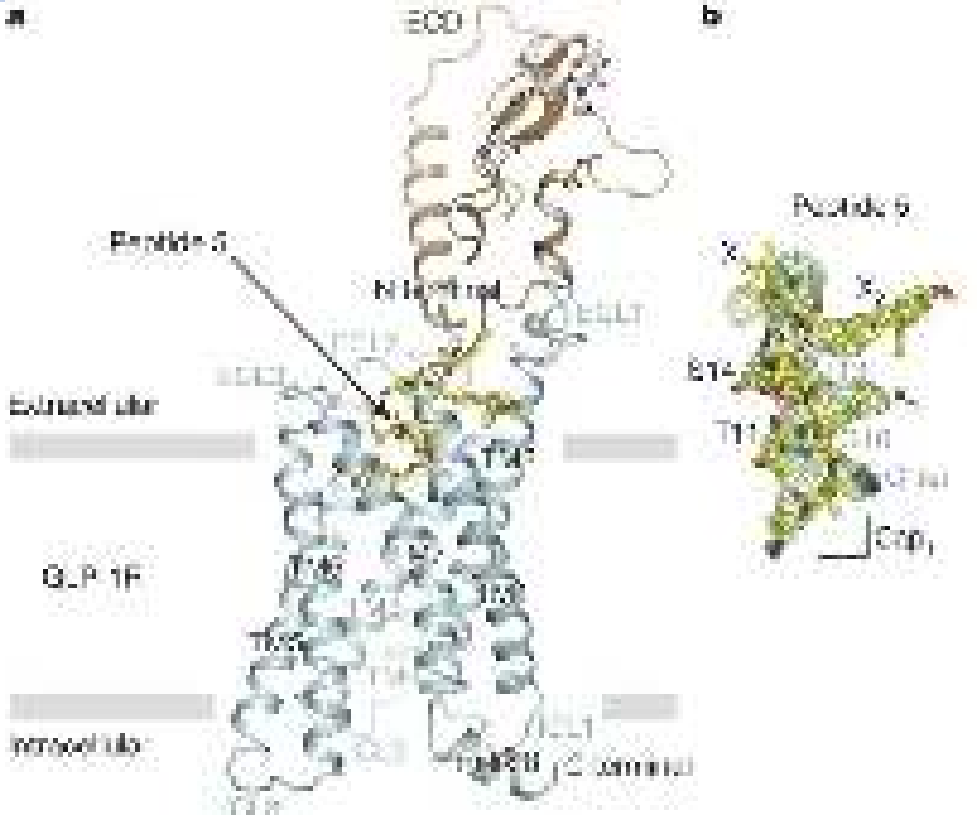
- In patients with T2D and DKD, finerenone reduced albuminuria with a lower risk of hyperkaliemia than observed with steroidal MRAs

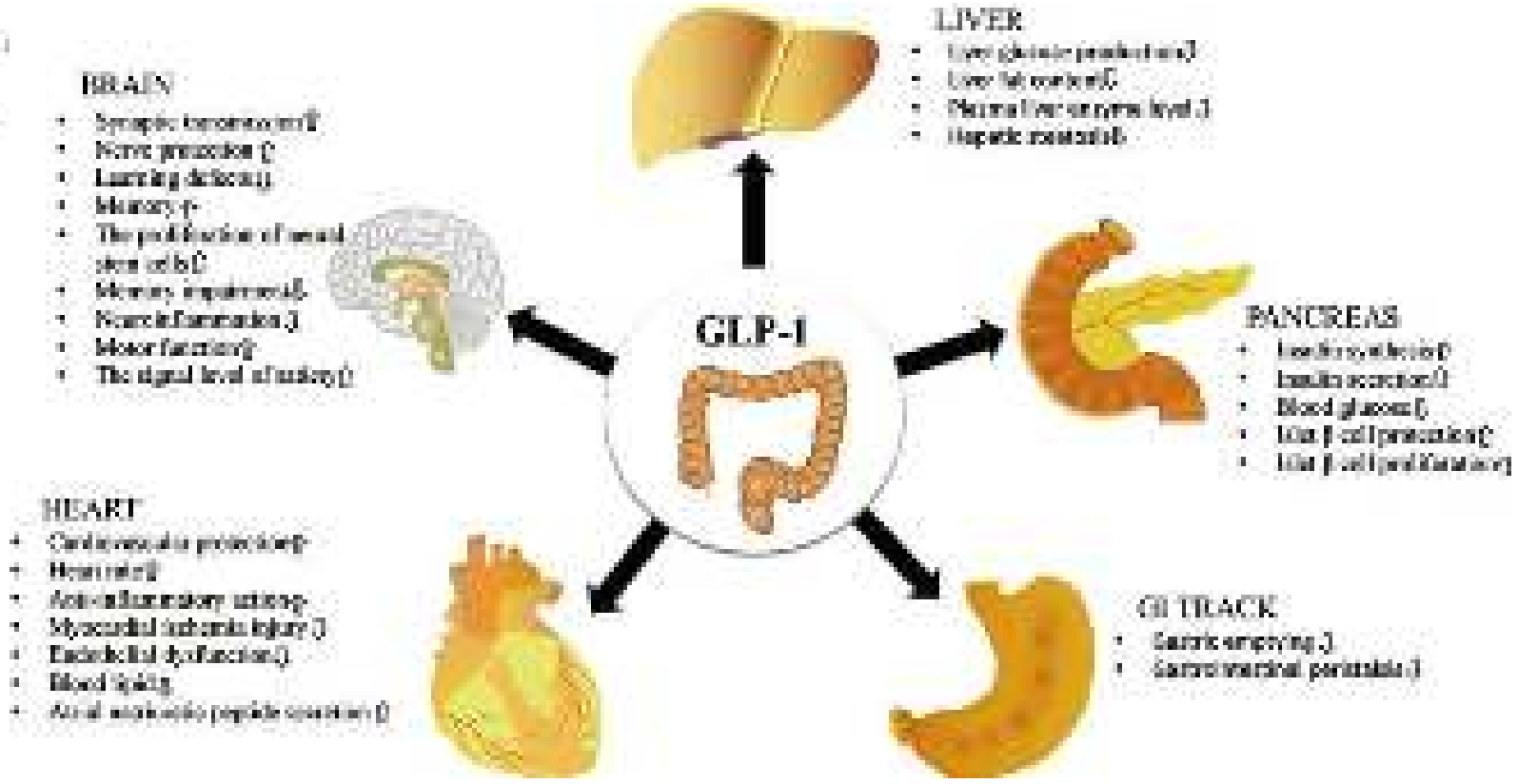
- Approved by the FDA to reduce the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks and hospitalization for CHF in patients with T2D

Glucagon-like peptide-1 receptor agonist



GLP-1 Receptor & GLP-RA





GLP-1 agonists

- Dulaglutide (Trulicity) (weekly)
- Exenatide extended release (Bydureon bcise) (weekly)
- Exenatide (Byetta) (BID)
- Semaglutide (Ozempic) (weekly)
- Liraglutide (Victoza, Saxenda) (QD)
- Lixisenatide (Adlyxin) (QD)
- Semaglutide (Rybelsus) (PO QD)
- Semaglutide (Wegovy) (weekly)

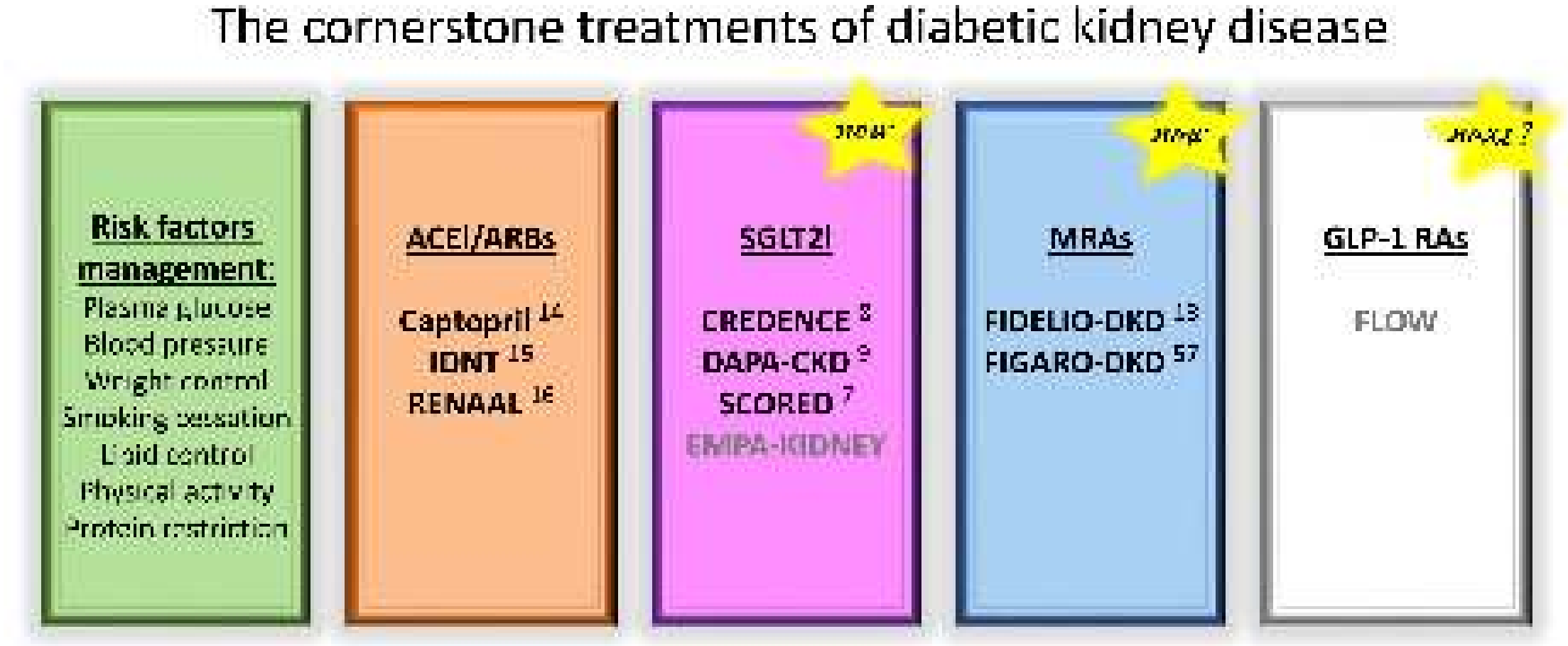
Some combined with Insulin

Summary of utilization in CKD

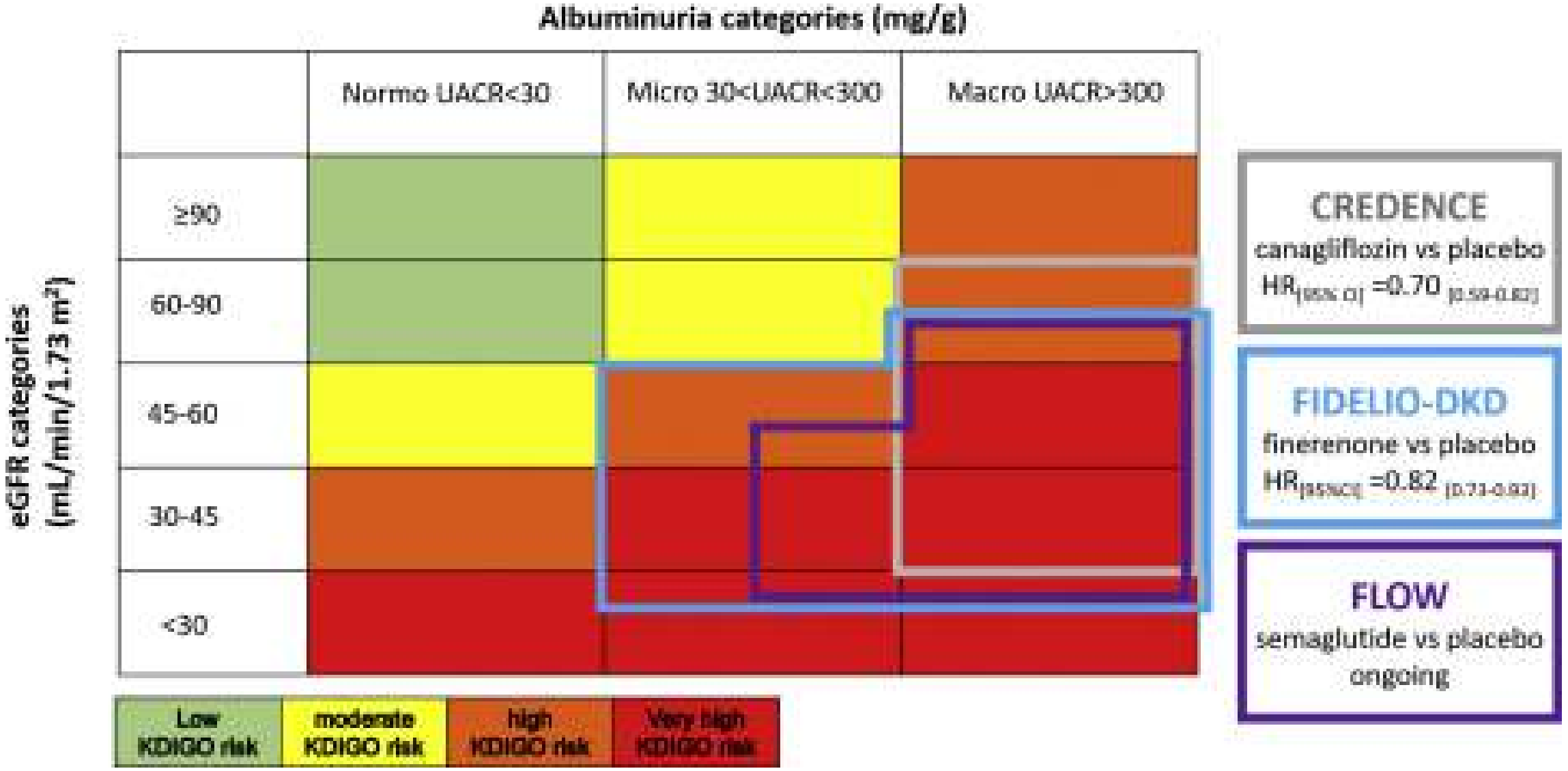
- Phase 2-3 trials, show that GLP-1 RAs are **safe & effective** in reducing glycemia and body weight, including in patients with **eGFR > 15** mL/min/1.73 m2
- As the **therapeutic options** for patients with CKD **limited**
- Data are **lacking** regarding the safety and efficacy of GLP-1 RAs in patients with **ESKD**
- **Limited** data on the effects in kidney **transplant**
- GLP-1 RAs have beneficial CV effects in patients w & wo CKD
  - Probably even greater in patients with CKD
- Most consistent finding is reduction of new **macroalbuminuria**
- Risk to develop ESKD have yet to be demonstrated

DKD treatment: FLOW

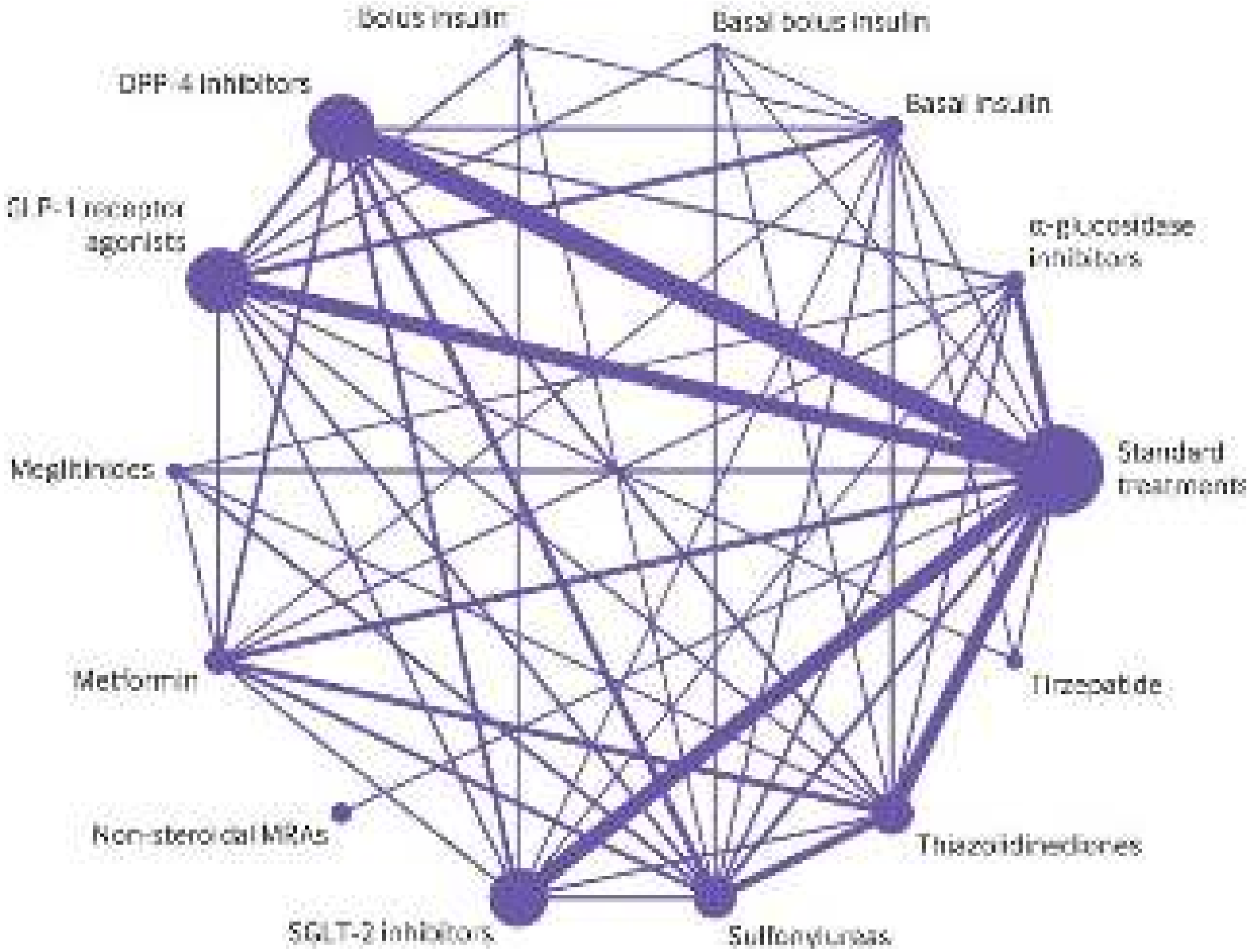
- FLOW trial is the first long-term kidney outcome trial, studying the effects of the GLP-1 RA, semaglutide, on kidney outcomes



DKD treatment: FLOW



Putting all together: 13 different drug classes



BMJ 2023 Apr 6;381

Benefits & harms of drug treatment for T2D: meta-analysis

Eligibility criteria for selecting studies:

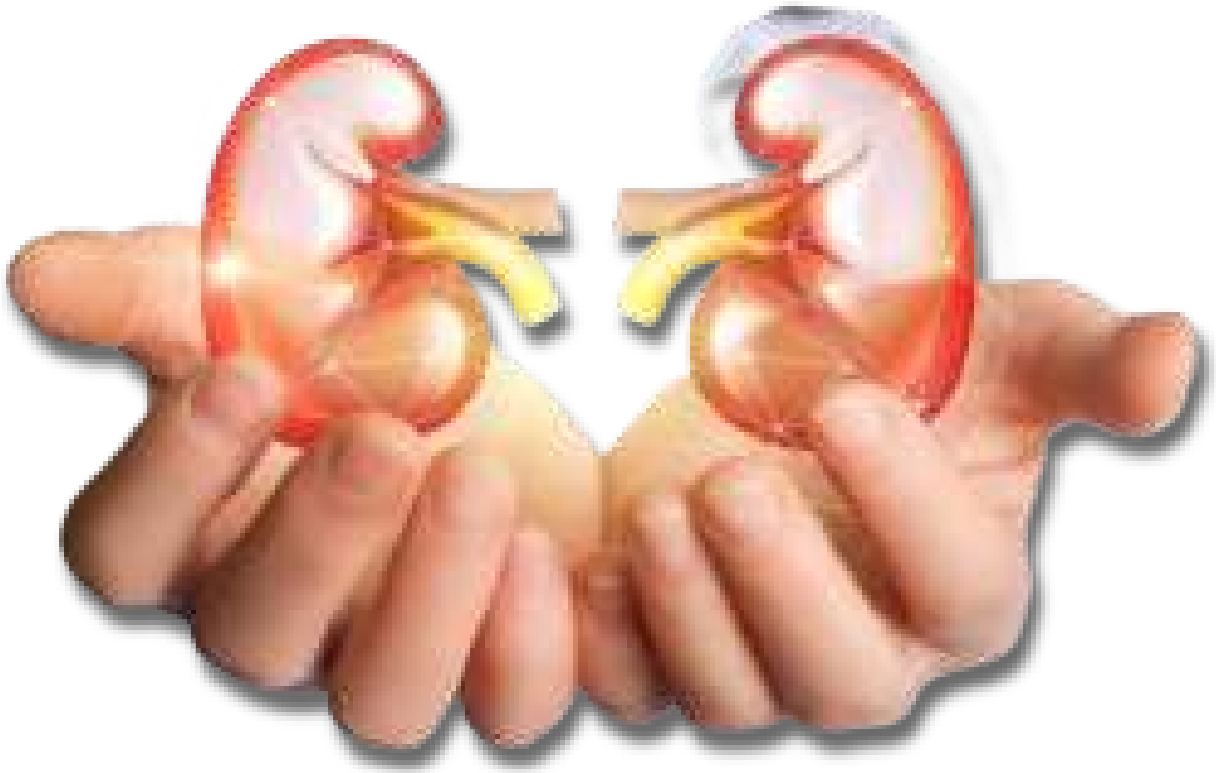
- Eligible RCT compared drugs of interest in adults with DM-II
- F/U > 24 wk

Results:

- 816 trials with 471 038 patients, evaluating 13 different drug classes
  - **SGLT-2** inhibitors (**OR 0.88**, 95% CI 0.83 to 0.94) & GLP-1 RA (**0.88**, 0.82 to 0.93) reduce **all cause death**
  - NS MRA (only with **finerenone**) probably reduce **mortality** (**OR 0.89**, 0.79 to 1.00)
  - **SGLT-2** inhibitors and **GLP-1 RA** reduce **CV death, non-fatal MI, admission to hospital for CHF, & ESRD**
  - Finerenone probably reduces admissions to hospital for CHF, & possibly CV death
  - Only **GLP-1 RA** reduce non-fatal **stroke**
  - **Tirzepatide** probably results in the largest **reduction in body weight** (mean difference **-8.57 kg**)
  - Basal **insulin** (difference **2.15 kg**) & **thiazolidinediones** (difference **2.81 kg**) probably result in the **largest increases in body weight**

BMJ 2023 Apr 6;381

Protect the beans!



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