The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

UPDATES IN THE MANAGEMENT OF DIABETIC KIDNEY DISEASE

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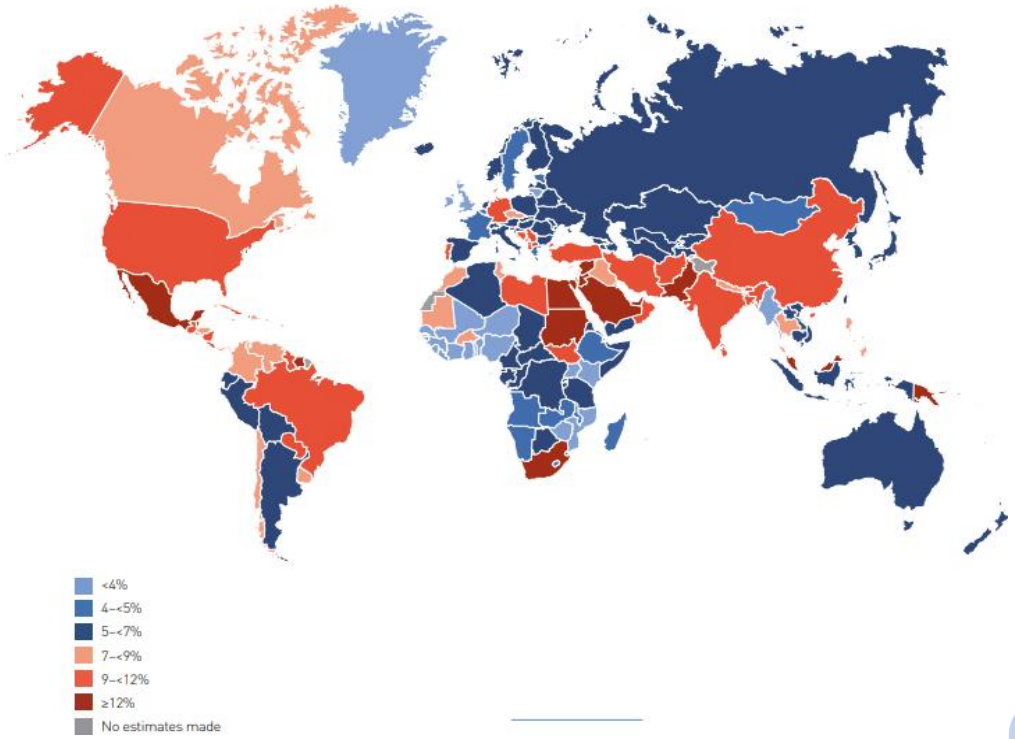
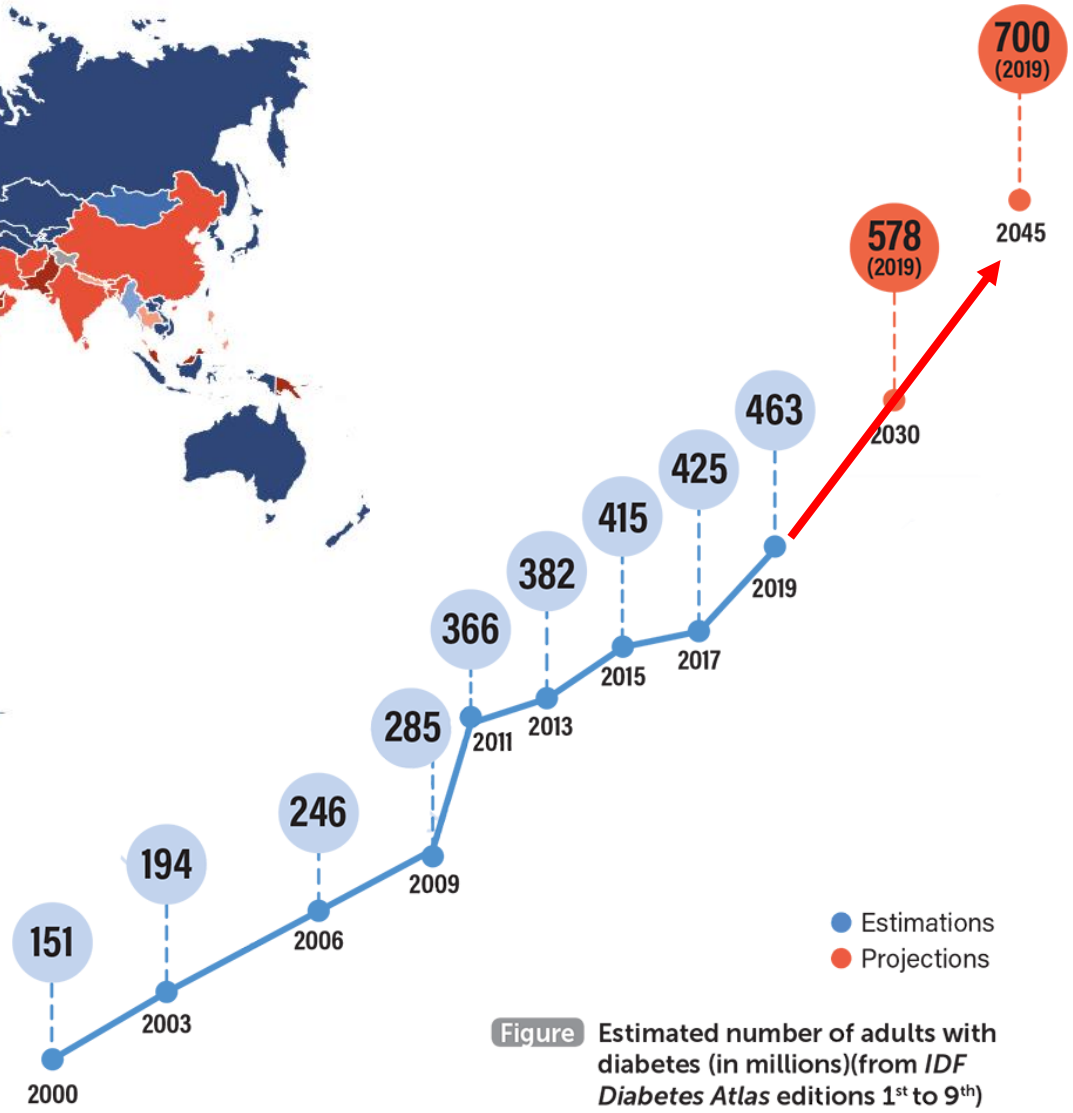
TEHRAN 2023

DIABETES IS AN ANCIENT DISEASE

- First defined in Anatolia by a healtcare provider of the time (A.C. 100-150 Cappadocia)
- “diabetes” (separate feet)
- First description included ‘all muscle and bones of people with diabetes turned into urine’
- Since ancient times diabetes has been in the interest of nephrology (ists)

Hesi Ra, 3rd Dynasty, Ancient Eygpt





3 fold increase in 20 years

Figure Estimated number of adults with diabetes (in millions)(from *IDF Diabetes Atlas* editions 1st to 9th)

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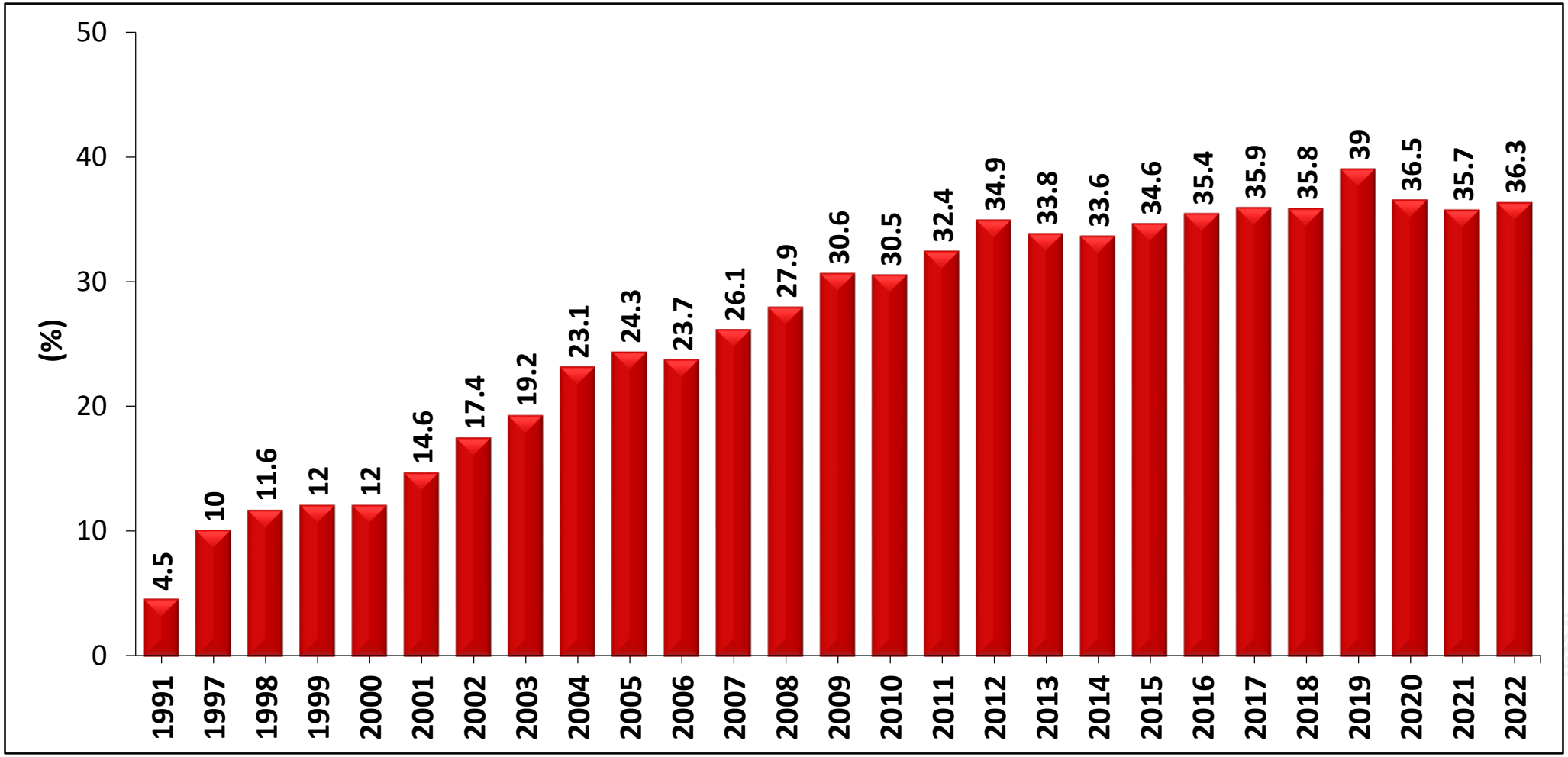
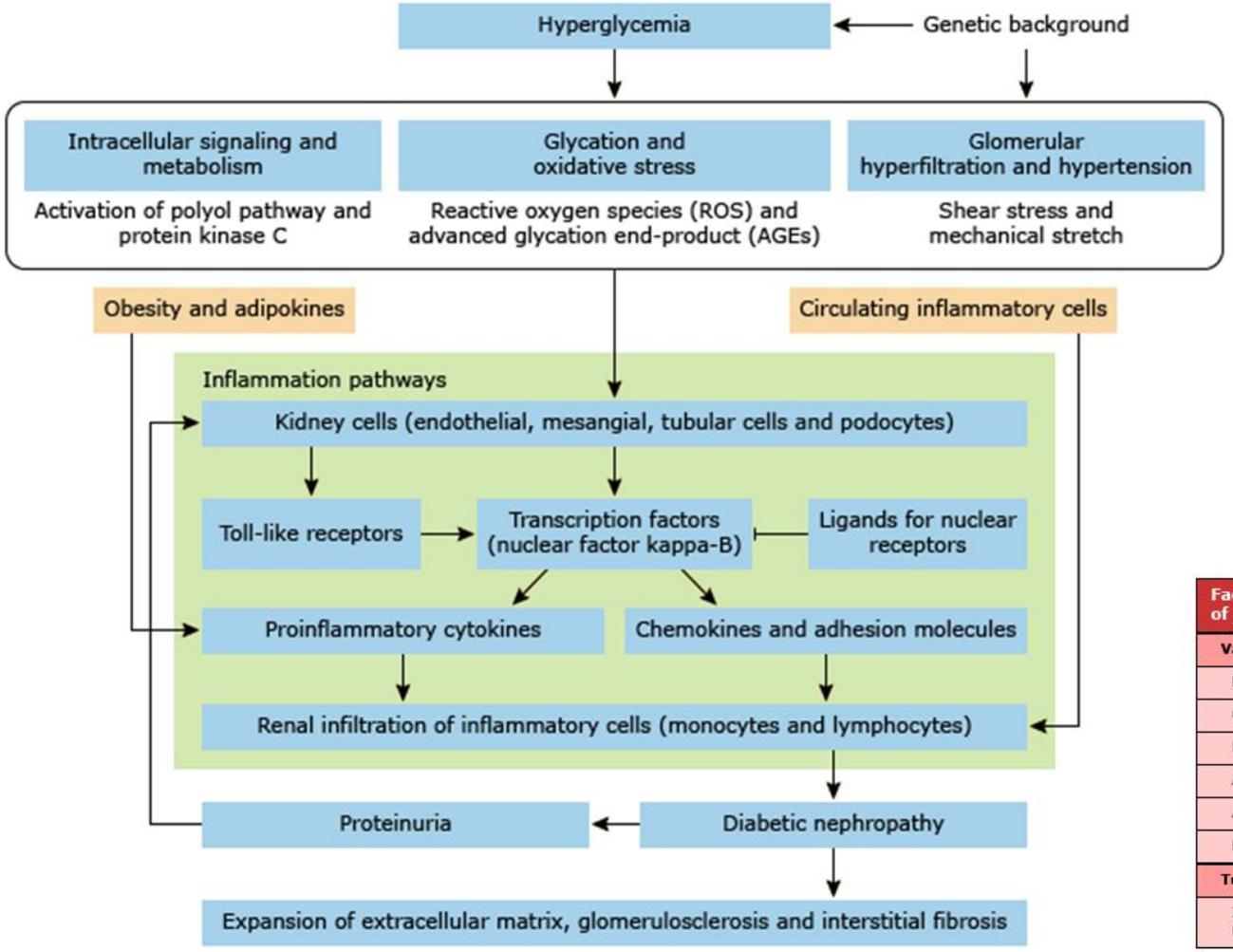
Diabetes Atlas 8th edition 2019

PREVALENT HD PATIENTS WITH DKD

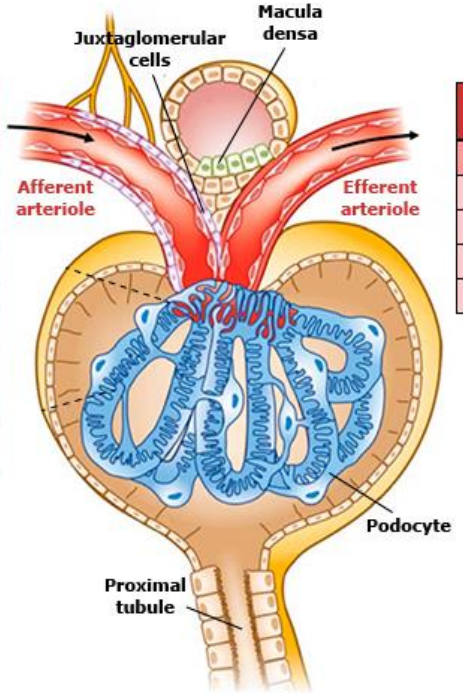


Registry of The Nephrology, Dialysis and Transplantation in Türkiye, 2022



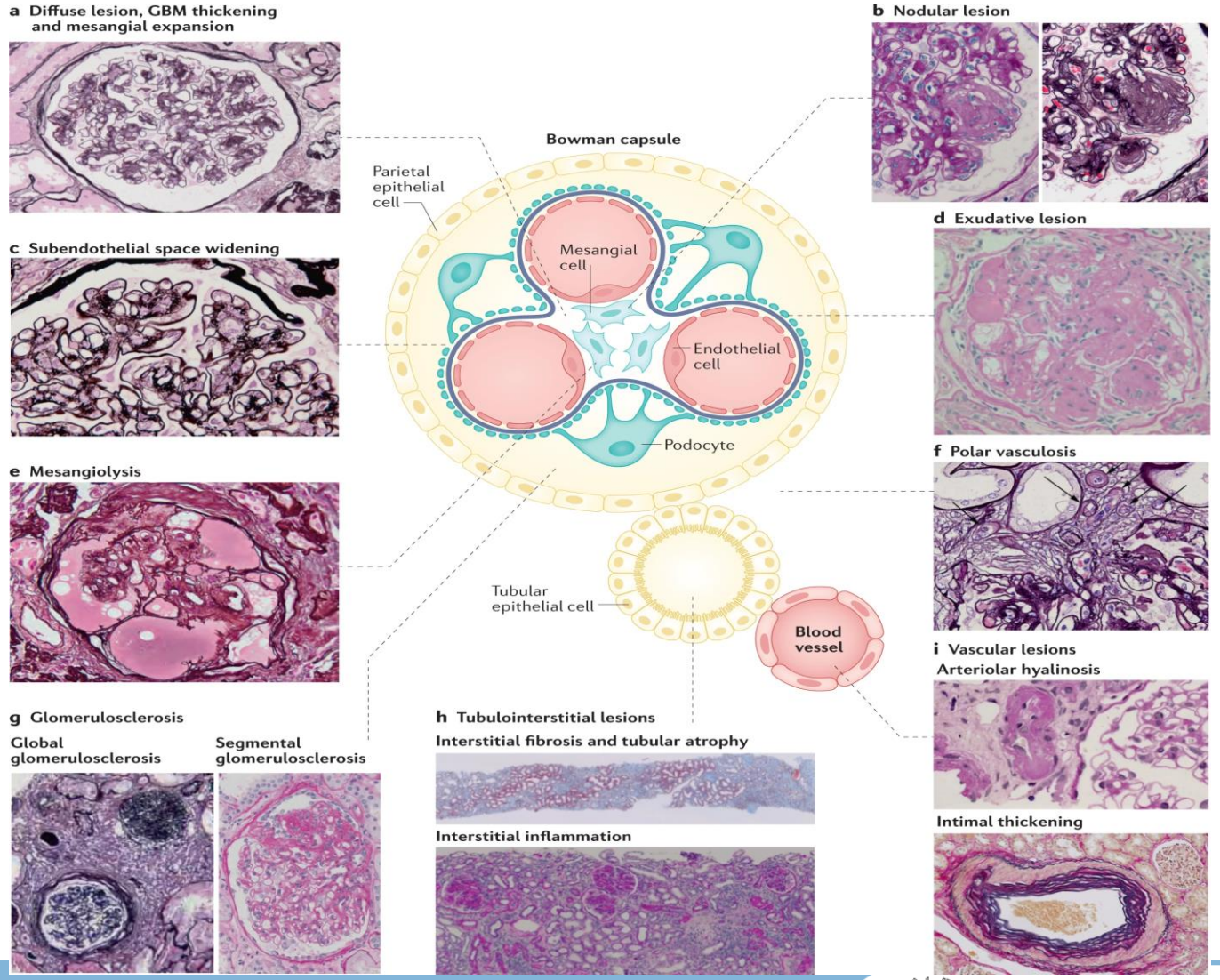
Hyperfiltration in diabetic kidney disease

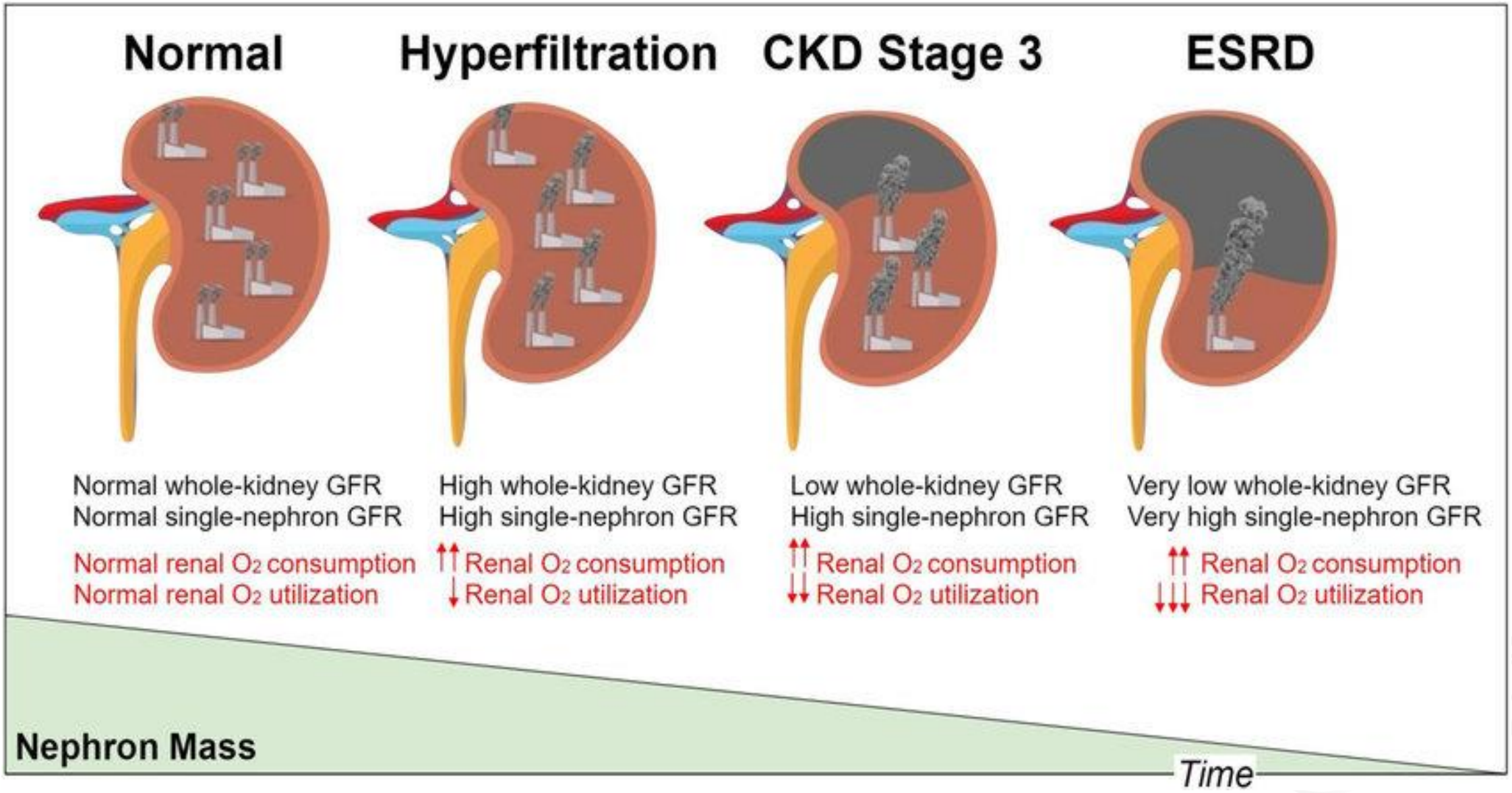
Factors causing a net reduction of afferent arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin (1-7)
Hyperinsulinemia per se
Tubular signals
Inhibition of TGF (macula densa signals)

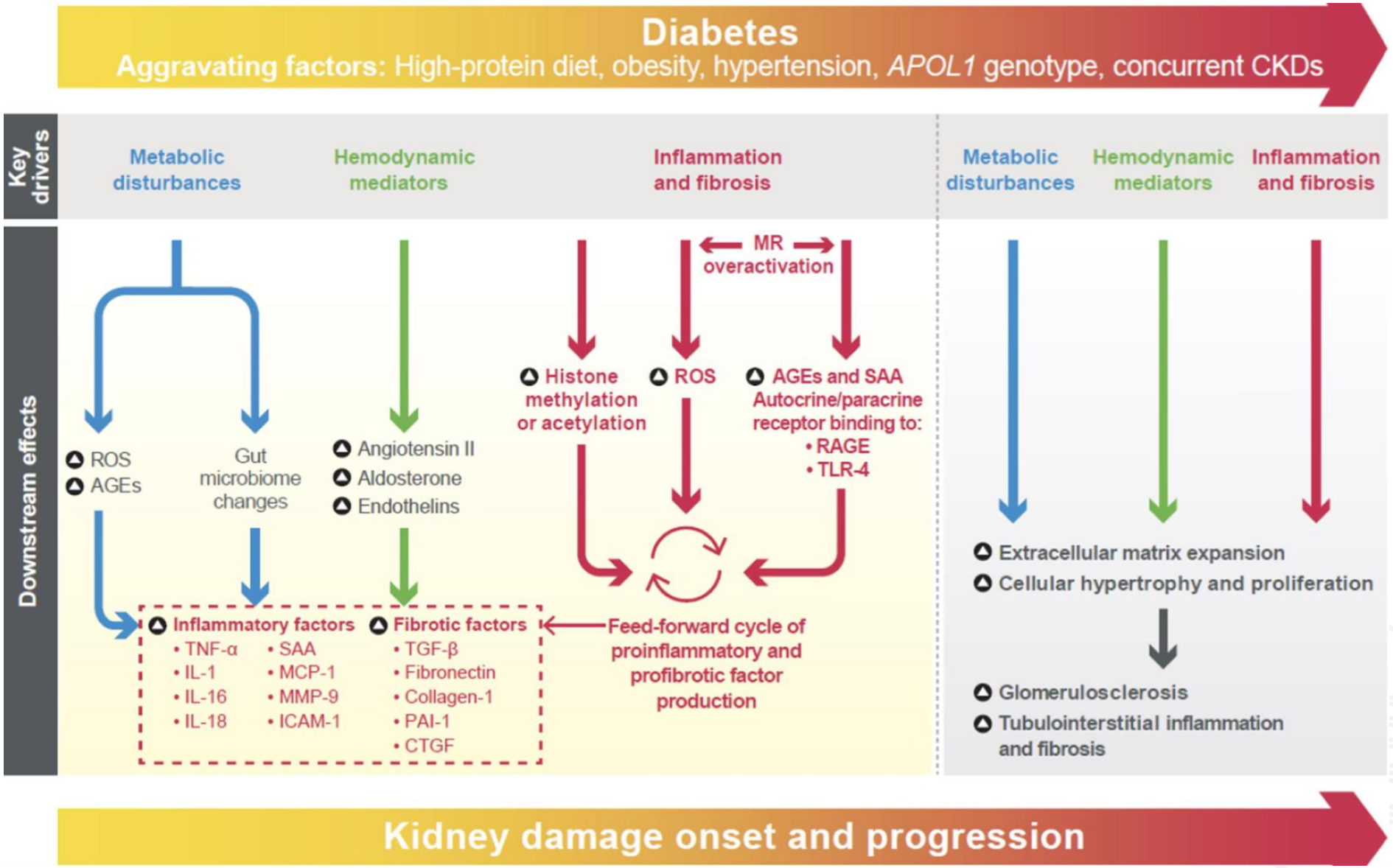


Factors causing a net increase of efferent arteriolar resistance
Vascular factors
Angiotensin II
Thromboxane A2
Endothelin 1 (ETA receptor)
Reactive oxygen species

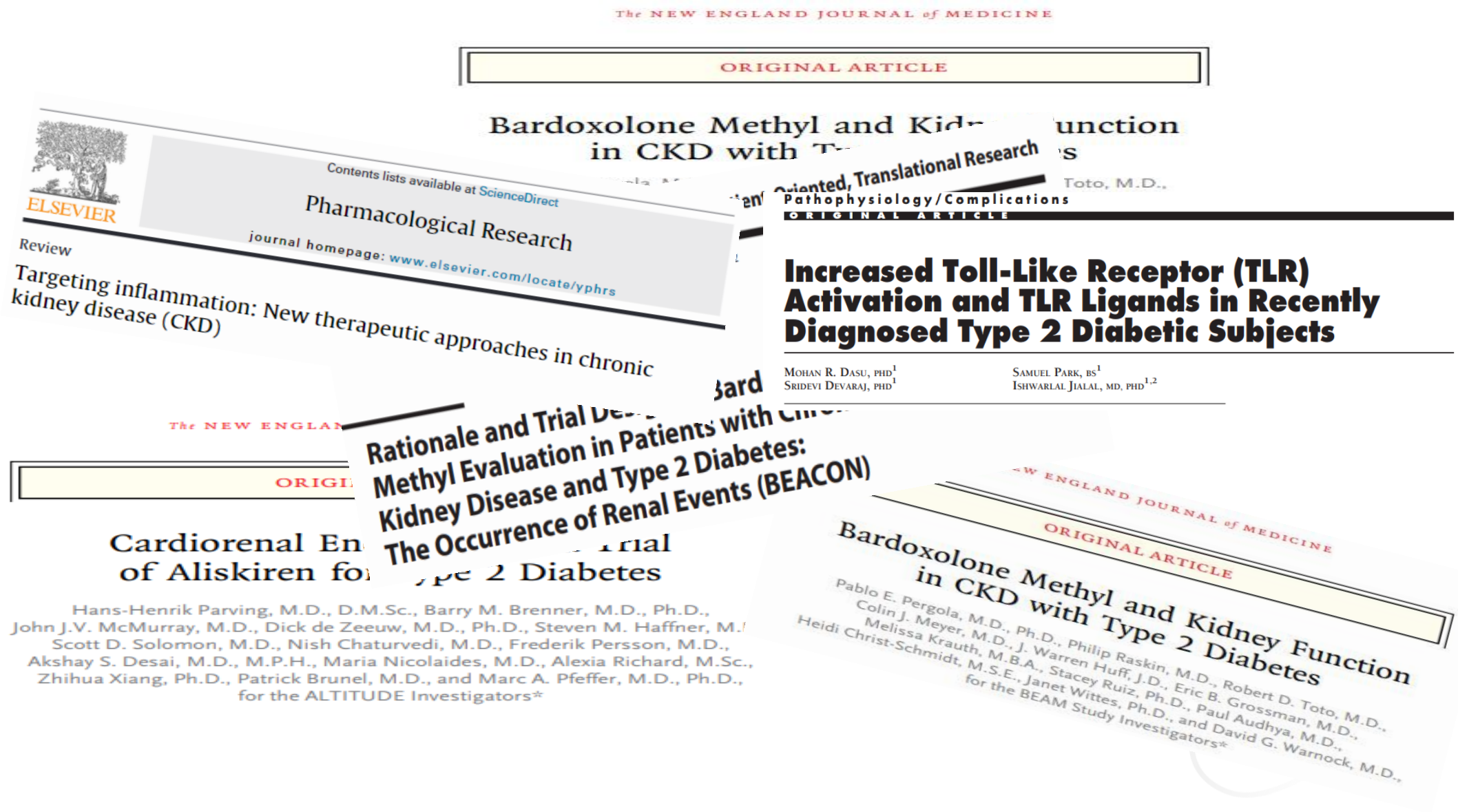
DIABETIC NEPHROPATHY




Normal
Hyperfiltration
CKD Stage 3
ESRD
Normal whole-kidney GFR
Normal single-nephron GFR
Normal renal O2 consumption
Normal renal O2 utilization
High whole-kidney GFR
High single-nephron GFR
↑↑ Renal O2 consumption
↓ Renal O2 utilization
Low whole-kidney GFR
High single-nephron GFR
↑↑ Renal O2 consumption
↓↓ Renal O2 utilization
Very low whole-kidney GFR
Very high single-nephron GFR
↑↑ Renal O2 consumption
↓↓↓ Renal O2 utilization
Nephron Mass
Time

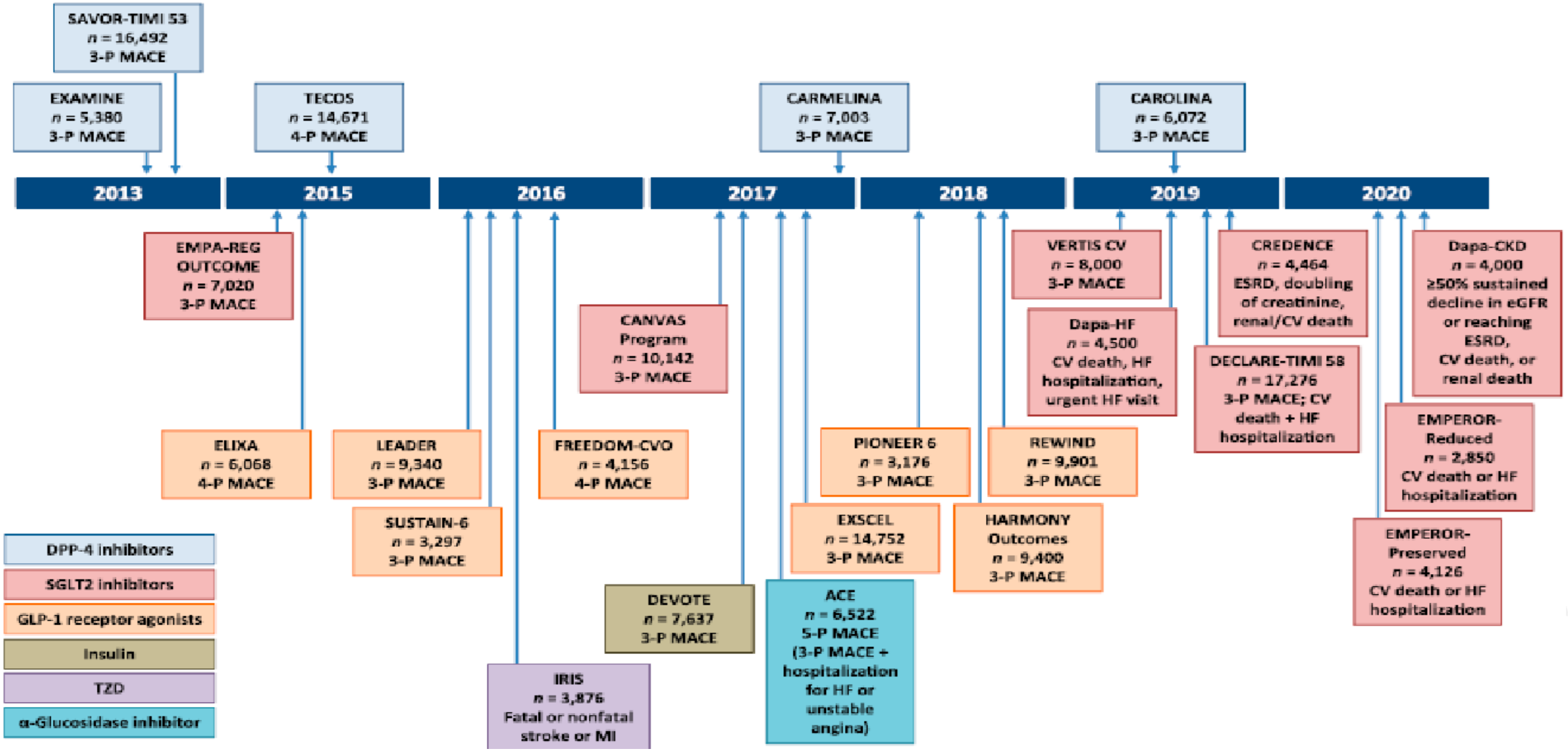


Joshua J et al. Clin Kidney J 2023;sfad285



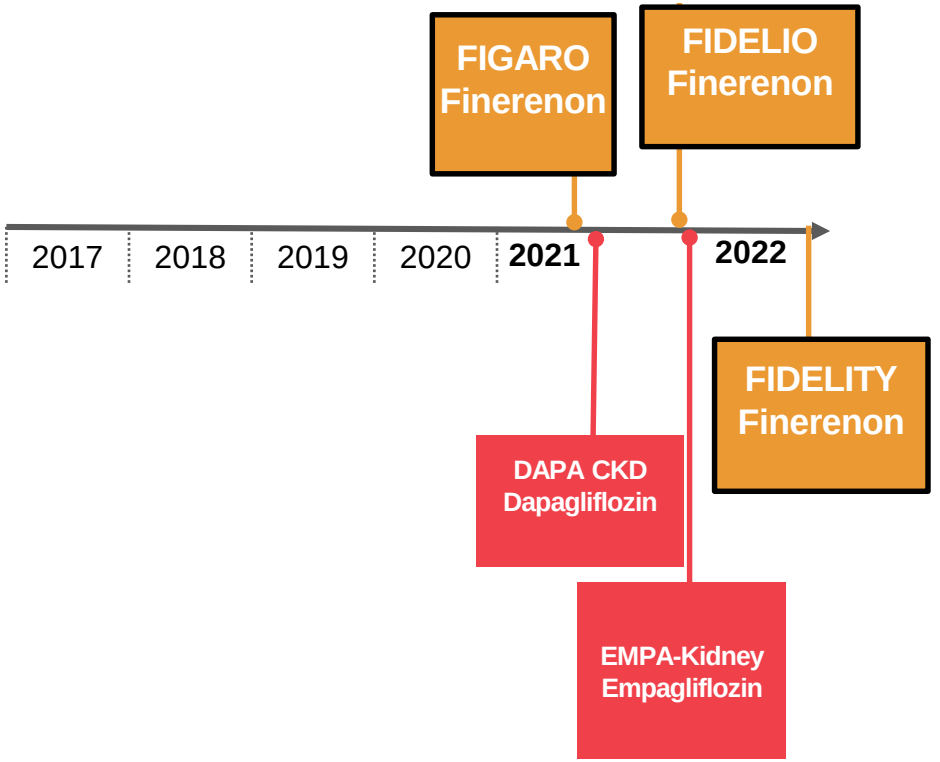
Avosentan, aliskiren, bardoloxone etc. were not as effective as they were expected.

CLINICAL TRIALS OF DIABETES DRUGS

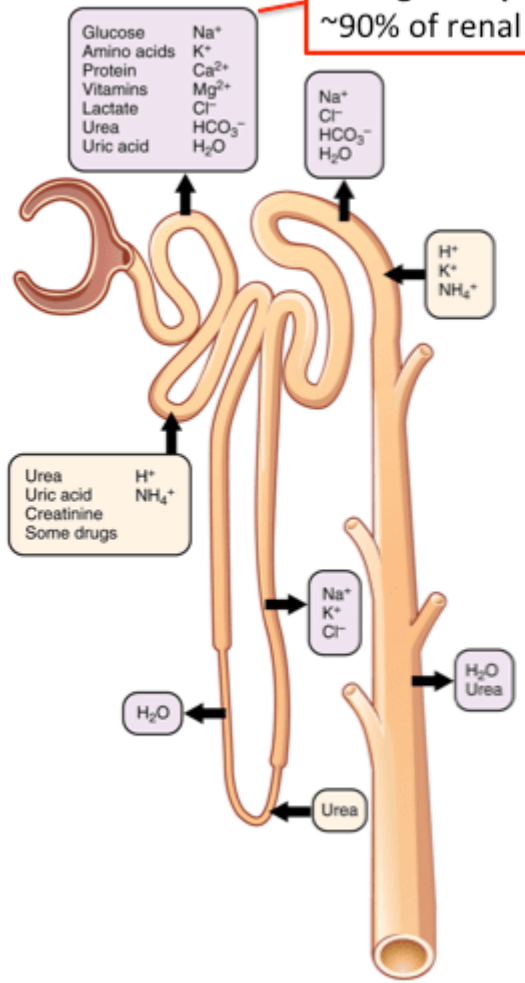


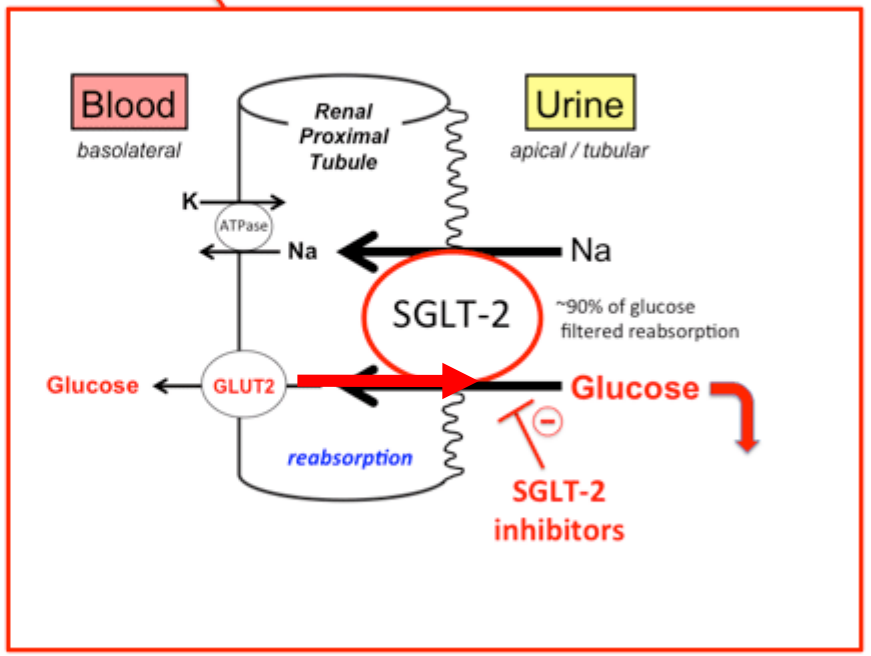
Cefalu W *et al, Diabetes Care* 2018

CLINICAL TRIALS OF NEW DIABETES DRUGS

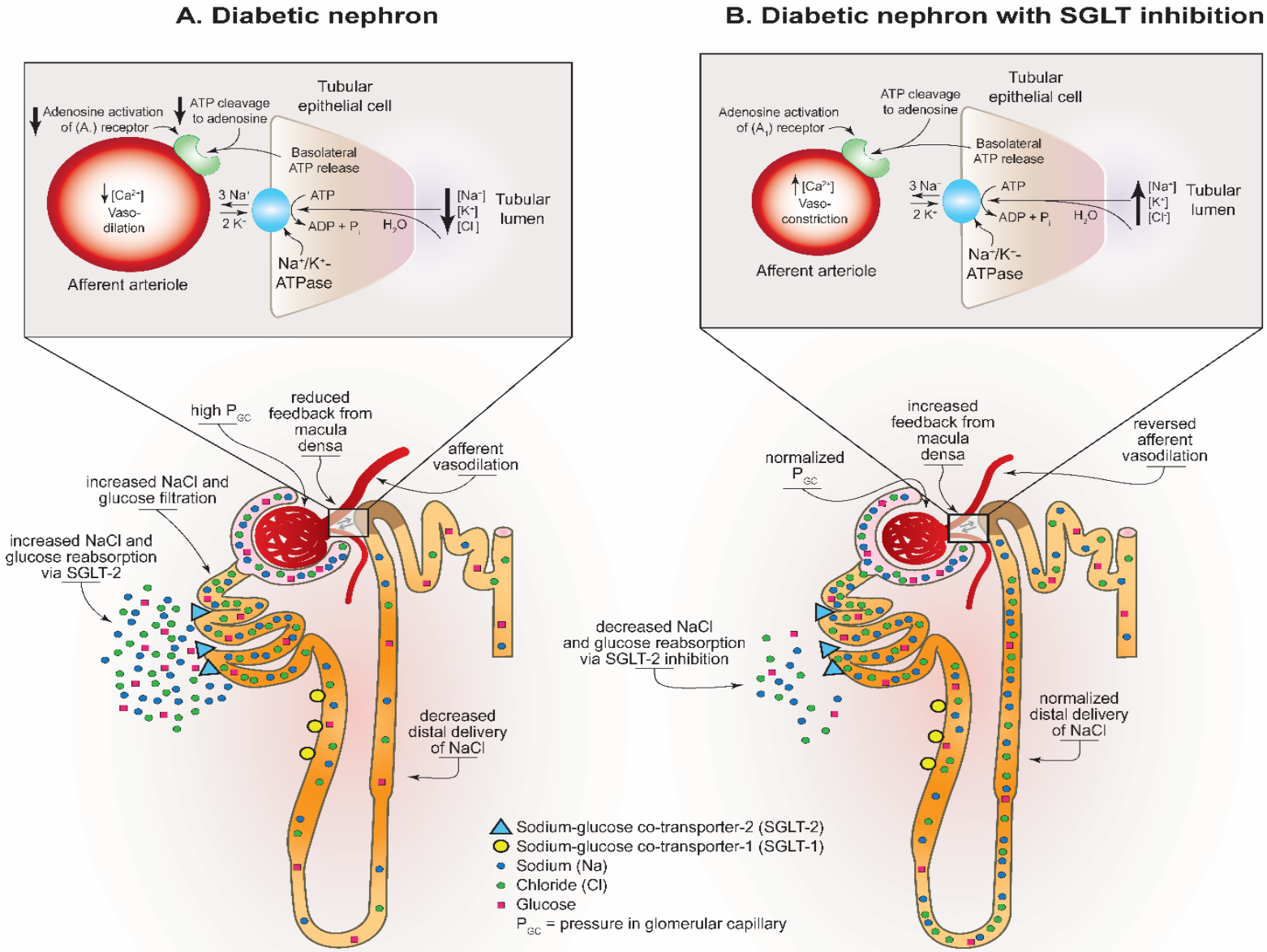


S1 segment proximal tubule:
~90% of renal glucose reabsorption





Glycosuria
HbA1c ↓ and…



Alicic RZ, et al. Am J Kidney Dis 2018;72:267-277

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, Christoph Wanner, John M. Lachin, EMPA-REG OUTCOME Investigators NEJM 2015 373.

#NephJC

Who was tested

Type 2 DM. Prior history of CV disease

N=7,020

- Age 63.1
- A1c 8.1%
- Diabetic nephropathy (>300 mg/g)11%
- Blood pressure 135/77
- ACEi or ARB in 81%
  Statins in 77%

What was done

- **Empagliflozin** 25 mg (N= 2,342)
- **Empagliflozin** 10 mg (N= 2,345)
- **Placebo** (N= 2,333)

2.6 years on treatment (3.1 years for outcomes)

What they found

The primary outcome was a composite of CV death, nonfatal MI, nonfatal stroke

	Primary Outcome	CV death	Total mortality
Empagliflozin	10.5%	3.7%	5.7%
Hazard Ratio	0.86 P<0.001	0.62 P<0.001	0.68 P<0.001
Placebo	12.1%	5.9%	8.3%

Hgb A1c

	12 weeks	94 weeks
10 mg	0.54%	0.42%
25 mg	0.60%	0.47%

Systolic BP 5 mmHg

The NEW ENGLAND JOURNAL of MEDICINE

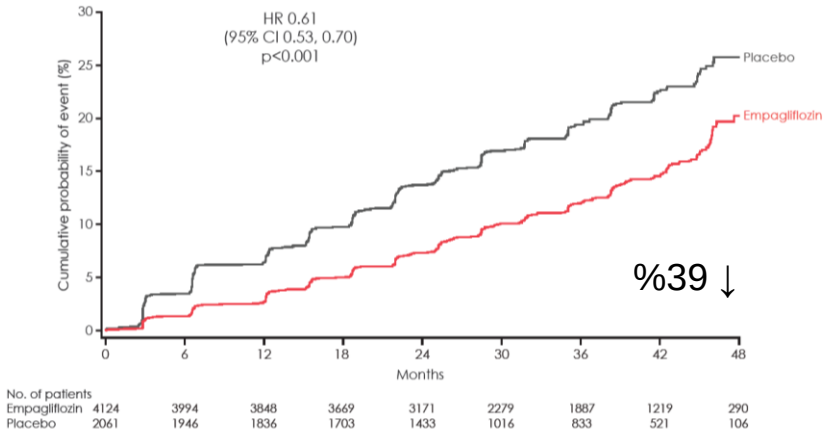
EMPA-REG OUTCOME®

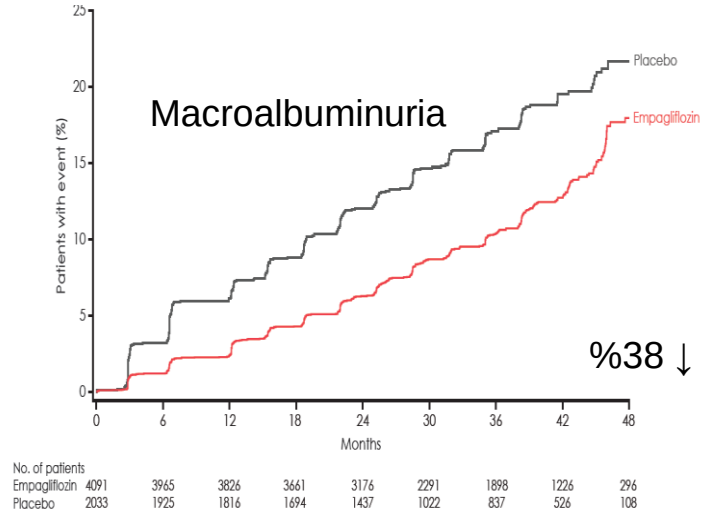
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Nephropathy risk





***Progression to macroalbuminuria, doubling of serum creatinine, KRT need or death due to CKD**

N Engl J Med 2015;373:2117

The NEW ENGLAND JOURNAL of MEDICINE

47% decrease in kidney outcome

Da… …nes
… Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

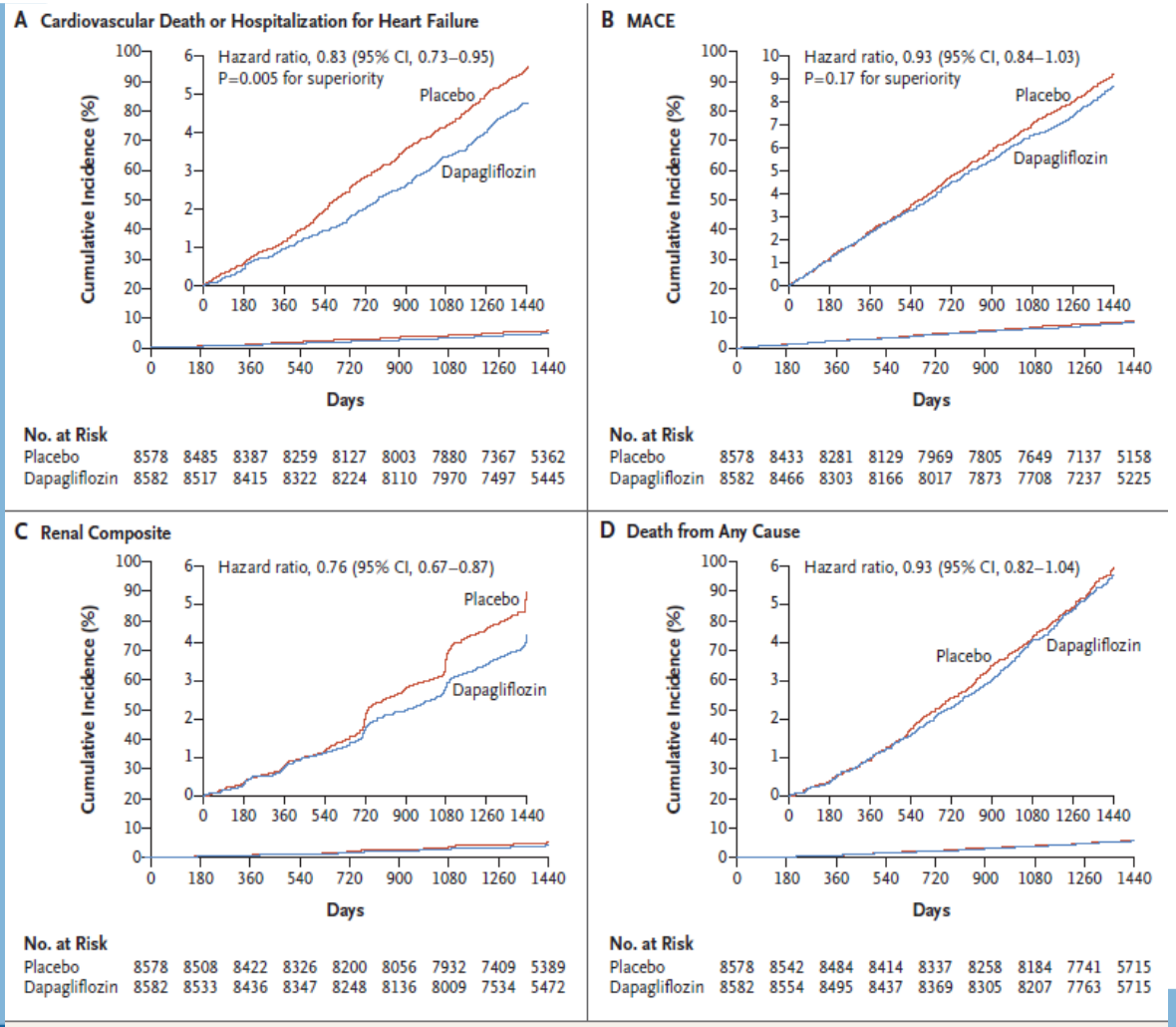


Figure 1. Major Cardiovascular and Renal Outcomes and Death from Any Cause.

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

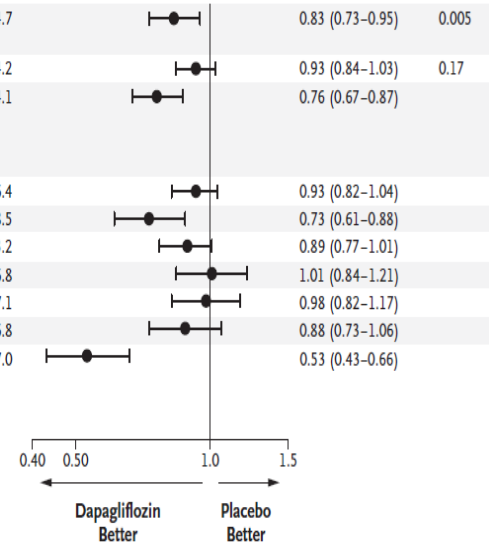


Table 2. Safety Events.*

Event	Dapagliflozin (N=8574) no. (%)	Placebo (N=8569) no. (%)	Hazard Ratio (95% CI)	P Value
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

N Engl J Med 2019;380:347-57

Diabetologia (2019) 62:1154–1166
https://doi.org/10.1007/s00125-019-4859-4

ARTICLE

Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease

Abstract

Aims/hypothesis The sodium–glucose cotransporter 2 (SGLT2) inhibitor canagliflozin slows progression of kidney function decline in type 2 diabetes. The aim of this study was t
progression of diabetic kidney disease (DKD).

Methods A canagliflozin mechanism of action (MoA
experiment in human proximal tubular cells and mol
model was mapped onto an established DKD netw
Overlapping areas in both networks were subsequer
therapy. These biomarkers were measured in 296 sto
paring canagliflozin with glimepiride.

Results Forty-four proteins present in the canagliflozi
model. These proteins were considered candidates for monitoring impact of canagliflozin on DKD pathophysiology. For ten of
these proteins, scientific evidence was available suggesting that they are involved in DKD progression. Of these, compared with
glimepiride, canagliflozin 300 mg/day decreased p
0.010), matrix metalloproteinase 7 (MMP7; 24.9
follow-up.

Conclusions/interpretation The observed reductio
reversing molecular processes related to inflamma
Trial registration ClinicalTrials.gov NCT0096881

Glimepirid vs canagliflozin

UACR > 1.7 mg / mmol 296 pts

2 years

Inflammatory parameters

TNF receptor 1 (9.2%; p <0.001)

IL-6 (26,6%; p = 0,010),

Matrix metalloproteinase 7 (24.9%; p = 0.011)

Fibronectin 1 (14.9%; p = 0.055)

Canagliflozin (SGLT2i) for type 2 DM: cardiovascular outcomes

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.
B Neal, V Perkovic, K W Mahaffey, Dick de Zeeuw CANVAS Program Collaborative Group. NEJM 2017 EPub.

#NephJC

N=4,330
CANVAS

Age 63.3 ± 8.3

A1c 8.2%

10,142

Hx of CVD 65%

GFR 76

CANVAS-R
N=5,812

Albuminuria
12 mg/g Cr

CANAGLIFLOZIN
29% drop out

188 Weeks
(3.6 years)

PLACEBO
30% drop out

PRIMARY OUTCOME

Composite: CV death, nonfatal MI, nonfatal stroke

26.9 per 1,000 patient years

DECREASE of 4.6 events/ 1000 patient years

31.5 per 1,000 patient years

95% CI, 0.75 to 0.97
P<0.001 for noninferiority;
P=0.02 for superiority

AMPUTATIONS

Non-traumatic amputations of toes, feet, or legs

6.3 per 1,000 patient years

INCREASE of 2.9 events/ 1000 patient years

3.4 per 1,000 patient years

95% CI, 1.41 to 2.75

Additional benefits from canagliflozin

Hgb A1c ↓ 0.58%

↓ 1.6 kg

↓ 3.9/1.4

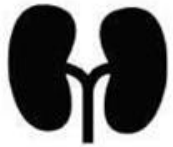
CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

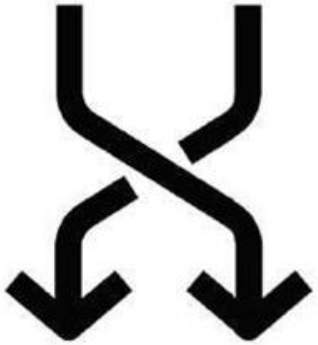


eGFR 57

UACR 927 mg/g

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

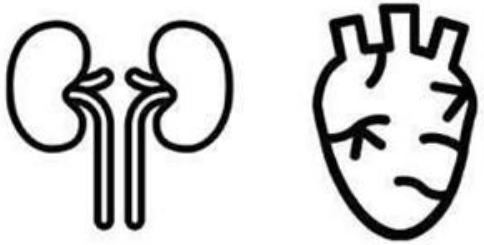


Canagliflozin **Placebo**

Outcomes

Primary outcome

(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

Fractures

HR 0.98
(95% CI 0.70-1.37)

Conclusion

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Perspective

Kidney360

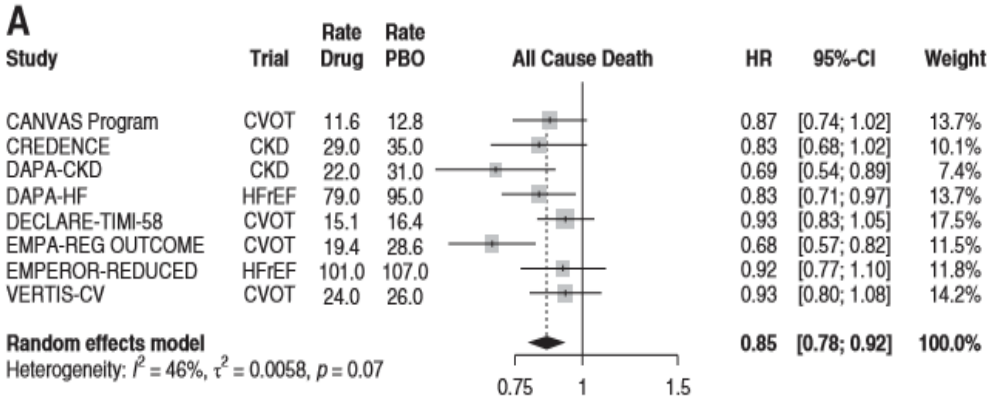
Are the Protective Effects of SGLT2 Inhibitors a "Class-Effect" or Are There Differences between Agents?

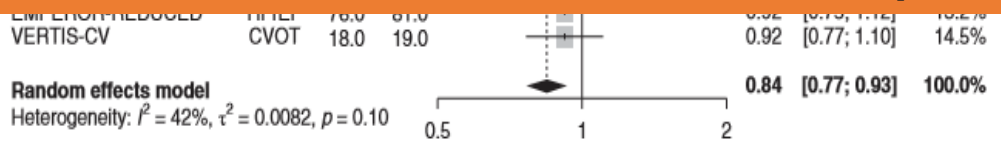
Darren W. Schmidt, Christos Argyropoulos, and Namita Singh

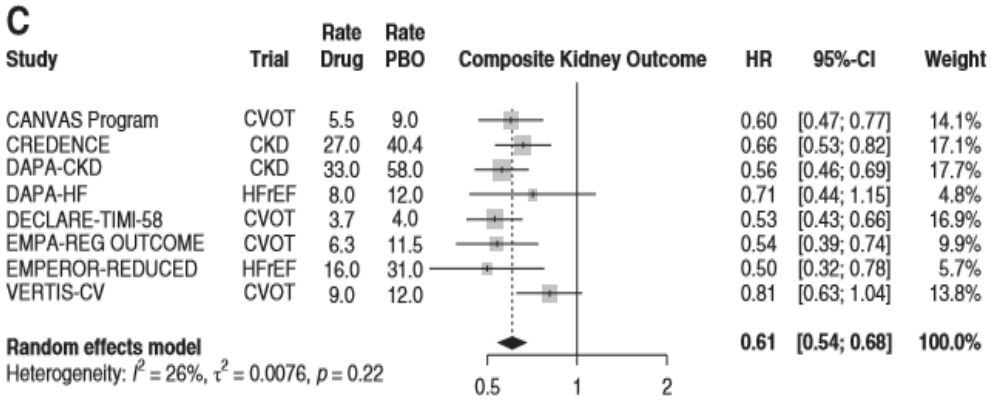
KIDNEY360 2: 881–885, 2021. doi: https://doi.org/10.34067/KID.0000622021

The cardiorenal benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) are transforming the care of CKD. An inherent challenge of practice-changing advances on this scale is how to best incorporate them into daily practice. In this vein, although there are four SGLT2is commercially available in the United States, the question remains whether these SGLT2is may be viewed as interchangeable or if specific agents offer unique benefits or harms in specific clinical settings. The more similarities between the agents within a pharmacologic class (*e.g.*, chemical structure, pharmacodynamics, and pharmacokinetics), the greater the likelihood of shared class effects. Preclinical data, starting with largely comparable chemical structures, provide a foundation where class effects might be anticipated. Nevertheless, on- and off-target effects may be expected to modify the response to any drug—an area of particular interest when considering the potential for drug, rather than class-specific, effects (1). Although translational, toxicologic, and pharmacologic investigations carried out in model systems late 1980s, a series of studies involving rat models of diabetes used phlorizin to gain additional insights into the antiglycemic effects of SGLT2 blockade (5). Further studies found that, in blocking glucose absorption in the proximal tubule, this agent was able to mitigate hyperfiltration and tubuloglomerular feedback was felt to be the likely mechanism of this action (6). Investigations marrying the evidence of FRG and the phlorizin rodent studies demonstrated that, in SGLT2-knockout mice given diabetes, hyperfiltration was attenuated (7), providing the rationale for testing these agents in (diabetic) CKD.

Notwithstanding these encouraging observations, phlorizin (which is a dual inhibitor of SGLT1 and SGLT2) was never developed for human use because of two unappealing properties. First, it has a limited oral bioavailability, necessitating the use of rather high doses to achieve a systemic exposure, and a significant potential for gastrointestinal side effects as a result of the inhibition of the glucose absorption in the small bowel (8). To overcome the limited bioavail-





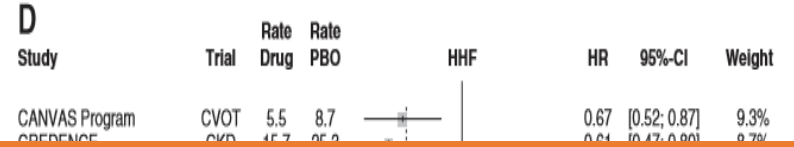


Perspective
Kidney360

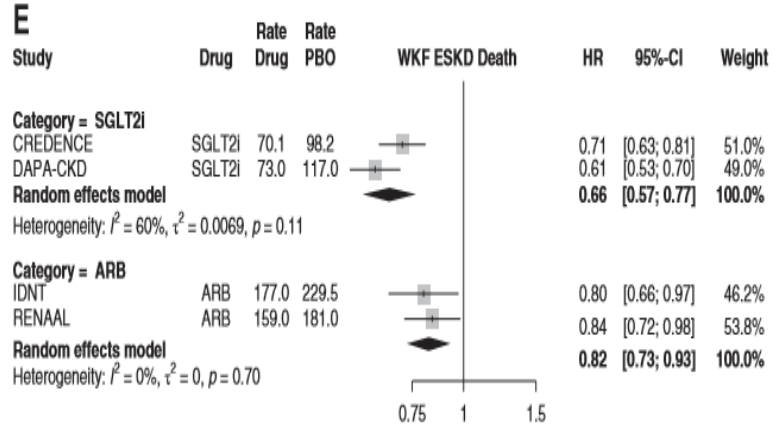
Are the Protective Effects of SGLT2 Inhibitors a "Class-Effect" or Are There Differences between Agents?

Darren W. Schmidt, Christos Argyropoulos, and Namita Singh

KIDNEY360 2: 881–885, 2021. doi: https://doi.org/10.34067/KID.0000622021



On the basis of the available clinical trial data thus far, and basic considerations from pharmacology and physiology, it can be inferred that both the benefit and the side effects of SGLT2is are part of their class features and not specific to individual drug members of the class.



SGLT2i reduce total and cardiovascular mortality, kidney outcomes, and heart failure. Effects of SGLT2is on (A) all-cause death and

Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis

Toyama & Neuen et al.

Diabetes, Obesity and Metabolism doi: 10.1111/dom.13648

@brendonneuen

27 included studies

Up to 7,363 participants

eGFR <60mL/min/1.73m²

Overall effect estimate

P-heterogeneity for differences between individual agents

CV death, nonfatal MI, nonfatal stroke	Hospitalization for heart failure	eGFR slope	Renal composite outcome
RR 0.81 (95% CI 0.70-0.94)	RR 0.61 (95% CI 0.48-0.78)	1.35mL/min/1.73m²/year (95% CI 0.78-1.93)	RR 0.71 (95% CI 0.53-0.95)
0.41	0.68	0.11	0.93

Conclusion: SGLT2 inhibitors reduce the risk of cardio-renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns beyond those already known for the class

The George Institute for Global Health

NONSTEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONIST

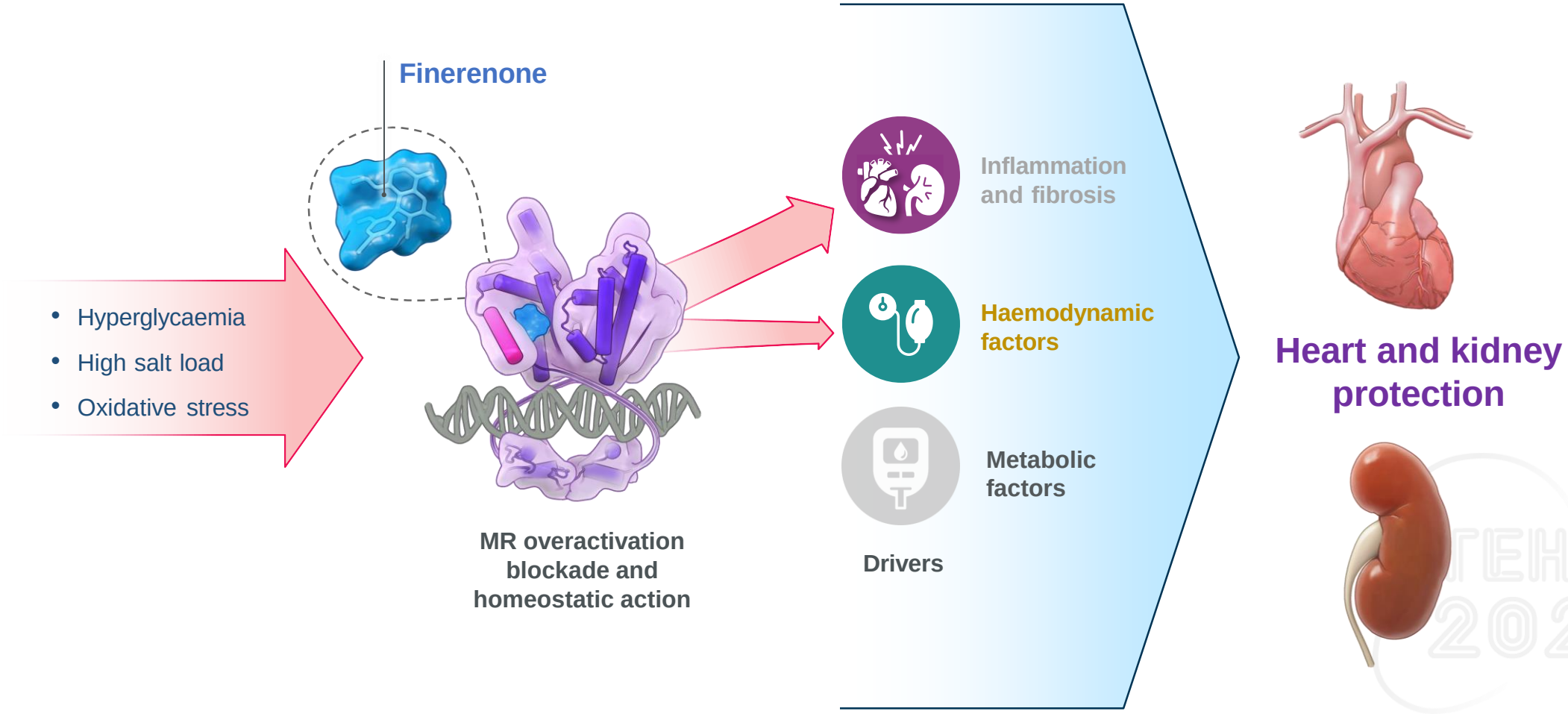
It has been well known that overactivation of MR is a key event for chronic inflammation by increasing the recruitment of neutrophil, macrophage and Th1 & Th17 cells and upregulating the expression of pro-inflammatory factors and fibrotic-related factors including TGF-α, endothelin 1, PAI-1, CTGF.

Martínez et al. found that finerenone regulated the activation of NF-kB signaling pathway through neutrophil gelatinase-associated lipocalin (NGAL) and inhibited the inflammation in cardiac remodeling after myocardial infarction.

Finerenone might alleviate the progression of chronic kidney disease and eliminate the kidney inflammation by reducing the expression of proinflammatory cytokines, such as MCP-1, TNF-α and Matrix metalloproteinase-12 (MMP-12).

Young and Rickard, 2015
Han et al., 2006
Huang et al., 2014
Martinez-Martinez et al., 2017

Finerenone, a nonsteroidal, highly selectively MRA blocks MR overactivation, which slows kidney and CV disease progression in patients with T2D



Kintscher U, et al. Br J Pharmacol 2021
Agarwal R, et al. Eur Heart J 2021;42:152–162
Amazit L, et al. J Biol Chem 2015;290:21876–21889
Agarwal R, et al. Nephrol Dial Transplant 2020;37:1014–1023

Does Finerenone Help Reduce Kidney Failure and Progression in Diabetic Kidney Disease ?

American Journal of Nephrology

FIDELIO-DKD

Randomized
Double-blind
Placebo-controlled

47 countries

5.5 years

eGFR ≥ 25 to < 75 *mL/min/1.73m²*

Urine Alb/Crea
≥ 30 to ≤ 500 *mg/g*

n = 5,734

To assess whether finerenone reduces cardiorenal morbidity and mortality in patients with Type 2 DM and CKD when used in addition to standard of care

PRIMARY EFFICACY ENDPOINT

Time to first occurrence of the composite onset of:

- **Kidney failure**
- **Sustained decrease of eGFR ≥ 40% from baseline over at least 4 weeks**
- **Renal death**

At least 90% power to detect a 20% reduction in the risk of primary outcome

Conclusion: FIDELIO-DKD will determine whether an optimally treated cohort of T2D patients with CKD at high risk of renal and CV events will experience cardiorenal benefits with the addition of finerenone to their treatment regimen.

Bakris G, Agarwal R, Anker S, Pitt B, Ruliope L, Nowack C, Kolkhof P, Ferreira A, 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: 10.1159/000503916

Visual Abstract by Edgar Lerma @edgarvlermamd

FINERENONE

FIDELIO-DKD

Patients with advanced CKD in T2D (N=5734)

- Finerenone significantly reduced the risk of CKD progression (≥40% eGFR composite outcome) by **18%** versus placebo
- Finerenone significantly reduced the risk of CV events by **14%** versus placebo

FIGARO-DKD

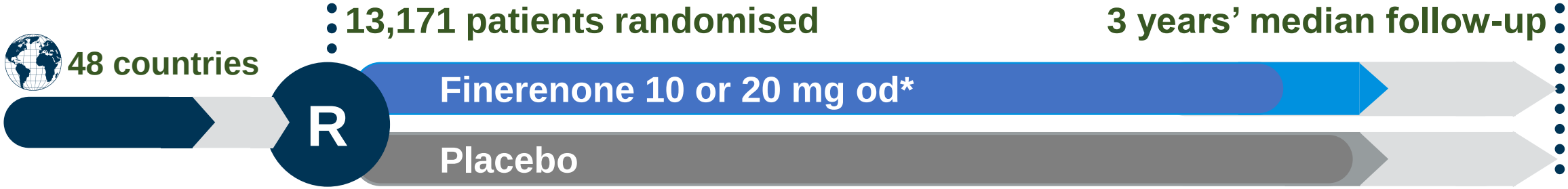
Patients with CKD stage 1–4 and T2D (N=7437)

- Finerenone significantly reduced the risk of CV morbidity and mortality by **13%** versus placebo
- Finerenone reduced the incidence of the ≥40% eGFR composite outcome by **13%** versus placebo (nonsignificant)
- Finerenone significantly reduced the incidence of ESKD by **36%** and the ≥57% eGFR composite outcome by **23%** versus placebo

FIGARO-DKD FIDELIO-DKD

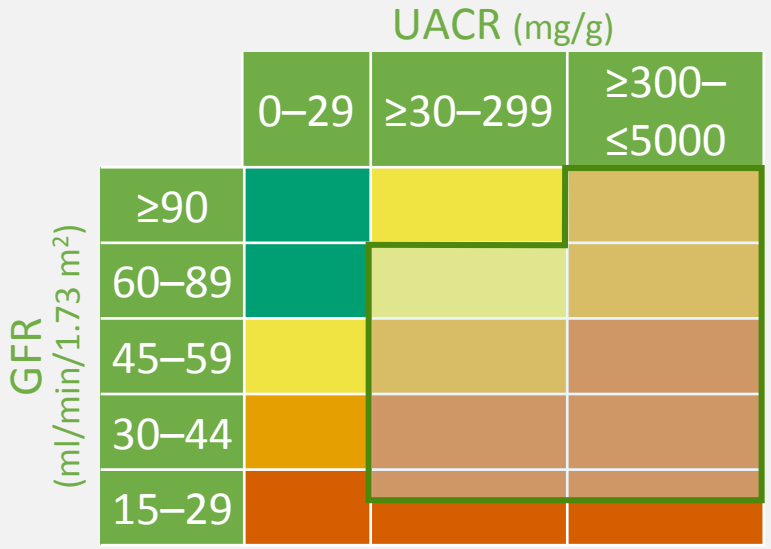
Bakris GL, et al. N Engl J Med 2020;383:2219–2229
Pitt B, et al. N Engl J Med 2021;385:2252–2263

FIDELITY is a large, prespecified pooled individual patient data analysis of FIDELIO-DKD and FIGARO-DKD



Key eligibility criteria

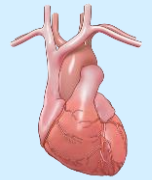
- ✓ T2D
- ✓ CKD
- ✓ On single RASi
- ✓ Serum [K^+] ≤4.8 mmol/l
- ✗ Symptomatic HFrEF



Key outcomes

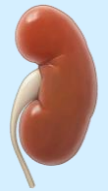
CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



57% eGFR kidney composite

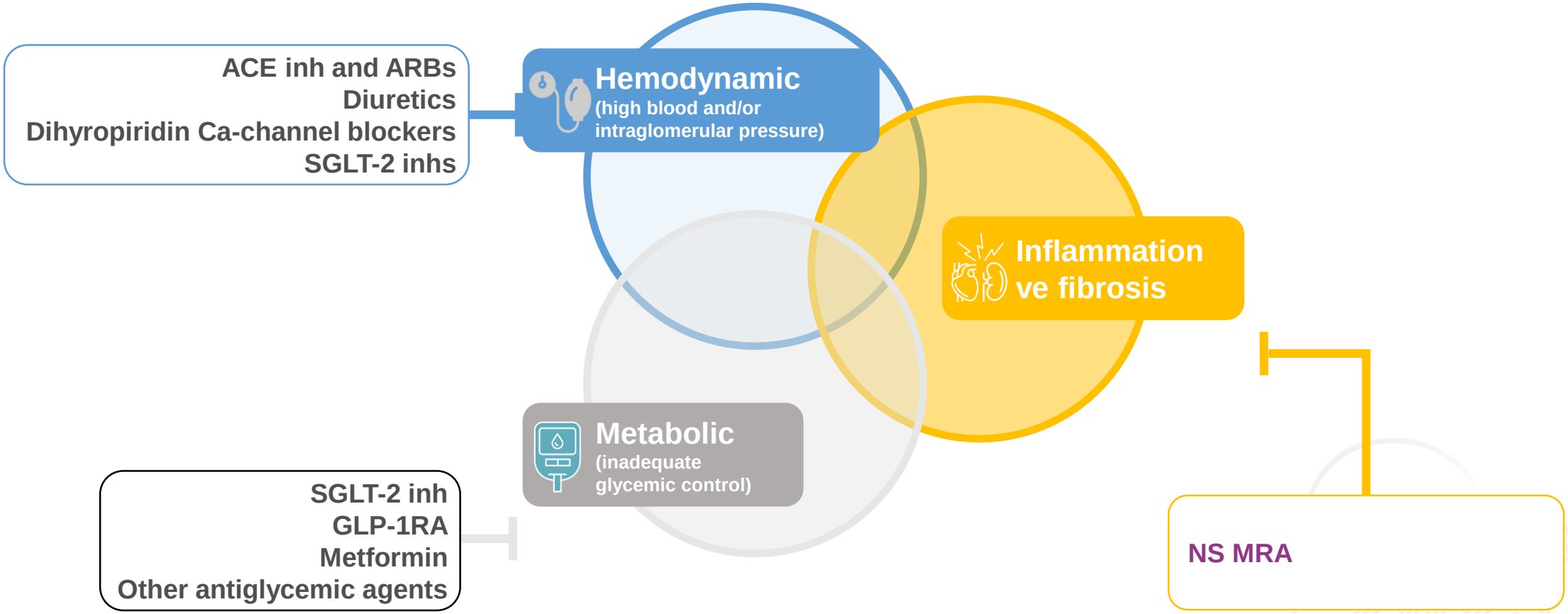
Time to kidney failure,# sustained ≥57% decrease in eGFR from baseline, or renal death



FIDELITY

Agarwal R, et al. Eur Heart J 2022;43:474–484

TARGETS OF THERAPY

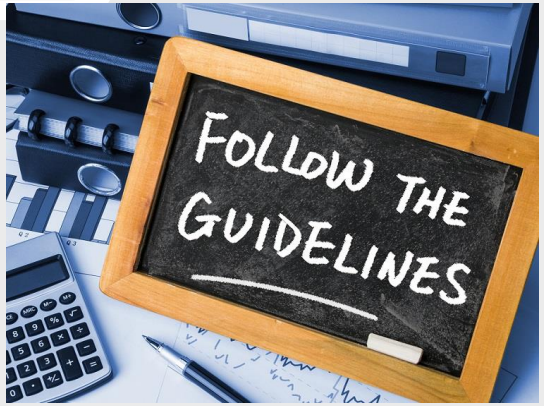


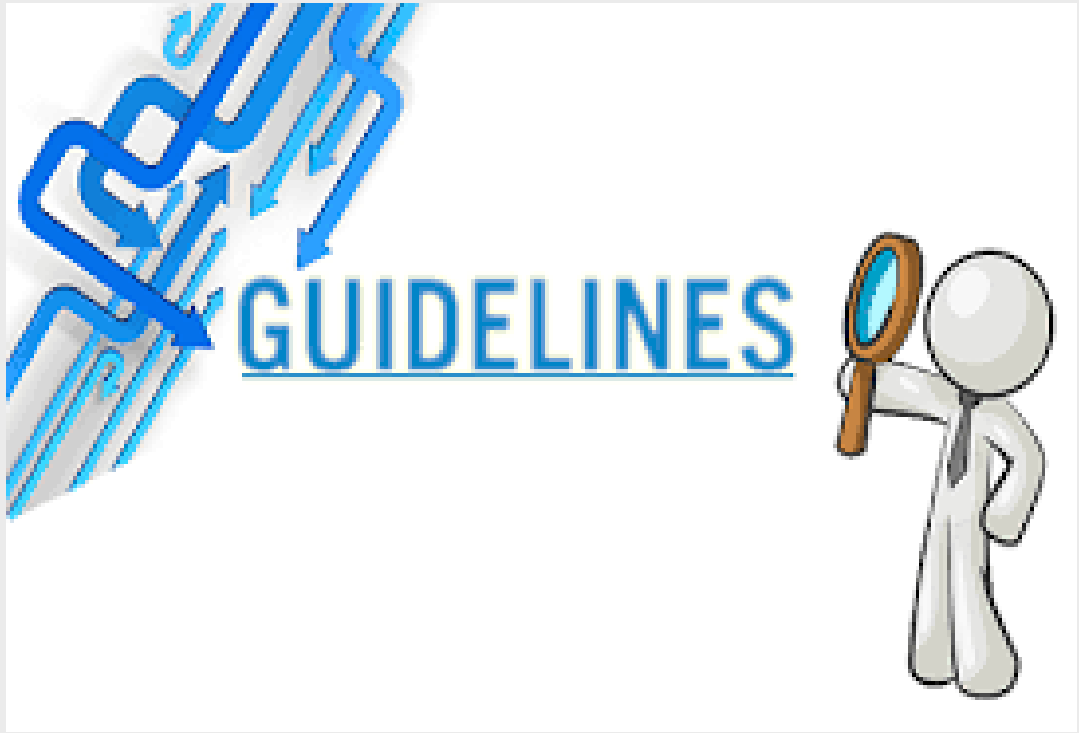
American Diabetes Association. Diabetes Care 2020;43:S135-151

Kidokoro K, et al. Circulation 2019:140;303–315

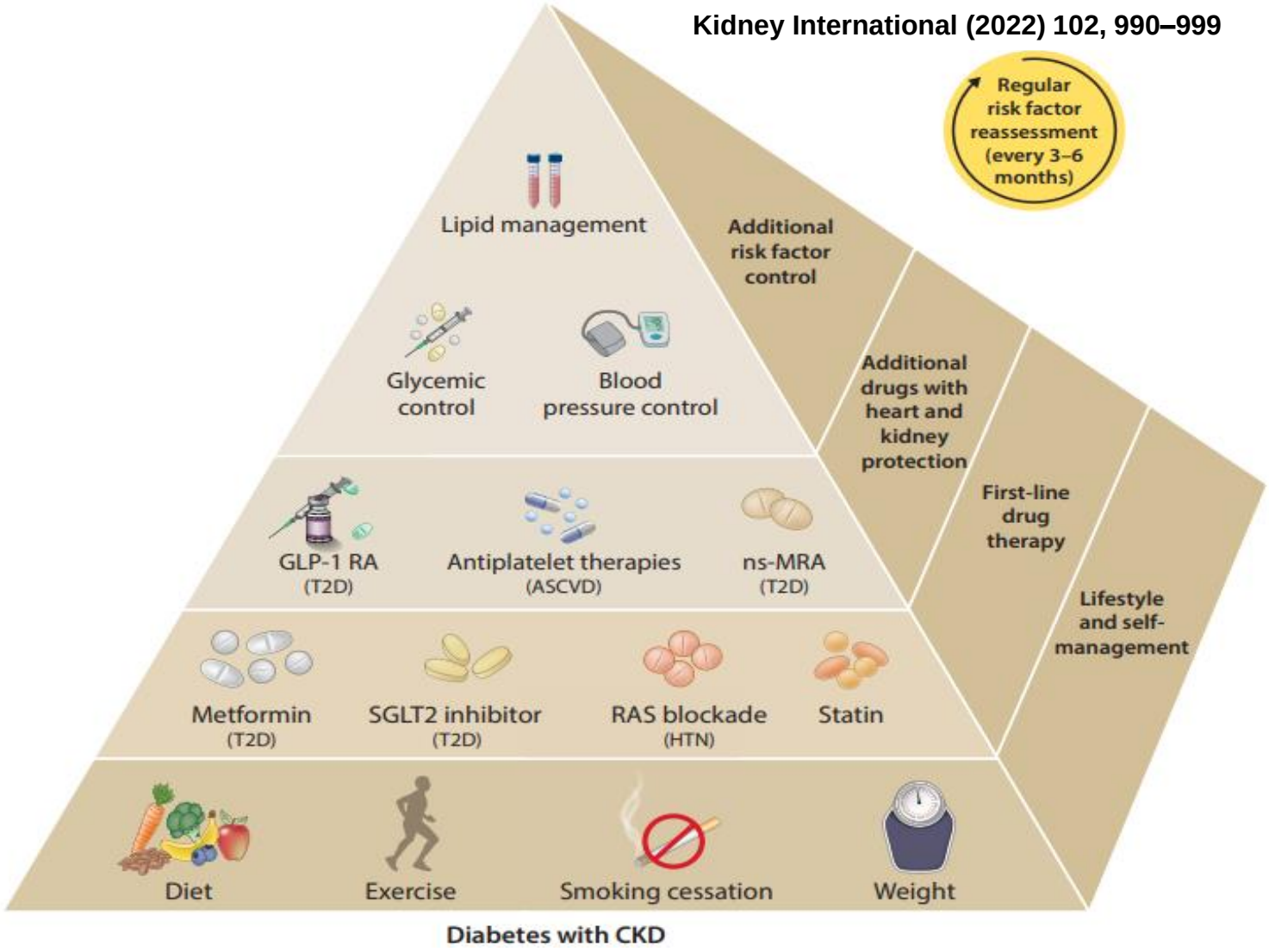
Zelniker TA & Braunwald E. J Am Coll Cardiol 2020;75:422–434

Alicic RZ, et al. Adv Chronic Kidney Dis 2018;25:1941–191

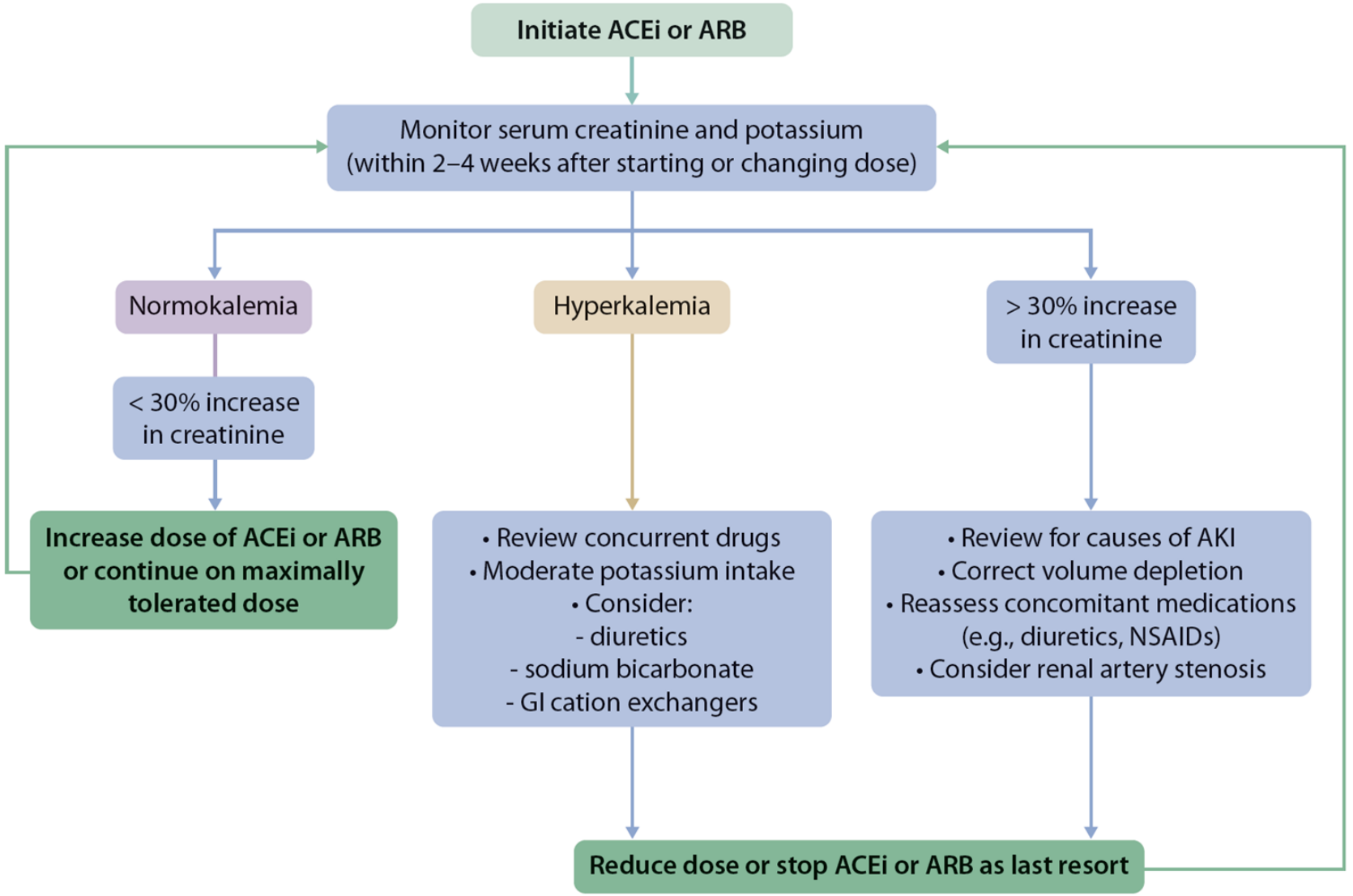

FOLLOW THE
GUIDELINES


GUIDELINES

Kidney International (2022) 102, 990–999



Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated *(1B)*.

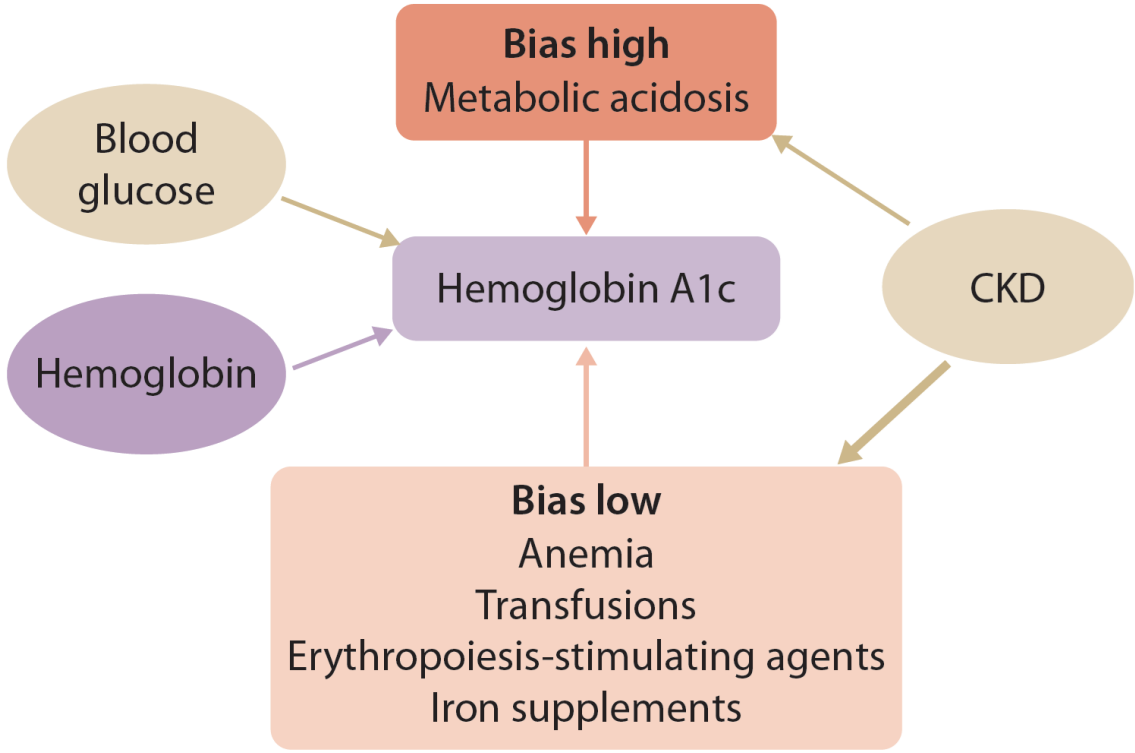


GLYCEMIC MONITORING IN PATIENTS WITH DIABETES AND CKD

Recommendation 2.1.1: We recommend hemoglobin A1c (HbA1c) to monitor glycemic control in patients with diabetes and CKD *(1C)*.

Practice Point 2.1.1: Monitoring long-term glycemic control by HbA1c twice per year is reasonable for patients with diabetes. HbA1c may be measured as often as 4 times per year if the glycemic target is not met or after a change in antihyperglycemic therapy.

Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4-G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.



GLYCEMIC TARGETS IN PATIENTS WITH DIABETES AND CKD

Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis *(1C)*.

< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

LIFESTYLE INTERVENTIONS IN PATIENTS WITH DIABETES AND CKD

Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g of protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis (*2C*).

Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis should consume between 1.0 and 1.2 g protein/kg (weight)/d.

Animal proteins

Meat, poultry, fish, seafood, eggs:
28 g (1 oz) = 6–8 g protein
1 egg = 6–8 g protein

Dairy, milk, yogurt, cheese:
250 ml (8 oz) = 8–10 g protein
28 g (1 oz) cheese = 6–8 g protein

Plant proteins

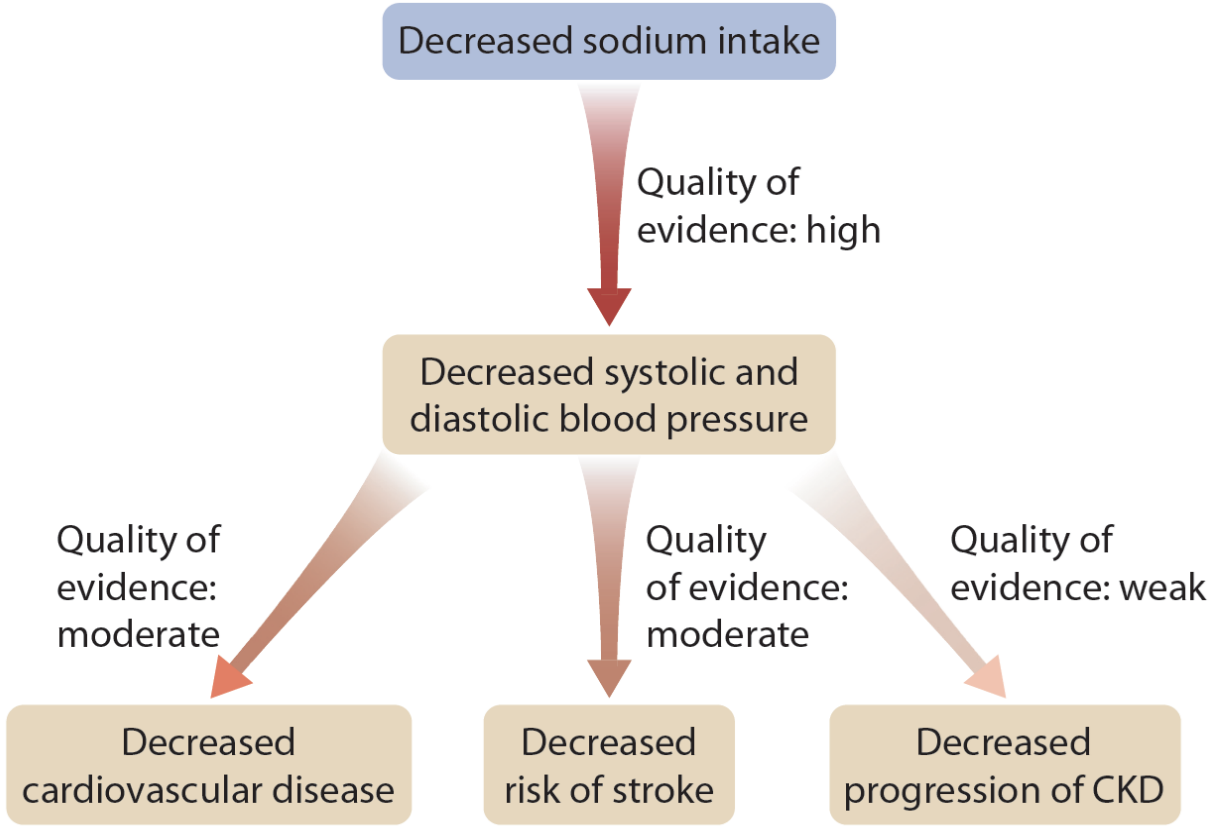
Legumes, dried beans, nuts, seeds:
100 g (0.5 cup) cooked = 7–10 g protein

Whole grains, cereals:
100 g (0.5 cup) cooked = 3–6 g protein

Starchy vegetables, breads:
2–4 g protein

LIFESTYLE INTERVENTIONS IN PATIENTS WITH DIABETES AND CKD

Recommendation 3.1.2: We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD *(2C)*.

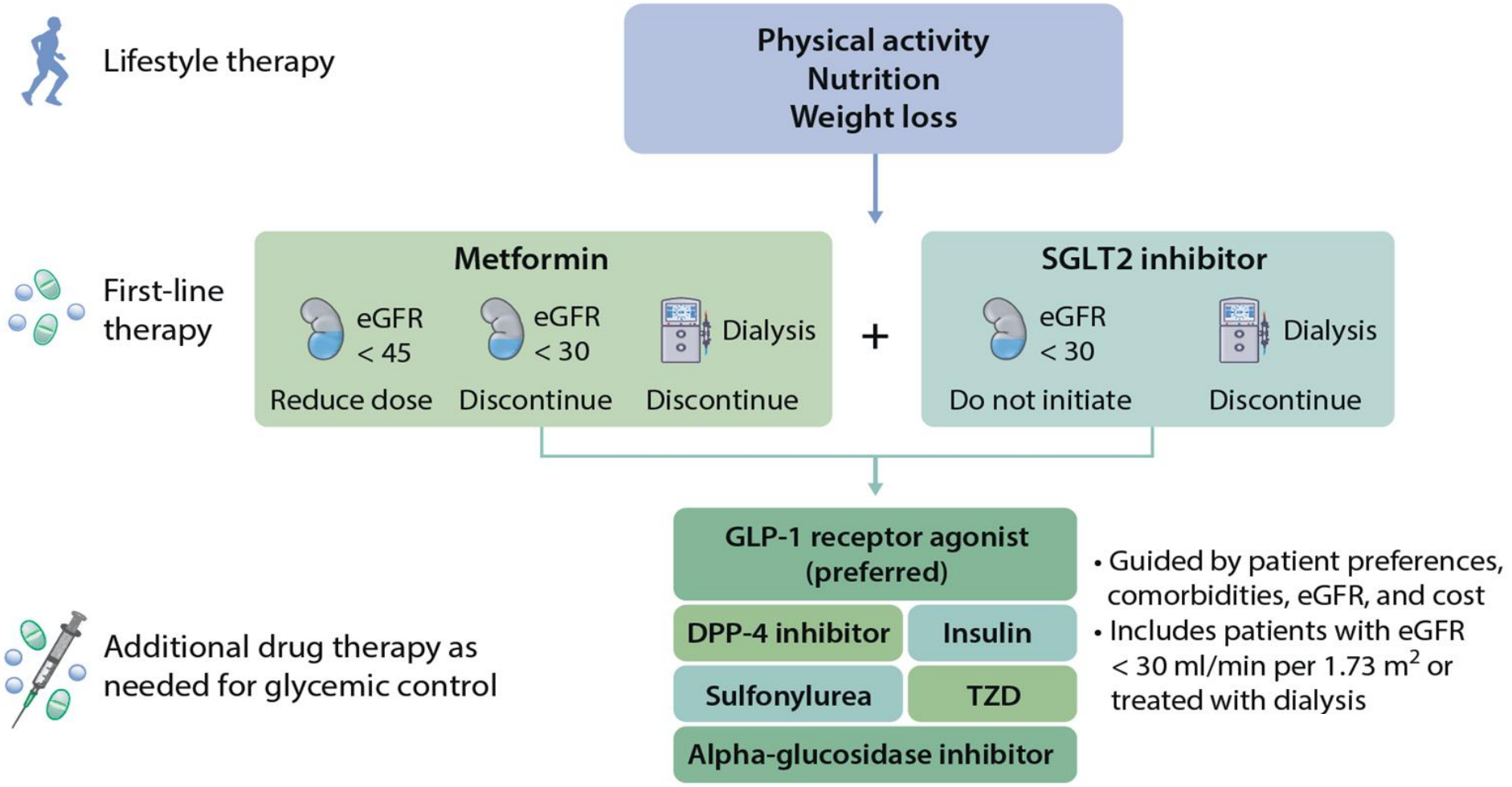


LIFESTYLE INTERVENTIONS IN PATIENTS WITH DIABETES AND CKD

Recommendation 3.2.1. We recommend that patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance *(1D)*.

Intensity of physical activity	METs	Examples
Sedentary	<1.5	Sitting, watching television, reclining
Light	1.6–2.9	Slow walking, household work such as cooking, cleaning
Moderate	3.0–5.9	Brisk walking, biking, yoga, swimming
Vigorous	>6	Running, biking, swimming, lifting heavy weights

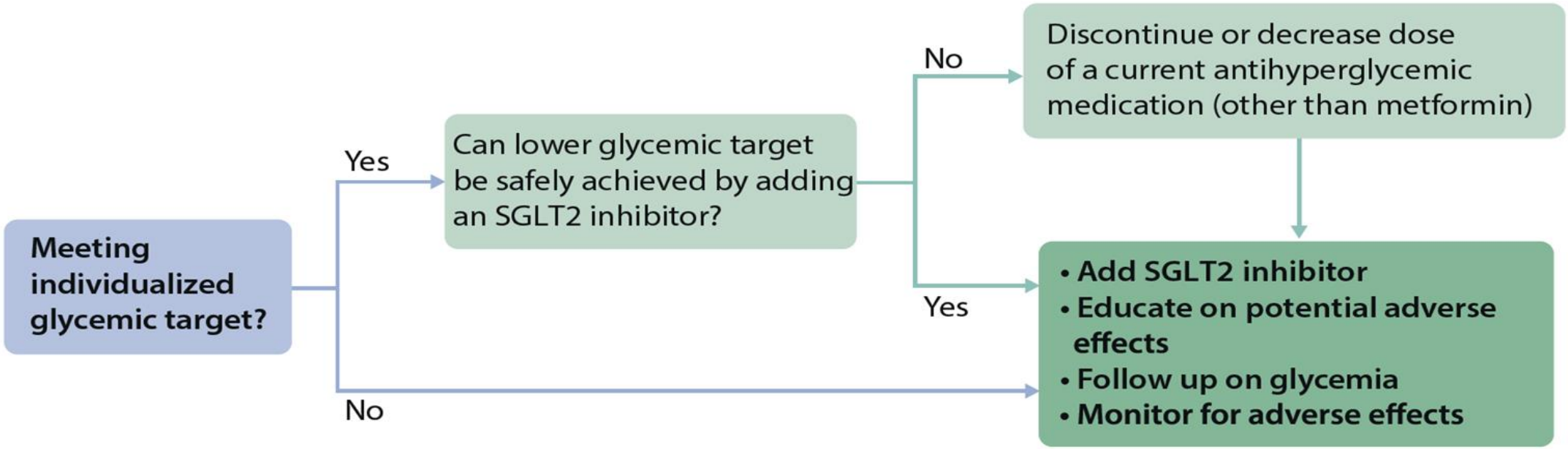
TREATMENT ALGORITHM



ANTI-HYPERGLYCEMIC THERAPIES

Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m² with an SGLT2i *(1A)*.

Practice Point 4.2.1: An SGLT2i can be added to other antihyperglycemic medications for patients whose glycemic targets are not currently met or who are meeting glycemic targets but can safely attain a lower target.



ANTI-HYPERGLYCEMIC THERAPIES

Practice Point 4.2.2: For patients in whom additional glucose-lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.

Practice Point 4.2.3: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 4.2.4: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 4.2.5: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

ANTI-HYPERGLYCEMIC THERAPIES

Practice Point 4.2.6: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 4.2.7: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if eGFR falls below 30 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

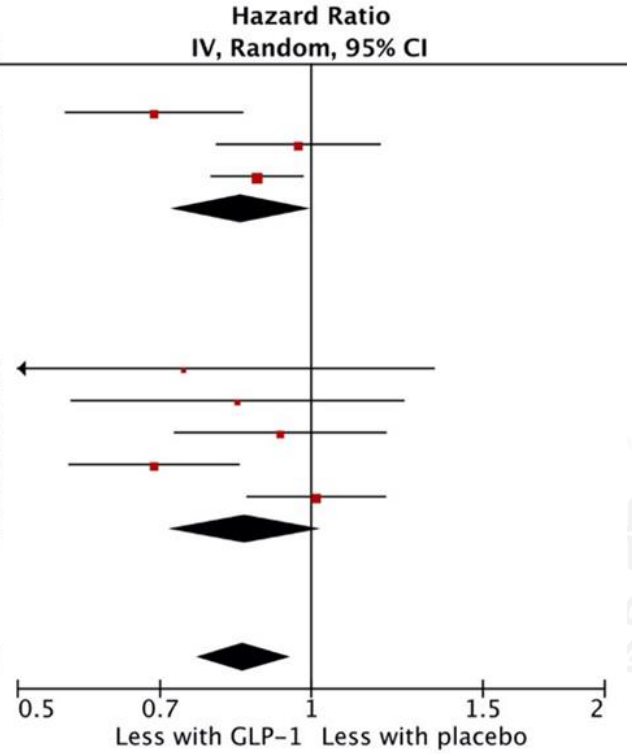
Practice Point 4.2.8: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i treatment does not apply to kidney transplant recipients.

ANTI-HYPERGLYCEMIC THERAPIES

Recommendation 4.3.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.

3-point Major Cardiovascular Events

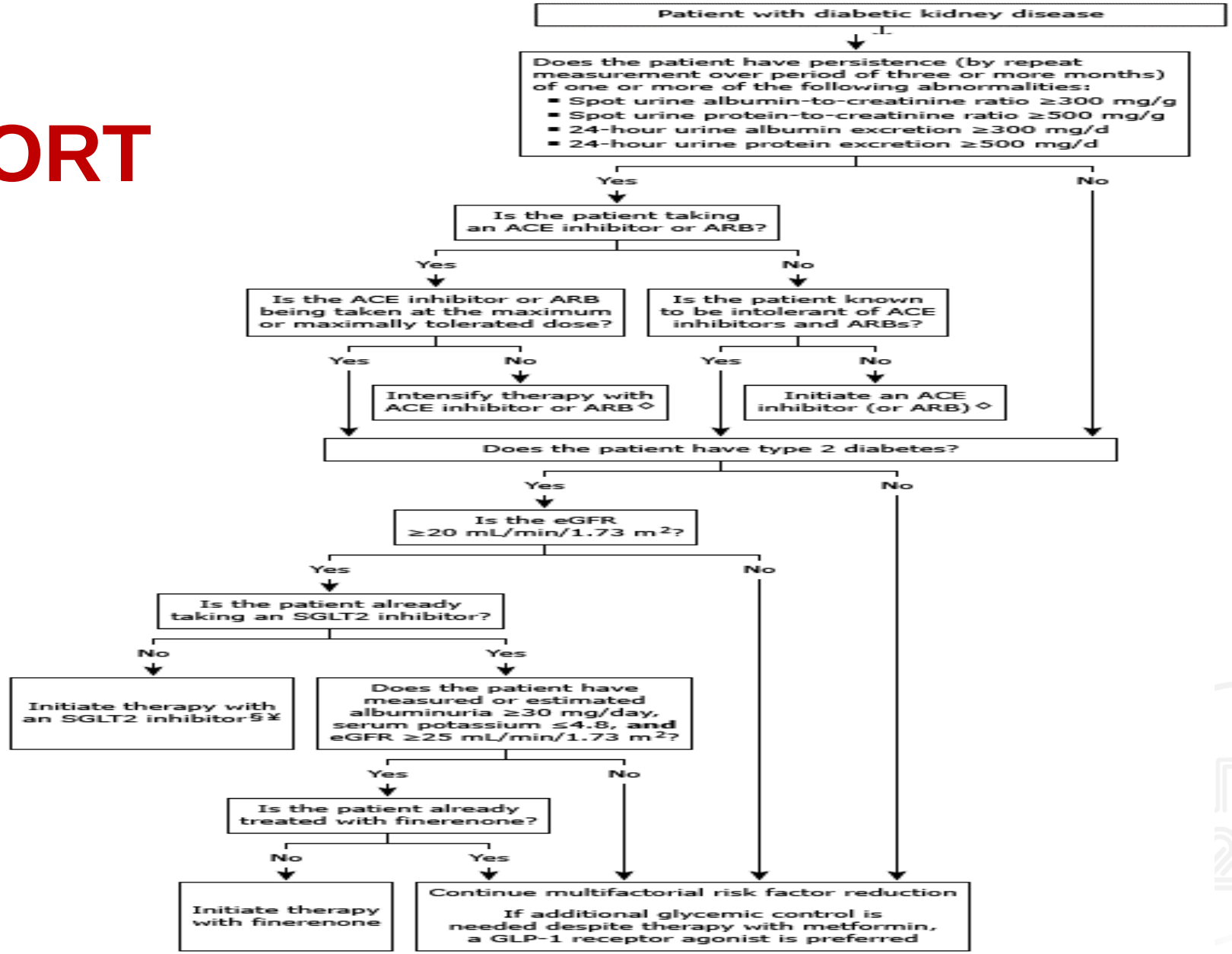
Study or Subgroup	log[Hazard Ratio]	SE	GLP-1 agonists Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
3.1.1 Stage 1-2 CKD						
Harmony Outcomes 2018	-0.3711	0.1065	2208	2209	13.5%	0.69 [0.56, 0.85]
LEADER 2017	-0.0305	0.0983	1932	1937	14.5%	0.97 [0.80, 1.18]
EXSCEL 2017	-0.1278	0.055	5769	5745	21.0%	0.88 [0.79, 0.98]
Subtotal (95% CI)			**9909**	**9891**	**49.0%**	**0.85 [0.72, 1.00]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.95$, df = 2 (P = 0.05); $I^2 = 66\%$						
Test for overall effect: Z = 1.97 (P = 0.05)						
3.1.2 Stage 3 -5 CKD						
PIONEER 6	-0.3011	0.3013	463	435	3.1%	0.74 [0.41, 1.34]
SUSTAIN-6 2016	-0.174	0.2	469	470	6.1%	0.84 [0.57, 1.24]
Harmony Outcomes 2018	-0.073	0.127	1098	1124	11.2%	0.93 [0.72, 1.19]
LEADER 2017	-0.371	0.102	1116	1042	14.1%	0.69 [0.57, 0.84]
EXSCEL 2017	0.012	0.083	1565	1626	16.7%	1.01 [0.86, 1.19]
Subtotal (95% CI)			**4711**	**4697**	**51.0%**	**0.85 [0.71, 1.02]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.07$, df = 4 (P = 0.06); $I^2 = 56\%$						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)			**14620**	**14588**	**100.0%**	**0.85 [0.76, 0.95]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 15.06$, df = 7 (P = 0.04); $I^2 = 54\%$						
Test for overall effect: Z = 2.84 (P = 0.005)						
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.94), $I^2 = 0\%$						



ANTI-HYPERGLYCEMIC THERAPIES

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with CrCl >30 ml/min
Liraglutide	0.6 mg, 1.2 mg, and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

IN SHORT



Uptodate 2023


Thank you for
your interest