Cardiorenal Protection in 2024: An Update on the Latest and Greatest for Clinicians

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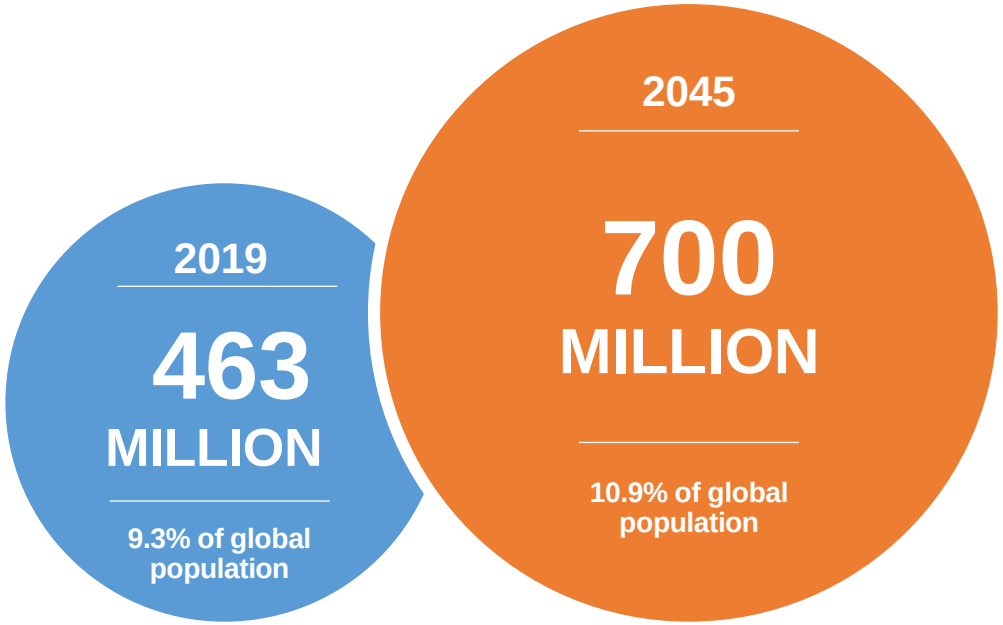
Objectives

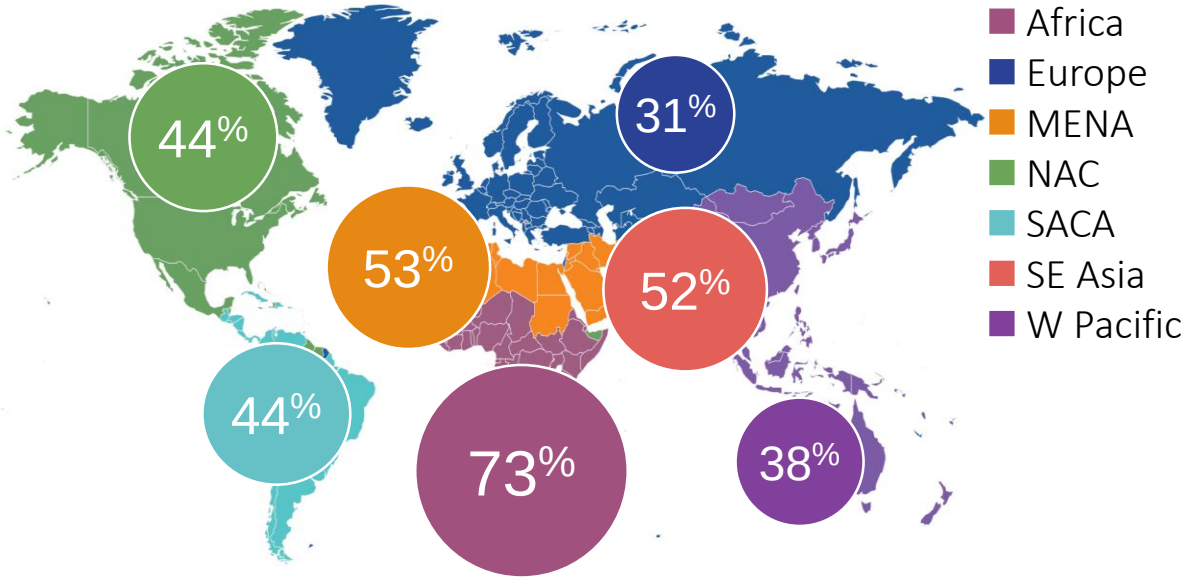
- Describe the epidemiology of CKD in diabetes
- Review recent clinical trials examining the cardiorenal effects of various medical interventions
- Summarize current guideline recommendations for treatment of CKD in diabetes mellitus

Diabetes mellitus is a major global threat: A growing medical problem associated with high mortality

Growing global incidence of diabetes in adults aged 20–79 years



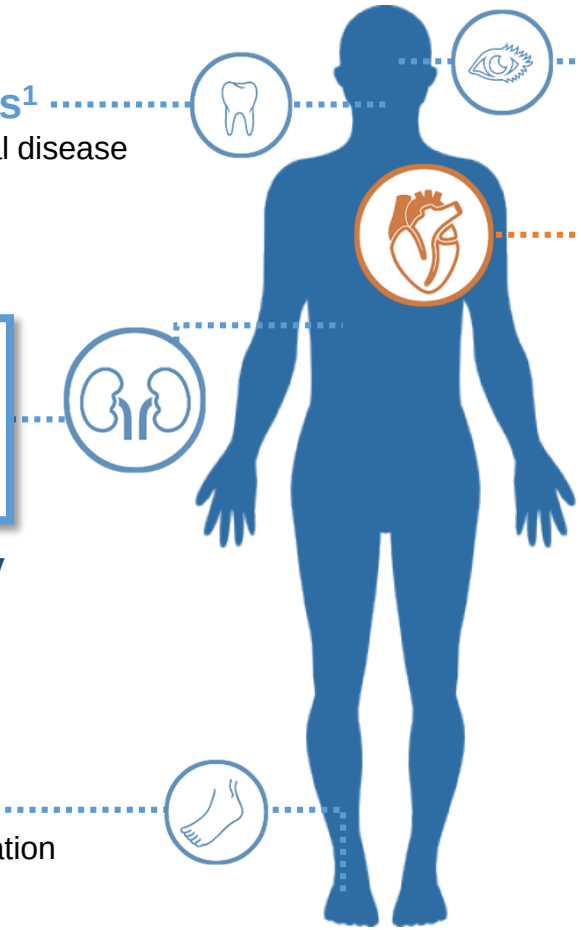
Proportion of all deaths due to diabetes occurring before age of 60 years



Diabetes accounted for an estimated 4.2 million deaths* in 2019

*In adults aged 20–79 years. MENA, Middle East and North Africa; NAC, North America and Caribbean; SACA, South and Central America; SE, Southeast; W, Western.
International Diabetes Federation. *IDF Diabetes Atlas*. 9th edn. Brussels, Belgium: International Diabetes Federation; 2019.

Diabetes has frequent co-morbidities that impose a health burden on patients



Oral health issues[1]
Higher risk of periodontal disease

Diabetic retinopathy[1,2]
Affects 1 in 3 patients with diabetes

Cardiovascular disease[1,2]
Two- to threefold increase in patients with diabetes

CKD in T2D[1]
10 times higher prevalence of kidney failure in patients with diabetes compared with people without diabetes

Diabetes is the leading cause of kidney failure in the USA[3–5]

Nerve damage and diabetic foot[1,2]
May lead to lower limb amputation

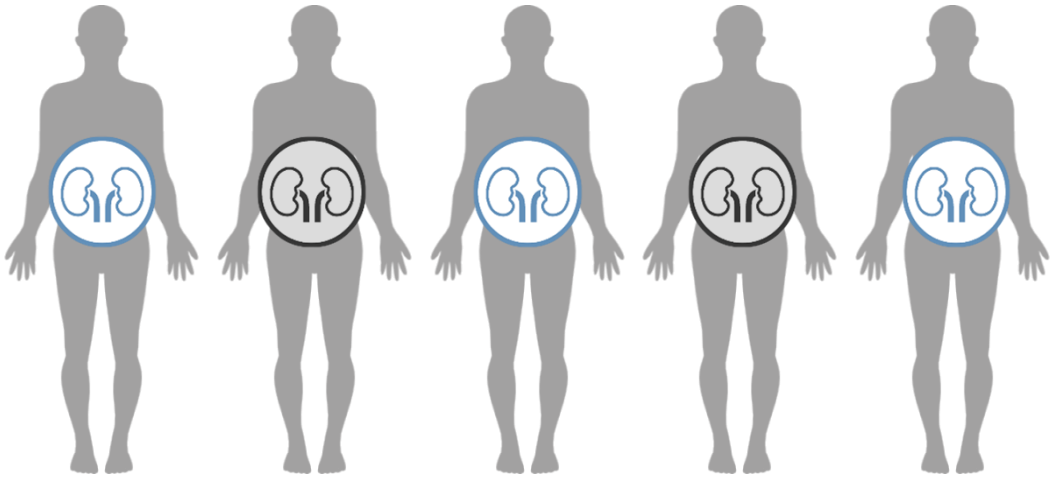
Microvascular complications

Macrovascular complications

CKD, chronic kidney disease; T2D, type 2 diabetes.

1. International Diabetes Federation. *IDF Diabetes Atlas*. 9th edn. Brussels: International Diabetes Federation; 2019; 2. National Kidney Foundation. *Am J Kidney Dis* 2007;49:S1–S180; 3. United States Renal Data System. *2018 USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* Vol. 2. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018. p. 291–332; 4. United States Renal Data System. *2018 USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* Vol. 2. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018. p. 549–594; 5. United States Renal Data System. *2019 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2019. p. 1–64.

Approximately 40% of patients with T2D have co-morbid CKD



CKD affects ~2 in 5 patients with T2D

An estimated

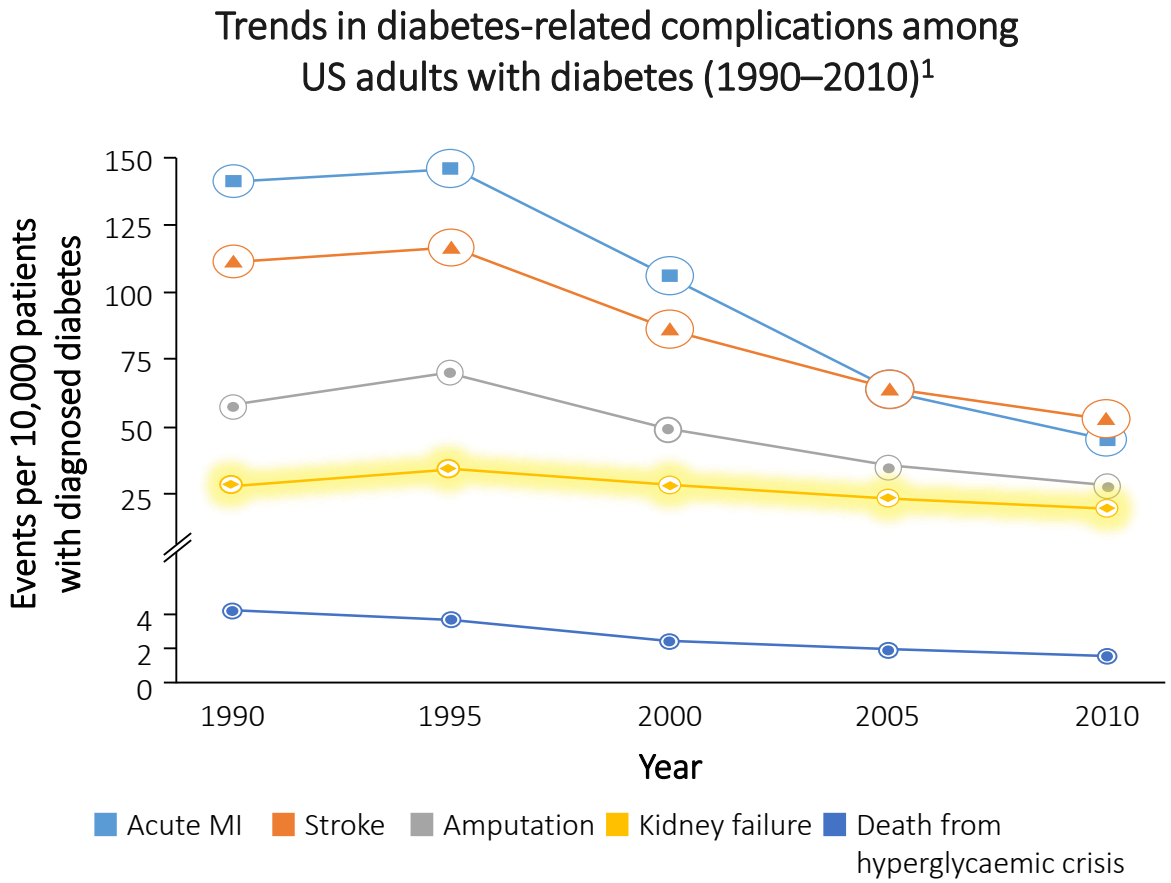
160 MILLION

adults were living with CKD and T2D* in 2019

*Aged 20–79 years.

Wu B *et al. BMJ Open Diabetes Res Care* 2016;4:e000154.

Despite advances in CV care, patients with T2D are still progressing to kidney failure

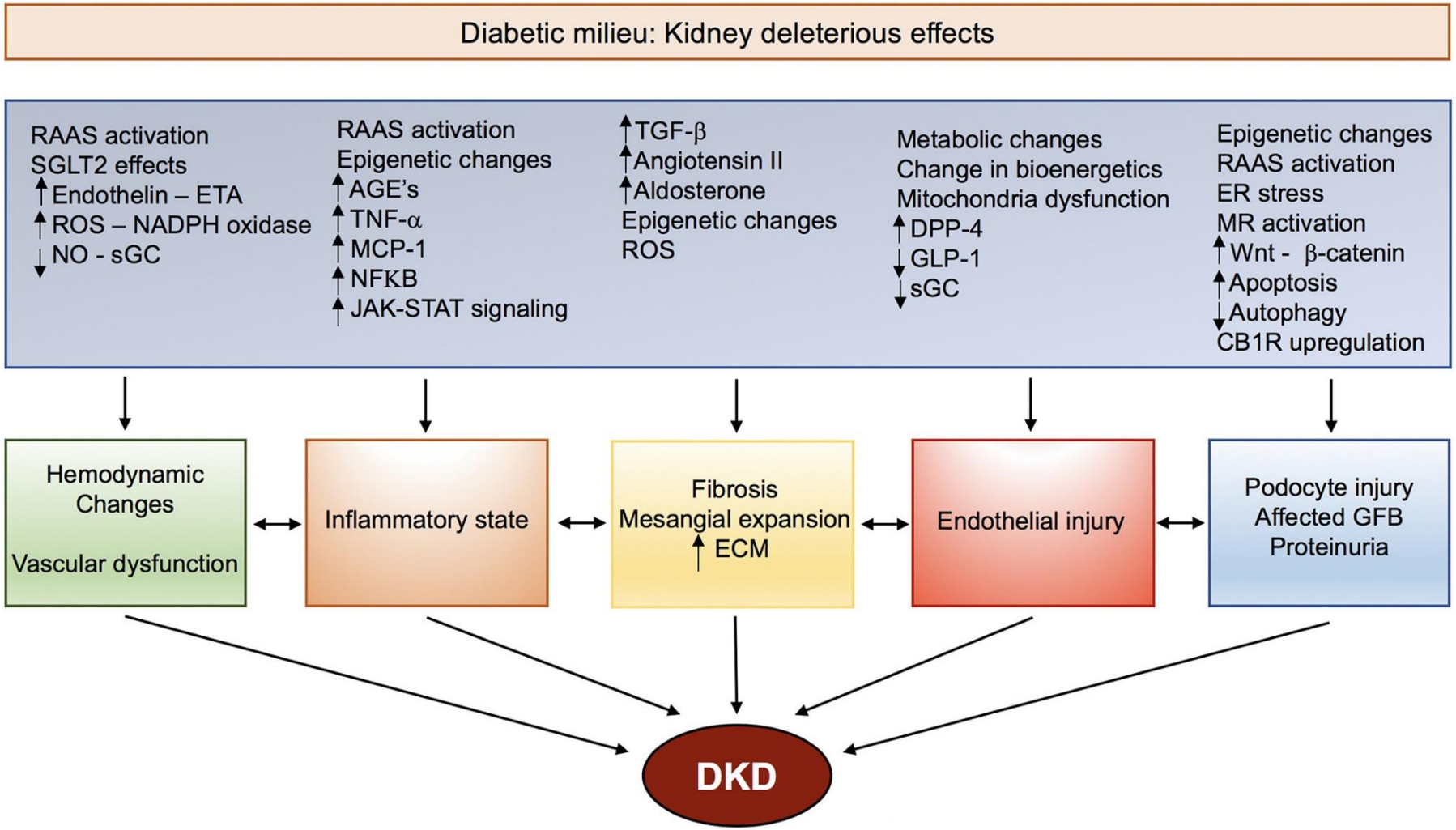


- Greatest relative decreases were observed for acute MI (−67.8%) and death from hyperglycaemic crisis (−64.4%)[1]
- Stroke and amputation both declined by approximately half (−52.7% and −51.4%, respectively)[1]
- **The smallest decline was observed for kidney failure (−28.3%)[1]**

In a US population-based cohort study (Jan 2008–Sept 2018), **CKD worsening was observed in approximately 10–17% of patients** with T2D and newly recognized CKD over a median follow-up of 2 years[2]

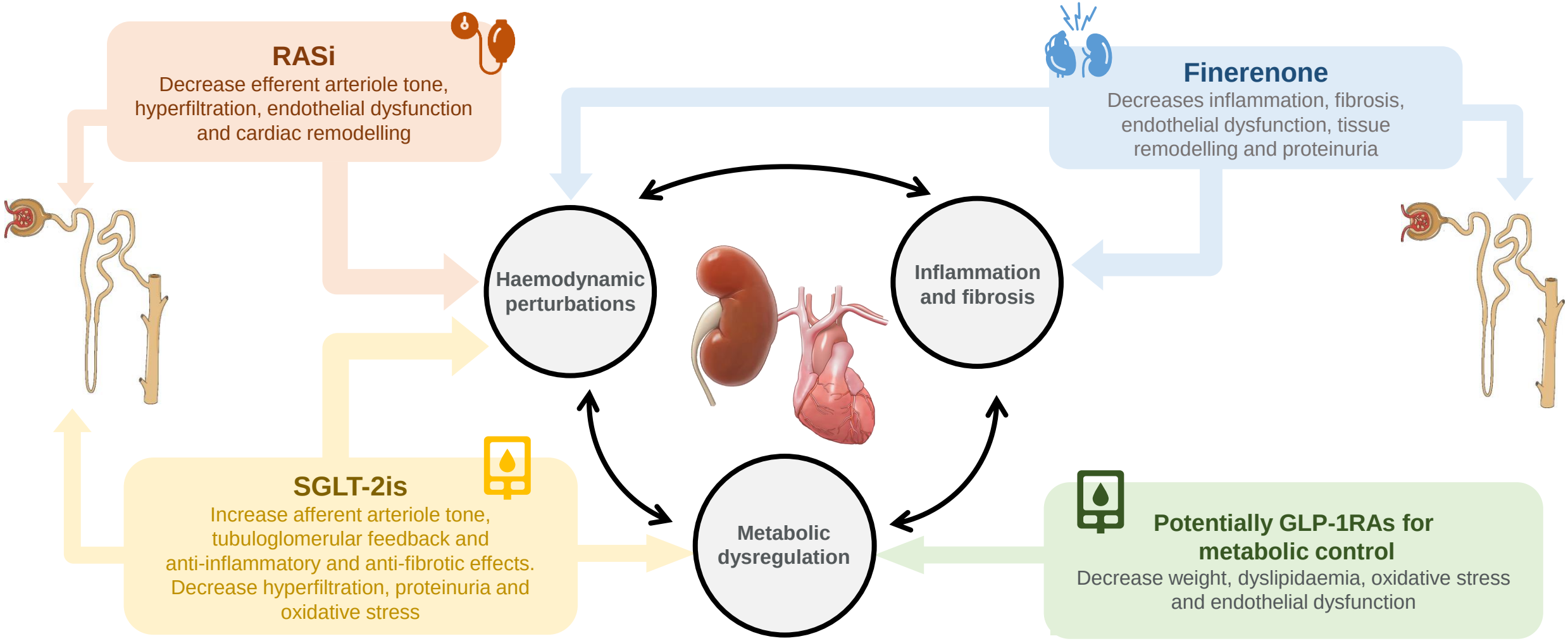
1. Gregg EW *et al. N Engl J Med* 2014;370:1514–1523; 2. Kovesdy CP *et al. Clin Kidney J* 2021;14:1657–1664.

Pathophysiologic mechanisms in diabetic kidney disease



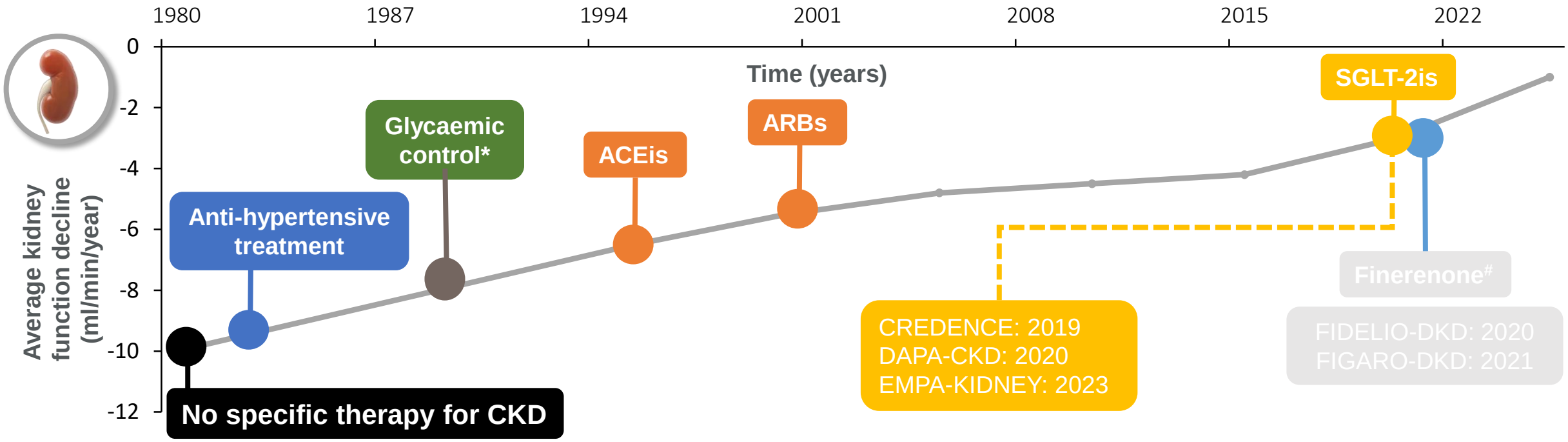
Barrera-Chimal J, Jaisser F. *Diabetes Obes Metab*. 2020;22 Suppl 1:16-31.

The complex pathophysiology underpinning CV and kidney disease in people with T2D calls for a holistic approach to treatment[1,2]



1. Naaman SC & Bakris GL. *Diabetes Care* 2023;46:1574–1586; 2. Neuen BL, *et al. Circulation* 2024;149:450–462

Therapies to slow CKD progression associated with T2D have evolved over the past 40 years[1–10]



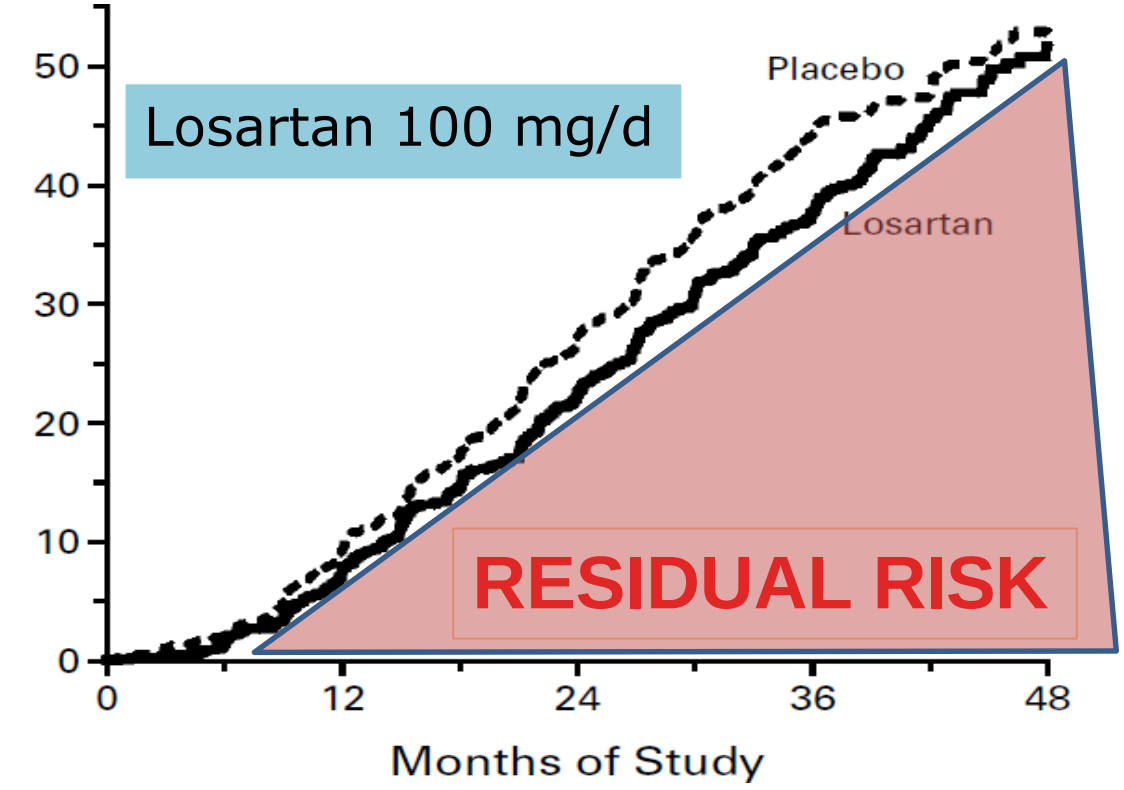
Recent findings on the kidney and CV benefits of **finerenone** and **SGLT-2is** have changed the therapeutic landscape for CKD and T2D

The Only Proven Treatment for Renoprotection in T2DM-RAS BLOCKERS: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

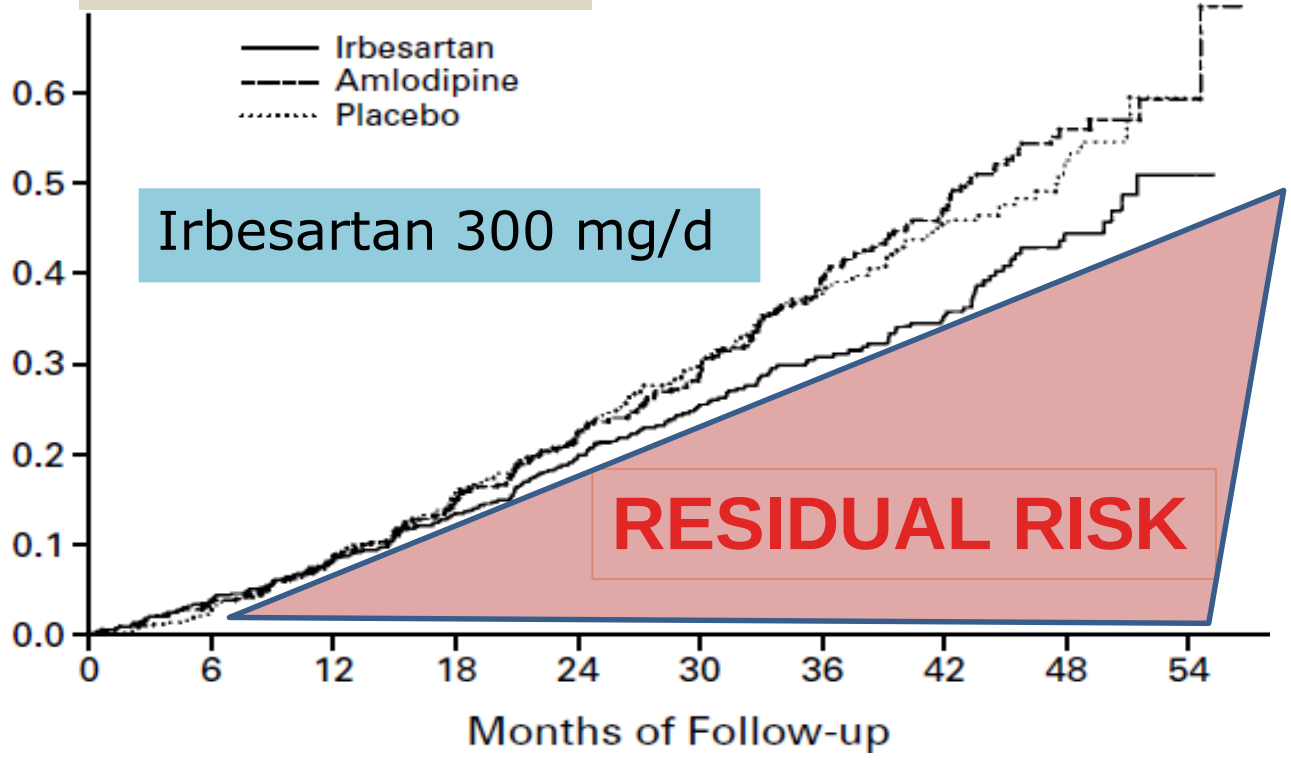
Risk reduction, 16%
P = 0.02

RENAAL



Risk reduction, 20%
P = 0.02

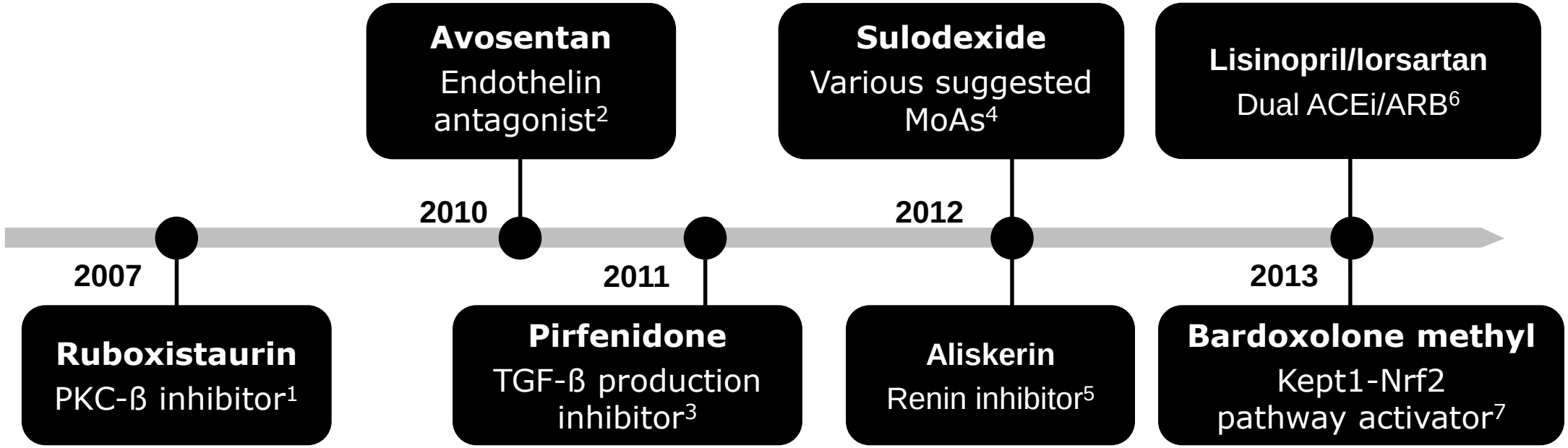
IDNT



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

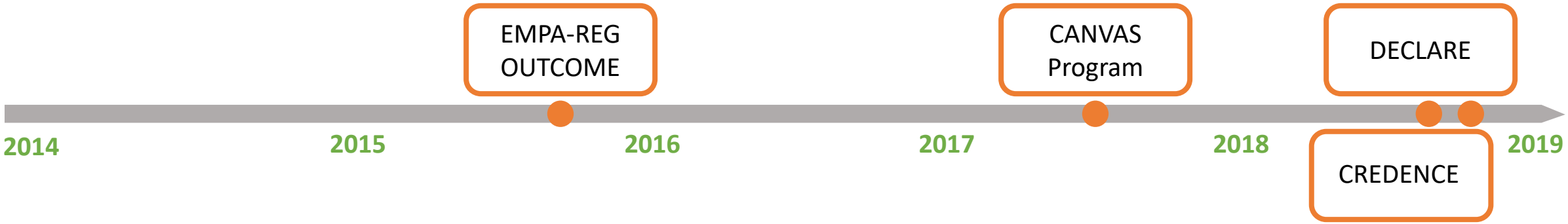
Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Since RENAAL and IDNT, New Therapeutic Strategies for Patients With T2DM and CKD Have Failed



1. Tuttle KR, et al. *Clin J Am Soc Nephrol.* 2007;2(4):631-636.
2. Mann JFE, et al. *J Am Soc Nephrol.* 2010;21(3):527-535.
3. Sharma K, et al. *J Am Soc Nephrol.* 2011;22(6):1144-1151.
4. Packham DK, et al. *J Am Soc Nephrol.* 2012;23(1);123-130.
5. Parving HH, et al. *N Engl J Med.* 2012;367(23):2204-2213.
6. Fried LF, et al. *N Engl J Med.* 2013;369(20):1892-1903.
7. de Zeeuw D, et al. *N Engl J Med.* 2013;369(26):2492-2503.

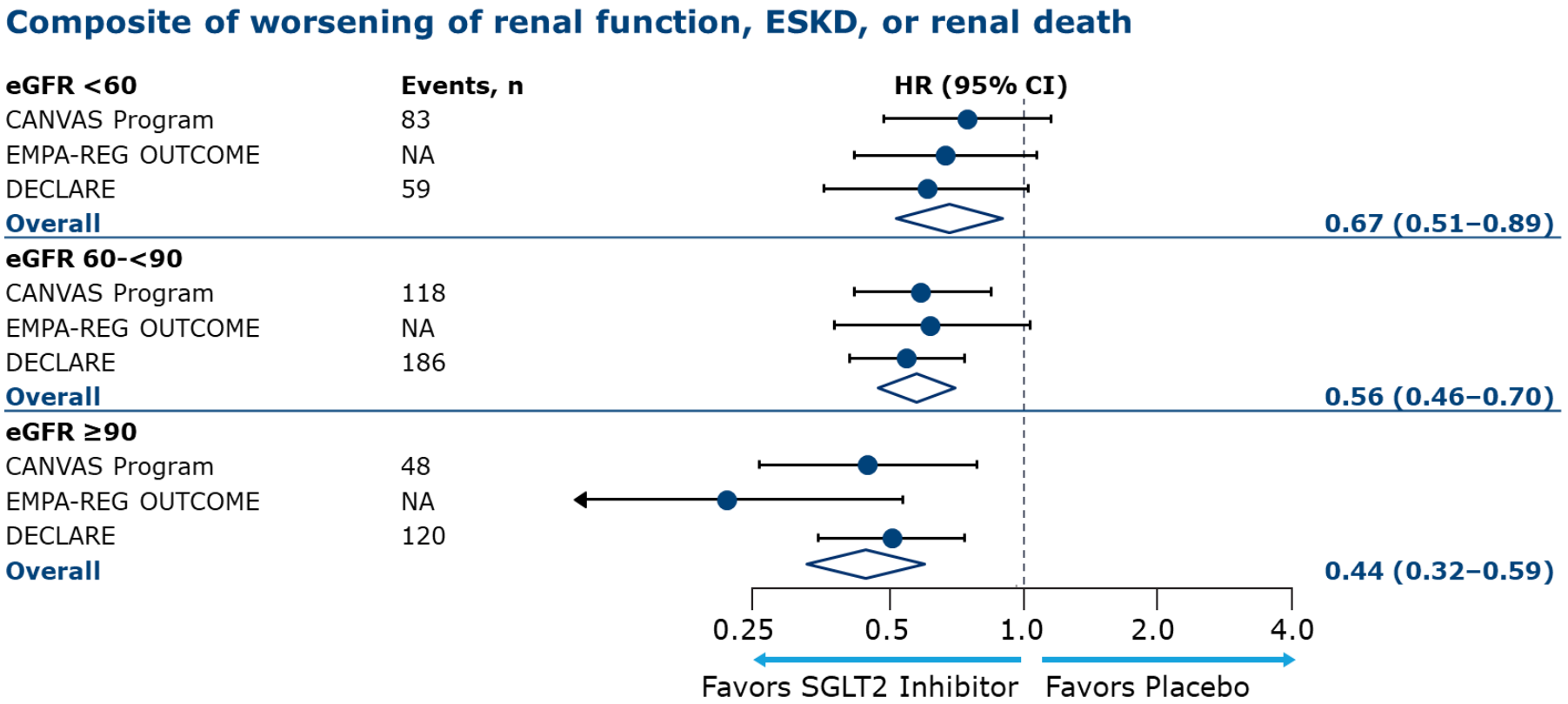
Timeline of Major SGLT2 Inhibitor Trials



- Renal effects were not the primary focus of the CV outcomes trials

Renal Outcomes in SGLT2i Trials

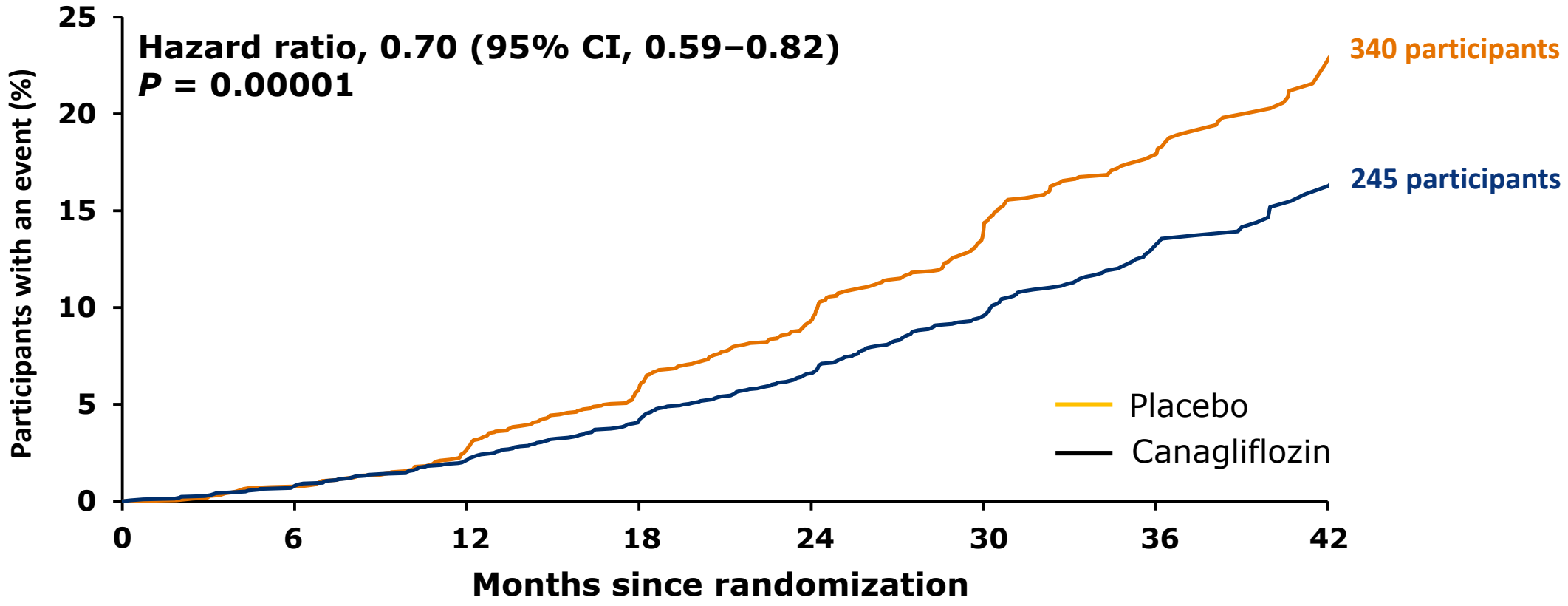
- CV outcomes trial results suggested possible attenuation of renal effects in patients with reduced kidney function



Interaction
P value = 0.0258

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

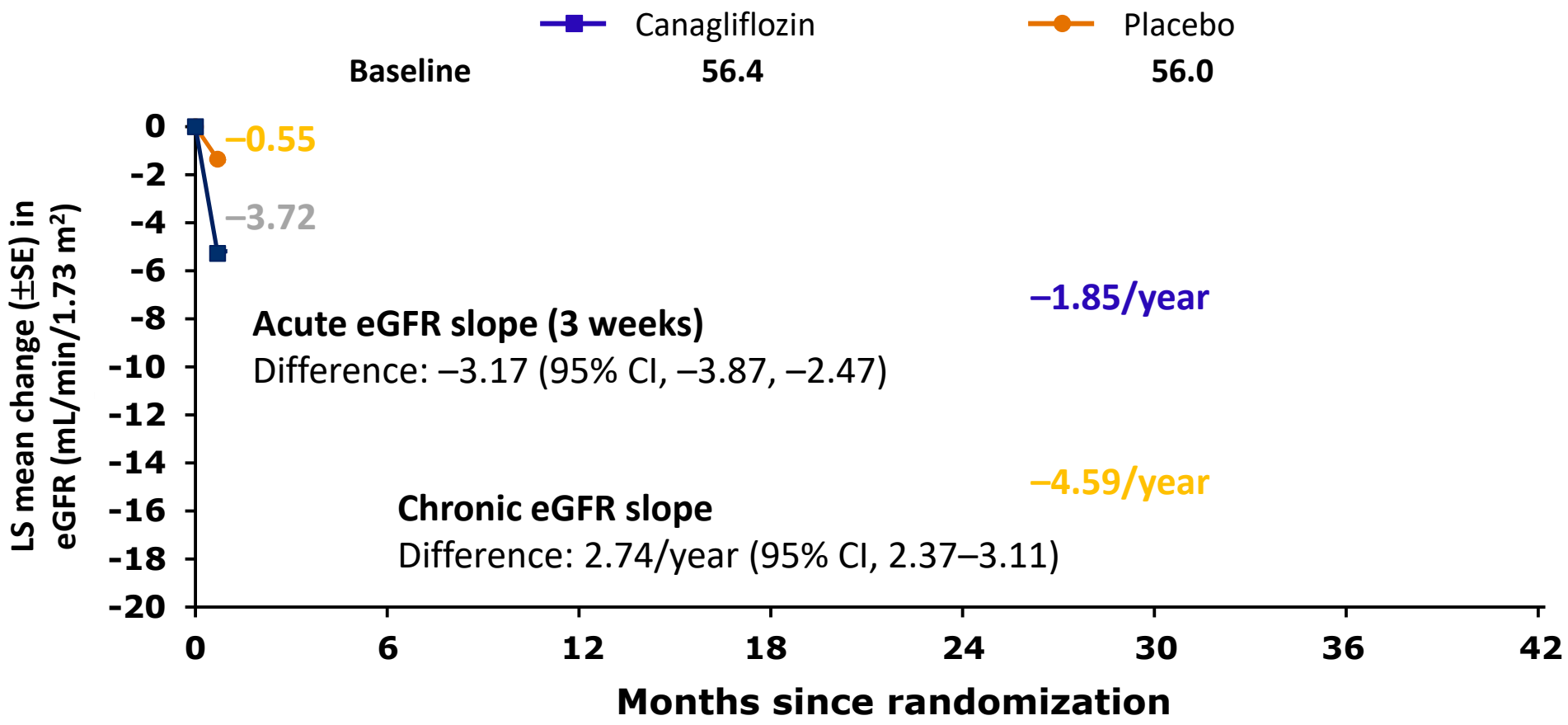
CREDENCE: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic et al. *N Engl J Med.* 2019; 380(24):2295-2306.

Effects on eGFR

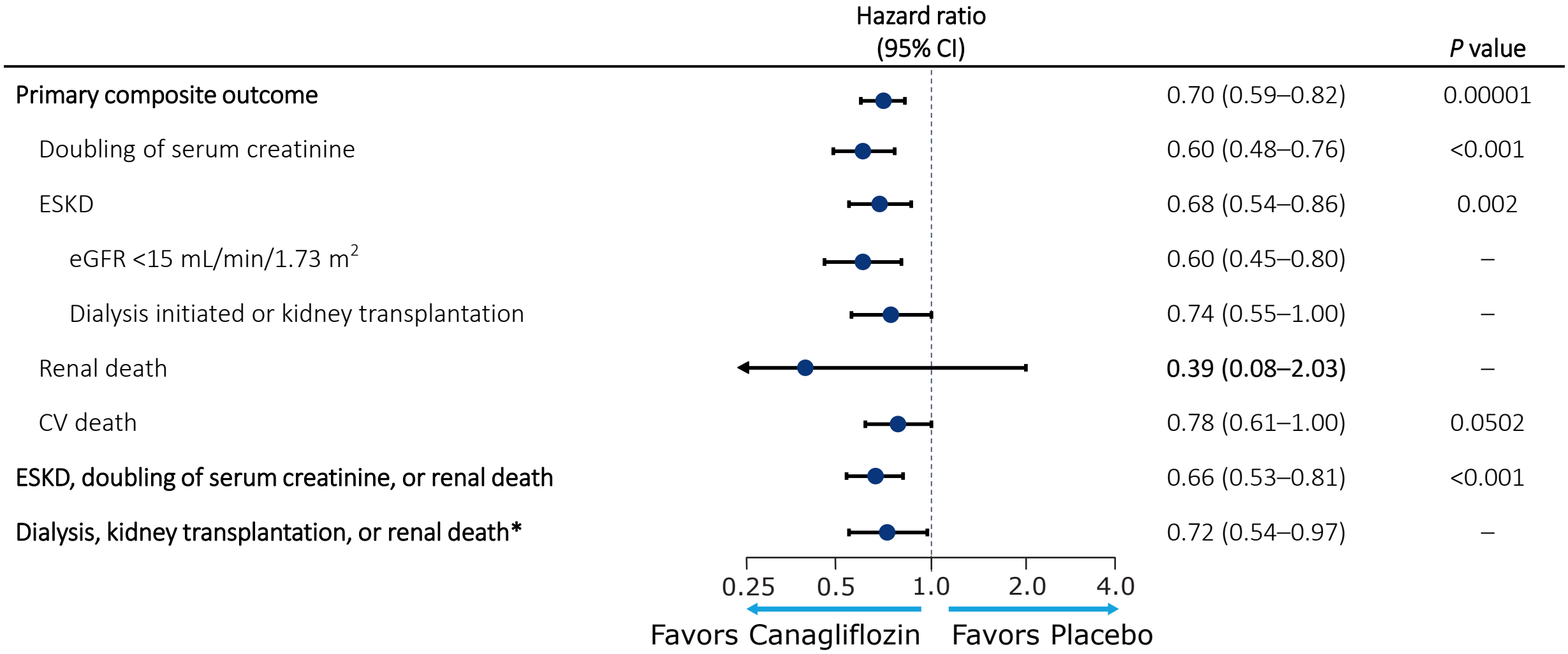


No. of Participants									
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

On treatment

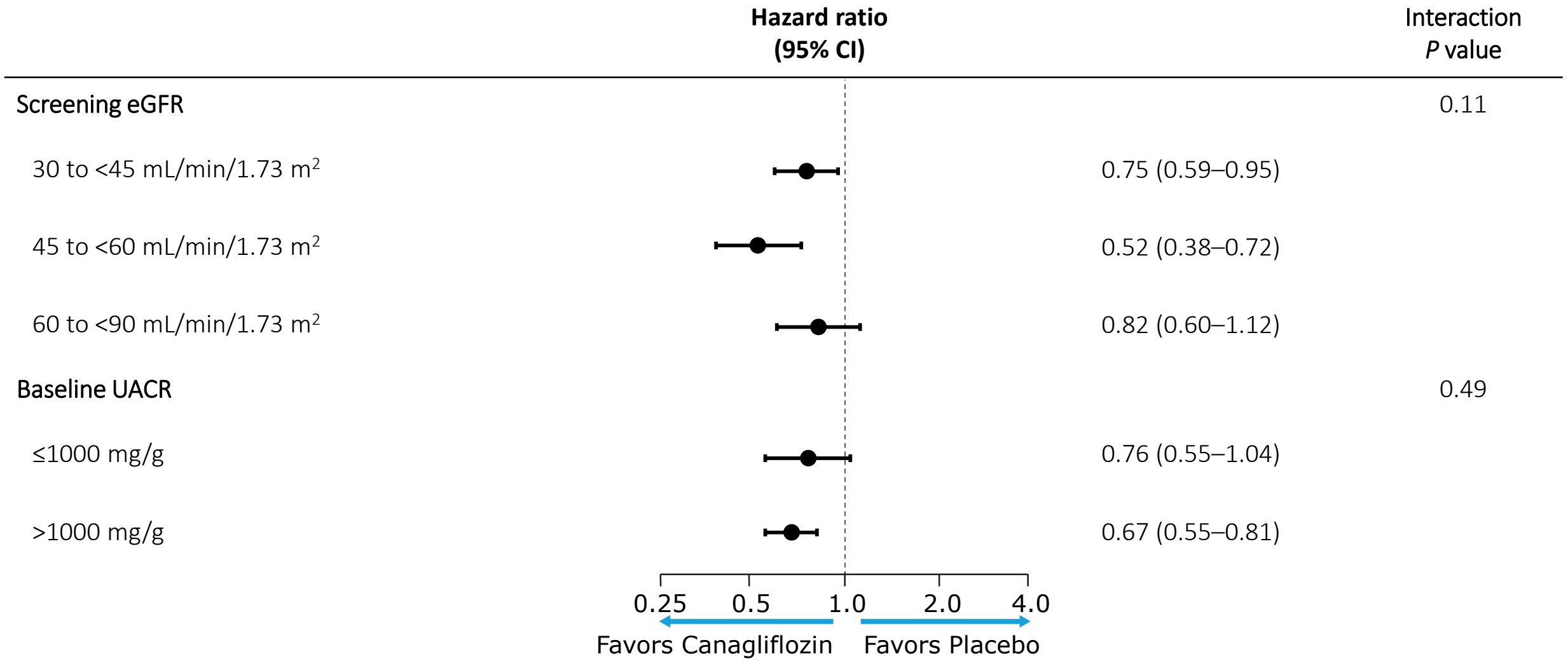
Perkovic et al. *N Engl J Med.* 2019;380(24):2295-2306.

Summary Forest Plot



Perkovic et al. *N Engl J Med.* 2019;380(24):2295-2306.

Primary Outcome by Screening eGFR and Albuminuria

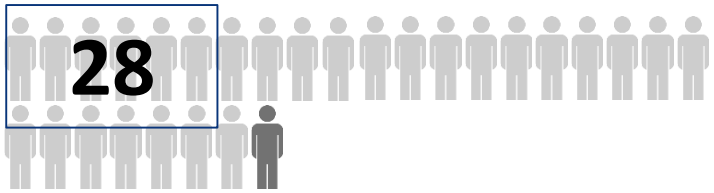


Perkovic et al. *N Engl J Med.* 2019;380(24):2295-2306.

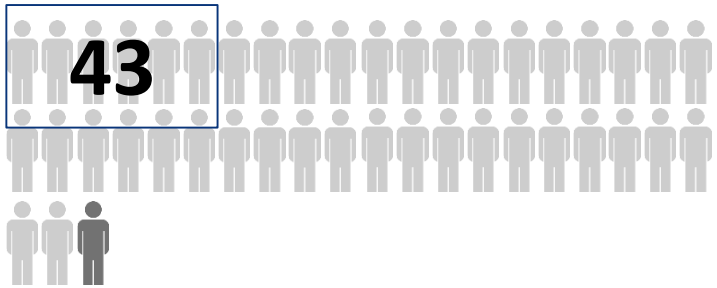
NNT for Renal and CV Outcomes Over 2.5 Years

Primary composite outcome

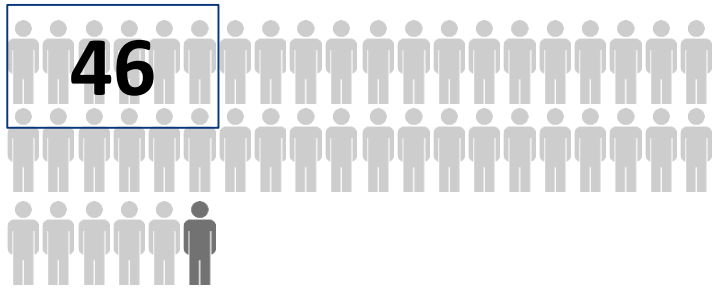
ESKD, doubling of serum creatinine, or renal death



ESKD



Hospitalization for heart failure



CV death, MI, or stroke

Primary composite outcome NNT in patients with eGFR 30 to <45 mL/min/1.73 m^2

Perkovic et al. *N Engl J Med.* 2019;380(24):2295-2306.

SGLT2i renoprotection: Class effect

- Other RCTs with primary renal end points for SGLT2 inhibitors
  - EMPA-KIDNEY
    - Includes non-diabetic patients
  - DAPA-CKD – stopped early due to overwhelming efficacy in interim analysis
    - Includes non-diabetic patients

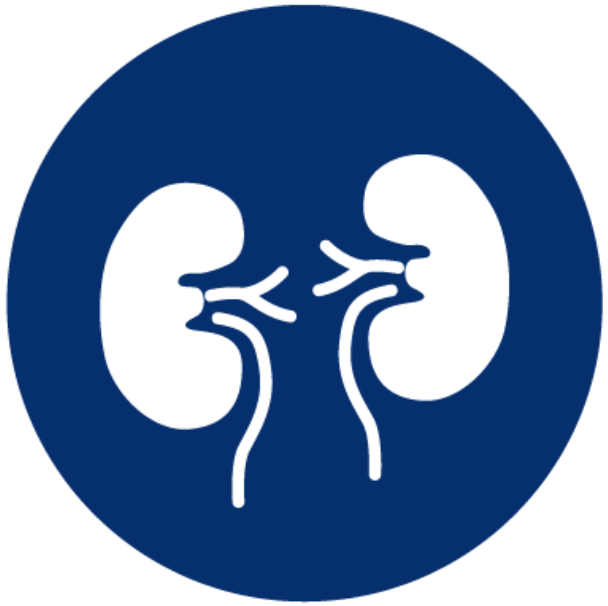
Many Renal Effects of SGLT2 Inhibition Have Been Proposed…

↓ Intraglomerular pressure

↓ Glucose

↓ BP/arterial stiffness

↓ Volume



↓ Albuminuria

↓ Oxidant stress

↓ Intrarenal angiotensinogen upregulation

↓ Inflammation/fibrosis

And many others…

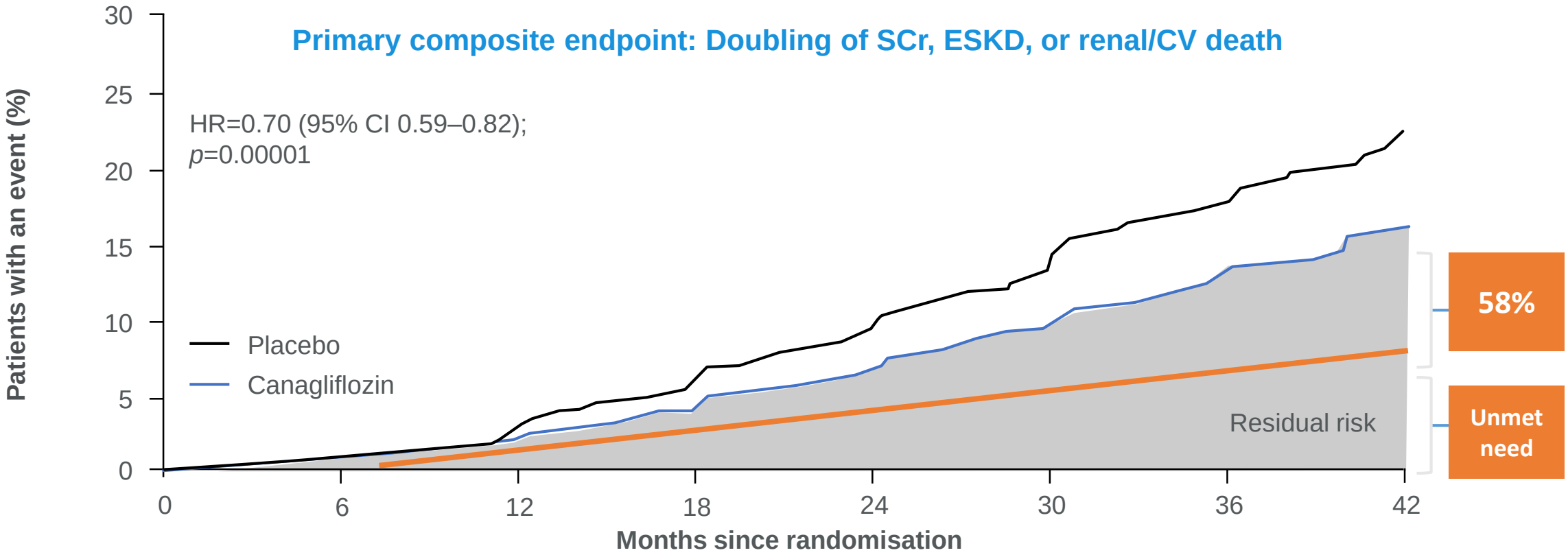
Hemodynamic and Non Hemodynamic Effects of SGLT2 inhibitors 2019

- Decrease GFR by tubuloglomerular feedback
- Blunt rise in angiotensinogen formation
- Reduce oxidative stress by more
- Reduce NLRP3 inflamma
- Attenuation of obe
- Inhibit

SGLT2 inhibitors act by both hemodynamic and anti-inflammatory mechanisms

Woods et.al. Am J Nephrol 2019;Yaribeygi H et.al. J Cell Physiol 2018;
Jung, U., & Choi, M Int. J of Molecular Sci 2014;
Guzik, T. J., & Touyz, R. M. Hypertension 2017;
Mora-Gutiérrez, J. M. et.al. J Magnetic Res Imaging 2017

Remaining Residual risk after SGLT2 inhibitors



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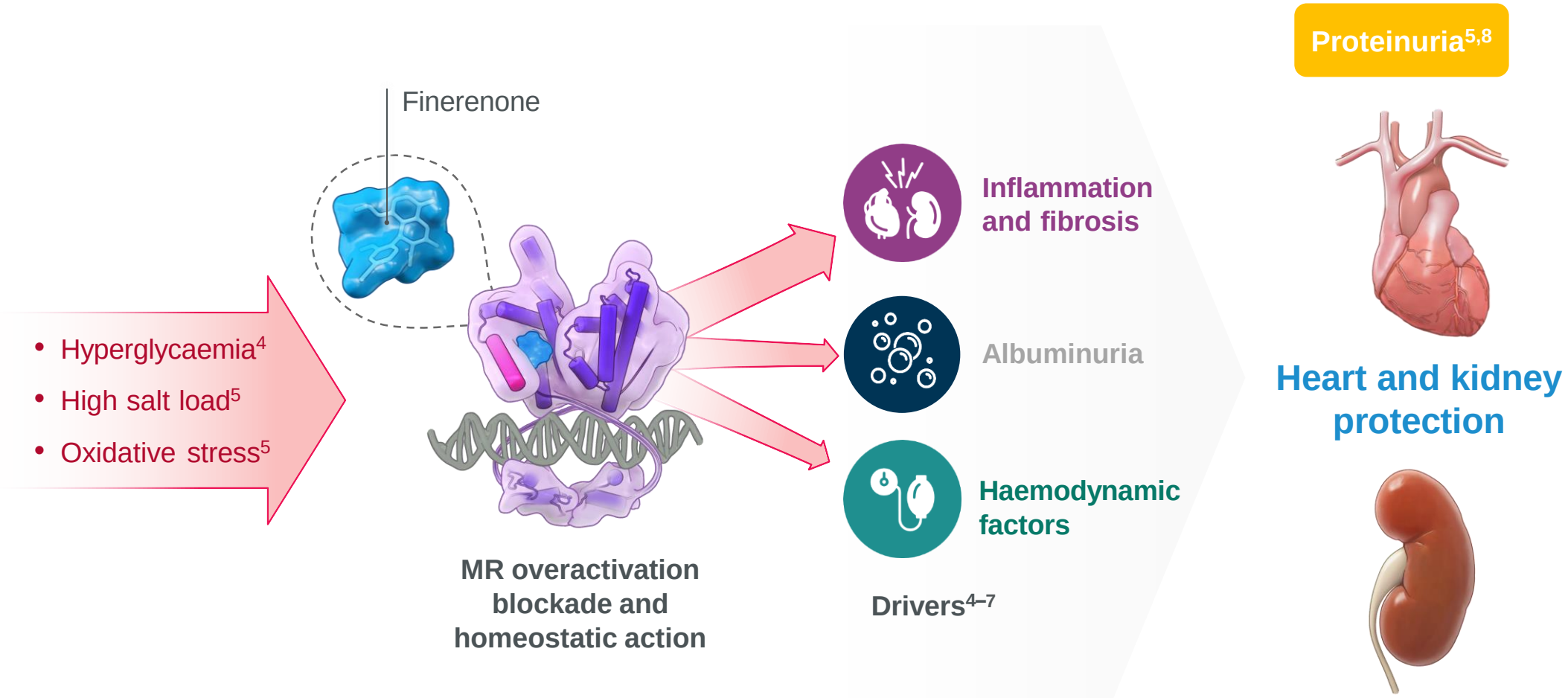
Placebo	2199	2178	2132	2047	1725	1129	621	170

Perkovic V, *et al*. *N Engl J Med* 2019;380:2295–2306

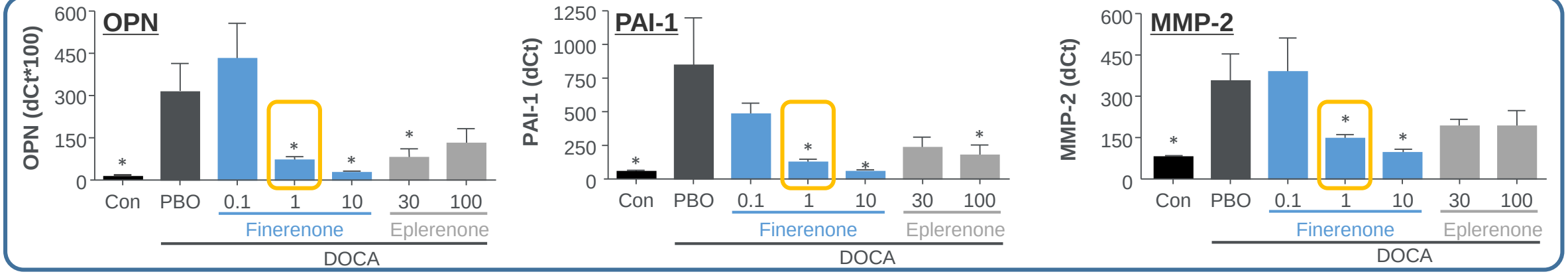
Finerenone, a selective, nonsteroidal MRA, blocks MR overactivation, which slows kidney and CV disease progression[1–3]



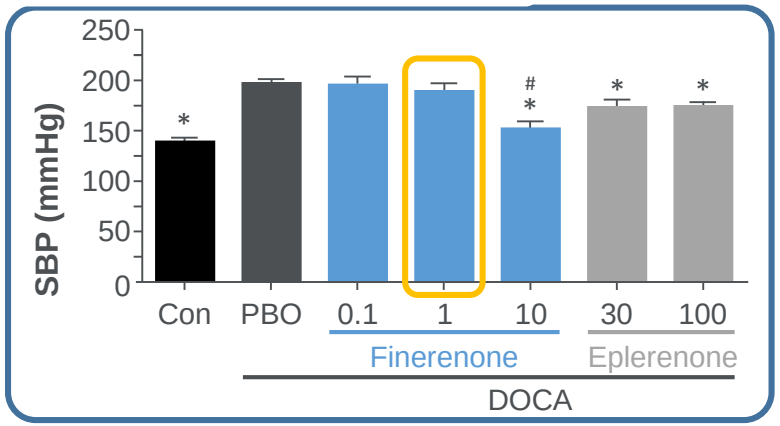
1. Kintscher U, *et al. Br J Pharmacol* 2022;179:3220–3234; 2. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 3. Agarwal R, *et al. Nephrol Dial Transplant* 2022;37:1014–1023; 4. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 5. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 6. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 7. Khan MS, *et al. JACC Rev* 2023;81:270–282; 8. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889

In preclinical models, finerenone reduced pro-inflammatory and pro-fibrotic marker expression without significantly affecting BP

Effect on mRNA expression of inflammatory and fibrotic markers in rat kidney tissue



Effect on SBP

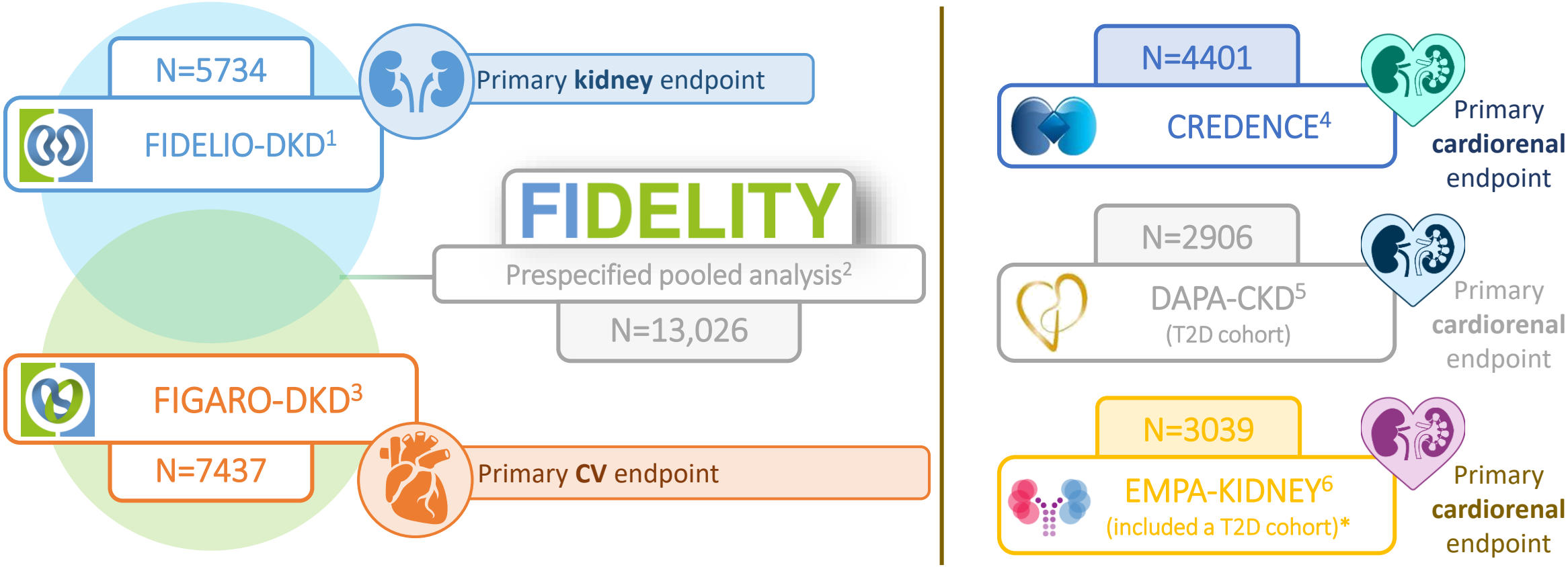


Finerenone reduced mRNA expression of pro-inflammatory and pro-fibrotic markers in kidney tissue to a greater extent than equinatriuretic doses of eplerenone in a rat DOCA–salt model of kidney injury

Finerenone 1 mg/kg/day inhibited inflammation and fibrosis without significantly affecting BP; however, eplerenone doses tested inhibited inflammation and fibrosis and significantly reduced BP

Kolkhof P, *et al*. *J Cardiovasc Pharm* 2014;64:69–78

Overview of completed finerenone and SGLT-2i studies in patients with CKD and T2D



1. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 2. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 3. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 4. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306; 5. Heerspink HJL, *et al. N Engl J Med* 2020;383:1436–1446; 6. The EMPA-KIDNEY Collaborative Group. *Nephrol Dial Transplant* 2022;37:1317–1329

In FIDELITY, finerenone demonstrated significant kidney and CV risk reductions in patients with CKD and T2D

FIDELITY (N=13,026) was a **prespecified pooled analysis** of individual patient data from the complementary **FIDELIO-DKD** and **FIGARO-DKD** trials

Key outcomes

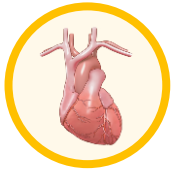
Kidney composite

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

23% RRR of kidney composite outcome (HR=0.77; 95% CI 0.67–0.88; *p*=0.0002)

ARR: 1.7% at 3 years

20% RRR of ESKD (HR=0.80; 95% CI 0.64–0.99; *p*=0.040)[#]



CV composite

Time to CV death, non-fatal MI, non-fatal stroke or HHF

14% RRR of CV composite outcome (HR=0.86; 95% CI 0.78–0.95; *p*=0.002)

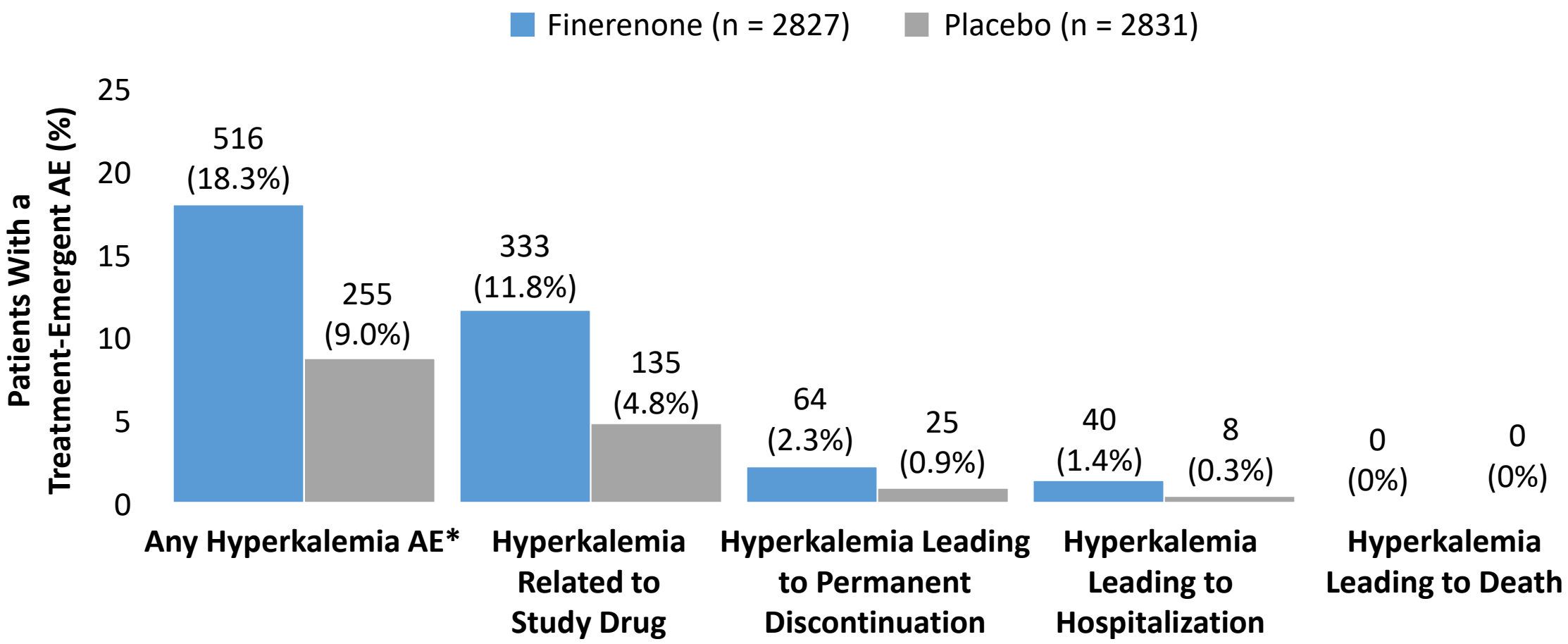
ARR: 2.2% at 3 years

22% RRR of first HHF[‡] (HR=0.78; 95% CI 0.66–0.92; *p*=0.003)

32% reduction in **UACR** (ratio of LS mean change from baseline 0.68; 95% CI 0.66–0.70)

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

FIDELIO-DKD: Treatment-Emergent Adverse Events Related to Hyperkalemia



*Investigator-reported treatment-emergent AEs using the MedDRA preferred terms “hyperkalemia” and “blood potassium increased.”

Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219-2229.

The THUNDERBALL programme is set to further investigate finerenone in patients with CKD and beyond…

FIND-CKD[1]

Efficacy and safety of finerenone in addition to SoC on the progression of kidney disease in patients with non-diabetic CKD (N=1584)

Population:
Patients with non-diabetic CKD (eGFR ≥25–<90 ml/min) with albuminuria

Primary outcome:
Mean rate of change as measured by the total slope of eGFR from baseline to month 32

CONFIDENCE[2]

Efficacy and safety of finerenone in combination with empagliflozin vs either therapy alone in patients with CKD and T2D (N=807)

Population:
Patients with CKD (eGFR ≥30–≤90 ml/min) and T2D with albuminuria (≥300–<5000 mg/g)

Primary outcome:
Relative change in UACR from baseline to 180 days

FIONA[3]

Efficacy, safety and PK/PD of an age- and body weight-adjusted oral finerenone regimen, in addition to an RASi, for the treatment of children with CKD and proteinuria (N=219)

Population:
Paediatric patients with CKD and proteinuria on maximum tolerated dose of RASi

Primary outcome:
Proportion of patients with UPCR reduction ≥30% from baseline to day 180

FINE-ONE[4]

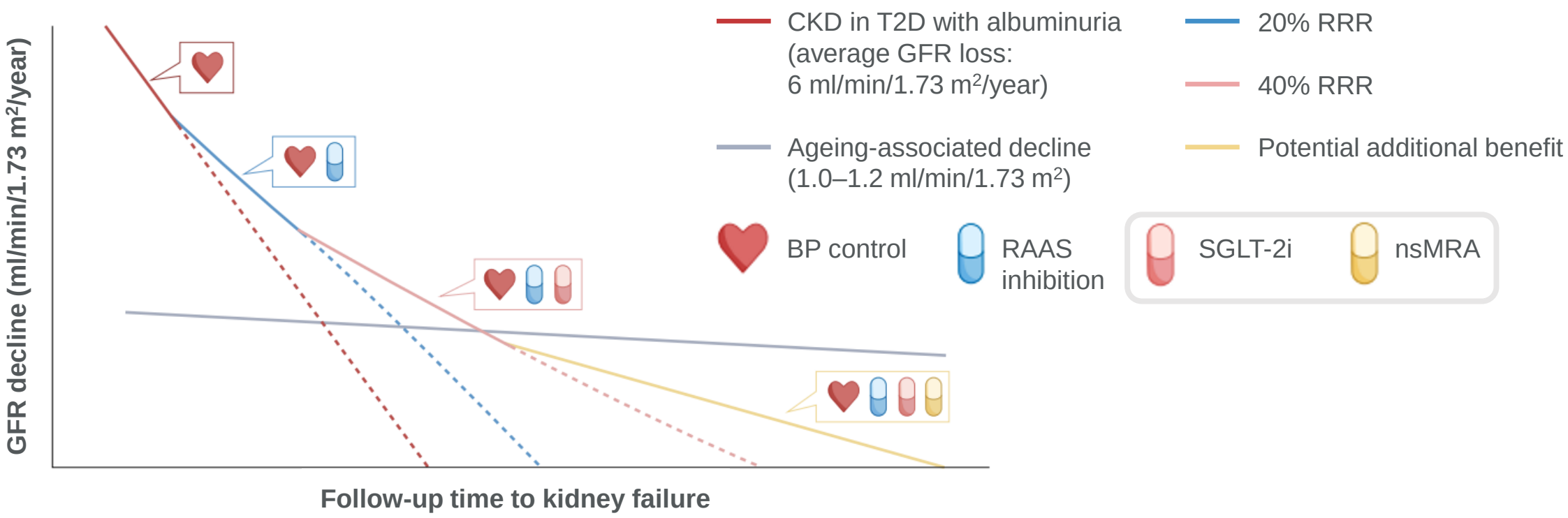
Efficacy and safety of finerenone in addition to SoC in patients with CKD and T1D (N=220)

Population:
Patients with CKD (eGFR ≥25–<90 ml/min/1.73 m² and UACR ≥200–<5000 mg/g) and T1D

Primary outcome:
Change in UACR from baseline to month 6

1. https://clinicaltrials.gov/ct2/show/NCT05047263; 2. Green JB, *et al. Nephrol Dial Transplant* 2022; doi.org/10.1093/ndt/gfac198; 3. https://clinicaltrials.gov/ct2/show/NCT05196035; 4. https://clinicaltrials.gov/study/NCT05901831

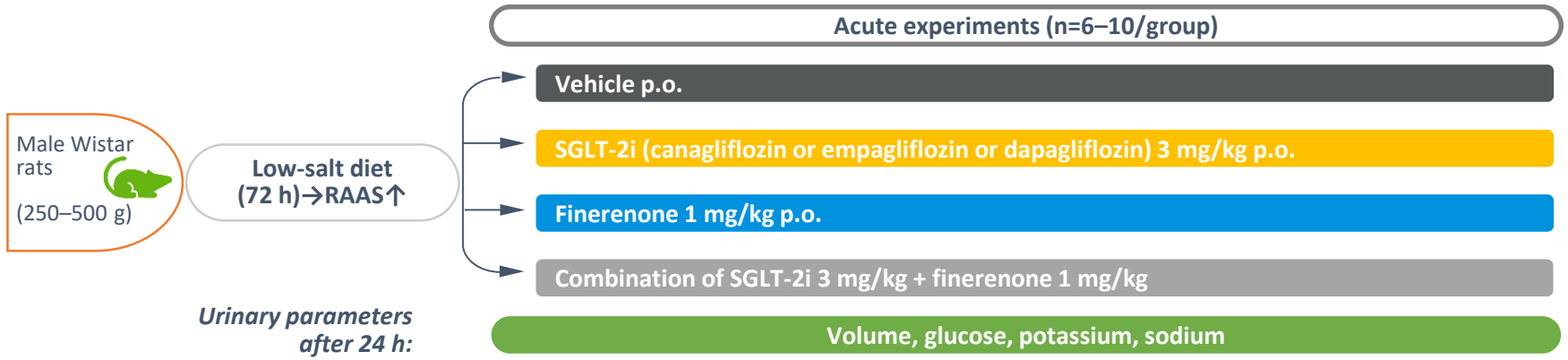
New and emerging therapies improve heart and kidney outcomes in CKD and T2D[1]



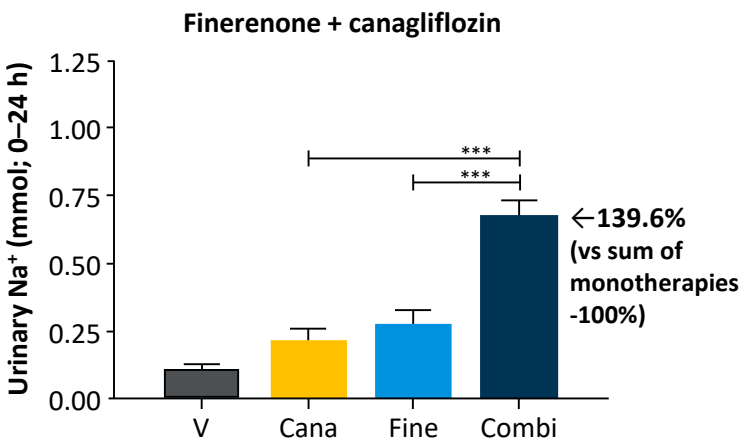
A joint analysis of RCT data on **combination treatment with nsMRA and SGLT-2i** (compared with conventional therapy) suggested a substantial **increase in the number of years free from kidney failure and mortality** in patients with CKD and T2D[2]

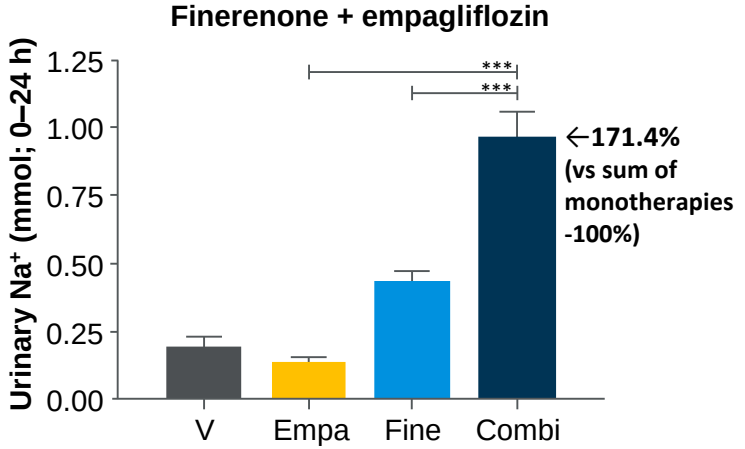
1. Fioretto P & Pontremoli R. *Nat Rev Nephrol* 2022;18:78–79; 2. Heerspink, HJL, *et al. Diabetes Obes Metab* 2023;25:3327–3336

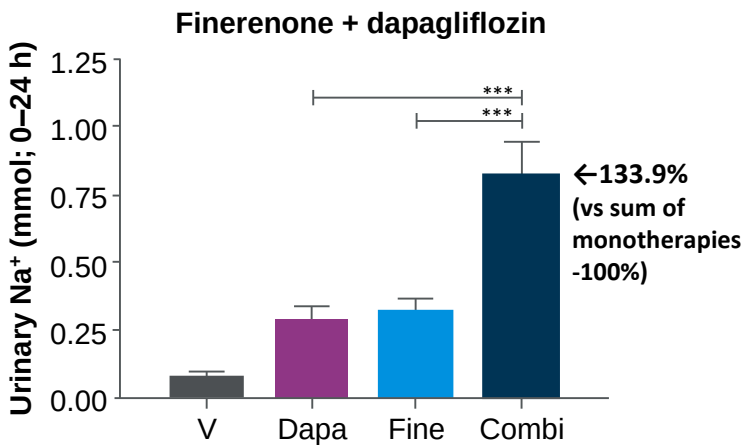
Preclinical data show over-additive effects of finerenone–SGLT-2i combination therapy in a rat model



Efficacious natriuresis can be an early trigger for beneficial effects on downstream signalling cascades, including inhibition of ROS generation and inflammation in the heart and the kidneys







Kolkhof P, *et al. ESC* 2023; Poster 80602

Cardio-renal effects of mono and combination therapy with Finerenone and Empagliflozin in preclinical model of Hypertension induced end organ damage

AJN
American Journal
of Nephrology

Hypertensive, proteinuric, L-NAME treated, renin-transgenic (mRen2)27 rats.

Intervention	Survival (Absence of mortality & severe morbidity)	Change in Proteinuria	Blood Pressure (mm Hg)	Cardiac & Renal Histology
Placebo	53%	100%	202 ±6.8	
Finerenone 1mg	85%	-27%	170 ±9.0	
Finerenone 3mg	86%	-87%	164 ±4.7	
Empagliflozin 3mg	71%	-38%	199 ±10.4	
Empagliflozin 10mg	62%	-64%	188 ±8.7	
Finerenone 1mg + Empagliflozin 3mg	93%	-86%	173 ±7.7	

Dose dependent Improvement in cardiac & renal histopathology parameters with maximum benefit with low dose combination therapy

Conclusion: Combination of nonsteroidal MR antagonism by finerenone and SGLT2 inhibition by empagliflozin confer CV protection in preclinical hypertension-induced cardiorenal disease indicating a strong potential for combined clinical use.

Kolkhof P, Hartmann E, Freyberger A, Pavkovic M, Mathar I, Sandner P, Droebner K, Joseph A, Hüser J, Eitner F: Effects of Finerenone Combined with Empagliflozin in a Model of Hypertension-Induced End-Organ Damage.
Am J Nephrol DOI: 10.1159/000516213

Visual Abstract by Aakash Shingada@aakashshingada

MRA combined with SGLT2i

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

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

46 patients

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

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

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

OUTCOMES

UACR change (%) from baseline

combination vs. dapa: p<0.001

combination vs. eple: p=0.0127

Change from baseline in serum K (mmol/L)

combination vs. dapa: p<0.0018

combination vs. eple: p=0.0296

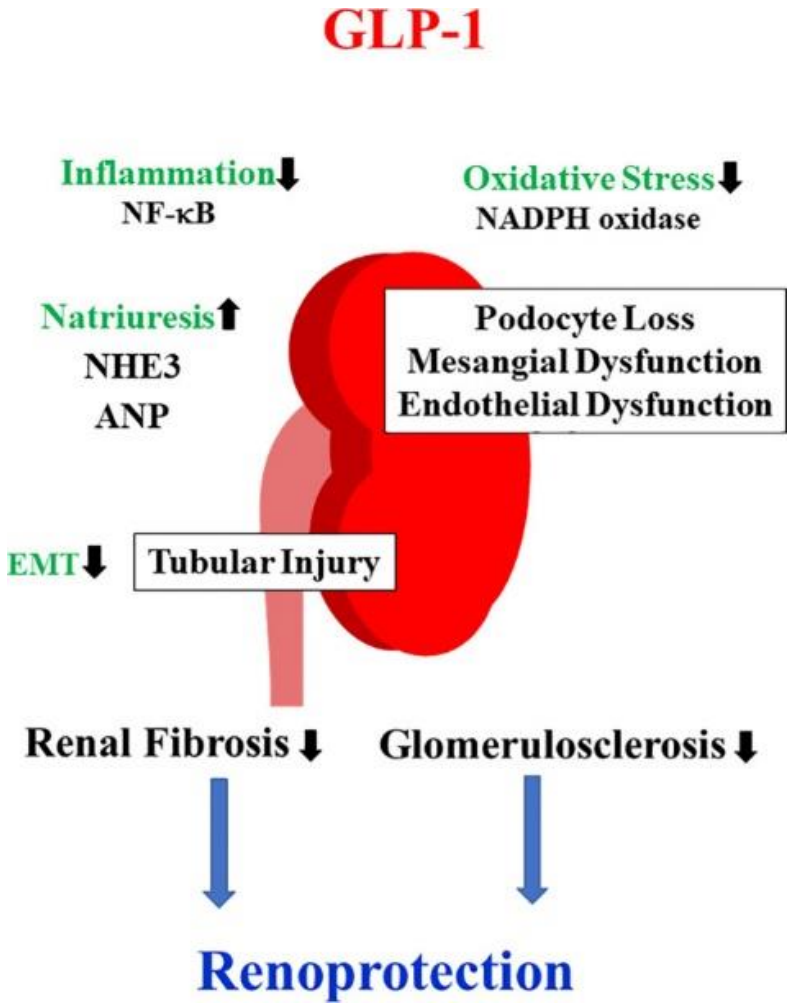
Conclusion

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

doi: 10.1681/ASN.2022020207

Provenzano et al., J Am Soc Nephrol. 2022 Apr 19. doi: 10.1681/ASN.2022020207. Online ahead of print

Many Renal Effects of GLP-1RA Have Been Proposed…



Kawanami D, Takashi Y. Front Pharmacol 2020;11:967.

Renal outcomes with Glucagonlike peptide-1 (GLP-1) receptor agonists

Trial	Agents, Follow-up Duration	Subjects	Renal Outcomes	Results
LEADER (n=9,340)	Liraglutide (1.8 mg) vs. placebo, 3.84 years	T2D with high CV risk	New-onset macroalbuminuria, doubling of the serum creatinine level, ESRD, renal death	HR 0.78 (95% CI: 0.67-0.92)
SUSTAIN-6 (n=3,297)	Semaglutide (0.5 mg, 1.0 mg) vs. placebo, 104 weeks	T2D Age >50 with established CVD or CKD stage 3-5 Age >60 with CV risk factors	New or worsening of nephropathy (persistent macroalbuminuria, doubling of the serum creatinine level and CCr < 45 mL/min/1.73 m2, RRT)	HR 0.64 (95% CI: 0.46-0.88)
REWIND (n=9,901)	Dulaglutide (1.5 mg) vs. placebo, 5.4 years	T2D with a previous CV event or CV risk factors	New onset of macroalbuminuria, sustained eGFR decline (≥30%) or RRT	HR 0.85 (95% CI: 0.77-0.93)
AWARD-7 (n=576)	Dulaglutide (0.75 mg, 1.5 mg) vs. placebo, 52 weeks	T2D with moderate to severe CKD (stage 3-4)	Changes in eGFR decline and UACR from baseline	eGFR decline: -1.1 (1.5 mg), -1.5 (0.75 mg), -2.9 (glargine) UACR: no significant differences among groups
ELIXA (n=6068)	Lixisenatide (10-20 μg) vs. placebo, 108 weeks	T2D with recent acute coronary syndrome	Percent change in UACR and eGFR from baseline	eGFR decline: no significant differences among groups

Kawanami D, Takashi Y. Front Pharmacol 2020;11:967.

Semaglutide for CKD in Patients with Type 2 Diabetes: "FLOW"ing with the Semaglu"TIDE"

#NephJC

METHODS

International, double-blind, placebo-controlled
28 countries

Type 2 DM and CKD:
GFR 50-75 ml/min + ACR 300-5000 mg/g
or
GFR 25-<50 ml/min + ACR 100-5000 mg/g

Median follow-up, 3.4 years

	Major kidney disease events	Death from any causes	Adverse event leading to discontinuation
Placebo n = 1766	7.5 events per 100 patient-years	279(15.8%)	211(11.9%)
	HR 0.76 (95% CI, 0.66-0.88)	HR 0.80 (95% CI, 0.67-0.95)	
Semaglutide n = 1767	5.8 events per 100 patient-years	227(12.8%)	233(13.2%)

Major kidney disease events- kidney failure, ≥50% reduction in GFR, death from CV or kidney-related causes

HR= Hazard ratio

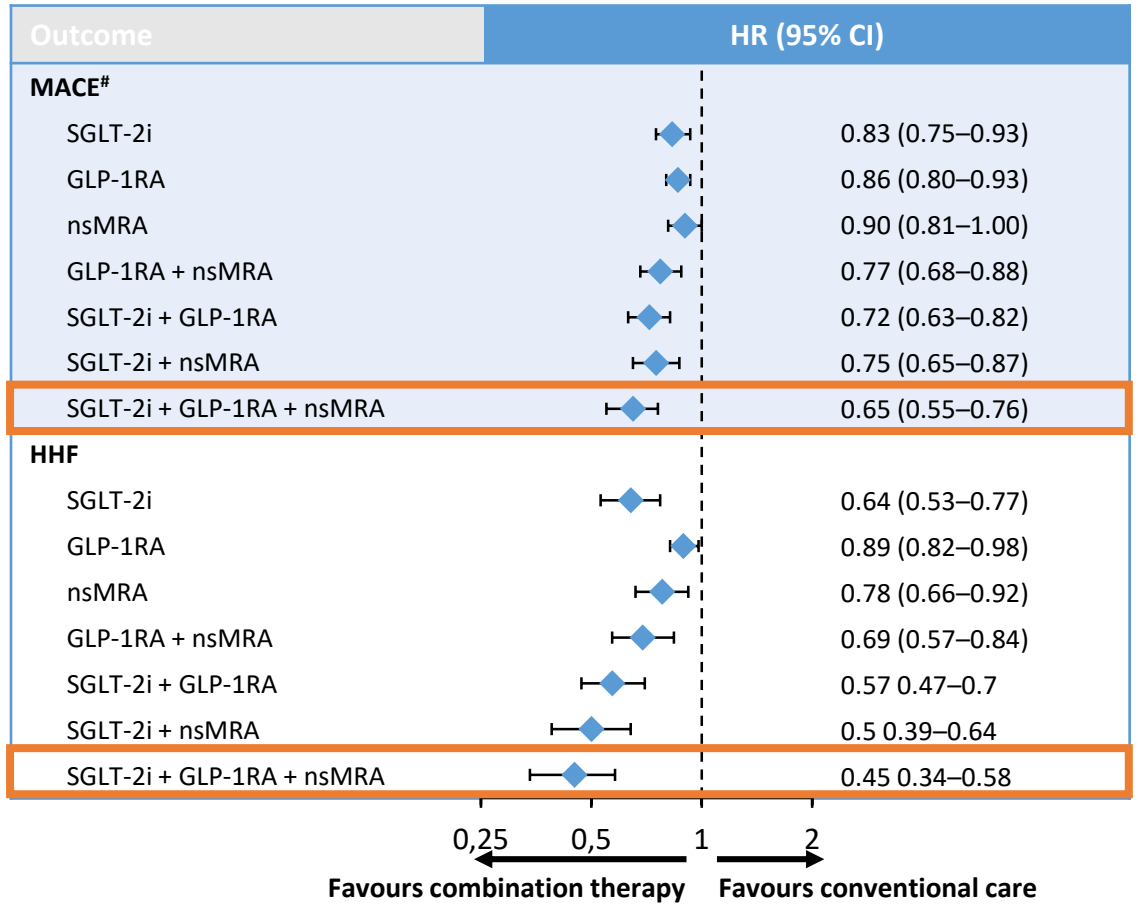
Reference: Perkovic,V et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. NEJM, May 2024.

VA by Anjana Gopal @anjanagopal9

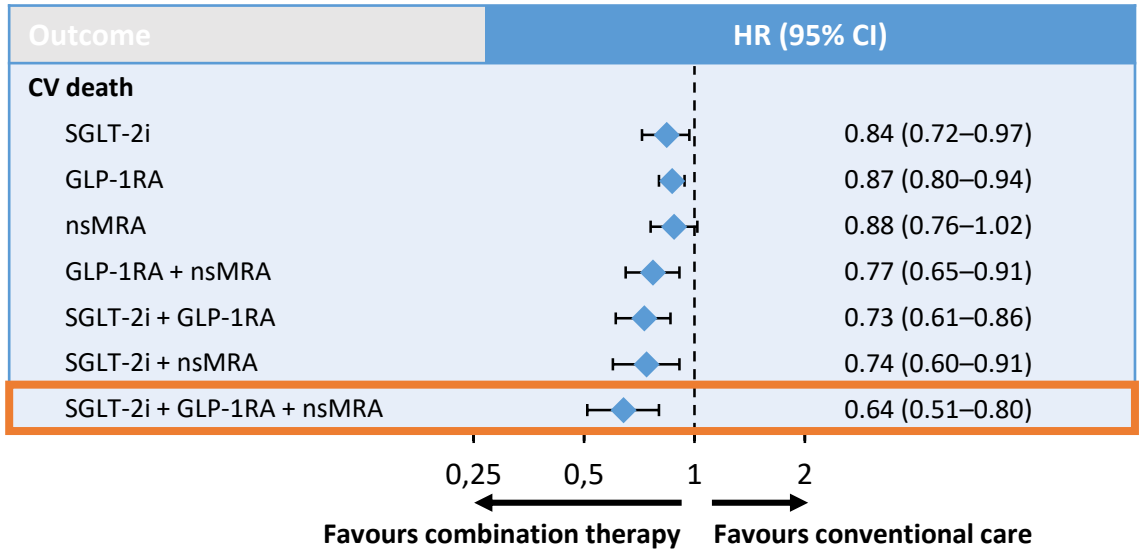
Conclusion: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Results from a cross-trial secondary analysis suggest potential CV benefits with SGLT-2i, GLP-1 RA and nsMRA combination treatment in patients with T2D and albuminuria

MACE and HHF



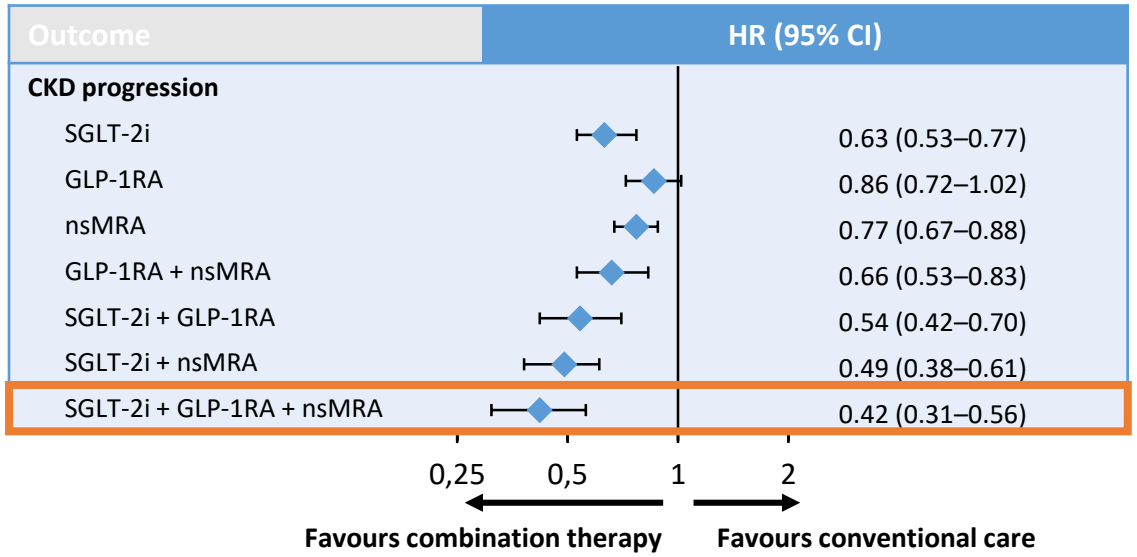
CV death



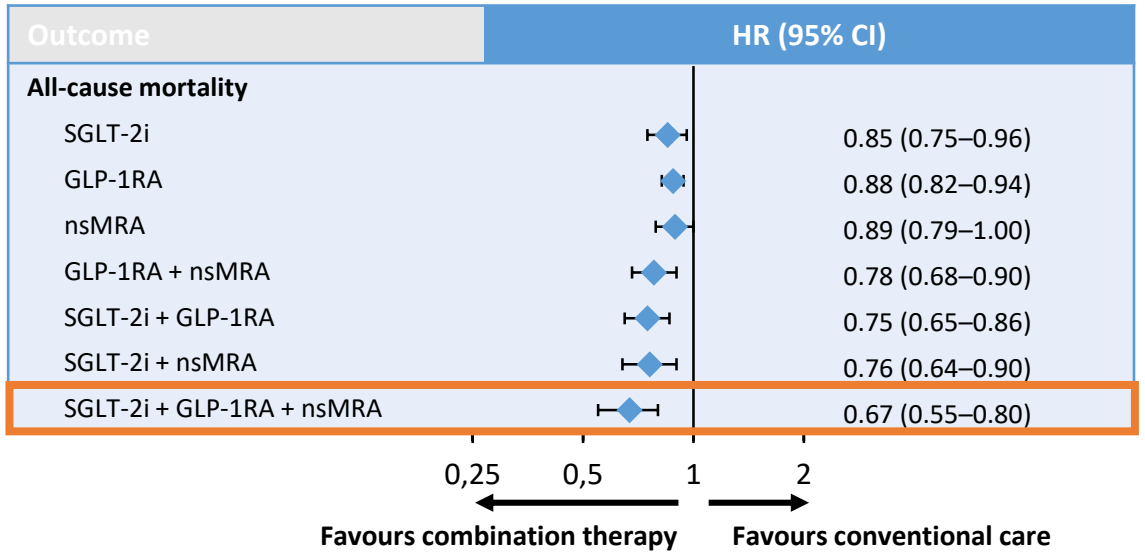
Neuen BL, *et al. Circulation* 2024;149:450–462

Combination treatment with an SGLT-2i, GLP-1 RA and nsMRA may also reduce the risk of CKD progression and all-cause mortality

CKD progression



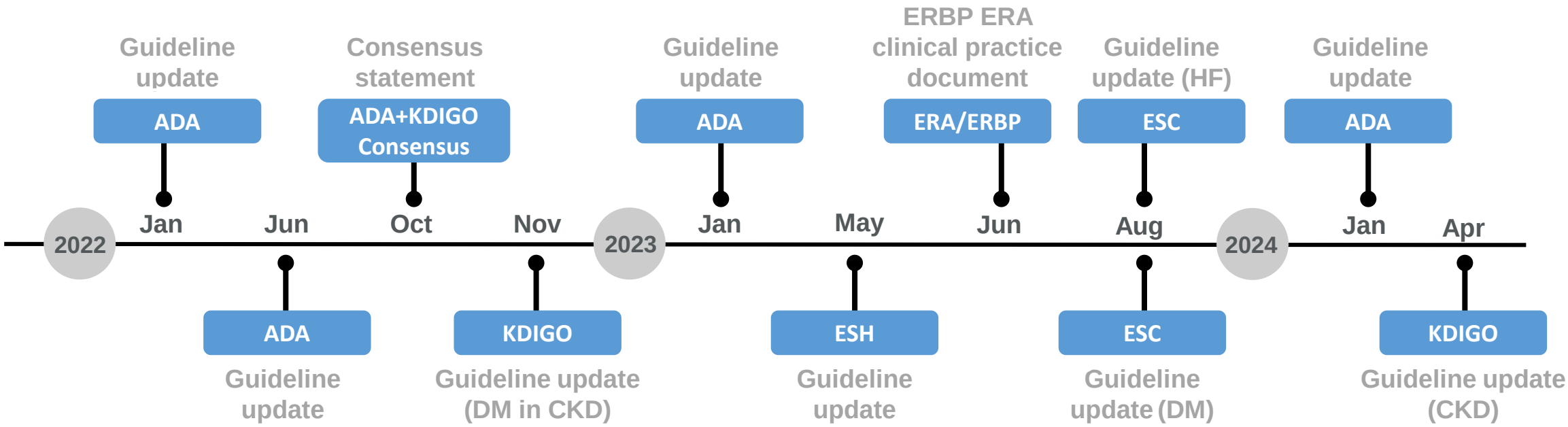
All-cause mortality



A **'pillar' approach** combining therapy with an **SGLT2i, GLP-1 RA and nsMRA**, in addition to **RAS blockade,** may be **beneficial for patients with T2D and albuminuria** as these drugs **target different complementary pathophysiological pathways** involved in CV and kidney diseases

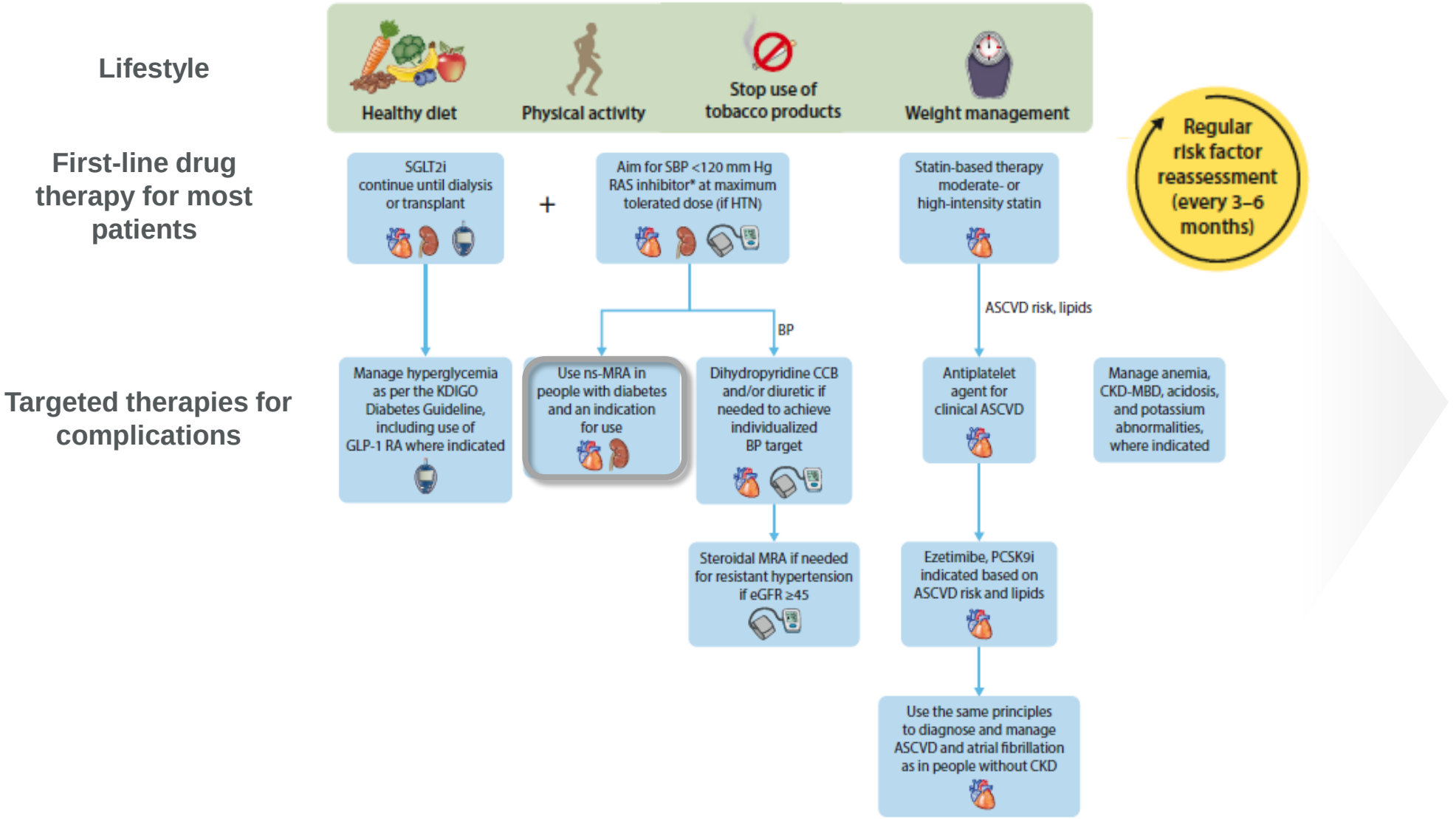
Neuen BL, *et al. Circulation* 2024;149:450–462

Recent clinical guideline updates reflect the evolving treatment landscape for CKD and T2D[1–13]



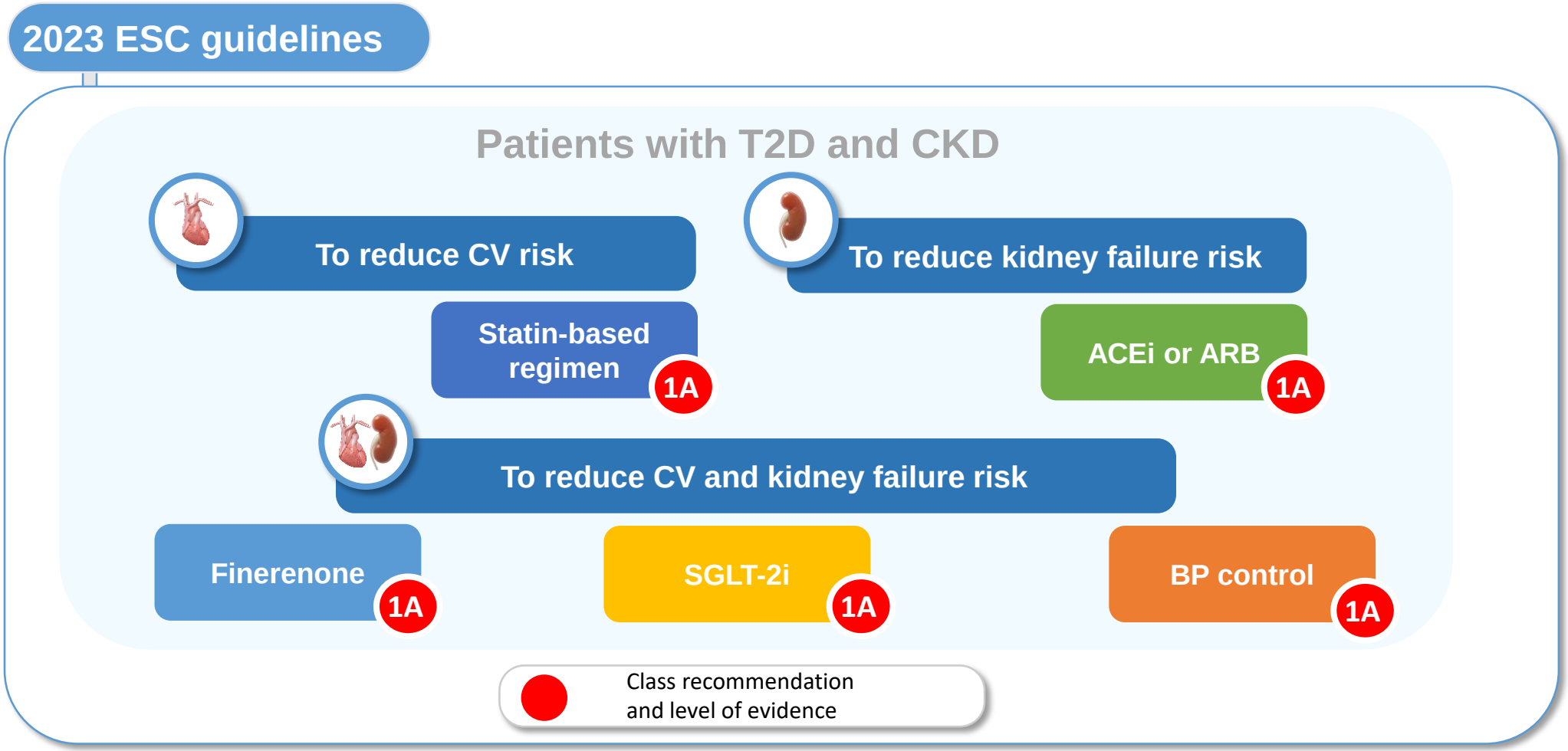
ADA, American Diabetes Association; CKD, chronic kidney disease; DM, diabetes mellitus; ESC, European Society of Cardiology; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcome

A holistic approach to treatment is recommended by the KDIGO 2024 guidelines for improving outcomes in patients with CKD and T2D



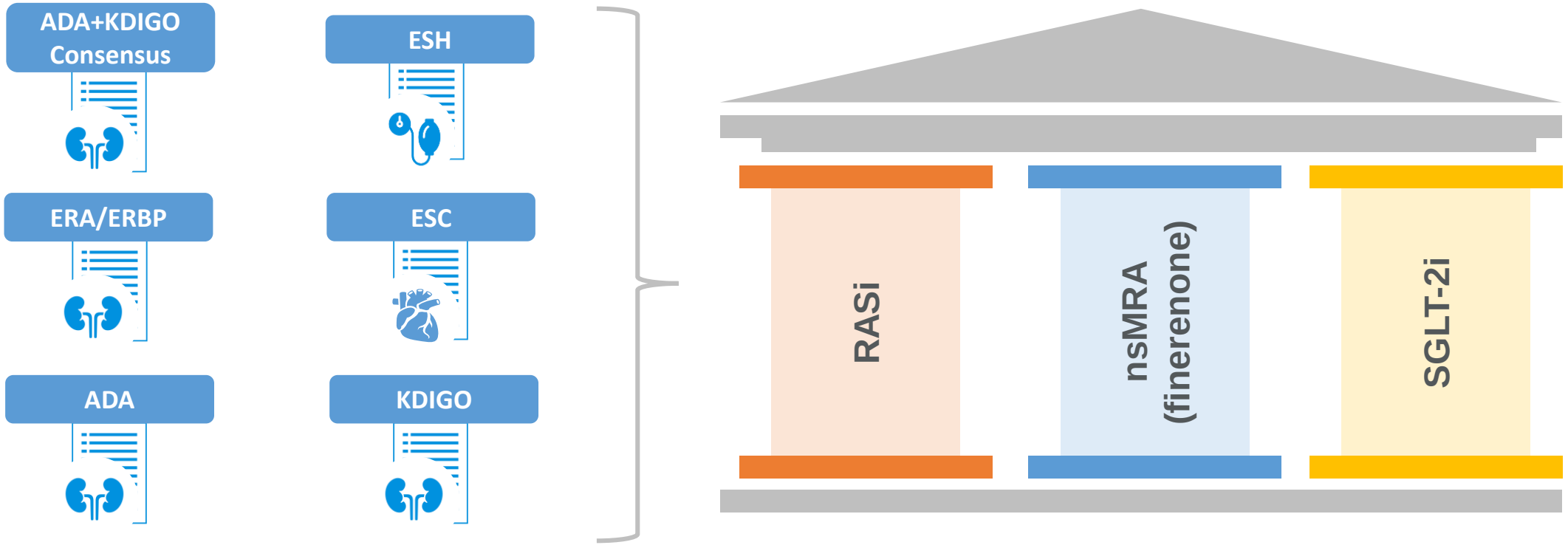
Kidney Disease: Improving Global Outcomes (KDIGO): *Kidney Int* 2024;105;S117–S314

The 2023 ESC guidelines for CVD management in patients with diabetes recommend finerenone for the reduction of CV and kidney disease risk



Marx N, *et al*. *Eur Heart J* 2023;44:4043–4140

Clinical guidelines for the management of CKD in T2D recommend a combination of drug therapies to optimally reduce risks[1–8]



This ‘pillar approach’ is aligned with the multifactorial and holistic approaches for the treatment of CKD and T2D recommended by ADA and KDIGO, respectively[1–3]

1. KDIGO Diabetes Work Group. *Kidney Int* 2022;102:S1–S127; 2. Kidney Disease: Improving Global Outcome (KDIGO): *Kidney Int* 2024;105;S117–S314;
3. American Diabetes Association. *Diabetes Care* 2024;47(Suppl 1):S179; 4. de Boer IH, *et al. Diabetes Care* 2022;45:3075–3090; 5. Sarafidis PA, *et al. Clin Kidney J* 2023;16:1885–1907;
6. Mancia G, *et al. J Hypertens* 2023;41:1874–2071; 7. Marx N, *et al. Eur Heart J* 2023;44:4043–4140; 8. Blazek O & Bakris GL. *Am Heart J Plus* 202 2;19:100187

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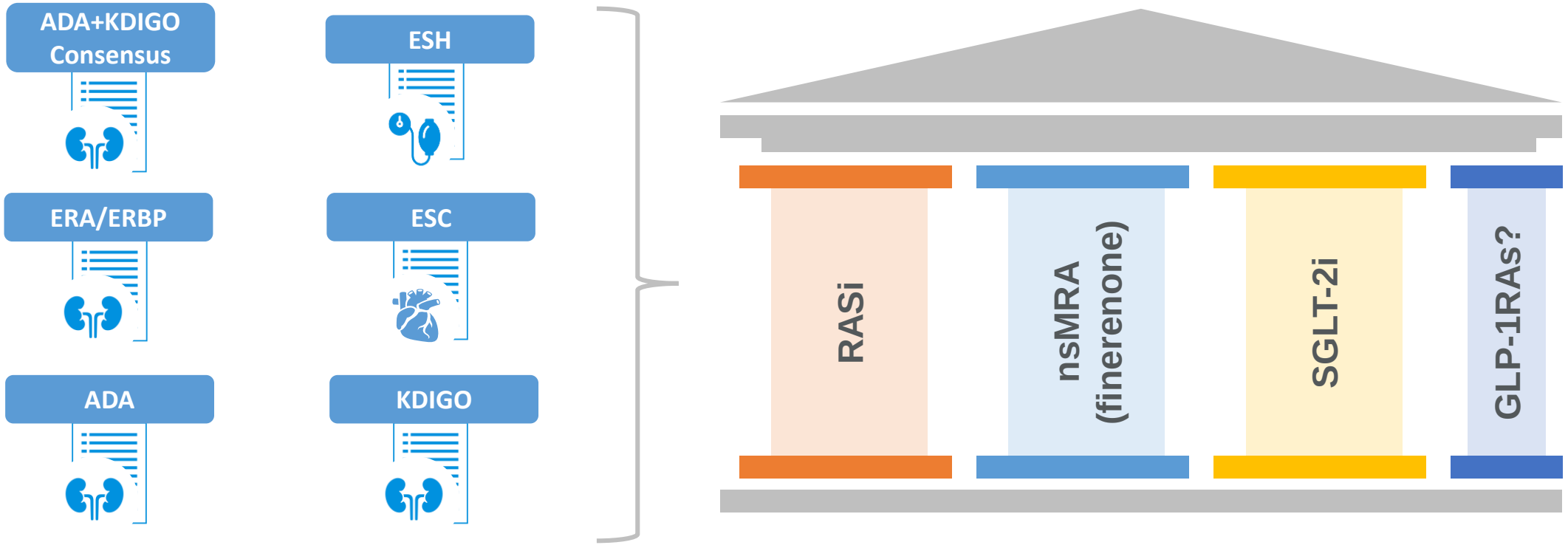

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Questions