Iran Endocrine Society | Research Insititute for Endocrine Sciences | Shahid Beheshti University of Medical Sciences | Iran University of Medical Sciences | Institute of Endocrinology and Metabolism

THE 14th INTERNATIONAL CONGRESS OF
ENDOCRINE DISORDERS
22nd - 24th November 2023

Diabetic kidney disease and Cardiovascular outcomes

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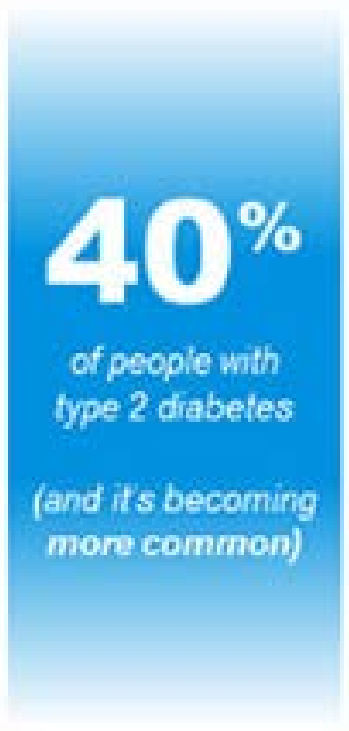
Iran University of Medical Sciences

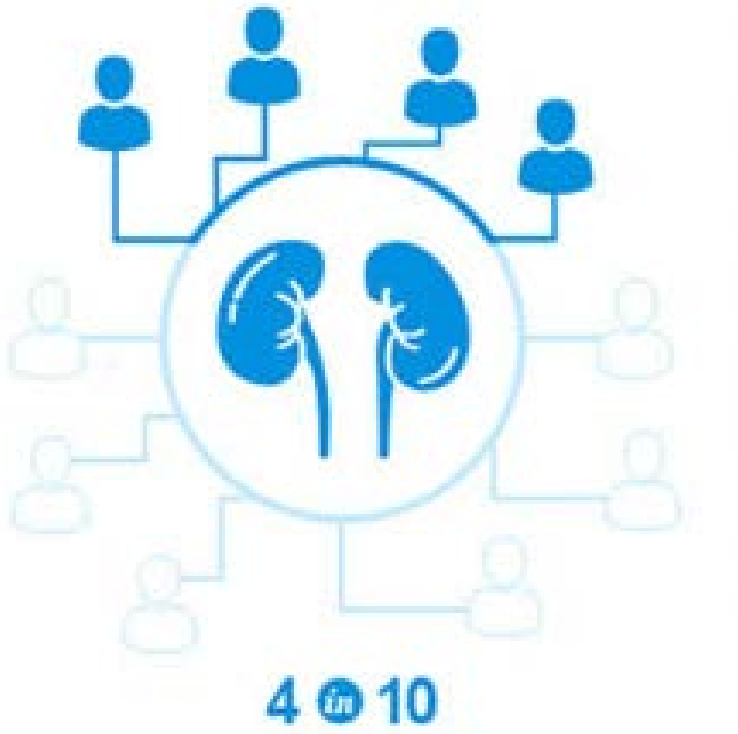
Agenda

- Introduction
  - Epidemiology and phenotypes of DKD
  - DKD phenotypes and cardiovascular risk
- The pillar approach with therapeutic target
  - RAS blockers
  - SGLT2 Inhibitors
  - GLP-1RAs
  - Non-steroidal mineralocorticoid receptor antagonists
- Summary

Diabetic kidney disease (DKD)

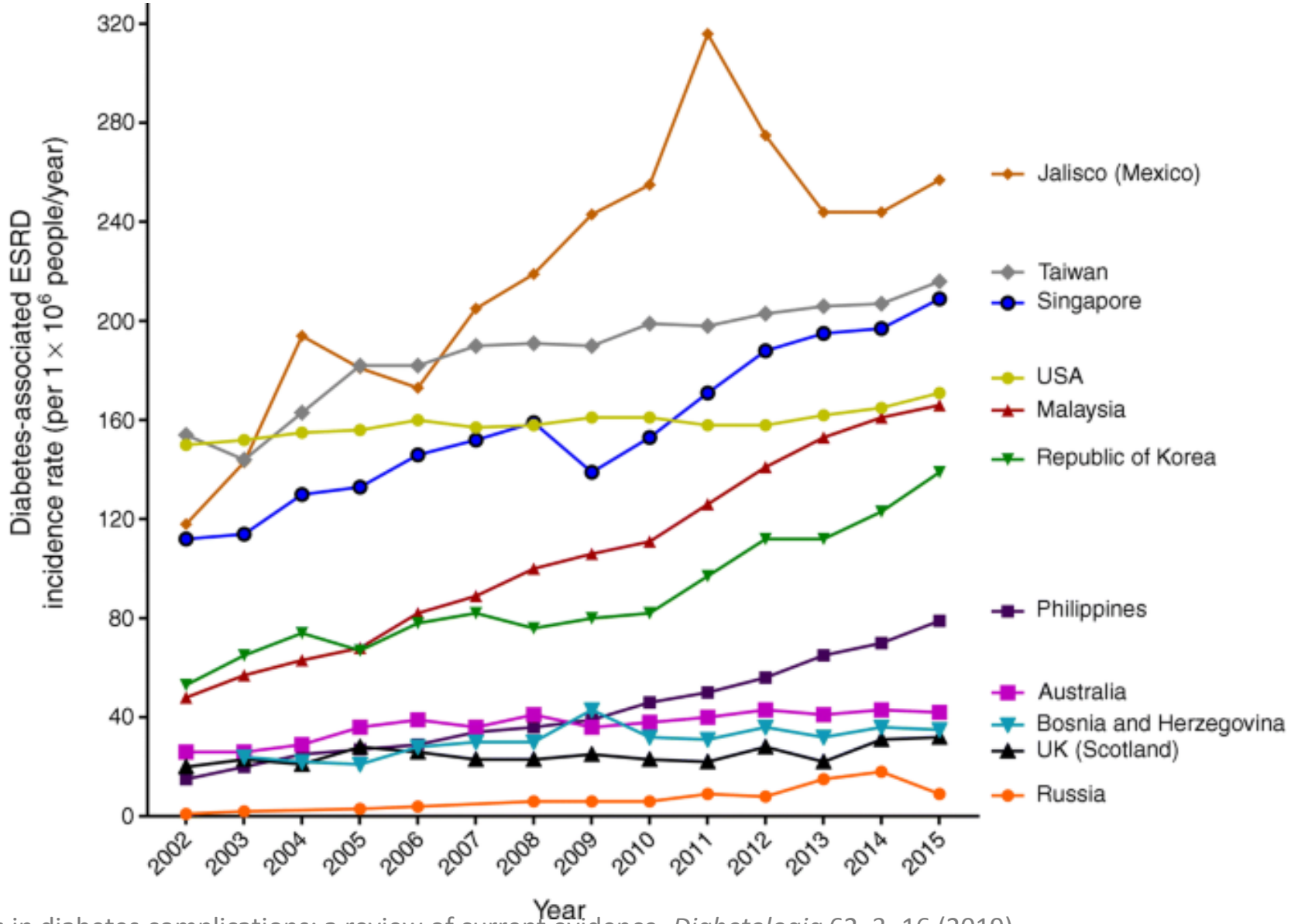
- **A common microvascular complication in DM**
- **The main cause of CKD and ESRD**
- **A major cause of mortality and morbidity**





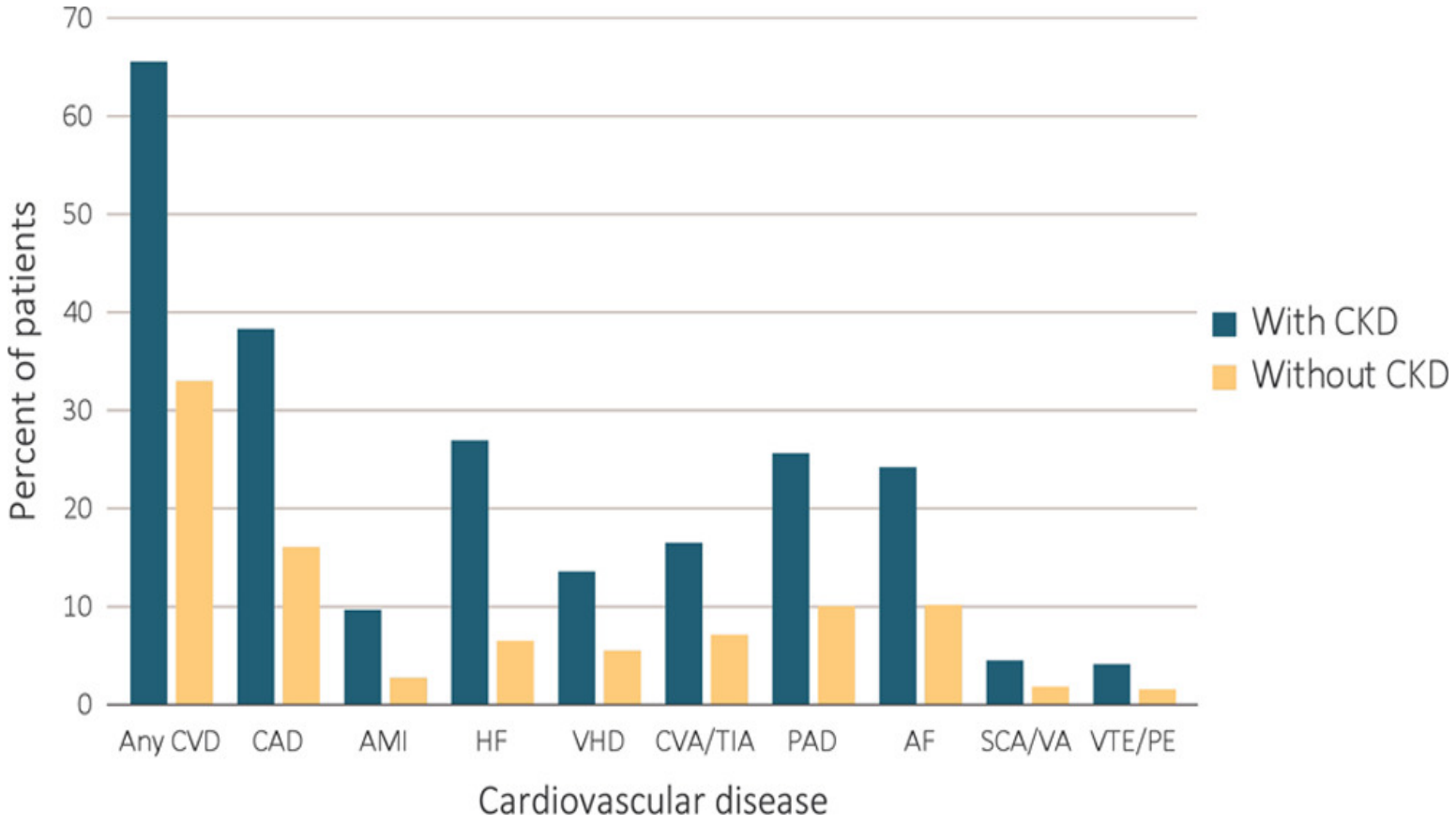
Postgraduate Medicine, 134:4, 376-387, DOI: 10.1080/00325481.2021.2009726

Global trends in DKD



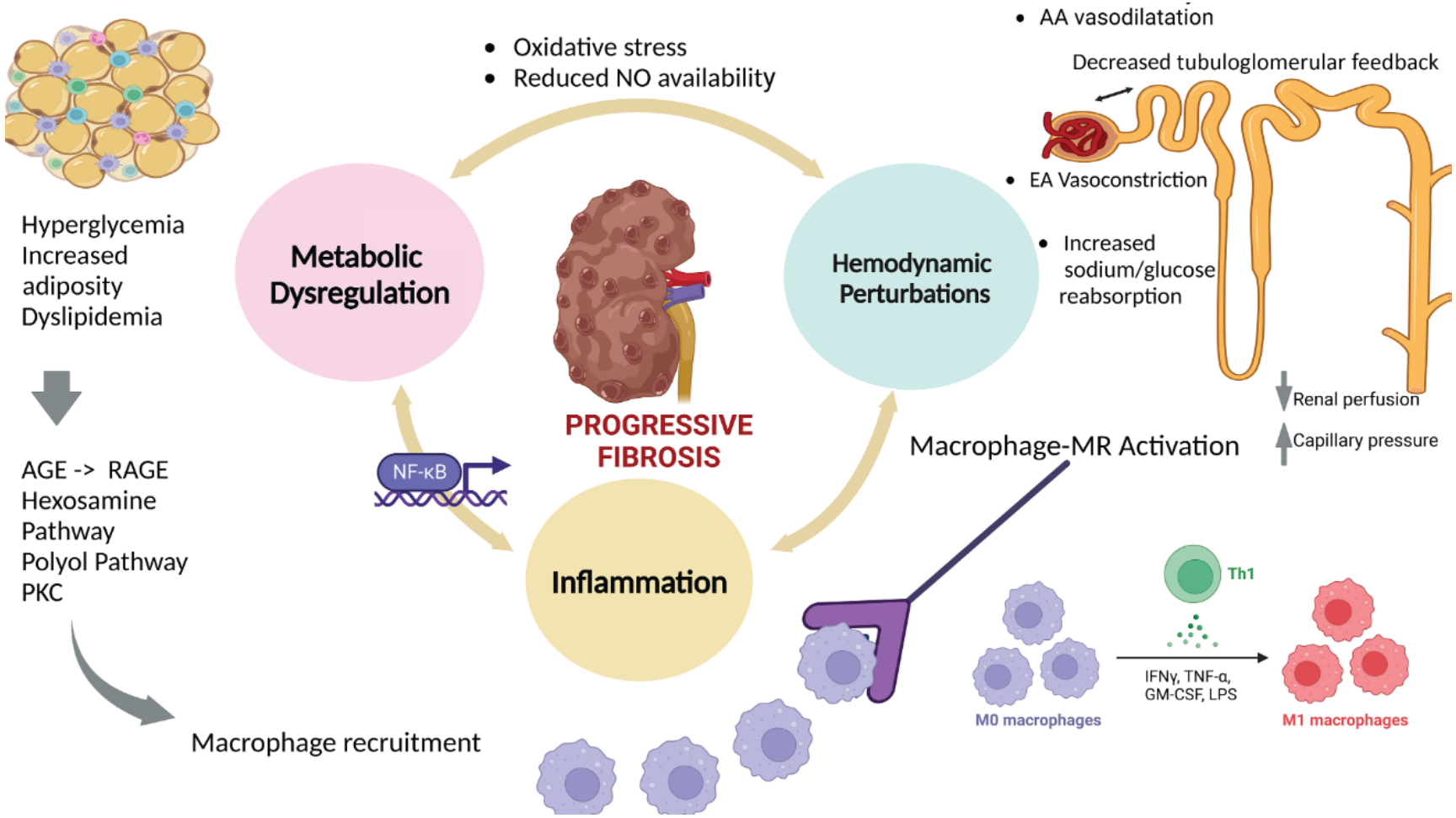
Harding, J.L. Global trends in diabetes complications: a review of current evidence. *Diabetologia* 62, 3–16 (2019).

CVD is More Prevalent in The Presence of CKD



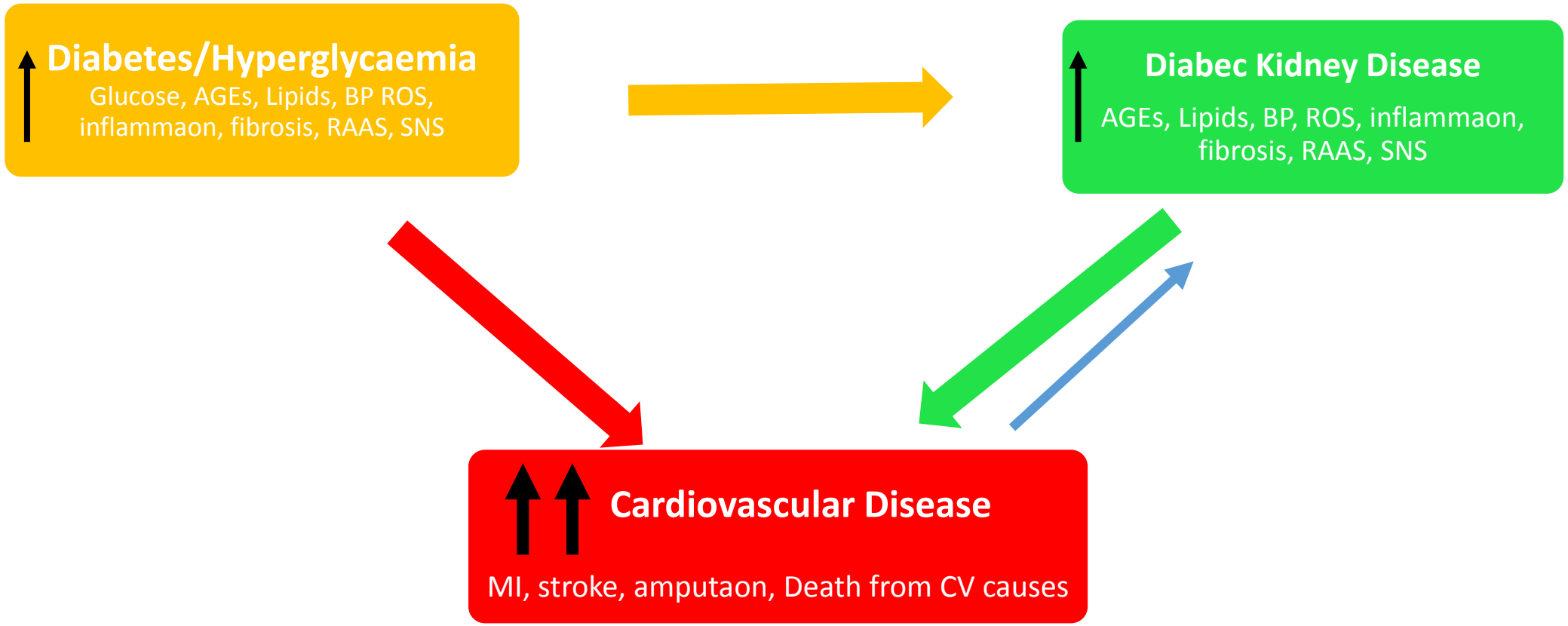
Salim S. Virani. Circulation. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association, 141, 9, e139-e596,

Metabolic, hemodynamic, and inflammatory pathways implicated in the underlying pathophysiology of DKD



Diabetes Care 2023;46(9):1574–1586 | https://doi.org/10.2337/dci23-0030

DM and concomitant DKD accelerate CVD



Cardiovascular Disease and Diabetic Kidney Diseasehttps://doi.org/10.1016/j.semnephrol.2018.02.003

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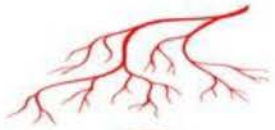
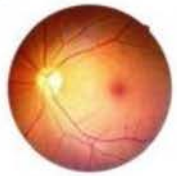
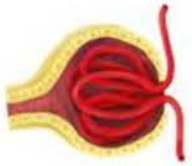
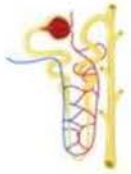
DKD presents more heterogeneously

Albuminuric DKD

Non-Albuminuric DKD

30% of participants ≥40 years

DKD is clinically heterogeneous

Albuminuric DKD		Non-albuminuric DKD
UACR > 30 mg/g	 	eGFR < 60 ml/min/1.73m^2 and UACR < 30 mg/g
Microangiopathy	 	Macroangiopathy
Correlation with retinopathy	 	No correlation with retinopathy
Glomerulosclerosis	 	Tubular and vascolar damage
Male sex	 	Female sex
Correlation with Hb1Ac	 	No correlation with Hb1Ac

Shi S, Ni L, Comparison of Nonalbuminuric and Albuminuric Diabetic Kidney :A Systematic Review and Meta-Analysis. *Front. Endocrinol.* .2022.

DKD phenotypes and CV risk / CV death

J Am Soc Nephrol. 2009 Aug; 20(8): 1813–1821.
doi: 10.1681/ASN.2008121270
PMCID: PMC2723977
PMID: 19443635

J Am Soc Nephrol

Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

Toshiharu Ninomiya,[*] Vlado Perkovic,[✉*] Bastiaan E. de Galan,[*†] Sophia Zoungas,[*] Avinesh Pillai,[*] Meg Jardine,[*] Anushka Patel,[*] Alan Cass,[*] Bruce Neal,[*] Neil Poulter,[‡] Carl-Erik Mogensen,[§] Mark Cooper,[‖] Michel Marre,[¶] Bryan Williams,[**] Pavel Hamet,[††] Giuseppe Mancia,[‡‡] Mark Woodward,[*§§] Stephen MacMahon,[*] and John Chalmers[*],
on behalf of the ADVANCE Collaborative Group

› Diabetologia. 2011 Jan;54(1):32-43. doi: 10.1007/s00125-010-1854-1. Epub 2010 Jul 30.

Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

P L Drury [1], R Ting, D Zannino, C Ehnholm, J Flack, M Whiting, R Fassett, J-C Ansquer, P Dixon, T M E Davis, C Pardy, P Colman, A Keech

CV risk on the basis of the presence or absence of albuminuria

10,640 patients with T2DM

Mean follow-up: 4.3 years

ADVANCE Post-Hoc Analysis (Ninomiya et al., 2009) [38] *

Cardiovascular events

	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminuria	1.00 (reference)	0.98 (0.78–1.22)	1.33 (1.02–1.75)
Microalbuminuria	1.48 (1.09–2.01)	1.54 (1.20–1.98)	2.04 (1.54–2.69)
Macroalbuminuria	1.18 (0.52–2.69)	1.67 (1.09–2.57)	3.23 (2.20–4.73)

9795 patients with T2DM

FIELD posthoc Analysis (Drury et al., 2011) [43] #

Cardiovascular events

	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminura	1.00 (reference)	1.11 (0.95–1.29)	1.63 (1.20–2.20)
Microalbuminuria	1.25 (1.01–1.54)	1.43 (1.18–1.72)	1.94 (1.37–2.73)
Macroalbuminuria	1.19 (0.76–1.85)	1.77 (1.33–2.36)	2.30 (1.48–3.55)

CV risk on the basis of the presence or absence of albuminuria

Non-Albuminuric DKD

ADVANCE Post-Hoc Analysis (Ninomiya et al., 2009) [38] *

Cardiovascular events

	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminuria	1.00 (reference)	0.98 (0.78–1.22)	1.33 (1.02–1.75)
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CV risk on the basis of the presence or absence of albuminuria

Albuminuric DKD

ADVANCE Post-Hoc Analysis (Ninomiya et al., 2009) [38] *			
Cardiovascular events			
	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminuria	1.00 (reference)	0.98 (0.78–1.22)	1.33 (1.02–1.75)
Microalbuminuria	1.48 (1.09–2.01)	1.54 (1.20–1.98)	2.04 (1.54–2.69)
Macroalbuminuria	1.18 (0.52–2.69)	1.67 (1.09–2.57)	3.23 (2.20–4.73)

Albuminuric DKD

FIELD posthoc Analysis (Drury et al., 2011) [43] #			
Cardiovascular events			
	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminura	1.00 (reference)	1.11 (0.95–1.29)	1.63 (1.20–2.20)
Microalbuminuria	1.25 (1.01–1.54)	1.43 (1.18–1.72)	1.94 (1.37–2.73)
Macroalbuminuria	1.19 (0.76–1.85)	1.77 (1.33–2.36)	2.30 (1.48–3.55)

CV death on the basis of the presence or absence of albuminuria

ADVANCE Post-Hoc Analysis (Ninomiya et al., 2009) [38] *

Cardiovascular death

	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminura	1.00 (reference)	1.22 (0.81–1.84)	1.85 (1.17–2.92)
Microalbuminuria	1.96 (1.16–3.32)	2.52 (1.65–3.84)	3.37 (2.15–5.30)
Macroalbuminuria	2.87 (1.01–8.18)	3.61 (2.02–6.43)	5.93 (3.45–10.20)

FIELD posthoc Analysis (Drury et al., 2011) [43] #

Cardiovascular death

	eGFR ≥ 90	*eGFR 60–89*	*eGFR < 60*
Normoalbuminura	1.00 (reference)	1.17 (0.80–1.72)	2.36 (1.29–4.31)
Microalbuminuria	1.73 (1.08–2.77)	1.38 (0.88–2.15)	2.96 (1.59–5.51)
Macroalbuminuria	1.89 (0.83–4.27)	2.59 (1.49–4.50)	5.26 (2.73–10.15)

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Summaries of landmark trials with the RAAS blockade

Trial	Publication Year	Treatment(s)	Primary Composite Kidney Outcome	Risk Reduction
CSG Captopril [11]	1993	Captopril vs. placebo	Doubling of the base-line serum creatinine concentration	48%
RENAAL [12]	2001	Losartan vs. placebo	Doubling of serum creatinine, ESKD or death	16%
IDNT [13]	2001	Irbesartan vs. amlodipine vs. placebo	Doubling of serum creatinine, ESKD or death	20% vs. placebo 23% vs. amlodipine

Therapeutic Advances in Diabetic Nephropathy,January 2022Journal of Clinical Medicine 11(2):378Follow journal,DOI: 10.3390/jcm11020378

Either an ACE inhibitor or an angiotensin receptor blocker

- **11.4a** In nonpregnant people with diabetes and hypertension
- recommended for those with urinary Alb/Cr: 30–299 mg/g creatinine. **B**
- strongly recommended for those with urinary Alb/Cr ≥300 mg/g creatinine and/or eGFR<60. **A**

- **11.4c** not recommended for the primary prevention of CKD in people with diabetes and normal BP, normal urinary Alb/Cr (<30 mg/g creatinine), and normal eGFR. **A**

Chronic Kidney Disease and Risk Management: ***Standards of Care in Diabetes—2023***

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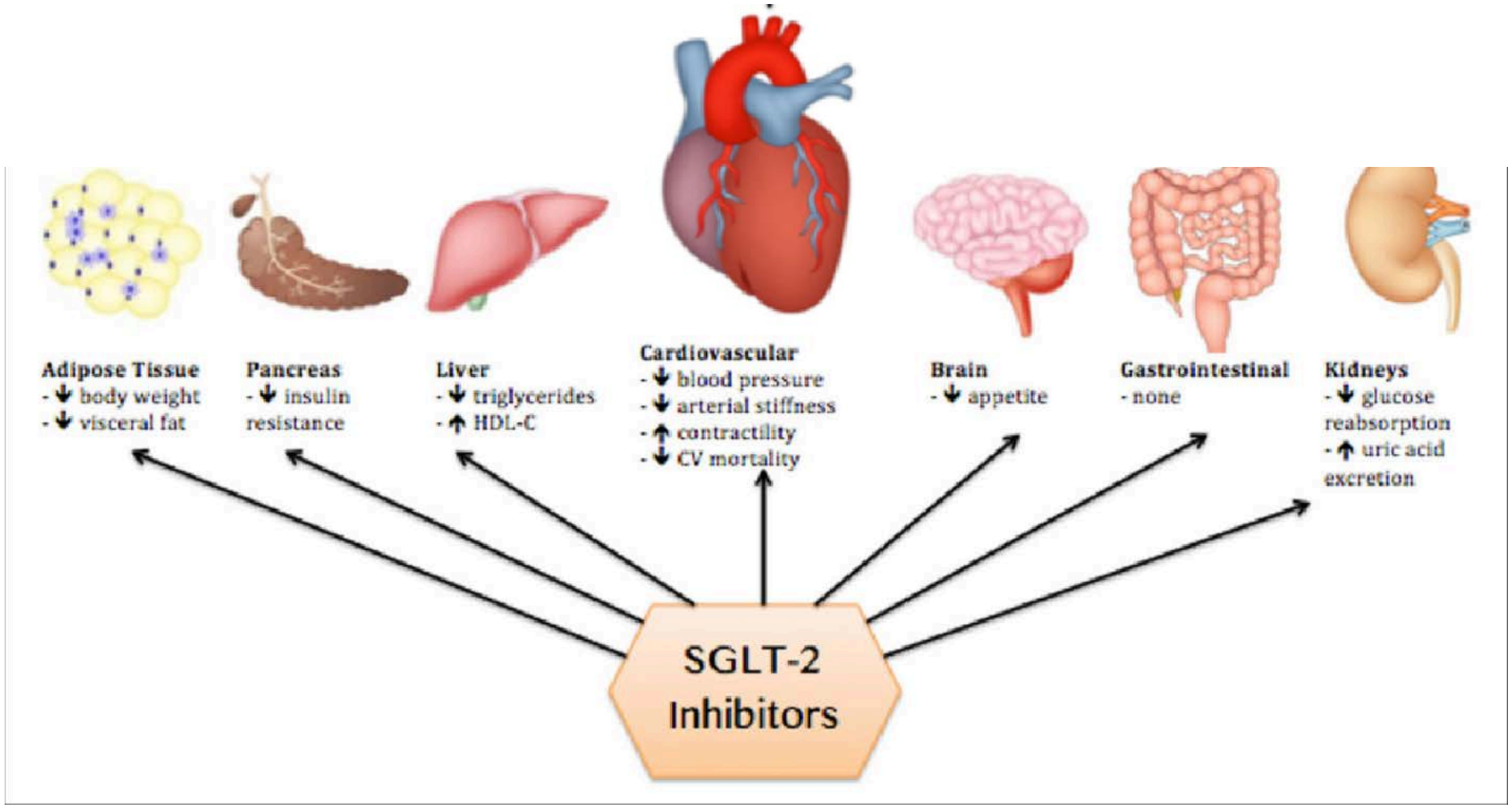
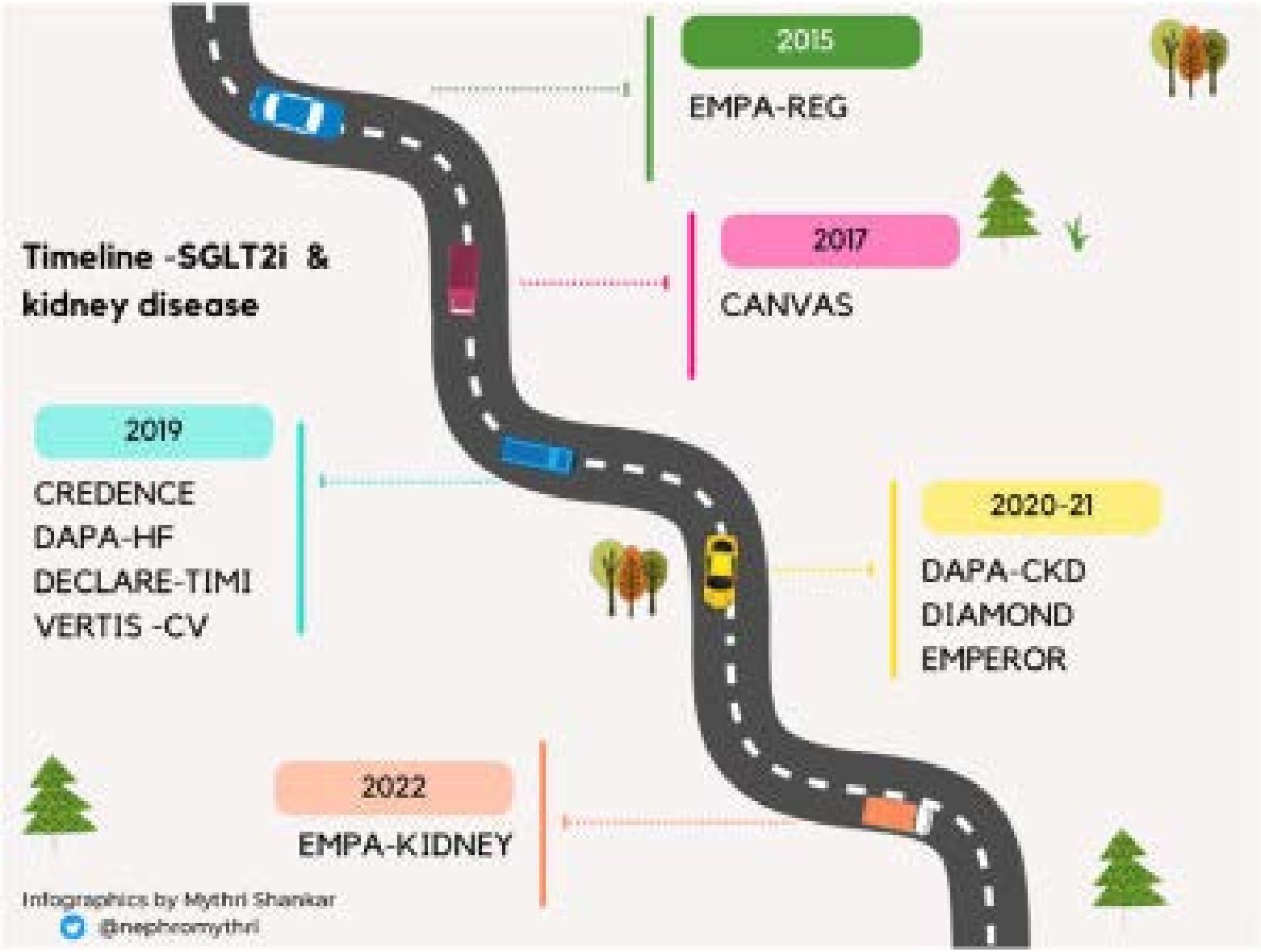
Pleiotropic effects of SGLT2 Inhibitors



Journal of Cardiovascular Pharmacology and Therapeutics. 2019

Timeline of trials involving SGLT2 inhibitors



Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10142	17160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

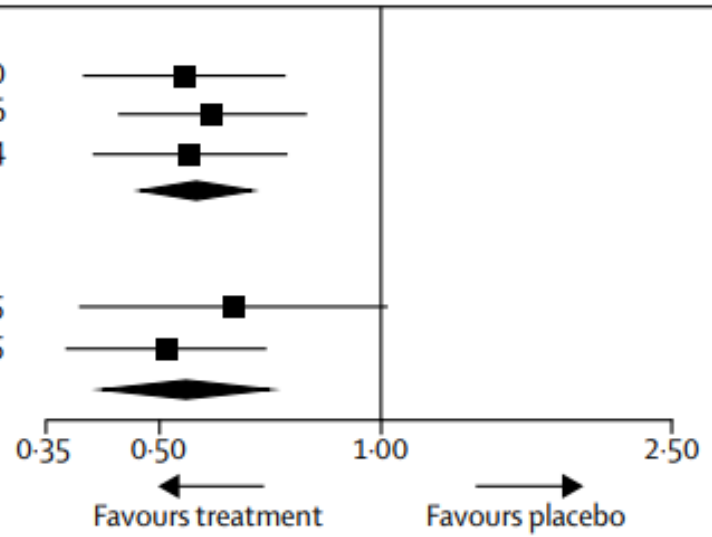
Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

Lancet,2019, https://doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death

The p value for subgroup differences: 0·71.

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645	2323	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756	2900	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474	3500	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108	5078	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**

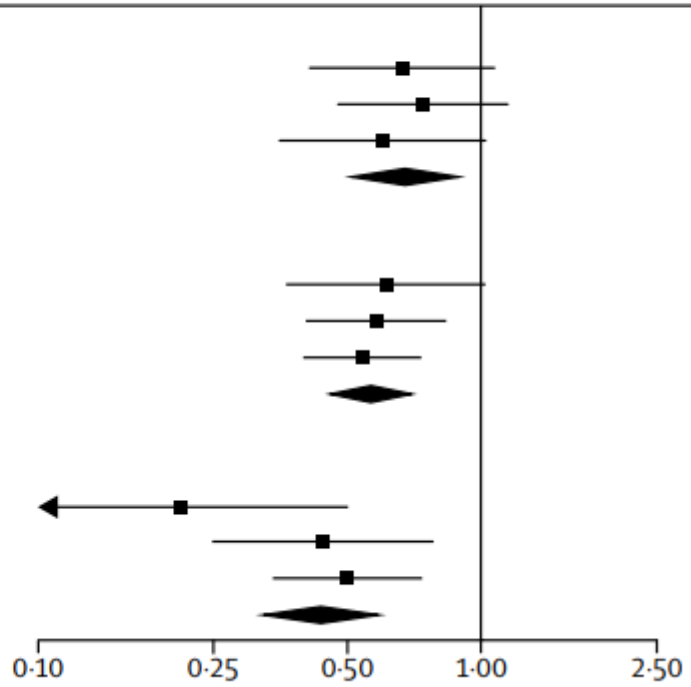


Lancet,2019, https://doi.org/10.1016/S0140-6736(18)32590-X

Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death

A

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196	605	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA	NA	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606	659	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406	1232	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA	NA	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838	3894	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043	486	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA	NA	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137	4025	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**



B

Lancet,2019, https://doi.org/10.1016/S0140-6736(18)32590-X

Landmark Trials of SGLT2 Inhibitors in CKD

	CREDENCE	DAPA-CKD	EMPA-KIDNEY
eGFR (mL/min/1.73 m^2)	30 to <90	25-75	20 to <45 or, 45 to <90 with albuminuria
Albuminuria (mg/g)	>300-5,000	200-5,000	Any level of albuminuria if eGFR 20 to <45 At least 200 if eGFR 45 to <90
Median (IQR) follow-up, y	2.62 (0.02-4.53)	2.4 (2.0-2.7)	2.0 (1.5-2.4)
Primary outcomes (HR, 95%CI)	0.70 (0.59-0.82) NNT:22	0.61 (0.51-0.72) NNT:19	0.72 (0.64-0.82) NNT:25
Key secondary outcomes (HR, 95%CI)			
Death from any cause	0.83 (0.68-1.02)	0.69 (0.53-0.88)	0.87 (0.70-1.08)
Hospitalization for heart failure or death from CV cause	0.69 (0.57-0.83)	0.71 (0.55-0.92)	0.84 (0.67-1.07)
Composite of decline in eGFR, ESKD, or death from renal cause	0.66 (0.53-0.81))	0.56 (0.45-0.68)	—

Kidney Medicine, 2023, DOI:https://doi.org/10.1016/j.xkme.2023.100608

Recommendation use of a SGLT2 Inhibitors in people with type 2 DM and DKD

- **11.5a** an eGFR ≥20 & urinary Alb/Cr ≥200. **A**

- **11.5b** an eGFR ≥20 & urinary Alb/Cr ranging from normal to 200. **B**

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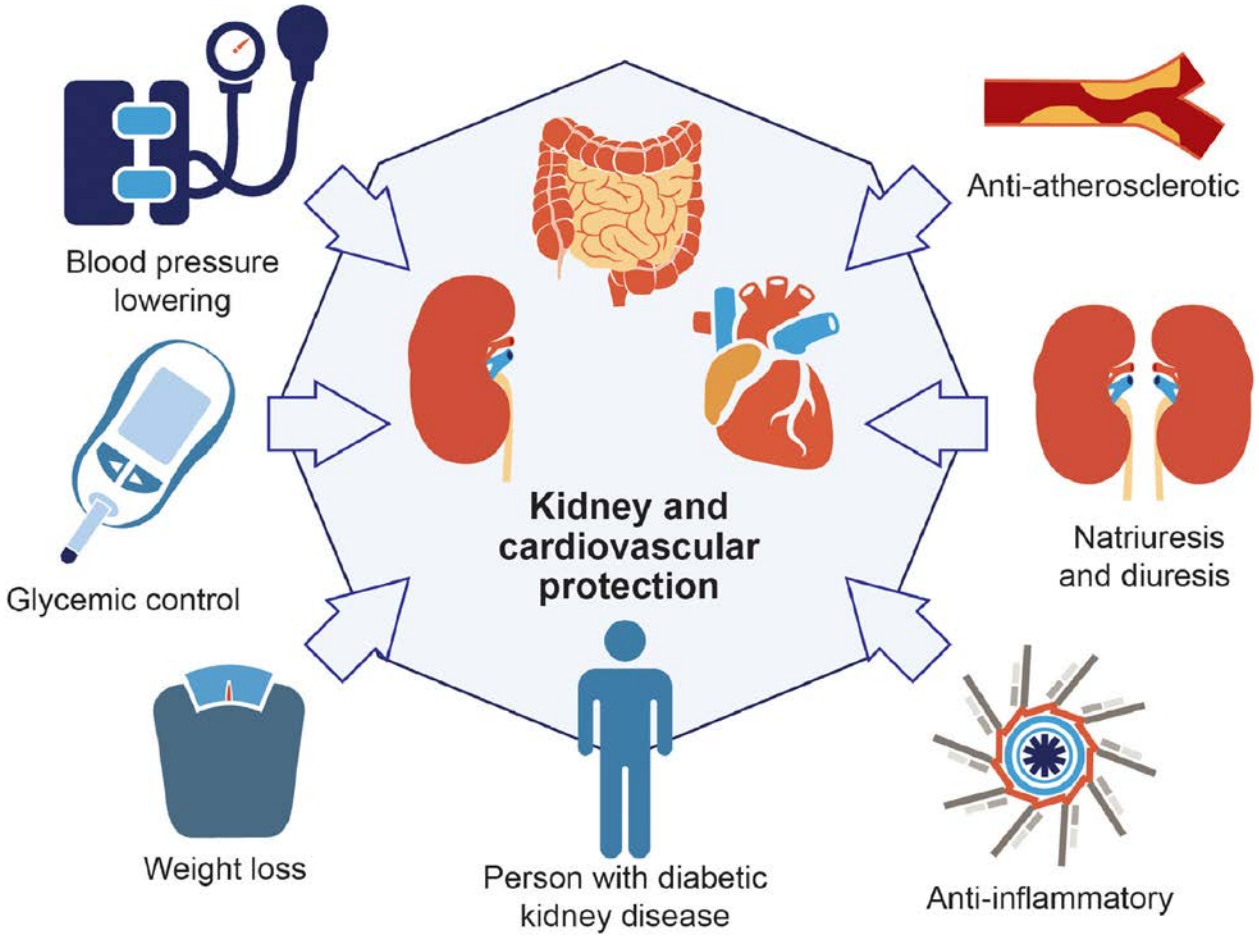
Potential mechanisms by which GLP1-RA confer kidney and cardiovascular protection



Michos, Erin D., et al. "Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: A review of their kidney and heart protection." *American Journal of Preventive Cardiology* (2023): 100502.

Renal endpoints in cardiovascular outcome trials of GLP-1 receptor agonists

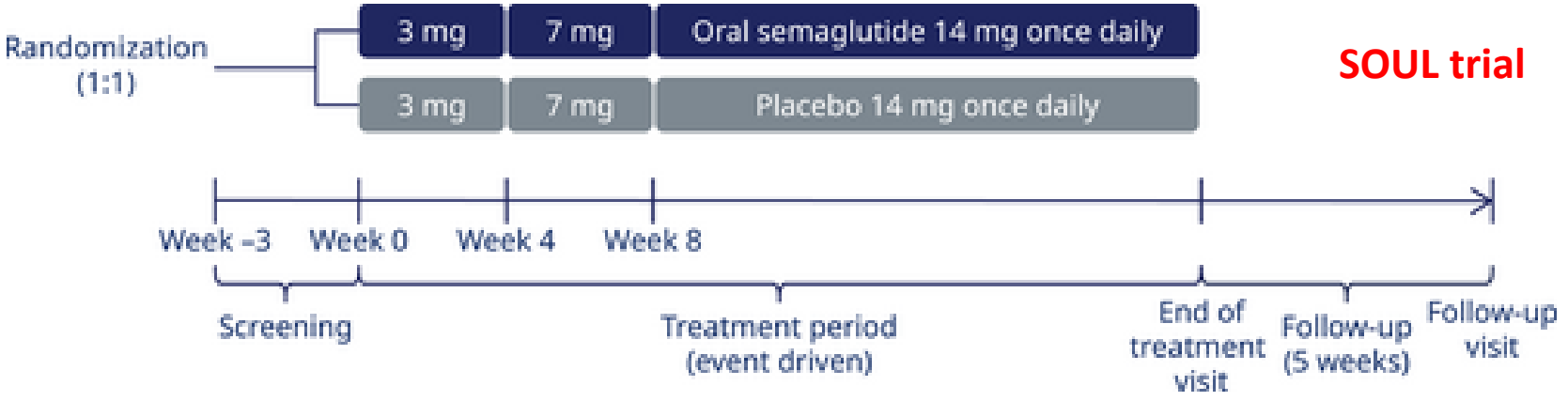
	LEADER [44]	SUSTAIN-6 [46]	REWIND [53]	AMPLITUDE-O [56]	ELIXA [42]	EXSCEL [48]
Drug	Liraglutide	Semaglutide	Dulaglutide	Efpeglenatide	Lixisenatide	Exenatide ER
Participants (n)	9,340	3,297	9,901	4,076	6,068	14,752
Median follow-up (yr)	3.8	2.1	5.4	1.8	2.1	3.2
Baseline HbA1c (%)	8.7	8.7	7.2	8.9	7.7	8
Baseline BP (mmHg)	136/77	136/77	137/78	135/77	130	135/78
Established CVD (%)	81	83.0	31	89.6	100	73.1
Baseline eGFR < 60 mL/min/1.73 m^2 (%)	23.1	24.1	22.2	31.6	23.2	21.6
Baseline eGFR, mL/min/1.73 m^2	80	80	75	72	78	77
Albuminuria (%)	11.0	NA	34.5	48.5	25.3	22.0
ACEI or ARB (%)	82.8	83.5	81.5	80.0	85.0	79.9
Renal composite outcomes[b]	0.78 (0.67–0.92)	0.64 (0.46–0.88)	0.85 (0.77–0.93)	0.68 (0.57–0.79)	0.84 (0.68–1.02)	0.88 (0.76–1.01)
New-onset persistent macroalbuminuria[b]	0.74 (0.60–0.91)	0.54 (0.37–0.77)	0.77 (0.68–0.87)	0.68 (0.58–0.80)	0.81 (0.66–0.99)	0.87(0.70–1.07)
Persistent doubling of serum creatinine[b]	0.89 (0.67–1.19)	1.28 (0.64–2.58)	NA	NA	1.16 (0.74–1.83)	NA
End-stage renal disease[b]	0.87 (0.61–1.24)	0.91 (0.40–2.07)	0.75 (0.39–1.44)	NA	NA	NA
Death due to renal disease[b]	1.59 (0.52–4.87)	NA	NA	NA	NA	NA

Yu, Ji Hee, et al. "GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions." *Kidney Research and Clinical Practice* 41.2 (2022): 136.

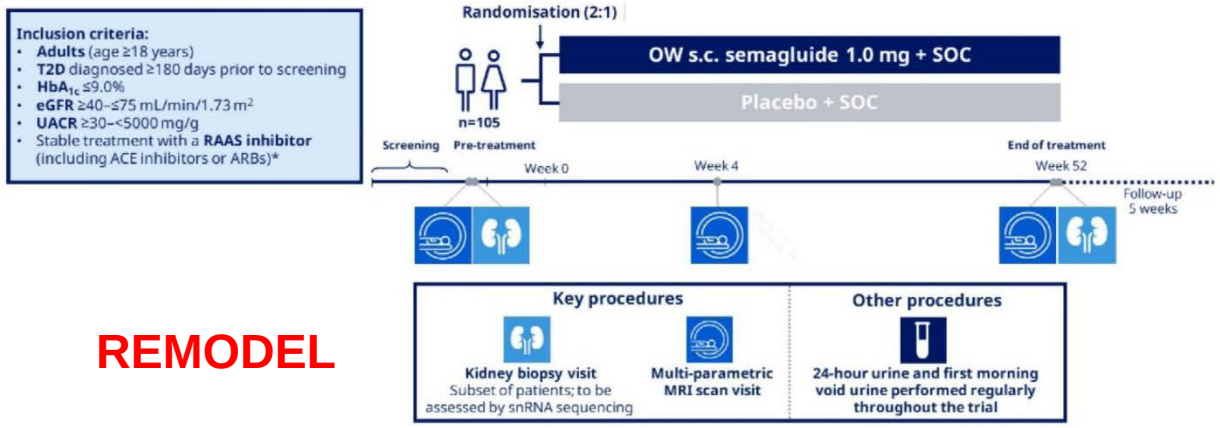
Renal endpoints in cardiovascular outcome trials of GLP-1 receptor agonists

	NNT:67	NNT:43	NNT:40	NNT:19		
	LEADER [44]	SUSTAIN-6 [46]	REWIND [53]	AMPLITUDE-O [56]	ELIXA [42]	EXSCEL [48]
Drug	Liraglutide	Semaglutide	Dulaglutide	Efpeglenatide	Lixisenatide	Exenatide ER
Participants (n)	9,340	3,297	9,901	4,076	6,068	14,752
Median follow-up (yr)	3.8	2.1	5.4	1.8	2.1	3.2
Baseline HbA1c (%)	8.7	8.7	7.2	8.9	7.7	8
Baseline BP (mmHg)	136/77	136/77	137/78	135/77	130	135/78
Established CVD (%)	81	83.0	31	89.6	100	73.1
Baseline eGFR < 60 mL/min/1.73 m^2 (%)	23.1	24.1	22.2	31.6	23.2	21.6
Baseline eGFR, mL/min/1.73 m^2	80	80	75	72	78	77
Albuminuria (%)	11.0	NA	34.5	48.5	25.3	22.0
ACEI or ARB (%)	82.8	83.5	81.5	80.0	85.0	79.9
Renal composite outcomes[b]	0.78 (0.67–0.92)	0.64 (0.46–0.88)	0.85 (0.77–0.93)	0.68 (0.57–0.79)	0.84 (0.68–1.02)	0.88 (0.76–1.01)
New-onset persistent macroalbuminuria[b]	0.74 (0.60–0.91)	0.54 (0.37–0.77)	0.77 (0.68–0.87)	0.68 (0.58–0.80)	0.81 (0.66–0.99)	0.87(0.70–1.07)
Persistent doubling of serum creatinine[b]	0.89 (0.67–1.19)	1.28 (0.64–2.58)	NA	NA	1.16 (0.74–1.83)	NA
End-stage renal disease[b]	0.87 (0.61–1.24)	0.91 (0.40–2.07)	0.75 (0.39–1.44)	NA	NA	NA
Death due to renal disease[b]	1.59 (0.52–4.87)	NA	NA	NA	NA	NA

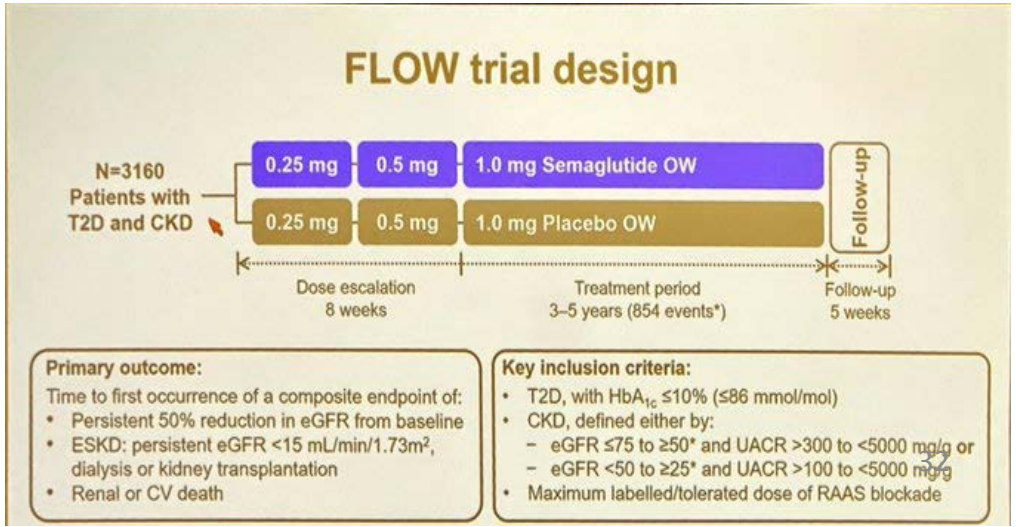
Future directions Renal outcome trials of GLP-1 receptor agonists in DKD



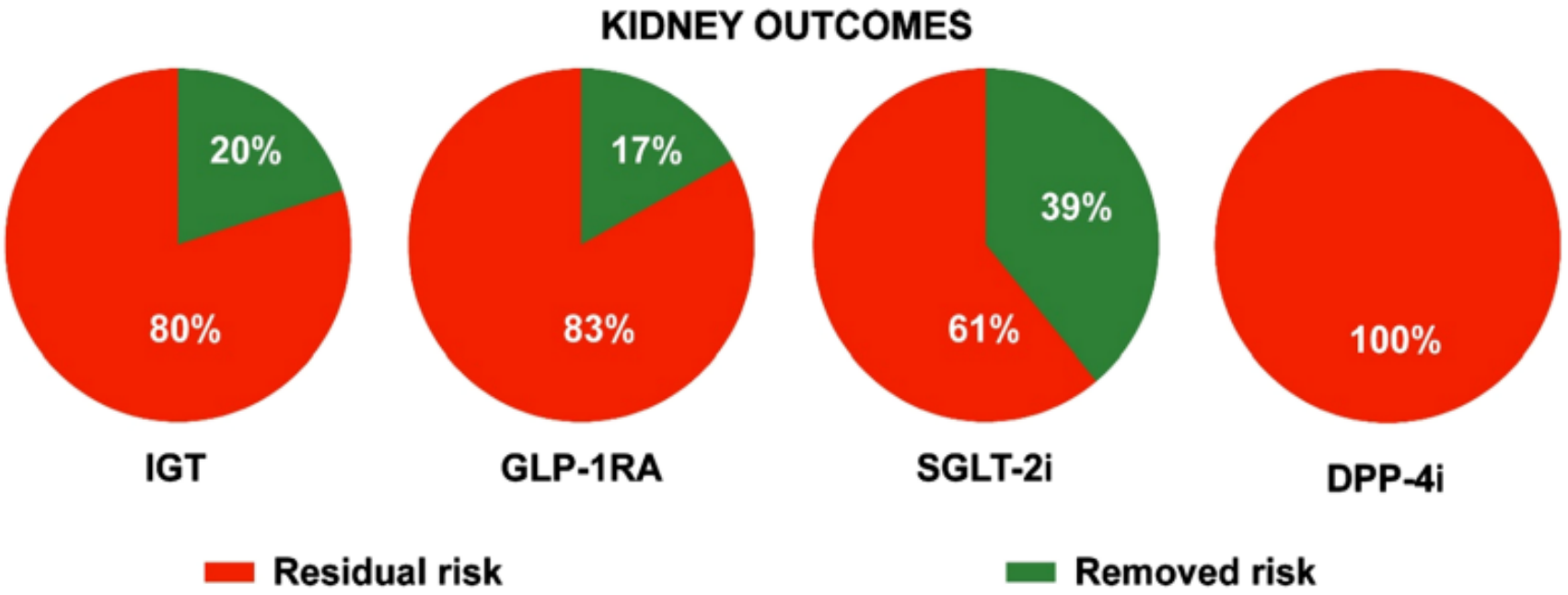
SOUL trial



REMODEL



Residual Risk for Kidney Outcomes

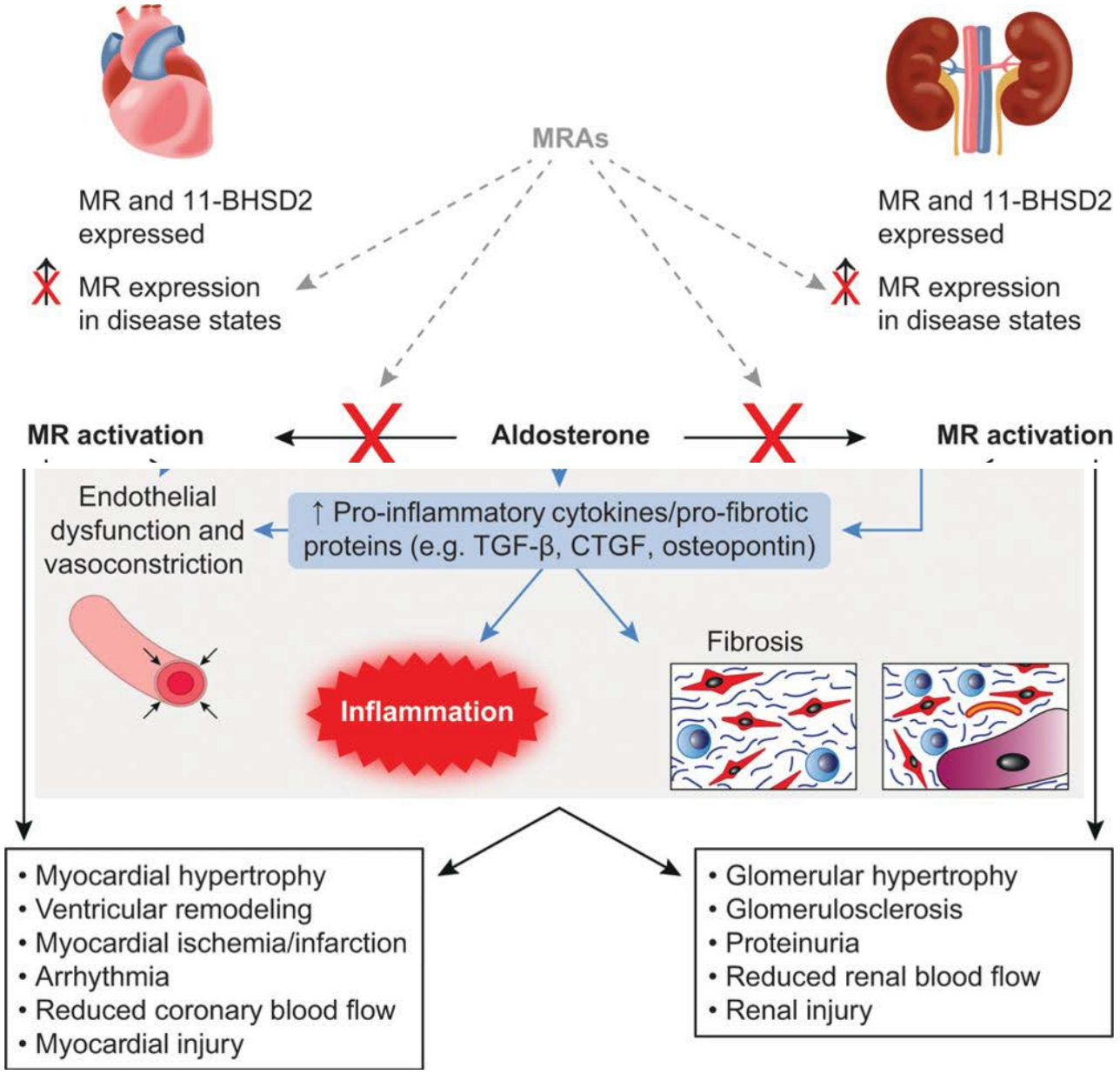


Cardiovasc Diabetol (2021) 20:36

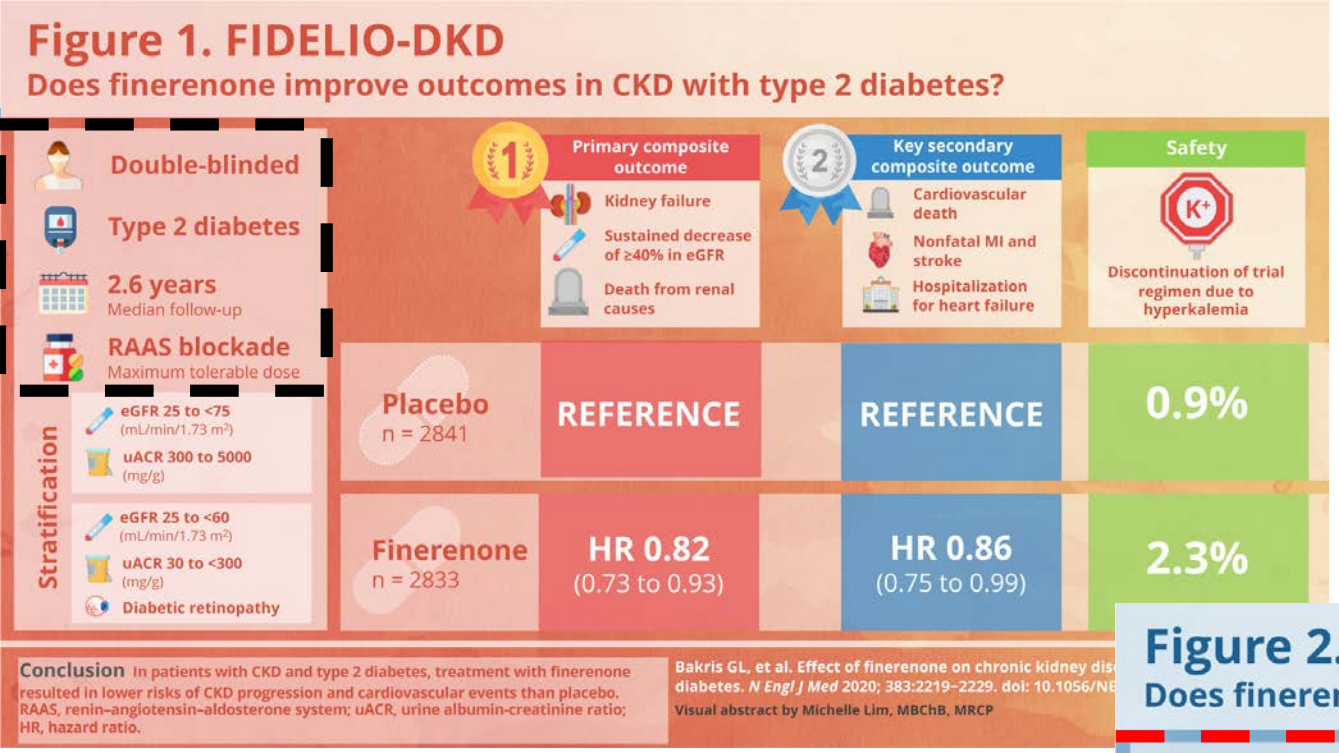
Agenda

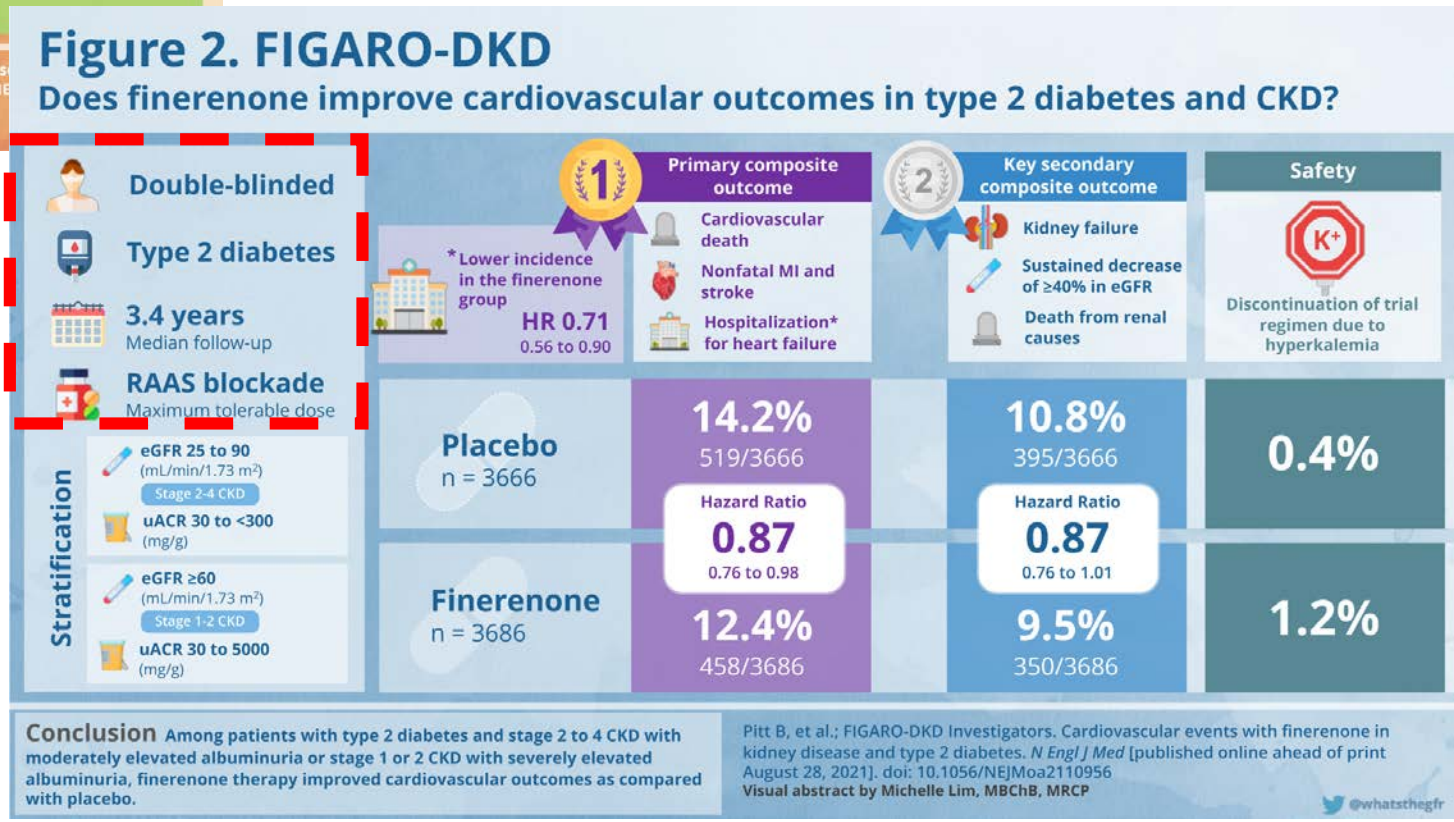
- **Introduction**
  - Epidemiology and phenotypes of DKD
  - DKD phenotypes and cardiovascular risk
- The pillar approach with therapeutic target
  - RAS blockers
  - SGLT2 Inhibitors
  - GLP-1RAs
  - **Non-steroidal mineralocorticoid receptor antagonists**
- Summary

The direct deleterious effects of aldosterone/MR activation in the heart and kidneys



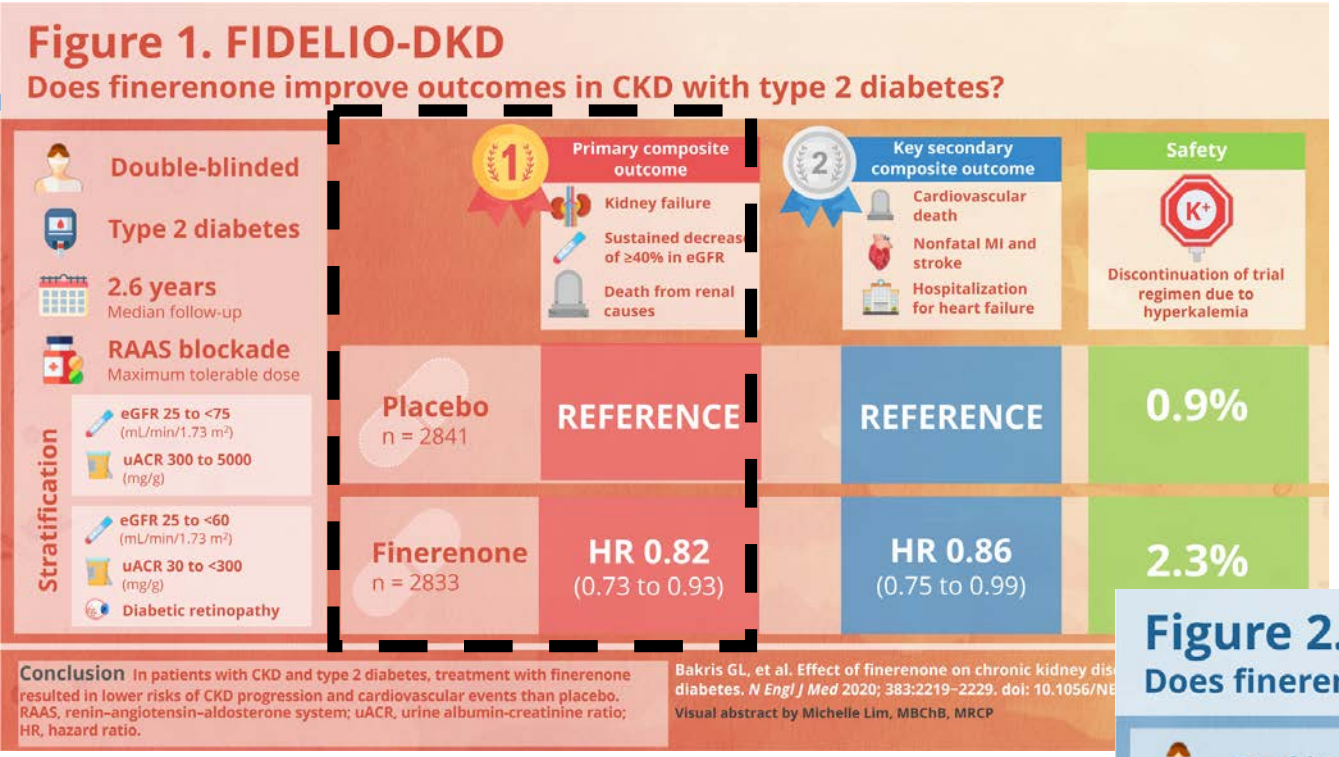
Mineralocorticoid Receptor Activation and Mineralocorticoid Receptor Antagonist Treatment in Cardiac and Renal Diseases. Hypertension. 2015;65(2):257-63.

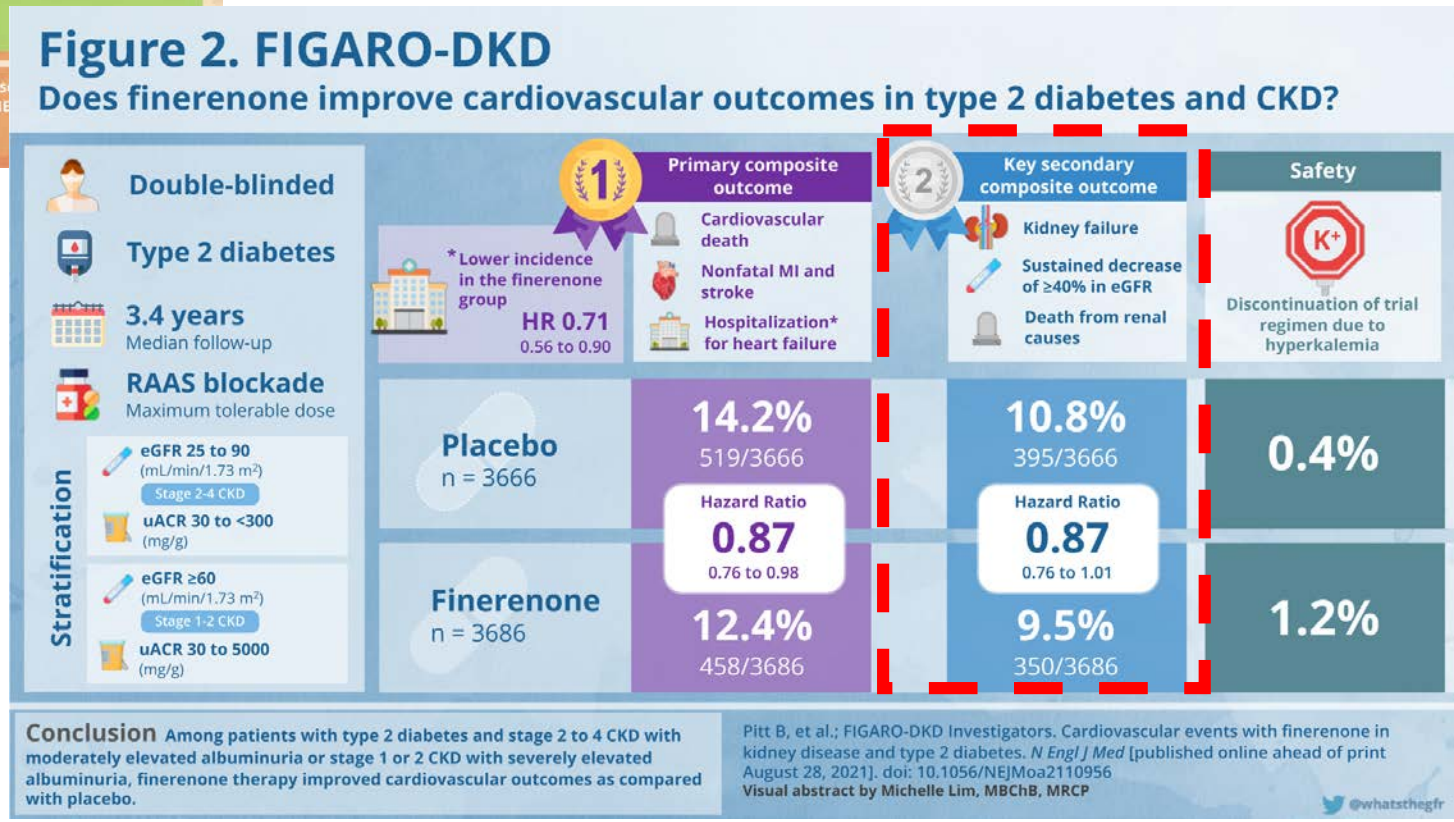




https://doi.org/10.1161/CIRCULATIONAHA.120.051898Circulation. 2021;143:540–552

https://doi.org/10.1161/CIRCULATIONAHA.121.057983Circulation. 2022;145:437–44





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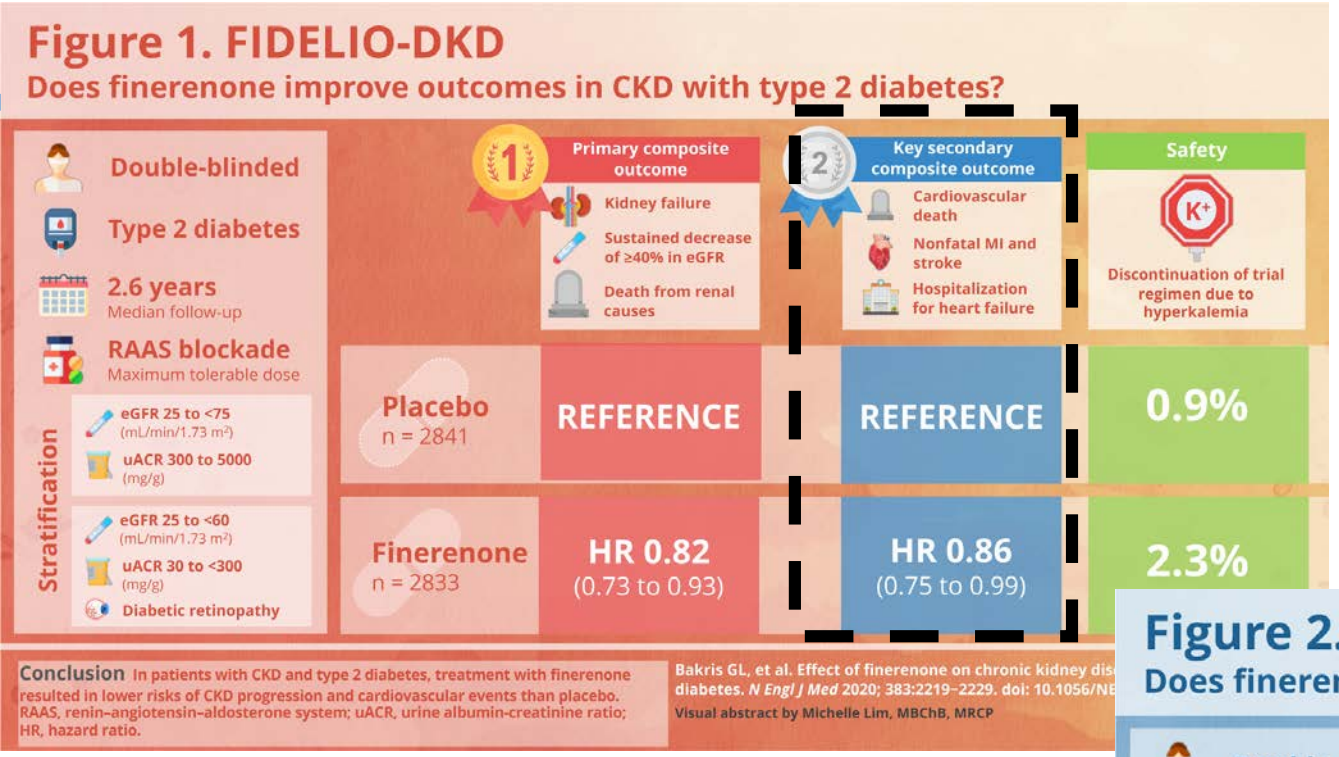

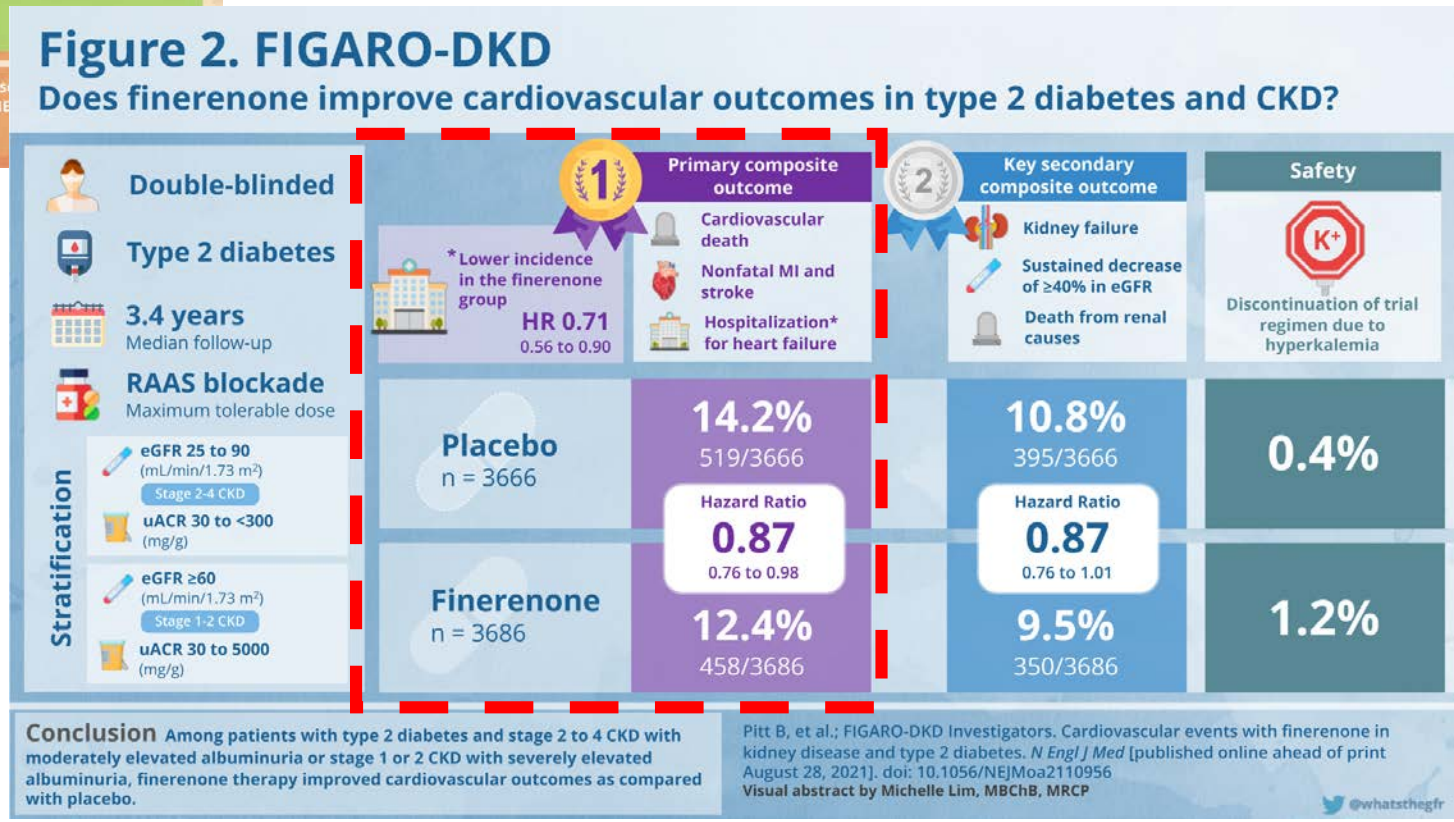

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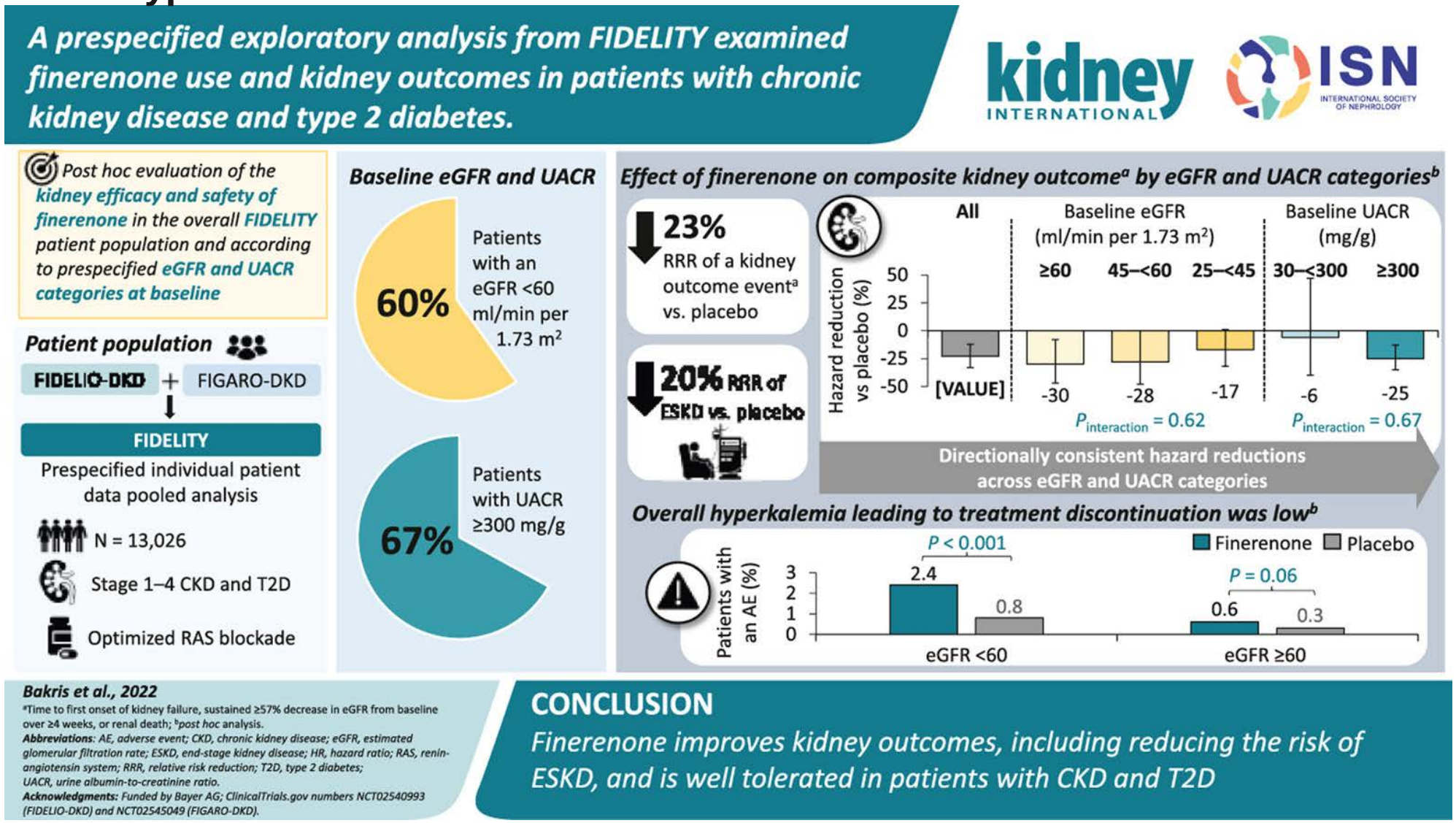
https://doi.org/10.1161/CIRCULATIONAHA.121.057983Circulation. 2022;145:437–44

FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes



Bakris et al., 2022

[a]Time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death; [b]*post hoc* analysis.

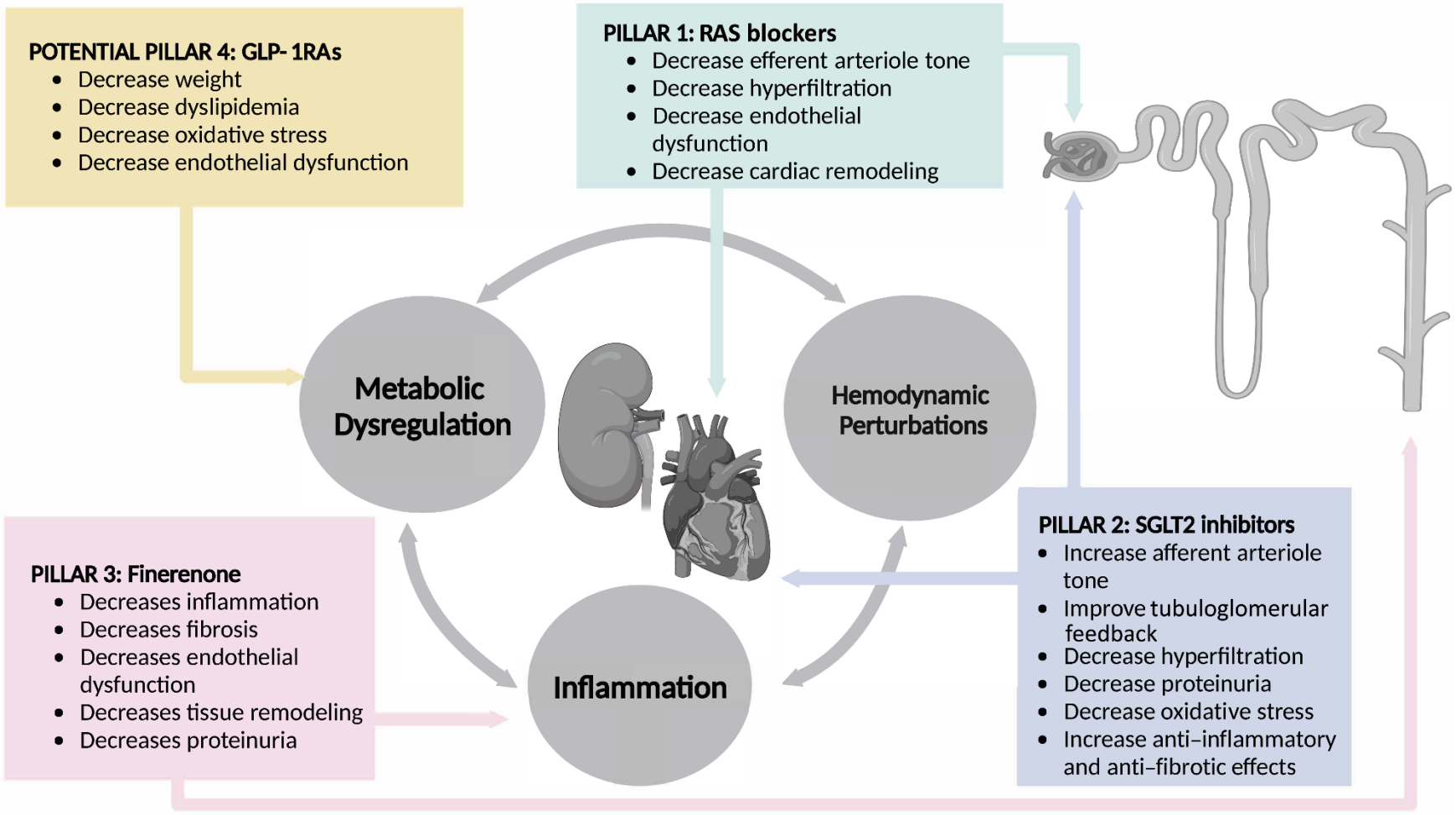
Abbreviations: *AE, adverse event; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; RAS, renin-angiotensin system; RRR, relative risk reduction; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.*

Acknowledgments: *Funded by Bayer AG; ClinicalTrials.gov numbers NCT02540993 (FIDELIO-DKD) and NCT02545049 (FIGARO-DKD).*

CONCLUSION

Finerenone improves kidney outcomes, including reducing the risk of ESKD, and is well tolerated in patients with CKD and T2D

A pillared approach with targeted therapies



Diabetic Nephropathy: Update on Pillars of Therapy Slowing Progression. *Diabetes Care* 1 September 2023;. https://doi.org/10.2337/dci23-0030

Holistic approach for improving outcomes in patients with diabetes and CKD

Life style

Physical activity

Healthy diet

Smoking cessation

Weight management

Regular risk factor reassessment (3-6 months)

T2D

T2D+T1D

First-line drug therapy

SGLT2i (Initiate eGFR ≥20; continue until dialysis or transplant)

Metformin (If eGFR ≥30)

RAS inhibitor at max tolerated dose (if HTN)

Mod-high intensity **statin**

A1c, CGM

UACR

BP

ASCVD risk, Lipids

Targeted therapy

GLP1-RA if needed to achieve individualized glycemic target or persistent albuminuria

ns-MRA if persistent albuminuria and normal K^+

DHP-CCB and/or diuretic if needed to achieve individualized BP target

Antiplatelet agent for clinical ASCVD

Other glucose-lowering drugs if needed to achieve individualized glycemic target

Steroidal MRA if needed to for resistance HTN if eGFR ≥45

Ezetimibe, PCSK9i, or icosapentethyl if indicated based on ASCVD risk and lipids

de Boer IH, et al. *Diabetes Care* 2022; 45(12):3075-3090. doi: 10.2337/dci22-0027.

Take Home Messages

- NADKD has been increasingly recognized, especially in DM2 (30% of DKD cases)
- Higher UACR levels and lower eGFR levels associated with an increased risk for CVD
- Either an ACEi Or ARB recommended for those with urinary Alb/Cr≥30 or eGFR<60
- Recommendation use of a SGLT2 Inhibitors in people with type 2 DM and DKD (an eGFR ≥20)
- Nonsteroidal MRA, finerenone slows CKD progression/CVD risk, with lower risks of hyperkalemia

Thank You!