Brigham and Women's Hospital
Founding Member, Mass General Brigham

Hot Topic in Nephrology: Imagine Stopping Progression of Kidney Disease in Type 2 Diabetes

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Medicine Residency @ University of South Carolina
Nephrology Fellowship @ Combined BWH & MGH
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- Clinical focus: Diabetic Kidney Disease
- Research focus: Medical Education and Implementation Science of Disease Modifying Therapies

DISCLOSURES

None

OBJECTIVES

- Typical and Atypical Presentations of DKD
- Progression of Diabetic Kidney Disease (DKD)
- Four pillars of DKD management
  - RAAS inhibitors
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
  - ns-MR agonists
- CKD Reassessment Recommendations

eGFR categories (mL/min/1.73 m²) Description and range	Albuminuria categories: A1 <30 mg/g <3 mg/mmol	A2 30–299 mg/g 3–29 mg/mmol	A3 ≥300 mg/g ≥30 mg/mmol
≥90 G1	Monitor (1)	Treat (1)	Treat & consult (3)
60–89 G2	Monitor (1)	Treat (1)	Treat & consult (3)
45–59 G3a	Treat (1)	Treat (2)	Treat & consult (3)
30–44 G3b	Treat (2)	Treat & consult (3)	Treat & consult (3)
15–29 G4	Treat & consult (3)	Treat & consult (3)	Treat & consult (4+)
<15 G5	Treat & consult (4+)	Treat & consult (4+)	Treat & consult (4+)

Low risk

Stable disease *OR* NO CKD in absence of other markers of kidney damage.‡ Requires measurements once a year or earlier in case of new symptoms / risk factors.

Moderately increased risk

Requires measurements at least once a year

High risk

Requires measurements at least twice a year

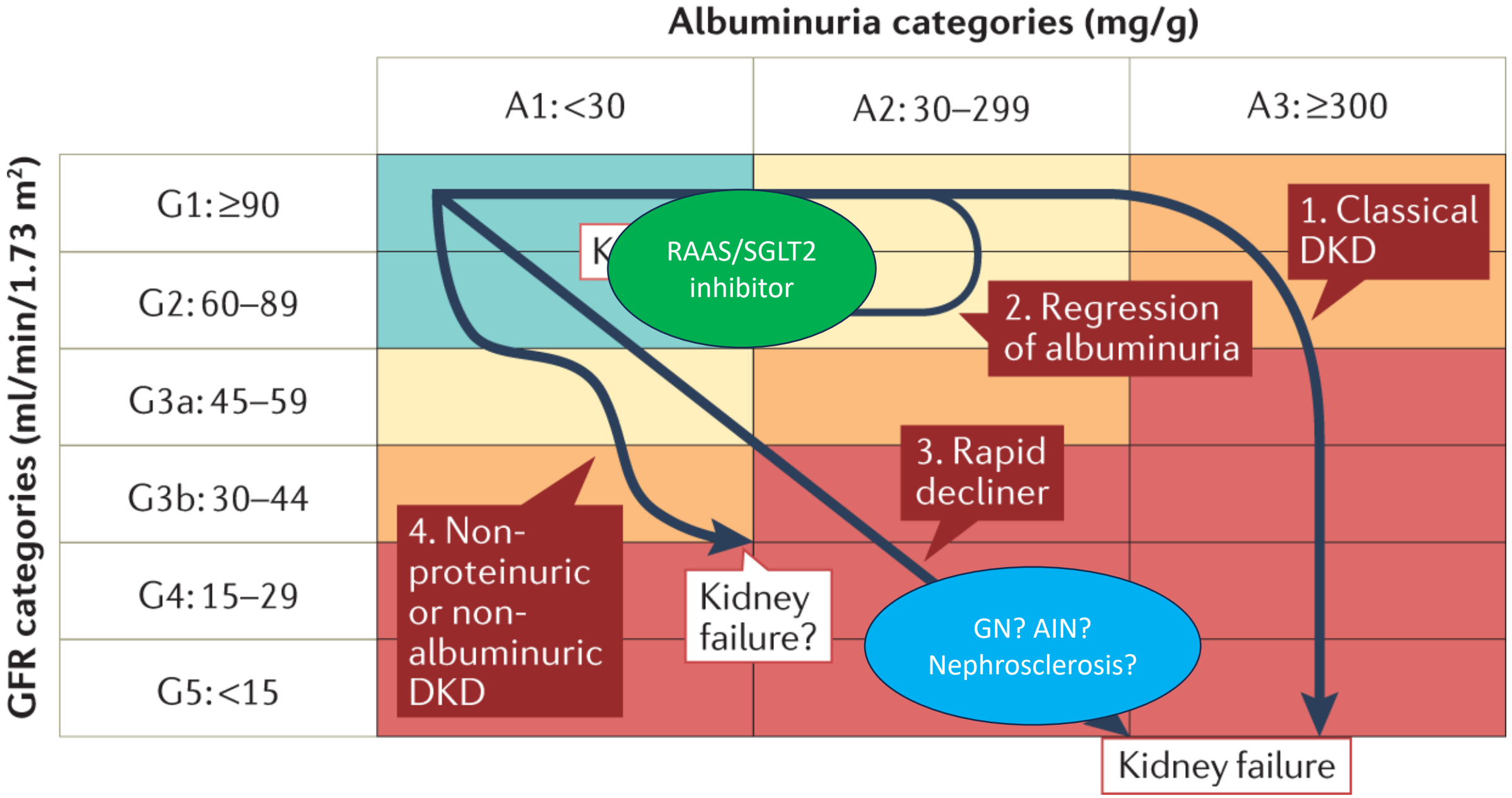
Very high risk

Treat in agreement with a nephrologist

Requires measurements at least three times a year

Requires the closest monitoring at least four times a year (every 1–3 months)

Adapted from de Boer *et al*. 2022[3]



Oshima M et al. Nat Rev Nephrol. 2021 Nov;17(11):740-750.

Presentation

Classic features (60%): Normal kidney size despite kidney failure and proteinuria>1g

Atypical (13%): Ischemic nephropathy

Coexist (27%): Known primary kidney disease

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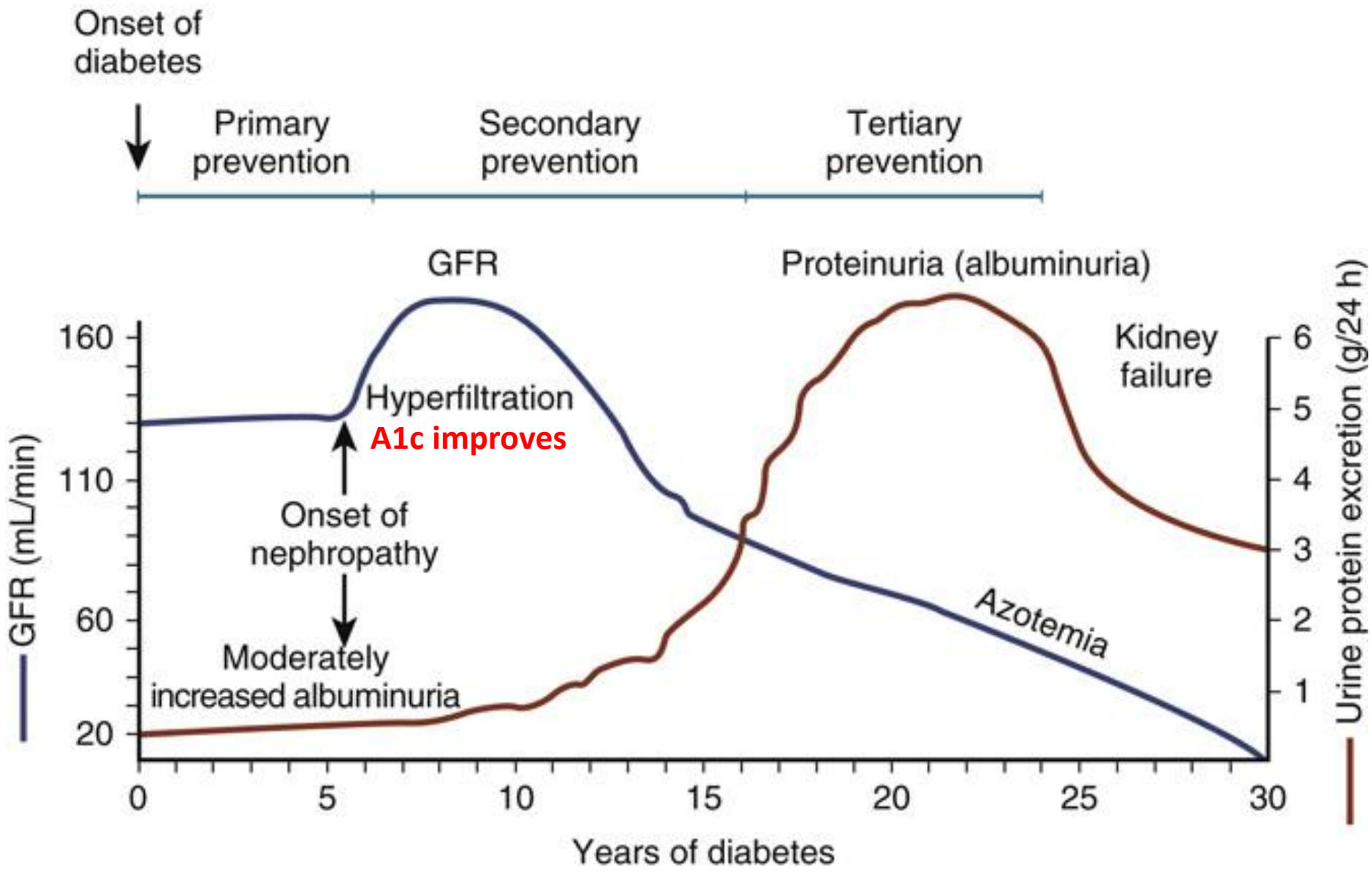
1. Hyperfiltration→ Larger kidneys
2. Moderately increased albuminuria (30-300mg/24hr or A2 by KDIGO) which may progress to severely increased albuminuria
3. Annual eGFR decline: **within 5ml/min/1.73m2** while on RAAS inhibitor

Natural History of Diabetic Nephropathy



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Non-albuminuric DKD phenotype: a breakthrough in DKD classic conception

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

Scilletta S, Di Marco M, et. al. Update on Diabetic Kidney Disease (DKD): Focus on Non-Albuminuric DKD and Cardiovascular Risk. Biomolecules. 2023 Apr 26;13(5):752.

RIACE (Penno et al., 2018) [44] @

All-cause death

	eGFR ≥90	*eGFR 75–89*	*eGFR 60–74*	*eGFR 45–59*	*eGFR 30–44*	*eGFR <30*
UACR <10	1.00 (ref.)	0.80 (0.67–0.96)	1.10 (0.83–1.12)	1.32 (1.97–1.62)	1.85 (1.40–2.44)	1.61 (0.88–2.97)
UACR 10–29	0.94 (0.78–1.12)	1.05 (0.89–1.25)	1.06 (0.88–1.27)	1.39 (1.14–1.69)	2.25 (1.79–2.82)	2.25 (1.49–3.37)
UACR 30–299	1.31 (1.08–1.60)	1.31 (1.09–1.58)	1.39 (1.15–1.68)	1.48 (1.22–1.80)	2.09 (1.69–2.59)	2.79 (2.09–3.70)
UACR ≥300	2.19 (1.55–3.11)	2.48 (1.82–3.38)	1.71 (1.23–2.36)	2.26 (1.71–3.00)	2.78 (2.14–3.63)	4.66 (3.59–6.05)

JDDM 54 (Yokoyama et al., 2020) [45] $

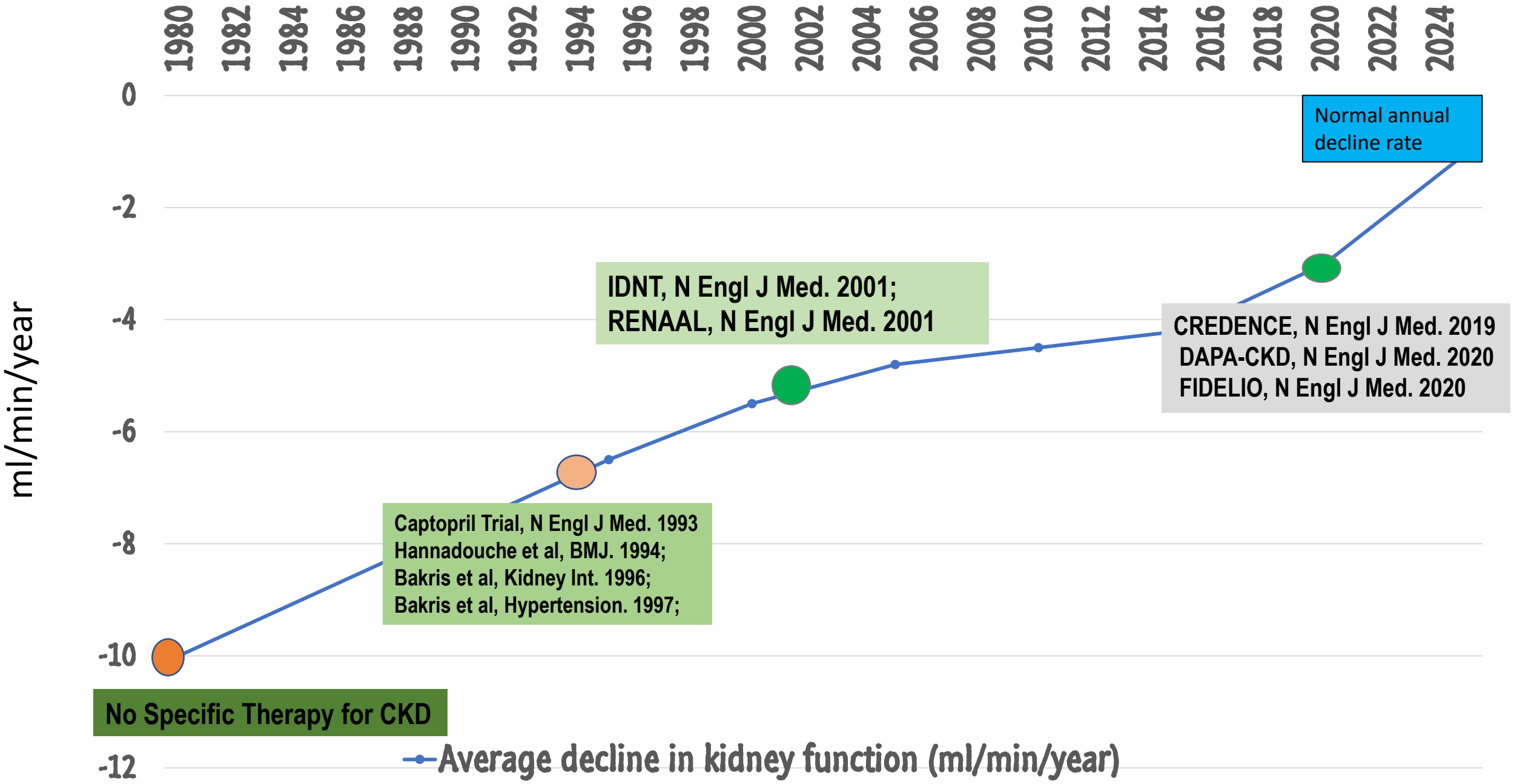
	Alb− eGFR−	*Alb+ eGFR−*	*Alb− eGFR+*	*Alb+ eGFR+*
CVD	1.00 (reference)	1.75 (1.32–2.34)	1.06 (0.63–1.79)	2.30 (1.57–3.39)
Death or CVD	1.00 (reference)	1.73 (1.35–2.21)	1.02 (0.66–1.60)	2.32 (1.67–3.24)

Analysis from Hong Kong Diabetes Biobank (Jin et al., 2022) [46] °

	Alb− GFR−	*Alb+ GFR−*	*Alb− GFR+*	*Alb+ GFR+*
All-cause mortality	1.00 (reference)	2.00 (1.52–2.63)	1.59 (1.04–2.44)	3.26 (2.43–4.38)
CVD	1.00 (reference)	1.19 (1.02–1.40)	1.14 (0.88–1.48)	1.47 (1.23–1.76)
Hospitalization for HF	1.00 (reference)	3.14 (2.09–4.73)	3.08 (1.82–5.21)	5.50 (3.63–8.34)

Scilletta S, Di Marco M, et. al. Update on Diabetic Kidney Disease (DKD): Focus on Non-Albuminuric DKD and Cardiovascular Risk. Biomolecules. 2023 Apr 26;13(5):752.

Historical Perspective on Slowing CKD progression associated with Type 2 diabetes



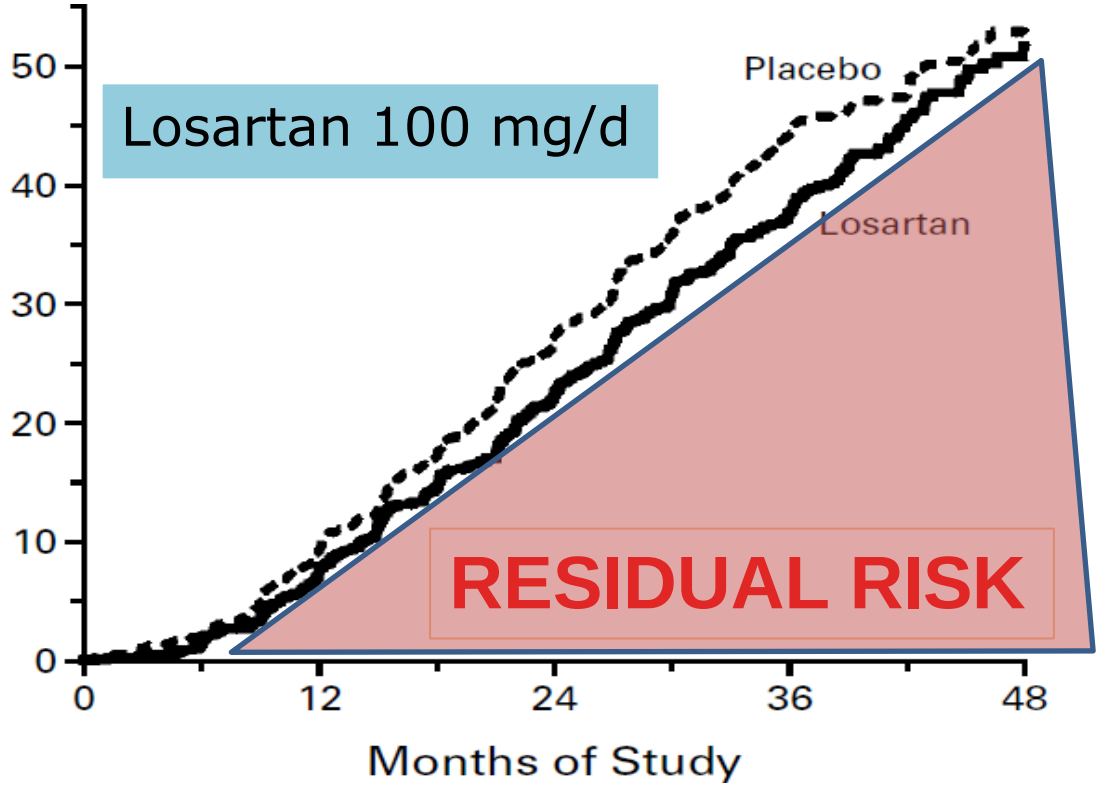
Naaman SC, Bakris GL.Diabetes.doi:10.2337/db20211-28): Arlington (VA), 2021, 28-32.

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

Doubling of serum creatinine, ESKD, or death

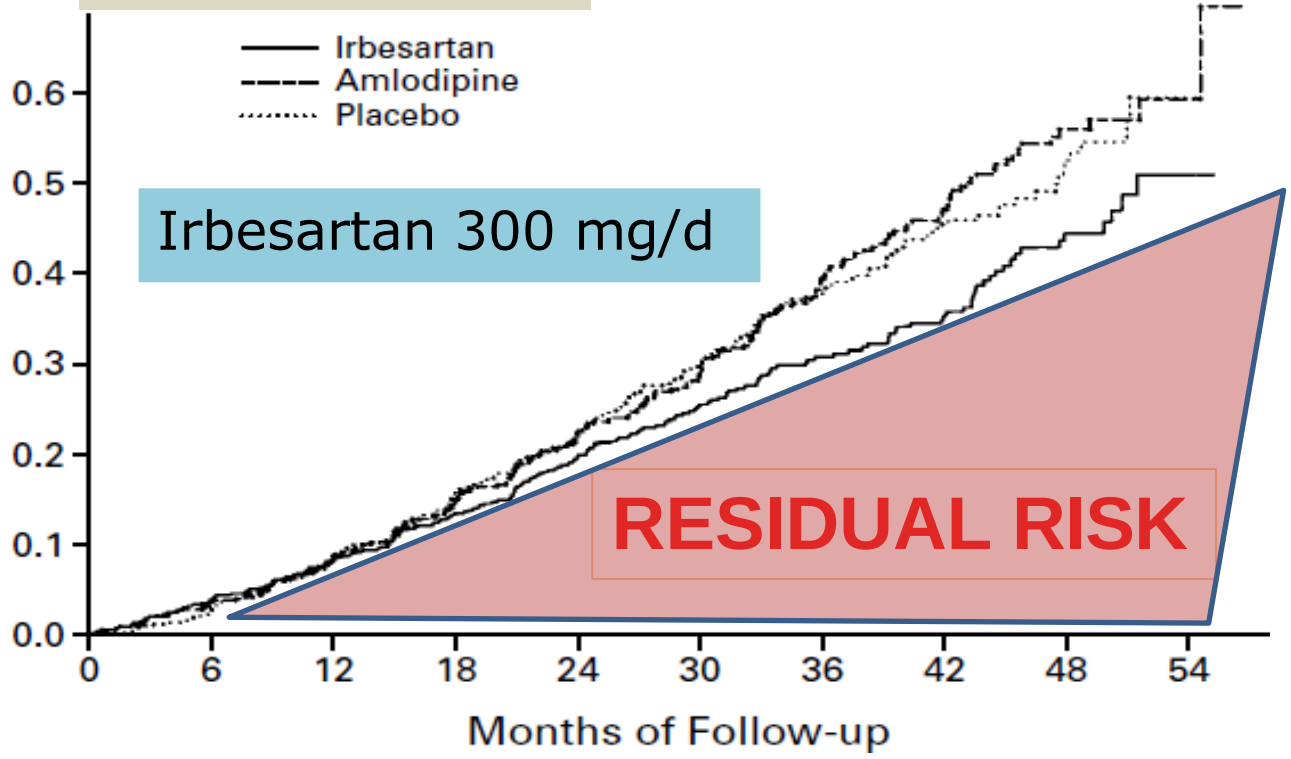
Risk reduction, 16%
P = 0.02

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.

Landmark Studies on Glucose Control

- **1987, DCCT:** reduction of progression to moderately increased albuminua with tight glucose control (Type I DM)
- **1998, UKDPS:** A1c reduction by 0.9%, reduces nephropathy
- **2008, ADVANCE:** Target A1c<6.5% associated with kidney failure reduction
- **2015, EMPA-REG:** Empagliflozin in T2DM, eGFR 20-90, associated with lower kidney events
- **2019, CREDENCE:** Canagliflozin in T2DM, eGFR 30-90, and albuminuria 300-5,000mg/g confers kidney protection
- **2020, DAPA-CKD:** Dapagliflozin in DKD or non-DKD, eGFR 25-75, and albuminuria 200-5,000mg/g confers kidney protection

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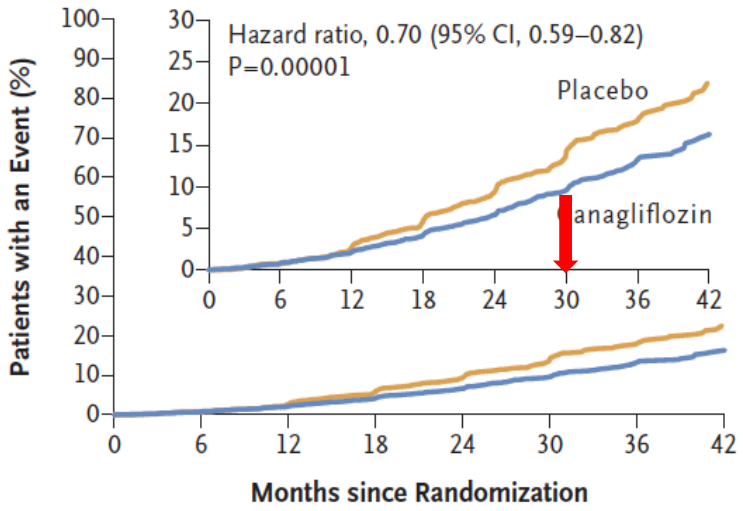
The Trilogy of SGLT2 Inhibitors for CKD

All SGLT2 inhibitor trials in CKD were stopped early based on clear evidence of benefit – A first in Nephrology

Primary outcomes: Substantial eGFR decline (40%, 50%, 57%), kidney failure, or death due to kidney or cardiovascular causes

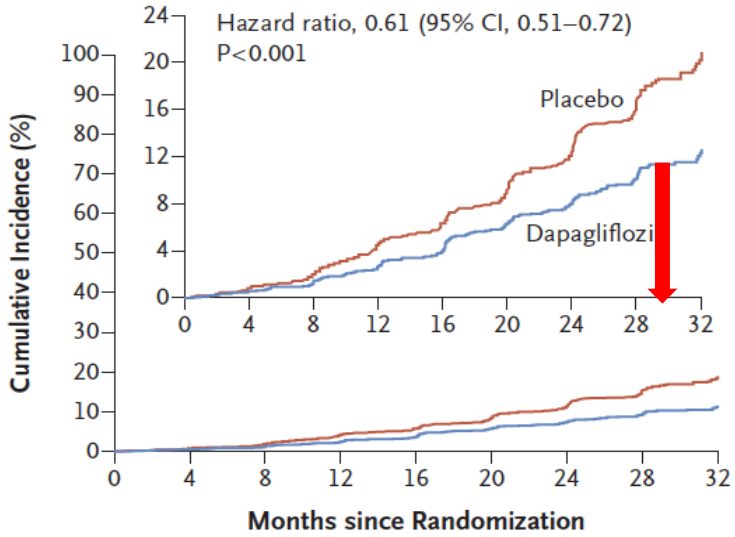
Residual risk



CREDENCE

Adults with type 2 diabetes, eGFR ≥30 mL/min/1.73 m2, UACR >300 mg/g (N=4401)

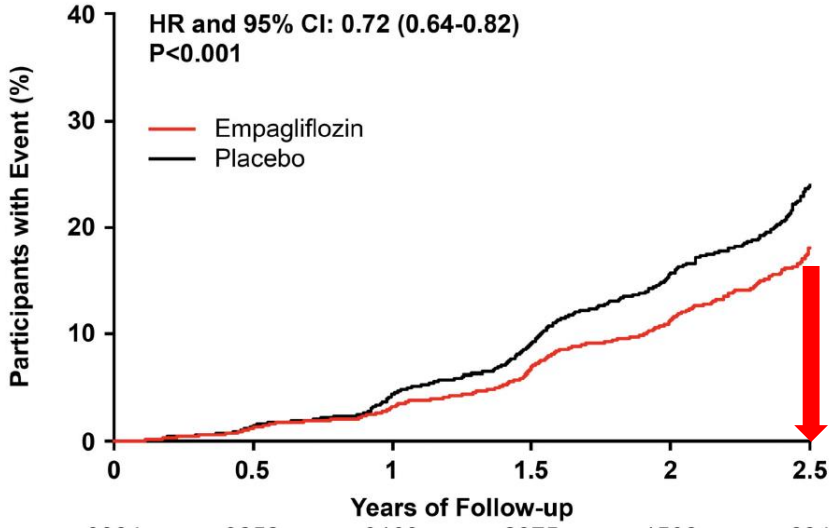
Perkovic V *et al. N Engl J Med*. 2019;380:2295-2306



DAPA-CKD

Adults with or without type 2 diabetes, eGFR ≥25 mL/min/1.73 m2, UACR >200 mg/g (n=2906).

Heerspink HJL et *al. N Engl J Med.* 2020;383(15):1436-1446

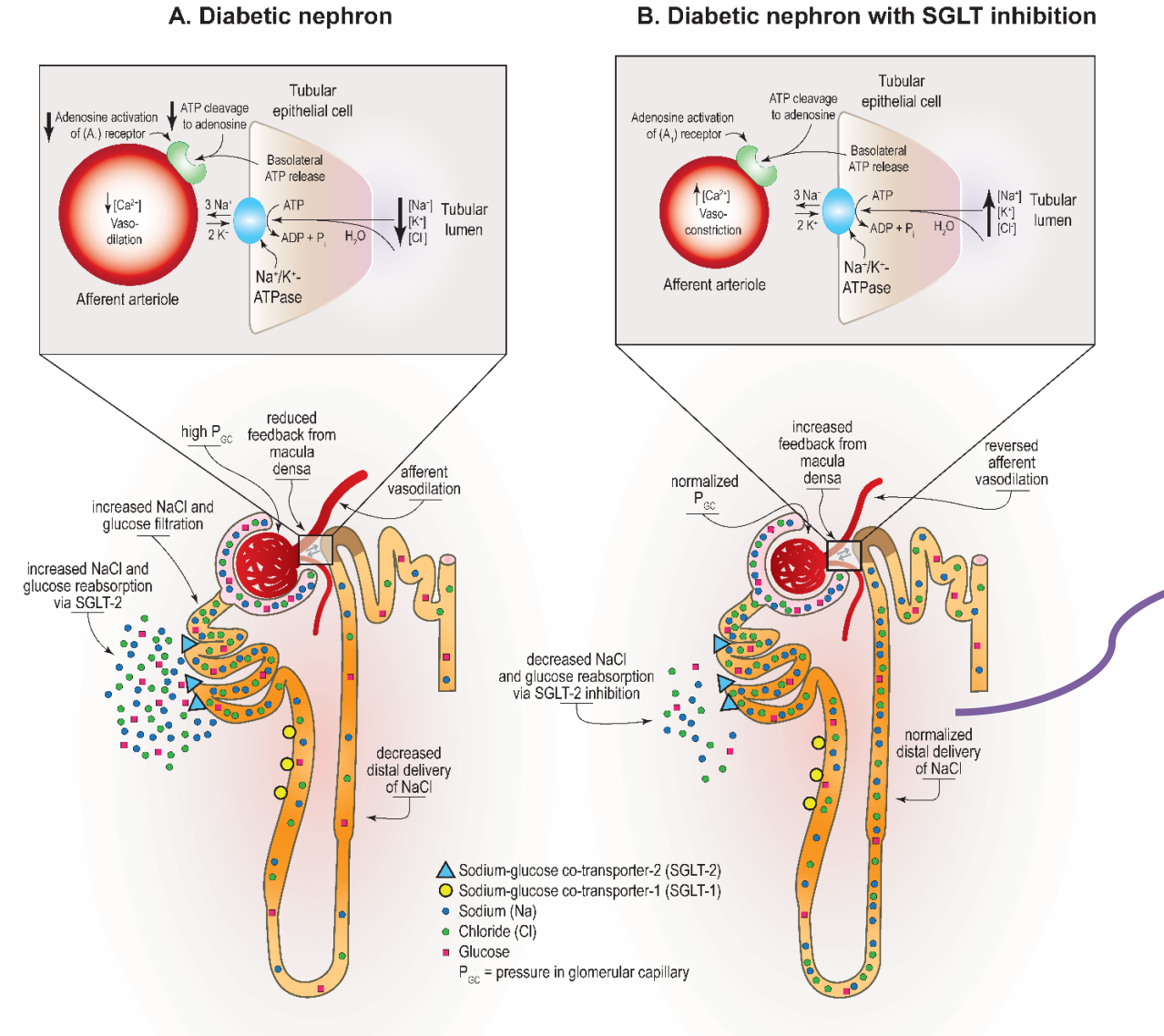


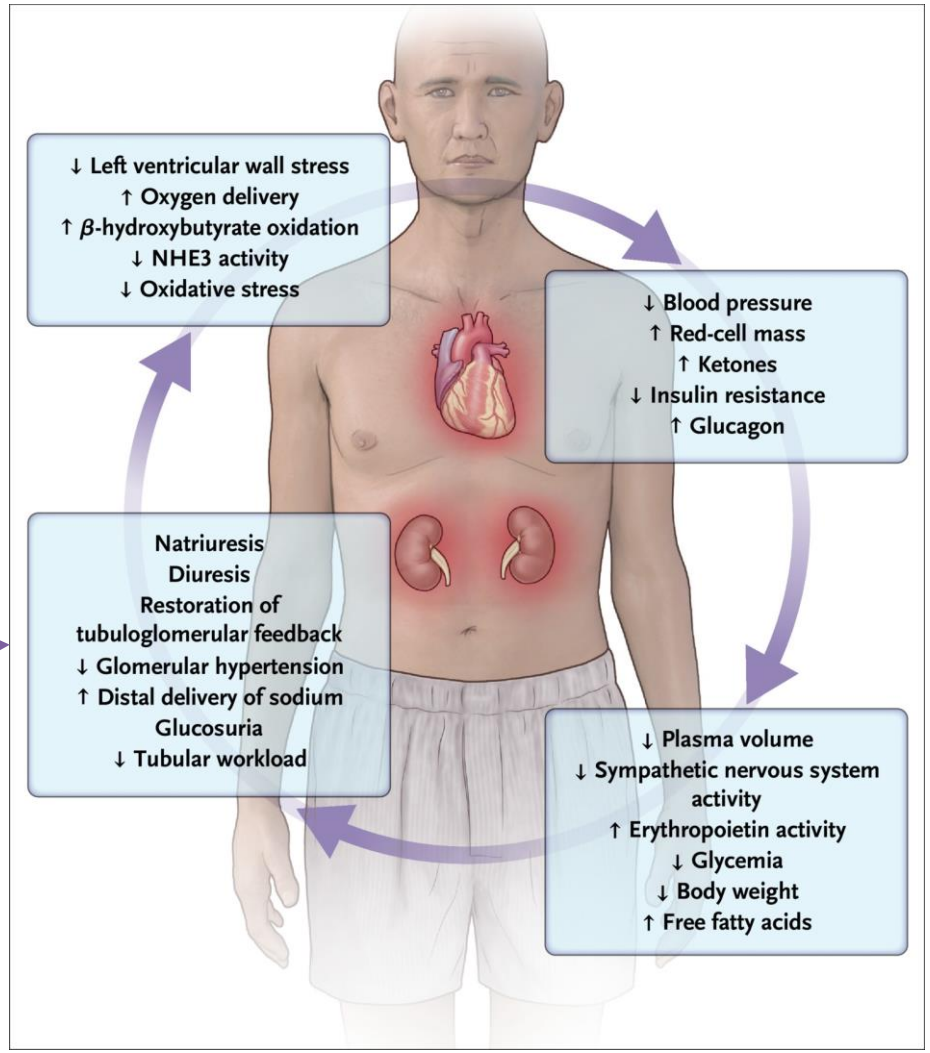
EMPA-KIDNEY

Adults with or without type 2 diabetes, eGFR ≥45 to <90 mL/min/1.73 m^2 and UACR ≥200 mg/g or ≥20 to <45 mL/min/1.73 m^2 irrespective of albuminuria (N=6609).

Herrington W *et al.* for the EMPA-KIDNEY Collaborative Group. *N Engl J Med.* 2023;388:117-127

The Kidney–Heart Connection for Organ Protection by SGLT2 Inhibitors





Alicic RZ, Johnson EJ, Tuttle KR. *Am J Kidney Dis* 2018;72:267-277
Tuttle KR *et al. Am J Kidney Dis.* 2021;77:94-109
Braunwald E. *N Engl J Med* 2022;386:2024-2034

KDIGO 2024 Recommendations

Recommendation 3.7.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Practice Point 3.7.1: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or KRT is initiated.

Practice Point 3.7.2: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when people may be at greater risk for ketosis).

Recommendation 3.7.2: We recommend treating adults with CKD with an SGLT2i for the following *(1A)*:

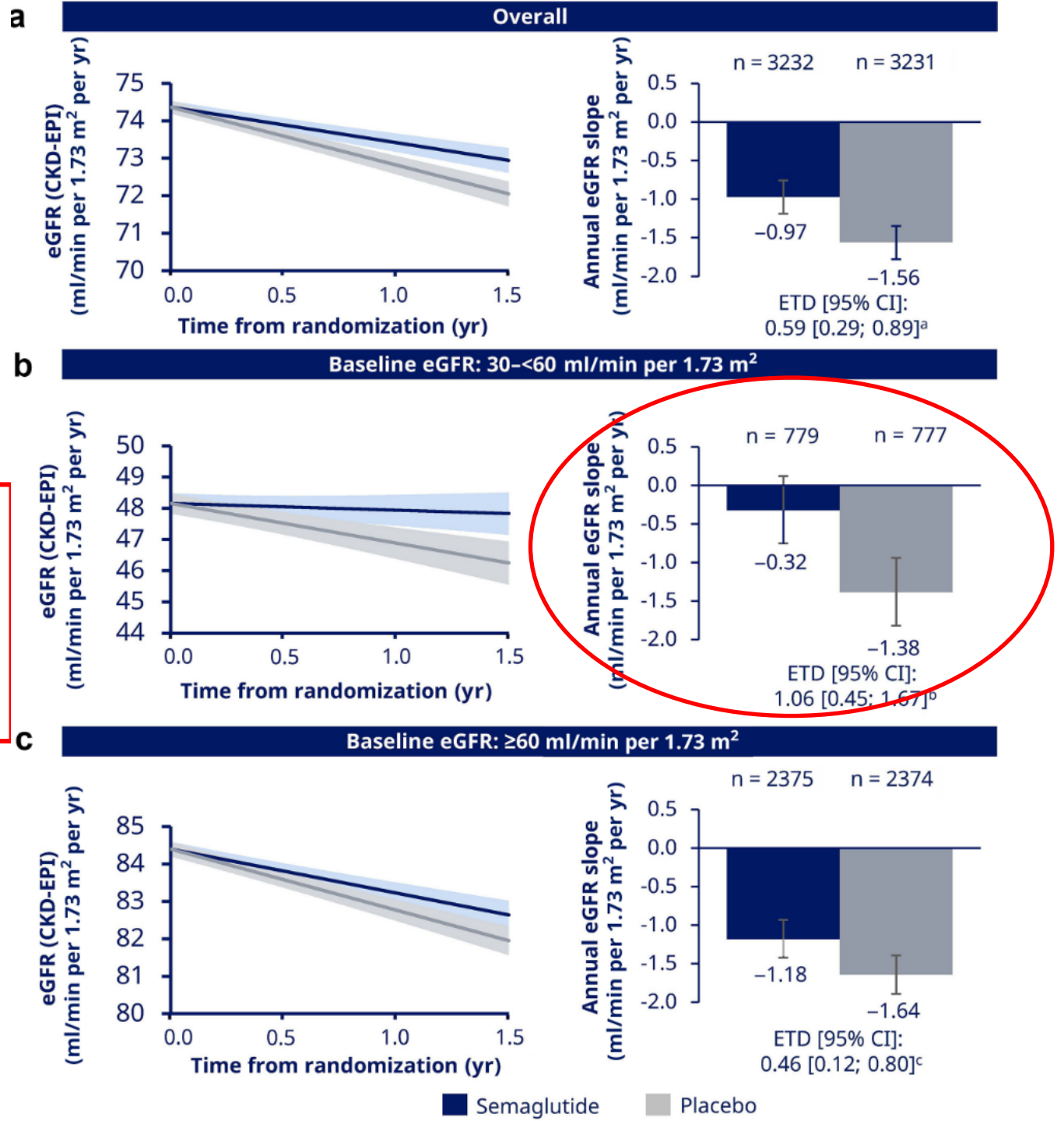
- **eGFR ≥20 ml/min per 1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or**
- **heart failure, irrespective of level of albuminuria.**

Practice Point 3.7.3: SGLT2i initiation or use does not necessitate alteration of frequency of CKD monitoring and the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

Recommendation 3.7.3: We suggest treating adults with eGFR 20 to 45 ml/min per 1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) with an SGLT2i *(2B)*.

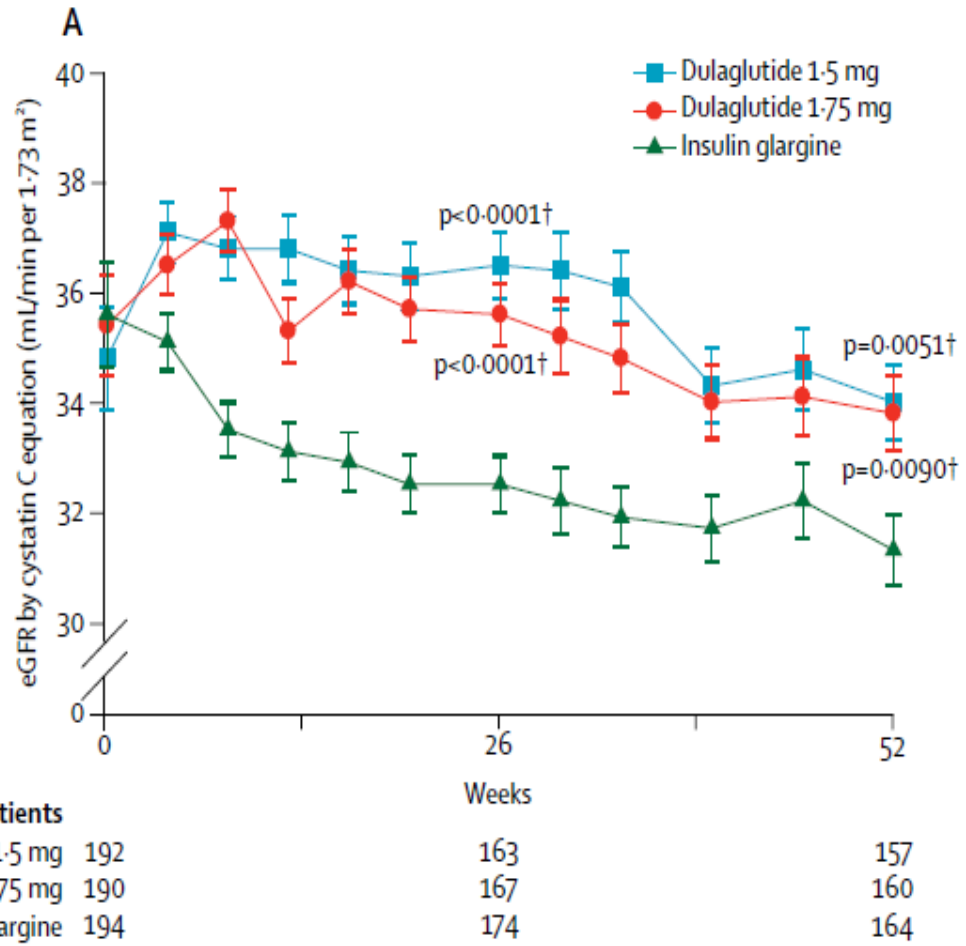
SUSTAIN-6 and PIONEER-6: Kidney Function Stabilized by Semaglutide

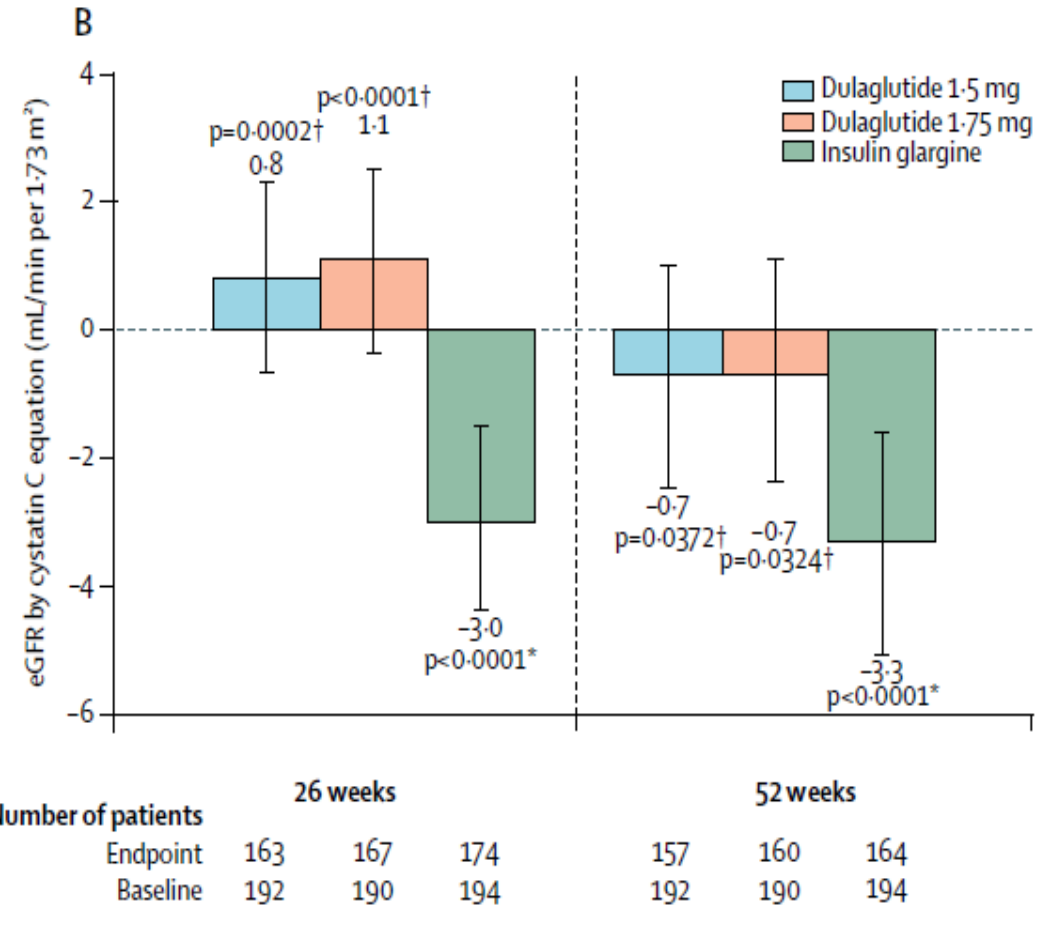
eGFR slope with estimated treatment difference (ETD) >0.75 mL/min/1.73m^2 per year predicts significantly lower risk of kidney failure versus placebo



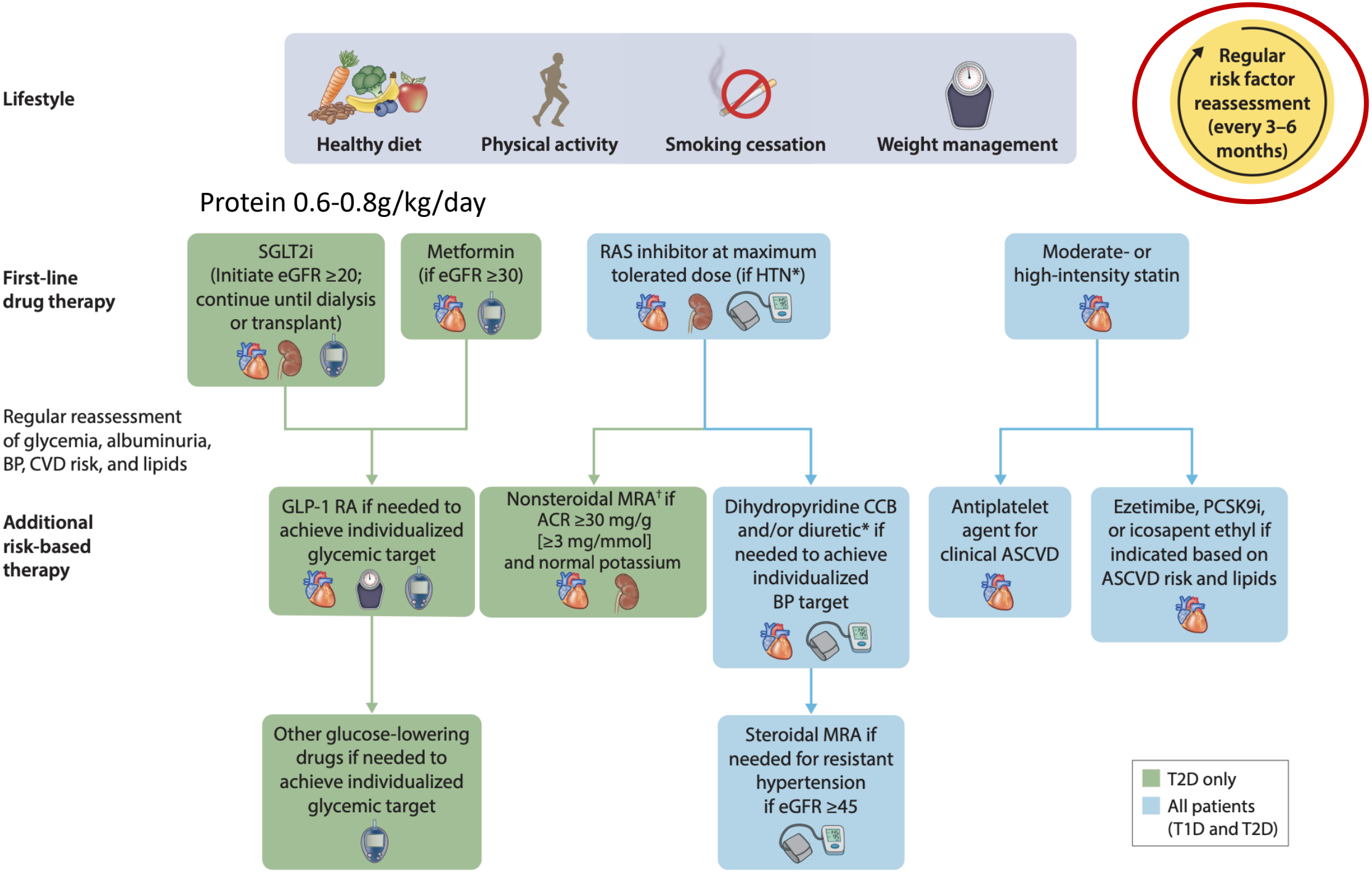
Tuttle KR *et al. Kidney Int* 2023;103:772-781
Inker LA *et al. J Am Soc Nephrol* 2019;30:1735-1745

AWARD-7: Dulaglutide versus Insulin Glargine in Type 2 Diabetes and Moderate-to-Severe CKD



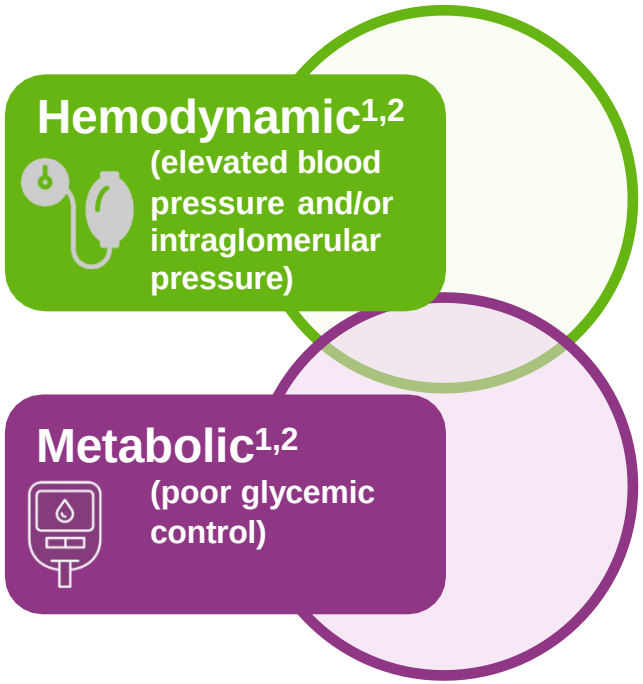


Tuttle KR *et al. Lancet Diabetes Endocrinol* 2018;6:605-617


Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
Protein 0.6-0.8g/kg/day
First-line drug therapy
SGLT2i (Initiate eGFR ≥20; continue until dialysis or transplant)
Metformin (if eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids
Additional risk-based therapy
GLP-1 RA if needed to achieve individualized glycemic target
Nonsteroidal MRA† if ACR ≥30 mg/g [≥3 mg/mmol] and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
T2D only
All patients (T1D and T2D)

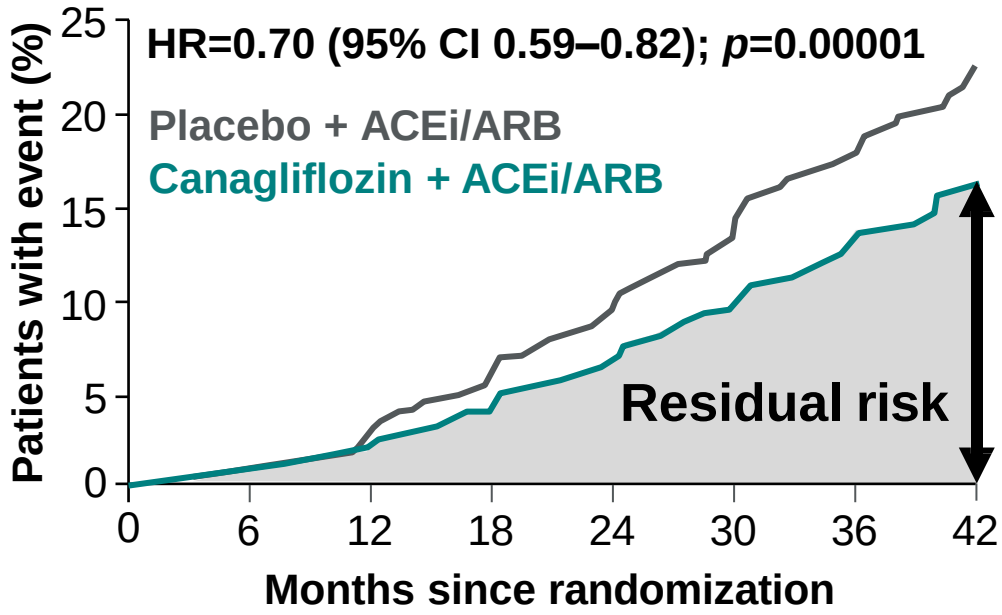
Adding NS-MRA rationale

High residual risk of CKD progression with current therapies



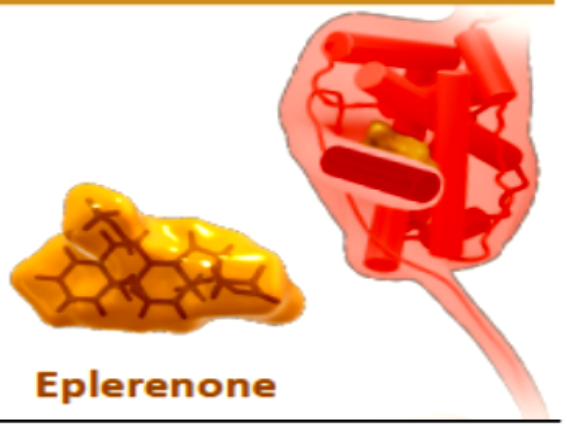
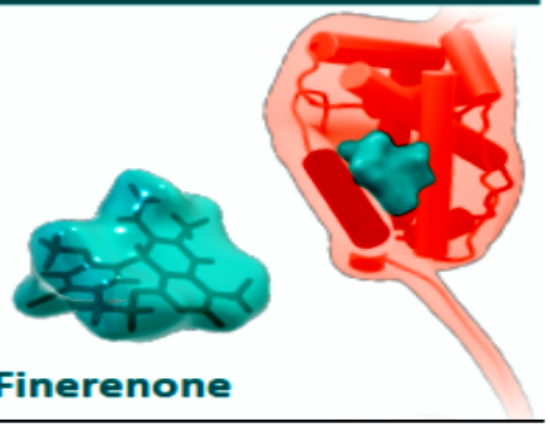
CREDENCE[3]

Cardiorenal composite endpoint*



1. Alicic RZ, *et al*. *Clin J Am Soc Nephrol* 2017;12:2032; 2. Mora-Fernández C, *et al*. *J Physiol* 2014;18:3997;
3. Perkovic V, *et al*. *N Engl J Med* 2019;380:2295

Comparison of MRA inhibitors: Steroidal and Non-steriodal

	Steroidal MRAs		Finerenone
	 Spironolactone	 Eplerenone	 Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	-
Sexual side effects	++	(+)	-
Half-life	> 20 hours	4-6 hours	2-3 hours
Active metabolites	++	-	-
Effect on BP	+++	++	+

Kintscher U, Bakris GL, and Kolkhof P. *Br J Pharmacol 2021, in press*

The FIDELITY[1] prespecified pooled analysis of FIDELIO-DKD[2] and FIGARO-DKD[3] showed significant risk reductions in CV and kidney outcomes with finerenone

FIDELIO-DKD N=5734

FIDELITY Prespecified pooled analysis N=13,171*

FIGARO-DKD N=7437

3 years median follow-up

R

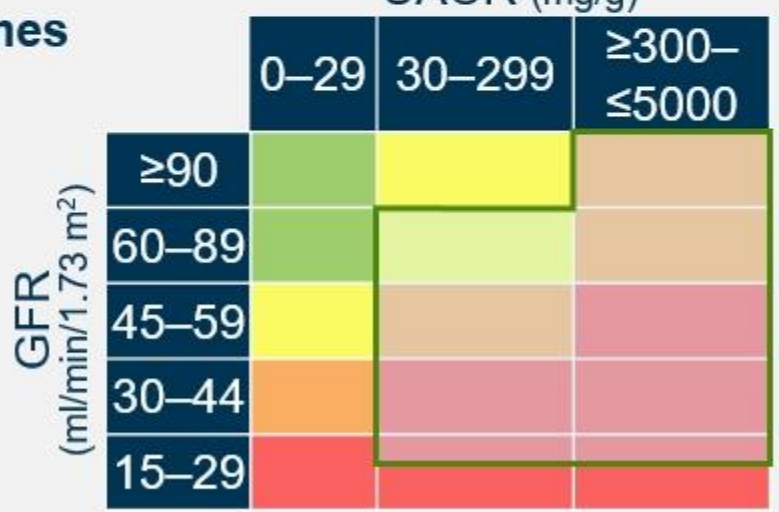
Finerenone 10 or 20 mg od (n=6519)

Placebo (n=6507)

FIDELITY Key eligibility outcomes

- T2D
- CKD
- On single RASi
- Serum [K⁺] ≤4.8 mmol/l#

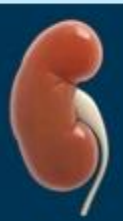
- Symptomatic HFrEF‡



FIDELITY Key endpoint outcomes

CV composite§ vs placebo (HR=0.86; 95% CI 0.78–0.95)

14%



Kidney composite¶ vs placebo (HR=0.77; 95% CI 0.67–0.88)

23%

*13,026 patients were included in the statistical analysis (145 were excluded due to critical GCP violations); #at run-in or screening visit; ‡run-in only; § Time to CV death, nonfatal myocardial infarction, nonfatal stroke or hospitalisation for heart failure, ¶ time to kidney failure, sustained ≥57% eGFR from baseline over ≥4 weeks decline or renal death

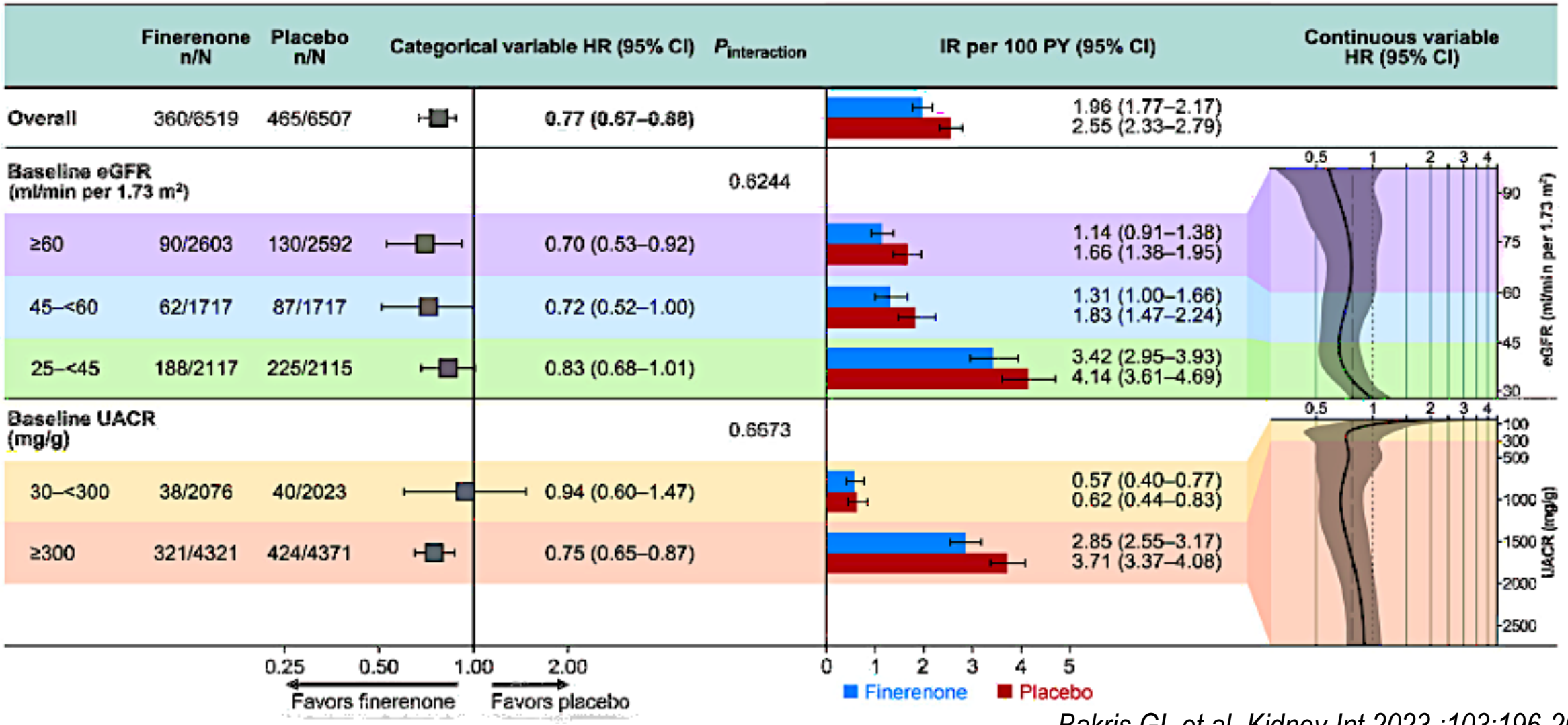
eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GPC, Good Clinical Practice; HbA1c, glycated haemoglobin; HFrEF, heart failure with reduced ejection fraction; [K⁺], potassium concentration;

NYHA, New York Heart Association; od, once daily; RASi, renin–angiotensin system inhibitor; UACR, urine albumin-to-creatinine ratio

1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263, 3. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELITY

Composite kidney outcome, including a >57% eGFR decrease component by baseline UACR and eGFR categories.



Bakris GL et.al. Kidney Int 2023 ;103:196-206

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

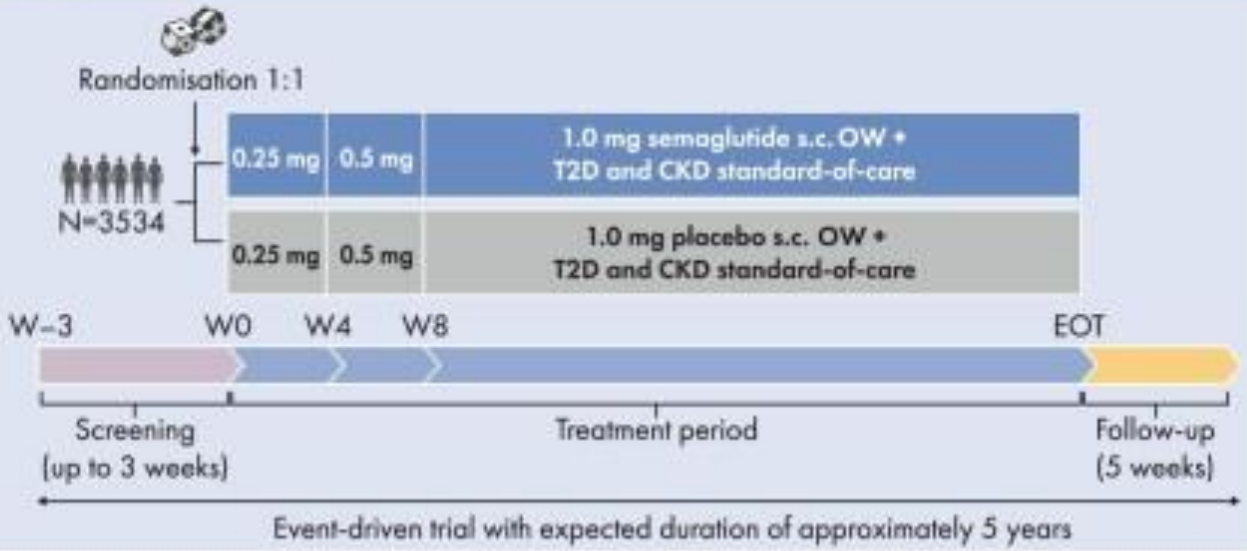
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.

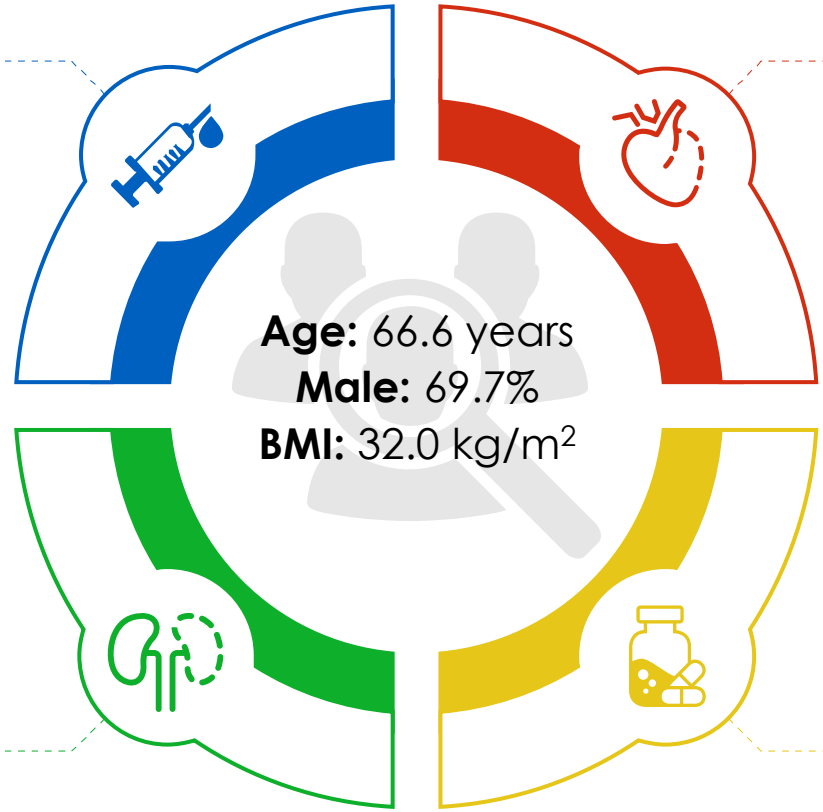
Rossing P et.al. *Nephrol Dial Transplant (2023) 0: 1–11*https://doi.org/10.1093/ndt/gfad009

FLOW Design: Kidney Disease Outcomes Trial in Persons with Type 2 Diabetes

Stopped early for clear positive efficacy

Perkovic V *et al. N Engl J Med.* 2024 Jul 11;391(2):109-121.
Rossing P et al. *Nephrol Dial Transplant* 2023;38:2041–2051

FLOW Participants with Type 2 Diabetes Had High- and Very-High-Risk CKD



T2D

- HbA_{1c}: 7.8%
- T2D duration ≥15 years: 56.8%

CVD

- BP: 138.6/76.4 mmHg
- Prior MI or stroke: 22.9%
- Chronic heart failure: 19.2%

CKD

- eGFR: 47.0 mL/min/1.73 m²
- Median UACR: 567.6 mg/g

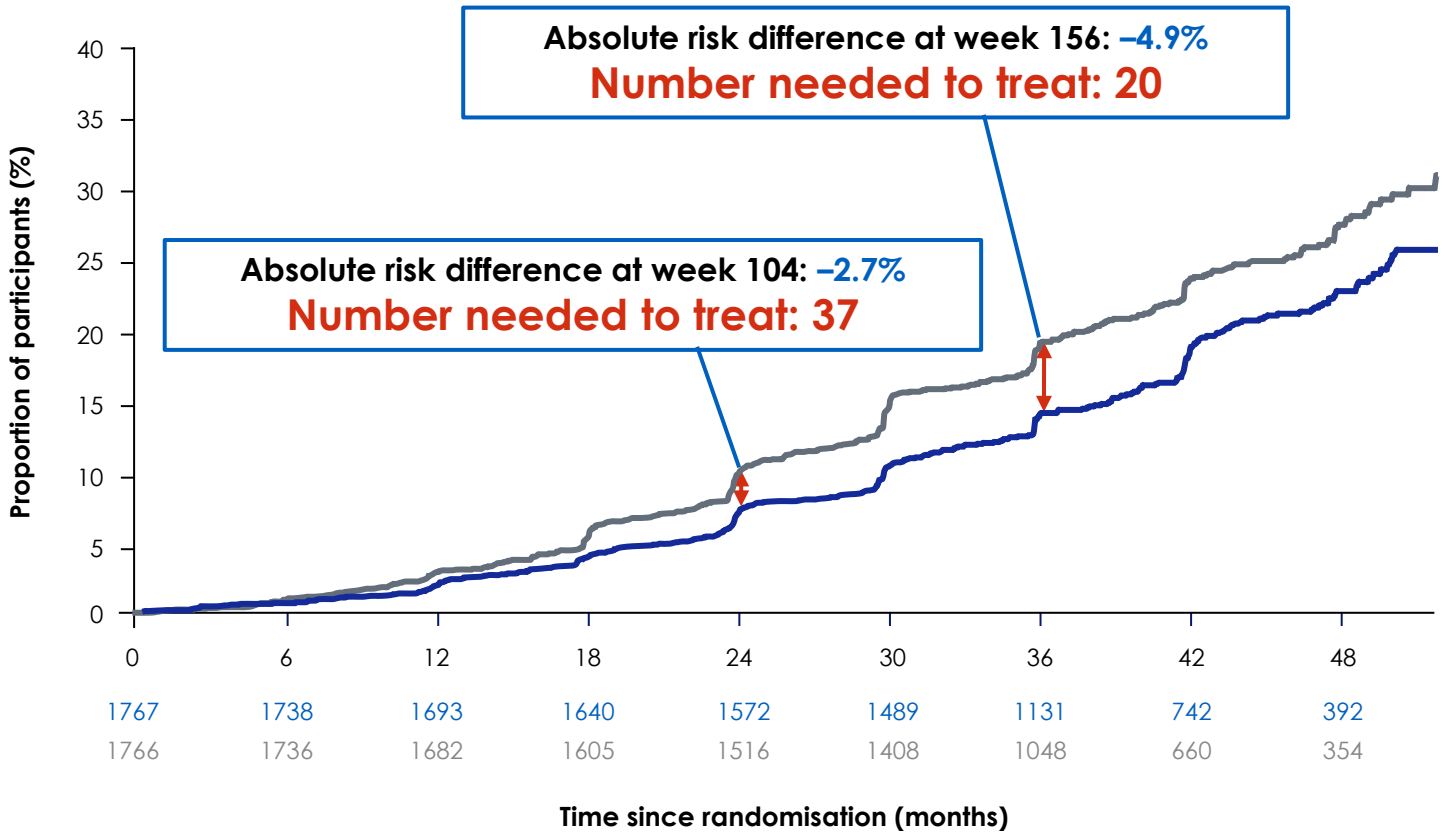
Medication use

- RAAS blocker: 95.3%
- SGLT2 inhibitor: 15.6%

Perkovic V *et al. N Engl J Med.* 2024 Jul 11;391(2):109-121.

Composite Kidney Outcome

Primary outcome



Placebo 23.2%
(410/1766)

Semaglutide 18.7%
(331/1767)

HR 0.76 (95% CI 0.66, 0.88)
p=0.0003

Superiority if two-sided
p value <0.0322

Perkovic V *et al. N Engl J Med.* 2024 Jul 11;391(2):109-121.

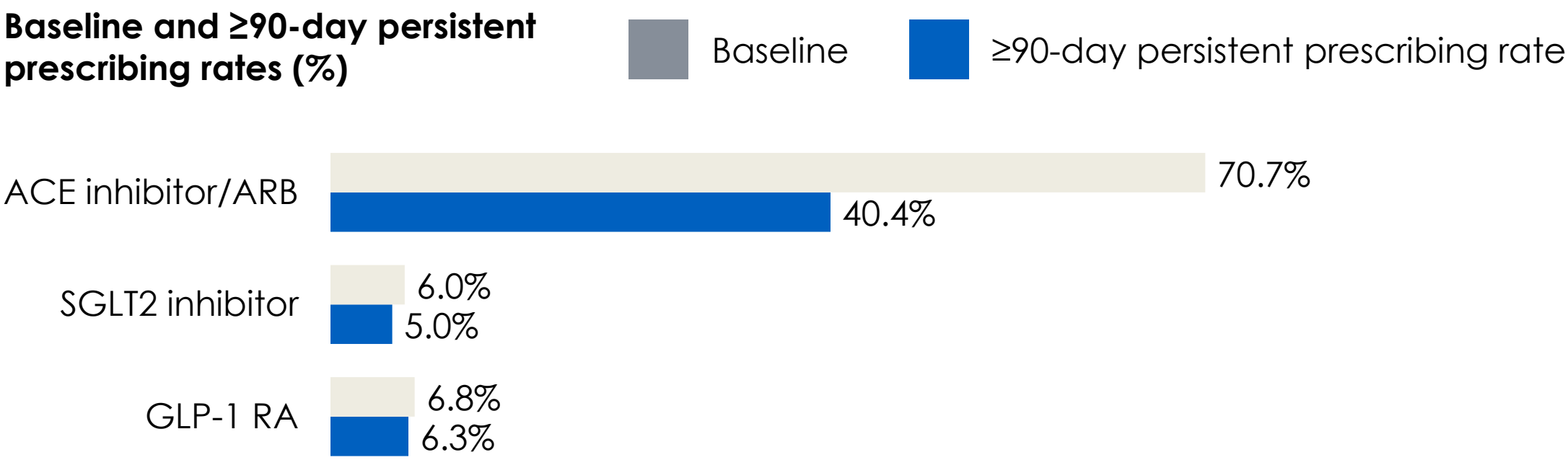
Albuminuria/Proteinuria Monitoring is Low in CKD CURE-CKD 2006-2017 (N=606,064)

	All CKD	CKD/DM/PDM/HTN	CKD/HTN	CKD/DM/PDM	CKD Alone
UACR, mg/g					
≤30	17 651 (2.9)	12 703 (4.2)	1776 (1.3)	2224 (2.7)	948 (1.1)
>30 to ≤300	27 227 (4.5)	21 435 (7.1)	1089 (0.8)	4066 (5.0)	637 (0.7)
>300	7673 (1.3)	5860 (2.0)	509 (0.4)	995 (1.2)	309 (0.3)
Not measured	553 513 (91.3)	260 159 (86.7)	131 126 (97.5)	73 981 (91.0)	88 247 (97.9)
UPCR, mg/g					
≤150	14 467 (2.4)	7823 (2.6)	2723 (2.0)	2076 (2.6)	1845 (2.0)
>150 to ≤500	5688 (0.9)	3087 (1.0)	1163 (0.9)	763 (0.9)	675 (0.7)
>500	4880 (0.8)	2978 (1.0)	785 (0.6)	696 (0.9)	421 (0.5)
Not measured	581 029 (95.9)	286 269 (95.4)	129 829 (96.5)	77 731 (95.7)	87 200 (96.7)
Age, median (IQR) [No.], y	70 (59-81) [606 064]	70 (60-79) [300 157]	72 (60-83) [134 500]	73 (63-83) [81 266]	64 (42-81) [90 141]
eGFR, median (IQR) [No.], mL/min/1.73 m^2	53 (41-61) [524 169]	54 (43-63) [266 838]	53 (44-59) [115 061]	49 (35-59) [74 366]	53 (41-66) [67 904]
SBP, mean (SD) [No.], mm Hg	129 (18) [365 561]	131 (18) [202 951]	132 (18) [92 051]	119 (17) [25 533]	119 (16) [45 026]
DBP, mean (SD) [No.], mm Hg	72 (11) [365 561]	72 (10) [202 951]	74 (11) [92 051]	67 (10) [25 533]	70 (10) [45 026]

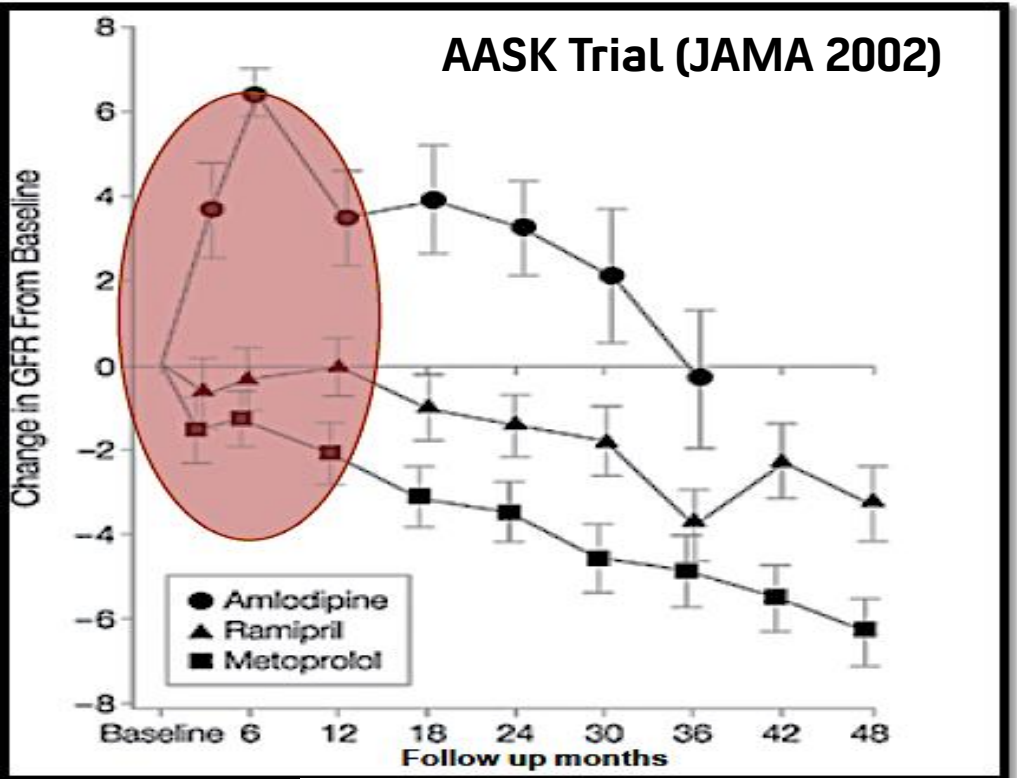
Tuttle KR *et al. JAMA Netw Open* 2019;2:e1918169

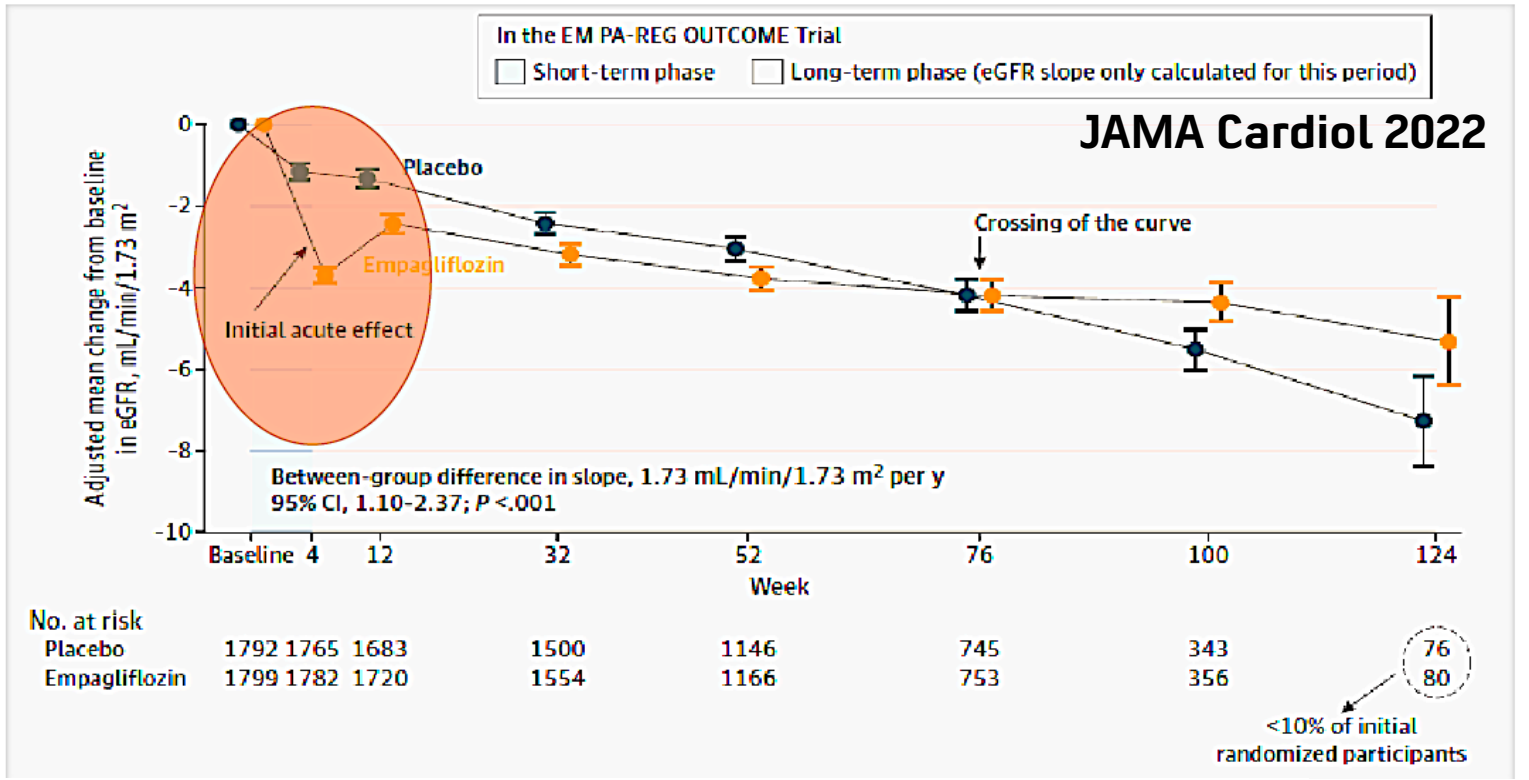
Prescription of Guideline-Directed Medical Therapy Is Suboptimal in Diabetes and CKD

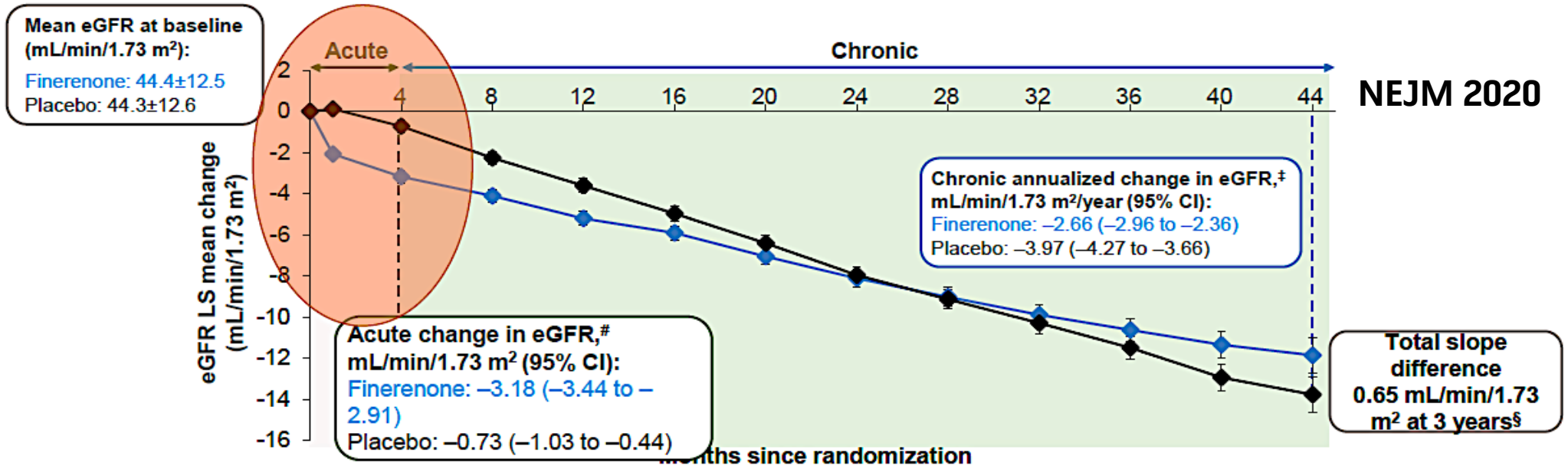
US CURE-CKD Registry study, an electronic health records database from Providence and UCLA Health system (2019–2020)



Nicholas SB *et al. Diabetes Obes Metab* 2023;25:2970–2979







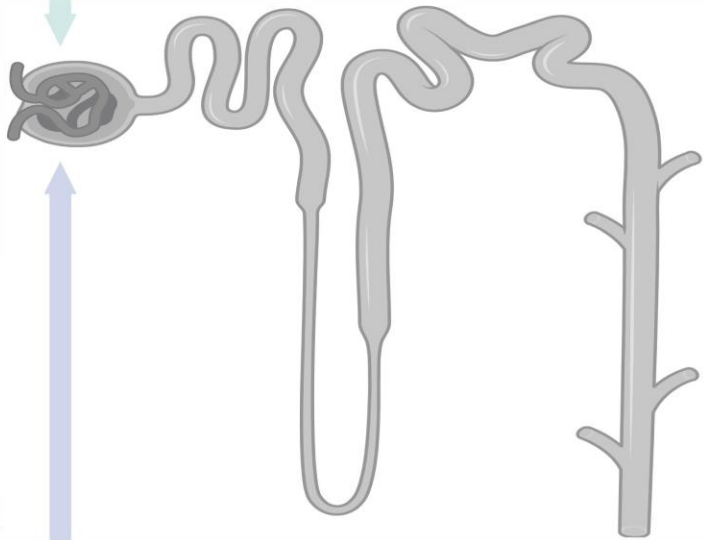
Bakris G and Weir M Am J Nephrol. 2022;53(7):513-515

POTENTIAL PILLAR 4: GLP- 1RAs

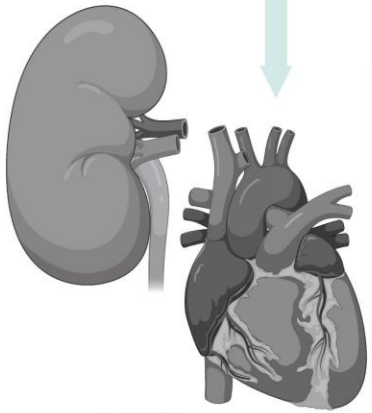
- Decrease weight
- Decrease dyslipidemia
- Decrease oxidative stress
- Decrease endothelial dysfunction

PILLAR 1: RAS blockers

- Decrease efferent arteriole tone
- Decrease hyperfiltration
- Decrease endothelial dysfunction
- Decrease cardiac remodeling



Metabolic Dysregulation



Hemodynamic Perturbations

Inflammation

PILLAR 3: Finerenone

- Decreases inflammation
- Decreases fibrosis
- Decreases endothelial dysfunction
- Decreases tissue remodeling
- Decreases proteinuria

PILLAR 2: SGLT2 inhibitors

- Increase afferent arteriole tone
- Improve tubuloglomerular feedback
- Decrease hyperfiltration
- Decrease proteinuria
- Decrease oxidative stress
- Increase anti–inflammatory and anti–fibrotic effects

Naaman S and Bakris GL Diabetes Care 2023;46:1574-1586

Take Home Points

- Screen for Diabetic Kidney Disease with **serum creatinine, cystatin C, and urine albumin to creatinine ratio** at 5 years after onset of Type I DM and at diagnosis of Type II DM.
- An **SGLT2** inhibitor and an **ACE inhibitor or an ARB** are **first-line** for patients with diabetes and CKD.
- A **GLP-1** receptor agonist and a **non-steroidal MRA** are currently considered **risk-based** disease modifying therapy for albuminuria, glycemia, weight, and CVD.
- Focused efforts for CKD detection and access to care are needed to remove barriers to receiving kidney-heart-lifesaving therapies.

Brigham and Women's Hospital
Founding Member, Mass General Brigham

THANK YOU!

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