



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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- Clinical focus: Diabetic Kidney Disease
- Research focus: Medical Education and Implementation Science of Disease Modifying Therapies



DISCLOSURES

None



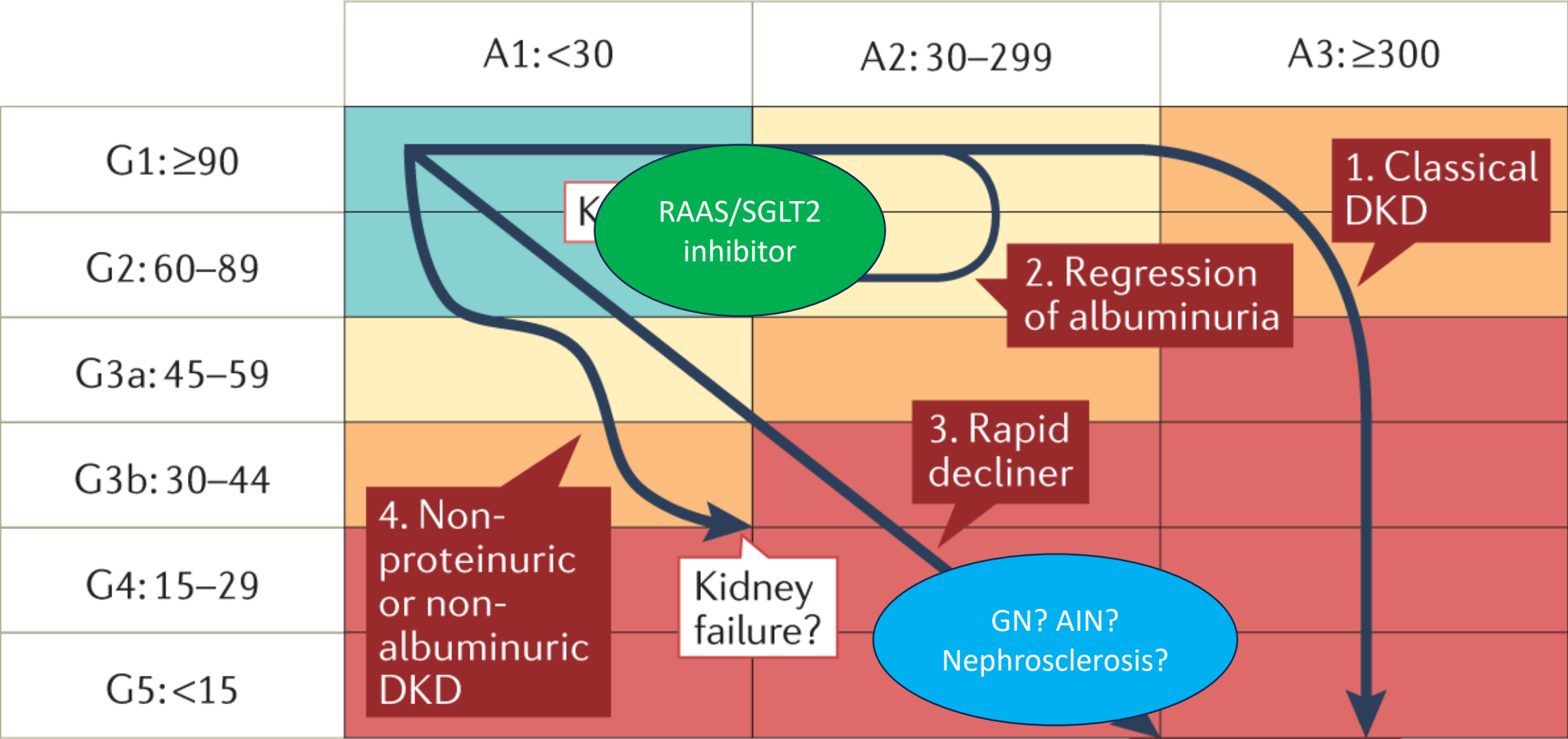
OBJECTIVES

- 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



Albuminuria categories (mg/g)

GFR categories (ml/min/1.73 m²)



Presentation

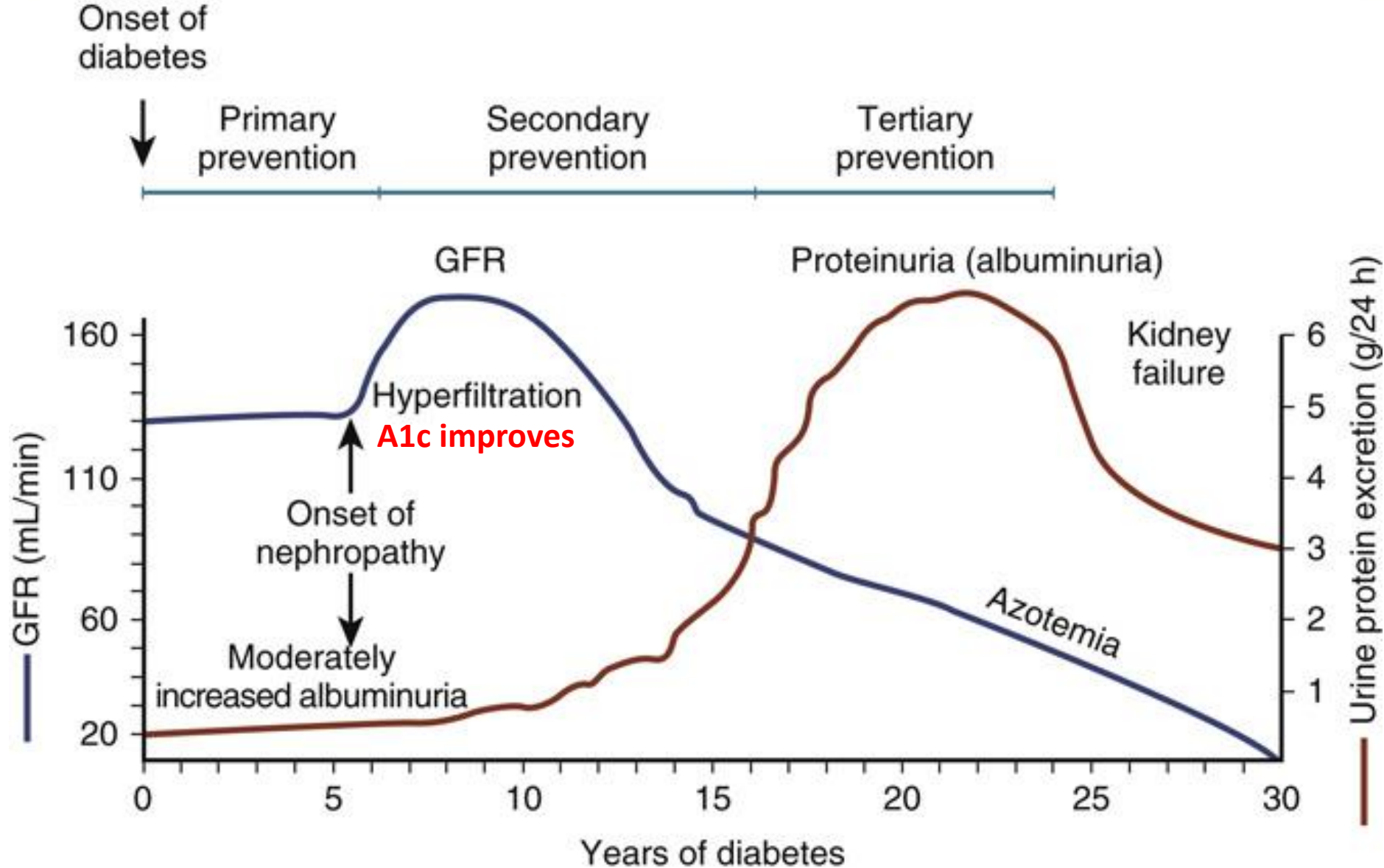
Classic features (60%): Normal kidney size despite kidney failure and proteinuria >1g

Atypical (13%): Ischemic nephropathy

Coexist (27%): Known primary kidney disease

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



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

Albuminuric DKD

UACR > 30 mg/g



Microangiopathy



Correlation with
retinopathy



Glomerulosclerosis



Male sex



Correlation with Hb1Ac



Non-albuminuric DKD

eGFR < 60 ml/min/1.73m² and
UACR < 30 mg/g



Macroangiopathy



No correlation with
retinopathy



Tubular and vascular
damage



Female sex

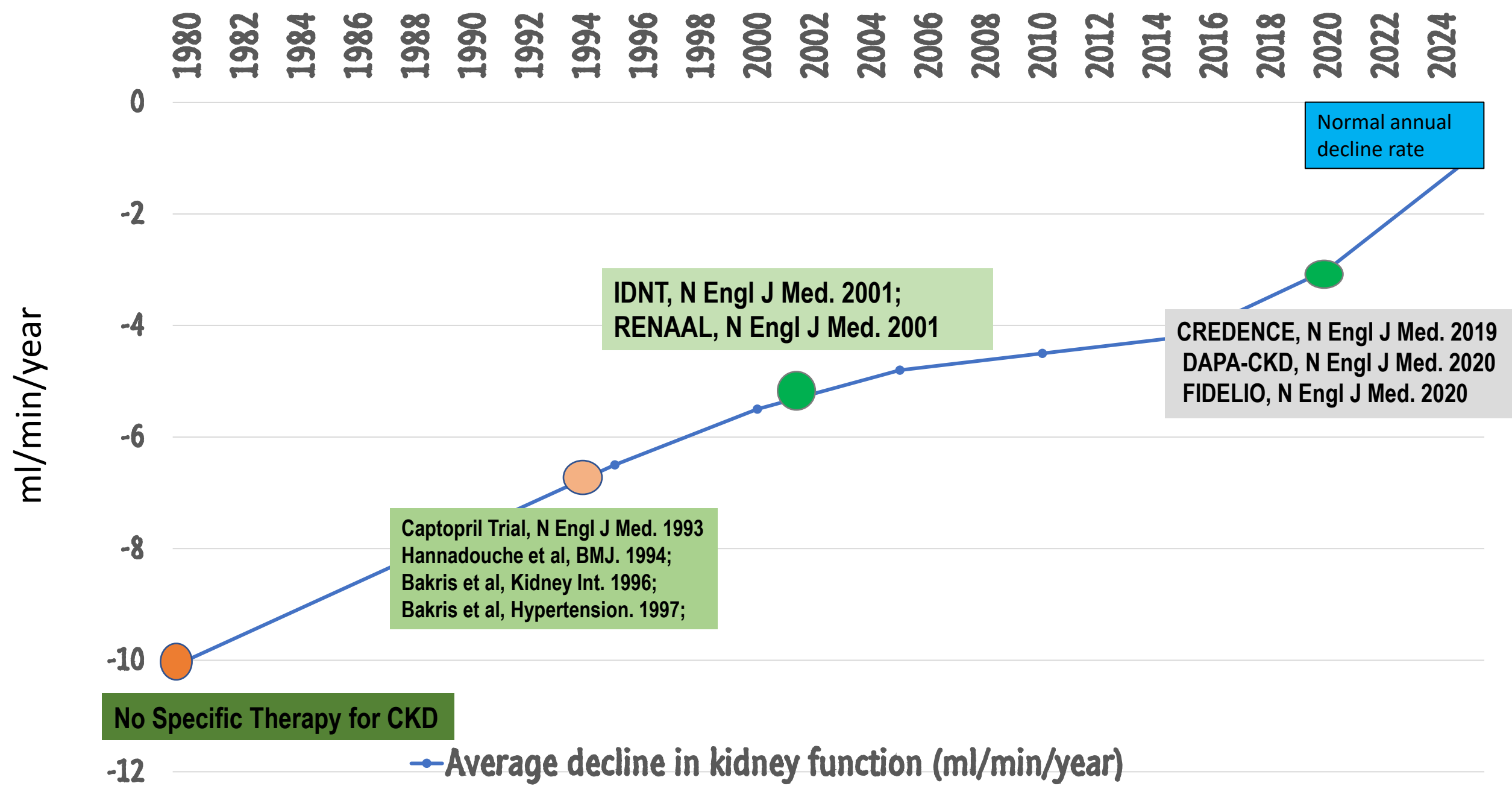


No correlation with Hb1Ac

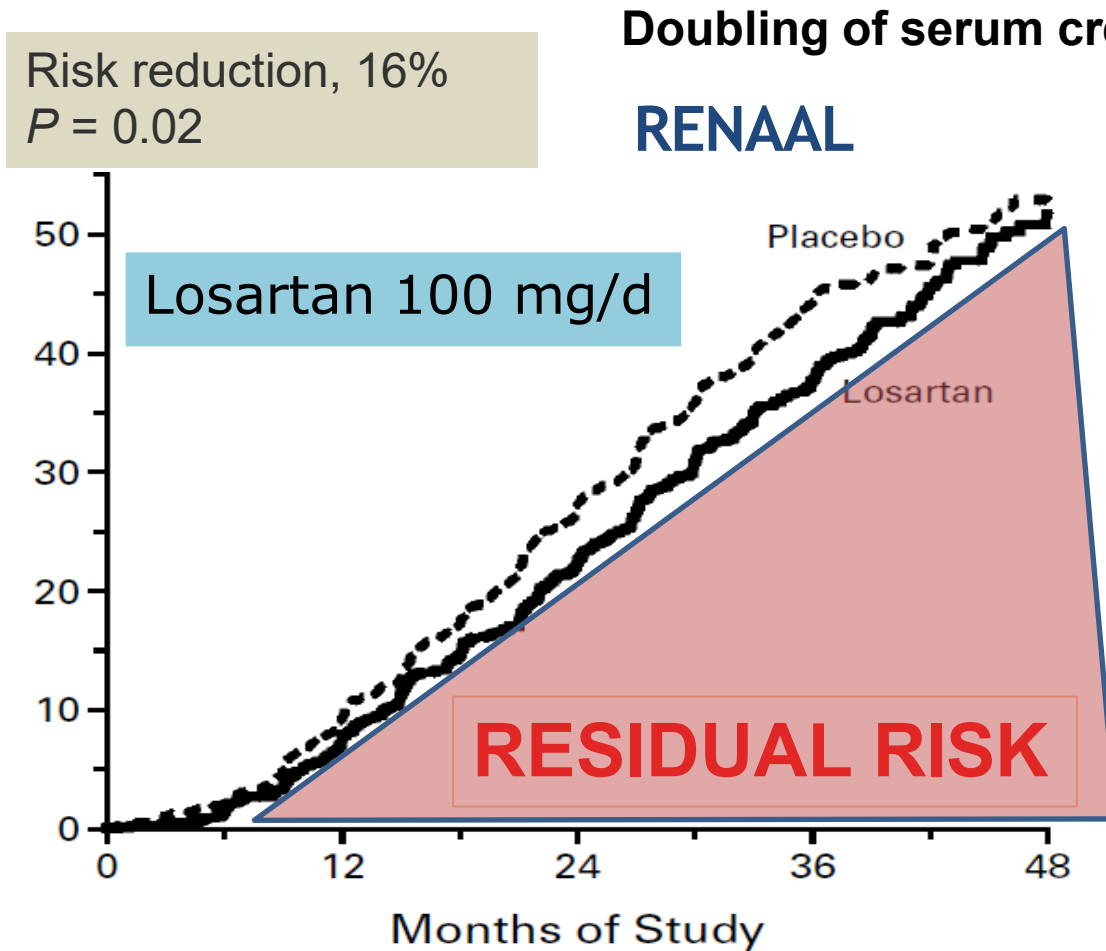


RIACE (Penno et al., 2018) [44] @						
All-cause death						
	<i>eGFR</i> ≥90	<i>eGFR</i> 75–89	<i>eGFR</i> 60–74	<i>eGFR</i> 45–59	<i>eGFR</i> 30–44	<i>eGFR</i> <30
<i>UACR</i> <10	1.00 (ref.)	0.80 (0.67–0.96)	1.10 (0.83–1.12)	1.32 (1.97–1.62)	1.85 (1.40–2.44)	1.61 (0.88–2.97)
<i>UACR</i> 10–29	0.94 (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)
<i>UACR</i> 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)
<i>UACR</i> ≥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] \$						
	<i>Alb</i> – <i>eGFR</i> –	<i>Alb</i> + <i>eGFR</i> –	<i>Alb</i> – <i>eGFR</i> +	<i>Alb</i> + <i>eGFR</i> +		
<i>CVD</i>	1.00 (reference)	1.75 (1.32–2.34)	1.06 (0.63–1.79)	2.30 (1.57–3.39)		
<i>Death or</i> <i>CVD</i>	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] °						
	<i>Alb</i> – <i>GFR</i> –	<i>Alb</i> + <i>GFR</i> –	<i>Alb</i> – <i>GFR</i> +	<i>Alb</i> + <i>GFR</i> +		
<i>All-cause</i> <i>mortality</i>	1.00 (reference)	2.00 (1.52–2.63)	1.59 (1.04–2.44)	3.26 (2.43–4.38)		
<i>CVD</i>	1.00 (reference)	1.19 (1.02–1.40)	1.14 (0.88–1.48)	1.47 (1.23–1.76)		
<i>Hospitalization</i> <i>for HF</i>	1.00 (reference)	3.14 (2.09–4.73)	3.08 (1.82–5.21)	5.50 (3.63–8.34)		

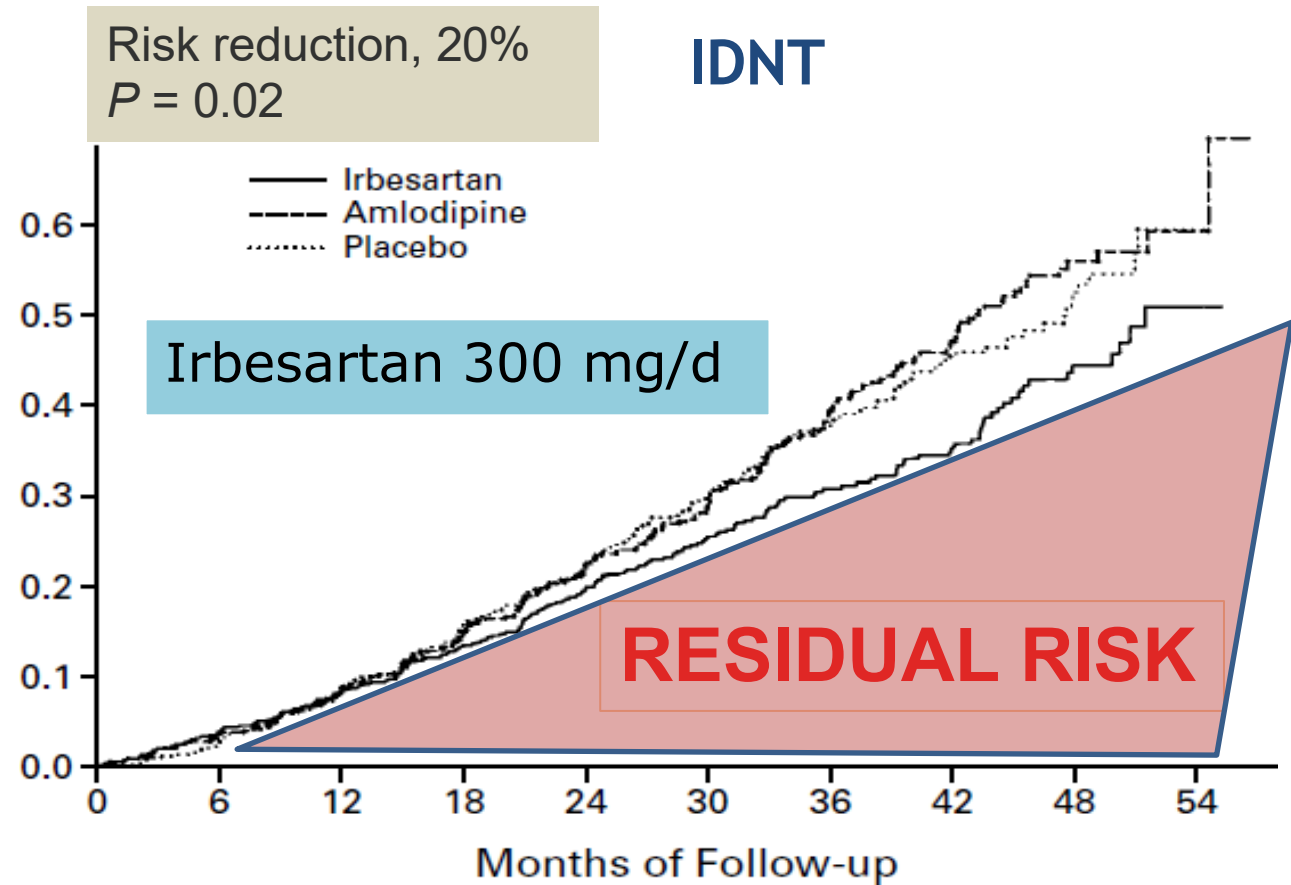
Historical Perspective on Slowing CKD progression associated with Type 2 diabetes



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



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



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

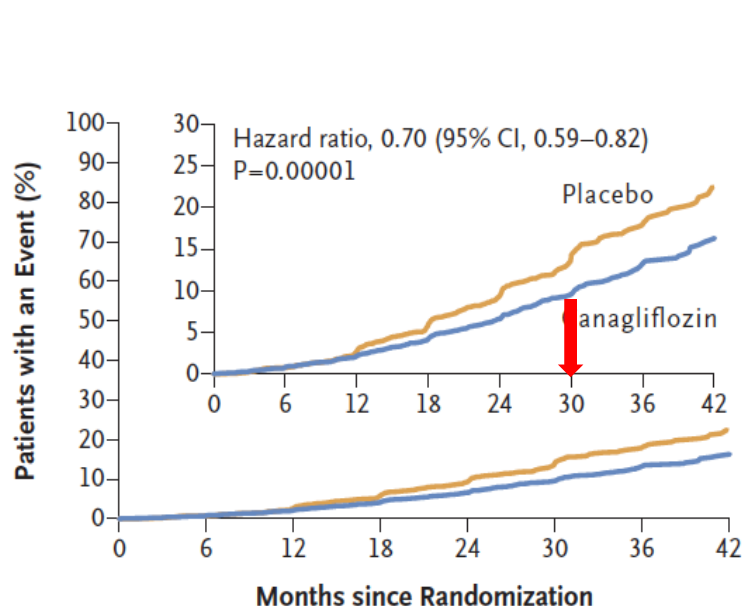
Landmark Studies on Glucose Control

- **1987, DCCT:** reduction of progression to moderately increased albuminuria 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

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

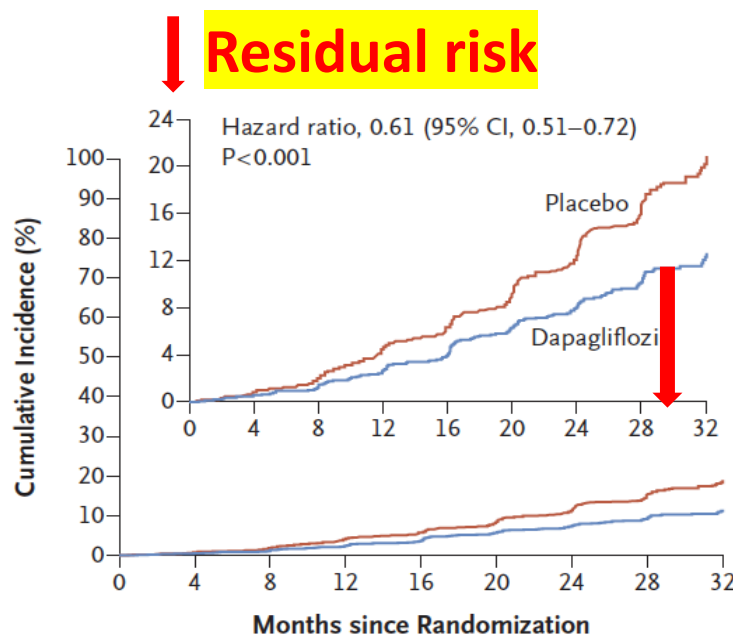
Primary outcomes: Substantial eGFR decline (40%, 50%, 57%), kidney failure, or death due to kidney or cardiovascular causes



CREDENCE

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

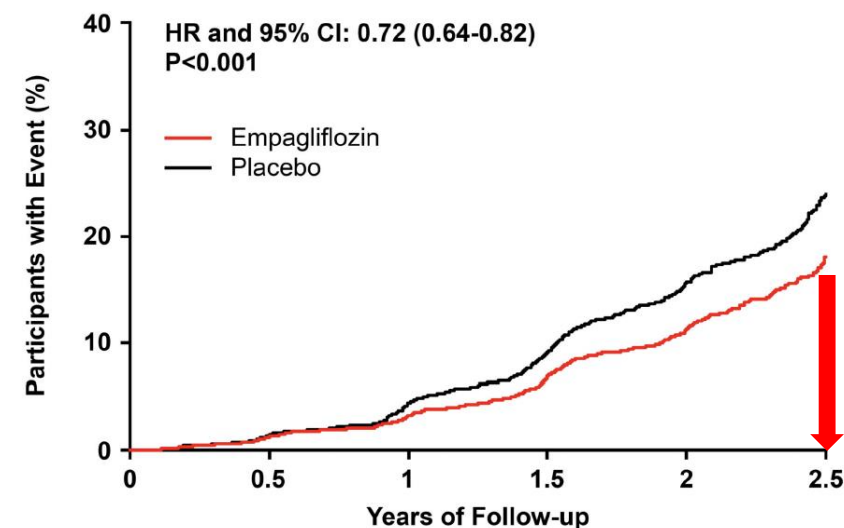
Perkovic V et al. *N Engl J Med.* 2019;380:2295-2306



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

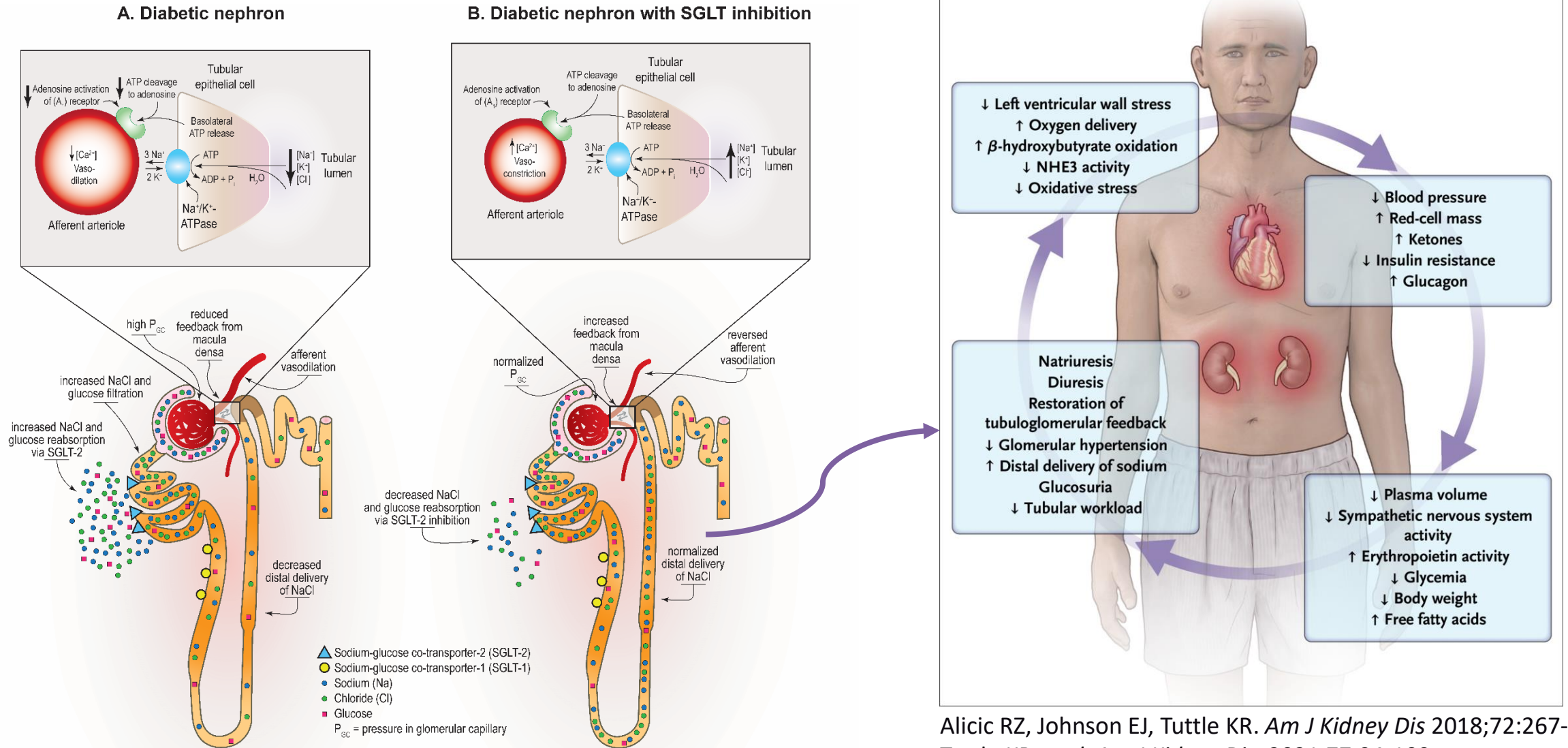


EMPA-KIDNEY

Adults with or without type 2 diabetes, eGFR ≥ 45 to <90 mL/min/1.73 m² and UACR ≥ 200 mg/g or ≥ 20 to <45 mL/min/1.73 m² 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 2026 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 $20 \text{ ml/min per } 1.73 \text{ m}^2$, 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):

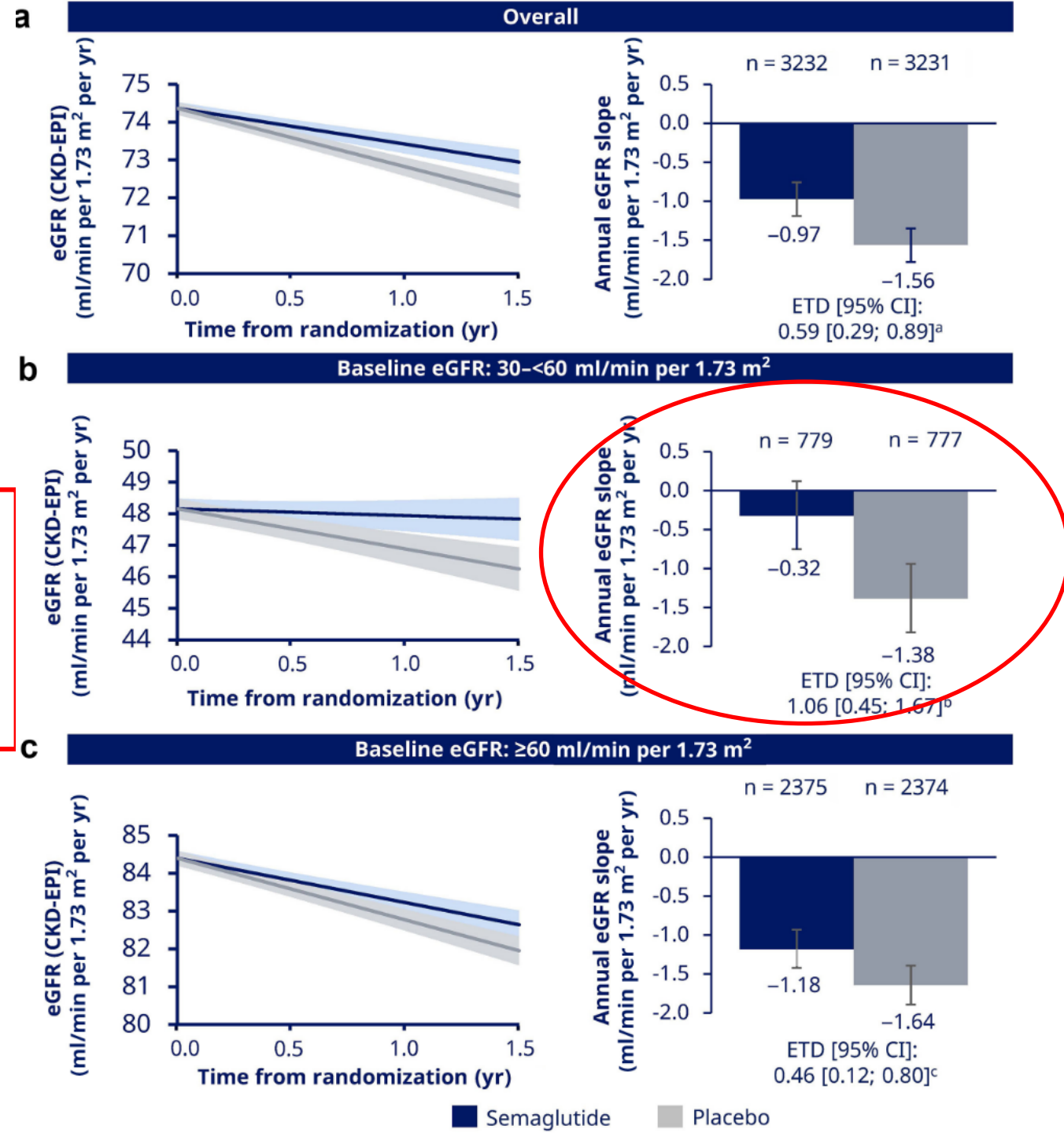
- eGFR $\geq 20 \text{ ml/min per } 1.73 \text{ m}^2$ with urine ACR $\geq 200 \text{ mg/g}$ ($\geq 20 \text{ mg/mmol}$), or
- heart failure, irrespective of level of albuminuria.

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 $45 \text{ ml/min per } 1.73 \text{ m}^2$ with urine ACR $< 200 \text{ mg/g}$ ($< 20 \text{ mg/mmol}$) with an SGLT2i (2B).

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

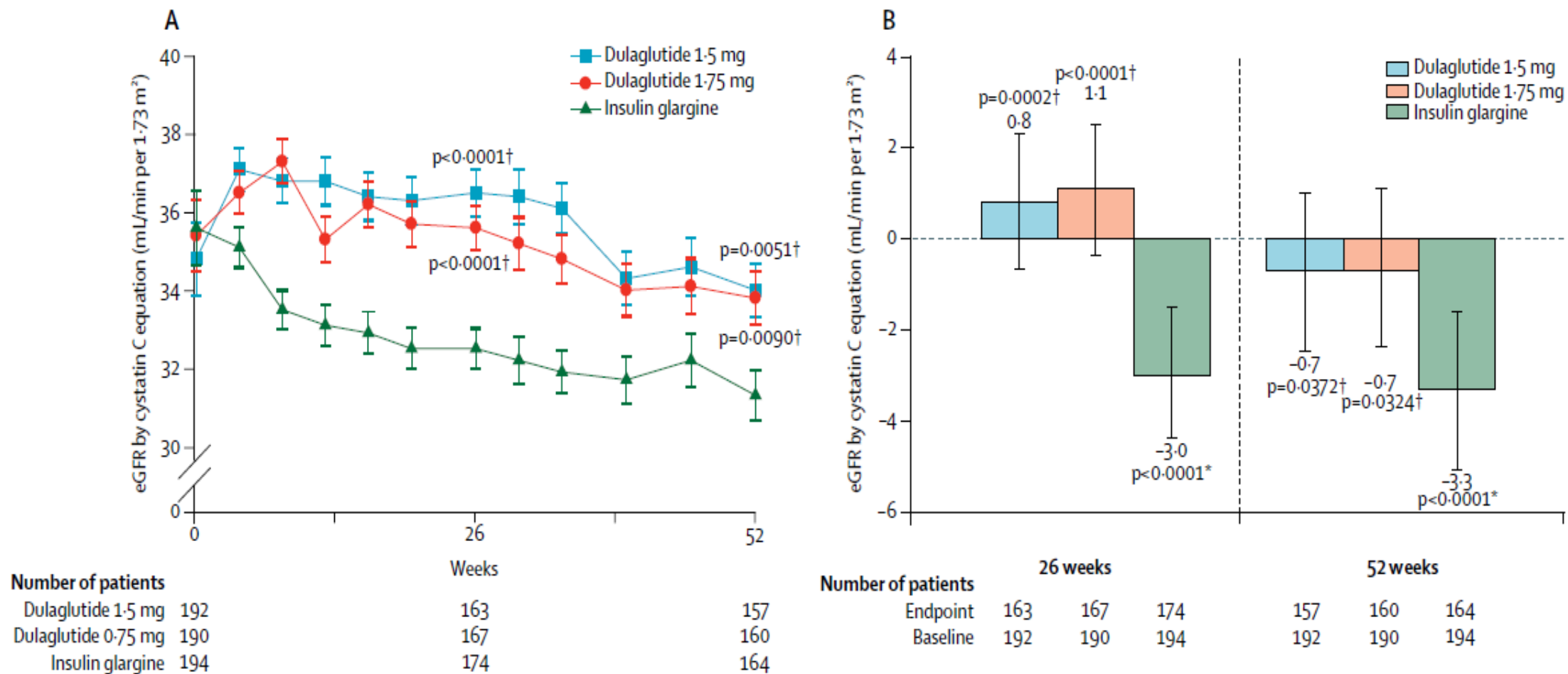
eGFR slope with estimated treatment difference (ETD) >0.75 mL/min/1.73m² per year predicts significantly lower risk of kidney failure versus placebo



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



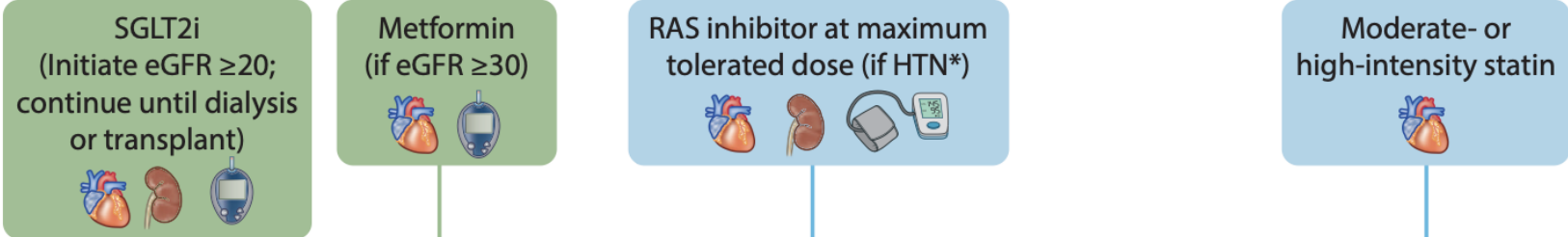


Lifestyle



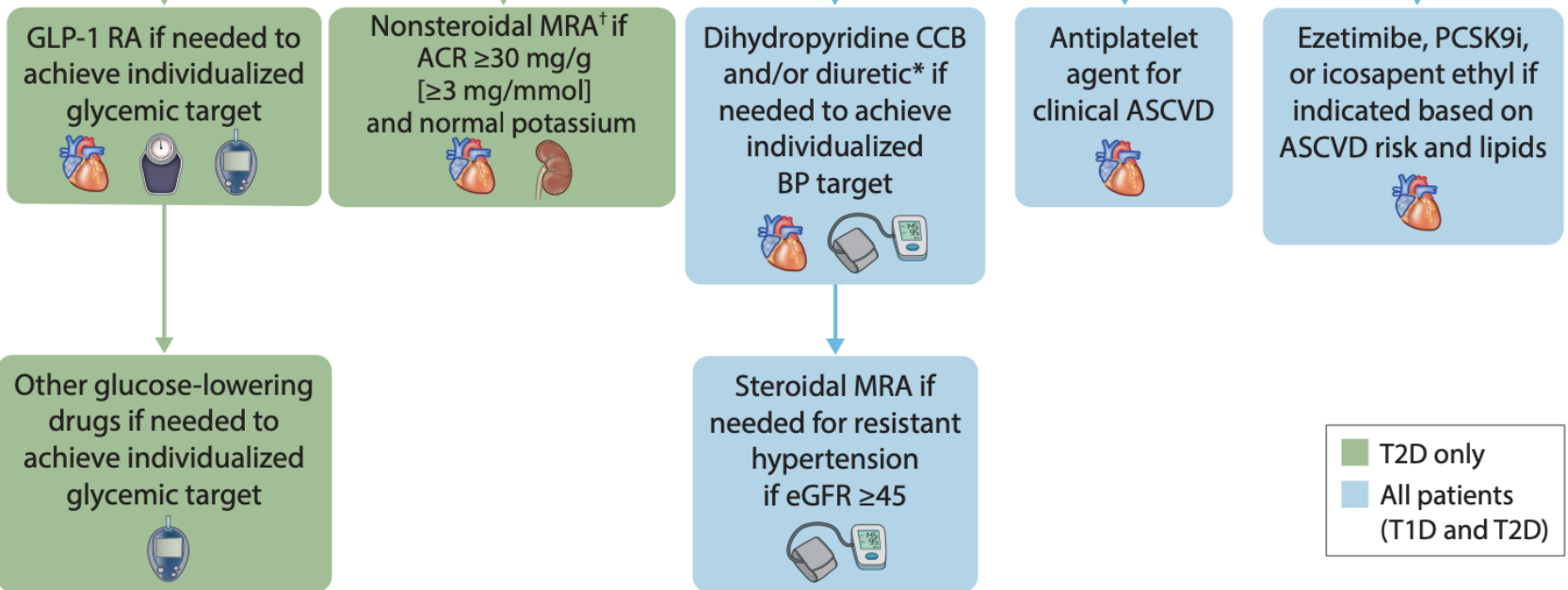
Protein 0.6-0.8g/kg/day

First-line drug therapy



Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids

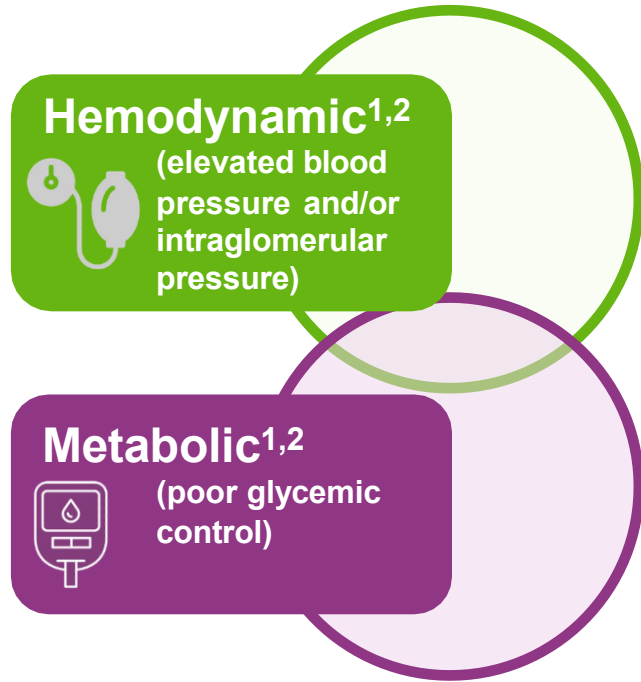
Additional risk-based therapy



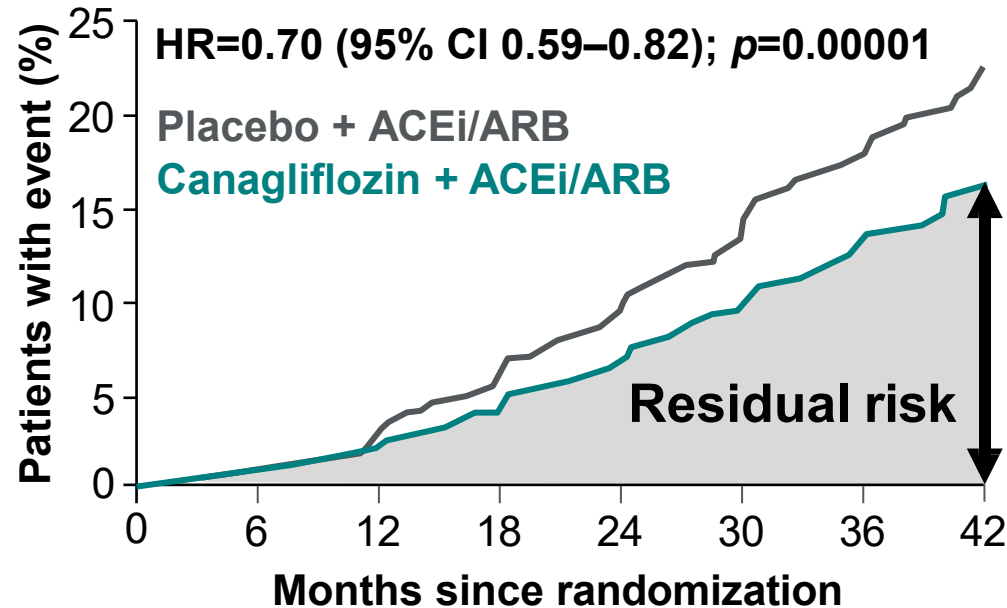
■ T2D only
■ All patients (T1D and T2D)

Adding NS-MRA rationale

High residual risk of CKD progression with current therapies



CREDENCE³ 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	+++	++	+

The FIDELITY¹ prespecified pooled analysis of FIDELIO-DKD² and FIGARO-DKD³ showed significant risk reductions in CV and kidney outcomes with finerenone



FIDELITY Key eligibility outcomes

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

- ✗ Symptomatic HFrEF[‡]

GFR (ml/min/1.73 m ²)	UACR (mg/g)		
	0–29	30–299	≥300– ≤5000
≥90			
60–89			
45–59			
30–44			
15–29			

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)

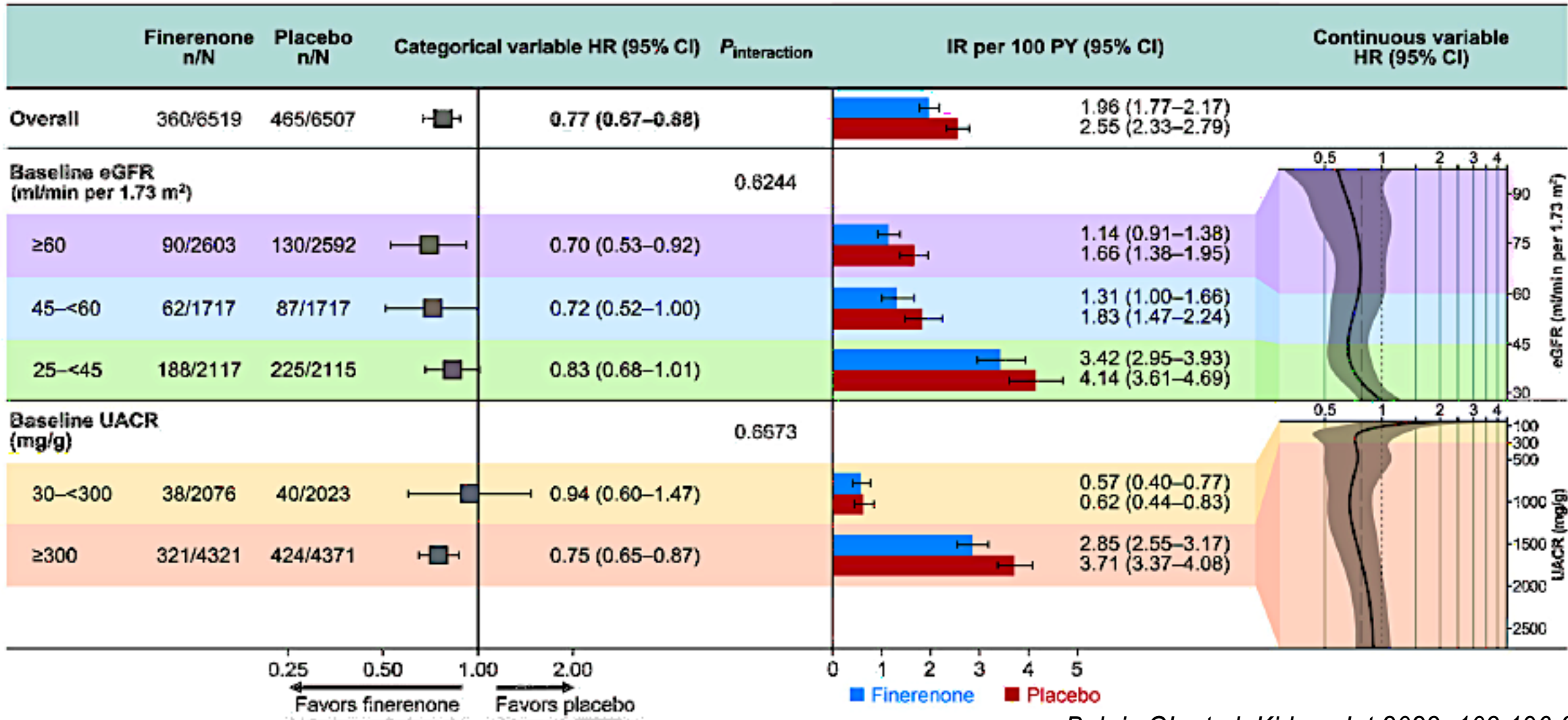
23%

*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;

⁴ 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

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



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-1 RAs 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 $\geq 50\%$ 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

Methods

Participants:

- Adults

• eGFR ≥ 30 ml/min/1.73 m² and
• A1cR >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 $\geq 50\%$ reduction in eGFR; or
- Death from kidney or CV causes

N=35

0.25 mg

0.5 mg

1.0 mg semaglutide s.c. OW +
T2D and CKD standard-of-care

placebo s.c. OW +
standard-of-care

W-3

Screening
(up to 3)

HR
0.76



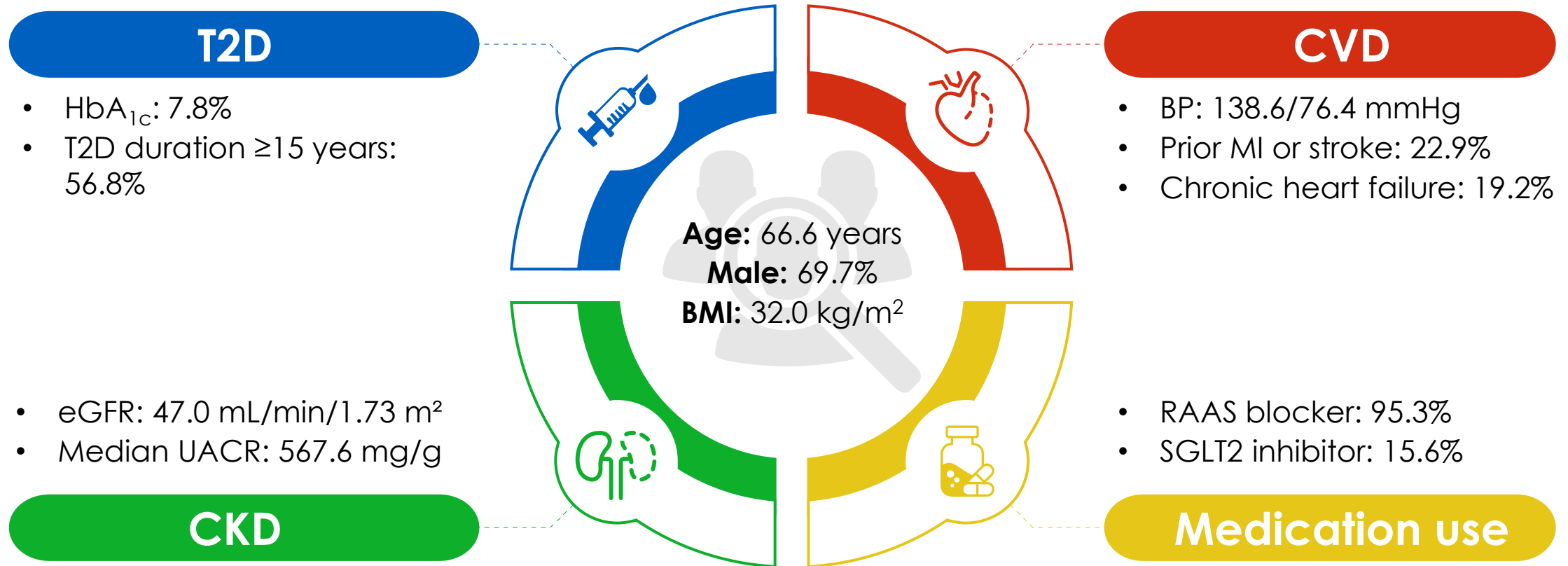
EOT

Period

Follow-up
(5 weeks)

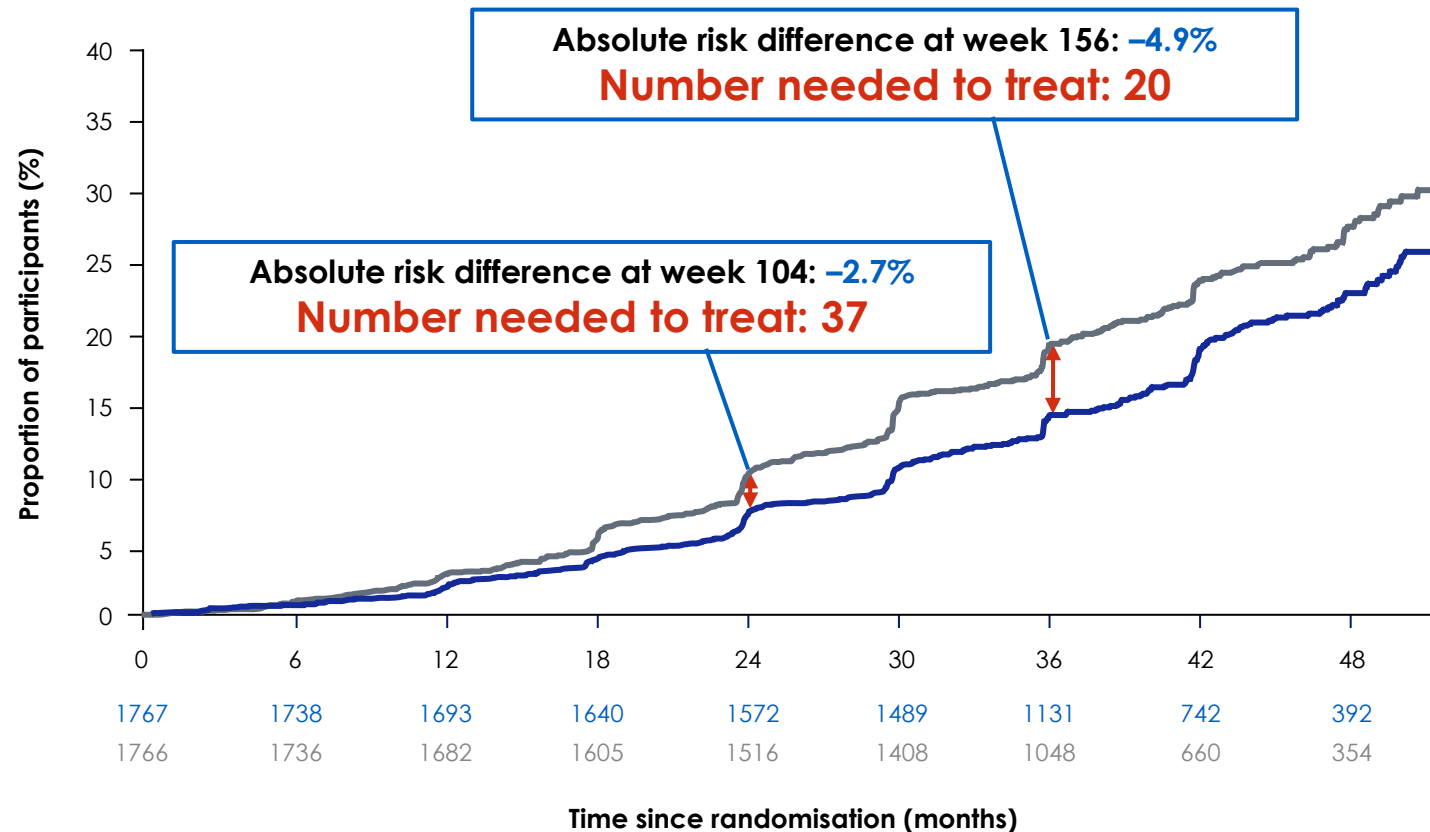
Duration of approximately 5 years

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



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

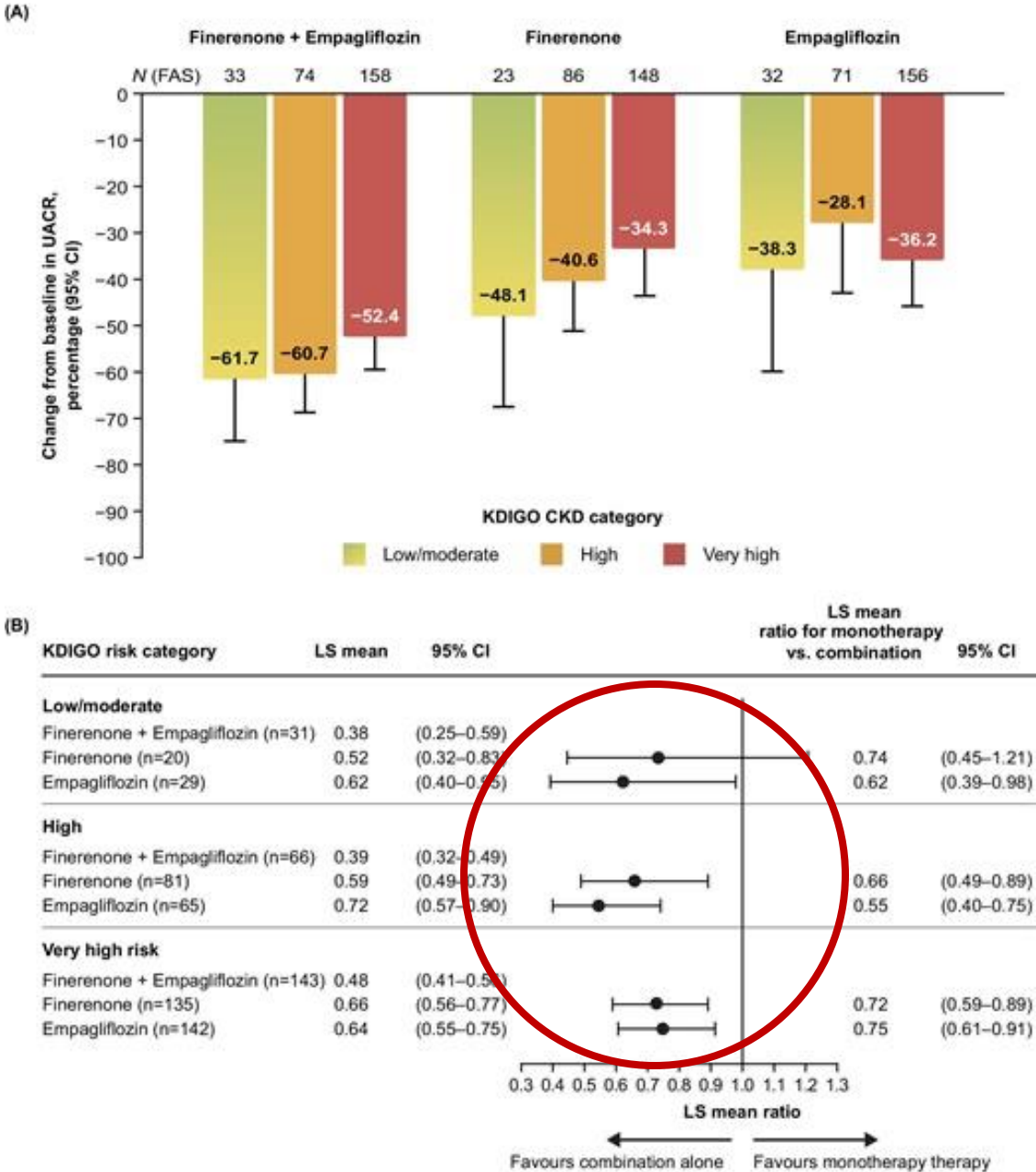
CONFIDENCE Trial

781 participants

- 11.3% low/moderate
- 29.6% high
- 59.2% very high

GFR categories (mL/min/1.73 m²)

		Albuminuria categories (mg albumin/g creatinine)		
Data presented as n (%)		A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
		<30	30 to 300	>300
G1	≥90	0 (0)	7 (0.9)	21 (2.6)
G2	60 to <90	1 (0.1)	80 (10.0)	164 (20.5)
G3a	45 to <60	0 (0)	46 (5.8)	181 (22.6)
G3b	30 to <45	0 (0)	65 (8.1)	191 (23.9)
G4	15 to <30	1 (0.1)	5 (0.6)	19 (2.4)
G5	<15	—	—	—



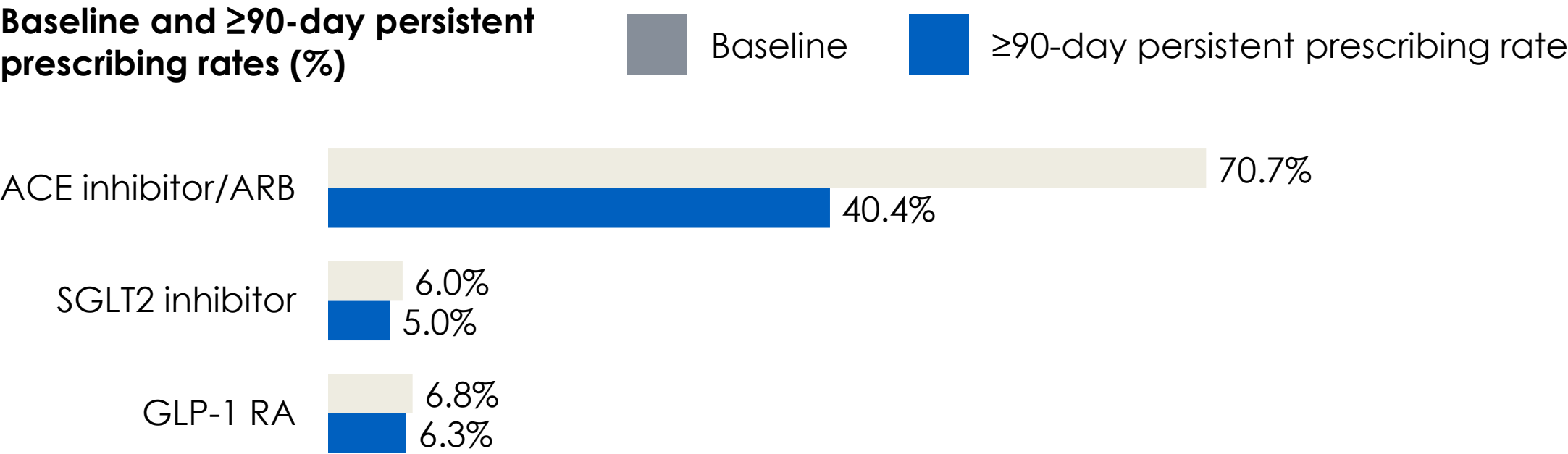
Albuminuria/Proteinuria Monitoring is Low in CKD

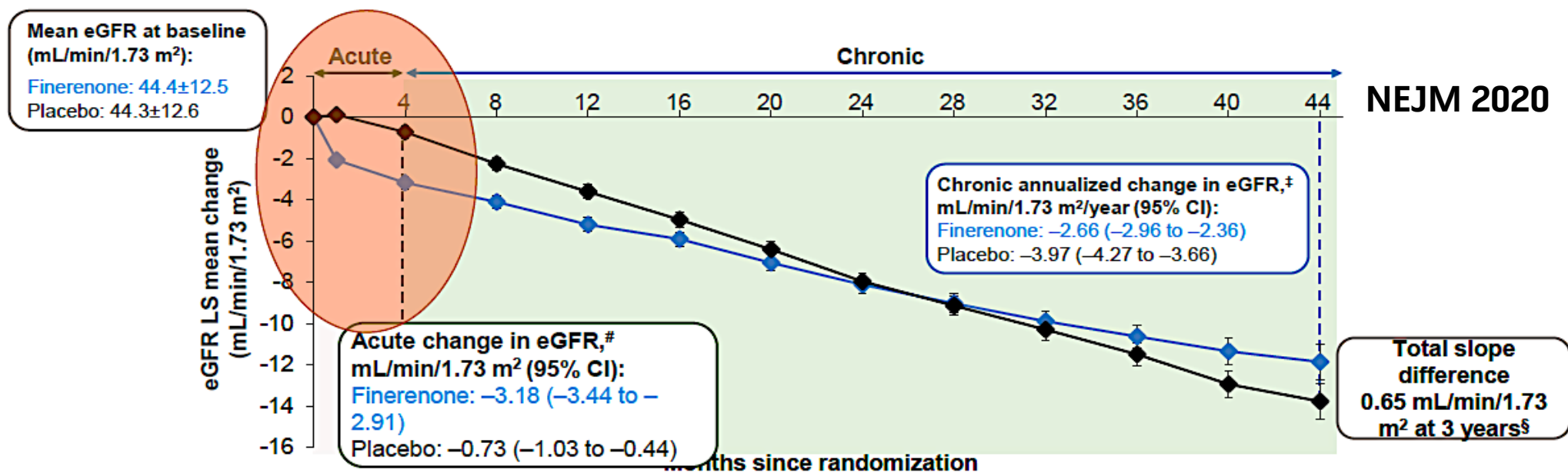
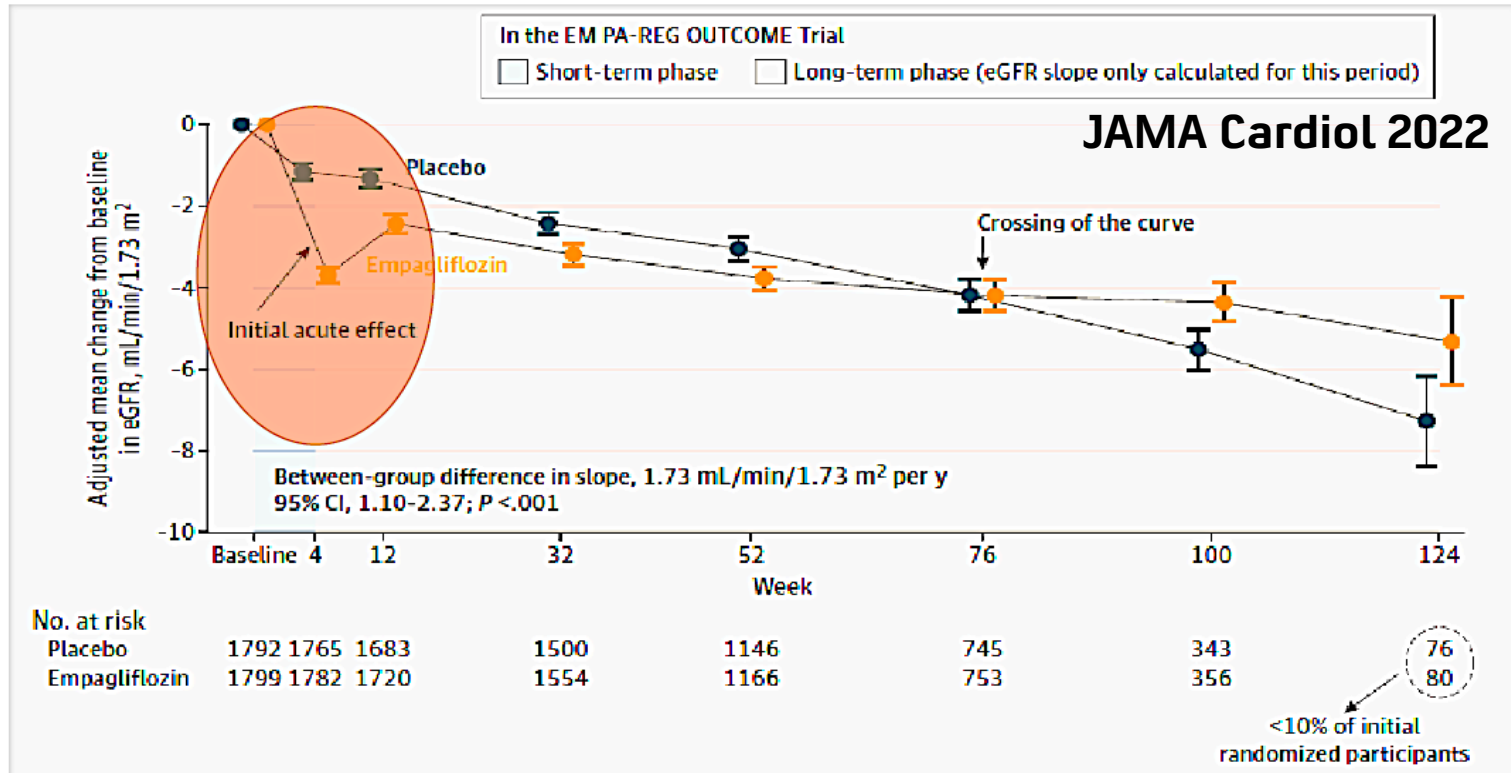
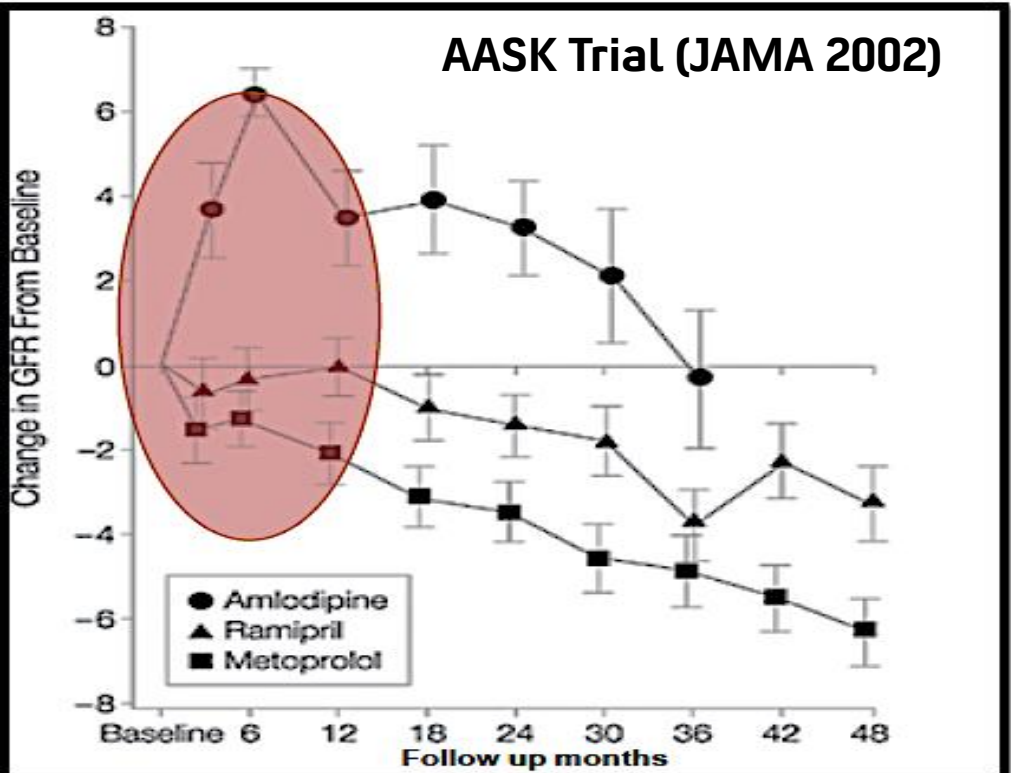
CURE-CKD 2006-2017 (N=606,064)

	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]

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)





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

PILLAR 3: Finerenone

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

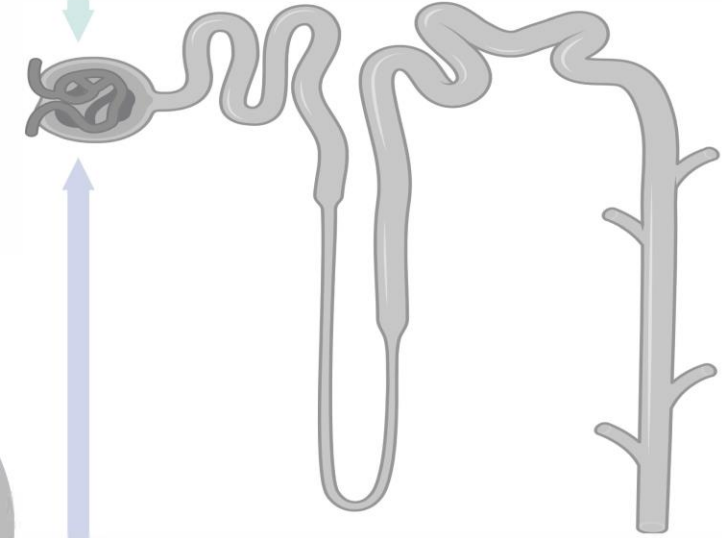
PILLAR 2: SGLT2 inhibitors

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

**Metabolic
Dysregulation**

**Hemodynamic
Perturbations**

Inflammation



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!

References

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