Medikamentöse Verhinderung der Progression von Nieren-erkrankungen: Wege und Irrwege

Johannes Mann

- KfH Nierenzentrum, München-Schwabing
- PHRI, McMaster University, Hamilton, ON, Canada
- Friedrich Alexander Universität Erlangen-Nürnberg

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I report the following potential duality/dualities of interest in the field covered by my lecture:

- **Author:** UpToDate Inc., KDIGO
- **Consultant:** Bayer, Novo Nordisk
- **Employee:** KfH
- **Research Support:** European Union, Canadian Institutes of Health Research, Iqvia, Cytel, WCG, Parexel, Bayer, Novo Nordisk, Sanofi
- **Speaker's Bureau:** AstraZeneca, Bayer, Hexal, Novo Nordisk

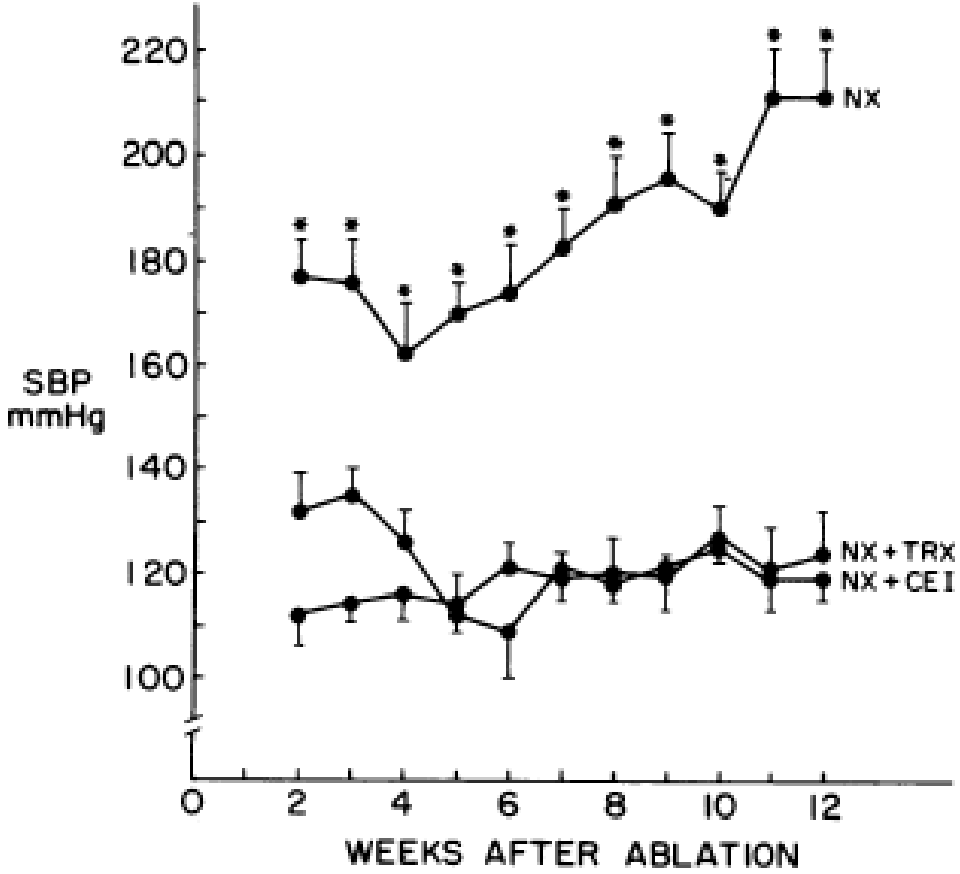
Verhinderung des Nierenversagens: Medikamentöse Wege und Irrwege

Johannes Mann, KfH Nierenzentrum München-Schwabing und
PHRI, McMaster University, Hamilton, ON, Canada

Wege: RAS Blockade, SGLT2-Hemmer, Aldosteron-Blocker, GLP1-RA, Polypille, (Endothelin-Blocker) Bikarbonat?

Irrwege: Doppelte RAS Blockade, Statine, Bardoxolon, Soludexide, DPP4-Hemmer, Vitamin B, D, E, Epoetin, TGF-Hemmer

Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat.
S Anderson, H G Rennke. B M Brenner J Clin Invest. 1986:77:1993-2000



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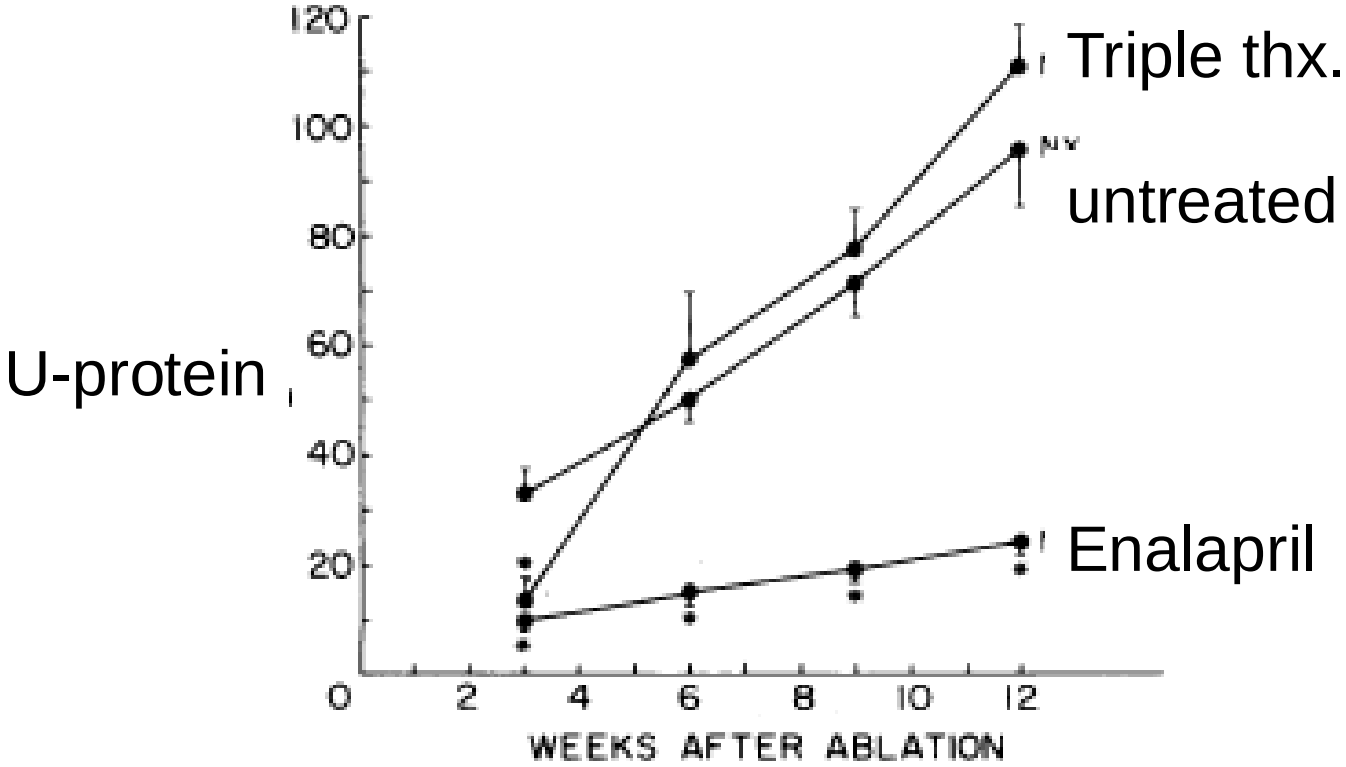

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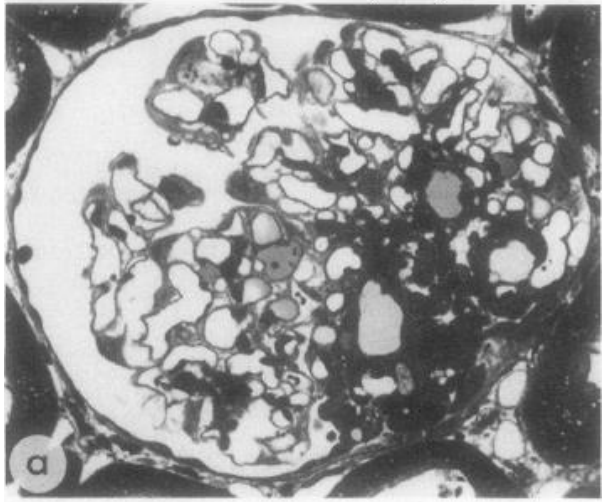
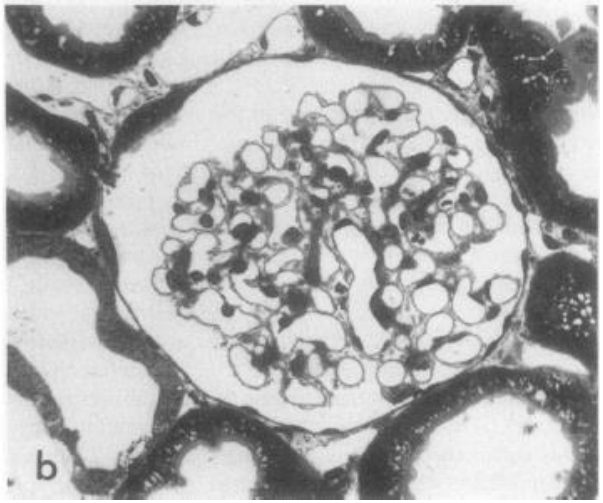
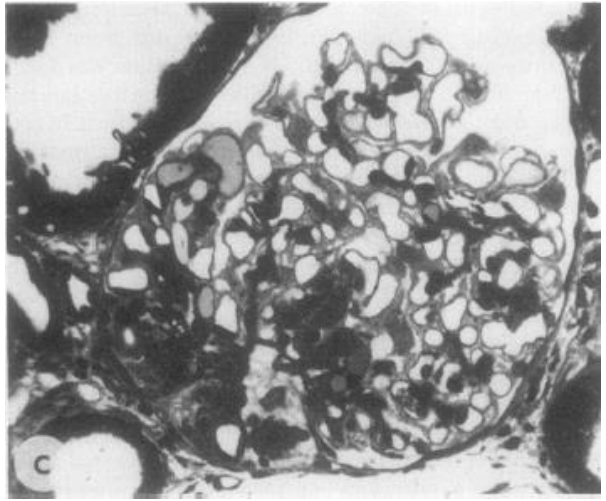






Untreated Enalapril Triple therapy

Mann & Ritz, 1987
Lancet 1987;330:622

PRESERVATION OF KIDNEY FUNCTION BY USE OF CONVERTING-ENZYME INHIBITORS FOR CONTROL OF HYPERTENSION

	ACE inhibitors (n = 39)	Alternative anti-hypertensive agents (n = 41)
Median blood pressure (mm Hg) at presentation		
Systolic	184 (120–250)	170 (130–230)
Diastolic	116 (80–175)	103 (65–140)
Blood pressure after 12 mo (mm Hg)		
Systolic	155 (110–235)	150 (120–200)
Diastolic	98 (70–150)	89 (70–120)
Serum creatinine (mg/dl) at presentation	2·33 (1·5–5·5)	2·39 (1·5–6·0)
Serum creatnine (mg/dl) after:		
1 mo	2·70 (1·5–6·6)	2·55 (1·5–7·6)
3 mo	2·61 (1·5–7·2)	2·69 (1·3–8·8)
6 mo	2·58 (1·5–9·4)	2·96 (1·3–9·6)
12 mo	2·65 (1·5–6·1)	3·45 (1·3–12·9)

ACE-inhibition in non-diabetic chronic kidney disease: kidney failure or doubling of serum-creatinine

- AIPRI –Study
- Maschio, Alberti, Mann .... Ritz
- NEJM 1996

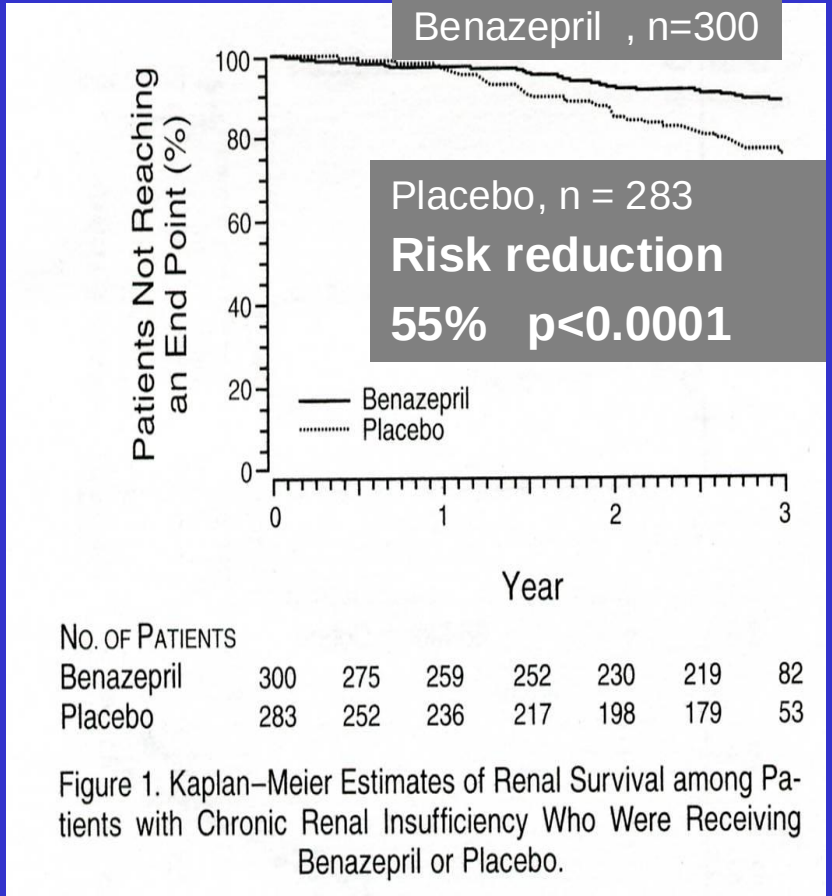
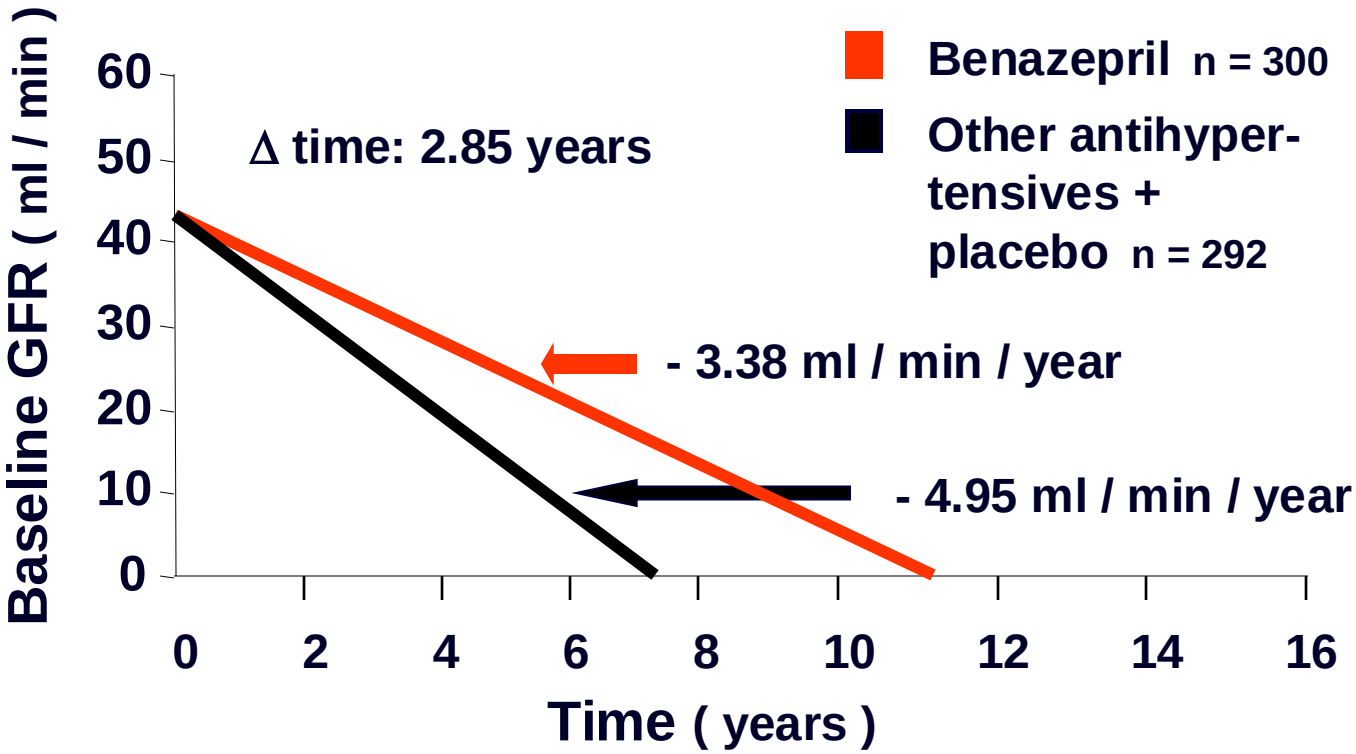


Figure 1. Kaplan–Meier Estimates of Renal Survival among Patients with Chronic Renal Insufficiency Who Were Receiving Benazepril or Placebo.

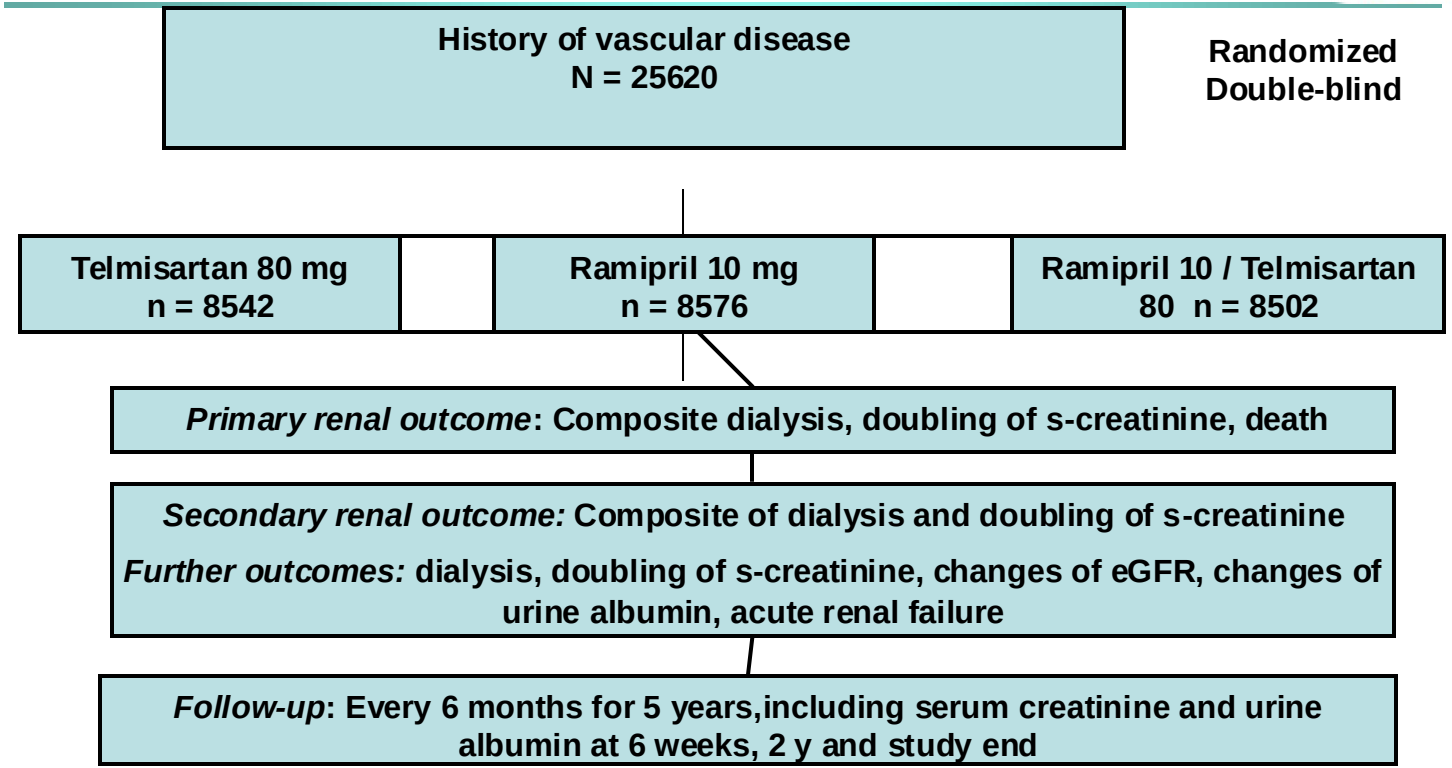
AIPRI study: Time to ESRD in non-diabetic CKD (Uprot 1.4 g/d)



Maschio, Alberti, Mann … Ritz et al, NEJM 1996

ONTARGET: Design

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE



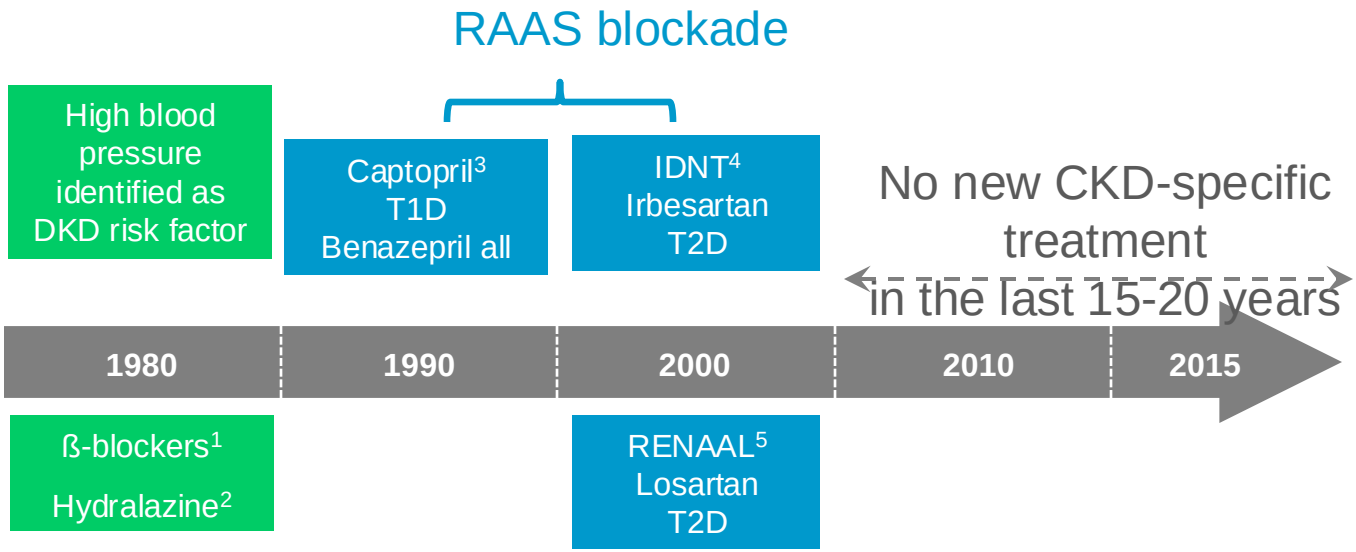
Ontarget Investigators *N Engl J Med. 2008;358: 1547-59*, *Lancet 2008;372:547-53*

ONTARGET: Renal side effects of combining ACEI and ARB

	Ramipril *(n = 8,576)*	Telmisartan *(n = 8,542)*	Combined *(n = 8,502)*	P *(combined vs ramipril)*
Any renal Impairment	871	906	1,148	<0.001
ESRD	33	31	34	0.85
Acute dialysis	**13**	**20**	**28**	**0.02**
Hyperkalemia	**283**	**281**	**480**	**<0.001**

Mann et al. *Lancet* 367: 547-553, 2008 , N= 25,620, F/U 5 years

No new treatments for progression of (diabetic) kidney disease identified for over 15-20 years



We cannot say we did not try … treating CKD

Dual blockade of RAS: ONTARGET, ALTITUDE, NEPHRON-D, ORIENT

Endothelin blockade: ASCEND, *SONAR*

Statins: CARDS

Vitamin D: PRIMO, VITAL

Vitamin B, E: DIVINE, HOPE, HOPE-2

Antioxidant/-inflammatory: BEACON, Pirfenidon

Epoetin: TREAT

Glycosaminoglycan (Soludexide): SUN-MACRO

Effect of B-Vitamin Therapy on Progression of Diabetic Nephropathy

A Randomized Controlled Trial

JAMA. 2010;303:1603-1609

What was done ?

- 238 Pt. with diabetic nephropathy
- Randomised to Folic acid + Vit B6 + Vit B12 or Placebo

Primary outcome: change of GFR

Secondary outcome: MI, stroke, Revascularisation, death

Effect of B-Vitamin Therapy on Progression of Diabetic Nephropathy

A Randomized Controlled Trial

JAMA 2010;303:1603-10

What was found ?

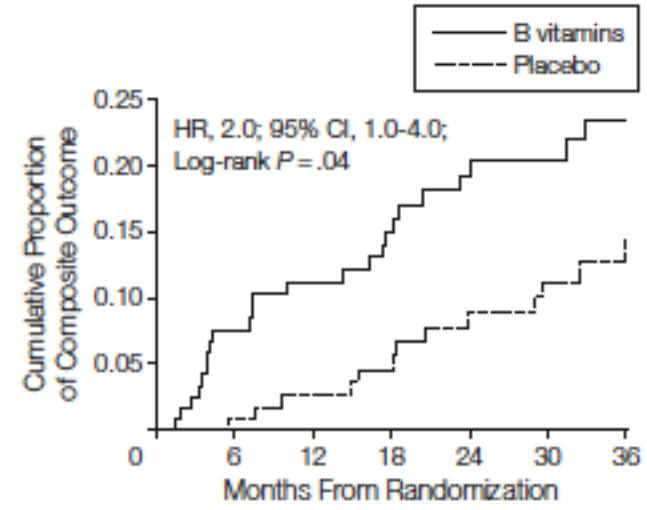
	Placebo	B-Vitamines	
GFR	-4.1 (ml/min/year)	-6.4	(P=0.02)
Mortality	7%	7%	
P-Hcy	+15%	-15%	(P=0.001)

Effect of B-Vitamin Therapy on Progression of Diabetic Nephropathy

A Randomized Controlled Trial

JAMA 2010;303:1603-10

Figure 2. Cumulative Proportion of Myocardial Infarction, Stroke, Revascularization, and All-Cause Mortality



No. at risk

B vitamins	119	107	96	87	70	59	45
Placebo	119	117	105	93	81	72	53

We cannot say we did not try … treating CKD

Dual blockade of RAS: ONTARGET, ALTITUDE, NEPHRON-D, ORIENT

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Epoetin: TREAT

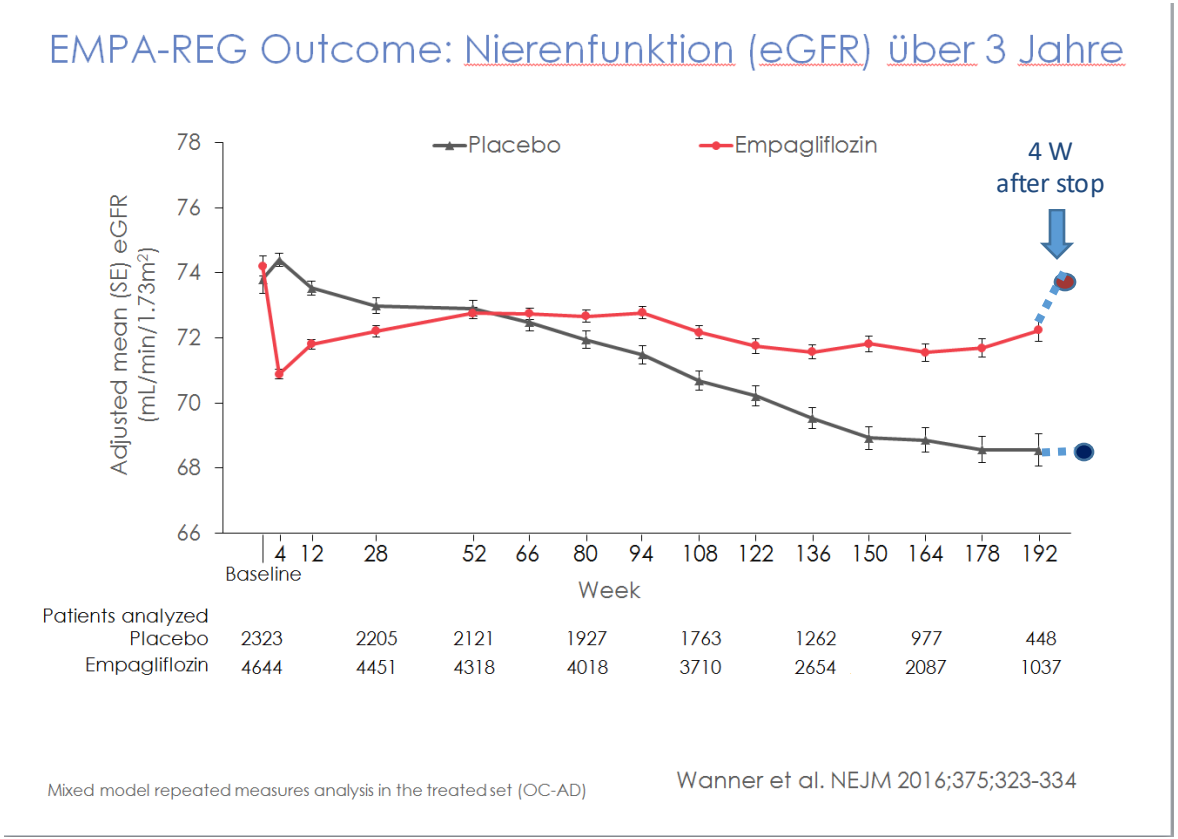
Glycosaminoglycan (Soludexide): SUN-MACRO

Why SGLT2i in people with CKD with/without T2D ?

3 trials: CREDENCE , DAPA-CKD, EMPA-KIDNEY

- Less CV outcomes (MACE), particularly less heart failure
- Less mortality outcomes
- Less kidney failure, dialysis, loss of GFR and lower UACR
- Consistent data for Cana-, Dapa- & Empagliflozin

EMPA_REG: eGFR before, on-drug, & off-drug



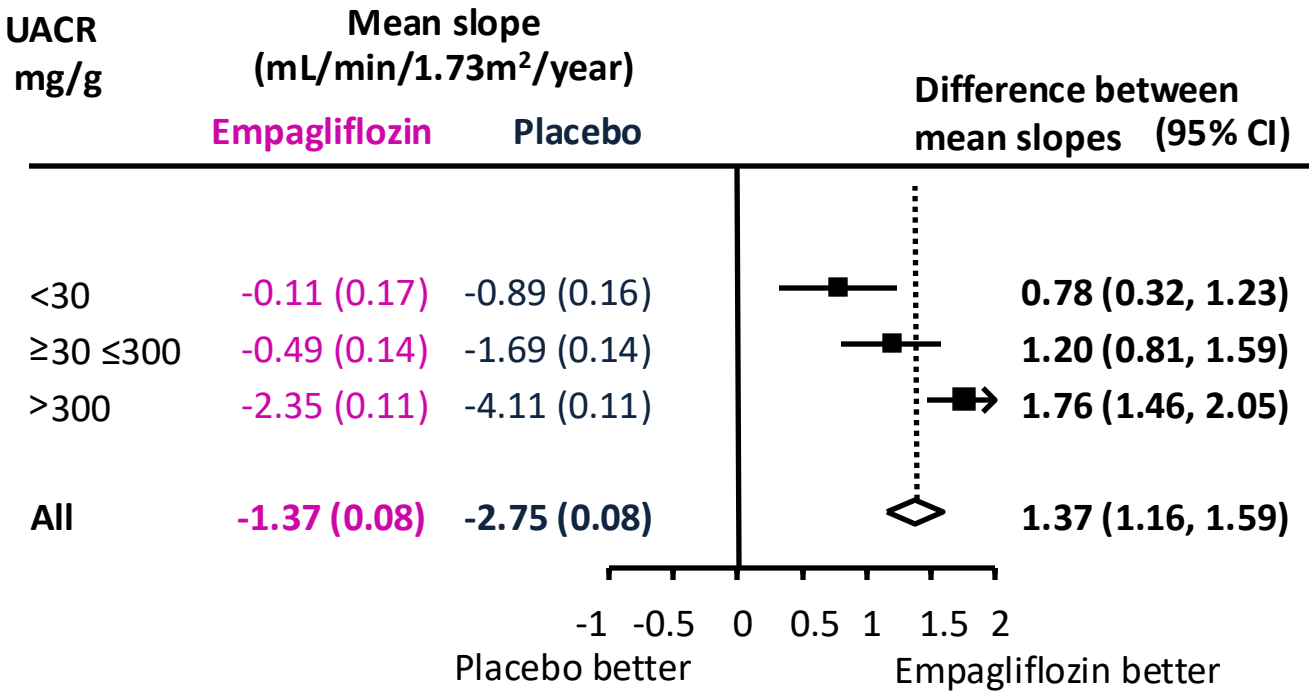
EMPA_REG Wanner C et al. N Engl J Med 2016;375:323-34

CREDENCE & DAPA_CKD & EMPA-KIDNEY (N= 4401, 4304, 6609 F/U 2 - 2.5y)

	Cana vs Plac	Dapa vs Plac	Empa vs Plac
• Dialysis	116 vs 165	109 vs 161	108 vs 158
• Death	168 vs 201	101 vs 146	148 vs 167
• Heart failure	89 vs 141	100 vs 138	72 vs 83

Perkovic et al., NEJM 2019:381:1442 Heerspink et al., NEJM 2020:383:1436 Empa-K Group NEJM 2023;388:117

EMPA KIDNEY: Chronische eGFR slopes gemäß UACR



NEJM 2023;388:117-127

Prespecified exploratory analyses

SGLT-2i: additional effects

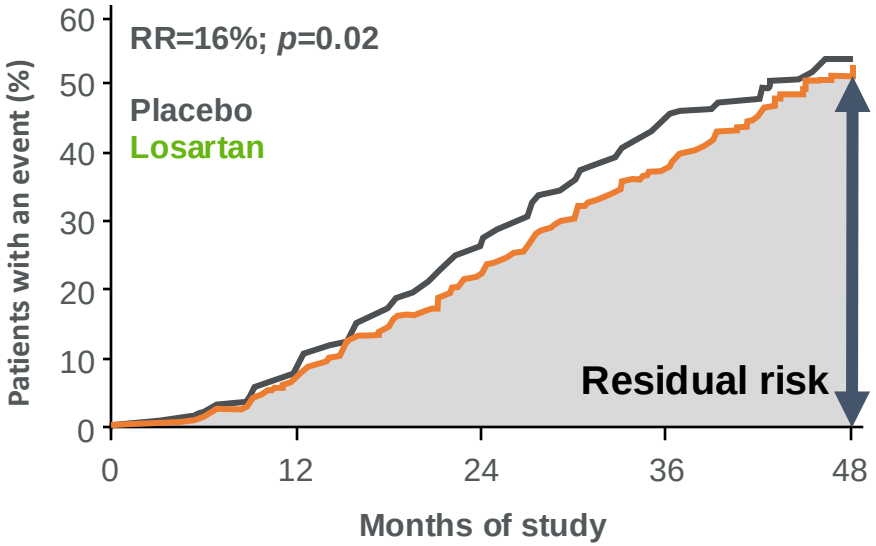
Improvements:

- Less hyper-K in CKD by 20-40%
- Less hypo-Na in SIADH
- Decrease in AKI incidence
- Hemoglobin increase (renal anemia) by 0.3-1 g/dl
- Decrease in serum uric acid & gout incidence
- Less edema

More: Fungal vaginitis and balanitis

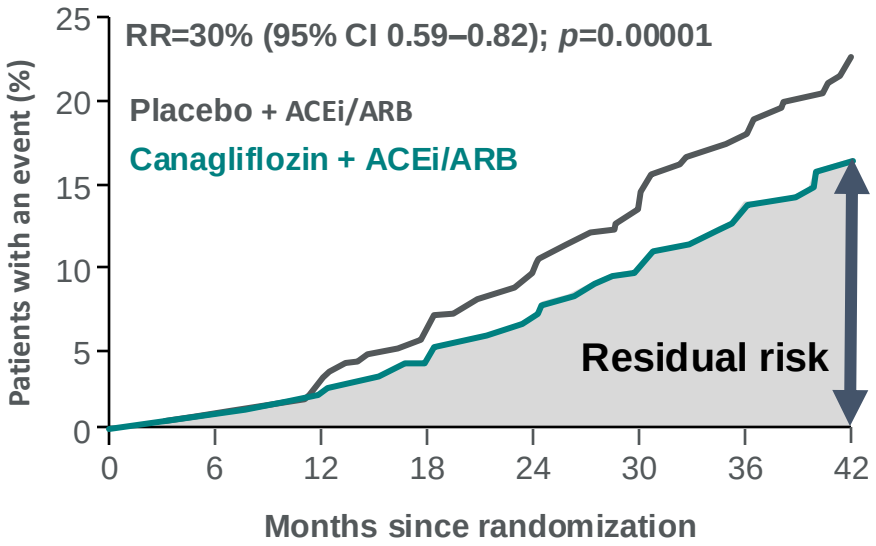
T2DM: ARB or ACE/ARB + SGLT2i

RENAAL
Composite of 2xSCr, ESKD or death*



Brenner *et al*. *NEJM* 2001;345:861

CREDENCE
Composite of 2xScr, ESKD or renal or CV death



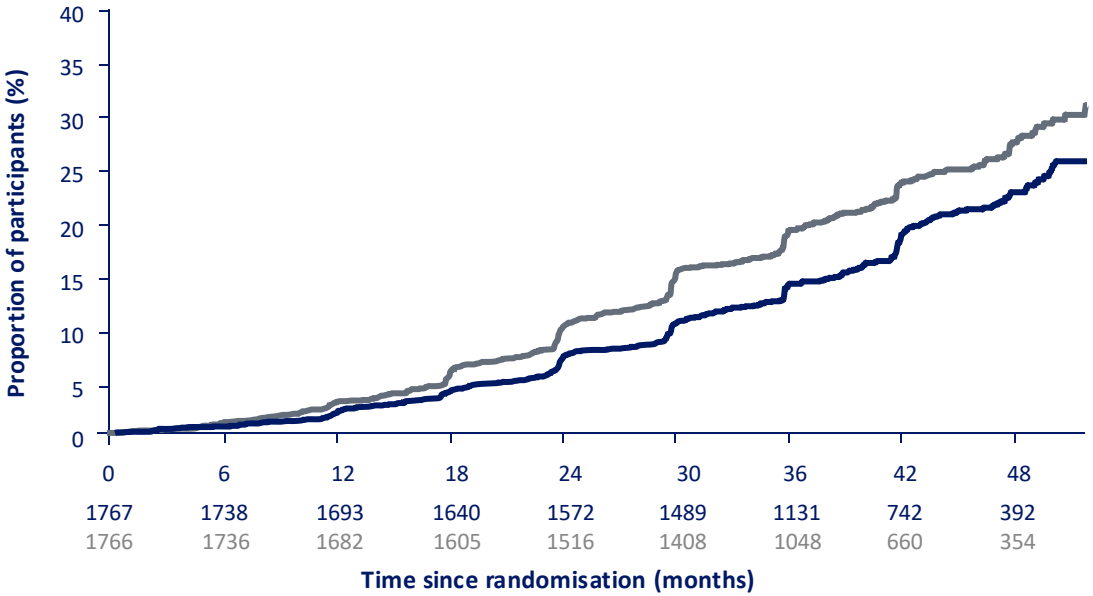
;
Perkovic *et al*. *NEJM* 2019;380:2295

Why GLP-1 Receptor Agonists in T2D with CKD ?

- Less CV outcomes (MACE)
- Less mortality outcomes
- Less kidney failure, loss of GFR, lower UACR

FLOW: Composite kidney outcome in CKD and T2D (N= 3553)

Primary outcome (eGFR reduction ≥50%, EGFR <15ml/min, dialysis or transplantation, renal death, CV death)



Placebo 23.2%
(410/1766)

Semaglutide 18.7%
(331/1767)

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

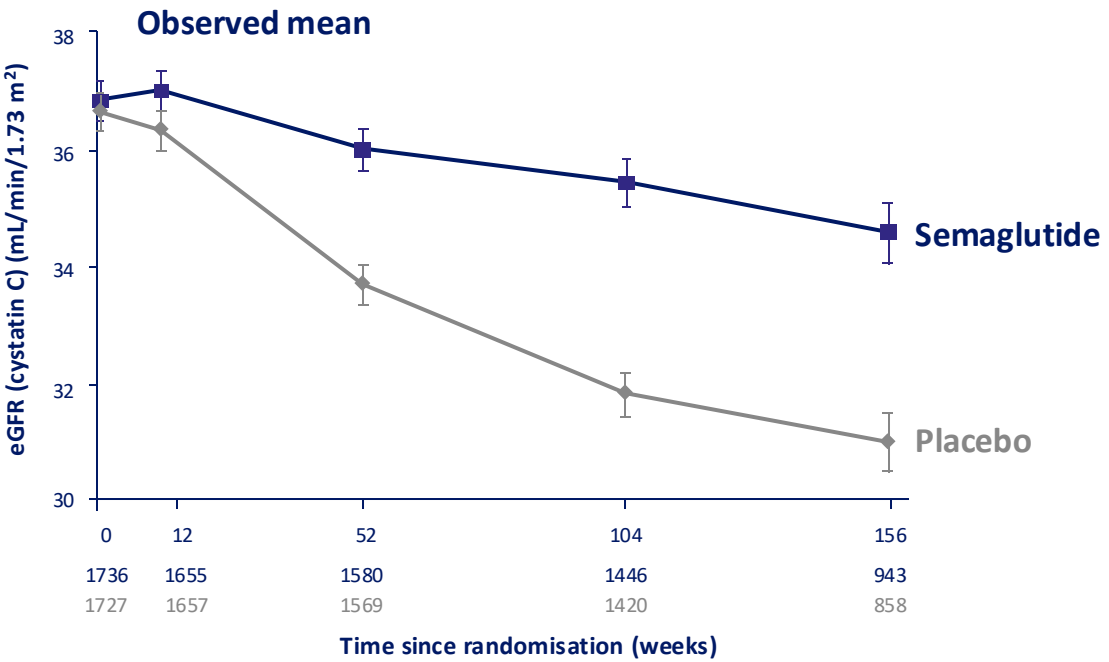
Effects independent of SGLT2-inhibition

FLOW
semaglutide | renal outcomes trial

Full analysis set. Data from the in-trial period. Numbers shown in the lower panels represent the number of participants at risk
Event rates: 5.8 and 7.5 per 100 patient-years of follow-up for participants receiving semaglutide and placebo, respectively
CI, confidence interval; HR, hazard ratio

Perkovic et al., NEJM 2024;391:109-121 & Mann et al Nature Med 2024;30: online

FLOW: Change in eGFR (calculated with cystatin C)



Calculated by cystatin C
ETD at **week 104**
1.70 mL/min/1.73 m2/year
(95% CI 2.63, 4.15)

FLOW semaglutide | renal outcomes trial

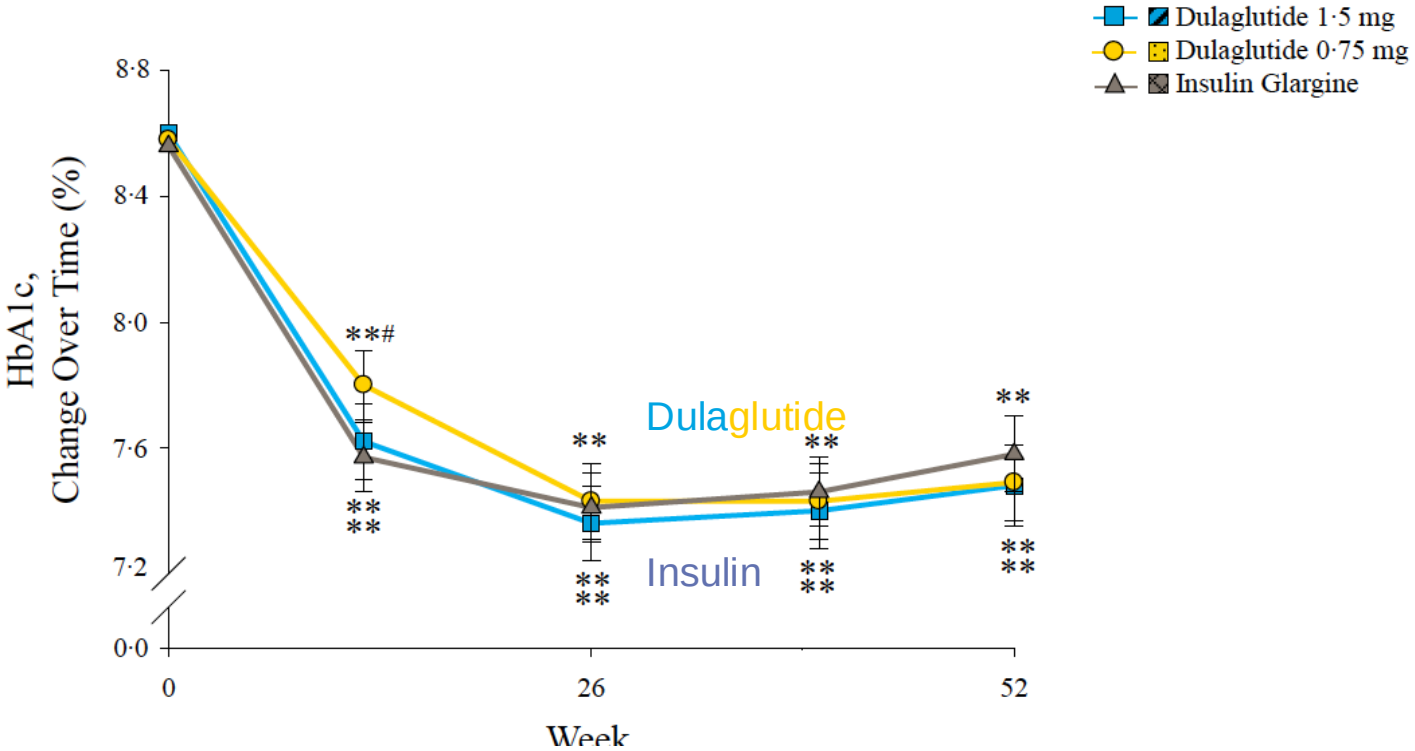
Full analysis set. Data from the in-trial period. Numbers shown in the lower panels represent the number of participants at risk
Error bars indicate ± the standard error
CI, confidence interval; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference

Perkovic et al., NEJM 2024;391:109-121 & Mann et al Nature Med 2024;30: online

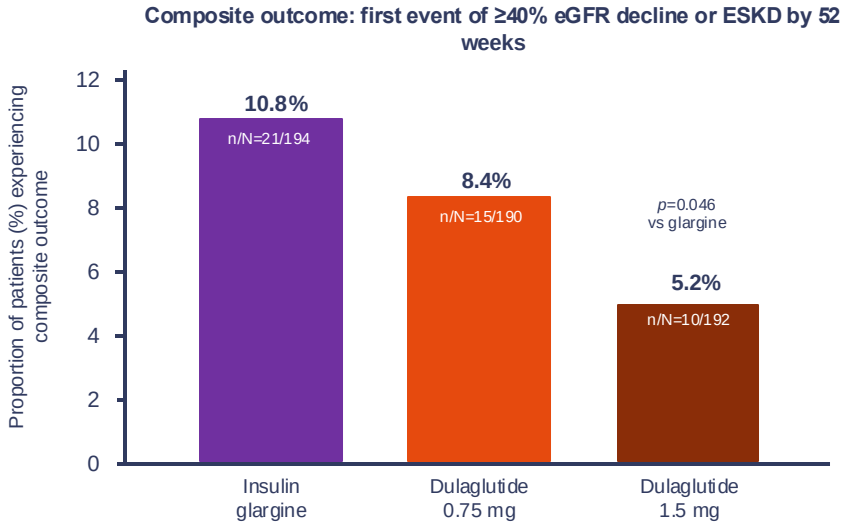
AWARD-7

Tuttle et al., Lancet Diab Endocrin, 2018;6:605

GLP-1 Agonist Dulaglutid (1,5 and 0,75 mg/Week) blunts GFR loss vs Insulin glargine



AWARD 7: ≥40% eGFR decline or ESKD; dulaglutide vs insulin glargine



Tuttle et al., Lancet Diab Endocrin, 2018;6:605

GLP-1 RA: pro & con

Improvements:

- Survival
- MACE
- Stroke
- **Body weight**
- LDL-cholesterol
- Less infections
- Less heart failure in obese

Adverse events:

- GI: nausea, vomiting, gallbladder problems

GLP-1 RA: pro & con

Improvements:

- Survival
- MACE
- Stroke
- **Body weight***
- LDL-cholesterol
- Less infections
- Less heart failure in obese

Adverse events:

- GI: nausea, vomiting, gallbladder problems

* Peter Rossing
Vortrag 14 Uhr

Why ns-MRA in people with T2D and CKD ?

2 trials: Fidelio and Figaro (both: FIDELITY)

- Less CV outcomes (MACE), particularly less heart failure
- Less kidney failure, dialysis, loss of GFR and lower UACR
- Trials in combination with SGLT2i underway
- Aldosteron-synthase blockers: trials underway

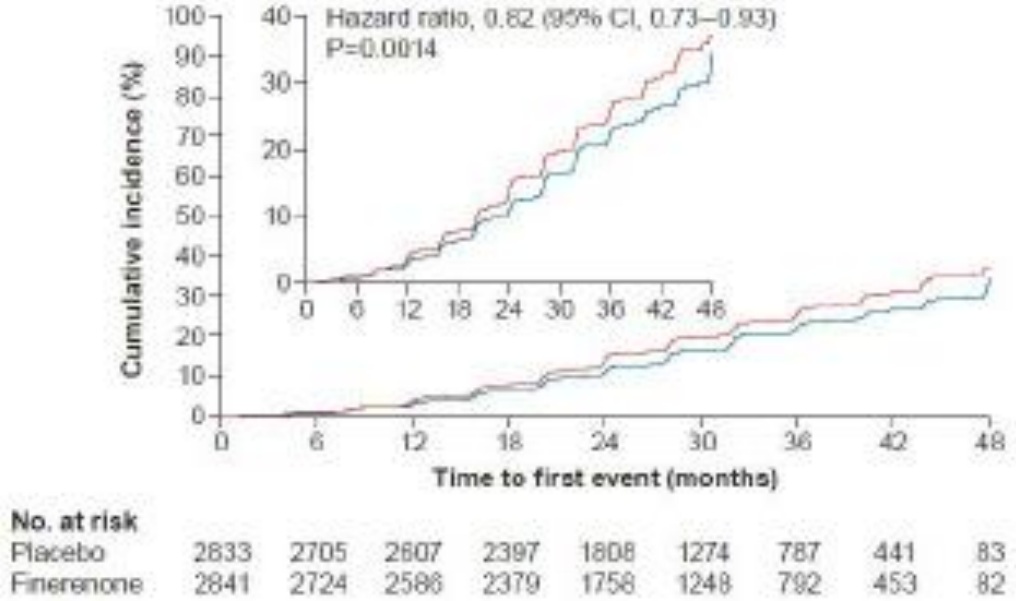
FIDELIO, results (N= 5674,mean follow-up 2.6 y; primary outcome in N=1004)

(Bakris et al, NEJM 2020, Oct 23 online)

Primary outcome:

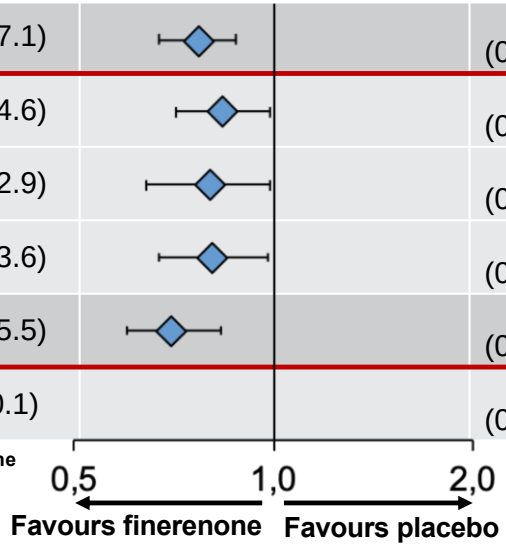
- Kidney failure
- ≥40% eGFR decline or
- Death due to kidney disease

A Primary Composite Renal Outcome (N= 1004 outcomes, 504 vs 600)



Finerenone significantly reduced incidences of most components of the kidney composite outcome

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	*p*-value
eGFR 57% composite kidney outcome	360 (5.5)	465 (7.1)	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD[#]	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040[‡]
eGFR <15 ml/min/1.73 m^2[¶]	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026[‡]
≥57% decrease in eGFR from baseline[¶]	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	–



≥57% decrease in eGFR is equivalent to doubling of serum creatinine

*Only 6 patients experienced renal death; [#]initiation of chronic dialysis for ≥90 days or kidney transplant; [‡]analysis for *p*-values not prespecified; [¶]confirmed by two eGFR measurements ≥4 weeks apart

*Cu
CI, (

A pillared approach to treat CKD in diabetes

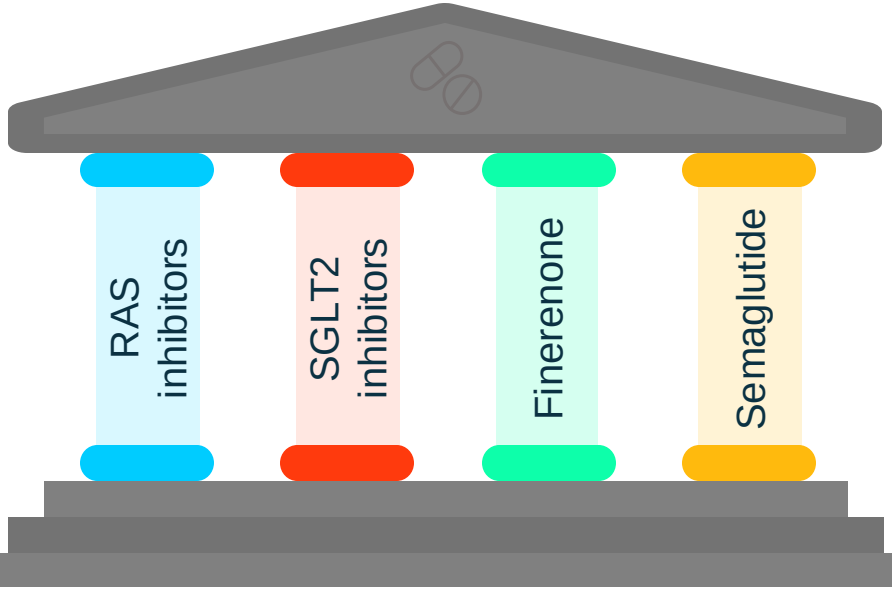
FLOW
semaglutide | renal outcomes trial

RAS inhibitors

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

SGLT2 inhibitors

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



Finerenone

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

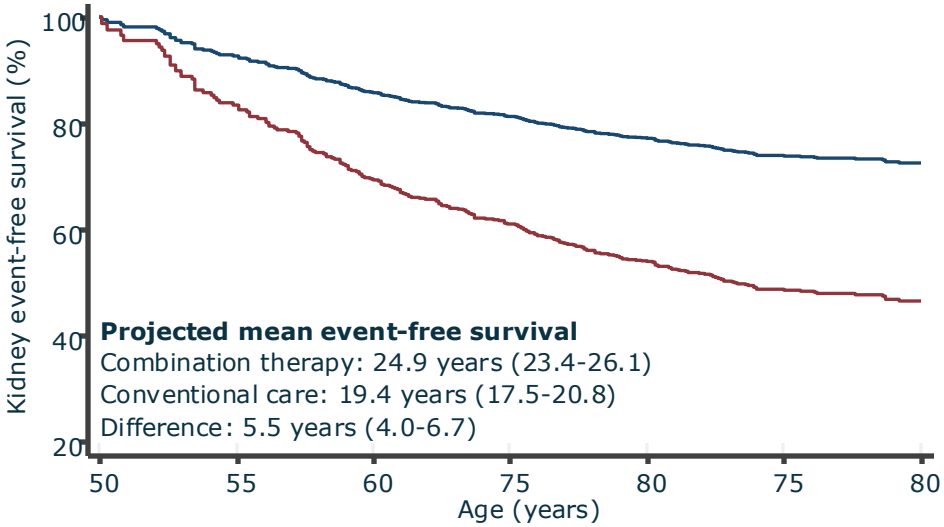
Semaglutide

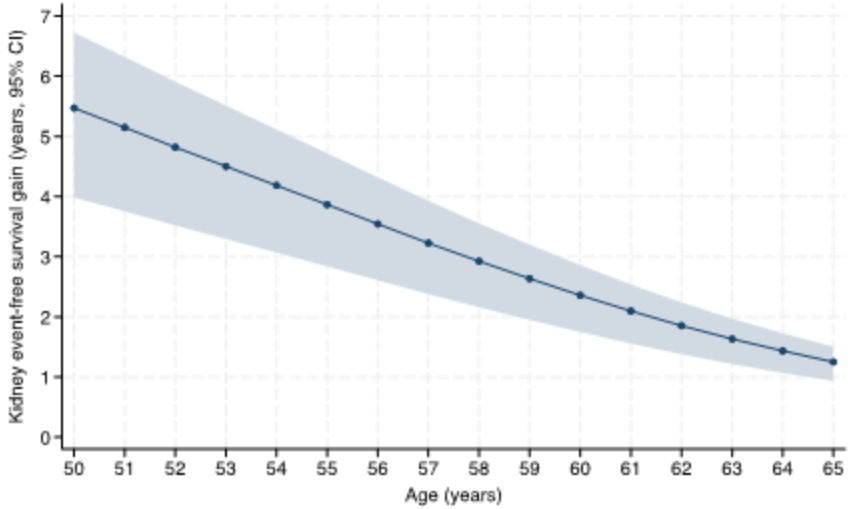
- Decrease weight
- Decrease dyslipidemia
- Decrease oxidative stress
- Decrease endothelial dysfunction

CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes.

Naaman SC, Bakris GL. *Diabetes Care* 2023;46:1574–1586.

Kidney event-free survival gains with combination therapy (RASi, SGLT2i, GLP1RA, MRA)



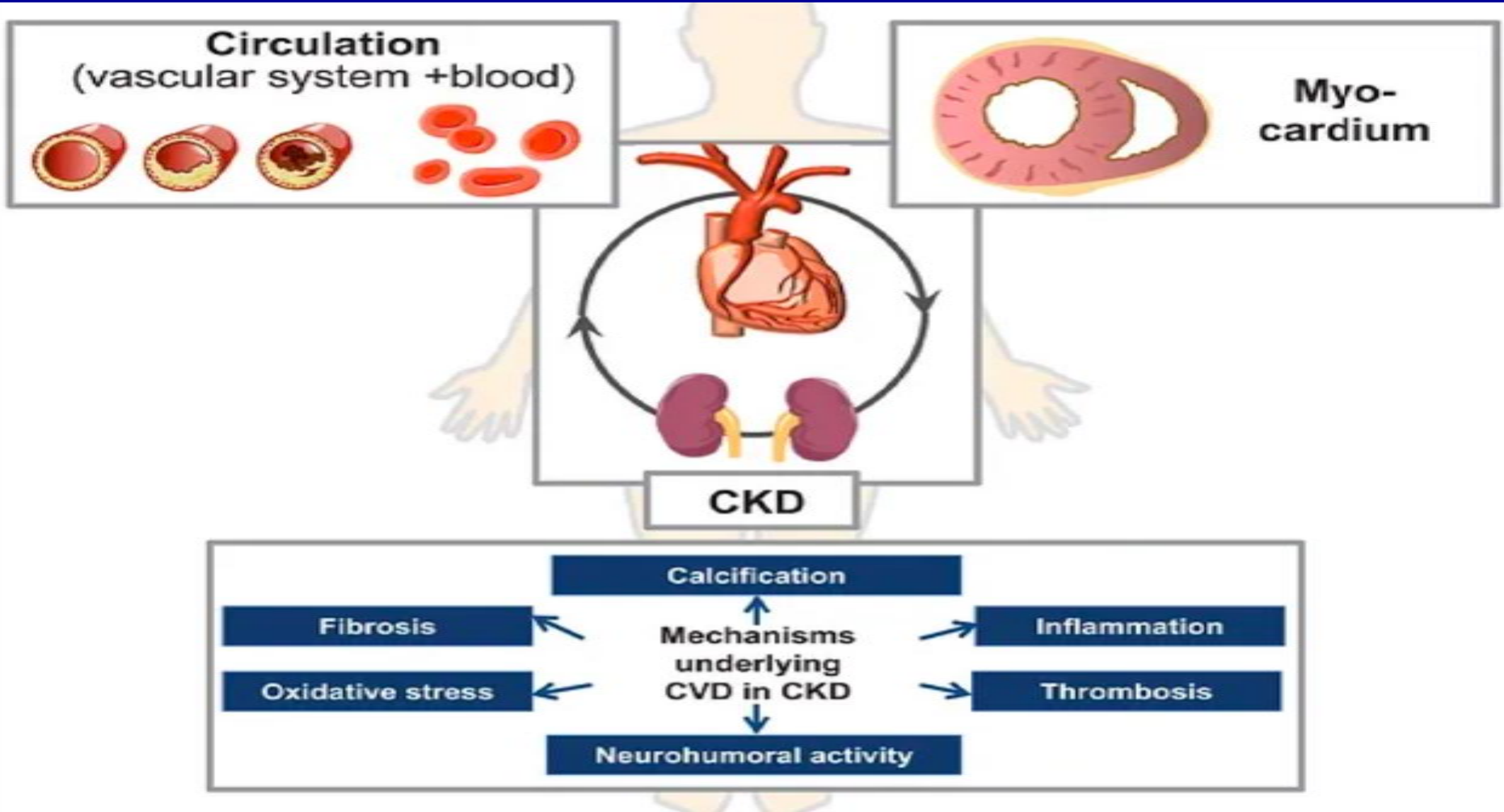


Neuen BL et al., Circulation 2024

What is coming next? Look out for ongoing trials

- Finerenone plus SGLT2i
- Aldosterone Synthase inhibitor plus SGLT2i
- Endothelin-Antagonist plus SGLT2i
- GLP-1 Rezeptor Agonist plus SGLT2i

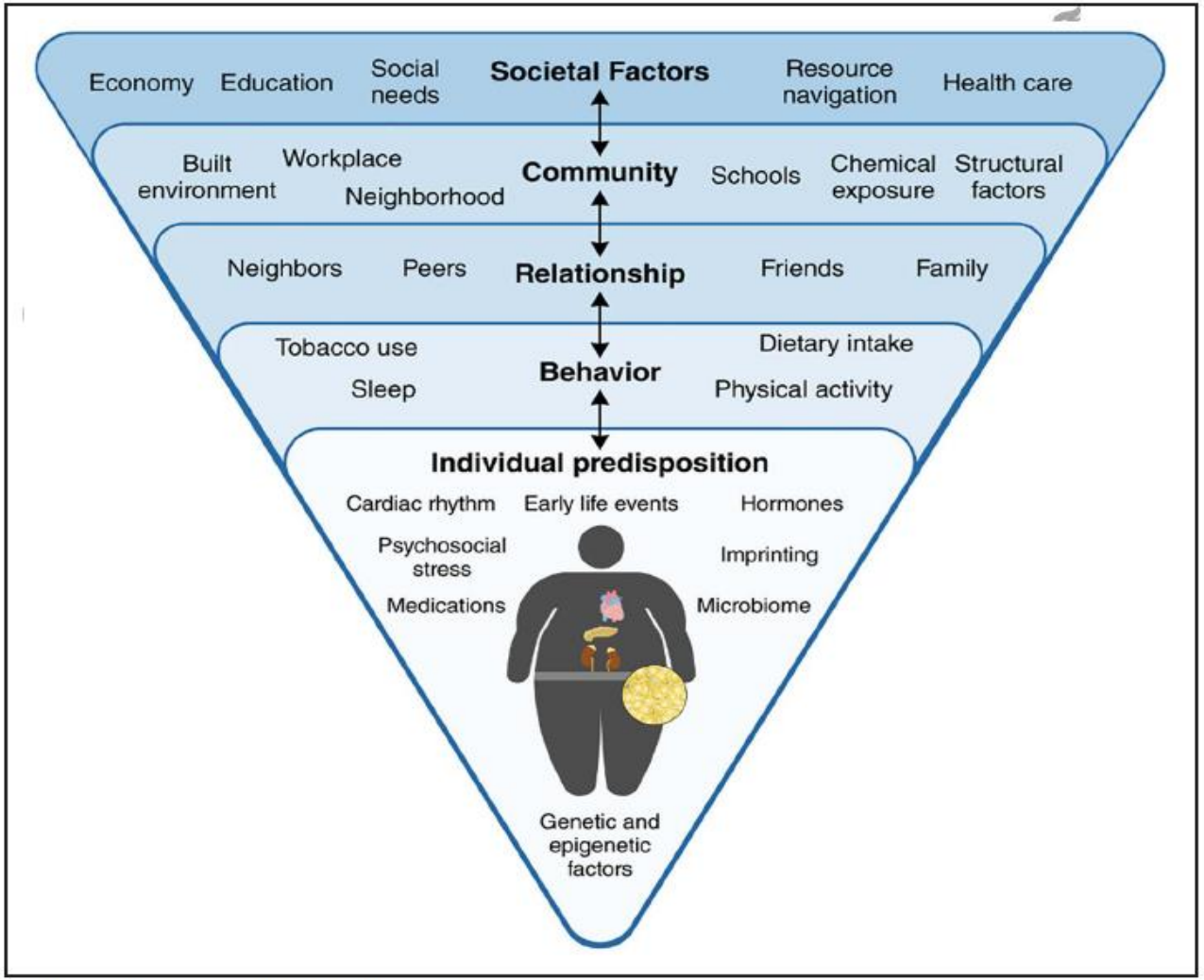
- Stay tuned for the next guidelines!! And the next trials!!


Circulation
(vascular system +blood)
Myo-
cardium
CKD
Calcification
Fibrosis
Inflammation
Mechanisms
underlying
CVD in CKD
Oxidative stress
Thrombosis
Neurohumoral activity

Ndumele et al.
Circulation 2023;148: online

CKM, Cardiovascular Kidney Metabolic syndrome,

an AHA scientific statement



Socioecological framework for CKM syndrome.

Ps 7.10 and 26.2; old testament
(James bible translation)

for the righteous God trieth the heart and the reins *

Examine me, O Lord, and prove me; try my reins* and my heart

* Reins = kidneys

Ritz & Wiecek Deut Med Wschr 2006;131:2616-9

E N D