Combining state-of-the-art therapies to maximize efficacy in mitigating diabetic kidney disease in type 2 diabetes.

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University of Colorado Anschutz Medical Campus

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Presenter Disclosure

- AstraZeneca: Consultancy, Advisory Board, Grant support
- Bayer: Consultancy, Advisory Board, Data Monitoring Committee Chair
- Boehringer Ingelheim: Consultancy, Advisory Board
- Bristol-Meyer Squibb: Consultancy
- Eli Lilly: Consultancy, Steering Committee, Grant Support
- LG Chem: Consultancy
- Horizon Pharma: Advisory Board and Grant Support
- Merck: Grant Support
- Novo Nordisk: Advisory Board, Consultancy and Grant Support
- Sanofi: Consultancy
- XORTX Scientific: Advisory Board

Photography allowed

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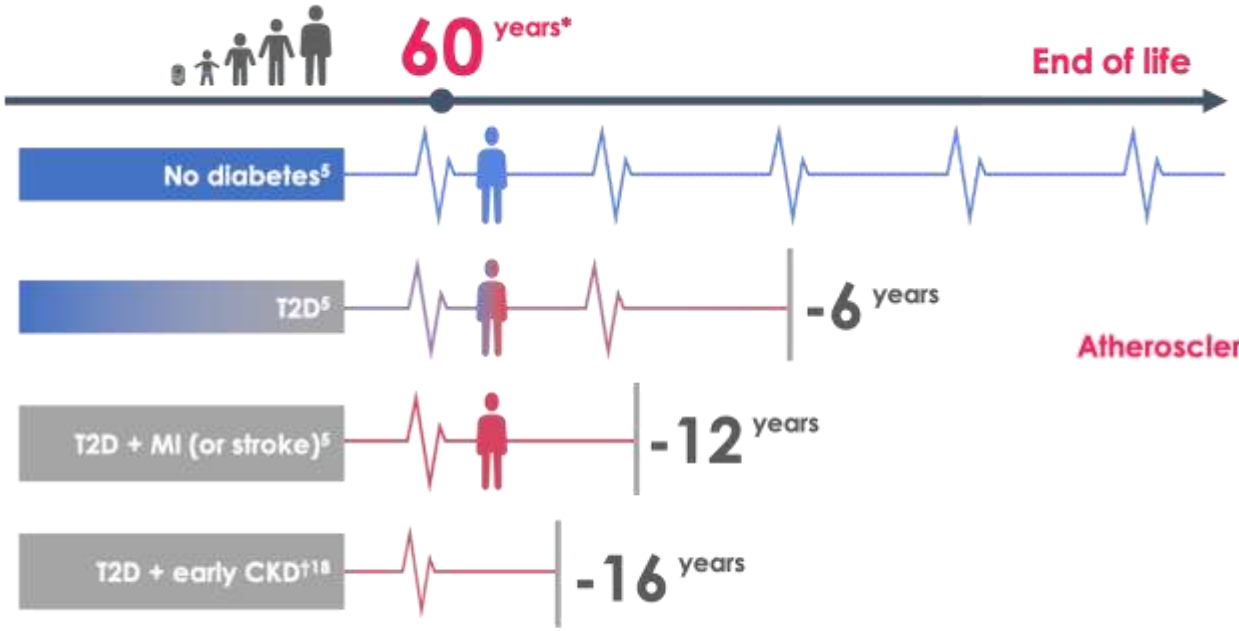
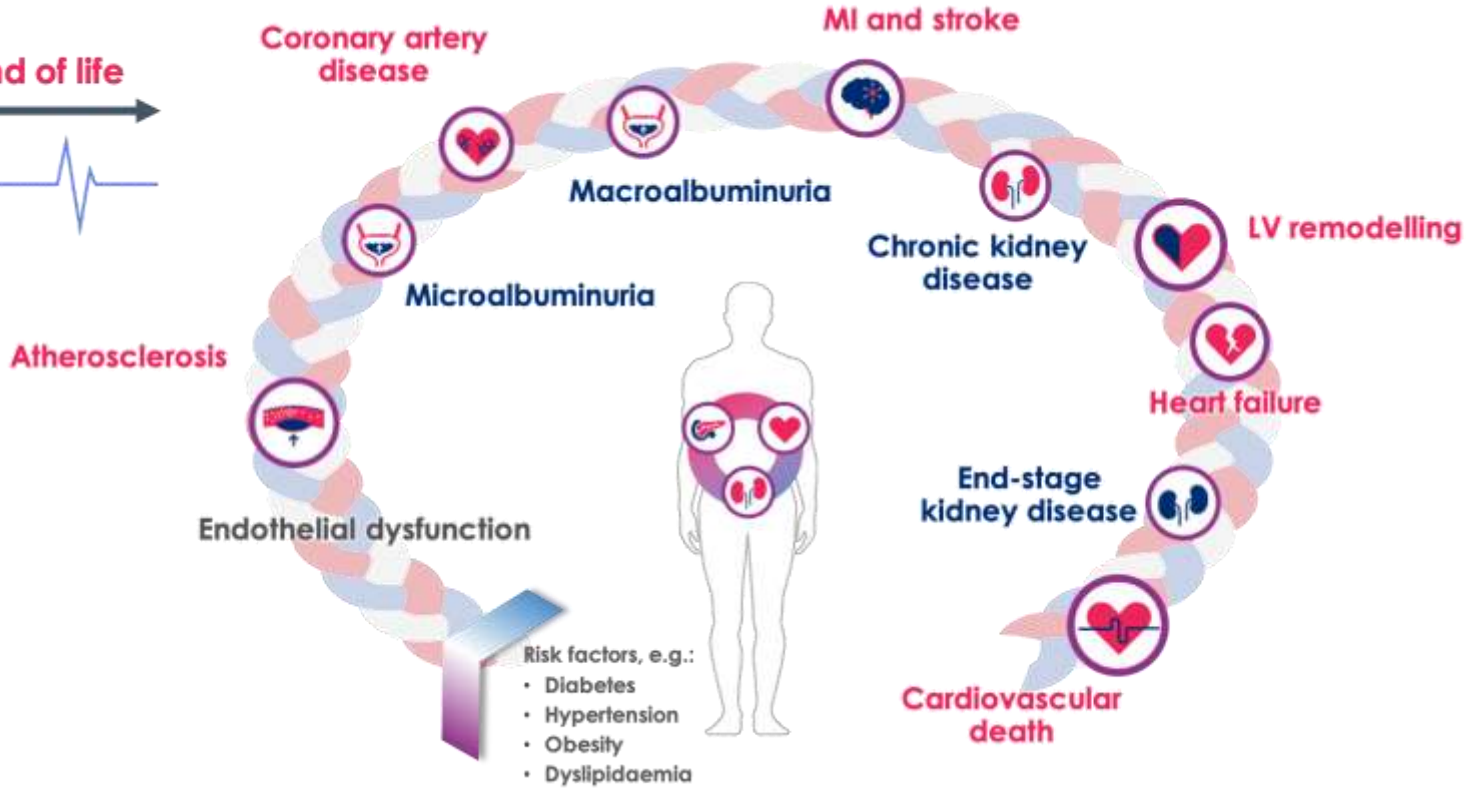
Reduced life expectancy in chronic kidney disease





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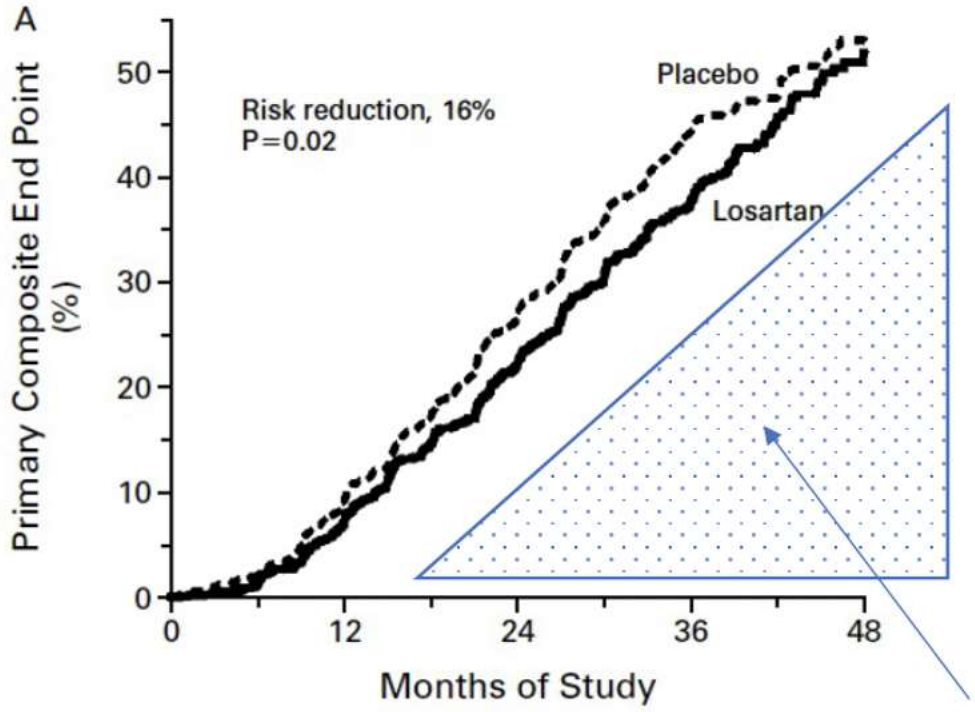
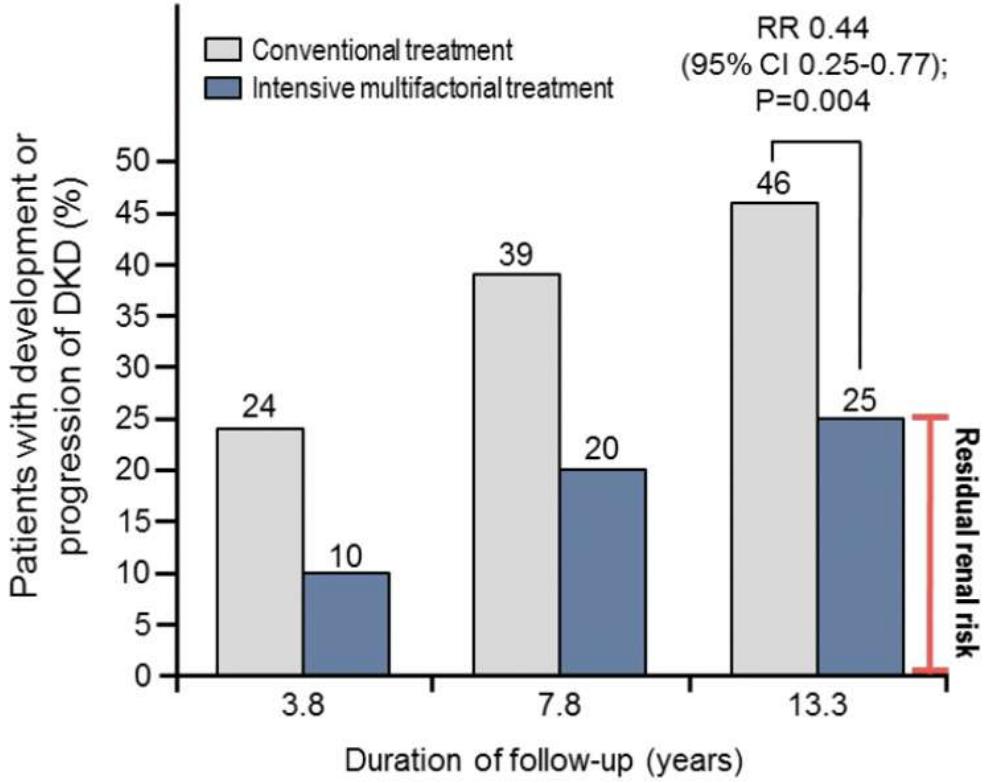
Kopyt N. *JAOA* 2005;105:207
Wen C. *Kidney Int* 2017;92:388

DKD: unmet medical need

Renin-angiotensin-aldosterone system (RAAS) blockers





No cardiovascular protection in RENAAL, IDNT, IRMA trials

RENAAL. Brenner et al. NEJM 2001

Gaede P. *N Engl J Med* 2003;348(5):383-93.

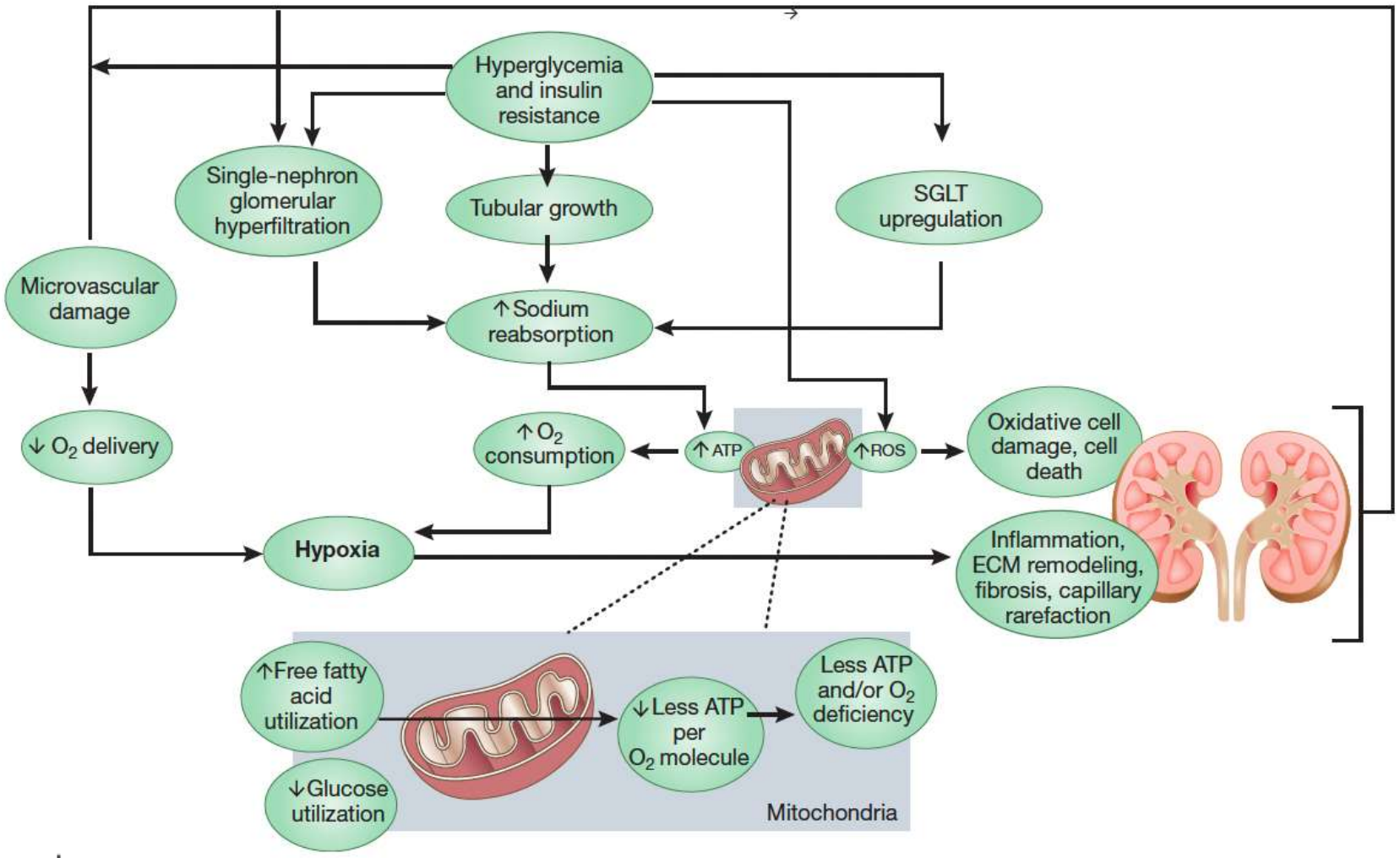
Glycemic and blood pressure control ≠ DKD mitigation

Addressing this unmet need proven to be challenging

Trial	Intervention	Renal endpoints met	Adverse effects
VA NEPHRON-D	**Losartan** + **Lisinopril** vs PBO	**- No**	↑ K+, acute kidney injury
ALTITUDE	**ACE-i/ARB** + **Aliskiren** vs PBO	**- No**	↑ K+, hypotension
Sun-trials	**ACE-i/ARB** + **Sulodexide** vs PBO	**- No**	-
ASCEND	**ACE-i/ARB** + **Avosentan** vs PBO	**- No**	Fluid overload, CHF, anemia
BEACON	**ACE-i/ARB** + **Bardoxolone methyl** vs PBO	**- No**	CHF, CVD

Packham et al. *JASN* 2012
Fried et al. *NEJM* 2013
Palmer et al. *Lancet* 2015
De Zeeuw et al. *NEJM* 2013
Mann et al. *JASN* 2009
Parving et al. *NEJM* 2012

The vicious cycle of renal tissue deterioration after hyperglycemia-induced renal hypoxia



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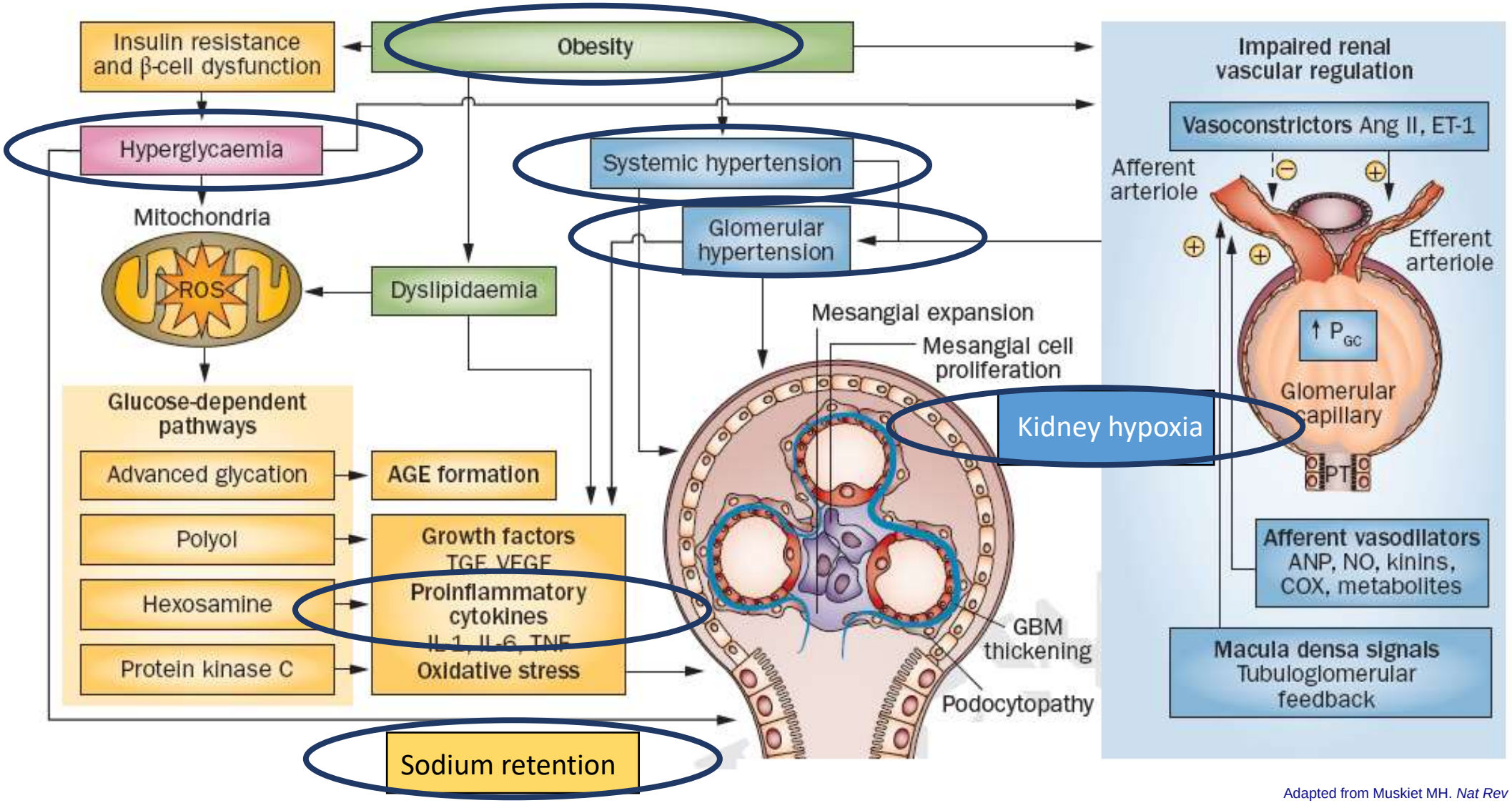
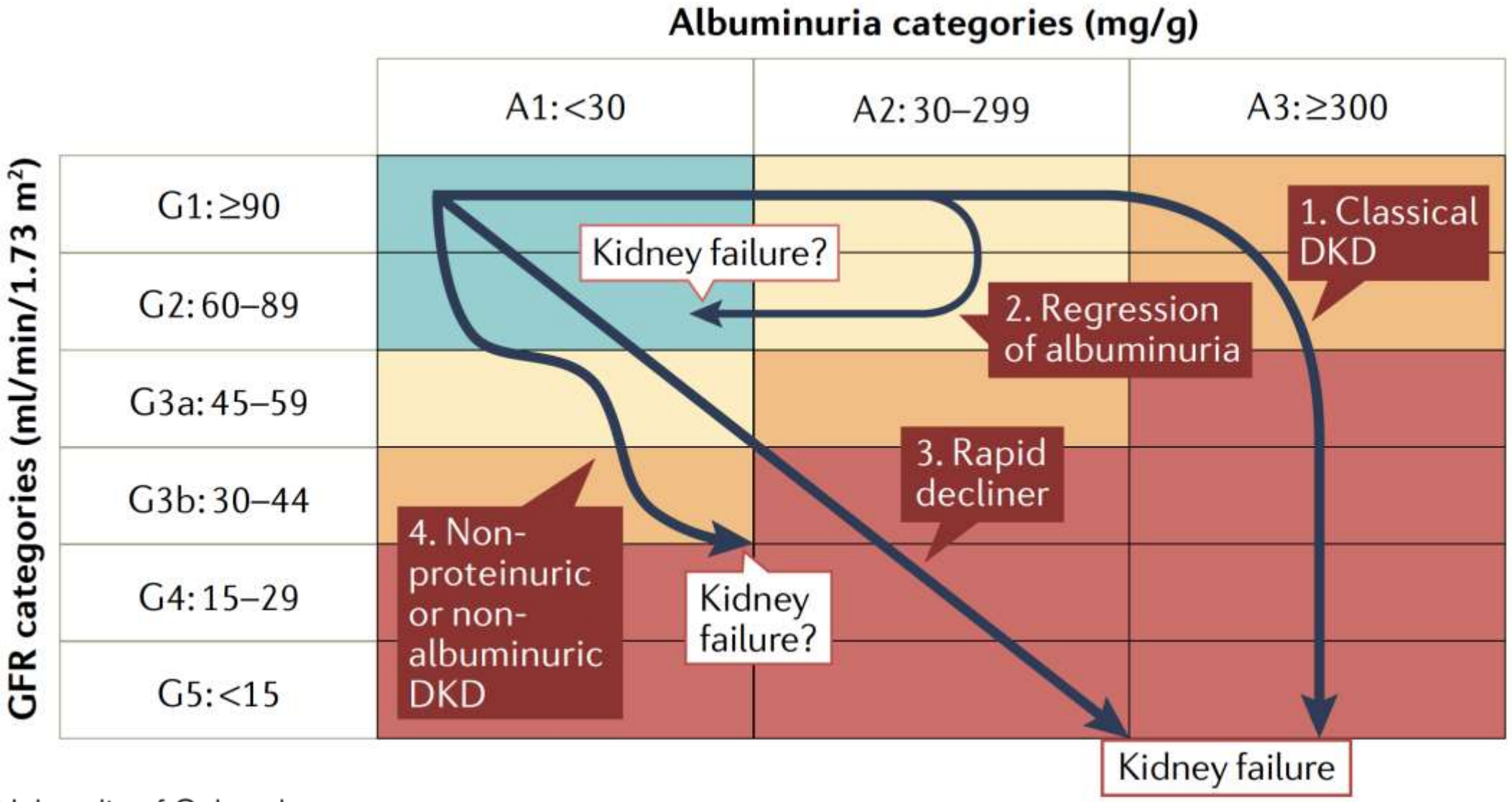
Hesp and Bjornstad et al *Kidney Int.* 2020

Complex pathophysiology of DKD



Adapted from Muskiet MH. *Nat Rev Nephrol* 2014;10(2):88-103.

Trajectories of Kidney Function in DKD



Oshima *Nat Rev Nephrol* 2021.

Trials in recent years have ended this drought

SGLT-2 inhibitors

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

Mineralocorticoid receptor antagonist (MRA): Finerenone

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

Endothelin receptor antagonist (ERA): Atrasentan

Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial

Glucagon-like peptide (GLP)-1 receptor agonist

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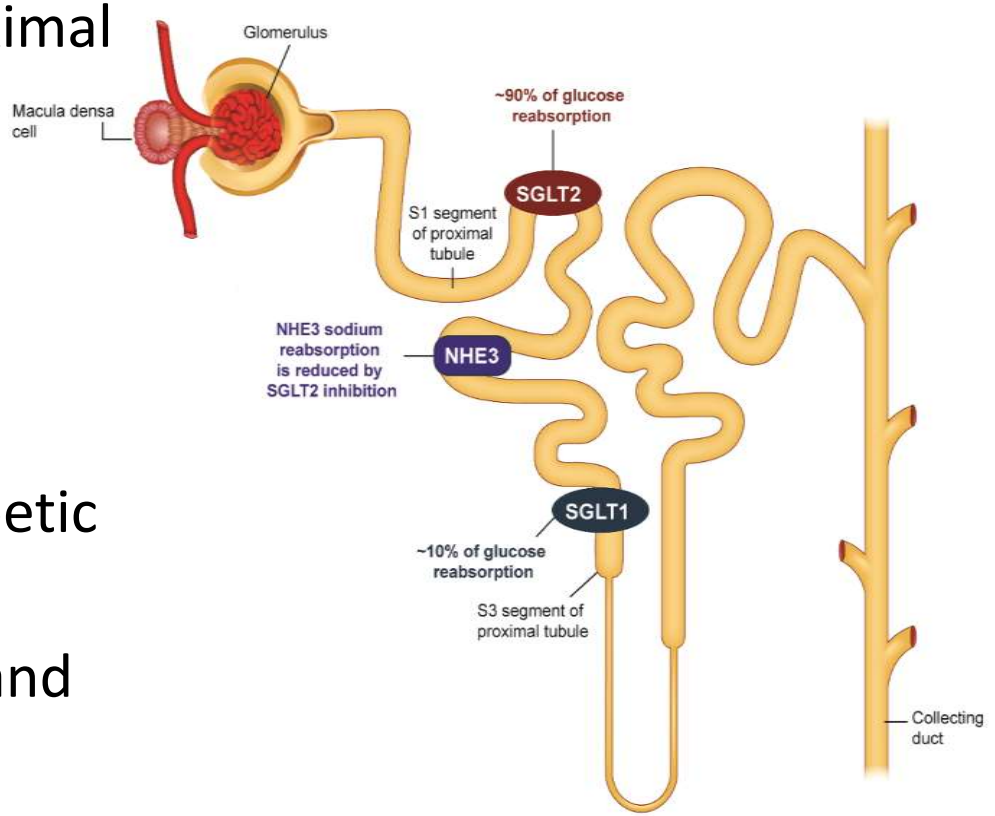
Perkovic et al. *NEJM* 2019 Heerspink et al. *Lancet* 2019

Bakris et al. *NEJM* 2021 RCT NCT 03819153

SGLT-2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors

- SGLT2 almost exclusively expressed in the proximal tubules (PT)
  - 90% of filtered glucose is reabsorbed in the apical membrane of the PT by SGLT2
- Modestly lower HbA1c
- Modestly lower SBP
- Durable and significant protection against diabetic kidney disease and cardiovascular disease
- Mechanism of protection likely multifactorial and incompletely understood

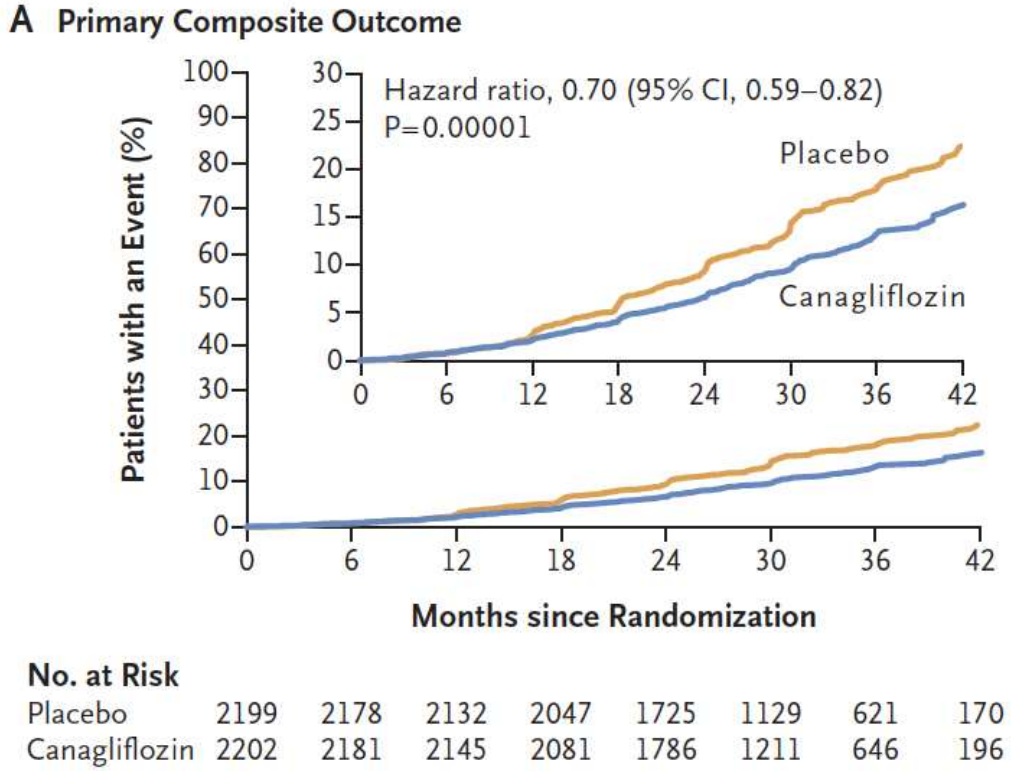


Lytvyn et al. *Endocrin Review. 2020*

SGLT-2 inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors

CREDENCE

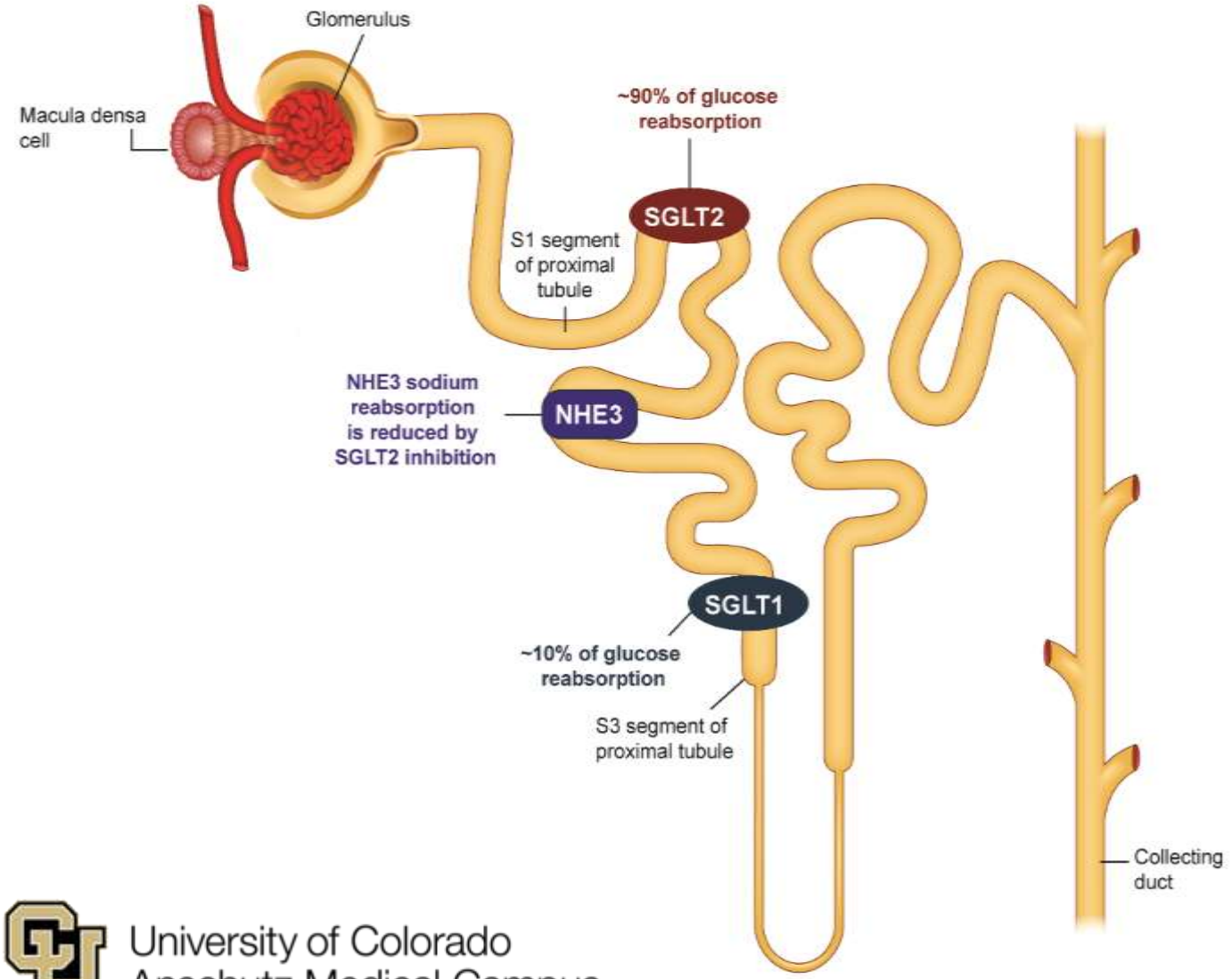


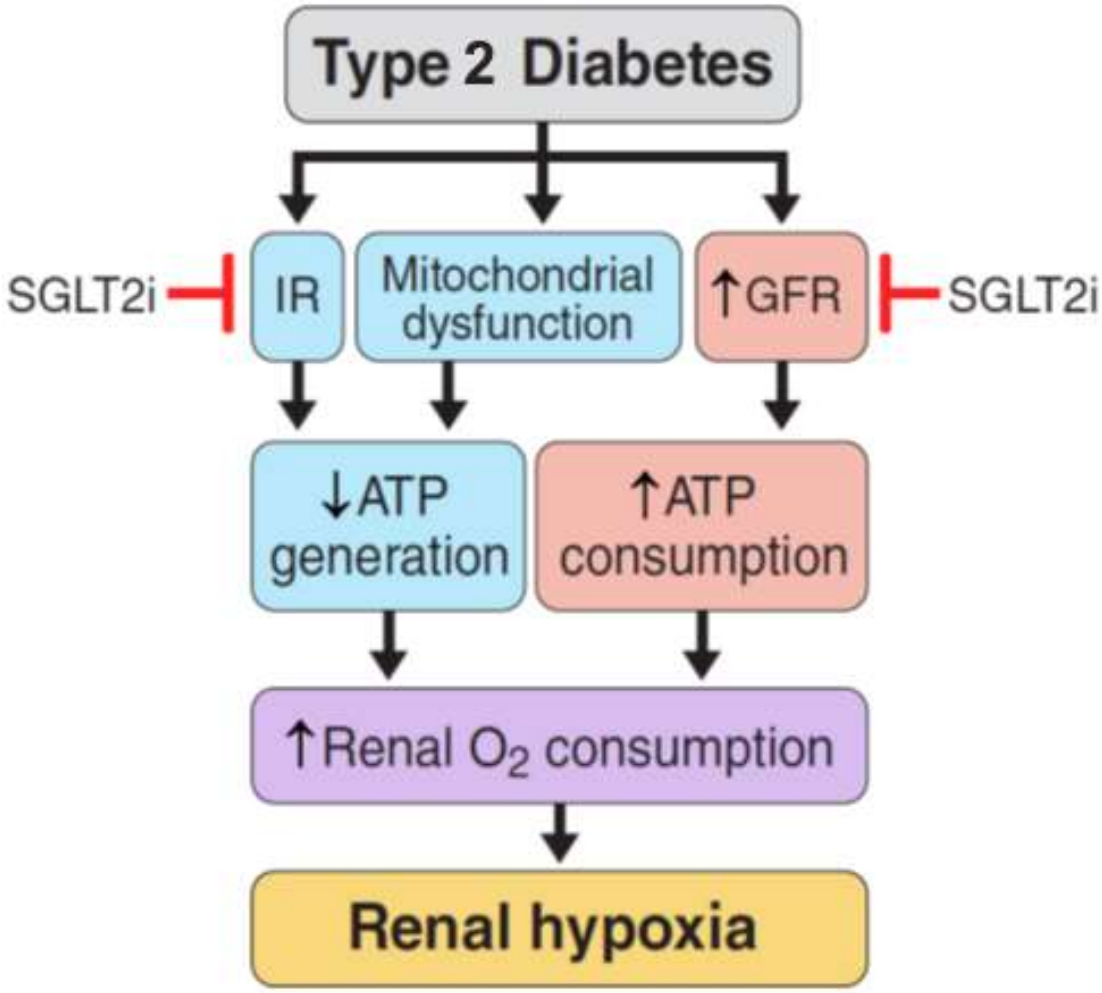
Primary composite outcome of kidney failure, doubling of the serum creatinine, or renal or CV death

EMPA-REG OUTCOME	November 26, 2015
DECLARE-TIMI 58	January 24, 2019
CREDENCE	June 13, 2019
DAPA-HF	November 21, 2019
DAPA-Kidney	October 8, 2020
EMPA-Reduced	October 8, 2020
EMPA-Preserved	October 14, 2021
DELIVER dapa in HFpEF	August 27, 2022
EMPA-Kidney	November 2022?

Courtesy of Dr. Topf, @kidney_boy

Potential mechanisms of SGLT2 inhibitors





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Kidney hypoxia early in the course of diabetes

N=60

N=26
T1D

N=10
HC

N=24
T2D

N=12
SGLT2i yes

N=12
SGLT2i no

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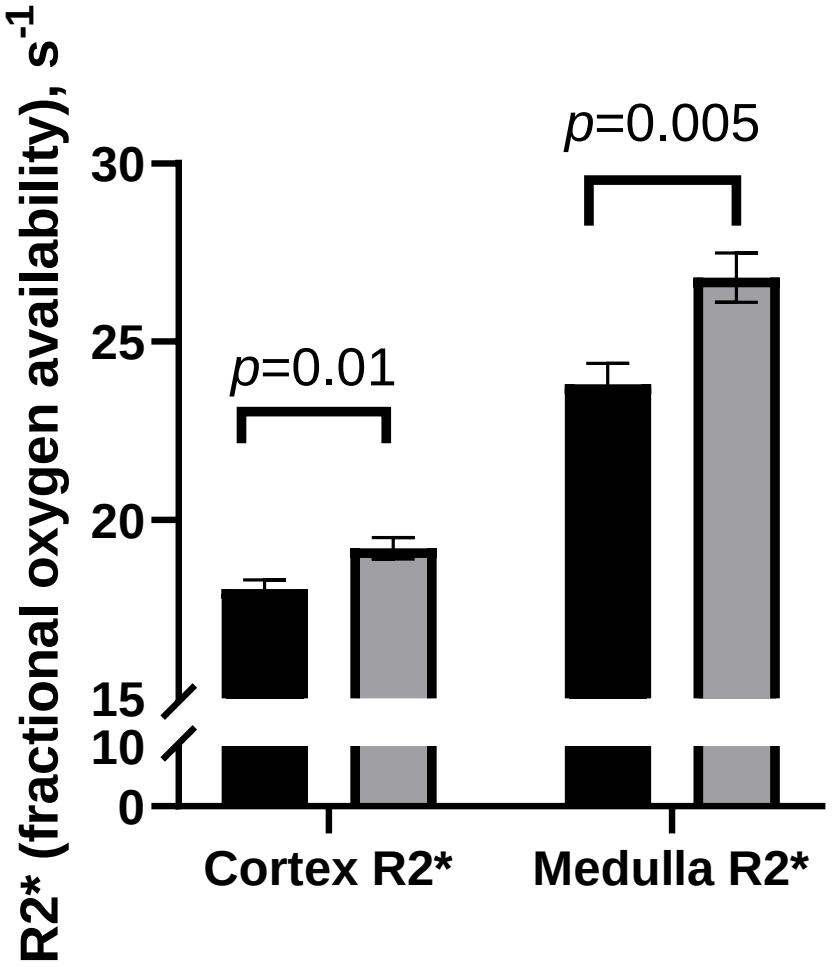
Bjornstad et al. https://www.medrxiv.org/content/10.1101/2022.07.23.22277943v1

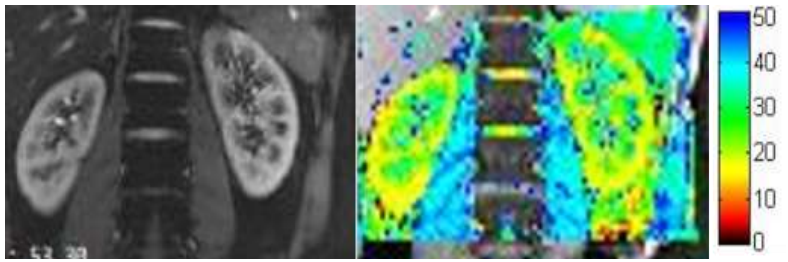
SGLT2 inhibitors in T2D



SGLT2 inhibitors

No SGLT2 inhibitors

N=24 with T2D



Adjusted for sex, GFR and BMI

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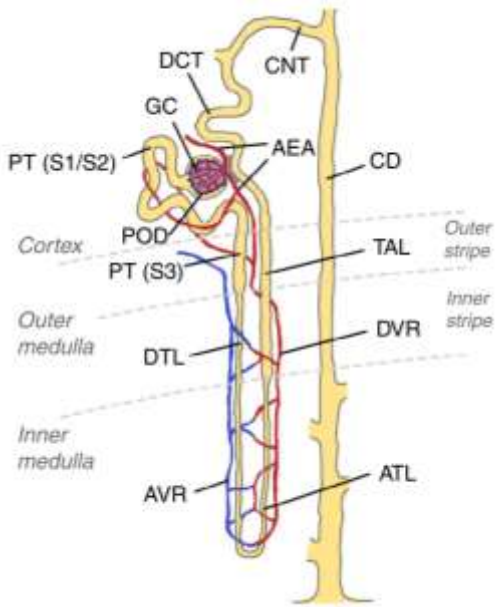
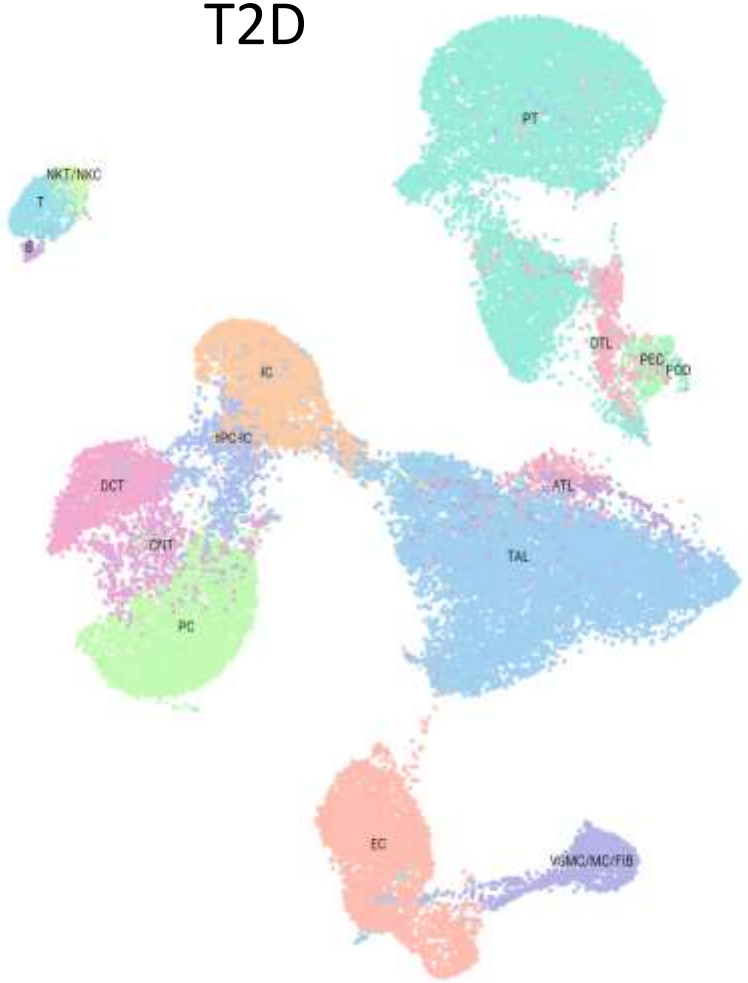
Bjornstad et al. https://www.medrxiv.org/content/10.1101/2022.07.23.22277943v1

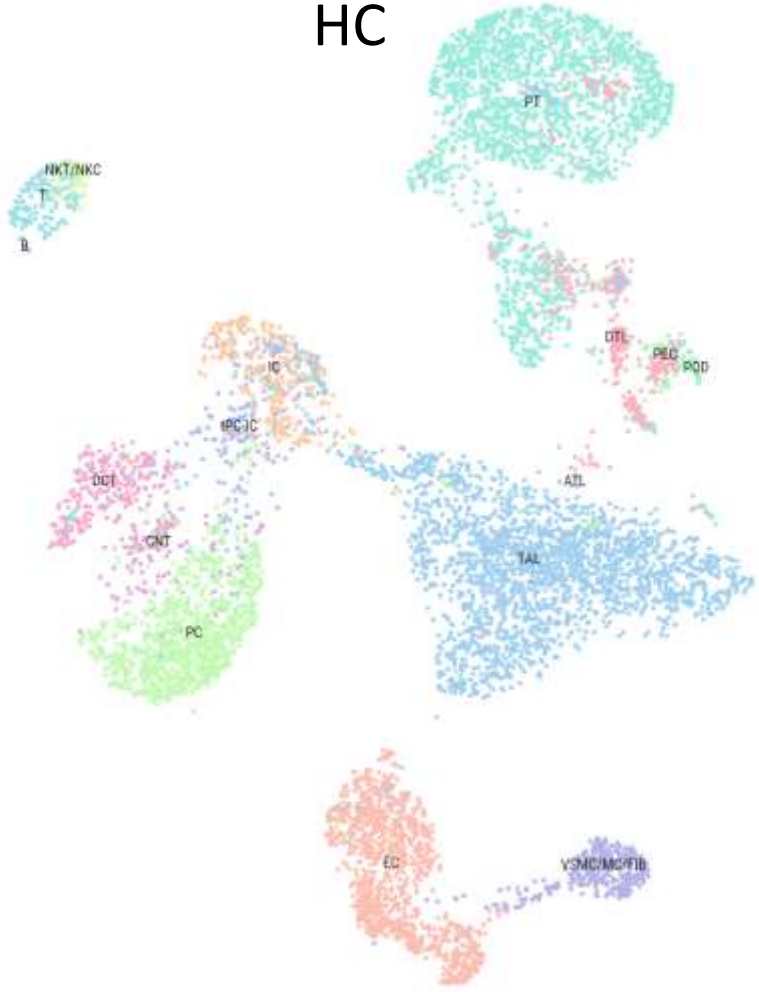
Single-cell RNA sequencing of kidney tissue



T2D

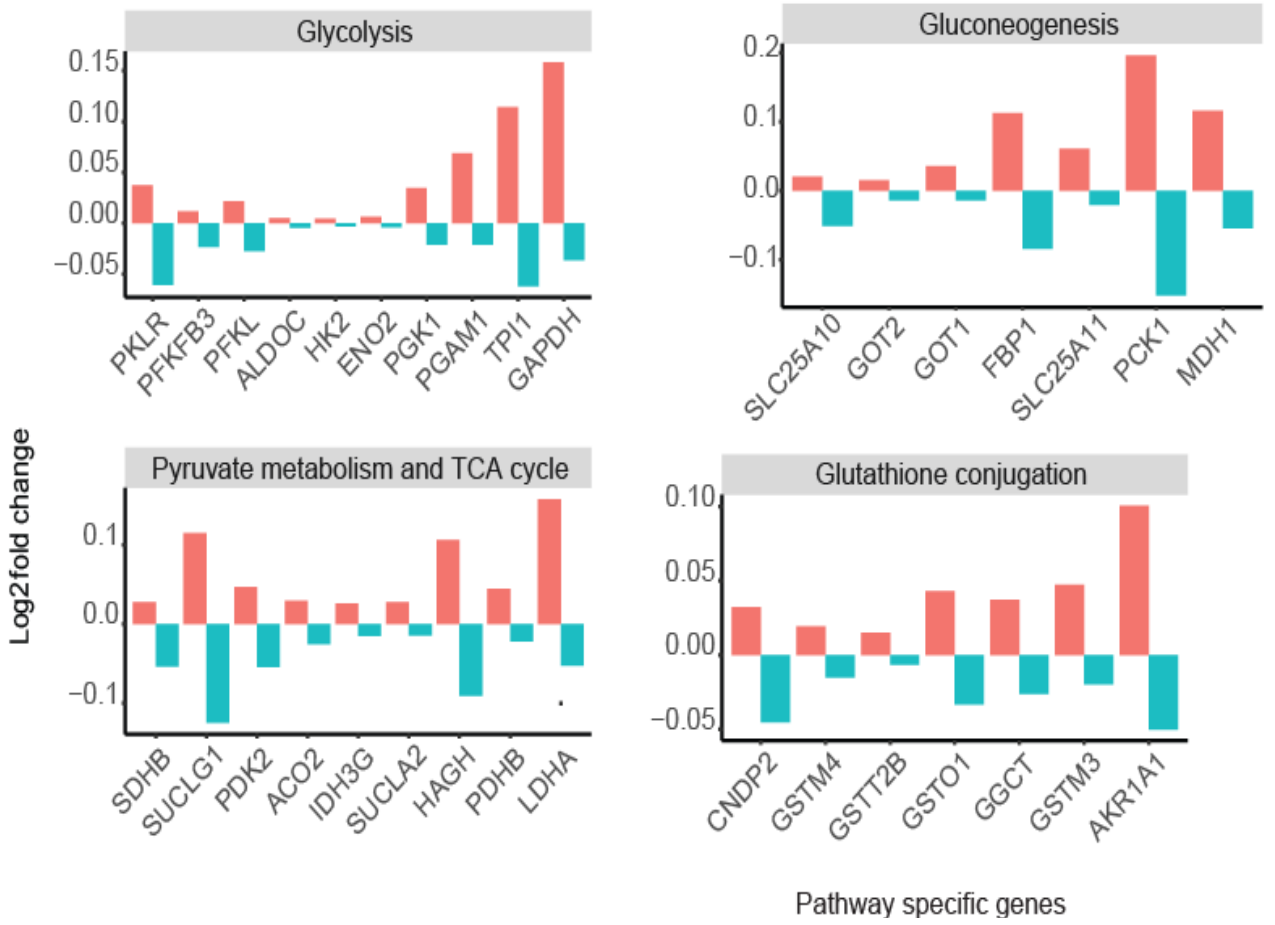


HC

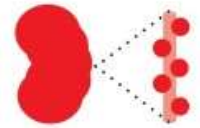


Bjornstad et al. https://www.medrxiv.org/content/10.1101/2022.07.23.22277943v1

Proximal tubular metabolic pathways reversed by SGLT2i



Kidney biopsy data



log2FC_T2D_HC (T2D vs. HC)

log2FC_T2Di_T2D (T2D + SGLT2i vs. T2D)

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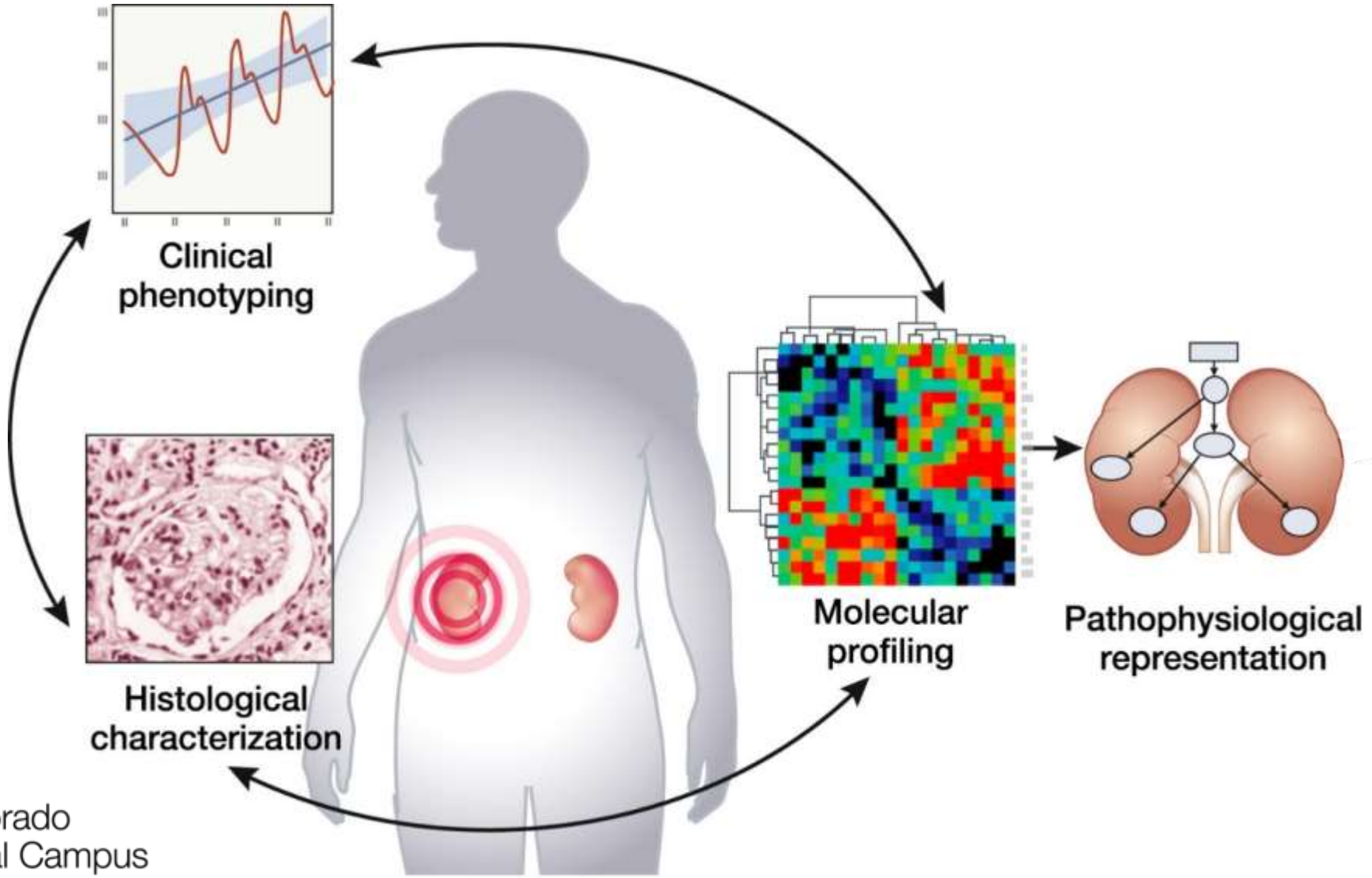
Bjornstad et al. https://www.medrxiv.org/content/10.1101/2022.07.23.22277943v1

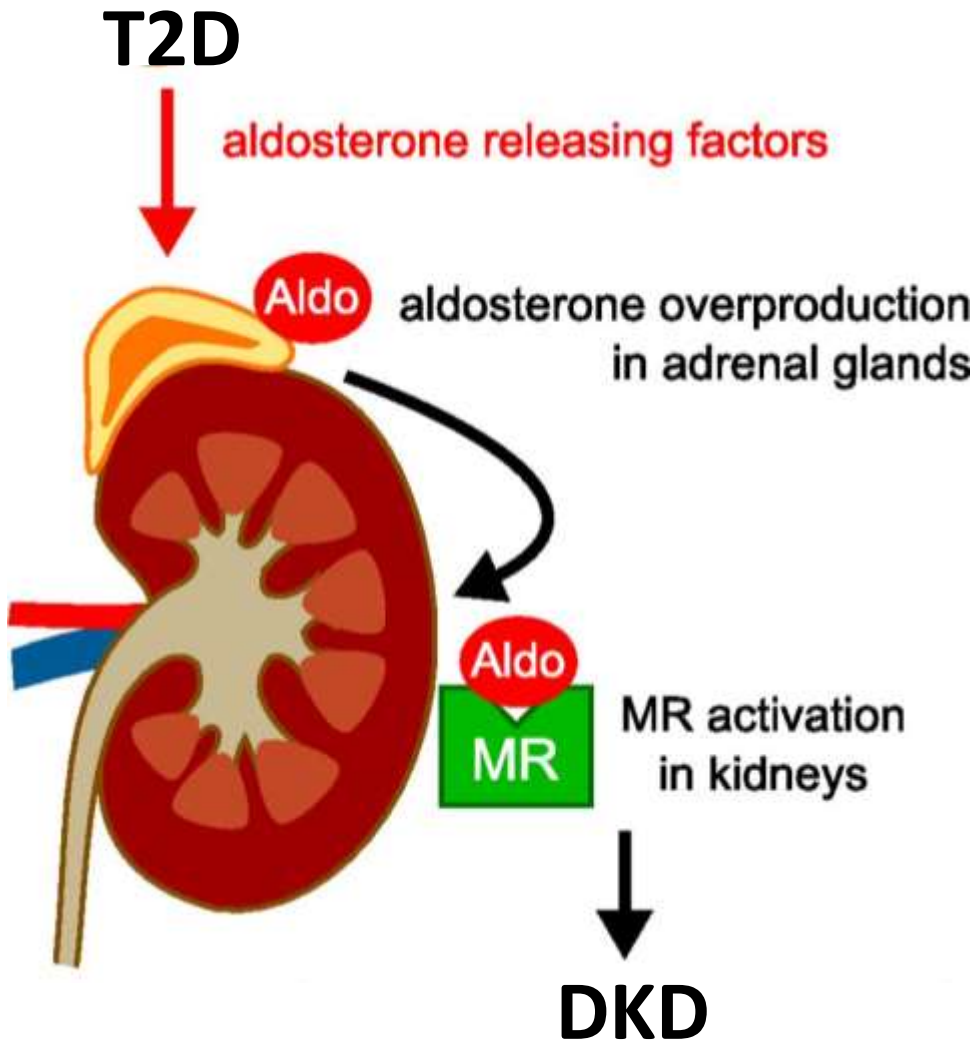
Single-sample Gene Set Enrichment Analysis



Mineralocorticoid receptor antagonist (MRA): Finerenone

Mineralocorticoid receptor (MR) antagonists

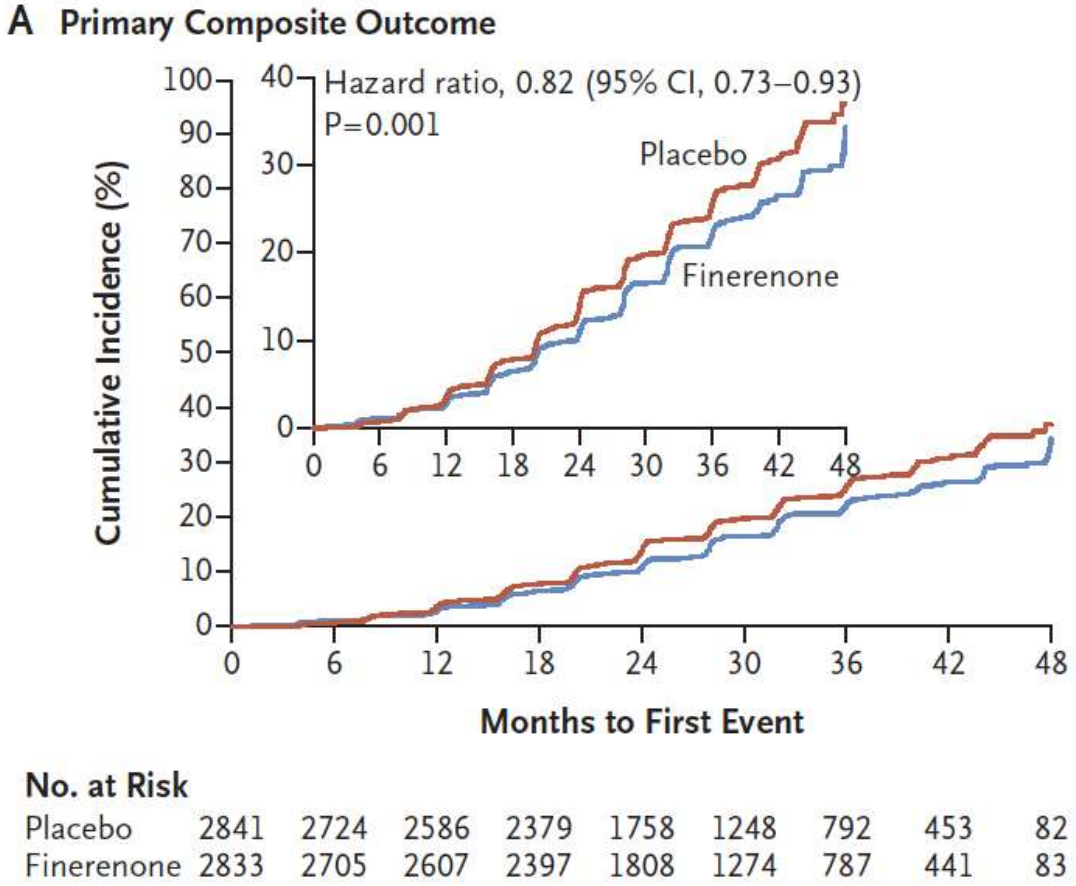
- T2D has been linked to inappropriate MR activation with resultant inflammation and fibrosis.
- Murine MR knockout models showed protection against kidney inflammation and fibrosis.
- In CRIC, higher serum aldosterone concentrations predicted greater risk of CKD progression in adults with and without T2D.



Verma et al. EHJ 2022

Mineralocorticoid receptor antagonist (MRA): Finerenone

Mineralocorticoid receptor (MR) antagonists



The primary composite outcome in FIDELIO-DKD: kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes.

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Bakris et al. *NEJM* 2021

Endothelin receptor antagonist (ERA): Atrasentan

Endothelin receptor antagonists

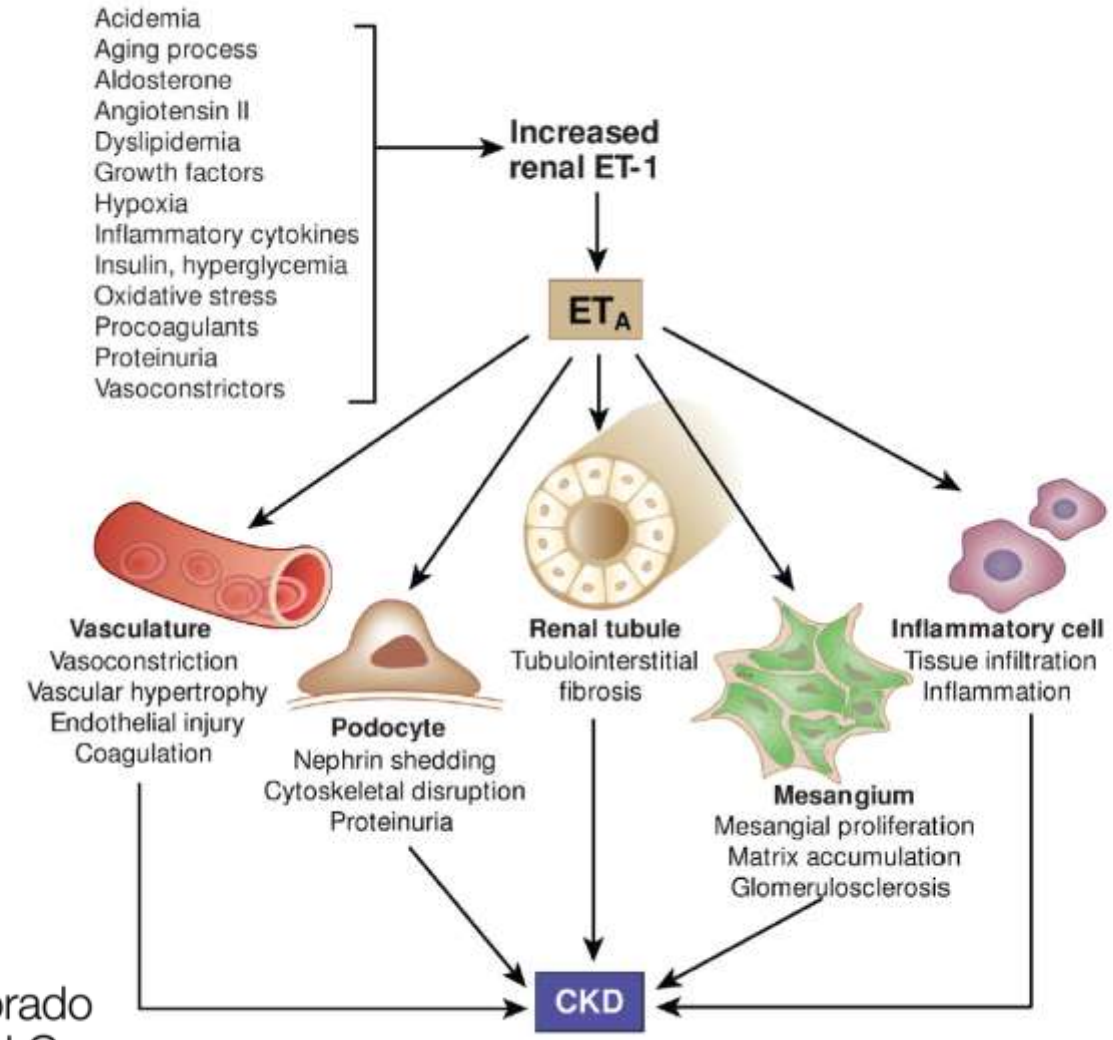
- Endothelins (1-3) linked to various diseases, including DKD
  - In CKD/DKD: increased kidney endothelin-1 production

- Endothelin receptor A (ERA) and Endothelin receptor B (ERB)
  - ERA activation induces pro-inflammatory and pro-fibrotic pathways, glomerular hyperfiltration through vasoconstriction efferent vasculature
  - ERB in collecting duct stimulate sodium excretion

Kohan et al. *Kidney Int* 2014
Dhaun et al. *Hypertension* 2009
Hunter et al. *Hypertension* 2009

Endothelin receptor antagonist (ERA): Atrasentan

Endothelin receptor A activation



ERA Blockade reduces:

- Systemic blood pressure
- Glomerular hypertension
- Efferent vasodilation
- Proteinuria

But increases sodium retention

Role of ERB blockade

Kohan et al. *Kidney Int* 2014

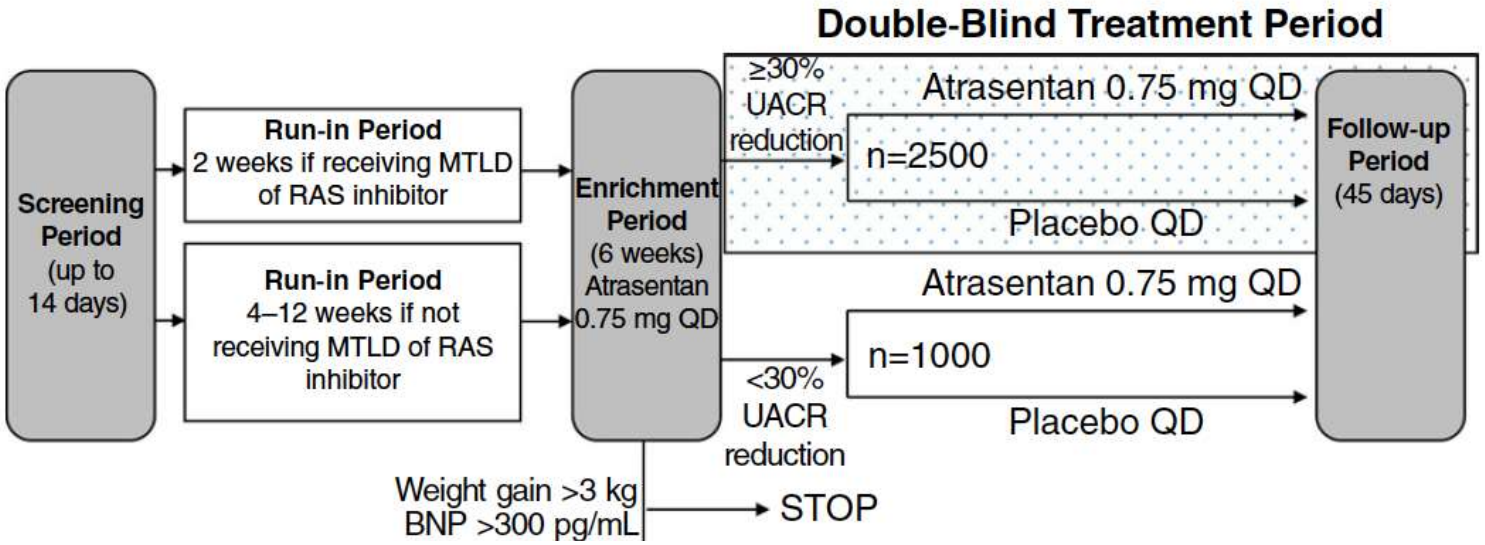
Dhaun et al. *Hypertension* 2009

Hunter et al. *Hypertension* 2009

Endothelin receptor antagonist (ERA): Atrasentan

Atrasentan ($ET_{A:B}$ 1200:1): design of the SONAR trial

Phase-3 trial
3500 T2D patients
Macroalbuminuria
CKD stages 2-4
BNP<200 pg/mL
Atrasentan 0.75 mg/d



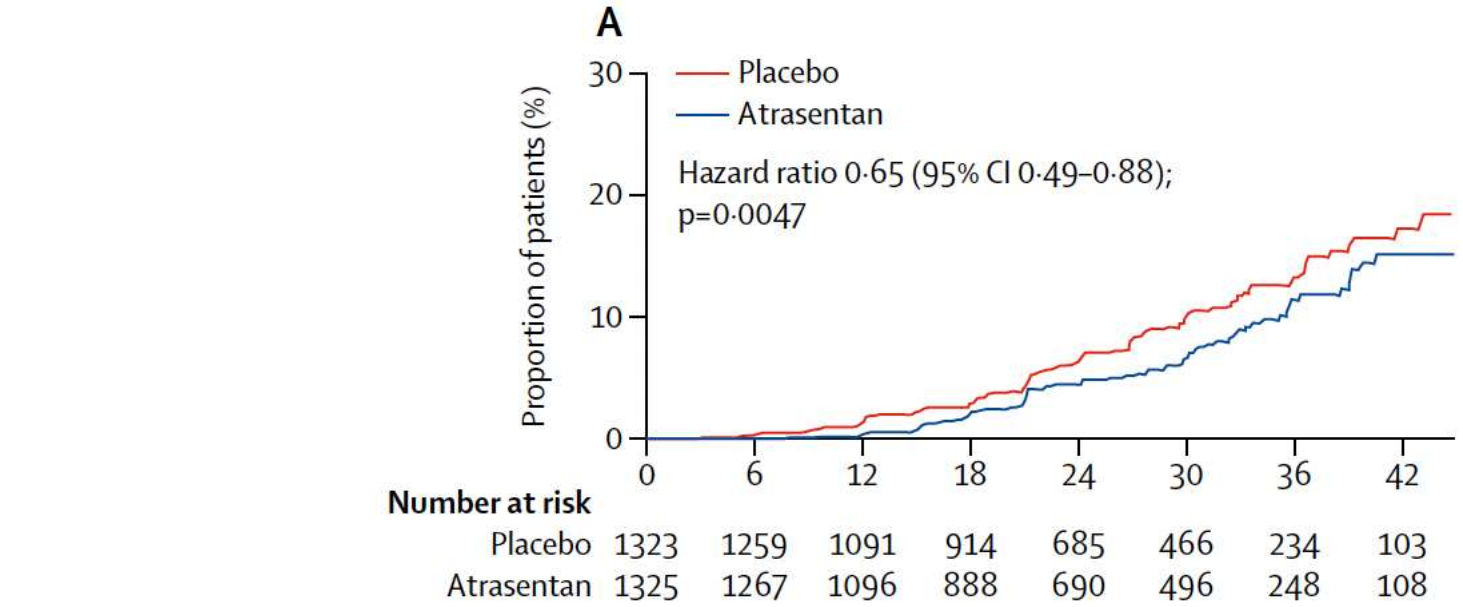
Primary composite endpoint:
1. Time to doubling of serum creatinine from baseline (confirmed by 30-day serum creatinine)
2. Time to ESRD defined as eGFR <15 mL/min/1.73 m^2, need for chronic dialysis (both confirmed after 90 days), renal transplantation or renal death

Prematurely ended due to few events

Heerspink et al. *DOM* 2018

Endothelin receptor antagonist (ERA): Atrasentan

Main outcomes of the SONAR trial



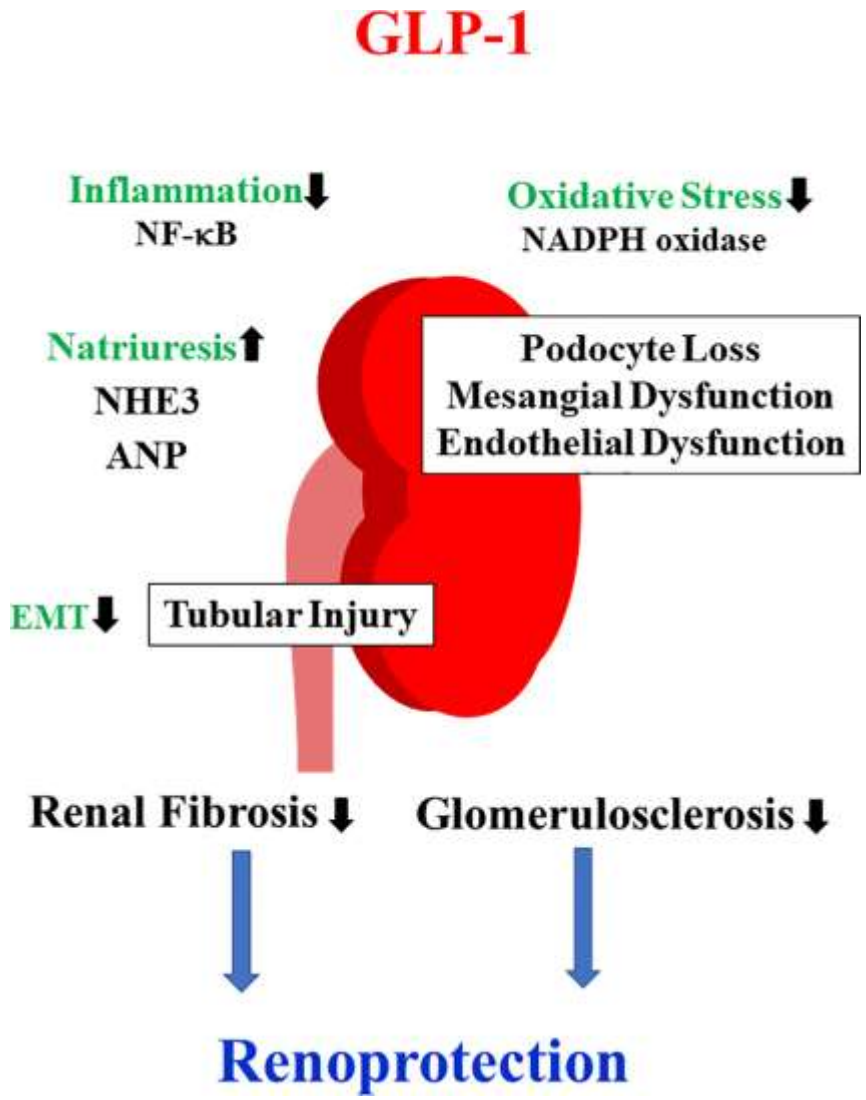
	Atrasentan (n=1325)		Placebo (n=1323)		Hazard ratio (95% CI)	p value*
	Number	Annual rate	Number	Annual rate		
Primary outcome						
Composite renal outcome	79 (6·0%)	2·8%	105 (7·9%)	3·7%	0·65 (0·49–0·88)	0·0047
Doubling of serum creatinine	56 (4·2%)	2·0%	78 (5·9%)	2·7%	0·61 (0·43–0·87)	0·0055
End-stage kidney disease	67 (5·1%)	2·4%	81 (6·1%)	2·9%	0·73 (0·53–1·01)	0·060

Heerspink et al. *Lancet* 2019

Glucagon-like peptide (GLP)-1 receptor agonist

Glucagon-like peptide-1 (GLP-1) receptor agonists

- GLP-1 peptide hormone released from L-cells of the distal ileum in response to oral glucose.
- GLP-1 receptor activation has many effects:
  - Insulin secretion
  - Insulin sensitization
  - Increased perfusion
  - Reduced fibrosis
  - Reduced inflammation
- GLP-1RAs lower albuminuria and may attenuate eGFR decline in high-risk people with T2D.



Glucagon-like peptide (GLP)-1 receptor agonist

GLP-1: preliminary evidence for kidney protection

- REWIND cardiovascular outcome trial with dulaglutide

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Main analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001

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Gerstein HC. Lancet. 20179; 394:131-8.

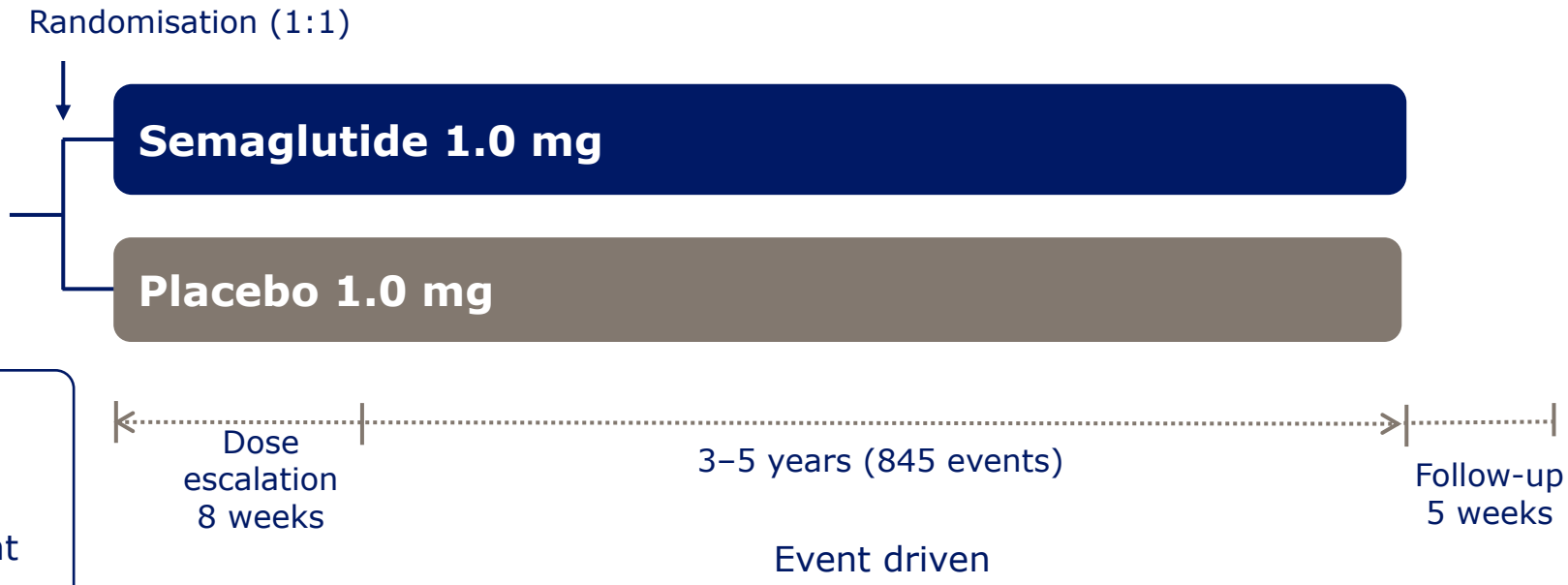
Glucagon-like peptide (GLP)-1 receptor agonist

FLOW: renal outcomes trial with semaglutide

TRIAL DESIGN

3,120 participants with T2D

- HbA_{1c} ≤10%
- RAAS blocker
- eGFR ≤75 and ≥50* and UACR >300 mg/g OR eGFR <50 and ≥25*and UACR >100 mg/g



Trial rationale

- To assess the effect of semaglutide vs placebo on the progression of renal impairment in subjects with T2D and CKD

Primary endpoint

- Composite of selected renal endpoints; renal death; CV death

Secondary confirmatory endpoints

- Change in eGFR (eGFR slope); MACE; all-cause mortality

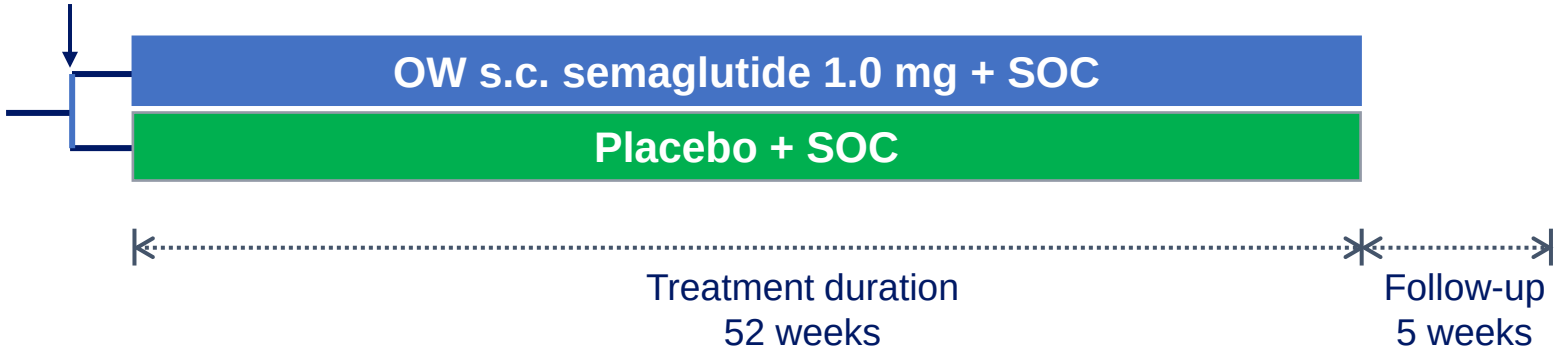
REMODEL: A Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People With Type 2 Diabetes and Chronic Kidney Disease

NCT04865770

105 participants with T2D

- HbA_{1c} ≤9.0% (≤75 mmol/mol)
- RAAS blocker treatment*
- eGFR ≥40 to <75 mL/min/1.73 m^2
- UACR ≥30 to ≤5,000 mg/g†
- Capped SGLT-2i use

Randomisation (2:1)



Trial information

- Multicentre trial
- Assessments included clinical + imaging, kidney biopsies (n=45); multiparametric MRI, GFR measurements, biochemistry and biobanking
- Conducted in Canada, France, Italy, Poland, South Africa, Spain, United States.

Key endpoints

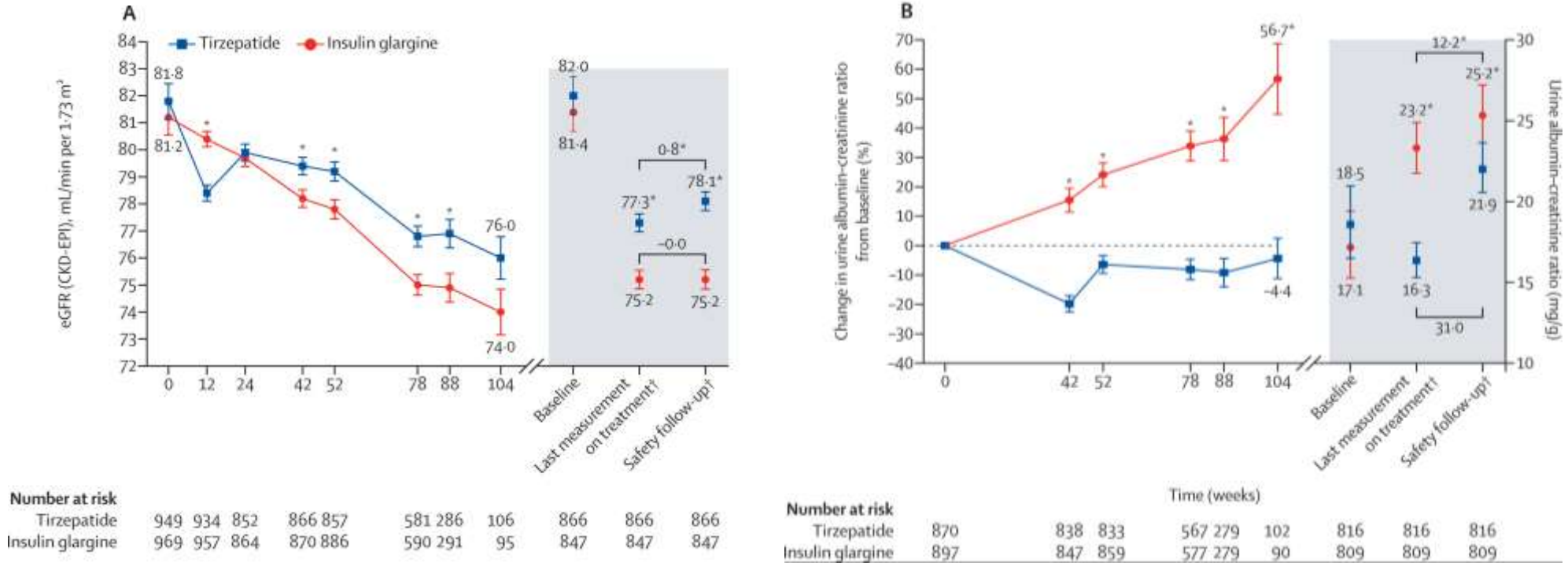
- **Clinical:** Change in UACR and mGFR
- **Anti-inflammation:** change in inflammatory gene expression (single-nucleus RNAseq; from biopsies), biomarkers and T1+T2 mapping (measured using MRI)
- **Oxidative stress:** change in ROS gene expression and biomarkers (circulating and urine)
- **Hemodynamics:** change in kidney hypoxia (measured using MRI) and RAAS biomarkers and gene expression; mean arterial flow & perfusion (measured using MRI)

Steering Committee

Participating countries

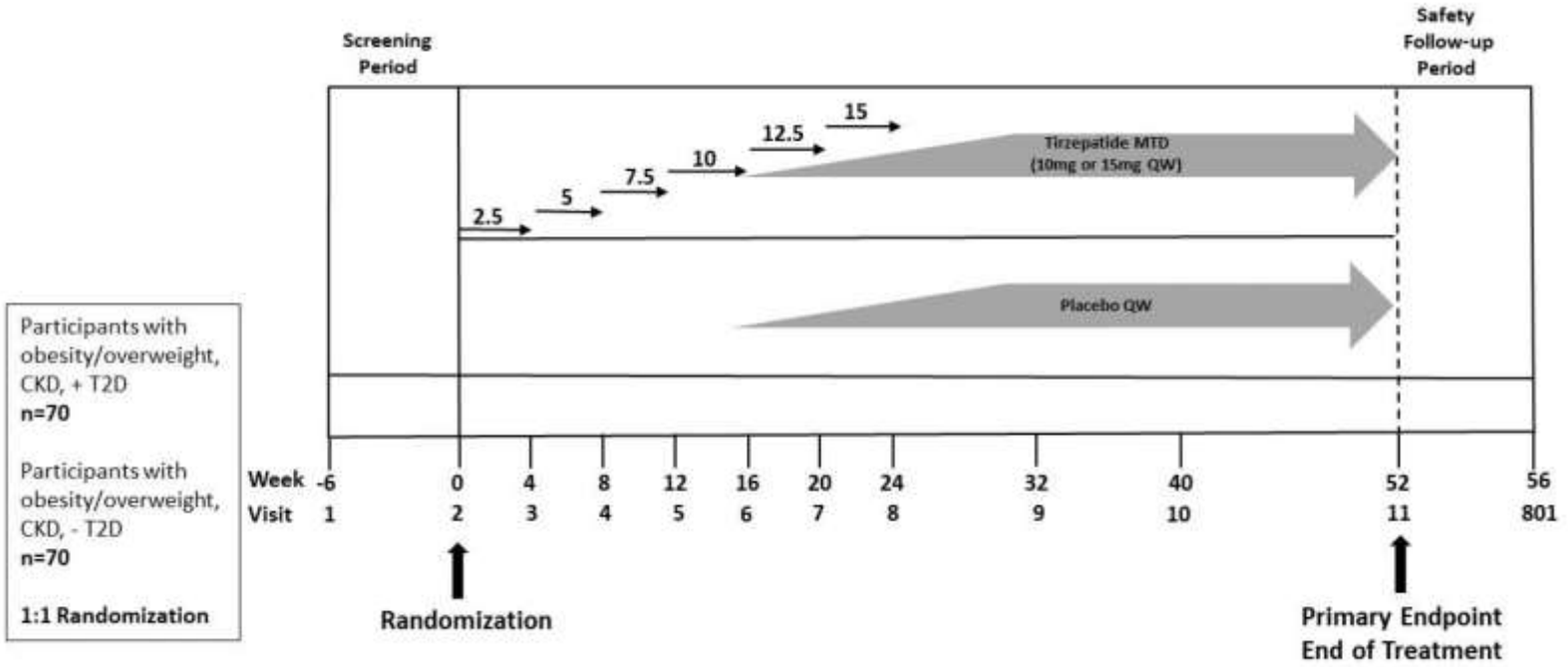
GLP-1/GIP: prelim. evidence for kidney protection

- Posthoc analysis of SURPASS-4 trial (tirzepatide):



Heerspink et al. Lancet Diabet. Endocrinol 2022

TREASURE CKD: Tirzepatide Mechanism of Action Study on Renal Function (TREASURE-CKD)



Key endpoints

- **Clinical:** Change in UACR and mGFR
- **Kidney oxygenation, perfusion and renal blood flow:** multiparametric MRI
- **Kidney oxidative metabolism:** C-11 acetate PET

Steering Committee


van Raalte


Cherney


Bjornstad

Trials in recent years have ended this drought

SGLT-2 inhibitors

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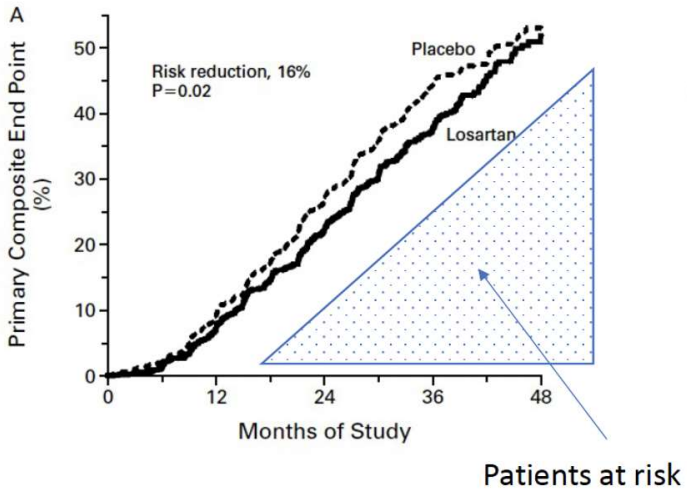
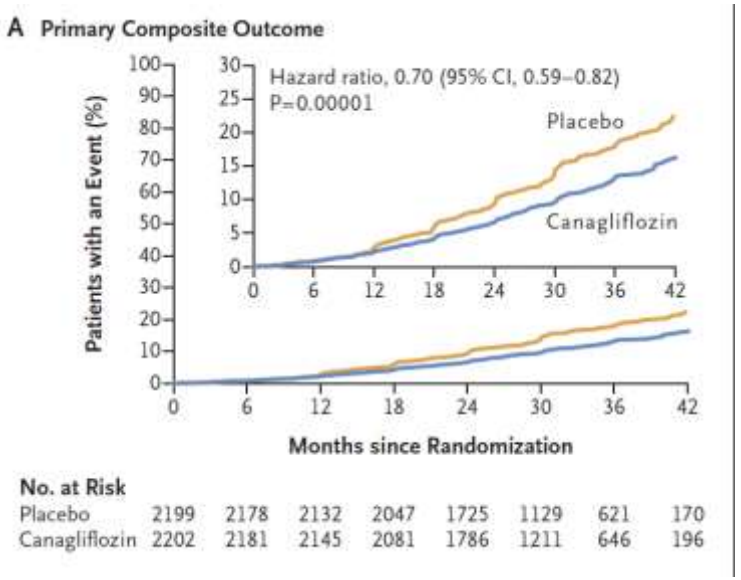
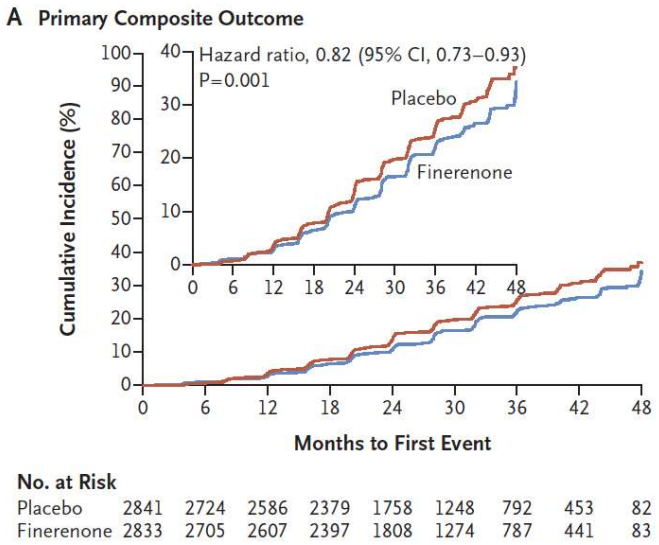
Perkovic et al. *NEJM* 2019 Heerspink et al. *Lancet* 2019

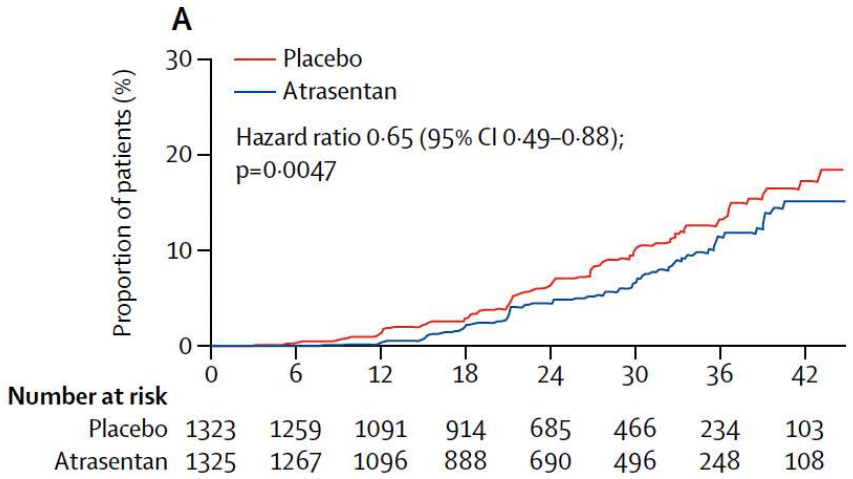
Bakris et al. *NEJM* 2021 RCT NCT 03819153

Do we need to combine these drugs?









How can we combine these drugs?

1) Do these drugs have additive effects (efficacy)? → Mechanism of action

2) Do these drugs have (potential) problematic interactions?

3) Can these drugs mitigate agent-specific adverse effects?

1) Individual kidney protective mechanisms

RAAS blockers

Amelioration of glomerular hyperfiltration

Endothelial effects angiotensin-II blockade

Resulting in postglomerular/efferent dilation

Reduction blood pressure

SGLT-2 inhibitors

Amelioration of glomerular hyperfiltration

Activation of tubuloglomerular feedback

Reduction kidney workload/kidney hypoxia

Reduction blood pressure

MRA: Finerenone

Reduction in fibrosis

Reduction in inflammation

ERA: Atrasentan

Reduction in inflammation

Reduction in glomerular pressure

Improved endothelial function

GLP-1RA

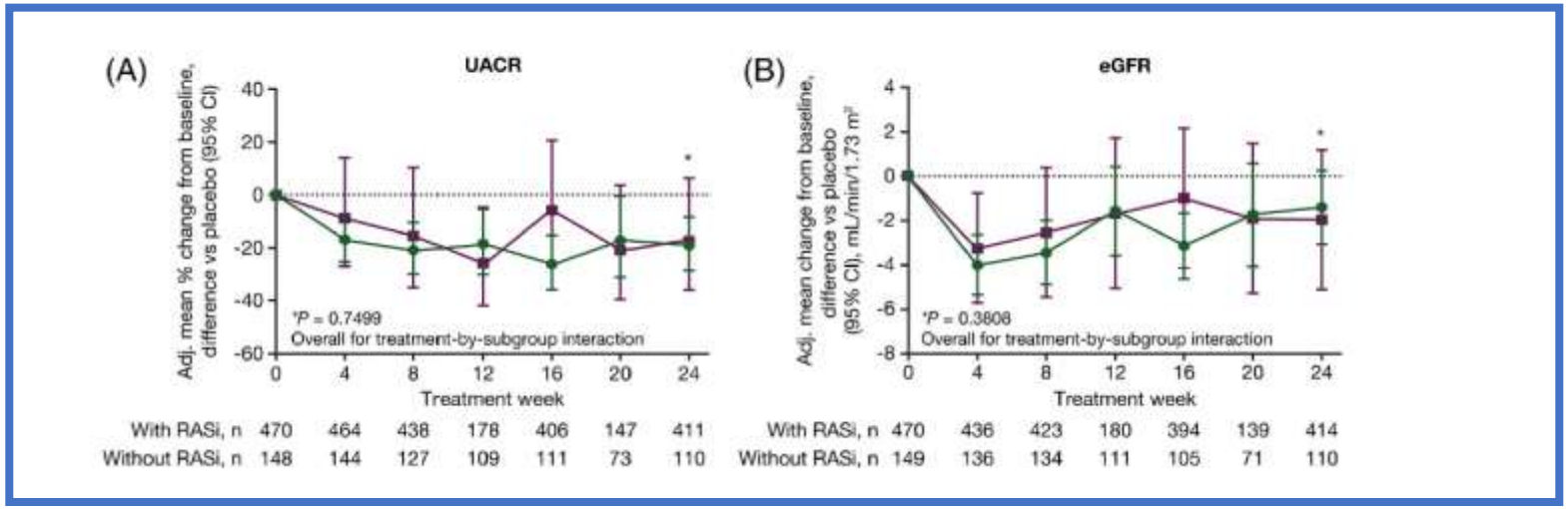
Reduction in fibrosis

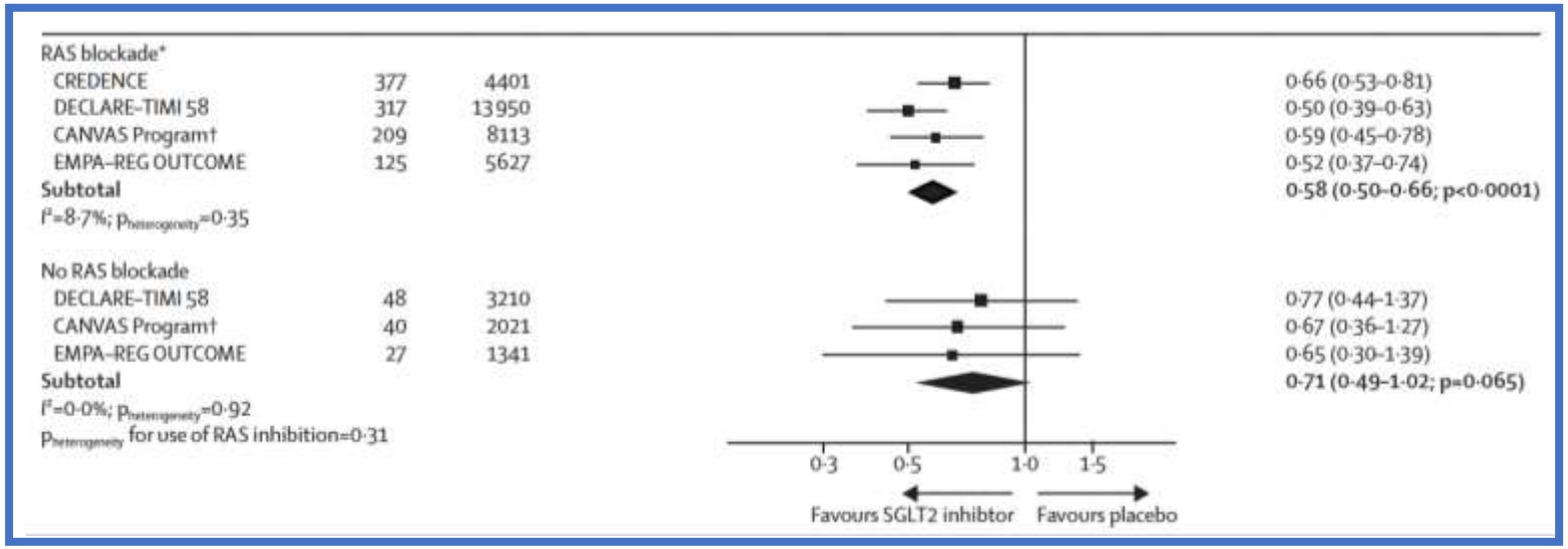
Reduction in inflammation

Improved energetics

Efficacy

RAAS blockers ⟷ **SGLT-2 inhibitors**

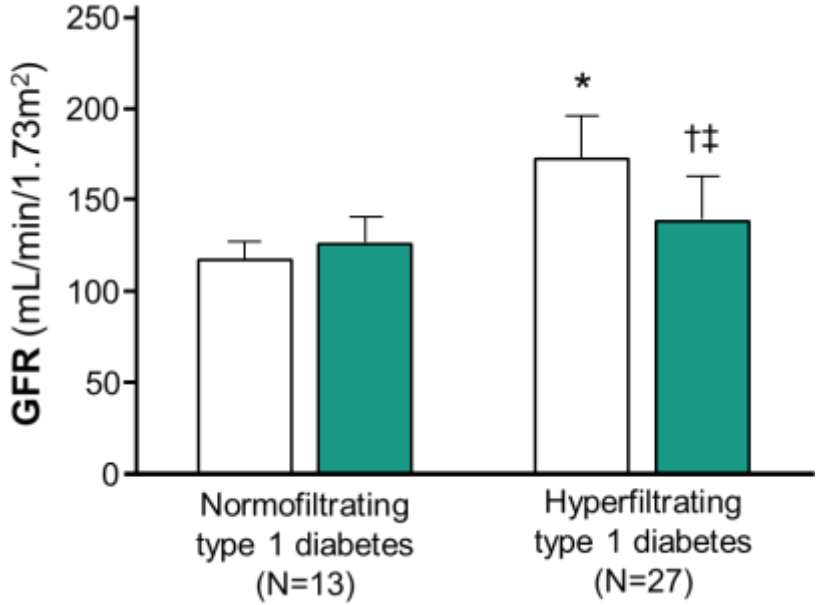


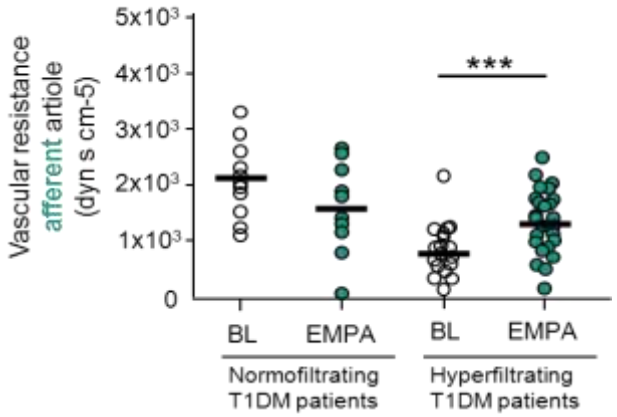


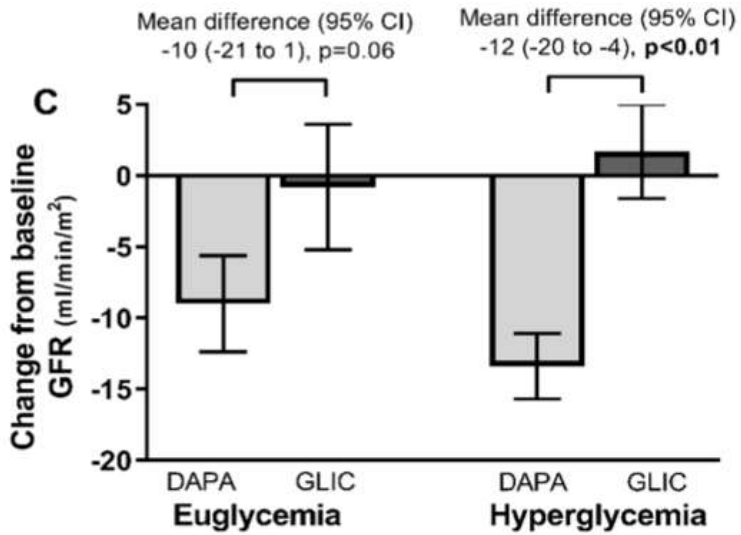
Scholtes, van Raalte et al. *Diab Obes Metab* 2020

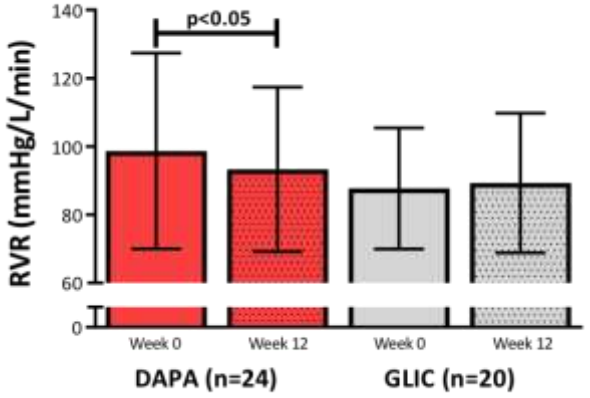
Neuen et al. *Lancet DE* 2019

A closer look at the kidney hemodynamic effects of SGLT2 inhibitors

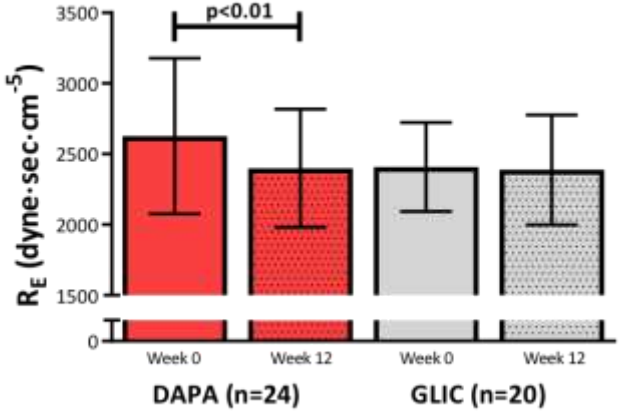




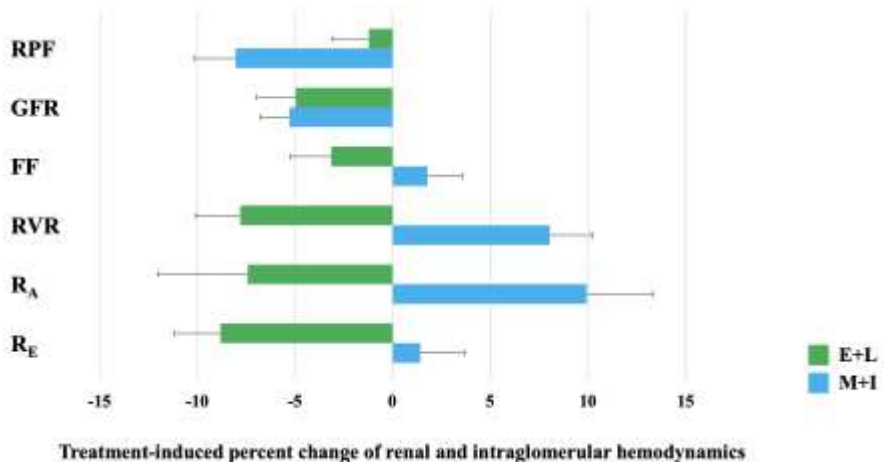




Renal vascular resistance



Estimated postglomerular arteriolar resistance



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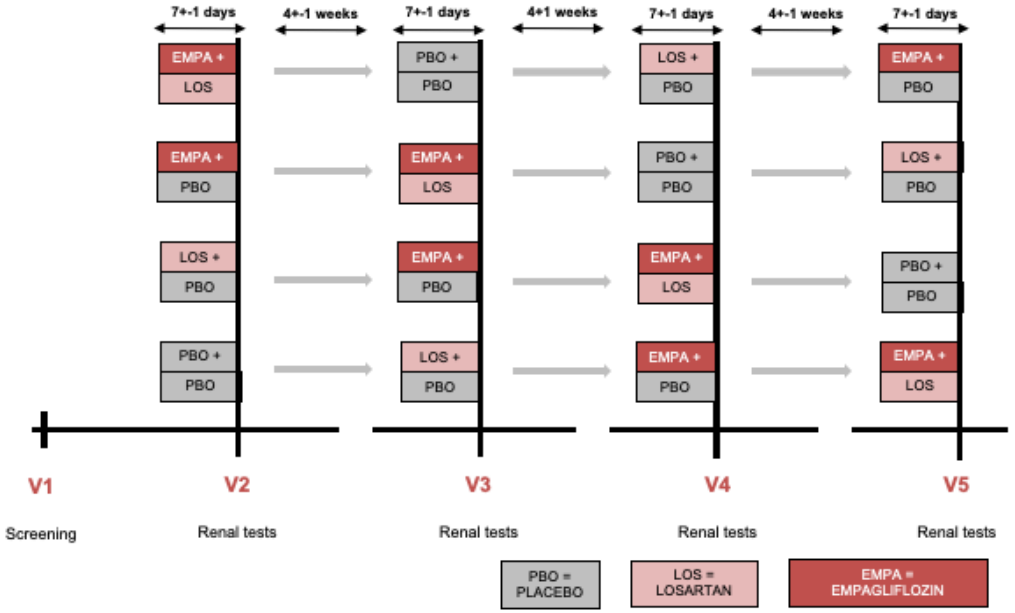
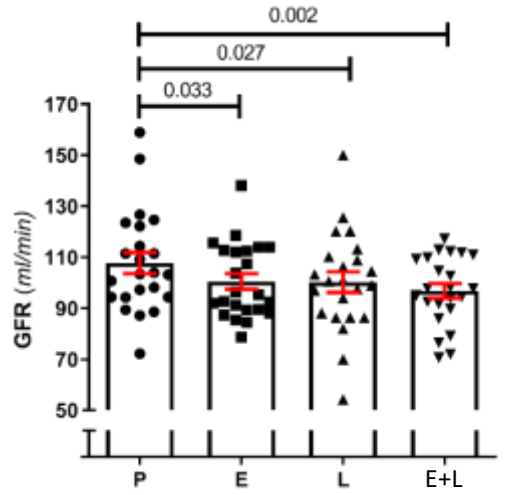
Cherney DZ. Circulation 2014;129(5):587-97.

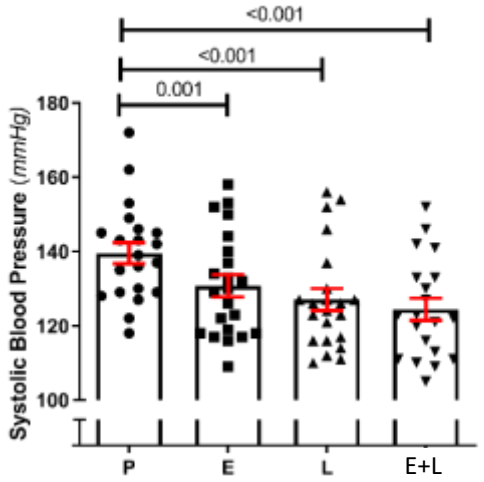
Van Bommel, van Raalte et al. Kidney International

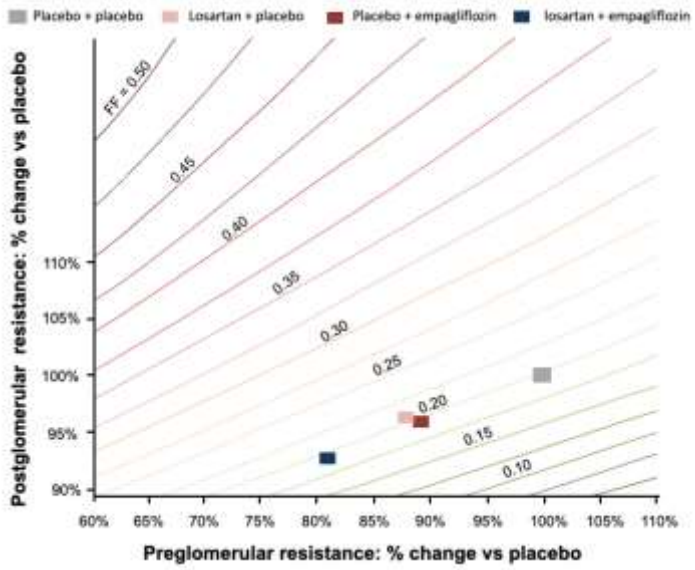
Ott, Schmieder. Cardiovascular diabetology

RECOLAR study









Equation of Hagen-Poisseulle

$$\Delta p = \frac{8\mu LQ}{\pi R^4} = \frac{8\pi\mu LQ}{A^2}$$

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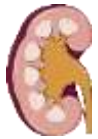
Scholtes, van Raalte,
Circulation 2022 *in press*

Participants & Methods: morphometry

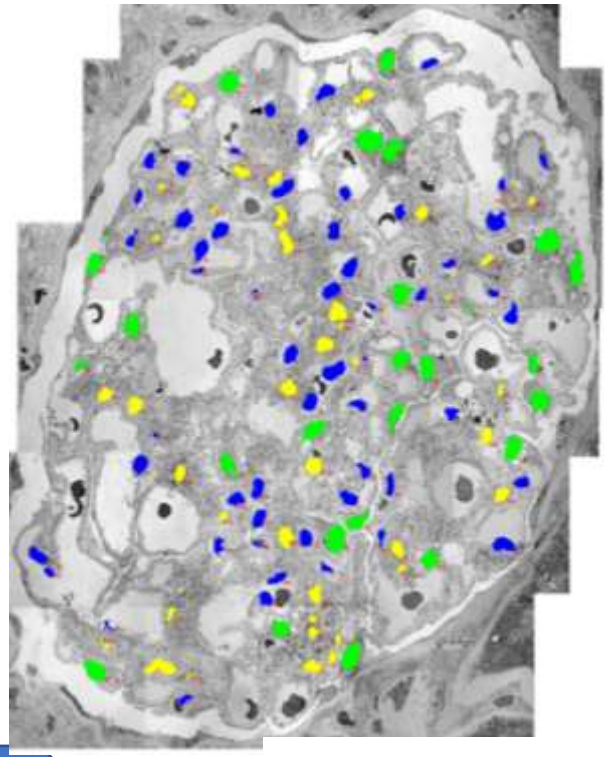
N=237 adults with T2D

Functional parameters

Research kidney biopsy



Median 2.4 months

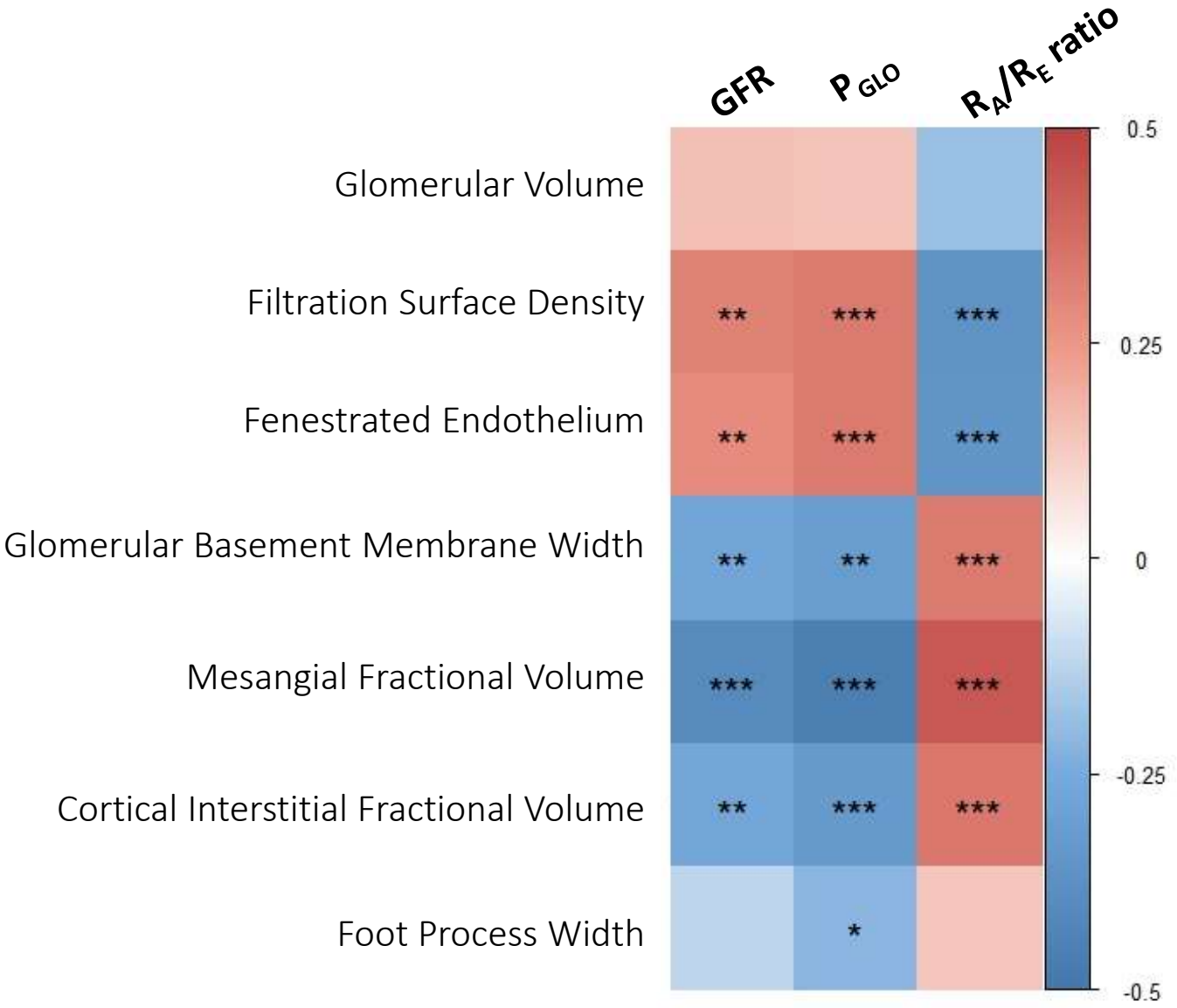


Podocytes
Endothelium
Mesangium

Cross-sectional

Saulnier, Bjornstad et al. Diabetes 2021

Correlations between kidney hemodynamics and structural lesions

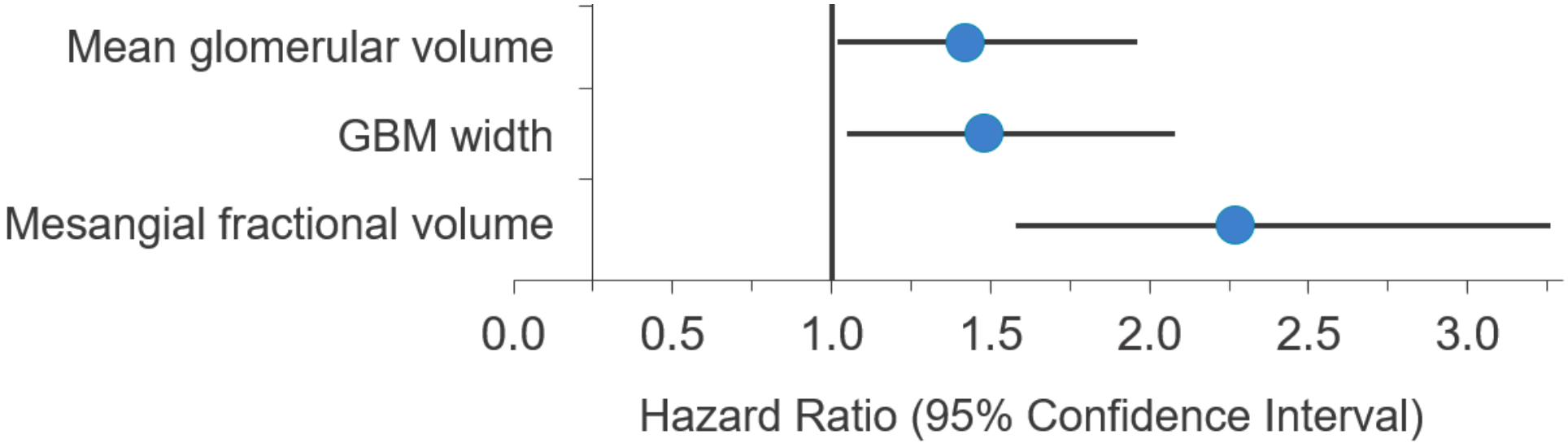


P-values *** <0.0001 **<0.01 *<0.05. Adjustment for age, sex, HbA1c and mean arterial pressure.

Saulnier, Bjornstad et al. Diabetes 2021

Associations of structural lesions and DKD progression

Hazard Ratio and 95% CI for ≥40% Loss of GFR per 1 SD Increment of Each Morphometric Variable

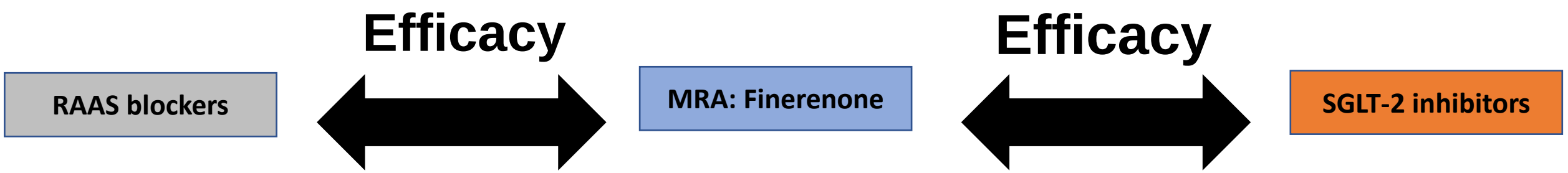


Fufa et al. Clin J Am Soc Nephrol, 2016

Efficacy

- Systematic review and meta-analysis by Li et al examining trials that combined SGLT2 inhibitors + GLP-1RA showed superior effects (compared to monotherapy) on reducing:
  - HbA1c
  - Body weight and BMI
  - SBP
  - LDL-C
- However, outcome trials with kidney endpoints are needed to determine additive effects.

Li et al. Front Pharmacol. 2022



- We have limited data regarding potential additive effects
- Mechanisms seem complementary
- Background FIDELIO: RAAS blockade 100%, SGLT2 inhibition 5%

A Study to Learn How Well the Treatment Combination of Finerenone and Empagliflozin Works and How Safe it is Compared to Each Treatment Alone in Adult Participants With Long-term Kidney Disease (Chronic Kidney Disease) and Type 2 Diabetes (CONFIDENCE)

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/1.73m²
- 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

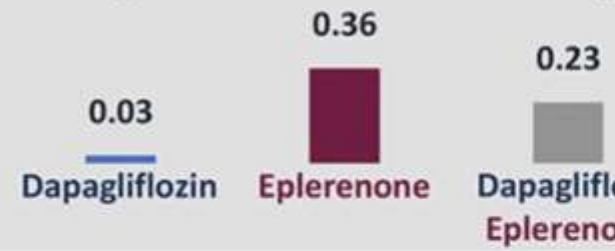
OUTCOMES

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

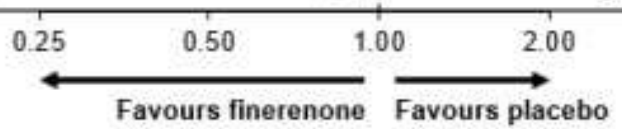
Heerspink et al, ROTATE 3 study, 2022

Efficacy

MRA: Finerenone ⟷ **GLP-1RA**

Figure 1. Analysis of efficacy outcomes in patients receiving/not receiving a GLP-1RA

	Finerenone n/N (%)	Placebo n/N (%)	Finerenone n per 100 PY	Placebo n per 100 PY	Hazard ratio (95% CI)	$p_{interaction}$
Cardiovascular composite						
Overall	825/6519 (12.6)	939/6507 (14.4)	4.34	5.01	0.86 (0.78, 0.95)	
GLP-1RA use at baseline	58/497 (11.7)	64/447 (14.3)	3.79	4.90	0.76 (0.52, 1.11)	0.63
No GLP-1RA use at baseline	767/6022 (12.7)	875/6060 (14.4)	4.38	5.02	0.87 (0.79, 0.96)	
Kidney composite (eGFR ≥ 57%)						
Overall	360/6519 (5.5)	465/6507 (7.1)	1.96	2.55	0.77 (0.67, 0.88)	
GLP-1RA use at baseline	22/497 (4.4)	27/447 (6.0)	1.47	2.10	0.82 (0.45, 1.48)	0.79
No GLP-1RA use at baseline	338/6022 (5.6)	438/6060 (7.2)	2.01	2.59	0.77 (0.67, 0.89)	
All-cause mortality						
Overall	552/6519 (8.5)	614/6507 (9.4)	2.76	3.10	0.89 (0.79, 1.00)	
GLP-1RA use at baseline	33/497 (6.6)	25/447 (5.6)	2.05	1.79	0.97 (0.56, 1.67)	0.41
No GLP-1RA use at baseline	519/6022 (8.6)	589/6060 (9.7)	2.83	3.20	0.89 (0.79, 1.00)	



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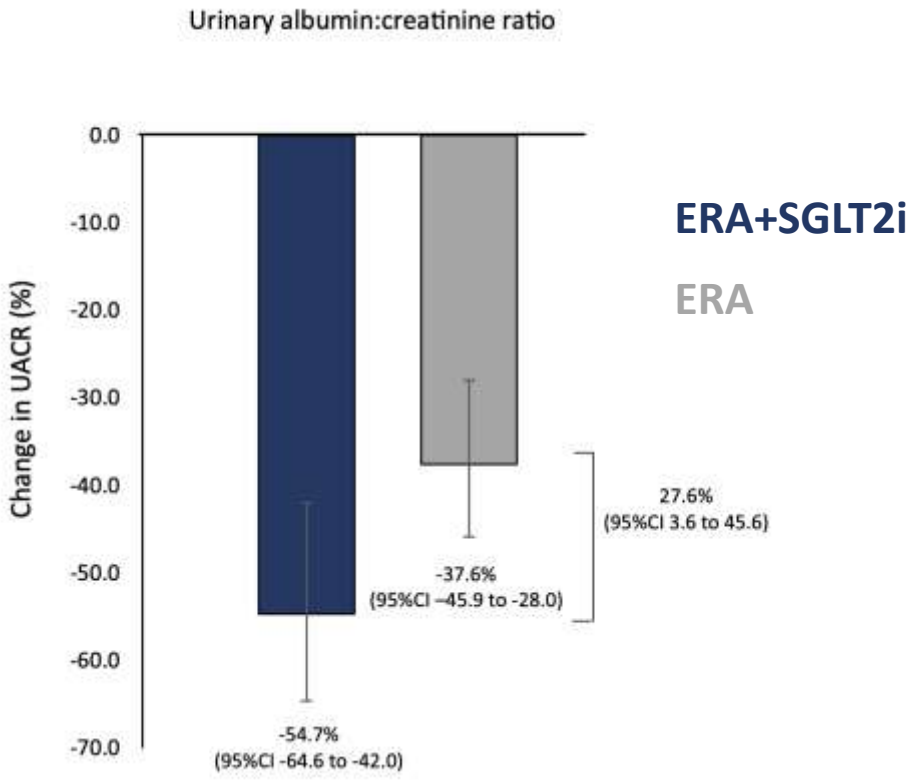
Rossing et al. DOM 2022

- We have limited data regarding additive effects
- Mechanisms seem complementary
- Background SONAR:
  - RAAS blockade 100%
  - SGLT2 inhibition 1-2%



Zibotentan and Dapagliflozin for the Treatment of CKD (ZENITH-CKD Trial) (ZENITH-CKD)

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Heerspink H. *Kidney interational* 2021.

2) Potential interactions between drugs; 3) safety/side effects

RAAS blockers

Hypotension/dehydration

Small increment in potassium levels

SGLT-2 inhibitors

Genital mycotic infections

Dehydration/hypovolemia

Fractures/amputations

Euglycemic DKA

MRA: Finerenone

Hyperkalemia

Little anti-androgen effects

ERA: Atrasentan

Edema/fluid retention

Hospitalization for heart failure

GLP-1RA

Gastrointestinal

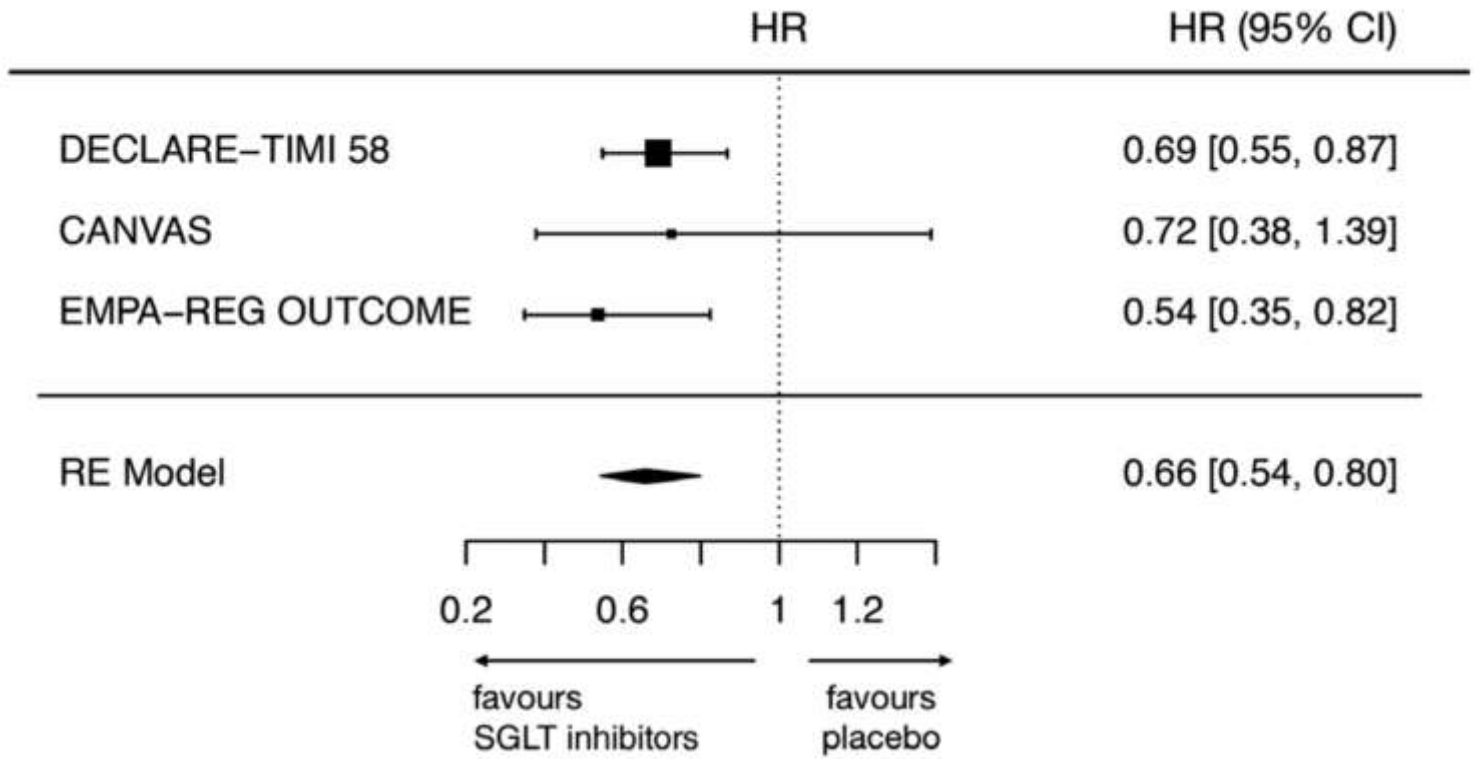
Hypoglycemia

Progression of retinopathy

Safety

RAAS blockers ⟷ **SGLT-2 inhibitors**

- Worries regarding potential increments in acute kidney injury (AKI)

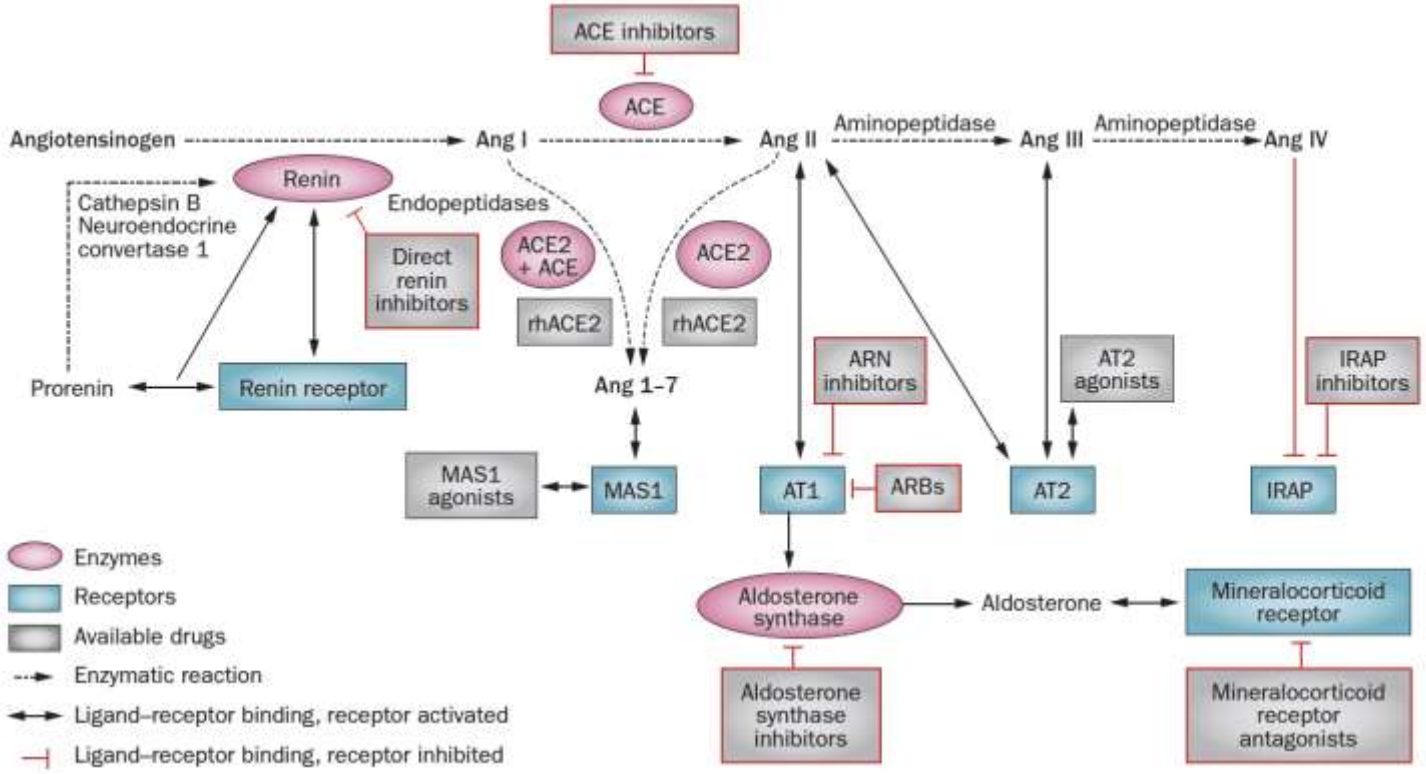


Gilbert, Diab Obes Metab 2019

Safety

RAAS blockers ⟷ **SGLT-2 inhibitors**

- SGLT2 increase plasma renin and aldosterone levels



MAS1 activation

- Antifibrotic effects
- Anti-inflammatory effects
- Increased baroreflex sensitivity
- Antiproliferative effect on vascular smooth muscle cells
- Nitric oxide release

Romero et al. *Nat Rev Endocrinol 2015*

- The main problem with finerenone is hyperkalemia (K > 5.0 mM excluded in outcome trials)

	SGLT2 inhibitors		Placebo		
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	Hazard Ratio (95% CI)
CANVAS Program	137/5795	8.2	85/4347	9.2	0.89 (0.67, 1.17)
CREDENCE	121/2202	21.6	154/2199	27.9	0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3	0.88 (0.71, 1.09)
DECLARE-TIMI 58	53/8582	1.6	78/8578	2.3	0.67 (0.47, 0.95)
EMPA-REG OUTCOME	216/4687	17.2	124/2333	20.5	0.83 (0.67, 1.04)
VERTIS CV	291/5493	18.7	157/2745	21.2	0.90 (0.74, 1.09)
Overall (I^2=0.0%; $P_{heterogeneity}$=0.71)					**0.84 (0.76, 0.93)** P<0.001

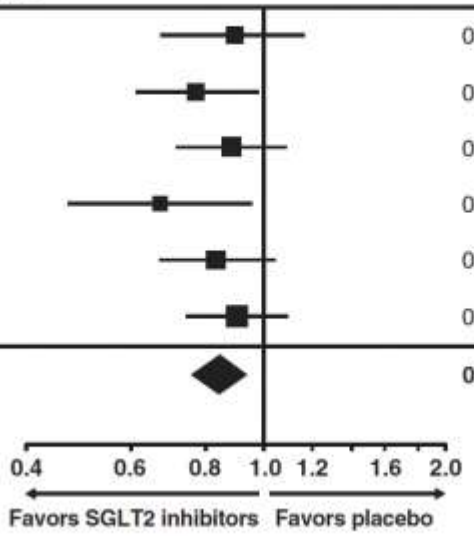


Figure 1. Effects of SGLT2 inhibitors on serious hyperkalemia (central laboratory–determined serum potassium ≥6.0 mmol/L).

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Neuen et al. *Circulation* 2022

Safety

Safety

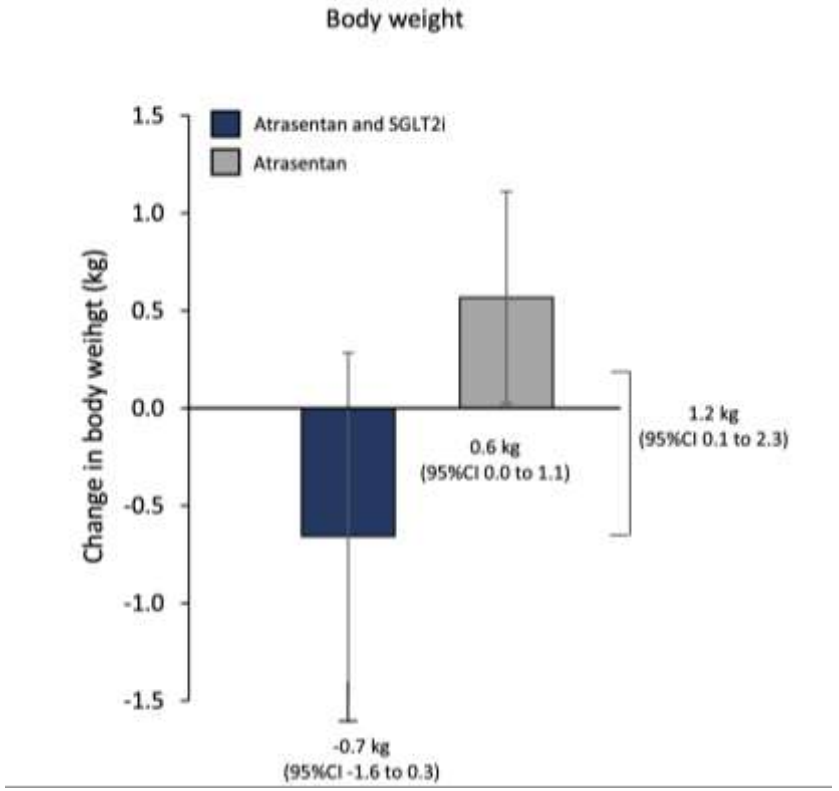
RAAS blockers

ERA: Atrasentan

SGLT-2 inhibitors

- The main problem with ERA is fluid retention and hypertensive HF (despite stringent NT-proBNP levels in exclusion criteria)

**Interaction studied in the ongoing ZENITH-CKD trial (Zibotentan and Dapagliflozin)*



Heerspink et al. Kidney Int. 2020

Conclusions

- Additive vasodilative kidney hemodynamic actions contributing to beneficial mGFR ”dip”
- Additive beneficial effects on systemic blood pressure
- Combination is safe
- Support early combination of these drugs to halt DKD

- Interaction studies are largely unavailable
- Based on different mechanism of action, efficacy could be additive
- No major safety concerns with respect to side effects
- SGLT2 could off-set specific adverse effects of ERA and MRA drugs

Current knowledge gaps

- Mechanism of action data for finerenone and ERA in humans
- Cross-over combination therapy studies
- DKD versus non-diabetes CKD studies
- Studies in people with T1D and youth with T2D
- Outcome trials for dual (e.g., tirzepatide) and triple incretin agonists

New Guidelines!

Screening recommendations

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:
- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

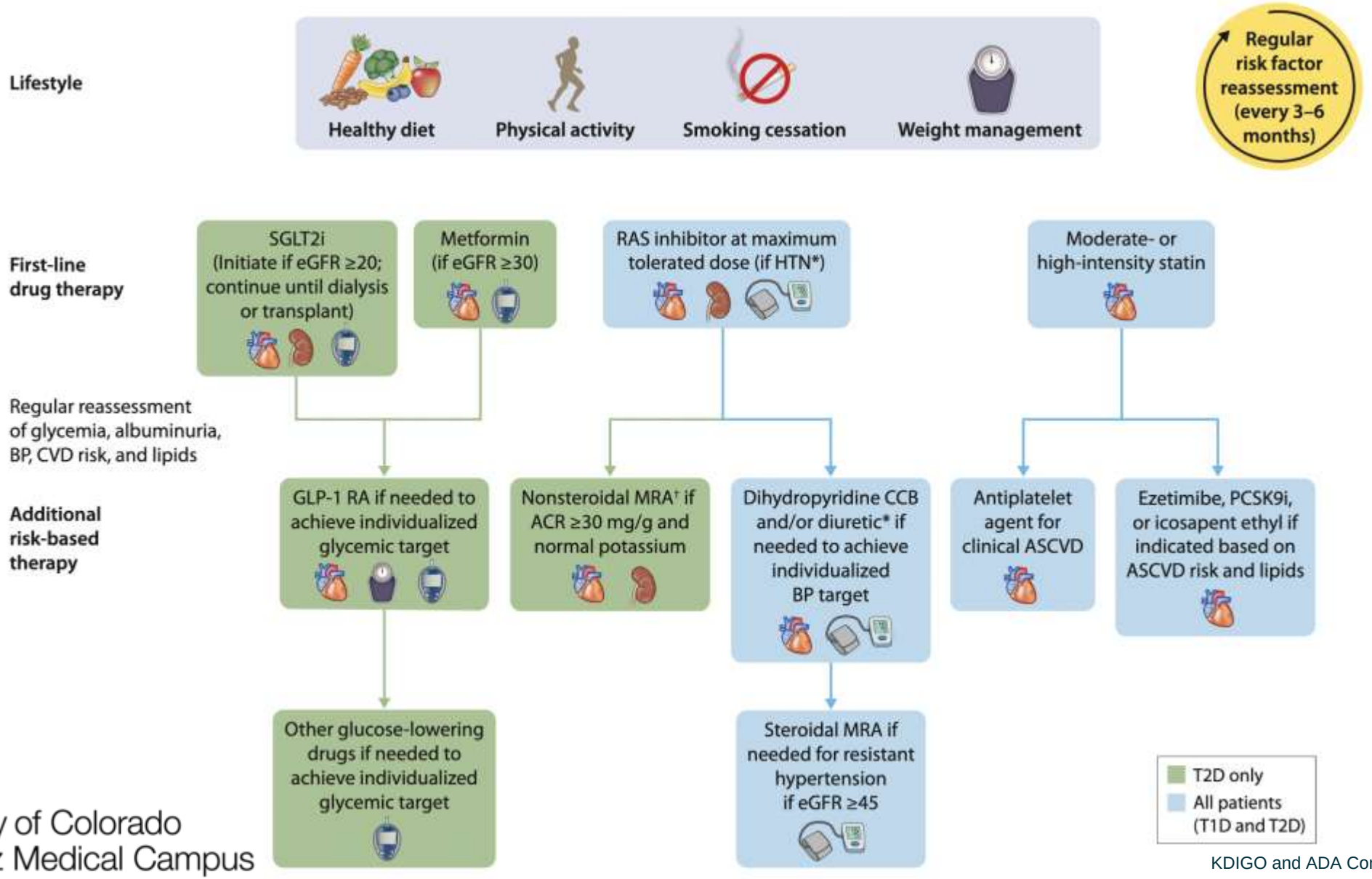
Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

KDIGO Consensus. Kidney Int. 2022

Management recommendations



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KDIGO and ADA Consensus. Diabetes Care 2022

Management recommendations

Table 2—Considerations for selecting glucose-lowering agents in patients with T2D and CKD (2,17)

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor			Potential				
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Missing MRA, ERA, and dual and triple incretin agonists

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

University of Colorado Anschutz Medical Campus

KDIGO and ADA Consensus. Diabetes Care 2022

Collaborators

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- David M. Maahs

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- Meda Pavkov

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- Chirag Parikh

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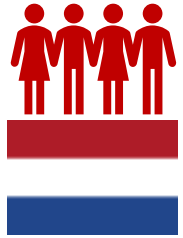
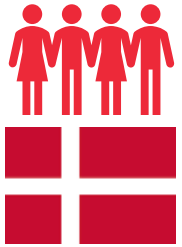
- Yuliya Lytvyn
- Erik Lovblom
- Etienne Sochett



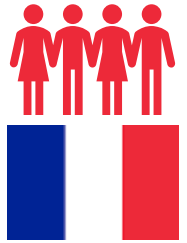
VU University Medical Center:
- Daniel van Raalte ← *Adapted some of his slides from ADA*

UMCG:
- Hiddo Lambers Heerspink

University of Helsinki:
- Daniel Gordin



Steno Diabetes:
- Peter Rossing
- Frederik Persson



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