SGLT2 remmers bij chronische nierschade zonder diabetes

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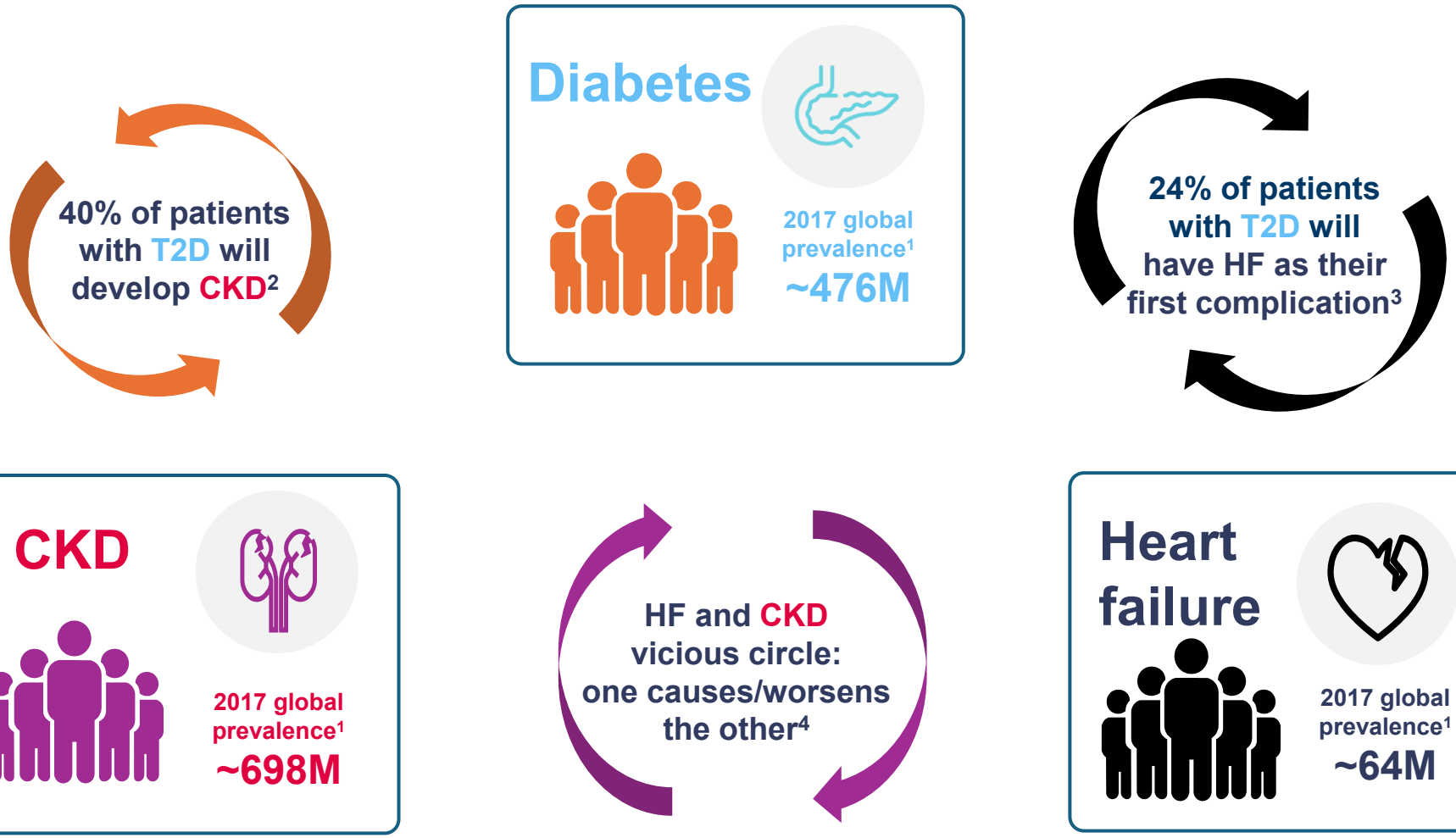
Overzicht

- Impact CKD en cardiokidney metabool syndroom (CKMS)
- Hoe werken SGLT2 remmers?
- CKD data in mensen met en zonder diabetes
- Overige ontwikkelen in non-diabetes CKD

CKD, heart failure, and T2D are interrelated, leading to a vicious circle of cardiac, renal, and metabolic risk



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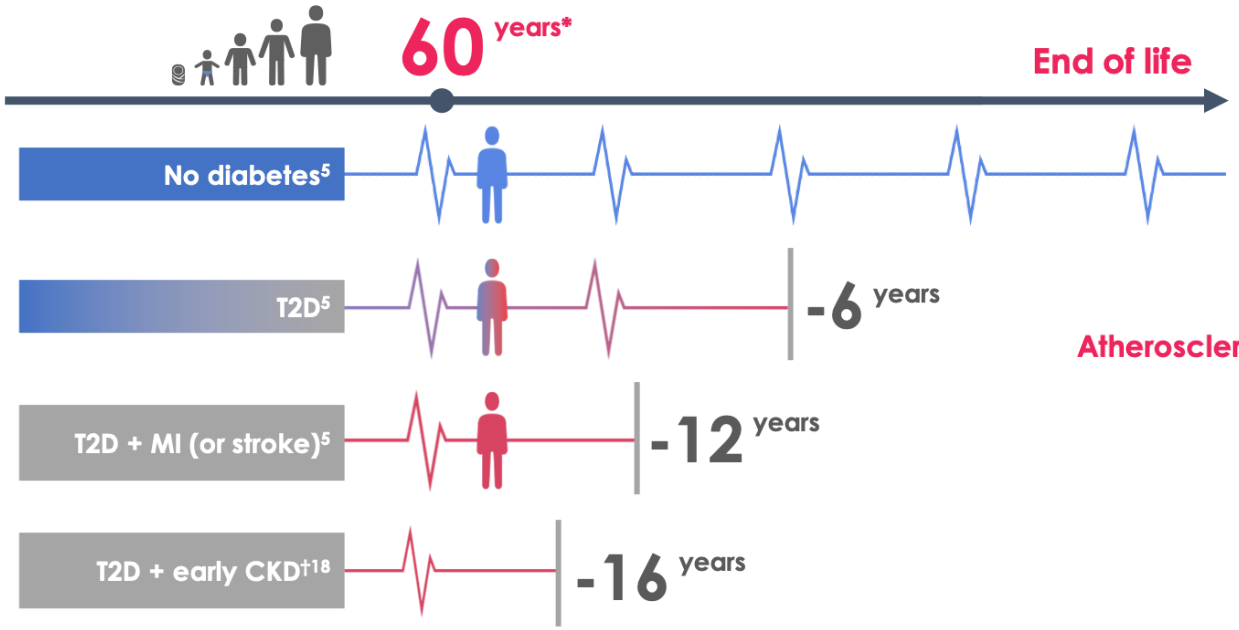
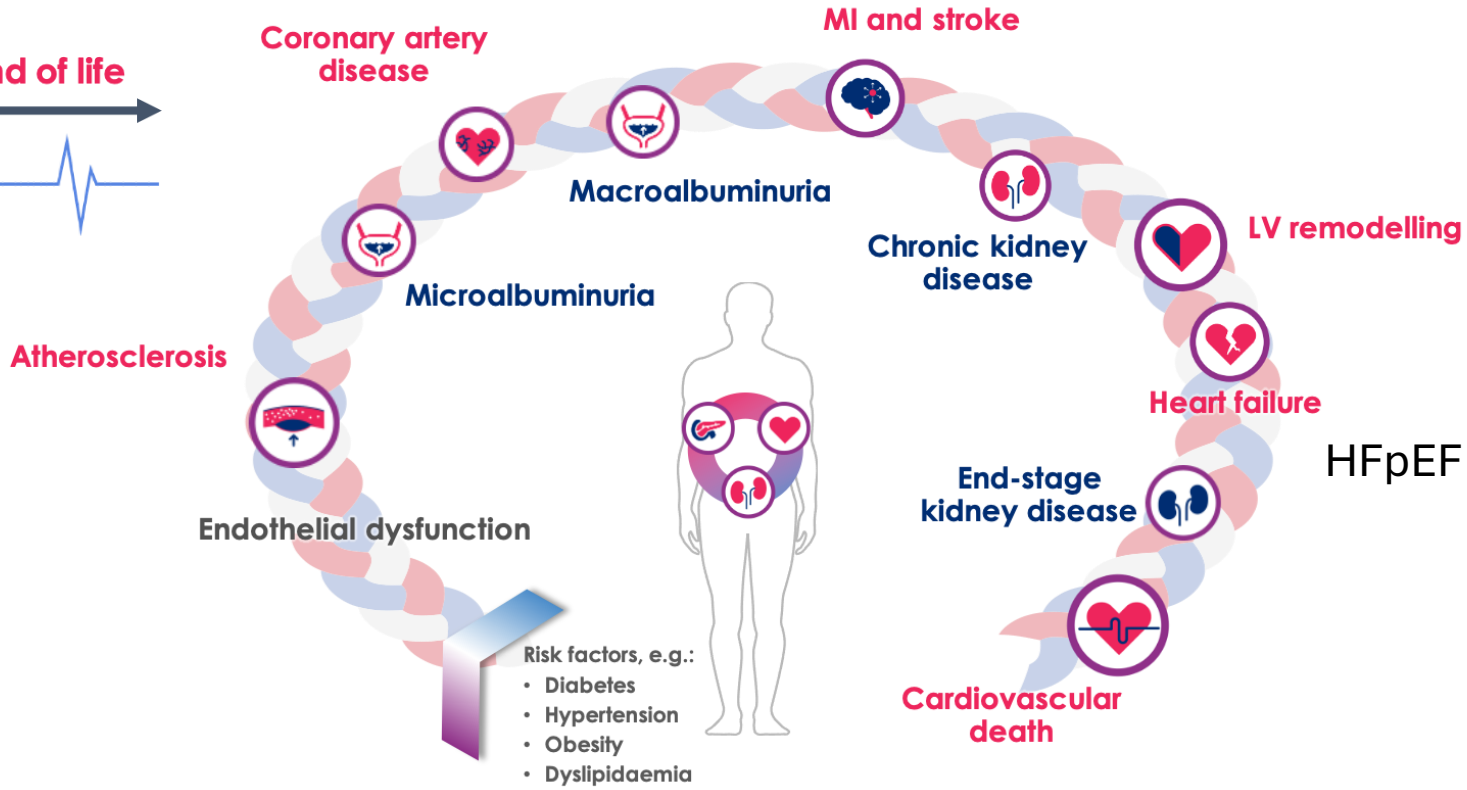
CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet* 2018;392:1789–1858; 2. Parving HH, et al. *Kidney Int* 2006;69:2057–2063; 3. Birkeland KI, et al. *Diabetes Obes Metab* 2020:22:1607–1618; 4. Ronco C, et al. *J Am Coll Cardiol* 2008;52:1527–1539

Reduced life expectancy in chronic kidney disease





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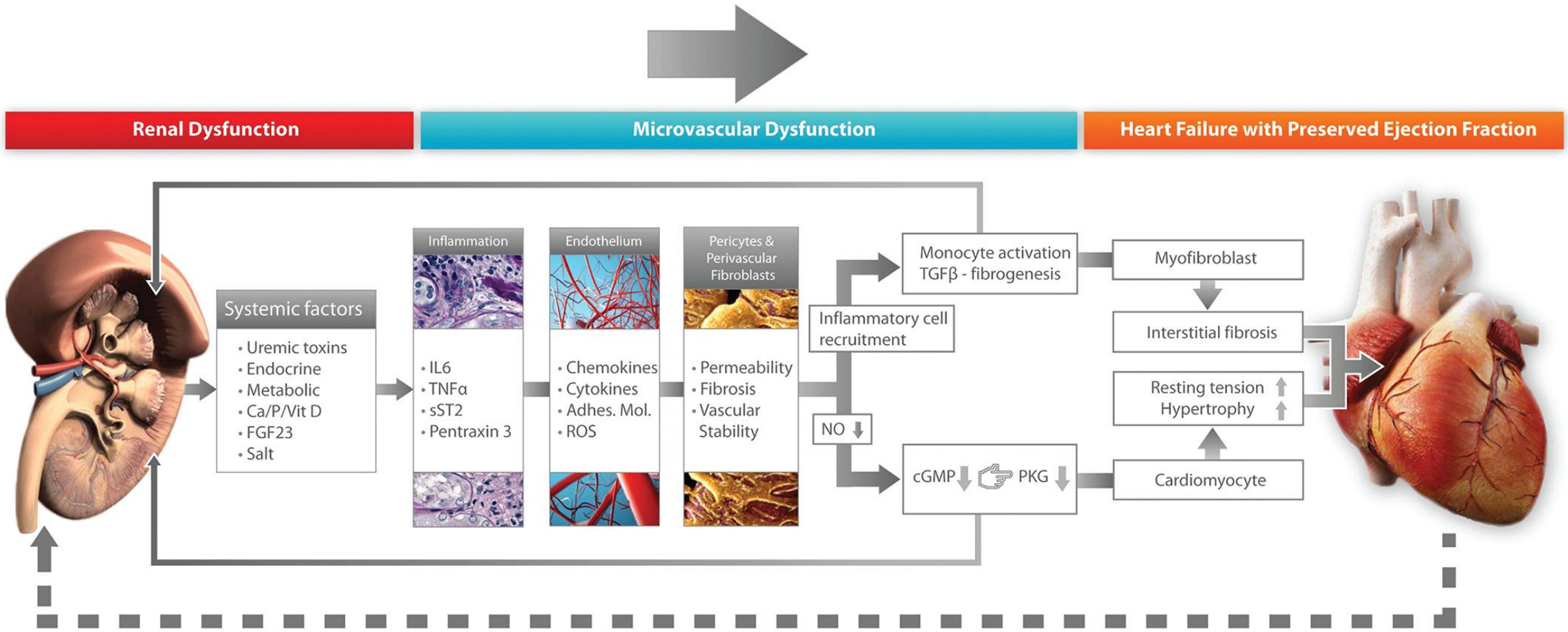
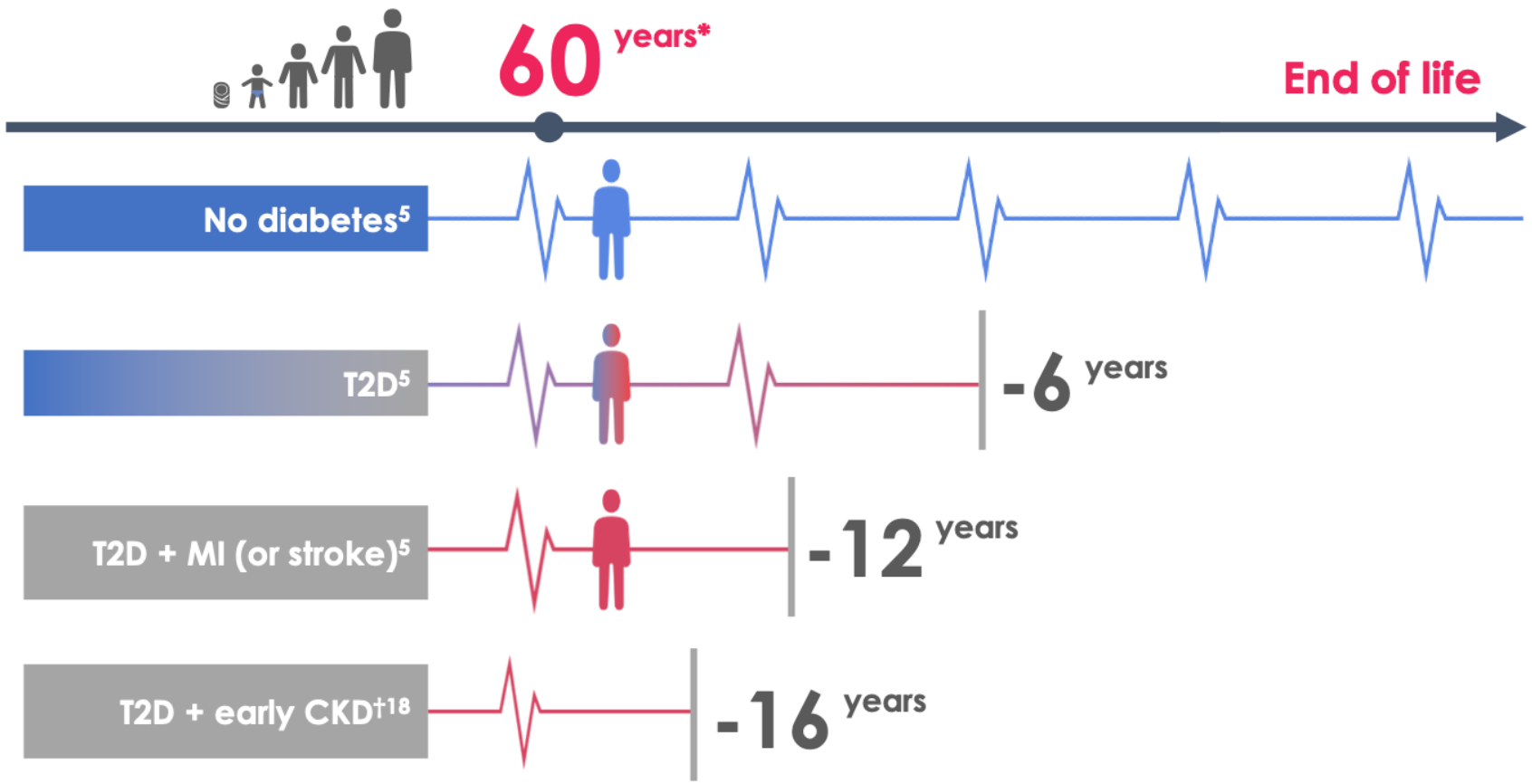
Kopyt N. *JAOA* 2005;105:207
Wen C. *Kidney Int*

Endothelial dysfunction and inflammation connect cardio kidney disease

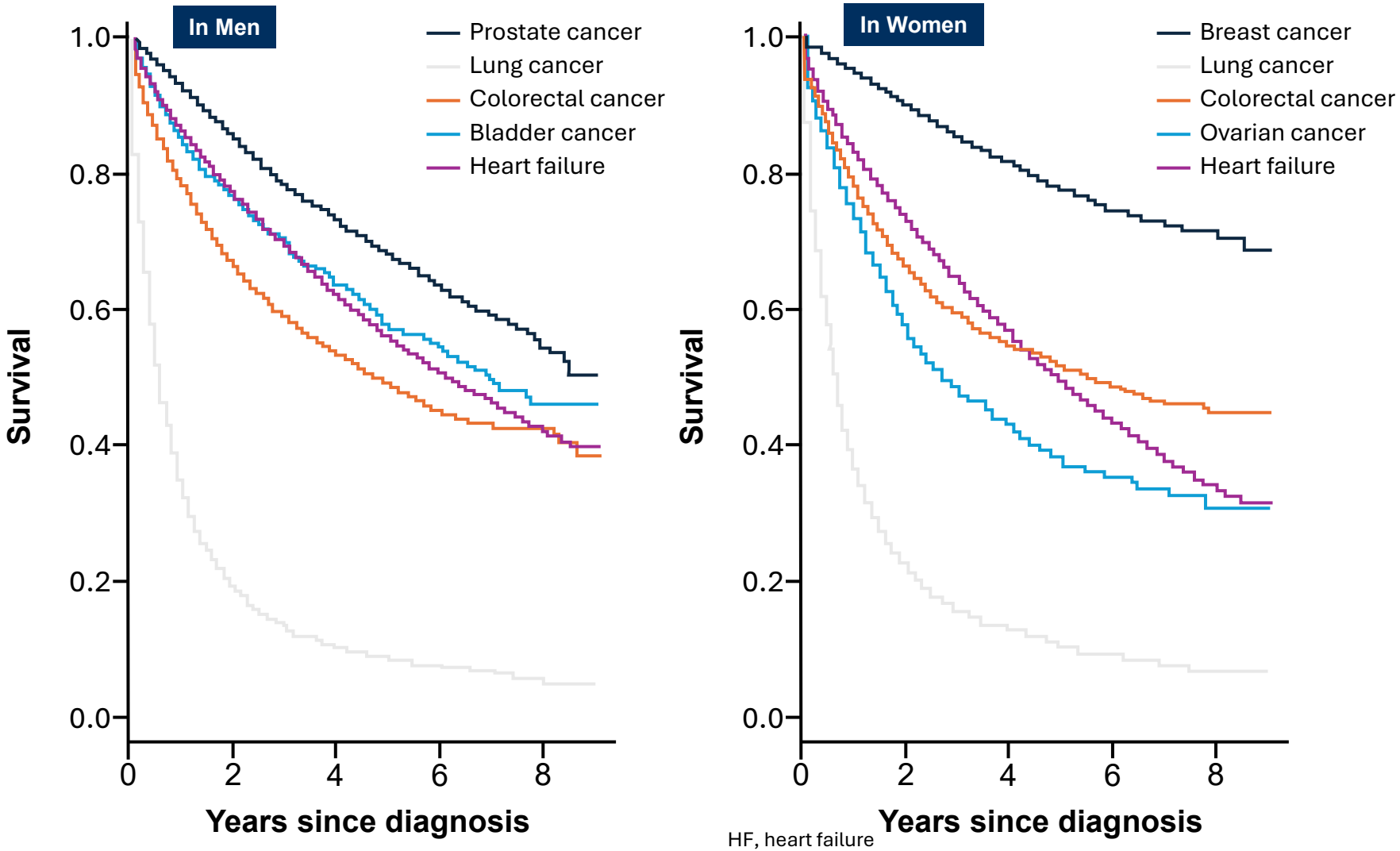


Why is it important to treat or prevent chronic kidney disease?



Hartfalen komt frequent voor en heeft een slechte uitkomst

Despite advances in care, men and women with a diagnosis of HF continue to have worse survival than patients with one of several common cancers



HF, heart failure

Mamas MA. et al. *Eur J of Heart Failure* 2017.19:1095–1104

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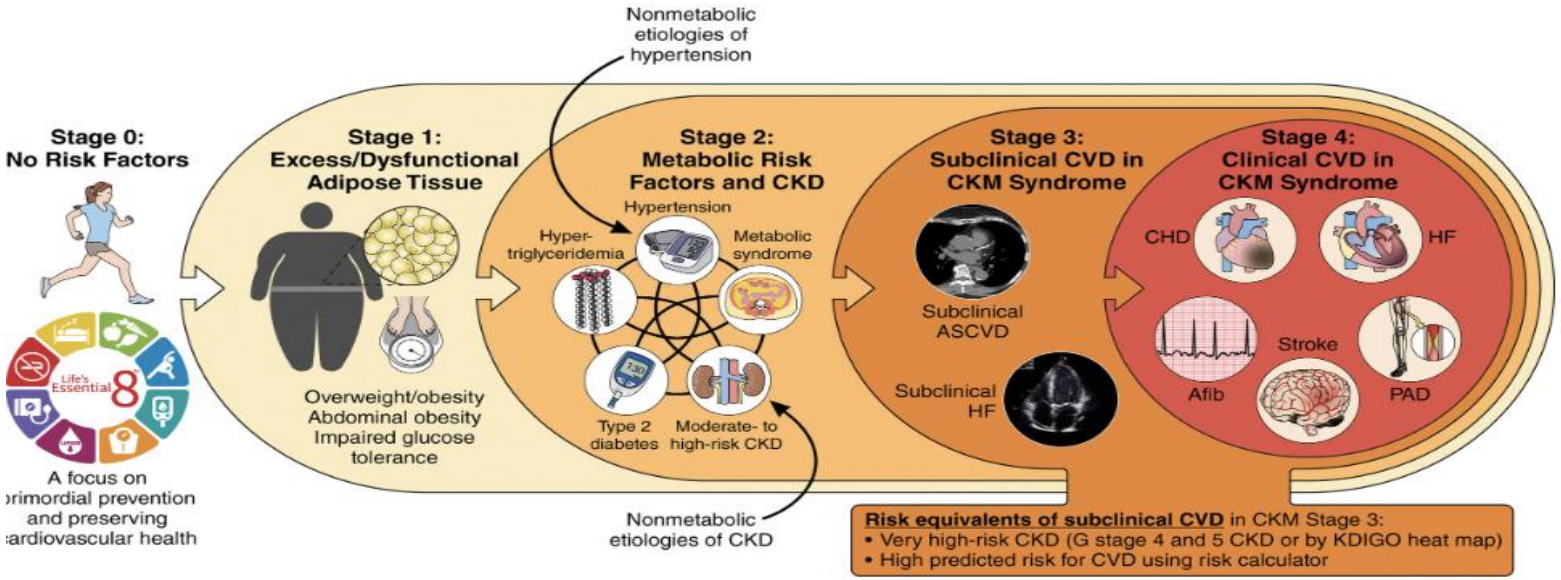
American Heart Association.

AHA PRESIDENTIAL ADVISORIES

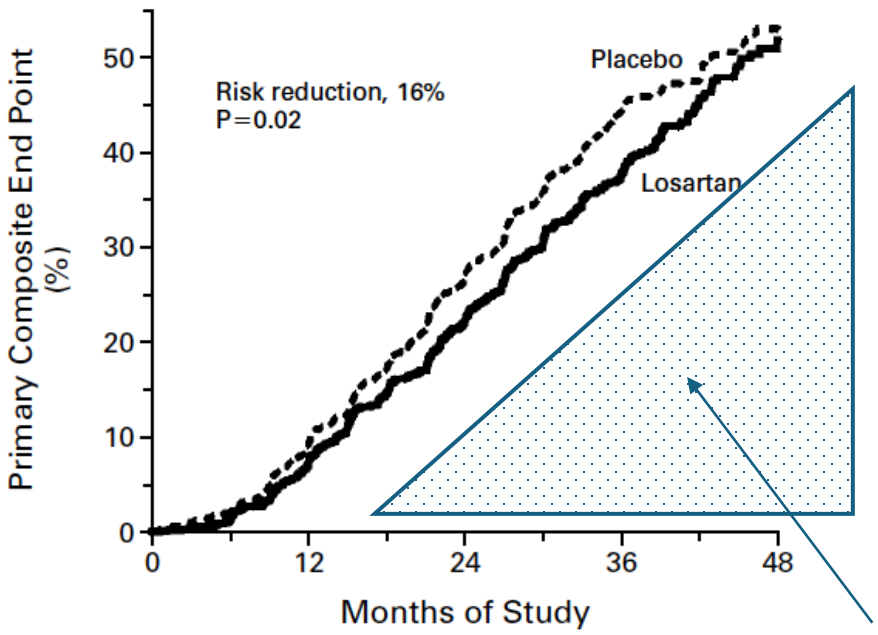
Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association



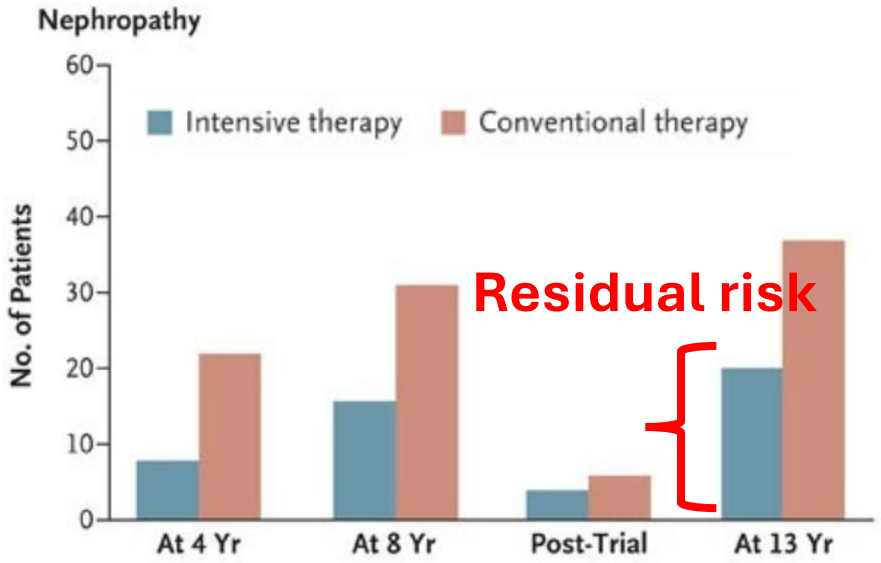
Residual risk remains high

Target risk factors:

1. Hyperglycemia (in case of diabetes)
2. Hypertension (RAAS blockers if albuminuric)
3. Obesity
4. Dyslipidemia
5. Sodium/protein intake



Patients at risk



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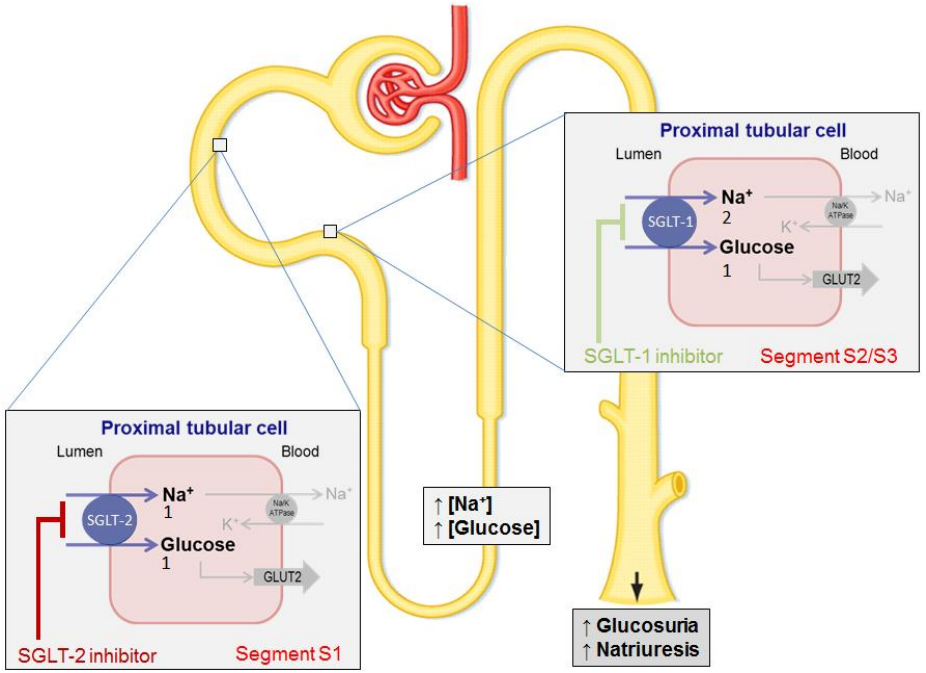
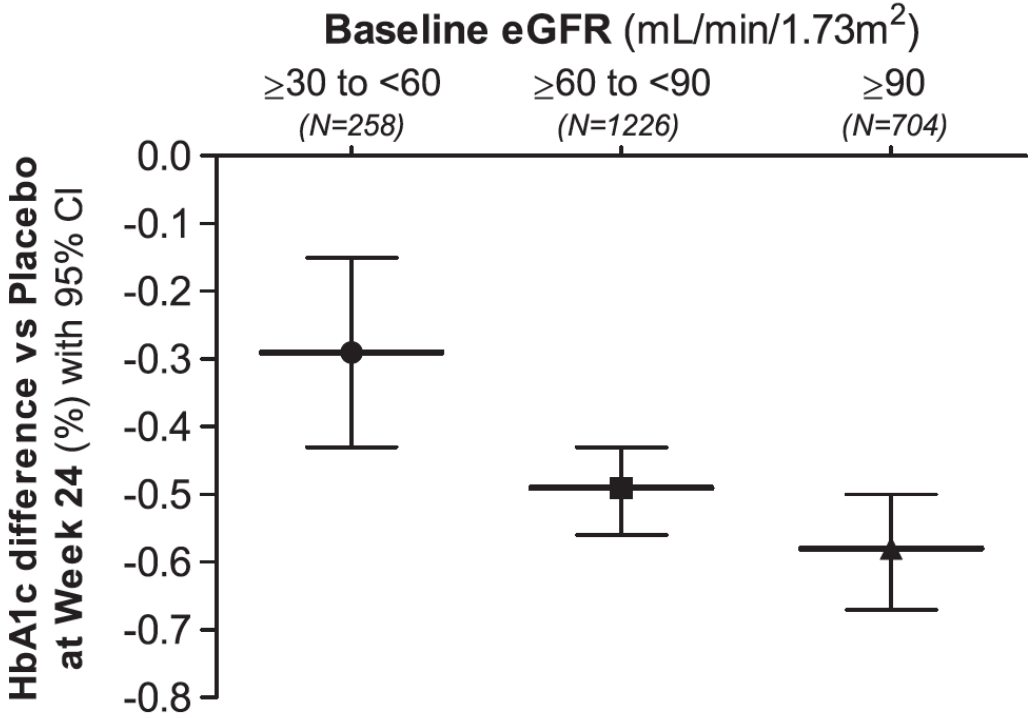
Gaede et al. *NEJM* 2008

RENAAL. Brenner et al. *NEJM* 2001

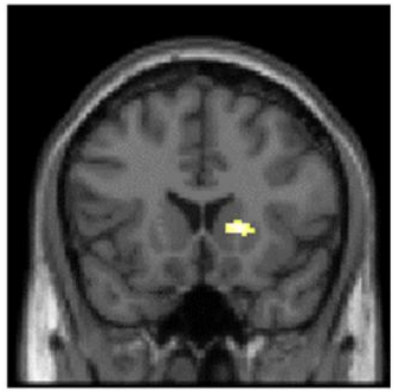
SGLT2 inhibitors: invented for glucose lowering

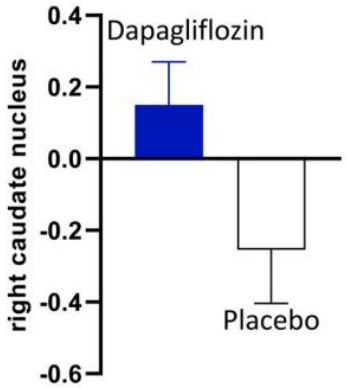


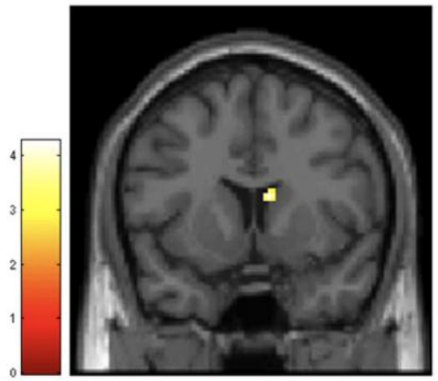


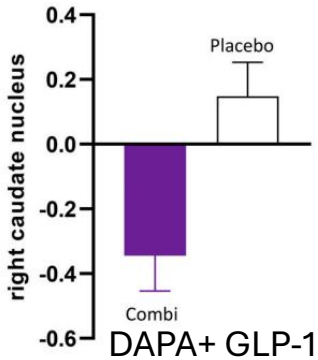
Counterregulatory responses

- SGLT2i: reduction of 250-450 kcal/day
- Expected weight loss: 8 kg
- Observed weight loss: 2-4 kg



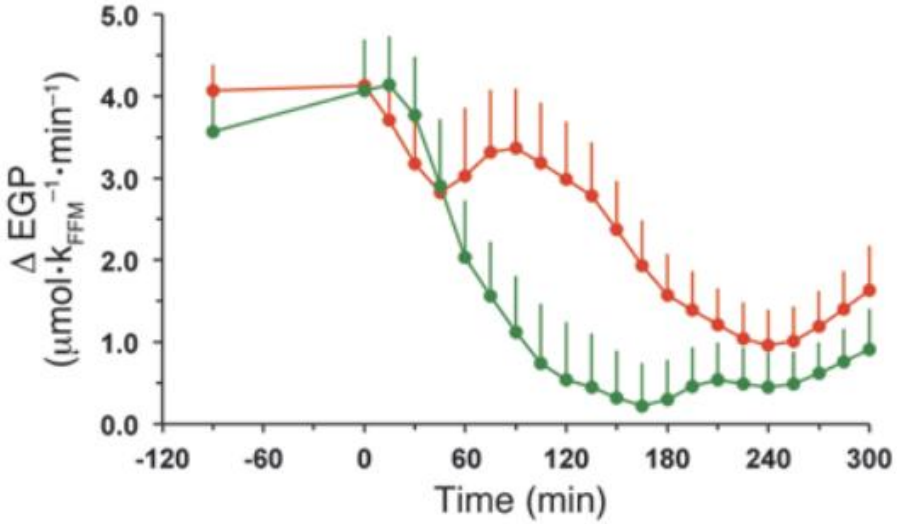






DAPA+ GLP-1

SGLT2i increase liver glucose production



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Ferrannini; JCI 2014

Van Ruiten; Diabetes Obes Metab 202

SGLT-2 inhibitors in T2D

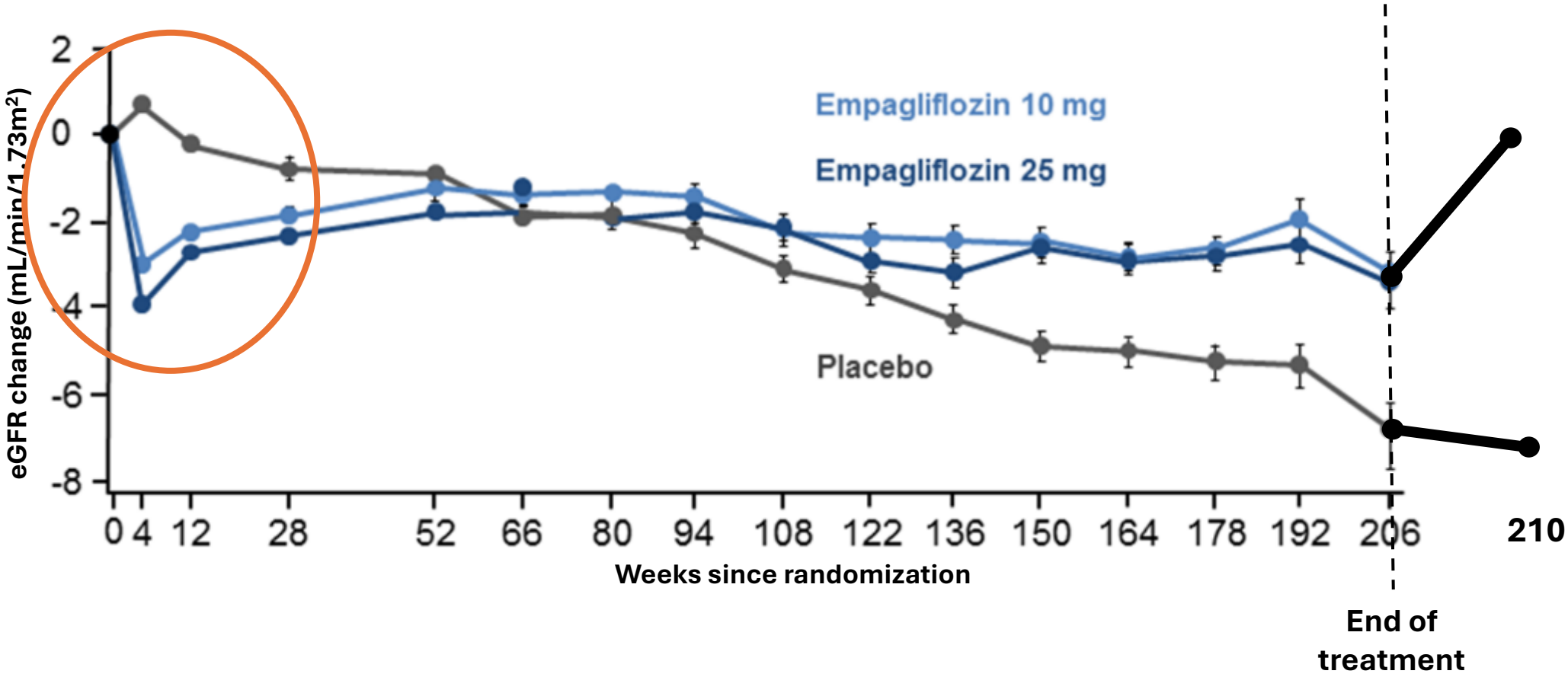
Advantages:

- Low risk of hypoglycemia
- Works in any type of patient with hyperglycemia

Disadvantages:

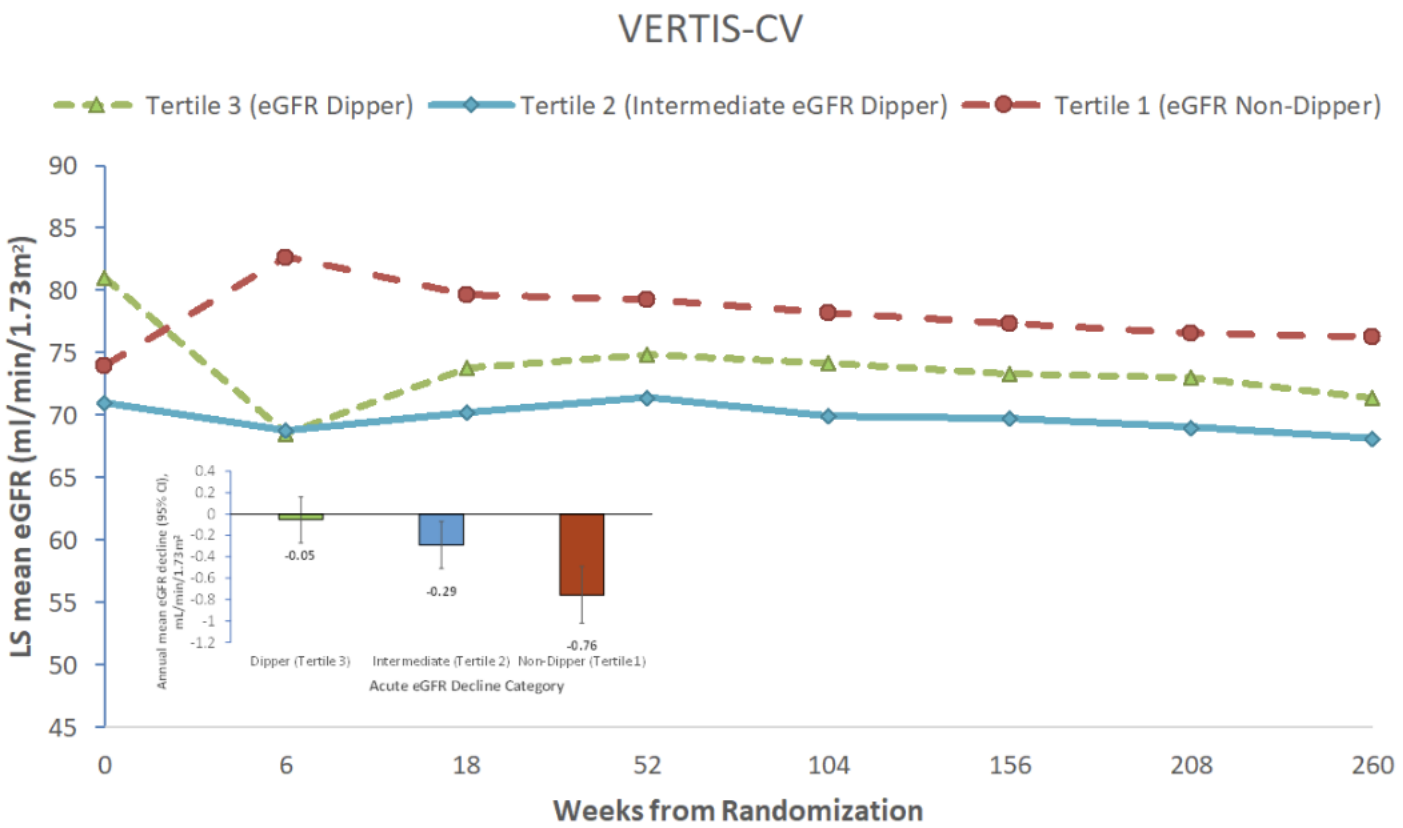
- Expensive versus other oral glucose lowering drugs
- Limited glycemic efficacy in CKD
- Genital mycotic infections
- Euglycemic DKA in type 1 diabetes
- Canagliflozin: more amputations and fractures

SGLT2 inhibitors have acute renal hemodynamic actions



Wanner et al. NEJM 2016

eGFR dip associates with lower kidney function decline!



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Cherney, van Raalte. Kidney International In Press

Meettechniek

Iohexol:

- Volledige filtratie
- Geen reabsorptie of secretie

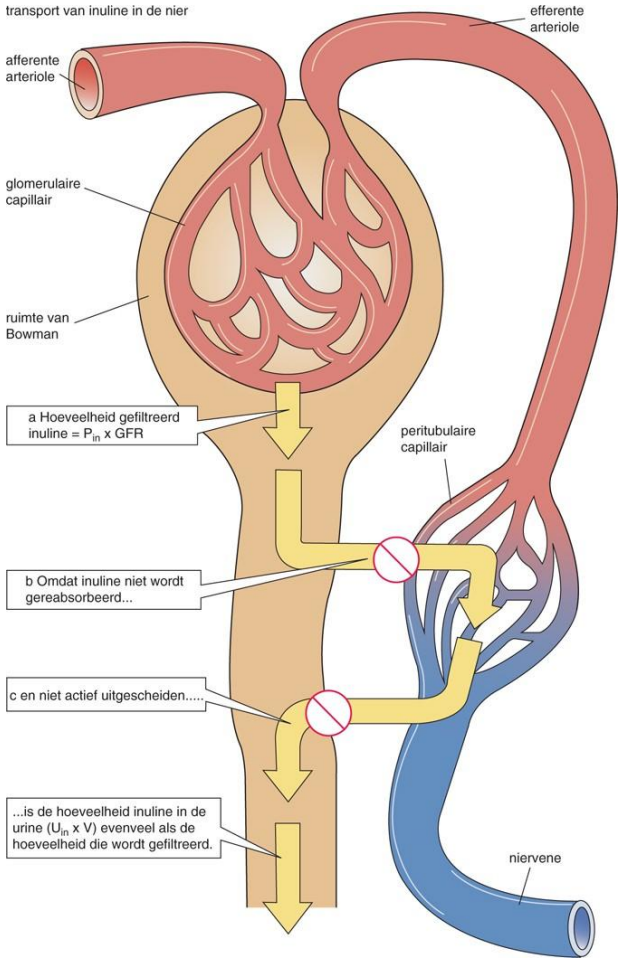
→ Measured GFR

PAH:

- Volledige filtratie en secretie
- Geen reabsorptie

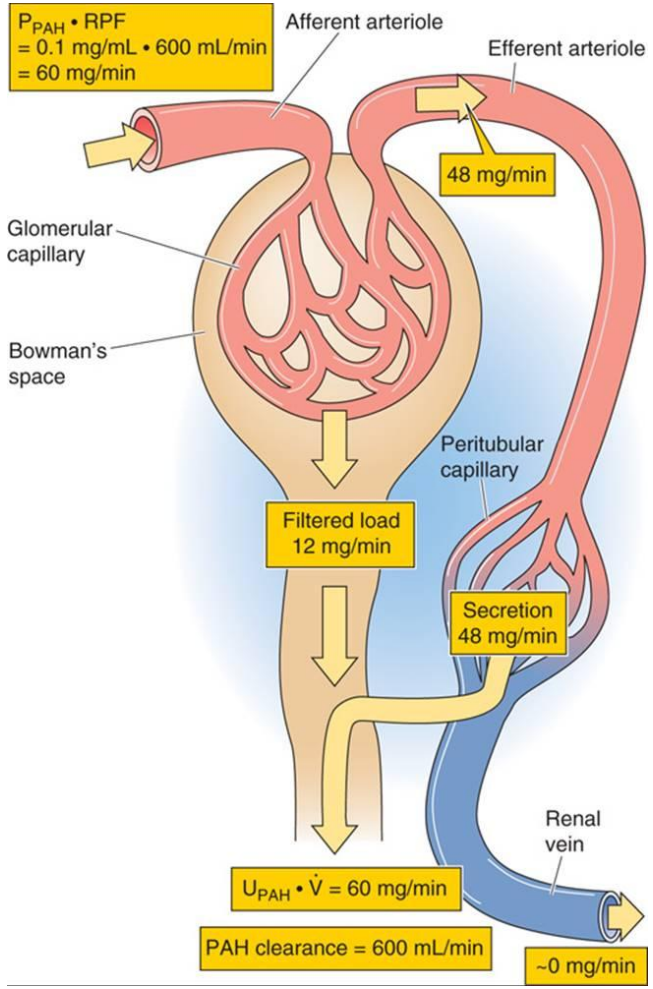
→ ERPF

Inuline / Iohexol

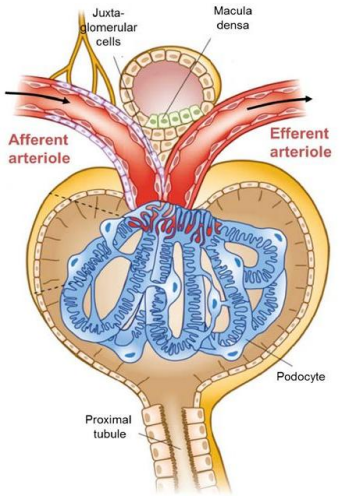


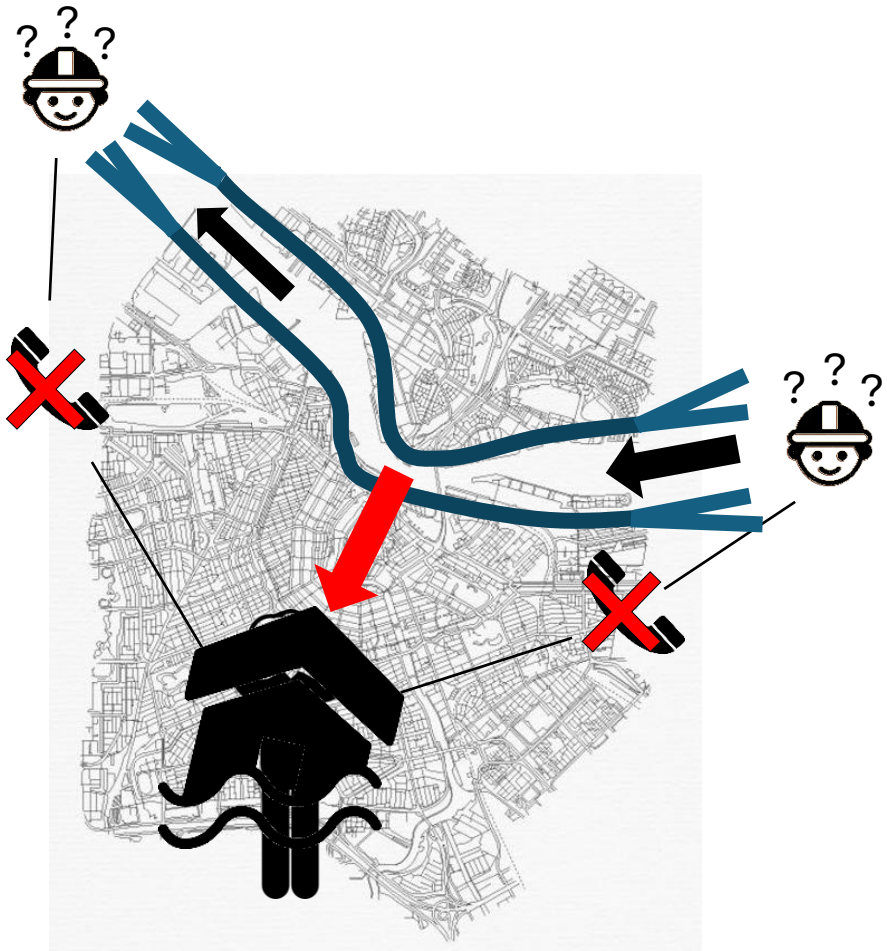
$$CL_x = \frac{U_x \times \dot{V}}{P_x}$$

PAH



Hyperfiltration – afferent/efferent pressures



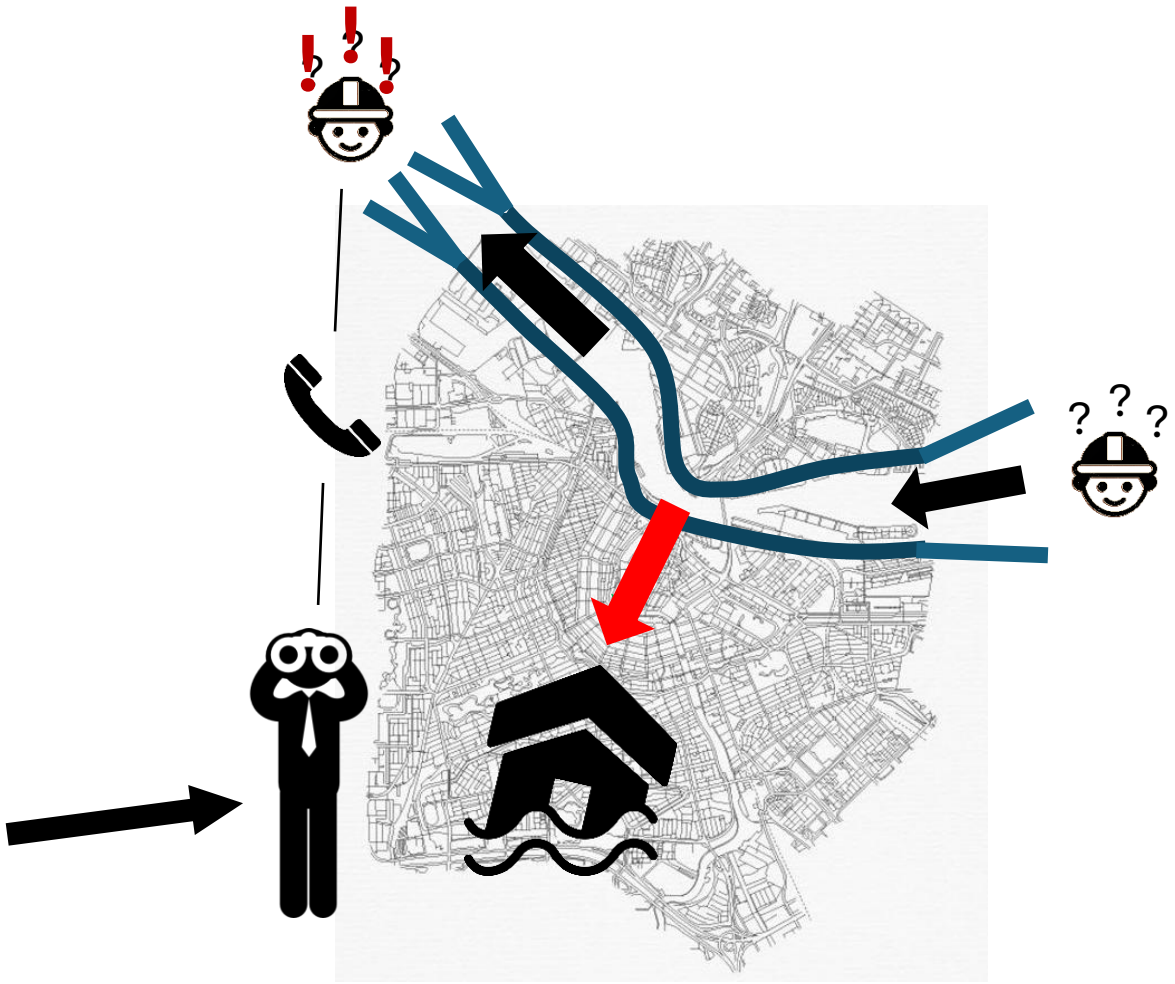


Hyperfiltration

Similar pathology in obesity, FSGS and other forms of CKD

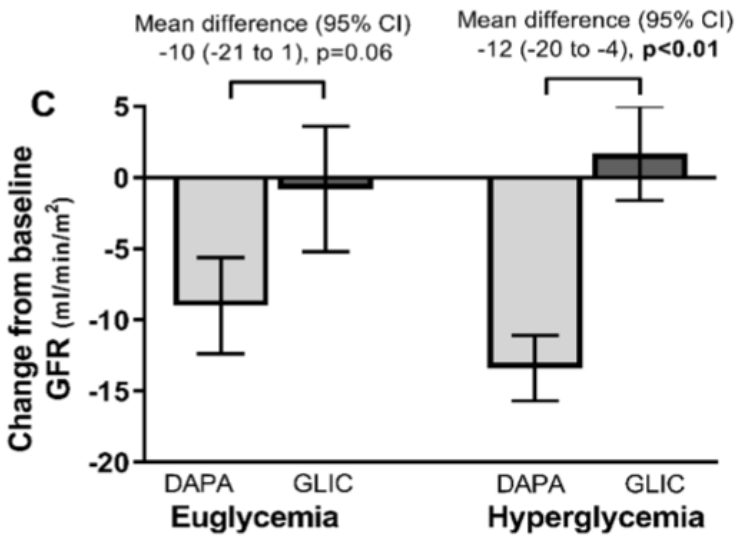


RAS blocker
SGLT2i

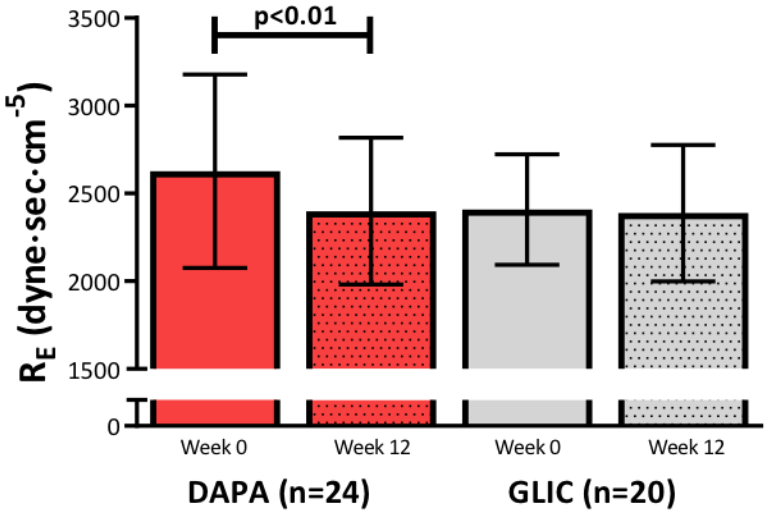


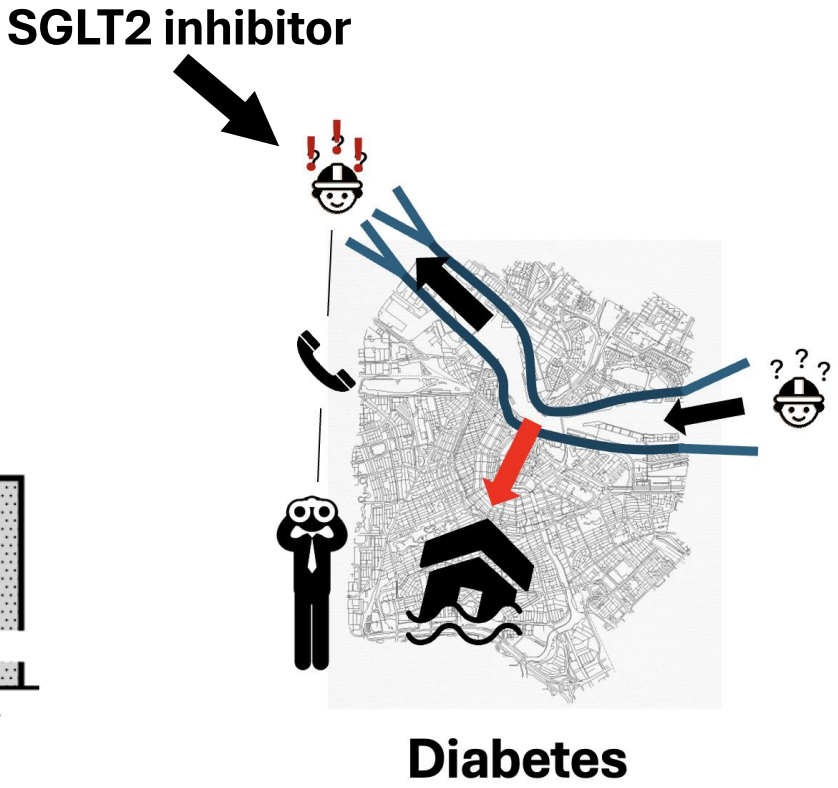
Type 2 diabetes

The Amsterdam RED study



Postglomerular resistance





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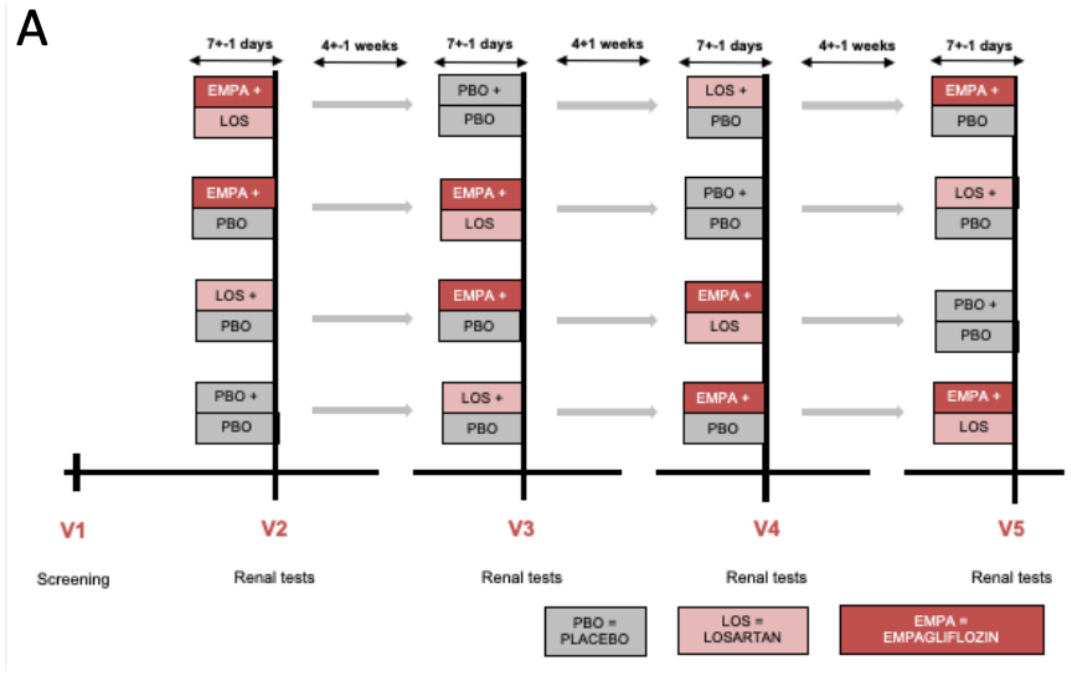
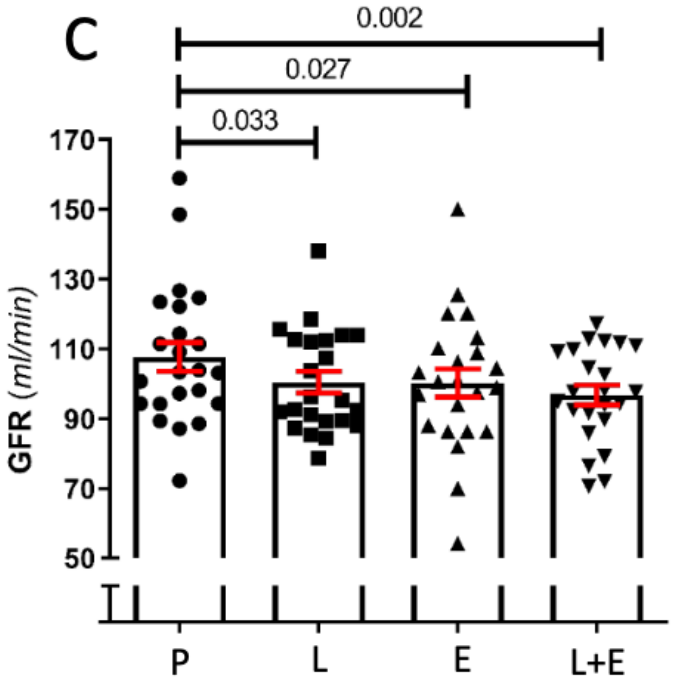
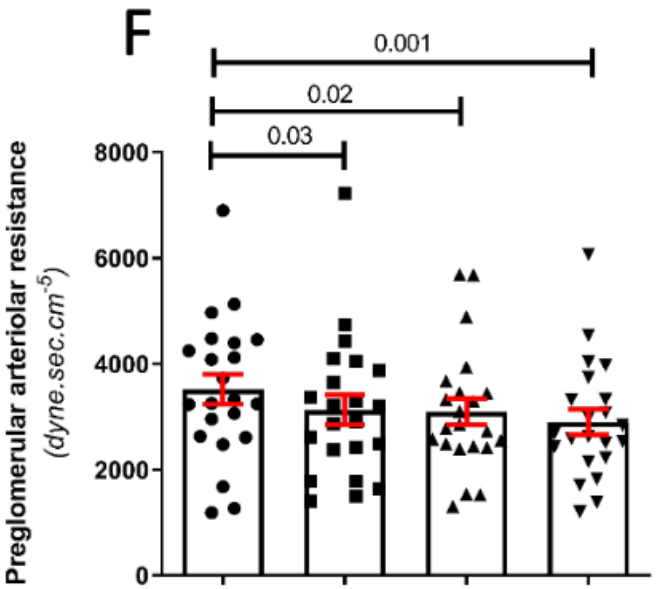
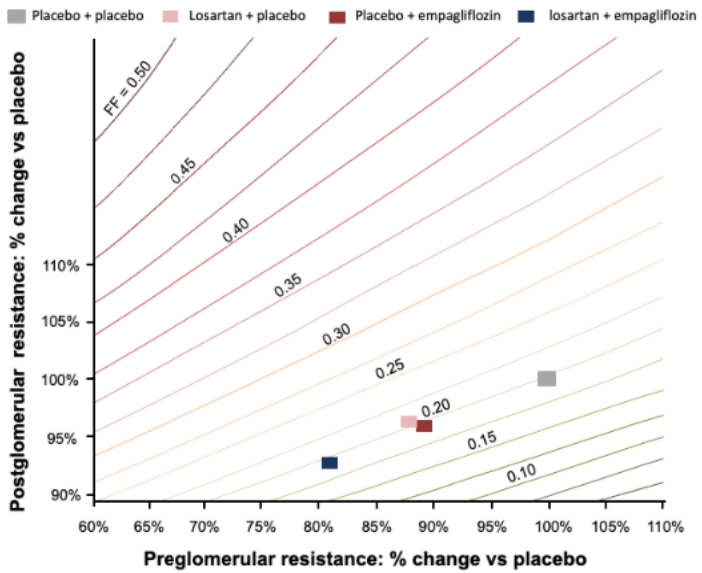
Van Bommel, ..., van Raalte et al. Kidney International 2020









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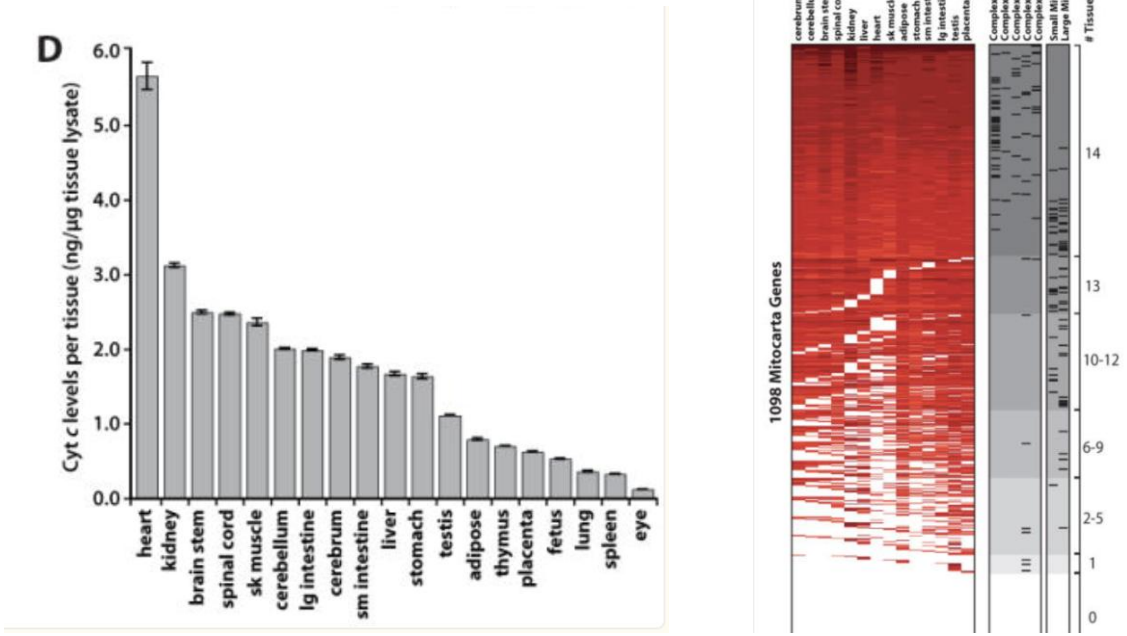
Scholtes, ..., van Raalte et al. Circulation 2022

Kidney metabolism

The kidney is one of the most energy-demanding organs in the human body. A study measuring the resting energy expenditure of various organs in healthy adults, ranging from 21 to 73 years of age, found that the kidney and heart have the highest resting metabolic rates[1]. The kidney has the second highest mitochondrial content and oxygen consumption after the heart[2,3]. The resting metabolic rate for the kidney is high because the kidney

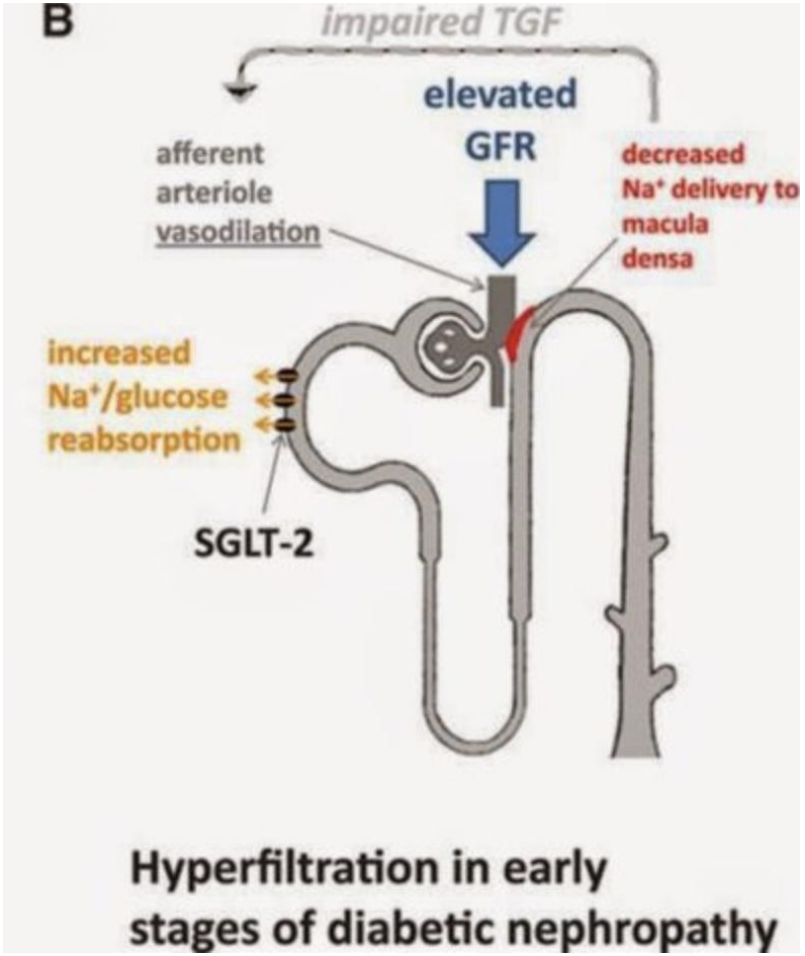


Pagliarini DJ, Cell 2008
Barghava P, Nat Rev Nephrol 2018

Potential Changes in Kidney Workload in People with Diabetes

Potential changes in diabetes due to hyperglycemia and hyperfiltration:

1) **Increased** sodium transport (T_{Na})
2) Change in metabolic efficiency (Q_{O2}/ T_{Na})
3) Increased kidney gluconeogenesis



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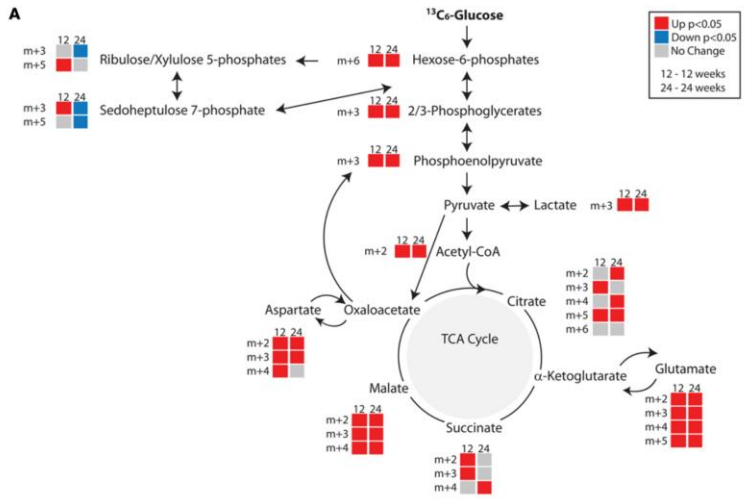
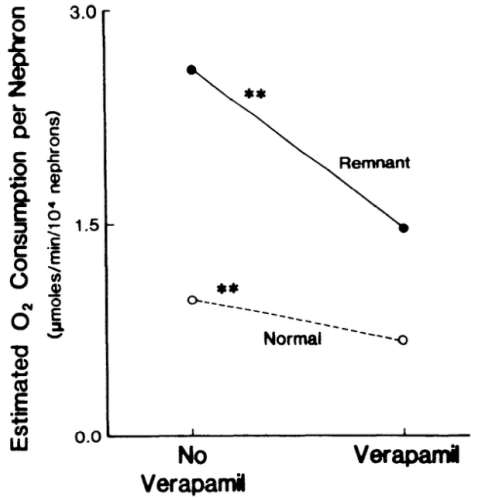
Cherney, Circulation, 2014

Kidney hypermetabolism is linked to damage

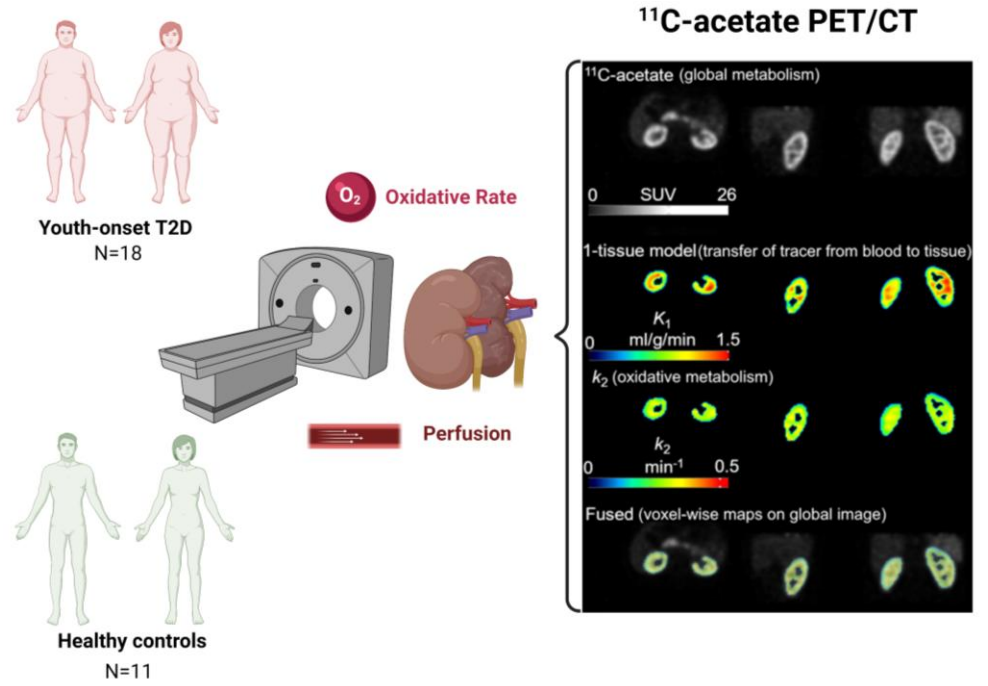
- Hypermetabolism related to metabolic reprogramming (obesity)

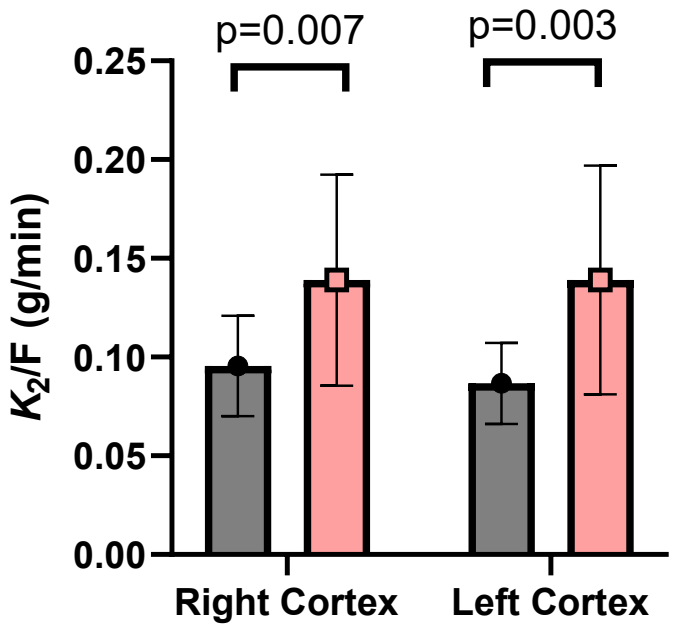


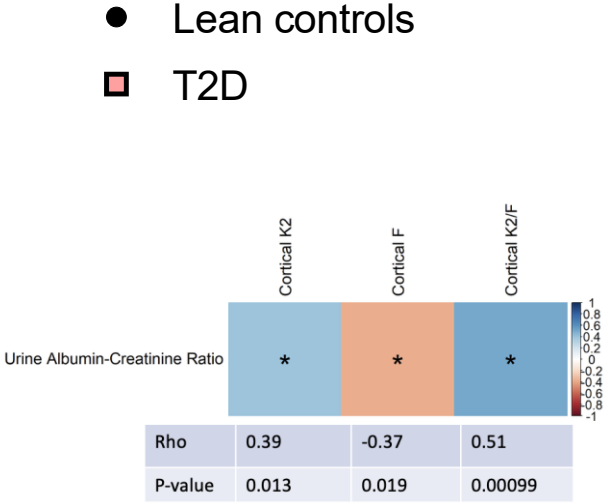


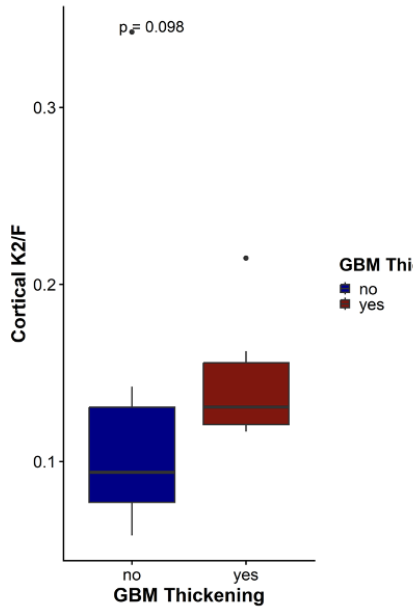
- Mitochondrial metabolites may activate RAAS and pro-fibrotic proteins
- Induction of oxidative stress
- Impairing kidney oxygen metabolism

Harris DC, AJP 1988
Sas KM, JCI Insight 2016

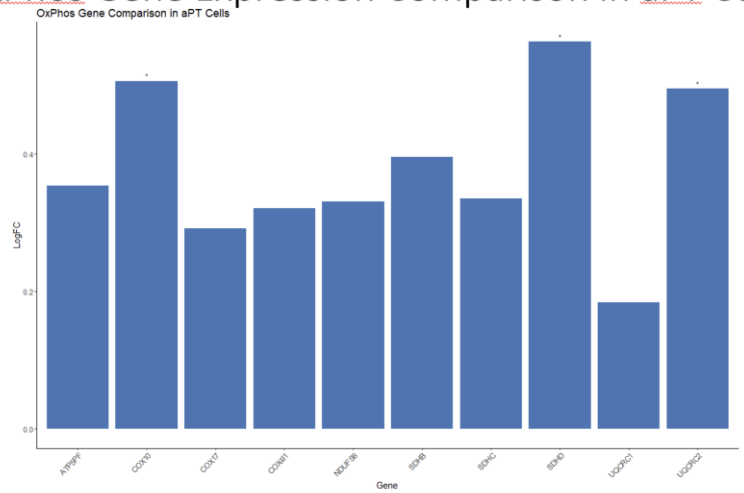




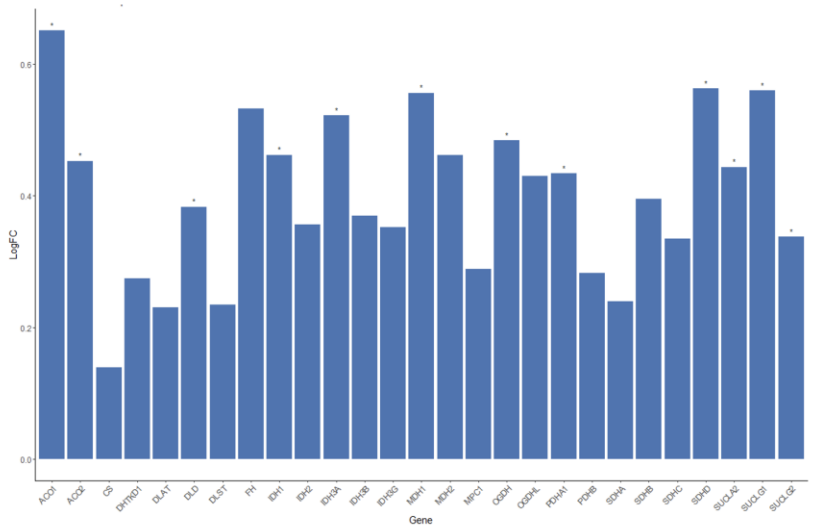




OxPhos Gene Expression Comparison in aPT Cells



TCA Gene Expression Comparison in aPT Cells



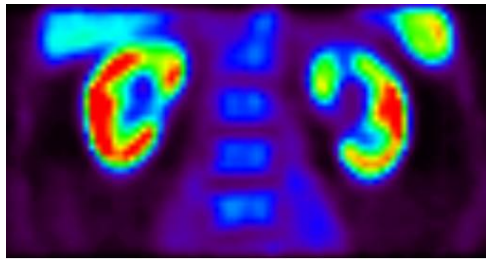


Petter Bjornstad, Colorado University

ROCKIES study: ertugliflozin

ROCKIES

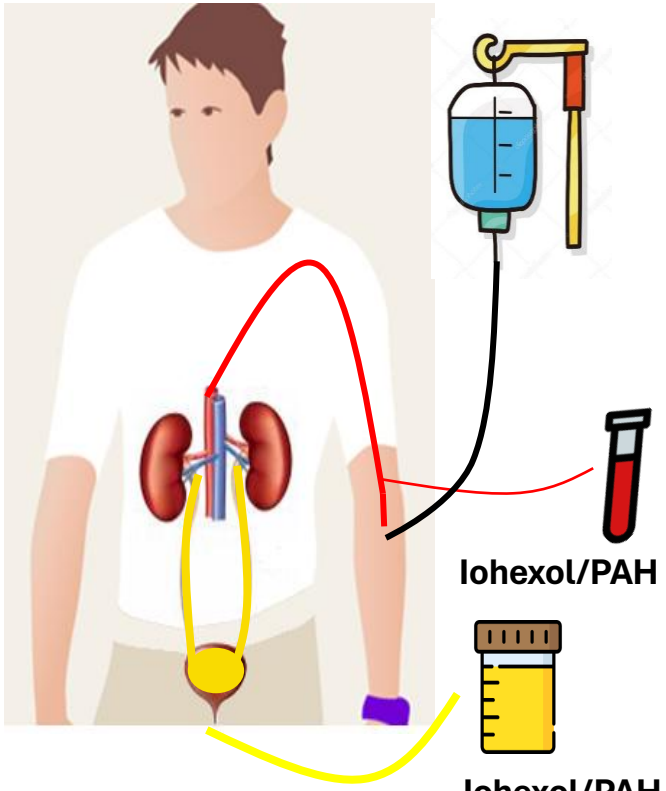




11c- acetate PET-CT
Oxygen consumption
K2/F

mGFR → iohexol

Renal plasma flow → PAH



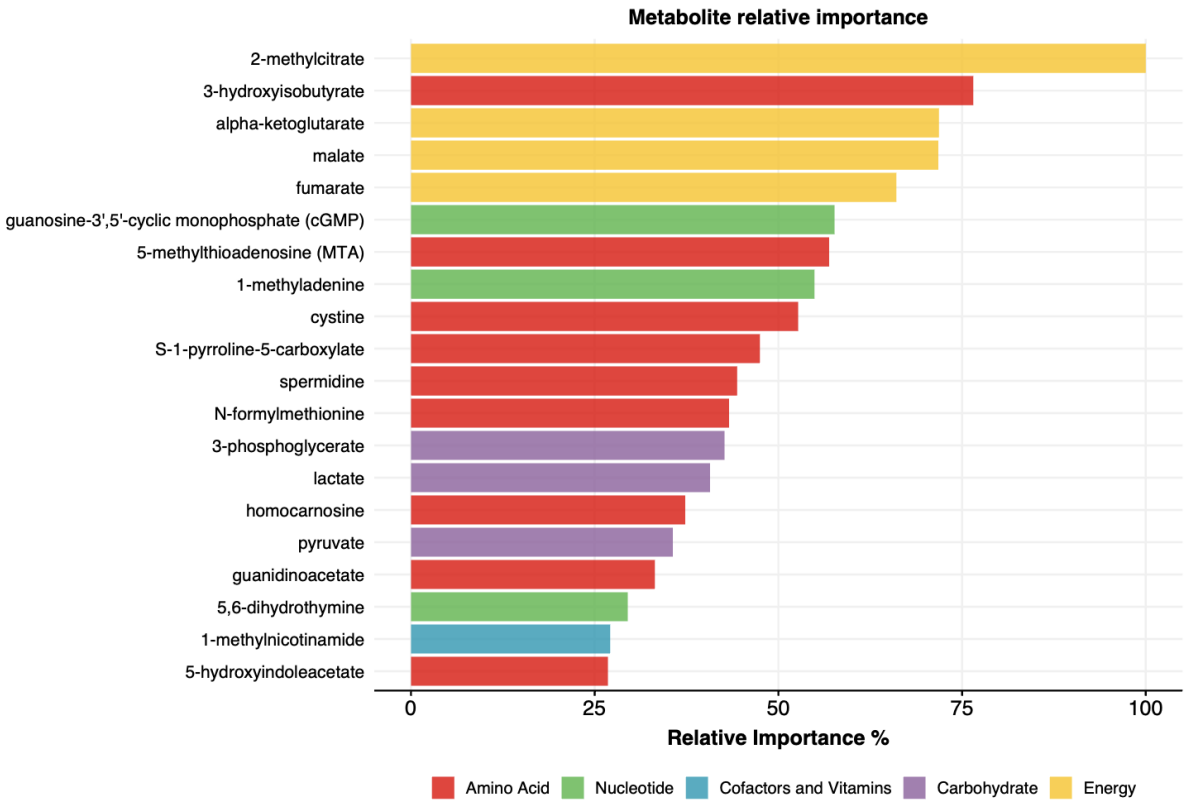
Sodium reabsorption → mGFR * arterial sodium – Urinary sodium

Insulin Sensitivity → Oral glucose insulin sensitivity (OGIS)



ROCKIES study

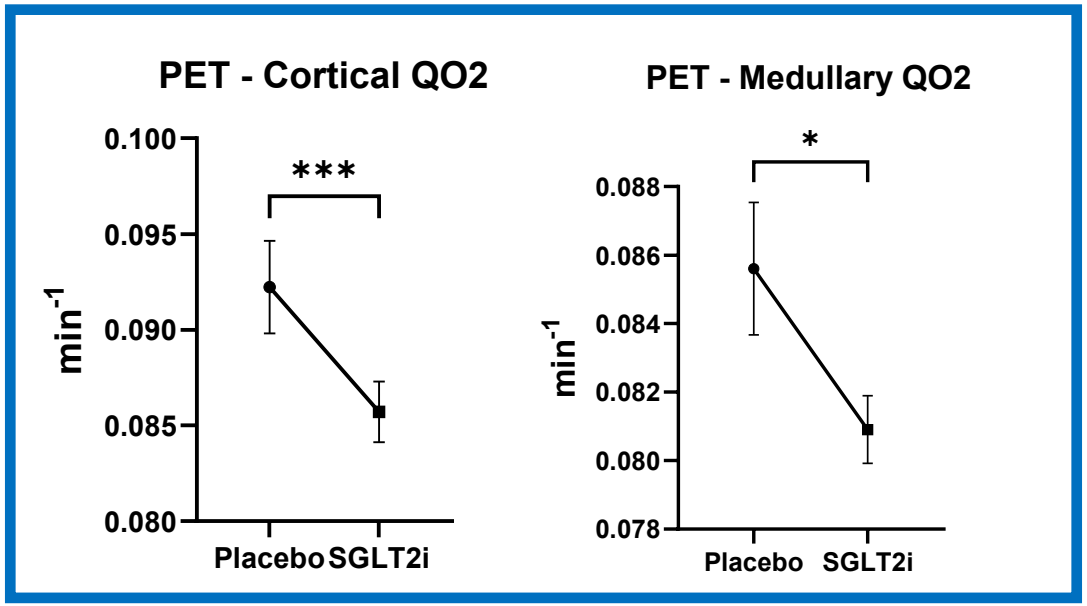
ROCKIES

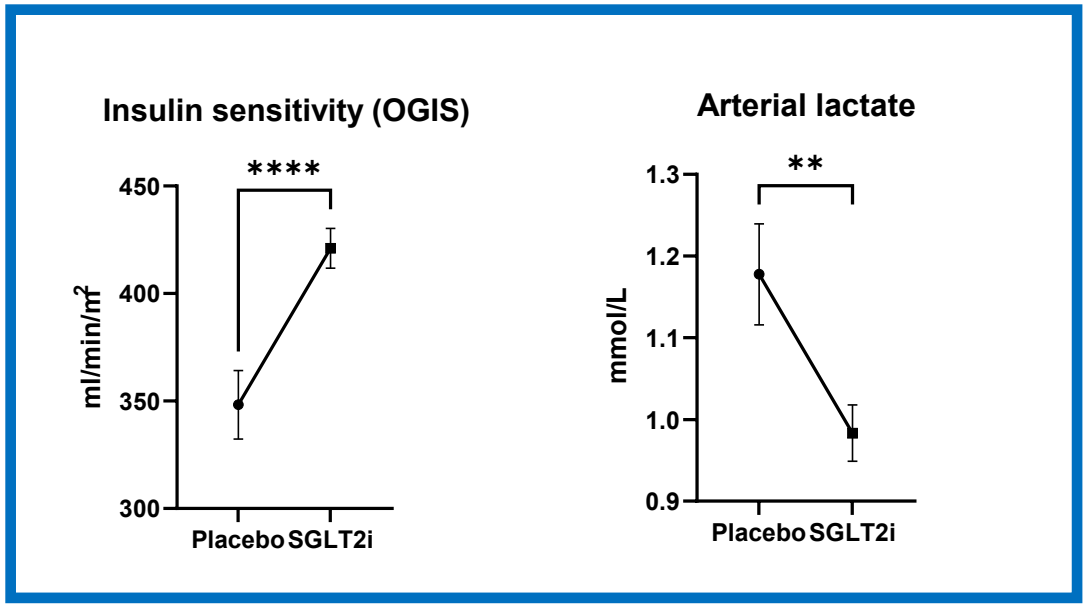


Higher cortical oxidative rate associated inversely with insulin sensitivity

ROCKIES study

ROCKIES







^{11}C-acetate PET/CT

Improvements in insulin sensitivity strongly associated with attenuation of increased oxidative rates

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DAPASALT – studie opzet

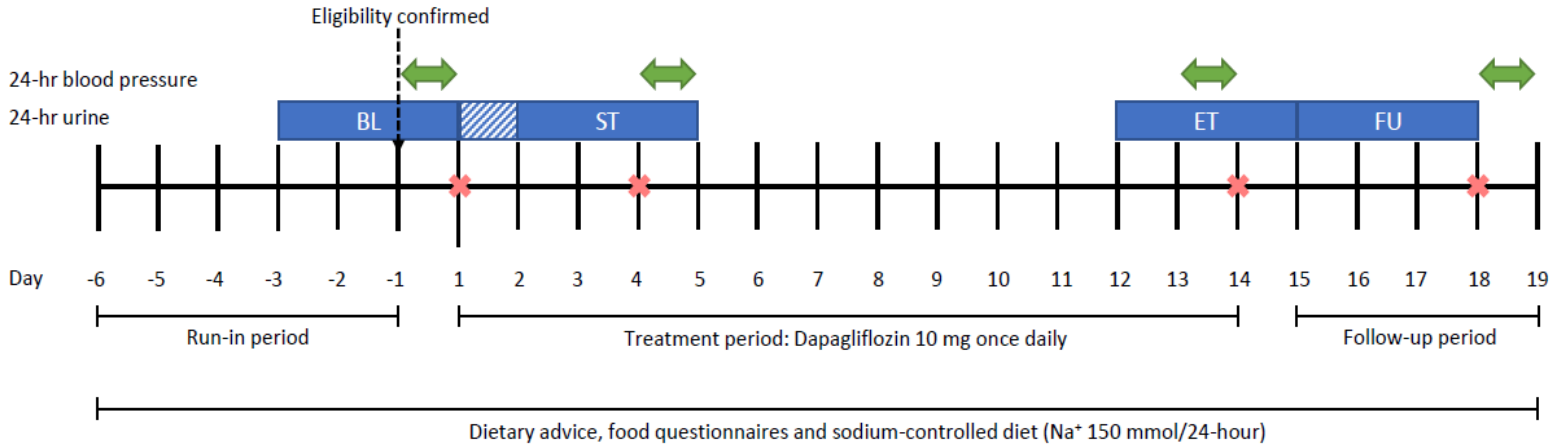
phase IV, multicenter, open-label, July 2017 t/m March 2020.

Het effect van dapagliflozin op natriurese (plasma volume, extracellular/intracellular volume en 24-u bloeddruk)

Vooraf:
Metformine / SU derivaat
+ stabiele dosering ARB
Geen diuretica

Dag -6 t/m dag 18:
Maaltijdbox ±9 gram zout per da

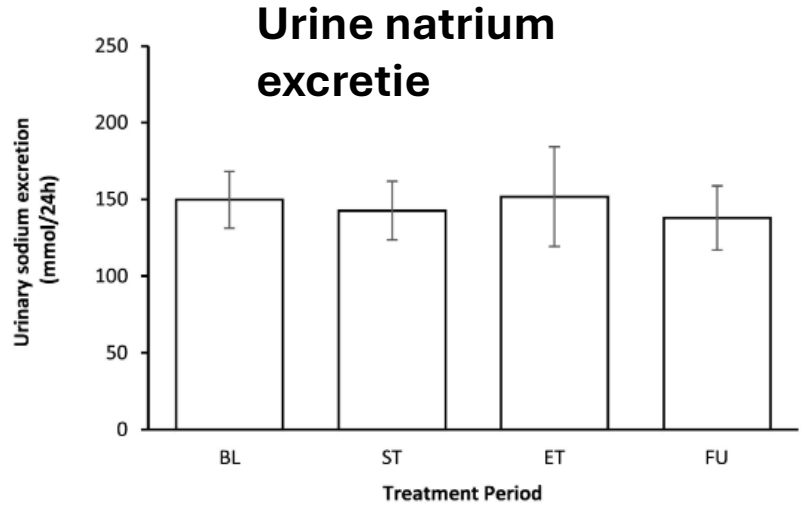
BL = baseline > urine collecties
ST = start of study > urine collecties
ET = end of study > urine collecties
FU = follow up > urine collecties



(Scholtes, Muskiet et al. 2021)

DAPASALT – Resultaten

14 deelnemers met T2D, ♀ = 5, BMI 31.9 (±4.2), eGFR 94.3 (±10.9), stabiele dosering ARB



BL = dag -3/-1
ST = dag 1 – 4
ET = dag 12 – 14
FU = dag 15 - 17

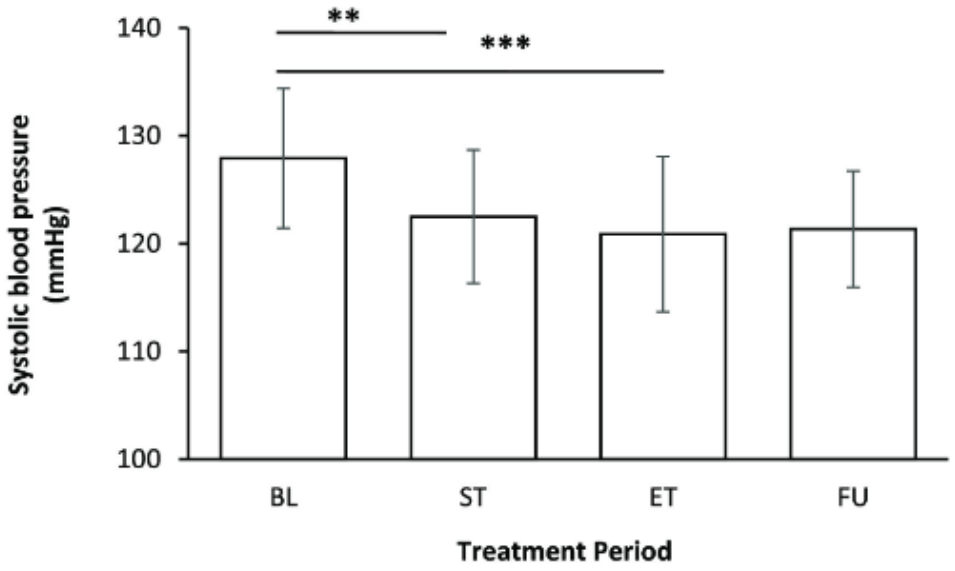
Mean change – BL vs ST: -7.0; 95% CI: -22.4, 8.4; p=0.34
Mean change – BL vs ET: 2.1; 95% CI: -28.8, 33.0; p=0.89
Mean change – ET vs FU: -13.8; 95% CI: -30.9, 3.2; p=0.10

=	Urine natrium excretie
=	Urine volume
↑	Urine glucose excretie
↑	Fractionele lithiumexcretie

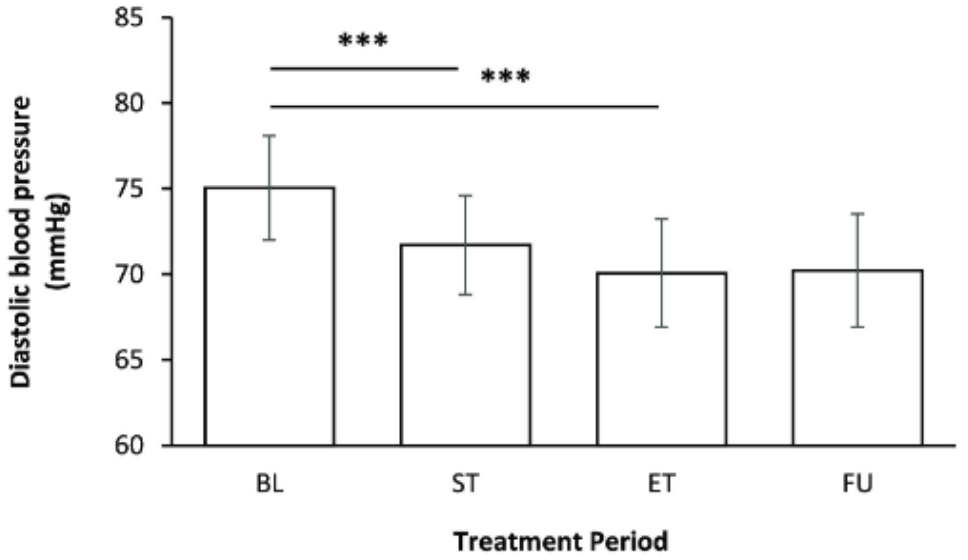
(Scholtes, Muskiet et al. 2021)

DAPASALT – Resultaten

Systolische bloeddruk

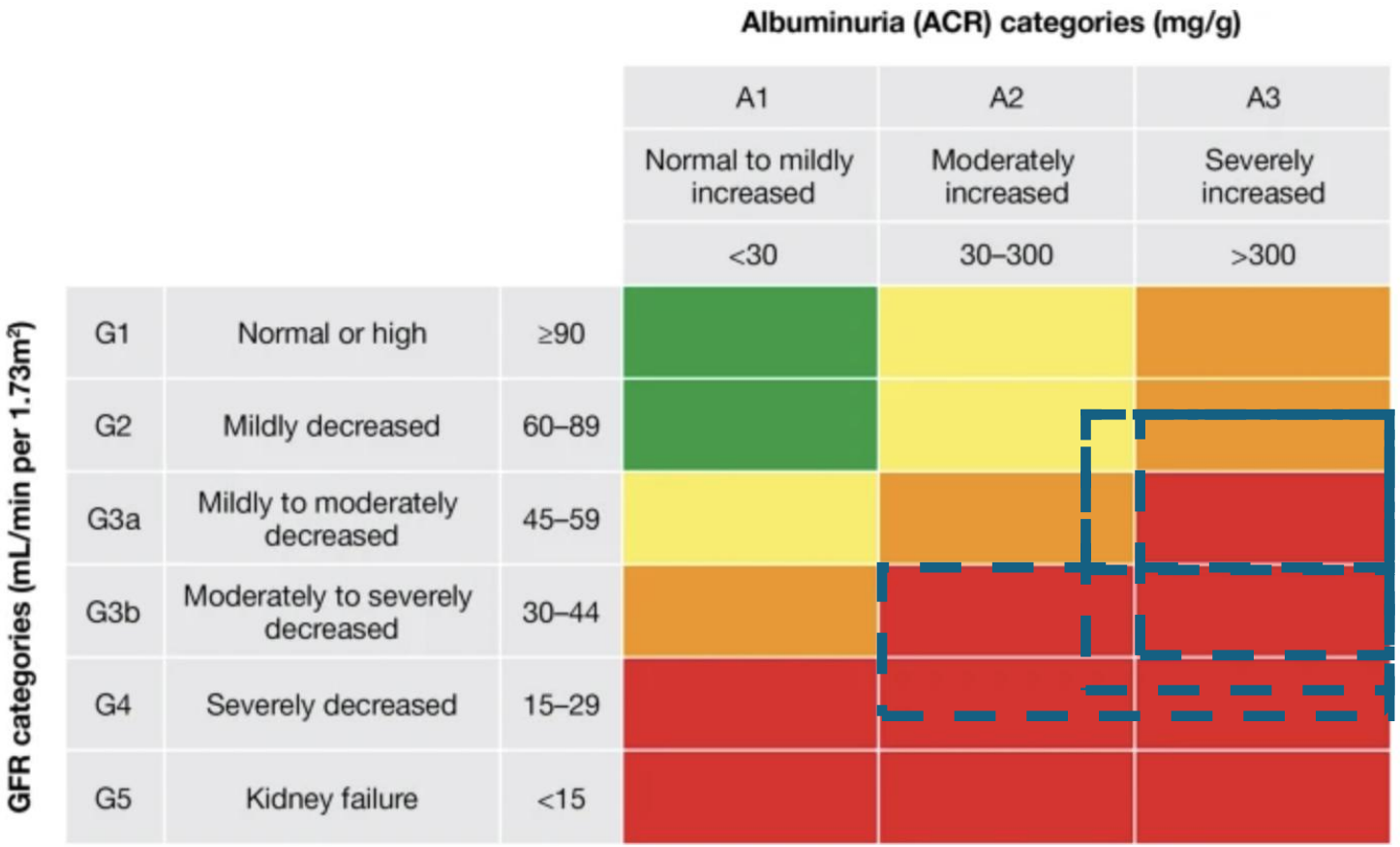


Diastolische bloeddruk



BL = dag -3
ST = dag 2 – 4
ET = dag 12 – 14
FU = dag 15 - 17

Welke T2D-CNS patients werden geincludeerd?



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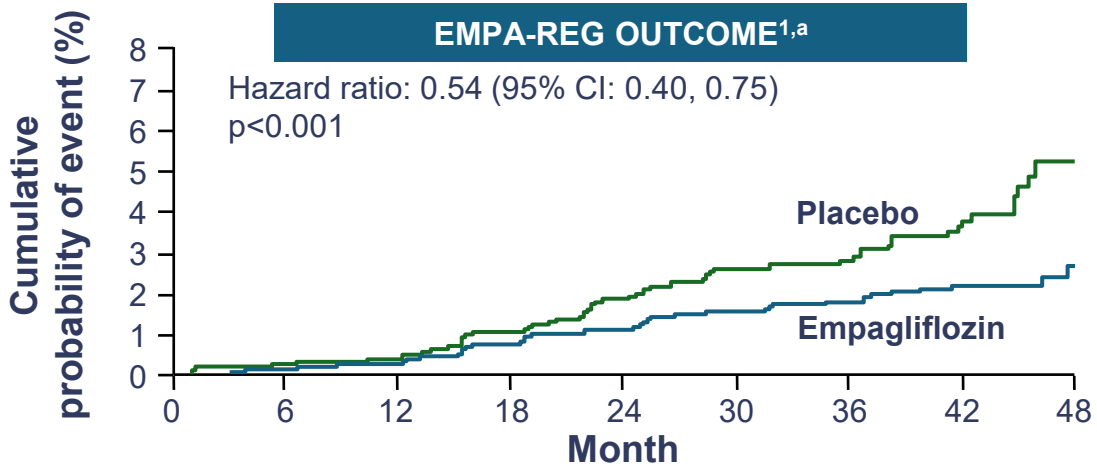
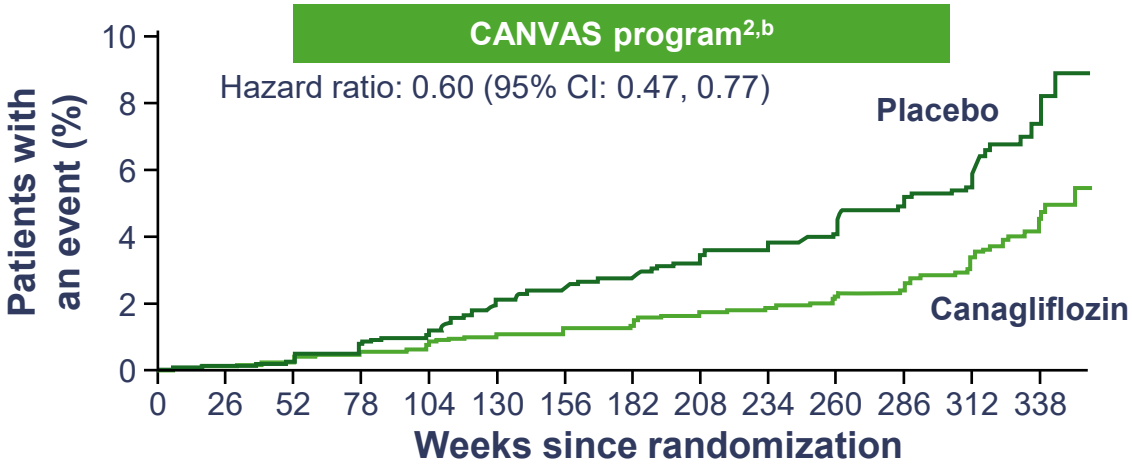
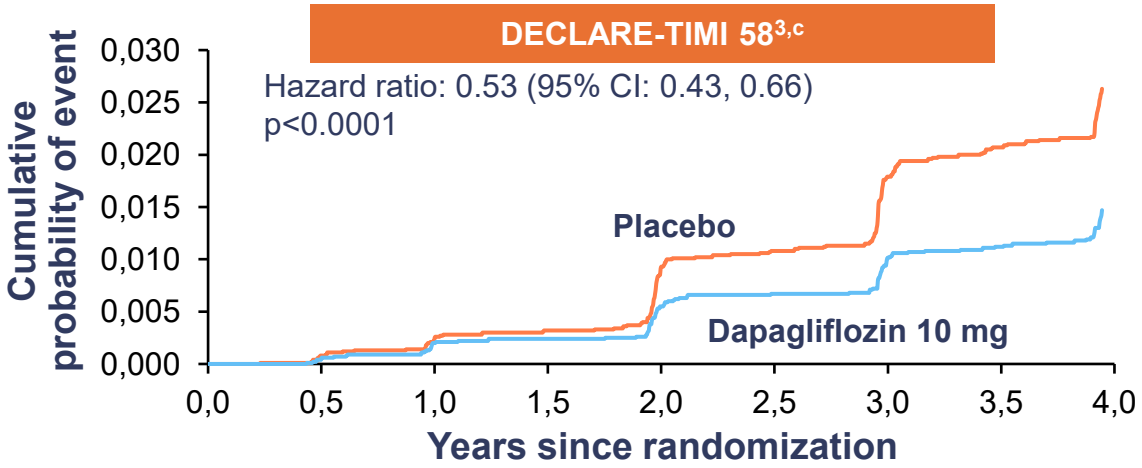
CREDENCE (canagliflozine) DAPA-CKD (dapagliflozine) EMPA Kidney (empagliflozine)

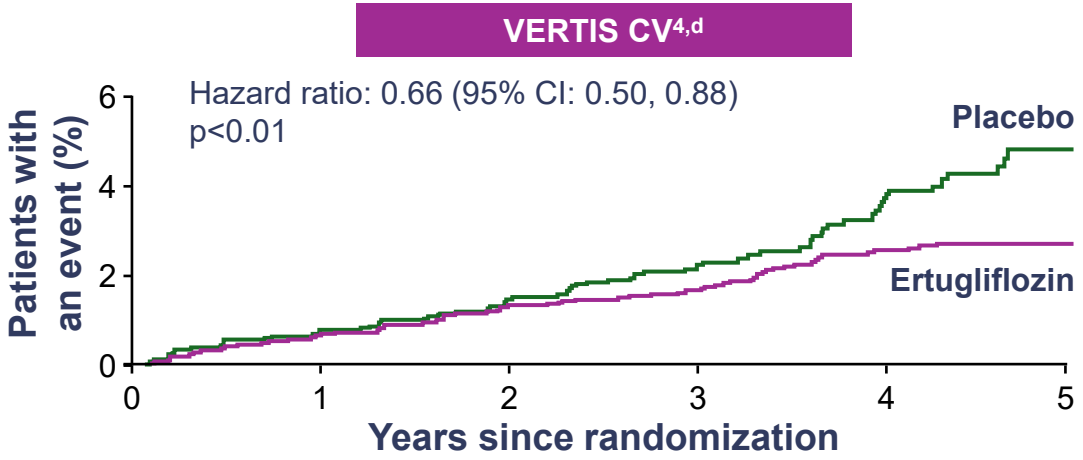
FIDELIO (finerenon) FLOW (semaglutide)

SGLT2 inhibitors have demonstrated a class effect in reducing risk of composite kidney disease endpoints in T2D



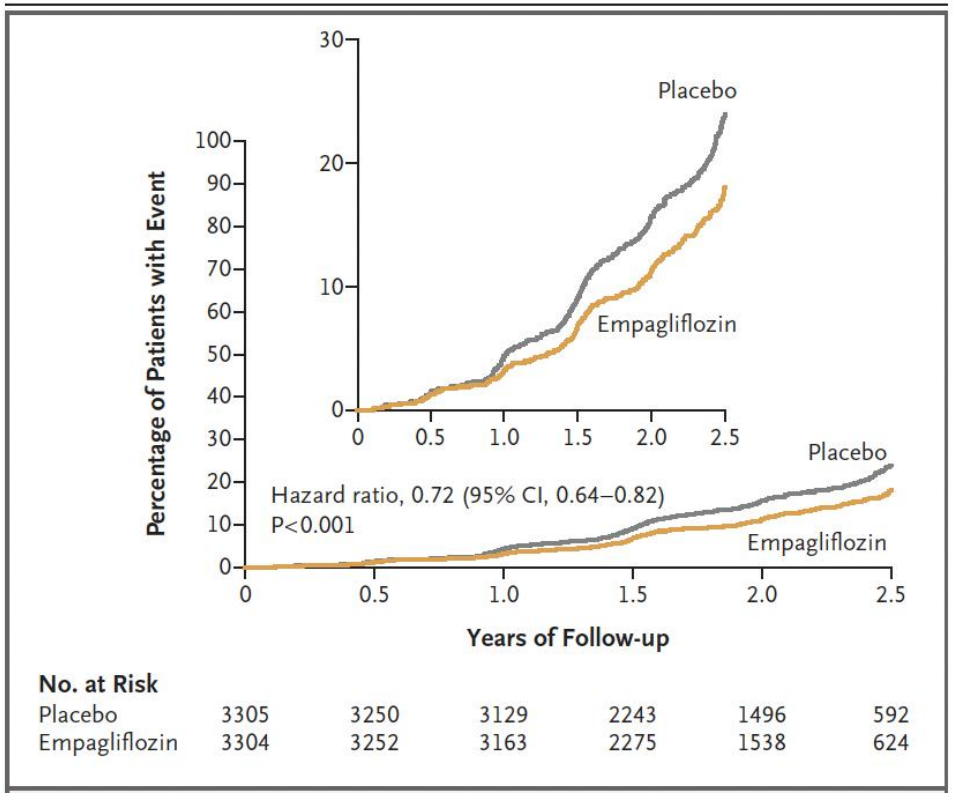


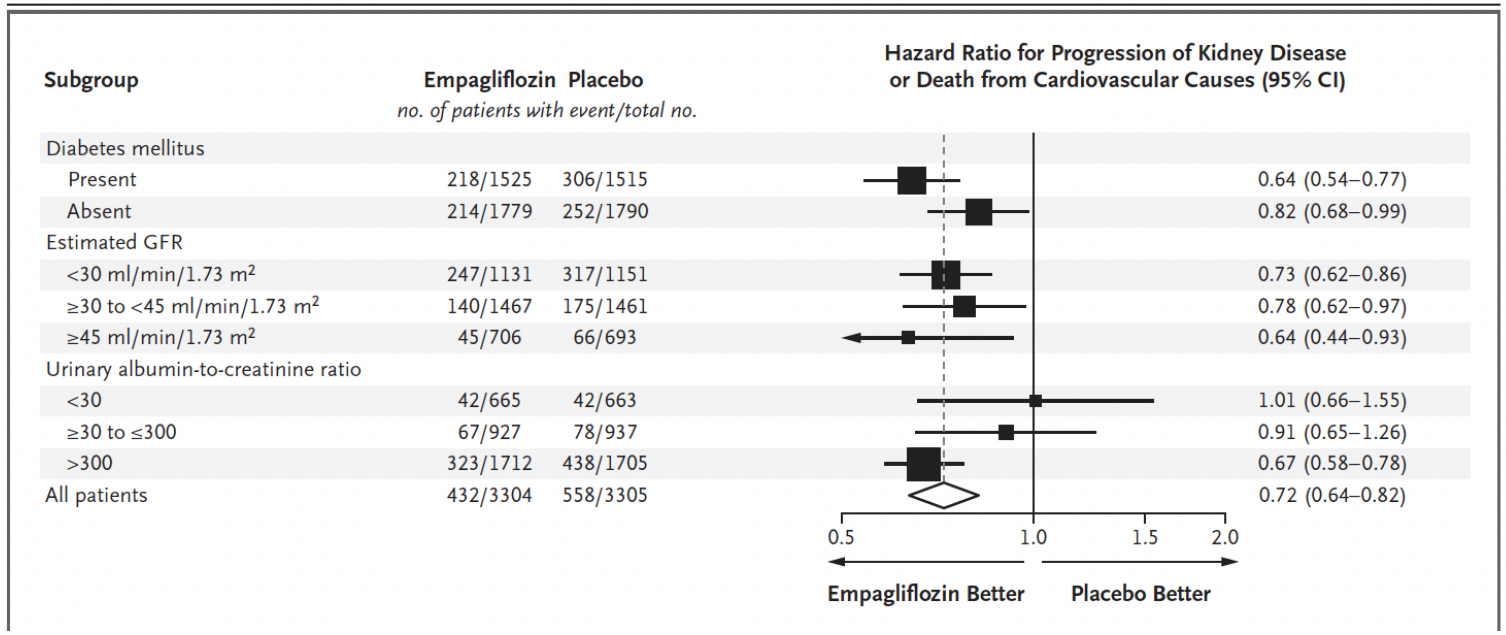




[a]Composite kidney disease endpoint defined as dSCr accompanied by eGFR ≤45 mL/min/1.73 m^2, RRT, or kidney death; [b]40% reduction in eGFR, KRT, or death from kidney causes; [c]eGFR decrease ≥40% to <60 mL/min/1.73 m^2, ESKD, or kidney death; [d]Exploratory endpoint defined as sustained 40% decrease from baseline in eGFR, chronic renal dialysis/transplant, or renal death
CI, confidence interval; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KRT, kidney replacement therapy; RRT, renal replacement therapy; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

1. Wanner C, et al. *N Engl J Med* 2016;375:323–334; 2. Neal B, et al. *N Engl J Med* 2017;377:644–657;
3. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617; 4. Cherney DZI, et al. *Diabetologia* 2021;64:1256–1267





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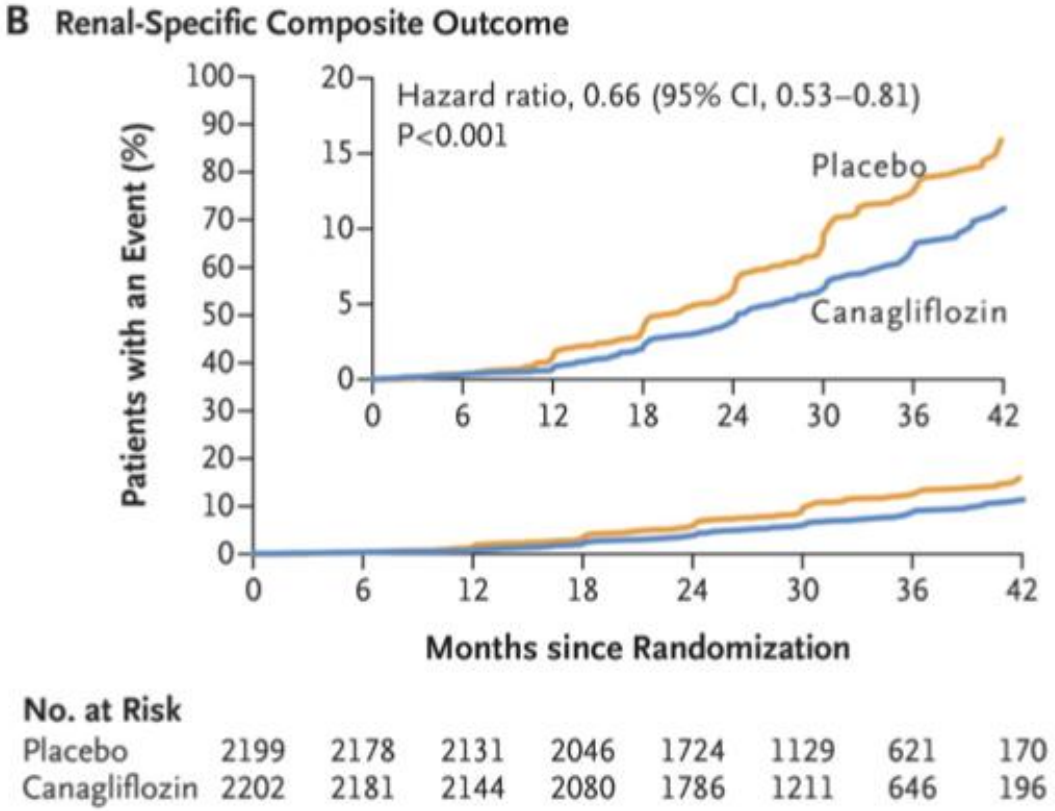
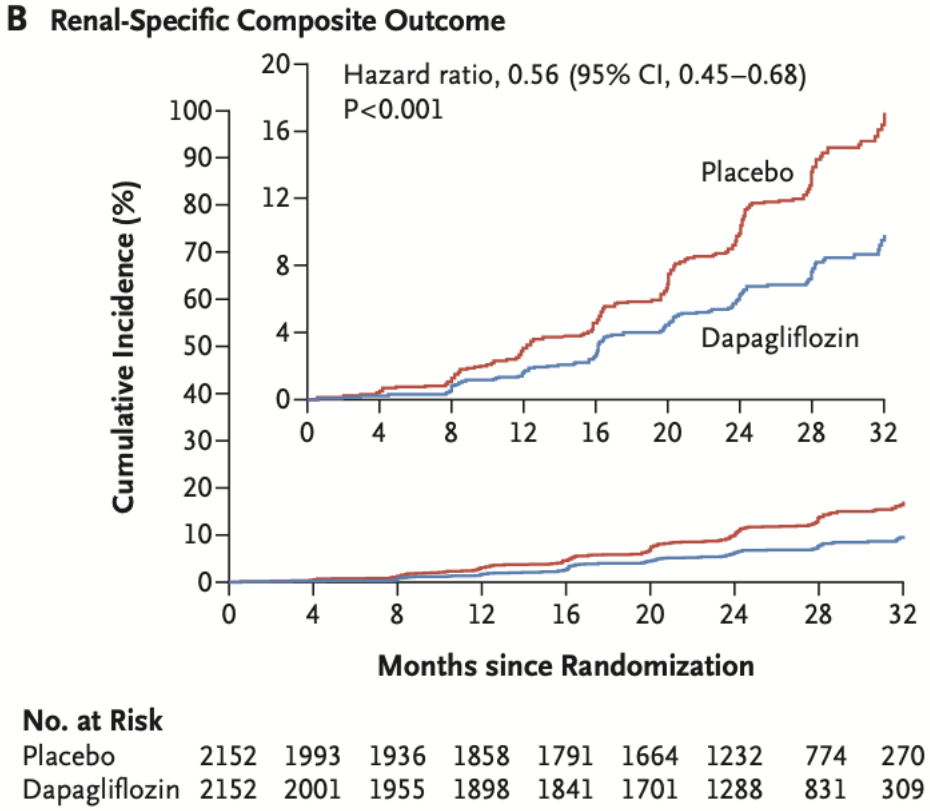
N Engl J Med 2023;388:117-127

Nier uitkomsten -> onafhankelijk van diabetes



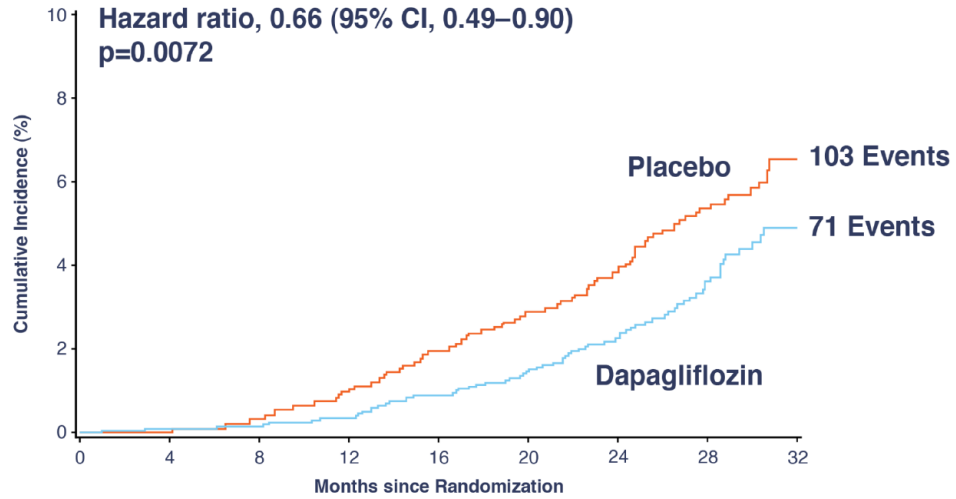
CREDENCE study NEJM



DAPA CKD study NEJM

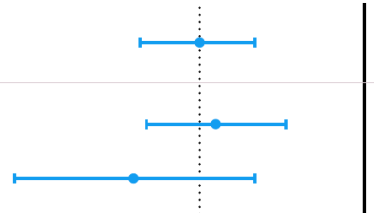
Kidney outcomes are independent of the presence of diabetes

Chronic dialysis, kidney transplantation, renal death

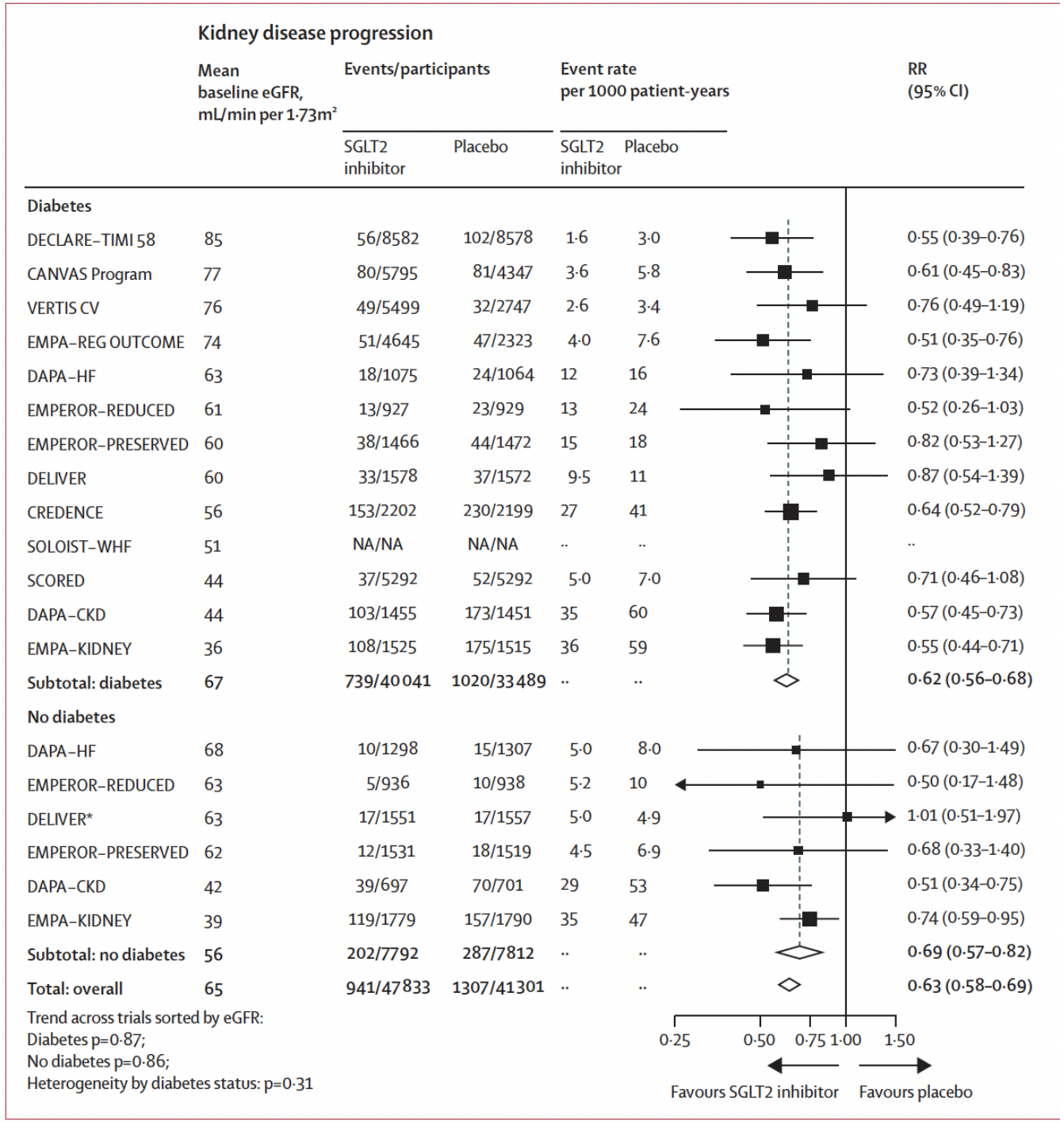


Primary outcome – pre-specified subgroup analysis

	Dapagliflozin events	Placebo events	Hazard Ratio (95% CI)	p-value interaction
All patients	197	312	0.61 (0.51, 0.72)	
With type 2 diabetes	152	229	0.64 (0.52, 0.79)	
Without type 2 diabetes	45	83	0.50 (0.35, 0.72)	0.24



Heerspink et al. NEJM 2020



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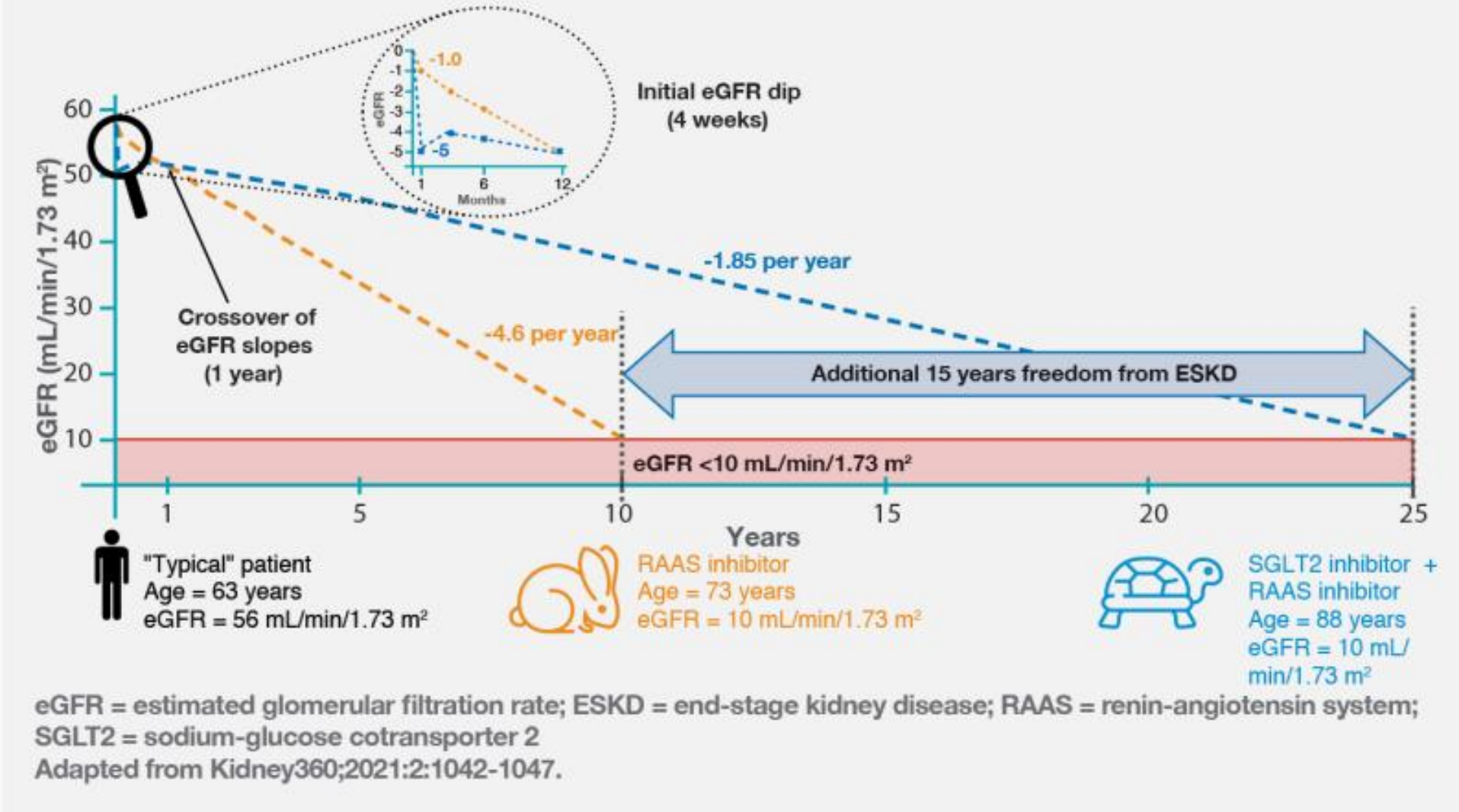
Lancet . 2022 Nov 19;400(10365):1788-1801.

How do these data translate to life years free of dialysis?



eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; RAAS = renin-angiotensin system; SGLT2 = sodium-glucose cotransporter 2

Adapted from Kidney360;2021:2:1042-1047.

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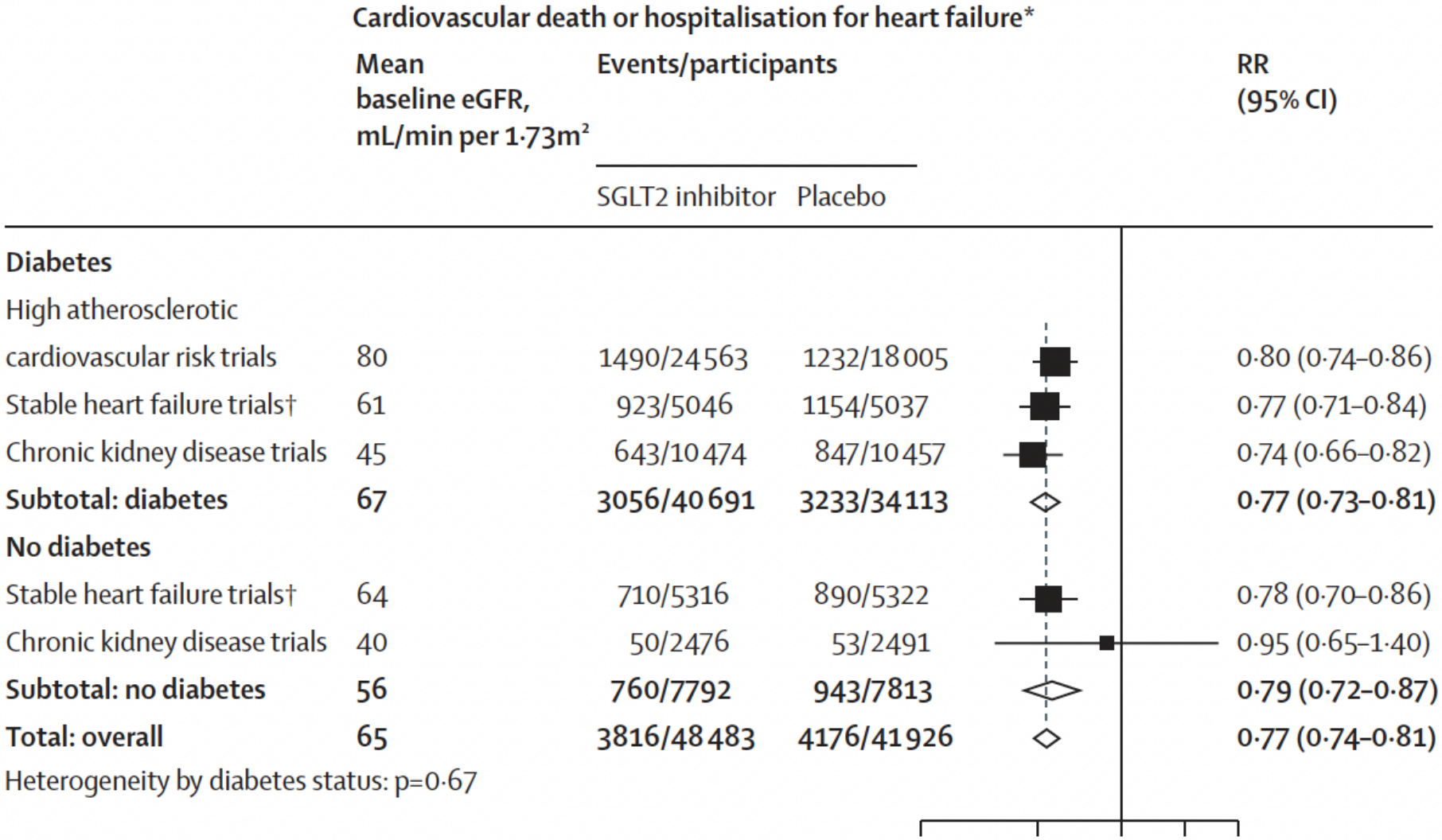
Meraz-Munoz. Kidney Int 2021



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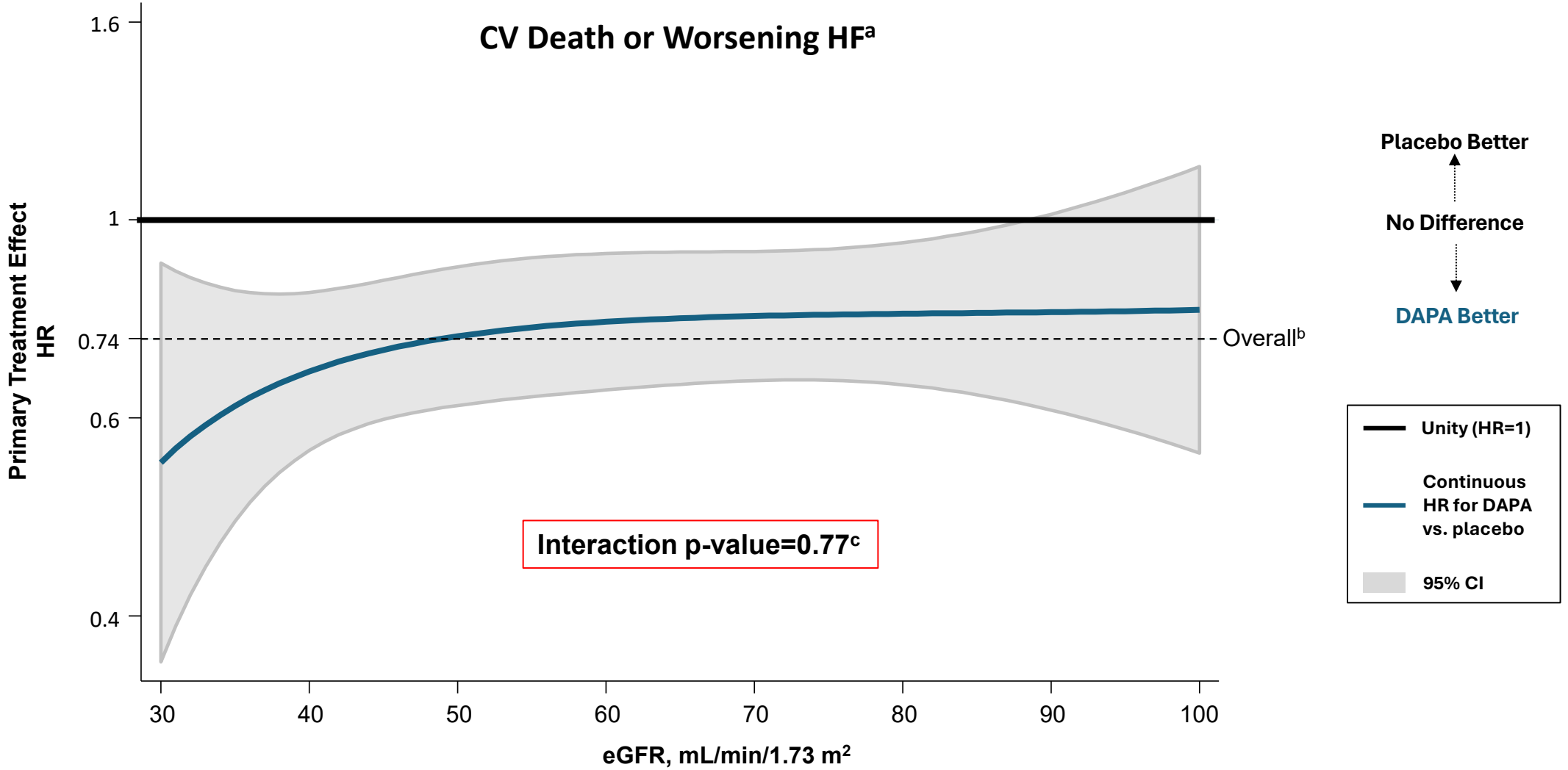
Lancet . 2022 Nov 19;400(10365):1788-1801.

Dapagliflozin Benefit Consistent Across the Spectrum of Baseline eGFR



[a]Worsening HF includes hHF or urgent HF visit; [b]Indicates HR for the overall DAPA-HF trial population; [c]A nonsignificant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.

1. Jhund PS et al. *Circulation*. 2021;143:298-309; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Mechanisms of cardiovascular protection

SGLT-2 induces natriuresis and osmotic diuresis

Leads to reduction in plasma volume (hemoconcentration)

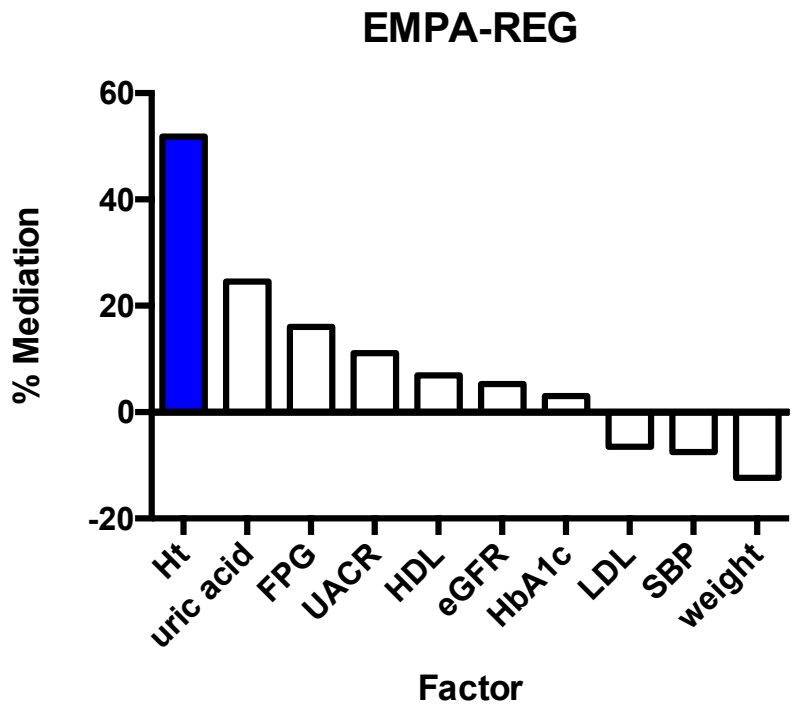
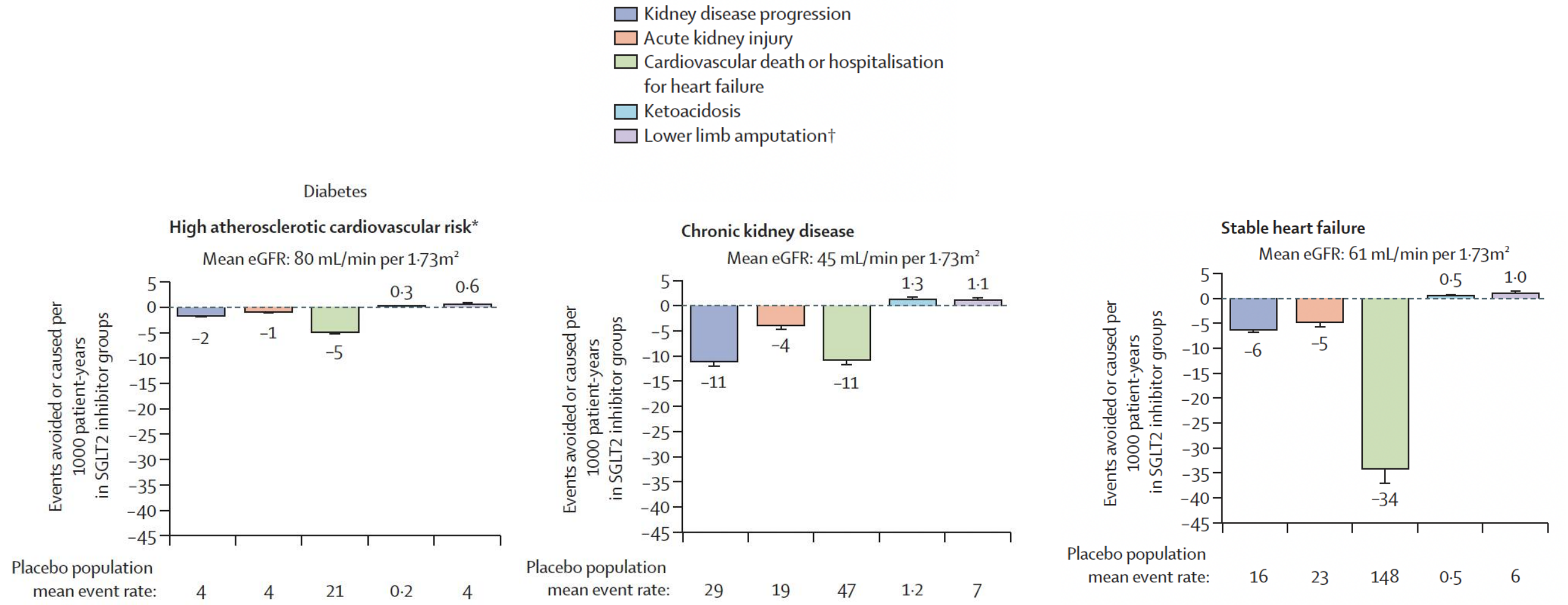


Figure modified from: Inzucchi et al, Diabetes Care 2018 Feb; 41(2): 356-363.
Subodh Verma, FRCSC The American Journal of Medicine (2019) 132:S39–S48;



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Lancet . 2022 Nov 19;400(10365):1788-1801.

Serious adverse events and prespecified adverse events of interest

	Empagliflozin (n=1863) – N (%)	Placebo (n=1863) – N (%)
Patients with any AEs	1420 (76.2)	1463 (78.5)
Serious AEs	772 (41.4)	896 (48.1)
Serious AEs of special interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Confirmed severe hypoglycaemic events‡	27 (1.4)	28 (1.5)
In patients with type 2 diabetes	20 (2.2)	22 (2.4)
In patients without type 2 diabetes	7 (0.7)	6 (0.6)
Urinary tract infections	91 (4.9)	83 (4.5)
Complicated urinary tract infections	19 (1.0)	15 (0.8)
Genital tract infections	31 (1.7)	12 (0.6)
Complicated genital tract infections	6 (0.3)	5 (0.3)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputation	13 (0.7)	10 (0.5)

‡Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dl or that required treatment
AE, adverse event
Packer M et al NEJM DOI: 10.1056/NEJMoa2022190

Contra-indicaties / voorlichting als SGLT2-remmer gestart wordt bij:

- eGFR <30 ml/min/1,73m^2
- Kwetsbare patient met levensverwachting < 5 jaar

  hypovolemie/dehydratie: cave diuretica; verlagen andere glucose medicatie

- Actief voetulcus
- Verhoogd risico op diabetische ketoacidose:
  - Alcoholisme
  - Ondervoeding
  - Intermitterend vasten
  - Dieet met zeer weinig koolhydraten per dag (ketogeen dieet)
- Recidiverende genitale schimmelinfectie

Should all people on CKD be on SGLT2? Be careful when:

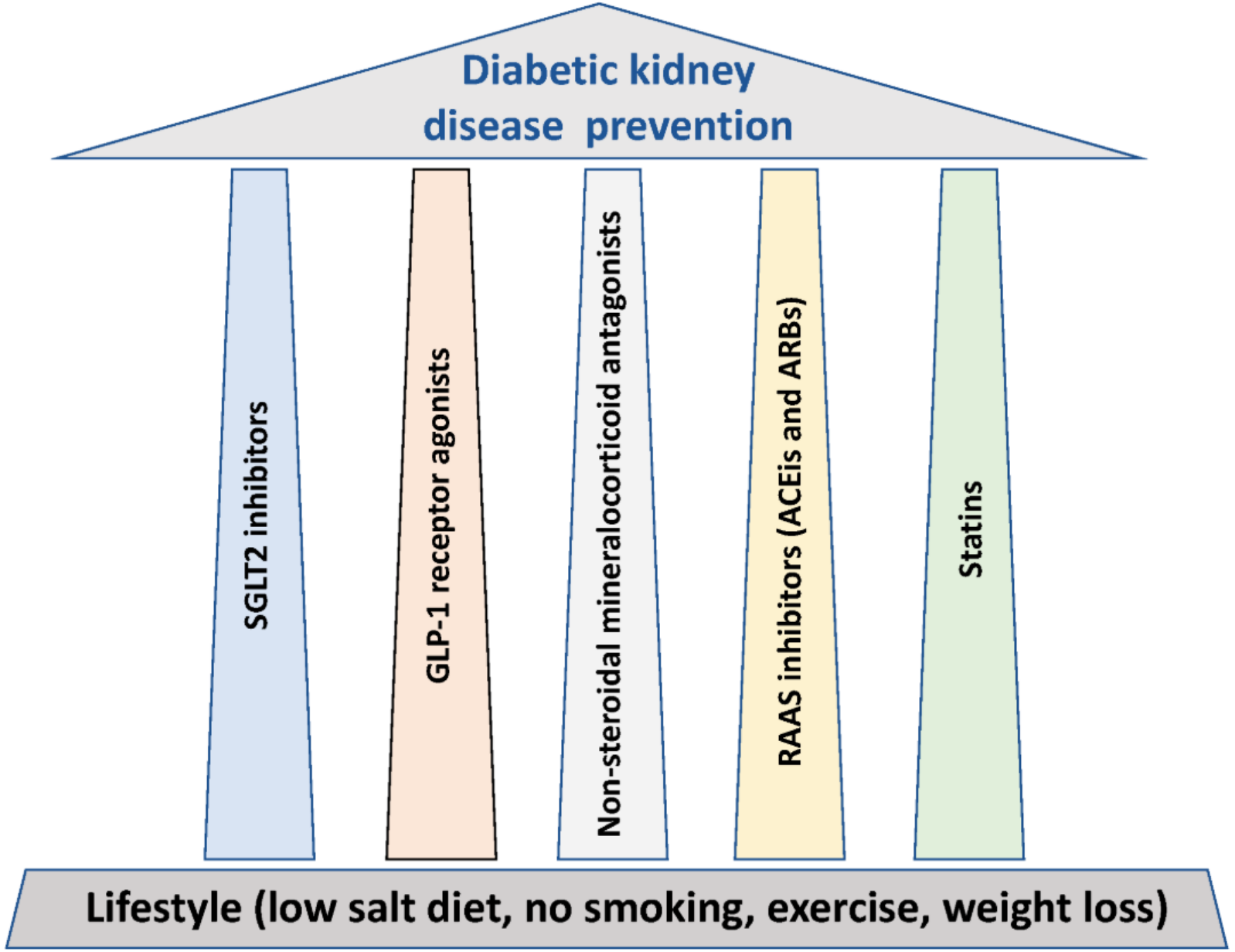
- Type 1 diabetes
- Stage 4-5 CKD / dialysis patients
- Kidney transplant recipients
- The elderly (with frailty)

- People ADPKD or glomerulonephritis



This may change in the next years with important studies ongoin

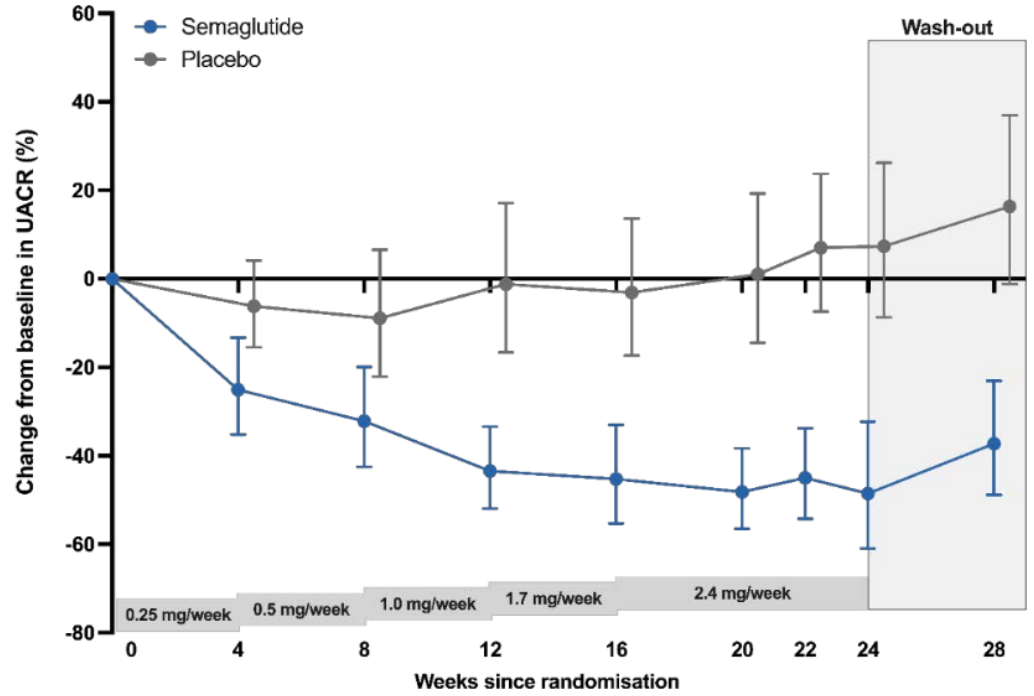
FIND CKD study

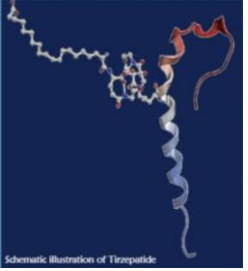


Kearney, 2023, Pharmaceutics

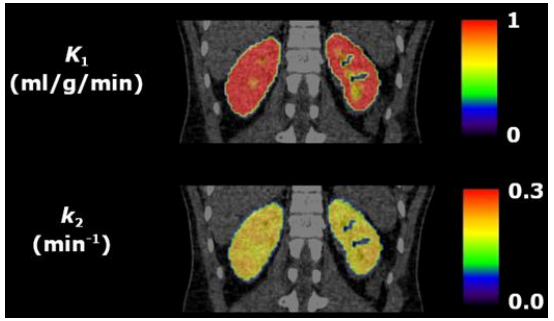
SMART study met Semaglutide

Figure 1. Change from baseline in UACR over the study treatment period.





TREASURE study - Tirzepatide



- People with DKD and non-diabetic CKD



- Effects on measured GFR (iohexol clearance)

- Multiparametric kidney MRI
- Kidney fat accumulation



- Kidney oxygen consumption using 11c Acetate PET



Conclusie

- Hoge morbiditeit en mortaliteit van CNS -> link met HVZ
- Grote studies tonen voordeel van SGLT2 remmers op harde eindpunten
- Andere middelen die in diabetes succesvol zijn geweest qua nierbeschermingen, worden nu onderzocht in CKD zonder diabetes