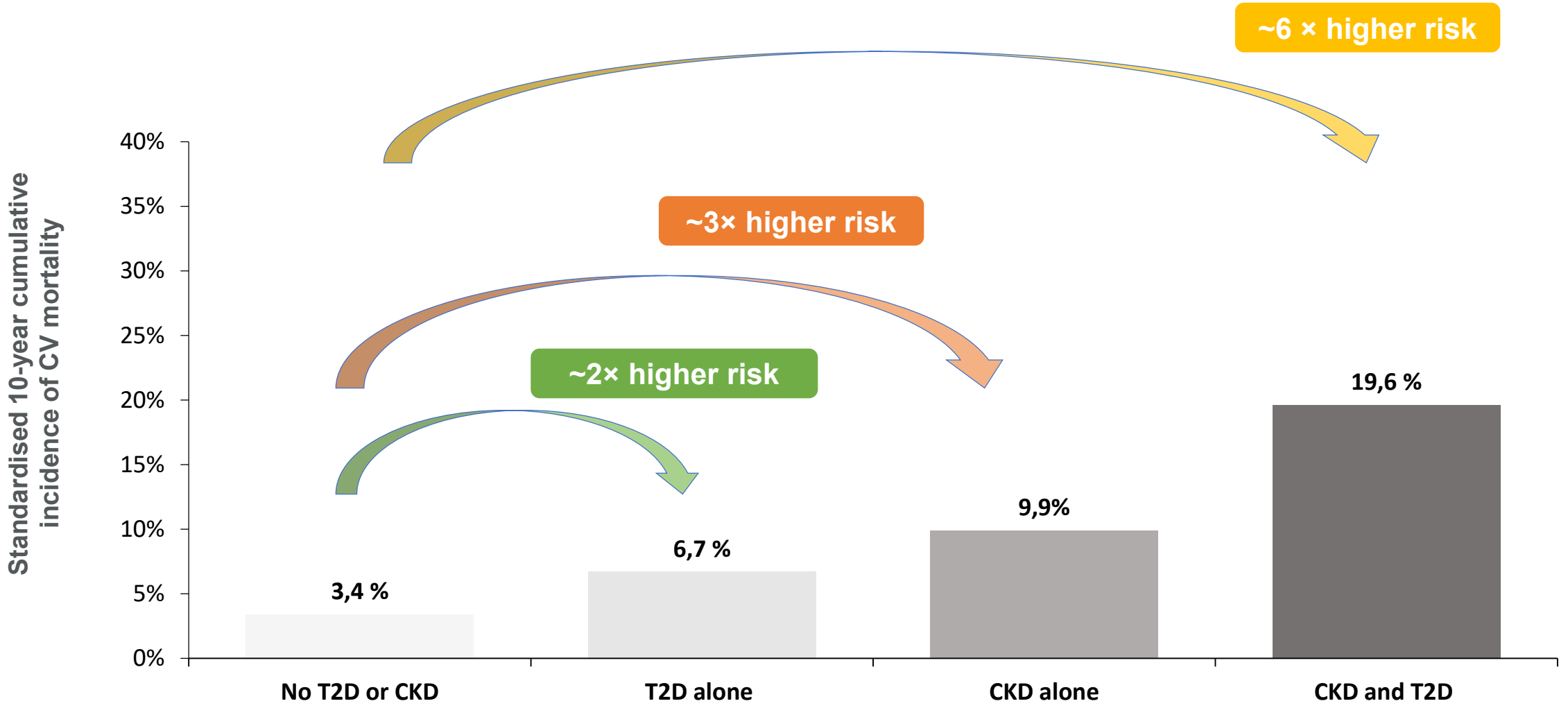
Mineralocorticoïd antagonisten

Dr. Johan Scharpé

Nefroloog GZA

Hoog CV risico (mortaliteit) bij DM 2 en CKD

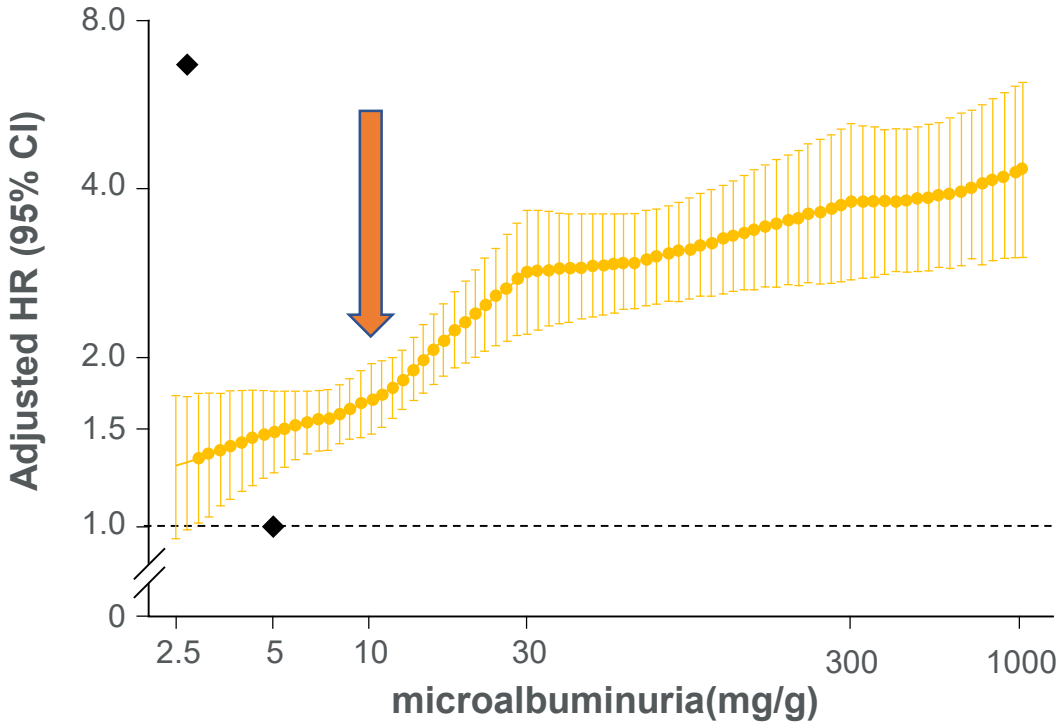


Afkarian M, *et al*. *J Am Soc Nephrol* 2013;24:302–308

Standardised 10-year cumulative incidence of CV mortality by diabetes and kidney disease status

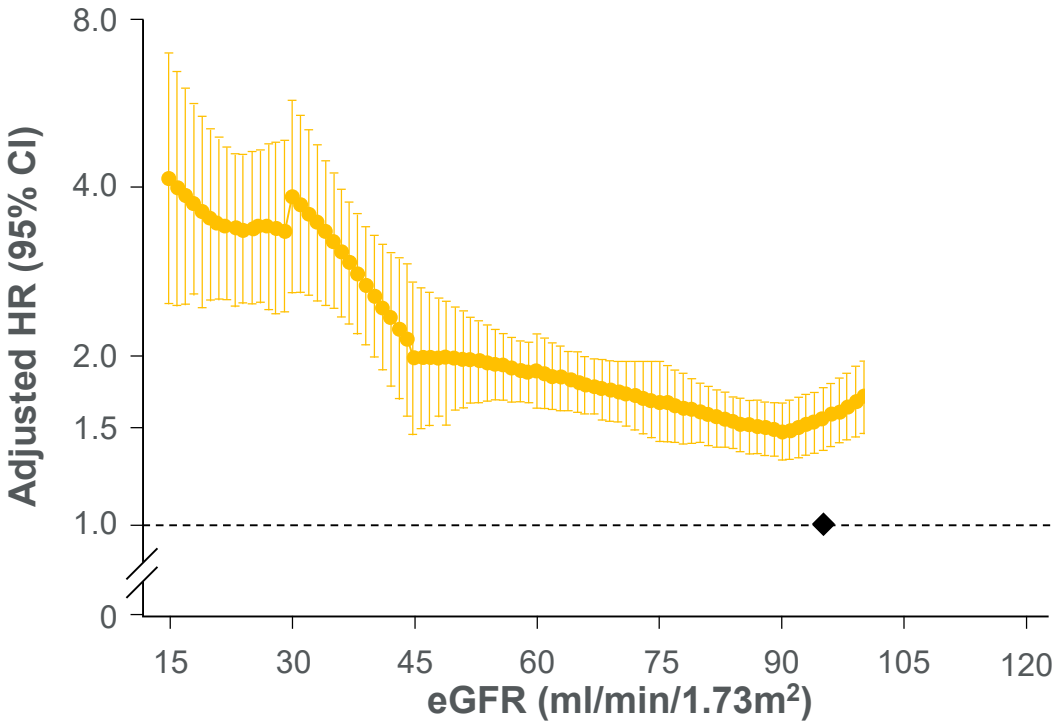
Risico op CV events bij patienten met diabetes verhoogt bij toenemende albuminuria en dalende GFR

CV mortality according to microalbuminuria



Risk of CV death is significantly increased as urinary alb/creat ratio rises above 10 mg/g

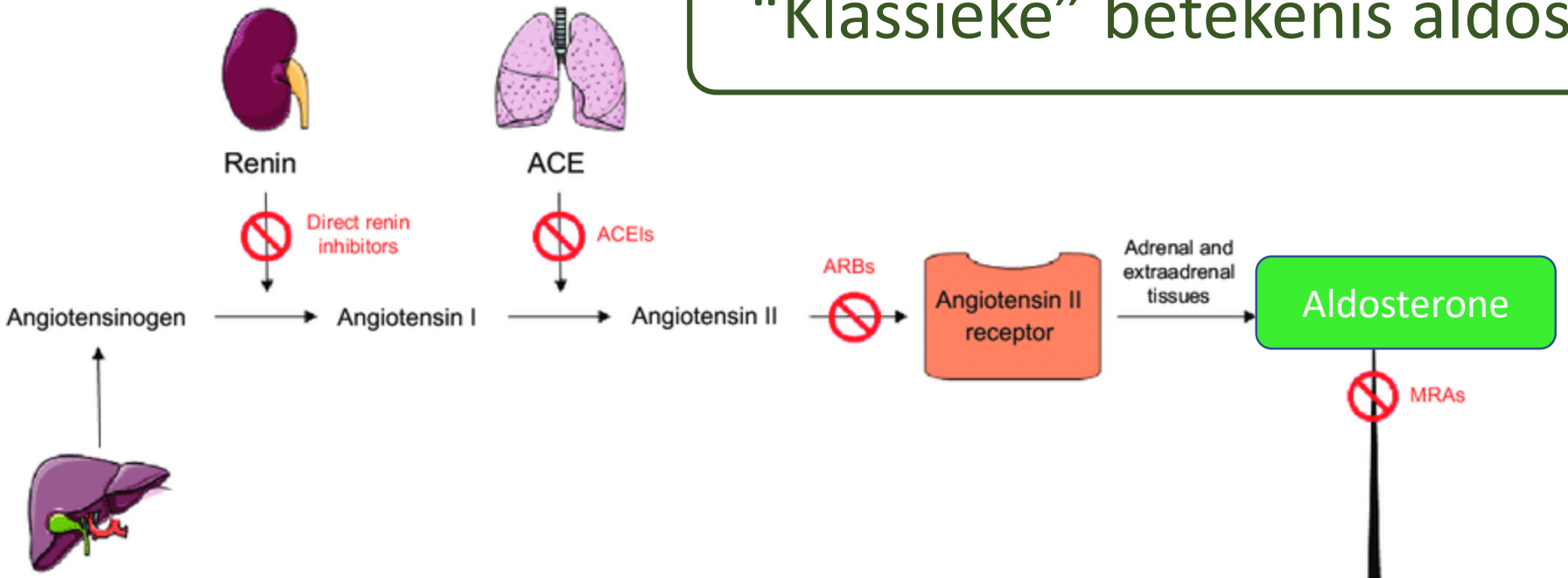
CV mortality according to eGFR



Risk of CV death is significantly increased as eGFR falls below 75 ml/min/1.73 m²

Fox CS, *et al. Lancet* 2012;380:1662–1673 . Meta analyse 128000 diabetes patienten

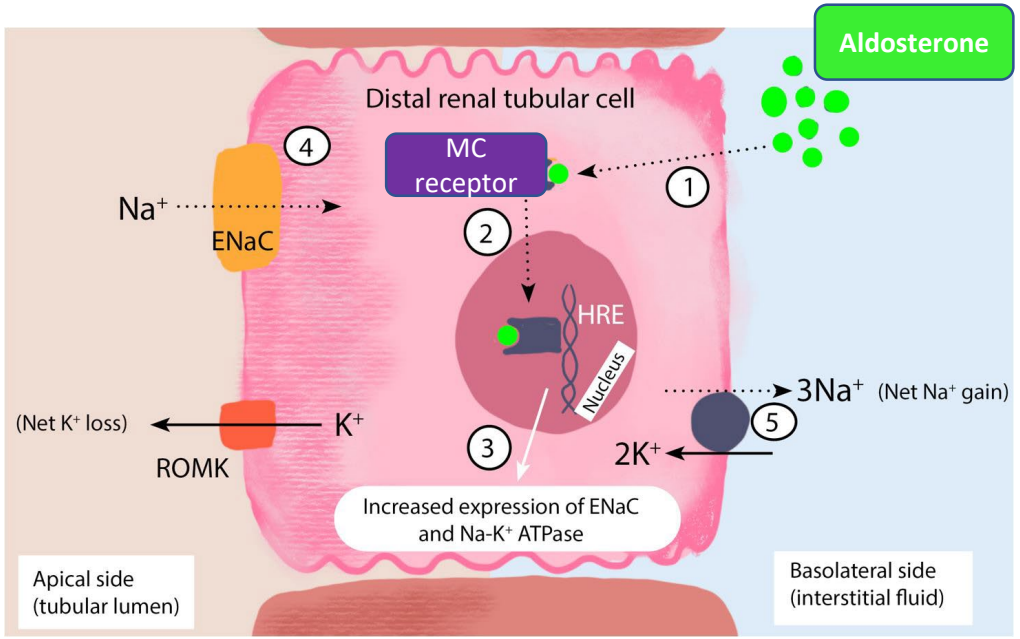
“Klassieke” betekenis aldosterone



Na/ H2O reabsorptie
K excretie
(K excretie colon)

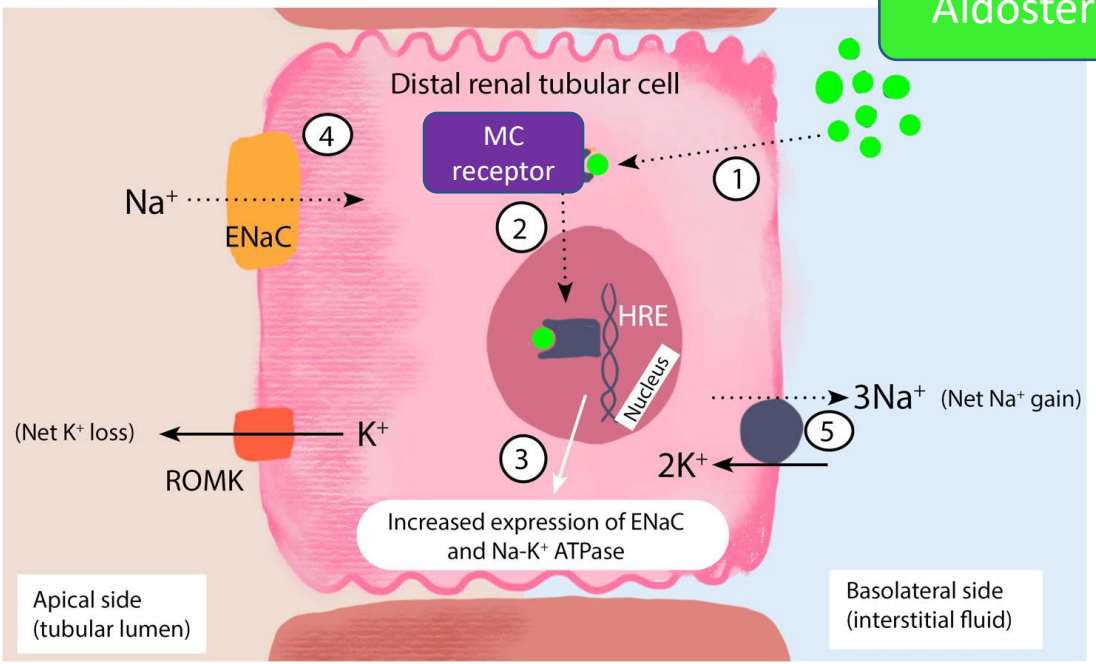
Basis voor ontwikkeling

Spironolactone
RAS blokkers



Aldosterone “klassiek” (50 j geleden)
MR receptor in distale tubuli

Aldosterone



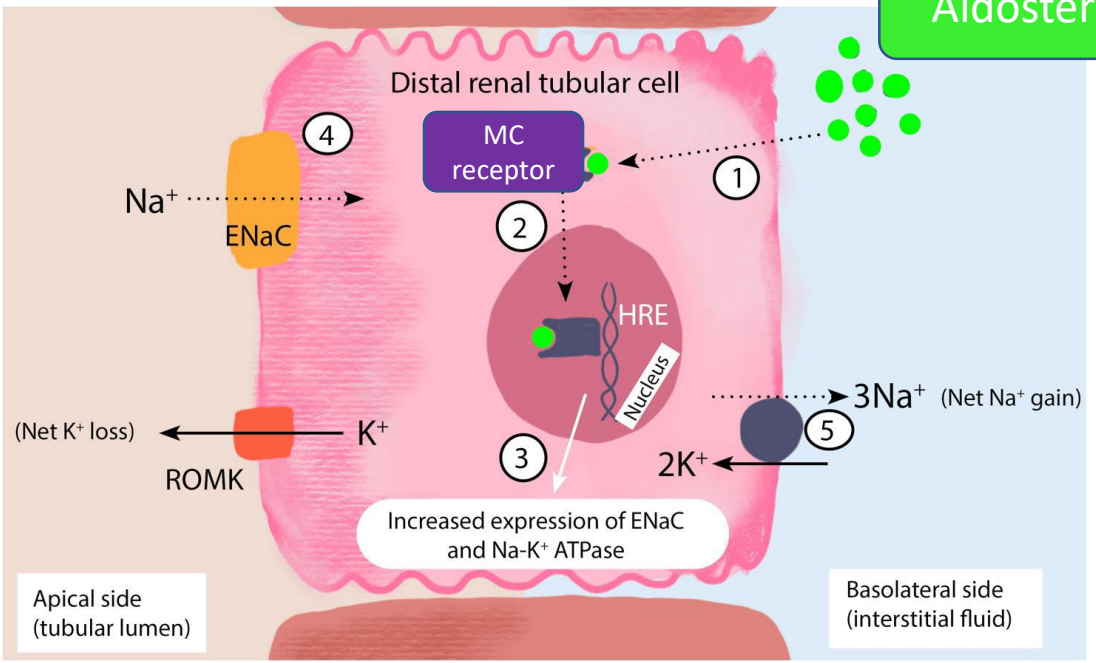
Na / H2O reabsorptie en K excretie
(ook K excretie colon)

Basis voor ontwikkeling
spironolactone
RAS

Aldosterone "klassiek" (50 j geleden)
MR receptor in distale tubuli

Aldosterone "nu"
MR receptor "overal"

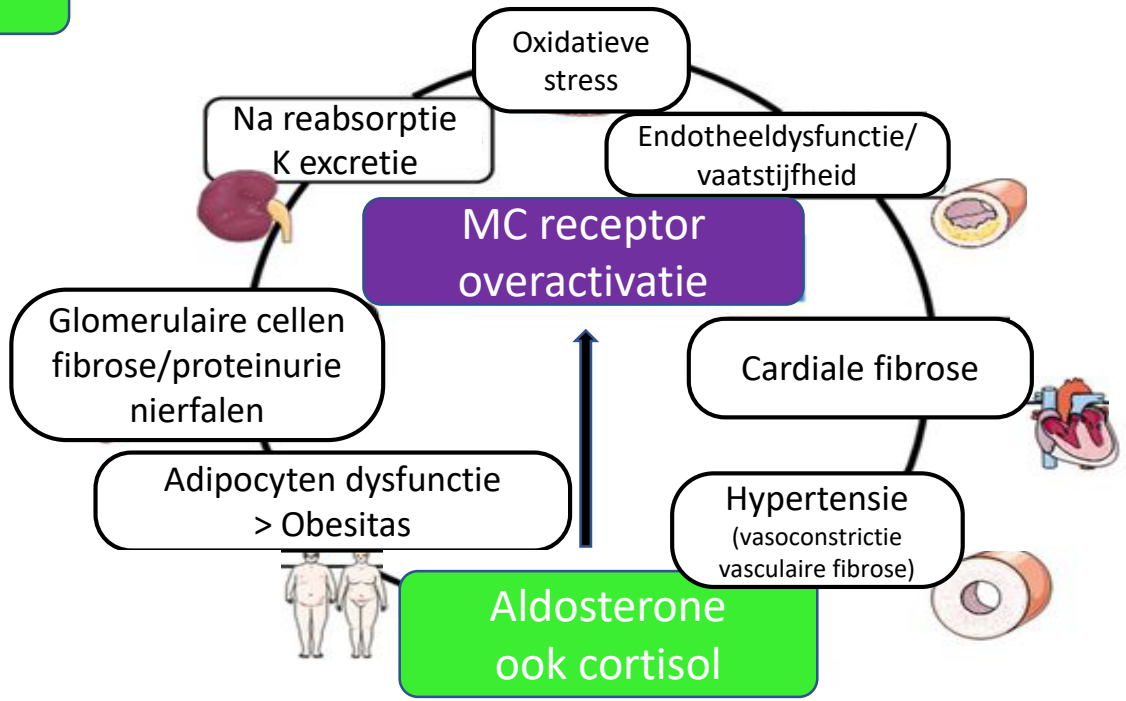
Aldosterone



Na / H2O reabsorptie en K excretie
(ook K excretie colon)

Basis voor ontwikkeling spironolactone RAS

Pleiotropic aldosterone actions contributing to the pathogenesis of cardiovascular disease.

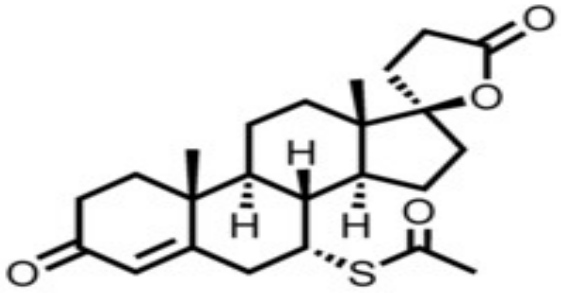


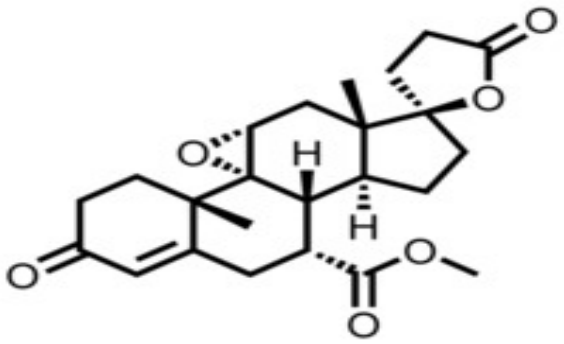
Inflammatie en fibrose (cardiaal /vasculair / renaal) vaatstijfheid

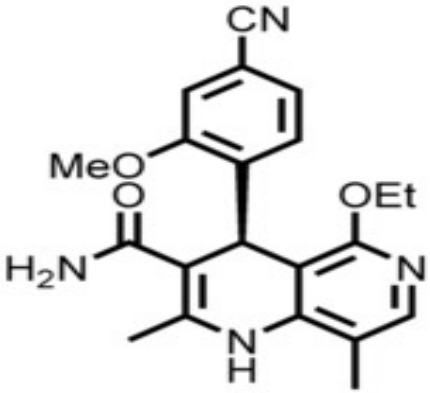
Spironolactone
nieuwe generatie MCR antagonisten

Mineralocorticoid Receptor Antagonists

1st generation | 2nd generation | 3rd generation







1950s | 2000s | 2015

Spironolactone | **Eplerenone** Inspra® | **Finerenone** Kerendia ®

	Steroidale		Niet-steroidale
Structural properties			
Potency against MR	+++	+	+++
Selectivity for MR	+	+++	+++++
Tissue distribution	Kidney>heart	Kidney>heart	Kidney = heart
Sexual side effects	++	(+)	–
Active metabolites	++	–	–
Effect on BP	+++	++	+
Effect on inflammation/fibrosis	+	+	+++

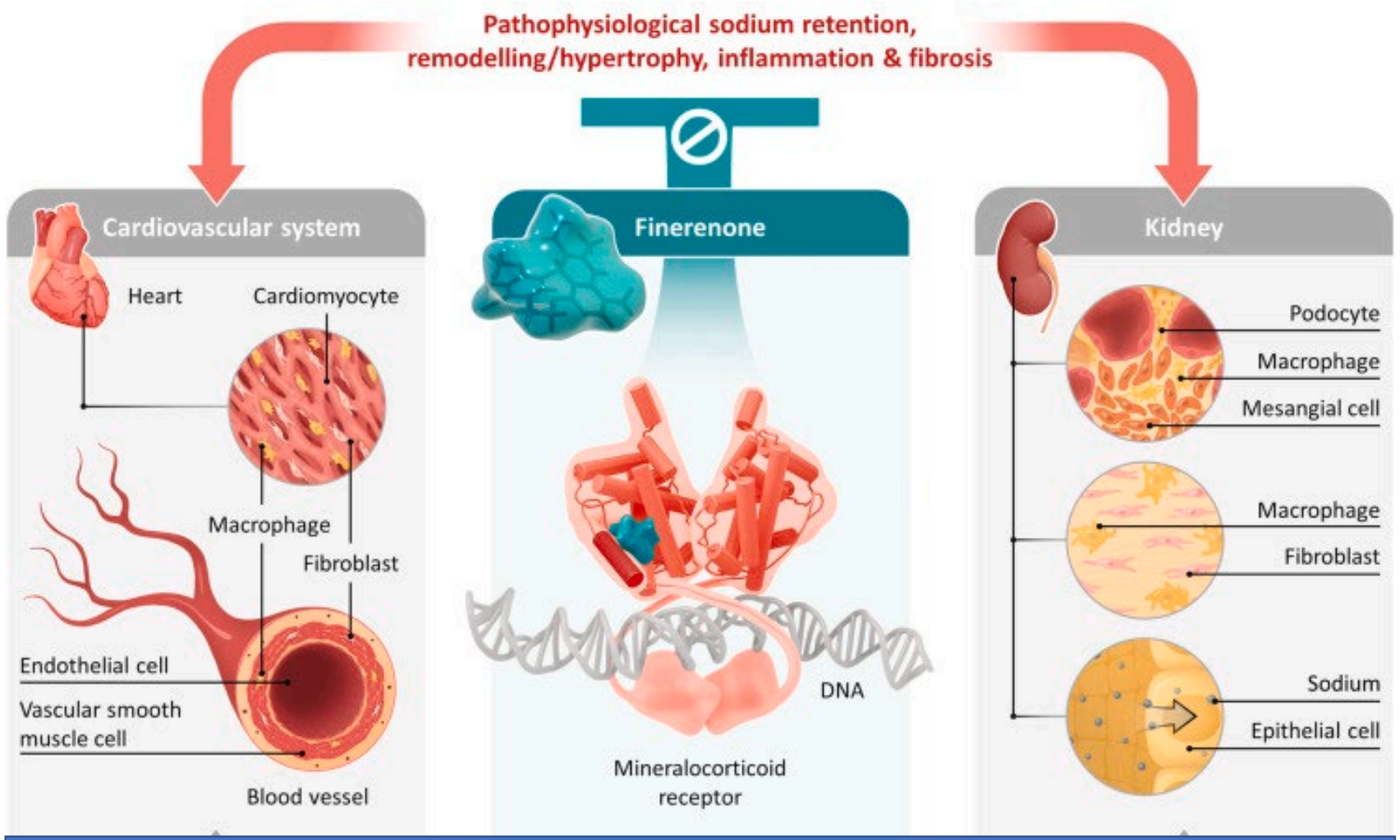
(Soms gevaarlijke) hyperkaliemie

Gynecomastie
Onregelm menses
Libidoverlies / impotentie

affiniteit androgene /progesterone receptor

GEEN affiniteit voor androgene/ progesterone / corticoid receptor

Mineralocorticoid receptor overactivatie = inflammatie / fibrose



Experimentele modellen tonen renoprotectie en cardiovasculaire protectie van finerenone

FIDELIO : finerenone bij CKD en DM type 2

Albuminurie / **GFR**	Alb < 30 / g creat	Alb 30-300 / g creat	Alb > 300 /g creat
> 90			
> 60			
45-59		GFR 25-60 en retinopathie	GFR 25-75
30-44			
15-29			
< 15 of dialyse			

RISICO

- Laag
- Matig
- Hoog
- Zeer hoog

Table 1. **Demographic and Clinical Characteristics of the Patients at Baseline.***

Characteristic	Finerenone (N=2833)	Placebo (N=2841)	Total (N=5674)
Age — yr	65.4±8.9	65.7±9.2	65.6±9.1
Male sex — no. (%)	1953 (68.9)	2030 (71.5)	3983 (70.2)
Estimated glomerular filtration rate			
Mean	44.4±12.5	44.3±12.6	44.3±12.6
Urinary albumin-to-creatinine ratio‡			
Median (IQR)	833 (441–1628)	867 (453–1645)	852 (446–1634)

Comedicatie

100% ACE/ARB
70% diureticum
5% SGLT2

NEJM 2000

FIDELIO

Finerenone (n = 2866)

Na 4-16 w maximalisatie ACE/ARB

K < 4,8

Placebo (n = 2868)

10 mg GFR < 60

20 mg GFR = of > 60

17,8 %

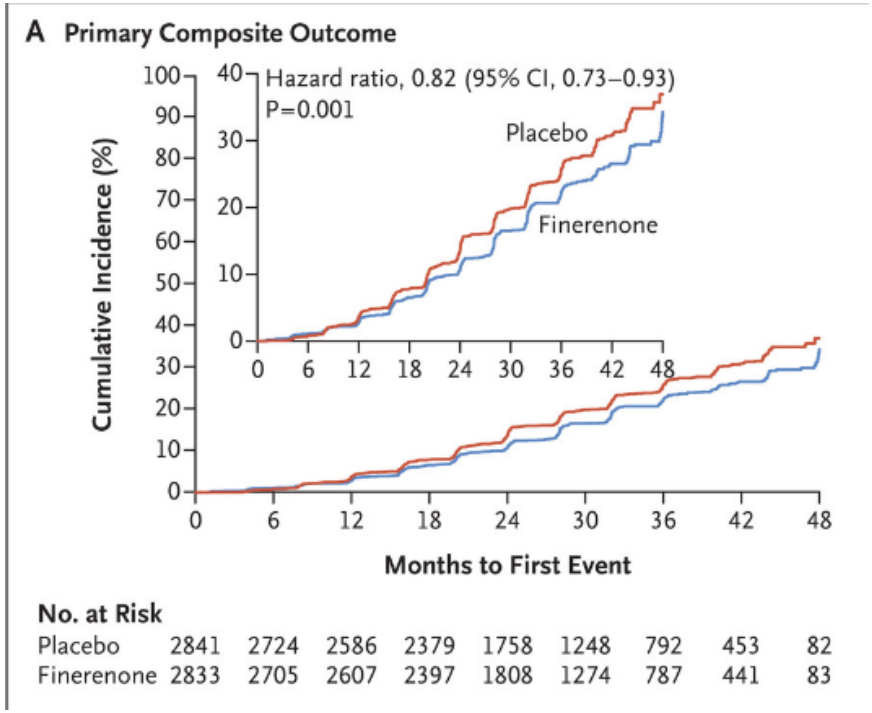
2,6 jaar

Composite outcome
- Death
- Dialysis
- 40% GFR daling

10 mg GFR < 60

20 mg GFR = of > 60

21,1 %



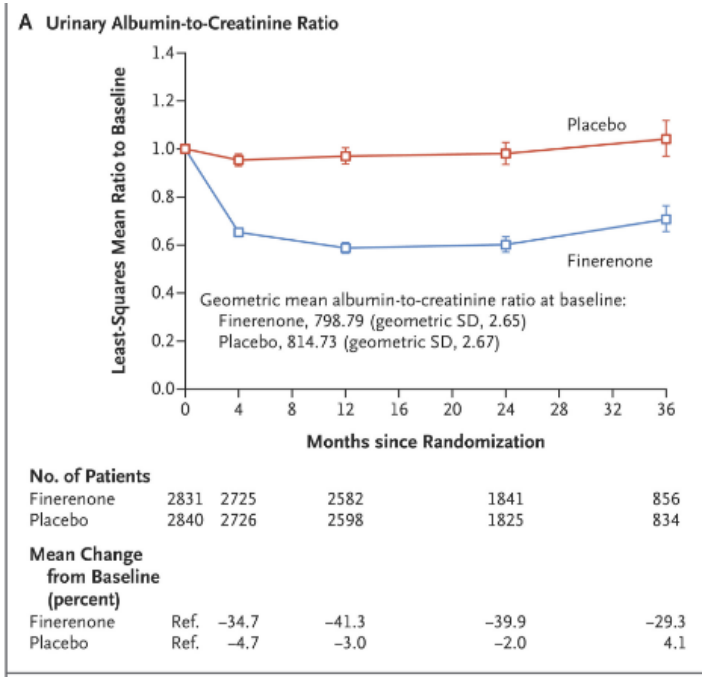
FIDELIO

	Kalium	> 5,5	> 6,0
Finerenone		21,7 %	4,5 %
Placebo		9,8 %	1,4 %

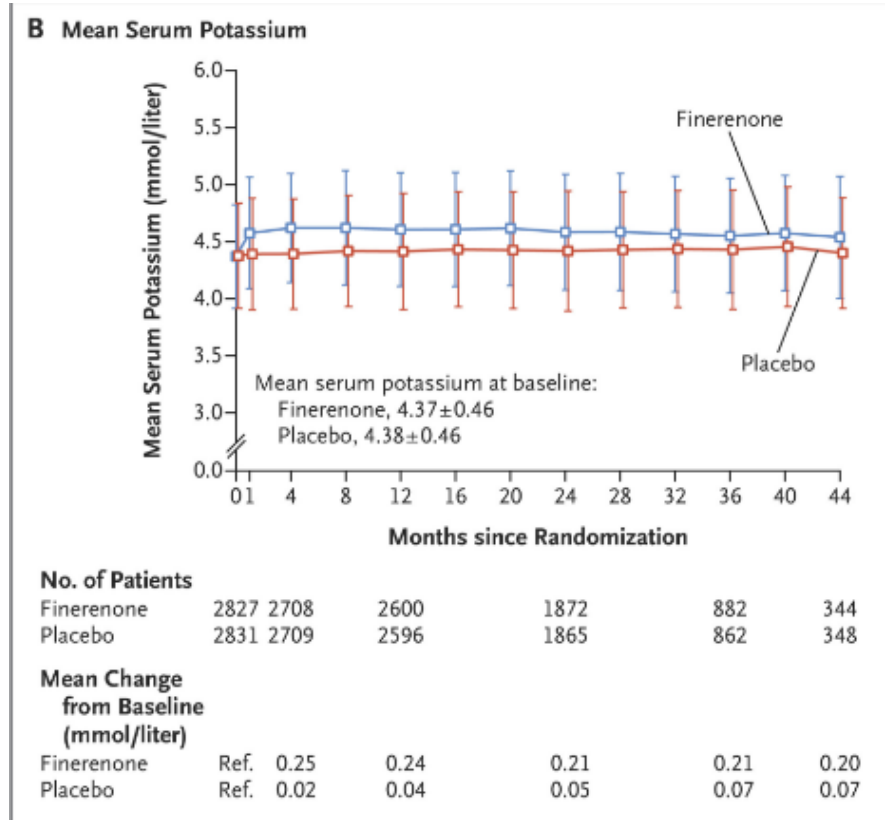
Finerenone

BD : - 2 a 3 mmHg systolisch
Reductie albuminurie

Door wat hogere zoutexcretie ?



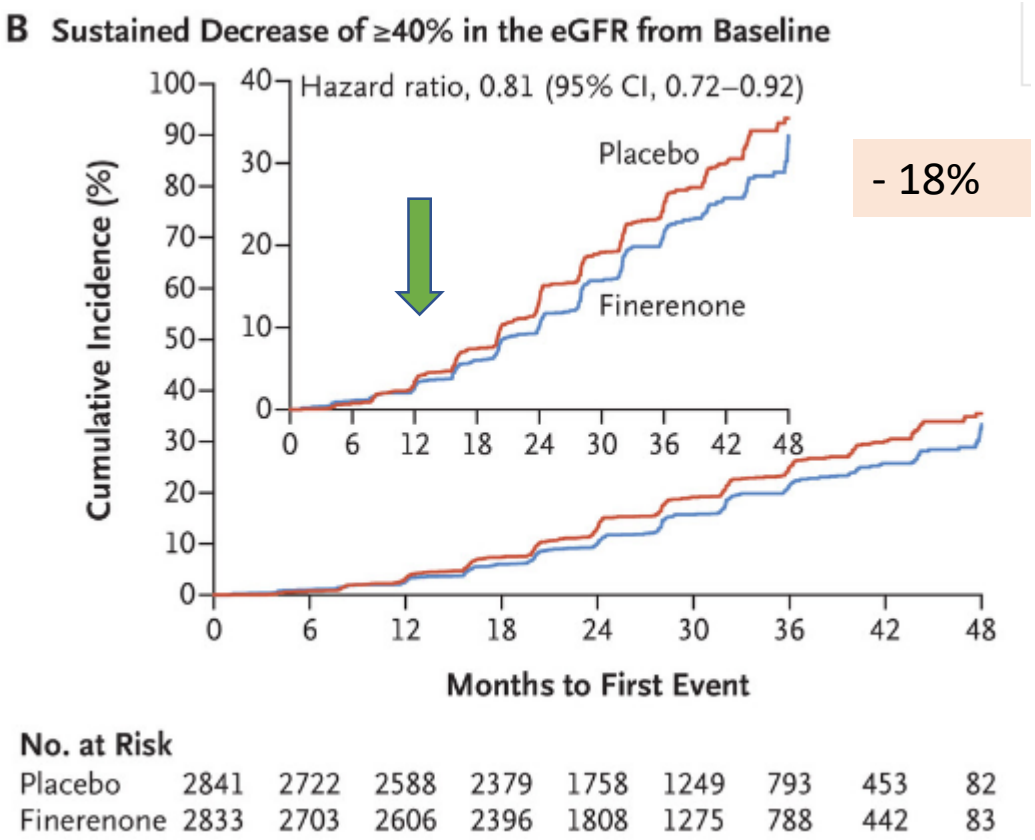
No. of Patients					
Finerenone	2831	2725	2582	1841	856
Placebo	2840	2726	2598	1825	834
Mean Change from Baseline (percent)					
Finerenone	Ref.	−34.7	−41.3	−39.9	−29.3
Placebo	Ref.	−4.7	−3.0	−2.0	4.1



No. of Patients						
Finerenone	2827	2708	2600	1872	882	344
Placebo	2831	2709	2596	1865	862	348
Mean Change from Baseline (mmol/liter)						
Finerenone	Ref.	0.25	0.24	0.21	0.21	0.20
Placebo	Ref.	0.02	0.04	0.05	0.07	0.07

FIDELIO. NEJM 2000. Bakris et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

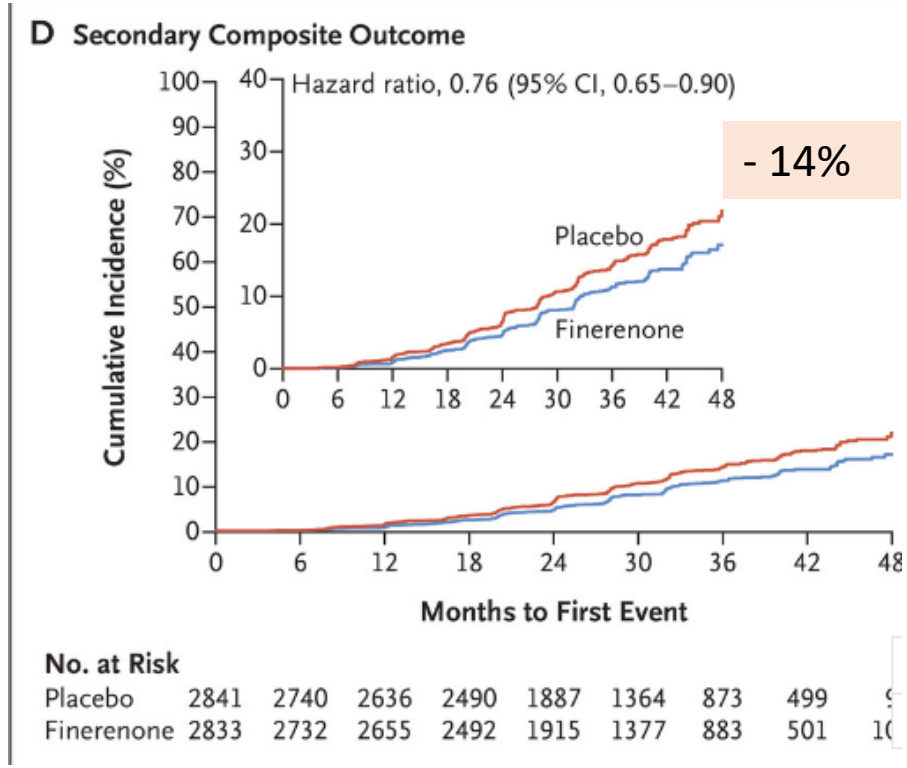
NEFROPROTECTIE



- 18%

Pas na 12 maand zichtbaar
> eerder door tissue remodeling dan door verhoogde zoutexcretie / hemodynamiek ?

CARDIOVASCULAIRE PROTECTIE



- 14%

Key secondary composite outcome
- Death from cardiovascular causes
- Nonfatal myocardial infarction
- Nonfatal stroke
- Hospitalization for heart failure

FIDELIO . NEJM 2000. Bakris et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

FIGARO : finerenone bij CKD en DM type 2

Albuminurie / **GFR**	Alb < 30 / g creat	Alb 30-300 / g creat	Alb > 300 /g creat
> 90			GFR >60
> 60		GFR 25-90	
45-59			
30-44			
15-29			
< 15 of dialyse			

RISICO

- Laag
- Matig
- Hoog
- Zeer hoog

Table 1. **Key Demographic and Clinical Characteristics of the Patients and Medications at Baseline.***

Characteristic	Finerenone (N=3686)	Placebo (N=3666)	Total (N=7352)
Age — yr	64.1±9.7	64.1±10.0	64.1±9.8
Male sex — no. (%)	2528 (68.6)	2577 (70.3)	5105 (69.4)
Estimated glomerular filtration rate			
Mean — ml/min/1.73 m^2	67.6±21.7	68.0±21.7	67.8±21.7
Urinary albumin-to-creatinine ratio‡			
Median (interquartile range)	302 (105–749)	315 (111–731)	308 (108–740)

Comedicatie

100% ACE/ARB
47% diureticum
8% SGLT2

NEJM 2021

FIGARO

Finerenone (n = 3686)

10 mg GFR < 60

20 mg GFR = of > 60

12,4%

maximalisatie ACE/ARB

K < 4,8

3,4 jaar

Composite outcome
- CV Death
- Myocardinfarct
- Stroke
- Hospitalisatie HF

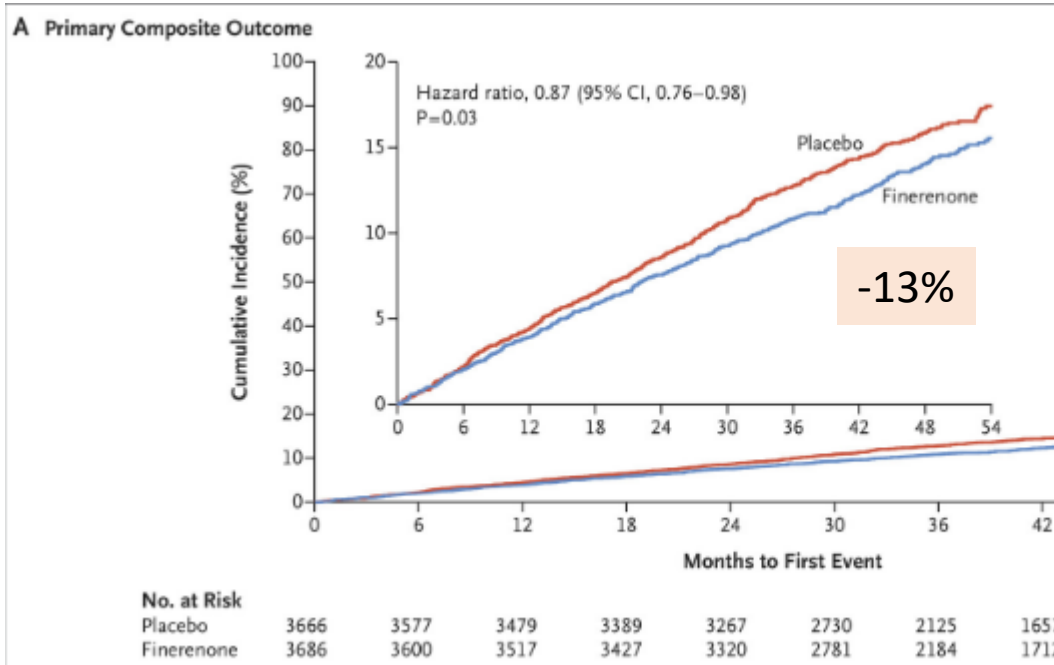
Placebo (n = 3666)

10 mg GFR < 60

20 mg GFR = of > 60

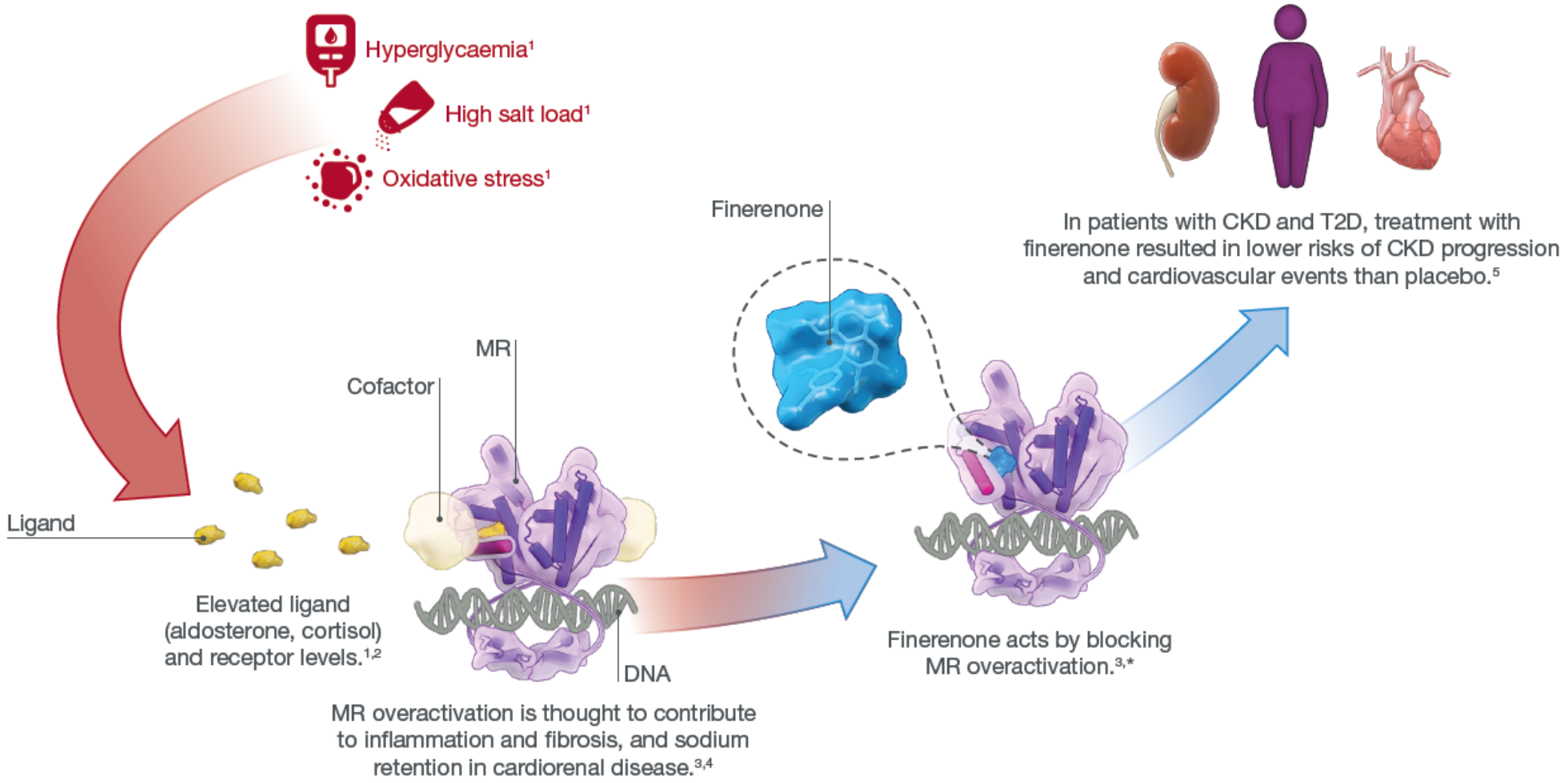
14,2 %

CARDIOVASCULAIRE PROTECTIE

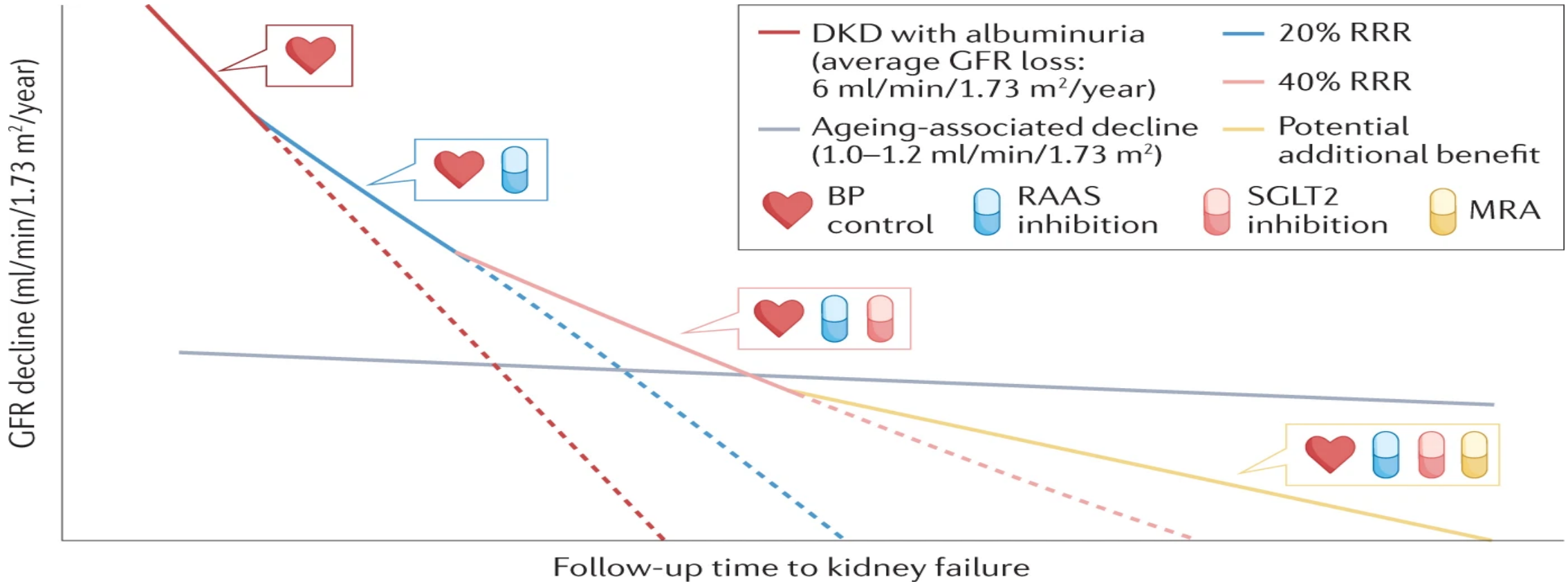


FIGARO; nejm 2021; Pitt; Cardiovascular events with finerenone in kidney disease and type 2 diabetes

SAMENVATTING : finerenone
een niet-steroidale, selectieve mineralocorticoid receptor antagonist
bij CKD en DM: renoprotectief / cardivasculair protectief in vgl placebo
en dit bovenop maximale RAS blokkade



Preventie nierfunctieachteruitgang bij DM en CKD



Plaats finerenone en SGLT2 bij CKD/DM

Start RAS blokker

+ SGLT 2

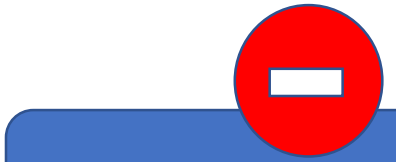
Maximaliseer RAS blokker

Optimaliseer BD

Residuele microalbuminurie ?

K < 4,8

Finerenone



Dubbele RAS blokkade

Expert opinion , state of art lecture Prof Topf (Detroit) voor BVN 12/2022

Nog openstaande vragen

- finerenone bovenop SGTL2 bij (non)diabetische nefropathie

FLAMINGO study: Combination of Finerenone and SGLT2 Inhibitors in People With Chronic Kidney Disease Together With Type 2 Diabetes by Using Routine Medical Care Data and Past Clinical Study Results

Eind 2023 ?

- finerenone bij niet-diabetische nefropathie

  (met/ zonder proteinurie)?

FIND-CKD study : finerenone versus placebo /standard care

2026 ?

- finerenone versus spironolactone bij hypertensie

Effect of Mineralcorticoid Recept Antagonist on Cardiovascular Disease in Patients With Hypertension and Hyperaldosteronemia : A Multicenter Randomized Controlled Study

Finerenone versus spironolactone versus placebo bij aldo > 12 ng/dl (excl primair hyperaldo): voordeel op cardiovasculaire outcome, onafh van bloeddrukcontrole ?

Eind 2026 ?

Clinicaltrials.gov

Nieuwe kaliumbinders

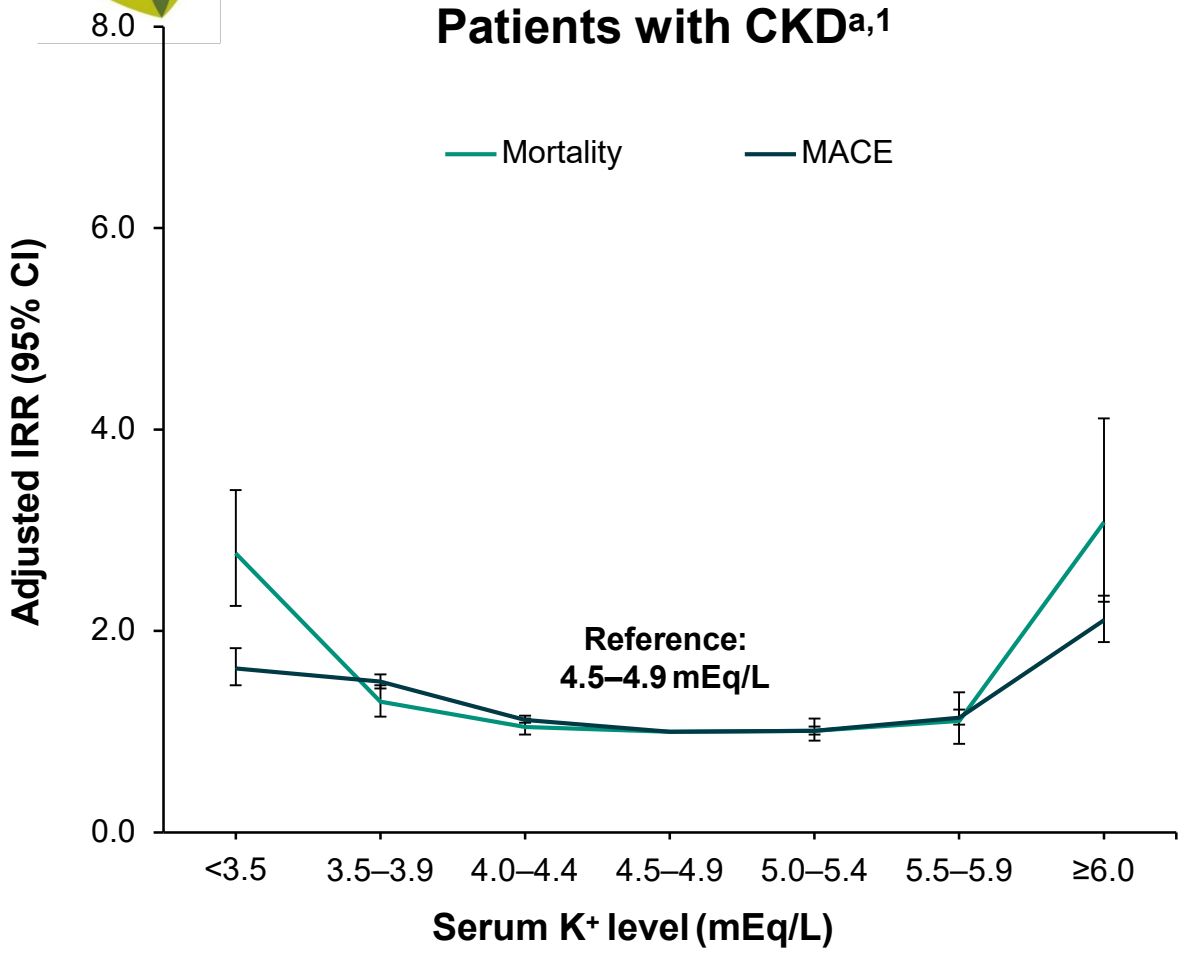
Vanessa Ooms

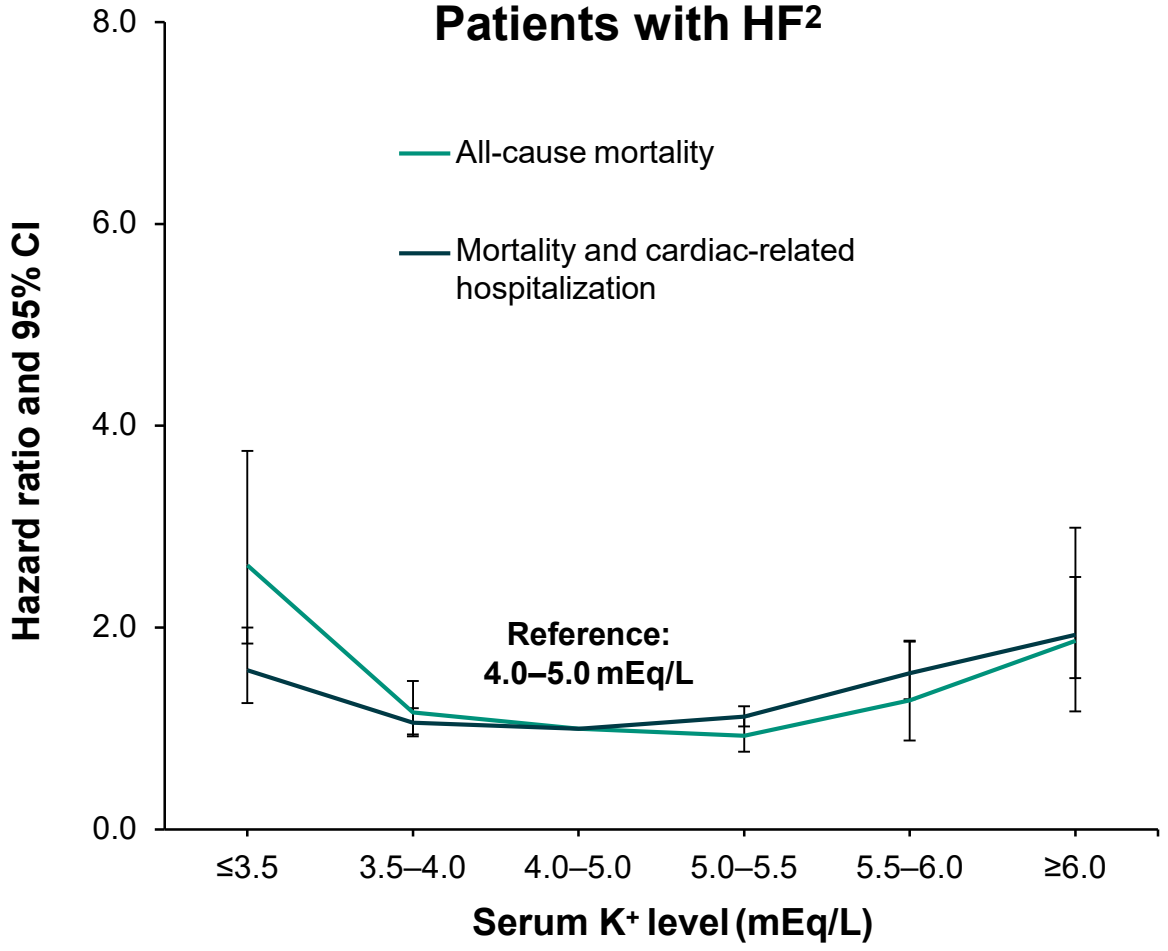
Nefroloog GZA

Hyperkalemie: K > 5,1 mmol/l

The incidence of HK in the general population is 2–3%[1]

High serum K^+ is associated with increased mortality and adverse outcomes in patients with CKD and those with HF

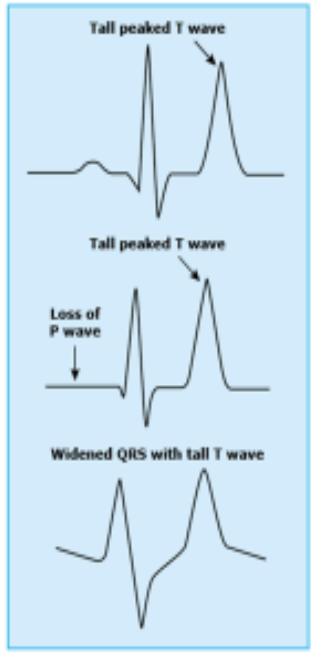




Symptomen ? Pas als K > 6,5 à 7 mmol/l

- Ernstige spierzwakte OL
- Hartritmestoornissen,
- geleidingsstoornissen
- Bij dialysepatiënten :
  - plotse dood (WE)

Typical electrocardiographic features of hyperkalemia



Serum potassium	Major change
5.5-6.5	Tall peaked T waves
6.5-7.5	Loss of P waves
7.0-8.0	Widening of QRS
8.0-10.0	Sine wave, ventricular arrhythmia, asystole

Adapted from: Mattu A, Brady WJ, Robinson DA. Electrocardiographic manifestations of hyperkalemia. Am J Emerg Med 2000; 18:721.

UpToDate

Hoe chronische (milde) hyperkalemie behandelen?

- Metabole acidose corrigeren : $NaHCO_3$ gellulen opstarten los van de maaltijd
- Bij overvulling: lis- of thiazide diureticum (kaliurese stimuleren)
- SGLT-2 inhibitor: kaliuretisch
- Uitlokkende (niet-essentiële) medicatie stoppen
  - NSAID's
  - Trimetoprim
- Kaliumarm dieet (mild)
- Kaliumbinder

Foods with high levels of potassium

Highest content (>25 mEq/100 g)
Dried figs
Molasses
Seaweed
Very high content (>12.5 mEq/100 g)
Dried fruits (dates, prunes)
Nuts
Avocados
Bran cereals
Wheat germ
Lima beans

High content (>6.2 mEq/100 g)
Vegetables
Spinach
Tomatoes
Broccoli
Winter squash
Beets
Carrots
Cauliflower
Potatoes
Fruits
Bananas
Cantaloupe
Kiwis
Oranges
Mangos
Meats
Ground beef
Steak
Pork
Veal
Lamb

Adapted from: Gennari FJ. Hypokalemia. N Engl J Med 1998; 339:451.

UpToDate®

Behandeling acute ernstige hyperkalemie

- Calciumgluconaat IV (cardiale stabilisatie)

- K shift naar intracellulair:
  - Hypertoon glucose 50% + insuline IV
  - NaHCO3 IV
  - Beta-2adrenerge agonisten

- K verwijderen
  - Lisdiuretica IV
  - Kaliumbinder GI
  - Acute dialyse

Selected characteristics of potassium binders

	Kayexalate/Sorbisterit (polystyreensulfonaat)	Veltassa (patiromer)	LOKELMA (zirconium cyclosilicaat)
Approval date	1958[a]	USA: 2015; EU: 2017	USA: 2018; EU: 2019
Mechanism	Nonspecific sodium cation-exchange resin; may also bind magnesium	Nonspecific cation-binding in exchange for calcium	Highly selective; preferentially captures K^+ ions
Onset	1–2 hours	4–7 hours[5]	1 hour
Starting dose	15 g/d	8.4 g once daily	10 g three times daily (starting dose); 5 g once daily (maintenance)
Location	Colon[3]	Predominantly distal colon[4]	Entire gastrointestinal tract

Sodium /calciumpolystyrene sulfonate SPS (Kayexalate/Sorbisterit)

- Kationuitwisselend hars
- Bij de kaliumrijke maaltijd innemen (1 maatje= 15g/d)
- 3uur voor/na andere medicatie (anders gedaalde absorptie)
- Slechte tolerantie GI (obstipatie, anorexie, nausea)
- Nevenwerkingen:
  - Ischemische colitis (colonnecrose) vooral als samen gebruikt met Sorbitol
  - Hypercalcemie, hypoMg

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Veltassa en Lokelma: terugbetaling aan te vragen door nefroloog, internist of cardioloog

- Diabetes of congestief hartfalen of proteinurie > 1g/d
  - En CNI GFR 15-60ml/min
  - En recidiverende hyperkalemie K > 5,1 (ondanks K arm dieet en correctie metabole acidose)
  - En RAAS blokker nodig
  - En K < 6,5 mmol/l
  - Geen VG darmobstructie, geen ingrijpende GI heelkunde

- Verlenging na 6 maanden
  - K moet < 5,1 zijn onder therapie

Veltassa en Lokelma: terugbetaling aan te vragen door nefroloog voor (pre)dialysepatiënten

- Predialyse GFR < 15 ml/min of chronische dialyse
  - En K >5,4 mmol/l, ondanks aanpassen dialysaat

- Verlenging na 6 maanden
  - K moet < 5,1 zijn onder therapie

Doel- nut nieuwe kaliumbinders ?

- Kalium onder controle en RAAS blokker en/of MRA (spironolactone/finerenone) kan verdergezet zonder streng kaliumarm dieet

Patiromer (Veltassa)

- Polymeer , wordt niet gereabsorbeerd, werkzaam in colon
- Best ‘s avonds (3uur voor /of na andere geneesmiddelen), met of zonder voedsel (metformine ciproxine, levothyroxine)
- Werkt na 4-7uur
- Zakjes poeder oplossen in 40ml water
- Goede tolerantie (obstipatie in 6%), natriumvrij
- Hypomagnesemie (Mg volgen)

Patiromer (Veltassa)

- Opstarten met zakjes van 8,4 g/d
- Labo na 1 week: kalium en Mg
- Labo na 1maand: als kalium > 5,1mmol/l: evt dosis naar 16,4g/d en opnieuw Mg volgen
- Daling van kalium gemiddeld -1 mEq/l

Selected characteristics of potassium binders

	Kayexalate/ Sorbisterit	Veltassa	LOKELMA[6]
Approval date	1958[a]	USA: 2015; EU: 2017	USA: 2018; EU: 2019
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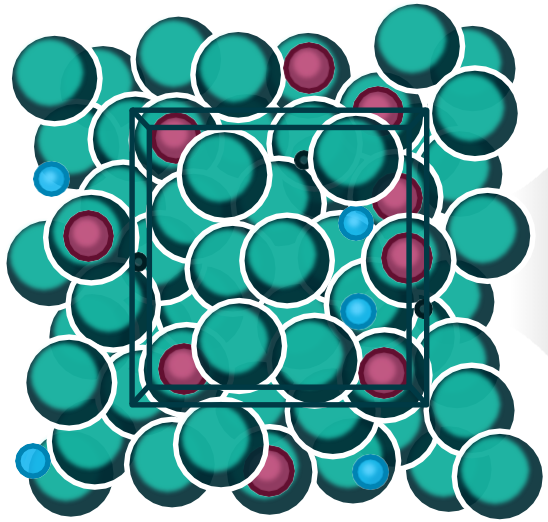
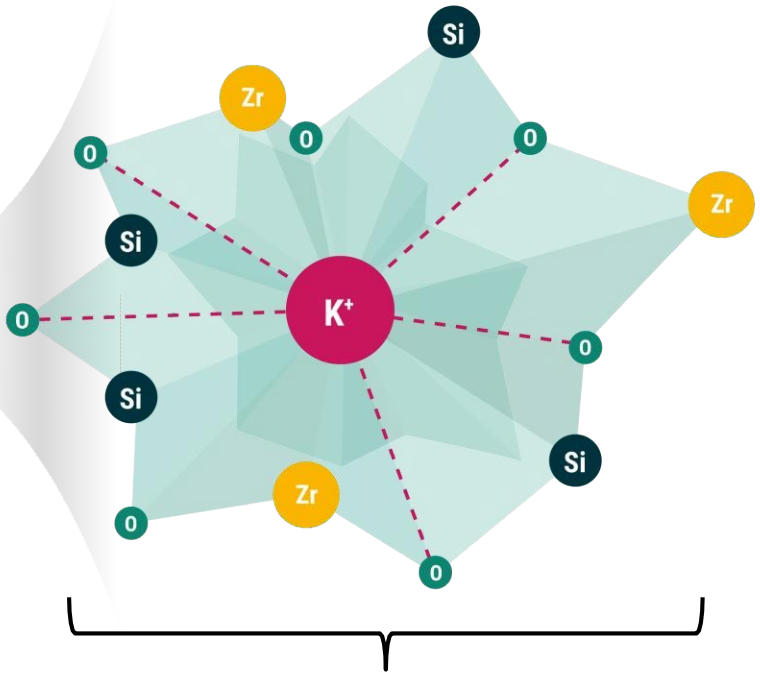
Location	Colon[3]	Predominantly distal colon[4]	Entire gastrointestinal tract

LOKELMA crystal

LOKELMA is indicated for the treatment of HK in adults[1]



Chemical formula:
$H_6Na_2O_9Si_3Zr^{+2}$

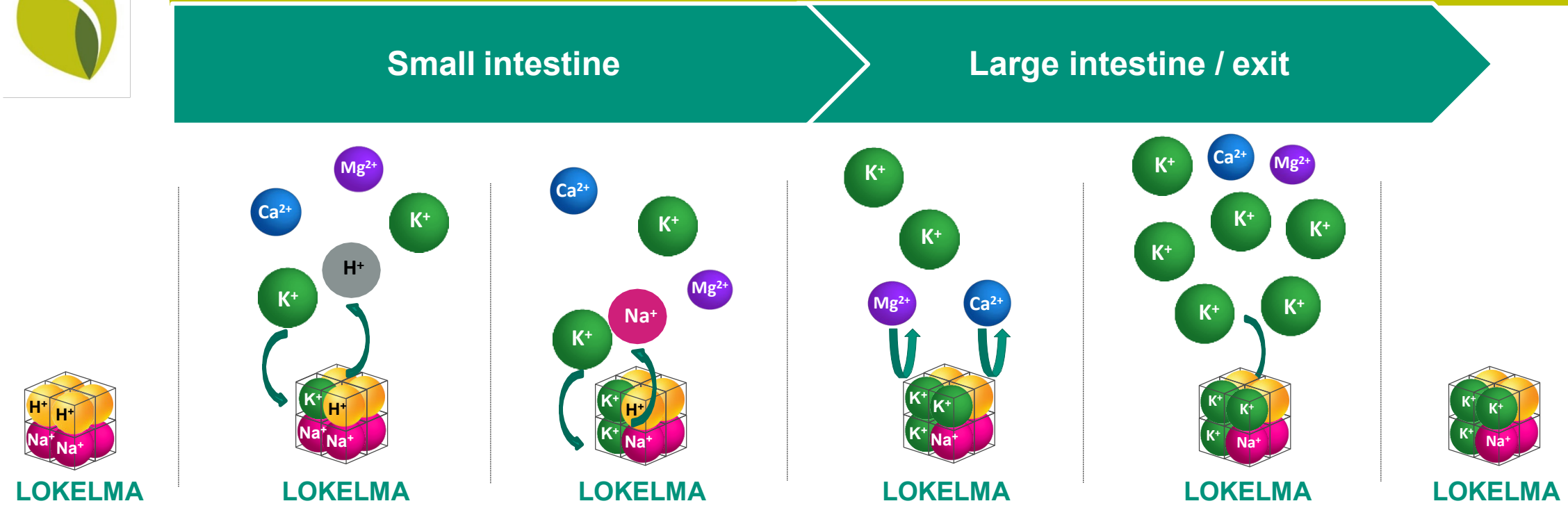


Average binding-site width: 3 Å

Key molecular characteristics:[1,3]

- Inorganic crystalline zirconium silicate compound
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed
- High affinity for K^+ [a]
- Exchanges Na^+ and H^+ for K^+

LOKELMA binds K^+ throughout the GI tract[a]

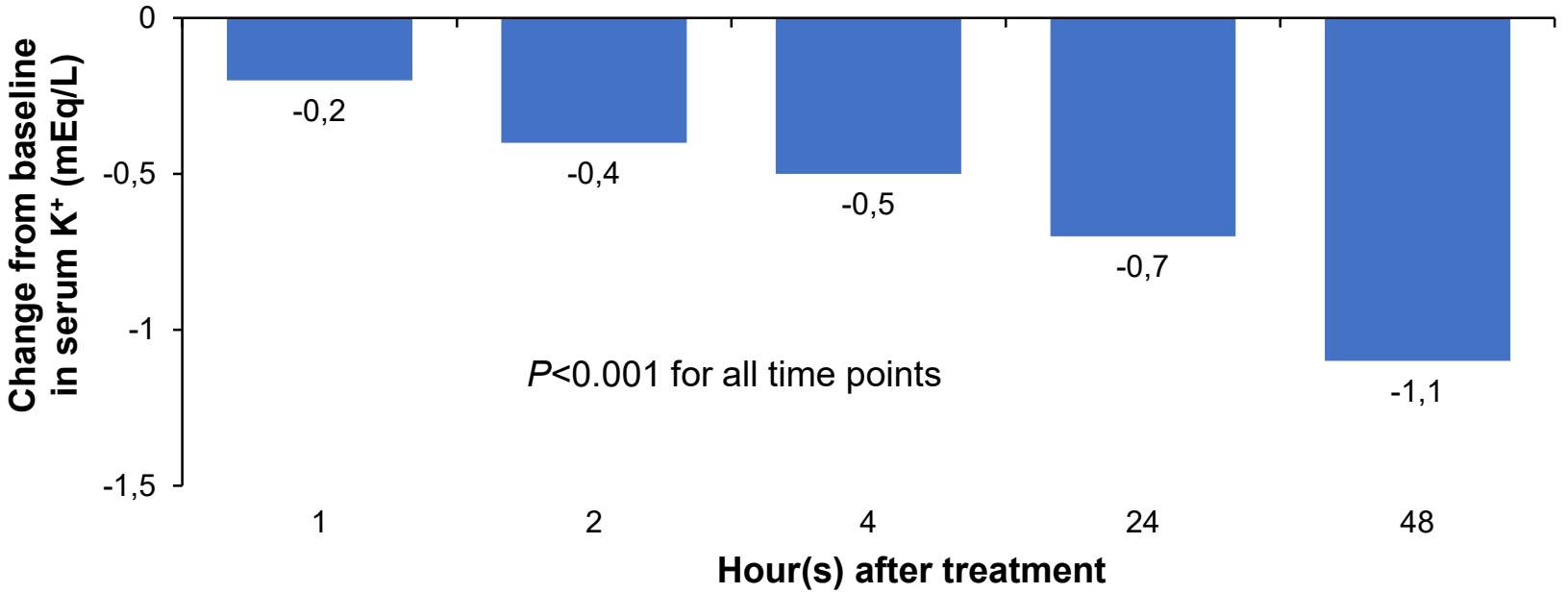


- Based on in vitro data, LOKELMA may begin working immediately in the small intestine to preferentially capture K^+
- K^+ is exchanged for sodium and hydrogen

LOKELMA: Onset of action at 1 hour

- **88% of patients achieved normokalemia** during the 48-hour correction phase
- The median time to serum K+ normalisation was 2.2 hours

Mean serum K^+ level with LOKELMA 10 g three times daily for 48 hours (N=258)[1a]

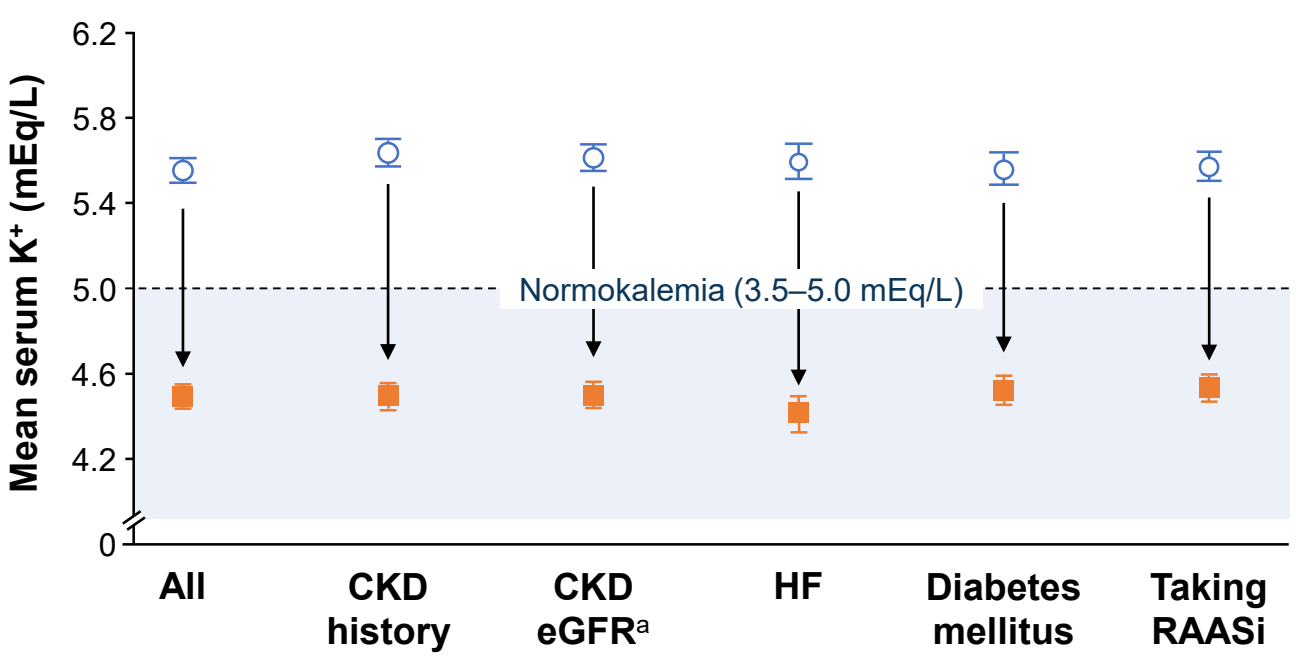


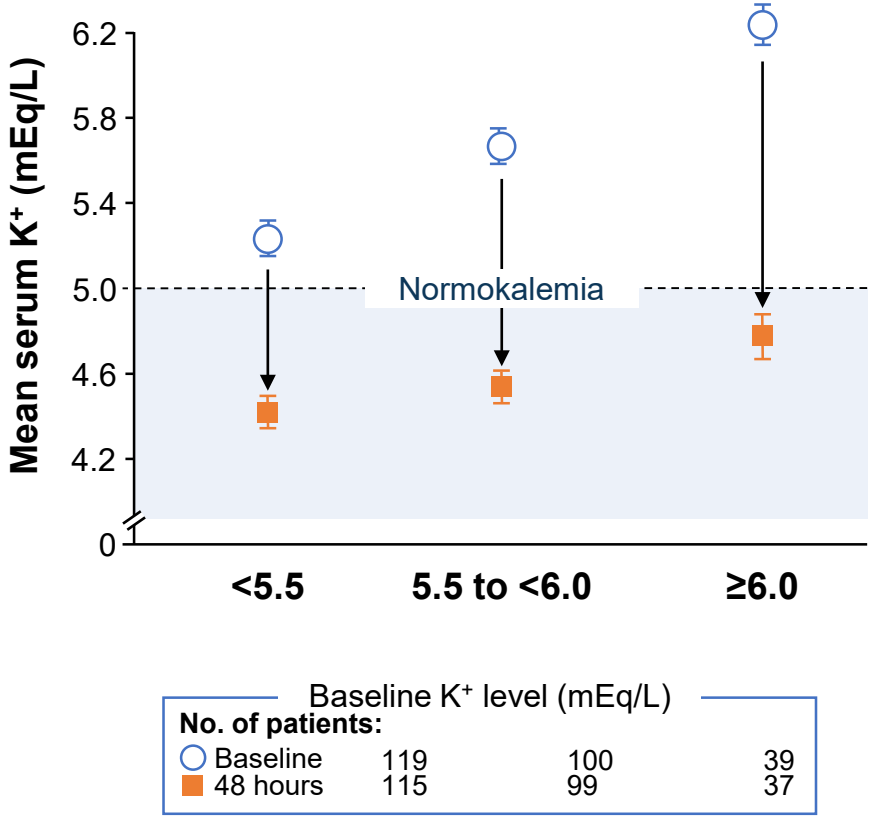
Open-label phase
mean baseline serum K^+:
5.6 mEq/L

Comorbidities/treatment at baseline: CKD (60%), HF (11%), T2DM (66%),[3b] and RAASi use (70%)[1]

LOKELMA reduced serum K^+ across patient types

Mean serum K^+ level at 0 and 48 hours across prespecified subgroups[2]

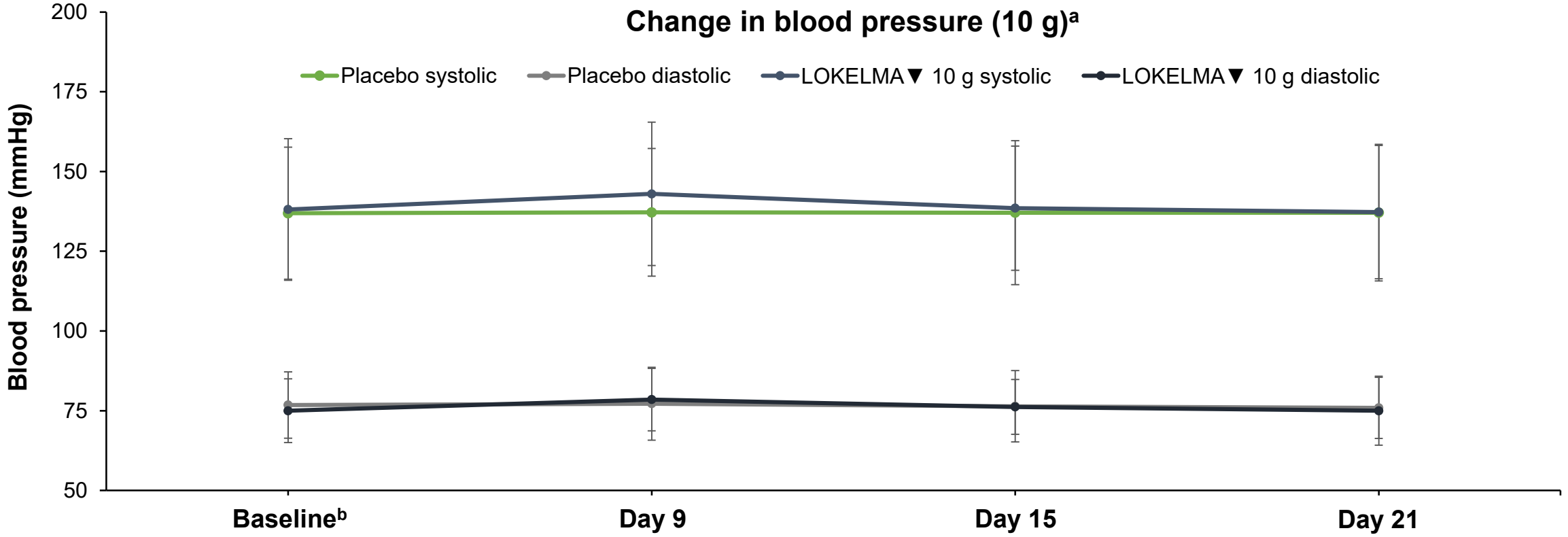




LOKELMA is considered high in sodium. This should be particularly taken into account for those on a low sodium diet.

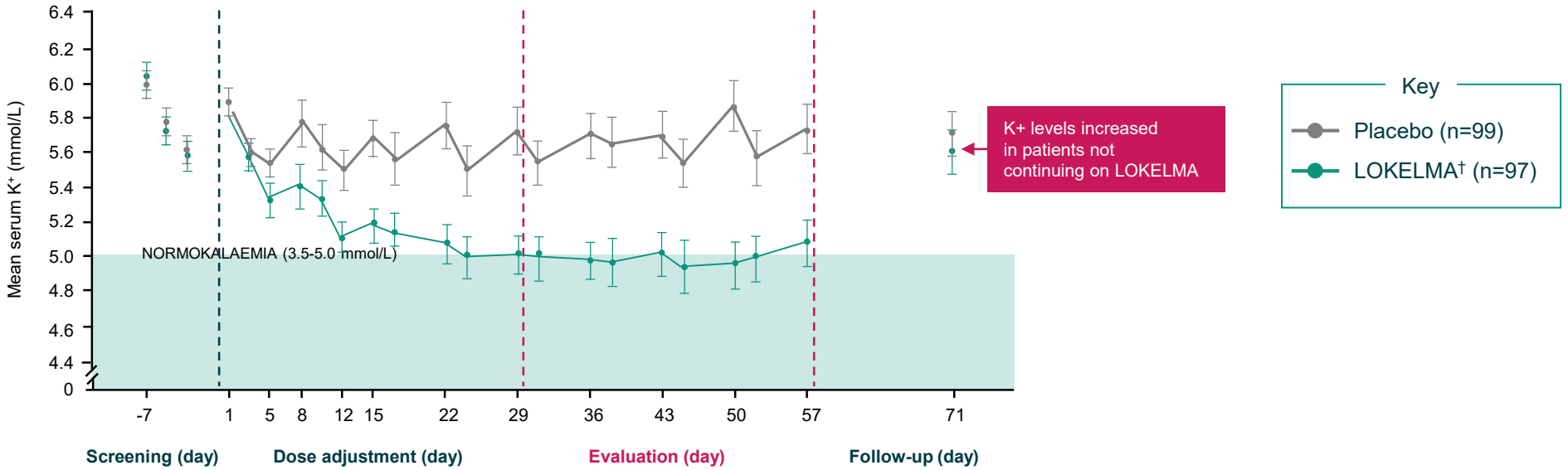
	LOKELMA 5 g[a]	LOKELMA 10 g	Bicarbonate 4.8 g[2]	SPS 60 g[3,b,c]
Estimated Na^+ content	400 mg	800 mg	1311 mg	6000 mg[d]
Salt equivalent:[4]	 ~1/6th tsp	 ~1/3rd tsp	 ~1/2 tsp	 ~2.5 tsp

No significant changes in SBP or DBP in the LOKELMA- and PBO-treated groups



LOKELMA REDUCED K^+ LEVELS AND SUSTAINED K^+ CONTROL IN HAEMODIALYSIS PATIENTS

Mean predialysis serum K^+ levels over time in patients on haemodialysis*[1]



- **LOKELMA is a powder for oral suspension, available in 5 g or 10 g doses[1]**
- **Mix LOKELMA with 45 mL of water for oral administration[1]**

- ✓ Tasteless and odourless[1,2]
- ✓ May be taken with many other medications and with or without food[a1]
- ✓ No special conditions for storage[1]

- **LOKELMA is a daily treatment option for hyperkalaemia[1]**
- **Recommended dosing of LOKELMA to achieve and sustain normokalaemia[1]**

FOR ADULT (NON-DIALYSIS) PATIENTS

Correction phase

3×  **/day[a,b]**

10 g
for 24 to 48 hours

until normokalemia is achieved[a,b]

Maintenance phase

1×  **/day[a,b]**

5 g
for up to 1 year

To establish minimum effective dose, LOKELMA may be titrated
- Up to **10 g once daily** or
- Down to **5 g once every other day**

No more than **10 g once daily** should be used for maintenance therapy

FOR HAEMODIALYSIS PATIENTS

RECOMMENDED STARTING DOSE

1×  **/non-dialysis days**

5 g

To establish normokalaemia, the dose may be titrated up or down weekly based on the predialysis serum K^+ after the long interdialytic interval

The dose could be adjusted at intervals of one week in increments of 5 g:
- **Up to 15 g once daily on non-dialysis days**

It is recommended to monitor serum K^+ weekly while the dose is adjusted. To maintain normokalaemia, it is recommended to monitor serum K^+ regularly (e.g., monthly or more frequently based on clinical judgement)

LOKELMA is indicated for the treatment of hyperkalemia in adults

MOA	Preferential K^+-binding in exchange for sodium and hydrogen[1]
Onset of action	As early as 1 hour after the first dose[2]
Efficacy data	Acute treatment and maintenance data
Drug–drug interactions	Should be administered at least 2 hours before or 2 hour after oral medications with clinically meaningful gastric pH-dependent bioavailability[2*]
Location of K^+-binding	Throughout GI tract[2]
Tolerability	Associated with:[2] • Hypokalemia • Edema-related events

- [a]Examples of medicines that should be administered before or after LOKELMA include azole antifungals (ketoconazole, itraconazole, and posaconazole); anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, and rilpivirine); tyrosine kinase inhibitors (erlotinib, dasatinib, and nilotinib)

Lokelma

- Selectievere binder, dus geen hypoMg

- Bindt ammonium GI waardoor serum HCO_3 stijgt en metabole acidose betert

Prijs ?

- **Publieksprijs incl. BTW (België)**

Lokelma 5 g, 30 zakjes

368,18 euro

Lokelma 10 g, 30 zakjes

502,50 euro

Veltassa

322,17 euro 30 zakjes (zowel 8,4 g als 16g)