Pasaules Nieru Diena

PASAULES NIERU DIENA 2024

Nieru veselību ikvienam

Nesteroīdie mineralokortikoīdu receptoru antagonisti (nsMRA) – renoprotektīvās īpašības.

Nefroloģijas rezidente Ieva Muižniece
Nefroloģijas centra vadītājs prof. Aivars Pētersons

Epidemiology of chronic kidney disease: an update 2022

kidney INTERNATIONAL supplements

ISN

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Extremely common

843,6 Million in 2017

Approximately **1** in 10

Increasing death rate

+41.5% 1990 to 2017

Large burden in low- and middle-income countries

Among the **top 10 causes** of death in Singapore, Greece, and Israel

Kovesdy, 2022

CONCLUSION

Chronic kidney disease (CKD) occurs frequently and has devastating consequences. This should prompt major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

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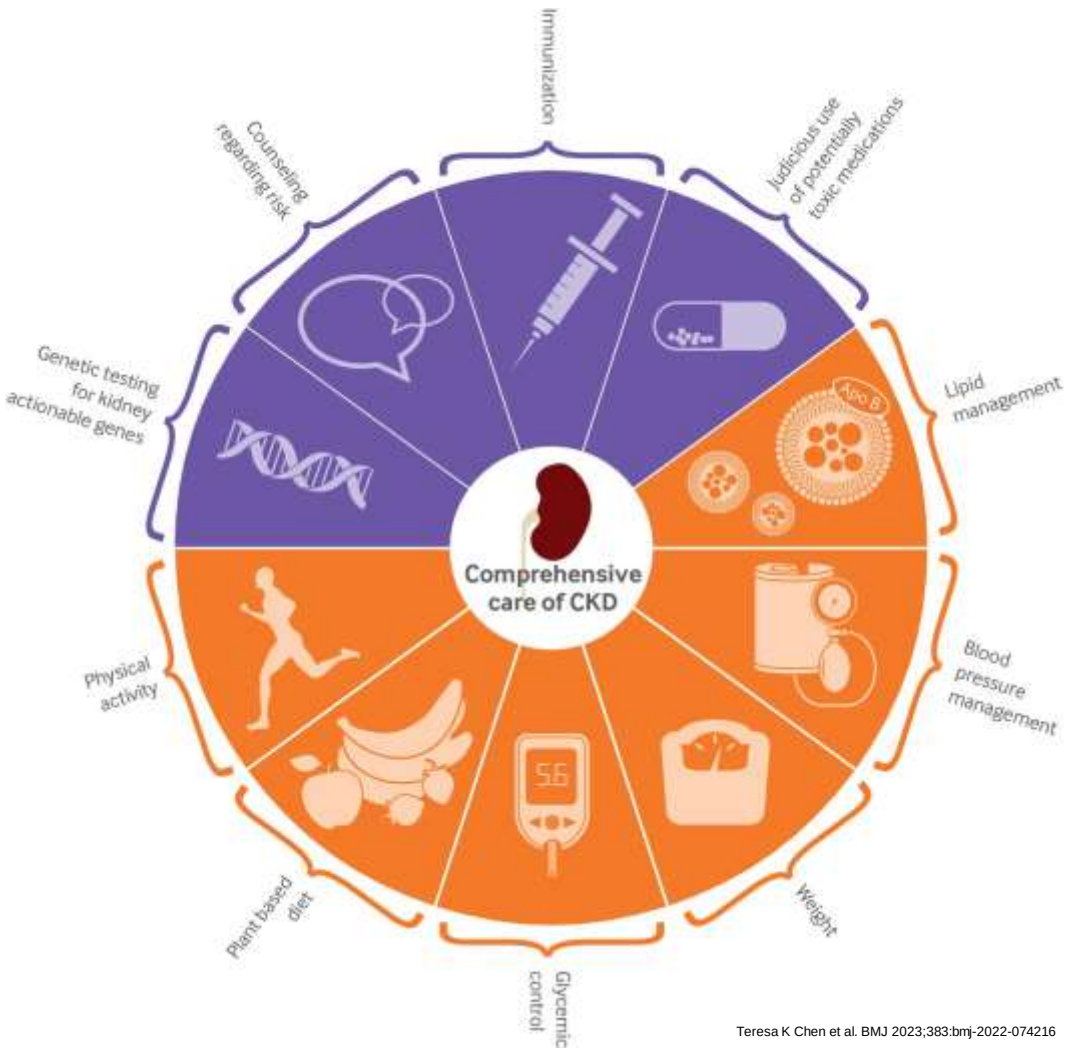
Kidney Int Suppl 2022 127-11DOI: (10.1016/j.kisu.2021.11.003)



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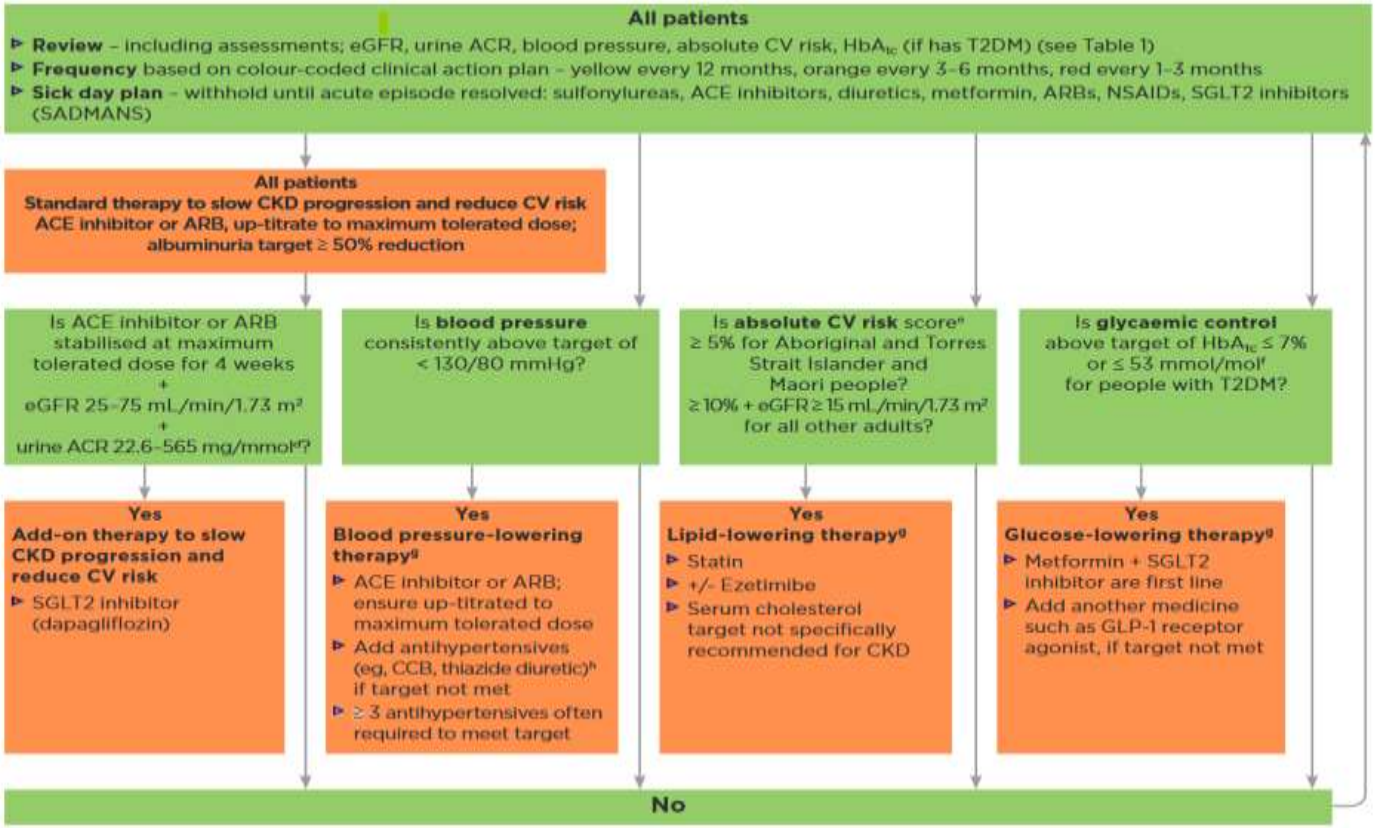
Teresa K Chen et al. BMJ 2023;383:bmj-2022-074216

FIGURE 2: Algorithm for medicines that slow CKD progression and reduce CV risk for people with CKD



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https://www.nps.org.au/assets/NPS/pdf/Medicines_for_CKD_a_practical-guide_PrintVersion.pdf

Aktualitāte

→ Lai arī esošās rekomendācijas mazina HNS progresiju, tās to neaptur un ir nepieciešami jauni medikamenti.

Mineralokortikoīdu (MR) receptoru ekspresija un funkcija

- MR receptori ir steroīdu receptori.

- Klasiski **MR receptori** tiek saistīti ar **nieru audiem**, kur tie atrodas nefrona distālajā kanāliņā, savācējvados. Tā ligandam – **aldosteronam** – iedarbojoties uz receptoriem, veicina **Na+ un ūdens reabsorbciju, K+ ekskrēciju;** ietekmē **arteriālo asinsspiedienu**.[1]

- Šobrīd ir zināms, ka MR receptori atrodas **arī sirdī (kardiomiocīti, fibroblasti, asinsvadi),** smadzenēs, plaušās, *colon*, ādā, skeleta muskuļos, siekalu un sviedru dziedzeros un taukos, **iekaisuma šūnas** (T-ly, MF, dendrītiskās š.).[2]

1. Claudia Grossmann, Brian Almeida-Prieto, Alexander Nolze, Diego Alvarez de la Rosa, «Structural and molecular determinants of mineralocorticoid receptor signalling», 22 November 2021
2. Biff F. Palmer, Deborah J. Clegg. «Extrarenal Effects of Aldosterone on Potassium Homeostasis», 2022 Jan 14., Kidney360

Ievadam

- Ne-klasiskie aldosterona efekti tiek pētīti jau kopš 1980 g.

- Gan HNS, gan sirds mazspējas gadījumā ↑aldosterona līmenis, kas ne tikai veicina Na+ retenci → hipertensija, bet spēlē lomu sirds un nieru fibrozes attīstībā[1]

[1] Thomas H. Hostetter, Hassan N. Ibrahim and ; Feature Editor «Aldosterone in Chronic Kidney and Cardiac Disease »JASN September 2003, 14 (9) 2395-2401; DOI: https://doi.org/10.1097/01.

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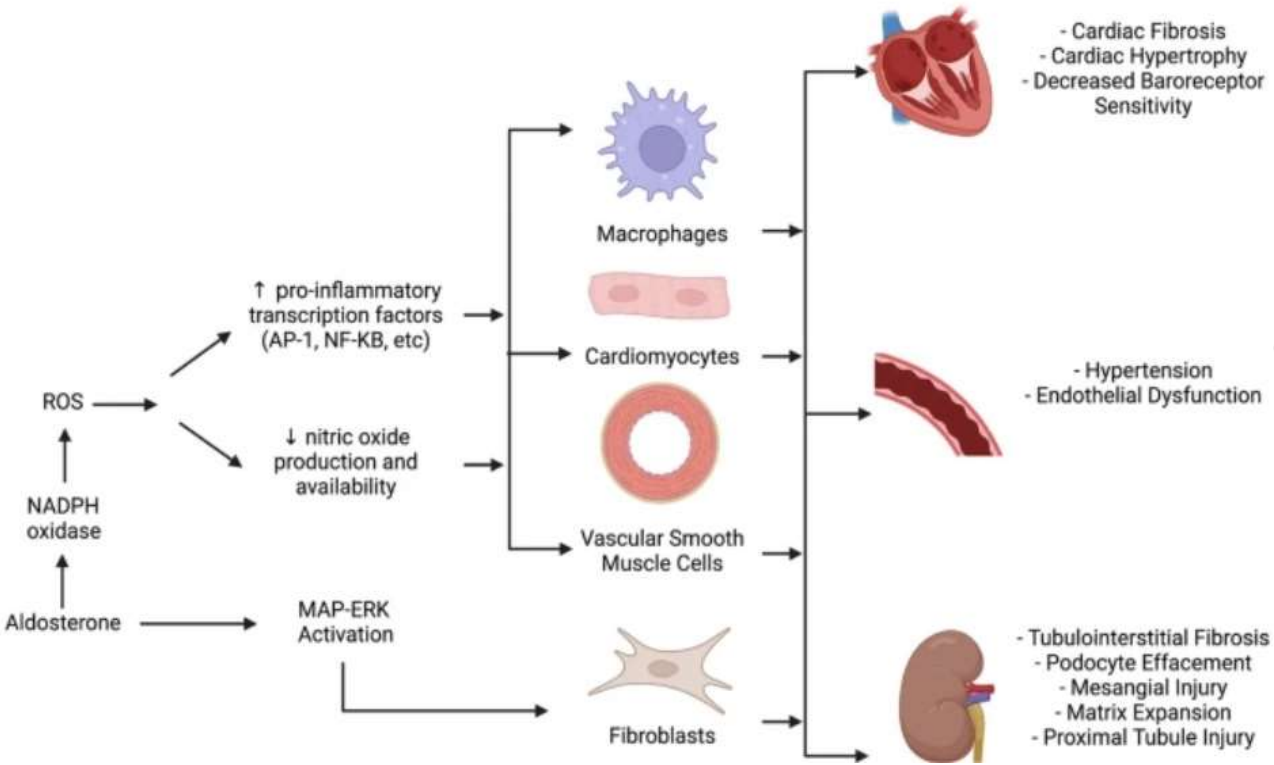
Pārmērīga MR aktivācijas efekti



https://link.springer.com/article/10.1007/s40119-022-00269-3

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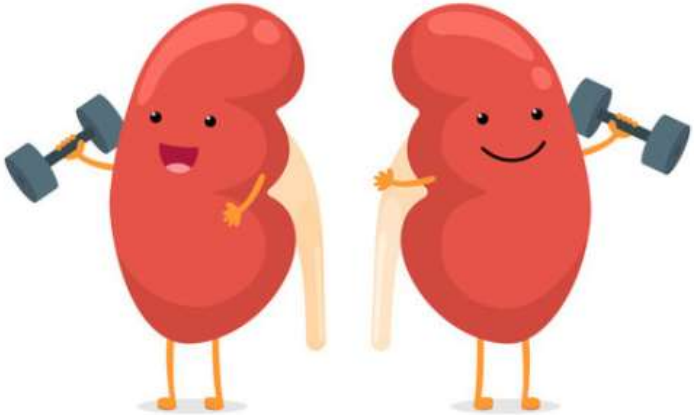
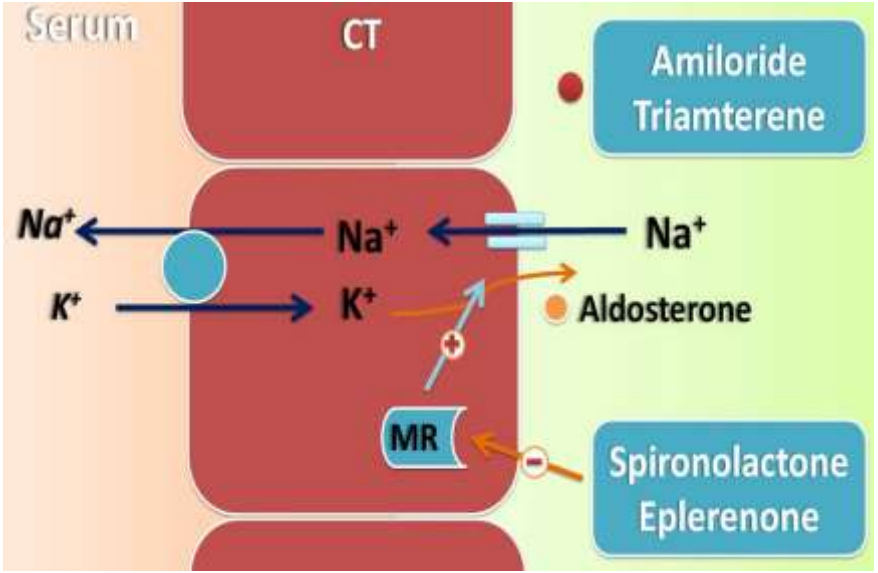


→ Novēršot pārmērīgu MR aktivāciju, mazinātu mērķorgānu bojājumu

Attēls: https://stock.adobe.com/search?k=kidney+cartoon

Mineralokortikoīdu receptoru antagonisti, vēsture

- Pēc tam, kad atklāts jauns **steroīdu-MRA *spironolacton*** (Kagawa et al, 1957), kas bloķē aldosteronu, tas tuvākajos gados tiek sākts plaši pielietots terapijā pacientiem ar primāru aldosteronismu, arteriālu hipertensiju un kā diurētiķis pie tūskām[1].
- Jau drīzumā ziņotas pirmās blaknes, kā ginekomastija, impotence un menstruāli traucējumi[1].
- Ņemot vērā augstāk minēto, otrās paaudzes **steroīdu-MRA *eplerenon* tikai sintezēts** (de Gasparo et al. 1987) – ar zemāku potenci, bet augstāku selektivitāti[1].



https://www.egpat.com/blog/potassium-sparing-diuretics

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1. Peter Kolkhof, Frederic Jaisser, So-Young Kim, Gerasimos Filippatos, Christina Nowack, Bertram Pitt Steroidal and Novel Non-steroidal Mineralocorticoid Receptor Antagonists in Heart Failure and Cardiorenal Diseases: Comparison at Bench and Bedside PMID: 27830348 DOI: 10.1007/164_2016_76

Ne-steroīdu MRA

- Jauna – trešā paaudze – MRA, kas veidota, domājot par drošību (hiperK, ANM, hipotensija) un mazinot blaknes (androgēnie efekti). Tādi, kā:
  - **Finerenon**
  - **Esaxerenone**
  - Apararenone
  - KBP-5074
  - PF-03882845
  - AZD9977

- Visi no tiem atrodas dažādās izvērtēšanas stadijās, sākot no preklīniskiem līdz III fāzes pētījumiem; daži pieejami tirgū – finerenon, esakserenon

Finerenon uzbūve un darbības mehānisms

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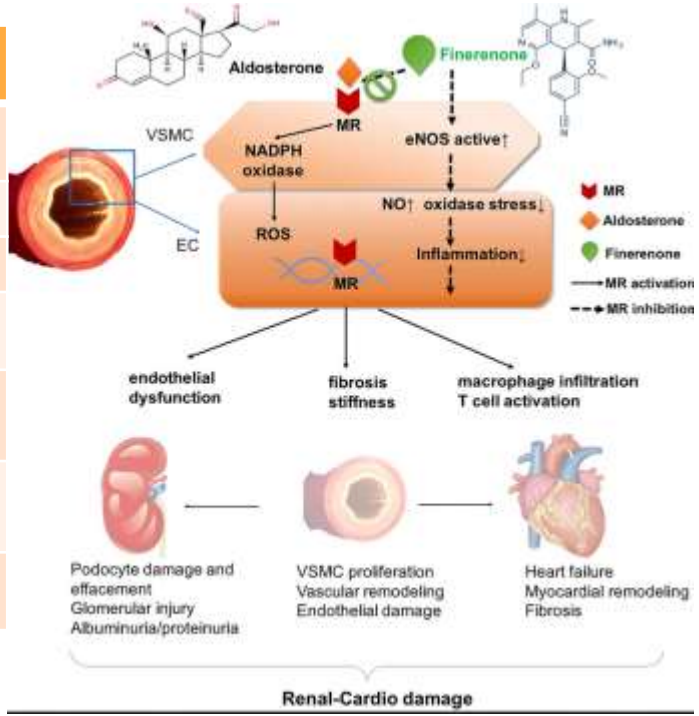
	Steroīdu MRA		Ne-steroīdu MRA
	Spironolakton	Eplerenon	Finerenon
Struktūra	Plakans	Plakans	Lielizmēra
MR-afinitāte	+++	+	+++
MR-selektivitāte	+	++	+++
Androgēni efekti	++	(+)	-
Pusizvades laiks	>20h	4-6h	2-3h
Ietekme uz TA	+++	++	+



Ulrich Kintscher, Frank Edelmann, «The non-steroidal mineralocorticoid receptor antagonist finerenone and heart failure with preserved ejection fraction», Cardiovascular Diabetology 2023

Nieru veselību ikvienam

Ruolin Lv, Lili Xu, Lin Che, Song Liu, Yangang Wang, Bingzi Dong «Cardiovascular-renal protective effect and molecular mechanism of finerenone in type 2 diabetic mellitus», Front. Endocrinol., 13 February 2023

Trial/phase	Primary end point	Patient involved	Intervention	Sample size/ duration	Results	Findings
FIDELIO-DKD III [16]	Time-to-event analysis: a composite of kidney failure, eGFR decrease ≥40% over 4 weeks, or death from renal causes	•Age ≥18 years •T2DM and CKD •UACR 30–300 mg/g, eGFR 25–60 mL/min/1.73 m^2 or UACR 300–5,000 mg/g eGFR 25–75 mL/min/1.73 m^2 •diabetic retinopathy •Maximal RAS inhibitor •Serum K^+ ≤4.8 mM	•Finerenone •eGFR 25–60 10 mg/day (1 month later up titrated to 20 mg based on K^+ and eGFR) •eGFR ≥60 mL/min/m^2 20 mg/day •Placebo	•5,734 people •2.6 years	•The primary composite outcome: finerenone versus placebo group: 504 (17.8%) and 600 (21.1%) patients (hazard ratio, 0.82; 95% CI: 0.73–0.93; $p = 0.001$) •Key secondary outcome (hospitalization for heart failure, death from cardiovascular causes, nonfatal MI, or nonfatal stroke) finerenone versus placebo group: 367 (13.0%) and 420 (14.8%) patients (hazard ratio: 0.86; 95% CI: 0.75–0.99; $p = 0.03$) •Hyperkalemia related adverse events: finerenone versus placebo group: 18.3% and 9.0% •Hyperkalemia leading to discontinuation of trial finerenone versus placebo group: 2.3% and 0.9% •Serum K^+ levels ≥5.5 and 6.0 mM: finerenone: 21.7%, 4.5%; placebo: 9.8%, 1.4%	•Finerenone improved cardiovascular and renal outcomes in patients with T2DM who had stage 3–4 CKD with moderately elevated albuminuria or stage 2–4 CKD with severely elevated albuminuria •Finerenone is associated with a higher risk of hyperkalemia than placebo discontinuation of the trial regimen due to hyperkalemia was infrequent
FIGARO-DKD III [17]	Time-to-event analysis: a composite of death from cardiovascular causes, hospitalization for heart failure, nonfatal stroke, or nonfatal MI	•Age ≥18 years •T2DM and CKD •UACR 30–300 mg/g, eGFR 25–90 mL/min/1.73 m^2 or UACR 300–5,000 mg/g eGFR ≥60 mL/min/1.73 m^2 •Maximal RAS inhibitor •Serum K^+ ≤4.8 mM	•Finerenone •eGFR 25–60 10 mg/day (1 month later up titrated to 20 mg based on K^+ and eGFR) •eGFR ≥60 mL/min/m^2 20 mg/day •Placebo	•7,437 people •3.4 years	•The primary composite outcome: finerenone versus placebo group: 458 (12.4%) and 519 (14.2%) patients (hazard ratio, 0.87; 95% CI: 0.76–0.98; $p = 0.03$) •Key secondary outcome (kidney failure, eGFR decrease ≥40%, death from renal causes) finerenone versus placebo group: 350 (9.5%) and 395 (10.8%) patients (hazard ratio,0.87; 95% CI: 0.76–1.01) •Hyperkalemia: finerenone versus placebo group: 10.8% and 5.3% •Hyperkalemia leading to discontinuation of trial: finerenone versus placebo group: 1.2% and 0.4%	•Finerenone improved cardiovascular outcomes in patients with T2DM who had stage 2–4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria •Finerenone is associated with a higher risk of hyperkalemia than placebo discontinuation of the trial regimen due to hyperkalemia was infrequent
ARTS-DN II [94]	Changes in UCRA	•CKD and T2DM •UACR 30 mg/g, eGFR >30 mL/min/1.73 m^2 •RAS inhibitor •Serum K^+ ≤4.8 mM	•Finerenone: 1.25, 2.5, 5 7.5, 10, 15, 20 mg/day •Placebo	•823 people •90 days	•Mean ratios of UACR at 90 days versus baseline 7.5 mg/day: 0.79 (90% CI, 0.68–0.91; $p = 0.004$) 10 mg/day: 0.76 (90% CI, 0.65–0.88; $p = 0.001$) 15 mg/day: 0.67 (90% CI, 0.58–0.77; $p < 0.001$) 20 mg/day: 0.62 (90% CI, 0.54–0.72; $p < 0.001$) •Hyperkalemia: 1.5 mg/day: 2.1%; 2.5 mg/day: 1.1% 5 mg/day: 1.0%; 7.5 mg/day: 2.1%; 10 mg/day: 0% 15 mg/day: 3.2%; 20 mg/day: 1.7%	•Finerenone exhibits dose-dependent UACR reduction at the four highest doses group versus placebo in patients with T2DM and CKD •Discontinuation of hyperkalemia occurred in 1.8% of patients receiving finerenone 7.5–20 mg/day, compared with no cases in the placebo group
ARTS-HF II [95]	Proportion of patients with >30% decline in NT-proBNP	•HFrEF, T2DM and/or CKD •eGFR >30 mL/min/1.73 m^2 in patients with T2DM or 30–60 mL/min/1.73 m^2 in those without T2DM •Therapy for HF for at least 3 months •Left ventricular ejection fraction of 40% or less	•Finerenone 2.5, 5, 7.5, 10, or 15 mg/day, titrated to 5, 10, 15, 20 or 20 mg/day, respectively, on day 30 •Eplerenone 25 mg every other day, increased to 25 mg/day on day 30, and to 50 mg/day on day 60	•1,066 people •90 days	•Proportion of patients with >30% decline in NT-proBNP: similar with finerenone versus eplerenone •Composite clinical endpoint of all-cause death, cardiovascular hospitalizations, or emergency presentation for worsening HF the incidence was lower in finerenone compared with eplerenone, except for finerenone 2.5→5 mg/day group •Hyperkalemia: finerenone: 3.6, 3.8, 3.7, 3.6, 6.3% (from low to high dose); eplerenone 4.7% •Serum K^+ level at day 90 was greater in eplerenone group (+0.262 mM) than in each of the finerenone dose groups (+0.119–0.202 mM)	•The 10 mg/day finerenone titrated to 20 mg/day after 30 days would provide the best balance of safety and efficacy for further investigation in larger clinical trials •Compared with eplerenone, finerenone decreased composite clinical endpoint •Serum K^+ is dose dependent in finerenone groups and similar to eplerenone group
ARTS II [96]	Change in serum potassium	•HFrEF and CKD •NYHA class II–III •left ventricular ejection fraction ≤40% •eGFR 60–90 (part A) or 30–60 mL/min/1.73 m^2 (B) •Therapy for HFrEF •Serum K^+ ≤4.8 mM	•Part A •finerenone: 2.5, 5.10 mg/day •placebo •Part B •finerenone: 2.5, 5.10 mg/day or 5 mg twice daily (bid) •open label spironolactone 25 or 50 mg/day •placebo	•Part A 65 people 28 days •Part B 393 people 28 days	•Part A: Finerenone of all doses is safe and tolerable •Part B •Finerenone 10 mg/day and 5 mg b.i.d. show greater increase in serum K^+ level from baseline $p = 0.0243$ and 0.0003, respectively •Serum K^+ level increase in finerenone is smaller than in spironolactone ($p < 0.0001$ for 2.5, 5, 10 mg/day and $p = 0.0107$ for 5 mg b.i.d.)	•For a significantly smaller increase in serum potassium, finerenone was equi-efficient in lowering albuminuria and cardiac biomarkers compared with spironolactone

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Galvenie Klīniskie Finerenon Klīniskie pētījumi

Wenyu Liu, Shengqiang Yu, «Nonsteroidal Mineralocorticoid Receptor Antagonist Eliciting Cardiorenal Protection Is a New Option for Patients with Chronic Kidney Disease», Kidney Dis 2023

FIDELIO-DKD – *The Finerenon In Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease*

- Trešās fāzes randomizēts, dubult-akls, *placebo*-kontrole*,* multicentru pētījums (norise 2015.-2018.g.).

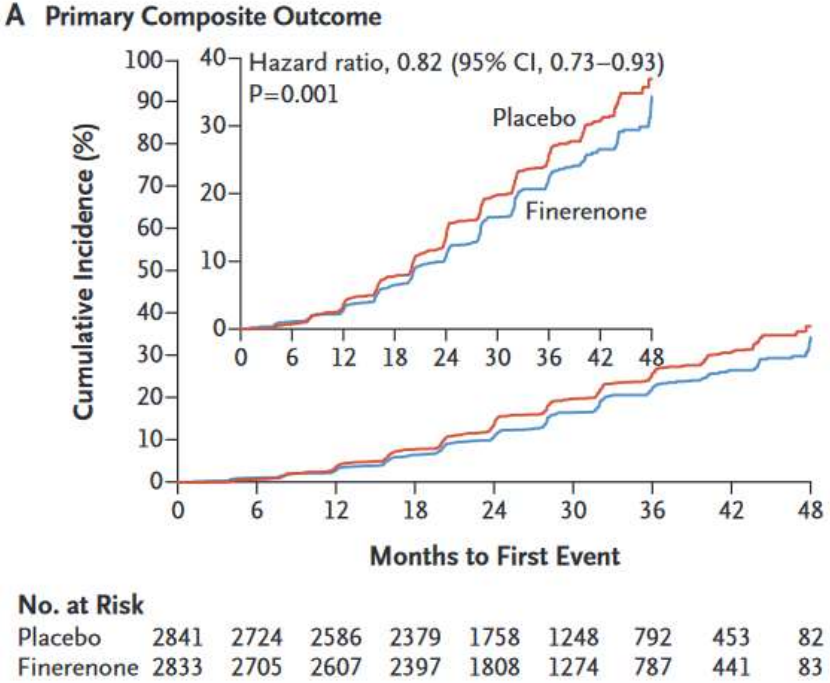
- Pētījuma hipotēze – vai finerenons palēlina HNS progresiju un samazina KVS saslimstību un mirstību pacientiem ar 2TCD un HNS.

- 13 911 pacienti skrīnēti, no kuriem randomizēti **5674 pacienti**

- **<u>Iekļauti pētījumā:</u>**
- ≥ 18 g.v. Ar 2TCD un saņem AKEi vai ARB maksimālā devā neradot nevēlamas blaknes.
  HNS tika definēta:
  - Persistējoša mikroalbuminuria (UACR 30-300 mg/dnn), eGFĀ ≥ 25 < 60 ml/min un diabētiska retinopātija
    VAI
    Persistējoša proteinūrija (UACR 300-5000 mg/dnn), eGFĀ ≥ 25 < 75 ml/min
  - Kālijs serumā skrīninga laikā ≤4,8 mmol/l.

Bakris GL, *et al.* N Engl J Med 2020; 383:2219-2229

FIDELIO-DKD. Primārie iznākumi.

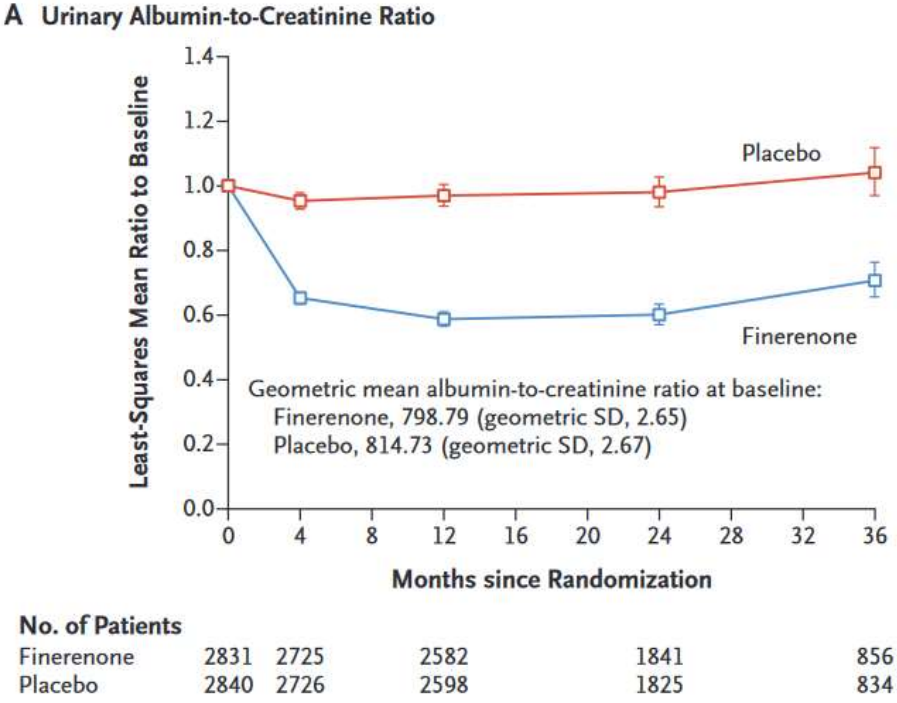


→Finerenon grupā terminmāla nieru mazspēja, noturīgs ≥40% eGFĀ, nāve nieru dēļ retāk nekā placebo 17,8% vs 21,1% (p=0.001)

Laiks līdz terminālai nieru mazspējai, noturīgs ≥40% eGFĀ, nāve nieru dēļ.

Bakris GL, *et al.* N Engl J Med 2020; 383:2219-2229

FIDELIO-DKD. Sekundārie iznākumi.



→ Finerenon mazina **ACR par 31% jau pēc 4 mēn**. no sākotnējā + tas saglabājas zemāks visu pētījuma laiku

Bakris GL, *et al.* N Engl J Med 2020; 383:2219-2229

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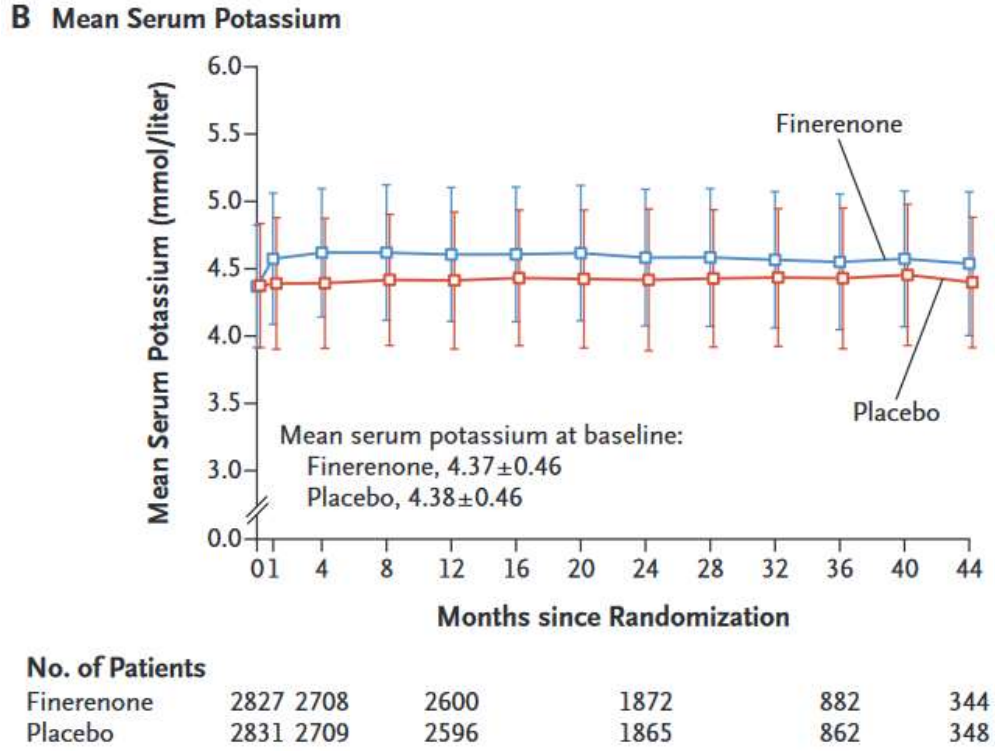
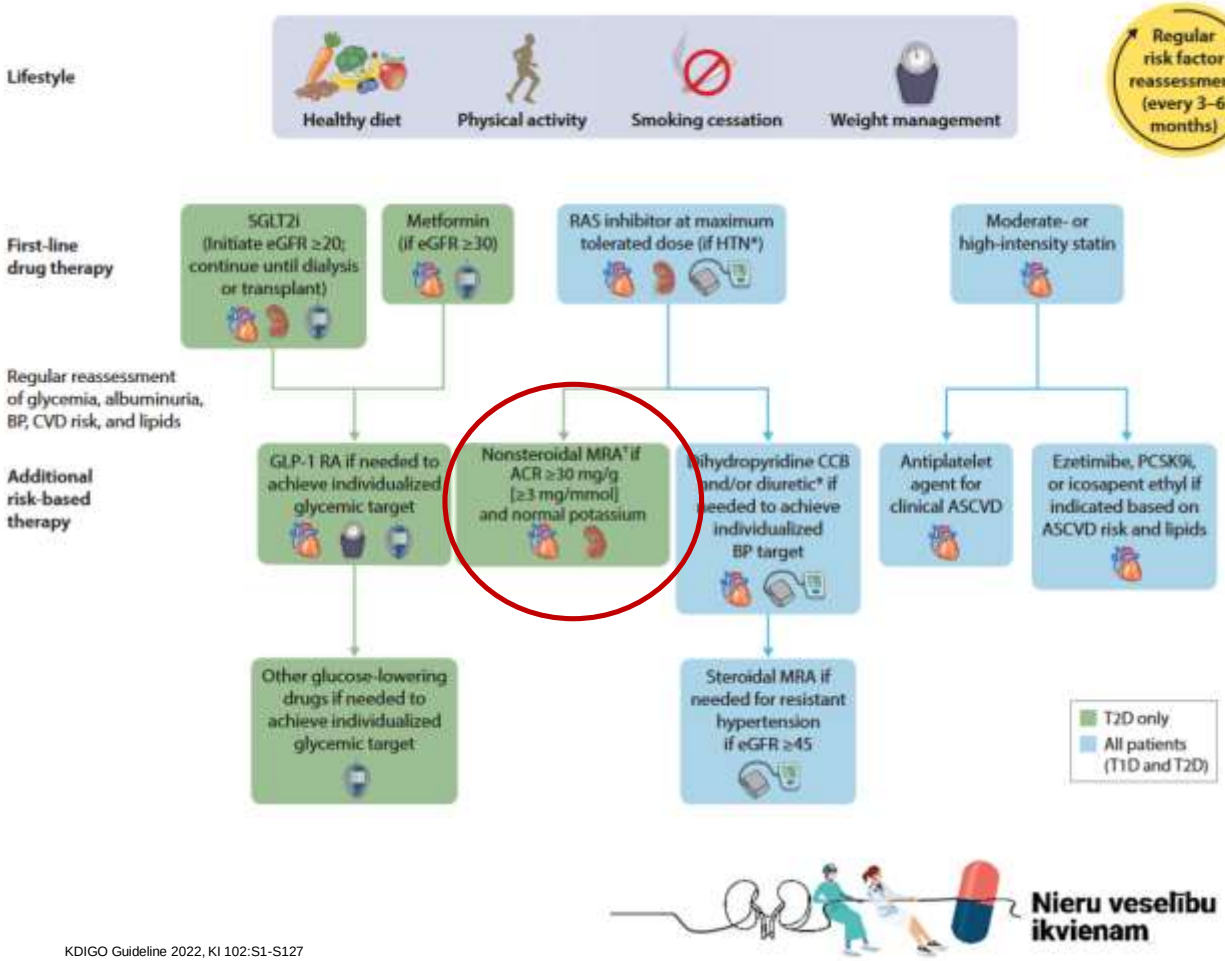
Finerenon un hiperkaliēmija



- → Hiperkalēmija bija biežāka finerenon grupā nekā placebo (18,3% vs 9%), lielākā vidējā starpība bija 0.23 mmol/l pēc 4 mēn.
- → Lai arī hiperkalēmija bija biežāka finerenon grupā, tās klīniskā nozīme mazāka.

Bakris GL, *et al.* N Engl J Med 2020; 383:2219-2229



KDIGO Guideline 2022, KI 102:S1-S127

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→ Rekomendē nsMRA pacientiem ar 2TCD un HNS, eGFĀ≥25 ml/min, normokalēmiju un albumināriju (≥30 mg/g vai ≥3 mg/mmol), kuri saņem maksimāli tolerējamas RASi devas

Nobeigumā

- Hroniskas nieru slimības incidence un prevalence pieaug; palielina mirstību.
- nsMRA ir relatīvi jauna medikamentu grupa ar daudzsološu pozitīvu ietekmi gan uz sirds-asinsvadu, gan nieru iznākumiem.
- Finerenon ir nefroprotektīva darbība – mazina nieru fibrozi – ievērojami aizkavē HNS progresiju, mazina proteinūriju.
- Finerenon iekļauts vadlīnijās pacientiem ar 2TCD un HNS kā *on-top* medikaments, lai sasniegtu maksimālus HNS aizkavēšanas mērķus, KVS notikumus.
- Nepieciešami plašāki pētījumi dažādās HNS grupās

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PALDIES PAR UZMANĪBU!

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