KLINIKA ZA NEFROLOGIJU

Novine u lečenju hipertenzije kod bubrežnih bolesnika

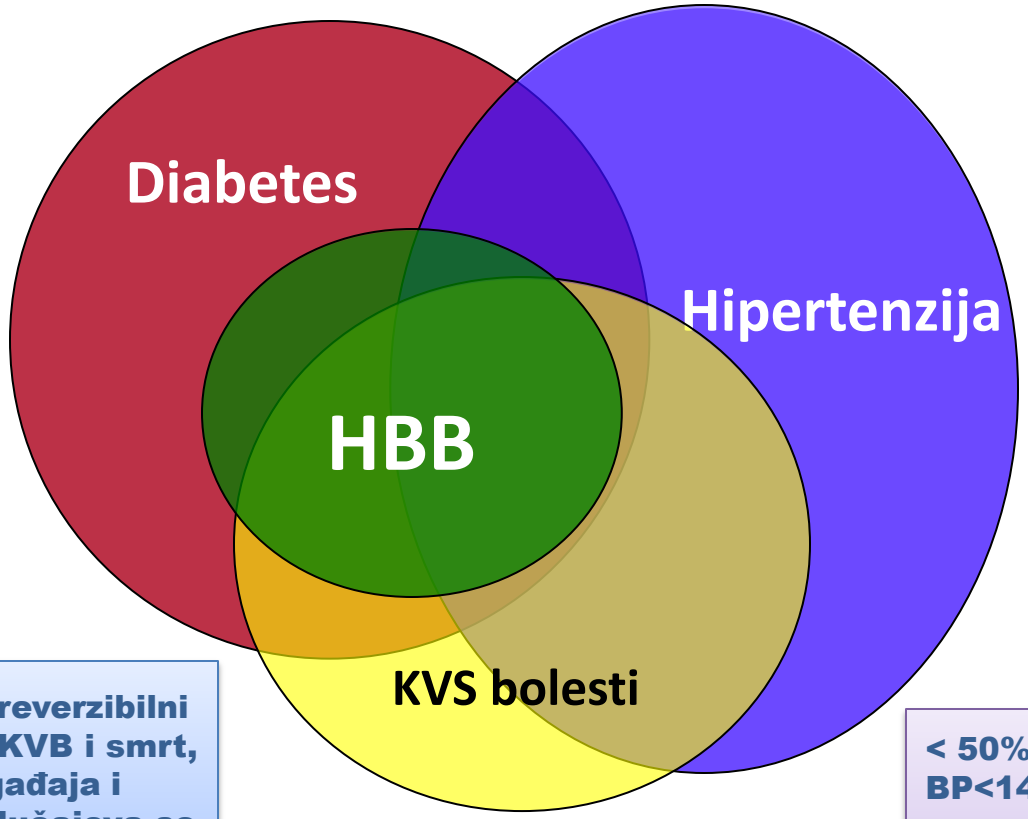
Radmila Veličković Radovanović

Klinika za nefrologiju UKC Niš ; Medicinski fakultet Niš; AMN SLD

XV Nedelja bolničke klinicke farmakologije 23-24 dec 2023

Sekcija za kliničku farmakologiju “dr Srdjan Djani Marković”, Srpsko lekarsko društvo

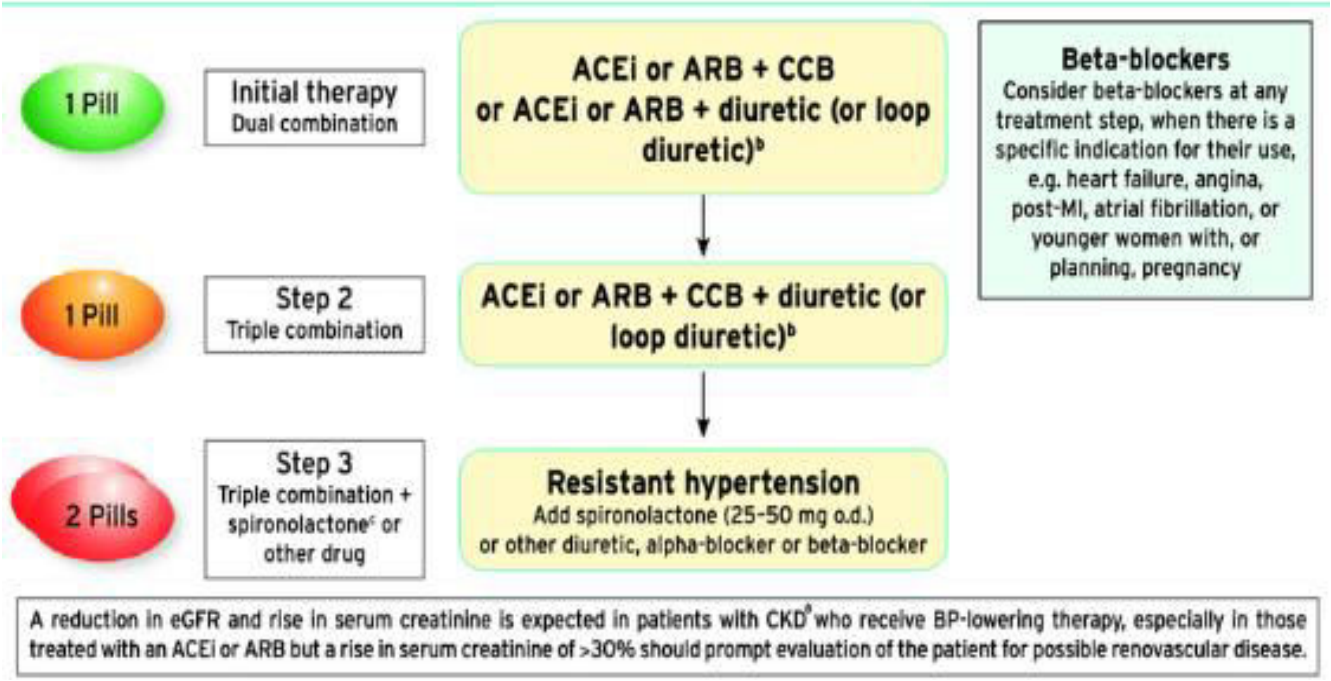
Značaj terapije hipertenzije



-HTA najvažniji reverzibilni faktor rizika za KVB i smrt,
> 50% KVB događaja i
- 17% smrtnih slučajeva se pripisuju hipertenziji

< 50% hipertoničara ima BP<140/90mmHg
--samo 35% žena i 23% muškaraca u Americi ima regulisan HTA
-10% rezistentna HTA

Campbell N. et all. *The Lancet Regional Health America* 2022

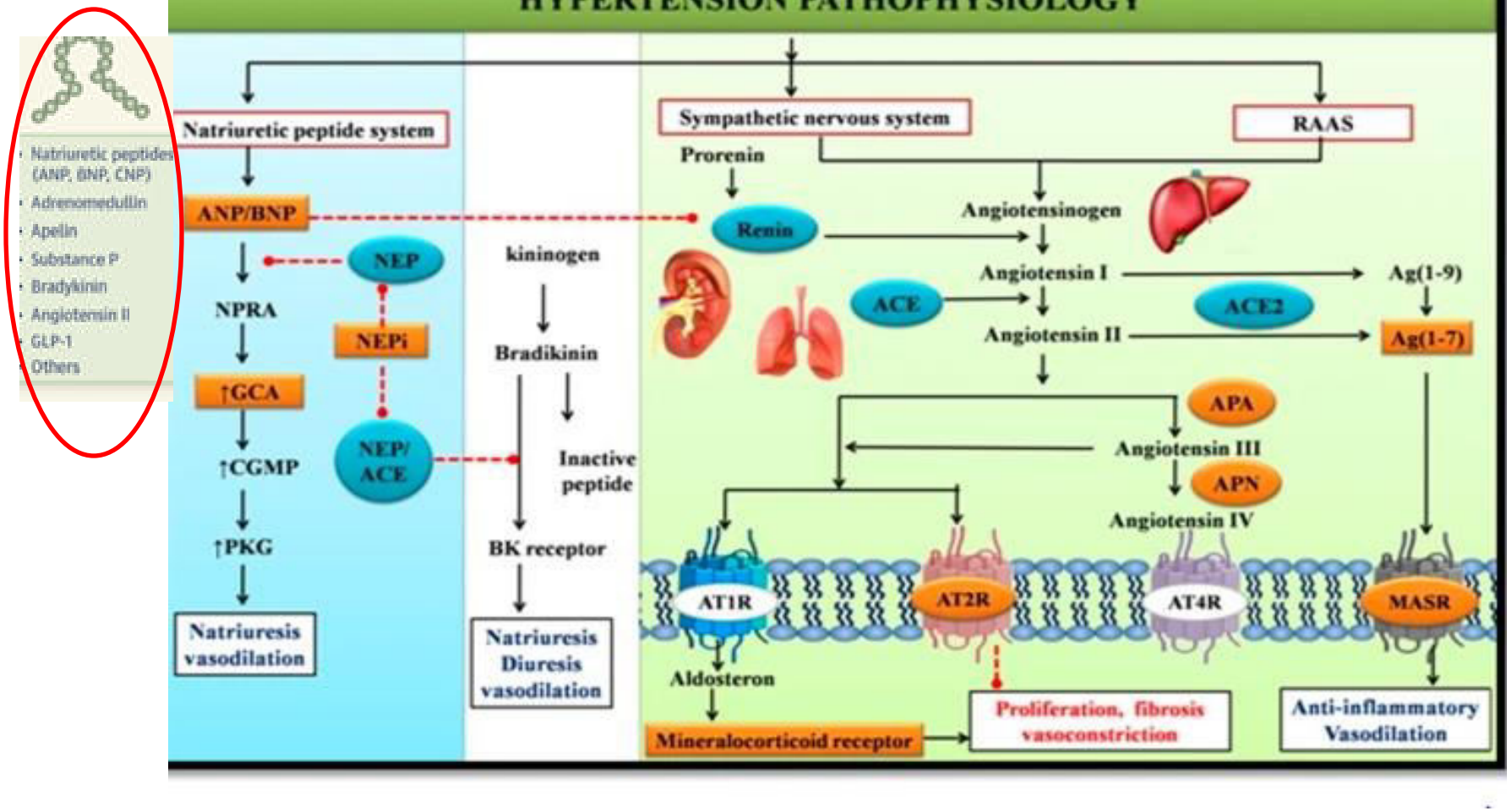


Nove kombinacije antihipertenzivnih lekova

-kandesartan cilexetil/nifedipin
-fimasartan/amlodipin
-olmesartan/ amlodipin
-valsartan/ amlodipin/hidrohlorotiazid
-valsartan/amlodipin/rosuvastatin
-valsartan/amlodipin/atorvastatin
-amlodipin/ telmisartan/hlorhalidon

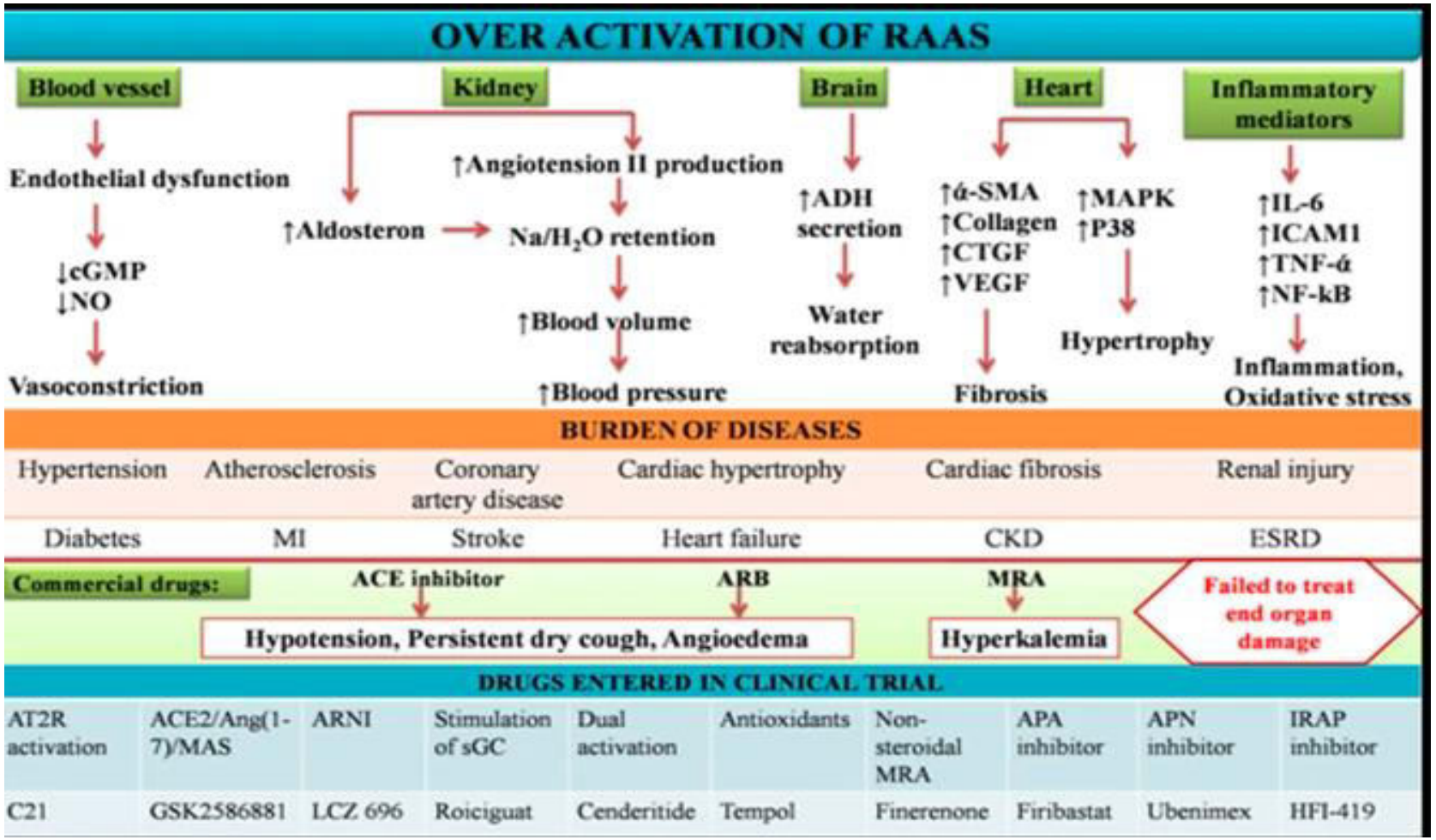
Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021.

Patofiziologija arterijske hipertenzije



T Ghatage. *Hypertens Res* 2021

Previše aktivirani RAAS utiče na različite ćelijske procese u vitalnim organima, što dovodi do komplikacija hipertenzije



T Ghatage. *Hypertens Res* 2021

Novi lekovi u lečenju hipertenzije

Farmakološka grupa	Lek	Način delovanja	Status
Aminopeptidaza A Inhibitori (APA inhibitor)	**Firibistat**	APA inhibitor – centralno antihipertenzivno dejstvo (blokada RAS i vasopresina)- vazodilatatorno i diuretsko dejstvo	registrovan
Nesterioidni. selektivni MRA	**Finerenon** Esaxerenon ocedurenon	Antagonisti aldosterona diuretsko, antifibrozno dejstvo, nefroprotekcija, kardioprotekcija	registrovani
Inhibitori vazopeptidaze	**Sakubitril/valsartan** omapatrilat	Inhibicija neprilizina NEP/ACEi	registrovani
Endotelin 1 antagonisti	Macitentan Darusentan **aprocitentan**	ETAr/ETBr antagonist Selektivni ETr antagonist ETAr/ETBr antagonist periferni vazodilatator	registrovani
SGLT2 inhibitori	**Dapagliflozin** **Empagliflozin** Canagliflozin	inhibitor Na-.glukoza kotransportera osmotska diureza, natriureza Kardio-nefroprotekcija	registrovani

T Ghatage. *Hypertens Res* 2021

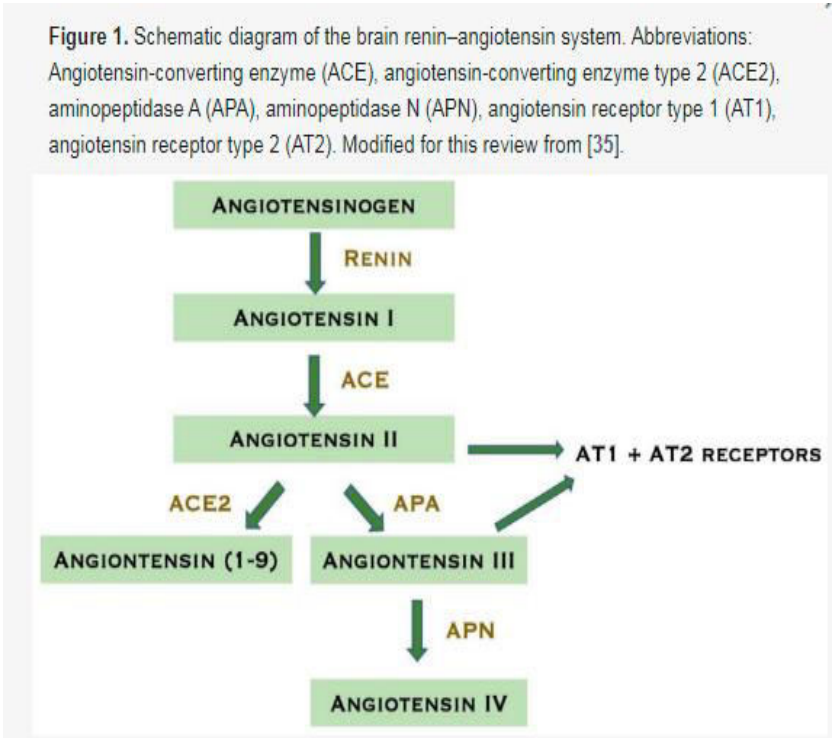
Firibastat

- Firibastat je prvi u novoj klasi antihipertenzivnih lekova

– inhibitor aminopeptidaze A, *inhibira konverziju ANG II u ANG III u mozgu*

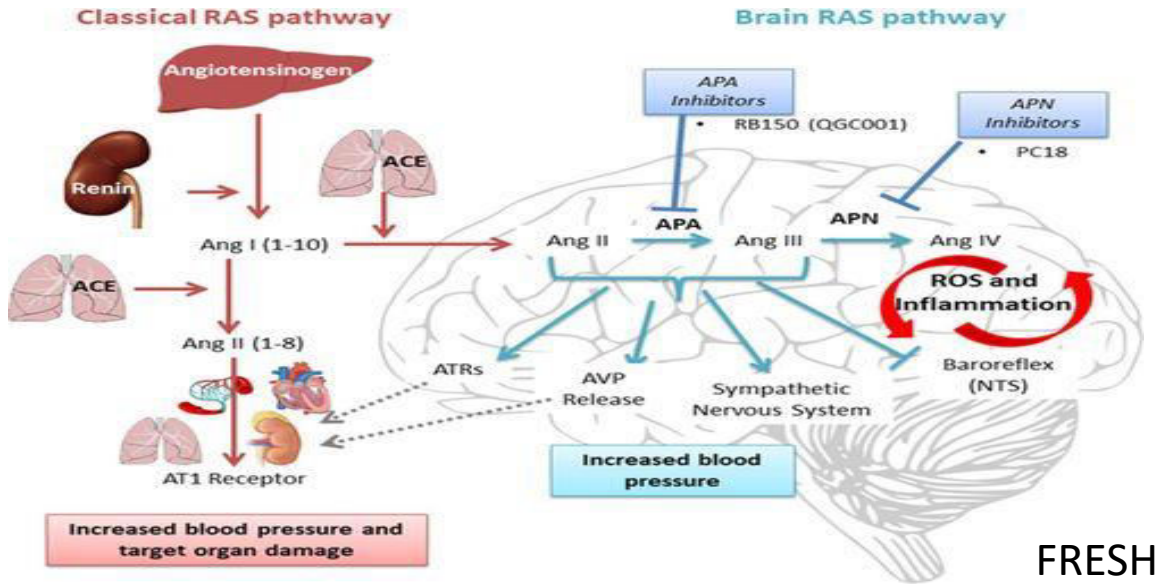
- Registrovan 2019 (FDA)
- Signifikantno redukuje krvni pritisak (prosečno 9,5/4,2mmHg)

Firibastat prolek - pri prelasku krvno-moždane barijere cepa se na dva aktivna molekula EC33. EC33 - aktivni molekul , inhibira aminopeptidazu A, koja pretvara angiotenzin II u angiotenzin III. Angiotenzin III ima tri centralna hipertenzivna mehanizma.



Hansen, E. *Int. J. Mol. Sci.* 2022

Farmakološka dejstva firibastata



FRESH study 2022

NCT02322450 [48,49]	34 participants Phase IIa	AEs: 14 patients with 16 reversible adverse events of mild intensity. One case of withdrawal due to rash, vestibular disorder and arthralgia each. For 8 weeks, the effect of twice daily administration of oral firibastat among hypertensive overweight/obese people of different races has been investigated. Firibastat reduced office SBP by 9.5 mmHg and office DPB by 4.2 mmHg. Significant de- creases in BP were found in all subgroups. Among obese people, SBP decreased by 10.2 mmHg, 10.5 mmHg among blacks and 8.9 mmHg among non-blacks. AEs: 14.1% related treatment-emergent AEs (headache, skin reactions most common), one serious related AE (erythema multiforme) resulted in discontinuation	Firibastat is effective in lowering the BP, also in the high-risk groups. Firibastat is a possible alternative when it comes to difficult-to-treat patients or resistant hypertension where monotherapy with standard treatment options is no longer effective.
Novel Evaluation with QGC001 in Hypertensive Overweight Patients of Multiple Ethnic Origins (NEW-HOPE) NCT03198793 [44,50]	Open-Label Dose-TitratingSafety and Efficacy Study 256 participants Phase IIb		
Firibastat in Treatment-resistant Hypertension (FRESH) NCT04277884 [51]	Double-blind, Placebo-controlled, Efficacy and Safety Study 502 participants Phase 3	This study is still recruiting and has not been completed yet. For that reason, the results are missing from this study. The objective of this study is to investigate the effect of firibastat in people ≥18 years with uncontrolled primary hypertension. Administrations of firibastat 500 mg orally twice daily over 12 weeks are compared with placebo. This study is still recruiting and has not been completed yet.	No conclusions can be drawn since the study is not completed.
Randomized Study of Extended Treatment with Firibastat in Treatment-Resistant Hypertension. (REFRESH) NCT04857840 [52]	Double-blind, Placebo-controlled and Open-label Efficacy and Long-term Safety Study 750 participants Phase 3	The objective is to investigate the efficacy and safety of 1000 mg (2 × 500 mg p.o.) firibastat in addition to their chronic antihypertensive therapies for up to 48 weeks in patients with difficult-to-treat/treatment-resistant HTN	No results have been reported yet

Hansen E, Grimm D, Wehland M. Current Knowledge about the New Drug Firibastat in Arterial Hypertension. Int J Mol Sci. 2022

MRA antagonisti

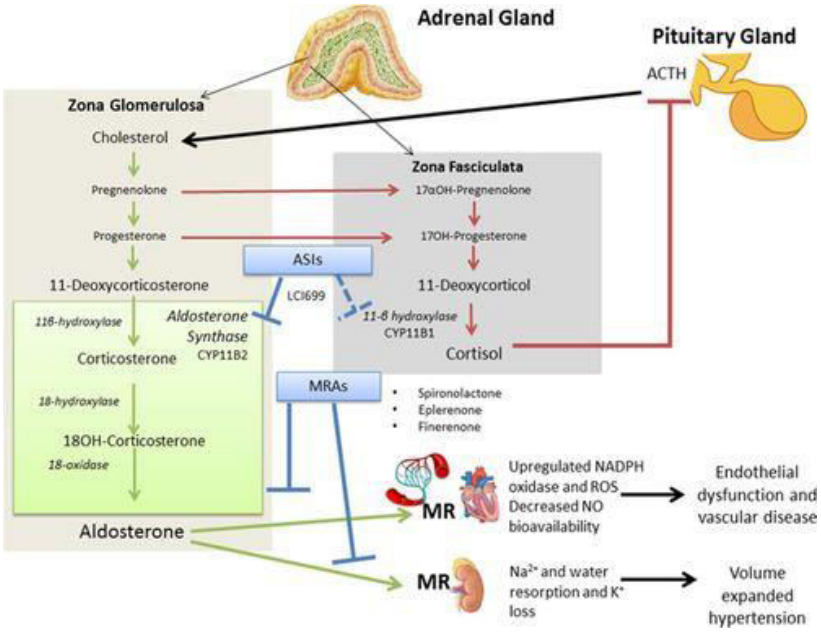
-spironolakton, eplerenon (selektivni MRA)

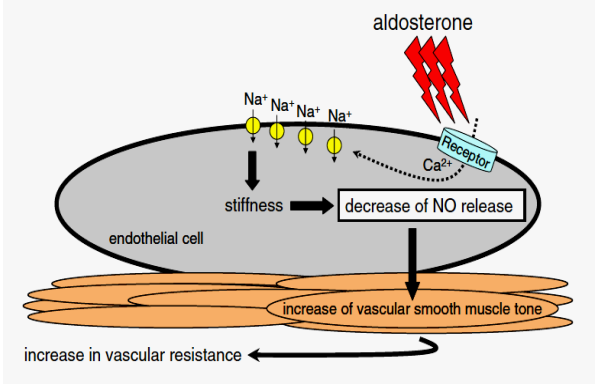
-nesteroidni MRA/ finerenon,esaxerenon, aparenon

Terapija rezistentne hipertenzije ↓ **mortalitet i nastanak fibroze**

Hronični KRS i RKS **Kontrola bubrežne funkcije i K+ !!!**

Kardio i nefroprotektvno dejstvo





Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?

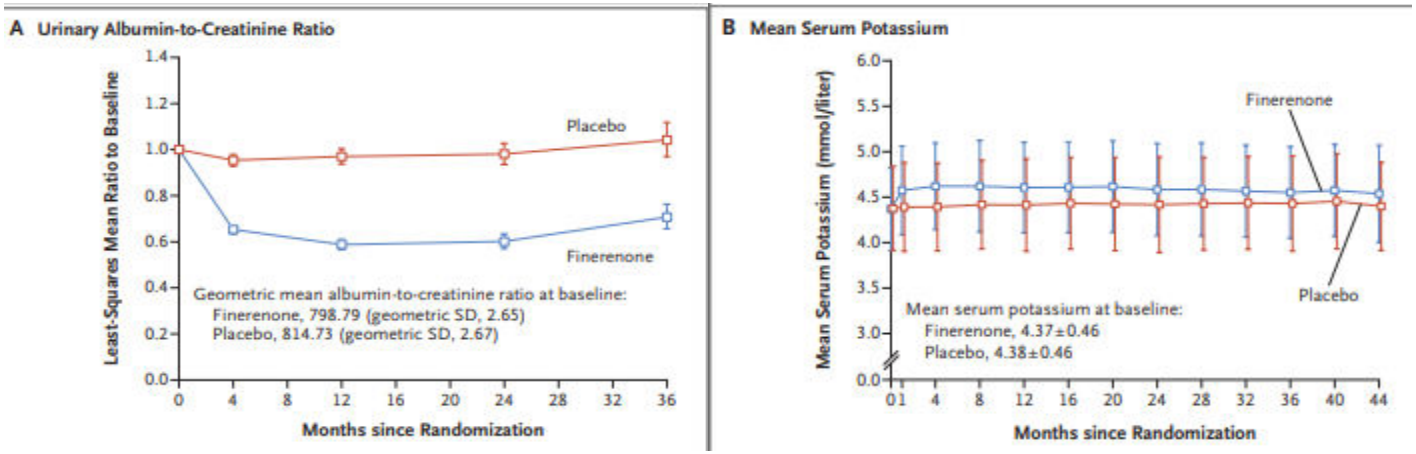
Andrew S Bomback*, Abhijit V Kshirsagar and Philip J Klemmer

Nature Clin.Practice Nephrol. (2009)

Finerenon (Kerendia) - **novi nesteroidni, antagonist mineralokortikoidnih receptora**

- veća selektivnost od spironolaktona
- jači afinitet vezivanja od eplerenona
- *Smanjuje rizik od bubrežne slabosti,usporava progresiju HBI, KVS smrti, nefatalnog srčanog udara i hospitalizacije od srčane insuficijencije kod odraslih sa HBB i dijabetesa tip 2*

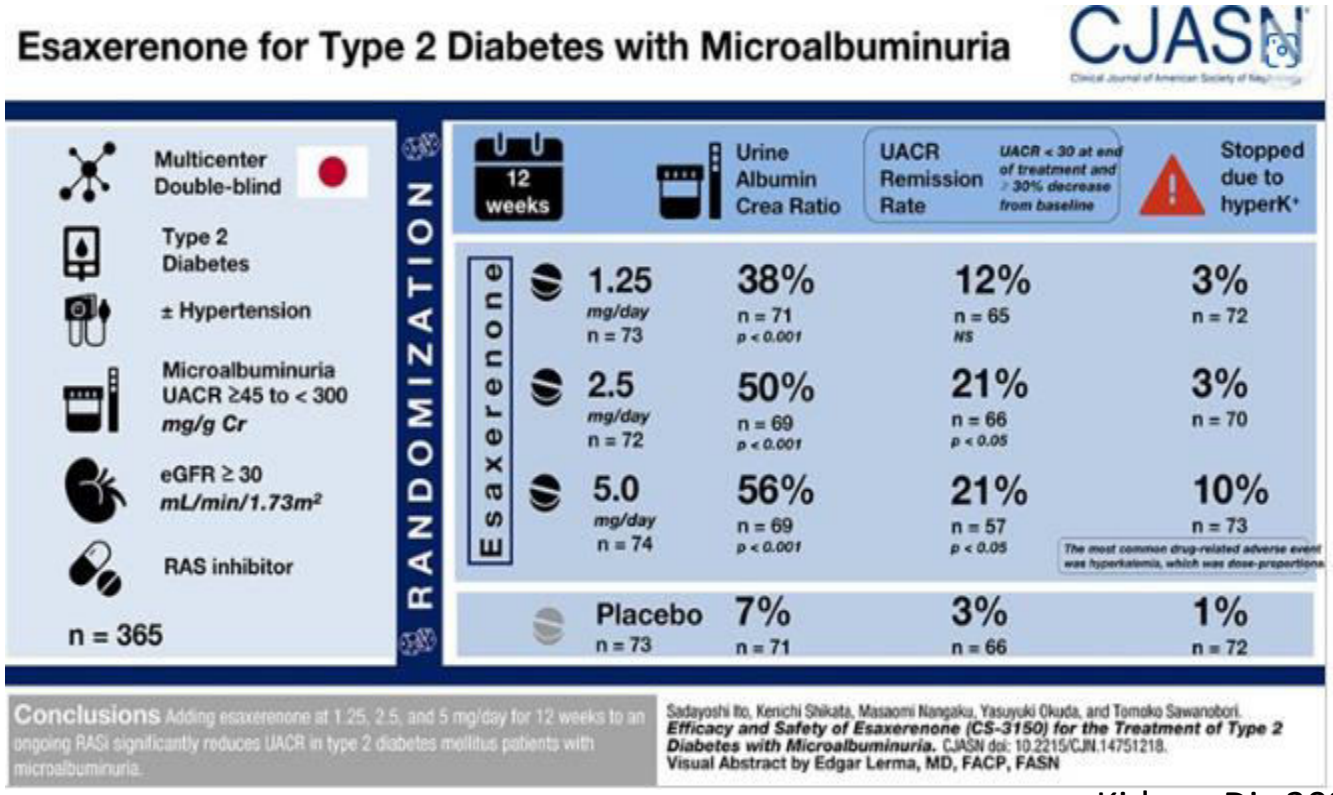
- ARTS study -Finerenone 5–10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing serum levels of BNP and pro-BNP, albuminuria, with lower incidence of hyperkalaemia (5.3% vs. 12.7%) in patients with systolic HF and CKD.
- FIDELIO-DKD ClinicalTrials In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo
- FIGARO-DKD trial, 2022



N Engl J Med 2020

Esaxerenon (MINNEBRO™)

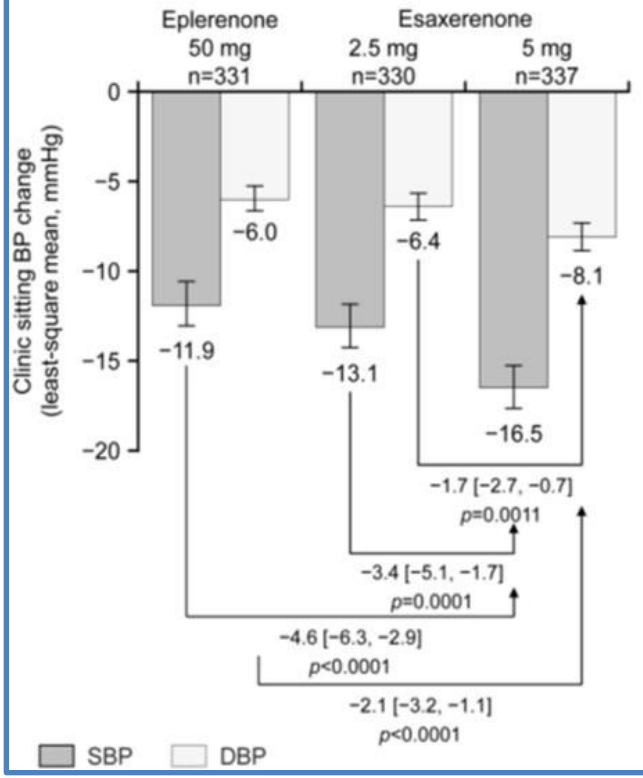
- Esaxerenone je efikasan i dobro podnošljiv antihipertenziv, smanjuje albuminuriju kod pacijenata sa T2MD i CKD.
- Potencijalno nova, perspektivna farmakoterapija koja modifikuje bolesti



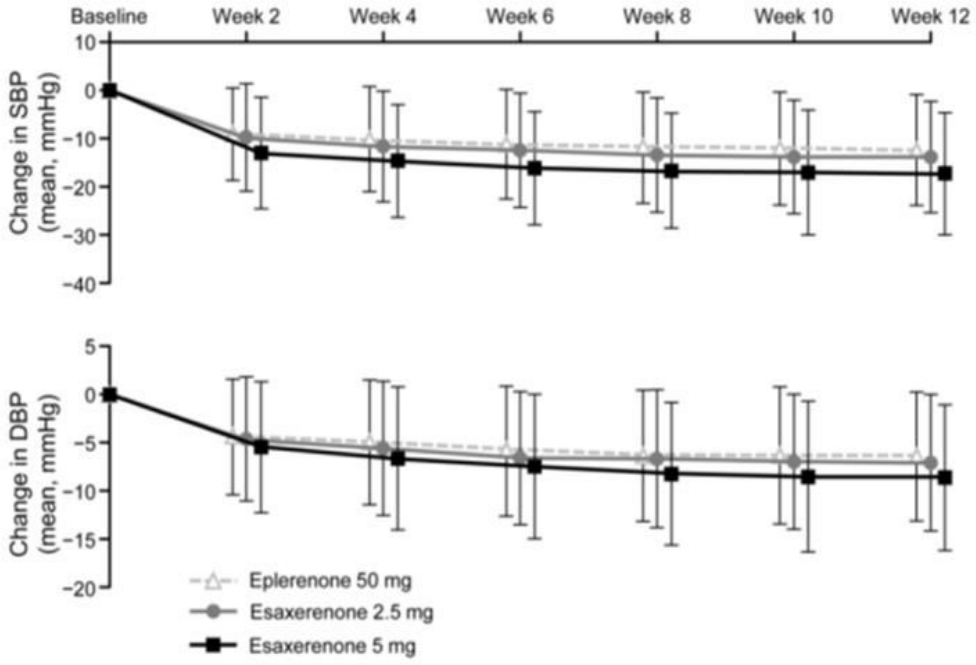
Wenyu Liu. Kidney Dis 2023;9:12–25

Mean change in clinic sitting BP in the full analysis set

End of treatment



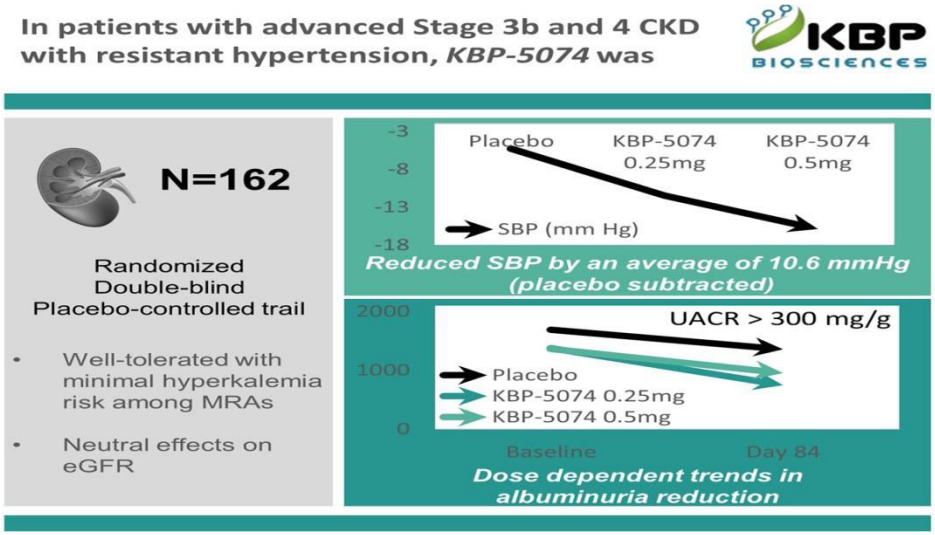
Mean change from baseline



Sadayoshi Ito. Hypertension. Double-Blind Randomized Phase 3 Study Comparing Esaxerenone (CS-3150) and Eplerenone in Patients With Essential Hypertension (ESAX-HTN Study),

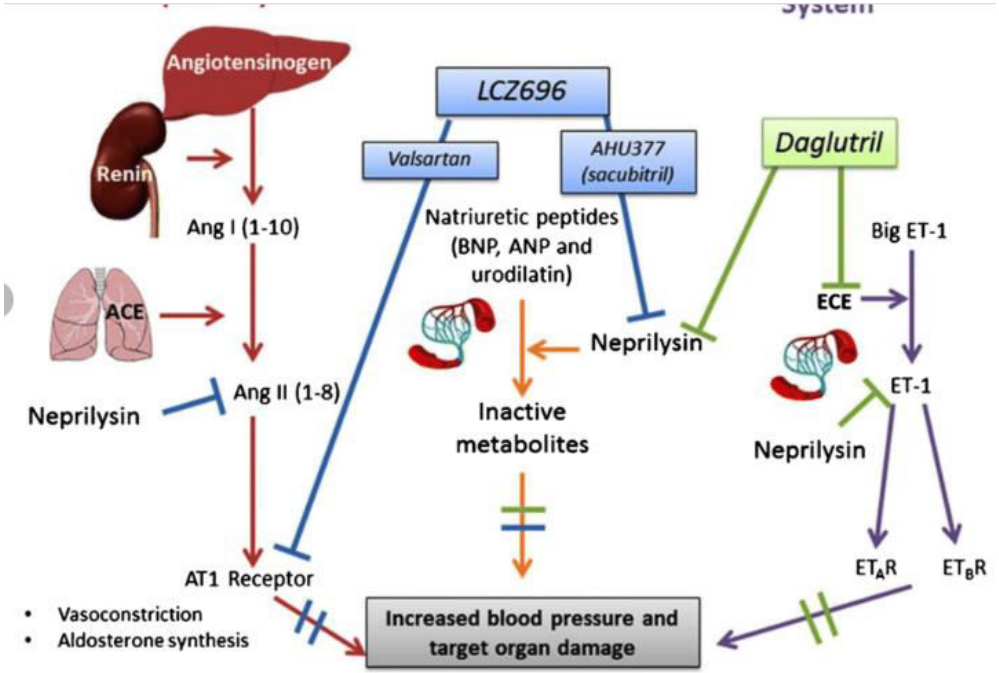
Ocedurenon

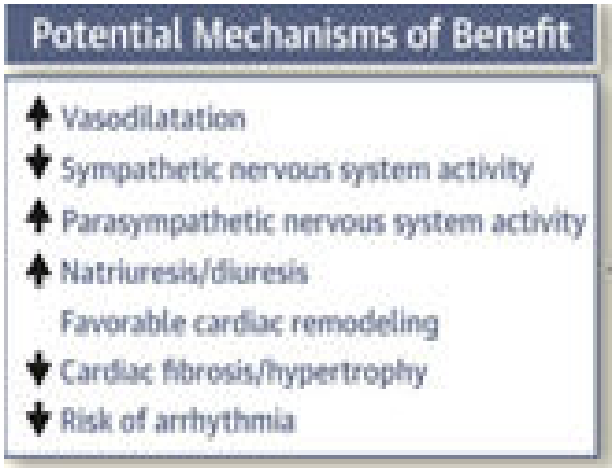
- Ocedurenone (KBP-5074) - ne steroidni, selektivni, visoki afinitet za MRA
- antihipertenzivno, kardio-renoprotektivno dejstvo
- kliničko ispitivanje Faze 3 (Clarion-CKD) -terapija CKD i nekontrolisane hipertenzije
- Pokazano je značajno snižavanje krvnog pritiska sa minimalnim rizikom od hiperK
- **Potencijalno nova terapijska opcija u lečenju neregulisane hipertenzije kod pacijenata sa odmaklom CKD**
- Blok-CKD faza 2b - dvostruko slepa, placebo kontrolisana, multicentrična studija za procenu efikasnosti, bezbednosti i PK ocedurenona 0,25 mg QD i 0,5 mg QD kod pacijenata sa umerenom do teškom CKD i nekontrolisanom hipertenzijom



KBP Biosciences. Efficacy and safety of KBP-5074 in uncontrolled hypertension and moderate or severe CKD (Clarion-CKD). NCT04968184.

Inhibitori vasopetidaze
valsartan-sacubitril



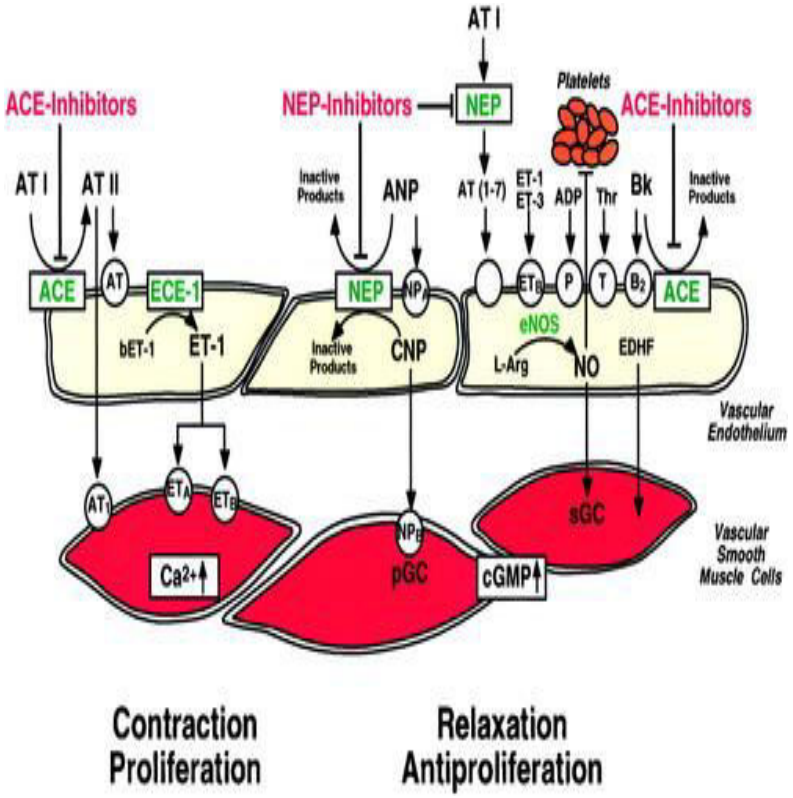


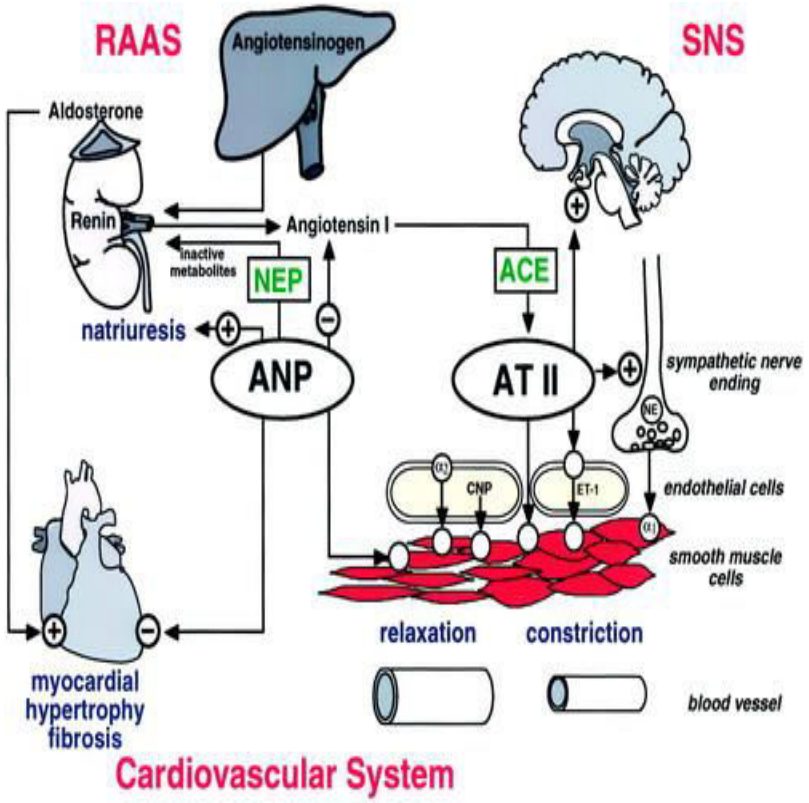
<u>Neželjena dejstva</u>

hipotenzija, hiperkalijemija, renalna insuficijencija, kašalj, angioedem

Inhibitori vazopeptidaze

- omapatrilat – dvojna inhibicija





Roberto Corti. Circulation. Vasopeptidase Inhibitors, Volume: 104, Issue: 15, Pages: 1856-1862,

Antagonisti endotelinskih receptora

Indikacije - terapiji rezistentne hipertenzije
- plućna hipertenzija

Endothelin-1	Bosentan	Nonselective ETR antagonists	Approved
	Macitentan	Dual ETAR/ETBR antagonist	Approved
	Darusentan	Selective ETR antagonists	Approved
	Aprocitentan	Dual ETAR/ETBR antagonist	Approved
	zibotentan	Selective ET1antagonist	

Neželjena dejstva

Edem/retencija tečnosti kod pacijenata lečenih aprocitentanom — oko 30% razvija edem, pri čemu je >95% bilo blagog do umerenog intenziteta.

-bosentan - hepatotoksičnost

-macitentan – anemija

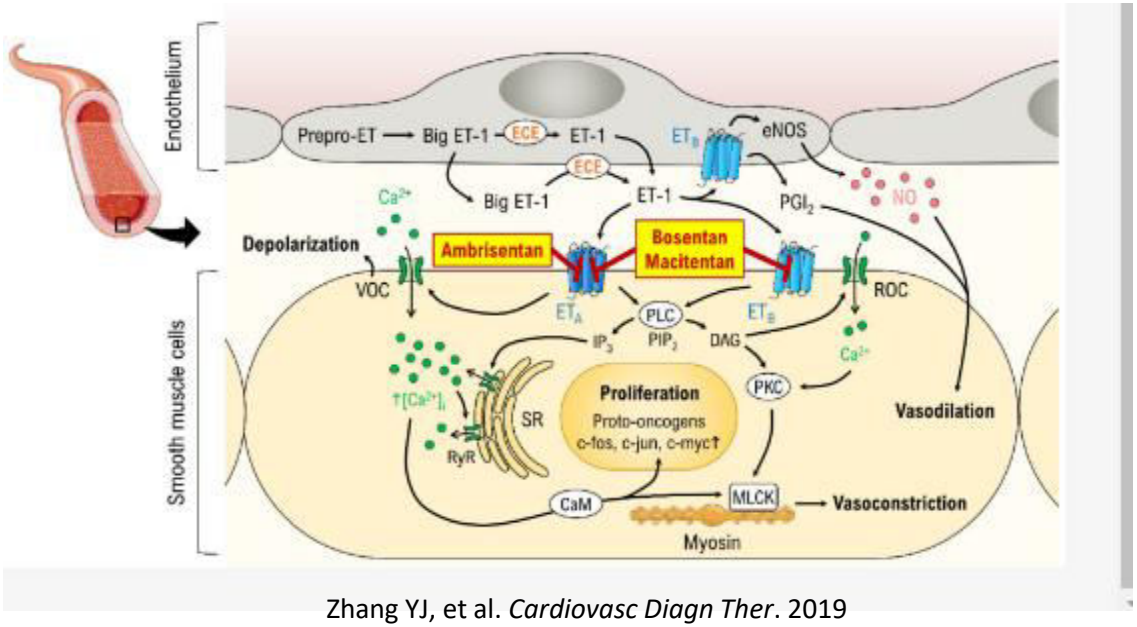
-ambrisentan- periferni edemi

-**zibotentan + dapagliflozin-**

Circulation Research. 2015

Aprocitentan (Idorsia Pharmaceuticals; Janssen)

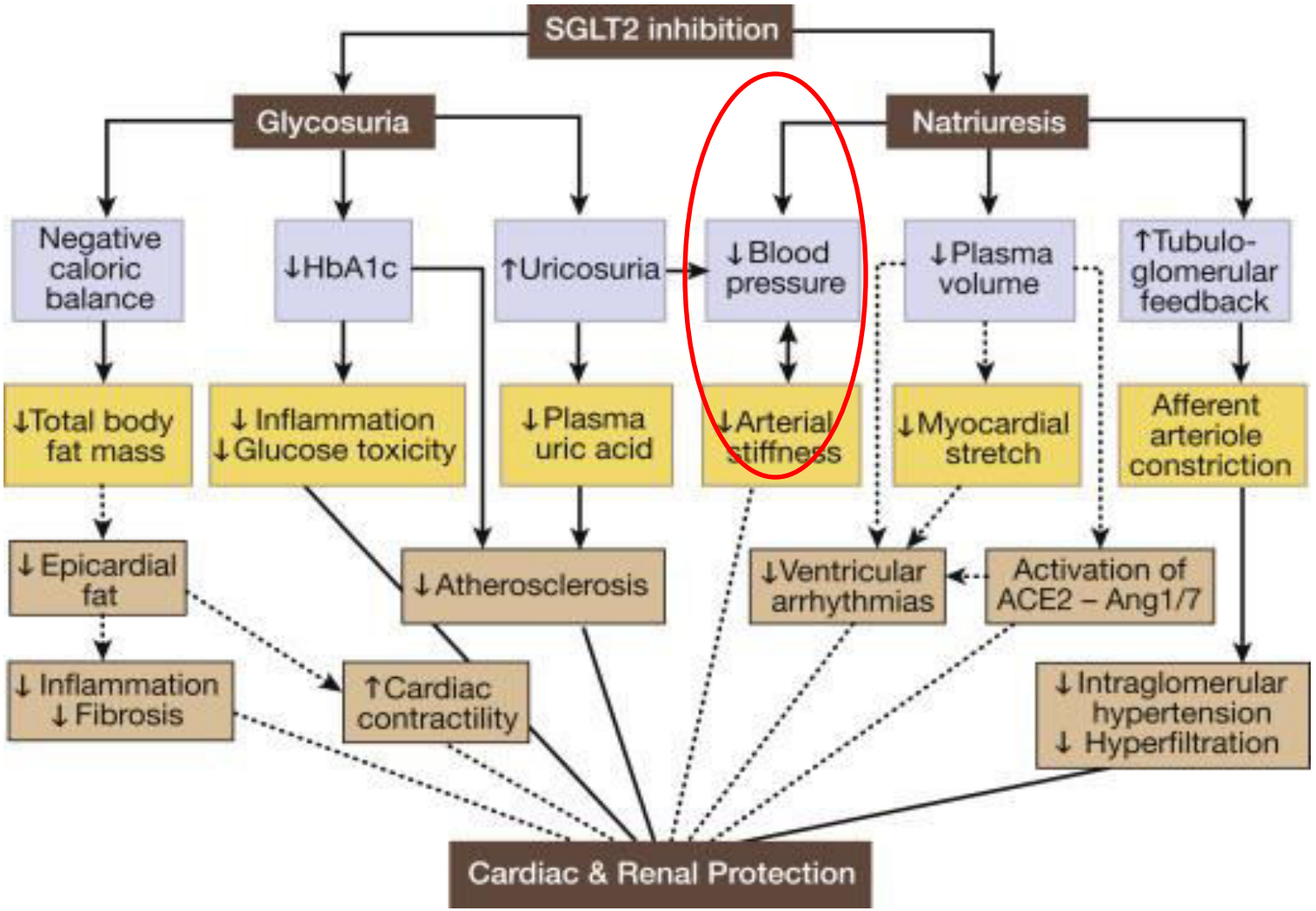
- Dvojni antagonist endotelinskih receptora ETAr/ETBr
- Signifikantno redukuje krvni pritisak (prosečno ↓ 7,65/5,92mmHg)
- U terapiji rezistentne hipertenzije (PRECISION study)
- FDA – nije odobrila
- Meta analiza 18 studija efikasnosti i bezbednosti ETAR



Zhang YJ, et al. *Cardiovasc Diagn Ther*. 2019

Schlaich MP et al; PRECISION investigators. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet. 2022.

SGLT2 inhibitori



Rajasekeran. Kidney International 2016.

Neuen BL, et al. NDT 2020;Lancet,2017

Heerspink HJL, et al. NDT 2020;

Kardiorenalni protektivni efekti novih antihipertenzivnih lekova

Renal Outcomes	Potential Mechanisms	Medication	Potential Mechanisms	Cardiovascular Outcomes
↓ Composite of dialysis, transplant, or death due to kidney disease ↓ ESRD ↓ AKI	↑ Vasoconstriction of afferent arteriole and decreased hyperfiltration, barotrauma, and proteinuria ↓ Oxidative stress ↓ Blood pressure	**SGLT2 inhibitors**	↓ Plasma volume, arterial stiffness, and blood pressure ↓ Oxidative stress ↑ Sensitivity to diuretics and natriuretic peptides	↓ CV death ↓ MI ↓ HHF ↔ Stroke
↓ Composite of development of new onset macroalbuminuria, decline in eGFR, ESRD, or death due to kidney disease	↓ Blood pressure ↓ Weight ↓ Dyslipidemia ↓ Oxidative stress ↓ Endothelial dysfunction	**GLP-1 receptor agonists**	↓ Blood pressure ↓ Weight ↓ Dyslipidemia ↓ Oxidative stress ↓ Endothelial dysfunction	↓ CV death ↓ MI ↓ HF ↓ Stroke
↓ Composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes	↓ Inflammation ↓ Fibrosis ↓ Blood pressure ↓ Endothelial dysfunction ↓ Tissue remodeling ↓ Proteinuria	**Selective nonsteroidal MR antagonists**	↓ Inflammation ↓ Fibrosis ↓ Blood pressure ↓ Endothelial dysfunction ↓ Tissue remodeling	↓ Composite of death from CV causes, nonfatal MI, nonfatal stroke, or HHF
↓ Onset of microalbuminuria ↓ Progression to macroalbuminuria ↓ ESRD	↓ Blood pressure ↓ Endothelial dysfunction ↓ Vasoconstriction of efferent arteriole and decreased hyperfiltration	**RAAS inhibitors**	↓ Blood pressure ↓ Vasoconstriction of coronary arteries ↓ Atherosclerosis ↓ Endothelial dysfunction ↓ Cardiac remodeling	↓ MI ↓ HHF

Hypertension. 2022.

Sinergistički efekat kombinacije sGLT-2 inhibitora i Finerenona

- Kombinacija empagliflozina i finerenona u malim dozama efikasne u smanjenju albuminurije i BP, creatinina i urikemije, cardio i renalne fibroze (FIDELIO-DKD trial)
- FIDELITY trial, smanjenje relativnog rizika od kardiorenalnih ishoda sa finerenonom bilo je slično bez obzira na upotrebu SGLT-2 inhibitora kao udruzene terapije
- Slično, DAPA-CKD, efekat dapagliflozina na renalne i kardiovaskularne ishode bio slican kod pacijenata koji su bili ili nisu lečeni steroidnom MRA
- Kombinovana terapija poboljšava efikasnost i povecava bezbednosti, s obzirom na rizik od hiperkalemije povezane sa upotrebom MRA-a a koji snižavaju SGLT2 inhibitora
- Istovremena primena SGLT2 inhibitora sa finerenonom smanjila je rizik od progresije CKD, esaxerenon je smanjio rizik od hiperkalemije kod pacijenata sa CKD i T2DM

Georgianos P. et all. Int. J. Mol. Sci. 2023, 24, 2803

Perspektive u lečenju hipertenzije

Farmakološka grupa	Lek	Način delovanja	Status
Vazoaktivni intestinalni peptid	Vasomera	VIP receptor agonist selectivni VPAC2-receptor agonist	Faza I
Na+/H+ exchanger 3 Intestinalni NHE3	Tenapanor SAR218034	NHE3 inhibitor	Registrovan 2021
NO	Pentaeritritol tetranitrat Vericinguat	NO	Faza I
Vakcine Gastrointestinalni mikrobiom		S1PR1 antagonist	Faza 1-2

Interventne procedure u lečenju rezistentne hipertenzije

T Ghatage. *Hypertens Res* 2021

ZAKLJUČAK

- Neadekvatna regulacija hipertenzije može se delimično unaprediti razvojem novih lekova i uređaja/procedura za lečenje hipertenzije i njenih komplikacija

- U budućnosti se očekuje primena novih klasa lekova (*inhibitori vazopeptidaza, aldosteron sinteze i novi MRA, agonisti natriuretskog peptida A i vazoaktivnog intestinalnog peptidnog receptora, inhibitori aminopeptidaze A)* u cilju optimalne regulacije kvnog pritiska i prevencije komplikacija hipertenzije

- Nesteroidni, selektivni MRA su potencijalno nova terapijska opcija kod bubreznih bolesnika sa T2DM zbog kardio-renoprotektivnog dejstva


rx
stroke
help
factors
vessels
diet
weight
health
systolic
high
obesity
genetic
blood
testing
men
heredity
HYPERTENSION
women
bp
people
care
heart
pressure
diastolic
normal
risk
control
research
bmi
medication
causes
rn
salt
cuff