Budućnost antagonista mineralokortikoidnih receptora u liječenju dijabetičke nefropatije

Future of Mineralocorticoid Receptor Antagonists in the Treatment of Diabetic Nephropathy

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SAŽETAK: Antagonisti mineralokortikoidnih receptora imaju važnu ulogu u liječenju rezistentne arterijske hipertenzije i srčanog popuštanja. Ne postoji kliničko istraživanje koje dokazuje da su lijek prvog izbora u liječenju ovakvih bolesnika. Najčešće ograničenje primjene lijekova iz ove skupine, čiji je najčešći predstavnik spironolakton, jesu hiperkalemija i spolna disfunkcija te ginekomastija, što je mnogo manje izraženo prilikom primjene selektivnijeg eplerenona u usporedbi sa spironolaktonom. Unatoč dokazanoj učinkovitosti i smanjenoj pojavnosti hiperkalemije u odnosu prema spironolaktonu još uvijek se eplerenon nedovoljno primjenjuje u svakodnevnoj praksi, posebno u bolesnika s dijabetičkom kroničnom bubrežnom bolesti, najčešće zbog straha od hiperkalemije. Novi nesteroidni selektivniji antagonist mineralokortikoidnih receptora finerenon pokazao je obećavajuće pozitivne ishode u kardiorenalnoj medicini, primarno prevenciju napredovanja kronične bubrežne bolesti u sklopu dijabetičke nefropatije uz mnogo manju pojavnost hiperkalemije. U randomiziranom istraživanju *FIDELIO-DKD* finerenon je znatno smanjio primarni i sekundarni ishod u usporebi s placebom, dovodeći do usporivanja progresije bubrežnog oštećenja u bolesnika s dijabetičkom kroničnom bubrežnom bolešću, čime je otvorena nova era liječenja dijabetičke bubrežne bolesti koja je danas najčešći uzrok završnoga stupnja bubrežne bolesti u svijetu.

KLJUČNE RIJEČI: antagonisti mineralokortikoidnih receptora, kronična bubrežna bolest, dijabetička bolest bubrega.

SUMMARY: Mineralocorticoid receptor antagonists (MRA) play a significant role in the treatment of resistant arterial hypertension and heart failure. There is no clinical study proving that they are the first drug of choice in the treatment of these patients. The most common limitation of the use of this group of drugs, whose most common representative is spironolactone, is hyperkalemia and sexual dysfunction, as well as gynecomastia, which is significantly less pronounced when using eplerenone, a more selective drug. Despite proven efficacy, the use of MRAs like eplerenone in patients with CKD is still limited and it is insufficiently applied in everyday practice. Finerenone, a nonsteroidal, novel, and selective antagonists of mineralocorticoid receptors shows promising differences from steroidal MRA, with a mechanism of action distinct from other agents for cardiorenal medicine in chronic kidney disease and diabetes mellitus type 2, which results in less hyperkalemia. In the FIDELIO-DKD randomized study, finerenone significantly reduced the both composite endpoints vs. placebo, suggesting that is possible postpone progression to kidney damage, thus ushering a new era in the treatment of diabetic kidney disease, which represents the most common cause of end-stage kidney disease in the world.

KEYWORDS: antagonists of mineralocorticoid receptors, chronic kidney disease, diabetic kidney disease.

CITATION: Cardiol Croat. 2021;16(3-4):157-63. | https://doi.org/10.15836/ccar2021.157

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TO CITE THIS ARTICLE: Prkačin I. Future of Mineralocorticoid Receptor Antagonists in the Treatment of Diabetic Nephropathy. Cardiol Croat. 2021;16(3-4):157-63. | https://doi.org/10.15836/ccar2021.157

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2021.157

RECEIVED:
February 8, 2021

UPDATED:
February 13, 2021

ACCEPTED:
February 28, 2021

Arterijska hipertenzija (AH) uz šećernu bolest tipa 2 (ŠB2) vodeći su uzroci pobolijevanja i smrtnosti u svijetu, te glavni uzroci kardiorenovaskularne (KRV) bolesti.[1] Procjenjuje se da će do 2025. godine od AH-a bolovati oko 1,56 milijardi ljudi, a unatoč kontroli arterijskoga tlaka i razine HbA1c u bolesnika sa šećernom bolešću (ŠB) ne zaustavlja se progresija kronične bubrežne bolesti (KBB), nego, upravo suprotno, ima

Along with type 2 diabetes, arterial hypertension (AH) is one of the leading causes of morbidity and mortality and one of the main cause of cardiorenovascular (CVR) disease in the world.[1] It is estimated that approximately 1.56 billion people will be suffering from AH by 2025, and despite efforts to control arterial pressure and HbA1c levels in patients with diabetes, the progression of chronic kidney disease (CKD)

pandemijske razmjere.[2] Antagonisti mineralokortikoidnih receptora (MRA) u terapiji AH-a i srčanog popuštanja imaju važnu ulogu.[3] Ne postoji kliničko istraživanje koje dokazuje da su MRA lijek prvog izbora za liječenje AH-a. Indicirani su primarno za liječenje primarnog hiperaldosteronizma (kada operacija nije indicirana), u stanjima sekundarnog hiperaldosteronizma zbog edema i ascitesa, te prema smjernicama ESH-a iz 2018. godine kao dodatna opcija liječenja rezistentne AH i srčanog popuštanja.[3] Posljednjih se nekoliko godina sve veća pažnja pridaje upravo ovoj skupini lijekova zbog dodatnoga pozitivnog učinka na sniženje albuminurije i djelovanja na usporivanje progresije KBB-a, posebice nesteroidne skupine MRA u bolesnika s dijabetičkom bubrežnom bolesti (DBB). U ovom će se članku prikazati spoznaje vezane za dosadašnje i najnovije spoznaje o ovoj važnoj skupini lijekova MRAs, koji se dijele u dvije skupine: steroidnu i nesteroidnu, a skupine se razlikuju u molekularnim i farmakološkim svojstvima.[4]

Skupina steroidnih antagonista mineralokortikoidnih receptora

SINTEZA ALDOSTERONA

Aldosteron je hormon nadbubrežne žlijezde koji se sintetizira iz kolesterola u stanicama zone glomeruloze. Izlučuje se na poticaj/promjene koncentracije angiotenzina II (AG II), adrenokortikotropnog hormona (ACTH) i kalija.[5] Sinteza aldosterona se odigrava se u dvjema fazama, akutnoj i odgođenoj. Akutnu fazu regulira protein StAR (*steroidogenic acute regulatory protein*) koji je odgovoran za dostavu kolesterola na unutarnju mitohondrijsku membranu. Kalij, ACTH i angiotenzin II preko sekundarnih glasnika reguliraju fosforilaciju i ekspresiju StAR proteina. Odgođena ili kronična faza sinteze aldosterona regulirana je enzimima na mitohondrijskoj membrani, a limitirajući čimbenik te faze jest aldosteron sintaza – CYP11B2.

GENOMSKO I NEGENOMSKO DJELOVANJE ALDOSTERONA

Aldosteron vezanjem za mineralokortikoidne receptore (MR) utječe na transkripciju i translaciju i to se djelovanje naziva genomskim.[5] Drugi je način djelovanja negenomski koje se ostvaruje preko membranskih receptora. MR su intracelularni citoplazmatski receptori, a pripadaju obitelji transkripcijskih faktora ovisnih o ligandu. Sam receptor ima 3 domene, N-terminalni kraj koji ima funkciju aktivacije transkripcije, središnji dio je domena koje se veže za specifični dio ciljanih DNA gena (SRE – *steroid response element*) i C-terminalni kraj na koji se veže aldosteron (LBD – *ligand binding domain*).[5] U inaktivnome stanju za receptor su vezani HSP (*heat-shock proteins*) koji mu onemogućuju vezanje za SRE. Nakon vezanja aldosterona za receptor dolazi do otpuštanja HSP-a i konformacijske promjene receptora koji se translocira u jezgru i veže za određenu sekvenciju DNA. Na taj način započinje transkripcija, a konačna se mRNA prenosi na ribosome, gdje se sintetiziraju proteini inducirani aldosteronom (AIP – *aldosterone induced proteins*). Inducira se ekspresija Na+ kanala, K+ kanala, Na+/K+-ATP-aze, luminalnog Na+/H+ antiportera, ali samo u proksimalnom kolonu, i luminalnog Na+/Cl- kotransportera osjetljivog na tijazide u distalnim tubulima nefrona. S obzirom na to da se proteini moraju sintetizirati, ova faza djeluje s odgodom od >2,5 sati pa se naziva kasnom fazom.

has not slowed down but has instead reached pandemic levels.[2] Mineralocorticoid receptor antagonists (MRA) play a significant role in therapy for hypertension and heart failure.[3] No clinical trial data has shown that MRA are first-line drugs for the treatment of AH. Instead, MRA are considered "go-to drugs" for the treatment of primary hyperaldosteronism (when surgery is not indicated) and in secondary hyperaldosteronism due to edema and ascites, although the ESH guidelines from 2018 consider them an additional option for with treatment-resistant hypertension and heart failure.[3] Over the last few years, this group of drugs has received increased attention due to their beneficial effect on reducing albuminuria and slowing progression of CKD, especially for nonsteroidal MRA in patients with diabetic kidney disease (DKD). Herein we shall present both past and most recent insights related to the MRA drug group, which are divided into two groups: steroidal and nonsteroidal, with important differences in molecular and pharmacological properties between the two types.[4]

Steroidal mineralocorticoid receptor antagonists

ALDOSTERONE SYNTHESIS

Aldosterone is an adrenal hormone which is synthesized from cholesterol in the cells of the zona glomerulosa. It is secreted based on stimulus from angiotensin II (AG II), adrenocortical hormones (ACTH), and potassium.[5] Aldosterone synthesis takes place in two phases, the acute phase and the chronic phase. The acute phase is regulated by the steroidogenic acute regulatory protein (StAR), which is responsible for delivering cholesterol to the inner mitochondrial membrane. Potassium, ACTH, and AG II regulate phosphorylation and StAR protein expression through secondary messengers. The chronic phase of aldosterone synthesis is regulated through enzymes on the mitochondrial membrane, and aldosterone synthase – CYP11B2 – is the limiting factor in this phase.

GENOMIC AND NONGENOMIC EFFECTS OF ALDOSTERONE

By binding to mineralocorticoid receptors (MR), aldosterone affects transcription and translation, which is called a genomic effect.[5] The other effect of aldosterone is nongenomic and is achieved through membrane receptors. MR are intracellular cytoplasmatic receptors belonging to the family of ligand-dependent transcription factors. MR themselves have 3 domains, an N-terminal domain that activates transcription, the central domain binding to a specific part of targeted DNA (SRE – steroid response element), and the C-terminal domain binding aldosterone (LBD – ligand-binding domain).[5] In the inactive state, heat-shock proteins (HSP) are bound to the receptor, disallowing it to bind to SRE. After aldosterone binds to the receptor, HSP are released and a conformation change in the receptor takes place, translocating it to the nucleus and binding to a specific DNA sequence. This initiates transcription, and the resultant mRNA transfers to ribosomes, where aldosterone-induced proteins (AIP) are synthesized. This induces expression of the Na+ channel, K+ channel, Na+/K+-ATPase, the luminal Na+/H+ antiporter, but only in the proximal tubule, and the luminal Na+/Cl- cotransporter sensitive to thiazides in distal nephron tubules. Since these proteins must be synthetized, this phase takes place with a >2.5 hour delay and is therefore called the late phase.

Rana, negenomska faza počinje s odgodom od 20 do 60 minuta aktiviranjem postojećih kanala i pumpe, čime se povećava kapacitet transporta stanice. Ta faza djeluje preko sekundarnih staničnih glasnika: intermedijarna tirozin-kinaza (IPYK), fosfolipaza-C (PLC), inozitol trifosfat (IP3), diacilglicerol (DAG), protein-kinaza-C (PKC) i povećanjem slobodnoga intracelularnog kalcija. Signalne kaskade koje su pokrenute preko sekundarnih glasnika djeluju na fosforilaciju natrijskih kanala membrane ili utječu na njihovu ekspresiju putem fosforilacije transkripcijskih faktora.[5] Ovakvo, negenomsko djelovanje aldosterona nije osjetljivo na mineralokortikoidne antagoniste. Zaključno, aldosteron vezanjem za mineralokortikoidne receptore (MR) potiče transkripciju i ekspresiju natrijevih kanala (ENaC – *Epithelial Sodium Channels*) koji resorbiraju natrij (nalaze se na apikalnoj membrani, aktivno se transportiraju putem Na+/K+-ATP-aze na bazolateralnoj membrani). Radi osmotske ravnoteže, Na+ za sobom povlači i vodu te se tako povećava i volumen cirkulirajuće krvi, što pridonosi nastanku AH.[5,6] Osim za MR u epitelnim stanicama nefrona i kolona, aldosteron se veže i za MR u kardiomiocitima, kardijalnim fibroblastima i glatkim mišićnim stanicama u stijenkama krvnih žila uzrokujući fibrozu miokarda, a u endotelu krvnih žila, osim profibrotskog odgovora, uzrokuju oksidativni stres blokirajući enzim glukoza-6-fosfat dehidrogenazu, što rezultira upalom i hipertrofijom žila, bubrega i srca s progresijom KRV bolesti.[7]

ULOGA ANTAGONISTA MINERALOKORTIKOIDNIH RECEPTORA

Lijekovi iz skupine MRA koji se danas primjenjuju jesu spironolakton (najčešće u dozama 12,5 – 50 mg) i eplerenon (u dozama 25 – 50 mg). Oba su lijeka jednako učinkovita u snizivanju tlaka, no eplerenon je selektivniji za MR, zbog čega ima manje neželjenih štetnih događaja (nuspojava) u usporedbi sa spironolaktonom, poput ginekomastije i/ili osjetljivosti dojki i bradavica, spolne i menstrualne disfunkcije. Prije uvođenja MRA-a u postojeću terapiju obvezno se procjenjuje bubrežna funkcija te, ako je procijenjena glomerularna filtracija (eGFR) <50 ml/L/1,73 m^2, ne preporučuje se viša dnevna doza od 25mg na dan upravo zbog hiperkalemije, koja je ograničavajući čimbenik primjene ove skupine lijekova.[8] Povišen rizik od nastanka hiperkalemije čine starija dob, ŠB i/ili KBB, dodavanje MRA uz terapiju inhibitora angiotenzin-konvertirajućeg enzima (ACEI) ili sartana (ARB) i/ili uzimanje nesteroidnih antiinflamatornih lijekova.[8] U istraživanjima sa **spironolaktonom** dokazan je renoprotektivni učinak sa sniženjem albuminurije i arterijskoga tlaka u bolesnika s KBB-om.[5] Na temelju pojedinačnih istraživanja učinkovitosti spironolaktona u bolesnika s KBB-om, liječenje tim lijekom u bolesnika s KBB 3. – 4. stadija bilo je udruženo sa sniženjem relativnog rizika od završnog stadija (ESRD) za 34 %, no uz triput viši rizik od hospitalizacije zbog hiperkalemije, koja je najčešći uzrok prekida liječenja.[9]

Eplerenon je u dosadašnjim istraživanjima pokazao učinkovitost u bolesnika s blagom do umjerenom AH, s jednakom učestalošću najčešćih neželjenih štetnih događaja poput dismenoreje, impotencije i ginekomastije kao u skupini s placebom. U usporedbi sa spironolaktonom zabilježen je manji porast razine aldosterona u plazmi, renina i hiperkalemije u odnosu prema skupini na spironolaktonom.[10] Eplerenon je kontraindiciran pri teškom oštećenju jetrene i bubrežne funkcije KBB 4. i 5. stadija (eGFR <30 mL/min/1,73 m^2).

The early nongenomic phase starts with a 20-60 minute delay upon the activation of existing channels and pump, thus increasing transport capacity in the cell. This phase takes place through second cell messengers: intermediary tyrosine kinase (IPYK), phospholipase C (PLC), inositol trisphosphate (IP3), diacylglycerol (DAG), protein kinase C (PKC), and increase in free intracellular calcium. Signal cascades initiated by second messengers act on the phosphorylation of membrane sodium channels or influence their expression through phosphorylation of transcription factors.[5] This nongenomic effect of aldosterone is not sensitive to mineralocorticoid antagonists. Finally, by binding to MR, aldosterone induces transcription and expression of epithelial sodium channels (ENaC) that resorb sodium (they are located on the apical membrane and actively transported via Na+/K+-ATPase on the basolateral membrane). In order to maintain osmotic balance, Na+ also binds water and thus increases circulating blood volume, contributing to AH.[5,6] Other than binding to MR in nephron and colon cells, aldosterone also binds to MR in cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells, causing myocardial fibrosis, and, in addition to a profibrotic response, also causing oxidative stress in the vascular endothelium by blocking the glucose-6-phosphate dehydrogenase enzyme, which results in inflammation and hypertrophy of blood vessels, kidneys, and the heart and consequently progression of CVR disease.[7]

THE ROLE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS

Medications from the MRA group that are applied today are spironolactone (usually in doses of 12.5-50 mg) and eplerenone (in doses of 25-50 mg). Both drugs are equally effective in reducing blood pressure, but eplerenone is more selective for MR, which is why it has less unwanted adverse events (side-effects) compared with spironolactone, such as gynecomastia and/or breast and nipple sensitivity as well as sexual or menstrual dysfunction. Renal function must be assessed before introducing MRA into an existing treatment regime, and if glomerular filtration (eGFR) is <50 ml/L/1.73 m^2, a daily dose above 25 mg per day is not recommended due to hyperkalemia, which is the limiting factor for this group of medications.[8] Factors for increased risk of hyperkalemia are advanced age, diabetes and/or CKD, adding MRA to therapy with angiotensin-converting enzyme inhibitors (ACEI) or sartans, and/or taking nonsteroidal anti-inflammatory drugs (NSAID).[8] Studies with **spironolactone** have demonstrated a renoprotective effect with a reduction in albuminuria and arterial pressure in patients with CKD.[5] Based on individual studies examining the effectiveness of spironolactone in patients with CKD, treatment with spironolactone in patients with stage 3-4 CKD was associated with a reduction in relative risk for end-stage renal disease (ESRD) of 34%, but with a three times higher risk of hospitalization for hyperkalemia, which is the most common cause for treatment discontinuation.[9]

In studies conducted so far, **eplerenone** was demonstrated to be effective in patients with mild to moderate AH, with the same incidence of the most common unwanted adverse events such as dysmenorrhea, impotence, and gynecomastia as in the placebo group. Compared with spironolactone, eplerenone resulted in a lower increase of plasma levels of aldosterone, renin, and hyperkalemia in comparison with the spironolactone group.[10] Eplerenone is contraindicated in severe damage to liver and kidney function in stage 4 and 5 CKD (eGFR<30 mL/min/1.73 m^2).

Istraživanja učinkovitosti eplerenona dokazana su u bolesnika s preboljelim infarktom miokarda sa sniženom ejekcijskom frakcijom (LVEF ≤40 %) i simptomima srčanog popuštanja.[11] Rezultati istraživanja *EPHESUS* (*Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, N* = 6642) pokazali su da je uzimanje eplerenona bilo povezano sa sniženjem rizika od smrtnosti za 15 % s obzirom na placebo, te sniženjem od 13 % relativnog rizika od KV smrtnosti i hospitalizacije u odnosu prema placebu.[10] Iako su podatci dobiveni u istraživanju *EPHESUS*, a koji se odnose na bolesnike sa ŠB2 i albuminurijom A2 ograničeni, uočena je u bolesnika sa ŠB2 veća pojavnost hiperkalemije koja raste sa smanjivanjem bubrežne funkcije.[10] Dodatno istraživanje iz 2011. godine *EMPHASIS-HF* (*Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, N = 2737*) pokazalo je dodatnu KV protekciju postignutu eplerenonom s obzirom na placebo, s redukcijom rizika od smrti i svih uzroka hospitalizacije u bolesnika s niskom ejekcijskom frakcijom (LVEF ≤30 %) koji su prethodno (unutar šest mjeseci) bili hospitalizirani zbog KV-a i/ili blagih simptoma srčanog popuštanja (NYHA II).[12]

U istraživanju *EMPHASIS-HF* hiperkalemija (razina kalija u serumu >5,5 mmol/L) zabilježena je u 11,8 % u skupini liječenoj eplerenonom te 7,2 % na placebu (p <0,001). S druge strane, vrlo često zanemaren problem hipokalemije posebice u bolesnika sa srčanim popuštanjem, koja se definira kao razina kalija u serumu <4,0 mmol/L, bila je statistički niža s eplerenonom u usporedbi s placebom (38,9 % za eplerenon u usporedbi s 48,4 % za placebo, p <0,0001).

Eplerenon se pokazao siguran i dobro podnošljiv u bolesnika s akutnim koronarnim sindromom i bez srčanog popuštanja u istraživanju *REMINDER* (*Impact of Eplerenone on Cardiovascular Outcomes in Patients Post Myocardial Infarction, N= 1012*). U tom istraživanju rana primjena MRA-a nije dokazala jasan dodatni boljitak ako je bila dodana standardnoj terapiji (*standard of care*, SOC) za infarkt miokarda.[13] Unatoč dokazanoj učinkovitosti i sigurnosti liječenja još uvijek je primjena eplerenona u bolesnika s KBB-om ograničena, ponajviše zbog pridruženog rizika od povišene vrijednosti kalija (hiperkalemija).[14,15]

Nova, nesteroidna generacija antagonista mineralokortikoidnih receptora

Rezultati ranijih istraživanja MRA-a i visoka pojavnost pridružene hiperkalemije u kliničkoj praksi rezultirali su identifikacijom potentnih, selektivnih, nesteroidnih MRA-a putem kloniranja humanih mineralokortikoidnih receptora komplementarnom DNA. Nedavna istraživanja pokazuju da lijekovi iz ove skupine novih MRA imaju dodatni učinak na smanjenje rezidualnog rizika od progresije bubrežne i srčane bolesti. Finerenon je novi, nesteroidni, selektivniji MRA od spironolaktona, s nešto višim MR afinitetom nego eplerenon, a distribuiran je podjednako između srca i bubrega (spironolakton i eplerenon imaju višu koncentraciju u bubrežnomu tkivu nego u srčanom). Njegova nesteroidna struktura omogućuje mu da se veže za MR s visokim afinitetom i inhibira transkripcijske koaktivatore uključene u ekspresiju profibrotskih gena.[4] Stoga ima mnogo manje neželjenih štetnih događaja poput ginekomastije i niske incidencije hiperkalemije. U istraživanjima kao što je *ARTS-DN* njegova je primjena dovela do znatnog

Studies have demonstrated the effectiveness of eplerenone in patients with previous myocardial infarction with reduced left ventricular ejection fraction (LVEF ≤40%) and symptoms of heart failure.[11] The results of the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, N = 6642) study have shown that taking eplerenone was associated with a reduction in risk of death by 15% in comparison with placebo and a reduction in relative risk and hospitalization of 13% in comparison with placebo.[10] Although the data obtained in the EPHESUS study are limited regarding patients with type 2 diabetes and A2 albuminuria, increased incidence of hyperkalemia was observed in patients with type 2 diabetes, which increased as renal function decreased.[10] EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, N = 2737), an additional study conducted in 2011, demonstrated that eplerenone provided an additional CV protective effect in comparison with placebo, with a reduction in the risk of death and all-cause hospitalizations in patients with low ejection fraction (LVEF ≤30%) in patients who had previously (within six months) been hospitalized for CV symptoms and/or mild heart failure symptoms (NYHA II).[12]

In the EMPHASIS-HF study, hyperkalemia (serum potassium >5.5 mmol/L) was observed in 11.8% of patients in the group treated with eplerenone and in 7.2% of patients in the placebo group (p <0.001). On the other hand, hypokalemia is a problem that has often been neglected, especially in patients with heart failure, with hypokalemia defined as serum potassium levels <4.0 mmol/L, which was statistically significantly lower with eplerenone in comparison with placebo (38.9% with eplerenone in comparison with 48.4% in the placebo group, p <0.0001).

Eplerenone was shown to be safe and well-tolerated in patients with acute coronary syndrome and no heart failure in the REMINDER study (Impact of Eplerenone on Cardiovascular Outcomes in Patients Post Myocardial Infarction, N= 1012). Early application of MRA in this study was not associated with a clear benefit when added to the standard of care (SOC) for myocardial infarction.[13] Despite the demonstrated effectiveness and safety of treatment with eplerenone, its application in patients with CKD is still limited, primarily due to the associated risk of elevated potassium levels (hyperkalemia).[14,15]

The new, nonsteroidal generation of mineralocorticoid receptor antagonists

The results of previous studies on MRAs and the significant incidence of associated hyperkalemia in clinical practice resulted in the identification of potent and selective nonsteroidal MRAs by cloning human MR-complementary DNA. Recent studies have shown that medications from this group of new MRAs have an additional effect on the reduction of residual risk of kidney and heart disease progression. Finerenone is a new, nonsteroidal, and more selective MRA compared with spironolactone and a somewhat higher MR affinity in comparison with eplerenone, and it is distributed approximately equally between the heart and kidneys (spironolactone and eplerenone have a higher concentration in kidney tissue compared with heart tissue). Finerenone's nonsteroidal structure allows it to bind to MR with a high affinity and inhibit co-activators involved in the expression of pro-fibrotic genes.[4] Consequently, it results in significantly fewer unwanted adverse events such as gynecomastia and has a lower incidence of

sniženja razine albumina u urinu (*albumin-to-creatinine ratio*, UACR) i pri početnim dozama od samo 7,5 mg uz temeljnu terapiju (ACEI ili ARB) nakon ukupno 90 dana liječenja.[16,17] Nastavak pozitivnih iskustava prvotnih istraživanja *ARTS-HF* (HFrEF) i *ARTS-DN* (KBB i A2/A3) faza je triju istraživanja finerenona u kardiorenovaskularnim ishodima bolesnika sa ŠB2 i KBB-om (*FIDELIO-DKD, Finerenone in reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease*). Uključni su kriteriji bili dob veća od 18 godina, DBB, uzimanje lijekova iz skupine ACEI ili ARB dulje od 4 tjedna, razina kalija <4,8 mmol/L te dijabetička retinopatija i albuminurija A2 i više. Isključni su kriteriji bili neregulirana ŠB s vrijednostima HbA1c >12 %, nepostojanje DBB-a, neregulirana AH, NYHA II-IV, srčano popuštanje s reduciranom ejekcijskom frakcijom). Primarni je ishod bila procjena utjecaja na albuminuriju i bubrežni ishod s gubitkom bubrežne funkcije i potrebom nadomjestne terapije (*kidney death*). Sekundarni ishodi bili su KV događaji, smrt ili hospitalizacija. Neželjenih štetnih događaja bilo je mnogo više u skupini na finerenonu, ukupno 18,3 % dok ih je u skupini s placebom bilo 9 %: od toga je akutnih bubrežnog oštećenja 4,6% u skupini na finerenonu, a 4,8 % u placebo skupini. Zbog hiperkalemije hospitalizirano je 1,4 % bolesnika u skupini na finerenonu i 0,3 % iz placebo skupine. Hiperkalemija kao uzrok prekida istraživanja utvrđena je u 2,3 % bolesnika na finerenonu i 0,9 % skupini s placebom, no nitko zbog hiperkalemije nije preminuo.

Rezultati istraživanja *FIDELIO-DKD* predstavljeni su potkraj studenoga 2020. godine, a pokazali su znatno sniženje albuminurije za 31 %, usporivanje propadanja bubrežne funkcije (za više od 40 %) i sniženje KV ishoda u usporedbi s placebom u bolesnika s KBB-om i ŠB2, s anamnezom KV bolesti i bez nje.[18] Pokazano je da broj bolesnika koje treba liječiti da se ovakav ishod postigne (NNT) iznosi 29 za primarni ishod i 42 za sekundarni ishod.[18]

Rasprava

Unatoč učinkovitosti lijekova iz skupine MRA u bolesnika sa srčanim popuštanjem vrlo je malo istraživanja s MRA u bolesnika s KBB-om. Osobitost bolesnika s KBB-om jest da najčešće umiru od komplikacija KV-a, što je još izraženije ako je riječ o bolesnicima sa ŠB2. Bolesnici s KBB-om i ŠB2 imaju trostruko viši rizik od smrti uzrokovane KV-om u usporedbi s onima koji nemaju KBB.[19] Razlog je prevelika aktivnost MR-a koja pridonosi upalnom odgovoru, fibroziranju s oštećenjem ciljnih organa (primarno srca, bubrega, periferne vaskulature), a povezana je s povišenim rizikom od KRV-a. Upravo je tu mjesto MRA, posebice nove skupine poput finerenona koji inhibira inflamatorni odgovor i smanjuje fibrozu omogućujući dodatnu zaštitu tkiva i organa ne uzrokujući hiperkalemiju koja je do sada bila glavni ograničavajući čimbenik primjene ove skupine lijekova.[8] Na temelju istraživanja *AMBER* koje je objavljeno 2019. godine sa spironolaktonom (i patiromerom koji je dodan kako bi snizivao kalij) čak je 23 % bolesnika isključeno iz istraživanja zbog hiperkalemije, a primjena je bila ograničena u slučaju višega stupnja bubrežnog oštećenja, tj. KBB-a 4. i 5. stadija (eGFR <30mL/min/1,73m^2).[20]

Više od dvadeset godina bolesnici sa ŠB2 i KBB-om s albuminurijom >300 mg/na dan imali su samo preporuku uzimanja lijekova iz skupine ACEI ili ARB (RAS blokatori).[3] Od sredine 2019. SGLT2 inhibitori preporučuju se u bolesnika sa ŠB2 s albuminurijom >300 mg/g uz eGFR >30 mL/min/1,73 m^2.[21]

hyperkalemia. In studies such as ARTS-DN, finerenone led to a significant reduction in urine albumin levels (albumin-to-creatinine ratio, UACR) even with initial doses of 7.5 mg in conjunction with basic treatment (ACE inhibitors or ARBs) after only 90 days of treatment.[16,17] The positive experiences of the initial studies, ARTS-HF (HFrEF) and ARTS-DN (KBB and A2/A3), were supported by a phase 3 finerenone trial on cardiovascular outcomes in patients with type 2 diabetes and CKD (FIDELIO-DKD, Finerenone in reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease). Inclusion criteria were being above 18 years of age, DKD, receiving medication from the ACE inhibitor or ARB group for longer than 4 weeks, potassium levels <4.8 mmol/L, diabetic retinopathy, and albuminuria A2 and higher. Exclusion criteria were unregulated diabetes with HbA1c >12%, lack of DKD, unregulated AH, NYHA II-IV, and heart failure with reduced ejection fraction. The primary outcome was the impact on albuminuria and kidney outcomes with loss of kidney function and the need for replacement therapy (kidney death). The secondary outcome was CV events, death, or hospitalization. Unwanted adverse events were significantly more common in the finerenone group, 18.3% in total in comparison with 9.0% in the placebo group, including 4.6% acute kidney damage in the finerenone group and 4.8% in the placebo group. In the finerenone group, 1.4% of patients were hospitalized for hyperkalemia, compared with 0.3% in the placebo group. Hyperkalemia was reported as the reason for leaving the study in 2.3% patients on finerenone and 0.9% in the placebo group, but it did not result in any deaths.

The results of the FIDELIO-DKD were presented in November 2020 and showed a significant reduction in albuminuria by 31%, a reduction in the deterioration of kidney function (by more than 40%), and reduced CV outcomes in comparison with placebo in patients with CKD and type 2 diabetes, with and without previous CV disease.[18] The number needed to treat (NNT) to achieve this outcome was 29 for the primary outcome and 42 for the secondary outcome.[18]

Discussion

Despite growing evidence for the effectiveness of MRA use in patients with heart failure, very few MRA trials have been performed in patients with CKD. Mortality in patients with CKD is characteristically caused by CV complications, especially if they also have type 2 diabetes. Patients with CKD and type 2 diabetes a three times higher risk of CV death compared with patients with those who do not have CKD.[19] This is due to MR overactivation in these patients, which drives inflammation and fibrosis formation, which can lead to target organ damage (primarily the heart, kidneys and peripheral vasculature) that is associated with increased CVR risk. This is where MRA can play a role, especially new groups such as finerenone that inhibit the inflammatory response and reduce fibrosis, providing an additional protective effect for tissue and organs without causing hyperkalemia, which has previously been the main limiting factor for the application of this group of drugs.[8] Based on the AMBER study published in 2019 that evaluated spironolactone (and patiromer added to reduce potassium), as many as 23% of patients were excluded from the study due to hyperkalemia, and application was limited in more advanced stages of kidney damage, i.e. stage 4 and 5 CKD (eGFR <30mL/min/1.73m^2).[20]

For more than 20 years, guidelines recommended that patients who had diabetes and CKD with albuminuria >300 mg/

Rizik od bubrežnog i srčanog zatajivanja u bolesnika s DBB-om dokazano je smanjen i lijekovima iz skupine inhibitora suprijenosnika natrija i glukoze 2 (SGLT2) uz RAS blokator, no nije zaustavljena progresija KBB-a.[21,22] Završni stupanj KBB-a (ESRD) ostao je neprihvatljivo visok, s dvaput bržom progresijom bubrežnog oštećenja nego u populaciji koja nema ŠB2.[21] Stoga ne začuđuju nastojanja prema pronalaženju lijekova iz drugih skupina kako bi se pokušala zaustaviti progresija KBB-a. Najnoviji podatci dodatne analize istraživanja dijabetičke nefropatije liječene atrasentanom (*SONAR*) pokazali su da kombinacijsko liječenje dovodi do većeg sniženja albuminurije nego samo monoterapija atrasentanom.[23]

Nova generacija MRA uključuje nove terapijske mogućnosti liječenja dijabetičke bolesti bubrega koja je još uvijek najčešći uzrok završnoga stupnja kronične bubrežne bolesti i potrebe nadomještanja bubrežne funkcije uz niz pridruženih mikrovaskularnih i makrovaskualrnih komplikacija koje znatno utječu na kvalitetu života bolesnika s DBB-om. Stoga novi lijekovi iz skupine MRA mogu omogućiti bolju i svjetliju budućnost pacijenata sa ŠB2.[23-25]

Buduća istraživanja

Podatci dobiveni u najnovijim istraživanjima podupiru hipotezu prolongirane i dugotrajnije protekcije bubrega kombiniranim liječenjem s naglaskom na multidisciplinarnu suradnju u translacijskoj medicini. U budućnosti očekujemo istraživanja učinkovitosti i sigurnosti istodobne primjene lijekova SGLT2 i nesteroidnih MRA-a u bolesnika s DBB-om.

Zaključak

Unatoč dokazanoj učinkovitosti sa sniženjem relativnog rizika za završni stadij KBB-a još uvijek je primjena MRA (poglavito spironolaktona, manje eplerenona) u bolesnika s KBB-om ograničena zbog povećanog rizika od hiperkalemije. Istraživanja s novim MRA poput finerenona čine novu eru liječenja bolesnika s KBB-om, primarno DBB-om s dokazano manjom pojavnošću hiperkalemije uz usporivanje progresije oštećenja ciljnih organa.

day should receive ACE inhibitors or ARBs.[3] Since mid-2019, SGLT2 inhibitors have been recommended for patients with diabetes with albuminuria >300 mg/g if the estimated glomerular filtration rate (eGFR) is >30 mL/min/1.73 m^2.[21] It has also been demonstrated that the risk of kidney and heart failure in patients with DKD is reduced by drugs in the sodium-glucose co-transporter-2 (SGLT2) group in combination with a RAS blocker, but CKD progression was not delayed.[21,22] The terminal stage of CKD (ESRD) remain unacceptably high, with ×2 more rapid progression of kidney damage than in the population without type 2 diabetes.[21] Attempts to find drugs from other groups that can prevent CKD progression are therefore not surprising. The newest data from additional analysis of a study on diabetic nephropathy with atrasentan (SONAR) have shown that combination treatment led to a greater reduction in albuminuria compared with monotherapy with atrasentan.[23]

This new generation of MRA opens up new possibilities in the treatment of diabetic kidney disease, which still represents the most prevalent cause of end-stage renal disease, while having to replace kidney function with the numerous associated micro- and macrovascular complications that significantly affect the quality of life in patients with DKD. These new drugs from the MRA group can therefore provide a better and brighter future for patients with type 2 diabetes.[23-25]

Future research

The data obtained in the latest studies support the hypothesis of prolonged and long-term renal protection with combined treatment, with an emphasis on multidisciplinary collaboration in translational medicine. Further studies are expected regarding the effectiveness and safety of by combination therapy with SGLT2 and nonsteroidal MRA for DKD in the future.

Conclusion

Despite proven efficacy with reduced relative risk for ESKD treatment, the use of MRA (especially spironolactone, eplerenone less so) in patients with CKD is still limited due to the increased risk of hyperkalemia. Studies with new MRAs such as finerenone represent a new era in the effective treatment of patients with CKD, primarily diabetic kidney disease, with a proven lower incidence of hyperkalemia and with a slowing of the progression of target organ damage.

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