Antagonist mineralokortikoidnih receptora eplerenon u suvremenom liječenju kardiovaskularnih bolesnika

Mineralocorticoid Receptor Antagonist Eplerenone in Cardiovascular Disease

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SAŽETAK: Velika randomizirana kontrolirana istraživanja dokazala su središnju ulogu antagonista mineralokortikoidnih receptora spironolaktona i eplerenona u liječenju bolesnika sa zatajivanjem srca. Svoje brojne pozitivne učinke ostvaruju blokiranjem reninsko-angiotenzinsko-aldosteronskog sustava, što uzrokuje smanjenje negativne remodelacije miokarda te u konačnici bolje ishode za bolesnika. Osim u zatajivanju srca, antagonisti mineralokortikoidnih receptora imaju ulogu u liječenju bolesnika s rezistentnom hipertenzijom. Ovaj pregledni članak usredotočen je na farmakokinetiku, farmakodinamiku, kliničku primjenu i sigurnosni profil eplerenona.

SUMMARY: Aldosterone and eplerenone are mineralocorticoid receptor antagonists with one of the main roles in the treatment of heart failure, as demonstrated by large randomized controlled trials. Effects on patient outcomes are the result of blocking the renin-angiotensin-aldosterone system, which improves cardiac remodeling. Besides heart failure, mineralocorticoid receptor antagonists are used in treatment of patients with resistant arterial hypertension. This review focuses on the pharmacokinetics, pharmacodynamics, clinical effects, and safety profile of eplerenone.

KLJUČNE RIJEČI: antagonisti mineralokortikoidnih receptora, eplerenon, zatajivanje srca, arterijska hipertenzija, hiperkalijemija.

KEYWORDS: mineralocorticoid receptor antagonists, eplerenone, heart failure, arterial hypertension, hyperkalemia.

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Uvod

Molekula aldosterona je otkrivena 50-ih godina 20. stoljeća te, iako su desetljeća bila potrebna samo za djelomično razumijevanje njegovih brojnih učinaka, već od pionirskih istraživanja mađarsko-kanadskog endokrinologa Hansa Selya poznata je njegova povezanost s nefrosklerozom i hipertrofijom miokarda u životinjskom modelu. Vrlo rano nakon otkrića aldosterona, sintetizirani su i prvi antagonisti (prekursori spironolaktona i spironolakton) koji, premda tada uglavnom nepoznata djelovanja, dovode do manje negativne remodelacije miokarda u životinjskim modelima.[1,2] Neki od ključnih koraka dugogodišnjeg istraživanja steroidnih hormona svakako su otkriće i sinteza mineralokortikoidnih receptora 80-ih godina prošloga stoljeća, koji omogućuju proizvodnju novih generacija antagonista mineralokortikoidnih receptora poput eplerenona.[1,2]

Introduction

Aldosterone was isolated in the 1950s, but further research of its physiology was relatively slow over the next decades. In spite of that, it was already in the early days that Hungarian-Canadian endocrinologist Hans Selye observed an increase in nephrosclerosis and myocardial hypertrophy in animal models exposed to high aldosterone levels. The first aldosterone antagonists were synthesized soon after aldosterone isolation (spironolactone precursors and spironolactone itself). Although their mechanisms of action were unknown, beneficial effects on cardiac remodeling were observed.[1,2] One of the key events in steroid hormone research was synthesis of mineralocorticoid receptors and discovery of its microstructure in the 1980s, allowing design and discovery of new mineralocorticoid receptor antagonists (MRA) such as eplerenone.[1,2]

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Fiziologija i patofiziologija aldosterona

Središnja je uloga reninsko-angiotenzinsko-aldosteronskog sustava (RAAS) u kardiovaskularnoj fiziologiji i patofiziologiji. Aktivacija RAAS-a povezana je s nepovoljnim ishodima te je u više randomiziranih kontroliranih istraživanja dokazana korist njegove blokade. Aldosteron se uglavnom proizvodi u kori nadbubrežne žlijezde, no poznato je da se proizvodi i lokalno na razini endotela i glatkomišićnih stanica krvnih žila brojnih organa.[3,4]

U normalnim fiziološkim uvjetima aldosteron regulira prijenos natrija i kalija u bubregu sporim, genomskim mehanizmom; vezivanjem za intracitosolne mineralokortikoidne receptore nastupa pozitivna stimulacija transkripcijskih faktora koji reguliraju aktivaciju gena kanalića za apsorpciju natrija i sekreciju kalija s posljedičnim povećanjem volumena plazme i povišenjem arterijskoga tlaka. Djeluje i na transkripciju gena koji uzrokuju fibrozu, poput kolagena i transformirajućeg faktora rasta-beta (TGF-beta) te gena koji djeluju proinflamatorno. Mineralokortikoidni receptori prisutni su u stanicama endotela, miokardu, makrofagima, stanicama sluznice gastrointestinalnog sustava i oka.[5-8]

Aldosteron djeluje i izravno na glatkomišićne stanice vaskulature negenomskim, brzim putem, i to prije svega nakon lokalne proizvodnje. Neki od dobro poznatih i klinički važnih negenomskih učinaka jesu vazokonstrikcija koronarnih arterija i povišenje sistemske vaskularne rezistencije.[8]

Na životinjskim je modelima dokazan negativan učinak aldosterona na miokard neovisno o povišenju arterijskoga tlaka. Aldosteron uzrokuje fibrozu miokarda i hipertrofiju klijetki, a primjenom inhibitora angiotenzin-konvertirajućeg enzima (ACE) dolazi do smanjenja hipertrofije, no ne i fibroze, što upućuje na to da se fibroza odigrava i dodatnim mehanizmima osim samom aktivacijom angiotenzina II. Aldosteron povećava proizvodnju tkivnog ACE-a i receptora angiotenzina 1 (AT1), što stvara začarani krug koji još dalje potencira njegove negativne učinke. Aktivacija tkivnog ACE-a i proizvodnja receptora AT1 u podlozi je fenomena „bijega aldosterona" koji se pojavljuje nakon nekoliko mjeseci liječenja ACE inhibitorima i može biti povezan s novim kliničkim pogoršanjem bolesnika sa zatajivanjem srca.[9]

Eplerenon

Eplerenon je kompetitivni antagonist mineralokortikoidnih receptora. Iako je eplerenon visoko selektivan za mineralokortikoidne receptore, njegov afinitet za te receptore jest 10 – 20 puta manji od spironolaktona *in vitro*, a klinička istraživanja pokazuju da je 50 – 75 % potentan kao spironolakton, što je rezultat kompenzacije lošijeg afiniteta boljom bioraspoloživosti. Vršne koncentracije eplerenona prosječno se postižu za 1,5 sati nakon peroralnog uzimanja, te hrana ne utječe na apsorpciju, dok mu je poluvrijeme eliminacije oko 4 – 6 sati.[2,8] Metabolizira se primarno preko jetre citkromom P450 (CYP3A4), što znači da lijekovi poput ketokonazola, ribonavira i klaritromicina mogu povisiti koncentracije eplerenona u krvi, dok fenobarbital djeluje suprotno.[4]

Eplerenon u usporedbi sa spironolaktonom ima mnogo niži afinitet za androgene i progesteronske receptore, što znači da njegova primjena nije povezana s nepovoljnim androgenim učincima – ne uzrokuje bolnu ginekomastiju i erektilnu disfunkciju u muškaraca ili menstrualne probleme u mlađih žena.[8]

Aldosterone physiology and pathophysiology

The renin-angiotensin-aldosterone system (RAAS) has a central role in cardiovascular physiology and pathophysiology. RAAS activation is associated with adverse outcomes, whereas its blockade has been shown to be beneficial in several randomized controlled trials (RCTs). Aldosterone is mainly produced by zona glomerulosa cells of the adrenal gland cortex. To a lesser extent it is also produced locally, by vascular endothelium and smooth-muscle cells of different organs.[3,4]

In normal conditions, aldosterone regulates renal sodium and potassium transport by genomic pathways. Aldosterone binds to intracytosolic receptors that are in fact transcription factors regulating gene expression for sodium absorption and potassium secretion channels. The net result is plasma volume expansion and blood pressure elevation. It also regulates expression of profibrotic (collagen and transforming growth factor-beta (TGF-beta)) and proinflammatory genes. Mineralocorticoid receptors can be found in the endothelium, myocardium, macrophages, gastrointestinal epithelium, and the eye.[5-8]

Aldosterone, predominantly when produced locally, also acts through fast non-genomic pathways directly in smooth-muscle vascular cells. Coronary artery vasoconstriction and increase in systemic vascular resistance are examples of non-genomic aldosterone actions.[8]

Adverse myocardial effects of aldosterone have been shown in animal models independently of blood pressure increase. Aldosterone causes myocardial fibrosis and myocardial hypertrophy. Although hypertrophy can be alleviated by angiotensin-converting enzyme (ACE) inhibitors, they have no effect on fibrosis, indicating mechanisms of fibrosis other than through angiotensin II. Aldosterone increases tissue ACE and receptors for angiotensin 1 (AT1), resulting in a vicious circle of adverse effects. Tissue ACE activation and AT 1 receptor production are responsible for "aldosterone escape", a phenomenon that occurs several months into treatment with ACE inhibitors and that may be associated with new worsening of heart failure symptoms despite ACE inhibitors therapy.[9]

Eplerenone

Eplerenone is a competitive MRA. Although it is highly selective for mineralocorticoid receptors, its affinity is 10-20 times lower than spironolactone. However, clinical research has shown that eplerenone has at least 50-75% of the potency of spironolactone due to compensating low affinity with better bioavailability. Peak eplerenone plasma concentrations are reached 1.5 h after oral intake, and concomitant food ingestion has no effect on absorption. Its half-life in plasma is 4-6 hours.[2,8] Eplerenone is metabolized primarily via hepatic cytochrome P450 (CYP3A4), indicating that ketokonazole, ribonavir, and clarithromycin increase its plasma concentrations while phenobarbital lowers them by inducing CYP3A4.[4]

In comparison with spironolactone, eplerenone has a much lower affinity for androgen and progesterone receptors, translating into no adverse androgen effects – no painful gynecomastia or erectile dysfunction in men or menstrual problems in young women.[8]

Eplerenon u liječenju bolesnika sa zatajivanjem srca

UTJECAJ NA SMRTNOST I BROJ HOSPITALIZACIJA

Randomizirano kontrolirano istraživanje RALES (*the Randomized Aldactone Evaluation Study*) prvo je rezultiralo jasnim dokazima prednosti liječenja bolesnika sa zatajivanjem srca antagonistom aldosterona u usporedbi s placebom. Podsjetimo se, kliničko istraživanje s 1663 bolesnika s kroničnim zatajivanjem srca i sniženom ejekcijskom frakcijom (prosječna EF u tom je ispitivanju bila 25 %), a koji su bili NYHA III. ili IV. funkcijskog statusa, te su primali tada standardno farmakološko liječenje ACE inhibitorima, diureticima i digoksinom, prekinuto je ranije nego što je bilo protokolom predviđeno zbog mnogo niže ukupne smrtnosti u skupini koja je primala spironolakton.[10] Neke od glavnih zamjerki bile su isključivanje bolesnika s kroničnom bubrežnom bolesti i mali postotak bolesnika koji su liječeni blokatorima beta-adrenergičnih receptora. Štoviše, rezultate RALES istraživanja u svakodnevnoj kliničkoj praksi ugrožavao je porast incidencije hiperkalijemije koja je zahtijevala hospitalno liječenje, te porast incidencije bubrežnog zatajenja u bolesnika liječenih spironolaktonom.[11] U tom se kontekstu od eplerenona, kao antagonista mineralokortikoidnih receptora s većom selektivnosti, očekivao bolji sigurnosni profil i šira rasprostranjenost u svakodnevnoj kliničkoj praksi. Tomu je uveliko pridonijelo randomizirano kontrolirano istraživanje EPHESUS (*Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study*). Ukupno su 6642 bolesnika randomizirana na liječenje eplerenonom ili placebom 3 – 14 dana nakon akutnog infarkta miokarda kompliciranog sistoličkom disfunkcijom lijeve klijetke (ejekcijska frakcija lijeve klijetke (LVEF) <40 %) i kliničkim znakovima popuštanja srca (ili samo sistoličkom disfunkcijom lijeve klijetke; LVEF <40 % u bolesnika sa šećernom bolesti). U usporedbi s istraživanjem RALES, u ovome je većina bolesnika liječena standardnim lijekovima za akutni infarkt miokarda kompliciran zatajivanjem srca (ACE inhibitori ili blokatori angiotenzinskih receptora, blokatori beta-adrenergičnih receptora, acetilsalicilatna kiselina, diuretici). Dokazana je mnogo niža učestalost kardiovaskularne smrtnosti, iznenadne srčane smrti i broja hospitalizacija zbog zatajivanja srca u bolesnika liječenih eplerenonom. Važno je naglasiti kako je ukupno niža kardiovaskularna smrtnost najvećim dijelom rezultat manje pojavnosti iznenadne srčane smrti (čak 21 % niže u ispitivanoj skupini) te da se taj učinak vidio već 30 dana nakon randomizacije, dakle vrlo rano u tijeku liječenja eplerenenom.[12] Jedna od dodatnih analiza istraživanja EPHESUS dokazala je kako se utjecaj primjene eplerenona na ishode u ovih bolesnika postiže samo ako je liječenje započeto unutar 7 dana od infarkta miokarda.[13] Navedeni podatak svrstava eplerenon u jedan od osnovnih lijekova za bolesnike s infarktom miokarda i zatajivanjem srca.

Ukupnoj težini dokaza pozitivnog učinka eplerenona u liječenju bolesnika sa zatajivanjem srca uvelike pridonose i rezultati kliničkog istraživanja EMPHASIS-HF (*Eplerenonein Mild Patients Hospitalization and Survival Study in Heart Failure*). U tom istraživanju na liječenje eplerenonom ili placebom randomizirano je 2737 bolesnika sa zatajivanjem srca i sniženom EF (<30 – 35 %) koji su NYHA II. funkcijskog statusa, te su ili hospitalno liječeni zbog kardiovaskularnog uzroka

Eplerenone in heart failure

MORTALITY AND HEART FAILURE HOSPITALIZATIONS

The RALES study (the Randomized Aldactone Evaluation Study) was the first to give evidence of improved outcomes of patients treated with spironolactone in comparison with placebo. The trial included 1663 patients with chronic heart failure with reduced ejection fraction (average ejection fraction (EF) in the trial was 25%), NYHA class III or IV, that were already treated with standard heart failure therapy at the time (ACE inhibitors, digoxin, diuretics). The trial was terminated early due to significantly lower overall mortality in the group receiving spironolactone.[10] Major objections to the study included exclusion of patients with significant chronic renal failure and the small percentage of patients treated with beta-blockers. The RALES results were not applied so well in clinical practice due to higher incidence of hyperkalemia and renal insufficiency in real-life post-marketing studies.[11] In this context, a better safety profile and wider clinical use was expected from eplerenone, a more selective MRA. The EPHESUS randomized controlled trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) significantly contributed to wider clinical use of eplerenone. 6642 patients were randomized to eplerenone or placebo 3-14 days after myocardial infarction with systolic dysfunction of the left ventricle (EF <40%) and signs of heart failure (or just systolic dysfunction of the LV in patients with diabetes mellitus). In comparison with the RALES study, most of the patients were now treated with standard therapy for myocardial infarction with heart failure (ACE inhibitors or angiotensin-receptor blockers (ARB), beta-blockers, acetyl-salicylic acid, and diuretics). Significantly lower cardiovascular mortality, rates of sudden cardiac death, and less hospitalizations were demonstrated in patients treated with eplerenone. It is important to emphasize that the overall lower rates of cardiovascular mortality were primarily due to lower rates of sudden cardiac death, and this effect was already observed at 30 days post randomization.[12] One of the EPHESUS trial sub-analyses showed that a positive effect of eplerenone on major outcomes was observed only if eplerenone was started early in the course of treatment, i.e. in the first 7 days following myocardial infarction.[13] Given that fact, eplerenone became one of the standard therapies for patients with myocardial infarction and heart failure.

Treatment with eplerenone is also supported by findings of the EMPHASIS-HF trial (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure). In this trial, 2737 patients with heart failure with reduced EF (<30-35%) and NYHA II class were randomized to eplerenone or placebo. Additional criteria that patients had to meet for eligibility was either a cardiovascular hospitalization 6 months prior to randomization or elevated biomarkers (BNP or NT-proBNP). Patients treated with eplerenone had 37% lower cardiovascular mortality and a lower number of heart failure hospitalizations.[14]

Patients with heart failure with preserved EF often have the same signs and symptoms as those with heart failure with reduced ejection fraction. Their mortality is also similar, with significant burden of sudden cardiac death.[15] Therefore, one of the leading problems of modern-day cardiology is the lack

unutar 6 mjeseci prije randomizacije ili su imali povišene koncentracije markera popuštanja srca (BNP ili NT-proBNP). Skupina bolesnika liječenih eplerenonom imala je čak 37 % nižu kardiovaskularnu smrtnost i manji broj hospitalizacija zbog zatajivanja srca.[14]

Bolesnici sa zatajivanjem srca i očuvanom EF u usporedbi s onima sa sniženom EF imaju vrlo često slične simptome i znakove te čak slične stope kardiovaskularne smrtnosti (s velikim udjelom iznenadne srčane smrti i smrti zbog zatajivanja srca).[15] Upravo zato jedan od velikih problema današnje kardiologije jest nedostatak adekvatnih dokaza izravnog utjecaja farmakoloških ili nefarmakoloških intervencija na ishode u toj skupini bolesnika. S obzirom na to da je u bolesnika sa zatajivanjem srca i očuvanom EF patofiziološki također riječ o patološkoj aktivaciji RAAS-a s posljedično negativnom remodelacijom miokarda u smislu intersticijske fibroze i hipertrofije lijeve klijetke, te da se disfunkcija endotela, prema nekim autorima, smatra jednim od ključnih događaja u patofiziologiji ovog sindroma, očekuje se i povoljan učinak antagonista mineralokortikoidnih receptora.[16,17] Manja su klinička istraživanja dokazala pozitivan učinak antagonista mineralokortikoidnih receptora na smanjenje hipertrofije LV-a i pokazatelje dijastoličke disfunkcije, dok utjecaj na ishode u velikim randomiziranim kontroliranim istraživanjima nije dokazan.[18] Jasan signal koristi od spironolaktona dobiven je iz ukupno gledano negativnoga randomiziranog kontroliranog istraživanja TOPCAT (*Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist*). Iako nije dokazan niži mortalitet u bolesnika s očuvanom EF liječenih spironolaktonom, dokazan je manji broj hospitalizacija zbog zatajivanja srca.[19] Dodatne analize ovog istraživanja koje su uključivale samo bolesnike iz Sjeverne i Južne Amerike pokazale su iznimnu geografsku različitost u ishodima, te povoljan utjecaj spironolaktona na kardiovaskularnu smrtnost.[20] Navedeni podatci upućuju na određene profile bolesnika sa zatajivanjem srca i očuvanom EF koji imaju povoljnije ishode liječenjem antagonistima mineralokortikoidnih receptora.[5,21]

UTJECAJ NA EKSCITABILNOST MIOKARDA

Rezultati EPHESUS istraživanja jasno pokazuju pozitivan učinak eplerenona na niže stope iznenadne srčane smrti u bolesnika rano nakon infarkta miokarda sa zatajivanjem srca.[12] Također, prema rezultatima EMPHASIS-HF istraživanja, eplerenon učinkovito snizuje pojavnost fibrilacije atrija u bolesnika sa zatajivanjem srca (čak 42 % u usporedbi s kontrolnom skupinom).[14,22]

EPLERENON U POSEBNIM SKUPINAMA BOLESNIKA

Eplerenon je u EMPHASIS-HF istraživanju zadržao svoj povoljan učinak na ishode čak i u podskupinama bolesnika s očekivano lošijim ishodima, poput onih s anamnezom kronične bubrežne bolesti, šećerne bolesti te u bolesnika starijih od 75 godina.[23]

Rezultati nekoliko manjih kliničkih istraživanja upućuju na moguću veću korist od eplerenona u usporedbi sa spironolaktonom u liječenju bolesnika sa zatajivanjem srca i šećernom bolesti. Naime, takvi bolesnici liječeni spironolaktonom imali su više koncentracije glikiranog hemoglobina i kortizola te lošiju funkciju endotela u usporedbi s onima liječenima eplerenonom, što je moguće posljedica njegove visoke selektivnosti. Ipak, navedene će rezultate trebati potvrditi velikim randomiziranim kliničkim istraživanjima.[24,25]

of evidence-based treatments for patients in this heart failure category. Heart failure with preserved EF shares similar pathophysiological pathways, including adverse activation of RAAS and subsequent negative cardiac remodeling in terms of interstitial fibrosis and left ventricular hypertrophy. Furthermore, some authors consider endothelial dysfunction to be one of the key mechanisms underlying this syndrome. All of these mechanisms indicate a potential role of MRA in patients with heart failure with preserved EF.[16,17] Small studies have shown positive effects of MRA on left ventricular hypertrophy and echocardiographic diastolic function indices, while positive effects on major outcomes have not yet been shown.[18] The clear beneficial signal of spironolactone in this patient population comes from the overall negative RCT TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist). Although the trial did not prove lower mortality overall in patients with heart failure with preserved EF treated with spironolactone, it did show lower incidence of heart failure hospitalizations.[19] Several sub-analysis of the trial focusing only on patients from North and South America showed geographical differences in outcomes and positive effect of spironolactone on cardiovascular mortality in those patients.[20] These data indicate the existence of specific patient profiles that clearly benefit from treatment with mineralocorticoid receptor antagonists.[5,21]

EFFECT ON MYOCARDIAL EXCITABILITY

The EPHESUS trial results showed positive effects of eplerenone on sudden cardiac death in patients soon after myocardial infarction with heart failure.[12] Furthermore, the EMPHASIS-HF study showed significant reduction of its secondary endpoint of atrial fibrillation incidence in the group of patients treated with eplerenone (42% reduction in comparison with the control group).[14,22]

EPLERENONE IN SPECIFIC PATIENT POPULATIONS

In the EMPHASIS-HF trial, outcome benefits of eplerenone were present even in subgroups with greater risk of worse outcomes, such as patients with chronic renal disease, diabetes mellitus, and in those older than 75 years.[23]

The results of a few small studies indicate greater benefit of eplerenone treatment in comparison with spironolactone for patients with heart failure and diabetes mellitus. Patients treated with spironolactone had higher HbA1c and cortisol and worse endothelial dysfunction in comparison with those treated with eplerenone. The selectivity of eplerenone may partially explain this observation. Nevertheless, the results of this studies require confirmation in large RCTs.[24,25]

Eplerenone in treatment of patients with myocardial infarction

Given the anti-inflammatory and anti-fibrotic properties of eplerenone, its early administration following myocardial infarction in patients without heart failure was also studied. The REMINDER clinical trial randomized 1012 patients with myocardial infarction without heart failure to early administration of eplerenone or placebo. Although it did not have the statistical power to assess major outcomes, it did show excellent eplerenone tolerability if administered within 24 hours of

Eplerenon u liječenju bolesnika s akutnim infarktom miokarda

S obzirom na protuupalno i protufibrozno djelovanje eplerenona, razmatrana je i njegova rana primjena u bolesnika s akutnim infarktom miokarda bez zatajivanja srca. U randomiziranom kontroliranom istraživanju REMINDER, 1012 bolesnika s akutnim infarktom miokarda bez zatajivanja srca randomizirano je na ranu primjenu eplerenona ili placeba. Istraživanje nije imalo statističke snage za procjenu velikih ishoda poput smrtnosti, no pokazalo je odličnu podnošljivost eplerenona primijenjenog unutar 24 sata od infarkta miokarda, te mnogo niže koncentracije NT-proBNP-a 30 dana do 18 mjeseci nakon inicijalnog događaja.[26]

Eplerenon u liječenju bolesnika s rezistentnom arterijskom hipertenzijom

Prema posljednjim smjernicama Europskoga kardiološkog društva za liječenje bolesnika s arterijskom hipertenzijom iz 2018. godine, rezistentna arterijska hipertenzija definirana je kao nemogućnost postizanja željenih vrijednosti arterijskoga tlaka (<140 sistoličkoga i/ili manje od 90 mmHg dijastoličkoga) standardnim strategijama liječenja (optimalne ili najviše podnošljive doze inhibitora ACE ili ARB, kalcijskih blokatora i tiazidskih diuretika), te kada su navedene vrijednosti potvrđene kontinuiranim mjerenjem arterijskog tlaka u bolesnika koji se pridržavaju propisanog liječenja. Razinu preporuke I B u liječenju rezistentne hipertenzije ima dodatak spironolaktona u dozi do 50 mg na dan te, u slučaju nepodnošenja spironolaktona, eplerenon u dozama 50 – 100 mg na dan (**Tablica 1**).[27]

Sigurnosni profil eplerenona

U skupinama bolesnika koji su liječeni eplerenonom u velikim randomiziranim kontroliranim istraživanjima zabilježen je znatan porast koncentracije kreatinina i kalija u usporedbi s kontrolnim skupinama, no bez znatnog porasta incidencije zatajenja bubrega. U svim dosadašnjim velikim randomiziranim kontroliranim istraživanjima nije zabilježen smrtni ishod povezan s hiperkalijemijom zbog primjene eplerenona.

myocardial infarction and patients receiving eplerenone had significantly lower NT-proBNP concentrations at 30 days as well as 18 months after myocardial infarction.[26]

Eplerenone in resistant arterial hypertension

The latest European Society of Cardiology guidelines for treating arterial hypertension define resistant arterial hypertension as not achieving target blood pressure values (systolic <140 mmHg and/or diastolic <90 mmHg) by standard treatment (optimal or maximally tolerated doses of ACE inhibitors/ARBs, calcium blockers, or thiazide diuretics), confirmed by ambulatory blood pressure monitoring in patients who are fully compliant to prescribed therapies. Adding spironolactone 50 mg daily, and, if not tolerated, eplerenone in a dose of 50-100 mg daily has the I B recommendation level for management of resistant arterial hypertension (**Table 1**).[27]

Eplerenone safety

In all of the large RCTs patients receiving eplerenone had significantly higher creatinine and potassium, but without difference in renal failure incidence. Furthermore, there was no death attributable to hyperkalemia in any of the trials. Viewed from a different perspective, there is significantly less hypokalemia and less deaths induced by ventricular arrhythmias as a consequence of hypokalemia. Generally, there is a low risk of hyperkalemia in patients with no preexistent renal disease. It is recommended to check potassium levels approximately one month after initiation of therapy. In patients with chronic renal disease, acute exacerbation of chronic renal disease, or who concomitantly take nephrotoxic drugs, potassium and renal function should be monitored more closely.[5,28-30]

Conclusion

Large RCTs have demonstrated the beneficial effects of eplerenone on survival of patients with heart failure with reduced EF. This is the reason why large cardiological societies included eplerenone as one of the essential treatments in

TABLE 1. Eplerenone in European Society of Cardiology Guidelines.

Guidelines	Recommendation	Level of evidence
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[28]	MRAs are recommended in all symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF to reduce mortality and HF hospitalizations.	I A
2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[29]	MRAs are recommended in patients with LV dysfunction (LVEF ≤40%) and heart failure or diabetes mellitus, who are already receiving ACE inhibitor and a beta blocker, provided there is no renal failure or hyperkalemia.	I B
2018 ESC/ESH Guidelines for the management of arterial hypertension[27]	Recommended treatment of resistant hypertension is addition of low-dose spironolactone to existing treatment, or the addition of further diuretic treatment if intolerant to spironolactone, with either eplerenone, amiloride, higher dose thiazide, or loop diuretic.	I B

ESC=European Society of Cardiology; MRA=mineralocorticoid receptor antagonist; ACEI=angiotensin converting enzyme inhibitor; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; ESH=European Society for Hypertension.

Ako na navedeno gledamo iz drugog kuta, postoji jasna korist od prevencije hipokalijemije i mogućih smrti povezanih s ventrikularnim aritmijama izazvanim niskim koncentracijama kalija. Općenito gledano, u bolesnika s normalnom bubrežnom funkcijom mali je rizik od ozbiljne hiperkalijemije. Preporuka je da se koncentracija kalija u serumu kontrolira otprilike mjesec dana nakon uvođenja eplerenona u liječenje. No svakako su češće kontrole kalija potrebne u bolesnika s kroničnom bubrežnom bolesti, akutnim pogoršanjem bubrežne funkcije ili istovremenoj primjeni drugih lijekova koji utječu na koncentraciju kalija.[5,28-30]

Zaključak

Velika randomizirana kontrolirana istraživanja dokazala su jasan učinak eplerenona na pobol i preživljenje u bolesnika sa zatajivanjem srca i sniženom EF, što je i razlog da ga velika svjetska kardiološka udruženja u svojim smjernicama preporučuju kao osnovno liječenje uz ACE inhibitore/blokatore angiotenzinskih receptora i blokatore beta-adrenergičnih receptora. Potrebna su daljnja randomizirana istraživanja kako bi se dobili jasni i izravni dokazi njegova utjecaja na ishode u bolesnika sa zatajivanjem srca i očuvanom EF te u bolesnika s akutnim koronarnim sindromom. Svakako, od velike su važnosti za svakodnevnu kliničku praksu sigurnosni profil eplerenona te njegova dobra podnošljivost koja pridonosi boljoj suradljivosti bolesnika.

their guidelines, in addition to ACE inhibitors/ARBs, and beta-blockers. Further RCTs are needed to confirm the effects of eplerenone on outcomes in patients with heart failure with preserved EF as well as in patients with myocardial infarction and no systolic dysfunction. Eplerenone safety profile is of great importance for everyday clinical practice, as well as its high tolerability that contributes to patient compliance.

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