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Mineralocorticoid-receptor antagonists in the management chronic heart failure: the effectiveness and promising opportunities

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Abstract

This article presents the results of randomized clinical trials on the use of mineralocorticoid-receptor antagonists in patients with myocardial infarction, chronic heart failure in combination with type 2 diabetes mellitus, with and without chronic kidney disease. The review highlights pathogenetic aspects of the implementation of these medications in patients with cardiorenal pathology and its effect on the prognosis. Issues of tolerability and limitations when prescribing various mineralocorticoid receptor antagonists representatives are discussed.

Keywords: *chronic heart failure, myocardial infarction, diabetes mellitus, chronical kidney disease, mineralocorticoid-receptor antagonists, spironolactone, eplerenone, finerenone.*

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Introduction

The prevalence of chronic heart failure (CHF) with clinical manifestations is about 4.5% of general population. Additionally, the amount of patients who require permanent diuretic therapy has increased by 2.5 times since 1998 [1]. The prognosis of patients with CHF can be serious especially in patients with III–IV functional class of CHF where median survival is estimated as 3.8 years [2]. Arterial hypertension (AH) and coronary artery disease (CAD) are the leading causes of CHF [2]. The role of diabetes mellitus (DM) has significantly increased in the development of CHF [2]. The development of micro- and marcrovacular complications of DM can aggravate the course of CHF and deteriorate the prognosis. Various classes of pharmacological agents have proved its efficacy in the decrease of mortality and admissions in patients with CHF with reduced ejection fraction (HFrEF) of the left ventricle, including patients with DM. These agents include: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or angiotensin/neprilysin receptor inhibitors (ARNIs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs). All of them affect the imbalance of neurohumoral systems that cause CHF.

Aldosterone effects

Aldosterone is one of the main components of the renin-angiotensin-aldosterone system (RAAS) that activates in both cardiovascular and renal pathologies. It is synthesized in the cells of the zona glomerulosa of the adrenal cortex from deoxycorticosterone and is considered as one of the most active mineralocorticoids. Aldosterone is locally synthesized in endothelial and smooth muscle cells of blood vessels and myocardium. Aldosterone affects mineralocorticoid receptors (MR) in epithelium as well as in myocardium, blood vessels, kidneys, and the central nervous system. By activating MR, which are nuclear receptors, aldosterone causes transcription of the $\alpha 1$, $\beta 1$ and γ genes that are the subunits of Na+/K+-ATPase in renal cells and, therefore, increases sodium transport across the basolateral cell membrane [4, 5].

Hyperaldosteronemia causes the decrease of potassium and magnesium microelements, followed by the prolongation of the QT interval that serves as a substrate for the development of life-threatening arrhythmias. It has been estabilished that aldosterone activates the Na+/H+ exchanger that leads to hydrogen secretion and sodium reabsorption. The expression of Na+/H+ exchanger isoform 3 (NHE3) in the epithelium of the nephron proximal tubule increases in patients with CHF [6]. The non-genomic effects of aldosterone are exposed through the activation of non-epithelial MR, that leads to the development of endothelial dysfunction in the long-term [7]. Aldosterone not only increases the expression of angiotensin-converting enzyme (ACE) mRNA in cardiomyocytes with local activation of angiotensin II, as well as increases the number of angiotensin II type 1 and endothelin receptors, but also activates the sympathetic nervous system. In addition to its hemodynamic effects and impact on electrolyte balance, aldosterone stimulates the synthesis of types I and III collagen, fibroblast proliferation, and free radical oxidation that leads to cell apoptosis [8, 9].

The effectiveness of spironolactone in patients with CHF

The effectiveness of MRAs that was revealed in randomized clinical trials lead to the inclusion of these pharmacological agents into the clinical guidelines for the management of patients with heart failure with reduced ejection fraction (HFrEF) as the third neurohumoral blocker. The first large-scale RALES trial showed the reduction in the risk of death from any cause by 30% (relative risk (RR) — 0.70; 95% confidence interval (95% CI) — 0.60–0.82; p<0.001), sud-

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den death from cardiac causes — by 31 % (RR 0.69; 95 % CI — 0.58–0.82; p<0.001), death from progressive heart failure — by 36 % (RR 0.64; 95 % CI — 0.51–0.80; p<0.001) in patients with HFrEF who were prescribed with spironolactone at a dose of 12.5–50 mg/day (average dose — 26 mg/day) in addition to ACE inhibitors for 24 months [10]. Most of the participants had NYHA class III of CHF with an average left ventricular ejection fraction (LV EF) of 25 %. The study excluded patients with primary operable valvular heart disease, acute coronary syndrome (ACS), patients who had undergone heart transplantation or were awaiting the procedure as well as with a plasma creatinine level of more than 221 μmol/l and a potassium level of more than 5.0 mmol/l. The RALES trial also showed the effectiveness and safety of combination use of ACE inhibitors and MCAs in patients with HFrEF with aldosterone escape phenomena after long-term therapy with ACE inhibitors or ARNIs. In the main group, the exacerbation of symptoms and the reduction admission risk due to CHF decreased by 35 % (RR 0.65; 95 % CI — 0.54–0.77; p<0.001). Not all the participants from RALES study received optimal therapy for HFrEF. Patients from the observational group received loop diuretics, about 95 % — ACE inhibitors, over 70 % — cardiac glycosides, and only 10 % of patients received BBs. The median creatinine concentration in the spironolactone group increased from 4 to 9 μmol per liter and the median potassium concentration increased by 0.30 mmol per liter compared with the placebo group (p<0.001). Unfortunately, about 10 % of patients did not tolerate the medication due to the development of gynecomastia or pain in the mammary gland. Adverse endocrine effects were more common in the spironolactone group compared with in the placebo group (10 vs. 1, p=0.006).

Evidence base of eplerenone effectiveness in patients with cardiovascular disease and CHF

The long-term use of MRAs in patients with CHF has high risk of side effects development that can lead to discontinuation of the medication, therefore, initiated the invention of selective MRAs. Eplerenone, another MRAs, was included into the guidelines for the patients with CHF. This agent has lower affinity to MR compared with spironolactone, but shows similar antialdosterone effect due to lower plasma protein binding. The high selectivity of eplerenone and low affinity to androgen and progesterone receptors provides better tolerability compared with spironolactone. The results of randomized placebo-controlled EPHESUS trial were published in 2003. The study evaluated the effectiveness of eplerenone in 6.632 patients 3 to 14 days after acute myocardial infarction (AMI), clinical manifestations of NYHA class I–IV CHF and reduced LV EF ⩽ 40 % (mean EF — 33 %) [11]. 32 % of patients had DM, about 15 % of patients had a history of CHF, and about 7 % of them had already been admitted to the hospital due to CHF. Exclusion criteria were the use of potassium-sparing diuretics, a serum creatinine concentration of more than 220 μmol per liter, and a serum potassium concentration of more than 5.0 mmol per liter. The average creatinine clearance (CC) according to the Cockcroft-Goult formula was 79 ml/min. Most of the participants received optimal pharmacotherapy for MI and CHF, including ACE inhibitors or ARNIs (86 %), BBs (75 %), diuretics (60 %), aspirin (88 %), statins (47 %). Coronary reperfusion therapy was performed in 45 % of patients. The mean dose-equivalent of the eplerenone was 42.6 mg. The mean follow-up period was 16 months. The two primary endpoints were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event, including CHF, recurrent AMI, stroke, or ventricular arrhythmia. Eplerenone significantly reduced both all-cause mortality by 15 % (RR 0.85; 95 % CI 0.75–0.96; p=0.008) and the hospitalization for cardiovascular events by 13 % (RR 0.87; 95 % CI 0.79–0.95; p=0.02). The risk of cardiovascular events was reduced by 17 % (RR 0.83; 95 % CI 0.72–0.94; p=0.005); risk of sudden cardiac death — by 21 % (RR 0.79; 95 % CI 0.64–0.97; p=0.03); the risk of hospitalization due to CHF — by 15 % (RR 0.85; 95 % CI 0.74–0.99; p=0.03), in the eplerenone group compared with the placebo group. Patients with LV EF < 30 % and symptoms of CHF showed more pronounced effect of therapy. Hyperkalemia (113 cases vs. 66 cases in the placebo group, p<0.001) and creatinine increase were more frequently registered in the eplerenone group. The rate of serious hyperkalemia (over 6 mmol/l) was more frequent in eplerenone group (180 cases vs. 126 in the placebo group, p=0.002), however, this condition did not increase mortality. The risk of severe hyperkalemia was higher in patients with reduced CC. On the other hand, it is very important to reduce the risk of hypokalemia that is often seen in patients with

CHF who regularly receive diuretics and can increase mortality [12].

In the EPHESUS trial, the risk of hypokalemia was more than twice as high as the risk of severe hyperkalemia, and eplerenone significantly reduced it. Thus, in the eplerenone group, cases of severe hypokalemia were significantly less frequent (potassium level less than 3.5 mmol/l) — 273 cases vs. 424 in the placebo group, p<0.001. Eplerenone did not aggravate the course of endocrine diseases, unlike spironolactone. The incidence of gynecomastia and erectile dysfunction among men in eplerenone group was comparable to the placebo that can be attributed to the fact that eplerenone has greater selectivity for the MR. The study showed the effectiveness of low dose (25 mg / day) of eplerenone in patients during first two weeks after AMI.

The placebo-controlled EMPHASIS-HF trial investigated the effects of eplerenone in patients with HFrEF. The study included 2737 patients with NYHA class II CHF and systolic dysfunction (LV EF of no more than 30% or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography, 26.2% on average) within 6 months after hospitalization for a cardiovascular reason or the plasma level of B-type natriuretic peptide (BNP) of at least 250 pg per milliliter or the plasma level of N-terminal pro-BNP of at least 500 pg per milliliter in men and 750 pg per milliliter in women [13]. Average duration of CHF was 4.7 years. Approximately 1/3 of patients had DM. Participants received medical therapy for CHF: ACE inhibitors and/or ARNIs — 94% of patients; BBs — about 87%; diuretics — 84–85%; antithrombotic agents — 88%. The mean estimated glomerular filtration rate (eGFR) was about 70 ml/min/1.73 m^2. More than 30% of patients had eGFR less than 60 ml/min/1.73 m^2. Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily provided the serum potassium level was no more than 5.0 mmol per liter. In case when the estimated GFR was 30 to 49 ml per minute per 1.73 m^2 the medication was started at 25 mg on alternate days, and increased to 25 mg daily. Then dose adjustment was carried out every 4 months, depending on the results of patients examination. If the serum potassium level was 5.5 to 5.9 mmol per lite, the dose of the medication was decreased, if the serum potassium level was 6.0 mmol per liter or more, it was withheld. Potassium level was remeasured within 72 hours after the dose reduction or study-drug withdrawal, and the study drug was to be restarted when level was below 5.0 mmol per liter. Average eplerenone dose was 39.1±13.8 mg/day. The median follow-up period was 21 months. Thus, the frequency of primary endpoint (cardiovascular event or hospitalization for CHF) decreased by 37% (RR 0.63; 95% CI 0.54–0.74; p <0.001) in the eplerenone group compared with placebo. In the eplerenone group, the risk of death from any cause or hospitalization for CHF was by 35% (RR 0.65; 95% CI 0.55–0.76; p<0.001) lower than in the control group. The drug also reduced the primary outcome in selected subgroups of high-risk patients: among patients aged over 75 years the risk decreased by 34% (RR 0.66; 95% CI 0.49–0.88; p=0.0044); in patients with LV EF less than 35% — by 35% (RR 0.65; 95% CI 0.53–0.78; p=0.0001); in patients with type 2 DM — by 46% (RR 0.54; 95% CI 0.42–0.70; p=0.0001); in patients with eGFR less than 60 ml/min/1.73 m^2 — by 38% (RR 0.62; 95% CI 0.49–0.79; p=0.0001); in patients with blood pressure less than 123 mmHg — by 38% (RR 0.62; 95% CI 0.51–0.79; p=0.0001). Eplerenone reduced both the risk of death from any cause by 24% (RR 0.76; 95% CI 0.62–0.93; p = 0.008) and the risk dearth from cardiovascular event by 24% (RR 0.76; 95% CI 0.61 to 0.94; p=0.01) compared with placebo. The medication significantly reduced the risk of hospitalization for any reason by 23% (RR 0.77; 95% CI — 0.67–0.88; p<0.001), the risk of hospitalization for CHF — by 42% (RR 0.58; 95% CI — 0.47–0.70; p<0.001). The total number of hospitalizations (including second and subsequent hospitalizations) was also lower in the eplerenone group (750, vs. 961 in the placebo group, for a 24% reduction; P<0.001), as were the total numbers of hospitalizations for cardiovascular reasons (509 vs. 699, for a 29% reduction; P<0.001) and hospitalizations for CHF (273 vs. 429, for a 38% reduction; P<0.001). It is also worth noting that the risk of hospitalizations due to renal function impairment and the development of hyperkalemia was comparable between groups.

At 1 month, the mean change in serum creatinine level from baseline was 13.3±30.9 μmol per liter in the eplerenone group, as compared with 6.2±25.6 μmol per liter in the placebo group. At the trial cutoff date, the serum creatinine level had increased from baseline by 8.0±32.7 μmol per liter in the main group and 3.5±35.4 μmol per liter — in the placebo group. At 1 month and at the trial cutoff date, the mean change

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in potassium level from baseline was 0.16±0.51 mmol per liter and 0.16±0.56 mmol per liter in the finerenone group, as compared with 0.04±1.16 mmol per liter and 0.05±0.53 mmol per liter, in the placebo group (P=0.001, p<0.001), respectively. A serum potassium level above 5.5 mmol per liter was reported more frequently (11.8 %) in the eplerenone group than in placebo group (7.2 %) (P<0.001). The frequency of serum potassium level above 6.0 mmol per liter was comparable between groups (p=0.29). A serum potassium level below 4.0 mmol per liter as well as below 3.5 mmol per liter was significantly less frequently reported in eplerenone group (38.8 % and 7.5 % of patients, respectively) compared with the placebo (48.4 % and 11.0 %, respectively) (p<0.001; P<0.001).

The analysis of the eplerenone effectiveness in subgroups showed that its positive effect was more pronounced in women, patients younger than 65 years of age, patients with eGFR less than 60 ml / min / 1.73 m^2, patients with DM. The incidence of gynecomastia did not differ significantly between groups. Algorithm for the prescription and titrating of MRAs doses in patients with CHF was developed based on the results of mentioned above trials and considered the level of eGFR and potassium. Eplerenone not only improved the prognosis and reduced the number of hospitalizations in patients with CHF, but also reduced the risk of CHF development after AMI.

The study of the eplerenone effectiveness in patients with AMI continued in multicentral, randomized placebo-controlled REMINDER trial that included 1012 patients with previously diagnosed CHF. The medication was administered in the first 24-hours after MI with ST-segment elevation [14]. About half of patients had the history of arterial hypertension, average eGFR was 86.5 ml/min/1.73m^2, the number of patients with DM and with eGFR less than 60 ml/min/1.73m^2 was lower in eplerenone group compared with placebo group 12.8 % and 15.4 %; 6.8 % and 10.0 %, respectively.

The study showed that the addition of eplerenone to standard treatment of AMI lead to the significant decrease of primary composite endpoint (cardiovascular mortality, rehospitalization, extended initial hospital stay due to diagnosis of CHF, sustained ventricular tachycardia or ventricular fibrillation, LV EF ⩽ 40 % at 1 month or later after randomization, BNP over reference data) by 42 % (RR 0.58; 95 % CI — 0.45–0.76; p<0.0001) compared with placebo. The effect was due to a 40 % lower risk of the increase of BNP, the main marker of CHF, in eplerenone group (RR 0.60; 95 % CI 0.45–0.79; p=0.0003) compared with placebo. BNP above 200 pg/mL or NT-proBNP above 450 pg/mL (in patients aged below 50); above 900 pg/mL (age 50–75 years), or above 1800 pg/mL (patients older than 75) after 1 month was considered as elevated. The results of the study showed the role of eplerenone in the prevention of CHF development in patients after AMI. The medication was well tolerated. As in other studies involving eplerenone, episodes of hyperkalemia were more frequently recorded in the drug group (p = 0.09). The incidence of severe hyperkalemia (over 6.0 mmol/l) was rare and did not differ from placebo group (p=0.11). Episodes of hypokalemia in patients administered with eplerenone developed significantly less frequently (1.4 %) than in placebo group (5.6 %; p = 0.0002) that is of special importance in patients with AMI since low serum potassium levels are associated with increased risk of arrhythmias and mortality.

Nephroprotective potential of MRAs in patients with CHF and chronic kidney disease (CKD)

According to various data, from 25 to 60 % of patients with CHF have impaired renal function. GFR below 60 ml/min/1.73 m^2 increases the risk of death by more than 2 times in patients with CHF, and by 3.8 times — in patients with HFrEF and renal failure [15]. The kidney dysfunction in patients with CHF is not only associated with poor prognosis, but also with higher risk of repeated hospitalizations (RR 1.95, p<0.001 and RR 1.30, p=0.022, respectively) [16]. The addition of MRAs to standard therapy with ACE inhibitors and ARNIs may provide additional nephroprotective effect. Several meta-analyses have been published in 2009, 2014, 2020 evaluating the effects of selective (eplerenone) and nonselective (spironolactone or canrenone) or nonsteroidal (finerenone) MRAs on major cardiovascular events and death, kidney function, progression to end-stage renal disease and safety of its use in patients with CKD [17]. The authors mention the antiproteinuric and hypotensive effects of MRAs. However, the effect of the addition of MRA to ACE inhibitors or ARNIs on the mortality risk, major cardiovascular events, and renal failure in patients with CKD and

proteinuria remains uncertain. The administration os pharmacological agents from this group can lead to the development of hyperkalemia, acute kidney injury, gynecomastia. The management of patients with CHF and CKD is a difficult task that requires additional monitoring of biochemical parameters and electrolyte balance, dose adjustment of many medications prescribed for pathogenetic therapy of HFrEF.

The effectiveness of finerenone in patients with CHF, type 2 DM and CKD

Finerenone proved to be a promising agent from the MRAs group in patients with concomitant CKD. Similar to eplerenone, the medication is selective mineralcorticoid receptor antagonist and does not affect glucocorticoid, androgen, progesterone and estrogen receptors. Therefore, the risk of side effects that are usually seen in non-selective MCRAs is lower. Unlike eplerenone, finerenone is a derivative of dihydropyridine and does not belong to steroids. The drug has high affinity to MR, and effectively inhibits collagen formation and prevents the development of interstitial fibrosis [18]. Finerenone is not registered in the Russian Federation.

Randomized, placebo-controlled phase 2 study that ended in 2012 showed comparable efficacy of finerenone at dose of 5–10 mg / day and spironolactone at dose of 25–50 mg / day in the reduction of BNP, proBNP and albuminuria in patients with HFrEF in combination with CKD. However, finerenone was associated with significantly lower mean increase of serum potassium level than spironolactone (0.04–0.30 and 0.45 mmol/L, respectively, p<0.0001–0.0107), and lower incidence of hyperkalemia (5.3 % and 12.7 %, respectively, p=0.048) and kidney function impairment [19]. The phase 2b ARTS-HF trial for the first time compared the effectiveness of various finerenone and eplerenone doses in patients with HFrEF decompensation (LV EF 40 % and lower over the last year) that required intravenous diuretics as well as with DM and/or CKD (eGFR of.30 mL/min/1.73 m^2 in patients with DM and 30–60 mL/min/1.73 m^2 in patients without DM) [20]. Over 60 % of patients had CAD, over 70 % had arterial hypertension, and about half of patients had a high/very high level of albuminuria. Most patients from observation group had class III CHF according to NYHA. The average LV EF was about 29 %. All patients received optimal pharmacological therapy for CHF. Participants who received spironolactone, eplerenone, renin inhibitors discontinued its intake 24 hours before randomization (48 hours for spironolactone). All of the 1066 patients included into the program were divided into 6 observation groups. Group 1 received 25 mg per day of eplerenone. The medication was increased to 25 mg once daily on day 30, and to 50 mg once daily on day 60. Patients of the remaining 5 groups received finerenone once-daily at a dose of 2.5, 5, 7.5, 10, or 15 mg, uptitrated to 5, 10, 15, 20, or 20 mg, respectively, on day 30 if the serum potassium level did not exceed 5.0 mmol/L. The medication was discontinued with hyperkalemia over 5.6 mmol/l. The duration of this therapy was 90 days. After that, patients were followed up for another month. The primary endpoint was the percentage of individuals with a decrease of 30 % in plasma NT-proBNP from baseline to day 90 that occurred in 37.2 % of patients in the eplerenone group and 30.9, 32.5, 37.3, 38.8, and 34.2 % in the finerenone groups, respectively (P=0.42–0.88). Except for the 2.5–5 mg finerenone group, the composite clinical endpoint of death from any cause, cardiovascular hospitalization, or emergency presentation for worsening chronic HF occurred numerically less frequently in finerenone-treated patients compared with eplerenone. It is noteworthy that of the parameter decreaseed in 10–20 mg group compared with eplerenone group (HR 0.56, 95 % CI -0.35; 0.90; P=0.02). This can be explained by positive dynamics of individual components of the secondary endpoint in the 10–20 mg finerenone group compared with the eplerenone group: death from any cause (RR 0.13; 95 % CI — 0.02–1.07), cardiovascular hospitalization (RR 0.56; 95 % CI: 0.34–0.93) and emergency presentation for worsening of CHF (RR: 0.58; 95 % CI: 0.33–1.02). The changes in concentrations of galectin 3 and N-terminal pro- collagen III peptide from baseline to Day 90 were not significant. Mean scores of the KCCQ and the EuroQoL Questionnaire improved in all treatment groups. The incidence of adverse events was comparable between groups. Hyperkalaemia (serum potassium concentration ⩾5.6 mmol/L) was observed in 44 patients (4.3 %) with a balanced distribution among the finerenone dose groups and the eplerenone group. Hyperkalemia ⩾5.6 mmol/l was registered in 44 patients (4.3 %) with a uniform distribution between the finerenone groups and the eplerenone group. Hyperkalemia >6.0 mmol/l was

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detected in five patients (1/212 (0.5 %) in the eplerenone group and in 1/164 (0.6 %) and 3/160 (1.9 %) in the finerenone groups at a dose of 7.5–15 mg and 15–20 mg, respectively). However, mean change from baseline to day 90 in serum potassium concentration was greater in the eplerenone group (+0.262 mmol/ L) than in each of the finerenone dose groups (+0.119–0.202 mmol/L). Mean systolic blood pressure decreased approximately by 3 mmHg in all treatment groups. Mean eGFR increased slightly in the two lowest finerenone groups and decreased in the other groups. There were isolated cases of decrease in eGFR by ⩾ 25, ⩾ 30, ⩾ 40 and ⩾ 57 % in all groups. There were five renal events leading to hospitalization: two in the eplerenone group and one each in the finerenone 2.5–5, 7.5–15, and 15–20 mg dose groups. The use of MRAs in patients with HFrEF is pathogenetically justified, but the prescription of medication at a therapeutic dose is often limited by the risk hyperkalemia, kidney function impairment, and the development of endocrine disorders (in nonselective drugs). Therefore, finerenone can become an alternative MR blocker, especially in groups of patients with high risk of hyperkalemia. The results of the ARTS-HF trial contributed to further investigation of new MRAs agents in patients with CHF at a dose of 10–20 mg/day.

The 2018 systematic review and meta-analysis of three studies that included 1520 patients with CHF showed the comparable effect of finerenone to steroidal MRA (spironolactone, eplerenone) in the reduction of the NT-proBNP level. The effectiveness of the medication depended its dose. Finerenone at the dose of 10 mg/day was superior to steroidal MRA (p>0.05). However, the frequency of side effects was significantly lower compared with steroidal MRA at the dose of 25–50 mg/day (RR=0.81; 95 % CI, 0.66–0.99; p=0.04). The serum potassium level in the 10 mg/day finerenone group was lower than in the 25–50 mg/day steroidal MRAs group, and eGFR was higher in patients who received finerenone compared with patients administered with steroidal MRAs (p = 0.05). Based on the meta-analysis, the researchers concluded that finerenone has dose-dependent effect in patients with CHF. The dose of 10 mg/day was comparable to steroidal MRAs at the dose of 25–50 mg/day. At the same time finerenone has less effect on potassium level and eGFR [21].

The investigation of finerenone effectiveness continued in several phase III trials involving over 18.600 patients with DM, CKD, CHF such as FIDELIO-DKD, FIGARO-DKD, FINEARTS-HF. The results of the FIDELIO-DKD study were published in autumn 2020 [22]. The multicentral, randomized, placebo-controlled trial included 5734 patients with CKD and type 2 DM. The study included patients with less than 4.8 mmol/l serum potassium level. The median follow-up period was 2.6 years. Finerenone was administered at 10 and 20 mg/day additionally to hypoglycemic therapy and high doses of RAAS inhibitors (ACE inhibitors and ARNIs). The primary outcome, (composite of kidney failure, a sustained decrease of at least 40 % in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes) decreased in finerenone group by 18 % (RR 0.82; 95 % CI — 0.73–0.93, p=0.0014) compared with placebo. Finerenone reduced the risk of kidney failure by 13 % (RR 0.87; 95 % CI 0.72–1.05), the risk of a sustained decrease in the eGFR ⩾ 40 % from baseline by 19 % (RR 0.81; 95 % CI — 0.72–0.92). During the study follow-up, 4 deaths from kidney disease were registered (2 in each group). The frequency of secondary composite outcome (cardiovascular event, non-fatal MI, non-fatal stroke, or hospitalization for CHF) was lower by 14 % compared with placebo (RR 0.86; 95 % CI 0.75–0.99; p=0.0339) as well as its individual components: cardiovascular event risk by 14 % (RR 0.86; 95 % CI — 0.68–1.08); nonfatal MI by 20 % (RR 0.80; 95 % CI 0.58–1.09) and the risk of hospitalization for CHF by 14 % (RR 0.86; 95 % CI 0.68–1.08). In February 2021, the randomized, placebo-controlled, phase III FIGARO-DKD trial that started in 2015 has ended [23, 24]. The median follow-up was 3.4 years. This trial included a population of patients with type 2 DM and CKD (7437 patients) similar to FIDELIO-DKD, but the primary outcome assessed the effectiveness and safety of finerenone in the reduction of cardiovascular events, non-fatal MI, non-fatal stroke, or hospitalization for CHF frequency. Secondary outcome included: time to kidney failure (sustained decrease from baseline of ⩾40 % in GFR, or death from renal cause); time to death from any cause; time to hospitalization for any reason; change of albumin / creatinine ratio 4 months after medication prescription compared with baseline; time to first occurrence of a combined endpoint (onset of kidney failure, a sustained decrease from baseline ⩾ 57 % eGFR for

at least 4 weeks, or death from renal cause). The study included patients with moderate albuminuria (albumin/creatinine ratio over 30 mg/g and less than 300 mg/g in the urine) and eGFR from 25 to 90 ml/min/1.73 m^2 (CKD stages 1–4) and patients with severe albuminuria (albumin/creatinine ratio from 300 mg/g to 500 mg/g) and eGFR of at least 60 ml/min/1.73 m^2 (CKD stages 1–2). Potassium level over 4.8 mmol/L was an exclusion criterion. The mean age of participants was 64.1±9.8 years. About 45% of patients had a history of cardiovascular disease. In the majority (over 60%) of patients, eGFR was over 60 ml/min/1.73 m^2, and the mean value of albumin/creatinine ratio was 308 mg/g. About 98% of patients permanently received hypoglycemic therapy, and only 8.4% received sodium-glucose co-transporter-2 (SGLT2) inhibitors and 7.5% — glucagon-like peptide-1 (GLT-1) agonists. The initial dose of medication depended on the eGFR. Patients with an eGFR of 25–60 ml/min/1.73 m^2 at the screening visit received an initial dose of 10 mg once daily, and those with an eGFR of ≥60 at the screening visit received an initial dose of 20 mg once daily. An increase in the dose to 20 mg was encouraged, in case when the serum potassium level was ≤4.8 mmol/L and the eGFR was stable. With hyperkalemia was over 5.5 mmol/l, the drug was discontinued. Finerenone showed its effectivenes in the significant reduction of the primary outcome by 13% compared with placebo (RR 0.87; 95% CI 0.76–0.98; p=0.03). The result was largely due to the decrease of the frequency of hospitalizations for CHF (RR 0.71; 95% CI 0.56–0.90). Events of the secondary combined outcome were less frequently recorded in the finerenone group (in 350 patients — 9.5%) than in the control group (in 395 patients — 10.8%) (RR 0.87; 95% CI — 0.76–1.01). The medication also demonstrates good tolerability that was comparable to placebo. However, in the main group, hyperkalemia was registered more often (in 1.2% of patients), which required discontinuation of the medication, compared with the placebo group (in 0.4% of patients). Episodes of hypokalemia were almost 2 times less common in the finerenone group. The analysis of the adverse events associated with COVID-19 development displayed lower number of complications in finerenone group, including severe cases, compared with placebo (38 — 1.0% vs. 63 — 1.7%). The results of performed studies showed that among patients with HFrEF, type 2 DM, CKD, finerenone can be an effective treatment choice. The FIGARO-DKD study revealed a positive effect of finerenone on the prognosis in patients with the initial stages of CKD (stages 1–2).

In 2020 the study of the the effectiveness and safety of finerenone in patients with symptomatic CHF with moderately reduced and preserved LV EF was initiated. Unfortunately, to this date, there is not enough evidence of a positive effect on the prognosis of any medication in this group of patients, therefore, the FINEARTS-HF study (NCT04435626) is highly relevant. According to the information published in the U.S. National Library of Medicine Clinical Trials Database, this is a multicenter, randomized, placebo-controlled study of 5.500 patients aged over 40 years with NYHA II–IV classes of CHF, LV EF ⩾ 40%, who regularly received diuretic treatment for at least 30 days prior to randomization, and have one of the following structural heart changes: left atrial diameter (LAD) ⩾3.8cm, left atrial area (LAA) ⩾20cm^2, left atrial volume index (LAVI) >30 mL/m^2, left ventricular mass index (LVMI) ⩾115 g/m^2 (in men)/ 95 g/m^2 (in women), septal thickness or posterior wall thickness ⩾1.1 cm. Patients with eGFR < 25 ml/min /1.73m^2, plasma potassium level > 5.0 mmol/l, acute myocarditis, MI, coronary artery bypass grafting, stroke or transient ischemic attack within 90 days prior to randomization, percutaneous coronary intervention within 30 days prior to randomization, with an alternative cause of CHF symptoms were excluded from the study. The planned follow-up period for patients is 42 months. The dose of finerenone depended on the eGFR. For participants with an eGFR ⩽60 mL/min/1.73m^2: starting dose is 10 mg per day and maximum dose — 20 mg per day. For participants with an eGFR >60 mL/min/1.73m^2 starting dose is 20 mg per day and maximum dose — 40 mg per day. The effectiveness of the medication will be assessed by its impact on the risk of cardiovascular event and the course of CHF. The study also intends to study the dynamics of patients' life quality by using the Kansas City Cardiomyopathy Questionnaire (KCCQ) after 6, 9, 12 months of treatment, renal outcomes (sustained decrease in estimated glomerular filtration rate (eGFR) ⩾40% relative to baseline over at least 4 weeks, or sustained eGFR decline <15ml/min/1.73m^2 or initiation of dialysis or renal transplantation), risk of death from any cause.

Conclusion

The review of clinical trials presented in this article clearly demonstrates the effectiveness of MRAs in patients with MI, CHF in combination with type 2 DM and CKD. The use of MRAs in patients with HFrEF is necessary, but in some cases it is limited by high risk of hyperkalemia and impaired renal function development, especially in groups of patients with concomitant DM and CKD. The evidence obtained for the effectiveness and safety of the non-steroidal MRA finerenone shows that it can be widely used in patients with severe course of the disease and poor prognosis. Further studies on the use of the combination therapy of finerenone and of hypoglycemic agents (such as SGLT2 inhibitors and GLT-1 agonists) with proven nephroprotective effect is required. This combination may contribute to the long-term reduction of cardiorenal risk. The results of ongoing trials, as well as the initiation of new ones involving patients with Herat failure with preserved ejection fraction, will allow to develop more specific patient-oriented guidelines for the management of patients with high risk and several comorbid pathologies.

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