The role of mineralocorticoid receptor antagonists in the prevention and treatment of chronic heart failure after acute myocardial infarction.

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Summary

This review article examines the role of mineralocorticoid receptor antagonists (AMP) in the treatment of heart failure (CH) in patients who have suffered acute myocardial infarction (AMI). The pathogenetic basis of the effect of AMPs on myocardial remodeling after AMI is considered. The pharmacological characteristics of drugs of this class are described: spironolactone and eplerenone. The results of the main studies proving the protective role of eplerenone in patients who have suffered AMI with HF of varying severity (EPHESUS, EMPHASIS-HF, ALBATROSS, REMINDER) are covered. The effectiveness of eplerenone was analyzed depending on the timing of its administration. The safety of the drug in comparison with spironolactone was considered. In conclusion, it was concluded that it is advisable to use these drugs in routine therapy in acute, subacute and long-term periods of ST-segment elevation AMI and with a left ventricular ejection fraction ≤40%, heart failure or diabetes mellitus, when patients already receive angiotensin-converting enzyme inhibitors and beta blockers and in the absence of renal failure or hyperkalemia. In this case, preference should be given to eplerenone as a drug having the most convincing evidence base and having a favorable tolerance profile. The introduction into medical practice of effective, accessible generics of eplerenone allows expanding its use in real clinical practice.

Key words: myocardial infarction, complications, heart failure,cardiac remodeling, eplerenone. Ipleron

Introduction

Heart failure (HF) is one of the most common causes of death and hospitalization in developed countries. According to epidemiological data published in 2007, the prevalence of HF in the Western world is 1–2%, and the incidence approaches 5–10 cases per 1000 people per year [1]. The prevalence of HF increases with age from <1% among those under 55 years of age to 10% among those 80 years of age [1]. In the Russian Federation, chronic heart failure (CHF) is also among the main nosologies in the structure of cardiovascular diseases (CVD). One of the main reasons for the development of CHF is still acute myocardial infarction (AMI) at the time of its manifestation or in history (post-infarction cardiosclerosis, PIC). The proportion of such patients in 2016 was 15.3% [2], while in 1998 it was only 9.8%, i.e., the importance of AMI as an etiological factor of CHF is increasing. The increase in the number of such patients is due to the longer survival of patients with acute coronary syndrome (ACS). Despite the constant improvement of treatment methods for ACS, allowing for timely myocardial revascularization [3], left ventricular (LV) dysfunction and acute HF (AHF) in AMI still develop quite often. According to a retrospective analysis, the incidence of AHF development is more than 30% at the time of hospitalization; in another 5–8% of patients with AMI, AHF develops during the hospital period [4]. These data have been confirmed in such large registers as ADHERE, EURO HART survey, NRMI [5].

Cardiac remodeling after AMI: features and mechanisms

The process of post-infarction remodeling of the heart, including dilatation of its cavities, changes in geometry and impaired contractility of the LV, begins in the first hours of AMI and ends by 2–6 months. diseases. Cardiac remodeling is defined as a general adaptation process that allows cardiomyocytes and the collagen network to adapt to a changed environment. Remodeling due to AMI has a number of features. For example, it is asymmetrical and associated with the localization of the necrosis zone [6]. The literature covers in detail the mechanisms of LV remodeling after AMI without restoration of reperfusion [7]. However, remodeling also occurs in patients with AMI and successful myocardial reperfusion. Early resumption of perfusion of the

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myocardial area subjected to acute ischemia limits the size of the zone of cardiomyocyte death, thereby reducing the likelihood of both death and the development of AHF [8]. But still, due to the initial loss of cardiomyocytes and, as a consequence, a decrease in the contractile function of the heart, all the main stages of remodeling are preserved. The pathophysiological basis of this process, according to modern concepts, is the activation of neurohumoral mechanisms. In response to the development of acute ischemia, levels of norepinephrine, cytokines, endothelin, vasopressin, angiotensin II (AT II) and aldosterone increase. An increase in aldosterone synthesis is realized through the activation of type 1 AT II receptors, an increase in the cardiac level of AT II and the activity of aldosterone synthase mRNA [9]. High levels of aldosterone in plasma and urine in patients with AMI are detected already in the first hours and reach a maximum by the 3rd day of the disease. In 58% of patients, aldosterone levels remain high in the long term [10]. Like any adaptation process, the initial activation of the sympathoadrenal system and the renin-angiotensin-aldosterone system (RAAS) serves as a protective mechanism, the action of which is aimed at compensating for developing hemodynamic disorders (decreased cardiac output, decreased circulating blood volume). However, during the chronic course of the disease, hyperactivation of these initially physiological processes occurs, as a result of which they acquire a pathological character. Thus, it was found that aldosterone plays a major role in the development of a number of negative clinical manifestations: sodium and fluid retention, endothelial dysfunction, LV hypertrophy and fibrotic changes in the myocardium [11, 12]. It has been proven that increased levels of aldosterone and AT II are associated with higher mortality in patients with CHF [13]. High aldosterone levels have shown to be a negative predictor of survival in patients after AMI. So, in patients with a high ($\geq$141 pg/ml) aldosterone concentration in the blood, the risk of death within 5 years after AMI is 2 times higher than with a low (<83.2 pg/ml) concentration [14].

The main result of exposure to ischemia and vasoactive peptides is an increase in the synthesis and concentration of collagen [15, 16], which prevails over its breakdown and, as a consequence, the progression of myocardial fibrosis. The cause of the development of CHF is, therefore, not only the loss of muscle tissue as a result of necrosis, but also the development of fibrosis, which is the decisive factor in this process. These mechanisms are closely interrelated. Several months after AMI, zones of hibernation and apoptosis in the myocardium still remain in combination with areas of fibrosis, with loss of myocardial substance and partial inability to adapt and regenerate. It is fibrosis that is the main marker of CHF and a decisive indicator of myocardial heterogeneity, which increases diastolic stiffness and the tendency to arrhythmias. Today, aldosterone, as the main participant in the fibrotic process, is considered as the most important neurohumoral factor in the development of the so-called electrical remodeling of the myocardium in CHF and after AMI. In particular, it has been proven that aldosterone is involved in changing the function of ion channels in the cardiomyocyte membrane and disrupting repolarization. In AMI, this process develops already in the early stages, preceding disturbances in the structure and function of the LV. It serves as a predictor of life-threatening ventricular arrhythmias and sudden cardiac death (SCD). Research in recent decades has proven that the negative role of hyperaldosteronism in CHF is also associated with the development of perivascular inflammation, endothelial dysfunction and vasculopathy, and the induction of oxidative stress in cardiomyocytes [9, 17, 18]. The important role of aldosterone in the pathogenesis of cardiac remodeling after AMI determines the leading role of blockade of the RAAS (and aldosterone) in the treatment and prevention of HF in these patients.

The role of mineralocorticoid receptor antagonists in the prevention and treatment of HF after AMI
Previously, it was believed that the use of angiotensin-converting enzyme inhibitors (ACEIs) and AT II receptor blockers (ARBs) provides sufficient suppression of aldosterone activity. However, it has been shown that in 38% of patients taking ACE inhibitors for a long time, on the contrary, there is an increase in aldosterone levels [19, 20].

In one study, patients receiving both an ACEI and an ARB II had significantly lower aldosterone levels at week 17. therapy, however, at the 43rd week. treatment, this effect was leveled out [21]. This phenomenon is called the "aldosterone escape effect." It is based on several pathophysiological mechanisms, and the leading one is the reactivation of AT II (stimulator of aldosterone release) during long-term therapy with ACE inhibitors [19]. Moreover, the "aldosterone escape effect" develops in patients regardless of the dose of ACEI [22]. In addition, there is evidence that some aldosterone is synthesized directly by endothelial cells,

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cardiomyocytes and smooth muscle cells of blood vessels, while ACE inhibitors and ARB II affect only the synthesis of aldosterone by the adrenal glands [23]. At the same time, there is an opinion that it is the local synthesis of aldosterone in the heart that plays a leading role in post-infarction remodeling [9].

Regardless of the mechanism, the "aldosterone escape effect" can reduce the effectiveness of ACE inhibitors and ARB II, which entails a worsening prognosis of patients with CHF. This serves as an additional argument in favor of prescribing drugs with "antialdosterone" action, mineralocorticoid receptor (AMP) aldosterone antagonists, to this category of patients.

Unfortunately, these drugs often remain unclaimed in real clinical practice. Moreover, low adherence to treatment with them concerns both patients ("why do I need diuretics if there is no swelling") and doctors. According to statistics in the USA, these drugs are prescribed to only 32% of those patients for whom they are indicated [24, 25]. In European countries, this figure was 33–36% in 2012 [26]. In the Russian Federation, the proportion of patients taking spironolactone, according to the EPOCHA study (2014) [2], is only 11%. It is these drugs that are most often "lost" during long-term therapy for CHF. Discontinuation of antimicrobial therapy in patients with CHF was noted in 54.7% of cases [2].

As you know, the AMP class includes 3 drugs: spironolactone, eplerenone and canrenone, which is not registered in the Russian Federation. Each of them has characteristics that distinguish it from the rest. Spironolactone, a non-selective competitive AMP, is structurally similar to progesterone. As a result, in addition to the basic properties inherent in AMP, it has the properties of a weak androgen and corticosteroid receptor antagonist and progesterone receptor agonist. This can naturally lead to side effects such as impotence, gynecomastia, menstrual irregularities, hirsutism and decreased libido [9]. Spironolactone is a prodrug; its active metabolites, canrenoate and canrenone, are formed in the liver, have a half-life of 17 to 22 hours and are eliminated in bile and urine. Eplerenone is a spironolactone derivative that is a selective AMP and therefore does not cause clinically significant sexual side effects. The half-life of eplerenone is 4–6 hours and is eliminated by the kidneys, liver, and gastrointestinal tract [9].

Clinical efficacy of mineralocorticoid receptor antagonists

Below we present data from the main studies that have proven the effectiveness of AMR for CHF, including those developed as a result of AMI. The first data on the positive effect of spironolactone on the course of severe CHF were obtained during the multicenter placebo-controlled study RALES (Randomized Aldactone Evaluation Study) in 1999 [27]. Taking spironolactone in addition to standard therapy for CHF in patients with severe CHF (NYHA functional class III–IV) with reduced LV ejection fraction (EF) of ischemic and non-ischemic etiology led to a reduced risk of serious complications and increased patient survival. The use of spironolactone reduced the number of cases of SCD and death from progressive circulatory failure, as well as the number of hospitalizations due to decompensated CHF [27]. Patients with PICS were not included in a separate group in this study. However, a number of studies have shown the promise of using this drug after AMI. It has been proven that taking spironolactone can prevent LV myocardial remodeling after AMI, even in patients taking ACE inhibitors. Spironolactone suppresses excess synthesis of the N-terminal fragment of procollagen III after AMI [28]. Similar results—suppression of myocardial fibrosis and remodeling—were obtained in a study in which eplerenone was administered in combination with an ARB II [29]. A number of studies have shown that blockade of aldosterone receptors in the early stages - within 7 days [30] or 4 weeks. [31] after AMI—reduced fibrosis in viable myocardium. Moreover, the addition of spironolactone to ACEI therapy in rats with HF after AMI significantly increased the bioavailability of nitric oxide [32]. Eplerenone experimentally reduced oxidative stress [33]. Animal and human studies have shown other cardiac and peripheral effects of AMPs, including eplerenone: inhibition of the development of inflammatory lesions of the coronary arteries, myocardial and atrial remodeling [34], improvement of vasomotor reactivity [35] and anti-inflammatory nephroprotective effect [36].

The effectiveness of eplerenone after AMI was studied in a large randomized, double-blind, placebo-controlled study, EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) [37]. The study included patients on days 3–14 after AMI with LVEF <40%. A mandatory condition was at least one-time registration of clinical symptoms of HF. An exception was made for patients with diabetes mellitus (DM), since in this case the risk of developing cardiovascular complications (CVD) is so increased that it was considered similar to that in patients with symptoms of HF but without DM. The study

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included 6642 patients. Patients received standard therapy for CHF, 87% received ACE inhibitors. In 16 months During follow-up, there were 478 deaths in the eplerenone group and 554 deaths in the placebo group (HR 0.85; p=0.008). Of these, 407 deaths in the eplerenone group and 483 in the placebo group occurred from cardiovascular causes (RR 0.83; p = 0.005) [37]. Eplerenone reduced the risk of the other primary endpoint of cardiovascular death or hospitalization for cardiovascular disease by 13% and the risk of the secondary endpoint of death from any cause or any hospitalization by 8% (p=0.02). There was also a reduction in the incidence of SCD (RR 0.79; p=0.03). Thus, the decrease in cardiovascular mortality was primarily due to a decrease in the incidence of SCD. The reduction in the risk of death due to progressive CHF and AMI was also significant, but not as impressive. The effectiveness of eplerenone was independent of age, serum potassium and creatinine concentrations, LVEF, pulse pressure, therapy received, and whether or not reperfusion therapy was performed. However, the authors make the caveat that this study was not sufficiently powered to responsibly assess the effectiveness of the drug in different subgroups [37]. Importantly, the positive effects of eplerenone on long-term survival and CVD are not determined by its early potassium-sparing or diuretic effects [38]. Apparently, it is due to the ability of the drug to eliminate electrical instability of the myocardium, which is especially significant in the early stages of the development of AMI. From a practical point of view, the analysis of the effectiveness of eplerenone depending on the timing of its administration, published by Ch. Adamopoulos et al. (Table 1) [39]. Early prescription was associated with a 31% reduction in the risk of all-cause death, CVD death and hospitalization for CVD by 24%, and SCD by 34% (Table 1). When adjusted for various additional risk factors, the benefit of early initiation of eplerenone therapy was a 36% reduction in the risk of all-cause death, CVD death or hospitalization for CVD by 18%, and SCD by 26%. The feasibility of early administration of MRA (single intravenous administration of potassium canrenoate followed by oral spironolactone) in AMI, regardless of the presence of LV dysfunction, was studied in the ALBATROSS study, the results of which were published in 2016 [40]. There was a reduction in the risk of death in the AMR group compared with the standard therapy group (HR 0.20; p = 0.0044) in the ST-segment elevation MI subgroup (1,229 people), but not in the non-STEMI subgroup (374 person). In the REMINDER (Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction) study, 1012 patients with AMI with pST without HF were randomized to receive eplerenone/placebo in the first 24 hours after onset of symptoms [41]. After 10.5 months. primary composite endpoint (cardiovascular death, readmission or prolonged hospital stay due to HF, sustained ventricular tachycardia or fibrillation, EF <40%, or increased B-type natriuretic peptide (BNP)/N-terminal natriuretic B-type peptide (NT-proBNP) was recorded in 18.2% of patients in the study group versus 29.4% in the placebo group (p < 0.0001), but the difference was mainly due to BNP levels. A logical extension of the EPHESUS study was The EMPHASIS-HF study [42, 43], which included 2737 patients with HF with NYHA class II and EF not more than 35%. Approximately half of those included had a history of AMI. The result was evidence that even in patients on adequate therapy and initially well compensated, the addition of eplerenone improved the clinical course and prognosis of CHF.The addition of eplerenone led to a reduction in the risk of death from cardiovascular causes or hospitalization due to CHF by 37% (p<0.001), a reduction in the risk of death from cardiovascular causes by 24 % (p=0.01) and the number of hospitalizations due to decompensation of CHF by 42% (p<0.001). Of particular note is that in the eplerenone therapy group the risk of atrial fibrillation was lower by 42%. The effect of eplerenone was independent of age, gender, race, concomitant therapy, blood pressure, renal function, LVEF and the etiology of CHF.

Table 1. Cardiovascular complications in patients with AMI and CHF depending on the timing of initiation of eplerenone therapy (EPHESUS study) [39]			
Cardiovascular complications	Early initiation (3-7 days),n=1388, eplerenone vs placebo	Late initiation (7-14 days), n=1925, eplerenone vs placebo	Early initiation vs late initiation

Death (all cases)	| OP 0.69 (95% CI: 0.57–0.85), p=0.001 |	OP 0.94 (95% CI: 0.80-1.10), p=0.45	OP 0.74 (95%CI: 0 I: 0.60-0.90), p=0.02
Sudden cardiac death	| OP 0.66 (95% CI: 0.55–0.88), p<0.0001 |	OP 0.69 (95% CI: 0.78–1.33), p=0.85	OP 0.82 (95%CI: (95%CI: 0.51 -0.99), p=0.04
Death from CVD or hospitalization for CVD	OP 0.76 (95% CI: 0.66-0.80), p<0.0001	OP 0.69 (95% CI: 0.841.05), p=0.30	OP 0.71 (95% CI: 0.71-0.94), p=0.006

Eplerenone or spironolactone:

Eplerenone has demonstrated a good safety profile. The most common side effect was the development of hyperkalemia. Thus, in the EPHESUS study [38], the incidence of significant hyperkalemia was 5.5% in the eplerenone group and 3.9% in the placebo group (p = 0.002). More often, this complication, as expected, occurred with initially low creatinine clearance (<50 ml/min). On the other hand, the incidence of hypokalemia (a non-less serious complication) was 8.4% in the eplerenone group versus 13.1% in the placebo group (p=0.002). Obviously, therapy with eplerenone, like spironolactone, requires careful monitoring of electrolyte balance and renal function. However, such control is necessary for all patients with CHF. The main conclusion to be drawn is that this hyperkalemia is predictable, manageable and non-fatal [44]. The dual route of elimination makes it easier to "manage" this drug. Another side effect of spironolactone is less well known. Studies have shown that it is able to increase the level of glycated hemoglobin (HbA1c) and aggravate endothelial dysfunction in patients with type 2 diabetes [45]. In direct comparison with eplerenone [46], spironolactone increased not only HbA1c but also cortisol levels, while simultaneously decreasing adiponectin levels. Eplerenone did not produce such effects. Therefore, eplerenone is the optimal choice for type 2 diabetes, visceral obesity, and metabolic syndrome [47].

To date, the efficacy and safety profile of spironolactone and eplerenone have not been directly compared. Recommendations for the treatment of CHF in AMI [48, 49] mention MRA without specifying a specific drug. Most doctors prefer the more familiar drug, spironolactone [9]. However, it should be remembered that, firstly, eplerenone has a wider evidence base. It is for him that the effectiveness of early initiation in AMI, as well as in patients with FC II CHF with low EF, has been proven. Secondly, eplerenone has a more favorable tolerability profile, therefore, patients taking this drug demonstrate higher adherence to therapy [50]. When choosing an AMR, price is often the determining factor. It is the high cost that prevents the widespread use of eplerenone. This problem is intended to be solved by the introduction into medical practice of more accessible and no less effective generics of eplerenone [9]. One of them, Ipleron (Sinton Spain, S.L.), is produced in Spain according to GMP standards. A comparative study of the bioequivalence of the original eplerenone (film-coated tablets, 50 mg) and Ipleron (film-coated tablets, 50 mg) gave positive results (Fig. 1).
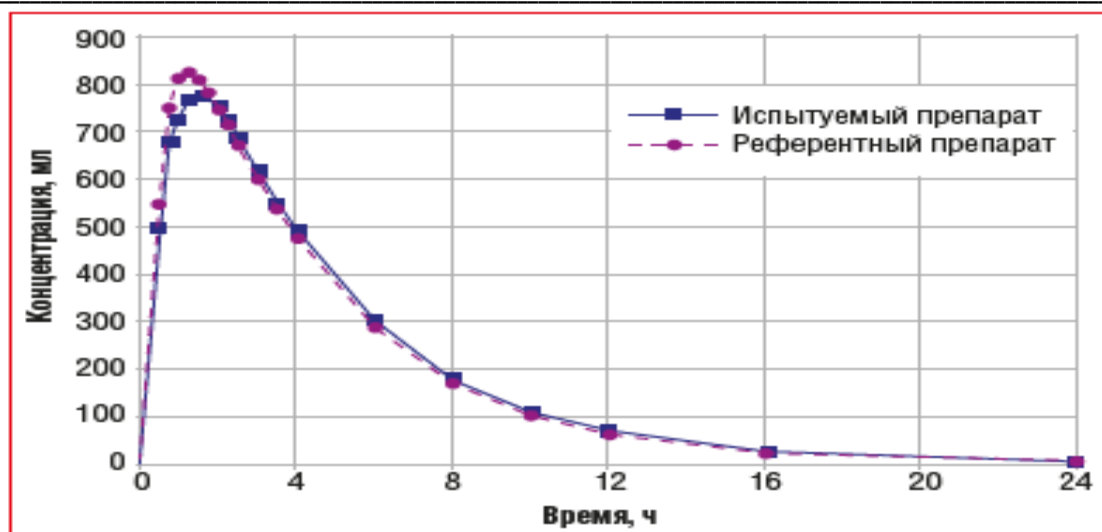
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Рис. 1. Концентрация эплеренона в плазме

Conclusion

Thus, in routine therapy in the acute, subacute and long-term periods of AMI with pST, AMPs are recommended for patients with LVEF ≤ 40%, HF or DM who are already receiving ACE inhibitors and beta-blockers, provided there is no renal failure or hyperkalemia [49]. Moreover, strictly speaking, these recommendations relate specifically to eplerenone as the drug that has the most convincing evidence base. The introduction of effective, affordable generic versions of eplerenone, such as Ipleron, is helping to expand its use in real-world clinical practice.

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