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Three ages of spironolactone. Evolution of views on spironolactone capabilities in the treatment of patients with heart failure

The article presents in a historical context the discovery of aldosterone and the creation of its antagonist, spironolactone. The article also describes the aldosterone effects related with stimulation of two receptor types, slow (nuclear or genomic) and rapid (membrane). These effects are evident not only as the influence on water-salt metabolism and extracellular fluid volume but also as regulation of vascular tone and vascular wall elasticity and, most interestingly, as the impact on heart remodeling. In the early period after spironolactone creation, it was considered exclusively as a drug for the regulation of water-salt metabolism, diuresis, and blood pressure. Later, the use of spironolactone covered a new field, systolic heart failure. This treatment was considered not only for enhancing safe diuresis but also for eliminating the aldosterone escape phenomenon of angiotensin-converting enzyme inhibitors. The change in the paradigm of heart failure towards the prevalence of its diastolic phenotype, which is based on excessive diffuse myocardial fibrosis, has put spironolactone in demand as an independent drug due to its strong antifibrotic effect that inhibits the entire complex of endo- and paracrine effects of aldosterone.

Keywords Aldosterone; HFpEF; spironolactone; fibrosis

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2024 will be the 70th anniversary of the discovery by Simpson and Tate of aldosterone, a steriod hormone of the adrenal cortex with mineralocorticoid activity. The history of studies and subsequent clinical application of aldosterone began with the works by J. Cohn, who described the syndrome of arterial hypertension and hypokalaemia in patients with autonomous adrenal cortex tumors [1]. The attention had been focused for a long time on stimulating of specific cytosolic (nuclear) receptors in the distal renal glomeruli with aldosterone, which resulted in the retention of sodium ions and water and the elimination of potassium ions. Thus, extracellular ion homeostasis and blood pressure (BP) sufficient for adequate perfusion of vital organs is supported. Blockade of these receptors by aldosterone antagonists (AA), such as spironolactone, on the contrary, leads to the elevation of serum K^+, and decrease in Na^+, increased urine output, and lower BP. On this ground, AAs were called "potassium-sparing diuretics" for a long time and were popular, mainly, as safe concomitant drugs to enhance the diuretic effect of loop or thiazide diuretics. However, since the early 1990s, after the discovery of multiple organ membrane receptors for aldosterone, it was shown that aldosterone influences the cardiovascular system not only through the kidneys and urine output, but also directly affecting the smooth muscle cells of the vascular walls, the skeletal muscles, and cardiomyocytes and fibroblasts of the myocardium [2]. The two types of receptors provide various short-term (membrane) and long-term (nuclear or genomic) effects of aldosterone, which manifest not only by the effects on water-salt metabolism and the volume of extracellular fluid, but also by the regulation of vascular tone, vascular wall elasticity, and, most interestingly, the effect on the cardiac remodeling processes. The latter is associated, including but not limited to, with the paracrine/autocrine activity of aldosterone synthesized by the myocardium [3]. Numerous factors stimulate aldosterone synthesis, including adrenocorticotropic hormone (ACTH), K^+ and Na^+ imbalance, endothelin, and some other neurohumoral modulators. However, the key factor is the stimulatory effect of angiotensin II (AII).

Fundamental studies of the chronic heart failure (CHF) mechanisms conducted by the end of the last century, created awareness of the role of the renin-angiotensin-aldosterone system (RAAS) hyperactivation in the pathogenesis of heart muscle damage, which manifests morphologically as structural changes in the heart muscle, i.e., cardiac remodeling. Heart muscle damage, commonly of ischemic nature, is followed by a decrease in cardiac output and results in reduced renal blood flow, which leads to a compensatory increase in the production of renin activating the cascade growth of AII synthesis, which, in turn, stimulates the synthesis of aldosterone. Excess aldosterone acts as an efferent remodeling tool based on fibroblast hyperstimulation in

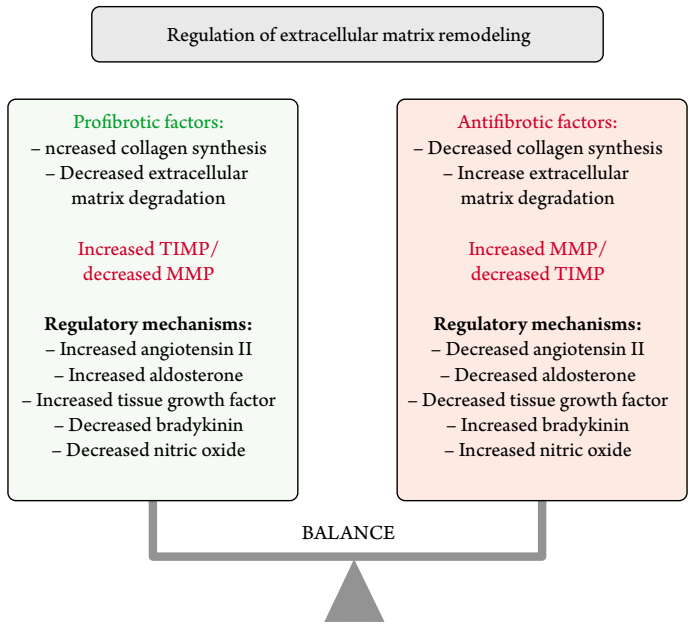
the heart muscle tissue with hypersynthesis of collagen (matrix) in the intercellular space. The mechanisms of the intercellular matrix balancing are complex (Figure 1), but aldosterone seems to have the priority role.

This neurohumoral concept of cardiovascular regulation was implemented in the therapeutic setting as RAAS blockade with the suppression of AII synthesis and the corresponding indirect reduction in aldosterone synthesis using angiotensin-converting enzyme (ACE) inhibitors. The first results of randomized clinical trials of this class of drugs in patients with systolic CHF showed that this approach is amazingly effective in reducing the relative risk of death by 23 % on average [4], and ACE inhibitors were first drugs to increase life expectancy in patients with this form of heart failure [5].

However, the administration of only ACE inhibitors could not solve the problem of CHF: firstly, we wanted to achieve a more significant result, and, secondly, ACE inhibitor therapy became ineffective in some patients over time. One of the causes of the lack of efficacy was detected later and named the phenomenon of "aldosterone escape". Numerous studies showed that, if a week after the beginning of ACE inhibitor therapy, the level of aldosterone significantly decreased, it began to increase again several weeks later and reached the same values in the coming months [6, 7]. Aldosterone escape is also observed during the use of AII receptor blockers (ARBs) and beta-blockers (BBs) [8]. This phenomenon can be explained by the activity of alternative pathways for aldosterone stimulation (Figure 2) after the elimination of the stimulating effect of AII due to ACE inhibitor therapy, and its levels increase again [6–8].

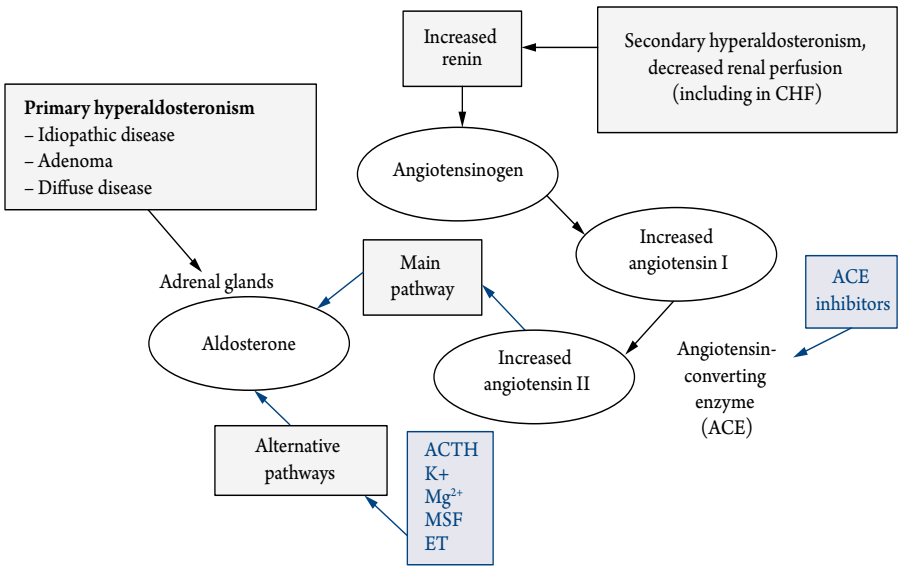
Concomitant administration of aldosterone receptor blockers, such as spironolactone, together with ACE inhibitors is an obvious way to solve this problem. During such blockade, the stimulating effect of aldosterone on fibroblasts becomes weaker irrespective of its plasma levels. The only serious risk of combining ACE inhibitors and spironolactone was the possible deterioration of renal function, which is manifested by elevated creatinine and, most importantly, the development of life-threatening hyperkalaemia. Since ACE inhibitors and spironolactone are potassium-sparing agents, this concern was reasonable, and the only way to overcome it could be a dedicated randomized clinical trial (RCT) evaluating

Figure 1. Balance of profibrotic and antifibrotic factors in maintaining extracellular matrix homeostasis



MMP, matrix metalloproteinases;
TIMP, tissue inhibitor of metalloproteinases [38].

Figure 2. Multiple factors stimulating aldosterone synthesis in the adrenal cortex



Increased renin and angiotensin II play a key role in CHD as a response to decreased renal perfusion. Adrenocorticotropic hormone (ACTH), plasma potassium and magnesium, melanization stimulating factor (MSF), endothelin (ET) are alternative stimuli of secondary hyperaldosteronism. ACE inhibitors block the synthesis and, thus, the stimulating effect of angiotensin II. Alternative pathways of aldosterone synthesis are activated over time in response.

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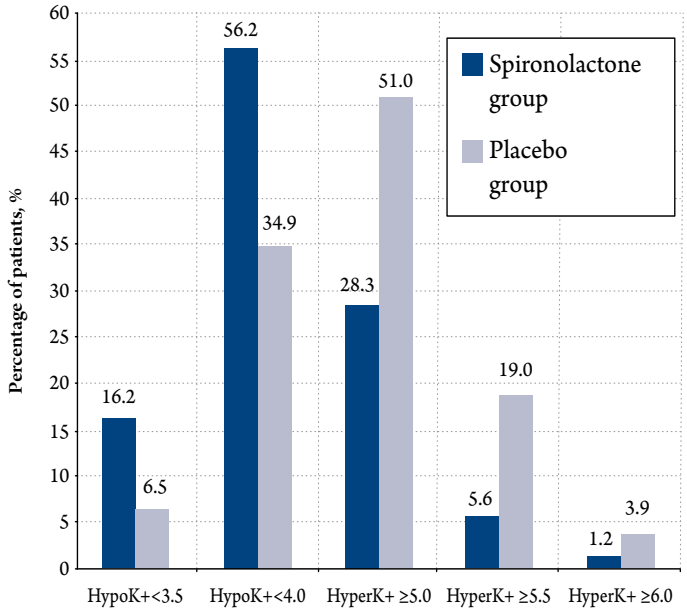
Figure 3. Percentage of patients with hypokalemia and hyperkalemia in the spironolactone group (light color) and the placebo group (dark color)



Values are not mutually exclusive, and each patient could experience both events during the period of follow-up.
HypoK, hypokalemia; HyperK, hyperkalemia.

the efficacy and safety of low-dose spironolactone in combination with ACE inhibitors in patients with symptomatic CHF. Randomized Aldactone Evaluation Study (RALES) was designed and conducted by Pitt et al., and the findings were published in the New England Journal of Medicine in 1999 [9]. This RCT included 1,663 patients with symptomatic CHF, with LVEF ≤35% who received the best-possible for that time drug therapy including ACE inhibitors. Patients were randomized to the spironolactone (12.5–50.0 mg, mean dose 26.0 mg) and placebo groups. The trial was terminated early, two years after it began, due to a significant 30 % reduction in the relative risk of death (95 % CI: 0.60-0.82; p<0.001), including the risk of death associated with heart failure and sudden death due to arrhythmia. Concomitant use of spironolactone with background ACE inhibitor therapy was also associated with a significant 35% reduction in the risk of hospitalization (95% CI: 0.54–0.77; p<0.001), and the improvement of a NYHA class of CHF (p<0.001). However, the main intrigue of the trial was an increased potential for excessive risk of life-threatening hyperkalemia in most patients in the spironolactone group: increased levels of plasma K^+ ≥6.0 mEq/L were detected in only 3.9% of the patients, which was relatively higher than in the placebo group (1.2%) (Figure 3). The in-depth analysis of the RALES findings showed that the more severe CHF, higher the baseline potassium level, and lower the glomerular filtration rate, the greater the risk of formal hyperkalemia ≥5.5 mEq/L during the concomitant use of spironolactone and ACE inhibitors/ARBs [10]. The key factor of hyperkalemia was the dose of spironolactone: the doses of 25 mg and 50 mg were associated with the 13.5% and 41.4% risk of hyperkalemia, respectively. However, the main conclusion of the study was that, irrespective of the drug dose, the mortality of patients who received spironolactone was significantly lower than those who did not, with K^+ <6.0 mEq/L (moderate hyperkalemia).

Another property of spironolactone, which should be taken into consideration during its use, was endocrinopathy, such as, gynecomastia and breast pain in male patients. The reason is that spironolactone is a steroid derivative able to block not only mineralocorticoid receptors (MCRs), but also, partially, androgen and progesterone receptors, which causes these symptoms. During the 2-year RALES study, the incidence of gynecomastia and breast pain was 10 %, and only 2 % of male patients discontinued treatment due to this reason. According to the authors, the risk of gynecomastia is not a reason to abandon spironolactone. And rightfully so: 30% reduction in the risk of death versus 2 % of refusal of the treatment [10].

However, the risks of hyperkalemia and gynecomastia prompted the search for safer MCR antagonists. Selective MCR antagonist (MCRA) eplerenone was developed. It has insignificant effect on sex hormone receptors, and its endocrinological side effect are virtually nil. More recent studies EPHESUS and EMPHASIS HF [11, 12] confirmed endocrinological safety of eplerenone; however, the risks of life-threatening hyperkalemia were approximately the same as for spironolactone, and the need to control blood electrolytes was indicated as mandatory in the summary of product characteristics. Moreover, a meta-analysis of the studies of eplerenone compared to the earlier AMCRs (spironolactone and canrenone) showed that spironolactone is more clinically effective and affordable than eplerenone [13].

Later studies of spironolactone showed its high efficacy for initial stages of CHD (NYHA FC I–II) as well as severe CHD (NYHA FC III–IV) [14].

The results of the RALES trial and some subsequent studies prompted clinicians to reassess spironolactone and see it not only as a mandatory pathogenetic agent that, in combination with an ACE inhibitor, significantly improves the quality of life and prognosis of patients with systolic CHD, but also as a concomitant potassium-sparing diuretic. The second wave of spironolactone recognition was so powerful that it caused unregulated misuse of high doses of the drug (more than 50 mg/day) in some clinics, which in turn resulted in an

increased incidence of hyperkalemia and nosocomial mortality [15]. The RALES trial was indeed a turning point in the history of spironolactone: it was considered exclusively as a potassium-sparing diuretic in the 1997 ESC Guidelines for the Management of CHD [16], but the 2001 Guidelines (immediately after RALES), spironolactone at the dose of 25–50 mg (together with ACE inhibitors) was recommended to decrease the prevalence and mortality of CHF NYHA FC III-IV [17]. The significance of spironolactone in the treatment of systolic CHF continued to grow in the future. In the 2005 and 2008 Guidelines, it was classified as IB [18, 19]; in 2012, it was designated as IA with the wording «add in case of insufficient effect of ACE inhibitor and BB» [20]; and since 2021, it has been designated as IA for all CHF patients with reduced left ventricular ejection fraction (LVEF) as a component of quadrotherapy [21].

However, despite obvious mandatory use of MCRAs in a complex treatment of patients with CHF, the results of the national 20-year epidemiological study EPOCH showed that by 2017, the rate of MCRA administration was only 25.3 % even in patients with severe CHF NYHA FC III–IV, which is significantly less than in case of ACE inhibitors/ARBs or BB, 92.7% and 75.3%, respectively [22]. When analyzing the potential causes for the limited MCRA administration in the real-world practice, the authors draw main attention to low clinician and patient adherence to multiple drug therapy of CHF. MCRAs, the third in a row after ACE inhibitors and BBs, are the first "victim" of such an approach. This apparent misunderstanding is a result of the subjective factor, namely physicians' inadequate awareness of the lack of treatment options for CHD and the significance of MCRAs.

However, there are also objectively reasonable causes. Primarily, this represents a shift in the epidemiological paradigm to patients with heart failure with preserved LVEF (HFpEF), the prevalence of which among all patients with CHD is above 50 % and, according to local studies, even 70 %. [23]. In fact, this is a new epidemic of HFpEF, and another, third wave of interest in spironolactone used as a pathogenetic treatment for HFpEF.

The main hypothesis of HFpEF development represents a pathophysiological model, when concomitant diseases such as arterial hypertension with LV hypertrophy, obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD), some others, induce and maintain low-intensity, chronic pro-inflammatory state, which causes the development of diffuse reactive fibrosis in the LV myocardium, higher chamber stiffness, and, as a result, diastolic dysfunction [24]. The problem of HFpEF treatment should have been handled theoretically by suppressing excessive myocardial fibrosis using ACE inhibitors or ARBs, but studies of several drugs of these classes [25–27] failed to demonstrate their adequate clinical efficacy. This failure is probably due to the lack of antifibrotic "power" of ACE inhibitors or ARBs alone, which is not enough to eliminate excess collagen in the myocardium being the main pathomorphological ground for diastolic dysfunction. Combining the antifibrotic effects of renin-angiotensin system blockers with MCRA may be the obvious solution to this problem. The soundness of this approach to the management of HFpEF patients was confirmed in a comparative study of the candesartan + spironolactone combination (32 mg and 25 mg, respectively) and monotherapy with candesartan 32 mg [28]. The study included 69 patients with clinical signs of CHD NYHA FC II–III, LVEF > 45 % and clear fibrotic phenotype, which was manifested by the presence of concentric LV hypertrophy (57 %), pseudo-normal/restrictive diastolic LV filling (mean E/A was 1.29±0.10), and/or elevated levels of NTproBNP [403 (212; 1011) pg/mL]. High (above 13 units) E/e' is a solid marker of fibrotic phenotype of HFpEF, and our patients reached 13.5±1.0. The two treatment tactics were compared after 24 weeks of treatment, and the candesar tan + spironolactone combination showed a statistically significant superiority in all clinical, hemodynamic, and biochemical parameters, especially in improving the collagen balance (increased MMP-1/TIMP-1 ratio) (Figure 4), that is, significant regression of fibrosis is achieved only in the presence of spironolactone.

In the Aldo-DHF study [29], Edelmann et al. received similar findings which studied the efficacy of spironolactone 25 mg concomitantly with the background ACE inhibitor therapy on diastolic function and exercise tolerance in patients with HFpEF. Despite the absence of an increase in the 6-minute walk distance, indicators of diastolic function improved statistically significantly in the spironolactone group as LV mass index and NTproBNP levels decreased, which confirms the pronounced antifibrotic effect of spironolactone.

The ability to positively influence collagen balance and reduce the severity of myocardial fibrosis with the combination of a RAAS blocker and spironolactone provided the grounds for a large-scale independent RCT of patients with HFpEF – Spironolactone for Heart Failure with Preserved Ejection Fraction (TOPCAT) [30]. The trial study included 3,445 patients from the USA, Canada, Argentina, Brazil, Russia, and Georgia with symptoms of CHF, LVEF > 45 %, and compliance

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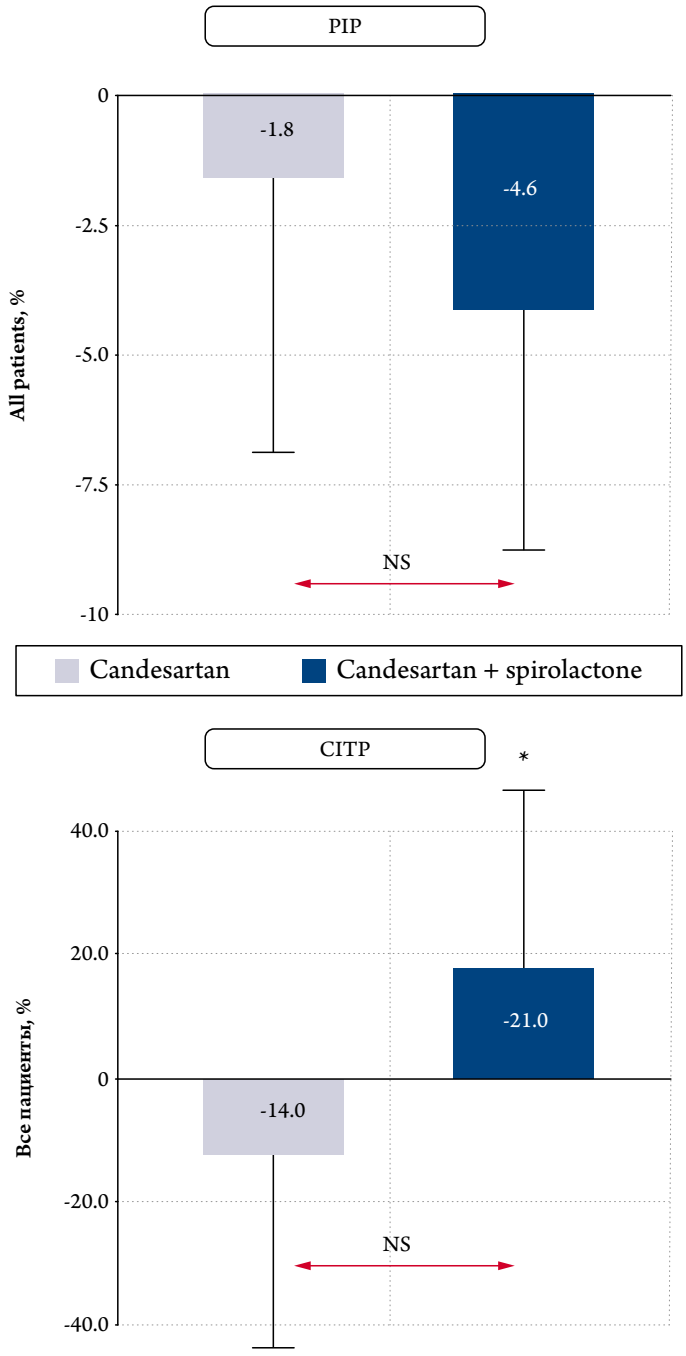
Figure 4. Changes in biochemical markers of the collagen balance during the therapy with candesartan and candesartan + spironolactone



* p<0.1. PIP, carboxyterminal propeptide of type I procollagen(marker of extracellular synthesis of collagen I), CITP, carboxyterminal telopeptide of collagen I (marker of extracellular degradation of collagen I) [28]. NS, not significant

with one of two criteria: a history of hospitalization for decompensated CHF within the past 12 months (criterion I) or elevated NTproBNP ≥ 360 pg/mL in sinus rhythm or > 900 pg/mL in atrial fibrillation (criterion II). Patients receiving best-possible drug therapy with RAAS blockers were randomized to the spironolactone 15–45 mg/day or placebo subgroups.

The main stage of trial lasted for 3.3 years on average and showed a statistically neutral result. However, additional analysis conducted after the completion of the main stage showed that the administration of spironolactone was accompanied by a significant decrease in the composite primary endpoint (cardiovascular death, resuscitation after cardiac arrest, and hospitalization for decompensated CHF) in four American countries, unlike Russia and Georgia, where the primary endpoint did not significantly decrease. There were several reasons for this difference [31], but the most objective explanation for a significant reduction in the risk of the primary endpoint by 18 % (p=0.026) among the patients in the American continent, and no such reduction in the subgroup of patients included in the trial from Russia and Georgia (10 %, p = 0.58), is obviously the predominance of severe stages of fibrosis in the American patients and more severe initial diastolic dysfunction. This is indirectly confirmed by the fact that more than half of American patients (56.4%) were included in the trial in compliance with the criterion of elevated NTproBNP, and there were only 12.4 % of such Russian and Georgian patients, and the main criterion for the inclusion was a history of hospitalization for HF (87.6%). The elevated levels of NTproBNP almost ensures a HFpEF patient has severe diastolic dysfunction as a consequence of excessive myocardial fibrosis (fibrotic phenotype), in which the combination of a RAAS blocker with spironolactone acts on the mature fibrotic substrate and is a positive prognostic factor. A history of hospitalization for HF without documented elevated levels of NTproBNP, on the contrary, do not guarantee the presence a mature fibrotic substrate in patients with HFpEF, and thus, do not guarantee the prognostic efficacy of the RAAS blocker + MCRA combination.

The correct selection of patients for pathogenetic therapy with spironolactone, such as patients with predominant fibrotic phenotype of HFpEF, would avoid errors in the interpretation of the TOPCAT findings and equivocality of the discussion. Pfeffer and Braunwald commented on the trial results that "… this drug (spironolactone – author's note) is universal, affordable, and generally well tolerated, although regular monitoring of electrolytes and creatinine is required to detect unexpected development of hyperkalemia and renal impairment…" [31].

Given patient selection error in the TOPCAT trial, a new RCT of spironolactone SPIRRIT [32] is currently conducted, in which the mandatory inclusion criterion is elevated NTproBNP (> 300 pg/mL). This RCT should make a final decision concerning the predominance of spironolactone in the management of HFpEF patients.

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There only two approved drugs for the treatment of CHF patients, the administration of which does not depend on LVEF: ARNIs (valsartan/sacubitrile) and sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin [33, 34]. Both drugs are positioned as universal treatments for patients with HFpEF [35] in an ideal combination with spironolactone without producing any adverse effects, especially hyperkalemia [36]. The position reflected in the latest ANA/ACC/HFSA Guidelines (2022), in which MCRA are designated as the drugs to be used in HFpEF of class of recommendation of IIb and high level of evidence, is a certain assurance that spironolactone will be formally approved for this indication. [37]. Class of recommendation and level of evidence for MCRA may be increased after the completion of the SPIRRIT study in 2022.

Thus, the 70-year history of the discovery of aldosterone, the key RAAS hormone, and later the development of spironolactone, a drug that blocks the action of aldosterone, is a clear example of how the complementary results of fundamental research successively open new hallmarks of biological laws, which is applied in real-world clinical practice.

Spironolactone created for the blockade of aldosterone receptors was initially regarded exclusively as a drug for water-salt metabolism regulation in the distal renal glomeruli, enhancing safe diuresis, and normalizing blood pressure. There is reason that its first was called a potassium-sparing diuretic. A new phase in the clinical use of this drug was marked by the discovery of membrane aldosterone receptors on the surface of endothelial and smooth muscle cells of vessels, cardiomyocytes, and notably fibroblasts. This discovery opened new possibilities, including the treatment of patients with resistant hypertension and the treatment of systolic CHF to support the escaping effect of ACE inhibitors. Clearly, the new term aldosterone antagonist better reflected the understanding of the spironolactone mechanisms of action. Finally, the use of spironolactone as a potent independent antifibrotic agent that blocks the entire complex of endocrine and paracrine effects of aldosterone, has expanded due to the shift in heart failure paradigm towards the prevalence of its diastolic phenotype based on excessive diffuse myocardial fibrosis. We appear to be at the beginning of the third wave of spironolactone use, now as a mineralocorticoid receptor antagonist.

The lifespan of spironolactone is undoubtedly longer than three ages, and new basic discoveries are likely soon that will result in new perspectives, new possibilities for the administration, and, probably, the development of new dosage forms.

No conflict of interest is reported.

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