Aldosterone antagonists in hypertension and heart failure

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La spironolactone, un antagoniste compétitif du récepteur de l'aldostérone, a été classiquement utilisé comme thérapie de premier choix dans le traitement de l'hyperaldostéronisme idiopathique et pour le traitement préopératoire de l'adénome de Conn.

La spironolactone est partiellement absorbée, largement métabolisée principalement par le foie et ses propriétés thérapeutiques sont dues à son métabolite actif, la canrénone. Aux doses thérapeutiques de 25 à 400 mg par jour, la spironolactone est capable de contrôler efficacement la pression artérielle et l'hypokaliémie dans la majorité des cas. Les effets adverses associés sont principalement la gynécomastie, une réduction de la libido et l'impotence chez l'homme et les irregularités menstruelles chez la femme. La canrénone et la forme saline K⁺-canrénoate sont aussi utilisées : ces dernières ne comportent pas la formation de métabolites ayant activité anti-androgène et progestative et donc sont caractérisées par une incidence réduite d'effets adverses. De plus, un nouvel antagoniste sélectif du récepteur minéralo-corticoïde (l'eplerenone), caractérisé par une faible affinité pour les récepteurs des hormones androgènes et de la progestérone, est actuellement en phase d'étude clinique.

Dans l'hypertension artérielle, l'aldostérone peut soutenir l'hypertension même et augmenter l'incidence d'hypertrophie cardiaque et d'accidents cardiovasculaires. D'ailleurs, l'inhibition du système rénine-angiotensine-aldostérone (SRAA) est associée à une réduction de la pression artérielle, avec une régression de l'hypertrophie cardiaque. C'est pour cela que les antagonistes de l'aldostérone (ARA) ont été proposés comme thérapie complémentaire associée aux inhibiteurs de l'enzyme de conversion (IEC) et aux antagonistes du récepteur de l'angiotensine II. L'aldostérone est impliqué aussi dans la physiopathologie de la décompensation cardiaque. Des données expérimentales obtenues chez le rat ont suggéré que l'aldostérone peut provoquer une fibrose cardiaque interstitielle et périvasculaire.

Le SRAA est chroniquement activé dans la décompensation cardiaque. Les diurétiques stimulent ultérieurement le SRAA et causent l'hypokaliémie. C'est ainsi que l'utilisation des ARA a été proposée initialement pour corriger la déplétion de potassium et magnésium. À présent, l'emploi des ARA est indiqué dans le traitement de l'hyperaldostéronisme primaire, dans les conditions associées à l'œdème et l'ascite, dans l'hypertension artérielle et dans les états hypokaliémiques. L'utilisation des ARA comme thérapie additionnelle dans le traitement de la défaillance cardiaque est actuellement sous investigation. En effet, il est bien connu que pendant le traitement avec IEC, même à dosage élevé, le SRAA n'est pas complètement supprimé : un phénomène de « escape » de l'aldostérone peut se réaliser à travers des mécanismes non angiotensine II-dépendants. L'addition de la spironolactone à l'IEC cause une diurèse marquée et une amélioration des symptômes.

Pendant les dernières années, l'étude RALES (Randomized Aldactone Evaluation Study) a été organisée pour enquêter sur l'efficacité de la thérapie combinée avec la spironolactone et un IEC dans un groupe de patients avec défaillance cardiaque en classe III ou IV NYHA. L'étude a été interrompue 18 mois avant la date prévue car les résultats étaient tellement significatifs que la poursuite de l'étude n'était pas justifiée.

Although the incidence of hypertension due to mineralocorticoid excess has been previously considered rather low, there is a significant proportion of patients with “essential” hypertension who respond to therapies affecting mineralocorticoid action, even though circulating levels of these steroids are likely within normal ranges and the patients are not hypokalemic [14, 17, 18].

More recently, the widespread introduction of the aldosterone/plasma renin activity ratio (Aldo/PRA) ratio in the screening of secondary forms of hypertension has clearly demonstrated that a significant number of so called « essential hypertensives » have indeed a mild form of primary aldosteronism.

Furthermore, a role of aldosterone has been advocated not only in the pathophysiology of hypertension but also in increasing the incidence of myocardial hypertrophy and cardiovascular events [11, 25, 28, 29]. Thus, in addition to the pharmacological inhibition of Renin-Angiotensin System (RAS), which is associated with a decrease in blood pressure, a regression of left ventricular hypertrophy and a reduction of target organ damage [19, 28, 31, 32], aldosterone receptor antagonists (ARAs) have been proposed as complementary treatment associated to ACE inhibitors and angiotensin in receptor antagonists.

Aldosterone is also known to play an important role in pathophysiology of congestive heart failure (CHF). In
plus éthique. Une réduction de 30 pour cent de la mortalité cardiovasculaire et des hospitalisations pour causes cardiaques a été reportée dans le groupe traité avec la spironolactone par rapport au groupe traité avec placebo.

**Mots-clés** : Hypertension artérielle, défaillance cardiaque, système rénine-angiotensine, aldostérone, antagonistes de l’aldostérone.

**Aldosterone antagonists in hypertension and heart failure**

Spironolactone, a competitive aldosterone receptor antagonist (ARA), has traditionally been the treatment of first choice in idiopathic hyperaldosteronism (IHA) and for preoperative management of aldosterone producing adenoma (APA).

Spironolactone is partially absorbed, is extensively metabolized mainly by the liver and its therapeutic properties are attributable to active metabolite canrenone.

At therapeutic doses of 25 to 400 mg per day, spironolactone effectively controls blood pressure and hypokalemia in the majority of cases. Endocrine side effect are often associated and mainly consist of gynecomastia, decreased libido and impotence in man and menstrual irregularities in women. Canrenone and the K+ salt of canrenoate are also in clinical use: they avoid the formation of intermediate products with anti-androgenic and gestational actions, resulting in a decreased incidence of side effects. Furthermore, a relatively new selective ARA compound (eplerenone) with reduced affinity for androgen and progesterone receptors, is currently undergoing clinical trials.

In essential hypertension aldosterone can contribute to hypertension and increases the incidence of myocardial hypertrophy and cardiovascular events. On the other hand, inhibition of Renin-Angiotensin-Aldosterone System (RAAS) is associated with a decrease in blood pressure, with a regression of left ventricular hypertrophy and a reduction of target organ damage. Thus, ARA have been proposed as complementary treatment associated to ACE inhibitors and angiotensin receptor antagonists.

Aldosterone is also known to play an important role in pathophysiology of congestive heart failure (CHF). In vitro and in vivo evidences suggest that aldosterone promotes myocardial fibrosis. This effect reflects direct, extra-epithelial actions of aldosterone via cardiac MR which are counteracted by ARAs in animal models.

The RAAS is chronically activated in CHF. Non potassium-sparing diuretics further stimulate the RAAS and cause hypokalemia. Thus, use of ARAs in CHF was first proposed to correct potassium and magnesium depletion.

At present ARAs are indicated in the management of primary hyperaldosteronism, in oedematous conditions in patients with CHF, in cirrhosis of the liver accompanied by oedema and ascites, in essential hypertension and in hypokalemic states. Its indication as adjunctive therapy of heart failure is currently under investigation. In fact, it is well known that even high doses of ACE inhibitors may not completely suppress the RAAS; aldosterone ‘escape’ may occur through non angiotensin II dependent mechanisms. Addition of spironolactone to an ACE inhibitor causes marked diuresis and symptomatic improvement.

During the last few years, the RALES study (Randomized Aldactone Evaluation Study) was organized to explore the efficacy of combination therapy with spironolactone and ACE inhibitor in patients with CHF, class III or IV NYHA. The study was stopped 18 months early because the results were so statistically and clinically significant that it would be unethical to continue the trial. It is reported a 30 percent decrease in mortality and hospitalisation for cardiac causes in spironolactone-treated group vs placebo group.

**Key words** : Hypertension, heart failure, renin-angiotensin, aldosterone system, aldosterone receptor antagonists.
gated channels. Corticotropin also stimulates aldosterone secretion, but its effect is short lived (less than 24 hours).

Aldosterone regulates electrolyte excretion and intravascular volume mainly though its effect on the distal tubules and cortical collecting ducts of the kidney, increasing sodium reabsorption and potassium excretion. Aldosterone increases the number of such channels that are open. This may reflect an increase in the percentage of time that each channel stays open or an actual increase in the number of channels. Aldosterone also raises potassium conductance through specific channels. Finally, it increases the synthesis of a Na+/K+-ATPase located on basolateral cell membranes, thus generating the electrochemical gradient that drives diffusion through the sodium and potassium channels.

Aldosterone exerts most of its biologic effects on cells by occupying an intracellular receptor, the type-I-mineralocorticoid receptor (MR), which then binds DNA and thereby influences the transcription of various genes (delayed genomic responses). MR can be demonstrated not only in epithelial cells (kidney, gastrointestinal mucosa, salivary glands and sweat glands) but also in non-classical, non-epithelial target tissues such as hippocampus, arterial smooth muscle cells, mammary gland and leukocytes.

Although these receptors are not specific for aldosterone and they have equivalent affinity for cortisol, in the epithelial aldosterone target tissues cortisol is normally excluded from both mineralocorticoid and glucocorticoid receptors by the action of the 11β-hydroxysteroid dehydrogenase enzyme type 2 (11β-HSD2), which catalyzes the conversion of cortisol to the hormonally inactive metabolite, cortisone. In the non-epithelial tissues, such as the circumventricular region of the brain, MR are not protected by 11β-HSD2 and their activation may lead to blood pressure elevation through different mechanisms. In rat models MR occupancy by corticosterone/cortisol or by an MR antagonist has no agonist effect but blocks the action of aldosterone. The findings that neither agonist nor antagonist effects via MR are mimicked or blocked by a glucocorticoid antagonist is interpreted as evidence for MR action via a specific mineralocorticoid response element (MRE) as opposed to the non selective hormone response element (HRE) in the classical epithelial aldosterone target tissues [15, 16].

Other non-epithelial MR-mediated effects of aldosterone have been described in producing experimental cardiac hypertrophy and fibrosis. Furthermore, a number of studies have demonstrated rapid in vitro and in vivo effects of aldosterone on sodium, potassium and calcium concentrations and cell volume of human mononuclear leukocytes (HML) as well as on the activity of the sodium-proton exchanger of the cell membrane in HML and vascular smooth muscle cells (VSMC). These effects, resulting in increase of peripheral vascular resistance and blood pressure, are not consistent with the genomic action via classical type-I-mineralocorticoid receptors, suggesting the existence of distinct receptors subsequently described in plasma membranes from pig kidney and liver [8, 9, 21].

**ALDOSTERONE AND HYPERTENSION**

A significant number of patients with essential hypertension (about 20%) are characterized by low plasma renin activity. These subjects have been classified in the past as a subgroup of patients with volume dependent hypertension, either as a consequence of a inappropriate «normal» levels of aldosterone for such a low renin levels, or as a sign of disturbance of some unidentified mineralocorticoid hormone secretion, or as the result of a salt retaining mechanism leading to volume expansion and hypertension. These patients were considered to be especially responsive to diuretic antihypertensive therapy. Even if other intra-renal factors have been advocated to explain the lowering of renin secretion, recent data are giving new strength to the hypothesis that at least a part of the so called low-renin hypertensives are indeed dependent on one of the mechanisms mentioned above.

First, with improved screening methodologies, in particular the measure of morning ambulatory paired random plasma aldosterone concentration (PAC) and plasma renin activity (PRA), in most hypertensive patients, including the normokalemic ones, the average number of primary aldosteronism (PA) detected per year has increased in some institution more than 10 fold (with a prevalence of 5 to 10% of all hypertensives), leading PA to be the most common form of curable secondary hypertension.

Secondly, recent advances in molecular genetics have allowed the elucidation of the pathogenesis of three inherited forms of salt-sensitive, low-renin hypertension: glucocorticoid remediable aldosteronism (GRA), in which a chimeric gene between the 11β-hydroxylase and aldosterone synthase genes results in aldosterone excess; Liddle’s syndrome, due to mutations in the epithelial sodium channels (ENaC) resulting in unopposed sodium retention; apparent mineralocorticoid excess (AME), an inherited form of severe hypertension involving the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) gene. Particularly, the observation that milder forms of AME due to homozygous mutations in 11β-HSD2 exist, and that the heterozygous state is associated with arterial hypertension, suggest the hypothesis that defective 11β-
HSD2 activity may be of relevance in patients currently labeled as having « essential » hypertension.

Moreover, polymorphisms of the promoter region of aldosterone synthase gene may also contribute to LRH and actually has been found associated with higher plasma aldosterone levels in hypertensive patients.

Furthermore many subjects appears to be salt sensitive when challenged with the Grim and Weinberger, test independently of their renin status.

**ALDOSTERONE AND CARDIOVASCULAR REMODELING**

Arterial hypertension is associated with an increased incidence of cardiovascular and renal events, and approximately half of the hypertensive population dies of an acute episode (myocardial infarction, stroke).

The activation of the renin-angiotensin-aldosterone system (RAAS) has been identified as a risk factor for the development of ischemic heart disease, cardiovascular remodeling and fibrosis, left ventricular hypertrophy (LVH) and congestive heart failure (CHF).

In the LVH that accompanies hypertension, the extracellular space is frequently the site of an abnormal accumulation of fibrillar collagen. This reactive and progressive interstitial and perivascular fibrosis accounts for abnormal myocardial stiffness and ultimately ventricular dysfunction and is likely a result of cardiac fibroblast growth and enhanced collagen synthesis [34]. However, the involvement of this non-myocyte cell is disproportionate in comparison with myocyte hypertrophy and LVH, suggesting that the growth of myocyte and non-myocyte cells is independent of each other. In vivo studies of experimental hypertension have demonstrated this abnormal fibrous tissue response in the hypertensive, hypertrophied left ventricle as well as in the normotensive, non-hypertrophied right ventricle [6]. Because LVH is not always associated with an increase in fibrillar collagen, despite comparable pressure or volume overload, non-hemodynamic factors such as circulating hormones may represent growth stimuli to cardiac fibroblasts. Comparable levels of systemic hypertension and LVH were observed in rats with unilateral renal ischemia (renovascular hypertension) and infrarenal aortic banding (non- renovascular hypertension) and in uninephrectomized animals receiving enhanced dietary sodium plus the mineralocorticoid aldosterone.

However, in the hypertrophied left ventricle that accompanied renovascular hypertension or hyperaldosteronism (i.e. uninephrectomized animals receiving aldosterone plus enhanced dietary sodium), the fibrillar collagen fraction was significantly increased. On the other hand the treatment with low or high doses of the aldosterone receptor antagonist (ARA), spironolactone was able to prevent myocardial fibrosis in rats with unilateral renal ischemia or hyperaldosteronism, even though it did not normalize arterial pressure or prevent LVH.

**ALDOSTERONE RECEPTOR ANTAGONISTS (ARAs)**

Pharmacological blockade of aldosterone actions was achieved in 1950s by the synthesis of the spirolactone class of compounds, which were demonstrated to competitively antagonize the effects of aldosterone and deoxycorticosterone on electrolytes excretion in rats, and to induce natriuresis in man (fig. 1). Spironolactone has been the most commonly used compound of this class of drugs in the past 30 years as treatment of primary aldosteronism and other sodium retaining states such as in congestive heart failure and liver cirrhosis; furthermore, there is evidence that this compound is also an effective antihypertensive drug in essential hypertension (see below).

Spironolactone is partially absorbed and extensively metabolized mainly by the liver. Its therapeutic properties are attributable to the active metabolite canrenone, which is in plasma in equilibrium with potassium canrenoate [12].

At therapeutic doses of 25 to 400 mg per day, spironolactone effectively controls blood pressure and hypokalemia in the majority of cases of primary aldosteronism.

ARAs represent also the standard initial therapy for the treatment of ascites and volume overload in edematous patients with secondary hyperaldosteronism (hepatic cirrhosis and nephrotic oedema) and they are frequently combined with furosemide in treating congestive heart failure to avoid the cardiotoxic effects of hypokalemia and hypomagnesemia. Endocrine side effects are often associated and mainly consist of gynecomastia, decreased libido and impotence in man and menstrual irregularities in women [2]. Canrenone and the K⁺ salt of canrenoate are also widely used in clinical practice. They avoid the formation of intermediate products with greater anti-androgenic and progestational actions, resulting in a decreased incidence of side effects. Furthermore, a relatively new selective ARA compound (eplerenone) with reduced affinity for androgen and progesterone receptors, is currently undergoing clinical trials.

**ARAs IN HYPERTENSION**

Spironolactone and its analogues represent the most specific treatment of mineralocorticoid excess syndro-
mes and particularly of primary aldosteronism. In patients with aldosterone producing adenoma this therapy is indicated preoperatively in order to better control hypokalemia, when present, and hypertension: in general, the response to spironolactone at doses of 50 to 200 mg is a good prognostic indicator of the outcome of surgery. Others and we have in fact demonstrated that normalization of blood pressure is obtained in half of the patients and a partial reduction in further 30% (fig. 2).

Long term ARAs treatment is also suggested in idiopathic primary aldosteronism with as low as possible amounts to decrease the incidence of side effects. However, in at least 30% of these patients ARAs alone are insufficient in controlling blood pressure, thus requiring additional antihypertensive drugs (especially calcium-channel blockers, but also α₁-antagonists, or even ACE-inhibitors) [20].

In essential hypertension, inhibition of Renin-Angiotensin-Aldosterone System (RAAS) by ACE-inhibitors and angiotensin receptor antagonists is associated with a decrease in blood pressure, a regression of left ventricular hypertrophy and a reduction of target organ damage. Benefit is also provided by suppression of aldosterone, which causes sodium retention, potassium and magnesium loss, vasoconstriction and cardiovascular fibrosis. However, there is the evidence that plasma aldosterone levels increase after several months of ACE-inhibition [26]; this phenomenon is known as « aldosterone escape » and has been demonstrated also with angiotensin receptor antagonists.

Furthermore, the findings referred above have provided arguments to consider ARAs as a helpful therapy not only in the extended group of primary aldosteronism but also in several selected subgroups of essential hypertensives.

As in other previous studies, Jeunemaitre et al. [18] confirmed the efficacy of long term therapy with spironolactone alone in essential hypertension. In 182 selected patients with mild to moderate essential hypertension, they found that 60 percent of the patients on treatment had a diastolic blood pressure (DBP) ≤ 90 mmHg while only 10 percent had > 100 mmHg. In agreement with previous reports, the dose range of 75 to 100 mg daily seemed to be the most appropriate, with no further decrease in BP for doses of 150 mg or higher (fig. 3). The increase in plasma potassium is dose-dependent and is greatly influenced by its initial level. Hyperkalemia was described, but especially in patients who received potassium chloride concurrently and/or...
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suffered of pre-existing renal failure, cardiac insufficiency, or hepatic cirrhosis. On the other hand, the lack of significant adverse metabolic effects seems to be of interest.

The spironolactone-induced gynecomastia is a reversible dose-dependent side effect. Its incidence greatly increases for doses higher than 150 mg daily.

In the last decade, potassium canrenoate, a slightly different aldosterone antagonist, and its active metabolite canrenone, are widely used as therapy of sodium retaining states and mineralocorticoid and essential hypertension [10]. Potassium canrenoate is a water soluble derivative of spironolactone, sharing the same active metabolite canrenone, but has probably a different pattern of metabolism which avoids the formation of intermediate products with anti-androgenic effects. As result it has a decreased incidence of side effects, as shown by several trials in essential hypertensive and cirrhotic patients.

Among others, a higher Na⁺-K⁺-Cl⁻ cotransport (and again a lower renin) has been found to be associated to a selective blood pressure control by potassium-canrenoate [14] (fig. 4).

Eplerenone, an ARA that has less anti-androgenic activity than spironolactone, has been found to possess blood pressure lowering effect in a dose-dependent fashion (with doses somewhat higher than spironolactone).

Moreover a significant correlation of serum aldosterone levels with left ventricular mass has been demonstrated. In the last few years, an accumulating body of knowledge has provided increasing evidence that aldosterone induces a remodeling in myocardial tissue and particularly in non-myocyte cells (i.e., endothelial cells and cardiac fibroblasts). In arterial hypertension, this may adversely affect myocardial structure, ultimately leading to myocardial fibrosis. Attenuation of the effects of elevated circulating aldosterone levels by antialdosterone therapy may become a new goal for the prevention and regression of pathologic LVH in essential arterial hypertension.
ARAs IN HEART FAILURE

In congestive heart failure (CHF) multiple neurohormonal systems are activated and several recent clinical trials have identified the presence of neurohumoral abnormalities in a broad spectrum of patients with CHF [1, 4]. These events may increase myocardial oxygen consumption by elevating heart rate and afterload, and may also induce coronary vasoconstriction. Activation of the RAAS gives an important contribute to the pathophysiological mechanisms in this clinical syndrome. Reductions in cardiac output result in increased plasma renin activity (PRA), angiotensin II, and aldosterone levels. Another mechanism which causes plasma aldosterone concentrations to triple or quadruple is a decreased rate of hepatic aldosterone clearance (25 to 50 % of the normal rate) with commensurate reduction in hepatic perfusion.

Increased levels of circulating aldosterone augment distal renal tubular reabsorption of sodium and water, with a consequent expansion of intravascular volume that produces a volume overload leading to deteriorating hemodynamic conditions. Cardiac output consequently decreases further, producing a drop in renal blood flow. This sets in motion a vicious circle through extra-stimulation of the RAAS.

In addition to promoting sodium and fluid retention, aldosterone enhances urinary potassium and magnesium excretion, aggravating the hypokalemia and magnesium depletion caused by treatment with loop diuretics [3]. The consequences of these electrolyte disturbances can include myocardial electrical instability, death of cardiac myocytes and increased risk of cardiac arrest. Others potentially harmful effects of aldosterone have been demonstrated in several experimental models and they include increased collagen synthesis and myocardial fibrosis, impaired baroreflex function, catecholamine uptake inhibition, and endothelial dysfunction (fig. 5).

The blockade of RAAS has been shown to be effective in reducing morbidity and mortality in patients with symptomatic and asymptomatic left ventricular dysfunction, as CONSENSUS and SAVE trials have demonstrated [28, 30, 31, 33]. However, it is well known that ACE inhibition is not sufficient to suppress aldosterone production, and the plasma aldosterone levels quite early return to baseline and even go over these values in a period of months (fig. 6). This « escape » of aldosterone could be due in part to non-ACE-dependent angiotensin II production and to the fact that the control of aldosterone production may be independent of angiotensin II, through the actions of atrial natriuretic factor (ANF), corticotropin, vasopressin, or serum potassium concentrations and salt reduction.

ARAs block aldosterone receptors, thus favourably influencing left ventricular hypertrophy, myocardial fibrosis, fluid retention, and arrhythmias induced by potassium and magnesium loss [37].

The use of aldosterone antagonists in CHF was first proposed to correct potassium and magnesium depletion, both of which are associated with enhanced diastolic toxicity and arrhythmogenesis, and it has recently been recommended by the North American Societies of Cardiology.
As aldosterone antagonists have been shown to decrease water and sodium retention in various states of CHF, especially in severely ill patients with refractory oedema, their use has also been recommended by European Society of Cardiology Working Group on Heart Failure.

De Valeriola et al. [10] reported that in a group of patients with CHF, receiving a daily dose of 200 mg of potassium canrenoate in conjunction with the conventional treatment over a period of two months, peripheral oedema had almost disappeared and dyspnoea appeared only on marked physical activity. 

During the last few years, the double-blind multicentric RALES study (Randomized Aldactone Evaluation Study) was organized to explore the efficacy of combination therapy with spironolactone and ACE inhibitor in 11 663 patients with CHF, classified as New York Heart Association (NYHA) class III or IV [22]. The study was stopped 18 months early because the results were so statistically and clinically significant that it would be unethical to continue the trial. It was found that treatment with spironolactone, at a dose of 12.5 to 50 mg daily (mean dose 26 mg daily), reduced the risk of death from all causes (30 %), death from cardiac causes (31 %), hospitalization for cardiac causes (30 %), and the combined end point of death from cardiac causes or hospitalisation for cardiac causes (32 %) among patients who had severe heart failure as a result of left ventricular systolic dysfunction and who were receiving standard therapy including an ACE-inhibitor. Spironolactone also improved the symptoms of heart failure, as measured by changes in the NYHA functional class. Severe hyperkalemia requiring the discontinuation of treatment was uncommon, occurring in one patient in the placebo group and three in the spironolactone group. The reductions in the risk of death and hospitalisation were observed after 2 to 3 months of treatment and persisted throughout the study (mean follow-up, 24 months) (fig. 7). These results are consistent with the current understanding of the effect of aldosterone in patients with heart failure. The effectiveness of a low dose of spironolactone (25 mg daily) does not appear to be due entirely to an effect on sodium retention or potassium loss. In fact, although in the RALES trial spironolactone had some effect on sodium retention, this effect would most likely be minor, as compared with that of the high doses of loop diuretics used. In addition, although there was a significant increase from baseline in serum potassium concentrations in the patients treated with spironolactone, this change was not clinically important. Thus, several other mechanisms of action should be considered, such as the blockade of the non-epithelial MR-mediated effects of aldosterone in the heart and blood vessels.

In summary, according to the results of this large clinical study, aldosterone antagonism added to conventional therapy with loop diuretics and ACE-inhibitors is able to improve the survival, and leads to beneficial effects on important end-points such as cardiac complications and quality of life.

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