Review Article

Spironolactone; the ultimate blocker of RAAS cascade in hypertensive patients with special reference to its cardiovascular benefits: Revisiting the forgotten ways

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Acknowledgement: All the authors would like to express their heartfelt thanks to Dr Jagadeesh Tangudu, Mtech, MS, PhD and Sowmya Jammula, M Tech for their immense and selfless contribution towards manuscript preparation, language editing and final approval of text. ***Abstract:*** Hypertension is a major risk factor for various macro and microvascular complications in a patient with diabetes. Control of hypertension is of paramount importance in the care of a diabetes subject. The goals for blood pressure in diabetes subjects are below 130/ 80 mmHg and below 125/75 mmHg if accompanying renal impairment is there. Spironolactone is a medication that has been used to treat high blood pressure since the 1960s. While there is some belief spironolactone reduces blood pressure, there are concerns due to the potential for this drug to cause adverse effects. Previous Meta analysis has shown that spironolactone reduces systolic/diastolic blood pressure by approximately 20/7 mmHg compared to placebo. Spironolactone has also been shown to decrease morbidity and mortality in patients with heart failure. We have tried to emphasize upon the usage of this old but important drug in management of resistant hypertension with reference to its mode of action, benefits and recent studies pertinent to cardiovascular benefits of spironolactone. ***Data Source:*** We searched PUBMED and MEDLINE database for relevant articles including key words. References of each article were further reviewed for final synthesis of the manuscript.

Key words: Hypertension, microvascular, macrovascular, spironolactone

Introduction: The renin-angiotensin-aldosterone system (RAAS) plays an integral role in regulation of blood pressure and has been a long target of pharmacologic approaches to control blood pressure (BP) and other conditions like diabetic nephropathy, heart failure, myocardial infarction and other nondiabetic nephropathies. Clinical interventions involving the RAAS have focused mainly on inhibiting the action of angiotensin II (Ang II) with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs), while limited attention has been focused on the direct inhibition of aldosterone 1. In recent years, advances in the role of aldosterone producing nephropathy and cardiovascular injury have brought to for the importance of aldosterone in the management of these conditions.

Aldosterone synthesis and regulation: brief overview.

Aldosterone in the circulation is produced in the zona glomerulosa of the adrenal cortex. A series of enzymatic steps lead to the conversion of dietary or endogenous cholesterol to aldosterone[2]. Its production is regulated at[2] critical steps: conversion of cholesterol to pregnenolone by cholesterol side chain cleavage enzyme, and conversion of corticosterone to aldosterone by aldosterone synthase. Many factors modify aldosterone secretion; angiotensin II and potassium are the most important factors. Other factors such as ACTH, neural mediators and natriuretic factors are also involved. The major effect of aldosterone is to increase the transport of sodium across the cell in exchange for potassium and hydrogen ions[2].

Aldosterone: Target organs and effects

In the past, the focus was on aldosterone and its target organs resided in the classical target, the kidneys.

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Increasing evidence now points towards the fact that aldosterone can be synthesized in extraadrenal tissue, in the heart and the vasculature[2]. Aldosterone synthase, the enzyme responsible for the last step in aldosterone biosynthesis is expressed in heart, blood vessels and brain[3]. These non epithelial tissues also express mineral corticoid receptors which have properties similar to that of renal receptors but produce a wide variety of effects. Apart from a role in maintaining the renal electrolyte balance, aldosterone promotes cardiac fibrosis[4], abnormal endothelial function[5] and regulates sympathetic tone in the central nervous system[6]; factors which contribute to increased systemic vascular resistance[7] and consequent hypertension and cardiovascular disease (Figure 1).

ALDOSTERONE	**CARDIOVASCULAR DISEASE**
1) Myocardial remodeling and fibrosis	1) Hypertension
2) Vascular inflammation and fibrosis	2) Heart failure
3) Reduced vascular compliance	3) Stroke
4) Thrombotic effects	4) Ischemia
5) Endothelial dysfunction	5) End-stage renal disease
6) Ventricular ectopy	
7) Catecholamine potentiation	
8) Baroreceptor dysfunction	
9) Angiotensin II potentiation	
10) Sodium and water retention	
11) Progressive renal dysfunction	

Figure I: Multiple effects of aldosterone

Aldosterone: Genomic and non genomic effects

Steroid hormones produce their actions by binding to intracellular receptors, this hormone-receptor complex further binds to DNA and activates or regresses transcription of target genes. However, all steroid hormones can also act through non-genomic mechanisms and alter the physiological processes[8]. The non-genomic effects have a rapid onset and are insensitive to inhibitors of transcription and translation. Similarly aldosterone also produces non-genomic effects on various target organs like vascular smooth muscle cells, endothelial cells, skeletal muscle cells, lymphocytes, cardiac myocytes, colonic epithelial cells and kidney cells. Kidneys are the classical target organ for the non-genomic as well as genomic effects, where aldosterone stimulates sodium reabsorption and potassium secretion [9]. Aldosterone as mediator of renal dysfunction.

Aldosterone binds with cytosolic the mineralocorticoid receptor and translocated into the nucleus where it binds to the regulatory region of the target gene promoters and enhances its expression. Sodium reabsorption in renal tubular cells depends mostly on aldosterone induced transcriptional regulation of Na+/ K+- ATPase. Aldosterone enhances the gene expression of profibrotic molecules like collagen and transforming growth factor ß (TGF- ß), matrix proliferating molecules like epithelial growth factor receptor (EGFR), and prothrombotic molecules like plasminogen Ativator Inhibitor type[1] (PAI-1). It also stimulates inflammation through the generation of reactive oxygen species (ROS), gene expression of proinflammatory molecules like intracelluler adhesion molecule[1] (ICAM-1), interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1). Non-genomic effects include upregulating the expression of pro-inflammatory transcription factors like extracellular signal regulated kinase 1and related molecules like. All these factors induce inflammation and extracellular matrix accumulation resulting in renal tissue fibrosis and ultimately renal scarring[10].

In fact, aldosterone is an important pathogenic factor in progressive renal disease. It has been demonstrated that patients with diabetic nephropathy with renal insufficiency have increased aldosterone levels when compared to healthy individuals. Furthermore, it has also been seen that the highest aldosterone levels are observed among those patients who have the greatest renal function impairment. Hene et al observed that at comparable serum potassium and plasma rennin activity and with creatinine clearance lower than 50% of normal, the plasma aldosterone is elevated in a majority of subjects[11].

Aldosterone as mediator of hypertension

Although, primary aldosteronism is known to be an important cause of secondary hypertension, initial studied of serum aldosterone levels in hypertensive patients' demonstrated inconsistent results. Vasan et al in the Framingham offspring Study observed increased serum aldosterone even within normal range was associated with an increased risk of developing hypertension[12]. The study analyzed the effect of increasing serum aldosterone in a cohort of 1688 nonhypertensive individuals. More than 40% of these subjects had blood pressures lower than 120/80 mmHg at the onset of observation period. Mean serum aldosterone levels were similar in men and women at onset (10.7 ng/dl vs 11.3 ng/dl, respectively). After a follow up period of approximately 4 years, a proportion of patients or were found to be hypertensive (Figure II).

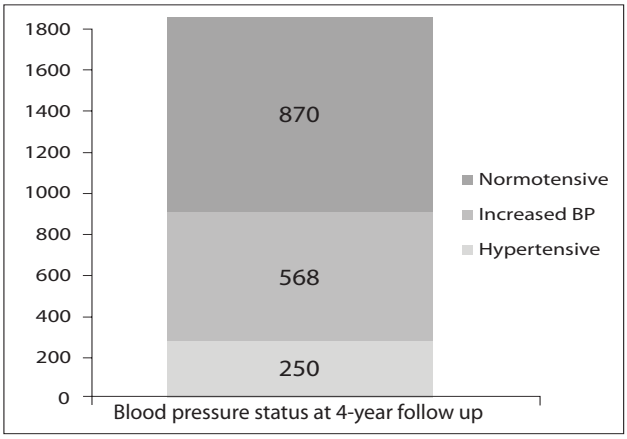

Figure II: Blood pressure status at 4 year follow up in 1688 normotensive patients in the Framingham Offspring study.

On further analysis it was observed that there was a 16% increased risk of hypertension for each quartile increment in the serum aldosterone level (Figure III).

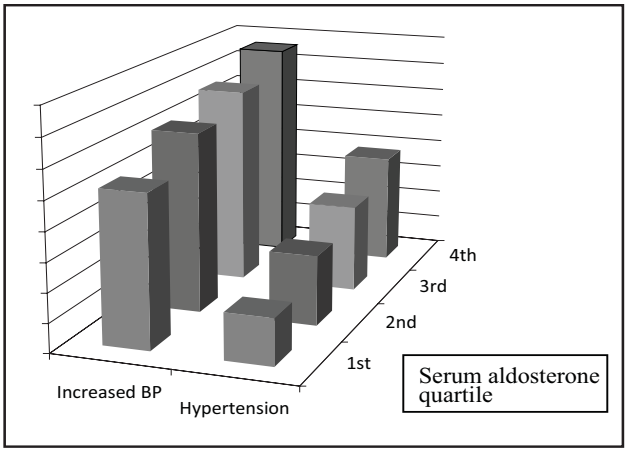

Figure III: Blood pressure outcomes at 4 years according to quartile of serum aldosterone level in the Framingham Offspring Study

These effects were even greater in those subjects with serum aldosterone in the highest quartile. There was no significant effect of age, gender, systolic blood pressure or body mass index on the aldosterone levels and the BP values.

Increased aldosterone levels within the physiologic range may predispose to hypertension through several possible mechanisms which include effects on renal sodium, Ang II, endothelial function, vascular compliance and central nervous system mechanisms (Figure IV).

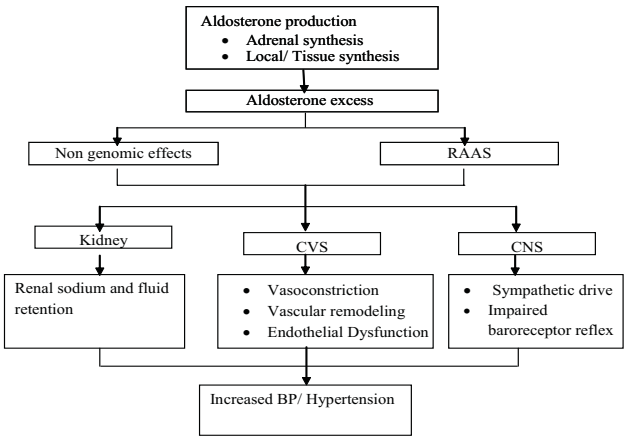

Figure IV: Mechanisms involved in aldosterone mediated hypertension

Since mineralcorticoid receptors are widely distributed throughout the vasculature, myocardium and central nervous system, serum levels of aldosterone may underestimate its true effects on blood pressure.

In addition to genomic effects, aldosterone also induces rapid non- genomic effects predominantly in the non epithelial tissue[13]. These effects are mediated by a wide variety of intracellular second messengers as well as by RAAS. There is cross talk between angiotensin II and type 1 angiotensin II receptor regulated pathways and aldosterone and the mineralocorticoid receptor in vascular smooth muscle cells and cardiomyocytes. Despite multiple and complicated actions, it may be stated that synergistic actions between aldosterone and angiotension II in endothelial cells and vascular smooth muscle cells cause direct target organ damage, and also directly promote vascular inflammation, fibrosis, remodelling and finally hypertension.

Aldosterone and cardiovascular disease

The mineralocorticoid receptors and the enzyme 11-hydroxysteroid dehydrogenase have been demonstrated in the heart, and in addition to its classical effects of fluid and sodium retention and potassium excretion, it also exerts direct effects on the myocardium. It promotes increased collagen accumulation and the development of fibrosis in hypertrophied cardiac ventricles, reduces myocardial perfusion and increases the incidence of cardiovascular events [14]. Significant relationship between plasma aldosterone and echocardiographic parameters of the left ventricle such as left ventricular size and mass, and cardiac index have been demonstrated[15,16]. Aldosterone causes autonomic imbalance, electrolyte abnormalities, contributing to myocardial dysfunction, arrhythmias, cardiovascular events and sudden cardiac death[17].

Further support comes from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) which established that elevated plasma aldosterone was associated with the pathogenesis and progression of heart failure[18]. All these observations indicate that direct and indirect actions of aldosterone play an important role in the myocardial structural changes that lead to pathological hypertrophy.

Inhibitors of aldosterone through mineralocorticoid receptor blockade

Blockade of the mineralocorticoid receptor has been demonstrated as a useful target for antihypertensive therapy and may be used as monotherapy or add-on therapy in the treatment of hypertension and other conditions such as heart failure. Patients with a clinical condition for an aldosterone receptor antagonist should be initiated on these drugs, only if, they have a baseline serum K+ < 5.0 meq/l and a serum creatinine <2.5 mg/ dl for men or 2,0 mg/ dl for women[19]. Serum K+ and creatinine levels should be monitored 4 weeks after the start of treatment or after 1 week in those patients with an increased risk of severe hyperkalemia (6.0 meq/l) such as patients with diabetes or reduced renal function with a glomerular filtration rate <60 ml/ minute

Amongst patients with left ventricular systolic dysfunction, almost 1/3rd have clinically important levels of aldosterone despite serological evidence of complete ACE inhibition[15]. This phenomenon as aldosterone breakthrough may explain the beneficial effects of aldosterone receptor antagonists when added to ACEIs in patients with symptomatic congestive heart failure[20].

Spironolactone

Spironolactone is a nonselective aldosterone receptor antagonist that is extensively metabolized to its active metabolites in the liver. The plasma half life of the drug is 1.4 hours, but this duration may increase by up to five fold in patients with congestive heart failure because of the hepatic congestion. Spironolactone is structurally similar to progesterone, thereby allowing sex-steroid receptor cross activity. This phenomenon accounts for the antiprogesterone and antiandrogen effects observed in some patients treated with spironolactone. Spironolactone is indicated for use in severe (NYHA class III-IV) CHF with LV systolic dysfunction, essential hypertension and primary hyperaldosteronism.

Spironolactone produces its actions chiefly by inducing natriuresis but it probably also produces other effects as it has been shown to reduce blood pressures even in anuric patients on maintenance hemodialysis[21]. Spironolactone has been demonstrated to lower blood pressure as effectively as thiazide diuretics in patients with low rennin levels and aldosterone to rennin ratio[22]. Spironolactone is also effective in patients with resistant hypertension when used as fourth line agent at very low doses[23, 24]. Another study has demonstrated the efficacy of low dose spironolactone in chronic kidney disease with resistant hypertension[25]. Adding spironolactone[25] mg/day to an angiotensin receptor blocker in patients with chronic glomerulonephritis resulted in further BP reduction and a 13% decrease in proteinuria[26].

Spironolactone was also found to be useful in New York Heart Association (NYHA) class III to IV patients with LV systolic dysfunction, in the RALES trial where it reduced the mortality by 30% over[24] months when added to an ACEI and loop diuretic therapy[27].

Eplerenone

Eplerenone is a second generation selective aldosterone receptor antagonist derived from spironolactone but with a major difference that it has limited affinity for the progesterone and androgen receptors and therefore lacks sex related adverse side effects. Eplerenone is metabolized by cytochrome P450 and

has a plasma half life of 4 to 6 hours; the steady state drug levels are usually achieved 48 hours after the first dose. Eplerenone is indicated for use in severe (NYHA class III- IV) CHF after myocardial infarction and hypertension. Aldosterone mediated increase in vascular tone is related to a non-genomic mechanism. It is interesting to note that eplerenone is effective in blocking the vasoconstrictor action of aldosterone and non-genomic effects on sodium proton exchanger activity or intracellular calcium responses[28]. Eplerenone has been found to be as effective as spironolactone for lowering the blood pressure and more effective than other commonly used drugs in the management of hypertension. An important observation with eplerenone has been the beneficial role in hypertensive patients with vascular remodeling; eplerenone prevents remodelling by inhibiting both, in-vitro cell stiffening and reduction in nitric oxide synthesis in endothelial cells[29].

In lines with results of RALES[27], the addition of eplerenone to optimal medical therapy in the EPHESUS (Eplerenone Post-Myocardial Infarction Heart Failure Efficacy and Survival) trial demonstrated that the drug contributed to the improvement in survival and hospitalization rates among patients with acute myocardial infarction complicated by left ventricular dysfunction[30]. The number of deaths from any cause was significantly lower in the eplerenone group in comparison to the placebo group. Similarly, deaths from cardiovascular cause or hospitalization for a cardiovascular event were also reduced with eplerenone therapy (Figure V).

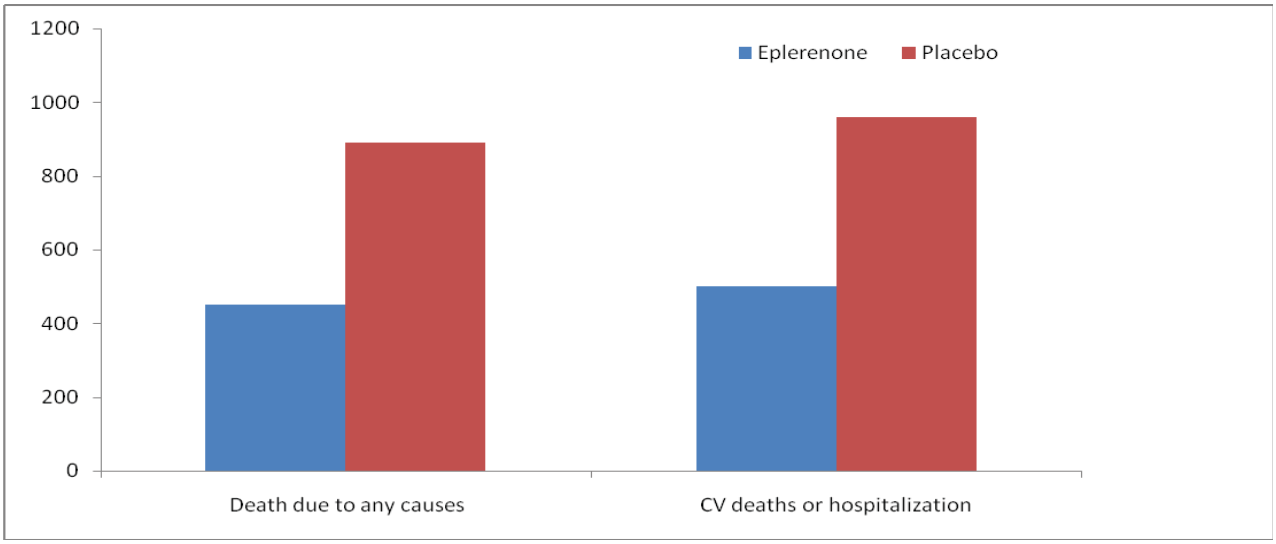

Figure V: Eplerenone therapy on primary outcomes in the EPHESUS trial

Eplerenone treatment also produced significant beneficial effects on the secondary endpoints (Figure VI).

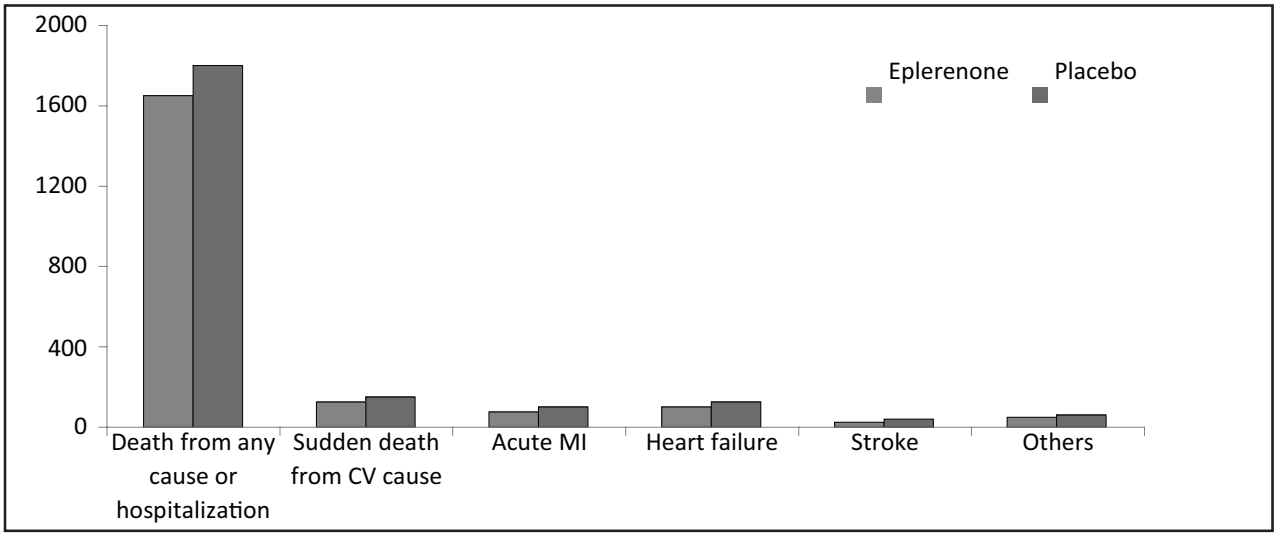

Figure VI: Eplerenone therapy on secondary end points in the EPHESUS trial

Eplerenone treatment led to an increased incidence of serious hyperkalemia, though there were no deaths in the eplerenone group attributable to hyperkalemia. The risk \was significantly increased among patients who had a decreased creatinine clearance at baseline (< 50 ml/ minute). Strict monitoring of serum potassium excluding patients with a baseline serum potassium concentration of more than 5 Meq/l, a baseline serum creatinine concentration of more than 2.5 mg/ dl, or both could help in optimizing the utilization of this drug.

Summary

Scientific advances have helped in improving our understanding about the relationship between hyperaldosteronism and cardiovascular dysfunction and expanded the spectrum of patients who may benefit from pharmacotherapy towards aldosterone blockade. These advances have also prompted the use of aldosterone receptor antagonists for the treatment of cardiovascular diseases, particularly hypertension where these agents are underused. Evidence from RALES and EPHESUS was a significant first step and will form the platform over which future trials in order to gain more evidence and improve our understanding and patient care.

References:

1) Black HR. Evolving role of aldosterone blockers alone and in combination with angiotension converting enzyme inhibitors or angiotensin II receptor blockers in hypertension management: a review of mechanistic and clinical data. *Am Heart Jour. 2004;* ***147*** (4): 564-572. http://dx.doi.org/10.1016/j.ahj.2003.10.034 PMid:15077068

2) Williams GH. Aldosterone biosynthesis, regulation and classical mechanism of action. *Heart failurereviews.*2005; *10(1):7-13*. http://dx.doi.org/10.1007/s10741-005-2343-3 PMid:15947886

3) Bonvalet JP, Alfaidy N, Farman N, Lombes M. Aldosterone: intracellular receptors in human heart. *Eur Heart J.* 1995; **16** (suppl N): 92-97.

4) Struthers AD. Aldosterone induced vasculopathy. *Mol cell Endocrinol*. 2004; **217**: 239-241. http://dx.doi.org/10.1016/j.mce.2003.10.024 PMid:15134823

5) Joffe HV, Adler GK. Effect of aldosterone and mineralocorticoid recetor blockade on vascular inflammation. *Heart fail Rev.* 2005; **10**: 31-37. http://dx.doi.org/10.1007/s10741-005-2346-0 PMid:15947889

6) Connell JM, Davies E. The new biology of aldosterone. *J Endocrinol.* 2005; **186**: 1-20. http://dx.doi.org/10.1677/joe.1.06017 PMid:16002531

7) Wehling M, Spes CH, Win N, et al. Rapid cardiovascular action of aldosterone in man. *J Clin Endocrinol* Metab. 1998; **83**: 3517-3522. http://dx.doi.org/10.1210/jc.83.10.3517

8) Losel R, Wehling M. Non-genomic action s of steroid hormones. Nat Rev. 2003; 4: 46-56. http://dx.doi.org/10.1038/nrm1009 PMid:12511868

9) Booth RE, Johnsons JP, Stockand JD. Aldosterone. *Adv Physiol Educ*. 2002; **26:** 8-20. PMid:11850323

10) Perico N, Benigni A, Remuzzi G. Present and future drug treatments for chronic kidney diseases: evolving targets in reno protection. *Nat Rev Drug Discov*. 2008; **7**(11): 936-953. http://dx.doi.org/10.1038/nrd2685 PMid:18846102

11) Hene RJ, Boer P, Koomans HA, Mees EJD. Plasma aldosterone concentrations in chronic renal disease. *Kidney International*. 1982; **21**: 98-101. http://dx.doi.org/10.1038/ki.1982.14

12) Vasan RS, Evans JC, Larson MG, et al. Serum aldosterone and the incidence of hypertension in nonhypertensive patients. *N Engl J Med.* 2004; **351**: 33-41. http://dx.doi.org/10.1056/NEJMoa033263 PMid:15229305

13) Grossman C, Gekle M. New aspects of rapid aldosterone signaling. *Mol Cell Endocrinol* 2009; **308**:53-62. http://dx.doi.org/10.1016/ j.mce.2009.02.005 PMid:19549592

14) Weber KT, Sun Y, Guarda E, katwa LC, Ratajska A, Cleutjens JPM, et al. Myocardial fibrosis in hypertensive heart disease: An overview of potential regulatory mechanisms. *Europ Heart J.* 1995; **16** (Suppl C): 24-28.

15) Brilla CG, Maisch B, Zhon G, Weber KT. Hormonal regulation of cardiac fibroblast function. *Europ Heart Jr.* 1995; **16** (Suppl C): 45-50. PMid:7556272

16) Rossi GP, Sacchetto A, Pavan E, Scognamiglio R,

Pietra M, Pessina AC. Left ventricular systolic function in parimary aldosteronism and hypertension. *J hypertens* 1998; **16**: 2075-2077. http://dx.doi.org/10.1097/00004872-199816121-00032 PMid:9886899

17) Struthers AD. Cardiovascular assault. *Amer Heart J* 2002; **144** (Suppl 5): S2-S7. http://dx.doi.org/10.1067/mhj.2002.129969, PMid:12422134

18) Swedberg K, Eneroth P, Kjeskhus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation.* 1990; **82**: 1730-1736. http://dx.doi.org/10.1161/ 01.CIR.82.5.1730 PMid:2225374

19) Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. ACCF/ AHA guidelines for the diagnosis and management of heart failure in adults.: a report of the American college of cardiology foundation/ American heart Association Task Force on Practsie guidelines; developed in collaboration with the international society for Heart and Lung Transplantation. *Circulation.* 2009; **119:** 1977-2016. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192064 PMid:19324967

20) Jorde UP, Vittorio T, Katz SD, Colombo PC, Latif F, Le Jemtel TH. Elevated plasma aldosterone levels despite complete inhibition of the vascular angiotensin-converting enzyme in chronic heartfailure.

21) Gross E, Rothstein M, Dombek S, et al. Effect of spironolactone on blood pressure and the renninangiotensin-aldosterone in oligo-anuric hemodialysis patients. *Am J Kidney Dis*. 2005; **46:** 94-101. http://dx.doi.org/10.1053/j.ajkd.2005.03.005 PMid:15983962

22) Hood SJ, taylor KP, AshbyMJ, Brown MJ. The spironolactone, amiloride, losartan and thiazide (SALT) double blind crossover trial in patients with low rennin hypertension and elevated aldosterone-renin ratio. *Circulation.* 2007: **116(3):** 268-275. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.690396 PMid:17606839

23) Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low dose spironolactone in subjects with resistant hypertension. *Am J Hypertension.* 2003; **16:** 925-930.http://dx.doi.org/10.1016/S0895-7061(03)01032-X

24) Lane DA, Shah S, Beevers DG. Low dose spironolactone in the management of resistant hypertension; a surveillance study. *J Hypertens.* 2007: **25** (4): 891-894.z http://dx.doi.org/10.1097/HJH.0b013e328014954d PMid:17351384

25) Abolghasmi R, Taziki O. Efficacy of low dose Spironolactone in Chronic Kidney Disease with Resistant Hypertension. *Saudi J Kidney Dis Transplant* 2011; **22(1)**: 75-78. PMid:21196617

26) Nitta K, Uchida K, Nihei H. Spironolactone and angiotensin receptor blocker in non diabetic renal disease. *Am J Med.* 2004; **117:** 44-445. http://dx.doi.org/10.1016/j.amjmed.2004.04.020 PMid:15380506

27) Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: randomized Aldactone Evaluation Study Investigators. *N Eng J Med.* 1999; **341**: 709-717. http://dx.doi.org/10.1056/NEJM199909023411001 PMid:10471456

28) Michea L, Delpiano AM, Hitschfeld C, et al. Eplerenone blocks non genomic effects of aldosterone on the Na+/ H+ exchanger, intracellular calcium levels and vasoconstriction in mesenteric resistance vessels. *Endocrinol.* 2004; **146** (3): 973-980. http://dx.doi.org/10.1210/en.2004-1130 PMid:15550504

29) Imanishi T, Ikejima H, Tsujioka H, Kuroi A, Kobayashi K, Muragaki Y, et al. Addition of eplerenone to an angiotensin converting enzyme inhibitor effectively improves nitric oxide bioavailability. *Hypertension.* 2008; **51**(3): 734-741. http://dx.doi.org/10.1161/HYPERTENSIONAHA.107.104299 PMid:18227404

30) Pitt B, Remme W, Zannad f, et al. The Eplerenone Post-Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348:** 1309-1321. http://dx.doi.org/10.1056/NEJMoa030207 PMid:12668699