



Published in final edited form as:

Circ Res. 2015 January 2; 116(1): 206–213. doi:10.1161/CIRCRESAHA.116.302706.

Translational Success Stories: Role of Mineralocorticoid Receptor Antagonists in Cardiovascular Disease

Carlos M Ferrario, MD¹ and Ernesto L Schiffrin, MD, PhD.²

¹Hypertension Translational Research Laboratory, Departments of Surgery, Internal Medicine-Nephrology, and Physiology-Pharmacology, Wake Forest University Health Science Center, Winston Salem, North Carolina 27157

²Department of Medicine, and Lady Davis Institute for Medical Research, SMBD-Jewish General Hospital, McGill University, Montreal, PQ, Canada H3T 1E2

Abstract

Aldosterone exerts its best known sodium homeostasis actions by controlling sodium excretion at the level of the distal tubules via activation of the apical epithelial sodium channel (ENaC) and the basolateral Na⁺/K⁺ ATPase pump. Recently, this mineralocorticoid hormone has been demonstrated to act on the heart and blood vessels. Excess release of aldosterone in relation to the salt status induces both genomic and non-genomic effects that by promoting endothelial dysfunction, and vascular and cardio-renal adverse remodeling, contribute to the target organ damage found in hypertension, heart failure, myocardial infarction and chronic renal failure. Mineralocorticoid receptor blockers have been shown to be highly effective in resistant hypertension and to slow down heart failure progression, and in experimental animals, the development of atherosclerosis. Blockade of the action of aldosterone and potentially other mineralocorticoid steroids has been increasingly demonstrated to be an extremely beneficial therapy in different forms of cardiovascular disease. This review provides a summary of the knowledge that exists regarding aldosterone actions in the cardiovascular system and, in providing the translational impact of this knowledge to the clinical arena, illustrates how much more needs to be achieved in exploring the use of mineralocorticoid receptor blockers in less advanced stages of heart, renal, and vascular disease.

Keywords

Hypertension; heart failure; chronic renal failure

Address for Correspondence: Carlos M Ferrario, MD, Department of Surgery, Wake Forest University Health Science Center, Medical Center Blvd., Winston-Salem, NC 27157, Phone: 336-716-5849, Fax: 336-716-6644, cferrari@wakehealth.edu.

Disclosures

CM Ferrario reports that there are no disclosures to be documented. EL Schiffrin reports that there are no disclosures to be documented.

INTRODUCTION

The renin-angiotensin-aldosterone (RAAS) system is a powerful hormone regulatory mechanism serving multiple functions as a key determinant of tissue perfusion pressure and cellular homeostasis. Since the original demonstration of renin in renal extracts characterization of the biochemical physiology and mechanisms of action of this system has become one of the major accomplishments of the biomedical research enterprise. It is also a fruitful example of translational medicine, with major impact on the therapy of cardiovascular disease as a consequence of the development of drugs that inhibit the pathological actions of angiotensin II (Ang II) and its interplay with the adrenocortical steroid aldosterone.

The knowledge of how the RAAS functions has taken diverse routes that entail exploring the pathways by which Ang II is produced in blood and tissues, the functions and signaling mechanisms for the action of the hormone, and its link to the processes by which aldosterone is formed and acts through its interplay with Ang II and the neuro-hormonal mechanisms regulating salt and water intake. The translational lessons derived from the original reports of Ang II and aldosterone biosynthesis embodies an extensive medical literature, the highlights of which resulted in the development of angiotensin converting enzyme (ACE) inhibitors, Ang II receptor antagonists (ARBs), direct renin inhibitors (DRI), and mineralocorticoid receptor (MR) antagonists. It would be a futile effort to detail accurately the complete history of these accomplishments, as they constitute a body of literature of several hundred papers and more than one hundred years of exemplary discoveries. This review provides a succinct summary of the translational therapeutic outcomes for aldosterone and Ang II given their key interplay in cardiovascular regulation through a narrative synthesis of accomplishments and the inclusion of the timeline of discoveries documented in Table 1.

Aldosterone Biosynthesis and Functions

The isolation of aldosterone can be traced back to the early 1930s when researchers succeeded in obtaining biologically active extracts free of contaminating compounds from the adrenal medulla. As narrated by Tai et al. ¹, this work was accomplished by several teams of investigators working at Columbia University ², the Mayo Clinic ³ and the Ciba group in Basel ⁴. Aldosterone crystals were obtained first from human urine collected from two patients with congestive heart failure (HF) ⁵. Table 1 documents the evolution of the research leading to the final synthesis of aldosterone by the Ciba group of investigators in 1955. Whereas the clinical role of aldosterone in disease processes continues to expand, the classification provided by Genest, Kuchel, and Nowacynski (1973) (Table 2) summarizes the involvement of this adrenal hormone in human hypertension ⁶.

Normal adrenal steroidogenesis leads to the production of glucocorticoids, mineralocorticoids, and sex hormones. While glucocorticoid secretion is regulated primarily by pituitary ACTH, Ang II acts as the primary stimulus for aldosterone secretion ⁷. The mechanisms by which aldosterone interplays with the regulation of blood pressure and the control of renal salt excretion (Figure 1) are mediated by the MR, a ligand-activated transcription factor that is a member of the nuclear receptor superfamily ⁸. The relatively

slow genomic aldosterone actions influence renal gene expression of proteins that regulate Na⁺/K⁺ ATPase activity and the renal epithelial sodium and outer medullary potassium channels⁹. Of importance, aldosterone has a significant influence in the activation of genes participating in the genesis of adverse cardiac and vascular remodeling. Aldosterone can exert direct vasoconstrictor actions^{10, 11} and in normal healthy volunteers the effects of aldosterone in forearm blood flow were dose-dependent¹². In vascular smooth muscle cells (VSMCs), aldosterone induces a proliferative response through increased expression of p53 binding protein¹³. Wehling and colleagues^{14–16} and Rautureau et al.⁸ provide a comprehensive discussion of aldosterone non-genomic effects, which are in the order of minutes rather than hours^{17, 18}. In addition, aldosterone can upregulate vascular angiotensin receptors¹⁹, a finding that is critically important in understanding vasoconstrictor and inflammatory mechanisms of the interplay among Ang II, aldosterone, and salt intake. Collagen deposition in the vasculature leading to vascular stiffness was prevented in VSMCs from mice with conditional inactivation of the MR²⁰. The authors concluded that the MR influences vascular elasticity by modulation of cell-matrix attachment proteins independent of major vascular structural changes²⁰.

The interactions between MRs and angiotensin receptors appear to explain many of the effects found when blocking either of these receptors²¹. These signaling pathways are important in explaining the mechanisms by which MRs induce cardiac and vascular collagen deposition, activation of pro-inflammatory cytokines, and increases in oxidative stress^{8, 22–27}. Recently, evidence has been produced of a role of placental growth factor in the mediation of aldosterone action²⁸. Furthermore, aldosterone proatherogenic effects may in part be mediated by stimulation of placental growth factor²⁹. The effects on atherosclerosis are mediated via MRs as demonstrated in mice with deletion of smooth muscle MRs²⁰ or administration of MR antagonists³⁰. Furthermore, the aldosterone contribution to atherosclerosis progression may include facilitation of aortic aneurysm formation³¹.

Atherogenic effects of aldosterone may relate to its role in inflammation, stimulation of oxidative stress, endothelial dysfunction, and prothrombotic activity^{26, 32, 33}. Aldosterone, in association with inflammatory mediators such as interferon- γ (IFN- γ) and tumour necrosis factor α (TNF- α), stimulate growth and proliferation of VSMCs, leading to adverse vascular remodeling³⁴. Moreover, new fascinating data shows prevention of vascular and renal inflammatory responses following administration of T-regulatory lymphocytes both to Ang II-infused³⁵ and to aldosterone-infused mice^{23, 34}. The finding that Ang II functions as an obligatory mediator pathway for the formation of aortic fatty streaks in the presence of hypercholesterolemia and no changes in arterial pressure was first demonstrated in monkeys³⁶. These findings led to the hypothesis that the RAAS is a critical contributor to the pathogenesis of atherosclerosis through stimulation of oxidative stress, inflammatory cytokines, and recruitment of monocytes into the subendothelial vascular spaces^{36–39}. Proatherogenic aldosterone mechanism occurs via induction of oxidative stress, endothelial dysfunction, activation of adhesion molecules, and up-regulation of ACE and AT₁ receptors (see²⁷ for review). Atherogenic actions of aldosterone can be prevented by eplerenone administration^{40–42}. In primary aldosteronism, plasma osteopontin (OPN) levels are higher than those in essential hypertensive subjects, and in OPN-knockout mice reduced renal

interstitial fibrosis is induced by aldosterone infusions^{43, 44}. An intriguing study showed that aldosterone can stimulate the release of Willebrand factor and IL-8 via exocytosis of Weibel–Palade bodies⁴⁵. This non-genomic effect is a potentially powerful mechanism for the activation of proinflammatory factors. Prothrombotic aldosterone actions include stimulation of plasminogen activator inhibitor-1 (PAI-1), a finding that may contribute to extracellular collagen deposition as PAI-1 inhibits the production of plasmin from plasminogen⁴⁶. The opportunity to advance the use of MR antagonists in prevention or management of coronary heart disease is a tantalizing proposition as mortality due to myocardial infarction worsens in the presence of hyperaldosteronism^{47–50}.

Adrenal glands contain the genes and proteins for local tissue production of bioactive angiotensins⁵¹. Cells in the zona glomerulosa contain the highest levels of renin activity and Ang II. The independence of this tissue system from that of the circulation or the kidney is based on the demonstration that renin activity is not suppressed in anephric rats, while increases in adrenal renin and aldosterone are independent of plasma or kidney renin concentrations^{52–54}. The role of this adrenal RAAS remains to be elucidated. Nevertheless, the interdependent nature of the interplay between aldosterone and Ang II in the regulation of cardiovascular function entails both a stimulatory action of the peptide in the systemic release of aldosterone and the ability of aldosterone to increase the expression of angiotensin receptors in vascular smooth muscle cells⁵⁵. In VSMCs intracellular mobilization of calcium (Ca^{2+}) by Ang II is augmented in the presence of aldosterone via increased expression of extracellular-signal-regulated kinase (ERK1/2) and c-Jun N-terminal kinase (JNK) pathways^{15, 56}. Moreover, eplerenone blocked mitogen-activated protein kinase (MAPK) activation, radical oxygen species (ROS) generation, and epidermal growth factor receptor (EGFR) transactivation⁵⁷. The aldosterone-induced activation of ERK1/2, JNK and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) has been reported to be dependent on the transactivation of AT_{1a} but not AT_{1b} receptors^{8, 21}. This interpretation agrees with two published studies showing that: a)- eplerenone inhibits aldosterone vasoconstrictor actions and non-genomic effects on the sodium-proton exchanger (NHE1) activity or intracellular Ca^{2+} responses of rat mesenteric vessels⁵⁸; and b)- aldosterone-mediated mesenteric artery vasoconstriction are blunted in AT_{1a} knockout mouse^{8, 21, 59}.

Mice in which a VSMC-specific deletion of MR (VSMC-MR) has been induced have lower blood pressure as they age⁶⁰. This occurs despite the absence of changes in sodium excretion, indicating that the kidney effects of aldosterone do not participate in these effects. There is also absence of vascular remodeling. Interestingly, the aged VSMC-MR mice exhibited a reduction in vascular myogenic tone and Ang II-dependent contraction, and this was associated with reduced expression and activity of L-type Ca^{2+} channels. Changes in myogenic tone appeared to be related to reduce density of the L-type Ca^{2+} channel Cav1.2. Thus, VSMC-MR seems to contribute to Ang II–induced vascular oxidative stress, contraction, and elevated blood pressure, and vascular MR-mediated vascular tone may participate in control of blood pressure as well as vascular aging⁶⁰.

Salt excess appears to be important for aldosterone to exert its hypertensive action in rodents, especially in rats^{61, 62}, whereas in mice even in the presence of salt, and despite powerful pro-inflammatory actions, aldosterone exerts little effect on blood pressure²³. The

reason for this difference is unclear. However, the effect of salt on aldosterone effects may explain that in essential hypertensive patients with stage 1 hypertension, blockade of MR has a mild antihypertensive action, whereas in uncontrolled or in resistant hypertension, often associated with excess consumption of salt, the effects of MR blockade are much more powerful. Salt consumption by hypertensive and HF patients probably is a confounder of the efficacy of MR blockade in clinical trials.

Translational Correlates

Dysregulation of MR participates in the pathogenesis of cardiovascular disease either via amplification of the proliferative, pro-inflammatory and prothrombotic effects of excess Ang II levels or excess secretion of aldosterone. Knowledge of the direct effects of hyperaldosteronism on cardiovascular function resulted from Conn's report of the association of high blood pressure and hypokalemia in a woman with a diagnosis of primary aldosteronism^{63, 64}. However, as early as 1937, Steigler and Reichstein⁶⁵ had reported a syndrome of hypokalemia and hypertension associated with the administration of synthesized deoxycorticosterone. A syndrome resembling primary aldosteronism without elevated aldosterone levels is associated with inhibition of 11- β -hydroxysteroid dehydrogenase enzyme (11- β -OHS) ⁶⁶⁻⁶⁸. This apparent mineralocorticoid excess process results from increased binding of cortisol to MR since the 11- β -OHS accounts for the conversion of cortisol to cortisone. Nevertheless, the contribution of aldosterone to cardiovascular pathology remained elusive until the publication of a sensitive radioimmunoassay⁶⁹ and a more comprehensive understanding of its role in the control of electrolyte homeostasis⁷⁰. Availability of a measure of aldosterone activity provided a tool to seek the contribution of this hormone to the pathophysiology of essential hypertension, an effort that led to identification of subsets of hypertensive subjects where aldosterone was associated with sodium retention and hypertension. Williams and Hollenberg^{71, 72} characterized a subset of essential hypertensive patients that they have named as "non-modulators". These individuals are now recognized to associate hypertension with salt-sensitivity, insulin resistance, and RAAS gene polymorphisms⁷³⁻⁷⁵. A state of hyperaldosteronism is also found in diseases associated with important alterations in body fluid volumes, particularly HF, cirrhosis accompanied by ascites, and the nephrotic syndrome⁵¹.

Although most studies in hypertensive subjects have not demonstrated elevations of plasma aldosterone except in few patients⁷⁶, quartiles of plasma levels of aldosterone in the Framingham study were directly associated with blood pressure levels⁷⁷. Moreover, treatment with MR blockers lowers blood pressure in patients with hypertension⁷⁸, and particularly in resistant hypertension⁷⁹. The MR blocker spironolactone prevented vascular fibrosis independently of blood pressure reduction in spontaneously hypertensive rats⁸⁰⁻⁸². The more selective but less potent MR blocker eplerenone also reduces small artery fibrosis and stiffness in stage 1 essential hypertension, possibly contributing to the antihypertensive actions of MR antagonism as well as improvement of tissue perfusion⁷⁸. Spironolactone has also been shown to block some of the effects of Ang II⁸², indicating that aldosterone mediates some actions often attributed to direct effects of the peptide. The effects with MR

blockers are mimicked by aldosterone synthase inhibitors, indicating that spironolactone and eplerenone effects are probably mediated by blockade of aldosterone actions⁸³.

The important role of aldosterone in the regulation of sodium and potassium balance led to the exploration of the potential clinical benefits that could be derived from blocking the MR. The synthesis of the first MR antagonist (spironolactone) by the chemists at Searle laboratories lagged for almost 30 years behind the identification of aldosterone^{84–87}. As commented by Delyani,^{88, 89} the drug was initially labelled as a potassium-sparing diuretic given that at that time the known aldosterone actions were limited to epithelial ion transport. Spironolactone (7-acetate of the γ -lactone of 17-hydroxy-7-mercapto-3-oxo-17- α -pregn-4-ene-21-carboxylic acid) acts as a competitive antagonist of the MR (but also other steroid receptors such as the androgen receptor, leading to both its adverse side effects and also some additional therapeutic indications as a consequence of its antiandrogenic effects). The drug is rapidly cleared from the circulation ($T_{1/2}$ 10 minutes) to two principal metabolites (canrenoate and canrenone)^{86, 87, 89}.

The most compelling results for the participation of aldosterone in the pathogenesis of cardiovascular disease derived from the use of MR antagonists in HF. The rationale for the exploration of blocking MRs in HF was based on the observation that ACE inhibitors had only a transient Ang II suppression action and that the same could be demonstrated for plasma aldosterone⁸⁹. It was therefore reasoned that addition of spironolactone on top of background ACE therapy could have a greater impact on the progression of HF. The Randomized ALdactone Evaluation Study (RALES) trial established the benefits of aldosterone antagonists in the evolution of severe HF (NYHA class III/IV)⁹⁰. In this trial, 1,663 subjects with a diagnosis of severe heart failure (ejection fraction < 35%) were randomized to conventional therapy (ACE inhibitor, loop diuretic and digoxin in most subjects) plus placebo or the combined use of conventional therapy plus spironolactone (25 mg/day). The trial was interrupted after a mean follow-up period of 24 months because an interim analysis showed a significant 35% reduction in all causes of death in the spironolactone-treated group compared to the placebo medicated subjects⁹⁰. The beneficial effects of spironolactone were associated in this trial with significant reductions in the frequency of hospitalization for worsening HF and HF symptomatology. Since the greatest benefits were observed in subjects in whom spironolactone was administered on top of background ACE inhibitor therapy, it is clear that combined suppression of Ang II formation and aldosterone production was enhanced through blockade of the MR.

The pleotropic actions of aldosterone on the cardiovascular system, particularly the aldosterone-mediated collagen synthesis that contributes to adverse left ventricular remodeling, prompted an examination of the action of MR antagonists in subjects' post-myocardial infarction. The trial was in part based on finding that adrenalectomy or eplerenone attenuated the adverse cardiac remodeling in an Ang II model of experimental hypertension⁶². The Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS) determined the effect of the MR antagonist eplerenone on morbidity and mortality among patients with acute myocardial infarction⁹¹. Eplerenone (pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ -lactone, methyl ester) is a selective MR antagonist devoid of the progestational and anti-androgenic side effects of

spironolactone and shows minimal activity on P450 enzymes. During a mean 16-month follow-up, patients with acute myocardial infarction complicated by left ventricular dysfunction and HF assigned to eplerenone and associated optimal medical therapy demonstrated significantly reduced morbidity and mortality⁹¹. The beneficial effect of aldosterone blockade in the evolution of HF can be shown even in those subjects with milder forms of the syndrome. This was found in another trial that recruited NYHA class II systolic HF subjects. Patients enrolled in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study showed a reduced rate of hospitalization and death when treated with eplerenone^{92, 93}.

The landmark studies using MR antagonists in HF have in part overshadowed the potential use of these agents in a broader patient population, such as individuals with cardiac arrhythmias, myocardial ischemia secondary to cardiac fibrosis, and diastolic dysfunction⁹⁴. Spironolactone can prevent cardiac collagen deposition in two experimental rat models of hypertension independent of the drug effect on blood pressure and cardiac hypertrophy^{94, 95}. Translational outcomes of these experimental studies are contained in a study where spironolactone improved echocardiographic measurements of myocardial relaxation in patients with exertional dyspnea and abnormal left ventricular filling patterns⁹⁶. These important findings need further confirmation as diastolic dysfunction associated with heart failure and preserved ejection fraction (HFpEF) has no known effective treatment^{97, 98}. The Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart (TOPCAT) has addressed the potential benefit of spironolactone on 3,445 patients with symptomatic heart failure and HFpEF^{99, 100}. However, results have been disappointing, since only hospitalization for heart failure was reduced by MR antagonism, whereas other endpoints such as the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF did not differ statistically with placebo¹⁰¹.

Other areas where additional research is needed relate to the observation that spironolactone suppresses QT-dispersion¹⁰² and sudden death in subjects that were enrolled in the RALES and EPHEsus trials. It is not known whether these antiarrhythmic actions of aldosterone antagonism are related to conservation of total body potassium and magnesium or reversal of cardiac fibrosis. An attractive alternative hypothesis for the antiarrhythmic effects of MR antagonists has been provided by studies using mice with conditional cardiac-specific overexpression of the human MR¹⁰³. In this experimental model, prolongation of ventricular repolarization and presence of severe ventricular arrhythmias due to overexpression of the human MR were prevented by spironolactone administration¹⁰³. Additionally, aldosterone arrhythmogenic actions may relate to myocyte gap junction remodeling through its dual effects on the expression of connexin 43 (Cx43)^{42, 104}. This is clearly an area of potential fruitful research.

Summary

Aldosterone's main physiological function maintains sodium homeostasis through its direct action on controlling sodium excretion at the level of the distal tubules via activation of the apical epithelial sodium channel (ENaC) and the basolateral Na⁺/K⁺ ATPase pump¹⁰⁵. An

excess production/release of aldosterone in relation to the salt status induces a genomic and non-genomic effect that in experimental animals leads to vascular remodeling, endothelial dysfunction and cardio-renal adverse remodeling including the structural and functional consequences of increased collagen deposition. In humans, the non-genomic actions of aldosterone through MR are somewhat more varied as vasoconstriction, vasodilatation or no effects have been observed¹⁰⁶. Amphibatic actions of aldosterone in humans may be related to doses employed, the baseline plasma aldosterone levels¹⁰⁷, as well as salt status. The more chronic effects of aldosterone play a critical role in contributing to target organ damage associated with hypertension, HF, myocardial infarction and chronic renal failure¹⁰⁵. MR antagonists are powerful treatment agents having a marked beneficial effect in HF progression and resistant hypertension, and in experimental animals, in atherosclerosis. The pleotropic actions of this mineralocorticoid hormone in human primary essential hypertension and the cardiometabolic syndrome await further investigation as emerging evidence demonstrates that the use of MR antagonists may be associated with potentially impressive outcomes^{22,25}.

Acknowledgments

The authors recognize the kind and valuable contribution of Jessica VonCannon, B.S. in proofreading the manuscript.

Sources of Funding

The work of ELS was supported by Canadian Institutes of Health Research (CIHR) grants 37917, 82790, and 102606, a Canada Research Chair on Hypertension and Vascular Research from CIHR/Government of Canada, and the Canada Fund for Innovation. The work of CMF is supported by grant HL-051952 from the National Heart, Lung and Blood Institute of the NIH.

Abbreviations

11-β-OHSD	11-β-hydroxysteroid dehydrogenase enzyme
ACE	angiotensin converting enzyme
Ang II	angiotensin II
ARBs	angiotensin II receptor blockers
Ca²⁺	calcium ion
Cx43	connexin 43
DRI	direct renin inhibitors
EGFR	epidermal growth factor receptor
ENaC	epithelial sodium channel
ERK	extracellular signal-regulated kinase
FMD	flow-mediated vasodilation
HF	heart failure
HFpEF	heart failure and preserved ejection fraction

IFN-γ	interferon γ
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein kinase
MR	mineralocorticoid receptor
NHE-1	sodium/hydrogen exchanger 1
NT	nitrotyrosine
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
Na⁺/K⁺ ATPase	sodium-potassium adenosine triphosphatase pump
OPN	osteopontin
RAAS	renin angiotensin aldosterone system
TNF-α	tumor necrosis factor α
VSMC	vascular smooth muscle cell

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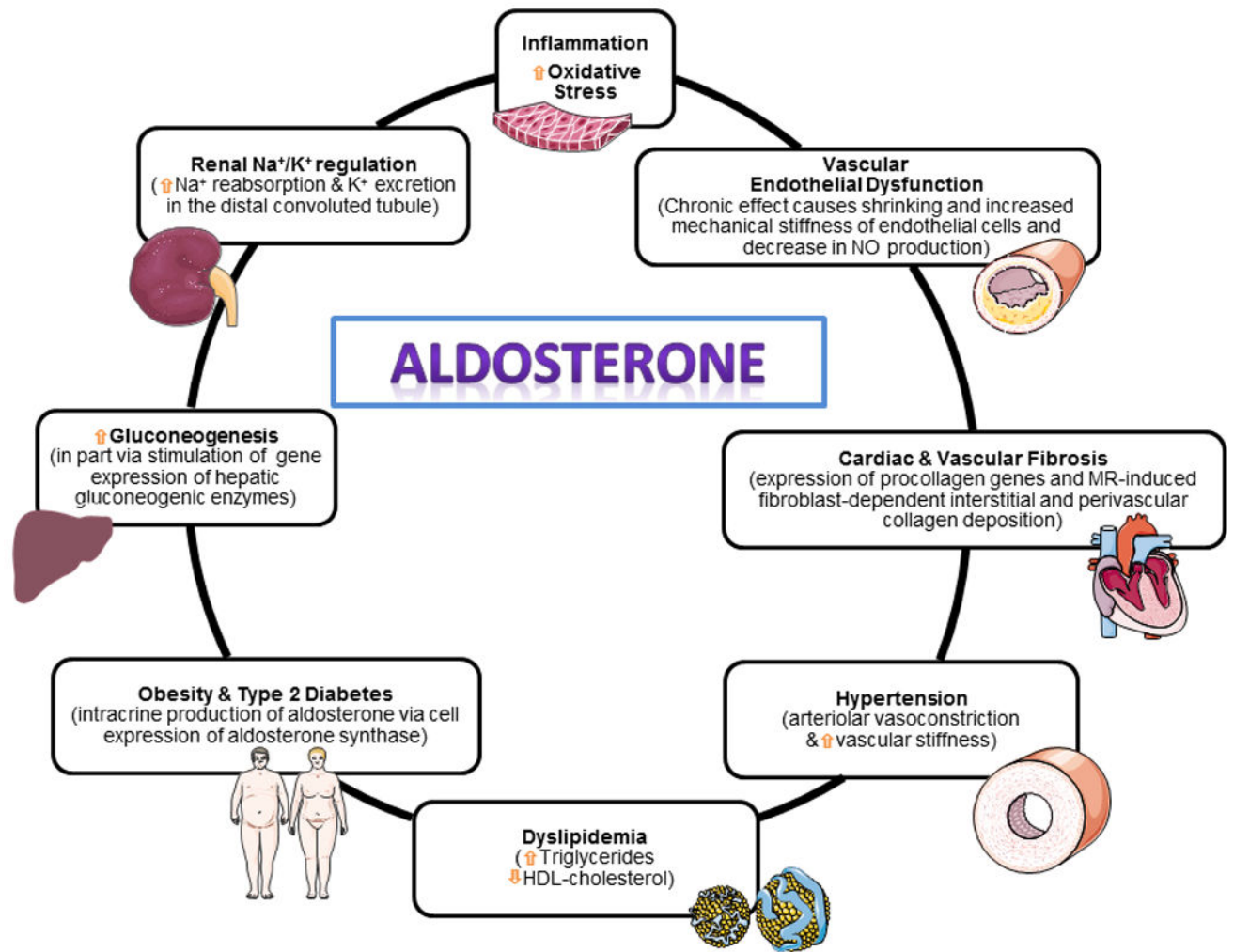


Figure 1. Pleiotropic aldosterone actions contributing to the pathogenesis of cardiovascular disease.

Table 1

Year	Discovery or Major Basic Research Accomplishment
1563	Bartolomeo Eustacchio description of the adrenal gland (glandulae Renibus incumentes). ¹⁰⁸
1855	Addison's first identification of the lethal association of pathological changes in the suprarenal capsules (adrenal glands) with anemia. ¹⁰⁹
1935	Development of biologically active extracts free of contaminating compounds from the adrenal medulla.
1939	Kuizinga and Cartland ¹¹⁰ show potent mineralocorticoid activity in the amorphous fraction of adrenocortical preparations.
1952–1955	Simpson and Tait ^{111–115} critical studies of adrenal mineralocorticoid activity culminate with the isolation of electrocortin, later rename as aldosterone. ¹¹⁶
1954	Aldosterone structure identified as 11_-21-dihydroxy-18-oxo-pregn-4-ene-3,20-dione ^{113,116}
1956	Luetscher et al. ⁵ obtain aldosterone crystals from human urine.
1955–1956	Aldosterone is synthesized by the Ciba group in Basel ^{117,118} .
1956	Giroud et al. ^{119,120} in Montreal, demonstrated that the zona glomerulosa of the rat exclusively produced aldosterone.
Clinical Translational Research	
1955	First description of the primary aldosteronism syndrome ⁶³ .
1999	The Randomized ALdactone Evaluation Study (RALES) trial demonstrates the role for aldosterone antagonists in chronic severe (NYHA class III/IV) systolic HF ⁹⁰ .
2003	The Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS) documents the benefit of aldosterone receptor antagonists in patients with an EF <40% after MI ⁹¹ .
2014	TOPCAT shows moderate effects of spironolactone in heart failure with preserved ejection fraction (HFpEF) since only hospitalization for heart failure benefited in this population from MR antagonism ¹⁰¹ .

Table 2**Adrenal Steroids in Hypertension**

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1. Hypertension caused by overproduction of mineralocorticoid hormones
 - Primary Aldosteronism (Conn's syndrome)
 - 17-alpha-hydroxylase deficiency (Biglieri's syndrome)
 - Virilizing adrenal hyperplasia due to 11-beta hydroxylase deficiency
 - Cushing's syndrome
 - Non-endocrine ACTH producing tumors
 - Adrenocortical carcinoma
 - Iatrogenic (i.e., anovulatory pills, licorice, glucocorticoids, excess salt intake)
 2. Hypertension associated with overproduction of mineralocorticoids
 - Malignant hypertension
 - Hypertension in terminal renal failure
 - True renovascular hypertension
 - Essential hypertension
 - Liddle's syndrome
 3. Congenital enzymatic defects associated with hypertension
 - 17-alpha hydroxylase deficiency
 - 11-beta hydroxylase deficiency
-

Adapted from reference ⁶.