A REVIEW OF EXPERIMENTAL AND CLINICAL PHARMACOLOGY OF ALISKIREN, A NOVEL DIRECT RENIN INHIBITOR(DRI)

An Essay

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by

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List of abbreviations

Abbreviation	Meaning
ACEIs	Angiotensin converting enzyme inhibitors
ACh	Acetylcholine
ACTH	Adrenocorticotrophic hormone
AEs	Adverse effects
ALLAY trial	Aliskiren Left Ventricular Assessment of Hypertrophy trial
ALOFT trial	Aliskiren Observation of Heart Failure Treatment trial
ALTITUDE trial	Aliskiren Trial in Type 2 Diabetes using Cardiovascular and Renal Disease Endpoints
Ang I	Angiotensin I
Ang II	Angiotensin II
ARBs	Angiotensin II type 1 receptor blockers
ASPIRE trial	Safety and Efficacy of Aliskiren in Post Myocardial Infarction Patients trial
AT 1	Angiotensin type 1 receptor
AVOID trial	Aliskiren in the Evaluation of Proteinuria in Diabetes trial
BMI	Body mass index
BNP	Brain-type natriuretic peptide
BP	Blood pressure
CCBs	Calcium channel blockers

CNS	Central nervous system
DBP	Diastolic blood pressure
DN	Diabetic nephropathy
DRI	Direct renin inhibitor
dTGR	Double transgenic rats
eGFR	Estimated glomerular filtration rate
eNOS-/-	Endothelial nitric oxide synthase–deficient
ERK	Extracellular signal-regulated kinase
HCTZ	Hydrochlorothiazide
HF	Heart failure
HOPE trial	Heart Outcomes Prevention Evaluation trial
JG	Juxtaglomerular
Ldlr-/-	LDL receptor-deficient
LV	Left ventricle
LV ANP	Left ventricular atrial natriuretic peptide
LVEF	Left ventricular ejection fraction
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MAP	Mitogen-activated protein
MHC	Major histocompatibility complex
MI	Myocardial infarction
MMP-9	Matrix metalloproteinase 9

msDBP	Mean sitting diastolic blood pressure
msSBP	Mean sitting systolic blood pressure
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form).
NO	Nitric oxide
NT-pro BNP	N-terminal prohormone brain-type natriuretic peptide
PRA	Plasma renin activity
PRC	Plasma renin concentration
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
RPF	Renal plasma flow
SBP	Systolic blood pressure
TGF-β	Transforming growth factor-beta
TG(mRen-2)27	Transgenic rats that harbor the mouse renin gene
WHHL	Watanabe heritable hyperlipidemic

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Introduction

High blood pressure (BP) is a major risk factor for stroke, myocardial infarction, heart failure, peripheral artery disease and renal failure **(Kannel, 1996).** The global prevalence of hypertension is believed to be 25% to 30% in the adult population and is steadily increasing in Western Societies **(Ong et al., 2007).** Among the elderly (>65 years) the prevalence of hypertension is even higher, reaching 50 to 70% **(Fagard, 2002)** and is an increasing public health concern. The condition confers a 3- to 4-fold increased risk of cardiovascular disease and renal failure and is associated with declining cognitive function among the affected patients **(Andersen, 2009).**

There is a continuous independent relationship between elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) and stroke and cardiovascular mortality for all age groups. The mortality risk is doubled for every 20 mmHg rise in SBP and 10 mmHg rise in DBP from the level of 115/75 mmHg **(Lewington et al., 2002).** Based on the steadily increasing proportion of elderly in the population, it can be predicted that cardiovascular and renal complications of high BP will increase even further in the coming decades unless appropriate preventive measures are taken **(Andersen, 2009).**

According to the chain of events, cardiovascular and renal disease, the most frequent causes of morbidity and mortality, can be regarded as progressing along a sort of continuum (Figure 1). The continuum starts with cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking, etc) and evolves with progression of atherosclerotic lesions and organ damage. Hence, the continuum may become clinically manifest with the major clinical syndromes (myocardial infarction [MI], stroke, heart failure [HF], end-stage renal disease), which may ultimately lead to death **(Dzau et al., 2006).**

The outcome associated with late stages of the continuum is remarkably poor. For example, one out of two patients with New York Heart Association (NYHA) stage IV congestive heart failure dies within one year, and approximately 80% of all patients with congestive heart failure die within 10 years **(Verdecchia et al., 2009).** It is important to note that therapeutic interventions at each step of the continuum can slow down or block its progression, with potentially measurable outcome benefits. In this setting, the blood pressure control remains a fundamental mechanism for prevention of cardiovascular disease **(Staessen et al., 2001).**

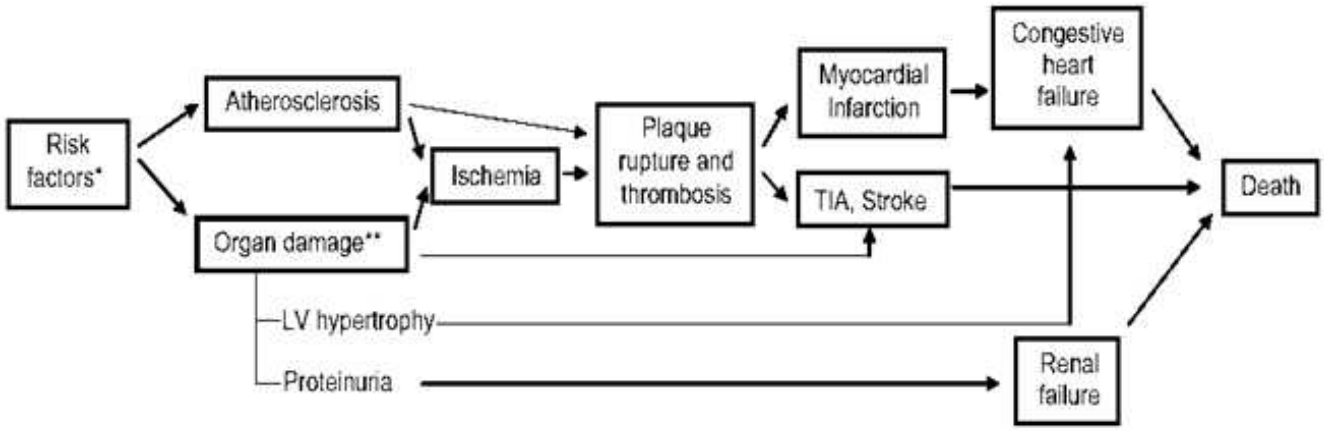

Figure 1: Cardiovascular disease continuum **(Dzau et al., 2006).**

*****Hypertension, diabetes, smoking, hypercholesterolemia, etc.
**LVH, proteinuria, vascular hypertrophy, plaques, asymptomatic cerebrovascular disease, hypertensive retinopathy, atrial fibrillation.
LV hypertrophy= left ventricular hypertrophy, TIA= transient ischemic attack.

Cardiac remodeling is one of the most detrimental effects of chronic hypertension. With an increased workload during hypertension, the heart eventually undergoes hypertrophic and fibrotic responses. Hypertrophy of the cardiac myoctyes without any accompanying fibrosis or vascular changes does not appear to have any adverse prognostic implications. Myocyte hypertrophy, when accompanied by fibrosis during remodeling, however, is a pathological process that can lead to a decrease in cardiac function. This cardiac hypertrophy and inappropriate interstitial collagen formation can contribute to increased wall stiffness and diastolic dysfunction **(Schaper, 1998).** Thus

the remodeling process, which could accompany hypertension, would consist of changes in the architecture of the heart, including perivascular and myocardial fibrosis, and medial thickening of intramyocardial coronary arteries, in addition to the myocyte hypertrophy. Various clinical trials have demonstrated that regression of left ventricular (LV) hypertrophy is a desirable target for therapy, because it is associated with improved long-term clinical outcomes **(Pitt et al., 2003)**.

In an attempt to attenuate the complications of hypertension, clinicians are faced with an array of antihypertensive agents. In many instances, the older generic drugs have been found as effective for BP lowering as the newly developed antihypertensive agents. However, only recently randomized clinical trials (RCTs) have provided insight into the relative efficacy of these agents to confer end organ protection which may be seen as the ultimate goal of BP treatment. Selection of antihypertensive treatment needs to be based on the presumed clinical benefit that may be obtained for different patient groups **(Andersen, 2009).** A group of these drugs are the drugs that act on renin-angiotensin-aldosterone system (RAAS).

Thiazide diuretics were the first tolerated efficient antihypertensive drugs that significantly reduced cardiovascular morbidity and mortality in placebo-controlled clinical studies. Although these drugs today still are considered a fundamental therapeutic tool for the treatment of hypertensive patients, the following considerations should be taken into account. Thiazide diuretics must be used at appropriate and/or optimal doses to achieve the optimal antihypertensive effect with the smallest occurrence of side effects, including alterations in glucose and lipid profiles and hypokalemia. Moreover, because thiazide diuretics can increase the incidence of new-onset diabetes, especially when combined with β- blockers, caution is advised in using these drugs above all in patients who are at high risk for developing diabetes, in whom thiazide diuretics should be used at the lowest active dose and possibly in combination with drugs that block the RAAS. It is believed that these drugs should not be considered

as the only first-choice drug but included among first-choice drugs **(Antonio and Lorenzo, 2006).**

Despite the wide use of β-blockers for the management of hypertension, their use in patients with uncomplicated hypertension has become increasingly controversial over the past few years **(Black and Sica, 2007).** This was in part due to the results of recent meta-analyses showing no difference between atenolol and placebo in risk reduction for mortality, myocardial infarction (MI), or stroke **(Carlberg et al., 2004)** and an increased risk of mortality and stroke with atenolol or propranolol in comparison to other antihypertensive drug classes including diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor blockers (ARBs), and calcium channel blockers (CCBs) **(Lindholm et al., 2005).**

The recently updated National Institute for Health and Clinical Excellence guidelines in Great Britain reflected this concern, having changed the indication for β-blockers from use as first-line agents for hypertension treatment to consideration as a fourth-line add-on therapy in patients requiring multiple drugs **(National Collaborating Centre for Chronic Conditions, 2006).** In addition, the most recent guidelines, the European Society of Hypertension / European Society of Cardiology recommend that β-blockers should not be preferred in hypertensives with multiple metabolic risk factors including metabolic syndrome, abdominal obesity, high normal or impaired fasting glucose, and impaired glucose tolerance, conditions that make the risk of incident diabetes higher **(Mancia et al., 2007)**.

CCBs are effective and safe antihypertensive drugs compared with placebo and reduce the cardiovascular morbidity and mortality of treated patients. Moreover, when CCBs were compared with conventional antihypertensive drugs, they demonstrated similar BP-lowering effects and similar reductions in cardiovascular morbidity and mortality, with the exception of a higher incidence of HF and fatal MI in some studies. Considering all the evidence available today, these drugs should be considered safe for

the treatment of the uncomplicated hypertensive patient in combination with other drugs **(Papadopoulos and Papademetriou, 2008).**

Over the last two decades, a growing number of experimental and clinical studies provided evidence of an important role played by angiotensin II (Ang II) along the different steps of the cardiovascular disease continuum **(Schmieder, 2005).** In clinical and experimental models, beneficial effects independent of BP lowering have been attributed to RAAS blockade. Chronic activation of the RAAS is detrimental to long term cardiovascular health through physiologic mechanisms that include BP elevation, chronic vasoconstriction, and cellular effects that promote atherosclerosis and cardiovascular remodeling. Blockade of the RAAS is valuable in patients with hypertension and becomes increasingly important in the presence of end-organ disease **(Gradman, 2009).**

Components of the renin-angiotensin-aldosterone system (RAAS)

The RAAS hormonal cascade begins with the biosynthesis of renin by the juxtaglomerular cells (JG) that line the afferent (and occasionally efferent) arteriole of the renal glomerulus. Renin is synthesized as a preprohormone, and mature (active) renin is formed by proteolytic removal of a 43-amino-acid prosegment peptide from the N-terminus of prorenin, the proenzyme or renin precursor.

Mature renin is stored in granules of the JG cells and is released by an exocytic process involving stimulus-secretion coupling into the renal and then the systemic circulation. In addition to this regulated pathway, it appears that the kidney also releases unprocessed prorenin via a constitutive pathway. In fact, prorenin accounts for about 70 to 90% of the immunoreactive renin in the human circulation. The potential biological significance of this finding is poorly understood at present.