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Renin Angiotensin System and Cardiovascular Risk- A Review

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ABSTRACT

The renin angiotensin system [RAS] forms a central role in the pathogenesis of cardiovascular and renal diseases. Angiotensin II, the main peptide of the system stimulates key components of atherosclerosis. Blocking RAS pathways exert potent antiatherosclerotic effects by their anti-hypertensive, anti -inflammatory, anti-proliferative and oxidative stress reducing mechanisms, thereby, decreasing atherosclerotic plaque progression and ischemic events. Thus, it forms a mainstay of strategies to improve the prognosis of patients with cardiovascular disease. This review discusses the members of RAS and their role in pathophysiology of the atherosclerotic diseases from molecular pathways, to human genetics and to the latest clinical trials.

Key words: Angiotensin II, AT1 receptor, RAS, Atherosclerosis, Inflammation.

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INTRODUCTION

Cardiovascular disease is the leading cause of mortality for men and women worldwide, which makes up 16.7 million or 29.2% of total global deaths [1]. Atherosclerosis is a chronic inflammatory disease [2] initiated by a variety of cardiovascular risk factors such as smoking, diabetes mellitus, hypertension and obesity [3]. The atherosclerotic plaques are composed of dysfunctional endothelial cells, smooth muscle cells, lipid laden macrophages and T-lymphocytes [4]. Myocardial infarction, stroke or sudden cardiac deaths are the fatal end points of the progressive atherosclerosis [5].

In this regard, the role of immuno - inflammatory response initiated by the mechanical stress and LDL-C stimulate a cascade of mechanisms involving cytokines, chemokines and eicosanoids. Since RAS regulate a host of biological functions in the body including maintenance of the vascular tone and as all the components of the RAS have been identified in the atherosclerotic tissues, RAS proves to be the central point of these pathophysiological processes [6]. Hence, RAS has become the key factor of intensive research activities for several decades for the protection of cardiovascular, cerebrovascular and renal systems. Pharmacologic inhibition of RAS is used as a treatment for hypertension, left ventricular dysfunction, acute myocardial infarction [AMI], diabetic nephropathy and atherosclerosis [7].

In animal models of atherosclerosis, RAS directly contributes to the coronary ischemic events, altered post infarct remodeling and reduced fibrinolysis [8]. This review briefly describes RAS and its uses to explore the pathophysiology and results of recent genetic and clinical trials in the atherothrombotic diseases.

OVERVIEW OF THE RAS

The RAS system is involved in the regulation of blood pressure and electrolyte metabolism. The primary hormone involved is angiotensin II, an octapeptide made from angiotensinogen [AGT], which is a α-globulin produced in liver and is 452 amino acid in length [9]. An enzyme produced in the juxtaglomerular cells of the renal afferent arteriole, renin, act upon angiotensinogen to form a decapeptide angiotensin I. Plasma angiotensin converting enzyme [ACE], converts angiotensin I to form angiotensin II [10]. ACE, also known as kininase II is a zinc containing large acidic glycoprotein metallozyme with a single polypeptide and is found in highest concentration in lungs, kidney, ileum, duodenum and uterus [11]. This enzyme is expressed primarily by endothelial, epithelial and neuroepithelial cells ACE. Plasma ACE which exists on endothelial cells throughout atherosclerotic plaques forms a small proportion of total body ACE [12]. Angiotensin II is a very potent vasoactive substance which causes vasoconstriction of the arterioles [13]. Angiotensin II by the action of enzyme aminopeptidase forms angiotensin III which stimulates aldosterone synthesis and inflammation [14]. Later, angiotensin II and angiotensin III are degraded by angiotensinases to form degradation products [15].

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HUMAN ANGIOTENSINOGEN

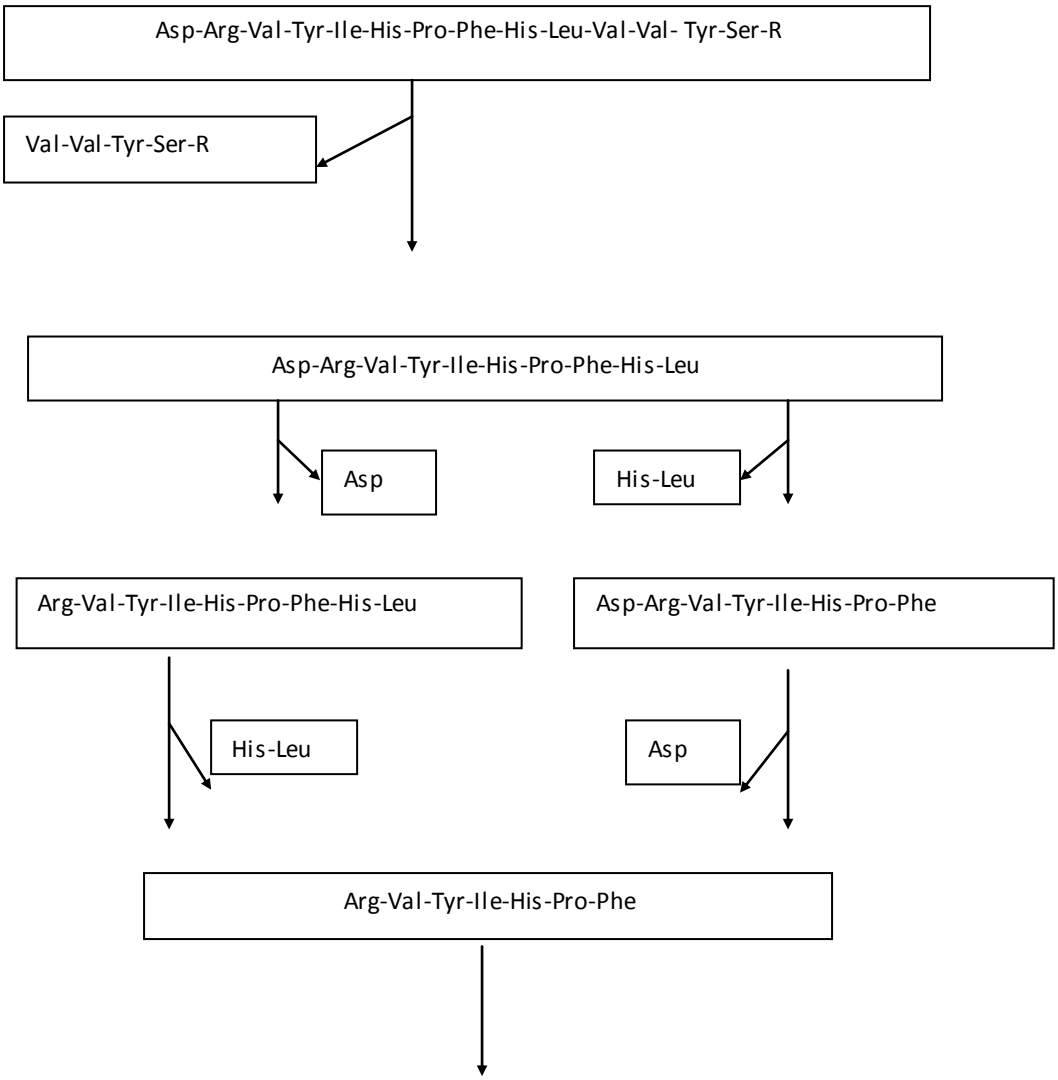

Fig 1[16] RAS Cascade in Humans

Angiotensin II acts through two type of receptors, type 1 [AT1] and type 2 [AT2]. AT1 is a seven transmembrane domain G- protein coupled receptor, which is abundantly distributed in tissues such as blood vessels, heart, kidney, adrenal gland, liver, brain and lungs [17]. The effects mediated by AT1 are cell growth, regulation of expression of vasoconstructive hormones, growth factors, cytokines, aldosterone and extracellular matrix components [18].

AT2 is mainly present in myocardium, vascular endothelium, uterus, brain, pancreas and adrenal gland. It is predominantly located in interstitial fibroblasts and is involved in progression of inflammation and fibrosis [19].It is increased with atherosclerotic processes, vascular injury, myocardial infarction and heart failure [20].

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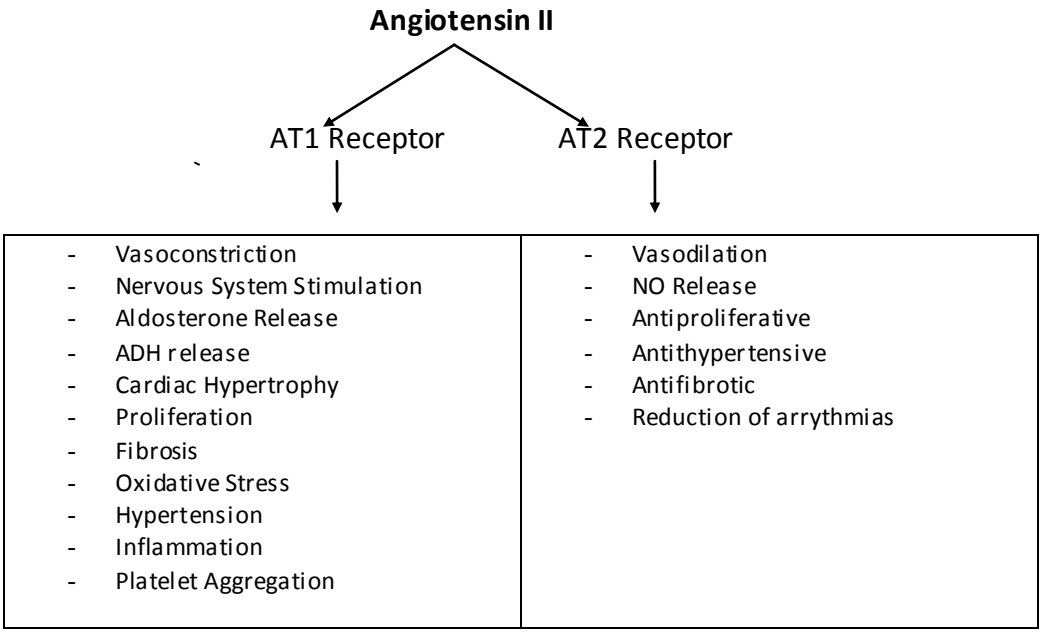

Fig2 [21] Actions of Angiotensin II

PATHWAYS OF RAS THAT LEAD TO ATHEROSCLEROSIS

Angiotensin II activates intracellular signaling pathways that promote atherothrombosis through inflammation, endothelial dysfunction, growth, altered fibrinolysis and increased LDL-C oxidation [22].

These processes are discussed as follows:

A) **INFLAMMATION**- Atherosclerosis is a chronic inflammatory disorder that leads to plaque formation [23] and RAS serves a major role in promoting this inflammation. Angiotensin II activates the proinflammatory transcription factors- nuclear factor kappa B [NF- κB] in monocytes , vascular smooth muscle cells [VSMC] and endothelial cells [24], causing increased production of intercellular adhesion molecule [ICAM-1], vascular cellular adhesion molecule [VCAM-1] and proinflammatory cytokines such as monocyte chemoattractant protein -1 [MCP-1], interleukin-6 [IL-6], TNF- α and cyclooxygenase -2 [25]. This inflammatory cascade activates the vascular inflammatory response by increasing inflammatory cell recruitment to the intima. Recruited cells produce more Angiotensin II, resulting in a positive feedback response, which maintains this inflammatory vicious cycle. The RAS modulated activation of complement system is implicated in both atherosclerosis and renal injury [26].In human heart, AT2 is located in interstitial fibroblasts hence; it also serves a role in inflammation and fibrosis [27].

B) **ENDOTHELIAL DYSFUNCTION**- It is one of the earliest detectable functional abnormalities in the coronary circulation at the onset of atherosclerosis [28]. Under normal conditions, endothelial function exerts its antithrombogenic effect by nitric oxide [NO] and

prostacyclins. NO inhibits platelet and leukocyte adhesion to the endothelium and inhibits the growth of VSMC [29].

RAS impairs NO release and activity through bradykinin degradation by ACE and oxidative stress [30]. Angiotensin II also, impairs NO activity by stimulating oxidative stress through NADH/ NADPH oxidase in VSMC and endothelial cells [31]. Thus, endothelial dysfunction causes stimulation of adhesion molecules, MCP-1 and cytokines that are proinflammatory [32].Also; in a study conducted it was observed that hypercholesterolemia was associated with AT1 receptor upregulation, endothelial dysfunction and inhibition of the oxidase. Reduction of early plaque formation by an AT1 receptor antagonist suggests a crucial role of angiotensin II mediated superoxide radical production in the early stage of atherosclerosis [33].

C) **GROWTH FACTORS** - Angiotensin II activates several growth associated kinase pathways such as Janus Kinase/ signal transducers and activators of transcription and mitogen activated protein pathways [34]. Angiotensin II also leads to the increased production of transforming growth factor β1 [TGF-β1] and platelet derived growth factor [PDGF] [35]. In VSMC, TGF- β1 promotes fibrosis and hence, cellular hypertrophy. Imbalances in these growth factors, possibly created by vascular injury leads to angiotensin II mediated proliferation [36].

D) **THROMBOSIS** - RAS inhibits the fibrinolytic system and enhances thrombosis by altering the coagulation cascade and platelet activity [37].RAS increases the production and release of platelet activated inhibitor [PAI-1] from endothelial cells and VSMC. This PAI-1 in turn inhibits the endogenous fibrinolytic system and serves as most important inhibitor of the tissue plasminogen activator [38]. Also, RAS increases levels of tissue factor, a member of the coagulation cascade that serves as an essential cofactor of factor VIII and is increased in atherosclerotic plaques and acute coronary syndromes [39].

E) **LDL-C OXIDATION** - Oxidized LDL-C impairs NO formation, promotes superoxide anion formation and induces endothelial adhesion molecules [ICAM-1, VCAM-1 and E- selectin], chemokines [MCP-1] and smooth muscle growth factors [40]. Angiotensin II enhances the oxidation of LDL-C via stimulation of lipooxygenase pathway and NADH in the macrophages [41]. Oxidized LDL-C and hypercholesterolemia increase expression of AT1 on human endothelial cells and VSMC [42].

GENETIC STUDIES ASSOCIATED WITH RAS IN ATHEROSCLEROSIS

Genetic components play an important role in the development of vascular disease which is evident by the clustering of premature atherosclerosis in families [43]. Various polymorphisms have been associated in the genes of the RAS. One of the major polymorphism of the RAS is an insertion [I] / deletion [D] polymorphism in the ACE. The ACE DD genotype is associated with higher circulating and tissue levels of ACE [44].

There is a proposed interaction between the molecular mechanisms of the RAS and cholesterol in promoting atherosclerosis. To define the relationship of RAS and lipids in humans, in a study, angiotensin II was administered to normocholesterolemic and hypercholesterolemic men and it was found that increase in blood pressure was exaggerated in the hypercholesterolemic subjects and this response was slowed down by LDL-C lowering agents [45].

Genes encoding components of the RAS have been associated with elevated blood pressure and increased risk of coronary artery disease [CAD]. A study was conducted in 301 white males, to observe the effect of the AGT M235T gene variant on plasma AGT levels and blood pressure in patients with CAD. It was found that AGT M235T gene polymorphism was a significant predictor of diastolic blood pressure and elevated circulating AGT in the pathogenesis of CAD [46].

Association of aortic stiffness and CAD is also observed in the AT1- 1166 A/C polymorphism [47]. Also, AT1- 810T/A polymorphism is linked to CAD and MI [48]. In a study conducted it was shown that C825T polymorphism in the G- protein beta 3 subunit gene [GNB3] with altered transmembrane signaling is linked to altered hypertension, CAD and MI [49].

Two studies conducted depicts that there is a synergistic interaction between the increased risks associated with the D allele of the ACE I/D polymorphism and the C allele of the AT1- 116 A/C polymorphism [50]. A recent study indicated a synergistic effect between AGT M235T and apolipoprotein E4, with an increased risk of MI observed in AGT TT and apolipoprotein E4 allele carriers [51].

It has been observed that angiotensin converting enzyme 2 [ACE 2], which catalyses the conversion of angiotensin I and angiotensin II, to angiotensin [1-9] and angiotensin [1-7] respectively, is linked with polymorphism in the ACE 2 gene in relation to the cardiovascular risk. The allele A of the rs2285666 polymorphism in this ACE 2 gene influences the fatal cardiovascular outcome in females [52].

Thus, these polymorphisms observed in atherosclerotic diseases are helpful in determining the role of the RAS in the cardiovascular events, risk stratification and therapeutics.

ACE INHIBITORS IN ATHEROSCLEROSIS

ACE inhibitors act by inhibiting the conversion of angiotensin I to angiotensin II. They also decrease the breakdown of bradykinin and increase tissue and plasma levels of angiotensin [53]. Since, tissue ACE is highly expressed in human atherosclerotic plaques [54] and is localized in the areas of clustered macrophages it becomes significantly increased in patients with unstable angina [55]. It is observed that blocking ACE will prevent plaque fissuring, thrombosis and rupture. But at the same time, the use of ACE inhibitors can lead to secondary increase in angiotensin II and aldosterone through the Secondary [non- ACE] pathways, also

known as ACE Escape. One of the most important non- ACE pathway leading to formation of angiotensin II is the Chymase pathway. Recent data suggests that this pathway is upregulated in the diabetic and hypertensive nephropathy and thus, ACE Escape may be more marked in patients with renal disease [56].

HUMAN CLINICAL TRIALS OF RAS INHIBITION

Several human clinical trials have been conducted to measure the impact of the RAS and its inhibition in inflammation and endothelial dysfunction.

In a study conducted known as SECURE [study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E], it was found that there was a significant reduction in the progression slope of mean maximal carotid intimal thickness [IMT] by 0.04mm [p= o.46] indicating early atherosclerosis [57].

In numerous clinical trials, ACE inhibition has been shown to decrease the risk of the coronary events and cardiovascular death in patients of MI [58].

Clinical trials of the SOLVD [studies of left ventricular dysfunction] treatment trial [59], the SAVE [survival and ventricular enlargement] trial [60], the AIRE [acute infarction ramipril efficacy] study [61] and the TRACE [trandopril cardiac evaluation] study [62] showed a 21% relative risk [RR] for MI [P=0.001].

The HOPE [heart outcomes prevention evaluation] study demonstrated that ACE inhibition with ramipril therapy decreased rates of death and MI in high risk patients with left ventricular dysfunction or heart failure where RR was 0.78 and p< 0.001 [63].

The PROGRESS [perindopril protection against recurrent stroke study] found that ACE inhibition in 6105 patients with a history of cardiovascular attacks reduced the secondary outcome of acute MI, where RR= 0.74 and p < 0.05 [64].

The LIFE [losartan intervention for endpoint reduction] in hypertension study showed in 9193 patients, aged 55- 80 years with moderate to severe hypertension; a 13% [p= 0.021] lower primary event rate in the losartan based treatment group [65].

In the ADVANCE [Action in diabetes and vascular disease- Preter Ax and Diamicron MR controlled evaluation] study, the significant antihypertensive effect of Perindopil/Indapamide given in addition to current therapy in patients with diabetes and hypertension was associated with improvement in morbidity and mortality compared with standard therapy, includind RAS inhibitors alone [66].

There is a recent evidence to show that angiotensin receptor blockers [ARB's] have efficacy similar to ACE inhibitors in reducing cardiovascular outcomes. In the CHARM [candesartan in heart failure study] and VAL-HeFT [valsartan heart failure trial] of patients with

severe heart failure, the addition of an ARB to an ACE inhibitor reduced cardiac mortality and lowered hospital admissions [67].

It has been observed that ARB's can improve endothelial function and reduce markers of atherosclerosis via AT1 receptor antagonism.The ARB- Olmesartan Medoxomil is shown to have utility of RAS suppression in reducing atherosclerosis. The recent trials of OLIVUS [Impact of Olmesartan on progression of coronary atherosclerosis: evaluation by intravascular ultrasound], EUTOPIA [European trial on Olmesartan and Pravastatin in inflammation and atherosclerosis], MORE [Multicenter Olmesartan atherosclerosis regression evaluation] and VIOS [Vascular improvement with Olmesartan Medoxomil study] studies proves the role of ARB's in reducing atherosclerotic plaque volume, improving plaque composition and stability and improving endothelial dysfunction, thereby, improving cardiovascular outcome[68].

CURRENT HUMAN TRIALS

There are numerous trials that are currently in progress to emphasize on the effects of RAS inhibition. The EUROPA [European trial on reduction of cardiac events with perindopril in stable coronary artery disease] study is examining 10500 patients with a follow up period of 5 years for effect of ACE inhibition on cardiac mortility, MI and unstable angina [69].

The PEACE [prevention of events with angiotensin converting enzyme inhibition] study will also review the 5 year outcome of cardiovascular death and MI IN 8100 CAD patients [70].

Another study, VALUE [valsartan antihypertensive long term use evaluation] trial will follow 14400 patients with hypertension and cardiovascular risk for 6years comparing cardiovascular events with amlodipine therapy [71].

The trials such as ONTARGET [ongoing telmisartan alone and in combination with ramipril global endpoint] trial will enroll about 23000 patients of > 55 years of age with a history of CAD, stroke or peripheral vascular disease [72].

Another trial TRANSCEND [telmisartan randomized assessment study in ACE inhibitor intolerant patients with cardiovascular disease] will compare telmisartan with placebo in 5000 similar patients, who cannot tolerate ACE inhibitors [73]. Newer clinical trials have also been started to investigate the possible effects of aliskiren – the oral renin inhibitor in cardiac remodeling after MI [AVANT GRADE, ASPIRE] and diabetic nephropathy [ALTITUDE] [74]. In a very recent study conducted, it was observed that left atrial [LA] strain and strain rate [SR] imaging improved after reduction of blood pressure with RAS inhibitors in the hypertensive patients. These values play a crucial role in detecting subclinical myocardial involvement in essential hypertension at an early stage [75].

CONCLUSION

Atherosclerosis is an ever growing threat to human population with 1 of every 2.5 deaths globally attributed to it. Current strategies aim to prevent and slow the progression of atherosclerosis by lifestyle modification and pharmacological treatment to control hyperlipidemia. But atherosclerosis may develop in many people without hypercholesterolemia. Therefore, there are other mechanisms promoting atherosclerosis, amongst them RAS has been recognized to play a crucial role in promotion of inflammation and endothelial dysfunction leading to atherogenesis. Inhibition of RAS reduces plaque development. Several RCT have shown decreased cardiovascular ischemic events in high risk patients receiving ACE inhibitors. Thus, the complex interactions between the RAS and hyperlipidemia in promoting atherosclerosis will elucidate new mechanisms to reduce ischemic events, decrease plaque formation and correct altered fibrinolytic balance.

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