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# The Renin-Angiotensin System and Its Blockers

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**SUMMARY**
Research on the renin-angiotensin system (RAS) has contributed significantly to advances in understanding cardiovascular and renal homeostasis and to the treatment of cardiovascular diseases. This review offers a brief history of the RAS with an overview of its major components and their functions, as well as blockers of the RAS, their clinical usage and current research that targets various components of the RAS. Because angiotensin-converting enzyme (ACE) metabolizes two biologically active peptides, one in the kallikrein-kinin system (KKS) and one in the RAS, it is the essential connection between the two systems. ACE releases very powerful hypertensive agent, angiotensin II and also inactivates strong hypotensive peptide, bradykinin. Inhibition of ACE thus has a dual effect, resulting in decreased angiotensin II and increased bradykinin. We described the KKS as well.
**Keywords:** renin-angiotensin system; angiotensin II; bradykinin; ACE inhibitors; angiotensin receptor blockers; aliskiren

## INTRODUCTION

Research on the renin-angiotensin system (RAS) has contributed significantly to advances in understanding cardiovascular and renal homeostasis and to the treatment of cardiovascular diseases. The RAS is well-known for its role in the regulation of blood pressure as well as fluid and electrolyte homeostasis. The history of the RAS began at the end of the 19th century, 115 years ago. Other components of the cascade (angiotensinogen, angiotensin I, angiotensin II, angiotensin converting enzyme), fragments of angiotensin, and various blockers of the RAS were discovered later during the 20th century. But that is not the entire history of the RAS; many questions remain to be answered. This review offers a brief history of the RAS, development of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blocking (ARB) agents, renin inhibitors, and a summary of current research developments related to the RAS, and clinical usage of the RAS blockers.

## RENIN-ANGIOTENSIN SYSTEM

The discovery of a hypertensive agent in extracts of rabbit kidney was recorded in 1898 [1]. The substance was named renin, but research remained dormant for 30 years until it was found that renin was involved in the rise of blood pressure in the experimental models of hypertension [2]. The history of angiotensin began in 1939 when two independent research groups located a great geographical distance apart, described the pressor substance released by renin [3].

### One peptide, two names

Two independent research groups, one in Buenos Aires led by Eduardo Braun-Menendez and other in Indianapolis, led by Irvine H. Page, linked ischemic renal disease with hypertension. Both based their conclusions upon results obtained in experimental animals where the renal artery was partially obstructed with a silver clip. They ultimately identified the substance that caused blood pressure increase. The Argentine researchers named it hypertensin, and the Indianapolis group named it angiotonin. From 1939 to 1957 this renin-derived hypertensive substance was known by both names, which led to some confusion. In 1957 Braun-Menendez and Page agreed to use a name derived from both of the two original ones: angiotensin. The renin substrate (produced by the liver) was named angiotensinogen, and enzymes that inactivated the peptide were termed angiotensinases. Despite the published agreement [4], the name hypertensin persisted for several more years, perhaps because of the well-known CIBA product Hypertensin.

### Angiotensin converting enzyme

Skeggs et al. [5] reported in 1956 that renin liberates a decapeptide, angiotensin I (Ang I). This peptide is converted by an angiotensin-converting enzyme (ACE) to a biologically active octapeptide, Ang II. Later on, it was found that the pulmonary circulation could convert Ang I even in the absence of blood, suggesting that the enzyme must be bound to pulmonary endothelium [6, 7]. Based upon infor-

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mation obtained from various researchers, the following sequence was established: first, the release of renin from juxtaglomerular cells into blood converts angiotensinogen to Ang I. Next, this peptide is hydrolyzed to Ang II both by ACE in blood and the enzyme bound to vascular endothelium. Ultimately, Ang II interacts with its vascular receptors to raise blood pressure.

Now, because of the pivotal position of ACE in this sequence, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blocking agents (ARBs) are currently the most often prescribed medications for various cardiovascular conditions. ACEIs decrease production of Ang II, reduce sympathetic nervous system activity, and increase bradykinin levels, thus slowing the progression of target organ damage.

Ang II was initially believed to act only as a circulating hormone by binding two receptor subtypes [8]. Activation of $AT_1$ receptors promoted vasoconstriction, aldosterone release stimulation, hypertension, decreased renal flow, and augmentation of peripheral noradrenergic activity. The activation of $AT_2$ receptors led to vasodilatation, inhibition of proliferation and modulation of the extracellular matrix. However, an expanded view of the RAS has gradually emerged. The idea that the RAS was an endocrine system had to be modified when it was discovered that Ang II levels were much higher in tissues than in plasma, and that ACE inhibitors lowered blood pressure in hypertensive patients even when concentrations of renin and Ang II in the circulation were normal. As a result, a new concept emerged indicating that the RAS operates at both systemic (endocrine) and tissue (paracrine and autocrine) levels [9]. It is now clear that, in addition to vascular and renal actions, Ang II has direct effects at the cellular level and can influence, for example, cell growth and differentiation, but also may play a role as a mediator of apoptosis.

A whole family of angiotensins can be derived from Ang I by the action of various enzymes. A few of these peptides are identified by Roman numerals, e.g. Ang II, and all can be named by Arabic numerals referring to their amino acid sequence starting with the N-terminal end:

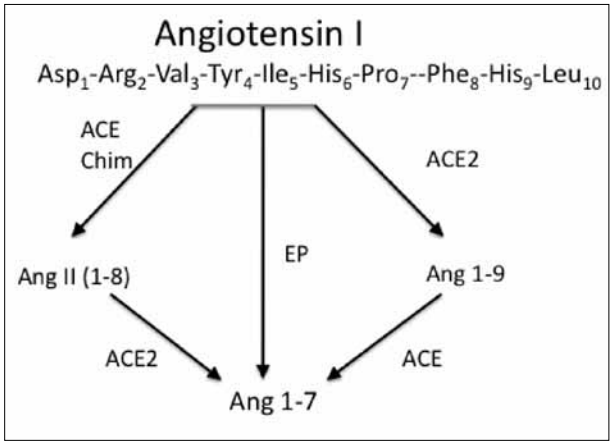


**Figure 1.** Main routes of angiotensin (Ang) II and Angiotensin 1–7 production

Chim – chimases; ACE – angiotensin I converting enzyme; ACE2 – a homologue of ACE; EP – tissue endopeptidases

Ang I (Ang 1-10), Ang II (Ang 1-8), Ang III (Ang 2-8), Ang IV (Ang 3-8), Ang 1-9, Ang 1-7, Ang 1-5. Some of the shorter angiotensin peptides (Ang 2-8, Ang 3-8, Ang 1-7) have biological actions. Ang 1-7 antagonizes many effects of Ang II, potentiates bradykinin actions, and has its own receptors. Because of its vasodilator action and stimulation of renal $Na^+$ excretion, Ang 1-7 could potentially counterbalance the hypertensive effects of Ang II. ACE2, a homologue of ACE [3], generates Ang 1-7 directly from Ang II, Ang I or indirectly (Figure 1). Chymase can generate Ang II directly, without the participation of renin [10].

## Properties of ACE

The ACE gene located on the chromosome 17 consists of 25 exons. Two forms of human ACE have been identified, somatic and germinal. Somatic ACE is associated with endothelial, epithelial and neuroepithelial cells, and it is a protein with two homologous N- and C-domains. Each domain has an active center with similar but distinct substrate specifications and chloride activation requirements. The somatic enzyme has a molecular weight of 150,000-180,000 D. Germinal ACE, expressed in the testes is only half the molecular size of the somatic enzyme [11]. Despite their different molecular sizes and immunological properties, the two forms of ACE exhibit similar enzymatic activities.

The main physiologic functions of the enzyme are attributed to the membrane-bound form. Blood vessels of the lung, retina, brain, and kidney are rich in ACE. Microvilli sructutres or epithelial linings in the brush border, choroid plexus, small intestine, and placenta are also very rich in ACE. High concentrations of ACE are found in both neurons and glial cells. [12]. Proteolytic cleavage releases cell-bound ACE into various body fluids, such as blood, urine, lymph, cerebrospinal fluid, and aqueous humor. Plasma ACE measurement is widely used for the diagnosis of sarcoidosis [13].

An insertion (II)/deletion (DD) polymorphism of ACE functions as a quantitative trait locus (QTL) which can account for the individual variability of ACE levels in plasma [13]. Individuals who are homozygous for the deletion allele have much higher levels of serum ACE and also an increased risk of cardiovascular and renal diseases and premature death. Recent technological advances that identify expression of QTLs now allow us to determine predispositions for human disease [13].

Conversion of Ang I by ACE depends upon the presence of chloride ion, while bradykinin hydrolysis can proceed in its absence, although at a lower rate. ACE has a pH optimum in the neutral range. At an acidic pH, $Zn^{++}$ dissociates from the active center and ACE activity decreases. The addition of $Zn^{++}$ maintains enzyme active to a pH as low as 5.5.

## Substrates of ACE

ACE releases C-terminal dipeptides from a variety of peptides, including Ang I, bradykinin, substance P, opioid

peptides (Met-enkephalin-Arg$^6$-Phe$^7$, β-neoendorphin, dynorphin1-8, dynorphin1-6), neurotensin, luteinizing hormone releasing hormone (LHRH) and cholecystokinin-8 [13]. The longest peptide cleaved on prolonged incubation is the b-chain of insulin that has 30 residues.

## KALLIKREIN-KININ SYSTEM

Another system that produces vasoactive peptides from plasma can be traced back to the 19$^{th}$ century when it was discovered that injection of urine caused a toxic reaction [14]. This substance in urine was called kallikrein, but it was soon discovered that kallikrein was not vasoactive per se; it releases biologically active peptides, called kinins, from a plasma protein. The main kinins are bradykinin and lys-bradykinin (kallidin) [15]. They are released by enzymes (kininogenases) from substrates known as kininogens (Figure 2). Two kininogenases, plasma and tissue (glandular) kallikreins, are two separate enzymes that produce bradykinin and lys-bradykinin (kallidin), respectively. Tissue kallikrein is the major kinin forming enzyme in arteries, heart and kidney [16]. Kininogens are synthesized in the liver and circulate in high concentrations in plasma. Plasma kallikrein releases bradykinin only from high-molecular weight kininogen. Aminopeptidase cleaves N-terminal lysine of kallidin to produce bradykinin.

Bradykinin was named after the slow contraction it causes in the guinea pig ileum. An electronic instrument to record isotonic contractions of isolated smooth muscles (eg. guinea pig ileum, rat uterus, and guinea pig colon) was designed in 1962 by Erdos et al. [17] and it was the first of its kind. Thus, the era of kymographs, which required smoker paper on a rotating drum and a fixative to preserve signal markings, was ended.

Almost all cells express kinin receptors, $B_1$ and $B_2$. Bradykinin and kallidin bind to both types of B receptors, but they bind more efficiently to the $B_2$ type. $B_1$ receptors are selectively activated by des-Arg$^9$-bradykinin and des-Arg$^{10}$-kallidin. The $B_2$ receptor normally predominates, while $B_1$ receptors are induced by tissue injury (myocardial ischemia, inflammation). $B_2$ receptors mediate vasodilation, increased vascular permeability, hypotension, contraction of intestinal smooth muscle, contraction of smooth muscle in airways, production of nitric oxide, and induction of pain [18]. Bradykinin was named after the slow contraction it causes in the guinea pig ileum.

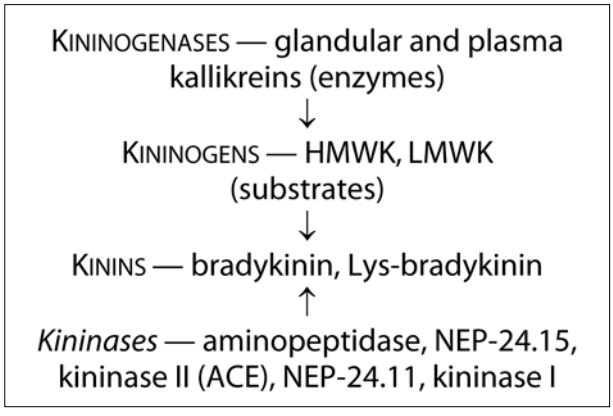


**Figure 2.** Schematic presentation of the kallikrein-kinin system

HMWK – high-molecular-weight kininogen; LMWK – low molecular weight kininogen; NEP – neutral endopeptidase.
Bradykinin is a peptide chain with following amino acid sequence: Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg.

Hydrolysis of any bond in bradykinin inactivates its effect on the $B_2$ receptor. This inactivation is done by kininases: ACE (kininase II), neutral endopeptidases, aminopeptidases, and carboxypeptidase N (kininase I). The name 'kininase II' was given to an enzyme found in the kidney and human plasma that releases the Phe$^8$-Arg$^9$ from bradykinin instead of the single Arg$^9$ released by carboxypeptidase N [19].

The functions of kinins include the regulation of blood flow in the heart and kidney, but there is evidence for other actions as well. For example, the glands of the gastrointestinal tract contain kallikrein. It is possible that kallikrein secretion during or after a meal releases kinins to promote vasodilatation and thus increase absorption. Kinins are known to be involved in sweating, vasodilatation and edema formation during inflammation. Low urinary kallikrein excretion in children is a predictor of familial (genetic) essential hypertension, while children with high urinary kallikrein excretion have a reduced risk for developing familial hypertension [18]. Urinary kallikrein is also decreased in individuals with renal hypertension.

## IDENTITY OF ACE AND KININASE II

The link between the kallikrein-kinin system and renin-angiotensin system was first recognized in the laboratory of Ervin G. Erdos when it was discovered that ACE and kininase II are identical [20, 21]. These findings were confirmed by purification of the protein from the lung. The purified enzyme yielded a single band on disc electrophoresis and had the same dual actions, activation of angiotensin and inactivation of bradykinin [7, 21].

Because ACE metabolizes two biologically active peptides, one in the kallikrein-kinin system and one in the RAS, it forms the essential connection between the two systems. ACE releases very powerful hypertensive agent, Ang II and also inactivates the strongest hypotensive peptide, bradykinin. Thus, the inhibition of ACE has a dual effect, resulting in decreased Ang II and increased bradykinin (Figure 3).

## ACE INHIBITORS

The discovery of renin, ACE, and Ang II suggested that inhibition of any of these components could be beneficial for the regulation of blood pressure in people with hypertension. The first clinically useful ACE inhibitor (ACEI), captopril, was discovered in 1974, and the next generation of ACEIs soon followed. Next, Ang II-receptor blockers were discovered. It took still more time and effort to find

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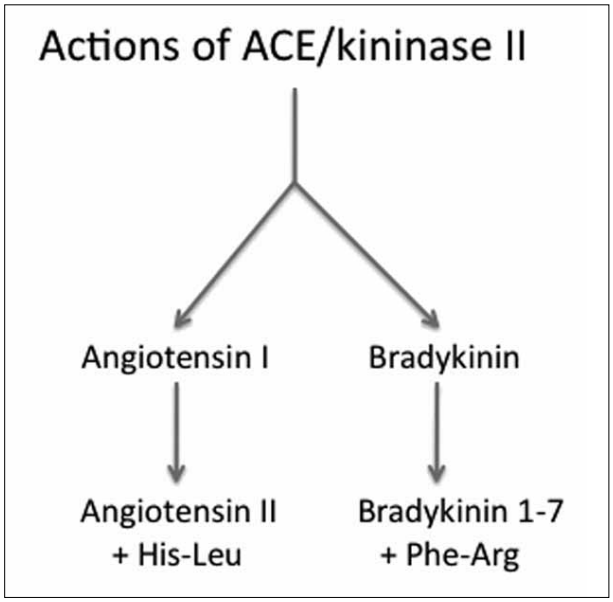


**Figure 3.** Dual actions of ACE

an orally active renin blocker. The story of captopril discovery is especially important because this drug initiated a new era of structure-based or rational drug design.

### From snake venom to discovery of captopril

Mauricio Rocha e Silva, a Brazilian biochemist, became interested in the fact that when workers at the banana plantations in Brazil were bitten by pit vipers (*Bothrops jararaca*), they suddenly collapsed with a dramatic drop in blood pressure. Dr. Roscha e Silva then began to study the effects of viper venom extracts in dogs and guinea pigs. One of his postdoctoral fellows traveled to London in the mid 1960s to work in the laboratory of a prominent pharmacologist, Sir John R Vane. He brought with him a vial of the pit venom. By 1970, Vane's laboratory had determined that the snake venom contained a potent ACEI.

Dr. Vane then suggested to researchers at Squibb Pharmaceutical Company that if a decrease in Ang II formation reduced blood pressure, the snake venom extract might prove to be a useful drug. The active agent, a peptide, was soon isolated, purified from venom and then synthesized. It was then established that this peptide blocks the conversion of Ang I to Ang II and reduces blood pressure in hypertensive patients. However, the peptide had to be injected, because oral administration resulted in inactivation by acid hydrolysis in the stomach.

A small but powerful inhibitor of carboxypeptidase A was described in 1973. It was constructed on the basis of x-ray crystallography that enabled researchers to visualize the three–dimensional structure of the enzyme. This finding helped the Squibb researchers to formulate a whole new approach to create an inhibitor of ACE. To design an ACEI, it was necessary to make a molecule that has positive and negative charges in exactly the right places to bind to ACE and block the contact of the enzyme with Ang I. A year later, more than 50 molecules were synthesized. Among them was captopril, the first orally active ACE inhibitor [22].

**Table 1.** Dosages of the ACEIs

| Drug (generic) name | Daily dose in mg (frequency/day) | |
|---|---|---|
| | Hypertension | Heart failure |
| Benazepril | 10-40 (1-2) | Not recommended |
| Captopril | 75-300 (2-3) | 18.75-150 (3) |
| Cilazapril | 1-5 (1) | 0/5-2/5 (1) |
| Enalapril | 5-40 (1-2) | 5-40 (2) |
| Fosinopril* | 10-40 (1) | 10-40 (1) |
| Lisinopril | 10-40 (1) | 5-20 (1) |
| Moexipril | 7.5-30 (1-2) | Not approved |
| Perindopril | 4-16 (1-2) | Not approved |
| Quinapril | 10-80 (1-2) | 10-40 (1-2) |
| Ramipril** | 2.5-20 (1-2) | 10 (2) |
| Trandolapril* | 1-8 (1-2) | 1-4 (1-2) |

* renal and hepatic elimination; ** indicated in high-risk vascular patients

Similar structure-based designs were then applied to create additional ACEIs, eleven of which are now on the market (Table 1). An analogous technique was used in the 1990s to make five effective ARBs.

## CLINICAL USAGE OF THE ACEIs AND ARBs

### ACE inhibitors as drugs

ACEIs are effective medications for several cardiac, renal, and vascular conditions, including hypertension, heart failure and diabetic nephropathy [23]. Most ACEIs are pro-drugs with improved absorption, but they require metabolic conversion (hydrolysis) in the liver or intestine to become active [24, 25]. Lisinopril and captopril are the only drugs that do not need such conversion. ACEIs have sulfhydryl (captopril), phosphinyl (fosinopril), or carboxyl (all other ACEIs) side groups that affect their disposition and metabolism. Captopril has -SH group and it reduces S-S bridges in proteins. Thus, dissociation of IgG by huge doses of captopril may cause the appearance of protein in urine [26]. It is not clear whether some of ACEIs, such as those that are highly lyophilic (quinapril and ramipril), penetrate better into specific tissues and are thus more effective.

ACEIs interfere both with the generation of Ang II and inactivation of bradykinin, thus decreasing the availability of Ang II and prolonging the half-life of bradykinin [13]. Decreased levels of Ang II in circulation (which suppresses release of renin) result in increased plasma renin activity and Ang I release. This, in turn, provides the Ang I substrate for alternative enzymes, such as chymase that contributes to the so called "Ang II escape".

The vasodilator actions of bradykinin are not due entirely to the direct actions of the peptide on blood vessels. Increased bradykinin stimulates the production of nitric oxide and induces prostacyclin release to further increase vasodilatation. When an ACEI is used together with nonsteroidal anti-inflammatory drugs, the bradykinin-lowering effect of the ACEI, especially captopril, may be suppressed.

### Indications for clinical usage of ACE inhibitors

The ACE inhibition or ARB is recommended for treating hypertension (especially in diabetics), heart failure, diabetic nephropathy (or stage 1 to 3 chronic kidney disease), myocardial infarction, and high-risk cardiovascular disease [24, 25]. ACE inhibitors are particularly useful in hypertensive diabetics. These drugs are useful for the treatment of isolated systolic hypertension or systolic-predominant forms of hypertension. In cerebrovascular disease, ACEIs preserve cerebral autoregulatory vascular ability despite a reduction of blood pressure. These drugs are effective in coronary artery disease, because they decrease myocardial oxygen consumption and ischemia.

On the basis of the data from several clinical trials or open trials, it is recommended to use the ACEIs as the first-choice drugs in all stages of heart failure. Significant reductions in heart failure mortality have been observed with enalapril, captopril, ramipril, quinapril, trandolapril, and lisinopril. These agents improve symptomatology of heart failure, as well. ACEIs reduce morbidity and mortality in post myocardial infarction patients, and they slow progression of target organ damage, including various nephropathies, especially if proteinuria is present. ACEIs are indicated for the primary prevention of stroke in high-risk patients and in patients with diabetes and hypertension.

Table 1 shows the usual dosage of ACEIs. Lower doses are recommended for initiation of therapy. Higher doses are generally used with continuing therapy to provide full 24-hour coverage. In individuals with renal dysfunction (creatinine clearance <30 ml/min) dosing should be adjusted accordingly. Fosinopril does not require dosage adjustment because the biliary excretion increases in renal dysfunction. ACEIs may be given in fixed-dose combinations that contain a low dose of thiazide diuretic (6.25 mg of hydrochlorothiazide) for an additive and beneficial action. Eighth Joint National Committee (JNC 8) of the 2014 recommends that thiazide-type diuretic, ACEI, ARB, or calcium channel blocker (CCB) should be used as initial treatment for uncomplicated hypertension in the general population of <60 years to lower blood pressure at 140/90 mm Hg, and for the general population of ≥60 years old <150/90 mm Hg [24]. Diabetics should be initially treated with the same types of drugs, and the goal blood pressure is <140/90 mm Hg. Chronic kidney disease should be initially treated with ACEI or ARB, and the goal blood pressure is <140/90 mm Hg. If goal blood pressure cannot be reached with two drugs, a third drug from the list (thiazide–type diuretic, CCB, ACEI, or ARB) should be added. An ACEI and an ARB should not be used together in the same patient [24].

### Adverse effects of ACEIs

Main ACEIs adverse effects include functional renal insufficiency, hyperkalemia, cough, and angioedema [25, 27]. ACEIs induce angioedema in 0.02-0.05% of patients. When ACE inhibitor is stopped, angioedema disappears within hours; if necessary adrenaline, antihistamine, and/or a glucocorticoid should be given. In the case of renal insufficiency, discontinuation of ACEIs or cautious volume repletion usually reverses the problem. Hyperkalemia may appear when glomerular filtration rate is reduced, but ACEIs actually minimize hypokalemia caused by diuretics. ACEIs, ARBs and aliskiren (an inhibitor of renin) are contraindicated in pregnancy because of developmental defects that may occur when the drugs are given in the second or third trimester. They are also contraindicated for individuals with renal artery stenosis. The prevalence of renal artery stenosis is estimated to be between 2% (unselected hypertensive patients) and 40% (older patients with atherosclerotic comorbidity) [28].

Angioedema and dry, nonproductive cough (in 5%-20% of patients) are the most important adverse effects of ACEIs. Women are affected more often than men. It seems that angioedema/cough is partly genetically determined. Decreased degradation of bradykinin may also be involved in these adverse reactions. When ACE is inhibited, bradykinin is metabolized by other enzymes, such as neutral endopeptidases, aminopeptidases and carboxypeptidase N (kininase I). If these enzymes are also inhibited, as may occur in the treatment of diabetes or transplant patients, the incidence of angioedema increases significantly [27]. The adverse effects of ACEIs are not dose related. A cough may begin one week to six months after therapy is initiated, but it will resolve spontaneously a few days to several weeks after discontinuation of the drug. Withdrawal of ACEI for four weeks is usually sufficient to determine whether the medication caused the cough. An ARB blocker may be substituted for the ACEI. However, for patients who developed angioedema with ACEI, the risk of developing subsequent angioedema when taking an ARB is between 2% and 17%.

## ANGIOTENSIN II RECEPTOR BLOCKERS

ARBs, orally active non-peptide compounds that specifically block Ang II binding to the $AT_1$ receptor, were developed in the early 1980s when the synthesis and testing of a series of imidazole-5-acetic acid derivatives attenuated pressor responses to Ang II.

The $AT_1$ receptor mediates most of the known physiologic actions of Ang II, including its hemodynamic and trophic effects. Ang II–induced vascular smooth muscle cell growth depends on cytochrome P450 1B1 (CYP1B1) [29]. Thus, it is believed that CYP1B1 contributes to the development and maintenance of Ang II-induced hypertension and associated vascular changes, which include hypertrophy, endothelial dysfunction, increased sensitivity to vasoactive drugs, cardiac hypertrophy, fibrosis, inflammation, and generation of reactive oxygen species. The $AT_2$ receptor appears primarily during fetal development, where it is believed to mediate apoptosis and tissue remodeling/healing [30].

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### Indications for clinical usage of angiotensin receptor blockers

ARBs are well tolerated and effectively reduce blood pressure, diminish left ventricular hypertrophy, and prevent chronic kidney disease in type 2 diabetic patients. ARBs may be used alone or in combination with other antihypertensive agents, especially thiazide diuretics [31]. Clinical trials have shown that ARB treatment of heart failure and renal insufficiency provides cardiovascular benefits similar to those of ACE inhibitors [24, 32].

Losartan Intervention for Endpoint (LIFE) trial that included 4.605 patients treated with losartan and 4.588 patients treated with atenolol studied morbidity and mortality. The patients (75-80 years) with left ventricular hypertrophy demonstrated by electrocardiogram were treated from 50 mg of either losartan or atenolol to 100 mg. If blood pressure of <140/90) was not achieved, hydrochlorothiazide and other agents could be added. In the subgroup with isolated systolic hypertension, a marked beneficial effect of losartan was observed for hypertension (25% reduction) and stroke (40% reduction) relative to atenolol. In the RENAAL study the effects of losartan were compared with conventional therapy (diuretics or b-adrenergic blockers) in diabetic hypertensive patients with proteinuria. Compared with conventional therapy, losartan reduced the primary composite end point by 16 %. Similar trials done with irbesartan (IDNT-Irbesartan type 2 Diabetic Nephropathy) and IRMA II (the Irbesartan Micro-Albuminuria II) demonstrated renal protective effects. Studies on heart failure have shown no meaningful differences between ARBs and ACE inhibitors on cardiovascular mortality and morbidity. The effects of combinations of ARB-ACE inhibitor are not superior to higher doses of either class given alone (Table 2).

Adverse effects of ARBs are not dose-related [32]. Cough and angioedema are much less common than with ACEIs. As with the other RAS blockers, ARBs are contraindicated in pregnancy.

**Table 2.** Daily doses of the ARBs

| Drug (generic) name | Daily dose* (mg) |
|---|---|
| Candesartan | 8-32 |
| Eprosartan | 600-800 |
| Irbesartan | 150-300 |
| Losartan | 25-100 |
| Olmesartan medoximil | 20-40 |
| Telmisartan | 40-80 |
| Valsartan | 80-320 |

* ARBs are usually administered once daily

### Renin inhibitors

Because secretion of renin is the first step in the renin-angiotensin cascade, a concentrated effort has been made to develop orally active renin inhibitors for clinical usage. Initially several agents were found to have potential. However, investigations at the clinical testing of the first generation renin inhibitors (e.g., zankiren and remikiren) were discontinued, because of their low potency and poor bioavilability, and for commercial reasons [33]. In fact, the success of ACEIs and ARBs influenced the pharmaceutical decision makers to avoid taking commercial risks with putative renin inhibitors.

The synthesis of aliskiren was based on X-ray crystallography, which helped in the structural design of the orally active renin inhibitor (the second generation) to become available for clinical use. Clinical data show that aliskiren is a safe drug with an antihypertensive effectiveness similar to that of other antihypertensive drugs [33], and potential for reducing kidney disease progression [34]. In contrast to other renin-angiotensin blockers, aliskiren directly decreases plasma renin activity.

Despite many recent clinical trials, the place of aliskiren (Tekturna in the USA, Rasilez in UK and elsewhere) in the management of essential hypertension remains unclear [35]. It is not yet clear if aliskiren provides better protection against end-organ damage in cardiovascular and renal diseases. Combined with other antihypertensive drugs, aliskiren (300 mg once/day) improves their hypotensive effects, and it may lessen their adverse effects. However, in high-risk patients, precautions should be taken when combining two or more RASIs, as tissue perfusion may be serious adverse effect. Although the first studies of aliskiren yielded favorable results, two other trials (ASPIRE and AVANT-GARDE) produced contradictory data. The ALTITUDE study was terminated early because of safety issues and lack of beneficial effects. The results of ongoing studies in other patient groups such as the ATMOSPHERE trial are still unavailable. With longer experience this drug may yet become a part of the standard treatment for hypertension.

## CONCLUSION

The RAS has evolved from a circulating and endocrine system to multiple endocrine, paracrine, and autocrine systems. At least four axes for the RAS have been explored, mainly classical renin/ACE/ANG/$AT_1$ and $AT_2$ receptor axis, and its role in the regulation of blood pressure, aldosterone synthesis, and body salt and fluid homeostasis.

The imbalance of actions induced by Ang II and smaller angiotensins (Ang1-7, Ang II and Ang IV) may lead to the development of hypertension and organ injury.

Although ACEIs and ARBs substantially improve the prognosis for patients with hypertension, heart failure and/or kidney disease, morbidity and mortality remain high. Patients treated chronically with either an ACEI or ARB may experience increased renin levels with potentially harmful consequences due to upregulation of pathways that lead to Ang II escape.

Therapeutic strategies could include inhibiting various points within the angiotensin/kinin cascade. ACE2 could enhance the production of Ang 1-7, and drugs that decrease proangiotensin-12 would reduce angiotensin formation by an alternate pathway (Figure 1) [10]. Such

treatments are still in the experimental stage. Development of additional kinin agonists may prove useful in managing of patients with cardiac ischemia, diabetes, renal disease or peripheral ischemia. Inhibitors (e.g., omapatrilat and valsartan-neprilysin) that block both ACE and neutral endopeptidase 24.11 or ARB and neprilysin might also be useful, as would inhibition of chymase. As it stands, these experimental agents have helped us to understand alternate mechanisms that might be used for cardiovascular protection [32]. Blocking antibodies for the components of an overly active RAS failed to reduce blood pressure in hypertensive patients. Ongoing trials with aliskiren, and continuing research studies with the blockers of prorenin, (pro)renin receptors, and gene therapy to reduce renin will reinforce the position of renin in cardiovascular diseases and indicate more effective treatments for cardiovascular and renal diseases.

Current research on the (pro)renin receptors and alternative pathways for Ang II production, suggests additional targets for management of cardiovascular and renal diseases. All new prospects for targeting the RAS can increase vascular protection and prevent end-organ damage. Even though individuals can be helped by novel drug therapies, a global approach to hypertension and cardiovascular diseases must focus on lifestyle changes and prevention as well as treatment.

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# Систем ренин-ангиотензин и његови блокатори

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**КРАТАК САДРЖАЈ**

Истраживања ренин-ангиотензин система (РАС) значајно су допринела разумевању кардиоваскуларне и реналне хомеостазе, али и лечењу кардиоваскуларне болести. У овом прегледном чланку дат је кратак историјат РАС, описане су његове главне компоненте и њихова функција, приказана је клиничка примена блокатора РАС и указано на текућа истраживања компонената овога система. Пошто ангиотензин-конвертујући ензим (*ACE*) метаболише два биолошки веома активна пептида, од којих један припада каликреин-кинин систему (ККС) а други РАС, тај ензим је важна веза између тих система. *ACE* ослобађа веома снажан хипертензивни пептид, ангиотензин *II*, а инактивира јак хипотензивни пептид брадикинин. Зато инхибиција *ACE* доводи до смањивања нивоа ангиотензина *II* и повећања нивоа брадикинина. Због тога смо овде описали и ККС.

**Кључне речи:** ренин-ангиотензин систем; ангиотензин *II*; брадикинин; *ACE*-инхибитори; блокатори ангиотензина; алискирен

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