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Review Article

ANGIOTENSIN II RECEPTOR BLOCKERS: AN OVERVIEW

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ABSTRACT

Blockage of the renin-angiotensin system (RAS) is now recognized as an effective approach to the treatment of hypertension and congestive heart failure. Today, it is possible to antagonize the effects of angiotensin II (AT-II) more specifically by blocking its receptors by using nonpeptide receptor antagonists. AT-II-receptor antagonists were developed as agents that would more completely block the RAS and thus decrease the adverse effects seen with Angiotensin Converting Enzyme (ACE inhibitors). AT-II-receptor antagonists include losartan, valsartan, irbesartan, candesartan, eprosartan and telmisartan. The adverse effects of AT-II-receptor antagonists dizziness, headache, upper-respiratory- tract infection, cough, and gastrointestinal disturbances occur at about the same rate as with placebo. Four of them have recently been launched on the market and several others are preregistered for the treatment of hypertension. These new molecules are as effective as ACE inhibitors, calcium antagonists and beta-blockers in lowering blood pressure in hypertensive patients. When compared to ACE inhibitors, they appear to have comparable favorable effects on systemic and renal hemodynamic properties. All available AT-II-receptor antagonists seem to be equally effective in reducing both systolic and diastolic blood pressure. Currently, AT-II-receptor antagonists are used either as monotherapy in patients who cannot tolerate ACE inhibitors or in combination with other antihypertensive agents. In this review we summarize the combined therapy of ACE inhibitors and AT-II receptor antagonists play in ischemic heart disease. In this respect the review will improve ideas for developing new formulations with combinations of these drugs in the future.

Keywords: Renin-angiotensin system, Hypertension, Angiotensin II receptor, Angiotensin Converting Enzyme inhibitors.

INTRODUCTION

Hypertension is not a single disease but a syndrome with multiple causes. In most instances, the cause remains unknown, and the cases are lumped together under the term essential hypertension (Table 1). However, mechanisms are continuously being discovered that explain hypertension in new subsets of the formerly monolithic category of essential hypertension, and the percentage of cases in the essential category continues to decline. Essential hypertension is often called primary hypertension, and hypertension in which the cause is known is called secondary hypertension, although this separation seems somewhat artificial. This chapter discusses the pathogenesis of hypertension and its complications in general terms and then discusses the specific causes of the currently defined subgroups and the unique features, if any, that each adds to the general findings in patients with high blood pressure.

Table 1: Estimated frequency of various forms of hypertension in the general hypertensive population.[1]

S. No.	Type of hypertension	% Population
1.	Essential hypertension	88.0
2.	Renal hypertension	
2.1	Renovascular	2.0
2.2	Parenchymal	3.0
3.	Endocrine hypertension	
3.1	Primary aldosteronism	5.0
3.2	Cushing's syndrome	0.1
3.3	Pheochromocytoma	0.1
3.4	Other adrenal forms	0.2
3.5	Estrogen treatment (contraceptive hypertension)	1.0
3.6	Miscellaneous (Liddle's syndrome, coarctation of the aorta, etc)	0.6

ABNORMALITIES OF THE RENIN-ANGIOTENSIN SYSTEM

Increased secretion of angiotensinogen from the liver can cause hypertension. Secretion of this angiotensin precursor is under endocrine control and is stimulated by estrogens. Consequently, it is increased in women taking contraceptive pills containing large amounts of estrogens. When circulating angiotensinogen is increased, more angiotensin II is formed and blood pressure rises. The normal compensation for this response is decreased secretion of renin because angiotensin II feeds back directly on the juxtaglomerular cells to reduce renin secretion. However, in some women, the compensation is incomplete and the estrogens cause a significant increase in blood pressure. The incidence of this pill hypertension in the general hypertensive population is about 1% (Table 1). Some of the women with the condition have underlying essential hypertension, which is triggered by the estrogens, but in others the hypertension is cured by stopping estrogen treatment. Mutations in the gene for angiotensinogen, which produce slight increases in circulating angiotensinogen, have been reported to be more common in patients with essential hypertension than in individuals with normal blood pressure.[1]

The Renin-Angiotensin Receptor System

The renin-angiotensin-aldosterone cascade is activated when renin, secreted by the juxtaglomerular cells of the kidneys, catalyzes the conversion of angiotensinogen to angiotensin I (AT-I) in the liver. AT-I is locally transformed into active AT-II via ACE. AT-II, a peptide hormone, is responsible for numerous effects, aldosterone production and release, afferent and efferent vasoconstriction, proximal tubular reabsorption of sodium, increased inotropism and chronotropism, stimulation of drinking behavior and sodium appetite, vagus suppression, and b-adrenergic-receptor stimulation. Two subtypes of AT-II receptors have been identified. Type 1 receptors are predominantly found on vascular endothelium and are linked to all the known physiological and pharmacologic actions of AT-II. Stimulation of type 1 receptors by AT-II induces vasoconstriction, renal tubular sodium reabsorption, aldosterone release, vascular smooth muscle remodeling, and stimulation of central and peripheral sympathetic activity, thus leading to increases in blood volume and blood pressure.[2] Antagonism of type 1 receptors lowers blood pressure by inhibiting these actions. Type 2 receptors are predominantly found in the adrenal medulla, uterus, and fetal tissue and may play a role in fetal growth and differentiation, although the exact function of these receptors has not been identified.[3]

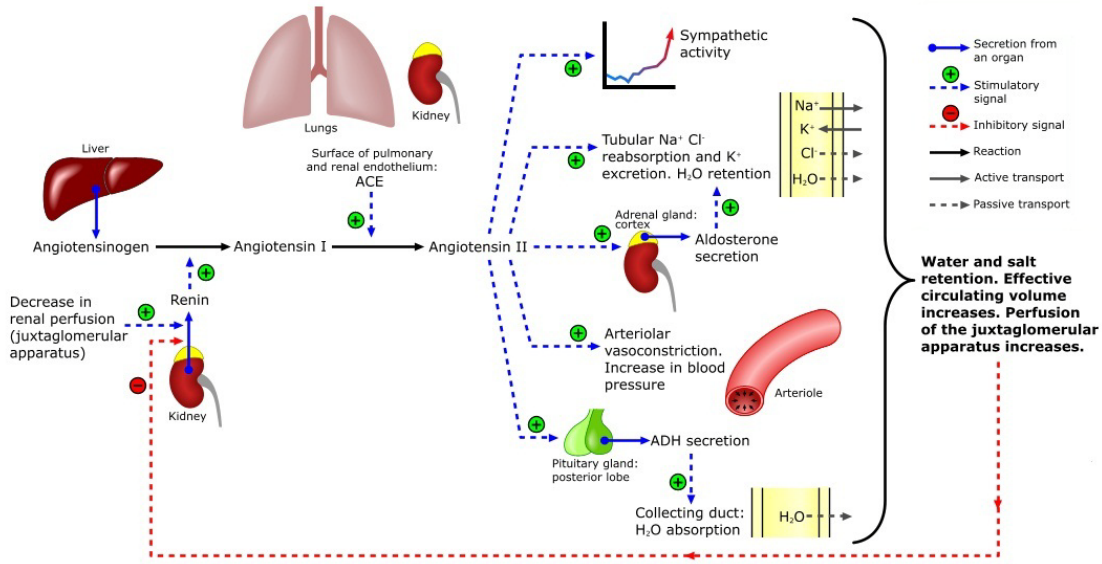

Fig. 1: Schematic representation of the renin angiotensin system and the different sites of potential pharmacological action[4]

PHARMACOLOGY

The renin-angiotensin system, specifically angiotensin II, is implicated in the pathogenesis of essential hypertension, renovascular hypertension, congestive heart failure, and renal diseases associated with albuminuria.[5,6,7] Blockade of the reninangiotensin system with ACE inhibitors has provided effective treatment of these conditions; however, some of the adverse effects of ACE inhibitors appear to be unrelated to angiotensin II blockade. For example, cough and angioedema are due to other effects of ACE inhibition, such as degradation of bradykinins and prostaglandins. The ARBs' mechanism of action, selective inhibition of angiotensin II by competitive antagonism of the angiotensin II receptors, has been speculated to reduce adverse effects and possibly improve clinical efficacy. ARBs displace angiotensin II from the angiotensin I receptor and produce their blood pressure lowering effects by antagonizing angiotensin II–induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic response.[6]

PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetic profiles of the agents in the ARB class are listed in Table 2. Losartan's major active metabolite, EXP- 3174, is 10 to 20 times more potent than losartan and has a longer duration of action.[5] The active metabolite is primarily responsible for the therapeutic effects. Candesartan and olmesartan are prodrugs that undergo metabolic activation during absorption from the gastrointestinal tract. [5, 6, 7] The parent compounds of candesartan and olmesartan have little or no clinical efficacy. Once olmesartan is rapidly converted to its active metabolite, it does not undergo further metabolism. [8]

Table 2: Pharmacokinetic parameters of angiotensin II receptor blockers[8,9]

Drug	Active metab	Bioavail (%)	Food effect	Half-life (hrs)		Protein binding (%)		Route of elimination(%)	
				Drug	metab	Drug	metab	Drug	metab
Losartan	Yes	33	No	2	6–9	98.7	99.8	35	60
Valsartan	No	25	Yes	9	-	95	-	13	83
Irbesartan	No	70	No	11-15	-	90-95	-	20	80
Candesartan	Yes	42	No	3.5-4.0	3-11	99.5	-	33	67
Telmisartan	No	43	No	24	-	>99	-	0.5	>97
Eprosartan	No	15	No	5-7	-	98	-	7	90
Olmesartan	Yes	26	No	~13	-	>99	-	35-50	50-65

*Metab indicates metabolite; †Bioavail indicates bioavailability.

Antagonist of the Renin- Angiotensin System

Blocking of the renin-angiotensin system (RAS) led to the discovery of ACE inhibitors, which proved efficacious in the treatment of hypertension, various cardiovascular disorders (e.g., congestive heart failure and coronary insufficiency), and renal diseases.[10] However, the high frequency of cough with ACE inhibitors (up to 20% of patients)[11,12] meant that another class of equally efficacious agents with a potentially more favorable adverse- effect profile was needed.

Conversion of AT-I to AT-II is not the only pathway for AT-II generation. AT-II is also formed via pathways involving cathepsin G, elastase, tissue plasminogen activator, chymostatin- sensitive AT-II-generating enzyme, and chymase; thus, ACE inhibition only partially reduces the formation of AT-II.[13] Agents that can specifically and selectively inhibit the action of AT-II could completely block the RAS. In addition, relative to other classes of antihypertensives, such agents might decrease the frequency of common adverse effects, such as dizziness, headache, fatigue, diarrhea, cough, and edema.[14]

Currently, two classes of drugs have the mechanistic potential to completely block the RAS: renin inhibitors and AT-II receptor antagonists. Competitive antagonism of renin would prevent the formation of AT-II by inhibiting AT-I formation; however, the development of such agents has progressed slowly because of continuing problems with bioavailability.[15] Saralasin, the first AT-II-receptor antagonist, was synthesized in 1971. An intravenous formulation of this AT-II peptide analogue was shown to lower blood pressure in direct proportion to the plasma level of renin. However, saralasin was not a feasible treatment for hypertension because it had poor bioavailability and a short duration of action and because it potentiated vasoconstriction and induced hypertensive effects in low-renin conditions.[16]

Table 3: Some famous brands of angiotensin II receptor blockers

Generic Name	Brand Name
Candesartan	Atacand
Eprosartan	Teveten
Irbesartan	Avapro
Losartan	Cozaar
Olmesartan	Benicar
Telmisartan	Micardis
Valsartan	Diovan

Losartan Potassium

Losartan potassium was the first orally bioavailable, long-acting, nonpeptide AT-II type 1-receptor antagonist to be used in humans.[14,17] It has been extensively studied in both animals and human volunteers.[17] Its effectiveness as an antihypertensive agent has been established.[17,18]

Losartan has a half-life of 2 hours (Table 2). It is rapidly absorbed from the gastrointestinal tract, independent of food intake. Losartan undergoes first-pass hepatic metabolism via cytochrome P-450 (CYP) isoenzymes 2C9 and 3A4 to its active carboxylic acid metabolite, EXP-3174, which reaches peak plasma concentration in two to four hours and has a half-life of six to nine hours.[19,20] Despite the biotransformation of losartan by CYP isoenzymes, no pharmacokinetic or pharmacodynamic interactions with warfarin or digoxin have been reported. The consequences of using losartan with potent CYP2C9 inhibitors have not been examined. In vitro studies have shown that oxidation of losartan to EXP-3174 is markedly inhibited by ketoconazole, a potent inhibitor of CYP3A4; however, the clinical consequences, if any, of this interaction have yet to be determined.[21]

The usual starting dosage of losartan potassium is 50 mg once daily. The dosage can be increased to a maximum of 100 mg daily. Doses exceeding 100 mg have not been found to produce any additional decrease in systolic or diastolic blood pressure.[22] In patients who have hepatic impairment or who may be volume depleted, such as those taking large doses of a diuretic, the starting dosage should be reduced to 25 mg once daily to minimize the occurrence of symptomatic hypotension.

Valsartan

Valsartan was the second nonpeptide AT-II type 1- receptor antagonist available for the treatment of hypertension. Valsartan is rapidly absorbed from the gastrointestinal tract after oral administration and can be administered without regard to food intake.[23] The peak effect of valsartan is evident in two to four hours; the bioavailability is 25%.[24] Valsartan has a half-life of nine hours and demonstrates antihypertensive effects for approximately 24 hours. Less than 10% of an orally administered dose of valsartan undergoes biotransformation in the liver; the enzymes responsible for its metabolism are unknown, and no active metabolites have been identified.[25] Elimination occurs primarily in the bile (83%) and to a lesser extent via the kidneys (13%), largely as unchanged drug.[26,27]

Dosages ranging from 80 to 320 mg once daily are effective for controlling blood pressure and are recommended in patients who are not volume depleted. Greater reductions in blood pressure are apparent with incremental increases in the dosage up to 320 mg/day; hence, it is recommended that valsartan be started at 80 mg/day and the dosage adjusted upward until the desired response is reached. The effectiveness of valsartan 80-320 mg/ day in reducing blood pressure was established by a randomized, double blind, placebo-controlled trial.[11]

The safety of valsartan has been assessed in various clinical trials.[28,29] Valsartan was well tolerated at dosages of 80-160 mg/day. At higher dosages (320 mg/day), dizziness became more prevalent. Headache, upper-respiratory-tract infection, diarrhea, and fatigue occurred most commonly (>1%), but at rates comparable to those in placebo recipients. In one study, dry cough was considerably less common with valsartan than with the ACE inhibitors lisinopril (71.1%).[30] In another study comparing valsartan with an ACE inhibitor (enalapril) and with placebo, study patients reported cough.[31]

Irbesartan

Irbesartan is a long-acting nonpeptide AT-II type 1-receptor antagonist with a plasma half-life of 11-15 hours. Irbesartan has no active metabolites and is 90-95% protein bound. The drug is absorbed rapidly after oral administration and has a bioavailability of 70%, the highest in its class.[32] Food intake has no effect on absorption. After oral administration, peak plasma concentrations are achieved in two hours. Irbesartan undergoes hepatic metabolism via glucuronide conjugation and oxidation; no active metabolites have been identified. After administration of a single 150-mg dose of irbesartan, 20% of the dose is excreted by renal route and about 80% is excreted in the bile. In vitro studies indicate that oxidation of irbesartan occurs primarily via CYP2C9. Warfarin and digoxin appear to have a negligible effect on CYP2C9 metabolism of irbesartan. When potential drug interactions were explored in patients taking warfarin, hydrochlorothiazide, or digoxin concurrently with irbesartan, no changes in the pharmacokinetics of digoxin or the pharmacodynamic effects of warfarin (prothrombin time) were noted.[33]

Antihypertensive effects are seen within two weeks of initiating therapy, with maximum effects occurring at between two and six weeks.[34-36] Effects on blood pressure are dose dependent over the range of 75-300 mg.[37,38] However, data from various double-blind, placebo-controlled trials show that daily doses of 150-300 mg, administered once daily or in divided doses, will effectively reduce blood pressure by 3.1-6.1 mm Hg.[37] The addition of hydrochlorothiazide 6.25-25 mg/day to irbesartan 75-300 mg/day further decreases blood pressure [39,40] to the same extent as treatment with enalapril 20-40 mg.[41]

In clinical studies of irbesartan there was no relationship between the dosage and the overall frequency of adverse reactions. The rates of serious adverse events were similar for irbesartan (1.0%) and placebo (1.9%).[42] The most common adverse reactions were upper-respiratory- tract infection (9.0% for irbesartan, 5.1% for placebo).

Candesartan

Candesartan another long-acting nonpeptide antagonist of AT-II type 1 receptors,[43] is a prodrug that is hydrolyzed to its active metabolite candesartan during gastrointestinal absorption.[44] The half-life of candesartan is about 3.5-4 hours, and it is 99.5% protein bound. About 33% of a dose is eliminated through the urine and 67% through the bile. Candesartan is not metabolized by CYP isoenzymes.

Candesartan lowers blood pressure in a dose-dependent manner (at doses of up to 32 mg).[45-47] The 16- and 32-mg daily doses seem to be more effective than lower doses (4 and 8 mg/day) in lowering blood pressure; mean reductions in blood pressure were 10.7 and 12.6 mm Hg for candesartan 16 and 32 mg, respectively, and 9.9 and 10.5 mm Hg for 4- and 8-mg doses.[45]After administration of 4-32 mg, peak plasma candesartan levels are achieved within three to four hours. Dosages of 4-16 mg/day have no effect on plasma aldosterone concentrations; however, a decrease in the plasma aldosterone concentration is seen when 32 mg/day is administered.

Candesartan is well tolerated, with no relationship seen between dosage or time of administration and occurrence of adverse events.[48-50] Upper-respiratory- tract infection (6%), pain (3%), and dizziness (4%) were among the most commonly reported adverse events, and these events generally resolved without discontinuation of therapy. Rates of adverse events were similar to those for placebo.[49]

Eprosartan

Eprosartan was the fourth selective nonpeptide AT-II type 1-receptor antagonist to gain approval for use in the treatment of hypertension in the United States. It was marketed by Unimed Pharmaceuticals in October 1999 under the name Teveten. After oral administration of a single dose of 300 mg of eprosartan, plasma

concentration peaks in one to two hours in the fasted state.[51] Eprosartan is less bioavailable than other AT-II-receptor antagonists (Table 3); this may be related to incomplete absorption. Eprosartan yields no active metabolites after oral administration. It is eliminated primarily in bile (90%) and to a lesser extent in urine (7%) as unchanged drug. There is negligible systemic accumulation of eprosartan with long-term use, so dosage adjustment is not warranted in patients with hepatic or renal disease.

When eprosartan is used as monotherapy in patients who are not volume depleted, a starting dosage of 600 mg once daily is recommended. If a further decrease in blood pressure is warranted, the dosage may be increased to 800 mg/day.[51,52] In most patients it may take two to three weeks of treatment to see a maximum response in blood pressure. When used in combination with other antihypertensive agents, such as thiazide diuretics and calcium channel blockers, an additive effect is seen [53,54], however, a recommended starting dosage in this situation has not yet been established. Hypotension may occur in volume- or salt-depleted patients, so caution is needed in treating this patient population, and these conditions should be corrected before starting eprosartan therapy.

Eprosartan does not inhibit CYP450 isoenzymes and is not metabolized via this pathway. Thus, eprosartan would not be expected to inhibit the metabolism of drugs that require this enzyme system for elimination (such as warfarin), nor should it be prone to drug interactions mediated by this pathway.[53,55] When administered with warfarin, eprosartan had no apparent influence on the anticoagulatory effect of warfarin, as determined by the International Normalized Ratio.[56] In conclusion, no dosage adjustments are necessary when eprosartan is administered with warfarin, digoxin, or glyburide. [55-57]

Telmisartan

Telmisartan a nonpeptide AT-II-receptor antagonist,[58] gained FDA approval for use in the treatment of hypertension in 1998. After oral administration, peak concentrations are reached in 0.5-1 hour. The absolute bioavailability of telmisartan is dose dependent.[59,60] A dose of 40 mg achieves 43% bioavailability, whereas 160 mg is 58% bioavailable. The bioavailability of oral telmisartan is reduced slightly, but not significantly, by food. The half-life is 24 hours, which allows for once-daily administration. About >97% of a telmisartan dose is eliminated unchanged in the feces via biliary excretion. Renal excretion does not contribute (~0.5%) to telmisartan's elimination.

The antihypertensive effects of telmisartan 20-160 mg were assessed in clinical trials in patients with mild to moderate hypertension. Reductions in systolic and diastolic blood pressure were on the order of 6-8 and 6 mm Hg, respectively, with 20 mg/ day; 9-13 and 6-8 mm Hg with 40 mg/day; and 12-13 and 7-8 mm Hg with 80 mg/day.[59,61] A further decrease in blood pressure was not seen with a larger dosage (120-160 mg/ day). It is recommended that telmisartan be initiated at 40 mg/day with or without food; the dosage may be increased to up to 80 mg/day if further blood pressure reduction is needed. In situations in which even further blood pressure reduction is needed (beyond that achieved with 80 mg/day), the addition of hydrochlorothiazide has been found to produce incremental reductions.[62] Antihypertensive activity begins within 3 hours and is maintained for 24 hours. A maximum reduction in blood pressure is evident in approximately four weeks. No reduction in the starting dosage is necessary in patients with mild to moderate renal impairment or the elderly. Caution should be used when administering telmisartan to patients with biliary obstructive disorders or hepatic insufficiency, since this agent is eliminated primarily by biliary excretion.

Tolerability Profile of Angiotensin II Receptor Antagonists

The adverse event profile of a new therapeutic agent is very important. One of the major characteristics of angiotensin II receptor antagonists as a class is the excellent tolerability with an incidence of side-effects that is generally similar to that of placebo. Studies performed with losartan and valsartan have clearly demonstrated that in contrast to ACE inhibitors, these agents do not induce cough. [63,64] This observation confirms that dry cough is due to the lack of specificity for the renin-angiotensin system of ACE inhibitors. The only difference among angiotensin II antagonists is the ability of losartan to increase urinary uric acid excretion and hence to lower plasma uric levels.[65] Whether this uricosuric effect of losartan, but not EXP 3174, represents an advantage or an inconvenience is still not clear. In patients pretreated with thiazide diuretics, losartan has been shown to blunt significantly the diuretic-induced increase in plasma uric acid. [66] In cyclosporine-treated heart transplant patients, losartan has also been shown to lessen the cyclosporine induced hyperuricemia. [67] Thus, in some clinical situations if not always–the uricosuric effect of losartan may be rather beneficial. Uric acid stone formation is not a complication of losartan because urinary pH tends to become slightly more alkaline during angiotensin II receptor blockage.

Table 4: Tolerability Profile of Angiotensin II Receptor Antagonists[8,9]

Adverse effect	Losartan n=1075	Valsartan n=2316	Irbesartan n=1965	Candesartan n= 2350	Telmisartan n=1455	Eprosartan n=1202	Olmesartan n=3278
CNS							
Dizziness	3.5	-	-	4	-	-	3
Fatigue	-	2	4	-	-	2	-
GIT							
Diarrhea	2.4	-	3	-	3	-	-
Dyspepsia	1.3	-	-	2	-	-	-
Abdominal pain	-	2	-	-	-	2	-
Muscles							
Arthralgia	-	-	-	-	-	2	-
Pain	-	-	-	3	1-3	-	-
Respiratory							
URTI	7.9	-	9	6	7	8	-
Cough	3.4	-	2.8	-	-	4	-
Sinusitis	-	-	-	-	3	-	-
Viral infection	-	3	-	-	-	2	-

*CNS Central nervous System; *GIT Gastrointestinal tract; *URTI upper respiratory tract infection; *n= no. of patients under trial

Drug Interactions

Of the AT-II-receptor antagonists, only candesartan has any clinically important interactions with digoxin, warfarin, and hydrochlorothiazide. Candesartan may increase serum concentrations of digoxin and may decrease warfarin concentrations; however, there is no apparent change in the International Normalized Ratio. Losartan is metabolized by the CYP isoenzyme system; however, the effects of potent inhibitors of CYP3A4 and CYP2C9 on losartan pharmacokinetics have not been clinically studied. When administered with losartan, phenobarbital causes a 20% reduction in serum concentrations of losartan and its metabolite, thus reducing its effectiveness.

Eprosartan, candesartan, irbesartan, valsartan, and telmisartan are not metabolized by the CYP system.

Table 5: Interactions of angiotensin II receptor blockers with other drugs[7,9]

Precipitant drug	Object drug	CYP450 substrates	Effect
Cimetidine	Losartan	-	↑losartan no effect EXP3174
Fluconazole	Losartan	3A4, 2C9	↑Losartan
Indomethacin	Losartan	-	↓hypotensive effect
Phenobarbital	Losartan	-	↓losartan ↓active metabolite
Rifampicin	Losartan	3A4, 2C9	↓ Losartan
Telmisartan	Digoxin	-	↑ Digoxin

Future trends of Angiotensin II Receptor Antagonists

Angiotensin II antagonists signify a key new advance in the management of hypertension and probably congestive heart failure and chronic renal failure. These agents are very effective in lowering blood pressure and present a unique tolerability profile. Additional studies are now necessary to evaluate their impact on the long-term morbidity and mortality of patients with various cardiovascular diseases. Several large trials are underway in various populations. The LIFE study (Losartan Intervention for End-point reduction in hypertension) is evaluating the effect of losartan on cardiovascular morbidity and mortality in hypertensive patients [68] and the RENAAL study examine the renal protective effect of losartan in patients with type II diabetes. The ELITE trial (Evaluation of Losartan in the Elderly) has compared the safety and efficacy of losartan and captopril in elderly patients with heart failure. [69] The first results of this study have shown that losartan is as safe as captopril, and no difference in renal dysfunction was found between the two drugs. Surprisingly, however, after one year of follow-up the mortality was significantly lower in the losartan than in the captopril group.

A second study (ELITE II) is now underway to confirm these promising preliminary results. Large interventional trials are also conducted with other angiotensin II receptor antagonists. Together, the results of these studies will help to more clearly define the future role of angiotensin II receptor antagonists in the management of patients suffering from hypertension, congestive heart failure and chronic nephropathies. Morbidity and mortality from cardiovascular diseases are still high, despite the use of the best available therapies. There is growing evidence that excessive renin-angiotensin system activation underlies much of the damaging and progressive nature of cardiovascular and kidney diseases. Today, ACE inhibitors and AT-II receptor antagonists have clearly demonstrated their efficacy in preventing target organ damage and in reducing cardiovascular morbidity and mortality in hypertension. So far, renin inhibitors have been very slow to develop but a new orally active, well-tolerated and promising compound is being developed. Renin inhibition may not only provide new opportunities to block the renin-angiotensin cascades specifically and effectively; it will also improve our understanding of the renin-angiotensin system as it may help to clarify the role of bradykinin and AT-II subtype 2 receptors in mediating the effects of ACE inhibitors and AT-II receptor antagonists.

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Declaration of Interest

The authors report no financial or non financial conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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