WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 3, 1688-1721 Review Article ISSN 2278 – 4357

ROLE OF ARBS IN THE MANAGEMENT OF HYPERTENSION, CARDIOVASCULAR DISEASES, RENOPROTECTION AND NEUROPROTECTION

Afshan Siddiq*, Hafiza Amna Batool and Sadia Ghousia Baig

Department of Pharmacology, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Karachi, 75270, Pakistan.

Article Received on
18 Jan. 2019,

Revised on 08 Feb. 2019,
Accepted on 28 Feb. 2019,
DOI: 10.20959/wjpps20193-13385

***Corresponding Author**
Afshan Siddiq
Department of Pharmacology, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Karachi, 75270, Pakistan.

ABSTRACT

The angiotensin II receptor blockers are well tolerated and highly beneficial antihypertensive therapy. They have ability to control blood pressure for 24 hours and administer only once a day. Efficacy and other clinical characteristics of ARBs are almost same and there is no significant difference. Several clinical trial have showed that angiotensin receptor blockers reduced mortality and morbidity associated with hypertension, diabetic mellitus, diabetic nephropathy, heart failure, myocardial infarction, stroke, atrial fibrillation, end stage kidney disease and hypertension with left ventricular hypertrophy. They provide beneficial effects in erectile dysfunction, protection of cognitive function as well as restoration of cognitive decline. ARBs are developed in 1995 to overcome the several deficiencies of angiotensin converting enzyme inhibitor. ARBs are given as an alternative to ACE inhibitor intolerant patients. ACE inhibitor causes cough and angioedema which are found less common in ARB. Compare with ACE inhibitor ARBs have overall lower withdrawal rate because of adverse events as compare to ACE inhibitor. ARBs is superior to ACE inhibitor because of fewer side effect but provide equal outcome efficacy for the treatment of hypertension or its compelling indications. ARBs may be prescribed as monotherapy for achieving blood pressure goal in initial stage and as well as add on- antihypertensive therapy. They may also give as a single pill fix dose combination of two or three agents by reducing their doses. Additive antihypertensive effects are observed when ARBs are given in combination with thiazide diuretics, calcium channel blocker and renin inhibitor.

KEYWORDS: angiotensin receptor blockers, angiotensin converting enzyme inhibitor, hypertension, stroke, heart failure, myocardial infarction, diabetic nephronathy, end stage renal disease, erectile dysfunction, cognitive function, antihypertensive effects.

INTRODUCTION

Renin angiotensin aldosterone system

The renin-angiotensin-aldosterone system (RAAS) take part a vital role in protecting vertebrates against cardiovascular collapse because of hypotension and volume loss owing to injury that involves blood loss.[1] Increase or inappropriate activity of the RAAS is responsible for the development of hypertension and causes an injury to critical organs such as the, heart, brain, kidneys, and blood vessels.[1,2,3] As knowledge of the pathological role of the RAAS in hypertensive vascular disease, developed antihypertensive medication by targeting pathway of this route.[1,4] The four classes of medications that are taken into account in this route contain angiotensin II receptor blockers, angiotensin converting enzyme inhibitor, direct renin inhibitors and aldosterone antagonists.[4] The first of the RAAS-blocking drugs were the aldosterone antagonists came on the market in the 1970s, followed by the angiotensin-converting enzyme inhibitors, captopril, in the 1980s and the angiotensin II receptor blockers, losartan, in 1995.[5]

Angiotensin receptor system

Angiotensin II binds two types of angiotensin II receptors (ATR) – ATR_1 and ATR_2. The ATR_1 receptors are present in the vessels, brain, heart, kidney, adrenal gland, and nerves while ATR_2 are mainly expressed in the fetus but decrease in amount during the postnatal and present in small quantity in the adult kidney, adrenal gland, heart, brain, uterus, and ovary.[6,7] Angiotensin II increases inositol triphosphate and various arachidonic acid metabolites and decreases cyclic adenosine monophosphate by activation of ATR_1.[4]

ARBs inhibit the binding of angiotensin II to the ATR_1 and thereby block its activation, despite of it synthesis by ACE-dependent or -independent pathways.[8, 9]

Angiotensin II activate the AT_1 receptor which produces generalized vasoconstriction from contraction of vascular smooth muscle, increases in aldosterone resulting in increased sodium reabsorption in the proximal tubule and cell growth and proliferation in the arteries and heart.[2,4,8,10,11] Sympathetic nervous system activity is increased due to secretion of catecholamine from the adrenal medulla and nerve endings by Angiotensin II.[1,4,8,10]

Angiotensin II is responsible for cardiovascular effects by ATR_1.Thus, ATR1 blockage decreases cardiac preload and afterload.[4]

The antihypertensive action of ARBs is mostly owing to lowering of peripheral vascular resistance.[11] Angiotensin II is believed to have an important mechanistic role in promoting cardiovascular diseases unrelated to its effect in blood pressure. Several animal studies demonstrate that it produce cardiac hypertrophy even in the absence of increased blood pressure.[12] Study showed that people who have elevated renin-sodium profile have greater risk of myocardial infarction than those with a normal or low profile.[13]

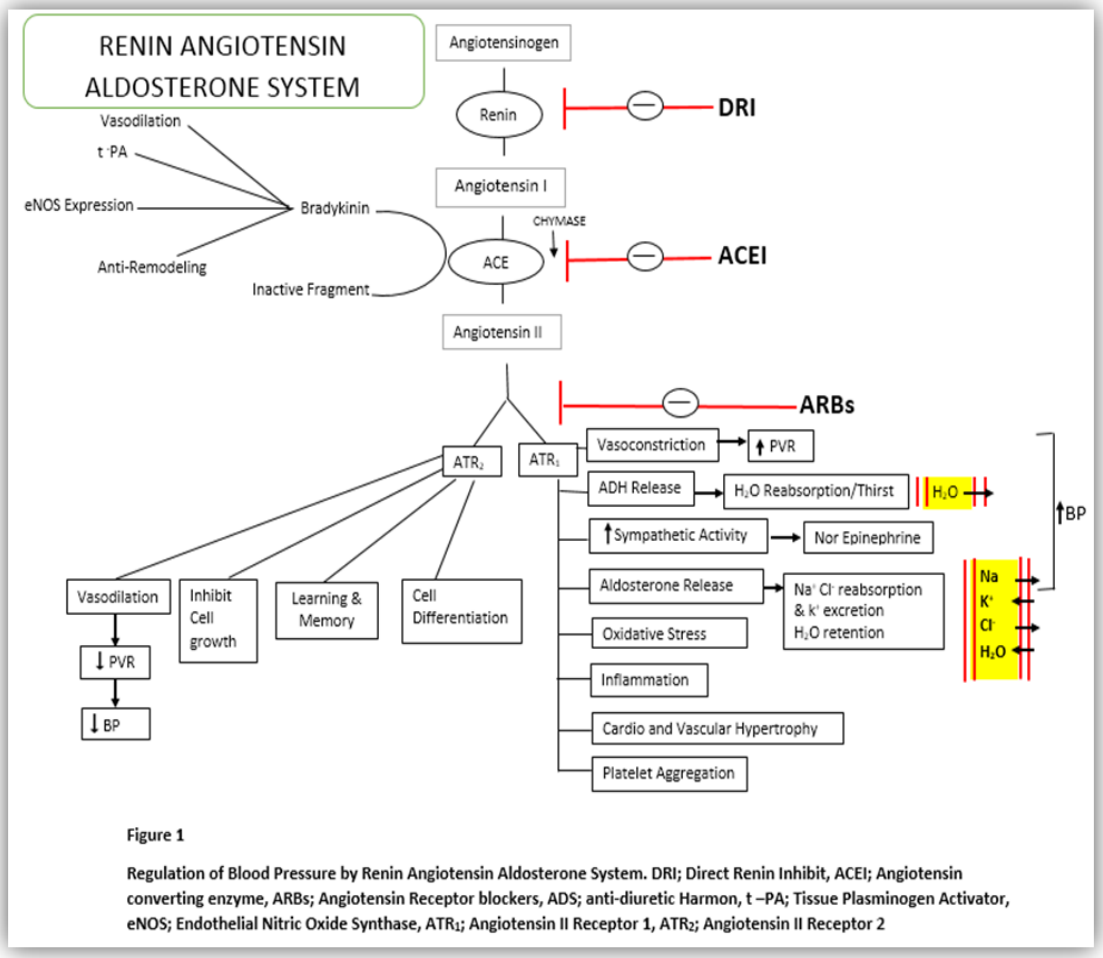

Figure 1

Regulation of Blood Pressure by Renin Angiotensin Aldosterone System. DRI; Direct Renin Inhibit, ACEI; Angiotensin converting enzyme, ARBs; Angiotensin Receptor blockers, ADS; anti-diuretic Harmon, t –PA; Tissue Plasminogen Activator, eNOS; Endothelial Nitric Oxide Synthase, ATR_1; Angiotensin II Receptor 1, ATR_2; Angiotensin II Receptor 2

ARBs increase circulating AT II concentrations by inhibiting the binding of AT II to the ATR_1 which, in turn, bind to the ATR_2.[2][9] ARBS may have promising cardiovascular actions due to 'over-stimulation' of the ATR_2 by ARBs.[9]

ATR_2 activation may inhibit cell growth, apoptosis, cell differentiation, and cause vasodilation.[7] However it may also have a beneficial effect in repair processes.[2] Animal studies show that AT_2 receptor activation enhance cardiac function and prevents cardiac remodeling post-myocardial infarction.[14]

ARBs do not increase bradykinin level because they do not block kininase II activity. Therefore, ARBs has a unique mechanism for inhibiting the RAAS, which is distinct from that of ACE-inhibitors. ARBS may be advantageous in CHF patients who are intolerant to ACE-inhibitors. ARBS may provide complete blockage of AT II (by blocking non-ACE-generated AT II).[9]

PHARMACOKINETIC

The ARBs are non-peptide and most of them share a common chemical structure biphenyl-tetrazole and imidazole group.[15,16,17] All ARBS contain carboxylic acid group except irbesertan.[11] Despite of their structural similarities and same mechanism of action, ARBs differ in pharmacokinetic properties. ARBs binds with AT1 receptor in different ways. Binding is classified as surmountable or insurmountable based on the ability to shift the angiotensin-II concentration-response curves to the right. Surmountable binding can be decreased by increasing concentrations of agonist or angiotensin II whereas insurmountable binding cannot be overcome by increasing concentrations of angiotensin II. However, surmountable antagonism does not associated with a change the maximal angiotensin II response whereas insurmountable antagonism reduces the response. Losartan, valsartan, azilsartan and eprosartan are surmountable (competitive) antagonists, whereas Irbesartan, candesartan, and telmisartan and olmisartan are insurmountable (noncompetitive) antagonists.[18,19,20]

Table 1: Pharmacological parameter of ARBs.

Drug	Prodrug	Active met	Bioav %	Food effect	Half life (h) D M	Protein binding % D M	Route of elimination % R B	Vd (l)	S or I Ant	Cyp P450 met
Losartan		EXP-3174	33	Yes¶	2 6-9	98.7 99.8	30 70	34/ 12	S/EXP=I	2C9,3A4,IA2
Valsartan		-	23(cap) 50(sol)	yes~	6 -	95 -	20 80	17	S	2C9(weak)
Irbesartan		-	60-80	no	11-15 -	90-95 -	25 75	53 93	I	2C9,3A4 (negligible)
Candesartan	prodrug		42	no	9-12	99.5 -	33 67	10	I	2C9(weak)
Telmisartan		-	43	no	24	>99 -	<1 >97	500	I	
Eposartan		-	13	yes^	5-7	98 -	10 90	13	S	
olmesertan	prodrug		26	no	13 ˜	>99 -	40 60	17	I	
azilsartan	prodrug		60		12		42 55	16	S	269,CYP2B6 (negligible) CYP2C8 (negligible)

Abbreviations: Met: metabolite, Bioav: bioavailability, D: drug, M: metabolite, R: renal, B: biliary, Vd: volume of distribution, S: surmountable, I: insurmountable, Ant: antagonist, CYP 450 met: cytochrome P450 metabolite

¶Absorption is delay by food and decrease its Cmax but the AUC of it and EXP-3174 are not significantly changed.

~High fat food increases bioavailability by 80% and AUC by 55% but slows gut absorption

^Bioavailability increases by 80% and AUC by 55% but slows gut absorption due to elevated fat food.

Candesartan, olmesartan and azilsartan are prodrug and require metabolic activation in gastrointestinal tract and liver to produce their therapeutic effect.[19,21,22] EXP-3174 (metabolite of losartan) is 10 -40 times more potent than lostatan and has a longer duration of action.[21,22] No other metabolite of ARBs significantly produce therapeutic effect.[11]

ARBs are highly protein bound (>90%) but they differ in their volume of distribution from 10L for candesartan to 500L for telmisartan.[23] ARBs are well absorbed after oral administration and peak plasma concentration reaches 0.5-4hour but they have different Bioavailability, ranges from 13% for eposartan to 60% to 80% for irbesartan.[24]

ARBs are highly protein bound (>90%) but they differ in their volume of distribution from 10L for candesartan to 500L for telmisartan.[23] ARBs are well absorbed after oral administration and peak plasma concentration reaches 0.5-4hour but they have different Bioavailability, ranges from 13% for eposartan to 60% to 80% for irbesartan.[24]

According to half-life losartan, valsartan, and eprosartan may be classified as shorter acting and candesartan, irbesartan and telmisartan, olmisartan, azilsartan as longer acting.

Elevated plasma concentration are seen in patient with impaired renal function for those drug which are primarily excreted through renal route, such as candesartan and eprosartan, so lowering of dose may be required.[23] Patient having severe hepatic impairment, lowering of losartan dose by half must be needed.

ARBs is better drug of choice in contrast to ACE inhibitor for the indication of hypertension in patient with impaired renal function because ARBs is primarily eliminated through hepatic route while ACE inhibitor are excreted predominantly through kidneys.[25,26]

If ARBs and ACE inhibitor are prescribed to patient having bilateral renal artery stenosis or unilateral renal artery stenosis and a solitary kidney, caution must be advised.[25] ARBs as a class of drug are not dialyzable but in certain cases ACE inhibitor are dialyzable.[27]

DOSING OF ARBS

Table 2: Starting and maintenance doses of ARBs.

Drug	Brand name	Starting dose (mg daily)	Maximum dose (mg daily)	Dosing interval
Losartan	Cozaar	50	100	OD or BID
Valsartan	Doovan	80	320	OD
Irbesartan	Irecon	150	300	OD
Candesartan	Advent	16	32	OD or BID
Telmisartan	Pressurex	40	80	OD
Eprosartan	Taveten	600	800	OD or BID
Olmesartan	Benser	20	40	OD
azilsartin	Aziltrend	40	80	OD

Abbreviations: OD: once a day, BID: twice a day.

Starting dose may be decreased by 50% in elderly or volume depletion person as well as renal dysfunction patient.

Lower starting dose of candesartan and valsartan in BID regimen are recommended for heart failure.

Based on daily mg dose, the antihypertensive potency of the ARBs has following sequence: candesartan > olmesartan > telmisartan = azilsartan > losartan > valsartan> irbesartan > eprosartan.

All ARBs are given once a day but losartan, valsartan and eprosartan may be given twice a day because of short half-life.

INDICATION

Table 3: Therapeutic indication of ARBs.

ARBs	Losartan	Valsartan	Irbesartan	Candesartan	Olmesartan	Telmisartan	Azilsartan	Eprosartan
Hypertension	yes	yes	yes	yes	yes	yes	yes	yes
Heart failure	yes	yes		yes				
Diabetic nephropathy	yes		yes					
Prevention of stroke	yes							
Cardiovascular risk reduction						yes		
Following myocardial infarction		yes						
Atrial fibrillation						yes		

Diabetic mellitus		yes				yes		
Hyperuricemia	yes							
Erectile dysfunction	Yes	yes	yes					
Cognitive decline	yes	yes	yes	yes		yes		yes

Yes: beneficial effect of ARBs

Hypertension

"The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and management of High Blood Pressure in adult (JNC 7) recommend to reduced blood pressure to a goal of systolic blood pressure <140/diastolic blood pressure 90 mm Hg in patients with uncomplicated hypertension and to systolic blood pressure <130/ diastolic blood pressure 80 mm Hg in patients of known clinical cardio vascular disease, diabetes mellitus or chronic kidney disease.[28]

Table 4: Clinical comparison of ARBs among as monotherapy.

Study design	Drug	Dosage	Duration	Sample	Result
8-week, double-blind, randomized, parallel group, multicenter, forced titration study. (CLAIM Study II)[29]	Candesartan Candesartan Losartan Losartan	16mg OD 32mg OD 50mg OD 100mg OD	2 weeks 6 weeks 2 weeks 6 weeks	307 304	At week 8, candesartan reduced the BP to a significantly more than losartan (P < 0.05). Response rates of candesartan were higher (58.8%) than losartan (52.1%) but the differences did not reach statistical significance.
12-week, randomized, double-blind, forced-titration study.[30]	Olmesartan Losartan Valsartan	20mg OD 40mg OD 50mg OD 100mg OD 50mg BID 80 mg OD 160 mg OD 320 mg OD	4 weeks 8 weeks 4 weeks 4 weeks 4 weeks 4 weeks 4 weeks 4 weeks	182 180 181	All 3 drugs significantly decreased mean SeDBP from baseline compared with placebo at weeks 4, 8, and 12 (P<.001). At week 8, olmesartan decreased mean SeDBP greater than losartan (P<.001); more patients in the olmesartan group achieved a blood pressure goal of <130/85mm Hg. Olmesartan did not decreased mean SeDBP significantly compared with valsartan, while more patients attained blood pressure goal with olmesartan (P=.031). At week 12, all 3 drugs reduced blood pressure less than 130/85 was equivalently.

1year, randomized,double blind, placebo-controlled study.[31]	Telmisartan Eprosartan	40mg OD 60mg OD	1 year 1 year	40 39	After 12 month, telmisartan or eprosartan produced a significant reduction (p<0.01) in SeSBP compared with baseline. Telmisartan decreased significantly more SeDBP than eposartan.
8 week, Single blind, placebo for 3 weeks then followed by randomized to take either drug for 5 weeks.[32]	Irbesartan Valsartan	150mg OD 80mg OD	8 weeks 8 weeks	211 215	Irbesartan showed more reductions than valsartan for mean change from baseline in diastolic ABP at trough (P = 0.035) and mean systolic ABP at trough (P < 0.01) and for mean 24-h diastolic ABP (P = 0.023) and systolic ABP (P < 0.01). Irbesartan was more beneficial than valsartan in reducing DBP and SBP at trough and in providing greater overall 24-h blood pressure- reducing efficacy
6 week, double-blind, placebo-controlled trial, randomized, forced titration, multicenter, forced titration study.[33]	Azilsartan Azilsartan Valsartan Olmesartan	40mg OD 80mg OD 320mg OD 40mg OD	6 weeks 6weeks 6weeks	280 825 282 290	Azilsartan at 80 mg dose exhibited superior efficacy to both valsartan 320 mg and olmesartan 40 mg using ambulatory blood pressure monitory. Azilsartan 80 mg showed a greater reduction in 24-hours systolic BP (-14.3 mm Hg) than valsartan 320mg (-10.0 mm Hg, P<0.001) and olmesartan 40mg (-11.7 mm Hg, P=0.009). At 40mg dose azilsartan was noninferior to olmesartan 40mg (difference: -1.4 mm Hg). Both doses of azilsartan 24mg and 80 mg were superior to the comparator ARBs for clinical systolic bold pressure.
8 week, randomized, double-blind, parallel-group, multicenter study.[34]	Olmesartan Irbesartan Valsartan Losartan	20mg OD 150mg OD 80mg OD 50mg OD	8week 8 week 8 week	145 145 142 146	Olmisartan was demonstrated greater reduction in mean 24-DBP and SBP (8.5 and 12.5 mm Hg respectively) than valsartan (5.6 and 8 mm Hg respectively) and losartan (6.2 and 9 mm of Hg respectively) and equivalent to irbesartan.(7.4 and 11.3 mm of Hg respectively)

Abbreviation: Se DBP: setting diastolic blood pressure, seSBP: setting systolic blood pressure, ABP: ambulatory blood pressure.

There is no clinical significance difference of reducing blood pressure among ARBs. Single drug therapy of ARBs reduce blood pressure effectively in 50% of population but if blood pressure goal does not achieve by single drug therapy than go to multidrug therapy. Multi drug therapy is either a fixed dose single pill combination of specific ARBs with other antihypertensive classes or drugs added after one another to achieve an effective multidrug regimen. Multi drug therapy will be required to attain blood pressure goal to <140/90 mm Hg or <130/80 mm Hg for diabetic, chronic kidney disease and cardiovascular disease patient as well as for those patient whose BP is more than 20 mm Hg above systolic goal or 10 mm Hg above diastolic goal. Fixed dose combination often show better BP reduction at lower doses of active agents. ARBs can be given in combination with thiazide diuretic, ACEI, CCB or beta blocker. In fixed dose combination one of the thiazide diuretic should be consider.[28,35-37]

Combination of drug exhibit less adverse effect as compared to single drug. Thiazide diuretic causes electrolyte and metabolic disturbances and it is less occur when combined with a RAS blocker. Similarly, when dihydropyridine CCBs such as amlodipine has given in combination with RAS blocker it reduced the frequency of peripheral edema.[38]

Combination therapy of ARBs eprosartan with thiazide diuretic hydrochlorothiazide reduced the systolic and diastolic BPs significantly more than diuretic eprosartan alone after 8 weeks in hypertensive patient.[39] Similarly in Japanese adult patients with mild-to-moderate essential hypertension, calcium channel blocker amlodipine was given with ARBs candesartan in a combination therapy has been observed more efficacious in reducing blood pressure than amlodipine or candesartan monotherapy.[40]

Initiate triple drug combination when a significant therapeutic goal of blood pressure not attain despite the use of dual combination medication. The European Society of Cardiology/European Society of Hypertension guidelines emphasize the use of an RAAS blocker with a CCB or diuretic as a triple-combination therapy.[41] Triple combination therapy of amlodipine, valsartan and hydrochlorothiazide reduced blood pressure more than dual therapy valsartan/ hydrochlorothiazide, valsartan/ amlodipine and amlodipine/ hydrochlorothiazide in mild to moderate hypertension patient in 12 week trial. Triple therapy combination was superior in attaining overall BP control (P<0.0001) and SeDBP and SeSBP (P< or =0.0002) verses dual combination therapy.[42]

Heart Failure

Valsartan, candesartan and losartan are prescribed for the second-line treatment of heart failure in cases of ACEI intolerance.[43]

Val-heft trial showed that valsartan decrease all-cause mortality by 33% and composite mortality and morbidity risk by 44% compared with placebo in heart failure patient who do not take ACEI. Valsartan has beneficial effect in New York heart association (NYHA) class, ejection fraction, and HF signs and symptoms and decreased the rate of hospitalization in the study population.[44]

RESOLVD study demonstrate that candesartan and enalapril had parallel effect in New York heart association functional classification (NYHA-FC) and on left ventricular function.[45] In the CHARM trial, treatment with candesartan show a significant reduction in the risk of CV deaths and hospital admissions for heart failure compared with placebo.[46]

The ELITE I and II trials have both demonstrated that in elderly HF patients, losartan had an effect similar to that of captopril in connection with all-cause mortality, resuscitated arrests or sudden death and also NYHA class improvement. In the first ELITE study, losartan showed a lower mortality mainly owing to a greater decrease in sudden cardiac death. Patient treated with losartan experienced less adverse effect as compared to captopril.[47][48]

Additional benefits effects seem with the use of 150mg losartan in contrast to 50 mg dose because it decrease the left ventricular ejection fraction, rate of death and admission for heart failure. However, it also show improvement in patient intolerance to ACH inhibitors.[49]

Stroke

Losartan is prescribed in hypertensive patient which are at a great risk of stroke.[43] In the LIFE study, losartan decreased the risk of any stroke, atherothrombotic stroke and fatal stroke predominantly more as compared to atenolol (by 40,45 and 70%, respectively).[50]

Evaluation of telmisartan in the PRoFESS and TRANSCEND trial demonstrated a nonsignificant reduction of recurrent stroke, major cardiovascular events, or diabetes in contrast to placebo; according to a post hoc analysis, from 6 months, the reduction in the frequency of strokes was significant.[51,52]

Use of candesartan treatment in elderly patient with isolated systolic hypertension associated with a significantly 42% relative risk reduction in stroke verses other antihypertensive medication[53] according to the ACCESS study, candesertan demonstrated beneficial effects after a 7-days course following an acute ischemic stroke, significantly decrease the rate of CV morbidity and mortality.[54]

Treatment with eposartan show a fewer cerebrovascular events compared to nitrendipine in high risk hypertensive stroke patients from 2.5 years of follow-up in the MOSES trial.[55]

Myocardial Infarction

Valsartan is prescribed for HF or asymptomatic left ventricular systolic dysfunction after a recent MI.[9] VALIANT trial evaluated that treatment with valsartan and captopril alone or in combination show almost identical effect in ejection fraction, infarct segment length between baseline, cardiac volume and 20 months after MI.[56]

Valsartan showed remarkably lower ratio of major adverse cerebro-cardiovascular event (MACCE) when administered 48 hours before percutaneous coronary intervention due to reduction reactive oxygen species (ROS) levels.[57]

TRANSCEND trial demonstrated a significant reduction in the occurrence of MIs in hypertensive patients as compared with normal blood pressure individual by using telmisartan. However, telmisartan may also suppress new onset of LVH.[58]

Treatment with telmisartan showed a similar rate of MI in patients with vascular disease or high-risk diabetes when compare with ramipril. Furthermore, combination of telmisartan and rampipril exhibited more adverse events without increasing any benefit.[59]

Atrial Fibrillation

Atrial fibrillation (AF) is the most common type of arrhythmia which enhance cardiovascular risk in hypertensive patients.[60] Atrial fibrillation occurs frequently in chronic heart failure patient and considered as negative prognostic factor.[61][62] Several studies have indicated that blocking the renin-angiotensin-aldosterone system may decrease the incidence of AF.[60,62]

According to life study, losartan was significantly reduce the new-onset AF and associated stroke verses atenolol.[63] in symptomatic congestive heart failure patient, administration of

candesartan decreased the incidence of atrial fibrillation compared to placebo in the CHARM program.[61]

In the VALUE trial, valsartan have found to decrease the risk of new-onset AF. selectively sustained AF in hypertensive patients compare with amlodipine.[62] However, addition of valsartan in prescribed therapy for HF patient significantly decrease the incidence of AF by 37% according to Val-HeFT.[64]

RAS inhibitors may be beneficial in preventing the incidence of paroxysmal atrial fibrillation (PAF). However, Losartan was associated with a lowering of the maximum duration and the total duration of paroxysmal AF in patients with sick sinus syndrome without effecting any significant hemodynamic change.[65]

Evaluating the effect of telmisartan, ramipril, and amlodipine on atrial fibrillation recurrence, telmisartan was more significantly reduce AF recurrence and severity or also improve P-wave dispersion (PWD). This may be linked to a specific effect of telmisartan on atrial electric remodeling.[66] Although, other studies also showed that telmisartan based treatment was more effective than amlodipine based treatment in reducing AF recurrences in hypertensive patients with paroxysmal AF.[67]

Evaluation of ARBs in recurrent AF in different studies are conflicting.Losartan was exhibited more effective than amlodipine in preventing new occurrence of AF in hypertensive patient.[68] The use of valsartan was more significant in preventing new episodes of AF in hypertensive type 2 DM patient verses amlodipine.[69] Although, preventive role of valsartan in patients who already had AF in their history could not conform in GISSI-AF trial.[70, 71] However Madrid et al studied associated with a significant reduction of recurrent AF by using irbesertan[72] Irbesartan did not show reduction in the risk of hospitalization and cardioversion in patient with persistent AF verses placebo in the in the ACTIVE-I trial.[73,74]

VF-HT-AF study evaluated a beneficial role of valsartan in the treatment of recurrent AF in hypertensive patients.[75]

Prevention of Diabetes Mellitus

Hypertension occur more commonly in diabetic patients as compared with non-diabetic population.DM is correlated with CV risk factor, it enhanced susceptibility to atherosclerosis,

and also causes HF, stroke and peripheral vascular disease. Adequate glycemic and blood pressure control are important in the treatment of diabetic patients and those at risk of DM.[76]

RAAS inhibitors show improvement in insulin sensitivity. The anti-diabetic properties of ARBs may also include activation of Peroxisome proliferator-activated receptor gamma (PPAR-γ), up regulation of glucose transporter expression in muscle and enhance blood flow to muscles, prevention of oxidative stress and anti-inflammatory action, improvement in β cell function and inhibition of fibrosis through blocking of transforming growth factor beta (TGF-β) as well as enhancement and modulation of insulin signaling.[77, 78, 79] In obese rats, the novel compound azilsartan associated with an insulin-sensitizing effects as well as downregulated 11β-hydroxysteroid dehydrogenase type 1 expression.[80]

Meta-analysis of eight trials was exhibited that telmisartan was superior to other ARBs in lowering of fasting plasma glucose and increasing adiponectin levels. Telmisartan may also decrease fasting plasma insulin levels as well as homeostasis model assessment of insulin resistance (HOMA-IR) by using 80mg dose.[81]

meta-analysis of placebo-controlled clinical trials was associated that ARBs therapy may lower the incidence of new onset diabetes with placebo in patients with high CV risk and hypertension.[82] According to meta-analysis of LIFE, SCOPE and VALUE trials have demonstrated that losartan, candesartan as well as valsartan can reduce the incidence of new onset diabetes relative risk ratio (RRR) of 0.80 for all the three agents.[83] Similarly, the meta-analysis of the TRANSCEND and PRoFESS trials had shown that treatment with telmisartan is associated with a 16% reduction in the risk of new onset DM compared with placebo.[83]

Renal End-Organ Protection

Hemodynamic changes occur during the adaptation to function loss of nephron in chronic kidney disease patient no matter what is the etiology of the renal failure. RAAS activation causes elevated intraglomerular pressure which lead to capillary damage, enhanced proteinuria and consequent interstitial inflammation and fibrosis. Proteinuria is an independent risk factor for end-stage renal disease (ESRD) and mortality; its reduction enhanced the rate of glomerular filtration rate. Therefore in hypertensive patients with or without DM lowering of proteinuria and adequate blood pressure control play an important role in CKD management.[84]

ARBs alone or in combination with ACE inhibitors are the most beneficial antihypertensive classes for the prevention of ESRD, showing significant improvement verses placebo in network meta-analysis.[85] Treatment with ARBs inhibits inflammation and oxidative stress in diabetic patients with nephropathy, also patients with elevated renal stress marker values get most beneficial in terms of oxidative stress marker and reduction in rate of excretion of urinary albumin as compared to trichlormethiazide.[86]

According to renal study, in patients with coexistent diabetic nephropathy administration of losartan in addition to conventional antihypertensive treatment reduced the level of urinary protein excretion by 35 % and decrease the risk of ESRD by 28% and lower the incidence of a doubling of the serum creatinine concentration by 25% verses placebo.[87]

In hypertensive patients with nephropathy due to DM, irbesartan is associated with a decrease risk of onset of ESRD and doubling serum creatinine levels by 23% and 33% respectively compared with placebo in the IDNT trial.[88] In comparison with amlodipine, irbesartan benefits were more profound. Even after withdrawal of all antihypertensive treatment, higher doses of irbesartan also showed a sustained long-term decrease in rate of albumin excretion.[89]

ONTARGET, TRANSCEND, DETAIL, INNOVATION, AMADEO and VIVALDI trial showed a beneficial effect of telmisartan for improvement of proteinuria or suppression of its progression in diabetic patient. Telmisartan also showed a significant decrease in percent changes urinary albumin/protein to creatinine ratio of urinary albumin/protein excretion and with telmisartan relative to other ARBs, ACEI and other therapy by 20, 14 and 40%, respectively.[90]

In the CALM study, use of candesartan is associated with a decrease urinary albumin/ creatinine ratio by 30%.[91]

Hyperuricemia

Several study show that hyperuricemia is an independent risk factor for CVD. Approximately 25% Hypertensive patients had showed elevated serum uric acid (SUA) levels; Use of loop and thiazide diuretic may further increase SUA level.[92,93] The renal uric acid transporter (URAT1) was involved in the anti hyperuricemia effect of ARBs. Losartan and pratosartan were shown to be potent blocker of URAT1. Candesartan, olmesartan and valsartan were not

associated with an inhibition of URAT1, although a trans-stimulation of URAT1 by these ARBs was found at grater concentrations and may lead to raise SUA level.[94]

Telmisartan was shown only a *cis*-inhibitory effect but not a *trans*-stimulatory effect on URAT1. No uricosuric effect of telmnisertan can be indicated clinically because telmisartan maily excreted through feases and urinary excretion is less than 0.02%.[94]

Losartan enhanced the excretion of uric acid and reduced the SUA level in both healthy and hypertensive subjects. However, Candesartan was associated with slightly but significantly increase uric acid levels.[95,96]

In patient with mild to moderate essential hypertension, eprosartan was not show any effect on SUA concentrations or urine uric acid excretion.[97] Use of ibesartan was found to be associated with the reduction of SUA levels only in those patients who had higher baseline SUA values.[98]

Role of ARBs on protection of cognitive function

The human brain is intensely based on/subjected to proper function of its vascular system. Several study supported that vascular dysfunction and hypertension lead to the progression of dementia and the decline of cognitive function.[99,100,101] There fore. hypertension and atrial fibrillation believe to elevate the risk and development of Alzheimer's disease by modifying risk factor which secondary prevent Alzheimer's disease.[102]

Prospective cohort study was exhibited a significant reduction in the frequency and progression of Alzheimer's disease and dementia compared with angiotensin converting enzyme inhibitors or other cardiovascular drugs.[103][104] However, combination of Angiotensin receptor blockers and angiotensin converting enzyme inhibitors gives an additive effect and showed a reduced risk of incident dementia. Angiotensin receptor blockers also showed a dose-response profile for incident dementia, candesartan, irbesartan, losartan and valsartan were associated with the strongest dose dependent decreased in incident dementia.[103]

Treatment with telmisartan showed a beneficial effect) in elderly hypertensive patients with AD due to increased regional cerebral blood flow (rCBF) in various region of brain.[105]

According to AT_2 hypothesis, ARBs selectively block the ATR_1 but ATR_2 receptor remains activated which provide protective effects of ARBs. These protective effects are not present in ACEI, for which ARBs are distinguish from ACEIs. Stimulation of ATR_2 in brain reduces inflammation, axon degeneration and superoxide production, enhances neuronal cell differentiation and activation of repair system.[103]

Studies in animal model showed that ARBs have cognitive protective action because of reduced production and oligomerization and enhanced degeneration of Aβ and their vascular effects (improve blood-brain barrier, reduced inflammation, regain endothelial function and elevated cerebral blood flow).[106] Losartan demonstrated protective action against the onset of cognitive dysfunction, even in the presence of elevated levels of Aβ plaque load and soluble Aβ species in adult and aged mice. Losartan show improvement by rescuing arterial, neurometabolic and hemodynamic responses even at an advanced pathological stage. However, losartan also associated with restoration of memory related AT_4 receptor.[107] Improvement in the ameliorated leakage from brain microvessels and cognitive decline by use of olmisartan was observed in hypertensive rats. Furthermore, olmesartan also reduced brain ATII levels, as well as increased mRNA levels of tight junctions (TJs) and collagen-IV in the hippocampus.[108]

Telmisartan exhibits protection against hypertension-associated cognitive decline via up-regulation of Brain-derived neurotrophic factor (BDNF) and its receptor TrkB in the hippocampus due to partly stimulation of PPAR-γ in the hippocampus in addition to ATR_1 blockade in hypertensive rat. Partly reduction in the protective action of telmisartan on cognitive decline by co-administration with PPAR-γ antagonist.[109] Telmisartan was found to be significantly repair cognitive functions damage by chronic stress and reduce forgetfulness.[110]

In mice, treatment with candesartan improve latency period, spatial memory. Pretreatment with candesartan also decrease oxidative stress, decrease free radicle and increase acetylcholine in brain of mice.[111]

In patients with essential hypertension, restoration on the overall mean Mini-Mental State Examination (MMSE) was observed with the 6 months of eprosartan treatment in OSCAR study.[112]

Treatment with ARBs exhibited preserved memory compared with other antihypertensive drugs. Patient who was taking blood brain barrier crossing ARBs showed greater memory performance over time verses other hypertensive drug and normotensive and also low white matter hyperintensities over time than non-blood brain barrier crossing hypertensive drugs.[113]

Human observational studied demonstrated that treatment with ARBs reduced amyloid deposition in the brain in Alzheimer's disease and may give protection against future cognitive decline in those with mild cognitive impairment and dementia.[106]

Erectile dysfunction

Erectile dysfunction is often known as impotence. It is the inability to get an erection long-lasting enough, or firm enough, for penetrative sexual intercourse in men. Blood pressure can damage your arteries by causing them to become thicker (atherosclerosis), or even to burst. This can limit blood flow to your penis and then may cause erectile dysfunction.[114]

Enhanced Blood pressure damage the lining of arteries to the penis as a result less blood is flow to the penis which resist strengthen an erection or make it difficult to achieve and maintain erection.[114,115]

High blood pressure may impede with ejaculation and decrease sexual desire (25) some antihypertensive medications may also have similar effect like β blocker or thiazide diuretic.[114,116]

Erectile dysfunction is an early predictor of silent coronary heart disease. ONTARGET/ TRANSCEND trials showed that ED causes CV death, MI, stroke and HF in men with CVD. However, trials also demonstrated that neither treatment with telmisartan alone or in combination with ramipril improve or worsen ED.[117,118]

RAAS system inhibitor would be a best choice in the indication of hypertension with ED because bradykinin-induced relaxation and angiotensin II-induced contraction both partially balance the tone of Penile cavernous smooth muscle and as well as the tissue and plasma levels of both peptides are maintainedby the RAAS.[119]

Some ARBs show beneficial effect on sexual function verses placebo in several study but not all studies have associated with significant improvement in sexual function.[116] Irbesartan

showed improvement in penile endothelial function by reduction of vascular and cavernosal oxidative stress and in apolipoprotein E (ApoE) mice[120] Although, olmesartan enhanced the malondialdehyde concentrations and increased messenger ribonucleic acid (mRNA) levels of endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) in the penis of hypertensive rat.[121]

A prospective study was demonstrated that valsartan treatment in hypertensive men greatly improve orgasmic function, intercourse and overall satisfaction in patient who were previously untreated and as well as who were switched from other treatment regimens (45%and 53% respectively).[122,123] However, long-term use of valsartanwas associated with significant improvement in sexual activity as compared with β-blockers carvedilol and atenolol in a comparison study.[124]

Erectile function, sexual satisfaction and frequency of sexual activity get improved by the use of losartan in hypertensive patients[125] Losartan alone or in combination with tadalafil is prescribed for the treatment ED in diabetic patients, those patient who have with mild to moderate ED get benefit most from its use.[126]

In hypertensive patients with the metabolic syndrome, use of irbesartan alone or in combination with hydrochlorothiazide improved erectile function, sexual desirea and frequency of sexual contacts.[127] Also, irbesartan enhanced erectile function recovery in prostatectomized patients.[128]

ONTARGET/TRANSCEND studies found that treatment with telmisertan neither improve or nor worsen ED.[117]

Adverse effects

ARBs are most commonly prescribed because of their excellent tolerability. ARBs do not have a specific dose dependent adverse effect. Compared to ACE inhibitor, incidence of cough and angioedema (0.1%-0.2%) are lower in patient taking ARBs because of no significant increase in bradykinin level.[129,130,131] According to meta-analysis which comparing tolerability of ARBs versus ACE inhibitors, diuretics and placebo, cough and angioedema frequency of ARBs was comparable to placebo. (RR 1.01 and 1.62 respectively). however ARBs is associated with increased incidence of hyperkalemia, hypotension and renal dysfunction compared with placebo (RR 3.37, 2.63, 2.07 respectively) (132)

Other common side effect include fatigue drowsiness headache, dizziness, diarrhea abdominal taste sensation digestion, hyperglycemia., sinusitis, bronchitis, upper respiratory tract infection, flu like symptoms.[11,133]

Hyperkalemia, Hypotension and renal dysfunction risk are high in elderly patient, diabetic patient, patient with lower base line function, patient taking potassium supplement or when given with renin angiotensin aldosterone system inhibitors, such as potassium sparing diuretic or ACE inhibitor.[134]

The most serious, but rare, side effects of ARBs are Liver failure (hepatitis), kidney failure, hyponatremia, anaphylaxis, pruritus, urticaria, neutropenia, leukopenia, agranulocytosis, alopecia, arthralgia, viral infection and vasculitis, including Henoch- Schönlein purpura.[134,135]

All of the ARBs have teratogenic potential and should not be prescribed in pregnancy (Category C for the first trimester and category D for the second and third trimesters).[134,135]

DRUG INTERACTIONS

Losartan is metabolized by CYP450 enzyme system and has grater drug interaction with other drugs. Olmesartanis not a substrate of CYP450 enzyme and has not shown significant interaction with digoxin, warfarin, rosuvastatin aluminium magnesium hydroxide. Eprosartan Irbesartan, valsartan, telmisartan and candesartan are not metabolized by CYP450 enzyme system and have not exhibited any significant drug interaction. Candesartan may increase digoxin level and decrease warfarin level but there is no significant change in INR.

Table 5: Interaction of ARBs with other drug.

Precipitant drug	Object drug	CYP 450 substrates	Effect
Fluconazole	Losartan	3A4, 2C9	↑ losartan
Telmisartan	Digoxin	-	↑ digoxin
Phenobarbital	Losartan	-	↓ losartan ↓ active metabolite
Rifampin	Losartan	3A4, 2C9	↓ losartan
Candesartan	digoxin	-	↑ digoxin
Indomethacin	Losartan	-	↓ hypotensive effect
candesartan	warfarin	-	↓ warfarin
Cimetidine	Losartan	-	↑ losartan no effect EXP3174
losartan	lithium	3A4, 2C9	↑ lithium

DISCUSSION

The goal of anhipertensive therapy to reduce the mortality, morbidity and cardiovascular events that is associated with hypertension. ARBs differ in efficacy due to their different binding ability with AT1 receptor. Insurmountable (noncompetitive) antagonists telmisartan, irbesartan, olmisartan and candesartan have long duration of action than surmountable (competitive) antagonists losartan, valsartan, azilsartan and eprosartan. ARBs are given once daily and provides 24 hour blood pressure control. Losartan, irbesartan and candesartan may be given once daily or two times a day.

All ARBs produced similar reduction in systolic blood pressure, diastolic blood pressure and ambulatory blood pressure. They are given as a single therapy and fixed dose combination with thiazide diuretics, CCBs and direct renin inhibitors. Fixed dose single pill combination therapy has superior in reduction of blood pressure at lower doses of active agent and causes less side effect than single therapy alone. Combination therapy act on different pathways to reduce blood pressure and have more patient compliance. Initiated dual therapy when patient do not respond well in single therapy and have high cardiovascular risks or 20/10mm of HG above BP goal. Despite of dual therapy, goal of reducing blood pressure is not achieved, start triple therapy.

Triple combination therapy of valsartan, amlodipine and hydrochlorothiazide attain blood pressure goal more effectively than dual combination therapy of same drug without increasing any side effect.

Val-heft, RESOLVD and The ELITE I and II trials showed that Valsartan, candesartan and losartan reduced the risk of CV death and rate of hospitalization for heart failure as well as improved left ventricular ejection fraction. Telmisartan and valsartan are used in myocardial infarction.

VALUE, LIFE, CHARM, Val-HeFT trials and post hoc analyses of the LIFE showed that Treatment with valsartan, losartan and candesartan causes a reduction in occurrence of new-onset AF. Telmisartan reduce recurrence and severity of AF as well as improve p-wave depression which may link to atrial electrical remodeling.

LIFE, SCOPE, VALUE, TRANSCEND and PRoFESS trial demonstrated that losartan, candesartan, valsartan and telmisartan can reduce the incidence of new onset DM. Use of

ARBs have a beneficial effect in preventing from ESRD, doubling serum creatinine level, protein urinary excretion. Losartan and eprosartan decreased the uric acid level by increasing their secretion.

Valsartan, irbesartan and losartan improve sexual activity in hypertensive men as well as erectile dysfunction or may be used in patient complaining sexual problems as a side effect due to use of other antihypertensive drug.

ARBs show a significant reduction in the frequency and progression of Alzheimer's disease and dementia. It also provide a dose dependent response in incident dementia. BBB crossing ARBs elicit more effect in reducing white matter lesion than non-crossing BBB ARBs. ARBs may improve memory decline due to their ability to improve cerebral blood flow, endothelial function, decreased inflammation, enhanced degradation of Aβ, enhanced antioxidant defense system of brain as well as reduce oxidative and nitrosative stress.

The adverse effect of ARBs is equivalent to placebo and as well as lower frequency of cough and angioedema compare to ACEI.

CONCLUSION

The ARBs are highly effective class of drugs for the treatment of hypertension and its comorbidities. They have excellent safety and tolerability profile which increase patient compliance and adherence to this antihypertensive class. They are also prescribed to those patient who are sensitive to take ACEI. ARBs seem to have beneficial effect on preservation of memory as well as cognitive function. It may consider a new therapeutic option for treatment of Alzheimer disease and stress related cognitive impairment.

ABBREVIATIONS

ARBs: Angiotensin II receptor blockers.

ACE: Angiotensin converting enzyme.

RAAS: Renin angiotensinaldosterone system

ATR_1: Angiotensin II receptor 1

ATR_2: Angiotensin II receptor 2

BP: Blood pressure

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

CCB: Calcium channel blocker

ACEI: Angiotensin converting enzyme inhibitor

RAS: Renin angiotensin system

HF: Heart failure

LVH: left ventricular hypertrophy

MI: Myocardial infarction

AF: Atrial fibrillation

DM: Diabetes mellitus

ESRD: End stage renal disease

CKD: Chronic kidney disease

CV: Cardiovascular

CVD: Cardiovascular disease

SUA: Serum uric acid

URAT1: Uric acid transporter

ED: Erectile dysfunction

INR: international normalized ratio

Aβ: Amyloid-β

BBB: Blood-brain barrier

REFERENCES

1. Taylor AA, Siragy H, Nesbitt S. Angiotensin receptor blockers: pharmacology, efficacy, and safety. J Clin Hypertens (Greenwich), 2011; 13(9): 677-86.
2. Unger T. The role of the renin-angiotensin system in the development of cardiovascular disease. Am J Cardiol, 2002; 89(2A): 3A-9A; discussion 10A.
3. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet, 1997; 349(9054): 747-52.
4. George M Brenner, Craig W Stevens. Pharmacology. 4th edition. Philadelphia: Pennsylvania. Saunders; 2013
5. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet, 2015; 385(9982): 2047-56.
6. Appel GB, Appel AS. Angiotensin II receptor antagonists: role in hypertension, cardiovascular disease, and renoprotection. Prog Cardiovasc Dis, 2004; 47(2): 105-15.

7. Bertram Katzung, Susan Masters, Anthony Trevor. Basic and Clinical Pharmacology 12th Edition.
8. Oparil S, Silfani TN, Walker JF. Role of angiotensin receptor blockers as monotherapy in reaching blood pressure goals. Am J Hypertens, 2005; 18(2 Pt 1): 287-94.
9. Theal M, Demers C, McKelvie RS. The role of angiotensin II receptor blockers in the treatment of heart failure patients. Congest Heart Fail, 2003; 9(1): 29-34.
10. Givertz MM. Manipulation of the renin-angiotensin system. Circulation, 2001; 104(5): E14-8.
11. Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens, 2000; 14 Suppl 1: S73-86.
12. Brunner HR. Experimental and clinical evidence that angiotensin II is an independent risk factor for cardiovascular disease. Am J Cardiol, 2001; 87(8A): 3C-9C.
13. Alderman MH, Madhavan S, Ooi WL, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med, 1991; 324(16): 1098-104.
14. Lauer D, Slavic S, Sommerfeld M, et al. Angiotensin type 2 receptor stimulation ameliorates left ventricular fibrosis and dysfunction via regulation of tissue inhibitor of matrix metalloproteinase 1/matrix metalloproteinase 9 axis and transforming growth factor β1 in the rat heart. Hypertension, 2014; 63(3): e60-7.
15. Miura S, Fujino M, Hanzawa H, et al. Molecular mechanism underlying inverse agonist of angiotensin II type 1 receptor. J Biol Chem, 2006; 281(28): 19288-95.
16. Masahiro Fujino, Shin-ichiro Miura, Yoshihiro Kiya, et al. A small difference in the molecular structure of angiotensin II receptor blockers induces AT_1 receptor-dependent and -independent beneficial effects. Hypertens Res, 2010 Oct; 33(10): 1044–1052.
17. Haitao Zhang, Hamiyet Unal, Cornelius Gati, et al. Structure of the Angiotensin Receptor Revealed by Serial Femtosecond Crystallography. Cell, 2015; 161(4): 833–844.
18. Richard A. Harvey, Michelle A. Clark, Richard Finkel, Jose A. Rey, Karen Whalen Lippincott's Illustrated Reviews: Pharmacology 5th edition.
19. Oparil S. Newly emerging pharmacologic differences in angiotensin II receptor blockers. Am J Hypertens, 2000; 13(1 Pt 2): 18S-24S.
20. Van Liefde I, Vauquelin G. Sartan-AT1 receptor interactions: in vitro evidence for insurmountable antagonism and inverse agonism. Mol Cell Endocrinol, 2009; 302(2): 237-43.

21. Amy Barreras, Cheryle Gurk-Turner. Angiotensin II receptor blockers. Proc (Bayl Univ Med Cent), 2003; 16(1): 123–126.
22. Hazel Mae A. Abraham, C. Michael White, William B. et al. The Comparative Efficacy and Safety of the Angiotensin Receptor Blockers in the Management of Hypertension and Other Cardiovascular Diseases. Drug Saf, 2015 Jan; 38(1): 33–54.
23. Taylor AA, Siragy H, Nesbitt S. Angiotensin receptor blockers: pharmacology, efficacy, and safety. J Clin Hypertens (Greenwich), 2011; 13(9): 677-86.
24. Miura S, Fujino M, Hanzawa H, et al. Molecular mechanism underlying inverse agonist of angiotensin II type 1 receptor. J Biol Chem, 2006; 281(28): 19288-95.
25. Textor SC. Renal failure related to angiotensin-converting enzyme inhibitors. Semin Nephrol, 1997; 17(1): 67-76.
26. Sica DA. Kinetics of angiotensin-converting enzyme inhibitors in renal failure. J Cardiovasc Pharmacol, 1992; 20 Suppl 10: S13-20.
27. Sica DA, Gehr TW, Fernandez. Risk-benefit ratio of angiotensin antagonists versus ACE inhibitors in end-stage renal disease. Drug Saf, 2000; 22(5): 350-60.
28. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension, 2003; 42(6): 1206-52.
29. Vidt DG, White WB, Ridley E, et al. A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM Study II. J Hum Hypertens, 2001; 15(7): 475-80.
30. Giles TD, Oparil S, Silfani TN, et al. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. J Clin Hypertens (Greenwich), 2007; 9(3): 187-95.
31. Derosa G, Ragonesi PD, Mugellini A, et al. Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertens Res, 2004; 27(7): 457-64.
32. Mancia G, Korlipara K, van Rossum P, et al. An ambulatory blood pressure monitoring study of the comparative antihypertensive efficacy of two angiotensin II receptor antagonists, irbesartan and valsartan. Blood Press Monit, 2002; 7(2): 135-42.
33. White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension, 2011; 57(3): 413-20.

34. Oparil S, Williams D, Chrysant SG, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. J Clin Hypertens (Greenwich), 2001; 3(5): 283-91, 318.
35. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003; 326(7404): 1427.
36. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. Drugs, 2002; 62(3): 443-62.
37. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension, 2003; 42(6): 1206-52.
38. Taylor AA, Shoheiber O. Adherence to antihypertensive therapy with fixed-dose amlodipine besylate/benazepril HCl versus comparable component-based therapy. Congest Heart Fail, 2003; 9(6): 324-32.
39. Sachse A, Verboom CN, Jäger B. Efficacy of eprosartan in combination with HCTZ in patients with essential hypertension. J Hum Hypertens, 2002; 16(3): 169-76.
40. Rakugi H, Ogihara T, Miyata Y, et al. Evaluation of the efficacy and tolerability of combination therapy with candesartan cilexetil and amlodipine besilate compared with candesartan cilexetil monotherapy and amlodipine besilate monotherapy in Japanese patients with mild-to-moderate essential hypertension: a multicenter, 12-week, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther, 2012; 34(4): 838-48.
41. Neutel JM, Smith DH. Hypertension management: rationale for triple therapy based on mechanisms of action. Cardiovasc Ther, 2013; 31(5): 251-8.
42. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. Hypertension, 2009 Jul; 54(1): 32-9.
43. https: //www. medicines. org. uk/emc/
44. Piérard L. Clinical study of the month. Effects of valsartan in chronic heart failure: the VAL-HeFT study. Rev Med Liege, 2002; 57(1): 57-9.
45. CMcKelvie RS, Yusuf S, Pericak D, et al. comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation, 1999; 100(10): 1056-64.

46. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet, 2003; 362(9386): 759-66.
47. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet, 1997; 349(9054): 747-52.
48. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet, 2000; 355(9215): 1582-7.
49. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet, 2009; 374(9704): 1840-8.
50. Kjeldsen SE, Lyle PA, Kizer JR, et al The effects of losartan compared to atenolol on stroke in patients with isolated systolic hypertension and left ventricular hypertrophy. The LIFE study. J Clin Hypertens (Greenwich), 2005; 7(3): 152-8.
51. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med, 2008; 359(12): 1225-37.
52. Diener HC. Preventing stroke: the PRoFESS, ONTARGET, and TRANSCEND trial programs. J Hypertens Suppl, 2009; 27(5): S31-6.
53. Papademetriou V, Farsang C, Elmfeldt D, et al. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). J Am Coll Cardiol, 2004; 44(6): 1175-80.
54. Schrader J, Lüders S, Kulschewski A, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke, 2003; 34(7): 1699-703.
55. Schrader J, Lüders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke, 2005; 36(6): 1218-26.
56. Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation, 2005; 111(25): 3411-9.
57. Noro T, Takehara N, Sumitomo K, et al Initial reduction of oxidative stress by angiotensin receptor blocker contributes long term outcomes after percutaneous coronary intervention. Am J Cardiovasc Dis, 2014; 4(4): 159-67.

58. Foulquier S, Böhm M, Schmieder R, et al. Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a Telmisartan Randomised Assessment Study in ACE iNtolerant subjects with cardiovascular Disease subanalysis. J Hypertens, 2014; (6): 1334-41.
59. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med, 2008; 358(15): 1547-59.
60. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol, 2005; 45(5): 712.
61. Ducharme A, Swedberg K, Pfeffer MA, et al. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J, 2006; 152(1): 86-92.
62. Schmieder RE, Kjeldsen SE, Julius S, et al Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens, 2008; 26(3): 403-11.
63. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol, 2005; 45(5): 712-9.
64. Maggioni AP, Latini R, Carson PE. et al. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J, 2005; 149(3): 548-57.
65. Takii E, Inage T, Yoshida T, et al. Beneficial effects of losartan for prevention of paroxysmal atrial fibrillation in patients with sick sinus syndrome: analysis with memory function of pacemaker. Heart Vessels, 2016; 31(3): 402-7.
66. Fogari R, Mugellini A, Zoppi A, et al. Effect of telmisartan and ramipril on atrial fibrillation recurrence and severity in hypertensive patients with metabolic syndrome and recurrent symptomatic paroxysmal and persistent atrial fibrillation. J Cardiovasc Pharmacol Ther, 2012; 17(1): 34-43.
67. Fogari R, Zoppi A, Maffioli P, et al. Effect of telmisartan on paroxysmal atrial fibrillation recurrence in hypertensive patients with normal or increased left atrial size. Clin Cardiol, 2012; 35(6): 359-64.

68. Fogari R, Mugellini A, Destro M, et al. Losartan and prevention of atrial fibrillation recurrence in hypertensive patients. J Cardiovasc Pharmacol, 2006; 47(1): 46–50.
69. Fogari R, Zoppi A, Mugellini A, et al. Comparative evaluation of effect of valsartan/amlodipine and atenolol/amlodipine combinations on atrial fibrillation recurrence in hypertensive patients with type 2 diabetes mellitus. J Cardiovasc Pharmacol, 2008; 51(3): 217–22.
70. Fogari R, et al. Effect of valsartan and ramipril on atrial fibrillation recurrence and P-wave dispersion in hypertensive patients with recurrent symptomatic lone atrial fibrillation. Am J Hypertens, 2008; 21(9): 1034–9.
71. Disertori M, et al. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med, 2009; 360(16): 1606–17.
72. Madrid AH, et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. Circulation, 2002; 106: 331–6.
73. Yusuf S, et al. Irbesartan in patients with atrial fibrillation. N Engl J Med, 2011; 364(10): 928–38.
74. Qi WW, et al. Upstream therapeutic strategies of valsartan and fluvastatin on hypertensive patients with non-permanent atrial fibrillation (VF-HT-AF): study protocol for a randomized controlled trial. Trials, 2015; 16(1): 336.
75. Y. Robert Li Cardiovascular Diseases: From Molecular Pharmacology to Evidence-Based Therapeutics. wiley; 2015.
76. Chia-Hsuin Chang, Yi-Cheng Chang, Li-Chiu Wu, et al. Different angiotensin receptor blockers and incidence of diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol, 2014; 13: 91.
77. James Matthew Luther and Nancy J. Brown. Renin-angiotensin-aldosterone system and glucose homeostasis. Trends Pharmacol Sci, 2011; 32(12): 734–9.
78. Van der Zijl NJ, Moors CC, Goossens GH, et al. Does interference with the renin-angiotensin system protect against diabetes? Evidence and mechanisms. Diabetes Obes Metab, 2012 Jul; 14(7): 586-95.
79. Zhao M, Li Y, Wang J, et al. Azilsartan treatment improves insulin sensitivity in obese spontaneously hypertensive Koletsky rats. Diabetes Obes Metab, 2011; 13(12): 1123-9.
80. Suksomboon N, Poolsup N, Prasit T. Systematic review of the effect of telmisartan on insulin sensitivity in hypertensive patients with insulin resistance or diabetes. J Clin Pharm Ther, 2012 Jun; 37(3): 319-27.

81. Tocci G, Paneni F, Palano F, et al. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and diabetes: a meta-analysis of placebo-controlled clinical trials. Am J Hypertens, 2011; 24(5): 582-90.
82. Cheung BM, Cheung GT, Lauder IJ, et al. Meta-analysis of large outcome trials of angiotensin receptor blockers in hypertension. J Hum Hypertens, 2006; 20(1): 37-43.
83. Kurtz TW, Klein U. Next generation multifunctional angiotensin receptor blockers. Hypertens Res, 2009; 32(10): 826-34.
84. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. N Engl J Med, 1998; 339(20): 1448-56.
85. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet, 2015; 385(9982): 2047-56.
86. Ogawa S, Mori T, Nako K, et al. Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy. Hypertension, 2006; 47(4): 699-705.
87. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med, 2001; 345(12): 861-9.
88. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med, 2001; 345(12): 851–60.
89. Andersen S, et al. Kidney function during and after withdrawal of long-term irbesartan treatment in patients with type 2 diabetes and microalbuminuria. Diabetes Care, 2003; 26(12): 3296–302.
90. Takagi H, et al. Effects of telmisartan on proteinuria or albuminuria: a meta-analysis of randomized trials. Int J Cardiol, 2013; 167(4): 1443–9.
91. Mogensen CE, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ, 2000; 321(7274): 1440–4.
92. Csiky B. The pleiotropic effects of losartan [Hungarian]. LAM, 2008; 18(10): 663–66.
93. Hainer BL, et al. Diagnosis, treatment, and prevention of gout. Am Fam Physician, 2014; 90(12): 831–6.

94. Iwanaga T, et al. Concentration-dependent mode of interaction of angiotensin II receptor blockers with uric acid transporters. JPET, 2007; 320: 211–7.
95. Fauvel JP, et al. Effects of losartan on renal function in patients with essential hypertension. J Cardiovasc Pharmacol, 1996; 28: 259–63.
96. Manolis AJ, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension: Losartan Trial Investigators. Clin Ther, 2000; 22: 1186–203.
97. Ilson BE, et al. The effects of eprosartan, an angiotensin II AT1 receptor antagonist, on uric acid excretion in patients with mild to moderate essential hypertension. J Clin Pharmacol, 1998; 38(5): 437–41.
98. Nakamura M, et al. Effects of irbesartan on serum uric acid levels in patients with hypertension and diabetes. Clin Pharmacol, 2014; 6: 79–86.
99. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet, 1996; 347(9009): 1141-5.
100. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging, 2000; 21(1): 49-55.
101. Elias MF, Wolf PA, D'Agostino RB, et al. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. Am J Epidemiol, 1993; 138(6): 353-64.
102. Mielke MM, Rosenberg PB, Tschanz J, et al. Vascular factors predict rate of progression in Alzheimer disease. Neurology, 2007; 69(19): 1850-8.
103. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ, 2010; 340: b5465.
104. Yasaman Arjmand Abbassi, Mohammad Taghi Mohammadi, Mahsa Sarami Foroshani, andJavad Raouf Sarshoori. Captopril and Valsartan May Improve Cognitive Function Through Potentiation of the Brain Antioxidant Defense System and Attenuation of Oxidative/Nitrosative Damage in STZ-Induced Dementia in RatAdv Pharm Bull, 2016; 6(4): 531–539.
105. Kume K, Hanyu H, Sakurai H, et al. Effects of telmisartan on cognition and regional cerebral blood flow in hypertensive patients with Alzheimer's disease. Geriatr Gerontol Int, 2012; 12(2): 207-14.
106. Hajjar I, Rodgers K. Do angiotensin receptor blockers prevent Alzheimer's disease? Curr Opin Cardiol, 2013; 28(4): 417-25.

107. Ongali B, Nicolakakis N, Tong XK, et al. Angiotensin II type 1 receptor blocker losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model. Neurobiol Dis, 2014; 68: 126-36
108. Pelisch N, Hosomi N, Ueno M, et al. Blockade of AT1 receptors protects the blood-brain barrier and improves cognition in Dahl salt-sensitive hypertensive rats. Am J Hypertens, 2011; 24(3): 362-8.
109. Kishi T, Hirooka Y, Sunagawa K. Telmisartan protects against cognitive decline via up-regulation of brain-derived neurotrophic factor/tropomyosin-related kinase B in hippocampus of hypertensive rats. J Cardiol, 2012; 60(6): 489-94.
110. Wincewicz D, Braszko JJ. Telmisartan attenuates cognitive impairment caused by chronic stress in rats. Pharmacol Rep, 2014; 66(3): 436-41.
111. Tota S, Kamat PK, Awasthi H, et al. Candesartan improves memory decline in mice: involvement of AT1 receptors in memory deficit induced by intracerebral streptozotocin. Behav Brain Res, 2009; 199(2): 235-40.
112. Hanon O, Berrou JP, Negre-Pages L, et al. Effects of hypertension therapy based on eprosartan on systolic arterial blood pressure and cognitive function: primary results of the Observational Study on Cognitive function And Systolic Blood Pressure Reduction open-label study. J Hypertens, 2008; 26(8): 1642-50.
113. Ho JK, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Memory is preserved in older adults taking AT1 receptor blockers. Alzheimers Res Ther, 2017; 9(1): 33.
114. http: //www. bloodpressureuk. org/BloodPressureandyou/Yourbody/Erectiledysfunction
115. https: //www. mayoclinic. org/diseases-conditions/high-blood-pressure/in-depth/high-blood-pressure-and-sex/art-20044209.
116. M. P. J. Nicolai, S. S. Liem, S. Both, et al. A review of the positive and negative effects of cardiovascular drugs on sexual function: a proposed table for use in clinical practice. Neth Heart J, 2014; 22(1): 11–19.
117. Böhm M, Baumhäkel M, Teo K, et al. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. Circulation, 2010; 121(12): 1439-46.
118. Doumas M, Viigimaa M, Papademetriou V. Combined antihypertensive therapy and sexual dysfunction: terra incognita. Cardiology, 2013; 125(4): 232-4.

119. Becker AJ, Uckert S, Stief CG, et al. Possible role of bradykinin and angiotensin II in the regulation of penile erection and detumescence. Urology, 2001 Jan; 57(1): 193-8.
120. Baumhäkel M, Custodis F, Schlimmer N, et al Improvement of endothelial function of the corpus cavernosum in apolipoprotein E knockout mice treated with irbesartan. Pharmacol Exp Ther, 2008; 327(3): 692-8
121. Shimizu S, Tsounapi P, Honda M, et al. Effect of an angiotensin II receptor blocker and a calcium channel blocker on hypertension associated penile dysfunction in a rat model. Biomed Res, 2014; 35(3): 215-21.
122. Della Chiesa A, Pfiffner D, Meier B, Hess OM. Sexual activity in hypertensive men. J Hum Hypertens, 2003 Aug; 17(8): 515-21.
123. Düsing R. Effect of the angiotensin II antagonist valsartan on sexual function in hypertensive men. Blood Press Suppl, 2003; 2: 29-34.
124. Fogari R, Zoppi A, Poletti L, et al. Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. Am J Hypertens, 2001; 14(1): 27-31.
125. Llisterri JL, Lozano Vidal JV, Aznar Vicente J, et al. Sexual dysfunction in hypertensive patients treated with losartan. Am J Med Sci, 2001; 321(5): 336-41.
126. Chen Y, Cui S, Lin H, et al. Losartan improves erectile dysfunction in diabetic patients: a clinical trial. Int J Impot Res, 2012; 24(6): 217-20.
127. Baumhäkel M, Schlimmer N, Böhm M; DO-IT Investigators. Effect of irbesartan on erectile function in patients with hypertension and metabolic syndrome. Int J Impot Res, 2008; 20(5): 493-500.
128. Segal RL, Bivalacqua TJ, Burnett AL, et al. Irbesartan promotes erection recovery after nerve-sparing radical retropubic prostatectomy: a retrospective long-term analysis. BJU Int, 2012; 110(11): 1782-6.
129. Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. Am J Health Syst Pharm, 2001; 58(8): 671-83.
130. ONTARGET Investigators, Yusuf S, Teo KK, et al Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med, 2008 Apr; 358(15): 1547-59.
131. Mary Anne Koda-Kimble, Lloyd Yee Young, Wayne A. Kradjan, B. Joseph Guglielmo, Brian K. Alldredge, Robin L. Corelli, Bradley R. Williams Applied therapeutics: clinical use of drugs Ninth Edition.
132. Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs, 2012; 12(4): 263-77.

133. Amy Barreras, Cheryle Gurk-Turner. Angiotensin II receptor blockers. Proc (Bayl Univ Med Cent), 2003; 16(1): 123–126.
134. https: //www. thecardiologyadvisor. com/cardiology/angiotensin-receptor-blockers/article/583490/
135. Mary Anne Koda-Kimble, Lloyd Yee Young, Wayne A. Kradjan, B. Joseph Guglielmo, Brian K. Alldredge, Robin L. Corelli, Bradley R. Williams Applied therapeutics: clinical use of drugs Ninth Edition.
136. Amit K, Khairnar, Dheeraj et al. Angiotensin II receptor blockers: an overview. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(3): 50-56.
137. Warner GT, Jarvis B. Olmesartan medoxomil. Drugs, 2002; 62(9): 1345-53; discussion 1354-6.
138. Roh H, Son H, Lee D, et al. Pharmacokinetic interaction between rosuvastatin and olmesartan: a randomized, open-label, 3-period, multiple-dose crossover study in healthy Korean male subjects. Clin Ther, 2014; 36(8): 1159-70.