A Review on a Novel Antihypertensive Drug Aliskiren Effective on CHF

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ABSTRACT

Hypertension is a key risk factor for cardiovascular illnesses, which are the main causes of death in the Western world, such as stroke, myocardial infarction, and heart failure. Inhibitors of the renin-angiotensin system (RAS) have proven to be effective hypertension therapies. Renin is the best target for RAS inhibition since it selectively catalyses the rate-limiting phase of the RAS. Several peptide-like renin inhibitors have previously been synthesised, but due to poor pharmacokinetic properties, these drugs were not clinically effective. For enhanced pharmacokinetic qualities, we used a combination of molecular modelling and crystallographic structure studies to create renin inhibitors without the long peptide-like backbone of previous inhibitors. Aliskiren is most likely to be useful in patients who are uncontrolled by or intolerant to other classes. A rational understanding of the renin system would maximise its utility, for example, by advocating greater use of natriuretic medications in patients with resistant hypertension in order to make their hypertension renin dependent. Aliskiren's blood pressure-lowering efficacy is comparable, if not superior, to that of other first-line antihypertensive drugs, and it is considerably boosted when coupled with different other antihypertensive medications, with no adverse drug interactions. Aliskiren is also an effective and well-tolerated medication in high-risk populations such as diabetics, obese people, and the elderly. Aside from its ability to reduce blood pressure, evidence from preclinical and clinical trials suggest that aliskiren has beneficial effects on markers of cardiovascular and renal damage. In CHF patients, RAS inhibition is a cornerstone of neuroendocrine blockade, and coupled RAS blockade is especially helpful in individuals who present with repeated cardiac decompensations. This review focuses on the therapeutic role of RAS inhibitors in chronic heart failure induced by systolic left ventricular dysfunction. The purpose of this review is to discuss the efficacy and safety of aliskiren in the treatment of hypertension.

KEYWORDS

Aliskiren, Antihypertensive drug, Renin-angiotensin system, Congestive Heart Failure, Pharmacokinetics, Treatment, Efficacy.

1. INTRODUCTION

Hypertension is a very common condition, especially in older people. Although it is not a disease in and of itself, it is a significant risk factor for cardiovascular mortality and morbidity. The manometric cut-off point between normotensives and hypertensives is arbitrary. In practice, 'hypertension' could be defined as the level of blood pressure at or above which long-term antihypertensive treatment reduces cardiovascular mortality. It is defined as 140 mm Hg systolic and 90 mm Hg diastolic by the JNC 7* (2003) and WHO-ISH@ guidelines (2003), though risk appears to increase even above 120/80 mm Hg [1]. Epidemiological studies have shown that the higher the blood pressure (systolic, diastolic, or both), the higher the risk of cardiovascular disease. Most cases are of essential (primary) hypertension, which means that the cause is unknown. The sympathetic and renin-angiotensin systems (RAS) may or may not be overactive in hypertensives, but they both contribute to blood vessel tone and c.o. Many antihypertensive medications interfere with these regulatory systems on some level. Antihypertensive medications, by chronically lowering blood pressure, may reset the barostat to function at a lower level of blood pressure [2]. According to recent World Health Organization estimates, hypertension is a major risk factor for cardiovascular diseases such as stroke, myocardial infarction, and heart failure [3]. In the year 2000, there were 7.1 million deaths worldwide (13% of total deaths) (World Health Report, 2002). Despite the known risks of hypertension [4], most hypertensive patients do not have their blood pressure controlled to target levels [5] indicating a clear need for novel approaches to hypertension management. Congestive heart failure is a complex progressive disorder or a condition in which the heart is unable to pump sufficient blood to meet the needs of the body or we can say CHF can be an increased workload imposed on the heart [6]. This is due to the reduced contractility of the cardiac muscles, especially those of the ventricles, which causes a decrease in cardiac output, increasing the blood volume of the heart (hence the term “congested”) [7]. As a result, systemic blood pressure and renal blood flow are both reduced, which often leads to the development of edema in the lower extremities and the lung (pulmonary edema) as well as renal failure.

Congestive heart failure is of two types:

1. Systolic (when heart contracts) disfunction

2. Diastolic (when the heart dilates) disfunction

1.1 Systolic (when heart contract) disfunction

Systolic heart failure is characterized by the **deficient pumping of the ventricles**, which leads to the **improper ejection of blood volume** into the systemic or pulmonary circulation. During this state, the ventricles are unable to develop sufficient wall tension, a physiological requirement governed by the relationship between intraventricular pressure and the ventricular radius. Consequently, the heart fails to meet the metabolic demands of the body due to this diminished contractile strength.

1.2 Diastolic (when the heart dilates) disfunction.

Diastolic heart failure is primarily characterized by thickened ventricular walls, which causes the heart muscle to become stiff and noncompliant. Because the muscle is unable to relax normally during diastole, the process of ventricular filling is significantly impaired, leading to reduced stroke volume even if the pumping strength remains intact. This condition is most commonly a chronic consequence of long-standing hypertension, as the heart continuously works against high pressure, leading to compensatory but ultimately dysfunctional wall thickening.

1.3 Role of physiological compensatory mechanism

The renin-angiotensin system (RAS) is a key regulator of blood pressure and body fluid volume that works primarily through the effects of angiotensin II, an octapeptide hormone (Ang II). The aspartic peptidase renin cleaves the Leu10-Val11 peptide bond of angiotensinogen to form angiotensin I (Ang I), which is then converted into Ang II by angiotensin-converting enzyme (ACE). Excess RAS activity is thought to be the root cause of many pathological conditions because Ang II raises blood pressure and has direct growth-promoting effects on cardiac [8] and renal [9] tissue, resulting in end-organ damage. Indeed, RAS inhibitors like ACE inhibitors and Ang II receptor blockers (ARBs) are effective treatments for hypertension and heart failure [10][11].

Renin inhibitors prevent the formation of Ang I and Ang II and so may act differently from ARBs, which increase angiotensin peptide levels, and ACE inhibitors, which increase Ang I levels and do not block ACE-independent Ang II production [12,13]. Over the last 20 years, a few stable peptide-like analogues of angiotensinogen's scissile peptide bond have been developed and have been shown to inhibit renin and lower blood pressure (BP) following intravenous administration to sodium-depleted marmosets [14]. We used a combination of renin-inhibitor complex crystal structure analysis and computational methods to create novel, low

molecular weight renin inhibitors without the extended peptide-like backbone of previous inhibitors and with favourable pharmacokinetic properties after oral administration [15].

1.4 DIRECT RENIN INHIBITOR DRUG

ALISKIREN

Aliskiren is direct renin inhibitors (DRIs) are the most recent class of RAS inhibitory drugs, with only one member [16], Aliskiren, now available for the treatment of cardiovascular and renal diseases currently treated with ACE inhibitors and ARBs. Aliskiren is a nonpeptide that binds selectively to the catalytic site of renin and competitively blocks angiotensinogen access to this site. As a result, Ang I is not produced, and the RAS chain is disrupted. While feedback increases plasma renin concentration, it decreases plasma renin activity (PRA). Ang I and Ang II levels decrease [17]. Aliskiren causes a drop in blood pressure, which is more pronounced in Na+ depleted subjects with high basal PRA [18]. Plasma aldosterone levels are reduced, as with ACE inhibitors, with mild natriuresis and a tendency to K+ retention. Aliskiren's antihypertensive efficacy is comparable to that of ACE inhibitors or ARBs [19]. The combination of these drugs with aliskiren causes a greater drop in blood pressure, at least in the short term. This could be due to ACE inhibitors/ARBs blocking the rise in PRA. Aliskiren's hemodynamic effect pattern is like that of ACE inhibitors; postural hypotension is not a problem [20]. Aliskiren has been shown in trials to reduce hypertensive left ventricular hypertrophy and benefit CHF patients, but its value in comparison to ACE inhibitors/ARBs as monotherapy and as an additional drug is unknown [21]. Aliskiren also has renoprotective properties for hypertension and diabetes mellitus. Its long-term benefits [22] and position in comparison to ACE inhibitors/ARBs are being assessed. Currently, aliskiren is recommended as an alternative antihypertensive drug (for those who do not respond/tolerate first-line drugs) and in combination with others for greater blood pressure control [23][24].

The chemical evolution of renin inhibitors that led to the discovery of aliskiren can be divided into three generations of compounds. Angiotensinogen analogues to inhibit renin's enzymatic action; second, peptidomimetic compounds that were dipeptide transition-state analogue inhibitors of the active site [25,26]. Third, non-peptide-like compounds, the most successful of which is aliskiren [27,28]. First-generation renin inhibitors were ineffective and metabolically unstable [29,30]. The second-generation compounds were potent (with activity in the nanomolar range) and reduced blood pressure in both animals and humans when administered parenterally [31,32,33]. These studies gave an insight into the endocrine and hemodynamic effects of renin

inhibitors in animal models [34]. Further development of the second-generation molecules resulted in longer durations of action and oral activity, although at extremely high doses in humans [35,36]. Although structural changes in the molecules were successful in improving metabolic stability, oral bioavailability, and the associated blood pressure reduction remained low [37,38]. Their clinical utility was limited not only by a lack of oral activity but also by a short duration of action [39]. The discovery of aliskiren was aided by advances in crystallography and a structure-based approach to drug design in the third generation of compounds [40,41]. Aliskiren was discovered to bind to the previously unknown sub-pocket S3sp of renin that extends from the S3-binding site [42,43]. Renin inhibitors have traditionally had prohibitively high commercial manufacturing costs. Indeed, because aliskiren has four chiral centres, the compound's initial synthesis was both difficult and costly [44,45]. This issue, which was a major impediment to the further development of the aliskiren, was resolved through the development of a new [46] and innovative synthetic route for commercial products based on the synthon approach [47].

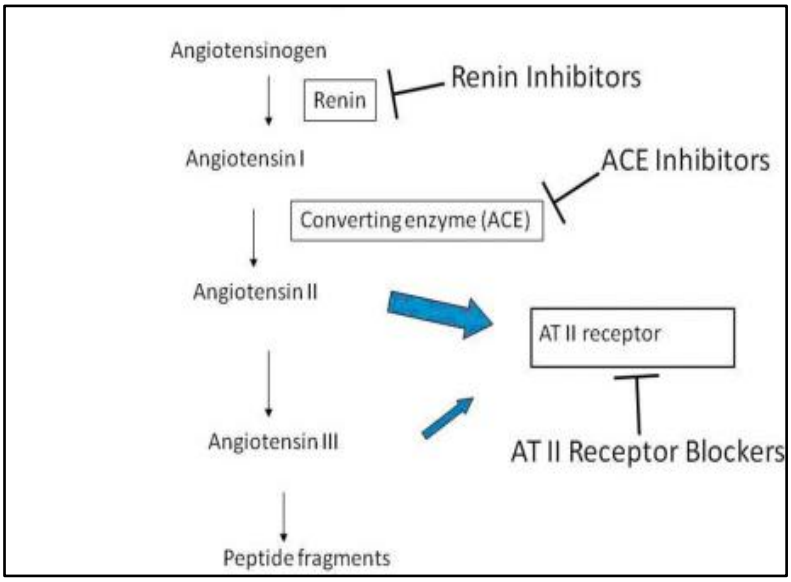

Figure No. 1- Inhibitors of Renin-Angiotensin System

*Source - Dowd FJ. Renin inhibitors.

1.5 ALISKIREN DRUG DESIGN BASED ON STRUCTURE

Molecular modelling methods were used to create compounds that did not have the P1-P4 spanning backbone of previous peptide inhibitors and instead took advantage of the extended hydrophobic surface of Renin's large S3-S1 cavity [48]. This design concept combined a dipeptide-like hydroxy ethylene transition state mimic with a directly linked P3-P1 pharmacophore to produce novel inhibitors [49][50]. Purified recombinant human renin was

inhibited at nanomolar concentrations, but activity was reduced in the presence of plasma. Lead optimization was guided by computational modelling and x-ray crystallographic resolution of enzyme-inhibitor complexes, to identify inhibitors with improved potency in the more physiologically relevant plasma renin assay [51][52]. Despite the hydrophobic nature of the S3 specificity site, the tertiary butyl residue in fig was replaced by the smaller, more polar OMe group, resulting in fewer lipophilic compounds with no loss of in vitro activity [53,54].

The length and position of the distal ether oxygen as H-bond acceptor from Tyr 14 of the S3sp sub-pocket appear to be optimal for the methoxypropoxy sidechain in fig. [55,56]

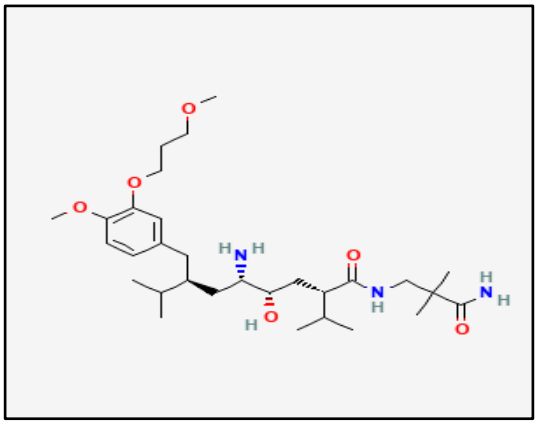

Figure No. 2- Structure of Aliskiren

In preliminary studies investigating the effects of oral administration on marmosets, the substitution of the methyl group for an isopropyl moiety had little effect on in vitro activity but improved the duration of action [57]. Extensive modifications to the P20 portion, such as replacing the n-butyl sidechain of fig with basic or neutral polar residues, resulted in inhibitors with comparable in vitro potency [58,59]. The terminal carboxamide group participates in an additional H-bonding interaction with Arg74, and the insertion of the geminal methyl residues into the P20 sidechain provides hydrophobic van der Waals interactions with the S20 site of renin, increasing affinity into the sub-nanomolar range [66][67]. Compound 9 is the hemi-fumarate salt of aliskiren, a non-peptide, small molecule transition-state mimetic human renin inhibitor [60][61].

2. PHARMACOKINETICS AND INTERACTION WITH OTHER DRUGS

Aliskiren's pharmacokinetic profile has been studied in healthy subjects as well as patients with the hepatic and renal disease after single oral and intravenous doses [70]. Aliskiren is rapidly absorbed after oral administration, with peak plasma concentrations occurring between 1 and 3 hours after dosing [62]. The absolute bioavailability is low, with less than 3% of the dose absorbed, but it is consistent and predictable. Aliskiren has linear pharmacokinetics at doses ranging from 75 to 600 mg. Following [14C]-aliskiren administration, 90% of the absorbed dose was eliminated via the faecal route, with less than 0.6% recovered in the urine, and the estimated elimination half-life was 44 hours [63][64]. The elimination pharmacokinetics of

aliskiren after a single oral 300 mg dose were similar in patients with the hepatic disease compared to matched healthy subjects, as measured by the area under the measured concentration curve (AUC) [65].

Aliskiren's steady-state pharmacokinetics have also been studied in patients with varying degrees of renal insufficiency [66]. A modest increase in exposure was associated with renal impairment (a 65% increase in AUC at a steady state). The increase in exposure, however, did not correlate with the severity of the renal disease. The increase in exposure, however, did not correlate with the severity of the renal disease. The authors concluded that the observed effects could be attributed to differences in non-renal drug distribution [67]. Aliskiren exhibited comparable pharmacokinetics in type 2 diabetes patients and healthy volunteers. However, no pharmacokinetic parameters showed statistically significant differences [68][69]. Overall, the findings of these trials indicate that aliskiren dose adjustments are unnecessary in patients with hepatic and renal disease, as well as in elderly or diabetic patients [70]. After single and multiple oral doses of aliskiren, conventional pharmacokinetic studies were conducted in rats, marmosets, and humans [71]. Aliskiren has a low bioavailability, but the exact mechanism has not been determined. Oral bioavailability in rats is 2.4%, 16% in marmosets, and approximately 2.5% in humans [72]. The mean AUC and Cmax are reduced by 71% and 85%, respectively, after a high-fat meal. Animal species have lower AUC and Cmax values than humans. Aliskiren has a slow terminal elimination in rats, marmosets, and humans, with plasma half-lives of 23, 26, and 23-70 h, respectively. The difference in human terminal half-life is most likely due to differences in post-dose sampling period duration [73]. In studies with a shorter post-dose sampling period (48 h), the half-life of aliskiren was between 24 and 30 hours, whereas studies with a longer post-dose sampling period (72-96 h) reported values around 40 hours [74,75]. With once-daily administration, steady-state blood levels are achieved in about seven to eight days. In humans, plasma proteins bind approximately 47-51% of aliskiren, regardless of concentration. Aliskiren is highly bound to plasma proteins in marmosets, with a 92% affinity [76,77]. Aliskiren is metabolized slightly in humans (about 20%) and approximately 50% in rodents [78]. According to in vitro research, the main enzyme responsible for aliskiren metabolism appears to be CYP3A4. Aliskiren has no effect on the CYP450 isoenzymes (CYP1A2, 2C8, 2C19, 2D6, 2E1, and CYP3A). Aliskiren metabolism is primarily accomplished through O-demethylation at the phenyl-proxy side chain or the 3-methoxypropoxy group, followed by oxidation to the carboxylic acid derivative [79][80]. Aliskiren metabolism in liver microsomes is qualitatively comparable in humans, marmosets,

and rats. Aliskiren is primarily eliminated through the feces in its unmetabolized form. One-fourth of the absorbed dose is also found in the urine as an unchanged compound [81]. This half-life, which is longer than the 24-hour dosing interval, is consistent with the observation that aliskiren plasma concentrations accumulate by about 2-fold at a steady state when compared to administration of a single dose. An open-label study was conducted to evaluate the pharmacokinetics of aliskiren in healthy volunteers and type 2 diabetes patients who were age, race, and weight-matched [82]. There was no significant difference in AUC, Cmax, time to maximum concentration, half-life, or Cl/F between the two populations after a single dose of aliskiren 300 mg [83]. Even though these subjects were not matched for gender, these pharmacokinetic parameters did not differ significantly between men and women in this study.

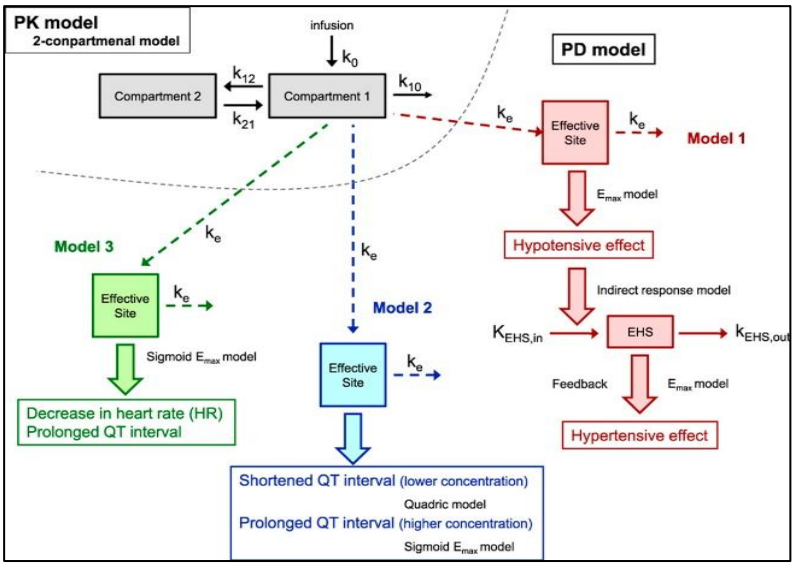

Figure no. 3 pk model of hypertensive effect

In addition, an open-label study was conducted to assess the pharmacokinetics and safety of aliskiren in healthy elderly subjects [84]. A single 300-mg dose of aliskiren was given to 29 elderly (65 years old) and 28 younger (18-45 years old) subjects who were matched for gender and weight. The elderly population had a significantly higher AUC and a significantly longer half-life after aliskiren administration than the younger group [85]. When compared to healthy subjects, the pharmacokinetics of a single 300-mg dose of aliskiren were not significantly different in patients with mild, moderate, or severe hepatic impairment.

Aliskiren pharmacokinetics were not significantly altered in patients with varying degrees of renal insufficiency [86,87,88]. There are few data to describe the effect of race and ethnicity on aliskiren pharmacokinetics.

2.1. DRUG INTERACTION

Aliskiren's absorption, distribution, metabolism, excretion, and interaction with other drugs that do not necessarily affect the RAAS have all been studied experimentally and clinically [89]. Studies on the disposition of [14C] aliskiren oral doses in rats, marmosets, and humans revealed that an oral dose was excreted almost entirely (>90%) in the feces, primarily as unchanged aliskiren. A small portion of the absorbed dose was excreted in the form of oxidized metabolites, which were most likely derived from cytochrome P450 oxidation (CYP) [90]. However, no interaction of aliskiren with cytochrome P450 isoenzymes was discovered in human liver microsomes in vitro, indicating that aliskiren has a low potential for clinically significant drug interactions [108]. Indeed, aliskiren did not show any clinically significant increases in exposure when co-administered with a wide range of potential concomitant medications [91]. In healthy volunteers, for example, no clinically relevant pharmacokinetic interactions were observed between aliskiren and the CYP substrates celecoxib, digoxin, lovastatin, warfarin, or the CYP inhibitor cimetidine [92]. Aliskiren is a substrate for the efflux transporter P-glycoprotein, which may play a role in the drug's hepatobiliary/intestinal excretion, according to animal and human studies. The lack of pharmacokinetic interaction between aliskiren and the P-glycoprotein substrate digoxin, on the other hand, indicates that aliskiren does not inhibit P-glycoprotein activity) [93,94]. Nonetheless, the coadministration of ketoconazole (200 mg twice daily) with aliskiren resulted in an 80% increase in aliskiren plasma levels. Furthermore, coadministration of aliskiren and furosemide significantly reduces later blood concentrations while having a minor effect on aliskiren pharmacokinetics. It is worth noting that cyclosporine raises aliskiren blood concentrations.

Aliskiren has a low potential for drug interactions because it does not affect cytochrome P450 enzyme activities, is minimally metabolized by CYP3A4, and is not extensively protein bound [95,96]. Clinical trials, however, revealed an interaction between aliskiren and certain medications. Aliskiren's Cmax is reduced by up to 50% when combined with irbesartan after multiple doses. Co-administration of furosemide reduces the AUC and Cmax by 30% and 50%, respectively. When aliskiren therapy is started, the therapeutic effects of furosemide may be reduced [97]. Ketoconazole at a dose of 200 mg twice daily causes an 80% increase in aliskiren plasma levels and may be the cause of increased adverse reactions [98]. The pharmacokinetics of valsartan, ramipril, amlodypine, atenolol, hydrochlorothiazide, lovastatin, and digoxin are not affected by co-administration of aliskiren. Concurrent administration of aliskiren and irbesartan reduced aliskiren Cmax and AUC by 27% and 18%, respectively, in healthy volunteers, and by 33% and 7% respectively, in patients with mild or moderate renal

impairment [99]. These changes, however, were not deemed statistically significant. In addition, no significant differences in the occurrence of adverse events associated with the concomitant use of aliskiren and irbesartan in these patient populations were reported.

Another study found that aliskiren did not the effect the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects. In a group of healthy volunteers, no significant drug interactions were observed between aliskiren and digoxin. Aliskiren exposure increased when co-administered with the P-glycoprotein (P-gp) inhibitors atorvastatin and ketoconazole, indicating that aliskiren is a P-gp substrate [100]. However, the lack of a clinically relevant effect of aliskiren on P-gp substrate exposure (digoxin or atorvastatin) indicated that aliskiren is not a P-gp-mediated transport inhibitor [101]. Aliskiren has no known clinically significant interactions with commonly used hypertension or diabetes medications [102]. In healthy subjects, co-administration with furosemide resulted in a 30% decrease in furosemide AUC and a 50% decrease in Cmax compared to single doses. Co-administration with furosemide resulted in a 30% decrease in furosemide AUC and a 50% decrease in Cmax in healthy subjects after single doses;[103] however, there was no adjustment of furosemide dose in clinical trials when the two drugs were administered together [104]. Aliskiren co-administration with valsartan, metformin, amlodipine, or cimetidine resulted in a 20-30% change in Cmax or AUC. Aliskiren AUC and Cmax were increased by 50% when combined with atorvastatin [105]. Aliskiren did not effect the pharmacokinetics of atorvastatin, valsartan, metformin, or amlodipine when taken together. The EMEA has determined that no dose adjustments for aliskiren or these co-administered medicines are required [106].

3. RECENT STUDIES ON ALISKIREN IN HYPERTENSIVE PATIENT

Early phase II trials with aliskiren compared its blood pressure-lowering effects and safety to placebo, losartan, and irbesartan [107].

In a 4-week trial involving 226 patients with mild-to-moderate essential hypertension, aliskiren (at doses of 37.5, 75, 150, and 300 mg once daily) and losartan (100 mg once daily) were compared. Aliskiren reduced blood pressure in a dose-dependent manner, with the changes in patients receiving 75-300 mg of aliskiren being comparable to those receiving 100 mg of losartan [108]. 652 hypertensive subjects were randomly assigned to receive either irbesartan (150 mg) or aliskiren in a comparative trial with the ARB irbesartan (150, 300/, and 600 mg). Aliskiren (150 mg) was as effective as irbesartan (150 mg) in lowering blood pressure with comparable safety and tolerability in the short term [109].

In a multicenter, randomized, placebo-controlled, 8-week trial of 1123 patients with mild-to-moderate hypertension, the BP-lowering effects of aliskiren (75, 150, or 300 mg) alone or in combination with the ARB valsartan (80, 160, or 320 mg) were compared (Pool et al 2007). In an additional comparator arm, patients were given valsartan/hydrochlorothiazide (160/12.5 mg) [110]. Aliskiren has been compared to other antihypertensive drugs in subsequent trials. In an 8-week placebo-controlled, factorial design trial involving 2776 hypertensive patients, Aliskiren (in doses of 75 mg, 150 mg, and 300 mg once daily) was compared to HCTZ (in doses of 6.25, 12.5, and 25 mg once daily), as well as the combination of the two agents [110]. This study found that HCTZ significantly improves aliskiren's antihypertensive efficacy.

The combination of aliskiren 300 mg and HCTZ 25 mg resulted in the greatest mean BP reduction (21.2/14.3 mmHg in systolic and diastolic BP, respectively). Aliskiren safety and efficacy data for long-term use have recently become available [111]. Thus, in a 12-month open-label study, the efficacy of aliskiren with or without the addition of HCTZ was investigated. Aliskiren 150 mg (n = 1178) or 300 mg (n = 773) was given to patients with mild-to-moderate essential hypertension. In patients with BP 140/90 mmHg after Month 2, dose titration (aliskiren 150 mg titrated to 300 mg) or addition of HCTZ (12.5 mg titrated to 25 mg if necessary) to aliskiren 300 mg was permitted [112].

During a 4-week double-blind withdrawal phase, a subset of patients who were still on aliskiren monotherapy at Month 11 was randomized to continue aliskiren (n = 132) or placebo (n = 129). The BP reductions at the study end were comparable in these patients (BP reduction of 18.7/12.1 mmHg) [112] and the patients who had responded adequately to aliskiren monotherapy (BP reduction of 17.4/13.3 mmHg) [113].

Aliskiren has not been associated with rebound hypertension. Long-term renin-inhibition therapy could theoretically induce pharmacologic tolerance with renin hypersecretion, as well as the phenomenon of rebound hypertension after abrupt discontinuation of chronic therapy [114]. However, few researchers shows that clinical experience with aliskiren does not support this, as demonstrated by a recent long-term study published. In another study of 672 patients with mild-to-moderate essential hypertension, aliskiren withdrawal after 8 weeks of therapy (in doses of 150, 300, or 600 mg) was not associated with rebound blood pressure or PRA, despite elevated plasma renin concentrations at the time of withdrawal; BP and PRA remained suppressed for 2-weeks after therapy discontinuation. [115].

recently published a pooled analysis of data from eight randomized multicenter studies with aliskiren, involving 8570 patients with mild to moderate hypertension (published so far only as abstract) [116]. The duration of treatment ranged from 6 to 52 weeks. In summary, these clinical studies show that once daily aliskiren administration effectively lowers blood pressure, being at least as effective as, if not more effective than, standard doses of established ACE inhibitors and ARBs [117].

Aliskiren's long half-life is expected to provide more consistent continuous BP control during the morning surge, which has been linked to an increase in cerebrovascular events. Aliskiren also has synergistic effects when combined with a thiazide diuretic, an ACE inhibitor, a calcium antagonist, and possibly an ARB [118].

The addition of aliskiren 75 or 150 mg/day produced significant reductions in the mean daytime and night-time ambulatory SBP and DBP measurements compared to ramipril monotherapy (p0.05 for all comparisons) in the aliskiren-ACE inhibitor combination study (21 patients) [119]. However, the additional blood pressure reduction achieved by increasing the aliskiren dose to 150 mg/day was not statistically significant when compared to the 75 mg/day dose. When compared to irbesartan monotherapy, the addition of aliskiren 75 mg/day resulted in a reduction in daytime SBP and DBP, but this difference was not considered statistically significant [120]. Furthermore, rather than resulting in a further decrease in daytime and nigh time SBP and DBP, increasing the dose of aliskiren to 150 mg/day increased these measurements; however, these changes were not deemed statistically significant [121].

Given that the combination of aliskiren and valsartan had previously been studied in normotensive people, 37 a larger study in a patient population with mild-to-moderate hypertension was conducted to further investigate the antihypertensive effects of this combination therapy [122].

In this 8-week, double-blind, multicentre study, 1123 patients with mild-to-moderate hypertension were randomly assigned to one of the following treatment groups after a 3-4-week placebo run-in period: aliskiren 75, 150, or 300 mg/day; valsartan 80, 160, or 320 mg/day; aliskiren 75 mg-valsartan 80 mg/day; aliskiren 150 mg-valsartan 160 mg/day; aliskiren 300 mg-valsartan 320 mg/day; valsartan 160 mg-hydrochlorothiazide 12.5 mg/day; or placebo [123].

Only the 300-mg group had significantly lower msDBP and msSBP (p=0.0001) when compared to the placebo when the antihypertensive effects of aliskiren monotherapy were evaluated [124]. When compared to previous trials, the lower antihypertensive efficacy of

aliskiren in this trial may be attributed in part to the large placebo effect (msSBP/msDBP were reduced by 10/8.6 mm Hg in the placebo group) [125].

The reduction in msSBP and msDBP achieved with all three aliskiren-valsartan combination regimens was numerically higher, but not significantly (in general) higher than with either drug alone [126]. Furthermore, the reduction in msSBP and msDBP with aliskiren 150 mg-valsartan 160 mg/day and aliskiren 300 mg-valsartan 320 mg/day was comparable to the reduction achieved with valsartan 160 mg-hydrochlorothiazide 12.5 mg/day. There was no significant difference in the proportions of patients who achieved adequate blood pressure control (msSBP/msDBP 140/90 mm Hg) between the aliskirenn valsartan combination groups and the respective monotherapy groups [127]. An even larger study in patients with mild-to-moderate hypertension looked at the efficacy of aliskiren and valsartan as monotherapy or in combination.

The primary endpoint was the difference in msDBP between baseline and week 8. Change in msSBP from baseline to week 8, change in 24-hour ambulatory blood pressure measurements from baseline to week 8 (in a subset of patients), the proportion of patients achieving blood pressure control, and changes in PRA and PRC were secondary endpoints [128]. At the end of

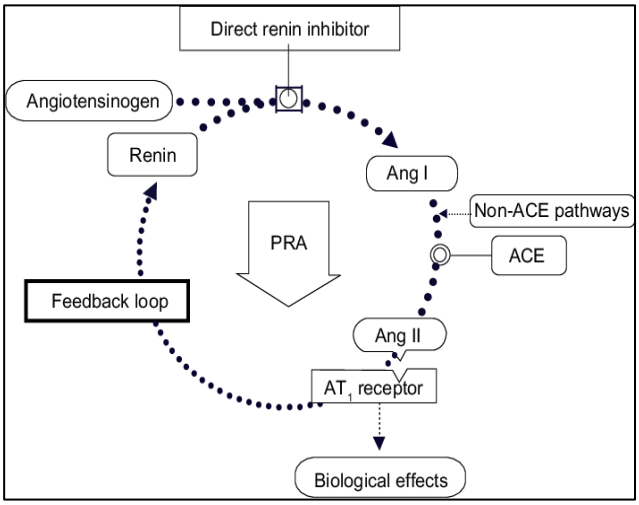

Figure no.4 Direct renin inhibition

week 8, the aliskiren-valsartan combination therapy was also significantly more effective than either drug alone in terms of blood pressure control (p=0.0005 compared to aliskiren monotherapy, p<0.0001 compared to valsartan monotherapy) [129]. All active treatments achieved significantly better blood pressure control rates than placebo (p<0.0001 for all comparisons) [130].

At the end of week 4, the combination of aliskiren 150 mg-valsartan 160 mg/day was significantly more effective than either drug alone or placebo in lowering msDBP ($p<0.0001$ compared to aliskiren monotherapy or placebo, $p=0.0004$ compared to valsartan monotherapy) and msSBP ($p<0.0001$ compared to aliskiren monotherapy,valsartan

monotherapy, or placebo) [131]. At the end of week 8, combination therapy (94 patients) was also superior at lowering blood pressure. Compared to either drug alone ($p<0.0001$ compared to aliskiren monotherapy [79 patients] or valsartan monotherapy [100 patients]) [132].

Patients with hypertension and a body mass index of 30 kg/m2 or higher who did not respond to hydrochlorothiazide 25 mg/day monotherapy for 4 weeks (msDBP 90-109 mm Hg) were randomly assigned in a double-blind fashion to receive one of the following therapies (in addition to hydrochlorothiazide) for 4 weeks: aliskiren 150 mg/day (122 patients), irbesartan 150 mg/day (122 patients) [133].

When these changes were compared to those in the respective monotherapy groups, statistical significance was obtained in all dosing groups except those treated with aliskiren 75 mg-hydrochlorothiazide 12.5 mg/day and aliskiren 150 mg-hydrochlorothiazide 6.25 mg/day (p0.05) [152]. Although more patients in the combination therapy group achieved adequate blood pressure control (msSBP/msDBP 140/90 mm Hg) than in the respective monotherapy groups, this difference was not statistically significant [153].

A smaller, randomized, double-blind trial was carried out to assess the efficacy of aliskiren or ramipril alone or in combination on blood pressure control in patients with concomitant hypertension and type 1 or type 2 diabetes [154]. For four weeks, patients were randomly assigned to receive once-daily aliskiren 150 mg (282 patients), ramipril 5 mg (278 patients), or aliskiren 150 mg-ramipril 5 mg (277 patients) treatment. The doses were then doubled in all treatment groups for an additional four weeks [155]. At the end of week 8, the aliskiren, ramipril, and aliskiren-ramipril groups had reduced their msSBP/msDBP by 14.7/11.3, 12.0/10.7, and 16.6/12.8-mmHg, respectively. The reduction in msSBP with the aliskiren-ramipril combination was only statistically significant ($p<0.0001$) when compared to ramipril monotherapy [156]. Using a noninferiority margin of 2- and 4-mm Hg for msDBP and msSBP, respectively, it was discovered that aliskiren monotherapy was non-inferior in reducing msDBP ($p=0.0002$) and superior in reducing msSBP ($p=0.021$) [157].

Although PRC was significantly increased in all treatment groups (aliskiren monotherapy 139%, ramipril monotherapy 72%, aliskiren-ramipril combination 331%, $p<0.0001$ for all

comparisons vs baseline), PRA was significantly reduced in the aliskiren monotherapy and aliskiren-ramipril combination groups ($p<0.001$) [158].

4. MECHANISM OF ACTION ALISKIREN AS A TREATMENT OF CHF (CONGESTIVE HEART FAILURE)

In the chronically failing heart, cardiac adrenergic drive increases, contributing to the loss of myocardial reserve and the progression of left ventricular (LV) dysfunction that characterizes heart failure. The "adrenergic hypothesis" of heart failure was developed in the early 1980s based on work in the explanted failing human heart. The hypothesis, which has been updated, has been continually tested by multiple investigators using a variety of approaches. Chronically increased adrenergic activity in the failing human heart may have two types of negative effects: signal transduction desensitization and adverse biologic effects on cardiac myocytes [159]. Although major components of this pathophysiologic construct remain unknown, additional research in the explanted human heart, intact human heart, cardiomyopathy animal models, isolated cardiac myocytes, and transgenic mice has consistently supported and refined this hypothesis [160].

First, in comparison to most other organs, the heart has significant and selective adrenergic activation. Second, in the failing human heart, adrenergic activation is regionally regulated. Third, cardiac adrenergic activation predicts outcomes better than systemic sympathetic markers [161]. Finally, new evidence suggests that cardiac adrenergic activation is the first neurohormonal abnormality detected in the progression of heart failure from asymptomatic LV dysfunction to the clinical syndrome.

The first type of detrimental effect of sustained cardiac adrenergic activation, as depicted in, is desensitization of b-adrenergic signal transduction mechanisms, which was the first adverse effect of chronic adrenergic stimulation identified in the chronically failing human heart [162]. The clinical consequences of a decrease in signal transduction are a decrease in myocardial reserve and an impairment in maximal exercise responses, both of which contribute to the clinical syndrome of heart failure. Increased levels of endogenous catecholamines are primarily responsible for changes in b-receptor signal transduction [163].

This is supported by findings that norepinephrine causes similar abnormalities in cultured heart cells as it does in the failing human heart and interventions that reduce cardiac adrenergic drive or catecholamine-receptor occupancy increases b-receptor density and correct other signal-

transduction abnormalities [164]. The second way that chronically increased cardiac adrenergic stimulation causes harm is through an adverse effect on the biology of the cardiac myocyte, which is mediated by the remaining 40-50% of b-adrenergic signal-transduction capacity [165]. The clinical manifestation of these effects is progressive LV dysfunction. Direct evidence that norepinephrine can decrease contractile function and alter gene expression in isolated cardiac myocytes, the effect of high levels of sympathetic drive on human myocardial function, and the beneficial effects of b-adrenergic-blocking agents on LV function in chronic heart failure all support the idea that sustained b-adrenergic stimulation of the failing heart leads to progressive LV dysfunction. The progressive nature of ventricular systolic dysfunction, like diminished exercise capacity, is a hallmark of the natural history of heart failure.

Clinical therapy for CHF in a child is intended to promote recovery, maintain stability, limit disease progression, and create an environment conducive to somatic growth and the best possible development of the child into an adolescent. Combinations of ACE inhibitors, beta-blockers, diuretics, and aldosterone antagonists are commonly used [166].

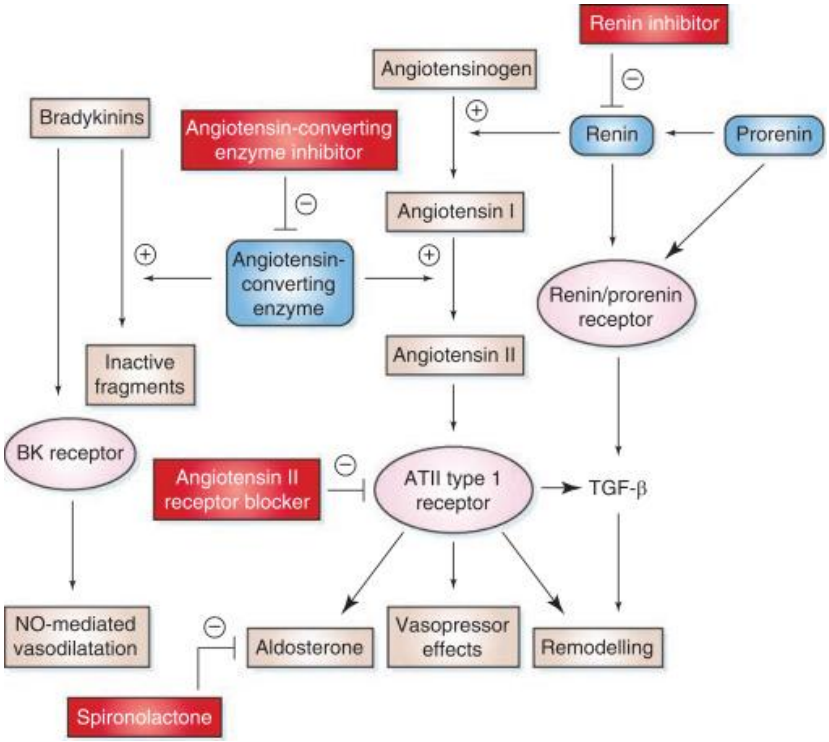

Figure no. 5- Aliskiren inhibits the activity of the enzyme renin at the onset of the conversion cascade within the renin–angiotensin system (RAS), eventually resulting in a decrease in blood pressure. ACE, angiotensin converting enzyme; ACE I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; AT-R, angiotensin-II receptor.

CHF disease with reduced systolic function is characterized by RAAS pathway activation, which is a physiological response to reduce renal perfusion. Renin promotes the process by which hepatic angiotensinogen is converted into angiotensin I, which is then processed by the ACE, primarily in the lungs, to produce angiotensin II, a potent blood vessel constrictor with long-term detrimental effects on CHF. ACE inhibitors' mechanism of action. This could be due to aldosterone release, which increases sodium reabsorption, as well as vasoconstriction of renal afferent arterioles [167]. When RAAS activation is not inhibited, vasoconstriction causes cardiomyocyte hypertrophy and death. ACE inhibitors can reverse remodelling, reduce vascular resistance, and improve vascular compliance. The remodelling properties appear to be higher with ACE inhibitors that have significant tissue penetration, such as lisinopril. Their beneficial hemodynamic changes include a reduction in cardiac preload, afterload, and systolic ventricular wall stress, resulting in increased cardiac output without an increase in oxygen consumption [168]. This hemodynamic change improves renal perfusion and increases salt excretion, allowing glomerular filtration to continue. ACE inhibitors' mechanism of action. This could be due to aldosterone release, which increases sodium reabsorption, as well as vasoconstriction of renal afferent arterioles. When RAAS activation is not inhibited, vasoconstriction causes cardiomyocyte hypertrophy and death. ACE inhibitors can reverse remodelling, reduce vascular resistance, and improve vascular compliance [169]. The remodelling properties appear to be higher with ACE inhibitors that have significant tissue penetration, such as lisinopril. Their beneficial hemodynamic changes include a reduction in cardiac preload, afterload, and systolic ventricular wall stress, resulting in increased cardiac output without an increase in oxygen consumption. This hemodynamic change improves renal perfusion and increases salt excretion, allowing glomerular filtration to continue [170].

Spironolactone, a mineralocorticoid antagonist commonly used in pediatrics, reduces aldosterone's competitive ability to bind to its receptor in the distal renal tubule, causing sodium to be excreted while potassium is preserved [171]. Spironolactone has a minor diuretic effect, but due to its potassium-saving properties, it is very effective in treating acute heart failure patients. Beta-blockers are the standard treatment for CHF with a low ejection fraction. Different drugs have varying selectivity for beta 1 or 2 receptors: some only partially activate the receptors (inherent sympathomimetic action), others have additional properties on adrenoceptors, or they may stimulate nitric oxide production [172]. Most used beta-blockers (metoprolol, carvedilol, propranolol, nebivolol, and bisoprolol) are contraindicated agonists at the beta 1 adrenoceptor, which means that exposure to the drug reduces a predominating basal

level and constitutionally reduced signal transduction from the receptor even in the absence of an agonist for the receptor [173].

5. RAAS INHIBITION IS A POTENT METHOD IN HYPERTENTION TREATMENT AND ALSO EEFECTIVE IN CHF

The enzyme renin initiates RAAS activity by cleavage the peptide angiotensinogen into the decapeptide angiotensin I (Ang I); the key product of the renin system is the octapeptide hormone angiotensin II (Ang II), which is formed from Ang I by the angiotensin-converting enzyme [174]. RAAS is essential for volume regulation and BP maintenance. Excessive renin system activity, on the other hand, is associated with hypertension and target organ damage, which is largely mediated by the actions of Ang II on the angiotensin AT1 receptor [175].

The introduction of ACE inhibitors heralded a new era of therapeutic options for patients suffering from hypertension, heart failure, and renal failure. However, physicians quickly discovered that, in terms of lowering blood pressure, ACE inhibitors were no more effective as monotherapy than existing antihypertensives and, like existing drugs, had to be combined with other treatments, particularly diuretics, to achieve BP control [176]. This was recently confirmed by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) researchers. The lower levels of BP control achieved in the ALLHAT ACE inhibitor arm may reflect, at least in part, the trial protocol's prohibition on ACE inhibitor/diuretic combinations.

This design feature most likely contributed to the trial's black patient subgroup's significantly poorer blood pressure control. Patients taking ACE inhibitors have lower circulating Ang II levels at first, but these levels frequently rise to earlier baseline levels. The same holds true for circulating aldosterone concentrations [177]. The phenomenon is known as "escape." The introduction of angiotensin receptor blockers (ARB), a drug class that can directly block the Ang II AT1 receptor, was expected to solve the RAAS problem by inhibiting all the negative effects of RAAS activation.

After all, Ang II actions such as salt retention, aldosterone release, vascular smooth muscle cell contraction, and growth factor activity all involve AT1 receptor activation. However, despite its undeniable clinical benefit, the introduction of this drug class may not adequately block the RAAS [178].

The suppression of the RAAS after treatment with either ACE inhibitors or ARBs is still insufficient. One important reason for this is that these therapies cause a reactive increase in renin activity by disrupting the short feedback loop through which Ang II normally inhibits renin release from the kidney [179]. Bernstein et al. used mouse models to demonstrate the importance of renin in blood pressure control. They discovered that mice with gene disruptions in angiotensinogen, renin, ACE, and the AT1 receptor all have a similar phenotype, with a 35-mmHg reduction in blood pressure. These experiments demonstrate the importance of the RAAS in BP control. Importantly, while ACE/ mice had barely detectable Ang II levels, ACE/ mice had normal Ang II levels but higher Ang I levels, resulting in an Ang II/Ang I ratio that was roughly half normal [180].

Another issue with ACE inhibitors and possibly ARB is that they may not effectively inhibit tissue RAAS activity. Crowley and colleagues recently demonstrated the significance of extrarenal AT1 receptors. They carried out challenging cross-transplantation experiments in AT1 receptor and wild-type mice [181]. When the AT1A receptor was deleted in the recipient animal, even transplantation of a wild-type donor kidney that expressed the AT1A receptor did not restore normal blood pressure; this discrepancy could not be explained by altered aldosterone generation.

It's worth noting that the researchers also demonstrated that disrupting the AT1 receptor-mediated short feedback loop in the kidney was insufficient to explain the marked stimulation of renin production caused by global AT1 receptor deficiency or receptor blockade. Nonetheless, this discovery highlights the variety of mechanisms that stimulate renin responses [182]. These findings suggest that using a renin inhibitor to suppress the reactive rise in renin activity, either alone or in combination with ACE inhibitors or ARB, has a high potential for preventing end organ damage in hypertension.

The RAAS has been demonstrated to play an important role in BP regulation. Renin is a low molecular weight enzymatic protein that is synthesised from juxtaglomerular cells (JGC) as the preprohormone prorenin when blood pressure (BP) is low. Mature renin is stored in JGC granules and released into the renal and, eventually, systemic circulation via an exocytic process involving stimulus secretion coupling [183].

Active renin secretion is primarily regulated by four interdependent factors: (1) a renal baroreceptor mechanism in the afferent arteriole; (2) changes in NaCl delivery to the distal

tubules' macula densa cells (which are close to the JGC and form the JG apparatus); and (3) sympathetic nerve stimulation via 1-adrenergic receptors.

Renin acts on angiotensinogen, cleaving it to produce Ang I, a biologically inert decapeptide. In fact, the biologically active molecule is formed by the hydrolysis of Ang I by angiotensin-converting enzyme (ACE), which produces Ang II, while renin remains in the circulatory system for 30 to 60 minutes, continuing to induce the production of Ang I [184].

Other Ang I and II metabolites may have significant biological activity, particularly in tissues. Ang III and IV are formed by sequentially removing amino acids from Ang II's N-terminus. The central nervous system contains Ang III. Ang IV is a hexapeptide that results from the further enzymatic degradation of Ang III.

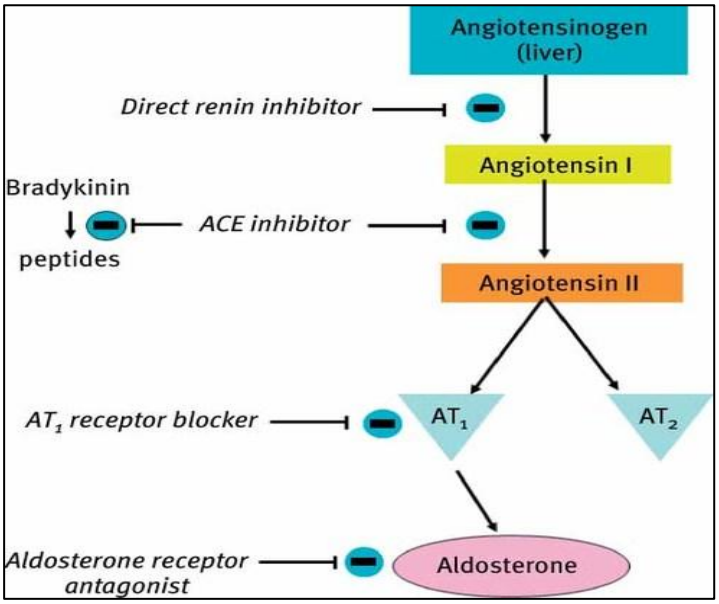

Figure no.6 Renin-angiotensin aldosterone system.

Ang IV appears to cooperate with Ang II signalling in preclinical studies. Several studies and experiments have demonstrated that Ang II is the. The renin-angiotensin-aldosterone (RAAS) and kallikrein-kinin (KK) systems [185]. A variety of RAAS-induced physiological and pathophysiological actions are mediated by this protein.

There are at least four angiotensin receptor subtypes known.

The type 1 (AT1) receptor regulates the cardiovascular system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy), the kidney (renal tubular sodium reabsorption, inhibition of renin release), the sympathetic nervous system, and the adrenal cortex (stimulation of aldosterone synthesis).

This receptor is found on a variety of cell types in Ang II target organs. The type 2 (AT2) receptor is abundant in the brain, kidney, and other tissues during foetal life, but its levels drop dramatically after birth [186]. It may mediate vasodilation, antiproliferative and apoptotic effects in vascular smooth muscle, as well as inhibit heart growth and remodelling. The significance of any of these AT2-mediated actions is unknown. The type 4 (AT4) receptors are thought to mediate the release of plasminogen activator inhibitor 1 by Ang II and the N-terminal truncated peptides (Ang III and Ang IV), but the type 3 (AT3) receptors' function is unknown. Ang II stimulates the production of aldosterone via the AT1 receptor. which regulates extracellular volume by regulating sodium and potassium balance. It promotes potassium excretion by increasing sodium and water reabsorption in the distal tubules and collecting ducts [187].

The RAAS plays an important role in the regulation of circulatory homeostasis; however, the system's continued or inappropriate activation is thought to contribute to the pathophysiology of diseases such as hypertension [188]. There is evidence that RAAS disruptions play a role in essential hypertension as well as the responses of cardiovascular and renal tissue to hypertensive and nonhypertensive injury.

6. ALISKIREN VS OTHER CLASS OF DRUG

Renin inhibitors' chemical progress can be separated into three generations of substances. There were peptide angiotensinogen analogues, which block the enzymatic action of renin, peptidomimetic agents, which are dipeptide transition-state analogue inhibitors of the active site, and nonpeptide-like compounds, of which aliskiren is the most successful example. The first- and second-generation drugs were constrained by poor metabolic stability and oral bioavailability, poor BP lowering potency, short duration of action, and high synthesis costs [189]. Advances in crystallography and a structure-based approach to drug design aided in the development of aliskiren, a third-generation molecule. The aliskiren molecule was designed and modified using molecular modelling, with the structure based on x-ray crystallographic studies of the active site of renin. Aliskiren interacts with multiple binding pockets located in different locations surrounding the active site of renin, specifically the renin subpocket (S3sp). Aliskiren has lower lipophilicity than peptidomimetic renin inhibitors, making it more resistant to intestinal breakdown. The hepatic extraction ratio (12%) suggests a low rate of first-pass metabolism, and the consequent bioavailability (approximately 2.6%) is much higher than that of previous renin inhibitors. Peak plasma concentrations are attained within 2.5-3.0 hours after a single 150 mg or 300 mg administration of the medication, and steady-state plasma

concentrations are reached within 7-8 days [190]. Pharmacokinetic investigations have indicated that there is no requirement for dose adjustment in individuals with renal or hepatic impairment, as well as in elderly or diabetic patients. Aliskiren has a low risk of medication interactions due to its lack of influence on cytochrome P450 isoenzyme activities.

6.1. Diuretics

Aliskiren 75-300 mg daily was consistently more effective than hydrochlorothiazide (HCTZ) 6.25 mg, 12.5 mg, and 25 mg for lowering blood pressure in hypertensive patients in a 2006 trial. The superiority of aliskiren became clearer at increasing doses [191]. Another direct comparison study involving 1124 hypertensive patients confirmed that aliskiren 150 mg force-titrated to 300 mg daily reduced systolic/diastolic BP values significantly more than HCTZ 12.5 mg/day titrated to 25 mg/day (20.3/14.2 mmHg versus 18.6/14.0 mmHg, P, 0.05).

6.2. Inhibitors of ACE

Aliskiren was compared to ramipril in three big studies. The first trial comprised 837 diabetic hypertensive patients who were given aliskiren 150 mg, ramipril 5 mg, or aliskiren 150 mg in conjunction with ramipril 5 mg. For the next four weeks, dosages were titrated to aliskiren 300 mg, ramipril 10 mg, and aliskiren 300 mg + ramipril 10 mg. After eight weeks, aliskiren monotherapy reduced systolic blood pressure more than ramipril alone (14.7 versus 12.0 mmHg, P, 0.05) and resulted in a higher responder rate (73% versus 66%, P, 0.05). Surprisingly, the incidence of cough was lower in aliskiren (2.1%) patients than in ramipril (4.7%) patients [192].

The AGELESS (Aliskiren for Geriatric Lowering of Systolic Hypertension) research provides more evidence of aliskiren's superior antihypertensive efficacy compared to ramipril.

Table 1: Pharmacological rationale of combination therapy

Combinations	Mechanisms	
ARB-Diuretic	ARBs cause the antagonism of angiotensin II at the vascular and myocardial level by direct AT-1 receptor blockade	Thiazide diuretic blocks sodium chloride reabsorption at the distal convoluted tubule
β-Adrenoceptor Antagonist-Diuretic	The β-adrenoceptor blocker inhibits activation by direct suppression of renin release, inhibit β-adrenergic sympathetic stimulation decreasing myocardial contractility and heart rate	Diuretics as above
ACEI-Diuretic	ACEI cause the removal of the angiotensin II effect (vasoconstriction, stimulation of aldosterone secretion) and enhancement of kinin-mediated vasodilation	Diuretics as above
ACEI-CCB	ACEI as above	The calcium antagonists de-crease vascular resistance by vascular smooth muscle relaxation
ARB-CCB	ARBs as above	CCBs as Above
ACE-ARB Inhibitors	ACEI as above	ARBs as above
Centrally Acting Agents-Diuretic	Clonidine acts by decreasing sympathetic outflow by stimulating pre synaptic α_2-adrenoceptors in the vasomotor centre of the CNS.	Diuretics as above

Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II type 1 Receptor Blockers (ARBs), Calcium Channel Antagonist (CCB)

6.3. Combination treatment

To obtain sufficient blood pressure control, most patients require two or more antihypertensive medications [193]. As a result, various studies have been conducted to evaluate the effects of aliskiren in combination with other antihypertensive medications.

6.4. Aliskiren in combined with amlodipine.

Adding aliskiren 150 mg daily to the regimen of hypertensive individuals who had insufficient blood pressure control with amlodipine 5 mg resulted in better BP decrease (11.0/8.5 mmHg) compared to continuing amlodipine 5 mg (5.0/4.8 mmHg). The BP-lowering impact of aliskiren-amlodipine was comparable to that of amlodipine 10 mg. The combined medication also resulted in higher rates of responder and BP control (64% and 43%, respectively) than amlodipine 5 mg alone (45% and 23%) [194]. In a recent study, the effects of aliskiren added to amlodipine on ankle edoema were specifically assessed, and the combination produced a significantly less marked increase in both ankle foot volume and pretibial subcutaneous tissue pressure (two objective measures of ankle edema) than amlodipine alone. Long-term open

research with 556 mild to moderate hypertensives recently demonstrated the antihypertensive efficacy and tolerability of aliskiren amlodipine combination therapy. After 12 months of treatment with aliskiren-amlodipine, there was a mean decrease in blood pressure of 24.2/15.5 mmHg, with a rate of BP normalisation of 74.3% [195]. Interestingly, the BP-lowering effect in this study was more pronounced in the subgroup of patients with Stage II hypertension (160/100 mmHg), who showed a mean BP reduction of 29.1/17.1 mmHg, demonstrating that the higher the baseline BP level, the greater the antihypertensive efficacy of the aliskiren-amlodipine combination [196].

6.5. Aliskiren in combined with hydrochlorothiazide.

In a large factorial design research, the combination of aliskiren 75-300 mg and HCTZ 6.25-25 mg reduced blood pressure much more than the component monotherapies.24 BP was lowered by a mean of 21.2/14.3 mmHg at the maximum combined dose of 300/25 mg. The combination also reduced the incidence of thiazide-induced hypokalaemia, and the HCTZ-induced elevation in PRA was neutralised by aliskire. In a recent study, the effects of aliskiren added to amlodipine on ankle edema were specifically assessed, and the combination produced a significantly less marked increase in both ankle foot volume and pretibial subcutaneous tissue pressure (two objective measures of ankle edema) than amlodipine alone [197]. Furthermore, the frequency of patients with clinically obvious peripheral edema was reduced in those who got the combination.

6.6. Aliskiren in combined with an ACE inhibitor.

The efficacy of combining aliskiren 300 mg with ramipril 10 mg in diabetic hypertensive individuals has been studied.26 When compared to each component monotherapy (10.7 mmHg with ramipril and 11.3 mmHg with aliskiren), combination therapy demonstrated a substantial further reduction in diastolic BP (12.8 mmHg) [198]. The combination also resulted in a bigger drop in systolic blood pressure and a higher responder rate than ramipril monotherapy. The combination also resulted in a bigger reduction in systolic blood pressure and a higher responder rate than ramipril monotherapy. Ambulatory blood pressure measures in a sample of 137 individuals revealed that adding aliskiren to ramipril resulted in a larger drop of mean 24-hour BP, enhancing BP control over 24 hours [199].

6.7. Aliskiren in combined with an ARB.

Oparil et al30 reported significantly greater BP reductions (17.2/12.2 mmHg) with an aliskiren 300 mg + valsartan 320 mg combination compared to aliskiren alone (13.0/9.0 mmHg, both P, 0.0001 versus the combination) in an eight-week study involving 1797 mild to moderate hypertensive patients [201]. Responder and BP control rates were also greater in combination therapy patients (66% and 49%, respectively) than in aliskiren (53% and 37%) and valsartan (55% and 34%) monotherapy recipients. In an ambulatory BP monitoring research, an aliskiren valsartan combination significantly reduced 24-hour ambulatory BP more than either component alone. The combined therapy reduced mean blood pressure by 14.4/10.3 mmHg, aliskiren by 9.8/7.1 mmHg, and valsartan by 10.1/7.1 mmHg.

In an ambulatory BP monitoring research, an aliskiren valsartan combination significantly reduced 24-hour ambulatory BP more than either component alone [202]. The combined therapy reduced mean blood pressure by 14.4/10.3 mmHg, aliskiren by 9.8/7.1 mmHg, and valsartan by 10.1/7.1 mmHg.

7. Superior Efficacy of Aliskiren in Blood Pressure Regulation and CHF Management

The renin-angiotensin-aldosterone system (RAAS) is essential in the physiology of blood pressure management and the pathophysiology of hypertension (HTN), influencing vascular tone, salt retention, and oxidative stress. Stress, fibrosis, sympathetic tone, and inflammation are all factors to consider [203].

Fortunately, RAAS inhibitors have been used to treat HTN since the 1970s, and more drugs are being developed. In this review, we will look at new antihypertensive medications that affect the RAAS [204], assess recent studies that help us understand which patients are more likely to benefit from RAAS blockade, and look at three recent pivotal randomised trials that involve newer RAAS blocking agents and inform clinical practise. Antihypertensive medications, both new and old, that act on the renin-angiotensin-aldosterone system. There are well-established drugs that interfere with the renin-angiotensin-aldosterone system (RAAS) at several sites, including (1) angiotensin-converting enzyme inhibitors (ACEIs), (2) angiotensin II type I (AT1) receptor blockers (ARBs), (3) direct renin inhibitors (DRIs), (4) mineralocorticoid receptor antagonists (MRAs), and even (5) beta blockers, the last of which may be considered partial inhibitor [205]. In this section, we will quickly examine trials demonstrating the benefits of ACEIs/ARBs, followed by a discussion of recent advancements and novel medicines that inhibit the RAAS at various sites.

Aliskiren significantly reduced both SBP and DBP when compared to placebo at all dosages. Aliskiren 300 mg demonstrated the greatest BP-lowering efficacy among all aliskiren dosages tested in the six included trials. The reduction in SBP and DBP with aliskiren 300 mg vs. placebo was substantially larger than with aliskiren 150 mg [206]. The extent of the BP reduction with aliskiren at the highest recommended dose of 300 mg daily is like that of ACE inhibitors (8/5 mm Hg) and ARBs (8/5 mm Hg). This finding is supported by a direct comparison of the three placebo-controlled trials included in this systematic review that compared aliskiren 150 mg and aliskiren 300 mg with ARBs. Aliskiren 150 mg vs. irbesartan 150 mg (SBP, 6.0 vs. 7.2 mm Hg and DBP, 6.0 vs. 7.2 mm Hg) 2.9 vs 2.5 mm Hg) and aliskiren 300 mg versus valsartan 320 mg (SBP, 5.1 to 13.0 vs 6.5 to 12.8 mm Hg; and DBP, 3.7 to 9.0 vs 2.7 to 9.7 mm Hg) [207]. This shows that blocking the renin-angiotensin system at various places does not result in clinically varied blood pressure lowering effects. Azilsartan, a new ARB, has been demonstrated to be more effective than olmesartan or valsartan in lowering blood pressure (BP)14-16. Azilsartan 80 mg lowers blood pressure more effectively than the optimal and best tolerated doses of both olmesartan (40 mg) and valsartan (320 mg), with no increase in adverse effects [208]. A recent German registry investigation supported these findings: among 3,849 patients with critical HTN, 61% of those started on azilsartan attained a BP target of less than 140/90 mmHg, compared to 56% of those started on an ACEI17. Azilsartan may be more effective at lowering blood pressure due to its greater capacity to block AT1 receptors. Only a prospective, randomised, dose-escalation trial can fully determine whether azilsartan is superior to other ARBs in decreasing blood pressure [209].

The efficacy of therapeutic RAAS blockage is now without doubt. Despite therapy with ACE inhibitors and ARBs, residual rates of hospitalisation and death in patients with CHF and rates of progression to renal failure in individuals with diabetic nephropathy remain high, even in the setting of recent controlled clinical studies. Although clinical inertia, poor adherence, and other pathophysiological pathways all play a role, at least some of the residual morbidity and mortality is thought to be due to insufficient RAAS blockade [210].

8. CONCLUSION

Although treatment guidelines for controlling blood pressure recommend using two medications in combination with any antihypertensive drug, even if this is ineffectual, blood pressure remains uncontrolled in half of all treated patients. Cardiovascular illnesses are the leading cause of death among hypertension-related conditions worldwide. A variety of large

clinical trials have revealed that inhibiting the RAS reduces cardiovascular morbidity and mortality. RAS inhibition, on the other hand, is not possible with ACE inhibitors or ARBs due to counter-regulatory processes. As an alternative to the current treatment of hypertension, ischemic heart disease, and heart failure, a new class of agents that effectively and specifically inhibit the RAS via a novel mechanism of action, with few side effects and a long half-life to allow once-daily dosing is required. Aliskiren is an effective blood pressure medication that is well tolerated, with side effects equivalent to placebo or ARBs. When taken with medications that cause a reactive rise in plasma renin activity, it has synergistic effects. Recent pharmacological investigations suggest that aliskiren may be effective as a substitute therapy in patients who are intolerant of ACE inhibitors and ARBs, for the treatment of illnesses in which Ang II plays a role in the aetiology, and for the secondary prevention of cardiovascular disease.

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Conflict of Interest

The authors declare no competing financial interests or personal relationships that could influence the work reported in this manuscript

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