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Review

Pharmacokinetics and pharmacodynamics of aliskiren, an oral direct renin inhibitor

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Abstract:
Intensive efforts have been spent to discover therapeutic, non-peptide and orally effective hypertensive drugs. One drug that emerged from this effort is aliskiren, a direct human renin inhibitor that blocks the conversion of angiotensinogen to angiotensin I (Ang I). In contrast to other antihypertensive agents, aliskiren decreases plasma renin activity (PRA). In healthy human subjects, doses of between 40 and 640 mg of aliskiren exert a dose-dependent reduction in PRA and Ang I and Ang II levels. The bioavailability of aliskiren is low (2%), peak plasma concentrations are reached within one to three hours and the binding with plasma proteins achieves approximately 47–51%. Aliskiren is slightly metabolized (20%) by CYP3A4. The most common adverse events include diarrhea, headache, back pain and gastrointestinal disorders. Aliskiren is well tolerated, and may be used alone or in combination with other antihypertensive agents.
Aliskiren belongs to a new class of agents that effectively and specifically inhibit the RAS. This drug functions through a novel mechanism of action and has the potential to become a true alternative to angiotensin converting enzyme inhibitors and angiotensin receptor blockers in the therapy of hypertension and other cardiovascular and renal disorders.

Key words:
angiotensin, renin inhibitor, aliskiren

Introduction

Hypertension is largely responsible for cardiovascular morbidity and mortality and the incidence of cardiovascular complications (predominantly stroke and coronary heart disease). The most recent reports (WHO, 2007) indicate that the number of people worldwide with elevated blood pressure (BP) that warrants treatment is increasing [19, 31]. Although angiotensin converting enzymes inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) and many others drugs with different mechanisms of action are currently being used to treat this disorder, the number of hypertensive patients is still growing. Therefore, because current treatments are not able to stop the progression of disease, the intensive search for a new therapeutic system must continue.

The renin-angiotensin system (RAS) plays a key role in the regulation of blood pressure, hydroelectrolyte balance and cell functions [10, 27]. Renin is secreted by the kidney and cleaves its substrate, angiotensinogen, forming the inactive decapeptide (Ang I) that is converted to an active octapeptide (Ang II) by angiotensin converting enzyme (ACE) [17, 26].

In the last 10 years, many findings indicated that Ang II exerts both local and systemic activities on the endothelium. Ang II is responsible for endothelial

dysfunction by inducing oxidative stress, promoting atherosclerosis, inhibiting nitric oxide (NO) synthesis and enhancing leukocyte infiltration and adhesion to the vascular wall. Ang II may be one of the risk factors for the development of thrombosis [9, 30]. Ang II is a powerful vasoconstrictor and induces the release of catecholamines from the adrenal medulla and prejunctional nerve ending [45]. It also promotes aldosterone secretion and sodium reabsorption and inhibits renin release, thus providing negative feedback to the system. To sum up, Ang II causes an increase in vascular resistance and blood pressure [12, 17].

Therapies with ACE-Is and ARBs that block the RAS system are proven to be highly successful treatments for hypertension and related cardiovascular disorders. However, ACE-Is and ARBs only partially suppress the RAS because they stimulate a compensatory increase in Ang II levels [28, 29, 53]. Indeed, higher Ang II levels are associated with end organ damage and cardiovascular events in patients with hypertension [3, 43]. It has also been observed that higher PRA levels are a predictor of cardiovascular disease in patients not being treated for hypertension [1]. Additionally, PRA levels are associated with a higher incidence of myocardial infarction (MI) among hypertensive patients [2].

Thus, the inhibition of renin activity and the blocking of the RAS cascade at its primary steps seem to be rate-limiting strategies. Thus, reducing both PRA and angiotensin II activity [35] could enhance the therapeutic potential of drugs affecting the RAS.

Aliskiren

The idea of RAS blocking has existed for more than 30 years, and numerous groups have searched for

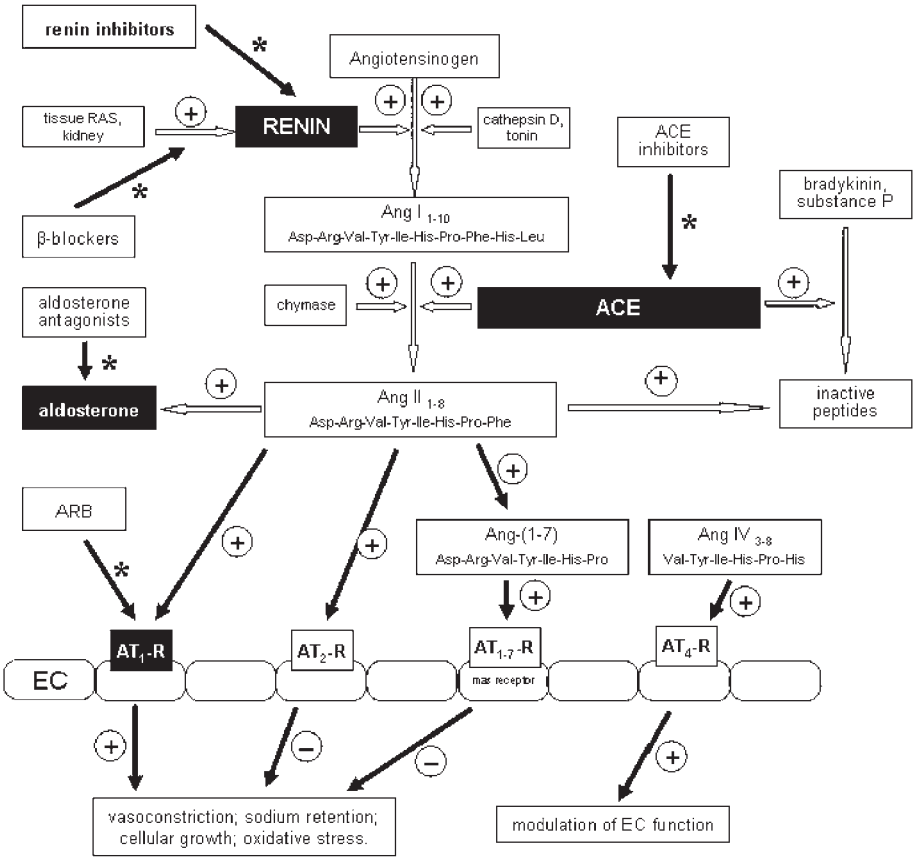

Fig. 1. The renin-angiotensin-aldosterone system and various points of RAS blockade. (*) –indicates points of blocking, (+) – indicates stimulation and (–) – indicates inhibition. AT_1-R – angiotensin receptor; EC – endothelial cells, EP – endopeptidases

an orally active renin inhibitor. The renin-angiotensin-aldosterone system can be blocked at various points (Fig. 1). Antihypertensive agents like β-blockers reduce the release of renin from the kidney [11]. ACE-Is block the conversion of Ang I to Ang II and inhibit the inactivation of bradykinin and substance P [34, 36, 41, 46]. ARBs compete with angiotensin II for AT_1 receptor [8]. All these drugs are potent blockers of the RAS at various steps, but only renin inhibitors suppress the RAS at its origin [21, 41, 56].

Several stable peptide-like renin inhibitors were synthesized previously. The first generation of orally active renin inhibitors was never used clinically [56]. Low bioavailability, rapid elimination and weak blood-pressure lowering activity after oral administration in patients eliminated these substances from clinical practice. In 2003, Wood et al. employed a combination of molecular modeling and crystallographic structure analysis to design renin inhibitors lacking the extended peptide-like backbone of earlier inhibitors in order to improve pharmacokinetic properties [57]. This led to the discovery of aliskiren, the first of a new class of non-peptide, orally effective renin inhibitors [42, 56]. Aliskiren has the chemical structure 2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-(4-methoxy-3-[3-methoxypropoxyl-]phenyl)-octanamide and a molecular weight of 551,8 g/mol [13]. The active substance of aliskiren is a hemifumarate salt [45, 52, 57]. It is optically active with four chiral carbons, but exists as a single diastereoisomer [18]. The molecular formula of aliskiren hemifumarate is: $C_{30}H_{53}N_3O_6 \times 0.5\ C_4H_4O_4$ [10, 32, 42] (Fig. 2).

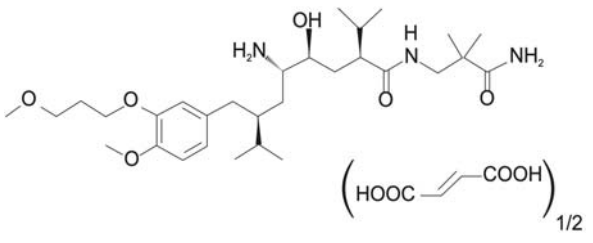

Fig. 2. Chemical structure of aliskiren hemifumarate

This small-molecule inhibitor that was identified by molecular modeling techniques has favorable physicochemical properties, such as remarkably good water solubility (log octanol/water partition coefficient [$\log P_{oct/water}$] = 2.45 at pH 7.4) and low lipophilicity [13, 42]. Aliskiren is also soluble in phoshate buffer and n-octanol [45]. It is resistant to rapid biodegradation by peptidases in the intestinal tract, circulation and liver. Because of its activity as a potent and specific *in vitro* inhibitor of human renin and good oral absorption in mammals, aliskiren has become a drug candidate for clinical development [42].

Mechanism of action

Aliskiren is a direct renin inhibitor. It has a high binding affinity for renin and this may be explained by a number of interactions with the enzyme's active site. Aliskiren appears to bind to both the hydrophobic S1/S3-binding pocket and to a large, distinct subpocket that extends from the S3-binding site towards the hydrophobic core of the enzyme [31, 42]. The enzyme specificity of aliskiren for human renin, human aspartic peptidase and HIV-1 peptidase was tested *in vitro*. Aliskiren is a potent competitive inhibitor of purified renin, but very poorly inhibits related aspartic peptidases. It is one of the most potent known renin inhibitors with high specificity for primate renin [41, 57]. Aliskiren is reported to have an IC_{50} (the half maximal inhibitory concentration) of 0.6 nmol/l for both purified human renin and human plasma renin [13].

In healthy human subjects, doses of between 40 and 640 mg of aliskiren exert a dose-dependent reduction in PRA, Ang I and Ang II levels. Aliskiren is superior in reducing PRA compared to ARBs. Aliskiren at a dose of 300 mg decreases PRA in hypertensive patients by approximately 50–80% [7, 45].

Aliskiren reduces PRA and plasma levels of Ang I and Ang II for 48 h [5, 41]. Urinary aldosterone was reduced at a dose of 80 mg or more, and sodium extraction was increased to 91% at a 640 mg dose [12]. Compared with valsartan, aliskiren more strongly decreases renin activity in the circulation and reduces urinary aldosterone excretion for a longer period [5, 37]. Published findings suggest that in lower doses, renin inhibitors and ARBs might exert synergistic effects on the RAS [41].

Pharmacokinetics properties

Conventional pharmacokinetic studies have been performed in rats, marmosets and humans after single and multiple oral doses of aliskiren. Aliskiren shows low bioavailability, but the exact mechanism of this property has not been elucidated. Oral bioavailability is 2.4% in rats, 16% in marmosets and about 2.5% in humans [12, 14, 41, 58]. After administration of a high fat meal, the mean AUC and C_{max} are decreased by 71% and 85%, respectively [45]. AUC and C_{max} values in animal species are lower than in humans [58].

Following oral administration, peak plasma concentrations of aliskiren are reached within one to three hours [5, 35, 45, 47, 48]. The plasma half-life of aliskiren in rats, marmosets and humans shows a slow terminal elimination at 23, 26 and 23–70 h, respectively [13, 14, 19, 41, 42, 45, 52, 55, 59]. The discrepancy in human terminal half-life is likely associated with differences in the duration of the postdose sampling period. The half-life of aliskiren was between 24 to 30 h in studies with a shorter postdose sampling period (48 h) [5, 35, 49], whereas studies with a longer postdose sampling period (72–96 h) reported values around 40 h [47, 48, 59]. Steady-state blood levels are reached in about seven to eight days with once-daily administration [12, 45]. The distribution volume of intravenously administered aliskiren is reported to be 135 l in normal volunteers, indicating extensive tissue uptake of the drug [13]. Approximately 47–51% of aliskiren is bound by plasma proteins in humans, independently of the concentration [12, 50, 52]. In marmosets, aliskiren is highly bound to plasma proteins by approximately 92% [18].

Aliskiren is slightly metabolized in humans (about 20%) and is approximately 50% metabolized in rodents. Based on *in vitro* studies, the major enzyme responsible for aliskiren metabolism appears to be CYP3A4 [12, 14, 35, 41, 47]. Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C19, 2D6, 2E1 and CYP3A) [45]. The major metabolic pathway for aliskiren metabolism is O-demethylation at the phenyl-proxy side chain or at the 3-methoxy-propoxy group, with further oxidation to the carboxylic acid derivative [52]. The metabolism of aliskiren observed in liver microsomes is qualitatively comparable in humans, marmosets and rats [18].

The main elimination route of aliskiren is *via* faeces in its unmetabolized form [41, 52]. About one-fourth of the absorbed dose also appears in the urine as unchanged compound [45].

The pharmacokinetic and pharmacodynamic differences of aliskiren between Caucasians and Japanese are minimal [45]. No clinically important pharmacokinetic differences were observed between patients with type 2 diabetes and healthy volunteers. The half-life of this drug was 40 and 44 h in healthy subjects and patients with diabetes, respectively [51, 59]. Aliskiren is well tolerated by all age groups, including the very elderly. It caused similar BP lowering effects in patients over 65 years of age and younger patients [49]. Aliskiren exposure following a single 300 mg dose was increased in elderly subjects compared with younger patients. AUC was increased by 57%, and the peak concentration was increased by 28% [12]. The pharmacokinetics have not been assessed in children [45], and gender differences in aliskiren pharmacokinetics have not been observed [59]. Special adjustment of drug administration in these groups of patients is not required [49]. In addition, there are no indications to change the recommended dose of aliskiren in patients with hepatic and renal insufficiency [45]. The peak concentration, AUC and half-life were only slightly greater in patients with hepatic dysfunction. Aliskiren exposure was also increased slightly in patients with renal function impairment, but these changes did not correlate with creatinine clearance [12].

Pharmacodynamics properties

Animal studies

Aliskiren was tested *in vivo* in marmosets, mice, spontaneously hypertensive rats and two group of transgenic rats: double transgenic rats (dTGR) that express human genes for renin and transgenic rats (TGR) that express mouse renin [5, 16, 39, 58].

The BP-lowering effects of aliskiren were investigated in sodium-platelet marmosets (oral dosing) and spontaneously hypertensive rats (dosing *via* subcutaneous minipumps). In sodium-platelet marmosets, single oral doses of aliskiren (1–30 mg/kg) lowered BP in a dose-dependent manner. At 3 mg/kg, peak ef-

fects were observed 1 h after administration (30 ± 4 mmHg), and the response persisted for more than 12 h. In hypertensive rats, aliskiren decreased BP in a dose-dependent manner (10–100 mg/kg per day). Aliskiren also intensified the antihypertensive effects of low doses of valsartan or benazeprilat (1–3 mg/kg) [58]. In marmosets and spontaneously hypertensive rats, aliskiren reduced blood pressure in a manner comparable with valsartan and benazepril, and intensified the antihypertensive effects of both drugs administrated together [12].

Because renin is only specific for its human substrate, renin inhibitors cannot be tested efficiently in conventional hypertensive rat models. Therefore, a dTGR model harbouring both human renin and angiotensinogen genes has been used [39]. In this model, aliskiren reduced BP and albuminuria and normalized serum creatinine. Aliskiren also reduced cardiac hypertrophy, decreased left ventricular wall thickness and improved survival in the treated rats compared to the untreated animals [39].

Investigations with TGRs show that minimal doses (0.3 mg/kg) of aliskiren provide target organ protection without significant effects on BP and that high doses (3 mg/kg) of the drug lower BP to a significant extent and protect completely against mortality. Albuminuria is reduced by half with low doses and is reduced completely by the high doses. The low doses significantly decrease cardiac hypertrophy compared to the high-doses [16]. Aliskiren administrated at a dose of 10 mg/kg effectively reduces albuminuria and glomerulosclerosis in diabetic animals [24]. The studies on Apo (–/–) mice with the 2-kidney, 1-clip renovascular hypertension model showed that aliskiren significantly prevented atherosclerosis progression. Compared with untreated animals, atherosclerotic plaques exhibited thinner fibrous caps, smaller lipid cores, decreased media degeneration and macrophage content and increased smooth muscle cell content [33]. This study provided evidence that direct renin inhibition mediates atherosclerotic plaque stabilization.

Human studies

Elevated PRA is independently associated with increased cardiovascular risk in hypertensive patients [1, 6, 50]. All agents that inhibit the RAS, including renin inhibitors, suppress the negative feedback loop that leads to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE-Is and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so the levels of Ang I and Ang II as well as PRA are all reduced [45].

The studies show that monotherapy with aliskiren has a linear dose relationship; as the dose increases, the reduction in blood pressure also increases [7, 23]. The reduction in blood pressure was measured in a double-blind, multicenter, randomized, eight-week trial that included 652 adult, hypertensive patients (systolic/diastolic) after daily doses of 150 mg, 300 mg and 600 mg aliskiren, 150 mg irbesartan or placebo. The results showed that three doses of aliskiren (150 mg, 300 mg and 600 mg) significantly reduced sitting diastolic blood pressure (DBP) by 9.3 ± 0.8, 11.8 ± 0.8 and 11.5 ± 0.8 mmHg, respectively, *versus* 6.3 ± 0.8 mmHg for the placebo group. The reduction in sitting systolic blood pressure (SBP) averaged between 11.4 ± 1.3, 15.8 ± 1.2 and 15.7 ± 1.2 mmHg, respectively, *versus* 5.3 ± 1.2 mmHg for the placebo group. The two highest aliskiren doses lowered DBP more significantly than irbesartan. Compared with 150 mg aliskiren, 150 mg irbesartan reduced the DBP by 8.9 ± 0.7 mmHg and reduced the SBP by 12.5 ± 0.8 mmHg). However the difference between the 300 mg and 600 mg doses of aliskiren was minimal [12, 23, 41, 54].

Administration of aliskiren in combination with ARBs or hydrochlorothiazyde at low doses gives the same DBP- and SBP-lowering effects as higher doses of individual monotherapy [7]. Studies including combination therapy have shown greater effects on treatment and better tolerance than when a single drug is used [50].

There is some evidence indicating that aliskiren may affect hemostasis. In *in vitro* studies with whole human blood, the therapeutic concentration of 0.5 μg/ml of aliskiren did not affect hemostatic biomarkers, except for a significant increase in AT-III. Higher aliskiren doses were associated with more profound biomarker changes. These changes are not likely to be clinically relevant since they show diverging (both mild antiplatelet and platelet-activating) trends and consider the 2- to 4-fold safety margin [40]. Thus, the antithrombotic properties of aliskiren should be further explored in clinical studies.

Preliminary studies have shown that short-term administration of aliskiren has beneficial antialbuminu-

ric effects in diabetic patients with chronic nephropathy and favourable neurohormonal effects in patients with chronic heart failure [4]. Aliskiren reduces the 24 h SBP, and this effect was associated with a reduction in albuminuria in type 2 diabetic patients [38].

Aliskiren may have lower hypertensive effects compared with ACE-Is because it does not block the degradation of bradykinin [18]. Aliskiren also does not block enzymes like cathepsin D or tonin that are located in the vascular wall and cause an increase in Ang I levels due to angiotensinogen degradation [18, 41].

Aliskiren at a concentration of 10 μM exhibited a slight effect on neurotransmitter receptors, including α_1-, α_2- and β-adrenoreceptors, 5-HT, histamine, opiate, benzodiazepine, adenosine, muscarinic cholinergic and NMDA glutamate receptors [57].

Drug interactions

Since aliskiren does not affect cytochrome P450 enzyme activities, is minimally metabolized by CYP3A4 and is not extensively protein bound, there is a low potential for drug interactions [12, 14, 35, 50]. However, clinical trials showed an interaction of aliskiren with some specific medications. Co-administration of aliskiren with irbesartan reduces aliskiren's C_{max} by up to 50% after multiple doses. Co-administration with furosemide reduces furosemide's AUC by 30% and its C_{max} is reduced by 50%. The therapeutic effects of furosemide may be reduced upon initiation of aliskiren therapy. Ketoconazole at a dose of 200 mg twice daily is associated with an 80% increase in aliskiren plasma levels and may be a reason for increased adverse reactions. Co-administration of aliskiren does not significantly affect the pharmacokinetics of valsartan, ramipril, amlodypine, atenolol, hydrochlorotiazide, lovastatin and digoxin [45, 50].

Adverse events, contraindications and warnings for aliskiren

The clinical trials do not report any major adverse effects of aliskiren [45]. It is generally well tolerated by all patients. The most common adverse events of aliskiren are diarrhea, headache, nasopharyngitis, dizziness, fatigue, back pain, gastrointestinal disorders, rash and renal stones [12, 14, 37, 45]. Because aliskiren directly inhibits the RAS, adverse events such as coughing and angioedema may also occur [12, 14, 45]. Cases of edema involving the face, lips, tongue, hands and whole body have been reported [14, 45]. These adverse events occur in more than 1% of patients treated with aliskiren, but also occur at a similar or greater rate in patients receiving placebo [45].

Aliskiren had no clinically important effects on total cholesterol, HDL, fasting triglycerides or fasting glucose. Laboratory abnormalities that may occur in some patients include a minor increase in blood urea nitrogen (BUN) and serum creatinine, small reductions in hemoglobin and hematocrit, an increase in serum potassium greater than 5.5 mEq/l, elevated uric acid levels and renal stones. There is no effect of aliskiren on the QT interval [45]. Aliskiren has the same contraindications as ACE-Is and ARBs, including hypersensitivity reactions to aliskiren, pregnancy and bilateral renal-artery stenoses [45]. Aliskiren belongs to Pregnancy Category C for first trimester and Pregnancy Category D for second and third trimester exposure. All direct RAS inhibitors can cause fetal injury or death when used during the second and third trimesters. Animal studies do not show evidence of teratogenicity action in early pregnancy [12]. Aliskiren therapy should be promptly discontinued when pregnancy is detected. Angioedema of the face, extremities, larynx and tongue are indications to discontinue therapy. Hyperkalemia may occur during monotherapy with aliskiren. Increased potassium in the serum is more frequently observed with the use of aliskiren in combination with ACE inhibitors, mainly in patients with diabetes. It is for this reason that patients with diabetes must be routinely monitored for electrolytes and renal function during combination therapy [45]. Hypotension may occur in patients who are volume- or salt-depleted because of diuretic therapy. Volume- or salt-depletion should be corrected before patients receive aliskiren alone or in combination with other antihypertensive agents [12].

Conclusion

Cardiovascular diseases are the most common causes of death worldwide from disorders dependent on hypertension [31]. A multitude of large clinical trials have shown that blockade of the RAS protects against cardiovascular morbidity and mortality. On the other hand, RAS blockade cannot be achieved with ACE

inhibitors or ARBs because of counter regulatory mechanisms [31]. Thus, a new class of agents that effectively and specifically inhibits the RAS with a novel mechanism of action, with few side effects and with a long half-life to allow once-daily dosing is needed as an alternative to the current treatment of hypertension, diabetic nephropathy, atherosclerosis, ischemic heart disease and heart failure [42].

Aliskiren treatment is likely to offer more optimal RAS blokade than ACE-Is and ARBs. It may have a pharmacokinetic advantage over other RAS blockers because it may already bind to renin on its way to tissue, whereas the other blockers must first penetrate into tissues in order to exert their effects. Because of its ability to bind to circulating renin, the renin inhibitor-renin complex will eventually replace "free" renin at tissue sites, thus gradually preventing tissue angiotensin generation [15, 20].

Recent pharmacological studies indicate that aliskiren might also be useful as a substitute therapy in patients intolerant of ACE inhibitors and ARBs, for the treatment of disorders in which Ang II contributes to the pathogenesis and for secondary prevention of cardiovascular disease [14, 41]. It was found that renin inhibitors are more effective in preventing the production of Ang I and Ang II, which usually increases in ACE-independent pathways when ACE-Is or ARBs are used [7].

Clinical studies [44] indicate possible cardioprotective and renoprotective effects that are similar to other inhibitors of the RAS cascade, but further studies are needed in humans. The current literature does not identify any published study that was performed to evaluate the effect of aliskiren in long-term cardiovascular outcomes. Nevertheless, present studies support the use of aliskiren alone or in combination with other antihypertensive drugs in patients with mild to moderate hypertension [14]. Moreover, renin inhibitors offer additional safety for patients with cardiovascular disease and renal dysfunction because they are preferentially eliminated *via* the liver without much interference from other drugs [25, 32]. Clinical trials that are currently underway will assess the effects of aliskiren combined with an angiotensin receptor blocker on intermediate markers of end organ damage [22]. The results of these studies will determine the place of aliskiren in the treatment of hypertension and related cardiovascular diseases. Thus, aliskiren possesses the potential to became the first orally active renin inhibitor that provides a true alternative to ACE-Is and ARBs in the therapy of hypertension and other cardiovascular and renal diseases.

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