Introduction

Activation of the renin-angiotensin (Ang)-aldosterone system (RAAS) plays an important role in the development of hypertension and end-organ damage. RAAS suppression is, therefore, an important goal of antihypertensive therapy, and RAAS inhibitors, such as Ang-converting enzyme (ACE) inhibitors and Ang receptor blockers (ARBs), have proven to be highly successful treatments for hypertension, heart failure and related cardiovascular disorders.[1,2] Although renin was discovered more than a century ago,[2,3] the significance of this system in the pathogenesis of cardiovascular and renal disorders has gained wide acceptance only during the past 3 decades, in large part because of the availability of specific pharmacologic agents that can block the system.[4] The concept of blocking the RAAS at its origin by inhibiting renin has existed for at least 50 years. The first synthetic renin inhibitor was pepstatin, which was followed by first-generation agents that were active but required parenteral administration. Oral agents that were subsequently developed, such as enalkiren, remikiren, and zankiren, had limited clinical use because they demonstrated poor bioavailability (<2%), short half-lives and weak antihypertensive activity.[4]

Aliskiren

Intensive efforts have been made to discover therapeutic, nonpeptide and orally effective hypertensive drugs. Drugs that inhibit renin have been available for many years but have been limited by low potency, bioavailability and duration of action. However, a new class of nonpeptide, low molecular weight, orally active inhibitors has recently been developed.[5] One drug that emerged from this effort is aliskiren, a direct human-renin inhibitor that blocks the conversion of angiotensinogen to Ang I.[6]

Aliskiren [Figure 1], a 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-methoxypropoxy]-phenyl)-octanamide, is the only orally active renin inhibitor that has successfully progressed to phase III trials and extensive clinical use.[7,8] The US Food and Drug Administration’s approval in March 2007 of aliskiren, the first commercially available direct renin inhibitor, for the treatment of hypertension, met with great enthusiasm. Despite the notable absence of human clinical data for this agent, many clinicians have touted aliskiren as the ideal agent to achieve additional suppression of the RAAS as a means to reduce the morbidity and mortality of chronic diseases of the cardiovascular and renal systems.[9]
Chemical properties

Aliskiren is a low-molecular-weight hydrophilic nonpeptide, which exerts a potent and specific competitive inhibition on renin in primates. The adverse effects of aliskiren are uncertain due to its 10,000-fold higher affinity for renin than for other aspartic peptidases. Because renin is a water-soluble protein that can be studied with crystallographic analysis, the opportunity arose to examine systematically the crystals of renin bond to renin inhibitors. Aliskiren was developed as a result of successive steps of molecular modeling on earlier renin inhibitors. These steps were aimed to increase the affinity and duration of action of drug.[8,9] Aliskiren is a transition-state mimetic, with favorable physicochemical properties including high aqueous solubility (>350 mg/ml at pH 7.4) and high hydrophilicity (log P oct/water = 2.45, pH 7.4). These properties are important prerequisites for improved oral bioavailability.[9]

Mechanism of aliskiren

Renin is an aspartic protease that is synthesized as prorenin, a proenzyme that is transformed into renin by cleavage of a 43-amino-acid segment from the N-terminal end. The binding of renin to its receptor with a single transmembrane domain has multiple and far-reaching consequences. Receptor binding induces a 4-fold increase in the catalytic conversion of angiotensinogen to Ang I, suggesting that the cell surface is an important site of Ang generation. Once bound, renin triggers a series of intracellular events that culminate in activation of the mitogen-activated protein kinases ERK1 (p44) and ERK2 (p42), which are involved in cell hypertrophy and proliferation.[4] Aliskiren 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 sub pocket that extends from the S3-binding site toward the hydrophobic core of the enzyme.[6] 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.[6] Aliskiren is reported to have an IC50 (the half maximal inhibitory concentration) of 0.6 nmol/L for both purified human renin and human plasma renin, this compares favorably with the earlier renin inhibitor compounds. Thus, the IC50 for enalikiren is 14 nmol/L, and remikiren and zamikiren are 0.8 and 1.1 nmol/L, respectively.[10,11] Aliskiren into the clinical arena has revived interest in renin and its precursor prorenin. Receptor activation by renin/prorenin may develop glomerulosclerosis and hypertension in the absence of changes in renin or Ang. Aliskiren prevents Ang I generation by receptor-bound prorenin but it will not be effective in receptor signaling. Published findings suggest that in lower doses, renin inhibitors and ARBs might exert synergistic effects on the RAAS.[12,13]

Pharmacokinetics character of aliskiren

The pharmacokinetics of aliskiren deviates from dose linearity, with an overproportional increase in area under the curve (AUC) and Cmax with respect to the administered dose. The mean terminal half-life is approximately 40 hours after multiple administrations of a single dose, and repeated once-daily administration leads to drug accumulation. The mean absolute bioavailability is 2.6%; administration with a high-fat meal reduces AUC and Cmax values by 71% and 85%, respectively, of those in the fasting state, so patients should be advised to take aliskiren in the same manner each day with respect to meal times. Peak plasma concentrations are reached 1 to 2 hours after dosing, and steady state is reached after five to eight days of once-daily administration.[4,6,11,14] 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. The plasma half-life of aliskiren in rats, marmosets and humans after a single oral dose of 10 mg/kg was between 24 to 30 h in studies with a shorter post-dose sampling period (48 h), whereas studies with a longer post-dose sampling period (72-96 h) reported values around 40 h. Steady-state blood levels are reached in about seven to eight days with once-daily administration. The distribution volume of intravenously administered aliskiren is reported to be 135 L, in normal volunteers, indicating extensive tissue uptake of the drug. Aliskiren binds only moderately to plasma proteins, with the binding concentrations being independent in the range of 10-500 ng/ml.[14] Approximately 47-51% of aliskiren is bound by plasma proteins in humans, independent of the concentration. In marmosets, aliskiren is highly bound to plasma proteins by approximately 92%.[9] Aliskiren is slightly metabolized in humans (about 20%) and is approximately 50% metabolized in rodents. The major metabolic pathway for aliskiren metabolism is O-demethylation at the phenyl-proxy side chain or at the 3-methoxyprooxy group, with further oxidation to the carboxylic acid derivative. The metabolism of aliskiren observed in liver microsomes is qualitatively comparable in humans, marmosets and rats.[6,12] The main pathway of elimination for aliskiren is via biliary excretion as unmetabolized drug. Less than 1% of an orally administered dose is excreted in urine.[10] Aliskiren is not metabolized by, and does not induce or inhibit cytochrome P450 enzymes and shows no clinically relevant pharmacokinetic interactions with warfarin, lovastatin, atenolol, celecoxib, cetimide, amiodipine, valsartan, hydrochlorothiazide (HCTZ) or ramipril. Coadministration of aliskiren with furosemide, reduced the AUC of furosemide by 28% and Cmax by 49%, but the clinical significance of this remains uncertain. The pharmacokinetics of aliskiren remains unaffected by ethnicity, age, gender, hepatic impairment, renal impairment and diabetes.[4,11] Aliskiren pharmacokinetics has been studied in marmosets. After a single oral dose of 10 mg/kg, peak plasma concentrations were reached in 1-2 h. The calculated bioavailability was 16.3% and mean half-life 2.3 h.[15] Aliskiren accumulates following multiple once-daily administrations as indicated by the accumulation ratios of 1.4-3.9, with the accumulation being more pronounced at higher doses. Study in healthy volunteers showed that the plasma concentration increased dose-dependently after oral aliskiren in doses of 40-640 mg/day, with peak plasma concentrations reached in 3-6 h. The mean plasma half-life was 23.7 h.[11,14]

Therapeutic potential of aliskiren

The therapeutic potential of aliskiren and other renin inhibitors are like monotherapy for hypertension, component of combination therapy for hypertension, with a diuretic, calcium channel blocker (CCB), ACE inhibitors and/or an ARBs, alternative to ACE inhibitors or ARBs in the management of hypertension and the prevention of organ damage, alternative to ACE inhibitors in patients with diabetic
nephropathy or cardiovascular disease, use in patients with diabetic nephropathy or in African American hypertensive patients.[26]

Evidence from research

The antihypertensive efficacy of aliskiren monotherapy has been compared with that of other RAAS antagonists and combinations of aliskiren with these agents. These studies have shown that aliskiren is equally effective as ARBs and may be slightly more effective than ACE inhibitors in lowering blood pressure. Aliskiren blocks the entire RAAS process, this results in greatly increased plasma renin concentration due to removal of Ang II-mediated feedback inhibition of renin release, which has raised concerns about whether direct renin inhibition improve anything to inhibition of downstream components of the RAAS cascade.[18]

Animal studies

The species specificity of renin is such that human-renin inhibitors can be tested practically only in the marmoset and the guinea pig. To get around this problem, Ganten, Mullins, Murakami and others generated two transgenic rat strains. One strain harbors the human-renin gene with its own promoter; the second harbors the human angiotensinogen gene with an albumin promoter. These strains are generating more amount of Ang II in the circulation and other tissues through activation of two transgenes.[19,20]

In first study, 6-week-old dTGR were matched by albuminuria (2 mg/dl) and divided into five groups. Untreated dTGR were compared with aliskiren-treated (3 and 0.3 mg/kg per day) and valsartan-treated (10 and 1 mg/kg per day) rats. The result of this study concluded that in dTGR, equieffective antihypertensive doses of valsartan or aliskiren attenuates end-organ damage. Thus, renin inhibition compares favorably to ARB in reversing organ damage in dTGR. In the second study, C-reactive protein (CRP) elevation; macrophages; T cells; TNF-α; complement C1q, C3, C3c, and C5b-9 expression all preceded albuminuria in untreated dTGR. Aliskiren and the ARB losartan reduced albuminuria; TNF-α; CRP; and complement C1q, C3, C3c, and C5b-9 expression to control levels. Blockade of the RAAS either by inhibiting renin directly or by blocking the AT1 receptor ameliorates target organ damage in this model.[20]

The blood pressure (BP)-lowering effects of aliskiren were investigated in sodium-platelet marmosets and spontaneously hypertensive rats. 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 effects 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). Because renin is only specific for its human substrate, renin inhibitors cannot be tested efficiently in conventional hypertensive rat models.[6,17,21,22] Aliskiren also reduced cardiac hypertrophy, decreased left ventricular wall thickness and improved survival in the treated rats compared to the untreated animals.[8] 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 with the high doses. Aliskiren administered at a dose of 10 mg/kg effectively reduces albuminuria and glomerulosclerosis in diabetic animals.[24] The studies on 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.[25] This study provided evidence that direct renin inhibition mediates atherosclerotic plaque stabilization.

Human studies

The studies show that monotherapy with aliskiren has a linear dose relationship; as the dose increases, the reduction in blood pressure also increases.[25] 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, 300 and 600 mg aliskiren, as well as 150 mg of irbesartan or placebo. The results showed that three doses of aliskiren significantly reduced sitting diastolic blood pressure (DBP) by 9.3 ± 0.81.18 ± 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 ± 1.31, 5.8 ± 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.[26] Administration of aliskiren in combination with ARBs or hydrochlorothiazide at low doses yields the same DBP- and SBP-lowering effects as higher doses of individual monotherapy. 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.[27] 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 antialbuminuric effects in diabetic patients with chronic nephropathy and favorable neurohormonal effects in patients with chronic heart failure.[28] Aliskiren reduces the 24-h SBP, and this effect was associated with a reduction in albuminuria in type-2 diabetic patients.[29] Aliskiren at a concentration of 10 μg exhibited a slight effect on neurotransmitter receptors, including α1-α2 and β-adrenoreceptors, 5-HT, histamine, opiate, benzodiazepine, adenosine, muscarinic cholinergic and NMDA glutamate receptors.[6,8] In a 4-week study, aliskiren 37.5, 75, 150 or 300 mg once daily was compared with losartan 100 mg once a day. Dose-dependent reductions from baseline in daytime ambulatory SBP (ASBP) were obtained with all doses of aliskiren.[30]

A systematic review reported that aliskiren caused a dose-related SBP/DBP lowering effect compared with placebo. This review found weak evidence that during 4- to 8-week use, aliskiren did not increase withdrawals due to adverse effects as compared with placebo. It has been concluded that aliskiren has a dose-related blood-pressure-lowering effect better than placebo and the magnitude of effect is similar to that determined for ACE inhibitors and ARBs.[31,32] In another study, it was reported that aliskiren was effective in promoting left ventricular (LV) mass regression in combination with losartan. These findings suggest that aliskiren was effective as an ARB in attenuating this measure of myocardial end-organ damage in hypertensive patients with LV hypertrophy.[33] Aliskiren treatment, both as monotherapy
and with optional addition of amlodipine, provided significantly greater BP reductions than the respective hydrochlorothiazide (HCT) regimens. Nickenig et al. evaluate the efficacy, safety and tolerability of a single-pill combination of the direct renin inhibitor aliskiren and HCT in patients with hypertension and an inadequate BP response to aliskiren monotherapy. Aliskiren/HCT single-pill combinations provide clinically significant additional BP reductions and improved BP control rates over aliskiren alone in patients who are nonresponsive to monotherapy with aliskiren 300 mg. Combination therapy with aliskiren and valsartan provided significantly greater BP reductions over aliskiren or valsartan monotherapy and is an appropriate option for management of BP in patients with stage 2 hypertension. Once-daily treatment with aliskiren 75,150 or 300 mg significantly lowered BP in Japanese patients with essential hypertension. This reduction was evident after only 2 weeks of treatment and was long lasting and dose-dependent. In addition, aliskiren demonstrated a safety profile similar to that of placebo, an important consideration in the largely asymptomatic condition of hypertension.

Recently, research found that aliskiren accumulates in renin granules, thus allowing long-lasting renin-Ang system blockade beyond the half-life of this drug. Aliskiren may be an appropriate substitute for beta-blocker treatment in patients with uncomplicated hypertension. Aliskiren also combined with atenolol to improve BP reductions and BP control with maintained tolerability compared with atenolol alone. A recent study reported that Aliskiren improved LV dysfunction after MI in a dose that did not affect blood pressure. Diabetes activates the cardiac intracellular RAAS, which increases oxidative stress and cardiac fibrosis. Aliskiren has a marked effect than ARBs and ACE inhibitors on these diabetes complications and may be clinically more efficacious. Aliskiren might have renoprotective effects that are independent of its blood-pressure-lowering effect in patients with hypertension, type 2 diabetes and nephropathy and are receiving the recommended renoprotective treatment. In placebo-controlled studies in hypertensive subjects, aliskiren produced a dose-related BP reduction at doses between 75 and 300 mg/day. There was little or no effect below 75 mg, and no additional BP-lowering effect above 300 mg. Most of the effect on BP occurred after 2 weeks, and a near maximal effect was noted after 4 weeks.

In a double-blind study, 1797 hypertensive patients were randomly assigned to receive aliskiren 150 mg/day alone, valsartan 160 mg/day alone, a combination of aliskiren and valsartan, or placebo for 4 weeks. Then the dose in each arm was doubled to the maximum recommended dose for another 4 weeks. At 8 weeks, the combination of aliskiren and valsartan lowered DBP from baseline by 12.2 mm Hg, more than monotherapy with aliskiren (-9.0 mmHg), valsartan (-9.7 mmHg) or placebo (-4.1 mmHg). This study concludes that the combination of aliskiren and valsartan provides greater reductions in BP than monotherapy with either agent, with a tolerability profile not dissimilar from that of monotherapies.

The clinical results obtained thus far on BP with the combination of aliskiren and valsartan and aliskiren and ramipril are in agreement with this pharmacologic concept, which attributes to the reactive rise in renin release and synthesis associated with all RAAS inhibitors a self-limiting role to their efficacy, as a result of the reappearance of Ang I and/or Ang II, in addition to Ang II producing enzymes other than ACE, such as chymase. The Aliskiren Observation of Heart Failure Treatment trial (ALOFT) was a randomized between-patient comparison of aliskiren 150 mg/day and placebo in patients with heart failure. The primary endpoint consisted in the changes in the plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP). Plasma levels of NT-proBNP increased by approximately 762 pg/mL with placebo and decreased by 244 pg/mL with aliskiren. Thus, the ALOFT study demonstrated that the addition of aliskiren to an optimal therapy in patients with heart failure has favorable neurohumoral effects and is very well tolerated.

The Aliskiren in the Evaluation of Proteinuria In Diabetes trial (AVOID) was a randomized between-patient comparison between aliskiren and placebo in addition to losartan in diabetic patients. Treatment of aliskiren reduced the mean urinary albumin-to-creatinine ratio by 20%. A reduction by 50% or more was noted in 24.7% of patients under aliskiren and 12.5% of patients under placebo. BP was 2/1 mmHg lower with aliskiren than with placebo and tolerability was the same in the two groups. The authors concluded that the renoprotective effects of aliskiren are independent of its antihypertensive effect in patients with hypertension, type 2 diabetes, and nephropathy who are being treated with an ARB.

Another trial ALTITUDE, an international, randomized, double-blind, placebo-controlled, parallel-group study, which includes three categories of high-risk patients with type 2 diabetes will determine whether dual RAAS blockade with the direct renin inhibitor aliskiren in combination with an ACE inhibitor or ARB will reduce major morbidity and mortality in a broad range of high-risk patients with type 2 diabetes. The dual therapy in the AVOID trial achieved the goal of reducing albuminuria; however, it is not known what the result would have been had the patients taken the medications for a longer period of time. Although adverse events were not marked, the participating patients were chosen carefully; patients with glomerular filtration rates of less than 30 ml/min or potassium levels greater than 5.1 mmol/L were excluded. Whether dual therapy to block the RAAS with aliskiren and another agent or agents would provide sustained renoprotection remains to be demonstrated.

Another study demonstrates that the aliskiren provides additional, significant BP reductions when administered in combination with the highest commonly used dosage of ramipril (10 mg) in patients with hypertension and diabetes. Aliskiren treatment was well tolerated and had no adverse effects on glycemic control when administered alone or in combination with ramipril. Combination with aliskiren may therefore represent a useful treatment option for patients who do not achieve BP control following first-line treatment with ramipril 10 mg.

Adverse events and contraindications

Aliskiren has been shown to be well tolerated in healthy subjects and in patients with hypertension, when given as single and multiple oral doses. The clinical trials do not report any major adverse effects of aliskiren. Aliskiren-based therapy was well tolerated and produced sustained blood pressure reductions in patients with hypertension during 6 months, greater than those with ramipril-based therapy. The incidence of adverse events with aliskiren and the number of study discontinuations as a result of adverse events during aliskiren treatment have been relatively low and were similar to results obtained in patients treated with placebo. The most common adverse events reported were hypotension, hyperkalemia, nasopharyngitis, headache, laryngopharyngitis fatigue, headache, dizziness, diarrhea, back pain, gastrointestinal disorders, rashes and renal stones. Aliskiren directly inhibits the RAAS and does not interfere with metabolism of bradykinin and substance P; therefore, side effects such as coughing and angioedema may not occur. But in some studies edema involving the face, lips, tongue, hands and whole body have been reported. 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. Aliksiren 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. In another study reported that the most frequent abnormality was elevated alanine aminotransferase, but its incidence was similar across the active treatment and placebo groups.

Aliksiren has the same contraindications as ACE inhibitors and ARBs, including hypersensitivity reactions to aliskiren, pregnancy and bilateral renal-artery stenoses. Aliksiren belongs to Pregnancy Category C for first trimester and Pregnancy Category D for second- and third-trimester exposures. All direct RAAS 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. Aliksiren therapy should be promptly discontinued when pregnancy is detected. Although aliskiren appears to be safe, additional data would be needed to assess the effects of aliskiren on renal function and biochemistry, especially serum potassium levels in patients with renal impairment, heart failure and diabetes mellitus.

**Future directions**

On the basis of the above considerations, hypertension and heart failure are the two conditions in which the effects aliskiren can be exploited the most. A robust clinical development program is ongoing to evaluate the renoprotective and cardioprotective effects of aliskiren in which surrogate markers and major clinical outcomes will be analyzed as primary endpoints. However, the efficacy of aliskiren in reducing major clinical events requires to be verified in large clinical trials. One of these trials, ALTITUDE, is ongoing. ALTITUDE is carried out in about 8600 patients with type 2 diabetes associated with persistent macroalbuminuria, persistent microalbuminuria, or a history of cardiovascular disease with reduced renal function. This is an event-driven study that will be concluded when 1628 patients will experience the primary end-point (composite of cardiovascular and renal events). Enrollment began in October 2007 and the study is expected to finish in 2012. Two other studies are being planned. The ATMOSPHERE (Aliksiren Trial to Mediate Outcome Prevention in Heart FailuRE) will address patients with heart failure similar to those included in ALOFT. Cardiovascular death and rehospitalization for heart failure will be the components of the primary end-point. The APOLLO (Aliksiren in Prevention Of Later Life Outcomes) will address elderly subjects with normal BP, no overt cardiovascular disease, and a high cardiovascular-risk profile, in order to test the efficacy of the drug in reducing the risk of major cardiovascular end-points. Furthermore, because aliskiren inhibits the initial and rate-limiting step of the RAAS, it might become a reasonable therapeutic choice also in a broad number of clinical conditions, sharing an increased cardiovascular risk, in which the inhibition of the RAAS has been shown to be beneficial. These conditions include stable coronary artery disease, cerebrovascular disease, diabetes and peripheral arterial disease. A recent trial suggests that the ARB telmisartan is as good as (“non inferior” to) ramipril in these patients, although the tolerability profile of telmisartan was superior to that of ramipril and the combination of the two drugs was not superior to the single ones. Aliksiren has the potential to be useful in this wide spectrum of conditions. This would require the demonstration of non-inferiority versus other drugs inhibiting the RAAS in properly designed clinical trials. 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 become the first orally active renin inhibitor that provides a true alternative to ACE inhibitors and ARBs in the therapy of hypertension and other cardiovascular and renal diseases.

**References**


