

Current and Emerging Pharmacotherapies for the Management of Hypertension, Focus on Aliskiren

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Abstract: Despite the availability of a wide range of antihypertensive medications, about 45.5% of treated patients in the US fail to achieve a blood pressure control target of <140/90 mmHg; for this reason, in the last two years, some emerging treatments have become available such as aliskiren, a renin inhibitor. A lot of trials showed that aliskiren proved to be safe and effective in monotherapy in reducing blood pressure, with a blood pressure-lowering effect similar, if not superior, to that of other first-line antihypertensive agents, and to be safe also in combination with various other antihypertensive medications. However, recently the European Medicines Agency decided to early terminate the ALTITUDE study, due to more cases of stroke, renal complications, hyperkalemia and hypotension in patients who received aliskiren compared with patients who received a placebo. Given these discrepancies, we conducted a review about the emerging pharmacotherapies for the management of hypertension focusing our attention on the latest class of antihypertensive drugs become available, such as renin inhibitor aliskiren. After an accurate review of all the most important studies conducted, we can conclude that aliskiren proved to be safe and well tolerated and to have some protective effects on heart and kidney, not observed with the other drugs. However, until further data will not be available, aliskiren should not be prescribed in combination with ACE inhibitors or ARBs. In combination with other anti-hypertensive drugs, instead, aliskiren should be considered for the treatment of hypertension in not well controlled hypertensive patients.

Keywords: aliskiren, anti-hypertensive drugs, hypertension, renin-angiotensin-aldosterone system, renin inhibitor

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Introduction

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) latest guidelines^{1,2} define hypertension as systolic (SBP) and diastolic (DBP) blood pressure values higher than some pre-defined cut-off values listed in Table 1.

The threshold for hypertension, and the need for drug treatment, should be considered as flexible based on the level and profile of total cardiovascular risk. When a patient's SBP and DBP fall into different categories, the higher category should apply for the quantification of total cardiovascular risk, decision about drug treatment and estimation of treatment efficacy. Furthermore isolated SBP should be graded (grades 1, 2 and 3) according to the same SBP values, indicated for systolic-diastolic hypertension. However, the association with a low DBP (eg, 60–70 mmHg) should be regarded as an additional risk. The latest ESH/ESC guidelines affirms that thiazide diuretics (as well as chlorthalidone and indapamide), β -blockers, calcium antagonists, ACE inhibitors (ACE-I) and angiotensin receptor antagonists (ARBs) can adequately lower blood pressure and significantly and importantly reduce cardiovascular outcomes.^{1,2} However, despite the availability of the wide range of antihypertensive medications, about 45.5% of treated patients in the US fail to achieve a blood pressure control target of <140/90 mmHg;³ for this reason, in the last two years, some emerging treatments have become available such as aliskiren, a renin inhibitor. A lot of trials showed that aliskiren proved to be safe and effective in monotherapy in reducing blood pressure, with a blood pressure-lowering effect similar, if not superior,

to that of other first-line antihypertensive agents, and to be safe also in combination with various other antihypertensive medications.⁴ However, recently some concerning data emerged: in fact, on 19 December 2011, Novartis, the company producing aliskiren, decided to early terminate the ALTITUDE study,⁵ aimed to determine whether aliskiren 300 mg once daily, reduces cardiovascular and renal morbidity and mortality compared with placebo when added to conventional treatment (including ACE inhibitors or Ang II receptor antagonists).

Termination of this placebo-controlled phase III trial was recommended by the independent Data Monitoring Committee overseeing the study, because the results showed that there was no benefit with aliskiren and that there were more cases of stroke, renal complications, hyperkalemia and hypotension in patients who received aliskiren compared with patients who received placebo. The Committee has asked the company to provide additional analyses to allow the Committee for Medicinal Products for Human Use to assess the impact of the results of the ALTITUDE trial on the overall benefit-risk profile of aliskiren-containing medicines and to determine the need for regulatory action.⁶

Given the discrepancies existing, we decided to conduct a review about the emerging pharmacotherapies for the management of hypertension focusing our attention on the renin inhibitor aliskiren.

Material and Methods

A systematic search strategy was developed to identify randomised controlled trials in both MEDLINE (National Library of Medicine, Bethesda, MD; 2001 through November 2011) and the Cochrane Register of Controlled Trials (The Cochrane Collaboration, Oxford, United Kingdom). The terms “hypertension treatment”, “renin inhibitors”, “aliskiren” were incorporated into an electronic search strategy that included the Dickersin filter for randomised controlled trials.⁷ The bibliographies of all identified randomised trials and review articles were reviewed to look for additional studies of interest. We reviewed all of the citations retrieved from the electronic search to identify potentially relevant articles for this review. We subsequently reviewed the potential trials to determine their eligibility. To qualify for inclusion, clinical trials were required to meet a series of predetermined criteria regarding study design, study population, interventions

Table 1. Definitions and classification of blood pressure levels.

| Category | SBP (mmHg) | | DBP (mmHg) |
|--------------------------------|------------|--------|------------|
| Optimal | <120 | and | <80 |
| Normal | 120–129 | and/or | 80–84 |
| High normal | 130–139 | and/or | 85–89 |
| Grade 1 hypertension | 140–159 | and/or | 90–99 |
| Grade 2 hypertension | 160–179 | and/or | 100–109 |
| Grade 3 hypertension | \geq 180 | and/or | \geq 110 |
| Isolated systolic hypertension | \geq 140 | and | <90 |



evaluated, and outcome measured. Studies were required to be randomised clinical trials comparing aliskiren at any dosage with placebo or any other anti-hypertensive drug in hypertensive patients. Eligible trials had to present results on blood pressure control or adverse events. Two different outcomes related to blood pressure control were of primary interest: (1) the proportion of individuals within each treatment group achieving clinically significant BP reduction, and (2) the mean amount decrease (in mmHg) of SBP, and DBP within each treatment group. The following data were abstracted onto standardized case report forms: authors; year of publication; country of study; source of funding; study goal; means of randomisation and blinding; duration of treatment; treatment characteristics; sex; quantity of and reasons for study withdrawal; HbA_{1c} and age characteristics of the treatment and control groups; outcomes; and adverse event data. A validated, 3-item scale was used to evaluate the overall reporting quality of the trials selected for inclusion in the present review. This scale provided scoring for randomisation (0–2 points), double-blinding (0–2 points), and account for withdrawals (1 point). Scores ranged between 0 and 5, and scores 3 indicated a study of high quality,⁸ and study selection was restricted to randomised controlled trials to ensure the inclusion of only high quality evidence.

Current Therapies

Diuretics

Diuretics act by diminishing sodium reabsorption at different sites in the nephron, thereby increasing urinary sodium and water losses. The ability to induce negative fluid balance has made diuretics useful in the treatment of a variety of conditions, particularly edematous states and hypertension. In particular thiazide-type diuretics act in the distal tubule and connecting segment (and perhaps the early cortical collecting tubule).^{9,10} Electrolyte abnormalities, including hypokalemia, hypomagnesemia, hyponatremia, and hypercalemia may occur. Elevated blood glucose levels have also been reported. Hyperuricemia is possible, therefore caution in patients who suffer from gout is recommended. Arrhythmias may be precipitated secondary to electrolyte abnormalities. Hyperlipidemia (increase in total cholesterol, triglycerides, and LDL cholesterol) has occurred. Dermatologic side effects include photosensitivity and an SLE-like syndrome.

Calcium channel blockers

Calcium channel blockers are peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. They work by blocking voltage-gated calcium channels in cardiac muscle and blood vessels; this decreases intracellular calcium leading to a reduction in muscle contraction. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in arterial diameter with vasodilation. Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output with a final blood pressure drop. Calcium channel blockers are especially effective against large vessel stiffness, one of the common causes of elevated SBP in elderly patients. First-generation dihydropyridine (nifedipine, isradipine, felodipine, nitrendipine and nicardipine) concentrations rapidly increase in plasma, with a consequent rapid onset of the vasodilator/antihypertensive effect. They have been demonstrated to produce reflex activation of the sympathetic nervous system,^{11,12} which may be disadvantageous in patients with cardiologic problems,¹³ as proved by the disappointing results recorded in some observational studies.¹⁴ On the other hand, second-generation dihydropyridines (modified release nifedipine, felodipine and isradipine) have a delayed or modified release mechanism. Third-generation agents (amlodipine, lercanidipine, lacidipine and manidipine), instead, are long acting, due to their long plasma or long receptor half-lives. Third generation agents minimize fluctuating plasma levels and cause a lower incidence of adverse events, including a lack of heart rate activation.^{15–17} Regarding adverse events, cardiovascular effects include atrio-ventricular heart block and peripheral edema. Central nervous system effects include headache and dizziness. Gingival hyperplasia has been reported with some agents. Gastrointestinal disturbances include constipation.

Alfa blockers

Selective blockade of α -1 receptors results in vasodilation. These agents decrease blood pressure by decreasing total peripheral resistance and venous return. Doxazosin is the most used α -blocker; in patients with type diabetes and hypertension, doxazosin proved to be not inferior to irbesartan in



reducing blood pressure and to be more effective in improving glucose metabolism and lipid parameters, with significant reductions in glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and HOMA-IR.¹⁸ The positive effect in improving metabolic control was confirmed in patients with impaired glucose tolerance.¹⁹ Doxazosin also proved to exert anti-inflammatory effects in addition to its antihypertensive properties in hypertensive patients, decreasing high-sensitivity C-reactive protein (hs-CRP) and increasing nitrites/nitrates.²⁰ Some doubts about α -blockers safety were raised by the ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), a randomized, double-blind, active-controlled study aimed to evaluate the effect of doxazosin, an α -blocker, with chlorthalidone, a diuretic, on incidence of cardiovascular disease in patients with hypertension as part of a study of 4 types of antihypertensive drugs: chlorthalidone, doxazosin, amlodipine, and lisinopril. Doxazosin showed a significantly higher incidence of combined cardiovascular events and, in particular, congestive heart failure events, compared to chlorthalidone. In addition, with essentially equal rates in the 2 treatment groups for the primary CHD outcome and total mortality, a beneficial effect of doxazosin at the scheduled trial termination was highly unlikely based on conditional power calculations. There were also negative trends for stroke and for combined CHD, particularly 2 of its components, coronary revascularizations and angina.²¹ Cardiac adverse effects of α -blockers include orthostatic hypotension, palpitations, bradycardia, and edema. Central nervous system side effects including dizziness, headache, fatigue, and anxiety have been reported. GI effects include nausea, diarrhea, constipation, and vomiting. Genitourinary side effects include nocturia, urinary frequency, impotence, and priapism.²²

Beta blockers

Beta blockers block the action of endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) in particular, on β -adrenergic receptors, part of the sympathetic nervous system. There are three types of β -receptor, designated β_1 , β_2 and β_3 receptors: β_1 -adrenergic receptors are located

mainly in the heart and in the kidneys; β_2 -adrenergic receptors are located, mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle; β_3 -adrenergic receptors are located in fat cells. Blockade of β_1 -receptors, primarily located in cardiac tissue, results in decreased heart rate, decreased contractility, slowed atrio-ventricular conduction, and suppression of automaticity. Beta-blocking therapy is effective in reducing the risk of death and re-infarction among infarct patients (secondary cardioprotection), and also proved to reduce the incidence of coronary events also in hypertensive patients with no clinical evidence of coronary heart disease (primary cardioprotection).²³ The MAPHY study demonstrated that starting anti-hypertensive treatment with the β_1 -selective blocker metoprolol instead of a thiazide diuretic led to lower total and cardiovascular mortality, mainly by reducing fatal CHD and fatal stroke.²⁴ Cardiac side effects include hypotension and bradycardia, neurologic side effects, include depression, headache, dizziness, and insomnia. Beta blockers may cause cholesterol abnormalities (increase in triglycerides and LDL, decrease in HDL). These agents may induce bronchospasm and antagonize the effects of bronchodilator medications used for the treatment of asthma. Beta blockers have been reported to cause sexual dysfunction, primarily decreased libido and impotence.

Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the homeostatic regulation of BP, fluid electrolytic balance, tissue perfusion, and vascular growth.²⁵ Renin catalyzes the cleavage of angiotensinogen, producing the decapeptide, angiotensin I (Ang I). Angiotensin-converting enzyme (ACE) then catalyzes the conversion of Ang I to the octapeptide Ang II, the primary effector of the RAAS. Angiotensin II (Ang II), the major actor of the RAAS, acts through two receptor subtypes: Ang II type 1 (AT1R) and type 2 (AT2R). Activation of AT1R leads to elevated BP through vasoconstriction increased cardiac output, aldosterone release and sodium reabsorption. In addition to these peripheral effects, AT1R also mediates the central effects of Ang II, including vasopressin release, water and salt intake and increased sympathetic drive, all of which contribute to the development of high BP. The binding of Ang II to



its AT1R, besides mediating its main biologic effects, including vasoconstriction, cell proliferation, hypertrophy, and aldosterone secretion, provides feedback inhibition of further renin release by the kidney.^{26,27}

ACE inhibitors reduce the activity of the RAAS by blocking the conversion of Ang I to Ang II. They, therefore, lower arteriolar resistance and increase venous capacity, increase cardiac output, cardiac index, stroke work, and volume, lower renovascular resistance, and lead to increased natriuresis. Renin increases in concentration in the blood due to negative feedback of conversion of Ang I to Ang II. ACE inhibitors may precipitate a dry, non-productive cough or angioedema. These effects most often disappear when the drug is discontinued. Cardiovascular effects include hypotension, angina, and palpitations. Dizziness, fatigue, headache, and weakness have been reported. Gastrointestinal disturbances include nausea, vomiting, diarrhea, constipation, and abnormal taste. Neutropenia is a rare side effect. Hyperkalemia or proteinuria may occur, especially in patients with renal dysfunction. Dermatologic effects include rash and flushing.

Ang II receptor antagonists block the activation of Ang II AT1 receptors. Blockage of AT1R directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone, amongst other actions. The combined effect reduces BP. Cardiovascular side effects include orthostatic hypotension and angioedema. Central nervous system side effects include headache, dizziness, and fatigue. Gastrointestinal disturbances, including dyspepsia and diarrhea, have been reported. Muscle cramping, rash and decreased renal function have also occurred with Ang II receptor antagonists use.

Combination Therapies

One solution for the problem of poor BP control is the use of combination therapies; the rationale of combination therapy in antihypertensive treatment is mainly to enhance the BP-reducing effect of antihypertensive drugs. Combinations may also serve to counteract counter-regulatory mechanisms that are triggered whenever pharmacological intervention is started, limiting the efficacy of the therapy. For example, in the combinations with diuretics, the compensatory rise in renin secretion induced by sodium depletion

may be the prominent cause of persistent high BP. Simultaneous blockade of the RAAS, with either an ACE inhibitor or an ARB breaks this vicious cycle and allows maximum benefit from sodium depletion. Thus, fixed combinations of diuretic and ACE inhibitor or ARB anti-hypertensives became increasingly used both as first- and second-line therapy in hypertension. For example irbesartan/HCT combination, proved to be safe, well tolerated and give better patients adherence.²⁸⁻³⁰ The TALENT study, instead, suggested that nifedipine and telmisartan as monotherapy have a similar effect on blood pressure, but a synergistic effect when taken simultaneously, both on clinical and ambulatory blood pressure.^{31,32} Given these positive results, recently fixed combination tablets containing both a calcium channel blocker and an ARB/ACE inhibitor have become available: one combination is enalapril/lercanidipine, this once-daily administration of a fixed-dose enalapril/lercanidipine, by bringing together two distinct and complementary mechanisms of action, reduces BP effectively and has the potential for improved target organ protection relative to either class agent alone.^{33,34} Also olmesartan/amlodipine is a valid option, in the COACH (Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure) study, the use of olmesartan/amlodipine allowed up to 54% of patients, with previously inadequate responses to amlodipine or olmesartan monotherapy, to achieve their BP goals.³⁵ Data from post-registration studies using tight BP control and forced titration regimens have further demonstrated the high efficacy of olmesartan/amlodipine in achieving BP goal rates. Moreover, consistent reductions in BP were observed over the 24-hour dosing interval using ambulatory measurements. Olmesartan/amlodipine was generally well tolerated over the short- and long-term, with a lower frequency of peripheral edema with olmesartan/amlodipine 40/10 mg than with amlodipine 10 mg monotherapy.³⁶

Emerging Therapies

Renin inhibitor

Aliskiren is a highly potent and selective direct renin inhibitor that was approved by the Food and Drug Administration (FDA) for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents.³⁷ The development



of aliskiren was preceded by a number of other renin inhibitors, such as enalakiren, remikiren, and zankiren³⁸ all of which were limited by their poor oral bioavailability, weak antihypertensive effect, and short duration of action. Consequently, further clinical development of these three agents was abandoned.

Mechanism of Action and Route of Elimination

By binding to the active site of renin, aliskiren functions by blocking the catalytic functions of this enzyme, which inhibits the conversion of angiotensinogen to Ang I and reduces Ang II concentrations.³⁹ Like ACE inhibitors and Ang II receptor blockers, aliskiren can reactively lead to an increase in plasma renin concentration; however, unlike these other inhibitors of the RAAS, the effects of renin are suppressed with aliskiren, resulting in a reduction in plasma renin activity (PRA).

Aliskiren is metabolized by the CYP3A4 enzyme, but it does not induce nor inhibit the CYP450 system. It has been found to decrease the maximum concentrations of furosemide by up to 50%. Irbesartan may reduce maximum aliskiren concentrations by up to 50%; atorvastatin and ketoconazole may increase maximum aliskiren concentrations by 50% and 80%, respectively. The main route for elimination is biliary, where most of the aliskiren is unchanged.

Clinical Recommendations

Aliskiren was approved by the FDA on March 6, 2007, for the treatment of hypertension, either as monotherapy or in combination with another antihypertensive agent.⁴⁰ Given the recently concerning data from the ALTITUDE study, doctors should not prescribe aliskiren containing medicines in combination with ACE inhibitors or ARBs.⁴¹ The recommended initial dose of aliskiren is 150 mg once daily, which may be increased to 300 mg daily if additional blood pressure control is needed. Higher doses were evaluated in some clinical trials, but they did not provide a better antihypertensive response, and their use was associated with increased gastrointestinal side effects. Maximal hypertensive effects of a given dose are typically achieved by 2 weeks. Caution should be exercised

when using aliskiren in patients with severe renal impairment as this patient population has not been studied. Peak plasma concentrations of aliskiren are reached within 1 to 3 hours. High-fat meals decrease aliskiren's absorption substantially, so it is recommended that patients time their aliskiren dosing around meals. Aliskiren is available as 150 mg and 300 mg tablets.

Adverse Events

The most common adverse events reported with the use of aliskiren in these trials were fatigue, headache, dizziness, diarrhea, nasopharyngitis, and back pain.^{42,43} Because aliskiren is an inhibitor of the RAAS, it seems logical to expect that its ability to cause hyperkalemia and renal dysfunction would be similar to that of ACE inhibitors and ARBs. The full effects of aliskiren on renal function and potassium handling are unknown. However, thus far in clinical trials, the rate of hyperkalemia (serum potassium concentration > 5.5 mEq/L) with the use of aliskiren monotherapy has been relatively low (0.9%).⁴⁴ The rate of hyperkalemia was higher when aliskiren was administered concomitantly with valsartan (4%) compared with aliskiren monotherapy (2%) or valsartan monotherapy (2%).⁴⁵

Clinical Practice

For a summary of all the following studies, see Table 2.

In the ATLAAS study⁴⁶ the authors report on an 8-week double-blind, randomized study of African American patients with stage 2 hypertension that compared brachial and central BP responses (substudy of 53 patients) to combination aliskiren/hydrochlorothiazide (HCT) and amlodipine monotherapy. Following a 1- to 4-week washout, initial therapy was aliskiren/HCT 150/12.5 mg or amlodipine 5 mg for 1 week, forced-titrated to aliskiren/HCT 300/25 mg or amlodipine 10 mg for 7 weeks. Mean seated SBP reductions from baseline was similar with both treatments -28.6 mmHg with aliskiren/HCT vs. -28.2 mmHg with amlodipine. In the substudy, significantly greater reductions in central SBP were observed with aliskiren/HCT vs. amlodipine -30.1 mmHg vs. -21.2 ; $P = 0.031$), although 24-hour mean ambulatory BP reductions between the two groups were similar. Pretreatment geometric mean PRA in randomly assigned patients

Table 2. Summary of the studies involving aliskiren cited in the review.

| Study | Subjects (n) | Duration | Drugs involved | Aim | Results |
|----------------------------|--------------|----------|--|---|--|
| ATLAAS ⁴⁶ | 332 | 8 weeks | Aliskiren/HCT 150/12.5 mg vs. amlodipine 5 mg monotherapy for 1 week, then aliskiren/HCT 300/25 mg or amlodipine 10 mg. | To evaluate the superiority in the change in SBP with combination aliskiren/HCT versus amlodipine. | Mean seated systolic BP reductions from baseline was similar with both treatments (–28.6 mmHg with aliskiren/HCT vs. –28.2 mmHg with amlodipine). Treatment with 300 mg of aliskiren daily, as compared with placebo, reduced the mean urinary albumin-to creatinine ratio by 20%, with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared with 12.5% of those who received placebo. |
| AVOID ⁴⁷ | 599 | 6 months | Aliskiren 150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months) or placebo, in addition to losartan 100 mg/day. | To evaluate the reduction in the ratio of albumin to creatinine, as measured in an early morning urine sample. | Aliskiren, with or without HCT, provides clinically significant BP reductions and may therefore be an effective treatment option in patients with stage 2 hypertension. Aliskiren/HCT therapy provides substantial BP reductions and may thus be a useful treatment option for older patients with stage 2 hypertension. |
| ACQUIRE ⁴⁹ | 688 | 12 weeks | Once-daily aliskiren/HCT 150/12.5 mg or aliskiren 150 mg for 1 week and then double the doses for 11 weeks. | To evaluate aliskiren therapy in patients with the lower ranges of stage 2 hypertension. | Aliskiren, with or without HCT, provides clinically significant BP reductions and may therefore be an effective treatment option in patients with stage 2 hypertension. Aliskiren/HCT therapy provides substantial BP reductions and may thus be a useful treatment option for older patients with stage 2 hypertension. |
| ACTION ⁵⁰ | 451 | 8 weeks | Once-daily aliskiren/HCT 150/12.5 mg or HCT 12.5 mg for 1 week, and then double the doses for 7 weeks. | To evaluate aliskiren/HCT compared with HCT monotherapy in older patients (55 years and older) with stage 2 systolic hypertension. | Aliskiren, with or without HCT, provides clinically significant BP reductions and may therefore be an effective treatment option in patients with stage 2 hypertension. Aliskiren/HCT therapy provides substantial BP reductions and may thus be a useful treatment option for older patients with stage 2 hypertension. |
| ALOFT ⁵¹ | 302 | 3 months | Placebo or aliskiren 150 mg/day added to an ACE inhibitor (or angiotensin receptor blocker) and β -blocker. | To evaluate the effects of adding the direct renin inhibitor aliskiren to an ACE inhibitor in patients with heart failure. | Addition of aliskiren to an ACE inhibitor (or angiotensin receptor blocker) and β -blocker had favourable neurohumoral effects in heart failure and appeared to be well tolerated. |
| Fogari et al ⁵² | 170 | 24 weeks | Aliskiren 300 mg or amlodipine 10 mg, both given once daily. | To evaluate the effect of aliskiren compared to amlodipine on QT duration and dispersion in hypertensive patients with type 2 diabetes. | Despite similar BP lowering effect, aliskiren, but not amlodipine, reduced QT duration and dispersion, which might be related to the ability of aliskiren to interfere with mechanisms underlying myocardial electrical instability in the heart of diabetic hypertensive patients. |

(Continued)

Table 2. (Continued)

| Study | Subjects (n) | Duration | Drugs involved | Aim | Results |
|----------------------------|--------------|----------|--|---|---|
| Fogari et al ⁶³ | 120 | 8 weeks | Amlodipine 10 mg or aliskiren 300 mg or their combination. | To assess the effect of aliskiren and amlodipine on ankle-foot volume (AFV) and pretibial subcutaneous tissue pressure (PSTP). | Aliskiren partially counteracts the microcirculatory changes responsible for calcium-channel-induced edema formation, possibly through preferential vasodilation of venous capacitance vessels. Despite a similar blood pressure effect, aliskiren decreased PAI-1 antigen and activity, and increased GIR. |
| Fogari et al ⁶⁴ | 76 | 12 weeks | Aliskiren 300 mg once a day or losartan 100 mg once a day. | To compare the effect of aliskiren and losartan on fibrinolysis and insulin sensitivity in hypertensive patients with metabolic syndrome. | |

was 0.35 ng/mL/h in the aliskiren/HCT group and 0.40 ng/mL/h in the amlodipine group. At end of study, combination aliskiren/HCT significantly reduced PRA by 40%. In contrast, amlodipine led to a 101% increase in PRA. Combination aliskiren/HCT raised plasma renin concentrations from baseline (geometric mean increase, 943%), as did amlodipine (geometric mean increase, 60%); however, the increase with aliskiren/HCT was significantly greater than with amlodipine ($P < 0.0001$).

In the AVOID study⁴⁷ 599 patients were enrolled. After a 3-month, open-label, run-in period during which patients received 100 mg of losartan daily, patients were randomly assigned to receive 6 months of treatment with aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months) or placebo, in addition to losartan. The primary outcome was a reduction in the ratio of albumin to creatinine, as measured in an early morning urine sample, at 6 months. By the end of the study period, treatment with aliskiren (150 mg daily for 3 months, followed by 300 mg daily for another 3 months) reduced the mean urinary albumin-to-creatinine ratio by 20%, as compared with placebo ($P < 0.001$). The mixed effects model yielded an identical reduction of 20% in the mean urinary albumin-to-creatinine ratio ($P < 0.001$). After adjustment for the change from baseline in SBP, the reduction was 18% ($P = 0.002$). By week 12, 150 mg of aliskiren daily, as compared with placebo, decreased the urinary albumin-to-creatinine ratio by 11% ($P = 0.02$). At week 24, the overnight urinary albumin excretion rate showed a similar pattern, with a reduction of 18% in the aliskiren group ($P = 0.009$ for the comparison with the placebo group). After adjustment for the change from baseline in SBP, the reduction was 17% ($P = 0.02$). Mean BP, measured while the patient was seated, was nearly identical at baseline in the two groups. By the end of the study period (week 24), the mean blood pressure in the aliskiren group was 2/1 mmHg lower than that in the placebo group ($P = 0.07$ for SBP, $P = 0.08$ for DBP). A reduction of 50% or more in albuminuria was seen in 24.7% of the patients who received aliskiren, as compared with 12.5% of the patients who received placebo ($P < 0.001$). A comparison of baseline characteristics between patients who had a heightened response (a reduction of 50% or more in albuminuria)



and those who had a normal response (a reduction of less than 50% in albuminuria) did not reveal any significant differences. The mean rate of decline in the estimated glomerular filtration rate during the 24-week study period was 2.4 ml per minute per 1.73 m² in the aliskiren group and 3.8 ml per minute per 1.73 m² in the placebo group ($P = 0.07$). There was no difference in the overall incidence of adverse events between the aliskiren group and the placebo group (66.8% and 67.1%, respectively).

Another study⁴⁸ compared the effects of aliskiren (300 mg daily), olmesartan (40 mg daily), and its combination therapy on urinary L-fatty acid binding protein (L-FABP), a marker of tubular injury in stage I or II CKD patients. Olmesartan or aliskiren monotherapy for 6 months comparably decreased SBP and DBP, proteinuria, and serum creatinine. Systolic and DBP, proteinuria and serum creatinine levels were reduced more by co-treatment of olmesartan and aliskiren; compared with each monotherapy, BP levels were significantly lower, and proteinuria and serum creatinine levels had a tendency to decrease in the olmesartan plus aliskiren group. After 6 months' treatment with olmesartan or aliskiren monotherapy, the urinary excretion level of L-FABP was reduced comparably, but the effects of each treatment on L-FABP were modest. On the other hand, olmesartan plus aliskiren treatment produced more incremental reduction in urinary L-FABP level relative to olmesartan or aliskiren therapy alone.

In the ACQUIRE⁴⁹ study patients with stage 2 hypertension (SBP ≥ 160 mmHg and/or DBP > 100 mm Hg) were evaluated; after a 2- to 4-week washout period, 688 patients were randomised to once-daily aliskiren/HCT 150/12.5 mg or aliskiren 150 mg for 1 week and then double the doses for 11 weeks. Aliskiren/HCT provided significantly greater mean reductions from baseline in SBP than aliskiren monotherapy at week 12 (-30.0 mmHg vs. -20.3 mmHg; $P < 0.0001$), corresponding to an additional mean reduction in SBP of -9.7 mmHg for patients receiving aliskiren/HCT compared with those on aliskiren monotherapy. Mean reductions in DBP were also significantly greater with aliskiren/HCT compared with aliskiren alone ($P < 0.0001$). Similar reductions in SBP and DBP were obtained at week 8. Both treatment regimens produced clinically significant reductions in BP as early as 1 week after starting treatment.

In patients receiving aliskiren/HCT, mean BP was reduced to $<140/90$ mmHg within 4 weeks of starting treatment, and these reductions were maintained throughout the study. Patients with isolated systolic hypertension who received aliskiren/HCT achieved a significant -10.6 mmHg additional reduction from baseline in SBP compared with those on aliskiren monotherapy at week 12. Similar reductions in SBP were observed at week 8. The proportion of patients achieving their BP goal with aliskiren/HCT combination therapy (54.6%) at week 12 was significantly higher than the proportion reaching goal with aliskiren monotherapy (32.2%; $P < 0.0001$). Similar findings were observed at week 8. Noncumulative responder rates were also significantly higher with aliskiren/HCT combination therapy than with aliskiren monotherapy at week 12 (75.4% vs. 56.7%; $P < 0.0001$) and week 8 (75.4% vs. 52.5%; $P < 0.0001$). Aliskiren alone and in combination with HCT provided significant reductions in PRA at week 12 ($P < 0.05$). The reductions in PRA with aliskiren monotherapy (-73%) were significantly greater ($P < 0.0001$) than those with aliskiren/HCT (-45%). Aliskiren was generally well tolerated as monotherapy or in combination with HCT during the study, with a similar incidence of adverse events observed in the two groups.

Similar results were obtained by the ACTION study,⁵⁰ a randomized double-blind trial that compared a single-pill combination of aliskiren and HCT with HCT monotherapy in older patients (older than 55 years) with SBP ≥ 160 mmHg and <200 mmHg. After a 1- to 4-week washout, 451 patients were randomized to once-daily aliskiren/HCT 150/12.5 mg or HCT 12.5 mg for 1 week, and then double the doses for 7 weeks. Aliskiren/HCT tablets provided a significantly greater reduction from baseline in SBP than HCT monotherapy at week 4 end point (least-squares mean reductions of 29.6 mmHg vs. 22.3 mmHg; $P < 0.0001$), with patients who received aliskiren/HCT gaining an additional mean reduction in SBP of -7.3 mmHg compared with those who received HCT monotherapy. Mean reductions in DBP were also significantly greater with aliskiren/HCT than with HCT monotherapy ($P < 0.005$). As specified by the protocol, patients whose SBP remained above 160 mmHg at weeks 4 or 6 could receive add-on amlodipine. A lower proportion of patients required add-on amlodipine in the aliskiren/HCT group than



in the HCT monotherapy group (12.8% vs. 22.0%; $P < 0.01$). Despite the use of add-on amlodipine, mean reductions in SBP and DBP at week 8 end point remained significantly greater in the aliskiren/HCT group than in the HCT monotherapy group ($P < 0.0001$ for SBP and DBP). Aliskiren/HCT treatment brought a significantly higher proportion of patients to BP goal than HCT monotherapy at week 4 end point (51.1% vs. 33.3%, $P = 0.0001$). This difference remained significant at week 8 end point (62.2% vs. 39.2%; $P < 0.0001$), when patients who were initially non responders were receiving amlodipine in addition to the aliskiren/HCT single-pill combinations or HCT. Aliskiren/HCT treatment was associated with a reduction from baseline in PRA (by 49% at week 4 and 57% at week 8), whereas HCT monotherapy led to an increase from baseline (122% at week 4 and 143% at week 8). Aliskiren/HCT combination therapy and HCT monotherapy were generally well tolerated with or without optional addition of amlodipine.

In the ALOFT trial⁵¹ patients with New York Heart Association class II to IV heart failure, current or past history of hypertension, and plasma brain natriuretic peptide (BNP) concentration 100 pg/mL who had been treated with an ACE inhibitor (or angiotensin receptor blocker) and β -blocker were randomized to 3 months of treatment with placebo or aliskiren 150 mg/die. The primary efficacy outcome was the between-treatment difference in N-terminal pro-BNP (NT-proBNP). Plasma NT-proBNP rose by a mean \pm SD of 762 ± 6123 pg/mL over the 12 weeks of treatment in the placebo group and fell by a mean \pm SD of 244 ± 2025 pg/mL with aliskiren treatment (between-treatment difference in change from baseline $P = 0.0106$). BNP decreased by a mean \pm SD of 12.2 ± 243 pg/mL in the placebo group and by 61.0 ± 257 pg/mL in the aliskiren group ($P = 0.0160$). Plasma aldosterone did not differ between groups, but urinary aldosterone excretion decreased more in the aliskiren group; the decrease with aliskiren was 9.24 ± 42.9 nmol/d, and the decrease with placebo was 6.96 ± 38.5 nmol/d ($P = 0.0150$). Plasma renin activity decreased more with aliskiren (decrease of 5.71 ± 11.27 ng \cdot mL⁻¹ \cdot h⁻¹ with aliskiren compared with a decrease of 0.97 ± 9.96 ng \cdot mL⁻¹ \cdot h⁻¹ with placebo; $P < 0.0001$). The mean \pm SD decrease in seated SBP was 1.7 ± 13.2 mmHg in the placebo

group and 4.1 ± 14.5 mmHg in the aliskiren group ($P = 0.2257$). The corresponding decreases in DBP were 0.2 ± 8.6 mmHg in the placebo group and 2.9 ± 9.0 mmHg in the aliskiren group ($P = 0.0599$). The mean increase in heart rate was 0.2 ± 10.3 bpm in the placebo group and 1.1 ± 13.6 bpm in the aliskiren group ($P = 0.6774$). Mean standing SBP decreased by 1.7 ± 13.1 mmHg in the placebo group and by 3.5 ± 16.1 mmHg in the aliskiren group ($P = 0.497$). The corresponding changes in DBP were a 0.7 ± 8.3 mmHg increase with placebo and a 3.5 ± 10.7 mmHg decrease with aliskiren ($P < 0.0045$). Standing heart rate decreased by 0.3 ± 11.4 bpm in the placebo group and increased by 0.7 ± 13.8 bpm in the aliskiren group ($P = 0.466$). Eleven (7.5%) placebo-treated and 14 (9.0%) aliskiren treated patients discontinued use of the study drug prematurely.

In a recent study recently published by Fogari et al,⁵² Authors evaluated the effect of aliskiren compared to amlodipine on QT duration and dispersion in hypertensive patients with type 2 diabetes. One hundred and seventy outpatients aged 50–75 years with mild to moderate hypertension (SBP > 130 and < 180 mmHg and DBP > 80 and < 100 mmHg) and type 2 diabetes were randomly treated with aliskiren 300 mg or amlodipine 10 mg, both given once daily for 24 weeks, according to a prospective, open label, blinded-end point, parallel group design. At 12 weeks 42% of patients in the aliskiren group and 39% of patients in amlodipine group required HCT addition due to insufficient BP control (SBP/DBP $> 130/80$ mmHg), with no significant difference between the two treatment groups. In no patient doses of HCT were escalated above 12.5 mg daily. A total of 161 patients, 81 in the aliskiren group and 80 in the amlodipine group completed the study. Both aliskiren and amlodipine significantly reduced sitting SBP (-28.2 mmHg and -28.6 mmHg respectively; both $P < 0.001$ vs. placebo) and DBP (-14.5 mmHg and -14.9 mmHg respectively; $P < 0.001$ vs. placebo), with no significant difference between the two treatments. Similar results were obtained for standing SBP/DBP values, which were reduced by both aliskiren ($-27.2/-14.3$ mmHg; $P < 0.001$ vs. placebo) and amlodipine ($-27.8/-14.2$ mmHg; $P < 0.001$ vs. placebo) with no difference between the two treatments. Aliskiren therapy significantly decreased QT max (-14 ms at 12 weeks and -17 ms at 24 weeks,



both $P < 0.05$ vs. placebo) and QTc max (-26 ms and -31 ms, both $P < 0.01$ vs. placebo) as well as QTd (-11 ms and -13 ms, both $P < 0.01$ vs. placebo) and QTcd (-18 ms and -19 ms, both $P < 0.01$ vs. placebo), while amlodipine did not induce any significant reduction in QT parameters, the difference between the two treatments being statistically significant ($P < 0.05$). No significant relationship between changes in BP and QTc dispersion was noted with either treatment regimens ($P = 0.55$ for SBP and 0.63 for DBP in aliskiren group; $P = 0.61$ for SBP and 0.58 for DBP in the amlodipine group).

Fogari et al⁵³ also conducted a study to assess the effect of aliskiren and amlodipine on ankle-foot volume (AFV) and pretibial subcutaneous tissue pressure (PSTP). After 4-week placebo, 120 outpatients with grade 1–2 hypertension were randomized to amlodipine 10 mg or aliskiren 300 mg or their combination for 8 weeks in three crossover periods. At the end of each treatment, blood pressure, AFV, PSTP, PRA and norepinephrine were assessed. Monotherapy with both amlodipine and aliskiren significantly lowered BP values: the mean decrease in SBP/DBP values was 16.8/13.1 mmHg with amlodipine ($P < 0.001$ vs. baseline) and 15.9/12.2 mmHg with aliskiren ($P < 0.001$ vs. baseline). Aliskiren/amlodipine combination produced a significantly greater decrease in BP values than either drug alone. The mean decrease was -24.6 mmHg for SBP ($P < 0.0001$ vs. baseline) and -20.9 mmHg for DBP ($P < 0.0001$ vs. baseline). As expected, aliskiren monotherapy did not affect AFV and PSTP as compared with baseline, whereas amlodipine monotherapy significantly increased both AFV ($+28.4\%$; $P < 0.01$ vs. baseline) and PSTP ($+80.4\%$; $P < 0.01$ vs. baseline). Compared with amlodipine alone, the aliskiren/amlodipine combination produced a significantly less pronounced increase in AFV ($+6.6\%$; $P < 0.05$ vs. baseline and $P < 0.01$ vs. amlodipine), the mean difference between the two treatments being statistically significant (286.7 ml) and in PSTP (20.1%; $P < 0.05$ vs. baseline and $P < 0.01$ vs. amlodipine), the mean difference between the two treatments being statistically significant (1.2 cmH₂O). An inverse correlation was found between AFV and PSTP changes. When the correlations between age and treatment induced changes in AFV and PSTP were considered, both amlodipine alone and aliskiren/amlodipine combination, although to a different extent, were found to produce

increases in AFV that were greater with increasing age. Conversely, the PRA was unaffected by amlodipine ($+23.6\%$), while it was significantly reduced by both aliskiren monotherapy (-77.7% ; $P < 0.01$ vs. baseline and vs. amlodipine) and aliskiren/amlodipine combination (-75.7% ; $P < 0.01$ vs. baseline and vs. amlodipine).

In another study by Fogari et al,⁵⁴ Authors compared the effect of aliskiren and losartan on fibrinolysis and insulin sensitivity in hypertensive patients with metabolic syndrome. After 2-week placebo period, 76 outpatients with mild to moderate hypertension and metabolic syndrome were randomized to aliskiren 300 mg once a day or losartan 100 mg once a day for 12 weeks. Both aliskiren and losartan induced a significant and similar SBP/DBP reduction ($-15.6/10.7$ mmHg and $-15.5/10.5$ mmHg, $P < 0.001$ vs. baseline, respectively). Both drugs decreased PAI-1 antigen and activity after 2 weeks of treatment; subsequently, only the decreasing effect of aliskiren was sustained throughout the 12 weeks [-7.5 ng/mL (-31%) $P < 0.05$ vs. baseline], while with losartan PAI-1 increased at week 12 [$+3.6$ ng/mL ($+15\%$), $P < 0.05$ vs. baseline and $P < 0.01$ vs. aliskiren]. The tPA activity showed no significant change with aliskiren and a decrease with losartan [-0.04 IU/mL (-8%), $P < 0.05$ vs. baseline and $P < 0.01$ vs. aliskiren]. Aliskiren significantly increased GIR [$+1.4$ mg/min/kg ($+28\%$), $P < 0.01$ vs. baseline], while losartan did not change it [$+0.2$ mg/min/kg ($+4\%$), not significant vs. baseline, $P < 0.05$ vs. aliskiren].

On the other side, the ALTITUDE study⁵ included three categories of high-risk patients with type 2 diabetes (aged ≥ 35 years): those with either urinary albumin/creatinine ratio (UACR) ≥ 200 mg/g; microalbuminuria (UACR) $\geq 20 < 200$ mg/g and eGFR $\geq 30 < 60$ mL/min/1.73 m²; and thirdly, those with a history of cardiovascular disease and eGFR $\geq 30 < 60$ mL/min/1.73 m² with or without microalbuminuria. The primary outcome measure was time to first event for the composite endpoint of cardiovascular death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease or doubling of baseline serum creatinine concentration. Secondary endpoints include a composite CV endpoint and a composite renal endpoint.⁵ The results showed that,



in this kind of patients, there was no benefit with aliskiren and that there were more cases of stroke, renal complications, hyperkalemia and hypotension in patients who received aliskiren compared with patients who received a placebo.

Discussion

The most of the studies reported above showed the efficacy and safety of aliskiren both in monotherapy and in combination therapy. Aliskiren proved to be effective not only on blood pressure control, but also on organ protection. For example the ALOFT⁵¹ trial showed that the addition of aliskiren to an ACE inhibitor (or angiotensin receptor blocker) and β -blocker had favorable neurohumoral effects in heart failure; aliskiren better decreased BNP compared to placebo, and reductions in BNP have consistently been associated with improved outcome in heart failure.⁵⁵ To better clarify this aspect the ongoing ATHMOSPHERE study⁵⁶ was designed: this study wants to evaluate the effect of both aliskiren and enalapril monotherapy and aliskiren/enalapril combination therapy on cardiovascular death and heart failure hospitalization in patients with chronic systolic heart failure, NYHA functional class II-IV symptoms, and elevated plasma levels of BNP. Patients tolerant to at least 10 mg or equivalent of enalapril will undergo an open-label run-in period where they receive enalapril then aliskiren. Approximately 7000 patients tolerating this run-in period will then be randomized to aliskiren monotherapy, enalapril monotherapy, or the combination. The primary endpoints of ATMOSPHERE are whether the aliskiren/enalapril combination is superior to enalapril monotherapy in delaying time to first occurrence of cardiovascular death or heart failure hospitalization and whether aliskiren monotherapy is superior or at least non-inferior to enalapril monotherapy on this endpoint.

Furthermore, when added to amlodipine, aliskiren also demonstrated to give a less pronounced increase in both AFV and PSTP, two objective measures of peripheral edema, and to lower the number of patients with clinical evidence of this side effect.⁵⁴ Moreover, aliskiren, but not amlodipine, reduced QT duration and dispersion, this action might be related to the ability of aliskiren to interfere with mechanisms underlying myocardial electrical instability in the heart of diabetic hypertensive patients.⁵² Any

drug that reduces BP may also reduce QT dispersion to some degree because of mechanic electrical feedback mechanism; however, a correlation analysis demonstrated that changes in QT duration and dispersion in the aliskiren treated patients did not relate to BP decrease, which suggests that at least some of this favorable effect of aliskiren on QT parameters may be independent of its antihypertensive effect. Aliskiren also proved to have nephroprotective effects that are independent from its blood pressure-lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended nephroprotective treatment.⁴⁷ In the AVOID study the estimated glomerular filtration rate was nearly identical in the two groups at baseline, whereas the decline in the glomerular filtration rate tended to be smaller among the patients who were treated with aliskiren for 6 months than among the patients who were given placebo. Long-term studies must be conducted to elucidate whether the beneficial effect on the kidney that is seen in the short term is sustained.⁴⁷

Regarding the data from the ALTITUDE study, surely they have created a lot of concern, at the point that the same Novartis, the manufacturer of aliskiren, informed physicians on potential risks of cardiovascular and renal adverse events in patients with type 2 diabetes and renal impairment and/or cardiovascular disease treated with aliskiren tablets and aliskiren-containing combination products. Novartis affirmed that aliskiren-containing products should not be used in combination with ACE inhibitors or ARB in patients with diabetes, and to stop aliskiren-containing treatment in this kind of patients.⁵⁷ Despite that, we have to consider that the patients enrolled in the ALTITUDE study were already at high risk at the baseline, they were affected by type 2 diabetes, and renal impairment that, as itself, can give hyperkalemia. Furthermore, in most patients, arterial blood pressure was adequately controlled at baseline, and aliskiren 300 mg was given in addition to standard of care, including an ACE inhibitor or ARB. So some adverse events, such as hyperkalemia and hypotension, should be expected with this kind of study design.

On February 17th, the EMA completed the review of aliskiren-containing medicines, concluding that the benefits of aliskiren continue to outweigh its risks, but



recommended changes to the product information to restrict its use. In particular, EMA stated that aliskiren must not be prescribed in combination with ACE inhibitors or ARBs to patients with diabetes or with moderate or severe kidney impairment. In addition, EMA added that the combination of aliskiren with ACE inhibitors or ARBs is not recommended in all other patients.⁴¹

A limitation of the above reported studies is that aliskiren efficacy in providing cardiovascular protection was not assessed. When the data from the ATMOSPHERE study will be available, also this aspect will be clarified.

Conclusion

Given the info reported above, aliskiren proved to be safe and well tolerated and to have some protective effects on heart and kidney, not observed with the other drugs. However, until further data will not be available, aliskiren should not be prescribed in combination with ACE inhibitors or ARBs. In combination with other anti-hypertensive drugs, instead, aliskiren should be considered for the treatment of hypertension in not well controlled hypertensive patients.

Author Contributions

Conceived and designed the experiments: GD, PM. Analysed the data: GD, PM. Wrote the first draft of the manuscript: GD, PM. Contributed to the writing of the manuscript: GD, PM. Agree with manuscript results and conclusions: GD, PM. Jointly developed the structure and arguments for the paper: GD, PM. Made critical revisions and approved final version: GD, PM. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is

unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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