

Aliskiren-Hydrochlorothiazide in Combination: Efficacy Review in Mild to Moderate Hypertension

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Abstract: Hypertension is one of the major cardiovascular and renal risk factors and is linked to high morbidity and mortality in patients worldwide. The control rates of hypertensive patients are still low, and this makes the issue of newer drugs highly necessary in order to improve control rates. Since this will be affected by efficacy as well as compliance to antihypertensive medications, we require drugs offering reducing properties against high blood pressure as well as a minimum of adverse effects. The drug class of renin angiotensin system inhibitors is the most-used class for treating hypertension in regard to efficacy as well as tolerability. Recently, a new player in this field was introduced: the direct renin inhibitor aliskiren. Here we review the efficacy and safety of aliskiren alone and in the combination with hydrochlorothiazide, an interesting combination partner since their mode of action allows synergistic effects in regard to lowering blood pressure as well as in reducing possible side effects of both drugs.

Keywords: aliskiren, hydrochlorothiazide, hypertension



Introduction

Arterial hypertension is one of the major independent risk factors for cardiovascular diseases. Thus, arterial hypertension followed by its target organ damage represents one of the leading causes of morbidity and mortality, both in industrialized and in developing countries. Hypertension affected 972 million patients in the year 2000, and is anticipated to increase to 1.54 billion patients in the year 2025 with a worldwide prevalence of approximately 26%.¹ The WHO suggested that hypertension accounts for 7.1 million deaths per year² and again, this number is assumed to rise even more in the next centuries. Therefore, treatment of hypertension with the target of controlling blood pressure is essential for the reduction of morbidity and mortality.³ After the initiation of lifestyle changes, medical treatment is the option of choice for controlling hypertension, which means a reach of blood pressure target goals in all patients. Different substance classes are available today and have been shown to reduce blood pressure and thus mortality in hypertensive patients. All classes are known to be effective and there is no specific recommendation on what might be the “best” starting class in treating hypertension according to current European guidelines.³

The recent reappraisal of the 2007 hypertension guidelines emphasize that combination therapies and fixed dose medication might be useful in regard to controlling hypertension.⁴ Moreover, classes yielding only few side effects might be favourable for compliance and adherence of antihypertensive medications. Again, this may allow better control rates in hypertensive patients.

The class of inhibitors of the renin-angiotensin-aldosterone-system (RAAS) is known to be potent in reducing blood pressure and thus improve morbidity and mortality as well as reducing target-organ damage in hypertensive patients. Moreover, side effects of RAAS inhibitors, especially angiotensin receptor blockers are known to be lower compared to other classes, e.g. beta-blocker or diuretics in monotherapy regimes,⁵ which makes them the most popular class in daily clinical practice. While angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are established drugs in the field of RAAS inhibitors, a new player was introduced recently: the first available direct renin inhibitor

aliskiren. This direct renin inhibitor (and other renin inhibitors not yet on the market) block the RAAS system at its rate limiting step, the conversion of angiotensinogen to angiotensin I by renin. Although this step was targeted early in the development of RAAS inhibitors, it is only now that the first drug in this new class is available.

Combination of aliskiren with a diuretic is one choice in treating hypertension, which might be of special interest due to the interaction with the plasma renin activity of both drugs (see in more detail below). The available studies for the efficacy and safety of the combination of aliskiren with hydrochlorothiazide will be reviewed and discussed here.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

The RAAS is essential for fluid and sodium retention, but also vasoconstriction, sympathetic activation, generation of oxidative stress, cellular hypertrophy leading to cardiac hypertrophy, and accumulation of fibrosis in different tissues, especially in the heart, are all known to be mediated by an activated RAAS.⁶ The pathological over-activation of the RAAS is therefore an important contributor to arterial hypertension and will ultimately favour target organ damage. Intensive research has increased our knowledge about the RAAS in the last decades and therefore, we can now tailor strategies to improve a patient's outcome by inhibiting the RAAS at different levels with different drug classes.

An increased plasma renin concentration increases cleavage from angiotensinogen to angiotensin I, which is again cleaved in the next step by the angiotensin converting enzyme to angiotensin II (Ang II). Most of the actions of the RAAS are attributed to the angiotensin II type 1 receptor as the pathological target receptor of the RAAS. Therefore, blockade of this receptor by angiotensin II receptor blockers (ARBs) or reduction of angiotensin II levels by angiotensin converting enzyme inhibitors (ACE-I) can reduce blood pressure and attenuate target-organ damage. This would result in a reduced morbidity and mortality in hypertensive patients. Direct renin inhibitors like aliskiren reduce angiotensin II levels by blocking the renin-based cleavage of angiotensin to angiotensin I (Fig. 1), thus lowering the pathologically increased plasma renin activity. Interestingly, ARBs and ACE-Is (and other

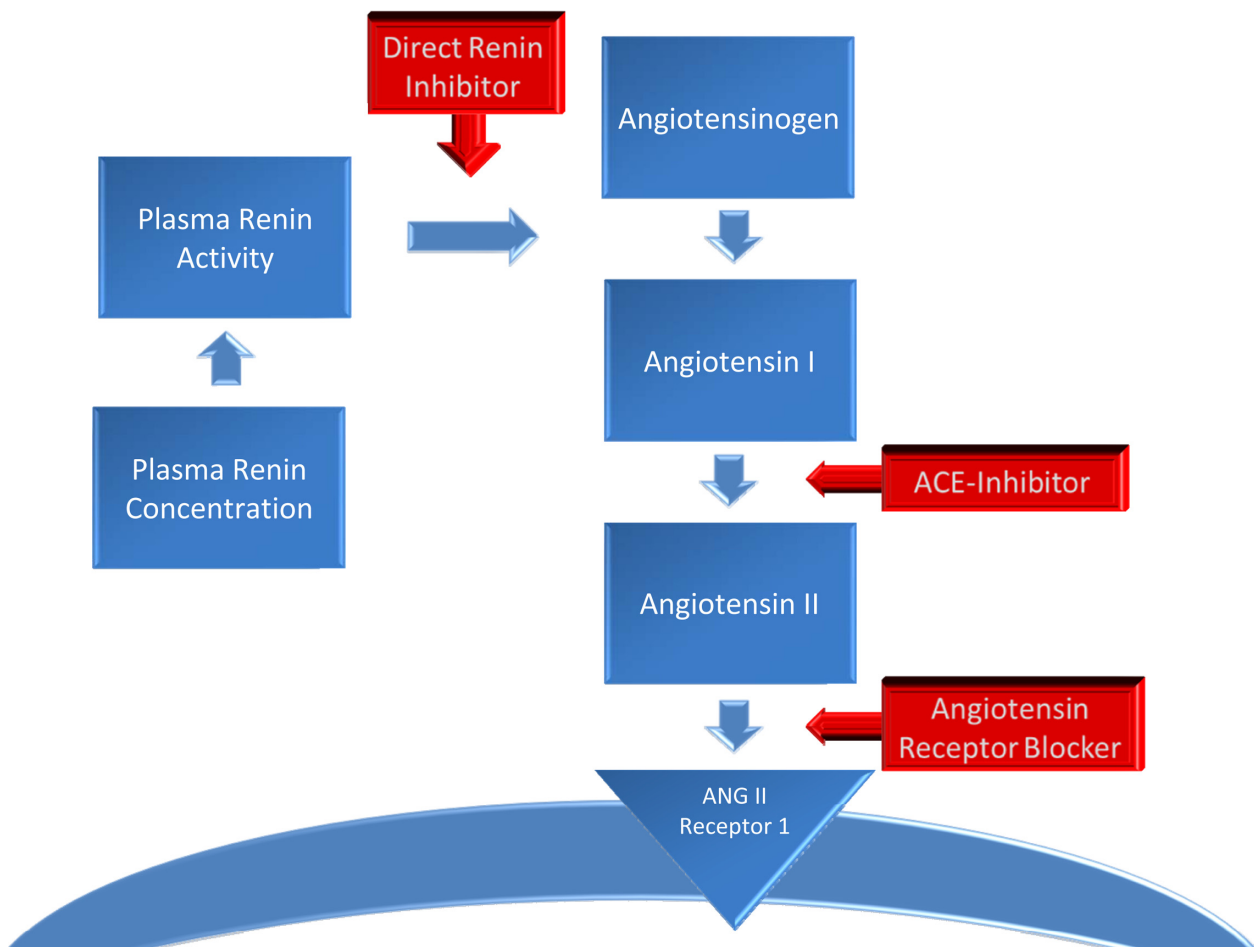


Figure 1. Scheme of the mode of action of the renin angiotensin system. Active renin cleaves angiotensinogen to angiotensin I, which is again cleaved by angiotensin converting enzyme to angiotensin II. Angiotensin II binds e.g. to the angiotensin II type 1 receptor to mediate ANG II (patho) physiology, which e.g. increases blood pressure. Interaction of current inhibitors are marked in red boxes. Plasma renin activity is lowered by direct renin inhibitors, thus reducing cleavage of angiotensinogen to angiotensin I. Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) reduce the ACE-based cleavage of angiotensin I to angiotensin II. Angiotensin receptor blockers (ARBs) block the angiotensin receptor, and therefore angiotensin II cannot activate this receptor.

anti-hypertensive medications such as diuretics) induce a secondary increment of the plasma renin concentration as a compensatory feedback mechanism. Also, the renin inhibitor aliskiren increases plasma renin concentration since juxtaglomerular cells spill out more renin into the plasma in response to a decrement of kidney angiotensin II levels. Indeed, it was suggested that aliskiren increases plasma renin concentration even more than ACE-Is or ARBs do, but the effects of this is still under discussion.⁷⁻⁹ Nevertheless, it is only a renin inhibitor which can effectively lower the plasma renin activity (PRA) and therefore it counteracts this compensatory mechanism leading to a more complete inhibition of the RAAS, and this implies a theoretical advantage of that substance over the other

RAAS inhibitors.^{10,11} PRA itself has been linked to a worsening of the outcome in heart failure, as could be shown in the Heart Outcomes Prevention Evaluation (HOPE) study (presented at the AHA 2009). Indeed, aliskiren reduced the PRA after 8 weeks of treatment in about 80% of the 672 patients receiving a hypertension-dependent dose, while placebo-treated patients showed a 19% increase of PRA.¹² This decrement of PRA due to aliskiren treatment is consistent also in patients treated with other drugs known to increase PRA.¹³ Therefore, aliskiren seems to be an optimal choice when the other administered agent increases PRA.¹¹

Especially hydrochlorothiazide is known to increase PRA¹⁴ and since it is an effective antihypertensive medication itself, it seems to be an ideal combination



partner for aliskiren (Fig. 2). Hydrochlorothiazides act at the distal tubule of the nephron to block sodium uptake. This decreases volume retention and lowers preload, which reduces blood pressure effectively in patients having hypertension.

The bioavailability of orally-administered aliskiren is low, with only 2.7%, and the plasma concentration (C_{max}) peaks after 1–3 hours.¹⁵ The half-life is relatively long, possessing values measured between 24–40 hours, which makes a once-daily administration possible. A steady state in plasma concentration is reached after 7 days of aliskiren administered once daily.¹⁶ Aliskiren is only slightly metabolised (20%) by the CYP450 isoenzyme CYP3 A4, and apparently not at all influenced by the isoenzymes 2C8, 2C19, 2D6, 2E1, and 3A. These facts suggest a low incidence of drug interactions, and this is quite favourable in patients treated with multiple drugs. The main excretion route of aliskiren is via faeces and urine in its unmetabolized form,¹⁷ which suggests no special need of individual dosing in patients with concomitant diseases.

The bioavailability of orally-administered hydrochlorothiazide is described as being high (50%–80%), and C_{max} peaks are reached after 1–2.5 hours.¹⁸ The half-life of hydrochlorothiazide is shorter than that of aliskiren, and has been documented to different extents, these varying between 2 and 15 hours.¹⁹ Similar to aliskiren, hydrochlorothiazide is not metabolized significantly (5%) and is excreted unchanged in the urine (95%).

Clinical Studies, Safety and Efficacy of Aliskiren and Hydrochlorothiazide

Antihypertensive efficacy of aliskiren in patients with hypertension has been investigated and reviewed

extensively^{20–25} and it was shown in all trials that a monotherapy using aliskiren reduces blood pressure in a dose-dependent manner after administration once daily of 150 mg and 300 mg aliskiren. One outstanding effect of aliskiren when compared with other antihypertensive medications might be explained by its relatively long half-life. Andersen et al documented that four weeks after stopping the administration of aliskiren (taken previously for 26 weeks) the PRA was still 52% below pre-treatment baseline and the blood pressure was lower when compared to baseline values before aliskiren treatment.¹³ Coherent with the prolonged inhibition of PRA, median blood pressure did not exceed the target of 140/90 mmHg four weeks after stopping aliskiren treatment (blood pressure 4 weeks after discontinuation: 138.7/90.0 mmHg with a blood pressure of 151.7/98.3 mmHg at the beginning of the study). This was recently confirmed by a meta analysis showing that aliskiren does not lead to paradoxical blood pressure rises after cessation¹⁰ but in fact does maintain its efficacy in blood pressure reduction after a missed dose.²⁶ Future studies will have to reveal information on any possibility that the relatively long half-life might induce problems concerning interaction with other drugs, although up to date this problem is not apparently evident.

Whether or not aliskiren is superior in regard to blood pressure reduction when compared to ACE-I or ARBS has, to our knowledge, never been tested directly, while that seems rather questionable when one examines currently available meta analysis which demonstrates similar blood pressure effects of all RAAS inhibitors.^{25,27–29}

Hydrochlorothiazide is one of the most-prescribed drugs for arterial hypertension in the United States.

	PRC	PRA	ANGII	Potassium
Direct Renin Inhibitor Aliskiren	↑↑	↓↓	↓	↑
Angiotensin Receptor Blocker	↑↑	↑	↑	↑
Angiotensin Converting Enzyme Inhibitor	↑↑	↑	↓	↑
Hydrochlorothiazide	↑	↑	↑	↓
Aliskiren—Hydrochlorothiazide combination	↑↑↑	↓	↓	↔

Figure 2. Different effects of different RAAS inhibitors and hydrochlorothiazide on plasma renin concentration (PRC), plasma renin activity (PRA) and angiotensin II levels are shown. Moreover, estimated changes in the amount of serum potassium due to different drugs in monotherapy and the combination of aliskiren with hydrochlorothiazide are shown.



Interestingly, almost all studies investigating monotherapy with hydrochlorothiazide and its effect on mortality and morbidity investigated higher doses than those usually prescribed today. Most studies used 50–100 mg of hydrochlorothiazide daily, compared to the 6.25–25 mg we use today in monotherapy as well as in all available combinations. It is important to note that for these low-dose treatments, little or no data exist today which show outcome improvements for hydrochlorothiazide. Another diuretic, namely chlorthalidon, seems to be more efficient in lowering blood pressure when compared to hydrochlorothiazide¹⁹ and it was recently proven to be as potent as lisinopril or amlodipine in lowering cardiovascular events.³⁰ which challenges clinicians' as well as pharmaceutical companies' preference for hydrochlorothiazide.

Nevertheless, hydrochlorothiazide is effective for blood pressure reduction alone as well as in most of the possible combinations. Given the different effects of hydrochlorothiazide and aliskiren on PRA, a combination might be one efficient and safe way to lower blood pressure, especially since the adverse events of both medications may counteract each other.

Villamil et al investigated in 2776 patients with increased diastolic blood pressure (MSDPP 95–109 mmHg) the use of hydrochlorothiazide and aliskiren, each alone, and also in combination. Both drugs significantly reduced blood pressure—interestingly enough by the same amount (using up to 300 mg aliskiren versus 25 mg hydrochlorothiazide)—but the different combinations were dose-dependently more efficient than the respective monotherapies. This was also seen in regard to control rates. Moreover, the incidence of hypokalaemia induced by hydrochlorothiazide was significantly decreased in combination with aliskiren and furthermore, the increase of PRA due to the diuretic treatment was neutralized by aliskiren.¹⁴ Recently, Schmieder et al showed a more pronounced effect of the aliskiren-based regime compared to the hydrochlorothiazide-based regime after an add-on of amlodipine in both arms where this was deemed appropriate in 1126 patients with hypertension.³¹ Unfortunately, no combination of aliskiren together with hydrochlorothiazide was tested in this large study.

In 489 obese and hypertensive patients, who were not adequately treated with 25 mg of hydrochloro-

rothiazide once daily, the addition of up to 300 mg aliskiren improved treatment in respect to a significant reduction of blood pressure when compared to hydrochlorothiazide alone. Interestingly, addition instead, with the ARB irbesartan (up to 300 mg) or the CCB amlodipine (up to 10 mg) achieved similar improvements in control rates when compared to those using aliskiren. In line with the PRA lowering properties of aliskiren, all treatment arms increased PRA despite aliskiren, which could decrease it significantly. The rates of adverse events were similar in irbesartan and aliskiren, with an increase of peripheral oedema in the amlodipine arm. Additionally, low serum potassium was seen more frequently in the amlodipine-based regime, but obviously not in both of the RAAS inhibitor arms.³²

In 901 elderly patients with systolic hypertension, an aliskiren-based regime (starting with 150 mg, and then moving up to 300 mg) with an add-on of hydrochlorothiazide (after 12 weeks, up to 25 mg) and amlodipine (after 22 weeks, up to 10 mg) was compared to a ramipril -based regime (starting with 5 mg, going up to 10 mg) with a similar add-on. Although the authors planned a non-inferiority trial only, the aliskiren-based regime was significantly better in regard to hypertension control rates in all of the various aliskiren-based treatment arms. This was further accompanied by a smaller number of patients requiring hydrochlorothiazide or hydrochlorothiazide plus amlodipine as an add-on to achieve control of hypertension. Moreover, cough—as the major adverse event of ACE-Is—was seen to occur less frequently in the aliskiren-based regime.³³

The recent reappraisal of the 2007 European Hypertension guidelines favours an early combination of different drug classes as well as that of a single pill regime, whenever available. Indeed, single pill combinations were shown to be superior in regard to compliance and efficacy when compared to free combinations in a meta analysis.³⁴ A single pill combination of aliskiren and hydrochlorothiazide is also available and its efficacy was tested recently.³⁵ After 4 weeks of hydrochlorothiazide the 722 non-responders (MSDBP over 90 mmHg) were randomly assigned to 8 weeks of a once-daily treatment with aliskiren/hydrochlorothiazide as 300/25 mg or 150/25 mg in a single pill combination, or they stayed on 25 mg of hydrochlorothiazide in monotherapy.

The single pill combination reduced blood pressure and increased control rates in a dose-dependent manner when compared to hydrochlorothiazide monotherapy. While this shows the efficacy of single pill aliskiren and hydrochlorothiazide, there are no direct comparisons of free combinations to single pill combinations available for aliskiren in any combination, although this would purport to a very high level of interest (Fig. 3). Moreover, taking into account the interesting results of a recent study³⁶ investigating the superiority of the combination of a RAAS-inhibitor (benazepril) together with amlodipine compared to the combination with hydrochlorothiazide, other combinations than those reviewed here, e.g. aliskiren combined with amlodipine might be promising as well, and these are already under development.

Patient Preference

Patients with hypertension have relatively low compliance. This seems to be negatively correlated with the number of pills patients have to take. Moreover, the success in controlling blood pressure also predicts a patient's compliance. This makes those anti-hypertensive medications attractive, which can be given only once daily and which are known to have the least amount of side effects. Dependent on comorbidities, RAAS-inhibitors might be an optimal

choice in starting medication in “uncomplicated” hypertension. Aliskiren produces few side effects (more so than ACE-Is, and similar to ARBs) and the addition of hydrochlorothiazide as a combination is effective. Moreover, the side effects in regard to potassium levels of both medications (diuretics lower these, aliskiren raises them) counteract each other, which makes them a preferred partner per se. This is especially the case, since hypokalaemia is associated with changes in glucose metabolism (one feared side effect of diuretics), and this may ultimately increase the risk of a new onset of diabetes. Thus, diuretics as a monotherapy may seem questionable to some patients. The use of a single pill combination, also available for aliskiren/hydrochlorothiazide has been suggested to increase compliance. Moreover, aliskiren is the newest addition in the long line of the antihypertensive armamentarium, which makes them especially attractive for many patients.

Place in Therapy

Aliskiren's place in antihypertensive therapy is established and it is one more drug to effectively lower blood pressure without any significant side effects. Nevertheless, the main goal of any anti-hypertensive is not only to lower blood pressure, but to improve as well the outcome in patients. Therefore, large-scale

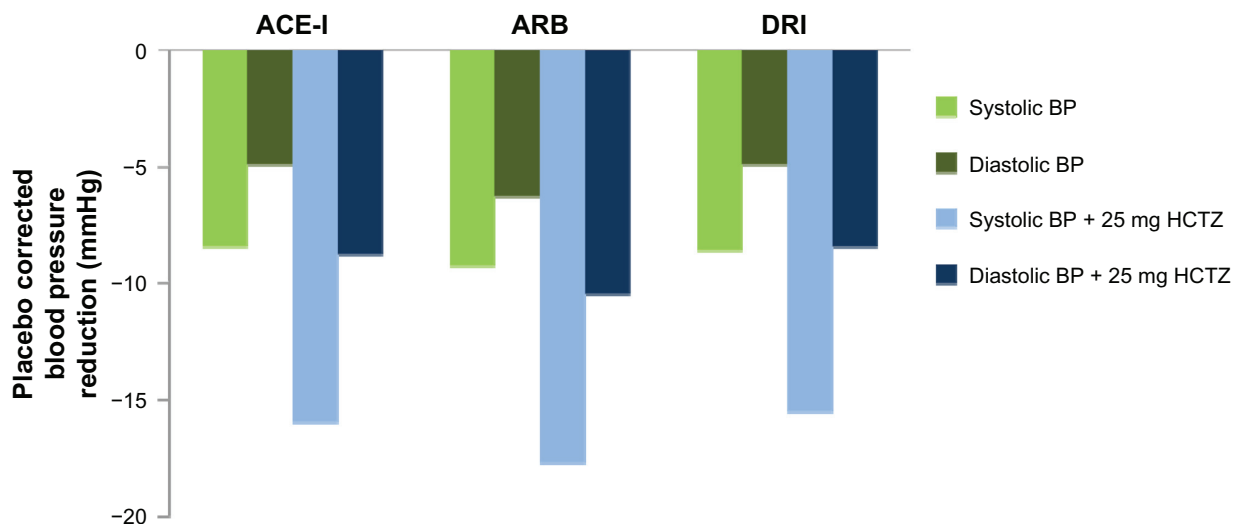


Figure 3. As based on the Cochrane Database System reviews which include studies in patients having hypertension treated with a RAAS inhibitor compared to placebo,^{25,27,28,53} this shows mean placebo-corrected systolic and diastolic blood pressure reduction of an ACE-I, an ARB or aliskiren (maximal dose in each group) in monotherapy and in combination with 25 mg of hydrochlorothiazide. A similar efficacy of all different RAAS inhibitors in regard to blood pressure reduction is suggested. Since no head-to-head trial was done for most class combinations, no direct comparisons can be made from an examination of the articles and reviews in the current literature.

Abbreviations: ACE-I, Angiotensin Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; DRI, direct rennin inhibitors; HCTZ, hydrochlorothiazide.



clinical trials were designed and some of them are already on their way to completion to test whether treatment with aliskiren can indeed reduce cardiovascular mortality.

Only a biomarker (or surrogate parameter) study has been finished which investigated the outcome with aliskiren. Such biomarker studies have already shown that aliskiren might be effective towards cardiac failure. The first study in heart failure population where aliskiren was tested involved the Aliskiren Observation of Heart Failure Treatment study (ALOFT).³⁷ In 302 patients with stable heart failure (NYHA II–IV) and hypertension it was documented that 150 mg of aliskiren was safe and well tolerated in addition to an ARB or an ACE (but not both). No increment in adverse events could be documented after aliskiren add-on therapy in regard to hyperkalaemia, hypotension or renal dysfunction. Moreover, it was shown that an add-on of aliskiren was beneficial towards biomarkers of heart failure. N-terminal proBNP (NT-proBNP), which is closely associated with the outcome in heart failure patients, showed a significant improvement after 3 months therapy with aliskiren. Another trial in cardiovascular patients measured the effects of aliskiren as an add-on therapy on the development of cardiac hypertrophy (ALiskiren in Left Ventricular Hypertrophy, ALLAY).³⁸ Cardiac hypertrophy is an important predictor of cardiovascular outcome and is known to be associated with arterial hypertension.^{39–41} In this study, 300 mg of aliskiren were compared to 100 mg of losartan, or the combination of both, over 36 weeks. The effect of this treatment on left ventricular mass as assessed by MRI in 465 patients with hypertension and left ventricular (LV) hypertrophy was investigated. In ALLAY it was shown that aliskiren, when compared to losartan, was similarly effective in reducing LV mass. The combination of both drugs did not result in any additional benefit, although the tolerability of 300 mg of aliskiren as an add-on to 100 mg of losartan was excellent and did not cause any increase in the number of adverse events. Promising effects of aliskiren in different models of cardiac failure were shown^{42–46} and therefore the effect in post myocardial remodelling was then investigated in the ASPIRE trial (Aliskiren Study in Post-MI Patients to Reduce REmodelling). There was no significant improvement in the primary endpoint, i.e. in the change in the LV

endsystolic volume between placebo or aliskiren after 36 weeks in patients after myocardial infarction and low ejection fraction. Nevertheless, double RAAS inhibition with aliskiren as an add-on on top of conventional therapy did increase significantly the risk of adverse events concerning increased renal dysfunction, hypotension and hyperkalaemia, although there was no significant change in more serious adverse events (e.g. creatinine above 3 mg/dl).

One established biomarker for renal protection is the reduction of the albuminuria.^{47,48} ARBs and ACE-Is were shown to be beneficial in regard to albuminuria in patients with diabetic nephropathy^{49–51} making a RAAS-inhibitor the standard of care in that disease. The AVOID (Aliskiren in the evaluation of proteinuria in Diabetes) study tested in 599 patients with diabetes mellitus, hypertension and proteinuria to what extent 300 mg of aliskiren versus placebo both as an add-on to 100 mg of losartan and optimal antihypertensive therapy would reduce albuminuria.⁵² A significant 20% reduction in urinary albumin/creatinine ratio—when compared to the addition of placebo—was seen with aliskiren after 6 months of treatment. In more than twice the number of the patients in the aliskiren group, compared to the placebo group, this reduction was 50% from baseline. Interestingly, blood pressure reduction of aliskiren was only mild in these optimal treated patients (2/1 mmHg further reduction compared to placebo) suggesting beneficial effects of aliskiren next to blood pressure reduction.

The outcome trials (ALTITUDE: Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints, and ATMOSPHERE: Aliskiren Trial to Minimize Outcomes in Patients with heart Failure) are on their way to completion and these results will finally benchmark the place of aliskiren in today's therapy.

Conclusions

Aliskiren in combination with hydrochlorothiazide is one possible way to lower blood pressure in patients with hypertension. It is not only effective, but also safe in regard to adverse events. The combination of both drugs is favourable, especially since adverse events will counteract each other and the addition of a PRA-increasing drug seems to be a logical option for aliskiren. Future studies will have to clarify its role in patients with refractory hypertension. The outcome studies, which are impatiently awaited by



many clinicians worldwide, will finally consolidate aliskiren's position in the hypertensive medication of today and tomorrow.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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