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Review article:

RENIN INHIBITORS IN DIABETES AND HYPERTENSION: AN UPDATE

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ABSTRACT

The coexistence of hypertension and diabetes increases the incidence of cardiovascular events and long-term morbidity and mortality. Blood pressure should be controlled with the most appropriate drugs as well as tight blood glucose control in patients with diabetes and hypertension. RAAS (Renin Angiotensin Aldosterone System) blockers have an important role in the treatment of these patients, in this sense, ACEi and ARB remained the major treatment option in hypertension guidelines. The most recent RAAS blocker to be approved by the FDA was aliskiren in 2007, a renin inhibitor. Studies showed that aliskiren is as effective as other antihypertensive drugs and has a safety profile similar to placebo. The potent renin inhibitor aliskiren directly inhibits the RAAS system at its rate limiting step and differently from other RAAS blockers; it decreases plasma renin activity (PRA). Although the relationship of increased PRA levels and cardiovascular risk has been shown, it is unclear if the PRA decrease provided by aliskiren has an impact on clinical outcomes and cardiovascular endpoints. On the other hand, large trials like ASPIRE, AVANT-GARDE, ALTITUDE, ASTRONAUT, which investigated the combination of aliskiren with other RAAS blockers, failed to show the expected outcomes or resulted with an increased incidence of adverse effects, which raised more questions. As a result of the ALTITUDE trial, combination of aliskiren with an ACEi or ARB is not recommended in patients with hypertension and diabetes, or at least moderate renal dysfunction. Trials designed to prove aliskiren's efficacy in new indications like diabetes, may face similar problems related to dual RAAS blockade because in the majority of cases, the optimal treatment is achieved with an ACEi or ARB. In this conjuncture, the increase in adverse events seen with aliskiren might be related to dual RAAS blockade rather than aliskiren directly. For instance, it is unclear whether the adverse event incidence would be the same, less, or higher if ALTITUDE was designed to investigate ACEi and ARB combination without aliskiren. In fact, every new molecular entity and mechanism of action faces the same barriers. For the time being, differentiating points like PRA lowering effects as an add-on therapy to calcium channel blockers or hydrochlorothiazide, and the populations that might have additional benefit, should be carefully investigated.

Keywords: Aliskiren, renin inhibitor, hypertension, diabetes

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INTRODUCTION

Hypertension is the most frequent condition in primary care settings that results with myocardial infarction, renal failure, stroke, retinopathy, and death if underdiagnosed or treated inappropriately. Diabetes Mellitus is as chronic, complex, and common disease as hypertension. Incidence of both in the same patient makes the outcomes worse.

The etiology of diabetes complications was unclear and much discussed until the 1990s. During that period, clinical trials demonstrated that intensive control of blood glucose in diabetes was correlated with microvascular complication decrease and angiotensin converting enzyme inhibitor (ACEi), independent from blood pressure (BP) lowering effects, reduced the progression of diabetic complications (Hsueh and Wyne, 2011). Nowadays, it is widely known that RAAS (Renin Angiotensin Aldosterone System) blocking agents prevent or delay the onset of diabetes complications. Moreover, trials with RAAS blockade and guidelines allowed ACEi and angiotensin II receptor blockers (ARB) to be the first-line treatment options in patients with hypertension and diabetes.

Diabetes and hypertension both affect the vascular tree and deteriorate same target organs including the heart, kidneys, eyes, and brain (Grossman and Messerli, 2008). The cardiovascular disease risk is four times higher when both diseases are present compared with hypertension alone (Aksnes et al., 2012). Moreover, Framingham cohort results showed that coexistent hypertension is attributed to excess risk of cardiovascular events in patients with diabetes (Chen et al. 2011). Thus, blood pressure targets in diabetes are important for treatment efficacy. The most common cause of end stage renal disease (ESRD) is hypertension and diabetes mellitus (Grossman and Messerli, 2008). Hypertension and diabetic retinopathy are important causes of blindness (Grossman and Messerli, 2008). The presence of hypertension and diabetes has a great effect on silent cerebral infarcts (Eguchi et al., 2003).

As a result of several studies, it is known that decreasing blood pressure reduces cardiovascular events. The therapeutic goals for diabetic hypertensive patients differ between guidelines. According to the recent American Diabetes Association (ADA) guidelines, the diabetic patients' treatment target for blood pressure is 140/90, excluding young patients (American Diabetes Association, 2014). In the Eighth Joint National Committee (JNC 8) guideline "Evidence-Based Guideline for the Management of High Blood Pressure in Adults," goals below 140/90 mm/Hg are recommended for diabetic hypertensive adult patients (James et al., 2014). Lower diastolic goals are proposed in the European Society of Hypertension/The European Society of Cardiology (ESH/ESC) 2013 guidelines for patients diagnosed as having diabetes and hypertension at <140/85 mm/Hg (Mancia et al., 2013). An earlier ADA 2013 recommendation was below 140/80 mm/Hg and the ESH/ESC 2009 recommendation was 130/80 mm/Hg.

Drug therapy recommendations for patients with diabetes and hypertension in ESC/ESH and ADA 2013 guidelines were ACEi/ARB; whereas the JNC 8 2014 guidelines claim that there is moderate evidence to support initiating drug treatments ACEi/ARB/calcium channel blockers (CCB) or thiazide-type diuretics (James et al., 2014). The ADA 2014 diabetes care recommendation for pharmacologic therapy for patients with diabetes and hypertension includes ACEi or ARB, and notes that multiple-drug therapy is generally needed to achieve the blood pressure goals. Interestingly with evidence level A, ADA 2014 recommends taking medication at bedtime (American Diabetes Association, 2014).

The most recently approved RAAS blocking antihypertensive is a renin inhibitor, aliskiren. In this review, we discuss the use of aliskiren in patients with hypertension and diabetes as a monotherapy or in combination with other agents, the adverse effects of aliskiren, dual RAAS blockade, and ALTITUDE and some other clinical trials.

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POTENTIAL ADVANTAGES OF ALISKIREN

It is known that higher plasma renin activity is associated with cardiovascular risk. Aliskiren, like ACEi and ARB, affects the negative feedback of RAAS and increases plasma renin concentration (Azizi et al., 2006). Unlike other antihypertensives excluding beta blockers, aliskiren decreases plasma renin activity (PRA) (Gradman and Traub, 2007). Therefore, aliskiren may provide additional benefit with its unique PRA lowering capacity. However, before drawing any conclusions, the clinical impact on cardiovascular end points via the PRA lowering effect of aliskiren in clinical trials should be documented. On the other hand, the treatment efficacy of aliskiren might be reduced due to lower baseline PRA, reactive PRA increase or inadequate reduction (Stanton et al., 2009).

Aliskiren has a good safety profile within its therapeutic dose range (150 - 300 mg) and can be used in patients with renal impairment because of its hepatic elimination. Drug interactions are rarely seen. Aliskiren should not be used during pregnancy and renal artery stenosis, which is the same for ACEi and ARBs.

In addition, the long half-life of aliskiren (nearly 40 h) could put this medicine one step ahead of other drugs. In a randomized double-blind trial, Palatini and colleagues measured 24 h mean ambulatory BP changes after a missed dose in 654 patients with hypertension who received aliskiren, ramipril or irbesartan. Aliskiren 300 mg maintained antihypertensive efficacy over 24 hours. The decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) was better maintained with aliskiren 300 mg (91/91 %) than irbesartan 300 mg (73/77 %) and ramipril 10 mg (64/65 %) (Palatini et al., 2010). This difference among groups might be explained by the long-duration half-life of aliskiren.

PRORENIN AND DIABETES

The function of prorenin, which is a precursor of renin, was investigated in several preclinical studies. Prorenin can be activated with or without proteolysis. Proteolytic activation requires prosegmentin separation. The non-proteolytic activation is achieved via binding with the recently discovered (pro)renin receptor ((P)PR).

Prorenin levels have been shown to be higher in patients with diabetes mellitus with microvascular complications. It is shown that this increase occurs earlier than high microalbumin levels and prorenin levels can be predictive for microalbuminuria, together with glycosylated hemoglobin (Danser et al., 1989; Luetscher et al., 1985). However, the reason for the increase in prorenin levels in this condition remains unknown.

On the other hand, studies show that increased prorenin levels are related with the development of several pathologic conditions such as heart failure, diabetic nephropathy, and diabetic retinopathy and that prorenin receptors may have a role in hypertension and end organ damage (Saris et al. 2006; Véniant et al., 1996).

All drugs that inhibit (directly or indirectly) the effects of angiotensin II increase prorenin levels through inhibition of the negative feedback loop. However, no data exists that shows that this prorenin increase causes excessive prorenin binding and harmful effects. Renin inhibitors bind to the active part of the enzyme and inhibits functionally, which is different from other antihypertensives (Uresin and Baran, 2009). Aliskiren has been shown to be a potent inhibitor of mature renin's free forms and renin or prorenin's receptor bound forms (Biswas et al., 2010).

TREATMENT EFFICACY AND SAFETY OF ALISKIREN

In the majority of patients, combination therapy with at least 2 antihypertensive drugs is needed to obtain a BP level below recommended guideline limits. In patients with

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high initial BP, combination therapy should be considered as a prioritized option (Mancia et al., 2013). In order to increase the efficacy of aliskiren in hypertension, it could be combined with agents that increase PRA such as ACEi, diuretics or ARBs (Andersen et al., 2008; Gradman et al., 2005; Oparil et al., 2007; Uresin et al., 2007; Villamil et al., 2007).

Aliskiren has been shown to have superior or similar efficacy and safety as a monotherapy in hypertension versus ACEi, ARB, HCTZ and CCB in many studies.

In a randomized 8 week trial by Villamil and colleagues, 2776 patients with hypertension were treated in 4 treatment arms with aliskiren, hydrochlorothiazide (HCTZ), their combination, or placebo. Both diastolic and systolic BP reduction was significantly better ($p<.0001$ and $p<.05$ respectively) in the combination arm excluding low dose 75 mg aliskiren – 12.5 mg HCTZ combination. PRA was decreased by aliskiren by up to 65 %. Conversely, PRA was increased by HCTZ by up to 72 %. The combination of aliskiren and HCTZ produced a 46.1-63.5 % decline in PRA (Villamil et al., 2007). In another study with HCTZ, either 25 or 12.5 mg in combination with 300 mg aliskiren showed better SBP/DBP decrease (15.9/11.0 mm/Hg or 13.5/10.5 mm/Hg) than aliskiren alone (8.0/7.4 mm/Hg; both $p < 0.001$). Also, tolerability of the combination treatment was similar to that of the aliskiren monotherapy (Nickenig et al., 2008). Patients with uncontrolled hypertension under 25 mg HCTZ treatment had a significant BP decrease after administration of 150/25 mg and 300/25 mg aliskiren/HCTZ combination (26 % vs 49 and 58 %, $p < .001$ both) in an 8-week trial with 722 patients (Blumenstein et al., 2009).

ACCELERATE (Aliskiren and the CCB Amlodipine Combination as an Initial Treatment Strategy for Hypertension Control) trial randomized patients in 3 treatment arms; aliskiren 150 mg plus placebo, amlodipine 5 mg plus placebo and aliskiren 150 mg plus amlodipine 5 mg. Between 16 and 32 weeks of the study, all patients were treated with 300 mg aliskiren plus 10 mg amlodipine. At the 24th week, patients with uncontrolled BP were allowed to receive HCTZ or placebo. The initial combination therapy arm had a 6.5 mm/Hg better SBP reduction versus monotherapy groups ($p < .0001$). The Amlodipine monotherapy arm had 11.4 % peripheral edema, which was the most common reason for withdrawal. Hypotension rates were 0.3 %, 0.6 % and 0.8 % with aliskiren, amlodipine, and combination arms, respectively (Brown et al., 2011).

Aliskiren has been compared with ACEi in many head-to-head trials. Uresin and colleagues compared the efficacy and safety of aliskiren in 837 patients with diabetes with hypertension. This trial showed that a combination of aliskiren and ramipril was superior versus aliskiren ($p=.043$) and ramipril alone ($p=.004$) in decreasing DBP. Also, the combination regimen was superior in SBP decrease vs ramipril monotherapy ($p<.0001$), but not aliskiren monotherapy ($p=.088$). Considering SBP, aliskiren monotherapy was superior to ramipril monotherapy ($p=.021$). Safety and tolerability measures were similar among the groups. The most common adverse effects seen with aliskiren monotherapy were headache (3.2 %), cough (2.1 %), nasopharyngitis (3.2 %) and diarrhea (1.1 %). Although cough was seen in 4.7 % of ramipril monotherapy, in the combination arm it was 1.8 %. Hyperkalemia was 5.5 %, 2.6 % and 2.2 % in the combination, ramipril and aliskiren arms, respectively (Uresin et al., 2007).

In a randomized clinical trial, the antihypertensive effect of aliskiren and valsartan alone or in combination was investigated in 1797 patients. The highest dose combination (300 mg of aliskiren and 320 mg of valsartan) reduced the mean DBP significantly better than either monotherapy (12.2 mm/Hg decrease with combination; versus 9.0 mm/Hg with aliskiren; 9.7 mm/Hg with valsartan 320 mg; 4.1 mm/Hg decrease with placebo). There was no difference in the rates of the adverse reactions, including hyperkalemia

and increased serum creatinine levels (Oparil et al., 2007).

White and colleagues showed the favorable safety profile of aliskiren in their meta-analysis. Twelve thousand patients with hypertension from 12 randomized controlled trials were pooled to analyze the adverse effect profile of aliskiren versus ACEi and ARB. Long-term adverse events were lower with aliskiren 150 mg and aliskiren 300 mg (33.7-43.2) compared with ACEi (60.1 %) and ARB (53.9 %). The number of serious adverse event incidents with aliskiren (3.4 %) was between ACEi (2.4 %) and ARB (8.4 %). Angioedema, urticaria and renal dysfunction were less than 0.5 % and hyperkalemia as low as 0.1 %. Hypotension (7.6 %) and peripheral edema (4.8 %) were the two most reported adverse events that occurred with aliskiren treatment. The incidence of cough with aliskiren treatment was 3.7 %, which was lower than that of ACEi treatment (12 %). Aliskiren at a dose of 600 mg was related with diarrhea (White et al., 2010).

Aliskiren combined with an ARB or HCTZ has a good safety profile, demonstrated by a meta-analysis of 10 randomized clinical trials and a total of 4814 patients. However, serum potassium levels should be carefully monitored when using aliskiren with another RAAS blocking agent. There is a greater risk of hyperkalemia when aliskiren is used with ARB or ACEi than when ACEi or ARB (RR 1.58, 95 % CI 1.24–2.02) or aliskiren (1.67, 1.01–2.79) are used as a monotherapies, respectively. There was no significant difference in acute kidney failure risk between the mono- and combined therapy (1.14, 0.68–1.89) (Harel et al., 2012).

AVOID, ALTITUDE AND DUAL RAAS BLOCKADE

In the AVOID (Aliskiren combined with losartan in type 2 diabetes and nephropathy) trial, 599 patients with hypertension and type 2 DM and nephropathy who were taking 100 mg losartan daily, received add-on aliskiren. This trial was randomized in 2 arms; patients in one arm received 150 mg aliskiren for the first 3 months then the aliskiren dose was doubled, and the second arm was given placebo. Compared with placebo, aliskiren 300 mg showed a 20 % decline in albumin/creatinine ratio (95 % confidence interval, 9 to 30; $p < .001$). There was no difference in adverse events and serious adverse events between the groups. Considering the similar blood pressure reductions between the groups (systolic, 2 mm/Hg lower [P=.07] and diastolic, 1 mm/Hg lower [P=.08] in the aliskiren group), the renoprotective effect of aliskiren might be independent of blood pressure reduction (Parving et al., 2008).

The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Disease Endpoints) study investigated 300 mg add-on aliskiren to ACEi or ARB in patients with diabetes whose glomerular filtration rate (GFR) was lower than 60 ml/min per 1.73 m^2 or with microalbuminuria. The primary outcome in ALTITUDE was time to first event for the composite endpoint of cardiovascular (CV) death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for heart failure (HF), onset of end-stage renal disease or doubling of baseline serum creatinine concentration (Parving et al., 2009). The study was terminated early by the safety board due to increased adverse events such as nonfatal stroke (2.6 % with aliskiren vs. 2 % placebo, unadjusted $p = .04$), renal impairment hyperkalemia and hypotension (McMurray et al., 2012). This study concluded that aliskiren should not be combined with ACEi and ARB in patients with hypertension and diabetes or in the presence of moderate or worse renal impairment.

In 2008, the ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial) trial demonstrated that a combination of ramipril and telmisartan decreased proteinuria better than both ramipril and telmisartan monotherapies. However, secondary renal outcomes, dialysis, and serum creatinine doubling was high-

er with ramipril and telmisartan combination therapy (Mann et al., 2008).

ONTARGET raised questions about combining two RAAS blocking agents and the predictive value of surrogate biomarkers such as microalbuminuria. This trial, which recruited patients with hypertension and atherosclerotic vascular disease or diabetes with end-organ damage who were prescribed co-medication of ACEi and ARBs, resulted in an increase renal adverse event incidence such as dialysis use and increased serum creatinine levels (Mann et al., 2008). On the other side, the ALTITUDE trial investigated cardio-renal hard endpoints of adding aliskiren to ACEi or ARB therapy in patients with diabetes and renal disease (GFR < 60 ml/min per 1.73 m^2 or microalbuminuria) (Parving et al., 2009). In this perspective, when ONTARGET and ALTITUDE were evaluated together in hypertensive patients with diabetes and renal disease; hyperkalemia, high serum creatinine, renal dysfunction and hypotension related with dual RAAS blockage increased. Interestingly, in ALTITUDE, adverse events like hyperkalemia and hypotension related with dual RAAS were predictable in trial hypertensive patients with diabetes and renal disease, but the increase in non-fatal stroke incidence was not and this finding sparked an argument concerning the use of dual RAAS blockade with aliskiren. This issue should be thoroughly investigated.

New components of the RAAS pathway are frequently being discovered and evaluated in clinical trials. For example, in recent years prorenin, angiotensin IV, Angiotensin 1-7 and ACE2 and more parameters of RAAS were investigated by researchers. However the roles or clinical impacts of these parameters are still not clear. In theory, inhibiting RAAS from two points could result in too much inhibition of positive components of RAAS and thus the expected improvement might not be seen.

The results of ATMOSPHERE (The Aliskiren Trial of Minimizing Outcomes for Patients with Heart Failure) trial has a very different design vs. ALTITUDE and by recruiting a different patient's population such as those with heart failure will give us additional information on dual RAAS blockade with aliskiren (McMurray at al., 2012)

CONCLUSION

The use of RAAS blockers in patients with diabetes and hypertension has positive effects and is recommended by guidelines. Aliskiren shows similar efficacy and safety when compared with the widely-used ACEi and ARBs. Though similar in efficacy and safety, in terms of pharmacoeconomics and place in therapy studies, as seen in every other new drug it has failed to show superiority versus current treatments. The first results of the ASPIRE-HIGHER program consisting of 14 major clinical trials and about 35 000 patients reported very positive results. The perspective towards aliskiren changed after AVANT-GARDE (Aliskiren and Valsartan Versus Placebo in Lowering NT-proBNP in Patients Stabilized Following an Acute Coronary Syndrome) and ASPIRE (Effect of the direct renin inhibitor aliskiren on left ventricular remodelling following myocardial infarction with systolic dysfunction), and recently ALTITUDE, which was expected to have very positive results and more recently ASTRONAUT (Six Months Efficacy and Safety of Aliskiren Therapy on Top of Standard Therapy, on Morbidity and Mortality in Patients with Acute Decompensated Heart Failure) because trials resulted with somehow disappointing results (Sen et al., 2013). However, it could be argued that the negative results were not solely related to aliskiren, but also to study designs, study population and dual RAAS blockade. In the next few years dual RAAS blockade, study populations, and surrogate markers like microalbuminuria will probably be discussed more.

After ONTARGET, the ALTITUDE trial evaluated hard endpoints with a different study design. Dual RAAS blockade was expected to have a positive effect in patients with hypertension and diabetes. However,

the results brought about more questions. For the time being, according to current data, the combination of aliskiren with an ACEi or ARB is not recommended for hypertensive patients with diabetes or at least renal dysfunction, especially when we consider the risk of developing new adverse events such as hyperkalemia and hypotension.

Dual RAAS blockade might have positive results in different patient groups such as those with heart failure or diabetes with other complications, excluding renal impairment. Moreover, specific patients with high baseline PRA might be candidates for future clinical trials.

According to regulations, in order to show efficacy of aliskiren in new indications, such as diabetes and heart failure, aliskiren should be added to the current optimal treatment. However, in these populations, the optimal treatment is mostly an ACEi or ARB. Considering this, aliskiren should provide its benefits with dual RAAS blockage without any increase in the rate of adverse reactions. There are no more trials other than CHARM-added (Effects of Candesartan in Patients with CHF and Reduced Left-ventricular Systolic Function Taking Angiotensin-converting-enzyme Inhibitors), Val-HeFT (A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure) and a few more highlighting benefits of dual RAAS blockage (McMurray et al., 2003; Nakao et al., 2003). Discordant results of different trials should be understood well; trial designs and endpoints should be analyzed. Another fact is that we need more and better surrogate markers to better predict hard endpoints. Pharmacoeconomic long-term benefits might also be investigated in clinical trials or real-life studies.

Future clinical trials may focus on aliskiren combinations with HCTZ and/or CCB due to the disappointing results of dual RAAS blockade studies. Current data have substantiated the effectiveness of aliskiren as a monotherapy or in combination with HCTZ and/or calcium channel blockers. It is known that CCB treatment does not affect or improve metabolic parameters such as blood glucose and lipids. When this issue is taken into account, a combination of aliskiren and CCB may be a new option for patients with hypertension and diabetes.

Although there was no evidence of harm with aliskiren treatment, the APOLLO trial, which was evaluating the effect of aliskiren alone and in combination with HCTZ or CCB on cardiovascular events in elderly people, was also terminated early. There is very limited information on the reason for termination of the APOLLO trial. On the other hand, initiation of aliskiren in addition to standard therapy demonstrated no beneficial effect in mortality or hospitalization in heart failure patients in the ASTRONAUT trial. At this time, no trials using aliskiren with hard endpoints are expected in the near future (Mancia et al., 2013).

Aliskiren is a relatively new drug that was approved by the FDA for the treatment of hypertension in 2007. Although in recent years it has proven its efficacy and placebo-like safety profile in clinical trials, there are several issues to be clarified. In particular, there is a requirement for the thorough documentation of the clinical impact of lowering PRA activity, dual RAAS blockade, and the effect of (P)RR.

As concluded by several studies, prorenin may have a role beyond angiotensin formation. Data on the function of (P)RR receptor remains preclinical and unclear. To understand the RAAS system better and develop new therapies in this area is exciting, but it remains unresolved for the time being. The effects of renin inhibitors on prorenin should be carefully investigated when we consider that high prorenin levels might be associated with diabetic complications in patients with hypertension.

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