Different Effects of Aliskiren and Losartan on Fibrinolysis and Insulin Sensitivity in Hypertensive Patients with Metabolic Syndrome

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Key words
- PAI-1 antigen
- tPA activity
- AT1R blockers
- renin inhibition

Abstract

The aim of this study was to compare the effect of aliskiren and losartan on fibrinolysis and insulin sensitivity (IS) 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 od or losartan 100 mg od for 12 weeks. Clinic blood pressure (BP), plasma PAI-1 antigen, and tPA activity were evaluated after 2, 4, 8, and 12 weeks of treatment. At the end of each treatment period patients performed an euglycemic hyperinsulinemic clamp and IS was assessed by glucose infusion rate (GIR). 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%), NS vs. baseline, $p<0.05$ vs. aliskiren)]. These results indicated that in this type of patients, despite similar BP reduction, aliskiren improved the fibrinolytic balance as well as IS, while losartan worsened the fibrinolytic balance and did not affect IS. The clinical relevance of these different effects remains to be clarified.

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Introduction

Hypertension and metabolic syndrome are conditions characterized by impaired fibrinolysis, mainly expressed as elevated plasma levels of plasminogen activator inhibitor-1 (PAI-1) and decreased tPA activity [1,2]. It is well known that increased PAI-1 is an independent risk factor for thromboembolic complications [3,4]. Elevated levels of PAI-1 are also considered to be a possible link between insulin resistance, type 2 diabetes mellitus, and atherosclerosis [1,5].

An amount of experimental and clinical evidence indicates that the renin-angiotensin-aldosterone system (RAAS), which plays an important pathophysiological role in both hypertension and the metabolic syndrome, can influence the fibrinolytic balance both by stimulating PAI-1 synthesis and by reducing tPA production [6,7].

Blockade of the RAAS by angiotensin-converting enzyme-inhibitors (ACE-Is) has been associated with a decrease in PAI-1 concentrations in most clinical trials [8–14]. This observation has been advocated as one possible explanation for the reduction of the rate of myocardial infarction observed during ACE-inhibition treatment [8,15].

The effects on fibrinolyis of the angiotensin receptor blockers (ARBs), which inhibit the RAAS by blocking the effects of angiotensin II (Ang II) at the AT1 receptor level, are more controversial, with some studies showing a reduction in PAI-1 plasma levels [16,17] and more numerous studies showing no effect [11–14,18,19]. Other mechanisms beyond Ang II inhibition, including Ang II metabolites and kinin mediated effects, have been advocated to explain the different effects of ACE-Is and ARBs on the fibrinolytic balance [20,21].

Recently a new drug that blocks the RAAS by direct renin inhibition, aliskiren, has become available in clinical practice for hypertension treatment [22]. In contrast with both ACE-Is and ARBs, which increase renin release and plasma renin activity (PRA) with reactive activation of the RAAS, because of interference with feedback inhibition of renin release, aliskiren, targeting the renin system at its point of activation, provides suppression of the RAAS without inducing reactive rises in PRA [23,24]. In clinical trials aliskiren has demonstrated to be effective in lowering BP alone or in combination with other drugs, with a good safety and tolerability profile [22–24].

To date, to the best of our knowledge, the effects of aliskiren on the fibrinolytic balance have not been investigated. Therefore, this study was undertaken in order to evaluate the effects of aliskiren as compared to the ARB losartan on plasma PAI-1 antigen and activity and on plasma tPA activity in hypertensive patients with metabolic syndrome. Due to the close relationship between the fibrinolytic system and insulin sensitivity [5], the effect of aliskiren and losartan on insulin sensitivity, as assessed by the euglycemic hyperinsulinemic clamp [25], was also evaluated.

Materials and Methods

Study design and patients

This was a 12-week, prospective, randomized, double-blind, and parallel group study, with 2 treatment arms. Male and female outpatients, aged 18–65 years, with stage I hypertension (defined as sitting SBP ≥140 and <160 mmHg and sitting DBP ≥90 and <100 mmHg after a 2-week placebo period) and metabolic syndrome (AHA/NHLBI criteria) [26] were considered for enrollment.

Patients with secondary hypertension, smoking habits, creatinine clearance <80 ml/min, total cholesterol (TC) ≥220 mg/dl, diabetes mellitus, history of myocardial infarction or stroke within 6 months prior to the study, congestive heart failure or any severe disease likely to interfere with the conduction of the study were excluded as were those with known contraindications or intolerance to the study drugs.

The study was performed in accordance with the Declaration of Helsinki and its amendments and all patients gave their written informed consent to participate in the study at the time of enrolment.

After a 2-week placebo period, patients fulfilling the inclusion criteria were randomized to receive aliskiren 300 mg or losartan 100 mg both given once daily (od) in the morning (at approximately 8 AM) for 12 weeks. The doses of the 2 drugs were chosen to be equipotent with respect to BP lowering. From the time of enrollment until the completion of the study, all participants maintained their usual diet and level of physical activity and avoided changes in body weight. No concomitant medication was allowed. Both aliskiren and losartan were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study. Randomization was done by drawing envelopes containing randomization codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in cases of an emergency. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. At baseline, we weighed participants and gave them a bottle containing a supply of study medication for at least 100 days. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

Laboratory parameters

Blood pressure, PAI-1 antigen level and activity, and tPA activity were evaluated at the end of the placebo period and after 2, 4, 8, and 12 weeks of treatment, while fasting plasma glucose (FPG), fasting plasma insulin (FPI), and insulin sensitivity were evaluated only at the end of the placebo and of each active treatment period.

The BP measurements were obtained from each patient (right arm) in the seated position by using a standard mercury sphygmomanometer (Korotkoff I and V) with a cuff of appropriate size. Measurements were taken in the morning before daily drug intake (i.e., 24 h after dosing, at trough) and after the subject had rested 10 min in a quiet room. 3 successive BP readings were obtained at 1-min intervals and averaged.

After BP measurements, venous blood was drawn from an antecubital vein for blood sampling at the same hour in the morning, approximately between 08:00 and 09:00 h, because PAI-1 concentration is at its peak during this period. Blood samples were collected on ice and centrifuged immediately at 0 °C for 20 min. All plasma or serum was separated and stored at –70 °C until assay. Blood for measurement of PAI-1 antigen was collected in Vacutainer tubes containing 0.105 mmol/l acidified sodium citrate, and antigen level was determined by using a 2-site enzyme-linked immunosorbent assay (Biopol AB). PAI-1 activity levels were measured with an assay based on the method of Veheijen et al. [27], with standardized commercial kits (Biopool Inc). Plasma tPA activity was determined by using an immunofunctional assay (Chromalize, Biopool AB).

Insulin sensitivity evaluation

Insulin sensitivity was assessed by the euglycemic, hyperinsulinemic clamp, according to the technique of De Fronzo et al. [25]. At 09:00 AM, after the subjects had fasted 12 h overnight, an intravenous catheter (18 g polyethylene cannula, Venflon, Viggo) was placed in an antecubital vein for infusion of insulin and 20% glucose. A second catheter was inserted retrogradely into a wrist vein. The hand was heated (about 70 °C) in a thermoregulated box with the aim of arterializing venous blood within 20–40 min. Plasma glucose was assessed at 5–10 min intervals during the clamp. A 10-min priming infusion of insulin (Humulin R, Lilly corporate, Indianapolis, Indiana, USA), was administered at rate of 1 mU per minute per kilogram for 2 h, during which the plasma glucose was held constant at the basal state (95 mg/dl) by a variable infusion of exogenous glucose. The amount of glucose required to maintain isoglycemia equals whole-body disposal of glucose, provided that exogenous glucose production is essentially absent. During insulin infusion, normal fasting blood glucose levels were maintained by adjustment of the infusion of a 20% glucose solution. The amount of glucose taken up (mg per minute per kilogram of body weight) was calculated for each 10 min interval after the first 20-min of the clamp. Insulin sensitivity was calculated from the mean glucose uptake rate for the last 30 min of the clamp and expressed as the amount of glucose infused during that time (glucose infusion rate: GIR) in mg per minute per kilogram of body weight.

Table 1 Baseline characteristics of the subjects at the beginning of the study

Parameters	Aliskiren (n = 38)	Losartan (n = 38)
Age (years)	54.5 ± 9.9	54.9 ± 9.8
Gender (Male/Female)	20/18	19/19
BMI (kg/m^2)	26.7 ± 1.46	26.5 ± 1.42
SBP (mmHg)	147.8 ± 6.5	148.5 ± 6.3
DBP (mmHg)	97.4 ± 4.9	97.5 ± 4.5
Total cholesterol (mg/dl)	189.4 ± 15.1	187.9 ± 13.8
HDL-cholesterol (mg/dl)	43.2 ± 5.8	42.5 ± 5.4
Triglycerides (mg/dl)	160.6 ± 30.4	165.3 ± 32.1
FPG (mg/dl)	91.2 ± 8.6	90.6 ± 8.3
FPI (μIU/ml)	13.7 ± 3.9	14.2 ± 4.1
Creatinine clearance (ml/min)	100.3 ± 12.2	99.7 ± 12.5
Duration of hypertension (years)	7.3 ± 2.6	7.5 ± 2.7

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; FPI: fasting plasma insulin

Table 2 Effect of treatment on blood pressure

Time	Aliskiren (n = 35)	Losartan (n = 35)
Seated SBP mmHg		
Baseline	147.5 ± 6.4	148.3 ± 6.2
Week 2	135.4 ± 5.4‡	139.4 ± 5.6**
Week 4	134.9 ± 4.9‡	135.8 ± 4.9‡
Week 8	133.5 ± 4.8‡	134.3 ± 4.7‡
Week 12	131.9 ± 4.5‡	132.8 ± 4.6‡
Seated DBP mmHg		
Baseline	97.2 ± 4.8	97.4 ± 4.6
Week 2	89.6 ± 3.9‡	92.6 ± 4.2**
Week 4	88.1 ± 3.6‡	89.3 ± 4.0‡
Week 8	87.2 ± 3.2‡	87.5 ± 3.5‡
Week 12	86.5 ± 2.9‡	86.9 ± 3.2‡

* $p < 0.05$; ** $p < 0.01$; ‡ $p < 0.001$ vs. baseline
SBP: systolic blood pressure; DBP: diastolic blood pressure

Statistical analysis

Continuous variables were tested using a 2-way repeated measures analysis of variance (ANOVA). ANOVA was also used to assess the significance within and between groups. Paired tests were also used: a one-sample *t*-test to compare values obtained before and after treatment administration and two-sample *t*-tests to compare the change score (final minus baseline) for a given parameter between the 2 groups. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 14.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean ± standard deviation (SD). For all statistical analyses, $p < 0.05$ was considered statistically significant.

Results

A total of 80 patients were screened between April and December 2009. At the end of the 2-week placebo period, 76 patients were randomized to aliskiren 300 mg (n = 38) or losartan 100 mg (n = 38). Their main demographic and clinical characteristics are shown in **Table 1**. The 2 treatment groups were comparable in terms of age, sex, BMI, baseline sitting BP, total cholesterol, HDL-cholesterol, triglycerides, FPG, creatinine clearance, and duration of hypertension. 6 patients withdrew after randomization (2 withdrew the informed consent, 2 refused to repeat the clamp, and 2 complained of side effects). A total of 70 patients, 35 in the aliskiren group and 35 in the losartan group, completed the study.

Table 3 Effect of treatment on metabolic parameters

Parameters	Aliskiren (n = 35)	Losartan (n = 35)
FPG (mg/dl)		
Baseline	90.9 ± 8.1	90.4 ± 8.2
Week 12	89.4 ± 7.8	89.8 ± 8.0
FPI (μIU/ml)		
Baseline	13.5 ± 3.7	14.0 ± 4.0
Week 12	13.0 ± 3.4	13.8 ± 3.9
GIR (mg/min/kg)		
Baseline	4.9 ± 1.7	4.8 ± 1.9
Week 12	6.3 ± 2.1*‡	5.0 ± 1.8

* $p < 0.01$ vs. baseline; ‡ $p < 0.01$ vs. losartan
FPG: fasting plasma glucose; FPI: fasting plasma insulin; GIR: glucose infusion rate

The BP effects are shown in **Table 2**. After 12 weeks of treatment, both aliskiren and losartan significantly reduced sitting SBP (−15.6 mmHg and −15.5 mmHg, respectively; both $p < 0.001$ vs. baseline) and DBP (−10.7 mmHg and −10.5 mmHg, respectively; both $p < 0.001$ vs. baseline), with no significant difference between them. The BP lowering effect was already evident after 2 weeks and sustained for the duration of the study.

The metabolic effects are shown in **Table 3**, which provides data on the effect of therapy on FPG, FPI and on insulin sensitivity. There were no significant effects of both drugs on FPG and on FPI, while the mean rate of glucose uptake for the last 30 min of the clamp (GIR), considered as an index of insulin sensitivity, was significantly increased by aliskiren (by a mean of 1.4 mg/min/kg, $p < 0.01$ vs. baseline), but not by losartan (+0.2 mg/min/kg, p = not significant).

Treatment with both aliskiren and losartan significantly decreased plasma PAI-1 antigen after the first 2 weeks (−6.9 ng/ml and −3.2 ng/ml, both $p < 0.05$ vs. baseline). Subsequently, only the PAI-1 lowering effect of aliskiren was sustained throughout the 12 week period (−7.5 ng/ml, $p < 0.01$ vs. baseline), while in the losartan group PAI-1 antigen returned to baseline values at 4 weeks and significantly increased at 12 weeks (+3.6 ng/ml, $p < 0.05$ vs. baseline and $p < 0.01$ vs. aliskiren) (**Table 4**). Similar results were obtained for PAI-1 activity, which paralleled PAI-1 antigen behavior in both treatment groups (**Table 4**). Moreover, the change in PAI-1 antigen over time in response to treatment was significantly less during losartan treatment compared with aliskiren treatment (**Fig. 1**).

The tPA activity was not significantly affected by aliskiren (+0.02 IU/ml at 12 weeks, NS) while significantly decreased during treatment with losartan (−0.04 IU/ml at 12 weeks, $p < 0.05$ vs. baseline and $p < 0.01$ vs. aliskiren) (**Table 4**). The change in tPA activity over time was significantly different in the 2 treatment group, showing a progressive decrease in the losartan group, which did not occur in the aliskiren group (**Fig. 2**).

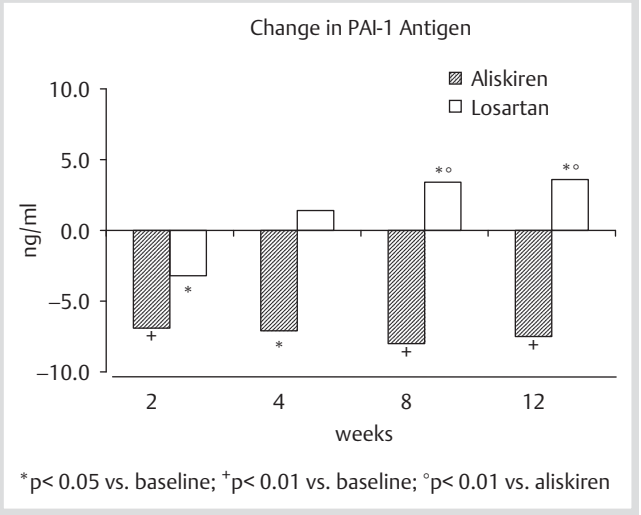
Discussion

The results of the present study showed that in patients with stage I hypertension and metabolic syndrome, aliskiren and losartan, despite a similar BP decreasing effect, displayed different effect on the fibrinolytic balance: after 12 weeks of treatment, aliskiren significantly reduced PAI-1 antigen and activity without affecting plasma tPA activity, whereas losartan increased

Table 4 Effect of treatment on plasma PAI-1 antigen, PAI-1 activity, and tPA activity

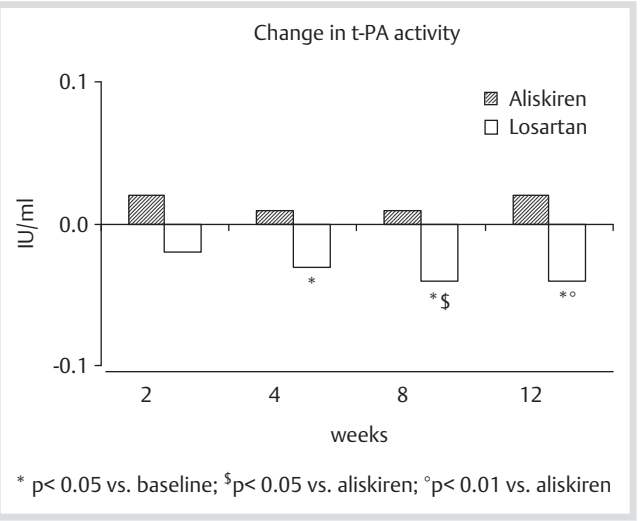
Time	Aliskiren (n = 35)	Losartan (n = 35)
PAI-1 antigen (ng/ml)		
Baseline	23.9 ± 11.8	23.1 ± 12.1
Week 2	17.0 ± 8.8*	19.9 ± 9.9*
Week 4	16.8 ± 7.5*	24.5 ± 11.2
Week 8	15.9 ± 7.4+	26.5 ± 9.4*‡
Week 12	16.4 ± 7.6+	26.7 ± 10.6*‡
PAI-1 activity (IU/ml)		
Baseline	8.9 ± 3.5	9.2 ± 3.7
Week 2	6.3 ± 2.6*	7.6 ± 2.9*
Week 4	6.5 ± 2.4*	8.5 ± 3.4
Week 8	6.8 ± 2.7*	9.4 ± 4.2
Week 12	6.1 ± 2.3*	10.9 ± 4.4*‡
tPA activity (IU/ml)		
Baseline	0.44 ± 0.14	0.45 ± 0.15
Week 2	0.46 ± 0.12	0.43 ± 0.13
Week 4	0.45 ± 0.11	0.42 ± 0.12*
Week 8	0.45 ± 0.12	0.41 ± 0.13*$
Week 12	0.46 ± 0.13	0.41 ± 0.12*‡

*p < 0.05 vs. baseline; +p < 0.01 vs. baseline; $p < 0.05 vs. aliskiren; ‡p < 0.01 vs. aliskiren. PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator



*p< 0.05 vs. baseline; +p< 0.01 vs. baseline; °p< 0.01 vs. aliskiren

Fig. 1 Change in mean plasma PAI-1 antigen level over time in response to treatment with aliskiren or losartan.



* p< 0.05 vs. baseline; $p< 0.05 vs. aliskiren; °p< 0.01 vs. aliskiren

Fig. 2 Change in mean tPA activity over time in response to treatment with aliskiren or losartan.

PAI-1 and decreased plasma tPA activity. When considering the effect of the 2 drugs on plasma PAI-1 antigen over time (**Fig. 1**), we observed a different time-course of effect in that short-term treatment with both aliskiren and losartan significantly reduced PAI-1 antigen plasma levels, whereas in the long term only aliskiren but not losartan decreased PAI-1 antigen. Similar results were obtained for PAI-1 activity. A different time-course of effects of aliskiren and losartan on plasma tPA activity was also observed, since it significantly decreased over time with losartan, but not with aliskiren (**Fig. 2**).

The different effect of aliskiren and losartan on the fibrinolytic balance observed in the present study cannot be explained by a difference in BP lowering, being the decrease in BP similar in the 2 treatment groups. It is well known that an energy-restricted diet favorably affects the fibrinolytic balance in both obese and nonobese patients [28, 29]. However, as all participants in the present study maintained their usual diet and avoided body weight changes, this factor should not have directly influenced the effect of the 2 drugs.

One possible explanation for the different effects of aliskiren and losartan on PAI-1 levels might be that Ang II increases PAI-1 synthesis not only directly through AT1 receptors at the level of vascular smooth muscle cells, but also through its hexapeptide catabolite, Ang IV, which binds to specific endothelial Ang type 4 receptor AT4 [20]. Thus, inhibition of the conversion of Angiotensin I to smaller peptides by aliskiren may prevent the expression of PAI-1 at endothelial level. By converse, blockade of Ang II at the AT1 receptor levels produces reactive rise in Ang II and its smaller fragments favoring PAI-1 expression via endothelial AT4 receptor stimulation. Upregulation of the AT4 receptors after 2 weeks of AT1 blockade might be one possible explanation for the reduction of PAI-1 observed with short-term losartan therapy. Another possible explanation is that AT1 receptor blockade requires some weeks to achieve the maximal Ang II increase and in this period of time the effect of AT1 blockade prevails on that of AT4 stimulation. Similarly to what observed in comparative studies between ACE-Is and ARBs [30], the different time-courses of aliskiren and losartan on PAI-levels might also have resulted from differences in the duration of suppression of tissue Ang II, which is suppressed by aliskiren but not by losartan.

Furthermore, the dissimilar effects of aliskiren and losartan on the fibrinolytic balance might also depend on their different effect on insulin sensitivity. Insulin is known to be one of the regulators of fibrinolysis and insulin resistance is frequently associated with increased PAI-1 levels [5]. Interventional studies aimed at reducing insulin resistance demonstrated a parallel decrease in plasma insulin and PAI-1 levels, thus confirming the link between insulin resistance and PAI-1 observed in cross-sectional studies [31]. In the present study, aliskiren improved insulin sensitivity, as assessed by the euglycemic hyperinsulinemic clamp, whereas losartan did not influence it.

Unlike aliskiren, that did not affect tPA activity, losartan reduced plasma tPA, which confirms previous observations [6, 32]. Since only a fraction of tPA is normally present in an enzymatically active form and most of it is complex-bound to PAI-1 [33], the observed reduction of tPA with losartan might partly depend on the increase of PAI-1 with the ARB.

Our study has some limitations, for example, the short observational period and the relatively small number of tested patients; furthermore, we did not evaluate if the beneficial effects on the various parameters were sustained after the cessation of therapy. We know that other studies have demonstrated the improvement of insulin resistance with ARB, but we did not find any improvement in insulin resistance probably because we considered different population and different drugs, and used different methodology (euglycemic hyperinsulinemic clamp, not HOMA).

Conclusions

The results of this study indicated that in hypertensive patients with metabolic syndrome a 12-week treatment with the renin inhibitor aliskiren and the ARB losartan, despite similar antihypertensive efficacy, displayed different effects on the fibrinolytic balance, which was improved by aliskiren, but not by losartan. These findings suggest that other mechanisms beyond Ang II inhibition, including angiotensin metabolite-mediated effects and the different effect on insulin sensitivity, might explain the dissimilar influence of the 2 drugs on fibrinolysis. Whether these differences between aliskiren and losartan could be of clinical relevance in terms of cardiovascular protection remains to be clarified.

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