Losartan and Perindopril Effects on Plasma Plasminogen Activator Inhibitor-1 and Fibrinogen in Hypertensive Type 2 Diabetic Patients

Roberto Fogari, Amedeo Mugellini, Annalisa Zoppi, Luca Corradi, Paola Preti, Pierangelo Lazzari, and Giuseppe Derosa

Background: This study compared the effects of losartan and perindopril on plasma plasminogen activator inhibitor-1 (PAI-1) and fibrinogen in hypertensive type 2 diabetic patients.

Methods: We studied 85 nonsmoking outpatients, aged 46 to 64 years, with mild to moderate essential hypertension (diastolic blood pressure [BP] >90 and <110 mm Hg) and well controlled type 2 diabetes mellitus. After a 4-week washout placebo period, patients were randomized to received perindopril 4 mg once daily (n = 42) or losartan 50 mg once daily (n = 43) for 12 weeks according to a double-blind, parallel-group design. At the end of the placebo and active treatment periods, BP was measured and plasma PAI-1 and fibrinogen were evaluated.

Results: Both perindopril and losartan reduced systolic and diastolic BP values (–16/15 mm Hg and –15/14, respectively; P < .001 vs placebo), with no difference between the two treatments. Plasma PAI-1 was reduced by perindopril (–10 ng/dL, P = .028 vs placebo) but not by losartan (+4 ng/dL, NS), the difference between the two treatments being statistically significant (P < .01). Plasma fibrinogen showed no significant change with both drugs, although a decreasing trend was noted with perindopril.

Conclusions: These findings indicate that perindopril but not losartan decreases PAI-1 in hypertensive type 2 diabetic patients, which suggests that the PAI-1 lowering effect is unrelated with AT1 receptor blockade and could rather be due to the fact that the endothelial receptors that mediate PAI-1 expression in response to angiotensin II are not type 1 receptor subtypes. Different effects of the two drugs on the bradykinin system might also be implicated.


Key Words: Perindopril, losartan, PAI-1 antigen, fibrinogen, hypertension, diabetes.

Impaired fibrinolytic potential, mainly expressed as elevated levels of plasminogen activator inhibitor (PAI-1),1,2 and hemostatic factors such as fibrinogen3 have been associated with increased risk for cardiovascular disease. Both in men and in women, the PAI-1 level has been shown to be positively related to blood pressure (BP).4,5 Recent reports have shown that PAI-1 levels and fibrinogen are elevated in hypertensive patients.6–8 Failure to influence PAI-1 and fibrinogen satisfactorily may be one of the possible explanations for the disappointing results of antihypertensive treatment on the incidence of coronary heart disease.4,7 Hypertension clusters with other risk factors such as insulin resistance. It has been shown that hypertensive patients with insulin resistance have higher PAI-1 levels in comparison with hypertensive patients without insulin resistance.6 In addition, PAI-1 is increased in blood7 and in coronary plaques in patients with type 2 diabetes.8 A significant correlation between PAI-1 and fasting plasma insulin has been evidenced in subjects with glucose intolerance9 and in overweight hypertensive individuals.10 Plasma fibrinogen levels are also increased in diabetes.3 The combination of hypertension and type 2 diabetes enhances the risk of developing cardiovascular disease.11

Accumulating data suggest that angiotensin II (Ang II) modulates fibrinolysis by increasing the expression of PAI-1 in endothelial cells.12–14 If the angiotensin type 1 (AT1) receptor is the major determinant of PAI-1 production in response to angiotensin, then one would hypothesize that angiotensin converting enzyme inhibitors (ACE

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0895-7061/02/$22.00
P11 0895-7061(01)02340-8

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Published by Elsevier Science Inc.
Table 1. Baseline demographic and clinical characteristics of patients in the two study groups

<table>
<thead>
<tr>
<th>Patients</th>
<th>Perindopril (n = 43)</th>
<th>Losartan (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>22/21</td>
<td>23/19</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.6 ± 7.9</td>
<td>58.1 ± 8.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.69 ± 0.08</td>
<td>1.68 ± 0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.2 ± 6.7</td>
<td>72.9 ± 6.4</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>163.2 ± 12.9</td>
<td>162.9 ± 12.6</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>102.8 ± 6.1</td>
<td>102.7 ± 5.9</td>
</tr>
<tr>
<td>HR (mm Hg)</td>
<td>76.3 ± 5.3</td>
<td>76.7 ± 4.9</td>
</tr>
<tr>
<td>Previously untreated (n)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Previously treated (n)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Clonidine</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

inhibitors) and Ang II receptor antagonists would have similar effects on vascular fibrinolytic balance. However, if other angiotensin receptors play an important role, then these agents may have different effects.

This study was performed to assess the effects on PAI-1 and plasma fibrinogen levels of the ACE inhibitor perindopril compared with the Ang II antagonist losartan in the treatment of hypertensive patients with type 2 diabetes.

Patients and Methods

Patients

The study population included 85 nonsmoking outpatients, 45 men and 40 women, aged 46 to 64 years (mean 58 years). All subjects had mild to moderate essential hypertension (diastolic BP >90 and <110 mm Hg) and concomitant type 2 diabetes mellitus (National Diabetes Data Group criteria) in stable metabolic control with diet and oral hypoglycemic agents. Their baseline demographic and clinic characteristics are shown in Table 1. Of the 85 patients, 44 had never been treated for hypertension; the other 41 had been treated with calcium antagonists (26 patients), clonidine (8 patients), and α-blockers (7 patients). Previously treated patients did not differ from the nontreated ones in terms of measured parameters.

Patients with secondary hypertension, previous or active ischemic heart disease, serum creatinine >1.5 mg/dL, evidence of chronic liver disease, obesity (body mass index [BMI] > 28), or pregnancy were excluded from the study.

Study Protocol

This was a randomized, double-blind, parallel-arm trial. The study protocol was approved by the local Ethics Committee and informed consent was obtained from each patient. After an initial 4-week wash-out placebo period, patients were randomly given perindopril 4 mg once daily (n = 42) or losartan 50 mg once daily (n = 43) for 12 weeks. At the end of the placebo and active treatment periods, BP, plasma PAI-1, and fibrinogen levels were evaluated. Blood pressure measurements were obtained from each patient (right arm) in the seated position, using a standard mercury sphygmomanometer (Korotkoff phases I and V) with a cuff of appropriate size. Measurements were taken in the morning before daily drug intake (ie, approximately 24 h after dosing) and after the subject had rested 10 min in a quiet room. Three successive BP readings were obtained at 1-min intervals and averaged. Body weight was measured in the fasting state with the subjects wearing only undergarments; BMI was computed as weight in kilograms divided by height in meters squared (kg/m²).

Chemical Analysis

For measurements of PAI-1 and fibrinogen levels, blood was drawn after a 12-h overnight fast, after at least 10 min rest in the recumbent position and always at the same hour (between 8 AM and 9 AM) to reduce interference by the diurnal variation of PAI-1 levels. Blood samples were collected in standard vacutainer tubes containing 0.105 mol/L sodium citrate and centrifugated immediately at 0°C for 20 min. Fibrinogen levels were measured by using a standard coagulation method; measurements were performed in duplicate and averaged. PAI-1 antigen levels were determined by a commercially available, two-site, enzyme-linked immunosorbent assay, after a procedure described by Ridker et al. The interassay and intra-assay coefficient of variation was 10% and 5% respectively. Metabolic parameters including fasting blood glucose, glycylated hemoglobin (HbA1c), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and total triglycerides (TG) as well as serum creatinine levels and body weight were also measured at the end of the placebo and active treatment periods. Body weight was measured in the fasting state with the subjects wearing only undergarments; BMI was computed as weight in kilograms divided by height in meters squared (kg/m²).

Statistical Analysis

Data are expressed as means ± standard deviations (SD). The homogeneity of pretreatment values of BP, PAI-1, fibrinogen, and other metabolic parameters was evaluated by one-way analysis of variance. Within-group and between-group variations of BP, PAI-1, fibrinogen and other metabolic parameters were compared using repeated measures analysis of variance. A P value < .05 was considered statistically significant.

Results

Of the 85 patients enrolled in the trial, three dropped out (two because of side effects and one because of failure to
appear at the visit), whereas 82 patients completed the study (41 in the perindopril group and 41 in the losartan group). Table 2 shows the results for patients who completed the study.

Both perindopril and losartan significantly reduced systolic BP (by a mean of 16 mm Hg and 15 mm Hg, respectively, \( P < .001 \) vs placebo) and diastolic BP (by a mean of 15 mm Hg and 14 mm Hg, respectively, \( P < .001 \) vs placebo), with no difference between the two treatments.

The PAI-1 antigen levels were significantly reduced by perindopril (by a mean of 10 ng/mL, \( P = .028 \) vs placebo) but not by losartan (+4 ng/dL, NS), the difference between the two treatments being statistically significant (\( P < .01 \)).

Fig. 1 shows the change in PAI-1 from placebo to perindopril and losartan in each subject of the two treatment groups. In the perindopril-treated group, most patients showed a decrease in PAI-1 levels, which was more evident in those with higher baseline values. By contrast, most patients in the losartan-treated group showed no change or even a slight increase in PAI-1 levels.

Fibrinogen plasma level did not show any significant change with both treatments (Table 2); however, a trend

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Perindopril</th>
<th>( P )</th>
<th>Placebo</th>
<th>Losartan</th>
<th>( P )</th>
<th>Comparison Between Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>162 ± 13</td>
<td>146 ± 10</td>
<td>.001</td>
<td>162 ± 14</td>
<td>147 ± 11</td>
<td>.001</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>102 ± 6</td>
<td>87 ± 5</td>
<td>.001</td>
<td>102 ± 6</td>
<td>88 ± 5</td>
<td>.001</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 0.9</td>
<td>27 ± 0.8</td>
<td>NS</td>
<td>26 ± 0.8</td>
<td>26 ± 0.7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PAI-1 (ng/mL)</td>
<td>42 ± 21</td>
<td>32 ± 17</td>
<td>.028</td>
<td>41 ± 19</td>
<td>45 ± 22</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>356 ± 74</td>
<td>312 ± 59</td>
<td>NS</td>
<td>344 ± 67</td>
<td>333 ± 59</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>112 ± 7.3</td>
<td>107 ± 6.9</td>
<td>NS</td>
<td>113 ± 7.5</td>
<td>111 ± 7.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>NS</td>
<td>1.1 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>NS</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>197 ± 23</td>
<td>186 ± 19</td>
<td>NS</td>
<td>191 ± 20</td>
<td>188 ± 19</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>44 ± 5</td>
<td>46 ± 6</td>
<td>NS</td>
<td>44 ± 5</td>
<td>44 ± 6</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>142 ± 49</td>
<td>127 ± 44</td>
<td>NS</td>
<td>145 ± 50</td>
<td>140 ± 48</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>HbA₁c (%)</td>
<td>7.2 ± 1.9</td>
<td>7.1 ± 1.7</td>
<td>NS</td>
<td>6.9 ± 2.0</td>
<td>7.0 ± 1.8</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant; BMI = body mass index; PAI-1 = plasminogen activator inhibitor; FBG = fasting blood glucose; HbA₁c = glycosylated hemoglobin; other abbreviations as in Table 1.

Data are given as mean ± SD.

Table 2. Effects of treatment with perindopril and losartan

FIG. 1. Change in plasminogen activator inhibitor (PAI-1) plasma levels (ng/mL) from placebo to perindopril and losartan in each subject of the two treatment groups.
toward a decrease was observed in the perindopril-treated group.

There was no significant change in BMI, fasting blood glucose, serum creatinine, TC, HDL-C, and TG during treatment with both losartan and perindopril (Table 2). Glycemic control, as assessed by HbA1c, was not influenced by either treatment, and none of the patients required changes in hypoglycemic therapy.

**Discussion**

The results of this study show that, in patients with mild to moderate hypertension and well controlled type 2 diabetes, despite a similar BP reducing effect, perindopril decreases PAI-1 level, whereas losartan does not. There was no difference in fibrinogen plasma level between the two treatment groups; however, a statistically nonsignificant trend toward a decrease in fibrinogen was observed in the perindopril-treated group.

The different effects of ACE inhibition and AT1 antagonism on PAI-1 observed in the present study cannot be explained by a difference in BP lowering, inasmuch as the decrease in BP was similar in the two groups.

The dissimilar effects of perindopril and losartan on PAI-1 antigen levels might result from different effects of the two drugs on insulin sensitivity. In fact, on one hand, ACE inhibitor have been shown to improve insulin sensitivity in diabetic patients, whereas losartan has been reported to have neutral effects; on the other hand, insulin resistance and proinsulin (which are typically elevated in patients with type 2 diabetes) contribute to increased plasma PAI-1 activity.

In a previous study regarding overweight hypertensive patients, perindopril enhanced insulin sensitivity whereas losartan did not.

In another study regarding normotensive nondiabetic patients, the ACE inhibitor quinapril has been shown to improve the fibrinolytic balance whereas losartan did not, although the two drugs had similar effect on the fasting glucose-insulin ratio.

In the present study, insulin sensitivity was not measured; however, fasting glucose and HbA1c values did not differ after treatment between the perindopril- and losartan-treated groups.

Another factor that could contribute to increased PAI-1 release is hypertriglyceridemia and the combination of hyperinsulinemia, hypertriglyceridemia, and hyperglycemia are likely to contribute to the hyperfibrinolysis of type 2 diabetes by increasing the blood levels of PAI-1.

Although in the present study a trend toward a decrease in plasma TG was observed in the perindopril group, this trend was not statistically significant and cannot explain the difference in PAI-1 between the two groups after 12 weeks of treatment.

Alternatively, although in the present study aldosterone concentrations were not evaluated, we cannot exclude possible differential effects of ACE inhibition and AT1 antagonism on serum aldosterone levels, which have been shown to correlate with PAI-1 concentrations.

Clinical use of ACE inhibitor has been shown to be associated with a reduction in PAI-1 and plasma fibrinogen in most, although not all, trials. One possible explanation for the conflicting findings about the effects of ACE inhibition on fibrinolytic balance is that studies have differed widely in their design. In fact, the effect of ACE inhibition on fibrinolysis may depend on the ACE inhibitor used, the population studied (eg, post–myocardial infarction, hypertensive, or normotensive) and the state of activation of the renin angiotensin aldosterone system. At present, few direct comparison studies on the effects of ACE inhibitor and Ang II AT1 receptor antagonists on fibrinolysis have been performed in human patients.

One study showed that both acute AT1 antagonism and ACE-inhibition were associated with a significant improvement in plasma fibrinolytic parameters in patients with heart failure. Two other trials also observed a decrease in PAI-1 with ACE inhibitor but not with losartan. This confirms data from Seljeflot et al, who observed no effect of losartan administration on PAI-1 levels in hypertensive patients, either at baseline or during acute hyperinsulinemia.

The mechanisms for the contrasting effect of ACE inhibitor and Ang II antagonists on fibrinolysis remains to be clarified. One explanation for the dissimilar effects of ACE-inhibition and AT1 antagonism on PAI-1 is the hypothesis that Ang II increases PAI-1 expression through its hexapeptide metabolite, Ang IV, and the Ang II type 4 receptor (AT4), that has been observed in vitro in endothelial cells. Thus, the effect of Ang II on endothelial PAI-1 expression is not blocked by either AT1 receptor or Ang II type 2 receptor antagonists, whereas inhibition of the conversion of Ang II to Ang IV blocks the effect of Ang II on PAI-1 expression.

Besides, ACE inhibitor may exert a beneficial effect on vascular fibrinolytic balance not only by reducing the production of Ang II but also by blocking the degradation of bradykinin, which, by contrast, is not affected by Ang II antagonists. Although Ang II is a potent stimulus for the production of PAI-1, bradykinin appears to be a potent stimulus for the production of tissue plasminogen activator.

Recent studies have demonstrated that clinical use of ACE inhibitor is associated with a reduction in plasma fibrinogen. In a trial performed in overweight patients, perindopril was associated with a reduction in plasma fibrinogen, whereas losartan was not. In the same trial, a positive relationship was found between the perindopril-induced reduction in plasma fibrinogen and the increase in insulin sensitivity. In the present study, the lack of a statistically significant fibrinogen decreasing trend might be explained by the difference in the populations studied: the diabetes treatment might have reduced the apparent effect of the ACE inhibitor. The present study confirms the absence of significant fibrinogen modification reported by another trial performed with another ACE inhibitor on hypertensive patients with type 2 diabetes mellitus.
In conclusion, the results of this study show that, in patients with mild to moderate essential hypertension and concomitant type 2 diabetes: 1) the ACE inhibitor perindopril and the Ang II antagonist losartan have no or few effect on plasma fibrinogen levels; 2) perindopril significantly decreases PAI-1 antigen levels, whereas losartan does not. This suggests that the decrease in PAI-1 is not related with AT1 receptor blockade and could instead be due to the fact that the endothelial receptors that mediate PAI-1 expression in response to Ang II are not type 1 receptor subtypes. Different effects of the two drugs on the bradykinin system might also be implicated. Further studies are needed to clarify these points.

References