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Effects of Lisinopril, Irbesartan, and Amlodipine on the Thrombogenic Variables in the Early and Late Stages of the Treatment in Hypertensive Patients

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Abstract

Regulation of the fibrinolytic balance between plasminogen activators and inhibitors is modulated by the renin–angiotensin system (RAS). Impaired fibrinolytic function, characterized by increased plasminogen activator inhibitor type 1 (PAI-1) levels and decreased tissue plasminogen activator (t-PA) activity, has been found in patients with hypertension and may account in part for the increased risk of atherosclerosis and its clinical complications in these patients. In this regard, data from the literature indicate that different antihypertensive drugs may vary in their influence on fibrinolysis. Angiotensin-converting enzyme (ACE) inhibitors (ACE-I) have generally been shown to improve the fibrinolytic balance by reducing plasma PAI-1 levels. Calcium-channel blockers (CCB) have been reported to increase t-PA activity, and angiotensin receptor blockers (ARB) seem to be neutral in their effect. In the light of these data, this study aimed to compare the effects of ACE-I, ARB, and CCB on the fibrinolytic system in the early and late stages of the treatment in hypertensive patients. These data that the beneficial effect of RAS inhibition on fibrinolysis related to decrease in Ang II during early period of treatment. Amlodipine may also improve thrombogenic risk related to lowering the effect on increased platelet activation reflected by p-selectin. The greater improvement in the early and late stages of the fibrinolytic balance because of the combined action of RAS inhibition and Ca antagonism represents a further indication to the use of combinations of RAS inhibition (ACE-I or ARB) and CCB in the treatment of hypertension.

Keywords: angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, calcium-channel blocker, fibrinolytic system, hypertension

INTRODUCTION

Hypertension is associated with decreased fibrinolytic potential, mainly expressed as elevated plasma plasminogen activator inhibitor type 1 (PAI-1) levels, and increased platelet aggregability, which may account in part for the increased risk of atherosclerosis and its clinical complications in hypertensive patients (1).

The mechanisms through which activation of the renin–angiotensin system (RAS) increases or angiotensin-converting enzyme (ACE) inhibition decreases the risk of ischemic cardiovascular events in selected populations are not known. One possible explanation involves an interaction between the RAS and the fibrinolytic system. Angiotensin (Ang) II and aldosterone increase PAI-1, the major physiological inhibitor of fibrinolysis in vitro and in vivo (2,3). Increased PAI-1 expression has been demonstrated in conditioned media from arterial segments with atherosclerotic changes (4) and in atherosclerotic plaques (5).

Angiotensin-converting enzyme inhibitors (ACE-I) and Angiotensin-1 (AT1) antagonists differ in their effects on the RAS. For example, Ang II concentrations increase versus baseline during AT1 antagonism, but not ACE inhibition (6). Unlike ACE inhibition, AT1 antagonists increase baseline Ang II concentrations (6). If the effect of endogenous Ang II on circulating PAI-1 concentrations in humans is mediated through a non-AT1 and non-AT2 receptor, then PAI-1 concentrations would be expected to increase, rather decrease, during AT1 antagonism. Furthermore, in addition to inhibiting the formation of Ang II, ACE-I block the degradation of bradykinin (7). Angiotensin-1 antagonists do not alter the metabolism of bradykinin when given for short time.

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Bradykinin is a potent stimulus to tissue plasminogen activator (t-PA) release in the human vasculature (8). For these reasons, ACE-I and AT1 antagonists might be expected to differ in their effects on the balance between PAI-1 and t-PA. It is now well established that elevated PAI-1 is an independent risk factor for thrombembolic complications (9).

The calcium-channel blockers (CCB) are one such group of drugs that appear to act directly on the platelets, as well as bringing about changes that are seemingly independent of lowering in blood pressure (BP) (10). Indeed, platelet activation results in the increase in intracellular calcium ions, and interfere with the entry of calcium into the cells could be a way of minimizing blocking platelet (11).

Restoration of endothelial function and reduction of increased platelet aggregation in essential hypertension are one of the aims of modern antihypertensive therapy. Therefore, the effects of the various antihypertensive drugs on endothelial and platelet functions are of interest. Thus, the purpose of the present study was to compare the effect of the ACE-I (lisinopril), angiotensin receptor blocker (ARB; irbesartan), and the CCB (amlodipine) on fibrinolytic system during early and late stages of the treatment in hypertensive patients.

MATERIAL AND METHODS

Total 181 outpatients (88 men and 93 women), referred to our hypertension unit, participated in this study. Each patient had a well-established history of chronically elevated BP without any underlying cause and had been treated for at least 3 years with one or more antihypertensive agents. All subjects underwent a complete history and physical examination before the investigation. Subjects with significant cardiovascular, renal, endocrine (including diabetes), or pulmonary disease, or who were taking vasoactive medications were excluded. Inclusion criteria consisted of the following: the presence of essential hypertension with an average sitting systolic blood pressure (SBP) >140 mm Hg, a sitting diastolic blood pressure (DPB) >90 mm Hg, or both, on three consecutive visits. Exclusion criteria consisted of the presence of the following: (i) secondary hypertension including renovascular hypertension; (ii) severe hypertension which is defined by sitting SBP >210 mm Hg and sitting DBP >115 mm Hg at any time while sitting in the run-in period; (iii) evidence of clinical cardiovascular disease (including stroke or myocardial infarction in the previous 6 months, angina, clinically significant arrhythmia or heart block, or congestive heart failure), or renal failure (serum creatinine >1.5 mg/dL); (iv) life-threatening medical conditions (cancer, and so forth); (v) hyperlipidemia and diabetes; (vi) a history of smoking; (vii) a history of alcoholism or other drug abuse; or (viii) the use of sedatives, tranquilizers, vasoactive medications, or oral contraceptives.

After 4 weeks of observation, the patients who matched with the aforementioned criteria were excluded. They were separated into three groups. Of the 181 hypertensive patients randomized to treatment, 62 were administered lisinopril (20 mg), 59 were administered irbesartan (300 mg), and 60 were administered amplodipine (10 mg). Drugs were administered in the morning at approximately 9 am after breakfast. During the study period, all patients continued on their usual diet and activities. These patients were followed at 4-week intervals for 6 months at the outpatient clinic.

An additional population of 30 normotensive healthy volunteers (14 men, 16 women), matched with the patients for approximate age, was selected as a control group. Control persons had no evidence or history of hypertension, cardiovascular disease, hyperlipidemia, or any other systemic diseases and no history of recent or regular drug use. Normotensive subjects had a SBP < 120 mm Hg and a DBP < 80 mm Hg.

Study Protocol

All patients gave informed consent to participation according to the ethical principles for human investigations as outlined in the Second Declaration of Helsinki. All patients were evaluated in an outpatient setting. Medical history and physical examination were recorded for each patient, and each patient underwent tests for routine biochemical and hematological monitoring. Blood pressure was measured with a mercury sphygmomanometer and cuffs were adapted to the arm circumference after 15 minutes in the recumbent position. Systolic blood pressure was taken as the appearance of Korotkoff sounds and DBP as the point of their disappearance (phase V). Secondary causes of hypertension, metabolic abnormalities, and evidence of damage to end organs were sought by studying each patient's history, performing a detailed physical examination, conducting electrocardiography, renal imaging, and performing laboratory tests including plasma renin activity (PRA), urinalysis, creatinine, electrolyte level, and, when clinically indicated, vanilmandelic acid excretion in the urine. A history was obtained for all healthy control subjects; all received a physical examination and underwent a urinalysis test. Blood samples for PAI-1 antigen and activity, and t-PA antigen and activity level were obtained at baseline from all patients. Once the SBP remained below 90 mm Hg for 12 weeks, we obtained plasma samples (at fasting) for these analyses. Hypertensive patients continued oral antihypertensive medication.

Blood Samples

The study was a cross-sectional determination of t-PA and PAI-1 antigen levels in plasma samples taken from hypertensive patients and from healthy volunteers. Each measurement was taken after the subject had been seated for 30 minutes. Following each measurement of BP, blood was drawn for measurement of PAI-1 activity, and t-PA antigen. Blood was drawn in the morning

because PAI-1 concentrations peak during this period. Blood for measurement of PRA and serum aldosterone was drawn at 8:00 am and 10:00 am. Blood for measurement of fasting glucose and insulin concentrations was drawn at 8:00 am. A light lunch was provided after the blood draw in noon.

After a 30-minute rest in the sitting position, blood samples were drawn from the large antecubital veins of patients. All venipunctures were carried out without interruption of venous flow and with a 19-G butterfly needle connected to a plastic syringe. Fifteen milliliters of blood was drawn and the first few milliliters was discarded; 4 mL or 5 mL was transferred immediately to Stabilyte tubes (Biopool, Umea, Sweden) for determination of PAI-1 activity. Plasma thrombomodulin level was determined by two-site enzyme-linked immunosorbent assay (ELISA) with two monoclonal antihuman thrombomodulin antibodies (ELISA, Asserachrom thrombomodulin, Diagnostica Stago, Asnières, France). Plasma von Willebrand Factor (vWF) level was evaluated by ELISA method and measured in international units per deciliter. Plasma p-selectin level was detected with alorimetric ELISA for human adhesion molecules method in nanograms per milligram.

Nine milliliters were transferred to polypropylene tubes containing 1 mL trisodium citrate (0.109 mol/L) to determine the levels of other analytes. The tubes were then centrifuged at 3000 rpm for 15 minutes at 10°C–18°C. The supernatant plasma samples were stored in plastic tubes at −30°C until assayed. Blood for measurement of t-PA antigen was collected in vacutainer tubes containing 0.105 mmol/L acidified sodium citrate, and antigen levels were determined using a two-site ELISA (Biopool AB, Umea, Sweden). Plasminogen activator inhibitor type 1 activity was determined by using an immunofunctional assay (Chromolize, Biopool AB). Blood for PRA and aldosterone was drawn into chilled tubes containing EDTA. Plasma renin activity was measured by radioimmunoassay for Ang I formation at pH 7.4 and at 37°C. Aldosterone was measured using a commercially available radioimmunoassay (Diagnostic Product Corp., Los Angeles, CA, USA). Serum cholesterol and triglycerides were determined using standard enzymatic methods on an automated system (ACE, Schiapparelli Bio Systems, West Caldwell, NJ, USA). Plasma glucose concentration was measured with a colorimetric assay (Johnson and Johnson Clinical Diagnostics, Inc., Rochester, NY, USA).

Assays

Plasma renin activity was analyzed radioimmunologically (Radioimmunoassay, Sorin, Renctz, CisBio Int., France), the reference (supine) range with normal salt intake being 0.2–5.7 ng/mL/h. Tissue plasminogen activator antigen levels were quantified with ELISA Tintelize kit (Biopool). Plasminogen activator inhibitor type 1 activities were measured by Chromogenic Assay (Biopool). The intra- and interassay coefficients of variation ranged from 5.2% to 8.7% and from 6.5% to 9.4%, respectively.

Blood for measurement of PAI-1 activity and t-PA antigen was collected in standard vacutainer tubes containing 0.105 mol/L sodium citrate (Becton Dickinson). Antigen levels were determined using a two-site ELISA (Biopool AB) as previously described. In our laboratory, the coefficients of variation for repeated measures of t-PA antigen and PAI-1 activity are 5.9% and 8.1%, respectively. Blood for PRA was collected in tubes containing EDTA. Plasma renin activity was measured by radioimmunoassay for Ang I formation at pH 7.4 and at 37°C. About 29 samples of serum aldosterone were assayed with a commercially available radioimmunoassay kit (Diagnostic Corporation). The intra- and interassay coefficients of variation were 6% and 10%, respectively.

Statistical Analysis

The differences in baseline t-PA antigen and activity, and PAI-1 antigen and activity between hypertensive patients and healthy volunteers were evaluated by applying the nonparametric Mann–Whitney *U*-test. Intergroup analyses were performed by using Wilcoxon paired signed rank test. The differences between pretreatment and posttreatment values for all analytes in the lisinopril, irbesartan, and amlodipine groups were also assessed by applying Wilcoxon paired signed rank test. Data were analyzed with SPSS software (v.11.0) for Windows (SPSS, Inc.) and expressed as mean ± SD. $P < .05$ was considered significant.

RESULTS

In Table 1, the baseline subject characteristics for the three treatment groups are shown. There were no differences in age, gender, ethnicity, body mass index, blood pressure, cholesterol, triglycerides, glucose, vWF, PRA, and aldosterone.

While the mean plasma basal levels of PAI-1 activity, serum Thrombomodulin (sTM), p-selectin were significantly higher in the hypertensive patients than in normal controls ($P < .005$), the mean plasma levels of t-PA activity did not differ in these groups (Table 2, Figure 1).

The mean plasma levels of the thrombogenic variables of all groups at baseline, 1 and 6 month(s) after treatment have been shown in Table 3 and Figure 2. While the mean plasma levels of the PAI-1 activity were reduced significantly at the first month period of the treatment in lisinopril and irbesartan groups, the reduction pronounced more at the sixth month of the treatment in both groups. In the amlodipine group, while the mean plasma PAI-1 levels did not differ at baseline and 1 month after treatment, these levels were reduced significantly at the sixth month of the treatment. However, the reduction was more pronounced in lisinopril and irbesartan groups than in amlodipine

Table 1. Baseline demographic characteristics of the treatment groups with mild and moderate hypertensive patients and controls

Parameter	Control group ($n = 30$)	Lisinopril group 1 ($n = 62$)	Irbesartan group 2 ($n = 59$)	Amlodipine group 3 ($n = 60$)
Mean age (y)	52 ± 24	54 ± 16	52 ± 18	53 ± 26
Gender(women/men)	16/14	17/15	15/14	15/15
BMI (kg/m^2)	22.6 ± 2.4	24.6 ± 3.2	24.9 ± 2.8	25.1 ± 3.4
SBP (mm Hg)	118 ± 1.2	170 ± 3.7	165 ± 3.9	$168 \pm 3.7^{\star}$
DBP (mm Hg)	78 ± 0.8	100 ± 4.8	101 ± 5.2	$101 \pm 5.1^{\star}$
Fasting plasma cholesterol (mg/dL)	182 ± 6	186 ± 8	183 ± 8	185 ± 7
Fasting plasma glucose (mg/dL)	84 ± 4	87 ± 5	88 ± 5	89 ± 6
Plasma uric acid (mg/dL)	6.9 ± 2.3	7.2 ± 3.6	7.0 ± 3.5	7.1 ± 3.8
Plasma creatinine (mg/dL)	0.96 ± 0.16	0.96 ± 0.23	0.93 ± 0.25	0.95 ± 0.25

Values are means ± SD. Abbreviations: BMI – body mass index; SBP – systolic blood pressure; DBP – dystolic blood pressure.
$^{\star}P < .05$ hypertensive patients versus controls.

Table 2. Basal mean arterial pressure (MAP), plasma PAI-1 activity, t-PA activity, sTM, vWF, and p-selectin levels of hypertensive patients and control group

Parameters	Hypertensive patients	Control group	P value
MAP (mm Hg)	123 ± 18	94 ± 16	$<.005$
PAI-1 activity (IU/mL)	$24.18 \pm 12.34^{\star}$	9.64 ± 4.2	$<.005$
t-PA antigen (ng/mL)	0.68 ± 0.42	0.70 ± 0.38	$>.05$
sTM (ng/mL)	$64.52 \pm 12.64^{\star}$	37.18 ± 6.18	$<.005$
p-selectin (ng/mL)	$72.4 \pm 16.4^{\star}$	24.6 ± 6.6	$<.005$
vWF (IU/dL)	83.7 ± 8.7	87.1 ± 6.4	$>.005$

Values are means ± SD. Abbreviations: MAP – mean arterial pressure; PAI-1 – plasminogen activator inhibitor type 1; t-PA – tissue plasminogen activator.
$^{\star}P < .05$ hypertensive patients versus controls.

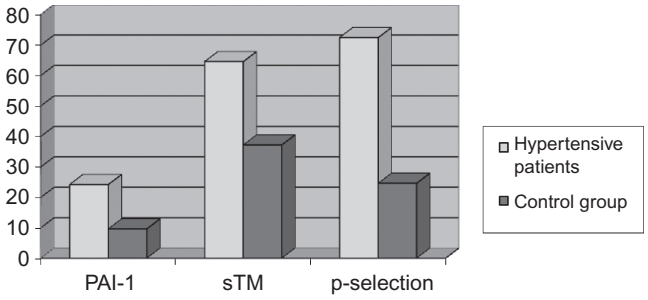

Figure 1. Mean arterial pressure (MAP), plasma PAI-1 activity (IU/mL), sTM (ng/mL), and p-selectin (ng/mL) baseline levels of hypertensive patients and control group.

group. Similar reduction response was found in plasma levels of sTM in all of the groups. While the mean plasma p-selectin levels did not differ at first month treatment period compared to baseline in lisinopril and irbesartan groups, those levels reduced at the end of the sixth month treatment period. The mean plasma levels of the p-selectin were significantly reduced at the end of the first and sixth treatment period in amlodipine group.

DISCUSSION

The changes in endothelial structure and function resulted in various mediator production caused by endothelium which is effective in the beginning and development of atherosclerotic process. Endothelial cells and platelets secrete vWF, which is an adhesion molecule and regarded as one of the markers of endothelium dysfunction or damage (12). It plays a key role in the process of platelet adhesion and aggregation and is elevated in hypertensive patients with target organ damage, such as left ventricular hypertrophy, ischemic heart disease, and stroke. Increased activity or antigen concentrations of PAI-1 represent decreased fibrinolytic function and increased activity of t-PA reflects higher fibrinolytic activity (13,14); hence, t-PA and PAI-1 play crucial roles in regulating the fibrinolytic function and can be used as measures of fibrinolytic function. The risk of thrombosis increases when the dynamic balance between t-PA and PAI-1 is disrupted.

Several recent reports (15,16) have shown that PAI-1 activity is elevated and t-PA activity is depressed in patients with systemic hypertension. Similarly, in the present study as compared to normotensive persons, PAI-1 activity levels were found to be increased in hypertensive patients. Thus, it is not surprising that ACE-I promote fibrinolysis and lead to a reduction in ischemic events (17,18).

The RAS plays a key role in the process of hypertension. Angiotensin II, which is the most important effector peptide of the RAS, can stimulate the generation of PAI-1 directly or indirectly, and ACE-I can decrease PAI-1 and increase the activity of the fibrinolytic system, although inconsistent conclusions have

Table 3. Mean arterial pressure (MAP), plasma PAI-1 activity, t-PA activity, sTM, and p-selectin levels before and 1 and 6 months after administration of lisinopril, irbesartan, and amlodipine

	Lisinopril groups			Irbesartan groups			Amlodipine groups		
Parameters	Basal	1 mo	6 mo	Basal	1 mo	6 mo	Basal	1 mo	6 mo
MAP (mm Hg)	124.2 ± 112	118.2 ± 66	106.4 ± 62	123.1 ± 106	119.4 ± 54*	108.4 ± 6	123.2 ± 110	116.6 ± 44	106.4 ± 66
PAI-1 activity (IU/mL)	23.3 ± 3.4	18.2 ± 2.3*	12.5 ± 3.5*	24.9 ± 1.7	16.2 ± 1.8*	12.4 ± 2.8*	24.4 ± 2.2	23.7 ± 2.1	16.3 ± 1.5*
t-PA antigen (ng/mL)	0.64 ± 0.46	0.62 ± 0.34	0.58 ± 0.42	0.72 ± 0.56	0.68 ± 0.64	0.7 ± 0.62	0.74 ± 0.54	0.76 ± 0.46	0.72 ± 0.38
sTM (ng/mL)	64.4 ± 2.4	52.5 ± 2.6*	32.4 ± 1.9*	66.1 ± 2.4	49.5 ± 2.7*	30.4 ± 1.6*	62.6 ± 2.6	48.5 ± 1.5*	30.6 ± 2.4*
p-selectin (ng/mL)	74.8 ± 6.3	68.7 ± 5.8	65.6 ± 4.6	72.6 ± 5.4	69.6 ± 4.1	64.7 ± 4.7	70.8 ± 4.2	56.6 ± 4.4*	30.4 ± 2.4*
Aldosterone (ng/dL)	46.7 ± 4.2	41.8 ± 4.8	39.4 ± 3.5	54.0 ± 5.5	48.4 ± 7.8	39.5 ± 4.2	51.2 ± 4.8	47.6 ± 5.2	45.7 ± 6.2
PRA (ngAngI/mL/h)	32.4 ± 5.6	44.6 ± 7.8	34.5 ± 4.7	29.7 ± 4.8	36.6 ± 6.4	32 ± 3.6	34.6 ± 7.5	33.4 ± 6.4	28 ± 3.8
vWF (IU/dL)	87.4 ± 4.4	84.1 ± 4.3	86.3 ± 5.2	91.4 ± 6.2	88.7 ± 4.6	84.6 ± 3.9	87.4 ± 8.2	83.7 ± 5.1	84.3 ± 4.7

Values are means ± SD. Abbreviations: MAP – mean arterial pressure; PAI-1 – plasminogen activator inhibitor type 1; t-PA – tissue plasminogen activator; PRA – plasma renin activity.

*$P < .05$ in with the values after and before treatment comparison of baseline values.

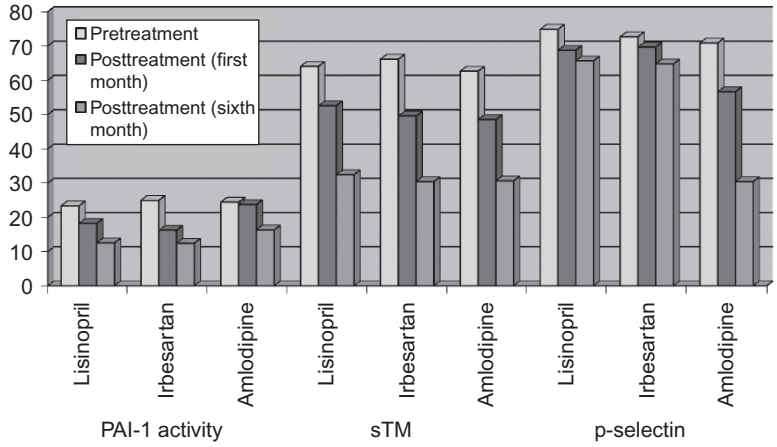

Figure 2. Mean arterial pressure (MAP), plasma PAI-1 activity (IU/mL), sTM (ng/mL), and p-selectin (ng/mL) levels before and 1 and 6 months after administration of lisinopril, irbesartan, and amlodipine.

been drawn from various trials (19,20). The present study demonstrated that PAI-1 and fibrinolytic parameters were significantly decreased in essential hypertensive patients treated with losartan and lisinopril and irbesartan group while at the end of the sixth month the reduction became even more significant, indicating a beneficial effect on the fibrinolytic system, as well as antihypertensive effects. In amplodipine group, in the first month, PAI-1 level did not differ at all. However, in the sixth month, even though not as pronounced as in lisinopril and irbesartan group, there is a significant reduction when compared to pretreatment period. Besides, in any of the three groups no differences were determined before and subsequent to the treatment for t-PA activity.

Many researches carried out with the patients who have the risk of developing atherosclerotic vascular diseases such as hypertension and diabetes revealed that their vWF and sTM levels were high (21,22). In fact, increase of these endothelial markers in the diseases causing functional and structural damage in endothelium is by no means surprising at all. Recent studies have demonstrated that vWF and sTM levels increase in parallel with plasma PAI-1 level in hypertensive patients (23). Besides plasma PAI-1 level, sTM and vWF basal levels in hypertensive patients, which are the markers of endothelial dysfunction and/or activation, are determined as significantly high when compared to the control group in our study. In comparison with the markers in pretreatment period, an explicit reduction in average plasma sTM and vWF levels is revealed in all three groups in the first and sixth month(s) of the treatment. Moreover, it is clearly seen that the levels in the sixth month are lower than the levels in the first month. In our study, average plasma p-selectin level, which is the indicator of platelet aggregation ability, has been detected in a clearly high levels. Thrombosis affects process of atherosclerotic vascular disease pathogenesis in different ways. Besides contributing to plaque growth, thrombosis causes lumen blockage, thereby causing myocardial infarction and stroke. These effects might be one of the possible mechanisms for the more positive effect of losartan on stroke risk than atenolol, as observed in the LIFE trial (24).

Having been understood that p-selectin, which belongs to vascular adhesion molecule family, might be used as the indicator of platelet aggregation, selectin tissue and plasma level have recently began to be used to investigate the possible role of thrombocytes in the pathogenesis of vascular diseases. The studies carried out have revealed close relation between thrombotic events and p-selectin level (25,26). While in the first month, the average plasma p-selectin level did not differ in lisinopril and irbesartan groups compared to pretreatment period, in the sixth month the levels showed a statistically insignificant reduction. As for the amlodipine group, both in the first and sixth month(s) after treatment statistically significant and sensible reduction was observed. However, the reduction in the sixth month was even more distinctive than that in the first month.

All these results revealed that compared to amlodipine, drugs causing RAS inhibition had more positive effects on PAI-1 level in relation to examining the samples taken from each group on the similar BP level. The data showed that the positive effects of lisinopril and irbesartan were independent from those of on BP reduction. But although not as significant as lisinopril and irbesartan group, in the amlodipine group observation of reduction in plasma PAI-1 level in the sixth month is significant because of the fact that it shows the positive contribution to BP reduction. In this study, distinctive decrease in average plasma sTM and vWF levels was observed in the first month when compared to the levels before treatment. However, in terms of this positive effect, lisinopril and irbesartan are not dominant over amlodipine in any way. This positive effect can be explained by BP regulation and it can be said that active BP control has reduced endothelial damage in the long run. This study is not adequate

in number. Nevertheless, it is important due to the fact that it has the data which directly compare the effects of various antihypertensive drugs on endothelial functions.

It was observed that in the group receiving amlodipine, the decrease in p-selectin level within the sixth month was more distinctive than the level in the first month. As for lisinopril and irbesartan group, in the sixth month decrease in p-selectin level to some extent was observed but it was not as pronounced as in amlodipine group. Consequently, the use of amlodipine in hypertensive patients showed positive effects on endothelial functions by creating a reflection like antigregan and this positive effect becomes more significant with the use of drugs in the long run.

In the sixth month, the decrease in p-selectin level in lisinopril and irbesartan group can be explained by the control of BP on account of drug use and eventually the decrease in endothelial damage.

As a consequence of our study, it is possible to say that keeping BP at a normal level alone is not adequate to reduce cardiovascular mortality and morbidity in hypertension treatment. In that case, the aim should be the treatment of endothelial dysfunction along with hypertension. These three groups of drugs having positive effects on endothelial, coagulation–fibrinolysis system, and platelet functions, besides reducing BP of all the groups in our study set us thinking that it may also have positive effects on cardiovascular mortality and morbidity.

In conclusion, the outcome of the study is that the drugs causing RAS inhibition, which has positive influence mainly over endothelial and fibrinolysis system, and CCB beneficial effects on thrombosis function may suppress atherosclerosis, thereby reducing cardiovascular mortality and morbidity. The greater improvement in the early and late stages of the fibrinolytic balance because of the combined action of RAS inhibition and Ca antagonism represents a further indication to the use of combinations of RAS inhibition (ACE-I or ARB) and CCB in the treatment of hypertension.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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