Original Article

Effects of Antihypertensive Treatment on Platelet Function in Essential Hypertension

Tomoko GOMI, Toshio IKEDA, Yuko SHIBUYA, and Reiko NAGAO

To evaluate the effect of antihypertensive therapy on platelet activation in essential hypertension, the plasma levels of β -thromboglobulin (β -TG) were examined in 45 patients with essential hypertension and 20 age-matched normotensive control subjects. Hypertensive patients were assigned to monotherapy with one of five different antihypertensive drugs for 6 months, and the change of plasma levels of β -TG was reexamined after the completion of the monotherapy. The plasma β -TG increased in hypertensive patients compared with levels in normotensive control subjects. Monotherapy with each drug resulted in sufficient blood pressure control in all hypertensive patients. The plasma β -TG decreased significantly after monotherapy with an α -blocker or an angiotensin-converting enzyme inhibitor (ACEI). The plasma β -TG increased with the use of a diuretic but did not change with the use of a β -blocker or calcium antagonist. The platelet activation observed in patients with essential hypertension is reversed by monotherapy with an α -blocker or an ACEI. It is possible that these drugs reduce the development of hypertensive vascular complications due to suppression of platelet activation in patients with essential hypertension. (*Hypertens Res* 2000; 23: 567-572)

Key Words: β -thromboglobulin, platelet activation, α -blocker, angiotensin-converting enzyme inhibitor

Introduction

The acceleration of platelet activity estimated *in vitro* and *in vivo* has been reported in patients with essential hypertension (1-4). We reported that the platelet function evaluated by the ratio of the plasma level of β -thromboglobulin (β -TG) to platelet factor 4 (PF-4) was activated in essential hypertensive patients and that this ratio increased with the progression of hypertensive vascular complications (1). Several reports have indicated that antihypertensive medications may improve platelet activation, but their exact influence remains unknown (2, 3). Even though a number of antihypertensive drugs have been reported to affect platelet function in hypertensive patients, we have only limited information on the long-term effects of antihypertensive medication following a

clinically relevant and properly designed study. For that reason, in this study we intended to determine whether the long-term monotherapy of antihypertensive drugs could affect the platelet function in patients with essential hypertension.

Methods

Subjects

This study was conducted on 45 patients (30 men and 15 women; mean age, 53.0 ± 9 years) with essential hypertension and 20 age-matched normotensive control subjects (10 men and 10 women, mean age 50.0 ± 3 years). Hypertension was diagnosed when blood pressure measured at the outpatient clinic was >160 mmHg in systolic and >95 mmHg in diastolic on 3 consecutive visits at least 1 week

From the Department of Medicine and Health Care Center, Nippon Telegram and Telephone (NTT) Kanto Medical Center, Tokyo, Japan.

Address for Reprints: Tomoko Gomi, M.D., Department of Medicine, NTT Kanto Medical Center, 5-9-22, Higashigotanda, Shinagawa-ku, Tokyo 141-8625, Japan.

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apart after 8 weeks of placebo treatment. Patients with other causes of hypertension, manifest atherosclerotic vascular complications, glucose intolerance, or kidney or heart failure were excluded from this study. The normotensive control subjects were selected from volunteers who visited the Health Care Center, NTT Kanto Medical Center, for physical checkups and who exhibited no abnormalities in routine laboratory tests.

The nature of the study and its potential associated risks were explained to all subjects, each of whom gave his or her signed informed consent before participating in the study. The study protocol was approved by the Institutional Review Board on Human Investigations of NTT Kanto Medical Center.

Study Protocol

Control studies were carried out during 12-h daytime fasting in hypertensive patients 8 weeks after a placebo "run-in" period and in normotensive control subjects. Subjects rested in the supine position in a temperature-controlled (25°C) and humidity-controlled (55%) quiet room. Blood pressure and pulse rate values used for analysis were averaged from five measurements taken by an automated measurement system (BP 203I, Nippon Colin Co., Tokyo, Japan) every 3 min after 30 min of resting in the supine position. Following the measurement of blood pressure and pulse rate, blood specimens were obtained to determine the plasma concentrations of β -TG and PF-4, hematocrit, and serum concentrations of albumin, glucose, creatinine, and lipids by careful venipuncture without stasis using a polypropylene disposable syringe and a 21-gauge needle.

After basal clinical and laboratory data were taken, the hypertensive patients were divided into five groups at random and administered one of five antihypertensive drugs monotherapeutically. The following groups were defined and treated with a diuretic: trichlormethiazide (group I, $n=9$); β -blocker: atenolol (group II, $n=9$); α -blocker: terazosin (group III, $n=9$); calcium (Ca) antagonist: nicardipine (group IV, $n=9$); angiotensin-converting enzyme inhibitor (ACEI): captopril (group V, $n=9$). The dose of each antihypertensive drug was increased every 4 weeks until the diastolic blood pressure fell below 90 mmHg. During the study, no patient was allowed to take any medication with vasoactive or antiplatelet properties. The same measurements as those made during the control period were repeated after 6 months of monotherapy with each antihypertensive drug.

Analytical Methods

To determine the plasma levels of β -TG and PF-4, immediately after collection, 2.5 ml of blood was placed in a pre-cooled collecting tube containing disodium ethylene-

diamine tetraacetate and theophylline. Each sample was centrifuged at $2,000\times g$ for 30 min at 4°C, and platelet-poor plasma was obtained from the upper part of the supernatant and kept frozen at -70°C until assayed. Plasma β -TG was determined by the radioimmunoassay (RIA) method of Ludlam *et al.* (5) with a β -TG RIA kit (Amersham International PLC, Amersham, UK). Plasma PF-4 was radioimmunoassayed by the method of Bolton *et al.* (6) with a PF-4 kit (Abbott Laboratories, Diagnostic Division, Chicago, USA). Serum concentrations of albumin, creatinine, and glucose were measured by an automatic analyzer (Model H736, Hitachi, Tokyo, Japan). Cholesterol and triglycerides were measured by an enzymatic technique with an automatic analyzer. High-density lipoprotein (HDL) cholesterol was measured after precipitation of low-density lipoprotein, very low-density lipoprotein, and chylomicrons with dextran sulfate, magnesium chloride, and polyethylene glycol.

Statistical Methods

All data in the text, tables, and figure are expressed as the mean $\pm$ SD of the mean. Significant differences among groups were analyzed by one-way fractional ANOVA. Pairwise mean comparisons among groups were done using Scheffe's test.

Results

Table 1 shows the clinical and laboratory variables in normotensive control subjects and hypertensive patients. Hypertensive patients had higher serum creatinine, glucose, and triglycerides and lower HDL cholesterol than did control subjects. There was no difference in hematocrit between the two groups. The averaged value of plasma β -TG in hypertensive patients was 52% higher than that of the control subjects; however, the averaged value of plasma PF-4 in hypertensives was similar to that of the normotensive control subjects.

Both systolic and diastolic blood pressures decreased significantly throughout the 6 months of monotherapy with each antihypertensive drug. The daily doses at the end of the trials were 3.3 ± 1.6 mg of trichlormethiazide in group I, 54 ± 9 mg of atenolol in group II, 3.5 ± 2.0 mg of terazosin in group III, 52 ± 19 mg of nicardipine in group IV, and 43 ± 12 mg of captopril in group V. The percentage decrease in systolic and diastolic blood pressure after the monotherapy trials were 11.7% and 12.1% in group I, 10.8% and 14.4% in group II, 11.2% and 14.9% in group III, 16.2% and 16.2% in group IV, and 12.5% and 15.4% in group V, respectively. Pulse rate decreased significantly by 11% only in group II, whose members were treated with the β -blocker atenolol. The fasting glucose declined significantly in group V, whose members were treated with the ACEI captopril. Serum creatinine decreased in

Table 1. Clinical and Laboratory Variables in Normotensive Control Subjects and Hypertensive Patients

	Control (n=20)	Hypertensive (n=45)	p
Age (years)	50±3	53±9	
Male/Female	10/10	30/15	
Systolic blood pressure (mmHg)	120±15	163±12	0.001
Diastolic blood pressure (mmHg)	76±9	103±9	0.001
Pulse rate (beats/min)	70±10	73±10	
Hematocrit	0.44±0.08	0.42±0.04	
Albumin (g/l)	42±2	42±3	
Creatinine (μmol/l)	56±12	79±19	0.001
Glucose (mmol/l)	5.2±0.5	5.6±0.6	0.02
Total cholesterol (mmol/l)	5.2±0.7	5.3±0.9	NS
HDL cholesterol (mmol/l)	1.6±0.2	1.3±0.4	0.02
Triglycerides (log (mmol/l))	0.15±0.22	0.20±0.15	0.001
β-Thromboglobulin (ng/ml)	21.2±9.8	32.1±13.7	
Platelet factor 4 (ng/ml)	6.7±3.7	6.8±1.7	

Values are mean±SD.

Table 2. Mean Levels and SD of Clinical and Laboratory Variables before and after Each Antihypertensive Treatments

Variables	Control	Group I	Group II	Group III	Group IV	Group V
Age (years)	50±3	56±10	53±8	52±10	53±10	50±9
Gender: Male/Female	10/10	5/4	6/3	5/4	7/2	7/2
Before treatment						
Systolic blood pressure (mmHg)	120±15	162±14 [#]	158±48 [#]	161±12 [#]	167±15 [#]	160±9 [#]
Diastolic blood pressure (mmHg)	76±9	99±8 [#]	104±12 [#]	101±5 [#]	105±10 [#]	104±11 [#]
Pulse rate (beats/min)	70±10	73±14	70±6	72±9	72±8	69±9
Hematocrit	0.44±0.08	0.40±0.04	0.42±0.04	0.42±0.06	0.42±0.04	0.43±0.04
Albumin (g/l)	42±2	42±2	42±2	43±2	41±4	43±3
Creatinine (μmol/l)	56±12	86±22 [#]	78±12 [#]	70±17 [#]	78±18 [#]	88±27 [#]
Glucose (mmol/l)	5.2±0.5	5.7±0.4 [#]	5.7±0.6 [#]	5.6±0.5 [#]	5.6±0.7 [#]	5.5±0.5
Total cholesterol (mmol/l)	5.2±0.7	5.2±1.0	5.6±0.7	5.4±0.9	5.7±0.8	5.1±0.8
HDL cholesterol (mmol/l)	1.6±0.5	1.3±0.7 [#]	1.2±0.3 [#]	1.3±0.3 [#]	1.3±0.1 [#]	1.3±0.3 [#]
Triglycerides (log (mmol/l))	0.15±0.22	0.36±0.39	0.28±0.11	0.23±0.11	0.20±0.22	0.26±0.15
After treatment						
Systolic blood pressure (mmHg)		143±16 [*]	141±14 [*]	143±6 [*]	140±12 [*]	140±13 [*]
Diastolic blood pressure (mmHg)		87±8 [*]	89±6 [*]	86±6 [*]	88±4 [*]	88±7 [*]
Pulse rate (beats/min)		70±6	62±3 [*]	78±16	74±13	66±9
Hematocrit		0.42±0.02	0.42±0.04	0.41±0.05	0.42±0.03	0.44±0.03
Albumin (g/l)		42±4	43±3	43±3	42±3	43±2
Creatinine (μmol/l)		71±18 [*]	70±14 [*]	56±13 [*]	69±22 [*]	71±18 [*]
Glucose (mmol/l)		5.6±0.3	6.6±1.6	5.4±0.7	5.5±0.8	5.3±0.3 [*]
Total cholesterol (mmol/l)		5.2±0.7	5.7±0.8	5.3±1.0	5.8±1.3	5.1±0.9
HDL cholesterol (mmol/l)		1.4±0.7	1.2±0.3	1.4±0.3	1.6±0.5	1.4±0.4
Triglycerides (log (mmol/l))		0.17±0.05	0.43±0.23	0.08±0.15	0.23±0.15	0.26±0.11

Values are mean±SD. ^{*}p<0.05 compared with before treatment. [#]p<0.05 compared with control. Group I, trichlor-methiazide; group II, atenolol; group III, terazosin; group IV, nicardipine; group V, captopril.

all groups, but no change was observed in other variables (Table 2).

Plasma β-TG and PF-4 levels before treatment were very similar in all treatment groups (29.5±9.9 and 7.0±

3.6 ng/dl in group I; 27.9±7.2 and 8.0±1.5 ng/dl in group II; 32.0±8.6 and 7.0±3.2 ng/dl in group III; 32.6±7.0 and 7.1±2.7 ng/dl in group IV; 37.0±10.1 ng/dl and 8.2±3.0 ng/dl in group V). Figure 1 shows the

Fig. 1. Plasma levels of β -thromboglobulin and platelet factor 4 in control subjects, before and after treatments of 5 kinds of antihypertensive drugs in patients with hypertension. Dotted bars show the levels of control subjects. Open bars show the levels before treatment and solid bars show the levels after treatment in hypertensive patients.

changes of plasma β -TG and PF-4 after each antihypertensive monotherapy together with those of control subjects. After treatment, a significant decrease of plasma β -TG was observed in group III, whose members were treated with the α -blocker terazosin, by 28% from 32.0 ± 8.6 to 23.0 ± 8.8 ng/ml, and in group V, whose members were treated with the ACEI captopril, by 40% from 37.0 ± 10.1 to 22.0 ± 4.2 ng/ml. Plasma β -TG increased by 123% in group I, whose members were treated with the diuretic trichlormethiazide, from 29.5 ± 9.9 to 67 ± 20.5 ng/ml. There was no change of plasma PF-4 after treatment in any of the groups.

Discussion

We observed that platelet function estimated by plasma β -TG was activated in essential hypertensive patients. Although cross-sectional studies suggest that plasma β -TG may correlate with end organ damage (1-3, 7, 8), prospective data linking plasma β -TG to clinically important vascular events such as stroke and myocardial infarction are lacking. Measurements of plasma β -TG and PF-4 allow us to quantify a platelet-releasing response *in vivo*, without being influenced by the addition of anti-coagulants or platelet aggregation-inducing agents (5, 6). A methodological problem in measuring β -TG as an index reflecting the status of platelet activation *in vivo* is how to rule out the platelet activation caused by minute stimulation during blood sampling and handling. Both β -TG and PF-4 are present in platelet α -granules in equal amounts and are released from platelets in similar quantities during platelet activation *in vivo* (9). The released β -TG is cleared from the systemic circulation with a half-life of 100 min, but the removal of PF-4 from plasma is extremely rapid and the half-life cannot be accurately determined

(10). This rapid removal of PF-4 has been attributed to PF-4 binding to vascular endothelial cells (11). When both β -TG and PF-4 levels were increased in the samples, increased β -TG was considered to be a result of *in vitro* platelet activation induced by blood sampling and handling. The plasma β -TG can be used as an index of platelet function *in vivo* when plasma PF-4 remains within normal values. The values of PF-4 in this study ranged from 6.2 to 8.1 ng/ml, which indicated that an activation of platelets during blood sampling and handling was avoided throughout the study.

We compared the effects of monotherapy with 5 different kinds of antihypertensive drugs, including a diuretic, β -blocker, α -blocker, Ca antagonist, and ACEI, on platelet function in patients with essential hypertension. Monotherapy with an α -blocker or ACEI decreases plasma β -TG levels, suggesting a beneficial effect on platelet function. These effects cannot be explained by the antihypertensive effect of these drugs, because the β -blocker or Ca antagonist had no effect on platelet function even though they have a similar antihypertensive effect as the α -blocker or ACEI. There are four reports available describing the following changes in platelet function after treatment with α -blockers in hypertensive subjects: increased plasma level of β -TG in hypertensive subjects were found to decrease to normal values after prazosin monotherapy (12); platelet aggregation induced by epinephrine, collagen, and adenosine diphosphate was inhibited by treatment with doxazosin (13) and terazosin (14); and Okrucka *et al.* (15) reported that short-term prazosin monotherapy for 7 days had no effect on plasma levels of β -TG or platelet aggregating ability, even though it showed a sufficient antihypertensive effect. Our data are in accordance with previous reports (12-14) indicating the beneficial effect of an α -blocker on platelet function,

but our findings were different from those of Okrucka *et al.* (15). Although the exact reason why our results, as well as those of the three previous reports, are different from those of Okrucka *et al.* is not clear, it may be due to a difference in the length of treatment. The α -adrenoceptor on platelets has been classified as an α_2 -adrenoceptor by platelet aggregation and binding studies. Because terazosin has a highly selective α_1 -adrenoceptor-blocking action, it seems unlikely that terazosin inhibits the platelet activation *via* the α_2 -adrenoceptor on the platelets. Hess (16) demonstrated that prazosin is 20 times more potent for inhibiting phosphodiesterase (PDE) in isolated rat hearts than theophylline, a standard PDE inhibitor. If this is the case in blood platelets, increases of cyclic adenosine monophosphate levels in platelets by an α -blocker may induce the inhibitory effect on platelet function. On the other hand, Alarayed *et al.* (17) reported that the selective α_1 -blockers naftopidil and doxazosin decreased platelet aggregation to adrenaline by inhibition of intracellular Ca^{2+} mobilization in blood platelets. They indicated that the α_1 -blockers inhibit Ca^{2+} mobilization in platelets and that this mechanism may be the means by which α_1 -blockers inhibit platelet aggregation. The α_1 -blocker is reported to improve insulin sensitivity (18) and lipid metabolism (19) in patients with essential hypertension. The mechanisms underlying these effects may be explained by the α_1 -blocker's catecholamine blocking effects and vasodilator effects (18). Although the exact mechanisms of our observation and those of others indicating the inhibitory effect of an α -blocker on platelet function remain to be clarified, it appears that the α -blocker's effect on platelets, insulin sensitivity, and lipid metabolism may be beneficial in preventing hypertensive end organ damage.

There are several reports that suggest monotherapy with an ACEI has a beneficial effect on platelets (20-22). Increased levels of plasma β -TG decreased from 69 to 45 ng/ml after monotherapy with the ACEI quinapril for 12 weeks in hypertensive patients (21). Islim *et al.* (3) compared the effects of antihypertensive drugs on platelet function in untreated and treated patients with hypertension and observed that the patients treated with the ACEI had significantly lower plasma β -TG levels than did the patients treated with other kinds of antihypertensive drugs. However, a double blind cross-over trial to evaluate the effect of quinapril on platelet function in hypertensive patients found no significant changes of β -TG and PF-4 between quinapril and a placebo period (22). In this study, plasma β -TG decreased significantly by 40% after the monotherapy with captopril in hypertensive patients, indicating that an ACEI might decrease the platelet activation *in vivo*. It was reported that human platelets had receptors for angiotensin II (23); however, angiotensin II itself has no direct effect on platelet function or change of intracellular Ca^{2+} in platelets. Physiological concentra-

tions of angiotensin II (10^{-11} mol) were observed to enhance adrenaline-induced platelet aggregation, while a high concentration (10^{-7} mol) had an inhibitory effect on platelet aggregation (24). Platelet aggregation induced by thrombin was enhanced in the presence of 10^{-9} mol angiotensin II (25). These findings suggest that the elevation of circulating angiotensin II may induce platelet activation *in vivo* and ACEI may inhibit platelet activation by reducing circulating angiotensin II. ACEI is reported to improve insulin sensitivity (26) and endothelial dysfunction (27) in patients with essential hypertension. These effects of ACEI will have beneficial effects in preventing hypertensive vascular damages.

According to previous reports, there continues to be controversy about the effects of Ca antagonists on platelet function in hypertensive patients (3, 28-30). Some reports indicated that isradipine and nitrendipine (28-30) suppressed platelet function, while another report found no effects on platelet function by nifedipine, nicardipine, or verapamil (3). We are aware of only one report, by Wigley *et al.* (31), in which the Ca antagonist nicardipine was used to evaluate its effect on platelet function. They observed that monotherapy with nicardipine with a dose of 30 mg per day resulted in no significant decrease in plasma β -TG by 5.0 ± 2.4 mg/ml in patients with primary and secondary Raynaud's phenomena. We observed that the chronic administration of nicardipine with an average dose of 52 mg per day showed a neutral effect on platelet function in hypertensive patients. We hypothesize that such a dose of nicardipine does not have any inhibitory effects on platelet function, unlike other dihydropyridine Ca-antagonists, for example isradipine and nitrendipine.

There is only one report on the effects of diuretics on platelet function *in vivo*. Islim (3) reported that plasma levels of β -TG in hypertensive patients treated with diuretics were not different from those of untreated hypertensive patients in a cross-sectional study. In our study, platelet function was activated and hematocrit showed the tendency to increase from 0.40 to 0.42 by treatment with trichlormethiazide. Volume contraction induced by the diuretic may participate in this process.

Conclusions

The platelet hyperactivity in patients with essential hypertension was reversed by an α -blocker or ACEI. These drugs may be useful for the treatment of hypertension.

References

1. Gomi T, Ikeda T, Yuhara M, Sakurai J, Nakayama D, Ikegami F: Plasma beta-thromboglobulin to platelet factor 4 ratios as indices of vascular complications in essential hypertension. *J Hypertens* 1988; 6: 389-392.
2. Wilson J, Orchard MA, Spencer AA, Davies JA, Pren-

- tice CRM: Anti-hypertensive drugs non-specifically reduce "spontaneous" activation of blood platelets. *Thromb Haemost* 1989; **62**: 776-780.
3. Islim IF, Beevers DG, Bareford D: The effect of anti-hypertensive drugs on *in vivo* platelet activity in essential hypertension. *J Hypertens* 1992; **10**: 379-383.
 4. Winther K, Gleerup G, Hedner T: Enhanced risk of thromboembolic disease in hypertension from platelet hyperfunction and decreased fibrinolytic activity: has antihypertensive therapy any influence? *J Cardiovasc Pharmacol* 1992; **19** (Suppl 3): S21-S24.
 5. Ludlam CA, Moore S, Bolton AE, Pepper DS, Cash JD: The release of a human platelet specific protein measured by a radioimmunoassay. *Thromb Res* 1975; **6**: 543-548.
 6. Bolton AE, Ludlam CA, Pepper DS, Moore S, Cash JD: A radioimmunoassay for platelet factor 4. *Thromb Res* 1976; **8**: 51-58.
 7. Petralito A, Fiore CE, Mangiafico RA, Malatino LS: Beta-thromboglobulin plasma levels in different stages of arterial hypertension. *Thromb Haemost* 1982; **48**: 241.
 8. Yamanishi J, Sano H, Saito K, Furuta Y, Fukuzaki H: Plasma concentrations of platelet-specific proteins in different stages of essential hypertension: interactions between platelet aggregation, blood lipids and age. *Thromb Haemost* 1985; **54**: 539-543.
 9. Kaplan KL, Broekman MJ, Chernoff A, Lesznik GR, Drillings M: Platelet alpha-granule proteins: studies on release and subcellular localization. *Blood* 1979; **53**: 604-618.
 10. Dawes J, Smith RC, Pepper DS: The release, distribution, and clearance of human beta-thromboglobulin and platelet factor 4. *Thromb Res* 1978; **12**: 851-861.
 11. Busch C, Dawes J, Pepper DS, Wasteson A: Binding of platelet factor 4 to cultured human umbilical vein endothelial cells. *Thromb Res* 1980; **19**: 129-137.
 12. Ikeda T, Nonaka Y, Goto A, Ishii M: Effects of prazosin on platelet aggregation and plasma beta-thromboglobulin in essential hypertension. *Clin Pharmacol Ther* 1985; **37**: 601-605.
 13. Hernández RH, Pajuelo JRG, Carvajal AR, *et al*: Evidence of an antiplatelet aggregation action of doxazosin in patients with hypertension: an *ex vivo* study. *Am Heart J* 1991; **121**: 395-401.
 14. Hernández RH, Angeli-Greaves M, Carvajal AR, Pajuelo JG, Padilla MCA, Armas-Hernández MJ: Terazosin: *ex vivo* and *in vitro* platelet aggregation effects in patients with arterial hypertension. *Am J Hypertens* 1996; **9**: 437-444.
 15. Okrucka A, Pechan J, Mikulecky M: The effect of prazosin therapy on platelet activation in essential hypertension. *Clin Exp Pharmacol Physiol* 1990; **17**: 813-819.
 16. Hess HJ: Prazosin: biochemistry and structure-activity studies. *Postgrad Med* 1975; Spec No: 9-17.
 17. Alarayed NA, Cooper MB, Prichard BNC, Betteridge DJ, Smith CCT: *In vitro* adrenaline and collagen-induced mobilization of platelet calcium and its inhibition by naftopidil, doxazosin and nifedipine. *Br J Clin Pharmacol* 1997; **43**: 415-420.
 18. Pollare T, Lithell H, Selinus I, Berne C: Application of prazosin is associated with an increase of insulin sensitivity in obese patients with hypertension. *Diabetologia* 1988; **31**: 415-420.
 19. Shieh SM, Sheu WH, Shen DC, Fuh MM, Chen YD, Reaven GM: Glucose, insulin, and lipid metabolism in doxazosin-treated patients with hypertension. *Am J Hypertens* 1992; **5**: 827-831.
 20. James IM, Dickenson EJ, Burgoyne W, *et al*: Treatment of hypertension with captopril: preservation of regional blood flow and reduced platelet aggregation. *J Hum Hypertens* 1988; **2**: 21-25.
 21. Blann AD, Lip GYH, Islim IF, Beevers DG: Evidence of platelet activation in hypertension. *J Hum Hypertens* 1997; **11**: 607-609.
 22. Gupta RK, Kjeldsen SE, Motley E, Weder AB, Zweifler AJ, Julius S: Platelet function during anti-hypertensive treatment with quinapril, a novel angiotensin converting enzyme inhibitor. *J Cardiovasc Pharmacol* 1991; **17**: 13-19.
 23. Moore TJ, Williams GH: Angiotensin II receptors on human platelets. *Circ Res* 1981; **51**: 314-320.
 24. Ding YA, MacIntyre DE, Kenyon CJ, Semple PF: Potentiation of adrenaline-induced platelet aggregation by angiotensin II. *Thromb Haemost* 1985; **54**: 717-720.
 25. Touyz RM, Schiffrin EL: Effects of angiotensin II and endothelin-1 on platelet aggregation and cytosolic pH and free Ca^{2+} concentrations in essential hypertension. *Hypertension* 1993; **22**: 853-862.
 26. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989; **321**: 868-873.
 27. Millgård J, Hägg A, Sarafi M, Lind L: Captopril, but not nifedipine, improves endothelium-dependent vasodilation in hypertensive patients. *J Hum Hypertens* 1998; **12**: 511-516.
 28. Sinzinger H, Virgolini I, Rauscha F, Fitscha P, O'Grady J: Isradipine improves platelet function in hypertensives. *Eur J Clin Pharmacol* 1992; **42**: 43-46.
 29. Tison P, Ulicna L, Jakubovska Z, Oravcova J, Fetkovska: Effects of dipyridines and their combination with aspirin on blood pressure and circadian platelet activity in patients with essential hypertension. *Am J Hypertens* 1994; **7**: 46s-49s.
 30. Belousov Y, Kushnaryov V: The effects of nisoldipine, diltiazem, nifedipine and verapamil on hemodynamic parameters and red blood cells-platelet interactions in patients with arterial hypertension. *J Cardiovasc Pharmacol* 1991; **18** (Suppl 9): S32-S35.
 31. Wigley FM, Wise RA, Malamet R, Scott TE: Nifedipine in the treatment of Raynaud's phenomenon. *Arthritis Rheum* 1987; **30**: 281-286.