Hypercoagulability in Cushing's syndrome: the role of specific haemostatic and fibrinolytic markers

Kaštelan, Darko; Dušek, Tina; Kraljević, Ivana; Polašek, Ozren; Giljević, Zlatko; Solak, Mirsala; Zupančić Šalek, Silva; Jelčić, Jozo; Aganović, Izet; Koršić, Mirko

Title: *Hypercoagulability in Cushing's syndrome: the role of specific haemostatic and fibrinolytic markers*

Running title: *Hypercoagulability in Cushing's syndrome*

Authors: Darko Kaštelan[1], Tina Dušek[1], Ivana Kraljević[1], Ozren Polašek[2], Zlatko Giljevic[1], Mirsala Solak[3], Silva Zupančić Salek[4], Jozo Jelčić[1], Izet Aganović[1], Mirko Koršić[1]

Institutions: [1]Division of Endocrinology, Department of Internal Medicine, University Hospital Zagreb, Zagreb, Croatia
[2]Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Štampar School of Public Health, Zagreb University School of Medicine, Zagreb, Croatia
[3]University Hospital for Pulmonary Diseases, Zagreb, Croatia
[4]Division of Haematology, Department of Internal Medicine, University Hospital Zagreb, Zagreb, Croatia

Corresponding author:

Darko Kaštelan, M.D., Ph.D.

Division of Endocrinology, Department of Internal Medicine, University Hospital Zagreb

Kišpatićeva 12, 10000 Zagreb

Croatia

Fax +385-1-2421-867

e-mail: dkastelan@inet.hr

Abstract

Objective: Hypercoagulability is a commonly described complication in patients with Cushing's syndrome. Recent clinical studies have indicated various abnormalities of coagulation and fibrinolysis parameters which may be related to that phenomenon. The aim of this study was to investigate the mechanisms underlying the hypercoagulable state in patients with Cushing's syndrome.

Research methods and procedures: A wide range of serum markers involved in the processes of blood coagulation and fibrinolysis was measured in a group of 33 patients with Cushing's syndrome and 31 healthy controls. No participant was taking medication which could influence the result or had known diseases, except hypertension and diabetes, which could affect blood coagulation or fibrinolysis parameters.

Results: Patients with Cushing's syndrome had higher levels of clotting factors II (P=0.003), V (P<0.001), VIII (P<0.001), IX (P<0.001), XI (P<0.001) and XII (P=0.019), protein C (P<0.001), protein S (P<0.001), C1-inhibitor (P<0.001) and PAI-1 (P=0.004). The activity of fibrinolytic markers, plasminogen (P<0.001), antithrombin (P<0.001) and antithrombin antigen (P=0.001) was also increased in the patient group.

Conclusion: The study has demonstrated hypercoagulability in patients with Cushing's syndrome manifest as increased prothrombotic activity and compensatory activation of the fibrinolytic system. We propose the introduction of thromboprophylaxis in the preoperative and early postoperative periods, combined with a close follow-up in order to prevent possible thromboembolic events in patients with Cushing's syndrome.

Key words

Cushing’s syndrome, coagulation, thrombosis, fibrinolysis, pulmonary embolism

Introduction

Hypercoagulability is a commonly described complication in patients with Cushing's syndrome. Thromboembolic events have been reported both in patients with endogenous cortisol hypersecretion and in those treated with glucocorticoids (1-6). However, the pathogenesis of the thrombotic tendency in these patients has not been appropriately explained. *In vitro* studies have demonstrated a lower fibrinolytic activity induced by corticosteroids due to the stimulated release of the plasminogen activator inhibitor type 1 (PAI-1) or to the suppression of plasminogen activator secretion (7-9). A study on a canine model reported an increase of the thrombin-antithrombin complex (10).

Recent clinical studies have indicated various abnormalities of different coagulation and fibrinolysis parameters which may be responsible for the increased risk of thromboembolism in patients with hypercortisolism (11-15). Increased levels of serum factor VIII, von Willebrand factor (vWF), plasminogen, tissue plasminogen activator (t-PA) antigen and PAI-1 activity has been observed in the patients with Cushing's syndrome as compared to healthy controls (11-13). Conversely, in another study patients with Cushing's syndrome had mean PAI-1, t-PA and vWF-Ag levels insignificantly different from those found in the controls (15). Similarly, a study by Fatti et al. disclosed no significant difference in the PAI-1 level between patients with Cushing's syndrome and controls (16).

Since data from different studies are inconsistent, the issue of hypercoagulability in patients with Cushing's syndrome remains to be reassessed. Accordingly, the aim of this study was to provide an additional contribution to existing knowledge and, possibly, an additional explanation on the mechanisms underlying hypercoagulability in patients with Cushing's syndrome through the analysis of the wide range of markers involved in the processes of blood coagulation and fibrinolysis.

Results

The haemostatic and fibrinolytic markers in patients and control subjects are summarized in Table 2. Alteration of at least two parameters was demonstrated in all patients with Cushing's syndrome. In 25 patients (75.8%) alteration was detected in 5 or more haemostatic and fibrinolytic parameters

As compared with the controls, serum levels of coagulation factors II ($P = 0.003$), V ($P < 0.001$), VIII ($P < 0.001$), IX ($P < 0.001$), XI ($P < 0.001$) and XII ($P = 0.019$) were significantly higher in patients with Cushing's syndrome. Similarly, protein C ($P < 0.001$), protein S ($P < 0.001$), antithrombin ($P < 0.001$), anthitrombin Ag ($P = 0.001$), C1 inhibitor ($P < 0.001$), plasminogen ($P <0.001$) and PAI-1 ($P = 0.004$) levels were also significantly higher in patients with Cushing's syndrome. Factor VII and fibrinogen levels were not significantly different from the controls. Patients with Cushing's syndrome had a significant shortening of APTT ($P <0.001$) whereas no differences were noted for PT and TT.

The amount of daily urine cortisol excretion in patients with Cushing's syndrome was positively correlated with antithrombin activity (r=0.46; P=0.01) and FVII level (r=0.36; P<0.05). In the comparison of patients with ACTH dependent and ACTH non-dependent Cushing's syndrome no significant differences in the level of coagulation parameters were noted.

The analysis of coagulation and fibrinolytic markers in patients with Cushing's syndrome and in the presence of diabetes, hypertension and a high BMI revealed no differences either between hypertensive and non-hypertensive, or diabetic and non-diabetic patients. With respect to BMI, patients with BMI ≥ 30 as compared to those with BMI < 30 showed significantly higher C1-inhibitor ($P = 0.04$) and factor II levels ($P = 0.03$).

Discussion

It is well known that patients with Cushing's syndrome are at an increased risk of thromboembolism (17), which can be explained by an increased level of procoagulation factors, reduced levels of fibrinolytic factors, or both. This impairment in the coagulation process may also contribute to the development of atherosclerosis (18) and subsequent cardiovascular morbidity and mortality (19, 20). However, the exact mechanism of the prothrombotic state associated with hypercortisolism is still not fully understood.

Some studies focused on coagulation and fibrinolysis parameters in patients with Cushing's syndrome, each reporting a number of abnormalities. Increased levels of PAI-I, t-PA, vWF-Ag, II, V, VIII, IX, XIII clotting factors, and depletion of antithrombin-III have been reported (4, 11-13). In a small series of patients with the active disease Fatti et al. observed significantly increased vWF-Ag, thrombin-antithrombin complex and plasmin-antiplasmin complex levels (16). They suggested that the prothrombotic state is related to an enhanced metabolic function of endothelial cells. In the same study, the PAI level, although higher, was not significantly different in active patients as compared to controls.

The data presented in this study suggest that patients with Cushing's syndrome display an increased risk of thromboembolism, determined by higher levels of clotting factors II (P=0.003), V (P<0.001), VIII (P<0.001), IX (P<0.001), XI (P<0.001) and XII (P=0.019), protein C (P<0.001), protein S (P<0.001), C1-inhibitor (P<0.001) and PAI-1 (P=0.004) as compared to healthy controls. The possible underlying mechanism was cortisol-induced up-regulation of mRNA transcription of various coagulation factors. The increased activity of fibrinolytic markers; plasminogen (P<0.001), antithrombin (P<0.001) and antithrombin antigen (P=0.001), was probably a secondary event due to the activation of coagulatiuon.

Although we did detect some correlation between coagulation markers and urine free cortisol, these two parameters were not significantly associated. A similar finding has also

been demonstrated in previous reports (14, 15). To some extent, this could possibly be attributed to the day to day variability of urinary free cortisol excretion. Furthermore, coagulation levels and fibrinolysis parameters depend not only on the degree of hypercortisolism but also on the duration of the disease.

It has recently been observed that patients with persistent hypercortisolism have a higher mortality rate during the first year after initial diagnosis (21) which can be attributed to thromboembolic events. A study by Boscaro et al. indicated that 10% of patients with Cushing's syndrome die due to thrombotic events (17). It has been observed that the early postoperative period is associated with a high thrombotic risk (11). Conversely, in another study involving 53 patients with Cushing's syndrome, six patients suffered deep venous thrombosis or pulmonary embolism. The authors of the study estimated that those thromboembolic episodes appeared as frequently as expected for patients undergoing any other major surgery (5). In our group, one patient had deep vein thrombosis, whereas two had an episode of pulmonary embolism during the disease. However, the values of thrombotic and fibrinolytic markers in those patients were not different when compared to patients without such events. Elevated concentrations of haemostatic and fibrinolytic markers present in all the patients who participated in the study can indicate a sub-clinical activation of the coagulation cascade without overt thromboembolic events.

On the basis of these observations, the main dilemma seems to be whether these patients need peri- and postoperative thromboprophylaxis different from other patients undergoing major surgery. In view of this consideration, the major task would be a prospective study with patients' outcomes after the implementation of prophylactic anticoagulation as a primary endpoint. A recent study involving a large group of patients with Cushing's syndrome indicated a huge reduction of morbidity and mortality due to thromboembolic events after the introduction of postoperative prophylactic anticoagulation

(17). In the study the patients were treated with warfarin (after a short-term postoperative heparin therapy) for at least four months. The treatment was discontinued when the cure of the disease and normalization of coagulation parameters were demonstrated. Therefore, the introduction of pre- and postoperative thromboprophylaxis in patients with Cushing's syndrome appears to be reasonable.

Considering the aetiology of hypercoagulability in patients with Cushing's syndrome we need to accept the possibility that hypercoagulation could be related to hypertension and diabetes per se. A higher vWF-Ag level has been found in hypertensive as compared to normotensive patients with Cushing's disease (16). In another study, a statistically significant difference in PAI-1 was found between diabetic and nondiabetic patients with hypercortisolemia (22). Furthermore, impairment of coagulation and fibrinolytic parameters could be associated with obesity (23). Finally, some patients with Cushing's syndrome presented clinically with polycythemia (24) which can also contribute to an increased risk of thromboembolism.

In the present study, 25 patients (75.8%) had hypertension, 9 (27.3%) had type 2 diabetes and 15 (45.5%) were obese. No significant differences in the activity of the analysed coagulation factors were found between patients with and without hypertension or diabetes. In contrast, BMI $\geq$ 30 was associated with significantly higher of C1-inhibitor and clotting factor II levels.

Several studies have recently showed that patients with clinically inapparent adrenal masses may present with clinical signs of a mild cortisol excess known as subclinical Cushing's syndrome (25-27). Patients with a subclinical Cushing's syndrome are at an increased cardiovascular risk demonstrated by changes in carotid intimal-medial thickness (28). With respect to these data it would be of interest to analyse whether adrenal incidentaloma is associated with an increased risk of thromboembolism. The only study in

this field involving a small series of twelve patients with adrenal incidentaloma observed higher PAI-1, tPA and vWF-Ag levels (15).

In conclusion, the present study has demonstrated hypercoagulability in patients with Cushing's syndrome manifest as increased prothrombotic activity and compensatory activation of the fibrinolytic system. Based on these data, in such patients we suggest the introduction of prophylactic anticoagulation in the preoperative and early postoperative periods.

Materials and methods

Patients

Our group comprised thirty-three consecutive patients (25 females, 8 males; mean age 45.4±2.3 yr) with Cushing's syndrome in the active phase of the disease, and thirty-one age and sex matched healthy controls (19 females, 12 males; mean age 48.7±2.5 yr). The study was conducted in the Department of Endocrinology, University Hospital Zagreb, and approved by the local Ethics Committee. All the patients and controls were informed about the study protocol and gave their written consent.

The clinical and demographic characteristics of patients with Cushing's syndrome and of the controls are shown in Table 1. No participant was taking drugs or had a disease, except hypertension and diabetes, which could affect blood coagulation or fibrinolysis parameters. The controls were recruited among hospital personnel and their friends. The diagnosis of Cushing's syndrome was based on characteristic clinical presentation and on the results of standard hormonal criteria (increased urinary free cortisol, absence of typical cortisol and ACTH diurnal rhythm, nonsuppressibility of cortisol secretion in the 1 mg overnight dexamethasone test and classic 2-days 2 mg dexamethasone test). Additionally, the high-dose dexamethasone test and inferior petrosal sinus catheterisation with basal and CRH-stimulated blood sampling were run where indicated in order to verify the distinction between ectopic ACTH secretion and Cushing’s disease. Twenty-five patients (75.8%) had pituitary disease whereas eight (24.2%) had cortisol producing adrenal adenoma. Twenty-five patients (75.8%) had hypertension and 9 (27.3.6%) type 2 diabetes. Fifteen patients (45.5%) were obese (BMI ≥ 30). One patient (3.0%) had deep vein thrombosis and 2 (6.0%) pulmonary embolism during the disease.

Laboratory tests

Venous blood was drawn from the participants and collected in glass tubes for determination of prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, factors II, V, VII, VIII, IX, XI, XII, plasminogen, protein C and protein S activity, antithrombin, antithrombin antigen, C1-inhibitor and plasminogen activator inhibitor-1 (PAI-1). Prothrombin time was determined by Innovin reagents. Activated partial thromboplastin time was determined by Actin FS reagents (Siemens Medical Solutions Diagnostics /Deerfield, IL, USA/). Fibrinogen was quantified by the modified Clauss method (Siemens Medical Solutions Diagnostics /Deerfield, IL, USA/). Standard one-stage clotting assays using a specific factor deficient plasma as a substrate were used for the determination of factors II, V, VII, VIII, IX, XI, XII (Siemens Medical Solutions Diagnostics /Deerfield, IL, USA/). Antithrombin, protein C activity, protein C1-inhibitor, PAI, and plasminogen were quantified by chromogenic determination (Siemens Medical Solutions Diagnostics /Deerfield, IL, USA/). Protein S activity was quantified by the clotting assay (Siemens Medical Solutions Diagnostics /Deerfield, IL, USA/). The antithrombin antigen was quantified by nephalometric determination (Siemens Medical Solutions Diagnostics /Deerfield, IL, USA/).

Statistics

Statistical analysis was run by using SPSS 13.0 (SPSS, Chicago, USA), with significance set at $P<0.05$. Non-parametric statistical methods were used in the analysis – medians and ranges as central tendency indicators, and Mann-Whitney and Spearmans tests in hypothesis testing.

Acknowledgments

The study was funded by Research Program No. 108-0000000-3496 of the Croatian Ministry of Science, Education and Sport.

References

1. Diez, J.J. and Iglesias, P. (1997). Pulmonary thromboembolism after inferior petrosal sinus sampling in Cushing's syndrome. Clin Endocrinol. 46, 775-777.
2. Obuobie, K., Davies, J.S., Ogunko, A., and Scanlon, M.F. (2000). Venous thrombo-embolism following inferior petrosal sinus sampling in Cushing's disease. J Endocrinol Invest. 23, 542-544.
3. Semple, P.L., and Laws, E.R. (1999). Complications in a contemporary series of patients who underwent transsphenoidal surgery for Cushing's disease. J Neurosurg. 91**,** 175-179.
4. La Brocca, A., Terzolo, M., Pia, A., Paccotti, P., De Giuli, P., and Angeli, A. (1997). Recurrent thromboembolism as a hallmark of Cushing's syndrome. J Endocrinol Invest. 20**,** 211-214.
5. Small, M., Lowe, G.D., Forbes, C.D., and Thomson, J.A. (1983). Thromboembolic complications in Cushing's syndrome. Clin Endocrinol. 19, 503-511.
6. Isacson, S. (1970). Effect of prednisolone on the coagulation and fibrinolytic system. Scand J Haematol. 7, 212-221.
7. Oikarinen, A., Hoythya, M., and Jarvinen, M. (1990). Dexamethasone-induced plasminogen activator inhibitor: characterization, purification and preparation of monoclonal anti-bodies. Arch Dermatol Res. 282, 153-158.
8. Laug, W.E. (1983). Glucocorticoids inhibit plasminogen activator production by endothelial cells. Thromb Haemost. 50, 888-892.
9. Barouski-Miller, P.A., and Gelehrter, T.D. (1982). Paradoxical effects of glucocorticoids on regulation of plasminogen activator activity of rat hepatoma cells. Proc Natl Acad Sci USA. 79, 2319-2322.

10. Jacoby, R., Owings, J., Ortega, T., Gosselin, R., and Feldman, E. (2001). Biochemical basis for the hypercoagulable state seen in Cushing syndrome. Arch Surg. 136, 1003-1007.
11. Casonato, A., Pontara, E., Boscaro, M., Sonino, N., Sartorello, F., Ferasin, S., and Girolami, A. (1999). Abnormalities of von Willebrand factor are also a part of the prothrombotic state of Cushing's syndrome. Blood Coag Fibrinol. 10, 145-151.
12. Sjoberg, H.E., Blomback, M., and Granberg P.O. (1992). Thromboembolic complications, heparin treatment and increase in coagulation factors in Cushing's syndrome. Acta Med Scand. 199, 95-98.
13. Patrassi, G.M., Sartori, M.T., Viero, M.L., Scarano, L., Boscaro, M., and Girolami, A. (1992). The fibrinolytic potential in patients with Cushing's disease: a clue to their hypercoagulable state. Blood Coag Fibrinol. 3, 789-793.
14. Patrassi, G.M., Dal Bo Zanon, R., Boscaro, M., Martinelli, S., and Girolami, A. (1985). Further studies on the hypercoagulable state of patients with Cushing's syndrome. Thromb Haemost. 54, 518-520.
15. Ambrosi, B., Sartorio, A., Pizzocaro, A., Passini, E., Bottasso, B., and Federici, A. (2000). Evaluation of haemostatic and fibrinolytic markers in patients with Cushing's syndrome and in patients with adrenal incidentaloma. Exp Clin Endocrinol Diabetes. 108, 294-298.
16. Fatti, L.M., Bottasso, B., Invitti, C., Coppola, R., Cavagnini, F., and Mannucci, P.M. (2000). Markers of activation of coagulation and fibrinolysis in patients with Cushing's syndrome. J Endocrinol Invest. 23, 145-150.
17. Boscaro, M., Sonino, N., Scarda, A., Barzon, L., Fallo, F., Sartori, M.T., Patrassi, G.M., and Girolami, A. (2002). Anticoagulant prophylaxis markedly reduces

thromboembolic complications in Cushing's syndrome. J Clin Endocrinol Metab. 87, 3662-3666.

18. Skrha, J. (2003). Pathogenesis of angiopathy in diabetes. Acta Diabetol. 40, 324-329.
19. Etxabe, J., and Vazquez, J. (1994). Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol. 40, 479-484.
20. Mancini, T., Kola, B., Mantero, F., Boscaro, M., and Arnaldi, G. (2004). High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clin Endocrinol. 61, 768-777.
21. Lindholm, J., Juul, S., Jorgensen, J.O.L., Bjerre, A.P., Feldt-Rasmussen, U., Hagen, C., Jorgensen, J., Kosteljanetz, M., Kristensen, L.O., Laurberg, P., Schmidt, K., and Weeke, J. (2001). Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 86, 117-123.
22. Prazny, M., Jezkova, J., Horova, E., Lazarova, V., Hana, V., Kvasnicka, J., Pecen, L., Marek, J., Skrha, J., and Krsek, M. (2008). Impaired microvascular reactivity and endothelial function in patients with Cushing's syndrome: influence of arterial hypertension. Physiol Res. 57, 13-22.
23. Martens, I., Considine, R.V., Van der Planken, M., and Van Gaal, L.F. (2006). Hemostasis and fibrinolysis in non-diabetic overweight and obese men and women. Is there still a role for leptin? Eur J Endocrinol. 155, 477-484.
24. Dusek, T., Kastelan, D., Solak, M., Basic Kinda, S., Aganovic, I., and Korsic, M. (2008). Polycythemia as the first manifestation of Cushing's disease. J Endocrinol Invest. 31, 940.
25. Reincke, M., Nieke, J., Krestin, G.P., Saeger, W., Allolio, B., and Winkelman, W. (1992). Preclinical Cushing's syndrome in adrenal „incidentalomas“: Comparison with adrenal Cushing's syndrome. J Clin Endocrinol Metab. 75, 826-832.

26. Terzolo, M., Ali, A., Osella, G., Cesario, F., Paccotti, P., and Angeli, A. (1998). Subclinical Cushing's syndrome in adrenal incidentaloma. Clin Endocrinol. 48, 89-97.
27. Barzon, L., Sonino, N., Fallo, N., Palu, G., and Boscaro, M. (2003). Prevalence and natural history of adrenal incidentalomas. Eur J Endocrinol.149, 273-285.
28. Tauchmanova, L., Rossi, R., Biondi, B., Pulcrano, M., Nuzzo, V., Palmieri, E.A., Fazio, S., and Lombardi, G. (2002). Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J Clin Endocrinol Metab. 87, 4872-4878.

Table 1. Clinical and demographic characteristics of the patients with Cushing's syndrome and controls

	Cushing's (n=33)	Controls (n=31)	*P* value
Age (years)	50 (38-60)	51 (22-83)	NS
Body weight (kg)	78 (77-88)	80 (58-100)	NS
Body height (cm)	158 (155-170)	170 (156-185)	NS
BMI (kg/m^2)	32 (27-36)	28.0 (21-34)	0.04
Male/female	8/25	12/19	NS
Hypertension (yes/no)	25/8	5/26	0.001
Diabetes (yes/no)	9/24	0/31	0.001
Cigarette smoking (yes/no)	6/27	5/26	NS

The results are medians (range)
NS – not significant; BMI-body mass index

Table 2. Haemostatic and fibrinolytic markers in patients with Cushing's syndrome and controls

	Cushings (n=33)	Controls (n=31)	*P* value
fibrinogen (g/l) (n.r. 1.8-4.1)	3.8 (1.8-4.2)	2.8 (2.3-4.4)	NS
antithrombin (%) (n.r. 75-125)	115.6 (57.5-120.4)	99 (69-114)	<0.001
antithrombin Ag (g/l) (n.r. 0.19-0.31)	0.31 (0.20-0.33)	0.28 (0.19-0.35)	0.001
F II:C (IU) (n.r. 0.75-1.20)	1.36 (0.94-1.51)	1.02 (0.84-1.27)	0.003
F V:C (IU) (n.r. 0.75-1.20)	1.57 (1.33-1.67)	1.24 (0.65-1.80)	<0.001
F VII:C (IU) (n.r. 0.70-1.20)	0.97 (0.89-1.32)	1.07 (0.58-1.89)	NS
F VIII:C (IU) (n.r. 0.60-1.80)	2.92 (1.53-3.08)	1.17 (0.76-1.96)	<0.001
F IX:C (IU) (n.r. 0.60-1.80)	1.47 (1.14-2.26)	1.04 (0.71-1.57)	<0.001
F XI:C (IU) (n.r. 0.75-1.20)	1.31 (1.11-1.55)	0.94 (0.73-1.40)	<0.001
F XII:C (IU) (n.r. 0.70-1.40)	0.57 (0.43-1.14)	1.00 (0.48-1.27)	0.019
protein C (%) (n.r. 70-140)	163.2 (93.7-169.6)	120 (88-198)	<0.001
protein S (%) (n.r. 48-120)	105.1 (84.5-113)	79 (47-124)	<0.001
C1 inhibitor (%) (n.r. 70-130)	129.6 (116.8-162.6)	112 (16-150)	<0.001
PAI-1 (U/ml) (n.r. 0.3-3.5)	7.02 (2.79-8.5)	3.6 (0.1-7.3)	0.004
Plasminogen (%) (n.r. 75-150)	115.6 (93.9-132.8)	104 (11-137)	<0.001
PT (ratio) (n.r. 0.70-1.30)	1.19 (0.81-1.29)	1.16 (0.93-1.49)	NS
APTT (s) (n.r. 24-33)	25.2 (25.1-30.9)	27 (25-29)	<0.001
TT (s) (n.r. 16-21)	18 (17.2-18.3)	19 (16-32)	NS

The results are medians (range)
NS – not significant; PAI-1-plasminogen activator inhibitor type 1; PT-prothrombin time; APTT-activated partial thromboplastin time; TT-thrombin time