Thrombodynamics Test in Assessing the Risk of Thrombus Formation in Patients with Atrial Fibrillation Taking Direct Oral Anticoagulants

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Aim. To evaluate thrombus characteristics in patients with atrial fibrillation (AF) taking different direct oral anticoagulants (DOACs) using Thrombodynamics test.

Materials and methods. Thrombodynamics test was performed in 100 patients with paroxysmal and permanent forms of AF taking different DOACs, dose choice was done in accordance with the instructions for drugs use. For analysis samples of fresh citrated platelet-free plasma were taken just before regular DOACs dose intake (trough concentration). Statistical data processing was carried out using R software packages.

Results. All patients had no history of thrombosis or bleeding before inclusion in this study. All parameters of Thrombodynamics test taken at residual concentration of DOACs were in general within reference values, that is in the area of normal coagulation: spatial clot growth rate (V) – 26.56 (25.0; 29.2) μm/min, the time to the start of clot growth (Tlag) – 1.05 (0.85; 1.27) min, initial spatial clot growth rate (Vi) – 44.3±7.7 μm/min, stationary spatial clot growth rate (Vst) – 26.5 (24.9; 28.4) μm/min, clot size (CS) – 999.7 (912.9; 1084.7) μm, clot density (D) – 22883.1±3199.9 arb. units. D was appeared to be higher in women [22947.7 (21477.5; 22947.7) vs men [22124.8 (19722.8; 22124.8), p=0.035] and Tlag was significantly higher in patients with chronic heart failure [1.2 (1.0; 1.2) vs 1.0 (0.8; 1.0), p=0.008]. A correlation was found between level of creatinine and Tlag parameter, glomerular filtration rate (GFR) and clot density. With an increase in the level of creatinine in the blood and a decrease in GFR, respectively, there was an increase in Tlag parameter (p-value 0.038); with an increase in GFR, clot density decrease (p-value 0.005).

Conclusion. All parameters of Thrombodynamics test on residual concentration of DOACs were within reference values that indicated optimal anticoagulant effect of all DOACs. The obtained data of normal coagulation at the residual concentration of the anticoagulant are consistent with the previously obtained data on the safety and effectiveness of DOACs using other methods. Further studies with clinical end points are needed to assess the clinical value of this method.

Keywords: blood clotting, atrial fibrillation, direct oral anticoagulants, laboratory assays, bleeding, thrombodynamics test.

For citation: Gebekova Z.A., Ivanov I.I., Asambayeva A., Skripka A.I., Sokolova A.A., Napalkov D.A., Vuimo T.A. Thrombodynamics Test in Assessing the Risk of Thrombus Formation in Patients with Atrial Fibrillation Taking Direct Oral Anticoagulants. *Rational Pharmacotherapy in Cardiology* 2022;18(5):544-552. DOI:10.20996/1819-6446-2022-09-07.

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Received: 13.04.2022
Accepted: 14.06.2022

Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmia [1] with an increasing incidence. According to global statistics, the prevalence of AF ranges from 2 to 4% in the adult population [1], and it is estimated that by 2030 in the EU countries it will reach 14-17 million people [2] due to an increase in life expectancy and improvement in diagnosis of subclinical AF [3].

The burden of AF and its social and economic impact are determined by a large number of unfavorable outcomes. AF is associated with a 2-fold increased risk of death and leads to a 5-fold times increase risk of stroke [4], which requires anticoagulant therapy associated with bleeding events.

It has been proven that direct oral anticoagulants (DOACs) currently are the basic drugs for thromboembolic prevention in patients with non-valvular AF [4].

Warfarin traditionally is used in clinical practice but has some serious disadvantages: firstly, the difficulty in achieving target international normalized ratio (INR) and, despite of that, high risk of major bleedings. In this regard, DOACs [5] are gaining an increasing role which is reflected in clinical guidelines [4]. Many large randomized controlled trials have shown that direct thrombin inhibitor dabigatran, as well as factor Xa inhibitors apixaban and rivaroxaban, have the same efficacy as warfarin [6], predictable pharmacodynamics, wide therapeutic range, and few interactions with other drugs and food.

Optimal assessment of hemostasis is necessary to adjust the doses of anticoagulants, taking into the consideration according to individual characteristics of the patient. However, the current clinical practice has no routine unified laboratory method for monitoring anticoagulant effect of DOACs. Routine tests, such as INR, prothrombin time (PT), activated partial thromboplastin time (aPTT) are low-informative for this purpose [7-10], since they describe isolated components of blood coagulation system, have low sensitivity to hypercoagulable states and are of a low predictive value for thrombotic complications. Therapeutic drug monitoring by direct measurement of the equilibrium concentrations of anticoagulant in blood plasma allows us to obtain objective data on the pharmacokinetics of the drug and its effect on clinical outcomes, however, the method is expensive, and its use does not yet go beyond scientific research. Moreover, at the moment, the optimal therapeutic concentrations of DOACs in blood plasma have not been determined [11,12]. Possibilities of global integral tests for assessing the dynamic characteristics of thrombus formation, which measure the overall result of all hemostasis reactions in conditions that simulate in vivo situation, have not been studied in detail [13]. There are several methods known [14-19]. One of the most promising in modern coagulology is Thrombodynamics test (TD).

Thrombodynamics test evaluates the qualitative and quantitative characteristics of the coagulation state of blood plasma by analyzing the spatio-temporal changes of clot formation in a heterogeneous environment *in vitro* [13]. This method is based on the idea that in human being the process of blood coagulation is activated at the site of damage to the endothelium of a blood vessel or on the surface of cells carrying tissue factor (TF). In this case, the growth of a fibrin clot begins from the activating surface and then spreads into the blood volume without contact with it. Previously, data have already been obtained on the greater informativeness of this test in comparison with the currently used thromboelastography (TEG) and thrombin generation test (TGT) [18,20], as well as routine coagulation tests in patients taking different heparins [18,20]. The technique has demonstrated a high sensitivity to changes in hemostasis both in hypo- and hypercoagulation [16,21-28]. Up-to-date there are no single study of thrombodynamics including patients with atrial fibrillation who are taking different DOACs.

Thus, the aim of this study is to evaluate thrombus formation in patients with AF taking various DOACs by using Thrombodynamics test.

Material and methods

Material

To carry out Thrombodynamics test the diagnostic laboratory system "Thrombodynamics Recorder T-2" (DLS TR T-2, HemaCore, Moscow, Russia) and the following diagnostic kits of consumables were used: two-channel polymer cuvettes for single use, two-channel inserts-activators with TF fixed at their ends [29], microtubes for control solutions I and II con-

taining a mixture of a contact activation inhibitor (corn trypsin inhibitor) and calcium salt, respectively.

Anticoagulant therapy was carried out using DOACs in accordance with their product instructions: dabigatran etexilate, rivaroxaban and apixaban.

Thrombodynamics test was performed using samples of fresh citrated platelet-free plasma (PFP) got at room temperature.

Patients

The clinical study was carried out in compliance with principles of Good Clinical Practice. In this study all procedures were performed in accordance with the ethical standards of the IRB and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The research protocol was approved by the local (interuniversity) Ethics committee (Protocol No. 31-20 of 11.11.2020). All patients signed an informed consent form to participate in the study.

The exclusion criteria of the study were as follows: patients under 18 years of age, pregnancy or lactation, reversible causes of AF (heart surgery, thyrotoxicosis, alcohol abuse), clinically significant bleeding episodes in previous 3 months, or conditions accompanied by a significant increase in the risk of bleeding (exacerbation of gastrointestinal ulcer disease, hemorrhagic stroke in previous 6 months, thrombocytopenia, concomitant intake of antiplatelets or other anticoagulants, etc.), severe comorbidities (hematological diseases, connective tissue diseases, malignancy, severe liver failure (Child-Pugh class B and C), chronic kidney disease (CKD) grade 4-5 or creatinine clearance (CrCl) <30 ml/min, deep vein thrombosis/ pulmonary embolism (PE) in previous 6 months, severe mental disorders), long-term intake of nephrotoxic drugs, low compliance to treatment.

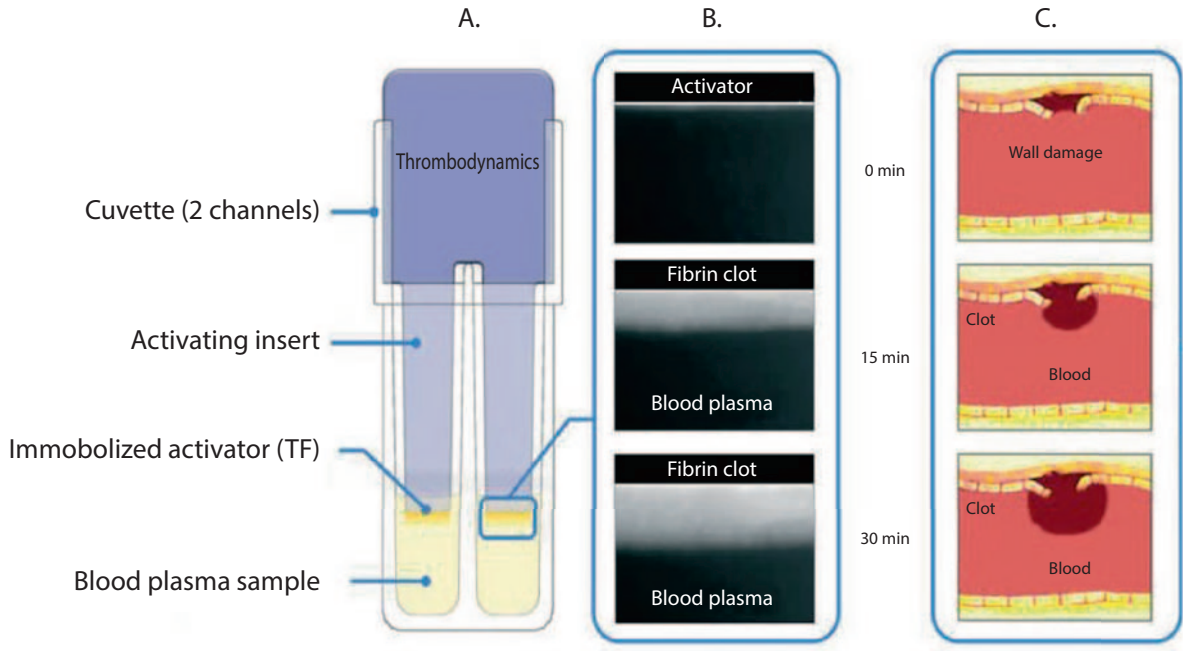
Blood collection and plasma preparation

Blood collection from patients was carried out immediately before taking scheduled dose of anticoagulants (not less than 5 tablets consequently to reach concentration in a "steady" state and to develop stable pharmacodynamic effect [30]). We were guided by standard rules for collecting blood from the cubital vein for coagulation tests. We used a type of vacuum tubes that had a minimal effect on the test results in healthy donors: Vacuette plastic 4.5 ml 3.8% citrate and CTAD (Greiner Bio-One; registration certificate No FSZ 2011/09572). The volume ratio of blood to citrate was equal to 9:1. Blood samples were centrifuged at 1,600 g for 15 minutes, and the upper part of the resulting plasma (75%) was taken. Subsequently, PFP was obtained by additional centrifugation of platelet-poor plasma for 5 minutes at 10,000 g. The upper part (~ 80%) of the received PFP was collected for analysis. The procedure was performed at ambient temperature.

Principle of the method and its parameters

The global coagulation "Thrombodynamics" test differs from other global tests because it simulates the spatial distribution of the blood coagulation process in blood vessels and assesses the spatio-temporal dynamics of blood clotting. Using video microscopy, it makes it possible to register clot formation initiated by TF immobilized on the surface. In this case, the clot initially forms on the activating surface, and then propagates in the plasma without mixing. This approach allows to take into consideration the heterogeneity of blood coagulation *in vivo* and simulates coagulation conditions close to biological model in comparison with other global tests. Schematic representation of an experimental cuvette and the processes of growth of a fibrin clot in this cuvette *in vitro* and in a damaged blood vessel are presented in Fig. 1. Pictures of clots, as well as calculated parameters on the graph are presented on Fig. P1 in Supplementary material.

In addition to the visual monitoring of clotting, the device performs mathematical processing and obtaining quantitative parameters of the clot growth. The main numerical parameters of the "Thrombodynamics" test, which characterize the clot growth curve, include: V (stationary) and Vi (initial) spatial clot growth rates (the slopes of the clot size curve vs. time for the segments of 15-25 min and 2-6 min from the clot growth start for V and Vi, respectively); Tlag (the time to the start of clot growth); CS (the clot size at 30 min after coagulation activation); D (the maximum optical density of the formed clot, which characterizes the clot quality); Tsp (the time of appearance of spontaneous clots in the sample, the presence of which indicates a high prothrombotic trend) [18].



(a) Schematic image of a plastic cuvette and an activator for TD measurement; (b) sequential photographs of the growth of a clot from the activator in vitro; (c) schematic image of clot growth from a damaged vessel wall in vivo. TF – tissue factor

Figure 1. "Thrombodynamics" test simulates a coagulation process *in vivo* [13]

The ranges of normal values of the parameters of the "Thrombodynamics" test were taken from the instructions of the used consumables from the manufacturer. The manufacturer checked the supplied batch of consumables in advance to determine the reference values of thrombodynamic parameters. The range of reference values for this pool of consumables corresponded to the control range of values of thrombodynamics parameters according to the Operation Manual of DLS TR T-2.

The deviation of the values of the parameters, both above and below the established reference ranges, indicates the development of a pathological condition. Along with quantitative parameters, the study report provides a sequence of pictures of a growing fibrin clot, which clearly characterize patient's hemostasis. The "Thrombodynamics" test showed a high sensitivity to hypo- and hypercoagulable states of various nature, as well as to therapy with various anticoagulants (Supplementary material Fig. P2- P5).

A protocol for the Thrombodynamics test

Previously prepared sample of PFP volume 120 ml, is placed in a microtube with control solution I, which contains contact activation inhibitor, for subsequent incubation at 37° C for 3 minutes. After incubation, the plasma sample is transferred into a microtube with control solution II. The resulting mixture is mixed using a pipette until the dry substance of calcium acetate is completely dissolved. The resulting mixture is placed in the channels of the measuring cuvette. Then the insert-activator with TF is introduced into the cuvette. The study is started on the device. The process of the formation and growth of a fibrin clot from the butt end of the insert-activator in the cuvette channel is recorded by the device in the mode of sequential photography by a digital camera using the dark field method for 30 minutes. The construction and calculation of the indicators of the fibrin clot growth curve is carried out using software developed by manufacturers for automatic data calculation.

Statistical analysis

Statistical data processing was carried out by standard methods of variational statistics using the statistical packages of the "R" software. The Shapiro–Wilk test and histograms were used to analyze the

normal distribution of values. The values of the normally distributed parameters were calculated as the arithmetic mean with standard deviation (±SD), for other parameters, the distribution of which differed from normal, the median and quartiles were used. To study the correlation, the nonparametric Spearman's R method was used. The result was considered statistically significant if the error probability was $p < 0.05$.

Results

The study included 100 patients with persistent or paroxysmal atrial fibrillation taking different DOACs in accordance with the product instructions. All patients had no history of thrombosis or bleeding before inclusion in this study. The basic demographic and other characteristics of the patients are presented in Table 1 and 2. The other characteristics of included patients are presented in Supplementary material in Fig. P6.

At the residual concentration of various DOACs, including at reduced doses in accordance with the product instructions, it was found that thrombodynamic parameters, such as V, Vi, Vst, Tlag, CS and D remained within the reference range, that is, in the area of normal coagulation (see Table 3). However, the Tlag parameter was higher than 1.5 min in 13 patients, and the V parameter was lower than 20 μm/min in 3 patients, which indicated hypocoagulation. In other 17 patients, an increase in the V parameter above 29 μm/min was observed and the formation of spontaneous clots was recorded in 2 patients. Statistically significant clinical and laboratory signs assuming hypercoagulation in these patients were not found, except for generally known (clinical conditions from the CHA_2DS_2-VASc score).

Considering the different pharmacodynamics of dabigatran and apixaban/rivaroxaban, we compared the thrombodynamic parameters separately in these subgroups. Vi – initial spatial clot growth rate and CS – clot size were significantly higher in patients taking apixaban/rivaroxaban compared with those on dabigatran (see Table 3). For reduced doses similar results were not obtained.

Table 1. The basic characteristics of patients

Characteristic	Dabigatran (n=75)	Rivaroxaban (n=15)	Apixaban (n=10)
Male, n (%)	28 (37.3)	11 (73.3)	4 (40.0)
Age, years	75.0 (68.0; 80.0)	68.0 (66.5; 74.0)	68.5 (67.0; 79.3)
Weight, kg	82.0 (72.0; 93.5)	85.0 (78.0; 95.0)	80.0 (72.8; 85.8)
AF paroxysmal/permanent type, n (%)	46 (61.3)/29 (38.7)	9 (60.0)/6 (40.0)	8 (80.0)/2 (20.0)
CHA_2DS_2-VASc	4.00 (3.00; 5.00)	4.00 (2.00; 4.50)	3.50 (2.25; 5.50)
HAS-BLED	2.00 (1.00; 2.50)	2.00 (1.00; 2.50)	1.50 (1.00; 2.75)
Creatinine, μmol/l	102.2 (91.1; 116.6)	99.6 (77.6; 109.3)	86.7 (82.6; 103.5)
Creatinine Clearance, ml/min	57.0 (48.1; 64.1)	72.8 (60.6; 93.5)	52.4 (43.8; 77.8)

The data are presented as Me (25%; 75%), unless otherwise specified

DOACs – Direct Oral Anticoagulants, AF – atrial fibrillation

Table 2. Drug groups taken by patients

Group	Dabigatran (n=75)	Rivaroxaban (n=15)	Apixaban (n=10)	p
ACE inhibitor/ARB, n (%)	63 (84)	12 (80)	6 (60)	0.170
BB, n (%)	55 (73)	10 (67)	9 (90)	0.441
Diuretics, n (%)	37 (49)	4 (27)	3 (30)	0.199
CCB, n (%)	29 (39)	5 (33)	5 (50)	0.653
Amiodarone, n (%)	24 (32)	7 (47)	3 (30)	0.595
Other antiarrhythmics, n (%)	49 (65)	11 (73)	6 (60)	0.774
Statins, n (%)	55 (73)	11 (73)	8 (80)	1.000

DOACs – Direct Oral Anticoagulants, ACE inhibitor - Angiotensin-Converting Enzyme inhibitor, ARB – Angiotensin II Receptor Blocker, BB – Beta blockers, CCB – Calcium channel blockers

Table 3. Parameters of the "Thrombodynamics" test in patients taking DOACs

Parameter	Reference range	For all DOACs	Dabigatran	Apixaban/Rivaroxaban	p*
Tlag, min	0.6-1.5	1.05 (0.85; 1.27)	1.05 (0.85; 1.45)	1.05 (0.95; 1.25)	0.698
Vi, μm/min	38-56	44.3±7.7	43.2±6.7	48.2±6.1	0.002
V, μm/min	20-29	26.6 (25.0; 29.2)	25.9 (24.3; 28.2)	27.4 (25.8; 28.4)	0.140
Vst, μm/min	20-29	26.5 (24.9; 28.4)	25.93 (24.3; 28.2)	27.4 (25.8; 28.4)	0.068
CS, μm	800-1200	999.7 (912.9; 1084.7)	970.46 (874.2; 1060.5)	1063.93 (999.7; 1110.6)	0.004
D, arb. units	15000-32000	22883.1±3199.9	23184.7±2679.9	23089.37±4075.8	0.927

* - dabigatran vs apixaban/rivaroxaban

The data are presented as Me (25%; 75%) or M±SD

DOACs – Direct Oral Anticoagulants, V (velocity) – spatial clot growth rate, Vi (initial velocity) – initial spatial clot growth rate, Vst (stationary velocity) – stationary spatial clot growth rate, Tlag (lag time) – the time to the start of clot growth, D (density) – clot density, CS – clot size

The clot density (D) was significantly higher in women [22947.7 (21477.5; 22947.7)] vs men [22124.8 (19722.8; 22124.8); p = 0.035].

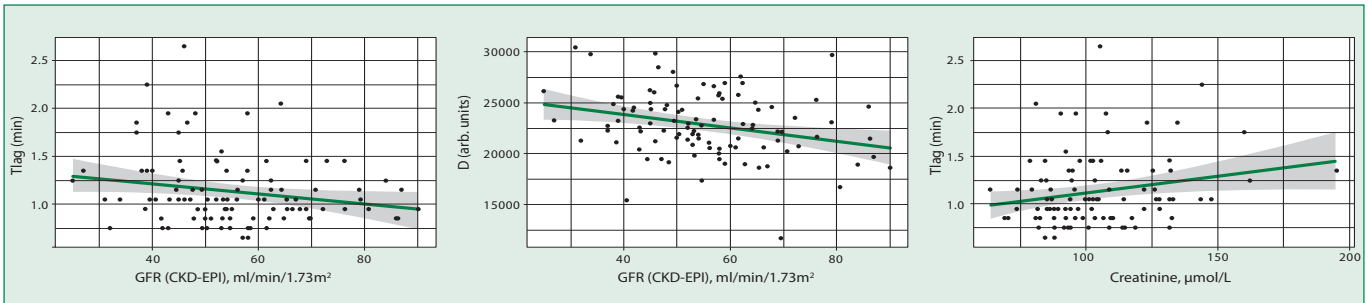
The Tlag parameter turned out to be significantly higher in people with chronic heart failure (CHF) [1.2 (1.0; 1.2) vs 1.0 (0.8; 1.0); p = 0.008]. However, the median of this indicator did not exceed normal values.

We analyzed correlation between renal function and all thrombodynamic parameters. As it can be seen in the diagrams (Fig. 2), statistically significant weak correlation according to Chaddock's scale was found between level of creatinine and T-lag parameter, glomerular filtration rate (GFR) and clot density. With an increase in the level of creatinine in the blood and a decrease in GFR, respectively, there was an increase in T-lag parameter (p-level 0.038); with an increase in GFR, clot density decrease (p-level 0.005).

Discussion

It is now commonly known that routinely used laboratory tests, such as aPTT, PTT, and INR, do not always provide a qualitative, and even more quantitative, assessment of hemostasis [10] in patients with AF taking direct oral anticoagulants. Efficacy and safety evaluation of DOACs use is even more difficult, since most of the tests have low specificity [10] and the possibility of global tests use in patients taking DOACs is still controversial [13]. The use of direct measurement of equilibrium concentrations of the drug in blood plasma does not go beyond the limits of research laboratories yet due to the high cost of the method and the absence of reliable data on optimal therapeutic concentrations of DOACs in blood plasma [11,12].

In few clinical studies carried out in various clinical conditions, "Thrombodynamics" has demonstrated high sensitivity to anticoagulant therapy (heparins, warfarin [31,32]) compared to aPTT, TGT and TEG [16,20,26,28]. Furthermore, the sensitivity of TD was comparable to that of the anti-Xa activity assay [20]. Up-to-date no such data has been published for DOACs. The TD test showed substantially good standardization and reproducibility. According to the



GFR – glomerular filtration rate

Figure 2. Correlation between renal function and TD parameters

study by E.I. Sinauridze et al. [18], interlaboratory deviations for repeated measurements of the TD parameters important for the measurement of heparins (V and Vi) were equal to approximately 6.0%, and the inter-individual variability of these parameters in a healthy population was equal to or not more than 7.6-8.0%, but for TEG and TGT these variations were more than 15-20%. In this connection, it seemed interesting to evaluate the parameters of TD in patients with atrial fibrillation taking DOACs. The limitations of the study were the absence of a control group of patients, the small sample size and relatively short follow-up period, which can affect the accuracy of the results obtained.

According to the results of the conducted study, at the residual concentration of DOACs in blood plasma, the average values of TD indicators were within the range of normal coagulation. The results obtained confirm the well-known data on the sufficient efficacy and safety of DOACs in patients with AF [4]. However, several observations were noted in which the thrombodynamic parameters went beyond the admissible limits. Hypocoagulation (increase in Tlag and/or decrease in Vi) before the next dose of a DOAC is an indicator of the efficacy of the anticoagulant; moreover, it does not guarantee the development of bleeding in the patient. The other side of the coin is the situation when, at the residual concentration of the anticoagulant, the blood plasma is in a state of hypercoagulability, which dramatically increases the risk of thrombosis. In such patients, this state of hemostasis is a reason to think about adjusting the dose of the DOAC or replacing it with another one off-label. After analyzing the possible factors that could be associated with an increase in the fibrin clot growth rate, no significant hypercoagulable factors were identified in 17% of patients: neither the AF form (p-value=0.58), nor reduced DOAC doses (p-value=0.79), nor a high CHA_2DS_2-VASc score (p-value= 0.72). In two women, there were recorded spontaneous clots, which indicates a high prothrombotic potential of plasma, and is probably associated with the presence of activated blood coagulation factors in the blood and an increased concentration of procoagulant vesicles. It was noteworthy that both patients took reduced doses of anticoagulant; in addition, one patient had severe anemia and a burdened oncological history. Unfortunately, we were unable to establish a link between clinical outcomes and thrombodynamic parameters due to the low frequency of hemorrhagic and thromboembolic events, as well as the practical impossibility of taking blood for analysis at the time of the event. Large prospective clinical trials are needed.

Compared our data with previously published study [20] which included patients taking low-molecular-weight and unfractionated heparin, we would like to notice that V parameter value in patients taking DOACs was in a much narrow diapason, especially for patients taking unfractionated heparin. Whereas majority of patients were in a normal coagulation state. This might point at more stable and predictable pharmacodynamics of DOACs in comparison with heparins. Though, we should note that the study had different clinical state patients, including postoperative, oncology and patients with deep vein thrombosis. Up to date we could find only one meta-analysis [33] comparing DOACs and low-molecular-weight heparin in patients with high thrombosis risk based on clinical outcomes. Potentially, "Thrombodynamics" test might give a better picture of DOAC's advantages and disadvantages over traditional anticoagulants.

Interesting data was obtained for individual TD parameters. Increase of the initial spatial clot growth rate and the size of the clot (p=0.002 and p=0.004, respectively), characterizing hypercoagulation, in patients taking Xa factor inhibitors, may indicate a lower anticoagulant activity of drugs at a residual concentration compared with a direct thrombin inhibitor, which may be due to an earlier termination of Xa inhibitors factor. However, the comparison groups were unequal: 25 people versus 75, in addition, most of the patients from the dabigatran group had CKD, which could affect the accuracy of the results obtained, and moreover, the objectives of the study did not include a direct comparison of DOACs with each other. It was found that the clot density is significantly higher in women than in men (p = 0.035). The clot density is an optical indicator equal to the intensity of light scattering by a fibrin clot, which characterizes the density and structure of the formed fibrin clot. An increase in this indicator

indicates an increased concentration of fibrinogen in the blood plasma, which, accordingly, indicates an increased ability of the blood to thrombus formation. It is known that the female sex itself is an independent risk factor of systemic embolism in patients with AF [34], which is shown in the CHA2DS2-VASc scale. The mechanisms of this phenomenon are still unknown: the influence of menopause, gender differences in hemodynamics or specific remodeling of the cardiovascular system [34], as well as the effect of a higher level of von Willebrand factor in older women [35] are supposed. Gram J. et al. studied the kinetics of fibrin polymerization, properties of fibrin fibers, lysis of fibrin clot and their gender differences in patients with AF. Women had higher rates of lateral aggregation of protofibrils during fibrin polymerization ($p<0.04$) and lower fibrin dissolution compared to men, which indicates a reduced clot dissolution and more aggressive fibrin polymerization profile in women [36,37]. The higher density of the fibrin clot in women is consistent with thrombodynamics data with the common concept of an enhanced prothrombotic profile compared with men.

A subanalysis for clotting parameters and renal function demonstrated statistically significant weak correlation according to Chaddock's scale between Tlag and GFR, clot density D and GFR, Tlag and creatinine level. It is known that DOACs are eliminated to a greater or lesser extent by kidneys and trough concentration of a drug would highly depend on a renal function. With decrease of renal function drug elimination slows down, prolonging anticoagulation effect, which can be manifested in Tlag increase indicating hypocoagulation. CKD is a risk factor for thrombosis though, and higher clot density probably can reflect more aggressive fibrin polymerization in them.

The values of the Tlag parameter were significantly a little higher in patients with CHF but within normal values. This parameter is sensitive to DOACs and also becomes longer at a severe deficiency of factors of the external and common coagulation pathways [13]. Although an increase in this parameter is observed at hypocoagulation, the presence of CHF is a well-known risk factor of thrombosis and thromboembolism [38-40]. This fact is still unclear and requires further study.

Conclusions

We conducted a study that resulted in descriptive data on the parameters of the "Thrombodynamics" test performed in patients with atrial fibrillation taking different DOACs. The obtained data of normal coagulation at the residual concentration of the anticoagulant are consistent with the previously obtained data on the safety and effectiveness of DOACs using other methods. The Vi and Tlag were the test parameters that showed the highest sensitivity to various states of hemostasis against the background of taking DOACs. Given the studies already carried out for heparins and warfarin, TD is a promising technique and may hold promise as a method of measuring the efficacy of any anticoagulant, especially in comorbid patients with CKD. However, to confirm the results obtained and have a more complete picture, further large clinical studies with the possibility of long-term follow-up of patients are required.

Relationships and Activities. None.

Funding: The study was performed with the support of the Sechenov University, Pirogov Russian National Research Medical University, Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology and Immunology.

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