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WARFARIN VERSUS NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS: HOW THE DEGREE OF ANTICOAGULATION DIFFERS DURING CATHETER ABLATION OF ATRIAL FIBRILLATION

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Aim. To evaluate intraoperative doses of administered heparin to achieve the target value of activated clotting time (ACT) in patients receiving preoperative anticoagulant therapy with warfarin or one of the non-vitamin K antagonists oral anticoagulants (NOAC).

Materials and methods. The study was of a retrospective. Inclusion criteria: patients with atrial fibrillation (AF) who have indications for catheter ablation in accordance with national clinical guidelines; age 18-75 years; absence of thrombus and the effect of echocontrasting 3-4 stage in the left atrium cavity according to transesophageal echocardiography or computed tomography with contrast enhancement; regular intake of anticoagulants prescribed at least 3 weeks before hospitalization. Exclusion criteria: additional intake of antiplatelet drugs; contraindications to the anticoagulant therapy, including intolerance to the components of drugs; weight more than 100 kg. According to the criteria for inclusion in the study 279 patients were included (211 of them received warfarin and 68 received one of the NOAC). The mean age of the patients was 59.2±8.9 years, the body mass index was 59.2±8.9 kg/m^2. Among them, men accounted for 155 (55,6%), diabetes mellitus was diagnosed in 28 (10%), arterial hypertension - in 224 (80.3%), coronary heart disease - in 103 (36.9%). Paroxysmal AF was observed in 185 (66.3%) of patients, persistent AF - in 77 (27.6%), and long-standing persistent AF - in 17 (6.1%). To ensure maximum comparability of the groups pseudorandomization was performed with the formation of 67 pairs of patients.

Results. A group of patients taking warfarin for preoperative preparation required lower doses of heparin to achieve the target ACT and amounted to 14.8±5.1 thousand ME compared to 17.9±4.4 thousand ME in the NOAC group (p=0.0001). Despite the lower dose of heparin the ACT level in the warfarin group was significantly higher than in patients taking NOAC (441.5±203.4 sec. and 345.4±148.8 sec. accordingly, p=0.0001).

Conclusions. A significantly lower dose of heparin was required in the warfarin group to achieve the target ACT (>300) than in the group of NOAC, while the maximum ACT value was higher. Thus, with the standard starting dose of heparin, the target anticoagulation was achieved faster in patients receiving warfarin.

Keywords: atrial fibrillation, catheter ablation, direct oral anticoagulants, indirect anticoagulants, activated platelet time

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Catheter ablation (CA) for atrial fibrillation (AF) has become an effective alternative to drug therapy and complex open-heart surgery in recent years [1-3]. Considering the high risk of thromboembolic complications (TE complication) caused by left atrial surgery (LA), radiofrequency ablation (RFA) should be performed against a background of mandatory anticoagulant therapy [4, 5].

The procedure of anticoagulation before, during and after CA is carefully prescribed in the guidelines of the Russian Society of Cardiology and ESC [1, 3]. For preoperative preparation, the recommendations allow the use of both warfarin with a target international normalised ratio (INR) of 2.0-3.0 and non-vitamin K antagonist oral anticoagulants (NOACs). Intraoperatively, all patients should receive intravenous heparin at a dose of 5000-15000 IU (or 90-200 IU/kg) with a target activated clotting time (ACT) of more than 300 s [6], but no standard dose is given in the guidelines.

There is evidence that preoperative preparation for NOACs requires a higher dose of heparin to achieve the target ACT [7]. Thus, there is a discrepancy between the standard initial intraoperative heparin dose regardless of the anticoagulant used for preoperative preparation. This topic is inadequately covered and requires further investigation.

Purpose of the study: To evaluate the intraoperative heparin dose administered to achieve the target value ACT

in patients receiving preoperative anticoagulant therapy with warfarin or one of the NOACs.

MATERIALS AND METHODS

The study was retrospective. A total of 492 patients who had undergone RFA for AF at our centre in 2020 were studied. 279 patients were included in the study.

Inclusion criteria:

- Patients with AF with indications for CA according to national clinical guidelines;
- Age 18-75 years;
- Absence of thrombus and grade 3-4 echocontrast in the LA cavity according to transoesophageal echocardiography (EchoCG) or absence of thrombus according to contrast-enhanced computed tomography (CT);
- Regular use of anticoagulants prescribed at least 3 weeks prior to hospitalisation;

Exclusion criteria:

- Additional intake of antiplatelet drugs;
- Contraindications to anticoagulant therapy, including intolerance to components of the medication;
- Weight of more than 100 kg.

The clinical and demographic characteristics of the patients included in the study are listed in Table 1. All patients were examined before surgery: general clinical tests, coagulogram, coronarography for men over 40 and women over 50 (this is the standard examination before RFA of AF in our clinic), EchoCG, transoesophageal EchoCG or CT with contrast enhancement to exclude a thrombus in the cavity LA.

Anticoagulant therapy was administered for at least 3 weeks prior to catheter ablation of AF. Patients taking warfarin achieved and maintained INR at a therapeutic level of 2.0-3.0 at least 3 weeks before hospitalisation. NOACs were discontinued 12 hours before surgery in all patients in our study. Patients taking warfarin did not discontinue the drug before surgery. The surgeries were performed under intravenous sedation with dexedemetomidine and fentanyl. Transseptal puncture (TSP) was performed twice under fluoroscopic control, and 2 unguided intravesicles were injected into the cavity LA. Intraoperatively, all patients received a heparin loading dose of 10,000 units (Republican Unitary Enterprise Belmedpreparaty, Republic of Belarus) in the preoperative period, regardless of anticoagulant therapy, according to TSP, and then a bolus infusion was administered until ACT time values above 300 s were reached. The heparin dose was 15.6±5.1 thousand IU. The first measurement of ACT level was performed every 10 min after the loading dose until the ACT target values≥300 s were reached, then every 30 min. The maximum value of ACT reached 418.1±197.3 s. Heparin solution was also continuously flushed through the infusion device at a rate of 250 r/h for intravenous tubing.

After pulmonary vein angiography, an anatomical map of LA was created using the CARTO 3 3D Mapping System (BiosenseWebster, Johnson & Johnson, USA). RFA was performed using EZ SteerNav and EZ SteerNav SF bidirectionally irrigated electrodes (BiosenseWebster, Johnson & Johnson, USA) without clamp force control. A Stockert RF energy generator (BiosenseWebster, Johnson

Table 1.

Clinical and demographic characteristics of patients who received warfarin or one of the NOACs

	Total (n=279)	Warfarin (n=211)	NOACs (n=68)	P	Warfarin* (n=67)	NOACs* (n=67)	P
Age, years	59.2±8.9	58.7±8.9	60.9±8.6	0.047	58.7±8.9	60.1±8.3	0.077
Male gender, n (%)	155 (55.6)	124 (59.1)	31 (44.9)	0.038	38 (56.7)	30 (44.8)	0.100
BMI, kg/m^2	29.5±3.9	29.3±3.8	29.8±4.1	0.377	29.8±3.9	29.8±4.0	0.387
Diabetes mellitus, n (%)	28 (10.0)	18 (8.5)	10 (14.7)	0.164	6 (8.9)	10 (14.7)	0.204
Arterial hypertension, n (%)	224 (80.3)	161 (76.3)	63 (92.6)	0.003	56 (83.6)	62 (92.5)	0.126
CHD, n (%)	103 (36.9)	73 (34.8)	30 (43.4)	0.408	32 (47.8)	30 (44.8)	0.473
Paroxysmal AF, n (%)	185 (66.3)	136 (64.8)	49 (71.0)	0.590	45 (67.1)	47 (71.1)	0.692
Persistent AF, n (%)	77 (27.6)	60 (28.6)	17 (24.6)		18 (26.9)	17 (25.4)	
LS AF, n (%)	17 (6.1)	14 (6.6)	3 (4.4)		4 (6.0)	3 (4.5)	
CHA_2DS_2-VASc (points)	1.92±1.23	1.85±1.25	2.16±1.13	0.042	1.94±1.24	2.02±1.12	0.143
Creatinine, μmol/l	96.6±20.1	97.9±19.1	92.6±22.3	0.080	94.3±17.1	92.5±22.3	0.112
Creatinine clearance, ml/min	68.5±15.8	68.1±15.7	69.6±15.8	0.483	66.9±17.7	69.5±15.9	0.454
Hemoglobin, g/l	142.9±13.5	143.5±13.5	141.3±13.3	0.255	144.1±13.6	141.2±13.4	0.299
Operation time, min	98.4±33.1	100.1±35.1	93.5±25.6	0.160	99.2±32.3	93.7±25.4	0.365
Complications, n (%)	8 (2.9)	5 (2.4)	3 (4.4)	0.413	2 (3.0)	3 (4.4)	0.434
Hemopericardium, n	4	3	1		1	1	
Arterio-venous junction, n	2	1	1		1	1	
Pulsating hematoma, n	2	1	1		0	1	

Note: NOACs, non-vitamin-K-dependent oral anticoagulants; *, after pseudorandomisation; P, significance of differences between groups; BMI, body mass index; CHD, coronary heart disease; AF, atrial fibrillation; LS, long-standing; CHA_2DS_2-VASc, ischemic stroke and systemic thromboembolism risk prediction scale for AF.

& Johnson, USA) was used in energy control mode. After ablation was completed and the introducers were removed from the LA cavity, 50 mg protamine sulfate (Ellara LLC, Pokrov city) was injected intravenously. A Z-shaped suture was placed at the puncture site in the groyne.

In the postoperative period, haemodynamics and electrocardiography were monitored with bedside monitors for 3 hours, and ultrasound examination of the pleural cavities and pericardium was performed. If haemorrhagic complications could be excluded, anticoagulant therapy was resumed in the postoperative period 4-6 hours after ablation and continued for at least 8 weeks.

Warfarin as an oral anticoagulant was taken by 211 of the 279 patients and 68 were taking one of the NOACs. The clinical and demographic characteristics of the patients are shown in Table 1. The patient groups differed on the basis of four parameters (age, sex, presence of arterial hypertension and CHA_2DS_2-VASc score). To exclude systematic errors and maximise group comparability, pseudorandomisation was performed (propensity score matching) using the 1:1 nearest neighbour method. The following 13 covariates were used (age, sex, body mass index, presence of diabetes mellitus, arterial hypertension and ischaemic heart disease, type of AF, CHA_2DS_2-VASc score, creatinine level and clearance, haemoglobin, time of surgery, presence of complications)..

Statistical analysis

All clinical data of the patients were taken from the electronic medical record («Medialog 7.10 B0119»). The results were statistically analysed using IBM® SPSS® StatisticsVersion 23 (23.0). All quantitative variables were checked for their distribution type using the Kolmogorov-Smirnov criterion, graphically using quantile diagrams and skewness and kurtosis indices. If the distribution was symmetrical, the results are reported as arithmetic mean and standard deviation (M±SD). If the distribution was not symmetrical, the values are represented by the median (Me) and the interquartile range as 25th and 75th percentiles. The Mann-Whitney test was used for the analysis. Frequencies and fractions (percentages) calculated by the Wilson method were used to describe qualitative data. Qualitative variables were compared using Pearson's χ^2 test. The critical significance level was set at ≤0.05.

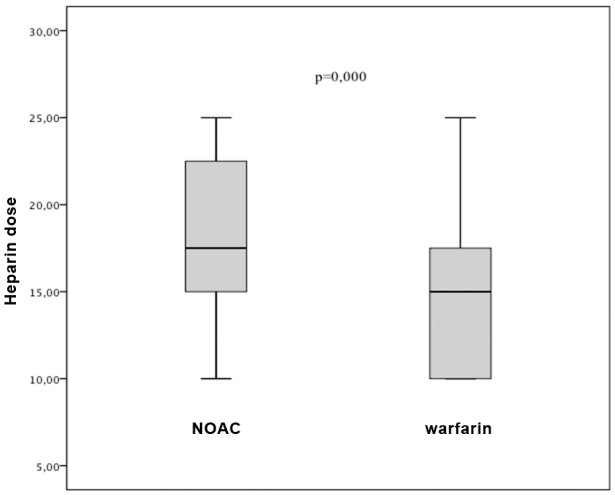

Fig. 1. Mean heparin dose to achieve target activated platelet time (ACT) in groups of patients treated with warfarin or one of the non-vitamin-K-dependent oral anticoagulants (NOACs).

RESULTS

After pseudorandomisation, the warfarin group (n=67 patients) and the NOACs group (n=67 patients) were comparable at baseline. The data are shown in table 1. INR was significantly higher in the warfarin group (2.36±0.82 versus 1.21±0.22 in the NOACs group, p=0.000), which is meaningful. Target INR was achieved in 49 (73.1%) patients treated with warfarin. Heparin doses to reach the target ACT were significantly higher in the NOACs group (17.9±4.4 thousand IU vs. 14.8±5.1 thousand IU in the warfarin group, p=0.0001). At the same time, the maximum value of ACT was higher in the warfarin group (441.5±203.4 s vs. 345.4+148.8 in the NOACs group, p=0.0001). The data are shown in figures 1 and 2.

The following drugs were used in the NOACs group: apixaban in 16 patients at a dose of 10 mg daily, rivaroxaban in 40 patients at a dose of 20 mg daily and dabigatran in 11 patients at a dose of 300 mg daily. The dose of heparin to achieve the target ACT did not differ by type of NOACs (16.6±4.6, 18.7±4.3, 16.8±4.3; p=0.594), nor did the maximum ACT value during surgery (335.1±39.1; 359.1±188.6; 309.5±37.3; p=0.175). The number of intraoperative complications related to anticoagulation therapy (haemopericardium, arteriovenous junction, pulsatile haematoma) was comparable in the warfarin and NOACs groups (3.0% and 4.4%, p=0.434). There were no strokes and transient ischaemic attacks in the postoperative period.

DISCUSSION

CA for AF has become an effective alternative to drug therapy and complex open-heart surgery in recent years [1-3, 8-10]. All patients with AF during paroxysm have some risk of TE complications [11, 12]. In addition, even in these patients, the catheter procedure increases the risk of TE complications caused by TSP and insertion of introducers into LA and radiofrequency damage to the atrial endothelium during ablation [13-15]. In addition, the atrial tissue may be anaesthetised for several weeks or months after ablation, leading to disruption of normal LA contraction and increased risk of thrombosis [16]. However, the prothrombotic state after the procedure is reversible. Therefore, patients with AF are at increased risk of thromboembolism during, immediately after and for several days or months after CA [17-20].

Therefore, cerebrovascular complications associated with CA for AF are relatively rare, usually occur either during the procedure or within the first 24 h after AF and have a benign course. In our study, there were also no cases of stroke or transient ischaemic attack in either group. Previous ischaemic stroke, mechanical heart valve and CHA_2DS_2-VASc≥3 risk of thromboembolic complications are independent predictors of such complications [19]. Consequently, careful monitoring of patients' anticoagulation levels before, during and after CA is crucial for AF to prevent the occurrence of thromboembolism.

At the same time, low anticoagulation levels contribute to some of the most common complications of the

procedure, including haemopericardium, cardiac tamponade and vascular complications. Therefore, care must be taken to achieve optimal, safe coagulation levels as soon as possible throughout the procedure. A number of authors also report that the incidence of AF ablation complications correlates directly with higher CHA_2DS_2-VASc scores, inversely with increasing operator experience and independently of the type of anticoagulant therapy (assessed both individually by drug and by class as a whole) [21, 22]. In our study, we obtained similar data, such that the number of intraoperative complications, such as haemopericardium, arteriovenous transition and pulsatile haematoma, was comparable in the warfarin and NOAC groups (3.0% and 4.4%, p=0.434).

There have been recent changes in the approach to anticoagulant therapy before, during and after catheter ablation. This is also due to the advent of NOACs, whose effective and safe use in patients with non-valvular AF has been demonstrated in the ARISTOTLE (apixaban), RELY (dabigatran), ROCKET-AF (rivaroxaban) trials [23, 24].

Many patients who underwent CA for AF are at high risk for TE complications (CHA2DS2VASc≥2 points), so they are prescribed anticoagulant therapy with warfarin under INR control with achievement and maintenance of a therapeutic INR of 2.0-3.0 or a direct thrombin inhibitor (dabigatran) or factor Xa (rivaroscaban, apixaban). In the case of preparation for CA, anticoagulant therapy is prescribed at least 3 weeks before the procedure, regardless of the risk of TE complications [1, 2, 5]. The mean CHA_2DS_2-VASc score in the patients in our study was 1.92±1.23, so anticoagulant therapy was administered as an outpatient more than 3 weeks before the planned hospitalisation.

A number of authors have also reported the need to perform a transoesophageal EchoCG or contrast-enhanced CT prior to the procedure to detect thrombus or spontaneous echo-contrast effect of the LA cavity regardless of the risk of TE complications, which is also included in the local protocol of patient examination prior to CA in our hospital. As the incidence of thrombus or echocontrast effects varies between 1.6% and 2.1% despite continuous anticoagulant therapy, it is directly proportional to the risk of TE complications on the CHA_2DS_2-VASc scale and the form of AF (persistent or long persistent), although not always [25, 26].

Thanks to a prospective, open-label, randomised, multicentre COMPARE study published in 2014 that found no differences in the risk of TE and haemorrhagic complications with catheter ablation of AF on a background of continuous warfarin therapy, many centres, including ours, have abandoned «bridge therapy» prior to catheter ablation of AF (i.e. discontinuing warfarin and switching to low-molecular-weight heparins) [4].

Unlike warfarin, NOACs have a faster onset of action, a shorter half-life, no association with food intake and a more predictable response to the prescribed dose. Several meta-analyses have shown NOACs to be similarly effective and safe compared with warfarin (CA) [7, 27, 28-31]. However, most of these studies omitted one or two doses of NOACs before CA for AF procedures. Based on the results of the RE-CIRCUIT (direct comparison of the performance of AF ablation in patients receiving continuous dabigatran and warfarin) and Venture- AF (comparison of the performance of AF ablation in patients receiving continuous rivaroxaban and warfarin) trials, the data are now considered sufficient to provide a class I recommendation for the implementation of CA for AF with continuous dabigatran (evidence level A) or rivaroxaban (evidence level A) and a class IIa recommendation for other Ha factor inhibitors for which no specific clinical trials have currently been conducted or are ongoing (as in the case of apixaban). Resumption of anticoagulant therapy is recommended 4-6 hours after ablation, provided that haemorrhagic complications are excluded.

All patients in our study who received NOACs were discontinued 12 hours before the procedure CA. Patients receiving warfarin did not discontinue the drug before the procedure. Therapy was resumed 4-6 hours after surgery, after haemorrhagic complications had been ruled out.

Optimal intraoperative anticoagulation with unfractionated heparin to achieve and maintain a target value ACT of 300 seconds or more (class I recommendation) also plays an important role in minimising haemorrhagic and TE complications. A number of researchers have observed that thrombi can form at the atrial septum and/or catheter almost immediately after TSP despite preoperative anticoagulant therapy and that early administration of heparin significantly reduces this risk. Therefore, in AF ablation procedures, it is recommended that heparin be administered before or immediately after TSP and that it be adjusted to achieve and maintain ACT target values of more than 300 seconds [7-9]. A meta-analysis of studies involving more than 7,000 patients also showed a reduced risk of TE complications without an increased risk of bleeding when the target ACT of more than 300 seconds was achieved during AF ablation [32]. ACT should be monitored at 10-15 minute intervals until therapeutic anticoagulation is achieved and then at 15-30 minute intervals throughout the procedure. Heparinised saline should be administered continuously through each intravenous line to further reduce the risk of thrombosis. The heparin infusion can be stopped after all catheters have been removed from

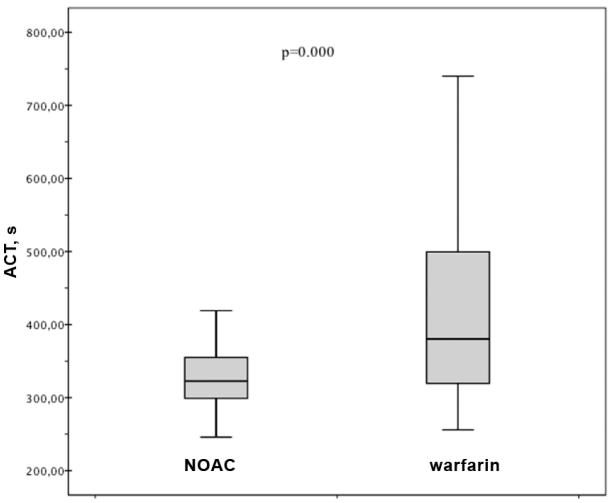

Fig. 2. Maximum activated platelet time (ACT) values in the groups of patients treated with warfarin or one of the non-vitamin-K-dependent oral anticoagulants (NOACs).

LA. At the end of surgery, it is possible to administer protamine to inactivate the effect of heparin (recommendation class IIA) [1].

A number of authors have found that patients receiving warfarin require lower doses of heparin and achieve their ACT goals more quickly than patients receiving NOACs [7, 32]. A survey of different author groups also found a wide variability in heparin loading protocols before ablation. The initial heparin bolus for patients taking warfarin was 50 U/kg, 75 U/kg for patients not taking an anticoagulant prior to CA for AF and 120 U/kg for patients taking one of the NOACs. Thus, a patient weighing 80-100 kg received an initial bolus of 4.0-5.0 thousand IU when using warfarin, 6.0-7.5 thousand IU without an anticoagulant preparation and 9.6-12.0 thousand IU before taking NOACs. The use of higher doses of heparin preoperatively with NOACs than in patients without anticoagulant treatment is quite surprising.

In our observational series, all patients received the first dose of heparin 10,000 IU, regardless of the anticoagulant administered. At the same time, in the warfarin group, the dose of heparin to reach the target value ACT (> 300) was significantly lower than in the NOACs group (14.8±5.1 thousand IU and 17.9±4.4 thousand IU, p=0.0001), and the maximum ACT value was higher (441.5±205.4 and 345.4±148.8, p=0.0001).

To understand and suspect the cause of this phenomenon, it is necessary to know the scheme of the coagulation cascade and the mechanism of action of each drug on the coagulation steps [33]. The coagulation cascade can be activated either internally or externally, leading to thrombin activation and subsequent fibrin formation.

Anticoagulants are divided into two groups: direct-acting anticoagulants (unfractionated heparin, low molecular weight heparins, directly activated X (Xa) factor inhibitors rivaroxaban and apixaban, direct-acting thrombin inhibitor dabigatran) and indirect-acting (warfarin).

Unfractionated heparin inhibits the activity of the factors IX, X, XI, XII, thrombin (IIa). Unlike warfarin, which blocks the formation of several clotting factors (factors II, VII, IX and X), NOACs block the activity of a single clotting step. Apixaban and rivaroxaban inhibit the clotting of factor Xa, while dabigatran is a direct inhibitor of thrombin.

NOACs are also characterised by a faster onset of action (apixaban and rivaroxaban reach maximum blood concentrations within 2to 4 hours and dabigatran - 0.5to 2 hours) and a shorter elimination half-life (for apixaban 12 hours, dabigatran 12to 17 hours, rivaroxaban 5to 13 hours). At the beginning of warfarin therapy, the clotting process is not blocked immediately because there is a «reserve» of circulating prothrombin and related clotting factors. The maximum effect of the drug occurs on the 3-5th day after starting the prescription and ends 3-5 days after stopping the drug.

As shown in the scheme of the coagulation cascade, the simultaneous interaction of heparin and NOACs blocks the activity of a common coagulation step. Thus, the interaction of direct inhibitors of clotting factor Xa and unfractionated heparin impairs the activity of factors IX, X, XI, XII, thrombin (IIa). The interaction of a direct thrombin inhibitor with unfractionated heparin also influences the activity of the factors IX, X, XI, XII, thrombin (IIa). In the case of an interaction between warfarin and unfractionated heparin, more factors are eliminated from the clotting process: II, VII, IX, X, XI, XII, which in turn can lead to a stronger hypocoagulation effect. And since warfarin initially already inhibits several clotting factors that are also affected by unfractionated heparin, a lower dose of heparin is required.

Another reason for the higher need for intraoperative heparin and the lower ACT levels in patients taking NOACs could be a shorter half-life of this group of drugs and the usual skipping of the dose on the eve of surgery. In our opinion, patients taking warfarin or any of the NOACs for preoperative preparation before CA for AF should receive different initial doses of heparin intraoperatively. In addition, the heparin dose should be higher in patients taking NOACs in the preclinical phase. Determining the optimal starting dose of heparin requires further study. A limitation of our study is its retrospective observational nature.

CONCLUSION

In our observational series, the warfarin group required a significantly lower dose of heparin to reach the target ACT (> 300) than the NOACs group, while the maximum ACT was higher. Thus, with a standard starting dose of heparin, target anticoagulation was reached faster in patients treated with warfarin.

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