



PHARMACODYNAMICS OF ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION IN THE ACUTE PERIOD OF ISCHEMIC STROKE

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Background. Every fifth ischemic stroke is caused by a patient's history of atrial fibrillation. Nowadays, direct and indirect oral anticoagulants are widely used to prevent thromboembolic complications in patients with atrial fibrillation. However, despite the prescription of this group of drugs, every year 1–2% of patients with atrial fibrillation have an ischemic stroke. In this situation, a number of questions take rise: if it is possible to carry out thrombolytic therapy in the patients who have been taking anticoagulants; if it is worth resuming anticoagulant therapy after a stroke; when exactly this should be done; and what drugs should be used to prevent another stroke.

The aim of this review was to summarize the available clinical guidelines and research results on the study of the anticoagulant therapy characteristics in patients with atrial fibrillation after an ischemic stroke.

Materials and methods. For this review, the information presented in the scientific literature from open and available sources, has been used. The information had been placed in the following electronic databases: PubMed, Scopus, Web of Science Core Collection, Cochrane Library, ClinicalTrials.gov; Elibrary, Cyberleninka, Google Academy. The covering period was 1997–2020.

The search queries were: "ischemic stroke + atrial fibrillation + anticoagulants"; "ischemic stroke + atrial fibrillation + direct oral coagulants" and "atrial fibrillation + ischemic stroke + warfarin" in both Russian and English equivalents.

Results and conclusion. Currently, the problem of the use of anticoagulants for the prevention of recurrent thromboembolic complications in patients with AF in the acute period of a stroke, is studied insufficiently. The difficulties are caused by the delivery of TLT in the patients who have been taking DOACs, first of all, due to the impossibility of an accurate assessment of the hemostasis state because of the unavailability of routine specific tests; and second, as a result of the lack of registered antidotes for most drugs, and their high costs. Besides, there are no RCTs dedicated to the study of the optimal time for the resumption or initiation of anticoagulant therapy in the acute period of an IS, and the optimal drugs for this group of patients. Most of the existing recommendations on these aspects, are based on the consensus of experts, and this fact indicates the need for further research in the area under review.

Keywords: atrial fibrillation, ischemic stroke, oral anticoagulants

Abbreviations: PTT – partial thromboplastin time; CI – confidence interval; IS – ischaemic stroke; INR – international normalized ratio; RR – risk ratio; DOAC – direct oral anticoagulant; RCT – randomized clinical trial; TT – thrombin time; TIA – transitory ischaemic attack; TLT – thrombolytic therapy; AF – atrial fibrillation; ECT – ecarin clotting time.

ФАРМАКОДИНАМИКА ОРАЛЬНЫХ АНТИКОАГУЛЯНТОВ У БОЛЬНЫХ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ В ОСТРОМ ПЕРИОДЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА

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Введение. Каждый пятый ишемический инсульт обусловлен наличием у пациента в анамнезе фибрилляции предсердий. Для предотвращения тромбоэмболических осложнений у пациентов с фибрилляцией предсердий в настоящее время широко применяются прямые и непрямые пероральные антикоагулянты. Однако, несмотря на назначение данной группы препаратов, ежегодно у 1–2% пациентов с фибрилляцией предсердий возникает ишемический инсульт. В данной ситуации встает ряд вопросов: возможно ли проведение тромболитической терапии у больных, принимавших антикоагулянты, стоит ли возобновлять антикоагулянтную терапию после перенесенного инсульта, когда именно это нужно делать и какие препараты для этого использовать.

Цель. Целью написания данного обзора было резюмировать имеющиеся клинические рекомендации и результаты исследований, посвященные изучению особенностей антикоагулянтной терапии у пациентов с фибрилляцией предсердий, перенесших ишемический инсульт.

Материалы и методы. Для обзора использовали сведения научной литературы из открытых и доступных источников за период 1997–2020 гг., размещенных в электронных базах данных: PubMed, Scopus, Web of Science Core Collection, Cochrane Library, ClinicalTrials.gov; Elibrary, Киберленинка, Google-академия. Поисковые запросы – «ишемический инсульт+фибрилляция предсердий+антикоагулянты»; «ишемический инсульт+фибрилляция предсердий+прямые оральные коагулянты» и «фибрилляция предсердий+ишемический инсульт+варфарин» как в русском, так и английском эквиваленте.

Результаты и заключение. Проблема применения антикоагулянтов для профилактики повторных тромбоэмболических осложнений у пациентов с ФП в остром периоде инсульта в настоящее время изучена недостаточно. Сложность вызывает проведение ТЛТ у пациентов, принимавших ПОАК, в первую очередь, из-за невозможности точной оценки состояния гемостаза в виду недоступности рутинного проведения специфических тестов, во вторую очередь, отсутствие зарегистрированных антидотов для большинства препаратов и их высокая стоимость. Также отсутствуют РКИ, посвященные изучению оптимального времени для возобновления или инициации антикоагулянтной терапии в остром периоде ИИ и оптимальных препаратов для данной группы пациентов. Большинство существующих рекомендаций по этим аспектам основаны на согласованном мнении экспертов, что говорит о необходимости дальнейших исследований в данной области.

Ключевые слова: фибрилляция предсердий, ишемический инсульт, оральные антикоагулянты

Список сокращений: АЧТВ – активированное частичное тромбопластиновое время, ДИ – доверительный интервал, ИИ – ишемический инсульт, МНО – международное нормализованное отношение, ОР – относительный риск, ПОАК – прямые оральные антикоагулянты, РКИ – рандомизированное контролируемое исследование, ТВ – тромбинспецифическое время, ТИА – транзиторная ишемическая атака, ТЛТ – тромболитическая терапия, ФП – фибрилляция предсердий, ЭВС – экариновое время свертывания.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a cardioembolic stroke as the most severe complication. From 20 to 30% of ischemic strokes (ISs) are associated with AF. IS in patients with AF is characterized by a higher risk of death and more often leads to disability compared with strokes of another etiology [1].

As the asymptomatic nature of the course of arrhythmia is rather frequent, in some cases IS is the first symptom of AF. If AF is detected earlier, anticoagulant therapy is indicated for all patients with a high risk of thromboembolic complications.

Currently, doctors have a number of drugs with proven efficacy in the prevention of a stroke and other systemic embolisms; they can include direct (dabigatran, rivaroxaban, apixaban, edoxaban) and indirect (warfarin) oral anticoagulants.

Despite the success achieved in the prevention of thromboembolic complications of AF, the incidence of IS in the patients taking anticoagulants, is 1–2% per year [2]. In such patients, adherence to therapy as well as alternative causes of a stroke, should be assessed.

An effective method of treating an acute IS with-

in 4.5 hours from the onset of symptoms is systemic thrombolysis with a recombinant tissue plasminogen activator [3]. However, the use of thrombolysis in patients receiving oral anticoagulant therapy, is difficult due to the high risk of bleeding. The question of the resumption timing of anticoagulant therapy after suffering an IS is also controversial.

THE AIM of this review was to summarize the available clinical guidelines and research results on the study of the anticoagulant therapy characteristics in the patients with atrial fibrillation after an ischemic stroke.

MATERIALS AND METHODS

For the review, the data from scientific literature from open and available sources over the period of 1997–2020 were used. The information was placed in the following electronic databases: PubMed, Scopus, Web of Science Core Collection, Cochrane Library, ClinicalTrials.gov; Elibrary, Cyberleninka, Google Academy. The search queries were: “ischemic stroke + atrial fibrillation + anticoagulants”; “ischemic stroke + atrial fibrillation + direct oral coagulants” and “atrial fibrillation + ischemic stroke + warfarin” in both Russian and English equivalents.

RESULTS AND DISCUSSION

Systemic thrombolysis in patients taking anticoagulants

Systemic thrombolysis is contraindicated for the patients administered with anticoagulants, on condition of effective hypocoagulation [4, 5].

Recombinant tissue plasminogen activator can be administered to the patients taking warfarin, if their international normalized ratio (INR) is lower than 1.7.

In this situation, thrombolytic therapy (TLT) did not lead to a significant increase in the risk of hemorrhagic complications [6, 7]. However, standard tests such as INR, activated partial thromboplastin time (APTT), prothrombin time are not suitable for assessing coagulation when using direct oral anticoagulants (DOACs) [8].

Plasma concentrations of dabigatran, causing a significant anticoagulant effect, did not lead to significant changes in prothrombin time and INR. The APTT index can be altered by the drug, but the relationship between the plasma concentration of dabigatran and the APTT is not linear [5].

To assess the effect of dabigatran, the best approach is to determine the thrombin clotting time (TT) and ecarin clotting time (ECT), but the dilute time of thrombin formation, which gives a quantitative assessment of the effect of dabigatran-Hemoclot (HyphenBioMed, "Neuville-sur-Oise", France), is especially highly sensitive to the action of the drug [9].

Although prothrombin time and APTT may be prolonged by direct Xa factor inhibitors (rivaroxaban, apixaban, edoxaban), these analyses do not quantify the anticoagulant effects of the drugs. Prothrombin time and APTT results can also depend on the reagent used, and must be calibrated in each laboratory to determine the effect of a particular drug [5]. The concentration of Xa factor inhibitors in plasma was most reliably reflected by the chromogenic anti-Xa assay [10, 11].

In real clinical practice, the above data are confirmed by the example of the German register RASU-NOA (Registry of Acute Stroke Under New Oral Anticoagulants), which included 290 patients receiving DOACs therapy, who had been hospitalized with a diagnosis of an acute IS to neurological departments throughout Germany from 2012 to 2015 [2]. Coagulation indices were analyzed in patients by conducting nonspecific (INR, APTT, TT, ECT) and specific (analyses for anti-factor Xa or hemoclot) tests.

According to the data obtained, about half (56.2%) of patients receiving dabigatran had a slightly elevated INR level. In contrast, TT was above the upper limit in the majority (94%) of patients receiving dabigatran,

and only in 14% of patients taking factor Xa inhibitors (rivaroxaban, apixaban). APTT was also more frequently prolonged with dabigatran (65%) than with rivaroxaban (32%) and apixaban (13%). A significant number of false negative results (11-44%) of INR and APTT, were detected even when the peak levels of DOACs concentration were exceeded.

Fewer than half of the patients receiving DOACs, were subjected to specific testing. The drug concentration levels varied greatly at admission even if similar intervals were observed, from the time of the last intake (according to patients). In 58% of patients, the concentration of drugs in the blood was within the expected range. In contrast, in 25% of the test persons, the concentration of the drug was below the minimum level. It is of interest that 17% of patients suffered a stroke even though their blood anticoagulant levels were above the peak range.

Based on the tests performed, only 9% of patients have gone systemic thrombolysis. The number of patients theoretically suitable for thrombolysis, based on the coagulation parameters. Hereby, the number of patients strongly depended on the parameters, the doctors would decide to use.

For example, if in the group of patients receiving rivaroxaban, the decision on TLT were made on the basis of normal anti-Xa values, then only 12% of the tested patients would be suitable candidates. Whereas, if doctors' decisions were based on normal APTT and TT values, the number of eligible patients would increase to 24%. This underlines the low sensitivity of nonspecific tests for determining the concentration of rivaroxaban.

It becomes apparent that standard coagulation tests are not reliable in predicting the actual level of DOACs in the blood. On the other hand, the possibility of conducting specific tests is not available in all medical institutions, even in large vascular centers. Thus, the use of DOACs for the prevention of thromboembolic complications in AF, is a barrier to TLT in the event of a stroke in patients.

According to the European Heart Rhythm Association's practical guidelines on the use of DOACs in AF, thrombolysis cannot be performed within 24 hours after the last dose of the drug due to its long half-life, which can also be prolonged in renal failure and in elderly patients [12]. The assessment of renal function is necessary for all patients receiving DOACs as antithrombotic therapy, in view of the presence of these drugs in varying degrees (27-80%) of the renal route excretion. Moreover, to calculate creatinine clearance, it is preferable to use the Cockcroft-Gault formula, since it was according

to this formula that renal function was assessed in all phase III randomized controlled trials (RCTs) to study the efficacy and safety of DOACs [13].

In addition to assessing renal function, an assessment of the hemostasis system is required before TLT. In accordance with the Consensus Document of the Interdisciplinary Expert Group on Emergency and Urgent Care for Patients Receiving DOAC, the determination of APTT and TT is sufficient for a qualitative assessment of the residual anticoagulant effect of dabigatran, while for direct inhibitors of factor Xa, only the chromogenic method for determination of anti-Xa activity is recommended [14].

Based on the opinion of the experts from the European Heart Rhythm Association, the use of a recombinant tissue plasminogen activator is allowed in the patients treated with coagulation factor Xa inhibitors, if, according to the data of specific tests carried out without a significant delay, their concentration is less than 30 ng/ml (when measured later than in 4 hours after drug administration) [12].

According to the European and Russian clinical guidelines for the treatment of AF, systemic thrombolysis is allowed in patients with normal APTT treated with dabigatran if more than 48 hours have passed since the last intake of the drug (based on the experts' consensus) [1, 15].

TLT in the patients taking dabigatran, is also allowed in the presence of a specific inhibitor, idarucizumab [16]. Idarucizumab is a fragment of a human monoclonal antibody that binds to dabigatran with a high affinity that exceeds the binding capacity of dabigatran to thrombin by about 300 times [17]. Immediately after the administration of the drug, the concentration of unbound dabigatran in the plasma decreases by more than 99%, which is accompanied by a rapid normalization of indicators reflecting the anticoagulant activity of dabigatran (TB, APTT, ECT, diluted thrombin time). This effect persists for at least 24 hours. By itself, idarucizumab does not have any procoagulant effect.

The largest prospective study investigating the effectiveness of the drug to neutralize the action of dabigatran in patients with bleeding or before an urgent surgery, is the RE-VERSEAD study, but it did not include the patients who had been scheduled for thrombolysis [18]. But there are retrospective studies demonstrating the efficacy and safety of using idarucizumab in this category of patients [19, 20]. In 2018, a systematic review of a series of TLT cases following a reversal dabigatran action, was also published [21]. It presents 55 cases of IS in patients taking dabigatran; a prolongation of APTT and thrombin time were recorded at their admission.

Thrombolysis after idarucizumab was successful in 81.9% of cases. Adverse outcomes (deaths/disabilities) were reported in 10.9% of patients. In Russia, a description of one successful case of using idarucizumab for reversing the action of dabigatran before thrombolysis, has been published [22].

Despite the fact that in the official instructions TLT is not an indication for the prescription of idarucizumab, the use of the drug in this clinical situation is regulated by the Protocol of Reperfusion Treatment of Acute Ischemic Stroke dated 2019 [16]. According to the instructions for medical use, the recommended dose of idarucizumab is 5 g (2 vials of 2.5 g). The drug is administered intravenously in the form of two successive infusions (2.5 g each) lasting no more than 5–10 minutes each, or as a bolus.

Since the specific antidote for Xa factor inhibitors, andexanet alfa, is not registered in the Russian Federation, thrombolysis is contraindicated in the absence of the possibility of determining anti-Xa activity.

The use of endovascular thrombectomy up to 7.3 hours after the onset of a stroke in patients with distal internal carotid artery occlusion or proximal middle cerebral artery occlusion who had not received anticoagulants, has been proven [12]. In the recommendations of the European Stroke Association, endovascular thrombectomy is mentioned as a first-line therapy in patients with contraindications to systemic thrombolysis [23]. Although the trials underlying these recommendations, included only a few patients on anticoagulants, a small amount of available data suggests that endovascular thrombectomy may be safe in these people as well [12].

The treatment tactics of a patient taking DOACs in the acute period of ischemic stroke, is shown in Fig. 1.

Resumption of anticoagulants after a transient ischemic attack or ischemic stroke

Patients with AF who have had a cardioembolic stroke, have a higher risk of a recurrent stroke within the first two weeks than the patients with other etiologies of ISs, and its frequency varies from 0.1 to 1.3% per day [24]. On the other hand, the presence of a large ischemic focus is a predisposing factor to the development of hemorrhagic transformation [25]. The CHA₂DS₂VASc and HAS-BLED scales, which are widely used to assess the risks of thromboembolic and hemorrhagic complications in AF for deciding on the prescription of anticoagulants, are not suitable for use in the acute period of a stroke [26]. Thus, the problem of prescribing anticoagulants after a previous AF is very hard.

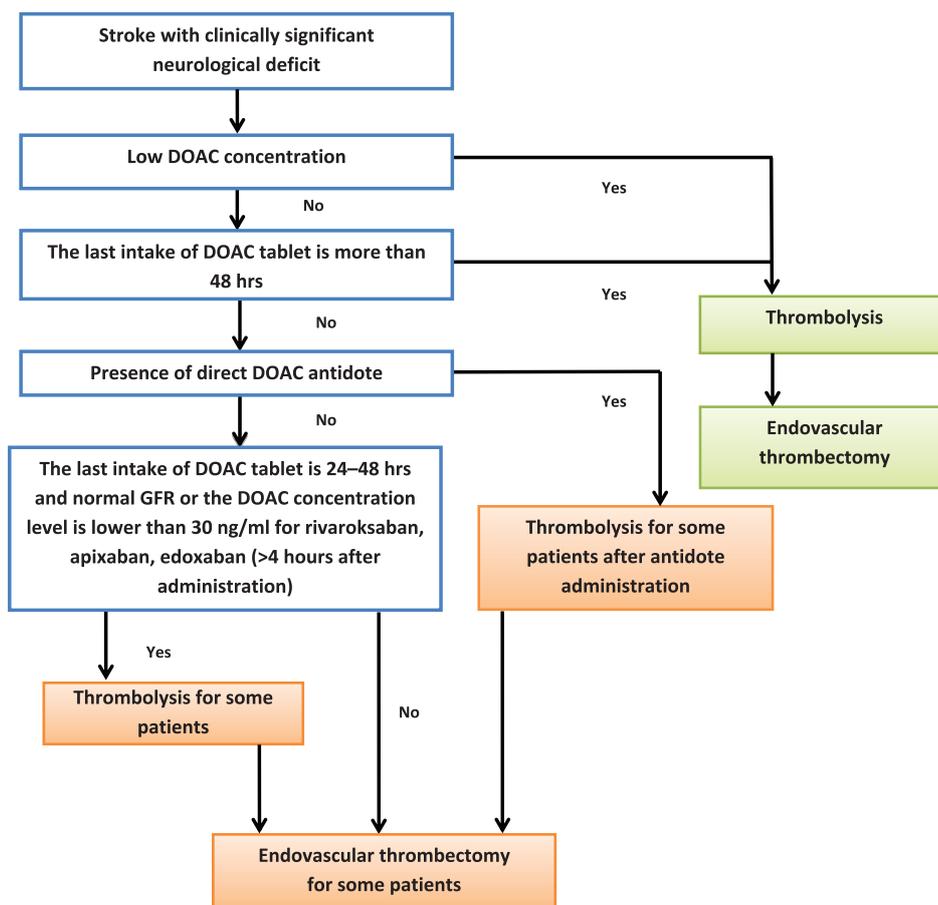


Figure 1 – Treatment tactics of a patient taking DOACs in the acute period of ischemic stroke (adapted by J. Steffeletal, 2018 [12])

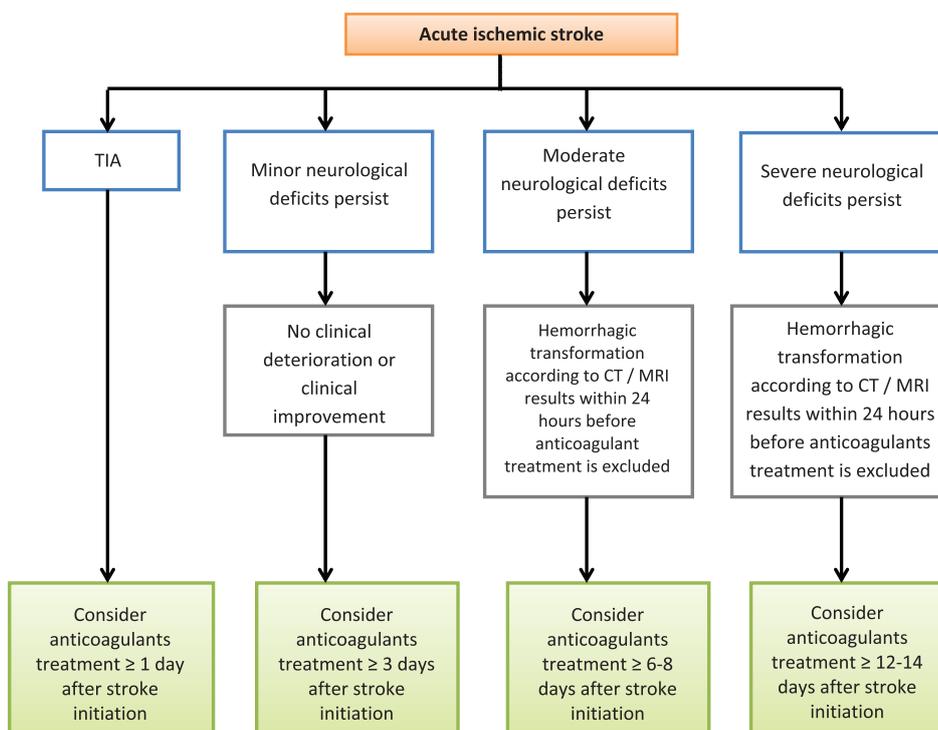


Figure 2 – Initiation/resumption of anticoagulant therapy after transient ischemic attack/ischemic stroke (adapted from J. Steffeletal, 2018 [12])

In the meta-analysis by Paciaroni M. et al. [24], which included seven RCTs involving 4,624 patients with an acute cardioembolic stroke, the administration of unfractionated and low molecular weight heparin within 48 hours from the onset of stroke, was assessed.

It was shown that the prescription of parenteral anticoagulants within 7–14 days after a stroke contributes to a slight decrease in the risk of recurrent ISs (relative risk (RR) 0.68, 95% CI 0.44–1.06), while there is still a significant increase in the likelihood of intracranial hemorrhage (RR 2.89, 95% CI 1.19–7.01).

In 2015, the results of the international prospective study RAF were published [27]. They included 1037 patients with AF from 29 stroke departments across Europe and Asia. The patients who were participating in the study, were monitored for 90 days after the onset of ISs on the development of a recurrent stroke or a transient ischemic attack (TIA), as well as bleeding (both intracranial and extracranial).

All in all, 1029 people were included in the analysis (8 people were excluded due to the lack of data); 766 of them received anticoagulant therapy: 113 (14.7%) patients were prescribed low molecular weight heparin, 284 (37.1%) – vitamin K antagonists, 93 (12.1%) took DOAC, 276 people received low molecular weight heparin followed by switching on to vitamin K antagonists. Out of 263 patients who did not receive anticoagulants, 231 people took antiplatelet agents, 32 people did not receive any antithrombotic therapy.

It was established that the patients who had been receiving only oral anticoagulants, had a significantly lower risk of bleeding compared with the patients who had been receiving low molecular weight heparin followed by switching on to oral anticoagulants or only low molecular weight heparin (this regimen was associated with the highest risk of bleeding). The patients taking only DOACs, had a low risk of both intracranial bleeding (2.1%) and recurrent ischemic events (4.3%). In addition, the study determined the most optimal time for starting treatment with anticoagulants. It has been shown that the administration of anticoagulant therapy from the 4th to the 14th day of the IS development, is both safe and effective compared to the start of the treatment, before or after this period.

However, the RAF study had some limitations associated with the lack of randomization and, as a result, the influence on the selection: the patients with a smaller lesion in the brain and with a more favorable course of the disease, probably, began to receive anticoagulant therapy earlier than the patients with severe strokes. The administration of only low-molecular-weight hepa-

rin in the early post-stroke period, could be also associated with the development of dysphagia and, probably, a more severe course of the disease in such patients.

Several prospective observational studies have investigated the potential risks and benefits of the early DOACs prescription in patients with ISs associated with AF. Three studies included patients with a recent cardioembolic stroke who were followed up for at least 3 months before clinical outcomes (recurrent ISs and intracranial bleeding) [28–30]. In all three studies, a significant proportion of patients took DOACs: NOACISP-155 (75%), SAMRUAI-NVAF – 475 (41%), RAF-NOAC – 1127 (100%). Their average age was 76–79 yrs, the severity of a stroke was assessed using National Institutes of Health Stroke Scale – NIHSS – and ranged from 3 to 8 points. The start of taking anticoagulants was on average 5 days after the acute event. The annual risk of recurrent ISs was roughly equal in all the studies, and it was 7.7% in NOACISP, 8.5% in SAMRUAI-NVAF, and 7.8% in RAF-NOAC. The risk of intracranial bleeding was low in the NOACISP and SAMRUAI-NVAF studies (1.3% and 1.2% per year, respectively) while in the RAF-NOAC study it was 6.4% per year. Most of intracranial bleedings in RAF-NOAC were associated with a later initiation of anticoagulant therapy.

An early administration of DOACs after a mild stroke, was studied in two small RCTs. One of the studies conducted in 14 academic medical centers in South Korea, included 183 patients. They were prescribed anticoagulant therapy 5 days after suffering cardioembolic ISs (the severity averaged 2 points, according to the National Institutes of Health Stroke Scale (NIHSS) [31]. The participants were randomized into two groups: the first group took rivaroxaban 10 mg per day for 5 days, followed by 15 or 20 mg per day; the second – warfarin with a target INR of 2.0–3.0. The primary endpoint was the combination of a new ischemic lesion or a new intracranial hemorrhage as seen by magnetic resonance tomography in 4 weeks. The rivaroxaban group (n = 95) and the warfarin group (n = 88) showed no differences in the primary endpoint (47 [49.5%] vs 48 [54.5%]; RR 0.91; 95% CI 0.69–1.20) or in its individual components (a new ischemic lesion: 28 [29.5%] vs 31 of 87 [35.6%]; RR 0.83; 95% CI 0.54–1.26; new intracranial hemorrhage: 30 [31.6%] vs 25 of 87 [28.7%], RR 1.10; 95% CI 0.70–1.71).

In the DATAS II study, dabigatran was compared with aspirin in 301 patients with TIAs or minor strokes (up to 9 points on the NIHSS), but without confirmed AF [32]. The medication was started within 72 hours from the acute event and continued for 30 days. Magnetic resonance tomography was performed before randomiza-

tion and repeated on day 30. Symptomatic hemorrhagic transformation was the primary endpoint. The symptoms of hemorrhagic transformation did not appear in any of the groups. Asymptomatic petechial hemorrhagic transformation developed in 11/142 (7.8%) patients administered with dabigatran and in 5/142 (3.5%) patients administered with aspirin (RR 2.301; 95% CI, 0.778–6.802). Thus, dabigatran has a risk of hemorrhagic transformation similar to aspirin in an acute non-severe noncardioembolic ISs or TIAs. Although these data cannot be extrapolated to patients with ISs associated with AF, the DATAS II study provides some confidence in the safety of an early initiation of anticoagulant therapy in these patients.

Currently, four RCTs are ongoing (ELAN, Switzerland; TIMING, Sweden; OPTIMAS, UK; START, USA). Up to 9000 people who had suffered ISs associated with AF, were involved into studies [26]. The study participants are prescribed DOACs in the acute period of a stroke. The endpoints in all RCTs are the onset of ischemic or hemorrhagic events, three of which also include cardiovascular or all-cause mortality. The research results are expected in 2021.

In 2013, the European Heart Rhythm Association from the European Society of Cardiology, proposed to use the rule of “1–3–6–12 days”, according to which the start of taking an anticoagulant depends on the severity of the stroke [33]. The earliest initiation or resumption of anticoagulant therapy, is recommended for patients with TIAs – the day after the acute event, and a mild stroke (NIHSS<8) – 3 days after the acute event; in the patients with a moderate stroke (NIHSS 8–15) and a severe stroke (NIHSS≥16), it is recommended to refrain from prescribing anticoagulants after an acute event for 6 and 12 days, respectively.

This strategy for the secondary IS prevention is retained in the subsequent edition of the recommendations, dated 2016 [34]. A similar approach is reflected in the Russian clinical guidelines “Diagnosis and treatment of atrial fibrillation”, dated 2017 [15]. However, both documents base their recommendations on the consensus opinion of experts, due to the lack of sufficient prospective studies.

In 2019, the recommendations of the European Stroke Organization for the secondary prevention of a stroke in patients with AF were published [35]. The authors of the document also point out the need for additional research to determine the optimal time to start anticoagulant therapy. In the absence of those, it was proposed to resume taking anticoagulants 3–4 days after a mild stroke, 7 days after a moderate stroke, and not

earlier than 14 days after a severe one. In addition, within 48 hours after an IS before the start of anticoagulant therapy, it is recommended to prescribe aspirin at the dosage of 100–300 mg to prevent thromboembolic complications. These recommendations are based on two large non-blinding RCTs (IST and CAST), which demonstrated that when aspirin was given within 48 hours of an acute event, mortality and a stroke recurrence were minimal [36, 37].

The 2018 American Heart Association and American Stroke Association Guidelines for the Early Management of IS patients, recommend oral anticoagulants 4–14 days after the development of neurological symptoms, based on the results of the RAF study [38].

Thus, most guidelines for the treatment of patients with AF and ISs, recommend starting anticoagulant therapy in the first 14 days after the development of acute symptoms, focusing on the severity of the disease and the size of the lesion (the algorithm for prescribing anticoagulants after TIAs or ISs is shown in Fig. 2). These recommendations are based on the expert consensus and several prospective studies currently available. More data from large RCTs are necessary to determine a more accurate management of these patients.

Nowadays, we do not have comprehensive data as to whether drugs should be preferred in the acute period of ISs either. Acute stroke patients were not included in the RCTs of phase 3 that investigated the effectiveness of DOACs. However, in these studies, there was a subgroup of patients who had previously suffered ISs or TIAs. Thus, in the RE-LY study, which examined the effectiveness of two dosages of dabigatran (110 mg or 150 mg twice a day) in comparison with warfarin, the subgroup of stroke patients who had suffered ISs, consisted of 2,428 people with a median follow-up of 2 years [39]. In the ROCKET AF study with rivaroxaban at the doses of 20 mg or 15 mg (with creatinine clearance of 30–49 ml/min), 7,468 participants with previous ISs or TIAs were followed for 1.85 years [40]. In RCTs with apixaban (ARISTOTLE) at the doses of 5 mg or 2.5 mg twice a day (for the patients with two or more of the following data: age ≥80 years, body weight ≤60 kg, serum creatinine ≥133 μmol/L), the number of the patients with a previous stroke was 3,436; the average follow-up was 1.8 years. In the ENGAGE AF-TIMI 48 study, where the efficacy of edoxaban with a single dose of high (60/30 mg) or low (30/15 mg) doses with warfarin was compared, a subgroup of 5,973 people with previous ISs or TIAs was followed-up for 2.8 years [42]. A pooled analysis of the results of these studies showed that DOACs use was associated with a significant reduction in hemorrhagic strokes (RR 0.43; 95% CI 0.29–0.64) and death from any

cause (RR 0.87; 95% CI 0.80–0.95) compared with warfarin. However, there was no significant difference in the risk of thromboembolic complications (RR 0.91; 95% CI 0.81–1.02) or recurrent ischemic stroke (RR 1.15; 95% CI 0.84–1.57) [35]. It should be notified that there was a significant reduction in thromboembolic complications and strokes in favor of DOACs when higher dose regimens of dabigatran and edoxaban were put into action, while the reduction in hemorrhagic strokes remained similar. Thus, based on the recommendations of the European Stroke Organization, DOACs should be given preference for the secondary prevention of ISs in comparison with warfarin because of their greater safety (a low risk of intracranial bleeding).

CONCLUSION

Summarizing all the above, it can be notified that

the problem of the anticoagulants use for the prevention of recurrent thromboembolic complications in patients with AF in the acute period of the stroke, is currently insufficiently studied.

Difficulties are caused by TLT in the patients taking DOACs, first of all, due to the impossibility of the accurate assessment of the hemostasis state because of the inaccessibility of routine specific tests, and second, due to the lack of registered antidotes for most drugs, and their high costs.

There are no RCTs devoted to the study of the optimal time for resumption or initiation of anticoagulant therapy in the acute period of ISs and the optimal drugs for this group of patients, either. Most of the existing recommendations on these aspects are based on the consensus of experts. This factor indicates the need for further research in this area.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

V.I. Petrov – planning and editing the review; A.S. Gerasimenko – writing the review;
V.S. Gorbatenko – collection of materials for the review; O.V. Shatalova – collection of review materials.

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