Difficult issues in the management of patients with atrial fibrillation: a neurologist's point of view

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The article evaluates recent perspectives about the role of oral anticoagulants in the secondary prevention of cardioembolic stroke. The timing of prescribing drugs for ischemic stroke and transient ischemic attack is discussed in accordance with current clinical guidelines and the results of clinical trials. The issues of prescribing oral anticoagulants in some problematic situations, such as the elderly and senile age, reperfusion therapy, presence of hemorrhagic transformation, combined atherosclerosis of major head and neck arteries, cerebral microangiopathy, history of intracerebral hemorrhage, cryptogenic stroke, and low patient compliance are considered. Finally, an anticoagulant therapy algorithm in the acute period of cardioembolic stroke is presented.

Keywords: *stroke; atrial fibrillation; prevention; direct oral anticoagulants.*
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Introduction. Cardioembolic stroke (CES) against the background of atrial fibrillation (AF) occupies 13–26% in the etiological structure of ischemic stroke (IS), its frequency increases with the age of patients [1]. The first few days after CES are characterized by both an increased risk of IS recurrence and the risk of hemorrhagic transformation (HT). Without prescribing anticoagulants, the frequency of recurrent IS in the first 14 days varies from 0.5% to 1.3% per day [2]. The risk factors for early recurrence of CES include advanced age, large infarction size and enlargement of the left atrium, which anatomically contributes to a high embolic potential [3, 4]. The administration of oral anticoagulants (OAC) – apixaban, dabigatran, rivaroxaban, edoxaban or warfarin, serves as the basis for the secondary prevention of CES against the background of AF [5]. A meta-analysis of data from 20,500 patients with AF and IS / TIA showed that, in comparison with vitamin K antagonists (VKA), direct oral anticoagulants (DOAC) are associated with higher efficacy in the secondary prevention of CES and greater safety in relation to the development of intracerebral hemorrhage (ICH) [6]. The advantages of DOAC over VKA in the secondary prevention of CES are indicated by the recommendations of ESC 2020 [7] and ESO 2019 [8]. However, real clinical practice poses many questions for the neurologist regarding the features of the application of DOAC in complex clinical situations, some of which are discussed in this article.

The role of DOAC in the secondary prevention of CES. All four randomized clinical trials (RCTs) devoted to DOAC (RELY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48) demonstrated the advantages of DOAC over VKA with a 19% reduction in the risk of stroke and systemic embolism by reducing the risk of hemorrhagic stroke by 51%, and a decrease in mortality by 10% [9]. The ARISTOTLE study (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, n=18201) showed that apixaban was superior to warfarin during 1.8 years of follow-up in terms of the incidence of strokes and systemic embolism (1.27% vs. 1.60 % – risk reduction by 21%), as well as the frequency of bleeding (2.13% versus 3.09% – risk reduction by 31%) [10]. Among DOAC, only apixaban was superior to warfarin in three key indicators: a decrease in the risk of stroke, including recurrent, and systemic embolism, a decrease in the number of major bleedings, and a decrease in overall mortality [11]. A recent analysis of data from the Norwegian national registry (n=52,476) showed no difference in the incidence of stroke and systemic embolism with dabigatran, rivaroxaban and apixaban in patients with AF, but dabigatran and apixaban were associated with a lower risk of major bleeding, including ICH [12].

The efficacy and safety indicators of DOAC in comparison with warfarin in the secondary prevention of IS in real clinical practice are comparable to those for RCTs [13]. With secondary prevention of IS, the incidence of systemic embolism is 4.9% for DOAC and 5.7% for warfarin, while the incidence of hemorrhagic stroke is halved with DOAC [14]. Data from real clinical practice show that the efficacy of apixaban and warfarin in the prevention of IS in AF is comparable, while the risk of major bleeding is significantly lower for apixaban in comparison with warfarin, dabigatran and rivaroxaban (reduction in the relative risk 38%, 35% and 46%, respectively). The risk of ICH is also significantly lower for apixaban than for warfarin and rivaroxaban (46% and 54%) and is comparable to acetylsalicylic acid. In addition, taking apixaban is associated with the lowest risk of gastrointestinal bleeding, which is important both in the acute period of IS (given the high frequency of stress ulcers) and in the long term [14, 15].

The timing of the administration of the OAC for IS and transient ischemic attack (TIA). For a long time, the Diener's rule was used to determine the optimal time for the initiation of the OAC, according to which, depending on the severity of the neurological deficit (TIA, minor, moderate and severe stroke according to the NIHSS result), the drug should be administered on days 1, 3, 6, and 12, respectively. At the same time, before the administration of OAC on days 6 and 12, it is necessary to repeat the CT scan of the brain to exclude HT [16]. Analysis of data from the K-ATTENTION register (Korean ATrial fibrillaTion

EvaluatioN regisTry in Ischemic strOke patieNts, n=2321, South Korea) showed that compliance with the Diener rule was associated with a lower risk of recurrence of any stroke (1.4% versus 3.4%) in comparison with non-compliance with these recommendations [17]. Nevertheless, a significant drawback of Diener's rule is the orientation in decision making on the severity of neurological deficit, rather than on the size of the infarction, which can lead to an incorrect assessment of the risk of HT, for example, in vertebrobasilar stroke (Fig. 1).

Clinical guidelines. Approaches to the administration of OAC in accordance with modern international clinical guidelines are presented in table. 1.

It should be noted that most recommendations are based on opinions of experts, since at the moment none of the planned RCTs has been completed.

Observational studies. Currently, the results of several multicenter observational studies with a follow-up period of at least 3 months have been published (Table 2) [1, 20–24].

The observational multicenter study RAF-NOACs (Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin K Oral Anticoagulants) was conducted in European countries and included 1127 patients, 80% of whom received DOAC (approximately equally – dabigatran, rivaroxaban and apixaban) in the first 15 days of the disease, on average, 7–8 days. The study showed that in patients with CES, DOAC treatment is associated with 5.2% of the combined incidence of ischemic and hemorrhagic events (stroke, TIA, clinically overt systemic embolism, clinically overt ICH, large extracerebral bleeding) within 90 days. ICH developed in 1.6% of patients. With the administration of an anticoagulant in the first two days, the combined indicator was 12.4%, with initiation from 3 to 14 days – 2.1% and with a start after 14 days – 9.1% [22]. On the other hand, analysis of data from the VISTA register (Virtual International Stroke Trials Archive, n=1644) showed that prescribing VKA on days 2+3 after stroke was associated with a lower recurrence rate compared with prescribing after 3 days without an additional increase in the risk of clinically apparent ICH. [25].

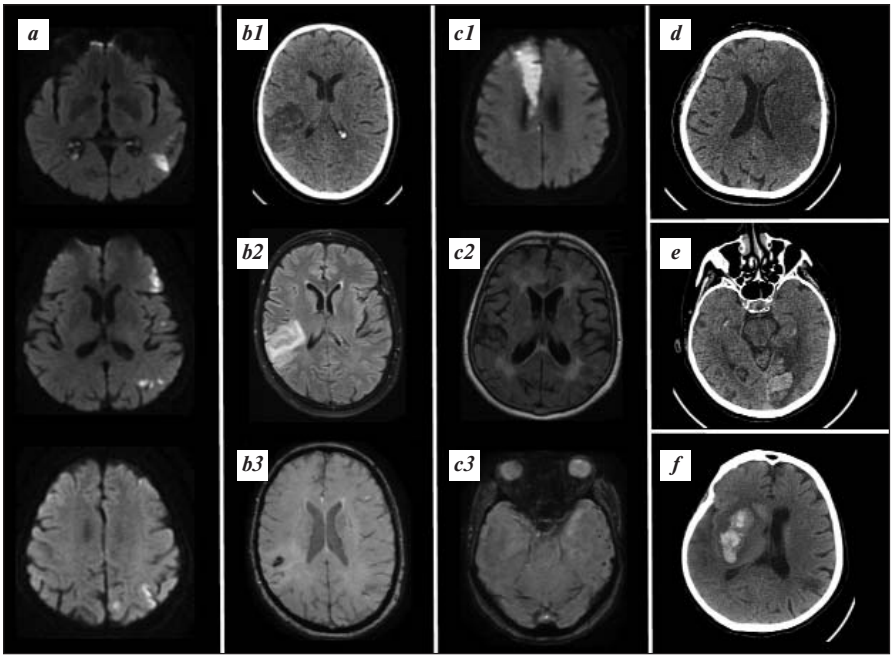

Fig. 1. *Determination of the time of the OACs initiation in different clinical situations. a – 72-year-old female, NIHSS upon admission – 6 points. Maximum infarct size – 2 cm (MRI, DWI), without hemorrhagic transformation. DOACs initiated on the 3rd day; b – 66-year-old female, NIHSS upon admission – 3 points. Maximum infarct size – 4 cm (b1 – CT, b2 – MRI FLAIR). Hemorrhagic infarction type 1 on CT (b1) and MRI SWAN (b3) scans. DOACs initiated on the 10th day; c – 76-year-old female, NIHSS upon admission – 3 points. Maximum infarct size – 8 cm (c1 – MRI DWI). No signs of hemorrhagic transformation, but lobar cerebral microbleeds on MRI SWAN scans (c3) and severe (Fazekas 3) white matter hyperintensities on MRI FLAIR (c2) are present. DOACs initiated on the 10th day; d – 68-year-old female, NIHSS upon admission – 15 points. Maximum infarct size on CT scan – 12 cm, without hemorrhagic transformation. DOACs initiated on the 10th day; e – 80-year-old female, hemianopia upon admission to the ASU (NIHSS – 1 point). Absence of infarct on CT scan, therefore DOACs were started on the 3rd day according to Diener's rule. CT control after 1 week revealed a hemorrhagic transformation into hemorrhagic infarction type 2, which was regarded as asymptomatic. DOACs were not discontinued; f – 80-year-old female, NIHSS upon admission – 14 points. Intravenous thrombolysis was administered. CT-control revealed a type 2 intraparenchymal hematoma. DOACs initiation was recommended in the outpatient setting on the 40th day*

The recently published multicenter observational study IAC (The Initiation of Anticoagulation after Cardioembolic Stroke, n=1289, USA) compared the efficacy and safety of OAC administration at 0–3 days, 4–14 days, and >14 days after CES. Outcome was assessed by relapses of IS, TIA, systemic embolism; clinically evident ICH and large extracranial hemorrhage within 90 days. The combined endpoint was recorded in 10.1% of patients, while there was no difference in the frequency of its development between the studied subgroups; the incidence of clinically apparent ICH and recurrent ischemic events did not differ either. Thus, the IAC study did not confirm that the interval of 4–14 days is advantageous for the administration of OAC after CES, which emphasizes the need for an RCT [24].

In an observational study, Yoshimura et al. (n=686, Japan) showed that early administration of apixaban (<48 hours) for IS due to large artery occlusion in patients with AF was as safe as later initiation. The average NIHSS result in the study was 14 points, intravenous thrombolysis was received by 39% of patients, endovascular treatment – 52% of patients, HT developed in 16.3% of patients [26]. In an observational study, Alrohimi et al. (n=100, Canada, Saudi Arabia) demonstrated the safety of early apixaban administration (on average after 2 days) in mild CES (average infarction volume 4 ml) [27].

Randomized clinical trials. The RCT Triple AXEL (Acute Stroke With Xarelto to Reduce Intracranial Hemorrhage, Recurrent Embolic Stroke, and Hospital Stay; n = 195, South

Korea) demonstrated that rivaroxaban administration in the first 5 days of small CES (with an average of 2 points on the NIHSS) is comparable efficacy and safety with warfarin [28]. RCT DATAS II (The Dabigatran Following Acute Transient Ischemic Attack and Minor Stroke II trial, n=305) showed that dabigatran administration in the first 72 hours of small (NIHSS+9; infarction +25 ml) noncardioembolic stroke does not differ in the incidence of clinically apparent HT from the administration of acetylsalicylic acid [29]. Thus, there is quite convincing evidence of the safety of the administration of DOAC in the early days of small CES or TIA.

In April 2021, the results of an RCT AREST (Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation) were published, which compared the safety of early administration of apixaban and warfarin. For TIA, apixaban was prescribed for 0–3 days, for stroke with infarction <1.5 cm – for 3–5 days, for stroke with an average size of infarction |1.5 cm, except for complete territorial cortical infarction – for 7–9 Day; warfarin was prescribed 1 week after TIA and 2 weeks after CES. The study showed that apixaban is characterized by a statistically similar, but generally lower frequency of recurrent strokes and TIA (14.6% versus 19.2%, p=0.78), death (4.9% versus 8.5%, p=0.68), fatal stroke (2.4% versus 8.5%, p=0.37), clinically overt hemorrhage (0% versus 2.1%), and a primary combined outcome including fatal stroke, recurrent stroke, and TIA (17.1% versus 25.5%, p=0.44) [30]. Thus, the result of RCT AREST expanded the area of safe application of DOAC in the early stages of CES and proved the validity of the approach to determining the time of initiation of therapy depending on the size of the cerebral infarction.

Table 1. *Approaches to prescribing OACs according to current international clinical guidelines*

Recommendations	Timing of OAC prescription
2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS (Diener's rule) [16]	1-3-6-12 days depending on the severity of stroke on the NIHSS scale: TIA, NIHSS <8 (minor stroke), NIHSS 8-15 (moderate stroke), NIHSS≥16 (severe stroke). For moderate to severe strokes, CT should be repeated before prescribing
AHA / ASA 2019 [18]	For most patients, days 4-14
ESO 2019 [8]	The optimal time is not known. Expert opinion: antiplatelet agents in the first 48 hours after CES. Start of the OAC on day 3-4 in patients with minor stroke and infarction <1.5 cm, on day 7 with moderate infarction, on day 14 with large infarction
ESC 2020 [7]	Optimal timing is unknown, but it is not recommended to prescribe in the first 48 hours
EHRA 2021 [19]	TIA - 1 day, TIA with acute infarction on neuroimaging - 1-3 days, persistent minor neurological deficit - ≥3 days, persistent moderate neurological deficit - ≥6-8 days (CT / MRI control), persistent severe neurological deficit - ≥12-14 days (CT / MRI control); with HT - ≥3-28 days (CT / MRI control)
AHA / ASA 2021 [5]	TIA - immediately, low risk of HT - 2-14 days, high risk of HT - after 14 days

Table 2. *Characteristics of multicenter observational studies focused on the OACs initiation after IS*

Study, year	Population	Average age of patients	Average NIHSS score	Average size of infarction	Average time of initiation	Recurrence of ischemic stroke	Intracranial hemorrhage
NOACISP, 2016	Switzerland, n = 204 / DOAC - 155	79 years	4	-	5 days for DOAC	7.7% per year / 5, 1% per year for DOAC ≤7 days versus 9.3% > 7 days	1.3% per year
SAMURAI-NVAF, 2016	Japan, n = 1192 / DOAC - 466	78 years	3	24% - small, 48% - medium, 28% - large	5 days for DOAC	10.1% per year for DOAC	0.8% per year for
RAF-NOAC, 2017	Europe, 1127 / DOAC - all	76 years	8	41% - small, 33% - medium, 22 % - large	8 days	7.8% per year	6.4% per year
Wilson et al., 2019	UK, 1355 / DOAC - 475	76 years	4	18% - large	11 days	5.7% per year	0.6% per year
IAC, 2020	USA, 1289 / DOAC - 68%	77 years	5 for an interval of 0-3 days, 10 for an interval of 4-14 days, 15 for an interval > 14 days A	Lesion with a volume of ≥60 ml occurred in 5.9% with initiation within 0-3 days, in 17.4%, patients with initiation within 4-14 days, in 32.8% with initiation within > 14 days	-	for interval 0-3 days - 7.3%, for interval 4-14 days - 6.0%, for interval > 14 days - 7.2%	for interval 0-3 days - 1.1%, for interval 4-14 days - 1.7%, for an interval > 14 days - 2.9%

Currently undergoing RCTs ELAN (NCT03148457; Switzerland), OPTIMAS (EudraCT, 2018-003859-38; UK), TIMING (NCT02961348; Sweden) and START (NCT03021928; USA). Thus, the search for the optimal term for the administration of DOAC continues.

The approximate timing of the administration of the OAC after CES / TIA in accordance with the stated data and approach are shown in Fig. 2 [31].

Administration of OAC in some difficult clinical situations

Elderly and senile age. An analysis of the prescription of OAC to patients |85 years old (mean age 89 years) in two Italian hospitals (n=117) showed that OAC were initiated in 80.5% (97% – DOAC) of patients on average 6 days after IS. The prescription of OAC was not associated with an increased risk of HT, which indicates that age, as an independent risk factor, should not affect the timing of OAC prescription after IS [32].

Reperfusion therapy. Analysis of data from studies of RAF and RAF-NOACs, in a population of which 26% of patients received intravenous thrombolysis (predominantly) or / and mechanical thrombectomy, demonstrated that reperfusion therapy does not affect the efficacy and safety of anticoagulant therapy prescribed on average after 7 days [33].

Hemorrhagic transformation. In the process of cerebral ischemia, the integrity of the microvascular bed is disturbed due to degradation of the basement membrane and extracellular matrix, which leads to a violation of the integrity of the blood-brain barrier and HT of ischemic tissue, which, according to the ECASS classification (European Cooperative Acute Stroke Study), can be represented by hemorrhagic infarctions 1 and 2

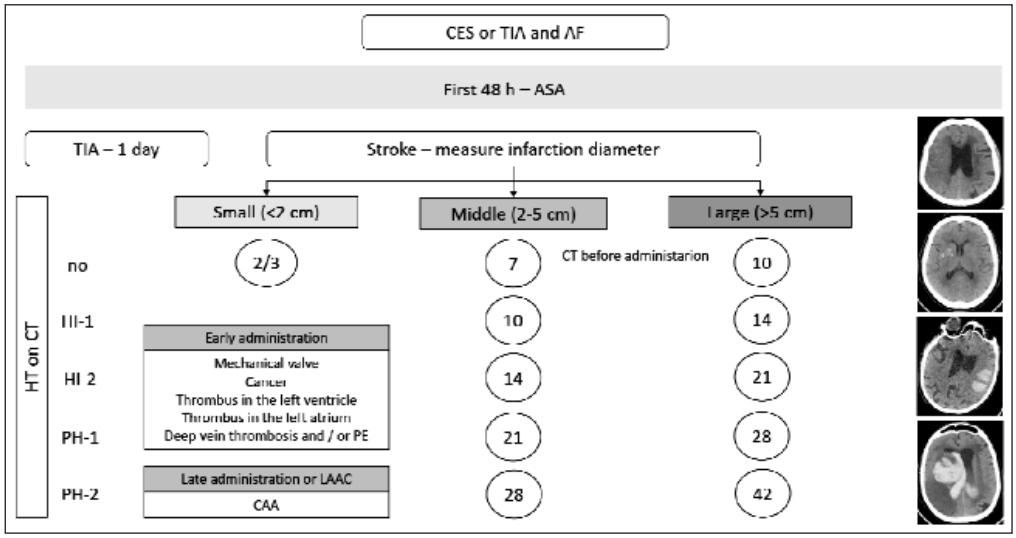

Fig. 2. *Approximate timing of the OACs initiation after CIS/TIA (from [31], with changes)*

type, as well as parenchymal hemorrhage of types 1 and 2. It is fundamentally important to distinguish clinically obvious HT, which is accompanied by neurological deterioration or leads to the death of the patient, and asymptomatic HT [1, 34]. HT is a common phenomenon in IS, even in the absence of reperfusion therapy. The risk of developing symptomatic HT without intravenous thrombolysis is 1–7% [35], and after intravenous thrombolysis it varies from 2 to 7% [34]. According to the WAKE-UP study, the frequency of HT was 17.4% in patients without intravenous thrombolysis and was mainly represented by type 1 and type 2 hemorrhagic infarctions [36].

The main risk factor for HT is the size of infarction: for infarction <2 cm, the risk of HT is 1.5%, with a size of 2–5 cm – 22%, with a size |5 cm – 58%. At the same time, the residual risk of HT decreases to 10% on day 6 with an average size of the lesion and by day 15 with large lesions, which necessitates a differentiated prescription of DOAC after IS [37].

It is assumed that early anticoagulant administration can induce or aggravate HT with potential negative clinical consequences, which often leads to delayed administration of the drug [38]. Higher mortality due to ICH in comparison with the recurrence of ischemic stroke is another limiting factor [1]. In the population of RAF and RAF-NOACs studies, the incidence of HT was 11%, while clinically overt HT was 3%. OAC initiation without HT was carried out on average after 12 days, in the presence of HT – after 23 days. It is noteworthy that this delay did not lead to an increase in the number of relapses of ischemic events [39]. The results of this study indicate that in the presence of HT, prescribing OAC too early is inappropriate.

Low patient compliance. Taking DOAC, in contrast to warfarin, does not require regular laboratory monitoring, which, in theory, should increase adherence to anticoagulant therapy [11]. However, Compliance with DOAC therapy varies from drug to drug. An analysis of 36,652 patients with AF in the UK showed that adherence to therapy (taking the drug as prescribed by the doctor) and constancy of therapy (continuing to take the drug) for 1 year were 55% and 65%, respectively, for all OAC. Among the studied drugs (VKA, dabigatran, rivaroxaban and apixaban), apixaban was characterized by the highest rates of adherence to therapy and its persistence [40]. According to the results of a meta-analysis of data from 594 784 patients with AF, the proportion of patients with good adherence is 71% for apixaban, 70% for rivaroxaban and 60% for dabigatran [41]. Another meta-analysis showed that the frequency of administration of DOAC (1 or 2 times a day) does not affect the effectiveness and safety of therapy [42].

Data from the Swiss registry indicate that the benefit of prescribing DOAC in patients with AF and recent stroke persists even in the presence of disability and dependence on others (modified Rankin scale 3–5 after discharge from the hospital) [43]. Nevertheless, in practice, severe dysphagia and mRS|4 points are risk factors for not prescribing the drug [32], although administration through the nasogastric zones does not affect the bioavailability of apixaban and rivaroxaban [19].

Combined atherosclerosis of the main arteries of the head and neck. Atherosclerotic plaques occur in 28+64% of patients with AF [44]. Moreover, there is evidence that patients with AF are more prone to carotid atherosclerosis than patients without AF. This may be due to a local change in hemodynamics due to arrhythmia [45]. Patients with a combination of AF and carotid atherosclerosis may require additional preventive measures – in particular, the combined administration of OAC and antiplatelet agents, strict control of risk factors and the use of surgical methods [46].

In the presence of stenosis of more than 50%, it is impossible to reliably determine the mechanism of development of a real stroke, if there is no involvement of different vascular territories. If the patient has a potentially clinically overt carotid stenosis, carotid endarterectomy is preferable, while stenting is undesirable due to the need for subsequent administration of dual antiplatelet therapy. However, if it is impossible to perform an open operation, the option of stenting can also be considered, followed by the administration of a combination of clopidogrel and DOAC for 1 month, which is allowed by the recommendations of ESC 2021 [47]. After carotid endarterectomy, the patient should take acetylsalicylic acid before initiating the OAC [19, 45].

Cerebral microangiopathy. Cerebral microangiopathy (CMA) is understood as a disease of small perforating arterioles, capillaries and, possibly, venules, causing a spectrum of neuropathological, CT and MRI changes, as well as a number of clin-

ical syndromes [48]. From the point of view of etiology, CMA is extremely heterogeneous and includes both a wide range of sporadic forms associated with arterial hypertension and other vascular risk factors, cerebral amyloid angiopathy (CAA), and rare genetic variants, primarily CADASIL [48–52]. CMA is the main cause of vascular cognitive impairment, lacunar stroke, and hypertensive ICH [53].

Thanks to the gradual introduction of the STandards for ReportIng Vascular changes on nEuroimaging, neuroimaging standards for cerebral vascular pathology, the neurologist is increasingly faced with the problem of interpreting phenomena such as white matter hyperintensity of vascular origin, lacunae, dilated perivascular spaces and cerebral microbleeds – CMB) [54]. CMB on MRI correspond to the foci of hemosiderin deposition [55]; in individuals |50 years of age, one or more CMB occurs in 17% of cases [56]. The presence of CMA can affect the safety of anticoagulant prophylaxis after IS or TIA – CMB increase the risk of developing ICH by 2.7–3.7 times, while moderate and severe white matter hyperintensity – 5.7 times [57, 58]. Moreover, even in the presence of CMB, the absolute risk of IS significantly exceeds the risk of CMB (5% versus 0.9%), regardless of the number and location of CMB, as well as the type of antithrombotic therapy, which justifies the inadmissibility of refusal to take OAC in this clinical situation [59].

CMB are considered as a marker of the severity of cerebrovascular disease and vascular fragility, which reflects the risk of further ischemic and hemorrhagic cerebral events [60]. In the recently proposed MINOC (Microbleeds International Collaborative Network) scale, the following indicators are used to predict the development of intracranial hemorrhage during the secondary prevention of CEI: the number of CMB, age, population, history of intracranial hemorrhage, history of IS, and the type of OAC (VKA or DOAC) [61]. Thus, the presence of CMB in itself should not influence the decision to prescribe OAC after IS or TIA [53, 60].

History of ICH. In a multicenter observational study (n = 4540, Taiwan), it was shown that among patients with AF and previous ICH, the use of DOAC is associated with a lower incidence of ICH and major bleeding compared with prescribing warfarin, while the incidence of ischemic events does not differ [62]. A subsequent meta-analysis confirmed that the use of DOAC versus VKA is associated with a reduced risk of stroke, death from any cause, and ICH in patients with a history of intracranial hemorrhage [63]. It is known that ICH due to CAA are characterized by a high risk of recurrence, but the cumulative ischemic risk, including extracerebral events, can be underestimated; therefore, a history of ICH is not a reason for not prescribing OAC after IS or TIA [60]. Only in the presence of severe CAA (with recurrent ICH, multiple CMB, disseminated cortical superficial siderosis) is it possible to abandon the OAC. The option of choice in this case is the occlusion of the left atrial appendage [5, 7].

Cryptogenic stroke. AF is one of the potential causes of cryptogenic embolic stroke (ESUS), especially in elderly and senile patients [64]. It is possible to formulate two strategies for searching for AF in ESUS – extended and targeted cardiac monitoring. It is known that the longer ECG monitoring is, the greater the likelihood of AF detection [65]: the frequency of arrhythmia detection varies from 4.3% with 72-hour Holter monitoring to 22% with 3-week monitoring [66, 67]. Prolonged cardiac monitoring using loop recorders can detect AF within 3 years in 41% of patients with ESUS, however, in Russia it is not readily available [68].

Targeted cardiac monitoring is based on the concept of atrial cardiopathy, according to which AF can be a marker of atrial dysfunction or "cardiopathy", which in turn is a direct cause of embolic events [69]. The main markers of atrial cardiopathy, that is, indicators of a high probability of AF detection after IS / TIA, include: age over 75 years, left atrial diameter more than 46 mm, the number of supraventricular extrasystoles at the first monitoring | 480 / day, the presence of an episode of supraventricular tachycardia lasting >20 cardiac cycles at the first monitoring and the NT-proBNP concentration> 400 pg / ml [70].

Prolonged monitoring in patients with markers of atrial cardiopathy is more effective: 12-month follow-up reveals AF in 33% of patients [71]. In routine practice, the most convenient biomarkers of atrial cardiopathy are structural and functional characteristics of the left atrium according to transthoracic echocardiography (diameter, volume index (LAVI), ejection fraction (LAEF)) [72], as well as serum concentration of natriuretic peptides, especially NT-proBNP [73–75]. It is advisable to use these markers to select patients for prolonged monitoring.

In a recent retrospective study, it was shown that the administration of OAC in a subgroup of patients with abnormal markers of coagulation and hemostasis or a pronounced increase in the left atrium (left atrial volume index |40 cm / m^2) is associated with a decrease in the frequency of recurrent stroke compared with antiplatelet therapy – 3% versus 14 % during the year without increasing the risk of intracranial hemorrhage [76].

Currently, the ARCADIA (The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial) study is evaluating the hypothesis that apixaban is superior to acetylsalicylic acid in the prevention of recurrent stroke in patients with ESUS and atrial cardiopathy established in the presence of |1 of the following markers: terminal P-wave index in lead V1 on ECG >5000 mV c ms, serum NT-proBNP level > 250 pg / ml and LA diameter index | 3 cm / m^2 by echocardiography [77].

Conclusion. Anticoagulant therapy is an effective and safe method of secondary prevention of CES, especially when using DOAC. Early initiation of anticoagulant therapy is a priority, but the timing should be determined individually, taking into account the size of the infarction and the presence of HT. Anticoagulant therapy remains highly effective and safe in various clinical situations that a neurologist of the vascular department may encounter – an elderly patient, undergoing reperfusion therapy, the presence of CMA, CMB, a history of hemorrhagic stroke, as well as functional limitations. In patients with embolic cryptogenic stroke in the presence of markers of atrial cardiopathy, prolonged ECG monitoring is advisable in order to detect latent AF and timely prescribe OAC. Any specialist prescribing a OAC should strengthen the patient's adherence to this type of secondary prevention.

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