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Oral anticoagulant therapy in patients after intracerebral hemorrhage

The presence of indications for long-term oral anticoagulant (OAC) therapy in a patient who has experienced an intracerebral hemorrhage (IUD) poses a difficult clinical dilemma for the physician. The article discusses the vectors of recurrence for different types of IUD and their neuroimaging markers. It describes approaches to the global assessment of risk factors for IUD in patients taking OACs. Detailed consideration is given to the situation of IUD concurrent with atrial fibrillation as the most common reason for prescribing OACs. There are data on the safety of restating OACs after IUD and on the risk of the latter in patients taking warfarin and direct OACs. The optimal OAC start or restart time after IUD, including that in patients with prosthetic valves, is discussed. An algorithm for decision making is recommended.

Keywords: *intracerebral hemorrhage; cerebral amyloid angiopathy; cerebral microbleeding; cortical superficial siderosis; oral anticoagulants.*
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Introduction

Intracerebral hemorrhage (ICH) is the most common type of intracranial hemorrhage that develops annually in 2 million people worldwide [1,2]. While early and personalized secondary prevention of ischemic stroke is a priority for specialists in the stroke units, a similar part of medical care for hemorrhagic stroke is not so actualized. At the same time, aging of the population predisposes to two overlapping age-associated conditions – cerebral amyloid angiopathy (CAA), which underlies cerebrovascular fragility with the development of aggressive lobar ICH, and atrial fibrillation (AF), requiring the administration of oral anticoagulants (OAC) [3]. This comorbidity currently is a barrier to the administration of an effective and safe secondary prevention.

In this work, we set out to objectively assess the benefits and risks of anticoagulant therapy in patients who have had ICH. Given the heterogeneity of ICH, the article focuses on two of its most common causes – hypertension and CAA, which underlie 4 out of 5 cerebral hemorrhages [1, 4]. Issues of identifying the causes of ICH and its classification were considered in our previous article [5].

Recurrence vector in patients with hypertensive and CAA-associated ICH

Most elderly patients with lobar ICH have a combination of hypertension and CAA [6].

The CAA-associated ICH accounts for one third of hemorrhages associated with cerebral small vessel disease and for more than a half in the structure of lobar hematomas [7, 8]. The neuroimaging signs of CAA-associated ICH include: lobar localization of the hematoma, its frequent combination with subarachnoid hemorrhage and the phenomenon of «finger-like projections», multiple expanded perivascular spaces in the region of the centrum semiovale, lobar hemispheric and strictly superficial cerebellar microbleeds (MBs), cortical superficial siderosis (cSS), more than 10 subcortical spots of white matter hyperintensity or its fronto-occipital gradient, as well as lobar lacunae [9–13].

Lobar ICH differ from non-lobar ICH by a twofold increase in the recurrence rate (7.8% vs 3.4% per year) [14], CAA-associated hemorrhage is characterized by a higher recurrence rate compared with hypertensive ICH (7.4% vs 1.1% per year) [7, 15]. With lobar localization of the hematoma, the frequency of recurrent ICH (7.9%) is higher than that for ischemic stroke (5.3%), while with hypertensive hemorrhage the risk of ischemic stroke significantly prevails (11.2% vs 3.2%) [16].

Neuroimaging markers of ICH recurrence

Cerebral microbleeds. MB is an MRI phenomenon that reflects the perivascular foci of hemosiderin deposition [17]. In cerebrovascular disease, MBs are a marker of the severity of vascular pathology and are observed in 60% of patients with ICH, although their presence does not allow predicting the development of the first or recurrent hemorrhage [18].

The presence of two or more MBs increases the risk of CAA-associated ICH recurrence by 3–4 times, while the likelihood of a repeated hypertensive ICH increases only with >10 MBs [15]. However, these results are criticized in the light of the modern understanding of the role of cSS [19].

Cortical superficial siderosis. cSS is a neuroimaging phenomenon that can be identified using T2* or SWI/SWAN MR sequences. Deposition of blood breakdown products in the cerebral cortex or subarachnoid space appears in the form of characteristic hypo-intensive «paths» along the cerebral gyri (Fig. 1). Development of cSS is associated with recurrent superficial cortical hemorrhages.

The phenomenon is associated with the APOE ?2 + genotype and is observed in 44% of patients with a history of CAA without ICH. cSS is a marker of increased fragility of the cortical

and leptomeningeal small vessels, high activity, and the progradient course of CAA [19, 20].

A meta-analysis of three cohorts of patients with CAA-associated ICH (n=443) showed that the recurrence rate of ICH is 6.9% per year. cSS is observed in 32% of patients and is disseminated in 21% of patients. Dissemination of cSS increases the risk of ICH recurrence by 4 times, and the presence and prevalence of cSS are the only independent predictors of recurrence of lobar ICH [19].

Global assessment of ICH risk factors in patients taking OAC.

The following factors associated with the risk of hemorrhage, including ICH, are well known: the presence of concomitant kidney or liver pathology, improper dose selection, inadequate control of blood pressure and international normalized ratio (INR) during therapy with warfarin, violation of OAC regimen, alcohol abuse, co-administration with antiplatelet agents, non-steroidal anti-inflammatory drugs and glucocorticosteroids [21–23].

Taking an anticoagulant in the absence of coagulopathy is not the cause of ICH, but only contributes to hemorrhage on the background of macro- or microvascular pathology, therefore, when prescribing an OAC to a patient, calculation of hemorrhagic risk with assessment of modifiable and non-modifiable bleeding risk factors is required [23]. Despite the fact that the popular HAS-BLED scale has been validated for predicting ICH with OAC, its predictive capabilities are very limited [24, 25].

The combination of ICH and AF

The comorbidity of AF and ICH should be considered in two aspects: (1) ICH, which developed in a patient with AF during the treatment with OAC, and (2) AF, which is detected in a patient with ICH and requires the administration of anticoagulant therapy.

According to the predicted increase in the occurrence of AF in the population, it can be assumed that the proportion of drug-related ICH will increase [26]: already at present, about 15% of ICH develop with the use of OAC, and within two years ICHs occur in 1.9% of patients with cardioembolic stroke taking OAC [27]. On the other hand, in 15% of patients, AF is diagnosed for the first time after a hemorrhagic stroke [3], and every fourth patient with a CAA-associated ICH has AF [28]. Thus, in approximately one third of cases of ICH a physician will face a difficult clinical dilemma.

Direct OAC (DOAC) compared with warfarin demonstrated a safety advantage in relation to the development of hemorrhagic stroke, therefore, a significant strategy to reduce the risk of ICH is to switch to DOAC in the absence of contraindications to their use [21].

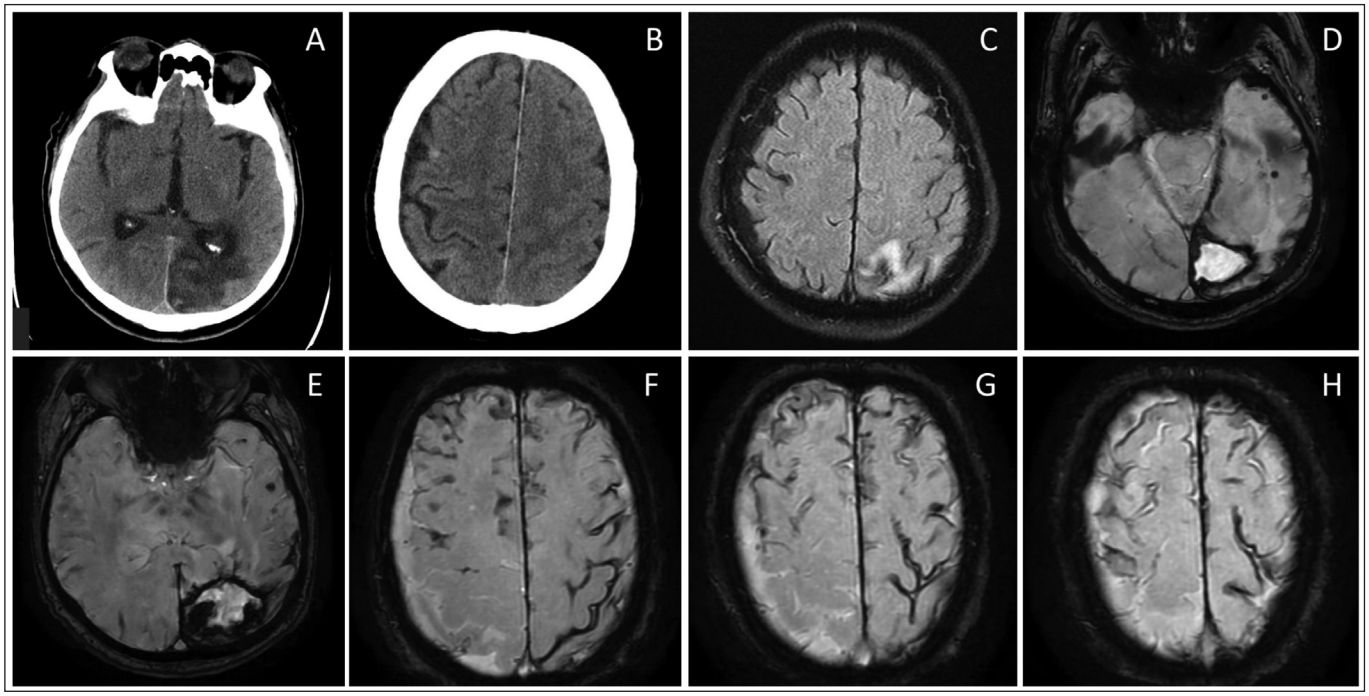

Fig. 1. *A patient, 80 years old, came for a consultation accompanied by his relatives, with complaints of decreased memory. Two months before, he suffered a stroke with the development of lobar intracerebral hematoma in the left parietal-occipital region. The patient was treated in the stroke department. During the examination in hospital, an atrial fibrillation was first detected, but due to the acute period of hemorrhage, antithrombotic therapy was not prescribed. On CT scans of the brain, cystic-atrophic changes in the left parietal and occipital lobes were visualized (A), as well as the focus of the convexal subarachnoid hemorrhage in the right parietal lobe (B). Brain MRI (SWAN) allowed to additionally determine strictly lobar cerebral microbleeds (D,E) and disseminated cortical superficial siderosis (F,G,H), not accompanied by hyperintensity on the FLAIR (C) Based on the modified Boston criteria, probable cerebral amyloid angiopathy was suggested. The hemorrhagic phenotype of the disease with dissemination of cortical superficial siderosis and the presence of lobar hematoma in the anamnesis determined absolute contraindications for the oral anticoagulants, therefore, left atrial appendage occlusion (LAAO) was recommended as a measure of preventing thromboembolic events.*

Safety of resuming OAC after ICH

Algorithms for risk assessment during the resumption of OAC after bleeding, including ICH, are presented in a number of documents [22, 29–31]. However, at the present time we do not have data from randomized clinical trials for the prescription of OAC after ICH, so the decision to resume anticoagulant therapy is individual. The resumption of treatment with OAC varies from 6–8 days [32, 33] to 4–8 weeks from the time of ICH [29].

A survey of specialists from the USA, Canada, Europe, Latin America, Russia and other countries (n=228) showed that the frequency of resuming of OAC after ICH in real clinical practice varies from 30% (in CAA) to 98% (in traumatic ICH). Late administration (> 3 months from the index event) or rejection of OAC are characteristic of large (> 30 cm^2), lobar hematomas and recurrent ICH. About 38% of respondents use MRI data for decision making and 36% use vascular imaging results [34].

Observational studies performed prior to 2014 showed conflicting data regarding the safety of resuming OAC administration [35–37]. In 2015, the German multicenter study RETRACE for the first time convincingly demonstrated that in patients admitted to a hospital with OAC-associated ICH (n=719), the resumption of OAC therapy reduced the incidence of ischemic stroke during the one year follow-up by 8.8% (3, 9% vs 12.7%) without a significant increase in the number of ICH [38]. Moreover, the resumption of OAC was associated with a significant reduction in mortality (8.3% vs 30.7%). In the same period, similar data were published on the analysis of the Danish registry (n=1752), which showed that the resumption of anticoagulant therapy after a OAC-provoked ICH was associated with a twofold reduction in the risk of ischemic stroke and systemic embolism compared with refusal of treatment or the administration of antiplatelet agents, without differences in the frequency of ICH during the period of observation (one year) [39]. Later, the presented results were reproduced in other observational studies [3, 40] and meta-analyzes [41–43].

When comparing the results of independent studies, the annual recurrence rate of ICH in patients not taking OAC is from 0 to 8.6%, while in those taking OAC it is 2.6–8.7% [3]. At the same time, the risk of ischemic stroke after ICH in the first group of patients ranged from 1.0 to 12.7%, and in the second group (taking OAC) – 0.8–5.6%. Thus, with a formal comparison of the frequency of ICH when taking OAC (on average, 4.5% per year) with the frequency of ischemic stroke when they are rejected (on average, 8.0% per year), the absolute value of the benefits of OAC is 3.5 % per year [3].

Taking into account concerns about the possibility of an error related to patient selection, a meta-analysis of individual data was performed (n=1012), which included only patients with AF and ICH. It confirmed the benefit of prescribing OAC [44]. In addition, the authors showed that the resumption of OAC increases the chance of achieving a favorable functional outcome after a year of observation by 4 times. The safety of OAC resumption is likely to persist in elderly patients [45].

Differences in the risk of developing ICH between patients taking warfarin and DOAC

It is known that the ICH, associated with the use of anticoagulants, develops in 0.3–3.7% of patients per year on the background of taking warfarin and in 0.2–0.5% of patients when taking DOAC. Warfarin causes 9–14% of all cases of intracranial hemorrhage and more than 10 times increases the risk of hemorrhagic stroke. Taking DOAC is associated with a twice lower risk of ICH compared with taking warfarin [26, 46]. Does this advantage persist if the patient has had an ICH?

Despite the obvious advantages of DOAC, there are no data on the features of their restart after ICH. An analysis of the Danish national registries, which included 622 patients with AF who had suffered ICH, showed that the annual risk of ischemic and hemorrhagic stroke for warfarin and DOAC groups is 7.9% vs 4.0% and 7.0% vs 5.1%, respectively. which indicates the priority of DOAC in this group of patients [47].

On the other hand, it is known that in the case of hemorrhagic complications, the further clinical scenario is uniform and does not depend on the type of OAC [46]. Considering that no convincing differences in the therapy with antagonists of vitamin K and DOAC after ICH have been identified, the main argument for choosing OAC is the availability of a neutralizing agent. Antidote substances are being actively studied [48]. The main representatives of the DOAC antidote groups include idarucizumab, adnexanet-alpha, and ciraparatag (aripazine). Idarucizumab is a prodrug, a fragment of human monoclonal antibodies that specifically bind to dabigatran and neutralize its action [49]. Adnexanet-alpha is a recombinant form of factor Xa that neutralizes the action of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). For heparin and all OAC, with the exception of warfarin, ciraparantag can be used. Also, as part of measures to normalize hemostasis in the development of life-threatening bleeding, the use of a prothrombin complex concentrate is discussed [22, 31, 50]. Currently, only idarucizumab is registered among the specific neutralizing agents for DOAC in the Russian Federation.

Time of start / resumption of OAC after ICH

A one-center observational study by Y. Sakamoto et al. (2019) (n=236) demonstrated the safety of OAC administration (n=41) in patients with AF (81%) or deep vein thrombosis on average 7 days after the primary ICH. During inpatient treatment (on average, 21 days), none of the patients demonstrated an increase in the size of the hematoma or recurrence of the ICH. It should be noted that in almost all patients, ICH was the first in their life, lobar hematoma was observed in every fourth patient, lobar MB in 56% of patients, probable CAA in 12% of patients [51]. The lack of a unified approach to the timing of the resumption of anticoagulant therapy is demonstrated in a study by Y. Kato et al. (2019), in which resuming of DOAC in patients with AF was performed in every second case after an average of 11 days [52].

Analysis of the data from the Swedish register (n=2619) showed that the optimal time interval for resuming OAC is 7–8 weeks [53], however, in observational studies, the average prescription period was 4–6 weeks. Thus, experts recommend resuming/prescribing OAC therapy within a period of 4–8 weeks, depending on the individual characteristics of the patient. Within this interval, an earlier administration is advisable with a significant predominance of thromboembolic risk over the risk of recurrent bleeding: a mechanical prosthesis in combination with AF or a history of ischemic stroke; a spherical or disk-shaped valve prosthesis; AF with a value of CHA2DS2-VASc ⩾6 points; the risk of developing ischemic stroke is ⩾10% per year; rheumatic mitral stenosis; venous thromboembolic disease less than 3 months before; a history of unprovoked venous thromboembolism; active cancer with a history of venous thrombosis; previous thromboem-

bolism with OAC discontinuation; thrombosis of the left chambers of the heart; artificial left ventricle) [30] (Fig. 2). Also, according to experts, refusal of OAC is possible if there are signs of a severe or hemorrhagic endophenotype of CAA (>10–20 MB, disseminated / multifocal cSS) [54].

Resumption of OAC therapy in patients with prosthetic valves

A special situation associated with the highest thromboembolic risk and requiring the urgent resumption of warfarin therapy develops in the presence of a mechanical valve prosthesis. A mechanical mitral valve prosthesis is associated with a five-fold increased risk of valve thrombosis and a 1.5-fold higher risk of thromboembolic events [32].

The position of the European Cardiology Society (2017) indicates that systemic anticoagulation with heparin can be started after 3 days with a switch to a vitamin K antagonist on day 7 [33]. The RETRACE I & II study involved 137 patients with ICH and a mechanical valve prosthesis. The resumption of the anticoagulant (heparin or warfarin), as such, is associated with a ten-fold increase in the risk of intra- and extracerebral hemorrhage, however, prescribing after 2 weeks can be safe. In high-risk patients, resuming may be considered after 1 week [55]. Also, in patients with prosthetic heart valves, ischemic risk assessment and the establishment of the period for the resumption of anticoagulant therapy should be carried out using the target INR data presented in the 2017 ESC / EACTS recommendations for the treatment of valvular heart disease [56].

Left atrial appendage occlusion as an alternative to OAC

Left atrial appendage occlusion (LAAO) with the WATCHMAN device has been approved by the US Food and Drug Administration for the prevention of stroke in patients with nonvalvular AF who require OAC but have reasonable contraindications to long-term therapy [57]. Existing data indicate that this procedure is not inferior to warfarin in relation to the development of stroke, systemic embolism and cardiovascular death, although it is associated with perioperative complications. According to European guidelines for managing patients with AF, LAAO can be considered for the prevention of stroke in patients with AF if there are contraindications to long-term therapy with anticoagulants [29, 33].

Decision-Making Algorithm

The lack of data from randomized clinical trials does not allow us to formulate clear recommendations on the administration/resumption of OAC after ICH. From a practical point of view, this decision is associated with the solution of three problems: (1) to determine the ratio of the individual thromboembolic and hemorrhagic risk of the patient, (2) to choose the optimal OAC and the time of its administration, (3) to achieve maximum control of factors that additionally increase hemorrhagic risk [54]. Based on a generalization of the studies reviewed, we formulated a decision-making algorithm for the administration / resumption of treatment for OAC after ICH (Fig. 2).

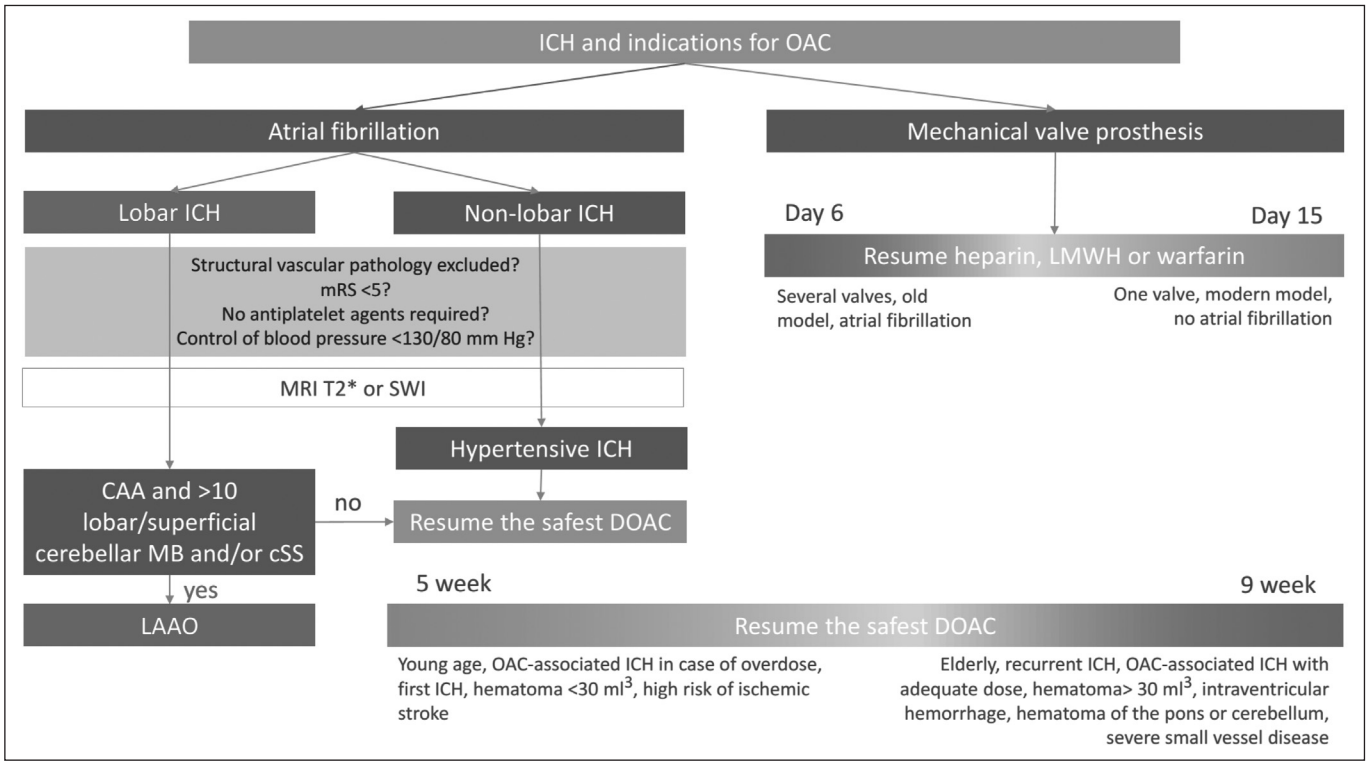

Fig. 2. *Decision-making algorithm for administration / resumption treatment for OAC after ICH.*
ICH – intracerebral hemorrhage, OAC – oral anticoagulants, mRS – modified Rankin scale, LMWH – low molecular weight heparin, CAA – cerebral amyloid angiopathy, MB – cerebral microbleeds, cSS – cortical superficial siderosis, left atrial appendage occlusion – LAAO, DOAC – direct oral anticoagulants.

Conclusion

ICH belongs to the category of life-threatening bleeding into a critical organ, which in the acute period requires the immediate discontinuation of all antithrombotic therapy. Over the past decade the data on the safety and efficacy of OAC therapy in a category of patients after ICH with a high thromboembolic risk have been accumulated. The concept of the neuroimaging markers of a high ICH recurrence risk and a comparative characteristic of OAC have been formed. The specific antidote of dabigatran idarucizumab and the performance of LAAO in the leading centers of the country also became available for use in the clinical practice of the Russian Federation. Further systematization of information will allow a team of specialists to make an informed decision on the issue of anticoagulant therapy in one of the most difficult clinical situations at the intersection of neurology and cardiology.

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