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REVIEW ARTICLE

Anticoagulative therapy after stroke in patients with atrial fibrillation

M. N. Mamedov

National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Author

Mekhman N. Mamedov, M.D., Ph.D., doctor of sciences, professor, head of the Laboratory of Interdisciplinary Approach for Prevention of Chronic Non-infectious diseases, National Research Centre for Preventive Medicine, Moscow, Russia.

Atrial fibrillation (AF) is one of the most serious complications in stroke patients. Meta-analysis of several studies showed that the risk of recurrent stroke is 2,5 higher in patients with AF and stroke/transient ischemic attack (TIA). According to current guidelines (ESC 2016) secondary stroke prevention in patients with AF include effective new oral anticoagulant (NOAC) and medication adherence measures. NOAC decreased cardiovascular mortality and the risk of major and intracranial bleeding compared with vitamin K antagonists in stroke/ TIA patients. The review article presents NOAC indications, dosing and administration recommendations.

Key words: *atrial fibrillation, stroke, anticoagulants, effectiveness, safety.*

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Atrial fibrillation (AF) is one of the most common cardiovascular disease (CVD) risk factors. The prevalence is 1,5–2,0 % among adults according to epidemiological studies. The prevalence of AF increases with age [1,2]. AF comorbidity with other diseases also has prognostic value. According to EORP AF data, among 3049 patients with AF and average age of 68,8 years, 71 % had arterial hypertension (AH), 47,5 % had chronic heart failure (CHF), 36,4 % — coronary artery disease (CAD), every third patient had cardiomyopathy and every fifth –type 2 diabetes mellitus (T2DM) (Table 1) [3].

There is an opinion, that clinically manifested strokes are the tip of an iceberg of vascular brain diseases. The number of investigations showed that 40 % of patients with 1–2 grade AH have organic vascular pathologies according to MRI data. In general, the frequency of intractable intracranial strokes is

* Corresponding author. Tel. 89262283309. E-mail: mmamedov@mail.ru

5–23 % according to imaging methods and biomarkers.

Table 1. **Comorbidities in patients with AF (according to EORP AF data)**

Average age, years	68,8
CAD, %	36,4 %
Congestive heart failure, %	47,5 %
AH, %	70,9 %
DM, %	20,6 %
Hypercholesterinemia, %	48,6 %
Cardiomyopathy, %	35,3 %
Other cardiovascular diseases, %	8,1 %
Chronic kidney disease, %	13,2 %

Atrial fibrillation and the risk of complications in stroke patients

AF is one of the most serious complications in patients after stroke. The meta-analysis of several studies showed that the risk of stroke increases by 2,5 times in patients with AF and stroke/ transient ischemic attack (TIA). The risk of ischemic stroke/ TIA is 7,6 % and the risk of symptomatic intracranial hemorrhage — 3,6 % during the first 90 days in stroke patients with AF. Mortality during the first year after stroke in patients with AF is 50 %. It is also remarkable that the frequency of AF is relatively high in stroke patients — 30 % [4].

In general, the history of thromboembolic complications is the risk factor of coronary events in patients with AF. However, CHF in patients with left ventricular ejection fraction (LVEF) ⩽40 %, age ⩾75 years and metabolic syndrome can also cause cardiovascular events [5].

According to current guidelines (ESC 2016), secondary prevention of stroke in patients with AF include effective new oral anticoagulant (NOAC) and medication adherence measures. NOACs are superior to vitamin K antagonists (VKA) or aspirin in patients with AF and history of stroke. Patients with TIA and stroke during anticoagulant therapy should underwent adherence estimation and optimize it if needed [1].

The effectiveness of new oral anticoagulants in stroke or transient ischemic attack patients with atrial fibrillation

The results of new studies on the effectiveness of NOAC compared with standard therapy — warfarin, have been published. The REAFFIRM study included the retrospective analysis of the US Truven MarketScan database from January 2012 to June 2015 in order to compare the effectiveness and safety of rivaroxaban, apixaban, dabigatran with warfarin for secondary stroke prevention and systemic embolism in patients with AF in clinical practice. The primary endpoint of the investigation was the general frequency of ischemic stroke and intracranial haemorrhage. NOAC was superior to other medications according to the results [6].

Three large studies (ROCKET AF — rivaroxaban, RE-LY — dabigatran, ARISTOTLE — apixaban) studied the effectiveness and safety of oral anticoagulants (OA) in patients with AF after stroke, the prevalence of which was from 19 % to 52 %. The results of these studies showed that recurrent strokes frequency reduced by 21 % (apixaban) and 26 % (dabigatran) compared with warfarin, and mortality reduced by 11 % and 14 %, respectively. NOACs reduce the risk of intracranial bleeding and large bleedings compared with warfarin [7–10].

Anticoagulative therapy guidelines

Patients with TIA or stroke during anticoagulative therapy should underwent anticoagulative therapy adherence estimation and optimize it (Figure 1).

The resumption of anticoagulant therapy in patients with AF after stroke / TIA depends on stroke severity and the presence of bleeding risk factors [11].

NOAC therapy can be resumed not only after a stroke, but also after intracranial bleeding.

The combination of NOAC and antiplatelet therapy in patients after TIA or stroke, is not recommended.

Patients after NOAC therapy had lower risk of ischemic events without differences in hemorrhagic complications compared with patients without OACs [12].

National Institutes of Health Stroke Scale [13] (NIHSS) is used for the estimation of stroke severity, neurological deficits, and consists of 11 items:

- Each item scores a specific ability between 0 and 4 — higher score indicative higher level of impairment.
- The maximum possible score is 42.

There are 5 gradations depending on the score:

- no stroke symptoms;
- minor stroke;
- moderate stroke;
- moderate to severe stroke;
- severe stroke.

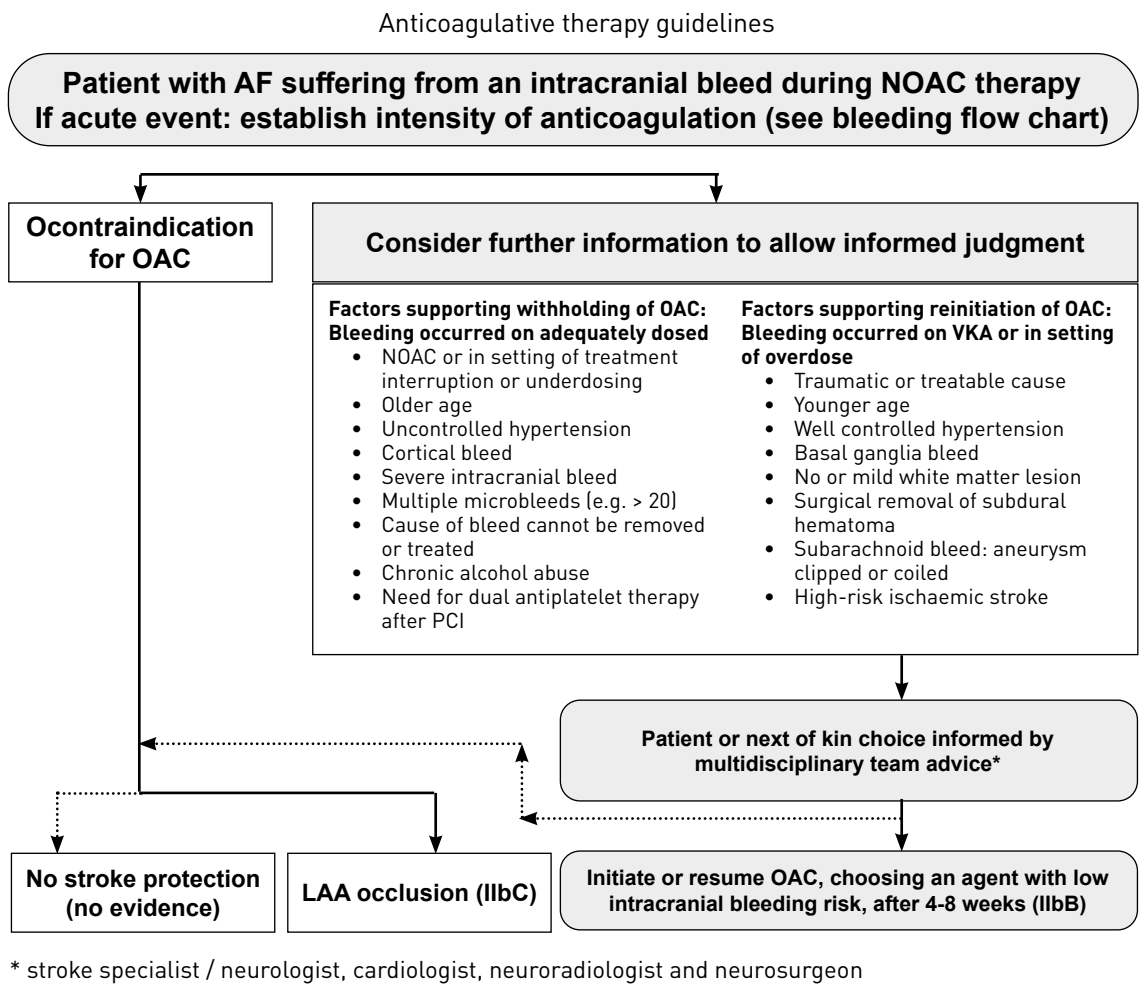

Figure 1. Anticoagulative NOAC therapy guidelines in patients with AF and intracranial bleeding

The estimation of additional risk factors, affecting earlier or later beginning of treatment with new oral anticoagulants

When initiating NOAC therapy in patients with AF after ischemic stroke / TIA we have to consider the following factors:

- bleeding occurred on VKA or in setting of overdose;
- traumatic or treatable cause;
- younger age;
- well controlled hypertension;
- basal ganglia bleed;
- no or mild white matter lesions;
- surgical removal of subdural hematoma;
- subarachnoid bleed: aneurysm clipped or coiled;
- high-risk of ischemic stroke.

The beginning/reinitiating of NOAC after ischemic stroke/ TIA depends on the severity of stroke. The 1–3–6–12 day rule is advocated. Patients with TIA can start OAC therapy in 1 week. Patients with NIHSS <8 or minor stroke — in 3 weeks. Patients with moderate stroke and NIHSS 8–15 — in 6 weeks. Patients with severe stroke and NIHSS >16 — have the longest interval when prescribing NOACs [1,12].

Anticoagulative therapy in patients with AF after intracranial bleeding can be reinitiated 4–8 weeks after.

Clinical situations supporting withholding of oral anticoagulants

In some cases, we have to reduce or withhold the NOAC in order to prevent possible complications. These cases are listed below:

- bleeding occurred on adequate or reduced dose;
- NOAC or in setting of treatment interruption;
- older age;
- uncontrolled hypertension;
- cortical bleed;
- severe intracranial bleed;
- multiple microbleeds (e.g. > 20);
- cause of bleed cannot be removed or treated;
- chronic alcohol abuse;
- need for dual antiplatelet therapy after PCI.

Conclusion

Patients with AF and the history of stroke/TIA have higher risk of stroke recurrence. These group of patients also have higher risk of intracranial bleeding. NOAC reduced cardiovascular mortality and the risk of major bleeding or intracranial bleeding in patients with the history of stroke/TIA compared with vitamin K antagonists therapy.

Conflicts of interest: None declared.

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