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Why do not all patients with atrial fibrillation at high risk of thromboembolism receive oral anticoagulation?

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Abstract

The CHA_2DS_2-VASc scale is commonly used to assess the risk of thromboembolism in patients with atrial fibrillation (AF). Oral anticoagulants are recommended for the prevention of stroke in patients with AF with a CHA_2DS_2-VASc score of ≥ 2 for men and ≥ 3 for women. There are known factors that have not been included in this scale, but they significantly increase the risk of thromboembolism. Not all patients with AF who are at high risk of thromboembolism receive anticoagulation therapy. This is mainly due to the contraindications to the use of drugs from this group.

Key words: atrial fibrillation, oral anticoagulants, stroke

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Introduction

Patients with atrial fibrillation (AF) are at significantly increased risk of thromboembolic complications. The presence of AF increases the risk of stroke by 5 times, and every 5th stroke can be attributed to this arrhythmia [1]. The risk of complications can be significantly reduced by the use of oral anticoagulants (OACs). Prophylaxis of thromboembolic complications depends on the risk of thromboembolism assessed using the CHA_2DS_2-VASc score. Oral anticoagulants are recommended for the prevention of stroke in patients with AF with a CHA_2DS_2-VASc score of 2 or more in men and 3 or more in women [2]. Prophylactic anticoagulation has been shown to be associated with a 60–70% reduction in the risk of thromboembolic complications and mortality [3].

Non-classical risk factors for thromboembolic complications in patients with AF

The guidelines of the European Society of Cardiology (ESC) recommend the use of the CHA_2DS_2-VASc score (Table 1) in the assessment of thromboembolic risk in patients with AF [2]. In 2020, a different risk score for the assessment of thromboembolic complications was also proposed — the ABC scale, which includes: age, biomarkers and clinical history [4]. The CHA_2DS_2-VASc and ABC scores have the highest predictive value in predicting thromboembolic risk in patients with AF. According to the 2020 ESC guidelines, the CHA_2D_2-VASc score should be used to assess the risk of thromboembolism and to qualify patients for anticoagulation treatment.

However, there are other factors known that are not included in the CHA_2DS_2-VASc score, but significantly increase the risk of thromboembolism. These factors include, but are not limited to, the type of AF, chronic kidney disease, and cancer. Piccini et al. [5] proved that in patients with non-valvular AF with a moderate to high risk of stroke, renal dysfunction is a strong predictor of stroke and systemic embolism, and concluded that the assessment of renal function should be included in the stratification of stroke risk in patients with AF. In the proposed R_2CHADS_2 score, 2 points were added to the $CHADS_2$ score if the creatinine clearance (CrCl) was below 60 mL/min. Decreased CrCl

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Table 1. Components of the CHA_2DS_2-VASc score (source [2])

	Risk factors and definition	Score	Definition
C	Congestive HF, symptomatic HF, moderate to severe LV dysfunction or HCM	1	Recent decompensated HF regardless of LVEF (HFrEF or HFpEF) or the presence (even asymptomatic) of moderate to severe LV systolic dysfunction in cardiac imaging
H	Hypertension	1	Resting blood pressure > 140/90 mm Hg in ≥ 2 measurements on different occasions or antihypertensive treatment
A	Age ≥ 75 years	2	2 points assigned for the age of > 75 years
D	Diabetes	1	Random venous blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) + symptoms Two fasting blood glucose measurements ≥ 126 mg/dL (≥ 7.0 mmol/L) OGTT ≥ 200 mg/dL (≥ 11.1 mmol/L)
S	Stroke/TIA/thromboembolism	2	History of stroke, systemic embolism or TIA
V	Vascular disease	1	Vascular disease defined as a history of myocardial infarction, atherosclerotic peripheral artery disease, atherosclerotic plaque in the aorta
A	Age of 65–74 years	1	1 point assigned for the age of 65–74 tears
Sc	Sex category, female	1	Increases the risk in the presence of ≥ 1 other risk factor
Maximum score		9	

HF — heart failure; LV — left ventricle; HCM — hypertrophic cardiomyopathy; LVEF — left ventricular ejection fraction; HFrEF — heart failure with reduced ejection fraction; HFpEF — heart failure with preserved ejection fraction; OGTT — oral glucose tolerance test; TIA — transient ischemic attack

was a strong independent prognostic factor for stroke and systemic embolism; and was only surpassed by a previous stroke or transient ischemic attack. According to the R_2CHADS_2 score, the reclassification rate increased by 6.2% compared to CHA_2DS_2-VASc and by 8.2% compared to $CHADS_2$. It can therefore be concluded that there is an independent association between renal impairment and an increased risk of stroke in patients with AF.

The relationship between the type of AF and stroke risk remains controversial. The CODE-AF registry has shown that paroxysmal AF may be associated with a lower incidence of stroke compared with non-paroxysmal AF. This was probably due to the fact that patients with persistent and permanent AF were older, had more comorbidities, and were prescribed anticoagulants much more often than patients with paroxysmal AF [6].

Many clinical risk factors for stroke, such as obstructive sleep apnea (OSA), are closely related to the components of the CHA_2DS_2-VASc, but taking them into account does not improve its predictive value. The relationship between smoking or obesity and the risk of stroke in patients with AF is still controversial [7]. Overweight and obesity have been shown to be risk factors for ischemic stroke, thromboembolism and death in patients with AF. Various biomarkers, such as troponin, natriuretic peptides, and von Willebrand coefficient, have shown predictive value in the assessment of stroke risk in AF patients treated with OACs [8, 9]. The level of the N-terminal pro-B-type natriuretic peptide (NT-proBNP) was significantly associated with the risk of thromboembolic events and cardiovascular mortality.

In addition, elevated levels of inflammatory markers such as interleukin 6 (IL-6) and C-reactive protein (CRP) are reported to be associated with greater difficulty in maintaining sinus rhythm and with increased risk of cardiovascular events and AF mortality. It has also been shown that the concentration of D-dimer may be associated with the risk of stroke in AF. Anticoagulation treatment reduces the concentration of this biomarker in the majority of treated patients [8].

Echocardiographic parameters are also among the risk factors for thromboembolism in patients with AF. It has been reported that left ventricular systolic dysfunction assessed by transthoracic echocardiography may be a strong and independent prognostic factor for stroke in patients with AF. In contrast, left atrial diameter and mitral regurgitation are not associated with a higher risk of thromboembolic events in patients with AF [10]. Table 2 lists risk factors that are significant in the stratification of the risk of stroke and other thromboembolic complications, but are not included in the CHA_2DS_2-VASc score.

Recommendations for thromboembolism prophylaxis in patients with AF at high risk of thromboembolic complications

Anticoagulation therapy is recommended in all patients with AF. Due to the fact that OACs significantly reduce the risk of stroke and mortality, the 2020 guidelines recommend considering the inclusion of OAC also in patients with CHA_2DS_2-VASc score of 1 point (non-gender related), i.e. in

Table 2. Stroke risk factors not included in the CHA_2DS_2-VASc score in patients with atrial fibrillation (AF) (based on [10–13])

Echocardiographic parameters	Coagulation marker	Biomarkers	Others
LAV, LAVI	D-dimers	BNP	CKD
LVEF	Fibrinogen	CRP	Neoplastic disease
Atherosclerotic plaque in the aorta	PAI-1	IL-6	LAA fibrosis (MRI)
LAA dysfunction	TAT	Cardiac troponins T and I	AF type
LAA shape (TOE, CT, MRI)	von Willebrand factor		Smoking
LAA count (TOE, TAT, MRI)	Cystatin C		Hyperlipidemia
			Amyloidosis
			Metabolic syndrome

LAV — left atrium volume; LAVI — left atrium volume index; LVEF — left ventricular ejection fraction; LAA — left atrial appendage; TOE — transechophageal echocardiography; CT — computed tomography; MRI — magnetic resonance imaging; TAT — thrombin–antithrombin III complex; PAI-1 — plasminogen activator inhibitor 1; BNP — B-type natriuretic peptide; CRP — C-reactive protein; IL-6 — interleukin 6; CKD — chronic kidney disease

patients with an intermediate risk of thromboembolism [2]. High-risk patients with AF absolutely require OAC therapy. They are in a group particularly at risk of thromboembolic complications. It should also be mentioned that antiplatelet drugs cannot be used in the prophylaxis of thromboembolic complications in patients with AF [2].

In line with guidelines that have changed in recent years, patients at high risk of stroke have always required anticoagulation therapy. The 2010 guidelines recommended that obtaining at least 2 points in the $CHADS_2$ scale was an indication for the use of a vitamin K antagonist (VKA, vitamin K antagonist), 1 point allowed the choice between VKA and acetylsalicylic acid (ASA), while obtaining 0 points meant that there are no indications for anticoagulant treatment [14]. Guidelines, which have changed in recent years, have always indicated that patients at high risk of stroke required anticoagulation therapy. The guidelines from 2010 recommended that the $CHADS_2$ score of at least 2 was an indication for the use of a vitamin K antagonist (VKA), 1 point allowed the choice between VKA and acetylsalicylic acid (ASA), while obtaining 0 points indicated that there were no indications for anticoagulant treatment [14]. For the first time, attention was drawn to the possibility of using two groups of novel OACs (NOACs) — direct thrombin inhibitors (e.g. dabigatran) and oral factor Xa inhibitors (e.g. rivaroxaban) — as part of antithrombotic prevention in patients with AF. In 2012, the update of the 2010 guidelines was released; further evidence has emerged in favor of the new OACs [15]. It has been proven that ASA in the prevention of stroke may be harmful and there is no evidence confirming its effectiveness in the prevention of thromboembolic complications in patients with AF [16]. In the following years, studies were conducted that assessed OAC in patients with AF. They included mainly people at high risk of stroke [17, 18]. Men with a CHA_2DS_2-VASc score of at least 2 points and women with a score of 3 have been shown to benefit from OAC. Vitamin K antagonists and NOACs have been found to be effective in the prevention of stroke in patients with AF and to be safe for use [19]. The 2020 ESC Guidelines [2] once again provide strong evidence for the efficacy and safety of NOACs, the role of which has been significantly strengthened. Due to their effectiveness, safety profile and convenience of use, they are the drugs of first choice among OACs in the prevention of stroke in patients with AF, which is confirmed by large registers from recent years [20].

Prophylaxis of thromboembolic complications in large registries

With new guidelines and research in AF, the approach to using oral anticoagulants has evolved. It is absolutely indicated in patients at high risk of thromboembolism. It should be noted that the use of OACs in daily practice has increased in recent years. According to the data from the registry of Ding et al. [21], in 2001–2004, OACs were used in only 23% of patients with a CHA_2DS_2-VAS score of at least 2 points while in 2012–2016 these drugs were used in as much as 84.3% of such patients in the study performed by Cools et al. [22], which is similar to the data from the EORP-AF [23] and PREFER in AF [24] registers. The results presented by Cowan et al. [25] and Holt et al. [26] are similar and concern a specific time periods, i.e. 2009–2012 and 2007–2010, respectively, in which the use of OAC was 55% and 53%. The GLORIA-AF II registry [27] shows a significant use of OACs in high-risk patients (83.2%), which contrasts with the results of phase I trial, in which ASA was most frequently prescribed. In the GARFIELD-AF and ORBIT-AF II registries, the use of OACs was 69% and 87%, respectively, in patients with a CHA_2DS_2-VASc score of at least 2 points, but with significant geographical heterogeneity [ranges of 31–93% (GARFIELD-AF) and 66–100% (ORBIT-AF II)] In patients with newly diagnosed AF, the use of non-vitamin K antagonist oral anticoagulants increased over time to 43% in 2016 for GARFIELD-AF and 71% for ORBIT-AF II, while antiplatelet monotherapy decreased from

Table 3. The use of oral anticoagulants (OACs) in patients with atrial fibrillation (AF) at high risk of stroke in clinical trials (based on [20–32])

Study/author	When the study was conducted (years)	Proportion of patients treated with OA (%)
ORBIT AF II [20]	2011–2014	87
ATRIUM, Meinertz et al. [28]	2009	87
PREFER IN AF [24]	2012–2013	85.6
GARFIELD-AF/Cools et al. [22]	2012–2016	84.3
GLORIA AF II/Huisman et al. [27]	2011–2014	83.2
Chae et al. [29]	2006–2008	82
Krittayaphong et al. [30]	2014–2017	81.6
EORP-AF [23]	2013–2016	About 80
GARFIELD AF/Dalgaard et al. [31]	2010–2016	73.1
Raji et al. [32]	2007	67.8
Cowan et al. [25]	2009–2012	55
Holt et al. [26]	2007–2010	53
Ding et al. [21]	2001–2004	23

36% to 17% (GARFIELD-AF) and from 18% to 8% (ORBIT--AF I and II) [20]. Table 3 [20–32] presents the results of anticoagulation in the prevention of thromboembolic complications in patients with AF and high risk of stroke in individual registries.

Limitations of anticoagulation in patients at high risk of thromboembolism

Restrictions on the use of OACs in patients at high risk of thromboembolism mainly concern contraindications to the use of drugs from this group. It is estimated that they occur in approximately 13% of patients. However, the ORBIT-AF study [33] found that they are often subjective and many patients who reported them received OACs, suggesting that the perceived benefit outweighed the potential risk of their use. In the study by Steinberg et al. [34] out of 26,684 patients with AF not treated with OAC, 8,283 (31%) had contraindications related to a high risk of bleeding, mainly abnormal blood counts — thrombocytopenia, anemia, hemoglobinopathies, neoplasms of the hematopoietic system and the lymphatic system (75%) or a history of gastrointestinal bleeding (40%). Contraindications to OAC therapy related to a high risk of bleeding are more common in elderly patients with AF. In the study by Polo García et al. [35], approximately 20% of patients with non-valvular AF did not receive anticoagulation. The main reasons were: refusal to monitor coagulation parameters by the patient (37.3%), high risk of bleeding (31.1%), uncontrolled hypertension (27.9%), and frequent falls (27.6%). In a study by Redfors et al. [36], out of 1,300,643 patients, 43,248 (3.3%) had contraindications to anticoagulant therapy and had not received OAC for the last 12 months or died in hospital.

The few absolute contraindications for taking OAC include active major bleeding (where its source must be identified and treated), comorbidities (e.g. severe thrombocytopenia < 50 platelets/L, severe anemia under diagnosis, *etc*.) or recent high-risk bleeding, such as intracerebral hemorrhage (ICH). In such cases, non-pharmacological options may be considered [2]. The limitations mainly apply to older people (over 90 years of age), patients with dementia, after a hemorrhagic stroke or bleeding, with extreme kidney and liver failure, and patients with cancer.

Regarding renal failure, none of the randomized trials of OAC use included patients with end-stage renal disease. Hemodialysis (HD) patients with AF have additional risk factors for stroke due to vascular disease, age, diabetes, and HD treatment. They are also at increased risk of serious bleeding from uremic platelet dysfunction. Anticoagulation treatment increases the risk of bleeding in patients with end-stage renal disease and HD-treated patients up to 10 times compared to warfarin-treated patients with normal renal parameters [37]. Arnson et al. [38] conducted an analysis assessing the safety of OAC use in patients with chronic kidney disease (CKD). The patients enrolled in the study were older and had more comorbidities. The group with the lowest rates of OAC treatment (27.6%) were patients with stages 4–5 of chronic renal failure (CRF). The use of OAC was associated with a reduced risk of stroke and ICH, regardless of the stage of CRF, and a reduced risk of death in patients with CRF in stages 1–3. The risk-benefit ratio of OAC in advanced CKD is a subject of ongoing debate and clinical consideration.

Patients with hepatic impairment may have a higher risk of bleeding with VKAs, while NOACs are associated with a lower risk of bleeding complications. In patients with a known cause of bleeding, preventive measures

should be taken and OAC therapy initiated as soon as possible, focusing on the greatest safety profile of the drug. Advanced liver disease increases the risk of bleeding and affects drug metabolism. Patients with active liver disease and AF are often excluded from clinical trials with OACs. This group of patients, especially those with abnormal blood clotting parameters, may be at greater risk of bleeding events. Kuo et al. [39] found, however, that in patients with cirrhosis, the benefit of reducing the risk of ischemic stroke with NOAC may outweigh the risk of bleeding, compared to the lack of treatment, which supports the use of these drugs.

Patients with cancer and AF are a special group in which anticoagulant therapy is used with caution. Recent analyzes [40, 41] clearly show that NOACs are safe and that compared to VKAs, they have fewer thromboembolic and bleeding complications. Vitamin K antagonists have a number of disadvantages that may particularly interfere with the therapy and treatment of neoplastic diseases. These include interactions with chemotherapy or other medications, food intolerance, and the need to stop treatment because of invasive procedures. Importantly, the risk of bleeding may be increased when using full doses of NOAC in patients with gastrointestinal neoplasms; therefore, special care should be taken in these patients [42].

Summary

Thromboembolism prophylaxis in patients with AF at high risk of thromboembolism is an important element of their management. Over the years, the profile of the patient described as "high-risk patient" has changed. Patients with high CHA_2DS_2-VASc scores always required anticoagulation treatment. It should be stated that risk factors, including comorbidities, can evolve and therefore the patient should be assessed by a physician depending on the specific clinical situation. Nevertheless, NOACs are the safest (and at the same time available) drugs in reducing the risk of thromboembolic complications. These drugs should be first considered when implementing anticoagulant therapy. There are some limitations, such as severe renal failure, liver failure or active cancer, but the latest research shows safety in this respect as well.

Conflict of interest

The authors declare no conflict of interest.

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