Review paper

Atrial fibrillation and atrial flutter – the state of the art. Part 1

Migotanie i trzepotanie przedsionków – aktualny stan wiedzy. Część 1

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Słowa kluczowe: leczenie, ryzyko, udar mózgu, migotanie przedsionków, trzepotanie przedsionków.

Abstract

Despite constantly updating our knowledge on atrial fibrillation and flutter, there are still many questions and doubts about the nature and extent of the arrhythmic and non-arrhythmic consequences of these arrhythmias. In part 1 of the state-of-the-art paper the diagnostic work-up of patients with the 2 arrhythmias has been summarized. The management of patients with atrial fibrillation and flutter requires a multidisciplinary approach in the risk assessment (including stroke) and treatment strategy. Regardless of the type of antiarrhythmic or anticoagulant therapy, benefits must always surpass or at least offset potential adverse effects and drug toxicity.

Streszczenie

Mimo stałego poszerzania i aktualizowania wiedzy na temat nadkomorowych zaburzeń rytmu serca, wiele pytań dotyczących natury i nasilenia arytmicznych oraz pozaarytmicznych konsekwencji migotania i trzepotania przedsionków pozostaje bez odpowiedzi. Stratyfikacja ryzyka ze szczególnym uwzględnieniem udaru mózgu oraz leczenie chorych z migotaniem lub trzepotaniem przedsionków wymaga zaangażowania wielodyscyplinarnego zespołu. Potencjalne ryzyko związane z leczeniem zarówno antyarytmicznym, jak i przeciwkrzepliwym zawsze powinno być mniejsze lub przynajmniej równoważone przez korzyści wynikające z tego postępowania. W pierwszej części niniejszego opracowania przedstawiono postępowanie diagnostyczne u pacjentów z migotaniem lub trzepotaniem przedsionków.

Introduction

Atrial fibrillation (AF) and atrial flutter (AFL) are the 2 forms of supraventricular arrhythmias that pose a significant clinical, social, and economic burden. Their impact on the human body goes beyond arrhythmic issues, and there are still questions and doubts about their nature and consequences.

Both arrhythmias, often coexisting, share some similarities regarding clinical management and possible complications [1, 2]; however, they differ in the underlying disease mechanism. Initially episodic arrhythmia frequently turns into persistent and eventually permanent, as a result of atrial electrophysiological disorganization and anatomical remodelling. AF is characterized by uncoordinated electrical activation of the atria and usually irregular ventricular rhythm (the ventricular rate depends on the electrophysiological properties of the atrioventricular node, the presence of accessory conduction pathways, the function of the autonomic nervous system, and drug therapy), which leads to loss of atrial systole and a decrease in cardiac output, providing a substrate for the development of heart failure (HF). In turn, AFL is characterized by a rapid, ordered atrial rhythm at an average rate of 240–250 bpm and usually a slow ventricular response.

Mechanisms responsible for triggering and sustaining AF are complex and can be divided into 2 categories: focal activity and reentry. The 2 mechanisms may coexist or transform from one into another. AFL can be classified as cavotricuspid isthmus (CTI)-dependent, which accounts for more than 90% of AFL, or atypical when the mechanism does not include the CTI [3]. In the CTI-dependent AFL, a reentrant circuit is in the right atrium, and the CTI between the inferior vena cava ostium and the tricuspid valve is the region of delayed conduction, which is critical for sustaining arrhythmia. In the remaining cases, the underlying mechanism of AFL is macroreentry or microreentry, located both in the left atrium (LA) and right atrium, but not in the CTI.

Diagnosis

Although the surface ECG remains the primary diagnostic tool, the mobile health technologies are

capable of fast screening and detecting AF with high sensitivity and specificity. When AF is detected by a screening tool, including mobile or wearable devices, a single-lead ECG tracing of ≥ 30 s or a standard 12-lead ECG showing AF confirmed by a physician with expertise in ECG interpretation is necessary to establish a definitive diagnosis of clinical AF [4].

In patients with AF, the ECG shows an irregular, multiform f wave occurring at a rate of more than 350 bpm, most prominent in precordial leads V1 and V2, absent P waves, and totally irregular QRS complexes (except complete heart block and a regular escape rhythm). In patients with typical CTI-dependent AFL, the ECG shows regular sawtooth F waves without an isoelectric line between them, best seen in leads II, III, and aVF. In case of atypical AFL, the morphology of the F waves depends on the reentrant circuit anatomy and electrophysiology. In addition, a 2 : 1 (3 : 1 or 4 : 1 less commonly) atrioventricular block is present resulting in a regular ventricular rate, usually of 130–160 bpm; however, the atrioventricular conduction ratio may be changeable [1, 5–8].

Epidemiology

In 2010, the number of individuals with AF was 33.5 million, i.e. approximately 0.5% of the global population, developing in 20.9 million men and 12.6 million women. The annual number of new cases with AF was close to 5 million, which, in line with rising tendency, indicates a rapid increase in the burden of AF, best seen in developed countries [9–12]. It is estimated that 1 in 4 middle-aged adults in Europe and the US will have AF [13] and by 2030 there will be 14–17 million individuals with AF in Europe with 120–215 thousand new cases each year (incidence of 0.23–0.41 per 1000 person/years) [14]. According to estimates the incidence rate will double by 2050 [15]. AF more frequently develops in older adults and in patients with arterial hypertension (HA), HF, coronary artery disease (CAD), valvular heart diseases, obesity, diabetes mellitus (DM), and chronic kidney disease (CKD) [12]. The clinically relevant problem is also postoperative AF, defined as new-onset AF in the immediate postoperative period, occurring in 20–50% of patients after cardiac surgery and less often after noncardiac surgery, with peak incidence between postoperative day 2 and 4. AF and AFL, detected in younger adults (< 60 years of age), without a medical history and/or echocardiographic signs of accompanying cardiovascular and/or respiratory diseases are classified as isolated (or lone) [16, 17]; however, with advances in diagnostic tests and updates on the aetiology of AF and AFL the terms are no longer recommended.

Epidemiological studies on AF are decidedly more numerous than those on AFL, but some of them address the 2 arrhythmias together; therefore, the true incidence of AFL is not clearly established. The Marshfield (Wisconsin) Epidemiologic Study Area (MESA) data on AFL comprising 181 subjects with new-onset AFL showed an incidence of 88/100,000 person/years. The incidence rates ranged from 5/100,000 in individuals < 50 years of age to 587/100,000 in subjects > 80 years of age. Men were 2.5 times more likely than women to have AFL. The incidence of AFL was 3.5-fold greater in patients with HF and 1.9-fold greater in those with chronic obstructive pulmonary disease (COPD). Only 3 patients with AFL (1.7%) had no accompanying diseases. In the MESA cohort, the incidence of AFL was 0.09%, whereas 58% of individuals with AFL also had AF. Deriving from the MESA population-based study, it was estimated that annually in the US there were 200,000 incident cases of AFL, more frequently in men, older people, and patients with HF and chronic obstructive heart disease [18]. Similarly to AF, AFL occurs more frequently in the elderly, those diagnosed with HA, DM, COPD, and HF, excessive alcohol use, and in athletes performing high-intensity interval training. Initially, AFL frequently alternates with AF [7, 8, 18–22].

Clinical consequences of arrythmia

The important clinical implications of AF and AFL include their negative impact on quality of life, increased incidence of HF, stroke, systemic thromboembolism, and an increased risk of death in this population of patients. Patients with AF are 3 times more likely to have HF and 5 times more likely to have stroke than subjects without AF. Patients with AF and stroke have a markedly increased additional risk of death, whereas individuals with AF and non-fatal stroke are at higher risk of serious disability than subjects with stroke without AF. AF increases the risk of hospital admissions [13, 14, 23–28]. Hospitalization is associated with a 2-fold increase in overall mortality in women and a 1.5-fold increase in men [12–14, 26]. It has been shown that postoperative AF is a risk factor for stroke, myocardial infarction (MI), and death like non-postoperative AF. Moreover, long-term stroke risk was substantially higher with non-cardiac than cardiac postoperative AF [4].

The clinical presentation of AFL largely depends on the heart rate, which is rapid in most cases and may cause arterial hypotension, angina symptoms, HF, syncope, and palpitations. The likelihood of stroke and thromboembolic events in patients with AFL is usually evaluated in relation to coexisting AF, which may influence the accuracy of risk assessment. The incidence of left atrial thrombus (LAT) and/or left atrial appendage thrombus (LAAT) and the probability of thrombotic events seem to be lower in patients with AFL than in those with AF, nevertheless thromboembolic risk in AFL is still high. Furthermore, frequent coexistence of the two arrhythmias provides a strong argument for antithrombotic prophylaxis in patients

with AFL on the same basis as in those with AF. However, randomized prospective studies are warranted to fully clarify this issue [8, 19–22, 29–38].

Thrombotic complications

In the context of AF, AFL and stroke, LAT and/or LAAT have been found to place patients at highest stroke risk. Moreover, original studies and a recent meta-analysis revealed evidence that the left-sided atrial septal pouch (LASP), in the presence of blood stasis of left atrium like in AF, may be a source of intracardiac thrombotic masses, and LASP is associated with increased stroke risk [39]. Studies in patients without anticoagulation therapy with valvular AF (in the current guidelines the term "valvular AF" refers to patients with AF and accompanying mitral stenosis (MS) and to patients with AF and mechanical valve prostheses) show that the incidence of LAT ranges from 25 to 55% [40–42], in patients without anticoagulation therapy with nonvalvular AF (in the current guidelines the term "nonvalvular AF" refers to patients with AF without the accompanying MS and to patients with AF without mechanical valve prostheses) the incidence of these events seems lower, but not well defined [43, 44]. In patients with valvular AF thrombi are located in the left atrial appendage (LAA) or in the LA in 57% of cases, and in patients with nonrheumatic AF thrombi are located in the LAA in 9% of cases [44]. Depending on the study group, in patients with AF on oral anticoagulation (OAC) the incidence of LAT and/or LAAT varies from 0.6 to 8.2% [45–53]. Currently, regardless of chronic OAC, transoesophageal echocardiography (TEE) is performed relatively widely, mainly in search of LAT and/or LAAT, before referral of patients with AF and AFL for direct current cardioversion (DCC) or electrophysiological procedures. If they are present, DCC and ablation are cancelled [12]; however, there are no clinical studies on intracardiac thrombi and the above-mentioned therapeutic procedures, as well as recommendations on patient management in this clinical context are based mainly on expert opinion. Several clinical studies evaluated the incidence of LAT and/or LAAT in patients with AF and AFL on chronic OAC therapy and referred for DCC. In a multicentre analysis of a large population (n = 1286) of patients with AF undergoing TEE before DCC thrombi were found in 4.7% of the patients, more frequently in patients receiving vitamin K antagonists (VKA) (5.3%) as compared with non-vitamin K oral anticoagulants (NOACs) (2.5%) (p = 0.02), and the independent risk factors for intracardiac thrombi included a history of embolism, arterial hypertension, tachyarrhythmia-induced cardiomyopathy, increasing body mass index (BMI), lack of anticoagulation, higher levels of creatinine, lower glomerular filtration rate, delayed flow through LAA, and spontaneous echocardiographic contrast (SEC) during TEE [47]. In a Korean study of 424 patients, thrombi were present in 2.2% of patients referred for DCC during VKA treatment as compared to 4.3% of patients receiving NOACs (p = 0.281) [46]. In a group of 510 Italian patients with AF lasting > 48 h treated with VKA (0.6%) and dabigatran (0.6%) the incidence of thrombi before DCC was very low [45]. In another study, in a large population of 2150 patients with AF undergoing DCC the rate of thromboembolic complications was very low, and in patients receiving VKA there were only 2 such cases (2/1466), and in those on NOACs only 1 event (1/684) (risk ratio (RR) = 1.07; 95% CI: 0.10–11.81); however, not all patients underwent TEE before DCC [54]. In a study by Kawabata *et al.* in a Japanese population of patients with "nonvalvular" AF on chronic OAC therapy, LAAT was diagnosed in 2.7% (15/559) of patients, and the incidence of thrombi was comparable in groups receiving warfarin and NOACs. Furthermore, thrombi did not occur in patients with a CHA_2DS_2-VASc score of 0, as well as in patients with paroxysmal AF without a history of TIA or stroke, whereas serum BNP concentration ≥ 173 pg/ml was an independent predictor of LAAT [55].

Thrombus risk assessment

The current guidelines recommend using the CHA_2DS_2-VASc scoring system to define risk factors for stroke and thromboembolic disease in patients with AF and AFL, but it is not yet established whether it is an adequate diagnostic tool for predicting the occurrence of LAT and/or LAAT in patients with "nonvalvular" AF and AFL lasting for more than 48 h and receiving chronic OAC therapy. In a study by Zoppo *et al.* the incidence of LAAT was 2.3% in patients on long-term warfarin anticoagulation referred for ablation due to drug-resistant AF and enlarged LA, and higher CHA_2DS_2-VASc scores were found to be independent risk factors for thrombi [56]. Dorenkamp *et al.* revealed that in patients with drug-resistant AF, who were referred for pulmonary vein isolation on chronic anticoagulant therapy, LAT/LAAT was diagnosed in 7 (2.1%) individuals, and DM, $CHADS_2 \geq 3$ and CHA_2DS_2-VASc ≥ 4 were identified as independent predictors of LAT/LAAT [57]. In a study by Yamamoto *et al.* in 564 patients who were candidates for ablation of symptomatic, drug-resistant AF, TEE revealed LAAT in 36 (6.4%) patients, and the independent predictors were higher $CHADS_2$ score, lower left ventricular ejection fraction (LVEF), increased SEC in LAA on TEE, larger LA volume, and an increased number of LAA lobes [58]. Scherr *et al.* detected 12 thrombi on 732 TEE scans, i.e. in 1.6% of patients referred for AF ablation on chronic OAC therapy, all these events developed in patients with LA size ≥ 45 mm, multivariate analysis showed that $CHADS_2 \geq 2$ and larger LA size were independent predictors of thrombi [59]. A meta-analysis by Zhan *et al.* demonstrated that arterial hypertension, conges-

tive HF, age, female gender, structural heart disease or cardiomyopathy, antiarrhythmic therapy, duration of atrial fibrillation, and higher $CHADS_2$ or CHA_2DS_2-VASc scores were clinical risk factors for LAT/LAAT in patients with AF. Additionally, BNP > 75 pg/ml, reduced LVEF, enlarged LA, low LAA flow velocity and SEC in LAA on TEE were the predictors of LAAT [60]. In a study by Kapłon-Cieślicka *et al*. in 1033 patients with AF on chronic anticoagulant therapy referred for ablation or DCC, LAAT was demonstrated on TEE in 59 (5.7%) patients, and multivariate analysis identified independent predictors of LAAT, i.e. HF, higher CHA_2DS_2-VASc scores, duration of AF (both persistent and permanent AF increased the risk of LAAT and the odds ratio was 5.76 and 13.02, respectively), eGFR < 56 ml/min/1.73 m^2, and age ≥ 75 years [50]. Some clinical studies demonstrate that the CHA_2DS_2-VASc score can be a valuable diagnostic tool for prediction of LAAT in patients with AF on anticoagulant therapy, whereas some other studies show single clinical variables incorporated into the CHA_2DS_2-VASc score as predictive factors for LAAT. Unfortunately, it is not clear whether the CHA_2DS_2-VASc scoring system is a sufficiently precise diagnostic tool to differentiate the patient with LAAT from the patient without LAAT and whether in this clinical context the system should be expanded to include additional parameters such as laboratory biomarkers or parameters evaluating the mechanics of individual heart chambers.

The incidence of LAT and/or LAAT in patients with AF on OAC therapy seems lower than in patients with AF not receiving OAC therapy. It should, however, be noted that studies directly comparing the 2 patient populations regarding the incidence of LAT and/or LAAT are lacking; therefore, conclusions on the prevalence of LAT and/or LAAT in patients with AF depending on the anticoagulation status may only be indirect. One should also remember that patient populations in different studies differed with respect to clinical characteristics. Unfortunately, with respect to LAT and/or LAAT in patients with AF and AFL on chronic OAC therapy, there are no studies that would define the actual health hazard related to these masses in this population of patients. In view of the foregoing, it is not clear whether it is justified to traumatize and expose the patient to potentially serious TEE-associated complications in an active search for LAT and/or LAAT. Currently, the only thing certain in relation to LAAT in patients with AF and AFL on OAC therapy is that the diagnosis of such a condition complicates the process of treatment, because DCC and ablation are cancelled.

The current guidelines for the management of AF and AFL recommend identification and treatment of accompanying structural heart diseases and other predisposing conditions, actions dedicated to symptom alleviation, improvement of quality of life and functional abilities, management aiming at reducing morbidity and mortality, and especially preventing tachycardia-induced cardiomyopathy, stroke, and generalized thromboembolic disease, which may indirectly decrease their incidence or prevent visits in emergent help centres or hospitalizations [12, 61, 62]. All these issues are equally important, but the key issue in patients with AF and AFL is prevention of stroke. It is very important to understand the mechanisms responsible for these events to stratify the risk and provide effective preventive treatment.

Stroke – epidemiology and risk assessment

The epidemiology of stroke in patients with AF is well documented. A 24-year follow-up of the Framingham population revealed that stroke was 17.56 times more common in patients with AF and rheumatic heart disease than in patients without AF, and 5.6 times more frequent in patients with AF and without rheumatic heart disease than in patients without AF, the annual incidence of stroke in both AF groups was approximately 4.2% [63]. In the AFASAK study, the annual incidence of thromboembolic events, mainly stroke, was 5.5% in patients with AF and without rheumatic heart disease receiving placebo [64]. In the Stroke Prevention in Atrial Fibrillation (SPAF) study the annual incidence of thromboembolic events and stroke was 7.4% in patients with AF receiving placebo [65]. In the Canadian Atrial Fibrillation Anticoagulation (CAFA) study the annual incidence of stroke was 5.2% in patients with AF receiving placebo [66].

In 2016, globally there were 67.8 million new cases of ischaemic stroke, with an increase of 2.7% in its incidence between 2006 and 2016 [67]. It is estimated that 15–31% of stroke cases are directly related to AF, and it has been suggested that the rate may be underestimated [37], but the direct relationship between stroke and AF/AFL should be described in terms of probability rather than certainty. Currently, there are no diagnostic tools which can confirm or exclude the association between these conditions, especially in patients receiving OAC therapy; therefore, the actual rate of stroke events directly related to these arrhythmias is not known. It is often taken for granted that a large number of strokes in patients with AF and AFL are caused by cerebral thromboembolism from the LA or LAA [38, 43, 44, 68, 69]; however, other pathophysiological mechanisms may be responsible for stroke in these patients, especially in the elderly. Therefore, the actual number of stroke cases directly related to these arrhythmias in the context of thromboembolism in comparison with other diseases (including diseases of the aorta and carotid arteries) is not known [70–76]. Regardless of doubts about the association between ischaemic stroke and AF/AFL, a characteristic feature of these arrhythmias is the most frequent (of all cardiovascular diseases) coexistence with ischaemic stroke.

However, correlation does not imply causation. In the Trial of Org 10172 in Acute Stroke Treatment (TOAST) cardioembolic stroke was diagnosed in patients with cerebral artery occlusion, probably caused by debris from a cardiac source in the patient with clinical features suggesting this aetiology, for instance in the presence of artificial heart valves, MS with accompanying AF, LAT/LAAT, AF, AFL, MI, dilated cardiomyopathy, segmental left ventricular wall motion abnormalities, myxoma, infective endocarditis, persistent patent ovale, congestive heart failure, after exclusion of potential embolism due to large artery atherosclerotic occlusive disease [77]. The TOAST study identified 5 subtypes of stroke depending on its aetiology, i.e.: 1) stroke related to intracranial large artery atherosclerosis, 2) cardioembolic stroke, 3) stroke related to small vessel occlusion, 4) stroke of other determined aetiology, and 5) stroke of undefined origin. This classification was established taking into account the clinical features of stroke and data collected using additional diagnostic tools such as brain imaging (computed tomography, magnetic resonance), cardiac imaging (echocardiography), extracranial ultrasound, arteriography, and laboratory tests for hypercoagulability. However, one should realize that the clinical features of stroke superimpose on brain imaging findings and are not specific for any subtype of ischaemic stroke [77]. Potentially, there are numerous causes of stroke, especially in the elderly with additional risk factors such as obesity, arterial hypertension, DM, or cigarette smoking. In this era of endovascular interventions mechanical thrombectomy has become not only a promising therapeutic option, but also provides a unique opportunity to obtain thrombotic material for further analysis and identification of the most likely mechanism of stroke. Thrombotic material, being a conglomerate of fibrin, blood platelets, erythrocytes, and leukocytes, differs markedly between cardiogenic and non-cardiogenic stroke. In cardioembolic stroke defined according to the TOAST classification the embolic material contains a higher proportion of fibrin than red blood cells as compared with non-cardiogenic embolic material [75, 78–80]. However, the controversy still exists. Kim *et al*. demonstrated that the cardiogenic embolic material contained a higher proportion of red blood cells than fibrin as compared with the non-cardiogenic embolic material [81]. In 2017, a systematic review of the correlation between stroke aetiology and histopathological picture of thrombi obtained during mechanical thrombectomy in acute ischaemic stroke revealed no relationship between thrombus histology and stroke origin [72]. Perhaps a unified approach to thrombus procurement during thrombectomy in acute stroke and standardization of histopathological evaluation of thrombotic material will allow for precise differentiation between cardiogenic and non-cardiogenic stroke to provide specific treatment. As we can see, the identification of stroke aetiology is a complex process that does not give definite answers. In view of the foregoing, AF and AFL (which frequently are not independent entities, but a symptom or result of another disease) should be regarded as risk markers for stroke encouraging an active search for and treatment of coexisting pathologies, which visibly increase the risk of stroke. With respect to thromboembolic aetiology of stroke it is important not only to define the underlying mechanism responsible for intracardiac thrombogenesis but also to identify pathophysiological processes responsible for thrombus migration to the systemic circulation. Having the right answers to these questions we could implement preventive interventions. In patients with AF, AFL and thrombotic stroke, clots may be in the LA, especially in the LAA [38, 43, 44, 68, 69]. The formation of thrombus in the LA and LAA appears a very complex process, which is probably dependent on factors that can be divided into 3 groups. The first group consists of factors related to mechanical function of the LA and LAA, the second group encompasses factors related to biochemical properties of blood flowing through the heart, and the third group includes factors related to the structure of endocardium and endothelium of the LA and LAA [82–84]. These factors in various combinations may be responsible for triggering the formation of LAT and/or LAAT. Bearing in mind the risk factors for stroke, patients with AF and AFL referred for DCC require special attention. Sinus rhythm restoration places patients at increased risk of stroke and thromboembolic events. Regardless of the type of cardioversion (electrical or pharmacological), in patients without prior OAC treatment cardioversion is associated with a 5–7% risk of stroke and thromboembolic complications [85]. Procedure-related risk of stroke and thromboembolic events may be reduced to 0.3–1.9% by using appropriate OAC [86–90]. In 1960, Goldman proposed that ischaemic stroke complicating cardioversion is a consequence of pre-existing thrombus in the LA migrating to the systemic circulation after the restoration of sinus rhythm [91]. Thrombi discovered during imaging before cardioversion are still considered as predictors of ischaemic stroke. Embolic complications after DCC in AF/AFL may also occur despite the absence of thrombi on TEE immediately before cardioversion [92]. This may be a result of transient atrial mechanical dysfunction, called atrial stunning, which is observed after cardioversion of AF and AFL and lasting even for a few weeks [30, 93–95]. The formation of LAT/LAAT and direct relationship between thrombus and stroke is an intricate process [96, 97] and a multidimensional, not solely mechanistic approach is needed. However, there is a paucity of evidence showing that AF or AFL is an indispensable component of intracardiac thrombogenesis. The newest clinical data suggest that the morphologically and

structurally altered atrium may be a substrate for thrombogenesis, leading to stroke even in the absence of arrhythmia [98]. Undoubtedly, both arrhythmias delay blood flow through the heart, particularly in the LAA, but from the clinical viewpoint it is doubtful whether such an isolated pathophysiological state can initiate thrombus formation. Isolated blood flow disorders, resulting only and exclusively from the pathophysiological nature of these arrhythmias, is not a sufficient substrate for intracardiac thrombogenesis. There should be additional variables, for instance altered morphology of the atrium, including the endothelium or disorders of blood coagulation [82, 84, 99–102], or much more severe blood flow abnormalities, which occur in patients with accompanying HF, especially with reduced LVEF or during atrial stunning after cardioversion. The process of atrial thrombogenesis is a very complex clinical problem, and a question of the health hazard is even more complicated after taking into account the fact that ischaemic stroke occurs at a comparable rate regardless of therapeutic strategy, i.e. rate control strategy or rhythm control strategy [103–105].

If we agree that LAT and/or LAAT are the main causes of stroke and systemic embolic events in patients with AF or AFL, the question arises of whether such a thrombus constitutes the same health hazard regardless of anticoagulation status. The risk of stroke attributed to LAAT in patients with AF and AFL on chronic OAC therapy appears lower than in patients without such therapy. Unfortunately, the actual health hazard associated with this pathological mass in different patient populations is not known. Additionally, the risk may be modified by a number of accompanying clinical states, degree of damage to cardiac structures, and medical interventions undertaken by the patient. There are several diagnostic tools to define the risk of stroke and thromboembolic complications with intention to treat. The $CHADS_2$ score is the primary tool that assigns 1 point each for congestive heart failure, high blood pressure, age ≥ 75 years, and DM and 2 points for a previous stroke or transient ischaemic attacks [106]. Unfortunately, this system insufficiently differentiates people with very low risk from people with low but clinically significant risk of stroke, in whom OAC therapy could have a good risk-benefit ratio. In these circumstances $CHADS_2$ has been expanded to include additional risk factors. The new CHA_2DS_2-VASc score assigns 1 point each for congestive heart failure/LVEF ≤ 40%, high blood pressure, DM, and vascular disease (a history of MI, peripheral vascular disease or aortic atherosclerosis), 1 point for female gender, 2 points for previous stroke/transient ischaemic attacks/a history of thromboembolic disease, and 2 points for age ≥ 75 years [107, 108]. The CHA_2DS_2-VASc score is now recommended for stratifying risk of stroke and thromboembolic complications in patients with AF (excluding patients with moderate and severe MS, mechanical valves, and hypertrophic cardiomyopathy) to establish indications for OAC therapy [12, 109].

The CHA_2DS_2-VASc score refers to risk of stroke and thromboembolic complications, where the score 0 is considered low, score 1 means moderate risk, and score ≥ 2 is high risk of stroke and thromboembolic events [107]. The score has not been validated to evaluate risk of stroke and thromboembolic complications in patients with AFL, but the current guidelines for the management of AF recommend this score both in patients with AFL and in patients with AF [12, 62, 110]. Although the CHA_2DS_2-VASc score is now a recommended tool, the questions arise of whether it is an optimal system, whether it encompasses all significant risk factors, and whether it adequately evaluates the parameters.

Anticoagulation and bleeding risk

Anticoagulation is associated with increased risk of bleeding. Therefore, risk assessments of both stroke and bleeding in patients with AF are necessary in clinical practice, and these risks should be balanced for optimal use of OAC. The HAS-BLED risk score is well established for assessment of the major bleeding risk and is a recommended in the current guidelines for AF. This diagnostic tool is designed to identify specific risk factors for bleeding and considers clinical states such as hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, old age (> 65 years), and drugs/alcohol concomitantly [111]. An HAS-BLED score of 3 or more indicates a high bleeding risk; however, in the absence of contraindications for OAC (such as relevant bleeding particularly with relapses, adverse drug reactions, frequent falls/frailty, occupational risk, the individual patient's refusal), the HAS-BLED score should not be used on its own to exclude AF patients from oral anticoagulation therapy [4, 12, 112]. Anticoagulant therapy in AF patients at high bleeding risk and in a population with recent major bleeding or previous intracranial haemorrhage (ICH) is always challenge. In patients with the bleeding event, attention should be directed towards addressing the predisposing pathology, and the reinstitution of the oral anticoagulant therapy may require a multidisciplinary team decision balancing stroke reduction against serious bleeding. The most serious and often deadly complication of anticoagulant therapy is the ICH. In these, who survived the ICH at high risk of AF-related ischaemic stroke, the reintroduction of OAC, with preference for NOACs over VKAs in NOAC-eligible patients should be considered. However, the optimal time for reinitiate of anticoagulation after ICH is unknown, but should be delayed beyond the acute phase, probably for at least 4 weeks. In case of high risk of recurrent ICH and/

or contraindications for long-term anticoagulant treatment, the percutaneous left atrial appendage occlusion (LAAO) may be considered for stroke prevention in select patients with nonvalvular AF. Nevertheless, the LAAO can cause serious complications including incidence of post-procedure bleeding or a device-related thrombus, especially early after implantation, before endothelization of the device [4, 113]. It should be noted that the non-inferiority of LAAO to VKA treatment was mostly driven by the prevention of haemorrhagic stroke, with a trend for more ischaemic strokes [4]. As mentioned, some agents like antiplatelet or non-steroidal anti-inflammatory drugs increase bleeding risk, particularly in anticoagulated patients with AF and an indication for the concomitant antiplatelet therapy. In these patients, it is recommended that NOACs be used in preference to VKA. In patients at high bleeding risk (HAS-BLED ≥ 3) in combination with single or dual antiplatelet therapy, reduced dosage of rivaroxaban, dabigatran, and VKA should be considered. After percutaneous coronary intervention for AF patients with acute coronary syndrome and chronic coronary syndrome, dual antiplatelet therapy is recommended for no more than a week when the risk of stent thrombosis is lower than the bleeding risk or bleeding risk prevails the risk of stent thrombosis, irrespective of the type of stent used. If the risk of stent thrombosis outweighs the bleeding risk, cessation of aspirin after one month is recommended and dual antiplatelet therapy with an OAC and P2Y12 inhibitor (preferably clopidogrel) should be continued [4].

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Conflict of interest

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