TOPICS IN REVIEW

Antithrombotic therapy in atrial flutter: To anticoagulate or not, that is the question

Fabian Wesołek, MD,[1] Przemysław Szyszka, MD,[1] Małgorzata Cichoń, MD, PhD,[1,2] Katarzyna Mizia-Stec, MD, PhD,[1,2,3] Maciej T. Wybraniec, MD, PhD[1,2,3]

From the [1]First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland, [2]Upper-Silesian Medical Center, Katowice, Poland, and [3]Member of the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart).

Atrial fibrillation (AF) represents an arrhythmia fraught with significant morbidity, mortality, and financial burden for the health care system. Less attention is given to atrial flutter (AFL), which may occur as a stand-alone arrhythmia or coexist with AF in the same patient. Moreover, it is known that AF frequently develops after AFL ablation. Despite different pathophysiologies of AF and AFL, current guidelines provide identical indications for anticoagulation therapy in both arrhythmias, given the lack of trials in patients with AFL. This study attempts at providing an up-to-date literature review on the thromboembolic risk profile in AFL, focusing on differences between AFL and AF. Echocardiographic studies showed that the presence of spontaneous echocardiographic contrast (SEC) and thrombus are much less prevalent in patients with AFL than in those with AF. Patients with AFL had overall better left atrial appendage (LAA) function and lower coagulation marker levels than did patients with AF. Observational studies showed a significantly lower risk of stroke in patients with AFL than in those with AF. One study found a significantly higher ischemic stroke incidence in the AFL cohort only at CHA_2DS_2-VASc scores from 5 to 9 than in patients without AF or AFL. These findings imply that the thromboembolic risk inherent in AFL seems lower than that in AF. This should be considered in the context of a high chance of permanent AFL termination after successful cavotricuspid isthmus ablation, in contrast to the chronic clinical nature of AF. Although thromboembolic risk exists in AFL, prospective studies are warranted to establish the true prothrombotic properties of AFL, allowing the reassessment of anticoagulant treatment strategy.

KEYWORDS Atrial flutter; Atrial fibrillation; Stroke; Thromboembolism; Anticoagulation

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Introduction

Atrial flutter (AFL) is an atrial macroreentrant tachyarrhythmia with an atrial rate between 250 and 350 beats/min. The prevalence of AFL is 88 cases per 100,000 person-years overall, and AFL is significantly rarer than atrial fibrillation (AF).[1,2] In clinical practice, 2 types of AFL are recognized: typical, which is dependent on cavotricuspid isthmus (CTI); and atypical, where the source of arrhythmia is independent of CTI, most commonly related with atrial scar–dependent macroreentry circuit within the left or right atrium.

It is well known that AF and AFL often coexist in 1 patient and that AFL may precede AF,[3] including patients undergoing successful CTI ablation.[4] Although AFL can occur as an isolated atrial arrhythmia, it is known that a significant proportion of patients later develop AF,[3] particularly after AFL ablation.[4] AF can degenerate into AFL after treatment with class Ic antiarrhythmic drugs (propafenone).[5–7] For this reason, treatment with Vaughan Williams class Ic drugs, such propafenone or flecainide, should prompt the simultaneous use of β-blockers in order to avoid the risk of rapid 1:1 conductance in the course of AFL.[8] Also, AFL typically represents a more symptomatic disorder than AF because of the initially high ventricular rate. Also, AFL is less prone to pharmacological cardioversion with class I and III antiarrhythmic drugs according to the Vaughan Williams classification (ibutilide and dofetilide being the most effective); hence, electrical cardioversion is the preferred initial option for rhythm control management.[9] Typical atrial AFL may be easily terminated using overdrive pacing.[10]

Both arrhythmias share identified and presumed multiple risk factors such as age, male sex, heart failure, valvular heart disease, hypertension, smoking, chronic obstructive pulmonary disease, and prolonged PR interval.[2,11–14] Furthermore, a meta-analysis by Youssef et al[15] has shown that obstructive sleep apnea is strongly associated with the development of AF. Recent studies present differences in risk factors for both arrhythmias.

Address reprint requests and correspondence: Dr Maciej T. Wybraniec, First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, 47 Ziołowa St, 40-635 Katowice, Poland. E-mail address: maciejwybraniec@gmail.com.

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KEY FINDINGS

- *Pathophysiology:* Preserved left atrial (LA) mechanical function observed in typical atrial flutter (AFL), reflected by mitral inflow, contradicts the necessity of antithrombotic treatment, while LA mechanical dysfunction present in atypical AFL and common atrial fibrillation (AF) and AFL coexistence speak in favor of anticoagulation.
- *Current evidence:* Echocardiographic studies showed that the presence of spontaneous echo contrast and thrombus are much less prevalent in patients with AFL than in those with AF. Patients with AFL had overall better left atrial appendage function and lower coagulation marker levels than did those with AF. Observational studies showed a significantly lower risk of stroke in patients with AFL than in those with AF.
- *Guidelines and suggested amendment:* According to current guidelines, chronic oral anticoagulation (OAC) in AFL regardless of its type should be applied on the basis of CHA_2DS_2-VA score or planned cardioversion or ablation procedure. One should strongly consider withdrawal of OAC after successful cavotricuspid isthmus ablation in typical AFL after 2 months of postprocedural anticoagulation therapy, as the success rate of the procedure is excellent, provided that no AF is detected on prolonged electrocardiographic monitoring.
- *Future:* Further studies, especially prospective ones comparing patients with AFL with low thromboembolic risk with and without anticoagulant treatment, are required.

Mareedu et al[16] compared patients with AFL and those with AF and found that patients with AFL were more likely to have a history of chronic obstructive pulmonary disease, heart failure, and smoking. On the contrary, patients with AF were more likely to have a history of hypertension.[16] In another study by Rahman et al,[12] individuals with AFL compared to AF were less likely to have valvular heart disease and had a longer PR interval. All in all, patients with AFL are more likely to have structural heart disease, especially in case of atypical AFL after surgical interventions. Typical AFL may be the first manifestation of coronary artery disease (CAD) and should prompt noninvasive stress imaging toward myocardial ischemia, as AFL conferred a 5-fold higher risk of significant coronary stenoses than did AF.[17]

Despite different pathophysiologies of AF and AFL translating into diverse mechanical function of atria and thromboembolic risk, current guidelines provide identical indications for anticoagulation therapy in both arrhythmias, given the lack of trials in patients with AFL. This study attempts at providing an up-to-date literature review on the thromboembolic risk profile in AFL, focusing on differences between AFL and AF.

Current recommendations

2024 European Society of Cardiology guidelines for the management of AF

According to the latest European Society of Cardiology guidelines for the management of AF, clinicians should follow the AF-CARE pathway, where AF stands for *a*trial *f*ibrillation, C for *c*omorbidity and risk factor management, A for *a*void stroke and thromboembolism, R for *r*educe symptoms by rate and rhythm control, and E for *e*valuation and dynamic reassessment. The current guidelines also recommend applying these principles to patients with solitary AFL, including periprocedural management of stroke risk.[18]

Long-term anticoagulant treatment

The overall thromboembolic risk assessment to decide whether patients with AF need oral anticoagulation (OAC) is based on the CHA_2DS_2-VA scale, and a score of ≥ 2 is recommended (class I, level C) while a score of 1 should be considered as an indicator of elevated thromboembolic risk (class IIa, level C). Direct oral anticoagulants (DOACs) are preferred over vitamin K antagonists on account of a lower risk of severe bleeding, including intracranial hemorrhage (class I, level A). These rules do not apply to patients with AF and prosthetic mechanical heart valves and moderate to severe mitral stenosis for which the guidelines recommend the use of vitamin K antagonists (class I, level A).

Periprocedural anticoagulant treatment

It is important to raise the subject of periprocedural management in AFL including cardioversion and catheter ablation. According to guidelines, anticoagulation treatment before procedures should be initiated as soon as possible.

Before cardioversion, the period of uninterrupted anticoagulation treatment should be 3 weeks; alternatively, transesophageal echocardiography (TEE) should be performed in order to exclude the presence of thrombus within the LAA[18] (class I, level B). In case of an arrhythmic episode of <48 hours, cardioversion may be pursued after a single DOACs or heparin dose. After cardioversion, a minimum of 4 weeks of OAC is required in patients with thromboembolic risk factors irrespective of whether sinus rhythm is achieved [8] (class I, level B).

In patients undergoing pulmonary vein isolation for AF, CTI ablation for typical AFL, or right or LA macroreentry tachycardia ablation for atypical AFL, OAC should be initiated at least 3 weeks before ablation (class I, level C). As an alternative, TEE may be performed so as to exclude the presence of thrombus within the LA. The local practice at the authors' institutions is to perform TEE before any LA ablation despite adequate anticoagulation. After ablation, a minimum of 2 months of treatment is required regardless of the CHA_2DS_2-VA score or rhythm outcome, after which

long-term continuation of treatment depends on the patient's stroke risk profile (class I, level C).

2023 Heart Rhythm Society/American College of Cardiology/American Heart Association guidelines for the management of AF

These guidelines recommend that every patient with AF should be assessed for the annual risk of thromboembolic events by using a validated scale such as CHA_2DS_2-VASc score (class I, level B).[19] Anticoagulation is recommended for patients with AF and an estimated annual thromboembolic risk of $\geq$2% per year (eg, CHA_2DS_2-VASc score of $\geq$2 in men and $\geq$3 in women) (class I, level A) and is deemed as reasonable for patients with AF and an estimated annual thromboembolic risk of $\geq$1% but $<$2% per year (equivalent to CHA_2DS_2-VASc score of 1 in men and 2 in women) (class IIa, level A). In patients with AF who are candidates for anticoagulation, DOACs are recommended over warfarin if patients do not have a history of moderate to severe rheumatic mitral stenosis or a mechanical heart valve (class I, level A).

These guidelines consider anticoagulation management in typical AFL, and anticoagulation therapy is recommended for the same risk profile as in AF (class I, level B) and in patients who undergo successful cardioversion or ablation, resulting in restoration of sinus rhythm; anticoagulation should be continued for at least 4 weeks postprocedure (class I, level C). Furthermore, patients with typical AFL after successful CTI ablation and with previously detected AF before AFL ablation should receive OACs after ablation, as indicated for AF (class I, level A). Patients with typical AFL who have undergone successful CTI ablation and are deemed to be at high thromboembolic risk, without any known history of AF, should receive close follow-up and arrhythmia monitoring to detect silent AF if they are not receiving ongoing anticoagulation in view of the significant risk of AF (class I, level B). In patients with typical AFL who have undergone successful CTI ablation without any known history of AF and who are at high risk of developing AF (eg, LA enlargement, inducible AF, chronic obstructive pulmonary disease, and heart failure), it may be reasonable to prescribe long-term anticoagulation if thromboembolic risk assessment suggests high risk (>2% annual risk) for stroke (class IIb, level B).

Diagnosis of AFL and differentiation from AF

Given the evidence of misdiagnosis of AFL and the lack of distinction between this arrhythmia and AF,[20–22] it is important to raise the topic of diagnosing these arrhythmias with an electrocardiogram (ECG), as an incorrect diagnosis may lead to inappropriate treatment, including anticoagulation therapy.[22]

In typical AFL, there is an atrial rate of 240–350 beats/min accompanied by the so-called sawtooth flutter pattern, that is, a regular continuous waveform with negative deflections in the inferior leads II, III, and aVF and low-voltage deflections in leads I and aVL.[23] Lead V_1 deflections can be positive, biphasic, or negative. On the contrary, reverse typical flutter shows round or bimodal positive deflections in the inferior leads II, III, and aVF, with a characteristic bimodal W-shaped negative wave in lead V_1.[23]

Atypical AFL is defined as any tachycardia that corresponds to a continuous waveform pattern on the ECG, but differs from the patterns described above.[23]

The 2024 European Society of Cardiology guidelines and the 2023 American College of Cardiology/American Heart Association guidelines similarly define AF on the ECG as irregular R-R intervals (when atrioventricular conduction is not impaired), no distinct P waves, and irregular atrial activation.[18,19] It is important to underscore the differentiation between atrial tachycardia (AT) and AFL, which may be cumbersome. In AT, the rate of atria is thought to be <240 beats/min and an isoelectric line is present between the P waves.[18,19]

It is also worth noting that in patients with cardiac implantable electronic devices such as pacemakers/implantable cardioverter-defibrillators, the so-called atrial high rate episodes (AHREs), that is, episodes with atrial rate > 180 beats/min, that last longer than 5 minutes are found. Although such a finding indicates the possibility of AF or AFL, it is not a clear diagnosis and, in such situations, differentiation between both arrhythmias on the basis of the electrogram may be challenging or even impossible. The indications for OAC in patients with AHREs, without ECG proof of AF or AFL, are the matter of debate, as 2 large randomized controlled trials have provided conflicting results.[24,25] The recent NOAH-AFNET 6 (Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) trial focused on comparing the efficacy and safety of edoxaban therapy vs no anticoagulation in $\geq$65 years old patients with AHREs detected by implantable devices and at least 1 additional stroke risk factor.[24] The *primary efficacy outcome event*, which was defined as cardiovascular death/stroke/systemic embolism, occurred in 83 patients (3.2% per patient-year) treated with edoxaban vs 101 patients (4.0% per patient-year) in the placebo group (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.60–1.08; $P = .15$). The incidence of stroke was similar in both groups at ~1% per patient-year, and edoxaban treatment led to a higher incidence of death or major bleeding (149 patients [5.9% per patient-year] vs 114 patients [4.5% per patient-year] in the placebo group) (HR 1.31; 95% CI 1.02–1.67; $P = .03$). On the contrary, the ARTESIA (The Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Subclinical Atrial Fibrillation) trial involved patients with subclinical AF detected by an implanted pacemaker, defibrillator, or cardiac monitor and stroke risk factors, treated with apixaban or aspirin, in whom the rates of stroke, systemic embolism, and major bleeding were assessed.[25] The use of apixaban significantly reduced the incidence of stroke/systemic embolism, which occurred in 55 patients (0.78% per patient-year) vs

86 patients in the aspirin group (1.24% per patient-year) (HR 0.63; 95% CI 0.45–0.88; $P = .007$). However, apixaban treatment resulted in a higher rate of major bleeding (1.71% per patient-year vs 0.94% per patient-year in the aspirin group) (HR 1.80; 95% CI 1.26–2.57; $P = .001$) and more fatal bleeding (5 patients vs 8 patients in the aspirin group). As the results of these studies are contradictory, this suggests that in patients with AHREs, ECG confirmation of AF/AFL may be crucial for the implementation of OAC and thus for better outcomes.

Diverse pathophysiology: AFL vs AF

AFL constitutes a relatively uncommon arrhythmia, which occurs ~10 times less frequently than AF.[2] Considering the pathophysiology of AFL, it is necessary to distinguish the types of this pathology. The most common type is typical AFL conditioned by the presence of a macroreentry circuit that is primarily located within the right atrium and which is traversed by the wavefront positioned around the tricuspid valve and isolated anteriorly. The circuit allows the wavefront to rotate in either a counterclockwise (vast majority) or a clockwise direction. The LA does not participate in the macroreentrant circuit, but it is activated passively.[26–28] The circuit is posteriorly delimited by structures including the crista terminalis, cava veins, coronary sinus orifice, and Eustachian ridge.[29] The wavefront structures serve as anatomical barriers that enable the self-maintenance of the reentry circuit.[30] Precise paths, referred to as isthmuses, are traveled along by the wavefront. Typical AFL depends on CTI, which is a slow conduction zone necessary for the maintenance of the macroreentrant circuit. It should be mentioned that typical AFL is characterized by regular continuous atrial activation, a cycle length of 170–250 ms.[31] Typical AFL has an atrial rate of 250–350 beats/min and can be interrupted by overdrive atrial pacing.[10]

Conversely, atypical AFL is also promoted by macroreentrant mechanisms but CTI is not involved. It usually has an atrial rate of 340–430 beats/min, and it cannot be interrupted by overdrive atrial pacing.[10] Osório et al[32] have shown that atypical AFL is characterized by lower left atrial appendage emptying velocity (34.5 cm/s vs 48.3 cm/s; $P = .001$) and that left ventricular ejection fraction is lower in atypical AFL (46.8% vs 56.8%; $P = .01$); however, arrhythmia cycle did not differ much between typical and atypical AFL.

Atypical AFL may be associated with both the right atrium and the LA. The source of arrhythmia is often related to heart scarring; most of the cases are linked to the history of heart operations, atrial septal defect occluder implantation, or pulmonary vein isolation, but sometimes it also occurs in patients previously considered as healthy without any structural heart disease. No matter what the underlying heart disease is, any structural modification can lead to the development of slow-conducting areas that are crucial in atypical AFL pathophysiology.[33] Different pathophysiologies of AFL and AF are summarized in Table 1.

AF after AFL ablation

With the understanding of the mechanism of AFL and its anatomical location, ablation has become a widely used method for its treatment. Despite the significant safety and high success rate of this therapy in both typical and atypical AFL, many patients experience new-onset AF after this procedure. A meta-analysis by Pérez et al[34] focused on the evaluation of long-term treatment outcomes with CTI ablation of typical AFL. The AF incidence was 23.1% (95% CI 17.5%–29.9%) in patients without a history of AF vs 52.7% (95% CI 47.8%–57.6%) in those with a history of AF before ablation ($P < .05$). AF occurred in 34.9% (95% CI 30.7%–39.3%) of patients with bidirectional block vs 22.5% (95% CI 15.8%–31.1%) of those without isthmus block ($P > .05$). Another meta-analysis by Maskoun et al[35] also included patients after AFL ablation and showed that in studies with <2 years of follow-up, AF occurred in 54% of patients with a history of AF vs 13.9% of those without a history of AF (odds ratio 7.43; 95% CI 4.96–11.11; $P < .00001$). In studies with >2 years of follow-up, AF occurrence was 51.3% in patients with a history of AF and 26.2% in those without prior AF (odds ratio 2.93; 95% CI 2.42–3.56; $P < .00001$).[35] Furthermore, data presented by Dudek et al[36] suggest that developing AF after CTI ablation is more likely in patients with preexisting atypical AFL (81 [17.5%] vs 21 [7.6%]; $P <$

Table 1 Different pathophysiologies of AFL and AF

Compared parameter	AFL	AF
Substrate area	Right atrium	Left atrium
Mechanism	Reentry loop involving CTI (typical AFL) Most commonly heart scarring due to surgery or ablation (atypical AFL)	Rapid focal discharges most commonly from the pulmonary vein and atriopulmonary vein junction
Regularity	Typically regular atrial activity with a consistent F-wave pattern on the ECG	Typically irregular atrial activity on the ECG
Atrial rate	Typical AFL: 250–350 beats/min Atypical AFL: 340–430 beats/min	350–600 beats/min
Reentry	Organized macroreentrant circuit	Disorganized multiple wandering microreentry wavelets
Wavelength	Longer	Shorter

AF = atrial fibrillation; AFL = atrial flutter; CTI = cavotricuspid isthmus; ECG = electrocardiogram.

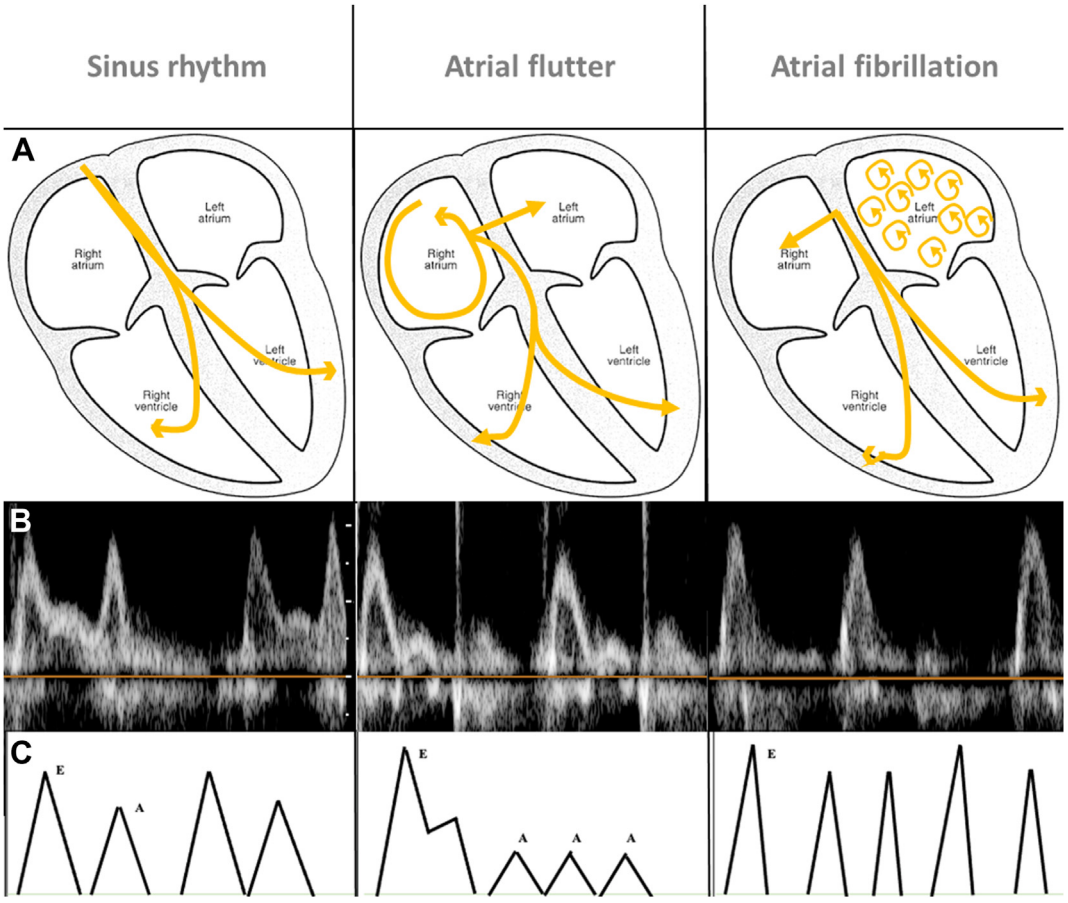

Figure 1 Electrophysiology substrate of arrhythmia and Doppler imaging—mitral inflow in sinus rhythm, typical atrial flutter, and atrial fibrillation. **A:** Electrophysiology substrate of arrhythmia. *Left:* Normal conduction from the sinoatrial node to the ventricles. *Middle:* Macroreentry tachycardia underlying atrial flutter. *Right:* Microreentry circuits in the left atrium responsible for atrial fibrillation and resultant loss of mechanical function of the atria. **B and C:** Mitral inflow reflecting mechanical function of the atria. *Left:* Presence of the early rapid filling (E wave) and single late diastolic filling with atrial contraction (A wave) in sinus rhythm, and presence of the E wave and multiple (2) A waves related with the F wave of atrial flutter. *Right:* Monophasic mitral inflow consistent with loss of active contraction of atria in atrial fibrillation.

.001). Yang et al[37] showed that in patients undergoing CTI ablation, although the incidence of AF was higher in atypical than in typical AFL (68% vs 38%; $P = .004$), the incidence of recurrent AF was similar (57% vs 48%; $P = .4$). (The mean follow-up duration was 28 ± 9 months for the atypical group and 18 ± 11 months for the typical group.) These data point to the need to assess patients after AFL ablation for risk factors, as in patients with AF, and to apply monitoring strategies for early detection of AF and thus appropriate treatment and that patients after ablation with a history of AF deserve special attention.

AF/AFL and CAD

In comparison to AF, AFL is burdened with 5 times higher risk of developing CAD.[12] AFL can also be a first manifestation of subclinical CAD, which can be chronic and asymptomatic in many patients. New onset of AFL in previously healthy patients should raise awareness of potentially developing cardiovascular disease.[17] There is evidence of increased mortality risk after AFL ablation because of undiagnosed and untreated CAD.[38] Despite the higher mortality risk related with CAD, thromboembolic risk according to Vadmann et al[38] is similar in AF and AFL. The pathophysiological basis of the relationship between AFL and CAD is not clear, as they both can potentially induce each other. On the one hand, AFL can lead to the onset of local inflammation, dysfunction of endothelium, and ischemia of the myocardium, that is, factors promoting CAD.[12] On the other hand, CAD, even if asymptomatic, can promote the development of slow conduction areas, which, if specifically localized, can induce reentry loop development, resulting in AFL.[12,17]

Echocardiographic parameters and the risk of LAA thrombus

Structural and functional dysfunction of LA increases thromboembolic risk. The use of echocardiography has become

crucial in the guidelines for the management of patients with AF/AFL.[18,19]

Atrial inflow filling in AFL and AF

The mitral inflow filling pattern in sinus rhythm consists of 2 forward flow velocities: early rapid filling (E wave) and late diastolic filling with atrial contraction (A wave). The A wave is commonly used as a measure of LA mechanical function. In AF, the A wave cannot be measured because of the absence of the atrial waveform. Because of the loss of contraction during AF, only the E wave characterized by interbeat variability could be observed (Figure 1).

The mitral inflow pattern in typical AFL consists of a single E wave and several waves representing atrial contraction, whose number corresponds to the flutter wave frequency on the ECG. This observation supports a preserved basal LA mechanical function in typical AFL. The properties of mitral inflow are summarized in Table 2, and review of the studies concerning mitral inflow in AF and typical and atypical AFL is presented in Table 3.

Table 2 Atrial inflow filling in AFL vs AF

Parameter	AFL	AF
Early rapid filling (E wave)	Single E wave present	Single E wave present with interbeat variability
Late diastolic filling with atrial contraction (A wave)	Multiple waves present corresponding to the flutter wave frequency	Absent
LA mechanical function	Preserved basal function indicated by multiple A waves	Impaired because of the absence of the A wave

AF = atrial fibrillation; AFL = atrial flutter; LA = left atrial.

LAA function in AFL and AF

LAA represents the location of the vast majority (90%) of thrombi forming within the LA in case of loss of LA mechanical function.[8] The individual propensity for thrombus formation may be related with LAA morphology.[49] The more complex the anatomy of the LAA is, the greater is the stasis and higher risk of thrombus formation.[49]

The LAA function measured by pulsed Doppler slightly diminishes with AFL presence, while a significant reduction in LAA emptying velocity (LAA-EV), but also loss of its organization, characterizes AF. Many studies have shown that its impaired function assessed in pulsed Doppler is related to cardioembolic events.[32,39,50–52]

There is no single variable that is significant to LAA thrombus presence; however, there are few parameters correlating with the absence of thrombus formation. Hemodynamic function of LA is strongly associated with LAA thrombus presence. Increased LA volume index and LA dimension correlates with the higher risk of thrombus formation.[53–55] Although a meta-analysis by Froehlich et al[56] suggests that in patients with AF the LA dimension index did not correlate with stroke and thromboembolic events, a significant proportion of participants with AF included in this study may have had anticoagulation treatment, which may have caused the bias, so the results are not clear in this regard. Also, it is shown that reduced LA emptying velocity and flow velocity as well as LAA-EV lead to blood stasis and thus thrombus formation.[57] All the above are associated with the occurrence of SEC, which may precede the formation of embolic material. In connection with atrial dysfunction, lower left ventricular ejection fraction and its ratio to LA volume index also increase the risk of thrombus formation.

Despite the above, there is an established parameter to determine the risk of thromboembolism in patients with AF, which is the LAA flow velocity (LAA-FV).[40] Its reduced value is believed to be associated with the occurrence of stroke and transient ischemic attack in this group of patients.[41,58,59] Another LAA function parameter, LAA emptying fraction (LAA-EF), has been found to have an inverse correlation with CHA_2DS_2-VASc score.[39] Another study has shown that higher stroke risk was related with decreased LAA-FV and LA ejection fraction and presence of significant mitral regurgitation.[60] LAA function is also described by a parameter of its movement, which is LAA flow time (LAA-FT). Narumiya et al[42] found that LAA-FT was shorter in patients with LAA thrombus confirmed (with thrombus 68.7 ms vs without thrombus 72.9 ms; $P < .01$).

One of the universal predictors of embolic formation in LA is SEC,[51,61] which takes the form of a swirling pattern of blood flow, and it can be confirmed through transthoracic echocardiography and TEE. SEC is strongly associated with lower LAA-FV.[62] The high CHA_2DS_2-VASc score category, a strong predictor of ischemic stroke occurrence in patients with AF, has a 88.7% sensitivity for SEC detection.[63]

Utility of LA strain

An echocardiographic parameter worth noting is LA strain, which correlates with the process of LA structural remodeling and deformation of myocardium,[64] whose reduction in patients with AF was associated with a higher risk of stroke/transient ischemic attack.[65,66] Costa et al[64] found in patients diagnosed with both AFL and AF that the reduced peak negative value of LAS correlates with the decreased rate of successful electrical cardioversion, and multivariate analysis of peak positive strain normalized by the LA maximum volume indexed by the body surface area correlates with higher thromboembolic risk, regardless of CHA_2DS_2-VASc score. Karabay et al[67] observed that in patients with sinus rhythm and suspected cardioembolic stroke, LA peak strain and LA precontraction strain values were significantly lower in the group with LAA thrombus (11.8% ± 1.4% vs 33% ± 12%; $P < .001$ and 5.8% ± 1.3% vs 14.2% ± 5.3%; $P < .001$). Moreover, these values were positively correlated with LAA-EV ($r = 0.74$; $P < .001$). The study showed that the presence of thrombus within

Table 3 Summary of different atrial functions in AFL vs AF

Study	AFL	AF
Osório et al[32]	Typical AFL vs atypical AFL • Higher LAA-EV (48.3 cm/s vs 34.5 cm/s; P=.001) • Higher LVEF (56.8% vs 46.8%; P=.01)	
Wu et al[39]	Isolated AFL • Higher LAA-FV (51.5 cm/s; P=.004) • Higher LAA-EF (36.5%; P=.024)	AFL + AF • Lower LAA-FV (31.9 cm/s) • LAA-EF (28.4%)
Handke et al[40]		LAA-FV • Paroxysmal AF (32 cm/s) • Chronic AF (27 cm/s)
Goldman et al[41]		LAA-FV • Lower in AF vs sinus rhythm (33 cm/s vs 61 cm/s)
Narumiya et al[42]	• Higher LAA-FV (52.6 cm/s; P<.001) • Longer LAA-FT (106 ms; P<.001)	• Lower LAA-FV in AF + thrombus, nonlone AF, lone AF (12, 20.5, 31.6 cm/s) • Shorter LAA-FT in each group (68.7, 72.9, 72.8 ms)
Sakurai et al[43]	• Higher LAA-FV (44 cm/s; P<.05) • Smaller LVEDD (47 mm; P<.05) • Smaller LAD (39 mm; P<.05)	• Lower LAA-FV (25 cm/s) • Greater LVEDD (52 mm) • Greater LAD (45 mm)
Santiago et al[44]	• Smaller left atrial area (5.3 cm^2; P<.05) • Higher LAA-FV (42 cm/s; P<.001)	• Greater left atrial area (6.7 cm^2) • Lower LAA-FV (17 cm/s)
Rozenberg et al[45]	• Smaller left atrial area (3.1 cm^2; P<.001) • Higher LAA-EV (47 cm/s; P=.03) • Less prevalent SEC (17%; P=.024)	• Greater left atrial area (6 cm^2) • Lower LAA-EV (30 cm/s) • More prevalent SEC (37%)
Grimm et al[46]	• Higher LAA-FV (42 cm/s; P<.001) • Less prevalent SEC (21%; P<.05)	• Lower LAA-FV (28 cm/s) • More prevalent SEC (50%)
Huang et al[47]	• Higher LAA-EV (63.3 cm/s; P<.001) • Less prevalent SEC (13%; P<.001)	• Lower LAA-EV (44.4 cm/s) • More prevalent SEC (34%)
Omran et al[48]	• Higher LAA-EF (52%; P=.008) • Higher LAA-EV (79 cm/s; P=.005) • Less prevalent SEC (11%)	AFL + intermittent AF • Lower LAA-EF (33%) • Lower LAA-EV (44 cm/s) • More prevalent SEC (36%)

AF = atrial fibrillation; AFL = atrial flutter; LAA-EF = left atrial appendage ejection fraction; LAA-EV = left atrial appendage emptying velocity; LAA-FT = left atrial appendage flow time; LAA-FV = left atrial appendage flow velocity; LAD = lef atrial diameter; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; SEC = spontaneous echocardiographic contrast.

the LAA was accurately predicted by transthoracic LA peak strain (area under the receiver operating curve 0.94; 95% CI 0.90–0.98; $P < .001$) and LA precontraction strain (area under the receiver operating curve 0.92; 95% CI 0.87–0.96; $P < .001$).[67] Thus, incorporation of automatic LAS calculation based on transthoracic echocardiography may help identify patients with a higher risk of LAA thrombus.

Impaired atrial function in AFL vs AF

A higher LAA-FV is observed in patients with AFL than in patients with AF, which suggests better LA function and more effective blood flow through the LAA, which may translate into lower risk of thrombus formation due to decreased blood stasis.[42,43]

The occurrence of SEC is more prevalent in AF than in AFL.[43–47] This has been confirmed by Cresti et al[68] in their study, where SEC was present in 35% of patients with AF vs 28% of patients with AFL ($P = .05$). Moreover, some studies have compared the frequency of SEC in patients with stand-alone AFL vs AFL with coexisting AF and SEC was also significantly less frequent in patients with isolated AFL.[44,48]

Miyoshi et al[69] measured LAA-FV in patients with supraventricular tachyarrhythmias. The lowest LAA-FV has been observed in patients with chronic AF (permanent AF 13.7 cm/s; paroxysmal AF 36.1 cm/s; AFL 44.5 cm/s; sinus rhythm 39 cm/s; $P < .00001$).[69]

As it is known that AFL can coexist with AF, it has to be taken into consideration when choosing the right anticoagulation approach path. The difference is crucial because significant differences have been observed during TEE in LAA function between patients with only AFL and those with AFL and paroxysmal AF. Wu et al[39] observed that LAA-EF and LAA-FV have been higher in patients with isolated AFL than in those with AFL and a history of AF. LAA-EF measured 28.4% in AFL + AF vs 36.5% in isolated AFL ($P = .024$). Similarly, LAA-FV measured 31.9 cm/s vs 51.5 cm/s ($P = .004$).[39] Grimm et al[46] also found that LAA-FV is higher in AFL than in AF (42 cm/s vs 28 cm/s, respectively; $P < .001$).

Another study showed that AF and AFL + AF had similarly chaotic LAA contractions with peak LAA-EV (18 and 17 cm/s) but isolated AFL had a regular pattern of LAA contractions and significantly higher LAA-EV (42 cm/s) ($P < .0001$).[44] The study also found differences in mean LAA

area (AF 6.7 cm^2; AF + AFL 6.3 cm^2 vs AFL 5.3 cm^2; $P <$ .05) as well as different prevalence of LAA thrombus (AF 29%; AFL + AF 40% vs AFL 0%; $P <$ .05) and SEC (AFL + AF 50%; AF 40% vs AFL 6%; $P <$ .05). Omran et al[48] also focused on comparing LAA function in patients diagnosed with AFL and those with AFL and paroxysmal AF. Decreased LAA-EF (AFL + AF 33% vs AFL 52%; P = .008) and LAA-EV (AFL + AF 44 cm/s vs AFL 79 cm/s; P = .005) have been observed in patients with paroxysmal AF.[48]

Narumiya et al[42] found that patients with AFL had higher LAA-FV (AFL 52.6 cm/s; AF without thrombus 31.6 cm/s; AF with thrombus 12.0 cm/s; $P <$ .001) and longer LAA-FT (AFL 106 ms; AF without thrombus 72.8 ms; AF with thrombus 68.7 ms; $P <$ .001) than did those with permanent AF; and in that research, thrombus has been confirmed only in patients with AF. Huang et al[47] performed a study in which thrombus has been found only in patients with AF and has not been found in patients with AFL (P = .01). SEC has been more prevalent in patients with AF than in those with AFL ($P <$ .001), and measured LAA-EV has been significantly lower in AF than in AFL (44.4 cm/s vs 63.3 cm/s, respectively; $P <$ .001).[47]

Rozenberg et al[45] showed significant differences in echocardiographic parameters between patients with AFL and those with AF, as LAA area was smaller (3.1 cm^2 vs 6.0 cm^2; P = .001), LAA SEC was less frequent (17% vs 37%; P = .024), and LAA-EV was higher (47 cm/s vs 30 cm/s; P = .03) in patients with AFL than in those with AF. In the study by Cresti et al,[68] the presence of LAA thrombus (5.9% vs 9.9%; P = .07) and SEC were less frequent (28% vs 35%; P = .05) in patients with AFL than in those with AF. There was a significant disparity in terms of LAA-EV in patients with AFL, depending on the presence of thrombus (thrombus group 25 cm/s vs nonthrombus group 42 cm/s; $P <$ .001); a similar situation has been found in the AF group (thrombus group 23 cm/s vs nonthrombus group 38 cm/s; $P <$ .01).[68]

Cardioversion itself may decrease LAA-FV because of the LA stunning effect. It was found by Grimm et al[46] that the decrease in patients with AFL has been less pronounced than that in patients with AF (AFL 42 cm/s decreased to 27 cm/s; AF 28 cm/s decreased to 15 cm/s; $P <$ .001). These findings are consistent with the work of Weiss et al,[70] who demonstrated that in patients with AFL, LAA-EV decreased 1 minute after cardioversion from 54 to 40 cm/s ($P <$ .01).

Biomarkers of prothrombotic state in AFL

As suggested earlier, organized atrial function in AFL should favor a lower thromboembolic risk than in AF, which should be reflected in thrombotic parameters such as d-dimer, high levels of which are suspected to be associated with thromboembolic incidents.[71–74] Sakurai et al[43] observed that d-dimer levels were significantly lower in AFL than in AF (1.0 ± 0.3 μg/mL vs 1.9 ± 0.4 μg/mL), suggesting a lower thromboembolic risk in AFL. In the same study, coagulation markers did not differ between patients with AFL and those in sinus rhythm.

Coagulation markers may differ between AFL types because of their different pathophysiology. Demir et al[75] found that fibrinogen (2.85 ± 0.7 g/L vs 4.44 ± 0.9 g/L; $P <$ .001), d-dimer (288.1 ± 99.7 ng/mL vs 532.7 ± 203 ng/mL; $P <$ .001), and thrombin-antithrombin III activity (97.9% ± 19.8% vs 165.5% ± 32.6%; $P <$ .001) are significantly lower in typical AFL than in atypical AFL, suggesting a lower thromboembolic risk in typical AFL.

Thromboembolic risk: AFL vs AF, other supraventricular tachycardias

Thromboembolic risk in AF is well described, and its presence is associated with a 5-fold increase in the risk of stroke.[76] However, to date, few studies have focused their attention on thromboembolic risk in AFL. In a retrospective study, Biblo et al[77] observed that patients with AFL (relative risk [RR] 1.41) have a higher risk of stroke than do patients in the control group (RR 1.00) but a lower risk than do patients with AF (RR 1.64). Moreover, patients with AFL who later experienced an episode of AF had a higher risk of stroke (RR 1.56) than did patients with AFL who never had another episode of AF (RR 1.11). Al-Kawaz et al[78] compared the risk of stroke in patients with AFL and patients with AF. The annual incidence of ischemic stroke was 1.38% (95% CI 1.22%–1.57%) in the AFL group compared with 2.02% (95% CI 1.99%–2.05%) in the AF group. Considering demographic and stroke risk factors, AFL was associated with a lower risk of stroke compared with AF (RR 0.69; 95% CI 0.60–0.79; $P <$ .05). After 1 year, 65.7% (95% CI 64.9%—66.4%) of patients with AFL switched to AF, but remained at a lower risk of ischemic stroke (RR 0.85; 95% CI 0.78–0.92). In the study by Lin et al[79] after stratification by CHA_2DS_2-VASc score, the incidence densities (IDs; in events per 100 person-years) of ischemic stroke were significantly lower in AFL (IDs 1.45; 95% CI 1.28–1.62) than in AF (IDs 3.08; 95% CI 3.03–3.13); moreover, the values of the AFL cohort are closer to those of the control cohort (ID 0.97; 95% CI 0.92–1.03). Ischemic stroke IDs in the AF cohort were significantly higher at all CHA_2DS_2-VASc scores than in the matched control cohort, while ischemic stroke IDs in the AFL cohort were significantly higher only at CHA_2DS_2-VASc scores from 5 to 9 than in the control cohort. The IDs of ischemic stroke with a CHA_2DS_2-VASc score of 1 in the AF cohort was similar to that of ischemic stroke with a CHA_2DS_2-VASc score of 2 in the AFL cohort, and the IDs of ischemic stroke with a CHA_2DS_2-VASc score of 2 in the AF cohort was similar to that of ischemic stroke with a CHA_2DS_2-VASc score of 4 in the AFL cohort. In addition, the authors observed that patients stratified by CHA_2DS_2-VASc score and diagnosed with solitary AF had a higher incidence of intracranial hemorrhage than did those with solitary AFL (stratified HR 1.29; 95% CI 1.08–1.55; P

Table 4 Factors in favor of or against chronic anticoagulation in patients with AFL

In favor of anticoagulation	Against anticoagulation
• Higher prevalence of thromboembolic events than in sinus rhythm • Lower LAA-FV than in sinus rhythm • Occurrence of SEC in some patients with AFL • Frequent coexistence with AF and higher risk of future AF episodes	• Lower incidence of SEC than in AF • Higher LAA-EF, LAA-EV, LAA-FT, and LAA-FV than in AF • Lower d-dimer level than in AF; no difference between hemostatic markers between AFL and sinus rhythm • High efficacy of ablation of cavotricuspid isthmus (95%) and low risk of typical AFL recurrence (10%) • Difficult differentiation between focal or multifocal AT and AFL based on the surface ECG

AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; ECG = electrocardiogram; LAA-EF = left atrial appendage emptying fraction; LAA-EV = left atrial appendage emptying velocity; LAA-FT = left atrial appendage flow time; LAA-FV = left atrial appendage flow velocity; SEC = spontaneous echocardiographic contrast.

= .005). The incidence of ischemic stroke or embolization has also been found higher in solitary AF and AFL accompanied by AF than in solitary AFL (HR 1.59; 95% CI 1.47–1.72; $P < .001$ and HR 1.69; 95% CI 1.53–1.87; $P < .001$, respectively). They also found that patients with solitary AFL receiving anticoagulation therapy had a lower risk of developing ischemic stroke and systemic embolization than did those without anticoagulation with CHA_2DS_2-VASc score ≥ 3 (HR 0.6; 95% CI 0.42–0.86; $P = .005$); however, at CHA_2DS_2-VASc score ≤ 3, anticoagulation therapy increases the risk of intracranial hemorrhage in patients with AFL (HR 2.48; 95% CI 1.39–4.42; $P = .002$). Further analysis concluded with the cutoff value of the CHA_2DS_2-VASc score being ≥ 4 when anticoagulation therapy has the best net clinical outcome, considering thromboembolic risk as well as major bleeding risk (HR 0.68; 95% CI 0.50–0.93; $P = .014$). These findings suggest that thromboembolic risk in AFL appears to be lower than that in AF, but still considerable; hence, possible different cutoff values of CHA_2DS_2-VA score for the initiation of anticoagulation in AFL should be proposed on the basis of randomized controlled trials in population with AFL.

It is also vital to refer to the lack of indication for chronic OAC in case of focal or multifocal AT. The difference between AFL and AT is based on the lower rate (100–250 beats/min) and presence of an isoelectric line between atrial waves of the latter arrhythmia.[80] There is obviously a borderline zone in which clinicians may use either the diagnosis of AT or AFL, which often causes concern about the need for anticoagulation. AT represents an arrhythmia with preserved atrial mechanical function, leading to the conclusion that chronic or preprocedural OAC is not indicated.[81] Still, current European guidelines on the treatment of supraventricular arrhythmias recommend anticoagulation in a special clinical scenario of focal AT associated with congenital heart disease, as the risk of thrombus formation is much higher in this population.[82] Of note, both atrioventricular nodal reentrant tachycardia and atrioventricular reentry tachycardia do not require chronic or preprocedural anticoagulation.[82]

A detailed comparison of factors in favor of and against anticoagulation in patients with AFL is presented in Table 4.

Conclusion

Given the limited amount of evidence in the field, it is difficult to draw firm conclusions about the indications for OAC use in AFL. Preserved LA mechanical function observed in typical AFL, reflected by mitral inflow, contradicts the necessity of antithrombotic treatment, while LA mechanical dysfunction present in atypical AFL and common AF and AFL coexistence speak in favor of anticoagulation. According to current guidelines, chronic OAC in AFL regardless of its type should be used on the basis of CHA_2DS_2-VA score or planned cardioversion or ablation procedure. One should strongly consider withdrawal of OAC after successful CTI ablation in typical AFL after 2 months of postprocedural anticoagulation therapy, as the success rate of the procedure is excellent, provided that no AF is detected on prolonged ECG monitoring. Further studies, especially prospective ones comparing patients with AFL with low thromboembolic risk with and without anticoagulant treatment, are required.

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