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REVIEW ARTICLE

Anticoagulation in atrial fibrillation and flutter

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Abstract Atrial fibrillation and atrial flutter are important risk factors for stroke. Based on a literature search, pathogenesis of thromboembolism, risk assessment in patients, efficacy of anticoagulation therapy and its alternatives are discussed. Special emphasis is put on issues like paroxysmal atrial fibrillation, atrial flutter and anticoagulation surrounding catheter ablation and cardioversion. A strategy for anticoagulation around the time of pulmonary vein ablation is suggested.

Introduction

Atrial fibrillation (AF) is an important public health problem affecting approximately 1% of the general population. As the frequency of AF increases with age, it is anticipated that the number of people with AF will double in the next 25 years [1]. One of the major goals in treating AF is a reduction in the incidence of thromboembolic stroke, the most feared complication of AF. It is estimated that about 17% of all strokes are caused by AF [2]. Ischaemic stroke associated with AF is nearly twice as likely to be fatal as non-AF stroke and the functional deficits among survivors more severe [2,3]. In the Framingham Study the risk of stroke in patients with non-valvular AF was increased five-fold in comparison with the general population [4]. Valvular AF increases this risk to 17-fold [5].

Atrial fibrillation and thromboembolism: pathogenesis and risk assessment

The loss of coordinated atrial contraction is important for thrombus formation in patients with AF [6].

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Patients with atrial flutter (AFL) and impaired left atrial appendage (LAA) function are also potentially at high risk for thromboembolism and might therefore require anticoagulation [7]. Approximately 90% of atrial thrombi in non-rheumatic AF are found in the LAA [8]. Patients less than 60 years of age, without cardiovascular disease, however, have a low risk of stroke. Other factors, such as age and associated cardiovascular disease play a greater role. Platelet activation, on the other hand, probably does not play a significant role in thrombus formation in these patients [9]. Five large, randomised trials of anticoagulation were pooled by The Atrial Fibrillation Investigators [10] and risk factors for stroke were defined. Age was shown to increase stroke risk by 1.4 per decade. Other risk factors include previous stroke or transient ischaemic attack (TIA), hypertension, diabetes mellitus, congestive heart failure, ischaemic or rheumatic heart disease, prior thrombo-embolism and female gender (Fig. 1). Patients with rheumatic heart disease, prosthetic heart valves, prior thromboembolism and persistent atrial thrombus detected by transoesophageal echocardiography (TOE) are considered to be at highest risk [11,12]. Risk stratification using schemes such as the $CHADS_2$ algorithm can help to quantify the stroke risk for patients with AF [13] (Table 1). $CHADS_2$ is a risk assessment algorithm derived from pooled data. Consistent with ACC/AHA/ESC guidelines [11] for patients with AF and additional risk factors, any patient with a $CHADS_2$ score ≥ 1 should be considered for long-term anticoagulation.

Transoesophageal echocardiography (TOE) is superior to transthoracic echocardiography both in assessment of left atrial, and left atrial appendage thrombus, as well as in detection of reduced flow velocities and spontaneous echo contrast in the left atrium and left atrial appendage [14]. TOE is also the method to detect a patent foramen ovale (PFO), a known cause of paradoxical emboli causing stroke or transient ischaemic attacks [15]. An association of PFO and septal aneurysms with stroke exists; a relation with AF is not described. Patients with AF and complex atherosclerotic plaques in the aorta have a substantially higher risk for stroke [16,17].

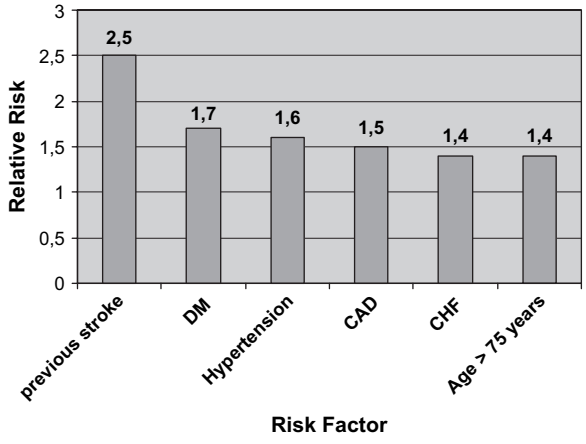

Figure 1 Relative risk compared with those with AF, but without these risks. CAD: coronary artery disease, CHF: congestive cardiac failure, DM: diabetes mellitus, TIA: transient ischaemic attack. *Adapted from reference [11].

Table 1 The $CHADS_2$ algorithm [1,3]

	$CHADS_2$ risk factors	Points
C	Recent clinical congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75 years	1
D	Diabetes mellitus (any form)	1
S	History of stroke or transient ischaemic attack	2

Efficacy of anticoagulation

Pooled data analysis for oral anticoagulation with coumadins has shown a relative risk-reduction for stroke of between 62 and 70% [10,18]. The risk reductions for stroke were 2.7% per year for patients without a history of stroke or transient ischaemic attack, and 8.4% per year for secondary prevention in patients with a prior stroke [12,19]. Recently, it was established that anticoagulants should be withheld during the first 14 days in AF patients with acute ischaemic stroke as the benefit was completely negated by a higher risk of intracranial bleeding [2].

Level of anticoagulation

Oral anticoagulation has a narrow therapeutic window. When the international normalized ratio (INR) is above 2.0 the risk of ischaemic stroke is low [20]. Above the level of 4.0, however, the risk of haemorrhagic complications, especially intracranial bleeding, increases significantly [21–23]. For those who continue to have TIAs or strokes despite a therapeutic INR or those who have a mechanical heart valve, many experts recommend a target INR of 2.5 to 3.5 [24]. Risk factors for major bleeding includes an INR ≥ 4.0, advanced

age, a history of stroke and hypertension [25,26] and unstable INR control [21]. A cohort study identified three risk factors for haemorrhage in an elderly population: alcohol abuse, chronic renal insufficiency and previous gastrointestinal bleeding [27].

Alternatives to standard oral anticoagulation

Aspirin alone or in combination with low dose warfarin [28] has been studied. The combination of aspirin with low dose warfarin does not improve the risk/benefit ratio [29]. Aspirin alone has a modest benefit. A meta analysis calculated a risk reduction of only 21% [30]. The new anti-thrombin drug ximelagatran has been reported to be a promising alternative to warfarin [31]. It has been shown to be equally effective, or at least not inferior to well controlled warfarin [32]. Further, it has the advantages of less drug interactions, an almost immediate anticoagulant action, the absence of the need for regular dose adjustments and a lower bleeding risk. However, drug-related liver injury, led the United States Food and Drug Administration not to approve its use [32,33].

Fondaparinux and idraparinux are investigational agents that prevent thrombin formation [34–37]. They are parenteral, specific, indirect, factor Xa inhibitors with a mechanism of action similar to that of heparin.

Because 90% of atrial thrombi in non-rheumatic AF are found in the left atrial appendage (LAA) [8], occlusion or resection of the LAA seems an alternative to anti-coagulation in the prevention of thromboembolic events in some patients. A newly developed device allowing percutaneous LAA occlusion (PLAATO) might be an alternative to oral anticoagulation for patients with a high thromboembolic risk and a contraindication to anticoagulation [38], and its value is currently being assessed.

Usage of anticoagulation

Several reports indicate that anticoagulation is actually underused in AF patients at high risk for thromboembolic complications [39,40]. Possible explanations for this underuse are doubts about the effectiveness of anticoagulation, the fear of haemorrhagic complications such as intracerebral bleeding and the limitations of its use, such as frequent coagulation monitoring and interactions with food, alcohol and other drugs. Patient self-testing and self-management has been shown to improve the accuracy and quality of oral anticoagulation [41,42] and may improve quality of life.

Special issues

Paroxysmal and persistent AF

In the trials of anticoagulation in AF, between 5 and 25% of the patients had what was labelled at that time paroxysmal or intermittent AF. In this group the same risk reduction for stroke was found as in patients with permanent AF. Patients with paroxysmal AF and with risk factors for stroke should therefore be treated with anticoagulation [43]. The AFFIRM [44] and RACE trials [45] both compared the benefits of rate in AF control versus rhythm control (sinus rhythm). In these two studies, most patients who experienced an ischaemic stroke either had a suboptimal INR or had discontinued anticoagulation. A very important observation was that 75% of the patients with an ischaemic stroke in the rhythm-control group in the AFFIRM trial were believed to be in sinus rhythm at the time of the event. Both trials give reason to reconsider the cessation of anticoagulation after a successful cardioversion in patients with stroke risk factors [46].

Atrial flutter

In recent literature, controversy exists about the need for anticoagulation surrounding cardioversion of lone atrial flutter [47,48]. The acute and chronic haemodynamic effects of flutter are not completely understood. After cardioversion of flutter, the atria remain stunned for up to 2 weeks, as has also been shown for AF [49]. The reported incidence of LAA thrombi in patients with lone atrial flutter varies from 1% [47] to 11% [50]. The prevalence of LAA thrombi also increases with age and with lower ejection fraction [51]. Lone atrial flutter has a similar stroke risk to lone atrial fibrillation, presumably because it carries a risk for subsequent development of atrial fibrillation that is higher than the general population. Furthermore, atrial flutter maybe the result of drug treatment of AF. In an unselected patient group with atrial flutter, Seidl et al. [52] found a remarkably high overall embolic rate of 7%. In this group the majority of patients were not receiving oral anticoagulation. Hypertension appeared to be the only independent risk factor. In patients with

atrial flutter, markers of a prothrombotic state (d-dimers and β-thromboglobulin) are not elevated, except for those patients with impaired LAA function as assessed by TOE. Anticoagulation should be considered for all patients with atrial flutter who are older than 65 years of age [53] and is mandatory in the period before and after electrical cardioversion [50,54,55].

In conclusion, anticoagulation in atrial flutter patients should use the same approach as in patients with atrial fibrillation [56,57].

Anticoagulation and prophylaxis of thromboembolism in radiofrequency (RF) ablation of atrial fibrillation and flutter

The treatment of AF entered a new era after the publication of the landmark observations of Haïssaguerre et al. [58]. The recognition of the role of the myocardial sleeves [59] within the pulmonary veins (PVs) in initiating AF changed both pathophysiological insights and therapeutic approaches. Segmental ostial catheter ablation [60] and left atrial encircling ablation of the PVs [61] have both been reported to be successful in the treatment of AF. RF ablation is a highly effective therapeutic approach in the treatment of typical isthmus dependent atrial flutter [62].

RF catheter ablation is complicated by thromboembolism in about 0.6% of patients [63]. The risk of stroke from RF ablation may be higher in paroxysmal AF patients with prior transient ischaemic attack [64]. As reflected by elevated plasma d-dimer levels, RF ablation has a thrombogenic effect that persists through the first 48 hours after the procedure [65]. Activation of the coagulation cascade in RF ablation procedures is not related to the delivery of RF energy, but is related to the placement of intravascular catheters and to the duration of the ablation procedure [66,67]. Furthermore, RF lesions themselves have been shown to be thrombogenic in acute studies [68]. The risk of a thromboembolic complication is higher for left sided ablations (1.8%—2.0%) [63]. By administering intravenous heparin immediately after introduction of the venous sheaths, haemostatic activation is significantly decreased [69]. There is also a significant risk for thromboembolism in patients referred for ablation of typical atrial flutter who have not been appropriately anticoagulated [70]. Radiofrequency ablation of chronic atrial flutter is associated with significant left atrial stunning [71].

The NASPE Policy Statement on Catheter Ablation [72] suggests anticoagulation for at least 3 weeks prior to ablation for AF and atrial flutter for patients who are in these arrhythmias. Discontinuation of anticoagulants 2 to 3 days before the procedure is possible. For high-risk patients, heparin to cover this period should be considered [72]. TOE shortly before pulmonary vein ablation to exclude left atrial thrombi is routine in many clinics [73,74]. We observed an atrial thrombus on TOE in 9% of patients referred to us for PV isolation (in press). Generally during left sided ablation, heparin should be administered, aiming at an activated clotting time (ACT) of 250—300 seconds. Higher levels of anticoagulation (ACT $\geq$ 300 seconds) are used for pulmonary vein ablations [72]. No clear guideline appears to exist regarding the use of anticoagulation after a successful pulmonary vein isolation procedure. However, it seems logical to continue oral anticoagulation for some time after the procedure. The duration will depend on pre-existing risk factors. Experienced groups continue anticoagulation therapy at least 3 months after a successful ablation [73,75,76].

Anticoagulation surrounding cardioversion for atrial tachyarrhythmias

Thromboembolic events after cardioversion in atrial tachyarrhythmias have been reported in 1% to 7% of patients not receiving prophylactic anticoagulation [77,78]. Anticoagulation is recommended for 3 to 4 weeks before and after cardioversion for patients with AF of unknown duration and for AF of more than 48 hours duration [11]. A reasonable alternative strategy is early cardioversion with a short period of anticoagulation therapy after exclusion of LA/LAA thrombi with TOE [79].

Anticoagulation in the elderly

Anticoagulation in those over 75 years of age has been poorly assessed, as this age group was not well represented in the majority of clinical trials of anticoagulation. Clearly, age increases the risk of complications of anticoagulation, but conversely these patients are also at the highest risk of stroke [80], so risk assessment and therapy should be individualised [81].

AF in association with valve prostheses

In patients with bioprosthetic valves and AF, similar levels of anticoagulation to those mentioned above seem adequate. In AF associated with mechanical valve prostheses, levels of anticoagulation recommended are less standardised,

Table 2 ACC/AHA/ESC atrial fibrillation guidelines-anticoagulation

Patient features	Antithrombotic therapy	Grade of recommendation
Age <60 years No heart disease (lone AF)	Aspirin (325 mg per day) or no therapy	1
Age <60 years Heart disease but no risk factors*	Aspirin (325 mg per day)	1
Age ≥60 years No risk factors*	Aspirin (325 mg per day)	1
Age ≥60 years With DM or CAD	Oral anticoagulation (INR 2.0—3.0) Addition of aspirin daily optional	12b
Age ≥75 years, especially women	Oral anticoagulation (INR approx 2.0)	1
Heart failure EF <0.35 Hypertension Thyrotoxicosis	Oral anticoagulation (INR 2.0—3.0)	1
Rheumatic heart disease Prosthetic heart valve Prior thromboembolism Persistent atrial thrombus on TOE	Oral anticoagulation (INR 2.5—3.5 or higher may be appropriate)	1

* Risk factors for thrombo-embolism include HF, LV EF <35% and history of hypertension. AF: atrial fibrillation, CAD: coronary artery disease, DM: diabetes mellitus, EF: ejection fraction, INR: international normalised ratio, LV: left ventricle, TOE: transoesophageal echocardiography. Adapted from reference [11].

but what is clear is that the risks for thromboembolism depend on the type of valve inserted and its position [82,83]. Accordingly, the target INR for these patients should be individualised and the presence or absence of AF has little influence on this target.

Conclusions

The evidence strongly supports the use of oral anticoagulation, aiming at an international normalised ratio (INR) between 2 and 3, in patients with AF who have an average or higher risk of stroke. This also includes the elderly. Only in younger patients without additional risk factors is the use of oral anticoagulation not indicated. Aspirin is advised by the guidelines (Table 2) for lower risk patients [11] but a true evaluation in this patient group is lacking [84]. Paroxysmal AF and atrial flutter should be treated in the same way as persistent and permanent forms of AF. For high-risk patients with a contraindication to anticoagulants, a left atrial occluder may be valuable, and is currently under investigation. Guidelines for the use of anticoagulation surrounding pulmonary vein isolation are not yet available, but a high level of anticoagulation is necessary during the procedure. It is appropriate to prescribe oral anticoagulation before and to re-initiate it after the procedure. A covering period with heparin until the INR reaches the level of 2 is advisable. It is possible that medical practice will change with the introduction of new antithrombin drugs and with further documentation of the efficacy of low molecular heparin in this area. The initial optimism over the introduction of ximelagatran has been tempered by criticism on the basis of its side effects [33].

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