Review Article

Optimisation of Anticoagulation in Patients with Atrial Fibrillation

Ankita Prasad, Patrick Pullicino

Abstract

Atrial fibrillation is a common cardiac arrhythmia associated with debilitating complications, one of which is stroke. Anticoagulants (warfarin and the non-vitamin K antagonist oral anticoagulants) are recommended for stroke prophylaxis, their utilisation however requires stroke risk reduction to be balanced against hemorrhage risk. Current review of the literature suggests that despite the presence of risk stratification tools such as the $CHADS_2$ and the newer CHA_2DS_2-VASc, clinicians often find it challenging to anticipate the risk-benefit ratio of anticoagulation. This results in both the underuse and overuse of anticoagulation in patients as well as uncertainty over whether to use anticoagulation in paroxysmal AF. This review looks at optimising anticoagulation by improving the assessment of bleeding risk and by improving the assessment of stroke risk. The percutaneous occlusion of the left atrial appendage is an emerging alternative to oral anticoagulation therapy.

Key words

anticoagulation, atrial fibrillation, stroke

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Abbreviations

AF: Atrial Fibrillation, $CHADS_2$: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischaemic attack score, CHA_2DS_2-VASc: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex score, CMBs: cerebral microbleeds, ECG: Electrocardiography, ICH: intracerebral haemorrhage, LAA: left atrial appendage, MRI: Magnetic Resonance Imaging, NOACs: non-vitamin K antagonist oral anticoagulants, NT-proBNP: N-terminal pro-brain natriuretic peptide OAC: oral anticoagulants, PAF: Paroxysmal Atrial Fibrillation

Introduction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in clinical practice.[1] In 2010 it was estimated that globally 33.5 million individuals had AF, and the prevalence is estimated to be increasing worldwide.[2] AF patients have a five-fold increase in their risk of ischemic stroke and strokes in AF patients have a higher chance of being fatal or disabling.[3] Oral anticoagulants are recommended for stroke prophylaxis but stroke risk varies in AF and risk reduction effect must be balanced against haemorrhage risk. Not all patients with AF have a stroke risk high enough to warrant anticoagulation. It may be difficult for the clinician to decide whether to anticoagulate a specific patient and anticoagulation is not always appropriately managed.[4] To use anticoagulants properly it is also important to look for occult intermittent AF in specific circumstances. When intermittent AF is detected, there is uncertainty about which patients should be anticoagulated.[5] This review will explore these key areas in which anticoagulation therapy may be optimised in AF patients.

Anticoagulants, stroke risk reduction and haemorrhage

The main anticoagulants, warfarin and the non-vitamin K antagonist oral anticoagulants (NOACs) - Dabigatran, Apixaban and Rivaroxaban, recommended for the use of stroke prophylaxis, have all been found to be effective in preventing stroke but are all associated with an increased risk of bleeding.[6] Successful use of anticoagulant treatment therefore needs to be able to achieve a balance between decreasing the risk of stroke

and increasing the risk of bleeding.[7]

The risks of stroke and bleeding in AF patients depend on individuals' vascular risk factors and clinical risk stratification schemes have been developed to assess the risk of stroke and bleeding.[8] These include the $CHADS_2$ (Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischaemic attack) score (Table 1) and the newer CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex) score (Table 2) to assess the risk of stroke and the HAS-BLED tool (Table 3) to assess the risk of bleeding.[4]

***Table 1**: Assessment of Stroke (CHADS2) in Atrial Fibrillation Patients*

$CHADS_2$ Risk	**Score**
Congestive Heart Failure	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

***Table 2**: Assessment of Stroke (CHA2DS2-VASc) in Atrial Fibrillation Patients*

CHA_2DS_2-VASc Risk	**Score**
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 – 74	1
Female	1

***Table 3**: Assessment of Bleeding Risk (HAS-BLED) in Atrial Fibrillation Patients*

HAS-BLED Tool	**Score**
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Previous Stroke	1
History of predisposition to bleeding	1
Labile INR	1
Elderly (> 65)	1
Drugs (Antiplatelets or NSAIDs)	1
Harmful Alcohol intake	1

Under the $CHADS_2$ tool AF patients are considered low risk for stroke if the score is 0 and high risk if the score is ≥ 2.[9] Under the newer CHA_2DS_2-VASc tool, AF patients are considered to have a low risk of stroke if they are below 65 with no risk factors other than their sex (this equates to a CHA2DS2-VASc score of 0 for men or 1 for women) and high risk if they have a CHA2DS2-VASc of ≥ 2,[9-10] (this means any woman over 65 or men with any added risk factor) Anticoagulation is indicated in any patient with a history of stroke.

Underuse of anticoagulants and optimisation

The underuse of oral anticoagulants in patients with a high risk of stroke can result in the occurrence of preventable ischemic stroke.[11] A recent study found that use of anticoagulants is poorly associated with the stroke risk. The international Global anticoagulant registry in the field (GARFIELD) study examined the use of warfarin and NOACs and found 38% of patients classified as having a high risk of stroke ($CHADS_2$ score ≥2) did not receive anticoagulant therapy. Similarly when risk was assessed using the CHA_2DS_2-VASc score, 40.7% of the patients with a high risk of stroke did not receive anticoagulant therapy.[12]

Underuse of anticoagulants is often due to an over-estimation of bleeding risks. The ESC and NICE guidelines recommend that the bleeding risk of patients with AF should be assessed using the HAS-BLED score.[13] The HAS-BLED score offers better prediction of bleeding compared with other bleeding risk scores such as HEMORR2HAGES (Table 4) and ATRIA (Table 5) but the effectiveness of HAS-BLED has largely been based on the prediction of bleeding events that were not considered major, i.e. gastrointestinal bleeds as opposed

to intracerebral haemorrhage (ICH).[14] A recent study showed that patients are prepared to accept 4.4 systemic major bleeds for every stroke prevented, so that the stroke risk reduction cannot be balanced against non-intracerebral bleeds.[15] The estimation of bleeding risk is difficult as many of the known factors that increase bleeding risk, overlap with stroke risk factors. Given that the prediction of bleeding risk can be challenging and that the HAS-BLED score does not directly address the bleeding event of greatest concern (ICH), an alternative approach to predicting the risk of bleeding such as brain MRI maybe necessary.[14] MRI can show cerebral microbleeds (CMBs) that are small areas of brain haemorrhage that may increase the risk of future intracerebral haemorrhage in AF patients.[16-17.] A recent meta-analysis of CMBs found the risk of ICH to increase up to 8 fold in ischemic stroke patients with CMBs compared to those without.[18]

There is limited data on cohorts exposed to OAC therapy but the presence of CMBs have been found to increase the risk of warfarin associated ICH. A case control study comparing warfarin users with ICH and warfarin users without ICH, found the number of CMBs were much higher in the ICH group (79.2% vs. 22.9%).[19] Assessing the microbleeds location and underlying cause of the ICH can help decide whether to restart anticoagulation after an ICH.[19] In patients on warfarin there is an increased risk of ICH with lobar microbleeds compared with deep CMBs.[20] Cerebral amyloid angiopathy and a high risk of recurrence are associated with lobar ICH in the aged population, whereas deep ICH are often associated with hypertension. Controlling the blood pressure can permit the resumption of anticoagulation in the case of deep ICH, whereas the presence of multiple lobar microbleeds on MRI will prevent the resumption.[19]

Findings such as these have prompted the recommendation that MRI screening for anticoagulation therapy should be necessary in patients with AF $\geq$ 60.[20] Larger prospective cohort studies such as the ongoing CROMIS-2 study are expected to establish whether brain MRI has the capacity to predict an individual's ICH risk and improve the personalised management of AF patients.[18] The use of MRI in such a way may have significant appeal, despite the economical and logistical issues, particularly for clinicians whose concern for haemorrhagic risk takes precedence over the benefit of stroke prevention when prescribing anticoagulants.[14] In patients in whom the risk of bleeding is too high, the percutaneous occlusion of the left atrial appendage (LAA) is an emerging alternative to oral anticoagulation therapy for stroke prevention as the LAA has been recognised as a major site of clot formation in non-valvular AF patients.[21] Haemorrhagic change in an ischaemic infarct should not be a reason not to anticoagulate.

***Table 4**: Assessment of Bleeding Risk (HEMORR(2)HAGES) in Atrial Fibrillation Patients*

HEMORR(2)HAGES	**Score**
Hepatic or renal disease	1
Ethanol abuse	1
malignancy	1
Older age	1
Reduced platelet count or function	1
Rebleeding risk	2
Hypertension	1
Anaemia	1
Genetic factors	1
Excessive Fall risk	1
Stroke	1

***Table 5**: Assessment of Bleeding Risk (ATRIA) in Atrial Fibrillation Patients*

ATRIA	**Score**
Anaemia	3
Severe renal disease	3
age $\geq$ 75 years	2
Previous haemorrhage	1
hypertension	1

Overuse of anticoagulants and optimisation

The overuse of anticoagulant therapy in low risk patients puts this population at an unnecessary risk of complications associated with bleeding.[9] The Global Anticoagulant Registry in the FIELD (GARFIELD) study which focused on the use of warfarin and NOACs, found when risk was assessed with the $CHADS_2$ score, 42.5% of low risk patients were on anticoagulant therapy and when risk was assessed with the CHA_2DS_2-VASc score even though fewer patients appeared to be on anticoagulant therapy (38.7%) the risk of overuse remained.[12]

Barnes et al.[9] found in their study that only 3.4% of low risk patients ($CHADS_2$ score of 0) were receiving inappropriate therapy with warfarin for stroke prophylaxis in AF, when procedure-based indications were considered. However the value of 3.4% in this study was achieved by utilising the total number of non-valvular AF patients involved in the study as the denominator. Whereas the earlier studies referred to in the paper such as Meiltz et al.'s study,[22] used the total number of patients with a $CHADS_2$ score of 0 as the denominator .The use of a larger denominator by Barnes et al.[9] may render the results misleading and thus the overuse of anticoagulants in low risk AF patients can still be seen as a problem.

The underuse and overuse of anticoagulants suggest that, the $CHADS_2$ and CHA_2DS_2-VASc tools are often not followed appropriately. Furthermore the tools have a limited capacity for the prediction of stroke as shown by their low c statistic scores (0.549 to 0.638).[7] A c-statistic of 1.0 offers perfect discrimination whereas a value of 0.5 means a tool is no better than random chance at making a prediction.[23] In light of this, biomarkers have been suggested as prognostic tools.

Elevated troponin and NT-proBNP levels are each independently associated with the rates of stroke and the addition of the biomarkers to the $CHADS_2$and CHA_2DS_2VASc clinical risk tools improves the prognostic ability of the tools [24]. The level of natriuretic peptides in AF can be associated with atrial dysfunction, which is an established risk factor for thrombus formation in AF. Currently no established explanation exists for the association between stroke and elevated troponin levels but the availability of troponin measurements in most hospitals means it a promising prognostic tool.[7]

The addition of both cardiac biomarkers to the $CHADS_2$ and CHA_2DS_2VASc scores, improves the c statistic more compared to the individual addition of the biomarkers.[25-26] In the future there may be a role for a multi marker strategy to improve risk stratification. It is important to note however that the results from these trials were derived from clinical trial populations and therefore it may not be possible to immediately extrapolate the findings to the general AF population until further trials are performed.[27] BNP levels show considerable variability and despite being a significant risk factor in a study population it is less likely that an isolated result in any patient will be a significantly robust stroke risk marker.

Use of Anticoagulation in Paroxysmal AF and Optimisation

The utilisation of anticoagulation in paroxysmal AF also poses problems. The terminology surrounding the different patterns of AF have been inconsistent in the past, however recent guidelines have proposed a consensus definition for the different types of AF.[28] Paroxysmal AF has been defined as episodes of AF that spontaneously end within 7 days. Persistent AF has been defined as episodes lasting more than 7 days and permanent AF has been defined as AF without any intervening periods of sinus rhythm.[29] The minimum duration of an AF episode that is acceptable as a risk factor for stroke is still unsettled,[5] however guidelines state anticoagulation should be considered after 48 hours of AF[29] Current guidelines recommend that the pattern of AF should not determine whether a patient is given anticoagulation or not. Patients with each type of AF should receive oral anticoagulant therapy dependant on the presence of individual stroke risk factors. [10] Previous data comparing the stroke risk of paroxysmal and permanent AF is believed to be restricted due to methodological problems, such as the use of small sample sizes or differing rates of anticoagulation in patients with differing patterns of AF.

Recent larger trials have found the stroke risk to be higher in non-paroxysmal AF compared to paroxysmal AF. A recent study found that within each CHA_2DS_2-VASc category the outcome rates of embolic events were lower in paroxysmal AF compared to persistent and permanent AF.[28] It is proposed that the electrical abnormalities and pathophysiological changes that predispose patients to thrombus formation and stroke are more pronounced in patients with permanent rather than paroxysmal AF. Thus the pattern of AF can be seen as a marker of increased susceptibility of stroke.[30]

In the above study patients with a CHA_2DS_2-VASc score of ≥ 2 and paroxysmal AF still had a minimum stroke risk of 2%, confirming recommendations that patients with a high clinical risk score of stroke should be anticoagulated regardless of the pattern of AF.[28] To optimise anticoagulation therapy in AF patients it is recommended that in patients where it is not clear whether a patient would benefit from anticoagulant therapy, the pattern of AF should be taken into account.

In low risk patients with paroxysmal AF the benefit of anticoagulation may not outweigh the risk of bleeding.[28] Similar recommendations have been made by Steinberg et al.[31] who prompt for further research regarding more thorough stroke prevention in patients with persistent AF compared to paroxysmal AF.

The detection of PAF itself is challenging due to its short, unpredictable and often asymptomatic nature.[32] There are a variety of strategies and devices available to detect PAF which include intermittent, event-triggered and continuous monitoring through both external and implanted devices. Although it has been established that prolonged ECG monitoring detects more paroxysmal AF the optimum method and duration for detection remain unclear.[33] This is an area which would aid from further research and help to further the optimisation of anticoagulation therapy in AF patients.

Conclusion

Optimal utilisation of anticoagulation in AF patients is challenging. The overuse and underuse of anticoagulation suggests uncertainty exists regarding when anticoagulation is appropriate. The current clinical risk stratification tools are still suboptimal at predicting the risks of stroke and of bleeding and this reduces the ability to accurately balance the risks of anticoagulation in an individual. The presence of novel promising risk stratification tools (biomarkers and MRI) and new techniques for risk assessment may help to manage anticoagulation better in the future. In our current state of knowledge, it is important to apply the CHADS2 or CHA2DS2VASC as well as the HAS-BLED scores as faithfully as possible to gauge the potential risk of stroke and bleeding. Gauging the risk of intracerebral haemorrhage is more of an art but patients with prior cerebral haemorrhage and multiple microbleeds should not be anticoagulated. In these patients and in patients with contraindications to anticoagulants, LAA occlusion should be considered.

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