ATRIAL FIBRILLATION IN DAILY PRACTICE
ATRIAL FIBRILLATION AND STROKE
Risk Stratification and New Anticoagulants

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder seen in clinical practice and is an independent risk factor for morbidity and mortality, primarily because it increases stroke risk [1].

The absolute risk of stroke is 4% per year among non-valvular AF patients, and co-morbid conditions increase the risk 15-20 fold. The risk of stroke is equal in men and women and similar whether the AF is paroxysmal or permanent [2-3].

Effective therapies and mainly oral anticoagulants have been shown to reduce dramatically the risk of AF-related stroke from 46.7‰ patient-years in 1992 to 19.5‰ patient-years in 2002 [4]. But these agents substantially increase the risk of bleeding [5].

THROMBUS FORMATION IN ATRIAL FIBRILLATION

As a result of the loss of organized atrial contraction and the reduced left atrial appendage (LAA) flow velocity there is stasis in the LAA and thrombus formation [6]. Within two days of AF, atrial thrombi may be seen in up to 14% on transesophageal echocardiography ranging from 0.2 to 4.2 cm in size [7].

ESTIMATING STROKE RISK

Other contributors to the AF may increase the risk. They are either clinical (congestive heart failure, hypertension, diabetes mellitus, and previous history of stroke or transient ischemic attack) or anatomical and functional characteristics of the left atrium, such as presence of ‘smoke’ in the left atrium and reduced flow velocity in the left atrial (LA) appendage as seen with Doppler imaging [8].

Control of blood pressure is very effective in reducing the risk of stroke in patients with AF. For example, in the Canadian atrial fibrillation study (1991) the mean systolic blood pressure was 142 mmHg and the observed stroke rate was 3.5% patient-years in the warfarin arm [9]. Conversely, in the RE-LY trial (2009), the mean systolic blood pressure was 131 mmHg and the stroke rate was 1.69% patient-years in the warfarin arm [10].

An easy approach is to consider the risk as mild, intermediate and high [11]. Table I

High-risk patients could be targeted for warfarin, low-risk patients given aspirin or warfarin. This was in the era prior to the availability of new oral anticoagulants.

Different schemes for risk estimation have been developed according to epidemiologic and observational studies.

THE CHADS² SCORE

As a result from the National Registry of Atrial Fibrillation, and after combining two schemes, a risk chart has been established according to clinical criteria such as congestive heart failure, hypertension, diabetes mellitus, and previous history of stroke or transient ischemic attack: the CHADS² score [8]. Table II

This risk stratification model has been popularized because of its ease of use and was established in clinical practice.

The ATRIA trial evaluated the predictive capacity of five well-known risk stratification schemes in a cohort of 13 559 patients [12]:
1. Atrial Fibrillation Investigators
2. Stroke Prevention in Atrial Fibrillation in 1999
3. CHADS² Score in 2001
4. Framingham Score in 2003

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Mild risk features</th>
<th>Moderate risk features</th>
<th>High risk features</th>
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</thead>
<tbody>
<tr>
<td>RISK FEATURES ASSOCIATED WITH STROKE IN ATRIAL FIBRILLATION</td>
<td>Age 65 to 74</td>
<td>Age ≥ 75</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>Symptomatic heart failure</td>
<td>Prior stroke, transient ischemic attack</td>
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<tr>
<td></td>
<td>Coronary artery disease</td>
<td>LVEF ≤ 35%</td>
<td>Prosthetic heart valve</td>
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<tr>
<td></td>
<td>Thyrotoxicosis</td>
<td>Hypertension</td>
<td>Hypertrophic cardiomyopathy</td>
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<td></td>
<td></td>
<td>Diabetes mellitus</td>
<td>Left atrial appendage thrombus</td>
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<td></td>
<td></td>
<td></td>
<td>Prior systemic embolism</td>
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<tr>
<td></td>
<td></td>
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<td>Dense spontaneous echocardiographic contrast</td>
</tr>
</tbody>
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Those schemes were comparable in their predictive capacities (although modest 0.56-0.62) but highly variable in their assignment of risk categories, with a 5-fold difference in their identification of high-risk patients (16.4% to 80.4%).

Lip et al. found that the CHADS$_2$ score suffers from limitations and they validated a new CHA$_2$DS$_2$VASc score [13] (Table III).

Applying this score to 73,538 patients, the stroke and thromboembolism event rate at one year follow-up ranges from 0.78 for score 0 to 23.64 for score 9 (Table IV).

The CHA$_2$DS$_2$VASc score is better in identifying “truly low-risk” patients with AF. Patients with AF who have ≥ 1 stroke risk factor are recommended to have effective stroke prevention therapy, which is essentially oral anticoagulation (OAC) with either well-controlled vitamin K antagonist (VKA) therapy (INR 2-3, with a high percentage of time in the therapeutic range, for example, at least 70%) or new oral anticoagulants.

In an attempt to refine this scheme some authors are looking for more risk factors like the role of transesophageal echo, genomics and serum biomarkers. They found that elevations of troponin I and NT-proBNP are common in patients with AF and independently related to increased risks of stroke and mortality and that TEE-based approach for fine-tuning stroke risk in AF patients with a moderate risk for stroke is feasible [14-15].

**THE BLEEDING RISK AND NET CLINICAL BENEFIT**

Bleeding is the most important concern while treating patients with AF. The risk of major bleeding in the AFFIRM trial was approximately 2% per year with warfarin [16]. This led many physicians to prescribe dual antiplatelet therapy, despite the similar rates of major hemorrhage observed with either warfarin or dual antiplatelet therapy in ACTIVE-W (2.21 vs. 2.42%/year, $p = 0.53$) [17].

Prevention of thromboembolism needs to balance the risk of stroke against the risk of major bleeding, especially intracranial hemorrhage. Recently, a simple bleeding risk score (HAS-BLED, Table V) has been proposed and used in the ESC [18] and Canadian guidelines [19]. The latter guidelines recommend formal bleeding risk assessment, and in patients with a HAS-BLED score of ≥ 3, caution and regular review is recommended. The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk, and importantly, makes clinicians think of the correctable risk factors for bleeding, for example, uncontrolled blood pressure, concomitant use of aspirin/NSAIDs, labile INRs, etc. The risk of bleeding is too high when the HAS-BLED is greater than the CHADS$_2$ score.

Singer et al., in an analysis of the ATRIA cohort, defined the net clinical benefit of warfarin anticoagulation as the estimated reduction in stroke and systemic embolism minus 1.5 times the estimated increase in the rate of intracranial hemorrhage [20].

**ORAL ANTICOAGULANTS**

**Warfarin**

Warfarin (a vitamin K antagonist) is a very effective drug to reduce the risk of stroke in patient with AF. Aspirin is an option reserved for patients with AF who have minimal or no risk factors for stroke or who are reluctant to the use of VKAs.

Warfarin has an unpredictable dose response and a narrow therapeutic window. It requires frequent laboratory monitoring of the international normalized ratio (INR) and subsequent dose adjustment to maintain patients within a goal INR.
Despite evidence-based recommendations for stroke prophylaxis with VKAs, they remain underprescribed in eligible patients with AF [21].

New oral anticoagulants (OAC)

Two broad categories of OACs were studied: the oral direct thrombin inhibitors (DTIs) and oral Factor Xa (FXa) inhibitors. Four large Phase 3 trials with new OACs have been published (RELY, ROCKET-AF, ARISTOTLE, AVERROES) and one is still ongoing (ENGAGE-AF with edoxaban).

Ximelagatran, the first DTI, was tested against warfarin in the SPORTIF III and V trials, which showed non-inferiority of ximelagatran to warfarin. However, the drug has since been withdrawn due to liver toxicity [22].

Dabigatran, the next DTI, was tested in two doses (110 mg twice a day [bid] and 150 mg bid) against warfarin in the huge RE-LY trial [10]. This trial showed that dabigatran 110 mg bid was non-inferior to warfarin for the primary efficacy endpoint of reducing stroke and systemic embolism, with a significant 20% reduction in major bleeding events.

Dabigatran 150 mg bid showed superiority (by 35%) over warfarin, with a similar rate of major bleeding events. Dabigatran 150 mg bid also resulted in significantly fewer ischaemic stroke events versus warfarin. Both doses of dabigatran were associated with significantly less hemorrhagic strokes and intracranial hemorrhage. There was a borderline reduction in all-cause mortality and a significant reduction in cardiovascular mortality.

Total bleeding events (i.e. the composite of major plus minor bleeds) were significantly reduced with both doses of dabigatran, compared to warfarin.

Rivaroxaban, the oral FXa inhibitor, was tested against warfarin in the ROCKET-AF trial, which targeted high-risk patients with AF for inclusion [23]. In this trial, rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint of stroke and systemic embolism, although there was a significant reduction in haemorrhagic strokes. When tested on a more conservative intention to treat analysis, rivaroxaban was not superior to warfarin, although an on-treatment analysis did suggest that superiority to warfarin was achieved (by 12%) for reducing stroke and systemic thromboembolism. Rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint of major plus clinically relevant non-major bleeds, with no significant difference in major bleeds, but an increase in gastrointestinal bleeding events. There was no significant difference in all cause mortality or cardiovascular mortality.

Apixaban, another FXa inhibitor was tested against warfarin in the ARISTOTLE trial [24], which showed a superiority over warfarin in reducing stroke and systemic thromboembolism (by 21%), driven by a 50% reduction in haemorrhagic stroke and no significant difference in ischemic stroke. Major bleeding was significantly less with apixaban (by 31%), as was total bleeding (major plus minor), with no excess of MI events. All-cause mortality was significantly reduced (by 11%) but there was no significant reduction in cardiovascular mortality. Apixaban was also tested against aspirin in a second Phase 3 trial, AVERROES [25], which included AF patients who had failed or refused VKA therapy. This trial was stopped early, due to a clear superiority of apixaban over aspirin (81 mg-324 mg daily), and the rate of major bleeding or intracranial hemorrhage (ICH) was not significantly different between apixaban and aspirin. Apixaban was also significantly better tolerated (as reflected by treatment discontinuations) compared to aspirin or warfarin.

CONCLUSION

There are enough data to explain the risk of stroke and thromboembolism in patients with AF. To have the maximum net clinical benefits, attempts are directed towards the class of patients with very low risk who do not need any anticoagulation. Even though CHADS\textscript2 score is commonly used in the US, using the CHA\textsubscript2DS\textsubscript2-VASc score will clearly identify low risk subjects.

Several questions are to be answered about new oral anticoagulants: Should we consider them as “alternatives to warfarin,” or being “preferred to warfarin.” Choosing of the drug available will depend on the patient preferred dosage schedule i.e. once or twice daily. The age of the patient, his kidney functions, the combination with medications that affect the P-glycoprotein (Pgp) are things to consider. While it is possible to remove dabigatran with hemodialysis in cases of toxicity, this is not the case for the other drugs. In all we still do not have a reliable test to determine the activity of the medications. The ability to tailor treatment based on the different characteristics of the new OACs will significantly reduce stroke and improve overall outcomes in the prevention of stroke in patients with AF.

Other area of research is still needed in the group of patients taking dual antiplatelet therapy, and those with valvular heart disease for usage of novel oral anticoagulants.

**TABLE V**

<table>
<thead>
<tr>
<th>BLEEDING RISK SCORE</th>
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<tbody>
<tr>
<td>Hypertension (e.g. systolic &gt; 160 mmHg)</td>
</tr>
<tr>
<td>Abnormal renal and liver function (1 point each)</td>
</tr>
<tr>
<td>Stroke 1</td>
</tr>
<tr>
<td>Bleeding tendency or predisposition</td>
</tr>
<tr>
<td>Labile International Normalized Ratio (INR) (only if on warfarin)</td>
</tr>
<tr>
<td>Elderly (e.g. age &gt; 65)</td>
</tr>
<tr>
<td>Drug (i.e. concomitant aspirin or non-steroidal anti-inflammatory drugs [NSAIDs]) or alcohol (1 point each)</td>
</tr>
<tr>
<td>Maximum score</td>
</tr>
</tbody>
</table>

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REFERENCES