Solutions to Reduce Cardiovascular Events in Patients with Atrial Fibrillation

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Abstract

AF is the most common sustained cardiac rhythm disorder and an established risk factor for ischemic stroke. Ischemic strokes which occur in patients with AF are particularly severe and disabling. In addition, stroke recurrence is more common in patients with AF compared with those without it. Previous cerebrovascular events, age, hypertension, diabetes, and heart failure are risk factors for stroke in patients with AF.

Various risk stratification schemes have been developed to quantify the risk for stroke in patients with AF. Currently, the most frequently used schemes to assess stroke risk in patients with AF are CHADS2, the ACC/AHA/ESC and American College of Chest Physicians (ACCP) schemes.

Current risk scores are largely derived from risk factors identified from clinical trials and many potential risk factors have not been properly considered. Consequently, the stroke risk in many patients could be underestimated, and these patients could receive a suboptimal antithrombotic prophylaxis.

There is substantial evidence for the benefit of vitamin K antagonists (VKA) in preventing stroke and reducing mortality. Novel oral anticoagulants are available for stroke prevention in patients with AF which overcome some of the difficulties associated with VKA. The introduction of novel oral anticoagulants in clinical practice and the advances in identifying patients at risk of stroke together may overcome many of the difficulties in providing effective stroke prevention for patients with AF.

Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke. Risk stratification for ischemic stroke in patients with AF is based on scores which incorporate several risk factors as previous cerebrovascular events, age, hypertension, diabetes, and heart failure. There are a number of risk factors for stroke that are not recognized by traditional risk scores, such as female gender, atherosclerotic vascular disease, valvular dysfunction and myocardial infarction. Consequently, the stroke risk in many patients could be underestimated, and these patients could receive suboptimal antithrombotic prophylaxis. At least two refinements of current risk scores are in development.

Antithrombotic therapy is tailored according to the level of risk, with vitamin K antagonists (VKA) reserved to medium-high risk patients. VKA are effective in preventing stroke and reducing mortality. Newer oral anticoagulants (direct thrombin inhibitors and direct Factor Xa) inhibitors are currently available for stroke prevention in patients overcoming some of the difficulties associated with VKAs.
In this review, we report on recent advances to optimize the risk scores and on the clinical development on the new oral anticoagulants. Improved risk scores and new oral agents together may overcome the current difficulties in providing effective stroke prevention in patients with AF.

**Epidemiology of Atrial Fibrillation**

AF is the most common sustained cardiac rhythm disorder. The prevalence of AF is probably underestimated due to under-diagnosis of asymptomatic cases. AF is relatively uncommon before the age of 60 years, but affects nearly 10% of individuals over the age of 80 years. After adjustment for age and predisposing conditions, men have a 1.5-fold greater risk of developing AF than women. Hypertension, diabetes mellitus, hyperthyroidism, alcohol abuse and obesity are additional risk factors for AF. In addition, after adjusting for cardiovascular risk factors, heart failure, valvular heart disease and myocardial infarction increase the risk of AF. Emerging risk factors for AF include reduced vascular compliance, atherosclerosis, insulin resistance, environmental factors, inflammation, increased level of natriuretic peptides and genetic predisposition.

The prevalence of AF is dramatically increasing. This is partly due to increase in the longevity of the general population.

**AF and Ischemic Stroke and Impact of AF on Stroke Severity and Risk of Recurrence**

AF is the most important independent risk factor for ischemic stroke. AF is associated with an approximate five-fold increased risk of stroke. Indeed, one in every four-five ischemic strokes occurs in patients with AF. Multivariate analysis revealed age, hypertension, diabetes mellitus, prior stroke or TIA, myocardial infarction and congestive heart failure as significant additional risk factors for stroke in patients with AF.

AF-related ischemic strokes are generally more severe and more disabling than strokes suffered by patients without AF. This might be due to several reasons: older age, larger size of the cerebral infarct, more common hemorrhagic transformations and more severe initial neurological impairment. Among stroke survivors, those with AF are more likely to suffer a recurrent stroke than those without AF.

Several clinical and observational studies found that the incidence of ischemic stroke in patients with paroxysmal AF was similar to that in patients with permanent AF.

**Antithrombotic Prophylaxis to Reduce the Risk of Stroke: Evidence from Clinical Trials**

Dose-adjusted VKA to maintain an international normalized ratio [INR] between 2.0 and 3.0 are effective for stroke prevention in patients with AF. A meta-analysis of six randomized trials showed that VKA provided about 65% risk reduction of ischemic stroke in comparison to placebo. A similar risk reduction is seen in patients who receive VKA for secondary prophylaxis. Aspirin 325 mg per day provides a 22% reduction in the incidence of stroke versus placebo. A meta-analysis of five randomized trials that compared dose-adjusted warfarin to ASA 325 mg per day showed that warfarin provided a 36% risk reduction for all strokes and a 46% risk reduction for ischemic strokes versus aspirin. VKAs prevent more severe and disabling strokes as compared to aspirin.

In the ACTIVE-W trial, warfarin was also significantly more effective than aspirin plus clopidogrel for stroke prevention in patients at high risk of stroke. However, among patients with AF for whom VKA therapy was considered unsuitable, the combination of clopidogrel and aspirin was associated with a reduction in the primary outcome of stroke, myocardial infarction, non-cerebral systemic embolism or death from vascular causes compared with aspirin alone. The difference was primarily due to a reduction in the rate of stroke. Major bleeding was significantly more common in patients assigned to the combination of clopidogrel and aspirin.

VKA are associated with an increased risk of
bleeding, particularly intracranial hemorrhage and gastrointestinal bleeding, with respect to aspirin or no treatment (0.3%, 0.2% and 0.1% per year respectively).\textsuperscript{18,19} VKA use accounts for a significant proportion of iatrogenic emergency room admissions. About 4% of admissions to Stroke Unit for intracranial hemorrhages are due to warfarin treatment within therapeutic range.\textsuperscript{24}

Stroke risk rises sharply when the INR falls below 2.0 and the risk of intracranial bleeding increases sharply when the INR increases beyond 3.0.\textsuperscript{25}

Identifying Patients at Risk of Stroke to Guide Antithrombotic Prophylaxis

The risk for stroke varies widely among patients with AF. Various risk stratification schemes have been developed \textsuperscript{7, 21-31} in attempts to evaluate and quantify individual risk. Currently, the most frequently implemented schemes for assessing stroke risk in patients with AF are CHADS\textsubscript2\textsuperscript{26} the ACC/AHA/ESC \textsuperscript{25} and American College of Chest Physicians (ACCP) \textsuperscript{30, 31} schemes.

In CHADS\textsubscript2, a cumulative score (range 0–6) is calculated according to the presence of defined risk factors. Different risk factors are given different weightings: two points are assigned for a previous stroke or TIA and one point is assigned for each of the following: age older than 75 years, hypertension, diabetes mellitus and recent cardiac failure. Scores of 0, 1 and ≥2 denote low, moderate and moderate-to-high risk of stroke, respectively.\textsuperscript{26, 27}

In contrast, the ACC/AHA/ESC \textsuperscript{25} and ACCP \textsuperscript{30, 31} schemes do not use a scoring system. Instead, they each categorize patients as being at low, moderate or high risk of stroke according specific combinations of risk factors.

The ACCP scheme does not take into consideration whether the patient has previously experienced a stroke or TIA, making this scheme less applicable to evaluating stroke risk for secondary stroke prevention (Table 1).

The current guidelines for antithrombotic prophylaxis \textsuperscript{25,31} recommend that patients with AF at low risk of stroke receive daily aspirin, those at high risk of stroke (or ‘moderate-to-high’ risk according to CHADS\textsubscript{2}) receive VKA therapy (unless contraindicated), and either aspirin or a VKA is recommended for patients classified as being at moderate risk of stroke. CHADS\textsubscript{2} is more likely than other schemes to classify a patient as being at moderate risk of stroke,\textsuperscript{32, 33} which may lead to uncertainty among physicians with regard to the choice of antithrombotic therapy for these patients (guidelines recommend either aspirin or VKA).

Limitations of Risk Stratification Scores

Current risk scores are largely derived from risk factors identified from trial cohorts and many potential risk factors have not been considered.\textsuperscript{34} The

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<td>Congestive heart failure: 1 point</td>
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<td>No moderate- or high-risk features</td>
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majority of patients with AF have at least one additional clinical condition that further increases their risk of stroke. Indeed, there are a number of risk factors for stroke that are not recognized by CHADS₂ as female gender, atherosclerotic vascular disease, valvular dysfunction and myocardial infarction. Consequently, many patients’ stroke risk could be underestimated, and they could receive suboptimal antithrombotic prophylaxis. In addition, several independent analyses have shown that assignment of stroke risk varies widely depending on the scheme used, which may contribute to inconsistent implementation of guideline recommendations for anticoagulation. Disagreement between risk scores comes in the critical range for decision-making; they all identify very low and very high risk pretty well, but diverge in the moderate classification.

An additional limitation of current risk stratification schemes is that they were all developed and validated in patients not receiving anticoagulants. Consequently, these schemes identify which patients are above a certain threshold of risk and would benefit from anticoagulation, but not those patients who remain at risk despite anticoagulation. A recent study found that carotid/vertebral atherosclerosis and hyperlipidemia are associated with an increased risk for ischemic events in patients with AF on adequate warfarin treatment. Stroke prevention in patients with AF might therefore be improved with more accurate schemes for stratifying stroke risk. It’s equally likely that treating everyone who is not low risk would just as good as try to predict risk. However, being able to communicate risk to the patient might improve adherence to medical recommendations. As the incidence of ischemic stroke is similar in patients with paroxysmal AF and those with permanent AF, antithrombotic therapy should not be guided by the clinical subtype of AF, but rather by the presence of additional risk factors for stroke.

Advances in Evaluating Stroke Risk: Building on CHADS₂

CHA2DS₂-VASc was recently developed with the aim of more accurately predicting stroke risk for patients with AF by taking into account some of the additional risk factors not recognized by CHADS₂. Like CHADS₂, a cumulative scoring system is used (see Table 2). However, the scoring for age is stratified and relatively younger age (≥65 years) is recognized as a risk factor whereas CHADS₂ only recognizes patients over the age of 75 years. In addition, female gender and vascular disease are included in the evaluation of stroke risk, whereas these risk factors are not recognized by CHADS₂. CHA₂DS₂-VASc was validated in the Euro Heart Survey; prediction of stroke risk was improved compared with CHADS₂ and only a small proportion of patients were categorized as being at ‘intermediate risk’ of stroke.

Another scheme for evaluation stroke risk in patients with AF has been developed by Rietbrock et al. As in CHADS₂, a cumulative score is calculated (see Table 2). However, this new scheme differs from CHADS₂ as follows: a greater weighting is placed on a previous stroke or TIA (six points compared with two points in CHADS₂), female gender is recognized, and the points assigned for age are

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<td>Age</td>
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<td>Previous stroke/TIA</td>
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<td>+6</td>
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<tr>
<td>Hypertension</td>
<td>+1</td>
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<tr>
<td>Female gender</td>
<td>–</td>
<td>+1</td>
<td>+1</td>
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<tr>
<td>Vascular disease</td>
<td>–</td>
<td>–</td>
<td>+1</td>
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<tr>
<td>Cumulative score</td>
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awarded on a sliding scale, with points assigned to patients ≥40 years of age, whereas in CHADS\(_2\) points for age are only assigned to those who are >75 years old. This scheme was evaluated in the UK General Practice Research Database (>51,000 patients with AF) and showed a modest improvement in the accuracy for predicting stroke over CHADS\(_2\). (C-statistic: 0.68 for CHADS\(_2\), 0.72 for the Rietbrock scheme).

In addition the accuracy of CHADS\(_2\) for predicting stroke risk might be improved by also taking into account AF burden (e.g. presence and duration of AF in addition to CHADS\(_2\) variables) since AF increases the risk of stroke in an independent manner.\(^{40,41}\)

**Antithrombotic Prophylaxis: Unmet Needs**

The Euro Heart Survey showed that VKA are not being used in accordance with the current guidelines and not in accordance with stroke risk.\(^{42-44}\) Only 61% of patients with AF were treated in accordance with the guidelines: 28% were undertreated, which was associated with a higher risk of thromboembolism and stroke; 11% were over-treated, which was associated with a trend towards a higher risk of bleeding.\(^{41}\)

The NABOR (National Anticoagulation Benchmark Outcomes Report) program, a performance improvement program designed to benchmark anticoagulation prophylaxis, treatment, and outcomes among participating hospitals, confirmed that VKA are under-prescribed to eligible patients with AF and conversely are prescribed to a high proportion of patients at low risk who do not require anticoagulation.\(^{45}\) Real-world data from registries and observational studies have also shown that patients with paroxysmal AF are much less likely to receive VKA prophylaxis than those with persistent or permanent AF.\(^{37,43,45}\)

Only 11% of patients admitted to the Stroke Unit of the University of Perugia for an ischemic stroke and known AF had received VKA prior to admission and only 40% of them were in the therapeutic range.\(^{11}\) A retrospective cohort study (ISAM) showed that 11–36% of patients (depending on country) are outside of the target INR range for >50% of the time,\(^{46}\) which leaves them either at increased risk of stroke (INR <2.0) or increased risk of bleeding (INR >3.0).

There is much concern with regard to the management of patients at moderate to high risk of stroke who are in need of anticoagulation but are deemed ineligible for VKAs for one reason or another. In the absence of alternative oral anticoagulants to VKAs, the only available option is the administration of antiplatelet agents (aspirin alone or aspirin plus clopidogrel combined), which is significantly less effective than VKAs (as discussed above) or no prophylaxis. Such patients are likely to receive only ASA (i.e. to be greatly undertreated and remain at risk of stroke). Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year) (relative risk, 1.57; 95% CI, 1.29 to 1.92; P<0.001).

**New Oral Anticoagulants In the Development of Stroke Prevention in AF**

The ideal profile of a new oral anticoagulant includes the following: a predictable pharmacological profile, so that INR monitoring and dose modifications are not required, rapid onset and offset of actions as well as fixed oral dosing that would be most convenient for patients and could potentially improve adherence to the prescribed regimen.

**Oral Direct Thrombin Inhibitors**

Ximelagatran was the first of these latest novels, and The SPORTIF trials \(^{47,48}\) showed that it was at least as effective as warfarin for the prevention of stroke, with no difference seen in the rate of total bleeding. Ximelagatran was withdrawn from the market in 2006 due to liver toxicity. Nevertheless, this drug provided the proof of concept for direct thrombin inhibition and showed that oral anticoagulation without regular INR monitoring could be safe and effective.

Dabigatran is a second-generation of direct thrombin inhibitors. In the landmark phase III RE-LY trial, dabigatran was the first oral anticoagulant to show its superiority to warfarin for stroke prevention in AF.\(^{49}\) Dabigatran 110 mg twice daily (bid) resulted in a rate of stroke and systemic em-
Oral Direct Factor Xa Inhibitors

The oral direct factor Xa inhibitor rivaroxaban was compared to warfarin in the ROCKET-AF study. This trial was a phase III, randomized, double-blind, event-driven non-inferiority trial with over 14,000 patients comparing rivaroxaban with warfarin in nonvalvular AF (at least two documented episodes) and a history of stroke, TIA, or non-CNS embolism or at least two independent risk factors for future stroke. Enrolment of patients without stroke, TIA, or systemic embolism and only two risk factors was capped at 10% of the overall study population; all subsequently enrolled patients were required to have at least three stroke risk factors or a history of stroke, TIA, or systemic embolism. A total of 86% of the population had a CHADS2 score of 3 or higher. Patients were randomized to rivaroxaban 20 mg once daily (or 15 mg once daily in patients with moderate renal impairment), or dose-adjusted warfarin titrated to a target INR of 2.5. The per-protocol, as treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism; if the non-inferiority criteria were satisfied, superiority was analyzed in the intent-to-treat population. Rivaroxaban was similar to warfarin for the primary efficacy endpoint of prevention of stroke and systemic embolism (event rate 1.71 versus 2.16 per 100 patient years for rivaroxaban versus warfarin; hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.66–0.96, P = 0.001 for non-inferiority). The stricter intention-to-treat analysis also showed rivaroxaban to be similar to warfarin but did not reach statistical significance for superiority: event rate 2.12 versus 2.42 per 100 patient years for rivaroxaban versus warfarin; HR 0.88, 95% CI 0.74–1.03, P = 0.117 for superiority. This superiority was only demonstrated in the per-protocol analysis of patients who continued to receive treatment for the 40-month trial period: event rate 1.70 versus 2.15 per 100 patient years for rivaroxaban versus warfarin; HR 0.79, 95% CI 0.65–0.95, P = 0.015 for superiority. Major and non-major clinically relevant bleeding was similar between the rivaroxaban and warfarin groups. The rivaroxaban group had significantly less fatal bleeding (0.2 versus 0.7 per 100 patient years; P < 0.001 for non-inferiority) but with a lower rate of major hemorrhage similar to that observed in warfarin-treated patients (3.11% per year vs. 3.36% per year, p=0.31). Dabigatran was also associated with higher rates of treatment discontinuation than warfarin, and dabigatran-treated patients had somewhat signals for more myocardial infarction, major GI bleeding and dyspepsia.

The AVERROES study was designed to evaluate the use of apixaban for stroke prophylaxis by comparing it to aspirin in patients unsuitable for warfarin. The study enrolled 5,600 patients with AF who could not take warfarin and compared apixaban 5 mg twice daily (2.5 mg twice daily for patients aged over 80 years, weighing less than 60 kg or with renal impairment) with aspirin 81–324 mg/day. The study was stopped because of an acceptable safety profile and benefit in favor of apixaban. After a year, patients taking apixaban were found to have a 55% reduction in the primary endpoint of stroke or systemic embolism (1.6% versus 3.7% per year, HR 0.45, 95% CI 0.32–0.62, P = 0.001). The rate of major bleeding was similar in both groups: 1.4% per year for apixaban and 1.2% per year for aspirin (HR 1.13, 95% CI 0.74–1.75, P = 0.57). Aspirin was the less well-tolerated therapy.

The ARISTOTLE trial compared apixaban to warfarin in patients with AF. It was a randomized phase III, double-blind, international trial comparing apixaban 5 mg twice/day versus warfarin titrated to an INR between 2 and 3 in over 18,000 patients. The primary outcome was stroke (either ischemic or hemorrhagic) or systemic embolism, and the trial was designed to test for non-inferiority. Secondary objectives included an analysis for superiority with respect to the primary outcome and to the rates of major bleeding and all-causes of mortality. The follow-up period was 1.8 years.
The rate of the primary outcome in ARISTOTLE was 1.27% per year in the apixaban group versus 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P = 0.001 for non-inferiority; P = 0.01 for superiority). This was primarily driven by a reduction in hemorrhagic stroke, as the rates of ischemic stroke were comparable with warfarin: 0.97% per year in the apixaban group versus 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P = 0.42). Conversely, the rates of hemorrhagic stroke were 0.24% per year in the apixaban group versus 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P = 0.001). Apixaban demonstrated a benefit with regards to all-causes of mortality compared to warfarin: rates of death from any cause were 3.52% in the apixaban group versus 3.94% in the warfarin group (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P = 0.047). Apixaban was found to be safer than warfarin with regards to major bleeding: 2.13% per year in the apixaban group versus 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.50 to 0.80; P = 0.001). Drug discontinuation occurred less frequently with apixaban compared to warfarin: 25.3% versus 27.5% (P = 0.001). The average time spent in therapeutic INR was 62.2% for the warfarin-treated patients. The reported adverse and serious adverse effects were similar in both groups.

Another randomized phase III trials exploring the use of oral direct Factor Xa inhibitors for stroke prevention in patients with AF is currently ongoing. This study is the ENGAGE AF TIMI 48 (NCT00781391): double-blind, randomized study comparing two different doses of edoxaban (30 mg or 60 mg once a day) with dose-adjusted warfarin.

Conclusions

- AF is a major risk factor for stroke, and its prevalence increases with older age
- Patients with AF vary widely with regard to their stroke risk and currently the choice of antithrombotic prophylaxis depends on an individual patient’s magnitude of risk. The role of risk stratification after the advent of newer agents is not entirely clear
- There is room for improvement in risk stratification and several refinements are in development. Better stratification of stroke risk may lead to better adherence to antithrombotic prophylaxis for individual patients
- VKAs are effective but are associated with a number of drawbacks in real-life practice
- Novel oral anticoagulants (including two major classes of agents: direct thrombin inhibitors and selective Factor Xa inhibitors) are available for stroke prevention in patients with AF which overcome some of the difficulties associated with VKAs.
- These advances in identifying patients at risk of stroke together with the introduction of novel oral anticoagulants into clinical practice may overcome many of the current difficulties in providing effective stroke prevention for patients at risk.

Disclosures

No disclosures relevant to this article were made by the authors.

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