

ATRIAL FIBRILLATION AND STROKE

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Introduction

Patients with atrial fibrillation have a 4 - to 5-fold increased risk of stroke due to embolism of thrombus in the left atrium [1]. Stroke risk varies depending on the presence or absence of several risk factors for cardiovascular disease [2,3], which were also used for creating a risk stratification schemes for thromboembolism. The risk of thromboembolism is divided into low, intermediate, and high risk strata [4]. Given the limitations of oral anticoagulation treatment with vitamin K antagonists, such risk stratification allows clinicians to target patients at “high risk” for treatment with vitamin K antagonists. For the intermediate risk category, guidelines recommend treatment with vitamin K antagonists or aspirin, and aspirin is recommended for the low risk category. Schemes for stratifying the risk of stroke have been largely derived from non-anticoagulation arms of clinical trial cohorts, in which many potential thromboembolic risk factors were not recorded. In these historical trials, less than 10% of patients screened were randomised, and over the past 15-20 years the evolution of risk schemes has not improved their predictive value for patients at high risk [5].

Clinical risk of stroke in atrial fibrillation

More recent data in patients at intermediate risk show that vitamin K antagonists are superior to aspirin in reducing the risk of thromboembolism and adverse events, [6-8] and aspirin does not reduce the risk of thromboembolism in atrial fibrillation patients at “low risk” [9]. Thus, a paradigm shift has been proposed whereby greater efforts are made to identify

“truly low risk” patients who may not need any antithrombotic treatment, whereas all others could be considered for oral anticoagulation [9-11].

The most widely used scheme for the risk of cardioembolic stroke includes the following criteria: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke / Transient ischemic attack - CHADS₂) [12]. Last two factors redouble risk factors for thromboembolism. Many have discussed the limitations of this assessment because of the large proportion of patients with the moderate risk (11). In 2006, the guidelines by the American Society of Cardiology (American Heart Association - AHA) added another possible risk factors with less evidence, including female gender, age 65-74 years, coronary artery disease and thyrotoxicosis [13]. The additional risk factors could easily identify patients with truly low risk. Therefore, they have been expressed in the CHA₂DS₂-VASc: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Previous Stroke / transient ischemic attack, Vascular disease, Age 65-74 years, Sex category. An analysis of 121,280 patients with atrial fibrillation has demonstrated that the risk of both scales, CHADS₂ and CHA₂DS₂-VASc was dependent from risk factors. The second scale has proven to be more valid for stroke prediction in patients categorised as being at low and intermediate risk by the CHADS₂ scheme. This is clinically important, as many of the patients at low risk according to CHADS₂ are not at “truly low risk” and treatment guidelines are not conclusive for those at intermediate risk. The risk associated with a specific risk score in both CHADS₂ and CHA₂DS₂-VASc depends on the risk factors composing the score. CHA₂DS₂-VASc performed better than CHADS₂ in predicting

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patients at high risk and can also be used to identify patients with non-valvular atrial fibrillation with a truly low risk of thromboembolism. [14,15,16].

Table 1. Risk stratification scheme for cardioembolic stroke in patients with atrial fibrillation according the CHADS2 [15]

Condition	Points
C Congestive heart failure	1
H Hypertension	1
A Age >75 years	1
D Diabetes mellitus	1
S2 Previous Stroke / transient ischemic attack	≥2

Table 2. Risk stratification scheme for cardioembolic stroke in patients with atrial fibrillation according the CHA2DS2-VASc [16]

Condition	Points
Congestive heart failure	1
Hypertension*	1
Age ≥75 years	2
Age 65-74 years	1
Previous Stroke / transient ischemic attack	2
Vascular diseases (myocardial infarction, peripheral arterial disease or plaque in the aorta)	1
Diabetes mellitus	1
Female	1

*History of hypertension

Patients with a certain risk factor or patients on a scale CHA (2) DS (2)-VASc reach one point or more are candidates for oral anticoagulation. Patients who are on a scale CHA(2)DS(2)-VASc do not reach one point, are a group of truly low-risk and require no anticoagulant treatment.

HAS-BLED SCORE

Despite extensive use of oral anticoagulation in patients with atrial fibrillation and the increased bleeding risk associated with such drugs use, no handy quantification tool of assessing this risk exists. HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score is a practical risk score to estimate the one-year

risk for major bleeding (intracranial, hospitalization, haemoglobin drop >2g/L and/or transfusion) in a patients with atrial fibrillation.

Table 3. HAS-BLED score assesses risk of major bleeding in atrial fibrillation patients [17]*

Condition	Points
H Hypertension (systolic pressure ≥ 160 mm Hg)	1
A Abnormal renal/liver function	1
S Stroke	1
B Bleeding history or predisposition	1
L Labile INR	1
E Elderly (>65)	1
D Drugs/alcohol concomitantly)	1

*HAS-BLED – Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; INR – International Normalized Ratio.

How to reduce stroke risk in atrial fibrillation patients?

Therapeutic cardio version and rhythm control do not reduce stroke risk [18]. Also percutaneous left atrial occlusion is of unclear overall benefit [19,20]. On the basis of consistent results from >12 randomized trials, anticoagulation is established as highly efficacious for prevention of stroke and moderately efficacious for reducing mortality [21].

Thirty-three randomized trials involving >60 000 participants have compared various antithrombotic agents with placebo/control or with one another [21, 22-24]. Treatment with adjusted-dose warfarin (target INR, range 2.0 to 3.0) provides the greatest protection against stroke [relative risk reduction (RRR) 64%; 95% CI, 49% to 74%], virtually eliminating the excess number of ischemic strokes associated with atrial fibrillation if the intensity of anticoagulation is adequate and reducing all-cause mortality by 26% (95% CI, 3% to 23%) (Table 3) [21]. Aspirin offers modest protection against stroke (RRR, 22%; 95% CI, 6% to 35%). There are no convincing data that favour one dose of aspirin (50 mg to 325 mg daily) over another. Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (RRR; 95% CI, 22% to 52%) (Table 3) [21].

?→ Table 3. *Efficacy of Warfarin and Aspirin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials** [21]

Comparison	No. of Trials	No. of Patients	Relative Risk Reduction, 95% CI	Estimated NNT for Primary Prevention
Adjusted-dose warfarin vs. control	6	2900	64 % (49–74)	40
Aspirin vs. control	7	3990	19 % (1–35)	140
Adjusted-dose warfarin vs. aspirin	9	4620	39 % (19–53)	90

CI indicates confidence interval, and NNT, No. needed to treat. No. needed to treat for 1 y to prevent 1 stroke, based on a 3.5%/y stroke rate in untreated patients with atrial fibrillation and without prior stroke or TIA.

Two randomized trials assessed the potential role of the combination of clopidogrel (75 mg daily) plus aspirin (75 mg to 100 mg daily) for preventing stroke in patients with atrial fibrillation. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) investigators compared this combination antiplatelet regimen with adjusted-dose warfarin (target INR, 2.0 to 3.0) in patients with atrial fibrillation with 1 additional risk factor for stroke in ACTIVE W and found a 40% relative risk reduction (95% CI, 18% to 56%, $P=0.001$) for stroke with warfarin compared with the dual antiplatelet regimen. ACTIVE A compared clopidogrel combined with aspirin with aspirin alone in atrial fibrillation patients deemed unsuitable for warfarin anticoagulation and who had at least 1 additional risk factor for stroke (approximately 25% were deemed unsuitable because of concern for warfarin-associated bleeding). Dual antiplatelet therapy resulted in a 28% relative risk reduction (95% CI, 17% to 38%; $P=0.0002$) in all strokes (including parenchymal ICH) over treatment with aspirin alone, but major bleeding was increased by 57% (increase in RR; 95% CI, 29% to 92%, $P<0.001$); overall and in absolute terms, major vascular events (the study primary end point) were decreased 0.8% per year, but major haemorrhages increased 0.7% per year (RR for major vascular events and major haemorrhages, 0.97; 95% CI, 0.89 to 1.06; $P=0.54$). Disabling/fatal stroke, however, was decreased by dual antiplatelet therapy (RRR, 26%; 95% CI, 11% to 38%; $P=0.001$) [21].

The initial 3 months of adjusted-dose warfarin are a particularly high-risk period for bleeding [25], and especially close monitoring of anticoagulation is advised during this interval. Treatment of hypertension in atrial fibrillation patients reduces the risk of both

ICH and ischemic stroke; hence, it has double benefits for atrial fibrillation patients who have received anticoagulation. [26–28]. Target systolic blood pressure should be <140 mm Hg. The benefits versus risks of the combined use of antiplatelet agents in addition to warfarin in elderly atrial fibrillation patients are inadequately defined. Combined use of warfarin with antiplatelet therapy increases the risk of intracranial and extracranial haemorrhage [29]. Adjusted-dose anticoagulation (target INR, 2.0 to 3.0) appears to offer protection against MI that is comparable to aspirin in atrial fibrillation patients [30]. Addition of aspirin to warfarin is not recommended for most atrial fibrillation patients with stable coronary artery disease. [31, 32]. Clopidogrel plus aspirin combined with warfarin has been suggested for 9 to 12 months after placement of bare-metal coronary stents [33]. Because drug-eluting stents require even more prolonged antiplatelet therapy, bare-metal stents are generally preferred for atrial fibrillation patients taking warfarin [34]. A lower target INR of 2.0 to 2.5 has been recommended [35].

New treatment of atrial fibrillation

Direct thrombin inhibitors offer an alternative treatment with warfarin in patients with atrial fibrillation. In a international multicenter study of long-term anticoagulation treatment (RE-LY - Randomized Evaluation of Long-term Anticoagulation Therapy) were enrolled 18,113 patients with atrial fibrillation who have had at least one additional risk factor for stroke. The study demonstrated the ability of dabigatran to reduce the occurrence of both stroke and haemorrhage in patients who had atrial fibrillation with high risks of stroke compared with patients who received warfarin. RE-LY was designed to compare

2 fixed doses (110mg or 150mg, twice daily) of dabigatran, each administered in a blinded manner, with open-label use of warfarin. In this study, in a population of patients with atrial fibrillation, dabigatran at 110 mg b.i.d was associated with stroke and systemic embolism rates similar to those associated with warfarin, and with lower rates of major haemorrhage. However, when dabigatran was administered at a dose of 150 mg, lower rates of stroke and systemic embolism and similar rates of major haemorrhage were found compared with warfarin [36]. Dabigatran has recently recognized by the Food and Drug Administration – FDA in the United States). In RE-LY, dabigatran demonstrated efficacy without the need for ongoing INR monitoring or dose adjustments. Furthermore, there were no food restrictions on those taking dabigatran in RE-LY. Therefore dabigatran will offer patients and doctors the first new treatment option for stroke prevention in atrial fibrillation in more than 50 years.

Table 4. Recommendations in primary stroke prevention in patients with nonvalvular atrial fibrillation [37]

Recommendations
1. Active screening for atrial fibrillation in patients >65 years of age in primary care settings using pulse taking followed by an ECG as indicated can be useful (Class IIa; Level of Evidence B).
2. Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with nonvalvular atrial fibrillation deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely (Class I; Level of Evidence A).
3. Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with atrial fibrillation, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring (Class I; Level of Evidence A).
4. For high-risk patients with atrial fibrillation deemed unsuitable for anticoagulation, dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding and might be reasonable (Class IIb; Level of Evidence B).
5. Aggressive management of BP coupled with antithrombotic prophylaxis in elderly patients with atrial fibrillation can be useful (Class IIa; Level of Evidence B).

Favourable preliminary results in the prevention of stroke in patients with atrial fibrillation also indicates the factor Xa inhibitor – rivaroxaban [38].

Recent changes to the guidelines for the management of stroke patients with atrial fibrillation are based on the results of the ACTIVE study. In the study arm ACTIVE A the combination of aspirin plus clopidogrel with aspirin alone were compared in patients who were not candidates for treatment with warfarin [21,22]. The results showed fewer ischemic strokes, but more bleedings in the treatment group with the combination compared with aspirin alone. The combination of these drugs brings the same risk of bleedings than warfarin and therefore is not recommended for the patients who have a contraindication to warfarin because of bleeding risk [39].

The novelty in the recommendations is that patients with atrial fibrillation and at high risk of re-stroke, who should temporarily break the oral anti-coagulants, introduce a bridging therapy with low molecular weight heparin [39].

Tabela 5. Recommendations in secondary stroke prevention in patients with nonvalvular atrial fibrillation [39].

Recommendations
1. Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with stroke or TIA and with nonvalvular chronic or intermittent atrial fibrillation should receive warfarin (Class I; Level of Evidence A).
2. Antiplatelet therapy with aspirin is recommended for some patients with atrial fibrillation with bleeding risk (Class I; Level of Evidence A).
3. Dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding. The combination of these drugs brings the same risk of bleedings than warfarin and therefore is not recommended for the patients who have a contraindication to warfarin because of bleeding risk (ClassIII; Level of Evidence B). New Recommendation!
4. Patients with atrial fibrillation and at high risk of re-stroke (CHADS2 5 or 6), who should temporarily break the oral anticoagulants, introduce a bridging therapy with low molecular weight heparin (Class IIa; Level of Evidence C). New Recommendation!

According the Canadian guidelines (The Canadian Cardiovascular Society – CCS) dabigatran is recommended for the patients with atrial fibrillation

and at high risk for stroke because of its advantages over warfarin [40].

Conclusion

Atrial fibrillation is a major, prevalent, independent risk factor for ischemic stroke, and adjusted-dose warfarin is highly efficacious for reducing stroke and death in high-risk patients with this condition. Adjusted-dose warfarin continues to be underused, particularly among very elderly atrial fibrillation patients.

Development of safer, easier-to-use oral anticoagulants might improve the benefit-risk ratio.

Novel oral anticoagulants (eg, direct thrombin inhibitors, factor Xa inhibitors) have and are being tested in several ongoing large randomized trials, and additional treatment options appear to be on the horizon.

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