Stroke Prevention in Patients with Atrial Fibrillation

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Stroke Prevention in Patients with Atrial Fibrillation

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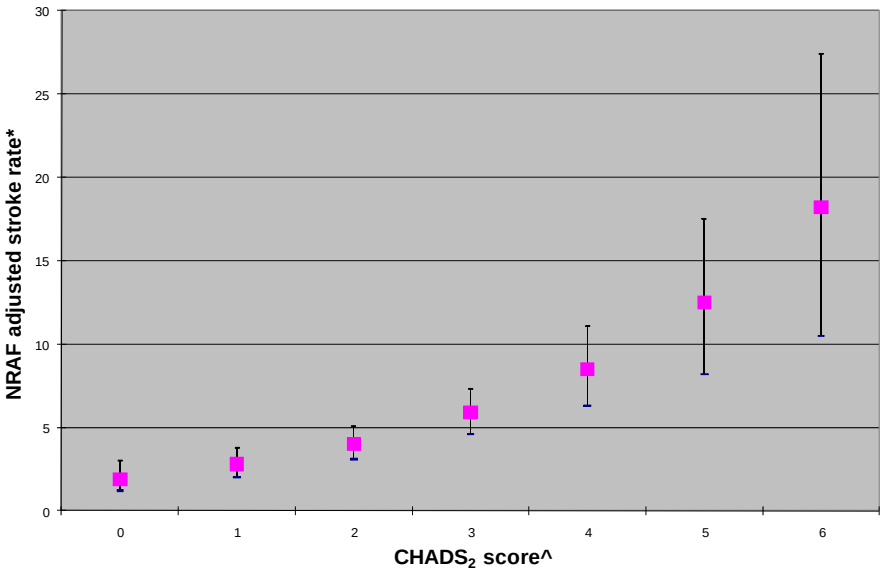
Introduction

Atrial fibrillation (AF) significantly increases a patient's risk of developing vascular events, such as stroke (one in six strokes occurs in patients with a background of AF), systemic embolism and vascular death. The risk of cerebral embolism in patients with AF and recent transient ischaemic events or previous strokes is around 12% per year with an annual mortality rate of 5%. The current evidence recommends that the best therapy in terms of risk prevention is anticoagulation; the ACTIVE W trial, which compared anticoagulation with a combination of aspirin and clopidogrel, was stopped early due to anticoagulation clearly being the superior option. However, in practice, anticoagulation is not always a suitable option. Medical contraindications such as intracranial bleeding, severe active bleeding, recent brain, eye, or spinal cord surgery, malignant hypertension, severe thrombocytopenia and other factors, e.g. compliance issues, reluctance to have regular INR checks, etc may preclude anticoagulant therapy. In such situations antiplatelet therapy and other treatment modalities appear to be more desirable options. In this short review we discuss the various treatment options under the umbrella term antithrombotic therapy and we also explore a surgical treatment, based on currently available evidence, for prevention of cardio-embolic strokes in patients with non-rheumatic AF.

Risk Stratification

Patients with AF can be stratified into high and low risk groups for developing strokes depending on their co-morbidities and risk factors, which may also influence how aggressive we are in our management. AF patients who are at high risk of developing strokes include patients over 65 years of age, those with previous strokes or transient ischaemic attacks (TIA), hypertensive, diabetics, or those with poor left ventricular function. The low risk group includes those less than 65 years of age with no other risk factors. The $CHADS_2$ scoring system has been developed to further classify patients where a patient scores 2 points if they have had a previous stroke or TIA and scores 1 point for each of the following risk factors: recent congestive heart failure, hypertension, age > 75 years or diabetes mellitus. As shown in figure 1, the risk of developing a stroke rises exponentially with every additional point. Hence prophylactic treatment should be started promptly especially for those in high risk categories.



^CHADS2 score is calculated by adding 2 points for having a prior stroke or TIA, and 1 point for the following – recent congestive heart failure, hypertension, age > 75 years, diabetes mellitus.
* The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model assuming that aspirin was not taken. – Pink squares indicate the adjusted stroke rate and the lines above and below indicate the 95% confidence interval.

Figure 1: Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$^ Score
Adapted from: Gage BF, Waterman AD, Shannon W, et al, 2001. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. *JAMA* 285(22):2864-2870.

Anticoagulation

Since 1989, there have been several randomized clinical trials investigating the use of anticoagulants for primary and secondary stroke prevention in patients with non-rheumatic atrial fibrillation. Five large primary prevention trials have shown a reduction in the incidence of ischaemic strokes by 65% with warfarin therapy. The recent Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA) compared the use of warfarin therapy adjusted to INR 2.5 with low dose aspirin (75mg) in patients over 75 years of age. In 973 patients who were prospectively followed up for 2.7 years, there were 24 significant events (21 strokes, 2 other intracranial haemorrhages and one systemic embolus) with warfarin therapy; 48 significant events (44 strokes, one other intracranial haemorrhage and three systemic emboli) occurred in the cohort assigned to aspirin therapy. The European Atrial Fibrillation Trial (EAFT), a large secondary prevention trial, randomized 1007 AF patients with recent TIA or minor stroke into anticoagulant, 300mg aspirin or placebo groups. After a mean follow-up of 2.3 years, 8% of patients on anticoagulant therapy developed a vascular event compared to 17% in the placebo group of patients. Haemorrhagic events in anticoagulated patients were 2.8% yearly with no intracranial bleeds identified.

Another antiplatelet drug, indobufen was compared with warfarin in the Studio Italinano Fibrillazione Atriale (SIFA). The incidence of any strokes for patients on indobufen was 5% compared with 4% for those on warfarin therapy. Patients on indobufen had a greater percentage of ischaemic strokes (3.9%) compared to 2.2% for those on warfarin, but this was partially offset by the slightly increased haemorrhagic strokes for patients on warfarin (0.88% compared to 0.2%).

Another approach which has been investigated in the Stroke Prevention in Atrial Fibrillation III (SPAFIII) and Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study (AFASKII) is whether low-dose warfarin which would require much less monitoring in addition to aspirin therapy would be efficacious in reducing thrombotic events. SPAFIII compared a regime of low-dose warfarin combined with 325mg aspirin against adjusted dose warfarin and was terminated after 1.1 years as patients on combination therapy developed a much higher rate of ischaemic strokes and systemic embolic events (7.9% per year as compared to 1.9% for those on adjusted dose warfarin). AFASKII randomized subjects into fixed low dose warfarin (1.25mg per day) alone, low dose warfarin and 300mg aspirin in combination, 300mg aspirin alone and compared the results against adjusted dose warfarin (INR 2.0-3.0). Findings from this trial indicated that in the first year patients on adjusted-dose warfarin had a lower rate of developing ischaemic strokes or systemic embolic events but after 3 years, there were no significant differences between the groups. Haemorrhagic events in both trials in all cohorts were insignificant.

Important clinical issues when starting warfarin therapy include the optimal intensity and when to initiate treatment. A case-control study found that risks of stroke rose steeply when INRs fell below 2.0 and that the risk of bleeding increased significantly when INR was above 4.0 with a steep increase of intracranial haemorrhages when INR reached 5.0 or above. The current guidelines recommend lifelong anticoagulation, maintaining INR levels between 2.0 and 3.0 which is in agreement with the published evidence. The International Stroke Trial randomized patients to 14 days of either aspirin or heparin therapy within the first 48 hours of developing an acute ischaemic stroke. Of the patients who were in AF, the heparin group had lower rates of recurrent ischaemic strokes but this was offset by increased rate of haemorrhagic strokes compared to the non-heparin cohort. Although not specifically investigated, patients with large strokes seem to be particularly prone to haemorrhagic transformation. Hence early anticoagulation in patients with AF particularly those with acute large strokes is not advised, especially not within the first 14 days.

Dual Antiplatelet Therapy

Another option in antiplatelet therapy to consider is if combined antiplatelet treatment is more effective than a single agent. As different agents have different modes of action, it would seem that using multiple treatments would be synergistic and give better protection against thrombotic events such as myocardial infarction and ischaemic stroke. The ACTIVE A trial enrolled 7554 patients with AF in whom anticoagulation was contraindicated, randomising them to receive aspirin (75-100mg OD) plus either clopidogrel (75mg OD) or a placebo. The patients taking clopidogrel were shown to have a significant reduction in vascular events (particularly disabling stroke) after 3.6 years compared to those taking the placebo. However, these patients were also shown to be at a much higher risk of bleeding complications, with a 57% higher incidence of major bleeding events (mainly GI bleeds). This suggests that, although dual antiplatelet therapy does reduce the risk of vascular events, the risk of bleeding does limit the use of these medications.

Other antithrombotic agents

Other emerging medical treatments include anti-Xa agents such as Rivaroxaban (Xarelto®) and Apixaban (Eliquis®) and oral direct thrombin inhibitor such as Dabigatran (Pradaxa®). Connolly et al ran a noninferiority trial involving 18,113 patients with AF and an increased risk of stroke, who received either a fixed dose of dabigatran (either 110mg or 150mg) or adjusted dose warfarin. They were followed up on average for 2 years (median duration), with the primary outcome being stroke or systemic embolism. It was found that those patients receiving 110mg dabigatran had a similar incidence of stroke/embolism compared to those on warfarin but lower rates of haemorrhage (3.36% in warfarin group compared to 2.71%, with p = 0.003). Those patients receiving 150mg dabigatran had a reduced incidence of stroke/embolism compared to those on warfarin (1.69% per year on warfarin compared to 1.11% with p < 0.001). However, the risk of major haemorrhage was similar in both groups. Results have been newly revised (fig. 2) but have not influenced the conclusions of the trial. As a result of this trial, the higher dose (150mg) but not the lower dose (110mg) of Dabigatran has recently been approved by the Food and Drug Administration (FDA) for risk reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In addition, Dabigatran would be easier to administer (since it is an oral preparation) and monitor, therefore, it may be suitable for some patients who cannot take warfarin for lifestyle reasons. Both Rivaroxaban and Apixaban′ also show promising results with comparable results to warfarin in terms of stroke prevention in patients with non-valvular AF and indeed may even have less risk of severe intracranial and major bleeds compared with warfarin.

Therapy	Trials	Participants	Relative Risk Reduction (95% CI)
Adjusted-dose warfarin compared to placebo	6	2900	62 (48 to 72)
Aspirin compared with placebo	6	3199	22 (2 to 38)
Adjusted-dose warfarin compared with aspirin	5	2837	36 (14 to 52)
Adjusted-dose warfarin compared with low-dose warfarin	3	893	38 (-20 to 68)
Aspirin compared with low-dose warfarin	2	934	15 (-42 to 49)
			Relative Risk (95% CI)
Adjusted dose warfarin compared with a)110mg Dabigatrin b) 150mg Dabigatran	1	18,113	a) 0.91 (0.74 to 1.11) [published] 0.90 (0.74-1.10) [revised] b) 0.66 (0.53 to 0.86) [published] 0.65(0.52-0.81) [revised]

Figure. 2: Summary of medical antithrombotic therapies
Adapted from Hart et al Ann Intern Med 1999

Surgical treatment

A novel method of managing patients with chronic AF is the percutaneous closure of the left atrial appendage as most cardio-embolic thrombi are formed in the left atrial appendage. The recently published multicentre randomized non-inferiority trial where AF patients scoring a $CHADS_2$ score of 1 or above were enlisted to undergo this procedure or to continue on warfarin therapy. The probability of non-inferiority was greater than 99.9% and the higher rates of adverse events (major bleeding, pericardial effusion and device embolism) were mostly due to periprocedural complications.

Other preventative measures

There are a number of issues to consider in optimizing the management of patients with AF who are at a high risk of a vascular event. Primary prevention, lifestyle changes and control of risk factors such as diabetes and hypertension are important, as for every extra point on the $CHADS_2$ score, the expected stroke rate in AF patients per 100 patient years increase exponentially with AF as illustrated above (fig. 1).

Management of AF itself is another factor, so efforts should be made to adequately control ventricular rate. Rhythm control strategies offer no survival advantage, hence rate control and anticoagulation is the best option for high risk patients.

Conclusion

Anticoagulation with adjusted-dose warfarin is currently the most effective stroke prevention therapy for patients in AF. For those with contraindications, antiplatelet therapy can be used to reduce recurrent ischaemic events, although to a lesser degree. Results of clinical trials with newer antithrombotic agents are promising. As these drugs have a number of advantages over warfarin, they may eventually replace it as the drugs of first choice.

References:

1. Hart RG, Halperin JL, 1999. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. *Ann Int Med.*131 (9):688-695.
2. Koudstaal PJ, Koudstaal A, 1999. Secondary stroke prevention in atrial fibrillation: indications, risks, benefits. *J Thrombosis and Thrombolysis*, 7(1): 61-65.
3. Hart R, Benavente O, McBride R, Pearce LA, 1999. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation; a meta-analysis. *Ann Intern Med*, 131(7):492-501.
4. Mant J, Hobbs FDR, Fletcher K, et al, 2007. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham atrial fibrillation treatment of the aged study, BAFTA): a randomized control trial. *Lancet* 370:493 -503.
5. EAFT Study Group, 1995. Optimal intensity of anticoagulant treatment in nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Eng J Med* 333: 5-10.
6. Morocutti C, Amabile G, Fattaapposta F, et al, 1997. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. *Stroke* 28:1015-1021.
7. Gullov AL, Koefoed BG, Petersen P, et al, 1998. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: second Copenhagen atrial fibrillation, aspirin and anticoagulation study. *Arch Intern Med.* 158(27):1513-21.
8. Stroke Prevention in Atrial Fibrilation Investigators, 1996. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. *Lancet*. 348 (9028):633-638.
9. Hylek EM, Skates SJ, Sheehan MA, Singer DE, 1996. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 335(8): 540-546
10. Hylek EM, Singer DE, 1994. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 120:897-902.
11. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP, Briët E, 1995. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 333:11-17.
12. International Stroke Trial Collaborative Group, 1997. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both or neither among 19,435 patients with acute ischaemic stroke. *Lancet* 349: 1569-1581.
13. Connolly, SJ et al. 2009. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 17;361(12):1139-51. Epub 2009 Aug 30.
14. Connolly S, Ezekowitz MD, Yusuf S, *et al.* Newly identified events in the RE-LY trial. 2010. *N Engl J Med.*. 363(19): 1875-1876.
15. Beasley B, Pharm D, Unger E, Temple R. 2011. Anticoagulat Options – Why the FDA approved a higher but not a lower dose of Dabigatran. *N Engl J Med* 364 (19):1788-1790
16. Patel MR, Mahaffey KW, Garg J et al 2011. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365(10):883-891.
17. Connolly SJ, Eikelboom J, Campbell J et al. 2011. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 364(9):806-817
18. Granger C, Alexander J, McMurray J et al, 2011. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 365 (11):981-992.
19. Holmes DR, Reddy VY, Turi ZG et al, 2009. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. *Lancet* 374(9689):534-542.
20. Gage BF, Waterman AD, Shannon W, et al, 2001. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. *JAMA* 285(22):2864-2870
21. Wyse et al 2002. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 347(23):1825-1833.

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