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EDITORIAL

Stroke prevention in atrial fibrillation

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ABSTRACT

The only major and potentially fatal risk for patients with atrial fibrillation is the development of systemic thromboembolism. Stroke occurs five times more frequently in patients with atrial fibrillation than in comparable patients in sinus rhythm. The yearly incidence of stroke in atrial fibrillation largely depends on the underlying heart disease: from 0.5% in 'lone' atrial fibrillation up to 20% in rheumatic heart valve disease.

Oral anticoagulation with vitamin K antagonists dramatically reduces the stroke risk by two-thirds, but is a laborious and patient-unfriendly therapy. Oral direct thrombin blockers and oral factor Xa antagonists, both without therapy monitoring, may replace warfarin for this indication, but there are safety and efficacy issues to be resolved. Oral antiplatelet agents are effective, but clearly less than warfarin. Angiotensin receptor blockers are currently under investigation.

Routine electrocardioversion for atrial fibrillation does not reduce the stroke risk, but promising techniques include electroablation of the left atrium and occlusion of the left atrial appendage.

KEYWORDS

Aspirin, atrial fibrillation, cardioversion, stroke, warfarin

The yearly incidence of stroke in patients with atrial fibrillation is about 5%,[1] which is five times higher than in comparable populations in sinus rhythm. The stroke risk largely depends on the underlying heart disease. In 'lone' atrial fibrillation (absence of heart disease), the stroke risk is only 0.5% per year,[2] whereas in atrial fibrillation associated with rheumatic valvular heart disease such as mitral valve stenosis it is very high. Needless to say, oral anticoagulation (with warfarin, acenocoumarol and phenprocoumon) has shown to be effective in the prevention of thromboembolism in patients with valvular and nonvalvular atrial fibrillation.[3] Severe bleeding with warfarin is seen in one in 100 patients per year, which is double the risk of stroke in lone atrial fibrillation. Therefore, anticoagulation is only indicated in atrial fibrillation patients with a stroke risk of 2% or more per year.

For several decades oral anticoagulants have been used in the treatment and prevention of venous thrombosis. Oral anticoagulants block the vitamin K dependent liver production of the plasma clotting factors II (prothrombin), VII, IX and X. They have a relatively narrow therapeutic window which requires close international normalised ratio (INR) monitoring: overdosing may result in life-threatening bleeding and underdosing in inefficacy. Recently, some major improvements in the monitoring of oral anticoagulation have been made: efficacy and safety of oral anticoagulation were found to be correlated with the INR values reached in trials in patients with atrial fibrillation,[4] in those with artificial heart valves[5] and in those after myocardial infarction.[6] Moreover, INR self-monitoring, which may even be more efficient than laboratory monitoring,[7] has become a reality.

Yet oral anticoagulation remains a laborious and poorly predictable therapy. Recently, oral direct thrombin inhibitors were introduced. These agents do not need anticoagulant monitoring. In a large clinical trial on venous thromboprophylaxis ximelagatran showed better efficacy than low-molecular-weight heparin[8] and in the large ESTEEM study in coronary artery disease ximelagatran plus aspirin showed superiority over aspirin alone.[9] After a proper dose-finding study[10] the drug has now been tested against warfarin in patients with atrial fibrillation in two large trials: SPORTIF-III[11] and SPORTIF-V.[12]

In 3407 patients with nonvalvular atrial fibrillation, ximelagratran 36 mg twice daily in an open-label design and in 3922 patients in a double-blind set-up proved not inferior to warfarin (INR 2 to 3) in stroke prevention with similar major (*table 1*), but less minor bleeding.

Table 1. *Efficacy of the direct thrombin blocker ximelagatran in patients with atrial fibrillation*

Trial	Stroke/systemic embolism		OR (95% CI)	P value
	Ximelagatran (36 mg bid)	Warfarin (INR 2 to 3)		
SPORTIF-III[11]	40/1704 (2.3%)	56/1703 (3.3%)	0.71 (0.48-1.07)	0.10
SPORTIF-V[12]	51/1960 (2.6%)	37/1962 (1.9%)	1.38 (0.91-2.10)	0.13
Total	91/3664 (2.5%)	93/3665 (2.5%)	0.98 (0.74-1.30)	0.94

Just as in the previous trials, transient liver enzyme elevations were seen in up to 3% with 24 mg,[6] and 6 and 7% with 36 mg twice daily in the SPORTIF trials and ESTEEM,[9] respectively. Recently, the new oral direct thrombin blocker dabigatran was evaluated in a 12-week dose-finding warfarin-controlled study in 502 patients with atrial fibrillation.[13] It shows an acceptable efficacy and safety profile, but liver enzyme elevation was only seen in less than 1% of patients on dabigatran (*table 2*). These results are the basis for the very large phase III trial of dabigatran *vs* warfarin (RELY).

Not only direct thrombin inhibitors have been tested in stroke prevention in atrial fibrillation. The novel once-weekly subcutaneous factor Xa-specific pentasaccharide idroparinux was compared with warfarin in the AMADEUS study (5700 patients). Unfortunately, this trial was prematurely terminated due to increased severe bleeding in the idroparinux-treated patients. Possibly, the very long-acting pentasaccharide cannot be adequately antagonised in case of bleeding. In the near future oral factor-Xa inhibitors will become available and will surely be evaluated against warfarin in atrial fibrillation.

Beside novel anticoagulants, antiplatelet therapy has been evaluated in stroke prevention. Aspirin has also shown to be protective against stroke in atrial fibrillation with a relative risk reduction of 36% compared with placebo,[14] much less than warfarin *vs* control (62% relative risk reduction). In direct comparison with warfarin, aspirin is less effective but can be used as an excellent alternative in patients not willing or capable of using the cumbersome oral anticoagulants. Also the platelet adenosine diphosphate (ADP) receptor antagonist clopidogrel, which has a good track record in the invasive and noninvasive treatment of coronary artery disease, has been tested against warfarin in aspirin-treated patients with atrial fibrillation in the 6500 patients of the ACTIVE-W study. This trial was also stopped prematurely, this time because of lack of efficacy relative to warfarin. The other ACTIVE studies are being continued. ACTIVE-A is a randomised trial of aspirin plus clopidogrel *vs* aspirin alone in patients with atrial fibrillation not willing or capable of using oral anticoagulants. ACTIVE-I is a randomised trial of irbesartan *vs* placebo on top of other therapy in patients with atrial fibrillation participating in the other ACTIVE studies.

If new drugs become registered for atrial fibrillation, it is very likely that warfarin will be replaced by these alternatives that are much easier to use. Although the first results look promising, there are unexpected safety and efficacy problems. Safety issues include bleeding and liver toxicity. Since warfarin use is associated with a yearly risk of at least 1% major bleeding, excess haemorrhagic complications of new drugs will not be easily found. Very long-acting drugs without proper antidotes such as idroparinux should be avoided. Although, to a lesser extent, liver enzyme elevations were observed in the early studies with statins, this turned out to be a minor problem. Whether this will also be the case for newer drugs is unknown and should be further tested. If after treatment initiation frequent liver enzyme testing proves to be necessary in the first six months, this will counterbalance the new drugs potential advantages with regard to drug monitoring. Furthermore, only patients similar to those in the large trials will be eligible for the trade-in of

Table 2. *Efficacy and safety of the new oral direct thrombin blocker dabigatran in a 12-week warfarin-controlled dose-finding study in atrial fibrillation*[13]

	Dabigatran (all doses) (n=472)	Warfarin (INR 2 to 3) (n=70)	P value
Stroke and thromboembolism	0.5%	0	0.61
Major bleeding	0.9%	0	0.98
All bleeding	18%	18%	
ALT elevation >3 times ULN	0.7%	0	0.85

ALT = alanine aminotransferase; ULN = upper limit of normal.

warfarin, because safety data on the new drugs in other atrial fibrillation patients are lacking. If safety seems good in a broader patient population, the drugs may find their way into general use in atrial fibrillation. But this process will take a while, and in the meantime aspirin-controlled studies with agents such as clopidogrel, which has a more established safety profile than the new drugs, will be finished. Depending of the outcome, physicians willing to trade-in warfarin in their atrial fibrillation patients must decide on which agent they will go for.

Finally, also nonpharmacological measures have been evaluated in stroke prevention in atrial fibrillation. For a long time routine electrocardioversion was thought to be the cure for atrial fibrillation with subsequent discontinuation of antiarrhythmic drugs and oral anticoagulation. However, this strategy has not been found to be superior to the combination of just rate control and proper oral anticoagulation.[15,16] More sophisticated techniques include internal electroablation of the left atrium and occlusion of the left atrial appendage. The effect on stroke prevention of these interventions, however, remains to be established.

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