The use of novel anticoagulants in non-valvular atrial fibrillation

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Atrial Fibrillation (AF) occurs in 1-2% of the general population, making it the commonest sustained cardiac arrhythmia. It becomes more common as one gets older, with a prevalence of 5-15% at 80 years of age. Atrial fibrillation is independently associated with doubling of mortality, mostly associated with a higher risk of stroke. One-fifth of strokes are due to AF, with a proportion of 'cryptogenic' also likely to have undiagnosed AF as a cause. Anti-thrombotic therapy is the only treatment which reduces deaths in patients with AF.[1]

The increased risk of stroke is present in all patients with AF, and no difference exists between patients with paroxysmal or permanent AF. However, numerous risk factors are independently related to an increased risk of thrombo-embolic disease. These risk factors include previous strokes/ transient ischaemic attacks/ thrombo-embolic episodes, age, diabetes, hypertension, congestive heart failure, structural heart disease, and gender. Risk-stratification tools, notably $CHADS_2$ and CHA_2DS_2-VASc scores (Table 1), have been created in order to better score and quantify the adjusted stroke rate for a given patient. A CHA_2DS_2-VASc score of 2 would confer a 2.2% yearly adjusted risk of stroke, while with a score of 6 the risk would go up to 9.8%.[1,2]

Over 2 decades ago, numerous large multi-centre trials have shown that Vitamin-K Antagonists (VKA) significantly reduce the risk of stroke when compared to placebo with a relative risk (RR) reduction of 64%.[3] The anti-coagulant effect of VKAs is mediated by blocking the production of Vitamin K-dependent coagulation factors II, VII, IX and X. Starting a patient on anti-coagulation therapy, however, is not without risks. The increased risk of bleeding, especially gastro-intestinal and cerebral bleeds, are dreaded complications. A balance between the patient's risk of stroke and his/her risk of bleeding has also to be taken into consideration.[1,3]

Studies comparing thrombo-embolic prophylaxis with aspirin versus VKA all showed significant superiority of the latter. In fact, the efficacy of aspirin in preventing stroke in AF is doubtful, as many studies comparing it to placebo failed to show a significant reduction of stroke. The few studies which showed a positive outcome for aspirin had their methodology heavily criticised. Notwithstanding, aspirin is still considered by some as an option in AF patients with no or a single stroke risk factor.[1]

Thrombo-embolic prophylaxis with VKA, with warfarin being the most common, has been at the forefront in the management of AF patients. VKA therapy is fraught with many problems, mainly related to inter- and intra-patient variation in their pharmacological effect. The anti-coagulation effect of VKAs, measured using INR, is dependent on a patient's genetic makeup and associated with significant drug, alcohol and food interactions. Patients therefore cannot be given a 'standard dose' and need to get frequent INR testing, with the dose being adjusted accordingly. In 'real-life' situations, over half of the time, patient on VKA are under-coagulated, and therefore are not getting the intended therapeutic benefit.

Table 1: CHA_2DS_2-VASc score adapted from the European Society of Cardiology guidelines for the management of AF[1]

Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)		**Adjusted stroke rate according to CHA_2DS_2-VASc score**		
Risk Factor	**Score**	**CHA_2DS_2-VASc score**	**Patients (n=7329)**	**Adjusted stroke rate (%/year)**
Congestive heart failure/Left Ventricular dysfunction	1	0	1	0%
Hypertension	1	1	422	1.3%
Age >75	2	2	1230	2.2%
Diabetes mellitus	1	3	1730	3.2%
Stroke/TIA/thrombo-embolism	2	4	1718	4.0%
Vascular disease	1	5	1159	6.7%
Age 65–74	1	6	679	9.8%
Sex category (i.e. female sex)	1	7	294	9.6%
Maximum score	**9**	**8**	**82**	**6.7%**
		9	**14**	**15.2%**

Many patients who, despite being on VKA therapy, develop thrombo-embolic episodes are in fact found to be inadequately anti-coagulated. Warfarin and other VKAs also have a long half-life and therefore pose a problem when emergency surgery is needed.[1]

Novel Oral Anti-Coagulants (NOACs) have recently become available, as a 'non-VKA' alternative, for thrombo-embolic prophylaxis in non-valvular AF patients.[4,5] What these drugs share in common is that they block a single step in the coagulation cascade. Three drugs are currently approved by the European commission for the prevention of stroke in patients with non-valvular AF: the direct thrombin-inhibitor dabigatran (Pradaxa®, Boehringer Ingelheim), and the direct factor Xa inhibitors rivaroxaban (Xarelto®, Bayer) and apixaban (Eliquis®, Pfizer/ Bristol-Myers Squibb). These 3 NOACs have been accepted as an alternative to VKAs on the strength of the results obtained in 3 clinical trials comparing them to warfarin. The RE-LY trial compared 2 different dabigatran doses (110mg and 150mg twice daily) to warfarin, the ROCKET-AF trial compared warfarin to rivaroxaban 20mg once daily, while ARISTOTLE compared warfarin to apixaban 5mg twice daily. These trials followed earlier trials which had shown success for NOACs in preventing venous thrombo-embolic events (VTE) in patients undergoing orthopaedic surgery.

The RE-LY trial was an open-label trial comparing dose-adjusted warfarin to a randomised dose of either 110mg or 150mg of dabigatran.[6] In this trial, dabigatran 150mg was superior to warfarin for the occurrence of stroke and systemic embolism, with no significant difference in major bleeding. Dabigatran 110mg was on the other hand non-inferior to warfarin, but with 20% fewer major bleeds. Rates of haemorrhagic stroke and intracranial haemorrhage were lower with both doses of dabigatran, but gastrointestinal bleeding was significantly increased with the 150mg dose. There was a non-significant numerical increase (28%) in myocardial infarction (MI) with both dabigatran doses. A meta-analysis of 7 dabigatran trials (including VTE prophylaxis trials) was carried out because of the concern of the small increase in myocardial infarctions.[7] Despite a 33% significant increase in MI, an 11% reduction in all-cause mortality was seen when compared to warfarin. The increased risk of MI with dabigatran is thought to be due to the protective effect of warfarin, rather than being caused by the new direct thrombin inhibitor.[8]

Rivaroxaban was approved for the prevention of stroke in non-valvular AF following the randomised double blinded ROCKET-AF trial.[9] This study showed that rivaroxaban 20mg once daily (reduced to 15mg in patients with renal failure) was non-inferior to warfarin, on an intention-to-treat basis, for the primary end-point of stroke and embolic episodes. Although the rates of mortality and ischaemic strokes were similar, patients on rivaroxaban had significantly less haemorrhagic strokes and intracranial haemorrhages.

The latest drug approved for anti-coagulation in non-valvular AF is apixaban, which was approved on the strength of the ARISTOTLE trial.[10] In this study 5mg twice daily apixaban (with dose reduction to 2.5mg in renal failure, > 80yrs, or < 60kg) was compared to warfarin in a randomized, double-blind, double-dummy manner. Apixaban showed superiority to warfarin with a 21% reduction in stroke and systemic embolism, a 31% reduction in major bleeding, and an 11% reduction in all-cause mortality.

The lack of head-to-head trials between different NOACs makes it inappropriate to make direct comparisons. The 3 major trials had different populations, with slightly different inclusion and exclusion criteria resulting in different baseline characteristics. For example, the ROCKET-AF trial had an older population with a higher $CHADS_2$ score than the other 2 trials. All drugs have some renal excretion (with 80% in dabigatran) and therefore all NOACs need to have their dosage reduced in renal failure. To date, there is no specific antidote to reverse their anticoagulant effects in case of emergencies; however they all have short half-lives. From a compliance point of view, rivaroxaban has the distinct advantage of being a once daily dose. As time goes by, NOACs will also find new indications, as seen by the recent EMA approval of rivaroxaban for acute coronary syndromes.

The recent launch of oral non-Vitamin K anticoagulants heralds a new era in stroke prophylaxis of non-valvular AF patients. In the next few years they will surely replace warfarin which, despite its effectiveness, is frowned upon for its cumbersome dosing regimen by both patients and clinicians. S

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