New Oral Anticoagulants for Non-Valvular Atrial Fibrillation - Safety Issues

Abstract:

One of the major adverse effects of atrial fibrillation (AF) is stroke which is more disabling and fatal than strokes due to other causes. An individual’s risk of AF related stroke may be reduced by two-thirds with effective anticoagulation with warfarin however it is underused and prescribed to only two thirds of appropriate candidates. Factors contributing to suboptimal warfarin use include drug and dietary interactions, the requirement for monitoring the INR and the risk of haemorrhage. Despite this over 35,800 patients receive warfarin (for all therapeutic indications) under the Community Drugs Scheme (CDS, GPS & LTI) accounting for over 90% of all patients being treated with oral anticoagulants.

The direct thrombin inhibitor dabigatran etexilate (Pradaxa) and factor Xa inhibitors rivaroxaban (Xarelto) and apixaban (Eliquis) are new oral anticoagulants that are at least as efficacious as warfarin. Advantages of these new agents include the predictable anticoagulant effect without the requirement for regular monitoring, lower rates of intracranial haemorrhage and the reduction in potential drug interactions. Currently there are over 3,350 patients in Ireland being treated with these new agents. The recently updated ESC guidelines for the management of AF recommend that one of the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban) should be considered rather than warfarin for most patients with non-valvular AF based on their net clinical benefit (apixaban is not yet reimbursed in Ireland for AF indication).

In the case of rivaroxaban it is contraindicated in patients with a CrCl less than 15 ml/min and a dose reduction to 11.25 mg daily is recommended for patients with moderate renal dysfunction i.e. CrCl between 30 – 49 ml/min. The manufacturers prescriber guide for rivaroxaban in patients with severe renal impairment (i.e. CrCl < 15 ml/min) suggests the 15 mg/day dose however prescribers should note that a CrCl less than 30 ml/min was an exclusion criteria in the main clinical trial for rivaroxaban in patients with non valvular AF. Therefore clinicians may wish to err on the side of caution by avoiding these products in patients with a CrCl < 30 ml/min if the bleeding risk is considered high.

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In the absence of a specific antidote to the haemorrhagic adverse effects of these new agents how can we as prescribers reduce the risk of such complications? One of the most important ways is through the identification of patients which may be at increased risk of haemorrhage which would then facilitate either dose adjusting or avoiding these drugs altogether if the risks are considered to outweigh the benefits. Patient populations considered at increased risk of bleeding include those with impaired renal function. Dabigatran is contraindicated in patients with a creatinine clearance (CrCl) less than 30 ml/min and a dose reduction to 110 mg twice daily is advised for those patients with a CrCl between 30 – 50 ml/min if the bleeding risk is considered high.

References