EDITORIAL

New oral anticoagulants versus vitamin K antagonists in countries with good INR control

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Routine monitoring of the international normalised ratio (INR) in patients treated with vitamin K antagonists (VKAs) is mandatory because of a narrow therapeutic index combined with an unpredictable and highly variable anticoagulant effect. The lowest risk of thrombotic and bleeding complications is reached by maximising the time in the therapeutic range (TTR). A low TTR indicates poor INR control and has been associated with increased risks of thrombotic and bleeding complications in patients with atrial fibrillation (AF).[1,2] The TTR is determined by individual characteristics, such as use of co-medication, as well as by the centre that manages the patient.[1] The mean TTR per centre (cTTR) thereby reflects the quality of management of VKA therapy of that specific centre.

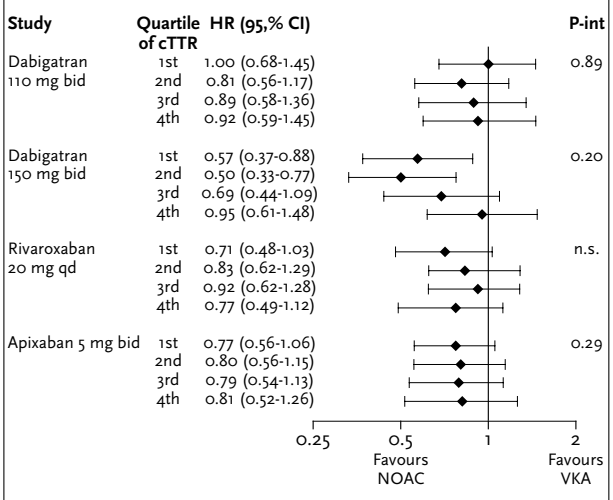
The new oral anticoagulants (NOACs) dabigatran etexilate, rivaroxaban and apixaban have been compared with VKA therapy in over 50,000 patients with AF.[3-5] The NOACs are used at a fixed dose without the need for routine coagulation monitoring and offer significant simplification of anticoagulant therapy. The results of the AF trials indicate that unmonitored NOACs are either non-inferior or superior compared with monitored VKAs. Concern has arisen if the benefits observed in the AF trials will apply in countries with a high quality of INR control of VKA therapy after the publication of a subgroup analysis of the RE-LY trial in 2010.[6] Although there was no significant interaction between the cTTR and treatment for the prevention of stroke or systemic embolism, the hazard ratio (HR) in the upper quartile of cTTR (>72.6%) of dabigatran etexilate 150 mg twice daily *vs* warfarin suggested a loss of superiority of dabigatran etexilate in centres with the highest TTR (HR 0.95, 95% confidence interval 0.61-1.48).[6]

Management of VKA therapy in the Netherlands is provided by a nationwide network of thrombosis services. In their annual reports, the percentage of INR results within the therapeutic range is consistently 70-80%.[7] However, the cross-sectional method used to calculate this percentage differs from the widely used Rosendaal method.[8] Moreover, the Dutch Federation of Thrombosis Services uses a wider therapeutic range (INR 2.0-3.5) than the therapeutic range in randomised controlled trials (INR 2.0-3.0). It is therefore hard to compare the quality of INR control in the Netherlands with the cTTRs from the trials. In this issue of the Netherlands Journal of Medicine, Bezemer and colleagues compare the Dutch cross-sectional method with the Rosendaal method in a representative sample of patients treated with VKA therapy in the Netherlands.[9] The results show that the two methods produce similar results with a TTR of 75% for the therapeutic range of 2.0-3.5. The TTR for the narrower INR target range of 2.5-3.5 was 60%. This study is the first to report the quality of INR control achieved in the Netherlands in terms that can be compared with international standards. The study shows that the quality of management of VKA therapy in the Netherlands is good, but not the best worldwide.

How should these results influence the expectations of the potential benefits of NOACs over VKA therapy in the Netherlands? Over two years have passed since the initial subgroup analyses by cTTR from the RE-LY trial. Similar analyses have now been presented for the two other atrial fibrillation trials, which allow a revaluation of the concept that NOACs may not provide the same benefits over VKAs in countries with good INR control.[10,11] The analyses of the three AF trials comparing NOACs with VKAs according to subgroups of cTTR for the primary efficacy outcome of stroke or systemic embolism are presented in *figure 1*. The results show that there is no significant interaction between quartiles of cTTR and treatment. This indicates that the benefits of NOACs over VKA apply to countries with poor INR control as well as in countries with good INR control. Although one may argue that a non-significant trend towards decreased superiority of dabigatran etexilate 150 mg twice daily *vs* VKA is present in centres with the highest cTTR, no such trend is visible

for rivaroxaban, apixaban or the low dose of dabigatran etexilate (*figure 1*). Moreover, the cTTR for the narrower INR range of 2.5-3.5 achieved by the Dutch Federation of Thrombosis Services is lower than the highest quartile of cTTR in each of the AF trials. With these new subgroup data from the AF trials, we should feel confident that most of the benefits of NOACs over VKA therapy will also apply to countries with good INR control including the Netherlands.

Figure 1. *Efficacy of NOACs compared with VKA therapy for prevention of stroke or systemic embolism in patients with AF, according to subgroups of cTTR*



cTTR = the mean time in therapeutic range per centre; HR = hazard ratio of the NOAC vs. VKA therapy; 95% CI = 95% confidence interval; P-int = p value for interaction between quartile of cTTR and treatment; NOAC = new oral anticoagulant; VKA = vitamin K antagonist; bid = twice daily; qd = once daily.

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