Editorial

Optimizing Vitamin K Antagonist Treatment in Patients with Mechanical Heart Valve Prosthesis

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Vitamin K antagonists (VKAs) have been the principal oral anticoagulation (OAC) option for the past 60 years. Although its management has much improved to optimize their efficacy and safety (and thus, patients outcomes), these drugs do still have important shortcomings. In spite of the development of non-VKA oral anticoagulants (NOACs), which offer a relative efficacy, safety and convenience compared with the VKAs, with fixed doses and less drug or diet interactions, there remain a huge number of patients who still use VKAs as their OAC of choice. These include patients with mechanical heart prosthesis and rheumatic valvular heart disease in association atrial fibrillation (AF).[1] Thus, all efforts should be directed to improve quality of anticoagulation control in these VKA users.

The most commonly used VKAs are 4-hydroxycoumarins derivatives, which included warfarin, phenprocoumon and acenocoumarol. Of these, phenprocoumon has the longest half-life and acenocoumarol has the shortest.[2] They exert an anticoagulant effect by interfering the synthesis of the vitamin K-dependent coagulation factors (factors II, VII, X and IX, and protein C, S and Z), leading to a decrease in the amount of reduced vitamin K required for the carboxylation of the vitamin K-dependent clotting factors.[3]

In general, the VKAs have major inter- and intra-individual variability and a narrow therapeutic range. This variability in the dose–response is influenced by several factors including drug interactions, dietary intake of vitamin K (especially nutritional supplements and herbal products), hepatic metabolism (and so dysfunction), renal dysfunction, alcohol intake and like other drugs, patient compliance.[4] Another important limitation is the slow onset and offset of action. These limitations make coagulation monitoring and frequent dose adjustments necessary to maintain the level of anticoagulation within therapeutic range to ensure efficacy and safety. Indeed, major bleeding and thrombotic complications are mainly related to the international normalized ratio (INR) levels out of range, age, comorbidities, polypharmacy and generally poor anticoagulation control, as reflected by time in therapeutic range (TTR).[2]

To date, we are perhaps able to explain up to 50% of variability in coumarin anticoagulants dose by knowing the following factor: age, ethnicity, comorbidities, concomitant medications and genetic patient profiles, mainly *VKORC1* and *CYP2C9*. However, pharmacogenetic dose adjustments have not been proven to be clinically beneficial.[5]

Laboratory anticoagulation monitoring for a patient taking VKA is made through the prothrombin time (which is sensitive to the decrease of factors II, VII and X) and is standardized thanks to the INR. The optimal target range for the INR is not the same for all indications, and bleeding is directly related to the intensity of anticoagulation.[6] In 1993, Rosendaal et al proposed a method to determine the optimal achieved intensity of anticoagulation (TTR) by the calculation of INR-specific incidence rates of adverse events (both thromboembolic or haemorrhagic) using a linear interpolation.[7]

In this issue of *Thrombosis and Haemostasis*, Gupta et al[8] report a systematic review and meta-analysis that evaluates the effect of a lower compared with higher INR target range on thrombotic and bleeding events, as well as mortality, in patients with mechanical heart valves. Along the time, the recommendations about the optimal INR range in patients with mechanical heart valves has been made with low or very low grades of evidence. Although, the authors recognize the low quality of data due to the high heterogeneity and the absence of standardization of variables and outcomes, this systematic review provides a good summary of the available data, and do not support the need of high INR target in patients with mechanical heart valves.

The intensity of anticoagulant therapy has been recognized as an important factor influencing the risk of bleeding.[3]

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However, most bleeding events occur within the therapeutic INR range (2.0–30)[9] and large INR fluctuations seem to be a more relevant risk factor given that a 'one off' random INR gives no indication of anticoagulation control.[10] Hence, the TTR or proportion of INRs in range (PINRR) are more important measures to determine the risks of bleeding and thromboembolism.[11] Notwithstanding some debates over the appropriateness of the method,[11,12] the Rosendaal method for calculating TTR remains widely used as a measure of the quality of anticoagulation control with the VKAs. Indeed, current guidelines recommend that we maintain a TTR of ~65 to 70% to ensure an optimal treatment.[13] Patients who spent at least 70% of time within therapeutic range have a lower risk for stroke, bleeding and death,[14,15] although after adjusting for clinical variables, only bleeding risk remained significantly correlated with TTR.[16]

Recently, a retrospective, non-randomized multi-centre cohort study including all patients with mechanical heart valve prosthesis registered in the Swedish National Quality Registry Auricula from 2006 to 2011 showed that the highest rates of bleeding were seen in patients with high INR variability, low TTR and high treatment intensity.[17] Of these, among patients with mitral valve replacement and high TTR value, only age and previous bleeding were associated with the risk of bleeding.[18]

VKAs efficacy and safety has improved during the last years thanks to the standardization of the biological control (i.e. INR), the implementation of anticoagulation clinics, computerized dosage systems and self-management programs.[2,19] Health care providers who manage OAC therapy should incorporate patient education, systematic INR testing, tracking, follow-up and good patient communication of results and dosing decisions.[3] Indeed, patients are best managed in specialized anticoagulation clinics, which usually achieves higher values of TTR and generally provides the best outcomes.[19]

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Conflict of Interest
None.

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