

## New Versus Old Anticoagulants in Atrial Fibrillation Management—A Clinical Dilemma

Vivian WY Lee\*

Department of Medicine and Therapeutics, School of Pharmacy, Faculty of Medicine, Chinese University of Hong Kong, Shatin, Hong Kong

**Keywords:** Oral anticoagulants; Atrial fibrillation; Medication adherence

Oral anticoagulants including Vitamin K Antagonists (VKA) such as warfarin have been widely used for the management of Atrial fibrillation (AF) patients for many years [1,2]. Warfarin, as well as other VKA is effective in reducing stroke by over 60% [3-5]. Yet, warfarin is limited by its narrow therapeutic range requiring frequent therapeutic drug monitoring and multiple drug-drug and drug-food interactions. Furthermore, it has been confirmed that over 90% of warfarin patients had at least 1 missed or extra pill-bottle opening during a 3.5-month period, causing a 40% rate of non-adherence with warfarin therapy [6]. The newer oral anticoagulants including the direct thrombin inhibitors and factor Xa inhibitors are approved for stroke prevention in AF patients as an alternative to warfarin therapy. Clinical trials have shown that these newer agents were either non-inferior or superior to warfarin depending on the dosages. Advantages of these newer agents include less blood monitoring and have less drug-drug as well as drug-food interactions. Then, the question is whether newer oral anticoagulants should replace warfarin and other VKA in the future.

In our recently published study, we aimed to compare clinical efficacy, safety and quality of life in patients with AF using dabigatran and warfarin in Hong Kong [7]. We concluded that the clinical efficacy and safety of dabigatran were comparable to that of warfarin and drug compliance and health related quality of life of using dabigatran and warfarin were similar after one year of use. In our study, we found that warfarin patients expressed their willingness to have more frequent monitoring and restriction so that their health states could be closely monitored. In contrast, patients on dabigatran expressed their concerns about the high cost and side effects of dabigatran in particular to the gastrointestinal upset. The most prominent side effect observed in our study for dabigatran was dyspepsia which had a significantly higher incidence than taking warfarin ( $p=0.01$ ). Since dabigatran is absorbed better at lower gastric pH, dabigatran is coated with tartaric acid to generate the acidic microenvironment. This decreased acidic condition in the stomach explained the higher rate of dyspepsia with dabigatran. The gastrointestinal side effects in Asians may be more common while using dabigatran as shown in our study and the Japanese subgroup analysis of the RE-LY trial [7,8]. We also observed that some patients may adjust their own dabigatran twice daily to once daily regimen in order to decrease monthly cost of the drug. In addition, we could not detect any difference in terms of drug compliance and quality of life between dabigatran and warfarin groups (drug compliance: 15.1% in dabigatran group versus 8.3% in warfarin group;  $p=0.121$ ; quality of life [utility score]:  $0.77 \pm 0.17$  in dabigatran group versus  $0.74 \pm 0.16$  in warfarin group;  $p=0.279$ ). The higher compliance rate in warfarin may be related to the patients' adaptation to the treatment.

Furthermore, a post-hoc univariate analysis was performed to investigate the possible risk factors for bleeding of any degree in patients using dabigatran in our study. We found that age and history of Chronic kidney disease (CKD) were significant positive predictors of bleeding of any degree in patients taking dabigatran ( $p=0.024$  for

age and  $p=0.015$  for CKD). We also determined the threshold of age for the highest bleeding risk. Patients with age greater than 70 years old had significantly higher risk of bleeding than those below 70 years ( $p=0.013$ ) using dabigatran. Unlike warfarin, there is no routine blood monitoring for dabigatran. It is particular important to closely monitor certain patient groups such as elderly and CKD when dabigatran is prescribed.

In addition to dabigatran, newer oral anticoagulants such as rivaroxaban and apixaban are in the market. However, post-marketing surveillance studies are required to observe the real world data in patients using these newer agents. It is because real world clinical data may be different than the published data from clinical trials. Our expectation of how patients should respond to the drugs may also be different due to various reasons including drug compliance, socioeconomic factors, and possible adverse effects.

In conclusion, both old and new oral anticoagulants have their role in the management in AF patients. However, not all patients are suitable for the newer oral anticoagulants and it is the same for warfarin as well. Therefore, it is important for clinicians to monitor the patients closely, listen to and understand the patients' points of view while they are on the medication. Post-marketing surveillance studies are vital to ensure the clinical efficacy and safety of the newer anticoagulants in the management of AF patients.

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\*Corresponding author: Vivian WY Lee, Department of Medicine and Therapeutics, School of Pharmacy, Faculty of Medicine, Chinese University of Hong Kong, Shatin, Hong Kong, E-mail: [vivianlee@cuhk.edu.hk](mailto:vivianlee@cuhk.edu.hk)

Received November 21, 2012; Accepted November 23, 2012; Published November 26, 2012

Citation: Lee VWY (2012) New Versus Old Anticoagulants in Atrial Fibrillation Management—A Clinical Dilemma. *J Clin Toxicol* 2:e114. doi:10.4172/2161-0495.1000e114

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