

# The Compelling Issue of Nonvitamin K Antagonist Oral Anticoagulant Adherence in Atrial Fibrillation Patients: A Systematic Need for New Strategies

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In 2019, 10 years have been passed since the introduction of dabigatran to the market with the specific indication of managing thromboembolic risk in atrial fibrillation (AF) patients.<sup>1</sup> Since then, three other nonvitamin K antagonist oral anticoagulants (NOACs) have been introduced and NOACs have become increasingly popular for stroke prevention in patients with AF.<sup>2</sup> One of the advantages of NOACs over vitamin K antagonists (VKAs) is the absence of continuous monitoring of the international normalized ratio (INR).<sup>3</sup> Indeed, while using VKA obtaining and maintaining an optimal quality of anticoagulation therapy control is essential to achieve a significant protection from thromboembolic events and mortality, without increasing bleeding risk.<sup>4</sup> However, adherence and persistence to oral anticoagulation for some patients is problematic and this requires efforts to improve appropriate prescriptions, to monitor NOAC adherence and implement strategies to improve adherence where it is found to be suboptimal.<sup>3,5</sup> For anticoagulation clinics, obtaining good INR control and time in the therapeutic range is the major objective of the clinical management. With less need for monitoring with NOACs, those patients who do not follow the prescribed regimen are likely to experience poorer adherence, and this may not be captured as adherence and may not be routinely assessed.<sup>6</sup>

In a recent narrative review, we reported how the rate of adherence and persistence in NOACs users ranged widely across studies, with varying settings and patients typology<sup>6</sup> and demonstrated how both adherence and persistence declined over time.<sup>6</sup>

In the previous issue of *Thrombosis and Haemostasis*, Hwang et al explored the issue of NOACs adherence in a

cohort of real-life AF patients enrolled in a single Korean tertiary referral cardiology department.<sup>7</sup> They evaluated the adherence to treatment, expressed as percentage of prescribed doses taken (PDT), and also evaluated adherence with the Morisky Medication Adherence Scale (MMAS)-8 tool. In a cohort of 719 AF patients prescribed one of the four NOACs (apixaban 47.8%, dabigatran 21.2%, rivaroxaban 18.4%, and edoxaban 12.6%), they found that over a mean (standard deviation [SD]) treatment period of 7.2 (5.7) months, the mean (SD) PDT for the once-daily NOACs (rivaroxaban and edoxaban) was 95.4 (9.1%) and 93.4% (12.7%) for the twice-daily NOACs (dabigatran and apixaban). Overall, 92.2% of patients reported high adherence (PDT  $\geq$  80%). Among the various NOACs, use of dabigatran was associated with the lowest adherence (PDT = 89.8%), while in general the twice-daily dosing was associated with an increased risk of reporting poorer adherence (PDT < 80%) in the univariate analysis (odds ratio [OR]: 2.15; 95% confidence interval [CI]: 1.06–4.34). A sensitivity analysis performed excluding dabigatran users found that twice-daily dosing no longer affected adherence.<sup>7</sup>

The MMAS-8 was a good predictor of poor adherence, showing an AUC of 0.751 ( $p < 0.001$ ), with a MMAS-8  $\geq 3$  exhibiting a 63.8% sensitivity and 78.5% specificity for poor adherence. In a multivariate logistic regression analysis, the twice-daily NOAC regimen was independently associated with a MMAS score of  $\geq 3$  (OR: 1.90; 95% CI: 1.35–2.67).<sup>7</sup>

The data presented appear reassuring in terms of good adherence with NOAC in this cohort, with less than 10% of patients reporting a PDT < 80%. However, the study does have some limitations, namely one Korean center only, relatively

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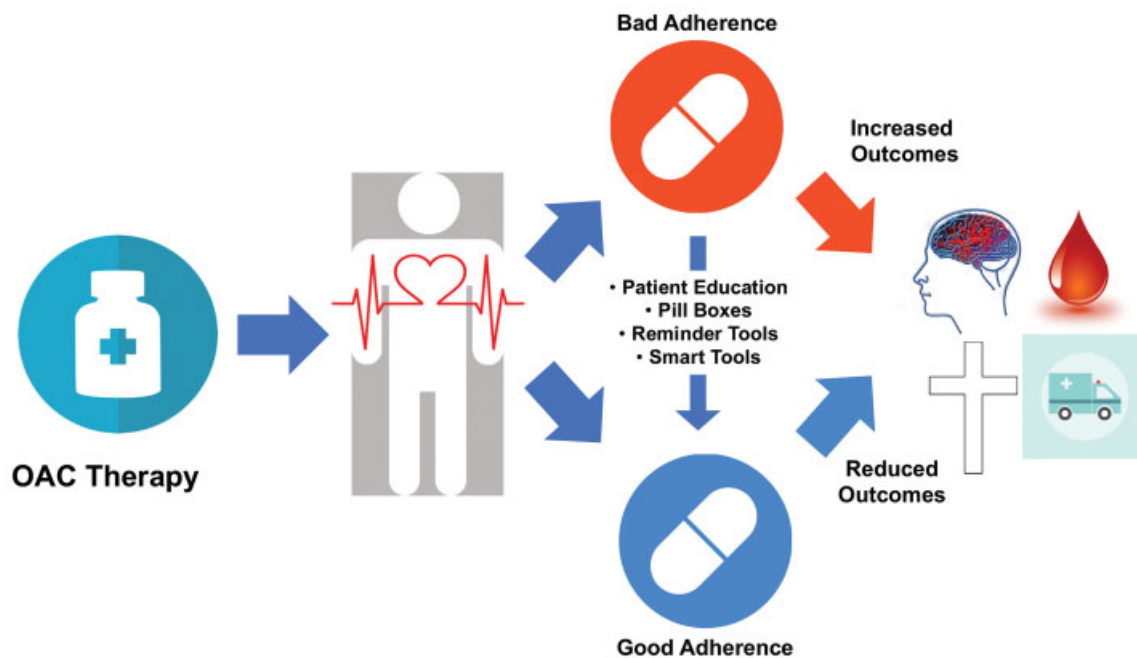
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**Fig. 1** Relationship between oral anticoagulant treatment, adherence, and outcomes in atrial fibrillation patients.

small cohort managed exclusively in a tertiary center with a limited follow-up period, which may impact the generalizability of the results.

A recent study performed among the UK primary electronic health records system (The Health Information Network), reports more concerning figures regarding OAC adherence. In this analysis, good adherence was defined as the proportion of days covered (PDC) of >80%. Good adherence among users of oral anticoagulant drugs was 55.2% overall, being lowest in VKA users (51.2%) and significantly higher in NOACs users (dabigatran 66.5%, rivaroxaban 63.1%, and apixaban 64.7%)<sup>8</sup> but still far from optimal. This study also showed that the rate of good adherence was lower in those patients with a shorter follow-up available. Previous data were similar indicating that over time the adherence rate was progressively lower, irrespective of the type of NOACs used.<sup>6</sup>

The paper by Hwang et al addresses an important issue regarding OAC management, that of adherence. Indeed, the ability of MMAS-8 to predict the occurrence of a poor adherence is useful in terms of clinical management of these patients and could be utilized alongside other tools to evaluate AF patients. Indeed, the SAME-TT<sub>2</sub>R<sub>2</sub> score has been designed to identify those AF patients that would more likely perform well if prescribed with VKA,<sup>9–11</sup> which is relevant since VKAs are still widely used OAC globally.

Despite all international guidelines currently recommending the use of NOACs over VKA for the majority of AF patients,<sup>12,13</sup> optimal management of these patients should evaluate the most appropriate oral anticoagulant as part of an integrated care approach for AF patients.<sup>14–16</sup> During the baseline evaluation of AF patients, use of MMAS-8 could help to identify those patients that more likely will have a poor

adherence to treatment and could be used to plan specific interventions to improve adherence.

Many factors are implicated in adherence to oral anticoagulant therapy among the patient-related factors are demographics, medical-related, behavioral factors, and patient understanding.<sup>6</sup> Although many strategies to address non-adherence have been proposed,<sup>6</sup> these need to be individually tailored to the patient based on the personal underlying cause (s) of non-adherence. Improving adherence to OAC in AF patients should be a priority of the clinical management of AF since data indicate that patients more adherent to NOACs are more likely to have better outcomes.<sup>17</sup> Starting anticoagulation is not enough, we need to ensure that patients are adherent lifelong by asking about medication adherence and where non-adherence is identified, working with the patient to develop strategies to improve adherence and ensuring these are implemented and maintained (► Fig. 1).

#### Conflict of Interest

D.A.L. reports grants from Bristol-Myers-Squibb and Boehringer Ingelheim (paid to the institution), and personal fees from Boehringer Ingelheim, Bristol-Myers-Squibb/Pfizer, Bayer, and Daichii-Sankyo, outside the submitted work. M.P. reports consultancy activity for Boehringer Ingelheim.

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