

## LETTER TO THE EDITOR

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### Adherence to treatment with non-vitamin K antagonist anticoagulants: once- vs. twice-daily regimens

With great interest, we read the article by Vrijens and Heidebuchel, recently published in *Europace*<sup>1</sup> focusing on adherence to non-vitamin K antagonists (NOACs) and translating studies on modelling HIV treatment to NOACs. We congratulate the authors for their excellent work. Indeed, reduced adherence might increase thrombo-embolic and bleeding complications and seriously impair the value of NOACs in clinical practice. We fully agree with the authors that clinical studies on predictors and consequences of non-adherence are urgently needed.

However, conclusions for or against a particular dosing regimen based on theoretical considerations might be premature due to several reasons. First, patients with atrial fibrillation are often in need of concomitant medication. Limiting the overall number of tablets taken per day might increase both, adherence and persistence, to all drugs prescribed. In addition, there is consistent evidence based on clinical data that adherence in once-daily (QD) regimen is superior to twice-daily (BID) application, in particular with regard to drugs used to treat cardiovascular diseases. This was

confirmed in a recent meta-analysis comprising all trials of drugs used in this setting.<sup>2</sup> Secondly, the pharmacokinetic model mentioned was created in the context of HIV drugs. However, overall treatment outcomes for QD and BID regimen in these patients were similar in a randomized controlled trial, and benefits for BID were shown in a subgroup of patients only.<sup>3</sup> In the case of rivaroxaban, pharmacokinetics of QD and BID treatments were extensively tested and no significant difference in terms of  $C_{max}$  and  $C_{trough}$  was established.<sup>4</sup> Finally, inter-patient variability of drug levels in NOACs is considerable<sup>5</sup> and no critically low trough-level is established. Since implementation of low molecular weight heparins we are aware that constant high drug levels are not absolutely necessary to achieve an effective anticoagulant treatment.

In conclusion, we fully agree with the authors that extent of adherence to NOACs as well as predictors and consequences of non-adherence are unclear. Clinical studies addressing these issues are urgently needed.

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