LETTERS 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 Heidbuchel, recently published in *Europace*[1] 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.[2] 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.[3] 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.[4] Finally, inter-patient variability of drug levels in NOACs is considerable[5] 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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Marcel Adler[1] and Michael Nagler[2,3,*]
[1]Department of Haematology and Central Haematology Laboratory, Inselspital, Bern University, Bern, Switzerland;
[2]Laboratory of Clinical Thrombosis and Haemostasis, and Cardiovascular Research Institute, Maastricht University Medical Center, P.O. Box 616, Maastricht 6229 ER, The Netherlands;
[3]Division of Haematology and Central Haematology Laboratory, Luzerner Kantonsspital, Lucerne 16 CH-6000, Switzerland
*Corresponding author. Tel: +31 433 88 42 63; fax +31 433 88 41 59. *E-mail address*: m.nagler@maastrichtuniversity.nl

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Medication adherence and non-vitamin K antagonist oral anticoagulants: what do we really know?

In their publication in *EP-Europace*, Vrijens and Heidbuchel[1] conclude twice-daily (BID) dosing of non-vitamin K antagonist (VKA) oral anticoagulants 'may be more forgiving in patients with suboptimal adherence' than once-daily (OD) dosing. The authors submit the above conclusion is 'exemplified' by the PLATO trial, which compared OD clopidogrel to BID ticagrelor in acute coronary syndrome patients; suggesting the reduced rate of cardiovascular events with BID ticagrelor was the result of a 'greater degree of continuity of drug action' in the presence of suboptimal adherence.[1,2] This theory ignores potential differences in antiplatelet potency between agents, in addition to, likely inferior platelet inhibition in some clopidogrel patients with CYP2C19 genetic polymorphisms.[3] These points are more likely to explain differences in PLATO event rates than variances in blood concentrations/activity subsequent to suboptimal adherence.

We agree with the authors that timing adherence (considering both the correct number of doses taken and their timing) is an important adherence metric to consider. If one embraces timing adherence, the authors statement that the pharmacological equivalent of missing a single dose of a QD regimen is missing three consecutive doses of a BID regimen (*Figure 2*, panel *C*) becomes representative of only an extreme instance of suboptimal adherence.[1] The European Heart Rhythm Association guidance[4] on new oral anticoagulants advises a forgotten dose can be taken as long as no more than half the dosing interval has passed. This means a patient taking an OD regimen need only remember to take their missed dose within 12-h of when it was scheduled to catch up; and consequently, need not go a full 48-h without a dose as depicted in panel *C*. It is also noteworthy that *Figure 2* is stated to represent a single hypothetical drug given OD vs. BID, and not a comparison of different non-VKA oral anticoagulants.

Perhaps most importantly, it is unclear what effect fluctuations in non-VKA oral anticoagulation (measured by drug concentration in the blood or degrees of factor Xa and/or thrombin inhibition) will have on efficacy and safety. Unlike antibiotics, for example, there is a paucity of data regarding what pharmacokinetic/pharmacodynamic parameters are most important in preventing thrombosis or bleeding. Perhaps the peak-to-trough ratio of the anticoagulant is most important (a kin to aminoglycoside antibiotics), or maybe only a minimal trough level of anticoagulation activity above a certain threshold is required to prevent or treat thrombosis?