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 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. 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. In the case of rivaroxaban, pharmacokinetics of QD and BID treatments were extensively tested and no significant difference in terms of Cmax and Ctrough was established. Finally, inter-patient variability of drug levels in NOACs is considerable 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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References

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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 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. This theory ignores potential differences in antplatelet potency between agents, in addition to, likely inferior platelet inhibition in some clopidogrel patients with CYP2C19 genetic polymorphisms. 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.

The European Heart Rhythm Association guidance 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 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 degree(s) 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 antibiotics), or maybe only a minimal trough level of anticoagulation activity above a certain threshold is required to prevent or treat thrombosis.

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In our opinion, the only way to assure patients prescribed a novel target anticoagulant in the real-world will obtain similar efficacy and safety as reported in its designated randomized trial is for their medication adherence to rival that in those at higher risk or showing suboptimal adherence; that adherence is only one of possible explanations to explain the PLATO results (although it is the factor on which we have the least information); that after forgetting a once-daily drug there is a longer interval to catch up (but the patient needs to be aware of the forgotten dose in the first place!); and that it is unclear what PK/PD parameters are most important for the antithrombotic non-vitamin K antagonist oral anticoagulant (NOAC) effect. It all underscores our ascertainment that many factors may play a role in the ultimate benefit/risk profile of once- vs. twice-daily drugs and that without reliable measurement and assessment, we will continue our guessing, and discuss based on opinion. Future clinical studies should address these issues by reliably measuring adherence and persistence, i.e. with electronic monitoring. Nevertheless, we would like to make some comments on other issues raised in both letters.

Coleman et al. have shown that when adherence to a dosing regimen is reported as an average percentage of prescribed pills taken, there is a 6.9% difference in favour of once-daily compared with twice-daily dosing regimens. However, such percentages are no sound pharmacometrical expression for concentration- and time-dependent drug actions. The key lesson from the Coleman et al. review is that even the use of once-daily regimens does not guarantee perfect adherence, with optimal adherence of once-daily dosing regimens ranging from 76.9 to 93.0%. In other words, there is evidence that among ambulatory patients prescribed once-daily dose cardiovascular drugs, 1 in ~14 to even 1 in ~4 doses have been omitted. Therefore, it is essential to understand the pharmacometric consequences of missing one or more (consecutive) doses, which was a key point of our paper.

Timing adherence is certainly another important metric to consider, especially when estimating drug exposure as input to PK/PD models. However, we do not think that once- and twice-daily dosing regimens can be compared using the same metric (i.e. percentage of doses taken within an assigned interval). The definition of assigned intervals varies across studies, but, often, is defined as allowing a 25% deviation in timing (i.e. 6 h for once-daily and 3 h for twice-daily). This threshold is inappropriate as it assumes that for twice-daily dosing, the prescription requires dosing every 12 h. In fact, given the higher trough plasma levels, timing deviation may be less critical for twice-daily than for once-daily NOAC with similar half-lifes (as we explained in our paper). Furthermore, giving less penalty (i.e. 6 h window) for once-daily dosing compared with only 3 h for twice-daily dosing does not make pharmacometric sense. Therefore, the claimed superiority of 22.9% for once-daily dosing compared with twice-daily is a mere arithmetic computation but is not necessarily medically relevant.

Basic pharmacology principles teach us that the pharmacokinetin profiles of NOACs do differ between once- and twice-daily dosing in terms of Cmax and Ctrough, even in the study cited by Adler and Nagler: for a given total daily dose of rivaroxaban, Cmax was consistently higher, and Ctrough was consistently lower in patients receiving the full dose once-daily compared with patients receiving half the dose twice-daily. Therefore, the peak to trough ratio is smaller with twice-daily dosing compared with once-daily dosing. Whether this translates into more or less net clinical benefit remains a topic of discussion in the NOAC field. But it is a consideration to keep in mind, and it should spur more research. As long as better insights are lacking, we agree with the statement of Baker and Coleman that we should strive to replicate the dosing scheme as used in the randomized trials to achieve the proven results.

Concerning the comment on using the HIV example is: the projections in Figures 2 and 3 in our paper are calculated as a pharmacokinetin model that is based on NOAC properties. This model is not derived from HIV or any other medical condition. The two examples of HIV and ACS were given for illustrational purpose only. We agree that the projections are theoretical. But again, it was the main aim of our paper to highlight the pharmacometric complexity beyond simple measures of ‘number of pills taken’ and even ‘timing of pills taken’. For the HIV example, the authors point out as an issue that the superiority in clinical outcome for twice-daily drug intake was shown in a subgroup only.7 It does not negate the finding, on the contrary. Dosing regimen advantages should not necessarily be expected in the average patient, or the very well adherent patient. But if there is increased effectiveness in those at higher risk or showing suboptimal adherence, this is an important consideration for the choice of treatment. We do not state that this is the factual case in NOAC-treated patients, but it certainly deserves study.

On that last count, that clinical studies addressing the important issue of adherence to NOACs (and to cardiovascular drugs in general) are urgently needed, we all agree!