From monitoring to vigilance about patient adherence to new oral anticoagulants

Ambivalence envelops the European Heart Rhythm Association Practical Guide\(^1\) on the use of new oral anticoagulants (NOACs). The Guide recites the NOACs’ marketing claim of ‘predictable effect without need for monitoring’, but proclaims that ‘therapy prescription with the new class of drugs requires vigilance’. ‘Monitoring’, thus renamed ‘vigilance’, draws prescribers into an array of partial measures of NOAC actions of limited value, e.g. interpretations where, to be viable, knowledge of the time since the last taken dose is required but where approximately one-third of patient-reported data on dose-timing are substantially erroneous, even in controlled clinical trials settings.

The Guide aptly emphasizes the need to minimize patient non-adherence, which is well-documented as the single, biggest source of variance in the effects of patient-administered drugs of all classes.\(^2\) However, the Guide adopts a ‘make it up as you go’ approach to minimizing non-adherence, failing to recognize the progress, summarized in\(^3\) that has occurred in the field of adherence research since the advent of highly reliable, electronic methods for quantifying patient adherence. The Guide calls for patient education to achieve and maintain good adherence, but two other essentials for sustained good adherence, often neglected, are patients’ motivation and their awareness of deviations from dosing instructions.\(^3\)

The Guide recommends that once-daily dosing is preferable to twice-daily dosing. This recommendation may not be the better choice, because continuity of drug action is more often the result of twice-daily than of once-daily dosing.\(^2\) It is true that patients prescribed once-daily dosing regimens take a somewhat higher percentage of prescribed doses than those prescribed twice-daily dosing, but it is the temporal sequence of doses taken that determines whether continuity of drug action prevails: percentages of doses prescribed do not activate receptors or other targets of drug actions.

The Guide suggests that NOAC prescribers should ask patients to bring their drug packages to follow-up visits, so that untaken doses can be counted by the prescriber. Two factors can nullify value in this recommendation: (i) the count of returned tablets is not interpretable without knowledge of when the packaged drug was dispensed by the pharmacist, whose necessary role in providing dispensing information is completely neglected by the Guide; (ii) the pill-count method of measuring adherence was thoroughly discredited 25 years ago.\(^2\) That conclusion has been repeatedly confirmed.

The need is indeed urgent to enable patients using NOACs to monitor and manage their medication adherence. Calendared blister packages designed to help patients track medication adherence have previously proven to make a meaningful impact. More comprehensive understanding comes from electronic measurements of patient adherence, which will, if history is a reliable guide, reveal a wide array of delayed or omitted doses, and some extra doses taken by patients prescribed NOACs.\(^2\) Increasing patient awareness of dosing errors, through blister package design and electronic compilation of dosing history data, provides patients with individualized dosing histories. Such data are gaining recognition as a strong force in minimizing dosing errors by ambulatory patients.\(^2,3\)

Conflicts of interest: B.V. and J.U. are employees of MWV Healthcare.

References

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Authors’ response: From monitoring to vigilance about patient adherence to new oral anticoagulants

We would like to thank Mr Vrijens and Dr Urquhart for their interest in the new oral anticoagulant (NOAC) Practical Guide, although they may have judged it by a false pars pro toto stating that ‘ambivalence envelops the Practical Guide’.\(^1\) We are confident that our document has created more concrete help than confusion for physicians working with NOAC patients. However, we are happy with the authors’ focus on the issue of medication adherence, which is of primordial importance in the NOAC arena. We have already devoted a whole section in the Guide to the issue of adherence (or compliance), and fully agree with the authors that non-adherence is a major threat to the effectiveness of these drugs in daily practice.\(^2\) Moreover, we have stressed repeatedly the importance of patient education, and re-education during follow-up (see e.g. the NOAC anticoagulation cards). Some specific suggestions by the authors (like calendared blisters, pharmacy involvement, and the use of electronic adherence recording devices) were already mentioned in our text. We have to remind the readership that the authors of the letter have a conflict of interest here, both being employees of a company.
that is active in the market of drug packaging and electronic adherence recording. Moreover, we have to wait for validation of whatever approach. In the absence of any available validated data, we had to restrict ourselves to a summary of the potential approaches to optimize adherence. Definitely, we ask for ‘vigilance’ among prescribers to tailor adherence approaches to their individual patients. Moreover, this required vigilance goes far beyond monitoring adherence, as we have highlighted important issues related to plasma levels and pharmacodynamic interactions in the Guide too. Inappropriate use of the correct drug, or with an inappropriate dose, carries a potential for harm. We agree that reliance on patient information like (last) drug intake is weak; in the section on cardiovascular, for instance, we stated that if any incorrect information is suspected, it may be safer to proceed with a transoesophageal echocardiography, rather than rely naively only on patient information. Physic-ians, be vigilant, indeed!

Only on-going randomized trials on adherence measures and large registries will be able to tell how well the results of controlled clinical trials are translated to the real world. In modern clinical NOAC trials, adherence was still measured in the old-fashioned way of pill counting, but we agree that the uncertainty of when a new drug package was delivered to the patient and opened for the first time, severely limits its usefulness in daily practice. We take that suggestion at heart and will ponder on how far the proposed NOAC card could be modified to also keep track of this information, to be filled out by pharmacists and patients.

We do object to the assertion of the authors that we stated in the Guide that once-daily NOAC dosing is preferable to twice-daily dosing. Exactly for the reasons spelled out by Vrijens and Urquhart, we suggested that it is unknown whether any regimen is superior in guaranteeing the clinical thromboembolic preventive effects and the safety profile as seen in the clinical trials.

Also, in this respect, more data are required. Again, registries will have to tell us to what extent the Phase 3 study results can be replicated in the overall population for different drugs and dosing schemes.

The NOACs marketed come in calendered blister packages or calendered boxes (containing the blisters), although the former do not all spell out the days of the week and the latter are not rated to be very practical by patients. Calendered pill boxes (also containing other medication) unfortunately cannot be used for dabigatran, which needs to be preserved in its original packaging. Electronic means certainly have high potential value concerning traceability and information sharing, and we look forward to studies on their use in the NOAC field. However, patients may also develop some wariness concerning such electronic surveillance. Again, we will need proof that the benefits outweigh the disadvantages in the field, and that such measures really translate into a clinically meaningful effect. Therefore, we all have to work on making patients adherent to their treatment to guarantee the intended safety and effectiveness. We certainly feel as partners of Vrijens and Urquhart on this issue.

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References

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Should catheter atrial fibrillation ablation be considered as a ‘high bleeding risk’ intervention?

We read with interest the last EHRA practical guide on the use of new oral anticoagulants (NOAC) in patients with non-valvular atrial fibrillation (AF) reported by Heidbuchel et al., and the problematic issue of NOAC during catheter AF ablation (CFA). Several studies have confirmed the reduction of both bleeding and thromboembolic (TE) complications when performing CFA during uninterrupted vitamin K antagonist therapy in comparison with a bridging strategy. Recent non-randomized studies with NOAC continued during CFA showed similar safety profiles while still considering TE and bleeding events.

In the absence of a specific classification including CFA procedures, the present guideline concerning the NOAC strategy was based on the exact definition of the bleeding risk associated which CFA, which can be ambiguous.

Careful reading of the text appears confusing in our opinion. In the text, the authors suggest NOAC interruption 48 h before a procedure that carries a ‘risk for major bleeding’ (p. 640), whereas in the corresponding Table 10, CFA is classified within the group of ‘high bleeding risk’ interventions. The table itself refers to a study reported in 2003 by Torn M et al. in which CFA was completely absent from that classification. Should we consider CFA as a procedure with ‘frequent’ bleeding complications?

There is a dissociation between these two concepts. On the one hand, the ‘risk of major bleeding’—this complication can be either frequent or exceptional—is defined by the gravity and/or consequence of peri- or post-procedural bleeding. On the other hand, ‘high bleeding risk’ procedures refer to the rate of bleeding complications—the consequence of which going from mild to fatal. This concerns both the rate of bleeding complications, and their severity. Low bleeding risk procedures designate procedures with clinical bleeding rates of 1.5% or less in the classification from the American Society for Gastrointestinal Endoscopy. The worldwide survey on CFA from Cappato et al. reports total bleeding rate events of 2.8% when adding tamponade, hemothorax, and groin complications. Then, according to the above-mentioned classification, CFA can be defined as a procedure associated with a bleeding risk which is not low. But then, does this imply that it is a ‘high bleeding risk’ procedure?

In fact, CFA is a procedure associated with major bleeding risk, because it can be complicated with transfusions, permanent disability (e.g. bleeding-induced stroke or myocardial infarction), and even death. Procedures that may result in intra-thoracic or pericardial bleeding are classified as major.

The other confusion concerns the distinction—even though this may appear elementary—in the same table, between single-(associated with low bleeding risk) and double-transseptal puncture procedures. No reference is provided to support this proposal.

To conclude, in the absence of specific validated bleeding risk classification, CFA can