EDITORIAL

On-label reduced doses of non-vitamin K anticoagulants prove safe and efficient; yet how to ensure the correct dose for the right patient?

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This editorial refers to «Efficacy and Safety of Reduced-dose Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials”, by K-L Wang et al, on page....

In the management of patients with atrial fibrillation (AF) stroke prevention with oral anticoagulants is crucial, and the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) altered the treatment scenario during few years.1 The individual NOACs have standard treatment doses suitable for most of the AF patients. However, all NOACs have different criteria for dose-reduction, which might be a challenge for the physician in daily practice.2 Real-world observational studies have found a frequent use of NOAC dosing regimens outside recommendations, and corresponding worse outcome for these patients.3 With four NOACs available (so far); all of them with individual dosages and different dose-reduction criteria, prescription of the correct dose to the right patient has become complicated.2

In this issue of the journal, Wang and co-workers present a meta-analysis investigating the outcomes of the three pivotal phase-III trials (ROCKET-AF, ARISTOTLE, and ENGAGE-AF)4-6 with regard to the subpopulations given on-label reduced-dose NOACs. They did not include the RE-LY study because RE-LY did not feature any dose-adjustment algorithm7, but in the supplement they showed additional analyses incorporating the RE-LY European label simulation data, confirming the results.8 The meta-analysis identified 7,351 patients with correctly reduced dose of NOACs from a total AF population of 46,426 patients (comprising 21%, 5% and 25% from ROCKET-AF, ARISTOTLE, and ENGAGE-AF, respectively). The main findings were that patients eligible for reduced-dose according to individual NOAC criteria were at higher risk of both thromboembolic and hemorrhagic complications on treatment. Furthermore, NOACs, when correctly dose adjusted, had the same reassuring effect and safety as standard doses of NOACs compared with Warfarin.

There are a number of limitations pertaining to this type of meta-analysis. The study populations in the three trials were profoundly different and a meta-analysis does not fully adjust for those dissimilarities. One reflection of these differences becomes obvious from the percentage of patients eligible for dose-reduction, with the above-mentioned variance from as low as 5% in ARISTOTLE to 25% in ENGAGE-AF. Another inconsistency lies in the actual degree of pre-defined dose reduction; from -25% for Rivaroxaban (i.e., reduction from 20mg to 15mg OD) to -50% for Apixaban and
Edoxaban (from 5mg to 2.5mg BID and from 60mg to 30mg OD, respectively). Finally, cross-trial comparisons depend on uniform definitions of outcome measures, which were not identical between the studies. For instance, diverging bleeding definitions were utilized for safety outcomes. Notwithstanding these limitations, the presented analysis by Wang and co-workers sheds an important light on the issue of NOAC dose adjustments.

Why is this topic so important? Firstly, due to the inevitable selection process of patients enrolled in RCTs, the percentages of patients who qualified for reduced NOAC dosages across the individual trials does not reflect the number of appropriate dose reductions in real life, which may be even higher. Secondly, one subgroup analysis from the ARISTOTLE trial has shown that patients who fulfilled only one of the three dose-reduction criteria had a higher risk of stroke and bleeding, but showed consistent benefits with the full NOAC dose regarding safety and efficacy, thus documenting that full-dose was appropriate for patients with only 1 dose-reduction criterion. Thirdly, we know from prescription statistics that the use of reduced NOAC doses even further exceeds these appropriate NOAC dose reductions, to an extend that is sometimes worrisome. Hence, to learn about the characteristics of the correctly down-titrated NOAC patients in these trials, and to comprehend their specific outcomes as compared to the full-dose study populations, provides an insightful aspect to the interpretation of the entire NOAC knowledge base.

Accordingly, what do we know about the extent of these inappropriate (often called “off-label”) prescriptions in general? Observational real-world data from Steinberg and co-investigators in the ORBIT-AF II Registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II) showed that, overall, 9.4% of NOAC-treated patients were under-dosed, and 3.4% were overdosed according to U.S. labeling, and both groups were associated with increased risk of adverse events compared to recommended doses. A recent publication on this issue from the same study group showed that a reduced NOAC dose was prescribed to 16% of the AF patients, and that the majority of these dose reductions (57%) were inconsistent with US Food and Drug Administration recommendations.

There may be many possible reasons for giving patients a reduced NOAC dose instead of the appropriate standard dose (Fig. 1). Perhaps the most important mechanism is the prescribing physician’s perception of frailty in a given patient. Frailty can be defined as “a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime”. In other words, frailty is a difficult-to-define syndrome of physiological decline in late life with an increased vulnerability to adverse health outcomes. This perception, together with the physicians fundamental oath of “do no harm”, may often trigger a mind-set of what is self-perceived as a guarded prescription strategy with NOACs. After all, for understandable reasons, physicians may be more afraid of a major bleeding than of thromboembolic events. Yet another mechanism pertains to those elderly patients who at time of prescription display borderline criteria for dose-reduction, which trigger a similar, cautious strategy in the prescriber due to the likelihood of an expected accentuation of one criterion (e.g., supposing a further decline in renal function).

On the other hand, as with all medications, giving too high doses of NOACs can also occur. This seems to be a less prevalent problem; however it is important, as all-cause mortality risk increases
compared with recommended doses. Possible reasons for giving patients the standard NOAC dose when criteria indicate a reduced dose are also displayed in Figure 1. One finds here again the scenario of patients with borderline creatinine values who might progress to worsening renal function reaching the criterion for reduced dose, either on a permanent basis or during intercurrent diseases. Indeed, the current recommendations for follow-up of NOAC patients explicitly state that renal function should be controlled regularly. A similar situation may arise in patients who experience weight-loss to below 60 kg during follow-up. Finally, yet another reason might be related to the complexity of drug combinations in patients with NOACs, and a reduced awareness of drug interactions when prescribing new medication. It was outside the scope of the meta-analysis to negotiate the complicated scenario of concomitant antiplatelet therapy, which also may prompt a decision to use lower doses of NOACs.

What can we learn from these investigations? (i) The appropriate dose-adjustment upon the presence of pre-defined dose-reduction criteria in a given patient deserves an unequivocal endorsement: it is a safe and efficient choice in this sub-population of patients with a higher stroke- and bleeding risk. (ii) On the other hand, when these criteria are not fulfilled, a full-dose regimen should generally be attempted. (iii) In between these options, the clinical judgment of the prescribing physician remains as important as ever, and difficult-to-define syndromes such as frailty may lead to deviations from those criteria-based rules that may claim a certain degree of appropriateness within the complex antithrombotic landscape.
References


Figure legend:

Factors influencing NOAC dosing regimens; on-label dosing regimens meaning NOAC doses in accordance with defined criteria; off-label dosing regimens meaning NOAC doses which deviate from defined criteria, i.e., either reduced dose of NOAC without correct dose reduction criteria (left panel) or standard dose of NOAC when criteria should indicate reduced dose (right panel).