Monitoring new oral anticoagulants, managing thrombosis, or both?

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Administration of oral anticoagulants is the cornerstone in the prevention of (chronic) morbidity and mortality due to arterial thromboembolic stroke (1) and, on the venous side, of pulmonary embolism and recurrent thrombosis (2). The largest population at risk of arterial thromboembolism is the elderly suffering from atrial fibrillation (AF). Advanced age contributes to a rise in the prevalence of AF, while more accurate diagnostic classification prompts earlier anticoagulant treatment in the vast majority of elderly subjects with AF (3). Long-term anticoagulation in AF (and venous thromboembolism [VTE] as well) aims at reducing a life-time risk of stroke (or recurrent VTE), and monitoring its effect would theoretically make sense in comparison with other chronic diseases or risk conditions like diabetes, hypertension and hypercholesterolaemia, where blood glucose, glycated haemoglobin (HbA1c), blood pressure and lipids are monitored and therapy is adjusted accordingly. While current oral anticoagulation with vitamin K antagonists (VKA) is being monitored by laboratory testing and dose adjustment, with the introduction of new oral anticoagulant agents (4) (NOACs) it appears that most physicians are willing or even eager to proceed with unmonitored therapy.

Since the introduction of the VKAs in the 1950s, monitoring the anticoagulant effect by prothrombin time, later expressed as international normalised ratio (INR), in order to adjust the VKA dose, has been routine practice. Through clinical trials, the therapeutic range for VKA was set at 2–3 for most indications, including AF (1, 2). Since fixed, low-dose therapy with warfarin does not offer sufficient protection, dose adjustment of VKA to the desired INR level is required. This is important, since many factors interfere with VKA uptake and metabolism by the liver, including food, medication, and comorbidity (5). Particularly in elderly subjects, many of these factors can be present concurrently. The time within the therapeutic range (TTR) is a good overall measure of the quality of antithrombotic treatment with VKA (6). However, it shows a wide variation by country. In an analysis by country of the RELY study data, excluding the first week of treatment, the average TTR varies from a very low level of 44% in Taiwan to a highest level of 77% in Sweden (7). Even at a good level of anticoagulant control of ∼75% (as in the Netherlands) this means that in around 25% of the time INR values are either too low (at risk of thrombosis), or too high (at risk of bleeding). In order to achieve proper laboratory control patients need blood drawing ∼20 times/year and, obviously, this poses a burden on their daily life. The quality of life, as well as the TTR, can be positively influenced with methods that provide (supported) self-management of VKA treatment, being increasingly popular among patients on long-term anticoagulant treatment (8, 9). However, even self-management requires a reliable support system, which may not be feasible throughout the world. In spite of all these practical limitations of VKA treatment, one of the main advantages is that at least the occurrence of potentially harmful situations (outside the “TTR”) are detected at some point in time, allowing dose adjustment, as well as actions taken to prevent recurrence of this situation. In the patient on VKA a number of measures can be taken to improve the TTR, including reminding the general practitioner to see the patient in order to deal with problems that may hamper adequate medication intake (poor cognitive function, lack of social network, treatment of comorbid conditions etc) so that appropriate action can be taken when needed. This may also include nurse-supervised medication intake (usually more than just the anticoagulants), involving family or neighbours in helping out etc. Such scenarios are frequently encountered in the daily practice of anticoagulation clinics, mainly because the majority of patients on anticoagulants are elderly and often frail, requiring blood drawing at home in 40% of cases, due to comorbidity (10).

The marked innovation in oral anticoagulant agents heralds a striking paradox in the management of patients with (risk of) thrombosis. While NOACs have been developed under the assumption that monitoring and dose adjustment would be abolished (illustrated by provocative paper headlines like “Funeral of the Anticoagulation Clinic”), the implication may be that patients are left with a prescription and a single advice, but without any kind of formalised support (including laboratory control). I consider this development potentially harmful to the patient, requiring critical consideration of causes and consequences. Pharmaceutical companies have invested heavily in the development of novel, targeted synthetic drugs that directly interfere with a specific coagulation protease, blocking its clotting activity. After many years of struggle (including the failure of ximelagatran to reach the market due to liver function problems), several NOACs have now successfully reached the clinical arena. Competition among several large companies is strong and rapid penetration of the most important segments of the market (including the AF population) is economically important.
The assumption is that NOACs, in contrast with VKA, neither require monitoring with laboratory tests, nor frequent dose adjustment, thanks to reduced food and drug interactions, contributing to increased pharmacokinetic stability. However, several issues should be considered. First, the NOACs are all prescribed on a fixed-dose basis. One size fits all, comparable to the poll-pill concept. In practice, this assumption has weaknesses; pharmacokinetic studies show that drugs like dabigatran show considerable variation in plasma drug concentrations (11), such that while the majority of patients will obtain an adequate plasma drug level, a measurable proportion will either achieve an insufficient, or a supra-therapeutic drug level, when given a fixed dose. Advocates of a fixed-dose policy will argue that the overall performance of NOACs in the large clinical trials is non-inferior or better, as compared to INR-adjusted warfarin. This may be so, but one should keep in mind that these were carefully selected patients to begin with (excluding those with assumed poor compliance, renal insufficiency, bleeding risks etc), while bleeding and other side effects were still encountered at significant percentages. One should not abolish the opportunity to further improve the efficacy and safety of new anticoagulants in practice, e.g. by searching for the optimal dose in the individual patient (tailored medication). This may, eventually, require laboratory based dose adjustment.

A second issue is that by not monitoring, there is a risk of losing track of the patient during long-term (often life-long) treatment. In the majority of patients with AF, there is no need for long-term follow up by the cardiologist, hence continuation of medication is maintained by prescription of the drug by the general practitioner. In the absence of a structured organisation, there will be no routine check on side effects, tolerance and adherence, while it is known that in unmonitored conditions medication adherence levels are not better than 50% (12). A third issue with NOACs is that there are many possible acute situations where one would like to measure the anticoagulant’s effect, by some assay. Such situations involve suspected under- or overdosing, comorbidity, potential interactions (as with frequently used medication like amiodarone and verapamil), interventions like surgery and cardioversion, renal failure (not typically the chronic slow progressive form but also rapid changes in clearance in situations such as dehydration, use of antibiotics etc) and other morbidity that is frequent in the elderly. Finally, getting an indication of an anticoagulant’s level may be appropriate in the setting of dual or triple antithrombotic therapy, such as in the patient with AF undergoing a percutaneous coronary intervention, when dual platelet inhibitors may be added to NOACs, given that such patients represent a complex management problem (13, 14).

In this issue of *Thrombosis and Haemostasis*, Douxfills et al. provide the results of a panel of common commercial assays for monitoring the effects of one of the NOACs, dabigatran, in plasma (15). Their comparative study nicely shows that an assay based on assessing the direct anti-thrombin effect is optimal for recording the anticoagulant effects over a wide range of relevant dabigatran concentrations, in part confirming previously published studies (as discussed in [15–17]). The authors correctly argue that such assays will be helpful in guiding and improving the quality of NOAC therapy, to reduce the risk of unwanted bleeding catastrophes. Also, for those active in acute medicine, management of patients with bleeding while on NOACs is no trivial matter, and lab tests that at least tell whether the drug is still present and in which quantities are urgently needed (19). In order to provide comprehensive advice for managing dabigatran, the recent overview by Huisman et al. gives a number of useful recommendations, also including laboratory testing. Having available a suitable point-of-care test on a 24-hour basis will be one of the precautions that hospitals need to take in order to be prepared for the daily management of NOAC therapy (20). In our country laboratory medicine is almost ready to deal with this, but is this also true for the world at large? Practical issues also arise in relation to the use of dabigatran (and other NOACs) in every day clinical practice, and the recent consensus document of the Italian Federation of Thrombosis Centers (FCSA) provides important answers to such questions (1).

At this stage I think that several actions become important, not strictly confined to the monitoring of NOACs, but addressing a number of issues involved in antithrombotic management of our patients. The first important action should be a general shift towards *thrombosis care*, with the principal aim of providing good quality management of patients with thrombosis. In our country, an initiative has been taken by the Federation of Anticoagulant Services (“FNT”), enforced by the Dutch government to organise integrated care for anticoagulant treatment. This initiative is also instigated by a critical report by the Health Inspection authorities based on an alarming rate of avoidable hospitalisation for bleeding complications during antithrombotic therapy (based on [21]). This integrated care policy will encompass describing and organising the entire chain of care (providers) in order to improve quality and to reduce risky situations (mainly involving bleeding complications). Key to a better organisation is optimal communication through protocols based on guidelines, which is critical in situations such as surgery, when interruption of anticoagulation must be carefully managed between surgeon, cardiologist, anaesthesiologist, general practitioner and last but not least, the patient. Strengthening the patient’s awareness and involvement is crucial in this process, but this requires cooperation of a capable patient (which can be a challenge in the elderly) and their family. Obviously, this is important for old as well as new anticoagulant agents.

Second, it is becoming more and more apparent that the absence of proper lab tests (as well as the lack of antidotes) is a major hurdle in the safe introduction of NOACs. It is critical that pharmaceutical companies take their responsibilities and provide and publish all relevant data on drug levels and coagulation test responses so that it becomes clear what the approximate therapeutic and harmful ranges of laboratory test outcomes are, for each anticoagulant agent. There is no good reason not to be transparent in these matters, even if it would entail the small risk that doctors would want to optimise therapy based on lab test results. It is time that we agree that thrombosis management is a complex matter that becomes only more complex with the increasing number of anti-thrombotic medications available. This is
the right time to collectively develop a decent model of thrombosis management, putting the patient in the lead where possible, but helping those patients that require support. This will also require having available the best laboratory assays on a 24-hour basis, to facilitate optimal drug management in conditions when things can go wrong, like peri-operatively. It is naïve to believe that new anticoagulant drugs will solve all practical problems. Fortunately, the pharmaceutical companies are aware of current uncertainty in the field and are increasingly willing to work together with all parties on improving thrombosis management for the future.

Conflicts of interest

H. ten Cate is chairman of the Board of the Dutch Federation of Anticoagulation Clinics (FNT). He has received speaker fees from Bayer, Stago, Roche, and GSK. He has received consultancy fees from Boehringer Ingelheim and Philips.

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