EDITORIAL COMMENT

Laboratory Monitoring of the Non–Vitamin K Oral Anticoagulants*

Andrew D. Blann, PhD, Gregory Y.H. Lip, MD

Although they are valuable when used to reduce the risk of thrombosis in several diverse clinical conditions, the vitamin K antagonists (VKAs) bring with them several challenges. These include the need for regular blood tests (perhaps 4 to 6 times weekly), which are expensive and inconvenient to manage; a narrow therapeutic window; interactions with many other drugs; alcohol and diet restrictions; teratogenicity; and a relatively long half-life (making them insensitive in the face of the need for a rapid change in activity). These and other problems have led to the development of other agents that do not act via vitamin K but directly on coagulation pathway factors. Because they are neither new nor novel these days, these agents are called target-specific oral anticoagulants, direct oral anticoagulants, and non–vitamin K oral anticoagulants (NOACs) (1,2). In a recent European consensus statement from the European Society of Cardiology Working Group on Thrombosis Anticoagulation Task Force, NOAC is the preferred acronym, which allows web search engines (e.g., Medline, Google Scholar) to find older literature that previously used the NOAC acronym (2).

An oft-cited advantage of these agents, compared with VKAs, is that like antiplatelet drugs, no routine monitoring is required (1,2). However, there are numerous situations in which the precise anticoagulant status of a particular patient is needed, such as before emergency surgery or other invasive procedure; in the face of evident or suspected hemorrhage; when there is suspicion of overdose; in acute thrombosis; in renal, liver, or heart failure; when proof of compliance is required; in potential drug-drug interactions; and in cases of trauma, acute medical disease, and malignancy (3). In these cases, some of which may be life threatening, the laboratory needs to be able to offer some support.

In this respect, the problem is that the “standard” laboratory coagulation tests of prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) simply cannot do the job adequately. Developed decades ago, these tests are perfectly acceptable for assessing the effects of VKAs and/or unfractionated heparin in many clinical situations. As effectively nonspecific screening tools, they are unsuitable for the specific nature of the NOACs that exert their effect in the direct inhibition of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban) (3). Dabigatran certainly prolongs “standard” PT; however, this effect has poor sensitivity, varies according to different reagents, and its relationship with APTT is curvilinear so that neither of these tests are recommended (3,4). Similarly, all 3 factor Xa inhibitors also prolong PT and APTT but at low sensitivity. With careful choice of reagents and analyzers, a modified PT can be used to monitor the effects of rivaroxaban (5–8). The standard TT is oversensitive for the assessment of dabigatran (3,4); however, if the plasma is diluted (i.e., dilute TT), TT can be used to monitor this drug (8,9). More precise methods are ecarin clotting time (ECT) for dabigatran (which has a correlation coefficient of 0.92 with the plasma concentration of this drug, compared with 0.86 for TT and 0.85 for PT) and
methods based on anti-factor Xa activity for the factor Xa inhibitors (4,9–11).

Although there are British (3), European (10), and U.S. recommendations (11), there is as yet no international consensus of the most effective tests for each particular agent and no systematic overview of the many research papers on this subject.

This void has been filled by the report in this issue of the Journal by Cuker et al. (12). Their systematic review of up to 17 papers on dabigatran, rivaroxaban, and apixaban confirms the widely held view that the standard PT and APTT tests are unsuitable but that the dilute TT, ecarin-based assays (clotting and chromogenic), and anti-Xa activity are preferred. However, Cuker et al. (12) found some inconsistencies between their overview and those of existing guidelines (3,11). Indeed, the field is rapidly developing as the 2014 update of the American Society of Hematology guideline (11) suggests that in the presence of a normal APTT, dabigatran is unlikely to contribute to bleeding and that if the PT is normal, rivaroxaban is unlikely to contribute to bleeding. Conversely, in the presence of a prolonged APTT, dabigatran may be contributing to bleeding, while if the PT is prolonged, bleeding may be due to rivaroxaban. The guideline fails to include apixaban in this opinion, but it suggests the therapeutic levels of apixaban may not elevate the PT and recommends the use of the dilute TT, ECT, or anti-factor Xa assays for the measurement of the anticoagulant activities of dabigatran and the factor Xa inhibitors, respectively. Table 1 summarizes guidance on the test for each drug (3,10,11).

So where does this leave the practitioner and the hematologist? With continuing pressure on laboratory budgets, the PT and APTT would be methods of choice but for their poor sensitivity and specificity and the lack of consensus regarding most suitable reagents and analyzers. However, their advantages of rapid turnaround time and universal accessibility are considerable, especially in an emergency setting. This must be weighed against the increased demands of the more complex ECT, dilute TT (the most cited method being that of the HEMOCLOT technique [3,4,9]), and the anti-factor Xa assays, which although preferable on scientific grounds, are slower and less accessible.

Until methods are widely agreed upon, each user must decide which is most appropriate in their own setting. The “fast and quick” tests (e.g., APTT and PT for dabigatran and rivaroxaban, respectively) are more qualitative and indicate an anticoagulant effect, rather than quantify anticoagulation intensity. These tests are certainly not for dose adjustment or assessment of drug compliance. In the same way that we have many options for oral anticoagulants and may be able fit the drug to the patient (and vice versa), this choice now comes with the task of fitting the coagulation test to the type of NOAC drug used, bearing in mind the urgency, practicality, and detail needed.

**TABLE 1** Laboratory Monitoring of NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Preferred Method In an Emergency</th>
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<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
</tr>
<tr>
<td>1. Ecarin clotting time</td>
<td>APTT (preferably with specific calibrated reagents)</td>
</tr>
<tr>
<td>2. Dilute thrombin time</td>
<td>APTT (preferably with specific calibrated reagents)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-factor Xa</td>
<td>PT (preferably with specific calibrated reagents)</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-factor Xa</td>
<td>Dilute PT</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-factor Xa</td>
<td>Few firm data</td>
</tr>
</tbody>
</table>

Opinion pooled from references 3, 10, and 11. APTT = activated partial thromboplastin time; NOAC = non-vitamin K oral anticoagulant; PT = prothrombin time.

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**REFERENCES**


KEY WORDS apixaban, coagulation tests, dabigatran, monitoring, non-vitamin K oral anticoagulant (NOAC), rivaroxaban