Dabigatran, an oral thrombin inhibitor, is licensed as an alternative to warfarin for stroke prevention in patients with atrial fibrillation. As the first of the new oral anticoagulants (NOACs) to gain approval for this indication, its use is increasing now that its safety has been confirmed using real-world data (1, 2), and clinical guidelines have given preference to NOACs over warfarin for stroke prevention in patients with atrial fibrillation (3-5).

Although dabigatran was designed to be given in fixed doses without monitoring, there are situations where assessment of its anticoagulant activity can be helpful (6). For example, detection of little or no dabigatran activity in plasma may identify patients who can safely undergo surgery, or receive thrombolytic therapy for management of acute ischaemic stroke. Conversely, excessive anticoagulant activity may indicate dabigatran accumulation in patients with deteriorating renal function, or may influence therapy in those with serious bleeding; common concerns in everyday clinical practice (6, 7). These scenarios highlight the need for simple, rapid and widely available monitoring tests for dabigatran.

How can the anticoagulant activity of dabigatran be assessed? Dabigatran prolongs the activated partial thromboplastin time (aPTT) more than the prothrombin time (Table 1). Although the effect of dabigatran on the aPTT is concentration-dependent, the aPTT begins to plateau with plasma dabigatran concentrations above 200 ng/ml (8-12). The thrombin time is very sensitive to dabigatran and even low concentrations of dabigatran produce a marked prolongation in the thrombin time. Dilution of the plasma prior to thrombin time determination renders the test less sensitive to dabigatran. The HemoClot assay capitalises on this phenomenon; to perform this test, patient plasma is diluted eight-fold prior to thrombin time determination (13). The plasma dabigatran concentration is then calculated by reference to a standard curve constructed using dabigatran calibrators. Although the test is rapid and simple, the HemoClot assay is only available in specialised coagulation laboratories, and the test is not licensed for patient use in the United States. The ecarin clotting time can also be used to determine plasma dabigatran concentrations, but this test is even less widely available than the HemoClot assay.

How do these coagulation tests perform in the real world setting? This is the focus of the study by Hapgood et al. (14) in a recent issue of Thrombosis and Haemostasis. These investigators used the HemoClot assay to determine drug concentrations in 75 plasma samples collected from 45 patients taking dabigatran. Dabigatran levels were then correlated with the aPTT, which was performed with four different reagents. Using linear regression analysis, they determined the aPTT range with each reagent that corresponded to dabigatran levels of 90 to 180 ng/ml, the range that the authors designated as therapeutic for dabigatran. The thrombin time also was correlated with dabigatran concentrations. Dabigatran concentrations over 60 ng/ml were associated with marked prolongation of the thrombin time; a finding that highlights the responsiveness of this test to dabigatran.

Although the study design is straightforward, do plasma concentrations of 90 to 180 ng/ml really represent the therapeutic range for dabigatran? As outlined by the authors, these values reflect the median trough and peak concentrations of dabigatran determined in subjects given the drug at a dose of 150 mg twice daily (15). However, the corresponding values in those taking 110 mg twice daily -- the dabigatran dose used in at least 50% of patients in most countries -- are about 65 and 130 ng/ml, respectively (16). Furthermore, even if the median trough and peak levels with the 150 mg dose of dabigatran are 90 and 180 ng/ml, respectively, this means that half of the patients will have dabigatran levels lower or higher than these values at trough and peak, respectively; findings that will complicate interpretation of aPTT results calibrated to this range. Therefore, 90 to 180 ng/ml cannot be considered the therapeutic range for dabigatran.

What can we learn from this study? The authors show that the aPTT values obtained with dabigatran concentrations ranging from 90 to 180 ng/ml differ with each of the aPTT reagents examined; a finding consistent with previous reports that aPTT reagents vary in their responsiveness to the anticoagulant effects of dabigatran (9-12). In addition to confirming this finding in samples collected from patients taking dabigatran, the results of this study suggest that each laboratory will need to determine the sensitivity of its aPTT reagent to dabigatran; a process analogous to determining the aPTT range that corresponds to therapeutic anti-Xa levels for heparin whenever the aPTT reagent lot number changes. It is uncertain whether...
plasma samples from patients taking dabigatran will need to be used for this task, as was done by Hapgood et al., or whether dabigatran calibrators will suffice. Widespread and rapid access to the Hemoclot assay would not only streamline calibration, but would also eliminate uncertainties arising from the use of the aPTT assay to determine dabigatran levels. With current cost constraints, however, many laboratories may be unwilling or unable to expand their repertoire of coagulation tests.

In hospitals without access to the Hemoclot assay, Hapgood et al. recommend holding dabigatran prior to elective surgery or interventions until both the aPTT and thrombin time are normal to ensure that there is no residual dabigatran activity. Is this really necessary, or is a normal aPTT a sufficient indicator of minimal dabigatran activity? This is an important question because normalisation of the thrombin time can be delayed for several days after the aPTT returns to normal. Such a delay can be problematic because withholding anticoagulation for an extended period of time may place patients at risk for thrombosis. Although confirmatory data are needed, it is likely that most surgical procedures can safely be performed with dabigatran concentrations of 50 ng/ml or less. With this level of dabigatran, the aPTT was normal or near normal in most of the patient samples studied by Hapgood et al. Therefore, a normal or near normal aPTT may be a sufficient indicator of little or no residual dabigatran activity in the majority of patients. Only in those undergoing procedures associated with a high risk of bleeding may it be prudent to withhold dabigatran until the aPTT and the thrombin time have both returned to normal.

Monitoring NOACs is an evolving science. Although the study by Hapgood et al. brings us one step further in our understanding of dabigatran monitoring, we still have a long way to go. Measuring plasma drug levels is only a first step. Next, we need to determine the relationships between low dabigatran levels and the risk of thrombosis and high drug levels and the risk of bleeding so that the therapeutic range for dabigatran can truly be defined.

Conflicts of interest

J. Eikelboom has received consulting fees and/or honoraria from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis and grants and/or in-kind support from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis. J. Weitz has received consulting fees and/or honoraria from Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, Daiichi Sankyo, Bayer, Portola, Merck and Janssen Pharmaceuticals.

This editorial reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

References

10. Douxfils J, Muller F, Robert S, et al. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PT/INR</th>
<th>aPTT</th>
<th>ECT</th>
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<th>dTT (Hemoclot)</th>
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<tr>
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<tr>
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<td>Log-linear</td>
<td>Linear</td>
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<td>Normal aPTT suggests minimal drug levels</td>
<td>Potentially suitable for monitoring</td>
<td>Normal TT excludes presence of drug</td>
<td>Potentially suitable for monitoring</td>
</tr>
</tbody>
</table>

aPTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECT, ecarin clotting time; PT/INR, prothrombin time/international normalised ratio; TT, thrombin time.