Atrial fibrillation (AF) is the most common cardiac rhythm disorder. The estimated prevalence of AF ranges from 0.4% to 2% in the general population and increases by age. AF is associated with a five-fold risk of stroke and a three-fold incidence of congestive heart failure, and higher mortality.\textsuperscript{1,2,3,4}

New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular AF.\textsuperscript{4}

The NOACs for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban). In contrast to VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in coagulation.\textsuperscript{4}

The NOACs so far tested in clinical trials have all shown non-inferiority compared with VKAs, with better safety, consistently limiting the number of intracranial hemorrhage. On this basis, ESC guideline recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF.\textsuperscript{4}

NOACs do not require routine monitoring of coagulation. However, the quantitative assessment of the anticoagulant effect drug levels may be needed in emergency situations, such as a serious bleeding or need for urgent surgery, or in patients with renal or hepatic insufficiency. In the paper we focus on the coagulation testing for new oral anticoagulants.

For dabigatran, the activated partial thromboplastin time (aPTT) may provide a qualitative assessment of the presence of dabigatran and the pro-thrombin time (PT) for rivaroxaban (and likely other factor Xa inhibitors), but these respective tests are not sensitive for the quantitative assessment of the NOAC. Quantitative tests for direct thrombin inhibitors (DTIs) and FXa inhibitors do exist, but they may not be routinely available in most hospitals. Point of care tests should not be used to assess the international normalized ratio (INR) in patients on NOACs. An overview of the inter-prediction of all the coagulation tests for different NOACs can be found in Table 1.

**Direct Thrombin Inhibitors (Dabigatran)**

For dabigatran, the ecarin clotting time (ECT) and thrombin clotting time are useful tests, and directly reflect thrombin inhibition; however, an activated partial thromboplastin time (aPTT) can also be used (especially in an emergency setting).\textsuperscript{4} The aPTT may provide a qualitative assessment of dabigatran (direct thrombin inhibitor) level and activity. The relation between dabigatran and the aPTT is curvilinear. Nevertheless, the sensitivity of the different aPTT reagents varies greatly. In patients receiving chronic therapy with dabigatran 150 mg twice daily (bid), the median peak aPTT was approximately two-fold that of control. Twelve hours after the last dose, the median aPTT was 1.5-fold that of control.

Therefore, if the aPTT level exceeds two times the upper limit of
normal, this may be associated with a higher risk of bleeding, and may warrant caution especially in patients with bleeding risk factors.

Dabigatran has little effect on the PT and INR at clinically relevant plasma concentrations. Prolongation of the PT is related linearly and dose-dependently to the plasma dabigatran concentration, but the responsiveness is low. The INR is therefore unsuitable for the quantitative assessment of the anticoagulant activity of DTIs.7

ECT prolongations above the basal value are related linearly and dose-dependently to the dabigatran concentration; responsiveness is also adequate. The ECT assay provides a direct measure of the activity of DTIs ≥3 times elevated ECT at trough is associated with a higher risk of bleeding in patients taking dabigatran.8

Thrombin time results depend on the coagulometer and the thrombin lot used. Unlike diluted thrombin time (dTT) test can more accurately predict the coagulation state. A dTT has been developed, with appropriate calibrators for interpretation in the context of dabigatran use (Hemoclotw). The dTT is suitable for the quantitative assessment of dabigatran concentrations. A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran. When dabigatran is used with twice daily dosing, a dTT measured at trough (≥12 h after the previous dose) with the Hemoclotw of ≥200 ng/ml dabigatran plasma concentration (dTT approximately >65 s), is associated with an increased risk of bleeding.13 still that there are no data on a cut-off dTT below which elective or urgent surgery is ‘safe’, and therefore its use in this respect cannot be recommended at this time.5

Factor XA Inhibitors (Rivaroxaban, Apixaban, Edoxaban)

Factor Xa-inhibitors prolongs the prothrombin time (PT) and aPTT varying degree and this might be used as a rough estimate of an anticoagulation effect. But the aPTT cannot be used for evaluation of FXa inhibitory effect because of the weak correlation and variability of assays.

The prolongation of the PT is related linearly and dose-dependently to the Factor Xa-inhibitor concentration, and the responsiveness is adequate. Nevertheless the effect on the PT depends both on the assay and on the FXa inhibitor. For rivaroxaban, the PT may provide some quantitative information, but the sensitivity of the different PT reagents varies greatly.

The INR is unreliable for the evaluation of FXa inhibitory activity. A better estimate for an anticoagulant effect for the oral Factor Xa inhibitors is an anti-Xa assay.4,5,9

Anti-FXa ‘chromogenic assays’ have been developed to assess plasma concentrations of the FXa-inhibitors and are commercially available. However, there are currently no data that associate a coagulation parameter or a drug level at trough or at peak with bleeding risk or risk for thrombo-embolism.

Impact Of NOACs On Coagulation System Assessment

The NOACs interfere with routine coagulation tests, thrombophilia tests or the measurement of coagulation factors. Abnormal coagulation tests should be interpreted with caution if the time window between blood sampling and NOAC intake is unknown. Therefore, a time window of at least 24 h is recommended between the last intake of a NOAC and blood sampling to assess coagulation parameters and this time window may be even longer for lupus anticoagulant measurements (≥48 h).10

Because NOACs may have an additional impact on the INR (especially the FXa inhibitors), influencing the measurement while on combined treatment during the overlap phase, it is important that the INR be measured just before the next intake of the NOAC during concomitant administration, and be retested 24 h after the last dose of the NOAC (during sole VKA therapy).

References


