Commentary

Viscoelastic monitoring of direct oral anticoagulants (DOAC)

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INTRODUCTION

The benefit of direct oral anticoagulants (DOAC) can become a challenge when the treated patient faces a critical bleeding emergency and withholding is not an option. Urgent monitoring to detect, quantify, and reverse remaining effects of anticoagulants is essential to make clinical decisions less empirical, with the help, if available, of protocols guiding the quantification of the anticoagulants' reversal. Qualitative identification of the type of DOAC at the time of the intervention is relevant, but most important is the quantitative evaluation of its effect, which corresponds to a residual plasma concentration.

To make an assessment prior to DOAC monitoring, dosage, time of last intake, and creatinine clearance data are required. In a non-urgent peri-procedural situation, the drug would be withheld for at least 24 hours, bridge therapy would not be necessary, and, with few exceptions, routine testing would not be recommended[1]. Predictors of residual DOAC levels were defined in a prospective study in elective surgery as older age, female sex, low weight, renal dysfunction, and shorter time of interruption[2]. Drug pharmacology, high inter-laboratory variability and low accuracy of conventional coagulation methods make viscoelastic analysis a good alternative for urgent monitoring of DOAC when rapid decision making is required. However, conventional viscoelastic assays will not always provide enough information for this quantification, and it will be essential to rely on specific reagents that detect the different drug and estimate their residual plasma levels. Guidelines for urgent reversal of DOAC cannot recommend widespread use of viscoelastic testing to monitor them because of the lack of randomized trials[3]. Nevertheless, the ability to perform a rapid, specific bedside analysis with a global hemostatic perspective and to stratify clinical decision making may be an optimal approach to DOAC monitoring that can always be complemented with laboratory data.

LABORATORY MONITORING OF DOAC

Conventional coagulation tests, such as prothrombin time (PT) for activated Factor X (FXa) inhibitors and, in particular, thrombin time (TT) and/or activated partial thromboplastin time (aPTT) for direct thrombin inhibitors (DTI), may be used non-specifically to screen for the presence of a DOAC[4]. However, PT and aPTT correlate poorly with plasma concentrations. Quantitative methods include diluted TT (dTT) and calibrated or chromogenic anti-Xa assay[5]. A normal TT can be used to exclude clinically relevant levels of dabigatran. Urine dipstick tests can rule out the presence of DOAC at plasma thresholds of >14 ng/mL (FXa inhibitors) and >19 ng/mL (DTI), allowing qualitative determination. However, this method is not recommended for quantitative monitoring[6].

The most common method used to quantify FXa inhibitors in plasma is the standardized anti-Xa assay, which may vary depending on the heparinoid, the automated laboratory analyzer, and the different available anti-Xa reagent[4]. It has been observed that the

anti-Xa assay may lose accuracy in the presence of significant antithrombin deficiency, pregnancy, obesity, end-stage renal disease, after thrombolysis, and in patients with hyperbilirubinemia[7,8]. Anti-Xa activity is linear over a wide range of drug levels for rivaroxaban and apixaban[5]. Undetectable anti-Xa activity likely excludes clinically relevant drug concentration. No predictive data on bleeding have been provided based on anti-Xa values.

Measurement of drug concentration in blood has also been shown to be a safe method for monitoring reversal of DOAC. In a pharmacokinetics study in a perioperative setting, the plasma concentration of ribaroxaban impacting blood loss was determined to be >100 ng/mL[9]. Monitoring efforts with thrombin generation assays have been unsuccessful, with critical influence of rheological conditions[10] and endogenous thrombin potential showing weak correlation with DOAC levels[11].

VISCOELASTIC MONITORING OF DOAC

Over the last decade, the evidence for DOAC monitoring with viscoelastic tests is growing[12]. Tests and parameters related to kinetics of thrombin generation were found to be the most useful. For the specific approach, attempts have been made to modify the test reagents by dilution or addition of tissue factor, but the specific agents for detection of DOAC in blood sample are as follows[13-16]. These available components are Russell's Viper Venom (RVV), isolated from the snake *Daboia russelii*, that activates FX directly and, in presence of FV, FII, Ca^{2+} and phospholipids, results in fibrin clot, and ecarin, which is a thrombin activator. Despite these advances, most studies have been observational and conducted in healthy volunteers, resulting in weak evidence. Consequently, while viscoelastic monitoring of DOAC appears to be convenient, its full potential remains largely unexplored and requires further investigation.

Viscoelastic monitoring with thromboelastography (TEG 5000® and TEG 6S® [Haemonetics, Boston, MA, USA])

First studies demostrated that RapidTEG activated coagulation time (ACT) and the intrinsic pathway activation test, kaolin, were able to detect and monitor DOAC, and the test to which a thrombin activator, ecarin, was added, was useful in differentiating between FXa inhibitors and DTI[17]. Other studies have determined sensitivity reaction time (R) values >2.5 min for dabigatran, >2.5 min for apixaban, >1.8 min for rivaroxaban to detect DOAC ≥50 ng/mL[18], with an R range of 0.6-1.5 min for FXa inhibitors and 1.6-2.5 min for DTI[19].

A prospective study with 189 patients with modified channels for DTI (ecarin) and FXa inhibitors (human factor FXa) demostrated R time linear correlation with dabigatran and R non-linear correlation with rivaroxaban and apixaban, with good sensitivity and negative predictive value for low DOAC levels[20]. This observation was later corroborated with healthy volunteers, obtaining sensitive R values for DOAC detection of 50 ng/mL[21].

Viscoelastic monitoring with thromboelastometry (ROTEM® [Werfen, Bedford, MA, USA] and CLOTPRO)

It was first observed, that extrinsic activation test EXTEM and fibrinogen effect test FIBTEM correlated with dabigatran but less with the intrinsic activation test INTEM[22]. It was defined a dose-dependent increase in clotting time (CT), poorly impacted from low levels of edoxaban, rivaroxaban or dabigatran, and little effect from apixaban, even at high concentrations[23].

A diagnostic test study of 66 patients with a modified EXTEM test detected FXa inhibitors about 25 ng/mL in poor platelet plasma with a 1.4-fold increase in CT, and was able to detect FXa inhibitors >30 ng/mL in whole blood with CT >197 sec[24]. Thirty patients with non-valvular atrial fibrillation and fifteen healthy volunteers as controls were tested with diluted EXTEM and modified EXTEM with ecarin (ECATEM) and anti II/Xa catchers (RO-DOA study) and were able to accurately identify DOAC[25]. In another *ex-vivo* study of 34 participants, clot formation appeared to be faster/firmer with increased dabigatran levels (non-dose-dependent effect of increased fibrin polymerization and dose-dependent effect of increased platelet sensitivity to thrombin). EXTEM CT was useful for qualitative monitoring of dabigatran and limited for rivaroxaban[26].

A prospective study of 50 anticoagulated patients and 20 healthy volunteers using algorithms and decision trees showed that standard tests can differentiate DOAC, vitamin K antagonists (VKA), dilutional coagulopathy and controls, but failed to differentiate FXa inhibitors, DTI and VKA[27]. A small preclinical study also showed, with highest sensitivity and specificity, that CT was able to detect DOAC >30 ng/mL, including apixaban, in modified ECATEM and

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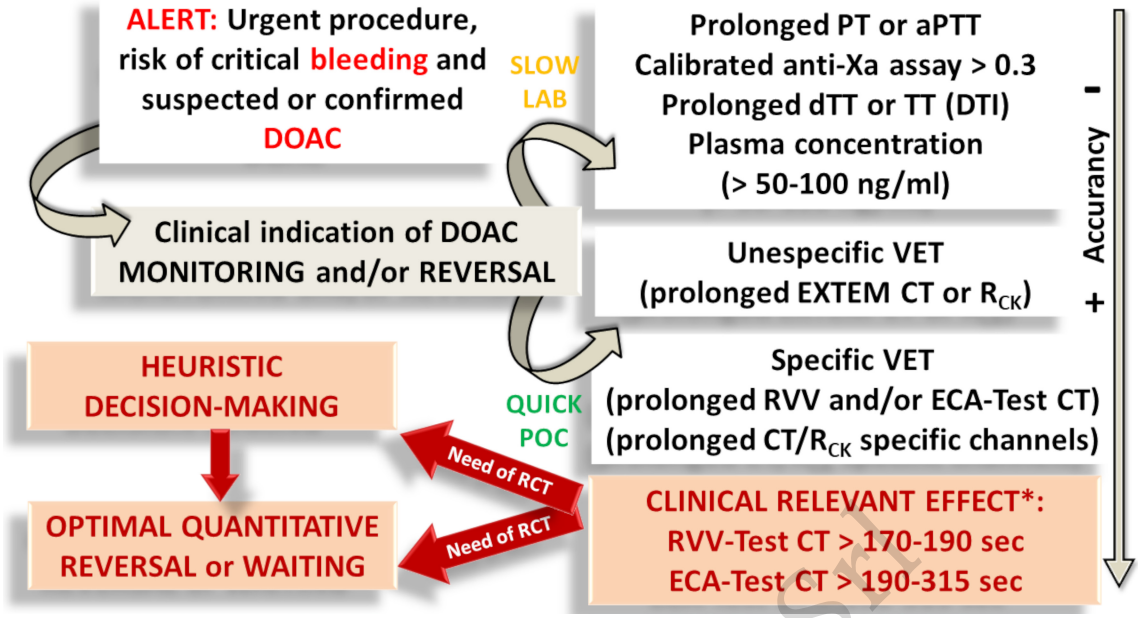

Figure 1 - DOAC monitoring algorithm for emergencies
DOAC: direct oral anticoagulants; LAB: conventional coagulation laboratory tests; PT: prothrombin time; aPTT: activated partial thromboplastin time; dTT: diluted thrombin time; TT: thrombin time; VET: viscoelastic tests; EXTEM: extrinsically activated thromboelastometric test; CT: clotting time; R_{CK}: citrated kaolin reaction time; POC: point of care; RCT: randomized control trial; RVV: Russell's Viper Venom; ECA: ecarin test; sec: seconds. *According to results of Oberladstätter *et al.*[13].

Tissue Factor thromboelastometric (TFTEM) assays[28]. An accurate prospective diagnostic study to date correlating plasma DOAC concentrations with thrombin generation times of the specific viscoelastic tests (RVV-Test and ECA-Test of CLOTPRO) was performed with over 200 measurements to identify cut-off points defining DOAC concentrations of 50 and 100 ng/mL. They found strong positive correlations between plasma levels and CT values in these specific assays, less so for apixaban[13]. The most relevant values of these results are summarized in **Figure 1**, linked to a clinical decision monitoring algorithm. The same research group conducted an *ex vivo* spiking study in a cohort of trauma patients, demonstrating the effect of idarucizumab and andexanet alfa on DOAC plasma concentration, evaluating CT in the specific tests[14].

A prospective observational study of 70 anticoagulated patients and 10 healthy volunteers concluded that, in emergency situations, specific viscoelastometric evaluation of whole blood samples can help determine the presence and type of anticoagulant class. RVV-Test CT was prolonged with dabigatran, FXa inhibitors, and unfractinated heparin (UFH) *vs* controls, and ECA-Test CT was increased with dabigatran *vs* controls. ECA-Test CT correlated with the plasma concentration of dabigatran and RVV-Test CT correlated with the plasma concentration of FXa inhibitors[16].

Recently, an *ex vivo* study in human blood anticoagulated with rivaroxaban demonstrated a concentration-dependent prolongation of the RVV-Test CT, which was not affected by the addition of 4-factor prothrombin complex concentrate, and the addition of andexanet shortened the RVV-Test CT, so this test may be an alternative to control reversal with andexanet alfa[29].

CONCLUSIONS

Viscoelastic assays provide rapid and essential point-of-care information on DOAC activity, and specific assays have been shown to be more sensitive. Identification and quantification of residual plasma DOAC concentration with non-specific viscoelastic tests is probably not sensitive enough compared to anti-Xa activity by conventional laboratory assays. Optimally, it would be desirable to have a rapid start-up and analysis device with sufficient automatization, but

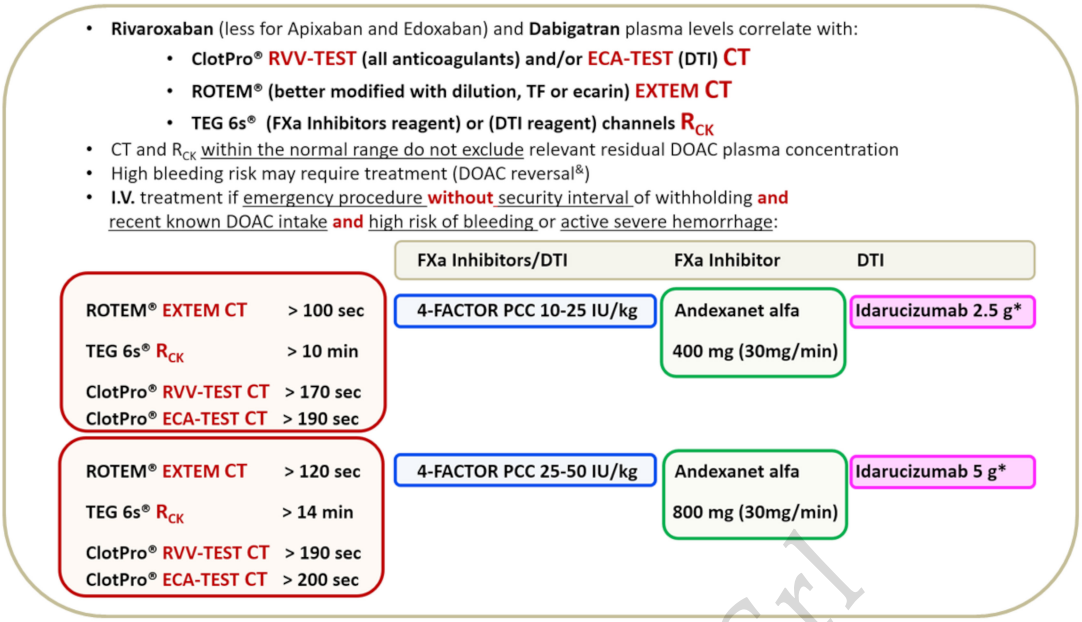

Figure 2 - Viscoelastic DOAC monitoring and management approach
DOAC: direct oral anticoagulants; RVV: Russell's Viper Venom; ECA: ecarin test; TF: tissue factor; CT: clotting time; EXTEM: extrinsically activated viscoelastometric test; FXa: activated Factor X; DTI: direct thrombin inhibitor; R: reaction time; R_{CK}: citrated kaolin reaction time; I.V.: intravenous; &: referenced European Guidelines of DOAC Reversal[3]; PCC: prothrombin complex concentrate; sec: seconds; min: minutes; *: first-line treatment.

also with the ability to discriminate and choose the most appropriate tests and, above all, with specific reagents that have demonstrated the best sensitivity and specificity, which until now are RVV and ecarin. If the possibility of viscoelastic monitoring of DOAC is not available, in case of emergency or critical bleeding risk, the best option to quantify the residual effect is the determination of thrombin time (better if diluted) for dabigatran and the anti-Xa assay for FXa inhibitors. The determination of plasma levels of DOAC provides additional and valuable information that is not usually available in every laboratory. A summary table of practical indications with a treatment proposal is reported in **Figure 2**.

The Authors declare no conflicts of interest.

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