

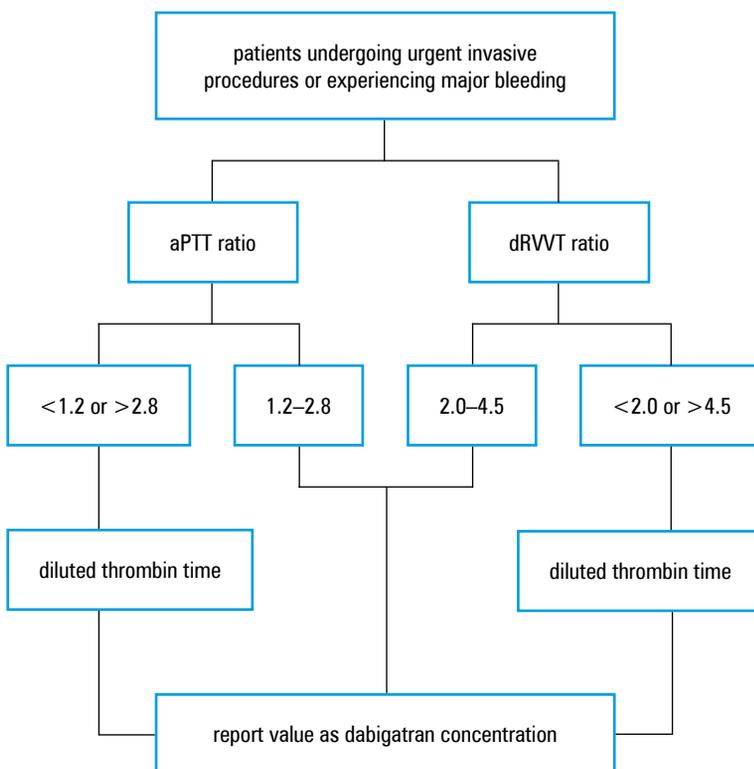
# Urgent monitoring of dabigatran plasma levels: sometimes less is more

**To the Editor** We read with interest an article by Czubek et al.,<sup>1</sup> who concluded that the urgent assessment of plasma dabigatran concentrations by means of a routine coagulation test such as measuring the activated partial thromboplastin time (aPTT) would be a feasible and reliable option in everyday practice. This information is indeed valuable and advantageous because the current standard for measuring direct oral anticoagulants such as dabigatran entails the use of expensive and cumbersome techniques including liquid chromatography–tandem mass spectrometry (LC-MS/MS) or, less routinely, the available procedures such as measurement of the diluted thrombin time (dTT).<sup>2</sup>

The alternative approach suggested by Czubek et al.<sup>1</sup> for the assessment of dabigatran in urgent settings has been previously examined in

our own environment. More specifically, normal pooled plasma samples spiked with a stock solution of plasma-containing dabigatran showed that the aPTT was linearly correlated with a dabigatran dose, displaying an excellent correlation coefficient ( $r = 0.996$ ), which was even greater than that of a commercial dTT assay (Hemoclote Thrombin Inhibitor, Hyphen BioMed, Neuville-sur-Oise, France;  $r = 0.968$ ).<sup>3</sup> The linearity of the dose-response of the former test to dabigatran concentrations was optimal in the range of concentrations between 30 ng/ml (aPTT, 1.2 ratio) and 600 ng/ml (aPTT, 2.8 ratio), thus fulfilling the need for urgent patient screening. Similar results were obtained using the dilute Russell viper venom time (dRVVT), wherein the dose-dependent linearity was proven excellent in the range of dabigatran concentrations between 100 ng/ml (dRVVT, 2.0 ratio) and 800 ng/ml (dRVVT, 4.5 ratio).<sup>3</sup>

Those results have allowed to develop local algorithms (reproduced in [FIGURE](#)),<sup>4</sup> entailing the performance of an aPTT or dRVVT assay as an initial step in patients who may require urgent assessment of plasma dabigatran levels (ie, those undergoing invasive procedures or experiencing major bleeding). An aPTT value in the range of the linearity of this assay (ie, between 1.2 and 2.8 ratio) would allow a reliable estimation of the drug concentration, while the use of a more sensitive assay (ie, dTT) would be required only if aPTT values were outside the range of linearity of this clotting assay (ie, <1.2 or >2.8 ratio). Similarly, a dRVVT ratio in the range of linearity (ie, between 2.0 and 4.5) would allow a reliable estimation of the drug concentration and, again, the use of dTT would only be required if a dRVVT ratio was outside the range of test linearity. Importantly, aPTT tests are widely available, and dRVVT tests (commonly used to assess lupus anticoagulant) are also more widely available than dTT tests. Interestingly, this approach is not only an effective way to decrease the turnaround time (the dRVVT and especially the aPTT are much faster than dTT or LC-MS/MS), but it is also less expensive than direct measurement of dabigatran concentrations in all patients by means of dTT (ie, 90% to 97% saved on the estimated cost of reagents).<sup>4</sup>



**FIGURE** Suggested approach to plasma dabigatran concentration screening based on activated partial thromboplastin time (aPTT) or dilute Russell viper venom time (dRVVT)

One caveat to these findings is that the utility of the aPTT and dRVVT assays in this setting may be reagent-dependent, and laboratories should evaluate their reagents for suitability before implementing this approach. Another caveat is that the concomitant existence of additional hemostatic defects, so that the aPTT or dRVVT may overestimate dabigatran concentrations in some patients (eg, patients with lupus anticoagulant or factor XII deficiency may have higher clotting times).<sup>5</sup> Thus, the use of lupus anticoagulant-insensitive aPTT and dRVVT reagents would be preferable in this setting.

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**Conflict of interest** The authors declare no conflict of interest.

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**Authors' reply** We are grateful for a number of insightful comments by Lippi and Favaloro<sup>1</sup> on dabigatran-induced alterations to coagulation tests that can be used in everyday practice; in particular, we appreciate the inclusion of the diagnostic algorithm for patients on dabigatran who may require urgent invasive procedures or experience major bleeding. In line with the paper by Lippi et al.,<sup>2</sup> our preliminary results have also shown a good correlation between plasma dabigatran concentrations (assessed using a commercially available diluted thrombin time [dTT] assay, Hemoclot Thrombin Inhibitor, Hyphen BioMed, Neuville-sur-Oise, France) and activated partial thromboplastin time (aPTT) in patients with atrial fibrillation.<sup>3</sup> Moreover, the algorithm proposed by Lippi and Favaloro<sup>1</sup> indicates that in urgent settings in patients with dabigatran concentrations exceeding 600 ng/ml, outside the range of

a linear relationship with aPTT, dTT may be more useful for dabigatran monitoring than aPTT. Unfortunately, we did not study patients with such high dabigatran concentrations; however, an approach suggested by Lippi and Favaloro<sup>1,2</sup> could be useful in emergency settings except for patients positive for lupus anticoagulant.

Interestingly, Lippi and Favaloro<sup>1</sup> favored the use of the dilute russell viper venom time (dRVVT) and a dRVVT ratio in the range of linearity (ie, between 2.0 and 4.5), reducing the need for the measurement of dTT to a small subset of patients with a dRVVT ratio below 2.0 or above 4.5. However, most reviews and expert opinions focus on the use of thrombin clotting time and ecarin clotting time to test the anticoagulant effect of dabigatran with the emphasis on aPTT as a readily available assay to determine relatively dabigatran-induced anticoagulant effects in clinical scenarios when the measurement of these actions of the thrombin inhibitor will be required. For example, Baglin et al.,<sup>4</sup> in the 2013 recommendation of the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis, did not mention dRVVT while presenting the effect of dabigatran on laboratory clotting tests. A special role of dRVVT in monitoring dabigatran use warrants further clinical validation studies and its implementation in hospital laboratories.

From a clinical point of view, the key issue remains, namely, the optimal management of patients on dabigatran or rivaroxaban who simultaneously require an immediate invasive procedure or have major bleeding complications. No tests to measure dabigatran levels have been convincingly shown to correlate with bleeding risk, although it has been reported that a dTT of more than 65 s is associated with an increased risk of bleeding in subjects on dabigatran.<sup>5</sup> The cut-off values of the tests to differentiate patients with "safe" residual drug levels from those on anticoagulation associated with significant hemorrhagic risk are not available.<sup>6</sup> Therefore, the interpretation of coagulation tests in patients on dabigatran is difficult and should include the time since the last dose, renal function, and clinical circumstances.

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