Routine Coagulation Tests in Patients With Nonvalvular Atrial Fibrillation Under Dabigatran and Rivaroxaban Therapy: An Affordable and Reliable Strategy?

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Abstract
Dabigatran and rivaroxaban, direct oral anticoagulants (DOACs), affect coagulation tests, and knowledge of their effects is important for therapeutic monitoring. Our aim was to examine the association between DOAC levels and routine coagulation tests in patients with nonvalvular atrial fibrillation. Samples from patients receiving dabigatran (150 mg) and patients receiving rivaroxaban (20 mg) were collected 2 hours after drug intake. Direct oral anticoagulant concentrations were determined using direct Hemoclot thrombin inhibitor (HTI) assay (HTI test) and a direct Xa inhibitor (Anti Xa-Riva). The routine coagulation measured included activated partial thromboplastin time (aPTT) and prothrombin time (PT). The median plasmatic dabigatran was 128.3 ng/mL (95% confidence interval [CI]: 93.7-222.6 ng/mL). The HTI exhibited a good correlation with aPTT ($R^2 = 0.74, P < .0001$). The median plasmatic rivaroxaban was 223.9 ng/mL (95% CI: 212.3-238.9 ng/mL). Anti-Xa-Riva correlated with PT ($R^2 = 0.69, P < .0001$) and aPTT ($R^2 = 0.36, P < .001$), but prolonged PT results were obtained, even below the rivaroxaban therapeutic range (20%). The routine coagulation tests were able to identify out of therapeutic range concentrations for dabigatran and rivaroxaban. We suggest the use of these screening tests to better understand and monitor the subtherapeutic concentrations of these DOACs.

Keywords
dabigatran, rivaroxaban, prothrombin time, activated partial thromboplastin time

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Introduction
Direct-acting oral anticoagulants (DOACs), such as dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor), are effective alternatives for anticoagulation in stroke prevention in patients with atrial fibrillation (AF).

Although these DOACs do not require any routine laboratory monitoring, there are some situations in which the precise anticoagulation status of a particular patient has to be considered, such as to determine the presence of very high levels of anticoagulant, in cases of suspected poor adherence or for planned invasive procedures. In these situations, the clinical laboratory needs to be able to provide some support.

In addition, there are no established thresholds for any coagulation test that indicate when surgery or invasive procedures

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can be safely performed without elevated bleeding risk. For patients taking DOACs, activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) should be used only as qualitative tests to confirm an anticoagulant effect. For dabigatran, the aPTT results should range from 2 to 3 times the normal value at drug peak level; moreover, the TT is very sensitive to the presence of the drug. For rivaroxaban, the PT is the recommended test, but a careful choice is necessary since there are “insensitive” PT tests available on the market for the assessment of rivaroxaban’s effect, like the Innovin from Siemens Dade (Marburg, Germany).

In both cases, quantitative biological methods developed to assess drug plasma concentrations are recommended, such as direct Hemoclot thrombin inhibitor (HTI) assay (HTI test) for determining the plasma concentration of dabigatran and the direct anti-Xa assay for determining rivaroxaban plasma concentration.

The aim of this exploratory study was to correlate specific chromogenic assays in their assessment of dabigatran and rivaroxaban concentrations with the results of screening coagulation tests, PT, aPTT, or TT in the plasma of patients receiving treatment for AF.

Materials and Methods

Patients diagnosed with nonvalvular AF attended in our clinical anticoagulation ambulatory and already receiving anticoagulation treatment (dabigatran or rivaroxaban) were invited to participate in the study. The Ethics Committee of the Heart Institute of the University of São Paulo approved the study, and written informed consent was obtained from all participants. Patients with abnormal coagulation tests, creatinine concentrations >2.0 mg/dL, and estimated glomerular filtration rates (Cockroft-Gault equation) <30 mL/min/1.73 m² were excluded.

Thirty (33%; male) patients taking 150 mg of dabigatran twice daily and 100 (55%; male) patients taking 20 mg per day of rivaroxaban were enrolled. Blood was collected during the second week of treatment. All patients were oriented to take the medicine in the presence of a health-care professional to ensure its proper intake. Blood collection was performed in the morning, on nonfasting patients, after 2 hours of the drug administration. After centrifugation, platelet-poor plasma was obtained by centrifugation performed at room temperature at 2500 x g for 10 minutes. Plasma samples were used in the screening coagulation tests on the day of collection and were stored at −80°C until use in specific coagulation assays.

All clotting assays were conducted in the same laboratory using a Destiny Max automated mechanical clot detection coagulometer purchased from TCoag (Bray, County Wicklow, Ireland). Coagulation screening assays included PT, aPTT, and TT obtained from TriniCLOT (Bray, County Wicklow, Ireland). A thromboplastin isolated from rabbit brains was used in the Quick PT method. The TriniCLOT reagents used in the PT assay had sensitivity to detect low concentrations of the drug. The mean of reference interval for PT was 12 seconds (9.8-14.0 seconds). The TriniCLOT aPTT reagents contained micronized silica as the contact activator and a similar mixture of purified phospholipids. The mean of reference interval for aPTT was 30 seconds (26-34 seconds). The TT assay directly assessed the activity of thrombin in the plasma samples. The mean of reference interval for TT was 13.1 seconds (11.8-14.5 seconds).

Dabigatran concentrations were measured by HTI test (Hyphen Biomed Neuville-sur-Oise, France), which contains highly purified human thrombin. Rivaroxaban concentrations were evaluated using the calibrated Biophen anti-activated Factor X Rivaroxaban kit from Hyphen Biomed. Duplicate analyses were performed for all samples. The results are expressed in ng/mL. All procedures were performed according to the manufacturers’ recommendations.

Expected Peak Drug Levels

Dabigatran administered at a dose of 150 mg twice daily resulted in a median peak concentration of 186 ng/mL (5th to 95th percentile: 64 to 443 ng/mL). For rivaroxaban, the therapeutic range, which was adopted based on phase II data and a dose of 20 mg once/day, resulted in a median peak level of 250 ng/mL (95% confidence interval [CI]: 177-361 ng/mL).

Statistical Analyses

The Kolmogorov-Smirnov normality test was used to analyze data normality. Data are expressed as the mean (standard deviation) or the median and 95% CI. Linear regression analyses were performed to determine the straight line that best describes the relationship between the coagulation test data and the corresponding plasma DOAC levels and to calculate linear regression equations.

Pearson’s correlation was used to determine the association between variables that were logarithmically transformed to obtain a normal distribution. Stepwise multivariable analyses were performed considering dabigatran or rivaroxaban as the dependent variable and PT, aPTT, sex, age, body mass index (BMI), and serum creatinine as independent variables. The same variables were used to calculate odds ratios (ORs). Variables with P < .1 were included in the regression model. Receiver operating characteristic (ROC) analyses were performed to determine optimal cutoff values for selected variables. The significance level adopted was <5% (P < .05).

Statistical analyses were performed using MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; 2014).

Results

Dabigatran

The basal characteristics of the patients (n = 30; 10 male) were as follows: mean age 66.0 (11) years, mean weight 71.6 (11.8) kg, and mean BMI 26.8 (3.8) kg/m². The mean creatinine level
was 1.0 (0.3) mg/dL, and the estimated glomerular filtration rate (Cockroft–Gault equation) was 56.2 (8.2) mL/min/1.73 m². Demographic characteristics of patients are shown in Table 1.

For the HTI test, the median peak level of plasmatic dabigatran was 128.3 ng/mL (95% CI: 93.7-222.6 ng/mL). For the screening test, the median aPTT result for all samples was 48.8 seconds (95% CI: 44.4-56.7), 1.6 times higher than the normal aPTT value (30 seconds). The best fit line of the effect of dabigatran plasma levels on aPTT obtained by linear regression was described by the equation: \( y = 0.0834x + 36.81 \). The \( R^2 \) value was 0.74 (\( P < .0001 \), pointing to a good correlation between the 2 measures.

The median PT for all of the samples was 20.4 seconds (CI 95%:18.4-22.4), 1.7 times higher than the normal PT value (12 seconds). The best fit line obtained by linear regression analysis of the relationship between dabigatran plasma levels and PT results was described by the equation: \( y = 0.043x + 13.94 \), and the \( R^2 \) was 0.73 (\( P < .0001 \)).

According to the therapeutic peak range obtained from Ezekowicz et al (64 to 443 ng/mL), only one patient presented an abnormally high dabigatran plasma concentration (770 ng/mL), which resulted in prolonged aPTT (3.6 times higher than the normal aPTT value) and PT (4.4 times higher than the normal PT value), while 5 (16.7%) patients with plasmatic concentrations below the lowest value of the therapeutic range presented normal aPTT and PT values (Table 2). In these cases, only TT remained prolonged (>200 seconds).

On multivariable regression analysis, aPTT was the independent variable (\( OR = 1.23, 95\% CI: 1.13-1.34, P < .0001 \)). The cutoff value of aPTT related to subtherapeutic levels of dabigatran obtained from the ROC curve (Table 3) was <42.8 seconds. The 6 remaining patients with dabigatran plasmatic concentrations below or above the therapeutic range did not present with bleeding or thrombosis events during the follow-up period of 1 year.

### Discussion

The major guidelines suggest coagulation screening tests for drug estimation and recommend that each laboratory acquires its own knowledge of local reagent sensitivity to a given DOAC to correctly interpret the coagulation tests. However, this reality is not uniform in all hospitals in the world, and this information is not available for laboratories that lack expertise in this area, resulting in inappropriate interpretation of test results.9,10

We analyzed samples from patients with nonvalvular AF from our laboratory’s daily clinical anticoagulation practice who were already under DOACs therapy. The knowledge of the effects of DOACs on coagulation testing (with specific brands of coagulation reagents) in our population was essential to determine the appropriateness of performing such tests and interpreting them correctly.

In the present study, due the small sample size, it was impossible to create our own reference values. Thus, we used the reference values from pharmacokinetic trials as representative of the therapeutic drug levels.
For the evaluation of dabigatran concentrations in patients’ samples, we performed a commercially dilute TT test with the HTI. This assay is a simple, rapid, sensitive method for the quantification of dabigatran concentrations in patient samples. Furthermore, data from this method exhibited a high correlation with data obtained by the gold standard method (liquid chromatography).

Twenty percent (n = 6) of patient sample concentrations were outside the normal range. Five patients presented dabigatran plasmatic concentrations below the therapeutic range, although none of them had thrombosis episodes during the follow-up period. One patient with a dabigatran level of 770 ng/mL, despite no signs of hemorrhage, had their medicine changed to another DOAC. The large variation on HTI test for dabigatran (95% CI: 93.7-222.6 ng/mL) could not be explained by patients age (mean value = 66 years) nor by creatinine values (mean value = 1.0 mg/mL). Also we must consider that for all of them, the blood collection was performed at the same time, 2 hours after the drug intake. This result should be investigated since it could be related to a genetic response to the drug.

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For aPTT, as described by others, the results presented a linear dose–response across the therapeutic range of dabigatran concentrations, with a plateau at high levels. According to our data, the aPTT was 1.8 times higher than the normal value on the therapeutic range and was associated with the presence of dabigatran. Variables that could be related to dabigatran due to their possible influence on the pharmacokinetics of the drug, such as sex, age, BMI, and creatinine, showed no association with aPTT. Results less than 42.8 seconds were indicative of subtherapeutic plasma levels of dabigatran.

It should be emphasized that the number of samples was very small; the test must be applied to a larger number of patients to confirm our findings. In addition, the test is not specific for DOACs and can also be prolonged by clotting factor deficiencies and lupus anticoagulant. In contrast to the results of other studies, the PT test presented a correlation with dabigatran concentration, although it was inferior to that of aPTT. One possible explanation for this difference is related to the reagent/instrument used in each study, since the sensitivity of the PT test is dependent on both factors. Helin et al showed that the PT measured using Quick-method reagents was 3 times higher than that measured with the Owren method.

According to other studies, normal results for aPTT and PT do not necessarily indicate the absence of plasma dabigatran, only the TT test presents a prolonged clotting time with minimal doses of this medication, thus serving as the best qualitative test for dabigatran. In our study, dabigatran levels greater than 30 ng/mL results in TT greater than 200 seconds.

### Table 2. Prothrombin Time and aPTT Results According to Different Ranges of Dabigatran and Rivaroxaban Concentrations.

| Dabigatran (ng/mL) | ≤63 (n = 5) | 64-443 (n = 25) | ≥444 (n = 1) |
|--------------------|------------|----------------|-------------|
| PT (sec)           |            |                |             |
| Median (95% CI)    | 14.2b      | 22.5 (20.2-24.7)| 53.4b       |
| Multiples PT       | -          | 1.87           | 4.45        |
| aPTT (sec)         |            |                |             |
| Median (95% CI)    | 35.6b      | 53.1 (48.4-57.7)| 107.6b      |
| Multiples aPTT     | -          | 1.77           | 3.60        |
| Rivaroxaban (ng/mL)| ≤176 (n = 20)| 177-361 (n = 78)| ≥361 (n = 2) |
| PT (sec)           |            |                |             |
| Median (95% CI)    | 27.1 (26.8-28.7)| 39.5 (37.2-40.0)| 50.9b       |
| Multiples PT       | 2.25       | 3.29           | 4.20        |
| aPTT (sec)         |            |                |             |
| Median (95% CI)    | 34.3 (33.3-35.7)| 37.1 (35.2-37.8)| 45.3b       |
| Multiples aPTT     | 1.14       | 1.23           | 1.51        |

### Table 3. ROC Curve Results.

| ROC Curve | Cutoff       | AUC    | 95% CI     | Se | Sp | Youden Index | P    |
|-----------|--------------|--------|------------|----|----|--------------|------|
| Dabigatran| aPTT <42.8 seconds | 0.990  | 0.862-1.000 | 96 | 100 | 0.96         | <.0001 |
|          | PT <30.5 seconds   | 0.950  | 0.886-0.984 | 89.6 | 95.2 | 0.85         | <.0001 |

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; PT, prothrombin time.

*The therapeutic peak ranges for dabigatran and rivaroxaban obtained from the PETRO trial and from phase II data (Bayer HealthCare Pharmaceuticals and Janssen Research & Development, LLC; data on file), respectively.

*Too few values for calculation.

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; PT, prothrombin time; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity.

*The results reflect the correlation between assays. They are not the values measured by outcome.
The great interpatient variability of dabigatran levels observed in our study was already described in the literature.\textsuperscript{17}

For the analysis of rivaroxaban, our results demonstrated a linear correlation between rivaroxaban plasma levels and PT results. These data are in agreement with those obtained in other studies that used the same thromboplastin reagent and showed a significant correlation between PT and rivaroxaban concentration.\textsuperscript{18,19} Importantly, TriniCLOT PT Excel S has already been demonstrated as the most sensitive reagent for detecting rivaroxaban, along with HemosIL HS PLUS from the Instrumentation Laboratory (Milan, Lombardy, Italy).\textsuperscript{18} In the multivariable regression model, PT was an independent variable associated with rivaroxaban presence. Here again, sex, age, BMI, and creatinine were not associated with DOAC. In addition, according to our data, PT results of less than 30.5 seconds were able to identify subtherapeutic levels of plasma rivaroxaban.

Despite the correlation between aPTT results and rivaroxaban plasma concentrations, aPTT lacks the sensitivity necessary for monitoring rivaroxaban plasma levels, since the results were close to normal in patients under drug therapy. This result was expected because direct factor Xa inhibitors have a greater effect on PT than on aPTT.\textsuperscript{20,21}

Although there is substantial variability in assay sensitivity, similar result was reported by Sholzberg and Xu\textsuperscript{22} who presented a clinical case in which the patient presented a PT value of 18.5 seconds and a rivaroxaban level of 167.5ng/mL, a subtherapeutic level.

The knowledge about the interpretation of screening coagulation tests (PT, aPTT, and TT) can help to qualitatively assess DOAC levels, which can be useful depending on the circumstances. The choice of reagents is extremely important when running these tests for DOAC monitoring since some reagents lack responsiveness to low concentrations of the drugs. Clinicians and laboratorians should establish a protocol of tests based on the kind of information they need, and to provide a multidisciplinary approach in its interpretation.

\textbf{Limitations}

The major limitation was the exploratory nature of the study, which would require further confirmation of the results. Furthermore, there was one measurement per patient and only at the time at which the peak plasmatic DOAC concentration occurs. The patients with concentrations values out of the range should be submitted to another blood collection to confirm the results. The small number of patients limited our findings and other studies must include patients with renal impairment and others cardiovascular diseases.

Additionally, we did not test patients using reduced doses of DOACs. Recent observations under real-world conditions have shown a high proportion of patients using such medicine with reduced doses and presenting a higher rate of stroke than that observed in the seminal trial.\textsuperscript{23,24}

\textbf{Conclusion}

The proportion of samples with results outside the normal range, although referring to only a single time point in the treatment, could indicate the importance of reevaluating the need for monitoring the plasma concentration of DOACs.

Our results point to the possibility of using simple screening tests to monitor DOAC concentrations. A TT test could be used to determine the presence or absence of dabigatran, and aPTT test could be used to identify out therapeutic range of the drug. A PT screening test may be suitable for assessing rivaroxaban concentrations, being an important candidate for the identification of patients out therapeutic range.

For best practice in daily routine analysis, we suggest using a combination of PT, aPTT, and TT data to analyze DOAC effects and to exclude other causes of coagulopathy in bleeding patients. Our results need to be replicated by other studies.

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