Comparative Assessment of the Anticoagulant Activity of Rivaroxaban and Dabigatran in Patients With Nonvalvular Atrial Fibrillation

A Noninterventional Study

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Abstract: There is a shortage of data in everyday clinical practice about the anticoagulant effects caused by the new oral anticoagulants (NOAs). Our aim was to estimate the intensity of anticoagulant activity induced by rivaroxaban 20 mg qd and dabigatran 110 mg bid among patients with nonvalvular atrial fibrillation (NV-AF). We studied 20 patients with NV-AF treated with dabigatran, and 20 patients treated with rivaroxaban. We performed conventional coagulation tests, thrombin generation (TG) test, thromboelastometry (ROTEM), and epinephrine-induced light transmission aggregometry (LTA) in all 40 patients and 20 controls. Hemoclot Thrombin Inhibitors (HTI) and Factor Xa Direct Inhibitor (DiXaI) assay were used to measure dabigatran and rivaroxaban plasma levels, respectively.

Measurements of all assays estimating anticoagulant activity across the 2 patient groups were similar, except for aPTT. Patients on dabigatran exhibited statistically significantly prolonged aPTT values ($P < 0.001$). In LTA, patients on dabigatran also showed decreased aggregation compared to those on rivaroxaban ($P = 0.045$). Regarding the TG test, there was no association between endogenous thrombin potential (ETP) and rivaroxaban plasma levels ($P = 0.33$) as opposed to dabigatran levels ($P < 0.001$), but significant correlations were observed between rivaroxaban plasma concentrations and kinetic parameters of TG assay (Tlag, $P = 0.045$; Tmax, $P = 0.016$; and Cmax, $P = 0.003$).

Based on ROTEM and TG assays, the anticoagulant effects induced by the 2 drugs given in the specific dose regimens in real-world patients were comparable. Only platelet aggregation was found to be more affected by dabigatran as compared to rivaroxaban.

Abbreviations: aPTT = activated partial thromboplastin time, AUC = area under curve, CBC = complete blood count, CFT = clot formation time, CHA2DS2-VASc = congestive heart failure hypertension age ≥75 years diabetes mellitus stroke/transient ischaemic attack vascular disease age 65–75 and female sex, Cmax = peak height, CT = clotting time, DiXaI = factor Xa direct inhibitor, Epi = epinephrine, ETP = endogenous thrombin potential, HTI = hemoclot thrombin inhibitors, IQR = interquartile range, LI 60 = lysis index at 60 min, LTA = light transmission aggregometry, MCF = maximum clot firmness, NATEM = nonactivated thromboelastometry, NOAs = new oral anticoagulants, NV-AF = nonvalvular atrial fibrillation, pNA = paranitroaniline, PPP = platelet-poor plasma, PRP = platelet-rich plasma, ROTEM = thromboelastometry, TG = thrombin generation, Tlag = lag time, Tmax = time to peak.

INTRODUCTION

Anticoagulant therapy is widely used for the prevention and treatment of venous and arterial thromboembolism. To optimize the profile of oral anticoagulants, new agents that target only single factors of the coagulation cascade have been developed. These new target-specific oral anticoagulants fall into 2 main categories: direct thrombin (Factor IIa) inhibitors and direct Factor Xa inhibitors. Although agents in the 2 categories target distinct enzymes within the coagulation pathway, they both have features in common including a rapid onset of action, few drug–drug interactions, and a predictable anticoagulant response that eliminates the need for routine coagulation monitoring.1

Although the treatment with the new oral anticoagulants (NOAs) does not require dose-adjustment on the basis of laboratory testing, assays to assess the level of anticoagulation may be of assistance in certain circumstances, such as in the case of overdose, in patients presenting with adverse events...
(thrombosis or hemorrhage) during treatment, undergoing scheduled or emergency surgery, those with liver failure or renal impairment and at the extremes of body weight. 2  

There is little real-world clinical experience with respect to the safety and efficacy of NOAs in everyday clinical practice settings, as no head-to-head trials or large-scale observational studies that reflect routine use of these agents are available. Only indirect comparisons of new anticoagulants have been performed based on data from their published warfarin-controlled randomized trials. 3,4 At the same time, there is a shortage of data about their relative effect on hemostatic parameters based on a direct comparison. 5 Studies propose a similar effect of dabigatran 100 mg bid with rivaroxaban 20 mg od for the prevention of thrombotic events. 5,6 However, a direct comparison of the effects of these 2 regimens on hemostatic variables in vitro has not been fully investigated. Thus, we conducted a pilot study that sought to detect significant differences in the intensity of anticoagulant activity between rivaroxaban 20 mg qd and dabigatran 110 mg bid in real-world patients with nonvalvular atrial fibrillation (NV-AF).

**METHODS**

In a recently published study by our research group, 7 we evaluated 20 diabetes mellitus, stroke/transient ischemic attack, vascular score (congestive heart failure, hypertension, age (110 mg per os, bid) for patients with high CHA2DS2-V ASc patients in group A received the standard dose of Pradaxa in the "Attiko" University Hospital, Athens, Greece. The 20 Department of Cardiology and Department of Haemostasis in the following performed assays are previously described. 7

**Hemoclot Thrombin Inhibitors (HTI)**

HTI (Hyphen BioMed, Neuville-sur-Oise, France) is an in vitro diagnostic device for the quantitative measurement of dabigatran in human citrated plasma, with a clotting method based on the inhibition of a constant and defined concentration of thrombin. For measuring DTI in plasma, first, the diluted plasma (1:8 to 1:20) was mixed with a normal pooled human plasma. Clotting was then initiated by adding a constant amount of highly purified human thrombin. The clotting time measured is considered to be directly related to the concentration of assayed DTI in the tested plasma.

**Thrombin Generation (TG)**

INNOVANCE ETP (Siemens Healthcare Diagnostics, Marburg Germany) is a global hemostasis function test to assess the endogenous thrombin potential (ETP) of plasma samples. The incubation of plasma with phospholipids, and activator and calcium ions leads to initiation and propagation of the coagulation processes, eventually resulting in the generation of thrombin. Thrombin generation and the subsequent inactivation were recorded by monitoring conversion of a specific thrombogenic substrate at a wavelength of 405 nm over time. The assay was performed using BCS XP System Hemostasis analyzer.

The estimated parameters of the TG curve included area under curve (AUC), also referred to as ETP; the lag time (tlag) that describes the time from the initiation of the reaction until TG is being observed; the time to peak (tmax) which is the time from the initiation of the reaction until the maximum TG is being observed; and finally the maximum TG depicted by peak height (Cmax).

**Light Transmission Aggregometry (LTA)**

The whole blood specimen was collected in 3.8% trisodium citrate and centrifuged at 200 g for 10 min to obtain platelet-rich plasma (PRP). The remaining specimen was centrifuged at 2000 g for 15 min to obtain platelet-poor plasma (PPP). The platelet count was adjusted to lie between 200 × 10^{12} /L and 300 × 10^{12} /L with PPP.

The test was conducted within 30 min from blood sampling. Aggregation was performed using a Biodata-PAP-4 aggregometer (Bio/Data Corp., PA). The 100% line was set...
using PPP and a 0% baseline established with PRP before addition of the agonist. Epi 5 μM (CHRONO-LOG Corporation HAVERTOWN, PA) was the agonist used. The test procedure included the transfer of 0.45 mL PRP into a cuvette incubated at 37 °C for 3 min. Subsequently, 25 μL of Epi were added into the PRP and the aggregation pattern was allowed to generate for 10 min.

**Thromboelastometry (ROTEM)**

Viscoelastic measurements were done using rotational thromboelastometry (ROTEM, Tem Innovations GmbH, Munich, Germany). Recalibrated whole blood was analyzed on the ROTEM analyser (Tem Innovations GmbH, Munich, Germany) using the nonactivated TEM (NATEM) assay. The NATEM test is a semi-quantitative in vitro diagnostic assay used on the ROTEM delta Thromboelastometry System to monitor the coagulation process, contact-activated by the surface of the measurement cell, in citrated whole blood specimens. The test was conducted within 30 min from blood sampling.

The following NATEM variables were measured: the Clotting time (CT [sec]) that was determined by the time elapsed from the start of measurement until the formation of a clot 2 mm in amplitude. The clot formation time (CFT [sec]) was the time elapsed from the end of the CT (amplitude of 2 mm) until a clot firmness of 20 mm was achieved. The angle (α°) was the angle between the central line (x axis) and the tangent of the TEM tracing at the amplitude point of 2 mm describing the kinetics of clot formation. The maximum clot firmness (MCF [mm]) reflects the final strength of the clot. The lysis index at 60 min (LI 60) is defined as the percentage of remaining clot stability in relation to the MCF following the 60 minutes observation period after CT and indicates the speed of fibrinolysis.

**Statistical Methods**

Descriptive statistics are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or percentages when appropriate. Because most of the variables were non-normally distributed, nonparametric tests (the Fisher’s exact test; the 2-sample Wilcoxon rank-sum [Mann–Whitney] test; and the Kruskal–Wallis [equality-of-populations] rank test) were used for the statistical evaluations. Correlations were assessed by the Spearman rank correlation coefficient and the respective P value. Spearman’s rho <0.20 is considered to indicate very weak correlation, 0.21 to 0.40 indicates weak correlation, 0.41 to 0.60 indicates moderate correlation, 0.61 to 0.80 indicates strong correlation, and higher than 0.81 indicates very strong correlation. For hypothesis testing, a probability level <0.05 was considered as statistically significant. All statistical tests were 2-sided. Stata software was used for all statistical analyses (Stata Corp., College Station, TX).
TABLE 2. Comparison of Coagulation Parameters Between Patients on Dabigatran (Group A, n = 20); Patients on Rivaroxaban (Group B, n = 20); and Controls (Group C, n = 20)

| Parameter                  | Group A             | Group B             | Group C             | K–W Test     | A vs B; P      | A vs C; P      | B vs C; P     |
|----------------------------|---------------------|---------------------|---------------------|--------------|---------------|---------------|---------------|
| INR                        | 1.32 ± 0.27; 1.19 (1.11–1.51) | 1.58 ± 0.60; 1.39 (1.15–1.83) | 0.99 ± 0.08; 0.99 (0.92–1.04) | P < 0.001    | P = 0.26; P < 0.001 | P < 0.001 | P < 0.001 |
| aPTT, seconds              | 54.8 ± 16.8; 51.7 (44.3–61.5) | 45.4 ± 15.3; 42.6 (38.9–48.4) | 30.5 ± 3.7; 29.2 (28.0–31.9) | P < 0.001    | P = 0.007; P < 0.001 | P < 0.001 | P < 0.001 |
| Fibrinogen, mg/dL          | 350.2 ± 76.7; 337.6 (288.1–398.1) | 372.4 ± 71.4; 369 (326–407) | 290.2 ± 94.5; 262 (213–343) | P = 0.005    | P = 0.27; P = 0.016 | P = 0.003 | P = 0.27 |
| D-dimers, ng/mL            | 20% had a value      | 15% had a value     | 20% had a value     | P = 0.42     | P = 0.87; P = 0.25 | P = 0.27 |
|                           | <170; 322 (170–762)  | <170; 297 (200–754) | <170; 275 (170–369) |             |               |               |
| CT, s                      | 1000 ± 362; 956 (761–1150) | 916 ± 414; 767 (678–1074) | 499 ± 116; 491 (412–584) | P < 0.001    | P = 0.25; P < 0.001 | P < 0.001 | P < 0.001 |
| CFT, s                     | 290 ± 268; 233 (140–278) | 310 ± 265; 188 (151–379) | 133 ± 31; 125 (113–163) | P = 0.002    | P = 0.94; P = 0.006 | P = 0.001 | P = 0.001 |
| A                          | 53.4 ± 14.8; 50 (43–68) | 50.5 ± 17.1; 56 (39–62) | 64.5 ± 5.0; 65.5 (59.5–68) | P = 0.004    | P = 0.90; P = 0.016 | P = 0.001 | P = 0.001 |
| MCF, mm                    | 60.3 ± 12.8; 56 (50–72) | 59.9 ± 6.2; 59 (56–64) | 58.8 ± 4.0; 58 (56–61) | P = 0.75     | P = 0.59; P = 0.58 | P = 0.52 |
| LI 60, %                   | 94.6 ± 4.3; 93 (92–100) | 95.4 ± 3.5; 95.5 (92.5–98.5) | 95.4 ± 2.8; 95.5 (94–97) | P = 0.85     | P = 0.62; P = 0.61 | P = 0.96 |
| LTA epinephrine, %         | 46.5 ± 27.1; 40.5 (21.5–71) | 63.3 ± 24.4; 70 (53–81) | 59.8 ± 25.4; 62.5 (41.5–82.5) | P = 0.096    | P = 0.045; P = 0.093 | P = 0.74 |
| Lag time, s                | 51.3 ± 13.4; 48.8 (10.3–60.8) | 48.2 ± 16.2; 47.5 (35.7–56.2) | 30.1 ± 5.0; 29.3 (27.0–31.7) | P < 0.001    | P = 0.45; P < 0.001 | P < 0.001 |
| Tmax, s                    | 99.0 ± 23.4; 98.9 (79.3–115.4) | 109.3 ± 47.1; 109.1 (70.6–124.2) | 83.6 ± 16.6; 80.3 (70.2–90.3) | P = 0.08     | P = 0.53; P = 0.035 | P = 0.08 |
| Cmax, %/min                | 81.0 ± 23.1; 86.8 (58.0–96.7) | 70.2 ± 18.8; 71.4 (58.7–84.2) | 113.4 ± 13.2; 112.2 (105.5–119.0) | P < 0.001    | P = 0.12; P < 0.001 | P < 0.001 |
| AUC, %                     | 73.7 ± 20.7; 77.5 (55–89) | 71.4 ± 18.7; 75 (60.5–85.5) | 101.5 ± 13.0; 97.5 (92.5–112.5) | P < 0.001    | P = 0.67; P < 0.001 | P < 0.001 |

a = angle; aPTT = activated partial thromboplastin time; AUC = area under curve; CFT = Clot formation time; Cmax = peak height; CT = clotting time; INR = international normalized ratio; LI 60 = lysis index at 60 minutes; LTA = light transmission aggregometry; MCF = maximum clot firmness; Tmax = time to peak.

Data are presented as means ± standard deviations; medians and interquartile ranges in parentheses, or percentages when appropriate. The nonparametric 2-sample Wilcoxon rank-sum (Mann-Whitney) test and the Kruskal-Wallis (equality-of-populations) rank test were used for the statistical evaluations.
TABLE 3. Correlation of Rivaroxaban Levels With Hemostatic Parameters

| Parameter          | Spearman’s rho | P Value | Interpretation                       |
|--------------------|----------------|---------|--------------------------------------|
| INR                | +0.73          | <0.001  | Statistically significant, strong positive correlation |
| apt                | +0.54          | 0.013   | Statistically significant, moderate positive correlation |
| CT                 | +0.28          | 0.22    | No correlation                       |
| CFT                | +0.37          | 0.10    | No correlation                       |
| a                  | −0.33          | 0.16    | No correlation                       |
| MCF                | +0.32          | 0.16    | No correlation                       |
| LI 60              | +0.23          | 0.34    | No correlation                       |
| LTA epinephrine    | +0.03          | 0.91    | No correlation                       |
| Lag time           | +0.45          | 0.045   | Statistically significant, moderate positive correlation |
| Tmax               | +0.53          | 0.016   | Statistically significant, moderate positive correlation |
| Cmax               | −0.62          | 0.003   | Statistically significant, strong inverse correlation |
| AUC                | −0.23          | 0.33    | No correlation                       |

a = angle; aPTT = activated partial thromboplastin time; AUC = area under curve; CFT = clot formation time; MCF = peak height; CT = clotting time; INR = international normalized ratio; LI60 = lysis index at 60 minutes; LTA = light transmission aggregometry; MCF = maximum clot firmness; Tmax = time to peak.

compared to rivaroxaban group (P = 0.045), but aggregation decrease in the dabigatran group did not reach statistical significance as compared to controls (P = 0.093).

The correlations of anti-Xa values with those of conventional clotting parameters, global coagulation assays, and aggregometry are shown in Table 3. Plasma rivaroxaban levels showed a strong and moderate positive correlation with INR (P < 0.001) and aPTT values (P = 0.013), respectively. No association was found among ROTEM variables, platelet aggregation, and anti-Xa values. Similarly, regarding TG, no correlation was found between ETP and rivaroxaban levels, but a moderate positive correlation was observed between rivaroxaban levels and lag time (P = 0.045) and Tmax (P = 0.016). A strong inverse correlation was also revealed between rivaroxaban plasma concentrations and Cmax (P = 0.003).

Data regarding the correlations of dabigatran levels with TG parameters have been previously presented.7

DISCUSSION

In this study, by using several coagulation assays, we have shown that there were no significant differences in the intensity of anticoagulant activity achieved by rivaroxaban 20 mg qd and dabigatran 110 mg bid in patients with NV-AF. To the best of our knowledge, there are few data available comparing head-to-head the anticoagulation intensity induced by the 2 agents in real-world patients,8–10 and most data are derived from testing plasmas of healthy subjects taking the drugs on the occasion of pharmacokinetic/pharmacodynamics studies or from testing pooled normal plasmas spiked in vitro with increased amounts of NOAs.9–12 Even about clinical efficacy and safety outcomes of NOAs in everyday clinical practice settings, only indirect estimations have been available by performing inter-trial comparisons.3,4,6,13 These indirect comparison studies are usually fraught with considerable limitations and hypotheses generated by them need to be further investigated.

It is well known that routine coagulation tests do not accurately reflect the circulating levels of NOAs and are not suitable for quantitative assessment of these agents exposure. On the other hand, specific tests are only available in specialized laboratories. HTI and DiXaI assay are considered as the gold standards to measure dabigatran and rivaroxaban plasma levels, respectively. Thus, in parallel with these assays, we performed haemostatic tests in order to evaluate anticoagulant activity caused by the 2 drugs used in certain dose treatments. Concerning conventional coagulation tests, aPTT was found to be more sensitive to dabigatran confirming the existing knowledge.14

Selective thrombin and factor Xa inhibitors have been reported to exhibit distinct effects on ROTEM analysis.7–10 In our study, all kinetic parameters of NATEM assay were significantly affected by the 2 drugs to a similar extent compared with controls. However, no statistically significant effect was detected on the final strength of the clot and the speed of fibrinolysis in both groups of patients, compared to controls. A notable finding was the detection of a statistically significant difference in Epi-induced LTA values between patients on dabigatran and those on rivaroxaban. Dabigatran group exhibited statistically significant lower aggregation values compared to patients receiving rivaroxaban. This is in keeping with the findings in a recent study of our research group indicating that dabigatran might affect platelet function in patients with stroke or transient ischemic attack and nonvalvular atrial fibrillation.15 The central role of thrombin in platelet adhesion16 and activation17 might be the biologically plausible mechanism underlying the antiplatelet effect. However, considering the limited number of patients and controls included in this pilot study, as well as the absence of a statistically significant difference between patients on dabigatran and controls, the clinical relevance of this finding remains vague and probably warrants further investigation.

Regarding the TG test, both anticoagulants have been previously shown to affect the various parameters of this assay.5,7,11,12,18 This was also confirmed by our findings. All parameters were significantly influenced in both groups of patients, related to controls. Moreover, rivaroxaban has been reported to reduce thrombin generation, with prolongations of the lag time and time to peak thrombin level and decrease in the peak thrombin level and ETP.5,11,12 Our findings also revealed a trend toward increase of the time to peak thrombin level and decrease in the thrombin peak height in patients on rivaroxaban as compared to those on dabigatran, but without reaching statistical significance. However, the amount of thrombin generated was similar in both patient groups. Regarding rivaroxaban, it is noteworthy the correlation between its plasma levels and kinetic parameters of TG assay, but not with ETP. This is in accord with the findings of Freyburger et al5 performing this test in patients receiving the drug in vivo in a
routine setting. These results enhance the view that rivaroxaban slows down the thrombin burst efficiently with a lower maximum thrombin concentration (decreased peak) that lasts longer.\textsuperscript{3,19} On the other hand, a statistically significant association had been observed between dabigatran levels, and this in line with conclusions arising from indirect comparisons of new oral anticoagulant drugs reporting no significant differences for rivaroxaban versus dabigatran 110 mg BID in preventing stroke and systemic embolism.\textsuperscript{3,13}

Certain limitations need to be acknowledged. As this is a pilot study, a sample size calculation is missing, and thus a relatively small number of patients have been analyzed. Furthermore, only certain dose regimens of the 2 drugs have been studied. The hypotheses generated by our findings have to be further investigated in larger patient samples, with other dose regimens and in relation to clinical findings. However, taking into account the high inter-individual variability in response to fixed doses,\textsuperscript{7} the necessity to assess the degree of anticoagulation response in patients receiving these drugs in certain clinical settings,\textsuperscript{5} and the fact we have assessed the anticoagulant effect of the NOAS in real-world patients using a comprehensive panel of hemostatic parameters, we consider that these findings may provide some insight concerning how to estimate anticoagulation response in everyday clinical practice settings.

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