The effect of contrast agents on the anticoagulant properties of oral factor Xa inhibitors

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Abstract
Background: Contrast agents may affect the anticoagulant properties of novel oral anticoagulants.
Purpose: To evaluate the effect of iohexol as a contrast agent on the anticoagulant activity of oral factor Xa inhibitors.
Material and Methods: The study included 65 individuals who underwent contrast computed tomography (CT). Group 1 comprised 20 patients using rivaroxaban, Group 2, 20 patients using apixaban, and Group 3, 20 patients using edoxaban. Group 4 was the control group of five healthy volunteers. Iohexol (60 mL) was used as a contrast agent. Blood samples of 2 mL were withdrawn into two tubes at 4 h after the drug dose and 1 h after the contrast CT (CT was performed 3 h after the drug was taken) from all the patients, and for the control group, at any time before and 1 h after contrast CT.

Results: The anti-factor Xa level was increased after using the contrast agent in the rivaroxaban group (0.66 ± 0.32 U/mL vs. 0.67 ± 0.32 U/mL; P = 0.01) and the edoxaban group (0.74 ± 0.35 U/mL vs. 0.76 ± 0.36 U/mL; P = 0.006). No significant difference was observed in the apixaban group (0.66 ± 0.33 U/mL vs. 0.66 ± 0.32 U/mL; P = 0.21) and control group (0.02 ± 0.01 U/mL vs. 0.03 ± 0.01 U/mL; P = 0.33).

Conclusion: The anticoagulant properties of rivaroxaban, apixaban, and edoxaban were evaluated using anti-factor Xa levels.

Keywords
Oral anticoagulant, contrast agent, anti-factor Xa, atrial fibrillation, renal function

Date received: 12 December 2021; accepted: 2 February 2022

Introduction
Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia. The prevalence of AF increases with age by up to 14% (1,2). AF increases the risk of ischemic stroke fivefold and approximately one-third of patients with ischemic stroke have AF (3,4). Vitamin K antagonists (VKA) reduce the incidence of stroke by 64% and 39% compared to any treatment and antiplatelet therapy (5). However, the quality of anticoagulation control is a challenging process and should be maintained in the therapeutic range (TTR) of >70% to improve the results (6). In patients with non-valvular AF, there is now widespread use of direct oral anticoagulants (DOAC) such as dabigatran, rivaroxaban, apixaban, and edoxaban. Rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors.

Contrast computed tomography (CT) examinations are frequently performed on patients who use oral factor Xa inhibitors. Contrast agents have different properties that are based on their osmolarity, chemical structure, and ionization status (7). Previous studies have shown that contrast agents have anticoagulant and antiaggregant effects (8,9).
However, there are no data in the literature showing whether the contrast agents affect the efficacy of oral factor Xa inhibitors. Therefore, the aim of the present study was to evaluate the effect of contrast agents on the anticoagulant activity of the oral factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.

**Material and Methods**

Approval for the study was granted by the Local Ethics Committee (decision number: 2019/01-01). This prospective study included 65 individuals who underwent contrast CT. The CT indications were thoracic aortic dilatation, chronic obstructive pulmonary disease, abdominal aortic dilatation, or chronic abdominal pain. The participants comprised 60 patients who were using oral factor Xa inhibitors (20 using rivaroxaban 20 mg OID, 20 using apixaban 5 mg BID, and 20 using edoxaban 60 mg OID) and five healthy volunteers not using any oral factor Xa inhibitors. Written informed consent was obtained from the study population in accordance with the study protocol. Patients using rivaroxaban were considered as Group 1 (20 patients), patients using apixaban as Group 2 (20 patients), patients using edoxaban as Group 3 (20 patients), and the control group volunteers as Group 4.

The inclusion criteria were as follows: (i) the use of oral factor Xa inhibitors (patients with non-valvular AF and CHA2DS2-VASc score ≥2); (ii) aged 21–80 years; (iii) no contraindications for anticoagulation use; (iv) GFR ≥30 mL/min; (v) voluntary participation in the study; and (vi) patients who needed to use contrast agent (iohexol) for CT examination. The study exclusion criteria were as follows: (i) coagulopathy; (ii) severe hepatic insufficiency; (iii) chronic systemic or inflammatory diseases; (iv) body weight <60 kg; (v) malignancy; (vi) creatinine value >1.5 mg/dL; and (vii) not providing consent to participate in the study.

**Study protocol**

The demographic characteristics of the patients were recorded, and physical examinations were performed. The baseline biochemical values and risk factors were recorded, and blood pressure (BP) was measured before the procedures. Patients were defined as hypertensive if they had a systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or if they were taking antihypertensive drugs. Patients were defined as diabetic if fasting blood glucose levels were ≥126 mg/dL in two consecutive measurements or if they were using oral antidiabetics or insulin. Body mass index (BMI) was calculated using the following formula: weight (kg)/height squared (m²). GFR was calculated using the Cockcroft-Gault formula: [[(140 − age) × patient weight (kg)]/[72 × serum creatinine value] ×0.85 for women] (10).

Four hours after taking the medication (oral factor Xa inhibitor), two tubes of 2 mL of blood were taken from the forearm of the 60 patients (20 rivaroxaban, 20 apixaban, and 20 edoxaban patients). The blood was taken from the forearm between 12:00 and 13:00 from all patients and volunteers. The anti-factor Xa, PT, INR, and aPTT levels were measured from the blood samples. The levels were also measured in the control group. Three days after the first evaluation of the levels, contrast CT was performed 3 h after taking the oral factor Xa inhibitor for the 60 patients. The second measurement of the anti-factor Xa, PT, INR, and aPTT levels was performed 1 h after the contrast CT evaluation for the 60 patients and five volunteers (Fig. 1). The blood was taken from the forearm between 12:00 and 13:00 from all patients and volunteers. Iohexol at the dose of 60 mL (350 mg I/mL) was used as the contrast agent for all patients and volunteers. BUN and creatinine values were checked at 48–72 h after the contrast CT in respect of contrast-induced nephropathy (CIN).

**Measurements of anti-factor Xa level and coagulation parameters**

The 2-mL blood samples were centrifuged immediately in the biochemistry laboratory at 5000 g for 10 min. The plasma samples were placed in an Eppendorf tube using a plastic pipette and stored at −20 °C until analysis. The anti-factor Xa level was measured from the obtained plasma samples with a Berichrom Heparin kit in a Sysmex cs 5100 device in the biochemistry laboratory. The Berichrom Heparin kit is a chromogenic test (Berichrom h-Heparin, Siemens Healthineers, Marburg, Germany). The kit contains AT III reagent. The Berichrom low molecular weight heparin calibrator was used to calibrate the anti-factor Xa measurement (11). INR, PT, and aPTT were measured as coagulation parameters. Venous blood samples in coagulation tubes were centrifuged at 5000 rpm for 10 min, and the INR, PT, and aPTT levels were measured in the biochemistry laboratory using a Sysmex cs 5100 device, with Dade Actin FS, activated PTT reagent, and thromborel S reagent. The researchers evaluating the anti-Factor Xa level were blinded to the patients groups.

**Statistical analyses**

Statistical analyses were performed using SPSS version 23 software (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation values, and categorical variables as number and percentage. In the comparison of continuous variables in the baseline characteristics of the four groups, the Kruskal–Wallis test was used, and for categorical variables, the chi-square test or Fisher’s
exact test was applied. The Wilcoxon signed rank test was used to evaluate repeated measurements. In a standard statistical analysis, a value of \( P < 0.05 \) was accepted as statistically significant. Intra- and inter-assay coefficients of variation were calculated for anti-factor Xa level measurements.

**Results**

**Patient characteristics**

Evaluation was made of 65 individuals (27 men [51.4%], 38 women [58.5%]; mean age = 66.4 years; mean BMI = 27.4 kg/m²). Hypertension was present in 51 (78.4%) patients, 18 (27.6%) were hyperlipidemic, 17 (26.1%) were diabetic, and 35 (53.8%) were smokers. The mean CHA2DS2-VASc score was 3 ± 1. The demographic and laboratory characteristics of the groups are shown in Table 1. The demographic and laboratory characteristics were similar in all the groups.

**Anti-factor Xa level and coagulation parameters**

The anti-factor Xa level was increased after contrast agent use in the rivaroxaban group (0.66 ± 0.32 vs. 0.67 ± 0.32: \( P = 0.01 \)) and edoxaban group (0.74 ± 0.35 vs. 0.76 ± 0.36: \( P = 0.006 \)). No significant difference was determined in the apixaban group (0.66 ± 0.33 vs. 0.66 ± 0.32: \( P = 0.21 \)) and control group (0.02 ± 0.01 vs. 0.03 ± 0.01: \( P = 0.33 \) (Table 2, Fig. 2). The INR level was increased after contrast agent use in the rivaroxaban group (1.20 ± 0.2 vs. 1.22 ± 0.2: \( P = 0.01 \)) and edoxaban group (1.33 ± 0.3 vs. 1.34 ± 0.3: \( P = 0.03 \)). No significant difference was determined in the apixaban group (1.20 ± 0.1 vs. 1.21 ± 0.1: \( P = 0.23 \)) and control group (0.85 ± 0.05 vs. 0.87 ± 0.06: \( P = 0.13 \) (Table 3). The anti-factor Xa intra assay coefficient of variation was 2.0%. The anti-factor Xa inter assay coefficient of variation was 3.9%.

The INR results were parallel to the anti-factor Xa level results (Table 3). When the aPTT values were compared, there was no statistically significant difference between the groups before and after contrast agent use (Table 3). With contrast agent, PT values were increased in the rivaroxaban group (16.23 ± 3.6 vs. 16.85 ± 4.1: \( P = 0.03 \)), edoxaban group (18.19 ± 5.4 vs. 18.87 ± 5.4: \( P = 0.004 \)), and the control group (11.26 ± 0.9 vs. 11.62 ± 0.9: \( P = 0.03 \)), and no significant difference was determined in the apixaban group (16.51 ± 2.7 vs. 16.86 ± 2.7: \( P = 0.10 \) (Table 3).
The BUN, creatinine, and GFR values did not change significantly before and after the contrast agent use (Table 4). CIN did not develop in any patients. In this study period, no clinically significant bleeding was observed with these oral factor Xa inhibitors in the study population.

### Discussion

The main results of this study were as follows: (i) the anti-factor Xa level increased with contrast agent use (iohexol) in patients with rivaroxaban and edoxaban treatment; (ii) the PT level increased with contrast agent use in patients with rivaroxaban and edoxaban treatment and the control group; (iii) the INR level increased with contrast agent use in patients with rivaroxaban and edoxaban treatment; (iv) the coagulation parameters did not change with contrast agent use in the apixaban group; and (v) there was concluded to be a need to test whether or not the small laboratory difference has a clinical effect.
AF-related complications (stroke) and venous thromboembolic complications lead to cardiovascular mortality and morbidity (12,13). Therefore, the use of an effective level of oral factor Xa inhibitors is very important. Contrast agents interact with the coagulation mechanism because they are ionic and non-ionic (8,9). Ionic contrast agents inhibit both intrinsic and extrinsic coagulation cascades at various stages, acting as a direct inhibitor of thrombin production. They also inhibit both platelet activation and aggregation, lead to increased bleeding time, and inhibit fibrinolysis enzymes (8,9,14).

Ionic contrast agents increase clotting time fourfold compared to non-ionic agents (15). Non-ionic contrast agents interact with the coagulation mechanism, although at a lower level than ionic contrast agents, by inhibiting the coagulation cascade after thrombin formation in the fibrin monomer polymerization stage (16,17). Therefore, both ionic and non-ionic contrast agents can prolong clotting time and increase the effects of anticoagulant and antiplatelet drugs (14,15).

In this study, iohexol (60 mL for all patients and volunteers) was used, which is a non-ionic and water-soluble contrast agent. Iohexol is excreted through the kidneys. Studies have shown that iohexol is freely filtered and does not cause glomerular damage. However, as it dissolves in water, it has been shown that it can be absorbed easily from the proximal tubule and cause cellular damage in the glomerulus (18). In CIN studies, it has been observed that every patient receiving iodine-containing contrast agents developed subclinical CIN, but it did not create apparent CIN clinically since healthy individuals had tubular repair mechanisms (19).

The oral bioavailability of oral factor Xa inhibitors is around 60%–80% for rivaroxaban, 50% for apixaban, and 62% for edoxaban (20). While the absorption of rivaroxaban and edoxaban is increased with food, apixaban absorption does not change (20). These three drugs reach maximum plasma concentration approximately 3 h after oral intake (20). Renal elimination is 35% for rivaroxaban, 27% for apixaban, and 50% for edoxaban (20,21).

The increasing anti-factor Xa level with iohexol in the rivaroxaban and edoxaban groups may be related to the renal elimination ratio of these agents. The low anti-factor Xa level increasing with 60-mL contrast may increase much more with more contrast use. The anti-factor Xa level was not changed in the apixaban group, and the renal elimination ratio was 27%. The renal elimination ratio is higher for rivaroxaban and edoxaban than apixaban. Both anti-factor Xa levels and PT and INR levels increased significantly after the contrast in the rivaroxaban and edoxaban groups, but there was no significant change in the apixaban group.

Rivaroxaban and edoxaban are used once a day and at a high dose. Drugs given at higher doses also have higher concentrations in the blood in the early period. The elimination rate of these drugs, which have a higher renal elimination rate and blood concentration, decreases because the renal elimination decreases as it is affected by the contrast agent. Due to this decreased elimination, high blood concentration causes an increase in the anti-factor Xa level.

Apixaban is taken at a lower dose and twice daily. Therefore, the blood concentration of apixaban is lower.

**Fig. 2.** Anti-factor Xa level before and after contrast agent use.
Apixaban has the lowest renal elimination rate and is minimally affected by the loss of renal function caused by the contrast agent. The increase in anti-factor Xa levels was higher in the edoxaban group with a renal elimination rate of 50% compared to the rivaroxaban group, which had a renal elimination rate of 35% (20,21). This supports the idea that the increase in anti-factor Xa levels may be related to the renal elimination of drugs. Recent studies have evaluated the efficacy and safety of DOACs on patients with hemodialysis and have shown that apixaban treatment has a lower bleeding risk compared with rivaroxaban treatment and a similar bleeding risk compared with warfarin (22,23). The results of those studies may support the current study findings.

Oral factor Xa inhibitors do not require routine monitoring as they are taken at a specific dose and have a predictable anticoagulant effect. However, routine coagulation tests have been conducted to determine patients with complications such as bleeding and to determine drug doses. In studies performed with standard coagulation tests such as PT, aPTT, and INR tests, it has been concluded that these tests are not suitable for use in evaluating oral factor Xa inhibitors because there is no clear correlation between drug doses and these tests (23–25). However, studies have shown the presence of PT values within normal limits within the therapeutic limits of oral factor Xa inhibitors (24–26).

Consistent with the anti-factor Xa test, the PT values in the current study increased in the rivaroxaban and edoxaban groups after contrast agent use. There was also a significant increase in the INR value calculated with PT values in the rivaroxaban and edoxaban groups. There was no change in aPTT values before and after contrast use. The slight increase in PT values in the control group can also be explained by the effect of contrast agents on PT. In a previous study, a significant increase in PT values was found with nonionic low osmolar iopamidol (27,28).

Intra-individual variability of the anti-Xa measurement method may be a significant parameter. The anti-Xa evaluation method (Berichrom Heparin kit, chromogenic test), which was used in this study, was tested recently in a rivaroxaban trial (29). The results of that study showed that the anti-Xa measurement method did not reveal any significant differences between three trough or between three peak levels, indicating that there are no essential changes in trough or peak values over time for individual patients in a stable clinical condition (29). In another trial the anti-Xa evaluation method (Berichrom Heparin kit, chromogenic test) was tested with an apixaban trial (30). The study reported no significant differences between three trough or between three peak levels, indicating that there are no essential changes in trough or peak values over time for individual patients in a stable clinical condition (29).

Table 3. PT, aPTT, and INR level before and after contrast agent use.

| Contrast agent | Before | After | P value |
|----------------|--------|-------|---------|
|                | PT (s) | aPTT (s) | INR | PT (s) | aPTT (s) | INR | PT | aPTT | INR |
| Rivaroxaban    | 16.23 ± 3.6 | 30.15 ± 4.6 | 1.20 ± 0.2 | 16.85 ± 4.1 | 30.36 ± 4.4 | 1.22 ± 0.2 | 0.03 | 0.82 | 0.01 |
| Apixaban       | 16.51 ± 2.7 | 30.31 ± 5.1 | 1.20 ± 0.1 | 16.86 ± 2.7 | 30.42 ± 4.5 | 1.21 ± 0.1 | 0.10 | 0.79 | 0.23 |
| Edoxaban       | 18.19 ± 5.4 | 32.25 ± 4.4 | 1.33 ± 0.3 | 18.87 ± 5.4 | 33.52 ± 3.4 | 1.34 ± 0.3 | 0.004 | 0.73 | 0.03 |
| Control        | 11.26 ± 0.9 | 19.84 ± 1.0 | 0.85 ± 0.05 | 11.62 ± 0.9 | 19.48 ± 0.83 | 0.87 ± 0.06 | 0.03 | 0.07 | 0.13 |

Values are given as mean ± SD. Bold number refers the significant statistical value.

aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

Table 4. BUN and creatinine level before and after contrast agent use.

| Contrast agent | Before | After | P value |
|----------------|--------|-------|---------|
|                | BUN (mg/dL) | Creatinine (mg/dL) | GFR (mL/min) | BUN (mg/dL) | Creatinine (mg/dL) | GFR (mL/min) | BUN | Creatinine | GFR |
| Rivaroxaban    | 18.47 ± 7.00 | 0.86 ± 0.17 | 83.10 ± 31.40 | 22.69 ± 8.51 | 0.98 ± 0.19 | 70.22 ± 19.67 | 0.61 | 0.09 | 0.12 |
| Apixaban       | 20.99 ± 10.04 | 0.99 ± 0.22 | 74.84 ± 18.03 | 25.83 ± 11.64 | 1.06 ± 0.26 | 69.14 ± 17.70 | 0.75 | 0.34 | 0.35 |
| Edoxaban       | 19.61 ± 8.19 | 0.89 ± 0.18 | 79.65 ± 21.04 | 25.94 ± 10.08 | 0.98 ± 0.36 | 77.36 ± 37.64 | 0.35 | 0.71 | 0.71 |
| Control        | 14.46 ± 4.68 | 0.92 ± 0.41 | 93.87 ± 32.62 | 18.69 ± 2.91 | 1.00 ± 0.41 | 84.75 ± 25.16 | 0.28 | 0.068 | 0.07 |

Values are given as mean ± SD.

BUN, blood urea nitrogen; GFR, glomerular filtration rate.
evaluated with the Berichrom Heparin anti-Xa test (30). Similar to previous studies, the anti-factor Xa intra- and inter-assay coefficient of variations were very low in the current study using the same anti-Xa evaluation method (Berichrom Heparin kit, chromogenic test).

The practical guide and guidelines support the results of this study (31). The guidelines advise dose reduction for rivaroxaban and edoxaban when GFR is <50 mL/min, and for apixaban when GFR is <30 mL/min.

The clinical implications of the present study are that decreased renal function may affect the anticoagulant properties of rivaroxaban or edoxaban, in particular. In the occurrence of such acute events in patients on DOAC treatment, great care must be taken in respect of complications. Future studies should evaluate this hypothesis.

The present study has some limitations. An important limitation was that this study was performed in a single center with a limited number of patients. Another limitation was that the blood concentrations of the drugs were not examined before and after the use of contrast media. A low molecular weight heparin evaluation kit was used for evaluation of the oral factor Xa inhibitors anti-factor Xa activity as previous studies have shown that this kit can be used for this purpose (11,32). A strong correlation has been shown between oral factor Xa inhibitors level and anti–factor Xa activity with the use of the Berichrom kit (11,32). The use of higher doses of contrast agent (iohexol) and the effects of different contrast agents were not evaluated. In addition, the study results could be tested on patients with CIN. Very small differences were found between the oral factor Xa inhibitors anti-factor Xa activity, but it is not known whether these small differences have any clinical effects or not, although the study intra- and inter-assay coefficient variations were small. Nevertheless, this study is the first to investigate the effects of contrast agents on the anticoagulant properties of oral factor Xa inhibitors and could guide large-scale studies.

In conclusion, the results of this study demonstrated that the anticoagulant activity of rivaroxaban and edoxaban tended to be increased by contrast agent use, while the anticoagulant activity of apixaban was not changed. The increase was small so there is therefore a need for these laboratory results to be validated with larger clinical trials. Large-scale studies are needed to determine whether dose adjustment is required for oral factor Xa inhibitors while using contrast agents.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship and/or publication of this article.

Informed consent was obtained from all individual participants included in the study.

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