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ORIGINAL RESEARCH ARTICLE

Therapeutic monitoring of direct oral anticoagulants — an 8-year observational study

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Abstract

Introduction: For years, anticoagulants have been the basic group of drugs that slow down, inhibit or prevent blood clotting by inhibiting thrombin formation or reducing its activity. Treatment with direct oral anticoagulants (DOACs) does not require routine anticoagulation monitoring due to their wide therapeutic index. However, there are circumstances where it may be necessary to know the drug levels to manage the risk of side effects or to confirm laboratory efficacy. In such a situation, an indication for DOAC laboratory testing could be the suspicion of excessively high or low DOAC levels. The aim of this article was to determine trends in concentrations of DOACs in a real life population of patients.

Material and methods: Consultations in clinical pharmacology extended with DOAC level assessments were performed in the Department of Cardiology and Clinical Pharmacology. The trial was designed as a retrospective analysis of laboratory analyses and included 480 laboratory tests performed in 236 patients.

Results: Mean CHA_2DS_2-VASc scoring 3.91 ±1.92 and HAS-BLED scoring 3.57 ±1.75 indicated high risks of both thrombosis and bleeding. Geometric mean of trough concentrations for dabigatran, rivaroxaban and apixaban were 91.53 ng/mL, 62.74 ng/mL and 124.81 ng/mL, whereas peak concentrations for all DOACs were significantly higher, at 220.80 ng/mL (p <0.0001), 116.59 ng/mL (p <0.0001) and 186.18 ng/mL (p =0.0354), respectively. Values for males and females did not differ significantly. Dose adjustment, performed according to rules described for every drug in registered drug characteristics, did not change significantly concentrations. Trough concentrations higher than 20 ng/mL were found at the 10th percentile for all DOACs, but higher at 40 ng/mL at the 5th percentile was found only for apixaban. Peak concentration lower than 400 ng/mL were for the 95th percentile for apixaban and for the 90th percentile for dabigatran and rivaroxaban.

Conclusion: Monitoring-based pharmacotherapy with DOACs should be restricted only to specific clinical settings; in the general population, it is not necessary. Recently, in many experienced centers, therapeutic drug monitoring of DOACs has gained great importance in selected clinical settings and it very likely will soon become commonplace in clinical practice.

Key words: therapeutic drug monitoring, TDM, dabigatran, rivaroxaban, apixaban, direct oral anticoagulant, DOAC

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Introduction

For years, anticoagulants have been the basic group of drugs that slow down, inhibit or prevent blood clotting by inhibiting thrombin formation or reducing its activity directly or indirectly, or by inhibiting the post-translational modification of clotting factors II, VII, IX, X and proteins C and S. The general indications for anticoagulant therapy are atrial fibrillation and flutter, acute coronary syndromes, venous thromboembolism, condition after prosthetic valve replacement, stenosis of the mitral valve, pulmonary hypertension, intracardiac thrombosis, percutaneous coronary interventions, and extracorporeal circulation [1]. For more than 60 years, pharmacological intervention was limited to only one option: treatment with the vitamin K antagonists (VKA) warfarin or acenocumarol.

In 2009, a new class of drugs was introduced into pharmacotherapy, which for the first time provided a viable alternative to VKA in the indications for the prevention of embolic complications in non-valvular atrial fibrillation and for the treatment of patients with deep vein thrombosis and pulmonary embolism. These new generation oral anticoagulants were originally referred to as novel oral anticoagulants (NOAC). As the group is no longer new, other abbreviations are now more appropriate. The best abbreviation is either direct oral anticoagulant (DOAC) or target specific oral anticoagulant (TSOAC) [1].

DOACs were approved for the treatment and prevention of thromboembolic events such as prevention of deep vein thrombosis, especially in its most dangerous form — pulmonary embolism. Next crucial indication is most important for atrial fibrillation adult patients. DOACs are now key drug used in stroke prevention as well as peripheral embolism. Rivaroxaban is the first DOAC approved for the prevention of atherosclerotic events in patients with a history of acute coronary syndrome, peripheral artery disease or stroke [2].

Nowadays, due to the favorable efficacy and safety profile of DOACs, the group has become the first line option for all patients without contraindications [1, 3].

DOACs fall into two main groups: Xa inhibitors (rivaroxaban, apixaban and edoxaban); and direct thrombin inhibitors (dabigatran) [1, 4]. These drugs are clinically similar, but their pharmacokinetics significantly differ.

Factor IIa (active thrombin) inhibition is possible with the reversible and competitive inhibitor, dabigatran. This kind of potent blockade prevents conversion from fibrinogen to fibrin. Dabigatran inhibits not only free thrombin but also fibrin-associated thrombin and fibrin-induced platelet activation [1].

The family of xabans include rivaroxaban, apixaban, edoxaban and betrixaban. These drugs act as direct inhibitors of factor Xa. They bind free and clot-bound forms and decrease thrombin concentration. In this condition, xabans block the enzyme involved in the production of thrombin. Generally, concentrations of dabigatran and xabans are higher in older people than in younger people [1, 5].

Dabigatran etexilate is effectively and completely converted to dabigatran. Its bioavailability is 6.5%, the T_{max} in healthy volunteers is 0.5–2 h, but in postoperative patients can be elongated especially on the day of surgery by up to 6 h. Bioavailability of dabigatran is not affected by food, but time necessary to obtain the maximal level can be extended by up to 2 hours. Plasma protein binding is 34–35%, half elimination time ($T_{0.5}$) is dose independent, in healthy volunteers it is 12–14 h. Volume of distribution (Vd) is 50–70 L. Dabigatran is excreted 85% in the urine, mainly unchanged, and 6% in the faeces. In patients with decreased creatinine clearance 50–30 mL/min, the effect of dabigatran is approximately 2.7 times greater than in patients without renal failure. For creatinine clearance <30 mL/min, the effect of dabigatran on the body is approximately six times greater, and $T_{0.5}$ twice as long as in patients with normal renal function, thus treatment with dabigatran is not recommended in that population. There are many drug/drug interactions, especially with verapamil, anti-cancer agents *etc.* [1, 6, 7].

Bioavailability of rivaroxaban depends on dose, for 10 mg is 80–100%; food has no effect on bioavailability or C_{max}. The drug at a dose of 15 mg and 20 mg has to be taken with a meal, as taking on an empty stomach significantly reduces its bioavailability. T_{max} is 2–4 h, Vd 50 L, $T_{0.5}$ 5–9 h and in older people 11–13 h. Plasma protein binding is 92–95%. Approximately 66% of the administered dose is metabolized and excreted equally by the kidneys and the liver. The remaining 33% is excreted unchanged by the kidneys, mainly by active renal secretion. The drug is metabolized by CYP3A4 and CYP2J2, and metabolism is independent of cytochrome P-450 [1, 6, 7].

Similarly to rivaroxaban, apixaban is rapidly absorbed and taking a 10 mg dose with a meal has no effect on AUC or C_{max}. Bioavailability for doses up to 10 mg is about 50%. T_{max} is 3–4 h, V_d 21 L. Apixaban binds to plasma proteins in 87%. 25% of the administered dose is excreted as metabolites, mainly in the faeces. The drug is also eliminated by the kidneys. $T_{0.5}$ is 12 h. Apixaban is metabolized mainly by CYP3A4/5 [1, 6, 7].

Edoxaban is rapidly absorbed, protein binding 55%, V_d 107 L, T_{max} 1–2 h, $T_{0.5}$ 10–14 h. Metabolism is minimal, elimination mainly by the kidneys. Betrixaban protein binding is 60%, T_{max} 3–4 h, $T_{0.5}$ 19–27 h, Elimination is mainly in the faeces (85%) and urine (11%). V_d 120 L [1, 6, 7].

Clinical trials have confirmed the efficacy and safety in typical populations of patients with atrial fibrillation, deep vein thrombosis, pulmonary embolism [7–10]. For all DOACs vs. VKA the significant reduction in the risk of major bleeding by 32% to 69% was revealed in randomized clinical trials [11]. The most important seems to be 50% reduction in the risk of intracranial bleeding in comparison to warfarin [12–14].

Pharmacotherapy monitoring

According to the current guidelines routine laboratory checks of coagulation parameters are not recommended because of very wide therapeutic index of DOACs [1]. However, there are clinical setting when therapeutic drug monitoring may help to manage the risk of side effects, especially bleeding, or confirm laboratory efficacy. Results of pre-registration trials suggests that one of key elements is body weight. Obesity or body weight over 110 kg may be risk factor of presence of low DOACs concentration, whereas body weight lower than 50 kg may lead to overdosage. DOACs laboratory testing may be useful tool to solve underdosage/overdosage problem especially in recurrent thrombotic episodes in adherent patients, or in pharmacokinetic disturbances such as malabsorption, elimination failure, as well as elderlies [15–17].

The presence of DOACs in plasma may be confirmed by routine clotting tests i.e. prothrombin time (PT) and activated partial thromboplastin time (APTT), but changes are not dependent on the type of drug and its concentration. Thrombin time (TT) and APTT are elongated in the presence of dabigatran, whereas PT elongation can be seen during treatment with xaban family agents. Coagulation reagents sensitivity vary for different DOACs e.g. lower sensitivity of PT chemicals is seen for apixaban in comparison to the rivaroxaban or edoxaban [18–20].

Laboratory monitoring of DOAC treatment

Laboratory monitoring can form the basis of classical laboratory tests or tests specific to DOACs. In the family of classical tests, there are TT, APTT and PT. TT is sensitive for dabigatran. Unfortunately, it is a kind of binary relationship, because at low concentrations of dabigatran, TT becomes maximal for method and therefore is not suitable for monitoring. APTT is recommended by registered drug characteristic for dabigartan as an indicatior of action. There are no linear relation between dabigatran concentration and APTT, moreover APTT elongation depends on reagents set type of and type of coagulometer, thus APTT cannot be used in therapy monitoring. APTT and PT, measured after high-dose xaban treatment, are prolonged, but the effect is variable. Moreover, high level of shaping of PT results depends on thromboplastin type used in a laboratory, especially for rivaroxaban. This is why these parameters are not recommended for monitoring of xaban treatment. To perform quantitative analysis for dabigatran, diluted thrombin time (dTT) or ecarin clotting time (ECT) should be used [21, 22].

According to the mechanism of xabans action measurement of anti-Xa activity is the best test to monitor its effectivity, but research to standardize and validate the assay are in progress [23].

The decision-making process based on laboratory testing is difficult because we have no detailed data and ranges for specific populations. In pre-registration pharmacokinetic trials, DOAC levels were distributed in a wide range of concentrations. For values below 20 ng/mL there is high probability of underdosage and risk of ineffective treatment, whereas results above 400 ng/mL suggest an increased risk of bleeding [23]. Personalized medicine in DOACs may improve decision taking in special populations where assessment of thrombosis or bleeding risk is crucial. Whereas for almost all patients therapeutic drug monitoring is not recommended, in some cases the changes in DOACs pharmacokinetics may make it necessary [15, 16, 24].

The main aim of this analysis was to determine trends in concentrations of DOACs in a real life population of patients.

Material and methods

Patients

Consultations in clinical pharmacology extended with DOAC level assessments were performed in the Department of Cardiology and Clinical Pharmacology between 2012 and 2021. The trial was designed as a retrospective analysis of laboratory analyses and included 480 laboratory tests performed in 236 patients. At that time, it was the only such center in the region that performed consultations in clinical pharmacology extended by therapeutic drug levels monitoring [15, 16, 24]. The study population took DOACs in the form of oral tablets or capsules (dabigatran).

Procedures

DOACs routine determination of the concentration in the serum was performed in all patients. To do this, we used Hemoclot assay and BIOPHEN DiXal assay (Hyphen Biomed, Neuville-sur-Oise, France), Direct Thrombin Inhibitor Assay by HemosIL cooperating with ACL TOP Family Analyzers (ACL TOP 700, ACL TOP 500 CTS, and ACL TOP 300 CTS), Liquid Anti-Xa's HemosIL cooperating with the ACL TOP Family Systems in conjunction with HemosIL, rivaroxaban and apixaban Calibrators. The range of detection values for dabigatran concentrations provided by the manufacturer is 20–2,000 ng/mL. The method's analytical sensitivity (lower limit of detection for the assay) is determined to be 2 ng/mL. A dabigatran concentration of 45 ng/mL is referred to as the 'low control' and 196 ng/mL as the 'high control'. The range of detection for rivaroxaban concentrations stated by the manufacturer is 20–1,000 ng/mL, and for apixaban 15–1,000 ng/mL. The analytical sensitivity of the method (lower limit of detection for the assay) is determined at 10 ng/mL for rivaroxaban and 6 ng/mL for apixaban. A rivaroxaban concentration of 79 ng/mL is defined as the low control and 299 ng/mL as the high control, whereas for apixaban it is 80 ng/mL and 322 ng/mL respectively.

Because in 2012 there were no therapeutic ranges, concentration ranges were divided into several. For trough values less than 30 ng/mL, treatment was considered ineffective. Therapeutic range was from 40 ng/mL to 400 ng/mL, but for values from 200 ng/mL to 400 ng/mL, additional analyses of risk factors of bleeding were performed. Values more than 400 ng were considered too high, thus clinical analysis of factors increasing the concentration was performed.

Statistics

Statistical software Statistica 12.0 in a Polish version (StatSoft, Tulsa, OK, USA) was used to calculate statistical parameters. The Shapiro-Wilk test assay revealed that the distribution of continuous variables did not comprise the criteria of normal distribution. According to that, quantitative variables were shown as medians and percentile ranges. To compare medians of independent variables, the Mann-Whitney test was performed. Values p <0.05 were treated as statistically significant. Values p ≥0.05 and <0.10 were treated as a trend towards statistical significance. Values p ≥0.10, being not significant, were replaced with the abbreviation ns (not significant).

Results

480 samples taken from 236 patients were analyzed. The clinical characteristics of the study population including DOAC drug therapy are set out in Table I. The average age of the study population was 68, weight 84 kg. The most common indication for treatment with DOAC was atrial fibrillation, in 98.96%. In five cases, the main indication was pulmonary embolism, for others comorbidity included atrial fibrillation and other diseases such as stroke, deep vein thrombosis, malabsorption syndrome or possible drug/drug interactions. Mean CHA_2DS_2-VASc scoring and HAS-BLED scoring indicated high risks of both thrombosis and bleeding. Creatinine clearance was calculated by the Cockcroft-Gault formula as 66.50 ±23.16. A plot of the DOAC concentration distribution is set out in Figure 1. Concentrations of DOACs are set out in Table II. Geometric mean of trough concentrations for dabigatran, rivaroxaban and apixaban were 91.53 ng/mL, 62.74 ng/mL and 124.81 ng/mL, whereas peak concentrations for all DOACs were significantly higher at 220.80 ng/mL (p <0.0001), 116.59 ng/mL (p <0.0001) and 186.18 ng/mL (p =0.0354), respectively. Values for males and females did not differ significantly. Dose adjustment, performed according to rules described for every drug in registered drug characteristics, did not change significantly concentrations. Trough concentrations higher than 20 ng/mL were found at the 10th percentile for all DOACs, but higher at 40 ng/mL at the 5th percentile were found only for apixaban. Peak concentration lower than 400 ng/mL were for the 95th percentile for apixaban and for the 90th percentile for dabigatran and rivaroxaban.

Table I. Clinical characteristics of study group

Study feature	Property value
Number of consultations (patients)	236
Number of tests	480
Age (years)	68.44 (43–98)
Body weight [kg]	84.0 (48.0–118.0)
Sex	
Men	245 (51.0%)
Women	235 (49.0%)
Main indication for treatment/consultation	
Atrial fibrillation	475 (98.96%)
Stroke	88 (18.33%)
Drug/drug interactions	24 (5.00%)
Pulmonary embolism/deep vein thrombosis	10 (2.08%)
Malabsorption	3 (0.63%)
CrCl [mL/min]	66.50 ±23.16*
CHA_2DS_2-VASc	3.91 ±1.92
HAS-BLED	3.57 ±1.75

*Creatinine clearance (CrCl) calculated by Cockcroft-Gault formula

Discussion

According to the current guidelines regarding therapy with DOACs, therapeutic drug monitoring can be considered in expert centers to manage risk of bleeding. This is why in specific clinical setting assessment of drug levels can be necessary. The most important conditions are serious bleeding especially in patients with drug-drug or drug-disease interactions, in obese patients or with very low body weight, in patients on DOACs with deplessed kidney function, before emergent surgery to confirm necessarity of reversal agent usage [15, 16, 23, 24]. The role of therapeutic drug monitoring (TDM) increased recently in experienced centers and probably next years become more common [1]. Lin et al. [25] described a similar population of Asian patients treated with dabigatran. Similar effects of monitoring were found. Pharmacokinetic analysis of the RE-LY study (a pre-registration clinical trial) by Reilly et al. [5] described a huge population of 9,183 patients. They concluded that there is a correlation between side effects, especially bleeding and high concentrations of dabigatran, thus they found monitoring in a specific population to be effective. A real life population of 44 patients receiving dabigatran was analyzed by Šinigoj et al. [26]. Patients with bleeding had significantly higher average trough dabigatran concentrations than patients without bleeding, while peak

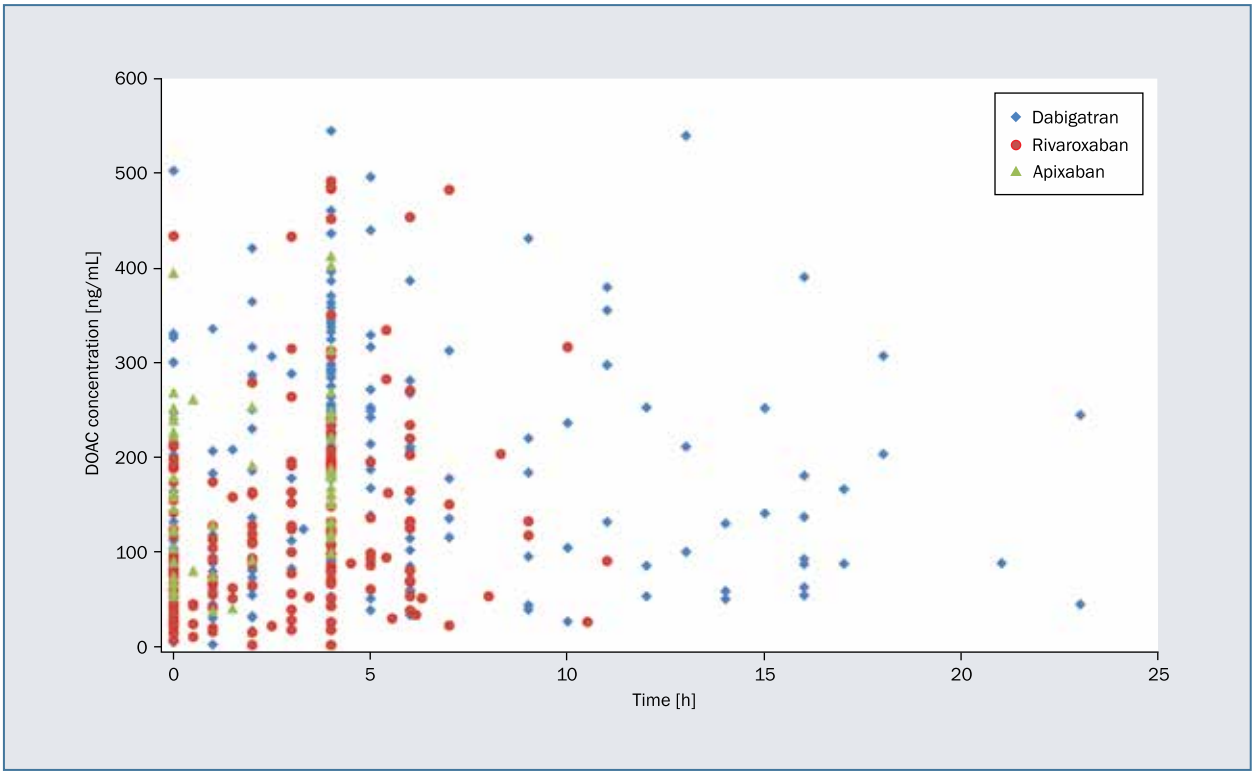

Figure 1. Concentrations of dabigatran, rivaroxaban and apixaban; DOAC — direct oral anticoagulant

dabigatran values had no predictive value. Dabigatran dose selection according to the guidelines resulted in appropriate trough concentrations with acceptable repeatability, whereas high trough concentrations predisposed to the risk of minor bleeding. These results supported the thesis that the most important factor is dosage that aligns with drug characteristics [26]. Monitoring of apixaban and rivaroxaban has been performed in many studies [27–30]. Generally, these have confirmed that DOACs are a safe group of anticoagulants, and that dose adjustment according to the drug characteristics will lead to effective and safe treatment, but it is extremely important to check all possible factors interfering with the drug pharmacokinetics during the first qualification to treatment visit. As DOACs are the first line option in many clinical settings due to safety and high efficacy, drug monitoring should be considered to enable the use of a better therapeutic option in a larger group of patients, including borderline patients.

Conclusion

Monitoring-based pharmacotherapy with DOACs should be restricted only to specific clinical settings. In the general population, it is not necessary. Recently, in many experienced centers therapeutic drug monitoring of DOACs has gained great importance in selected clinical settings, and it very likely will soon become more common in everyday clinical practice.

Authors' contributions

GG — sole author.

Conflict of interest

The author received honoraria from Bayer, Boehringer Ingelheim and Pfizer for lectures.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

Table II. Plasma concentrations of direct oral anticoagulants: dabigatran, rivaroxaban and apixaban

		C_{trough}	C_{peak}	F	M	Reg. dose	Adj. dose
DABIGATRAN [ng/mL]							
N	200	57	65	100	100	57	143
gMean	137.82	91.53	220.80**	146.21	129.90$^{\#}$	127.69	142.07$^{\#\#}$
gCV [%]	62.04	73.77	37.20	55.25	68.30	64.65	60.81
Median	166.81	95.09	249.00	175.50	159.20	135.25	173.00
P5	32.25	25.20	84.05	43.79	29.84	42.96	31.14
P10	51.93	39.00	99.00	52.26	51.88	51.71	52.54
P90	349.57	268.20	379.44	363.70	337.40	346.48	348.40
P95	396.64	337.20	438.49	396.64	387.99	380.39	429.02
Min	2.49	2.49	38.53	4.61	2.49	2.49	4.61
Max	544.00	502.00	544.00	538.80	544.00	544.00	538.08
RIVAROXABAN [ng/mL]							
N	170	64	57	77	93	125	45
gMean	87.80	62.74	116.60**	98.49	79.83$^{\#}$	89.21	83.98$^{\#\#}$
gCV [%]	69.15	57.29	69.96	62.30	73.73	64.68	70.69
Median	92.85	69.51	125.70	98.00	85.85	90.51	93.31
P5	17.85	15.19	24.34	20.37	16.73	17.85	20.27
P10	25.76	21.45	41.41	27.58	26.01	26.07	26.38
P90	264.44	184.03	328.41	292.11	231.78	237.59	274.97
P95	342.59	196.86	457.34	339.24	340.15	416.38	312.60
Min	2.01	7.10	2.01	7.10	2.01	2.01	7.10
Max	490.90	433.00	490.90	482.70	490.90	490.90	432.40
APIXABAN [ng/mL]							
N	56	30	22	31	25	42	14
gMean	145.28	124.81	186.18*	155.29	133.76$^{\#}$	151.05	129.26$^{\#\#}$
gCV [%]	38.60	40.82	24.70	32.01	45.04	34.86	39.40
Median	160.80	126.85	173.85	162.00	160.00	161.80	132.95
P5	53.50	53.50	116.20	71.05	43.34	53.76	62.15
P10	67.45	58.18	121.02	74.60	53.50	68.75	68.96
P90	264.60	252.81	308.58	253.10	265.32	268.74	243.28
P95	333.25	264.96	397.36	353.50	268.68	389.95	245.37
Min	38.30	38.30	99.10	58.70	38.30	38.30	53.50
Max	412.00	394.00	412.00	412.00	401.80	412.00	247.90

*p =0.0354, **p <0.0001 vs. C_{trough}; $^{\#}p$ ns vs. F group; $^{\#\#}p$ ns vs. reg. dose group; C_{trough} = concentration at steady state taken just before test dose, trough concentration; C_{peak} = concentration at steady state, after test dose, for time predicting maximal concentration, peek concentration; F — females; M — males; reg. dose = regular dose, dabigatran 150 mg bid, rivaroxaban 20 mg qd, apixaban 5 mg bid; adj. dose = adjusted dose, dabigatran 110 mg bid, rivaroxaban 15 mg qd, apixaban 2.5 mg bid; gCV = geometric coefficient of variation; gMean = geometric mean; P5 = 5th percentile; P10 = 10th percentile; P90 = 90th percentile; P95 = 95th percentile

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