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Methods for Detection of Direct Oral Anticoagulants and their Role in Clinical Practice

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Abstract

Introduction: Atrial fibrillation (AF) is the most common arrhythmia that increases by age, doubles for every decade after age of 50 years and reaches about 10% patients ≥ 80 years. Despite direct oral anticoagulants (DOACs') predictable pharmacokinetics and pharmacodynamics, the laboratory tests are necessary for effective and safe medical treatment, also for prediction and detection of thrombotic and bleeding events, as well as in situations when temporary discontinuation could be desirable.

Aim: of this study was to identify and analyze the need of coagulation tests for AF patients with high cardiovascular risk in clinical practice.

Methods: Quantitative, analytic, cross-sectional clinical trial, during the period from October 2016 till June 2017, was performed at Pauls Stradins Clinical University Hospital, Center of Cardiology, Latvia. There were collected data about patients with non-valvular AF, under anticoagulative therapy ≥ 3 months, defined as a high-risk group by CHA_2DS_2-VASc score-more or equal to 2 or 3, men and women respectively. Data were analyzed using SPSS.

Results: There were collected data about 143 patients of whom 46.2% (n=66) were male; the mean age was 69.7 (SD ± 9.9) years. About 2/3 (73.1%) of all patients the AF were longer than 1 year. The mean CHA_2DS_2-VASc score was 4.2 (SD ± 1.5). The most common comorbidies were arterial hypertension (65.0%; 93), chronic heart failure (48.3%; 69), coronary artery disease (32.9%; 47), diabetes mellitus (24.5%; 35), and dyslipidemia (25.9%; 37). Almost half of patients (46.2%; 66) used DOACs, 31.5% rivaroxaban and 14.7% dabigatran respectively; furthermore, 1.4% patients used DOACs' with antiaggregants. 49.7% (71) patients had increased risk of possible drug-drug interactions, most frequently with proton pump inhibitors (16.8%; 24), amiodarone (24.5%; 35), anti-inflammatory drugs (49.0%; 70). The use of DOACs and possible drug-drug interactions increases by risk score, reaching the maximum score 3 (16.1%; 23) and the mean frequent score 4.4 of 86 (60.1%) AF patients respectively.

Conclusion: Coagulation tests were applicable more than half of patients (60.1%) to detect DOACs concentration in plasma. Despite DOACs' expected pharmacokinetics and pharmacodynamics, the anticoagulant tests are necessary for effective and safe medical treatment, also for prediction and detection of thrombotic and bleeding events, as well as in situations when temporary discontinuation is desirable.

Keywords: Pharmacokinetics; Cardiovacsular; Pharmacology; Drug

Abbreviations: DOACS: Direct Oral Anticoagulants; AFIB: Atrial Fibrillation; AXF: Anti-Xa Factor; DTI: Direct Thrombin Inhibitors; DI: Drug-drug Interactions; CHA2DS2: VASc Risk Score.

Introduction

As the world population ages, the burden of AFib (atrial fibrillation) and venous thromboembolism disease is expected to increase, and prescriptions for long-term anticoagulation will climb [1-3]. Anticoagulated patients are vulnerable to spontaneous, traumatic and perioperative bleeding. Warfarin is a vitamin K antagonist that has been used for decades to prevent and treat arterial and venous thromboembolism [4]. But due to the need of regular monitoring, non-vitamin K antagonists/oral anticoagulants are now widely used as alternatives to warfarin for stroke prevention in atrial fibrillation and management of venous thromboembolism. These are dabigatran etexilate (Pradaxa, Boehringer Ingelheim, Germany) [5], rivaroxaban (Xarelto, Bayer AG, Germany) [6], apixaban (Eliquis, Pfizer and Bristol-Myers Squibb, NY) [7] and edoxaban (Savaysa, Daiichi Sankyo Inc., Japan). DOACs are associated with comparable risk of stroke, systemic embolism, major bleeding and death compared with warfarin [8]. They have more predictable therapeutic effect, pharmacokinetic and pharmacodynamics properties, as well as do not require routine monitoring, have fewer potential drug-drug interactions and no restrictions on dietary [2].

In clinical practice there is still widespread uncertainty on how to manage patients on DOACs who have risk of bleeding. In addition, the lack of specific antidotes and measurement methods/assays, as well as the role of renal function are critical points for patients' management with AFib.

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Pharmacokinetics and pharmacodynamics of direct oral anticoagulants (DOACs)

The new oral anticoagulants differ in their pharmacology and pharmacokinetics (Table 1). Although their onset of action and half-life are quite similar, other properties such as their respective mechanism of action, bioavailability, metabolism and creatinine clearance are different (Boehringer Ingelheim Summary of Product Characteristics, 2017; Bayer Pharma AG Summary of Product Characteristics, 2017; Bristol-Myers Squibb Company Summary of Product Characteristics, 2017; Daiichi Sankyo Europe GmbH Summary of Product Characteristics, 2017). All agents have rapid onset of action, a wide therapeutic window, little or no interaction with food and other drugs, minimal inter-patient variability, and similar pharmacokinetics in different patient populations. Since DOACs are substrates, co-administration with cytochrome P450 system isoenzymes and permeability glycoprotein (P-gp) inhibitors and inducers can result in substantial changes in plasma concentrations [2]. Clinicians should be aware and take into account before appointment of anticoagulative therapy.

Usually the pharmacokinetic profile of DOACs in healthy subjects is not substantially affected by age or sex. However, its profile is affected by mild impairment in hepatic function or extremes in bodyweight. In subjects with moderate hepatic impairment, the drug concentration is twofold higher than in controls, with an associated moderate increase of anti-coagulation and prolongation of prothrombin time [9]. In addition, patients with mild, moderate and severe renal impairment, the overall inhibition of coagulation cascade also could increase. Therefore, it is not expected to be dialyzable and their use are not recommended for patients with CrCl<15 ml/min [10].

Coagulation tests might be considered upon attainment of stable anticoagulation (1-2 weeks after initiation) to provide the level of anticoagulation achieved chronically. This information could be useful to interpret subsequent results.

Drug anticoagulative levels could be measured occasionally at

Properties	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Prodrug	Yes; dabigatran etexilate is hydrolysed to dabigatran by plasma and hepatic esterases (no involvement of CYP450)	No	No	No
Onset	Rapid	Rapid	Rapid	Rapid
Bioavailability	6.50%	80-100%	50%	62%
Administration	With or without food. The capsule should be swallowed intact; it should not be opened, broken or chewed. Oral bioavailability may increase by 75% if drug pellets are administered without the capsule.	With food	With or without food	With or without food
T_{Max}	2-3 hours	3 hours	3 hours	1-2 hours
T1/2	8-10 hours after a single dose, 14-17 hours after multiple doses; in older healthy subjects 12-14 hours, 28 hours in subjects with CrCl <30 ml/min.	5-9 hours in healthy young subjects; 11-13 hours in elderly subjects.	8-15 hours	10-14 hours
Metabolites	Conjugated with glucuronides to form metabolites with minor activity; substrate of P-glycoprotein.	Transformed into inactive metabolites through CYP3A4 and CYP2J2; substrate of P-glycoprotein.	Transformed into inactive metabolites mainly through CYP3A4; substrate of P-glycoprotein.	Conjugated or oxydated by CYP3A4/5 to form metabolites with minor activity; substrate of P-glycoprotein.
Protein binding	35%	>90%	87%	55%
Elimination	80% renal	66% renal (36%rivaroxaban + 30% inactive metabolites) 33% feces (inactive metabolites by HB route)	25% renal 56% feces (HB route)	50% renal
Creatinine clearance (ClCr)	Contraindicated for subjects with CrCl <30 ml/min.	Depends on renal impairement: mild (ClCr 50-80 ml/min) AUC increases 1.4 fold, factor Xa inhibition increases 1.5 fold; moderate (ClCr 30-49 ml/min) AUC increases 1.5 fold, factor Xa inhibition increases 1.9 fold; severe (ClCr 15-29 ml/min) AUC increases 1.6 fold, factor Xa inhibition increases 2.0 fold.	Subjects with mild and moderate renal impairement the dose adjustment is necessary; subjects with severe renal impairement should receive the lower dose of apixaban (2.5 mgbid).	For subjects with CrCl 50-80 ml/min AUCt increases by 32 %, CrCl 30-50 ml/min AUC increases by 74%, CrCL<30 ml/min AUC increases by 72%.
Hepatic impairement	Contraindicated if hepatic impairement or liver disease expected to have any impact on survival.	Contraindicated for subjects with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.	Contraindicated for subjects with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.	Contraindicated for subjects with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
Interactions	Potent P-gp inhibitors	Potent CYP3A4 inhibitors and P-gp inhibitors	Potent CYP3A4 inhibitors	Potent P-gp inhibitors, P-gp inducers, P-gp substrates, anticoagulants, antiplatelets and non-steroidal inflammatory drugs
Dosing AFib	110 mg or 150 mg bid	20 mg od	5 mg bid	30 mg od

HB: hepatobiliary; Tmax: Time to obtain maximum drug concentration in the blood; AUC: Area under the concentration-time curve; BID: Twice daily; Od: Once daily

Table 1: Pharmacology and pharmacokinetic properties.

the time of medical visits to assess adherence to treatment, to detect possible drug interactions and side effects. It should be realized that given the DOAC with short half-life (e.g. 8-15 hours), a dose missed a few days earlier that testing might not be detected in the laboratory.

Taking into account the CH_2ADS_2-VASc scale, individuals with extreme body weights may benefit from dose adjustment to avoid under- or over-anticoagulation (Table 2) [8].

The laboratory and direct oral anticoagulants

Although direct oral anticoagulants do not need laboratory testing for dose adjustment, there are instances when laboratory measurement of the drug anticoagulant effect may be useful. In addition, none of the standard coagulation tests constitutes a sensitive or accurate measure of their therapeutic activity. An assessment of the drug concentration or residual activity could be helpful for patients with low renal function or old age, before initiation of treatment, before surgical or invasive procedures, on occasion of hemorrhagic or thrombotic events, and whenever immediate reversal of anticoagulation is needed [11]. The comparative description of coagulation tests shown in Table 3.

Taking into account the different sensitivity and availability of coagulation tests in clinical practice, clinicians should be aware to reduce the risk of bleeding and stroke. However, the chromogenic anti-Xa assay and DTI assay are mostly appropriate tests to detect drug concentration and assess the safety of medical therapy and expected effect. Based on available data the coagulative laboratory testing is recommended for patients on high-risk groups, with CH2ADS2-VASc score ≥ 3 respectively [12,13].

Aim

The aim of this study was to define and assess the necessity of coagulation tests use in practice for patients with AFib in high-risk groups.

Materials and Methods

Quantitative, cross-sectional study was conducted at Pauls Stradins Clinical University Hospital, Latvia, in time from January 2013 to April 2015.

Patients were involved based on following inclusion criteria:

- At least 18 years old.
- Diagnosed non-valvular (as defined by European Society of Cardiology) AFib at least in one of the risk evaluation scores (CHA_{2D2-}VASc score more or equal to 2).
- Use DOACs more than 3 months.
- Have no life-dangerous, serious comorbidities, which can affect patients' mortality (e.g. cancer).
- Agreed to participate in this research and confirmed it by signed informed consent form.

Main patients' characteristics were collected, e.g. demographic data, comorbidies and used medicines. Laboratory assessments, diagnosis were defined during the interview and clarified with doctor if applicable. Patients demographic data, disease anamnesis, main comorbidies and used medicines was obtained. Laboratory test results, additional examinations were specified [14-18].

Results

A total of 143 patients were included in this study, of whom 46.2% (n=66) were male. The mean age was 69.7 (SD ± 9.9) years. About 2/3 (73.1%) of all patients the AF were longer than 1 year. Almost half of patients (46.2%) used DOACs', 16.1% dabigatran and 33.6% rivaroxaban respectively. The main characteristics are collected in Table 4.

The mean CHA_{2DS2-}VASc score was 4.2 (SD ± 1.5), 3.8 in dabigatran group and 4.1 in rivaroxaban group respectively. From all patients the most common comorbidies were arterial hypertension (65.0%; 93), chronic heart failure (48.3%; 69), coronary artery disease (32.9%; 47), diabetes mellitus (24.5%; 35), and dyslipidemia (25.9%; 37).

Almost half of patients (46.2%; 66) used DOACs, 31.5% rivaroxaban and 14.7% dabigatran respectively; furthermore, 1.4% patients used DOACs' with antiaggregants. 49.7% (71) patients had increased risk of possible drug-drug interactions, most frequently with proton pump inhibitors (16.8%; 24), amiodarone (24.5%; 35), anti-inflammatory drugs (49.0%; 70). Frequently used medicines are shown in Table 5.

Factors	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Body weight	Weight >50 kg is associated with C_{max} 21% higher than for subjects weighing 50 to 100 kg, and 53% higher than subjects weighing ≥ 100 kg.	Weight ≤ 50 kg and ≥ 120 kg has small influence on rivaroxaban concentration (approx. 25%).	For low body weight (≤ 50 kg): Increases C_{max} by 30%, AUC by 20%. For high body weight (≥ 120 kg): Decreases C_{max} by 30%, AUC by 20%. Body weight does not affect creatinine clearance.	For low body weight ≤ 60 kg recommended dose is 30 mg. For low body weigh <55 kg C_{max} increases by 40% and AUC by 13%.
Sex	In women ≥ 75 years C_{max} increases by 30% than in men.	Not applicable.	After 20 mg od >65 years elderly subjects: in women C_{max} increases by 18% and AUC by 15% than in men.	After accounting for body weight, gender had no additional clinically significant effect on pharmacokinetics.
Age	In subjects ≥ 75 years C_{max} increases by 68%, and 30% higher in women.	In subjects >75 years AUC increases by 41%; it arises from reduced renal and non-renal clearance.	In subjects >65 years AUC increases by 32%.	After taking renal function and body weigh into account, age had no additional clinically significant effect on pharmacokinetics.
Co-morbidities	Subjects with renal impairement dose reduction may need to be considered.	Subjects with CrCl <50 ml/min for 15 mg and 20 mg adjustment no needed, except those, who are elderly, had low body weight or impaired renal function. Not recommended in subjects with CrCl <15 ml/min or end-stage renal disease. Contraindicated for subjects with hepatic disease associated with	Subjects with CrCl 51-80 ml/min AUC increases by 16%, with CrCl 30-50 ml/min by 29% and with CrCl 30-50 ml/min by 44%. Contraindicated in subjects with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.	Subjects with CrCl >50-80 ml/min AUC increases by 32%, with CrCl 30-50 ml/min by 74% and with CrCl <30 ml/min by 72%, due to the higher quantity of active metabolites. Contraindicated in subjects with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

CrCl: Creatinine clearance; AUC: Area under the concentration-time curve

Table 2: The effects of body weight, sex, age and co-morbidities on the anticoagulants pharmacokinetics.

Assay	Type of DOAC	Utility	Laboratory experience	Sensitivity*/ specificity	Dependence of the reagent	Cut-off for a risk of bleeding
aPTT	Dabigatran	Limited: poorly reflects the intensity of anticoagulation.	Not required	± 100 ng/ml No specificity	Yes	Yes: depends on the indication and the reagent
TT	Dabigatran	Limited: only to exclude the presence of dabigatran. Useful in the perioperative setting.	Not required	Too sensitive No specificity	Yes	Not established
dTT	Dabigatran	Proven: accurately estimates the plasma concentrations-results expressed in ng/ml.	Required: requirement of calibrators and controls	± 10 ng/ml No specificity	No	Yes: depends on the indication(ng/ml)
ECT	Dabigatran	Limited: standardisation and validation required	Required: interlot variability probably requiring calibrators and controls	± 15 ng/ml No specificity	Probably not, but an interlot variability has been reported	Yes: depends on the indication (ratio and seconds)
ECA	Dabigatran	Proven: accurately estimates the plasma concentrations-results expressed in ng/ml.	Required: requirement of calibrators and controls	± 10 ng/ml No specificity	No	Yes: depends on the indication (ng/ml)
PT	Rivaroxaban	Limited: poorly reflects the intensity of anticoagulation.	Not required	From ±100 to >500 ng/ml (depending on the reagent) No specificity	Yes	Not established
Chromogenic anti-Xa assay	Rivaroxaban, apixaban	Proven: accurately estimates the plasma concentrations-results expressed in ng/ml.	Required: requirement of calibrators and controls	±10 ng/ml Specificity: depending on the anti-Xa assay	No	Not established
DRVV-T	Dabigatran, rivaroxaban, apixaban	Partially proven: confirmation should be done in plasma samples from patients treated with dabigatran and apixaban.	Not required	±100 to 200 ng/ml (depending on the reagent and type of DOAC) No specificity	Yes, but less importantly than for PT and aPTT	Not established

Aptt: Activated partial thromboplastin time; TT: Thrombin time; dTT: Dilute thrombin time; ECT: Ecarin clotting time; ECA: Ecarin chromogenic assay; PT: Prothrombin time; DRVV-T: Dilute Russell's viper venom time. *Sensitivity is defined as the concentration required to double or to halve the clotting time (for chronometric assays) or the OD/min (for chromogenic assays)

Table 3: Coagulation tests that could be used to estimate plasma concentrations of DOACs.

	Dabigatran (n; %)	Rivaroxaban (n; %)
Sex		
Female	12 (52.2)	24 (50.0)
Male	11 (47.8)	24 (50.0)
Age (years; mean)	65.4 (SD ± 10.1)	69.9 (SD ± 10.1)
Comorbidies		
Arterial hypertension	18 (80)	37 (78.1)
Chronic heart failure	10 (45)	27 (56.2)
Coronary artery disease	7 (30.0)	18 (37.5)
Diabetes mellitus	5 (21.7)	8 (16.7)
Dyslipidemia	5 (21.7)	7 (14.6)
Stroke	2 (8.7)	2 (4.2)
Myocardial infarction	2 (8.7)	3 (6.3)
Cardiomyopathy	-	6 (9.4)
CHA_2DS_2-VASc score	3.8 (SD ± 1.6)	4.1 (SD ± 1.7)
HAS-BLED score	2.6 (SD ± 1.5)	2.5 (SD ± 1.1)

Table 4: Baseline characteristics.

According to CHA2D2-VASc score, 60.2% patients were in high-risk group: score 3-23 (16.1%), score 4-22 (15.4%), score 5-20 (14.0%) and score 6-21 (14.7%). The use of DOACs and possible drug-drug interactions increases by risk score, reaching the maximum score 3 (16.1%; 23) and the mean frequent score 4.4 of 86 (60.1%) AF patients respectively. Based on CHA2D2- VASc score and clinically relevant possible drug-drug interactions, the DOACs' concentration in plasma could be affected, in result of increased risk of bleeding and/or thrombotic events. Furthermore, analyzing data by HAS-BLED score, it is shown that 72.7% (104) patients had increased risk of bleeding. The most common comorbidies and their correlation with CHA2D2- VASc score is shown in Figure 1.

Medicines	Dabigatran (n; %)	Rivaroxaban (n; %)
Proton pump inhibitors	6 (26.1)	14 (29.2)
Rhythm-control drugs	14 (60.9)	27 (56.3)
Amiodarone	4 (17.4)	14 (29.2)
Anti-inflammatory drugs	1 (4.3)	2 (4.2)
Antihypertensive drugs	13 (56.5)	36 (75)
Statins	8 (34.8)	21 (43.8)
Omega-3 fatty acids	3 (13.0)	8 (16.7)
Electrical cardioversion	14 (60.9)	17 (35.4)

Table 5: Most frequently used medicines and possible drug-drug interaction.

To detect the possible drug-drug interactions, patients were divided into two risk groups-medium and high. In dabigatran group most frequent potential drug interactions were with amiodarone (16.7%) and proton pump inhibitors (13.8%), in rivaroxaban group-amiodarone (29.2%) and anti-inflammatory drugs (4.2%) respectively (Table 6). In addition, 1.4% patients used DOACs' with antiagregants as triple therapy [19-21].

Discussion

The use of DOACs without routine monitoring of anticoagulant effect is likely safe and effective treatment for non-valvular atrial fibrillation in many patients, but there are circumstances, such as treatment failure, bleeding, renal and/or hepatic failure and perioperative monitoring, in which reliable assays of DOAC activity are needed. DOAC dosing recommendations are currently based on patient characteristics rather than measurement of drug effect, and emerging data from the largest trials of DOACs support this strategy. However, specific coagulation assays, depending on the DOACs, should be used in order to provide the more reliable information on plasma

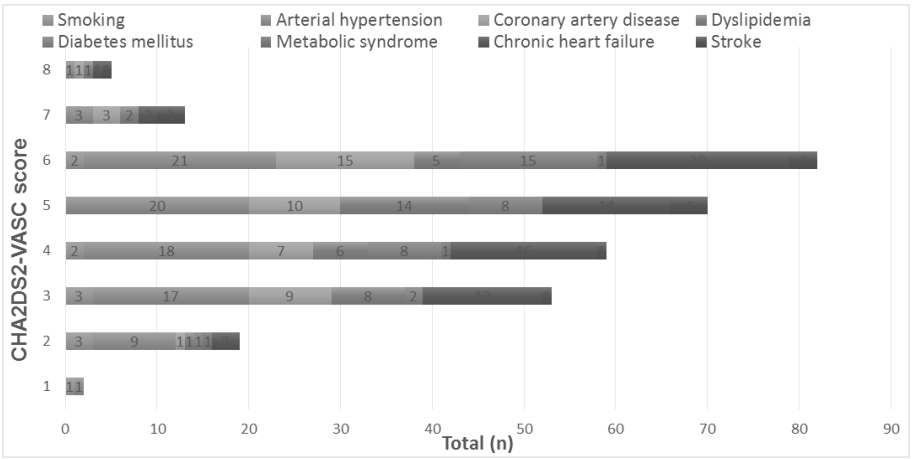

Figure 1: The most common comorbidies and their correlation with CHA_2D_2-VASc score.

	Dabigatran (n; %)	Rivaroxaban (n; %)
Medium	11 (52.4)	19 (42.2)
Amiodarone	4 (17.4)	14 (29.2)
Proton pump inhibitors	6 (26.1)	14 (29.2)
High		
Anti-inflammatory drugs	1 (4.3)	2 (4.2)

Table 6: Possible drug-drug interactions divided in medium and high risk groups.

concentrations. Standard assays, e.g. a PTT, PT, TT, of anticoagulation are generally insufficient for measuring DOAC activity, except in certain circumstances of extremely high or low drug levels and in the case of some factor Xa inhibitors. The use of calibrated chromogenic anti-Xa and DTI assays should be recommended for the assessment of DOACs, factor anti-Xa assay for rivaroxaban, apixaban and edoxaban, and DTI assay for dabigatran respectively. Unfortunately global coagulation tests, such PT and a PTT, are not useful at all and can lead to misinterpretation that could have clinical implications if the result is not fully understood (Lee, 2011) [12].

The use of dedicated assays may probably improve the benefit-risk profile of DOACs by identifying poor- and high- responders. Monitoring of therapies may be useful to provide guidance in case of bleeding, thrombosis recurrence, to assess the pharmacodynamics of high-risk groups responders, such as high age, low body weight, low renal function, before urgent surgery or procedure and for those with several co-morbidities. However, results should be interpreted with caution if responsiveness is unknown.

Conclusion

DOACs' usage correlates with CHA_{2D2-}VASc score with mean frequent score 4.4 of 86 (60.1%) AFib patients respectively. From all high-risk AFib patients (score ≥ 3) 47.7% had potentially moderate or major risk of drug-drug interactions. According to data by HAS-BLED score, it is shown that 72.7% (104) patients had increased risk of bleeding. In summary, for 60.2% AFib patients appropriate monitoring of anticoagulative therapy should be considered. Anticoagulative laboratory testing for patients on high-risk group could prevent safer anticoagulative therapy for patients with AFib.

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