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Methods for detection of direct oral anticoagulants and their role in clinical practice

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SOUHRN

Úvod: Fibrilace síní (FS) je nejčastější arytmií, jejíž incidence se zvyšuje s věkem; u osob ve věku 50 let se každých deset let zdvojnásobuje a u pacientů ve věku ≥ 80 let dosahuje přibližně 10 %.[1] Přes předvídatelnou farmakokinetiku a farmakodynamiku přímých perorálních antikoagulancií (direct oral anticoagulant, DOAC) je nutno v zájmu účinné a bezpečné léčby, stejně jako pro predikci a detekci trombotických a krvácivých příhod, provádět laboratorní vyšetření, a to i v situacích, kdy by dočasné vysazení léků mohlo být žádoucí.[2]
Cíl: Cílem této studie bylo stanovit a analyzovat nutnost provádění koagulačních testů u pacientů s FS a vysokým kardiovaskulárním rizikem v klinické praxi.
Metody: V období od října 2016 do června 2017 byla v kardiocentru fakultní nemocnice Pauls Stradins Clinical University Hospital v lotyšské Rize provedena kvantitativní, analytická, průřezová klinická studie. V této studii se shromažďovaly údaje pacientů s nevalvulární FS léčených antikoagulancii po dobu ≥ 3 měsíců, definovaných na základě skóre CHA_2DS_2-VASc (≥ 2 nebo 3) jako vysoce riziková skupina mužů i žen. Pro analýzu údajů byl použit software SPSS.
Výsledky: Celkem byly získány údaje 143 pacientů, z nichž 46,2 % (n = 66) byli muži; průměrný věk dosahoval 69,7 (SD ± 9,9) roku. Přibližně u dvou třetin (73,1 %) pacientů se FS vyskytovala po dobu více než jednoho roku. Průměrná hodnota skóre CHA_2DS_2-VASc byla 4,2 (SD ± 1,5). Nejčastějšími přidruženými onemocněními byly arteriální hypertenze (65,0 %; 93), chronické srdeční selhání (48,3 %; 69), ischemická choroba srdeční (32,9 %; 47), diabetes mellitus (24,5 %; 35) a dyslipidemie (25,9 %; 37). Přibližně polovina (46,2 %; 66) užívala DOAC, z toho 31,5 % rivaroxaban a 14,7 % dabigatran; navíc 1,4 % pacientů užívalo DOAC s antiagregancii. U 71 (49,7 %) pacientů existovalo zvýšené riziko možných lékových interakcí, nejčastěji s inhibitory protonové pumpy (16,8 %; 24), amiodaronem (24,5 %; 35) a protizánětlivými léky (49,0 %; 70). Užívání DOAC a možné lékové interakce zvyšují skóre rizika s maximální hodnotou 3 (16,1 %; 23) a průměrným častým skóre 4,4 u 86 (60,1 %) pacientů s FS. Koncentrace léků v krvi byly nižší, než se očekávalo, a dosahovaly hodnoty přibližně 75,2 % C_{max}.
Závěr: Užívání DOAC koreluje se skóre CHA_2DS_2-VASc s průměrnou častou hodnotou 4,4 u 86 (60,1 %) pacientů s FS. Koagulační testy pro stanovení koncentrací DOAC v plazmě byly provedeny u více než poloviny pacientů (60,1 %).

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.[1] 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.[2]
Aim: The aim of this study was to identify and analyze the need of coagulation tests for AF patients with high cardiovascular risk in clinical practice.

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Methods: Quantitative, analytic, cross-sectional clinical trial, during the period from October 2016 till June 2017, was performed at Center of Cardiology, Pauls Stradins Clinical University Hospital, 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 comorbidities 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. The drug concentration in blood was lower than expected, reaching about 75.20% of C_{max}.

Conclusion: DOACs' usage correlates with CHA_2DS_2-VASc score with mean frequent score 4.4 of 86 (60.1%) AF patients, respectively. Coagulation tests were applicable more than half of patients (60.1%) to detect DOACs concentration in plasma.

Keywords:
Atrial fibrillation
Anti-Xa factor
Direct oral anticoagulants
Direct thrombin inhibitors
Drug-drug interactions
CHA_2DS_2-VASc risk score

Introduction

As the world population ages, the burden of AF (atrial fibrillation) and venous thromboembolism disease is expected to increase, and prescriptions for long-term anticoagulation will climb.[3] AF is associated with significant morbidity, mortality, and socioeconomic burden, particularly form stroke and systemic thromboebolism. The later risks depend on patients age and the presence or absence of various stroke risk factors, which have resulted in the development of clinical scores to aid risk stratification for patients with AF. 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. 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,[4] rivaroxaban,[5] apixaban[6] and edoxaban.[7] 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 requirements.[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 are critical points for patients' management with AF.

Risk factors on 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.[4–7] 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. Patient lifestyle and comorbidities are the main risk factors of anticoagulative therapy. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65–74 years, female) is recommended by guidelines for stroke assessment in AF.[9] Patients with higher CHA_2DS_2-VASc score have had a higher risk of stroke, systemic thromboembolism or transient ischemic attack. Taking into account the CHA_2DS_2-VASc scale, individuals with extreme body weights may benefit from dose adjustment to avoid under- or over-anticoagulation (Table 2).[8]

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 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.

The laboratory and direct oral anticoagulants

Although direct oral anticoagulants do not need laboratory testing for dose adjustment, there are instances when

Table 1 – Pharmacology and pharmacokinetic properties

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 hydrolyzed to dabigatran by plasma and hepatic esterases (no involvement of CYP450)	No	No	No
Onset	Rapid	Rapid	Rapid	Rapid
Bioavailability	6.5%	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
$T_{1/2}$	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 impairment: 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	In the subjects with mild and moderate renal impairment the dose adjustment is necessary; subjects with severe renal impairment should receive the lower dose of apixaban (2.5 mg bid)	For subjects with CrCl 50–80 ml/min AUC increases by 32%, CrCl 30–50 ml/min, AUC increases by 74%, CrCl <30 ml/min AUC increases by 72%
Hepatic impairment	Contraindicated if hepatic impairment or liver disease is 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 AF	110 mg or 150 mg bid	20 mg od	5 mg bid	30 mg od

AUC – area under the concentration-time curve; bid – twice daily; CrCl – creatinine clearance; HB – hepatobiliary; od – once daily; T_{max} – time to obtain maximum drug concentration in the blood.

Table 2 – The effects of body weight, sex, age, and comorbidities on the anticoagulants pharmacokinetics

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 weight into account, age had no additional clinically significant effect on pharmacokinetics
Comorbidities	Subjects with renal impairment 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 coagulopathy and clinically relevant bleeding risk.	In 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.

AUC – area under the concentration-time curve; CrCl – creatinine clearance.

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 before initiation of treatment, before surgical or invasive procedures, on occasion of hemorrhagic or thrombotic events, and whenever immediate reversal of anticoagulation is needed.[10]

The comparative description of coagulation tests is 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. According to available data 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 in high-risk groups, with CHA_2DS_2-VASc score ≥3, respectively.

AIM

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

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 the following inclusion criteria:

- at least 18 years old;
- diagnosed non-valvular (as defined by European Society of Cardiology) AF at least in one of the risk evaluation scores (CHA_2DS_2-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, comorbidities and used medicines. Laboratory assessments, diagnosis were defined during the interview and clarified with doctor if applicable.

Patients' demographic data, disease anamnesis, main comorbidities and used medicines were obtained. Laboratory test results, additional examinations were specified.

On time of data collection the chromogenic anti-Xa assay and DTI assay was introduced at Pauls Stradins Clinical University Hospital. Therefore, additional data about DOAC concentration in plasma were collected as clinical cases and compared with study results.

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

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

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: standardization 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; DRVV-T – dilute Russell's viper venom time; dTT – dilute thrombin time; ECA – ecarin chromogenic assay; ECT – ecarin clotting time; PT – prothrombin time; TT – thrombin 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).

(SD ± 9.9) years. About in two thirds (73.1%) of all patients the AF occurred longer than one 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_2DS_2-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 comorbidities 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 the 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.

According to CHA_2DS_2-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 CHA_2DS_2-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 comorbidities and their correlation with CHA_2DS_2-VASc score is shown in Fig. 1.

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 antiaggregants as triple therapy.

Table 4 – Baseline characteristics

	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)
Comorbidities		
Arterial hypertension	18 (80.0)	37 (78.1)
Chronic heart failure	10 (45.0)	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 5 – Most frequently used medicines and possible drug-drug interaction

Medicines	Dabigatran (n; %)	Rivaroxaban (n; %)
Proton pump inhibitors	6 (26.1)	14 (29.2)
Rhythm-control drugs Amiodarone	14 (60.9) 4 (17.4)	27 (56.3) 14 (29.2)
Anti-inflammatory drugs	1 (4.3)	2 (4.2)
Antihypertensive drugs	13 (56.5)	36 (75.0)
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)

Data about 5 clinical cases were analyzed during the study. The samples to detect drug concentration in blood were took in different time intervals – 3, 6 and 12 hours after use of drug. The mean age was 65 years. We would like to highlight one patient data. The main characteristics are collected in Table 7.

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

	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 7 – Baseline characteristics for clinical case

Sex	Male
Age	71
Height (m)/Weight (kg)	1.80/99
BMI (kg/m^2)	30.56
AF time	2 months
Smoking status	No
Bleeding	Gastrointestinal bleeding, hospitalization required
Comorbidities	Arterial hypertension (NYHA II) Coronary artery disease Chronic heart failure
CHA_2DS_2-VASc score	4
HAS-BLED score	4

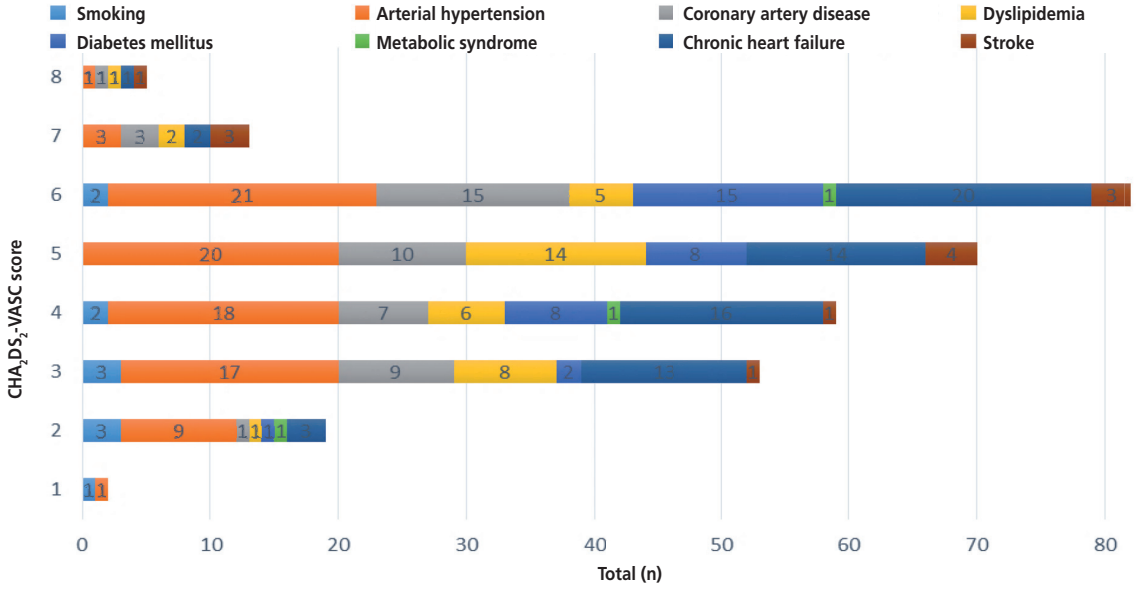

Fig. 1 – The most common comorbidities and their correlation with CHA_2DS_2-VASc score

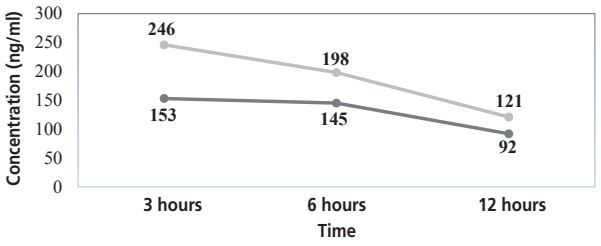

Fig. 2 – Rivaroxaban concentration in blood in different time-intervals

Patient received rivaroxaban 20 mg twice a day, amiodarone, ramipril, bisoprolol, atorvastatin, amlodipine, etoricoxib and omeprazole. Three hours after use of drug the anticoagulant concentration in blood was 153 ng/ml, what was less than expected – 246 ng/ml, respectively. The pharmacokinetic linearity, which is representative to rivaroxaban concentration in blood, was not observed, decreasing only by 5.2%, respectively. The concentration is shown in Fig. 2.

Taking into account the CHA_2DS_2-VASc score, which is 4, and changes in drug concentration in blood, which can affect anticoagulative effect, the patient had increased risk of stroke, systemic thromboembolism or transient ischemic attack.

As shown in clinical cases the drug concentration in blood was lower than expected, reaching about 75.2% of C_{max}. Although there is sufficient information to generalize the data, however, it was observed that patients with higher CHA_2DS_2-VASc score were more complicated and received multiple pharmacotherapy, which could affect DOAC concentration and effect. The study data confirmed necessity to detect anticoagulants concentration in clinical practice for high-risk patients (CHA_2DS_2-VASc score more or equal to 2).

Discussion

The use of DOACs without routine monitoring of anticoagulant effect is likely safe and effective treatment for non-valvular AF 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 concentrations. Standard assays, e.g. aPTT, 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 as PT and aPTT, are not useful at all and can lead to misinterpretation that could have clinical implications if the result is not fully understood.[11]

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 comorbidities. However, results should be interpreted with caution if responsiveness is unknown.

Conclusions

DOACs' usage correlates with CHA_2DS_2-VASc score with mean frequent score 4.4 of 86 (60.1%) AF patients, respectively. From all high-risk AF 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. The drug concentration in blood was lower than expected, reaching about 75.20% of C_{max}. In summary, for 60.1% AF patients appropriate monitoring of anticoagulative therapy should be considered. Anticoagulative laboratory testing for patients on high-risk group could prevent safer anticoagulation therapy for patients with AF.

Conflict of interest

None.

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