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Potential drug-drug interactions between oral anticoagulants for high-risk patients with atrial fibrillation in Latvia

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SOUHRN

Úvod: Fibrilace síní (FS) je onemocnění postihující mnoho lidí, zvláště starší osoby. U všech z nich je přítomno zvýšené riziko tromboembolické příhody. Ke snížení rizika se u těchto nemocných provádí antikoagulační léčba. K dispozici jsou dva typy antikoagulancií – antagonista vitaminu K warfarin a nová (neboli přímá perorální) antikoagulancia dagibatran a rivaroxaban. Protože osoby s FS obvykle mají několik dalších onemocnění a jiné komplikace, např. riziko krvácení a tromboembolie, užívají současně několik léčiv, což při jejich metabolické přeměně zvyšuje riziko lékových interakcí společných pro P-glykoprotein a CYP450. Větší pozornost věnovaná zdravotníky monitorování účinku farmakoterapie a edukace pacientů o nejčastějších lékových interakcích při užívání perorálních antikoagulancií by mohla pomoci zajistit bezpečnější a účinnější antikoagulační léčbu.

Cíl: Definovat a analyzovat nejčastější možné lékové interakce u perorálních antikoagulancií – warfarinu, dabigatranu a rivaroxabanu – nejčastěji podávaných vysoce rizikovým pacientům s FS v Lotyšsku.

Materiály a metody: Na kardiologické klinice fakultní nemocnice Paulse Stradinse (Lotyšsko) se v období od října 2016 do června 2017 prováděla průřezová studie s následnou kvantitativní analýzou údajů získaných od vysoce rizikových nemocných s FS, kteří denně užívali perorální antikoagulancia. Po podepsání informovaného souhlasu pacientů se shromažďovaly jejich demografické údaje, zjišťovaly informace o pravidelně a často užívané medikaci a potravinových doplňcích. Výsledky laboratorních testů a echokardiografického vyšetření byly zkombinovány s osobní anamnézou pacientů. Statistická analýza získaných údajů se prováděla s použitím softwaru SPSS Statistics.

Výsledky: Do studie bylo zařazeno celkem 143 pacientů; z tohoto počtu bylo 46,2 % mužů a 53,8 % žen průměrného věku 69,7 (SD 9,9) roku. Z medikace jich 53,8 % užívalo warfarin, 16,1 % dabigatran a 33,6 % rivaroxaban. U 49,7 % pacientů bylo zjištěno zvýšené riziko možných lékových interakcí. U osob užívajících warfarin se nejčastěji jednalo o možné lékové interakce s potravinovými doplňky obsahujícími omega-3 kyseliny (20,8 %), s amiodaronem (16,7 %) a s inhibitory protonové pumpy (13,8 %). V případě pacientů léčených dabigatranem byly zaznamenány nejčastější potenciální interakce s inhibitory protonové pumpy (26,1 %), s amiodaronem (17,4 %) a s potravinovými doplňky obsahujícími omega-3 kyseliny (13,0 %). U pacientů užívajících rivaroxaban se jednalo o nejčastější možné lékové interakce s amiodaronem (29,2 %), s potravinovými doplňky obsahujícími omega-3 kyseliny (16,7 %) a s nesteroidními protizánětlivými léky (4,2 %).

Závěr: Ze všech vysoce rizikových pacientů s FS bylo u 47,7 % zjištěno středně vysoké nebo vysoké riziko možných lékových interakcí, nejčastěji ve spojení s užíváním potravinových doplňků. Celkem 50,3 % pacientů užívalo antagonistu vitaminu K warfarin. Nejčastější možné lékové interakce ve skupině s warfarinem byly zaznamenány ve spojení s potravinovými doplňky obsahujícími omega-3 kyseliny (20,8 %) a amiodaronem (16,7 %), ve skupině užívající dabigatran to byly inhibitory protonové pumpy (26,1 %) a amiodaron (17,4 %); ve skupině užívající rivaroxaban byly zjištěny možné lékové interakce s amiodaronem (29,2 %) a s potravinovými doplňky obsahujícími omega-3 kyseliny (16,7 %). Povědomí zdravotníků o těchto interakcích by mohlo přispět k vyšší bezpečnosti a účinnosti antikoagulační léčby vysoce rizikových osob s fibrilací síní.

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ABSTRACT

Introduction: Atrial fibrillation (AFib) is a disease that affects many people, especially elderly ones. All of these persons have an increased risk of thromboembolic event. For lowering the risk these patients use anticoagulation therapy. There are two types of oral anticoagulants – vitamin K antagonist warfarin and new, known also as direct oral anticoagulants, dabigatran and rivaroxaban. Due to several comorbidities and other complications, e.g. the risk of bleeding and thromboembolism, AFib patients are using different medication simultaneously, therefore increasing the risk of drug-drug interactions because of one metabolism path through P-glycoprotein and CYP450. Monitoring of medical therapy and patient education about most frequent drug-drug interactions using oral anticoagulants could raise attention of health care professionals to the possible drug-drug interactions and promote safe and effective anticoagulation therapy.

Aim: To define and analyze the most common potential drug-drug interactions for most frequent used oral anticoagulants – warfarin, dabigatran, rivaroxaban – in patients with high-risk AFib in Latvia.

Materials and methods: Quantitative analytic cross-section research was made in time period from October 2016 till June 2017 in Pauls Stradins clinical university hospital, Center of Cardiology in Latvia. The data about patients with high-risk AFib who used oral anticoagulants daily were selected. After signed patients consent form the demographic data, regularly and frequently used medication and food supplements were obtained. Laboratory analysis and echocardiography data were specified with the help of case anamnesis. For statistical data analysis were used SPSS Statistics database.

Results: Altogether 143 patients were enrolled in this study, from which 46.2% were male, 53.8% female, with the mean age 69.7 (SD 9.9) years. 53.8% used warfarin, 16.1% dabigatran and 33.6% used rivaroxaban. 49.7% of patients had increased risk of possible drug-drug interactions. For warfarin users the most frequent potential interactions were with omega-3 supplements (20.8%), amiodarone (16.7%) and proton pump inhibitors (13.8%). For dabigatran users the most frequent potential interaction was with proton pump inhibitors (26.1%), amiodarone (17.4%) and omega-3 supplements (13.0%). For rivaroxaban users the most frequent potential drug interaction was with amiodarone (29.2%), omega-3 supplements (16.7%) and non-steroidal anti-inflammatory drugs (4.2%).

Conclusion: From all high-risk AFib patients 47.7% had potentially moderate or major risk of drug interactions, most frequently with food supplements. 50.3% patients used warfarin, K vitamin antagonist. The most frequent potential drug interaction in warfarin group was with omega-3 supplements (20.8%) and amiodarone (16.7%), in dabigatran group with proton pump inhibitors (26.1%) and amiodarone (17.4%), in rivaroxaban group with amiodarone (29.2%) and omega-3 supplements (16.7%). Awareness of these interactions between health care professionals could promote the safety and effectiveness of anticoagulation therapy for high-risk atrial fibrillation patients.

Keywords:
CYP450 inhibitors
Dabigatran
Monitoring drug use
Patient education
Risk of bleeding
Rivaroxaban
Warfarin

Introduction

Atrial fibrillation (AFib) is a problem that affects 1.5% of Latvia's population (1,5%)[1]. The prevalence of AFib increases with age, in a group of 60–70-year-olds presenting in 3,7–4,2% of cases but in a group of 80 and older reaching 10–17% prevalence.[2]

Persons with this condition, depending on individual risk factors, are in an increased ischemic stroke risk group.[3] To lower this risk patients are required to use antithrombotic prophylaxis with oral anticoagulants. For many years the only oral anticoagulant was K vitamin antagonist warfarin. Warfarin is rather complex to use because of the regular needed laboratory tests, diet restrictions, difficulties maintaining the INR (international normalized ratio) in its therapeutic range and the large number of medication that has the potential of interacting with it, raising its levels in the blood and leading to overdosing.

Almost ten years ago in the market appeared novel oral anticoagulants (NOACs), dabigatran and rivaroxaban, that did not need regular laboratory testing, were easier to use, had lower risk of drug-drug interactions and altogether provide a better safety profile.[4]

For all of these potential drug-drug interactions a big role plays P-glycoprotein and CYP450.[5] P-glycoprotein, also called multidrug resistance protein 1, that is an efflux transporter, mainly is found in tissues with excretory function, such as in intestine, liver and kidneys, pumping foreign substances out of the cell back into the lumen and decreasing their concentration in blood. P-glycoprotein is also a part of dabigatran and rivaroxaban metabolism path.[6] A spectrum of commonly prescribed cardiovascular drugs are also P-glycoprotein substrates and can have clinically relevant interactions with anticoagulants.[7]

Another very important metabolic pathway is through CYP-450, which is a protein of a superfamily that contains heme and cofactors. CYP-450 is responsible for about 75% of drug metabolism paths,[8] also for warfarin and rivaroxaban metabolism.[9,10] In a situation, where oral anticoagulant is used with other drugs or food supplements that can influence CYP450 activity, there is a potential risk, that it can disrupt the concentration level of anticoagulant and leading to toxic levels.

AFib patients use daily around four drugs,[11] leading to high possibility that these medications have the potential to interact with one-another. To lower this risk it is important to start focusing not only on separate drugs to treat the disease, but also on the metabolism path for these medications and how these drugs can potentially dangerously interact with one another.

Aim

To define the most common potential drug interactions for oral anticoagulant, warfarin, dabigatran and rivaroxaban, users in Latvian society with high-risk atrial fibrillation.

Materials and methods

Quantitative analytic cross-section research was performed in time period from October 2016 to June 2017 in Pauls Stradins clinical university hospital, Center of Cardiology.

Research was made by selecting patients that met all the inclusion criteria and did not have any exclusion criteria.

Inclusion criteria:

- patient is at least eighteen years old;
- patient is hospitalized in Cardiology Center of Latvia during the interview;
- patient agrees to participate in this research and signs an informed consent document, indicating that they understand the purpose of this study and are willing to participate in the study;
- person during the interview has full consciousness;
- person is a non-valvular (as defined by European Society of Cardiology)[12] high-risk atrial fibrillation patient at least in one of the risk evaluation scores (CHA_2D_2-VASc score for men more or equal to 2, for woman more or equal to 3; HAS-BLED score more or equal to 3, ORBIT score more or equal to 4, ATRIA score more or equal to 6);
- patient uses oral anticoagulants daily.

Exclusion criteria:

- patient does not agree to participate in this research;
- patient does not use oral anticoagulants daily;
- patient is a valvular AFib patient;
- patient uses oral anticoagulant for any other reason that is not AFib.

The interview included demographic questions, questions about previous echocardiography results, disease anamnesis, daily and frequently used medication and food supplements, laboratory tests. Data precision was made with case anamnesis reviewing. The interview was held orally and in case of any unclear questions they were explained and clarified.

After the interview all collected data were entered in SPSS Statistics and quantitative analysis was made.

The most common drugs and food supplements that AFib patients use and that have the potential to interact were de-

Table 1 – Potential drug interaction severity for different oral anticoagulants

	Antiplatelets	SSRIs, SNRIs	NSAIDs	Amiodarone	Omega-3 supplements	Proton pump inhibitors	Spironolactone
Warfarin	Major	Moderate	Major	Major	Moderate	Moderate	No interr.
Dabigatran	Moderate	Moderate	Major	Moderate	Moderate	Moderate	Moderate
Rivaroxaban	Major	Moderate	Major	Moderate	Moderate	No interr.	No interr.

Table 2 – Main characteristics of study groups

	Warfarin users	Dabigatran users	Rivaroxaban users
Variables	72	23	48
Female, %	56.9	52.2	50.0
Men, %	43.1	47.8	50.0
Age, years	71.0 (SD 9.4)	65.3.9 (SD 10.1)	69.9 (SD 10.1)
Hypertension, %	84.1	80.0	78.1
Chronic heart failure, %	66.7	45.0	56.2
Percutaneous coronary interventions, %	12.7	10.0	15.6
Cerebral infarction, %	14.2	10.0	9.3
Artificial cardiac pacemaker, %	23.8	0	21.8
Cardiomyopathy, %	6.3	0	9.4
Coronary heart disease, %	46.0	30	37.5
Paroxysmal atrial fibrillation, %	11.5	33.3	29.0
Persistent atrial fibrillation, %	54.1	50.0	48.4
Permanent atrial fibrillation, %	34.4	16.7	22.6
LVEF, %	51.13 (SD 14.10)	61.08 (SD 6.30)	58.36 (SD 9.10)
LA, mm	46.23 (SD 9.69)	43.93 (SD 4.81)	45.04 (SD 7.98)
LAVI, ml/m^2	46.10 (SD 17.41)	40.50 (SD 7.28)	40.19 (SD 13.93)
CHA_2DS_2-VASc	4.4 (SD 1.4)	3.8 (SD 1.6)	4.1 (SD 1.7)
HAS-BLED	2.7 (SD 1.3)	2.6 (SD 1.5)	2.5 (SD 1.1)
ORBIT	1.6 (SD 1.4)	1.7 (SD 1.9)	1.7 (SD 1.9)
ATRIA	6.5 (SD 2.5)	5.1 (SD 2.9)	5.8 (SD 2.7)

fined antiplatelet agents, non-steroidal anti-inflammatory drugs, antiarrhythmics, such as amiodarone, omega-3 food supplements, proton pump inhibitors, such as omeprazole and pantoprazole, serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) and spironolactone for interactions with dabigatran.

In Table 1 you can see the defined most common drug interactions for warfarin, dabigatran and rivaroxaban users and the potential of interaction.

These medications used together have the potential of interacting with one another and that puts a higher bleeding risk for those patients (https://www.drugs.com/drug_interactions.php).

If the patient daily or frequently used all the other medication except anticoagulants, at least 3 times a week or, in NSAIDs case, at least once in two weeks, it was noted as a medication that patient uses.

Results

Altogether 143 patients were included in this research and were hospitalized in Center of Cardiology in Latvia. From all the patients 46.2% were male and 53.8% were female. The mean age was 69.7 (SD 9.9) years. From all the included patients 50.3% used warfarin, 16.1% dabigatran and 33.6% used rivaroxaban. The main group characteristics you can see in Tables 2 and 3.

There was discovered that 49.7% of patients using daily oral anticoagulants have potential drug interactions because of one metabolism path through P-glycoprotein and CYP450.

Warfarin

Warfarin was the most frequent chosen anticoagulant for ischemic stroke prophylaxis – in 50.3% of cases.

From all the patients 54.2% (39) had potential drug interaction of which 30.56% (22) were major drug interactions and 33.33% (24) moderate drug interactions. 15.3% (11) of all the warfarin users had multiple potential drug interactions, but 38.9% (28) had single potential interaction. In Table 4 you can see all the medication that was detected and had potential drug interactions with warfarin in descending order, starting from the most common potential drug interactions and leading to least popular. Medication combinations that have potentially major drug interactions were written in bold.

Table 3 – Mean laboratory test results

	Warfarin	Dabigatran	Rivaroxaban
Leukocyte, × 10^9/L	9.1 (SD 7.7)	8.1 (SD 3.6)	7.3 (SD 1.8)
Erythrocyte, × 10^{12}/L	4.7 (SD 0.7)	4.7 (SD 0.5)	4.6 (SD 0.6)
Hemoglobin, g/L	128.6 (SD 27.6)	128.9 (SD 32.5)	131.9 (SD 18.0)
Hematocrit, %	40.5 (SD 5.8)	40.9 (SD 3.7)	40.5 (SD 5.4)
APTT, s	50.0 (SD 18.3)	50.2 (SD 14.2)	39.2 (SD 6.8)
INR	2.2 (SD (1.2)	1.2 (SD 0.2)	1.2 (SD 0.2)
ALAT, U/L	28.8 (SD 15.8)	33.9 (SD 24.8)	32.0 (SD 24.1)
ASAT, U/L	33.8 (SD 22.0)	26.0 (SD 13.4)	30.3 (SD 18.6)
Glucose, mmol/L	6.9 (SD 1.9)	6.2 (SD 1.5)	6.8 (SD 3.1)
Creatinine, mmol/L	93.1 (SD 26.5)	75.0 (SD 35.5)	93.4 (SD 17.1)
Potassium, mmol/L	4.4 (SD 0.5)	4.5 (SD 1.0)	4.6 (SD 0.4)
Triglycerides, mmol/L	1.6 (SD 0.7)	1.4 (SD 0.6)	1.5 (SD 1.0)
Cholesterol, mmol/L	4.5 (SD 1.4)	4.2 (SD 2.0)	4.3 (SD 1.7)
HDL, mmol/L	1.3 (SD 0.4)	1.3 (SD 0.4)	1.3 (SD 0.3)
LDL, mmol/L	2.6 (SD 1.1)	2.9 (SD 1.5)	2.5 (SD 1.2)
CRO, mg/L	16.1 (SD 57.5)	7.8 (SD 18.6)	2.5 (SD 2.1)

Table 4 – Most frequent drug interactions for warfarin users

Nr.	Drug/food supplement	Percentage of patients that use this medication	Number or patients that use this medication
1.	Omega-3 supplements	20.8%	15
2.	**Amiodarone**	**16.7%**	**12**
3.	Proton pump inhibitors	13.8%	10
4.	**NSAIDs**	**12.5%**	**9**
5.	Rosuvastatin	5.6%	4
6.	**Aspirine**	**4.2%**	**3**
7.	**Clopidogrel**	**1.4%**	**1**

Dabigatran

Dabigatran as anticoagulant for ischemic stroke prophylaxis was chosen in 16.1% of cases. From all the patients 47.8% (11) had potential drug interaction. From all the dabigatran users 4.3% (1) had major drug interactions and 47.8% (11) moderate drug interactions. 13.0% (3) of the persons who use dabigatran had multiple potential drug interactions, but 34.8% (8) – single drug interaction.

In Table 5 you can see the most frequent drug interactions between dabigatran and other drugs and food supplements for patients with high-risk atrial fibrillation.

Rivaroxaban

Rivaroxaban as anticoagulant for ischemic stroke prophylaxis was chosen in 33.6% of cases and from this group a potential drug-drug interaction was found in 43.8% (21) of cases. From all the patients 4.2% (2) had major drug interactions and 39.6% (19) moderate drug interactions. 8.3% (4) of the persons had multiple potential drug interactions, but 35.4% (17) single drug interaction. In Table 6 you can see the most frequent drug interactions between rivaroxaban and other drugs and food supplements for patients with high-risk atrial fibrillation.

Discussion

Potential drug-drug interaction is a threat for almost half of all the high-risk atrial fibrillation patients that use oral anticoagulants daily. These interactions can dangerously rise or lower the anticoagulant levels in blood serum depending whether it inhibits or stimulates P-glycoprotein or CYP-450, leading to bleeding episodes. Identifying these drug combinations that are used most frequently and have the potential to increasing bleeding risk, could help draw health care professional and patient attention to these interactions. Emphasizing how import is to evaluate all the metabolism paths for all the drugs and food supplements that the patient uses daily could encourage health care professionals to make adjustments to the therapy for lowering the potential drug interaction risk and reducing the bleeding risk to minimum, gaining the most benefits.

Drug-drug interactions (DDI) are not just a problem in cardiology and anticoagulant usage. There have been studies in different medicine field, for example in surgical departments, where as high as in 89% of all cases there had been potential drug-drug interactions,[12] whereas in a 2012 study in Brazil, it was calculated that 63% of patients that used drugs had potential drug interactions, risk increasing if patient used 3–5 drugs to 6 or more drugs.[14] In 2016 a study was made, where was calculated that for each physician there were 1.3% of woman and 1.2% of men that had used at least one contraindicated potentially interacting drug-drug combination during the past 12 months. Also it was analyzed that the highest probability to be exposed to DDI was in general practitioner and cardiologist patient care. From anticoagulants the most frequent potential drug-drug interaction was mentioned in warfarin with high dose salicylate.[15]

If we analyze what are the most common potential DDI in other studies, we can see parallels with our study, where the number of potential drug interactions have been around 35% of cases, but the most common ones have been NSAIDs,[16] but in others with amiodarone[17] or antiplatelets, such as acetylsalicylic, clopidogrel, statins and proton pump inhibitors.[18] Also an important fact, why attention to this problem should be raised is because there has been researches where it is concluded that concomitant use of drugs that has the potential to interact is involved in majority of warfarin-associated bleeding events.[19]

The research data were collected from patients during their hospitalization time. There is a possibility that these data could differ from society. This probability can be taken into account, because in hospital concentrate patients that have other cardiac conditions for which they may had been hospitalized and for example use more drugs daily than people, who have not been hospitalized.

The potential drug-drug interactions are not enough emphasized when talked about oral anticoagulants. Con-

Table 5 – Most frequent drug interactions for dabigatran users

Nr.	Drug/food supplement	Percentage of patients that use this medication	Number or patients that use this medication
1.	Proton pump inhibitors	26.1%	6
2.	Amiodarone	17.4%	4
3.	Omega-3 supplements	13.0%	3
4.	NSAIDs	4.3%	1
5.	Spironolactone	4.3%	1

Table 6 – Most frequent drug interactions for rivaroxaban users

Nr.	Drug/food supplement	Percentage of patients that use this medication	Number or patients that use this medication
1.	Amiodarone	29.2%	14
2.	Omega-3 supplements	16.7%	8
3.	NSAIDs	4.2%	2
4.	SSRIs	2.1%	1

sidering the fact that AFib patients have a higher prevalence of comorbidities[20] that requires adequate therapy as written is those corresponding guidelines, there is a risk that these guidelines have not foreseen guideline overlapping. There is possibility that health care professionals choose the most appropriate drug for each disease separately, predominantly not checking whether there are some drug with the potential to interact with each other and therefore leading to the increased bleeding risk.

Drawing more attention to this topic could improve medical therapy, gaining the most benefits for the least risk.

Conclusions

From all high-risk atrial fibrillation patients 47.7% of them has a potentially moderate or major drug interactions with other drugs or food-supplements.

The main part, 50.3% of the patients uses warfarin as oral anticoagulant.

The most frequent potential drug interaction in warfarin group was with omega-3 supplements (20.8%) and amiodarone (16.7%), in dabigatran group with proton pump inhibitors (26.1%) and amiodarone (17.4%) and in rivaroxaban group with amiodarone (29.17%) and omega-3 supplements (16.67%).

Awareness of these potential interactions between health care workers could lead to safer conservative treatment for high-risk atrial fibrillation patients.

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Conflict of interest

None.

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