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Bleeding risk and drug interactions in patients with atrial fibrillation taking oral anticoagulants

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Abstract

Patients with atrial fibrillation (AF) have an increased risk of thromboembolic stroke and all-cause mortality. In addition to antiarrhythmic drugs, the treatment of AF also includes the use of anticoagulants, which significantly reduce the risk of ischaemic stroke, but also carry a bleeding risk. The aim of this study was to assess the risk of bleeding in patients with AF on oral anticoagulants, and to determine the frequency of potentially clinically significant drug-drug interactions (pDDIs) that may further increase the risk of bleeding. A retrospective observational study was conducted at the Department of Cardiology of the Clinical Hospital Center "Bežanijska Kosa". The quantification of bleeding risk was performed using the HAS-BLED score. *Lexi-Interact* was used to identify pDDIs. The study included 124 patients (mean age 72 years, women 50.8%). A high risk of bleeding due to anticoagulant therapy was found in 10.5%. The prevalence of pDDIs, which can additionally increase bleeding risk was 18.5%. The pDDIs were combinations of vitamin K antagonists with selective serotonin reuptake inhibitors, proton pump inhibitors, levothyroxine, sulfonylureas, statins and propafenone. In the treatment and monitoring of patients with AF receiving oral anticoagulant therapy, the use of bleeding risk scores should

be complemented by information on drug interactions, to optimise the benefit/risk ratio of anticoagulant therapy.

Key words: ischaemic stroke, thromboembolic event, anticoagulant therapy, drug interactions, bleeding

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Introduction

Atrial fibrillation (AF) is the most common form of sustained arrhythmia, defined as lasting longer than 30 seconds. The incidence of AF is increasing in the general population due to increased life expectancy, increased prevalence of risk factors for AF, and improved survival after myocardial infarction (1). This type of arrhythmia affects approximately 1–4% of the world's population, with the incidence increasing significantly with age (1). In Europe, an estimated 8 million people suffer from AF and the number is predicted to rise to 18 million by 2060 (2, 3). The treatment of AF is well described in numerous clinical guidelines (4, 5). Treatment includes drugs that have prognostic significance (anticoagulants and cardiovascular disease therapy) and drugs that primarily improve symptoms (heart rate or rhythm control therapy). As already mentioned, anticoagulants are an essential part of the treatment of patients with AF. Oral anticoagulants reduce the risk of stroke due to AF by 60–70%, while the use of antiplatelet agents as monotherapy offers very little or no protection against cerebral infarction in this patient group, and increases the risk of intracranial haemorrhage similar to oral anticoagulants, especially in older patients (4, 6, 7). The following oral anticoagulants are available: the vitamin K antagonist warfarin, which inhibits the synthesis of the vitamin K-dependent coagulation factors II, VII, IX and X; or the direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban and edoxaban. The dose of warfarin should be adjusted to the international normalised ratio (INR), which should be in the range of 2–3. INR monitoring should be performed at least weekly during the initiation of anticoagulant therapy and at least monthly once anticoagulation is stable (INR in range) (8). The use of DOACs is recommended if the INR value cannot be maintained within the therapeutic range, if adverse effects have occurred, or if the patient is unable or unwilling to monitor the INR values.

Guidelines from representative organizations, such as the NICE guidelines or the European Society of Cardiology (ESC) guidelines for AF, recommend using the CHA_2DS_2-VASc score to estimate the risk of stroke in an individual patient (4, 5). The CHA_2DS_2-VASc score was developed to aid the initial decision-making regarding the use of anticoagulants in the treatment of AF. CHA_2DS_2-VASc is a validated score that estimates the one-year risk of a thromboembolic event in patients with nonvalvular AF if they were not taking anticoagulants (9, 10). Its use is recommended in all patient groups – symptomatic or asymptomatic paroxysmal, persistent or permanent AF. Various tools or scores have been developed to assess the bleeding risk, in order to make it easier for doctors to evaluate the benefit/risk ratio. The HAS-BLED score was the first to be developed (11) and is therefore the most widely used and well-validated score in a large number of studies (12–14). According to AF guidelines, it is used simultaneously with the CHA_2DS_2-VASc score, when initiating anticoagulant therapy, to assess whether the benefit of using oral anticoagulants outweighs the risk (5). The risk factors for bleeding in patients that are included in the calculation of the HAS-BLED score include: hypertension (uncontrolled), renal disease, liver disease, history of stroke, prior major

bleeding or predisposition to bleeding, labile INR, age over 65, alcohol consumption and taking drugs that tend to cause bleeding.

However, HAS-BLED only considers drug interactions when anticoagulants are taken concomitantly with aspirin, clopidogrel or non-steroidal anti-inflammatory drugs (NSAIDs), whereas anticoagulants are susceptible to numerous potential drug-drug interactions due to their pharmacokinetic and pharmacodynamic properties (15). Real-world studies document the association of DDIs with bleeding, regardless of comorbidities. These findings emphasised the need to be more vigilant of the impact of interacting drugs on bleeding risk in patients taking oral anticoagulants (16, 17). Nevertheless, the studies reported NSAIDs and antiplatelets, as most commonly associated with bleeding, while the exposure to other medications affecting pharmacokinetics processes is not well described. Therefore, the primary objective of the study was to assess the risk of bleeding in patients with AF taking oral anticoagulants. Additionally, the aim was to identify and characterise potential clinically significant drug-drug interactions (pDDIs) that may increase the risk of bleeding, and have not previously been included in the calculation of the bleeding risk score.

Methodology

A retrospective observational study was conducted from June 2012 to February 2013, in which consecutively hospitalised patients from the Cardiology Department of the Clinical Hospital Center "Bežanijska Kosa" were included. The inclusion criteria for adult patients were the presence of AF in the anamnesis and the use of oral anticoagulants. The study was approved by the Ethics Committee of the Clinical Hospital Center "Bežanijska Kosa" (decision number 222/3) and the Ethics Committee for Biomedical Research of the Faculty of Pharmacy of the University of Belgrade (decision number 1027/2). The patients' data were collected at the time of the admission to the cardiology department. Sociodemographic data (age, gender, living conditions, smoking status, alcohol consumption), medical history, data on complete therapy administered prior to hospitalisation (drug, dose, dosage regimen), and the reason for hospitalisation. The risk of ischaemic stroke was assessed using the CHA_2DS_2-VASc score. Bleeding risk was quantified using the HAS-BLED score (score 0–1 is considered low bleeding risk, 2 is intermediate, and ≥3 is high) (11, 18). The identification of pDDIs involving anticoagulants with other concomitantly administered drugs was performed using the Lexi-Interact electronic database (Lexicomp Online®, Lexi-Comp, Inc., Hudson, Ohio). Potentially clinically significant pDDIs are considered risk levels C (monitor therapy), D (modify regimen) and X (avoid combination).

Quantitative continuous variables are presented as mean and standard deviation, with an overall range (minimum-maximum value); quantitative ordinal variables are presented as median and interquartile range (25th and 75th percentile; interquartile range, *IQR*), with an overall range (minimum-maximum value); while qualitative, nominal variables are presented as the number of patients with a percentage. The difference between the mean or median values of the compared groups was tested with the t-test or

Mann-Whitney U-test. The assessment of the association of anticoagulant pDDIs with the identified high bleeding risk was performed using the Chi-square test of independence, i.e. Fisher's test. The value $p<0.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS, IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software was used for statistical analysis.

Results

A total of 124 patients with AF on anticoagulant therapy were included in the analysis. The mean age was 72.1 ± 8.6 years, with a range of 51–88 years. Approximately 80% of the patients were 65 years or older. The gender distribution was almost equal (63 women vs. 61 men). The patients had a median Charlson Comorbidity Index (CCI) of 3 [*IQR* 2–4], with more than a third of the patients having significant morbidity (CCI >3). Polypharmacy was prevalent, with 73.4% of the patients taking 5 or more drugs. The median number of drugs was 6 drugs [*IQR* 4–8], while the overall range was 2–15 drugs.

Among the cardiovascular comorbidities, hypertension was most common in 80 patients (64.5%), followed by heart failure in 62 patients (50%) and angina pectoris in 33 patients (26.6%). The prevalence of additional risk factors for the occurrence of cardiovascular or cerebrovascular events was: diabetes mellitus 25.8% (32 patients), dyslipidaemia 8.9% (11 patients), while 5.6% (7 patients) consumed alcohol. A detailed presentation of the demographic and clinical characteristics of the patients is summarised in Table I.

Table I Demographic and clinical characteristics of the patients

Tabela I Demografske i kliničke karakteristike pacijenata

Characteristics	**Number of patients (%)** **Mean ± SD (total range)** **Median [*IQR*]**
Age, years	72.1 ± 8.6 (51–88)
>65 years old	98 (79%)
Gender, female	63 (50.8%)
Length of hospitalisation, days	9.4 ± 5.7 (0–38)
Number of drugs	6.3 ± 2.8 (2–15) 6 [4–8]
1–4	33 (26.6%)
5–9	79 (63.7%)
≥10	12 (9.7%)

Characteristics	Number of patients (%) Mean ± SD (total range) Median [*IQR*]
Charlson Comorbidity Index (CCI)	3.1 ± 1.6 (1–8) 3 [2–4]
CCI >3	44 (35.5%)
Comorbidities	
hypertension	80 (64.5%)
heart failure	62 (50%)
angina pectoris	33 (26.6%)
diabetes mellitus	32 (25.8%)
myocardial infarction in anamnesis	13 (10.5%)
respiratory disease	12 (9.7%)
dyslipidaemia	11 (8.9%)
endocrine disease, excluding diabetes mellitus	7 (5.6%)
gastrointestinal disease	6 (4.8%)
blood and blood forming organs disease	5 (4%)
chronic renal disease	5 (4%)
infection	4 (3.2%)
stroke in anamnesis	3 (2.4%)
liver disease	3 (2.4%)
central nervous system disease (neurodegenerative or mental)	2 (1.6%)
previous bleeding	2 (1.6%)
Reason for hospitalisation	
heart failure	62 (50%)
arrhythmia	46 (37.1%)
hypertension	4 (3.2%)
angina pectoris	4 (3.2%)
thromboembolic event	2 (1.6%)

IQR – interquartile range; SD – standard deviation

The mean CHA_2DS_2-VASc score in the study group was 3.3 ± 1.4 (range 0–7), indicating a high average risk of ischaemic stroke due to AF (score ≥2). About 92% of the patients belonged to the high-risk group, in which the benefit of administering oral anticoagulants was convincing. The HAS-BLED score has indicated that 10.5% (13 patients) had a high estimated risk of bleeding. In the group of patients at high risk of ischaemic stroke (n=114), 64 patients (56.1%) used oral anticoagulants, while 50 patients (43.9%) used dual antiplatelet and anticoagulant therapy. The highest prevalence of criteria included in the calculation of the HAS-BLED score was: patient aged over 65 years (79%, 98), followed by the use of drugs that increase the risk of bleeding (41.9%, 52). A detailed presentation of the HAS-BLED score and the associated risk factors can be found in Table II.

Table II HAS-BLED score values and prevalence of criteria for its assessment
Tabela II Vrednosti HAS-BLED skora i zastupljenost kriterijuma za njegovu procenu

	Number of patients (%) **Mean ± SD (total range)** **Median [*IQR*]**
HAS-BLED, score	1.5 ± 0.9 (0–4) 2 [1–2]
low bleeding risk (0–1)	60 (48.4%)
intermediate bleeding risk (2)	51 (41.1%)
high bleeding risk (3–5)	13 (10.5%)
very high bleeding risk (>5)	0
Criteria	
Hypertension (uncontrolled, systolic >160 mmHg)	17 (13.7%)
Renal disease (dialysis, transplant, serum creatinine concentration >2.26 mg/dL or >200 μmol/L)	5 (4%)
Liver disease (cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal)	3 (2.4%)
Stroke history	3 (2.4%)
Prior major bleeding or predisposition to bleeding	2 (1.6%)
Labile INR (unstable/high INRs, time in therapeutic range <60%)	n.a.
Age >65 years old	98 (79%)

	Number of patients (%) **Mean ± SD (total range)** **Median [*IQR*]**
Drug use predisposing to bleeding (aspirin, clopidogrel, NSAIDs)	52 (41.9%)
Alcohol use (≥8 drinks/week)	7 (5.6%)

ALT – serum alanine aminotranspherase; AST – serum aspartate aminotranspherase; AP – serum alkaline phosphatase; *IQR* – interquartile range; INR – international normalised ratio; n.a. – not available; NSAID – non-steroidal anti-inflammatory drug; SD – standard deviation

Following the characterisation of bleeding risk associated with the oral anticoagulant use, the second phase of the study was dedicated to the identification of pDDIs associated with the oral anticoagulants that were present in the patients' therapy prior to hospital admission. In addition to the known pharmacodynamic interactions between antiplatelet agents and anticoagulants resulting in an increased risk of bleeding, labelled risk level D, the purpose of the study was to identify other pDDIs with the expected bleeding outcome that had not been considered in the previous calculation of the HAS-BLED score. The prevalence of pDDIs, excluding those already included in the HAS-BLED score, was 18.5% (23 patients). All interactions were categorised as risk level C and required patient monitoring. Six different types of pDDIs of vitamin K antagonists were identified, namely with drugs used for depression (SSRI, 2 patients, 1.6%), hyperacidity disorders (proton pump inhibitors, 1 patient, 0.8%), hypothyroidism (levothyroxine, 3 patients, 2.4%), oral antidiabetics – sulfonylurea derivatives (7 patients, 5.6%), statins (8 patients, 6.5%), and propafenone (2 patients, 1.6%). The characteristics of the identified pDDIs are listed in Table III.

Table III The characteristics of identified potentially clinically significant drug-drug interactions (pDDIs) of oral anticoagulants

Tabela III Karakteristike identifikovanih potencijalno klinički značajnih interakcija (pLLI) oralnih antikoagulanasa

pDDIs	Interacting drug pairs	Mechanism; risk class; severity	Management of the interaction
Vitamin K antagonists / Selective serotonin reuptake inhibitors (SSRI)	acenocoumarol + sertraline, warfarin + sertraline	**dual mechanism, pharmacodynamic** (SSRIs reduce the concentration of serotonin within platelets, which affects their aggregation) and **pharmacokinetic** (inhibition of VKA metabolism mediated by	The monitoring of patients is necessary due to the increased risk of bleeding; sertraline and citalopram are better choices than other SSRIs in terms of pharmacokinetics.

pDDIs	Interacting drug pairs	Mechanism; risk class; severity	Management of the interaction
		CYP2C9, CYP2D6); C risk class; moderate severity	
Vitamin K antagonists / Sulfonylurea derivatives	acenocoumarol + gliclazide, acenocoumarol + glimepiride, warfarin + gliclazide, warfarin + glimepiride	**pharmacokinetic mechanism** (displacement from plasma protein complexes and competition for hepatic enzymes, especially CYP2C9); C risk class; moderate severity	The monitoring of the increased therapeutic effect of anticoagulants should be performed when introducing or increasing the dose of sulfonylureas, and vice versa. It is also advisable to monitor for increased hypoglycemic effect when starting or increasing the dose of vitamin K antagonists, while a decrease in the hypoglycemic effect can be expected when reducing the dose or discontinuing anticoagulant therapy.
Vitamin K antagonists / Esomeprazole	acenocoumarol + esomeprazole, warfarin + esomeprazole	**pharmacokinetic mechanism** (inhibition of CYP2C19-mediated hepatic metabolism); C risk class; moderate severity	Esomeprazole may increase serum concentrations of vitamin K antagonists. Therefore, an increased monitoring of patients on acenocoumarol or warfarin therapy is advised. The monitoring includes the monitoring of INR values as well as signs of bleeding. There are spontaneous reports of increased prothrombin time or INR associated with the concomitant use of esomeprazole and warfarin during post-marketing surveillance.
Vitamin K antagonists / HMG-CoA reductase inhibitors	acenocoumarol + rosuvastatin, acenocoumarol + simvastatin, phenprocoumon + simvastatin, warfarin + pravastatin, warfarin + rosuvastatin or warfarin + simvastatin	**not clear, pharmacokinetic mechanism** (the displacement of warfarin from plasma protein complexes or competition for hepatic metabolic); C risk class; moderate severity	An increased monitoring of the anticoagulant effect is advised when changing therapy involving statins. An increased anticoagulant effect is expected when introducing a statin into therapy, as well as with each dose increase, and vice versa. A more frequent monitoring of INR values and correction of the dosage regimen of vitamin K antagonists are required. An exception to this interaction is atorvastatin.
Vitamin K antagonists / Propafenone	acenocoumarol + propafenone, warfarin + propafenone	**pharmacokinetic mechanism** (inhibition of CYP1A2-mediated hepatic metabolism of warfarin); C risk class; moderate severity	An increase in the anticoagulant effect is expected when propafenone is introduced into therapy, or when the dose is increased, when there is an increase in systemic exposure to

pDDIs	Interacting drug pairs	Mechanism; risk class; severity	Management of the interaction
			warfarin. The monitoring includes a more frequent monitoring of INR and the appearance of signs of bleeding.
Vitamin K antagonists / Levothyroxine	acenocoumarol + levothyroxine, warfarin + levothyroxine	**dual mechanism, pharmacodynamic and pharmacokinetic**: (a) hypothyroid patients may metabolize vitamin K-dependent coagulation factors more slowly than euthyroid patients; b) plasma protein binding of warfarin may be reduced in hypothyroidism; c) thyroid hormones may increase the affinity of vitamin K-dependent epoxide reductase for warfarin; d) although there is limited evidence at present, thyroid antibodies may modify the effect of warfarin; C risk class; moderate severity	An increased monitoring is advised to detect an increased anticoagulant effect if levothyroxine is introduced into therapy or its dose is increased, while a decrease in the anticoagulant effect is expected when the levothyroxine dose is reduced.

Four patients (3.2%) with an estimated high bleeding risk were exposed to pDDIs, which further increased the bleeding risk. The association between the presence of pDDIs and the estimated HAS-BLED bleeding risk was not statistically significant (Table IV). In the following analysis, we investigated whether the bleeding risk score differs in the presence of pDDIs, which can increase the risk of bleeding. Slightly lower mean and median HAS-BLED scores were found in patients exposed to pDDIs, but the difference was not statistically significant (Table IV).

Table IV The presence of potentially clinically significant drug-drug interactions (pDDIs) of oral anticoagulants in relation to bleeding risk stratification

Tabela IV Prisustvo potencijalno klinički značajnih interakcija lekova (pLLI) u odnosu na stratifikaciju rizika od krvarenja

	Presence of pDDIs with the expected outcome "bleeding" Number of patients (%)		**Test statistics**	**p-value**
HAS-BLED score, high risk of bleeding, number of patients (%)	yes	no		
yes	4 (3.2%)	9 (7.3%)	$X^2 = 1.936$	0.707
no	19 (15.3%)	92 (74.2%)		
HAS-BLED score				
mean ± SD	1.4 ± 0.9	1.5 ± 0.8	t = 1.967	0.473
median [*IQR*]	1 [1–2]	2 [1–2]	U = 1.681	0.455

IQR – interquartile range; SD – standard deviation; t – t-test; U – Mann-Whitney U-test; X^2 – Chi-square test

Discussion

The assessment of bleeding risk is an essential part of the therapy management in patients with AF, in order to achieve the greater safety of anticoagulant therapy. The current European Society of Cardiology (ESC) guidelines recommend the use of the HAS-BLED classification system to assess bleeding risk in patients with non-valvular AF (5). Our results provide a detailed insight into the bleeding risk associated with oral anticoagulants using the HAS-BLED score.

Although our study was conducted in a smaller sample of 124 patients, the results were very similar to numerous large studies. The mean age of the patients of 72 years fits within the narrow range of the mean age of 71–75 years reported in other studies (19–23). A similar result was found for the mean CHA_2DS_2-VASc score. In our study, the mean score was 3.3, or a median of 3, which is fully consistent with the results of other studies (19, 21, 22). Accordingly, 92% of the patients were found to be at high risk of ischaemic stroke (CHA_2DS_2-VASc ≥2), which is in line with literature data of 81–92.2% (19, 20, 22, 24). The latest available data from Serbia on the AF patient population reported a mean CHA_2DS_2-VASc score of 3.20 and a HAS-BLED score of 1.86, which was confirmed in our study (3.29 and 1.51, respectively) (24).

In our study, among the criteria used to assess the HAS-BLED score, the concomitant use of drugs that increase the risk of bleeding (aspirin, clopidogrel or

NSAIDs) was most common in 41.9% of patients. Of the other potentially modifying factors, uncontrolled hypertension was present in 13.7% of the patients, and alcohol consumption was reported by 5.6% of the patients. Previous data on a larger sample of patients with AF reported alcohol abuse in 3–4.1% of cases (23, 24). Non-modifying risk factors for bleeding were less common: chronic kidney disease in 4% (about 7% in the literature) (23), liver disease in 2.4% (about 4% in the literature) (23), history of stroke or transient ischaemic attack in 2.4% (11.6–25.1% in the literature) (19, 23, 24), and previous bleeding in 1.6% of patients (9–14% in the literature) (20, 21, 23).

The use of antiplatelet therapy was recorded in 41.9% of the patients, whereas in other studies this percentage ranged from 7% to 39.1% (19, 21–23). The differences in our study may also be explained by the design, or patient selection. The inclusion criterion in the study was the presence of anticoagulant therapy (100%) in patients with AF, to assess the risk of bleeding depending on the actual therapy. Other studies that included patients with AF (established or newly diagnosed), as well as studies that examined adherence to guideline prescribing recommendations (e.g. ESC), reported a lower prevalence of oral anticoagulants, approximately 90% (24). The authors of a large prospective multicentre study on the AF treatment in the Balkans (n=2663) concluded that aspirin alone or aspirin together with oral anticoagulants is inadequate in patients with stable coronary artery disease (24, 25). The recommendations for patients with AF and stable vascular disease favour the use of oral anticoagulants alone, as the risk of major bleeding increases significantly with dual use, without any additional reduction in the risk of thromboembolism (26, 27). The concomitant use of NSAIDs significantly increases the risk of bleeding and is included as a criterion in the evaluation of the HAS-BLED score. Interestingly, this percentage varied between 5% and 22.4% in the studies, although the studies report almost the same mean age of patients and one would expect a similar prevalence of musculoskeletal disorders requiring chronic NSAID use (19, 21, 23).

According to the HAS-BLED classification, the risk of bleeding was categorised as high in 10.5% of the patients, intermediate in 41.1%, and low in 48.4%. There is a difference in the classification of patients in the high-risk group compared to other studies, in which high risk was reported in 24–36% of the patients (19, 23, 24). One explanation for this is that our study lacked data on the trend of INR values in the period before hospitalisation, i.e. the time spent in the therapeutic range. The low proportion of patients with previous stroke in our study sample also contributes to this result. This difference was subsequently translated to a slightly higher representation of the intermediate-risk subgroup of patients (41.1%), compared with the literature data of 25–37% (23, 24). There is greater consistency in the classification of patients in the low-risk group (27–53.2%) (21, 23, 24).

Although extensive patient registries with detailed documentation and somewhat more regular follow-up of patients are used to validate the scores, it should be noted that data/indicators on the degree of patient adherence to oral anticoagulant therapy are often missing, possible interactions with other drug groups not included in the score criteria are not considered (e.g. SSRIs), and data on polymorphisms that may affect the body's

exposure to the drug, whether vitamin K antagonists or DOACs, are lacking. These aspects could explain the variability of the study results. As shown in the results of the second part of the study, the prevalence of pDDIs, excluding those already included in the corresponding scores for the initial assessment of bleeding, was 18.5% (23 patients). All interactions were classified as risk level C, i.e. they required patient monitoring. Six different types of interactions of vitamin K antagonists, with drugs for the treatment of depression (SSRIs), hyperacidity (esomeprazole), hypothyroidism (levothyroxine), antidiabetics (sulfonylurea derivatives), statins (except atorvastatin) and propafenone were identified. The interactions were described by different mechanisms, at the level of pharmacokinetics or pharmacodynamics. Our findings point to the need for a comprehensive therapy assessment in patients with AF taking oral anticoagulants, as patients of advanced age have multiple comorbidities and consequently additional therapy that may jeopardise the efficacy or safety of anticoagulant therapy. An insight into pDDIs monographs not only provides a risk assessment, but could also inform clinicians about the alternative drugs available or other prospective measures to reduce the risk of adverse bleeding events.

According to the results of the statistical analysis, the mean value of the HAS-BLED score was lower in the patients who simultaneously had a potential drug interaction with the expected bleeding outcome, i.e. which could potentially further increase the risk of bleeding, which is a positive result of the study, even if it is not confirmed by the level of statistical significance. Furthermore, of the 23 patients exposed to pDDIs that could further increase the risk of bleeding, only four patients were categorised as being at high risk of bleeding according to the HAS-BLED score. However, what is not evident from the general classification of drug interaction risks in the Lexi-Interact database is the presence of other risk factors in the patient that may increase the possibility of the manifestation of a drug interaction, i.e. the occurrence of an adverse drug event. The presence of cardiovascular disease has been shown to be a significant factor in the pharmacokinetic and pharmacodynamic variability of drugs, in addition to the expected increase in systemic exposure to the drug in the presence of liver or kidney disease as the main elimination organs (28–31).

The estimated high bleeding risk should help the clinician when initiating anticoagulation therapy in patients with AF, and later when monitoring patients on anticoagulation therapy by “signalling” which patient needs more frequent monitoring and control, which is particularly important in the era of electronic health records. The use of the above-mentioned score is also important from the point of view that some risk factors are potentially modifiable (e.g. uncontrolled hypertension, concomitant use of aspirin or NSAIDs, alcohol consumption). Therefore, a useful classification system should recognise these modifiable risk factors and alert the clinician to the need to address them in a timely manner (18, 21). Bleeding risk assessment is also a dynamic process that should be available and applicable at all stages of the management of patients with AF: at diagnosis, while they are not yet receiving antithrombotic therapy, and after the initiation of therapy. An estimated high risk of bleeding is not a reason to discontinue or

withhold treatment with oral anticoagulants, as the estimated benefit of reducing the risk of ischaemic stroke outweighs the risk even in these patients (21).

The main limitations of the study emerge from its retrospective design. The data on the patients' therapy and indications were collected from medical charts, limiting the reliability and completeness of data. A prospective study with more detailed patient information, follow-up and laboratory parameters would be necessary. A multicentre study would diminish possible differences in prescribing patterns or ethnic background, enabling better generalisability of the data. Other limitations are closely related to the drug interaction screening software, with significant differences and shortcomings being identified among pDDI screening databases. To improve the sensitivity during pDDIs detection, one of the solutions could be the combined simultaneous use of two such software programs (32).

Conclusions

In our study, an increased risk of bleeding due to use of oral anticoagulants was found in a total of 10.5% of the patients. The concomitant use of drugs that may increase the risk of bleeding was included as a criterion in the HAS-BLED score, with only aspirin, clopidogrel and NSAIDs listed. However, a prevalence of 18.5% of potentially clinically significant drug interactions that may increase the risk of bleeding and were not already included in the corresponding bleeding score was identified. Six different types of interactions of vitamin K antagonists, with drugs for the treatment of depression (SSRIs), hyperacidity (proton pump inhibitors), hypothyroidism (levothyroxine), antidiabetics (sulfonylurea derivatives), statins and propafenone were identified. There is a higher risk of potentially clinically significant interactions that may increase the risk of bleeding due to older age, the presence of concomitant diseases and the associated polypharmacy. The present study has several limitations due to its retrospective design and the use of a single pDDIs screening software. Although the generalisability of the results is limited, our study highlights the need for more vigilant, continuous follow-up of the patients, accompanied with the research on patients' knowledge, adherence, medicine-related practices and use of supplements which could interact with anticoagulants. When treating and monitoring patients with AF who receive oral anticoagulant therapy, the use of scores to assess the risk of bleeding should be supplemented by information from drug interaction sources in addition to the mandatory clinical assessment, in order to optimise the benefit/risk ratio of anticoagulant therapy.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest to disclose, including financial, personal or other relationships.

Author contributions

MK: conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft; SVK: conceptualization, data curation, writing – editing; MĆ: investigation, writing – editing; MJ: investigation, writing – editing; KV: investigation, writing – editing; **PS**: conceptualization, data curation, supervision, writing – editing; SR: conceptualization, investigation, data curation, supervision, writing – editing; BM: conceptualization, data curation, supervision, project administration, writing – editing.

All authors were responsible for critically revising this work for important intellectual content. All authors are accountable for all aspects of this work.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author MK upon reasonable request.

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Rizik od krvarenja i interakcije lekova kod pacijenata sa atrijalnom fibrilacijom koji su na oralnoj antikoagulantnoj terapiji

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Kratak sadržaj

Pacijenti sa atrijalnom fibrilacijom (AF) imaju povećan rizik od tromboembolijskog moždanog udara i mortaliteta od svih uzroka. Pored antiaritmika, lečenje AF podrazumeva upotrebu antikoagulanasa, koji značajno smanjuju rizik od ishemijskog moždanog udara, ali nose rizik od krvarenja. Ova studija je imala za cilj da proceni rizik od krvarenja kod pacijenata sa AF na oralnoj antikoagulantnoj terapiji i da odredi učestalost potencijalno klinički značajnih interakcija lekova (pLLI) koje mogu dodatno povećati rizik od krvarenja. Urađena je retrospektivna opservaciona studija na Odeljenju za kardiologiju Kliničko-bolničkog centra „Bežanijska kosa". Kvantifikacija rizika od krvarenja je izvršena korišćenjem HAS-BLED skora. *Lexi-Interact* je korišćen za identifikaciju pLLI. Studija je obuhvatila 124 pacijenta (srednja starost 72 godine, žene 50,8%). Kod 10,5% pacijenata procenjen je visok rizik od krvarenja usled primene oralne antikoagulantne terapije. Prevalenca pLLI koje mogu dodatno povećati rizik od krvarenja iznosila je 18,5%. Interakcije su obuhvatile kombinacije antagonista vitamina K sa selektivnim inhibitorima ponovnog preuzimanja serotonina, inhibitorima protonske pumpe, levotiroksinom, derivatima sulfonilureje, statinima i propafenonom. Prilikom vođenja i praćenja pacijenata sa AF na oralnoj antikoagulantnoj terapiji, korišćenje skorova za procenu rizika od krvarenja treba da bude dopunjeno informacijama o interakcijama lekova, kako bi se optimizovao odnos koristi i rizika antikoagulantne terapije.

Ključne reči: ishemijski moždani udar, tromboembolijski događaj, antikoagulantna terapija, interakcije lekova, krvarenje