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ORIGINAL ARTICLE

Comparison of vitamin K and non-vitamin K oral anticoagulants and the bleeding frequency in the emergency department

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Abstract

Introduction Safety studies of anticoagulant therapy have so far been conducted on many subjects in controlled conditions (i.e., clinically monitored) and demonstrated the noninferiority of new ones over old anticoagulant drugs. Data on the propositions for the presence of symptoms and signs of bleeding among various anticoagulants in the emergency department indicate that these data do not match the data published so far.

Aim The aim of the study was to investigate the differences in the frequency of bleeding and bleeding-related symptoms as a reason for emergency department attendance in patients on anticoagulant therapy.

Methods The study included patients from the emergency department of University Hospital for one year, who were on anticoagulant therapy and who met the inclusion criteria. Out of a total of 595 patients, 409 were on warfarin (68.74%), and the rest were taking direct oral anticoagulants (DOAC): dabigatran 71 (11.93%), rivaroxaban 66 (11.09%) and apixaban 49 (8.23%).

Results Out of 409 patients taking warfarin, 34.4% were adequately anticoagulated with the frequency of bleeding 13.7%, while in 57.2% of patients, PT INR was higher than the reference values with the frequency of bleeding 15.0%. A comparison between all DOAC groups and adequately anticoagulated warfarin patients in the frequency of bleeding and bleeding-related symptoms as a reason for emergency attendance yielded a difference that was marginally statistically significant (Pearson Chi-Square = 7.554, p = 0.052).

Conclusion Monitoring the frequency of bleeding and bleeding-related symptoms in patients on oral anticoagulant therapy as a reason for emergency department attendance may be a new safety and efficacy factor in real-life patient scenarios.

Keywords Warfarin · Direct oral anticoagulants · Emergency department · Safety

1 Introduction

Oral anticoagulants (OAC) are drugs that are prescribed to treat or prevent arterial and venous thromboembolic events (VTE). The most common indications for their use are the treatment of deep vein thrombosis of the lower extremities (DVT), pulmonary embolism (PE), and the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (NVAF) [1]. Due to the aging of the world's population, primarily in Western countries, there is an increase in the prescription of anticoagulant drugs [2].

The oldest and most prescribed OAC is the vitamin K antagonist, warfarin. The main advantages of warfarin compared to direct oral anticoagulants (DOAC) is the ability to control its effectiveness routinely adequately, by measuring prothrombin time international ratio (PT INR) and

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the existence of antidotes, vitamin K. Warfarin is currently the only OAC that is indicated in patients with implanted artificial heart valves [3]. Disadvantages of warfarin are the higher rate of bleeding, its narrow therapeutic range, the influence of many external factors such as diet and other drugs on its effectiveness, and consequently the need for frequent determination of PT INR [4]. One of the major warfarin limitations is that it takes time to reach the therapeutic range. Although the anticoagulant effect dominates, an initial procoagulant effect is possible in the initiation of warfarin, which requires the initial concomitant administration of warfarin with low molecular weight heparin [3].

After 2007, DOAC began to appear on the market. In randomized clinical trials, equal efficacy in the treatment of NVAF and VTE (if not better) was demonstrated while from the point of view of side effects, they were also comparable to warfarin [5]. The main advantage over warfarin is that they are administered in fixed doses (once or twice a day) and the dosing is titrated mostly according to renal function based on estimated glomerular filtration rate (eGFR) [6].

Dabigatran is a direct inhibitor of thrombin (factor II). Since it is eliminated mostly in the urine and to a lesser extent in the feces, its dosage depends on the eGFR value. The advantage of dabigatran over other DOAC is that there is a monoclonal antibody that reverses its effect immediately after application—idarucizumab [7].

Rivaroxaban and apixaban are direct inhibitors of factor Xa. Rivaroxaban has a dual excretion: glomerular filtration and tubular secretion and feces after metabolic degradation in the liver [8], and therefore the dose should be reduced when treating NVAF if the eGFR is < 50 ml/min/m^2. The main advantage of rivaroxaban is that it is administered once daily in the chronic application and after the end of the acute phase of treatment due to better patient adherence [9]. Apixaban is administered twice daily, and the dose is adjusted for eGFR as well as other DOACs. Compared to other DOACs, apixaban is the least excreted in the urine, and its safety has been confirmed in patients with reduced eGFR [10]. Studies conducted on many subjects taking DOAC as their significant advantage showed eGFR preservation over time compared to those taking warfarin [11].

The dose efficacy of DOAC is not routinely assessed by coagulation parameters (it can be measured by measuring the thrombin time or by determining factor Xa levels) but the eGFR-adjusted dose is mostly considered to be adequately effective. The data obtained for the purpose of DOAC safety in randomized clinical trials were in controlled conditions in which patients were regularly and adequately monitored by investigators [12]. In real life, significant proportions of patients do not come to the prescribed examination appointment or do not have adequate monitoring as on study visits. Also, checking the patient's adherence to the prescribed method of taking the medicine and not skipping doses is not easily feasible.

In this study, we sought to determine the differences in the frequency of symptoms and signs of bleeding as a reason for emergency attendance between different OACs and to answer the question of the significance of the results obtained.

2 Methods

2.1 Study design and ethics statement

This retrospective study included patients on OAC examined through the internal medicine emergency department at University Hospital Merkur in the period from January 1, 2018. to December 31, 2018. The study was conducted following the Declaration of Helsinki and approved by the Hospital's Ethics Committee. All patients included in the study received both written and oral information about the study and signed written informed consent.

2.2 Patients

There was a total of 595 patients who met the criteria for the study [age > 18 years, eGFR > 30 ml/min/m^2, patients on anticoagulant therapy: warfarin 409 (68.74%), dabigatran 71 (11.76%), rivaroxaban 66 (11.09%), apixaban 49 (8.23%)]. Demographical data were collected (age, gender), anthropometric (body weight and height, based on which the body mass index (BMI) was calculated) and anamnestic data (arterial hypertension, diabetes type 2, hyperlipidemia, heart disease), laboratory findings of serum creatinine and estimated glomerular filtration rate (eGFR). Exclusive criteria were factors that increase the tendency of bleeding: known malignancy, chronic renal disease with eGFR $<$ 30 ml/min/m^2, and in women, pregnancy and puerperium, oral contraception, and hormone therapy as well as patients with inflammatory bowel disease given the increased risk of major bleeding in patients during anticoagulation [13, 14].

Patients who presented with manifest gastrointestinal and urinary bleeding were included in the study. Also, patients who had subcutaneous hematomas were included as patients with signs of bleeding. All patients with signs of bleeding were included in the group of patients with positive symptoms and signs of bleeding. Patients with symptoms of anemia (weakness, fatigue, malaise, lethargy, etc), but with normal hemoglobin concentration weren't included in the group of patients with symptoms and signs of bleeding. In case of a positive laboratory test for anemia (hemoglobin values lower than the lower normal limit) and with symptoms of anemia, these patients were included in the study.

2.3 Anticoagulant therapy

The study counted patient arrivals because some patients repetitively reported to the emergency department. In all patients, the adequacy of the dose of DOAC therapy was checked by measuring renal function at each emergency attendance. The value of eGFR was calculated using a creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [15].

Only adequately DOAC-dosed patients taking more than one month (dabigatran 2 × 150 mg, rivaroxaban 20 mg, apixaban 2 × 5 mg) were included in the study. Patients in the rivaroxaban group who used small doses (10 mg for DVT and PE prevention) were not included in this investigation as well as all the DVT patients on rivaroxaban while there were no patients with this indication in the dabigatran and apixaban group.

Warfarin dosing adequacy was measured by PT INR values [3]. Thirty-four patient-arrivals did not have analyzed coagulation status (PT INR) while the others were divided according to PT INR values into two groups: adequately anticoagulated, PT INR in therapeutic width (141 patient-arrivals) and inadequately anticoagulated (PT INR higher than the therapeutic range) (234 patient-arrivals). PT INR for adequately anticoagulated patients with a mechanical heart valve is in the range of 2.5–3.5 and for others the range of 2.0–3.0 [16].

2.4 Statistical analysis

The normality of data distribution was analyzed by the Shapiro-Wilk test. Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± SD (standard deviation) for normally distributed continuous variables or as the median and interquartile range (IQR) for continuous variables with the nonparametric distribution. Groups were compared by independent sample t-test for normally distributed continuous variables or by Mann-Whitney or Kruskal-Wallis test for continuous variables with a nonparametric distribution. Categorical variables were compared by Pearson chi-square (χ^2) or Fisher exact test as appropriate. All statistical tests were two-sided and intergroup differences with $\alpha < 0.05$ were considered significant. All reported P values were uncorrected unless stated otherwise. Statistical analysis was performed using SPSS Statistics software (IBM Corp., Armonk, NY, USA).

3 Results

Indications for the use of OAC in the study population are listed in Table 1. There were no statistical differences in demographical data and BMI (kg/m^2) between four groups of patients (28.49 (3.8) for warfarin (27.47 inadequately/29.02 for adequately), 28.47 (3.7) for dabigatran, 28.42 (3.6) for rivaroxaban, and 27.7 (3.5) for apixaban group, p = 0.20). Patients in the apixaban and dabigatran group have 3 and more than 3 comorbidities (diabetes, hyperlipidemia, arterial hypertension, heart disease) as well as patients in group of inadequately anticoagulated patients than others (less than 3 comorbidities).

28% of patients in apixaban, 25% in dabigatran, 15% in rivaroxaban, 21% (30/141) in the adequately anticoagulated and 29% (70/234) in the inadequately anticoagulated warfarin group took concomitant medication (acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs), or statin) due to comorbidities. In addition, 90% of patients in the rivaroxaban group, 50% of patients in the apixaban group, 60% of patients in the dabigatran group, and all patients in the warfarin group were on proton pump inhibitors therapy.

The basic data of the examined patients are shown in Table 2. Out of 409 patients taking warfarin, 141 were adequately anticoagulated (34.4%), while in 234 patients (57.2%) PT INR was higher than the reference values (with

Table 1 Indication for oral anticoagulants therapy use

Indication for oral anticoagulants	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Atrial fibrillation	303 (72.26%)	68 (95.77%)	63 (95.38%)	44 (87.80%)
Deep venous thrombosis	64 (15.69%)	0	0	0
Pulmonary embolism	13 (3.19%)	1 (1.41%)	1 (1.54%)	0
Atrial fibrillation and deep venous thrombosis	4 (0.98%)	1 (1.41%)	1 (1.54%)	0
Atrial fibrillation and pulmonary embolism	2 (0.49%)	0	0	1 (2.44%)
Atrial fibrillation, deep venous thrombosis and pulmonary embolism	1 (0.24%)	0	0	4 (9.76%)
Deep venous thrombosis and pulmonary embolism	11 (2.70%)	1 (1.41%)	1 (1.54%)	0
Artificial mechanical heart valve	8 (1.96%)	0	0	0
Atrial fibrillation and artificial mechanical heart valve	1 (0.24%)	0	0	0
Coronary heart disease	1 (0.24%)	0	0	0

Table 2 Patients characteristics

	Overall (N = 595, %)	Warfarin (N = 409, %) Well/poor controlled (N = 141/234)	Dabigatran (N = 71, %)	Rivaroxaban (N = 66, %)	Apixaban (N = 49, %)	P-value overall
Age (years)	76.0 (67.0-84.0)	76.0 (72.0/80.0) (67.0-81.0)	78.0 (71.0–83.0)	76.0 (69.75–80.0)	78.0 (69.5–84.0)	0.089
Gender						**0.007**
Male	289 (48.6)	215 (52.6) (N = 116/99)	22 (31.0)	29 (43.9)	23 (46.9)	
Female	306 (51.4)	194 (47.4) (N = 90/104)	49 (69.0)	37 (56.1)	26 (53.1)	
Bleeding						**0.037**
Yes	93 (15.6)	56 (N = 20/36) (13.7/ 15.0)	16 (22.5)	8 (12.1)	13 (26.5)	
No	502 (84.4)	353 (86.3)	55 (77.5)	58 (87.9)	36 (73.5)	
Gastrointestinal bleeding						0.056
Yes	65 (10.9)	40 (9.8) (N = 11/29, 7.5/11.9)	12 (16.9)	4 (6.1)	9 (18.4)	
No	530 (89.1)	369 (90.2)	59 (83.1)	62 (93.9)	40 (81.6)	
Urinary bleeding						0.351
Yes	7 (1.2)	4 (1.0) (N = 1/3)	2 (2.8)	1 (1.5)	0 (0.0)	
No	588 (98.2)	405 (99.0)	69 (97.2)	65 (98.5)	49 (100.0)	
Skin bleeding						0.290
Yes	18 (3.0)	10 (2.4) (N = 1/9)	2 (2.8)	3 (4.5)	3 (6.1)	
No	577 (97.0)	39 (97.6)	69 (97.2)	63 (95.5)	46 (93.9)	
Epistaxis–nose bleeding						0.349
Yes	3 (0.5)	2 (0.5) (N = 0/2)	0 (0.0)	0 (0.0)	1 (2.0)	
No	592 (99.5)	407 (99.5)	71 (100.0)	66 (100.0)	48 (98.0)	
Transfusion						0.186
Yes	31 (5.2)	19 (4.6) (N = 3/16)	3 (4.2)	3 (4.5)	6 (12.2)	
No	564 (94.8)	390 (95.4)	68 (95.8)	63 (95.5)	43 (87.8)	
Hospitalization						0.175
Yes	195 (32.8)	135 (33.0) (24.8/38.0)	21 (29.6)	17 (25.8)	22 (44.9)	
No	400 (67.2)	274 (67.0)	50 (70.4)	49 (74.2)	27 (55.1)	

the range PT INR of 4-5.6 in inadequately anticoagulated patients, with the frequency of bleeding 15 %) (34 patients did not have PT INR measured).

The frequency of bleeding and bleeding-related symptoms as a reason for emergency attendance in OAC patients differed between the study groups and was highest in the apixaban group (26.5%) compared to dabigatran (22.5%), adequately anticoagulated warfarin (13.7%), and rivaroxaban group (12.1%) (Pearson Chi-Square = 8.654, p = 0.037). A comparison between all DOAC groups and adequately anticoagulated warfarin patients in the frequency of bleeding and bleeding-related symptoms as a reason for emergency attendance yielded a difference that was marginally statistically significant (Pearson Chi-Square = 7.554, p = 0.052). In the study, patients taking apixaban had more frequent transfusion treatment (12.2%) in the emergency department (Pearson Chi-Square = 7.427, p = 0.079) compared with the groups on other anticoagulants (warfarin all patients 4.6%, warfarin adequately anticoagulated 3.5%, dabigatran 4.2%, rivaroxaban 4.5%).

Hemoglobin values differed significantly between the study groups and were lowest in the group of patients taking apixaban (123 g/l [104–136]) while in the other groups, they were for warfarin (adequately anticoagulated) 133 g/l [115.5–146.5], warfarin (all patients) 128 g/l [109–142.25], dabigatran 127 g/l [103–135], rivaroxaban 134 g/l

[119.5–145.25], p = 0.022. There were also significant differences between the groups on apixaban and warfarin (adequately anticoagulated) (p = 0.039), apixaban and rivaroxaban (p = 0.041), dabigatran and warfarin (adequately anticoagulated) (p = 0.040) and dabigatran and rivaroxaban (p = 0.047).

The frequency of hospitalization was highest in patients on apixaban (44.9%), compared with the group with adequately anticoagulated warfarin (24.8%), dabigatran (29.6%), and rivaroxaban (25.8%) (Pearson Chi-Square = 7.550, p = 0.175). There was a significantly higher percentage of hospitalized in the group of inadequately anticoagulated patients (38%) compared to 24.8% of adequately anticoagulated patients on warfarin (Pearson Chi-Square = 6.939, p = 0.009).

4 Discussion

This retrospective study from one Hospital Center investigated the difference in the frequency of emergency attendance due to symptoms and signs of bleeding in patients on different OACs. This study did not examine differences in the efficacy of different OACs. Bleeding is the most common side effect of anticoagulant treatment, and previous research has shown that patients taking DOAC therapy due to atrial fibrillation had a slightly higher risk of bleeding compared with those on warfarin [17]. In this study, the frequencies of bleeding and bleeding-related symptoms were observed as a reason for emergency department attendance among all reasons in patients taking OAC therapy that meet inclusion criteria. According to the data obtained from the Croatian Institute of Public Health for 2018 (and data on OAC vendors), the ratio of prescribing warfarin and DOAC in the Republic of Croatia was 2:1 (in our study 2.2:1) which roughly corresponds to the general ratio [2]. From the above, we can see that the data in our study are proportional to the data in the general population.

DOACs are generally compared to warfarin as an older commonly accepted drug. Such studies are generally controlled, and patients are intensively monitored by the competent physician who prescribed anticoagulant therapy and there is a possibility of deviation from the actual data (real-life scenario). These data can be obtained from national registries for a particular diagnosis such as those for NVAF [18]. In this study, we used data from only patients that meet the criteria and who are taking warfarin. We also included a special group of patients on warfarin who were adequately anticoagulated but adequately controlled patients on warfarin are not more than a half and this could be limitation (PT INR in reference values at the time of measurement). Since DOACs are dosed mostly according to eGFR values in the study we did not include patients with severely impaired renal function. Safety studies of different OACs have generally been performed in patients with NVAF for comparability with warfarin. These studies mostly did not include patients suffering from DVT and PE, which then provides only safety data in patients with NVAF. All these studies suggest mostly similar data and suggest that rivaroxaban would be associated with a higher frequency of bleeding, while apixaban and dabigatran had a lower frequency of bleeding [19, 20].

In this retrospective observational study, we observed a higher frequency of symptoms and signs of bleeding in emergency patients, in patients taking dabigatran and apixaban compared to rivaroxaban. Yet, we observed the highest number of hospitalizations in the apixaban group compared to other DOACs. Patients in the apixaban and dabigatran group have more comorbidities which might explain more frequent bleeding events. A large proportion of patients (28% in apixaban and 25% in the dabigatran group) take concomitant medication (acetylsalicylic acid or NSAIDs or statins) due to comorbidities and this may also lead to a higher frequency of bleeding. In addition, 90% of patients in the rivaroxaban group, 50% of patients in the apixaban group, 60% of patients in the dabigatran group, and all patients in the warfarin group were on proton pump inhibitors therapy. The authors of the ORBIT-AF II Registry state that over and underdosing is associated with an increased risk of adverse events and that 1 in 8 respondents does not have an adequate dose of DOAC [21]. Due to twice daily administration, it is to be expected that patients taking DOAC twice daily will be more likely to forget their therapy, ie to be hypo-dosed. In this way, we would expect these patients to have the less frequent side effect of DOAC (ie bleeding). The above can sample a reduced concentration of the drug in the blood and better safety. In our study, patients who took DOACs prescribed twice a day had a higher frequency of symptoms and signs of bleeding as a reason for presenting to the emergency department.

In a systematic review and meta-analysis of data from randomized controlled trials, authors confirmed that there was no significant difference in the risk of major gastrointestinal bleeding between patients receiving DOAC vs conventional treatment [22]. Analyzing the differences in the frequency of hospitalization among the groups that were on warfarin, a significantly higher percentage of hospitalized was in the group of inadequately anticoagulated (61.38%) versus adequately anticoagulated (33.01%). Our data which included also urinary tract bleeding and subcutaneous hematoma suggest that there is a difference in the frequency of symptoms and signs of bleeding as a reason for emergency department attendance.

Different risk factors are distributed differently in different populations, so if we observe only one population, we cannot apply the data to other populations. One example is

blood groups that are known to have a lower susceptibility to venous thromboembolisms (blood group zero) where there is a different distribution of blood groups among different populations that may affect these results, efficacy, and safety [23]. The specific disadvantages of DOAC therapy regarding the region in the Republic of Croatia are that they require additional payment. Three different DOACs were present on the Croatian market during the duration of this study: dabigatran, rivaroxaban, and apixaban. We have previously shown that patients with NVAF who are on DOACs and are taking more than 3 different medications have a greater propensity for adverse events and that drug-drug interaction (DDIs) is one of the most important problems in everyday practice. Coadministration of statins with dabigatran worsens clinical outcomes and a similar interaction might be seen with verapamil and amiodarone [16].

It is known that many drugs can interfere with the metabolism of different OACs, but this is rarely considered in the emergency department [23]. As the elderly population suffers from numerous comorbidities, the frequency of polypragmatism is extremely frequent, which can lead to more frequent episodes of toxicity or ineffectiveness of prescribed therapy. Therefore, future research should take this type of analysis as an additional parameter [24]. In the group of patients taking dabigatran, the majority were women, which could be an additional confounding factor given that potential vaginal bleeding has not been included in this study. It is planned to conduct additional research in the emergency gynecological department to determine if there are differences in the frequency of bleeding in women taking OAC therapy. A further study should be conducted that would include all patients who come to the emergency department and thus include those at most risk, ie those with very low eGFR.

Blood hemoglobin values during emergency treatment differed between groups. Hemoglobin values were lower in the apixaban and dabigatran group in comparison to the adequately anticoagulated warfarin group and rivaroxaban group. This correlates with the fact that major bleedings are more common in the apixaban and dabigatran groups [25, 26]. The results indicated that there was a difference in the frequency of bleeding and bleeding-related symptoms as a reason for reporting to the emergency department in patients taking OAC. Although this study was conducted in the emergency department of only one hospital and only one specialty of the emergency service (internal medicine) in a period of one year, it showed statistically significant results so we can claim a significant difference between the examined groups. Further research is needed to include a larger number of respondents in different emergency services (gynecology, otorhinolaryngology, etc) and in several centers (multicenter studies). Additional parameters (more detailed description of the population, DDI, comorbidities) should be examined to determine the real potential of the proposed research.

This study did not examine the effectiveness of different OACs, but only the difference in the frequency of symptoms and signs of bleeding as the main reason for presenting to the emergency department. In this research, we presented all patients who met the inclusion criteria, and the population of patients included in the analysis was of an older age.

4.1 Limitations

The disadvantage of comparing the study population to the general population on OAC therapy is the inability to obtain stratification data from the Croatian Institute of Public Health for 2018. Also, as a disadvantage of this research, it can be stated that it was conducted on patients that are medically processed in internal medicine emergency service and who had the necessary laboratory parameters for comparison. The main tendency of the research was to determine whether there are differences between these groups and to open the possibilities of new research in this field. One of the additional disadvantages of this study is the possible DDI, which we did not investigate because not all patients had the necessary data for comparison, and which could have an impact on the results of the study [27, 28].

4.2 Conclusion

The reasons for patients who take OAC therapy for the emergency department attending are different among different OACs. Our experience from this study indicates that rivaroxaban did not show the same frequency of symptoms and signs of bleeding as a reason for emergency department attendance as other DOACs, but generally, patients taking DOAC are not at increased risk of bleeding and do not have a higher frequency of emergency attendance due to symptoms and signs of bleeding compared to warfarin, which further confirms their safety.

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Data availability statement The data presented in this study are available on a specific request from the corresponding author.

Declarations

Institutional review board statement The study was conducted following the Declaration of Helsinki and approved by the Hospital's Ethics Committee.

Informed consent All patients included in the study received both written and oral information about the study and signed written informed consent.

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