BLEEDING AS A MAJOR CAUSE OF EMERGENCY ATTENDANCE IN PATIENTS ON DIFFERENT ORAL ANTICOAGULANTS

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Background: Anticoagulant therapy is increasingly used in the world because the population is getting older and conditions that require anticoagulant treatment are more frequent. Since bleeding occurs in patients taking warfarin, as well as in patients taking direct oral anticoagulants, the goal of this study was to determine whether there was a difference in the frequency of bleeding as a major cause of emergency attendance between these two groups. *Methods*: The study included 83 patients examined in Emergency Unit, Merkur University Hospital from December 1, 2018 until June 1, 2019, who were taking anticoagulant therapy and had chronic kidney disease (stage 2-4). Group A included 22 patients (8 male) using warfarin and group B included 61 patients (19 male) taking direct oral anticoagulants. The median age was 80.77 years in group A and 80.95 years in group B. There were no differences in comorbidities. Doses of anticoagulants were adjusted to the glomerular filtration rate. *Results*: In group A, the main cause of emergency attendance was bleeding (mostly gastrointestinal) in 15 (68.18%) group A patients, whereas in group B bleeding was the main cause in 21 (34.42%) patients. The χ^2-test was used to assess difference in the frequency of bleeding as the cause of emergency attendance (χ^2=7.501; $p<0.01$). *Conclusion*: Study findings suggested that patients using direct oral anticoagulants as anticoagulant therapy adjusted to renal function had significantly less bleeding as the cause of attendance at Emergency Unit as compared to patients taking warfarin.

KEY WORDS: anticoagulant therapy, bleeding, emergency department, chronic kidney disease

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INTRODUCTION

Anticoagulant drugs are used to prevent the occurrence of complications of certain conditions (prophylactic use), whereas in some states it is administered as a medication (therapeutic use). Atrial fibrillation (AF), deep vein thrombosis, pulmonary embolism, and other hypercoagulable conditions are the most common causes for the introduction of anticoagulant therapy (1). Mostly, anticoagulants are divided into two groups: vitamin K antagonists (VKA) such as warfarin, and nonVKA or direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban. Warfarin has been the major anticoagulant drug for many years, affecting its wide application and low cost (1). It blocks the enzyme vitamin K epoxide reduc-

tase, which turns vitamin K into its active form. Without sufficient amount of active vitamin K formulation, there will be no adequate formation of factors II, VII, IX and X that reduce blood coagulability. Warfarin is administered *per os* once daily, provided that the dose is titrated to the values of the International Normalized Ratio (INR, blood coagulation parameter). When warfarin is introduced, heparin therapy is required until the target INR is reached. The INR is generally maintained in the range of 2-4. Warfarin is removed from the body *via* liver enzymes (1). The fact that optimal doses of INR are difficult to achieve and that the therapeutic width of the drug itself is very narrow has led to the need for new medicines. DOACs have appeared on the market in the last 10 years. Dabigatran is a factor IIa inhibitor, whereas rivaroxaban, edoxaban and apixaban are factor Xa inhibitors (2). The advantage over warfarin is that they are applied at fixed doses and their application does not require INR control to evaluate efficacy. Caution is advised when dosing DOAC in patients with impaired renal function and with drug interactions (3,4). Renal function is estimated by glomerular filtration rate (eGFR). In case of eGFR less than 50 $mlmin^{-1}1.73m^2$, it is necessary to adjust the dose of dabigatran and rivaroxaban (4). Bleeding (gastrointestinal and genitourinary) is the most common complication of taking anticoagulant therapy (5). The CHADS-VASc score is used to assess the risk in patients with AF and includes the following: congestive heart failure (or systolic left ventricular dysfunction), hypertension, age >65 years, diabetes mellitus, previous stroke or transient ischemic attack or thromboembolism, vascular disease and female sex, with a number of points the sum of which (0-9) ultimately show the degree of the risk of stroke in these patients (6). The HAS-BLED score (includes hypertension data, abnormal renal and liver function, stroke in history, previous bleeding, INR that is difficult to maintain in the set values, age and drug or alcohol consumption) shows the risk of major bleeding with points on this scale (0-9) (7).

The likelihood of bleeding increases with age due to the older population having many associated diseases and taking more therapy medications. Drugs that affect the permeability of glycoprotein reagents (P-gp) and particular CYP enzymes in the liver can significantly affect the concentration of dabigatran; statins can increase dabigatran concentration in the blood by 200% and result in increased efficacy of dabigatran (8).

The aim of this study was to determine the prevalence and type of bleeding between warfarin and DOACs in emergency patients taking these agents for the previously known indications adjusted to the degree of kidney disease.

PATIENTS AND METHODS

The study included 83 patients (out of 3488 patients examined within 7 months) from Emergency Unit, Department of Internal Medicine, Merkur University Hospital during the period from December 1, 2018 until June 1, 2019. All patients involved in the study were taking anticoagulant therapy and had AF.

Patients were divided into two groups, as follows: group A (22 patients, 8 male) were receiving warfarin and group B patients (61 patients, 19 male) were taking DOACs (dabigatran 29, rivaroxaban 20 and apixaban 12 patients). Rivaroxaban was started at a dose of 20 mg once daily and dabigatran at a dose of 150 mg twice daily in patients with eGFR ≥50 $mlmin^{-1}1.73m^2$. In patients with eGFR >30 and <50 $mlmin^{-1}1.73m^2$, rivaroxaban was started at a dose of 15 mg once daily and dabigatran at a dose of 110 mg twice daily. Apixaban was started at 5 mg twice daily. The mean age was 80.72±7.89 years in group A and 80.95±6.78 years in group B. All patients were under appropriate therapy for other comorbidities (duration of hypertension 12±5 years, duration of AF 6±3 years, body mass index (BMI) 34.6±4.1 kg/m^2).

Patients were compared and stratified according to the CHADS-VASc score (3.65 and 3.74 in group A and B, respectively) and HAS-BLED score (5.35 and 4.7 in group A and B, respectively), as well as according to eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (42.71±15.02 and 47.42±16.19 $mlmin^{-1}1.73m^2$ in group A and B, respectively). A HAS-BLED score ≥3 suggests an increased risk of experiencing bleeding complications (7). This study was approved by the local Ethics Committee and a written informed consent to participate was provided by study patients.

The STATISTICA 13.1 software was used to compare total bleeding between the groups and χ^2-test to test differences between the groups.

RESULTS

The main cause of emergency attendance was visible bleeding in 43 (51.81%) patients. Total number of patients divided according to localization of verified bleeding depending on the drug used is shown in Table 1. There were no statistically significant between-group differences in renal function, age, duration of hypertension, AF and CHADS-VASc score (Table 1).

Table 1. *Percentage of bleeding according to localization and drug used*

Verified bleeding	Warfarin, % (n)	DOACs, % (n)
Bleeding from lower gastrointestinal tract	46.67% (7/15)	42.86% (9/21)
Bleeding from upper gastrointestinal tract	33.33% (5/15)	28.57% (6/21)
Hematuria	13.33% (2/15)	23.81% (5/21)
Skin hematoma	6.67% (1/15)	4.76% (1/21)
Total (all patients taking certain drug)	68.18% (15/22)	34.42% (21/61)

DOACs = direct oral anticoagulants

Patients on DOAC on more than 3 different drugs such as atorvastatin or pantoprazole or amiodarone were more prone to bleeding. The number of active bleeding according to the chronic kidney disease (CKD) stage is shown in Table 2. The χ^2-test was used to compare total bleeding between the groups (χ^2=7.51; p=0.006). Bleeding was statistically significantly lower in group B (DOAC) than in group A (warfarin).

Difference in gastrointestinal bleeding was compared between the groups by use of χ^2-test (χ^2=7.78; p=0.005). Gastrointestinal bleeding was statistically significantly more frequent in group A as compared with group B (Table 2).

Table 2. *Number of bleeding patients according to kidney function and type of drug*

eGFR CKD EPI stage (mlmin^{-1}1.73m^2)	Warfarin, n (%)	DOACs, n (%)
G2 (60-89)	5/6 (83.33%)	5/14 (35.71%)
G3 (30-59)	6/10 (60.00%)	12/36 (33.33%)
G4 (15-29)	4/6 (66.66%)	4/11 (36.36%)
Total (all patients taking certain drug)	15/22 (68.18%)	21/61 (34.42%)

eGFR = estimated glomerular filtration rate (CKD-EPI formula, mL/min/1.73m^2); DOACs = direct oral anticoagulants

DISCUSSION

Patients with AF often present to emergency department because of symptoms such as shortness of breath, chest pain and palpitations, as well as bleeding (9). Prescribing of DOACs is increasing in every day medicine and ever more AF patients take these drugs (2,3), as also demonstrated in the present study. DOACs do not require bridging or INR monitoring, which is an important advantage of DOACs. They may improve patient adherence, but long-term medication may cause bleeding, as shown in this study. With initiation of a new long-term medication, it is recommended that these patients be followed over time to ensure the dosage is correct and adverse effects are managed (9).

This study confirmed that bleeding was the most common side effect of taking anticoagulant therapy. It occurs more frequently in elderly population and in the population using multiple drugs in their chronic therapy. Drugs that have effects on anticoagulant medication, especially on warfarin and dabigatran, include various agents; they act as the permeability glycoprotein (P-gp) inducers (rifampin and St. John's wort), or as inhibitors (statins, antiarrhythmics, antifungals, antiviral drugs, and many others) (9). Caution should be exercised by the family medicine physician when ordering additional medication in these patient groups. This primarily refers to prescribing particular antibiotics and education of patients taking nonsteroidal anti-inflammatory drugs (10).

Dosage of certain drugs depends on eGFR, which makes it a very important factor in this group of patients. In case of decreased eGFR, it is necessary to adjust doses of dabigatran and rivaroxaban. In the literature, improper dosing of these drugs or unrecognized kidney disease may increase their toxicity and consequently the frequency of side effects of this treatment, as shown in our previous articles (9,11). Patient education is also of utmost importance in order to reduce excessive analgesic consumption or other factors that may have an effect on this drug group (12). The effects of DOACs may be prolonged in patients with underlying undiagnosed CKD. Therefore, important questions to ask a patient having some bleeding while on DOACs include the timing of their last DOAC ingestion and whether they have any underlying renal disorders. The decision to use a reversal agent in patients having bleeding while taking DOACs must be made on a case-by-case basis with the help of a multi-disciplinary treatment team (13-15). Given our results with much more patients on DOACs than VKA (warfarin), we believe that both physicians and patients are becoming more accustomed to the use of DOACs in clinical practice. Many questions on how to optimally use these agents in specific clinical situations remain unresolved (14). The European Heart Rhythm Association coordinates a unified way of informing physicians on the use of different DOACs (14). The real world population is sicker and more fragile than patients in randomized controlled trials. These sicker, more fragile group of patients are at a higher risk of bleeding. Future work is needed to establish reliable follow-up of these patients in healthcare system.

CONCLUSIONS

The results of this study confirmed the safety of DOACs in elderly population (>80 years) with 3 and more comorbidities. Bleeding as a cause of emergency response was significantly more frequent in patients on warfarin compared to patients taking DOACs. Additional studies are needed to check the difference between individual DOACs and to determine difference between warfarin and DOACs in patients with severely impaired renal function.

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SAŽETAK

KRVARENJE KAO GLAVNI UZROK HITNOSTI U BOLESNIKA NA ANTIKOAGULANTNOJ TERAPIJI

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Starenjem populacije stanja koja zahtijevaju antikoagulantnu terapiju ima sve više, čime uporaba antikoagulantne terapije u svijetu raste. Budući da krvarenje nastaje kod uporabe varfarina kao i direktnih antikoagulansa, cilj ovoga istraživanja bio je pokazati postoji li razlika u učestalosti krvarenja kao glavnog uzroka hitnosti u ovih bolesnika ovisno o primijenjenom antikoagulansu. *Metode:* U istraživanje su bila uključena 83 bolesnika na antikoagulantnoj terapiji s kroničnom bubrežnom bolešću stadija 2-4, pregledana u Hitnom prijmu Kliničke bolnice Merkur u razdoblju od sedam mjeseci. Skupina A obuhvaćala je 22 bolesnika (8 muškaraca) na varfarinskoj terapiji, a skupina B 61 bolesnika (19 muškaraca) na direktnoj oralnoj antikoagulantnoj terapiji. Srednja dob u skupini A bila je 80,77 godina, a u skupini B 80,95 godina. Nisu nađene razlike u komorbiditetima među skupinama. Doze antikoagulantnih lijekova bile su prilagođene bubrežnoj funkciji. *Rezultati:* U skupini A je glavni uzrok hitnosti bilo krvarenje u 15/22 (68,18%) bolesnika (većinom gastrointestinalnog podrijetla), dok je u skupini B krvarenje pronađeno u 21/61 (34,42%) bolesnika. Za provjeru statističke značajnosti razlike krvarenja kao glavne hitnosti među dvjema skupinama bolesnika primijenjen je $\chi 2$-test ($\chi 2=7,501$; $p<0,01$). *Zaključak:* Primjenom direktnih oralnih antikoagulantnih lijekova u dozi prilagođenoj bubrežnoj funkciji bilježi se statistički značajno manje krvarenja kao glavnog uzroka hitnosti u usporedbi s varfarinom.

KLJUČNE RIJEČI: antikoagulantna terapija, krvarenje, hitna medicina, kronična bubrežna bolest