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Original Article

A real-world, retrospective, observational study of dabigatran and rivaroxaban in Turkey: elderly patients receive inappropriately low dose of rivaroxaban

Omer Yiginer[1], Mehmet Tezcan[2], Emrah Erdal[3], Gokhan Degirmencioglu[1], Gurkan Acar[4], Mehmet Ergelen[5], Serkan Cay[6], Hande Cetin[6], Fatih Ozcelik[7], Mehmet Dogan[8], Alptug Tokatli[9], Namik Ozmen[1], Omer Uz[1], Fethi Kilicaslan[10]

Departments of [1]Cardiology, [7]Biochemistry, GMMA Haydarpasa Training Hospital, Istanbul, Turkey; [2]Department of Cardiology, Gumussuyu Military Hospital, Istanbul, Turkey; [3]Department of Cardiology, Diyarbakir Military Hospital, Diyarbakir, Turkey; [4]Department of Cardiology, Faculty of Medicine, Kahramanmaras Sutcuimam University, Kahramanmaras, Turkey; [5]Department of Cardiology, Faculty of Medicine, BezmialemVakif University, Istanbul, Turkey; [6]Department of Cardiology, YuksekIhtisas Training and Research Hospital, Ankara, Turkey; [8]Department of Cardiology, Ankara Mevki Military Hospital, Ankara, Turkey; [9]Department of Cardiology, Golcuk Military Hospital, Kocaeli, Turkey; [10]Department of Cardiology, Faculty of Medicine, Medipol University, Istanbul, Turkey

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Abstract: Thromboembolic complications are the most important outcomes of atrial fibrillation (AF). New oral anticoagulants (NOACs) have been presented to protect non-valvular AF patients from thromboembolic complications. In this study, we aimed to evaluate effectiveness and safety of NOACs and also reveal prescribing habits of physicians, retrospectively. NOACs and their effectiveness and safety retrospectively. Patients with non-valvular AF using either rivaroxaban or dabigatran were included in the study in five different tertiary centers. Patients were identified by scanning their medication reports. Appropriate patients were called and face-to-face interviews were done. Follow-ups were carried out on the phone. 183 out of 201 identified patients, taking rivaroxaban and dabigatran, were reached. General clinical characteristics were not significantly different between drug groups. Vascular disease and persistent AF were significantly higher in the rivaroxaban group. The rate of low dose medication in the dabigatran group was higher compared to the rivaroxaban group. Average age of the patients taking low dose medication were prominently higher in both groups. Between high and low dose users of the dabigatran group, creatinine clearance (CrCl) were not differed. Among rivaroxaban group, CrCl of the low dose users were lower than of the high dose users. However, among low-dose-prescribed patients, only 6 out of 38 patients had a CrCl value in the range of 30-49 ml/min, revealing that remaining 32 patients were receiving inappropriately low rivaroxaban dose. The rate of all-cause mortality, thromboembolism and bleeding complications were not statistically significant between the medication groups. While prescribing NOAC for non-valvular AF patients, physicians seem to consider patients' ages rather than CrCl values. In terms of protecting from thromboembolism, rivaroxaban and dabigatran seem to be equally effective and safe.

Keywords: Atrial fibrillation, dabigatran, rivaroxaban

Introduction

Atrial fibrillation (AF) is an illness affecting approximately 2% of the population and an important health problem of the 21st century of which incidence is increasing due to society's aging [1]. Thromboembolic complications are one of the most important outcomes of AF [2]. Vitamin K antagonists (VKA) have been used for years in order to protect the patients from thromboembolic events; however, the necessity of constant monitoring and dose adjustment of VKAs has compelled researchers to develop alternative medications [3, 4]. In randomized clinic studies, 4 different medications were shown to be as effective as VKAs and just as safe as them [5-8]. Therewith, new oral anticoagulants (NOACs) have appeared in AF guidelines as alternatives to VKAs [9, 10].

In Turkey, the NOACs including dabigatran and rivaroxaban have been put up for sale for about

Table 1. Clinical characteristics of the patients

Features	Overall (n=183)	Dabigatran (n=95)	Rivaroxaban (n=88)	*P*
Age (mean ± S.D.)	72±8.8	72.2±9	71.8±9	n.s.
Gender (male), n (%)	77 (42%)	37 (39%)	40 (45%)	n.s.
Creatinine Clearance (mL/min)	71.9±20.2	68.9±16.4	74.7±22.9	n.s.
Mean clinical follow-up duration (months)	17±7.7	17±8	17±7.5	n.s.
Persistent atrial fibrillation	108 (59%)	46 (48%)	62 (70%)	P=0.0027
CHA2DS2-VASc score	3.6±1.5	3.6±1.6	3.6±1.4	n.s.
HAS-BLED score	2.3±0.9	2.4±1	2.2±0.8	n.s.
Congestive heart failure	30 (16%)	12 (12.6%)	18 (20.4%)	n.s.
Hypertension	140 (76.5%)	72 (75.8%)	68 (77.3%)	n.s.
Previous thromboembolism (Stroke, TIA, systemic embolism)	27 (14.8%)	17 (17.7%)	10 (11.4%)	n.s.
Diabetes mellitus	43 (23.5%)	25 (26%)	18 (20.4%)	n.s.
Vascular disease	59 (32%)	22 (22.9%)	37 (42%)	P=0.0073
Previous VKA treatment	154 (84.1%)	76 (79.2%)	78 (88.6%)	n.s
Usage of low dose of the drug*	111 (60.7%)	73 (76.8%)	38 (43.2%)	P<0.0001
Usage of additional antiplatelet agents	20 (22.7%)	10 (10.5%)	10 (11.3%)	n.s.

*Low dose implies 110 mg for dabigatran, 15 mg for rivaroxaban. TIA: transient ischemic attack; VKA: vitamin K antagonists.

four years and apixaban for about two years. After having been started to be used worldwide, many registries have been done revealing the effectiveness and safety of NOACs' in real-world practice [11, 12]. In this study, we aimed to evaluate effectiveness and safety of NOACs and reveal prescribing habits of physicians, retrospectively.

Materials and methods

Patients diagnosed with non-valvular AF who were started either rivaroxaban or dabigatran treatment were included in the study in five different tertiary centers. The design of this multicenter, non-interventional observational study was approved by Istanbul Medipol University ethical committee (26.02.2016/10840098-604.01.01.E.3186). All subjects gave written informed consent to participate.

Patients were identified by scanning their medication reports retrospectively. Appropriate patients were called and face-to-face interviews were done at least once. During face-to-face visits, patients' anamneses were obtained; their medical histories were questioned, physical examinations were done, EKGs were performed and blood tests were examined. Creatinine clearance (CrCl) of the patients was calculated using Cockcroft-Gault formula [13]. In order to quantify the thromboembolic risk, CHA2DS2-VASc scores of the patients were calculated; heart failure, hypertension, being between 65 and 74 years old, diabetes mellitus, being female and vascular disease were given one point; being 75 years old and above, and having prior stroke or thromboembolism history were given two points. Furthermore, HAS-BLED scores were calculated in order to quantify bleeding risk of the patients; hypertension, hepatic and renal function tests, stroke history, bleeding history, labile INR, being 65 years old and above and using alcohol or taking additional medication were given one point.

Following the face-to-face interview visits, follow-ups were carried out on the phone. Follow-up duration was determined as at least 6 months from the start of medication and patients were called in six-month periods. During the phone calls, major adverse cerebrovascular and cardiac events (MACCE) and hemorrhage side effects were questioned.

Stroke is defined as an immediate, focal, neurological dysfunction occurring in the cerebral territory supplied by a cerebral artery. All hemorrhages requiring blood transfusion and symptomatic hemorrhage in critical organs were accepted as major hemorrhage.

Statistical analysis

SPSS 15 software was used for statistical analysis. For the comparison of categorical inde-

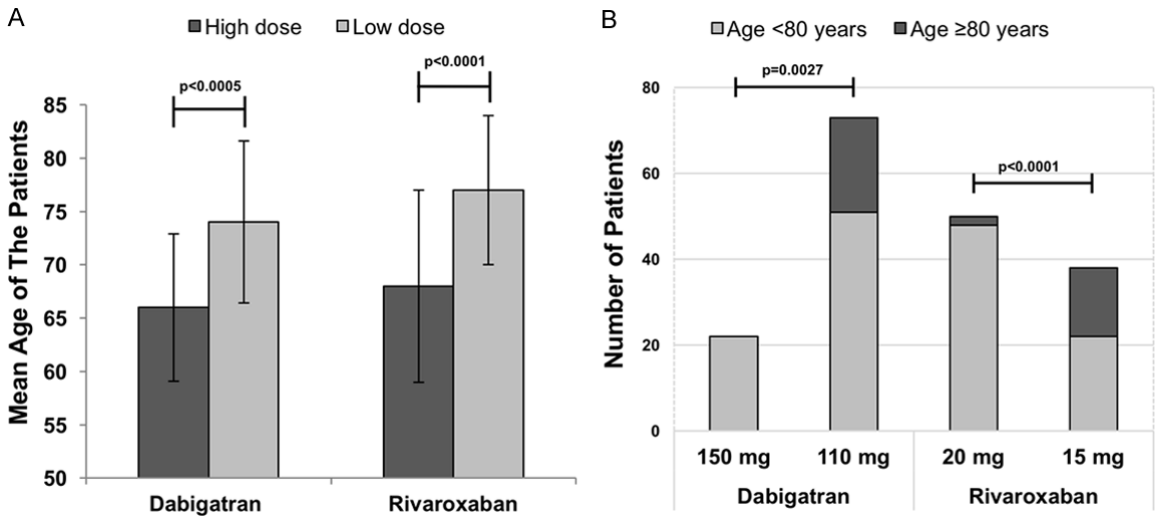

Figure 1. A. Comparison of the mean ages of the patients. In both dabigatran and rivaroxaban groups, mean age of the patients in low dose medication subgroups was prominently higher than of the high dose medication subgroups. B. Comparison of the patients aged above and under 80 years. It is seen that low dose drug prescriptions were significantly higher in patients aged ≥80 in each group.

pendent groups, the Fisher exact chi-square test was used; for the comparison of dependent groups the chi-square test for dependent groups (McNemar) was used. To compare continuous data, according to distribution analysis, dependent or independent t tests were used. Non-parametric tests were used for groups in which data were not distributed normally; the comparison of independent groups was performed using the Mann-Whitney U test and, for dependent groups, the paired Wilcoxon two-sample test.

Among all the groups using NOACs, all the factors that may be associated with bleeding (the drug, usage of high dose of the drug, usage of additional antiplatelets, the gender of the patient, the age of the patient, the scores of CHA2DS2-VASc and HAS-BLED) were chosen as independent variables and Binary Logistic Regression analysis was performed. Logistic regression analysis was not performed for thromboembolism because there was only one thromboembolic event. Mortality events were also evaluated using logistic regression analysis. Statistical significance was defined as $P<0.05$.

Results

183 out of 201 identified patients, taking rivaroxaban and dabigatran, were reached. General clinic features of the patients were presented in **Table 1**. Ninety-five of the patients were receiving dabigatran and 88 of them were receiving rivaroxaban. Mean age and gender distribution of the patients were similar. There was not a significant difference between medication groups in terms of CrCl. Average clinical follow-up duration for each group was 17 months without significant difference. The rate of persistent atrial fibrillation among the patients taking rivaroxaban was significantly higher than the dabigatran group (70% vs 48%, respectively; p=0.0027).

In terms of CHA2DS2-VASc and HAS-BLED scores, we didn't find statistically difference between the groups (CHA2D2-VASc: 3.8±1.6 vs. 4±1.4; HAS-BLED: 2.4±1 vs. 2.2±0.8; dabigatran vs. rivaroxaban, respectively). Additionally, the presence of heart failure, diabetes mellitus, and history of prior thromboembolism were not differed. However, the existence of vascular disease was prominently higher in rivaroxaban group compared to the dabigatran group (42% vs 22.9%, respectively; P=0.0073).

Eighty-four percent of the patients had taken VKAs previously, which was not differed between the groups. Ten patients in each group were taking antiplatelet agents in addition to NOACs but it is also off significance between the groups.

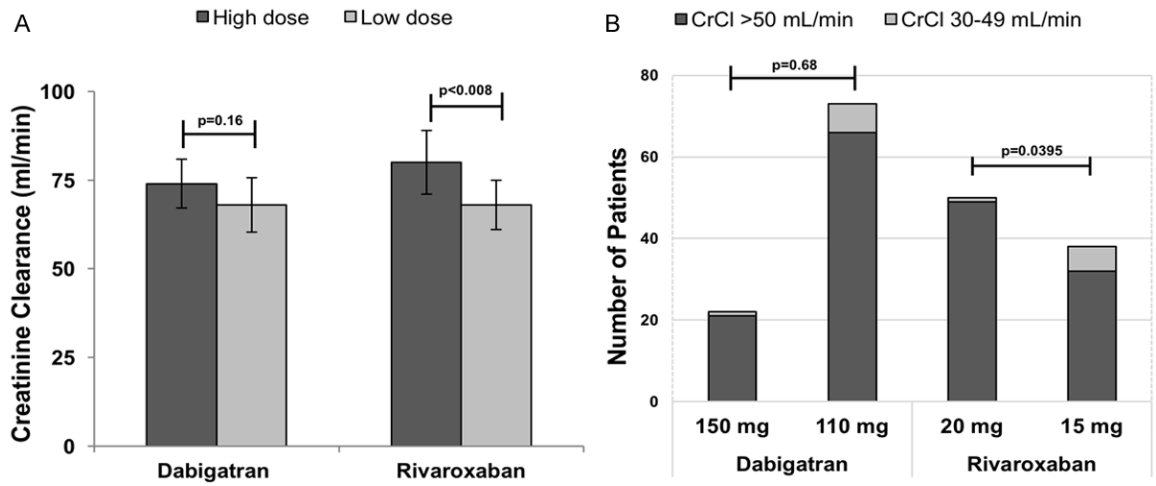

Figure 2. A. Comparison of the mean CrCl values in each group. In dabigatran group, mean CrCl of low dose patients was lower compared to high dose patients without statistically significance. However, in rivaroxaban group, we demonstrated a significant difference between the low and high dose subgroups regarding the mean CrCl. B. Comparison of the patients with a CrCl of 30-49 ml/min and above 50 ml/min in each group. After stratifying patients based on CrCl values, we found a significant difference in the rivaroxaban group implying low dose drugs were prescribed higher for the patients having a CrCl of 30-49 ml/min. In the dabigatran group, it was off significance.

In the dabigatran group, 22 patients were receiving high dose (150 mg BID) and 73 patients were taking low dose (110 mg BID). In the rivaroxaban group, 50 patients were receiving high dose (20 mg QD) and 38 patients were taking low dose (15 mg QD). Low dose medication rate among the dabigatran group was higher compared to the rivaroxaban group (77% vs. 43%, respectively; p<0.0001). In both group, mean age of low dose medication subgroups was prominently higher than of the high dose ones (**Figure 1A**). Twenty-two patients taking dabigatran were at age of ≥80. All octogenarian patients in the dabigatran group were taking low doses. In the rivaroxaban group, 18 patients were at age of ≥80. Sixteen of them were taking low dose and 2 of them were taking high dose of rivaroxaban. There was a significant difference in both medication group regarding low dose drug prescriptions in patients aged ≥80 (**Figure 1B**).

Mean CrCl of low dose dabigatran patients was lower compared to high dose patients, but it was not significant (74±14 vs. 67.3±17; respectively, p=0.16; **Figure 2A**). On the other hand, CrCl of low dose rivaroxaban patients were prominently lower compared to high dose patients (81±24 vs. 66.9±19; respectively, p=0.008; **Figure 2A**). Among the low dose dabigatran patients, seven patients had a CrCl of 30-49 ml/min. In the high dose dabigatran group, only one patient had a CrCl in the range of 30-49 ml/min (**Figure 2B**). CrCl of only 6 out of 38 low dose rivaroxaban patients were in the range of 30-49 ml/min. In the high dose rivaroxaban group, only one patient was found to have a CrCl in the range of 30-49 ml/min. After all, in terms of determining doses according to the CrCl, we found significant difference in the rivaroxaban group but not for the dabigatran group, (p=0.0395 for rivaroxaban, p=0.68 for dabigatran group; **Figure 2B**). HAS-BLED scores were not differed between low and high dose subgroups (**Figure 3A**). Additionally, having a HAS-BLED score of 3 and above were not significant in the groups (**Figure 3B**).

Clinical events were given in **Table 2**. Among all patients, 15 all-cause mortalities (10 in the dabigatran group and 5 in the rivaroxaban group) occurred. Among all the groups using NOACs, all the factors that may be associated with exitus (the drug, usage of high dose of the drug, usage of additional antiplatelets, the gender of the patient, the age of the patient, the scores of CHA2DS2-VASc and HAS-BLED) were chosen as independent variables and Binary Logistic Regression analysis was performed. Only the age of the patients was found to have a significant relationship with mortalities (p=0.008). However, this relationship was losing its significance when the drugs were

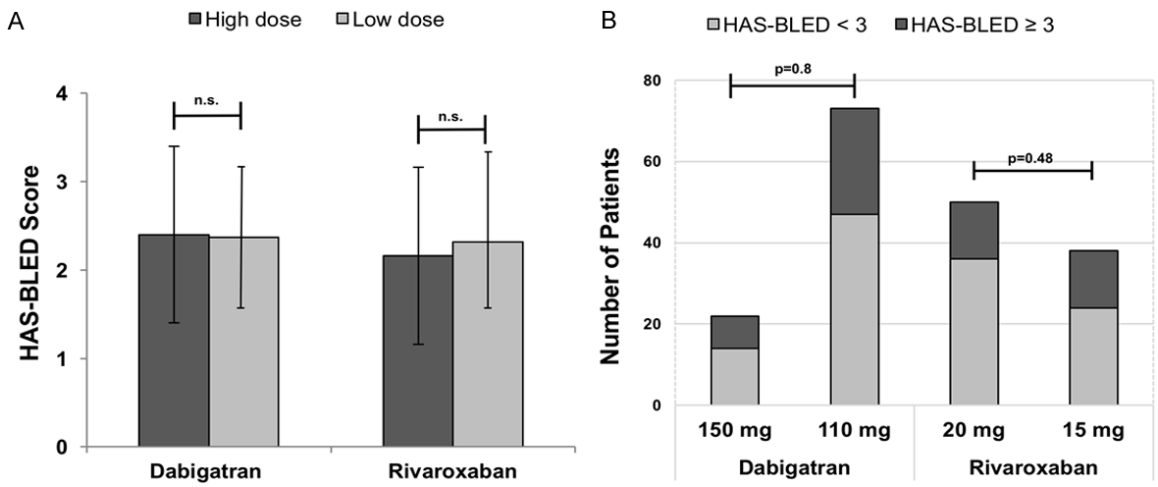

Figure 3. A. Comparison of HAS-BLED scores. HAS-BLED scores were similar between low and high dose subgroups in each group. B. Comparison of the patients with a HAS-BLED score of above and under 3. It is shown that it was off significance between low and high dose subgroups.

Table 2. Clinical outcomes of the patients

Events	Dabigatran	Rivaroxaban	*P*
All cause death	10 (10.5%)	5 (5.7%)	n.s.
Thromboembolism	0	1 (1.1%)	n.s.
Bleeding (major+minor)	17	18	n.s.
Intracranial hemorrhage	1 (1%)	1 (1.1%)	n.s.
GIT hemorrhage	7 (7.3%)	4 (4.5%)	n.s.
Hemorrhage requiring blood transfusion	5 (5.3%)	1 (1.1%)	n.s.
Minor bleeding	10 (10.5%)	14 (15.9%)	n.s.

GIT: gastrointestinal tract.

taken into account separately (p=0.072 for dabigatran, and p=0.058 for rivaroxaban).

Causes of deaths were given in **Table 3**. An embolization-type cerebrovascular thromboembolic event occurred in only one patient aged 63, who was taking low dose rivaroxaban. This patient didn't survive. One patient taking dabigatran had intracranial hemorrhage and died. Another patient taking rivaroxaban had subdural hemorrhage. Seven patients taking dabigatran and 4 patients taking rivaroxaban had gastrointestinal tract (GIT) bleeding. Hemorrhage requiring transfusion occurred in 5 patients in the dabigatran group and in 1 patient in the rivaroxaban group. A total of 24 patients (10 in the dabigatran group and 14 in the rivaroxaban group) had minor hemorrhagic complications with 8 epistaxis, 5 skin and subcutaneous hemorrhage, 4 hematuria, 4 hemorrhoidal, 2 conjunctival, 2 gingival, and 1 external ear canal hemorrhage. Overall, in terms of hemorrhagic events, logistic regression analysis did not show any relationship between bleeding complications and the potential factors (the drug, usage of high dose of the drug, usage of additional antiplatelets, the gender of the patient, the age of the patient, the scores of CHA2DS2-VASc and HAS-BLED).

The rates and causes of discontinuation of the medication were also examined (**Table 4**). Ten patients in the rivaroxaban group and 16 patients in the dabigatran group discontinued their medications for various reasons, which were off statistically significance between the groups (p=0.51). Three patients in the dabigatran group and 4 patients in the rivaroxaban group were not started any oral anticoagulants again. The most common reason for discontinuation was GIT bleeding. GIT intolerance also caused 3 patients in the dabigatran group discontinue their medications. Only one patient in the dabigatran group discontinued the medication due to elevated liver enzymes.

Discussion

The most important results of this study are as follows: i) While physicians are prescribing NOAC, they seem to take patient's age into too much consideration. ii) In prescribing rivaro-

Table 3. Cause of the deaths in the dabigatran and rivaroxaban groups

Dabigatran group	Gender	Age	Dosage	Cause
Patient 1	Male	76	150 mg BID	Noncardiac (trauma)
Patient 2	Female	85	110 mg BID	Noncardiac
Patient 3	Female	66	110 mg BID	Intracranial hemorrhage
Patient 4	Male	81	110 mg BID	Myocardial infarction
Patient 5	Male	72	110 mg BID	Suicide
Patient 6	Female	85	110 mg BID	Multiple organ failure
Patient 7	Female	83	110 mg BID	Heart failure
Patient 8	Female	75	110 mg BID	GIT hemorrhage
Patient 9	Male	74	110 mg BID	Lung cancer
Patient 10	Male	80	110 mg BID	Sudden death
Rivaroxaban group	Gender	Age	Dosage	Cause
Patient 1	Male	63	15 mg QD	Acute CVA
Patient 2	Female	82	15 mg QD	Noncardiac
Patient 3	Male	86	15 mg QD	Pneumonia
Patient 4	Male	79	15 mg QD	Noncardiac
Patient 5	Male	87	15 mg QD	Lung cancer

CVA: cerebrovascular accident.

Table 4. The reasons of the drug discontinuation in the groups

The Reason	Dabigatran	Rivaroxaban	Difference
Gastrointestinal bleeding	3	3	n.s.
Gastrointestinal intolerance	3	0	n.s.
Minor bleedings	2	4	n.s.
Renal failure	1	0	n.s.
Physicians preference	5	2	n.s.
Fatigue	1	0	n.s.
Increase in the serum level of liver enzymes	1	0	n.s.
Reimbursement issues	0	1	n.s
Total	16	10	n.s.

xaban, physicians prefer low dose (15 mg) while ignoring the GFR. iii) Dabigatran and rivaroxaban are equally effective protecting patients from thromboembolism. iv) They are also equally safe, in terms of side effect profile.

NOACs were brought into routine use in Turkey as an alternative to warfarin four to five years ago. The ESC and American guidelines presents NOACs as the best option in the protection from thromboembolism [10]. However, in Turkey, taking VKA previously is a mandatory issue as a term of payment for NOACs. Therefore, majority of our patients (84%) were composed of patients taking VKA previously.

In our study, it is seen that the rate of females was 58%, which is much higher than the rates in international NOAC studies. In clinical studies in which the effectiveness of rivaroxaban and dabigatran were examined, the rates of females were approximately 40% [6, 7]. Regarding the NOAC studies carried out in Turkey, the rate of females was reported to be 53% to 65% [14, 15]. In AFTER study, an epidemiological study carried out in Turkey, approximately 60% of the patients were females. These results show that AF prevalence in Turkey might be higher in women and this situation, by affecting CHA-2DS2-VASc score, increases the necessity of oral anticoagulants. [16].

Mean age of the patients in our study comply with those of international clinical studies and the registries [6, 7, 11, 12]. Ages of patients with AF are important on thromboembolism risk and frequency of hemorrhagic side effects. Our study also demonstrated that the age of the patients was the only independent variable to have a significant relationship with mortalities. In the dose selection of the drugs, patient's ages were not taken into account directly in RELY and ROCKET-AF studies [6, 7]. Patient's ages seem to affect dose adjustment indirectly while calculating CrCl. In our study, it was shown that higher doses of medication were preferred for younger patients and age affected dose selection regardless of the CrCl. In both RELY and ROCKET-AF studies, the patients having a CrCl of less than 30 mL/min were excluded [6, 7]. Also, in the ROCKET-AF study, patients whose CrCl values were between 30 and 50 mL/min were given rivaroxaban 15 mg/day [7]. In the RELY study, an additional dose adjustment

according to the CrCl was not done for dabigatran. Thus, the positive effects of dabigatran were observed in both doses regardless of CrCl. However, in the ROCKET-AF, 15 mg dose was applied to patients whose CrCl values were between 30 and 50 mL/min and positive effects in this group were observed only in patients who had mild renal dysfunctions. No randomized clinical study exists showing the effect of low dose rivaroxaban in patients with normal renal functions. Because rivaroxaban is partially eliminated via the kidneys, drug-blood concentrations in patients with normal renal functions might be decreasing to sub-therapeutic levels with low doses [17]. In the present study, CrCl of only 6 patients prescribed low dose rivaroxaban were found to be below 50 mL/min and this gives rises to thoughts that 84% of the low dose rivaroxaban patients do not take medication in effective dose.

In our study, only one patient taking 15 mg of rivaroxaban suffered from thromboembolic cerebrovascular accident. The patient was 65 years old and the CrCl of of this patient was 81 mL/min. This event might suggest that rivaroxaban was not in the adequate blood concentration. In one of the previous studies, it was also revealed that rivaroxaban was used in an inappropriately low dose [14]. In the XANTUS study, the greatest international registry of rivaroxaban, it was identified that in 15% of approximately 3800 patients whose CrCl were above 50 mg/min were given inappropriately low doses of rivaroxaban [11].

It was observed that while choosing between rivaroxaban and dabigatran, physicians decided independently of patients' ages, genders, GFR, CHA2DS2-VASc and HAS-BLED scores. In patients with persistent AF, rivaroxaban seemed to be preferred more. In the ROCKET-AF study, the rate of patients with persistent AF was 80%, whereas it was 30% in the RELY study [6, 7]. Being aware of this situation might lead the physicians to prefer rivaroxaban in those patients. Moreover, in patients with a history of vascular disease, rivaroxaban was preferred more. The most important cause of this might be the RELY study which reported myocardial infarction (MI) incidence to be higher in dabigatran patients compared to VKAs. In research reports of U.S. Food and Drug Administration (FDA) published in 2014, dabigatran did not increase MI risk [18]. However, new meta-analyses reporting dabigatran to increase MI risk continue to appear [18]. Despite the FDA report, these publications create confusions for the physicians and decrease the frequency of prescription of dabigatran in patients with vascular disease.

We are aware of the fact that our study does not include rather reliable data in terms of effectiveness and safety because it was not prospectively randomized and the number of patients was relatively insufficient. Our main aim on NOACs was to reveal prescribing habits of physicians in Turkey in the planning phase, but when we examined the data we obtained, we realized that our data was similar to high-scale randomized clinical studies and real-world data. When follow-up duration is considered, our data is important for a retrospective analysis with 17 months of follow-ups. In our study, age distribution of the patients shows similarities with those of randomized clinical studies and real-world data. CHA2DS2-VASc and HASBLED scores were also similar to those of international studies. Despite the quantitative differences between the two groups regarding effectiveness and side effect profile, no statistically significance was found.

GIT hemorrhage is among the most frequent causes of hospitalization in patients receiving NOAC treatment. In the RELY study, incidence rates of GIT hemorrhage in the 150-mg-dabigatran group were significantly higher compared to VKA group [6]. In the ROCKET AF study, rates of major hemorrhage from GIT were higher in the rivaroxaban group compared to the VKA group [7]. In a meta-analysis of about 150,000 patients, increased GIT hemorrhage rates due to NOACs were revealed [19]. In our study, GIT hemorrhage occurred at a rate of 6% during the follow-up process, which is similar to those identified in international studies. Additionally, in terms of GIT bleeding, we didn't find statistically difference between the drug groups, similarly to the previous reported study [20]. In the real-world data obtained from the study composed of nearly 46,000 patients taking dabigatran, rivaroxaban, and warfarin, GIT hemorrhage occurred mostly in dabigatran and least in rivaroxaban users [21]. In one study carried out with about 18,000 patients, there was found to be no difference between

rivaroxaban and warfarin in terms of GIT hemorrhage [22]. GIT hemorrhage is among the most frequent reason for discontinuing the medication. About 23% of our patients discontinued the medication due to GIT hemorrhage. Gastrointestinal intolerance is also another important reason for discontinuation. Three patients in our study discontinued dabigatran due to gastrointestinal intolerance. Minor hemorrhages are also important reasons leading to discontinuation. A significant difference was not identified between our groups in terms of minor hemorrhages. The most frequent minor hemorrhage causing discontinuation was epistaxis. Only in one patient among all, the liver enzymes increased and dabigatran was discontinued subsequently. Although it was previously reported that NOACs did not cause hepatotoxicity [23], there are many case reports reporting liver injury due to NOACs. Compiling these reports proposed that all NOACs in the market had hepatotoxicity risk which seems to be an idiosyncratic response and rivaroxaban seems to have higher risk compared to apixaban and dabigatran [24].

Study limitations

The most important limitation of our study is the scarcity of patients and the non-randomized study design. However, the fact that general clinical features of the patients and events' frequency were similar to those of major clinical studies, it made us think that our data could be used to interpret the medications' effectiveness and safety.

In conclusion, while prescribing NOAC for patients with non-valvular AF, physicians seem to consider patients' ages rather than CrCl. This situation does not constitute a significant change in patients prescribed dabigatran in terms of efficiency. However, among the patients who were prescribed low dose rivaroxaban, effective blood concentration might not be reached in patients with a CrCl above 50 ml/min, leaving them unprotected from thromboembolism. Hence, while prescribing NOAC and especially rivaroxaban, it would be appropriate to calculate patients' CrCl and determine the dose accordingly. In terms of protecting patients with non-valvular AF from thromboembolism, rivaroxaban and dabigatran seem to be equally effective and safe.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mehmet Tezcan, Department of Cardiology, Gumussuyu Military Hospital, Beyoglu, 34437, Istanbul, Turkey. Tel: +90 505 7648268; E-mail: drmehmettezcan@gmail.com

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