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The implication of new oral anticoagulant agents in gastrointestinal bleeding

Gastrointestinal sistem kanamalarında yeni kuşak oral antikoagülan ilaçların yeri

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Background and Aims: *This study was designed to (i) address the position of new oral anticoagulants in the etiology of bleeding in patients admitted to our hospital for gastrointestinal bleeding while using any anticoagulant and/or any antiaggregant drug and (ii) assess the relationships between the drug groups and severity of bleeding and the clinical picture in the first years of new oral anticoagulant use.* ***Material and Methods****: A total of 178 patients (mean age: 70±14 years) who were admitted to our clinic for gastrointestinal bleeding while using an anticoagulant and/or antiaggregant agent were recruited retrospectively. Patients were divided into the following three primary categories: patients using antiaggregant drugs (n=124), anticoagulant drugs (n=43), and both (n=11). The groups were compared according to their demographic data, biochemical parameters, 24-h follow-up period, maximum decrease in hemoglobin levels, amount of blood transfused, and mortality rates.* ***Results:*** *A total of 70% of the patients were taking antiaggregant drugs, 20% were using warfarin, 4% were taking new oral anticoagulants, and 6% of them were taking a combination of anticoagulants and antiaggregants. A total of 75% of the patients were using aspirin, 84% were taking warfarin, and 16% were taking new oral anticoagulants. There was no difference between the groups in terms of mortality rate (p=0.50), transfusion amount (p=0.72), and maximum hemoglobin decrease (p=0.39). There was also no difference in morbidity and mortality rates between patients taking new oral anticoagulants and those taking warfarin.* ***Conclusion:*** *Use of new oral anticoagulants has been listed as a cause for gastrointestinal bleeding. Although there was no difference between warfarin and new oral anticoagulant treatment with regard to mortality and morbidity rates, with the increasing use of these drugs in the forthcoming years, augmentation of their position in gastrointestinal bleeding etiology should be considered.*

Key words: *Anticoagulant, antiaggregant, gastrointestinal bleeding, new oral anticoagulants*

Giriş ve Amaç: *Yeni oral antikoagülanların kullanıma girdiği bu ilk yıllarda herhangi bir antikoagülan ve/veya antiagregan kullanmakta iken gastrointestinal kanama sebebiyle hastanemize başvuran ve gastrointestinal sistem kanaması tanısıyla yatırılan hastalarda gastrointestinal sistem kanama sebepleri arasında yeni oral antikoagülanların yerini belirlemek ve ilaç grupları ile kanama ciddiyeti ve klinik tablo arasındaki ilişkilerin değerlendirilmesidir.* ***Gereç ve Yöntem:*** *Bu retrospektif çalışmaya antikoagülan ve/veya antiagregan kullanmakta iken gastrointestinal sistem kanama nedeniyle kliniğimize yatan toplam 178 hasta (ortalama yaş: 70±14 yaş) alındı. Hastalar yalnız antiagregan kullanan (n=124), yalnız antikoagülan kullanan (n=43) ve kombine ilaç kullanan (n=11) olarak üç ana gruba ayrıldı. Gruplar demografik veriler, biyokimyasal değerleri, 24 saatlik takip dilimlerinde maksimum hemoglobin düşüşleri, kan transfüzyonu miktarı ve mortalite oranlarına göre karşılaştırıldı.* ***Bulgular:*** *Hastaların ilaç kullanımına göre dağılımı; %70'inin antiagregan ilaç, %20'sinin varfarin, %4'ünün yeni oral antikoagülan, %6'sının kombine ilaç kullanımı şeklinde idi. Antiagregan ilaç grubunda %75 oranında aspirin kullanımı vardı. Antikoagülana bağlı kanamalarda ise varfarin %84, yeni oral antikoagülan ilaçlar %16 oranında tespit edildi. Antiagregan, antikoagülan ve kombine ilaç kullanım grupları arasında mortalite oranı (p=0.50), transfüzyon miktarı (p=0.72) ve maksimum hemoglobin düşüşleri (p=0.39) arasında fark saptanmadı. Yeni oral antikoagülanlar ile varfarin arasında morbidite ve mortalite oranlarında farklılık saptanmadı.* ***Sonuç:*** *Sonuç olarak yeni oral antikoagülanlar, antikoagülan ve/veya antiagregan kullanımı sonrası gastrointestinal kanama nedenleri arasında yer almaya başlamıştır. Varfarin ve yeni oral antikoagülanlarla ilişkili kanamaya bağlı morbidite ve mortalite oranları arasında anlamlı fark saptanmamıştır ancak bu ilaçların önümüzdeki yıllarda daha yaygın kullanımı ile gastrointestinal kanama etiyolojisindeki yerinin daha da artabileceği göz önüne alınmalıdır.*

Anahtar kelimeler: *Antikoagülan, antiagregan, gastrointestinal kanama, yeni kuşak oral antikoagülan*

INTRODUCTION

Despite the developments in medical and endoscopic treatments, gastrointestinal bleeding (GIB) still remains a severe cause of mortality and morbidity (1). In the USA, GIB leads to approximately one million hospital admissions annually, and mortality rates due to upper GIB and lower GIB have been estimated at 4%–10% and 3.9%, respectively (2). Vital findings at the time of admission, including comorbidities such as age, heart failure, malignancy, and renal insufficiency and accompanying drug use, are known to affect mortality (3). These drugs include antiaggregants (AAs) and anticoagulants (ACs) that are well known to increase the incidence of both lower and upper GIB (4).

Today, owing to the increase in life span of people, the prevalence of cardiovascular diseases is also increasing, resulting in the widespread use of AAs and ACs. Unfortunately, the most important side effect of antithrombotic drugs is bleeding, and hence it is necessary to balance the effectiveness of these agents with the risk of bleeding in secondary cardiovascular protection. One of the most frequent localizations of bleeding is the gastrointestinal system, and these agents are known to provoke the onset of uncontrollable bleeding. While AA drugs produce ulcers and erosion, leading to bleeding, AC agents increase the risk of bleeding in the existing lesions (5). It has been reported that when the new generation of oral

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ACs (NOACs) are compared with warfarin, dabigatran leads to an increased risk for GIB and rivaroxaban leads to intracranial and fatal bleeding less than warfarin, but they exhibit similar total bleeding rates (6,7). Although the relationship between NOACs and GIB is known, there are still no sufficient data on this subject.

The present study was conducted on patients who were admitted to the hospital with complaints of GIB while using AC and/or AA drugs. The primary purpose of this study was to determine the position of NOACs in the etiology of GIB in the first years of its use, and the secondary aim was to evaluate the relationship among the drug groups, the severity of bleeding, and the clinical picture.

MATERIAL and METHODS

This study was conducted using the data of patients hospitalized in our hospital with a diagnosis of GIB while using AC and/or AA drugs for a medical cause. The study was approved by the hospital ethics committee (Date: July 18, 2014, decision number: 2014/0122).

Patients aged below 18 years; patients who had been hospitalized due to disseminated intravascular coagulation, hemophilia, hematological malignancy, immune thrombocytopenic purpura, and hemolytic uremic syndrome; and patients who had variceal bleeding developing on the basis of cirrhosis and bleeding secondary to thrombocytopenia were excluded.

Data were retrospectively obtained from the hospital database, patient files, and patient epicrisis. Demographic characteristics (age, gender, chronic comorbid diseases); complaints at the time of admission; vital findings; presence of shock at the time of admission (blood pressure <90/60 mmHg, pulse >100/min); use of ACs, AAs, and other drugs; serum hemoglobin level at the time of admission; white blood cell count; thrombocyte count; prothrombin time (PT); activated partial thromboplastin time (aPTT); international normalized ratio (INR); aspartate aminotransferase (AST); alanine aminotransferase (ALT); glucose; blood urea nitrogen (BUN); creatinine level; endoscopic findings; etiology of bleeding; transfusion requirement; medical and endoscopic treatment; maximum level of hemoglobin decrease in daily follow-ups; and requirement for surgery and total duration of hospital stay were recorded. AC and AA use and the combined use of these drugs were compared between the patient groups and between the subdrug groups. In-hospital mortality, surgical requirement, and intensive care requirement were additionally determined.

Rockall scores and Blatchford scores were calculated for all patients, and additionally HAS-BLED scores were calculated for patients taking AC drugs (8-10). Risk scores between groups were compared.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 14.0 (SPSS Inc.; Chicago, IL, USA). The categorical variables were presented as frequency, continuous numerical variables were presented as mean±standard deviation when they were normally distributed, and continuous variables were presented as median (minimum to maximum) when they were not normally distributed. A Chi-square test was used for the comparison of categorical variables. If normally distributed, Student's t-test was used for the comparison of categorical variables for binary groups and one-way analysis of variance (ANOVA) was used for the comparison of categorical variables for more than one group. If not distributed normally, Mann–Whitney U test was used for the comparison of categorical variables for binary groups and Kruskal–Wallis test was used for the comparison of categorical variables for more than one group. If a significant difference was found in the comparison of the three groups, Tukey and Bonferroni post hoc tests were applied to determine the group that produced the difference. The Kaplan–Meier test was used for the comparison of in-hospital survival of the patients using AA and AC drugs.

RESULTS

The files of 2,835 patients, who had been hospitalized in the Gastroenterology Clinic of our hospital between July 2012 and November 2014 with the diagnosis of GIB, were retrospectively investigated. Of these patients, 178 patients who had been under AC and/or AA treatment were included in the study. Among these, 65 patients were female (36.5%) and 113 were male (63.5%). Oral AC drugs were used by 43 patients (24.2%), oral AA drugs were used by 124 patients (69.7%), and combined oral AC and AA drugs were used by 11 patients (6.2%).

Hemoglobin levels were 9.86±2.7, 8.87±2.2, and 9.32±2.6 mg/dL in the AA, AC, and combined therapy groups, respectively, and there was no statistically significant difference between the groups in terms of initial hemoglobin levels (p=0.09).

Upper GIB was present in 100 patients (80.6%) and lower GIB was present in 24 patients (19.4%) who were under AA therapy. In patients who were under AC therapy, upper GIB was present in 30 patients (69.8%) and lower GIB in 13 patients (30.2%). Among those under combined drug therapy, upper GIB was observed in eight patients (72.7%) and lower GIB in three patients (27.3%). Overall, upper GIB was detected in a total of 138 patients (77.5%) and lower GIB was detected in a total of 40 patients (22.5%) (Table 1).

Regarding the drug usage among the patients, 93 patients (52.2%) were using aspirin, 36 patients (20.2%) were us-

Table 1. Patient demographics

	Antiaggregant group	Anticoagulant group	Combined group	p value
Number (%)	124 (69.7)	43 (24.2)	11 (6.2)	-
Gender (%)				
Male	71	58	64	0.001
Female	29	42*	36	
Age	74±7	69±14	77±7	0.016
Hypotension (%) (BP <90/60 mmHg)	12.9	11.6	27.3	-
Tachycardia (%) (pulse>100)	83.9	76.7	72.7	-
Hemoglobin (mg/dl)	9.86±2.7	8.87±2.2	9.32±2.6	0.09
Level of bleeding (%)				
Upper GIB	80.6	69.8	72.7	
Lower GIB	19.4	30.2	27.3	
Comorbidities (%)**				
DM	33.9	23.3	36.4	
HT	65.3	72.1	54.5	
CAD	58.9	34.9	72.7	
CHF	8.9	32.6	27.3	
CKD	16.1	16.3	18.2	
Malignancy	6.7	10.2	33.3	

*The number of females was significantly higher than that in the other two groups.
**DM: Diabetes mellitus HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal Failure

ing warfarin, 10 patients were using clopidogrel, six patients (3.4%) were using dabigatran, one patient (0.6%) was using rivaroxaban, and one patient (0.6%) was using ticlopidine. Twenty patients (11.2%) were using clopidogrel and aspirin and 11 patients (6.2%) were using combined AA and AC drugs (Figure 1).

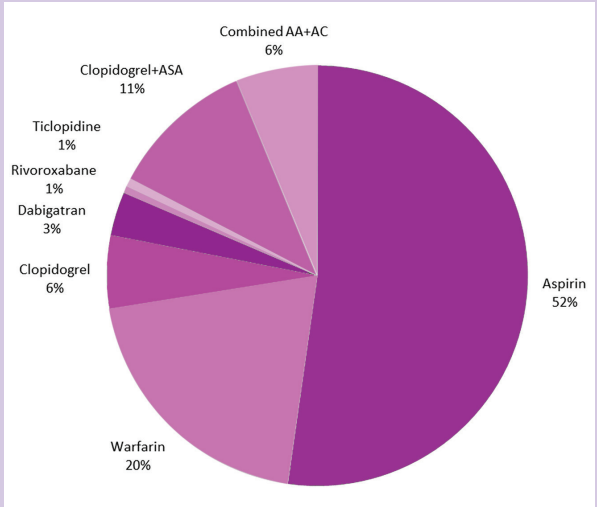

Figure 1. Distribution of medication use.

Endoscopic evaluation could not be performed in 18 patients because of their comorbidities and clinical conditions; however, in patients in whom endoscopic evaluation was performed (160 patients), at least one of the findings such as visible vessel, viscous clot, active bleeding, blood leakage, and/or red spot bleeding was detected in 32 patients in the AA therapy group, in four patients in the AC therapy group, and in one patient in the combined therapy group. Regarding the endoscopic findings, ulcer was detected in 80 patients, malignancy was detected in 12 patients, erosion was detected in 38 patients, dieulafoy lesion was detected in three patients, diverticulosis was detected in 16 patients, and angiodysplasia was detected in 11 patients. There was no statistically significant difference in the distribution of endoscopic lesions between the groups (p=0.3).

Rebleeding in 25 patients (20.2%) in the AA therapy group and in 10 patients (23.3%) in the AC therapy group was observed at the time of hospitalization or during their rehospitalization after discharge. No recurrent bleeding was detected in the combined therapy group.

Five patients (4%) in the AA therapy group and one patient (9.1%) in the AC group required follow-up in the intensive

care unit. Surgical intervention was required for three patients in the AA group, whereas it was not required in the other groups.

The maximum decrease in hemoglobin levels in the 24-h follow-up period was 2.12±1.2 mg/dL in the AA therapy group, 2.3±1.2 mg/dL in the AC therapy group, and 2.59±1.5 mg/dL in the combined therapy group with no significant difference between the groups (p=0.39).

The total amount of erythrocyte transfusion was 2.6±2.9 units in the AA therapy group, 3.0±2.4 units in the AC therapy group, and 2.5±2.3 units in the combined therapy group with no significant difference between the three groups (p=0.728).

The duration of hospital stay was 5.3±3.7 days in the AA therapy group, 7.3±4.3 days in the AC therapy group, and 5.9±2.8 days in the combined therapy group, indicating a significantly longer duration in the AC therapy group than in both the AA and combined therapy groups (p=0.01).

Mortality was detected in five patients (4%) in the AA therapy group, in four patients (10%) in the AC therapy group, and in one patient (9%) in the combined therapy group, with no statistically significant difference between the groups (p=0.506) (Table 2).

No statistically significant difference was observed between the 36 patients taking warfarin and the six patients taking dabigatran in terms of hemoglobin levels at the time of ad-

Table 2. Clinical follow-up between groups

	Antiaggreagant group	Anticoagulant group	Combined group	p value
Decrease in hemoglobin (mg/dl)*	2.12±1.2	2.30±1.2	2.59±1.5	0.39
Erythrocyte transfusion**	2.58±2.9	2.95±2.4	2.45±2.3	0.72
Duration of hospital stay (days)	5.31±3.73	7.28±4.28	5.82±2.82	0.01¶
Mortality (n)	5	4	1	0.5

*The maximum decrease in hemoglobin levels in the 24-h follow-up period.
**The total amount of erythrocyte transfusion.
¶The duration of hospital stay in the anticoagulant therapy group was longer.

Table 3. Clinical evaluation between warfarin and dabigatran groups

	Warfarin (n=36)	Dabigatran (n=6)	p value
Laboratory			
Hb (mg/dL)*	8.7±2.1	9.7±2.8	0.71
Decrease in Hb (mg/dL)**	2.2±1.2	3.0±1.1	0.85
PT (s)*	47.5±24.0	24±13.4	0.12
INR*	5.1±7.4	2.2±1.5	0.38
aPTT (s)*	61.25±27.58	42.31±19.71	0.11
Risk scores			
HAS-BLED	3.56±1.08	3.67±0.81	0.81
Rockall 1	3.75±1.02	3.83±1.47	0.86
Rockall 2	5.00±1.20	4.25±1.25	0.25
Blatchford	11.89±3.68	10.83±3.81	0.52
Erythrocyte transfusion (unit)^	3.0±2.4	2.5±2.1	0.61
Duration of hospital stay (days)	7.6±4.4	4.3±1.8	0.07
Mortality (n)	3	1	0.14

Hb: Hemoglobin level, PT: Prothrombin time, INR: International normalized ratio, aPTT: Activated partial thromboplastin time.
*Patients' PT, INR, and aPTT levels at the time of hospitalization.
**The maximum decrease in hemoglobin levels in the 24-h follow-up period.
^Total amount of erythrocyte transfusion.

mission, decrease in hemoglobin levels within 24 h, duration of hospital stay, and the amount of erythrocyte transfusion. The mean INR value was 5.19±7.41 in patients using warfarin, whereas it was 2.25±1.58 in patients taking dabigatran. However, the difference in INR values between these two groups was not statistically significant (p=0.34), which could be due to the small number of patients (six) using dabigatran. The mean aPTT level was 61.25±27.58 in patients using warfarin, while it was 42.31±19.71 in patients using dabigatran, and the difference between the two groups was not statistically significant (p=0.11). Mortality was detected in three patients (8.3%) using warfarin and in one patient (16.6%) using dabigatran, with no statistically significant difference between the two groups (p=0.14).

The mean Blatchford score was 11.89±3.68 in patients who were diagnosed with upper GIB and who were using warfarin, and it was 10.83±3.81 in the dabigatran group, with no significant difference between the two groups (p=0.52). There was also no significant difference in the mean Rockall scores before endoscopy between patients taking warfarin (3.71±1.02) and those using dabigatran (3.83±1.47) (p=0.86). For the 30 patients in whom endoscopy could be performed, the mean Rockall score was 5.00±1.20 following endoscopy, while it was 4.25±1.25 in the four patients taking dabigatran following endoscopy (p=0.25). Similarly, there was no significant difference in the mean HAS-BLED scores between the patients using warfarin (3.56±1.08) and those taking dabigatran (3.67±0.81) (p=0.81) (Table 3).

When the 93 patients using aspirin and the 36 patients taking warfarin were examined, the duration of hospital stay was 5.3±3.9 days in the aspirin group and 7.6±4.4 days in the warfarin group, and the difference was statistically significant (p=0.04). However, there was no statistically significant difference between the two groups in terms of mean age (p=0.13). Regarding the hemoglobin levels in these two groups, patients taking warfarin had significantly lower levels (8.7±2.11 mg/dl) than the levels of patients using aspirin (9.89±2.62 mg/dl) (p=0.01).

A significant difference was also observed in the Rockall scores before the endoscopies between patients taking aspirin (3.18±1.48) and those using warfarin (3.75±1.02) (p=0.03). However, after endoscopy, the Rockall scores were found to be 4.51±1.71 in patients taking aspirin and 5.00±1.20 in those using warfarin, with no significant difference (p=0.14). Table 4 shows the results of clinical evaluation between patients taking aspirin and those taking warfarin.

DISCUSSION

In the current study, which is important as it determines the changes in drug-related GIB ratios within the first years of using new-generation oral ACs, AA drug use was detected in 70% of patients who were admitted to the hospital with a diagnosis of GIB, warfarin use was detected in 20%, new-generation oral AC use (NOAC) was observed in 4%, and the combined use of AA and AC drugs was detected in 6% of patients. No difference was detected among the AC, AA, and combined AC and AA therapy groups in terms of mortality rates, the amount of transfusion, and the maximum level of hemoglobin decrease.

AA use constituted the leading cause of drug-related GIB in the present study. Aspirin use constituted 75% of this group with the highest ratio. In all the populations, aspirin, used at a rate of 19.3%, was being used as an AA drug (11). It was observed that 16% of patients using aspirin took it due to its analgesic and/or anti-inflammatory effects. Previous studies have reported that aspirin-related GIB is observed at a rate of 45%–52% among the etiologies of drug-related GIB (12,13). The rate of aspirin-related bleeding was 52% in the current study. However, this ratio does not include those patients with mild bleeding who had not been admitted to the hospital due to aspirin use.

Table 4. Clinical evaluation between aspirin and warfarin groups

	Aspirin (n=93)	Warfarin (n=36)	p value
Risk scores			
Rockall 1**	3.18±1.48	3.75±1.02	**0.03***
Rockall 2***	4.51±1.71	5.00±1.20	0.14
Blatchford	10.33±3.80	11.89±3.68	**0.03***
Erythrocyte transfusion (unit) ^	2.63±3.06	3.06±2.49	0.46
Duration of hospital stay (days)	5.3±3.9	7.6±4.4	**0.04***

*Statistically significant with $p < 0.05$
** Rockall score before endoscopy
*** Rockall score after endoscopy
^Total amount of erythrocyte transfusion

Patients using warfarin constituted 20% in the current study. In the USA, more than 30 million warfarin prescriptions are done in a year, and the rate of bleeding caused by this drug was found to be 0.4%–7.2% (14,15). In a study conducted before use of NOACs, warfarin was attributed for 15% of cases of drug-induced bleeding (12). In the RE-LY study, in which a new-generation oral AC, dabigatran, was compared with warfarin, a 110 mg dose of dabigatran was found to be similar to warfarin in terms of efficacy and with lower rate of major complications, whereas the efficacy of 150 mg dabigatran was more effective than warfarin and the rate of major complications was similar. However, the risk of GIB was significantly higher than that by warfarin (7). Similar to the results of the RE-LY study, in a retrospective cohort study performed by Graham et al.(16), the incidence of GIB in females above 75 years of age and in males aged more than 85 years was found to be high, and the risk of mortality was found to be increased in the dabigatran group. Although limited in number, there are studies demonstrating that the incidence of dabigatran-induced GIB is lower or similar (16,17). In the current study, 36 patients (20%) were using warfarin and seven patients (4%) were using NOAC in the AC group. In the NOAC group, six patients (86% of the NOAC group) were using dabigatran and one patient was using rivaroxaban (14% of the NOAC group). However, it is inevitable that these results are affected by the rate of use of these drugs and the approvement course in the population for whom we work. If a drug that rarely causes GIB is used more than a drug with a lower risk, the rate of GIB with that drug might be misleadingly high. Therefore, the rate observed in the present study might be misleading. Therefore, to minimize this limitation, we attempted to estimate the utilization rates of ACs in the population for whom we work. According to unpublished marketing and sales data of NOACs in Turkey, approximately seven million boxes of warfarin, 300 thousand boxes of dabigatran, and 240 thousand boxes of rivaroxaban have been used across the country during the study period, and according to the obtained data, 93% of these three ACs were warfarin, 4% were dabigatran, and 35% were rivaroxaban. During this period, the rate of dabigatran use was approximately 1.27 times higher than that of rivaroxaban and the rate of warfarin use was approximately 25-fold that of rivaroxaban. If the risk of bleeding had been equal, there would have been two patients using dabigatran and 25 patients using warfarin for every one patient using rivaroxaban. In the current study, GIB was detected in one patient after using rivaroxaban, in six patients after using dabigatran, and in 36 patients after using warfarin. In this case, when compared with rivaroxaban use, the rates of bleeding were found to be higher in patients using dabigatran and warfarin. As the incidence of warfarin use in the population is 25-fold higher, we suggest that dabigatran-induced bleeding is higher than that induced by warfarin.

Previous studies have reported that low doses of aspirin increase the risk of major bleeding two-fold higher than a placebo (18). It has been established that this risk further increased with AC therapy (19). In the current study, no significant difference was detected among the AA, AC, and combined drug groups in terms of hemoglobin levels at the time of admission, maximum daily decrease of hemoglobin, amount of erythrocyte transfusion, and mortality rates. Abu Daya et al. (20) compared the characteristics of GIB in patients using aspirin and ACs and reported that the number of adverse events defined as in-hospital mortality, rebleeding, and surgical requirement was lower and the duration of hospital stay was shorter in patients using aspirin than in those taking ACs. The authors also reported that blood transfusion requirement was highest in patients taking ACs. Similar to the findings of that study, we also observed in the present study that the duration of hospital stay was significantly longer in the AC group than in other groups. One possible reason for this finding could be that the longer hospital stay would increase the hospital costs and the risk of some morbidities such as hospital infection.

Although it is not necessary to follow up dose management in NOAC drugs, it has been demonstrated that dabigatran could cause the prolongation of aPTT but has less effect on PT and INR (21,22). In the current study, the mean PT, INR, and aPTT levels at the time of hospital admission were above the normal range in both warfarin and dabigatran groups. However, no statistically significant difference was detected between the groups in terms of coagulation parameters. Although a numerical difference was observed in PT levels between the two groups, it was not statistically significant and could be related to the small number of patients taking dabigatran. No difference was detected in the amount of erythrocyte transfusion, TDP transfusion, and mortality rates. The duration of hospital stay was found to be longer in the warfarin group. While there was no patient with chronic renal failure in the dabigatran group, chronic renal failure was detected in seven of the 36 patients using warfarin. As the majority of dabigatran clearance is through the kidneys and the drug is not used in case of terminal-phase renal failure, it is not primarily used in patients with renal failure (22). This could have affected the mortality and other clinical results in the comparison between warfarin and dabigatran groups.

Although clinically important results have been obtained in the current study, there are also certain limitations. One of them is that it is a retrospective study. Furthermore, the small number of patients in the NOAC group might have caused a limitation in the interpretation of the data.

In conclusion, new-generation oral ACs contributed to 4% of all cases of AA- and/or AC-related GIB who were admitted to our hospital. AAs (75% are acetylsalicylic acid) are the most

frequent reason for AA- and/or AC-related GIB, with a rate of 70%. Warfarin contributed to 84% of AC-related bleedings, whereas NOACs contributed to only 16%. No statistically significant difference was observed between the AC and AA groups in terms of mortality rates, and it was observed that the duration of hospital stay was longer in the AC group. The results of the present study have not supported the anticipated idea that NOACs could cause higher mortality and morbidity rates related to bleeding, as they have no antidotes on the market in Turkey. As the current study was performed at the beginning of the use of new-generation oral ACs, the frequency of NOAC-related GIB cases would be increased with the wider use of these drugs in the future.

Ethics Committee Approval

This study was approved by the ethics committee of our institution (Date: July 18, 2014, Decision number: 2014/0122).

Informed Consent

Written informed consent was obtained from the patients who participated in this study.

Peer-review

Externally peer-reviewed.

Author Contributions

Concept: S.K.T. - Design: Y.Ç., A.O. - Supervision: E.Ş., A.O., İ.T. - Resource: E.Ş., Y.Ç. - Materials: S.K.T., M.V.K. - Data collection and/or processing: S.K.T., M.V.K. - Analysis and/or interpretation: E.Ş., S.K.T, A.O., H.D. - Literature search: S.K.T., Y.Ç., E.Ş. - Writing: S.K.T., E.Ş., A.O. - Critical review: E.Ş., A.O., Y.Ç.

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