

# Comparative follow-up results of novel oral anticoagulants in daily practice

## Günlük uygulamada yeni oral antikoagülanların karşılaştırmalı takip sonuçları

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### ABSTRACT

**Objectives:** This study aims to examine the patients using dabigatran or rivoraxaban to compare their effectiveness and adverse events.

**Patients and methods:** Our study includes a total of 174 patients (82 male, 92 female; mean age 70.7±8.8 years), using dabigatran (n=113) and rivoraksaban (n=61), who were admitted to our outpatient clinic consecutively between August 2013 and April 2014. Physical examination was performed, patient history, electrocardiogram and biochemical results were recorded. Bleeding and ischemic stroke risk scores (HAS-BLED and CHA2DS2-VASc scores) were calculated. Patients were followed for adverse events.

**Results:** Patients were followed for an average of 12.9±2.4 months. The CHA2DS2-VASc scores were non-significant between the two groups (3.60±1.30 for dabigatran vs 3.90±1.22 for rivoraxaban, p>0.05). The patients using rivoraxaban had significantly higher HAS-BLED scores than the patients using dabigatran (2.01±0.95 vs 1.60±0.85, p=0.004). During the follow-up period, 12 of the patients had minor bleeding, two had gastrointestinal bleeding, two had intracranial hemorrhage and seven had ischemic stroke. Adverse events were non-significant between the rivoraxaban and dabigatran using patients (p>0.05 for each).

**Conclusion:** Bleeding and ischemic stroke are rare adverse effects among all the patients. No significant difference was observed between both of the groups in terms of preventing ischemic stroke. Rivoraxaban can be a better option in the patients with high HAS-BLED score to avoid bleeding.

**Keywords:** Atrial fibrillation; CHA2DS2-VASc; HAS-BLED score; dabigatran; oral anticoagulation; rivoraxaban.

### ÖZ

**Amaç:** Bu çalışmada dabigatran veya rivoraksaban kullanan hastalar, bu ilaçların etkinlikleri ve yan etkilerini karşılaştırmak için araştırıldı.

**Hastalar ve yöntemler:** Ağustos 2013 - Nisan 2014 tarihleri arasında ardışık olarak polikliniğimize başvuran ve halihazırda dabigatran (n=113) ve rivoraksaban (n=61) kullanan toplam 174 hasta (82 erkek, 92 kadın; ort. yaş 70.7±8.8 yıl) çalışmamıza dahil edildi. Hastaların fizik muayeneleri yapıldı, öyküleri, biyokimyasal değerleri ve elektrokardiyogramları kaydedildi. Kanama ve iskemik inme risk değerleri (HAS-BLED ve CHA2DS2-VASc) hesaplandı. Hastalar yan etkiler açısından takip edildi.

**Bulgular:** Hastalar ortalama 12.9±2.4 ay takip edildi. İki grup arasında CHA2DS2-VASc skoru anlamlı değildi (dabigatran için 3.60±1.30'a karşın rivoraksaban için 3.90±1.22, p>0.05). Rivoraksaban kullanan hastaların HAS-BLED skorları dabigatran kullananlarınkinden anlamlı olarak yüksekti (2.01±0.95'e karşın 1.60±0.85, p=0.004). İzlem süresince hastaların 12'sinde minör kanama, ikisinde gastrointestinal kanama, ikisinde intrakraniyal kanama ve yedisinde iskemik inme meydana geldi. Dabigatran ve rivoraksaban kullanan hastalar arasında yan etkiler açısından anlamlı fark gözlenmedi (her biri için p>0.05).

**Sonuç:** Kanama ve iskemik inme tüm hastalar arasında nadir yan etkilerdir. İskemik inmeden koruma açısından her iki grup arasında anlamlı farklılık gözlenmedi. Kanamayı önlemek için HAS-BLED skoru yüksek olan hastalarda rivoraksaban daha iyi bir seçenek olabilir.

**Anahtar sözcükler:** Atrial fibrilasyon; CHA2DS2-VASc; HAS-BLED skoru; dabigatran; antikoagülasyon; rivoraksaban.

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Atrial fibrillation (AF) is the most common ongoing heart rhythm disturbance with a prevalence of 1.5-2% in developed countries.<sup>[1]</sup> Systemic thromboembolic events, especially ischemic stroke due to AF, cause high morbidity and mortality. Ischemic stroke morbidity secondary to AF is much worse than other causes.<sup>[2]</sup> Warfarin is the most efficient anticoagulant drug for preventing thromboembolism in AF.<sup>[3]</sup> Difficulties in using warfarin such as frequent monitoring, drug-drug and drug-food interactions limit the effective usage of this drug.<sup>[4]</sup>

These disadvantages have propelled the emergence of new oral anticoagulant drugs. Novel oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) are manufactured and used in AF and are not related to valvular heart disease. Dabigatran; an oral anticoagulant directly inhibiting thrombin inhibitor and rivaroxaban; an oral anticoagulant directly inhibiting Factor Xa, have been proven effective and used in daily practice.<sup>[5,6]</sup>

In our previous study, we evaluated the prescribing patterns of dabigatran and rivaroxaban in daily practice.<sup>[7]</sup> In this study, we aimed to evaluate the comparative effectiveness and safety of dabigatran and rivaroxaban.

## PATIENTS AND METHODS

Our prospective observational study included 174 patients (82 males, 92 females; mean age  $70.7 \pm 8.8$  years) who suffered from atrial fibrillation and were already using dabigatran and rivaroxaban for anticoagulation. These patients admitted to Okmeydanı Training and Research Hospital between August 2013 and April 2014. Follow-up examined incidences of ischemic stroke and bleeding complications (minor, gastrointestinal bleeding and intracranial hemorrhage) for  $12.89 \pm 2.36$  months.

After a systematic, detailed history and physical examination took place, echocardiography, electrocardiography, and biochemical tests were performed. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation. All the patients provided written informed consent in accordance with the Declaration of Helsinki and the Local Ethics Committee approved the study protocol. In order to determine the risk of bleeding and stroke, HASBLED score

(Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly) and CHA<sub>2</sub>DS<sub>2</sub>-VASc score [Congestive heart failure, Hypertension, Age<sub>75</sub> years (doubled), Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category] were calculated. Patients were clinically re-evaluated at regular three-month intervals at our outpatient clinic. Patients who were unable to come to our clinic were evaluated over the phone.

The severity of bleeding was categorized according to the International Society on Thrombosis and Hemostasis (ISTH) criteria.<sup>[8]</sup>

## Statistical analysis

Continuous variables were expressed as mean  $\pm$  standard deviation and categorical variables were expressed as percentage (%). Categorical variables were compared using the chi-square test. Student's t-test was used to compare the continuous variables. All analyses were performed using PASW version 17.0 software for Windows (SPSS, Inc., Chicago, Illinois, USA). A two-sided *P* value less than 0.05 was considered statistically significant within a 95% confidence interval (CI).

## RESULTS

The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score of the study population was  $3.7 \pm 1.2$  and mean HAS-BLED score was  $1.74 \pm 0.9$ . Forty-one patients had coronary artery disease, 53 patients had congestive heart failure, 127 patients had arterial hypertension, 14 patients had diabetes mellitus and 17 patients had cerebrovascular disease.

Patients were followed prospectively for a mean follow-up period of  $12.89 \pm 2.36$  months. There were no deaths during the follow-up period. Ischemic stroke outcomes are given in Table 1. Ischemic stroke occurred significantly more frequently in older patients ( $p=0.05$ ), with a higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $p=0.006$ ) and higher HAS-BLED score ( $p=0.043$ ).

General characteristics, safety and efficacy outcomes are given comparatively in Table 2. There were no age and gender difference between patients using dabigatran and rivaroxaban. Patients using rivaroxaban had significantly higher bleeding risks than patients using dabigatran ( $2.01 \pm 0.95$  vs  $1.6 \pm 0.85$ ,  $p=0.004$ ). There were

**Table 1.** Ischemic stroke outcomes

General characteristics	Ischemic stroke (+) (n=7)			Ischemic stroke (-) (n=167)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			79.9±6.9			70.3±8.8	0.05
Gender							
Female	5	71.4		87	52.1		0.315
eGFR (mL/min)			60.3±10.4			63.7±8.8	0.116
HAS-BLED score			2.4±1.3			1.7±0.9	0.043
CHA <sub>2</sub> DS <sub>2</sub> -VASc score			5.0±1			3.7±1.3	0.006

SD: Standard deviation; eGFR: Estimated glomerular filtration rate HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; CHA<sub>2</sub>DS<sub>2</sub>-VASc score: Congestive heart failure, Hypertension, Age >75 years doubled, Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category.

no statistically significant differences for safety and efficacy outcomes between the 2 NOACs.

## DISCUSSION

In this prospective study, we followed patients using dabigatran and rivaroxaban with an indication of AF in order to determine safety and efficacy outcomes. Dabigatran and rivaroxaban were found to be safe and efficient in this group.

The mean age in our study population was similar to RE-LY and ROCKET-AF trials.<sup>[5,6]</sup> CHA<sub>2</sub>DS<sub>2</sub>-VASc score of the entire group was high. CHA<sub>2</sub>DS<sub>2</sub>-VASc score was introduced and physicians were advised to use it as a guideline in the 2012 focused update for the management of atrial fibrillation.<sup>[1]</sup> The RE-LY and ROCKET-AF trials were published before the updated guideline, so we are unable to directly compare our group with these trials. Larsen et al.<sup>[9]</sup> investigated a Danish cohort for comparative effectiveness of dabigatran, rivaroxaban and

apixaban. Our study group had higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores than the Danish cohort. Patients using rivaroxaban had lower renal functions than the dabigatran users. Dabigatran is excreted mostly from urine and should be used cautiously with renal impairment.<sup>[10]</sup> Thus, rivaroxaban was preferred over dabigatran in patients with low renal functions in our study.

Safety and efficacy outcomes showed similar results between rivaroxaban and dabigatran users. Most of the studies comparing NOACs were against warfarin.<sup>[11]</sup> Comparative follow-up results using real world data were first investigated by Larsen et al.<sup>[9]</sup> They compared all NOACs against warfarin and found the risks of death, bleeding and major bleeding were significantly lower for apixaban and dabigatran users, compared with warfarin. In our study, rivaroxaban was found to be a better option for patients with lower renal function and higher risk of bleeding.

**Table 2.** General characteristics, safety and efficacy outcomes of groups

General characteristics	Dabigatran (n=113)			Rivaroxaban (n=61)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			69.9±9.1			72.2±8.2	0.098
Gender	58	51.3		34	55.7		0.578
Female							
eGFR (mL/min)			74.1±17.5			67.8±15.6	0.019
HAS-BLED score			1.6±0.9			2.01±1.0	0.004
CHA <sub>2</sub> DS <sub>2</sub> -VASc score			3.6±1.3			3.9±1.2	0.141
Safety and efficacy outcomes							
Ischaemic stroke	5	4.4		2	3.3		0.714
Intracranial hemorrhage	1	0.9		1	1.6		0.656
Acute coronary syndrome	1	0.9		0	0		0.649
Gastrointestinal bleeding	1	0.9		1	1.6		0.656
Minor bleeding	6	5.3		6	9.8		0.206

SD: Standard deviation; eGFR: Estimated glomerular filtration rate HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; CHA<sub>2</sub>DS<sub>2</sub>-VASc score: Congestive heart failure, Hypertension, Age >75 years doubled, Diabetes mellitus, Prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category.

The limitations of the study included the small sample size and single-center experience. We did not have a control group of patients using warfarin, but our aim was comparing two NOACs, not to compare NOACs against warfarin. The inability to know if patients adhered to their drug regimen was also a limitation to our study.

In conclusion, bleeding and ischemic stroke are rare amongst all the patients. One is not greater than the other for preventing stroke. Rivoraxaban can be a better option in the patients with high HAS-BLED score in order to avoid bleeding.

#### **Declaration of conflicting interests**

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