Comparison of Non-Vitamin K Antagonist Oral Anticoagulants on Ischemic Stroke and Bleeding

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ABSTRACT

Objective: Non-vitamin K antagonist oral anticoagulants (NOACs) have become widely utilized for various clinical indications, including non-valvular atrial fibrillation (NVAF), deep vein thrombosis (DVT), and apical thrombus. Despite their increasing popularity, limited comparative data exist on the clinical outcomes associated with different NOACs. This study aims to address this gap by directly comparing NOACs in terms of ischemic stroke, hemorrhagic stroke, and gastrointestinal bleeding.

Materials and Methods: A retrospective search of the electronic database was conducted to identify patients using NOACs for NVAF, DVT, and apical thrombus. Clinical outcomes, including ischemic stroke, hemorrhagic stroke, and gastrointestinal bleeding, were directly compared among different NOACs. The chi-square test and Fisher's exact test were employed to assess the relative incidence of stroke and extracranial complications across four patient groups.

Results: Among the 4,112 retrospectively analyzed patients, 55 were included in the study. Demographic and clinical profiles showed no significant differences among patients in the four different drug groups (p > 0.05). Ischemic stroke was observed in 90.9% of the patients, hemorrhagic stroke in 5.8%, and gastrointestinal bleeding in 3.3%. A statistically significant difference was identified between drug doses and the rate of ischemic stroke (p < 0.001).

Conclusion: The findings of this retrospective study carry significant implications, especially considering the widespread global use of NOACs. The study revealed no discernible difference in the risk of ischemic stroke among patients using different NOACs. Notably, the risk of hemorrhagic stroke was dose-dependent in the dabigatran group, while rivaroxaban was associated with the highest risk of gastrointestinal bleeding. Given the elevated rate of thromboembolism in patients and the relatively short half-life of NOACs, the study concludes that further optimization of NOAC use is imperative.

Keywords: New oral anticoagulants (NOACs), Atrial fibrillation (AF), Stroke, Thromboembolism

INTRODUCTION

Atrial fibrillation (AF) is a common cause of ischemic stroke. Anticoagulant therapy is necessary to prevent stroke or systemic embolism and all-cause mortality in patients with AF and one or more risk factors for stroke. A stroke triggered by atrial fibrillation is usually more severe and debilitating and requires a longer hospital stay (than a stroke without atrial fibrillation) (1). Randomized controlled trials have shown that non-vitamin K antagonist oral anticoagulants (NOACs) are at least as effective as warfarin in reducing the risk of stroke and are associated with similar or lower rates of major bleeding (2).

Warfarin, long used for anticoagulation, has an anticoagulant effect by inactivating vitamin K-dependent posttranslational modifications of coagulation factors formed in the liver 2,7,9, and 10 (3). Although warfarin shows significant superiority compared with placebo and aspirin in patients with AF, some difficulties in its use (nutrient-drug interactions, narrow therapeutic window, frequent INR controls that are difficult and costly, long elimination time, prolonged half-life, changes in blood levels due to liver dysfunction) are the main reasons for the need to find oral anticoagulants of a new generation. Recently, new oral anticoagulants (NOACs) have become available for the prevention of thromboembolic events, particularly the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban (4).
These NOACs have a wide therapeutic window and limited drug and food interactions. They can be administered in fixed doses without periodic coagulation testing. However, there are some pharmacological differences between the NOACs, such as the mechanism of action, food effect, and renal clearance (5).

This study aims to compare the pathogenesis and risk factors for ischemic-hemorrhagic cerebrovascular events and gastrointestinal bleeding during the treatment of patients with NOACs. Our systematic review and meta-analysis aimed to analyze the differences between the various NOACs from different perspectives and provide data to support clinical, individualized treatment.

**MATERIAL and METHODS**

In this study, we aimed to investigate the possible characteristics of ischemic cerebrovascular events, hemorrhagic cerebrovascular events, GIS bleeding, and other complications in patients using new oral anticoagulants (dabigatran, apixaban, rivaroxaban, edoxaban) in the real world. Our study was designed retrospectively.

4112 patients who presented to Ankara Numune Training and Research Hospital’s neurology clinic within two years were analysed retrospectively.

When patients were admitted to the emergency department for a neurological reason, a consultation from the neurology department was routinely requested. Fifty-five patients hospitalized with ischemic stroke, hemorrhagic stroke, and extracranial hemorrhage while taking new oral anticoagulants were included in the study. AF; physical examination, bedside 12-lead ECG, and 24-hour rhythm were determined by Holter monitoring. NOACs were found to be used in 2 patients because of deep venous thrombosis and in 1 patient because of apical thrombus.

Age, sex, concomitant risk factors (hypertension, diabetes mellitus (DM), congestive heart failure, hyperlipidemia), transthoracic and/or transesophageal echocardiogram, bilateral Doppler ultrasound of the carotid-vertebral artery, cranial MRI and MRA examinations, GFR (glomerular filtration) value were retrospectively reviewed in 55 patients in whom new oral anticoagulants were used. Stroke etiology was classified according to the Causative Classification System for Ischemic Stroke (CCS) criteria, and stroke severity was calculated using the National Institutes of Health Stroke Scale (NIHSS) score.

The 2015 American Heart Association/American Stroke Association criteria were used as a guide. Patients were divided into four groups, taking dabigatran, rivaroxaban, apixaban, and edoxaban.

The inclusion criteria for the study were as follows: be over 18 years of age, have suffered an ischemic-hemorrhagic stroke while taking NOAC, or have a history of extracranial hemorrhage.

Statistical analysis of the data was performed with the SPSS 20.0 program. Descriptive statistics of the data, mean, standard deviation, median, frequency, and ratio values were used.

The distribution of the variables was measured using the Kolmogorov-Smirnov test. In the analysis of quantitative independent data, the one-factor analysis of variance (ANOVA) was used when normality and variance homogeneity were given, and in cases where the assumptions were not given, the Kruskal-Wallis test was used. In the analysis of qualitative independent data, the chi-square test was used when the conditions were not met, and Fisher's exact test was used.

p <0.05 was considered significant.

The ethical committee of Ankara Numune Training and Research Hospital approved the study.

**RESULTS**

Out of the 4,112 patients, 55 participants (33 women, 22 men) were enrolled in the study. Among these patients, 90.9% experienced ischemic stroke, while 5.8% had a hemorrhagic stroke, and 3.3% suffered from gastrointestinal bleeding (GIS).

No significant differences were observed among patients in the four distinct drug groups regarding age, gender distribution, the reason for initiating the drug, and the duration of use (p > 0.05).

Echocardiography and electrocardiography confirmed the initiation of NOAC in 52 out of 55 patients due to nonvalvular atrial fibrillation (AF). It was noted that NOAC was commenced in 2 patients due to deep vein thrombosis and in 1 patient due to apical thrombus (refer to Table 1).

Among the participants, two patients with hemorrhagic stroke exhibited parenchymal hematoma, and one patient presented with a subdural hematoma. Notably, all three patients were under the prescription of dabigatran at a dosage of 2x150 mg.

Additionally, one patient experienced gastrointestinal bleeding while using NOAC, specifically rivaroxaban (refer to Table 2).

The reason for switching to NOACs was the detection of nonvalvular AF in 63.6% of the patients, failure of INR regulation in 18.2%, other reasons in 5.5%, and unknown in 12.7%. There was no significant difference between the available data in terms of switching to 4 different drug groups (P > 0.05).

There was no significant difference between the four groups in congestive heart failure (CHF), diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), and hyperlipidemia (HL) comorbidities (p > 0.05).

There was no significant difference between the four groups in terms of GFR score, CHA2DS2VASc scores, NIHSS arrival scores, and NIHSS exit scores (p = 0.865, p = 0.956, p = 0.640, p = 0.815, respectively). Since four patients died, there are 51 patients with exit NIHSS values in the study.

There was no statistically significant difference between infarct sizes and medications (p = 0.806). The four groups had no significant difference in comorbidities (p>0.05).
A statistically significant difference was found between the dose of the drug in relation to the stroke ratios of the drugs used by the patients (p < 0.001). The effect size level between the two variables was found to be very strong (Cramer's V = 0.87). Of the 18 patients taking dabigatran, those with a drug dose of 2x150 mg (14) had more strokes. Eleven of these patients had ischemic stroke, and 3 had a hemorrhagic stroke (2 parenchymal hematomas, one nontraumatic subdural hematoma). Of 24 patients taking rivaroxaban, patients taking a drug dose of 10 mg (11) had more strokes, and one patient taking 20 mg had a history of GIS bleeding. Of the 11 patients taking apixaban, the drug dose of 2x2.5 mg (8) had more strokes. In 2 patients with stroke taking edoxaban, the drug dose was 30 mg (Figure 1).

Table 1: NOAC Groups Epidemiologic Feature

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran n=18</th>
<th>Rivaroxaban n=24</th>
<th>Apixaban n=11</th>
<th>Edoxaban n=2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.8±8.9</td>
<td>70.9±9.4</td>
<td>76.5±8.1</td>
<td>77.5±10.9</td>
<td>73.5±3.5</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 60%</td>
<td>13 54.2%</td>
<td>72.7%</td>
<td>2 100.0%</td>
<td>0.580</td>
</tr>
<tr>
<td>Male</td>
<td>22 40%</td>
<td>11 45.8%</td>
<td>27.3%</td>
<td>0 0.0%</td>
<td></td>
</tr>
<tr>
<td>NOAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>52 94.5%</td>
<td>24 100.0%</td>
<td>11 100.0%</td>
<td>2 100.0%</td>
<td>0.22</td>
</tr>
<tr>
<td>Start</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>2 3.6%</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
<td>0.000</td>
</tr>
<tr>
<td>Reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical thrombus</td>
<td>1 1.8%</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 2: Stroke and Extracranial Bleeding Distribution

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran n=18</th>
<th>Rivaroxaban n=24</th>
<th>Apixaban n=11</th>
<th>Edoxaban n=2</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Parenchymal hematoma</td>
<td>2 4%</td>
<td>2 8.3%</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
</tr>
<tr>
<td></td>
<td>Subdural hematoma</td>
<td>1 1.8%</td>
<td>1 6.3%</td>
<td>0 0.0%</td>
<td>0 0.0%</td>
</tr>
<tr>
<td>Extracranial Bleeding</td>
<td>GIS Bleeding</td>
<td>1 3.3%</td>
<td>0 0.0%</td>
<td>1 4.5%</td>
<td>0 0.0%</td>
</tr>
</tbody>
</table>

Figure 1: NOACs Groups and Ischemic Stroke Percentage
DISCUSSION

Cerebrovascular diseases contribute to around 11.8% of global mortality (6). Atrial fibrillation (AF) stands out as the most prevalent permanent cardiac arrhythmia linked to stroke (7).

In the context of nonvalvular AF, NOACs have gained popularity due to their favorable pharmacodynamic attributes, absence of routine monitoring requirements, minimal side effects, rapid onset of action owing to a short half-life, and convenient dose adjustment compared to warfarin, making them a preferred choice for preventing ischemic cerebrovascular events (8).

Our study retrospectively assessed the rate of ischemic and hemorrhagic stroke, GIS bleeding, and other complications in patients treated with new oral anticoagulants (dabigatran, apixaban, rivaroxaban, edoxaban). In both clinical practice and published literature, the rate of nontraumatic intracranial hemorrhage and GIS hemorrhage has decreased significantly in patients taking NOACs, whereas the rate of ischemic stroke has increased significantly (9).

The study by Max Shpak et al. is one of the few studies comparing warfarin with NOACs and NOACs with each other in regard to the risk of ischemic stroke. While the risk of stroke was high for dabigatran and apixaban in the study, no statistically significant difference was found for edoxaban due to the small number of patients (10). In our study, when comparing the four drug groups, no statistically significant difference was found between the preferred drug groups in terms of the stroke rate of the drugs used, but a statistically significant difference was found between the drug doses (< 0.001). In other words, while there is no difference between the efficacy or complication rates of the different drug groups, the drug dose makes a difference in terms of the risk of ischemic and hemorrhagic stroke.

The different medication use groups formed in our study did not differ significantly among the medication groups in terms of patient age, gender distribution, the reason for starting medication, and duration of medication use (p > 0.05). It was concluded that there was no bias between groups.

It was noted that there was a significant difference between the number of patients in our study since the NOACs were FDA-approved and launched at different times. (Edoksaban, the newest drug, was approved in 2015, and there are only 2 patients in the study.) Of the 55 patients, 18 were taking dabigatran, and those with a dose of 2x150 mg (n = 14) had more strokes. Eleven of these patients were admitted to the neurology department with a diagnosis of ischemic stroke and three patients with hemorrhagic stroke (2 parenchymal hematomas and one nontraumatic subdural hematoma). The reason for this increased prevalence of stroke in the dabigatran group is probably because three patients experienced a hemorrhagic stroke during treatment with dabigatran 2x150 mg. The high prevalence of stroke in the dabigatran group may be attributed to this situation.

In our study, the number of patients receiving rivaroxaban was the highest. Taking a single tablet per day may have contributed to this high number. In the study ROCKET-AF, which compared warfarin and rivaroxaban, gastrointestinal bleeding occurred more frequently in the rivaroxaban group (3.2%) than in the warfarin group (2.2%) (11). The administration of appropriate oral anticoagulant therapy for stroke prevention in elderly patients with atrial fibrillation is difficult due to bleeding problems. Rivaroxaban is not suitable for these patients (12). In our study, gastrointestinal bleeding was observed in only one patient, and this patient was using rivaroxaban 20 mg, which is consistent with the literature.

The reason for the increase in the rate of ischemic stroke in all drug groups with NOACs is probably the fact that their half-life is short. Another reason could be that, unlike warfarin, regular monitoring of blood levels is not required, so patients and their relatives do not get the idea that skipping pills could cause any problems (13).

The main limitation of our study is that the number of patients evaluated varied widely between groups and the records in the retrospective study were inadequate.

Study Limitations:

One limitation of our study is the exclusion of patients using warfarin. Although previous research has consistently demonstrated the superiority of NOACs over warfarin in numerous aspects, our study design intentionally excluded warfarin users. Nonetheless, it is essential to approach the findings of this study, rooted in observational data, with a comprehensive consideration of various factors when making clinical drug choices.

CONCLUSION

The aim of this article was to update and summarize the data on the clinical pharmacology of NOACs and to review real-world data to know their comparative efficacy and safety. Our work is primarily aimed at drawing attention to the conditions that should be considered before taking NOACs in patients who are planning to take NOACs and the conditions that should be considered, especially when taking NOACs.

The comparison between the NOACs showed that rivaroxaban has the highest risk of bleeding. There was no significant difference between the drugs in terms of the risk of ischemic stroke. Hemorrhagic strokes occurred more frequently in dabigatran users.

Overall, the study results showed that they were similar to the original data from the Phase III clinical trials and concluded that their use in practice largely overlapped with these.

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Author Contributions: BÖ, OK: Designed and directed the study. Literature search, Data collection, analysis and interpretation of results BÖ: Article writing, Final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.

REFERENCES