

Comparison of non-vitamin K antagonist oral anticoagulants and well-controlled warfarin in octogenarians with non-valvular atrial fibrillation: Real-world data from a single tertiary center

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ABSTRACT

Objective: Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and its prevalence increases with age. Nevertheless, data about the use of oral anticoagulants (OACs) among patients with ≥ 80 years remains limited. This study aimed to evaluate the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in octogenarians with non-valvular AF (NVAF).

Methods: Medical records of 387 patients who were ≥ 80 years and diagnosed with NVAF in our hospital between January 2017 and December 2019 were evaluated retrospectively. Patients with NVAF were divided into 2 groups (NOACs and warfarin), and the incidence of stroke/systemic embolism and major bleeding were analyzed.

Results: A total of 322 patients were included in the study. The median follow-up duration was 10.9 months for the NOACs group and 12.1 months for the warfarin group. The primary efficacy outcome was stroke/systemic embolism, and the primary safety outcome was major bleeding. A total of 220 patients were taking NOACs, and the most preferred NOACs were apixaban (53.6%), rivaroxaban (29.5%), dabigatran (13.2%), and edoxaban (3.6%) in this order. During a mean follow-up of 302.7 patient-years, the incidence of stroke or systemic embolic events was slightly higher among patients with warfarin but the difference was not statistically significant ($p=0.862$). The incidence rates of major bleeding events were similar between the treatment groups ($p=0.824$).

Conclusion: Our study revealed that the safety and efficacy outcomes are similar between the 2 treatment groups in octogenarians with NVAF.

Keywords: atrial fibrillation, embolism, octogenarian, anticoagulants, stroke

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Introduction

The incidence of atrial fibrillation (AF) increases with age (1-3). Age is an overlapping risk factor in both the CHA₂DS₂-VASc and the HAS-BLED scores and a strong predictor for both ischemic and bleeding events (4, 5). Therefore, anticoagulation is a major challenge in octogenarians (>80 years). Although age is not an absolute contraindication for anticoagulation, oral anticoagulants are often underused in extremely elderly patients owing to the concerns about the risk of bleeding, falling, complications, and comorbidities (6, 7).

The first prospective multicenter AF study in our country was the Atrial Fibrillation in Turkey Epidemiologic Registry study. The mean age of the patients was 66.8 years, and there were not enough data about the extremely elderly patients (8).

ReAl-life multicenter survey evaluating stroke prevention strategies in non-valvular atrial fibrillation study is the largest study in Turkish patients with non-valvular atrial fibrillation (NVAF), and the mean age was 69.7 years; no data were reported about octogenarians (9).

Despite the lack of evidence of treatment effect in Turkish octogenarians, we aimed to evaluate the efficacy and safety of

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HIGHLIGHTS

- We know that age is a strong predictor for both ischemic and bleeding events. Oral anticoagulants are often used inadequately in extremely elderly patients owing to the concerns of complications and comorbidities.
- We evaluated the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in octogenarian patients with non-valvular atrial fibrillation (NVAf).
- Our study shows that well-controlled warfarin and NOACs have similar safety and efficacy profiles, and NOACs were preferred over warfarin in octogenarian patients with NVAf.

non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in Turkish octogenarians with NVAf in a real-world tertiary center setting.

Methods

Study population

This was a single-center retrospective study. Medical records of 387 patients who were ≥ 80 years old and diagnosed with NVAf in our hospital between January 2017 and December 2019 were evaluated retrospectively. Baseline characteristics, laboratory parameters, and medications of all the patients were recorded.

NVAf is defined as the rhythm disturbance occurring in the absence of a prosthetic heart valve, mitral valve repair, or rheumatic mitral valve disease (10). The CHA₂DS₂-VASc and the HAS-BLED scores were calculated according to the European Society of Cardiology (ESC) clinical guidelines (11). The research protocol was approved by the Başkent University Institutional Review Board (project no: KA20/42).

Adequacy of anticoagulant therapy

The international normalized ratio (INR) between 2.0 and 3.0 in patients on warfarin, maintaining $\geq 70\%$ time in the therapeutic range (TTR) was used to determine the adequacy of treatment. For patients on NOACs, the adequacy of dosing was evaluated according to dose adjustment recommendations of the ESC according to age, renal function, weight, and hepatic function (12).

Efficacy and safety outcomes

The efficacy outcome was the composite of systemic embolism or stroke. Stroke was defined as the focal neurological deficit lasting at least 24 hours and confirmed by a neurologist. Systemic embolism was defined as documentation of an acute vascular occlusion by any imaging modality. The safety outcome was the incidence of major bleeding defined as fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial,

retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding causing a ≥ 2 g/dL decrease in the hemoglobin level or leading to the transfusion of ≥ 2 units of whole blood or red cells (13).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences version 21.0 (IBM Corporation, Armonk, NY, USA) software. Data were expressed in mean \pm standard deviation and median (range) for continuous variables and percentages for categorical variables. Continuous variables were evaluated with the Kolmogorov–Smirnov normality test to demonstrate distribution. Continuous variables with normal distribution were compared using the independent samples t-test. Continuous variables with abnormal distribution were compared using the Mann-Whitney U test. The Chi-square test was used to compare the categorical variables. A p value to evaluate the efficacy and safety outcomes was calculated by the Cox's regression model. The Kaplan-Meier method was used to estimate the survival-free rate of major bleeding between groups, and the survival rates were compared using the log-rank test. A p value of <0.05 was considered statistically significant.

Results

We performed a computer-based search in our hospital's database and found 387 patients who were ≥ 80 years and with NVAf. Patients who were not receiving oral anticoagulants were excluded. A total of 322 patients were included in the study. A total of 220 (68.3%) patients were treated with NOACs, and 102 (31.7%) patients were treated with warfarin. Their mean age was 86.2 years. The baseline clinical characteristics and laboratory parameters of patients are presented in Table 1.

The overall patient follow-up duration was 302.7 patient-years. The median follow-up duration was 10.9 months (5.4–17.1 months) for the NOACs group and 12.1 months (5.3–18.7 months) for the warfarin group. Comorbid conditions were consistent with previous registries from Turkey and other Western Caucasian populations. The mean CHA₂DS₂-VASc score was higher in the NOACs group (4.8 \pm 1.5 in the warfarin group versus 5.1 \pm 1.3 in NOACs group, $p=0.025$). A total of 23 (7.1%) patients were receiving concomitant antiplatelet therapy, and none of the patients were receiving dual antiplatelet therapy. There was no significant difference in the number of patients on concomitant antiplatelet use between the groups (7.8% in the warfarin group versus 6.8% in NOACs group, $p=0.816$).

Of the 220 patients who received NOACs, 118 (53.6%) received apixaban (95 on 2.5 mg twice per day and 23 on 5 mg twice per day), 65 (29.5%) received rivaroxaban (51 on 15 mg per day and 14 on 20 mg per day), 29 (13.2%) received dabigatran (26 on 110 mg twice daily and 3 on 150 mg twice daily), and 8 (3.6%) received edoxaban (7 on 30 mg daily and 1 on 60 mg daily) (Fig. 1).

In the warfarin group, 93% of patients achieved $\geq 70\%$ time in TTR. The dose of NOACs was compatible with the ESC recommendations in 98.6 % of patients in the NOACs group.

Table 1. Baseline clinical characteristics and laboratory parameters of patients

Variables	Total (n=322)	NOACs (n=220)	Warfarin (n=102)	P
Age, years (mean±SD)	86.2±4.7	86.2±4.9	86.2±4.4	0.940
Sex, male, n (%)	130 (40.4)	84 (38.1)	46 (45.1)	0.272
Follow-up duration (months)	11.9 (5.3–18.7)	10.9 (5.4–17.1)	12.1 (5.3–18.7)	0.098
Antiplatelet use, n (%)	23 (7.1)	15 (6.8)	8 (7.8)	0.816
Heart failure, n (%)	56 (17.4)	37 (16.8)	19 (18.6)	0.752
Hypertension, n (%)	301 (93.5)	206 (93.6)	95 (93.1)	0.814
Diabetes mellitus, n (%)	93 (28.9)	61 (27.2)	32 (31.4)	0.511
Previous stroke/systemic emboli, n (%)	144 (44.7)	99 (45.2)	45 (44.1)	0.905
Coronary artery disease, n (%)	147 (45.7)	100 (45.5)	47 (44.6)	1.000
Peripheral artery disease, n (%)	39 (12.1)	25 (11.4)	14 (13.7)	0.583
CHA ₂ DS ₂ -VASc, mean±SD	5.0±1.3	5.1±1.3	4.8±1.5	0.025
HAS-BLED, mean±SD	1.9±0.9	1.9±1.0	1.8±1.0	0.489
Medications, n (%)				
β blocker	239 (74.2)	167 (75.9)	72 (70.6)	0.339
Calcium channel blocker	64 (19.9)	41 (18.6)	23 (22.5)	0.454
Digoxin	53 (16.5)	37 (16.8)	16 (15.7)	0.873
Hemoglobin, mean±SD	11.7±1.1	11.7±0.9	11.6±1.1	0.849
Creatinine, mg/dL, mean±SD	1.1±0.4	1.1±0.3	1.2±0.5	0.030
Creatinine clearance, mL/min, mean±SD	50.3±13.3	50.9±12.7	49.7±14.1	0.331

NOACs - non-vitamin K antagonist oral anticoagulants; SD - standard deviation

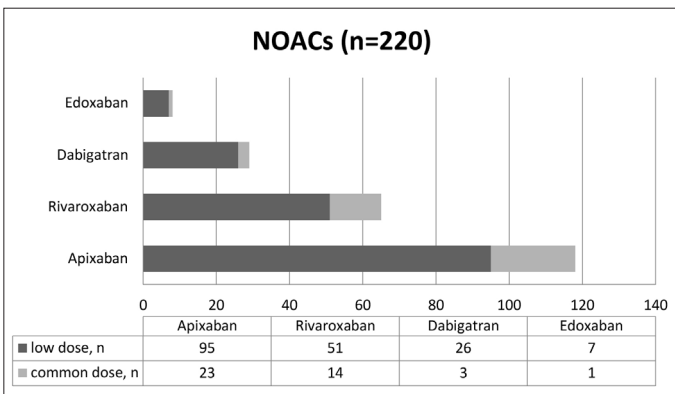


Figure 1. Distribution of non-vitamin K antagonist oral anticoagulant types and doses

NOACs - non-vitamin K antagonist oral anticoagulants

The efficacy and safety outcomes according to treatment groups are shown in Table 2.

The incidence rates of stroke or systemic embolic events were 5.1/100 patient-years in the NOACs group and 5.8/100 patient-years in the warfarin group. There were no significant differences between the groups (p=0.862).

Bleeding events occurred in 24 patients, and 16 of these met the criteria for major bleeding. The incidence rates of major bleeding events were similar between the treatment groups

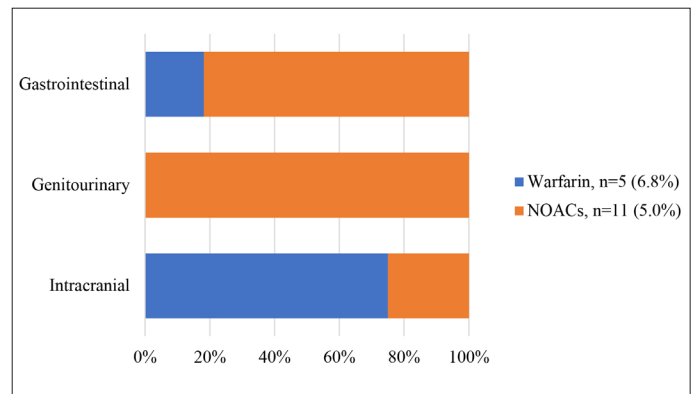


Figure 2. Sites of major bleeding

NOACs - non-vitamin K antagonist oral anticoagulants

(5.5/100 patient-years in the NOACs group versus 4.9/100 patient-years in the warfarin group, p=0.824).

Major bleeding occurred in 11 (5.0%) patients in the NOACs group and 5 (6.8%) patients in the warfarin group. Gastrointestinal bleeding was the most common cause of major bleeding in all the patients. Intracranial bleeding occurred in 1 (0.5%) patient in the NOACs group and 3 (4.0%) patients in the warfarin group (Fig. 2). These results were not statistically analyzed owing to the low number of events.

HAS-BLED score was not associated with an increased incidence of major bleeding in the Cox regression analysis (haz-

Table 2. Efficacy and safety outcomes according to treatment groups

Variables	NOACs (n=220)		Warfarin (n=102)		P
	Events (N)	Event rate (N/100 patient-years)	Events (N)	Event rate (N/100 patient-years)	
Stroke or systemic embolism	10	5.1	6	5.8	0.862
Major bleeding	11	5.5	5	4.9	0.824

P value between treatment groups was achieved for the overall follow-up duration by univariate Cox regression model.
N - number; NOACs - non-vitamin K antagonist oral anticoagulants

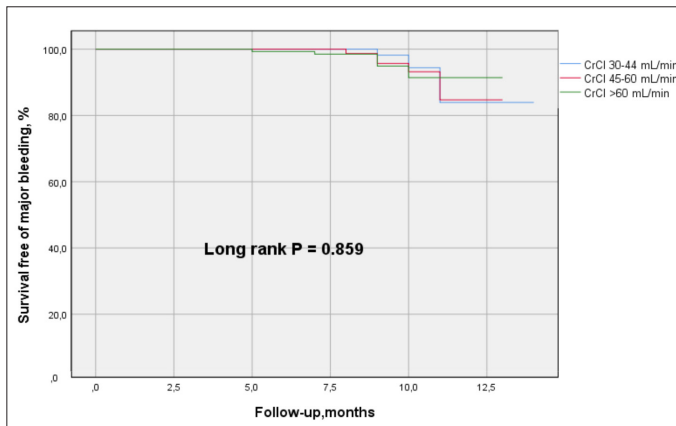


Figure 3. Kaplan-Meier curves showing the probability of survival free of major bleeding during follow-up according to renal function
CrCl - creatinine clearance

ard ratio: 0.421, 95% confidence interval: 0.848–2.377, $p=0.183$). Concomitant antiplatelet use was similar between the groups, and a major bleeding event occurred only in 1 patient in the warfarin group; this result was not statistically analyzed. Although creatinine levels were slightly higher in the warfarin group (1.1 ± 0.3 mg/dL versus 1.2 ± 0.5 mg/dL, $p=0.030$), creatinine clearance was similar between the groups (50.9 ± 12.7 mL/min versus 49.7 ± 14.1 mL/min, $p=0.331$).

The Kaplan-Meier analysis revealed no significant difference in the incidence of major bleeding according to the renal function (Fig. 3).

Discussion

Our study was a retrospective analysis to compare the NOACs with warfarin in Turkish octogenarians with NVAf. The main findings were that the safety (major bleeding) and efficacy outcomes (a stroke or systemic embolism) were similar between patients treated with NOACs and warfarin.

The most prevalent comorbid condition in our patients was hypertension (93.5%) followed by coronary artery disease (45.7%) and previous stroke/systemic emboli (44.7%). These findings were compatible with the literature (14).

The incidence of embolic events was 5.1 per 100 patient-years in the NOACs group and 5.8 per 100 patient-years in the warfarin group among our patients. Previous studies have reported different rates of stroke or systemic embolism in differ-

ent series. Asian studies have reported lower rates of embolic events ranging from 1.26% to 2.6% per year with NOACs and from 2.61% to 3.4% per year with warfarin (15, 16). In these studies, the mean age of the study population was approximately 70 years, whereas the mean age of our patients was 86.2 years. This could be an explanation for the higher rates of embolic events in our study population. Our study results were also slight higher than a retrospective analysis including 15,576 patients, 90 years and older, which showed that the annual risk of embolic events was 4.07% in patients treated with warfarin and 4.59% in patients treated with NOACs (17).

The incidence of embolic events was similar between our study groups ($p=0.862$). Importantly, CHA₂DS₂-VASc score was significantly higher in the NOACs group (4.8 ± 1.5 in the warfarin group versus 5.1 ± 1.3 in the NOACs group, $p=0.025$). Although a definite scientific result cannot be obtained because of the design and methodology of our study, this result can be interpreted as NOACs may be superior to well-controlled warfarin treatment in very elderly patients with high CHA₂DS₂-VASc scores.

A retrospective analysis including 293 consecutive patients with AF aged 80 years and older treated with either NOACs (50.5%) or warfarin (49.5%) showed that major bleeding events occurred in a significant number of patients in both the treatment groups without a significant difference (8.96% versus 12.46%; $p=0.290$) (18). The authors attributed this result to a real-world setting and concluded that the risk of major bleeding in octogenarian patients seems to be markedly high with both OACs. The incidence rates of major bleeding events were lower in our study population (5.5 per 100 patient-years in the NOACs group versus 4.9 per 100 patient-years in the warfarin group). These lower rates may be explained by well-controlled INR levels in the warfarin group (93%) and high adherence to the current guideline recommendations in the NOACs group (98.6%). Furthermore, there are multiple potential factors affecting the anticoagulation control in patients treated with warfarin and NOACs. Regular monitoring, adjusting additional medical treatments, and good patient education plan are important for successful treatment with warfarin. In addition, easy access to cardiologists in our center and the sociocultural influence levels of the patients may also have affected the results.

Our results are compatible with another subgroup analyses, which reported that the incidence of major bleeding was 4.43–5.10 per 100 patient-years on NOACs in patients ≥ 75 years (19).

HAS-BLED score is an important tool to identify the bleeding risk, and a HAS-BLED score ≥ 3 is attributed to high bleeding risk.

The mean HAS-BLED score was 1.9 in our study population, and we did not find any association with increased incidence of major bleeding according to the HAS-BLED score among our patients. This result could be attributed to the fact that the study population included patients with relatively low risk of bleeding because of the low HAS-BLED score.

A large Danish cohort study of patients with AF showed that the risk of major bleeding was significantly associated with the level of renal function (20). Kwon et al. (18) have found that major bleeding events were significantly higher in patients with a creatinine clearance of 30–44 mL/min among patients with NVAf aged 80 years and older. We did not find any significant difference in the incidence of major bleeding events according to the renal function (Fig. 2). We think that this finding can be explained by the fact that the majority of patients included in the study were already on NOAC treatment and had acceptable creatinine clearance values.

Because of the lack of data on head-to-head comparison of the NOACs in octogenarians, it is not possible to simply recommend one NOAC over another; however, according to a nonsystematic review of the literature by Russo et al. (21), apixaban or edoxaban should be considered over VKAs in octogenarians with AF and history of falls or at increased risk of falls regarding the safety profile. It is not possible to comment on this subject with the data we obtained from our study, but we can say that apixaban was the most preferred NOAC in our cardiology department.

Study limitations

There were several limitations to our study. It was based on a retrospective electronic data analysis. The study population was relatively small, and the follow-up duration was relatively short. Different kinds and doses of NOACs were prescribed, and subgroup analysis could not be performed owing to the small number of patients. Patient adherence to the prescribed NOAC regimen was not evaluated. Another limitation of our study was that the median follow-up periods of the patients were different. We could not add patients who had severe bleeding or stroke when using anticoagulants to our statistical data, but no patients died because of these reasons during our research process.

Despite these limitations, we believe that our results are meaningful because it is the first study evaluating the incidence of stroke or systemic embolic events and major bleeding risks in the NOACs or warfarin groups in Turkish octogenarians in a real-world clinical setting.

Conclusion

There remains a considerable risk for stroke and major bleeding in octogenarian patients with NVAf. Treatments with both well-controlled warfarin as well as NOACs seem to have similar safety and efficiency profiles. The findings also showed that NOACs are preferred over warfarin for anticoagulation in octogenarian patients with NVAf.

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