# Safety of once- or twice-daily dosing of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with nonvalvular atrial fibrillation: A NOAC-TR study

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## ABSTRACT

Once-daily dosing of non-vitamin K antagonist oral anticoagulants (NOACs) may increase patient adherence to treatment but may also be associated with a higher risk of bleeding. In this study, we investigated the adherence to once- or twice-daily dosing of NOACs and the risk of bleeding in nonvalvular atrial fibrillation (NVAF) patients. This multicenter cross-sectional study, conducted between 1 September 2015 and 28 February 2016, included 2214 patients receiving NOACs for at least 3 months, due to NVAF. Patients receiving once-daily or twice-daily NOAC doses were 1:1 propensity score matched for baseline demographic characteristics and the presence of other diseases. The medication adherence was assessed by the 8-item Morisky Medication Adherence Scale. Risk factors were investigated in relation to minor and major bleeding. The mean age of patients was 71 ± 10 years, and 53% of the patients were women. The medication adherence was lower in patients receiving twice-daily NOAC doses compared to once-daily-dose group (47% versus 53%, $p = 0.001$), and there was no difference between the groups in terms of minor (15% versus 16%, $p = 0.292$) and major bleeding (3% versus 3%, $p = 0.796$). Independent risk factors for bleeding were non-adherence to medication (OR: 1.62, 95% CI: 1.23–2.14, $p = 0.001$), presence of 3 or more other diseases (OR: 10.3, 95% CI: 5.3–20.3, $p < 0.001$), and HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score (OR: 4.84, 95% CI: 4.04–5.8, $p < 0.001$). In summary, the once-daily dose of NOACs was associated with increased patient adherence to medication, while it was not associated with bleeding complications.

KEY WORDS: Daily dosing; bleeding; medication adherence; non-vitamin K antagonist oral anticoagulants; self-report; NOACs; nonvalvular atrial fibrillation; NVAF

DOI: http://dx.doi.org/10.17305/bjbms.2017.2279 *Bosn J Basic Med Sci. 2018;18(2):185-190. © 2018 ABMSFBIH*

## INTRODUCTION

Medication adherence to oral anticoagulants is important for safe and efficient treatment of atrial fibrillation (AF) [1]. In recent years, non-vitamin K antagonist oral anticoagulants (NOACs) have been widely used in non-valvular AF (NVAF) treatment, and their efficacy and safety in NVAF patients has been demonstrated in several randomized controlled trials [2-6]. NOACs are fixed-dose combination drugs with a rapid onset time, for which routine monitoring is not required [7]. However, similarly as with vitamin K antagonists (VKA), poor compliance to NOACs can result in ineffective

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Submitted: 16 July 2017/Accepted: 31 August 2017

treatment, and therefore, the assessment of medication adherence in patients receiving NOACs is important. For example, in a previous study, we showed that non-adherence to NOACs was associated with increased bleeding and thromboembolic cardiovascular events in patients with NVAF [8].

Among the main factors that may affect medication adherence in patients receiving NOACs is the dosage regimen (e.g., once- and twice-daily dosing regimen). In patients with AF, once-daily dosing was found to be more efficient than twice-daily dosing in terms of medication adherence [8-10]; similarly, real-world studies showed favorable results for once-daily dosing regimens [9,11,12]. However, once-daily dosing may be associated with a higher risk of bleeding complications because of pharmacokinetic properties as well as higher peak and lower trough serum concentrations, as demonstrated previously [13]. So far, the cause-effect relation between daily dosing, NOAC adherence, and bleeding outcomes has not been explained.

Based on these information, we aimed to investigate whether the adherence to once- or twice-daily dosing of NOACs is a risk factor for bleeding complications in NVAF patients.

## MATERIALS AND METHODS

This multicenter cross-sectional study is a part of a larger study on NOAC adherence in Turkish patients with NVAF (NOAC-TR study) [8], which evaluated 2738 patients receiving NOACs for at least 3 months due to NVAF, between September 1, 2015 and February 28, 2016. The NOAC-TR study [8] was conducted in a total of 45 centers from all regions of Turkey. The approval was obtained from the Afyon Kocatepe University ethics committee (decision no. 2015/340). The study was registered at ClinicalTrials.gov (identifier no. NCT02480920). Patients ≥18 years old who received NOACs (dabigatran [110–150 mg], rivaroxaban [15–20 mg], or apixaban [2.5–5 mg]) for at least 3 months due to NVAF, and were confirmed for once-a-month prescription, were included in the study. The 8-item Morisky Medication Adherence Scale (MMAS-8) was applied to the patients during the outpatient admission, to assess their medication adherence [14]. According to the MMAS-8, patients with the total score of 6 and higher were considered adherent and those below 6 were considered nonadherent. The socio-demographic characteristics, use of additional medication, and presence of other diseases were evaluated in all patients. In addition, the CHA2DS2-VASc (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled] – vascular disease, 65–74 years of age, and sex category [female]) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g. age 65 years and frailty], drugs/alcohol concomitantly) scores were calculated for all patients. To minimize the confounding factors, propensity scores of patients receiving once-daily and twice-daily doses were calculated using the $CHA_2DS_2$-VASc, HAS-BLED scores, data on demographics and additional diseases, and were matched with each other. According to this analysis, the remaining 2214 patients were included in this study.

The safety endpoints were minor and major bleeding complications. Major bleeding was defined as the reduction of hemoglobin level of more than 2 g/dl, occurrence of bleeding complications requiring surgical intervention, requirement of blood transfusion of more than 2 units, or bleeding in a critical organ or region. All other bleeding events were considered as minor bleeding.

### Statistical analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Numerical data were presented as mean and standard deviation, and categorical data as frequencies and ratios. A comparison between groups was made with the independent t-test for numerical data and chi-square test for categorical data. The factors found to be associated with bleeding were evaluated with multivariate logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with standard methods. The limit of statistical significance (Type I error) was considered as $p < 0.05$ in all analyses.

## RESULTS

The mean age of patients was 71 ± 10 years and 53% were women. All patients underwent NOAC treatment for at least 90 days. The mean duration of NOAC use was 327 ± 206 days. Twice-daily dose was received by 1214/2214 (55%) of patients. The demographic characteristics, clinical risk factors, CHA2DS2-VASc, and HAS-BLED scores of patients receiving once- or twice-daily doses were matched similarly [$p > 0.05$] (Tables 1 and 2). When these factors were matched, the medication adherence was lower in patients receiving twice-daily NOAC doses ($p < 0.05$).

Bleeding complications developed in 18% of patients during monitoring period. Minor bleeding was detected in 15% and major bleeding in 3% of patients. Minor (16% vs. 15%, $p = 02.92$) and major bleeding rates (3% vs. 3%, $p = 0.796$) were similar in patients receiving once- and twice-daily doses, respectively.

In Tables 3 and 4, demographic and clinical characteristics were compared between patients with and without bleeding

complications. Duration of NOAC use, medication non-adherence, use of additional medications, presence of additional diseases, and alcohol addiction were higher in patients with bleeding complications ($p < 0.05$), while the knowledge about medication and frequency of taking the drug was lower ($p < 0.05$).

The CHA2DS2-VASc, HAS-BLED scores, and the rate of using nonsteroidal anti-inflammatory drugs and antiaggregants were higher in patients with bleeding complications ($p < 0.05$). Hypertension, diabetes mellitus, heart failure, coronary artery disease, and stroke rate were similar in both groups ($p > 0.05$). In addition, rate of other diseases was higher in patients who developed bleeding complications ($p < 0.05$).

According to the multivariate logistic regression analysis, medication non-adherence (OR: 1.62, 95% CI: 1.23–2.14, $p = 0.001$), presence of 3 or more additional diseases (OR: 10.3, 95% CI: 5.3–20.3, $p < 0.001$), and HAS-BLED score (OR: 4.84, 95% CI: 4.04–5.8, $p < 0.001$) were independent risk factors for bleeding complications (Table 5).

**TABLE 1.** Baseline demographic characteristics of matched once- and twice-daily direct oral anticoagulant cohorts of patients with nonvalvular atrial fibrillation

| Demographic characteristics | Once daily n=1000 | Twice daily n=1214 | *p* |
|---|---|---|---|
| Age, years (mean±std) | 70.7±10.4 | 70.5±10.3 | 0.539 |
| Gender, female n (%) | 529 (53) | 647 (53) | 0.853 |
| Duration of anticoagulant use, days (mean±std) | 335±204 | 320±207 | 0.163 |
| Education level n (%) | | | |
| Illiterate | 298 (30) | 388 (32) | 0.100 |
| Elementary school | 470 (47) | 552 (45) | |
| Secondary school | 119 (12) | 148 (12) | |
| High school | 84 (8) | 74 (6) | |
| University | 29 (3) | 51 (4) | |
| Occupation n (%) | | | |
| Unemployed | 528 (53) | 607 (51) | 0.273 |
| Employed | 401 (40) | 513 (43) | |
| Retired | 60 (6) | 59 (5) | |
| Living place n (%) | | | |
| City | 316 (32) | 347 (29) | 0.436 |
| Town | 441 (44) | 532 (45) | |
| Village | 238 (24) | 302 (26) | |
| Live alone | 109 (11) | 128 (10) | 0.809 |
| Use of additional oral medications n (%) | | | |
| 1-4 | 460 (46) | 534 (44) | 0.343 |
| 5 and more | 540 (54) | 680 (56) | |
| Drug abuse n (%) | 4 (0.4) | 7 (0.6) | 0.555 |
| Alcohol abuse n (%) | 12 (1) | 26 (2) | 0.090 |
| Knowledge about drug usage and indication n (%) | 742 (74) | 902 (74) | 0.957 |
| Forgetfulness n (%) | 360 (36) | 424 (35) | 0.599 |
| Drug adherence n (%) | 533 (53) | 570 (47) | 0.003 |

Std: Standard deviation

## DISCUSSION

To the best of our knowledge, this multi-center study included the largest population of patients with NVAF, in which the once- and twice-daily NOAC adherence was investigated in relation to bleeding complications. Although medication adherence was higher in patients receiving once-daily doses of NOACs, no difference was found between once- and twice-daily-dose groups in terms of minor and major bleeding rates.

It is assumed that decreasing daily dosage frequency increases the adherence to the treatment [15]. In a study evaluating patients with AF, once-daily dosing of antihypertensive drugs including antidiabetics, calcium channel blockers, and diuretics was more effective than twice-daily dosing, with regard to treatment adherence and persistence. However, oral anticoagulants were not assessed in that study [9]. In phase 3

**TABLE 2.** Baseline clinical characteristics of matched once- and twice-daily direct oral anticoagulant cohorts of patients with nonvalvular atrial fibrillation

| Clinical characteristics | Once daily n=1000 | Twice daily n=1214 | *p* |
|---|---|---|---|
| $CHA_2DS_2$-VASc score mean±std, median, (IQR) | 3.45±1.39, 3 (1–5) | 3.40±1.38, 3 (1–5) | 0.143 |
| HAS-BLED score mean±std, median, (IQR) | 3.28±1.03, 3 (2–4) | 3.20±1.01, 3 (2–4) | 0.083 |
| Hypertension n (%) | 801 (80) | 948 (78) | 0.248 |
| Diabetes mellitus n (%) | 257 (26) | 276 (23) | 0.104 |
| Smoking n (%) | 171 (17) | 200 (16) | 0.741 |
| Hyperlipidemia n (%) | 267 (27) | 356 (29) | 0.169 |
| Heart failure n (%) | 262 (26) | 302 (25) | 0.477 |
| Coronary heart disease n (%) | 293 (29) | 324 (27) | 0.176 |
| Stroke n (%) | 110 (11) | 145 (12) | 0.480 |
| Peripheral arterial disease n (%) | 25 (2) | 46 (4) | 0.087 |
| Chronic renal disease n (%) | 79 (8) | 76 (6) | 0.134 |
| Psychiatric disease n (%) | 59 (6) | 64 (5) | 0.527 |
| Dementia n (%) | 104 (10) | 154 (13) | 0.096 |
| Depression n (%) | 115 (11) | 130 (11) | 0.559 |

$CHA_2DS_2$-VASc (congestive heart failure/left ventricular dysfunction, hypertension, age≥75 years [doubled], diabetes, stroke [doubled] – vascular disease, 65–74 years of age, and sex category [female]); HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly (e.g., age 65, and frailty), drugs/alcohol concomitantly). IQR: Interquartile range; Std: Standard deviation

**TABLE 3.** Comparison of demographic parameters in patients with nonvalvular atrial fibrillation, with and without bleeding

| Demographic parameters | Bleeding, Yes n=394 | Bleeding, No n=1801 | *p* |
|---|---|---|---|
| Age, years (mean±std) | 70.2±11.8 | 70.7±10 | 0.374 |
| Gender, female n (%) | 224 (56) | 952 (52) | 0.224 |
| Duration of anticoagulant use, days (mean±std) | 365±234 | 319±198 | <0.001 |
| Non-adherence n (%) | 255 (64) | 856 (47) | <0.001 |
| Twice daily dosing n (%) | 210 (52) | 1004 (55) | 0.273 |
| Education level n (%) | | | |
| Illiterate | 142 (35) | 544 (30) | 0.247 |
| Elementary school | 169 (42) | 853 (47) | |
| Secondary school | 50 (12) | 217 (12) | |
| High school | 28 (7) | 130 (7) | |
| University | 12 (3) | 68 (4) | |
| Occupation n (%) | | | |
| Unemployed | 205 (52) | 930 (52) | 0.928 |
| Employed | 169 (43) | 745 (42) | |
| Retired | 23 (6) | 96 (5) | |
| Living place n (%) | | | |
| City | 126 (32) | 537 (30) | 0.197 |
| Town | 161 (41) | 812 (46) | |
| Village | 108 (27) | 432 (24) | |
| Live alone | 38 (10) | 199 (11) | 0.427 |
| Use of additional oral medications n (%) | | | |
| 0-4 | 148 (37) | 846 (47) | <0.001 |
| 5 and more | 253 (63) | 967 (53) | |
| Additional disease | | | |
| 0 | 19 (5) | 106 (6) | <0.001 |
| 1-2 | 170 (43) | 972 (54) | |
| 3 and more | 210 (53) | 726 (42) | |
| Drug abuse n (%) | 0 (0) | 11 (0.6) | 0.118 |
| Alcohol abuse n (%) | 12 (3) | 26 (1.4) | 0.030 |
| Knowledge about drug usage and indication n (%) | 277 (69) | 1367 (55) | 0.009 |
| Taking drug n (%) | 267 (67) | 1400 (77) | <0.001 |
| Forgetfulness n (%) | 199 (50) | 585 (32) | <0.001 |

Std: Standard deviation

**TABLE 4.** Comparison of clinical parameters in patients with nonvalvular atrial fibrillation, with and without bleeding

| Clinical parameters | Bleeding, Yes | Bleeding, No | *p* |
|---|---|---|---|
| $CHA_2DS_2$-VASc score, meas±std, median (IQR) | 3.65±1.43 4 (2-6) | 3.36±1.37 3 (1-5) | <0.001 |
| HAS-BLED score mean±std, median (IQR) | 4.24±1.11 4 (3-5) | 3.01±0.86 3 (1-5) | <0.001 |
| NSAID usage n (%) | 112 (28) | 258 (14) | <0.001 |
| Antiaggregant use n (%) | 64 (16) | 213 (12) | 0.021 |
| Hypertension n (%) | 324 (81) | 1425 (79) | 0.328 |
| Diabetes mellitus n (%) | 109 (27) | 424 (23) | 0.108 |
| Smoking n (%) | 84 (21) | 287 (16) | 0.013 |
| Hyperlipidemia n (%) | 132 (33) | 491 (27) | 0.018 |
| Heart failure n (%) | 97 (24) | 467 (26) | 0.514 |
| Coronary heart disease n (%) | 120 (30) | 497 (27) | 0.313 |
| Stroke n (%) | 57 (14) | 198 (11) | 0.063 |
| Peripheral arterial disease n (%) | 30 (7) | 41 (2) | <0.001 |
| Chronic renal disease n (%) | 43 (11) | 112 (6) | 0.001 |
| Depression n (%) | 57 (14) | 188 (10) | 0.027 |
| Dementia n (%) | 86 (21) | 172 (9) | <0.001 |
| Other psychiatric diseases n (%) | 36 (9) | 87 (5) | 0.001 |

$CHA_2DS_2$-VASc (congestive heart failure/left ventricular dysfunction, hypertension, age≥75 years [doubled], diabetes, stroke [doubled] – vascular disease, 65–74 years of age, and sex category [female]); HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g., age 65 and frailty], drugs/alcohol concomitantly) NSAID: Nonsteroidal anti-inflammatory drug; IQR: Interquartile range; Std: Standard deviation

trials, adherence to NOACs was moderately high. However, selection of patients who are at lower risk for non-adherence, frequent visits during the study, and impact of researchers on patients to take the drug make hard the objective evaluation of medication adherence in relation to dosage frequency. In the real-world study performed by Alberts et al. [16], medication persistence was higher in NVAF patients receiving once-daily dose NOAC combination than those receiving twice-daily dose [16]. In the analysis of healthcare claims from the Humana database, medication adherence of patients receiving rivaroxaban (72.7%) was better compared to patients receiving dabigatran (67.2%) and apixaban (69.5%) [10]. Similarly, medication adherence in NVAF patients receiving rivaroxaban was higher than in patients receiving dabigatran [11,12].

Other studies focused only on the adherence or persistence of NVAF/AF patients to different anticoagulant drugs and did not investigate the effect of dosage frequency [17-20]. In a large-scale prospective cohort study, the adherence was significantly higher with rivaroxaban compared to dabigatran but it was lower compared to apixaban [17]. Similarly, Brown et al. [18] found that rivaroxaban was more effective than dabigatran but less effective than apixaban in terms of adherence. In the studies of Castellucci et al. and Luger et al., the adherence was not different between patients receiving new oral anticoagulants (NOACs) and those taking VKAs [19,20]. Nevertheless, when interpreting the above-described results, the variability in patient groups, risk level, methods for adherence assessment, and indicators of medication use should be taken into account.

Non-adherence associated with once-daily dosing may lead to a higher risk of bleeding complications due to pharmacokinetic characteristics of drugs [21]. In our study, although adherence was lower in patients receiving twice-daily doses of NOACs, there was no difference in the rate of bleeding complications between once-daily and twice-daily-dose groups. The medication non-adherence (OR: 1.62, 95% CI: 1.23–2.14, $p = 0.001$), presence of 3 or more additional diseases (OR: 10.3, 95% CI: 5.3–20.3, $p < 0.001$), and HAS-BLED score (OR: 4.84, 95% CI: 4.04–5.8, $p < 0.001$) were independent risk factors for bleeding outcomes. There are several potential reasons why twice-daily dosing was associated with decreased adherence

**TABLE 5.** Independent risk factors for bleeding in multivariate logistic regression analysis

| Risk factor | OR | 95% CI | *p* |
|---|---|---|---|
| Additional disease (3 and more) | 10.3 | 5.3–20.3 | <0.001 |
| HAS-BLED score | 4.84 | 4.04–5.8 | <0.001 |
| Non-adherence | 1.62 | 1.23–2.14 | 0.001 |

HAS-BLED (Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g., age 65 and frailty], drugs/alcohol concomitantly)

and had no impact on bleeding outcomes. First, in addition to twice-daily dose regimen, other independent risk factors may be associated with non-adherence, and the combined action of most or all of these factors may be required for the development of bleeding complications. Second reason is associated with the pharmacokinetics of dosing regimens. Several observations were made in a simulation analysis of non-adherence to once and twice-daily dosing [22]. The peak-to-trough ratio was much smaller for a half the dose of a drug given twice-daily compared to a single dose given once-daily. When a single dose was missed in a twice-daily regimen the resulting concentration of the drug was similar to the trough concentration of once-daily dosing. Skipping a single dose in a once-daily regimen was equal to missing three consecutive doses in a twice-daily dosing regimen. A much higher peak was observed for an extra dose in a once-daily compared to twice-daily dosing regimen. In other words, fluctuation in the blood levels of medication is expected to be higher in the case of non-adherence to once-daily dose intake. Thus, an extra dose in a once-daily regimen is considered to be more risky in terms of developing bleeding complications, compared to twice-daily dosing, and non-adherence to twice-daily dosing regimens appears to be more tolerable [22].

Among the limitations of this study is its retrospective design, and prospective studies are required to investigate the association between medication adherence and bleeding complications. We also did not evaluate the impact of active drug substances on bleeding. Moreover, although there is no gold standard for the evaluation of medication adherence in clinical practice, less accurate results may be obtained with self-reported adherence that was also used in this study.

## CONCLUSION

Despite twice-daily dosing of NOACs was associated with decreased adherence in our patients, it was not an independent risk factor for bleeding complications, suggesting that not all factors related to medication non-adherence have an effect on development of bleeding and that the relationship between those factors may be more complex. Ideally, each patient should be evaluated for medication adherence and bleeding complication risks and appropriate NOAC dosage regimen should be determined on an individual basis.

## ACKNOWLEDGMENTS

The authors thank to NOAC-TR study group investigators for their great support in recruiting patients. We also thank to Emin ALİOĞLU for English editing.

## DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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