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# Do novel oral anticoagulant drugs used in patients with nonvalvular atrial fibrillation act only as anticoagulants?

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**Abstract. – OBJECTIVE: Although inflammation has an important role in the pathogenesis of atrial fibrillation (AF), the effect of novel oral anticoagulants (NOAC) used to reduce the risk of ischemic stroke and embolism on inflammation remains unknown. In this study, we aimed to investigate the effects of NOAC, which have been shown to have anticoagulant properties, on inflammation and platelet reactivation, which have an important role in the pathogenesis of AF.**

**PATIENTS AND METHODS: A total of 530 patients, including 380 patients with nonvalvular AF using NOAC and 150 patients with nonvalvular AF who did not use any NOAC were included in the study. Neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count. Mean platelet volume (MPV), red cell distribution width (RDW), and neutrophil-to-lymphocyte ratio (NLR) values of both groups were assessed both on admission and at three-month follow-up.**

**RESULTS: When the complete blood count (CBC) changes of the groups included in the study were compared, the RDW, MPV, and NLR values showed a greater decrease in the NOAC group compared to the non-NOAC group ($p$=0.000 for all).**

**CONCLUSIONS: The results indicated that the NOAC used in anticoagulation treatment do not only act as anticoagulants but also reduce inflammation and platelet reactivation, which have an important role in the pathogenesis of AF and thromboembolism.**

*Key Words:*
Atrial fibrillation (AF), Novel oral anticoagulants (NOAC), Stroke, Inflammation, Mean platelet volume (MPV), Red cell distribution width (RDW), Neutrophil-to-lymphocyte ratio (NLR).

## Introduction

Diabetes Atrial fibrillation (AF) is a common cardiac arrhythmia encountered in clinical practice and its prevalence has increased in recent years[1,2]. Since AF is independently associated with increased cardiovascular morbidity and mortality, it is inarguably a major public health concern[1,2]. In order to reduce the risk of ischemic stroke and embolism, AF patients are given anticoagulants during the treatment. Persistence to novel oral anticoagulants (NOAC) therapy is generally higher than to vitamin K antagonist therapy (VKA), being facilitated by a better pharmacokinetic profile of NOACs[3]. Therefore, NOAC are frequently used in patients with nonvalvular AF.

Inflammation plays a key role in thrombus formation and stimulation of the coagulation cascade and also plays a role in the pathogenesis of atrial fibrillation[4]. White blood cells (WBC) and their subtypes have been associated with cardiovascular risk factors[5,6]. Red cell distribution width (RDW) and the neutrophil-to-lymphocyte ratio (NLR) have recently emerged as popular inflammatory markers in the evaluation of prognosis in various diseases[7-10]. However, to our knowledge, there is no data in the literature regarding the effect of NOAC use on inflammation in patients with nonvalvular AF. In this study, we aimed to compare RDW and NLR between patients with nonvalvular AF using NOAC and patients with nonvalvular AF patients who do not use NOAC as well as to investigate the effects of NOAC on inflammation and platelet reactivation.

## Patients and Methods

### Study Population and Design

In The study included patients aged over 18 years who applied to our cardiology inpatient and outpatient clinics over the four-year period



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between January 1, 2016, and December 12, 2019. Patients were divided into two groups: (i) NOAC group included patients who had a diagnosis of nonvalvular AF and had been using NOAC (any of dabigatran, rivaroxaban and apixaban) for at least three months and (ii) non-NOAC group included patients who had a diagnosis of nonvalvular AF and had never received anticoagulant medication for any reason. Patients who had a diagnosis of AF but had no indication for the initiation of oral anticoagulants according to CHA2DS2-VASc scores, those who started NOAC but discontinued the treatment, those who had been using another anticoagulant (i.e., warfarin) within the last three months, those with more than 50% stenosis in the coronary arteries, history of malignancy, moderate-to-severe renal failure (estimated glomerular filtration rate [GFR] <60 mL/min) and hepatic dysfunction (presence of cirrhosis or alanine amino transferase [ALT] and/or aspartate amino transferase [AST] >3×ULN and total bilirubin>2×ULN), patients previously treated for anemia, and those with active inflammatory diseases and alcohol/substance abuse were excluded from the study. After applying the exclusion criteria, the remaining 530 patients were included in the study, comprising 380 patients in the NOAC group and 150 patients in the non-NOAC group.

### Procedures

Atrial fibrillation (AF) was defined as the detection of irregular R-R intervals with no discernible repetitive P waves of ≥30 seconds on a standard 12-lead electrocardiogram (ECG) or Holter monitoring[11]. Hypertension (HT) was defined as a systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg or use of any antihypertensive medication[12]. Diabetes mellitus (DM) was defined as a fasting blood glucose level of ≥126 mg/dL, a blood glucose level of ≥200 mg/dL two hours after oral glucose tolerance test, an HbA1c value of >6.5, or a randomly measured blood glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemic crisis[13]. Chronic obstructive pulmonary disease (COPD) was defined as having a Forced Expiratory Volume measured during the first forced breath (FEV1) / Forced Vital Capacity (FVC) ratio of less than 70 on spirometry or the use of any COPD medication[14]. The drugs used by the patients for these diseases (antidiabetics, antihypertensives, COPD drugs, antiaggregants and antihyperlipidemias) were recorded. Complete blood count (CBC) parameters including WBC count, hemoglobin (Hb), hematocrit (HCT), platelet (PLT), mean platelet volume (MPV), RDW, platelet distribution width (PDW), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platocrit, neutrophil, lymphocyte, monocyte, erythrocyte, basophil, and eosinophil were measured both on admission and at three-month follow-up. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

### Statistical Analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Variables and results were compared between the NOAC and non-NOAC groups to detect potential differences between the two groups. Normal distribution of continuous variables was assessed using Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD). For parametric data, groups were compared using Independent Samples *t*-test. Baseline and three-month CBC values were compared using Paired Samples *t*-test. Categorical variables were expressed as percentages (%) and were compared using Chi-square test or using Fisher's exact test in the case of low frequencies. A $p$-value of <0.05 was considered significant.

## Results

Our study was conducted with 530 patients who applied to cardiology clinic. The study population was divided into two groups to examine the results of NOAC treatment. The first group of the study included 380 cases using NOAC therapy for the diagnosis of nonvalvular AF, and the second group included 150 patients with AF who were selected as the control group and did not use any anticoagulant medication. Clinical characteristics of both groups are summarized in Table I. There was no significant difference between the two groups with regard to demographic characteristics including age, gender, and history of DM, HT, and COPD. Mean age was 71.3±9.7 years in the NOAC group as opposed to 70.3±10.2 years in the non-NOAC group ($p$>0.05).

Table II presents a comparison of the two groups with regard to antiplatelet (acetyl sali-

**Table I.** Demographic characteristics.

| Characteristics | NOAC (+) n (%) | NOAC (-) n (%) | p |
|---|---|---|---|
| Age (years) * | 71.3 ± 9.7 | 70.3 ± 10.2 | 0.482 |
| Gender (male)** | 143 (38.0) | 66 (42.9) | 0.302 |
| Diabetes mellitus** | 92 (24.5) | 29 (18.8) | 0.160 |
| Hypertension** | 291 (77.4) | 120 (78.4) | 0.795 |
| COPD** | 95 (25.3) | 30 (19.5) | 0.112 |

NOAC: Novel oral anticoagulants; COPD: Chronic obstructive pulmonary disease. *Independent samples *t*-test was used in the analysis of variable. **Chi-square test was used in the analysis of variables.

cylic acid and clopidogrel), anti-ischemic, antihypertensive, antidiabetic, antiarrhythmic, and antihyperlipidemic treatments that are commonly used in clinical practice. No significant difference was found between the two groups with regard to the use of these drugs ($p>0.05$).

Table III presents a comparison of CBC parameters measured on admission and at three months after the first evaluation. In the NOAC group, no significant change was observed in the Hb values, whereas the HCT values decreased significantly (HCTΔ: 0.49±4.1; $p=0.007$). In the non-NOAC group, however, no significant change was noted in the Hb and HCT values ($p=0.081$ and $p=0138$, respectively). On the other hand, the decrease in the RDW values of both groups was found to be statistically significant, whereas no significant change was found in both groups with regard to leukocyte and erythrocyte counts. Although the PLT count showed a significant change in the NOAC group, no significant difference was found in the non-NOAC group (non-NOAC group PLTΔ: 5.6±61; $p=0.035$). Similarly, the PDW value showed a significant change only in the NOAC group. The decrease in the MPV values in both groups was statistically significant ($p<0.05$). NLR decreased significantly in the NOAC group ($p=0.000$; $p<0.001$), while no significant change was observed in the non-NOAC group ($p=0.538$; $p>0.05$). The monocyte count increased significantly in the NOAC group, whereas no significant change was noted in the non-NOAC group (NOAC group MONOΔ:0.02±0.2; $p=0.022$). Both the eosinophil and basophil counts showed no significant change in both groups ($p>0.05$ for both).

**Table II.** Drugs used by the patients.

| | NOAC (+) n (%) | NOAC (-) n (%) | p |
|---|---|---|---|
| ASA | 50 (13.3) | 25 (16.2) | 0.457 |
| Beta blockers | 222 (59.0) | 93 (60.4) | 0.774 |
| Diltiazem | 91(24.2) | 34 (22.1) | 0.601 |
| Amlodipine | 92 (24.5) | 29 (18.8) | 0.160 |
| Furosemide | 109 (29.0) | 53 (34.4) | 0.218 |
| Spironolactone | 88 (23.4) | 27 (17.5) | 0.136 |
| Hydrochlorothiazide | 199 (52.9) | 84 (54.5) | 0.734 |
| ACEI | 99 (26.3) | 48 (31.2) | 0.259 |
| ARB | 120 (31.9) | 57 (37.0) | 0.259 |
| Amiodaron | 11 (2.9) | 8 (5.2) | 0.308 |
| Digoxin | 103 (27.4) | 53 (34.4) | 0.107 |
| Statin | 43 (11.4) | 23 (14.9) | 0.336 |
| Nitrate | 27 (7.2) | 14 (9.1) | 0.570 |
| Clopidogrel | 9 (2.4) | 6 (3.9) | 0.389 |
| Metformin | 59 (15.7) | 21 (13.6) | 0.641 |
| Insulin | 23 (6.1) | 8 (5.2) | 0.836 |
| Other antidiabetics | 53 (14.1) | 20 (13.0) | 0.843 |

NOAC: Novel oral anticoagulants; ASA: Acetylsalicylic acid; ACEI: Angiotensin-converting-enzyme inhibitors; ARB: Angiotensin receptor blockers. Chi-square test was used in the analysis of variables.

**Table III.** Diagnostic evaluation of independent predictors of PPI by ROC curve analysis.

| | NOAC (+) | | | NOAC (-) | | |
|---|---|---|---|---|---|---|
| | Baseline | 3-month | p | Baseline | 3-month | p |
| Hb | 13.5 ± 1.8 | 13.4 ± 2.0 | NS | 13.3 ± 1.7 | 13.1 ± 1.6 | NS |
| HCT | 41.1 ± 5.1 | 40.6 ± 5.3 | 0.007 | 40.2 ± 4.6 | 39.8 ± 4.4 | NS |
| MCV | 86.6 ± 7.2 | 85.8 ± 8.4 | 0.001 | 86.3 ± 6.3 | 86.1 ± 6.3 | NS |
| RDW | 14.6 ± 2.0 | 10.6 ± 5.3 | 0.000 | 15.3 ± 2.3 | 14.8 ± 2.9 | 0.048 |
| WBC | 8.18 ± 2.5 | 8.16 ± 2.8 | NS | 7.62 ± 2.1 | 7.55 ± 1.9 | NS |
| RBC | 6.72 ± 3.2 | 4.71 ± 0.6 | NS | 4.66 ± 0.4 | 4.63 ± 0.4 | NS |
| PLT | 245.3 ± 77 | 239.7 ± 71 | 0.035 | 234.7 ± 68 | 233.5 ± 63 | NS |
| MPV | 9.87 ± 1.4 | 9.20 ± 1.2 | 0.000 | 9.72 ± 1.9 | 9.42 ± 1.5 | 0.033 |
| PDW | 14.4 ± 2.6 | 14.0 ± 2.7 | 0.000 | 14.8 ± 2.9 | 14.8 ± 3.0 | NS |
| NLR | 3.36 ± 3.4 | 2.56 ± 3.4 | 0.000 | 3.03 ± 2.7 | 2.88 ± 2.0 | NS |
| MONO | 0.61 ± 0.2 | 0.63 ± 0.2 | 0.022 | 0.62 ± 0.1 | 0.60 ± 0.2 | NS |
| EOS | 0.17 ± 0.1 | 0.17 ± 0.1 | NS | 0.18 ± 0.1 | 0.18 ± 0.1 | NS |
| BAS | 0.03 ± 0.03 | 0.04 ± 0.03 | NS | 0.04 ± 0.03 | 0.04 ± 0.03 | NS |

NOAC: Novel oral anticoagulants; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; RDW: Red cell distribution width; WBC: White blood cell; RBC: Red blood cell; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil-to-lymphocyte ratio; MONO: Monocyte; EOS: Eosinophil; BAS: Basophil; NS: Non-significant ($p$>0.05). Paired samples t-test was used in the analysis of variables.

An analysis of the CBC changes of the groups included in the study indicated that the RDW, MPV, and NLR values showed a greater decrease in the NOAC group compared to the non-NOAC group ($p$=0.000 for all; $p$<0.001) (Table IV).

## Discussion

The results indicated that the RDW, MPV, and NLR values showed a greater decrease in the NOAC group compared to the non-NOAC group. To the best of our knowledge, this is the first study to evaluate the effect of NOAC use on RDW, MPV, and NLR values. The results also showed that the NOAC used in anticoagulation treatment do not only act as anticoagulants but also reduce inflammation and platelet reactivation, which have an important role in the pathogenesis of AF and thromboembolism.

Chronic inflammation is frequently seen in chronic diseases such as DM, HT, chronic kidney failure, connective tissue diseases, and cancer[15-17]. In addition, increased inflammation is associated with a poor prognosis in coronary artery disease[18]. CBC parameters including RDW, MPV, and NLR have been used as inflammatory markers in cardiovascular diseases[19-21]. Inflammation is involved in a variety of AF-related pathological processes including oxidative stress, fibrosis, and thrombogenesis[22]. Although it is not clear whether AF-related inflammation is a cause or a consequence of arrhythmia, the development of atrial fibrosis in AF, which is caused by inflammation and inflammation-induced endothelial damage, platelet and endothelial cell activation, and activation of the coagulation cascade, shows that inflammation contributes to the pathophysiology of AF[22].

Saliba et al[19] showed that the risk of stroke in patients with AF was directly related to RDW in a dose-response manner and that this association was independent of the stroke risk factors included in the CHADS2 and CHA2DS2-VASc scores. The authors also noted that the RDW

**Table IV.** Comparison of RDW, MPV, and NLRchanges.

| | NOAC (+) (n=380) | NOAC (-) (n=150) | p |
|---|---|---|---|
| RDW | 4.05 ± 5.6 | 0.51 ± 3.09 | 0.000 |
| MPV | 0.67 ± 1.1 | 0.29 ± 1.69 | 0.000 |
| NLR | 0.79 ± 0.05 | 0.15 ± 3.03 | 0.009 |

NOAC: Novel oral anticoagulants; RDW: Red cell distribution; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio. Independent samples t-test was used in the analysis of variables.

value predicted stroke independent of anemia status and revealed that the accuracy of CHADS2 and CHA2DS2-VASc scores in stroke prediction increased with the addition of RDW. The biological mechanisms to explain the relationship between RDW and cardiovascular disease remain unclear. As a possible mechanism, it is argued that oxidative stress and inflammation shorten the survival time of red blood cells, resulting in more heterogeneous red blood cell volumes[23,24]. Cha et al[25] showed that increased RDW values were associated with increased thromboembolic events in patients with nonvalvular AF. The authors recommended the cut-off values to be used in the prediction of increased thromboembolic risk as ≥13.9% in patients with AF and as 15% in patients with concurrent AF and heart failure[25]. Taken together, these two studies[19,25] emphasize the close relationship between AF and RDW. We consider that this relationship, albeit unclear, is based on inflammation. Elevated RDW levels are an important indicator of inflammation. Also elevated RDW levels may even be associated with the degree of inflammation[26]. In the present study, the RDW value was significantly lower in the NOAC group compared to the non-NOAC group and we consider that NOAC treatment, beside its anticoagulant properties, may also reduce the risk of stroke through another mechanism, possibly by acting on inflammation through the abovementioned mechanisms.

Makowski et al[20] explored whether AF causes increased platelet reactivity independent of other risk factors. Patients with lone AF who did not have other comorbidities known to affect platelet activation were included in the study to confirm the hypothesis and the results indicated that the changes in platelet activation and MPV observed after the restoration of sinus rhythm in patients without concomitant diseases suggested that arrhythmia essentially leads to increased platelet reactivity and that the increased platelet expression of adhesion molecules despite the restoration of sinus rhythm implicates that the anticoagulant therapy should be continued. The authors also noted that the changes in platelet reactivity observed in patients after the restoration of sinus rhythm demonstrate that arrhythmia naturally leads to increased platelet reactivity[20]. MPV is a commonly used marker of platelet reactivity since it is associated with increased platelet reactivity[27]. MPV is considered a risk marker of thrombogenesis in AF[20]. Additionally, MPV has been shown to be positively associated with the severity of ischemic strokes[28] and a poor outcome[29]. In the present study, MPV values were significantly lower in the NOAC group compared to the non-NOAC group, which implicates that NOAC may cause a reduction in platelet reactivation.

The neutrophil-to-lymphocyte ratio (NLR) has been implicated as a risk marker of AF development after coronary artery bypass grafting (CABG)[21]. In addition, NLR is considered a predictor of early recurrence of AF following radiofrequency catheter ablation[30]. Elevated NLR has been shown to increase the risk of thromboembolic stroke in patients with nonvalvular AF[31]. Shao et al[32] suggested that NLR is a newly recognized and potent predictor of AF and that it is a simple, inexpensive, and routinely assessed CBC parameter that can be a promising and useful predictor of AF recurrence after surgery or cardioversion. Either neutrophilia or lymphopenia can increase the NLR, which allows us to explicate the potential mechanism of the increasing NLR in the systemic inflammatory status[33]. In our study, we determined that NLR was significantly lower in the NOAC group compared to the non-NOAC group. Based on our findings, we consider that NOAC will both reduce thromboembolism and decrease the recurrence of AF by reducing NLR, which is a key marker of AF recurrence. This mechanism provides another answer to our hypothesis "Are NOAC anticoagulants only?".

In studies[34,35] examining atherosclerosis-induced mice and stroke-induced rats, it has been reported that tissue mRNA levels of inflammatory cytokines including interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNF-α), and monocyte chemo attractant protein-1 (MCP-1) are decreased with rivaroxaban treatment. Terry et al[36] established a rat model of central venous catheter (CVC) dysfunction and found that CVC was significantly more patent in rivaroxaban-treated mice compared to the control group (93.8% *vs.* 62.9%). Additionally, significant changes were observed in plasma IL-6 or TNF-α levels in rivaroxaban-treated mice and the authors suggested that this mechanism was due to the effect of rivaroxaban on inflammation. Our study supports the hypothesis of that study. However, unlike that study, our study was conducted on humans and evaluated other inflammatory parameters (RDW, MPV, NLR) as well.

### Limitations

Our study had some limitations. First, the study was a single-center, retrospective case-control

study. Second, NOAC were not compared among themselves, long-term results were not evaluated, and inflammatory parameters other than CBC parameters were not examined.

## Conclusions

In conclusion, beside NOAC well-known properties, the following potential were found:

- bypass an important pathway in the pathogenesis of AF by suppressing inflammation through their effects on the RDW level,
- maintain the continuity of sinus rhythm in patients with paroxysmal AF, which will reduce the NLR level, which is considered to be a promising and useful predictor for AF recurrence,
- prevent platelet reactivation by reducing the MPV level, which is considered a risk marker of thrombogenesis in AF. Further larger scale studies investigating long-term effects of NOAC are needed to substantiate our findings.

### Conflict of Interest

The Authors declare that they have no conflict of interest.

### Ethics Approval

The study protocol was conducted in accordance with the Declaration of Helsinki and the study was approved by Inonu University Medical School Clinical Research Ethics Committee (Date: June 17, 2020; No: 2020/98).

### Informed Consent

Informed consent was obtained from all subjects before the start of the study.

### Authors' Contribution

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

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