

## Reply to Letter to the Editor: "Anticoagulation in Real-Life Patients with Atrial Fibrillation: Impact of Renal Disease"

To the Editor,

We would like to thank the esteemed author Anetta Undas for reading our manuscript with interest and for her contributions. We would like to contribute to the author's valuable comments and answer her questions.

The renal elimination rate of nonvitamin K antagonist anticoagulants (NOACs) can vary within a wide range. Around 80% of dabigatran, 50% of edoxaban, 35% of rivaroxaban, and 27% of apixaban can be eliminated by kidney.<sup>1</sup> Renal function should be monitored at least once a year in all patients using NOACs.<sup>2</sup> Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved for use in patients with severe chronic kidney disease (CKD) in Europe [stage 4, i.e., creatinine clearance (CrCl) 15-29 mL/min] on a reduced dose regimen. In Europe, NOACs should not be prescribed for patients with atrial fibrillation (AF) and severe CKD (CrCl < 15 mL/min).<sup>3</sup> It is recommended to monitor CrCl at least once a year using the Cockcroft–Gault (CCG) method in patients receiving NOAC therapy and not having CKD.<sup>2</sup> In 2018, the European Heart Rhythm Association (EHRA) reported that the current use of edoxaban, rivaroxaban, and apixaban may be inadequate in patients with "hyper-normal" kidney function [i.e., glomerular filtration rate (GFR) > 95 mL/min/1.73 m<sup>2</sup>].<sup>4</sup> In all NOAC registry studies comparing NOAC group drugs with warfarin, GFR was evaluated with the CCG–CrCl formula.<sup>5-9</sup> Despite the undisputed superiority of the Chronic Kidney Disease Epidemiology Collaboration formula over CCG–CrCl and other creatinine-based formulas, EHRA, European Society of Cardiology (ESC), and North American consensus documents and guidelines on AF still recommend the CCG formula for assessing renal function in patients considering NOAC therapy and in patients currently receiving treatment.<sup>3,4,10,11</sup> In another study, although the CCG method has traditionally been used to calculate kidney function in all NOAC studies, it has been reported that this method can no longer be considered an accurate way to evaluate kidney function.<sup>12</sup> In our AFTER-2 study, we calculated the GFR value using the CCG formula. The CCG formula may have found lower GFR values in some patient groups. We classified it as follows: GFR ≥ 90 as stage I, 60 ≤ GFR < 90 as stage II, 30 ≤ GFR < 60 as stage III, 15 ≤ GFR < 30 as stage IV, GFR < 15 as stage V. In our study, the age ratio and female gender ratio were relatively high. In addition, patients with GFR < 60 were evaluated as CKD. Therefore, we found that the most common comorbid condition in patients was CKD.<sup>13</sup> In addition, we had 327 (12.6%) patients with GFR ≥ 90, 479 (18.5%) patients with 60 ≤ GFR < 90, 1141 (44%) patients with 30 ≤ GFR < 60, 499 (19.3%) patients with 15 ≤ GFR < 30, and 146 (5.6%) patients with GFR < 15. Among our patient population, rivaroxaban was the most commonly used NOACs, followed by dabigatran. We think that the reason for this is that these molecules were included in the scope of reimbursement earlier in our country. Dabigatran has been reimbursed in Turkey since May 2013 and rivaroxaban since October 2013.<sup>14</sup> In addition, we think that the single dose use of rivaroxaban may be effective in the choice of treatment. It is known that reducing the dosage frequency increases drug compliance. The distribution of patients using warfarin and NOAC group drugs according to GFR intervals is shown in Table 1 in detail.



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## LETTER TO THE EDITOR REPLY

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**Table 1. Oral Anticoagulation Use According to Glomerular Filtration Rate Ranges**

Parameters	GFR ≥ 90	60 ≤ GFR < 90	30 ≤ GFR < 60	15 ≤ GFR < 30	GFR < 15	Total Number of Patients
Dabigatran 150 mg (%)	3 (0.1)	15 (0.6)	38 (1.5)	3 (0.1)	0	59 (2.3)
Dabigatran 110 mg (%)	14 (0.5)	39 (1.5)	205 (7.9)	80 (3.1)	15 (0.6)	353 (13.6)
Rivaroxaban 20 mg, (%)	0	10 (0.4)	34 (1.3)	13 (0.5)	0	57 (2.2)
Rivaroxaban 15 mg (%)	29 (1.1)	64 (2.5)	307 (11.8)	152 (5.8)	28 (1.08)	580 (22.37)
Apixaban 5 mg (%)	8 (0.3)	20 (0.8)	6 (0.2)	1 (0.0)	0	35 (1.35)
Apixaban 2.5 mg (%)	55 (2.1)	101 (3.9)	89 (3.4)	19 (0.73)	8 (0.3)	272 (10.5)
Edoxaban 60 mg (%)	3 (0.3)	7 (0.27)	5 (0.19)	0	0	15 (0.57)
Edoxaban 30 mg (%)	3 (0.3)	9 (0.34)	16 (0.61)	3 (0.1)	1 (0.03)	32 (1.23)
NOAC (%)	115 (4.4)	265 (10.2)	700 (27.0)	271 (10.4)	52 (2.0)	1403 (54.1)
Warfarin (%)	110 (4.2)	136 (5.24)	359 (13.8)	146 (5.63)	57 (2.19)	808 (31.17)

GFR, glomerular filtration rate; NOAC, nonvitamin K antagonist oral anticoagulant.

The coexistence of AF and CKD includes serious risks in terms of both thromboembolic events and major bleeding.<sup>15</sup> Insufficient and inappropriate doses of NOACs are not uncommon in clinical practice. Physician preference and experience, age, comorbid conditions, patient's lifestyle, and patient preference are among the reasons for this.<sup>16</sup> In a study, lower doses of NOACs were prescribed in 30% of AF patients despite the indication for a standard treatment dose.<sup>17</sup> Around 16.4% of the patients received a reduced dose of NOACs instead of a full dose.<sup>17</sup> In particular, 7% of patients treated with rivaroxaban received a full dose of NOACs instead of reduced doses.<sup>17</sup>

Although the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score was high in our study, the number of patients who did not use any OAC was 558 (24.9%). The mean age of these patients was 68.6 ± 10.9 years, and 308 (55.1%) patients had a high HASBLED score (HASBLED score ≥ 3). When we examine the GFR intervals of this patient group, we identified 89 (15.9%) patients with GFR ≥ 90, 123 (22%) patients with 60 ≤ GFR < 90, 179 (32.1%) patients with 30 ≤ GFR < 60, 132 (23.7%) patients with 15 ≤ GFR < 30, and 35 (6.3%) patients with GFR < 15. The rate of inadequate dose of NOACs was relatively high in our study. The causes of inappropriate doses of NOACs can be explained by patient preference and high HASBLED scores. However, the 2018 ESC AF guidelines emphasize that the HASBLED score should not be used for NOAC prescriptions.<sup>4</sup> In the case of drugs such as Non-steroidal anti-inflammatory drugs (NSAIDs) and steroid, alcohol consumption and lifestyle recommendations, anticoagulation dose reduction may be considered. Finally, patients who have high HASBLED score require more outpatient clinic visits. Physicians and patients should be encouraged to use NOACs, especially in patients with high CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score with GFR ≥ 30.

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