Appropriateness of dabigatran dosing in patients with nonvalvular atrial fibrillation (NVAF): A retrospective study conducted in a tertiary care university hospital in the eastern province of Saudi Arabia

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Background: Establishment of thromboembolism prevention remains a challenge despite the widespread consensus that thromboprophylaxis safely reduces patient morbidity and mortality. Dabigatran is a nonvitamin K antagonist oral anticoagulant (NOAC) which reduces the risk of thromboembolism. Proper dosing is important to achieve the maximum prophylactic benefit with a maintained safety profile.

Objective: To evaluate the appropriateness of dabigatran dosing for stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation (NVAF).

Methods: This is a retrospective cohort study of adults with NVAF. The data were collected from the electronic filing system of the hospital. Patients receiving dabigatran therapy were divided into two treatment groups according to the dose of dabigatran received. The indications for dabigatran as an oral direct anticoagulant, including age, risk of bleeding, creatinine clearance (CrCl), were collected. Appropriateness of dose reduction included any of the following factors: HAS-BLED score >2 points, age ≥75 years, or CrCl of 30–50 mL/min. The two groups were evaluated according to dose appropriateness.

Results: Dabigatran dose of 110 mg was found to be inappropriately low in a large number of patients (31.3%). Multivariate regression analysis showed significant association of age and dose appropriateness ($p < 0.001$).

Conclusion: This study revealed inappropriate prescription of reduced doses of dabigatran in a large number of patients. Age was identified as the main driving factor for underdosing. Physicians’ and pharmacists’ awareness regarding this type of high-risk medication should be improved to ensure appropriate and safe use of this commonly used drug.

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1. Introduction

Nonvitamin K oral anticoagulants (NOACs) are considered to be a major advance in oral anticoagulation and have been demonstrated to significantly reduce stroke and systemic embolization associated with nonvalvular atrial fibrillation (NVAF) [1,2]. Four NOACs are licensed for clinical NVAF treatment: dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban [3], and edoxaban, which act as factor Xa inhibitors [4,5]. Dabigatran was the first NOAC approved for NVAF treatment [1], and is increasingly being used in clinical practice for thromboprophylaxis in atrial fibrillation as a convenient therapy which does not require drug or anticoagulation level monitoring [6]. Dabigatran, 150 mg, has been demonstrated to be superior to warfarin in stroke prevention, while maintaining a similar safety profile [1]. In addition, dabigatran 110 mg is non-inferior to warfarin in stroke prevention, but has a superior safety profile [1]. The dose selection for dabigatran is determined by age, glomerular filtration rate (GFR), and bleeding risk (HAS-BLED score). The pharmaceutical manufacturer of dabigatran, Boehringer Ingelheim, Al Khobar, Saudi Arabia recommends dabigatran dose reduction (110 mg twice daily) in the presence of the following patient factors: age >75 years, creatinine clearance (CrCl) of 30–50 mL/min, or increased bleeding risk while contraindicated if CrCl is <30 mL/min. Moreover, this recommendation was also endorsed by the NOAC guidelines established by the Clinical Excellence Commission [6]. By contrast, the Practical Guidelines set out by the European Heart Rhythm Association [7] recommend dabigatran dose reduction in the presence of the following patient factors: age >80 years, concomitant use of verapamil, or increased risk of gastro-intestinal bleeding, and contraindicate dabigatran when CrCl is <30 mL/min. We noticed that most of the patients who are prescribed dabigatran receive the reduced dose (110 mg twice daily), despite the higher efficacy of the standard dose. The main goal of the present study is to evaluate the appropriateness of the dabigatran dose reduction in our institution in order to provide recommendations for the prescribing physicians.

2. Materials and methods

The present study is a retrospective cohort study of adults treated for NVAF, conducted during the period between April 2018 and July 2018. All of the patients receiving dabigatran in our out-patient settings were identified in this study. Exclusion criteria included receiving dabigatran for indications other than NVAF and missing clinical information. The demographic data, including CHA2DS2-VASc score, HAS-BLED score, the estimated CrCl using the Cockcroft–Gault formula along with liver panel, history of gastrointestinal bleeding, and concomitant use of other drugs such as verapamil and antiplatelet, were collected from the Quadramed electronic filing system. The patients were divided into two groups based on received dabigatran dose. Group A included patients receiving the standard dabigatran dose (150 mg twice daily), and Group B included patients receiving the reduced dabigatran dose (110 mg twice daily). We chose to determine the appropriateness of dose reduction and standard dose using a more conservative approach than endorsed by the manufacturer and the clinical excellence commission NOAC guidelines [6]. Dose reduction was considered appropriate if any of the following requirements were met: HAS-BLED score ≥2 points, age ≥75 years, or CrCl of 30–50 mL/min. Both groups were further subdivided into appropriate and inappropriate dose categories and data analysis was carried out between the subgroups. Statistical analyses were performed using Student t test assuming unequal variances for continuous variables and Chi-square test for nominal variables.

Multivariate regression was performed to determine factors associated with inappropriate dose reduction.

3. Results

A total of 211 patients receiving dabigatran were identified, out of which 60 patients were excluded (22 for taking dabigatran for indications other than NVAF and 38 for missing data). The remaining 151 patients were, therefore, included in the analysis.
A total of 49 patients (32.5%) were identified as receiving the standard dabigatran dose (Group A) and 102 patients (67.5%) as receiving the reduced dabigatran dose (Group B). The patients’ characteristics are summarized in Table 1. Our results demonstrate that mean age (±SD) for patients in Group A was 58 (±11) years compared with 74 (±10) years in Group B (p < 0.0001). Moreover, mean CrCl was 109 (±40) mL/min for patients in Group A compared with 71 (±32.5) mL/min for patients in Group B (p < 0.0001). The mean CHA2DS2-VASc score was 3 (±1) compared with 4 (±2) for patients in Group B (p < 0.0001). The patients in the two study groups were further categorized according to dabigatran dose appropriateness (Tables 2 and 3). The reduced dabigatran dose was found to be inappropriate in a total of 34 patients (33.3%), out of which 32 patients were receiving inappropriately reduced dose while being eligible for the standard dose, and two patients were receiving dabigatran despite contraindications. Further analysis revealed the mean age of 78 (±7) years, 65 (±9) years (p < 0.0001), CrCl or 64 (±25) mL/min and 89 (±30) mL/min (p = 0.0012), CHA2DS2-VASc score of 2 (±1) and 1 (±1) (p < 0.0001), HAS-BLED score of 1 (±1) and 2 (±1) (p < 0.0001) for the appropriate and inappropriate conditions, respectively. Multivariate regression analysis revealed significant correlation of age and dose reduction.

Table 1. Patient characteristics.

| Patient characteristics | Group A (Dose of 150 mg), n = 49 | Group B (Dose of 110 mg), n = 102 | p   |
|-------------------------|----------------------------------|----------------------------------|-----|
| Age (yr), mean ± SD     | 58 ± 11                          | 74 ± 10                          | <0.0001 |
| CrCl (mL/min), mean ± SD| 109 ± 40                         | 71 ± 32.5                        | <0.0001 |
| CHA2DS2-VASc, mean ± SD | 3 ± 1                            | 4 ± 2                            | <0.001  |
| HAS-BLED score, mean ± SD| 1 ± 1                            | 2 ± 1                            | <0.001  |

CrCl = creatinine clearance; SD = standard deviation.

Table 2. Patient characteristics based on appropriateness of dabigatran dosing in Group A.

| Patient characteristics | Appropriate dose n = 36 | Inappropriate dose, n = 11 | p       |
|-------------------------|-------------------------|----------------------------|---------|
| Age (yr), mean ± SD     | 55 ± 9                  | 70 ± 7                     | <0.0001 |
| CrCl (mL/min), mean ± SD| 115 ± 40                | 80 ± 24                    | 0.0018  |
| CHA2DS2-VASc, mean ± SD | 2 ± 1                   | 4 ± 1                      | <0.001  |
| HAS-BLED score, mean ± SD| 1 ± 1                  | 3 ± 1                      | <0.0001 |
| Heart failure, %        | 33.3                    | 18.1                       | 0.34    |
| Hypertension, %         | 52.7                    | 100                        | <0.005  |
| Diabetes mellitus, %    | 52.7                    | 45.4                       | 0.67    |
| History of stroke, %    | 13                      | 54.5                       | 0.0053  |
| Peripheral arterial disease, % | 0.00          | 18.1                       | 0.0089  |
| Gastrointestinal bleeding, % | 0.00          | -                          | -       |
| Use of antiplatelet drugs, % | 11.1                   | 18.1                       | 0.5385  |

CrCl = creatinine clearance; SD = standard deviation.

Table 3. Patient characteristics based on appropriateness of dabigatran dosing in Group B.

| Patient characteristics | Appropriate dose n = 68 | Inappropriate dose n = 32 | p       |
|-------------------------|-------------------------|----------------------------|---------|
| Age (yr), mean ± SD     | 78 ± 7                  | 65 ± 9                     | <0.0001 |
| CrCl (mL/min), mean ± SD| 64 ± 25                 | 89 ± 30                    | 0.0012  |
| CHA2DS2-VASc, mean ± SD | 2 ± 1                   | 1 ± 1                      | <0.0001 |
| HAS-BLED score, mean ± SD| 1 ± 1                  | 2 ± 1                      | <0.0001 |
| Heart failure, %        | 54.4                    | 40.6                       | 0.1984  |
| Hypertension, %         | 85.2                    | 75                         | 0.2133  |
| Diabetes mellitus, %    | 67.6                    | 56.2                       | 0.26803 |
| History of stroke, %    | 35.2                    | 3.1                        | <0.001  |
| Peripheral arterial disease, % | 4.4                 | 0.00                       | 0.22766 |
| Gastrointestinal bleeding, % | 5.8                   | 3.1                        | 0.55508 |
| Use of antiplatelet drugs, % | 29.4                   | 15.6                       | 0.13749 |

CrCl = creatinine clearance; SD = standard deviation.
inappropriateness \([p < 0.001, 95\% \text{ confidence interval (CI)} = 0.014–0.03]\). There was no significant association between other factors considered and inappropriate dose reduction (Table 4).

### 4. Discussion

Appropriate dosing of NOAC is critical for achieving their beneficial therapeutic effects. Our results reveal that the majority of patients receiving dabigatran in our institute (102/151 cases) were prescribed the reduced dose which was found to be inappropriately low in 33.3\% of all cases. Age appeared to be the single significant factor in physicians’ dosing decision. Although age is an important decision factor for NOACs dose regimen, our results suggest that the physicians tend to prescribe the reduced dose inappropriately to patients older than 65 years. In addition, using a more liberal approach to determine the dose regimen as recommended by the European Heart Rhythm Association Practical Guidelines [7] would also result in a higher incidence of prescription of inappropriately reduced dose of dabigatran. A recent retrospective study by Whitworth et al. [8] has demonstrated similar results, with inappropriate doses of NOACs prescribed in 33.0\% of patient cases. In another study, Carlin et al. [9] found that 53\% of their patient cohort had been prescribed inappropriate doses of apixaban. Further, when Park et al. [10] had evaluated the appropriateness of NOAC dosing in family medicine practice, it was found that 15 out of 64 patients (23\%) received incorrect doses of NOAC. Another study carried out in a community hospital by Armbruster et al. [11] found that 76 out of 458 patients (16.0\%) were prescribed inappropriate dose regimen of dabigatran to prevent stroke and venous thromboembolism.

It has been previously demonstrated that the standard dabigatran dose is more effective in reducing thromboembolic events compared with the reduced dose [1] and, therefore, should be prescribed in the absence of contraindications (Table 5). In our study, we found a low threshold in terms of prescribing the reduced dose of dabigatran among treating physicians. Therefore, increased effort to improve physicians’ and pharmacists’ knowledge, attitude, and practice regarding the appropriate dabigatran dosing is warranted. We recommend the following for reduction in the incidence of inappropriate dosing of dabigatran: (1) the contributory factors resulting in reducing the dose of dabigatran should be addressed according to the guidelines; (2) utilization of a special form for NOAC prescription that includes patient age, CrCl, and bleeding risk, along with the recommended dose; and (3) reassessment of the patient’s condition upon each visit, because the patient’s characteristics may vary.

#### 4.1. Limitations

Because this is a relatively small retrospective study conducted in a single-center setting, the source of the data was limited to the electronic medical filing system of the hospital. In addition, physicians’ and pharmacists’ awareness regarding dabigatran dosing and up-to-date recommendations for its use was not evaluated in this study. This study did not intend to evaluate clinical outcome of different dose regimens; however, Randomized Evaluation of Long Term Anticoagulant

### Table 4. Multivariate regression result for factors associated with dose appropriateness.

| Patient characteristics | OR   | 95\% CI (lower, upper) | \(p\)  |
|-------------------------|------|------------------------|-------|
| Age, per 1-y increase   | 1.02 | 0.01, 0.03             | <0.0001|
| CrCl mL/min per 1 mL/min decrease | 0.99 | 0.01, 0.48             | 0.06  |
| CHA2DS2-VASc per 1-unit increase | 1.04 | 0.025, 0.11            | 0.22  |
| HAS-BLED score per 1-unit increase | 1.09 | 0.04, 0.22             | 0.19  |
| History heart failure   | 0.95 | 0.22, 0.11             | 0.56  |
| History hypertension    | 0.83 | 0.42, 0.05             | 0.12  |
| History diabetes mellitus | 1.1  | 0.05, 0.25             | 0.21  |
| History of stroke       | 1.04 | 0.18, 0.27             | 0.69  |
| History of peripheral arterial disease | 0.96 | 0.44, 0.36             | 0.84  |
| History of upper gastrointestinal bleeding | 1.21 | 0.13, 0.50             | 0.23  |
| Use of antiplatelet drugs | 1.0  | 0.20, 0.20             | 0.99  |

\(\text{CI} = \text{confidence interval}; \text{CrCl} = \text{creatinine clearance.}\)
Therapy trial has demonstrated the superiority of using the standard dose of dabigatran over the reduced one in stroke prevention [1].

5. Conclusion

We found that one third of the patients treated with the reduced dabigatran dose of 110 mg twice daily are eligible for the standard dose and therefore, their dosing regimen is considered inappropriate. Age was the most important contributing factor for underdosing. Thus, continuous medical education of practicing physicians and pharmacists is of utmost importance to improve knowledge, attitude, and practice regarding the proper dosing of NOAC.

Conflicts of interest

The authors declare that there is no conflict of interest. There is no financial relationship with pharmacological companies or other institutions.

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