Retrospective Comparison of Patients $\geq$ 80 Years With Atrial Fibrillation Prescribed Either an FDA-Approved Reduced or Full Dose Direct-Acting Oral Anticoagulant

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ABSTRACT

Direct-acting oral anticoagulants (DOACs) represent the standard for preventing stroke and systemic embolization (SSE) in patients with atrial fibrillation (AF). There is limited information for patients $\geq$ 80 years. We report a retrospective analysis of AF patients $\geq$ 80 years prescribed either a US Food and Drug Administration (FDA)-approved reduced ($n = 514$) or full dose ($n = 199$) DOAC (Dabigatran, Rivaroxaban, or Apixaban) between January 1st, 2011 (first DOAC commercially available) and May 31st, 2017. The following multivariable differences in baseline characteristics were identified: patients prescribed a reduced dose DOAC were older ($p < 0.001$), had worse renal function ($p = 0.001$), were more often prescribed aspirin ($p = 0.004$) or aspirin and clopidogrel ($p < 0.001$), and more often had new-onset AF ($p = 0.001$). SSE and central nervous system (CNS) bleed rates were low and not different (1.02 vs 0 %/yr and 1.45 vs 0.44 %/yr) for the reduced and full dose groups, respectively. For non-CNS bleeds, rates were 10.89 vs 4.15 %/yr ($p < 0.001$, univariable) for the reduced and full doses, respectively. The mortality rate was 6.24 vs 1.75 %/yr ($p = 0.001$, univariable) for the reduced and full doses. Unlike the non-CNS bleed rate, mortality rate differences remained significant when adjusted for baseline characteristics. Thus, DOACs in patients $\geq$ 80 with AF effectively reduce SSE with a low risk of CNS bleeding, independent of DOAC dose. The higher non-CNS bleed rate and not the mortality rate is explained by the higher risk baseline characteristics in the reduced DOAC dose group. Further investigation of the etiology of non-CNS bleeds and mortality is warranted.

1. Introduction

Atrial fibrillation (AF) is a modern epidemic with a prevalence of up to 23.5 % in the rapidly growing elderly population $\geq$ 80 years [1–3]. AF is associated with an increased risk of stroke and systemic embolization (SSE), as well as mortality [4–5]. In addition, strokes related to AF tend to be more debilitating and severe than strokes not associated with AF [6–8].

Since 2009, four direct-acting oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban, and edoxaban, have been compared to warfarin in prospective randomized clinical trials for stroke prevention in patients with atrial fibrillation [9–12]. Reduced and full doses of all DOACs have been approved by the US Food and Drug administration (FDA) on the basis of these trials to prevent SSE in patients with AF,
| Variable                                | Reduced dose, total (n = 514) | Full dose, total (n = 199) | P-value* | D75, (n = 53) | D150, (n = 57) | P-value* | R15, (n = 224) | R20, (n = 74) | P-value* | A2.5, (n = 236) | A5, (n = 68) | P-value* |
|----------------------------------------|------------------------------|---------------------------|----------|---------------|---------------|----------|---------------|---------------|----------|----------------|-------------|----------|
| Age (mean +/- 1SD)                     | 86.8 ± 3.9                  | 83.2 ± 1.4                | <0.001   | 86 ± 3.3      | 82.7 ± 1.4    | <0.001   | 86.8 ± 3.8    | 82.5 ± 4.2    | <0.001   | 87.1 ± 4.1    | 84.5 ± 0.7  |          |
| Men, n (%)                             | 206 (40.2)                  | 97 (48.7)                 |          | 30 (56.6)     | 24 (42.1)     |          | 83 (37.2)     | 39 (52.7)     |          | 92 (38.8)     | 34 (50)     |          |
| BMI (kg/m$^2$)                         | 25.4 ± 5.13                 | 27.2 ± 1.2                | <0.001   | <0.033        | 26.2 ± 4.3    | 27.9 ± 3   | 25.7 ± 5.4    | 26.4 ± 3.2    | <0.001   | 24.9 ± 4.9    | 27.4 ± 3.3  | 0.004    |
| AF Type                                |                             |                           |          |               |               |          |               |               |          |               |             |          |
| New-onset AF, n (%)                    | 182 (35.4)                  | 45 (22.6)                 | <0.001   | <0.001        | 12 (22.6)     | 4 (7)     | 78 (35)       | 16 (21.6)     | <0.001   | 91 (38.4)     | 25 (36.8)   |          |
| Paroxysmal AF, n (%)                   | 220 (42.8)                  | 87 (43.7)                 |          | <0.033        | 27 (50.9)     | 29 (50.9)  | 98 (43.9)     | 33 (44.6)     |          | 95 (40.1)     | 25 (36.8)   |          |
| Chronic AF, n (%)                      | 107 (20.8)                  | 67 (33.7)                 |          |               |               |          |               |               | <0.001   |               |             |          |
| Aspirin use, n (%)                     | 209 (45.34)                 | 52 (26.1)                 | 0.004    | <0.001        | 15 (26.3)     |            | 103 (46)      | 16 (21.6)     | 0.003    | 86 (36)       | 21 (30.9)   |          |
| Clopidogrel use, n (%)                 | 10 (2.17)                   | 5 (2.5)                   |          |               |               |          |               |               |          |               |             |          |
| Aspirin + Clopidogrel use, n (%)       | 50 (10.85)                  | 3 (1.5)                   | <0.001   | <0.033        | 1 (1.9)       | 2 (3.5)    | 4 (1.8)       | 3 (4.1)       |          | 5 (2.1)       | 0           |          |
| Creatinine clearance (mL/min)          | 44.1 ± 16.0                 | 59.4 ± 14.1               | <0.001   | <0.001        | 54.5 ± 60.8   | 45.7 ± 15.3 | 59.3 ± 0.7    | 42.5 ± 31.7   | <0.001   | 58.4 ± 16.3   | <0.001      |          |
| Serum Creatinine                       | 1.22 ± 0.67                 | 0.99 ± 0.21               |          |               |               |          |               |               |          |               |             |          |
| Hemoglobin (g/dL)                      | 12.52 ± 1.7                 | 12.9 ± 1.5                |          |               |               |          |               |               |          |               |             |          |
| WBC count (x 10$^9$/L)                 | 7.48 ± 3.7                  | 7.8 ± 1.1                 |          |               |               |          |               |               |          |               |             |          |
| Platelet count (x 10$^9$/L)           | 213.94 ± 74                 | 217.2 ± 45.3              |          |               |               |          |               |               |          |               |             |          |
| Stroke/TIA, n (%)                      | 99 (19.3)                   | 33 (16.6)                 |          |               |               |          |               |               |          |               |             |          |
| Systemic embolism, n (%)               | 2 (0.4 %)                   | 0                        |          |               |               |          |               |               |          |               |             |          |
| Myocardial infarction, n (%)           | 73 (14.2)                   | 15 (7.5)                  |          |               |               |          |               |               |          |               |             |          |
| Valvular Heart Disease, n (%)          | 365 (71)                    | 124 (62.3)                |          |               |               |          |               |               |          |               |             |          |
| Valve replacement/repair, n (%)        | 35 (6.8)                    | 6 (3)                     |          |               |               |          |               |               |          |               |             |          |
| Heart failure, n (%)                   | 163 (31.7)                  | 27 (13.6)                 |          |               |               |          |               |               |          |               |             |          |
| Diabetes Mellitus, n (%)               | 87 (16.9)                   | 32 (16.1)                 |          |               |               |          |               |               |          |               |             |          |
| Hypertension, n (%)                    | 364 (70.8)                  | 151 (75.9)                |          |               |               |          |               |               |          |               |             |          |
| Coronary Artery Disease, n (%)         | 169 (36.8)                  | 67 (33.7)                 |          |               |               |          |               |               |          |               |             |          |
| Peripheral Artery Disease, n (%)       | 33 (6.4)                    | 9 (4.5)                   |          |               |               |          |               |               |          |               |             |          |
| Cardioid disease, n (%)                | 43 (8.4)                    | 10 (5)                    |          |               |               |          |               |               |          |               |             |          |
| Hypercoagulable State, n (%)           | 3 (0.6)                     | 1 (0.5)                   |          |               |               |          |               |               |          |               |             |          |
| Coronary Stent(s), n (%)               | 99 (19.3)                   | 23 (11.6)                 |          |               |               |          |               |               |          |               |             |          |
| CABG, n (%)                            | 46 (8.9)                    | 14 (7)                    |          |               |               |          |               |               |          |               |             |          |
| Pacemaker, n (%)                       | 137 (26.7)                  | 42 (22.1)                 |          |               |               |          |               |               |          |               |             |          |
| Ablation, n (%)                        | 62 (12.1)                   | 21 (10.5)                 |          |               |               |          |               |               |          |               |             |          |
| Left atrial appendage (LAA) closure, n | 4 (0.8)                     | 1 (0.5)                   |          |               |               |          |               |               |          |               |             |          |
| Prescription as per label, n (%)       | 268 (52.1)                  | 167 (83.9)                | <0.001   | <0.001        | 15 (28.3)     | 55 (100)   | 135 (60.3)    | 49 (70)       |          | 119 (63)      | <0.001      |          |

D75 = Dabigatran 75 mg twice daily; D150 = Dabigatran 150 mg twice daily; R15 = Rivaroxaban 15 mg once daily; R20 = Rivaroxaban 20 mg once daily; A2.5 = Apixaban 2.5 mg twice daily; A5 = Apixaban 5 mg twice daily.

* All p-values are from multivariable stepwise regression.
representing a significant medical advancement [13–14]. The reduced doses of the DOACs were tested in pivotal clinical trials, except for Dabigatran 75 mg twice daily (D75), which was approved by the FDA based on pharmacokinetic modeling and simulation [15–17]. Following the approval of D75, a study of patients with chronic kidney disease (CKD) confirmed the exposure levels predicted by the dosing simulations [18].

In a prior publication, we performed a retrospective analysis of patients ≥ 80 years with atrial fibrillation from the Bryn Mawr Medical Specialists Association (BMMSA) database who were prescribed either the reduced dose DOAC or warfarin [19]. The reported rates of SSE trended lower in the reduced dose DOAC group [19]. The rate of central nervous system (CNS) bleeds was low in both groups [19]. The rates of major bleeding and all-cause mortality were higher in the reduced dose DOAC group compared to warfarin [19].

In this report, we extend the review of the BMMSA database to include patients ≥ 80 years of age with AF who were prescribed a full dose DOAC. Thus, a direct comparison in a real-world population of the reduced dose DOAC with the full dose DOAC was possible.

2. Methods

This study is an institutional review board-approved retrospective analysis of the BMMSA outpatient electronic records and the inpatient Mainline Health SmartChart database between January 1st, 2011, when Dabigatran was first commercially available, and May 31st, 2017. Two teams of investigators collected the data. Team 1 had access to patient records and collected the data in a de-identified format. Team 2 entered the data into the Microsoft Excel database without knowledge of patient identity [19]. We identified 514 patients who were prescribed the FDA-approved reduced dose DOACs and 199 who were prescribed the FDA-approved full dose DOACs. The baseline characteristics of these patients were compared, as shown in Table 1.

The clinical outcomes collected were SSE, CNS bleeding, non-CNS bleeding, and all-cause mortality. All outcomes were reported as the time-to-first-event. Additional data collected included time to switching anticoagulants, discontinuation of anticoagulation, and the number of patients lost to follow-up. The time periods after these events were excluded from the analysis. Patients who completed the observation period without any outcome event were identified (Fig. 1).

A stroke was defined as a sudden focal neurological deficit confirmed with either CT or MRI as a proven embolic event that persisted beyond 24 hours. CNS bleeding was defined as intracranial and/or spinal bleeds as identified by imaging. A non-CNS bleed was defined as any non-neurological bleeding event that led to DOAC discontinuation for more than 2 weeks. Mortality data were obtained from the BMMSA and Main Line Health databases and publicly available death notices. The cause of death was only available if the death occurred in a hospital setting or if the office database included notice of hospice status for a particular cause. Patients lost to follow-up were defined as any patient who was last seen 3 months or more before the last date of this retrospective analysis, May 31st, 2017.

The first analysis compared the baseline characteristics of all patients prescribed either a reduced dose or a full dose DOAC, independent of the specific DOAC used. The second analysis compared individual reduced and full dose DOACs. Both analyses began with univariable testing followed by a multivariable test of those characteristics that showed a difference in the univariable analysis. The univariable tests included unpaired t-tests for normally distributed numeric variables, Mann-Whitney U tests for non-normal numeric variables, and Chi-square or Fisher Exact tests for non-numeric variables. These analyses were followed by a stepwise multivariable logistic regression in which all characteristics that were univariably different at p ≤ 0.10 were entered into the model, thus ensuring that confounding variables were considered. The stepwise model retained variables that attained p ≤ 0.05.

Outcome events were compared between the reduced and the full
dose DOAC groups using Kaplan-Meier curves and log-rank tests. These analyses were then followed by multivariable proportional hazards models to adjust for the baseline variables that were significantly different between reduced and full dose DOACs (p ≤ 0.05) in the stepwise multivariable logistic regression analyses. To obtain person-year rates, the number of outcome events was divided in each group by the total years of follow-up for that specific group. P-values were generated by log-rank tests.

The reduced and full doses of DOAC were defined based on the published US consensus statement for the management of patients with atrial fibrillation [13–14].

For apixaban, the full dose is 5 mg twice daily (A5). The dose is reduced to 2.5 mg twice daily (A2.5) if the patient meets 2 out of the 3 following criteria: age ≥ 80 years, weight ≤ 60 kg, or creatinine ≥ 1.5 mg/dL.

For dabigatran, the full dose is 150 mg twice daily (D150) if creatinine clearance is > 30 mL/min. The dose is reduced to 75 mg twice daily (D75) if creatinine clearance is 15–30 mL/min. Of note, D75 outcome data has not been reported outside the BMMSA database [19].

For rivaroxaban, the full dose is 20 mg daily (R20). The dose is reduced to 15 mg daily (R15) if creatinine clearance is 30–49 mL/min.

3. Results

3.1. Baseline characteristics

Thirty-three baseline characteristics were collected (Table 1). The first analysis combined all the DOACs in a multivariable comparison of patients prescribed either a reduced or full dose DOAC. The following variables were identified as being significantly different: compared to the full dose group, patients prescribed the reduced dose were older (p < 0.001), had lower creatinine clearance (p = 0.001), were more often on antiplatelet therapy (ASA p = 0.004, ASA + clopidogrel p < 0.001), and had a higher prevalence of new-onset AF (p = 0.001). In contrast, full dose DOAC patients were more likely to have chronic AF (p = 0.011).

A second analysis of the baseline characteristics of patients prescribed either the reduced or full dose of the individual DOACs was conducted. Edoxaban was prescribed to only one patient, hence no further analysis of the edoxaban group was performed. When D75 was compared to D150 (Table 1), patients prescribed the reduced dose were older (p < 0.001), more often had new-onset AF (p = 0.033) and had worse renal function (p = 0.037). The number of patients prescribed their respective dabigatran dose on label was 28.3 % for the reduced dose and 100 % for the full dose, showing a significant univariable difference (p < 0.001). However, multivariable testing to assess the difference could not be done because all the patients in the full dose group were prescribed the dose on label. Compliance with the guidelines was determined in all but 2 patients in the D150 group.

When patients were prescribed either R15 or R20 daily, the differences were similar to those found for dabigatran (Table 1). Notably, those receiving R15 were older (p < 0.001), more often had new-onset AF (p < 0.001) and had a worse renal function with higher serum creatinine (p < 0.001). In addition, patients in the R15 group were more often men (p < 0.001), more often treated with aspirin (p = 0.006), and less likely to have a pacemaker (p = 0.011), and less likely to be prescribed the reduced dose as per label (p = 0.03).

When patients were prescribed either A2.5 or A5, those receiving A2.5 had a lower body mass index (p = 0.004), more commonly were prescribed aspirin and clopidogrel (p = 0.044), had lower creatinine clearance (p < 0.001), were more likely to have heart failure (p = 0.004) and were less likely to be prescribed the reduced dose as per label (p < 0.001) (Table 1). As expected, based on the dosing guidelines the reduced dose DOAC groups had worse kidney function.
3.2. Outcomes

At the end of the observation period, 245 (48 %) patients remained on the reduced dose DOAC, and 118 (59 %) patients remained on the full dose DOAC without an outcome event (Fig. 1). Outcomes were reported as time-to-first-event (Tables 2 and 3, Figs. 1 and 2). The rate of SSE for the reduced dose group was 1.02%/yr, and for the full dose group 0%/yr. (Fig. 1, Table 2). The rate of CNS bleeds was similarly low in both groups and was 1.45%/yr. for the reduced group and 0.44%/yr for the full dose group (p = 0.11 univariable). The rate of non-CNS bleeds was 10.89 and 4.15%/yr (p < 0.001 univariable) for the reduced dose and full dose groups, respectively. When the rates of non-CNS bleeds were corrected for differences in baseline characteristics using a multivariable analysis, the significant difference between the reduced and the full dose DOAC groups (Table 2) was no longer present (p = 0.249). For all-cause mortality, the rate was higher in the reduced dose DOAC group (6.26%/yr.) compared to the full dose DOAC group (1.75%/yr.), (p < 0.001 univariable). This difference remained significant after correcting for baseline differences (p = 0.013 multivariable) (Table 2). The comparison of the clinical outcomes for the reduced and full dose of individual DOACs mirrored the comparison of the combined DOAC groups (Table 3).

4. Discussion:

This retrospective analysis of a multi-specialty practice database from a single center was designed to fill a knowledge gap by comparing patients ≥ 80 years old with atrial fibrillation prescribed either a reduced or full dose DOAC. While DOAC use in octogenarians with AF has been reported in both randomized and observational studies, these previously published analyses have focused on comparisons between DOACs and warfarin [9–12,19–23].

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**Fig. 2.** Kaplan-Meier curves for time to SSE (A), death (B), non-CNS bleed (C), and CNS bleed (D) for all reduced dose and full dose DOAC groups.

**Table 4**

Event rates from post hoc age-related analyses of the RE-LY, ROCKET-AF, and ARISTOTLE trials.

| Events       | Dabigatran (RE-LY) | Rivaroxaban (ROCKET-AF) | Apixaban (ARISTOTLE) |
|--------------|---------------------|-------------------------|----------------------|
| Age (years)  | 80–84 (n = 2305)    | ≥85 (n = 722)           | ≥75 years (n = 3111) |
|              | ≥75 years (n = 5678) |                       |                      |
| Dose         | D110                | D150                    | R15 or R20*          |
|              |                      | D110                    | R20                  |
|               | 1.95                | 1.73                    | 2.15                 |
| SSE (%/yr)   | 1.61                | 2.15                    | 4.86                 |
| Major bleeding (%/yr) | 5.01 | 5.91  | 3.29  |
| Intracranial bleeding (%/yr) | 0.35  | 0.23  | 0.43  |
| All-cause mortality (%/yr) | 6.05  | 9.23  | 5.42  |

D110: Dabigatran 110 mg twice daily; D150: Dabigatran 150 mg twice daily; R15: Rivaroxaban 15 mg daily, R20: Rivaroxaban 20 mg daily; A2.5: Apixaban 2.5 mg twice daily, A5: Apixaban 5 mg twice daily.

*Analysis did not differentiate between R15 and R20.
With respect to baseline characteristics, this study reports that patients prescribed a reduced DOAC were older, had worse renal function, and were more often prescribed anti-platelet agents. With regards to outcomes, the rates of SSE and CNS bleeds were low independent of the individual DOAC prescribed, the DOAC dose, and the baseline risk. This finding is consistent with reported results from the pivotal clinical trials that led to the approval of each DOAC [9–12](Table 4). Non-CNS bleed rates were higher in the reduced dose DOAC group. This difference was no longer statistically different when correcting for baseline characteristics. By contrast, mortality was found to be higher in the reduced dose DOAC group and was independent of the baseline characteristics. A limitation of the mortality analysis was that the cause of death in most patients could not be accurately determined.

The impact of DOACs on outcomes has been studied extensively, but data comparing reduced and full dose treatment is sparse, particularly in patients ≥80 years. Thus, despite the limitation of this single-center retrospective study, our analysis provides useful information that could be used in further research involving larger patient groups.

This study also raises important questions regarding appropriate dosing of DOACs in octogenarians with AF. A significant number of patients in this analysis were inappropriately prescribed the reduced and full dose DOAC according to the current FDA-approved dosing guidelines. Only 52.1% of the patients receiving the reduced dose DOAC and 83.1% of those receiving the full dose DOAC were prescribed the doses according to the guidelines. These findings are consistent with an observational study from Naples, Italy which evaluated the appropriateness of DOAC dosing in AF patients ≥80 years [22]. They reported that out of 178 patients, 19 patients (25.6%) were overdosed, and 56 patients (74.4%) were underdosed according to guidelines. They also reported that survival was significantly reduced in underdosed patients compared to those who received the guideline-directed DOAC dose (p < 0.001).

Renal function is a critical variable concerning the safety of all DOACs [24–27] and requires continuous monitoring for dose adjustment [27]. In our report, patients who were prescribed the reduced dose DOAC had worse renal function compared to those prescribed the full dose, with a CrCl of 44.1 ± 16.0 for the reduced group and 59.4 ± 14.1 for the full dose group (p < 0.001). The pivotal DOAC clinical trials did not include patients with a CrCl < 30 (re-LY, ROCKET-AF, and ENGAGE-AF) [9–10,12] or with a CrCl < 25 in the ARISTOTLE trial [11]. Current guidelines recommend the use of DOACs in CKD stages I-IV. The exception is dabigatran which is not used in CKD stage IV [28]. The use of oral anticoagulants in CKD stage IV remains at the discretion of the prescribing clinician [29]. Apixaban is approved for use in patients with ESRD based on observational studies [30]. In addition, current guidelines do not require dose reduction for renal dysfunction alone, which includes patients on dialysis [31].

Between 17 and 46.5% of patients with atrial fibrillation have coronary artery disease [32–34]. The management of these patients is challenging because of the perceived need for concomitant use of antiplatelet therapy, which increases the risk of bleeding [35–36]. In this analysis, the concomitant use of antiplatelet agents was one factor associated with increased non-CNS bleeding.

5. Conclusions and limitations

We acknowledge that post-hoc analyses lack the scientific rigor of randomized prospective trials. However, despite limitations, this real-world analysis reports SSE and CNS bleeds in both reduced and full dose DOAC-treated patients ≥80 years old with AF are low and similar to the rates reported in prospective clinical trials in younger patients. These findings were independent of the individual DOAC prescribed. Non-CNS bleed rates were higher in the reduced dose DOAC group. This difference was not statistically different when correcting for baseline differences. By contrast mortality was found to be higher in the reduced dose DOAC group but was independent of the baseline characteristics.

Thus topics requiring further research should focus on outcomes related to compliance with guideline-directed dosing and evaluating the incidence and etiology of non-CNS bleeds and the cause of death in octogenarians with AF.

6. Disclosures

Dr. Ezekowitz is a member of the “Guideline Committee on Atrial Fibrillation” for the AHA, ACC, and HRS and a consultant for Boston Scientific and Sanofi. Dr. Ezekowitz was Co-Principal Investigator of the re-LY and EMANATE trials and served on the executive committee of the X-VERT, ENSURE-AF, and ENGAGE-AF trials. Dr. Harper was a participant in the EMANATE trial. All other co-authors have no disclosures.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Michael D. Ezekowitz reports financial support was provided by Boston Scientific. Michael D. Ezekowitz reports financial support was provided by Sanofi-Aventis US LLC. Glenn Harper reports a relationship with Pfizer, Bristol Myers Squibb that includes: funding grants. Michael D. Ezekowitz reports a relationship with Pfizer, Bristol Myers Squibb that includes: funding grants. Michael D. Ezekowitz reports a relationship with Boehringer Ingelheim that includes: funding grants. Michael D. Ezekowitz reports a relationship with Johnson and Johnson that includes: funding grants.]

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References

[1] M.C. Fang, J. Chen, M.W. Rich, Atrial Fibrillation in the Elderly, Am. J. Med. 120 (6) (2007) 481–487, https://doi.org/10.1016/j.amjmed.2007.01.026.
[2] M. Zoni-Berisso, F. Lercari, T. Carazza, S. Domenicucci, Epidemiology of atrial fibrillation: European perspective, Clin. Epidemiol. 6 (1) (2014) 213–220.
[3] V. Russo, A. Carbone, A. Rago, P. Golino, G. Nigro, Direct oral anticoagulants in octogenarians with atrial fibrillation: it is never too late, J. Cardiovasc. Pharmacol. 73 (4) (2019) 207–214.
[4] A.S. Go, E.M. Hylek, V. Chang, K.A. Phillips, L.E. Hensault, A.M. Capra, N. G. J esenovsl, J.V. Selby, D.E. Singer, Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? J. Am. Med. Assoc. 290 (20) (2003) 2685.
[5] J.P. Bassand, S. Virdone, S.Z. Goldhaber, A.J. Camm, D.A. Fitzmaurice, K.A. Fox, G. Horgan, E.B. Williams, K.L. Furie, P.J. Kelly, Stroke associated with atrial fibrillation, Circulation 139 (6) (2019) 787–798.
[6] P.S.J. Miller, P.L. Anderson, J. Krala, Are cost benefits of anticoagulation for stroke prevention in atrial fibrillation underestimated? Stroke 36 (2) (2005) 360–366.
[7] N. Hannon, O. Sheehan, L. Kelly, M. Marzane, A. Merwick, A. Moore, L. Kyne, J. Duggan, J. Moroney, P.M.E. McCormack, L. Daly, N. Fitz-Simon, D. Harris, G. Horgan, E.B. Williams, K.L. Furie, P.J. Kelly, Stroke associated with atrial fibrillation: incidence and early outcomes in the north Dublin population stroke study, Cerebrovasc Dis. 29 (1) (2010) 43–49.
[8] N.E. Andrew, A.G. Thrift, D.A. Cadilhac, The prevalence, impact and economic implications of atrial fibrillation in stroke: what progress has been made? Neuroepidemiology 40 (4) (2013) 227–239.
[9] J.S. Connolly, M.D. Ezekowts, S. Yusuf, J. Eikelboom, J. Oldgren, A. Parekh, J. Pogue, P.A. Reilly, E. Themoses, J. Varrone, S. Wang, M. Alings, D. Xavier, J. Zhu, R. Diaz, B.S. Lewis, H. Darius, H.-C. Diener, C.D. Joyner, L. Wallentin,idarbitran versus Warfarin in Patients with Atrial Fibrillation, N. Engl. J. Med. 361 (10) (2011) 883–891.
[10] R. Taoutel et al. IJC Heart & Vasculature 43 (2022) 101130
[11] C.B. Granger, J.H. Alexander, J.J.V. McMurray, R.D. Lopes, E.M. Hylek, M. Hanna, H.R. Al-Khalidi, J. Ansell, D. Atar, A. Avezum, M.C. Bahit, R. Diaz, J.D. Easton, J. A. Ezekowitz, G. Flaker, D. Garcia, M. Geraldes, B.J. Gersh, S. Golitsyn, S. Goto, A. G. Hermosillo, S.H. Hohnloser, J. Horowitz, P. Mabas, P. Jansky, R.S. Lewis, J.
Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment, J. Clin. Pharmacol. 52 (9) (2012) 1373–1378.

J. Friedman, Dabigatran etexilate in atrial fibrillation patients with severe renal impairment: dose identification using pharmacokinetic modeling and simulation, J. Clin. Pharmacol. 52 (9) (2012) 1373–1378.

J.L. Martin, M.G.D. Bates, Management of atrial fibrillation and concomitant coronary artery disease, Contin Cardiol. Educ. 3 (2) (2017) 47–53.

V. Russo, E. Attena, M. Di Maio, et al., Non-vitamin K vs vitamin K oral anticoagulants in patients aged >80 years with atrial fibrillation and low body weight, Eur. J. Clin. Invest. 50 (11) (2020) e13335.

V. Russo, E. Attena, M. Di Maio, C. Mazzone, A. Carbone, V. Parisi, A. Ragno, A. D’Onofrio, P. Golino, G. Nigro, Clinical profile of direct oral anticoagulants versus vitamin K antagonists in octogenarians with atrial fibrillation: a multicentre propensity score matched real-world cohort study, J. Thromb. Thrombolysis. 49 (1) (2020) 42–53.

A. Carbone, P. Santelli, R. Bottino, E. Attena, C. Mazzone, V. Parisi, A. D’Andrea, P. Golino, G. Nigro, V. Russo, Prevalence and clinical predictors of inappropriate direct oral anticoagulant dosage in octogenarians with atrial fibrillation, Eur. J. Clin. Pharmacol. 78 (5) (2022) 879–886.

V. Russo, E. Attena, M. Baroni, R. Trotta, M.C. Manu, P. Kirchhof, R. De Caterina, Clinical performance of oral anticoagulants in elderly with atrial fibrillation and low body weight: insight into Italian cohort of PREFER-AF and PREFER-AF prolongation registries, J. Clin. Med. Res. 11 (13) (2022) 3791.

K.F. Chan, R.P. Giugliano, M.R. Patel, et al., Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF, J. Am. Coll. Cardiol. 67 (24) (2016) 2888–2899.

J. Lutz, K. Jurk, H. Schmaier, Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations, Int. J. Nephrol. Renovasc. Dis. 10 (2017) 135–143.

J. Weber, A. Olyaei, J. Shatzel, The efficacy and safety of direct oral anticoagulants in patients with chronic renal insufficiency: a review of the literature, Eur. J. Haematol. 102 (4) (2019) 312–318.

V. Aursuleiene, I.I. Costache, Anticoagulation in chronic kidney disease: from guidelines to clinical practice, Clin. Cardiol. 42 (8) (2019) 774–782.

S. Roguda, A. Goeteck, T. Mazurek, E.P. NAVARESE, J. Szarzak, K.J. Filipiak, Safety and efficacy of DOACs in patients with advanced and end-stage renal disease, Int. J. Environ. Res. Public Health 19 (3) (2022), https://doi.org/10.3390/ijerph19031436.

S. Hariharan, R. Madabushi, Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment, J. Clin. Pharmacol. 52 (1 Suppl) (2012) 119S–125S.