

Efficacy and safety of non-vitamin K antagonist oral anticoagulants in very elderly patients with atrial fibrillation: a single-center experience

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Introduction Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly used in atrial fibrillation (AF), regardless of age, and they are now preferred over vitamin K antagonists (VKAs).¹ Atrial fibrillation occurs in 10% to 17% of the population over 80 years old^{1,2} and increases the risk of ischemic stroke at least 4 fold.³

While treating very elderly patients with NOACs, it is important to consider several comorbid diseases such as increased risk of falls, dementia, chronic kidney disease, and liver disease as well as drug-drug interactions to ensure the safety of anticoagulation.⁴

A large global registry showed that 82.3% of patients over 85 years with newly diagnosed AF receive anticoagulation, of which nearly 46% are treated with NOACs,⁵ most commonly with apixaban.⁶ The current European Society of Cardiology guidelines indicate that very elderly patients with AF do better on oral anticoagulants than not and on NOACs rather than VKAs.⁷ In elderly patients with AF, safety concerns represent the main reason for insufficient use of oral anticoagulants.⁸

The aim of this case series was to evaluate the efficacy and safety of apixaban, rivaroxaban, and dabigatran in real-life AF patients aged 85 years or older, who were followed at a single institution on a long-term basis.

Methods We enrolled 40 consecutive patients over 85 years old, who were diagnosed with non-valvular AF and in whom NOAC treatment was initiated in January 2015. We excluded patients

with a history of serious gastrointestinal or intracranial bleeding, known cancer, hemoglobin levels of less than 9 g/dl, thrombocytopenia ($<50 \times 10^3/\mu\text{l}$), chronic kidney disease stage 5, or potent drug-drug interactions. All patients were recruited in outpatient clinics at John Paul II Hospital in Kraków, Poland. The study protocol was approved by the bioethics committee, and all patients gave informed consent to participate in the study.

The HAS-BLED and CHA₂DS₂-VASc scores were used to evaluate bleeding and thromboembolic risk, respectively. Definitions of all comorbidities were derived from our previous study.⁹ Major bleeding and clinically relevant nonmajor bleeding (CRNMB) were defined according to International Society on Thrombosis and Hemostasis criteria.¹⁰

Patients were followed on a 6-month basis (a visit at the center or telephone contact). We recorded the incidence of ischemic stroke, transient ischemic attack, systemic embolism, and bleeding. Stroke was diagnosed based on the occurrence of a new and abrupt focal neurologic deficit persisting for more than 24 hours and confirmed by positive imaging findings. Transient ischemic attack was defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, lasting less than 24 hours.

Apart from routine laboratory investigations, electrochemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany) were used to measure growth differentiation factor 15 (GDF-15) and N-terminal fragment of

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the prohormone brain natriuretic peptide (NT-proBNP). ARCHITECT i1000SR (Abbott Laboratories, Abbott Park, Illinois, United States) was used to assess cardiac troponin I (cTnI) levels.

Statistical analysis was performed with the Statistica 12.5 software (StatSoft, Tulsa, Oklahoma, United States). Continuous variables were expressed as median (interquartile range [IQR]) or mean (SD), while qualitative variables, as numbers (percentages). The 2 patient groups were compared using the Mann–Whitney test or χ^2 test or Fisher exact test. A *P* value of less than 0.05 was considered significant.

Results and discussion We enrolled 40 patients aged from 85 to 93 years (women, 57.5%). Baseline characteristics of patients are presented in TABLE 1. Three-fourths of the study group had permanent AF and all patients had a high thromboembolic risk. Patients most frequently received apixaban (2.5 mg twice daily, 50% of patients; 5 mg twice daily, 12.5%), while dabigatran (110 mg twice daily, 20%) or rivaroxaban (15 mg/d, 17.5%) were used less commonly. Fourteen patients (35%) used an inappropriate NOAC dosing regimen, with a predominance of those on apixaban, 2.5 mg twice daily (78.5%), instead of apixaban, 5 mg twice daily. There were no differences in demographic, clinical, and laboratory parameters between patients on apixaban and those receiving dabigatran or rivaroxaban (TABLE 1).

During a median follow-up of 23.5 months (IQR, 20–27 months), 2 strokes (2.5%/year) and 1 episode of systemic embolism (1.2%/year) were reported. Ischemic stroke was reported in 2 patients receiving apixaban, 2.5 mg twice daily, in the 20th and 17th month of follow-up (including 1 patient after discontinuation of NOACs while on prophylactic enoxaparin during hospitalization for pneumonia). Systemic thromboembolism occurred after a 5-day discontinuation of apixaban, 5 mg twice daily, due to cataract surgery. Eight patients died (4%/year), including 5 due to cardiovascular causes (1 death from acute pulmonary embolism and 1 from acute myocardial infarction on reduced-dose apixaban). Major bleeds and CRNMB were reported in 4 patients each (5%/year), including 1 nonfatal intracranial bleeding on dabigatran, 110 mg twice daily. Four gastrointestinal bleeds (5%/year), all on reduced-dose apixaban, occurred in the first year of follow-up without coadministration of aspirin. The rates of thromboembolic and bleeding outcomes were similar in both treatment groups (TABLE 1).

The concentrations of GDF-15 were higher in 8 patients with clinically relevant bleedings as compared with the remaining patients (3228 pg/ml [IQR, 1571–3328 pg/ml] vs 1519 pg/ml [IQR, 1075–2560 pg/ml]; *P* = 0.046). No similar differences were noted for NT-proBNP and

cTnI levels. No significant differences in any of the 3 biomarkers were noted between 3 patients with thromboembolic events as compared with the remainder.

This case series shows acceptable rates of ischemic cerebrovascular events as well as major bleeding and CRNMB in patients aged 85 years or older, who were treated with NOACs. The rates of major bleeding were similar to those reported in seminal NOAC trials for AF patients over the age of 75 years (5.7%/year)¹¹; however, stroke or systemic embolism was more common in our study (1.7%/year).¹¹ We failed to demonstrate better safety of apixaban compared with rivaroxaban, 15 mg once daily, and dabigatran, 110 mg twice daily, in very elderly patients with AF.

Kim et al¹³ reported the results for 403 patients with AF treated with NOACs at a mean (SD) age of 83.4 (3.2) years, who received dabigatran (35%), rivaroxaban (39%), or apixaban (26%). They found a similar thromboembolic risk (2.4%/year) to that in our study, with a lower risk of major and gastrointestinal bleeds (2%/year each). Since our patients were older, all above 85 years, it might be speculated that this difference contributes to the higher bleeding risk in the current series, together with a low level of knowledge on AF and anticoagulation, related in part to cognitive impairment.⁸

Regarding dosing regimens, the current guidelines recommend using reduced-dose NOACs in elderly patients mainly with impaired renal function.^{1,5} However, reduced-dose dabigatran should be used in patients older than 80 years, while apixaban, 2.5 mg twice daily, is recommended in the presence of creatinine levels of 133 $\mu\text{mol/l}$ or higher or weight of 60 kg or lower in this elderly population.¹ The overrepresentation of AF patients on reduced off-label doses of NOACs is observed worldwide, which leads to an increased risk of stroke with unaltered bleeding risk.^{5,12} In the present study, we did not observe an increase in embolic events; however, we noted a higher risk of bleeding in patients who received too low a dose of apixaban.

Our novel finding is that elevated GDF-15 levels at baseline in very elderly patients with AF starting NOAC treatment might be useful in the prediction of bleeding, which is consistent with a study by Hijazi et al,¹³ although they analyzed patients aged 72 years on average. GDF-15, known to be a marker of oxidative stress and inflammation, has been shown to be independently associated with bleeding and thromboembolic events in AF. The current finding, if validated in a larger group, might help identify patients aged 85 years or older who require closer surveillance.

The study has several limitations. First, the group was small, but the findings are

TABLE 1 Baseline characteristics and clinical outcomes of the studied patients

Parameter	All patients (n = 40)	Apixaban (n = 25)	Dabigatran or rivaroxaban (n = 15)	P value	
Age, y	86.5 (86–89)	87 (86–89)	86 (85–90)	0.49	
Male sex, n (%)	17 (42.5)	13 (52)	4 (26.7)	0.12	
Body mass index, kg/m ²	24.9 (21.5–26.1)	25.3 (23.7–26.1)	24.1 (20.5–26.3)	0.2	
Former smoking, n (%)	16 (40)	12 (48)	4 (26.7)	0.18	
Time since AF diagnosis, y	6 (3–14)	5 (3–12)	9 (3–15)	0.32	
CHA ₂ DS ₂ -VASc	6 (5–6)	6 (5–6)	6 (5–6)	0.93	
HAS-BLED	2 (2–3)	2 (2–3)	2 (2–3)	0.96	
Comorbidities, n (%)	Diabetes mellitus	18 (45)	12 (48)	6 (40)	0.62
	Peripheral arterial disease	23 (57.5)	14 (56)	9 (60)	0.8
	Chronic kidney disease	28 (70)	16 (64)	12 (80)	0.48
	Coronary heart disease	24 (60)	14 (56)	10 (66.7)	0.5
	Prior stroke	7 (17.5)	5 (20)	2 (13.3)	0.69
	Ulcer disease	4 (10)	3 (12)	1 (6.7)	0.99
Hemoglobin, g/dl	12.9 (1.2)	12.9 (1.2)	12.9 (1.1)	0.93	
White blood cells, × 10 ³ /μl	6 (5–6.8)	6 (4.9–6.8)	6.2 (5–6.9)	0.58	
Fasting blood glucose, mmol/l	6.1 (5.6–6.7)	6.2 (5.7–6.9)	6.1 (5.3–6.5)	0.32	
Creatinine clearance, ml/min	50.6 (12.4)	50.6 (12.6)	50.6 (12.6)	0.91	
Platelet count, × 10 ³ /μl	202.4 (44.8)	200.8 (44.5)	205.1 (46)	0.78	
NT-proBNP, pg/ml	912 (421–1620)	713 (401–1476)	1193 (545–1992)	0.26	
GDF-15, pg/ml	1654 (1167–3029)	1532 (1141–2030)	2574 (1193–3265)	0.23	
cTnI, ng/l	6.8 (5.3–9.4)	7.5 (5.1–9.2)	6.3 (5.4–11)	0.68	
Medications, n (%)	Statin	26 (65)	17 (68)	9 (60)	0.61
	ASA	6 (15)	5 (20)	1 (6.7)	0.38
	Proton pump inhibitor	24 (60)	16 (64)	8 (53.3)	0.5
Follow-up	Duration, mo	23.5 (20–27)	23 (20–26)	25 (19–30)	0.2
	Stroke/TIA/systemic embolism	3 (7.5)	3 (12)	0 (0)	0.28
	Major bleeding/CRNMB	8 (20)	5 (20)	3 (20)	0.99
	Death	8 (20)	7 (28)	1 (6.7)	0.22
	Cardiovascular death	5 (12.5)	5 (20)	0 (0)	0.38

Data are shown as number (percentage), median (interquartile range) or mean (SD).

Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid, CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex; CRNMB, clinically relevant nonmajor bleeding; cTnI, cardiac troponin I; GDF-15, growth differentiation factor 15; HAS-BLED, hypertension, abnormal liver function, history of stroke or thromboembolism, history of bleeding, age ≥65 years, use of nonsteroidal anti-inflammatory drugs, alcohol abuse; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; TIA, transient ischemic attack

representative of very elderly Polish patients with AF. Secondly, our results could not be referred to elderly AF patients with prior major bleeds, who were ineligible. Given large differences between regions in Poland in terms of anticoagulation used in AF, which is in part related to the type of center,¹⁴ the rates in other centers

might be higher. We did not measure NOAC concentrations, which might have helped optimize anticoagulation in high-risk groups.¹⁵

In conclusion, our single-center experience supports the use of NOACs as a safe and effective anticoagulation treatment in AF patients aged 85 years or older.

ARTICLE INFORMATION

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