Brief Reports

Real-life Performance of Edoxaban in Elderly Patients With Atrial Fibrillation: a Multicenter Propensity Score–Matched Cohort Study

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ABSTRACT

Purpose: The purpose of the current study was to compare the efficacy and safety of edoxaban versus vitamin K antagonist (VKA) therapy among a cohort of elderly patients (ie, those aged ≥75 years) with atrial fibrillation (AF) in a real-life setting.

Methods: A propensity score–matched cohort observational study was performed comparing the safety and efficacy of edoxaban versus VKA therapy among a cohort of elderly (aged ≥75 years) patients with AF in a real-life setting. Follow-up data were obtained through outpatient visits at 1, 3, and every 6 months. The primary safety outcome was major bleeding. The primary efficacy outcome was the composite of stroke, transient ischemic attack, and systemic embolism.

Findings: A total of 130 patients receiving edoxaban 60 mg (EDO) treatment were compared with the same number of VKA recipients. The mean follow-up was 16 (2.6) months. The cumulative incidence of thromboembolic events in the EDO and VKA groups was 1.5% (2 of 130) and 2.3% (3 of 130), respectively ($P < 0.6$). The cumulative incidence of major bleeding events was 1.5% (2 of 130) in the EDO group and 3.1% (4 of 130) in the VKA group ($P < 0.4$). The total anticoagulant therapy discontinuation rate was 2.3% (3 of 130) in the EDO group and 4.6% (6 of 130) in the VKA group ($P < 0.3$). A nonsignificant trend in improved adherence was observed between the EDO and VKA groups (81% vs 78%; $P = 0.6$).

Implications: Edoxaban therapy showed a good real-life performance among elderly patients (aged ≥75 years) with AF. (*Clin Ther*. 2019;41:1598–1604)

Key Words: Real life, Atrial fibrillation, Edoxaban, Efficacy, Safety, Vitamin K antagonists.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and its prevalence increases with age, ranging from 0.1% in patients aged <55 years to >9% in octogenarian patients.[1] As a result of increased life expectancy, the number of elderly patients (ie, those

Accepted for publication April 18, 2019
https://doi.org/10.1016/j.clinthera.2019.04.041
0149-2918/$ - see front matter

aged ≥75 years) with AF is expected to significantly increase in the next years. Patients with AF have a 5-fold increased risk of ischemic stroke, and older age increases the risk of both thromboembolic and hemorrhagic events.[2] The management of oral anticoagulant therapy in elderly patients represents a unique challenge due to higher comorbidities and concerns about frailty and the risk of major bleeding events.[3–5] Non–vitamin K antagonist oral anticoagulants (NOACs) are a well-established effective and safe therapy for stroke prevention in patients with nonvalvular AF, and current guidelines recommend their use over vitamin K antagonists (VKAs).[6] Edoxaban, a direct factor Xa inhibitor, has been shown to be noninferior to warfarin in preventing stroke or systemic embolic events and superior to warfarin in reducing major bleeding events in patients with AF in a randomized controlled trial, with a greater absolute numeric reduction in the rates of major bleeding among elderly patients with AF.[7,8] However, to the best of our knowledge, no data comparing real-life outcomes between edoxaban and VKAs in elderly patients with AF are available. The objective of the current propensity score–matched cohort study was to compare the safety and efficacy of newly initiated edoxaban versus well-controlled VKA therapy among elderly patients (aged ≥75 years) with AF.

PATIENTS AND METHODS

Data for this study were obtained from the prospectively maintained Atrial Fibrillation Research Database shared by 6 Italian cardiologic centers (Monaldi Hospital, Naples; University of Campania "Luigi Vanvitelli," Naples; University of Naples Federico II, Naples; Maggiore Hospital, Trieste; Ruggi D'Aragona Hospital–University of Salerno, Salerno; and Roccadaspide Hospital, Salerno). The database includes all patients with AF followed up by these centers through outpatient visits at 1, 3, and every 6 months. All patients provided written informed consent before inclusion in the database, and the study was approved by the local institutional review committee.

During the follow-up visits, the clinical status, adherence to treatment, occurrence of stroke, transient ischemic attack (TIA), systemic embolism, major bleeding events, minor bleeding events, and other side effects were evaluated. Ischemic stroke was defined as a focal neurologic deficit lasting for at least 24 h with no signs of hemorrhage on cerebral imaging and was verified radiologically. TIA was defined as an acute focal neurologic deficit lasting <24 h. Systemic embolism was defined as an acute vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion and not associated with another likely cause. Major bleeding was defined as a fatal bleeding or symptomatic bleeding in a critical area or organ or bleeding causing a fall in hemoglobin level of ≥2 g/dL or leading to transfusion of two or more units of whole blood or red blood cells.[9] Minor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but requiring medical intervention or temporary interruption of the anticoagulant drug. Adherence to treatments was assessed by using proportion of days covered at each follow-up visit. One-year adherence to treatment was defined by using the cutoff point for proportion of days covered of ≥80%. The database was queried for patients with AF aged ≥75 years who were prescribed edoxaban 60 mg once daily (n = 264) or VKA (n = 810). Patients with AF who had follow-up ≥360 days after the first qualifying anticoagulant prescription were considered for the primary efficacy (composite of stroke, TIA, and systemic embolism) and safety (major bleeding events) end points and for the secondary efficacy (all-cause death) and safety (minor bleeding events) end points. Potentially eligible patients receiving edoxaban (n = 186) and VKA (n = 764) were propensity score matched to generate an analysis cohort with minimal differences in baseline characteristics.

Descriptive statistics of patient characteristics were evaluated; in particular, frequency and percentage were reported for the categorical variables, and mean and SD were used to summarize continuous variables. The incidence of bleeding was calculated both as incidence rate (the ratio between the number of new events that occurred during the follow-up and the person-time accrued from the study members) every 100 patient-years and as cumulative incidence. Continuous variables were compared by using *t* tests, and categorical variables were compared by using χ^2 tests. Propensity score matching was used to balance the differences in baseline characteristics between patients receiving edoxaban versus VKA.[10] The model included all pretratment variables that could affect the treatment assignment and/or the outcome. The 1:1 nearest according first to clinical judgment

and/or previous evidence in literature and, only in third instance, in case of doubt, considering the results of our exploratory regression analysis for treatment assignment and study end points (less reliable due to risk of overfitting). The 1:1 nearest neighborhood caliper matching was used to match patients based on the logit of the propensity score by using a caliper equal to 0.2 of the SD of the logit of the propensity score.

The adequacy of matching was assessed by comparing the status of each covariate and the standardized differences of means between the 2 groups, with a value <10% indicating between-group balance.[11] A Kaplan–Meier analysis and log-rank test were used to compare the event rates of primary end points over time. All statistical analyses were performed by using STATA version 11.1SE (StataCorp, College Station, Texas).

RESULTS

Propensity score logit matching identified 130 edoxaban recipients and the same number of VKA recipients who were comparable with respect to demographic and clinical characteristics. International normalized ratio was not included in matching because it would be inherently higher in the VKA group. Baseline characteristics of the study population before and after propensity score matching are summarized in the Table. The mean follow-up was 16 (2.6) months. Five patients experienced thromboembolic events (ischemic stroke, TIA, and systemic embolism) during follow-up. The cumulative incidence of thromboembolic events in the EDO and VKA groups was 1.5% (2 of 130) and 2.3% (3 of 130), respectively ($P < 0.6$).

Six patients had a major bleeding event. The cumulative incidence of major bleeding events was 1.5% (2 of 130) in the EDO group and 3.1% (4 of 130) in the VKA group ($P < 0.4$). Figures 1 and 2 show the Kaplan–Meier cumulative probability of event-free survival for major bleeding and thromboembolic events, respectively, in the EDO and VKA treatment groups. Three patients died during the follow-up: 1 cardiovascular death occurred in a patient receiving VKA; 2 additional noncardiovascular deaths were reported (1 lung cancer–related death in the edoxaban group and 1 prostate cancer–related death in the VKA group). Minor bleeding events were reported in 5 (3.8%) of 130 patients in the EDO group and in 8 (6.1%) of 130 patients in the VKA group ($P < 0.4$). The total anticoagulant therapy discontinuation rate was 2.3% (3 of 130) in the EDO group and 4.6% (6 of 130) in the VKA group ($P < 0.3$). Optimal adherence to anticoagulation therapy was observed in 81% of EDO-treated patients and in 78% of VKA-treated patients ($P = 0.6$).

DISCUSSION

Despite the incidence of thromboembolic events being higher in the elderly and outweighing the risk of major bleeding events,[12] oral anticoagulation is often underprescribed in elderly patients in clinical practice.[13] Long-term anticoagulation with VKAs has been shown to reduce the incidence of ischemic stroke versus aspirin in patients with AF aged ≥75 years without increasing the incidence of major bleeding events[14,15]; however, difficulties in keeping a target time in therapeutic range, increased risk of falling and bleeding events, and potential drug–drug interactions are the main reasons for suboptimal use of VKAs among elderly patients with AF in the real-world setting.[4,16–18] NOACs lack the limitations associated with VKAs and may offer benefits and increased convenience in older subjects; in particular, a meta-analysis of randomized controlled trials of NOACs in patients with AF aged ≥75 years found significantly lower rates of stroke and systemic embolism than conventional treatment, with no increased risk of bleeding.[19]

Of 21,105 subjects enrolled in the ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial, 8474 patients were ≥75 years of age (40.1%), representing the largest number of elderly patients enrolled in NOAC pivotal trials. The annualized rates of stroke and systemic embolism in patients aged ≥75 years were similar with edoxaban versus warfarin (2.3% vs 1.9%), whereas major bleeding was significantly lower with edoxaban (4.8% vs 4.0%), with a higher clinical benefit in older patients as age increased.[8] Among the 3488 elderly patients who met dose reduction criteria, the lower-dose edoxaban regimen conserved the same clinical benefits versus warfarin than the higher-dose edoxaban regimen, providing a greater reduction in major bleeding events compared with similar patients in the warfarin group. These results

Table. Study population baseline characteristics before and after propensity matching (PSM). Unless otherwise indicated, values are given as percentages.

	Before PSM			After PSM		
	EDO	VKA	*P*	EDO	VKA	*P*
n	186	764		130	130	
Age (mean (sd))	78.52 (13.1)	83.54 (5.5)	0.0027	80.5 (4.5)	80.4 (3.8)	0.811
Male sex (%)	0.55	0.50	0.103	0.55	0.57	0.856
Weigh (mean (sd))	70.81 (14.00)	72.51 (13.83)	0.094	70.84 (14.02)	71.33 (13.92)	0.652
COPD (%)	18.2	13.9	0.126	17.3	15.3	0.347
CAD (%)	22.1	28.1	0.079	12.3	14.1	0.418
DM (%)	13.4	20.6	0.042	22.4	21.3	0.975
Hypertension (%)	28.5	60.5	0.001	52.9	51.8	0.846
CKD (%)	41.5	37.0	0.237	41.2	38.9	0.581
Dyslipidemia (%)	39.1	42.8	0.342	39.3	40.1	0.896
Heart Failure (%)	18.5	25.3	0.001	12.9	13.1	0.807
Previous Stroke/TIA (%)	22.9	14.0	0.001	23.0	18.7	0.188
Vascular disease (%)	7.9	9.5	0.528	7.9	9.3	0.619
Past Bleeding (%)	19.8	15.9	0.189	19.8	17.7	0.528
Antiplatelet drugs (%)	2.4	3.3	0.620	2.6	3.1	0.302
ASA (%)	12.3	17.6	0.063	13.8	14.4	0.572
Antinflammatory drugs (%)	1.2	1.4	0.989	1.2	1.2	0.999
Hepathopathy (%)	1.6	2.2	0.782	1.6	1.7	0.665
Pericardial disease (%)	2.8	2.0	0.633	1.6	1.7	0.665
Pulmonary embolism (%)	2.4	2.4	0.999	2.2	2.2	0.999
Anaemia (%)	11.1	13.2	0.446	11.5	11.6	0.968
$CHADS_2$	2.8 (1.1)	2.4 (1.2)	0.04	2.8 (1.0)	2.7 (1.1)	0.193
CHA_2DS_2 -VASc	3.8 (1.1)	4.2 (1.2)	0.04	3.4 (1.1)	3.4(1.1)	0.415
HASBLED	2.9 (1.0)	2.7 (1.1)	0.06	2.8 (1.0)	2.8 (1.0)	0.999

ASA = acetylsalicylic acid; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; TIA = transient ischemic attack; $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke /TIA /Thromboembolism; CHA_2DS_2-VASc = Congestive heart failure (or Leftventricular systolic dysfunction), Hypertension, Age ≥75 years, Diabetes Mellitus, Prior Stroke/TIA /thromboembolism, Vascular disease, Age 65—74 years, Sex category.

are most consistent with those of a prespecified analysis of the ENGAGE AF-TIMI 48 trial, in which the edoxaban treatment in 900 patients (median age, 77 years) judged at increased risk of falling exhibited a greater reduction in major bleeding events and all-cause mortality compared with the warfarin group.[20]

Real-world evidence focused on clinical performance of NOAC use in the elderly is relevant to address current unmet medical needs and to better define the specific role of such agents in this subset of patients. To date, the only extensive real-world data regarding NOAC use and outcomes in elderly patients (aged ≥75 years) with AF were extracted from the Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation (PREFER in AF).[21,22] Data from this large European prospective registry indicated that, compared with VKAs, NOAC use was associated with a better net clinical benefit in elderly patients with AF, primarily due to lower rates of major bleeding. However, it has

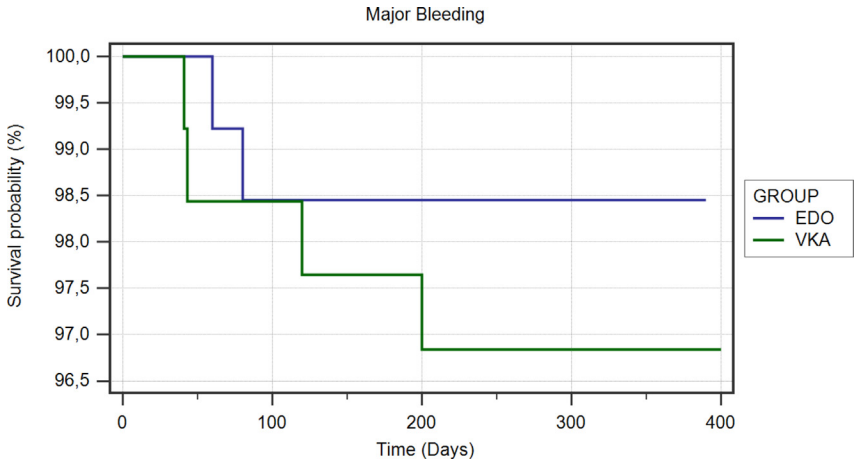

Figure 1. Kaplan–Meier cumulative probability of major bleeding event-free survival in recipients of edoxaban (EDO) and vitamin K antagonist (VKA) treatment.

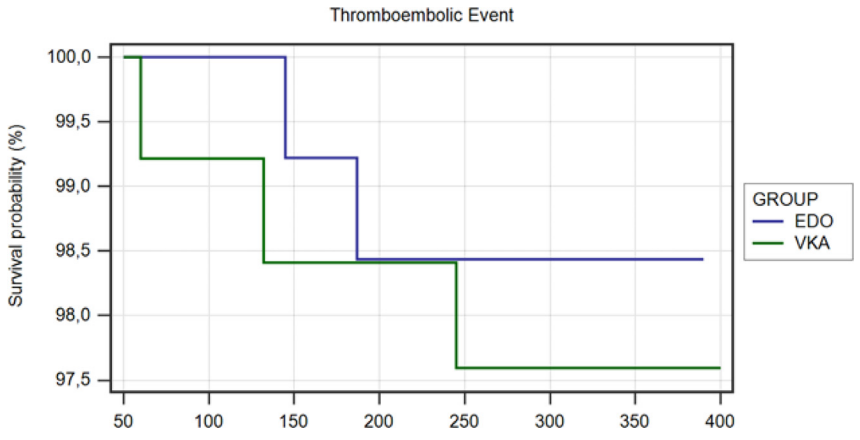

Figure 2. Kaplan–Meier cumulative probability of thromboembolic event-free survival in recipients of edoxaban (EDO) and vitamin K antagonist (VKA) treatment.

included only patients with AF receiving VKAs, dabigatran, rivaroxaban, and apixaban therapy; no information about edoxaban therapy in an older population with AF is available. The current study investigated the safety and efficacy of edoxaban versus VKAs among elderly patients with AF in a real-life setting. Edoxaban therapy showed, compared with VKAs, a trend indicating a reduction in the incidence of major bleeding and thromboembolic events, with a low discontinuation rate and high adherence among the cohort of elderly (aged ≥75 years) patients with AF in this real-life setting.

Despite the novelty, our study is limited by small sample size, a small number of observed events, the exclusion of patients receiving edoxaban 30 mg, and lack of randomization.

CONCLUSIONS

Edoxaban therapy showed a good real-life performance among elderly (ie, aged ≥75 years) patients with AF.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

Dr. Russo was responsible for project administration, conceptualization, supervision, review, and editing; Drs. Attena and Mazzone were responsible for methodology, data curation, and formal analysis; Drs. Melillo and Rago were responsible for data collection, manuscript writing, and reviewing; Drs. Galasso, Riegler, Parisi, and Rotunno were responsible for data collection and curation, investigation, and methodology; and Drs. Nigro and D'Onofrio were responsible for conceptualization, supervision, and validation.

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