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Original Research

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Optimal Dose of Edoxaban for Very Elderly Atrial Fibrillation Patients at High Risk of Bleeding: The LEDIOS Registry

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AUTHOR'S SUMMARY

Optimal anticoagulation for stroke prevention in very elderly patients with atrial fibrillation (AF) is challenging due to the high risk of anticoagulant-induced bleeding, particularly among those who have additional risk factors. We evaluated outcomes of on-label reduced-dose edoxaban (30 mg) in very elderly patients who had additional risk factors for bleeding. In very elderly AF patients with comorbidities associated with greater risk of bleeding, the incidence of major bleeding events was significantly increased without increase in stroke incidence. However, there were no significant differences in stroke incidence and there were no significant differences for either factor after adjusting for age and sex.

ABSTRACT

Background and Objectives: Optimal anticoagulation in very elderly patients is challenging due to the high risk of anticoagulant-induced bleeding. The aim of this study was to assess outcomes of on-label reduced-dose edoxaban (30 mg) in very elderly patients who had additional risk factors for bleeding.
Methods: This was a multi-center, prospective, non-interventional observational study to evaluate the efficacy and safety of on-label reduced-dose edoxaban in atrial fibrillation (AF) patients 80 years of age or older and who had more than 1 risk factor for bleeding.
Results: A total of 2448 patients (mean age 75.0±8.3 years, 801 [32.7%] males) was included in the present study, and 586 (23.9%) were 80 years of age or older with additional risk factors for bleeding. Major bleeding events occurred frequently among very elderly AF patients who had additional bleeding risk factors compared to other patients (unadjusted hazard ratio

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Kim JY, Han SJ, On YK; Data curation: Kim JY, Han SJ, Kim DK, Park YM, Lee SH, Park JS, On YK; Formal analysis: Kim JY; Funding acquisition: On YK; Investigation: Park SJ, On YK; Methodology: Kim JY, On YK; Project administration: On YK; Resources: On YK; Supervision: Kim J, Park SJ, Park KM, On YK; Visualization: Kim J, Park KM, On YK; Writing - original draft: Kim JY; Writing - review & editing: Kim JY, On YK.

[HR], 2.16; 95% confidence interval [CI], 1.16–4.02); however, there were no significant differences in stroke incidence (HR, 1.86; 95% CI, 0.98–3.55). There were no significant differences for either factor after adjusting for age and sex (adjusted HR, 1.65; 95% CI, 0.75–3.62 for major bleeding; adjusted HR, 1.13; 95% CI, 0.51–2.50 for stroke).
Conclusions: In very elderly AF patients with comorbidities associated with greater risk of bleeding, the incidence of major bleeding events was significantly increased. In addition, risk of stroke showed tendency to increase in same population. Effective anticoagulation therapy might be important in these high-risk population, and close observation of bleeding events might also be required.

Trial Registration: ClinicalTrials.gov Identifier: NCT03554837

Keywords: Atrial fibrillation; Edoxaban; Elderly; Bleeding; Stroke; Risk factors

INTRODUCTION

The prevalence of atrial fibrillation (AF) is increasing as the population ages, and most elderly AF patients require anticoagulation treatment for stroke prevention as the associated risk increase greatly with age.[1)2)] Nevertheless, oral anticoagulation remains underutilized due to the risk of bleeding.[3)4)] Recently, the Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial reported that off-label underdosing of edoxaban (15 mg once daily) resulted in stroke risk reduction compared to placebo without increasing the risk of bleeding in very elderly patients.[5)] Optimal anticoagulation for stroke prevention in very elderly AF patients who have additional risk factors for bleeding is challenging. Therefore, the ELDERCARE-AF trial concluded that, in very elderly patients who were not appropriate candidates for standard doses of oral anticoagulants, using a reduced dose is preferable to not using anticoagulation. However, these patients are also at high risk of stroke. Therefore, it is critical to achieve an appropriate balance between efficacy and safety. In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI) trial, edoxaban was non-inferior to warfarin for stroke prevention in higher-dose regimens, while the event rate of ischemic stroke was greater for a lower-dose edoxaban regimen (LDER) than for warfarin.[6)] In a pre-specified analysis of the ENGAGE AF-TIMI trial, the incidence of net clinical outcome of stroke/major bleeding/death in AF patients treated with a LDER was lower than for a higher-dose edoxaban regimen (HDER).[7)]

The aim of this study was to assess outcomes of on-label reduced dose edoxaban (30 mg) treatment of very elderly AF patients who had additional risk factors for bleeding in real-world practice.

METHODS

Ethical statement

This study was approved by the local Institutional Review Board (IRB) of Samsung Medical Center in South Korea (IRB number: SMC IRB 2017-12-051). All patients provided informed consent and were registered at ClinicalTrials.gov (NCT03554837).

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Study population

The Safety and Effectiveness of Low Dose Edoxaban in Patients with Non-Valvular AF (LEDIOS) registry is a multi-center, prospective, non-interventional cohort study to evaluate the safety and efficacy of low-dose edoxaban in patients with AF, who met any of the dose reduction criteria. The study design and details have been described previously.[8] In brief, the present study included patients who were indicated to receive non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention, were prescribed 30 mg of edoxaban, and who met the dose-reduction criteria. The LEDIOS_ELDERCARE-like group comprised AF patients who were older than 80 years of age and who also had risk factors for bleeding, including one or more of the following criteria: a history of bleeding from a critical organ, creatinine clearance (CrCl) 15–30 mL/min, body weight ≤45 kg, continuous use of nonsteroidal anti-inflammatory drugs (NSAIDs), or current use of an antiplatelet drug. LEDIOS_other group defined as patients who were older than 80 years of age and who did not have any risk factors for bleeding, and all the patients who were younger than 80 years of age with or without risk factors for bleeding.

Data collection and study outcomes

Basic demographic data and the medical history of each individual were collected, including age; sex; body mass index (BMI); body weight; renal function; and history of congestive heart failure, hypertension, diabetes mellitus, or thromboembolism. The primary safety outcome was major bleeding during treatment, as defined by the International Society on Thrombosis and Haemostasis criteria.[9] The efficacy outcome was ischemic stroke including transient ischemic attack or systemic embolism. The net clinical outcome was defined as the composite of stroke, systemic embolism, major bleeding, and all-cause mortality. Data were collected at baseline and during a follow-up period of at least 12 months. Patients were censored at outcome occurrence, at discontinuation of edoxaban treatment during the observation period, or at the end of the study period. Patients who were included in the ELDERCARE-like group were compared with the other patients not included in this group.

Statistical analysis

The baseline characteristics are presented as the mean ± standard deviation for continuous variables and as frequency with percentage for categorical variables. Continuous variables were compared using the unpaired t-test, and categorical variables were compared using either the χ^2 test or Fisher's exact test, as appropriate. Event rate curves were obtained using a Kaplan-Meier analysis and compared using the log-rank test. The outcomes were assessed using a Cox proportional hazards model, with Model 1 adjusted for age and sex and Model 2 for sex, body weight, CrCl, history of diabetes, and hypertension; the results are presented as the hazard ratio (HR). The p values <0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences® software, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinical characteristics

A total of 2,448 patients was included in the analysis. Among these, 932 (38.1%) patients were ≥80 years of age and 586 (23.9%) had more than one risk factor for bleeding (LEDIOS_ELDERCARE-like group) (**Figure 1**).

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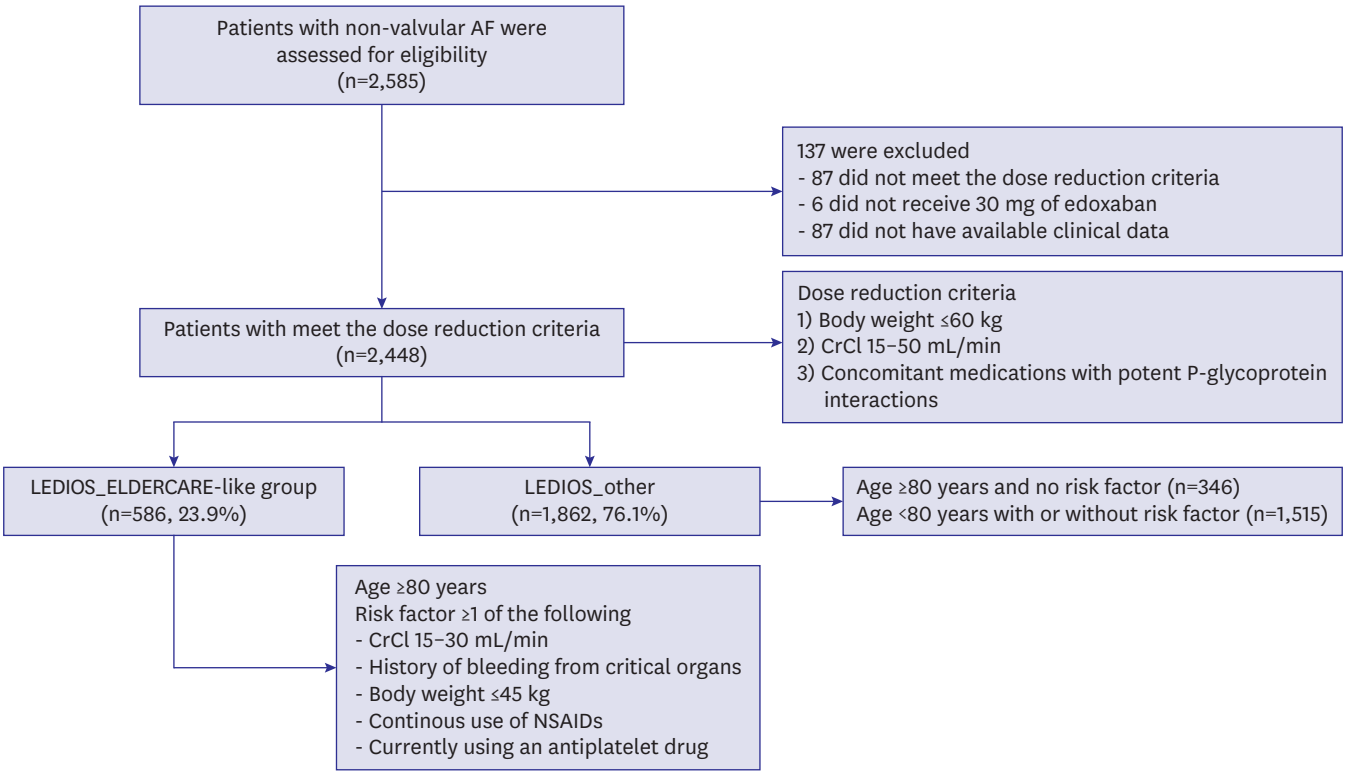

Figure 1. Flow chart of patient selection process for the study.
AF = atrial fibrillation; CrCl = creatinine clearance; NSAIDs = nonsteroidal anti-inflammatory drugs.

The baseline characteristics of the LEDIOS_ELDERCARE-like group were as follows: the mean age was 84.4±3.7 years, and 181 (30.9%) patients were men; the mean CHA_2DS_2-VASc score was 4.5±1.2; the mean body weight was 52.8±8.9 kg; and mean CrCl was 38.0 ± 13.4 mL/min. With regard to medical history, 31 (5.3%) had history of bleeding from a critical organ, 51 (8.7%) were continuously using NSAIDs, 402 (68.6%) were currently using an antiplatelet drug, 135 (23.0%) had body weight ≤45 kg, and 187 (31.9%) had CrCl 15–30 mL/min. The baseline characteristics of the patients are summarized in **Table 1**.

Outcome

In the LEDIOS_ELDERCARE-like group, major bleeding events occurred in 17 patients, and the event rate was 1.95% per year. The event rate of stroke and systemic embolism in LEDIOS_ELDERCARE-like group was 1.72%/yr. The overall net clinical outcome of composite of stroke, systemic embolism, major bleeding, and all-cause mortality occurred in 46 patients, an event rate of 5.34%/yr. The incidence rate of major bleeding in LEDIOS_other group was 0.95%/yr, stroke and systemic embolism was 0.95%/yr, and net clinical outcomes was 1.82%/yr. The survival curve demonstrated a significant increase in the major bleeding event rate in the LEDIOS_ELDERCARE-like group compared with the other patients (log-rank p=0.01; HR, 2.16; 95% confidence interval [CI], 1.16–4.02) (**Figure 2**). There was no significant difference in stroke rate between the two groups (log-rank p=0.06; HR, 1.86; 95% CI, 0.98–3.55). The survival curve showed a significant increase in the net clinical outcome in the LEDIOS_ELDERCARE-like group compared with the other patients (log-rank p<0.001; HR, 1.94; 95% CI, 1.34–2.81). There was no significant difference in all cause death rate between the two groups (log-rank p=0.14; HR, 1.61; 95% CI, 0.85–3.03) (**Supplementary Figure 1**). Cox proportional hazards model analysis was performed. In Model 1 (adjusted for age and sex), there were

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Table 1. Baseline characteristics of the study population

	LEDIOS_ELDERCARE-like patient group	LEDIOS_other patient group	p value
No. of patients	586 (23.9)	1,862 (76.1)	NA
Age (years)	84.4±3.7	73.6±7.7	<0.001
Sex, male	181 (30.9)	620 (33.3)	0.289
BMI (kg/m^2)	22.5±3.3	23.0±2.9	0.010
Body weight (kg)	52.8±8.9	55.8±7.9	<0.001
CrCl (mL/min)	38.0±13.4	55.5±19.1	<0.001
CHA_2DS_2-VASc	4.5±1.2	3.5±1.4	<0.001
Medical history			
Hypertension	469 (80.0)	1,288 (69.2)	<0.001
Diabetes	155 (26.5)	494 (26.5)	1.000
Heart failure	193 (32.9)	454 (24.4)	<0.001
Stroke	81 (13.8)	191 (10.3)	0.019
Risk factor			
Bleeding history	31 (5.3)	51 (2.7)	0.004
NSAID use	51 (8.7)	78 (4.2)	<0.001
Antiplatelet use	402 (68.6)	672 (36.1)	<0.001
Body weight ≤45 kg	135 (23.0)	115 (6.2)	<0.001
CrCl 13–30 mL/min	187 (31.9)	78 (4.2)	<0.001

Values are presented as mean ± standard deviation or number (%).
BMI = body mass index; CrCl = creatinine clearance; NA = non-available; NSAIDs = nonsteroidal anti-inflammatory drugs.

no significant differences between the two groups (adjusted HR, 1.65; 95% CI, 0.75–3.62 for major bleeding, adjusted HR, 1.13; 95% CI, 0.51–2.50 for stroke, and adjusted HR, 1.17; 95% CI, 0.74–1.84 for net clinical outcome). In Model 2 (adjusted for sex, body mass index, CHA_2DS_2-VASc, hypertension, history of heart failure and stroke), adjusted HR (95% CI) was 2.88(1.38–6.02) for major bleeding, 2.09 (0.98–4.46) for stroke, and 2.04 (1.30–3.21) for net clinical outcome (**Table 2**).

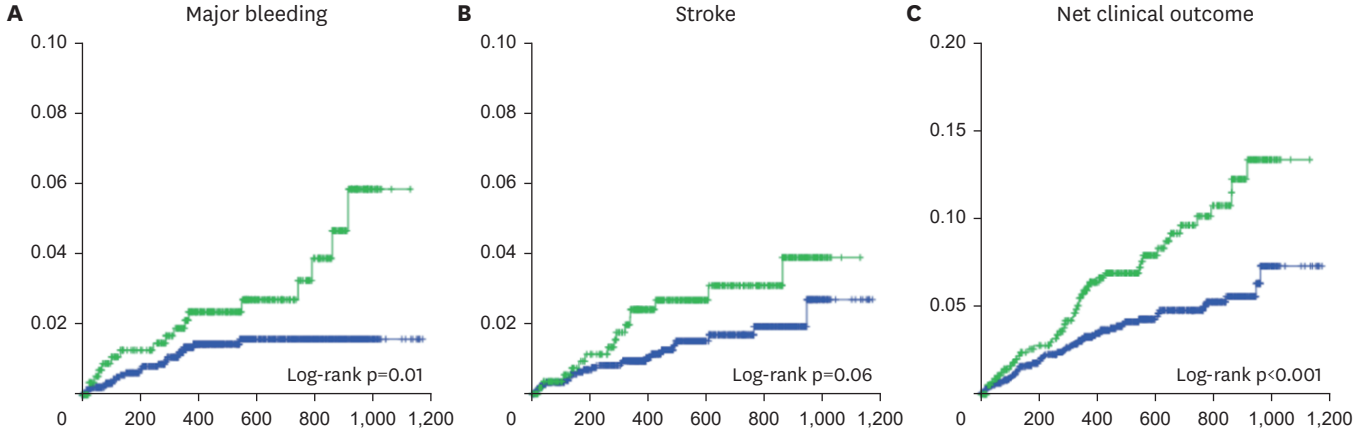

Figure 2. Kaplan-Meier curves for the primary outcome. (A) Freedom from major bleeding, (B) Freedom from ischemic stroke or systemic embolism, and (C) Freedom from net clinical outcomes. Green indicates the ELDERCARE-like group and blue indicates the other patients.

Table 2. HRs for outcomes in LEDIOS_ELDERCARE-like patient group versus other patients (events divided by 100 person-years [%/yr])

	No. of subjects	Stroke				Bleeding				Net clinical outcome			
		Incidence rate	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)	Incidence rate	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)	Incidence rate	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)
LEDIOS_ ELDERCARE-like patient group	568	1.72	1.86 (0.98–3.55)	1.13 (0.51–2.50)	2.09 (0.98–4.46)	1.95	2.16 (1.16–4.02)	1.65 (0.75–3.62)	2.88 (1.38–6.02)	5.34	1.94 (1.34–2.81)	1.17 (0.74–1.84)	2.04 (1.30–3.21)

CI = confidence interval; HR = hazard ratio.
*Adjusted for risk factors, age, and sex.
†Adjusted for risk factors, sex, body mass index, CHA_2DS_2-VASc, hypertension, history of heart failure and stroke.

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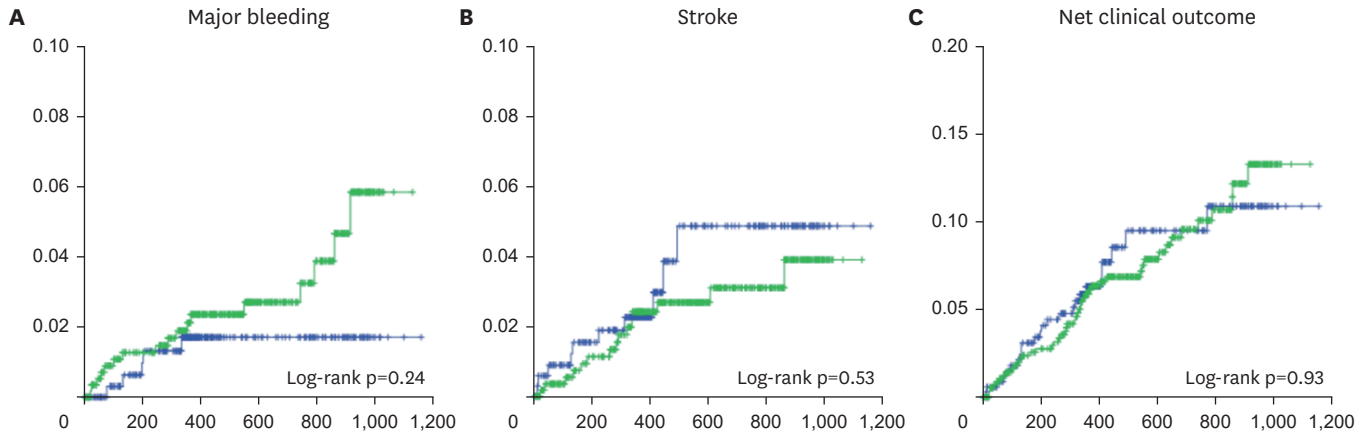

Figure 3. Kaplan-Meier curves for the primary outcome in very elderly patients with atrial fibrillation treated with edoxaban. (A) Freedom from major bleeding, (B) Freedom from ischemic stroke or systemic embolism, and (C) Freedom from composite clinical outcomes. Green indicates the ELDERCARE-like group and blue indicates patients ≥80 years of age without any risk factors for bleeding.

Outcomes in very elderly patients

The comparison was performed between the LEDIOS_ELDERCARE-like group and other AF patient ≥80 years of age without any risk factors for bleeding. The baseline characteristic between the two groups are summarized in **Supplementary Table 1**. The incidence rate of stroke and systemic embolism was 2.34%/yr, bleeding was 1.17%/yr, and net clinical outcome was 5.68%/yr in very elderly patients without risk factors. The analysis found a tendency toward increased bleeding risk in the LEDIOS_ELDERCARE-like group without significance (log-rank p=0.24; **Figure 3**). The survival curve for stroke and the net clinical outcome demonstrated a similar event rate in the ELDERCARE-like group compared with other patients ≥80 years of age without any risk factors for bleeding (log-rank p=0.53 and p=0.93). Adjusted HR (95% CI) was 1.00 (0.67–2.69) for stroke, 0.33 (0.09–1.16) for major bleeding, and 0.75 (0.40–1.40) for net clinical outcome in very elderly patients without risk factors.

DISCUSSION

This study revealed the true high-risk group for bleeding events among very elderly AF patients, and the finding may guide safer use of oral anticoagulation in such patients while maintaining efficacy. The study analyses provided three main findings. First, bleeding risk was increased in patients in the LEDIOS_ELDERCARE-like group compared to other AF patients, while the ischemic stroke risk showed tendency to increase. Second, the risk was offset after adjustment for age. Third, in patients ≥80 years of age, bleeding risk and stroke event were similar according to the presence of bleeding risk factors.

Current guidelines recommend that older AF patients should receive oral anticoagulants to achieve more favorable outcomes.[10] However, oral anticoagulants are underutilized or underdosed in an off-label manner in patients at high risk of stroke.[1][11] Factors associated with label adherence were old age, history of bleeding, renal dysfunction, and low body weight. In the ELDERCARE trial, comorbidities associated with risk factors for bleeding were history of bleeding from a critical organ, CrCl 15–30 mL/min, body weight ≤45 kg, continuous use of NSAIDs, and currently using an antiplatelet drug. The risk of bleeding is often cited as the reason for off-label underdosing of NOACs or not prescribing oral anticoagulants. In our study, concomitant use of antiplatelet agents was observed in 68%

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of cases. The ENTRUST-AF PCI (edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with AF) study reported that 60 mg edoxaban once daily plus an anti-platelet P2Y12 inhibitor was non-inferior for bleeding compared with a vitamin K antagonist combined with a P2Y12 inhibitor and aspirin.[12] However, the event rate for major bleeding in this study was 20.7%/yr in the edoxaban group. The event rate of major bleeding in the ELDERCARE trial was 3.3%/yr in the edoxaban group. These findings support the use of reduced-dose edoxaban in combination with antiplatelet agents in AF, especially for elderly patients. Indeed, in our study, the crude risk of bleeding and net clinical outcome rate were increased in very elderly AF patients who also had other risk factors for bleeding compared to other patients who did not have these risk factors, although the risk of stroke was similar, and neither bleeding nor stroke risk was significantly different in the 2 groups after adjustment for age. Moreover, when analyzing patients older than 80 years, there were no significant differences in outcomes according to the presence or absence of the risk factors examined. Therefore, in our study, the most powerful risk factor of increasing bleeding risk was age. Several reports have assessed the efficacy and safety of oral anticoagulants in patients older than 90 years.[13-15] In most studies, the use of NOACs was associated with a lower risk of clinical outcomes compared to that of warfarin. Furthermore, in very elderly patients over 90 years of age, NOACS were associated with a lower risk of composite adverse events compared to non-oral anticoagulant users, even for those with a history of intracranial hemorrhage (ICH), gastro-intestinal bleeding, or renal dysfunction. Brønnum Nielsen et al.[16] reported that the risk of ischemic stroke events after an ICH in patients with AF was greater than in non-ICH patients. Another study reported that warfarin use may be more beneficial than not using antithrombotic therapy with respect to net clinical outcome in patients who have AF and experience of ICH with a high stroke risk.[17] In other words, among AF patients, the high-risk group for bleeding is also at high risk of ischemic stroke, and careful consideration of the appropriate anticoagulation therapy is important in these patients.

Appropriate dosage of anticoagulants is important in patients at high risk of bleeding. Underdosing of apixaban in patients with normal or mildly impaired renal function was reported to be associated with a higher risk of stroke (HR of 4.87), but the risk of major bleeding events did not differ.[18] The ENGAGE AF-TIMI 48 trial, comparing two dose regimens of edoxaban with warfarin, showed that the rate of ischemic stroke was greater for the LDER (30/15 mg) compared with warfarin. In anticoagulation use, both efficacy and safety are important. Therefore, a net clinical outcome comprising stroke, bleeding, and mortality rate represents the balance of efficacy and safety. Steffel et al.[7] reported that a LDER reduced the primary net clinical outcome compared with a HDER, and a LDER may be considered in patients at high risk of bleeding. Based on this extension, the ELDERCARE-AF trial results suggest a lower dose of edoxaban in very elderly patients who had additional risk factors for bleeding. Our study results also showed increased risk of bleeding in our ELDERCARE-like patient group. However, the statistical significance of this result was reduced after adjustment for other variables including age. Age is known to be the most important risk factor for stroke. In addition, many studies have reported the safety of NOACs in elderly patients.[13][14] In our study, there were also no significant differences in outcomes among patients over 80 years of age according to the risk factors assessed. Based on these results, we suggest that an on-label dose of NOAC might be considered in elderly patients at high risk of bleeding, and close monitoring of bleeding events is important. In patients who have difficulty in maintaining a standard 30 mg dose of edoxaban, a reduced dose of 15 mg edoxaban might be an alternative treatment strategy.

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This study had some limitations. First, this study was a non-interventional single-arm observational study. Therefore, we could not compare the outcomes with a no-antithrombotic group or a 15 mg edoxaban group. However, we can conclude that our ELDERCARE-like group was a truly at high risk of bleeding events. Furthermore, age is the most powerful risk factor for bleeding. Second, the incidence of each outcome assessed was relatively low. Given this was a real-world study, our study outcomes showed reasonable event rates. Further, a strength of our study was that we included patients indicated for on-label 30 mg of edoxaban in a real-world observational study.

In AF patients who had comorbidities associated with elevated risk of bleeding, major bleeding was significantly increased in very elderly patients. In addition, risk of stroke showed tendency to increase in same population. Bleeding and stroke risk was similar according to the presence of risk factors for bleeding among AF patients older than 80 years. Our findings suggest that not only the risk of bleeding, but also the risk of stroke is increased in very elderly patients. Effective anticoagulation therapy might be important in these high-risk population, and close observation of bleeding events might also be required.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics

Supplementary Figure 1

Kaplan-Meier curves for all cause death. Green indicates the ELDERCARE-like group and blue indicates the other patients.

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