# Prognosis of elderly non-valvular atrial fibrillation patients stratified by B-type natriuretic peptide: ELDERCARE-AF subanalysis

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**Background** B-type natriuretic peptide (BNP) is a risk factor for stroke and cardiac death in patients with atrial fibrillation. We hypothesized the prognostic outcomes of very elderly non-valvular atrial fibrillation patients ineligible for standard anticoagulation treatment would vary according to BNP stratification.

**Methods** In this subanalysis of the ELDERCARE-AF trial, patients were stratified by BNP levels at enrollment, and clinical outcomes compared among BNP subgroups. Hazard ratios were adjusted for age, atrial fibrillation type, body mass index, creatine clearance, congestive heart failure, and D-dimer. BNP levels were measured using chemiluminescence enzyme immunoassays.

**Results** In total, 984 patients (average age: 86.6 years) not considered eligible for oral anticoagulant therapy at approved doses for stroke prevention were included. The BNP levels at enrollment were <200 (low), 200 to <400 (moderate), and ≥400 (high) pg/mL in 428, 300, and 256 patients, respectively. The number (%) of patients with stroke or systemic embolism (SSE) was 7 (1.2%), 24 (5.9%), and 28 (8.6%) in the low, moderate, and high BNP subgroups, respectively (adjusted hazard ratio 3.82, $P = .0025$ for low vs moderate BNP and 4.76, $P = .0007$ for low vs high BNP). There was no significant difference in major bleeding incidence between the BNP subgroups. Edoxaban 15 mg was associated with a consistent reduction in SSE vs placebo in all BNP subgroups.

**Conclusions** Stratification by BNP level was associated with the incidence of SSE for very elderly non-valvular atrial fibrillation patients ineligible for standard anticoagulation treatment, and the effect of edoxaban 15 mg was consistent across BNP levels. (Am Heart J 2022;250:66–75.)

## Background

The prevalence of atrial fibrillation (AF) increases with age,[1,2] and both AF and aging are independent risk factors for stroke and heart failure (HF).[3-5] Nevertheless, at present, many physicians are reluctant to prescribe oral anticoagulants for stroke prevention because of the perceived risk for bleeding in very elderly AF patients.[6,7] It is well known that age-related HF is an important risk factor for stroke, and effective and safe anticoagulant treatment options are needed, especially in elderly AF patients with comorbid HF.

The biomarkers N-terminal pro- B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are predictors for increased risk of stroke/systemic embolism (SSE) and cardiac mortality in patients with AF.[8-11] BNP and NT-proBNP are secreted from the atrial and ventricular myocytes, and their secretion is increased under various cardiovascular conditions.[10] These biomarkers can help improve the stroke and mortality risk assessment in patients with AF.[10,11] Both the ARISTOTLE trial and a substudy of the RE-LY trial demonstrated that NT-proBNP levels were associated with an increased risk of

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stroke or death in patients with AF.[8,9] The Fushimi AF Registry[12] showed that a high BNP level at baseline is an independent risk factor for SSE in patients with AF and HF. The ORBIT AF study also evaluated the association between BNP and combined clinical outcomes of major vascular or neurological adverse events and major bleeding.[13] The level of BNP is also shown to be associated with the level of frailty among the general elderly population,[14] and therefore a higher BNP level in very elderly AF patients would be associated with increased risk of adverse cardiovascular events. However, little is known about the relationship between outcomes and BNP levels in very elderly AF patients.

The ELDERCARE-AF trial was a multicenter, randomized, double-blind, placebo-controlled phase 3 study that reported on the efficacy and safety of edoxaban 15 mg once daily in very elderly Japanese patients (≥80 years of age) with non-valvular AF (NVAF) who were considered ineligible for standard anticoagulant treatment.[6,7] The results showed that edoxaban 15 mg was superior to placebo in preventing SSE, without significantly increasing the risk of bleeding compared with placebo in this patient population.

In this subanalysis of ELDERCARE-AF, we tested the hypothesis that BNP stratification might be useful in identifying patients at higher risk of adverse events and in improving prognostic outcomes of very elderly NVAF patients at high bleeding risk with edoxaban 15 mg.

## Methods

### Study design

This was a subanalysis of a multicenter, randomized, double-blind, placebo-controlled, event-driven, superiority phase 3 trial, and details of the study design have been published previously.[7] BNP values were assessed at ELDERCARE-AF trial enrollment, and patients were stratified according to the BNP value.

The study was approved by the institutional review board at each participating study center and conducted according to the standards specified in the Pharmaceutical and Medical Device Act of Japan and with the International Council for Harmonisation guidelines for Good Clinical Practice, as well as the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment. The main study was registered at ClinicalTrials.gov under the identifier number NCT02801669.

### Patients

Eligible patients were ≥80 years of age, had a history of NVAF verified by electrocardiogram or monitor recording within 1 year of consent, and had a $CHADS_2$ score of ≥2. The $CHADS_2$ score is an index of stroke risk among AF patients. Scores range from 0 to 6, and higher scores indicate a greater risk of stroke. Patients also had to be considered ineligible for oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the recommended therapeutic strength (warfarin) or approved doses for ≥1 of the following reasons: (a) low creatinine clearance (CrCl) (15-30 mL/min), (b) history of bleeding from a critical area/organ or gastrointestinal bleeding, (c) low body weight (≤45 kg), (d) continuous use of nonsteroidal anti-inflammatory drugs, and (e) current use of an antiplatelet drug. The full list of the inclusion and exclusion criteria has been published previously.[7]

### Biochemical analyses

Blood for BNP analysis was collected in 2 mL vacuum blood sampling tubes with EDTA-2Na 3.0 mg at the time of enrollment in the study. After blood collection, the tubes were refrigerated for up to 6 hours to allow for plasma separation and then immediately cryopreserved. BNP was measured at a central laboratory (SRL, Inc, Tokyo, Japan) using the chemiluminescence enzyme immunoassay method with a measurement range of 2.0 to 5,000 pg/mL (limit of detection of 2.0 pg/mL); the reference value was ≤18.4 pg/mL. The intra-assay coefficient of variance was ≤2.28 and the inter-assay coefficient of variance was ≤3.03.

### Randomization and blinding

Patients were randomly assigned in a 1:1 ratio to receive edoxaban 15 mg once daily or placebo. Randomization (in permuted blocks of four) was performed using an interactive response technology system and was stratified according to $CHADS_2$ score (2 points or ≥3 points). Patients, investigators, and the sponsor were blinded to the trial-group assignments. The use of tests that could compromise the masking of the trial-group assignments, such as pharmacodynamics and biomarker data, was prohibited at trial sites.

### Efficacy and safety endpoints

The primary efficacy endpoint was the composite of SSE. The primary safety endpoint was the International Society on Thrombosis and Haemostasis major bleeding. Secondary efficacy endpoints included the composite of stroke, systemic embolism, or cardiovascular mortality; major adverse cardiovascular events (defined as the composite of nonfatal myocardial infarction, nonfatal stroke, nonfatal systemic embolism, or death from cardiovascular causes or bleeding); the composite of stroke, systemic embolism, or all-cause mortality; net clinical benefit composite outcome; and all-cause mortality. The net clinical benefit composite outcome was the composite of SSE, major bleeding, or all-cause mortality. Secondary safety endpoints included the composite of major bleeding or clinically relevant non-major bleeding, clinically relevant non-major bleeding, minor bleeding, and all bleeding events. The definitions for efficacy and safety endpoints

have been published previously.[7] All efficacy and safety outcome events were adjudicated by an independent clinical events committee, blinded to randomized treatment assignment.

This subanalysis was prespecified to evaluate outcomes according to the baseline BNP level data of patients from the ELDERCARE-AF trial. Background characteristics and incidences of clinical outcomes were compared between the BNP subgroups at enrollment (BNP level <200 pg/mL [low], 200 to <400 pg/mL [moderate], and ≥400 pg/mL [high]). The BNP cut-off levels of 200 and 400 pg/mL were set based on the likelihood of HF according to BNP level described in the Japanese Circulation Society/Japanese Heart Failure Society guideline on the diagnosis and treatment of acute and chronic HF[15] and the increased mortality risk in HF patients according to BNP level reported in a previous study,[16] respectively.

### Statistical methods

The ELDERCARE-AF trial was event-driven, with a target of 65 patients experiencing a primary efficacy endpoint event. Patient demographic and clinical characteristics are described using distributions and summary statistics. Event rates for primary and secondary endpoints were calculated for each BNP stratification group. The cumulative incidences of SSE, major bleeding, and all-cause mortality were estimated by the Kaplan–Meier method. The influence of BNP level on the efficacy and safety outcomes was evaluated using a Cox proportional hazards model. The adjustment factors of the multivariate model for the primary efficacy endpoint were as follows: age, body mass index, CrCl, type of AF, congestive heart failure, and D-dimer. The relationship between the annual cumulative incidence of events and continuous BNP were evaluated by the restricted cubic splines method as an *ad hoc* analysis.[17] Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

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## Results

### Patients

Between August 5, 2016 and November 5, 2019, 984 out of 1086 enrolled patients from 164 institutions underwent randomization (edoxaban, $n = 492$; placebo, $n = 492$). Of the 102 patients who were excluded, 20 withdrew consent, 3 died, and 79 did not meet eligibility criteria. The median BNP value in the 984 patients was 230.0 pg/mL (25th-75th percentile, 120.0-405.5 pg/mL). Among them, 428, 300, and 256 had a BNP level at enrollment of <200 (low), 200 to <400 (moderate), and ≥400 pg/mL (high), respectively.

**Table I** shows the baseline characteristics of patients according to BNP stratification. There were many significant differences in patient characteristics among the BNP subgroups, including age, type of AF, weight, CrCl, history of falling, $CHA_2DS_2$-VASc score, history of intracranial bleeding, use of antiplatelet drugs, and history of oral anticoagulant therapy. Conversely, there were no significant differences in sex, HAS-BLED score, history of gastrointestinal bleeding, or use of nonsteroidal anti-inflammatory drugs. Among patients who underwent frailty assessment, the proportion of robust patients tended to decrease with increasing BNP level subgroup.

### Efficacy and safety outcomes by BNP stratification

The primary efficacy and safety endpoints by BNP stratification are shown in **Table II**. The incidence of SSE was significantly higher in the moderate (5.9%) and high BNP subgroups (8.6%) vs the low BNP subgroup (1.2%), with unadjusted hazard ratios of 5.03 ($P = .0002$ for the moderate vs low BNP subgroup) and 7.07 ($P < .0001$ for the high vs low BNP subgroup). The incidences of major adverse cardiovascular events were 3.4%, 11.1%, and 17.8% in the low, moderate, and high BNP subgroups, respectively ($P < .0001$ for the moderate vs low and high vs low BNP subgroup) (**Supplementary Table I**). The net clinical benefit composite outcomes were 7.2%, 16.6%, and 25.3% and the incidences of all-cause mortality were 4.9%, 10.9%, and 18.1% in each BNP subgroup, respectively (for net clinical benefit composite outcome, $P < .0001$ for the moderate vs low and high vs low BNP subgroup, and all-cause mortality, $P = .0007$ for the moderate vs low and $P < .0001$ for the high vs low BNP subgroup) (**Supplementary Table I**). Additional analysis excluding patients with a history of heart failure was performed. The low BNP subgroup had an incidence of ischemic stroke of 1.5%, and the moderate BNP subgroup had an incidence of ischemic stroke of 1.4%. The incidence of ischemic stroke (8.5%) and systemic embolism (1.7%) were highest among patients in the high BNP subgroup (**Supplementary Table II**). The incidence of major bleeding was 1.6% in the low BNP subgroup, 3.5% in the moderate BNP subgroup, and 3.0% in the high BNP subgroup. There were no statistically significant differences in the incidences of major bleeding (including intracranial hemorrhage and gastrointestinal bleeding), major/clinically relevant non-major bleeding, clinically relevant non-major bleeding, minor bleeding, and all bleeding according to BNP stratification (**Table II** and **Supplementary Table I**). The Kaplan–Meier curves for the primary efficacy endpoint (SSE), primary safety endpoint (major bleeding), and all-cause mortality by BNP

**Table I.** Baseline patient demographic and clinical characteristics according to BNP stratification

| | Low BNP group <200 pg/mL (*n* = 428) | Moderate BNP group 200 to <400 pg/mL (*n* = 300) | High BNP group ≥400 pg/mL (*n* = 256) | *P* value |
|---|---|---|---|---|
| Age*, years, mean ± SD | 85.6 ± 3.9 | 86.9 ± 4.4 | 87.8 ± 4.3 | <.0001 |
| Median (range) | 85 (80-98) | 86 (80-100) | 87 (80-100) | |
| Sex | | | | |
| Male | 189 (44.2) | 125 (41.7) | 105 (41.0) | .6720 |
| Female | 239 (55.8) | 175 (58.3) | 151 (59.0) | |
| Type of atrial fibrillation* | | | | |
| Non-paroxysmal | 154 (36.0) | 190 (63.3) | 177 (69.1) | <.0001 |
| Paroxysmal | 274 (64.0) | 110 (36.7) | 79 (30.9) | |
| Weight, kg, mean ± SD | 51.8 ± 11.0 | 51.0 ± 11.4 | 48.1 ± 10.0 | <.0001 |
| BMI*, kg/m$^2$, mean ± SD | 22.5 ± 3.8 | 22.3 ± 3.8 | 21.4 ± 3.3 | .0007 |
| Creatinine clearance*, mL/min, mean ± SD | 41.0 ± 14.6 | 35.4 ± 14.8 | 29.4 ± 10.1 | <.0001 |
| Median (range) | 40.1 (15.4-120.9) | 31.5 (15.1-85.9) | 27.8 (15.0-76.6) | |
| Coronary artery disease | 111 (25.9) | 85 (28.3) | 61 (23.8) | .4804 |
| Dementia | 58 (13.6) | 55 (18.3) | 47 (18.4) | .1299 |
| Dyslipidemia | 213 (49.8) | 128 (42.7) | 109 (42.6) | .0834 |
| History of falling | 120 (28.0) | 127 (42.3) | 93 (36.3) | .0003 |
| $CHADS_2$ score, mean ± SD | 2.9 ± 1.1 | 3.2 ± 1.1 | 3.2 ± 1.0 | .0008 |
| 2 | 202 (47.2) | 99 (33.0) | 62 (24.2) | <.0001 |
| ≥3 | 226 (52.8) | 201 (67.0) | 194 (75.8) | |
| Risk factor of thromboembolism | | | | |
| Congestive heart failure* | 152 (35.5) | 179 (59.7) | 202 (78.9) | <.0001 |
| Hypertension | 364 (85.0) | 241 (80.3) | 205 (80.1) | .1434 |
| Age ≥75 yrs | 428 (100) | 300 (100) | 256 (100) | - |
| Diabetes mellitus | 99 (23.1) | 73 (24.3) | 53 (20.7) | .5879 |
| History of TIA or cerebral infarction | 104 (24.3) | 81 (27.0) | 51 (19.9) | .1468 |
| $CHA_2DS_2$-VASc score, mean ± SD | 4.7 ± 1.2 | 5.0 ± 1.3 | 5.1 ± 1.3 | <.0001 |
| HAS-BLED score, mean ± SD | 2.3 ± 0.9 | 2.4 ± 0.9 | 2.3 ± 1.0 | .4839 |
| Hemorrhage risk | | | | |
| Severe renal impairment | 109 (25.5) | 134 (44.7) | 160 (62.5) | <.0001 |
| History of bleeding from critical area or organ | 106 (24.8) | 63 (21.0) | 53 (20.7) | .3472 |
| Intracranial | 45 (10.5) | 26 (8.7) | 9 (3.5) | .0048 |
| Gastrointestinal | 54 (12.6) | 33 (11.0) | 40 (15.6) | .2612 |
| Intraocular | 4 (0.9) | 1 (0.3) | 2 (0.8) | .6292 |
| Other | 4 (0.9) | 7 (2.3) | 3 (1.2) | .2704 |
| Low body weight (≤45 kg) | 143 (33.4) | 114 (38.0) | 117 (45.7) | .0059 |
| Continuous use of acidic NSAIDs | 148 (34.6) | 95 (31.7) | 74 (28.9) | .2981 |
| Using antiplatelet drug | 251 (58.6) | 157 (52.3) | 121 (47.3) | .0129 |
| Aspirin | 137 (32.0) | 88 (29.3) | 66 (25.8) | .2237 |
| Clopidogrel | 57 (13.3) | 41 (13.7) | 36 (14.1) | .9625 |
| Other | 59 (13.8) | 29 (9.7) | 19 (7.4) | .0255 |
| Frailty assessment | | | | |
| Tested | 409 (95.6) | 283 (94.3) | 252 (98.4) | .0990 |
| Robust (0) | 41 (9.6) | 14 (4.7) | 6 (2.3) | <.0001 |
| Pre-frail (1 or 2) | 209 (48.8) | 156 (52.0) | 116 (45.3) | |
| Frail (≥3) | 159 (37.1) | 113 (37.7) | 130 (50.8) | |
| Unevaluable | 10 (2.3) | 6 (2.0) | 1 (0.4) | |
| Missing | 9 (2.1) | 11 (3.7) | 3 (1.2) | |
| History of oral anticoagulant therapy | 155 (36.2) | 148 (49.3) | 120 (46.9) | .0007 |
| Warfarin | 90 (21.0) | 87 (29.0) | 66 (25.8) | .0440 |
| Direct oral anticoagulants† | 91 (21.3) | 88 (29.3) | 72 (28.1) | .0261 |
| Other | 1 (0.2) | 1 (0.3) | 1 (0.4) | .9318 |
| No history | 273 (63.8) | 152 (50.7) | 136 (53.1) | |
| D-dimer*, μg/mL, mean ± SD | 1.7 ± 2.7 | 2.1 ± 2.7 | 2.9 ± 3.1 | <.0001 |

Data in the table are *n* (%), unless otherwise specified.

*BMI*, body mass index; *BNP*, B-type natriuretic peptide; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SD*, standard deviation; *TIA*, transient ischemic attack.

* The adjustment factors of the multivariate model for the endpoint.

† Direct oral anticoagulants included dabigatran, rivaroxaban, apixaban, and edoxaban.

**Table II.** Primary endpoints by BNP stratification

| | Low BNP group <200 pg/mL Event *n* (%) | Moderate BNP group 200 to <400 pg/mL Event *n* (%) | High BNP group ≥400 pg/mL Event *n* (%) | Unadjusted Hazard ratio* (95% CI) | *P* value | Adjusted by multi-factors† Hazard ratio* (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| *Primary efficacy endpoints* | *n* = 428 | *n* = 300 | *n* = 256 | | | | |
| Stroke/systemic embolism | 7 (1.2) | 24 (5.9) | 28 (8.6) | 5.03 (2.17-11.67) | .0002 | 3.82 (1.60-9.12) | .0025 |
| | | | | 7.07 (3.09-16.18) | <.0001 | 4.76 (1.93-11.76) | .0007 |
| Stroke | 7 (1.2) | 19 (4.7) | 26 (8.0) | 3.98 (1.67-9.46) | .0018 | 3.30 (1.35-8.08) | .0089 |
| | | | | 6.55 (2.84-15.10) | <.0001 | 4.86 (1.94-12.18) | .0007 |
| Ischemic | 7 (1.2) | 18 (4.4) | 26 (8.0) | 3.77 (1.57-9.02) | .0029 | 3.12 (1.27-7.69) | .0134 |
| | | | | 6.56 (2.85-15.11) | <.0001 | 4.80 (1.91-12.05) | .0008 |
| Hemorrhagic | 0 (0.0) | 2 (0.5) | 0 (0.0) | - | - | - | - |
| | | | | - | - | - | - |
| Fatal | 0 (0.0) | 0 (0.0) | 4 (1.2) | - | - | - | - |
| | | | | - | - | - | - |
| Systemic embolism | 0 (0.0) | 7 (1.7) | 2 (0.6) | - | - | - | - |
| | | | | - | - | - | - |
| *Primary safety endpoints* | *n* = 426 | *n* = 300 | *n* = 256 | | | | |
| Major bleeding | 9 (1.6) | 13 (3.5) | 9 (3.0) | 2.19 (0.93-5.16) | .0739 | 1.34 (0.55-3.22) | .5203 |
| | | | | 1.79 (0.72-4.50) | .2133 | 0.82 (0.29-2.30) | .7025 |
| Intracranial hemorrhage | 2 (0.4) | 2 (0.5) | 2 (0.7) | 1.49 (0.21-10.70) | .6921 | 1.28 (0.14-11.69) | .8288 |
| | | | | 1.77 (0.25-12.55) | .5680 | 1.57 (0.11-22.83) | .7420 |
| Gastrointestinal bleeding | 6 (1.1) | 7 (1.9) | 6 (2.0) | 1.75 (0.58-5.29) | .3229 | 0.99 (0.35-2.83) | .9888 |
| | | | | 1.81 (0.59-5.59) | .3032 | 0.82 (0.26-2.57) | .7375 |

Data are *n* (%), unless otherwise specified.
*BNP*, B-type natriuretic peptide; *CI*, confidence interval.
* Hazard ratio; Upper: Low vs Moderate; Lower: Low vs High.
† The adjustment factors of the multivariate model for the endpoint were age, body mass index, creatinine clearance (mL/min), type of atrial fibrillation, congestive heart failure, and D-dimer.

stratification are shown in **Figure 1**. The BNP category was independently associated with the risk of primary (**Table II**) and secondary efficacy endpoints and all-cause mortality even after adjusting for multiple factors (**Supplementary Table I**).

### Effects of edoxaban 15 mg by BNP stratification

The effects of edoxaban on primary efficacy and safety endpoints and all-cause mortality according to BNP stratification are shown in **Table III**. In the moderate BNP subgroup, the incidence was 2.6% in patients who received edoxaban and 9.0% in those who received placebo (unadjusted hazard ratio 0.27, 95% confidence interval [CI] 0.10-0.73; $P = .0098$). In the high BNP subgroup, the incidence of SSE was 4.3% in patients who received edoxaban and 12.7% in those who received placebo (unadjusted hazard ratio 0.34, 95% CI 0.15-0.81; $P = .0141$). There were no significant interactions according to BNP stratification for SSE (**Figure 2**). Additional analysis using the restricted cubic spline method and estimated event rates at 1 year revealed a non-linear relationship between BNP and efficacy endpoints. The estimated event rate increased from 0 to 200 pg/mL of BNP before plateauing in patients receiving edoxaban (**Supplementary Figure 1**). Among the subgroups according to BNP stratification, there were no significant differences in major bleeding and all-cause mortality between the edoxaban and placebo groups (**Table III**). Moreover, there were no significant differences in the incidence of intracranial hemorrhage, gastrointestinal bleeding, and fatal bleeding between the edoxaban and placebo groups according to BNP stratification (**Supplementary Table III**).

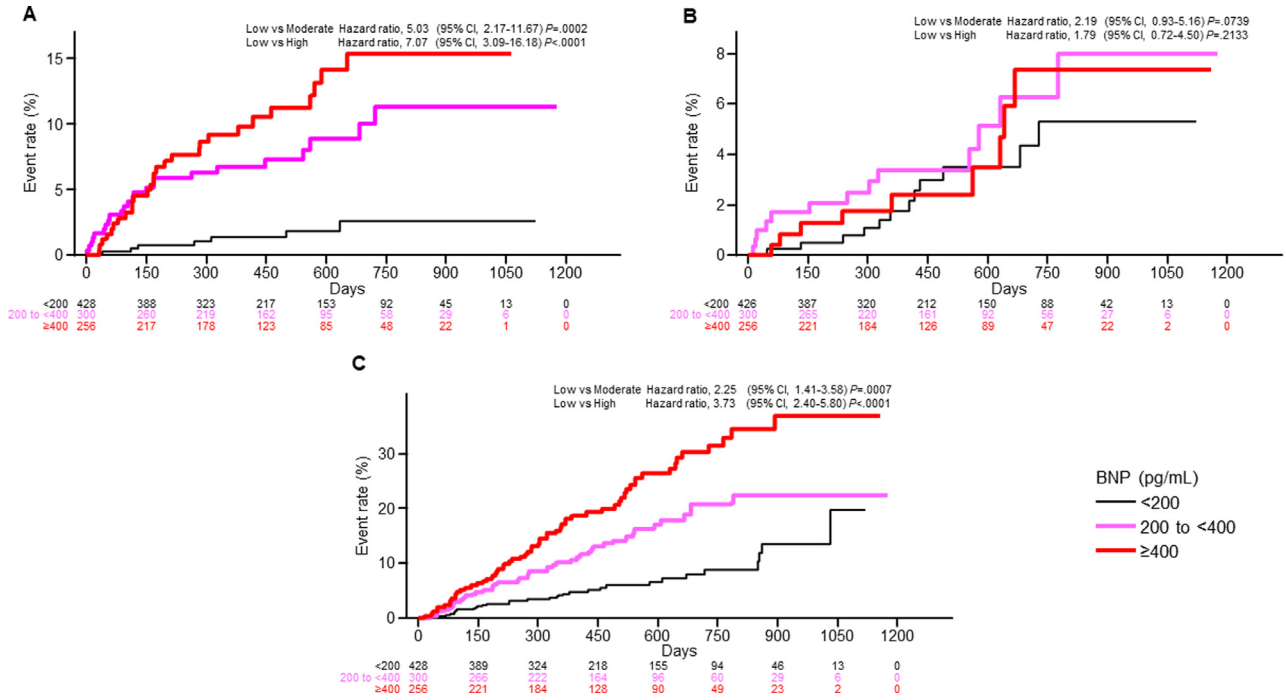
The Kaplan–Meier curves for the effect of edoxaban vs placebo on the primary efficacy and safety endpoints according to BNP stratification are shown in **Figures 3** and **4**, respectively.

## Discussion

The main findings of the present study are as follows: in very elderly patients with NVAF ineligible for standard anticoagulation treatment, the incidence of SSE increased with increasing BNP level; however, there was no significant difference in major bleeding among the BNP subgroups; there were no significant interactions according to BNP stratification with regard to the effects of edoxaban 15 mg vs placebo; and even after adjusting for multiple factors, the BNP level was independently associated with the primary efficacy endpoint.

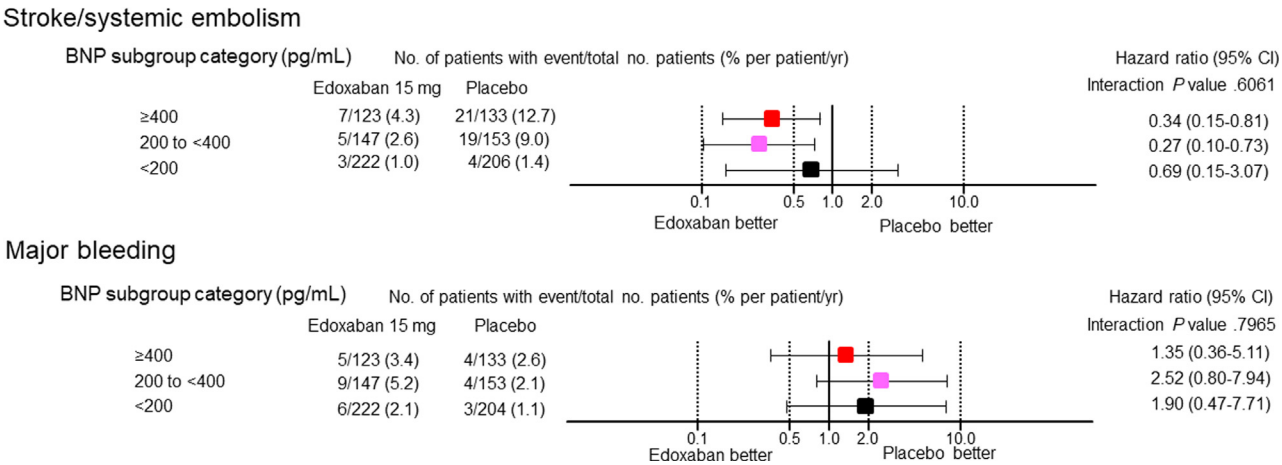
The results of the present subanalysis are consistent with those of previous studies in AF patients. The Fushimi AF Registry found that high BNP level at baseline (defined as above the median) was an independent

**Figure 1**




Kaplan–Meier curves for **A**, the primary efficacy endpoint, **B**, primary safety endpoint, and **C**, all-cause mortality, by BNP stratification overall. The event rates for the primary efficacy and safety endpoints and all-cause mortality increased with increasing BNP level. *BNP*, B-type natriuretic peptide; *CI*, confidence interval.

**Figure 2**



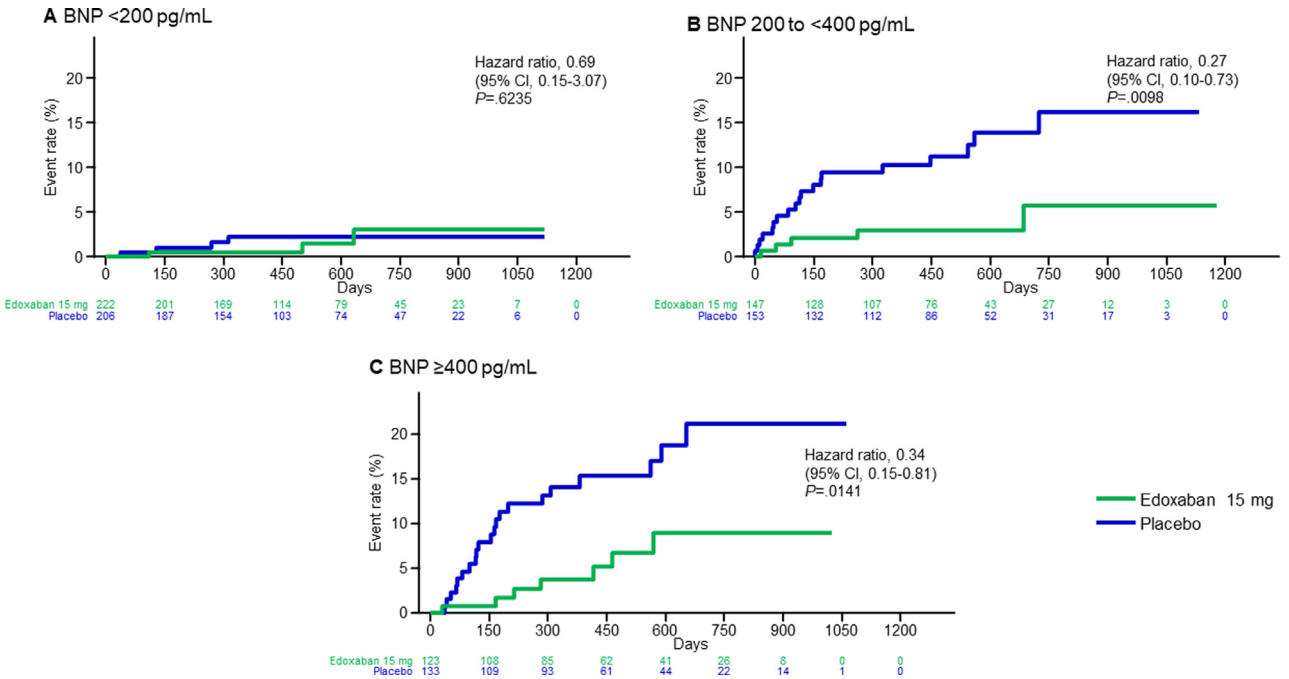

Effect of edoxaban on major study outcomes according to BNP stratification. There were no significant interactions according to BNP stratification for stroke or systemic embolism and major bleeding. *BNP*, B-type natriuretic peptide; *CI*, confidence interval; *yr*, year.

**Table III.** Effect of edoxaban on major outcomes according to BNP stratification

| | Edoxaban | | | Placebo | | | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|---|
| | *N* | Event *n* (%) | Patient/Year | *N* | Event *n* (%) | Patient/Year | | |
| *Stroke/systemic embolism* | | | | | | | | |
| Low BNP group: <200 pg/mL | 222 | 3 (1.0) | 308.4 | 206 | 4 (1.4) | 285.5 | 0.69 (0.15-3.07) | .6235 |
| Moderate BNP group: 200 to <400 pg/mL | 147 | 5 (2.6) | 195.2 | 153 | 19 (9.0) | 210.2 | 0.27 (0.10-0.73) | .0098 |
| High BNP group: ≥400 pg/mL | 123 | 7 (4.3) | 161.3 | 133 | 21 (12.7) | 165.4 | 0.34 (0.15-0.81) | .0141 |
| *Major bleeding* | | | | | | | | |
| Low BNP group: <200 pg/mL | 222 | 6 (2.1) | 284.6 | 204 | 3 (1.1) | 269.2 | 1.90 (0.47-7.71) | .3692 |
| Moderate BNP group: 200 to <400 pg/mL | 147 | 9 (5.2) | 173.6 | 153 | 4 (2.1) | 194.2 | 2.52 (0.80-7.94) | .1161 |
| High BNP group: ≥400 pg/mL | 123 | 5 (3.4) | 148.1 | 133 | 4 (2.6) | 156.5 | 1.35 (0.36-5.11) | .6623 |
| *All-cause mortality* | | | | | | | | |
| Low BNP group: <200 pg/mL | 222 | 12 (3.9) | 309.2 | 206 | 17 (5.9) | 288.2 | 0.66 (0.31-1.38) | .2650 |
| Moderate BNP group: 200 to <400 pg/mL | 147 | 26 (13.2) | 197.6 | 153 | 19 (8.8) | 214.8 | 1.49 (0.82-2.69) | .1903 |
| High BNP group: ≥400 pg/mL | 123 | 28 (17.3) | 162.2 | 133 | 33 (19.0) | 174.0 | 0.93 (0.56-1.54) | .7727 |

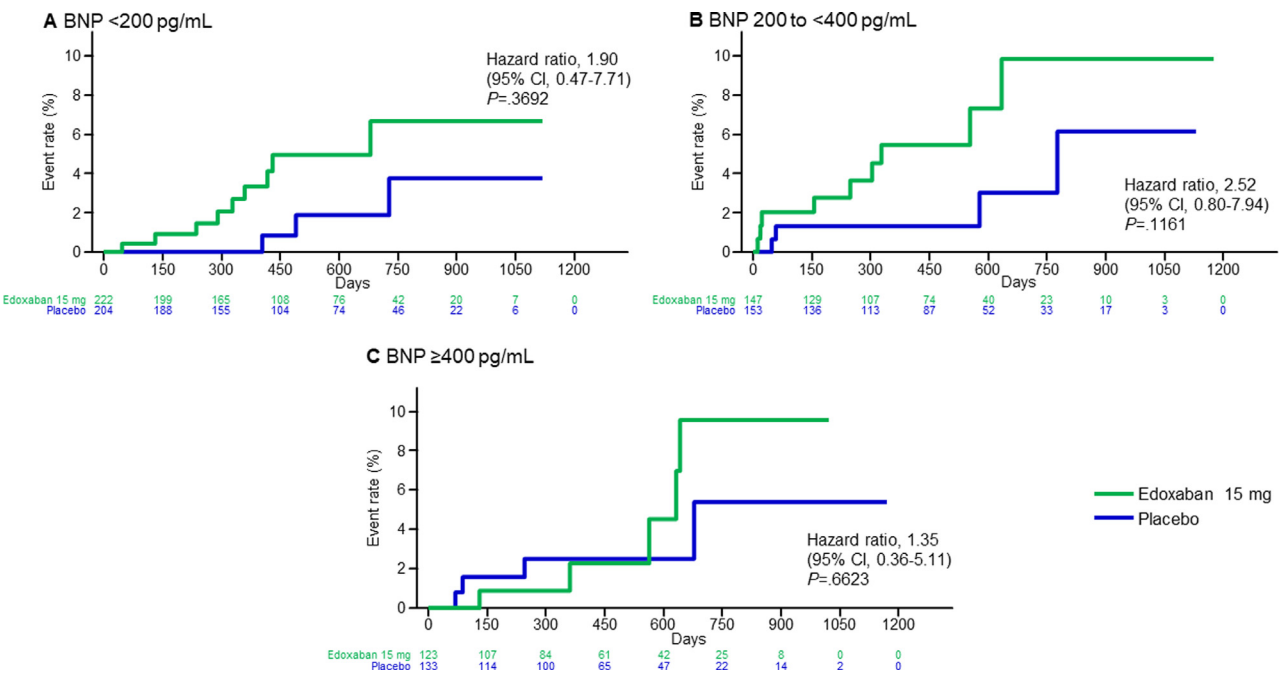
*BNP*, B-type natriuretic peptide; *CI*, confidence interval.

**Figure 3**




Kaplan–Meier curves for the effect of edoxaban vs placebo on the primary efficacy endpoint by BNP stratification: **A**, BNP <200 pg/mL, **B**, BNP 200 to <400 pg/mL, and **C**, BNP ≥400 pg/mL (intention-to-treat analysis set; overall study period). A notable event suppression effect on the primary efficacy endpoint was shown with edoxaban vs placebo, according to BNP stratification. *BNP*, B-type natriuretic peptide; *CI*, confidence interval.

**Figure 4**




Kaplan–Meier curves for the effect of edoxaban vs placebo on the primary safety endpoint by BNP stratification: (**A**) BNP <200 pg/mL, (**B**) BNP 200 to <400 pg/mL, and (**C**) BNP ≥400 pg/mL (modified intention-to-treat analysis set; overall study period). There was no significant difference in the incidence of major bleeding between the edoxaban and placebo groups in each BNP subgroup. *BNP*, B-type natriuretic peptide; *CI*, confidence interval.

predictor of SSE in Japanese patients with HF.[12] The Hokuriku-Plus AF Registry showed that a high BNP level at baseline (defined as BNP ≥147 pg/mL) was associated with the risk of thromboembolic events and death in Japanese patients with NVAF.[18] A subanalysis of data from the ENGAGE AF-TIMI 48 trial that assessed the predictive performance of biomarker-based ABC (age, biomarker, clinical history) scores, which included the assessment of N-terminal BNP, to evaluate the risk of stroke and systemic embolic events found that ABC-stroke and -bleeding scores were useful in identifying patients likely to benefit from anticoagulant therapy.[19] The ORBIT AF study showed that the risk of major adverse cardiovascular or neurological events increased with increasing BNP values.[13] Of note, the median BNP level in the present study (230.0 pg/mL) was notably higher than that in the Fushimi AF Registry (83.8 pg/mL)[12] and Hokuriku-Plus AF Registry (104 pg/mL).[18] These differences were likely due to the differences in population characteristics.

One of the most important aspects of the present ELDERCARE-AF trial is its study design: a randomized, placebo-controlled, double-blind, superiority trial. Because of the absence of a standard of care in the very elderly NVAF patients who were considered ineligible for standard oral anticoagulants for their high bleeding risks, placebo was selected as a comparator to edoxaban 15 mg. Considering that BNP levels are known to be associated with the risk of frailty in elderly patients,[14] the present subanalysis provides important information, showing that very elderly, high-risk patients with AF and high BNP levels who remain untreated with anticoagulants have a substantially higher risk of SSE (9.0% in the moderate BNP subgroup and 12.7% in the high BNP subgroup) than reported previously.[3,13,18] As BNP and NT-proBNP are known risk factors for stroke/SSE and cardiac death in those with established AF[8,9,12,13,20] and rising levels of NT-proBNP over a 12 month period were associated with a higher risk of stroke/SSE among those with AF treated with anticoagulation,[21] the findings of the present study taken together support the idea that the risk of SSE increases substantially with increasing BNP level in very elderly patients with AF and therefore, some therapeutic approaches should be considered. It should be pointed out that no association was observed between BNP levels and risk of major bleeding, which is consistent with the results of previous studies.[13,22]

When evaluating the effects of edoxaban 15 mg vs placebo by BNP stratification, our results showed a significant reduction in the incidence of SSE in patients who received edoxaban over those who received placebo, particularly among those with moderate and high BNP levels at baseline. Furthermore, edoxaban did not increase the incidence of major bleeding (including intracranial bleeding and gastrointestinal bleeding) and all-cause mortality over placebo, regardless of the patients' BNP level at baseline. Individualized therapy for patients with NVAF, including high-risk elderly patients, according to their BNP level may help improve patient outcomes, particularly in those with moderate and high BNP levels. The findings of the present study support the use of edoxaban 15 mg as a treatment option in this patient population.

The present subanalysis has some limitations. A considerable proportion of patients from the main study (16.1%) withdrew during the trial (158 in total, 81 from the edoxaban group, and 77 from the placebo group). As this study was conducted in Japanese patients with AF, the generalizability of the findings is limited to the Japanese population. The trial was not designed to evaluate changes over time in BNP levels and ejection fraction. Thus, the classification of HF could not be evaluated.

In conclusion, in very elderly Japanese patients (≥80 years of age) with NVAF who are considered ineligible for standard anticoagulant treatment, BNP is associated with the incidence of SSE and is not associated with major bleeding. Edoxaban 15 mg is more effective for preventing SSE than placebo, regardless of the BNP category, and thus, may be a treatment option that can be adopted for individualized medical care, particularly in very elderly patients with elevated BNP levels.

## Author contributions

Conceptualization: K Tanizawa, T Hayashi, M Akao, K Okumura, and T Yamashita. Data curation and investigation: O Okazaki, Y Higashino, K Yokoya, Y An, M Akao, and K Okumura. Formal analysis, writing and final approval of the manuscript: O Okazaki, Y Higashino, K Yokoya, Y An, K Tanizawa, Y Imamura, T Hayashi, M Akao, K Okumura, and T Yamashita.

## Data sharing statement

Anonymized data related to the present study will be made available at https://search.vivli.org/ to other researchers upon reasonable request to the corresponding author and pending approval by Daiichi Sankyo.

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## Disclosures

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.05.009.

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