Effectiveness and Safety of Apixaban in Japanese Elderly Atrial Fibrillation Patients With Extremely Low Body Weight

Takahide Kadosaka
Hokkaido University: Hokkaido Daigaku
Toshiyuki Nagai (nagai@med.hokudai.ac.jp)
Hokkaido University: Hokkaido Daigaku https://orcid.org/0000-0002-1043-0608
Shinya Suzuki
The Cardiovascular Institute
Ichiro Sakuma
Caress Sapporo Hokko memorial Clinic
Masaharu Akao
National Hospital Organisation Kyoto Medical Center: Kokuritsu Byoin Kiko Kyoto Iryo Center
Takeshi Yamashita
The Cardiovascular Institute
Ken Okumura
Saiseikai Kumamoto Hospital: Saiseikai Kumamoto Byoin
Toshihisa Anzai
Hokkaido University: Hokkaido Daigaku

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Abstract

Purpose

Although direct oral anticoagulants are effective and safe in preventing stroke in atrial fibrillation (AF) patients with low body weight, data remain limited in AF patients with extremely low body weight (< 50 kg). We aimed to investigate the effectiveness and safety of apixaban in this category of patients.

Methods

The J-ELD AF Registry is a large-scale, multicenter prospective observational study of Japanese non-valvular AF patients aged ≥ 75 years taking on-label doses of apixaban. The entire cohort (3,025 patients from 110 institutions) was divided into three body weight subgroups: >60 kg (n = 1,019, 33.7 %), 50–60 kg (n = 1,126, 37.2 %), and < 50 kg (n = 880, 29.1%).

Results

The event incidence rates (/100 person-years) were 1.69, 1.82 and 1.23 for stroke or systemic embolism (P = 0.60); 1.37, 1.73 and 2.73 for bleeding requiring hospitalization (P = 0.154); 2.02, 2.67 and 4.92 for total death (P = 0.003); and 0.73, 0.95 and 1.23 for cardiovascular death (P = 0.57), respectively. After adjusting for confounders by Cox regression analysis, body weight < 50 kg was an independent risk for total death but not for stroke or systemic embolism, bleeding requiring hospitalization or cardiovascular death.

Conclusions

The incidence of events in each body weight group was comparable for stroke or systemic embolism, bleeding requiring hospitalization, and cardiovascular death, and significantly higher for total death in the body weight < 50 kg group in Japanese non-valvular AF patients aged ≥ 75 years taking on-label doses of apixaban.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the elderly, and its prevalence in the general population aged 80 years and older is reported to be 7-14 % in Western countries and 2-3 % in Japan. [1-3] The risk of thromboembolism, such as stroke or systemic embolism, is higher in elderly patients with AF. [4, 5] Recently, the benefit of direct oral anticoagulants (DOACs) in the prevention of thromboembolism in patients with AF has been demonstrated, with a number of studies showing non-inferiority of apixaban and other DOACs to warfarin on effectiveness outcomes and a significant reduction in bleeding complications. [6-9] As a consequence, the proportion of patients receiving DOACs

for non-valvular AF has been increasing over time. [10, 11] On the other hand, the incidence of major bleeding remains around 3.5 % in non-valvular AF patients with low body weight (<50 kg) receiving DOACs, and it also increases with age, possibly due to elevated blood concentrations of the agents. [12-15]

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial demonstrated that low body weight (<60 kg) did not affect the effectiveness and safety of apixaban in patients with AF. [16] In contrast, age over 75 years and extremely low body weight (<50 kg) were shown to be significant key risk factors for bleeding complications in AF patients in the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET AF). [17, 18] Therefore, the effectiveness and safety of apixaban in elderly patients with extremely low body weight (<50 kg) have not been fully examined.

Accordingly, we sought to investigate the effectiveness and safety of apixaban in patients with extremely low body weight (<50 kg) using data from the J-ELD AF Registry, [19] a large-scale, multicenter prospective observational study of Japanese non-valvular AF patients aged ≥75 years taking apixaban.

Methods

Study Design

Data from the J-ELD AF Registry, obtained between September 2015 and August 2016 at 110 nationwide institutions, were retrospectively evaluated in different body weight groups. Details of the J-ELD AF Registry have been described previously. [19] Briefly, the J-ELD AF Registry is a large-scale, multicenter, prospective observational study of Japanese non-valvular AF patients aged ≥75 years taking apixaban. The inclusion criteria were Japanese patients with non-valvular AF aged ≥75 years who had attended the participating facilities after the start of the registry, and who had been taking or started taking apixaban. Patients with any of the following during the enrolment period were excluded: (1) history of hypersensitivity to apixaban, (2) active bleeding symptoms, (3) liver disease with coagulation disorder, and (4) creatinine clearance (CCr) < 15 mL/min. Also, patients who did not meet the apixaban dose reduction criteria but had received a reduced dose were excluded. Apixaban was given at a reduced dose (2.5 mg bid) to those who met two or three criteria for reduced apixaban dose administration of age ≥80 years, body weight ≤60 kg, and serum creatinine (S-Cre) ≥1.5 mg/dL, and at a standard dose (5 mg bid) to those who did not meet the above criteria. The observation period for each patient was 1 year.

Prior to the start of the registry, the investigators in charge received a review from the ethics committee of their main participating facility and acquired approval. Prior to enrolment, the contents of the study were explained to the patients using explanatory documents and consent documents, and written consent was obtained. If a patient withdrew consent during the observational period, all existing data collected from the patient were discarded. The study plan and its design were registered in the UMIN Clinical Trial Registry (UMIN000017895).

Data were collected using an Electronic Data Capture system for the observation and inspection items defined in the clinical trial protocol. Data regarding date of signature for informed consent, age, sex, body weight, type of heart disease, dose of apixaban, starting date of apixaban administration, presence or absence of co-administration with antiplatelet drugs, S-Cre, and CCr were collected at registration. Collected outcome data were the presence or absence of an event during the observation period of each patient, date of occurrence, and situation regarding apixaban administration during the week that the event occurred. Events included stroke, systemic embolism, bleeding requiring hospitalization, total death, cardiovascular death, acute myocardial infarction, antithrombotic drugs (anticoagulants and antiplatelet drugs) during the observation period, change or no change in dose, and date of change. Patient data were anonymized and imported into the Electronic Data Capture in a non-personal identity format. Data were securely managed by an external third-party commissioned by the Cardiovascular Institute Academic Research Organization.

Study Population

Among the original population of 3,066 patients, 41 were excluded (withdrawal of consent, n = 9; dropout, n = 26; no data of body weight, n = 6), and the remaining 3,025 patients were included in the current analysis. The target population for the analysis was divided into three groups according to body weight (>60 kg, 50-60 kg, and <50 kg) (Fig. 1).

Clinical Endpoints

The primary efficacy endpoint was stroke or systemic embolism, and the primary safety endpoint was bleeding requiring hospitalization. The secondary endpoint was total death or cardiovascular death.

Statistical Analysis

First, event incidence rate and 95% confidence interval (CI) (Poisson distribution) of the primary and secondary endpoints were calculated for each body weight group. The cumulative event incidences were displayed as Kaplan-Meier curves, and the differences between body weight groups were tested by log-rank test. Next, univariable and multivariable models were identified by Cox regression analysis. In the multivariable model, body weight groups were forcibly introduced, and factors showing a significant association with each endpoint in univariable analysis were also forcibly entered for adjustment. The factors for adjustment consisted of relevant thromboembolic or bleeding risk scores (i.e., $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores): age (≥85 years), female sex, heart failure, hypertension, diabetes mellitus, history of cerebral infarction or transient ischemic attack, history of myocardial infarction or peripheral artery disease, history of bleeding requiring hospitalization, liver dysfunction, habitual drinking, and use of antiplatelet drugs. Among these, the component of age was different from the original definition of each risk score, but we modified it to secure statistical power for the adjustment (model 1). In addition, another multivariable model was developed using age and body weight as continuous variables (model 2). For primary efficacy and safety endpoints, multivariable models with the Fine-Gray method were further developed to take account of competing risks with total death in assessing the relative

hazards. To assess the interaction between body weight and apixaban dose on the primary and secondary outcomes, multivariable models were identified by Cox regression analysis for each dosage. Statistical analysis was performed using SAS Ver. 9.4 (SAS Institute Inc., Cray, NC). In all analyses, $P < .05$ was taken to indicate statistical signification.

Results

Baseline Characteristics

The distribution of body weight in the present analysis is shown in **Fig. 2A** (mean body weight; 56.3 kg ± 11.2 kg), and the distributions of body weight in the reduced and standard apixaban dose groups are shown in **Fig. 2B** (mean body weight; 51.2 ± 8.6 kg, 63.3 ± 10.5 kg, respectively). The numbers of patients in the body weight >60 kg, 50 to 60 kg and <50 kg groups were 1,019 (33.7 %), 1,126 (37.2 %) and 880 (29.1 %), respectively (**Table 1 and Fig. 1**). Most patients in the body weight >60 kg group received the standard apixaban dose, and most in the body weight <50 kg group received the reduced apixaban dose. The mean age and number of patients with age ≥85 years increased significantly as body weight decreased. The lower body weight group included predominantly female patients and showed a higher prevalence of paroxysmal AF and heart failure, as well as lower prevalence of hypertension, diabetes mellitus, peripheral artery disease, myocardial infarction and liver dysfunction as comorbidities, and there was a tendency for less habitual drinking and taking antiplatelet drugs when compared to the higher body weight group. There were no significant differences in history of cerebral infarction and transient ischemic attack, or bleeding requiring hospitalization among body weight groups. The CHA_2DS_2-VASc and HAS-BLED scores showed significant differences, whereas there was no significant difference in $CHADS_2$ score among body weight groups.

Outcomes

Stroke or Systemic Embolism

The incidence rates of stroke or systemic embolism are shown in **Table 2**. There were no significant differences among the three groups (**Fig. 3A**). In the univariable and multivariable models of Cox regression analysis, low body weight was not significantly associated with stroke or systemic embolism (**Table 3**). The clinical factors independently associated with stroke or systemic embolism in the multivariable model were history of cerebral infarction or transient ischemic attack and history of bleeding requiring hospitalization. In the univariable and multivariable models of Fine-Gray regression analysis, low body weight was not significantly associated with these events, and the only independent predictor was history of cerebral infarction or transient ischemic attack (**Supplement Table S1**).

Bleeding Requiring Hospitalization.

The incidence rates of bleeding requiring hospitalization are shown in **Table 2**. There were no significant differences among the three groups (**Fig. 3B**). In the univariable and multivariable models of Cox

regression analysis, low body weight was not significantly associated with bleeding requiring hospitalization (**Table 3**). The clinical factors independently associated with bleeding requiring hospitalization in the multivariable model were history of bleeding requiring hospitalization and eGFR <45 mL/min/1.73m^2. Low body weight was not significantly associated with these events in the univariable and multivariable models of Fine-Gray regression analysis. There was no independent predictor of these events in the multivariable models of Fine-Gray regression analysis (**Supplement Table S1**).

Total Death.

The incidence rates of total death are presented in **Table 2**. Patients with body weight <50 kg had the highest incidence rate, and there were significant differences among the three groups (**Fig. 3C**). In the univariable and multivariable Cox regression models, body weight as a continuous variable was significantly and independently associated with total death, respectively. Although the category of body weight <50 kg was significantly associated with total death in the univariable model, it was not significant in the multivariable model (**Table 4**). The other independent determinants of total death in the multivariable model were age (both categories of ≥85 years old and continuous variable) and heart failure.

Cardiovascular Deaths.

The incidence rates of cardiovascular death are shown in **Table 2**. There were no significant differences among the three groups (**Fig. 3D**). In the univariable and multivariable models of Cox regression analysis, low body weight was not significantly associated with cardiovascular death (**Table 4**). The clinical factors independently associated with cardiovascular death in the multivariable model were age (continuous variable) and heart failure.

Subgroup Analysis.

We assessed the interaction between body weight and apixaban dose on the primary and secondary outcomes with the multivariable models of Cox regression analysis. There were no significant interactions on the primary and secondary outcomes between body weight and apixaban dose (Supplement Figure 1).

Discussion

In the present subanalysis of the J-ELD AF Registry, we evaluated the association between body weight and event occurrence in elderly AF patients taking on-label doses of apixaban. The main finding was that extremely low body weight (<50 kg) was not significantly associated with stroke or systemic embolism and bleeding requiring hospitalization in Japanese non-valvular AF patients aged ≥75 years, suggesting that apixaban would be safe and efficacious regardless of body weight even when it is extremely low.

Low body weight (<60 kg) is associated with increased blood apixaban level and bleeding events under exposure to apixaban, and therefore, constitutes one of the criteria for reduction of apixaban dose. However, the clinical significance of extremely low body weight (<50 kg) under treatment with apixaban in AF patients has not been fully evaluated. Pharmacokinetically, in healthy subjects, those with extremely low body weight (<50 kg) had approximately 27 % and 20 % higher apixaban C_{max} and $AUC_{0-\infty}$, respectively, compared with those with normal body weight defined as 65-85 kg. [15] There have been few reports from previous clinical trials and registries on the efficacy and safety of apixaban in patients with extremely low body weight (<50 kg) because there were a very small number of eligible cases in this category. Generally, East Asian AF patients are smaller in stature than Western AF patients. In clinical trials with AF patients, body weight in East Asian patients was much lower than that in non-East Asian counterparts (67 kg vs. 84 kg). [20] In fact, post-hoc analysis of the ARISTOTLE trial demonstrated that the mean body weight in patients over 75 years of age was 76.5 kg, around 20 kg heavier than that in our study (56.3 ± 11.2 kg). [21] Furthermore, the mean body weight of our entire cohort was also lower than in other clinical studies in Japanese AF patients such as the Fushimi AF Registry (58.5 kg [mean age, 74.2 years]), [22] the ARISTOTLE-J study (reduced dose: 67.6 kg [mean age, 69.3 years]; standard dose: 65.0 kg [mean age, 70.0 years]), [23] and the EXPAND Study (62.8 kg [mean age, 71.6 years]) [24] because the J-ELD AF Registry focused on more elderly patients (mean age, 81.7 years). Taking these results together, our registry would be suitable for evaluation of the efficacy and safety of apixaban in elderly patients with extremely low body weight.

In the present subanalysis of the J-ELD AF Registry, we identified the clinical characteristics of patients with extremely low body weight, which included patients with older age, higher female ratio, higher prevalence of heart failure, and lower prevalence of various cardiovascular risk factors such as hypertension and diabetes. It has been estimated that 10.7 % of the elderly have frailty, [25] and generally, weight loss is associated with frailty. [26] Therefore, one of the more significant features of patients with extremely low body weight in our subjects would be frailty, although we unfortunately did not have this information. Frailty and malnutrition are closely associated with each other, and moreover, they synergistically increase mortality as they progress. [27] Consistent with this, in our patients, body weight <50 kg was independently associated with total death, but not with cardiovascular death.

We evaluated the thromboembolic risk of extremely low body weight in elderly AF patients under apixaban treatment. The $CHADS_2$-VASc scores for the <50 kg, 50-60 kg and >60 kg groups in the J-ELD AF Registry were 4.7 ± 1.2, 4.4 ± 1.2 and 4.2 ± 1.2, respectively, which were much higher than those for the ≤60 kg, 60-120 kg and >120 kg groups in the ARISTOTLE trial [16] of 3.95 ± 1.52, 3.39 ± 1.50 and 2.71 ± 1.30, respectively. In the ARISTOTLE trial, the incidence rates of stroke and systemic embolism were numerically higher in patients with lower body weight in the apixaban group (≤60 kg, 60-120 kg groups; 2.01, 1.23 / 100 person-years, respectively) as well as in the warfarin group (≤60 kg, 60-120 kg groups; 3.20, 1.44 / 100 person-years, respectively), although these did not reach statistical significance. However, in the present subanalysis of the J-ELD AF Registry, these events were comparable among the groups (<50 kg, 50-60 kg, >60 kg groups; 1.23, 1.82, 1.69 / 100 person-years, respectively, $P = 0.60$). Given the

high $CHADS_2$-VASc scores regardless of body weight in the J-ELD AF Registry, the results above suggest that, at least under treatment with apixaban, the apparent high incidence rate of stroke and systemic embolism in low body weight subjects in the ARISTOTLE trial would be a confounding factor with age, and, when assessed in elderly AF patients, low body weight or extremely low body weight did not affect the incidence of stroke and systemic embolism. Notably, 84.4 % of our extremely low body weight group received a reduced apixaban dose, which was associated with a lower blood level of apixaban compared to the standard dose in a previous subanalysis of the J-ELD AF Registry. [28] Nevertheless, there was no significant difference in the occurrence of stroke or systemic embolism among the body weight groups, which suggests that apixaban level does not affect stroke and systemic embolism irrespective of apixaban dose. [28] There was no evidence that should take into account the effect of competing risk of total death, because there was no obvious difference in HR of the extremely low body weight group between the Cox model and the Fine-Gray model (**Supplement Table S1**). When comparing the risk of low body weight or extremely low body weight on stroke or systemic embolism between standard and reduced doses, there was no significant interaction between body weight and apixaban dose, which may partially confirm the validity of the criteria for reduction of apixaban dose in view of the effect of low body weight (**Supplement Figure 1**).

We evaluated the bleeding risk of extremely low body weight in elderly AF patients under treatment with apixaban. HAS-BLED scores for the <50 kg, 50-60 kg and >60 kg groups in the J-ELD AF Registry were 2.3 ± 0.7, 2.4 ± 0.8 and 2.6 ± 0.8, respectively, which were numerically similar among the body weight groups. However, although not statistically significant, the extremely low body weight group showed a numerically increased risk of bleeding requiring hospitalization (HR 1.9, 95% CI: 0.95-3.8, $P = 0.068$) in our study population. As noted, 84.4 % of our extremely low body weight group received a reduced dose of apixaban. Given that there was an obvious difference in the occurrence of bleeding requiring hospitalization between subjects with high and low blood apixaban levels in patients receiving a reduced apixaban dose in the subanalysis of the J-ELD AF Registry[28], the existence of a further high-risk subpopulation in the extremely low body weight group should have been presumed, which unfortunately could not be determined from our current data. There was no evidence that should take into account the effect of competing risk of total death, because there was no obvious difference in HR of the extremely low body weight group between the Cox model and the Fine-Gray model (**Supplement Table S1**). Comparing the risk of bleeding complications at standard and reduced doses among the weight groups, there was no significant interaction between body weight and apixaban dose, which may partially confirm the validity of the criteria for reduction of apixaban dose in view of the effect of low body weight (**Supplement Figure 1**).

Limitations

There are several potential limitations of the present study which should be acknowledged. First, the J-ELD AF Registry was a prospective, single-arm, observational study, and there was no control arm with which the effect of apixaban was compared. Second, selection bias may have occurred because investigators enrolled in this registry patients who were appropriately treated with apixaban. Third, it was

possible that patients with well-controlled AF may have been included because of the eligibility of patients who were able to attend a medical institution with cardiovascular specialists on the staff. Fourth, since the observation period was only one year, we may not be able to fully assess the occurrence of long-term events. Fifth, there may be differences in the definition of each event because the outcome events were reported by each participating center, and central adjudication was not performed. Sixth, the status of adherence, discontinuation, or change to other anticoagulants, which would affect patient outcomes, was not recorded in the present study. Seventh, the number of adverse events was relatively small, and the statistical power for detecting differences in negative data was limited. Lastly, this registry does not include patients taking an off-label under dose, which is common in real-world clinical practice. The benefit of under dose DOACs is an important matter of debate, but this was not within the scope of the present study.

Conclusion

This subanalysis examined the effect of body weight on events in >3,000 Japanese AF patients taking on-label doses, focusing on the risk of extremely low body weight. The incidence rates of events in each body weight group were comparable for stroke or systemic embolism and bleeding requiring hospitalization, and extremely low body weight (<50 kg) was identified as an independent risk factor for total death but not for cardiovascular death.

Declarations

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Conflict of Interest

Dr. Kadosaka reports no conflict. Dr. Nagai received honoraria from Daiichi Sankyo Co., Ltd., a clinical research grant from JSPS KAKENHI Grant-in-Aid for Scientific Research, and research grants from the Takeda Science Foundation, the Japan Foundation for Aging and Health, and the Uehara Memorial Foundation. Dr. Suzuki received research funding from Daiichi-Sankyo and Mitsubishi-Tanabe. Dr.

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Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Code Availability: Statistical analysis was performed using SAS Ver. 9.4 (SAS Institute Inc., Cray, NC).

Authors' Contributions: Contributions by each author according to the Contributor Roles Taxonomy (CRediT; https://www.casrai.org/credit.html):

Takahide Kadosaka: conceptualization, methodology, formal analysis, writing – original draft

Toshiyuki Nagai: conceptualization, methodology, formal analysis, writing – original draft

Shinya Suzuki: data curation, formal analysis, investigation, writing – review & editing

Ichiro Sakuma: investigation, writing – review & editing

Masaharu Akao: investigation, project administration, writing - review & editing

Takeshi Yamashita: funding acquisition, investigation, project administration, supervision, writing - review & editing

Ken Okumura: funding acquisition, investigation, project administration, supervision, writing - review & editing

Toshihisa Anzai: conceptualization, methodology, formal analysis, writing - review & editing

Ethics Approval: This study was performed in conformity to the ethical norms based on the Declaration of Helsinki (revised in 2008) and Ethical Guidelines for Medica and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare in Japan, issued in 2014).

Consent to Participate: Prior to enrollment, the contents of the study were explained to the patients using explanatory documents and consent documents, and written consent was obtained. If a patient withdrew consent during the observation period, all existing data collected from the patient were discarded.

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Tables

Table 1. Baseline characteristics

	Total	BW <50 kg	BW 50-60 kg	BW >60 kg	*P* value
	(N=3025)	(n = 880, 29.1 %)	(n = 1126, 37.2 %)	(n = 1019, 33.7 %)	
Dose					<0.001
Standard dose (5 mg bid), n (%)	1282 (42.4)	137 (15.6)	295 (26.2)	850 (83.4)	
Reduced dose (2.5 mg bid), n (%)	1743 (57.6)	743 (84.4)	831 (73.8)	169 (16.6)	
Gender					<0.001
Male, n (%)	1567 (51.8)	167 (19.0)	589 (52.3)	811 (79.6)	
Female, n (%)	1458 (48.2)	713 (81.0)	537 (47.7)	208 (20.4)	
Age, year	81.7 ± 4.6	83.5 ± 4.7	82.1 ± 4.5	79.7 ± 3.9	<0.001
Age ≥ 85y, n (%)	841 (27.8)	371 (42.2)	339 (30.1)	131 (12.9)	<0.001
Body weight, kg	56.3 ± 11.2	43.6 ± 4.5	55.0 ± 3.0	68.8 ± 6.8	<0.001
Systolic BP, mmHg	127.3 ± 17.4	124.9 ± 18.1	127.4 ± 17.8	129.1 ± 15.9	<0.001
Diastolic BP, mmHg	70.7 ± 12.3	68.4 ± 12.4	70.5 ± 12.0	72.9 ± 12.2	<0.001
Pulse rate, beat/min	74.1 ± 15.0	74.6 ± 14.7	74.0 ± 15.0	73.7 ± 15.1	0.45
S- Cre, mg/dL	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	<0.001
S- Cre >2.26 mg/dL, n (%)	10 (0.3)	3 (0.3)	1 (0.1)	6 (0.6)	0.131
eGFR, mL/min/1.73m^2	52.9 ± 15.4	52.1 ± 16.6	52.8 ± 15.5	53.8 ± 14.2	0.052
eGFR < 45mL/min/1.73m^2, n (%)	914 (30.2)	304 (34.5)	346 (30.7)	264 (25.9)	<0.001
AF type, n (%)					0.014
Paroxysmal	1485 (49.1)	462 (52.5)	565 (50.2)	458 (44.9)	
Persistent	488 (16.1)	123 (14.0)	171 (15.2)	194 (19.0)	

Permanent	1020 (33.7)	286 (32.5)	380 (33.7)	354 (34.7)	
Unknown	32 (1.1)	9 (1.0)	10 (0.9)	13 (1.3)	
EHRA score, n (%)					0.002
1	1653 (54.6)	448 (50.9)	600 (53.3)	605 (59.4)	
2	1056 (34.9)	338 (38.4)	396 (35.2)	322 (31.6)	
3	174 (5.8)	52 (5.9)	78 (6.9)	44 (4.3)	
4	27 (0.9)	12 (1.4)	6 (0.5)	9 (0.9)	
Unknown	115 (3.8)	30 (3.4)	46 (4.1)	39 (3.8)	
Heart failure, n (%)	1068 (35.3)	387 (44.0)	388 (34.5)	293 (28.8)	<0.001
Hypertension, n (%)	2715 (89.8)	768 (87.3)	1006 (89.3)	941 (92.3)	0.001
Diabetes mellitus, n (%)	700 (23.1)	137 (15.6)	260 (23.1)	303 (29.7)	<0.001
History of CI /TIA, n (%)	530 (17.5)	142 (16.1)	214 (19.0)	174 (17.1)	0.22
History of PAD /MI, n (%)	286 (9.5)	66 (7.5)	105 (9.3)	115 (11.3)	0.019
History of bleeding requiring hospitalization, n (%)	54 (1.8)	21 (2.4)	17 (1.5)	16 (1.6)	0.28
Abnormal values in liver enzyme, n (%)	486 (16.1)	122 (13.9)	180 (16.0)	184 (18.1)	0.046
Habitual drinking, n (%)	407 (13.5)	48 (5.5)	139 (12.3)	220 (21.6)	<0.001
Antiplatelet drugs, n (%)	558 (18.4)	133 (15.1)	201 (17.9)	224 (22.0)	<0.001
$CHADS_2$ score					
Continuous value	2.8 ± 1.1	2.8 ± 1.0	2.8 ± 1.1	2.8 ± 1.1	0.39
Category, n (%)					0.14
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	164 (5.4)	57 (6.5)	60 (5.3)	47 (4.6)	
2	1186 (39.2)	332 (37.7)	448 (39.8)	406 (39.8)	

3	972 (32.1)	308 (35.0)	347 (30.8)	317 (31.1)	
4	448 (14.8)	114 (13.0)	165 (14.7)	169 (16.6)	
5	206 (6.8)	59 (6.7)	85 (7.5)	62 (6.1)	
6	49 (1.6)	10 (1.1)	21 (1.9)	18 (1.8)	
$CHADS_2$-VASc score					
Continuous value	4.4 ± 1.2	4.7 ± 1.2	4.4 ± 1.2	4.2 ± 1.2	<0.001
Category, n (%)					<0.001
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
2	87 (2.9)	13 (1.5)	34 (3.0)	40 (3.9)	
3	612 (20.2)	90 (10.2)	219 (19.4)	303 (29.7)	
4	1064 (35.2)	330 (37.5)	413 (36.7)	321 (31.5)	
5	725 (24.0)	267 (30.3)	248 (22.0)	210 (20.6)	
6	356 (11.8)	110 (12.5)	145 (12.9)	101 (9.9)	
7	143 (4.7)	58 (6.6)	48 (4.3)	37 (3.6)	
8	33 (1.1)	10 (1.1)	18 (1.6)	5 (0.5)	
9	5 (0.2)	2 (0.2)	1 (0.1)	2 (0.2)	
HAS-BLED score					
Continuous value	2.4 ± 0.8	2.3 ± 0.7	2.4 ± 0.8	2.6 ± 0.8	<0.001
Category, n (%)					<0.001
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	197 (6.5)	75 (8.5)	84 (7.5)	38 (3.7)	
2	1653 (54.6)	536 (60.9)	608 (54.0)	509 (50.0)	
3	899 (29.7)	219 (24.9)	333 (29.6)	347 (34.1)	
4	253 (8.4)	44 (5.0)	94 (8.3)	115 (11.3)	

5	22 (0.7)	6 (0.7)	7 (0.6)	9 (0.9)
6	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
9	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are mean ± standard deviation, median (interquartile range) or percentages. BW, body weight; BP, blood pressure; S- Cre, serum creatinine; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation; EHRA, European Heart Rhythm Association; CI, cerebral infarction; TIA, transient ischemic attack; PAD, peripheral artery disease; MI, myocardial infarction.

Table 2. Event incidence rates

		No. of events	Person-years	Incidence rate (/ 100 person-years)	95%CI	
					Lower	Upper
Stroke or systemic embolism	Total	45	2800	1.61	1.20	2.15
	BW >60 kg	16	946	1.69	1.04	2.75
	BW 50-60 kg	19	1045	1.82	1.16	2.84
	BW <50 kg	10	810	1.23	0.67	2.27
Bleeding requiring hospitalization	Total	53	2796	1.90	1.45	2.48
	BW >60 kg	13	948	1.37	0.80	2.35
	BW 50-60 kg	18	1043	1.73	1.09	2.73
	BW <50 kg	22	805	2.73	1.80	4.14
Total death	Total	89	2816	3.16	2.57	3.89
	BW >60 kg	21	953	2.20	1.44	3.37
	BW 50-60 kg	28	1050	2.67	1.85	3.85
	BW <50 kg	40	813	4.92	3.61	6.70
Cardiovascular death	Total	27	2816	0.96	0.66	1.40
	BW >60 kg	7	953	0.73	0.36	1.52
	BW 50-60 kg	10	1050	0.95	0.52	1.75
	BW <50 kg	10	813	1.23	0.67	2.26

BW, body weight; 95% CI, 95% confidence interval.

Table 3. Cox proportional hazard models for stroke or systemic embolism and bleeding requiring hospitalization

	Univariable model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Stroke or systemic embolism						
BW >60 kg	Reference		Reference			
BW 50-60 kg	1.08 (0.55–2.09)	0.83	1.07 (0.55–2.09)	0.84		
BW <50kg	0.73 (0.33–1.61)	0.44	0.73 (0.33–1.61)	0.44		
BW (continuous value)	1.00 (0.98–1.03)	0.77			1.00 (0.98–1.03)	0.78
Age ≥ 85	1.33 (0.71–2.47)	0.37				
Age (continuous value)	1.04 (0.98–1.11)	0.198				
Heart failure	0.53 (0.26–1.06)	0.073				
Hypertension	1.63 (0.51–5.26)	0.41				
Diabetes mellitus	1.07 (0.54–2.10)	0.86				
History of CI/ TIA	2.34 (1.26–4.35)	0.007	2.29 (1.23–4.27)	0.009	2.32 (1.25–4.31)	0.008

Female sex	0.85 (0.47–1.53)	0.59				
History of PAD/ MI	0.96 (0.34–2.67)	0.93				
History of bleeding requiring hospitalization	4.11 (1.27–13.25)	0.018	4.11 (1.27–13.29)	0.018	4.01 (1.24–12.94)	0.020
eGFR < 45mL/min/1.73m^2	0.85 (0.44–1.64)	0.62				
Abnormal values in liver enzyme	1.16 (0.54–2.49)	0.71				
Habitual drinking	1.86 (0.92–3.76)	0.083				
Antiplatelet drugs	1.14 (0.55–2.36)	0.73				
Bleeding requiring hospitalization						
BW >60 kg	Reference		Reference			
BW 50-60 kg	1.26 (0.62–2.57)	0.53	1.28 (0.63–2.62)	0.50		
BW <50kg	1.90 (0.95–3.80)	0.068	1.90 (0.94–3.81)	0.073		
BW (continuous value)	0.98 (0.96–1.01)	0.120			0.98 (0.96–1.01)	0.124
Age ≥ 85	1.53 (0.87–2.68)	0.142				

Age (continuous value)	1.05 (0.99–1.11)	0.123				
Heart failure	1.07 (0.61–1.87)	0.83				
Hypertension	0.89 (0.38–2.08)	0.78				
Diabetes mellitus	0.89 (0.45–1.72)	0.72				
History of CI/ TIA	0.97 (0.47–1.99)	0.93				
Female sex	0.99 (0.57–1.70)	0.97				
History of PAD/ MI	2.06 (1.01–4.23)	0.048	1.46 (0.66–3.26)	0.35	1.43 (0.64–3.20)	0.38
History of bleeding requiring hospitalization	3.50 (1.09–11.23)	0.035	3.46 (1.07–11.18)	0.038	3.61 (1.12–11.63)	0.032
eGFR < 45mL/min/1.73m^2	2.00 (1.16–3.46)	0.012	1.82 (1.05–3.16)	0.032	1.84 (1.06–3.19)	0.030
Abnormal values in liver enzyme	1.44 (0.74–2.80)	0.28				
Habitual drinking	1.00 (0.45–2.22)	0.995				
Antiplatelet drugs	2.02 (1.12–3.64)	0.019	1.81 (0.94–3.48)	0.077	1.81 (0.94–3.50)	0.076

BW, age and serum creatinine were entered as categorical and continuous variables into the multivariable model 1 and 2, respectively. BW, body weight; CI, cerebral infarction; TIA, transient ischemic attack; PAD, peripheral artery disease; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; 95% CI, 95% confidence interval.

Table 4. Cox proportional hazard models for the total and cardiovascular death

	Univariable model		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Total death						
BW >60 kg	Reference		Reference			
BW 50-60 kg	1.21 (0.69–2.13)	0.51	1.05 (0.59–1.87)	0.86		
BW <50kg	2.24 (1.32–3.79)	0.003	1.72 (0.99–3.00)	0.054		
BW (continuous value)	0.97 (0.95–0.99)	<0.001			0.98 (0.96–1.00)	0.028
Age ≥ 85	2.25 (1.49–3.42)	<0.001	1.64 (1.05–2.55)	0.029		
Age (continuous value)	1.09 (1.05–1.14)	<0.001			1.05 (1.00–1.10)	0.037
Heart failure	2.85 (1.86–4.36)	<0.001	2.21 (1.42–3.45)	<0.001	2.19 (1.40–3.41)	<0.001
Hypertension	1.17 (0.57–2.43)	0.67				
Diabetes mellitus	1.15 (0.71–1.85)	0.57				
History of CI/ TIA	0.65 (0.35–1.22)	0.184				
Female sex	0.66	0.056				

	(0.43–1.01)					
History of PAD/ MI	1.98 (1.13–3.44)	0.016	1.46 (0.79–2.71)	0.23	1.45 (0.78–2.69)	0.24
History of bleeding requiring hospitalization	1.95 (0.62–6.16)	0.26				
eGFR < 45mL/min/1.73m^2	2.08 (1.37–3.15)	<0.001	1.48 (0.96–2.28)	0.074	1.46 (0.95–2.25)	0.088
Abnormal values in liver enzyme	1.27 (0.75–2.15)	0.38				
Habitual drinking	0.64 (0.31–1.32)	0.23				
Antiplatelet drugs	1.76 (1.11–2.79)	0.017	1.57 (0.94–2.62)	0.086	1.59 (0.95–2.67)	0.077
Cardiovascular death						
BW >60 kg	Reference		Reference			
BW 50-60 kg	1.30 (0.49–3.41)	0.60	1.16 (0.44–3.06)	0.76		
BW <50kg	1.68 (0.64–4.41)	0.29	1.28 (0.48–3.41)	0.62		
BW (continuous value)	0.99 (0.95–1.02)	0.48			1.01 (0.97–1.05)	0.62
Age ≥ 85	2.11 (0.99–4.51)	0.054				
Age (continuous value)	1.13	0.002			1.09	0.028

	(1.05–1.21)				(1.01–1.19)	
Heart failure	5.27 (2.23–12.47)	<0.001	4.36 (1.80–10.55)	0.001	3.92 (1.61–9.56)	0.003
Hypertension	1.45 (0.34–6.13)	0.61				
Diabetes mellitus	1.94 (0.89–4.24)	0.096				
History of CI/ TIA	0.58 (0.17–1.92)	0.37				
Female sex	0.45 (0.20–1.03)	0.057				
History of PAD/ MI	2.78 (1.12–6.88)	0.027	2.25 (0.9–5.64)	0.084	2.31 (0.93–5.75)	0.073
History of bleeding requiring hospitalization	4.47 (1.06–18.87)	0.042	3.89 (0.91–16.6)	0.067	4.43 (1.04–18.86)	0.044
eGFR < 45mL/min/1.73m^2	2.5 (1.18–5.32)	0.017	1.72 (0.79–3.73)	0.171	1.54 (0.71–3.36)	0.28
Abnormal values in liver enzyme	1.54 (0.62–3.81)	0.35				
Habitual drinking	0.81 (0.24–2.69)	0.73				
Antiplatelet drugs	1.89 (0.83–4.32)	0.130				

BW, age and serum creatinine were entered as categorical and continuous variables into the multivariable model 1 and 2, respectively. BW, body weight; CI, cerebral infarction; TIA, transient ischemic attack; PAD, peripheral artery disease; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; 95% CI, 95% confidence interval.

Figures

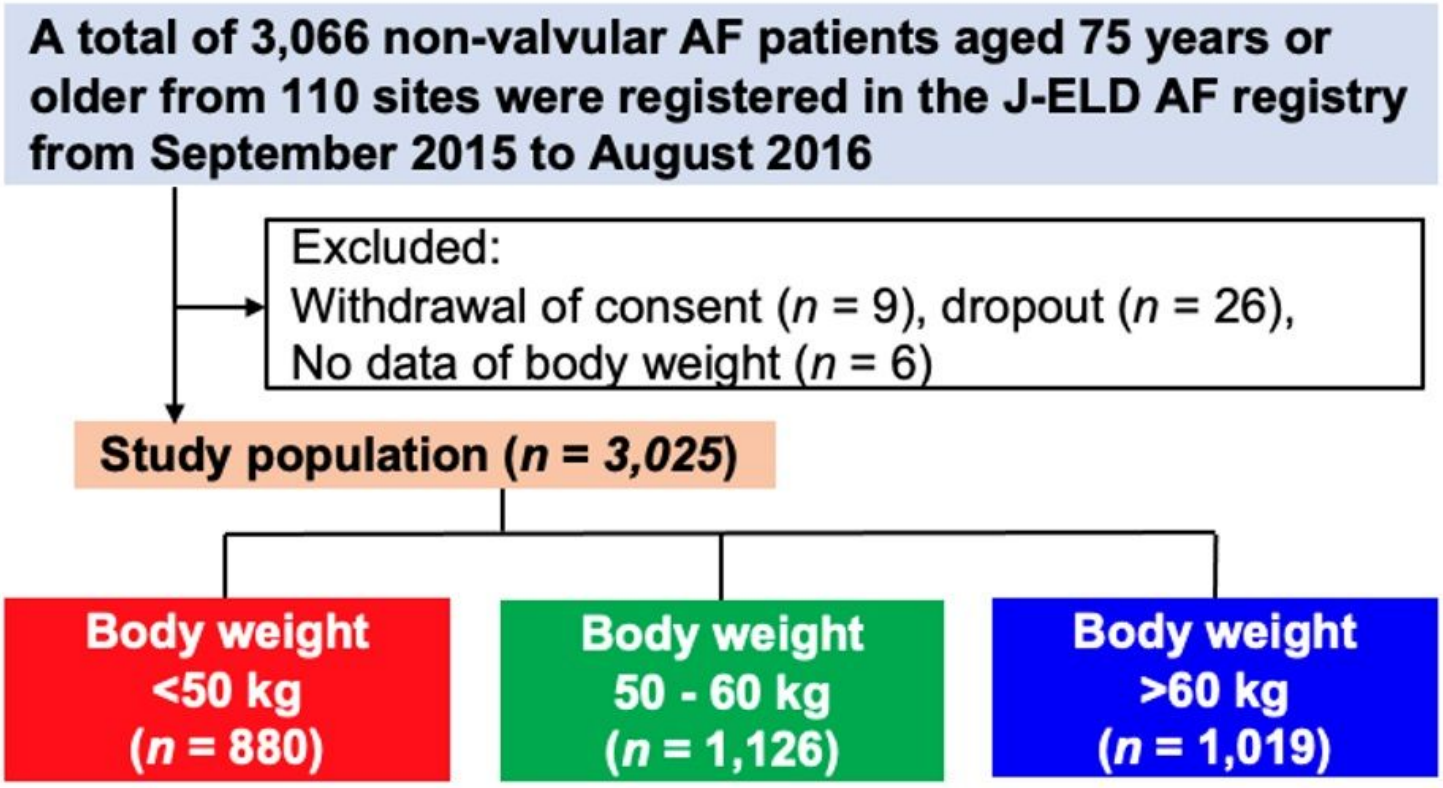

Figure 1

Flow diagram of present study. AF, atrial fibrillation.

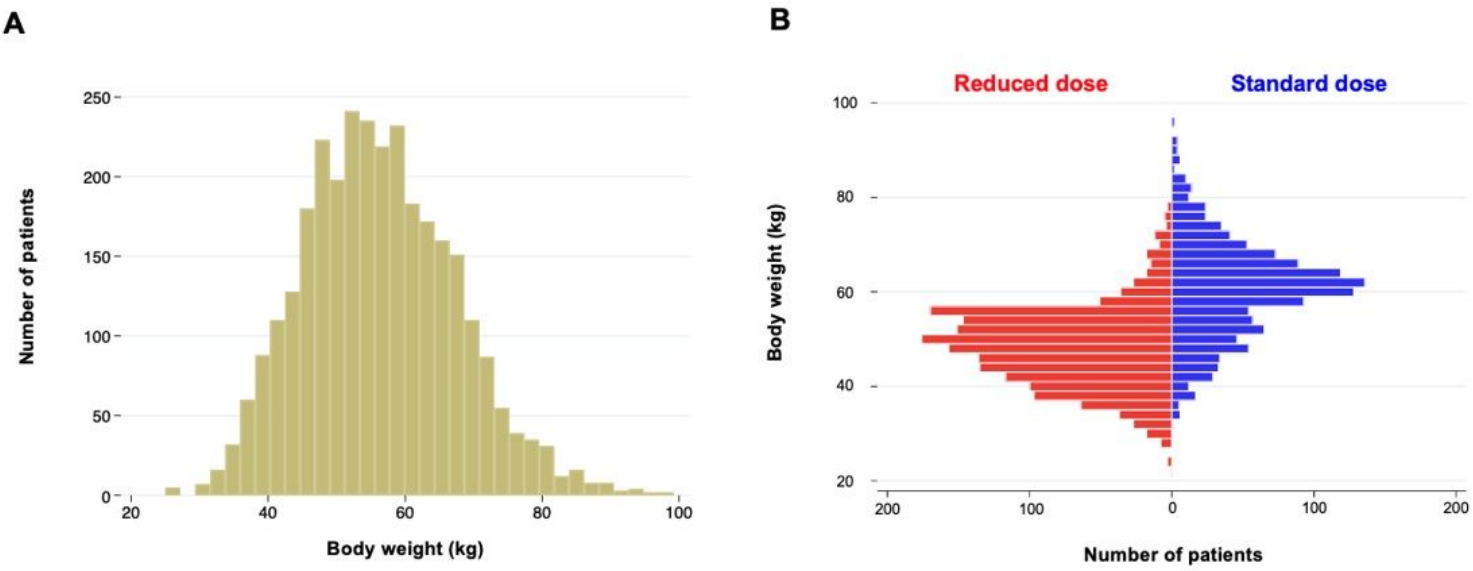

Figure 2

Distribution of body weight. (A) Entire cohort. (B) Classified by apixaban dose (standard dose; blue, reduced dose; red).

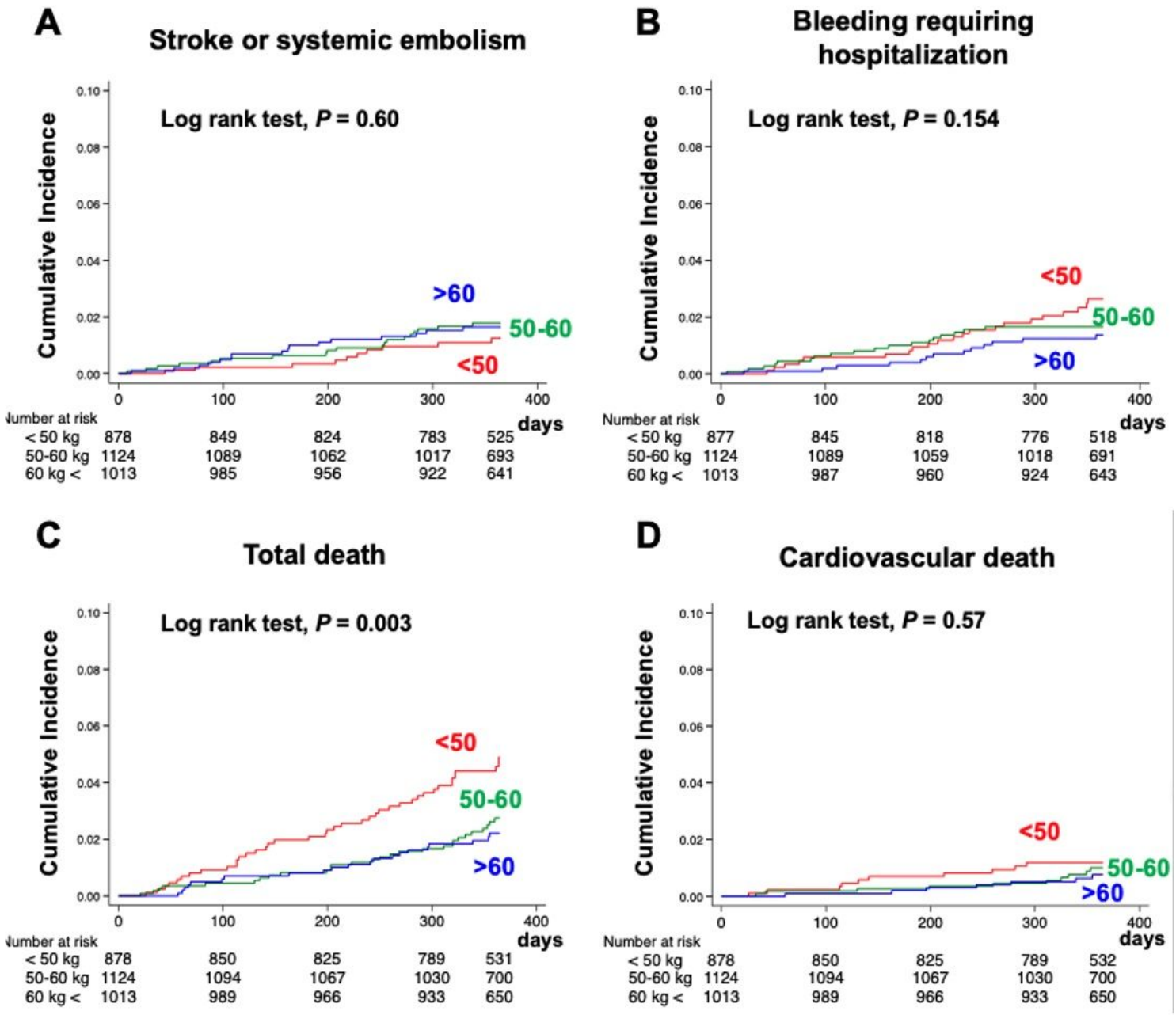

Figure 3

Cumulative incidence rates. (A) Stroke or systemic embolism. (B) Bleeding requiring hospitalization. (C) Total deaths. (D) Cardiovascular deaths.

Supplementary Files

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