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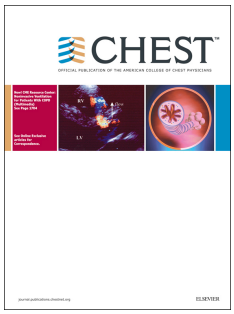

Clinical characteristics and outcomes in extreme elderly (age ≥85) Japanese patients with atrial fibrillation: The Fushimi AF Registry

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Short title: The extreme elderly with AF

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Disclosures

Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim and Bayer Healthcare. Dr Lip has served as a consultant for Bayer, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations list

AF=atrial fibrillation; APD=antiplatelet drugs; CI=confidence interval; CKD=Chronic kidney disease; HR=hazard ratio; OAC=oral anticoagulant; PT-INR=prothrombin time international normalized ratio; SD=standard deviation; SE=systemic embolism; TTR=time in therapeutic range

Abstract

Background: Atrial fibrillation (AF) is increasingly prevalent with age, and increasing age is an independent risk factor for ischemic stroke. Oral anticoagulant (OAC) therapy use in the extreme elderly (age ≥85 years) is challenging.

Methods: The Fushimi AF Registry is a community-based prospective study of Japanese AF patients (79 participating medical institutions in Fushimi-ku, Kyoto). The enrollment of patients was started in March 2011, and follow-up data were available for 3,304 patients as of July 2014. We compared clinical characteristics and outcomes between the extreme elderly group (n=479, 14.5%) and others.

Results: The extreme elderly had a higher prevalence of major co-morbidities and risk scores for stroke, but received less OAC. After a mean follow-up of 2.0 years, endpoints in the extreme elderly group were as follows: all-cause death 17.6, stroke or systemic embolism (SE) 5.1, and major bleeding 2.0 per 100 person-years, respectively. The extreme elderly group was associated with a higher incidence of combined stroke/SE and all-cause death (hazard ratio (HR) 3.20, 95% confidence interval (CI) 2.66-3.84, p<0.01), higher incidences of stroke/SE (HR 2.57, 95% CI 1.77-3.65, p<0.01) and mortality (HR 3.48, 95% CI 2.84-4.25, p<0.01), compared with others (aged ≤84). The incidence of major bleeding was not significantly different (HR 1.40, 95% CI 0.78-2.36, p=0.25).

Conclusions: In our community-based prospective cohort, Japanese extreme elderly AF patients had a higher incidence of stroke but similar major bleeding risks compared with the younger AF population.

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Key Words: atrial fibrillation; elderly; stroke; bleeding

Introduction

Atrial fibrillation (AF) is common among the elderly, and increases the risks for stroke and death[1]. The prevalence of AF increases with age, affecting 10% of those aged 80 years and 18% of those age >85 years[2]. The management of AF in elderly patients is of paramount importance, not only because of its increasing prevalence with age, but also because increasing age is an independent risk factor for ischemic stroke[3].

The use of oral anticoagulants (OAC) reduces stroke by 64% and all-cause mortality by 26%, compared with controls[4]. Thus, several sets of guidelines recommend that elderly AF patients aged over 75 years be offered OAC[5]. However, OAC therapy remains widely under-used in clinical practice, and only 15% to 50% of eligible elderly patients are prescribed warfarin therapy[6-9].

The management of OAC in the extreme elderly (age ≥85 years of age) patients is challenging due to the need to balance carefully the risk of thromboembolism with that of hemorrhage. To date, clinical trials have not specifically targeted extreme elderly patients, and most study subjects are not representative of the extreme elderly. Indeed, data on clinical characteristics and outcomes in the extreme elderly are limited, with no previous publications from Asia, including Japan. Our aim was to evaluate the clinical characteristics, including the status of OAC therapy and outcomes, in extreme elderly AF patients in 'real-world' clinical practice.

Methods

The Fushimi AF Registry is a community-based prospective survey of AF patients who visited the participating medical institutions in Fushimi district, Kyoto, Japan, which is a densely populated urban area with a total population of 283,000. The detailed study design, patient enrollment, definition of the measurements, and subjects' baseline clinical characteristics of the Fushimi AF Registry have been previously described (UMIN Clinical Trials Registry: UMIN000005834)[10, 11]. This study was conducted in accordance with the amended Declaration of Helsinki. The study protocol was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center (the approval number 14-033). Since the present research involves an observational study not using human biological specimens, written informed consent was not obtained from each patient according to the ethical guidelines for epidemiological research issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan.

Age data were collected at the time of entry into the registry. We defined the extreme elderly as those aged ≥85 years. We compared the background and the incidence of clinical events during a mean follow-up of 2.0 years (739 days) between the extreme elderly group and others (aged ≤74 years and aged 75-84 years). Chronic kidney disease (CKD) was diagnosed if there was persistent proteinuria or if estimated glomerular filtration rate was <60 mL/min/1.73 m^2 for more than 3 months[12]. OAC included warfarin, dabigatran, rivaroxaban and apixaban. The assignment to the

OAC group was based on use of OAC at the time of enrollment. The values of prothrombin time international normalized ratio (PT-INR) were collected at the time of enrollment for patients taking warfarin. Japanese guidelines set different target PT-INR ranges for patients taking warfarin: 1.6~2.6 for elderly patients (≥70 years old) and 2.0~3.0 for younger patients (<70 years old)[13]. Anti-platelet drugs (APD) included aspirin, clopidogrel, ticlopidine and cilostazol.

The $CHADS_2$ scoring adds together the points that correspond to the following conditions: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack (two points)[14]. The CHA_2DS_2-VASc scoring is a refinement of the $CHADS_2$ score and extends it by including additional common stroke risk factors: age (patients ≥75 years old get two points and patients 65-74 years old get one point), vascular disease and female gender[15]. We assessed hypertension (systolic blood pressure >160 mmHg), abnormal renal function (the presence of chronic dialysis or serum creatinine ≥200 mmol/L), abnormal liver function (aspartate aminotransferase or alanine aminotransferase 3 times the upper limit normal), stroke history, bleeding history, elderly (age >65 years), anti-platelet drugs, and excess alcohol (≥ 8 units alcoholic consumption per week) for calculating the HAS-BLED score[16]. Labile INR data, the values of bilirubin, and details on non-steroidal anti-inflammatory drugs were unavailable in our study.

The primary endpoint in the analysis was the composite of stroke, systemic embolism (SE) and all-cause death during the follow-up period. The secondary endpoints were stroke/SE, all-cause death and major bleeding. Stroke was defined as the sudden onset of a focal neurologic deficit in a location

consistent with the territory of a major cerebral artery, and the diagnosis of ischemic or hemorrhagic stroke was confirmed by computed tomography or magnetic resonance imaging. Major bleeding was defined as a reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ, following the definition by International Society on Thrombosis and Haemostasis[17].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are presented as absolute numbers and percentages. We compared continuous variables between the 2 groups using Student's t-test or Wilcoxon rank sum test on the basis of the distribution. Comparisons of the continuous variables of baseline data between the 3 groups were performed by 1-way analysis of variance (ANOVA). We compared categorical variables of baseline data using the Chi-square test when appropriate; otherwise, we used Fisher's exact test. Kaplan-Meier analysis was used to estimate event-free survival, and the log-rank test was used to compare survival across the groups. The univariate Cox proportional hazard model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the incidence of clinical events between each age group. A 2-sided P-value <0.05 was considered statistically significant. All statistical analyses were performed with JMP10.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of 3,666 patients who were enrolled into the Fushimi AF Registry by the end of July 2013, follow-up data (collected every year) were available for 3,304 patients (90.1%) by the end of July 2014. The age distribution in the entire cohort is shown in Figure 1A. The extreme elderly group accounted for 14.5% (479 patients).

The extreme elderly group was more often female (65.8%), with low body weight (49.0 kg) and low body mass index (21.1), and had many co-morbidities such as heart failure, coronary heart disease and chronic kidney disease (Table 1). Mean CHADS2 scores were as follows; 1.35 at age ≤74 years, 2.61 at age 75-84 years and 2.83 at age ≥85 years ($p<0.01$). Mean HAS-BLED score were as follows; 1.51 at age ≤74 years, 1.88 at age 75-84 years and 1.77 at age ≥85 years ($p<0.01$). Patients whose HAS-BLED scores were ≥3 accounted for 18% (371 patients).

Figure 1B shows the status of OAC and APD prescription according to age. OAC was used most frequently in those aged 75-79 years (60.1%) and its use decreased gradually with increasing age. On the other hand, APD were used most frequently in those aged 85-89 years (34.9%). Figure 1C shows the distribution of the number of patients according to $CHADS_2$ score in each age group: aged ≤74 years, aged 75-84 years and the extreme elderly (aged ≥85 years). Figure 1D shows OAC and APD prescription according to CHADS2 score in the age groups. In patients aged ≤74 years and 75-84 years, the use of OAC increased as the $CHADS_2$ score increased, up to about 70% in the high-risk patients. In the extreme elderly group, the rate of OAC prescription was generally low, from about

30% to 50% in all of the $CHADS_2$ subpopulations, with a weak association with the $CHADS_2$ score. In contrast, APD prescription rates were similar in all of the $CHADS_2$ subpopulations, for both the extreme elderly group and others.

The status of OAC therapy in each age group is shown in Table 1. Warfarin was the major OAC used in the study period. The prescription rates of OAC were as follows; 51.2% at age ≤74 years, 60.0% at age 75-84 years and 41.3% at age ≥85 years ($p<0.01$). The intensities of warfarin control as measured by mean PT-INR values at enrollment were comparable among the age groups (1.82 at age ≤74 years, 1.83 at age 75-84 years and 1.83 at age ≥85 years; $p=0.97$), but PT-INR values were unavailable in more than 30% of the extreme elderly patients.

The incidence rates of major clinical events in the entire cohort during the mean follow-up of 2.0 years (a total of 6,694 patient-years) were as follows: composite endpoint of stroke/SE and all-cause death in 538 (8.2 per 100 person-years), stroke/SE in 154 (2.3 per 100 person-years), ischemic stroke in 116 (1.8 per 100 person-years), all-cause death in 430 (6.4 per 100 person-years) and major bleeding in 95 (1.5 per 100 person-years). Kaplan-Meier curves for the incidences of stroke/SE and all-cause death, stroke/SE, all-cause death and major bleeding in each age group are shown in Figure 2. As shown in Table 2, the annual incidence rates of stroke/SE, all-cause death and major bleeding in the extreme elderly group were 5.1 per 100 person-years, 17.6 per 100 person-years and 2.0 per 100 person-years, respectively. The extreme elderly group was significantly associated with a higher incidence of stroke/SE (HR 2.57, 95% CI 1.77-3.65, $p<0.01$), a worse mortality rate (HR 3.48, 95%

CI 2.84-4.25, p<0.01), and a higher incidence of the composite of stroke/SE and all-cause death (HR 3.20, 95% CI 2.66-3.84, p<0.01), compared with those aged ≤84 years. The incidence of major bleeding was not significantly different (HR 1.40, 95% CI 0.78-2.36, p=0.25, compared with those aged ≤84 years).

Baseline characteristics, co-morbidities, medications and incidence rates of endpoints in the extreme elderly according to OAC use at baseline are shown in Table 3. The mean $CHADS_2$ score and CHA_2DS_2-VASc score were comparable between those with and without OAC ($CHADS_2$ score: 2.95 vs. 2.74, p=0.06; CHA_2DS_2-VASc score: 4.66 vs. 4.59, p=0.55), and so were the major co-morbidities, except for a higher prevalence of previous stroke in those with OAC (36.4% vs. 23.5%, p<0.01). The mean HAS-BLED score was also comparable between those with and without OAC (1.73 vs. 1.80, p=0.53).

Kaplan-Meier curves for stroke/SE and all-cause death, stroke/SE, all-cause death and major bleeding between patients taking and not taking OAC in the extreme elderly group are shown in Figure 3. The incidence rates of the composite of stroke/SE and all-cause death in extreme elderly patients were comparable between those with and without OAC (HR 0.94, 95% CI 0.69-1.28, p=0.71). The incidences of stroke/SE in those taking OAC were higher than those not taking OAC (HR 2.70, 95% CI 1.42-5.41, p<0.01), and the mortality rate was marginally lower, but this was not statistically significant (HR 0.75, 95% CI 0.53-1.06, p=0.11). The incidences of major bleeding in those with OAC were comparable to that in those without OAC (HR 0.88, 95% CI 0.30-2.45,

p=0.81).

Discussion

This is one of the largest community-based prospective cohorts of elderly Asian subjects with AF, where we describe the clinical characteristics and outcomes of Japanese extreme elderly (age ≥85) patients with AF in 'real-world' clinical practice. We found an under-use of OAC, but a high risk of stroke/SE and mortality, alongside a similar risk of bleeding. Second, there was a paradoxical finding that the incidence of stroke/SE was higher in extreme elderly patients with OAC compared to those without OAC use.

Despite the proven benefit of OAC for preventing stroke in patients with AF, its under-use has been reported, particularly among those aged ≥80 years[6]. Our study shows that the proportion of usage of OAC decreases gradually as patients age, and only 41.3% of extreme elderly patients were taking OAC. Our study also shows that extreme elderly patients with AF had a weak association with OAC prescription according to stroke risk scores, again consistent with a previous report from Japan showing modest relationship between $CHADS_2$ risk score and warfarin use[18]. The decision to prescribe long-term OAC therapy in extreme elderly patients with AF remains challenging because of the lack of clinical data concerning the risk of both thromboembolism and bleeding.

Thromboembolism in the extreme elderly with AF

One reported study found that the overall annual incidence of ischemic stroke among elderly Chinese AF patients aged ≥80 years was as high as 11.3% per year[19]. Our study showed that the incidence of stroke/SE was 5.1 per 100 person-years in Japanese extreme elderly patients with AF, which may reflect differences in study populations (hospitalized vs. community setting) and OAC use.

The present study demonstrates the paradoxical finding that the incidence of stroke/SE was higher in extreme elderly patients with OAC than in those without OAC use. It was unlikely that hemorrhagic stroke was more common in the OAC-treated group (0.7 per 100 person-years in patients with OAC vs. 0.6 in patients without OAC). $CHADS_2$ and CHA_2DS_2-VASc scores were comparable between those with and without OAC, but history of stoke were more frequent in those with OAC (36.4% vs, 23.5%; $p<0.01$), and other unidentified risk factors may have been associated. Insufficient intensity of warfarin (under-dose of warfarin) may also have been the underlying reason for the higher incidence of stroke in OAC-treated patients. The mean PT-INR value was not particularly low in the extreme elderly, but PT-INR values were missing in more than 30% of patients in the extreme elderly. Particular care is therefore needed when managing this elderly patient age group, given their high stroke risk overall, especially the need for careful thromboprophylaxis and treatment adherence to optimize stroke prevention in these patients. Indeed, OAC treatment is not simply prescribing the drug (ie. warfarin), but paying attention to the quality of anticoagulation control, as reflected by the time in therapeutic range (TTR).

Bleeding in the extreme elderly with OAC

Many studies have suggested that the major bleeding risk with OAC therapy is higher in older patients than in younger ones. Some studies have reported major bleeding rates with vitamin K antagonists in older patients of 1.1–5.1% per year[19-24]. Another observational study reported a higher prevalence of 13.1% per year[25]. Our study showed that the incidence rate of major bleeding in the extreme elderly with OAC was only 1.8 per 100 person-years, and there was no significant difference compared with younger age strata. This could have been due to some of the extreme elderly who received OAC at enrollment stopping taking OAC at the follow-up. Alternatively, under-dosing of warfarin therapy may have decreased the risk of bleeding. Analysis of TTR should be used to assess the quality of warfarin control, but unfortunately we do not have data on TTR in this study.

Benefit-risk balance of OAC in extreme elderly patients with AF

Several recent studies have demonstrated that OAC therapy provides a net clinical benefit in the elderly[26-30]. However, it is difficult to choose the appropriate OAC therapy in the extreme elderly with AF. Although risk scores are useful guides to clinical decision making in practice, in the "real world" they do not capture other factors which clinicians and patients consider when starting on long term OAC, such as age-related cognitive state, new co-morbidities, general frailty/mobility for attending monitoring and even socio-economic factors. Above all, their shorter life expectancy can also influence decision-making. In our study, the annual risk of all-cause death was 17.6 per 100 person-years. Decisions on OAC use in extreme elderly patients with AF should be based on

consideration of absolute individual benefits and the risks of treatment and patient preference.

Study limitations

This study has several limitations. First, this is an observational study and provides only associative evidence, not causative. Second, OAC data were collected only at the time of entry into the study, so we were unable to explore the relationship between changes in OAC and clinical events. Third, we investigated neither the TTR for patients taking warfarin during follow-up nor the adherence of OAC therapies, and therefore it would be difficult to know how the quality of warfarin control and the adherence of OAC therapies influenced outcomes. Fourth, about 10% of patients were missed during follow-up. As shown in the Supplementary Table, the population with 'missing data' was older, more often female, and had a higher $CHADS_2$ score than the followed patients, which could induce a selection bias. Finally, this study was conducted in Japanese AF patients, and it is uncertain whether the study results can be generalizable to other populations.

Conclusions

Our community-based large prospective cohort shows that Japanese extreme elderly patients with AF had a higher incidence of stroke, but similar major bleeding risk, compared with a younger AF population. Particular care is therefore needed when managing this elderly patient age group, given their high stroke risk overall.

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M. Akao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions: YY analyzed the data and wrote the paper. YH, GL helped data analysis and interpretation. HW helped statistical analysis. ME, YC, HT, HW, KH, and M. Abe are executive members of the organizing committee of the Fushimi AF Registry. M. Akao is a principal investigator of the Fushimi AF Registry, and the corresponding author of this paper.

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Figure Legends

Figure 1.

The distribution of age in the entire cohort (A). The distribution of OAC and APD prescription according to age (B). The distribution of patients according to $CHADS_2$ score in the extreme elderly group (aged ≥85 years) and others (aged ≤74 years, aged 75-84 years) (C). The distribution of OAC and APD prescription according to $CHADS_2$ score in the extreme elderly group and others (D). OAC, oral anticoagulant; APD, antiplatelet drug.

Figure 2.

Kaplan-Meier curves for the incidences of stroke/SE and all-cause death, stroke/SE, all-cause death and major bleeding. Data are presented as HR (95% CI). SE, systemic embolism; HR, hazard ratio; CI, confidence interval.

Figure 3.

The comparison of stroke/SE and all-cause death, stroke/SE, all-cause death and major bleeding in the extreme elderly group according to OAC use. Data are presented as HR (95% CI). SE, systemic embolism; HR, hazard ratio; CI, confidence interval; OAC, oral anticoagulant.

Table 1. Baseline characteristics, co-morbidities, oral anticoagulant (OAC) prescription, and warfarin control by age category

	Entire cohort	-74	75-84	85-	p value
Number	3,304	1,606 (48.6%)	1,219 (36.9%)	479 (14.5%)	
Baseline characteristics					
Age (years)	73.7 ± 10.9	65.0 ± 8.4	79.1 ± 2.8	88.8 ± 3.6	<0.01
Female	1330 (40.3%)	490 (30.5%)	525 (43.1%)	315 (65.8%)	<0.01
Body weight (kg)	59.1 ± 13.3	63.8 ± 13.2	56.9 ± 11.5	49.0 ± 10.9	<0.01
Body mass index (kg/m^2)	23.0 ± 4.0	23.7 ± 4.1	22.8 ± 3.6	21.1 ± 3.7	<0.01
Systolic blood pressure (mmHg)	124.7 ± 19.0	125.2 ± 18.6	124.0 ± 18.9	125.0 ± 20.5	0.23
Diastolic blood pressure (mmHg)	70.6 ± 12.9	73.0 ± 12.5	68.4 ± 12.3	67.7 ± 14.1	<0.01
Heart rate (beats/min)	77.7 ± 15.8	77.8 ± 15.7	77.2 ± 15.5	78.6 ± 16.5	0.25
Estimated glomerular filtration rate (mL/min/1.73 m^2)	61.0 ± 23.1	66.8 ± 24.3	57.4 ± 19.7	51.7 ± 22.3	<0.01
Calculated creatinine clearance (mL/min)	58.5 ± 35.3	72.3 ± 40.4	50.5 ± 24.3	34.9 ± 18.6	<0.01
Hemoglobin (g/dL)	12.9 ± 2.0	13.6 ± 1.9	12.7 ± 1.9	11.5 ± 1.8	<0.01
Dialysis	80 (2.4%)	47 (2.9%)	27 (2.2%)	6 (1.3%)	0.07
Tobacco history	1063 (46.8%)	621 (55.0%)	358 (43.0%)	84 (27.3%)	<0.01
Previous catheter ablation	201 (6.1%)	144 (9.0%)	50 (4.1%)	7 (1.5%)	<0.01
Left ventricular ejection fraction (%)	63.1 ± 11.6	63.2 ± 11.4	63.6 ± 11.5	61.7 ± 12.3	0.02
Left atrial diameter (mm)	43.9 ± 8.5	43.3 ± 8.1	44.5 ± 8.6	44.3 ± 9.3	<0.01
Co-morbidities					
Mean $CHADS_2$ score	2.03 ± 1.33	1.35 ± 1.11	2.61 ± 1.19	2.83 ± 1.20	<0.01
Mean CHA_2DS_2-VASc score	3.36 ± 1.70	2.37 ± 1.44	4.18 ± 1.35	4.62 ± 1.33	<0.01
Mean HAS-BLED score*	1.68 ± 0.94	1.51 ± 0.95	1.88 ± 0.90	1.77 ± 0.85	<0.01
Heart failure	882 (26.7%)	311 (19.4%)	366 (30.0%)	205 (42.8%)	<0.01
Hypertension	2028 (61.4%)	958 (59.7%)	781 (64.1%)	289 (60.3%)	0.05
Diabetes mellitus	767 (23.2%)	385 (24.0%)	291 (23.9%)	91 (19.0%)	0.06
Dyslipidemia	1429 (43.3%)	746 (46.5%)	531 (43.6%)	152 (31.7%)	<0.01
Coronary heart disease	488 (14.8%)	176 (11.0%)	230 (18.9%)	82 (17.1%)	<0.01
Chronic kidney disease	1143 (34.6%)	387 (24.1%)	480 (39.4%)	276 (57.6%)	<0.01
Peripheral arterial disease	138 (4.2%)	52 (3.2%)	67 (5.5%)	19 (4.0%)	0.01
History of stroke	612 (18.5%)	232 (14.5%)	242 (19.9%)	138 (28.8%)	<0.01
History of major bleeding	83 (2.5%)	24 (1.5%)	37 (3.0%)	22 (4.6%)	<0.01
Medications					
Aspirin	847 (25.7%)	369 (23.0%)	342 (28.2%)	136 (28.5%)	<0.01

Clopidogrel	140 (4.3%)	55 (3.4%)	68 (5.6%)	17 (3.6%)	0.01
Digitalis	443 (13.5%)	192 (12.0%)	183 (15.1%)	68 (14.3%)	0.05
Verapamil	358 (10.9%)	169 (10.5%)	132 (10.9%)	57 (12.0%)	0.69
Beta blocker	942 (28.6%)	487 (30.4%)	359 (29.6%)	96 (20.1%)	<0.01
Angiotensin converting enzyme inhibitor	298 (9.1%)	121 (7.5%)	114 (9.4%)	63 (13.2%)	<0.01
Angiotensin II receptor blocker	1186 (36.0%)	586 (36.5%)	455 (37.6%)	145 (30.4%)	0.02
Calcium antagonist	1007 (30.6%)	479 (29.9%)	378 (31.2%)	150 (31.5%)	0.67
Statin	763 (23.2%)	374 (23.3%)	306 (25.3%)	83 (17.4%)	<0.01
Loop diuretic	737 (22.4%)	255 (15.9%)	310 (25.6%)	172 (36.1%)	<0.01
Anti-arrhythmic drug	677 (20.6%)	389 (24.3%)	230 (19.0%)	58 (12.2%)	<0.01
OAC prescription	1,751 (53.0%)	822 (51.2%)	731 (60.0%)	198 (41.3%)	<0.01
Details of OAC					
Warfarin	1,623 (49.1%)	748 (46.6%)	690 (56.6%)	185 (38.6%)	<0.01
Dabigatran	104 (3.2%)	61 (3.8%)	31 (2.5%)	12 (2.5%)	0.11
Rivaroxaban	21(0.6%)	12 (0.8%)	8 (0.7%)	1 (0.2%)	0.43
Apixaban	3 (0.1%)	1 (0.1%)	2 (0.2%)	0 (0.0%)	0.52
Warfarin control					
PT-INR value	1.83 ± 0.46	1.82 ± 0.47	1.83 ± 0.45	1.83 ± 0.48	0.97
Missing value	374 (23.0%)	151 (20.2%)	166 (24.1%)	57 (30.8%)	
Therapeutic range of PT-INR					
-1.6	382 (30.6%)	181 (30.3%)	161 (30.7%)	40 (31.3%)	0.38
1.6-2.6	803 (64.3%)	385 (64.5%)	338 (64.5%)	80 (62.5%)	
2.6-3.0	42 (3.4%)	19 (3.2%)	20 (3.8%)	3 (2.3%)	
3.0-	22 (1.8%)	12 (2.0%)	5 (1.0%)	5 (3.9%)	

Data are presented as mean ± SD or number (%).

ANOVA for continuous variables and the Chi-square test for categorical variables were performed.

OAC: oral anticoagulants, PT-INR: prothrombin time international normalized ratio.

* HAS-BLED scores were unavailable in 1,277 patients due to incomplete data entry (systolic blood pressure data were missing in 26 patients, renal function data in 229, liver function data in 226, and alcoholic consumption data in 1,151).

Table 2. Incidence rates (/100 person-years) of major clinical events

Outcomes	**Extreme elderly group (85-)**	**Others (-84)**	**Extreme elderly (85-) vs. Others (-84)**	p value
	incidence rates (total events)	**incidence rates (total events)**	**HR (95% CI)**	
Number	479 (14.5%)	2825 (85.5%)		
Stroke/SE/All-cause death	21.2 (166)	6.4 (372)	3.20 (2.66-3.84)	<0.01
Stroke/SE	5.1 (40)	2.0 (114)	2.57 (1.77-3.65)	<0.01
Ischemic stroke	4.5 (35)	1.4 (81)	3.16 (2.10-4.66)	<0.01
Hemorrhagic stroke	0.6 (4)	0.4 (24)	1.44 (0.42-3.73)	0.52
All-cause death	17.6(142)	4.9 (288)	3.48 (2.84-4.25)	<0.01
Major bleeding	2.0(15)	1.4 (80)	1.40 (0.78-2.36)	0.25

The log-rank test for incidence rates were performed.

SE: systemic embolism, HR: hazard ratio, CI: confidence interval.

Table 3. Baseline characteristics and co-morbidities and incidence rates (/100 person-years) of events in the extreme elderly

	85-	With OAC	Without OAC	p value
Number	479 (14.5%)	198 (41.3%)	281 (58.7%)	
Baseline characteristics				
Age (years)	88.8 ± 3.6	88.1 ± 3.0	89.4 ± 3.9	<0.01
Female	315 (65.8%)	122 (61.6%)	193 (68.7%)	0.12
Body weight (kg)	49.0 ± 10.9	50.5 ± 11.3	47.9 ± 10.4	0.02
Body mass index (kg/m^2)	21.1 ± 3.7	21.4 ± 3.7	20.9 ± 3.7	0.16
Calculated creatinine clearance (mL/min)	34.9 ± 18.6	36.0 ± 17.3	34.2 ± 19.5	0.31
Hemoglobin (g/dL)	11.5 ± 1.8	11.6 ± 1.7	11.3 ± 1.9	0.09
Dialysis	6 (1.3%)	3 (1.5%)	3 (1.1%)	0.67
Tobacco history	84 (27.3%)	36 (29.8%)	48 (25.7%)	0.43
Previous catheter ablation	7 (1.5%)	4 (2.0%)	3 (1.1%)	0.40
Left ventricular ejection fraction (%)	61.7 ± 12.3	61.5 ± 12.5	61.8 ± 12.1	0.87
Left atrial diameter (mm)	44.3 ± 9.3	46.1 ± 9.2	43.0 ± 9.1	<0.01
Co-morbidities				
Mean $CHADS_2$ score	2.83 ± 1.20	2.95 ± 1.21	2.74 ± 1.18	0.06
Mean CHA_2DS_2-VASc score	4.62 ± 1.33	4.66 ± 1.34	4.59 ± 1.31	0.55
Mean HAS-BLED score	1.77 ± 0.85	1.73 ± 0.85	1.80 ± 0.86	0.55
Heart failure	205 (42.8%)	87 (43.9%)	118 (42.0%)	0.71
Hypertension	289 (60.3%)	112 (56.6%)	177 (63.0%)	0.18
Diabetes mellitus	91 (19.0%)	34 (17.2%)	57 (20.3%)	0.41
Dyslipidemia	152 (31.7%)	59 (29.8%)	93 (33.1%)	0.49
Coronary heart disease	82 (17.1%)	26 (13.1%)	56 (19.9%)	0.06
Chronic kidney disease	276 (57.6%)	119 (60.1%)	157 (55.9%)	0.40
Peripheral arterial disease	19 (4.0%)	6 (3.0%)	13 (4.6%)	0.48
History of stroke	138 (28.8%)	72 (36.4%)	66 (23.5%)	<0.01
History of major bleeding	22 (4.6%)	7 (3.5%)	15 (5.3%)	0.39
Medications				
Aspirin	136 (28.5%)	40 (20.2%)	96 (34.4%)	<0.01
Clopidogrel	17 (3.6%)	2 (1.0%)	15 (5.4%)	<0.01
A combination of aspirin and clopidogrel	11 (2.3%)	2 (1.0%)	9 (3.2%)	0.09
Anti-arrhythmic drug	58 (12.2%)	26 (13.1%)	32 (11.5%)	0.59
Institutions in which patients were treated				
Cardiovascular center	164 (34.2%)	58 (29.3%)	106 (37.7%)	0.05

Incidence rates (/100 person-years)				
Stroke/SE/All-cause death	21.2	20.4	21.8	0.71
Stroke/SE	5.1	8.0	2.9	<0.01
Ischemic stroke	4.5	7.3	2.2	<0.01
Hemorrhagic stroke	0.6	0.7	0.6	0.76
All-cause death	17.6	14.6	19.9	0.11
Major bleeding	2.0	1.8	2.1	0.81

Data are presented as mean ± SD or number (%). Student's t-test or Wilcoxon rank sum test on the basis of the distribution for continuous variables, the Chi-square test when appropriate; otherwise, Fisher's exact test for categorical variables, and the log-rank test for incidence rates were performed.

OAC: oral anticoagulants, SE: systemic embolism.

Supplementary Table. Baseline characteristics, co-morbidities and medications in follow-up cases and missing cases.

	Entire	Missing cases	Follow-up cases	p value
Number	3,666	362 (9.9%)	3304 (90.1%)	
Baseline characteristics				
Age (years)	73.9 ± 11.0	75.4 ± 11.8	73.7 ± 10.9	<0.01
Female	1501 (40.9%)	171 (47.2%)	1330 (40.3%)	0.01
Body weight (kg)	58.8 ± 13.3	56.2 ± 12.6	59.1 ± 13.3	<0.01
Body mass index (kg/m^2)	22.9 ± 4.0	22.4 ± 3.8	23.0 ± 4.0	0.02
Systolic blood pressure (mmHg)	125.1 ± 19.2	128.8 ± 20.5	124.7 ± 19.0	<0.01
Diastolic blood pressure (mmHg)	70.7 ± 12.9	72.3 ± 13.2	70.6 ± 12.9	0.02
Heart rate (beats/min)	78.0 ± 16.0	80.6 ± 17.8	77.7 ± 15.8	<0.01
Estimated glomerular filtration rate (mL/min/1.73 m^2)	61.0 ± 23.1	61.6 ± 23.5	61.0 ± 23.1	0.66
Hemoglobin (g/dL)	12.9 ± 2.0	12.8 ± 2.1	12.9 ± 2.0	0.19
Dialysis	94 (2.6%)	14 (3.9%)	80 (2.4%)	0.11
Left ventricular ejection fraction (%)	63.0 ± 11.6	61.6 ± 11.5	63.1 ± 11.6	0.05
Left atrial diameter (mm)	43.7 ± 8.4	41.8 ± 8.0	43.9 ± 8.5	<0.01
Co-morbidities				
Mean $CHADS_2$ score	2.04 ± 1.34	2.19 ± 1.42	2.03 ± 1.33	0.03
Mean CHA_2DS_2-VASc score	3.38 ± 1.72	3.59 ± 1.86	3.36 ± 1.70	0.02
Heart failure	998 (27.2%)	116 (32.0%)	882 (26.7%)	0.03
Hypertension	2258 (61.6%)	230 (63.3%)	2028 (61.4%)	0.53
Diabetes mellitus	837 (22.8%)	70 (19.3%)	767 (23.2%)	0.10
Dyslipidemia	1557 (42.5%)	128 (35.4%)	1429 (43.3%)	<0.01
Coronary heart disease	540 (14.7%)	52 (14.4%)	488 (14.8%)	0.88
Chronic kidney disease	1261 (34.4%)	118 (32.6%)	1143 (34.6%)	0.48
History of stroke	683 (18.6%)	71 (19.6%)	612 (18.5%)	0.52
History of major bleeding	89 (2.4%)	6 (1.7%)	83 (2.5%)	0.37
Medications				
Aspirin	916 (25.1%)	69 (19.1%)	847 (25.7%)	<0.01
Clopidogrel	157 (4.3%)	17 (4.7%)	140 (4.3%)	<0.01
Warfarin	1,731 (47.4%)	108 (29.8%)	1,623 (49.1%)	<0.01

Data are presented as mean ± SD or number (%).

Student's t-test for continuous variables and the Chi-square test for categorical variables were performed.

Figure 1

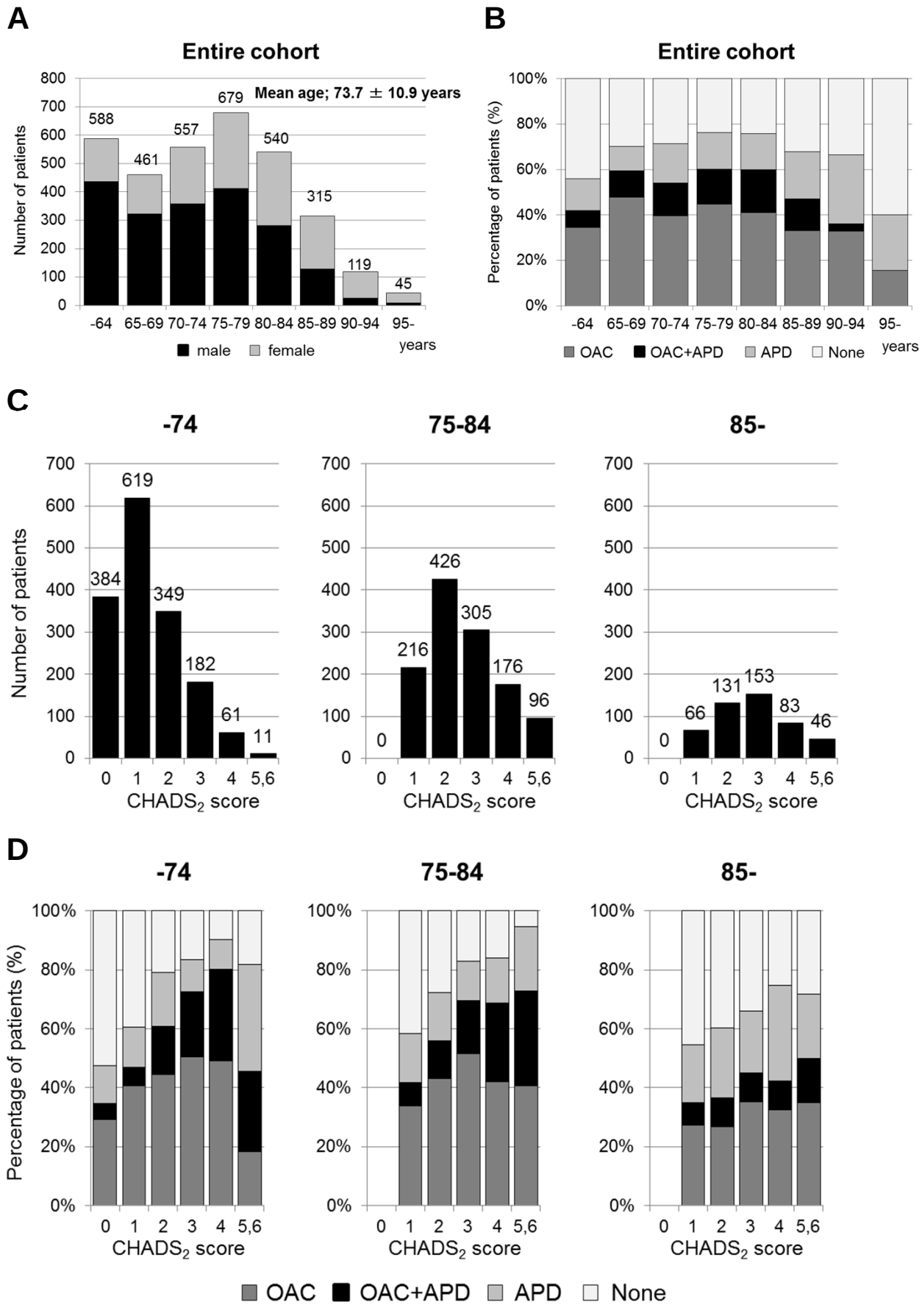

A
Entire cohort
Mean age; 73.7 ± 10.9 years
Number of patients
588
461
557
679
540
315
119
45
-64
65-69
70-74
75-79
80-84
85-89
90-94
95-
years
male
female
B
Entire cohort
Percentage of patients (%)
OAC
OAC+APD
APD
None
C
-74
75-84
85-
Number of patients
384
619
349
182
61
11
0
216
426
305
176
96
0
66
131
153
83
46
CHADS2 score
D
-74
75-84
85-
Percentage of patients (%)
CHADS2 score
OAC
OAC+APD
APD
None

Figure 2

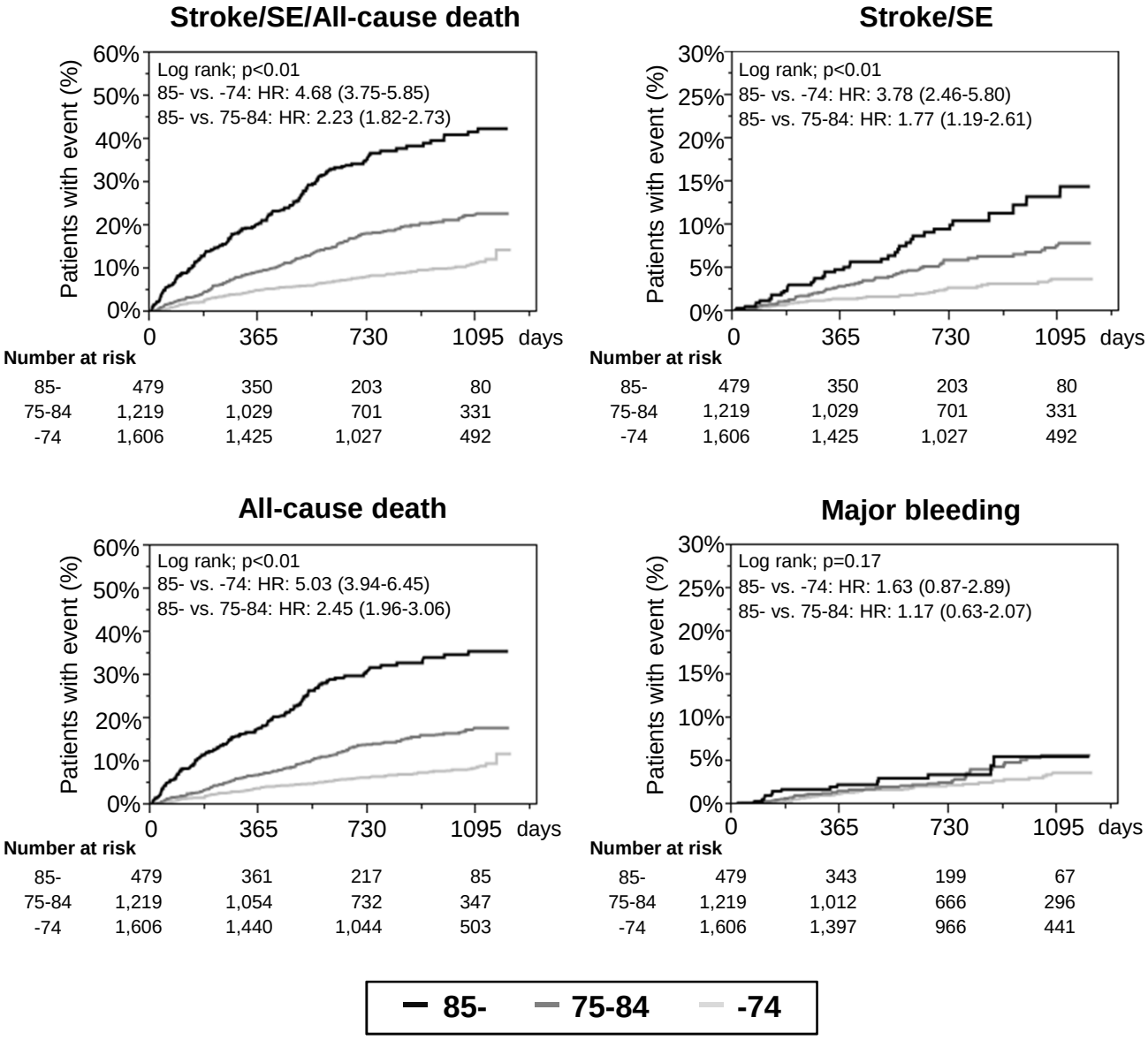
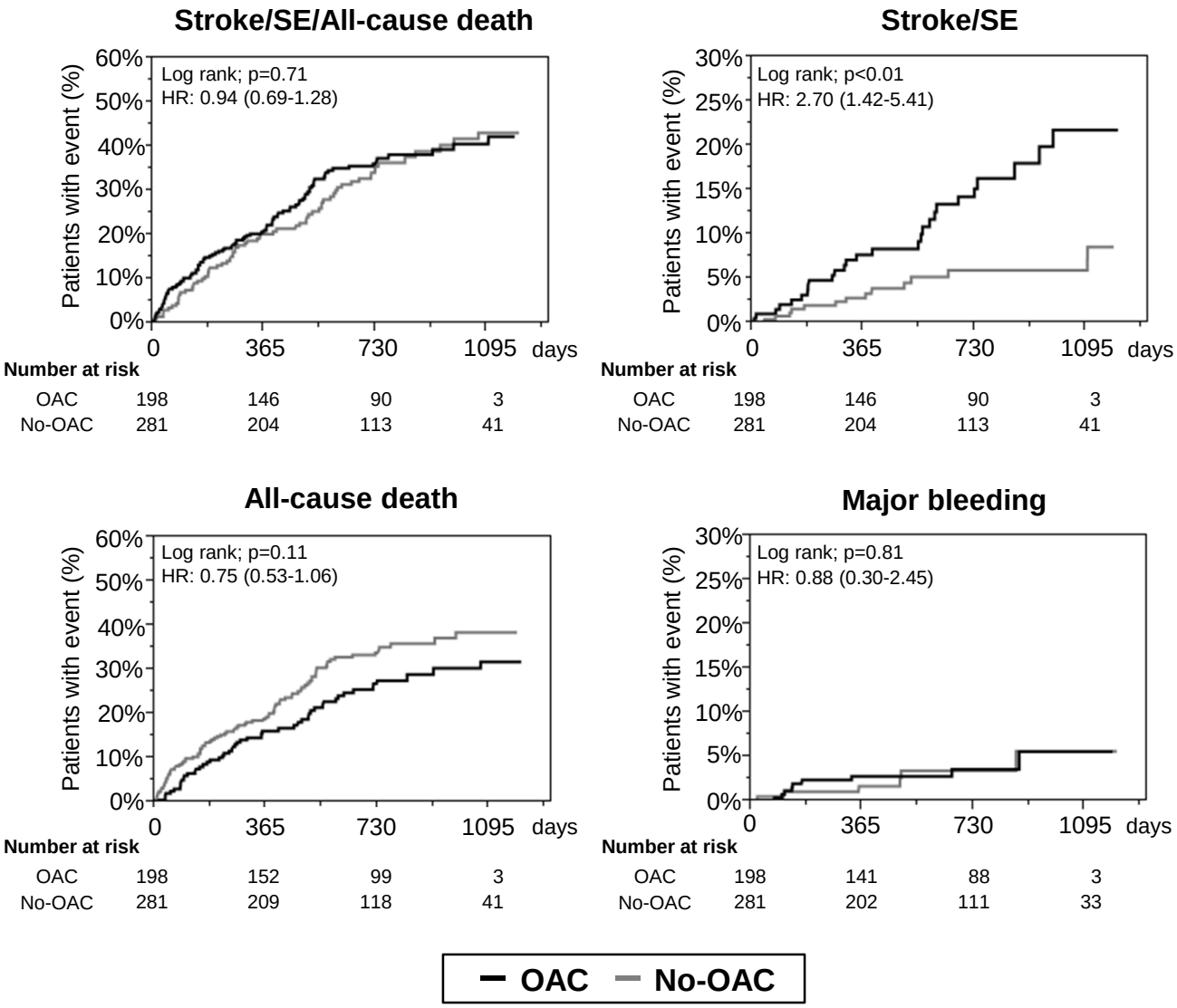

Stroke/SE/All-cause death
Patients with event (%)
60%
50%
40%
30%
20%
10%
0%
Log rank; p<0.01
85- vs. -74: HR: 4.68 (3.75-5.85)
85- vs. 75-84: HR: 2.23 (1.82-2.73)
0
365
730
1095
days
Number at risk
85- 479 350 203 80
75-84 1,219 1,029 701 331
-74 1,606 1,425 1,027 492
Stroke/SE
Patients with event (%)
30%
25%
20%
15%
10%
5%
0%
Log rank; p<0.01
85- vs. -74: HR: 3.78 (2.46-5.80)
85- vs. 75-84: HR: 1.77 (1.19-2.61)
0
365
730
1095
days
Number at risk
85- 479 350 203 80
75-84 1,219 1,029 701 331
-74 1,606 1,425 1,027 492
All-cause death
Patients with event (%)
60%
50%
40%
30%
20%
10%
0%
Log rank; p<0.01
85- vs. -74: HR: 5.03 (3.94-6.45)
85- vs. 75-84: HR: 2.45 (1.96-3.06)
0
365
730
1095
days
Number at risk
85- 479 361 217 85
75-84 1,219 1,054 732 347
-74 1,606 1,440 1,044 503
Major bleeding
Patients with event (%)
30%
25%
20%
15%
10%
5%
0%
Log rank; p=0.17
85- vs. -74: HR: 1.63 (0.87-2.89)
85- vs. 75-84: HR: 1.17 (0.63-2.07)
0
365
730
1095
days
Number at risk
85- 479 343 199 67
75-84 1,219 1,012 666 296
-74 1,606 1,397 966 441
85-
75-84
-74

Figure 3


Stroke/SE/All-cause death
Log rank; p=0.71
HR: 0.94 (0.69-1.28)
Patients with event (%)
60%
50%
40%
30%
20%
10%
0%
0
365
730
1095
days
Number at risk
OAC 198 146 90 3
No-OAC 281 204 113 41
Stroke/SE
Log rank; p<0.01
HR: 2.70 (1.42-5.41)
Patients with event (%)
30%
25%
20%
15%
10%
5%
0%
0
365
730
1095
days
Number at risk
OAC 198 146 90 3
No-OAC 281 204 113 41
All-cause death
Log rank; p=0.11
HR: 0.75 (0.53-1.06)
Patients with event (%)
60%
50%
40%
30%
20%
10%
0%
0
365
730
1095
days
Number at risk
OAC 198 152 99 3
No-OAC 281 209 118 41
Major bleeding
Log rank; p=0.81
HR: 0.88 (0.30-2.45)
Patients with event (%)
30%
25%
20%
15%
10%
5%
0%
0
365
730
1095
days
Number at risk
OAC 198 141 88 3
No-OAC 281 202 111 33
OAC
No-OAC