UNIVERSITY OF BIRMINGHAM

University of Birmingham
Research at Birmingham

Clinical characteristics and outcomes in extreme elderly (age 85 years) Japanese patients with atrial fibrillation

Yamashita, Yugo; Hamatani, Yasuhiro; Esato, Masahiro; Chun, Yeong-hwa; Tsuji, Hikari; Wada, Hiromichi; Hasegawa, Koji; Abe, Mitsuru; Lip, Gregory Y.h.; Akao, Masaharu

Document Version
Peer reviewed version

Link to publication on Research at Birmingham portal

Accepted Manuscript

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

Yugo Yamashita, MD, Yasuhiro Hamatani, MD, Masahiro Esato, MD, PhD, Yeong-Hwa Chun, MD, PhD, Hikari Tsuji, MD, PhD, Hiromichi Wada, MD, PhD, Koji Hasegawa, MD, PhD, Mitsuru Abe, MD, PhD, Gregory Y.H. Lip, MD, Masaharu Akao, MD, PhD
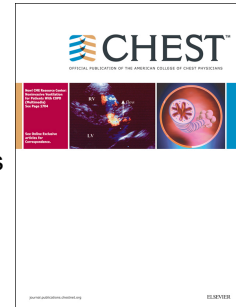
Please cite this article as: Yamashita Y, Hamatani Y, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M, Clinical characteristics and outcomes in extreme elderly (age ≥85) Japanese patients with atrial fibrillation: The Fushimi AF Registry, *CHEST* (2015), doi: 10.1378/chest.15-1095.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Word counts: Text 2757   Abstract 236

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

Short title: The extreme elderly with AF

Yugo Yamashita, MD[1]; Yasuhiro Hamatani, MD[1]; Masahiro Esato, MD, PhD[2]; Yeong-Hwa Chun, MD, PhD[2]; Hikari Tsuji, MD, PhD[3]; Hiromichi Wada, MD, PhD[4]; Koji Hasegawa, MD, PhD[4]; Mitsuru Abe, MD, PhD[1]; Gregory Y.H. Lip, MD[5]*; Masaharu Akao, MD, PhD[1]*

[*joint senior authors]

[1]Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

[2]Department of Arrhythmia, Ijinkai Takeda General Hospital, Kyoto, Japan

[3]Tsuji Clinic, Kyoto, Japan

[4]Division of Translational Research, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

[5]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; and Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Address correspondence to: Masaharu Akao, MD, PhD

Department of Cardiology, National Hospital Organization Kyoto Medical Center,

1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan

E-mail: akao@kuhp.kyoto-u.ac.jp

Disclosures

Sources of Funding

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.

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

Clinical Trial Registration: URL: http://www.umin.ac.jp/ctr/index.htm

Unique identifier: UMIN000005834.

Key Words: atrial fibrillation; elderly; stroke; bleeding

4

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

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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 $CHADS_2$ 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 $CHADS_2$ 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

9

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%

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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,

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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).

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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

14

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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.

Acknowledgement

registry and the clinical research coordinators (Shinagawa T, Mitamura M, Fukahori M, Kimura M,

Fukuyama M, Kamata C).

References

1.   Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA*. 2001;285(18):2370-2375.

2.   Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369-2429.

3.   Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J*. 2012;76(10):2289-2304.

4.   Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals Intern Med*. 2007;146(12):857-867.

5.   Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: An update of the 2010 ESC guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14(10):1385-1413.

6.   Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: The challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke*. 2006;37(4):1075-1080.

7.   Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol*. 2005;46(9):1729-1736.

8.   Nieuwlaat R, Capucci A, Lip GY, et al. Antithrombotic treatment in real-life atrial fibrillation patients: A report from the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2006;27(24):3018-3026.

9.   Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: A systematic review. *Am J Med*. 2010;123(7):638-645.

10.   Akao M, Chun YH, Wada H, et al. Current status of clinical background of patients with atrial fibrillation in a community-based survey: The Fushimi AF Registry. *J Cardiol*. 2013;61(4):260-266.

11.   Akao M, Chun YH, Esato M, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circ J*. 2014;78(9):2166-2172.

12.   Evidence-based practice guideline for the treatment of CKD. *Clin Exp Nephrol*. 2009;13(6):537-566.

13.   JCS Joint Working Group. Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). *Circ J*. 2014;78(8):1997-2021.

14.   Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

15. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137(2):263-272.

16. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.

17. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3(4):692-694.

18. Furusho H, Takamura M, Takata S, et al. Current status of anticoagulation therapy for elderly atrial fibrillation patients in japan: From hokuriku atrial fibrillation trial. *Circ J.* 2008;72(12):2058-2061.

19. Siu CW, Tse HF. Net clinical benefit of warfarin therapy in elderly chinese patients with atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2014;7(2):300-306.

20. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke prevention in atrial fibrillation II study. *Lancet.* 1994;343(8899):687-691.

21. Copland M, Walker ID, Tait RC. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. *Arch Intern Med.* 2001;161(17):2125-2128.

22. Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with

nonrheumatic atrial fibrillation and risk of bleeding. A multicenter inception cohort study.

Thromb Haemost. 2001;85(3):418-422.

23. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Bleeding risk during oral

anticoagulation in atrial fibrillation patients older than 80 years. *J Am Coll Cardiol*.

2009;54(11):999-1002.

24. Poli D, Antonucci E, Testa S, Tosetto A, Ageno W, Palareti G. Bleeding risk in very old

patients on vitamin K antagonist treatment: Results of a prospective collaborative study on

elderly patients followed by italian centres for anticoagulation. *Circulation*.

2011;124(7):824-829.

25. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and

tolerability of warfarin in the first year of therapy among elderly patients with atrial

fibrillation. *Circulation*. 2007;115(21):2689-2696.

26. Olesen JB, Lip GY, Lindhardsen J, et al. Risks of thromboembolism and bleeding with

thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a

'real world' nationwide cohort study. *Thromb Haemost*. 2011;106(4):739-749.

27. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral

anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial

fibrillation population: A modelling analysis based on a nationwide cohort study. *Thromb

Haemost*. 2012;107(3):584-589.

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

28. Van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: The atrial fibrillation investigators. *Stroke*. 2009;40(4):1410-1416.

29. Lip GY, Lane DA. Stroke prevention with oral anticoagulation therapy in patients with atrial fibrillation--focus on the elderly. *Circ J*. 2013;77(6):1380-1388.

30. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. *Stroke*. 2015;46(1):143-150.

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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.

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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$_2$DS$_2$-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

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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%)	
1.6-2.6	803 (64.3%)	385 (64.5%)	338 (64.5%)	80 (62.5%)	0.38
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).

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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

Outcomes	Extreme elderly group (85-) incidence rates (total events)	Others (-84) incidence rates (total events)	Extreme elderly (85-) vs. Others (-84) HR (95% CI)	p value
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.

26

Yamashita, et al. The extreme elderly with AF (CHEST-15-1095)

ACCEPTED MANUSCRIPT

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$_2$DS$_2$-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.

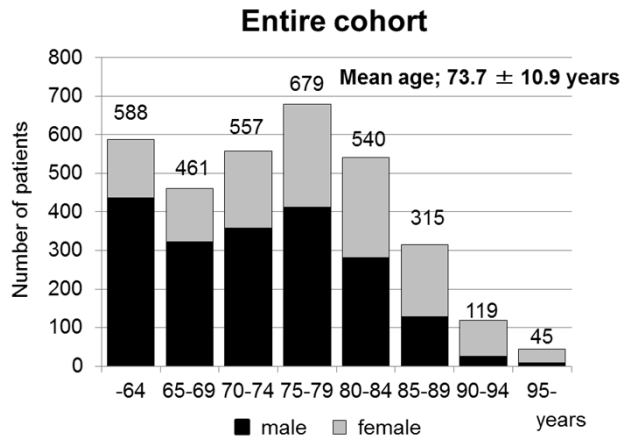|	Entire	Missing cases	Follow-up cases	p value
Number	3,666	362 (9.9%)	3304 (90.1%)	
Baseline characteristics				
Age (years)	73.9 ± 11.0	75.4 ± 11.8	73.7 ± 10.9	<0.01
Female	1501 (40.9%)	171 (47.2%)	1330 (40.3%)	0.01
Body weight (kg)	58.8 ± 13.3	56.2 ± 12.6	59.1 ± 13.3	<0.01
Body mass index (kg/m^2)	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$_2$DS$_2$-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 (%).

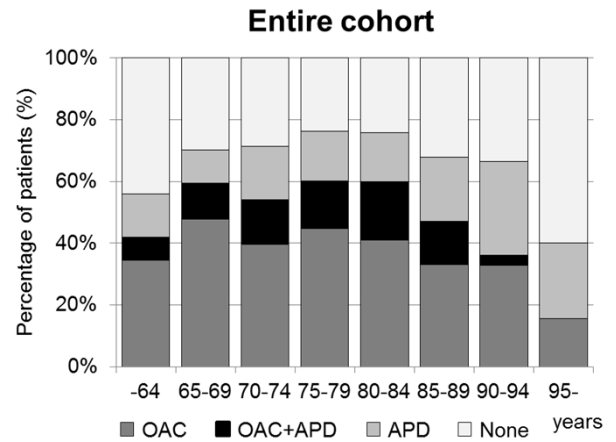Student's t-test for continuous variables and the Chi-square test for categorical variables were performed.

Figure 1

Figure 2

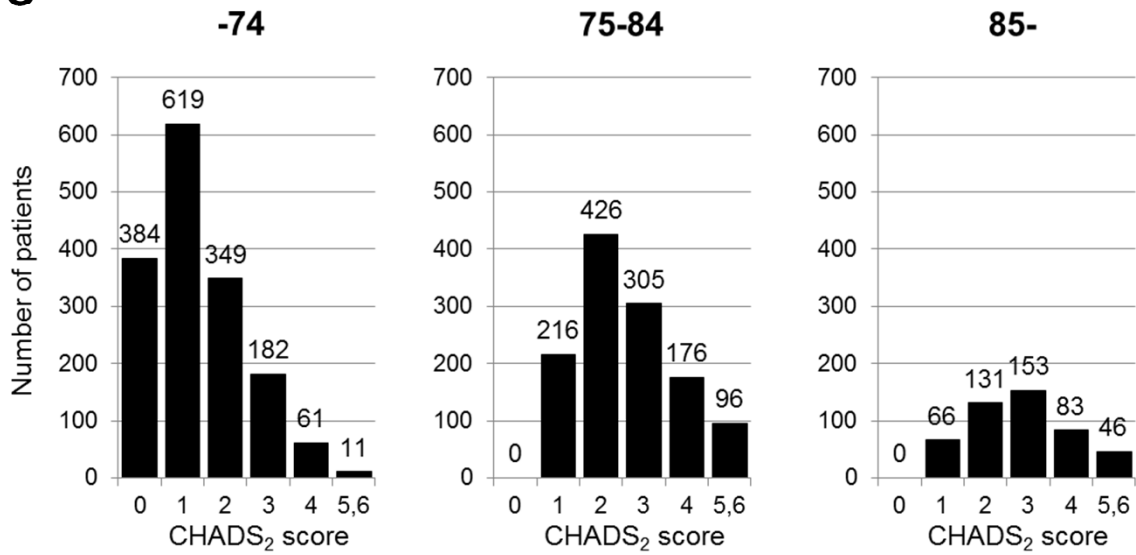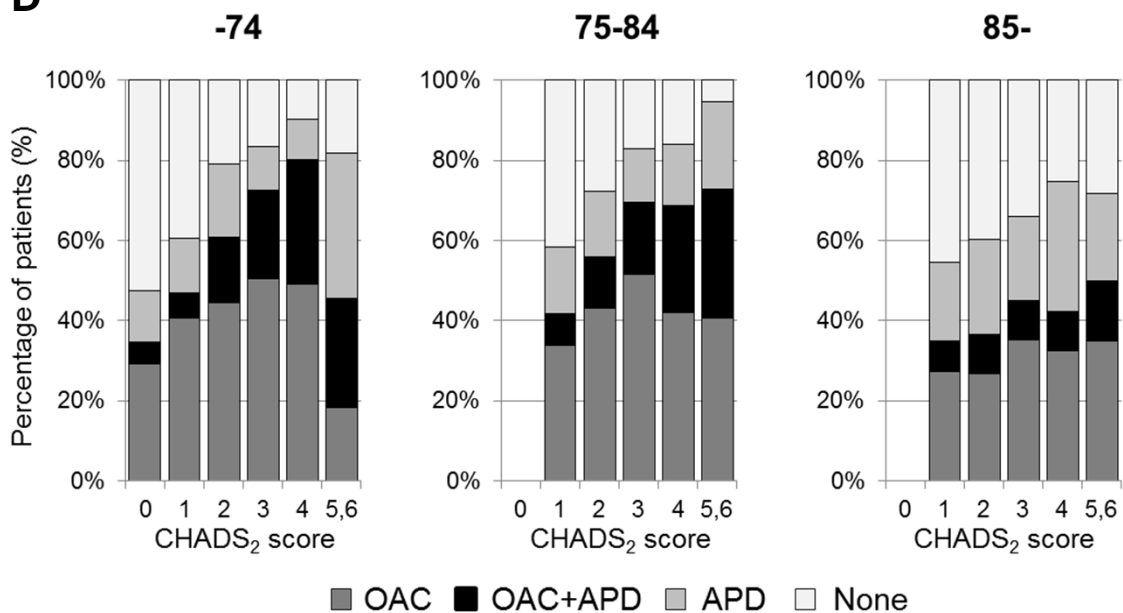## Stroke/SE/All-cause death

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)

Patients with event (%)

60%
50%
40%
30%
20%
10%
0%

0   365   730   1095   days
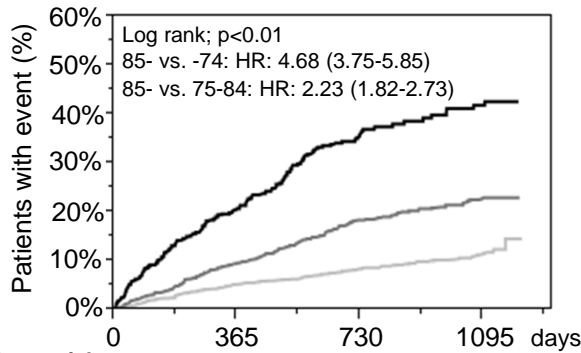
Number at risk

85-	479	350	203	80
75-84	1,219	1,029	701	331
-74	1,606	1,425	1,027	492

Stroke/SE

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)

Patients with event (%)

30%
25%
20%
15%
10%
5%
0%

0   365   730   1095   days
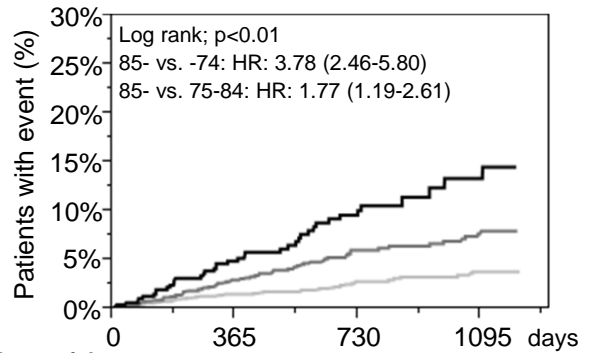
Number at risk

85-	479	350	203	80
75-84	1,219	1,029	701	331
-74	1,606	1,425	1,027	492

All-cause death

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)

Patients with event (%)

60%
50%
40%
30%
20%
10%
0%

0   365   730   1095   days
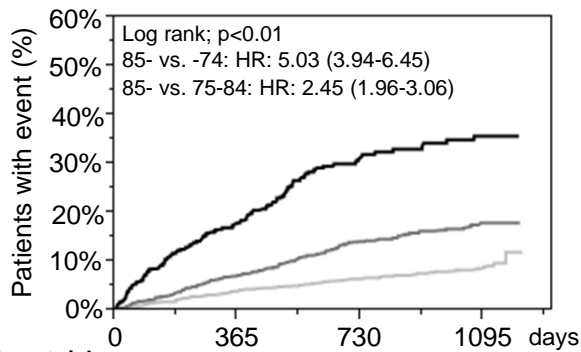
Number at risk

85-	479	361	217	85
75-84	1,219	1,054	732	347
-74	1,606	1,440	1,044	503

Major bleeding

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)

Patients with event (%)

30%
25%
20%
15%
10%
5%
0%

0   365   730   1095   days
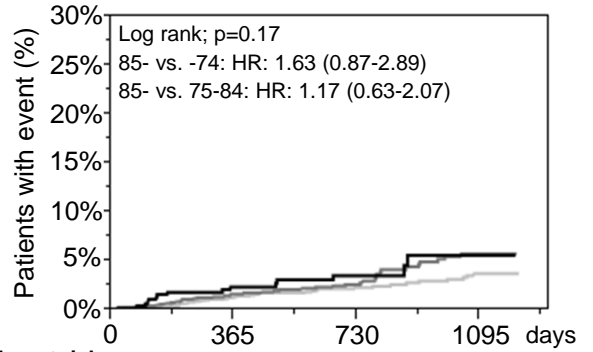
Number at risk

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

Patients with event (%)

Log rank; p=0.71
HR: 0.94 (0.69-1.28)

60%
50%
40%
30%
20%
10%
0%

0   365   730   1095   days
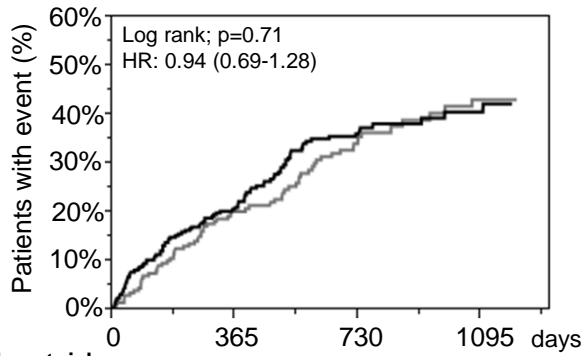
Number at risk

OAC	198	146	90	3
No-OAC	281	204	113	41

Stroke/SE

Patients with event (%)

Log rank; p<0.01
HR: 2.70 (1.42-5.41)

30%
25%
20%
15%
10%
5%
0%

0   365   730   1095   days
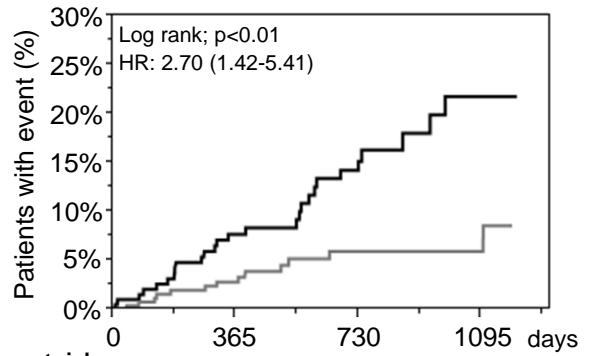
Number at risk

OAC	198	146	90	3
No-OAC	281	204	113	41

All-cause death

Patients with event (%)

Log rank; p=0.11
HR: 0.75 (0.53-1.06)

60%
50%
40%
30%
20%
10%
0%

0   365   730   1095   days
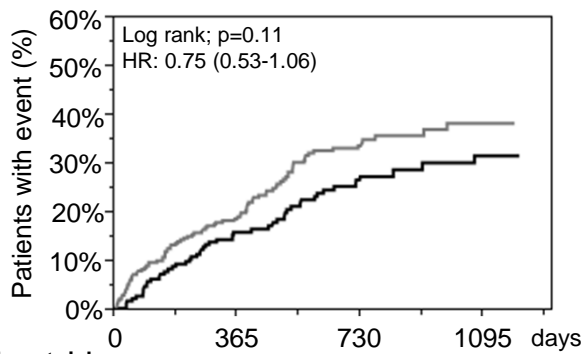
Number at risk

OAC	198	152	99	3
No-OAC	281	209	118	41

Major bleeding

Patients with event (%)

Log rank; p=0.81
HR: 0.88 (0.30-2.45)

30%
25%
20%
15%
10%
5%
0%

0   365   730   1095   days
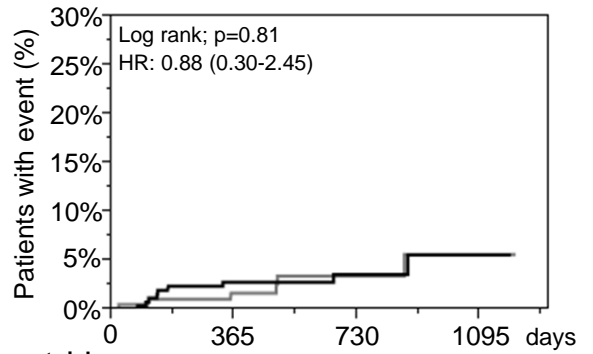
Number at risk

OAC	198	141	88	3
No-OAC	281	202	111	33

— OAC — No-OAC