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Causes of death in Japanese patients with atrial fibrillation:

The Fushimi AF Registry

Short title: Causes of death in AF patients

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Abstract

Aims: To investigate the causes of death and the associated clinical factors in patients with atrial fibrillation (AF) in the contemporary clinical practice.

Methods and Results: The Fushimi AF Registry is a community-based prospective survey of AF patients since March 2011 in Fushimi-ku, Kyoto. We investigated causes of death and the clinical indicators of cardiovascular (CV) and non-CV death in 4,045 patients with available follow-up data by the end of November 2016. The mean age was 73.6 ± 10.9 years and the mean CHA₂DS₂-VASc score was 3.38 ± 1.69 . Oral anticoagulants (OAC) were prescribed in 55% of patients. During a median follow-up of 1,105 days, there were 705 all-cause deaths (5.5%/year); 180 CV (26% of total deaths), 381 non-CV (54%), and 144 undetermined causes (20%). The most common causes of CV and non-CV death were heart failure (14.5%), malignancy (23.1%) and infection/sepsis (17.3%), while mortality due to stroke was only 6.5%. Mortality due to infection/sepsis and undetermined causes increased with aging. On multivariate analysis, the strongest indicator of CV death was pre-existing heart failure (hazard ratio [HR]: 2.42, 95% confidence interval [CI]: 1.66-3.54, $P < 0.001$) and that of non-CV death was anemia (HR: 2.84, 95% CI: 2.22-3.65, $P < 0.001$).

Conclusions: In a Japanese community-based AF cohort, CV death was not mainly

related to stroke but to heart failure. Non-CV death, mainly malignancy and infection, comprised more than a half of all deaths, which increased substantially in accordance with aging. Clinical factors that were associated with CV and non-CV death were distinct.

Keywords: atrial fibrillation; causes of death; community-based registry

Introduction

While the risk of stroke associated with atrial fibrillation (AF) is well-recognized, this common arrhythmia also independently increases the risk of all-cause mortality.^{1, 2} Recent several studies focused on increased risk of death and its specific causes in both randomized control trials (RCTs)³⁻⁶ and real-world cohorts among patient with AF⁷⁻⁹. In general, stroke-related death accounted for only 7 to 10% of all-cause mortality despite the high risk for stroke.¹⁰ Importantly, causes of death and their incidences vary substantially across study designs¹¹, regions¹², and periods at enrollment of patients¹³. Those with AF in routine clinical practice often have several cardiovascular (CV) risk factors and other non-CV co-morbidities, all of which may contribute to an increased mortality, especially amongst the elderly.¹⁴ However, there are limited data on the proportions of specific causes of death across age groups and the indicators of both CV and non-CV deaths, especially in Asian cohorts where the burden of AF is greatly increasing.¹⁵

The objective of this analysis was to describe cause-specific death between age groups and to identify factors associated with all-cause, CV, and non-CV mortality using data from the Fushimi AF Registry; a community-based cohort of Japanese AF patients.

Methods

The detailed study design, patient enrollment, the definition of the measurements, and subjects' baseline clinical characteristics of the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834).^{16, 17} The inclusion criterion for the registry is the documentation of AF on a 12-lead electrocardiogram or Holter monitoring at any time. There were no exclusion criteria. A total of 80 institutions participated in the registry of Fushimi district, Kyoto, Japan. We started to enroll patients from March 2011. Collection of follow-up information was mainly conducted through review of the inpatient and outpatient medical records, and additional follow-up information was collected through contact with patients, relatives and/or referring physicians by mail or telephone. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

Group Assignment and Definition

Baseline characteristics at the entry into the registry were described in this overall population and compared between the patients alive at the end of the follow-up and those who died during the follow-up. We also compared baseline characteristics and clinical outcomes among the 3 groups by age (≤ 74 years, 75-84 years, and ≥ 85 years),

as previously reported.¹⁴

The risk of stroke was assessed by the CHADS₂¹⁸ score and CHA₂DS₂-VASc score¹⁹. The type of AF was classified into 2 groups; paroxysmal AF and sustained AF which was defined as the combination of persistent AF and permanent AF.²⁰ Anemia was defined according to the World Health Organization criteria (hemoglobin level <13.0 g/dL in men and <12.0 g/dL in women). Renal dysfunction was diagnosed as the estimated glomerular filtration rate (eGFR) <60ml/min/m² at baseline. Oral anticoagulant (OAC) included warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Anti-platelet drug (APD) included aspirin, clopidogrel, ticlopidine, and cilostazol. OAC and APD usage were based on the prescription data at enrollment.

Study Endpoints

The primary endpoint in the analysis was all-cause death and its specific cause(s) during the follow-up period. Causes of death were adjudicated after consideration of all the available information, and were classified according to the following prespecified groups: CV, non-CV as well as undetermined death when the quality of the information could not allow the investigators to appropriately identify cause of death. CV deaths were further subclassified as cardiac (heart failure, acute coronary syndrome, or dysrhythmia), vascular (ischemic stroke, systemic embolism,

hemorrhagic stroke, other intracranial hemorrhage such as epidural/subdural hematoma, or extracranial bleeding), and others (which included other vascular causes and those vascular deaths with insufficient information to definitively assign a subclassification). Non-CV deaths included those resulting from malignancy, respiratory failure, infection/sepsis, renal failure, and others.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation, or median and interquartile range according to the distributions and compared using Student's t-test or Wilcoxon rank-sum test on the basis of the distribution. Categorical variables are presented as numbers and percentages and compared using the chi-square test when appropriate; otherwise, we used Fisher's exact test. The cumulative incidences of clinical outcomes were estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test.

We carried out multivariate analysis for the indicators of all-cause death, CV death, and non-CV death using the Cox proportional hazards model. The covariates chosen to be included were age (per 10 years), female (versus male), body mass index as the 3 categorical variable ($<18.5 \text{ kg/m}^2$, $18.5 \text{ to } <25.0 \text{ kg/m}^2$, $\leq 25.0 \text{ kg/m}^2$), sustained AF (versus paroxysmal AF), pre-existing heart failure, hypertension, diabetes mellitus,

previous stroke or transient ischemic attack (TIA), peripheral artery disease (PAD), prior myocardial infarction, anemia, chronic obstructive pulmonary disease (COPD), renal dysfunction, dyslipidemia, previous major bleeding, prescription of renin-angiotensin system inhibitor, each prescription of β -blocker, APD, OAC, diuretics, digitalis, and statin at baseline. We used JMP version 12 (SAS Institute, Cary, NC) to perform all of these analyses. Two-sided P values less than 0.05 were considered statistically significant.

Results

Of 4,441 patients who were enrolled by the end of November 2015, follow-up data (collected annually) were available for 4,066 patients (91.6%) as of November 2016. Of these 4,066 patients, 21 patients were excluded because their baseline prescription data were unavailable at baseline. Finally, a total of 4,045 patients at baseline were included in the current analysis.

During the median follow up of 1,105 (interquartile range: 669-1,825) days, a total of 705 patients (17.4%) died. These patients were older than 3,340 patients who were alive at the end of follow-up, and had higher prevalence of various co-morbidities such as previous stroke/TIA and pre-existing heart failure with higher CHA₂DS₂-VASc score (Table 1).

Table 2 shows the causes of death in the entire study population. CV causes accounted for 25.5% of all-cause deaths; heart failure; 16.3%, ischemic stroke; 4.8%, and hemorrhagic stroke; 1.7%. Non-CV causes consisted of a substantial proportion (54.6%) including malignancy; 23.1%, and infection/sepsis; 17.3%. Causes of death were not determined in 20.4% of patients who died during the follow-up. As shown in Figure 1, the event rate of all-cause, non-CV, and cardiac death, and death due to stroke were 5.5, 3.1, 0.9, and 0.4 per 100 person-years during the follow-up, respectively.

Table 3 shows the comparison of baseline characteristics and co-morbidities among age subgroups (≤ 74 years, 75-84 years, and ≥ 85 years). With higher ages, greater prevalence of co-morbidities became evident, especially previous stroke/TIA, pre-existing heart failure, renal dysfunction and anemia.

The proportions of specific causes of death between the three age subgroups at baseline are shown in Figure 2. CV death accounted for about 25% of all-cause death, with similar proportions of each cause of cardiac and intracranial deaths between the three groups. The proportion of each cause of non-CV death varied substantially by age subgroup, with an increasing proportion of infection-related death and deaths of undetermined cause with age strata.

Mortalities of specific causes of death increased in accordance with age strata (Figure 3A). Unadjusted hazard ratios (HRs) for cardiac death were 2.16 (95% confidence interval [CI]: 1.38-3.44) at age 75-84 years, and 5.83 (95% CI: 3.62-9.44) at age ≥ 85 years, compared with those aged ≤ 74 years (Figure 3B). With regard to non-CV death, those due to infection were higher in accordance with aging. Deaths of undetermined cause were also higher as age increased.

On multivariate Cox regression analysis, baseline variables associated with a highest risk of all-cause death were anemia (HR: 2.52, 95% CI: 2.10-3.02) (Figure 4),

followed by PAD, previous stroke/TIA, older age (per 10 years increase), pre-existing heart failure, COPD, prescription of digitalis, and renal dysfunction. Female gender, OAC prescription and that of statin was associated with a significantly lower risk of all-cause death. As shown in Figure 5, the strongest indicators for higher risk of CV death was pre-existing heart failure (HR: 2.42, 95% CI: 1.66-3.54) and that of non-CV death was anemia (HR: 2.84, 95% CI: 2.22-3.65). Some differences between CV and non-CV deaths existed in the predictive values of clinical factors. The prescription of OAC at baseline was significantly associated with a lower incidence of non-CV death, but not with that of CV death.

There was a higher prevalence of the CV co-morbidities such as pre-existing heart failure, previous stroke/TIA in patients with OAC at baseline (Table S1). The cumulative incidence of non-CV death was higher in patients with OAC than in those without, although there was no significant difference in CV death (Figure S1), due to the differences in mortality due to malignancy and infection (Figure S2).

Discussion

The principal findings of this study in a Japanese community-based AF cohort were as follows: (1) the most common cause of CV death was not stroke-related, but that of heart failure, which was one of major causes of death next to malignancy and infection; (2) the mortality due to infection and undetermined cause increased substantially in accordance with age; and (3) CV death was most strongly associated with pre-existing heart failure and non-CV death was with anemia. There were some differences about clinical indicators for CV and non-CV deaths.

Causes of death in AF patients

Cardiac death, mainly heart failure, was the most common CV death in the present study, in agreement with the findings in both RCTs³⁻⁶ and real-world cohorts⁷⁻⁹. Meanwhile, the mortality due to stroke accounted for 6.5% of all-cause deaths (0.4 per 100 person-years). This proportion was also comparable with those in the prior published reports.³⁻⁹ On the contrary, non-CV death varied across their study designs and populations. Indeed, the proportion of non-CV cause among all-cause death was 29.7% in the meta-analysis of 4 RCTs of non-vitamin K oral anticoagulants (NOAC).³ By comparison, there was higher proportion of non-CV death in real-world cohorts such as 35.8% in the international GARFIELD-AF registry⁷, 42.7% in a French regional

registry⁸, and 66.0% in a French nationwide database⁹. In the present study, non-CV deaths, mainly due to malignancy and infection/sepsis, accounted for more than half (54%) of all-cause deaths. These differences perhaps reflect the higher prevalence of co-morbidities in patients in routine clinical practice, compared to the selected patients enrolled in RCTs.

In the present study, deaths of undetermined cause occurred in 20.4%, which was comparable with that in the GARFIELD-AF registry (23.7%)⁷. Causes of death cannot be determined definitely in a certain proportion of patients in the routine clinical practice. As for the proportions among specific causes of death between three age groups, the total proportion of CV causes of death were almost identical between each of three age groups. Meanwhile, some differences across age groups exists for non-CV causes, for example, the proportion of death due to infection/sepsis and undetermined cause increased with age strata.

Factors associated with death

Anemia is a component of several algorithms that are used to determine the individual risk of bleeding in these patients.²¹⁻²³ Moreover, a recent sub-analysis of a RCT showed a strong association of anemia not only with bleeding but also all-cause

mortality in patient with AF receiving OAC, irrespective of warfarin or apixaban use.²⁴

The present study in a real-world cohort also demonstrated that anemia was strongly associated with both CV and non-CV mortality in AF patients. While not specifically examined in this study, multiple possible mechanisms may exist for the association between anemia and death; occult bleeding, general vascular frailty, renal dysfunction, nutrition status, and aging per se.

Pre-existing heart failure was identified as a strong indicator of all-cause death and CV death, not non-CV death in the present study, consistent with the sub-analysis from the RE-LY trial.⁴ Optimal management of heart failure as well as optimal antithrombotic therapy again appears to be the cornerstone for improving survival in patients with AF. In the present study, the prescription of OAC was associated with a lower incidence of all-cause death, mainly due to the lower incidence of non-CV death. Patients not using OAC may also have had various comorbidities with poor general clinical condition, and may have been considered unsuitable for OAC use.

Study limitations

The results of the present study have several limitations. First, the results were derived from a prospective observational study; therefore, it only shows association and

not causality with the limitations inherent to the design such as selection bias and unmeasured confounders. Since the present study was conducted in an urban district in Japan, the results cannot be easily extrapolated to other rural areas or countries. Second, the statistical analysis was based only on clinical details at the time of enrollment. Thus, changes of clinical backgrounds and treatments including prescriptions were not taken into consideration during the follow-up periods. Third, quality of anticoagulation with time in therapeutic range by warfarin and OAC adherence were also not investigated during the follow-up. Fourth, the percentage of deaths due to undetermined cause among all-cause death was substantially large (20.4%), especially with increasing rates in the elderly, which may result in underestimation of the incidence of each specified cause of death such as stroke or other CV causes. However, cause of death is sometimes difficult to determine, even in prospective randomized trials with close and strict data monitors. Especially, elderly patients are unlikely to be given full examination to pinpoint the cause of death in routine clinical practice. There is a wide variety in the proportion of undetermined causes in observational studies: 20.5% in the present study, compared with 3.2%⁸, none⁹, and 23.7%⁷. Unlike uniform medical information from retrospective analyses in a single center⁸ and from nationwide database in hospitalized AF patients⁹, large-scale multi-institutional observational registries such as ours and the

GARFIELD registry⁷ show higher percentage of undermined cause, probably due to heterogeneities in the quality of medical information across the participating institutions. Fifth, deaths recorded due to infection/sepsis, which increased with aging, might also have occurred as a consequence from the preceding CV event such as stroke or heart failure in the elderly AF patients. Sixth, there was no adjudication committee for outcome events. Finally, we did not have a control group (patients without AF) that would have allowed us to compare the distribution and predictors of each of the specific causes of mortality in patients with AF.

Conclusions

In a community-based Japanese AF cohort, CV deaths were not mainly related to stroke but to heart failure, irrespective of age groups. Non-CV deaths, especially death due to infection/sepsis, varied with different age strata. Clinical factors that were associated with CV and non-CV death were distinct. These findings provide important insights into the development of effective targeted interventions and reducing overall mortality in an increasing population with associated AF.

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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: YA analyzed the data and wrote the paper. YH, GL helped data analysis and interpretation. HO, YY, MI, NM, ME, 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.

Other contributions: We sincerely appreciate the efforts of the clinical research coordinators (T. Shinagawa, M. Mitamura, M. Fukahori, M. Kimura, M. Fukuyama, and C. Kamata).

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Conflict of interest: Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. Dr Lip has served as a consultant for Bayer, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic. No personal fees directly received.

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Role of the sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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Figure legends

Figure 1

Cumulative mortality of patients with atrial fibrillation in the entire cohort during the follow-up period. CV = cardiovascular

Figure 2

Causes of death between 3 groups categorized across age.

Figure 3

(A) Event rate of specific causes of death between 3 groups categorized across age. (B) Unadjusted hazard ratio for specific causes of death between age groups. CV = cardiovascular; CI = confidence interval.

Figure 4

Indicators of all-cause death. Data are presented hazard ratio and 95% confidence interval (CI). Hazard ratio were adjusted by age, female, body mass index, sustained AF (versus paroxysmal AF), pre-existing heart failure, hypertension, diabetes mellitus, previous stroke or TIA, PAD, prior myocardial infarction, anemia, COPD, renal dysfunction, dyslipidemia, previous major bleeding, prescription of renin-angiotensin system inhibitor, each prescription of β -blocker, APD, OAC, diuretics, digitalis, and statin at baseline. AF = atrial fibrillation; TIA = transient ischemic attack; PAD =

peripheral artery disease; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; OAC = oral anticoagulant

Figure 5

Indicators of cardiovascular and non-cardiovascular death. Data are presented hazard ratio and 95% confidence interval (CI). Hazard ratio were adjusted by the similar covariates chosen in the analysis for indicators of all-cause death. See Figure 4 legend for expansion of abbreviation and the covariates chosen to be included.

Figure S1

Kaplan-Meier curves for the crude incidences of (A) all-cause death, (B) cardiovascular death, and (C) non-cardiovascular death between in patients with oral anticoagulant and those without. OAC = oral anticoagulant.

Figure S2

Unadjusted event rate of specific causes of death in patients with oral anticoagulants and those without. CV = cardiovascular; OAC = oral anticoagulant.

Table 1. Baseline characteristics, co-morbidities, and prescription in patients alive and those who died during the follow-up

	Overall	Patients alive at the end of follow-up	Patients who died during the follow-up	P value
Number	4,045	3,340	705	
Baseline characteristics				
Female	1,634 (40%)	1,322 (40%)	312 (44%)	0.022
Age (years), mean $\pm$ SD	73.6 $\pm$ 10.9	72.3 $\pm$ 10.8	79.6 $\pm$ 9.0	<0.001
Age groups				<0.001
≤74 years	1,983 (49%)	1,790 (54%)	193 (27%)	
75 - 84 years	1,479 (37%)	1,192 (36%)	287 (41%)	
≥85 years	583 (14%)	358 (11%)	225 (32%)	
BMI (kg/m ²), mean $\pm$ SD	23.1 $\pm$ 4.0	23.4 $\pm$ 3.9	21.6 $\pm$ 4.1	<0.001
Systolic blood pressure (mmHg), mean $\pm$ SD	125.0 $\pm$ 18.5	125.0 $\pm$ 18.5	123.8 $\pm$ 20.7	0.15
Diastolic blood pressure (mmHg), mean $\pm$ SD	70.9 $\pm$ 12.9	71.4 $\pm$ 12.6	68.2 $\pm$ 13.9	<0.001
Pulse rate (beats/min), mean $\pm$ SD	78.2 $\pm$ 16.5	77.7 $\pm$ 15.9	80.5 $\pm$ 19.0	<0.001
Sustained AF	2,071 (51%)	1,671 (50%)	400 (57%)	0.001
Previous cardiac device implantation	315 (8%)	253 (8%)	62 (9%)	0.27
Estimated GFR (ml/min), median, (25%, 75%)	60.1 (47.2, 73.2)	61.6 (49.4, 74.2)	52.7 (34.8, 61.1)	<0.001
Co-morbidities				
CHADS ₂ score, mean $\pm$ SD	2.03 $\pm$ 1.32	1.90 $\pm$ 1.28	2.66 $\pm$ 1.37	<0.001
CHA ₂ DS ₂ -VASc score, mean $\pm$ SD	3.38 $\pm$ 1.69	3.19 $\pm$ 1.65	4.22 $\pm$ 1.66	<0.001
Previous stroke/TIA	738 (18%)	538 (16%)	200 (28%)	<0.001
Pre-existing heart failure	1,105 (27%)	795 (24%)	310 (44%)	<0.001
Hypertension	2,530 (63%)	2,088 (63%)	442 (63%)	0.93
Diabetes mellitus	938 (23%)	754 (23%)	184 (26%)	0.044
Dyslipidemia	1,769 (44%)	1,512 (45%)	257 (36%)	<0.001
Coronary artery disease	600 (15%)	451 (14%)	149 (21%)	<0.001
Prior myocardial infarction	249 (6%)	180 (5%)	69 (10%)	<0.001
Peripheral artery disease	167 (4%)	113 (3%)	54 (8%)	<0.001
Renal dysfunction	1,878(49%)	1,437 (46%)	441 (64%)	<0.001

Chronic obstructive pulmonary disease	212 (5%)	150 (4%)	62 (9%)	<0.001
Anemia	1,400 (37%)	941 (30%)	459 (67%)	<0.001
History of major bleeding	166 (4%)	119 (4%)	47 (7%)	<0.001
Prescription at baseline				
Oral anticoagulant	2,205 (55%)	1,861 (56%)	344 (49%)	<0.001
Warfarin	1,781 (44%)	1,458 (44%)	323 (46%)	0.29
NOAC	424 (10%)	403 (12%)	21 (3%)	<0.001
Anti-platelet drug	1,140 (28%)	898 (27%)	242 (34%)	<0.001
Diuretics	1,154 (29%)	866 (26%)	288 (41%)	<0.001
Loop diuretics	918 (23%)	670 (20%)	248 (35%)	<0.001
Thiazide diuretics	163 (4%)	139 (4%)	24 (3%)	0.34
Spironolactone	398 (10%)	287 (9%)	111 (16%)	<0.001
Renin-angiotensin system inhibitors	1,822 (45%)	1,495 (45%)	327 (46%)	0.43
Digitalis	481 (12%)	373 (11%)	108 (15%)	0.003
Beta-blocker	1,211 (30%)	1,017 (30%)	194 (28%)	0.1200
Statins	978 (24%)	847 (25%)	131 (19%)	<0.001

Categorical data are presented as number (%). Continuous data are presented as mean $\pm$ standard deviation (SD), or median and interquartile range (25%, 75%) according to the distribution. AF: atrial fibrillation, TIA: transient ischemic attack, Renal dysfunction: estimated glomerular filtration rate < 60 ml/min/m², NOAC: non-vitamin K oral anticoagulant

Table 2. Causes of death in overall patients

Event	Number	%
All-cause death	705	
Cardiovascular causes	180	25.5
Cardiac	115	16.3
Heart failure	102	14.5
Acute coronary syndrome	9	1.3
Dysrhythmia	4	0.6
Vascular	65	9.2
Ischemic stroke	34	4.8
Systemic embolism	1	0.1
Hemorrhagic stroke	12	1.7
Other intracranial hemorrhage	3	0.4
Extracranial bleeding	7	1
Other vascular/unknown	8	1.1
Non-cardiovascular causes	381	54
Malignancy	163	23.1
Respiratory failure	29	4.1
Infection/sepsis	122	17.3
Renal failure	23	3.2
Others	44	6.2
Undetermined causes	144	20.4

Table 3. Baseline characteristics, co-morbidities, and prescription among age subgroups.

	≤74 years	75-84 years	≥85 years	P value
Number	1,983	1,479	583	
Baseline characteristics				
Female	603 (30%)	646 (44%)	385 (44%)	<0.001
Age (years), mean ± SD	65.1 ± 8.4	79.1 ± 2.8	88.7 ± 3.6	<0.001
BMI (kg/m ²), mean ± SD	23.9 ± 4.2	22.8 ± 3.7	21.3 ± 3.7	<0.001
Systolic blood pressure (mmHg), mean ± SD	125.3 ± 18.5	124.2 ± 18.7	124.7 ± 20.8	0.21
Diastolic blood pressure (mmHg), mean ± SD	73.3 ± 12.4	68.8 ± 12.4	67.8 ± 14.2	<0.001
Pulse rate (beats/min), mean ± SD	78.1 ± 16.2	77.7 ± 16.3	79.8 ± 17.8	0.066
Sustained AF	947 (48%)	782 (53%)	342 (59%)	<0.001
Previous cardiac device implantation	101 (5%)	147 (10%)	67 (11%)	<0.001
Estimated GFR (ml/min), median, (25%, 75%)	66.5 (53.5, 79.0)	56.7 (44.9, 68.5)	49.5 (37.0, 62.1)	<0.001
Co-morbidities				
CHADS ₂ score, mean ± SD	1.36 ± 1.11	2.61 ± 1.18	2.87 ± 1.19	<0.001
CHA ₂ DS ₂ -VASc score, mean ± SD	2.39 ± 1.42	4.19 ± 1.34	4.67 ± 1.35	<0.001
Previous stroke/TIA	282 (14%)	289 (20%)	167 (29%)	<0.001
Pre-existing heart failure	403 (20%)	449 (30%)	253 (43%)	<0.001
Hypertension	1,192 (60%)	969 (66%)	369 (63%)	0.005
Diabetes mellitus	474 (24%)	247 (23%)	117 (20%)	0.14
Dyslipidemia	925 (47%)	649 (44%)	195 (33%)	<0.001
Coronary artery disease	232 (12%)	269 (18%)	99 (17%)	<0.001
Prior myocardial infarction	92 (5%)	108 (7%)	49 (8%)	<0.001
Peripheral artery disease	60 (3%)	80 (5%)	27 (5%)	0.002
Renal dysfunction	657 (36%)	818 (58%)	403 (71%)	<0.001
Chronic obstructive pulmonary disease	86 (4%)	95 (6%)	31 (5%)	0.024
Anemia	416 (23%)	615 (44%)	369 (66%)	<0.001
History of major bleeding	62 (3%)	67 (5%)	37 (6%)	0.002
Prescription at baseline				
Oral anticoagulant	1,052 (53%)	905 (61%)	248 (43%)	<0.001
Warfarin	820 (41%)	755 (51%)	206 (35%)	<0.001

NOAC	232 (12%)	150 (10%)	42 (7%)	0.007
Anti-platelet drug	473 (24%)	469 (32%)	198 (34%)	<0.001
Diuretics	429 (22%)	472 (32%)	253 (43%)	<0.001
Loop diuretics	324 (16%)	379 (26%)	215 (37%)	<0.001
Thiazide diuretics	77 (4%)	61 (4%)	25 (4%)	0.89
Spironolactone	159 (8%)	157 (11%)	82 (21%)	<0.001
Renin-angiotensin system inhibitors	862 (43%)	699 (47%)	261 (45%)	0.084
Digitalis	210 (11%)	198 (13%)	73 (13%)	0.037
Beta-blocker	636 (32%)	437 (30%)	138 (24%)	<0.001
Statins	483 (24%)	385 (26%)	110 (19%)	0.003

Categorical data are presented as number (%). Continuous data are presented as mean $\pm$ standard deviation (SD), or median and interquartile range (25%, 75%) according to the distribution. See Table 1 legend for expansion of abbreviations.

Table S1. Baseline characteristics and co-morbidities in patients with and without oral anticoagulants

	With OAC	Without OAC	P value
Number	2,205	1,840	
Baseline characteristics			
Female	836 (38%)	798 (43%)	<0.001
Age (years), mean $\pm$ SD	74.0 $\pm$ 9.2	73.1 $\pm$ 12.6	0.003
Age groups			<0.001
≤74 years	1,052 (48%)	931 (51%)	
75 - 84 years	905 (41%)	574 (31%)	
≥85 years	248 (11%)	335 (18%)	
BMI (kg/m ²), mean $\pm$ SD	23.4 $\pm$ 4.0	22.8 $\pm$ 4.0	<0.001
Systolic blood pressure (mmHg), mean $\pm$ SD	123.5 $\pm$ 18.6	126.4 $\pm$ 19.3	<0.001
Diastolic blood pressure (mmHg), mean $\pm$ SD	70.6 $\pm$ 12.7	71.2 $\pm$ 13.1	0.157
Pulse rate (beats/min), mean $\pm$ SD	77.9 $\pm$ 16.4	78.6 $\pm$ 16.6	0.21
Paroxysmal AF	833 (38%)	1,141 (62%)	<0.001
Previous cardiac device implantation	192 (9%)	123 (7%)	0.017
Estimated GFR (ml/min), median, (25%, 75%)	58.6 (46.4, 71.0)	62.5 (48.2, 76.7)	<0.001
Co-morbidities			
CHADS ₂ score, mean $\pm$ SD	2.25 $\pm$ 1.30	1.77 $\pm$ 1.31	<0.001
CHA ₂ DS ₂ -VASc score, mean $\pm$ SD	3.61 $\pm$ 1.62	3.10 $\pm$ 1.75	<0.001
Previous stroke/TIA	499 (23%)	239 (13%)	<0.001
Pre-existing heart failure	739 (34%)	366 (20%)	<0.001
Hypertension	1,427 (65%)	1,103 (60%)	0.002
Diabetes mellitus	553 (25%)	385 (21%)	0.002
Dyslipidemia	1,011 (46%)	758 (41%)	0.003
Valvular heart disease	463 (21%)	246 (13%)	<0.001
Coronary artery disease	306 (14%)	294 (16%)	0.061
Prior myocardial infarction	125 (6%)	124 (7%)	0.161
Cardiomyopathy	81 (4%)	31 (2%)	<0.001
Peripheral artery disease	97 (4%)	70 (4%)	0.34
Renal dysfunction	1,122 (54%)	756 (44%)	<0.001
Chronic obstructive pulmonary disease	129 (6%)	83 (5%)	0.057
Anemia	741 (35%)	659 (38%)	0.054

History of major bleeding	83 (4%)	83 (5%)	0.23
Prescription at baseline			
Warfarin	1,781 (81%)	-	
NOAC	424 (19%)	-	
Anti-platelet drug	517 (23%)	623 (34%)	<0.001
Diuretics	771 (35%)	383 (21%)	<0.001
Loop diuretics	616 (28%)	302 (16%)	<0.001
Thiazide diuretics	104 (5%)	59 (3%)	0.015
Spironolactone	278 (13%)	120 (7%)	<0.001
Renin-angiotensin system inhibitors	1,145 (52%)	677 (37%)	<0.001
Digitalis	321 (15%)	160 (9%)	<0.001
Beta-blocker	836 (38%)	275 (20%)	<0.001
Statins	597 (27%)	381 (21%)	<0.001

Categorical data are presented as number (%). Continuous data are presented as mean $\pm$ standard deviation (SD), or median and interquartile range (25%, 75%) according to the distribution. OAC: oral anticoagulant. See Table 1 legend for expansion of abbreviations.

Figure 1

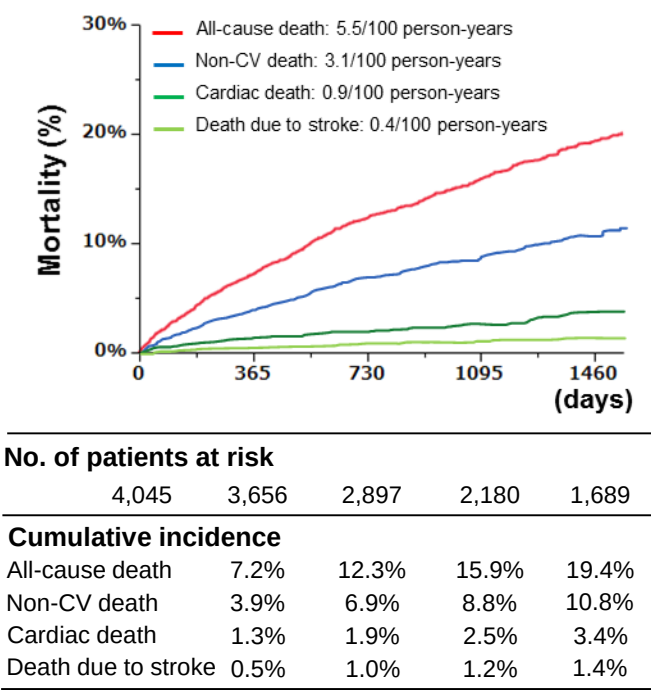


Figure 2

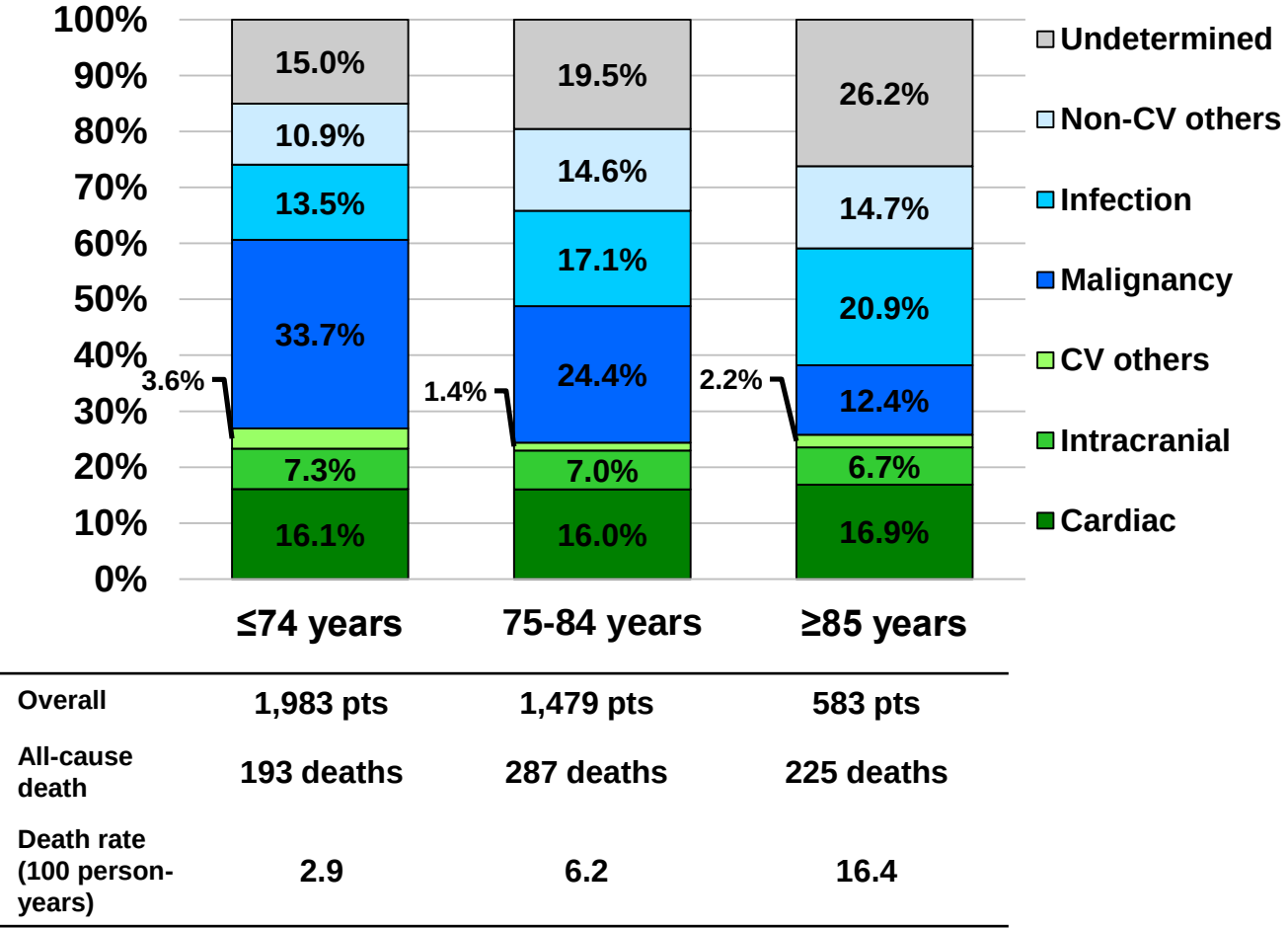
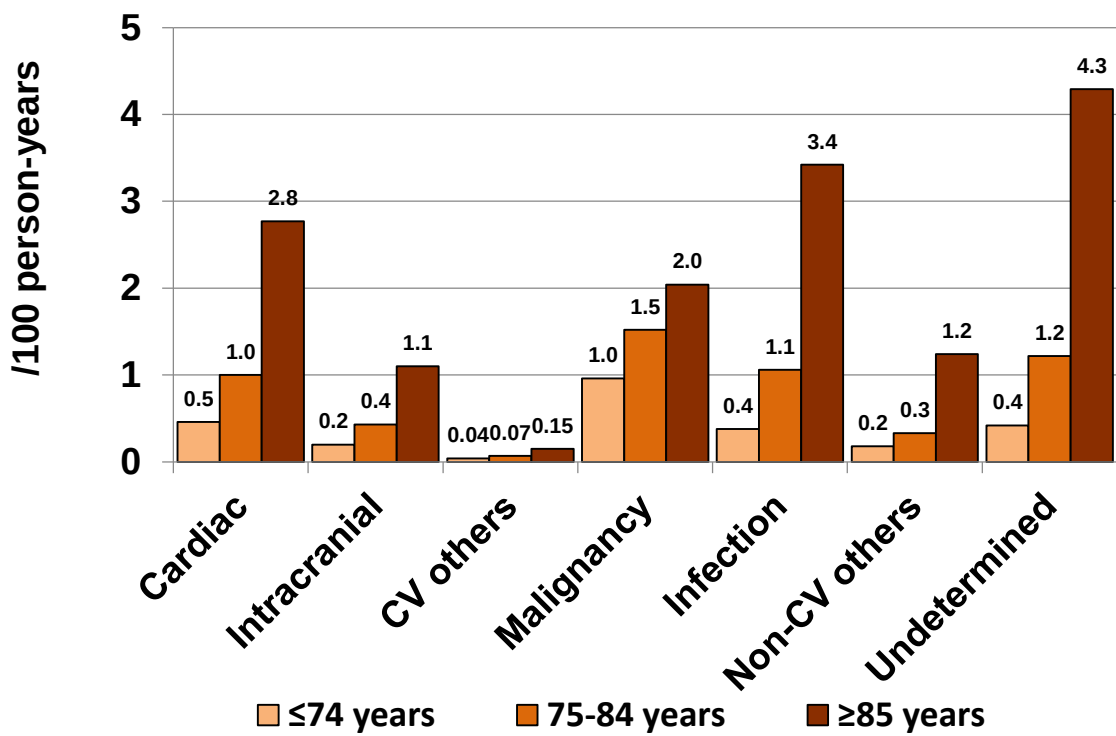


Figure 3

A



B

Unadjusted hazard ratio (95% CI)		
	75-84 years (versus ≤74 years)	≥85 years (versus ≤74 years)
Cardiac	2.16 (1.38-3.44)	5.83 (3.62-9.44)
Intracranial	2.04 (1.04-4.12)	4.74 (2.27-9.96)
CV others	1.44 (0.27-7.78)	3.13 (0.41-19.0)
Malignancy	1.55 (1.11-2.18)	1.98 (1.25-3.05)
Infection	2.74 (1.72-4.48)	8.58 (5.35-14.1)
Non-CV others	1.78 (0.84-3.90)	6.41 (3.07-13.8)
Undetermined	2.80 (1.80-4.44)	9.61 (6.21-15.2)

Figure 4

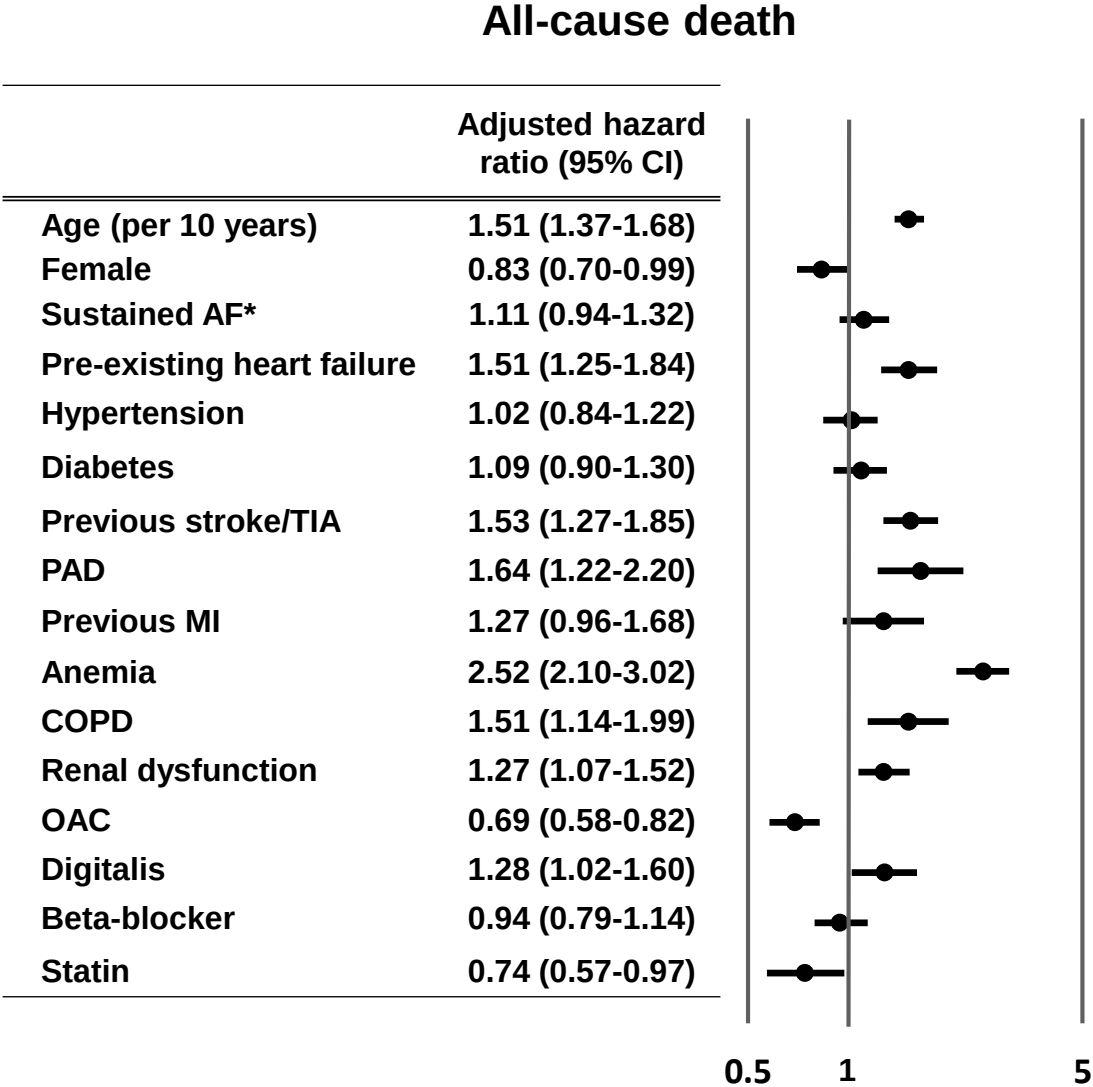


Figure 5

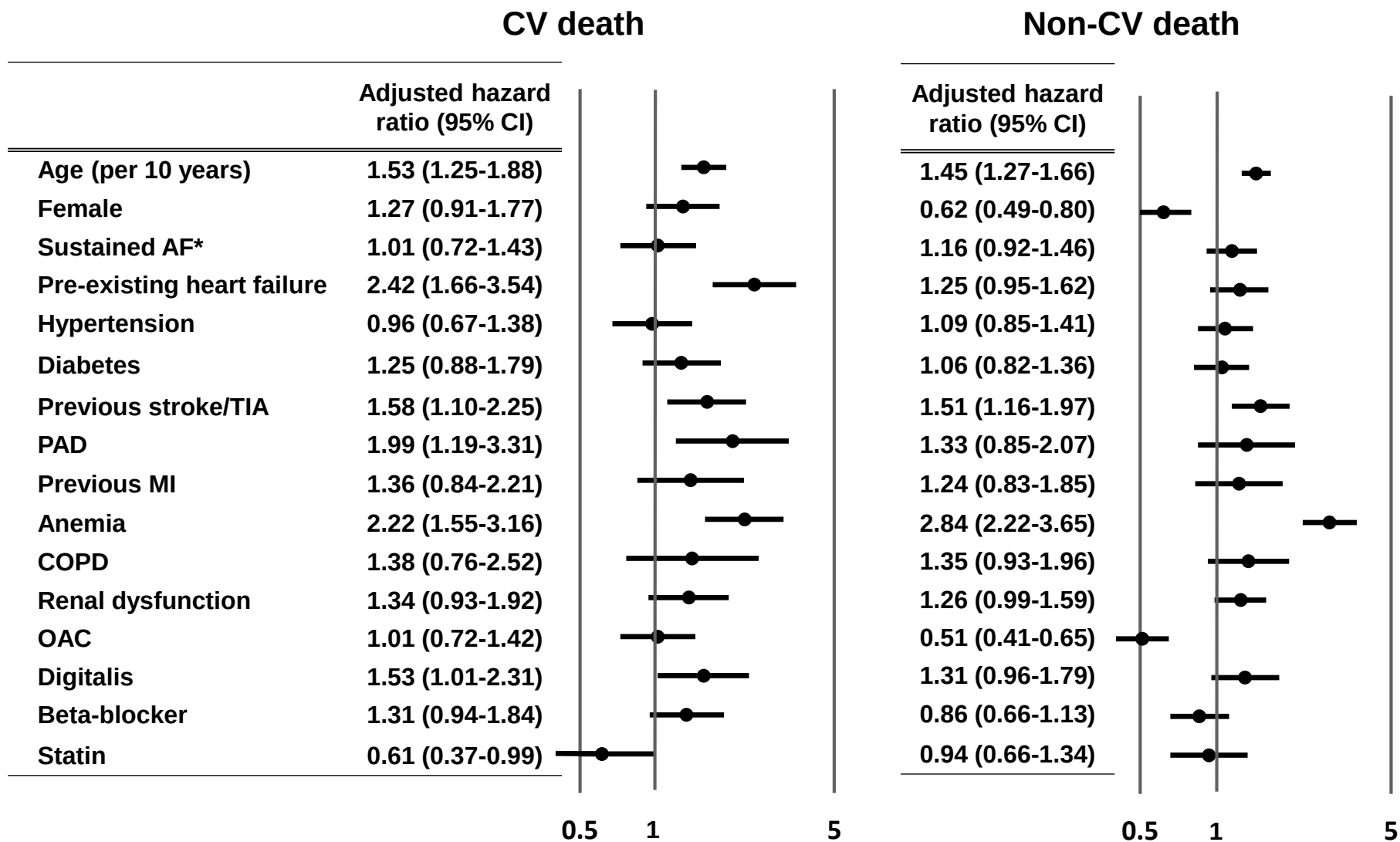
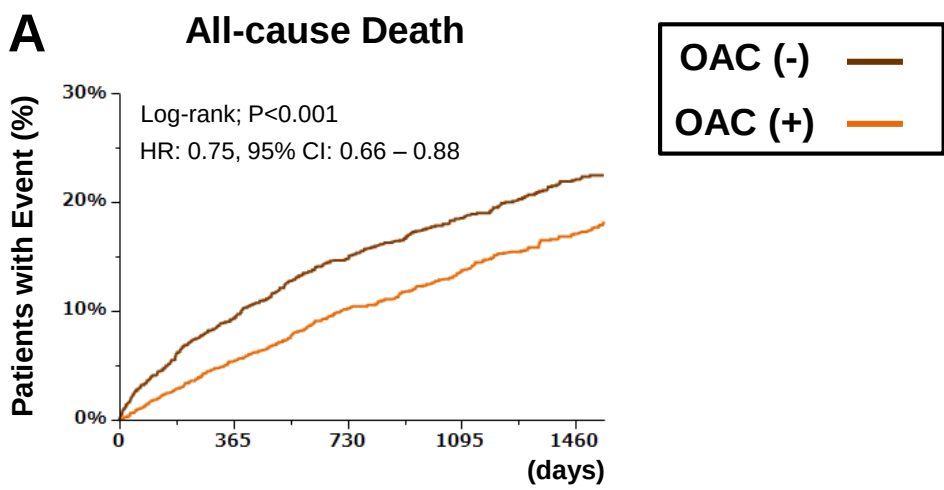
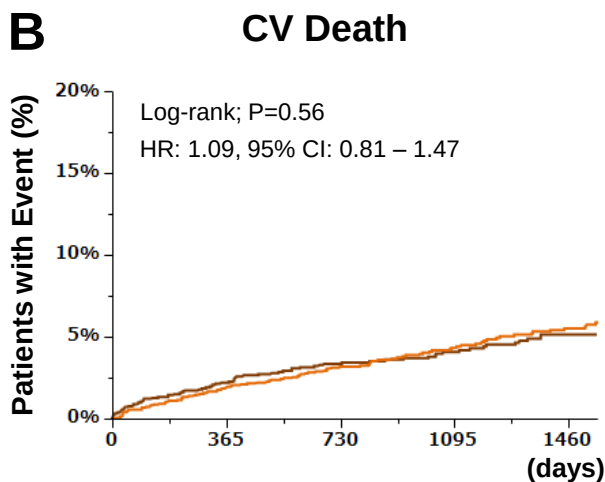


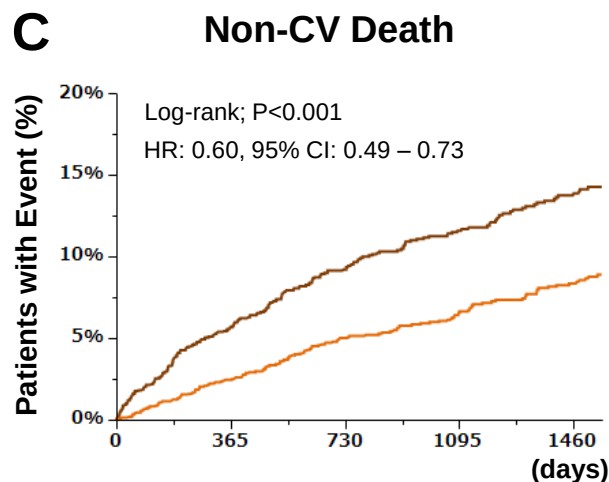
Figure S1



No. of patients at risk					
OAC (-)	1,840	1,624	1,284	962	736
OAC (+)	2,205	2,032	1,613	1,218	953
Cumulative incidence					
OAC (-)		9.3%	14.8%	18.5%	22.1%
OAC (+)		5.4%	10.2%	13.7%	17.1%



No. of patients at risk					
OAC (-)	1,840	1,624	1,284	962	736
OAC (+)	2,205	2,032	1,613	1,218	953
Cumulative incidence					
OAC (-)		2.2%	3.4%	4.1%	5.1%
OAC (+)		1.9%	3.2%	4.3%	5.5%



No. of patients at risk					
OAC (-)	1,840	1,624	1,284	962	736
OAC (+)	2,205	2,032	1,613	1,218	953
Cumulative incidence					
OAC (-)		5.7%	9.2%	11.6%	13.9%
OAC (+)		2.4%	5.0%	6.6%	8.3%

Figure S2

