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ORIGINAL ARTICLE
Epidemiology

Cause of Death and Associated Factors in Elderly Patients With Atrial Fibrillation

— Long-Term Retrospective Study —

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Background: Oral anticoagulant (OAC) therapy reduces the risk of stroke in patients with atrial fibrillation (AF). This study elucidated the causes of death and related factors in elderly Japanese AF patients.

Methods and Results: Over a median (interquartile range [IQR]) follow-up period of 46 (20–76) months, there were 171 all-cause deaths (28% cardiovascular, 46% non-cardiovascular, and 26% unknown causes) among 389 AF patients (median [IQR] age 80 [74–85] years; $CHAD_2DS_2$-VASc score 5 [4–6]). Cox regression analysis indicated that diabetes was associated with an increase in all-cause death (hazard ratio [HR] 1.48; 95% confidence interval [CI] 1.02–2.13), whereas hypercholesterolemia (HR 0.53; 95% CI 0.35–0.79), pre-existing heart failure (HR 0.67; 95% CI 0.48–0.95), and OAC use (HR 0.62; 95% CI 0.44–0.88) were associated with reductions in all-cause death. Pre-existing heart failure was associated with both cardiovascular (HR 3.03; 95% CI 1.33–8.20) and non-cardiovascular (HR 0.44; 95% CI 0.30–0.65) deaths, in opposite directions. OAC use was associated with a reduction in cardiovascular death (HR 0.34, 95% CI 0.17–0.69). The predominance of non-cardiovascular death and death-related factors were equivalent regardless of when observations started (before 2009 or in 2009 and later).

Conclusions: The predominant cause of death in elderly Japanese AF patients was non-cardiovascular. Distinct clinical factors were associated with cardiovascular and non-cardiovascular death.

Key Words: Atrial fibrillation; Cause of death; Cohort study; Elderly

Atrial fibrillation (AF) is a common arrhythmia in elderly patents. The prevalence and incidence rate of AF increase with age, with more than 70% of those diagnosed with AF being ≥65 years of age.[1,2] Although comorbidities increase with age,[3] elderly AF patients are likely to have a greater number of comorbidities.[2,4,5] The risk of developing embolic events is 5-fold higher in patients with AF than in those with sinus rhythm,[6] leaving patients bedridden or requiring long-term care, and increasing the mortality rate.[7] Oral anticoagulants (OACs) significantly reduce the incidence of stroke in patients with AF. All-cause mortality and causes of death among patients with AF were recently examined in both randomized control trials[8] and in cohort studies.[9–12] The real-world cohort studies demonstrated that stroke-related deaths account for approximately 5–8% of all-cause deaths, with non-cardiovascular (CV) death being the predominant cause of death.[9–12]

Against this background, the present study investigated differences in the clinical characteristics, prescription of OACs, incidence of death, and cause of death in elderly AF patients, and evaluated whether OACs and comorbidities are independently associated with prognosis in these patients.

Methods

Study Patients and Data Collection

The present study was a hospital-based retrospective observational study. All patients with AF (paroxysmal or sustained) as of 2017 according to the electronic medical record (EMR) system were picked up from 1997. Cardiologists and biomedical engineers reviewed the electrocardiograms (ECGs) and medical records, and ECG-documented

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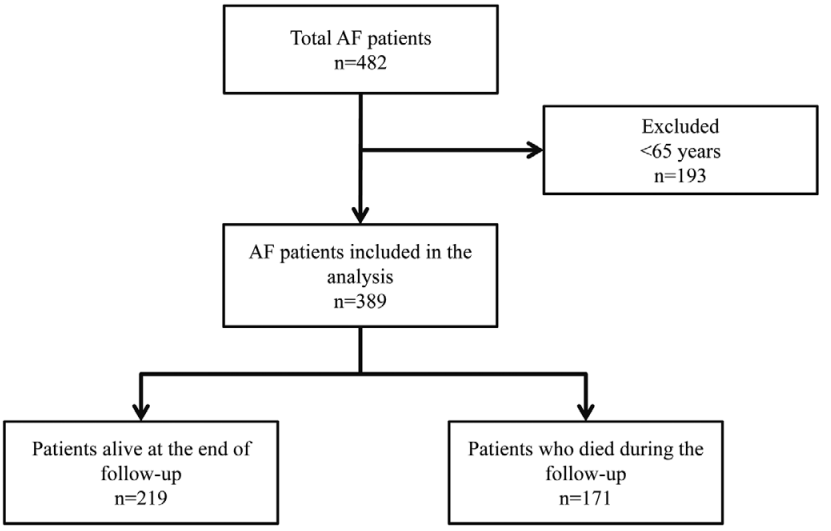

Figure 1. Diagram showing patient disposition in the present study. AF, atrial fibrillation.

cases of AF were included in the present study. In the case of patients without ECG records, patients were considered to have AF if the attending physician diagnosed and treated them for AF. Patients <65 years of age were excluded from the study. All data, including comorbidities, drug use, and patient prognosis, were evaluated by reviewing the hospital EMR for each patient (**Figure 1**).

Definition of Clinical Diseases

Comorbidities diagnosed clinically according to the following criteria were taken into account. Patients were diagnosed with hypertension if they were documented to have a blood pressure of at least 140/90 mmHg or were already on antihypertensive therapy.[13] Diabetes was defined as fasting plasma glucose levels of 126 mg/dL (7 mmol/L), HbA1c of 6.5%, and/or patients clinically identified and treated as having diabetes.[14] Hypercholesterolemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL (5.69 mmol/L)[15] or statin use. Patients with coronary artery disease were defined as those who had significant coronary lesions within the major coronary tree or a history of myocardial infarction (MI), percutaneous coronary intervention, or coronary artery bypass graft. Stroke was defined as a history of brain thromboembolism or bleeding. Peripheral artery disease (PAD) was defined as an ankle–brachial index <0.9,[16] or a history of percutaneous transluminal angioplasty or bypass graft. Heart failure was defined as a history of admission for congestive heart failure Stroke risk was assessed using the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior MI, PAD, or aortic atherosclerosis], age 65–75 years, female sex).

Study Endpoint

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 available information and were classified as either CV, non-CV, or undetermined (when the quality of information did not allow the investigators to appropriately identify the cause of death). CV deaths included those resulting from coronary artery disease, cerebral infarction, cerebral hemorrhage, subdural hematoma, aortic dissection, systemic embolism, constrictive pericarditis, congestive heart failure, aortic aneurysm rupture, pulmonary embolism, arterial sclerosis obliterans, and sudden death. Sudden death was defined as an unexpected sudden death from onset to death within 24 h. Non-CV deaths included those resulting from malignant neoplasm, pneumonia, other infectious diseases, ileus, gastrointestinal perforation, renal failure, choking, sarcoidosis, and senility. Senility was defined as the absence of any other fatal disease despite recovery from the underlying disease. Two cardiologists reviewed each medical record to confirm the diagnosis.

Statistical Analysis

The clinical characteristics of the study population according to survival at the end of follow-up period were compared using a t-test or Wilcoxon signed-rank test for continuous variables depending on whether the data were normally distributed, and the Chi-squared test for categorical variables. The normality of distribution was evaluated using the Kolmogorov-Smirnov test. Continuous data are presented as the median with interquartile range (IQR), whereas categorical data are presented as frequencies. The cumulative incidence of clinical outcomes was estimated by the Kaplan-Meier method, and the significance of differences was assessed with the log-rank test.

A multivariate Cox regression model was used on potential confounders to identify factors associated with all-cause death, CV death, and non-CV death. The covariates included age (per 10 years), male sex (vs. female sex), hypertension, diabetes, hypercholesterolemia, coronary artery disease, stroke, heart failure, PAD, sustained AF (vs. paroxysmal AF), and the use of OACs at baseline. To assess death-related factors in the later years of life, a separate Cox analysis was performed for individuals aged ≥75 years. In addition, considering the significant changes in AF therapeutic strategies after the launch of the Guidelines for the Pharmacotherapy of Atrial Fibrillation

Table 1. Baseline Characteristics of the 389 Patients in the Present Study (A), Stratified According to Treatment Era (B)

(A) Variable	Patients alive at the end of follow-up		P-value
	Yes (n=218)	No (n=171)	
Age (years)	78 [72–82]	83 [77–88]	<0.0001
Age group (%)			
65–74	34	15	
75–79	25	23	
≥80 or over	41	62	
Male sex (%)	107 (49)	87 (51)	0.7597
Sustained AF (%)	136 (62)	130 (76)	0.0043
Hypertension (%)	168 (77)	136 (80)	0.6215
Diabetes (%)	62 (28)	61 (36)	0.1532
Dyslipidemia (%)	87 (40)	36 (21)	0.0001
CAD (%)	51 (23)	38 (22)	0.8089
Stroke (%)	88 (40)	87 (51)	0.0407
Heart failure (%)	138 (63)	110 (64)	0.9154
PAD (%)	13 (6)	19 (11)	0.0930
Hemodialysis (%)	6 (3)	5 (3)	1.000
CHA_2DS_2-VASc score	5 [4–6]	5 [4–7]	0.9999
Oral anticoagulants (%)	156 (72)	85 (50)	<0.0001

(B) Variable	Observations started		P-value
	Before 2009 (n=61)	In 2009 or later (n=328)	
Age (years)	74 [70–79]	81 [75–86]	<0.0001
Age group (%)			
65–74	51	21	
75–79	34	22	
≥80	15	57	
Follow-up duration (months)	111 [94–125]	38 [15–61]	<0.0001
Male sex	30 (49)	164 (50)	1.000
Sustained AF	45 (74)	221 (67)	0.3702
Hypertension	46 (75)	258 (79)	0.6131
Diabetes	22 (36)	101 (31)	0.4514
Dyslipidemia	24 (39)	99 (30)	0.1801
CAD	17 (28)	72 (22)	0.3215
Stroke	26 (42)	149 (45)	0.7795
Heart failure	44 (72)	204 (62)	0.1494
PAD	3 (5)	29 (9)	0.4466
Hemodialysis	4 (7)	7 (2)	0.0767
CHA_2DS_2-VASc score	5 [4–6]	6 [4–6]	0.5734
Oral anticoagulants	44 (72)	197 (60)	0.0852

Unless indicated otherwise, data are expressed as the median [interquartile range] or n (%). The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, PAD, or aortic atherosclerosis], age 65–75 years, female sex) was used to assess stroke risk. AF, atrial fibrillation; CAD, coronary artery disease; PAD, peripheral artery disease.

(JCS2008),[17] the prognosis of patients in the study was assessed by categorizing them into 2 groups according to when observations began (i.e., before 2009 or in 2009 and later).

Statistical analyses were performed using JMP 9.0.2 (SAS Institute, Cary, NC, USA). All statistical tests were 2-sided, and $P<0.05$ was considered statistically significant.

This study was conducted following the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Social Medical Corporation Yuaikai, Okinawa, Japan (H30R009).

Results

In all, 389 patients who were retrospectively enrolled from 1997 to 2016 were followed for a median duration of 46 months (IQR 20–76 months). The baseline characteristics of the patients stratified according to prognosis are presented in **Table 1**. The median age of the patients was 77 years (IQR 68–84 years), 54% were men, and the median CH_2DS_2-VASc score was 5 (IQR 4–6). Hypertension (78%) was the most prevalent comorbidity, followed by heart failure (64%), stroke (45%), hypercholesterolemia (32%), diabetes (32%), and coronary artery disease (23%). Of the

Table 2. Causes of Death Among 389 Patients in the Present Study Stratified According to Patient Age (A), and Treatment Era (B)

(A) Cause of death	All patients who died (n=171)	Patients aged 65–74 years (n=97)	Patients aged ≥75 years (n=276)	P-value
All-cause death	171 (100)	26 (26)	145 (50)	<0.0001
CV death	48 (28)	9 (19)	39 (81)	0.2914
CAD death	0 (0)	0 (0)	0 (0)	
Heart failure	22 (13)	2 (9)	20 (91)	0.0791
Sudden death	15 (9)	5 (33)	10 (67)	0.5475
Stroke	4 (2)	1 (25)	3 (75)	1.000
Others	7 (4)	1 (14)	6 (86)	0.6829
Non-CV death	79 (46)	9 (11)	70 (89)	0.0008
Malignant neoplasm	32 (19)	2 (6)	30 (94)	0.0580
Pneumonia	19 (11)	1 (5)	18 (95)	0.0334
Senility	11 (6)	0 (0)	11 (100)	0.0731
Infection	8 (5)	1 (13)	7 (88)	0.6857
Others	9 (5)	5 (56)	4 (44)	0.0525
Unknown cause of death	44 (26)	8 (8)	36 (82)	0.2737

(B) Cause of death	Observations started		P-value
	Before 2009 (n=61)	In 2009 or later (n=328)	
All-cause death	25 (41)	146 (45)	0.6743
CV death	4 (7)	44 (13)	0.2009
CAD death	0 (0)	0 (0)	1.0000
Heart failure	2 (3)	20 (6)	0.5505
Sudden death	1 (2)	14 (4)	0.4832
Stroke	0 (0)	4 (1)	1.0000
Other	1 (2)	6 (2)	1.0000
Non-CV death	12 (20)	67 (20)	1.0000
Malignant neoplasm	2 (3)	30 (9)	0.2005
Pneumonia	4 (7)	15 (5)	0.5165
Senility	0 (0)	11 (3)	0.2258
Infection	2 (3)	6 (2)	0.3648
Others	4 (7)	5 (2)	0.0375
Unknown cause of death	9 (15)	35 (11)	0.3782

Unless indicated otherwise, data are expressed as n (%). CAD, coronary artery disease; CV, cardiovascular.

389 patients, 61% were taking OACs. There were 171 deaths during the follow-up period. The patients who died during the follow-up period were significantly older and had a higher prevalence of comorbidities, such as previous stroke and sustained AF, but the CHA_2DS_2-VASc scores were equivalent between those who died and those who did not (**Table 1A**).

Table 2A details of the cause of death in all patients and in patients stratified according to age. Of the patients who died during the follow-up period, approximately 30% died of CV causes, <50% died of non-CV causes, and 25% died of unknown causes. CV death included heart failure (13%), sudden death (9%), and stroke (only 2%). Non-CV death included malignant neoplasm (19%), pneumonia (11%), senility (6%), and infection (5%). Elderly AF patients were likely to die from non-CV causes. The survival curves stratified by cause of death for the entire study population are shown in **Figure 2**. The event rate of all-cause death, non-CV death, and CV death was 2.6%, 1.2%, and 0.7% per year, respectively.

In the multivariate Cox regression analysis (**Figure 3A**), baseline variables associated with all-cause death were age (hazard ratio [HR] 1.75; 95% confidence interval [CI] 1.53–2.00), male sex (HR 1.39; 95% CI 1.00–1.93), and diabetes (HR 1.48; 95% CI 1.02–2.13), followed by hypercholesterolemia (HR 0.53; 95% CI 0.35–0.79), heart failure (HR 0.67; 95% CI 0.48–0.95), and OAC use (HR 0.62; 95% CI 0.44–0.88). These results were almost the same for patients aged ≥75 years (**Table 3A**). Characteristic findings of this study were that pre-existing heart failure was associated with poor CV mortality (**Figure 3B**), but with better non-CV mortality (**Figure 3C**). Diabetes was associated with higher CV and non-CV mortality, but hypercholesterolemia was associated with lower CV mortality. OAC use significantly reduced CV but not non-CV mortality (**Figure 3B**,**C**).

Because the therapeutic strategies for AF changed after the publication of the Guidelines for the Pharmacotherapy of Atrial Fibrillation (JCS2008),[17] patients' background information and prognostic factors were also assessed by categorizing them into 2 groups depending on whether they started to be observed before 2009 or in 2009 and later. Patients who started being observed before 2009 were significantly younger than those who began being observed in 2009 or later, but there were no significant

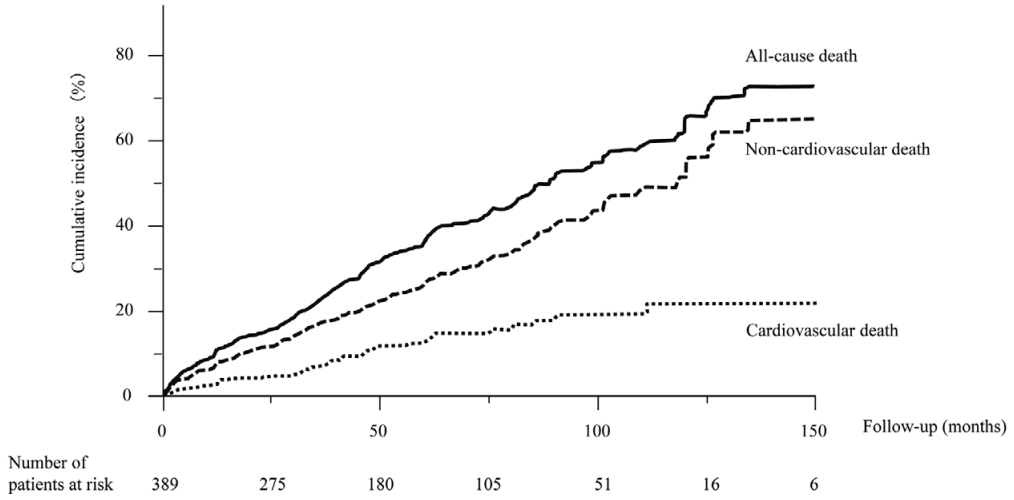

Figure 2. Kaplan-Meier curves of the 389 patients in the present study stratified by cause of death.

differences in the other factors between the 2 groups (**Table 1B**). The cause of death did not differ significantly between the 2 groups (**Table 2B**). The incidence of all-cause death was 1.1% per year for patients who started being observed before 2009 and 4.1% per year for patients who started being observed in 2009 or later. Multivariable Cox regression analysis indicated that the factors associated with all-cause death in patients who started being observed before 2009 were age (HR 1.15; 95% CI 1.07–1.25), diabetes (HR 5.23; 95% CI 1.80–15.97), and sustained AF (HR 5.70; 95% CI 1.40–30.58). In patients who started being observed in 2009 or later, the factors associated with all-cause death were age (HR 1.11; 95% CI 1.08–1.14), male sex (HR 1.56;, 95% CI 1.09–2.23), hypercholesterolemia (HR 0.64; 95% CI 0.40–0.98), pre-existing heart failure (HR 0.63; 95% CI 0.44–0.90), and OAC use (HR 0.52; 95% CI 0.35–0.76; **Table 3B**).

Discussion

The present analysis revealed that almost half the deaths in elderly AF patients were due to non-CV causes and that one-third of deaths were from CV causes. The most common cause of CV death was heart failure, which was the second leading cause of death after malignant neoplasm, followed by pneumonia. Only 2% of all-cause death was due to stroke. Diabetes was the factor most strongly associated with a higher incidence of non-CV death. Pre-existing heart failure was associated with CV and non-CV death, but in opposite directions.

Cause of Death in Elderly AF Patients

Compared with previous cohort studies,[9–12] the patients in the present study were older, had a higher CHA_2DS_2-VASc score, a longer observation period, and equivalent OAC use and mortality. The causes of death were similar to those reported in previous studies,[9–12] including the predominance of non-CV death, malignant neoplasm, heart failure, and pneumonia, and fewer stroke deaths. A distinguishing feature of the present study is that 6% of total deaths were due to senility. Understanding the characteristics of these patients, including their background and treatment details, may provide the key to optimal medical therapy[18] for elderly AF patients. The median age at death of these patients was 91 years (IQR 85–94 years), and only 36% were treated with OACs. The clinical significance of OACs for AF patients is evident.[19] Elderly patients are often prescribed many drugs for their comorbidities, which is likely to reduce renal function,[20] making physicians hesitant to prescribe OACs due to concerns about poor compliance and bleeding risks related to cognitive issues and drug interactions, respectively.[21] Furthermore, OACs for elderly patients with a high fall risk increase the risk of mortality from falling.[21,22] Therefore, introducing OACs for elderly AF patients requires comprehensive judgment after considering comorbidity, activities of daily living, and life expectancy. Healthcare providers may avoid introducing OACs in high-risk patients for the aforementioned reasons, leading to a better prognosis in patients using OACs.

Differences According to Treatment Era

To evaluate the effect of treatment era, patients were divided into 2 groups according to when they started to be observed: before 2009 or in 2009 and later. Patients who started to be observed before 2009 were significantly younger than those who started to be observed in 2009 or later (median [IQR] age 74 [70–79] vs. 81 [75–86] years, respectively; $P<0.0001$), but other background factors were equivalent between the 2 groups. There was no significant change in the composition of the causes of death over time, but the total mortality rate was lower in patients who started to be observed before 2009. On the basis of this information, it is presumed that elderly patients with AF who were not in good general condition may have ignored their AF and not been followed-up in the earlier time period. However, even in this biased group of patients, the predominance of non-CV deaths among all-cause deaths was the same as that for patients who started to be observed in 2009 and later.

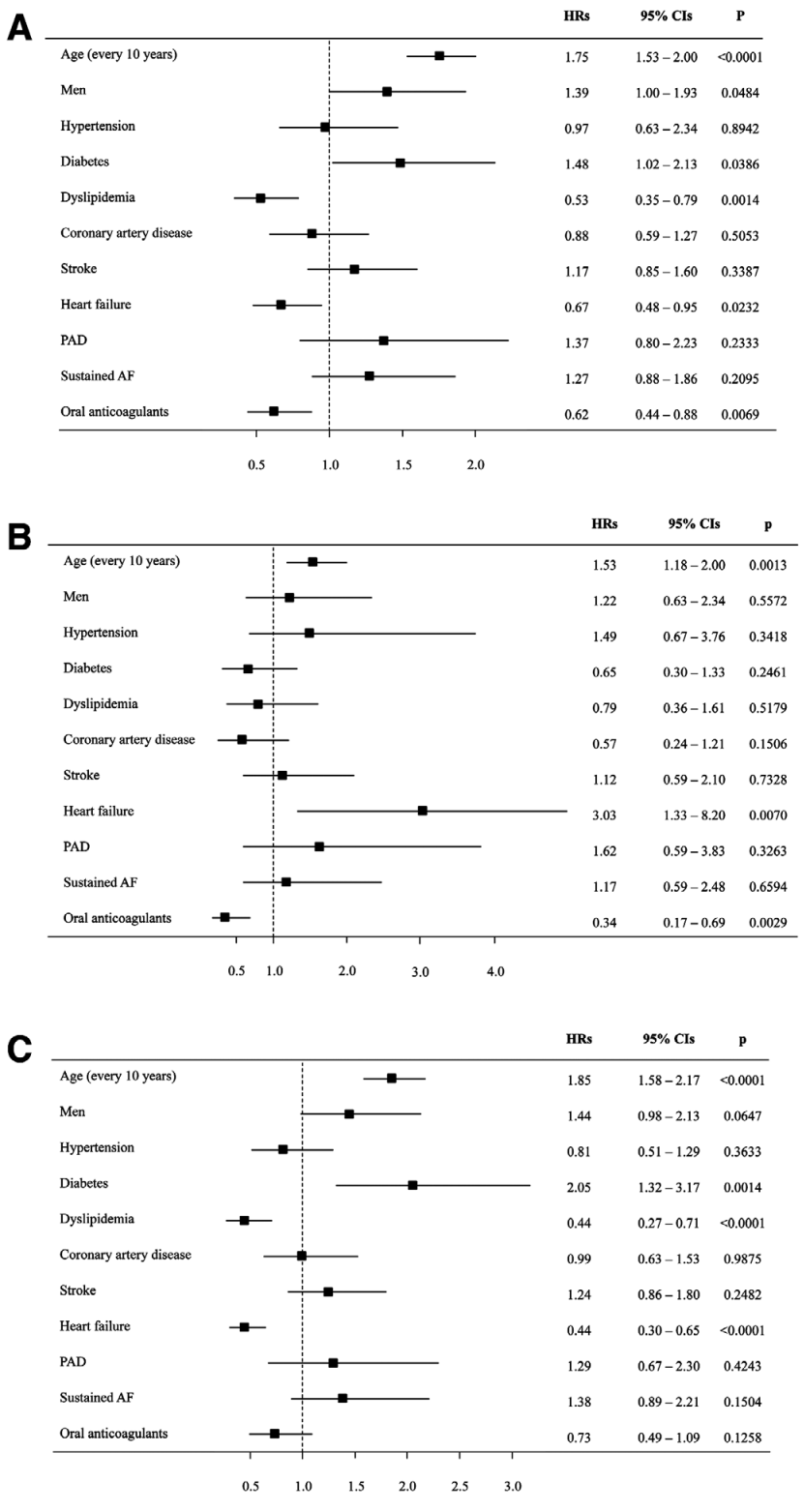

Figure 3. Cox regression analyses for (**A**) all-cause death, (**B**) cardiovascular death, and (**C**) non-cardiovascular death. Data are presented as hazard ratios (HR) with 95% confidence intervals (CIs) in the multivariate model for all patients. In the multivariate model, the covariables were forcibly included. AF, atrial fibrillation; PAD, peripheral artery disease.

Comorbidities and Mortality Risk

The significant finding of the present analysis was that the mortality risk associated with pre-existing heart failure differs between CV and non-CV deaths. Pre-existing heart failure was associated with a worse CV, but better non-CV outcome. It is unclear why pre-existing heart failure was associated with better non-CV mortality. No studies to date have demonstrated that pre-existing heart failure is associated with better mortality risk. The Fushimi AF Registry demonstrated that pre-existing heart failure was

Table 3. Cox Regression Analysis for All-Cause Death in All Patients and Those Aged ≥75 Years (A), and Stratified According to Treatment Era (B)

(A) Variables	All patients (n=373)			Patients aged ≥75 years (n=276)		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (every 10 years)	1.75	1.53–2.00	<0.0001	1.64	1.38–1.95	<0.0001
Male sex	1.39	1.00–1.93	0.0484	1.32	0.93–1.87	0.1204
Hypertension	0.97	0.66–1.47	0.8942	0.99	0.65–1.56	0.9705
Diabetes	1.48	1.02–2.13	0.0386	1.54	1.02–2.31	0.0394
Hypercholesterolemia	0.53	0.35–0.79	0.0014	0.56	0.35–0.85	0.0066
CAD	0.88	0.59–1.27	0.5053	0.98	0.64–1.47	0.9267
Stroke	1.17	0.85–1.60	0.3387	1.22	0.87–1.72	0.2440
Heart failure	0.67	0.48–0.95	0.0232	0.62	0.43–0.91	0.0154
PAD	1.37	0.80–2.23	0.2333	1.22	0.69–2.04	0.4836
Sustained AF	1.27	0.88–1.86	0.2095	1.18	0.80–1.77	0.4224
Oral anticoagulants	0.62	0.44–0.88	0.0069	0.60	0.41–0.87	0.0074
(B) Variable	**Observations started**					
	Before 2009 (n=61)			**In 2009 or later (n=328)**		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age (every 10 years)	1.15	1.07–1.25	0.0001	1.11	1.08–1.14	<0.0001
Male sex	0.98	0.31–2.88	0.9750	1.56	1.09–2.23	0.0153
Hypertension	0.62	0.19–2.13	0.4345	1.03	0.68–1.62	0.8799
Diabetes	5.23	1.80–15.97	0.0025	1.18	0.78–1.75	0.4445
Hypercholesterolemia	0.72	0.21–2.14	0.5674	0.64	0.40–0.98	0.0395
CAD	1.68	0.63–4.22	0.2908	0.83	0.54–1.26	0.3881
Stroke	0.96	0.36–2.54	0.9264	1.18	0.84–1.65	0.3510
Heart failure	0.73	0.19–2.90	0.6430	0.63	0.44–0.90	0.0127
PAD	0.98	0.04–8.67	0.9866	1.34	0.78–2.20	0.2789
Sustained AF	5.70	1.40–30.58	0.0138	1.25	0.85–1.88	0.2642
Oral anticoagulants	0.48	0.17–1.45	0.1886	0.52	0.35–0.76	0.0008

Hazard ratios (HR) and 95% confidence intervals (CIs) are for the multivariate model, in which the covariables were forcibly included. AF, atrial fibrillation; CAD, coronary artery disease; PAD, peripheral artery disease.

associated with high CV mortality, but not non-CV mortality.[10] Studies evaluating the association between pre-existing heart failure and non-CV death indicated greater mortality[12] or no association.[10] One potential reason for this paradoxical finding is the diagnosis of heart failure. In the present study, patients were diagnosed with heart failure if they had a history of heart failure, regardless of heart failure status. As a result, many survivors are likely to be well treated. Elderly AF survivors with pre-existing heart failure may be well treated, resulting in a better prognosis. They may be a biased population, leading to reverse causation.

Cardiometabolic risk factors such as hypertension, dyslipidemia, diabetes, and obesity are well-known factors that accelerate the lifetime risk for CV disease.[23] Current guidelines require optimal levels of these metabolic factors for the prevention of CV disease.[13–15] In contrast, in elderly AF patients, the association of these cardiometabolic factors with mortality has not been fully evaluated. Some studies report that hypertension is associated with a better prognosis.[9,11,24] The Fushimi AF registry demonstrated that statin use, suggestive of dyslipidemia, is associated with better all-cause mortality.[10] Moreover, the trajectories of blood pressure[25] and total cholesterol levels[26] exhibit an accelerated decline in the last years of life through frailty. In a previous evaluation of cardiometabolic risk control in frail outpatients, we found that the more controlled the cardiometabolic risk factors, such as blood pressure, lipids, and body weight, the greater the risk of frailty.[20] The patients in the present study were older and more likely to be frail than the other cohorts, resulting in hypertension and hypercholesterolemia being associated with a better prognosis. Because elderly AF patients have many comorbidities, both anticoagulation therapy for stroke prevention and optimal treatment of each comorbidity are required for a better prognosis in this group of patients. To establish the ideal treatment for prolonging a healthy life expectancy of these patients, we must pay attention not only to a single disease, but also to the whole body and all comorbidities.

Future Perspectives

The treatment of AF patients has been focused on the prevention of thromboembolism. Direct oral anticoagulants have not only enabled the effective prevention of stroke, but also enhanced the safety of this group of patients.[27–30] However, the results of real-world cohort studies indicate that although OACs reduce all-cause mortality, their reduction of stroke deaths, a primary purpose for their use, is minimal. Moreover, heart failure, renal failure, anemia, and lung disease are associated with a poor prognosis. Geriatric patients have many comorbid conditions, most of which are associated with their prognosis; as a result, interventions targeting a single disease may have limited efficacy in this population.[3] A single disease-specific therapeutic strategy for patients with this condition may have little effect on the morbidities or mortality of the individual.

The Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2) trial investigated type 2 diabetic patients with albuminuria and demonstrated additive reductions in CV events and death by lowering lipid and blood pressure levels in addition to blood glucose control, indicating the importance of comprehensive risk control for improving the prognosis of these patients.[31] The current treatment of elderly AF patients may focus too much on stroke prevention and too little on the management of comorbidities. Because of the likelihood of comorbidities in AF patients, comprehensive treatment for multiple disorders is required to prolong the healthy life expectancy of these patients.

Study Limitations

The present study has several limitations. First, the results of the study were derived from a retrospective observational study, showing only the association and not the causation. Second, the quality of anticoagulation by warfarin and adherence to OAC regimens were not investigated. Third, the percentage of deaths of unknown cause among all-cause deaths was relatively high (26%), resulting in an underestimation of each specified cause of death, such as stroke or other CV causes. However, this percentage is comparable with other real-world cohort studies, such as the GARFIELD-AF and FUSHIMI registries.[9,10] Fourth, the present study was conducted in a relatively limited area and number of institutes, and so the results cannot be generalized. Finally, this study included patients who started to be observed in an era when direct oral anticoagulants were not available. However, a study evaluating the long-term prognosis in new-onset AF patients indicated no difference in mortality across the different time periods.[32] These issues should be considered when interpreting the results of the present analysis.

Conclusions

In elderly Japanese AF patients, non-CV deaths (mainly infection and pneumonia) predominated. Heart failure, not stroke, was the predominant CV death regardless of the age group. Clinical factors that were associated with CV and non-CV deaths were distinct. These findings provide important information for the optimal treatment of elderly AF patients for a better prognosis.

Author Contributions

T.I., T.S., and K.O. participated in the study design. T.I. and K.O. drafted the manuscript. H.A. performed the statistical analysis and drafted the manuscript. M.T. and O.A. participated in study coordination. All authors read and approved the final manuscript.

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Disclosures

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IRB Information

This study was conducted following the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Social Medical Corporation Yuaikai, Okinawa, Japan (H30R009).

References

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: Analysis and implications. *Arch Intern Med* 1995; **155:** 469–473.
2. Go AS, Hylek EM, Phillips KA, Chang YC, Henault LE, Selby JV, 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. *J Am Med Assoc* 2001; **285:** 2370–2375.
3. Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J* 2014; **44:** 1055–1068.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death. *Circulation* 1998; **98:** 946–952.
5. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, et al. Incidence and prevalence of atrial fibrillation and associated mortality among medicare beneficiaries: 1993–2007. *Circ Cardiovasc Qual Outcomes* 2012; **5:** 85–93.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; **22:** 983–988.
7. Okumura K, Metoki N, Hagii J. Epidemiology and severity of cardioembolic stroke. *Jpn J Electrocardiol* 2011; **31:** 292–296.
8. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Causes of death in anticoagulated patients with atrial fibrillation. *Am J Coll Cardiol* 2016; **68:** 2508–2521.
9. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KAA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. *Eur Heart J* 2016; **37:** 2882–2889.
10. An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, et al. Causes of death in Japanese patients with atrial fibrillation: The Fushimi Atrial Fibrillation Registry. *Eur Heart J Qual Care Clin Outcomes* 2019; **5:** 35–42.
11. Fauchier L, Samson A, Chaize G, Gaudin AF, Vainchtock A, Bailly C, et al. Cause of death in patients with atrial fibrillation admitted to French hospitals in 2012: A nationwide database study. *Open Heart* 2015; **2:** e000290.
12. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, et al. Causes of death and influencing factors in patients with atrial fibrillation. *Am J Med* 2016; **129:** 1278–1287.
13. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res* 2019; **42:** 1235–1481.
14. Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, et al. Japanese clinical practice guideline for diabetes 2016. *J Diabetes Investig* 2018; **9:** 657–697.
15. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Umemoto S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. *J Atheroscler Thromb* 2018; **25:** 846–984.
16. Desk R, Williams L, Health K. Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106:** 3143–3421.
17. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): Digest version. *Circ J* 2010; **74:** 2479–2500.
18. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356:** 1503–1516.
19. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013): Digest version. *Circ J* 2014; **78:** 1997–2021.
20. Matsuoka M, Inoue T, Shinjo T, Miiji A, Tamashiro M, Oba K, et al. Cardiovascular risk profile and frailty in Japanese outpatients: The Nambu Cohort Study. *Hypertens Res* 2020; **43:** 817–823.
21. Oqab Z, Pournazari P, Sheldon RS. What is the impact of frailty

on prescription of anticoagulation in elderly patients with atrial fibrillation?: A systematic review and meta-analysis. *J Atr Fibrillation* 2018; **10:** 1870.
22. Inui TS, Parina R, Chang DC, Inui TS, Coimbra R. Mortality after ground-level fall in the elderly patient taking oral anticoagulation for atrial fibrillation/flutter: A long-term analysis of risk versus benefit. *J Trauma Acute Care Surg* 2014; **76:** 642–649.
23. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012; **366:** 321–329.
24. Andersson T, Magnuson A, Bryngelsson IL, Frøbert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: A Swedish nationwide long-term case-control study. *Eur Heart J* 2013; **34:** 1061–1067.
25. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: Cohort study using electronic health records. *Circulation* 2017; **135:** 2357–2368.
26. Charlton J, Ravindrarajah R, Hamada S, Jackson SH, Gulliford MC. Trajectory of total cholesterol in the last years of life over age 80 years: Cohort study of 99,758 participants. *J Gerontol A Biol Sci Med Sci* 2018; **73:** 1083–1089.
27. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361:** 1139–1151.
28. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; **364:** 806–817.
29. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365:** 981–992.
30. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369:** 2093–2104.
31. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358:** 580–591.
32. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, et al. Mortality trends in patients diagnosed with first atrial fibrillation: A 21-year community-based study. *Am J Coll Cardiol* 2007; **49:** 986–992.