Cardiovascular Events and Mortality in Patients With Atrial Fibrillation and Anemia (from the Fushimi AF Registry)

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Data regarding the associations of anemia (hemoglobin level <13.0 g/dl in men and <12.0 g/dl in women) with clinical outcomes in patients with atrial fibrillation (AF) remains scarce. This study sought to investigate the associations of anemia with the incidences of stroke or systemic embolism, major bleeding, heart failure (HF) hospitalization, and all-cause mortality including its causes, using the data from a Japanese community-based survey, the Fushimi AF Registry. A total of 4,169 AF patients were divided into the 3 groups, based on the baseline hemoglobin level: no (n = 2,622), mild (11.0 to <13.0 g/dl for men and <12.0 g/dl for women; n = 880), and moderate/severe anemia (<11.0 g/dl; n = 667). During a median follow-up of 1,464 days, the incidences of major bleeding, HF hospitalization, and mortality increased with higher rates of cardiac death, in accordance with anemic severity. On multivariate analyses, the higher risk of moderate/severe anemia, relative to no anemia, for major bleeding remained statistically significant (hazard ratio [HR]: 2.00, 95% confidential interval [CI]: 1.48 to 2.72). The risks of those with anemia, relative to no anemia, for HF hospitalization (mild; HR: 1.87, 95% CI: 1.51 to 2.31, and moderate/severe; HR: 2.02, 95% CI: 1.59 to 2.57) as well as for mortality (mild; HR: 1.80, 95% CI: 1.50 to 2.16, and moderate/severe; HR: 2.95, 95% CI: 2.45 to 3.55) were also higher, but not for stroke/systemic embolism. These relations were consistent, regardless of the use of oral anticoagulants. In conclusion, anemia was associated with higher risks of HF hospitalization, mortality, and major bleeding in AF patients. **(Am J Cardiol 2020;134:74−82)**

Anemia is a common condition and its prevalence becomes higher along with an aging population,[1] as well as with atrial fibrillation (AF).[2] Importantly, pre-existing anemia has been shown to be associated with a 2-fold higher risk of major bleeding among AF patients on oral anticoagulant (OAC) in the subanalyses of clinical trials.[3,4] However, the results might not be extrapolated to all of the patients with anemia, given that those with moderate to severe anemia were excluded from those trials. In addition, although the higher risk of all-cause mortality in AF patients with anemia has also been shown in some clinical studies,[3−5] data on specific causes of death in addition to mortality are limited in the clinical practice. The objective of this study was to examine the differences in the incidences of cardiovascular (CV) events and all-cause mortality including its causes, depending on the severity of anemia, in a community-based cohort of Japanese AF patients.

Methods

The detailed study design, patient enrollment, the definition of the measurements, and baseline clinical characteristics of the Fushimi AF Registry were previously described

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(UMIN Clinical Trials Registry: UMIN000005834).[6] 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 81 participating institutions comprised 2 CV centers, 9 small- and medium-sized hospitals, and 70 primary care clinics, all of which are members of Fushimi-Ishikai (Fushimi Medical Association). We started to enroll patients from March 2011. 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.

The study patients were categorized into 3 groups based on the hemoglobin (Hb) values at the time of enrollment, according to the standard World Health Organization classification of anemia: no anemia (Hb ≥13.0 g/dl for men, and ≥12.0 g/dl for women), mild anemia (Hb: 11.0 to <13.0 g/dl for men and <12.0 g/dl for women), and moderate (Hb: 8.0 to <11.0 g/dl)/severe anemia (Hb <8.0 g/dl).[7] The definition of pre-existing heart failure (HF) used in this study was having one of the following at enrollment: (1) history of hospitalization for HF prior to the enrollment, (2) symptomatic HF (New York Heart Association class ≥2), or (3) decreased left ventricular ejection fraction (<40%).[8] Type of AF was classified into 2 groups: paroxysmal AF and sustained (persistent or permanent) AF.[9] Renal dysfunction was diagnosed as the estimated glomerular filtration rate <60 ml/min/m^2 at baseline. OAC included warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Antiplatelet drugs (APD) included aspirin, clopidogrel, ticlopidine, and cilostazol. OAC and APD usage were based on the prescription data at enrollment.

The end points in this study were the incidences of stroke or systemic embolism (SE), major bleeding, HF hospitalization, and all-cause death during the follow-up period. Causes of death were adjudicated after consideration of all the available information, as reported previously.[10] Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery, and the diagnosis of ischemic or hemorrhagic stroke was confirmed by computed tomography or magnetic resonance imaging. SE was defined as an acute vascular occlusion of an extremity or organs. Major bleeding was defined based on the criteria of the International Society on Thrombosis and Haemostasis.[11] Admission for HF was determined by the attending physician based on history, clinical presentation, chest radiography, echocardiography, cardiac catheterization findings, and in-hospital course.

Continuous variables were expressed as mean ± standard deviation, or median and interquartile range according to the distributions and compared using 1-way analysis of variance or Kruskal-Wallis test on the basis of their distributions. 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. To adjust for the clinically relevant variables, we used the multivariable Cox proportional hazard model to estimate the hazard ratio (HR) and their 95% confidence interval (CI) for the risk of mild and moderate/severe anemia, respectively, relative to no anemia for clinical outcomes. In addition to anemic severity as categorical variables, we selected clinical variables for adjustment, based on the previous reports and consideration of clinical relevance as follows: (1) 10 risk-adjusting variables for stroke/SE based on the CHA_2DS_2-VASc score,[12] the type of AF,[13] the usage of OAC, and the creatinine clearance[14]; (2) 9 risk-adjusting variables for major bleeding on the basis of the HAS-BLED score[15] (except for the factor "L" (labile international normalized ratio), the usage of OAC, and the creatinine clearance[14] for adjustment of renal function; (3) 14 risk-adjusting variables for HF hospitalization[9]; and (4) 21 risk-adjusting variables for all-cause death,[10] as described in the footnote of Table 1. To reduce the effect of potential confounding in this observational study, we performed rigorous adjustment for the differences in the baseline characteristics using propensity score matching. The covariates entered into the propensity score were clinically relevant factors including all of the risk-adjusting variables for end points above-mentioned in (1 to 4), as described in the footnote of Tables S1 and S2. The propensity score-matched pairs were created by matching mild-anemia versus no anemia, and M-S anemia versus no anemia groups, on the basis of the nearest neighbor pair-matching algorithm with a 0.20 caliper width using JMP version 15 (SAS Institute, Cary, NC). A matching ratio of 1:1 was used. Two-sided p values less than 0.05 were considered statistically significant.

Results

Of 4,875 patients who were enrolled by the end of November 2017, follow-up data (collected annually) were available for 4,454 patients as of November 2018 (follow-up rate: 91.3%). Of these, the current study population consisted of 4,169 patients with available Hb values at diagnosis, after excluding 285 patients due to the absence of baseline characteristics including Hb value at enrollment. The median follow-up period was 1,464 (interquartile range: 725 to 2,219) days.

The distribution of Hb level among the entire study population, and those of males and females are shown in Figure 1. There were 2,622 patients (63%) without anemia, 880 (21%) patients with mild anemia, 667 patients (16%) with moderate/severe (moderate: 615 patients, and severe: 52 patients) anemia. The baseline patient characteristics were different in several aspects across the three groups (Table 1). Patients with anemia were older and more often had lower body mass index, and co-morbidities. Consequently, risk scores for thromboembolism ($CHADS_2$ and CHA_2DS_2-VASc scores) were higher in patients with anemia. The use of APDs and diuretics were more prevalent depending on the severity of anemia, whereas OACs were prescribed less commonly in patients with moderate/severe anemia.

The cumulative incidences of stroke/SE, major bleeding, HF hospitalization, and all-cause death were all significantly higher in patients with moderate/severe anemia, as well as in those with mild anemia compared with those

Table 1
Baseline clinical characteristics

Variable	Overall n = 4,169	No anemia n = 2,622	Mild anemia n = 880	Moderate/severe anemia n = 667	p Value
Women*,‡,§	1,692 (41%)	1,018 (39%)	304 (35%)	370 (55%)	<0.001
Age (years)‡,§, mean ± SD	73.8 ± 10.7	71.2 ± 10.5	77.5 ± 8.9	79.3 ± 9.9	<0.001
Age groups					<0.001
≤64†	700 (17%)	591 (23%)	66 (8%)	43 (6%)	
65-74*	1,319 (32%)	955 (36%)	228 (25%)	136 (20%)	
≥75*	2,150 (51%)	1,076 (41%)	586 (67%)	488 (73%)	
BMI (kg/m^2)‡,§, mean ± SD	23.1 ± 4.1	23.8 ± 3.9	22.4 ± 3.7	21.4 ± 4.3	<0.001
Type of AF*,‡,§					0.010
Paroxysmal AF	2,044 (49%)	1,242 (47%)	468 (53%)	334 (50%)	
Sustained AF (persistent/permanent)	2,124 (51%)	1,380 (53%)	412 (47%)	333 (50%)	
Previous cardiac device implantation	311 (7%)	171 (7%)	76 (9%)	64 (10%)	0.010
Calculated CrCl (ml/min)*,†, median, (25%, 75%)	54.1 (35.0, 74.1)	61.7 (44.0, 80.8)	47.3 (32.3, 64.6)	33.8 (18.6, 49.3)	<0.001
Excess alcohol†	794 (19%)	576 (22%)	151 (17%)	67 (10%)	<0.001
$CHADS_2$ score, mean ± SD	2.07 ± 1.32	1.86 ± 1.28	2.34 ± 1.28	2.57 ± 1.36	<0.001
CHA_2DS_2-VASc score, mean ± SD	3.43 ± 1.68	3.11 ± 1.64	3.77 ± 1.57	4.22 ± 1.60	<0.001
History of stroke/TIA*,†,‡,§	809 (19%)	474 (18%)	175 (20%)	100 (24%)	0.003
Pre-existing HF*,†,‡,§	1,190 (29%)	574 (22%)	317 (36%)	299 (45%)	<0.001
Hypertension*,†,‡,§	2,673 (64%)	1,675 (64%)	567 (64%)	431 (65%)	0.92
Diabetes mellitus*,‡,§	1,009 (24%)	594 (23%)	236 (27%)	179 (27%)	0.010
Dyslipidemia§	1,897 (46%)	1,317 (50%)	342 (39%)	238 (36%)	<0.001
Renal dysfunction‡,§	2,047 (50%)	1.067 (41%)	502 (57%)	478 (72%)	<0.001
Liver dysfunction†	62 (1%)	34 (1%)	13 (1%)	15 (2%)	0.22
Valvular heart disease‡	739 (18%)	370 (14%)	183 (21%)	186 (28%)	<0.001
Prior myocardial infarction*,‡,§	259 (6%)	116 (4%)	81 (9%)	62 (9%)	<0.001
Cardiomyopathy‡	119 (3%)	81 (3%)	23 (3%)	15 (2%)	0.44
Peripheral artery disease*,‡,§	178 (4%)	95 (4%)	48 (5%)	35 (5%)	0.030
Chronic obstructive pulmonary disease‡,§	228 (5%)	134 (5%)	66 (8%)	28 (4%)	0.010
History of major bleeding†,§	195 (5%)	76 (3%)	59 (7%)	59 (9%)	<0.001
Prescription at baseline					
Oral anticoagulant*,†,§	2,347 (56%)	1,507 (57%)	518 (59%)	322 (48%)	<0.001
Warfarin	1,720 (41%)	1,077 (41%)	380 (43%)	263 (39%)	0.32
NOAC	627 (15%)	430 (16%)	138 (16%)	59 (9%)	<0.001
Anti-platelet drug†,§	1,141 (27%)	640 (24%)	273 (31%)	228 (34%)	<0.001
Diuretics§	1,240 (30%)	616 (23%)	314 (36%)	310 (46%)	<0.001
ACE-I/ARB§	1,896 (45%)	1,146 (44%)	429 (49%)	321 (48%)	0.011
Digitalis§	468 (11%)	304 (12%)	97 (11%)	67 (10%)	0.51
Beta-blocker§	1,298 (31%)	805 (31%)	270 (31%)	223 (33%)	0.38
Statins§	1,057 (25%)	712 (27%)	220 (25%)	125 (19%)	<0.001

CrCl = creatinine clearance; AF = atrial fibrillation; TIA = transient ischemic attack; Renal dysfunction = estimated glomerular filtration rate <60 ml/min/m^2; HF = heart failure; NOAC = non-vitamin K oral anticoagulant; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

Categorical data are presented as number (%). Continuous data are presented as mean ± standard deviation (SD), or median and interquartile range (25%, 75%) according to the distribution.

* Potential variables for the multivariable Cox regression model to estimate the risk for stroke/SE, as follows; the components of CHA_2DS_2-VASc score (the factor "V" is defined as the composite of previous myocardial infarction and peripheral artery disease), the type of AF, oral anticoagulant, and CrCl as the 3 categorical variables (CrCl <30 ml/min, CrCl 30 to 49 ml/min, and CrCl ≥50 ml/min).

† Potential variables for the multivariable Cox regression model to estimate the risk for major bleeding, as follows; the components of HAS-BLED score except for the factor "L" (labile international normalized ratio), oral anticoagulant, and CrCl as the 3 categorical variables (CrCl <30 ml/min, CrCl 30 to 49 ml/min, and CrCl ≥50 ml/min) for adjustment of renal function.

‡ Potential variables for the multivariable Cox regression model to estimate the risk for HF hospitalization, as follows; age (per 10 years), women (vs men), body mass index, sustained AF (vs paroxysmal AF), pre-existing HF, hypertension, diabetes mellitus, history of stroke or TIA, peripheral artery disease, previous myocardial infarction, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, and renal dysfunction.

§ Potential variables for the multivariable Cox regression model to estimate the risk for all-cause death, as follows; age (per 10 years), women (vs men), body mass index, sustained AF (vs paroxysmal AF), pre-existing heart failure, hypertension, diabetes mellitus, history of stroke or TIA, peripheral artery disease, previous myocardial infarction, chronic obstructive pulmonary disease, renal dysfunction, dyslipidemia, previous major bleeding, prescription of ACE-I/ARB, β-blocker, antiplatelet drug, oral anticoagulant, diuretics, digitalis, and statin.

without anemia (Figure 2). This was evident in both patients with and without OAC (Figures S1 and S2). The specific causes of death between the 3 subgroups stratified by the severity of anemia are shown in Figure 3. The proportions of malignancy and infection were comparable among the 3 groups. The percentage of cardiac deaths was higher with anemic severity. As Figure 4 shows, all of the event rates of specific causes of death were higher with worsening anemia. The event rates of each cause of death were largely higher in patients without OAC compared

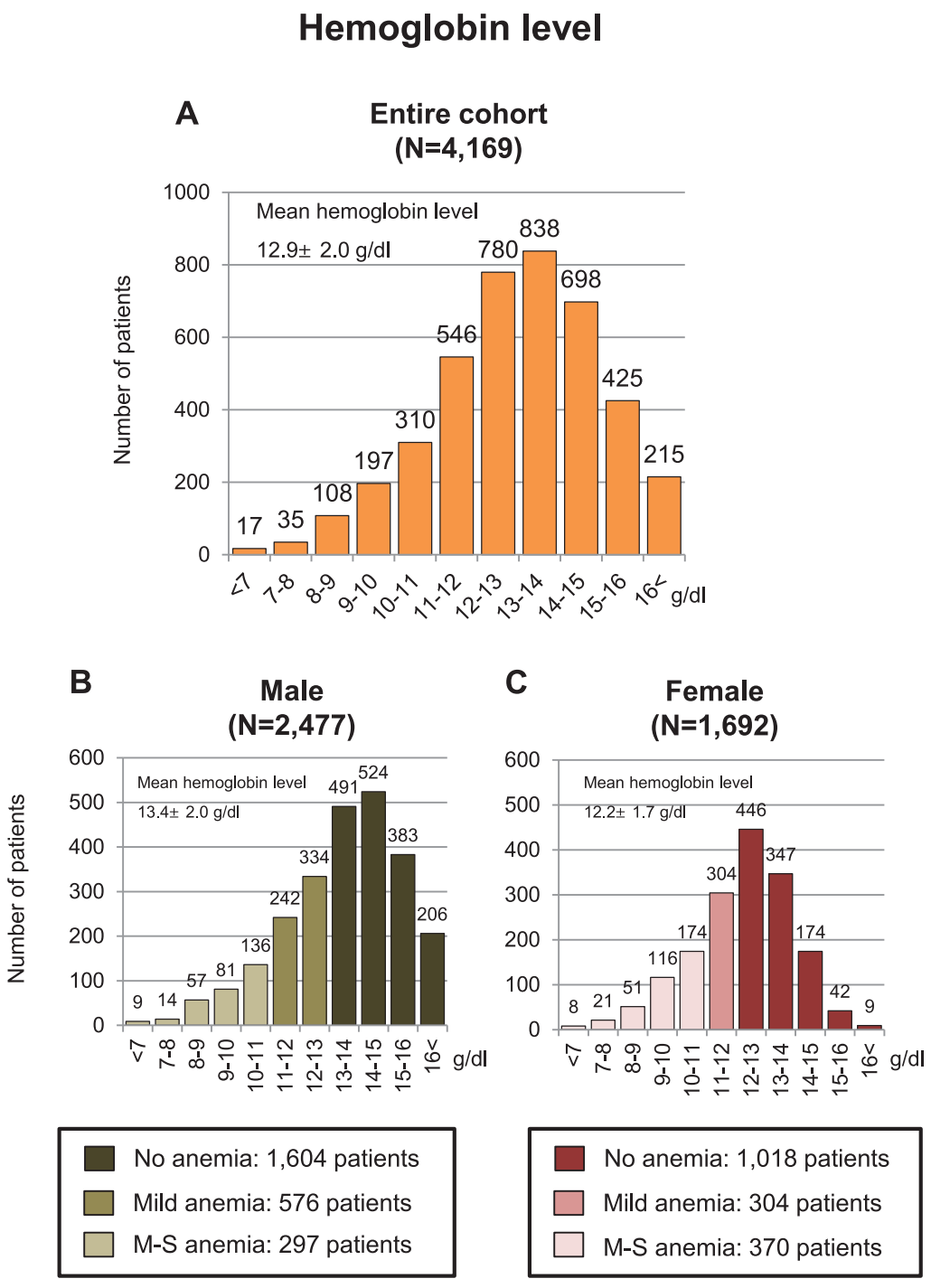


Figure 1. The distributions of hemoglobin level (*A*) in the entire cohort, and among (*B*) male and (*C*) female patients. M-S = moderate/severe.

with those with OAC, even when their anemic status was mild (Figures S3 and S4). The unadjusted HRs for cardiac death, mainly due to HF, were particularly high; 3.50 (95% CI: 2.27 to 5.39) in patients with mild anemia, and 8.57 (95% CI: 5.79 to 12.8) in those with moderate/severe anemia (Figure 4). Multivariate analysis was not performed for each specific cause of death given the limited number of events.

On multivariate Cox regression analysis (Table 2), the risks for stroke/SE in patients with mild and moderate/severe anemia were not different from patients without anemia. This was also the case in both patients with and without OAC at baseline. The risks for major bleeding in patients with mild (adjusted HR: 1.35, 95% CI: 1.03 to 1.79) and moderate/severe anemia (adjusted HR: 2.00, 95% CI: 1.48 to 2.72) were significantly higher than that in patients without anemia. Both mild and moderate/severe anemia were significantly associated with increased risk for HF hospitalization (mild; adjusted HR: 1.87, 95% CI: 1.51 to 2.31; moderate/severe; adjusted HR: 2.02, 95% CI: 1.59

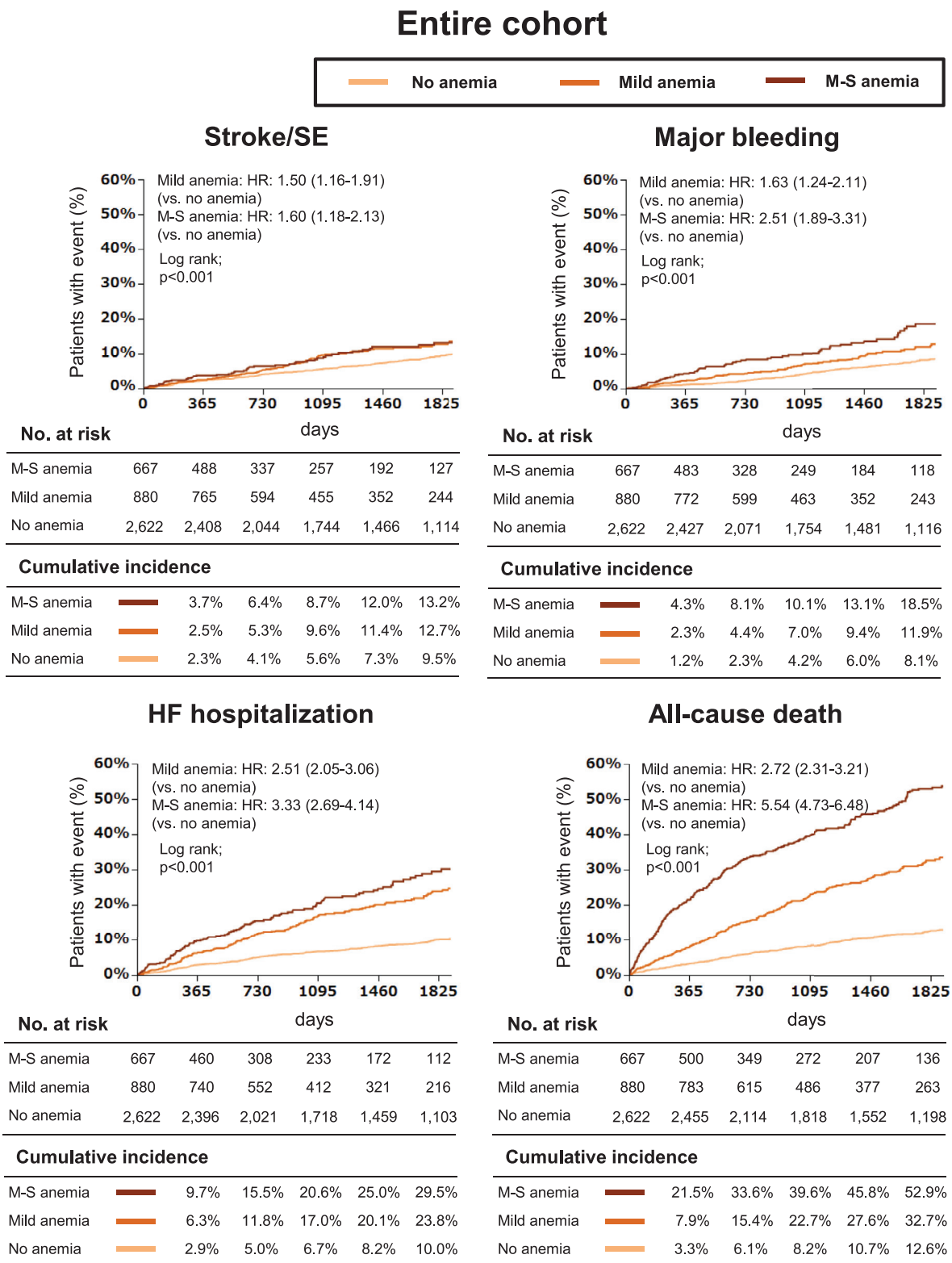
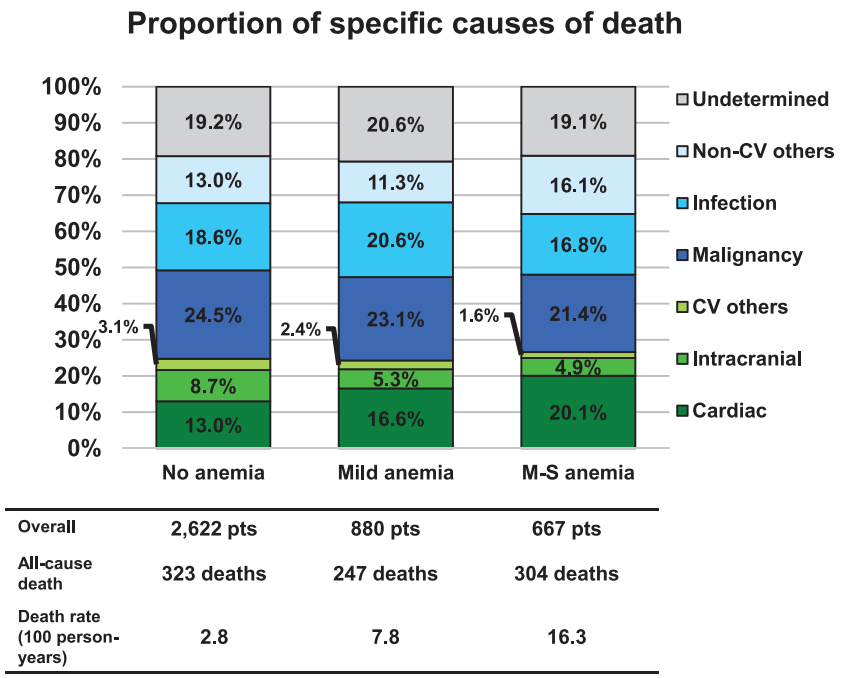


Figure 2. Kaplan-Meier curves for the incidences of (*A*) stroke/SE, (*B*) major bleeding, (*C*) HF hospitalization, and (*D*) all-cause death among the three groups in the entire cohort. SE = systemic embolism. HF = heart failure; M-S = moderate/severe.

to 2.57), and all-cause death (mild; adjusted HR: 1.80, 95% CI: 1.50 to 2.16; moderate/severe; adjusted HR: 2.95, 95% CI: 2.45 to 3.55), compared with those without anemia. These relations were also observed consistently among patients both with and without OAC. Since the clinical characteristics among the 3 groups were substantially different, we further perform propensity score matching analysis; 705 matched pairs of mild anemia versus no anemia



	No anemia	Mild anemia	M-S anemia
Overall	2,622 pts	880 pts	667 pts
All-cause death	323 deaths	247 deaths	304 deaths
Death rate (100 person-years)	2.8	7.8	16.3

Figure 3. The proportions of specific causes of death among the three groups in the entire cohort. M-S = moderate/severe; CV = cardiovascular. CV others as a cause of death include all of the CV causes such as systemic embolism or extracranial bleeding, except for cardiac and intracranial ones. Non-CV others as a cause of death include all of the non-CV causes such as renal failure, except for malignancy and infection.

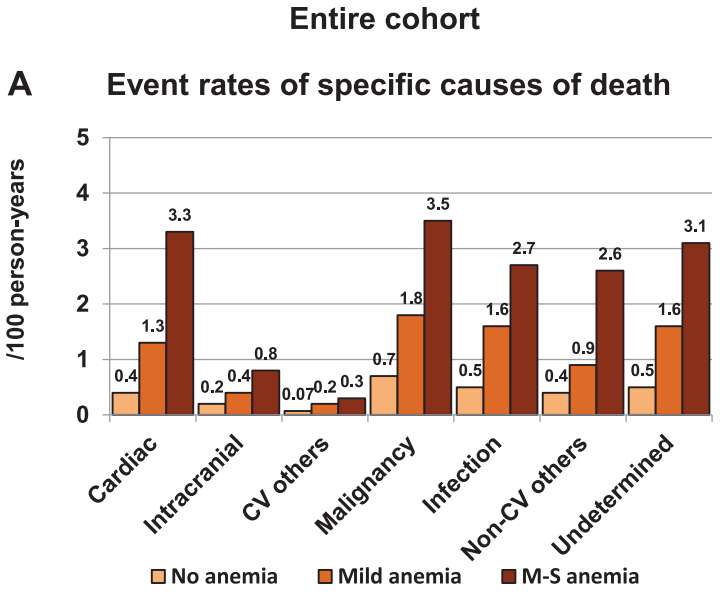
groups, and 429 matched pairs of M-S anemia versus no anemia group were compared (baseline characteristics shown in Tables S1 ad S2). Mild anemia was associated with higher incidences of HF hospitalization and all-cause death (Figure S5), whereas moderate/severe anemia was associated with higher incidences of major bleeding, HF hospitalization, and all-cause death (Figure S6).

Discussion

The principal findings of the current study in a Japanese community-based AF cohort were as follows: (1) moderate/severe anemia compared with no anemia in AF patients was associated with a significantly higher risk for long-term major bleeding events; (2) anemia, even if mild, was associated with higher risks for HF hospitalization and all-cause death, particularly due to cardiac causes, but was not related to that of stroke/SE.

Anemia has been previously shown to be associated with an increased risk of bleeding events in patients with AF[3,4,16] and other conditions, such as venous thromboembolism[17] and CV interventions.[18] In AF, the randomized clinical trials of nonvitamin K antagonist OACs[3,4] excluded patients with moderate/severe anemia (Hb <10 g/dL or 9 g/dL, respectively), the relation between anemia and clinical events was not fully investigated in clinical trial patients with AF. In a recent analysis of data from the Danish nationwide registry between 1997 and 2012,[16] a total of 14% of patients had moderate/severe anemia at baseline, and they were associated with an increased risk of bleeding, regardless of whether or not patients received OAC prescription. This relation was consistent with the present study, where 16% of the entire cohort had moderate/severe anemia at baseline. Anemia itself might be a good indicator of occult bleeding and/or general vascular frailty, both likely to be associated with the further major bleeding events, although the detailed mechanism for this relation still remains uncertain. Meanwhile, the relation of anemia to the risk of thromboembolic events is controversial where a significant relation has been observed in some studies,[3] but not in others.[4] The present study also revealed no significant relation between the risk of stroke/SE and anemia. These findings in the present study suggest that greater awareness, and more careful mitigation strategies against bleeding events should be warranted among patients with moderate/severe anemia, balancing the harm and benefit of treatment. Indeed, regular assessment and mitigation of modifiable bleeding risks can be associated with a reduction in bleeding outcomes, and an improvement in OAC use among AF patients.[19] Further investigation will be needed to clarify whether anemia should be included in bleeding risk scores.

Anemia was associated with increased mortality in patients with various CV and non-CV diseases such as coronary artery disease,[20] HF,[21] and cancer.[22] Among patients with AF, a significant relation between anemia and increased mortality has been shown in randomized controlled trials[3,4] and observational studies.[5,23] In the present study, not only moderate/severe anemia but also mild anemia is associated with higher all-cause mortality, compared with those without anemia. Meanwhile, the incidences of death and major bleedings tended to be higher in patients without OAC than those with OAC, although they were not compared statistically. We speculated that these differences might have been due to less likelihood of patients with high mortality or bleeding risk to receive OAC. A recent study also revealed that major bleeding during OAC treatment in patient with AF was associated with a substantially



B Hazard ratios for specific causes of death

	Unadjusted hazard ratio (95% CI)	
	Mild anemia (vs. no anemia)	M-S anemia (vs. no anemia)
Cardiac	3.50 (2.27-5.39)	8.57 (5.79-12.8)
Intracranial	1.65 (0.83-3.15)	3.07 (1.59-5.71)
CV others	2.63 (0.86-7.56)	3.60 (1.08-10.8)
Malignancy	2.56 (1.81-3.59)	4.87 (3.49-6.76)
Infection	3.10 (2.13-4.51)	5.19 (3.55-7.56)
Non-CV others	2.39 (1.47-3.86)	6.88 (4.54-10.5)
Undetermined	2.92 (2.01-4.23)	5.53 (3.85-7.93)

Figure 4. (*A*) Event rate and (*B*) unadjusted hazard ratio of specific causes of death among the 3 groups in the entire cohort. M-S = moderate/severe; CV = cardiovascular; CI = confidence interval.

increased subsequent risk of both death and of thrombotic events such as ischemic stroke or myocardial infarction.[24] This might be caused by rebound pro-thrombotic reactivity due to the discontinuation of OAC after bleeding. Importantly, in the present study, each mortality due to the specific causes was higher in accordance with the severity of anemia, being greatest in cardiac death, mainly from HF. This was consistent with the higher incidence of HF hospitalization in patient with anemia. Previous reports[25,26] have demonstrated that anemia was associated with an increased risk for cardiac events in patients with AF. This association can be explained by the fact that anemia is associated with CV compensatory changes including high cardiac output, low systemic vascular resistance, and sodium and water retention increasing the cardiac workload,[27] leading to left ventricular hypertrophy and subsequent HF worsening. In addition, the present study showed the negative impact of anemia on mortality in non-CV causes as well as CV ones. It remains uncertain whether anemia is a direct cause of the increased mortality, or a marker of the co-morbidities and a greater frailty, linking to the worse prognosis. Further studies will be needed whether the identification, precise evaluation, and treatment of anemia, especially if related to modifiable factors, might lead to an improvement in outcomes for patients with AF.

The present study has several limitations. First, the statistical analysis was based only on clinical details at the time of enrollment. Thus, longitudinal changes in clinical backgrounds including Hb level and treatments were not taken into consideration during the follow-up period. Second, the results were derived from a prospective observational study; therefore, we show associations and not a causality, with the limitations inherent to the study design such as selection bias and unmeasured confounders, despite adjustment for clinically relevant factors by using multivariate analyses as well as propensity score matchings. Third,

Table 2
Event rates and multivariate adjusted hazard ratios for the end points among subgroups

Variable	Overall (n = 4,169)				With OAC (n = 2,347)				Without OAC (n = 1,822)			
	Event number	Event rate	Adjusted HR (95% CI)	p Value	Event number	Event rate	Adjusted HR (95% CI)	p Value	Event number	Event rate	Adjusted HR (95% CI)	p Value
Stroke/SE												
No anemia	214	1.9%	Reference		126	2.0%	Reference		88	1.8%	Reference	
Mild anemia	88	2.9%	1.21 (0.93-1.57)	0.16	55	3.0%	1.20 (0.86-1.67)	0.29	33	2.8%	1.26 (0.82-1.93)	0.29
M-S anemia	56	3.1%	1.17 (0.85-1.61)	0.33	27	2.9%	1.10 (0.71-1.72)	0.66	29	3.3%	1.32 (0.82-2.10)	0.25
Major bleeding												
No anemia	181	1.6%	Reference		120	1.9%	Reference		61	1.2%	Reference	
Mild anemia	78	2.6%	1.35 (1.03-1.79)	0.031	46	2.5%	1.22 (0.86-1.74)	0.27	32	2.7%	1.65 (1.06-2.60)	0.028
M-S anemia	68	3.9%	2.00 (1.48-2.72)	<0.001	37	4.2%	2.04 (1.37-3.03)	<0.001	31	3.6%	2.00 (1.24-3.24)	0.004
HF hospitalization												
No anemia	248	2.3%	Reference		156	2.5%	Reference		92	1.9%	Reference	
Mild anemia	162	5.7%	1.87 (1.51-2.31)	<0.001	108	6.4%	1.86 (1.43-2.42)	<0.001	54	4.7%	1.91 (1.31-2.77)	<0.001
M-S anemia	127	7.7%	2.02 (1.59-2.57)	<0.001	77	9.5%	2.40 (1.79-3.24)	<0.001	50	5.9%	1.59 (1.04-2.41)	0.032
All-cause death												
No anemia	323	2.8%	Reference		177	2.7%	Reference		146	2.9%	Reference	
Mild anemia	247	7.8%	1.80 (1.50-2.16)	<0.001	123	6.4%	1.69 (1.25-2.06)	<0.001	124	10.0%	2.04 (1.56-2.67)	<0.001
M-S anemia	304	16.3%	2.95 (2.45-3.55)	<0.001	136	14.0%	3.09 (2.40-3.96)	<0.001	168	18.8%	2.87 (2.18-3.77)	<0.001

CI = confidence interval; OAC = oral anticoagulant; HR = hazard ratio; M-S = moderate/severe.
Event rates are presented at percentage of 1 person-year.
The total numbers of subgroups among overall population; no anemia: 2,622, mild anemia: 880, and M-S anemia: 667.
Those among patients with OAC; no anemia: 1,507, mild anemia: 581, and M-S anemia: 322.
Those among patients without OAC; no anemia: 1,115, mild anemia: 362, and M-S: 345.

the present study was conducted in an urban district in Japan, and the results cannot be easily extrapolated to other rural areas or countries. Fourth, about 9% of patients were lost during follow-up, and about 6% were excluded from this study population due to the lack of baseline data including Hb level, which could result in a selection bias. Fifth, we did not evaluate the causes of anemia or the time since diagnosis of anemia. Some clinical situations such as occult bleeding and/or malignancy could have potentially influenced Hb levels. There may be some differences in characteristics and prognostic impacts of anemia between patients with chronic anemia and those who developed incident anemia. Sixth, the quality of anticoagulation with time in therapeutic range by warfarin and OAC adherence were not investigated during the follow-up. In addition, we did not collect the data on dementia or any cognitive impairment disorder, which is often associated with adherence of medical treatment. Finally, we did not have a control group (patients without AF) that would have allowed us to compare the prognostic impacts of anemia on cardiovascular events, mortality, and its causes between in patients with and without AF.

Author Contribution

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Mitsuru Ishii: Data Curation
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Disclosures

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Supplementary materials

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