Received: 22 March 2023 | Revised: 26 May 2023 | Accepted: 5 June 2023

DOI: 10.1002/joa3.12885

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Impact of anemia on major bleeding in patients taking oral anticoagulants for nonvalvular atrial fibrillation

Norito Kinjo MD[1,2] | Shinichiro Ueda MD, PhD[3] | Kazutaka Uchida MD, PhD[1,2] | Fumihiro Sakakibara MD[1,2] | Mari Nezu MD[1] | Hideki Arai MD[1] | Takeshi Morimoto MD, PhD, MPH[1]

[1]Department of Clinical Epidemiology, Hyogo Medical University, Nishinomiya, Japan

[2]Department of Neurosurgery, Hyogo Medical University, Nishinomiya, Japan

[3]Department of Clinical Pharmacology and Therapeutics, University of the Ryukyus, Nishihara, Japan

Correspondence
Takeshi Morimoto, Department of Clinical Epidemiology, Hyogo Medical University, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan.
Email: morimoto@kuhp.kyoto-u.ac.jp

Funding information
Bristol-Myers Squibb

Abstract

Background: Anemia is encountered in patients with nonvalvular atrial fibrillation (NVAF) on oral anticoagulants (OACs) but the prognostic impact was not well scrutinized in real-world settings.

Methods: We conducted a historical multicenter registry of patients with NVAF taking OACs at 71 centers in Japan. Those with mechanical heart valves or a history of pulmonary thrombosis or deep venous thrombosis were excluded. Anemic patients were divided into three groups of hemoglobin (Hb) level: moderate/severe (Hb < 11.0 g/dL), mild (men: Hb of 11.0–12.9 g/dL; women: Hb of 11.0–11.9 g/dL), and no anemia. The endpoints included major bleeding, hemorrhagic stroke, ischemic events, ischemic stroke, and all-cause mortality.

Results: Among 7558 consecutive patients (mean age, 73 years; men 67%) registered in February 2013 and followed until February 2017, 2100 (28%) patients had anemia. The anemic patients were older (moderate/severe: 79 years; mild: 77 years; no anemia: 71 years, $p < .001$), and HAS-BLED score was significantly higher in the anemic patients ($p < .001$). The cumulative incidences at 4 years of major bleeding in moderate/severe, mild, and no anemia group, were 14.9%, 10.7%, and 6.4%, respectively. The adjusted hazard ratios (HRs) (95% confidential intervals (CIs)) of major bleeding of moderate/severe and mild anemia group were 1.96 (1.49–2.58) and 1.48 (1.17–1.87) compared to no anemia group. The adjusted HRs (95% CIs) for ischemic events were 0.63 (0.39–0.99) and 1.03 (0.76–1.39).

Conclusions: The severity of anemia in the patients with NVAF on OACs was associated with major bleeding.

KEYWORDS
anemia, atrial fibrillation, bleeding, oral anticoagulants, registry

1 | INTRODUCTION

Anticoagulation is the standard of care for patients with thrombotic risk due to nonvalvular atrial fibrillation (NVAF), which is inevitably associated with the risk of hemorrhagic complications.[1] We thus need to pay attention to patients with high bleeding risks. The commonly used bleeding risk score for such patients is the HAS-BLED score, which consists of hypertension, history of stroke, renal or liver dysfunction, history of major bleeding, labile anticoagulation control, elderly patients (>65 years), and concomitant use of drugs or alcohol.[2] The HAS-BLED score is well established and routinely used in clinical practice, but the definition of each component should be investigated. One of the components of HAS-BLED is B, which was defined as a history of bleeding events or predisposition of bleeding. However, there are no reports, including original studies, that defined anemia as a bleeding predisposition.

Patients with NVAF were generally senile, and the mean age was reported as 75 years in Asia and 70 years in the United States from the claim database.[3,4] As a result, these patients had many comorbidities or abnormalities in laboratories when oral anticoagulants (OACs) were administered. Although anemia is one of the commonly encountered conditions of the elderly in daily clinical practice, the data on the prevalence and effects of anemia in patients with NVAF in daily clinical practice are scant.[5]

In addition, randomized clinical trials of OACs generally excluded those with severe anemia (hemoglobin (Hb) < 10 g/dL in RE-LY trial; Hb < 9 g/dL in ARISTOTLE trial).[6,7] Even without evidence of efficacy and safety of OACs in such populations, as well as the prevalence of severe anemia, physicians or patients should consider the use of OACs in conjunction with the current risk stratification on HAS-BLED score for anemia. Thus, it should be helpful in clinical practice to estimate the prevalence of anemic patients among those with NVAF on OACs and compare the bleeding risks according to the degree of anemia. We thus analyzed a large historical registry of consecutive patients with NVAF taking OACs in daily clinical practice.

2 | METHODS

We conducted a historical registry study at 71 centers in Japan. We enrolled patients with NVAF taking OACs on February 26, 2013, and followed them until February 25, 2017. We included patients who received a vitamin K antagonist on February 26, 2013, and excluded those with mechanical heart valves or a history of pulmonary thrombosis or deep vein thrombosis (DVT). The institutional review boards of all 71 participating centers approved the study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and waived the need for written informed consent.

2.1 | Data collection and definitions

A review of hospital charts provided the clinical information at baseline, 1, 2, 3, and 4 years of follow-up. Contacting patients or referring physicians was utilized if necessary. We collected data on patient characteristics, laboratory data, risk of ischemic strokes ($CHADS_2$ score), and risk of hemorrhagic stroke (HAS-BLED score) at baseline. Definitions of baseline characteristics were described previously.[8] The $CHADS_2$ score was developed to estimate stroke risks in patients with NVAF,[9] and the HAS-BLED score was developed to predict major bleeding in anticoagulation for such patients.[2]

Baseline Hb at the inclusion of each cohort was used. World Health Organization (WHO) defined anemia as an Hb level < 13.0 g/dL for men and < 12.0 g/dL for women.[10] According to the WHO definition, we categorized all patients into three groups: moderate/severe anemia (Hb level < 11.0 g/dL both for men and for women); mild anemia (Hb level of 11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women), and no anemia (Hb level ≥ 13.0 g/dL for men and ≥12.0 g/dL for women). The patients without baseline Hb data were excluded from this analysis.

2.2 | Endpoints

The primary endpoint was major bleeding. Major bleeding was defined by the International Society on Thrombosis and Hemostasis criteria.[11] Other endpoints included hemorrhagic stroke, including intracerebral hemorrhage and subarachnoid hemorrhage, ischemic events, ischemic stroke including transient ischemic attack, and all-cause mortality. Intracerebral hemorrhage was defined as a high-density area on computed tomography (CT) or a hyperintensity area on magnetic resonance imaging (MRI) T1-weighted images, indicating bleeding in the brain parenchyma.[12] Subarachnoid hemorrhage was defined as a high-density area on CT or a hyperintensity area on MRI with fluid-attenuated inversion recovery in the subarachnoid space. Ischemic events were defined as ischemic stroke, including transient ischemic attack and systemic embolism.[13]

2.3 | Statistical analysis

We compared patient characteristics and endpoints among the moderate/severe anemia, mild anemia, and no anemia groups. Continuous variables are presented as mean and standard deviation or median and interquartile range, and categorical variables are numbers and percentages. Continuous variables were compared using ANOVA or the Kruskal–Wallis test based on their distribution and categorical variables using the chi-square test. All patients were censored on the day of the first major bleeding, ischemic events, death, or the last visit if patients were not followed up until the 4-year study period. We estimated the incidence of endpoints with cases per 1000 patient-years stratified by the groups. The cumulative incidence was estimated using the Kaplan–Meier method, while intergroup differences were assessed using the log-rank test.

The risks of moderate/severe anemia or mild anemia relative to no anemia for endpoints were estimated using Cox proportional

hazard models and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). We simultaneously included the variables of moderate/severe anemia and mild anemia as the dummy variables in the models, and no anemia was considered as a reference. We adjusted the clinically relevant variables to estimate the adjusted HRs in the multivariable Cox proportional hazard models. The adjusters for hemorrhagic events were HAS-BLED score, history of coronary artery disease (CAD), and statin use. The adjusters for ischemic events were $CHADS_2$ score, CAD, history of major bleeding, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or hemodialysis (HD), and statin use. The adjustment for all-cause mortality was a combination of these factors. As exploratory analyses, we divided patients in the moderate/severe anemia group into moderate anemia and severe anemia separately and constructed the same Cox proportional hazard models. Because the number of patients with severe anemia was small, these analyses should be considered as exploratory. We also conducted sensitivity analyses by dividing the total cohort into cohort with warfarin only (warfarin alone stratum) and cohort switched to DOACs (switch to DOACs stratum) during the study period and constructed the same Cox proportional hazard models for major bleeding and all-cause mortality. The missing values for the binary variables were considered "normal" because data should have been available if abnormalities were suspected. Platelet measurements were missed in 19 patients and were not imputed in this study. There were no further missing data on continuous variables except for Hb and platelets.

We constructed the same multivariable Cox proportional hazard models for the primary endpoint in the subgroups to estimate the adjusted HRs for each subgroup and the interaction *p* values. The subgroups included age (≥75 or <75 years), sex, history of stroke, history of chronic liver disease, history of malignancy, eGFR (≥60, <60 but ≥30, <30 or HD), $CHADS_2$ score (≥2 or <2), HAS-BLED score (≥3 or <3), and use of antiplatelets.

All statistical analyses were conducted using JMP 15.2 (SAS Institute Inc.). All reported *p* values were two-tailed, and *p* values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

We initially registered 8366 patients; of them, 560 were excluded due to conflicting eligibility criteria ($n=16$), unclear information in medical records with OAC use ($n=519$), or erroneous data ($n=5$). In addition, 268 patients without hemoglobin data were excluded from this study (Figure 1). The mean age of the 7558 included patients was 73 years, and 5082 (67%) were men. A total of 2100 (28%) patients had moderate/severe or mild anemia. (Table 1).

The mean age was significantly different among the three groups, and the patients with anemia were older than those without anemia (moderate/severe: 79 years; mild: 77 years; no: 71 years, $p<.001$) (Table 1). There were significantly fewer men in the moderate/severe anemia group than other groups (moderate/severe: 49%; mild: 69%; no: 69%, $p<.001$). The more anemic, the higher number of patients who had a BMI of <25 among the three groups (moderate/severe: 75%; mild: 69%; no: 56%, $p<.001$). Anemic patients were more likely to have a history of ischemic stroke, major bleeding, hypertension, diabetes, heart failure, CAD, and malignancy (Table 1). The anemic patients were significantly less likely to be current smokers (6% vs. 9% vs. 15%, $p<.001$).

In the moderate/severe and mild anemia groups, the $CHADS_2$ score was significantly higher than in the no anemia group ($p<.001$), as was the HAS-BLED score ($p<.001$; Table 1). The prevalence of B score was low even in the moderate/severe anemia group (50/726, 7%). Among 7558 patients on warfarin at baseline, 2097 (28%)

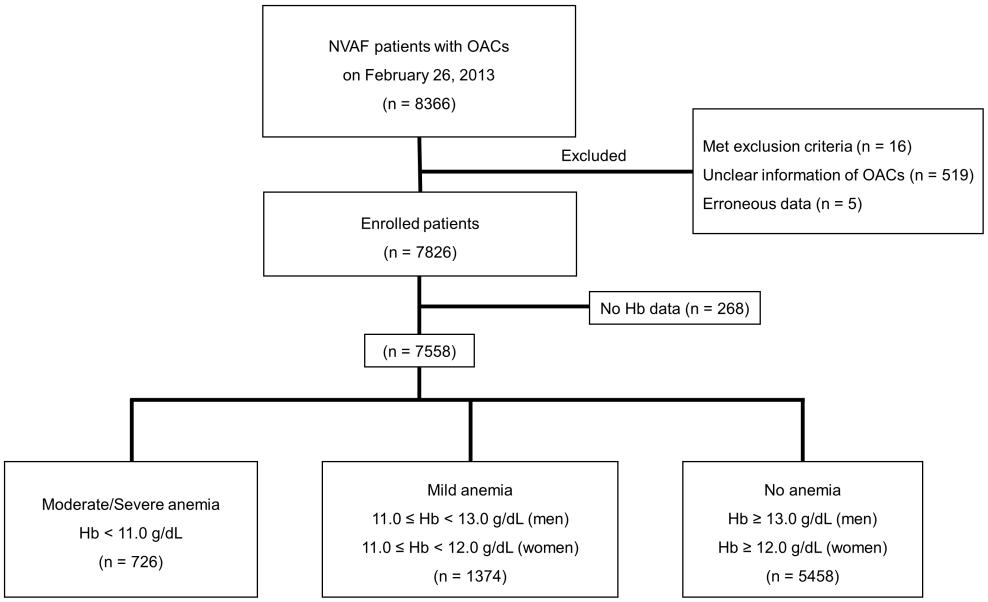


FIGURE 1 Study flowchart. Hb, hemoglobin; NVAF, nonvalvular atrial fibrillation; OACs, oral anticoagulants.

TABLE 1 Patients' characteristics.

	Total ($n=7558$)	Moderate/Severe anemia ($n=726$)	Mild anemia ($n=1374$)	No anemia ($n=5458$)	p value
Age-years, mean (SD)	73 (10)	79 (9)	77 (9)	71 (10)	<.001
Age ≥ 75 years, *n* (%)	3650 (48)	540 (74)	924 (67)	2186 (40)	<.001
Male, *n* (%)	5082 (67)	356 (49)	950 (69)	3776 (69)	<.001
Systolic BP-mmHg, median [IQR]	126 [116–137]	124 [112–135]	126 [113–138]	127 [117–137]	<.001
Heart rate-beats/min, median [IQR]	72 [64–83]	72 [64–81]	71 [63–82]	73 [65–84]	.0003
BMI-kg/m^2, median [IQR]	24 [22–27]	22 [20–25]	23 [21–26]	24 [22–27]	<.001
BMI < 25.0, *n* (%)	4071 (61)	501 (75)	860 (69)	2710 (56)	<.001
TTR-%, median [IQR]	84 [39–100]	71 [28–100]	79 [34–100]	86 [43–100]	<.001
Type of AF					
Paroxysmal, *n* (%)	2532 (34)	253 (35)	507 (37)	1734 (33)	.02
Persistent or permanent, *n* (%)	4065 (54)	378 (52)	693 (50)	2931 (55)	
Unknown, *n* (%)	961 (13)	95 (13)	174 (13)	664 (12)	
History of stroke, *n* (%)	1854 (25)	208 (29)	383 (28)	1263 (23)	<.001
Hemorrhagic stroke, *n* (%)	146 (2)	15 (2)	26 (2)	105 (2)	.96
Ischemic stroke, *n* (%)	1744 (23)	199 (27)	363 (26)	1182 (22)	<.001
History of major bleeding, *n* (%)	271 (4)	50 (7)	58 (4)	163 (3)	<.001
Hypertension, *n* (%)	5916 (78)	594 (82)	1109 (81)	4213 (77)	.0009
Diabetes, *n* (%)	2362 (31)	274 (38)	448 (33)	1640 (30)	<.001
Insulin therapy, *n* (%)	188 (2)	34 (5)	42 (3)	112 (2)	<.001
Heart failure, *n* (%)	3224 (43)	446 (62)	675 (50)	2103 (39)	<.001
History of coronary artery disease, *n* (%)	2030 (27)	248 (34)	445 (33)	1337 (25)	<.001
ACS, *n* (%)	790 (10)	106 (15)	179 (13)	505 (9)	<.001
Peripheral vascular disease, *n* (%)	627 (8)	86 (12)	145 (11)	406 (7)	<.001
COPD, *n* (%)	324 (4)	36 (5)	64 (5)	224 (4)	.4
Chronic liver disease, *n* (%)	584 (8)	57 (8)	112 (8)	415 (8)	.8
Malignancy, *n* (%)	856 (11)	135 (19)	243 (18)	478 (9)	<.001
Current smoker, *n* (%)	2298 (30)	187 (26)	415 (30)	1696 (31)	.014
$CHADS_2$ score, median [IQR]	2 [1–3]	3 [2–3]	3 [2–3]	2 [1–3]	<.001
≥2, *n* (%)	5606 (74)	648 (89)	1162 (85)	3796 (70)	<.001
HAS-BLED score, median [IQR]	2 [1–3]	2 [2–3]	2 [1–3]	2 [1–2]	<.001
≥3, *n* (%)	1973 (26)	311 (43)	471 (34)	1191 (22)	<.001
B score, *n* (%)	271 (4)	50 (7)	58 (4)	163 (3)	<.001
eGFR-mL/min/1.73 m^2, median [IQR]	59 [47–71]	40 [27–57]	51 [40–64]	62 [51–73]	<.001
60 ≤ eGFR, *n* (%)	3587 (47)	151 (21)	458 (33)	2978 (55)	<.001
30 ≤ eGFR<60, *n* (%)	3465 (46)	356 (49)	758 (55)	2351 (43)	
eGFR<30 or Hemodialysis, *n* (%)	506 (7)	219 (30)	158 (12)	129 (2)	
Platelets-×10^4/μL, median [IQR]	180 [151–215]	181 [141–230]	176 [143–214]	181 [154–214]	.03
Platelets<100×10^9/L, *n* (%)	234 (3)	50 (7)	61 (4)	123 (2)	<.001
Switch to DOACs, *n* (%)	2097 (28)	149 (21)	345 (25)	1603 (29)	<.001
Antiplatelet therapy, *n* (%)	1954 (26)	245 (34)	445 (32)	1264 (23)	<.001
Aspirin, *n* (%)	1652 (22)	210 (29)	355 (26)	1087 (20)	<.001
Clopidogrel or Prasgrel, *n* (%)	340 (5)	52 (7)	86 (6)	202 (4)	<.001

(Continues)

TABLE 1 (Continued)

	Total ($n=7558$)	Moderate/Severe anemia ($n=726$)	Mild anemia ($n=1374$)	No anemia ($n=5458$)	p value
Cilostazol, *n* (%)	158 (2)	27 (4)	49 (4)	82 (2)	<.001
Statin, *n* (%)	2518 (33)	174 (24)	433 (32)	1911 (35)	<.001
Beta-blocker, *n* (%)	3246 (43)	306 (42)	617 (45)	2323 (43)	.3
ACE-I/ARB, *n* (%)	3947 (52)	406 (56)	734 (53)	2807 (51)	.046
Calcium channel blocker, *n* (%)	3498 (46)	324 (45)	634 (46)	2540 (47)	.6
PPI or H2-blocker, *n* (%)	3377 (45)	438 (60)	729 (53)	2210 (41)	<.001
NSAIDs, *n* (%)	305 (4)	44 (6)	51 (4)	205 (4)	.01

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure, COPD, chronic obstructive pulmonary disease, DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; SD, standard deviation; TTR, time in therapeutic range.

switched to DOACs during the follow-up period. Those switched to DOACs were less common in the moderate/severe anemia group than in other groups (moderate/severe: 21%; mild: 25%; no: 29%, $p<.001$).

3.2 | Endpoints

At 4 years, 59% of patients completed the follow-up, and the median follow-up was 3.9 years. The cumulative incidences at 4 years of major bleeding in the moderate/severe, mild, and no anemia groups were 14.9%, 10.7%, and 6.4%, respectively (Figure 2A). The incidence of major bleeding with cases per 1000 patient-years among these three groups was 45.2 versus 28.6 versus 16.0, respectively (Table 2). The adjusted HRs (95% CIs) of moderate/severe and mild anemia for major bleeding were 1.96 (1.49–2.58) and 1.48 (1.17–1.87) compared to the no anemia group (Table 2). The cumulative incidences at 4 years of hemorrhagic stroke in the moderate/severe, mild, and no anemia groups were 0.8%, 1.1%, and 1.0%, respectively (Figure 2B). The incidence of hemorrhagic stroke with cases per 1000 patient-years in these three groups was 2.8 versus 2.6 versus 2.5, respectively (Table 2).

The cumulative incidences at 4 years of ischemic events in the moderate/severe, mild, and no anemia groups were 7.2%, 6.0%, and 5.2%, respectively (Figure 2C). The incidence of ischemic events with cases per 1000 patient-years among these three groups was 12.8 versus 15.9 versus 11.8, respectively (Table 2). The adjusted HRs (95% CIs) of moderate/severe and mild anemia for ischemic events were 0.63 (0.39–0.99) and 1.03 (0.76–1.39) compared to the no anemia group (Table 2). The cumulative incidences of ischemic stroke at 4 years among these three groups were 7.0%, 5.6%, and 4.8%, respectively (Figure 2D). The incidence of ischemic stroke with cases per 1000 patient-years in these three groups was 11.7 versus 14.5 versus 10.8 (Table 2).

The cumulative incidences of all-cause mortality at 4 years among these three groups were 21.2%, 15.7%, and 5.2%, respectively (Figure 2E). The incidence of all-cause mortality with cases per 1000 patient-years in these three groups was 69.5 versus 36.7 versus 12.5 (Table 2). The adjusted HRs (95% CIs) of moderate/severe and mild anemia for all-cause mortality were 3.77 (2.95–4.83) and 2.44 (1.95–3.05) compared to the no anemia group (Table 2).

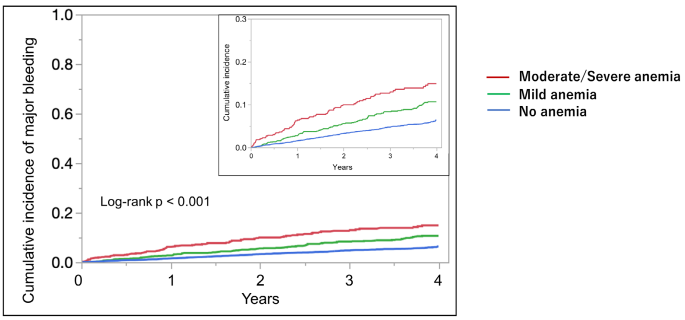
The exploratory analyses revealed the adjusted HR (95% CI) of severe anemia for major bleeding was 5.17 (1.99–13.40) and a linear trend from mild to severe anemia was observed (Table S1). The adjusted HR (95% CI) of severe anemia for all-cause mortality was 5.56 (2.13–14.5) and a linear trend also existed (Table S1). The moderate/severe anemia group had consistently higher HRs in subgroups for major bleeding (Figure S1), and subgroup analyses suggested significant interactions between the severity of anemia and eGFR (interaction $p=.04$). The sensitivity analyses revealed that the adjusted HRs (95% CIs) of moderate/severe and mild anemia for major bleeding were 2.81 (2.09–3.78) and 1.74 (1.33–2.29) compared to the no anemia in the warfarin alone stratum, but those were 1.22 (0.65–2.27) and 1.24 (0.81–1.90) in the switch to DOACs stratum, respectively (Table S2).

4 | DISCUSSION

Analyzing a nationwide registry of consecutive patients in daily clinical practice, we demonstrated the prevalence of anemia and the association between anemic status and bleeding risk in NVAF patients taking OACs. It was found that 28% of NVAF patients taking oral OACs had mild to severe anemia, including 9.6% with moderate or severe anemia. The anemic status was significantly associated with the incidence of major bleeding. The elevated risk of major bleeding was prominent in those with moderate/severe anemia, whose incidence was 14.9% at 4 years, but those with mild anemia were also at higher risk of major bleeding, adjusting for other clinically relevant variables. However, ischemic events or strokes were not associated with the presence or degree of anemia among those patients.

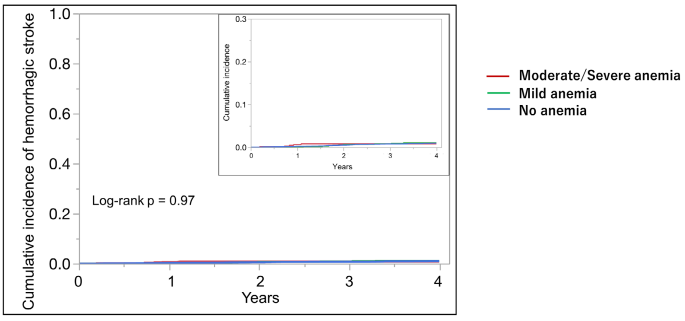
All conditions which necessitated anticoagulants or antiplatelets for preventing ischemic events have a similar dilemma. For example, the prevalence of mild to severe anemia was reported to be 34% among patients with venous thromboembolism (VTE) who started anticoagulants.[14] Among hospitalized Japanese patients with VTE, 54%

(A)



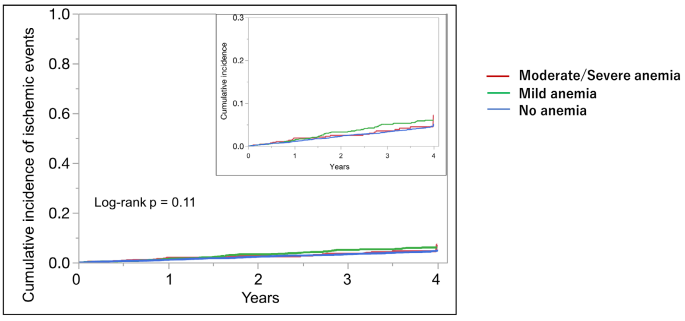
Follow-up, years		0	1	2	3	4
Moderate/Severe anemia	Number at risk, n	726	525	398	305	27
	Cumulative event, n	0	42	60	71	78
	Cumulative incidence, %	0	6.4	10.0	12.7	14.9
Mild anemia	Number at risk, n	1374	1127	885	716	55
	Cumulative event, n	0	36	66	90	107
	Cumulative incidence, %	0	2.8	5.6	8.3	10.7
No anemia	Number at risk, n	5458	4715	4099	3561	166
	Cumulative event, n	0	81	160	219	267
	Cumulative incidence, %	0	1.6	3.3	4.8	6.4

(B)



Follow-up, years		0	1	2	3	4
Moderate/Severe anemia	Number at risk, n	726	543	425	309	30
	Cumulative event, n	0	4	5	5	5
	Cumulative incidence, %	0	0.6	0.8	0.8	0.8
Mild anemia	Number at risk, n	1374	1145	912	728	56
	Cumulative event, n	0	0	7	9	10
	Cumulative incidence, %	0	0	0.7	0.9	1.1
No anemia	Number at risk, n	5458	4756	4173	3547	177
	Cumulative event, n	0	13	25	36	42
	Cumulative incidence, %	0	0.3	0.5	0.8	1.0

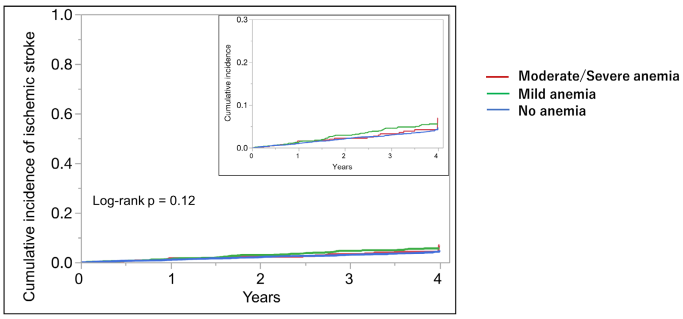
(C)



Follow-up, years		0	1	2	3	4
Moderate/Severe anemia	Number at risk, n	726	538	420	323	29
	Cumulative event, n	0	12	15	19	23
	Cumulative incidence, %	0	1.9	2.5	3.6	7.2
Mild anemia	Number at risk, n	1374	1134	893	725	53
	Cumulative event, n	0	17	38	53	60
	Cumulative incidence, %	0	1.3	3.3	5.1	6.0
No anemia	Number at risk, n	5458	4722	4112	3583	168
	Cumulative event, n	0	56	111	152	195
	Cumulative incidence, %	0	1.1	2.3	3.3	5.2

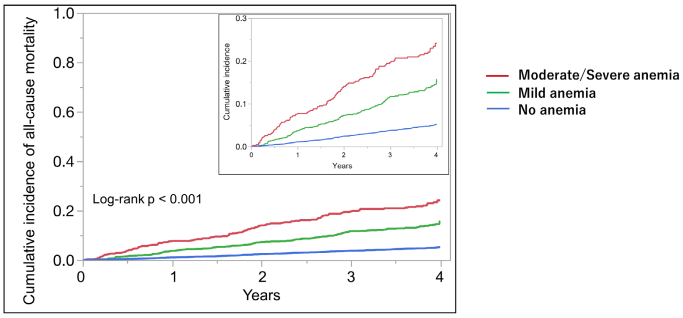
FIGURE 2 Cumulative incidence of endpoints. (A) Major bleeding. (B) Hemorrhagic stroke. (C) Ischemic events. (D) Ischemic stroke. (E) All-cause mortality.

(D)



Follow-up, years		0	1	2	3	4
Moderate/Severe anemia	Number at risk, n	726	538	420	323	29
	Cumulative event, n	0	10	13	17	21
	Cumulative incidence, %	0	1.6	2.2	3.3	7.0
Mild anemia	Number at risk, n	1374	1135	896	711	53
	Cumulative event, n	0	16	34	40	55
	Cumulative incidence, %	0	1.2	2.9	4.9	5.6
No anemia	Number at risk, n	5458	4726	4119	3483	168
	Cumulative event, n	0	51	101	148	177
	Cumulative incidence, %	0	1	2.1	3.3	4.8

(E)



Follow-up, years		0	1	2	3	4
Moderate/Severe anemia	Number at risk, n	726	543	426	328	30
	Cumulative event, n	0	52	86	112	126
	Cumulative incidence, %	0	7.7	14.0	19.6	21.2
Mild anemia	Number at risk, n	1374	1145	915	730	56
	Cumulative event, n	0	48	87	130	149
	Cumulative incidence, %	0	3.7	7.3	12.0	15.7
No anemia	Number at risk, n	5458	4763	4186	3670	179
	Cumulative event, n	0	55	117	172	217
	Cumulative incidence, %	0	1.1	2.4	3.8	5.2

FIGURE 2 (Continued)

were reported to have mild to severe anemia.[15] These trends were also observed in acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) which had a 30% prevalence.[16] The 28% prevalence of mild to severe anemia in our registry was consistent with these reports. Our study shed light on anemia being a common comorbidity in patients for whom anticoagulation is necessary.

It was reported that patients with anemia had significantly higher rates of major bleeding than those without anemia with relative risk of 2.84 among patients with VTE.[14] Among hospitalized Japanese patients with VTE, the HRs for 5 years of moderate/severe and mild anemia relative to no anemia for major bleeding were 1.91 and 1.41, respectively.[15] In our study, the 4-year HRs were 1.96 and 1.48 for moderate/severe and mild anemia relative to no anemia for major bleeding, respectively. These results were very close to previously reported data and the bleeding risk became higher when anemia became worse in patients requiring OACs.

On the other hand, the risk of ischemic events was not increased by the degree of anemia in our study. The HRs for ischemic events in NVAF patients with moderate/severe and mild anemia to those without anemia were 0.63 and 1.03, respectively. A post hoc analysis of the ARISTOTLE trial, which included over 18,000 patients with AF randomized to warfarin or apixaban showed that anemia was not associated with stroke or systemic embolism (adjusted HR, 0.92; 95% CI, 0.70–1.21).[17] Another study showed that in patients with VTE taking OACs, the rate of DVT recurrences was similar in patients with mild anemia relative to no anemia (relative risk 1.07; 95% CI 0.88–1.30) and the rate of pulmonary embolism (PE) recurrences was somewhat higher in patients with mild anemia but no significant difference was found (relative risk 1.23; 95% CI 1.00–1.56).[14] Considering these observations together, it is considered that anemia does not strongly affect the risk of ischemic events in patients on OACs.

TABLE 2 Clinical outcomes.

All cohort	Number (/1000PY)	Crude HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
Major bleeding							
Moderate/Severe anemia	78 (45.2)	2.34	1.80–3.05	<.001	1.96	1.49–2.58	<.001
Mild anemia	107 (28.6)	1.64	1.30–2.07	<.001	1.48	1.17–1.87	.001
No anemia	260 (16.0)	1.0	–	–	1.0	–	–
Hemorrhagic stroke							
Moderate/Severe anemia	5 (2.8)	0.89	0.35–2.27	.82	0.76	0.29–1.95	.56
Mild anemia	10 (2.6)	0.95	0.47–1.89	.87	0.86	0.43–1.74	.68
No anemia	42 (2.5)	1.0	–	–	1.0	–	–
Ischemic events							
Moderate/Severe anemia	23 (12.8)	0.88	0.57–1.37	.67	0.63	0.39–0.99	.046
Mild anemia	60 (15.9)	1.23	0.92–1.66	.17	1.03	0.76–1.39	.87
No anemia	193 (11.8)	1.0	–	–	1.0	–	–
Ischemic stroke							
Moderate/Severe anemia	21 (11.7)	0.89	0.56–1.41	.61	0.64	0.39–1.03	.07
Mild anemia	55 (14.5)	1.24	0.91–1.69	.17	1.04	0.76–1.43	.79
No anemia	176 (10.8)	1.0	–	–	1.0	–	–
All-cause mortality							
Moderate/Severe anemia	126 (69.5)	5.07	4.01–6.42	<.001	3.77	2.95–4.83	<0.001
Mild anemia	149 (36.7)	2.94	2.36–3.65	<.001	2.44	1.95–3.05	<.001
No anemia	207 (12.5)	1.0	–	–	1.0	–	–

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, patient-years.

We thus assumed that anemia became a risk stratification variable for bleeding risk in patients with NVAF due to these reasons. The most frequently used risk score for 1-year major bleeding in AF patients is the HAS-BLED score, which refers to hypertension, abnormal renal or liver function, history of stroke, history of bleeding events or predisposition of bleeding, labile international normalized ratio, elderly (>65 years), and antiplatelet use or alcohol abuse.[2] In this score, anemia was considered a predisposition of bleeding and the B score was counted if anemia was present. Although bleeding history was well defined as history of any bleeding event requiring hospitalization or causing a decrease in Hb level of >2 g/L or requiring blood transfusion, there was no definition of anemia as predisposition.[2] As a result, anemia was not well recognized as a risk for bleeding events and B score did not reflect the anemic status in calculating the HAS-BLED score.

In fact, the prevalence of patients with mild to severe anemia but no B score in the assessment of physician in charge was 95% (1992/2100) in our study. Even in patients with the moderate/severe anemia, 93% (676/726) were not considered to have predisposition of bleeding. Our study shed light on there being more patients than expected in daily clinical practice who were at risk for bleeding but whose risk was overlooked, and OACs were started irrespective to the risk of bleeding. Therefore, it is clinically relevant to clarify the impact of anemia severity on bleeding risk among such patients. In the Euro Heart Survey, the odds ratio (OR) for history of major bleeding as a risk factor for major bleeding after taking anticoagulants within 1 year was 7.51 (3.00–18.78).[2] Our exploratory analyses revealed the HR of severe anemia (Hb <8 g/dL) for major bleeding was 6.86 (2.68–17.55) compared to the no anemia group, which was close to the results from the Euro Heart Survey. This category of severe anemia could be a criterion for anemia incorporating the HAS-BLED score, but further careful validation should be necessary because only 0.3% (23/7558) of the patients in this cohort had severe anemia.

Another important issue is how to deal with NVAF patients with anemia in daily clinical practice. We should investigate the cause of anemia before considering the use of OACs, and several underlying conditions could be corrected before the use of OACs. In addition, if anemia was considered a risk for future major bleeding, blood transfusion before starting OACs could be an option. However, blood transfusion had been reported to increase postoperative mortality and cardiovascular events in patients undergoing PCI.[18] The restrictive red blood cell transfusion was also shown to be non-inferior to liberal strategies for postoperative mortality, cardiovascular events, or new-onset renal failure in cardiac surgery patients.[19] Because the pathophysiology was different between ischemic heart disease or structure cardiac disease and NVAF, we should carefully pay attention to the benefit or risk of correction of anemia in NVAF patients even if the anemia itself was a poor prognostic marker.

4.1 | Limitations

This study had several limitations. First, the underlying cause of anemia was not identified, and the history of mild bleeding was not examined. These factors could be unadjusted confounding factors. However, most of the included patients were post-menopausal and the subgroup analysis for malignancy revealed consistent results to the main analyses. We thus considered the effects of these unmeasured factors should be small. Second, all included patients started with warfarin at the start of the cohort and the changes from warfarin to DOACs were determined by the physician in charge. The decision of changes might be influenced by the risk of bleeding and with higher risk of selection bias. We thus conducted the sensitivity analyses which revealed the increased risk of major bleeding in moderate/severe anemia and mild anemia groups were apparent in the warfarin alone stratum, but not apparent in the switch to DOACs stratum. Because 72% of patients continued the warfarin, the finding was not influenced significantly. However, the increased risk of major bleeding due to anemia should be carefully considered in patients on DOACs. Third, we did not collect the details of major bleeding. Because some causes of major bleeding could be associated with anemia, but others were not, the investigation of causes of major bleeding should be carefully considered. Fourth, this study used the baseline Hb at the inclusion of the cohort. Such measurements could be affected by acute conditions such as dehydration and might change over time, leading to misclassification of anemia, but we did not collect the changes in Hb during the hospital stay or other measurements related to dehydration or other conditions. However, such misclassification should occur randomly in the anemia and no anemia groups and the estimates of the effects of anemia should be weakened by the random transitions. Therefore, the estimates with statistical significance should be robust in the large-scale study. Finally, the patients of this study were selected from participating hospitals, and these findings might not be applicable to patients in other settings. Therefore, the findings of this study should be attested in other settings including patients with different geographic or ethnic backgrounds.

5 | CONCLUSIONS

Anemia was frequently encountered in patients with NVAF on OACs in daily clinical practice. The severity of anemia in such patients was associated with a higher risk of major bleeding and mortality but not with the incidence of ischemic events. Our findings were relevant to reduce bleeding complications in patients who were taking OACs. When OACs are considered in patients with NVAF, anemic status should be carefully monitored.

AUTHORS' CONTRIBUTIONS

Dr. Norito Kinjo carried out study conception and design, statistical analysis, interpretation of data, management, and drafting of the manuscript. Dr. Shinichiro Ueda was involved in study conception and design, data acquisition, and critical revision of the manuscript. Dr. Kazutaka Uchida carried out statistical analysis, interpretation of data, and critical revision of the manuscript. Dr. Fumihiro Sakakibara, Dr. Mari Nezu, and Dr. Hideki Arai were involved in interpretation of data and critical revision of the manuscript. Dr. Takeshi Morimoto: study conception and design, data acquisition and management, interpretation of data, management, and drafting of the manuscript. All authors: final approval of the manuscript.

ACKNOWLEDGMENTS

We are indebted to the data managers of the Institute for Clinical Effectiveness (Ms. Makiko Ohtorii, Ms. Ai Sunagawa, Ms. Kaori Yamamoto, Ms. Sachiko Kitamura, Ms. Hirono Saito, and Ms. Saeko Nagano) for managing the data and performing the statistical analyses.

FUNDING INFORMATION

This study was supported by Bristol-Myers Squibb. The funders did not participate in any part of the study, from conception to article preparation.

CONFLICT OF INTEREST STATEMENT

Dr. Kinjo, Dr. Sakakibara, Dr. Nezu, and Dr. Arai have no disclosures to report. Dr. Uchida reports lecturer's fees from Daiichi Sankyo. Dr. Ueda reports receiving a research grant from Bristol-Myers Squibb, Chugai, Kowa, MSD, Pfizer, and Takeda, lecturer's fee from Boehringer Ingelheim, MSD, and Taiho, and manuscript fees from Kowa. He served on an advisory board for Otsuka.

Dr. Morimoto reports lecturer's fees from Bayer, Daiichi Sankyo, Japan Lifeline, Kyocera, Mitsubishi Tanabe, Novartis, and Toray; the manuscript fees from Bristol-Myers Squibb and Kowa; served advisory boards for Asahi Kasei, Boston Scientific, Bristol-Myers Squibb, and Sanofi.

ETHICS APPROVAL STATEMENT

The institutional review boards of the University of the Ryukyus (No. 597) and all 71 participating centers approved the study protocol (Supplemental Table). The institutional review boards waived the need for written informed consent and approved the study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

PATIENT CONSENT STATEMENT

Not Applicable.

CLINICAL TRIAL REGISTRATION

Not Applicable.

ORCID

Norito Kinjo https://orcid.org/0000-0003-1555-0614
Takeshi Morimoto https://orcid.org/0000-0002-6844-739X

REFERENCES

1. Culebras A, Messé SR. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation: report of the guideline development Subcommittee of the American Academy of neurology. Neurology. 2014;83:1220. https://doi.org/10.1212/wnl.0000000000000831
2. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the euro heart survey. Chest. 2010;138:1093–100. https://doi.org/10.1378/chest.10-0134
3. Chang SH, Chou IJ, Yeh YH, Chiou MJ, Wen MS, Kuo CT, et al. Association between use of non-vitamin K Oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. JAMA. 2017;318:1250–9. https://doi.org/10.1001/jama.2017.13883
4. O'Neal WT, Sandesara PB, Claxton JS, MacLehose RF, Chen LY, Bengtson LGS, et al. Influence of sociodemographic factors and provider specialty on anticoagulation prescription fill patterns and outcomes in atrial fibrillation. Am J Cardiol. 2018;122:388–94. https://doi.org/10.1016/j.amjcard.2018.04.022
5. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. Clin Interv Aging. 2014;9:1187–96. https://doi.org/10.2147/cia.S61125
6. 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;361:1139–51. https://doi.org/10.1056/NEJMoa0905561
7. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92. https://doi.org/10.1056/NEJMoa1107039
8. Morimoto T, Uchida K, Sakakibara F, Kinjo N, Ueda S. Effect of concomitant antiplatelet therapy on ischemic and hemorrhagic events in patients taking oral anticoagulants for nonvalvular atrial fibrillation in daily clinical practice. Pharmacoepidemiol Drug Saf. 2021;30:1321–31. https://doi.org/10.1002/pds.5228
9. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of atrial fibrillation. JAMA. 2001;285:2864–70. https://doi.org/10.1001/jama.285.22.2864
10. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968;405:5–37.
11. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x
12. Butzer JF, Cancilla PA, Cornell SH. Computerized axial tomography of intracerebral hematoma. A clinical and neuropathological study. Arch Neurol. 1976;33:206–14. https://doi.org/10.1001/archneur.1976.00500030062014
13. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). J Am Coll Cardiol. 2015;66:403–69. https://doi.org/10.1016/j.jacc.2014.12.018
14. Kuperman A, López-Reyes R, Bosco LJ, Lorenzo A, José B, Farge Bancel D, et al. Anemia and bleeding in patients receiving anticoagulant therapy for venous thromboembolism. J Thromb Thrombolysis. 2018;45:360–8. https://doi.org/10.1007/s11239-018-1610-9
15. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al. Influence of baseline anemia on long-term clinical outcomes in patients with venous thromboembolism: from the COMMAND VTE registry. J Thromb Thrombolysis. 2019;47:444–53. https://doi.org/10.1007/s11239-018-1791-2
16. Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, et al. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J. 2007;28:1936–45. https://doi.org/10.1093/eurheartj/ehm194
17. Westenbrink BD, Alings M, Granger CB, Alexander JH, Lopes RD, Hylek EM, et al. Anemia is associated with bleeding and mortality, but not stroke, in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Am Heart J. 2017;185:140–9. https://doi.org/10.1016/j.ahj.2016.12.008
18. Kwok CS, Sherwood MW, Watson SM, Nasir SB, Sperrin M, Nolan J, et al. Blood transfusion after percutaneous coronary intervention and risk of subsequent adverse outcomes: a systematic review and meta-analysis. JACC Cardiovasc Interv. 2015;8:436–46. https://doi.org/10.1016/j.jcin.2014.09.026
19. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or Liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44. https://doi.org/10.1056/NEJMoa1711818

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kinjo N, Ueda S, Uchida K, Sakakibara F, Nezu M, Arai H, et al. Impact of anemia on major bleeding in patients taking oral anticoagulants for nonvalvular atrial fibrillation. J Arrhythmia. 2023;39:556–565. https://doi.org/10.1002/joa3.12885