ORIGINAL RESEARCH

Safety and Effectiveness of Non–Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation and Anemia: A Retrospective Cohort Study

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Background—Major randomized trials assessing non–vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation generally excluded patients with hemoglobin <10 g/dL. This study evaluated the safety and effectiveness of NOACs in patients with atrial fibrillation and anemia.

Methods and Results—A cohort study based on electronic medical records was conducted from 2010 to 2017 at a multicenter healthcare provider in Taiwan. It included 8356 patients with atrial fibrillation who had received oral anticoagulants (age, 77.0±7.3 years; 48.0% women). Patients were classified into 2 subgroups: 7687 patients with hemoglobin ≥10 g/dL and 669 patients with hemoglobin <10 g/dL. A Cox regression analysis was performed to assess the risks of ischemic stroke/systemic embolism, bleeding, and death associated with NOAC versus warfarin in both subgroups, respectively. In patients with hemoglobin ≥10 g/dL, NOAC (n=4793) was associated with significantly lower risks of ischemic stroke/systemic embolism, major bleeding, and gastrointestinal tract bleeding than warfarin (n=2894); there was no difference in the risk of death. In patients with hemoglobin <10 g/dL, NOAC (n=390) was associated with significantly lower risks of major bleeding (adjusted hazard ratio, 0.43; 95% CI, 0.30–0.62) and gastrointestinal tract bleeding than warfarin (n=279), but there was no difference in the risk of ischemic stroke/systemic embolism (adjusted hazard ratio, 0.79; 95% CI, 0.53–1.17) or death. Subgroup analyses suggested that NOAC was associated with fewer bleeding events, irrespective of cancer or peptic ulcer disease history.

Conclusions—In patients with atrial fibrillation with hemoglobin <10 g/dL, NOAC was associated with lower bleeding risks than warfarin, with no difference in the risk of ischemic stroke/systemic embolism or death. **(*J Am Heart Assoc*. 2019;8:e012029. DOI: 10.1161/JAHA.119.012029.)**

Key Words: anemia • anticoagulation • atrial fibrillation • bleeding • outcome

Anemia is frequently observed in patients with atrial fibrillation (AF), and it may be associated with an increased risk of new-onset AF.[1,2] AF increases the risks of ischemic stroke (IS) and systemic embolism (SE). Vitamin K antagonists reduce the risks of IS/SE in AF but also increase the risk of bleeding, especially in patients with anemia.[3–5] In anticoagulated patients with AF, anemic patients have a higher prevalence of comorbidities, greater CHA_2DS_2-VAS_C (Congestive Heart Failure, Hypertension, Age ≥75 Years [doubled], Diabetes Mellitus, Prior Stroke, Transient Ischemic Attack, or Thromboembolism [doubled], Vascular Disease, Age 65–74 Years, Sex Category) and HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly) scores, and increased risks of major bleeding, mortality, and anticoagulant discontinuation

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Accompanying Tables S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012029

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Clinical Perspective

What Is New?

- Non–vitamin K antagonist oral anticoagulants, compared with warfarin, were associated with a significantly lower risk of major bleeding or gastrointestinal tract bleeding, but there was no difference in ischemic stroke, systemic embolism, or death in anemic patients with atrial fibrillation patients and hemoglobin <10 g/dL.

What Are the Clinical Implications?

- Non–vitamin K antagonist oral anticoagulant is a favorable alternative to warfarin in patients with atrial fibrillation and anemia, ≥65 years.

than those without anemia.[1,6] Physicians are, thus, faced with a treatment dilemma when choosing anticoagulant therapies in patients with AF and anemia.

Anemia is closely associated with peptic ulcer disease and cancer-related bleeding.[7,8] Peptic ulcer disease is the most common cause of bleeding in patients receiving long-term warfarin therapy.[9] Warfarin therapy in patients with a history of peptic ulcer bleeding raises management difficulties on the balance between the thromboembolic risk secondary to anticoagulation interruption and the hemorrhagic risk associated with a history of bleeding.[9] Treating AF with oral anticoagulants in patients with cancer is also a challenge because cancer may result in an increased risk of thromboembolism or bleeding.[10] Therefore, such patients may respond unpredictably to anticoagulant therapy; thus, thromboembolic and bleeding-risk prediction scores may not be reliable.[10.]

Non–vitamin K antagonist oral anticoagulants (NOACs) are now widely used as alternatives to warfarin for preventing stroke in AF because NOACs are as effective as but safer than warfarin.[11–14] The working dosage of NOACs is generally easier to ascertain because there is less variation among individuals and the drugs have a faster action onset and offset and exhibit fewer drug-food and drug-drug interactions than warfarin does.[15] However, most major randomized controlled trials of NOACs have excluded patients with hemoglobin <10 g/dL.[11,13,14,16] In addition, there is no specific recommendation for anticoagulant therapy in anemic patients with AF and hemoglobin <10 g/dL in current guidelines.[17–19] Hence, the aim of the present study was to compare the safety and effectiveness of NOAC and warfarin when prescribed for stroke prevention in patients with AF and hemoglobin <10 g/dL.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

In this retrospective cohort study, patient data were collected from the Chang Gung Research Database, a deidentified database derived from the electronic medical records of the Chang Gung Memorial Hospital system in Taiwan. The Chang Gung Memorial Hospital is currently the largest Taiwanese medical care system, comprising 4 tertiary-care medical centers and 3 major teaching hospitals. This medical care system, with >10 000 beds and >280 000 inpatients per year, provides ≈10% of all medical service used by the Taiwanese people annually.[20–22] The hospital identification number of each patient was encrypted and deidentified to protect individuals' privacy. The diagnoses and laboratory data could be linked and continuously monitored using consistent data encryption. The institutional review board of Chang Gung Memorial Hospital approved the study protocol (approval serial No. 21080666B0). The institutional review board waived the need for informed consents from the patients and prentices/guardians because the database used in this study consists of unidentifiable, secondary data released to the public for research.

Study Cohort

This study was conducted on the basis of electronic medical records in the Chang Gung Memorial Hospital system in Taiwan from 2010 to 2017. A total of 19 632 patients, aged ≥65 years, who had been diagnosed with AF (*International Classification of Diseases, Ninth Revision* [*ICD-9*], code 427.31 or *International Classification of Diseases, Tenth Revision* [*ICD-10*], codes I48.0, I48.1, I48.2, or I48.91) and had had at least 1 prescription filled for oral anticoagulant therapy after diagnosis were included. We enrolled patients with AF, aged ≥65 years, because the Taiwan National Health Insurance only reimburses for NOAC prescriptions for these patients. The oral anticoagulant therapy consisted of warfarin or an NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban). Patients were excluded if they had the following: (1) had deep vein thrombosis or pulmonary embolism up to 6 months before the index day (n=1040), (2) had received joint surgery (n=254) or a heart-valve replacement (n=653) up to 6 months before the index date, (3) had end-stage renal disease before the index date (n=2331), (4) had IS or SE or died up to 7 days after the index date (n=3799), or (5) had not had data on hemoglobin levels for the 2 years before the index date (n=3199). After the exclusion, 8356 patients remained eligible for the study, and these patients were divided into 2 subgroups: patients with hemoglobin ≥10 g/dL (n=7687, 92.0%) and those with hemoglobin <10 g/dL (n=669, 8.0%).[9–11,14] The Figure is the flowchart of the enrollment process and the subdivision of the eligible study cohort into the 2 subgroups. The index date was defined as the first date on which warfarin or NOAC therapy was initiated. The risks of IS/SE, bleeding, and death were compared between NOAC and warfarin therapies in these 2 subgroups of anticoagulated patients with AF. The

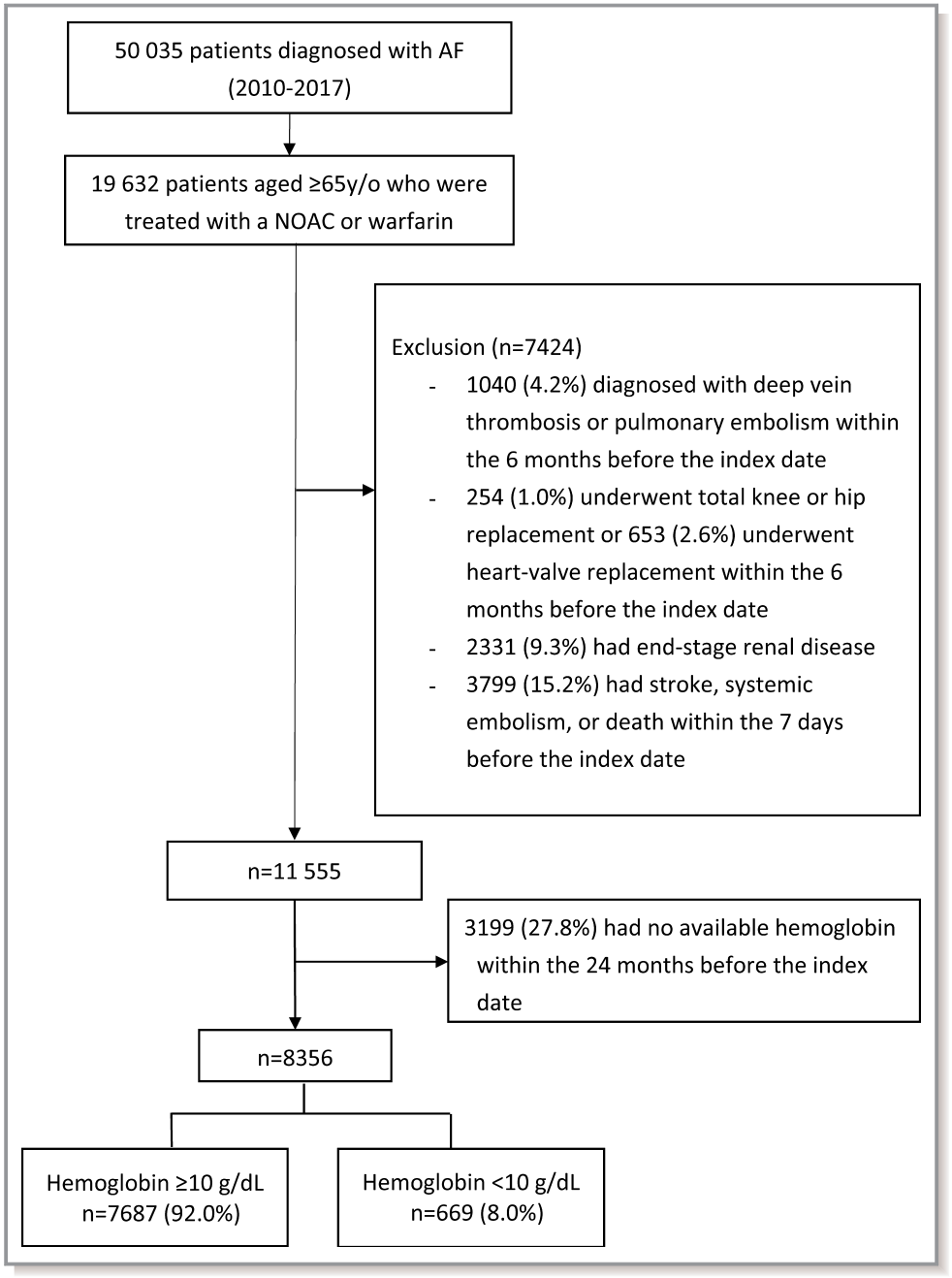

Figure. Enrollment of patients, aged ≥65 years, with nonvalvular atrial fibrillation (AF). From January 1, 2010, to December 31, 2017, this study evaluated a total of 7687 patients with hemoglobin ≥10 g/dL and 669 patients with hemoglobin <10 g/dL. NOAC indicates non–vitamin K antagonist oral anticoagulant.

identified patients were followed up until the outcome event or the end of 2017, whichever occurred first.

Assessment of Other Covariates

Baseline comorbidities of the study cohort included diabetes mellitus, hypertension, chronic kidney disease, chronic liver disease, and histories of heart failure, myocardial infarction, transient ischemic attack, IS, SE, bleeding, peptic ulcer disease, and cancer. Laboratory data included serum hemoglobin, platelet counts, estimated glomerular filtration rate, liver function tests, and lipid profiles. Baseline medications were identified from medical records for the 180-day period before the index date, including antiplatelets, nonsteroidal anti-inflammatory drugs, statins, amiodarone, digoxin, and proton pump inhibitors.

Outcome Measures

The efficacy end point was the occurrence of IS/SE or death. The safety end point was the occurrence of major bleeding or gastrointestinal tract bleeding. Major bleeding was defined as clinically overt bleeding associated with at least a 2-g/dL decrease in hemoglobin or requiring a transfusion of at least 2 units of packed red blood cells or whole blood, fatal bleeding, or intracranial hemorrhage during the period of drug use or within the 14-day period after the last day of drug use. Gastrointestinal tract bleeding was defined as hospitalization with a primary diagnosis of bleeding in any segment of the gastrointestinal tract, from the esophagus to the rectum, during the drug-use period or within the 14-day period after the last day of drug use. The follow-up period was defined as the time from the index date to the first occurrence of any study outcome or the end date of the study period (December 31, 2017), whichever came first. The anticoagulant type was treated as a time-dependent exposure. A 14-day period was the censoring window for drug switches. If an event occurred during the initial therapy period or within the 14-day period after the switch, the event and time were ascribed to the initial therapy. If an event occurred ≥15 days after the switch, the event and time were ascribed to the switch therapy. The diagnostic codes used to identify the study outcomes and the baseline covariates are summarized in Table S1.

Statistical Analysis

Data were presented as the mean±SD or median (interquartile range) for continuous variables and as proportions for categorical variables. Differences between continuous values were assessed using Wilcoxon's rank-sum test. Differences between nominal variables were compared with a χ^2 test. We calculated event rates as the number of events divided by 100 person-years. The Cox proportional hazard regression with time-dependent exposure (anticoagulant type) was used to compare event rates between NOAC and warfarin therapies in the 2 groups of patients. When comparing the risk of IS/SE, major bleeding, gastrointestinal tract bleeding, or death between NOAC and warfarin therapies, the analyses were adjusted for covariates, including patient characteristics, baseline comorbidities, laboratory information, and baseline medications. Statistical significance was based on the level of α=0.05. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Sensitivity and Subgroup Analyses

We performed 3 sensitivity analyses to validate our findings and check for potential selection biases. First, given the high mortality risk in patients with AF and anemia, we reanalyzed the data accounting for competing risks of death. Second, we reanalyzed the data by using 7 days as a censoring window for drug switches to assess whether the primary findings would have been changed if differential censoring windows between drug switches had been used. Third, we reanalyzed the data after excluding patients with missing values of covariates in the models to determine if missing data would change the results. Subgroup analyses were performed to explore the effects of anticoagulant types in patient subgroups with and without a history of peptic ulcer disease or cancer.[23,24]

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of anticoagulated patients with AF and different hemoglobin levels. The 7687 patients in the patient subgroup with hemoglobin ≥10 g/dL were a mean±SD age of 76.7±7.2 years, had a mean±SD CHA_2DS_2-VASc score of 3.8±1.6, and had a mean±SD HAS-BLED score of 3.1±1.1. The 669 patients in the patient subgroup with hemoglobin <10 g/dL were a mean±SD age of 79.4±7.6 years, had a mean±SD CHA_2DS_2-VASc score of 4.3±1.8, and had a mean±SD HAS-BLED score of 3.7±1.0. Of the 669 patients with hemoglobin <10 g/dL, 446 (66.7%), 184 (27.5%), 25 (3.7%), and 14 (2.1%) had hemoglobin levels of 9 to 9.9, 8 to 8.9, 7 to 7.9, and <7 g/dL, respectively. Both CHA_2DS_2-VASc and HAS-BLED scores were significantly higher in the patient subgroup with hemoglobin <10 g/dL. Patients with hemoglobin <10 g/dL tended to be older, to be women, and to have more comorbidities and a history of heart failure or stroke. In summary, patients with hemoglobin <10 g/dL were older and weaker than those with hemoglobin ≥10 g/dL. A separate comparison between NOAC and warfarin users in the patient subgroup with hemoglobin <10 g/dL is given in Table 2. Within the group, patients using NOAC or warfarin had similar demographic characteristics and comorbidities, except for older age in NOAC users.

Patients With Hemoglobin ≥10 g/dL

The crude event rates per 100 person-years in the NOAC and warfarin groups were 5.10 and 6.67 for IS/SE, 7.35 and 12.36 for major bleeding, 4.27 and 5.76 for gastrointestinal tract bleeding, and 3.06 and 2.97 for death, respectively (Table 3, upper section). NOAC therapy (n=4793) was associated with significantly lower risks of IS/SE (adjusted hazard ratio [aHR], 0.68; 95% CI, 0.61–0.77; *P*<0.001), major bleeding (aHR, 0.51; 95% CI, 0.46–0.56; *P*<0.001), and gastrointestinal tract bleeding (aHR, 0.67; 95% CI, 0.59–0.77; *P*<0.001); and it showed no difference in the risk of death (aHR, 0.91; 95% CI, 0.78–1.07; *P*=0.267) compared with warfarin therapy (n=2894).

Table 1. Baseline Characteristics of Anticoagulated Patients With AF and Hemoglobin ≥10 g/dL and Hemoglobin <10 g/dL

Characteristic	All Patients (n=8356)	Hemoglobin, g/dL		*P* Value
		≥10 (n=7687)	<10 (n=669)	
Age, y	77.0±7.3	76.7±7.2	79.4±7.6	<0.001
Aged 65–74 y, n (%)	3283 (39.3)	3100 (40.3)	183 (27.4)	
Aged 75–84 y, n (%)	3670 (43.9)	3372 (43.9)	298 (44.5)	
Aged ≥85 y, n (%)	1403 (16.8)	1215 (15.8)	188 (28.1)	
Women, n (%)	4009 (48.0)	3612 (47.0)	397 (59.3)	<0.001
Comorbidity at index date, n (%)				
Diabetes mellitus	2116 (25.3)	1927 (25.1)	189 (28.3)	0.069
Hypertension	4789 (57.3)	4430 (57.6)	359 (53.7)	0.047
Chronic liver disease	1427 (17.1)	1335 (17.4)	92 (13.8)	0.018
Heart failure	3389 (40.6)	3068 (39.9)	321 (48.0)	<0.001
Prior myocardial infarction	1835 (22.0)	1681 (21.9)	154 (23.0)	0.490
Prior stroke	1874 (22.4)	1695 (22.1)	179 (26.8)	0.005
Peripheral artery occlusive disease	196 (2.4)	165 (2.2)	31 (4.6)	<0.001
Prior transient ischemic attack	305 (3.7)	282 (3.7)	23 (3.4)	0.760
Bleeding history	3711 (44.4)	3430 (44.6)	281 (42.0)	0.191
Cancer	1244 (14.9)	1099 (14.3)	145 (21.7)	<0.001
Peptic ulcer disease	2767 (33.1)	2547 (33.1)	220 (32.9)	0.896
CHA_2DS_2-VASc score*	3.9±1.7	3.8±1.6	4.3±1.8	<0.001
HAS-BLED score†	3.2±1.1	3.1±1.1	3.7±1.0	<0.001
Laboratory data				
eGFR, mL/min per 1.73 m^2	70.7±25.1	70.9±24.3	67.2±33.3	0.001
eGFR <60 mL/min per 1.73 m^2, n (%)	2275 (27.2)	2026 (23.3)	249 (37.2)	<0.001
Hemoglobin, g/dL	13.0 (11.6–14.4)	13.2 (12.0–14.5)	9.3 (8.7–9.6)	<0.001
Platelets, $\times 10^3/\mu L$	189 (152–234)	188 (152–231)	208 (149–283)	<0.001
Aspartate aminotransferase, U/L	27 (21–36)	27 (22–36)	28 (21–41)	0.109
Alanine aminotransferase, U/L	20 (15–30)	21 (15–30)	18 (13–29)	<0.001
Total bilirubin, mg/dL	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.7 (0.4–1.0)	<0.001
LDL-C, mg/dL	91.2±26.5	91.6±26.4	85.4±27.6	0.005
Cholesterol, mg/dL	163.4±32.0	164.1±31.4	153.1±38.7	<0.001
Medications, n (%)				
Statins	3039 (36.4)	2873 (37.4)	166 (24.8)	<0.001
Amiodarone	3181 (38.1)	2909 (37.8)	272 (40.7)	0.150
ß Blockers	5724 (68.5)	5275 (68.6)	449 (67.1)	0.421
ACEIs or ARBs	5748 (68.8)	5326 (69.3)	422 (63.1)	0.001
Calcium channel blockers	2914 (34.9)	2667 (34.7)	247 (36.9)	0.247
Loop diuretics	4341 (52.0)	3859 (50.2)	482 (72.1)	<0.001
Aspirin	3572 (42.8)	3314 (43.1)	258 (38.6)	0.023
Digoxin	2475 (29.6)	2264 (29.5)	211 (31.5)	0.260
Clopidogrel	1697 (20.3)	1539 (20.0)	158 (23.6)	0.027
Ticagrelor	154 (1.8)	142 (1.9)	12 (1.8)	0.921

Continued

Table 1. Continued

Characteristic	All Patients (n=8356)	Hemoglobin, g/dL		*P* Value
		≥10 (n=7687)	<10 (n=669)	
Nonsteroid anti-inflammatory drugs	2972 (35.6)	2756 (35.9)	216 (32.3)	0.065
Proton pump inhibitors	2529 (30.3)	2227 (29.0)	302 (45.1)	<0.001
Warfarin	3173 (38.0)	2894 (37.7)	279 (41.7)	0.038
NOACs	5183 (62.0)	4793 (62.4)	390 (58.3)	0.038
Dabigatran, 110 mg	1635 (19.6)	1569 (20.4)	66 (9.9)	
Dabigatran, 150 mg	238 (2.9)	231 (3.0)	7 (1.1)	
Rivaroxaban, 10 mg	1183 (14.2)	1088 (14.2)	95 (14.2)	
Rivaroxaban, 15 mg	2024 (24.2)	1917 (24.9)	107 (16.0)	
Rivaroxaban, 20 mg	942 (11.3)	886 (11.5)	56 (8.4)	
Apixaban, 5 mg	1768 (21.2)	1611 (21.0)	157 (23.5)	
Edoxaban, 30 mg	701 (8.4)	652 (8.5)	49 (7.3)	
Edoxaban, 60 mg	305 (3.7)	298 (3.9)	7 (1.1)	
Patients with anticoagulant switch, n (%)	1459 (17.5)	1397 (18.2)	62 (9.3)	
No. of anticoagulant switches				
Warfarin to NOAC	1705	1648	57	
NOAC to warfarin	624	609	15	

Values are given as mean±SD or median (interquartile range), except as noted. The CHA_2DS_2-VASc score awards 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex (sex category) and 2 points each for age ≥75 years and previous stroke or transient ischemic attack. The HAS-BLED score awards 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age ≥65 years, and antiplatelet drug or alcohol use. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NOAC, non–vitamin K antagonist oral anticoagulant.

*Congestive Heart Failure, Hypertension, Age ≥75 Years (doubled), Diabetes Mellitus, Prior Stroke, Transient Ischemic Attack, or Thromboembolism [doubled], Vascular Disease, Age 65–74 Years, Sex Category.

†Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly.

Patients With Hemoglobin <10 g/dL

The crude event rates per 100 person-years in the NOAC and warfarin groups were 7.29 and 8.30 for IS/SE, 7.61 and 14.27 for major bleeding, 3.76 and 7.18 for gastrointestinal tract bleeding, and 8.10 and 5.94 for death, respectively (Table 3, lower section). NOAC therapy (n=390) was associated with lower risks of major bleeding (aHR, 0.43; 95% CI, 0.30–0.62; *P*<0.001) and gastrointestinal tract bleeding (aHR, 0.45; 95% CI, 0.28–0.71; *P*<0.001), with no significant differences in the risks of IS/SE (aHR, 0.79; 95% CI, 0.53–1.17; *P*=0.249) and death (aHR, 0.99; 95% CI, 0.66–1.48; *P*=0.951) compared with warfarin therapy (n=279).

Sensitivity and Subgroup Analyses

The results were similar for IS/SE and bleeding when death was treated as a competing risk factor in the Cox model (Table 3). We reanalyzed the data by using 7 days as a censoring window for drug switches and found similar results to those obtained with a 14-day censoring window (Table S2). Table S3 shows the analysis results after excluding patients with missing values of covariates; the results were similar to the main results. For the subgroup analysis of patients with and without a history of cancer (Table 4) or peptic ulcer disease (Table 5), the results were generally consistent with the main results. The lower risks of major bleeding and gastrointestinal tract bleeding associated with NOAC therapy were similar in patients with and without a history of cancer or peptic ulcer disease. However, extreme caution needs to be taken when interpreting the subgroup analyses because of the limited sample size and number of events. The number of events is way below the general rule of thumb.

Discussion

The main findings of the present study are as follows: (1) Approximately 8% of patients with AF had a hemoglobin <10 g/dL when they were anticoagulated. (2) In patients with AF and hemoglobin <10 g/dL, NOAC therapy was associated with a significantly lower risk of major bleeding or gastrointestinal tract bleeding when compared with warfarin therapy, and there was no statistical difference between the 2 therapies in terms of their risk of IS/SE or death. This better

Table 2. Baseline Characteristics of NOAC and Warfarin Users in Patients With Hemoglobin <10 g/dL

Characteristic	NOAC Users (n=390)	Warfarin Users (n=279)	*P* Value
Age, y	81 (75–86)	78 (72–83)	<0.001
Aged 65–74 y, n (%)	86 (22.1)	97 (34.8)	
Aged 75–84 y, n (%)	176 (45.1)	122 (43.7)	
Aged ≥85 y, n (%)	128 (32.8)	60 (21.5)	
Women, n (%)	229 (58.7)	168 (60.2)	0.70
Comorbidity at index date, n (%)			
Diabetes mellitus	112 (28.7)	77 (27.6)	0.75
Hypertension	219 (56.2)	140 (50.2)	0.13
Chronic liver disease	59 (15.1)	33 (11.8)	0.22
Heart failure	175 (44.9)	146 (52.3)	0.06
Prior myocardial infarction	98 (25.1)	56 (20.1)	0.13
Peripheral artery occlusive disease	19 (4.9)	12 (4.3)	0.73
Prior stroke	97 (24.9)	82 (29.4)	0.19
Prior transient ischemic attack	12 (3.1)	11 (3.9)	0.55
Bleeding history	167 (42.8)	114 (40.9)	0.61
Cancer	85 (21.8)	71 (25.5)	0.27
Peptic ulcer disease	132 (33.9)	88 (31.5)	0.53
CHA_2DS_2-VASc score*	4.3±1.7	4.3±1.9	0.67
HAS-BLED score†	3.7±1.0	3.7±1.1	0.81
Laboratory data			
eGFR, mL/min per 1.73 m^2	61 (45–85)	55 (43–85)	0.25
eGFR <60 mL/min per 1.73 m^2, n (%)	149 (38.2)	100 (35.8)	0.53
Hemoglobin, g/dL	9.3 (8.8–9.7)	9.2 (8.6–9.6)	0.05
Platelets, $\times 10^3/\mu L$	211 (163–284)	200 (131–281)	0.09
Aspartate aminotransferase, U/L	27 (21–37)	29 (20–51)	0.11
Alanine aminotransferase, U/L	18 (13–29)	18 (13–29)	0.99
Total bilirubin, mg/dL	0.7 (0.4–0.9)	0.7 (0.4–1.0)	0.43
LDL-C, mg/dL	83 (66–105)	81 (65–95)	0.20
Cholesterol, mg/dL	150 (131–176)	151 (125–179)	0.84
Medications, n (%)			
Statins	83 (21.3)	83 (29.8)	0.012
Amiodarone	134 (34.4)	138 (49.5)	<0.001
ß Blockers	251 (64.4)	198 (71.0)	0.07
ACEIs or ARBs	224 (57.4)	198 (71.0)	<0.001
Calcium channel blockers	136 (34.9)	111 (39.8)	0.19
Loop diuretics	248 (65.6)	234 (83.9)	<0.001
Aspirin	118 (30.3)	140 (50.2)	<0.001
Digoxin	96 (24.6)	115 (41.2)	<0.001
Clopidogrel	75 (19.2)	83 (29.8)	0.002
Ticagrelor	8 (2.1)	4 (1.4)	0.55

Continued

Table 2. Continued

Characteristic	NOAC Users (n=390)	Warfarin Users (n=279)	*P* Value
Nonsteroidal anti-inflammatory drugs	111 (28.5)	105 (37.6)	0.012
Proton pump inhibitors	147 (37.7)	155 (55.6)	<0.001

Values are given as mean±SD or median (interquartile range), except as noted. The CHA_2DS_2-VASc score awards 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex (sex category) and 2 points each for age ≥75 years and previous stroke or transient ischemic attack. The HAS-BLED score awards 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age ≥65 years, and antiplatelet drug or alcohol use. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NOAC, non–vitamin K antagonist oral anticoagulant.

*Congestive Heart Failure, Hypertension, Age ≥75 Years (doubled), Diabetes Mellitus, Prior Stroke, Transient Ischemic Attack, or Thromboembolism [doubled], Vascular Disease, Age 65–74 Years, Sex Category.

†Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly.

safety profile of NOAC therapy was consistent with the results in patients with hemoglobin ≥10 g/dL. (3) In anemic patients, the differences between NOAC and warfarin therapies in their effects on IS/SE, bleeding, and mortality were similar in patients with and without a history of cancer or peptic ulcer disease.

These findings fill a knowledge void on the safety and effectiveness of NOAC therapy for patients with AF and hemoglobin <10 g/dL. Such patients were typically excluded from the major randomized controlled trials that have investigated the efficacy and safety of NOACs for preventing stroke in patients with AF, namely, the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, the ROCKET AF (Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), the ENGAGE AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation) trial, and the AVERROES (A Phase III Study of Apixaban in Patients With Atrial Fibrillation).[11,12,14,16] The superiority of NOAC over warfarin for preventing stroke in patients with AF and mild anemia (hemoglobin, 9–12.9 g/dL in men and 9–11.9 g/dL in women) has been demonstrated in a post hoc analysis in the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial.[1] In that trial, patients with mild anemia were older, had higher $CHADS_2$ (Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack or Thromboembolism [doubled]) and HAS-BLED scores, and were more likely to have had prior bleeding events than those without anemia.[1] Apixaban therapy resulted in similar reductions in stroke and bleeding events relative to warfarin therapy in patients with

Table 3. Event Rate and Risk of IS/SE, Bleeding, and Death in Anticoagulated Patients With AF

Variable	Event Rate/100 Person-Years		Crude Data		Adjusted Data*		Competing Risk†	
	NOAC Users (n=4793)	Warfarin Users (n=2894)	HR (95% CI)	*P* Value	Adjusted hazard ratios (95% CI)	*P* Value	Adjusted hazard ratios (95% CI)	*P* Value
Hemoglobin ≥10 g/dL (n=7687)								
IS/SE	5.10	6.67	0.62 (0.55–0.69)	<0.001	0.75 (0.66–0.85)	<0.001	0.74 (0.65–0.84)	<0.001
Major bleeding	7.35	12.36	0.46 (0.42–0.51)	<0.001	0.53 (0.48–0.59)	<0.001	0.52 (0.46–0.58)	<0.001
Gastrointestinal tract bleeding	4.27	5.76	0.58 (0.51–0.65)	<0.001	0.69 (0.60–0.78)	<0.001	0.67 (0.59–0.77)	<0.001
Death	3.06	2.97	0.95 (0.81–1.10)	0.492	1.05 (0.89–1.23)	0.576		
Hemoglobin <10 g/dL (n = 669)								
IS/SE	7.29	8.30	0.59 (0.41–0.86)	0.006	0.71 (0.47–1.06)	0.106	0.64 (0.42–0.97)	0.035
Major bleeding	7.61	14.27	0.37 (0.25–0.52)	<0.001	0.41 (0.28–0.60)	<0.001	0.40 (0.28–0.59)	<0.001
Gastrointestinal tract bleeding	3.76	7.18	0.37 (0.24–0.58)	<0.001	0.42 (0.26–0.68)	<0.001	0.41 (0.25–0.67)	<0.001
Death	8.10	5.94	1.07 (0.73–1.56)	0.743	1.11 (0.74–1.68)	0.643		

AF indicates atrial fibrillation; HR, hazard ratio; IS, ischemic stroke; NOAC, non–vitamin K antagonist oral anticoagulant; SE, systemic embolism.

*IS/SE or death, adjusted for age, sex, hypertension, diabetes mellitus, history of heart failure, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, cancer, vascular disease, history of stroke, statins, hypertension medications, and antiplatelets; major bleeding or gastrointestinal tract bleeding, adjusted for age, sex, hypertension, diabetes mellitus, chronic liver disease, history of heart failure, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, cancer, history of peptic ulcer disease, history of bleeding, history of stroke, nonsteroidal anti-inflammatory drug, proton pump inhibitors, and antiplatelets.

†Death was considered as a competing risk factor in the Cox model.

Table 4. Event Rate and Risk of IS/SE, Bleeding, and Death in Anemic Patients With AF, Stratified by Cancer History

Hemoglobin <10 g/dL	Events/Total Years		Event Rate/100 Person-Years		Crude Data		Adjusted Data*	
	NOAC Users (n=390)	Warfarin Users (n=279)	NOAC Users (n=390)	Warfarin Users (n=279)	HR (95% CI)	*P* Value	Adjusted hazard ratios (95% CI)	*P* Value
Patients with a history of cancer (n=145)								
IS/SE	10/143	9/153	7.01	5.89	0.68 (0.27–1.74)	0.393	1.12 (0.33–4.02)	0.870
Major bleeding	8/117	24/110	6.83	21.88	0.21 (0.09–0.45)	<0.001	0.22 (0.08–0.53)	0.001
Gastrointestinal tract bleeding	8/138	15/140	5.81	10.70	0.30 (0.12–0.70)	0.007	0.19 (0.06–0.49)	0.004
Death	13/147	19/138	8.87	13.73	0.50 (0.24–1.05)	0.061	0.49 (0.20–1.15)	0.194
Patients without a history of cancer (n=524)								
IS/SE	41/557	56/631	7.36	8.88	0.58 (0.39–0.88)	0.010	0.75 (0.48–1.15)	0.203
Major bleeding	39/500	66/521	7.80	12.67	0.43 (0.28–0.63)	<0.001	0.49 (0.32–0.75)	<0.001
Gastrointestinal tract bleeding	20/607	45/696	3.29	6.47	0.39 (0.22–0.65)	<0.001	0.50 (0.28–0.87)	0.016
Death	49/619	34/754	7.92	4.51	1.37 (0.88–2.15)	0.187	1.28 (0.80–2.06)	0.321

AF indicates atrial fibrillation; HR, hazard ratio; IS, ischemic stroke; NOAC, non–vitamin K antagonist oral anticoagulant; SE, systemic embolism.
*IS/SE or death, adjusted for age, sex, hypertension, diabetes mellitus, history of heart failure, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, vascular disease, history of stroke, statins, hypertension medications, and antiplatelets; major bleeding or gastrointestinal tract bleeding, adjusted for age, sex, hypertension, diabetes mellitus, chronic liver disease, history of heart failure, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, history of peptic ulcer disease, history of bleeding, history of stroke, nonsteroidal anti-inflammatory drug, proton pump inhibitors, and antiplatelets.

and without mild anemia.[1] In patients with moderate anemia (hemoglobin <10 g/dL), NOAC seems to be an equally effective but safer anticoagulant than warfarin for preventing stroke for anemic patients with AF and hemoglobin <10 g/dL. The lower risk of major bleeding associated with NOAC therapy was consistently observed in anemic patients with or without a history of cancer or peptic ulcer disease. For patients with a history of cancer or peptic ulcer disease, NOAC may be a better oral anticoagulant than warfarin.

Anemia is common in patients with AF,[18] and the choices of anticoagulant for patients with AF and anemia have been puzzling. A sizable proportion of patients with AF would not have been eligible for the 4 major clinical trials of NOACs, and the most common reason for their exclusion from these trials was anemia (15.1%).[25] In the 2016 European Society of Cardiology guidelines for managing AF, anemia is considered as a potentially modifiable bleeding risk factor; and it is an important predictor of bleeding in $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Rebleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), and ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) scores.[3–5,17] Anemic patients with AF requiring anticoagulation were less likely to receive warfarin therapy because of bleeding concerns, and they more often discontinued warfarin therapy than nonanemic patients with AF.[26] In a subgroup analysis of the J-ROCKET AF (Japanese-ROCKET AF) trial, baseline anemia with warfarin therapy was one of the independent predictors of bleeding events.[6] In addition, patients with AF and anemia were also associated with a higher prevalence of stroke, a higher CHA_2DS_2-VASc score, and a greater risk of IS/SE.[1] Similar to the study of patients with mild anemia in the ARISTOTLE trial,[1] the present study found that patients with hemoglobin <10 g/dL were older, more likely to be women, and more likely to have experienced prior heart failure and stroke than patients with hemoglobin ≥10 g/dL. Both CHA_2DS_2-VASc and HAS-BLED scores were significantly higher in the anemic group. In these patients, NOAC therapy resulted in a similar reduction in the event rates of IS/SE and death and a significantly lower risk of major bleeding or gastrointestinal tract bleeding than warfarin.

Anemic patients with AF receiving anticoagulant therapy require more extensive follow-up because of their increased risks of bleeding and the high probability of anticoagulant interruptions. In the present cohort, 8% of the patients initiating oral anticoagulant therapy had a baseline hemoglobin level <10 g/dL. Before NOAC therapy can be initiated in such patients, their history of bleeding and clinical conditions that are likely to result in bleeding (ie, peptic ulcer disease, impaired renal or liver function, anemia, and thrombocytopenia) should be investigated, and corrected, if reversible.[17,18] Medications that could increase the risk of major bleeding, such as nonsteroidal anti-inflammatory drugs or antiplatelets, should be avoided or balanced with the risk and benefit of anticoagulant therapy. For patients receiving an NOAC therapy, it may be recommended to follow up the hemogram 1 month after anticoagulant initiation and then every 6 to

Table 5. Event Rate and Risk of IS/SE, Bleeding, and Death in Anemic Patients With AF, Stratified by Peptic Ulcer Disease History

Hemoglobin <10 g/dL	Events/Total Years		Event Rate/100 Person-Years		Crude Data		Adjusted Data*	
	NOAC Users (n=390)	Warfarin Users (n=279)	NOAC Users (n=390)	Warfarin Users (n=279)	HR (95% CI)	*P* Value	Adjusted hazard ratios (95% CI)	*P* Value
Patients with a history of peptic ulcer disease (n=220)								
IS/SE	26/226	19/258	11.48	7.37	1.14 (0.62–2.14)	0.685	1.62 (0.80–3.40)	0.208
Major bleeding	24/185	38/127	12.98	29.82	0.32 (0.19–0.54)	<0.001	0.36 (0.21–0.61)	<0.001
Gastrointestinal tract bleeding	11/253	25/235	4.35	10.62	0.30 (0.14–0.61)	0.001	0.36 (0.16–0.74)	0.010
Death	22/275	22/270	8.00	8.16	0.92 (0.49–1.72)	0.791	0.80 (0.41–1.58)	0.571
Patients without a history of peptic ulcer disease (n=449)								
IS/SE	25/474	46/526	5.28	8.75	0.40 (0.24–0.64)	<0.001	0.53 (0.31–0.91)	0.029
Major bleeding	23/432	52/503	5.32	10.33	0.35 (0.21–0.57)	<0.001	0.49 (0.29–0.82)	0.006
Gastrointestinal tract bleeding	17/492	35/600	3.46	5.83	0.42 (0.23–0.75)	0.004	0.51 (0.27–0.94)	0.023
Death	40/490	31/622	8.16	4.98	1.15 (0.72–1.87)	0.567	1.09 (0.66–1.82)	0.742

AF indicates atrial fibrillation; HR, hazard ratio; IS, ischemic stroke; NOAC, non–vitamin K antagonist oral anticoagulant; SE, systemic embolism.
*IS/SE or death, adjusted for age, sex, hypertension, diabetes mellitus, history of heart failure, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, cancer, vascular disease, history of stroke, hypertension medications, and antiplatelets; major bleeding or gastrointestinal tract bleeding, adjusted for age, sex, hypertension, diabetes mellitus, chronic liver disease, history of heart failure, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, cancer, history of bleeding, history of stroke, nonsteroidal anti-inflammatory drug, proton pump inhibitors, and antiplatelets.

12 months thereafter may be advisable. If hemoglobin levels remain stable, NOAC therapy can be continued.

Study Strengths

The strengths of our study include using a large, well-defined population sample; available baseline hemoglobin, platelet count, renal function, and liver function data before the initiation of oral anticoagulant therapy; and a direct comparison of NOAC and warfarin therapies in patients with hemoglobin levels <10 g/dL and ≥10 g/dL. To our knowledge, this is 1 of the only 2 studies that have compared NOAC therapy and warfarin therapy in patients with AF and hemoglobin <10 g/dL.[1]

Study Limitations

This study has several limitations. First, miscoding and misclassification are potential sources of biases in a database that relies on physician-reported diagnoses. However, such miscoding and misclassification are unlikely to have differed systematically between the 2 subgroups of patients, and our findings that NOAC was safer than warfarin and equally effective in patients with hemoglobin ≥10 g/dL agreed with meta-analysis and real-world data.[27,28] Second, because this study was a retrospective data analysis rather than a randomized controlled trial, both selection bias and unmeasured confounders were evident, despite statistical adjustments. Third, we did not assess the quality of warfarin control by calculating the time in therapeutic range because there were many missing values for prothrombin time from the follow-up period. In Taiwan, the measured time in the therapeutic range measured in one study is 56.6%,[29] which is lower than for the white or Japanese populations. The observed benefit of lower bleeding risks in NOACs might disappear when they were compared with well-managed warfarin.[30] Further studies to generalize and apply the findings of this study to other populations are, thus, warranted. Fourth, the sample size for patients with hemoglobin <10 g/dL was only 669. The small sample may not be sufficient to establish the efficacy and safety of NOACs and limit the generalization of the results. Similarly, given the limited patient number and event number in each subgroup, extreme caution is needed in the interpretation of subanalysis results.

Conclusions

In patients with AF and hemoglobin <10 g/dL, NOAC therapy was associated with lower risks of major bleeding or gastrointestinal tract bleeding than warfarin therapy, and the 2 therapies showed no significant difference in the risk of IS/SE or death.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9-CM and ICD-10-CM codes used to define the comorbidities and outcomes.

Comorbidities and outcomes	*ICD-9* codes	*ICD-10* codes	Diagnosis definition
End stage renal disease	585	N185, N186	Discharge
Pulmonary embolism	415.1, 415.11, 415.19	I26	Discharge
Deep vein thrombosis	451.11, 451.19, 451.2, 451.81, 451.9, 453.40, 453.41,453.42,453.8, 453.9	I82.4, I82.5, I82.6, I82.7	Discharge
Total knee replacement, total hip replacement	81.51, 81.54, V43.64, V43.65	Z96.64, Z96.65	Discharge
Heart valve replacement	68016, 68017, 68018		Discharge
Ischemic stroke	433, 434, 435,436	I63, I64, I65, I66, G458, G459, I6789	Discharge
Systemic embolism	444	I74	Discharge
Intracranial hemorrhage	430, 431, 432, 852, 853	I60, I61, I62	Discharge
GI bleeding	456.0, 456.2, 455.2, 455.5, 455.8, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 569.3, 535.01, 535.11, 535.21, 535.31, 535,41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12 562.13 568.81, 569.3, 569.85, 578	K250, K260, K270, K280, K290	Discharge
Other critical site bleeding	423,0, 459.0, 568.81, 593.81, 599.7, 623.8, 626.32, 626.6, 719.1, 784.7, 784.8, 786.3	D62, J942, H113, H356, H431, N02, N95, R04, R31, R58	Discharge
Congestive heart failure	428	I11.0, I13.0, I13.2, I42.0,I50, I50.1, I50.91	Discharge

Hypertension	401, 402	I10, I11	Outpatient department ≥2
Diabetes mellitus	250	E10, E10.1, E10.9, E11.0, E11.1, E11.9	Outpatient department ≥2
Chronic lung disease	490, 491.0, 491.1, 491.20-491.22, 491.8, 491.9, 492.0, 492.8, 493.00-493.02, 493.10-493.12, 493.20-493.22, 493.81, 493.82, 493.90-493.92,494.0, 494.1, 495.8, 495.9, 496, 500, 502, 503, 504, 505, A323, A325	J44	Discharge
Chronic liver disease	570, 571, 572	B150, B160, B162, B190, K704, K72, K766, I85	Outpatient department ≥2
Chronic kidney disease	580-589	I12, I13, N00, N01, N02, N03, N05, N07, N11, N14, N17, N18, N19,Q61	Outpatient department ≥2
Myocardial infarction	410, 411,412	I21-I25	Discharge
Peripheral artery occlusive disease	440.2	I70.2-I70.9, I71, I73.9	Discharge
Transient ischemic attack	435	G45	Discharge
Cancer	140-208	C00-C96, C7A	Discharge
Peptic ulcer	531, 532, 533, 534	K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9	Discharge

ICD-9 indicates International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Table S2 Event Rate and Risk of IS/SE, Bleeding, and Death in Anticoagulated AF Patients Using 7 days as a Censoring Window for Drug Switches.

	Event Rate/ 100 Person-Years		Crude		Adjusted*	
	NOAC (n=4793)	Warfarin (n=2894)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Patients with hemoglobin ≥10 g/dL (n=7687)						
IS/SE	5.08	6.63	0.62 (0.55–0.69)	<0.001	0.69 (0.61–0.77)	<0.001
Major bleeding	7.33	12.26	0.46 (0.42–0.51)	<0.001	0.51 (0.46–0.57)	<0.001
GI bleeding	4.25	5.72	0.58 (0.51-0.66)	<0.001	0.68 (0.60–0.77)	<0.001
Death	3.03	2.91	0.96 (0.82–1.12)	0.62	0.92 (0.79–1.08)	0.327
Patients with hemoglobin <10 g/dL (n=669)						
IS/SE	7.29	8.17	0.60 (0.41–0.88)	0.008	0.80 (0.54–1.19)	0.296
Major bleeding	7.61	14.27	0.37 (0.25–0.52)	<0.001	0.43 (0.29–0.62)	<0.001

GI bleeding	3.76	7.18	0.37 (0.24–0.58)	<0.001	0.44 (0.27–0.70)	<0.001
Death	8.10	5.94	1.07 (0.73–1.56)	0.743	0.99 (0.66–1.48)	0.951

AF indicates atrial fibrillation; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; IS/SE, ischemic stroke or systemic embolism; NOAC, non-vitamin K antagonist oral anticoagulants.

*IS/SE or death, adjusted for age, sex, hypertension, diabetes mellitus, history of heart failure, estimated glomerular filtration rate <60 mL/min/1.73m^2, cancer, vascular disease (myocardial infarction or peripheral vascular disease), history of transient ischemic attack, ischemic stroke, or systemic embolism, statins, hypertension medications, and anti-platelets; major bleeding or GI bleeding, adjusted for age, sex, hypertension, diabetes mellitus, chronic liver disease, history of heart failure, estimated glomerular filtration rate <60 mL/min/1.73m^2, cancer, history of peptic ulcer disease, history of bleeding, history of stroke, nonsteroidal anti-inflammatory drug, proton pump inhibitors, and anti-platelets.

Table S3. Hazard ratio with 95% confidence interval of outcomes (NOACs vs warfarin) in patients with missing values included or excluded.

	Patients with missing values included		Patients with missing values excluded	
	HR* (95% CI)	*P* value	HR* (95% CI)	*P* Value
Hemoglobin ≥10 g/dL	(n=7687)		(n=6082)	
IS/SE	0.68 (0.61–0.77)	<0.001	0.68 (0.59–0.79)	<0.001
Major bleeding	0.51 (0.46–0.56)	<0.001	0.52 (0.46–0.58)	<0.001
GI bleeding	0.67 (0.59–0.77)	<0.001	0.67 (0.58–0.77)	<0.001
Death	0.91 (0.78–1.07)	0.266	0.92 (0.77–1.10)	0.338
Hemoglobin <10 g/dL	(n=669)		(n=482)	
IS/SE	0.79 (0.53–1.17)	0.249	0.85 (0.54–1.34)	0.513
Major bleeding	0.43 (0.30–0.62)	<0.001	0.37 (0.24–0.56)	<0.001

GI bleeding	0.45 (0.28–0.71)	<0.001	0.45 (0.26–0.76)	0.004
Death	0.99 (0.66–1.48)	0.951	0.94 (0.58–1.54)	0.826

*IS/SE or death, adjusted for age, sex, hypertension, diabetes mellitus, history of heart failure, estimated glomerular filtration rate <60 mL/min/1.73m^2, cancer, vascular disease, history of stroke, statins, hypertension medications, and anti-platelets; major bleeding or GI bleeding, adjusted for age, sex, hypertension, diabetes mellitus, chronic liver disease, history of heart failure, estimated glomerular filtration rate <60 mL/min/1.73m^2, cancer, history of peptic ulcer disease, history of bleeding, history of stroke, nonsteroidal anti-inflammatory drug, proton pump inhibitors, and anti-platelets.