ORIGINAL RESEARCH

Effectiveness and Safety of Non–Vitamin K Antagonist Oral Anticoagulant and Warfarin in Cirrhotic Patients With Nonvalvular Atrial Fibrillation

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***Background*—**Liver cirrhotic patients with nonvalvular atrial fibrillation have been excluded from randomized clinical studies regarding oral anticoagulants for stroke prevention. Whether non–vitamin K antagonist oral anticoagulants (NOACs) are superior to warfarin for these patients remains unclear.

***Methods and Results*—**This nationwide retrospective cohort study, with data collected from the Taiwan National Health Insurance Research Database, enrolled 2428 liver cirrhotic patients with nonvalvular atrial fibrillation taking apixaban (n=171), dabigatran (n=535), rivaroxaban (n=732), or warfarin (n=990) from June 1, 2012, to December 31, 2016. We used propensity score–based stabilized weights to balance covariates across study groups. Patients were followed until the occurrence of an event or the end date of study. The NOAC group (n=1438) showed risk of ischemic stroke/systemic embolism and intracranial hemorrhage comparable to that of the warfarin group (n=990) after adjustment. The NOAC group showed significantly lower risk of gastrointestinal bleeding (hazard ratio: 0.51 [95% CI, 0.32–0.79]; *P*=0.0030) and all major bleeding (hazard ratio: 0.51 [95% CI, 0.32–0.74]; *P*=0.0003) compared with warfarin group. Overall, 90% (n=1290) of patients were taking a low-dose NOAC (apixaban 2.5 mg twice daily, rivaroxaban 10–15 mg daily, or dabigatran 110 mg twice daily). The subgroup analysis indicated that both dabigatran and rivaroxaban showed lower risk of all major bleeding than warfarin. The advantage of lower gastrointestinal and all major bleeding with NOACs over warfarin is contributed by those subgroups with either nonalcoholic or nonadvanced liver cirrhosis.

***Conclusions*—**NOACs have a risk of thromboembolism comparable to that of warfarin and a lower risk of major bleeding among liver cirrhotic Asian patients with nonvalvular atrial fibrillation. Consequently, thromboprophylaxis with low-dose NOACs may be considered for such patients. **(*J Am Heart Assoc*. 2019;8:e011112. DOI: 10.1161/JAHA.118.011112.)**

Key Words: atrial fibrillation • direct thrombin inhibitor • factor Xa inhibitor • hemorrhage • ischemic stroke • liver cirrhosis • mortality • warfarin

Liver cirrhosis is a condition associated with thrombocytopenia and decreased synthesis of several pro- and anticoagulant factors, which affects the hemostasis of several organs.[1] The abnormalities in hemostasis related to liver cirrhosis may increase the risk of either bleeding or thrombosis.[2,3] Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a global prevalence of 2% to 3%, and significantly increases the risk of thromboembolic events, hospitalization, and mortality.[4,5] Cirrhotic patients with AF may have a higher risk of ischemic stroke or cerebral hemorrhage,

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Clinical Perspective

What Is New?

- Liver cirrhotic patients have been excluded from randomized clinical trials regarding non–vitamin K antagonist oral anticoagulants for stroke prevention among patients with nonvalvular atrial fibrillation.
- Our study indicated that the group taking non–vitamin K antagonist oral anticoagulants showed risk of ischemic stroke/systemic embolism and intracranial hemorrhage comparable to that of the warfarin group and significantly lower risk of gastrointestinal bleeding and major bleeding among liver cirrhotic patients with nonvalvular atrial fibrillation.

What Are the Clinical Implications?

- Thromboprophylaxis with non–vitamin K antagonist oral anticoagulants may be considered for liver cirrhotic Asian patients with nonvalvular atrial fibrillation in clinical practice.

and previous studies indicated that cirrhotic AF patients taking warfarin may be associated with better clinical outcomes compared with those taking an antiplatelet agent or going without treatment.[6] However, because of the lack of established guidelines and the impaired synthesis of clotting factors interfacing the value of prothrombin time and international normalized ratio, prescription of warfarin remained challenging among cirrhotic AF patients. Several clinical trials have demonstrated that non–vitamin K antagonist oral anticoagulants (NOACs) have efficacy similar to or better than warfarin and are safer alternatives to warfarin.[7–10] However, those studies excluded cirrhotic AF patients because of poor underlying condition, and the effectiveness and safety profiles of NOACs among cirrhotic AF patients in clinical practice are limited. The objective of this study was to use data from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the effectiveness and safety of NOACs, including apixaban, dabigatran, and rivaroxaban, compared with warfarin for cirrhotic AF patients in clinical practice.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

This study was approved by the institutional review board of Chang Gung Memorial Hospital. We analyzed the medical data of the Taiwan National Health Insurance system, which is a mandatory universal health insurance program and provides comprehensive medical care coverage to nearly all Taiwanese citizens. As of 2014, there were >23 million enrollees and a >99% coverage rate of the entire population.[11] By using a consistent encrypting procedure, each patient's original identification number in NHIRD was encrypted and deidentified to protect patient privacy. Therefore, informed consent was waived by the institutional review board of Chang Gung Memorial Hospital.

Study Design

A dynamic cohort with 2 study groups (NOACs and warfarin) was used in the study. A flowchart of the study enrollment is shown in Figure 1. A total of 279 776 patients diagnosed with AF (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 427.31 from January 1, 2010, to December 31, 2015, or *ICD-10-CM* code I48 from January 1, 2016, to December 31, 2016) were identified. Among those, 11 206 patients were recognized as having liver cirrhosis according to diagnosis using *ICD* codes indicating liver cirrhosis (*ICD-9-CM* codes 571.2, 571.5, and 571.6 or *ICD-10-CM* codes K72, K74, K70.2, K70.3, and K70.4).[12–14] Those cirrhotic AF patients were included with their first prescription of a NOAC, including dabigatran as of the approval date of June 1, 2012; rivaroxaban as of February 1, 2013; or apixaban as of June 1, 2014, or warfarin after June 1, 2012. The index date for each group was defined as the first date of prescription for any NOAC or for warfarin after June 1, 2012. The follow-up period was defined as the index date until the occurrence of any thromboembolic or major bleeding event or the end date of study period (December 31, 2016), whichever came first.

Exclusion Criteria

Those patients with diagnoses indicating venous thromboembolism (pulmonary embolism or deep vein thrombosis), joint replacement therapy, or valvular AF (mitral stenosis or valvular surgery) within 6 months before the index date were excluded from this study to establish a cohort of NVAF patients taking an oral anticoagulant for the primary purpose of stroke prevention. Patients who took >1 kind of NOAC during their whole treatment course were also excluded from this study.

Study Outcomes

Four study outcomes were defined to determine the effectiveness and safety for cirrhotic AF patients taking NOACs and warfarin: ischemic stroke/systemic embolism (IS/SE),

intracranial hemorrhage (ICH), major gastrointestinal bleeding (GIB), and all major bleeding events. All study outcomes were required to be a discharge diagnosis to avoid misclassification. ICH was defined with the use of codes for atraumatic hemorrhage. Major GIB was defined as a hospitalized primary code indicating bleeding in the gastrointestinal tract.[15–17] All major bleeding events were defined as the total hospitalized events of ICH, major GIB, and other critical-site bleeding. The diagnosis codes for NHIRD shifted from *ICD-9-CM* to *ICD-10-CM* after January 1, 2016. The *ICD-9-CM* and *ICD-10-CM* codes used to identify the study outcomes and the baseline covariates are summarized in Table S1. The same patient may have had >1 study outcome during the study duration, and all study outcomes were reported independently in the study.

Covariates

Baseline covariates referred to any claim record with the noted diagnoses or medication codes before the index date. Bleeding history was confined to events within 6 months preceding the index date. History of prescription for medicine was confined to at least once within 3 months preceding the index date. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65–74 years, female sex) was adopted to predict the risk of ischemic stroke or thromboembolic events in AF patients, and the HAS-BLED score (hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age ≥65 years, and antiplatelet drug or alcohol use) was adopted to predict the risk of bleeding in AF patients treated with oral anticoagulant.[18,19]

Statistical Analysis

The method of propensity score–based stabilized weights (PSSWs), which attempts to approximate the randomized clinical trial for observational cohort data by balancing covariates across the study groups,[20] was used to estimate the 4 study outcomes of NOACs and warfarin. The advantage of using PSSWs is preservation of the sample size of the original data to appropriately estimate the variance of the main effect and to maintain the designated type I error. The nonparametric generalized boosted model was used to obtain the PSSWs for optimal balance among study groups. The advantage of the generalized boosted model is automatic selection of which covariates to include and the best functional form including interactions.[21] The covariates in Table 1 were included in the generalized boosted model except for CHA_2DS_2-VASc and HAS-BLED scores, which were a combination of other covariates. The balance of potential confounders at baseline (index date) between study groups was assessed using the absolute standardized mean difference rather than statistical testing because balance is a property of the sample and not of an underlying population. An absolute standardized mean difference ≤0.1 indicated an insignificant difference in potential confounders between the study groups.[22] When comparing baseline characteristics among 3 NOAC groups, ANOVA, the χ^2 test, and the Fisher exact test were used, as appropriate (Table 2). The incidence rates were computed using the total number of study outcomes during the follow-up period divided by person-years at risk. The risk of study outcomes for NOACs versus warfarin (reference) was obtained using survival analysis (Kaplan–Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis). Specific subgroups were analyzed to determine whether the NOAC group continued to have a lower risk of study outcomes compared with the warfarin group. As noted, the PSSWs were reestimated for each subgroup analysis so that the NOAC and warfarin groups maintained a balance of covariates across groups. Statistical significance was defined as $P<0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute).

Results

Among the 11 206 AF patients with liver cirrhosis, we identified 1438 and 990 patients taking NOACs and warfarin, respectively (Figure 1). The mean follow-up periods were 1.13 and 1.30 years for the NOAC and warfarin groups, respectively. Overall, 27% (n=381) of NOAC users previously took warfarin. Among the NOAC group, 171, 535, and 732 patients were taking apixaban, dabigatran, and rivaroxaban, respectively. Of patients taking apixaban, 69.0% (n=118) were prescribed the low dose (2.5 mg twice daily) and 31.0% (n=53) were prescribed the standard dose (5 mg twice daily). For dabigatran, 88.8% (n=475) were taking a low dose (110 mg twice daily) and 11.2% (n=60) were taking the standard dose (150 mg twice daily). For rivaroxaban, 95.2% (n=697) of patients were taking the low dose (10–15 mg once daily), whereas only 4.8% (n=35) were taking the standard dose (20 mg once daily).

Before PSSWs, the NOAC group had higher prevalence of age, hypertension, and stroke history but lower prevalence of chronic kidney disease and congestive heart failure than the warfarin group. The NOAC group had higher CHA_2DS_2-VASc and HAS-BLED scores than the warfarin group before propensity score weighting (absolute standardized mean difference >0.1). After PSSWs, both study groups were well balanced in all characteristics (all absolute standardized mean difference <0.1; Table 1). For the effectiveness outcome, the NOAC group had cumulative risk of IS/SE similar to the warfarin group after PSSWs. For the safety outcome, the NOAC group showed significantly lower risk of

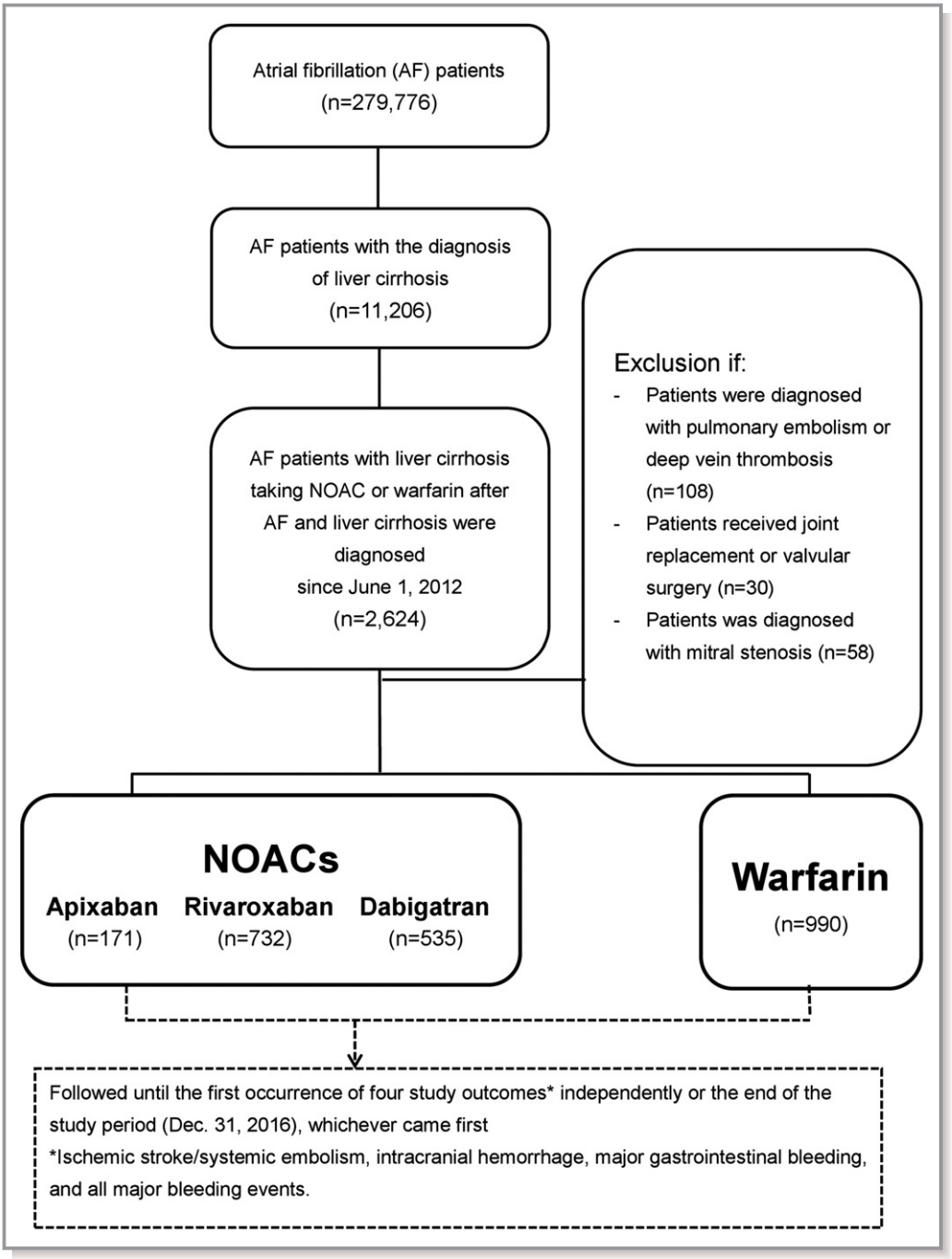

Figure 1. Enrollment of patients with liver cirrhosis and nonvalvular atrial fibrillation. From June 1, 2012, to December 31, 2016, a total of 171, 535, and 732 NVAF patients with liver cirrhosis taking apixaban, dabigatran, and rivaroxaban and 990 patients taking warfarin were enrolled in the study. AF indicates atrial fibrillation; NOAC, non–vitamin K antagonist oral anticoagulant.

major GIB (hazard ratio [HR]: 0.51 [95% CI, 0.32–0.79]; *P*=0.0030) and all major bleeding (HR: 0.51 [95% CI, 0.32–0.74]; *P*=0.0003) compared with the warfarin group after PSSWs. The cumulative risk showed clear separation of event curves for GIB and all major bleeding for the NOAC group versus the warfarin group either before or after PSSWs (Figure 2 and Figure S1).

After PSSWs, the annual incidence of IS/SE (3.2% versus 3.7% per year, *P*=0.4296) and ICH (1.0% versus 1.6% per year, *P*=0.1021) were comparable between the NOAC and warfarin groups. The NOAC group had significantly lower annual incidence of major GIB (1.9% versus 3.6% per year, *P*=0.0030) and all major bleeding (2.9% versus 5.4% per year, *P*=0.0003) compared with the warfarin group (Figure 2). Subgroup

Table 1. Baseline Characteristics of NVAF Patients With Liver Cirrhosis Taking Oral Anticoagulants Before and After PSSWs

	Before PSSWs			After PSSWs		
	NOAC (n=1438)	Warfarin (n=990)	ASMD	NOAC (n=1397)	Warfarin (n=946)	ASMD
Age, y, mean±SD	74.35±10.50	69.93±12.42	0.3848	72.80±11.05	72.41±11.21	0.0357
Age group						
<65	16.97	33.94		22.93	24.32	
65–74	27.33	26.06		26.94	27.22	
75–84	40.47	28.38		36.37	35.15	
>85	15.23	11.62		13.76	13.31	
Male sex	62.38	65.56	0.0662	63.65	63.70	0.0010
CHA_2DS_2-VASc, mean±SD	3.88±1.53	3.41±1.72	0.2895	3.72±1.57	3.66±1.65	0.0386
HAS-BLED, mean±SD	3.76±1.04	3.62±1.21	0.1226	3.71±1.08	3.69±1.11	0.0162
Hypertension	86.37	80.91	0.148	84.29	83.52	0.0211
Diabetes mellitus	46.31	44.55	0.0355	46.00	44.89	0.0223
Dyslipidemia	42.14	38.89	0.0663	41.02	39.80	0.0249
Chronic kidney disease	34.42	46.46	0.2472	38.67	39.80	0.0231
Chronic lung disease	3.96	3.33	0.0336	3.80	3.69	0.0055
Gout	30.81	30.81	0	30.93	29.85	0.0236
Congestive heart failure	20.51	25.45	0.1176	22.75	22.29	0.0108
Chronic ischemic heart disease	12.80	12.02	0.0235	12.71	12.41	0.0089
PAD	0.07	0.10	0.0108	0.07	0.12	0.0148
Stroke	20.58	15.45	0.1338	18.86	18.24	0.0161
TIA	2.71	2.93	0.0131	2.64	2.64	0.0001
Malignancy	20.38	16.77	0.0929	19.50	18.94	0.0141
PCI	5.42	5.56	0.0058	5.54	5.47	0.0030
CABG	0.35	1.21	0.0984	0.51	0.76	0.0305
History of bleeding	4.66	5.56	0.0407	4.78	4.89	0.0050
Use of NSAIDs	26.36	25.86	0.0113	26.46	25.34	0.0256
Use of PPI	19.19	27.27	0.1922	21.89	22.69	0.0192
Use of H_2 blocker	39.36	41.92	0.0521	39.92	40.62	0.0143
Use of ACEI/ARB	17.32	23.43	0.1523	19.44	20.28	0.0211
Use of amiodarone	28.44	34.44	0.1295	30.71	31.71	0.0215
Use of dronedarone	2.09	1.82	0.0194	2.00	2.31	0.0211
Use of β-blocker	57.51	59.39	0.0382	58.69	58.12	0.0115
Use of diltiazem/verapamil	25.80	25.05	0.0172	25.76	24.61	0.0263
Use of digoxin	25.24	32.73	0.1655	28.23	29.20	0.0215
Use of statin	7.93	8.69	0.1480	8.17	8.55	0.0136

Data are shown as percentages except as noted. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; ASMD, absolute standard mean difference; CABG, coronary artery bypass grafting; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65–74 years, female sex; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio (could not be determined from claims and was excluded from our scoring), age ≥65 years, and antiplatelet drug or alcohol use; NOAC, non–vitamin K antagonist oral anticoagulant; NVAF, nonvalvular atrial fibrillation; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PSSW, propensity score–based stabilized weights; TIA, transient ischemic attack.

analysis was performed to determine whether different NOACs were superior to warfarin regarding the risk of IS/SE and bleeding among subgroups. No heterogeneity was obvious among the 3 NOAC groups (most $P>0.05$; Table 2). The subgroup analysis indicated that dabigatran showed a significantly lower risk of all major bleeding (2.9% versus 5.3%

Table 2. Baseline Characteristics of NVAF Patients With Liver Cirrhosis Taking Apixaban, Dabigatran, and Rivaroxaban

	Apixaban (n=171)	Dabigatran (n=535)	Rivaroxaban (n=732)	*P* Value
Age, y, mean±SD	75.36±10.26	73.57±10.45	74.68±10.59	0.0722*
Age group				
<65, y	11.70	18.32	17.21	
65–74, y	33.92	27.85	25.41	
75–84, y	36.26	40.19	41.67	
>85, y	18.13	13.64	15.71	
Male sex	55.56	65.98	61.34	0.0353
CHA_2DS_2-VASc, mean±SD	3.98±1.57	3.82±1.46	3.90±1.57	0.4457*
HAS-BLED, mean±SD	3.90±1.04	3.82±1.46	3.90±3.76	0.1306*
Hypertension	87.72	86.54	85.93	0.8192
Diabetes mellitus	43.86	46.36	46.86	0.7781
Dyslipidemia	41.52	40.37	43.58	0.5134
Chronic kidney disease	41.52	29.91	36.07	0.0085
Chronic lung disease	3.51	3.36	4.51	0.5577
Gout	30.41	28.41	32.65	0.2698
Congestive heart failure	18.71	21.50	20.22	0.7064
Chronic ischemic heart disease	15.79	11.78	12.84	0.3919
PAD	0.00	0.00	0.14	1.0000†
Stroke	20.47	21.50	19.95	0.7962
TIA	2.92	2.06	3.14	0.4930
Malignancy	26.32	21.31	18.31	0.0513
PCI	7.02	4.30	5.87	0.0513
CABG	0.58	0.37	0.27	0.6838
History of bleeding	4.68	4.49	4.78	0.9700
Use of NSAIDs	30.99	24.11	26.91	0.1827
Use of PPI	19.88	18.13	19.81	0.7332
Use of H_2 blocker	38.60	37.94	40.57	0.6240
Use of ACEI/ARB	5.85	24.67	14.62	0.0001
Use of amiodarone	32.16	25.05	30.05	0.0769
Use of dronedarone	2.34	1.50	2.46	0.4805
Use of β-blocker	60.82	54.77	58.74	0.2381
Use of diltiazem/verapamil	25.15	25.42	26.23	0.9282
Use of digoxin	17.54	27.29	25.55	0.0370
Use of statin	4.09	10.09	7.24	0.0253

Data are shown as percentages except as noted. *P* values were calculated with the χ^2 test except as noted. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; CABG, coronary artery bypass grafting; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65–74 years, female; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio (could not be determined from claims and was excluded from our scoring), age ≥65 years, and antiplatelet drug or alcohol use; NVAF, nonvalvular atrial fibrillation; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; TIA, transient ischemic attack.

*ANOVA.

†Fisher exact test.

per year; HR: 0.54 [95% CI, 0.33–0.89]; *P*=0.0145) than warfarin. Rivaroxaban has a significantly lower risk of major GIB (1.6% versus 3.8% per year; HR: 0.38 [95% CI, 0.20–0.72]; *P*=0.0028) and all major bleeding (2.3% versus 5.7% per year; HR: 0.38 [95% CI, 0.23–0.65]; *P*=0.0004) than warfarin (Figure 3).

We also divided the cirrhotic patients taking oral anticoagulants into 2 subgroups: alcoholic versus nonalcoholic liver cirrhosis (Figure 4) and advanced versus nonadvanced liver cirrhosis (Figure 5). The definition of advanced liver cirrhosis was those cirrhotic patients who presented with any complications including ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or esophageal varicose bleeding. In total, 222 (15%) and 143 (14%) patients with alcoholic liver cirrhosis were taking NOACs and warfarin, respectively. For those patients with alcoholic liver cirrhosis, NOACs had risks of thromboembolism and major bleeding comparable to those of warfarin. In the contrast, those patients with nonalcoholic liver cirrhosis taking NOACs had lower risks of major GIB (HR: 0.40 [95% CI, 0.24–0.68]; *P*=0.0006) and major bleeding (HR: 0.45 [95% CI, 0.29–0.69]; *P*=0.0002) than those taking warfarin (Figure 4). There were 271 (19%) and 273 (27%) patients with advanced liver cirrhosis taking NOACs and warfarin, respectively. For those patients with advanced liver cirrhosis, it is noted that the NOAC group had a lower risk of ICH (HR: 0.17 [95% CI, 0.03–0.96]; *P*=0.0449) than the warfarin group. For those patients with nonadvanced liver cirrhosis, the NOAC group had lower risk of major GIB (HR: 0.45 [95% CI, 0.26–0.78]; *P*=0.0045) and major bleeding (HR: 0.51 [95% CI, 0.33–0.79]; *P*=0.0027) than the warfarin group (Figure 5).

Discussion

This is the first nationwide population-based and large-scale study to investigate the effectiveness and safety of NOACs versus warfarin in cirrhotic AF patients during a long following-up period. Our results indicated that the NOAC group had risk of IS/SE similar to that of the warfarin group and lower risk of GIB and all major bleeding events. In subgroup analyses, dabigatran and rivaroxaban were associated with lower risk of

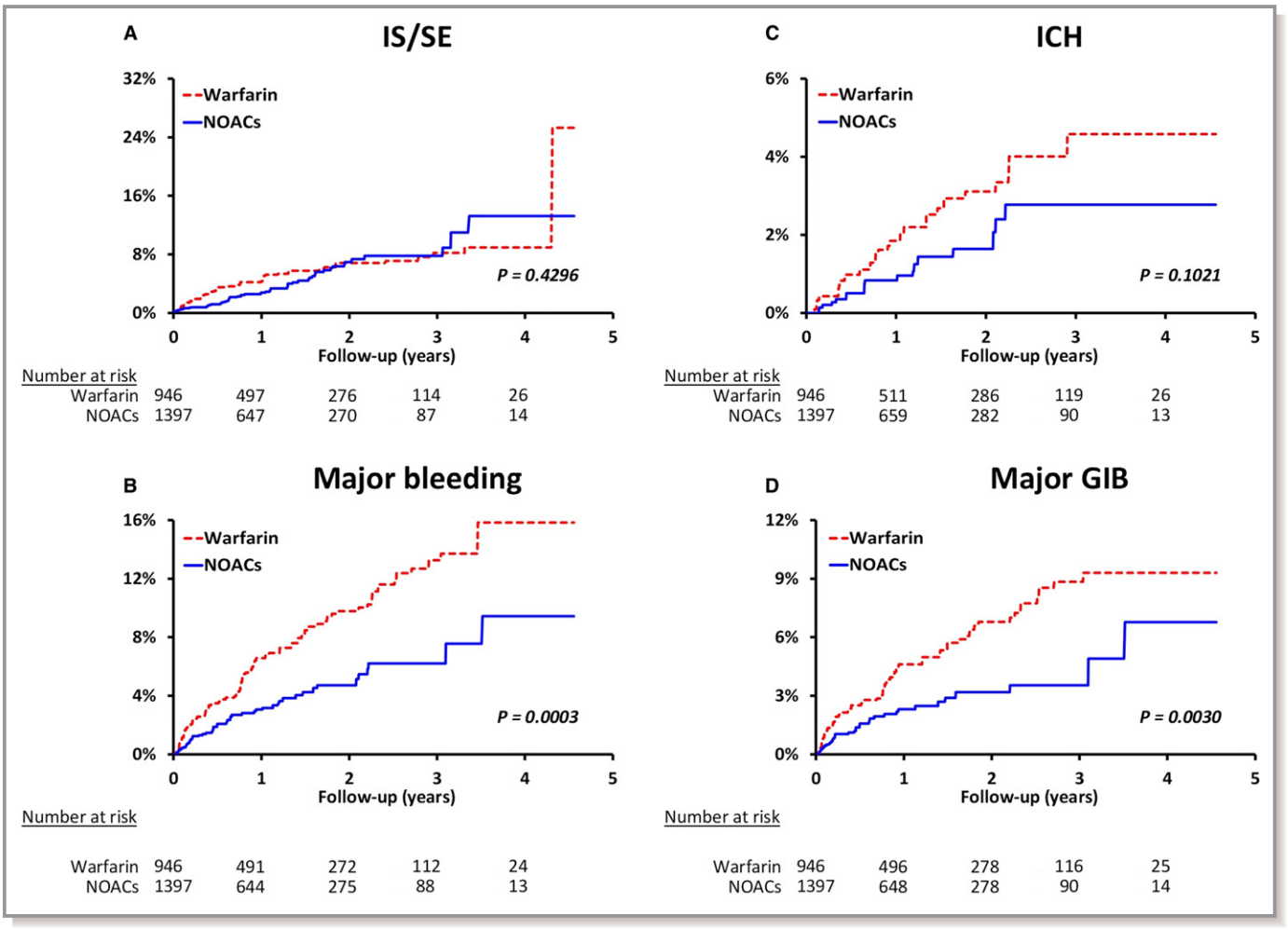

Figure 2. Cumulative incidence curves of IS/SE (**A**), all major bleeding (**B**), ICH (**C**), and major GI bleeding (**D**) for liver cirrhotic patients with nonvalvular atrial fibrillation according to initiated treatment after propensity score–based stabilized weighting. The NOAC group showed risk of IS/SE comparable to that of the warfarin group after adjustment. For the safety outcome, the NOAC group showed significantly lower risk of major GIB and all major bleeding than the warfarin group. GIB indicates gastrointestinal bleeding; ICH, intracranial hemorrhage; IS/SE, ischemic stroke/systemic embolism; NOAC, non–vitamin K antagonist oral anticoagulant.

all major bleeding events compared with warfarin. Furthermore, those patients with either nonalcoholic or nonadvanced liver cirrhosis taking NOACs were associated with lower risk of major GIB and all major bleeding than those patients taking warfarin.

The liver is a solid organ that produces most important factors involved in the coagulation and anticoagulation process, with the exception of von Willebrand factor, which is secreted by endothelial cells. Cirrhotic patients are considered to have higher risk of bleeding given decreased production of procoagulation factors II, V, VII, IX, X, and XI. Meanwhile, those patients are also prone to development of thrombosis given the decreased levels of antithrombin and anticoagulant proteins C and S and increased levels of procoagulation components factor VIII.[1–3,23] Furthermore, the coagulation laboratory tests commonly used to monitor the therapeutic effects of anticoagulants may not be useful in cirrhotic patients. Prolongation of prothrombin time and activated partial thromboplastin time are commonly found in cirrhotic patients. In contrast to prothrombin time and activated partial thromboplastin time, a lower level of antifactor Xa has been noted and correlates well with antithrombin in cirrhotic patients.[24,25]

Warfarin is a vitamin K antagonist that inhibits the synthesis of vitamin K–dependent clotting factors including factor II, VII, IX, and X in the liver. In addition to several limitations, including low therapeutic index, multiple food–drug and drug–drug interactions, and a requirement for regular coagulation monitoring, warfarin use is challenging in cirrhotic patients with innately elevated international normalized ratio. It is well known that warfarin is involved in a complex pathway of drug metabolism by human cytochrome P 450 (CYP; CYP1A2, CYP2C9, and CYP3A4), which contributes a wide range of warfarin–drug interactions.[26] Liver cirrhosis can affect the enzymes of warfarin metabolism.[27] Instead, drug–drug interaction through CYP metabolism is generally not an important issue for NOACs except for

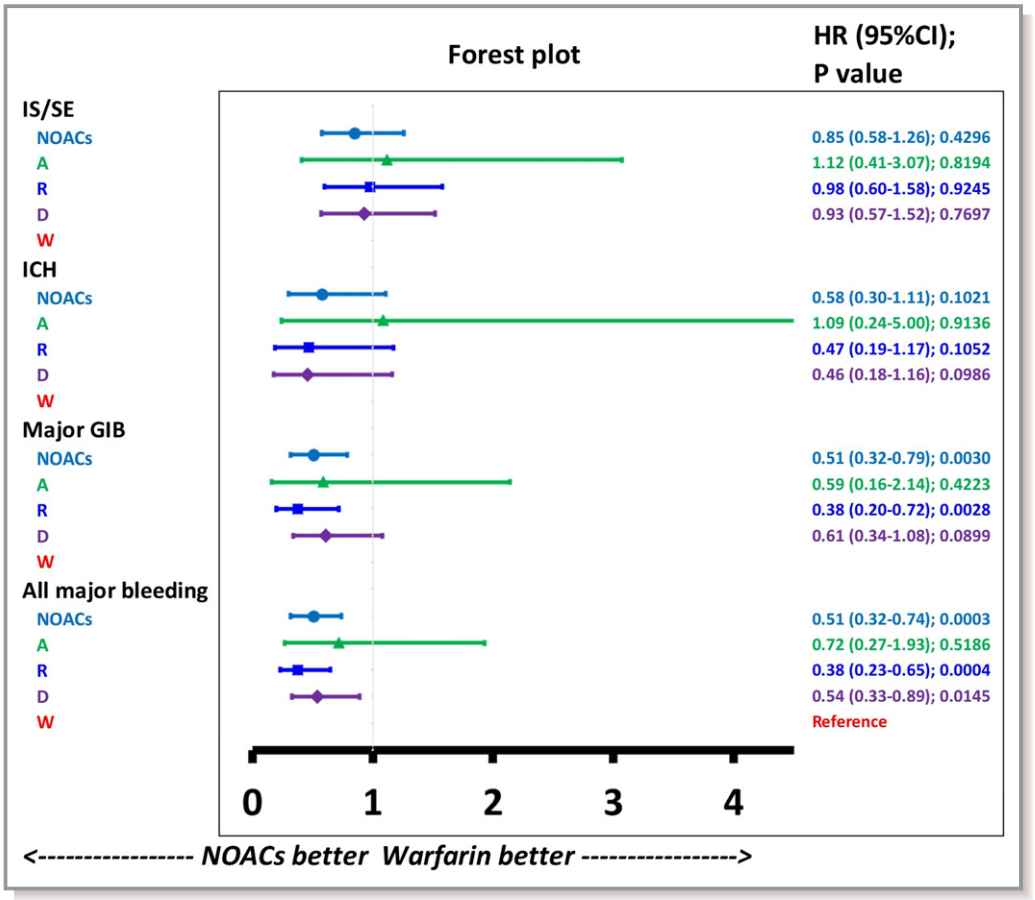

Figure 3. Forest plot of the hazard ratio for each NOAC vs warfarin among liver cirrhotic patients with NVAF taking oral anticoagulants. The NOAC group was associated with reduced risk of major GIB and all major bleeding compared with the warfarin group. Among NOACs, rivaroxaban was associated with lower risk of major GIB and all major bleeding than warfarin. Dabigatran was associated with lower risk of all major bleeding than warfarin. A indicates apixaban; D, dabigatran; GIB, gastrointestinal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; IS/SE, ischemic stroke/systemic embolism; NOAC, non–vitamin K antagonist oral anticoagulant; R, rivaroxaban; W, warfarin.

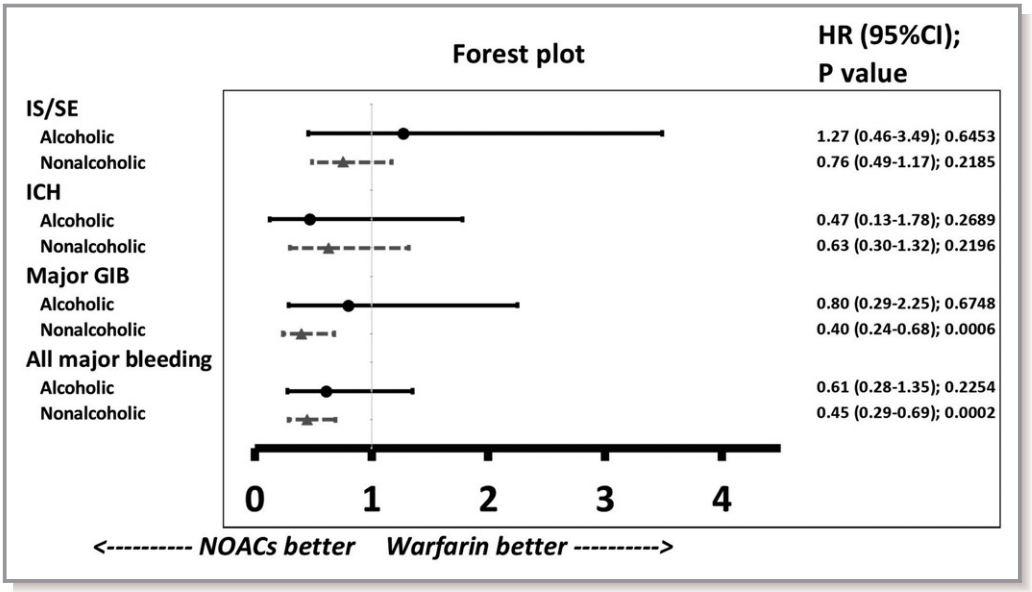

Figure 4. Forest plot of HRs for NOAC vs warfarin among patients with either alcoholic or nonalcoholic liver cirrhosis taking oral anticoagulants. In total, 222 (15%) and 143 (14%) patients with alcoholic liver cirrhosis were taking NOACs and warfarin, respectively. For those patients with alcoholic liver cirrhosis, the NOAC group has risks of thromboembolism and all major bleeding comparable to those of the warfarin group. For those patients with nonalcoholic liver cirrhosis, the NOAC group has lower risks of major GIB and all major bleeding than the warfarin group. GIB indicates gastrointestinal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; IS/SE, ischemic stroke/systemic embolism; NOAC, non–vitamin K antagonist oral anticoagulant.

rivaroxaban (66% CYP metabolism).[28] Consequently, NOACs seem to have advantages over warfarin in cirrhotic AF patients. Apixaban and rivaroxaban directly inhibit Xa factor, and dabigatran directly inhibits thrombin (factor IIa). Those NOACs have proven to be safer and convenient alternatives to warfarin without requiring regular coagulation monitoring.[7–9] However, cirrhotic patients were excluded from all large clinical trials of NOACs,[7–10] and little is known about the clinical outcomes of NOACs on cirrhosis AF patients. Until now, most data have been restricted to small retrospective clinical studies.[29–31]

Whether cirrhotic AF patients have to receive oral anticoagulants for prevention of thromboembolism remains uncertain. Several studies have indicated that cirrhotic AF patients have a higher risk of ischemic stroke than those without AF.[6,32] In addition to the risk of ischemic stroke, cirrhotic patients also have a higher risk of venous thromboembolism including pulmonary embolism, deep vein thrombosis, and splanchnic vein thrombosis.[33] A previous study demonstrated that cirrhotic AF patients taking warfarin may have better clinical outcomes than those taking antiplatelet therapy or going without treatment.[6] Furthermore, our present study demonstrated that in cirrhotic AF patients, NOACs have effectiveness similar to warfarin and a better safety profile. Nevertheless, further randomized and prospective studies are necessary to evaluate the effectiveness and safety of NOACs in this population with liver cirrhosis.

In subgroup analyses, patients treated with dabigatran or rivaroxaban, but not apixaban, were associated with a lower risk of major bleeding compared with those treated with warfarin. Several reasons may explain why apixaban did not have an advantage of lowering major bleeding events in cirrhotic AF patients. First, the apixaban group had a higher proportion of standard-dose prescriptions compared with the dabigatran and rivaroxaban groups in the present study (31.0%, 11.2%, and 4.8%, respectively). Second, the apixaban group had a trend of lowering major bleeding events, and the small sample size of the apixaban group may be insufficient for statistical significance. Third, apixaban had a higher proportion of hepatobiliary and intestinal elimination (≈75–80%) and a lower proportion of renal elimination (≈20–25%) compared with dabigatran and rivaroxaban.[34–36] Cirrhotic patients treated with apixaban may thus have an increased level of drug exposure, which may cause a higher risk of major bleeding. In addition, our study showed that the advantage of lower risk of major GIB or all major bleeding for NOACs was observed only in those patients with nonalcoholic or nonadvanced liver cirrhosis. A possibility is that the size of the sample with alcoholic or advanced liver cirrhosis may be insufficient for statistical significance. Nevertheless, our study indicated that NOACs may not have advantages over warfarin for those advanced cirrhotic patients with a worse condition that reduces drug-metabolizing enzymes or impairs hepatobiliary excretion.

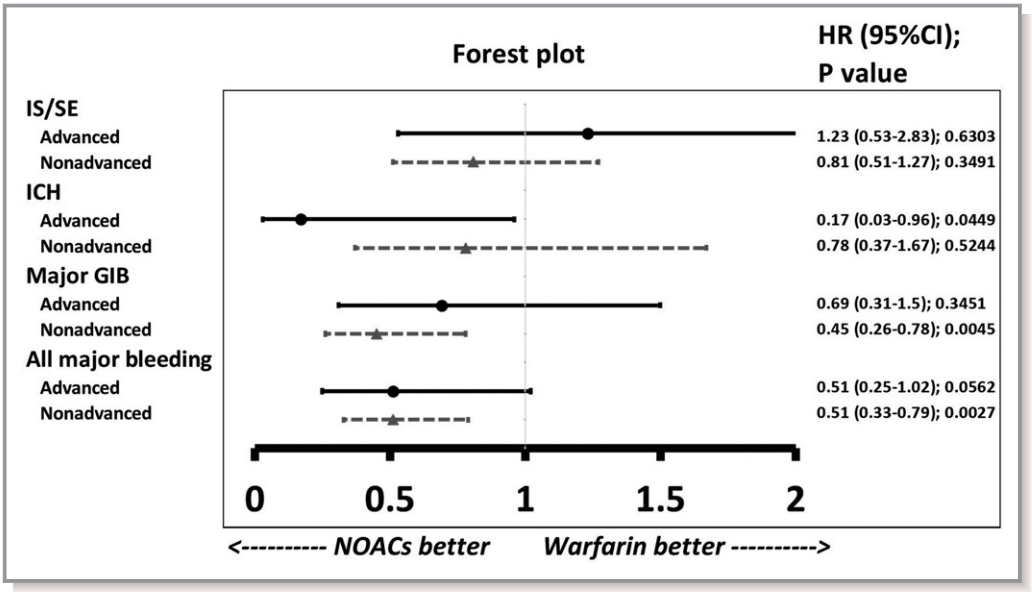

Figure 5. Forest plot of HRs for NOAC vs warfarin among patients with either advanced or nonadvanced liver cirrhosis taking oral anticoagulants. In total, 271 (19%) and 273 (27%) patients with advanced liver cirrhosis were taking NOACs and warfarin, respectively. For those patients with advanced liver cirrhosis, the NOAC group has lower risk of intracranial hemorrhage than the warfarin group. For those patients with nonadvanced liver cirrhosis, the NOAC group has lower risks of major GIB and all major bleeding than the warfarin group. GIB indicates gastrointestinal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; IS/SE, ischemic stroke/systemic embolism; NOAC, non–vitamin K antagonist oral anticoagulant.

The present study had several limitations. First, NHIRD does not include important laboratory data for prognostic scores of liver cirrhosis, such as Child–Pugh scores.[37] These nonmeasured covariates not included in PSSWs may affect our results. It remains unclear whether the grading of cirrhosis is associated with risk of thromboembolism in cirrhotic AF patients. A previous study reported that Child–Pugh score did not demonstrate a statistically significant difference between venous thromboembolism incidence in Child A versus Child B/C cirrhosis,[38] in which it may be due to decreased levels of both pro- and anticoagulation factors to achieve rebalanced hemostasis, even in patients with advanced liver cirrhosis.[1–3,23] Second, although some studies reported that adjustment of NOAC dosage may not be necessary in patients with Child A cirrhosis, limited data are available for patients with Child B or C cirrhosis.[29] Each physician's choice of treatment regarding to a specific NOAC and its dosage constitutes a major limitation of the present study. Third, the dominance of hepatitis B–related liver cirrhosis and a high prevalence of low-dose NOAC prescription in cirrhotic Asian patients may result in a different outcome from that of cirrhotic non-Asian patients.[39] Asian patients have a higher risk of bleeding when taking warfarin compared with non-Asian patients, and previous studies have indicated that NOACs may be more effective and safer in Asian than non-Asian patients.[40–42] Consequently, whether our results can be extrapolated to the non-Asian population remains uncertain.

Conclusions

Our data indicated that NOACs may be an effective and safe alternative to warfarin among the Asian patients with AF complicated by liver cirrhosis, especially for those with nonalcoholic or nonadvanced liver cirrhosis. Thromboprophylaxis with low-dose NOACs may be considered for such patients, and further prospective study is necessary to evaluate the effectiveness and safety of NOACs versus warfarin among the cirrhotic population.

Acknowledgments

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Disclosures

None.

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Supplemental Material

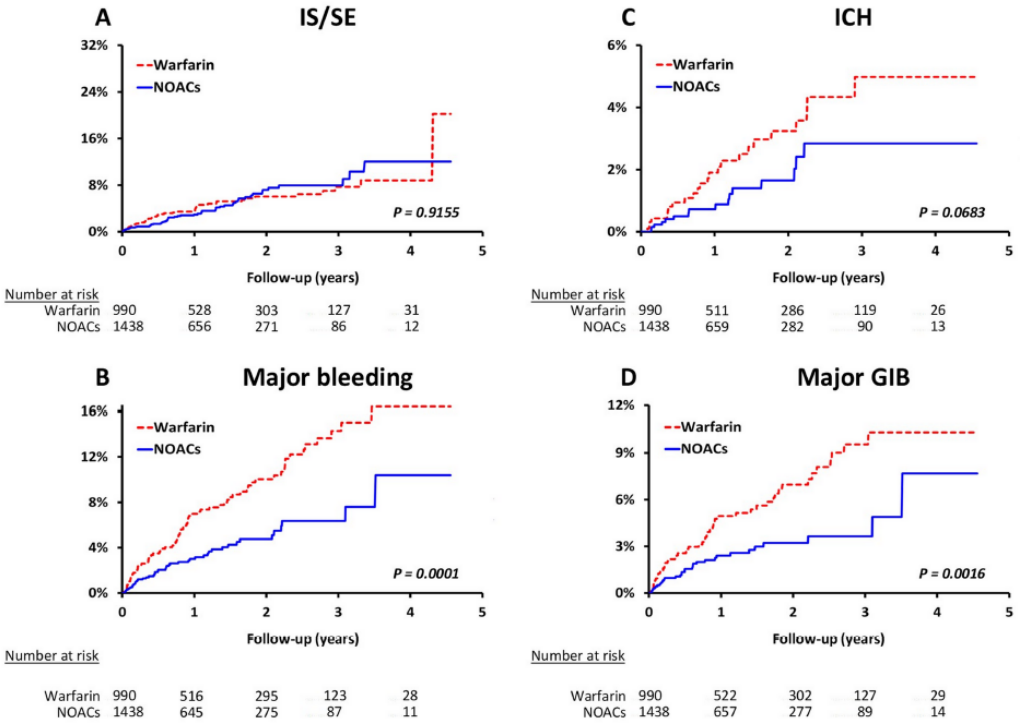
Table S1. International Classification of Disease (9th and 10th edition) Clinical Modification (ICD 9-CM and ICD 10-CM) codes used to define the co-morbidities and clinical outcome in the study cohort.

Disease	ICD-9 Codes	ICD-10 Codes	Diagnosis definition
Atrial fibrillation	427.31	I48	Discharge or outpatient department ≥2
Ischemic stroke	433, 434, 436	I63, I64	Discharge
Transient ischemic attack	435	G45	Discharge
Peripheral arterial occlusive disease	440.2	I70.2-I70.9, I71; I73.9	Discharge
Myocardial infarction	410, 411, 412	I21-I25	Discharge
Congestive heart failure	428	I11.0, I13.0, I13.2, I42.0, I50, I50.1, I50.9	Discharge
Hypertension	401, 402	I10-I16	Outpatient department ≥2
Diabetes mellitus	250	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9	Outpatient department ≥2
Hyperlipidemia	272	E78	Outpatient department ≥2
Chronic gout	274.0, 274.10, 274.11, 274.19, 274.81, 274.82, 274.89, 274.9	M10, M1A	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,	J44	Discharge

	A325		
Chronic kidney disease	580-589	I12, I13, N00, N01, N02, N03, N04, N05, N07, N11, N14, N17, N18, N19, Q61	Outpatient department ≥2
Chronic liver disease	570, 571, 572	B150, B160, B162, B190, K704, K72, K766, I85	Outpatient department ≥2
Liver cirrhosis	571.2, 571.5, 571.6	K72, K74, K70.2, K70.3, K70.4	Outpatient department ≥2
Non-alcoholic cirrhosis	571.5, 571.6	K740.0, K74.60, K74.69, K74.3, K74.4, K74.5	Outpatient department ≥2
Alcoholic cirrhosis	571.2	K70.30	Outpatient department ≥2
Ascites	789.5x	R18.8	Discharge
Hepatic encephalopathy	572.2	K72.91	Discharge
Spontaneous bacterial peritonitis	567.2x, 567.8x, 567.9x	K65.0, K65.2, K65.8, K65.9	Discharge
Esophageal varices bleeding	456.0, 456.20	I85.01, I85.11	Discharge
Malignancy	140.0-208.9	C	Outpatient department ≥2
Intracranial hemorrhage	430, 431, 432, 852, 853	I60, I61, I62	Discharge
Gastrointestinal bleeding	456.0, 456.2, 455.2, 455.5, 455.8, 530.7, 530.82, 531.0-531.6, 532.0-532.6, 533.0-533.6,	K250, K260, K270, K280, K290	Discharge

	534.0-534.6, 535.0-535.6 537.83, 562.02, 562.03, 562.12 562.13 568.81, 569.3, 569.85, 578.0, 578.1, 578.9		
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

Figure S1. Cumulative incidence curves of thromboembolism and bleeding for NVAF patients with liver cirrhosis according to initiated treatment before propensity score-based stabilized weights method.



The NOAC group showed a comparable risk of ischemic stroke/systemic embolism compared with warfarin group after adjustment. For the

safety outcome, the NOAC group showed significantly lower risks of major gastrointestinal bleeding and all major bleeding than the warfarin group. GIB = gastrointestinal bleeding; ICH = intracranial hemorrhage; IS/SE = ischemic stroke/systemic embolism. NOAC = non-vitamin K antagonist oral anticoagulants; NVAF = non-valvular atrial fibrillation.