ORIGINAL RESEARCH

Liver Cirrhosis in Patients With Atrial Fibrillation: Would Oral Anticoagulation Have a Net Clinical Benefit for Stroke Prevention?

Ling Kuo, MD; Tze-Fan Chao, MD; Chia-Jen Liu, MD; Yenn-Jiang Lin, MD; Shih-Lin Chang, MD; Li-Wei Lo, MD; Yu-Feng Hu, MD; Ta-Chuan Tuan, MD; Jo-Nan Liao, MD; Fa-Po Chung, MD; Tzeng-Ji Chen, MD; Gregory Y. H. Lip, MD; Shih-Ann Chen, MD

***Background*—**Patients with liver cirrhosis have been excluded from randomized clinical trials of oral anticoagulation therapy for stroke prevention in atrial fibrillation. We hypothesized that patients with liver cirrhosis would have a positive net clinical benefit for oral anticoagulation when used for stroke prevention in atrial fibrillation.

***Methods and Results*—**This study used the National Health Insurance Research Database in Taiwan. Among 289 559 atrial fibrillation patients aged ≥20 years, there were 10 336 with liver cirrhosis, and 9056 of them having a CHA_2DS_2-VASc score ≥2 were divided into 3 groups, that is, no treatment, antiplatelet therapy, and warfarin. Patients with liver cirrhosis had a higher risk of ischemic stroke (hazard ratio=1.10, *P*=0.046) and intracranial hemorrhage (hazard ratio=1.20, *P*=0.043) compared with those without. Among patients with liver cirrhosis, patients taking antiplatelet therapy had a similar risk of ischemic stroke (hazard ratio=1.02, 95%CI=0.88-1.18) compared to those without antithrombotic therapies, but the risk was significantly lowered among warfarin users (hazard ratio=0.76, 95%CI=0.58-0.99). For intracranial hemorrhage, there were no significant differences between those untreated and those taking antiplatelet therapy or warfarin. The use of warfarin was associated with a positive net clinical benefit compared with being untreated or receiving only antiplatelet therapy.

***Conclusions*—**For atrial fibrillation patients with liver cirrhosis in the current analysis of an observational study, warfarin use was associated with a lower risk of ischemic stroke and a positive net clinical benefit compared with nontreatment, and thus, thromboprophylaxis should be considered for such patients. **(*J Am Heart Assoc*. 2017;6:e005307. DOI: 10.1161/JAHA.116.005307.)**

Key Words: atrial fibrillation • intracranial hemorrhage • ischemic stroke • liver cirrhosis

Liver cirrhosis may be associated with a coagulopathy, and such patients have been excluded from randomized clinical trials of oral anticoagulation (OAC) therapy for stroke prevention in atrial fibrillation (AF). This may be of concern, as alcohol is a common predisposition to liver cirrhosis as well as AF. Nonetheless, there are limited data on the epidemiology and stroke or bleeding risks associated if liver cirrhosis is concomitantly present with AF. In Asian countries hepatitis carrier status and hepatitis-related liver cirrhosis are commonly encountered,[1] and a major clinical dilemma is how to decide on thromboprophylaxis in such patients.

Stroke and bleeding risks in AF are not homogeneous and are dependent on the presence of established risk factors incorporated within established risk scores, such as the CHA_2DS_2-VASc and HAS-BLED scores.[2,3] These scores have not been validated in patients with liver cirrhosis, and the

From the Divisions of Cardiology (L.K., T.-F.C., Y.-J.L., S.-L.C., L.-W.L., Y.-F.H., T.-C.T., J.-N.L., F.-P.C., S.-A.C.) and Hematology and Oncology (C.-J.L.), Department of Medicine, and Department of Family Medicine (T.-J.C.), Taipei Veterans General Hospital, Taipei, Taiwan; Institutes of Clinical Medicine (L.K., T.-F.C., Y.-J.L., S.-L.C., L.-W.L., Y.-F.H., T.-C.T., J.-N.L., F.-P.C., S.-A.C.) and Public Health and School of Medicine (C.-J.L.), and Cardiovascular Research Center (L.K., T.-F.C., Y.-J.L., S.-L.C., L.-W.L., Y.-F.H., T.-C.T., J.-N.L., F.-P.C., S.-A.C.), National Yang-Ming University, Taipei, Taiwan; University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L.).

Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/6/6/e005307/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Tze-Fan Chao, MD, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan. E-mail: eyckeyck@gmail.com

Gregory Y. H. Lip, MD, University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom. E-mail: g.y.h.lip@bham.ac.uk

Received January 31, 2017; accepted May 9, 2017.

Clinical Perspective

What Is New?

- Patients with atrial fibrillation associated with liver cirrhosis have been excluded from randomized trials of oral anticoagulation therapy for stroke prevention.
- In this nationwide registry study, atrial fibrillation patients with liver cirrhosis had a higher risk of ischemic stroke and intracranial hemorrhage compared with those without.
- Among atrial fibrillation patients with liver cirrhosis, the risk of ischemic stroke was lowered and the risk of intracranial hemorrhage was similar among warfarin users compared with those without antithrombotic therapies.
- The use of warfarin was associated with a positive net clinical benefit compared with being untreated or receiving only antiplatelet therapy.

What Are the Clinical Implications?

- For atrial fibrillation patients with liver cirrhosis, warfarin use was associated with a lower risk of ischemic stroke and positive net clinical benefit compared with nontreatment, and thus, thromboprophylaxis should be considered for such patients.

impact of OAC use in such patients is uncertain. Indeed, many such patients are perceived as being at too high risk for OAC and are often prescribed aspirin instead. This is despite the latter having minimal efficacy for stroke prevention and having a negative net clinical benefit (NCB) once ischemic stroke reduction is balanced against serious bleeds.[4]

We hypothesized that patients with chronic liver cirrhosis would have a positive NCB for OAC used for stroke prevention in AF. We tested this hypothesis in a nationwide cohort based on the Taiwan national insurance database.

Methods

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance system is a universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed healthcare data from >23 million enrollees, representing >99% of Taiwan's population. In this cohort data set the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the National Health Insurance database and can be followed continuously. The large sample size of this database provided a good opportunity to study the risk of increased intracranial hemorrhage (ICH) and benefits of stroke risk reduction with warfarin use in AF patients with liver cirrhosis.

Study Population

The study protocol of the present study was similar to those of our previous studies.[5-11] From January 1, 2000 to December 31, 2011, a total of 289 559 AF patients aged ≥20 years (10 336 with liver cirrhosis) were identified from the NHIRD. AF was diagnosed using the International Classification of Diseases, 9th Revision, Clinical Modification codes (427.31) registered by the physicians responsible for the treatment of patients. To ensure the accuracy of diagnosis, we defined patients with AF only when it was a hospital discharge diagnosis or confirmed at least 2 times in the outpatient department. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[12,13] The risk of ischemic stroke and ICH for AF patients with (n=10 336) or without liver cirrhosis (n=279 223) stratified based on the strategies for stroke prevention was compared (Figure 1).

Among 10 336 patients with liver cirrhosis, 9056 of them having a CHA_2DS_2-VASc score ≥2 were divided into 3 groups, that is, no treatment (n=5532, 61.1%), antiplatelet therapy (n=2770, 30.6%), and warfarin (n=754, 8.3%). The risk of ICH and benefit of stroke risk reduction were analyzed between patients without use of any antithrombotic agent and those with antiplatelet agents or warfarin use. The flowchart of study design and patient enrollment is shown in Figure 1.

Calculation of Score and Definition of Clinical End Point

The CHA_2DS_2-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes mellitus, recent cardiac failure, vascular disease (myocardial infarction or peripheral artery disease), and female sex, and 2 points each for a history of a stroke, TIA, or age ≥75 years.[2]

The clinical end point was the occurrence of ischemic stroke with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in Taiwan's NHIRD has been reported to be around 94%.[14] Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with positive predictive value and sensitivity of 88.4% and 97.3%, respectively.[15] The safety end point was the occurrence of ICH (International Classification of Diseases-9 code

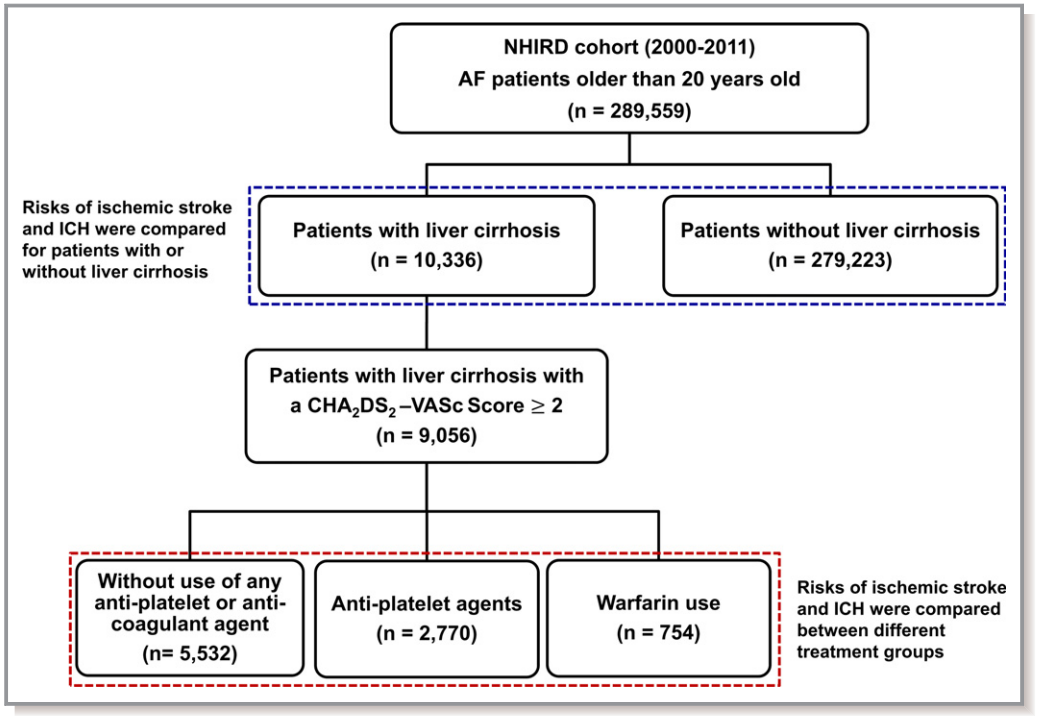

Figure 1. A flowchart of the enrollment of the study cohort. From January 1, 2000 to December 31, 2011, a total of 289 559 AF patients aged ≥20 years (10 336 with liver cirrhosis) were identified from the NHIRD. The risks of ischemic stroke and ICH were compared for patients with and without liver cirrhosis. Among 10 336 patients with liver cirrhosis, 9056 had a CHA_2DS_2-VASc score ≥2. These were divided into 3 groups, that is, no treatment (61.1%), antiplatelet therapy (30.6%), and warfarin (8.3%). The risk of ICH and benefit of stroke risk reduction were analyzed between patients without use of any anti-thrombotic agent and those with anti-platelet agents or warfarin use. AF indicates atrial fibrillation; ICH, intracranial hemorrhage; NHIRD, National Health Insurance Research Database.

430.x-432.x), which necessitated admissions to intensive care units.

Analysis of Net Clinical Benefit

The NCB for the use of warfarin or antiplatelet therapy compared with no treatment was calculated using the formula:

$$\begin{aligned}&(\text{Ischemic stroke rate}_{\text{no treatment}}\\&\quad-\text{Ischemic stroke rate}_{\text{anti-thrombotic therapies}})\\&\quad-\text{weighting factor}\times(\text{ICH rate}_{\text{anti-thrombotic therapies}}\\&\quad-\text{ICH rate}_{\text{no treatement}})\end{aligned}$$

The weighting factor reflects the relative impact, in terms of death and disability, of an ICH while receiving warfarin or antiplatelet agents versus experiencing an ischemic stroke while on no treatment.[4,16,17] The NCB with 95%CI were calculated from rate differences of ischemic stroke and ICH of the present study based on the weights previously produced and reported in the studies by Singer et al,[16] Connolly et al,[17] and Lip et al.[4] A positive NCB favors treatment (ie, warfarin) over no treatment.

Propensity Match Analysis

We performed propensity score–matched analyses for 2 kinds of comparisons among patients with liver cirrhosis: antiplatelet agents versus no antithrombotic therapy and warfarin versus no antithrombotic therapy. We calculated propensity scores for the likelihoods of receiving antiplatelet agents and warfarin compared to no antithrombotic therapy by multivariate logistic regression analyses, conditional on all baseline covariates listed in Table 1. After that, we matched patients in the antiplatelet-agent group to those in the no-antithrombotic-therapy group with a 1:1 ratio on the basis of the closest propensity score for the use of antiplatelet agents within a threshold of ±0.01. If more than 1 patient in the no-antithrombotic-therapy group could be matched to the corresponding subject in the antiplatelet-agent group, 1 patient from the no antithrombotic therapy group was selected randomly without repeat sampling. Similar matching processes were performed for the comparisons of warfarin versus no-antithrombotic therapy based on the propensity scores for the use of warfarin.

Table 1. Baseline Characteristics of Patients

Variables	AF Patients With Liver Cirrhosis Having a CHA_2DS_2-VASc Score ≥2 (n=9056)				*P* Value*
	All	No Antithrombotic Therapy (n=5532)	Antiplatelet Agents (n=2770)	Warfarin (n=754)	
Age, y	73.1±11.2	73.5±11.7	73.4±9.9	68.9±11.4	<0.001
Sex (male), n (%)	5506 (60.8)	3264 (59.0)	1771 (63.9)	471 (62.5)	<0.001
CHA_2DS_2-VASc score	4.7±1.8	4.6±1.8	4.9±1.8	4.6±1.8	<0.001
Medical history (components of the CHA_2DS_2-VASc score), n (%)					
Hypertension	7554 (83.4)	4503 (81.4)	2454 (88.6)	597 (79.2)	<0.001
Diabetes mellitus	4096 (45.2)	2443 (44.2)	1327 (47.9)	326 (43.2)	0.003
Congestive heart failure	4995 (55.2)	2929 (52.9)	1582 (57.1)	484 (64.2)	<0.001
Previous stroke/TIA	3812 (42.1)	2194 (39.7)	1272 (45.9)	346 (45.9)	<0.001
Previous vascular disease	2628 (29.0)	1251 (22.6)	1098 (39.6)	279 (37.0)	<0.001
Medical history (other than the components of the CHA_2DS_2-VASc score), n (%)					
COPD	4675 (51.6)	2918 (52.7)	1448 (47.7)	309 (41.0)	<0.001
Hyperlipidemia	2682 (29.6)	1435 (25.9)	1014 (36.6)	233 (30.9)	<0.001
Malignancy	1333 (14.7)	912 (16.5)	342 (12.3)	79 (10.5)	<0.001
Autoimmune diseases	834 (9.2)	507 (9.2)	271 (9.8)	56 (7.4)	0.137
End-stage renal disease	504 (5.6)	358 (6.5)	132 (4.8)	14 (1.9)	<0.001
HBV infection	1362 (15.0)	848 (15.3)	384 (13.9)	130 (17.2)	0.044
HCV infection	1981 (21.9)	1278 (23.1)	558 (20.1)	145 (19.2)	0.002
Hepatic encephalopathy	628 (6.9)	514 (9.3)	89 (3.2)	25 (3.3)	<0.001
EV with bleeding	421 (4.6)	339 (6.1)	64 (2.3)	18 (2.4)	<0.001
Degree of urbanization, n (%)					
Urban	4062 (44.9)	2408 (43.5)	1291 (46.6)	363 (48.1)	0.030
Suburban	3181 (35.1)	1983 (35.8)	950 (34.3)	248 (32.9)	
Rural	1813 (20.0)	1141 (20.6)	529 (19.1)	143 (19.0)	
Income level, n (%)					
Low	4940 (54.5)	3107 (56.2)	1443 (52.1)	390 (51.7)	0.004
Median	3199 (35.3)	1879 (34.0)	1037 (37.4)	283 (37.5)	
High	917 (10.1)	543 (9.9)	290 (10.5)	81 (10.7)	

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; EV, esophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; TIA, transient ischemic attack.
**P* value between groups with different strategies for stroke prevention (no antithrombotic therapy, antiplatelet agents, and warfarin).

Statistical Analysis

Data were presented as the mean value and standard deviation for normally distributed continuous variables and proportions for categorical variables. Differences between continuous values were assessed using an unpaired 2-tailed t test or 1-way ANOVA for the comparisons of 3 groups. Differences between nominal variables were compared by the chi-squared test. The incidence of ischemic stroke and ICH were calculated from dividing the number of events by person-time at risk, with the 95%CI estimated by exact binomial probabilities. The risk of ischemic stroke and ICH was assessed using the Cox regression analysis. For the comparisons of the risk of ischemic stroke and ICH among patients with or without liver cirrhosis, the analysis was adjusted for age, sex, CHA_2DS_2-VASc score, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, autoimmune diseases, end-stage renal disease, degree of urbanization, and income level. Among patients with liver cirrhosis without the propensity match, the comparisons of the risk of ischemic stroke and ICH between different treatment groups were adjusted for age, sex, CHA_2DS_2-VASc score, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, autoimmune diseases, end-stage renal disease, hepatitis B virus infection, hepatitis C virus infection, hepatic encephalopathy, esophageal varices with bleeding, degree of

urbanization, and income level. Statistical significance was set at a $P<0.05$.

The present study was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taipei, Taiwan, and the informed consent of study subjects was waived.

Results

Risk of Ischemic Stroke and ICH for AF Patients With or Without Liver Cirrhosis

Baseline characteristics of patients with or without liver cirrhosis are shown in Table S1. Figure 2 shows the risk of ischemic stroke and ICH for AF patients with liver cirrhosis compared to those without liver cirrhosis, stratified based on the strategies for stroke prevention. For patients who did not receive antithrombotic therapies, the risk of ischemic stroke and ICH was higher for AF patients with liver cirrhosis compared with those without after the adjustment for age, sex, CHA_2DS_2-VASc score, chronic obstructive pulmonary disease, hyperlipidemia, malignancy, autoimmune diseases, end-stage renal disease, degree of urbanization, and income level, with an adjusted hazard ratio (HR) of 1.10 (95%CI=1.00-1.20, P=0.046) and 1.20 (95%CI=1.01-1.43, P=0.043), respectively (Figure 2). For patients treated with warfarin, the adjusted risk of ischemic stroke and ICH was similar between patients with and without liver cirrhosis (Figure 2). Among patients treated with antiplatelet agents, patients with liver cirrhosis had a similar risk of ischemic stroke but a higher risk of ICH compared with those without (Figure 2).

Ischemic Stroke, ICH, and NCB on Antiplatelet Therapy and Warfarin Among Patients With Liver Cirrhosis Having a CHA_2DS_2-VASc Score ≥2

Clinical and demographic characteristics of patients with liver cirrhosis having a CHA_2DS_2-VASc score ≥2 are summarized in Table 1. There were significant differences in age with warfarin users being significantly lower than non–warfarin users, and mean CHA_2DS_2-VASc score was higher in antiplatelet therapy users. Of associated comorbidities, warfarin users tended to have less hypertension, diabetes mellitus, and heart failure, wherefore 45.9% of those on warfarin (or antiplatelet therapy) had had a prior stroke/TIA. Warfarin users tended to have fewer comorbidities with CHA_2DS_2-VASc score components and fewer complications of

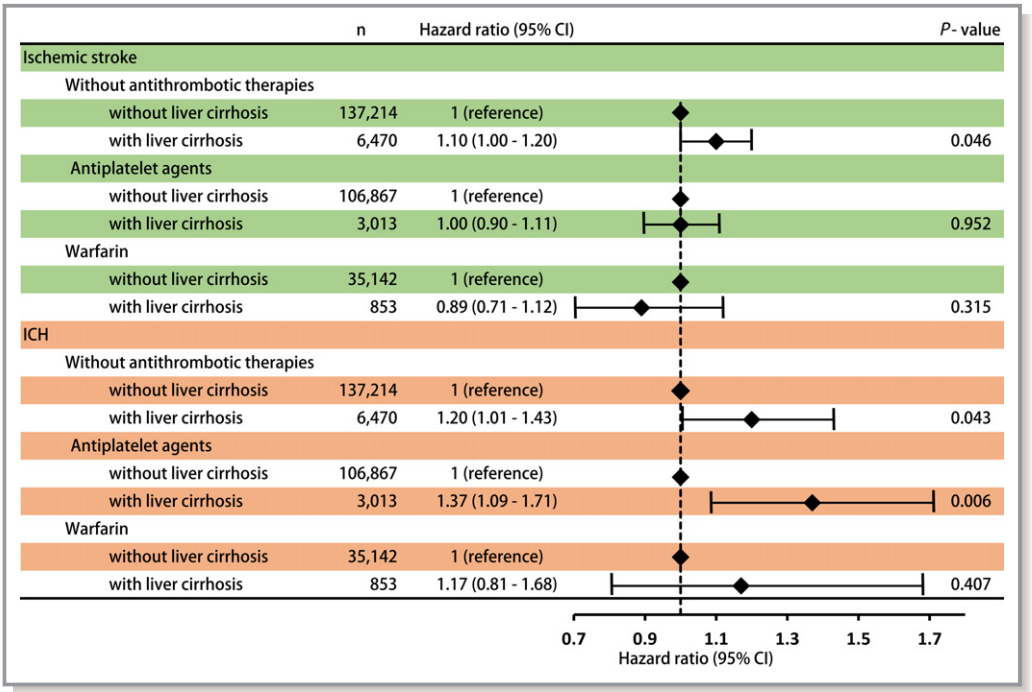

Figure 2. Risk of ischemic stroke and ICH for AF patients with or without liver cirrhosis, stratified based on the strategies for stroke prevention. For patients who did not receive antithrombotic therapies, the risk of ischemic stroke and ICH was higher for AF patients with liver cirrhosis compared with those without. For patients treated with warfarin, the risk of ischemic stroke and ICH was similar between patients with or without liver cirrhosis. The hazard ratio was adjusted for age, sex, CHA_2DS_2-VASc score, COPD, hyperlipidemia, malignancy, autoimmune diseases, end-stage renal disease, degree of urbanization, and income level. CI indicates confidence interval; ICH, intracranial hemorrhage.

Table 2. Risk of Ischemic Stroke and ICH Stratified Based on the Strategies for Stroke Prevention

Stroke Prevention Strategy	n	Ischemic Stroke				ICH			
		No. of Event	Incidence (95% CI)*	Adjusted HR† (95% CI)	*P* Value	No. of Event	Incidence (95% CI)*	Adjusted HR† (95% CI)	*P* Value
No antithrombotic therapy (reference group)	5532	447	4.09 (3.72-4.46)	Reference	…	107	0.92 (0.75-1.09)	Reference	…
Antiplatelet agents	2770	338	4.13 (3.70-4.56)	1.02 (0.88-1.18)	0.784	77	0.87 (0.68-1.06)	0.96 (0.71-1.30)	0.811
Warfarin	754	65	2.79 (2.12-3.46)	0.76 (0.58-0.99)	0.040	27	1.11 (0.69-1.53)	1.27 (0.82-1.95)	0.284

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; EV, esophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ICH, intracranial hemorrhage.

*Per 100 person-years of follow-up.

†Adjusted for age, sex, CHA_2DS_2-VASc score, COPD, hyperlipidemia, malignancy, autoimmune diseases, end-stage renal disease, HBV infection, HCV infection, hepatic encephalopathy, EV with bleeding, degree of urbanization, and income level.

liver cirrhosis such as hepatic encephalopathy and esophageal varices with bleeding. Minor differences in degree of urbanization and income level were evident.

The adjusted risks for ischemic stroke and ICH are shown in Table 2. Compared to those on no antithrombotic therapy (references), patients taking antiplatelet therapy had a similar risk of ischemic stroke (HR=1.02, 95%CI=0.88-1.18), but the risk was significantly lowered among warfarin users (HR=0.76, 95%CI=0.58-0.99) (Table 2). For ICH, there were no significant differences between those untreated and those taking antiplatelet therapy or warfarin (Table 2). The effect sizes (95%CI) of these analyses comparing the risk of ischemic stroke and ICH of different treatment groups are shown in Table S2. When assessing the NCB, we found that that use of warfarin had a positive NCB when compared with being untreated or using antiplatelet therapy (Table 3).

Propensity-Matched Analysis

For the propensity-matched cohorts of no antithrombotic therapy versus antiplatelet therapy, and no antithrombotic therapy versus warfarin, patient clinical and demographic characteristics are summarized in Table 4. Propensity scores between 2 groups in each comparison were similar. Age, sex, comorbidities, degree of urbanization, and income level were not significantly different between the groups in each comparison.

The risks for ischemic stroke and ICH for the 2 propensity-matched cohorts are shown in Table 5. Compared to those on no antithrombotic therapy (references), patients taking antiplatelet therapy had a similar risk of ischemic stroke (HR=1.00, 95%CI=0.85-1.18, *P*=0.970), but the risk was significantly lowered among warfarin users (HR=0.71, 95% CI=0.51-0.99, *P*=0.047) (Table 5). For ICH, there were no significant differences between those untreated and those taking antiplatelet therapy or warfarin (Table 5). The effect sizes (95%CI) of these analyses comparing the risk of ischemic stroke and ICH of different treatment groups are shown in Table S3.

Discussion

There are limited data on the stroke and ICH risks in AF patients with associated liver cirrhosis, and in this analysis we

Table 3. The Net Clinical Benefit Analyses for Each Treatment According to Different Weight Models

Stroke Prevention Strategy	NCB Based on Different Weight Models, % Per Year (95%CI)		
	Relative Weight of ICH Compared to Ischemic Stroke According to Singer et al[16] Weight=1.5	Relative Weight of ICH Compared to Ischemic Stroke According to Connolly et al[17] Weight=3.08	Relative Weight of ICH Compared to Ischemic Stroke According to Lip et al[4] Weight=2.44
Compared to no antithrombotic therapy (reference group)	…	…	…
Warfarin	1.02 (0.98-1.05)	0.71 (0.63-0.80)	0.84 (0.77-0.90)
Compared to antiplatelet drugs (reference group)	…	…	…
Warfarin	0.98 (0.93-1.03)	0.60 (0.49-0.71)	0.75 (0.70-0.84)

ICH indicates intracranial hemorrhage; NCB, net clinical benefit.

Table 4. Baseline Characteristics of AF Patients After the Propensity Match

Variables	Antiplatelet Agents Vs No Antithrombotic Therapy			Warfarin Vs No Antithrombotic Therapy		
	No Antithrombotic Therapy (n=2770)	Antiplatelet Agents (n=2770)	*P* Value	No Antithrombotic Therapy (n=754)	Warfarin (n=754)	*P* Value
Age, y	73.3±11.8	73.4±9.9	0.696	68.3±12.9	68.9±11.4	0.309
Sex (male), n (%)	1780 (64.3)	1771 (63.9)	0.801	465 (61.7)	471 (62.5)	0.750
CHA_2DS_2-VASc score	4.93±1.8	4.95±1.8	0.638	4.51±1.9	4.58±1.8	0.454
Medical history (components of the CHA_2DS_2-VASc score), n (%)						
Hypertension	2445 (88.3)	2454 (88.6)	0.705	607 (80.5)	597 (79.2)	0.521
Diabetes mellitus	1322 (47.7)	1327 (47.9)	0.893	320 (42.4)	326 (43.2)	0.755
Congestive heart failure	1616 (58.3)	1582 (57.1)	0.355	486 (64.5)	484 (64.2)	0.914
Previous stroke/TIA	1250 (45.1)	1272 (45.9)	0.553	338 (44.8)	346 (45.9)	0.679
Previous vascular disease	1077 (38.9)	1098 (39.6)	0.564	264 (35.0)	279 (37.0)	0.421
Medical history (other than the components of the CHA_2DS_2-VASc score), n (%)						
COPD	1485 (53.6)	1448 (52.3)	0.319	318 (42.2)	309 (41.0)	0.638
Hyperlipidemia	966 (34.9)	1014 (36.6)	0.178	242 (32.1)	233 (30.9)	0.618
Malignancy	347 (12.5)	342 (12.3)	0.839	75 (9.9)	79 (10.5)	0.734
Autoimmune diseases	278 (10.0)	271 (9.8)	0.753	56 (7.4)	56 (7.4)	1.000
End-stage renal disease	150 (4.7)	132 (4.8)	0.271	16 (2.1)	14 (1.9)	0.712
HBV infection	380 (13.7)	384 (13.9)	0.876	120 (15.9)	130 (17.2)	0.489
HCV infection	560 (20.2)	558 (20.1)	0.947	143 (19.0)	145 (19.2)	0.896
Hepatic encephalopathy	98 (3.5)	89 (3.2)	0.503	21 (2.8)	25 (3.3)	0.549
EV with bleeding	71 (2.6)	64 (2.3)	0.542	16 (2.1)	18 (2.4)	0.729
Degree of urbanization, n (%)						
Urban	1281 (46.2)	1291 (46.6)	0.788	355 (47.1)	363 (48.1)	0.680
Suburban	960 (34.7)	950 (34.3)	0.777	262 (34.7)	248 (32.9)	0.446
Rural	529 (19.1)	529 (19.1)	1.000	137 (18.2)	143 (19.0)	0.691
Income level, n (%)						
Low	1475 (53.2)	1443 (52.1)	0.389	406 (53.8)	390 (51.7)	0.410
Median	985 (35.6)	1037 (37.4)	0.147	268 (35.5)	283 (37.5)	0.423
High	310 (11.2)	290 (10.5)	0.387	80 (10.6)	81 (10.7)	0.934
Mean propensity score	0.37±0.1	0.37±0.1	0.064	0.18±0.1	0.18±0.1	0.985

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; EV, esophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; TIA, transient ischemic attack.

clearly show that, when compared to those on no antithrombotic therapy, patients taking antiplatelet therapy had a similar risk of ischemic stroke, but the risk was significantly lowered among warfarin users. For ICH, there were no significant differences between those untreated and those taking antiplatelet therapy or warfarin. Importantly, the NCB with warfarin was positive when compared to being left untreated or if antiplatelet therapy was used.

One previous study has demonstrated that the incidence of ICH was higher among patients with liver cirrhosis due to thrombocytopenia or prolonged international normalized ratio.[18] Indeed, abnormal liver function and cirrhotic liver disease are categorized as potentially and nonmodifiable bleeding risk factors, respectively, in the 2016 AF guidelines of the European Society of Cardiology and are important components of bleeding risk assessment, such as the HAS-BLED score.[3,19]

Interestingly, liver cirrhosis is associated not only with a bleeding tendency but also with a hypercoagulation status due to the decreased synthesis of anticoagulant factors or impaired degradation of prothrombotic factors.[20] We are not aware of any specific data showing that liver cirrhosis

Table 5. Risk of Ischemic Stroke and ICH With Different Strategies for Stroke Prevention After the Propensity Match

Stroke Prevention Strategy	n	Ischemic Stroke				ICH			
		No. of Event	Incidence (95%CI)*	HR (95%CI)	*P* Value	No. of Event	Incidence (95%CI)*	HR (95%CI)	*P* Value
Antiplatelet agents vs no antithrombotic therapy									
No antithrombotic therapy (reference group)	2770	238	4.20 (3.68-4.72)	Reference	···	56	0.93 (0.69-1.17)	Reference	···
Antiplatelet agents	2770	338	4.13 (3.70-4.56)	1.00 (0.85-1.18)	0.970	77	0.87 (0.68-1.06)	0.99 (0.70-1.39)	0.942
Warfarin vs no antithrombotic therapy									
No antithrombotic therapy (reference group)	754	74	4.03 (3.13-4.93)	Reference	···	17	1.08 (0.58-1.58)	Reference	···
Warfarin	754	65	2.79 (2.12-3.46)	0.71 (0.51-0.99)	0.047	27	1.11 (0.69-1.53)	1.10 (0.62-1.94)	0.756

COPD indicates chronic obstructive pulmonary disease; HR, hazard ratio; ICH, intracranial hemorrhage.
*Per 100 person-years of follow-up.

independently contributes to a higher risk of ischemic stroke in AF, but as our population profile shows, such patients are at high risk given the associated comorbidities and high CHA_2DS_2VASc scores. Transient liver function test abnormalities (eg, γ-glutamyl transferase) have been noted in stroke patients, but these would not necessarily reflect underlying liver cirrhosis.[21]

In the present study we clearly showed that AF patients with liver cirrhosis did have a higher risk of ischemic stroke and ICH compared with those without liver cirrhosis who did not receive antithrombotic therapies (Figure 2). Given the higher risks of both ischemic stroke and ICH, how to determine the optimal stroke prevention strategy for AF patients with liver cirrhosis is a clinically difficult scenario. Our data provide evidence that thromboprophylaxis should be considered for AF patients with liver cirrhosis to avoid the risk of AF-related stroke given the positive NCB with OAC compared to being left untreated or if antiplatelet therapy was used in such patients, as shown in Table 3. The results of the present study showed that patients taking antiplatelet therapy had a similar risk of ischemic stroke as those not treated, and therefore, antiplatelet agents should not be used for stroke prevention among AF patients with liver cirrhosis. On the contrary, the risk of ischemic stroke was significantly lowered among warfarin users. For ICH, there were no significant differences between those untreated and those taking antiplatelet therapy or warfarin, and these findings may further support the use of OACs for AF patients with liver cirrhosis.

Study Limitations

Our data were based on warfarin, and whether the findings would apply to patients taking non–vitamin K antagonist oral anticoagulants is uncertain. In keeping with registry design, we did not have data on quality of anticoagulation control (as reflected by time in therapeutic range) given the close relationship between time in therapeutic range and thromboembolism or bleeding. Also, we did not have laboratory data to provide information on degree of liver function derangement, and prognostic scores of liver cirrhosis, such as model for end-stage liver disease and Child-Pugh scores, were not available. We were only able to regard a history of hepatic encephalopathy and esophageal varices with bleeding as the proxies of disease severity of liver cirrhosis. It should be noted that although we have adjusted for baseline differences between different treatment groups in multivariable regression and propensity-matching analyses, other unmeasured confounders may still exist that could confound the analyses. Also, we did not adjust for multiple testing. Furthermore, the number of patients who received warfarin treatment was small, and therefore, the further analysis of NCB in different age strata or subgroups was not feasible. Besides, the NCB model only included ischemic stroke and ICH, the most devastating bleeding complications, and did not consider other bleeding events because the severity of other bleeding varied greatly and is difficult to be ascertained in the registry database. Last, the present study only enrolled Taiwanese patients, and whether the results can be extrapolated to other populations remains uncertain. Due to these limitations mentioned above, our data should be regarded as hypothesis generating, and further prospective studies are needed.

Conclusion

AF patients with liver cirrhosis had a higher risk of ischemic stroke and ICH compared with those without. For AF patients with liver cirrhosis in the current analysis of an observational study, warfarin use was associated with a lower risk of

ischemic stroke and positive NCB compared with nontreatment, and thus, thromboprophylaxis should be considered for such patients.

Acknowledgments

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

Sources of Funding

This work was supported in part by grants from the Ministry of Science and Technology (MOST 104-2314-B-075-024-MY3), and Taipei Veterans General Hospital (V105B-023).

Disclosures

None.

References

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis*. 2005;5:558–567.
2. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272.
3. 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;138:1093–1100.
4. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA_2DS_2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost*. 2015;114:826–834.
5. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Using the CHA_2DS_2-VASc score for refining stroke risk stratification in "low-risk" Asian patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;64:1658–1665.
6. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Should atrial fibrillation patients with 1 additional risk factor of the CHA_2DS_2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol*. 2015;65:635–642.
7. Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Liao JN, Chen TJ, Chiang CE, Lip GY, Chen SA. Age threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. *J Am Coll Cardiol*. 2015;66:1339–1347.
8. Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Chen SA. Rate-control treatment and mortality in atrial fibrillation. *Circulation*. 2015;132:1604–1612.
9. Chao TF, Liu CJ, Liao JN, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Chen TJ, Lip GY, Chen SA. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. *Circulation*. 2016;133:1540–1547.
10. Chao TF, Liu CJ, Tuan TC, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Hsieh MH, Lip GY, Chen SA. Impact on outcomes of changing treatment guideline recommendations for stroke prevention in atrial fibrillation: a nationwide cohort study. *Mayo Clin Proc*. 2016;91:567–574.
11. Li CH, Liu CJ, Chou AY, Chao TF, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chung FP, Liao JN, Chen TJ, Wu TJ, Chen SA. European Society of Cardiology guideline-adherent antithrombotic treatment and risk of mortality in Asian patients with atrial fibrillation. *Sci Rep*. 2016;6:30734.
12. Lin LJ, Cheng MH, Lee CH, Wung DC, Cheng CL, Kao Yang YH. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation—a nationwide descriptive study in Taiwan. *Clin Ther*. 2008;30:1726–1736.
13. Chang CH, Lee YC, Tsai CT, Chang SN, Chung YH, Lin MS, Lin JW, Lai MS. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. *Atherosclerosis*. 2014;232:224–230.
14. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011;20:236–242.
15. Hsieh CY, Chen CH, Li CY, Lai ML. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. *J Formos Med Assoc*. 2015;114:254–259.
16. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009;151:297–305.
17. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, de Caterina R, Hohnloser S, Hart RG; ACTIVE Steering Committee and Investigators. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med*. 2011;155:579–586.
18. Niizuma H, Suzuki J, Yonemitsu T, Otsuki T. Spontaneous intracerebral hemorrhage and liver dysfunction. *Stroke*. 1988;19:852–856.
19. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; Authors/Task Force Members. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2016;37:2893–2962.
20. Northup PG, Argo CK, Shah N, Caldwell SH. Hypercoagulation and thrombophilia in nonalcoholic fatty liver disease: mechanisms, human evidence, therapeutic implications, and preventive implications. *Semin Liver Dis*. 2012;32:39–48.
21. Peck K, Shinton R, Beevers G. Is serum gamma-glutamyl transferase a good marker of alcohol intake in stroke patients? *Postgrad Med J*. 1990;66:710–713.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients with or without liver cirrhosis

	With liver cirrhosis (n = 10,336)	Without liver cirrhosis (n = 279,223)	P value
Age, years	70.1 ± 12.6	71.5 ± 13.3	<0.001
Sex (male), n (%)	6,703 (64.9)	153,482 (55.0)	<0.001
CHA_2DS_2-VASc score	4.2 ± 2.1	4.1 ± 2.1	<0.001
Medical history (components of the CHA_2DS_2-VASc score), n (%)			
Hypertension	7,785 (75.3)	206,663 (74.0)	<0.001
Diabetes mellitus	4,234 (41.0)	85,206 (30.5)	<0.001
Congestive heart failure	5,225 (50.6)	117,594 (42.1)	<0.001
Previous stroke/TIA	3,812 (36.9)	103,743 (37.2)	0.254
Previous vascular disease	2,664 (25.8)	75,587 (26.0)	0.310
Medical history (other than the components of the CHA_2DS_2-VASc score), n (%)			
COPD	4,989(48.3)	107788 (38.6)	<0.001
Hyperlipidemia	2,892 (28.0)	81695 (29.3)	<0.001
Malignancy	1,504 (14.6)	16294 (5.8)	<0.001
Autoimmune diseases	883 (8.5)	18076 (6.5)	0.137
End-stage renal disease	534 (5.2)	6595 (2.4)	<0.001
Degree of urbanization, n (%)			
Urban	4,712 (45.6)	145696 (52.2)	
Suburban	3,592 (34.8)	91686 (32.8)	<0.001
Rural	2,032 (19.7)	41841 (15.0)	
Income level, n (%)			
Low	5,611 (54.3)	141807 (50.8)	
Median	3,667 (35.5)	100574 (36.0)	<0.001
High	1,058 (10.2)	36841 (13.2)	

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

Table S2. Effect size (95% CI) of the analysis comparing the risk of ischemic stroke and ICH of different treatment groups

Stroke prevention strategy	Ischemic stroke		ICH	
	Effect size	(95% CI)	Effect size	(95% CI)
No antithrombotic therapy (reference group)	-	-	-	-
Anti-platelet agents versus no antithrombotic therapy	0.41	(0.38 – 0.43)	0.43	(0.41 – 0.46)
Warfarin versus no antithrombotic therapy	0.46	(0.42 – 0.50)	0.45	(0.41 – 0.49)

CI = confidence interval; ICH = intracranial hemorrhage

Table S3. Effect size (95% CI) of the analysis comparing the risk of ischemic stroke and ICH of different treatment groups after the propensity match

Stroke prevention strategy	Ischemic stroke		ICH	
	Effect size	(95% CI)	Effect size	(95% CI)
No antithrombotic therapy (reference group)	-	-	-	-
Anti-platelet agents versus no antithrombotic therapy	0.37	(0.34 – 0.40)	0.39	(0.37 – 0.42)
Warfarin versus no antithrombotic therapy	0.24	(0.18 – 0.29)	0.24	(0.19 – 0.29)

CI = confidence interval; ICH = intracranial hemorrhage