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Recurrent thromboembolism, bleeding, and mortality in Asian patients with venous thromboembolism receiving different oral anticoagulants

A nationwide analysis

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Abstract

Venous thromboembolism (VTE) is associated with a high risk of morbidity and mortality. However, data on the association between oral anticoagulants and the hazards of VTE complications in Taiwanese patients with VTE is limited. This study aimed to compare the hazards of recurrent VTE, bleeding, and mortality between patients with VTE receiving rivaroxaban, a non-vitamin K antagonist oral anticoagulant (NOAC), and those receiving heparin or low-molecular-weight heparin (LMWH) followed by warfarin. Patients with VTE treated with rivaroxaban, or heparin or LMWH followed by warfarin were enrolled from 2 million random samples from Taiwan's National Health Insurance database between 2013 and 2016. Hazards of recurrent VTE (deep vein thrombosis and pulmonary embolism), major bleeding, and mortality in rivaroxaban and warfarin users were investigated. Survival analyses were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Users of rivaroxaban (183) and warfarin (456) were included in the study. Patients receiving rivaroxaban did not have significantly lower hazards of developing recurrent VTE (HR, 0.72 [CI, 0.37–1.37], $P = .31$) and mortality (HR, 0.86 [CI, 0.49–1.50], $P = .59$) than those receiving heparin or LMWH followed by warfarin. In addition, the hazard ratio of major bleeding was not significantly different between the 2 regimens (HR, 1.80 [CI, 0.39–8.29], $P = .45$). Rivaroxaban was not associated with lower risks of recurrent VTE and mortality and higher hazards of major bleeding than heparin or LMWH followed by warfarin in Taiwanese patients with VTE. Clinicians may tailor oral anticoagulants for VTE patients according to the patient's characteristics, cost-effectiveness and healthcare system policy.

Abbreviations: CI = confidence interval, DVT = deep vein thrombosis, HR = hazard ratio, INR = international normalized ratio, LMWH = low-molecular-weight heparin, NOAC = non-vitamin K antagonist oral anticoagulant, OAC = oral anticoagulant, PE = pulmonary embolism, RCT = randomized controlled trials, VTE = venous thromboembolism.

Keywords: rivaroxaban, venous thromboembolism, warfarin

1. Introduction

Venous thromboembolism (VTE) includes pulmonary embolism (PE), with 2-thirds manifesting as deep vein thrombosis (DVT). Overall, the incidence rate of VTE is approximately 1 case per 1000 people per year, and the recurrence rate is approximately 7% within 6 months.[1] In Taiwan, the crude incidence rate of VTE is 15.9 per 100,000 person-years, and the recurrence rate is 5.1% per person-year.[2] The incidence rate is lower than that in Western countries.[1,3,4]

Heparin or low-molecular-weight heparin (LMWH), followed by warfarin, is the standard regimen for VTE treatment. The international normalized ratio (INR) should be evaluated during warfarin use to ensure it is within the therapeutic range (2.0–3.0). If the INR is <2, VTE recurrence increases. For INR >3, the bleeding risk increases.[5] To balance the efficacy and safety,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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keeping INR within 2 to 3 is very important in clinical practice, but it is challenging. Rivaroxaban was the first non-vitamin K antagonist oral anticoagulant (NOAC) approved in Taiwan for VTE treatment. The EINSTEIN DVT[6] and EINSTEIN-PE[7] trials showed that rivaroxaban was as effective as the standard regimen for VTE or fatal PE recurrences. Furthermore, rivaroxaban is available in fixed doses and does not require blood draws to monitor the INR.

Although some observational cohorts showed that NOACs could lower the risk of VTE recurrence compared to warfarin, the risks of major bleeding between the 2 regimens did not have consistent results across the studies.[8–10] Besides, when taking oral anticoagulants (OACs), Asians have a higher risk of bleeding,[11] and the relevant data focusing on East Asian VTE patients are still sparse. Therefore, we conducted a retrospective cohort study to compare the risks of rivaroxaban and warfarin treatment for VTE patients in a real-world setting in Taiwan.

2. Methods

2.1. Database and study population

Taiwan National Health Insurance was implemented on March 1, 1995, and >99.6% of the Taiwanese population enrolled in this program. In 2016, the Health and Welfare Data Science Center collected research sampling datasets comprising 2 million subjects. Data were collected using stratified random sampling by age, sex, and registry of regions from the entire database population. It contains comprehensive claims data, including the cause of death, cancer registry, major illnesses, and hospital information datasets. Hence, random dataset sampling represents the national population.[12]

We used the VTE definition as stated by the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes. Patients with PE (ICD-9-CM code 415.1 or ICD-10-I26 code)[13,14] and DVT (ICD-9-CM code 453 or ICD-10-I82 code)[15] diagnosed between January 1, 2013, and December 31, 2017, were enrolled in our study. To increase the accuracy of the ICD codes, we recruited patients with at least once diagnosis code recorded at discharge or >3 times with the code at outpatient clinics. The index date was defined as the date when the VTE was first diagnosed. Patients below 20 years of age with atrial fibrillation, end-stage renal disease, joint replacement, previous surgery for any valvular disease, or those who used anticoagulants before the index date were excluded.

2.2. Exposure to study drugs

During the study period, Taiwanese patients with VTE were reimbursed for rivaroxaban and heparin or LMWH followed by warfarin. Besides, dabigatran, apixaban, and edoxaban were approved for use in Taiwan during the period. Hence, patients who received other anticoagulants 60 days before the index date were excluded. In the primary analysis, patients were censored when they switched to other anticoagulants after the initiation of treatment. Patients first exposed to the study drugs within the index date plus 7 days were included.

2.3. Covariates and outcomes

For each patient, we retrieved the comorbidities for VTE from both the inpatient and outpatient claims databases for the year before the index date. Comorbidities were recorded using the ICD-9-CM and ICD-10-CM codes. A history of bleeding was classified as critical site bleeding, gastrointestinal bleeding, or intracranial hemorrhage (Table S1, Supplemental Digital Content, http://links.lww.com/MD/H309).[16,17] Malignancy history was adopted from cancer registry datasets. In addition, antiplatelet agents were considered covariates because of their association with bleeding.

Our primary outcome was the VTE recurrence rate, identified from the inpatient claim database. The event with VTE diagnosis listed in the first 3 discharge diagnoses was calculated, which may improve the accuracy and avoid bias. The secondary outcomes were critical site bleeding and all-cause mortality. We obtained the individual death outcomes from the death datasets. All outcomes were observed after 3 days of drug exposure, up to 90 days after diagnosis or December 31, 2017.

2.4. Statistical analysis

The baseline characteristics of the included patients, divided into 2 groups, rivaroxaban and heparin or LMWH followed by warfarin, were described as a percentage or mean ± standard deviation. Differences between patients' demographic information and other covariates in each group were determined by appropriate test. Following the law of large numbers, the 2-sample t test is performed for continuous variables. According to the result of folded F test, test the equality of variances across samples, pooled or Satterthwaite estimator of variance is used in 2-sample t test. Differences in categorical variables are evaluated by Chi-square test or Fisher exact test, if appropriate. The incidence rates for each outcome were calculated based on the number of outcomes and person-years of follow-up. We calculated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) using a multivariate Cox proportional hazards model and adjusted covariates including sex, age, treatment duration, malignancy, diabetes mellitus, hypertension, peripheral arterial occlusion disease, chronic kidney disease, chronic liver disease, history of bleeding, and combination with antiplatelet agents to compare the primary and secondary outcomes between the 2 study groups.

In addition, we conducted subgroup analyses to examine the results of DVT and PE according to different baseline characteristics. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). Statistical significance was defined at $P < .05$.

2.5. Ethical statement

The study protocol was approved by the Ethics Committee of the Chi-Mei Medical Center (approval number 10801-E02).

3. Results

In this cohort study, we identified 2466 adults with newly diagnosed VTE. After excluding patients who had atrial fibrillation, end-stage renal disease, joint replacement, anticoagulant treatment before VTE diagnosis, and no records of study anticoagulants, 639 patients who had taken rivaroxaban or heparin or LMWH followed by warfarin were included. There were 183 patients in the rivaroxaban group and 456 patients in the heparin or LMWH followed by the warfarin group (Fig. 1).

The proportion of PE was 22.95% (42/183) for rivaroxaban and 35.53% (162/456) for heparin or LMWH followed by warfarin. The mean follow-up duration was 266.2 ± 111.90 days for rivaroxaban treatment and 328.2 ± 82.12 days for heparin or LMWH followed by warfarin treatment. The prescription periods for rivaroxaban were 40.98% (75/183) within 3 months, 32.24% (59/183) within 6 months, and 26.78% (49/183) within 12 months. For heparin or LMWH followed by warfarin, the prescription periods were 37.50% (171/456) within 3 months, 19.30% (88/456) within 6 months, and 43.20% (197/456) within 12 months. There were 39.89% (73/183) of patients aged ≤65 years in the rivaroxaban group and 39.91% (182/456) in heparin or LMWH followed by warfarin group. The rivaroxaban group (18.58%, 34/183) had a lower proportion of cancer

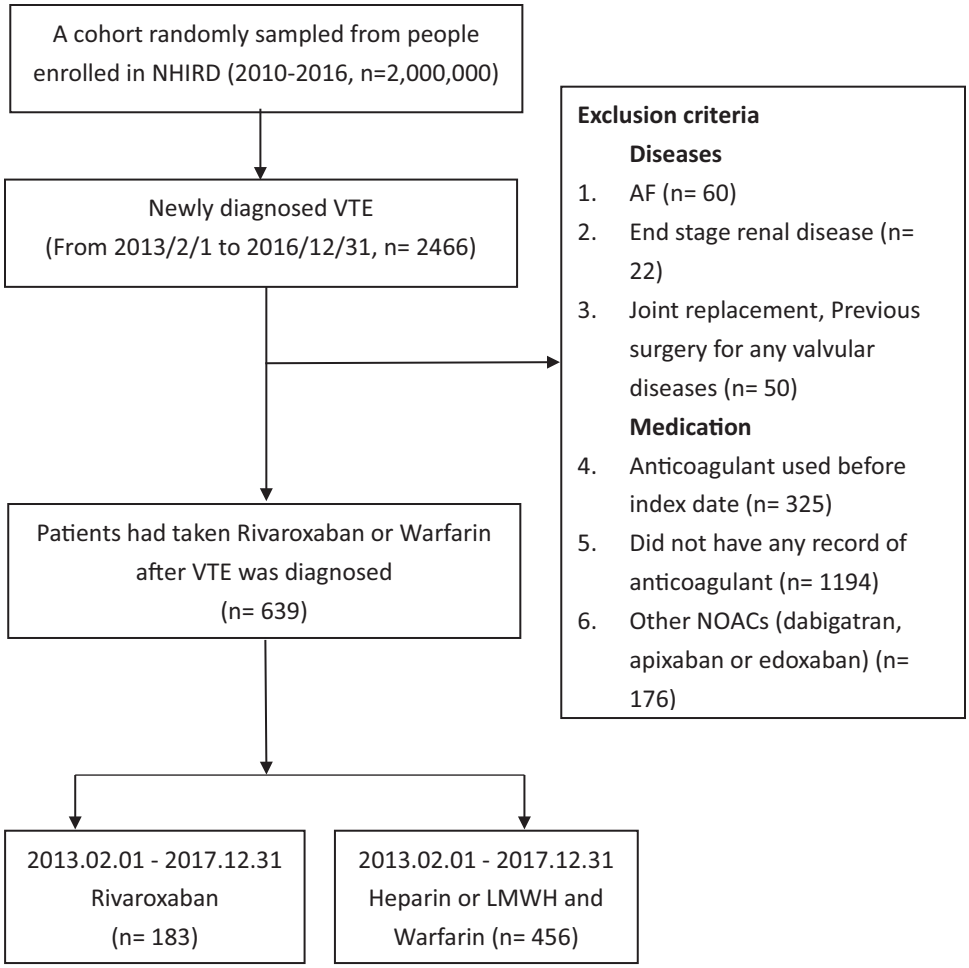

Figure 1. The flow chart of patient enrolled.

history than the heparin or LMWH followed by warfarin group (26.10%, 119/456). The other baseline characteristics did not differ significantly between the 2 study groups. This study had older patients and a greater percentage of cancer, compared with the EINSTEIN-DVT and EINSTEIN-PE trials[6,7] (Table 1).

There were 12 and 42 VTE recurrence events in the rivaroxaban (6.56%) and heparin or LMWH followed by warfarin group (9.21%), respectively (HR, 0.72; 95% CI, 0.37, 1.37, $P = .31$). The critical site bleeding rate was 1.64% (3 events) for rivaroxaban and 0.88% (4 events) for heparin or LMWH followed by warfarin group (HR, 1.80; 95% CI, 0.39, 8.29, $P = .45$). Furthermore, 16 patients (8.74%) died in the rivaroxaban group and 64 patients (14.04%) died in the heparin or LMWH followed by warfarin group (HR, 0.86; 95% CI, 0.49, 1.50, $P = .59$) (Table 2).

There were no significant differences in VTE recurrence and all-cause mortality between the PE and DVT subgroups (Table 3). In the other subgroups of VTE recurrence, we found no significant differences in age, duration of treatment, months, and history, except for male patients (HR, 0.35; 95% CI, 0.12, 1.00, $P = .05$) (Table 4).

4. Discussion

Our claims database analysis showed that rivaroxaban, as a part of routine clinical practice, had no difference in recurrent VTE, critical site bleeding, and all-cause mortality compared with the traditional regimen (heparin or LMWH followed by warfarin). However, patients in our cohort had a higher PE proportion and more comorbidities than those in randomized controlled trials (RCTs).[6,7] We found more VTE recurrence and a higher mortality rate in the real world than in RCTs.[6,7] Nonetheless, there was no statistically significant difference between rivaroxaban and the traditional treatment.

Our results are consistent with many previous cohort studies. There were similar findings in African-Americans[18] and morbid obese patients (weight > 120 kg or BMI >40 kg/m^2),[19] with these retrospective cohorts indicating no significant difference in recurrent VTE and major bleeding between patients receiving rivaroxaban or warfarin. Particularly, for safety, Jun et al presented that there was no significant difference between NOACs (94.6% rivaroxaban) and warfarin in major bleeding and all-cause mortality among VTE patients in Canada and the United States.[8] However, another study showed that rivaroxaban is associated with lower risks of recurrent VTE and bleeding events than warfarin.[10] The difference may be due to the proportion of cancer. Our study enrolled 18.58% of cancer patients in the rivaroxaban group and 26.10% in the warfarin group. There were only 4.5% of cancer patients in each group in Coleman et al study, and their subgroup analysis showed no statistical difference in cancer patients.[10]

The time in therapeutic range (TTR) for vitamin K antagonists was 58% and 63% in the EINSTEIN DVT[6] and EINSTEIN-PE[7] trials, respectively. Based on the previous study by Shen et al, Asians are considered to have a higher risk of bleeding when taking warfarin.[11] Furthermore, the TTR was lower in Asian patients than in non-Asian patients. Asian patients even had more time below the therapeutic range.[20] Subtherapeutic INR is associated with higher VTE recurrence.[21] In real-world practice, clinicians tend to maintain a lower INR; therefore,

Table 1

Baseline characteristics of patients using rivaroxaban vs warfarin.

	Cohort			EINSTEIN-DVT		EINSTEIN-PE	
n (%)	Rivaroxaban n = 183	Heparin or LMWH–warfarin n = 456	*P* value	Rivaroxaban n = 1731	LMWH-VKA n = 1718	Rivaroxaban n = 2419	LMWH-VKA n = 2413
Subgroup of VTE			<.01†				
PE	42 (22.95)	162 (35.53)		12 (0.69)	11 (0.64)	2419 (100)	2413 (100)
DVT	108 (59.02)	249 (54.61)		1708 (98.67)	1697 (98.78)	–	–
Both PE and DVT	33 (18.03)	45 (9.87)		–	–	–	–
Follow-up duration, d (mean, SD)	266.2 (111.90)	328.2 (82.12)	<.01†	–	–	263	268
Actual duration of treatment, mo			<.01†				
3-mo group	75 (40.98)	171 (37.50)		208 (12.0)	203 (11.8)	127 (5.3)	122 (5.1)
6-mo group	59 (32.24)	88 (19.30)		1083 (62.6)	1083 (63.0)	1387 (57.3)	1387 (57.5)
12-mo group	49 (26.78)	197 (43.20)		440 (25.4)	432 (25.1)	905 (37.4)	904 (37.5)
Age, yr			.32	55.8 ± 16.4	56.4 ± 16.3	57.9 ± 7.3	57.5 ± 7.2
≤ 65	73 (39.89)	182 (39.91)		–	–	–	–
65–75	29 (15.85)	94 (20.61)		–	–	–	–
≥ 75	81 (44.26)	180 (39.47)		–	–	–	–
Female	104 (56.83)	248 (54.90)	.57	738 (42.63)	751 (43.71)	1110 (45.89)	1166 (48.32)
Medical history							
Cancer	34 (18.58)	119 (26.10)	.04†	118 (6.8)	89 (5.2)	114 (4.7)	109 (4.5)
Diabetes mellitus	31 (16.94)	72 (15.79)	.72	–	–		
Hypertension	90 (49.18)	221 (48.46)	.87	–	–		
PAOD or CAD	35 (19.13)	80 (17.54)	.64	–	–		
Ischemic stroke	5 (2.73)	13 (2.85)	.93	–	–		
CKD	29 (15.85)	64 (14.04)	.56	–	–		
Chronic liver disease	11 (6.01)	30 (6.58)	.79	–	–		
History of bleeding	33 (18.03)	85 (18.64)	.86	–	–		
History of antiplatelet agents*	6 (3.28)	14 (3.07)	.89	–	–		

CAD = coronary artery disease, CKD = chronic kidney disease, DVT = deep vein thrombosis, LMWH = low-molecular-weight heparin, PAOD = peripheral arterial occlusion disease, PE = pulmonary embolism, VKA = vitamin K antagonist, VTE = venous thromboembolism.

*Including, aspirin clopidogrel, ticagrelor, dipyridamole, cilostazol, or ticlopidine.

† Statistically significant difference.

Table 2

The effectiveness and safety outcomes.

	Rivaroxaban group, no. of event (%)			Heparin or LMWH follow by warfarin group, no. of event (%)			Univariate analysis		Multivariate analysis	
	Cohort	EINSTEIN-DVT	EINSTEIN-PE	Cohort	EINSTEIN-DVT	EINSTEIN-PE	HR [95% CI]	*P* value	HR[95% CI]	*P* value
VTE	12 (6.56)	36 (2.1)	50 (2.1)	42 (9.21)	51 (3.0)	44 (1.8)	0.75 [0.39, 1.42]	.38	0.72 [0.37, 1.37]	.31
Critical site bleeding	3 (1.64)	3 (0.2)	26 (1.1)	4 (0.88)	3 (0.2)	52 (2.2)	2.09 [0.47, 9.36]	.33	1.80 [0.39, 8.29]	.45
All-cause mortality	16 (8.74)	39 (2.3)	58 (2.4)	64 (14.04)	49 (2.9)	50 (2.1)	0.78 [0.45, 1.35]	.37	0.86 [0.49, 1.50]	.59

CI = confidence interval, DVT = deep vein thrombosis, LMWH = low-molecular-weight heparin, PE = pulmonary embolism.

Table 3

Subgroup of PE and DVT.

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	*P* value	HR [95% CI]	*P* value
PE				
VTE	0.70 [0.16, 3.14]	0.64	0.61 [0.13, 2.82]	0.52
Critical site bleeding	–	–	–	–
All-cause mortality	0.26 [0.04, 1.93]	0.19	0.30 [0.04, 2.34]	0.25
DVT				
VTE	0.53 [0.22, 1.28]	0.16	0.61 [0.15, 1.55]	0.29
Critical site bleeding	1.66 [0.28, 9.95]	0.58	1.72 [0.28, 10.70]	0.56
Al-cause mortality	0.85 [0.44, 1.62]	0.62	1.21 [0.62, 2.36]	0.58

CI = confidence interval, DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism.

Table 4

Subgroup of VTE.

	Univariate analysis		Multivariate analysis	
Subgroup, no. of VTE (%)	**HR [95% CI]**	***P* value**	**Adjusted HR [95% CI]**	***P* value**
Sex				
Male	0.39 [0.14, 1.12]	.08	0.35 [0.12, 1.00]	.05
Female	1.43 [0.60, 3.40]	.42	1.48 [0.61, 3.61]	.39
Age, yr				
≤ 65	0.37 [0.11, 1.23]	.10	0.39 [0.12, 1.32]	.13
65–75	1.65 [0.30, 9.00]	.56	1.65 [0.28, 9.74]	.58
≥ 75	0.99 [0.41, 2.38]	.97	0.90 [0.37, 2.19]	.82
Duration of treatment, mo				
3-mo group	0.71 [0.35, 1.44]	.34	0.77 [0.38, 1.56]	.46
6-mo group	0.42 [0.09, 2.01]	.28	0.42 [0.09, 2.03]	.28
12-mo group	–	–	–	–
Cancer				
With	0.18 [0.02, 1.31]	.09	0.16 [0.02, 1.22]	.08
Without	1.23 [0.60, 2.54]	.57	1.11 [0.53, 2.31]	.78
Diabetes mellitus				
With	1.63 [0.39, 6.86]	.50	1.93 [0.42, 8.79]	.40
Without	0.63 [0.31, 1.31]	.218	0.61 [0.29, 1.28]	.19
Hypertension				
With	0.96 [0.43, 2.14]	.92	0.78 [0.34, 1.76]	.54
Without	0.53 [0.18, 1.57]	.25	0.64 [0.22, 1.90]	.42
PAOD or CAD				
With	0.55 [0.12, 2.53]	.44	0.67 [0.14, 3.28]	.62
Without	0.81 [0.40, 1.64]	.55	0.78 [0.38, 1.61]	.51
CKD				
With	0.88 [0.23, 3.31]	.85	0.89 [0.22, 3.55]	.86
Without	0.70 [0.34, 1.47]	.35	0.68 [0.33, 1.43]	.31
Chronic liver disease				
With	0.86 [0.09, 8.27]	.90	0.47 [0.05, 4.54]	.51
Without	0.74 [0.38, 1.45]	.38	0.74 [0.38, 1.47]	.39
History of bleeding				
With	1.19 [0.41, 3.42]	.75	1.05 [0.34, 3.26]	.93
Without	0.59 [0.26, 1.35]	.21	0.59 [0.26, 1.34]	.20
Ischemic stroke				
With	–	–	–	–
Without	0.78 [0.41, 1.50]	.46	0.74 [0.39, 1.4]	.37
History of antiplatelet agents				
With	–	–	–	–
Without	0.77 [0.40, 1.46]	.42	0.71 [0.37, 1.36]	.30

CI = confidence interval, VTE = venous thromboembolism.

the warfarin group in our cohort study had a higher rate of VTE recurrence and a lower rate of bleeding than the RCTs. In addition, we found that VTE recurrence and bleeding event rates were higher in patients on rivaroxaban than in the RCTs. Overall, the mortality rate of patients with real-world VTE was much higher than that of RCTs. Therefore, complete drug therapy is essential to reduce mortality in clinical practice.

We observed that rivaroxaban was associated with lower risks of VTE recurrence in men; however, the results were not in women. The possible reasons may be the different rates of VTE recurrence between genders. The previous study analyzing Caucasians, African-Americans and Hispanics showed that men have a significantly higher rate of recurrent VTE than women.[22] Despite the findings, the results should be interpreted cautiously, and more studies are warranted to assess the difference of efficacy between men and women. Besides, the cancer percentage in our study was relatively higher than in the previous trials. RCTs generally have strict inclusion and exclusion criteria. For example, the EINSTEIN DVT[6] and EINSTEIN-PE[7] trials excluded patients using systemic azole antifungal agents, commonly prescribed for cancer patients to prevent candida infection. The strict selections may decrease the cancer percentage in their study populations. Since our study analyzed the general population, including various cancers, this can explain why we had a higher cancer percentage.

Although the use of warfarin is inconvenient, its price is only 1/14 that of rivaroxaban in Taiwan. Rivaroxaban is an effective alternative to warfarin in patients with atrial fibrillation from a Taiwan national payer perspective,[23] but the economic analysis in VTE treatment remains insufficient. Warfarin is an inexpensive and effective drug in many populations, including young patients without specific comorbidities and patients who can accept dietary control and regular blood tests. On the other hand, potential drug interactions may affect the patient's INR when a patient has polypharmacy. This situation makes INR control difficult. Rivaroxaban may be more suitable than warfarin for these patients. Despite the advantages, some determinants may influence the clinical application. The rivaroxaban dose should be adjusted according to renal function, and it is not indicated according to the current clinical evidence in patients with advanced chronic kidney diseases (creatinine clearance <15 mL per minute). Besides, the patient's underlying diseases may influence the prescription decision, e.g., atrial fibrillation or cancer. Clinicians should prescribe OACs tailored to the characteristics of different patients.

We included the Taiwanese population using a national database, and the incidences of VTE, DVT, and PE were thoroughly investigated. We also compared the differences between the real world and RCTs, and performed a subgroup analysis based on relevant comorbidities. All of these are the strengths

of our study. However, our study had some limitations. We only discussed rivaroxaban and warfarin, and did not consider other NOACs, including dabigatran, apixaban, and edoxaban. We did not have individual INR data, and thus, we could not determine the effects of different TTR ranges. Further, we could not confirm whether patients' medication adherence was 100% during the study period. Therefore, the event rate might have been overestimated. The treatment duration for patients in the EINSTEIN DVT and EINSTEIN-PE trials was between 3 and 6 months, and the efficacy and safety of the extended period are still unknown. In our study, the effectiveness and safety of the extended treatment period are unknown. Also, the number of patients enrolled in this study was insufficient. A larger cohort study is needed to confirm the effectiveness and safety of rivaroxaban in the Asian population.

5. Conclusion

Our study found that rivaroxaban may not have significantly different hazards for VTE recurrence, major bleeding, and mortality compared to heparin or LMWH followed by warfarin in Taiwanese patients with VTE. The data may provide evidence that when tailoring the treatment strategy with different anticoagulants for VTE patients, the clinicians can consider the individual characteristics, cost-effectiveness and healthcare system's policy more comprehensively. Future large-scale and real-world studies are warranted.

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Conceptualization: Mei-Chuan Lee, Chia-Te Liao, and Wei-Ting Chang.
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