Changing Treatment Patterns in Patients With Venous Thromboembolism in Taiwan

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Background: In Asia, little information is available about contemporary real-world treatment patterns for venous thromboembolism (VTE).

Methods and Results: Consecutive patients (n=11,414) from the Taiwan National Health Insurance Research Database with initial VTE and taking oral anticoagulants between May 1, 2014 and June 30, 2016 were included. The temporal trends of using oral anticoagulants and pharmacomechanical therapy during the study period were evaluated. The efficacy and safety of nonvitamin K antagonist oral anticoagulants (NOACs) vs. warfarin were compared. Propensity score analysis (NOACs n=3,647 vs. warfarin n=3,647) was used to balance covariates between groups, and Cox proportional hazards models with adjustment were used to estimate the risks of clinical outcomes. The use of NOACs increased from 0.3% to 60.2% for VTE treatment during the study period. Pharmacomechanical therapy was used in 9.60%, 8.22%, and 5.63% from 2014 through 2016. NOACs were associated with a 16% risk reduction (adjusted hazard ratio [aHR] 0.84, 95% confidence interval [CI] 0.77–0.93) in all-cause mortality and a 21% risk reduction (aHR 0.79, 95% CI 0.65–0.96) in recurrent VTE vs. warfarin. Overall, NOACs were associated with a lower risk of major bleeding compared with warfarin (aHR 0.804, 95% CI 0.648–0.998).

Conclusions: In real-world practice, NOACs have become the major anticoagulant used for Asians with VTE. Although NOACs had a lower risk of recurrent VTE and major bleeding compared with warfarin in Taiwan, we still need a large-scale randomized controlled trial to confirm the findings.

Key Words: Deep vein thrombosis; Nonvitamin K antagonist oral anticoagulants; Pulmonary embolism; Venous thromboembolism; Warfarin

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), are serious and sometimes life-threatening conditions that require immediate medical attention. Heparin or low-molecular-weight heparin and warfarin are the traditional standard treatments for VTE. Development of nonvitamin K dependent oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, has revolutionized the treatment of VTE. Randomized clinical trials have demonstrated that NOACs are as effective as traditional standard anticoagulation therapy at reducing recurrent VTE with similar or reduced rates of major bleeding. Although evidence of long-term efficacy is lacking, pharmacomechanical therapy with catheter-directed thrombolysis, thrombus aspiration or maceration, or percutaneous transluminal balloon venoplasty with or without stent placement, or a combination of procedures is used to treat selected cases of severe VTE for rapid symptom relief. The incidence of VTE in Asians is lower than that reported from Western populations. However, our previous study in Taiwan showed that the cumulative rates of VTE recurrence at 6, 12, and 24 months after the index event were 6.7%, 9.4%, and 12.4%, which were comparable to Western populations. Anticoagulant therapy reduces the risk of VTE recurrence but must be balanced against the associated increased risk of bleeding. Asian
subgroup analysis from randomized clinical trials of NOACs for atrial fibrillation showed that NOACs carried a lower risk of major bleeding than warfarin.\textsuperscript{12–15} Unfortunately, randomized clinical trials of NOACs for VTE in Asian-specific populations are lacking. There was 1 meta-analysis of randomized controlled trials to evaluate the efficacy and safety of NOACs in VTE in Asian-specific populations which showed that the efficacy of NOACs was comparable with warfarin irrespective of ethnicity, and NOACs could be safer alternatives in Asian patients.\textsuperscript{16} The clinical trials have selective inclusion criteria and the reproducibility of their findings needs to be reassessed in the broader patient populations that are seen in routine clinical practice. Most post-marketing prospective or retrospective cohort studies assessing the efficacy and safety of NOACs for treatment of acute VTE also come from the Western countries.\textsuperscript{17–22} In fact, little information is available about the treatment of VTE in Asia in recent years. There are also no published data that directly compare efficacy and safety in Asians with VTE who are treated with NOACs vs. warfarin.

The purposes of this study were to investigate the pharmacoepidemiology of VTE patients who developed an initial DVT or PE from 2012 through 2016 by using the National Health Insurance Research Database (NHIRD) in Taiwan. The predisposing risk factors and associated comorbid diseases of these patients were evaluated. We also analyzed the trends of oral anticoagulant treatment and pharmacomechanical therapy during the study period. The risks of recurrent VTE, bleeding events, and all-cause death were compared between NOACs and warfarin in this real-world population of Asians with VTE.

### Methods

#### Study Design

A nationwide population-based cohort study was performed to observe the trends of treatment of VTE and compare the efficacy and safety of NOACs and warfarin in adult patients with an initial VTE and at least 6-month follow-up in Taiwan. The study (B-EX-107-044) was approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan. This study used the NHIRD released by the Taiwan National Health Research Institute. The National Health Insurance in Taiwan is a mandatory universal health insurance program that offers comprehensive medical care coverage to almost all Taiwanese residents (>99% of Taiwan’s population). Our previous verification studies demonstrated a high validity for the diagnosis of common medical diseases and death in the NHIRD.\textsuperscript{23,24} The accuracy for identifying procedures and medications was also high, with a positive predictive value >0.90.\textsuperscript{23,24} In this cohort dataset, the patients’ original identification numbers were encrypted to protect privacy. By using a consistent encrypting procedure, it was feasible to link and continuously follow all of the claims belonging to the same patient within the NHIRD.

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**Figure 1.** Flow chart of patient disposition. NOAC, nonvitamin K antagonist oral anticoagulant; VTE, venous thromboembolism.
Study Population

The Taiwan NHIRD from January 1, 2008 to December 31, 2016 was used for this study. Because the first NOAC (rivaroxaban) was approved for reimbursement by the Taiwan National Health Insurance from May 1, 2014, adult patients (≥18 years old) with their first attack of VTE (DVT, PE, or both) treated with anticoagulant therapy between May 1, 2014 and June 30, 2016 (inclusive) were enrolled in the study. Inclusion criteria were hospitalization with the major diagnosis of VTE or major diagnosis of VTE 2 times consecutively within 1 month in outpatient clinics. The exclusion criteria were: (1) treatment with anticoagulants in previous 3 years before the index event; (2) VTE diagnosed only in outpatient clinic but not fulfilling the inclusion criteria; (3) death during admission for VTE or with incomplete follow-up information (Figure 1). The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes and ICD-9-CM treatment codes were used (Supplementary Table 1).

For the first VTE event recorded in the database, and for each subsequent VTE event, the following information was captured: patient’s characteristics, medical history, provoking risk factors (e.g., major surgery/major trauma) within the previous 3 months, and type of VTE (DVT, PE or both) according to the ICD codes. We respectively ascertained the in-hospital and outpatient clinic use of warfarin, heparin/LMWH, antiplatelet agents, and NOACs by using the anatomic therapeutic chemical classification system. Recurrent VTE was defined as a new VTE hospitalization. The primary efficacy outcome was recurrent VTE, including DVT, PE or both. The breakdown incidences of recurrent DVT, recurrent PE, all-cause death, and myocardial infarction were also recorded. The primary safety outcome was major bleeding associated with hospitalization, including intracranial hemorrhage, major gastrointestinal (GI) bleeding, and other critical site bleeding (intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal).
nature of the study, propensity score analysis was performed to minimize any selection bias caused by differences in the clinical characteristics between groups. The propensity score is defined to be the probability of exposure to the treatment conditional on a study subject’s baseline characteristics.

In this study, the propensity score for the likelihood of receiving NOACs or warfarin was computed using multivariate logistic regression analysis, conditional on covariates including the index year, age, sex, medications during index hospitalization, medications 90 days before the index hospitalization, VTE provoking factors, and comorbidities, including coronary artery disease, heart failure, peripheral artery disease, hypertension, diabetes mellitus, hyperlipidemia, chronic lung disease, peptic ulcer, liver cirrhosis, cancer, atrial fibrillation, chronic kidney disease, and concomitant antiplatelet therapy.

The breakdown incidence of these bleeding events was also reported. Note that the same patient could have >1 study endpoint and have the same study endpoint many times during the study duration; only the study endpoint that appeared first was counted. The follow-up period was calculated from the index date until the occurrence of any study endpoint or to the end of the study period (December 31, 2016), whichever came first.

### Statistical Analysis

Demographic data are expressed as mean (±standard deviation) or percentage. In general, differences in proportions were tested with the chi-square test or Fisher’s exact test, and differences in continuous variables were tested with an unpaired Student’s t-test. Because of the nonrandomized nature of the study, propensity score analysis was performed to minimize any selection bias caused by differences in the clinical characteristics between groups. The propensity score is defined to be the probability of exposure to the treatment conditional on a study subject’s baseline characteristics. In this study, the propensity score for the likelihood of receiving NOACs or warfarin was computed using multivariate logistic regression analysis, conditional on covariates including the index year, age, sex, medications during index hospitalization, medications 90 days before the index hospitalization, VTE provoking factors, and comorbidities, including coronary artery disease, heart failure, peripheral artery disease, hypertension, diabetes mellitus, hyperlipidemia, chronic lung disease, peptic ulcer, liver cirrhosis, cancer, atrial fibrillation, chronic kidney disease, and concomitant antiplatelet therapy.
used to examine the effect of other potential unmeasured confounders on the treatment groups. A sensitivity analysis was performed using the R package “obsSens” to estimate the range of hazard ratios (HRs) between the treatment groups for 3 outcomes, including recurrent VTE, all-cause death, and the primary safety endpoint. We added a hypothetical unmeasured confounder with a favorable protective effect to observe the range of HRs confounded by this add-on factor with different prevalence in the warfarin and NOACs groups. The duration of anticoagulation therapy could be widely different according to the risk of recurrence in the real world and these differences should be taken into account. Therefore, we performed a time-dependent Cox regression model for the NOACs effect on primary efficacy and safety outcomes after propensity score matching and

| Table 2. Different Cancer Type Distribution Between NOACs and Warfarin Users After Propensity Score Matching | All cancer patients (n=1,624) | Warfarin (n=814) | NOACs (n=810) |
|---------------------------------------------------------------|-------------------------------|----------------|---------------|
| Malignancy of oral cavity and pharynx                          | 65 (4.00)                    | 38 (4.67)      | 27 (3.33)     |
| Malignancy of digestive organs                                 | 494 (30.42)                  | 243 (29.85)    | 251 (30.99)   |
| Malignancy of respiratory system                               | 339 (20.87)                  | 161 (19.78)    | 178 (21.98)   |
| Malignancy of bone, soft tissue                                | 173 (10.65)                  | 92 (11.30)     | 81 (10.00)    |
| Malignancy of genito-urinary system                            | 398 (24.51)                  | 204 (25.06)    | 194 (23.95)   |
| Malignancy of nervous system                                   | 21 (1.29)                    | 10 (1.23)      | 11 (1.36)     |
| Malignancy of endocrine glands                                  | 20 (1.23)                    | 8 (0.98)       | 12 (1.48)     |
| Hematology malignancy                                          | 83 (5.11)                    | 39 (4.79)      | 44 (5.43)     |
| Other\*                                                        | 31 (1.91)                    | 19 (2.33)      | 12 (1.48)     |

\*Unknown origin of malignancy.

| Table 3. NOACs Effect on Primary Efficacy Outcomes for a Cohort With VTE When Compared With Warfarin After Propensity Score Matching |
|---------------------------------------------------------------|-------------------------------|----------------|---------------|
| Primary efficacy endpoint                                      | Warfarin (n=3,647)          | NOACs (n=3,647) |
| Recurrent VTE, n (%)                                           | 233 (6.39)                   | 182 (4.99)    |
| Crude HR (95% CI)                                              | 1                            | 0.787 (0.648–0.955) |
| Adjusted HR (95% CI)                                          | 1                            | 0.788 (0.649–0.956) |
| CRR (95% CI)                                                  | 1                            | 0.790 (0.651–0.959) |
| Recurrent DVT, n (%)                                          | 145 (3.98)                   | 135 (3.70)    |
| Crude HR (95% CI)                                             | 1                            | 0.942 (0.745–1.190) |
| Adjusted HR (95% CI)                                          | 1                            | 0.943 (0.746–1.192) |
| CRR (95% CI)                                                  | 1                            | 0.943 (0.746–1.193) |
| Recurrent PE, n (%)                                           | 76 (2.08)                    | 42 (1.15)     |
| Crude HR (95% CI)                                             | 1                            | 0.559 (0.384–0.815) |
| Adjusted HR (95% CI)                                          | 1                            | 0.535 (0.366–0.781) |
| CRR (95% CI)                                                  | 1                            | 0.555 (0.380–0.812) |
| All-cause death, n (%)                                        | 880 (24.13)                  | 757 (20.76)   |
| Crude HR (95% CI)                                             | 1                            | 0.856 (0.777–0.944) |
| Adjusted HR (95% CI)                                          | 1                            | 0.844 (0.765–0.930) |
| Myocardial infarction, n (%)                                  | 34 (0.93)                    | 27 (0.74)     |
| Crude HR (95% CI)                                             | 1                            | 0.809 (0.488–1.341) |
| Adjusted HR (95% CI)                                          | 1                            | 0.804 (0.485–1.334) |
| CRR (95% CI)                                                  | 1                            | 0.805 (0.486–1.333) |

Patients treated with warfarin were recognized as reference group. Adjusted variables included sex, age, comorbidities, and concomitant medication. CI, confidence interval; CRR, competing risk regression; HR, hazard ratio; NOAC, nonvitamin K antagonist oral anticoagulant.

disease, and endstage renal disease. We used a greedy-matching algorithm to generate matches with a caliper of 0.25 of the standard deviation of the logit of the propensity score. Time-to-event Kaplan-Meier curves for each cohort were constructed for death from any cause and VTE, compared by means of log-rank test. The estimates of relative risk, with 95% confidence interval (CI), were derived from Cox proportional hazards models, adjusted for potential confounders including comorbidities. Fine and Gray competing risk regression models were used to examine the risk of acute myocardial infarction, recurrent VTE and bleeding events accounting for the competing risk of death. The SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA) was used for data collection and all subsequent statistical analyses. Sensitivity analysis was
Figure 3. Kaplan-Meier curves for event-free survival during follow-up for (A) recurrent VTE, (B) all-cause death, and (C) primary safety outcomes, including intracerebral hemorrhage, major gastrointestinal bleeding, and other critical site bleeding. NOAC, nonvitamin K antagonist oral anticoagulant; VTE, venous thromboembolism.
fitting duration of anticoagulation therapy as a time-dependent covariate.

### Results

Overall, identified in the database from May 1, 2014 to June 30, 2016 were 20,628 patients with a diagnosis of VTE. After exclusions, 11,414 patients (mean age 67.4±16.4 years, 44.4% male) were enrolled and formed the basis of this study (Figure 1). Figure 2 shows the temporal trends of oral anticoagulants and pharmacomechanical therapy for VTE from 2013 to 2016 in Taiwan. In anticoagulant-treated patients, warfarin use decreased progressively from 100% in 2013 Q1 to 39.8% in 2016 Q4, whereas NOACs use increased from 9% to 60.2% (Figure 2A). Among VTE patients in 2016 Q4, 56.3% of patients were treated with rivaroxaban, 3.1% with apixaban, and 0.8% with edoxaban. Unlike the gradually increasing use of NOACs, the proportion of patients who underwent pharmacomechanical therapy did not change significantly during the study period (Figure 2B).

Among the 11,414 patients enrolled in this study, 7,743 (68%) were given warfarin and 3,671 (32%) were given NOACs. The age, sex and other baseline clinical characteristics varied between the different treatment groups (Supplementary Table 2). After 1:1 propensity score matching, 7,294 patients were selected, and the baseline characteristics between patients treated with warfarin (n=3,647) and NOACs (n=3,647) became more balanced (Table 1). In the 7,294 oral anticoagulant-naïve patients, 4,957 (68%) of them had DVT, 1,688 (23%) had PE, and 649 (9%) had concurrent DVT and PE. The mean duration of warfarin use was 122 days after the VTE event and the mean duration of NOACs was 142 days. The most common identifiable risk factors were major surgery (30.9%), cancer (22.3%), and major trauma (9.9%). In Table 2, we list the different cancer types in the 2 groups. Table 3 shows the number of events for the primary efficacy endpoint. The duration of follow-up was similar between the warfarin (488.59±229.39 days) and NOACs groups (474.06±223.74 days). Overall, 415 patients developed recurrent VTE during follow-up, with 233 (6.39%) in the warfarin group and 182 (4.99%) in the NOACs group. NOACs were associated with lower rates of recurrent VTE compared with warfarin (adjusted HR [aHR] 0.788, 95% CI 0.649–0.956). A competing risk analysis showed a similar result (Table 3). The effects of NOACs were consistent among subgroups that were defined according to age, sex, and comorbidities (Supplementary Figure 1). Restricting the analyses to recurrent DVT or PE yielded an aHR of 0.943 (95% CI 0.746–1.192) for recurrent DVT and an aHR of 0.535 (95% CI 0.366–0.781) for recurrent PE. For all-cause death, NOACs was associated with a lower risk compared with warfarin (aHR 0.844, 95% CI 0.765–0.930) (Table 3). Subgroup analysis found patients without cancer had more benefit in mortality risk reduction with NOACs (Supplementary Figure 2). Figure 3 displays the cumulative event-free curves and shows that recurrent VTE and all-cause death were significantly decreased in patients treated with NOACs. Table 4 shows the number of events for the primary safety endpoint. Overall, NOACs were associated with a lower risk of major bleeding compared with warfarin (aHR 0.804, 95% CI 0.648–0.998). If mortality was taken into consideration, a competing risk analysis also showed that NOACs were associated with a significantly lower risk of bleeding compared with warfarin (aHR 0.805, 95% CI 0.648–0.999). Subgroup analysis showed that the benefit of NOACs for the primary safety endpoint was more significant in male patients and in those who took antiplatelet agents concomitantly (Supplementary Figures 3–5).

Sensitivity analysis was performed with an add-on unmeasured confounder for the 3 outcomes: recurrent VTE, all-cause death, and primary safety endpoint. Figure 4 displays the trend of estimates for the hazard using a

| Table 4. NOACs Effect on Primary Safety Outcomes for a Cohort With VTE When Comparing With Warfarin After Propensity Score Matching |
|---|
| **Warfarin** (n=3,647) | **NOACs** (n=3,647) |
| **Primary safety endpoint** | | |
| Major bleeding, n (%) | 185 (5.26) | 150 (4.25) |
| Crude HR (95% CI) | 1 | 0.818 (0.659–1.014) |
| Adjusted HR (95% CI) | 1 | 0.804 (0.648–0.998) |
| CRR (95% CI) | 1 | 0.805 (0.648–0.999) |
| Intracranial hemorrhage, n (%) | 62 (1.70) | 45 (1.23) |
| Crude HR (95% CI) | 1 | 0.734 (0.500–1.077) |
| Adjusted HR (95% CI) | 1 | 0.712 (0.485–1.047) |
| CRR (95% CI) | 1 | 0.712 (0.484–1.048) |
| Major GI bleeding, n (%) | 78 (2.14) | 67 (1.84) |
| Crude HR (95% CI) | 1 | 0.867 (0.626–1.202) |
| Adjusted HR (95% CI) | 1 | 0.861 (0.621–1.193) |
| CRR (95% CI) | 1 | 0.859 (0.619–1.192) |
| Other critical site bleeding, n (%) | 59 (1.62) | 50 (1.37) |
| Crude HR (95% CI) | 1 | 0.862 (0.592–1.257) |
| Adjusted HR (95% CI) | 1 | 0.851 (0.584–1.241) |
| CRR (95% CI) | 1 | 0.852 (0.585–1.240) |

Patients treated with warfarin were recognized as reference group. Adjusted variables included sex, age, comorbidities, and concomitant medication. Abbreviations as in Table 3.
Discussion

This is the first population-based study to observe the changing pattern of VTE treatment and compare the effects of NOACs with warfarin on VTE in Asian patients. Our study showed that NOACs have become the major anticoagulants for VTE treatment in recent years in this Asian cohort. A relatively fixed ratio of patients still needs pharmacomechanical intervention to treat VTE. Compared with warfarin, NOACs seemed to be associated with lower risk for recurrent VTE, all-cause death, and major bleeding.

Overall, 94% of the NOACs-treated patients were given rivaroxaban, which was the first NOAC reimbursed by the
Taiwan National Health Insurance from 2014 for VTE treatment. The EINSTEIN program, including EINSTEIN-DVT and EINSTEIN-PE studies, were randomized clinical trials that compared rivaroxaban with traditional therapy (enoxaparin/VKA) for treatment of DVT and PE, respectively. Pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies showed that the risk of recurrent VTE was similar between rivaroxaban and traditional therapy (HR 0.89, 95% CI 0.66–1.19) and major bleeding was significantly lower in the rivaroxaban group (HR 0.54, 95% CI 0.37–0.79). In a meta-analysis of all clinical trials including dabigatran, rivaroxaban, apixaban, and edoxaban for VTE treatment, NOACs were shown to be as effective as traditional therapy to decrease recurrence of VTE, and the risk of major bleeding was lower in patients treated with NOACs. More cancer patients were noted in our cohort (22%) compared with the EINSTEIN program (5.6%). A recent clinical trial recruiting only cancer patients with VTE demonstrated that rivaroxaban had a better effect in reducing recurrent VTE than dalteparin (HR 0.43, 95% CI, 0.19–0.99), but rivaroxaban showed a non-significant increase in major bleeding (HR 1.83, 95% CI 0.68–4.96). Another randomized clinical trial with edoxaban also showed similar results: the rate of recurrent VTE was lower but the rate of major bleeding was higher with edoxaban than with dalteparin in cancer patients with VTE. The higher proportion of cancer patients in our study could possibly explain the difference between our results and the data from randomized clinical trials. In addition, the quality of warfarin therapy is often represented by the time patients spend within the therapeutic range (percent time in therapeutic range, TTR). The correlation between TTR and the occurrence of complications during warfarin therapy has been established. According to previous trials (RELY, ROCKET-AF, ARISTOLE, ENGAGE AF–TIMI), warfarin TTR is lower in Asians than non-Asians (56.5% vs. 68.9%, 47.1% vs. 55.7%, 60% vs. 67%, 61.7% vs. 68.6%, respectively). In the ROCKET-AF subgroup analysis, TTR in Taiwan, China, Singapore, Hong Kong was 38% vs. 47% vs. 64% vs. 66%, respectively. Even in the randomized controlled trial, TTR in Taiwan was still far below the standard recommendation. We think that this could be an important reason why NOACs provide different results in Taiwan.

Despite advancements in vascular interventional therapy, only a minority of this study’s patients received pharmacomechanical therapy and that percentage did not increase in recent years. Our observation was similar to a recently published global registry study, The Global Anticoagulant Registry in the FIELD–Venous Thromboembolism (GARFIELD-VTE), showing that only 5.1% of patients received pharmacomechanical therapy. Lack of robust evidence to prevent recurrent VTE and risk of bleeding are the major reasons preventing the wide-spread use of pharmacomechanical therapy. In the current study, the absolute risk of recurrent VTE was 6.3% in the warfarin group and 4.99% in the NOAC group, which were in line with our previous report of an approximately 5.1% recurrent rate of VTE per person-year in Taiwan. The absolute risk of recurrent VTE was higher in our study compared with that in the EINSTEIN pooled analysis (2.3% in VKA and 2.1% in rivaroxaban group). This is probably because the mean age of our patients was older (57 years in the EINSTEIN pooled analysis vs. 68 years in our study) and more of our patients had cancer. These groups of patients carry a higher risk of VTE recurrence.

Most real-world studies of the use of NOACs in VTE treatment are from Western countries. In the Xa inhibition with rivaroxaban for Long-term and Initial Anticoagulation (XALIA) registry of DVT, rivaroxaban was associated with comparable effects in reducing recurrent VTE (HR 0.91, 95% CI 0.54–1.54) and major bleeding (HR 0.77, 95% CI 0.40–1.50) compared with warfarin. In the Danish health registries including only unprovoked VTE, the rate of recurrent VTE at 6 months was lower in the rivaroxaban-treated patients (HR 0.74, 95% CI 0.56–0.96), and major bleeding was similar between users of rivaroxaban and warfarin (HR 1.19, 95% CI 0.66–2.13). Although there is increasing use of NOACs for VTE treatment in Asia, their efficacy and safety have only been investigated in very small case numbers. Large-scale real-world data for the efficacy and safety of NOACs in Asian VTE patients are also lacking. In the EINSTEIN program, 439 Chinese patients were included. The risks of recurrent VTE and clinically relevant bleeding were similar between the rivaroxaban and enoxaparin/warfarin groups. The J-EINSTEIN study was a clinical trial that randomized only 81 Japanese patients with VTE to either rivaroxaban or intravenous unfractionated heparin (UFH) followed by warfarin. The composite endpoint of symptomatic recurrent VTE or asymptomatic deterioration occurred in 1.4% of rivaroxaban group and in 5.3% the UFH/warfarin group. No major bleeding occurred. Clinically relevant non-major bleeding occurred in 7.8% of the rivaroxaban group and 5.3% of the UFH/warfarin group. Our study is the largest to compare NOACs with warfarin in an Asian population and confirmed the efficacy and safety of NOACs in Asian VTE patients. The main advantage of our study was the use of a nationwide database with a large case number.

Study Limitations

There are several limitations. First, the accuracy of VTE diagnosis has not been verified in the NHIRD, so potential disease misclassification bias could exist. Second, some detailed clinical information, such as the international normalized ratio, was not available from the NHIRD and, thus the TTR of warfarin could not be analyzed in our study. The favorable effects of NOACs with regard to lower risk of VTE recurrence could be partly caused by low TTR of warfarin, which is a common practice behavior of physicians in Asia. Third, although an extensive number of variables were selected in the propensity score-matching analysis, some residual unmeasured confounding factors cannot be completely excluded. Fourth, the NHIRD could not provide clear cause of death and we only recorded the incidence of all-cause death in this study. Fifth, we could not well explain why recurrent PE was lower in NOACs users than in those treated with warfarin, but the risk of recurrent DVT was comparable between these groups.

Conclusions

NOACs have become the major anticoagulants used for Asian patients with VTE in recent years. Only a minority of VTE patients were treated with pharmacomechanical therapy. Although NOACs had a lower risk of recurrent VTE and major bleeding compared with warfarin, we still need a large-scale randomized controlled trial in Taiwan to confirm the findings.
Addendum

C.-H.L. and C.-C.F. initiated and designed the study, obtained approvals, prepared the data, did the analysis and interpretation, and wrote the first draft of the paper. L.-M.T. and P.-S.C. contributed to the development of the protocol, to the design, analysis, and interpretation, and to drafting the paper. S.-H.L. contributed to the protocol, interpretation, and drafting the article. H.-W.L. undertook the data processing and statistical analysis. Y.-H.L. coordinated the conduct of study, established the strategy of data processing of the claims data, and participated in the manuscript preparation. All authors approved the final draft.

Role of Sponsors

This study was funded by National Cheng Kung University-Show Chwan Memorial Health Care System R&D Project (NCKUSCMH10811). The funding organizations had no role in the design, performance or analysis of this study or decision to submit the manuscript for publication.

Disclosures

The authors declare no conflicts of interest.

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Supplementary Files
Please find supplementary file(s):
http://dx.doi.org/10.1253/circj.CJ-19-0741