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EDITORIAL

Utility of Rivaroxaban for Real-World Patients With Venous Thromboembolism

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Anticoagulation therapy is essential for the treatment and second prevention of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT). Vitamin K antagonists (VKA), including warfarin, were the only available oral anticoagulant in the past, but several direct oral anticoagulants (DOAC), such as rivaroxaban, have been introduced as novel treatments for VTE. The EINSTEIN PE/DVT trial, a large-scale multinational randomized clinical trial (RCT), demonstrated similar efficacy and safety of rivaroxaban, compared with conventional treatment using VKA,[1,2] which was also confirmed in a Japanese population in the J-EINSTEIN PE/DVT trial.[3] Based on the RCT results and ease of use, rivaroxaban has prevailed in daily clinical practice in Japan.[4] However, RCTs are conducted under idealized and rigorously controlled conditions, with highly selected patients, who might not be broadly representative of real-world practice. Because the clinical outcomes of rivaroxaban in the real world might not necessarily coincide with the clinical outcomes in RCTs, the effectiveness and safety of rivaroxaban in unselected real-world patients could be important. Furthermore, it is also clinically relevant whether this is the case in the Japanese population.

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In this issue of the Journal, Fukuda et al[5] report the clinical outcomes of rivaroxaban in the real-world patients in Japan using the open-label, prospective observational study, XASSENT (NCT02558465). A previous multicenter, prospective observational study, J'xactly, which

Table. Characteristics of Patients in XASSENT and the COMMAND VTE Registry

	XASSENT (n=2,387)	COMMAND VTE Registry (n=3,027)
Baseline characteristics		
Age (years)	66.6±15.0	67.2±15.3
Women	1,383 (58%)	1,858 (61%)
Body weight (kg)	60.9±13.9	57.9±13.7
Body mass index (kg/m^2)	23.9±4.2	23.2±4.4
Comorbidities		
Renal disease	221 (9.3%)	572 (19%)
Active cancer	406 (17%)	695 (23%)
Chronic lung disease	286 (12%)	271 (9.0%)
History of VTE	285 (12%)	178 (5.9%)
Presentation		
PE with or without DVT	1,187 (50%)	1,715 (57%)
Massive	71 (3.0%)	179 (5.9%)
Cardiac arrest/collapse	14 (0.6%)	80 (2.6%)
DVT only	1,199 (50%)	1,312 (43%)
Proximal DVT	694 (29%)	921 (30%)
Isolated distal DVT	409 (17%)	391 (13%)

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

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evaluated 1,039 patients with VTE in Japan, showed that rivaroxaban was a useful treatment for a broad range of VTE patients.[6] However, XASSENT had the strength of including over 2,500 patients with VTE treated with rivaroxaban, including a variety of patients with VTE. The study population in XASSENT was older, had lower body weight and a higher proportion of renal dysfunction compared with Western populations, which was consistent with a previous all-comer cohort study in Japan (**Table**).[7] In these various patients with VTE, including a relatively high-risk real-world population, XASSENT successfully demonstrated consistent effectiveness and safety of rivaroxaban for Japanese patients with VTE compared with those in the RCTs, which could be useful information for clinicians in daily clinical practice.

Notably, XASSENT showed a higher proportion of active cancer (17%), whereas the J-EINSTEIN PE/DVT trial included only 2 patients with active cancer (8.7%).[3] In line with the current study, the previous all-comer cohort study in Japan also showed a high proportion of active cancer (23%),[7] which suggests that patients with active cancer account for a certain proportion of patients with VTE in daily clinical practice in Japan. Although a previous RCT, the SELECT-D trial, showed that rivaroxaban could be a potential alternative standard treatment to low-molecular-weight heparin for cancer-associated VTE,[8] there still could be concerns of bleeding complications related to rivaroxaban, including gastrointestinal bleeding. Considering the numerically similar risk of recurrence between patients with and without active cancer in XASSENT, rivaroxaban might be a reasonable treatment option for cancer-associated VTE in Japan. However, further study of whether the current results can be applied to all types of patients with active cancer is warranted.

Another notable issue in XASSENT is a relatively higher proportion of isolated distal DVT. Although the previous RCTs did not include patients with isolated distal DVT,[1–3] the current study suggested that patients with isolated distal DVT were common in daily clinical practice in Japan, and these patients were treated with rivaroxaban. Very recently, a RCT evaluating the optimal duration of rivaroxaban in patients with symptomatic isolated distal DVT, the RIDTS study, demonstrated that longer duration of rivaroxaban treatment could have a potential benefit of reducing the risk of recurrence without increasing the risk of bleeding.[9] However, optimal management strategies for isolated distal DVT are still a matter of active debate, and further study of the optimal indication and duration of anticoagulation therapy is warranted.

From a practical point of view, in addition to the evidence from RCTs, the real-world evidence of VTE treatment is also important, and considering the current results, rivaroxaban could be a useful treatment option for a variety of patients with VTE in the era of DOACs. Finally, the authors should be congratulated for reporting the current clinically relevant study of rivaroxaban from XASSENT. Although solid evidence from RCTs might be still needed to recommend rivaroxaban for some specific VTE populations, the study by Fukuda et al could provide complementary information about an unresolved and clinically relevant issue in the VTE field.

Conflicts of Interest

Y.Y. received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare.

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