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The association of recurrence and bleeding events with mortality after venous thromboembolism: from the COMMAND VTE Registry

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Background/Introduction: Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), has a long-term risk for recurrence, which can be prevented by anticoagulation therapy. The duration of anticoagulation therapy after VTE should be based on the balance between risks of recurrent VTE and bleeding. However, there is uncertainty about the impact of these events on subsequent mortality.

Purpose: We sought to evaluate the impact of recurrent VTE events and bleeding events on subsequent mortality in patients with VTE in a large retrospective observational database in Japan.

Methods: We evaluated the association of recurrent VTE and major bleeding with mortality among 3026 patients in the COMMAND VTE Registry. We estimated the risks of recurrent VTE events and major bleeding events for subsequent all-cause death with the multivariable Cox proportional hazard model. We incorporated the recurrent VTE events and major bleeding events during follow-up into the multivariable Cox model as time-updated covariates together with the clinically-relevant 16 risk-adjusting factors. We expressed the adjusted risks of each covariate as hazard ratios (HR) and their 95% confidence intervals (CI). Furthermore, to assess the risks of recurrent PE and recurrent DVT events for subsequent all-cause death respectively, we divided recurrent VTE events into recurrent PE (PE with or without DVT) and recurrent DVT (DVT only), and incorporated these events as well as major bleeding events into the multivariable Cox model as time-updated covariates.

Results: In the current study population, the mean age was 67 years, 61% were women, and mean body weight and body mass index were 57.9 kg and 23.2 kg/m², respectively. During the median follow-up period of 1,218 days, 763 patients died, 225 patients developed recurrent VTE events, and 274 patients developed major bleeding events. The time-updated multivariable Cox proportional hazard model revealed that both the recurrent VTE events and the major bleeding events were strongly associated with subsequent mortality risk (recurrent VTE events: HR 3.24, 95% CI 2.57–4.08, $P < 0.001$; major bleeding events: HR 3.53, 95% CI 2.88–4.31, $P < 0.001$). Both the recurrent PE events and the recurrent DVT events were associated with subsequent mortality risk with the numerically greater magnitude of effect with the recurrent PE events than with the recurrent DVT events (recurrent PE events: HR 4.42, 95% CI 3.28–5.95, $P < 0.001$; recurrent DVT events: HR 2.42, 95% CI 1.75–3.36, $P < 0.001$).

Conclusions: In the real-world patients with VTE, both recurrent VTE events and major bleeding events were strongly associated with subsequent mortality risk with the comparable effect size. Recurrent PE and recurrent DVT events were also associated with increased risks for mortality, although the magnitude of the effect on mortality was numerically greater with the recurrent PE events than with the recurrent DVT events.