

## Risk factors for major bleeding during prolonged anticoagulation therapy in cancer-associated venous thromboembolisms: from the COMMAND VTE registry

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**Funding Acknowledgement:** Type of funding source: Foundation. Main funding source(s): Research Institute for Production Development, Mitsubishi Tanabe Pharma Corporation

**Background/Introduction:** Patients with cancer-associated venous thromboembolisms (VTEs) are at a high risk for recurrent VTEs and are recommended to receive prolonged anticoagulation therapy if they are at a low risk for bleeding. However, there are no established risk factors for bleeding during prolonged anticoagulation therapy.

**Purpose:** We aimed to identify the risk factors for major bleeding during prolonged anticoagulation therapy in cancer-associated VTE patients.

**Methods:** The COMMAND VTE Registry is a multicenter retrospective registry enrolling 3027 consecutive patients with acute symptomatic VTEs among 29 Japanese centers between January 2010 and August 2014. After excluding those without active cancer (N=2332), patients with major bleeding (N=15), death (N=17), and lost to follow-up (N=10) within 10 days after the diagnosis, and those without anticoagulation therapy beyond 10 days after the diagnosis (N=61), the present study population consisted of 592 cancer-associated VTE patients with anticoagulation therapy beyond 10 days after the diagnosis. The outcome measurement was International Society of Thrombosis and Hemostasis (ISTH) major bleeding during anticoagulation therapy beyond 10 days, which occurred before the first discontinuation of the anticoagulation therapy. We constructed a multivariable Cox proportional hazard model to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of the potential risk factors for major bleeding.

As a sensitivity analysis, we used Fine and Gray's method to estimate the HR and 95% CI, taking into account the competing risk of all-cause death.

**Results:** During a median follow-up period of 199 days, major bleeding occurred in 72 patients (31 patients within 3 months; 41 beyond 3 months). The cumulative incidence of major bleeding was 5.8% at 3-months, 13.8% at 1-year, 17.5% at 2-year, and 28.1% at 5-years. The most frequent major bleeding site was gastrointestinal (47%), followed by intracranial (17%) and genitourinary (11%). Major bleeding tended to occur from the sites of the cancer, however, the sites of the cancer and sites of major bleeding were not necessarily concordant. The multivariable Cox regression model demonstrated that terminal cancer (adjusted HR, 4.17; 95% CI, 2.22–7.85,  $P < 0.001$ ), chronic kidney disease (adjusted HR, 1.89; 95% CI 1.06–3.37,  $P = 0.031$ ), and gastrointestinal cancer (adjusted HR, 1.78; 95% CI, 1.04–3.04,  $P = 0.037$ ) were independently associated with an increased risk of major bleeding. After taking into account the competing risk of all-cause death, the multivariable Cox regression model demonstrated almost consistent results with the main analysis.

**Conclusions:** Major bleeding events were common during prolonged anticoagulation therapy in real-world cancer-associated VTE patients. Terminal cancer, chronic kidney disease, and gastrointestinal cancer were the independent risk factors for major bleeding.