Direct Oral Anticoagulant Therapy for Cancer-Associated Venous Thromboembolism in Routine Clinical Practice

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Background: The efficacy and bleeding complications of direct oral anticoagulant (DOAC) therapy for cancer-associated venous thromboembolism (VTE) in routine clinical practice remain unclear. Moreover, data on long-term outcomes in patients with cancer-associated VTE who received DOAC therapy are limited.

Methods and Results: This retrospective study enrolled 1,096 consecutive patients with acute VTE who received warfarin or DOAC therapy between April 2014 and May 2017. The mean follow-up period was 665±490 days. The number of cancer-associated VTE patients who received DOAC therapy was 334. Patients who could not be followed up and those prescribed off-label under-dose DOAC were excluded. Finally, 303 patients with cancer-associated VTE were evaluated. The number of cases of major bleeding and VTE recurrence was 54 (17.8%) and 26 (8.6%), respectively. In the multivariate analysis, the factors correlated with major bleeding were high cancer stage, high performance status, liver dysfunction, diabetes mellitus, and stomach cancer; those correlated with recurrent VTE were initial diagnosis of pulmonary embolism, uterine cancer, and previous cerebral infarction. Major bleeding was an independent risk factor of all-cause death. In the Kaplan-Meier analysis, those who received prolonged DOAC therapy had lower composite major bleeding and recurrent VTE risks than those who did not.

Conclusions: In DOAC therapy for cancer-associated VTE, major bleeding prevention is important because it is an independent risk factor of death.

Key Words: Cancer; Direct oral anticoagulants; Venous thromboembolism

Cancer is a major cause of venous thromboembolism (VTE). Cancer itself increases coagulability and, in addition, surgery, chemotherapy, and usage of central venous catheters for cancer therapy also increase the occurrence of VTE.1 In Japan, unfractionated heparin or warfarin is traditionally used for VTE, whereas in other Western countries, low-molecular-weight heparin is used. In September 2014, direct oral anticoagulant (DOAC) therapy was approved for VTE, and the Japan Circulation Society (JCS) recommended DOAC usage for VTE (Class I).2 Several randomized control trials (RCTs) revealed equivalent efficacy and safety between DOAC therapy and ordinary warfarin therapy.3,4 However, only a few patients with cancer-associated VTE were enrolled in those RCTs, and the efficacy and bleeding complications of DOAC therapy have not been fully elucidated. Moreover, few studies have reported the long-term outcomes of patients with cancer-associated VTE treated with DOACs. Herein, we aimed to evaluate the current state of DOAC therapy for cancer-associated VTE.

Methods
This physician-initiated retrospective study enrolled 1,096 consecutive patients with acute VTE who received oral anticoagulant therapy, comprising warfarin or DOAC, between April 2014 and May 2017 in Yokohama City University Hospital and Yokohama City University Medical Center. Patient data, including age, sex, VTE etiology, and other VTE-related factors, were collected from hospital charts. VTE was diagnosed on the basis of the patient’s symptoms and lower limb ultrasound, contrast-enhanced computed tomography, and ventila-
Major bleeding was defined by the International Society of Thrombosis and Hemostasis criteria: reduction in the hemoglobin level by at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. In the present study, each physician ordinarily prescribed DOACs for 3 months and withdrew them after confirmation that the thrombus had disappeared. When the thrombus remained, prolonged therapy was considered. VTE recurrence was defined as the presence of a new thrombus confirmed by objective imaging examinations. The timing of evaluation for recurrent VTE depended on the judgment of each physician in the presence of the following symptoms: leg pain, leg swelling, and dyspnea. As for asymptomatic cases, an increased D-dimer level was considered an indication for objective imaging examinations to monitor for new thrombus formation.

Patients with cancer-associated VTE included those receiving treatment for cancer, such as chemotherapy or radiotherapy, those scheduled to undergo cancer surgery, those with metastasis to other organs, and those with terminal cancer (expected life expectancy ≤6 months) at the time of diagnosis according to a previous study. We confirmed the specific tumor types, performance status (PS), cancer stage, and performance of chemotherapy at the time of VTE diagnosis. The cancer stage was determined using the TNM classification. Cancers with distal metastasis or the highest malignant grade were classified as stage 4. Liver dysfunction was defined as the presence of a chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin level >2× upper limit or aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase level >3× the upper limit). This definition was derived from the HAS-BLED score.

We evaluated the incidence and characteristics of VTE recurrence, major bleeding, and all-cause death. We also evaluated the composite risk of major bleeding and recurrent VTE between patients who received prolonged therapy and those with non-prolonged therapy. Prolonged therapy was defined as anticoagulant therapy with DOAC and/or initial intravenous anticoagulant for >3 months (90 days).

This study was approved by the Ethics Committee of Yokohama City University Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was given by all of the patients.

**Statistical Analysis**

All continuous variables are reported as mean±SD and all categorical variables as frequency (percentage). An unpaired t-test was used to compare the continuous variables, and the chi-square test was used to test the difference in the qualitative variables between groups. For all comparisons, P<0.05 was considered statistically significant.

For the factors that were significantly associated with major bleeding, recurrent VTE, and all-cause death by unpaired t-test or chi-square test, a univariate Cox regression analysis was performed. Thereafter, factors with a P-value <0.05 were validated in a multivariate Cox regression analysis. The Kaplan-Meier method was used to compare the composite risk of major bleeding and recurrent VTE between patients receiving prolonged or non-prolonged therapy. SPSS ver. 21 (IBM, NY, USA) was used for the statistical analysis.
Results

Between April 2014 and May 2017, 1,096 patients with acute VTE were treated with OAC therapy in our institutions. Among them, 780 and 316 patients were treated with DOACs and warfarin, respectively. In the DOAC group, there were 334 patients with cancer-associated VTE; 7 patients could not be followed up, and 24 patients were prescribed with off-label under-dose DOAC. Finally, 303 patients with cancer-associated VTE were evaluated in this study (Figure 1). The mean follow-up period was 665±490 days.

Table 1 shows the characteristics of the 303 patients with cancer-associated VTE. As for the primary site of cancer, digestive organ cancers had the greatest number of cases. The number of blood cancer cases was as follows: malignant lymphoma (n=4), multiple myeloma (n=2), myelodysplastic syndrome (n=1), and leukemia (n=1). The number of head and neck cancer cases was as follows: thyroid cancer (n=3), pharyngeal cancer (n=2), nose cancer (n=1), oral cavity cancer (n=1), and submaxillary cancer (n=1). As for the treatment in the acute phase, single-drug therapy with 15mg rivaroxaban BID or 5mg apixaban BID was used. The intravenous anticoagulants used were unfractionated heparin in 63 patients and argatroban in 5 patients. Patients not examined for the presence of pulmonary embolism (PE) included those not examined for the presence of PE according to the judgment of the attending physicians at the time of initial diagnosis of deep vein thrombosis (DVT). The number of patients with PE only was 29. The number of patients with PE and
Table 2. Comparison Between Patients With and Without Major Bleeding

|                                | Bleeding (n=54) | No bleeding (n=249) | P value |
|--------------------------------|-----------------|---------------------|---------|
| Age (years)                    | 72.8±9.0        | 72.1±10.4           | 0.64    |
| Female sex                     | 28 (51.9%)      | 113 (45.4%)         | 0.39    |
| Body weight (kg)               | 53.5±11.8       | 54.7±11.8           | 0.52    |
| Body mass index (kg/m²)        | 21.7±4.3        | 21.7±4.0            | 0.95    |
| ≥30 kg/m²                      | 4 (7.4%)        | 7 (2.8%)            | 0.10    |
| PE                             | 29 (53.7%)      | 116 (46.6%)         | 0.34    |
| Not examined for presence of PE| 5 (9.3%)        | 15 (6.0%)           | 0.39    |
| Proximal DVT                   | 15 (27.8%)      | 66 (26.5%)          | 0.85    |
| Distal DVT                     | 39 (72.2%)      | 190 (76.3%)         | 0.53    |
| Symptomatic VTE                | 23 (42.6%)      | 87 (34.9%)          | 0.29    |
| Primary site of cancer         |                 |                     |         |
| Stomach                        | 13 (24.1%)      | 31 (12.4%)          | 0.028   |
| Colorectum                     | 13 (24.1%)      | 68 (27.3%)          | 0.63    |
| Pancreas                       | 4 (7.4%)        | 26 (10.4%)          | 0.5     |
| Esophagus                      | 2 (3.7%)        | 4 (1.6%)            | 0.32    |
| Bile duct                      | 3 (5.6%)        | 15 (6.0%)           | 0.89    |
| Gallbladder                    | 0 (0.0%)        | 4 (1.6%)            | 0.35    |
| Liver                          | 2 (3.7%)        | 4 (1.6%)            | 0.32    |
| Lung                           | 6 (11.1%)       | 18 (7.2%)           | 0.34    |
| Breast                         | 1 (1.9%)        | 12 (4.8%)           | 0.33    |
| Uterus                         | 4 (7.4%)        | 12 (4.8%)           | 0.44    |
| Ovary                          | 3 (5.6%)        | 11 (4.4%)           | 0.72    |
| Prostate                       | 1 (1.9%)        | 7 (2.8%)            | 0.69    |
| Urinary bladder                | 0 (0.0%)        | 7 (2.8%)            | 0.21    |
| Kidney                         | 0 (0.0%)        | 4 (1.6%)            | 0.35    |
| Blood                          | 1 (1.9%)        | 7 (2.8%)            | 0.69    |
| Head and neck                  | 1 (1.9%)        | 7 (2.8%)            | 0.69    |
| Nerve                          | 0 (0.0%)        | 5 (2.0%)            | 0.29    |
| Skin                           | 0 (0.0%)        | 3 (1.2%)            | 0.42    |
| Bone                           | 0 (0.0%)        | 1 (0.4%)            | 0.64    |
| Unknown origin                 | 0 (0.0%)        | 3 (1.2%)            | 0.42    |
| Cancer stage                   |                 |                     |         |
| 1–3                            | 19 (35.2%)      | 163 (65.5%)         | <0.001  |
| 4                              | 35 (64.8%)      | 86 (34.5%)          |         |
| Performance status             |                 |                     |         |
| 0                              | 7 (13.0%)       | 112 (45.0%)         | <0.001  |
| 1                              | 32 (59.3%)      | 109 (43.8%)         | 0.038   |
| 2–4                            | 15 (27.8%)      | 28 (11.2%)          | 0.0016  |
| Chemotherapy                   | 40 (74.1%)      | 133 (53.4%)         | 0.0054  |
| Hypertension                   | 28 (51.9%)      | 94 (37.8%)          | 0.055   |
| Diabetes mellitus              | 15 (27.8%)      | 27 (10.8%)          | 0.001   |
| Previous stroke                | 4 (7.4%)        | 8 (3.2%)            | 0.15    |
| Liver dysfunction              | 11 (20.4%)      | 17 (6.8%)           | 0.0018  |
| Laboratory results at diagnosis|                 |                     |         |
| D-dimer level (μg/mL)          | 12.6±12.9       | 10.3±13.9           | 0.26    |
| eGFR (mL/min/1.73m²)           | 68.1±23.5       | 70.4±19.8           | 0.48    |
| Hemoglobin level (g/dL)        | 10.8±1.79       | 11.4±1.91           | 0.035   |
| Platelet count (×10⁴/dL)       | 25.5±12.1       | 23.5±9.7            | 0.18    |
| Treatment in the acute phase   |                 |                     |         |
| Single-drug therapy            | 7 (13.0%)       | 41 (16.5%)          | 0.52    |
| Intravenous anticoagulant      | 19 (35.2%)      | 49 (19.7%)          | 0.013   |
| Medications at diagnosis       |                 |                     |         |
| Antiplatelet agents            | 6 (11.1%)       | 20 (8.0%)           | 0.46    |
| Non-steroidal antiinflammatory drugs | 10 (18.5%) | 24 (9.6%) | 0.061   |
| Corticosteroids                | 3 (5.6%)        | 11 (4.4%)           | 0.72    |
| Median duration of anticoagulant therapy (days) | 86 | 188 | <0.001 |

Abbreviations as in Table 1.
Table 3. Comparison Between Patients With and Without VTE Recurrence

|                        | Recurrence (n=26) | No recurrence (n=277) | P value |
|------------------------|-------------------|-----------------------|---------|
| Age (years)            | 67.0±16.4         | 72.5±9.8              | 0.058   |
| Female sex             | 14 (53.8%)        | 127 (45.8%)           | 0.43    |
| Body weight (kg)       | 55.6±15.6         | 54.1±11.6             | 0.11    |
| Body mass index (kg/m²)| 21.8±5.4          | 21.6±4.0              | 0.17    |
| ≥30 kg/m²              | 2 (7.7%)          | 9 (3.2%)              | 0.25    |
| PE                     | 18 (69.2%)        | 127 (45.8%)           | 0.022   |
| Not examined for PE    | 0 (0.0%)          | 20 (7.2%)             | 0.16    |
| Proximal DVT           | 8 (30.8%)         | 73 (26.4%)            | 0.63    |
| Distal DVT             | 20 (76.9%)        | 209 (75.5%)           | 0.87    |
| Symptomatic VTE        | 12 (46.2%)        | 98 (35.4%)            | 0.27    |
| Primary site of cancer |                   |                       |         |
| Stomach                | 1 (3.8%)          | 43 (15.5%)            | 0.11    |
| Colorectum             | 8 (30.8%)         | 73 (26.4%)            | 0.63    |
| Pancreas               | 1 (3.8%)          | 29 (10.5%)            | 0.28    |
| Esophagus              | 0 (0.0%)          | 6 (2.2%)              | 0.45    |
| Bile duct              | 2 (7.7%)          | 16 (5.8%)             | 0.69    |
| Gallbladder            | 0 (0.0%)          | 4 (1.4%)              | 0.53    |
| Liver                  | 0 (0.0%)          | 6 (2.2%)              | 0.45    |
| Lung                   | 3 (11.5%)         | 21 (7.6%)             | 0.47    |
| Breast                 | 2 (7.7%)          | 11 (4.0%)             | 0.37    |
| Uterus                 | 4 (15.4%)         | 12 (4.3%)             | 0.015   |
| Ovary                  | 1 (3.8%)          | 13 (4.7%)             | 0.84    |
| Prostate               | 0 (0.0%)          | 8 (2.9%)              | 0.4     |
| Urinary bladder        | 1 (3.8%)          | 6 (2.2%)              | 0.59    |
| Kidney                 | 1 (3.8%)          | 3 (1.1%)              | 0.24    |
| Blood                  | 1 (3.8%)          | 7 (2.5%)              | 0.69    |
| Head and neck          | 1 (3.8%)          | 7 (2.5%)              | 0.69    |
| Nerve                  | 0 (0.0%)          | 5 (1.8%)              | 0.49    |
| Skin                   | 0 (0.0%)          | 3 (1.1%)              | 0.59    |
| Bone                   | 0 (0.0%)          | 1 (0.36%)             | 0.76    |
| Unknown origin         | 0 (0.0%)          | 3 (1.1%)              | 0.59    |
| Cancer stage           |                   |                       |         |
| 1–3                    | 13 (50.0%)        | 169 (61.0%)           | 0.27    |
| 4                      | 13 (50.0%)        | 108 (39.0%)           | 0.27    |
| Performance status     |                   |                       |         |
| 0                      | 11 (42.3%)        | 108 (39.0%)           | 0.74    |
| 1                      | 13 (50.0%)        | 128 (46.2%)           | 0.71    |
| 2–4                    | 2 (7.7%)          | 41 (14.8%)            | 0.32    |
| Chemotherapy           | 16 (61.5%)        | 157 (56.7%)           | 0.63    |
| Hypertension           | 14 (53.8%)        | 108 (39.0%)           | 0.14    |
| Diabetes mellitus      | 4 (15.4%)         | 38 (13.7%)            | 0.81    |
| Previous stroke        | 3 (11.5%)         | 9 (3.2%)              | 0.038   |
| Liver dysfunction      | 4 (15.4%)         | 24 (8.7%)             | 0.26    |
| Laboratory results at diagnosis |    |                       |         |
| D-dimer level (µg/mL)  | 10.6±8.5          | 10.7±14.1             | 0.98    |
| eGFR (mL/min/1.73m²)   | 67.9±23.0         | 70.0±20.4             | 0.99    |
| Hemoglobin level (g/dL)| 10.8±2.55         | 11.3±1.9              | 0.89    |
| Platelet count (×10⁶/dL)| 22.7±5.8          | 24.0±10.5             | 0.64    |
| Treatment in the acute phase |            |                       |         |
| Single-drug therapy    | 4 (15.4%)         | 44 (16.1%)            | 0.95    |
| Intravenous anticoagulant | 4 (15.4%)        | 64 (23.1%)            | 0.37    |
| Medications at diagnosis |                 |                       |         |
| Antiplatelet agents    | 2 (7.7%)          | 24 (8.7%)             | 0.87    |
| Non-steroidal antiinflammatory drugs | 4 (15.4%) | 30 (11%)             | 0.48    |
| Corticosteroids        | 1 (3.8%)          | 13 (4.7%)             | 0.84    |
| Prolonged therapy      | 14 (53.8%)        | 186 (67.1%)           | 0.17    |
| Median duration of anticoagulant therapy (days) | 211 | 427 | 0.76 |

Abbreviations as in Table 1.
**Table 4. Comparison Between Patients Who Survived or Died**

|                          | Died (n=173) | Survived (n=130) | P value |
|--------------------------|-------------|------------------|---------|
| Age (years)              | 72.2±10.9   | 72.3±9.0         | 0.94    |
| Female sex               | 73 (42.2%)  | 68 (52.3%)       | 0.08    |
| Body weight (kg)         | 52.6±11.5   | 57.0±11.8        | 0.0013  |
| Body mass index (kg/m²)  | 21.0±4.1    | 22.6±3.8         | <0.001  |
| ≥30kg/m²                 | 6 (3.5%)    | 5 (3.8%)         |         |
| PE                       | 88 (50.9%)  | 57 (43.8%)       | 0.23    |
| Not examined for presence of PE | 13 (7.5%) | 7 (5.4%) | 0.46 |
| Proximal DVT             | 55 (31.8%)  | 26 (20%)         | 0.02    |
| Distal DVT               | 122 (70.5%) | 107 (82.3%)      | 0.018   |
| Symptomatic VTE          | 67 (38.7%)  | 43 (33.1%)       | 0.31    |
| Primary site of cancer   |             |                  |         |
| Stomach                  | 28 (16.2%)  | 16 (12.3%)       | 0.34    |
| Colorectum               | 39 (22.5%)  | 42 (32.3%)       | 0.057   |
| Pancreas                 | 23 (13.3%)  | 7 (5.4%)         | 0.023   |
| Esophagus                | 5 (2.9%)    | 1 (0.77%)        | 0.19    |
| Bile duct                | 9 (5.2%)    | 9 (6.9%)         | 0.53    |
| Gallbladder              | 4 (2.3%)    | 0 (0.0%)         | 0.08    |
| Liver                    | 2 (1.2%)    | 4 (3.1%)         | 0.23    |
| Lung                     | 17 (9.8%)   | 7 (5.4%)         | 0.16    |
| Breast                   | 7 (4.0%)    | 6 (4.6%)         | 0.8     |
| Uterus                   | 11 (6.4%)   | 5 (3.8%)         | 0.33    |
| Ovary                    | 7 (4.0%)    | 7 (5.4%)         | 0.58    |
| Prostate                 | 3 (1.7%)    | 5 (3.8%)         | 0.26    |
| Urinary bladder          | 3 (1.7%)    | 4 (3.1%)         | 0.44    |
| Kidney                   | 0 (0.0%)    | 4 (3.1%)         | 0.02    |
| Blood                    | 5 (2.9%)    | 3 (2.3%)         | 0.75    |
| Head and neck            | 3 (1.7%)    | 5 (3.8%)         | 0.26    |
| Nerve                    | 4 (2.3%)    | 1 (0.77%)        | 0.3     |
| Skin                     | 1 (0.58%)   | 2 (1.5%)         | 0.4     |
| Bone                     | 0 (0.0%)    | 1 (0.77%)        | 0.25    |
| Unknown origin           | 2 (1.2%)    | 1 (0.77%)        | 0.74    |
| Cancer stage             |             |                  |         |
| 1–3                      | 64 (37%)    | 118 (90.8%)      | <0.001  |
| 4                        | 109 (63%)   | 12 (9.2%)        |         |
| Performance status       |             |                  |         |
| 0                        | 28 (16.2%)  | 91 (70%)         | <0.001  |
| 1                        | 107 (61.8%) | 34 (26.2%)       |         |
| 2–4                      | 38 (22%)    | 5 (3.8%)         |         |
| Chemotherapy             | 113 (65.3%) | 60 (46.2%)       | <0.001  |
| Hypertension             | 66 (38.2%)  | 56 (43.1%)       | 0.39    |
| Diabetes mellitus        | 27 (15.6%)  | 15 (11.5%)       | 0.31    |
| Previous stroke          | 11 (6.4%)   | 1 (0.77%)        | 0.014   |
| Liver dysfunction        | 24 (13.9%)  | 4 (3.1%)         | 0.0013  |
| Laboratory results at diagnosis |     |                  |         |
| D-dimer level (µg/mL)    | 11.5±12.5   | 9.6±15.1         | 0.25    |
| eGFR (mL/min/1.73 m²)    | 69.6±20.6   | 70.5±20.5        | 0.7     |
| Hemoglobin level (g/dL)  | 11.0±1.9    | 11.6±1.8         | 0.0055  |
| Platelet count (×10⁴/dL) | 25.0±10.5   | 22.4±9.5         | 0.03    |
| Treatment in the acute phase |       |                  |         |
| Single-drug therapy      | 27 (15.6%)  | 21 (16.2%)       | 0.89    |
| Intravenous anticoagulant| 39 (22.5%)  | 29 (22.3%)       | 0.56    |
| Medications at diagnosis |             |                  |         |
| Antiplatelet agents      | 16 (9.2%)   | 10 (7.7%)        | 0.63    |
| Non-steroidal antiinflammatory drugs | 26 (15%)  | 8 (6.2%) | 0.015 |
| Corticosteroids          | 11 (6.4%)   | 3 (2.3%)         | 0.096   |
| Major bleeding           | 51 (29.5%)  | 3 (2.3%)         | <0.001  |
| Recurrent VTE            | 15 (8.7%)   | 11 (8.5%)        | 0.95    |
| Median duration of anticoagulant therapy (days) | 141 | 232 | <0.001 |

Abbreviations as in Table 1.
DVT was 116, and that of patients with DVT only was 138. The number of cases not examined for the presence of PE was 20.

Figure 2 shows the Kaplan-Meier curve estimates for the rate of discontinuation of anticoagulation. In the follow-up period, 264 patients discontinued DOAC, and of them 103, 103, 54, 2, 1, and 1 patients discontinued DOAC because of difficulty with oral intake due to progression of cancer, disappearance of thrombus, bleeding complication, difficulty of oral intake due to cerebral infarction, bowel perforation, and suicide, respectively.

In the follow-up period, 54 (17.8%) patients developed major bleeding, and 26 (8.6%) patients developed recurrent VTE. A total of 20, 20, 4, 3, 2, 2, 1, and 1 patients had major bleeding in the upper digestive tract, lower digestive tract, brain, urinary bladder, genitals, nasopharynx, hemothysis, spleen, and heart (rupture), respectively. The number of fatal bleeding complications under DOAC therapy was only 2 (hemoptysis and heart rupture). Among the patients with recurrent VTE, 1, 1, 13, 5, and 6 had massive PE, sub-massive PE, non-massive PE, proximal DVT, and distal DVT, respectively. No patients with recurrent VTE died from VTE. Table 2 shows the comparison between patients with and without major bleeding. Table 3 shows the comparison between patients with and without recurrent VTE. The median duration of anticoagulant therapy for patients with and without recurrence was not significantly different. Table 4 shows the comparison between patients who survived and those who died. In the present study, 173 patients died. A total of 160, 4, 1, 1, 1, and 1 patients died because of progression of cancer, cerebral infarction, pneumonia, hemothysis, heart rupture, rupture of a thoracic aortic aneurysm, bowel perforation, and suicide. Table 5 indicates the independent factors that correlated with major bleeding, recurrent VTE, and all-cause death after adjustments in the Cox regression analysis. In the multivariate analysis, high cancer stage, high PS, stomach cancer, diabetes mellitus, and liver dysfunction correlated with major bleeding. Initial diagnosis of PE, uterine cancer, and previous cerebral infarction correlated with recurrent VTE. Conversely, high cancer stage, high PS, pancreatic cancer, liver dysfunction, and major bleeding independently correlated with all-cause death.

Figure 3 shows the Kaplan-Meier curve estimates for the composite outcome of major bleeding and recurrent VTE between patients who received prolonged therapy or non-prolonged therapy. The patients who received prolonged therapy had significantly lower composite risks than those who received non-prolonged therapy (log-rank P<0.001).

Discussion

Some studies have reported the incidence of major bleeding after DOAC therapy for cancer-associated VTE. The SELECT-D study reported that the 6-month cumulative incidence of major bleeding was 6% for rivaroxaban.10 The Hokusai VTE Cancer study revealed that major bleeding occurred in 32 of 522 (6.1%) patients administered with

| Major bleeding | Univariate HR (95% CI) | P value | Multivariate HR (95% CI) | P value |
|---------------|------------------------|--------|--------------------------|--------|
| Stomach cancer | 2.168 (1.16-4.05)      | 0.015  | 2.515 (1.306-4.844)       | 0.006  |
| Stage 4       | 3.466 (1.957-6.08)     | <0.001 | 1.948 (1.047-3.625)       | 0.035  |
| Performance status | 2.363 (1.677-3.33) | <0.001 | 2.01 (1.306-3.093)        | 0.001  |
| Chemotherapy  | 2.109 (1.146-3.878)    | 0.016  | 1.132 (0.589-2.178)       | 0.71   |
| Diabetes mellitus | 2.771 (1.526-5.031) | 0.001  | 1.968 (1.011-3.83)        | 0.046  |
| Liver dysfunction | 4.325 (2.217-8.44) | <0.001 | 2.759 (1.301-5.853)       | 0.008  |
| Hemoglobin level | 0.824 (0.712-0.954) | 0.010  | 0.926 (0.786-1.092)       | 0.36   |
| Intravenous anticoagulant usage | 1.643 (0.909-2.969) | 0.10   |                        |        |
| Recurrent VTE |                        |        |                          |        |
| PE            | 2.519 (1.095-5.796)    | 0.030  | 2.417 (1.029-5.677)       | 0.043  |
| Uterine cancer | 3.629 (1.238-10.63)   | 0.019  | 3.276 (1.083-9.910)       | 0.036  |
| Previous stroke | 5.183 (1.536-17.50)  | 0.008  | 6.511 (1.876-22.60)       | 0.003  |
| All-cause death |                        |        |                          |        |
| Body mass index (kg/m²) | 0.929 (0.89-0.971) | 0.001  | 0.966 (0.926-1.008)       | 0.113  |
| Proximal DVT  | 1.407 (1.021-1.938)    | 0.037  | 0.942 (0.674-1.315)       | 0.724  |
| Pancreatic cancer | 2.152 (1.373-3.372) | 0.001  | 3.207 (1.958-5.180)       | <0.001 |
| Stage 4       | 5.703 (4.121-7.892)    | <0.001 | 4.063 (2.755-5.991)       | <0.001 |
| Performance status | 2.541 (2.111-3.058) | <0.001 | 1.907 (1.487-2.445)       | <0.001 |
| Chemotherapy  | 1.624 (1.185-2.226)    | 0.003  | 0.776 (0.550-1.094)       | 0.148  |
| Previous stroke | 2.157 (1.169-3.980)   | 0.014  | 1.126 (0.572-2.218)       | 0.731  |
| Liver dysfunction | 3.157 (2.042-4.882)  | <0.001 | 1.703 (1.064-2.726)       | 0.026  |
| Hemoglobin level | 0.874 (0.805-0.949)  | 0.001  | 1.032 (0.939-1.134)       | 0.512  |
| Platelet count | 1.015 (1.001-1.030)   | 0.038  | 1.006 (0.991-1.021)       | 0.434  |
| Non-steroidal antiinflammatory drug usage | 1.685 (1.109-2.561) | 0.015  | 1.059 (0.659-1.702)       | 0.811  |
| Major bleeding | 3.158 (2.257-4.418)    | <0.001 | 1.677 (1.143-2.461)       | 0.008  |

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.
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bleeding while on anticoagulant therapy. Studies report that liver dysfunction is a risk factor of dysfunction have been excluded in several RCTs. Some function is not fully elucidated because patients with liver dysfunction also need to use DOACs carefully. In Japan. A higher prevalence of stomach cancer suggests the current study might reflect well the routine clinical practice of stomach cancer than other Western populations; thus, the incidence of stomach cancer in the current study. In the SELECT-D study, the incidence was 14.5%. It is well known that the Japanese population has a higher prevalence of stomach cancer than other Western populations; thus, the current study might reflect well the routine clinical practice in Japan. A higher prevalence of stomach cancer suggests individuals need to use DOACs carefully.

The relationship between DOAC usage and liver dysfunction is not fully elucidated because patients with liver dysfunction have been excluded in several RCTs. Some studies report that liver dysfunction is a risk factor of bleeding while on anticoagulant therapy. However, all those studies mainly evaluated ordinary warfarin therapy. The present study revealed that liver dysfunction also influenced the incidence of major bleeding in DOAC therapy in routine clinical practice. Two other studies support this result and reported that the pharmacokinetics and pharmacodynamics of DOACs were influenced by hepatic impairment.

Regarding recurrent VTE, only 1 massive PE and 1 submassive PE were observed in our study than in those previous studies, which may be mainly attributed to the higher incidence of stomach cancer in the current study. In the SELECT-D study, the incidence of stomach cancer was only 3%, and in the Hokusai VTE Cancer study, the incidence was 1.9%. In the current study, the incidence was 14.5%. It is well known that the Japanese population has a higher prevalence of stomach cancer than other Western populations; thus, the current study might reflect well the routine clinical practice in Japan. A higher prevalence of stomach cancer suggests individuals need to use DOACs carefully.

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Conclusions

In DOAC therapy for cancer-associated VTE, prevention of major bleeding is important because it is an independent risk factor of death.

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Data Availability

The deidentified participant data will not be shared.

Institutional Review Board Information

Yokohama City University, Center for Novel and Exploratory Clinical Trials (reference no. B160401015).

Disclosure

K.K., M.K. are members of Circulation Journal Editorial Team.

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