**A retrospective study on efficacy and safety of rivaroxaban and dalteparin for long-term treatment of venous thromboembolism in patients with lung cancer**

Running title: Rivaroxaban for VTE in lung cancer

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**Abstract**

**Background**

Standard therapy for cancer-associated venous thromboembolism (VTE) is low-molecular-weight heparin. The use of direct oral anticoagulants (DOACs) for cancer-associated VTE has increased; however, their efficacy and safety in lung cancer patients remain unclear.

**Objectives**

We examined the efficacy and safety of rivaroxaban compared with dalteparin for cancer-associated VTE in patients with primary lung cancer.

**Methods**

A single-center retrospective study of 204 patients with primary lung cancer who were prescribed rivaroxaban (N=131) or dalteparin (N=73) for VTE was performed. The primary endpoint was a composite event including recurrence and major or clinically relevant non-major bleeding. Secondary endpoints included the incidence of recurrence, major and clinically relevant non-major bleeding, all-cause mortality, and bleeding or pulmonary embolism-related mortality.

**Results**

The composite event occurred in 38 (29.0%) and 12 (16.4%) patients in the rivaroxaban and dalteparin (P=0.045) groups, respectively. The multivariate Cox proportional hazards model for age, ECOG PS, and bleeding risk factors revealed the rivaroxaban group showed a 1.176-fold composite event risk without statistical significance (0.595–2.324, P=0.641). There was no statistically significant inter-group difference for the incidence of VTE recurrence (5.3% in the rivaroxaban group vs. 2.7% in the dalteparin group, P=0.495) and major or clinically relevant non-major bleeding (23.7% in the rivaroxaban group vs. 13.7% in the dalteparin group, P=0.089). There was no significant difference in the all-cause mortality rate (HR 0.864, 0.624–1.196, P=0.337).

**Conclusions**

There was no difference in the safety and efficacy profile of rivaroxaban compared with dalteparin. Therefore, rivaroxaban may be a valuable treatment option for lung cancer-associated VTE.

**Keywords**

Anticoagulation; Dalteparin; Lung cancer; Rivaroxaban; Thromboembolism; Retrospective study

**Abbreviation list**

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; DOAC: direct oral anticoagulant; ECOG PS: Eastern Cooperative Oncology Group performance score; CT: computed tomography; HR: hazard ratio; CI: confidence interval

**Introduction**

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a well-recognized complication of malignancy. Cancer-associated VTE accounts for 20% of all cases of incidental VTE, and the incidence of PE in cancer patients is 1 in 200, which is 100 times that observed in the general population [1-5]. Among various cancer types, lung cancer has the highest incidence of VTE [6]. Since patients with lung cancer have compromised lung function and more severe symptoms, adequate treatment of VTE is a priority for clinicians also treating lung cancer.

Currently, the standard therapy for cancer-associated VTE is low-molecular-weight heparin [7-9]. Raskob et al. reported the non-inferiority of edoxaban compared with dalteparin in terms of the composite event of recurrent VTE and major bleeding [10]. Young et al. reported an association between lower recurrence rates and higher clinically relevant non-major bleeding rates and the use of rivaroxaban as opposed to dalteparin in cancer associated VTE [11]. Although these results indicate the potential of direct oral anticoagulants (DOACs) for cancer-associated VTE, various cancer types and a relatively small number of lung cancer patients were included in that study. Therefore, additional studies of the efficacy and safety of DOACs in lung cancer are needed.

Rivaroxaban, one of the DOACs, is a direct factor Xa inhibitor [12, 13]. Similar to dalteparin, a standard therapeutic drug for cancer-associated VTE, rivaroxaban can also inhibit factor Xa; thus, rivaroxaban is an attractive treatment option for cancer-associated VTE. Although several studies support the use of rivaroxaban for cancer-associated VTE, there is no definitive study of the safety and efficacy of rivaroxaban in lung cancer patients [14, 15].

DOACs including rivaroxaban are known to increase gastrointestinal bleeding and decrease intracranial bleeding compared to warfarin [16]. Although the specific mechanisms remain unclear, it is possible that DOACs might differentially affect these organs compared with other anticoagulants [16, 17]. Because mucosal injury from visceral malignancies is an important bleeding risk factor in cancer patients, the safety and efficacy of DOACs for various cancer types should be assessed [18].

In this study, we compared the incidence of recurrence and major or clinically relevant non-major bleeding, a so-called composite event, in patients with primary lung cancer who received either rivaroxaban or dalteparin for long-term treatment of cancer-associated VTE.

**Materials and Methods**

Study design and patients

We performed a single-center retrospective study at Asan Medical Center in South Korea. Eligible patients were selected based on rivaroxaban and dalteparin prescribing information in the electronic medical record system. The study inclusion criteria were (1) diagnosis of primary lung cancer, (2) diagnosis of PE and/or DVT, and (3) treatment of the VTE with rivaroxaban or dalteparin between 1 January 2012 and 31 December 2016. Exclusion criteria were (1) rivaroxaban or dalteparin use for 7 days or less, (2) use of other anticoagulants before rivaroxaban or dalteparin for more than 7 days, (3) follow-up loss after the 1st visit, and (4) inadequate dosing.

PE was diagnosed via computed tomography (CT) or ventilation-perfusion scanning performed by a certificated radiologist. DVT was diagnosed via lower extremity Doppler ultrasonography or CT venography. Follow-up examinations were performed in cases of suspected recurrence or for patients requiring periodic evaluation of cancer staging.

Asan Medical Center’s Institutional Review Board (IRB no. 2017-0652) approved the study. Informed consent was not mandatory because of the retrospective nature of the study. All patient data were anonymized.

Rivaroxaban and dalteparin administration

Since there was no standardized protocol for selecting the anticoagulants (rivaroxaban or dalteparin) during the study period, treatment choice was made based on the judgment of the responsible clinicians. Rivaroxaban was administered orally at 15 mg twice daily for 21 days followed by 20 mg once daily. Dalteparin was administered subcutaneously at 200 IU/kg once daily for one month followed by 150 IU/kg once daily.

Measurements

We retrieved all patient data from electronic medical records at Asan Medical Center.

The primary outcome in this study was a composite of recurrent VTE and major bleeding or clinically relevant non-major bleeding. VTE recurrence was defined as CT or ultrasonographic evidence of an increase in thrombosis or embolism at a new site during anticoagulant therapy [10]. We defined major and clinically relevant non-major bleeding as in the SELECT-D trial [11]. Major bleeding included any bleeding event occurring during the treatment period with rivaroxaban or dalteparin that (1) was related to death, (2) took place at a fatal site (intracranial, intraocular, retroperitoneal, intraspinal, or pericardial), or (3) required a transfusion of at least 2 units of packed red blood cells or led to a hemoglobin decrease of at least 2.0 g/dL [19]. Clinically relevant non-major bleeding was defined as any overt bleeding occurring during the treatment period with rivaroxaban or dalteparin that did not fulfill the criteria for major bleeding but resulted in medical attention, unappointed visits, a discontinuance of anticoagulants, or a decrease in daily activities [20]. We assessed bleeding events during the treatment period.

Secondary outcomes were the recurrence or symptomatic recurrence of PE or DVT, any bleeding event, clinically relevant non-major bleeding or major bleeding, all-cause mortality, and PE-related or bleeding-related mortality. We assessed the survival status of patients until 28 February 2018.

We also analyzed clinical and demographic characteristics including age, sex, Eastern Cooperative Oncology Group performance score (ECOG PS), smoking history, underlying kidney or liver disease, platelet count on 1st day of treatment, histological diagnosis of lung cancer, metastatic status, co-existing cancer, history of chemotherapy or radiotherapy, occurrence of PE, history of VTE, recent operation in the past 2 weeks, therapeutic duration, and bleeding risk factors. The risk factors for bleeding included surgery in the 2-weeks before anticoagulant therapy, concurrent use of antiplatelet agents, a primary or metastatic brain tumor, regionally advanced or metastatic cancer, co-existing gastrointestinal or urothelial cancer, and bevacizumab use within a 6-week period [10].

Statistical analysis

We compared all baseline characteristics and outcomes between both groups. Categorical variables are expressed as a number with the proportion of subjects. Differences between both groups were analyzed using the chi-square test or Fisher’s exact test. Continuous variables are presented as the means with standard deviations. Differences in continuous variables were analyzed using an independent two-sample t-test. The time to composite event or all-cause mortality was analyzed using the Cox proportional hazard model. Time-to-event curves were calculated by Kaplan-Meier curves.

We performed a multivariate analysis to observe the effects of the anticoagulants on composite events and all-cause mortality. Covariates included in the multivariate analysis were age, ECOG PS, and bleeding risk factors, which were statistically different between the two study groups (P<0.1).

Statistical significance was set at P<0.05. We used SPSS version 21 (IBM Corporation, Armonk, NY, USA) analytical software for statistical analysis.

**Results**

Baseline characteristics

Between 1 January 2012 and 31 December 2016, 259 primary lung cancer patients were diagnosed with PE and/or DVT. Of these, 53 patients were unsuitable for the study and excluded. 42 of those 53 patients were prescribed other anticoagulants before the study for more than 7 days. 10 patients took rivaroxaban or dalteparin for 7 days or less, and 2 patients were transferred to other hospitals after their 1st outpatient visit. Furthermore, 1 patient was prescribed a subtherapeutic dose for treatment of VTE because of concern for bleeding. A total of 204 patients were included in the present study, which included the rivaroxaban group (N=131) and the dalteparin group (N=73, Figure 1).

Table 1 presents the baseline characteristics of both groups. Except for metastatic status and therapeutic duration, most baseline characteristics did not show a statistically significant difference between the two groups. In both groups, the most common cancer type was adenocarcinoma (82.2% in the dalteparin group and 64.9% in the rivaroxaban group), followed by squamous cell carcinoma and small cell carcinoma. Patients in the rivaroxaban group had favorable cancer staging and longer therapeutic duration compared with those in the dalteparin group. 18 patients (24.7%) in the dalteparin group and 50 patients (38.2%) in the rivaroxaban group were incidentally diagnosed with VTE.

The composite event (primary endpoint) occurred in 38 patients (29.0%) in the rivaroxaban group and 12 patients (16.4%) in the dalteparin group. There was a statistically significant difference noted between the two groups (P=0.045, Table 2). Figure 2 shows the time to occurrence of the composite event. A Cox proportional hazards model for multivariate analysis was used to assess the incidence and timing of the composite event during the observational period. The hazard ratio (HR) for the composite event was 1.176-fold (95% confidence interval (CI) 0.595–2.324, P=0.641) higher in the rivaroxaban group without a significant difference (Table 3). Age, ECOG PS, and bleeding risk factors, which were adjusted for multivariate analysis, were not associated with the occurrence of the composite event (Table 3, Figure 2). Our study included 56 patients with metastatic brain lesions: 25 patients in the dalteparin group; 32 patients in the rivaroxaban group. A bleeding event occurred in 4 patients in the dalteparin group and 8 patients in the rivaroxaban group. There was no intracranial bleeding in either group.

In the rivaroxaban group, 7 patients (5.3%) had a recurrence of VTE; 5 patients with PE, 1 patient with DVT, and 1 patient with PE and DVT. 4 (3.1%) of them exhibited symptoms. In the dalteparin group, 2 patients (2.7%) had a recurrence of PE, and all of them exhibited symptoms. There was no significant difference in the recurrence rate between both groups (recurrence: P=0.495; symptomatic recurrence: P>0.999). Bleeding events occurred in 31 patients (23.7%) in the rivaroxaban group and 10 patients (13.7%) in the dalteparin group (P=0.089). Major bleeding events occurred in 8 patients (6.1%) in the rivaroxaban group and 2 patients (2.7%) in the dalteparin group. There was no significant difference between the two groups (P=0.500, Table 2). Table 4 shows the bleeding sites of both groups. The respiratory tract was the most common site of bleeding in both groups

By 28 February 2018, 170 patients had died. In the rivaroxaban group, 106 patients (80.9%) died; of those, 3 deaths were related to PE and 3 deaths were related to bleeding. In the dalteparin group, 64 patients (87.7%) died; of those, 2 deaths were associated with PE. There was no significant difference between the two groups in all-cause (P=0.215), PE-related (P>0.999), or bleeding-related (P=0.554) mortality (Table 2). The Cox proportional hazards model was used to assess the incidence and timing of all-cause mortality until 28 February 2018. The HR for all-cause mortality was not significantly different in multivariate analysis (HR 0.864, 95% CI 0.624–1.196, P=0.337, Table 5). Older age, higher ECOG PS, and bleeding risk factors were associated with a higher HR (Table 5).

**Discussion**

To our knowledge, no previous study has investigated the efficacy and safety of rivaroxaban in primary lung cancer patients. The present study is the first to compare recurrence and bleeding incidence in primary lung cancer patients treated with rivaroxaban or dalteparin for VTE.

In our study, both groups had similar clinical and demographic characteristics except for therapeutic duration and metastatic status. These differences may result from the tendency of practitioners to prescribe more dalteparin, a standard therapy for cancer-associated VTE, to patients with an unfavorable cancer stage. Rivaroxaban was prescribed for longer periods of time; however, dalteparin was used for a relatively short period because it had to be subcutaneously injected by patients. The recurrence and bleeding events between both groups in univariate analysis were significantly different. After adjusting for age, ECOG PS, and bleeding risk factors, the rivaroxaban group showed an increased HR for the composite event; however, there was no statistical significance in the Cox proportional hazard model. These findings might result from the fact that rivaroxaban was used for longer periods of time and in patients who had less bleeding risk factors. This increase suggests clinicians used rivaroxaban with caution and large-scale studies are required.

The Hokusai VTE Cancer trial revealed the non-inferiority of edoxaban for the treatment of cancer-associated VTE [10]. However, it did not indicate that these findings could be applied to other DOACs. Cohen et al. reported the higher HR of rivaroxaban compared with apixaban, dabigatran, and edoxaban in cases of clinically relevant non-major bleeding [21]. These studies suggest that the bleeding risk of rivaroxaban is higher than that of other DOACs in the treatment of cancer-associated VTE [10, 22, 23]. In the SELECT-D trial, rivaroxaban showed an increased incidence of clinically relevant non-major bleeding than dalteparin in cancer-associated VTE [11]. Several studies have reported that serum anti-Xa activity is associated with the anticoagulant effect of DOACs, and the peak serum anti-Xa activity of rivaroxaban is higher than that of other DOACs [24-27]. Therefore, rivaroxaban is not recommended for patients with a high bleeding risk [28, 29].

In the present study, the most frequent bleeding site was the respiratory tract in both groups. This result is consistent with the higher bleeding risk of mucosal lesions with visceral malignancy [18]. In general, rivaroxaban is thought to increase gastrointestinal bleeding [16, 17, 30-32]. In primary lung cancer patients, most mucosal lesions are located in the respiratory tract. Therefore, the effect of DOACs on bleeding risk may be relatively low.

There were no significant inter-group differences for secondary endpoints including symptomatic recurrence and major or clinically relevant non-major bleeding incidence, except for all-cause mortality. However, after adjusting for age, ECOG PS, and bleeding risk factors, there was no significant difference in all-cause mortality between both groups. In our study, older age, poor performance status, and bleeding risk factors, which included metastasis and brain lesions, were associated with a higher HR for all-cause mortality.

There are several concerns about using DOACs in cancer patients, including drug interactions that alter the serum DOAC level , changes in DOAC bioavailability due to gastrointestinal tract problems, and increased bleeding incidence (especially gastrointestinal tract bleeding) [16, 17, 30-33]. To our knowledge, no study has clearly described the changes in the pharmacokinetics of DOACs in cancer patients. Although the results of the present study suggest that rivaroxaban might be used with chemotherapy to treat lung cancer, further studies are needed to elucidate the interactions between DOACs and chemotherapy agents [17].

The present study has several limitations. First, the retrospective study design with a small number of patients may have resulted in selection bias. Second, there were significant differences in some of the baseline characteristics between both groups. Although most of the clinical and demographic characteristics were similar in both groups, there were significant differences in metastatic status and therapeutic duration; a time-dependent multivariate analysis was performed to address this. Finally, this study only included a relatively small number of patients. A large randomized controlled study would be required to confirm the effect and safety of rivaroxaban in the treatment of VTE in patients with primary lung cancer.

**Conclusions**

The present study demonstrated the safety and efficacy of rivaroxaban in the management of PE and DVT in patients with primary lung cancer. Because of its ease of administration, rivaroxaban may be considered an attractive alternative treatment option for cancer-associated VTE. Further randomized controlled studies are required to confirm precisely the results of this study.

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**Table 1.Baseline characteristics of the study cohort**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Dalteparin ( N=73 ) | Rivaroxaban ( N=131 ) | P value |
| Sex (Female) | 30 (41.1%) | 52 (39.7%) | 0.882 |
| Age | 64.25±8.66 | 66.79±11.32 | 0.074 |
| ECOG PS  0  1  2  3  4 | 4 (5.5%)  25 (34.2%)  20 (27.4%)  17 (23.3%)  7 (9.6%) | 12 (9.2%)  64 (48.9%)  29 (22.1%)  22 (16.8%)  4 (3.1%) | 0.078 |
| Smoking  Current  Ex-smoker | 13 (17.8%)  23 (31.5%) | 19 (14.5%)  45 (34.4%) | 0.802 |
| GFR <50 ml/min/1.73m2\* | 2 (2.7%) | 4 (3.1%) | >0.999 |
| Liver cirrhosis\* | 1 (1.4%) | 1 (0.8%) | >0.999 |
| Platelet count<100,000/µl\* | 6 (8.2%) | 6 (4.6%) | 0.355 |
| Cancer type  Adenocarcinoma  Squamous cell carcinoma  Small cell carcinoma  Large cell carcinoma  Others | 60 (82.2%)  6 (8.2%)  4 (5.5%)  1 (1.4%)  2 (2.7%) | 85 (64.9%)  21 (16.0%)  18 (13.7%)  1 (0.8%)  6 (4.6%) | 0.104 |
| Metastasis | 68 (93.2%) | 103 (78.6%) | 0.009 |
| Coexisting cancer\*  Metastatic brain lesion | 2 (2.7%)  25(34.2%) | 6 (4.6%)  33(25.2%) | 0.714  0.104 |
| History of chemotherapy | 60 (82.2%) | 98 (74.8%) | 0.294 |
| Chemotherapy in 4 weeks | 52 (71.2%) | 88 (67.2%) | 0.637 |
| History of radiotherapy | 33 (45.2%) | 51 (38.9%) | 0.458 |
| Radiotherapy in 4 weeks | 11 (15.1%) | 22 (16.8%) | 0.844 |
| Pulmonary embolism | 64 (87.7%) | 103 (78.6%) | 0.131 |
| History of VTE\* | 2 (2.7%) | 2 (1.5%) | 0.618 |
| Recent operation\* | 2 (2.7%) | 3 (2.3%) | >0.999 |
| Therapeutic duration | 53.44±56.52 | 109.35±92.29 | <0.001 |
| Risk factors for bleeding  0  1  2  3 | 1 (1.4%)  39 (53.4%)  32 (43.8%)  1 (1.4%) | 13 (9.9%)  73 (55.7%)  41 (31.3%)  4 (3.1%) | 0.054 |

Difference between both groups was analyzed by the chi-square test, Fisher’s exact test or independent two-sample t-test. \* indicated variables analyzed by Fisher’s exact test.

ECOG PS: Eastern Cooperative Oncology Group performance score; GFR: glomerular filtration rate; VTE: venous thromboembolism

**Table 2.Primary and secondary endpoints in both groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Dalteparin  (N=73) | Rivaroxaban  (N= 131) | P value |
| Composite event | 12 (16.4%) | 38 (29.0%) | 0.045 |
| Recurrence\* | 2(2.7%) | 7(5.3%) | 0.495 |
| Symptomatic recurrence\* | 2 (2.7%) | 4 (3.1%) | >0.999 |
| Bleeding | 10 (13.7%) | 31 (23.7%) | 0.089 |
| Major bleeding\*  CRNM bleeding | 2 (2.7%)  8 (11.0%) | 8 (6.1%)  23 (17.6%) | 0.500  0.208 |
| All-cause mortality  PE-related mortality\*  Bleeding-related mortality\* | 64 (87.7%)  2 (2.7%)  0 (0.0%) | 106 (80.9%)  3 (2.3%)  3 (2.3%) | 0.215  >0.999  0.554 |

Difference between both groups was analyzed by the chi-square test or Fisher’s exact test. \* indicated variables analyzed by Fisher’s exact test.

CRNM: clinically relevant non-major; PE: pulmonary embolism

**Table 3.Hazard ratio for the composite event in the Cox proportional hazards model**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Covariate | Univariate analysis | | Multivariate analysis | |
| HR (95% CI) | P value | HR (95% CI) | P value |
| Anticoagulants  Dalteparin  Rivaroxaban | 1  1.038 (0.532~2.025) | 0.913 | 1  1.176 (0.595~2.324) | 0.641 |
| Age | 0.992 (0.967~1.018) | 0.529 | 0.986 (0.960~1.013) | 0.311 |
| ECOG PS  0  1  2  3  4 | 1  1.280 (0.377~4.346)  2.862 (0.824~9.940)  2.633 (0.732~9.477)  1.666 (0.276~10.060) | 0.693  0.098  0.138  0.578 | 1  1.247 (0.366~4.246)  3.022 (0.857~10.654)  2.533 (0.695~9.235)  2.040 (0.315~13.230) | 0.725  0.085  0.159  0.455 |
| Bleeding risk factor  0  1  2  3 | 1  3.017 (0.721~12.616)  2.153 (0.483~9.588)  2.490 (0.224~27.627) | 0.130  0.314  0.458 | 1  2.646 (0.625~11.206)  1.700 (0.372~7.778)  2.277 (0.199~26.091) | 0.186  0.494  0.508 |

ECOG PS: Eastern Cooperative Oncology Group performance score; HR: hazard ratio; CI: confidence interval

**Table 4.Bleeding site in both groups**

|  |  |  |  |
| --- | --- | --- | --- |
| Site | Total (N=41) | Dalteparin (N=10) | Rivaroxaban (N=31) |
| GI tract bleeding  Respiratory tract bleeding  Urinary tract bleeding  Pleural cavity bleeding  Skin bleeding  Intracranial bleeding  Genital tract bleeding | 7 (17.1%)  24 (58.5%)  3 (7.3%)  1 (2.4%)  3 (7.3%)  1 (2.4%)  2 (4.9%) | 2 (20.0%)  6 (60.0%)  0 (0.0%)  0 (0.0%)  1 (10.0%)  0 (0.0%)  1 (10.0%) | 5 (16.1%)  18 (58.1%)  3 (9.7%)  1 (3.2%)  2 (6.5%)  1 (3.2%)  1 (3.2%) |

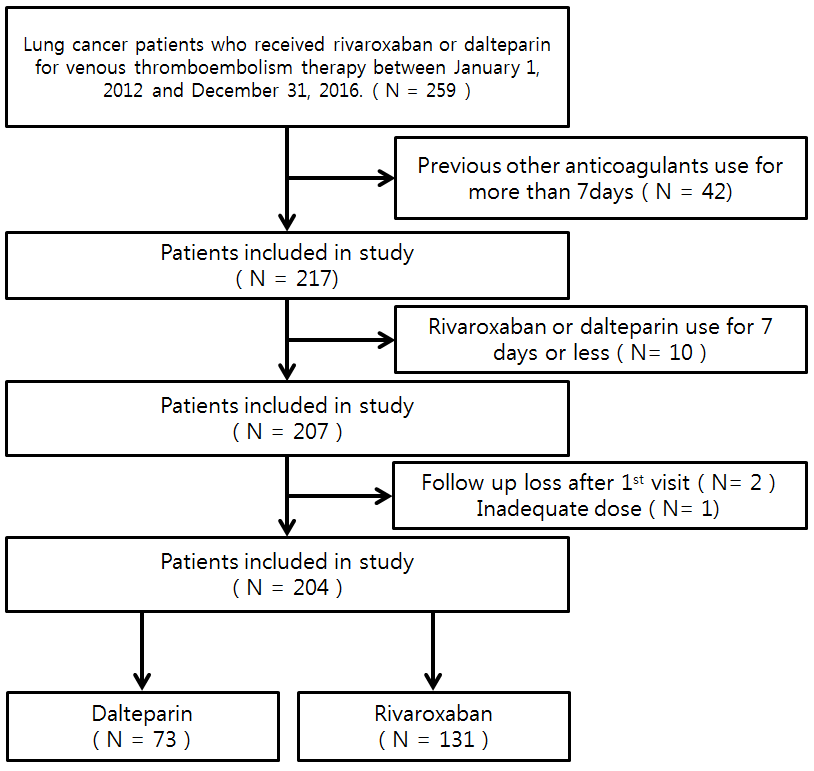
GI: gastrointestinal

**Table 5.Hazard ratio for the all-cause mortality in the Cox regression hazards model**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Covariate | Univariate analysis | | Multivariate analysis | |
| HR (95% CI) | P value | HR (95% CI) | P value |
| Anticoagulants  Dalteparin  Rivaroxaban | 1  0.668 (0.490~0.913) | 0.011 | 1  0.864 (0.624~1.196) | 0.337 |
| Age | 0.990 (0.976~1.003) | 0.124 | 0.982 (0.968~0.996) | 0.012 |
| ECOG PS  0  1  2  3  4 | 1  2.215 (1.016~4.833)  6.218 (2.784~13.886)  6.097 (2.690~13.818)  8.810 (3.359~23.104) | 0.046  <0.001  <0.001  <0.001 | 1  1.974 (0.903~4.316)  5.388 (2.410~12.044)  5.135 (2.246~11.741)  7.946 (2.954~21.372) | 0.089  <0.001  <0.001  <0.001 |
| Bleeding risk factor  0  1  2  3 | 1  5.189 (1.905~14.134)  6.547 (2.379~18.017)  6.271 (1.565~25.134) | 0.001  <0.001  0.010 | 1  3.805 (1.385~10.458)  4.001 (1.430~11.195)  5.501 (1.359~22.269) | 0.010  0.008  0.017 |

ECOG PS: Eastern Cooperative Oncology Group performance score; HR: hazard ratio; CI: confidence interval

**Figure 1.Patient flow diagram**

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**Figure 2.**Kaplan-Meier cumulative event rates for the primary outcome

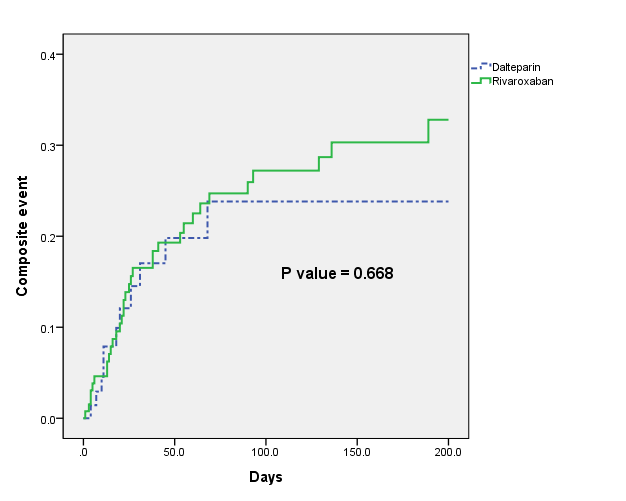
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Figure 2 presents occurrence of composite events during therapeutic period with study drugs. X-axis presents the day from the start day of study drugs to composite event day or end of study drugs. Y-axis presents the proportion of patients with composite events. We calculated P-value by Log-rank tests.