



Effectiveness and safety of oral direct factor Xa inhibitors for the treatment of venous thromboembolism in patients with cancer and/or older age

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Abstract

Venous thromboembolism (VTE) is a multifactorial disease. Cancer and older age are risk factors for both recurrent VTE and bleeding under anticoagulant therapy. Oral direct factor Xa inhibitors (Xa inhibitors) have been widely used to treat VTE. However, their effectiveness and safety in cancer and elderly patients have not been fully elucidated. A total of 187 consecutive patients who started Xa inhibitors for VTE therapy between September 2014 and September 2016 were recruited. Patients' demographics, changes in VTE amount, VTE recurrence, clinically relevant bleeding, and death until February 2017 were compared between 92 cancer and 95 non-cancer patients, and 57 elderly (≥ 75 years) and 130 non-elderly patients. Compared with non-cancer patients, cancer patients had a significantly higher incidence of deep vein thrombosis (DVT) in the proximal legs, superior vena cava, and upper extremities ($p=0.034$), although the patients' demographics and incidence of pulmonary thromboembolism (PE) were similar between the two groups. There were no significant differences in VTE recurrence ($p=0.328$) and clinically relevant bleeding ($p=0.078$) between the two groups. Death occurred in 29 cancer patients, 23 of whom died of cancer, while there were no deaths among the non-cancer patients. Elderly patients had a lower body weight and creatinine clearance than non-elderly patients. No significant differences between the two groups were found in relation to PE ($p=0.544$), DVT site ($p=0.054$), recurrent VTE ($p=0.194$), clinically relevant bleeding ($p=0.130$) and death ($p=0.241$). In comparisons among the four groups (elderly and non-elderly patients with and without cancer), recurrent VTE and clinically relevant bleeding were comparable ($p=0.493$ and 0.227 , respectively), while death was more frequent in cancer patients regardless of age ($p<0.001$). The efficacy and safety of Xa inhibitors as VTE treatment were comparable between cancer and non-cancer patients, and in elderly and non-elderly patients. This suggests that Xa inhibitors may be promising drugs for VTE treatment, irrespective of age and comorbid cancer.

Keywords Venous thromboembolism · Oral direct factor Xa inhibitors · Cancer · Elderly

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major healthcare problem associated with significant morbidity and mortality. In particular, PE is recognized as the third most common cause of death from cardiovascular disease after

heart attack and stroke in the US [1]. In Japan, Nakamura et al. showed that the number of PE cases has increased 4.6-fold in the past 15 years, with the annual incidence estimated to be 126 per 1,000,000 people in 2011 [2].

VTE is a multifactorial disease, which is thought to result from a complex interaction between genetic predisposition and environmental factors. The latter can be provoked (e.g., cancer, surgery, trauma or fracture, immobilization, pregnancy and the postpartum period, long-distance travel, hospitalization, catheterization and acute infection) or unprovoked (e.g., age, sex, race/ethnicity, body mass index and obesity, oral contraceptive or hormone therapy use, corticosteroid use, diet, physical activity, sedentary life and air pollution) [3]. Cancer patients are known to have a four to

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sevenfold higher risk of developing VTE [4, 5]. The Japan VTE Treatment Registry (JAVA) study also showed that a history of cancer is the most common risk factor for VTE and was present in 27.0% of VTE patients [6]. Therefore, cancer is a major cause of VTE. Elderly persons are more affected by VTE than younger persons and have a higher proportion of severe and fatal VTE. The global annual incidence of symptomatic VTE was 1.83 per 1000 patients, but reached 10 per 1000 patients aged 75 years or older in France [7]. A post hoc analysis of the MEDENOX study showed that age ≥ 75 years was an independent risk factor for VTE [8]. Therefore, with increasing life expectancy, the resultant increase in the number of elderly people will likely lead to an increase in the number of VTE patients [9]. Noteworthy, patients with the risk factors of cancer and advanced age also have a risk of bleeding while on VTE treatment with anticoagulants [9, 10].

Vitamin K antagonists (VKAs), unfractionated heparin, low-molecular-weight heparin, and factor Xa inhibitors are the anticoagulants available for VTE therapy. Considered as gold standard therapy for many decades, anticoagulation with VKA can, however, be inconvenient to use in clinical practice because of the narrow therapeutic margin and known interactions with drugs and nutrition. In contrast, oral direct factor Xa inhibitors (Xa inhibitors) do not require laboratory monitoring or dose adjustment. Therefore, Xa inhibitors may be clinically attractive drugs for the treatment of VTE. Recently, results of trials using Xa inhibitors for VTE therapy demonstrated that Xa inhibitors were not inferior to the standard heparin/VKA regimen in terms of efficacy and safety [11–14]. However, their efficacy and safety in cancer and/or elderly patients have not been fully elucidated. Currently, three Xa inhibitors, edoxaban, rivaroxaban, and apixaban, are available for use as VTE therapy in Japan. The aim of this study was to examine the differences in the efficacy and safety of Xa inhibitors between cancer vs. non-cancer patients, and elderly vs. non-elderly patients.

Materials and methods

Patients' charts were reviewed retrospectively, and 187 consecutive patients who either started VTE treatment with the Xa inhibitors, edoxaban (Lixiana[®], Daiichi–Sankyo, Tokyo, Japan), rivaroxaban (Xarelto[®], Bayer, Leverkusen, Germany), and apixaban (Eliquis[®], Bristol–Myers Squibb/Pfizer, New York, NY, USA), or were switched from other oral anticoagulants to Xa inhibitors for the treatment of VTE between September 2014 and September 2016 at Nagasaki University Hospital were recruited. The presence of VTE was confirmed by ultrasonography of the lower extremities, contrast-enhanced computed tomography or magnetic resonance imaging. VTE and the DVT site were classified

as reported previously [15]. Briefly, VTE was classified as DVT alone or PE with and without DVT, and the site of DVT was classified as proximal (between the inferior vena cava and knee joint), distal (below the knee joint) and upper (between the superior vena cava and upper extremities) DVT. Hematological data from within 1 week before starting the administration of Xa inhibitors were evaluated.

The approved doses of Xa inhibitors for the treatment of VTE in Japan are as follows: edoxaban: 30 mg or 60 mg daily, depending on body weight, renal function and concomitant medications; rivaroxaban: 15 mg twice daily for 3 weeks followed by 20 mg once daily; and apixaban: 10 mg twice daily for a week followed by 5 mg twice daily.

The definitions of recurrence of VTE and clinically relevant bleeding used were as reported previously [15]. The occurrence of death was examined from the initiation of drug administration to February 28, 2017. When the status of survival or death was unknown, as in patients who transferred to other hospitals, they were defined as “uncertain”. Changes in the amount of thrombosis were examined in 148 patients who underwent at least two imaging tests, such as ultrasonography of the lower extremities and contrast-enhanced computed tomography, and before and after administration of Xa inhibitors. The classification of changes in the amount of thrombus was based on the judgement of radiologists, sonographers and cardiologists, as follows: normalized (no thrombus in the legs and lungs); improved (improvements in both the legs and lungs or improvement in either the legs or lungs without deterioration at the other site); unchanged (unchanged results for both legs and lungs); and deteriorated (any deterioration in either legs or lungs) [16]. When the patients underwent more than two imaging tests after starting Xa inhibitors, the earliest test in which changes in VTE became stable was adopted as the post-treatment test [15].

In the present study, the effects of Xa inhibitors for VTE treatment on VTE recurrence, clinically relevant bleeding and death were examined in patients with and without cancer (92 cancer and 95 non-cancer patients) and in elderly (≥ 75 years, 57 patients) and non-elderly patients (< 75 years, 130 patients).

This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Nagasaki University Hospital approved the protocol. Since this was a retrospective study, an opt-out consent method was used instead of directly obtaining informed consent from the patients.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation for normally distributed variables, and as median (interquartile range) for skewed variables; these variables were compared using the unpaired *t* test and the

Mann–Whitney *U* test, respectively. Categorical variables are presented as absolute numbers and/or percentages and were compared using the chi-squared test. Kaplan–Meier analysis was used to estimate the cumulative incidence of events, and the log-rank test was used to compare survival between the groups. Patients who developed VTE recurrence, clinically relevant bleeding, stopped drug administration or died were censored. The significance level was set at $p < 0.05$. Statistical analysis was performed using EZR software version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [17].

Results

Entire patient cohort

In the patient cohort as a whole, median age was 67 years (59.5–77 years), females predominated (62.0%), and average body weight was less than 60 kg (57.9 ± 13.5 kg). The proportion of usage of the three Xa inhibitors was 85%:11%:4% for edoxaban, rivaroxaban and apixaban, respectively, and the median administration duration was 70.0 days (17–205.5 days).

Non-cancer vs. cancer patients

The characteristics of patients with and without cancer are shown in Table 1. There were no significant differences between the two groups. The primary cancer lesion was mostly in the uterus and ovary ($n = 26$, 28.3%), followed by the gastrointestinal tract ($n = 18$, 19.6%), hepatobiliary and pancreatic organs ($n = 10$, 10.9%), brain ($n = 8$, 8.7%), blood ($n = 8$, 8.7%), and kidney and bladder ($n = 6$, 6.5%). Histopathological findings indicated that most cancers were adenocarcinomas ($n = 36$, 39.1%), followed by squamous cell carcinomas ($n = 17$, 18.5%), malignant lymphomas ($n = 7$, 7.6%) and glioblastomas ($n = 6$, 6.5%).

The prevalence of DVT and PE was comparable between the two groups ($p = 0.994$, Fig. 1a). Cancer patients had more DVT at the proximal and upper sites ($p = 0.034$,

Fig. 1b). In terms of changes in the amount of thrombus, 87.3% and 82.6% of non-cancer and cancer patients, respectively, showed normalization or improvement in the thrombus, with no significant differences between the two groups ($p = 0.526$, Fig. 1c). The interval between the two imaging tests did not differ significantly [72.0 (14–160) days in non-cancer patients vs. 61.5 (20.5–144.3) days in cancer patients, $p = 0.327$].

One non-cancer patient and two cancer patients developed recurrent VTE. The incidence was 1.1% and 2.2%, respectively, indicating no significant difference between the two groups ($p = 0.328$, Fig. 2a). Clinically relevant bleeding occurred in three non-cancer (3.2%) and nine cancer patients (9.8%), although there was no significant difference between the two groups ($p = 0.078$, Fig. 2b). Among them, gastrointestinal bleeding occurred in two and three patients, and cerebral bleeding in one and two patients in the non-cancer and cancer groups, respectively. During the observation period, death occurred in 29 cancer patients (23 patients died from cancer). Therefore, the mortality rate was significantly higher in cancer than non-cancer patients ($p < 0.001$, Fig. 2c). Twenty-four non-cancer and ten cancer patients were classified as “uncertain” patients, because these patients could not be followed.

Non-elderly vs. elderly patients

Elderly patients had significantly lower body weight and creatinine clearance than non-elderly patients (Table 2). D-dimer levels did not differ significantly between non-elderly and elderly patients (4.5 vs. 5.7 $\mu\text{g/ml}$, $p = 0.260$). The duration of Xa inhibitor therapy was not significantly different between the two groups. The proportion of cancer was significantly higher in non-elderly patients (56.2% in the non-elderly vs. 38.6% in the elderly, $p = 0.038$).

The incidence of PE did not differ significantly between elderly and non-elderly patients ($p = 0.544$, Fig. 3a), while DVT at the distal site tended to be more frequent in elderly patients ($p = 0.054$, Fig. 3b). There were no significant differences in change in the amount of thrombus ($p = 0.212$, Fig. 3c) and in the interval between the two imaging tests

Table 1 Characteristics of cancer and non-cancer patients with venous thromboembolism

	Non-cancer	Cancer	<i>p</i> value
Gender (male:female)	39:56	32:60	0.380
Age (years)	68 (56–78)	67 (60–73)	0.537
Body weight (kg)	58.5 ± 13.8	57.2 ± 13.2	0.535
Body mass index (kg/m^2)	23.3 ± 4.4	22.9 ± 4.5	0.549
Creatinine clearance (ml/min)	66.2 (50.0–99.5)	72.5 (53.9–88.9)	0.704
D-dimer ($\mu\text{g/ml}$)	4.35 (1.70–14.10)	5.70 (3.20–10.60)	0.234
Administration duration (days)	51 (13–218)	77 (23–189)	0.873

Variables are expressed as mean \pm SD or medians (interquartile 25% and 75%)

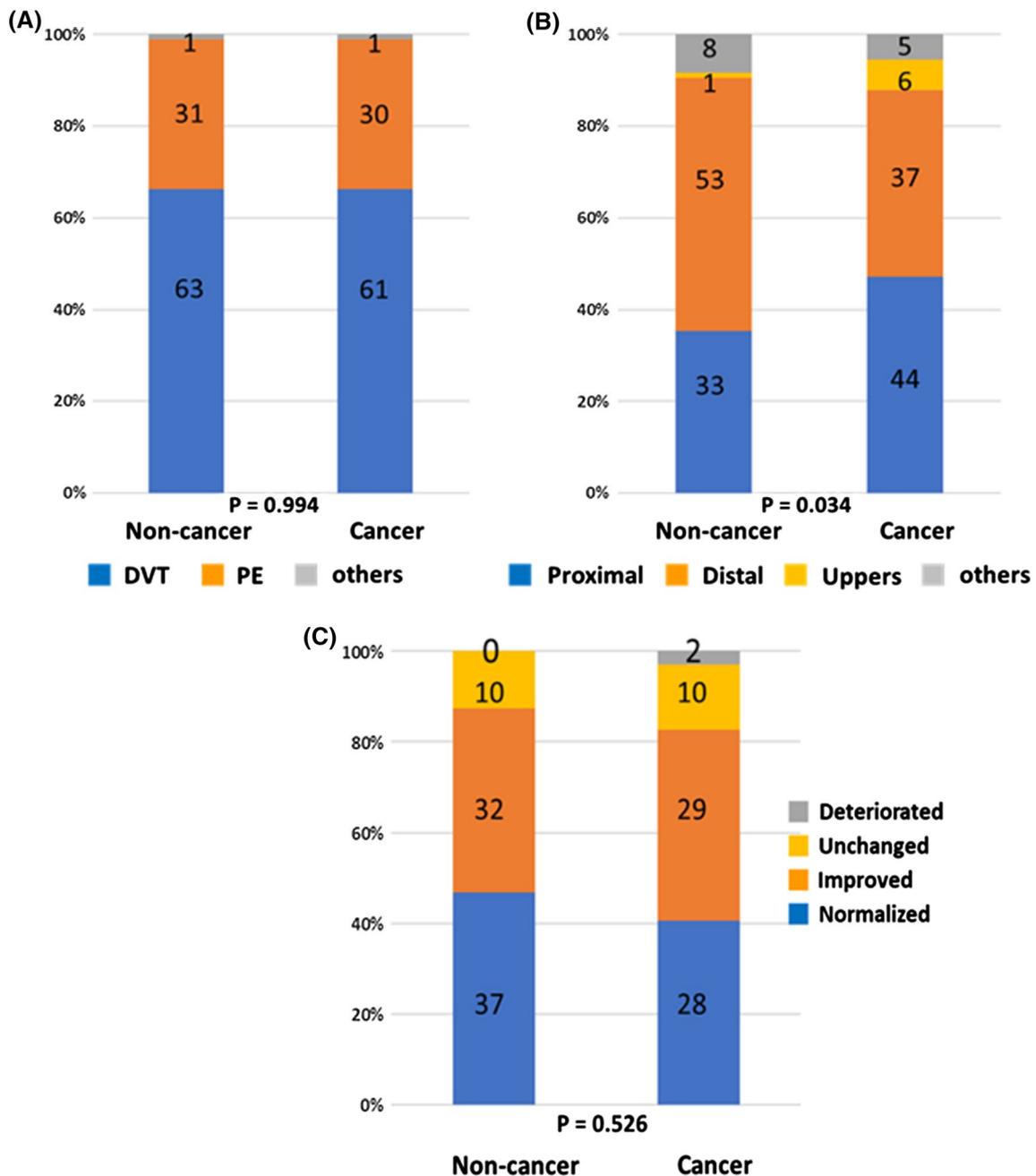


Fig. 1 Comparison of the type of venous thromboembolism (deep vein thrombosis alone or with pulmonary thromboembolism) (a), the site of deep vein thrombosis (b) and the changes in thrombus amount (c) between cancer and non-cancer patients. *DVT* deep vein thrombosis, *PE* pulmonary thromboembolism, *Proximal* thrombosis between the inferior vena cava and knee joint, *Distal* thrombosis below the

knee joint, *Upper* thrombosis between the superior vena cava and upper extremities, *Normalized* no thrombus in the legs and lungs, *Improved* improved results for both legs and lungs, or improvement in either legs or lungs without deterioration at the other site, *Unchanged* unchanged results for both legs and lungs

between the two groups [67.5 (16.5–151.8) days in non-elderly patients vs. 66 (14–140.5) days in elderly patients, $p = 0.743$].

No significant differences in the incidence of recurrent VTE ($p = 0.194$, Fig. 4a) and clinically relevant bleeding ($p = 0.130$, Fig. 4b) were found between the elderly and

non-elderly patients. Mortality rate also did not differ significantly between the two groups ($p = 0.241$, Fig. 4c), although the number of cancer patients was significantly higher in the non-elderly group ($p = 0.038$, Table 2).

Finally, the differences in incidences of VTE recurrence, clinically relevant bleeding and death were

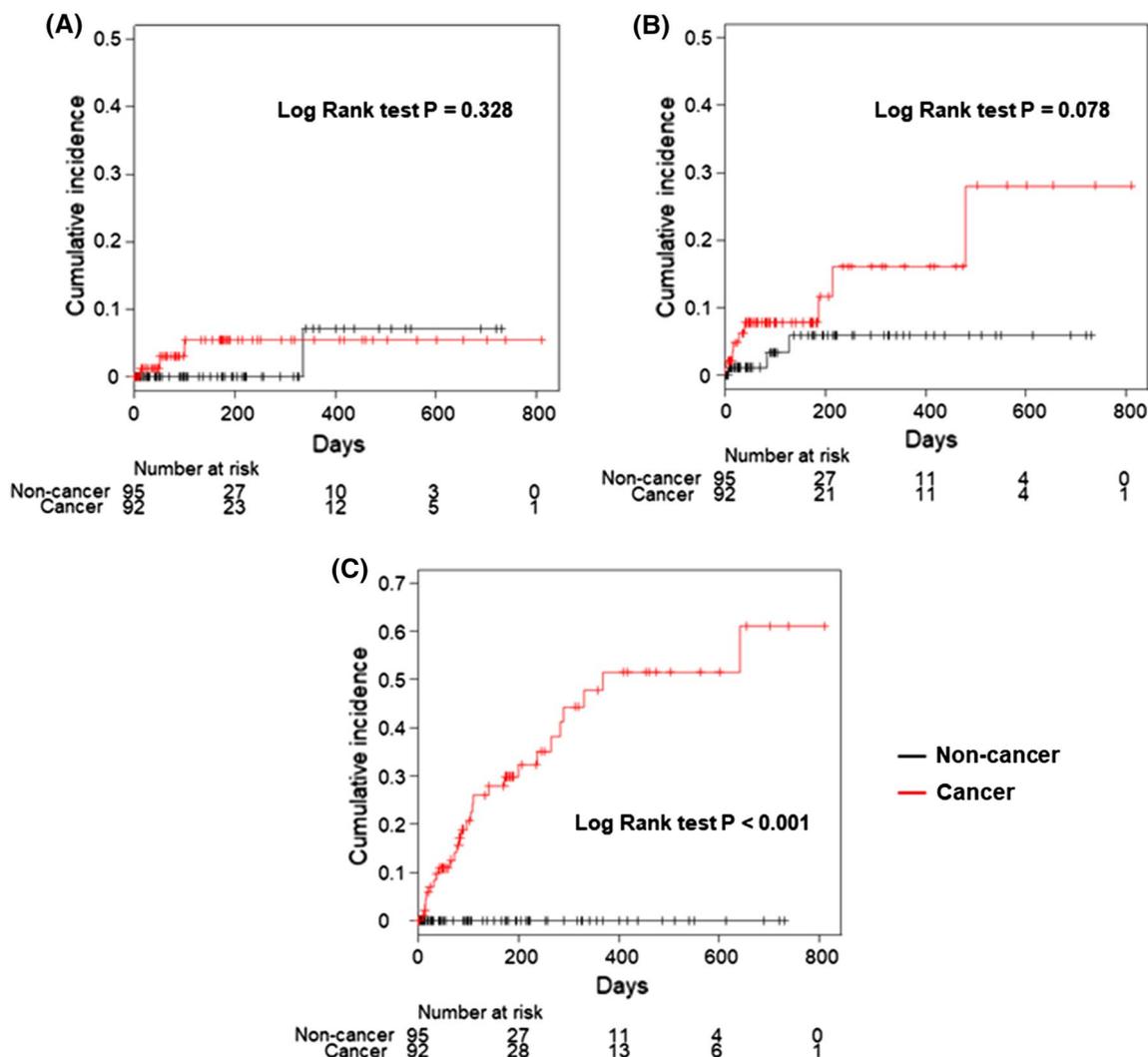


Fig. 2 Comparison of the cumulative incidence of recurrent venous thromboembolism (a), clinically relevant bleeding (b) and death (c) between cancer and non-cancer patients

Table 2 Characteristics of elderly and non-elderly patients with venous thromboembolism

	Non-elderly	Elderly	<i>p</i> value
Gender (male:female)	54:76	17:40	0.143
Age (years)	63 (54–68)	79 (77–82)	<0.001
Body weight (kg)	59.9 ± 13.9	53.3 ± 11.1	0.002
Body mass index (kg/m ²)	23.4 ± 4.7	22.5 ± 3.9	0.185
Creatinine clearance (ml/min)	82.3 (59.7–105.1)	53.7 (44.2–63.3)	<0.001
D-dimer (µg/ml)	4.50 (2.13–11.33)	5.70 (3.55–15.05)	0.260
Administration duration (days)	67 (18–206)	80 (17–195)	0.419
Cancer (– : +)	57:73	35:22	0.038

Variables are expressed as mean ± SD or medians (interquartile 25% and 75%)

examined among the four groups (non-elderly and elderly, and with and without cancer groups). As shown in Fig. 5a, b, the incidences of recurrent VTE and clinically relevant bleeding were not significantly different between the four

groups. Mortality rate was significantly higher in cancer than in non-cancer patients, regardless of age ($p < 0.001$, Fig. 5c).

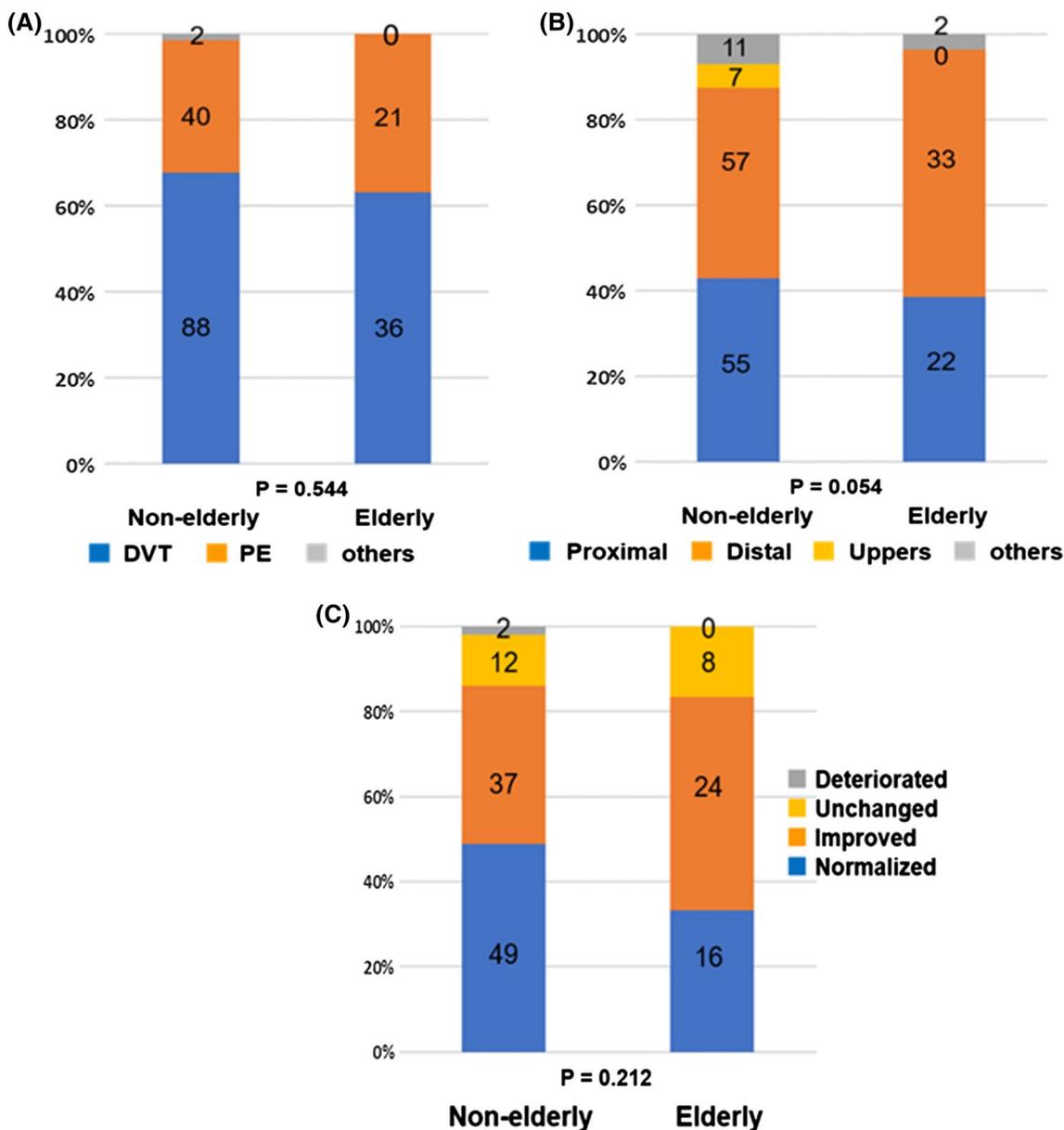


Fig. 3 Comparison of the type of venous thromboembolism (deep vein thrombosis alone or with pulmonary thromboembolism) (a), the site of deep vein thrombosis (b) and the changes in thrombus amount (c) between elderly and non-elderly patients. *DVT* deep vein thrombosis, *PE* pulmonary thromboembolism, *Proximal* thrombosis between the inferior vena cava and knee joint, *Distal* thrombosis below the

knee joint, *Upper* thrombosis between the superior vena cava and upper extremities, *Normalized* no thrombus in the legs and lungs, *Improved* improved results for both legs and lungs, or improvement in either legs or lungs without deterioration at the other site, *Unchanged* unchanged results for both legs and lungs

Discussion

The main findings of the present study were that the incidence of recurrent VTE and clinically relevant bleeding after the administration of Xa inhibitors for VTE treatment was comparable between cancer and non-cancer as well as elderly and non-elderly patients, and that the mortality

rate was higher in cancer patients, with most deaths caused by cancer.

VTE is a major complication of cancer and it is the second most common cause of death in cancer patients [18]. The incidence of symptomatic VTE in cancer patients has been reported as 2–30% [19, 20]. The recurrence of VTE is also more frequent in cancer patients, with a fourfold greater incidence than in non-cancer patients [10]. Tumor

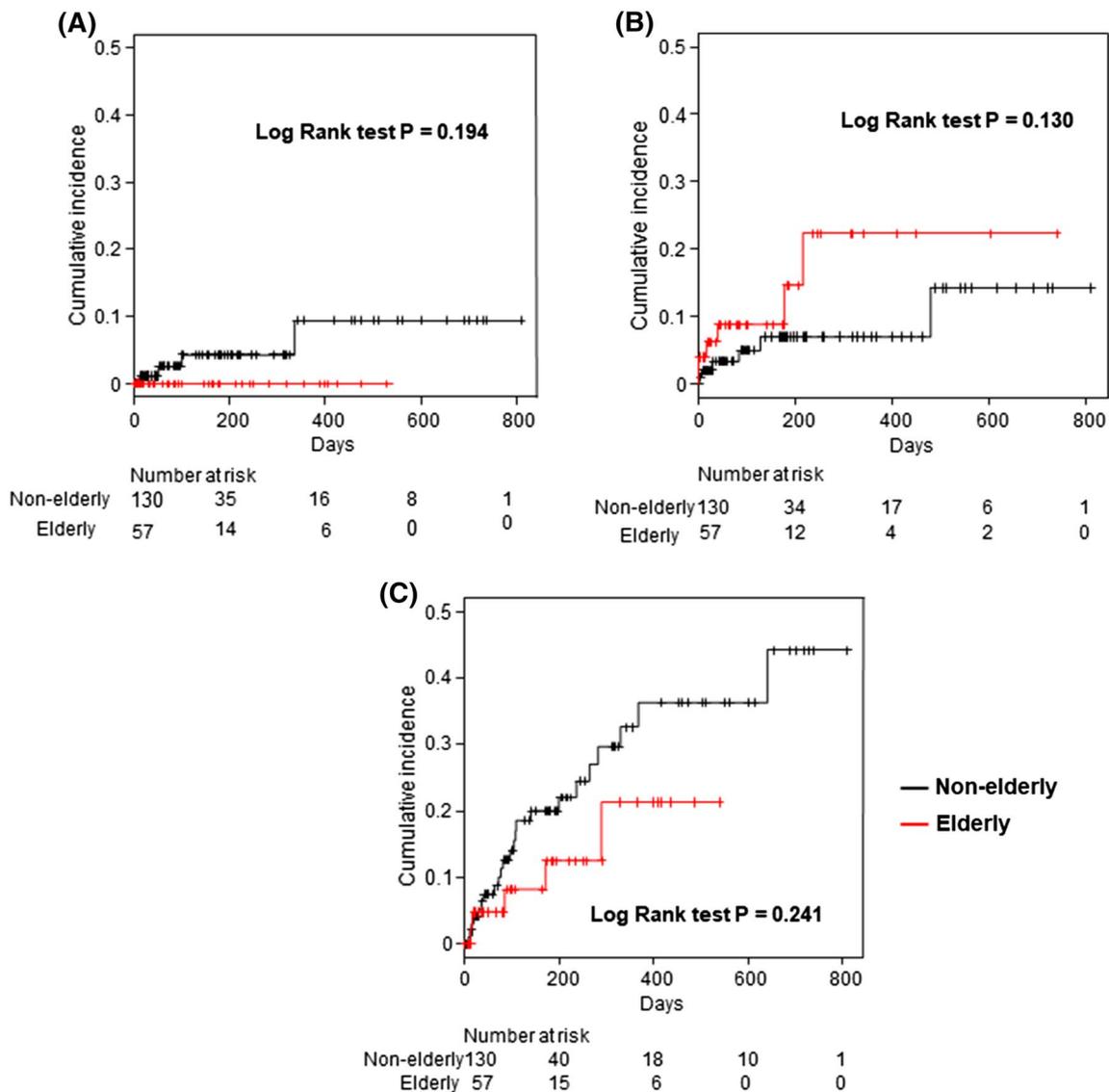


Fig. 4 Comparison of the cumulative incidence of recurrent venous thromboembolism (a), clinically relevant bleeding (b) and death (c) between elderly and non-elderly patients

cells can trigger coagulation through different pathways, including procoagulant, antifibrinolytic, and pro-aggregating activities, release of pro-inflammatory and pro-angiogenic cytokines, and interaction with vascular and blood cells through adhesion molecules [21]. Not only cancer itself, but also the treatments initiated in cancer patients (such as surgery, chemotherapy, anti-angiogenic agents and hormone therapy) and the presence of indwelling central venous catheters, as well as the demographic characteristics and comorbidities of patients contribute to the development of VTE [22]. Noteworthy, cancer also enhances the risk of anticoagulant-induced bleeding, even when anticoagulation is appropriately controlled [10]. Hence, anticoagulants with a reduced risk of recurrent VTE and reduced risk of bleeding

are required for the treatment of VTE in cancer patients. Currently, the guidelines from the US and Europe recommend low-molecular-weight heparin (LMWH)-based therapy over warfarin-based therapy as both the initial and long-term treatments for VTE in cancer patients [23]. Recently, two trials, in which the effects of oral factor Xa inhibitors and dalteparin, a LMWH, as VTE treatment were compared in a head-to-head manner in cancer patients, were reported. The Hokusai VTE Cancer trial showed that edoxaban was non-inferior to subcutaneous dalteparin with respect to the composite outcome of recurrent VTE and major bleeding [24]. In the SELECT-D trial, the incidence of VTE recurrence was relatively lower, but clinically relevant non-major bleeding was higher with rivaroxaban therapy than

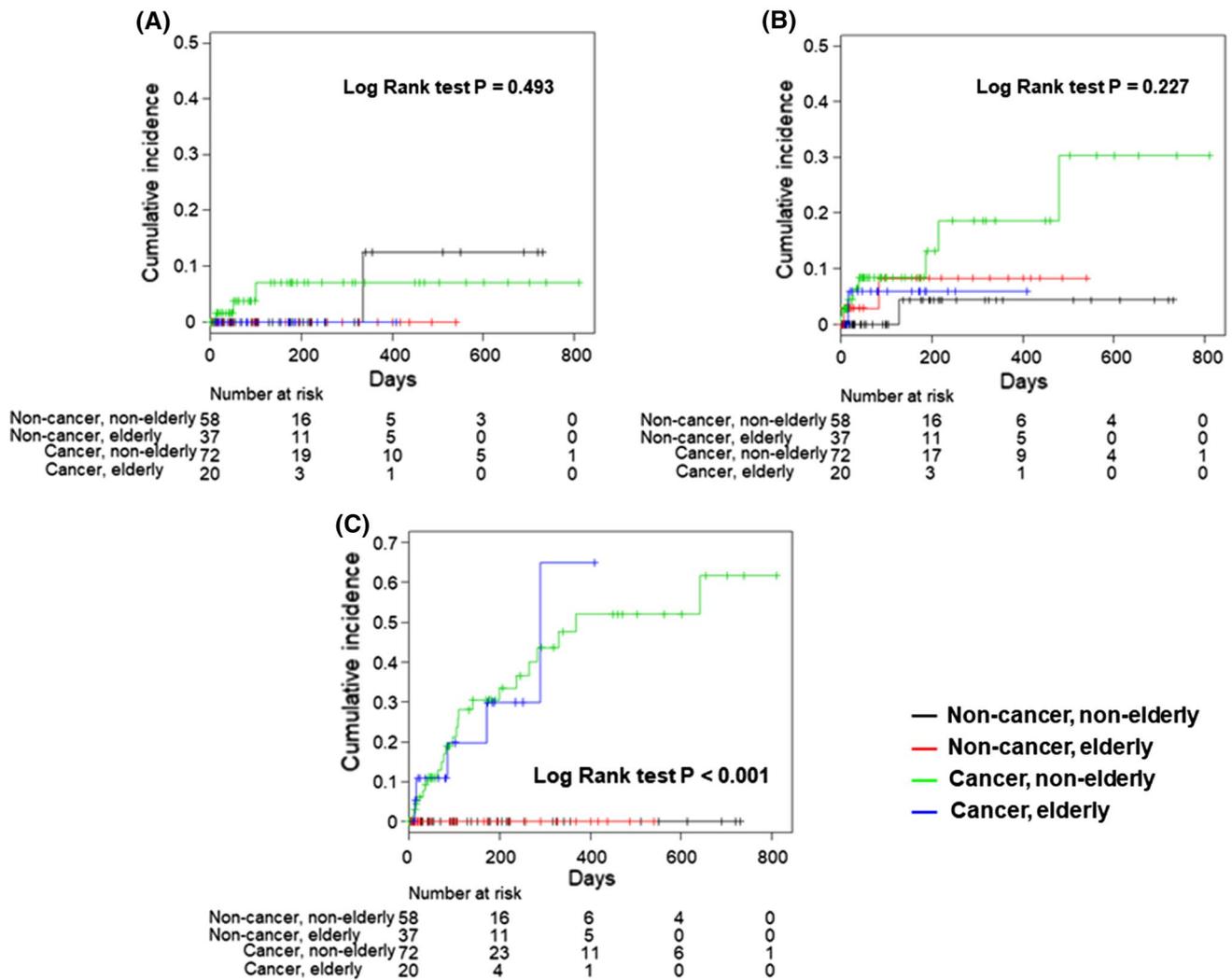


Fig. 5 Comparison of the cumulative incidence of recurrent venous thromboembolism (a), clinically relevant bleeding (b) and death (c) among elderly and non-elderly patients with and without cancer

with dalteparin therapy [25]. These results suggest that Xa inhibitors are clinically useful and appropriate alternative anticoagulants for the treatment of VTE in cancer patients, given that oral administration is more convenient than daily subcutaneous injections. However, since LMWH is not approved for VTE therapy in Japan, the effectiveness and safety of Xa inhibitors in VTE treatment between cancer and non-cancer patients were compared in the present study. The demographic characteristics of patients and the proportion of PE were similar in patients with and without cancer, although DVT in the proximal legs and upper sites was more common in patients with than without cancer. Our results showed that VTE recurrence and clinically relevant bleeding were comparable between the two groups. Death was significantly more common among cancer than non-cancer patients, although the cause of death in most cases was cancer, and not VTE- or bleeding-related deaths. These findings

suggest that Xa inhibitors may be the first-line anticoagulant therapy for VTE in cancer patients in Japan.

The elderly have a higher incidence of VTE, and various age-related demographic characteristics are associated with VTE occurrence, such as general frailty, surgery, hospitalization, nursing home confinement, trauma, neurological diseases, previous VTE, indwelling central venous catheters and cancer [26]. However, it is still not clear how prothrombotic factors relate to the age-related increase in thrombosis risk. Regarding the coagulation system, circulating levels of D-dimer, factor VIII and thrombin fragment F1 + 2 increase with age, although their association with VTE is not known [27]. In contrast, elderly patients with VTE have a higher incidence of bleeding complications while on therapeutic doses of anticoagulants [28]. VKAs have been used for the prevention and treatment of VTE. In patients ≥ 75 years old, the incidence of VKA-related bleeding increases to 5% per

year [29]. When using VKA treatment in elderly patients, the different risk factors—some of which increase with old age—such as drug interactions, malnutrition, liver dysfunction, dehydration and hypertension, complicate achievement of the target prothrombin time internationalized ratio [28]. Large randomized trials of VTE treatment have shown that Xa inhibitors are non-inferior in terms of VTE recurrence and have a tendency to a lower incidence of major bleeding compared with VKAs [11–14]. A meta-analysis including these trials concluded that Xa inhibitors were superior in terms of VTE recurrence and VTE-related deaths in VTE patients aged ≥ 75 years, with no difference in bleeding events [30]. This suggests that Xa inhibitors are more useful agents for VTE treatment in elderly patients at high risk of VTE and treatment-related bleeding. The results of the present study showed no differences in VTE recurrence, clinically relevant bleeding and death between non-elderly and elderly patients. This suggests that Xa inhibitors are useful for VTE treatment irrespective of age.

The presence of cancer in elderly patients is considered to be a predictor of VTE recurrence [27], bleeding [31], and mortality [32]. However, Lauber et al. reported that only two factors, unprovoked VTE and proximal DVT, were independently associated with recurrent VTE, indicating that the traditional risk factors for VTE recurrence (e.g., cancer) may be less relevant in elderly patients [33]. Thus, in this study, VTE recurrence, clinically relevant bleeding and death were compared among the four groups: non-elderly patients without cancer, elderly patients without cancer, non-elderly patients with cancer, and elderly patients with cancer. As shown in Fig. 5, no significant differences in these outcomes were found among the four groups, although cancer was more frequent in non-elderly than in elderly patients. In summary, the present study suggests that Xa inhibitors may be promising agents for the treatment of VTE irrespective of age and the presence of cancer, when adhering to the administration regime. To clarify the efficacy and safety of Xa inhibitors for VTE treatment in elderly and cancer patients, future prospective, randomized, controlled trials with large cohorts are required.

Limitations

This study is a retrospective, observational study evaluating a small population at a single institution. The changes in thrombosis were judged by comparing the changes on two imaging tests performed before and after Xa inhibitor treatment, irrespective of the absolute amount of thrombus or the VTE site before Xa inhibitor therapy. Since the analyses were based on a chart review at our hospital, events that were not recorded by doctors and paramedical personnel could not be analyzed. In addition, the events under investigation,

i.e., recurrent VTE and clinically relevant bleeding, were analyzed only during the administration of Xa inhibitors and within 1 week after stopping them, because the goal was to examine the direct effects of Xa inhibitors on these events. The proportion of patients receiving the three Xa inhibitors differed due to the difference in approval dates for VTE treatment of each agent.

In conclusion, the present study demonstrated that the effectiveness and safety of Xa inhibitors for VTE treatment are comparable among elderly/non-elderly patients with and without cancer. Therapy with Xa inhibitors may be clinically useful regardless of age and comorbid cancer.

Compliance with ethical standards

Conflict of interest Satoshi Ikeda received lecture fees from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb and Pfizer. Masamichi Eguchi received a research grant from Daiichi-Sankyo. Koji Maemura received lecture fees from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb and Pfizer, and research grants from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb and Pfizer.

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