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ORIGINAL ARTICLE

Low dose apixaban as secondary prophylaxis of venous thromboembolism in cancer patients – 30 months follow-up

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Abstract

Background: There are no data on the effect of low-dose anticoagulation as secondary prophylaxis for venous thromboembolism (VTE) in cancer patients. We assessed the efficacy and safety of low-dose apixaban for 30 months, after initial 6 months of full-dose treatment.

Methods: We included 298 patients with cancer and any type of VTE in a single arm interventional clinical trial. All patients were treated with full-dose apixaban (5 mg twice daily) for 6 months. Total 196 patients with active cancer after 6 months treatment continued with apixaban 2.5 mg twice daily for another 30 months. The main endpoints were recurrent VTE, major bleeding and clinically relevant non-major bleeding.

Results: During the 30 months of treatment with low-dose apixaban 14 (7.6%; 95% confidence interval (CI) 4.0%–11.7%) patients experienced recurrent VTE, six (3.1%;

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95% CI 1.1%–6.5%) experienced major bleeding and 16 (8.1%, 95% CI: 4.7%–12.8%) experienced clinically relevant non-major bleeding. The incidence rate per person month of recurrent VTE was 0.8% (95% CI 0.41–1.6) at 2–6 months with full-dose apixaban, and 1.0% (95% CI 0.5–1.9) at 7–12 months with low-dose apixaban. The incidence rate of major bleeding was 1.1% (95% CI 0.6–2.0) at 2–6 months, and 0.3% (95% CI 0.1–1.0) at 7–12 months. Between 12 and 36 months the incidence rate of recurrent VTE and major bleedings remained low.

Conclusion: Dose reduction of apixaban to 2.5 mg twice daily seems safe after 6 months of full-dose treatment. After 12 months the incidence rate of recurrent VTE and major bleeding remained low.

KEYWORDS
anticoagulants, apixaban, clinical trial, neoplasms, venous thromboembolism

1 | INTRODUCTION

Cancer increases the risk of venous thromboembolism (VTE).[1–3] Until recently, low molecular-weight heparin (LMWH) was the recommended VTE treatment for cancer patients. In the past 3 years, new data exploring oral factor Xa-inhibitors in cancer patients has emerged and they are now suggested as first-line treatment for deep vein thrombosis and pulmonary embolism in adult cancer patients.[4–6] Four randomized clinical trials assessing the factor Xa inhibitors apixaban, rivaroxaban and edoxaban are essential to the new guidelines.[7–10] In these trials, patients were treated with a factor Xa inhibitor for 6 months, except in the Hokusai VTE Cancer trial where treatment continued for up to 12 months.[7] The results showed that factor Xa inhibitors are non-inferior to LMWH in preventing recurrent VTE, although the results trended towards fewer recurrent VTEs in the patients randomized to factor Xa inhibitors. As for major bleeding, rivaroxaban and edoxaban,[8,11] but not apixaban,[12] showed a tendency towards more bleeding compared with LMWH, especially in patients with gastrointestinal cancer. A meta-analysis of the four studies concluded that factor Xa inhibitors resulted in less VTE than LMWH with the same likelihood of major bleeding.[13] Another meta-analysis which excluded the ADAM-VTE study did not find statistically significant differences between factor Xa inhibitors and LMWH regarding recurrent VTE and major bleedings.[14]

Current guidelines recommend anticoagulant treatment as long as the patient has active cancer.[5] Treatment beyond 6 months are documented in three cancer population studies where therapeutic doses of LMWH or rivaroxaban were administered up to 12 months.[15–17] In the general population, secondary prophylaxis with low-dose apixaban protects against recurrent VTE without increasing the rate of major bleeding.[18] Secondary prophylaxis with rivaroxaban 20 mg or 10 mg also show an acceptable safety profile in the general population.[19] In cancer-associated VTE there are no data on low-dose anticoagulation as secondary prophylaxis. Guidelines therefore recommend full-dose if the patient needs more than 6 months treatment. The efficacy and safety of dose reduction is important to explore, because cancer patients have an increased bleeding risk even without anticoagulation.[20] In our study we aimed to assess the efficacy and safety of low-dose apixaban treatment for 30 months, after initial 6 months of full dose treatment.

Essentials

- Low-dose anticoagulation has not been investigated in cancer associated thrombosis
- We gave patients low-dose apixaban for 30 months after 6 months of full-dose
- Low-dose apixaban resulted in low major bleeding rates from 6 to 12 months
- From 12 to 36 months there were few recurrent venous thrombosis and few bleedings

2 | METHODS

2.1 | Design, aims, follow-up, patients and inclusion criteria

"Apixaban as treatment of venous thrombosis in patients with cancer" (the CAP study) is an investigator-initiated, single-arm, interventional, multicenter study conducted in Norway. The aim of the study was to assess the efficacy and safety of apixaban as treatment and secondary prophylaxis for VTE in cancer patients. The trial is registered with identifier NCT02581176 in ClinicalTrials.gov.

The primary endpoints were recurrent venous thromboembolism (VTE), major bleeding and clinically relevant non-major bleeding (CRNMB) after full-dose treatment for up to 6 months. These data have already been reported.[21] The secondary endpoints were recurrent VTE, major bleeding and CRNMB after secondary prophylaxis

with low-dose apixaban for up to 24 months. Due to suggestions from the ethical committee we ended up with a total follow-up period of 36 months instead of 24 months as originally stated in the protocol. Low-dose apixaban was administered in the last 30 months of the intervention period, and those are the main data presented here. Written informed consent was obtained from all patients. Ethics approval was obtained from the Norwegian Regional Committees for Medical and Health Research Ethics and the local data protection officer at each participating hospital. The study was carried out in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The trial protocol is available from the corresponding author on request.

We recruited 300 patients from nine hospitals in Norway from April 2016 to May 2018. Two of the patients had to be excluded retrospectively because of wrong inclusion. 298 patients received full dose apixaban for up to 6 months. During the first 6 months, 102 patients left the study, leaving 196 patients to receive low-dose apixaban 2.5 mg twice daily for up to 30 months as secondary prophylaxis. Inclusion criteria for the first part of the study with full-dose apixaban were; new objectively verified VTE and a diagnosis of cancer or treatment for cancer, excluding basal cell and squamous cell carcinoma, within 6 months before inclusion. Both symptomatic and asymptomatic VTEs were included, with no restriction of VTE site. VTE was verified by compression ultrasound, venography, computer tomography, pulmonary angiography or venography or ventilation/perfusion lung scintigraphy. Patients eligible for further treatment with low-dose apixaban after 6 months of full-dose treatment were those who still had active cancer. Study visits from 7 to 36 months were obtained at 12, 24 and 36 months. At study visits the patients were assessed for efficacy and safety endpoints, new medication and blood samples were drawn.

2.2 | Treatment

From 7 months all 196 patients received 2.5 mg twice daily as secondary VTE prophylaxis for up to 30 months. Apixaban was temporarily discontinued when thrombocyte counts were below 25×10^9/L. It was allowed for the treating physician to shift anticoagulant treatment from apixaban to LMWH for shorter periods, e.g., in relation to procedures or severe thrombocytopenia.

2.3 | Outcomes and assessments

Primary efficacy and safety endpoints were any type of objectively verified recurrent VTE, major bleeding or CRNMB, respectively, during the first 6 months of full-dose treatment as previously reported.[21] The current article reports the secondary efficacy and safety endpoints during 30 months of low-dose treatment. The secondary efficacy endpoint was any type of objectively verified symptomatic or non-symptomatic recurrent VTE during low-dose treatment. The secondary safety endpoints were major bleeding and CRNMB in the same time period. Major bleeding and CRNMB were defined according to the criteria of the International Society of Thrombosis and Haemostasis.[22,23] The current article reports a post-hoc composite endpoint defined as the combination of recurrent VTE or major bleeding from 1–6 months to 7–36 months. The last secondary outcome was all-cause mortality during the full 36 months treatment period.

All serious adverse events were monitored by a medical monitor. Events obviously related to the cancer disease or cancer treatment was not reported as adverse events. Endpoints were assessed by an independent adjudication committee.

2.4 | Reasons for end of study

During the 30 months of low-dose follow-up, patients left the study at any time if considered cancer free. All patients experiencing recurrent VTE or major bleeding during low-dose treatment were taken out of the study. Other reasons for leaving the study were voluntary discontinuation, lost-to follow up, severe non-compliance and all other reasons that would make it unsafe to continue anticoagulant treatment (e.g., kidney failure, liver failure, interactions, dysphagia, terminal cancer etc.). Experiencing a CRNMB was not automatically a reason for leaving the study Appendix 1.

2.5 | Statistical analyses

The analysis of efficacy and safety is based on the time from the start of low-dose follow-up to the first recurrent thromboembolic event or major bleeding from 7 to 36 months. The intention-to-treat population consists of all patients who received at least one dose of low-dose apixaban. Endpoints are described as proportions with 95% confidence intervals (CIs). The risk of recurrence over time was analyzed using Kaplan-Meier method. The incidence rate of the main endpoints is reported as percent per person-month with 95% CI based on the Poisson distribution.[24]

3 | RESULTS

We included 300 patients in the study. Two patients had to be excluded retrospectively because of wrong inclusion. After 6 months treatment with full dose apixaban, 196 patients continued with apixaban 2.5 mg twice daily (low-dose) up to an additional 30 months (Figure 1).

Table 1 presents the patient characteristics at baseline and for those who continued with low-dose apixaban after 6 months. The age of the low-dose population was somewhat higher than the full-dose population (median 75 years vs. 68.5 years). The gender distribution, proportion of metastatic disease and the distribution of cancer types were fairly similar at baseline and at 7 months. Median follow-up time during low-dose treatment (30 months) was 16.8 months.

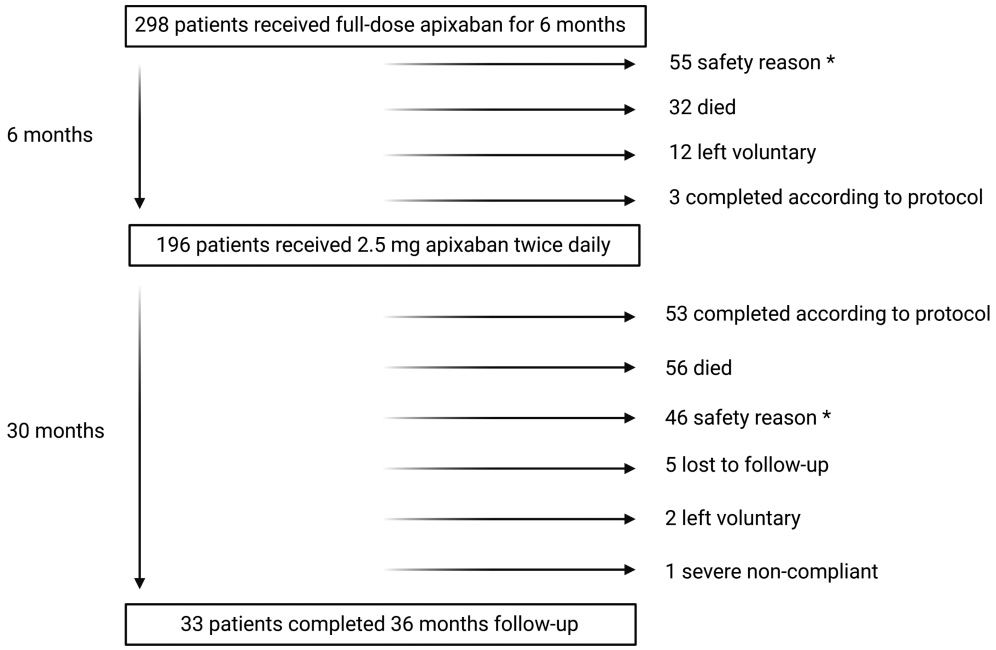

FIGURE 1 Flow chart

3.1 | Recurrent VTE

During the first 6 months of full-dose anticoagulation 12 of 298 patients had recurrent VTE (4.0%, 95% CI 2.1–6.9), as previously reported.[21] During the next 30 months with low-dose apixaban 14 of 196 (7.1%, 95% CI 4.0–11.7) patients experienced recurrent VTE (Table 2). The highest incidence rate of recurrent VTE was seen during the first month of full-dose anticoagulation, with an incidence rate of 1.4% (95% CI 0.5–3.6) per person-month (Table 3). After the first month, the incidence rate decreased to 0.8% (95% CI 0.4–1.6) from 2 to 6 months, and then increased slightly to 1.0% (95% CI 0.5–1.9) during 7–12 months after the dose of apixaban was reduced. After 12 months there were a steady decrease of recurrent VTE until the end of the study (Table 3 and Figure 2).

3.2 | Bleedings

During the first 6 months of full-dose anticoagulation 16 patients experienced major bleeding (5.4%, 95% CI 3.1–8.6) and 26 patients experienced one or more episodes of CRNMB (8.7%, 95% CI 5.8–12.5).[21] During the next 30 months of low-dose apixaban treatment six patients (3.1%, 95% CI: 1.1–6.5) experienced major bleeding and 16 (8.2%, CI 4.7–12.9) patients experienced CRNMB (Table 2). The incidence rate of major bleeding peaked the first month of full-dose treatment with 1.7% (95% CI 0.7–4.1) per person-month. After dose reduction, the incidence rate of major bleeding was reduced to 0.3% (95% CI 0.1–1.0) per person-month at 7–12 months and remained low during the subsequent 30 months (Table 3 and Figure 2).

During the first 6 months with full-dose apixaban six out of 16 major bleedings were in patients with gastrointestinal cancers, four in patients with un-resected tumors and two in patients with resected tumors. During the next 30 months there were 2/82 (2.4%, 95% CI 0.30–8.5) episodes of major bleeding in patients with gastrointestinal cancer, compared to 4/114 (3.5%, 95% CI 1.0–8.7) in all the other groups of cancer. Urogenital cancer had 2/43 (4.5%, 95% CI: 0.57–15.8) major bleedings during low-dose follow-up. The last two major bleeding episodes in the low-dose follow-up period occurred in sarcoma and lung cancer (Appendix 2: Tables A1–A4).

Four patients experienced intracranial bleeding during the low-dose apixaban treatment; one traumatic bleeding, one cerebral hemorrhage, and two metastatic bleedings. The two patients with metastatic bleed did not have verified cerebral metastases at inclusion. None of the seven patients with cerebral metastases at inclusion experienced intracranial bleeding during follow-up.

3.3 | Composite endpoint and survival

The incidence rate of the composite endpoint of major bleeding or recurrent VTE was highest during the first 9 months and then steadily decreased (Table 4). The highest incidence rate was observed during the first month with full-dose treatment (3.1% per month, 95% CI 1.6–6.0) and during 4–6 months (2.8% per month, 95% CI 1.6–4.8). During the 3 months immediately following dose reduction (7–9 months), the incidence rate was 1.6% per month (95% CI 0.80–3.2).

After 36 months follow-up, 33 patients continued with anticoagulation because of active cancer. During 0–36 months, 88 of 298

TABLE 1 Patient characteristics at inclusion and at 7 months

Characteristic	0–6 months (*n* = 298) No. /median (%, range)	7–36 months (*n* = 196) No. /median (%, range)
Age	68.5 (19–91)	75 (19–86)
Gender, female	130 (44%)	80 (40%)
BMI	25 (14.5–45)	25.4 (18.8–45)
Metastatic (solid tumor)	204 (68%)	139 (70.1%)
Previous venous thrombosis	30 (10.1%)	25 (12.8%)
Primary cancer		
Gastrointestinal[a]	126 (42.3%)	82 (42%)
Resected	66/126 (52%)	43/82 (52%)
Unresected	60/126 (48%)	39/82 (48%)
Urogenital[b]	59 (19.7%)	43 (22.4%)
Hematological	29 (9.7%)	21 (10.7%)
Breast	28 (9.4%)	19 (9.7%)
Lung	27 (9.1%)	12 (6.1%)
Pancreatic	25 (8.4%)	10 (5.1%)
Melanoma	11 (3.7%)	7 (3.5%)
Female genital[c]	7 (2.3%)	4 (2%)
Cholangiocarcinoma	4 (1.3%)	3 (1.5%)
Brain	4 (1.3)	1 (0.5%)
Other	7 (2.3%)	7 (3.5%)

[a]Esophageal, gastric, cholangiocarcinoma, liver, pancreas, small bowel, colorectal.

[b]Prostate, bladder, kidney, testicle.

[c]Ovaries, endometrial.

patients died while they were in the study, resulting in an overall survival rate of 70%.

3.4 | Adverse events and reasons for ending the study participation

There were 65 serious adverse events. Most abundant were infections and arterial thrombosis (Appendix 3: Table A5). Fatal outcomes and completion of the study according to protocol were the two most frequent reasons for leaving the study from 7 to 36 months, 56/196 (29%) and 86/196 (44%) respectively (Appendix 4: Table A6).

4 | DISCUSSION

Our results show that dose reduction of apixaban to 2.5 mg twice daily after 6 months treatment with full dose apixaban is reasonably safe and effective in our population. The incidence of recurrent VTE increased slightly after dose reduction, but was more than outweighed by the reduction in major bleedings. The highest incidence rate of recurrent VTE as well as major bleeding occurred during the first month of treatment with full-dose apixaban. As illustrated by the overlapping confidence intervals for the incidence rates, it is, however, uncertain if the changes in recurrent VTE and bleedings are true or coincidental (Appendix 5: Table A7).

The current study is to our knowledge the first to report low-dose anticoagulant treatment for cancer associated VTE, and the first to report data beyond 12 months treatment. Most studies have reported 6 months treatment of VTE in cancer patients, but there are four trials reporting data of treatment up to 12 months. The Daltecan[17] and the TiCat[15] trials investigated 12 months treatment with the LMWHs dalteparin and tinzaparin, while the Hokusai VTE Cancer trial[7] and the Select-D[8] study investigated the factor Xa inhibitors edoxaban and rivaroxaban. All patients in these studies were treated with full dose anticoagulation. Appendix 2 Table A4 shows recurrent VTE and major bleedings in these four studies during 6–12 months compared with the current study. The Select-D study had a second randomization between rivaroxaban and placebo at 6 months, but included few patients, which makes the estimates very uncertain. The Hokusai VTE Cancer study included 567 patients in the edoxaban arm for up to 12 months and reported fewer recurrent VTEs and more major bleedings. The same tendency is seen when the current study results are compared with the Daltecan and the TiCat studies. These comparisons indicate that lowering the dose of anticoagulation after 6 months may result in an increase in recurrent VTE and a decrease in major bleedings. This will not be answered properly before a randomization between full dose and reduced dose anticoagulation is done. There are currently at least two ongoing randomized trials to answer this question, the APICAT study NCT0369206 and the EVE trial NCT03080883.[25,26]

Because the incidence of both recurrent VTE and major bleedings fell markedly after 9–12 months treatment, the exact right time for dose reduction remains unclear. It could be beneficial for the patients to use full-dose anticoagulation as long as nine or 12 months before reducing the dose.

Although we believe that the dose reduction of apixaban was the reason for the change in recurrent VTE and major bleedings, we cannot be sure. The Daltecan study[17] reported less major bleeding after 6 months without dose reduction of dalteparin. Hence, it might be that the patients with the highest risk of bleeding and recurrent VTE has left the study during the first 6 months.

How to treat patients with cerebral metastases who needs anticoagulation is a difficult subject. In our study, metastatic brain bleed only occurred in patients without verified cerebral metastases at inclusion. Several retrospective studies indicate a comparable safety profile between oral factor Xa inhibitors and LMWHs in patients with cerebral metastases and primary cerebral tumors.[27–29] The current data illustrates that the actual rate of patients with cerebral metastases is uncertain if you do not do cerebral CT-scan at inclusion.

There were more major bleedings in patients with gastrointestinal cancers treated with rivaroxaban and edoxaban compared with

TABLE 2 Clinical outcomes 0–36 months

Clinical outcomes	0–6 months No. (%; 95% CI)	7–36 months No (%; 95% CI)	0–36 months No (%; 95% CI)
No. at risk	298	196	298
Recurrent venous thrombosis	12 (4.0%, CI: 2.1–6.9)	14 (7.1%, CI: 4.0–11.7)	26 (8.7%, CI: 5.8–12.5)
DVT leg	2	2	4
DVT arm	1	0	1
Pulmonary embolism	6	4	10
Abdominal	2	5	7
CVC	0	2	2
Other	1	1	2
Incidental VTE at inclusion	162 (54%)		
Incidental index VTE with recurrent VTE	7/12	6/15	13/27
Symptomatic index VTE with recurrent VTE	5/12	8/15	13/27
Major bleeding	16 (5.4%, CI: 3.1–8.6)	6 (3.1%, CI: 1.1–6.5)	22 (7.4%, CI: 4.7–11)
Gastro-intestinal bleeding	8	2	10
Hematuria	2	1	3
Cerebral[a]	1	3	4
Surgery	3	0	3
Epistaxis	1	0	1
Intra-abdominal	1	0	1
Major bleeding in un-resected GI-cancer	4/60 (6.7%, CI: 1.9–16)	1/39 (2.6%, CI: 0.06–13)	5/60 (8.3%, CI: 2.8–18)
Major bleeding in resected GI-cancer	2/66 (3.0%, CI: 0.37–11)	1/43 (2.3%, CI: 0.06–12)	3/66 (4.6%, CI: 0.95–13)
CRNMB	26 (8.7%, CI: 5.8–12.5)	16 (8.2%, CI: 4.7–12.9)	42 (14.1, CI: 10.4–18.6)
Arterial thrombosis	12 (4%, CI: 2.1–6.9)	4 (2%, CI: 0.6–5.1)	16 (5.4%, CI: 3.1–8.6)
Death	32 (11%)	56 (29%)	88 (30%)
Serious adverse events[b]	33	32	65

Note: From 0 to 6 months patients received apixaban 5 mg bid, from 7 to 36 months patients received 2.5 mg bid.

Abbreviation: CVC, central venous catheter.

[a]One hemorrhage after trauma, one intra-cerebral bleed, two metastatic bleeds.

[b]Serious adverse events are described in more detail in the Appendix 3: Table A5.

LMWH in the Select-D and Hokusai VTE Cancer Trial.[8,11] This was not observed in the Caravaggio study on apixaban,[12] where all the major bleedings in patients with gastrointestinal cancer occurred in those with un-resected cancer. In our study, we observed major bleedings in patients with both resected and un-resected tumors. During the 30 months observation of low-dose apixaban, we did not observe any difference in major bleeding between gastrointestinal cancers and other cancers. The confidence intervals were, however, too wide to make a firm conclusion.

We captured mortality in those who died during the study, however, we have no follow-up data on those who left the study as they approached the terminal phase of their cancer disease. Thus, the mortality rates do not accurately reflect the exact rates in the study population.

Study limitations includes the lack of randomization. This prevents a comparison between low-dose and full-dose apixaban. A strength of the study is that we had broad inclusion criteria, making the results representative of a "real world" population, and long term follow-up.

5 | CONCLUSION

We observed a small transient increase in VTE and a substantial decrease in major bleedings on apixaban 2.5 mg twice daily after 6 months full-dose apixaban. After 12 months the incidence of recurrent VTE and major bleeding remained low. The study shows that reducing apixaban to 2.5 mg twice daily is reasonably safe after 6 months.

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TABLE 3 Incidence rates of recurrent VTE and major bleeding

Time (months)	Apixaban dose	No. patients at risk	Recurrent VTE (n/ months at risk)	Incidence rate recurrent VTE (%/month)	95% CI	Major bleeding (n/ months at risk)	Incidence rate major bleeding (%/month)	95% CI
0–1	5 mg × 2	298	4/287	1.4	0.53–3.6	5/287	1.7	0.73–4.1
2–6	5 mg × 2	272	8/980	0.82	0.41–1.6	11/980	1.1	0.62–2.0
7–12	2.5 mg × 2	196	9/928	1.0	0.51–1.9	3/928	0.32	0.10–1.0
13–18	2.5 mg × 2	132	2/658	0.30	0.076–1.2	1/658	0.15	0.021–1.1
19–24	2.5 mg × 2	92	0/491	-	-	1/491	0.20	0.029–1.4
25–30	2.5 mg × 2	73	1/364	0.27	0.039–1.9	1/364	0.27	0.039–1.9
31–36	2.5 mg × 2	53	2/308	0.65	0.16–2.6	0/308	-	-

Larhammer, and Elin Sandanger Haugen, as well as study coordinator Line-Theres Carolin.

CONFLICT OF INTEREST

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Trine-Lise Hannevik: Pfizer/Bristol Myers Squibb (honorarias). Herish Garresori: Pfizer, Amgen, Bayer (Honorarias). Jorunn Brekke: No competing interests. Tone Ronnaug Enden: No competing interests. Hege Froen: Bristol-Myers Squibb (Honororia), Amgen (advisory committee) Eva-Marie Jacobsen: No competing interests. Petter Quist-Paulsen: No competing interests. Alina Carmen Porojnicu: Bristol-Myers Squibb (Honororia). Anne Hansen Ree: No competing interests. Dag Torfoss: No competing interests. Elin Velle: No competing interests. Hilde Skuterud Wik: No competing interests. Waleed Ghanima: Amgen (Honororia, advisory committee), Novartis (Honororia, advisory committee, research funding), MSD (advisory committee), Bayer (research funding), Pfizer/Bristol-Myers Squibb (research funding), Janssen (research funding) Per Morten Sandset: No competing interests. Anders EA Dahm: Pfizer (Honoraria), Novartis (Honoraria), Pfizer/Bristol-Myers Squibb (advisory committee, research funding).

AUTHOR CONTRIBUTIONS

Trine-Lise Larsen: Data curation; Formal analysis; Investigation; Project administration; Validation; Visualization; Roles/Writing – original draft. Herish Garresori: Data curation; Investigation; Project administration; Resources; Validation; Writing – review and editing. Jorunn Brekke: Data curation; Investigation; Project administration; Resources; Validation; Writing – review and editing. Tone Enden: Conceptualization; Project administration; Writing – review and editing. Hege Frøen: Data curation; Investigation; Project administration; Resources; Writing – review and editing. Eva Marie Jacobsen: Data curation; Investigation; Project administration; Resources; Validation; Writing – review and editing. Petter Quist-Paulsen: Data curation; Investigation; Project administration; Resources; Writing – review and editing. Alina Carmen Porojnicu: Data curation; Investigation; Project administration; Resources; Writing – review and editing. Anne Hansen Ree: Investigation; Resources; Writing – review and editing. Dag Torfoss: Investigation; Resources; Writing – review and editing. Elin Osvik Velle: Data curation; Investigation; Project administration; Resources; Writing – review and editing. Hilde Skuterud Wik: Conceptualization; Project administration; Validation; Writing – review and editing. Waleed Ghanima: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review and editing. Per Morten Sandset: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing – review and editing. Anders Erik Astrup Dahm: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration;

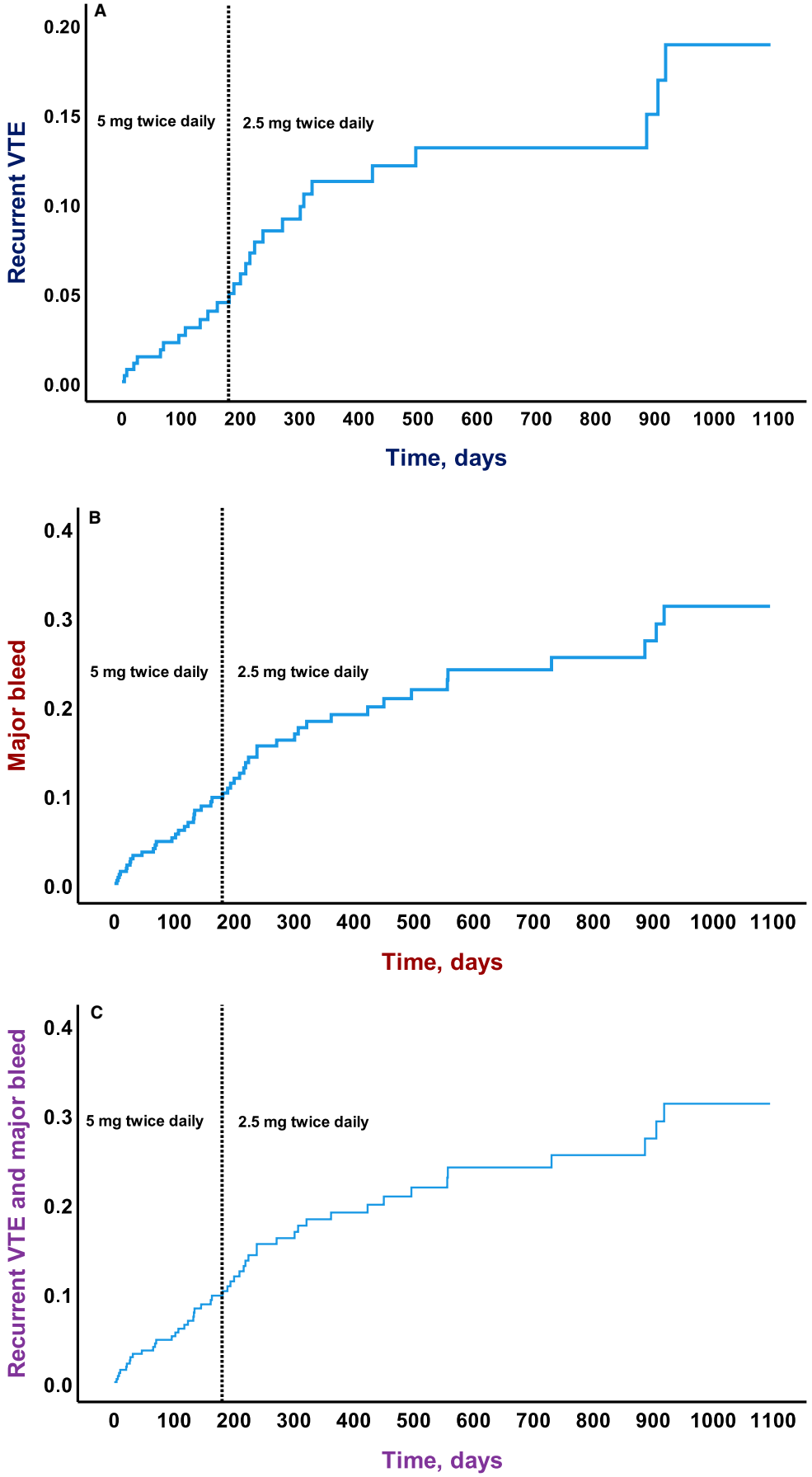

FIGURE 2 Kaplan-Meier survival curves. Recurrent venous thromboembolism (A), major bleeding (B), and recurrent venous thromboembolism or major bleeding (C)

TABLE 4 Incidence rates of the composite endpoint of recurrent VTE or major bleeding

Time (months)	Apixaban dose	No. patients at risk	Composite endpoints (*n*/months at risk)	Incidence rate composite endpoint (%/month)	95% CI
0–1	5 mg × 2	298	9/287	3.1	1.6–6.0
2–3	5 mg × 2	272	6/514	1.2	0.53–2.6
4–6	5 mg × 2	245	13/466	2.8	1.6–4.8
7–9	2.5 mg × 2	196	8/504	1.6	0.80–3.2
10–12	2.5 mg × 2	153	4/424	0.9	0.36–2.5
13–15	2.5 mg × 2	132	2/356	0.6	0.14–2.2
16–18	2.5 mg × 2	108	1/302	0.3	0.05–2.3
19–21	2.5 mg × 2	92	1/259	0.4	0.05–2.7
22–24	2.5 mg × 2	80	0/232	-	-
25–27	2.5 mg × 2	73	1/193	0.5	0.07–3.7
28–30	2.5 mg × 2	60	1/171	0.6	0.08–4.1
31–33	2.5 mg × 2	53	2/150	1.3	0.34–5.3
34–36	2.5 mg × 2	49	0/158	-	-

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APPENDIX 1

Describes inclusion and exclusion criteria.

INCLUSION CRITERIA

- Age >18 years, male and female
- A diagnosis of cancer, other than basal-cell or squamous-cell carcinoma of the skin, within six months before enrollment. Any treatment for cancer within the previous six months, or recurrent or metastatic cancer.
- Objectively verified VT
- Informed consent

EXCLUSION CRITERIA

- Anticoagulant therapy in therapeutic doses prior to trial entry for >96 h.
- Severe thrombocytopenia (platelets < 50 10^9/L)
- Severe renal failure – creatinine clearance < 30 ml/min
- The patients will be treated with catheter directed thrombolysis for DVT or systemic thrombolysis for severe pulmonary embolism
- Pregnancy or breastfeeding
- Childbearing potential without proper contraceptive measures such as oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to avoid pregnancy for the entire study.
- Drug abuse or mental disease that may interfere with treatment and follow-up.
- Severe malabsorption so that oral treatments are expected to have reduced effect
- Mechanical heart valves
- Known allergy to apixaban
- Active bleeding or severe risk of bleeding so that the risk of bleeding is considered a greater danger than the risk of not treating the VT
- Clinically significant liver disease (e.g., acute hepatitis, chronic active hepatitis, or cirrhosis)
- Concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g., human immunodeficiency virus protease inhibitors or systemic ketoconazole, voriconazole or posaconazole) or inducers (e.g., rifampicin, carbamazepine, or phenytoin). Fluconazol is allowed.

PRIOR AND CONCOMITANT MEDICATION

Therapeutic dosages of low molecular heparins/fondaparinux are allowed up to a maximum of 96 h prior to inclusion. The duration of prophylactic dosages of low molecular heparins, e.g., dalteparin 5000 U once daily or enoxaparin 40 mg once daily, are not restricted. A single pre-inclusion dose of vitamin K antagonist is also allowed.

APPENDIX 2

Description of the endpoints recurrent VTE and major bleeding.

TABLE A1 (a) Recurrent VTE and major bleeding type and distribution among cancer types. Time 0–6 months. (b) Recurrent VTE type and distribution among cancer types. Time 7–36 months

a		
Type cancer	**Type recurrent VTE**	**Day**
Pancreas	Pulmonary embolism	4
Cholangiocarcinoma	Pulmonary embolism	7
Lymphoma	DVT arm	20
Lung	Pulmonary embolism	26
Pancreas	Pulmonary embolism	63
Kidney	DVT leg	64
Gastric. KLL	Brachiocephalic, jugular vein and subclavia left side	89
Pancreas	Abdominal	107
Bladder	Pulmonary embolism/DVT leg	132
Anal	DVT leg	145
Small bowel	Abdominal	161
Anal	Pulmonary embolism	161
b		
Type cancer	**Type RVT**	**Day RVT**
Colon sigmoideum	Central venous line	189
Melanoma	Pulmonary embolism	189
Bladder	DVT Leg	215
Colon sigmoideum	Abdominal	224
Lymphoma	Abdominal/vena cava	230
Prostate	DVT Leg	238
Pancreas	Pulmonary embolism	269
Myeloma	Pulmonary embolism	301
Colon	Abdominal	307
Pancreas	Abdominal	423
Myeloma, anal	Pulmonary embolism	496
Pancreas	Abdominal/portal vein	883
Prostate	Internal jugular	905
Breast	Central venous line	918

TABLE A2 (a) Major bleeding type and distribution among cancer types. Time 0–6 months. (b) Major bleed type and distribution among cancer types. Time 7–36 months

a

Type cancer	Type major bleeding	Day major bleeding	Resected tumor
Anal	GI lower	2	No
Lung	Intraabdominal	6	No
Prostate	Surgery	10	Yes
Bladder	GI, lower	21	Yes
Colon	Upper GI	27	No
Lymphoma	Hematuria	31	Yes
Small bowel	GI, tumor	46	No
Hair-cell leukemia	Upper GI	68	No
Lung	Surgery	76	No
Prostate	Epistaxis	102	Yes
Colon	Upper GI	117	Yes
Breast	Surgery breast	121	Yes
Lung	Brain metastases	123	Yes
Lymphoma	Hematuria	133	Yes
Small bowel	GI, lower	134	Yes
Colon	GI, lower	153	No

b

Type cancer	Type major bleeding	Day major bleeding	Resected tumor
Osteosarcoma	GI	194	Yes
Lung	Cerebral, traumatic	219	No
Prostate	Cerebral hemorrhage	238	No
Bladder	Brain metastases	362	Yes
Cholangiocarcinoma	GI lower	455	Yes
colon	hematuria	730	No

TABLE A3 Risk of recurrent VTE and major bleeding presented as incidence rate per person-month for 6 months intervals and 3 months intervals

Time (months)	Apixaban dose	No. patients at risk	RVTE[a]	RVTE IR	95% CI	MB[a]	MB IR	95% CI	CE[a]	CE IR	95% CI
0–1	5 mg × 2	298	4/287	1.4	0.5–3.6	5/287	1.7	0.7–4.1	9/287	3.1	1.6–6.0
2–3	5 mg × 2	272	2/514	0.4	0.1–1.6	4/514	0.8	0.3–2.1	6/514	1.2	0.53–2.6
4–6	5 mg x2	245	6/466	1.3	0.32–1.8	7/466	1.5	0.7–3.1	13/466	2.8	1.6–4.8
7–9	2.5 mg × 2	196	5/504	1.0	0.41–2.4	3/504	0.6	0.2–1.8	8/504	1.6	0.80–3.2
10–12	2.5 mg × 2	153	4/424	0.9	0.36–2.5	0/424	-	-	4/424	0.9	0.36–2.5
13–15	2.5 mg × 2	132	1/356	0.3	0.04–1.2	1/356	0.3	0.04–2.0	2/356	0.6	0.14–2.2
16–18	2.5 mg × 2	108	1/302	0.3	0.05–2.3	0/302	-	-	1/302	0.3	0.05–2.3
19–21	2.5 mg × 2	92	0/259	-	-	1/259	0.4	0.05–2.7	1/259	0.4	0.05–2.7
22–24	2.5 mg × 2	80	0/232	-	-	0/232	-	-	0/232	-	-
25–27	2.5 mg × 2	73	0/193	-	-	1/193	0.5	0.07–3.7	1/193	0.5	0.07–3.7
28–30	2.5 mg × 2	60	1/171	0.6	0.08–4.1	0/171	-	-	1/171	0.6	0.08–4.1
31–33	2.5 mg × 2	53	2/150	1.3	0.34–5.3	0/150	-	-	2/150	1.3	0.34–5.3
34–36	2.5 mg × 2	49	0/158	-	-	0/158	-	-	0/158	-	-
2–6	5 mg × 2	272	8/980	0.8	0.41–1.6	11/980	1.1	0.6–2.0	19/980	1.9	1.2–3.0
7–12	2.5 mg × 2	196	9/928	1.0	0.5–1.9	3/928	0.3	0.1–1.0	12/928	1.3	0.74–2.3
13–18	2.5 mg × 2	132	2/658	0.3	0.08–1.2	1/658	0.2	0.02–1.1	3/658	0.5	0.15–1.4
19–24	2.5 mg × 2	92	0/491	-	-	1/491	0.2	0.03–1.4	1/491	0.2	0.03–1.4
25–30	2.5 mg × 2	73	1/364	0.3	0.04–1.9	1/364	0.3	0.04–1.9	2/364	0.6	0.14–2.2
31–36	2.5 mg × 2	53	2/308	0.6	0.16–2.6	0/308	-	-	2/308	0.6	0.16–2.6

Abbreviations: CE, composite endpoints; IR, incidence rate, rates are given as % per person-month; MB, Major bleed; RVTE, recurrent venous thromboembolism.

[a]Number of events/subject months at risk.

TABLE A4 Comparison of the proportions of recurrent VTE and major bleedings during 6–12 months in studies of anticoagulant treatment of cancer associated VTE

Trial	Design	No. patients left in study at month 7	Treatment	Recurrent VTE (n, %)	95% confidence interval	Major Bleedings (n, %)	95% confidence interval
Daltecan	Single-armed	194	Dalteparin	8/194, 4%	1.8–8.0	8/194, 4%	1.8–8.0
TiCat	Single-armed	189	Tinzaparin	2/184, 1.1%	0.1–3.9	5/189, 2.6%	0.9–6.1
Hokusai	RCT	567	Dalteparin	3/273, 1.1%	0.2–3.2	3/273, 1.1%	0.2–3.2
			Edoxaban	2/294, 0,7%	0.08–2.4	5/294, 1.7%	0.5–3.9
Select-D	RCT	86	Placebo	6/44, 14%	5.2–27	0/44, 0%	-
			Rivaroxaban	1/44, 2.3%	0.06–12	2/42, 5%	0.6–16.2
CAP	Single-armed	196	Apixaban	9/196, 4.6%	2.1–8.5	3/196, 1.5%	0.32–4.4

APPENDIX 3

Description of serious adverse events

TABLE A5 Serious adverse event time 0–36 months

Type event	0–6 months	7–36 months
Infections	11	15
Arterial thrombosis	12[a]	4[b]
Reduced general condition	1	1
Trauma		5
Pain	1	1
Ketoacidosis		1
Neuropathy	1	
Dyspnea	2	
Surgery complication	1	
Decubitus		1
Epilepsy	1	
Chest pain		1
Thrombocytopenia	1	
Atrial fibrillation		1
Bell's palsy	1	
Skin rash	1	
Leg pain		1
Edema leg		1
Total	33	32

[a]11 strokes, 1 myocardial infarction.

[b]3 strokes, 1 peripheral arterial embolism.

APPENDIX 4

TABLE A6 Reasons for leaving the study. Numbers represent number of patients

Reasons for leaving the study	0–6 months	7–36 months
Death	32	56
Voluntary discontinuation	12	2
Non-compliant	-	1
Lost to follow-up	-	5
Completed according to protocol	3	86
Safety reasons	55[a]	46
RVT	12	15
Major bleeding	16	6
CRNMB	6	4
Liver failure	-	2
Liver transplant	-	1
Stroke	2	1
Terminal phase	4	4
Cerebral metastases	-	1
General bad condition	3	1
Dysphagia	2	-
Side-effects	1	-
Treatment-resistant thrombus not registered as RVTE	2	-
Unknown safety reason	4	5
Interactions	4	4
Atrial fibrillation	-	1
Surgery	-	1

Note: Not all CRNMBs made the patient leave the study.

[a]1 person had one major bleed related to surgery at day 76 and was not taken out of the study, was later taken out because of recurrent VTE day 181.

APPENDIX 5

TABLE A7 Distribution of cancer types at inclusion and at 7 months

Cancer type	0–6 months	7–36 months
Anal	20	15
Appendix	1	-
Bladder	13	8
Brain	4	2
Breast	27	18
Cholangiocarcinoma	4	3
Colon	57	44
Endometrial	1	-
Esophageal	4	2
Hematological	29	-
Lymphoma	17	11
Hair-cell leukemia	1	-
CLL	3	3
Myeloma	8	8
Gastric	8	5
Gingival	1	1
Kidney	7	4
Lung	27	12
Melanoma	11	7
Nasopharyngeal	1	-
Neuroendocrine	1	1
Sarcoma	2	2
Ovaries	5	4
Paget	1	1
Pancreas	25	10
Peritoneal carcinomatosis	1	1
Prostate	35	27
Retroperitoneum	1	1
Small bowel	6	2
Testicles	4	4
Tonsils	1	1
Uterus	1	-