Original Article

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

J Oncol Pharm Practice
0(0) 1–7

DOI: 10.1177/1078155217718382
journals.sagepub.com/home/opp
SAGE

Retrospective comparison of low molecular weight heparin vs. warfarin vs. oral Xa inhibitors for the prevention of recurrent venous thromboembolism in oncology patients: The Re-CLOT study

Saeed K Alzghari[1], Susan E Seago[2], Jessica E Garza[2], Yasmeen F Hashimie[2], Kimberly A Baty[1], Martha F Evans[3], Courtney Shaver[4] and Jon D Herrington[1,3,5]

Abstract

Background: There is increasing evidence indicating oral factor Xa inhibitors can be used for secondary prevention of venous thromboembolism. Studies are needed to compare oral factor Xa inhibitors, low molecular weight heparins, and warfarin in the oncology population. The purpose of this study is to evaluate the recurrent venous thromboembolism incidence in oncology patients utilizing oral Xa inhibitors, low molecular weight heparins, or warfarin.

Methods: Using retrospectively collected data, we compared the recurrent venous thromboembolism incidence in oncology patients taking rivaroxaban/apixaban, enoxaparin, or warfarin with at least three months of follow-up. Patients were included if they had an active cancer, venous thromboembolism, and taking warfarin, enoxaparin, or rivaroxaban/apixaban. The primary endpoint was the first episode of recurrent venous thromboembolism at three months. Secondary endpoints included recurrent venous thromboembolism after six months, major bleeding, and mortality.

Results: Of 127 venous thromboembolism patients, 48 received rivaroxaban or apixaban, 23 received enoxaparin, and 56 received warfarin. The three most common cancer diagnoses were lung (21%), colorectal (14%), and breast (14%). There was no difference in venous thromboembolism recurrence at three months between the rivaroxaban/apixaban (0%), warfarin (3.6%), and the enoxaparin cohorts (4.4%) ($p = 0.8319$). Major bleeding at three months was only seen in one patient in the enoxaparin arm (4.2%). Mortality at three months was 0%, 3.6%, and 17.4% in the rivaroxaban/apixaban, warfarin, and enoxaparin cohorts, respectively.

Conclusion: The results of this retrospective study suggest that oral factor Xa inhibitors are potential options for cancer patients with venous thromboembolism. However, randomized, controlled trials are needed to confirm these results.

Keywords
Venous thromboembolism, enoxaparin, warfarin, rivaroxaban, apixaban

Date received: 4 January 2017; accepted: 11 June 2017

Introduction

A frequent complication among cancer patients is venous thromboembolism (VTE), which is a significant cause of morbidity and mortality in this population. Approximately 15% of cancer patients will experience a VTE with incidence rates ranging from 3.8 to 30.7%.[1] The etiologies of increased VTE risk in cancer patients

[1]Department of Pharmacy, Scott & White Medical Center – Temple, Baylor Scott & White Health, USA
[2]Department of Medicine, Scott & White Medical Center – Temple, Baylor Scott & White Health, USA
[3]University of Texas College of Pharmacy, USA
[4]Office of Biostatistics, Baylor Scott & White Health Research Institute, USA
[5]Texas A&M University College of Medicine, USA

Corresponding author:
Jon D Herrington, Department of Pharmacy, Scott & White Medical Center, 2401 South 31st Street, Temple, TX 76508, USA.
Email: Jon.Herrington@BSWHealth.org

include surgery, chemotherapy, hormonal agents, immobilization, central venous catheter insertion, and the prothrombotic and fibrinolytic nature of tumor cells.[2] The risk of recurrent VTE is threefold greater in cancer patients as compared with patients without cancer.[3]

Currently, low molecular weight heparins (LMWH) are first line for the secondary prevention of VTE in cancer patients. The American College of Chest Physicians has a grade 2B recommendation for cancer patients utilizing LMWH over vitamin K antagonist (VKA) therapy for VTE.[4] Furthermore, a grade 2C recommendation is in place for cancer patients with VTE to be treated with LMWH over rivaroxaban, apixaban, edoxaban, or dabigatran.[4] Although much emphasis has been placed on LMWH and VKA therapies, both come with drawbacks. For VKAs such as warfarin, undue burden comes in the form of regular INR monitoring and maintaining INRs between 2 and 3, which can be difficult in patients with variable dietary vitamin K intake. Furthermore, LMWH are only dispensed in injectable forms leading to a potential barrier in administering this agent. Rivaroxaban and apixaban are direct oral anticoagulants (DOAC) used in the secondary prevention of VTE. Rivaroxaban studies have shown non-inferiority in regard to VTE recurrence in comparison to warfarin as well as similar or superior reduction in major bleeding events.[5,6] Apixaban also displays non-inferiority to warfarin in regard to VTE recurrence and major bleeding.[7] A pooled analysis was performed in cancer patients on rivaroxaban compared to warfarin with similar rates of VTE recurrence and major bleeding.[8]

With increasing evidence suggesting DOACs have the potential to be used as an alternative therapy requiring no anticoagulation monitoring and a favorable oral formulation, we conducted an analysis comparing rivaroxaban/apixaban to LMWH and VKA therapy for the secondary prevention of VTE in cancer patients.

Methods

This IRB approved study evaluated oncology patients receiving anticoagulants via retrospective chart review from June 2013 to September 2015. Patients 18 years or older with active cancer diagnosis and a VTE with an expected three-month follow-up period were included. Patients had to be receiving enoxaparin, oral Xa inhibitor, or warfarin for at least 75% of total time on anticoagulants. Patients were excluded if they entered hospice, were pregnant, received systemic fibrinolytic therapy, had known adherence problems, experienced an underlying clotting or bleeding disorder, received a vena cava filter, received a mechanical heart valve, or received primary prophylactic anticoagulants. In the warfarin cohort with a goal INR of 2 to 3, the time in therapeutic range (TTR) was calculated using the Rosendaal method.[9]

The primary objective of this study was to evaluate the incidence of recurrent VTE in oncology patients within three months. Secondary objectives included VTE recurrence after three months, mortality and major bleeding within three months and beyond. Major bleeding was defined as bleeding leading to death, symptomatic bleeding in a critical area, bleeding resulting in >2 g/dL drop in hemoglobin or requiring ≥ 2 units of packed red blood cells, or bleeding requiring major medical or surgical intervention.

Statistical analyses

Characteristics of the sample were summarized using descriptive statistics. Means and standard deviations (or medians and ranges, if appropriate) were reported for continuous variables. Frequencies and percentages were reported for categorical variables. Variables were compared by anticoagulant regimen using the Kruskal–Wallis test, the chi-square test, Fisher's exact test, and one-way analysis of variance (ANOVA), as appropriate. If the three regimens were found significantly different, then the appropriate pairwise comparisons were made to determine which regimens differed from the others. A Kaplan–Meier plot was created for time to VTE recurrence and groups were compared using the log rank test. Statistical significance is indicated by $p < 0.05$.

Results

Over the study time period, 698 patients were identified for evaluation. We excluded 146 patients that entered hospice, 80 patients with inferior vena cava filter placed, 29 patients with an underlying clotting or bleeding disorder, 14 patients received the study anticoagulant for less than 75% of total anticoagulant time, 2 patients received systemic fibrinolytic therapy, 2 patients with mechanical heart valves, and 298 patients with incomplete data. Ultimately, 127 patients were included in our study with 23 enoxaparin patients, 56 warfarin, and 48 (44 rivaroxaban and 4 apixaban) DOAC patients (Table 1). Among the study population, 54% were female and 46% male. Warfarin patients on average were 10 years older compared to the other groups; pairwise ANOVA tests found that warfarin differed from DOAC ($p < 0.0001$) and enoxaparin ($p = 0.0005$). With respect to weight, the warfarin patients differed from DOAC ($p < 0.0001$) and enoxaparin groups ($p = 0.0027$), whereas the DOAC and enoxaparin groups were not

Table 1. Patient characteristics.

Characteristic	Enoxaparin (n = 23)	Warfarin (n = 56)	DOAC (n = 48)
Age (years)			
Mean ± SD	62.4 ± 13.9	72.6 ± 10.2	62 ± 13.8
Sex			
Female	14 (61)	31 (55)	24 (50)
Weight (kg)			
Median (range)	64.5 (50–113)	79.5 (49–178)	83.0 (50–164)
Ethnicity, N (%)			
Caucasian	16 (70)	45 (80)	32 (67)
African American	6 (26)	9 (16)	10 (21)
Hispanic	–	2 (4)	5 (10)
Asian	1 (4)	–	1 (2)
Initial VTE event, N (%)			
DVT	9 (39)	26 (46)	17 (35)
PE	11 (48)	18 (32)	23 (48)
PE & DVT	3 (13)	12 (21)	8 (17)
Presence of metastases, N (%)			
Yes	16 (70)	15 (27)	16 (33)
Brain metastases			
Known presence	4 (17)	2 (4)	2 (4)
Length of anticoagulation, days			
Median (range)	136 (2–590)	446 (33–2144)	204 (63–708)

DOAC: direct oral anticoagulant; SD: standard deviation; VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism.

Table 2. Active cancer diagnosis at initial venous thromboembolism event.

Cancer diagnosis	Enoxaparin (n = 23), N (%)	Warfarin (n = 56), N (%)	DOAC (n = 48), N (%)
Lung	10 (43)	9 (16)	8 (17)
Colorectal	3 (13)	9 (16)	6 (13)
Breast	2 (9)	7 (13)	9 (17)
Gynecologic	5 (22)	4 (7)	7 (15)
Prostate	1 (4)	7 (13)	5 (10)
Miscellaneous	2 (9)	20 (35)	13 (28)

DOAC: direct oral anticoagulant.

Table 3. Chemotherapy regimen at initial venous thromboembolism event.

Chemotherapy regimen at initial VTE (%)	Enoxaparin (n = 23), N (%)	Warfarin (n = 56), N (%)	DOAC (n = 48), N (%)
Platinum, taxane	4 (17)	2 (4)	4 (8)
Miscellaneous platinum containing regimens	3 (13)	5 (9)	11 (23)
Capecitabine or 5-FU alone	2 (9)	2 (4)	4 (8)
Bevacizumab containing regimens	2 (9)	–	3 (6)
Hormonal therapy	2 (9)	3 (5)	4 (8)
Miscellaneous	6 (26)	8 (14)	8 (17)
None	4 (17)	36 (64)	14 (29)

DOAC: direct oral anticoagulant; Platinum: carboplatin, cisplatin, or oxaliplatin; Taxane: paclitaxel or docetaxel; 5-FU: fluorouracil.

different ($p = 0.90$), using pairwise Kruskal–Wallis tests.

Of the 24 cancer locations reported, the three most common were lung (21%), colorectal (14%), and breast (14%). Enoxaparin group contained 43% lung cancer patients compared with only 17% and 16% in the DOAC and warfarin groups, respectively (Table 2).

Overall 57% of the patients presented with their initial VTE while receiving concomitant chemotherapy or hormonal therapy. Of that group, 83% of the enoxaparin group had their initial VTE while on therapy compared to 71% in the DOAC group and only 36% in the warfarin arm (Table 3). During the recurrent VTE phase, 56% of study groups were receiving concomitant chemotherapy.

At three months after initial VTE occurrence, the VTE recurrence rates were similar between cohorts (Table 4). One patient presented with a recurrent pulmonary embolism (PE) in the enoxaparin cohort (4.3%), two patients (one with a recurrent deep venous thrombosis (DVT) and another with a recurrent PE) in the warfarin cohort (3.6%), and one DOAC patient presented with a recurrent DVT (2.1%). Fisher's exact detected no significant difference was detected (p = 0.8319). At six months, the VTE recurrence rate in the enoxaparin arm experienced a 13% compared to 5.4% with warfarin and 2.1% with DOAC (p = 0.73). When evaluating the VTE recurrence during the entire data set, the DOAC cohort had an 8.3% recurrence rate while the warfarin and enoxaparin cohorts 12.5% and 21.7%, respectively (Table 4). The median time to recurrence was 125 days in the enoxaparin cohort compared with 210 days with warfarin and 206 days with DOAC. Kaplan-Meier plot analysis showed no significant differences in VTE recurrence over time amongst the three groups (Figure 1; p = 0.10)

Table 4. Recurrent venous thromboembolism.

	Enoxaparin (n = 23), N (%)	Warfarin (n = 56), N (%)	DOAC (n = 48), N (%)
Recurrent VTE at 0–3 months			
Total	1 (4.4)	2 (3.6)	–
DVT		1	
PE	1	1	
Recurrent VTE at 0–6 months			
Total	3 (13)	3 (5.4)	1 (2.1)
DVT	1	2	1
PE	1	1	
DVT/PE	1		
Recurrent VTE, 0 to >6 months			
Total	5 (21.7)	7 (12.5)	4 (8.3)
DVT	2	5	3
PE	2	2	1
DVT/PE	1	–	–
Time to recurrent VTE (days), median (range)	125 (86–628)	210 (63–990)	206 (94–312)

No statistically significant differences between the groups at three and six months.
DOAC: direct oral anticoagulants; VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism.

In the warfarin patients with a goal INR of 2 to 3, the TTR at three months, six months, and the complete data set had a mean (±SD) TTR of 46.7% ± 19.6, 48.6% ± 18.4, and 53.7% ± 17.4, respectively.

Major bleeding rates are displayed in Table 5. The rate of major bleeding was highest in the warfarin cohort (7.1%) compared to the DOAC or enoxaparin cohorts, 6.3% and 4.4%, respectively (p = 1.000). No patient with brain metastases or a brain primary had a major bleeding event.

Overall mortality is depicted in Table 5 in which the patients in the enoxaparin arm experience a higher rate of death compared with the other arms. At three

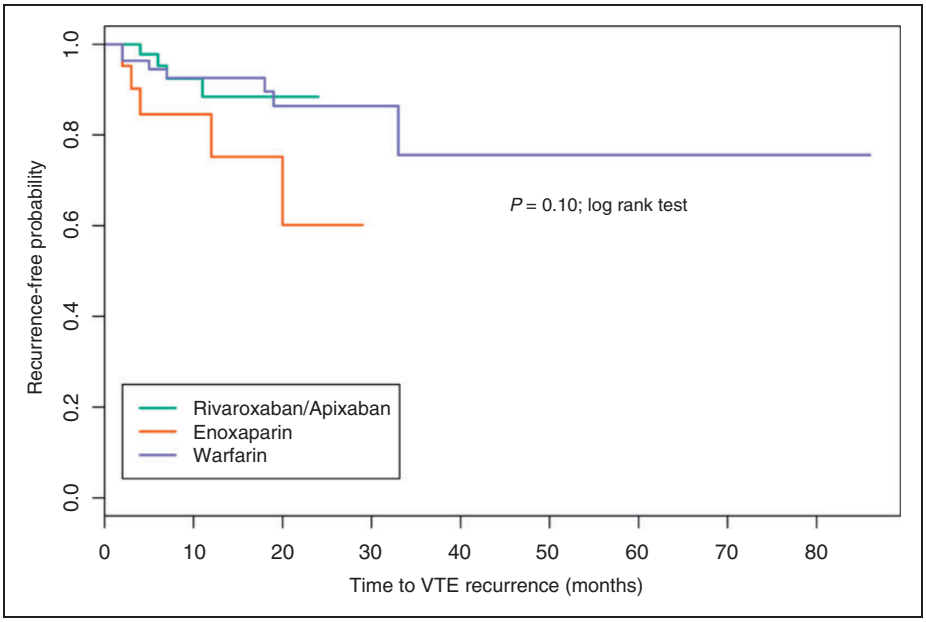

Figure 1. Time to venous thromboembolism (VTE) recurrence.
P = 0.10; log rank test

months, no death was noted in the DOAC cohort while 3.6% and 17.4% of patients died in the warfarin and enoxaparin cohorts, respectively. Over the entire study period, 56.5% of the enoxaparin group died compared with 23.2% and 14.6% of the warfarin and DOAC groups, respectively ($p = 0.0007$). The DOAC group and the warfarin group were not statistically different ($p = 0.2656$).

Discussion

In cancer patients with active malignancies, recurrent VTE is a potential risk that may impact morbidity and mortality. From this evaluation, there is a low rate of VTE recurrence at three months in cancer patients receiving a DOAC, warfarin, or enoxaparin. The recurrence rate in the DOAC cohort is similar to other retrospective or pooled-analyses in oncology patients (Table 6).[10–13]

In terms of safety, only one patient had a major bleed at the three-month period (Table 5). The enoxaparin lung cancer patient developed a noncritical subdural bleed. As time progressed seven more patients eventually developed a major bleed. In the warfarin group, four patients had major bleeds with two patients having INRs greater than 3 after receiving over three months of therapy. Three patients developed gastrointestinal (GI) bleeds and one patient suffered a noncritical subdural bleed in a prostate cancer patient who fell with an INR less than 2. Unfortunately, one warfarin patient who presented with an elevated INR greater than 3 died from the GI bleed. In the DOAC group, three patients without known kidney disease had major bleeding. One apixaban patient developed a GI bleed and two rivaroxaban patients with one having hematuria and the other patient with vaginal bleeding in a cervical cancer patient.

The rate of major bleeding with DOACs seen in our trial was higher than the rates seen from other retrospective or pooled-analyses (Table 6).[10–13] Our major bleeding rates ranged from 4.2 to 7.1% during the six-month period; however in Table 6, major bleeds were seen in up to 5% of the patients. Explanations for this difference would be the small sample size of our current trial, the low warfarin TTR, unknown adherence issues, concomitant anti-platelet therapy, and the patient population. Of note, none of the patients who experienced a major bleed in this study had known brain metastases or a brain primary tumor.

An interesting finding in our study was that the warfarin TTR was variable throughout the different time periods of three months, six months, and the entire data set, ranging from 47 to 54%. This TTR is lower than a meta-analysis of 40 studies consisting of more than 26,000 participants showing achieved TTR ranges from 56% to 75% in patients receiving warfarin for a VTE regardless of oncology status.[14] In comparison to the trial by Lee and colleagues, their TTR was 46% and the incidence of recurrent VTE at six months was 15.7%.[15] The VTE recurrent rate of our warfarin cohort was 5.4% at six months with a TTR of 49%.

Table 5. Mortality and major bleeding.

	Enoxaparin (n = 23), N (%)	Warfarin (n = 56), N (%)	DOAC (n = 48), N (%)
Mortality			
0–3 months	4 (17.4)	2 (3.6)	–
0–6 months	9 (39.1)	4 (7.1)	5 (10.4)
0 to >6 months	13 (56.5)	13 (23.2)	7 (14.6)
Major bleeding			
0–3 months	1 (4.2)	–	–
0–6 months	1 (4.2)	4 (7.1)	3 (6.2)
0 to >6 months	1 (4.2)	4 (7.1)	3 (6.2)

DOAC: direct oral anticoagulants.

Table 6. Risk of recurrent venous thromboembolism and major bleeding in active cancer patients receiving rivaroxaban or apixaban.

Reference	Anticoagulant	Recurrent VTE (%)	Cutoff point for recurrent VTE	Major bleeding (%)
Agnelli et al.[10]	Apixaban	3/81 (3.7)	6 months	2/87 (2.3)
	Enoxaparin/warfarin	5/78 (6.4)	6 months	4/80 (5)
Bott-Kitslaar et al.[11]	Rivaroxaban	4/118 (3.4)	3 months	3/118 (2.5)
Prins et al.[12]	Rivaroxaban	6/258 (2.3)	Not defined[a]	5/257 (1.9)
	Enoxaparin/warfarin	8/204 (3.9)	Not defined[a]	8/202 (4)
Wells et al.[13]	Rivaroxaban	9/237 (3.8)	Not defined[b]	3/237 (1.3)

VTE: venous thromboembolism.
[a]Over 60% of patients had a treatment duration of six months.
[b]Median time to VTE recurrence was 113 days.

It is curious why the Lee trial had almost three times greater recurrence rate compared to our evaluation and other trials. The incidence of recurrent VTE in cancer patients receiving warfarin in our trial (5.4%) is similar to recurrence rate (2.8 to 6.4%) seen in other warfarin containing trials.[5–7,10,12]

Over the entire study period, 56.5% of the enoxaparin group died compared with 23.2% and 14.6% of the warfarin and DOAC groups, respectively. This difference can be explained by the presence of more lung cancer patients (43%) in the enoxaparin group compared with only 16–17% in the other groups. In addition, 70% of the enoxaparin group had metastatic disease compared with 27–33% in the comparative arms.

Limitations of our study include that it is a single center evaluation, small sample size, and its retrospective nature. However, our study is comprised of real-world data in cancer patients without the restrictions imposed by randomized trials. The DOAC arm had a median follow-up of 318 days (range 90–736 days) after the initial VTE event with a VTE recurrence rate of 2.1% at six months. Our data suggest that DOACs may be used for extended periods of time in patients with cancer in a real-world setting.

The use of DOACs for the secondary prevention of VTE in oncology patients would be a step in right direction. These agents are once to twice a day and do not require intensive INR monitoring or require injections. The clinician needs to be mindful of their drug interaction potential and adjust or avoid DOACs in patients with renal dysfunction. The use of warfarin and adjusted dose LMWHs are still great options in those patients with renal dysfunction. In addition, those patients with potential drug interactions still have the option of LMWH products.

An interesting on-going prospective study is the CANVAS trial.[16] It is a randomized, interventional study to determine the effectiveness of LMWH, warfarin, or a DOAC (either rivaroxaban, apixaban, edoxaban, or dabigatran) for preventing recurrent VTE in oncology patients. Their primary outcome measure is VTE recurrence at six months, and their secondary outcome measures include major bleeding, health-related quality of life, burden of anticoagulation therapy, and mortality. The results of this study may corroborate our findings.

Conclusion

Our current data suggest oral Xa inhibitors are a potential option for cancer patients with VTE. The benefits of low recurrence rates and major bleeding in a real-world setting are intriguing, but prospective, randomized, controlled trials are needed to confirm these results. The pending results of the CANVAS trial will be of interest to elucidate the role of oral Xa inhibitors for the prevention of VTE in cancer patients.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Deitcher SR. Cancer-related deep venous thrombosis: clinical importance, treatment challenges, and management strategies. *Semin Thromb Hemost* 2003; 29: 247–258.
2. Prandoni P, Falanga A and Piccioli A. Cancer and venous thromboembolism. *Lancet Oncol* 2005; 6: 401–410.
3. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore)* 1999; 78: 285–291.
4. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149: 315–352.
5. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499–2510.
6. EINSTEINPE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366: 1287–1297.
7. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; 369: 799–808.
8. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; 11: 21. DOI: 10.1186/1477-9560-11-21.
9. Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; 69: 236–239.
10. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost* 2015; 13: 2187–2191.
11. Bott-Kitslaar DM, Saadiq RA, McBane RD, et al. Efficacy and safety of rivaroxaban in patients with venous thromboembolism and active malignancy: a single-center registry. *Am J Med* 2016; 129: 615–619.
12. Prins MH, Lensing AWA, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism

in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol* 2014; 1: e37–46.
13. Wells PS, Theberge IA, Bowdridge JC, et al. PO-41 – Rivaroxaban is effective therapy for high risk cancer patients with venous thromboembolic disease. *Thromb Res* 2016; 140(Suppl 1): S191–S192.
14. Erkens PM, ten Cate H, Büller HR, et al. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. *PloS One* 2012; 7: e42269.
15. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349: 146–153.
16. Clinicaltrials.gov. Direct Oral Anticoagulants (DOACs) versus LMWH +/− warfarin for VTE in cancer (CANVAS), https://clinicaltrials.gov/ct2/show/NCT02744092 (2016, accessed 10 June 2017).