Treatment of Cancer-Associated Venous Thromboembolism: 12-month outcomes of the placebo versus rivaroxaban randomisation of the SELECT-D Trial. (SELECT-D: 12m)

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ESSENTIALS:

- The ideal duration of treatment for cancer-associated venous thromboembolism (VTE) is unknown
- Patients were randomised to rivaroxaban or placebo after approximately 6 months of anticoagulants
- There was a trend towards a reduction in VTE recurrence with rivaroxaban compared to placebo.
- The absence of residual deep vein thrombosis defined a low VTE recurrence risk group.

ABSTRACT

Background: The SELECT-D trial demonstrated reduction in recurrent venous thromboembolism (VTE) but increased bleeding with rivaroxaban compared to dalteparin for treatment of acute VTE in cancer patients, at 6 months. Uncertainty remains around optimal duration of anticoagulation.

Objectives: To assess VTE recurrence and bleeding, with anticoagulation or not, beyond 6 months

Patients/Methods: In SELECT-D, after 6 months of trial treatment for VTE, patients with active cancer and residual deep vein thrombosis (RDVT) or index pulmonary embolism (PE) were eligible for randomisation to a further 6 months of rivaroxaban or placebo. Patients with no RDVT stopped anticoagulation. Primary outcome was VTE recurrence at 12 months. The second randomisation closed prematurely due to low recruitment when 92 of the planned 300 patients were recruited.

Results: 92 of 136 eligible patients were randomised to rivaroxaban or placebo. The cumulative VTE recurrence after 6 months from the second randomisation, was 14% with placebo and 4% with rivaroxaban (Hazard Ratio 0.32; 95% CI 0.06-1.58). The major and clinically-relevant non-major bleeding rates were 0% and 0% with placebo; and 5% (95% CI 1-18%) and 4% (95% CI 1-17%) with rivaroxaban. In an exploratory analysis, 7 (15.2 %) of 46 placebo patients with RDVT or an index PE experienced recurrent VTE compared to none in the 35 patients in the RDVT-negative cohort (P=0.03).

Conclusion: The SELECT-D trial was underpowered to detect a statistically significant reduction in recurrent VTE with extended anticoagulation. The absence of RDVT and/or index PE, defined a population at low risk of recurrence.

KEYWORDS: Cancer-associated thrombosis; treatment duration; direct oral anticoagulant; venous thromboembolism recurrence; bleeding

INTRODUCTION

Venous thromboembolism (VTE) in cancer patients is a common occurrence and can be clinically challenging. In many countries, low molecular weight heparin (LMWH) has been the standard of care for the treatment and prevention of recurrent VTE in cancer for over 15 years (1, 2). Direct oral anticoagulants (DOACs) are emerging as an alternative treatment to LMWH for cancer patients with VTE based on the results of two recent randomised controlled trials (RCTs): the Hokusai VTE Cancer trial (3) and the SELECT-D trial (4). In the Hokusai VTE Cancer trial, initial dalteparin for at least 5 days followed by edoxaban was compared with dalteparin alone, both treatments intended for 6 to 12 months (3). The primary outcome was a composite of VTE recurrence and major bleeding at 12 months post-randomisation. Edoxaban was found to be non-inferior to dalteparin. At 12 months, the recurrent VTE rate was higher in the dalteparin arm than in the edoxaban arm and the rate of major bleeding was significantly lower with dalteparin compared to edoxaban. The excess of major bleeding with edoxaban was confined to patients with gastrointestinal cancer. (5). In the SELECT-D trial, patients received rivaroxaban or dalteparin for 6 months (4). Using rivaroxaban reduced the 6-month VTE recurrence rate compared to dalteparin (hazard ratio (HR) = 0.43; 95% confidence interval (CI) 0.19-0.99). The rate of major bleeding was similar between groups (HR=1.83; 95%CI 0.68-4.96), but more clinically relevant non-major bleeding (CRNMB) was experienced by patients receiving rivaroxaban compared to dalteparin (HR=3.76; 95% CI 1.63-8.69). A recent meta-analysis of the efficacy and safety of DOACs, vitamin K antagonists (VKAs) and LMWH in patients with cancer associated thrombosis (CAT) found only these two aforementioned studies comparing DOAC and LMWH (6).

The duration of anticoagulant treatment in cancer patients with acute VTE is an unanswered question. Clinical practice guidelines have recommended continuing treatment for patients with risk factors for VTE recurrence or progression, including the presence of metastases or ongoing chemotherapies (7). Duration of treatment was hitherto based on the duration of treatment utilised in randomised trials (usually 6 months); extrapolated from patients with unprovoked VTE and not on published data; the duration differed depending on the anticoagulants used and the clinical circumstances.

There are also some data to suggest that the absence of residual deep vein thrombosis (RDVT) on compression ultrasound (CUS) predicts a low risk group for recurrent VTE (8). Based on these considerations, the SELECT-D trial included a second randomisation designed to investigate this important question of the clinical course of VTE, with anticoagulation or not, beyond 6 months. Patients in SELECT-D who had the presence of RDVT at approximately 5.5 months after randomisation or whose index VTE was a pulmonary embolism (PE) i.e. patients deemed at higher risk of VTE, were randomly allocated to continue rivaroxaban or placebo. The absence of RDVT mandated discontinuing anticoagulant therapy at 6 months. Rivaroxaban was the anticoagulant of choice as we were able to guage the safety of rivaroxaban in the cancer population in the first six months post-randomisation. The focus of this manuscript is the clinical course of patients who entered the second randomisation.

METHODS

Study design and patient population

The SELECT-D trial design and the population including inclusion and exclusion criteria, have been previously defined (4). Briefly, patients with active cancer presenting with a primary objectively confirmed symptomatic lower-extremity proximal deep vein thrombosis (DVT), symptomatic or incidental PE, were randomised to dalteparin or rivaroxaban.

At around 5.5 months post randomisation, patients with an index DVT had a CUS to detect the absence or presence of a RDVT. If the CUS showed RDVT or if patients had presented with a PE, they were eligible to be randomly assigned to a further 6 months of rivaroxaban at 20mg orally once daily or placebo (second randomisation). To be eligible, patients should have received trial treatment for 6 months, not had a VTE recurrence, have an ECOG performance status of $\leq$2; and have adequate haematologic, hepatic, and renal function. A previous VTE in the first six months excluded patients from participating in the second randomisation. However, having a bleed was not an exclusion criterion, leaving the decision to futher randomise or not to the discretion of the clinician. Patients with an absence of RDVT were not eligible for the second randomizaiton and were mandated to discontinue anticoagulant therapy at 6 months.

All patients entering the first randomisation were assessed at 3-monthly intervals until month 12 and then 6-monthly until month 24. The trial was approved by the Coventry & Warwickshire Research Ethics Committee, the Health Research Agency and the Medicines and Healthcare Products Regulatory Agency, UK.

Random Assignment and Study Interventions

Patients consenting to the second randomisation were randomised centrally by telephoning Warwick Clinical Trials Unit and randomly assigned to rivaroxaban or placebo in a 1:1 ratio using a computer-based minimisation algorithm. Patients were stratified by the trial treatment during the first 6 months of the trial, type of VTE, risk of clotting by tumour type, stage of disease and platelet count, at the time of the second randomisation.

Rivaroxaban and placebo were supplied by Bayer AG. The tablets were packaged, labelled and distributed by an independent company; the tablets and packaging were indistinguishable by patient or clinician. Each bottle of tablets had a unique drug pack number, allocated to a patient by the randomisation system. Emergency unblinding could be requested on safety grounds by the treating clinician by contacting an independent Emergency team. The treatment allocation was blinded to the patient, clinician and those evaluating outcomes. The treatment allocation was only unblinded to the trial statistician at the of the final analysis.

Outcomes

The predefined primary outcome for the patients entering the SELECT-D second randomisation was VTE recurrence at 12 months post first randomisation. Reported VTE events were adjudicated by a central committee unaware of treatment allocation after the last patient was entered. Predefined secondary outcomes for SELECT-D comprised major bleeding (9); CRNMB (10), overall survival and VTE recurrence at 12 months for the subgroup of patients with no RDVT. Bleeding events were adjudicated by an independent committee of experienced clinicians unaware of treatment allocation.

Statistical Considerations

In SELECT-D, the assumption was made that a sample size of 530 patients would allow sufficient numbers (300 in total) to continue onto the second randomisation to provide estimates for a future definitive duration study. However, the second randomisation closed on 1st September 2016 with only 92 patients recruited, based on a recommendation from the Data and Safety Monitoring Committee who recognised the futility of continued recruitment. Any patient randomised after 1st September 2016 was not eligible for the second randomisation. In addition, the protocol was also amended to exclude patients with esophogeal and gastro-esophogeal

cancer because of a bleeding signal. This exclusion did not effect the patients entering the second randomisation.

For the patients in the second randomisation, the time to a VTE recurrence was calculated from the date of second randomisation to the date of first VTE recurrence event, or censored at the date last known to be VTE recurrence-free or at 6 months post entry to second randomisation, whichever came first. Overall survival was calculated from the date of second randomisation to the date of death from any cause, or censored at the date last known to be alive or at 6 months.

Cumulative incidence curves for the time to a VTE recurrence were estimated using the complement of the Kaplan-Meier estimates. A competing risk analysis was performed using the cumulative incidence competing risk method to account for death as a competing risk (11). Kaplan-Meier estimates were also obtained for bleeding and overall survival. A Cox model was used to obtain hazard ratios (HRs) and associated 95% confidence interval (CIs). An exploratory comparison of patients with no RDVT and those with RDVT or PE on the placebo arm in terms of VTE recurrence was performed using the log rank test.

All analyses were performed on an intention-to-treat basis with the SAS statistical package version 9.4. SELECT-D was not powered for statistical testing between trial arms at 12 months.

RESULTS

Between 6th September 2013 and 22nd December 2016, 406 patients were randomised into the SELECT-D trial. Two-hundred fourteen patients (53%) were males, the median age was 67 years (range 22-87 years), 234 (58%) had metastatic disease and 211 (52%) patients had an incidental PE (Table 1). The primary analyses of recurrent VTE and bleeding at 6 months have been published (4).

A total of 371 patients were randomised into the SELECT-D trial before participation in the second randomisation was closed; the remaining 35 patients were not considered for the second randomisation. Of the 371 patients, 94 (25%) died, 33 (9%) withdrew before 6 months, 10 (3%) had a DVT on entry but were not assessed for RDVT (as they had already stopped anticoagulation, had recurrent VTE or were found to be ineligible), 35 (9%) were assessed and found to be RDVT negative, leaving 199 (54%) patients with RDVT on CUS or PE at presentation to be considered for the second randomisation (Figure 1). Of these, 63 were excluded as they did not meet the inclusion criteria, resulting in 136 patients eligible for the second randomisation.

Forty-four eligible patients declined to participate or their clinicians advised them not to (Figure 1); 4 (9%) had an index DVT, 29 (66%) had an incidental PE and 11 (35%) had a sympomatic PE. There were 2 VTE recurrences and 6 deaths in this patient group between 6 and 12 months post first randomisation.

Only 92 patients were randomised (46 to rivaroxaban and 46 to placebo). The patients entering the second randomisation tended to have better ECOG performance status, early/locally advanced disease, incidental PE, and a lower risk of VTE tumour type compared to those 107 that were not randomised (Table 1). The patient and clinical characteristics were reasonably comparable between randomised treatment arms. (Table 2). Four patients were randomised despite having a bleed (1 major [haematoma] and 3 CRNMB) on anticoagulation within the first six months of the trial.

Fifty-eight (63%) of the 92 patients participating in the second randomisation completed 6 months of additional trial treatment, six (7%) failed to start the trial treatment and 28 (30%) stopped treatment early due to various factors including death, VTE recurrence, bleeding and clinical decision (Figure 1). Two patients had their second randomised treatment unblinded in order to treat the patient safely; one patient had a pleural effusion and the other, a haematemesis associated with grade 4 thrombocytopenia.

There were six patients on the placebo arm and two patients on the rivaroxaban arm that had VTE recurrence within 6 months from second randomisation. Two of the placebo events were incidental PEs . The Kaplan-Meier estimates of VTE recurrence were 14% (95% CI 7-29%) for patients on the placebo arm and 4% (95% CI 1-16%) for patients on the rivaroxaban arm at 6 months from second randomisation (HR=0.32; 95% CI 0.06-1.58, Figure 2). The incidence of VTE recurrence per subject month at risk for months 1-6 from the second randomisation was 3.0% (6/237) for the placebo arm patients and 0.8% (2/246) for those on rivaroxaban. There was no significant interaction between the first and second treatment arms (p=0.99) in terms of VTE recurrence i.e. the initial anticoagulation allocation did not impact on the VTE recurrence outcomes for patients in the second randomisation.

Two patients, one with lung cancer; one with colorectal cancer, on the rivaroxaban arm experienced major bleeds (both upper gastrointestinal haemorrhages) at 1 month and 6 months from the second randomisation, respectively; resulting in a major bleeding rate of 5% (95% CI 1-18%). Neither resulted in death. The major bleeding rate was 0% on the placebo arm. An

additional two patients on the rivaroxaban arm had CRNMBs at 1 and 3 months from second randomisation for a 4% (95% CI 1-17%) CRNMB rate, due to bruising of the eye (gastric primary) and bleeding from the nipple (breast primary) respectively. The CRNMB rate was 0% on the placebo arm.

Of the 92 patients participating in the second randomisation, 11 patients died of their cancer (five on the placebo arm; six on the rivaroxaban arm) within 6 months of second randomisation. The overall survival rate for those patients on the rivaroxaban arm at 6 months from second randomisation was 89% (95% CI 75-95%) and 87% (95% CI 73-94%) for those on the placebo arm (HR=1.16; 95% CI 0.36-3.81).

Of the 35 patients who had no RDVT on CUS around 5.5 months from the first randomisation and for whom the protocol specified stopping anticoagulation at 6 months, six had additional anticoagulation treatment beyond 6 months, advised by their clinicians. Three of the six patients had already switched from trial treatment to alternative anticoagulation (one at 1 month, and two at 5 months from first randomisation). For the other three patients, their hospital/clinician reported that they considered it appropriate to continue on anticoagulation as patients had active cancer and therefore still at risk due to the disease. None of the 35 RDVT-negative patients experienced a VTE recurrence between 6 and 12 months from trial entry; four patients died within this time frame (three as a result of their cancer and one from kidney failure). In an exploratory comparison, patients with no RDVT were significantly less likely to have a VTE recurrence than the RDVT positive and PE patients receiving placebo (log rank p=0.03).

DISCUSSION

There is limited evidence on the duration of anticoagulation specifically in cancer patients with VTE. Clinical Practice Guidelines have recommended 6 months of anticoagulant therapy (7). Beyond the initial six months, guidelines recommend that anticoagulation should be considered in patients with active cancer, such as those on chemotherapy treatment (7, 12). The clinical course of patients in SELECT-D who received anticoagulation or not between 6 and 12 months has provided us with the opportunity for potential insights on the duration of anticoagulation in cancer patients.

For those patients who participated in the second randomisation, there was a higher VTE recurrence rate in the placebo arm in comparison to the rivaroxaban arm, but the difference was not statistically significant. The failure to detect a significant difference between 6 and 12 months of anticoagulation is likely to be the result of a lack of power from the small sample size. Extended treatment comes with a potential cost of bleeding. Major bleeding and CRNMBs on rivaroxaban in patients randomised at 6 months was 5% and 4% respectively. There were no major or CRNMBs for patients on placebo between 6 and 12 months.

In the venous thrombosis literature, there is a school of thought that the duration of anticoagulant therapy can be tailored to the underlying risk of thrombosis i.e. provoked or unprovoked (13). In planning SELECT-D, we hypothesized that cancer patients with VTE who had received approximately 6 months of anticoagulant treatment could be stratified into low and high risk groups for recurrent VTE based on underlying risk for thrombosis. RDVT was chosen as the risk stratification approach at the time of the trial design as the results of the EXTENDED Cancer-DACUS had demonstrated that in patients without RVT, a short period of treatment with a LMWH is sufficient. In those with persistent RVT, treatment extended to 2 years substantially reduced, but did not eliminate, the risk of recurrent thrombosis (14). We also postulated that having had an index PE also predicted for recurrence. In the group of patients whom we postulated would be at low risk of recurrent VTE i.e. RDVT-negative (8), there were no subsequent events after 6 months. In contrast, there was a significant increase in recurrent VTE in the placebo patients who were deemed at higher risk of VTE defined by RDVT positivity or having an index PE. This exploratory analysis supports the hypothesis that the RDVT negative patients are a low risk group for VTE recurrence. However a much larger cohort would be required to provide robust evidence that risk stratification can help tailor duration of anticoagulant therapy.

For patients participating in the first and second randomisations, there was a similar major bleeding rate on rivaroxaban between the first and second 6 months. The more than 3-fold reduction in CRNMBs between the second 6 months and first 6 months for the respective periods, suggests that patients entering the second 6-month period were fitter and at lower bleeding risk.

Forty-four percent of the initial 406 patients stayed on trial for 12 months; the attrition rate was higher in the first 6 months of the study. The survival rates were considerably higher for those entering the second randomisation, confirming those patients had a more favourable prognosis. In addition, 50% of all enrolled patients had an incidental PE, whereas this increased to 66% of patients in the second randomisation, which may also reflect a more favourable attitude (physician and/or patient) towards randomizing a patient who has not associated their symptoms to a PE.

Although the acceptance rate for those patients approached for the second randomisation was reasonably high at 68%, the number of eligible patients was lower than predicted. Twenty-five percent of patients had died and 9% had withdrawn from the trial before the 6-month time point. Clinicians alongside the patients were choosing whether to enter the second randomisation, mostly likely on the basis of clinical factors, reasons similar to a UK anticoagulation duration study in cancer patients which failed to recruit (15). However, the type of VTE at trial entry and the clinical outcomes for the 44 eligible patients who did not participate in the second randomisation were similar to the 92 who did participate.

Hokusai VTE Cancer (n=1050) and SELECT-D (n=406) have recently driven the use of DOACs for selected cancer patients with VTE. The 12-month trial outcomes for both studies are not directly comparable; nevertheless, the 12-month VTE recurrence for patients on a DOAC are similar; recurrent VTE occurred in 7.9% in the edoxaban group in the Hokusai VTE Cancer trial and 10% of those randomised initially to rivaroxaban in SELECT-D. Similarly, major bleeding at 12 months, occurred in 6.9% of the edoxaban group and 5% in the rivaroxaban group. The heterogeneous nature of the anticoagulation over time should be noted; 46 patients in SELECT-D were randomised to 6 months of placebo and 16 patients chose not to continue with anticoagulation, thus having no active treatment, which may explain the slightly higher VTE recurrence rate and lower bleeding rate with SELECT-D in comparison to the rates in the Hokusai VTE Cancer trial.

SELECT-D is not without limitations. It was small in size, the patient population was heterogeneous and potentially biased toward being the fitter patients that successfully completed the intitial 6 month course of anticoagulation, and clinicans did not always follow the study protocol. Furthermore, as SELECT-D was open to all cancer types and only stage of

disease could be accounted for in the stratification due to the sample size, there was an imbalance between treatment arms for some cancer types in particular colorectal cancer and ovarian cancer, which could have confounded the results.

It is unclear whether there will ever be a large randomised trial that specifically addresses the duration of anticoagulant therapy in cancer patients. Meanwhile, correlative biomarker research may improve risk stratification (16). In concusion, individualised, informed decision-making between patient and clinician based on the trade-off of the risk of continuing thrombosis, and bleeding is recommended. SELECT-D provides numerical values of the risk of recurrent VTE as well as risk of major bleeding and CRNMB when anticoagulation is continued beyond six months. These data can be helpful for informed decision making.

Addendum: Authorship Details

A Young, A Marshall, M Levine, O Chapman, A Lokare, JA Dunn, FDR Hobbs, S Petrou, V Wilkie, A Kakkar were responsible for the conception and design. J Thirlwall, C Hill, D Hale, K French, A Maraveyas, A Arif were responsible for the collection and assembly of data. A Marshall and M Maredza were responsible for the data analysis. A Marshall, A Young and M Levine were responsible for the drafting of the manuscript. All authors contributed to the interpretation and reviewing of the manuscript.

Conflicts of Interest

Andrea Marshall; Research Funding: Bayer AG (Inst)
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Danielle Hale; Research Funding: Bayer AG (Inst)
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Karen French; Honoraria from Bayer, Bristol-Myers Squibb and Aspen
Ajay Kakkar;
Honoraria: Bayer, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, Janssen, Verseon
Consulting or Advisory Role: Bayer, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, Janssen,

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Anand Lokare; no relationship to disclose
Anthony Maraveyas
Honoraria: Bayer AG, Bristol Myers Squibb
Consulting or Advisory Role: Bayer AG, Bristol Myers Squibb Speaker's Bureau: Bristol Myers Squibb, Pfizer

Oliver Chapman; no relationship to disclose
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Mandy Maredza; *Research Funding: Bayer AG (Inst)*
F.D. Richard Hobbs *Honoraria: Bayer, Boehringer Ingelheim*
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Role of the funding source

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REFERENCES

1. Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, et al. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomised Clinical Trial. Jama. 2015;314(7):677-86.
2. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. The New England journal of medicine. 2003;349(2):146-53.
3. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. The New England journal of medicine. 2018;378(7):615-24.
4. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomised Trial (SELECT-D). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(20):2017-23.
5. Kraaijpoel N, Di Nisio M, Mulder FI, van Es N, Beyer-Westendorf J, Carrier M, et al. Clinical Impact of Bleeding in Cancer-Associated Venous Thromboembolism: Results from the Hokusai VTE Cancer Study. Thrombosis and haemostasis. 2018;118(8):1439-49.
6. Rossel A, Robert-Ebadi H, Combescure C, Grosgurin O, Stirnemann J, Addeo A, et al. Anticoagulant therapy for acute venous thrombo-embolism in cancer patients: A systematic review and network meta-analysis. PloS one. 2019;14(3):e0213940.
7. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Bockenstedt PL, Chesney C, et al. NCCN Guidelines Insights: Cancer-Associated Venous Thromboembolic Disease, Version 2.2018. Journal of the National Comprehensive Cancer Network : JNCCN. 2018;16(11):1289-303.
8. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, Imberti D, et al. Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(32):3607-12.
9. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis : JTH. 2005;3(4):692-4.
10. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. The New England journal of medicine. 2010;363(26):2499-510.
11. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in medicine. 1999;18(6):695-706.
12. Watson HG, Keeling DM, Laffan M, Tait RC, Makris M. Guideline on aspects of cancer-related venous thrombosis. British journal of haematology. 2015;170(5):640-8.
13. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. Journal of thrombosis and haemostasis : JTH. 2016;14(7):1480-3.
14. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(17):2405-9.
15. Noble SI, Nelson A, Fitzmaurice D, al e. A feasibility study to inform the design of a randomised controlled trial to identify the most clinically effective and cost-effective length of Anticoagulation with Low-molecular-weight heparin in the treatment of Cancer-Associated Thrombosis (ALICAT)2015 1st February 2019. Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta19830/#/abstract.
16. Yamanaka Y, Sawai Y, Nomura S. Platelet-Derived Microparticles are an Important Biomarker in Patients with Cancer-Associated Thrombosis. International Journal of General Medicine. 2019;12:491–7.

17. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, et al. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. Circulation. 2012;126(4):448-54.

Table 1: Baseline patient characteristics for a) all 406 SELECT-D trial patients; b) those 92 patients that entered the second randomisation; c) those 107 with residual deep vein thrombosis (RDVT) positive or a pulmonary embolism (PE) at presentation that did not go onto the second randomisation ; and d) the 35 RDVT negative patients.

Characteristic	All patients		Second randomisation		RDVT positive/PE but not randomised		RDVT negative	
	n	%	n	%	n	%	n	%
Number of patients	406		92		107		35	
Sex								
Male	214	53	47	51	56	52	18	51
Female	192	47	45	49	51	48	17	49
Age years (Median(Range))	67 (22-87)		68 (30-87)		68 (42-85)		67 (34-82)	
BMI (Median(Range))	26.7 (14.9-50.4)		27.7 (17.8-42.9)		28.5 (15.1-50.4)		28.1 (16.8-46.2)	
ECOG performance status								
0	120	30	36	39	31	29	13	37
1	185	46	40	44	53	49	16	46
2	95	23	14	15	22	21	5	14
Unknown	6	1	2	2	1	1	1	3
Ethnicity								
White	389	95	88	96	104	97	33	94
Mixed	3	1	1	1	1	1	1	3
Asian or British Asian	3	1	2	2	1	1	0	0
Black or Black British	6	1	1	1	1	1	0	0
Chinese or other ethnic group	3	1	0	0	0	0	0	0
Unknown	2	1	0	0	0	0	1	3
STRATIFICATION VARIABLES								
Stage of disease at randomisation								
Early/locally advanced disease	164	40	44	48	46	43	25	71
Metastatic disease	232	57	44	48	57	53	10	29
Haematological malignancy	10	3	4	4	4	4	0	0
Platelet count at randomisation								
<=350,000/µl	336	83	84	91	89	83	32	91

>350,000/µl	70	17	8	9	18	17	3	9
Type of VTE								
Symptomatic VTE	195	48	32	35	40	38	35	100
PE	80	20	22	24	26	26	0	0
DVT	110	27	10	11	14	12	35	100
PE and DVT	4	1	0	0	0	0	0	0
Unknown	1	<1	0	0	0	0	0	0
Incidental PE	211	52	60	65	67	62	0	0
Risk of clotting by tumour type								
High risk	339	84	72	78	90	84	28	80
Low risk	67	16	20	22	17	16	7	20
First randomised trial treatment								
Dalteparin	203	50	42	46	55	51	17	49
Rivaroxaban	203	50	50	54	52	49	18	51
Tumour type								
Bladder	14	3	3	3	5	5	1	3
Breast	41	10	16	16	10	9	5	14
Brain	3	1	0	0	0	0	1	3
Cancer Unknown Primary (CUP)	6	2	2	2	0	0	0	0
Chronic Lymphoid Leukaemia	4	1	2	2	1	1	1	3
Colorectal	102	25	20	22	33	31	14	40
Gallbladder	4	1	0	0	0	0	0	0
Gastric	12	3	3	3	4	4	0	0
Gynaecological	13	3	2	2	5	5	0	0
Kidney	7	2	3	3	2	2	1	3
Lung	47	12	8	9	11	10	2	6
Lymphoma	22	5	10	11	5	5	1	3
Multiple myeloma	5	1	2	2	2	2	0	0
Oesophageal/gastro-oesophageal	29	7	7	8	4	4	3	8
Ovarian	30	7	6	7	10	9	2	6
Pancreatic	30	7	2	2	6	5	0	0
Prostate	21	5	5	6	7	6	0	0

Sarcoma	2	1	0	0	0	0	0	0
Other	12	3	1	1	2	2	3	8
Unknown	2	1	0	0	0	0	1	3
Characteristics at 5.5. months								
ECOG performance status at 5.5 months								
0	100	25	43	47	27	25	15	43
1	96	24	36	39	34	32	14	40
2	24	6	7	8	13	12	2	6
3	14	3	1	1	7	7	3	8
4	1	<1	0	0	1	1	0	0
Unknown	171	42	5	5	25	23	1	3
Stage of disease at 5.5. months								
Early/locally advanced disease	158	39	44	48	44	41	24	69
Metastatic disease	238	59	44	48	59	55	11	31
Haematological malignancy	10	2	4	4	4	4	0	0
Current status of cancer								
Complete Remission	35	9	15	16	13	12	4	11
Partial response	34	8	18	20	9	9	4	11
Stable disease	61	15	21	23	23	21	7	20
Progressive disease	48	12	10	11	23	21	8	23
Non-evaluable	6	1	3	3	2	2	1	3
Unknown	222	55	25	27	37	35	11	32

Table 2: Patient characteristics by the second randomisation trial allocation

Characteristic	Placebo		Rivaroxaban		Total	
	n	%	n	%	n	%
Number randomised	46	50	46	50	92	
Sex						
Male	18	39	29	63	47	51
Female	28	61	17	37	45	49
Age years (Median(Range))	68 (30-87)		68(32-87)		68 (30-87)	
BMI (Median(Range))	28.7 (17.8-42.9)		25.8 (18.4-41.6)		27.7 (17.8-42.9)	
ECOG performance status						
0	20	44	16	35	36	39
1	17	37	23	50	40	44
2	7	15	7	15	14	15
Unknown	2	4	0	0	2	2
Ethnicity						
White	43	94	45	98	88	96
Mixed	0	0	1	2	1	1
Asian or British Asian	2	4	0	0	2	2
Black or Black British	1	2	0	0	1	1
STRATIFICATION VARIABLES						
Stage of disease at second randomisation						
Early/locally advanced disease	24	52	20	43	44	48
Metastatic disease	21	46	23	50	44	48
Haematological malignancy	1	2	3	7	4	4
Platelet count at second randomisation						
<=350,000/µl	42	91	42	91	84	91
>350,000/µl	4	9	4	9	8	9
Type of VTE						
Symptomatic VTE	16	35	16	35	32	35
PE	10	22	12	26	22	24

DVT	6	13	4	9	10	11
Incidental PE	30	65	30	65	60	65
Risk of clotting by tumour type						
High risk	36	78	36	78	72	78
Low risk	10	22	10	22	20	22
First randomised trial treatment						
Dalteparin	21	46	21	46	42	46
Rivaroxaban	25	54	25	54	50	54
Tumour type						
Bladder	1	2	2	4	3	3
Breast	9	18	7	15	16	16
Cancer Unknown Primary	1	2	1	2	2	2
Chronic Lymphoid Leukaemia	0	0	2	4	2	2
Colorectal	6	13	14	31	20	22
Gastric	2	4	1	2	3	3
Gynaecological	2	4	0	0	2	2
Kidney	2	4	1	2	3	3
Lung	3	7	5	11	8	9
Lymphoma	4	9	6	13	10	11
Multiple myeloma	1	2	1	2	2	2
Oesophageal/gastro-oesophageal	4	9	3	7	7	8
Ovarian	6	13	0	0	6	7
Pancreatic	2	4	0	0	2	2
Prostate	2	4	3	7	5	6
Cholangiocarcinoma	1	2	0	0	1	1
Ottawa score*						
Low risk (<0)	10	22	16	35	26	28
Moderate risk (=0)	25	54	22	48	47	51
High risk (>1)	11	24	8	17	19	21

*Louzada et al. Circulation 2012 (17)

FIGURE LEGENDS

Figure 1: Consort diagram for the second randomisation

Figure 2: VTE recurrence for those in the second randomisation

Figure 1: Consort diagram for the second randomisation

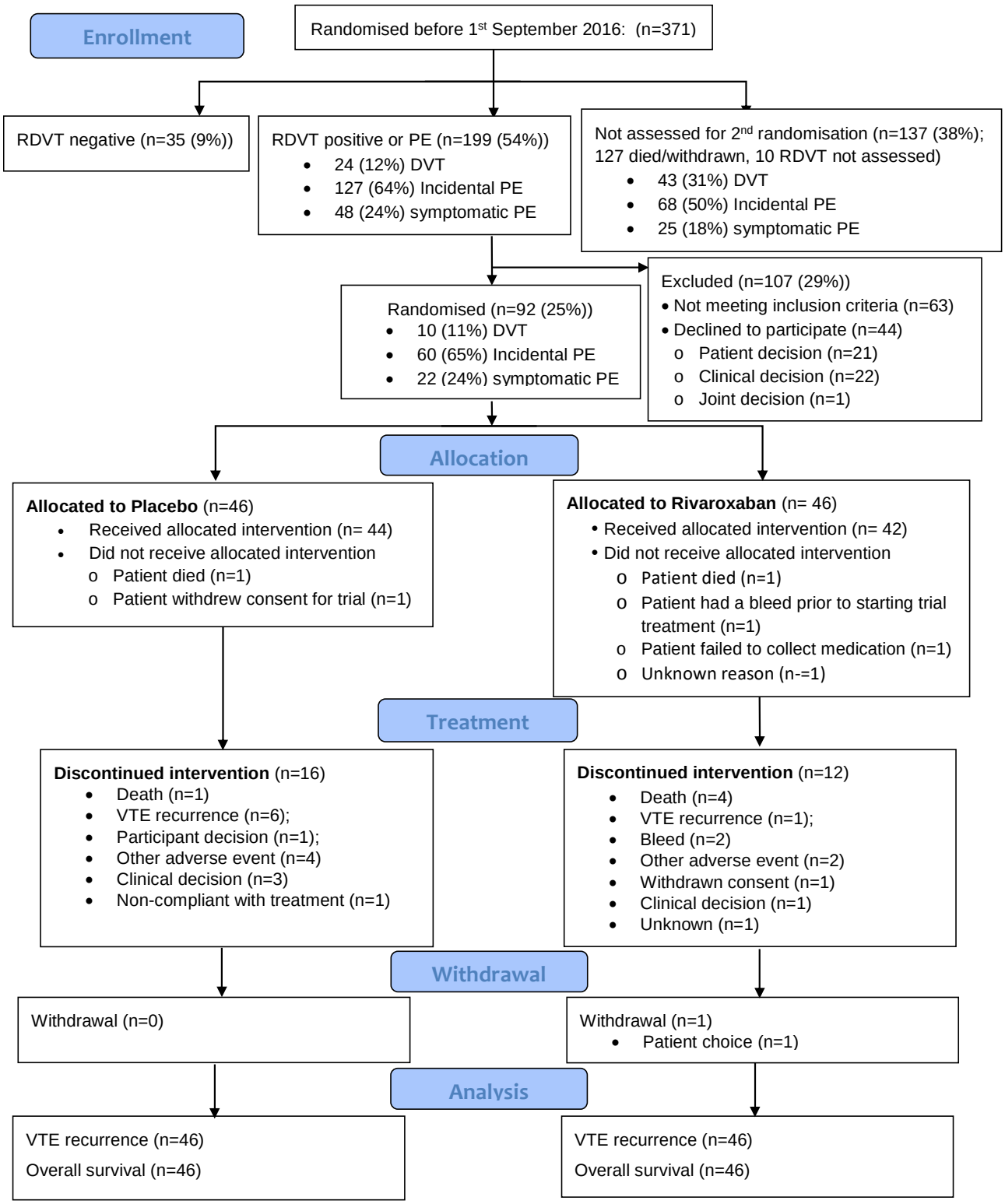
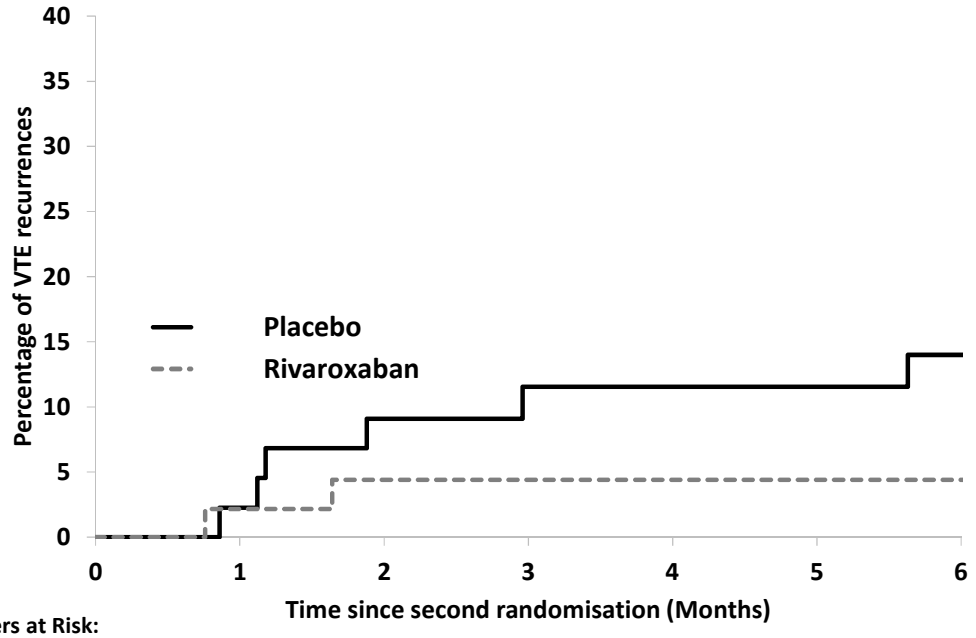


Figure 2: VTE recurrence for those in the second randomisation



Numbers at Risk:				
Placebo	46	40	36	35
Rivaroxaban	46	42	38	37