Comparison of an Oral Factor Xa Inhibitor with Low Molecular Weight Heparin in Cancer Patients with Venous Thromboembolism

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on behalf of the select-d Collaborative Group

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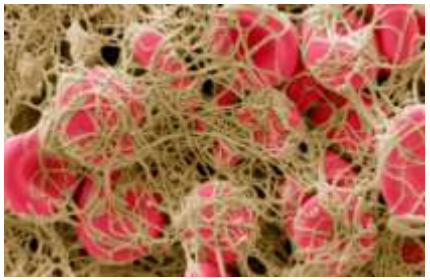
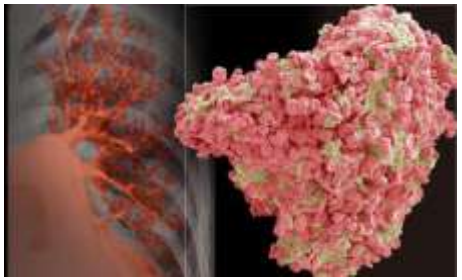
ICTHIC





Disclosures

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Honoraria from:

- Helsinn
- Bayer AG
- Leo Pharma

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Background

- LMWH remains the recommended standard for treatment and prevention of recurrent VTE in cancer patients in the current guidelines
- Direct oral anticoagulants (DOACs) are recommended for the management of patients with VTE *without* cancer
- There were limited data for DOACs in patients with cancer-associated thrombosis

Main research objectives

- **To assess VTE recurrence in cancer patients with a first VTE, treated with rivaroxaban or dalteparin**
- To assess rates of major and clinically relevant non-major bleeding
- To assess extended anticoagulation treatment beyond 6 months in selected patients

Study design (1)

Prospective, randomised, open-label, multicentre pilot phase III trial

n=530

Study population:
Active cancer with symptomatic DVT and/or any PE
ECOG PS ≤ 2

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Dalteparin
200 IU/kg od for the first 30 days followed by 150 IU/kg od

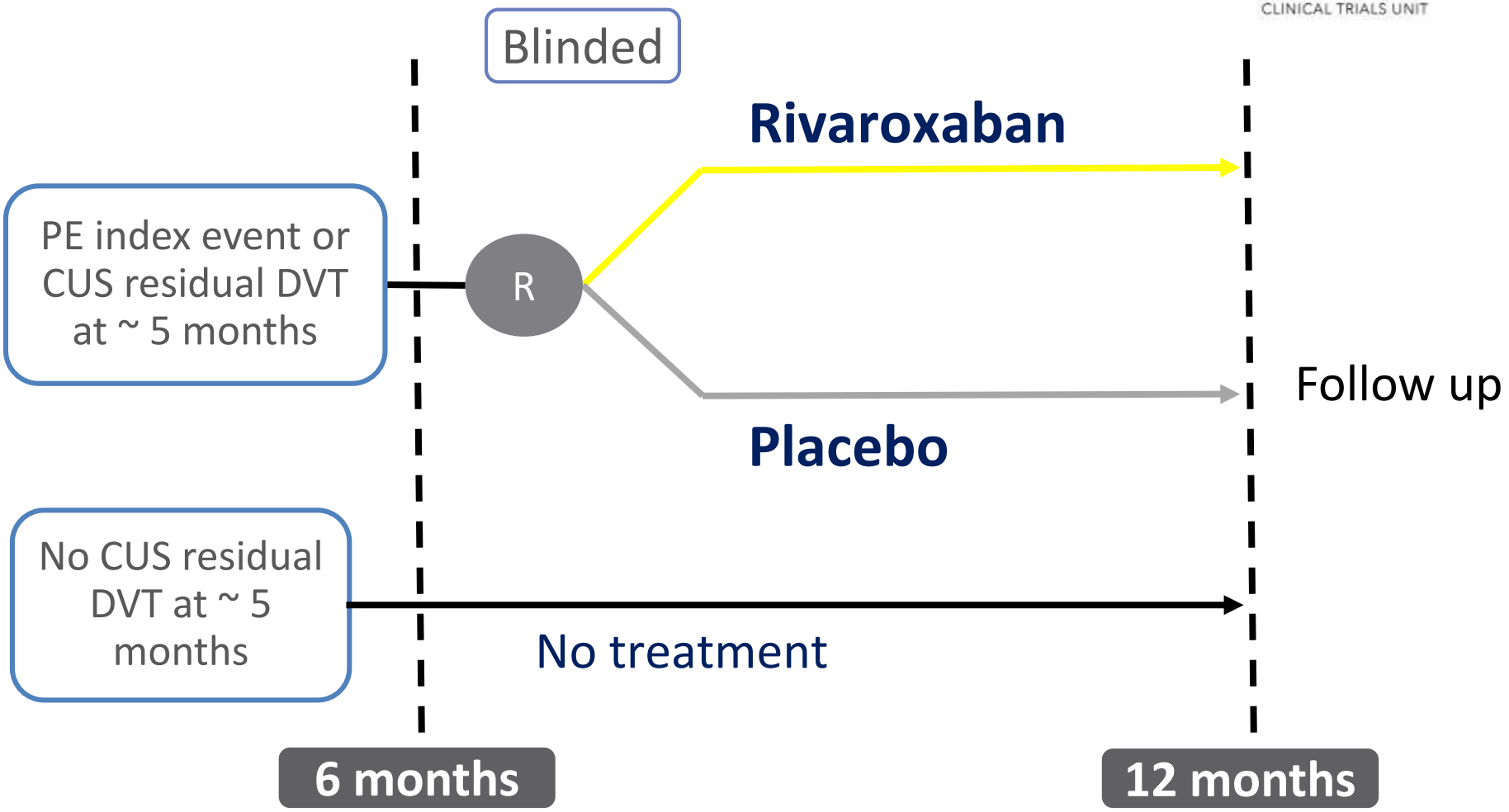
Rivaroxaban
15 mg bid for 21 days followed by 20 mg od

6 months

Stratification variables:

- Stage of disease
- Baseline platelet count
- Type of VTE
- Risk of clotting by tumour type

Study design (2)



Statistical considerations

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- A sample size of 530 patients would provide:
  - estimates of VTE recurrence rates at 6 months to within +/- 4%, assuming a VTE recurrence rate at 6 months of 10%
  - 300 patients for the second randomisation, assuming 70% eligible at 6 months and 80% agreed to participate

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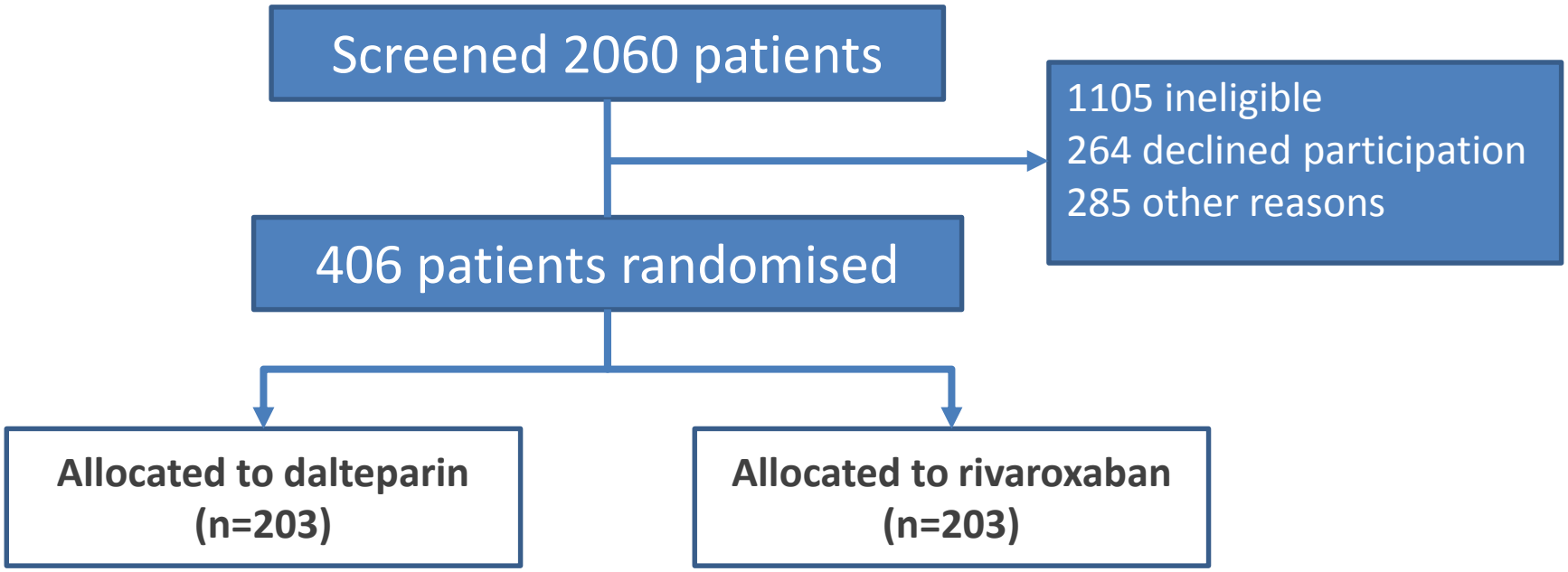
Trial progress

- First patient randomised in October 2013
- Changes to protocol based on DMC recommendations in June 2016
  - The second randomisation was closed to patients randomised into the trial after 31st August 2016 due to low recruitment (n=92)
  - Sample size reduced from 530 to 400 patients (increased the width of the 95% CI for VTE recurrence rate from 8% to 9%)
  - Patients with oesophageal and gastro-oesophageal cancer were excluded due to apparent imbalance in major bleeding rates compared to other tumour types

Recruitment



- Recruitment between October 2013 and December 2016 from 58 sites across the UK

Baseline characteristics

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Factor	Dalteparin % (n=203)	Rivaroxaban % (n=203)
Age: years, median (range)	67 (34–87)	67 (22–87)
Gender: male	48	57
Stage of Cancer: - metastatic	58	58
ECOG PS: - 0,1 - 2	77 21	73 26
Qualifying VTE: - symptomatic VTE - incidental PE	48 52	47 53

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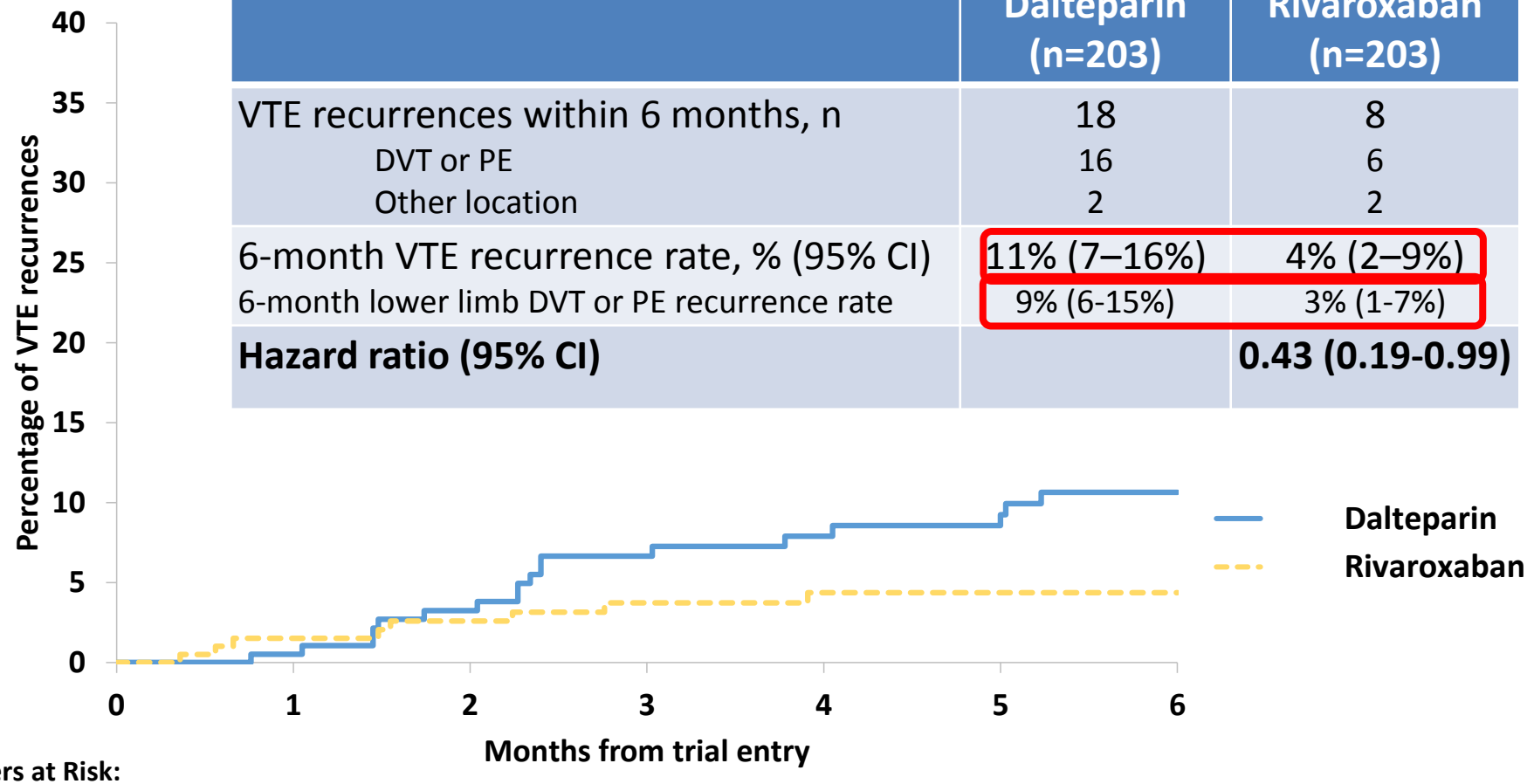
Primary tumour type

	Dalteparin, % (n = 203)	Rivaroxaban, % (n = 203)
Colorectal	23	27
Lung	12	11
Breast	10	10
Ovarian	9	6
Pancreatic	5	9
Lymphoma	6	5
Oesophageal/gastro-oesophageal	9	5
Prostate	4	7
Bladder	2	5
Other	20	15

VTE recurrence

	Dalteparin (n=203)	Rivaroxaban (n=203)
VTE recurrences within 6 months, n	18	8
DVT or PE	16	6
Other location	2	2
6-month VTE recurrence rate, % (95% CI)	11% (7–16%)	4% (2–9%)
6-month lower limb DVT or PE recurrence rate	9% (6-15%)	3% (1-7%)
Hazard ratio (95% CI)		**0.43 (0.19-0.99)**

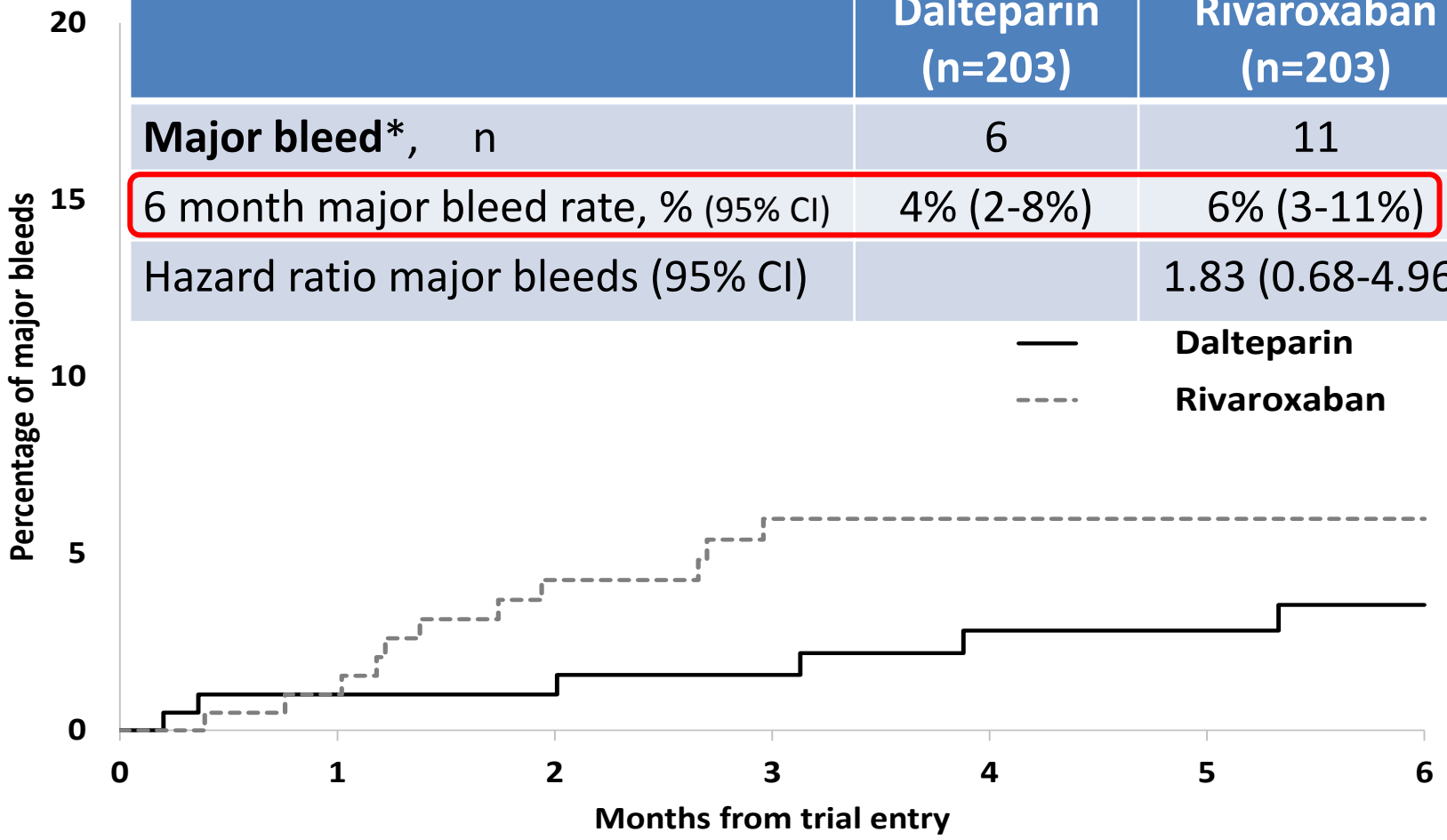


Numbers at Risk:

Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

Major bleeds

	Dalteparin (n=203)	Rivaroxaban (n=203)
Major bleed*, n	6	11
6 month major bleed rate, % (95% CI)	4% (2-8%)	6% (3-11%)
Hazard ratio major bleeds (95% CI)		1.83 (0.68-4.96)



Numbers at Risk:

Dalteparin	**203**	**176**	**147**	**122**
Rivaroxaban	**203**	**172**	**149**	**134**

*1 fatal bleed in each arm

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Clinically relevant non-major bleeds

	Dalteparin (n=203)	Rivaroxaban (n=203)
Clinically relevant non-major bleed	7	25
6 month CRNMB rate, % (95% CI)	4% (2-9%)	13% (9-19%)
Hazard ratio for CRNMB (95% CI)		3.76 (1.63-8.69)

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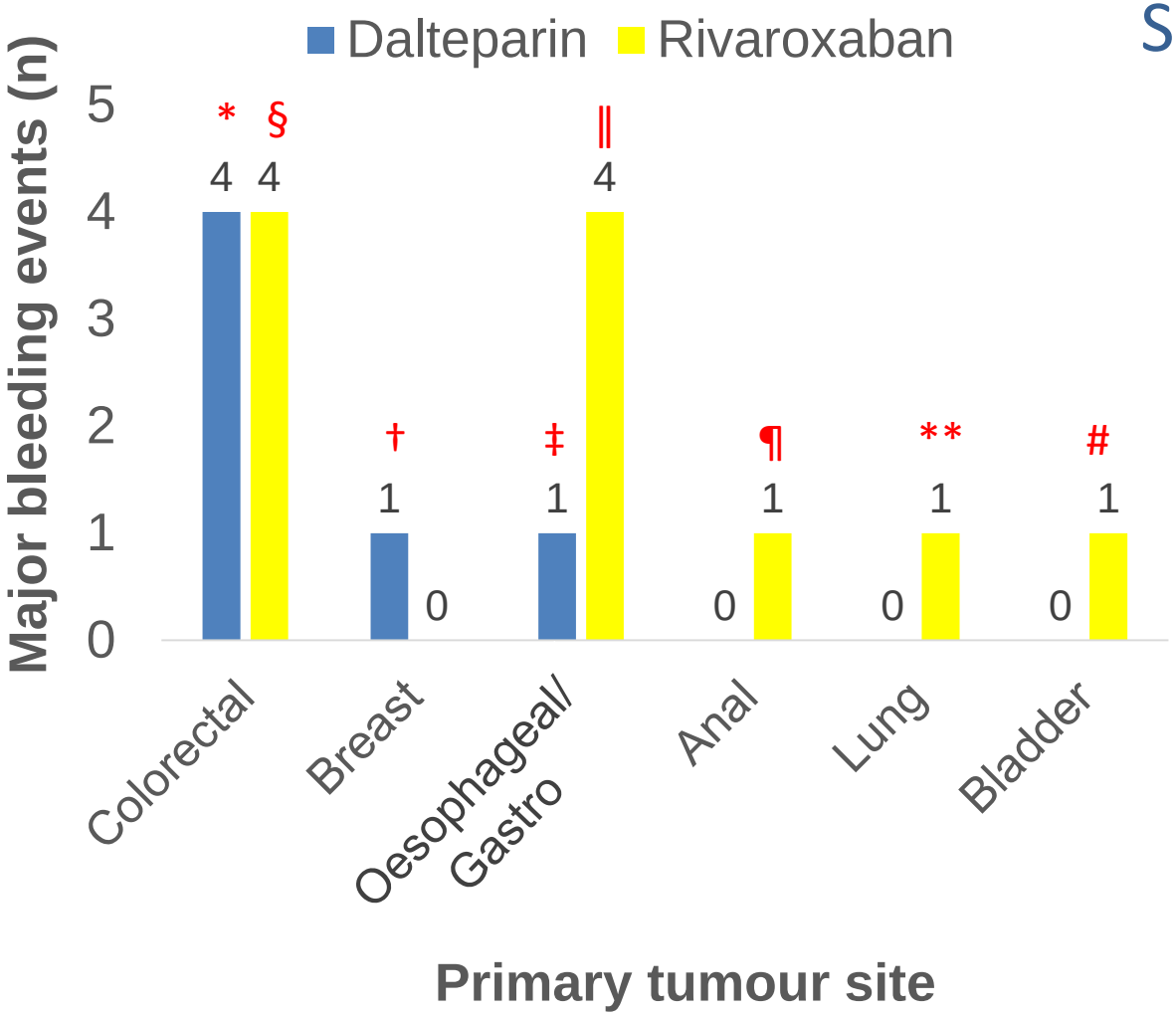
Details of major bleeds: Primary tumour site



Sites of major bleed

§Stomach (n=2), intra-operative haematuria, intra-abdo haematoma

‖Oesophageal (n=3), †Stomach

GI

‡Oesophageal

¶Epistaxis

**GI

#Lower GI

Overall survival

	Dalteparin	Rivaroxaban
Number of deaths	56	48
6-months overall survival, % (95% CI)	70% (63–76%)	75% (69–81%)

- 92 (88%) died from progressive cancer
- 2 (2%) fatal PEs

Summary

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- Overall, 1 in 5 patients who were screened, participated in the study
- Recurrent VTE was significantly reduced in favour of rivaroxaban: HR 0.43 (0.19-0.99)
- No difference in major bleeding: HR 1.83 (0.68-4.96)
- CRNMB was significantly greater in the rivaroxaban arm: HR 3.76 (1.63-8.69)
- The high mortality and clinician choice made the second randomisation non-feasible

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Main conclusion

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- DOACS are a feasible option for the treatment of CAT, reducing VTE recurrence
- Careful risk assessment, individual clinical circumstances and patient preference need to be taken into account regarding the bleeding risk

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Thank you to all the patients who participated in select-d

TMG

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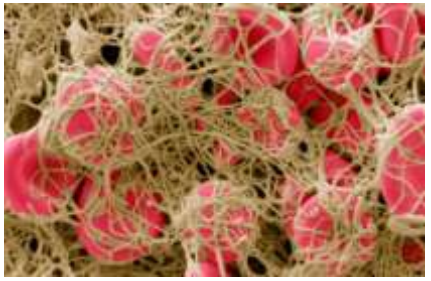

*JCO – in press

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