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Oral Option for the Treatment of Venous Thromboembolism in Cancer Patients?

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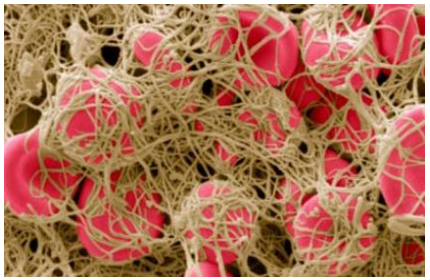
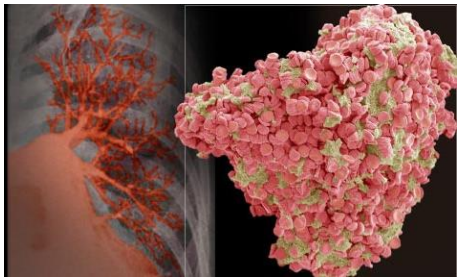


on behalf of the select-d Collaborative Group



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Disclosures

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Honoraria from:

- Helsinn
- Bayer AG
- Leo Pharma

Educational grant from:

- Bayer AG

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Adverse Consequences of Cancer-associated Thrombosis (CAT)

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- Greater Risk of Early Mortality[1]
- Increased Morbidity – hospitalisation[2]
- Increased risk of recurrent VTE[3]
- Bleeding Complications on anticoagulation[3]
- Cancer Treatment Delays
- Increased Healthcare Costs[2]

- Patient Perspectives

1. Chew HK et al. 2006 *Arch Intern Med* **166** (4): 458-464
2. Lyman GH et al. 2016 Blood **128**:4751
3. Prandoni P et al. 2002 Blood **100**: 3484-3488

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Impact of CAT on cancer patients

- Only 7/37 patients had been aware of their increased risk of VTE and what to look out for.
- Most misattributed their symptoms to e.g. effects of cancer treatment, delaying help-seeking.

No-one had told me that it could happen, or if they had told me they hadn't said it enough, not so you can remember - P12

I'd been in pain with my leg for a good week or so but you just think it's part of the cancer. - P2

Hutchinson, A., Rees, S., Maraveyas, A., Young, A. Date, K., and Johnson, M. In print - Palliative Medicine

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Patient Perspectives on tablet vs injection anticoagulant

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- Most patients experienced unwanted effects as result of injections, but these were acceptable in context of being a cancer patient
- Tablet was seen as better but only if as effective

Obviously you're covered in bruises so you don't look great, but I'm now covered in scars and colostomy bags and that sort of things, it seems a very small price to pay. It becomes a bit relative really. - P21

If a tablet would serve the same purpose then I would certainly sooner take a tablet, but…if the injections are an advantage then it's worth putting up with the discomfort. - P11

Hutchinson, A., Rees, S et al. In print Palliative Medicine

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Background

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- LMWH remains the recommended standard for treatment and prevention of recurrent VTE in cancer patients
- 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
- *From previous studies of VTE in clots in cancer patients with a central venous catheters, we had a network of practice-based and research nurses who were keen to recruit*

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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

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Study design (1)

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

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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

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Study design (2)

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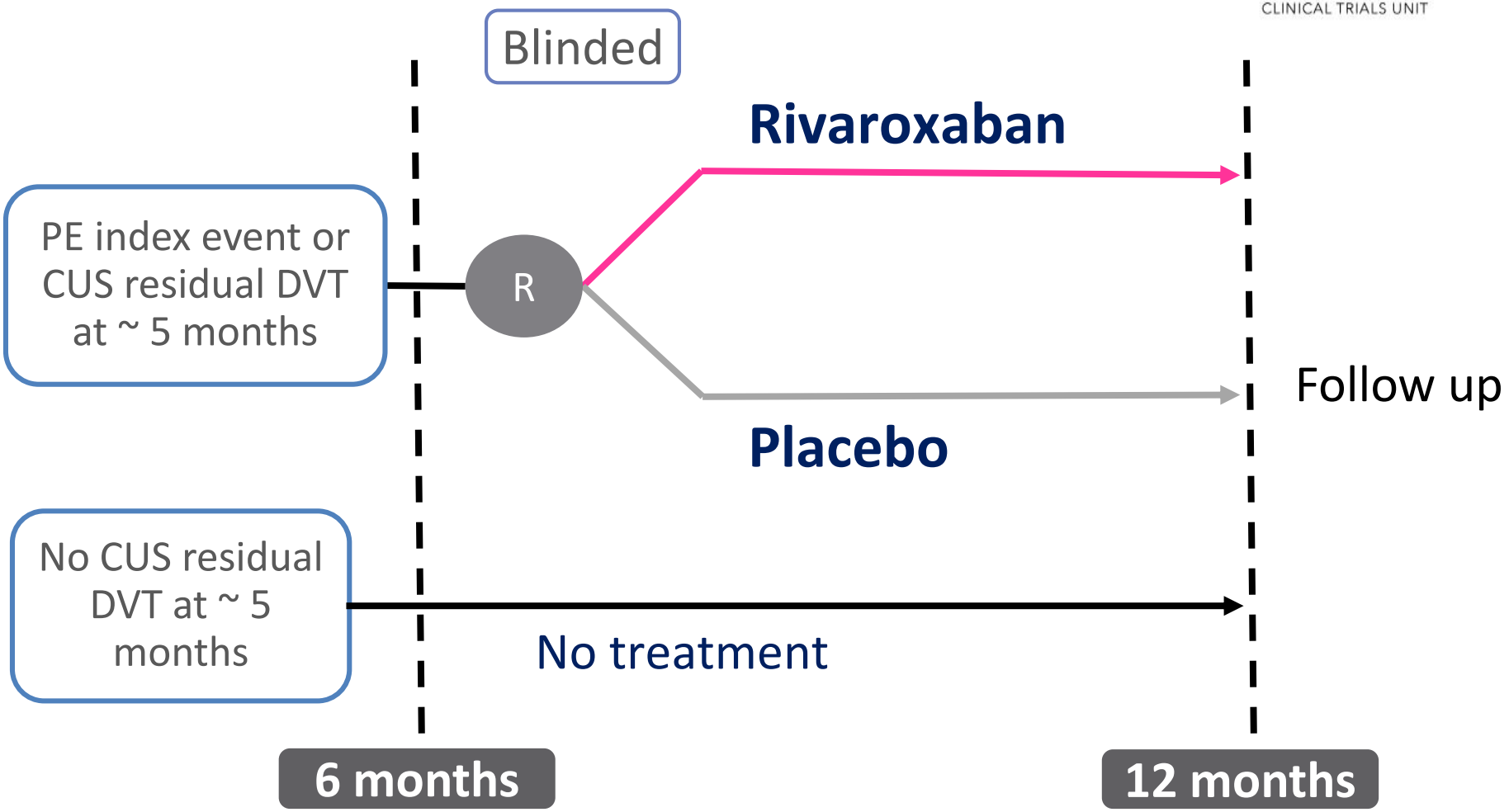

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Trial progress

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- 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

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Baseline characteristics

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
Primary Tumour type: -Colorectal -Lung -Breast -Ovarian	23 12 10 9	26 11 10 6

VTE recurrence

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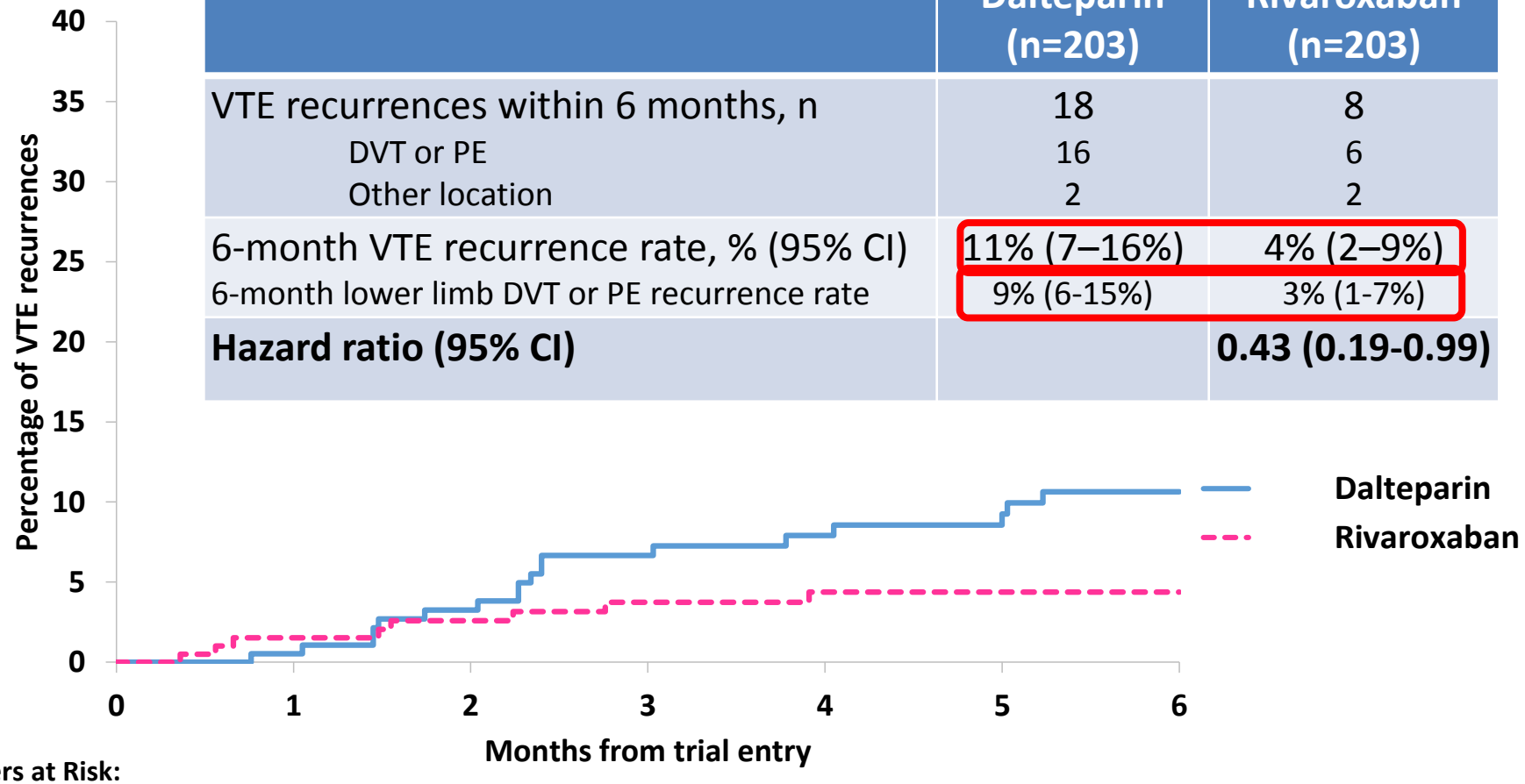
	Dalteparin (n=203)	Rivaroxaban (n=203)
VTE recurrences within 6 months, n	18	8
DVT or PE	16	6
Other location	2	2
6-month VTE recurrence rate, % (95% CI)	11% (7–16%)	4% (2–9%)
6-month lower limb DVT or PE recurrence rate	9% (6-15%)	3% (1-7%)
Hazard ratio (95% CI)		**0.43 (0.19-0.99)**



Numbers at Risk:

Dalteparin	203	171	139	115
Rivaroxaban	203	174	149	134

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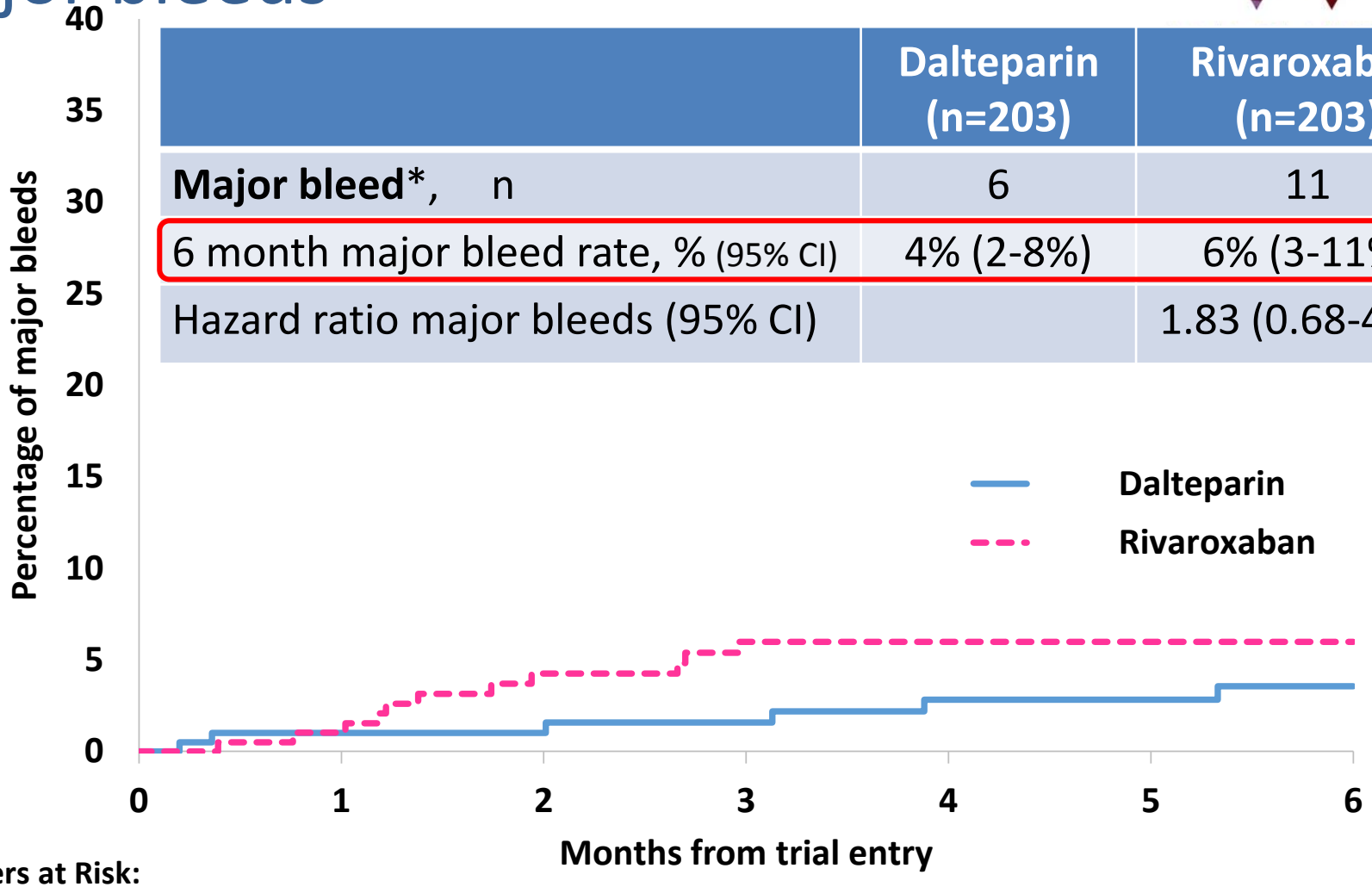
Major bleeds

	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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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

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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

Results consistent with HOKUSAI-Cancer trial >1000 patients: edoxaban vs LMWH

Raskob GE, et al. N Engl J Med 2018; 378:615-624

**** NEW GUIDANCE*

Khorana AA et al. 2018 *Journal of Thrombosis and Haemostasis*, 16: 1–4

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Young AM, Marshall A, Thirlwall J et al : *JCO* 2018, 6(20):2017-2032

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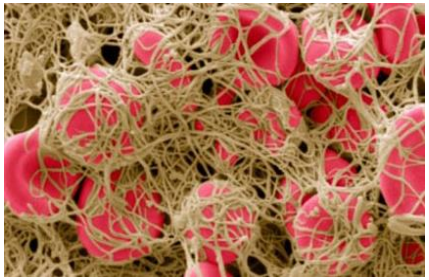

Thank you to all the patients who participated in select-d

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