Recurrent Venous Thromboembolism in Patients with Cancer

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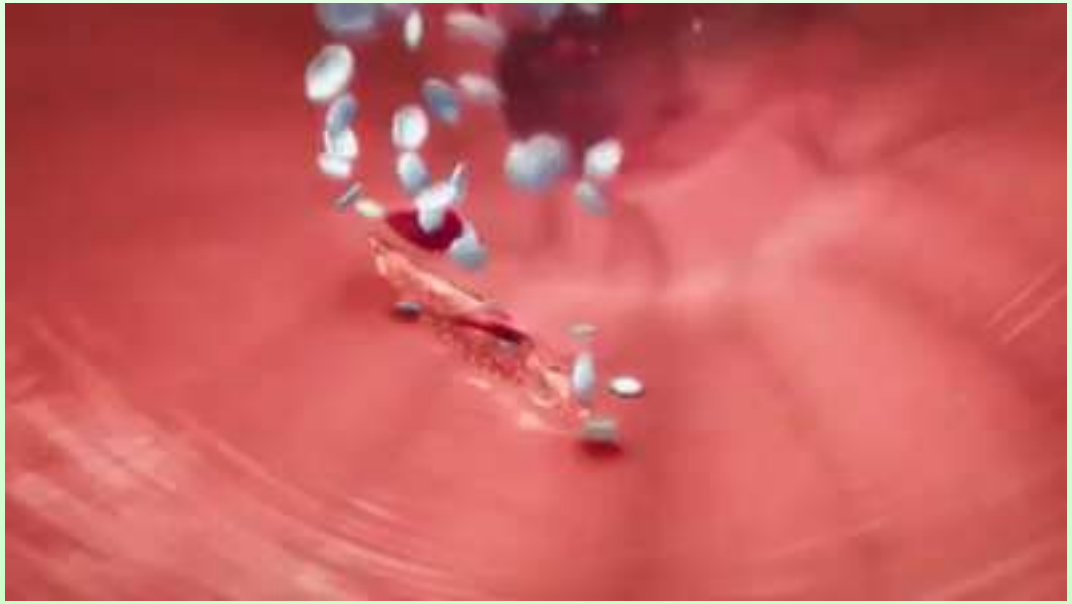
Disclosures

- I have received honoraria for work in study committees from
  - Boehringer Ingelheim
  - Bayer
  - Alnylam
  - Sanofi
  - Pfizer
- Research grants from
  - Boehringer Ingelheim
  - Octapharma
- Drugs that might not yet approved in some countries will be discussed – only for educational purposes

Agenda

- Management of patients with cancer and thrombosis
- Management of recurrent VTE in cancer



High VTE risk in cancer

Table 1. Effect of Malignancy on the Risk of Venous Thrombosis Depending on the Duration Between Diagnosis of Cancer and Venous Thrombosis

Duration Between Malignancy and Venous Thrombosis	No. of Individuals (%)		Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	Patients (n = 3220)	Control Participants (n = 2131)		
No malignancy	2831 (87.9)	2062 (96.8)	1.00	1.00
All malignancies	389 (12.1)	69 (3.2)	4.1 (3.2-5.3)	4.3 (3.3-5.6)
Time after index date (diagnosis)†				
0 to ≤3 mo	80 (20.6)	1 (1.5)	58.2 (8.1-419.1)	53.5 (8.6-334.3)
>3 mo to ≤1 y	92 (23.7)	5 (7.6)	13.4 (5.4-33.0)	14.3 (5.8-35.2)
>1 to ≤3 y	67 (17.2)	14 (21.2)	3.5 (2.0-6.2)	3.6 (2.0-6.5)
>3 to ≤5 y	43 (11.1)	11 (16.7)	2.8 (1.5-5.5)	3.0 (1.5-5.7)
>5 to ≤10 y	47 (12.1)	14 (21.2)	2.4 (1.3-4.5)	2.6 (1.4-4.7)
>10 to ≤15 y	19 (4.8)	6 (9.0)	2.3 (0.9-5.8)	2.3 (0.9-5.8)
>15 y	23 (5.9)	15 (22.7)	1.1 (0.6-2.1)	1.1 (0.6-2.2)

Abbreviation: CI, confidence interval.
*Adjusted for age and sex.
†Eighteen patients and 3 control participants did not report a date of diagnosis.

Blom JW, et al. JAMA; 2005;293(6):715-22

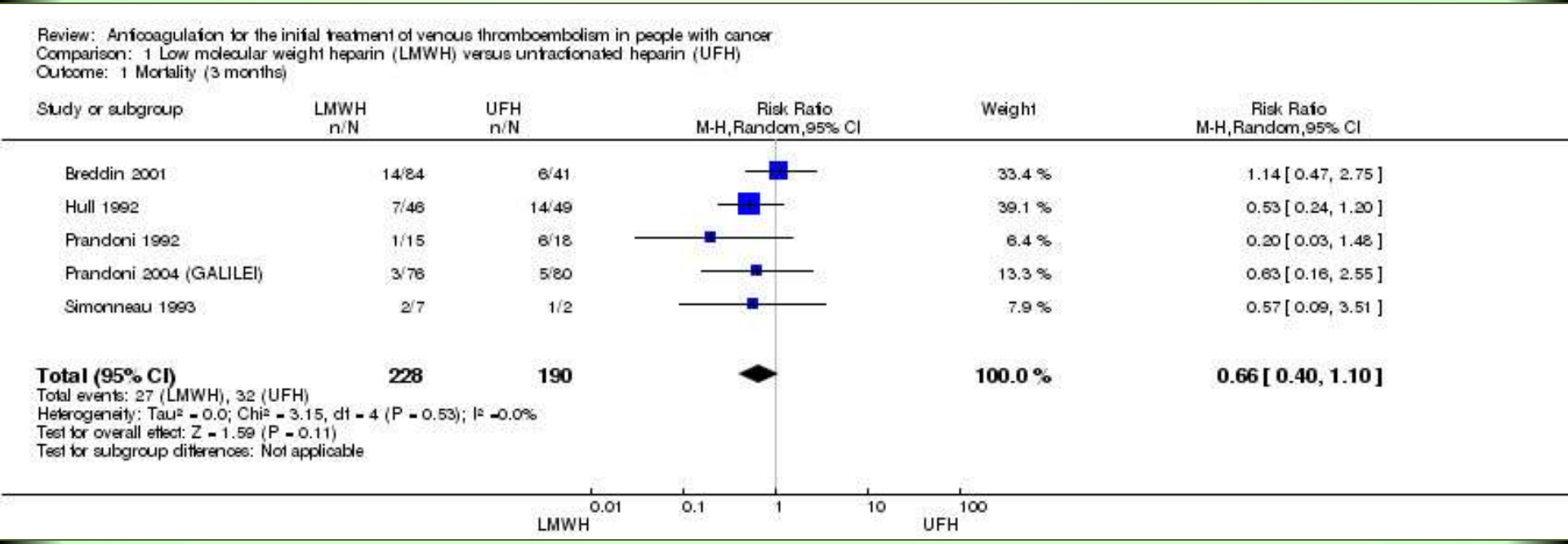
High mortality rate

Exposure	PY	Deaths (n)	MR per 100 PY (95% CI)	HR (95% CI)
None	277 713	1750	0.63 (0.60-0.66)	1.0 (reference)
VT only	1317	67	5.1 (4.0-6.4)	2.6 (2.0-3.3)
Cancer only	5650	721	12.7 (11.9-13.7)	7.4 (6.8-8.2)
Cancer-related VT	131	72	55.0 (43.6-69.3)	31.2 (24.6-39.6)

Adjusted for age and sex. Based on the Tromsø study 1994-2007

Timp JF et al. 2013;122(10):1712-23.

Initial treatment – month 0-3 Mortality



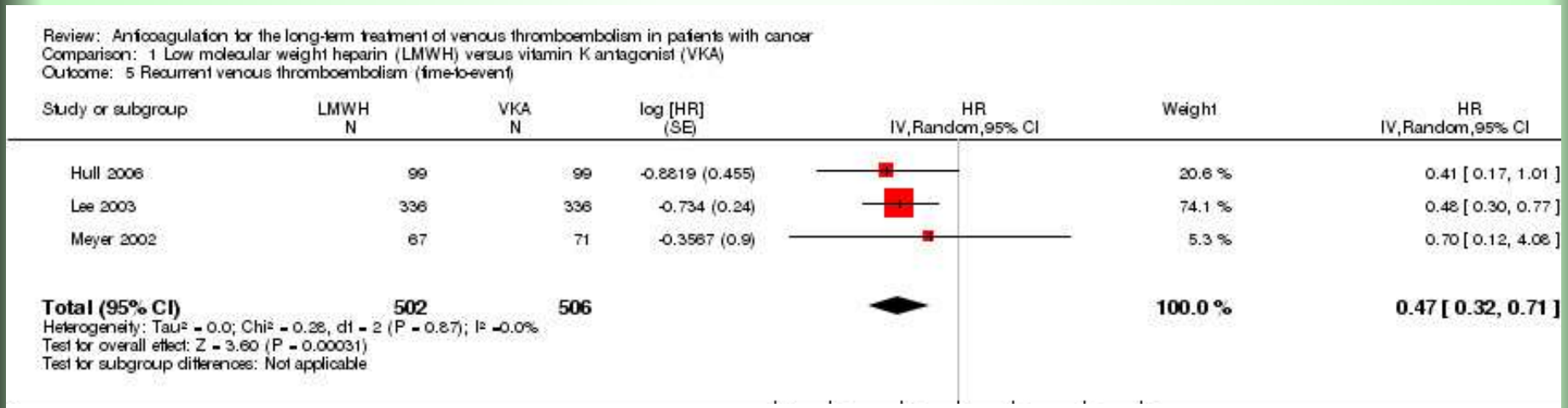
Recurrent VTE: RR 0.69 (0.27;1.76)

Hakoum MB et al. Cochrane Database Syst Rev. 2018 Jan 24;1:CD006649.

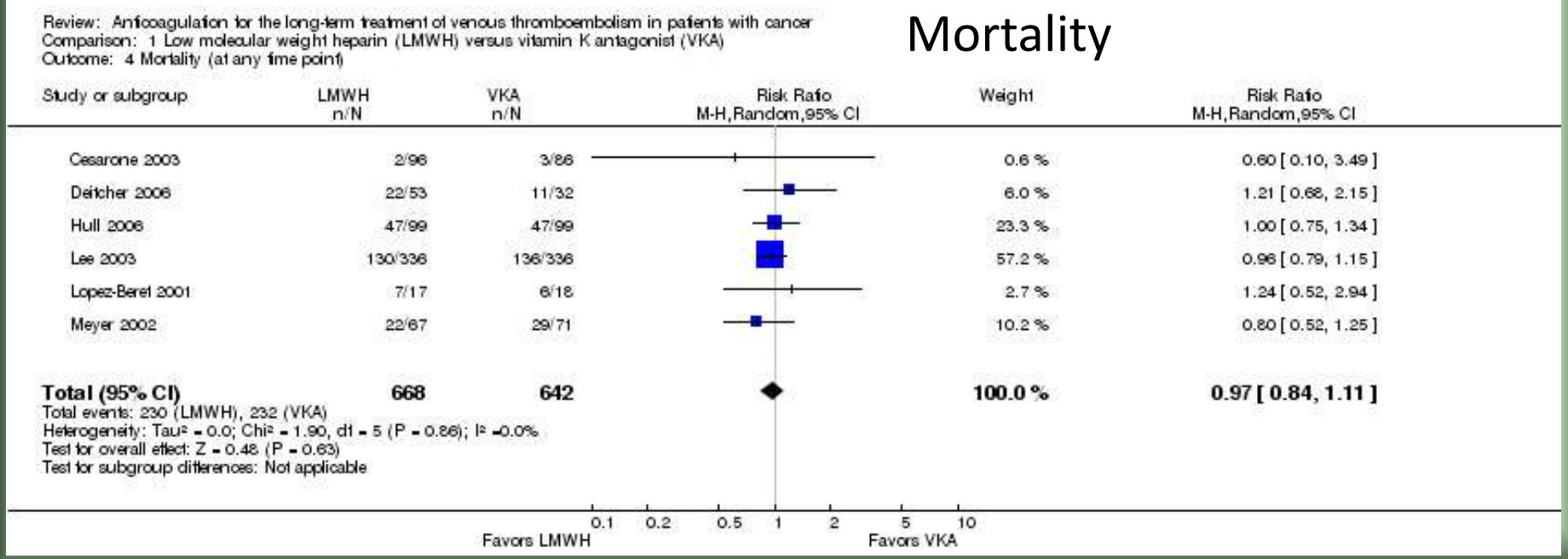
Akl EA et al. Cochrane Database Syst Rev. **2014**;(7):CD006650.

Long-term treatment – month 3-6

Recurrent VTE – time to event

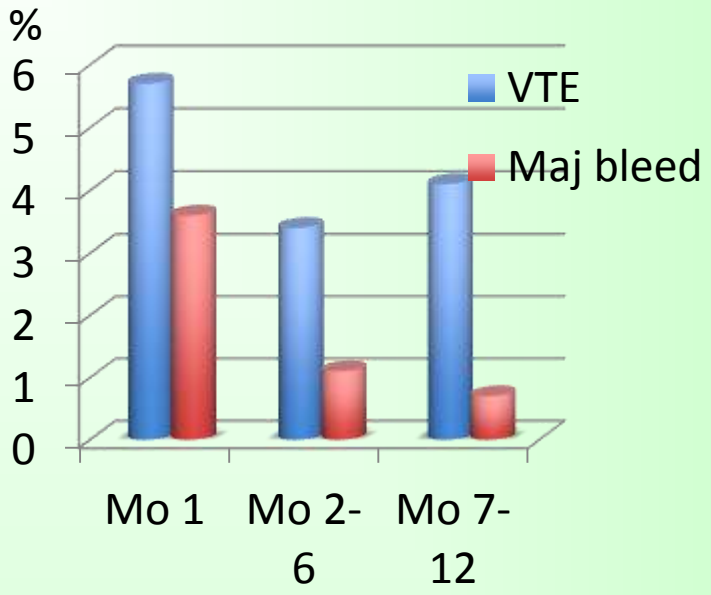


Mortality

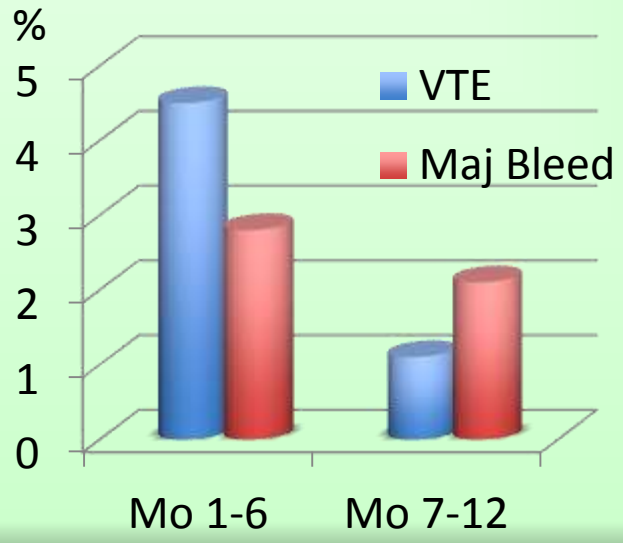


Extended treatment

- DALTECAN, n=334



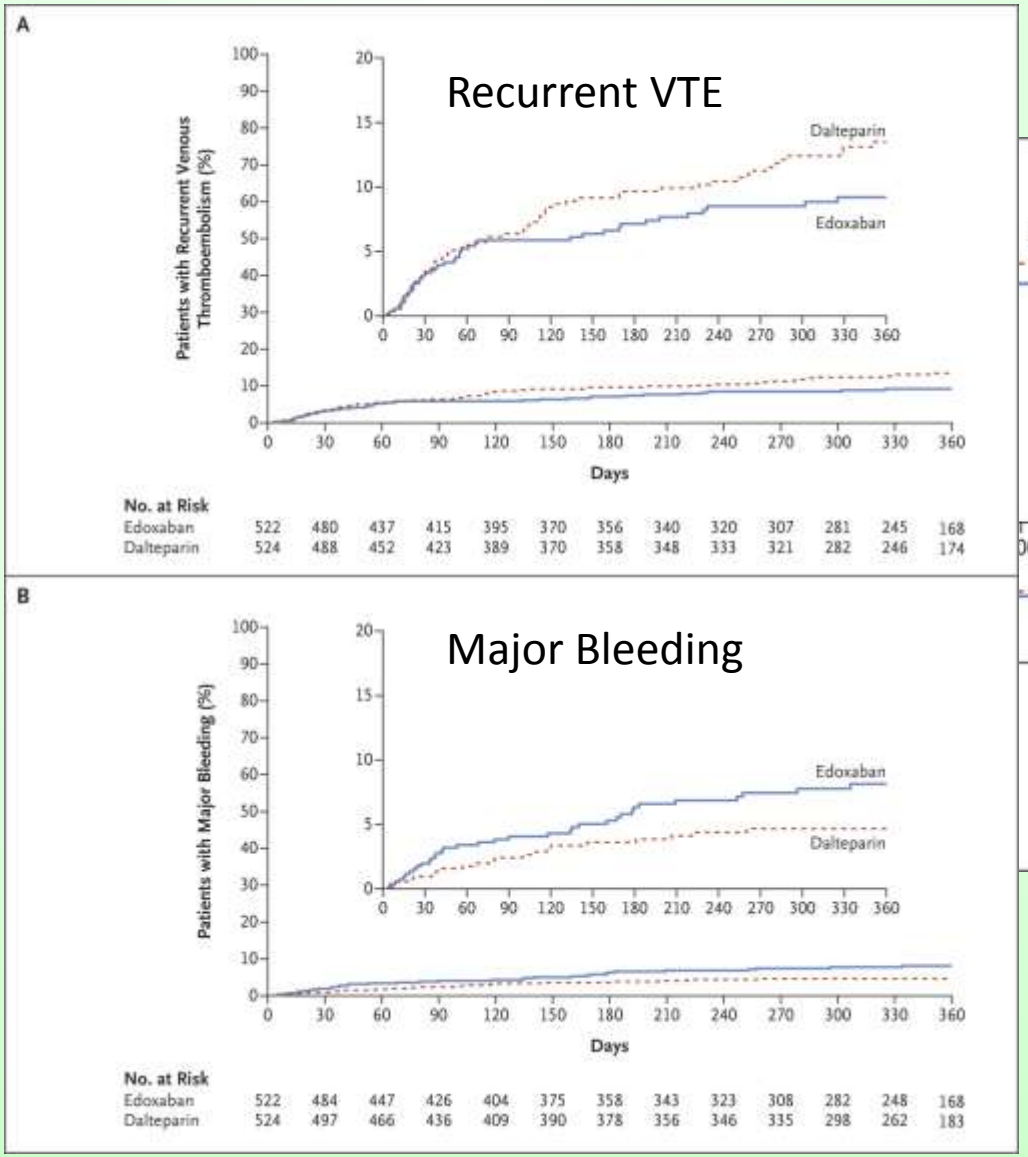
- TiCAT, n=247

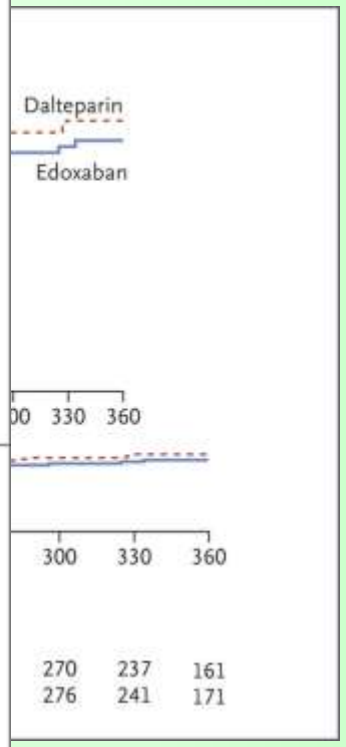


Francis CW et al. JTH 2015;13:1028-35
Jara-Palomares L et al. Thromb Res 2017;157:90-6

NOACs vs. LMWH

- N=1046

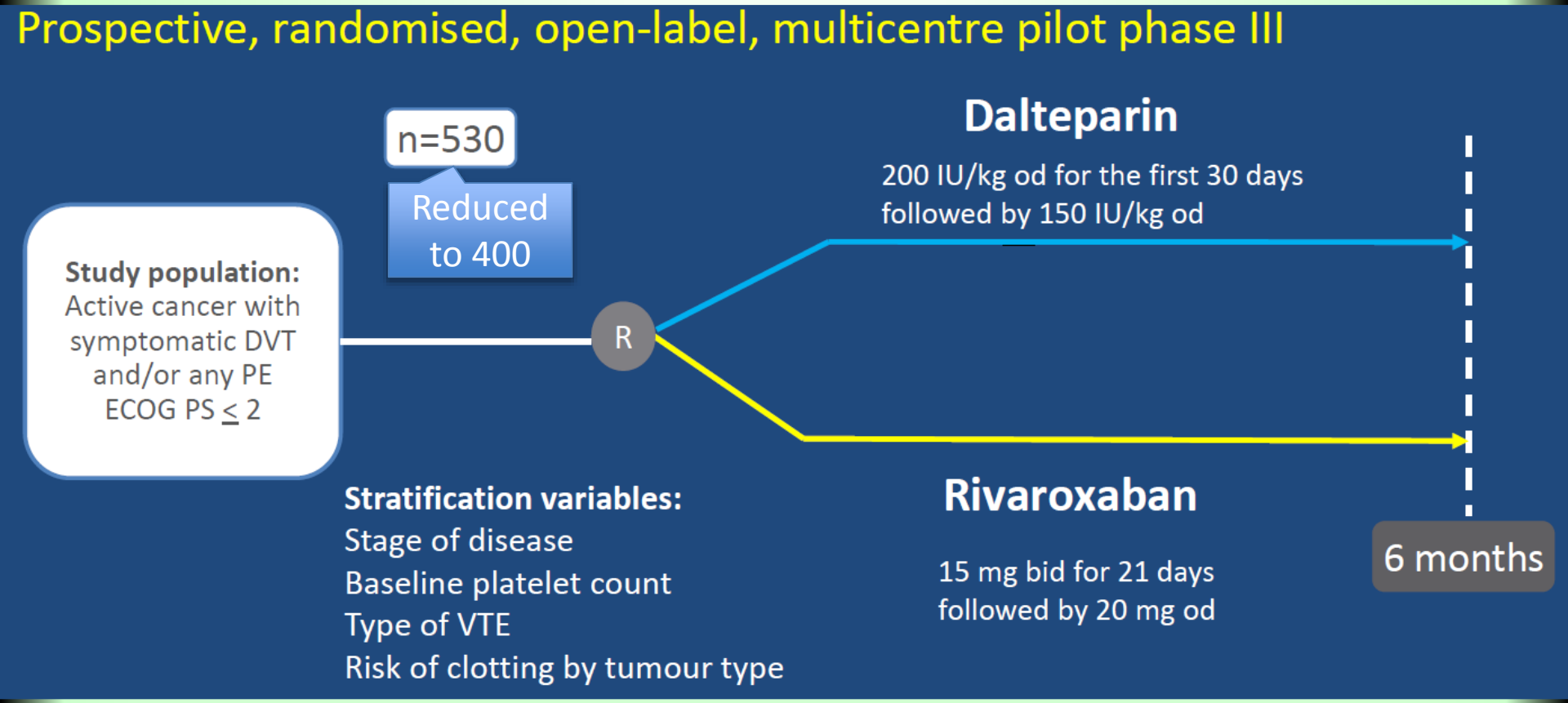




Raskob GE et al. N Engl J Med 2018; 378:615-24

Rivaroxaban vs. LMWH

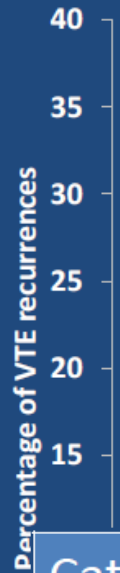
- SELECTeD, started in Oct 2013



Young A et al. Thromb Res 2016 Apr;140 Suppl 1:S172-3

SELECTeD interim data

VTE recurrence



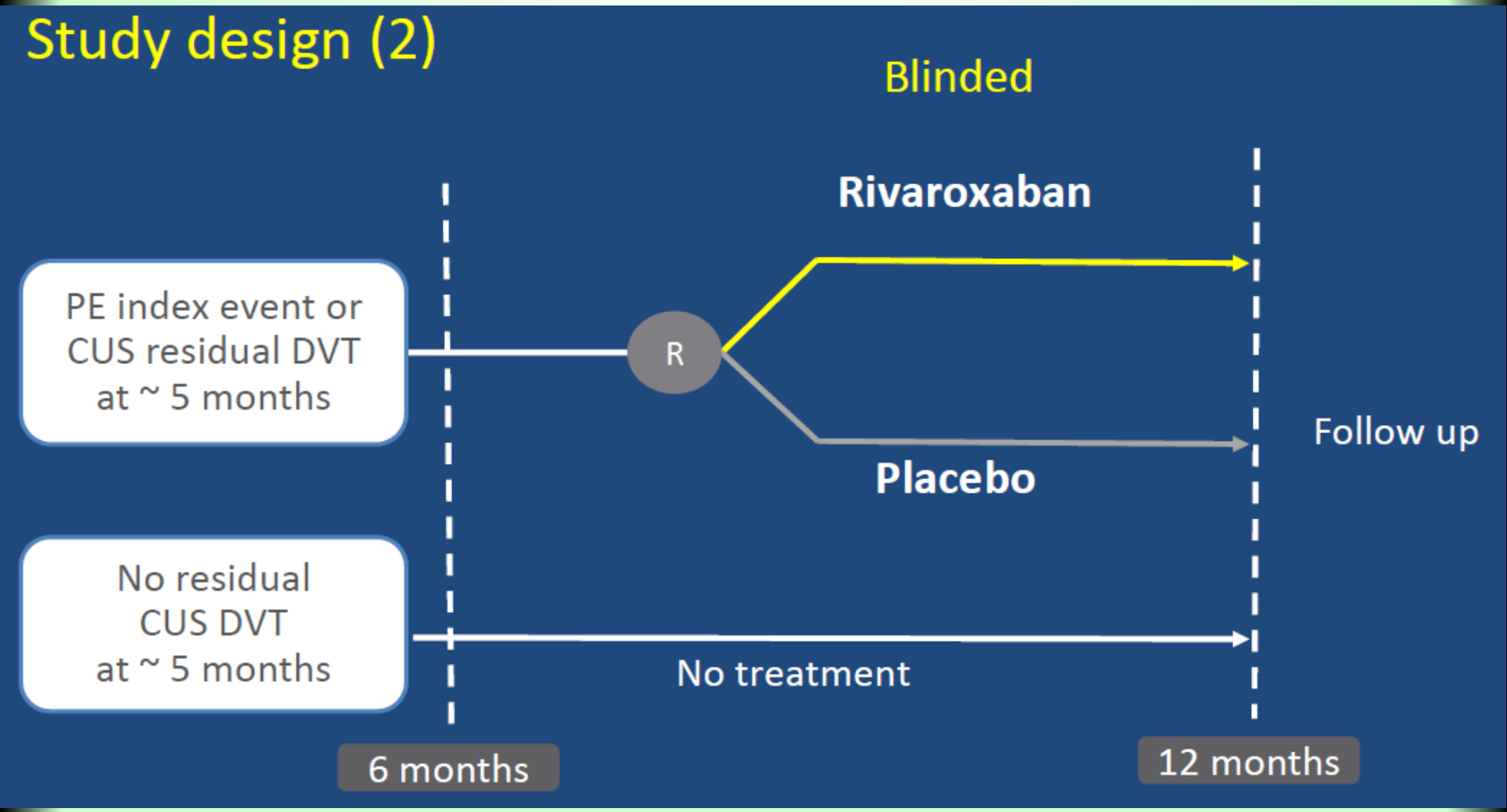
	Dalteparin (n=203)	Rivaroxaban (n=203)
VTE recurrences within 6 months, n	18	8
DVT or PE	16	6
Other location	2	2
6-month VTE recurrence rate, % (95% CI)	11% (7–16%)	4% (2–9%)
6-month lower limb DVT or PE recurrence rate	9% (6-15%)	3% (1-7%)

Category of bleeding	Dalteparin (n=203)	Rivaroxaban (n=203)
Major*	6 (3%)	11 (5%)
Clinically relevant non-major	6 (3%)	25 (12%)
Total	12 (6%)	36 (17%)

Numbers a
Dalteparin
Rivaroxaba

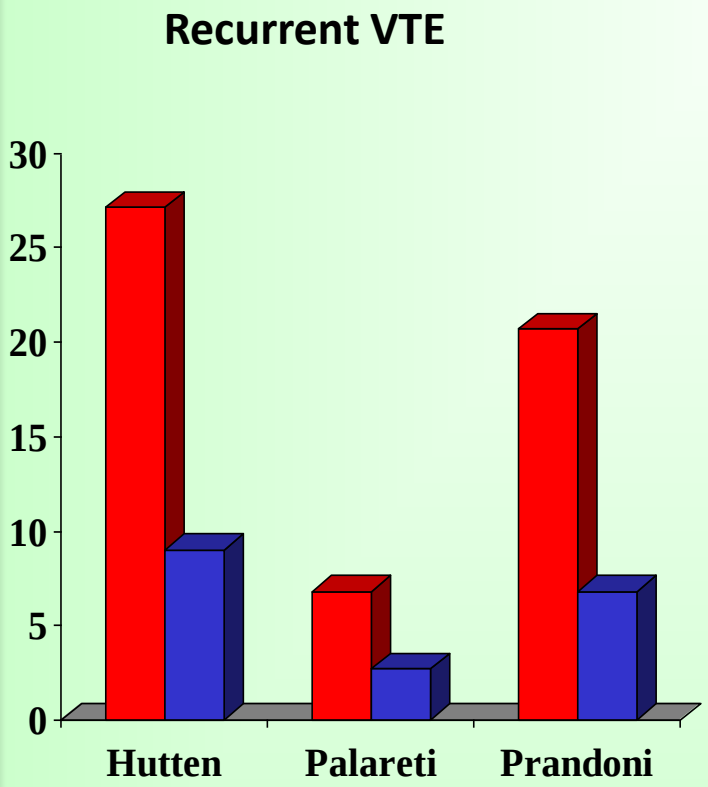
Young A et al. Thromb Res 2016 Apr;140 Suppl 1:S172-3

SELECTeD randomization #2



Stopped after 90 patients – too slow recruitment

Recurrent VTE on therapy



Risk factors for recurrence

- Age <65
- PE at study entry
- Ca diagnosis <3 months
- Cancer site
- Cancer stage
- Adenocarcinoma

Hutten BA et al. J Clin Oncol 2000;18:3078-83.
Palareti G et al. Thromb Haemost 2000;84:805.
Prandoni P et al. Blood 2002;100:3484-8.
Trujillo-Santos J et al. Thromb Haemost 2008; 100:435-9.
Louzada ML et al. Blood Coagul Fibrinolysis 2011;22:86-91

DACUS-Cancer

- 347 patients treated for 6 m with LMWH
- Higher risk of recurrence if residual vein thrombosis on US – off anticoagulation (21.9% vs. 2.8%)
- Extended LMWH to 12 months did not reduce risk significantly

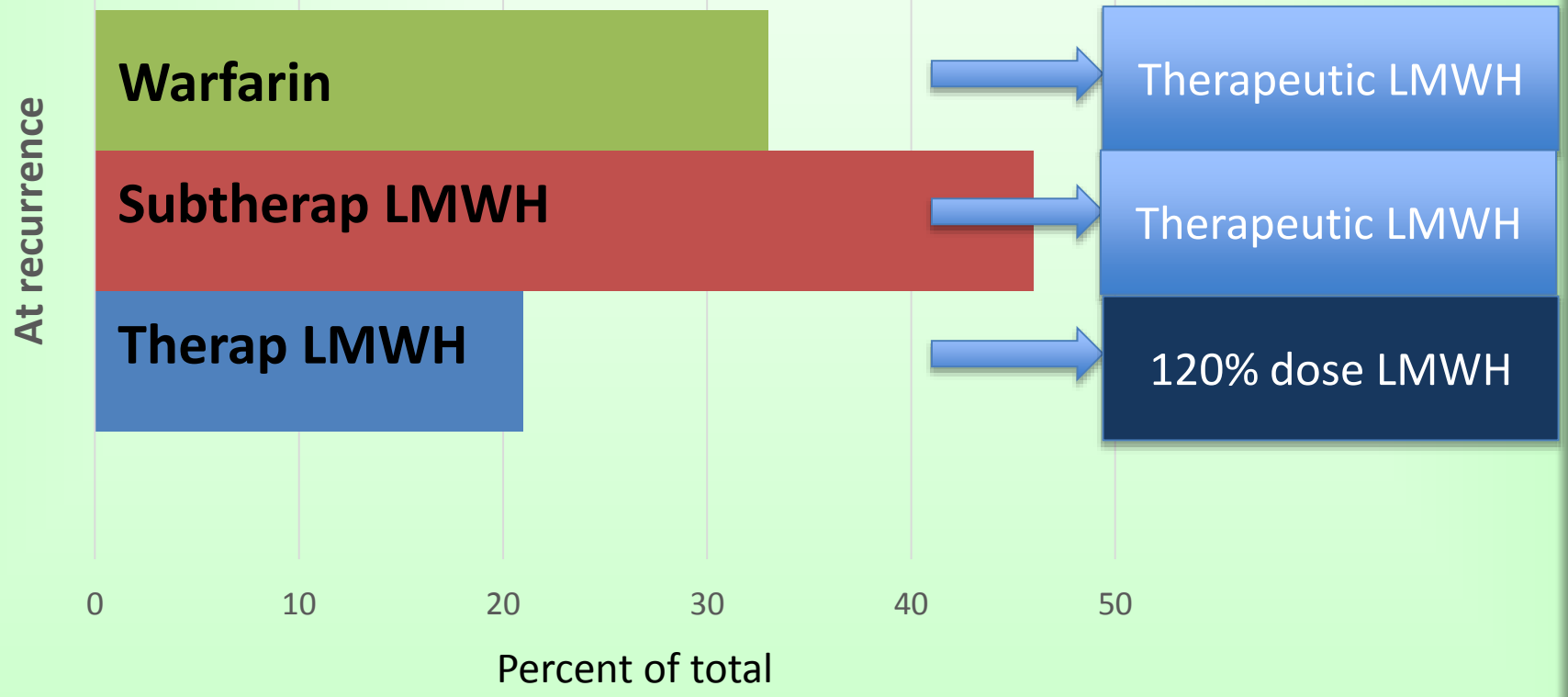
Napolitano M et al. J Clin Oncol 2014;32: 3607-12

Reasons for recurrence

- Cancer related (progression)
- Anticoagulation stopped
  - Hemorrhage
  - Thrombocytopenia
  - Poor compliance
- HIT
- Catheter-related or tumor obstruction

Dose escalation of LMWH

- Retrospective analysis, 70 patients with cancer & recurrent VTE on anticoagulation



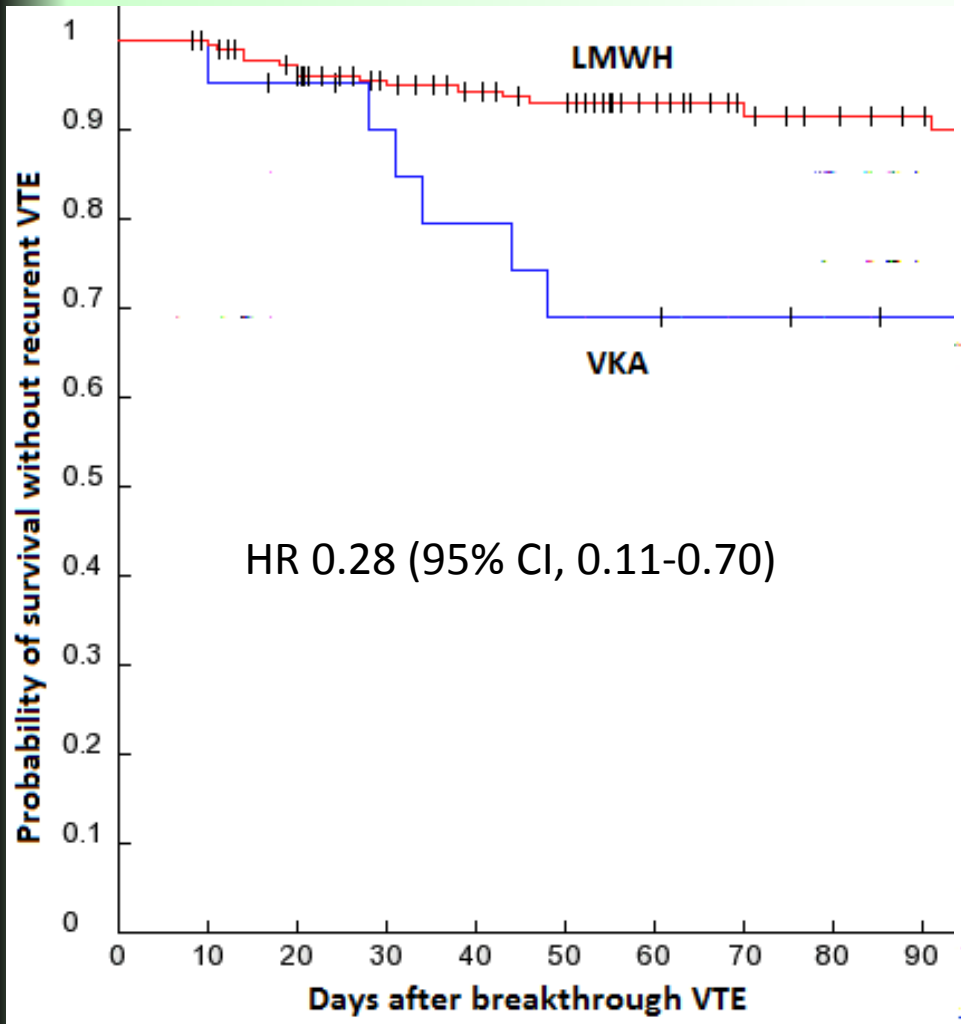
Carrier M et al. J Thromb Haemost 2009;7: 760-5

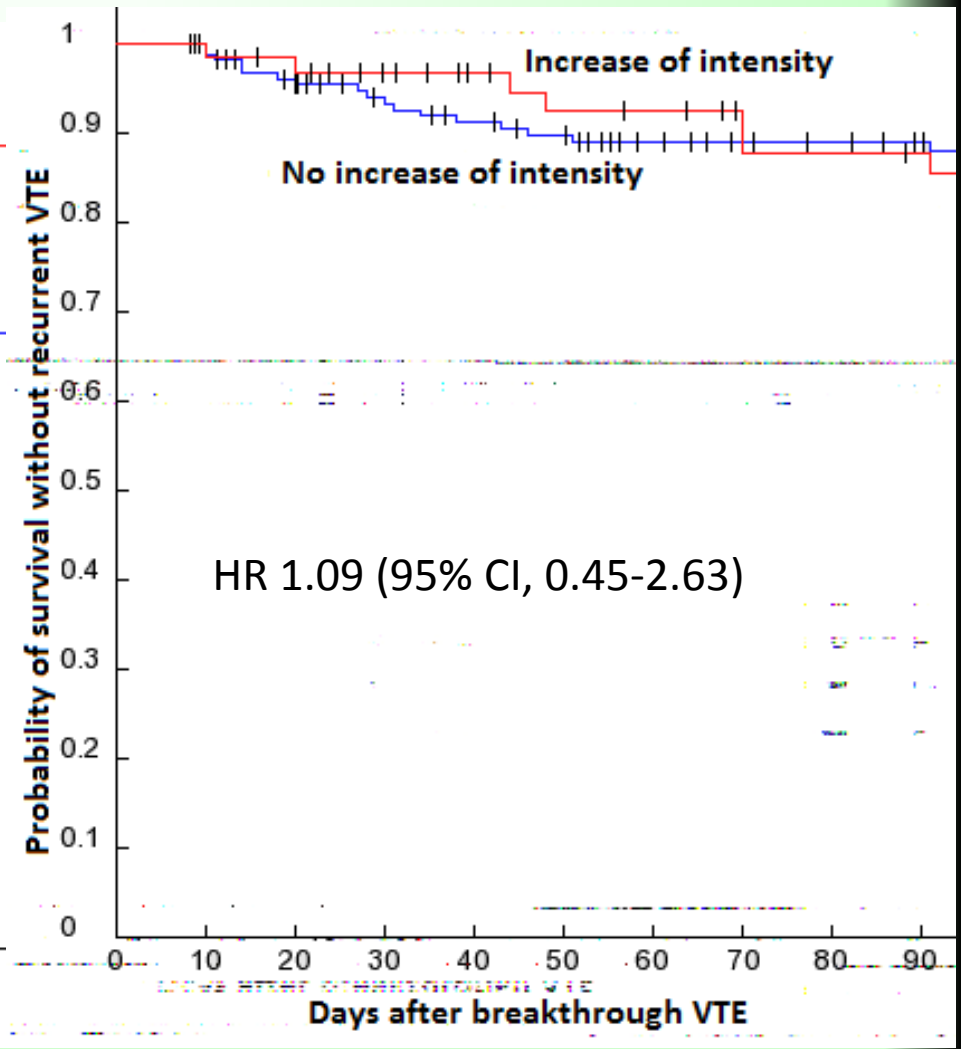
ISTH registry

- 212 patients with break-through VTE
- 59% had adenocarcinoma
- 73% had known metastases
- 70% were on LMWH, 27% on a VKA
- 70% had therapeutic dose or higher
- Patients followed for 3 months after the event

Schulman S et al. Thromb Haemost 2015;13:1010-8

New VTEs during 3 months

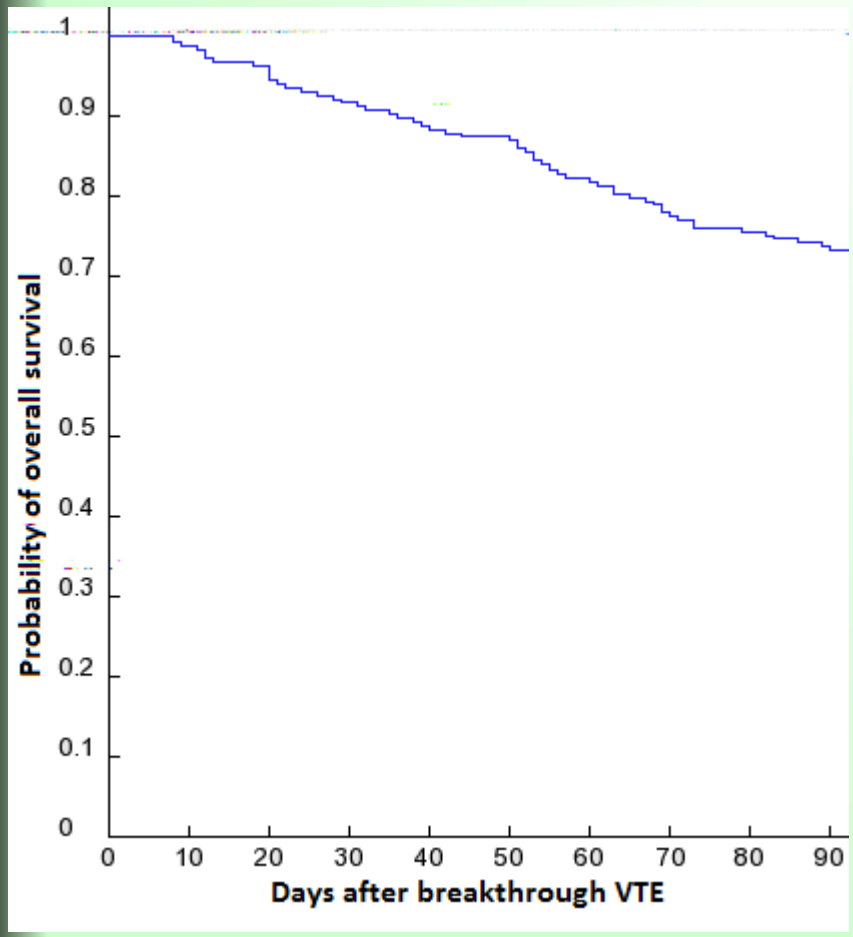




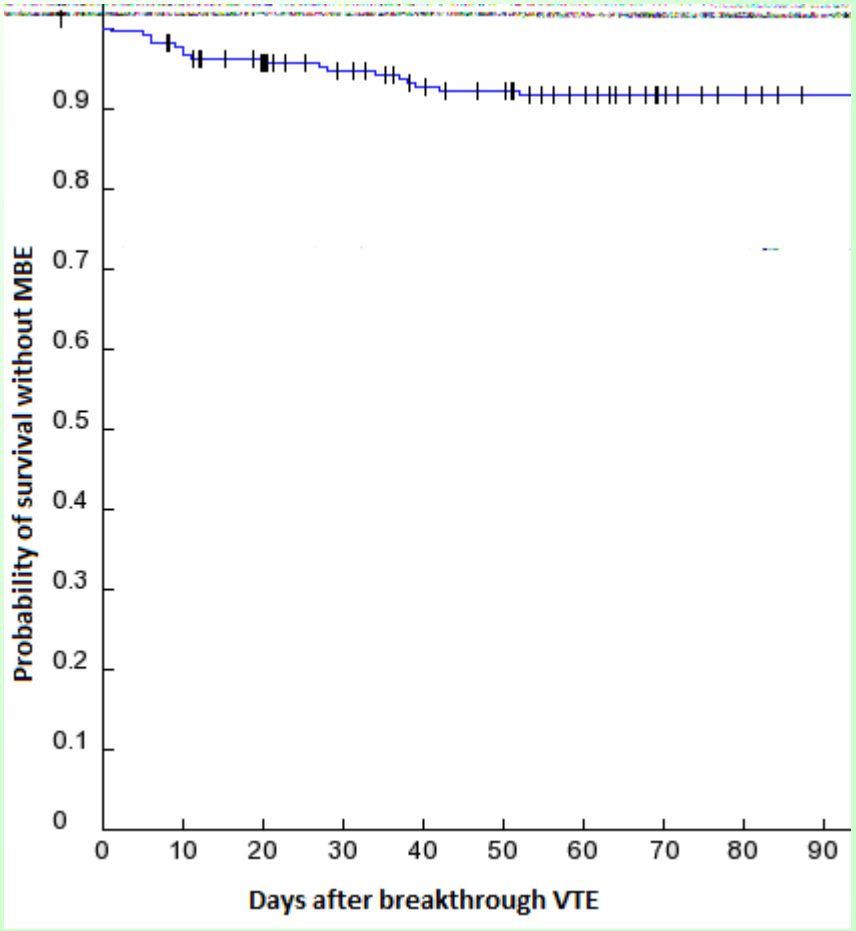
Schulman S et al. Thromb Haemost 2015;13:1010-8

Other outcomes after 3 months

Mortality



Major bleeds



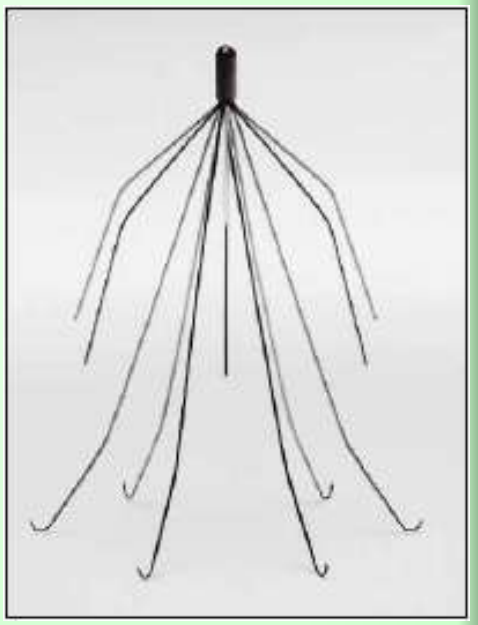
Schulman S et al. Thromb Haemost 2015;13:1010-8

Guideline recommendations in case of recurrence

- On therapeutic VKA → LMWH
  - Or increase target INR to 3.5 (ESMO)
- On prophylactic LMWH → Therapeutic LMWH
- On therapeutic LMWH
  - → increase by ¼ to ⅓ (ACCP)
  - → increase by 20-25% (ASCO)
  - Or guided by peak anti-Xa
    - LMWH q.d. – 1.6-2.0 U/mL
    - LMWH b.i.d. – 0.8-1.0 U/mL

IVC filter

- Possible option for recurrent VTE (ASCO, NCCN)
- Or as last resort (bleeding, severe thrombocytopenia) (ACCP, ESMO)



Conclusions

- VTE is a major cause of morbidity and mortality in cancer
- Anticoagulate as long as cancer is active
- For recurrence on warfarin – switch to LMWH
- If on LMWH – consider dose escalation.