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INNOVTE
F-CRIN NETWORK
INvestigation Network On Venous Thrombo-Embolism

Findings from the recent published clinical trials on thromboprophylaxis in cancer

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INSERM U1059 / F-CRIN network - INNOVTE

Disclosures: Bayer Healthcare, BMS, Boehringer-Ingelhein, Daiichi Sankyo, LEO, Pfizer, Portolla, SANOFI

Venous thromboembolic (VTE) prophylaxis in cancer pts

Rational for the use of thromboprophylaxis in cancer pts

1. **acute medical illnesses / immobilization**
2. **surgical/invasive procedures / immobilization**

extended/short term?
30 days / 7 days

3. **ambulatory setting**

long term? *3-6 months*

- **increase in overall survival**

- anti-tumoral effect?

- **decrease in VTE risk**

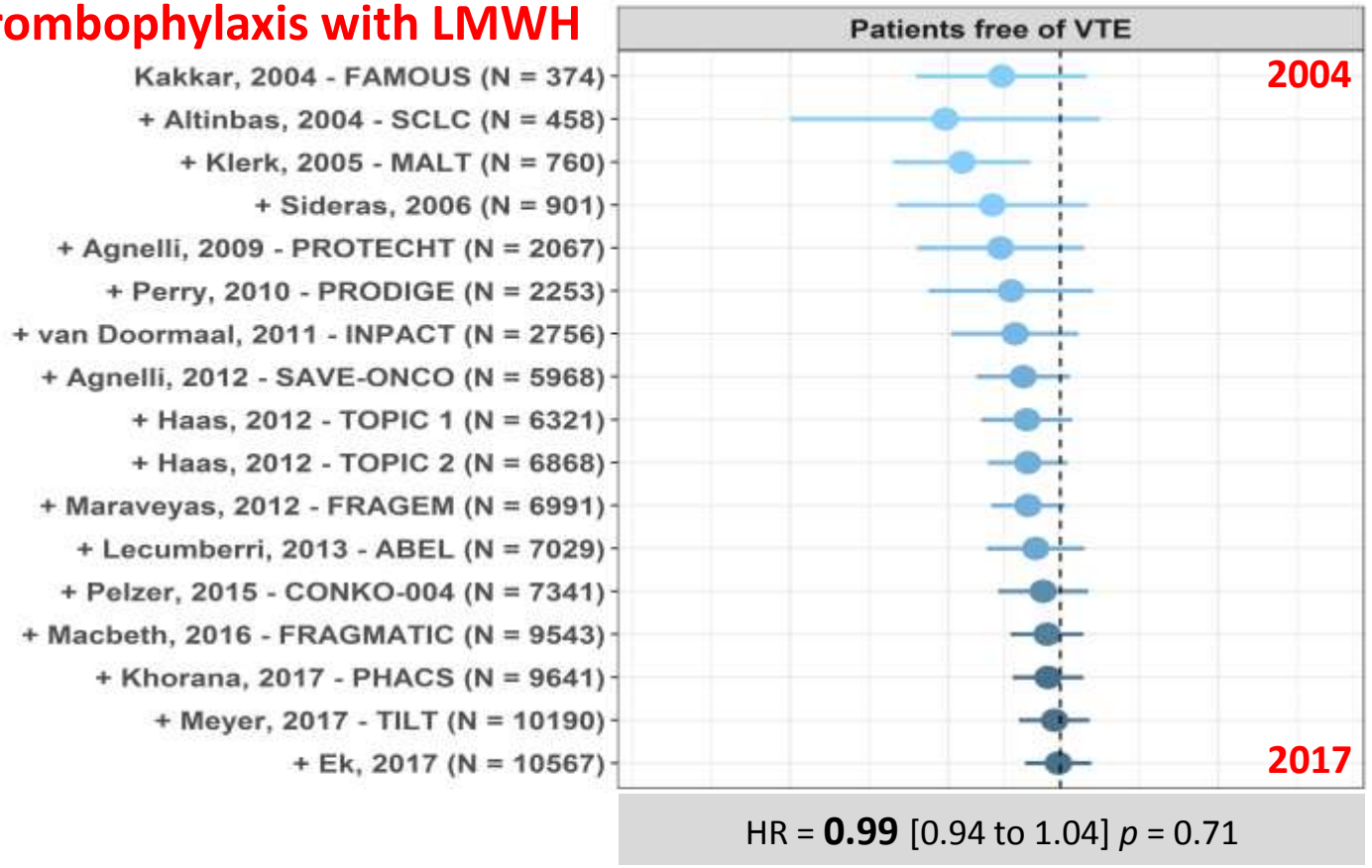
- antithrombotic effect?

  - tumor site and classification, vascular compression
  - chemotherapy / endocrine therapy / CVC
  - patients characteristics

Anti-tumoral effect of LMWH: impact on overall survival? updated cumulative meta-analysis

effect on overall mortality

Thrombophylaxis with LMWH



Laporte et al. *in press*

Thromboprophylaxis: → **no effect on overall survival**

→ **effect on VTE = main objective…**

VTE prophylaxis in ambulatory cancer pts & chemotherapy

LMWH *versus* **no thromboprophylaxis**: **meta-analysis** of 13 RCTs, 6,336 pts

	n RCTs	n pts	RR [CI95%] LMWH vs no prophylaxis	p
symptomatic VTE	9	3 284	**0.54** [0.38 ; 0.75]	0.0003
• **incidental VTE**	4	4 354	**0.66** [0.41 ; 1.08]	0.099
major bleeding	13	6 336	**1.44** [0.98 ; 2.11]	0.065
CR‡ bleeding	4	3 105	**3.40** [1.20 ; 9.63]	0.022
1-year mortality	8	2 304	**0.93** [0.80 ; 1.09]	0.37

‡ Clinically Relevant

Di Nisio et al. *Cochrane Databse Syst Rev* 2016;issue 12.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

SAVE-ONCO: **Semuloparin** *vs* **placebo -** median treatment duration **3.5 months**

	semuloparin n=1 608	**placebo** n = 1 604	RR [CI95%]	p
symptomatic VTE	**1.2** %	**3.4** %	**0.36** [0.21 ; 0.60]	<0.001
major bleeding	**1.2** %	**1.1** %	**1.05** [0.55 ; 2.00]	-
CRNM‡ bleeding	**1.6** %	**0.9** %	**1.86** [0.98 ; 3.68]	-
mortality	**43.4** %	**44.5** %	**0.96** [0.86 ; 1.06]	0.40

‡ Clinically Relevant Non Major

Agnelli et al. *New Engl J Med* 2012;366:601-9.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

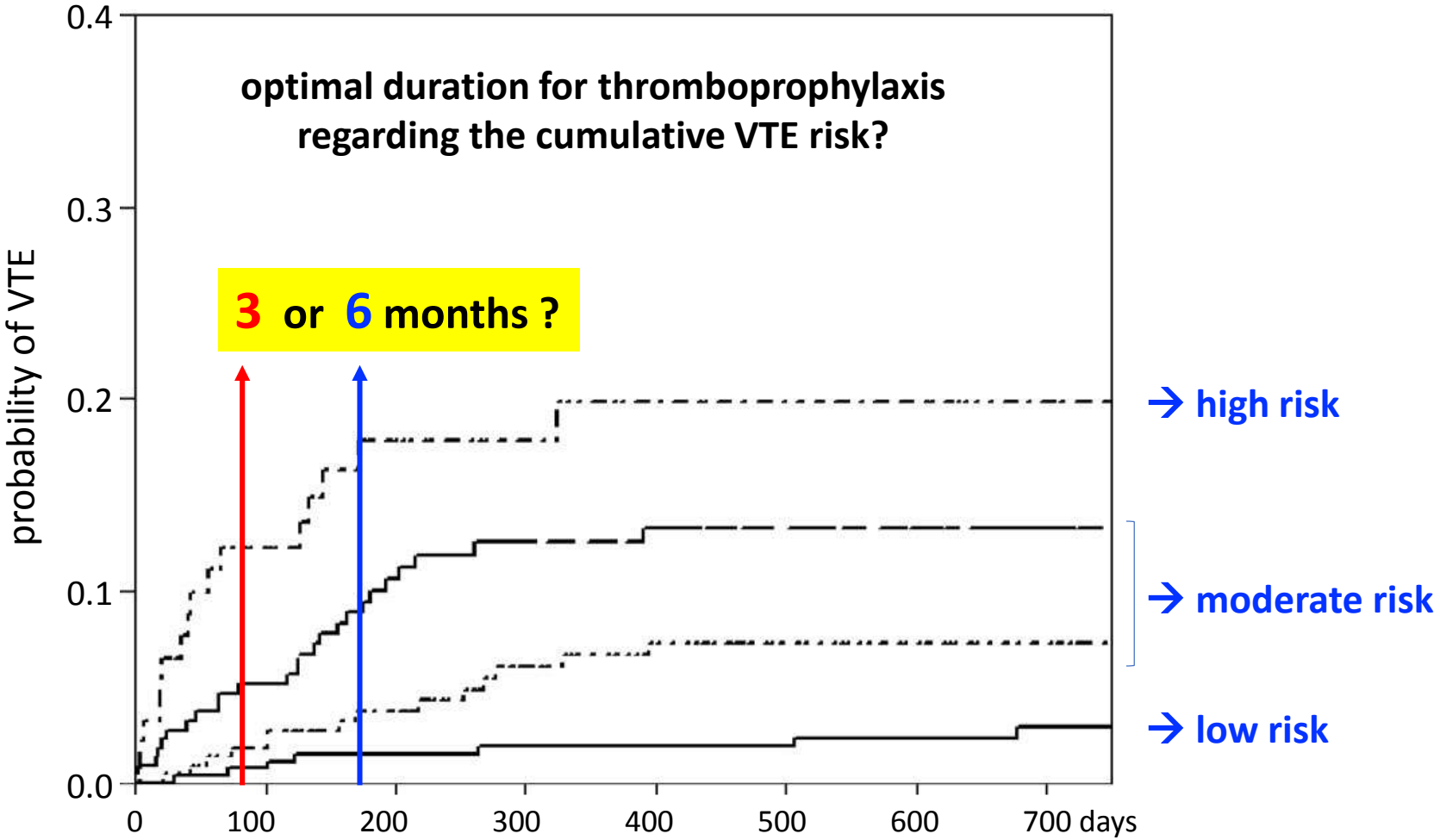
SAVE-ONCO study: tumor type and related VTE risk

	frequency	VTE risk	
Pancreas Bladder	~10 %	~10 %	very high
Lung	~40 %	~5 %	high
Colon / Rectum Stomach	~40 %	~2 %	moderate
Ovary	~10 %	<1 %	low

Agnelli et al. *New Engl J Med* 2012;366:601-9.

Optimal duration of VTE proph. in ambulatory cancer pts

819 cancer patients, 66% receiving chemotherapy, 37% with metastatpic disease



Ay et al. *Blood* 2010;116:5377-82.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

VTE prophylaxis: effective and safe but not routinely recommended / used…

- heterogeneous VTE risk - tumor / patients / chemotherapies
- bleeding risk
- parenteral anticoagulants - short duration despite cumulative VTE risk…
- competing risks - high mortality rate not related to VTE / bleeding

Further evaluations of VTE prophylaxis…

→ Homogeneous tumor and chemotherapy rather than broad indications…

→ Homogeneous study population *by using RAM* / VTE and bleeding risks…

→ Direct Oral Anticoagulants (DOACs) for 6 months rather shorter duration…

→ Systematic assessment of incidental VTE on top of symptomatic VTE…

FRAGMATIC trial: lung cancer (NSCLC + SCLC)

PROBE design - Dalteparin 5000 IU od for 24 weeks versus no LMWH
2,202 pts, 129 centres, median follow-up: 23 months, metastases: 61%, chemotherapy:83%

	LMWH	no LMWH	
NSCLC / SCLC	904 / 196	905 / 196	
1-year survival	**41.3** %	**42.5** %	HR = 1.01 [0.93 – 1.10] p=0.81
VTE outcomes	**5.5** %	**9.7** %	HR = 0.57 [0.42 – 0.79] p<0.001
• incidental PE	**1.3** %	**2.0** %	
Major bleeding	**1.1** %	**0.7** %	ns
M + CRNM bleeding ‡	**5.6** %	**1.3** %	p<0.001

‡ major and clinically relevant non major bleeding

McBeth et al. *J Clin Oncol* 2016;34:488-94.

Risk Assessment Model for VTE prophylaxis in cancer pts

Khorana score (KS)

- site of cancer
  - ✓ very high risk: stomach pancreas, brain → **2**
  - ✓ high risk: lung lymphoma, gynecologic, bladder, testicular → **1**
- prechemotherapy platelet count ≥ 350 G/L → **1**
- Hemoglobin level ≤100 g/L or use of cell growth factors → **1**
- Prechemotherapy leukocyte count ≥ 11 G/L → **1**
- BMI ≥ 35 kg/m^2 → **1**

Khorana et al. *Blood* 2008;111:4902-7.

KS = **0**	- VTE risk = **1.5%**	→ **low** risk
KS = **1**	- VTE risk = **3.8%**	→ **intermediate** risk
KS = **2**	- VTE risk = **9.6%**	
KS **≥ 3**	- VTE risk = **17.7%**	→ **high** risk

Ay et al. *Blood* 2010;116:5377-82.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

SAVE-ONCO: impact of Khorana score & VTE risk factors on VTE risk / placebo group

	n	% population	VTE risk
KS # =0 → low risk	312	20 %	1.6 %
KS=1-2 → intermediate	1,017	63 %	3.5 %
KS ≥ 3 → high	272	17 %	5.2 %
TOTAL	1,601	100 %	3.4 %

x 2,5

x 4.1

Khorana score : tumor type, platelet, red cell, leukocyte, obesity

Chen et al. *Am J Hematol* 2017;392:E101-E103.

PHACS (Prophylaxis of High-risk Ambulatory Cancer patients Study) study: KS ≥ 3

Open design - Dalteparin 5000 IU od for 12 weeks versus no LMWH

- cancer patients with a **Khorana score ≥ 3**
- new chemotherapy (first or new regimen), CUS‡ / 4 weeks & CT scan at 12 weeks

	LMWH 50	no LMWH 48	
pancreas, stoach	46 %	48 %	
lung, gynecologic,lymphoma	30 %	27 %	
all VTE	**12 %**	**21 %**	HR = **0.69** [0.23 – 1.89] ns
symptomatic VTE	4 %	4 %	
incidental PE	2 %	6 %	
proximal DVT (CUS)	4 %	10 %	
Major bleeding	2.0 %	2.1 %	ns
Major + CRNM bleeding	**12 %**	**2.1 %**	HR = **7.02** [1.24 – 131] p=0.025

‡ Compression Ultrasonography

Khorana et al. *Thromb Res* 2017;151:89-95.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

LMWH *versus* **no thromboprophylaxis**: updated meta-analysis

		weighted incidence [CI95%]			
		LMWH	**no treatment**	RR [CI95%]	p
symptomatic VTE	11 RCTs 5,284 pts	**3.9** % [3.2 - 4.6]	**7.7** % [6.7 - 8.8]	**0.56** [0.45 ; 0.69]	<0.0001
major bleeding	13 RCTs 6356 pts	**2.0** % [1.6 - 2.5]	**1.5** % [1.0 - 1.9]	**1.44** [0.98 ; 2.11]	0.065

NNT = 26 **NNH = 200**

personnal data

Risk Assessment Model for VTE prophylaxis in cancer pts

To optimize the Khorana score (KS)

→ **to identify a higher proportion of patients at risk** <20% with a KS ≥3

Chen et al. *Am J Hematol* 2017;392:E101-E103.

→ **to better identify patients at low risk** VTE >5% with a KS =0

Cella et al. *The Oncologist* 2017;22:1-8.

40% of the score are related to the tumor type

60% of the score are related to prechemotherapy blood cells counts & obesity

adding - specific biomarkers (D-Dimers, P-selectin…) Vienna CATS Ay et al. Blood 2010

- data regarding chemotherapy (platinum…) PROTECHT Verso et al. Intern Emerg Med 2013

- some clinical risk factors (history of VTE…) ONKOTEV Cella et al. The Oncologist 2017

VTE prophylaxis in ambulatory cancer pts & chemotherapy

SAVE-ONCO: impact of Khorana score & VTE risk factors on VTE risk / placebo group

	n	frequency	VTE risk
KS [#] =0 → low risk	312	20 %	1.6 %
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Chen et al. *Am J Hematol* 2017;392:E101-E103.

		n	frequency	VTE risk
risk factor for VTE [‡]	= 0	1,855	58 %	2.5 %
	≥ 1	1,357	42 %	4.8 %

‡ central venous line, obesity, age ≥ 75 yr, chronic heart or respiratory failure, venous insufficiency / history of VTE

Agnelli et al. *New Engl J Med* 2012;366:601-9.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

ONKOTEV study: multivariate analysis taking into account the competing risk in **843** ambulatory pts, median follow-up **8.3 months**, **VTE = 8.6%**

Independant predictors	sHR‡ [CI95%]	score
• **Khorana score > 2**	**2.51** [1.3-5.0]	**1**
• **metastatic disease**	**3.09** [1.7-5.5]	**1**
• **vasc/lymph. compression.**	**2.64** [1.5-4.7]	**1**
• **history of VTE**	**2.09** [1.1-3.9]	**1**

ONKOTEV score	% pop	VTE risk	increase in VTE risk (sHR)
• score **>2**	6%	33.9%	
• score **=2**	9%	19.4%	x 13.7
• score **=1**	43%	9.7%	x 6.5
• score **=0**	37%	3.5%	x 3.3

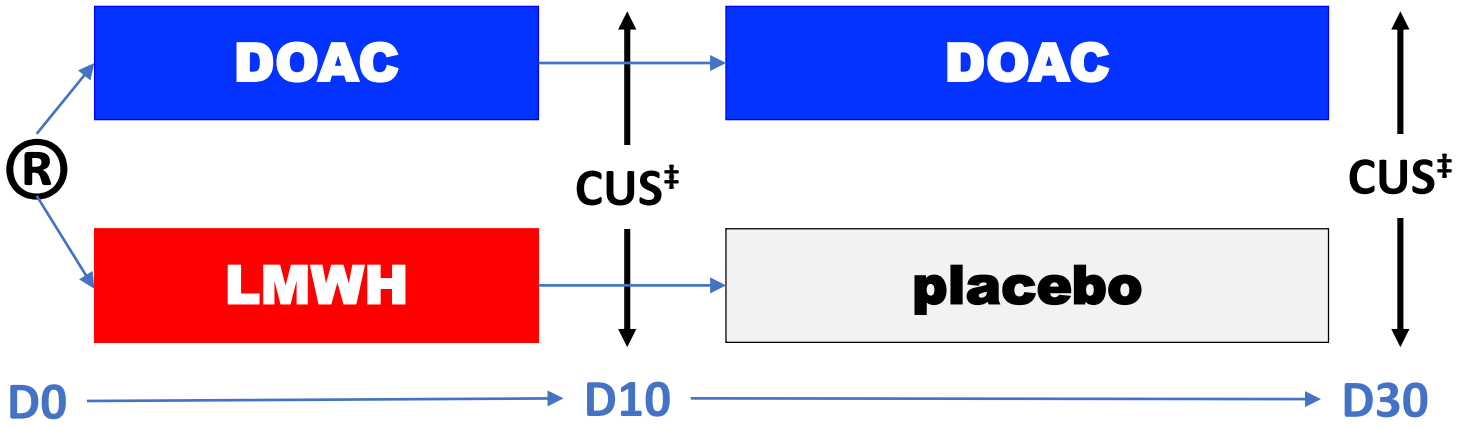
‡ subdistribution Hazard Ratio / fine & Gray model

Cella et al. *The Oncologist* 2017;22:1-8.

DOACs in cancer pts: Extended vs short term prophylaxis in hospitalized medically ill patients

- **MAGELLAN** rivaroxaban vs enoxaparin — Cohen et al. *New Engl J Med* 2013;368:513-23.
- **ADOPT** apixaban vs enoxaparin — Goldhaber et al. *New Engl J Med* 2011;365:2167-77.
- **APEX** betrixaban vs enoxaparin — Gibson et al. *N Engl J Med* 2016;375:634-44.

→ 3 studies = 21,831 patients - **13% with an history of cancer**

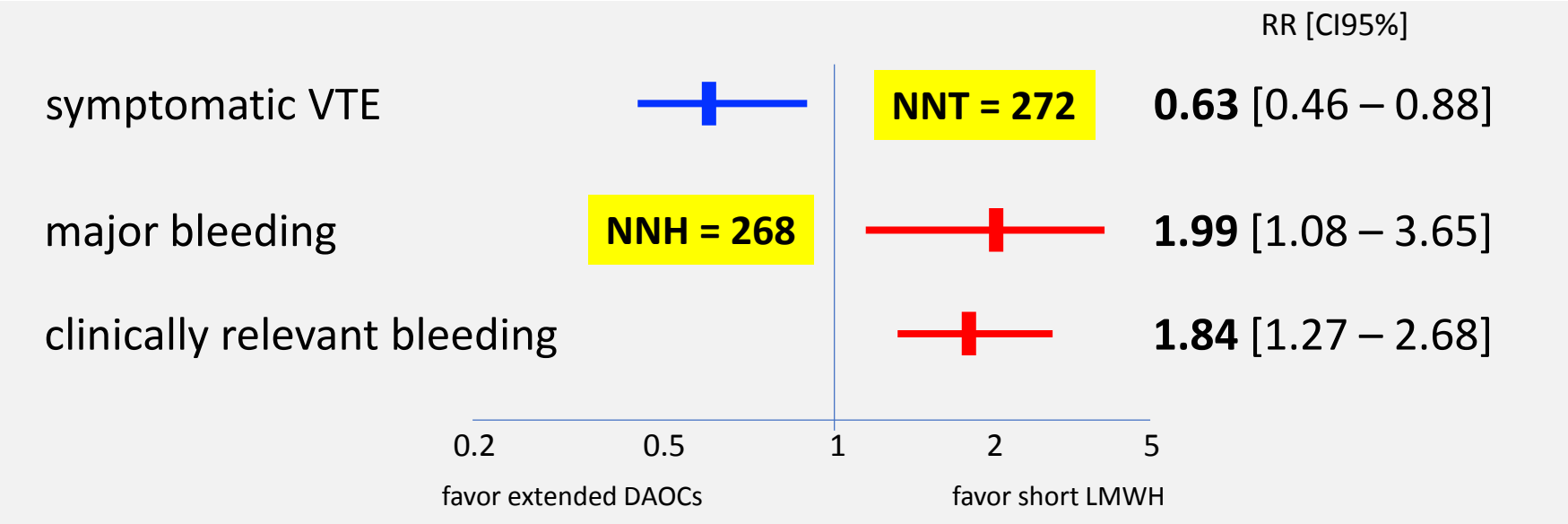


‡ Compression UltraSonography

→ at D10 only for MAGELLAN & ADOPT
→ at D30 for the 3 studies

Extended VTE prophylaxis with DOACs in medically ill pts

Meta-analysis of ADOPT, APEX, MAGELLAN: *extended* DOACs vs *short* LMWH



Al Yami et al. *J Blood Med* 2018;9:25-34.

Treament of CAT with DOACS: Hokusai cancer – edoxaban vs Daltepatin

→ significant increase in major bleeding (especially gastrointestinal)

HR major bleed. edox vs dalte **= 1.77** [CI95% 1.03 – 3.04], p=0.04

Raskod et al. *N Engl J Med* 2018;378:615-624.

First experience with DOAC for thromboprophylaxis in ambulatory cancer patient undergoing chemotherapy

phase II study from june 2006 → sept 2008 – early stop / slow recruitment:
patients with advanced or metastatic cancer receiving either 1st or 2nd-line chemotherapy

treatment duration: 12 weeks	**Apixaban 5 mg od** n=32	**Apixaban 10 mg od** n=29	**Apixaban 20 mg od** n=32	**placebo** n=29
M+CRNM bleeding‡	**3.1 %**	**3.4 %**	**12.3 %**	**3.4 %**
Major bleeding	**0.0 %**	**0.0 %**	**6.3 %**	**3.4 %**
Symptomatic VTE	**0.0 %**	**0.0 %**	**0.0 %**	**10.3 %**

‡ major + clinically relevant non major bleeding

Levine et al. *J Thromb Haemost* 2012;10:807-14.

VTE prophylaxis in ambulatory cancer pts & chemotherapy

AVERT study NCT02048865

- **apixaban 2.5 mg bid** versus **placebo** for 6 months for thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

- outcomes: - symptomatic and asymptomatic VTE
  - major and minor bleedings

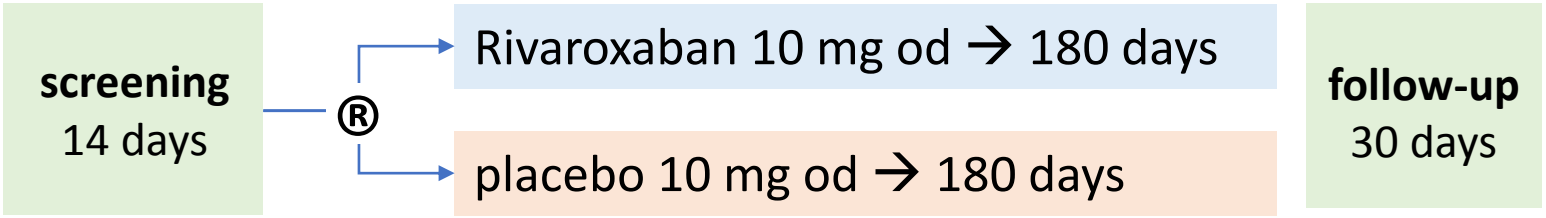
- 574 participants, planned from january 2014 → august 2019

- contacts: M. Carrier, Canada

VTE prophylaxis in ambulatory cancer pts & chemotherapy

CASSINI study NCT02555878

- **centrally randomized, double-blind, centrally adjudicated study**



- **inclusion criteria** - ≥18 years, ECOG PS 0-2, Khorana score ≥2, CrCl ≥30 mL/mn
  - solid tumors locally advanced or metastic

- **outcomes / 180d ± 3** - symptomatic + incidental VTE + asymptomatic proximal DVT
  - major bleeding (ISTH)

- **700 pts** with 6% vs 14.5% / 2-sided type I error = 5%, power = 80% / competing risks

Khorana et al. *Thromb Haemost* 2017

Thromboprophylaxis in ambulatory cancer patients

Unclear benefit-to-risk ratio but favourable background and promising results

1. Improvement of cancer therapy → decrease in competing risk

- easier to identify strong predictors of VTE risk: biomarkers
- easier to develop effective / easy-to-use RAM for both VTE & bleeding risk

2. Development of DOACs

- oral / no drug monitoring / favourable safety profile in other indications
- no evidence for strong drug-drug interaction with chemotherapy

Pending these results, thromboprophylaxis with LMWH could be discussed as following:

→ **ambulatory long-term** for cancer patients at very high risk

→ **extended** in case of major surgery / invasive procedure

→ **short-term** in case of acute medical event with restricted mobility