CASSINI

Alok A. Khorana, MD, FACP

@aakonc

Sondra and Stephen Hardis Chair in
Oncology Research

Professor of Medicine, Cleveland Clinic
Lerner College of Medicine/Case
Western Reserve University

Taussig Cancer Institute

Cleveland Clinic

DISCLOSURES

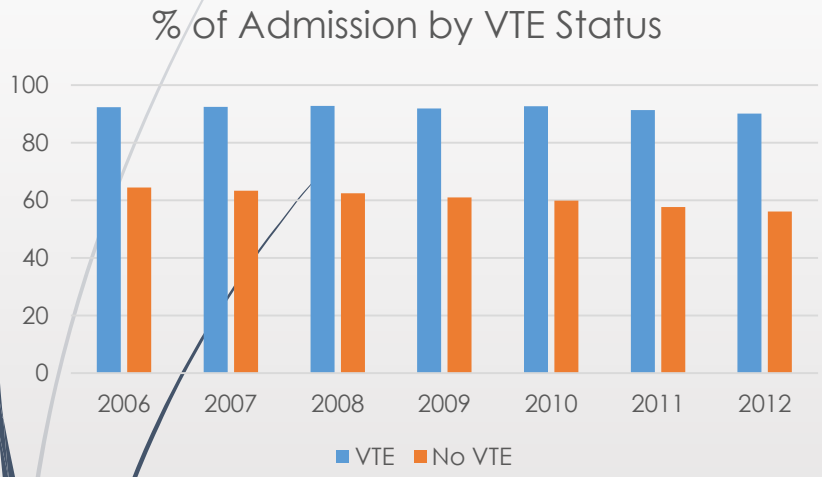
- Janssen
- Sanofi
- Halozyme
- Bayer
- Pfizer
- AngioDynamics

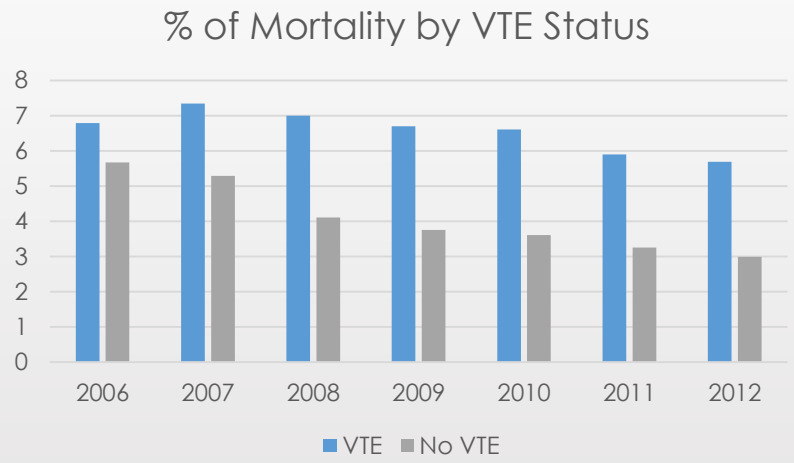
CAT Is Consequential

- Cancer patients with VTE had
  - 3-fold increase in all-cause hospitalizations (mean 1.38 versus 0.55 per patient)
  - 3-fold increase in days in hospital (10.19 versus 3.37) (all $P < 0.0001$).
- Cancer patients with VTE incurred
  - higher overall all-cause inpatient costs (mean $21,299 versus $7459 per patient),
  - outpatient costs ($53,660 versus $34,232 per patient), and
  - total health care costs ($74,959 versus $ 41,691 per patient) (all $P < 0.0001$).
- Mean VTE-related costs : $9247 / patient / year
- Adjusted mean incremental all-cause costs of VTE : $30,538 /patient

Khorana et al, *Clin Econ Outcomes Res* 2013

Results: Rates of Admission and Mortality In Patients With and Without VTE





92% vs 61%, p-value< .0001

6.5% vs 4%, p-value< .0001

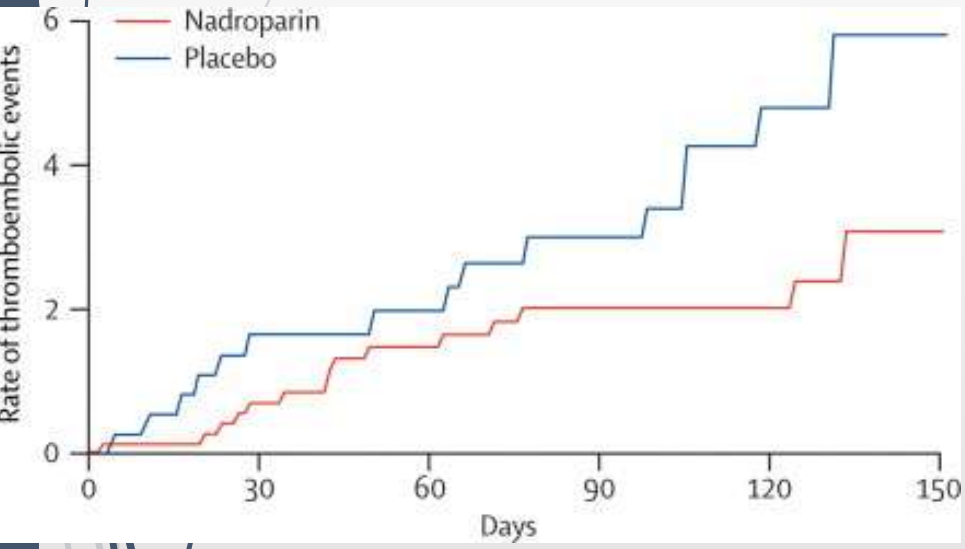
*AOR: 6.7, 95% CI: 6.54-6.80, p-value: <.0001

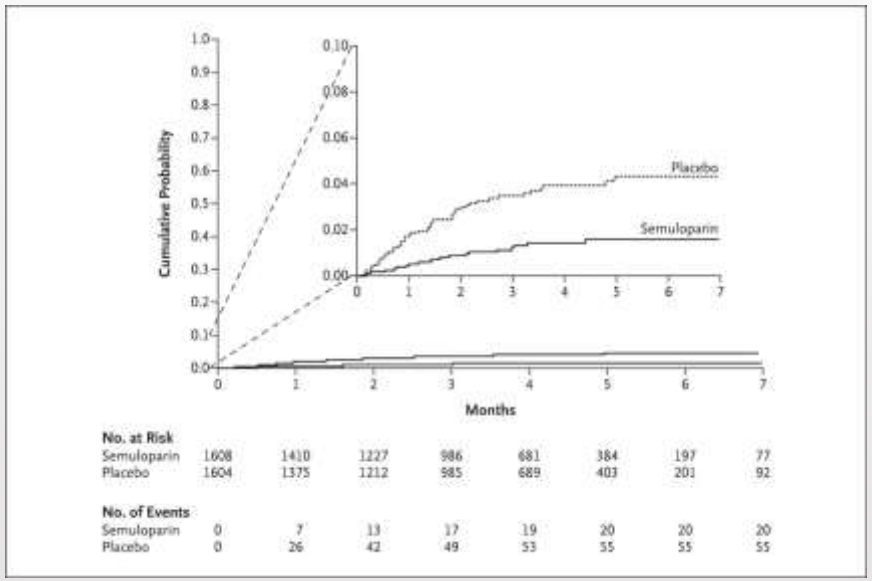
*AOR: 1.25, 95% CI: 1.23-1.28, p-value< .0001

*Models were adjusted for age, sex and cancer types

Chen et al, ASH 2017

VTE in Large Outpatient Studies: *Statistically But Not Clinically Significant*





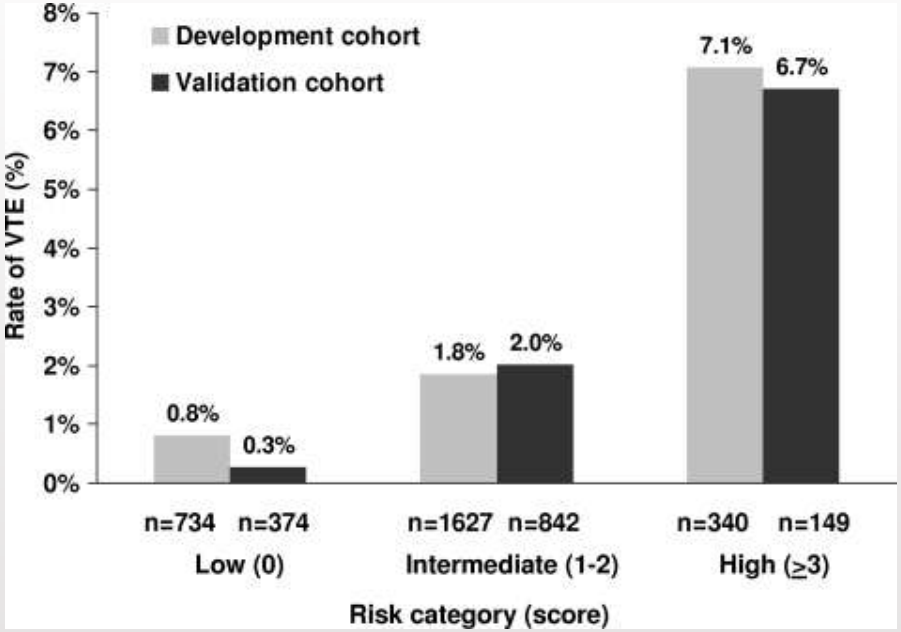
PROTECHT: N=1,150

SAVE ONCO: N=3,212

Agnelli et al *Lancet Onc* 2009
Agnelli et al NEJM 2012

Risk Score Development and Validation

Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1



Khorana AA et al. *Blood* 2008

Funding: NCI K23CA120587

Validation of Risk Score
N>15,000

Table 2 Selected external validation studies of the Khorana score

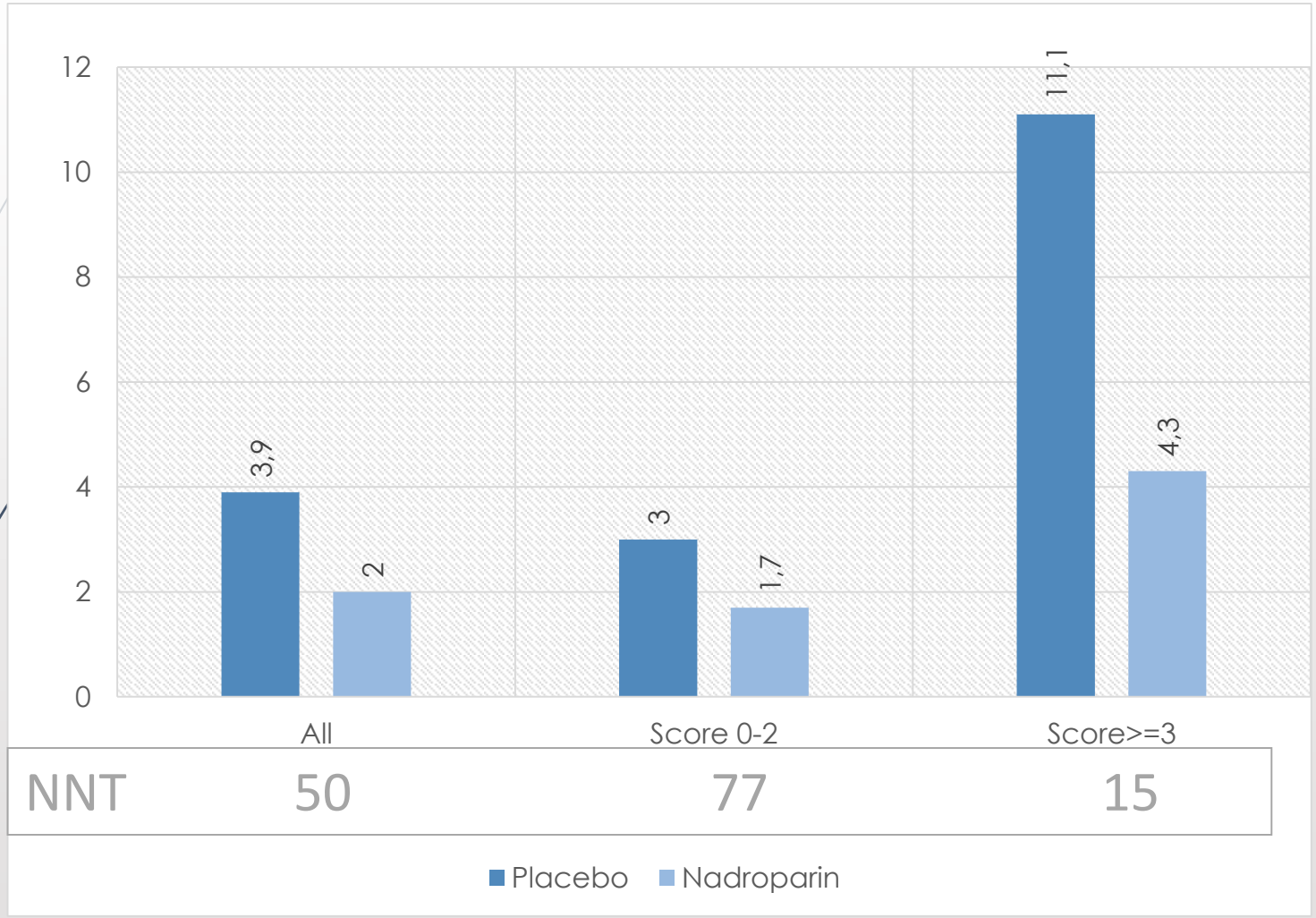
Study	Type, specific patient population	Duration	No. of patients Total $n = 12{,}064$	Low-risk (score = 0); rate of VTE	Intermediate-risk (score = 1–2); rate of VTE	High-risk (score ≥ 3); rate of VTE
Kearney et al (2009)[54]	Retrospective	2 y	112	5%	15.9%	41.4%
Price et al (2010)[55]	Retrospective, pancreatic	NA	108	NA	14%	27%
Ay et al (2010)[56]	Prospective	643 d	819	1.5% (0.6–3.9%)	Score = 1; 3.8% (1.9–7.4%) Score = 2; 9.6% (6.2–14.7%)	17.7% (95% CI: 11.0–27.8%)
Moore et al (2011)[57]	Retrospective, tx with cisplatin		932	13%	17.1%	28.2%
Mandala et al (2012)[58]	Retrospective, phase I	2 mo	1,415	1.5%	4.8%	12.9%
Verso et al (2012)[13]	Retrospective	113 d	378	3%		11.1%
Sharma et al (2012)[59]	Retrospective	NA	150	1.9%	3.9%	9.1%
Moinat et al (2014)[60]	Prospective, CVP	3 mo	1,097	NA	NA	OR: 3.5 (95% CI: 1–12.3)
Khorana et al (2014)[22]	Prospective	3 mo	35	NA	NA	23%
Lustig et al (2015)[61]	Prospective	3 mo	580	4%	NA	11% (score ≥2)
Srikanthan et al (2015)[62]	Retrospective, disseminated GCT	11 y	254	NA	NA	OR: 11.8; $p < 0.001$
Santi et al (2015)[63]	Pooled analysis, NHL	NA	1,717	2.2% (95% CI, NA)	4.5% (95% CI: 2.3–6.7)	6.6% (95% CI: 24–10.8)
Posch et al (2016)[30]	Prospective	2 y	1,685		Score = 1; HR:3.23 (1.53–6.81, $p = 0.002$) Score = 2; HR:4.63 (2.20–9.75, $p < 0.001$)	HR 6.47 (2.99–14.00, $p < 0.001$)
Patell et al (2016)[44]	Retrospective	1 y	2,782	NA	Score ≥ 2 OR: 1.71 (1.16–2.59)	OR: 2.54 (1.29–5.03)

Abbreviations: CVP, central venous port; GCT, germ cell tumor; HR, hazard ratio; NA, not available; NHL, non-Hodgkin lymphoma; OR, odds ratio; tx, treatment.

Angelini & Khorana, *Sem Throm Hem* 2017

Risk Assessment and Prophylaxis

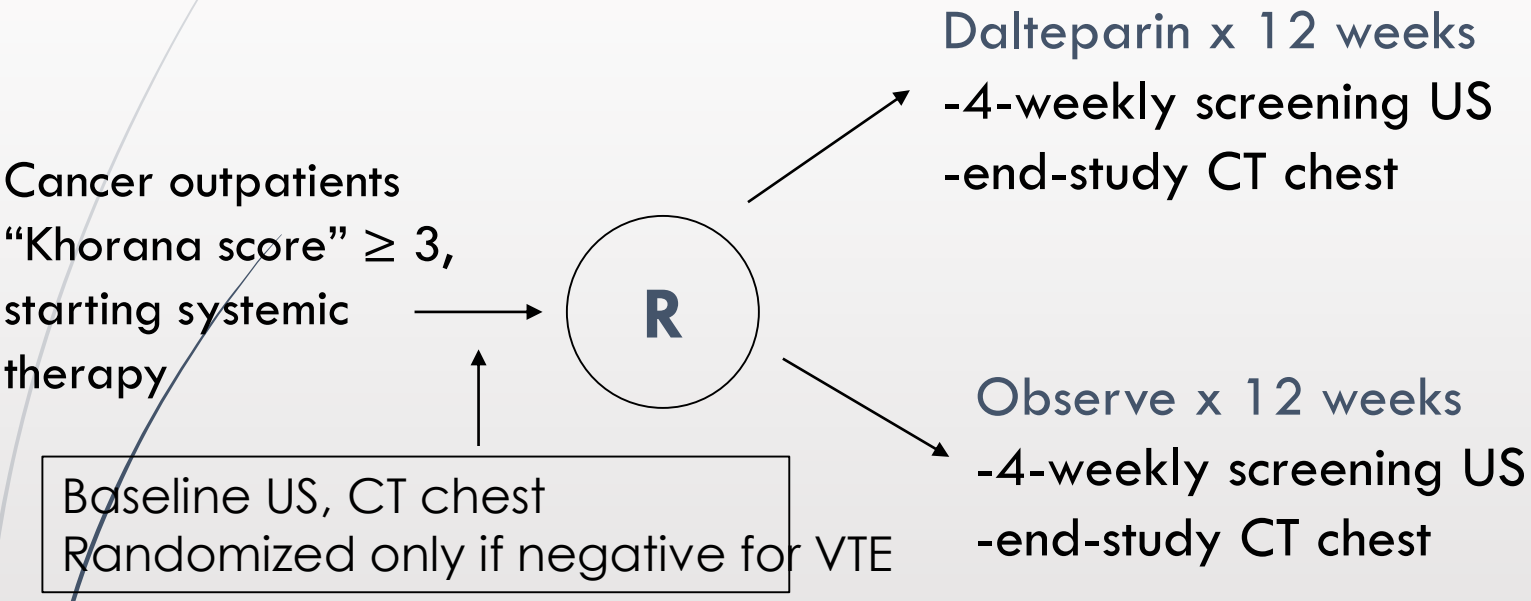
PROTECHT by Risk Score



Verso et al, *Int Emerg Med* 2012

PHACS Study Design

Objective: To compare the safety and efficacy of prophylaxis with dalteparin to observation in reducing VTE in high-risk ambulatory cancer patients initiating chemotherapy



PI: CW Francis (UR) Sites: University of Rochester (lead), Duke, University of Ottawa, University of California-Davis, Roswell Park

US= compression ultrasonography of lower extremities

Khorana et al, *Throm Res* 2016

PHACS

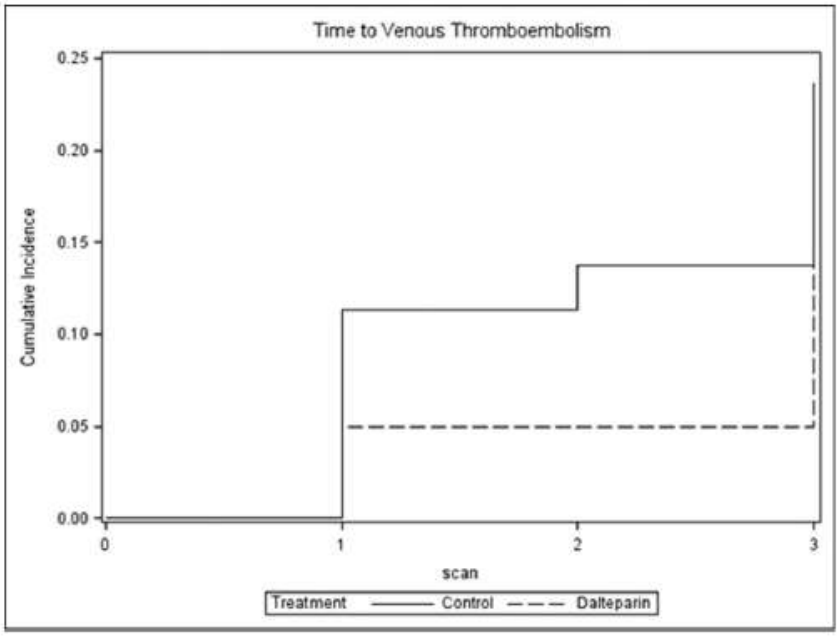


Table 3
Primary and secondary efficacy outcomes in PHACS[a].

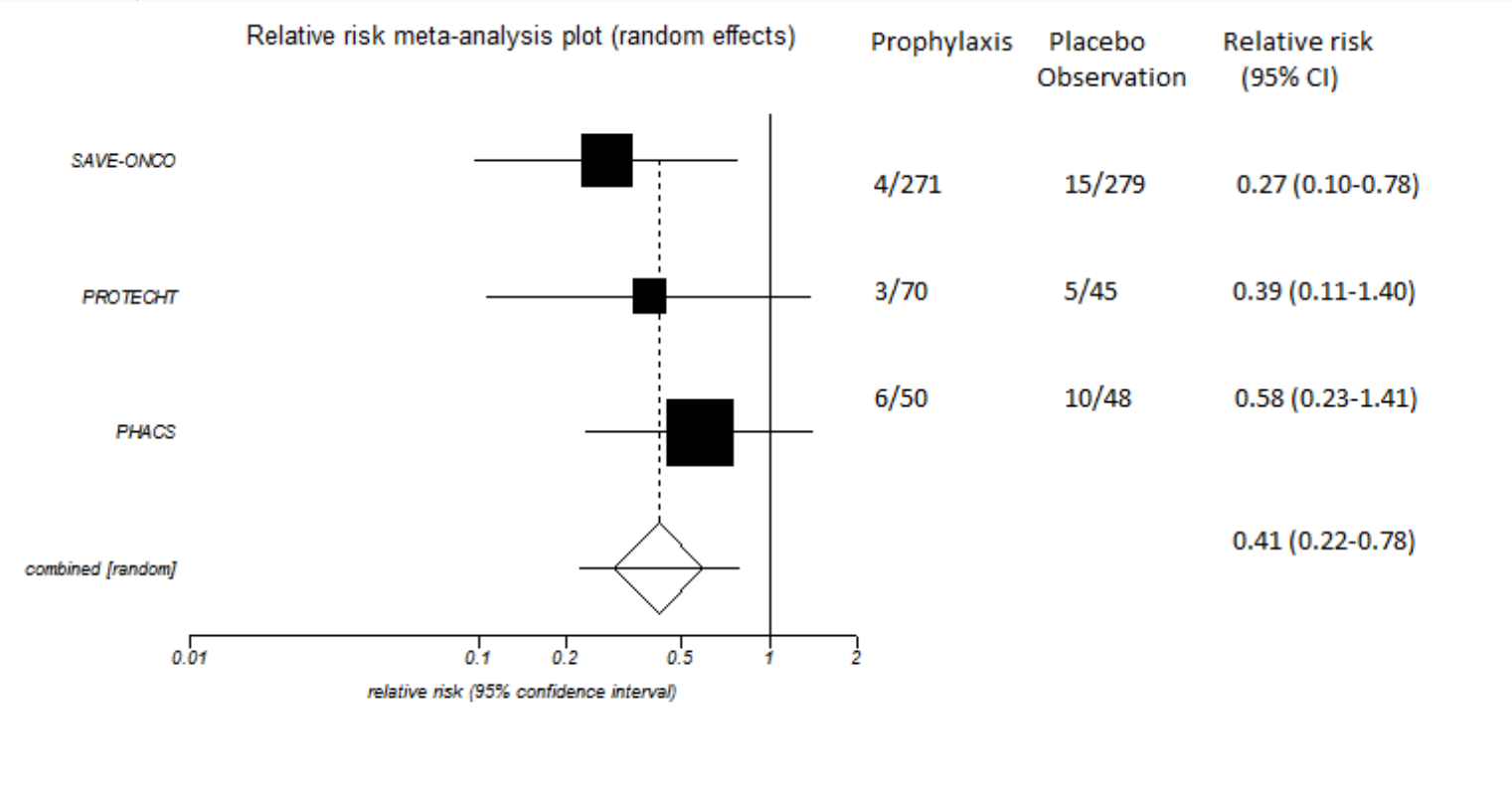
	Dalteparin (n = 50)	Observation (n = 48)
All VTE, n (%)	6 (12%)	10 (21%)
Symptomatic DVT, n (%)	0 (0%)	1 (2%)
Symptomatic non-fatal PE, n (%)	2 (4%)	1 (2%)
Fatal PE, n (%)	0 (0%)	0 (0%)
Screen-detected proximal DVT, n (%)	2 (4%)	5 (10%)
Screen-detected PE, n (%)	2 (4%)	3 (6%)

[a] Events occurring during the 12 week intervention period.

Khorana et al, *Throm Res* 2016

Meta-analysis of study patients with "Khorana score" ≥ 3: SAVE-ONCO[1], PROTECHT[2] and PHACS[3]

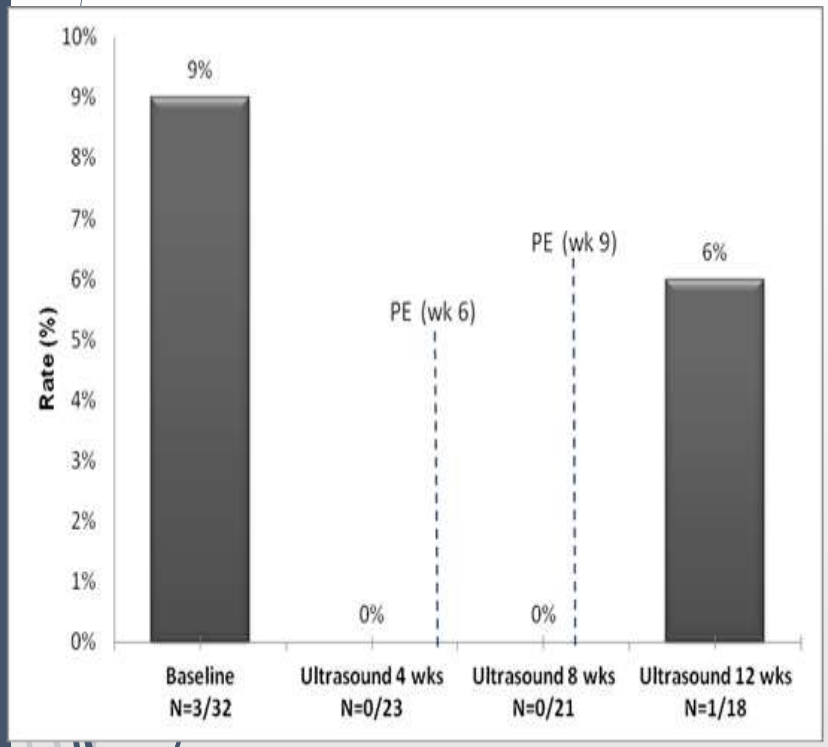
N=763 patients with score ≥ 3



Pooled RR for VTE with prophylaxis 0.41 (95% CI: 0.22 to 0.78); P = 0.006

[1]George et al 2011; [2]Verso et al 2012
[3]Khorana et al *Throm Res* 2016

Applying Risk Assessment
Early Detection



UR single institution, KS>=3

Baseline characteristics of study population.

	Dalteparin	Observation	Total
Enrolled (n)	–	–	117
Baseline VTE, n (%)	–	–	10 (9%)

PHACS, multicenter KS>=3

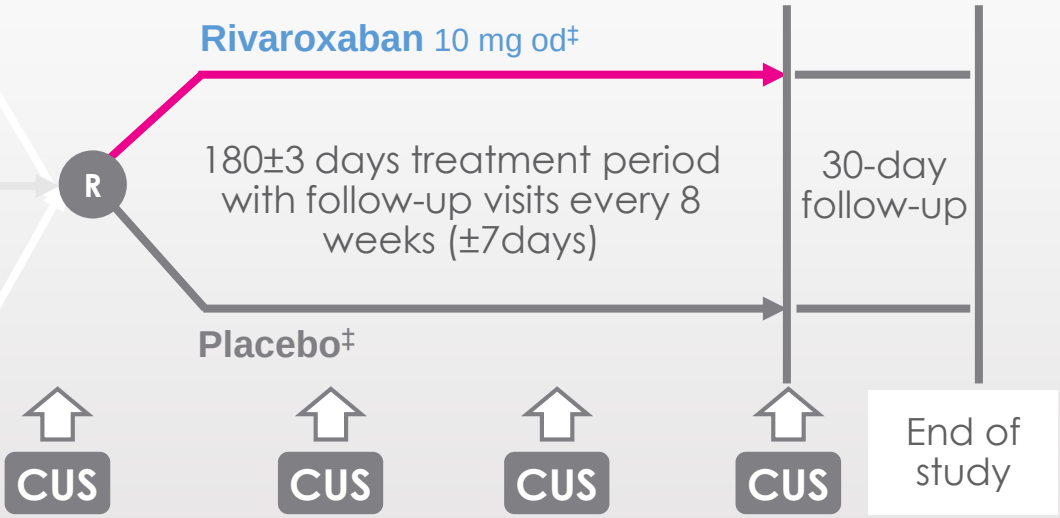
Khorana AA et al *Throm Res* 2014
Khorana AA et al *Throm Res* 2016

CASSINI Trial Design

VTEp Phase IIIb Study in Cancer Patients at High Risk of VTE

Rationale: Assess the efficacy and safety of rivaroxaban versus placebo for VTE prophylaxis in ambulatory cancer patients initiating systemic cancer therapy and at high risk of VTE[1]

Patients with various cancer types initiating systemic chemotherapy at high risk of VTE*
N~700#



Short design: Multinational, multicentre, randomized, double-blind, placebo-controlled phase IIIb superiority study

Indication: VTEp patients with cancer

FPFV: Q4/2015
LPLV: TBC

*As indicated by a Khorana risk score ≥ 2[1]; #subjects will be stratified at randomization by tumour type (pancreatic or other; up to appr. 25% of the subjects randomly assigned are those with advanced pancreatic cancer); ‡systemic cancer therapy will be initiated within 72 hrs of the first dose of study drug when at all possible, or within ±1 week of receiving the first dose of study drug with the intention of continuing systemic cancer therapy during the double-blind treatment period
CUS: compression ultrasound (at screening and Follow-up visits)

1. NCT02555878 (https://clinicaltrials.gov/ct2/show/NCT02555878?term=rivaroxaban+ambulatory&rank=1) 2. Khorana AA *et al*, *Blood* 2008;111:4902–4907

Study Update

- Last patient enrolled early 2018, N=841
- Anticipate completion of study follow-up period late 2018
- Hoping for presentation of topline data late 2018 or early 2019