# SHOULD PRIMARY THROMBOPROPHYLAXIS BE OFFERED TO ALL AMBULATORY CANCER PATIENTS? MY POSITION : NO

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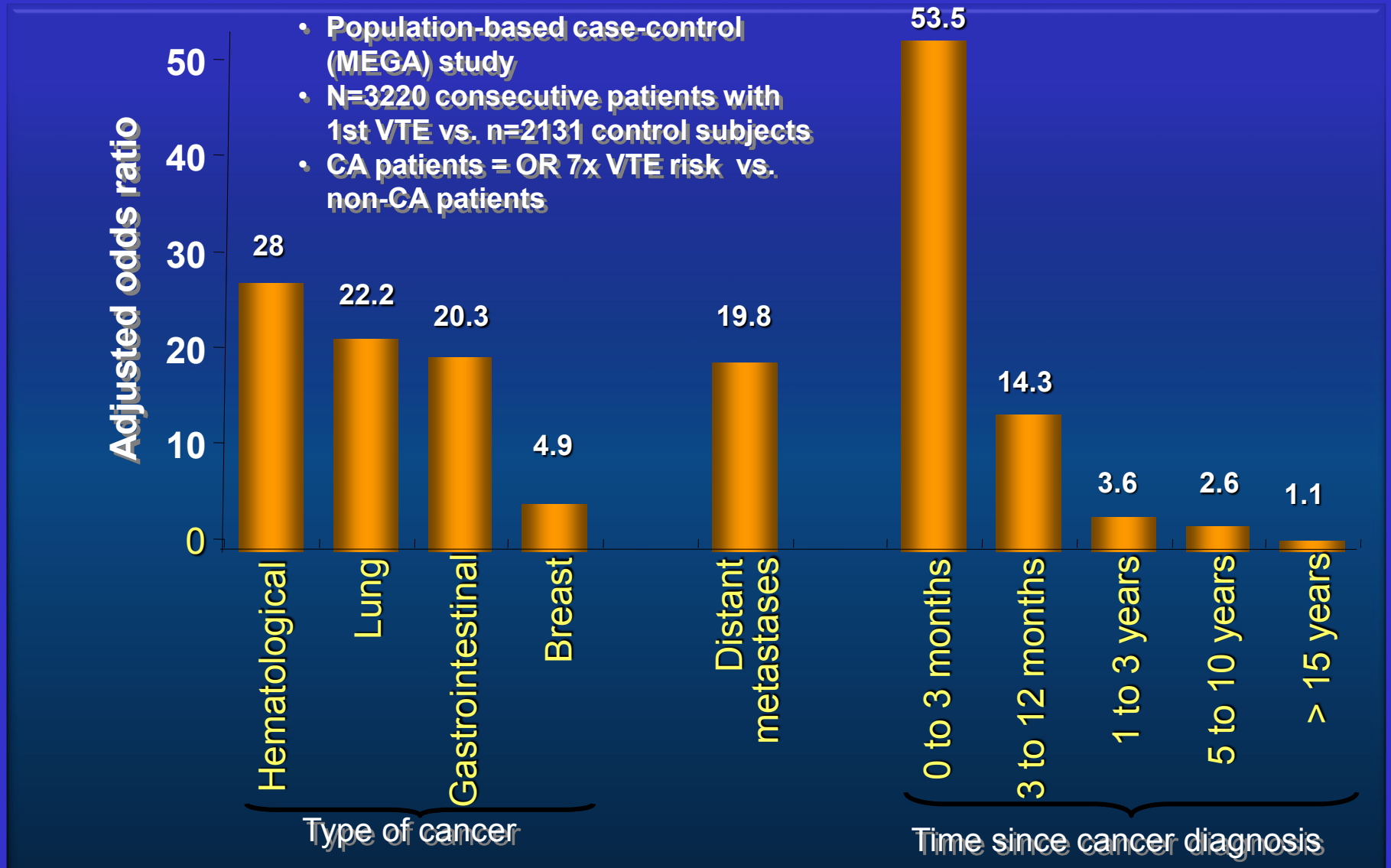
# NO CONFLICT OF INTEREST

# Venous thromboembolic disease in cancer

- Thromboembolism is the second leading cause of death in cancer patients[1,2]
- VTE occurs in over 20% of cancer patients through their lifetime[3]
- VTE may be present in as much a 50% of patients at the time of death[4]

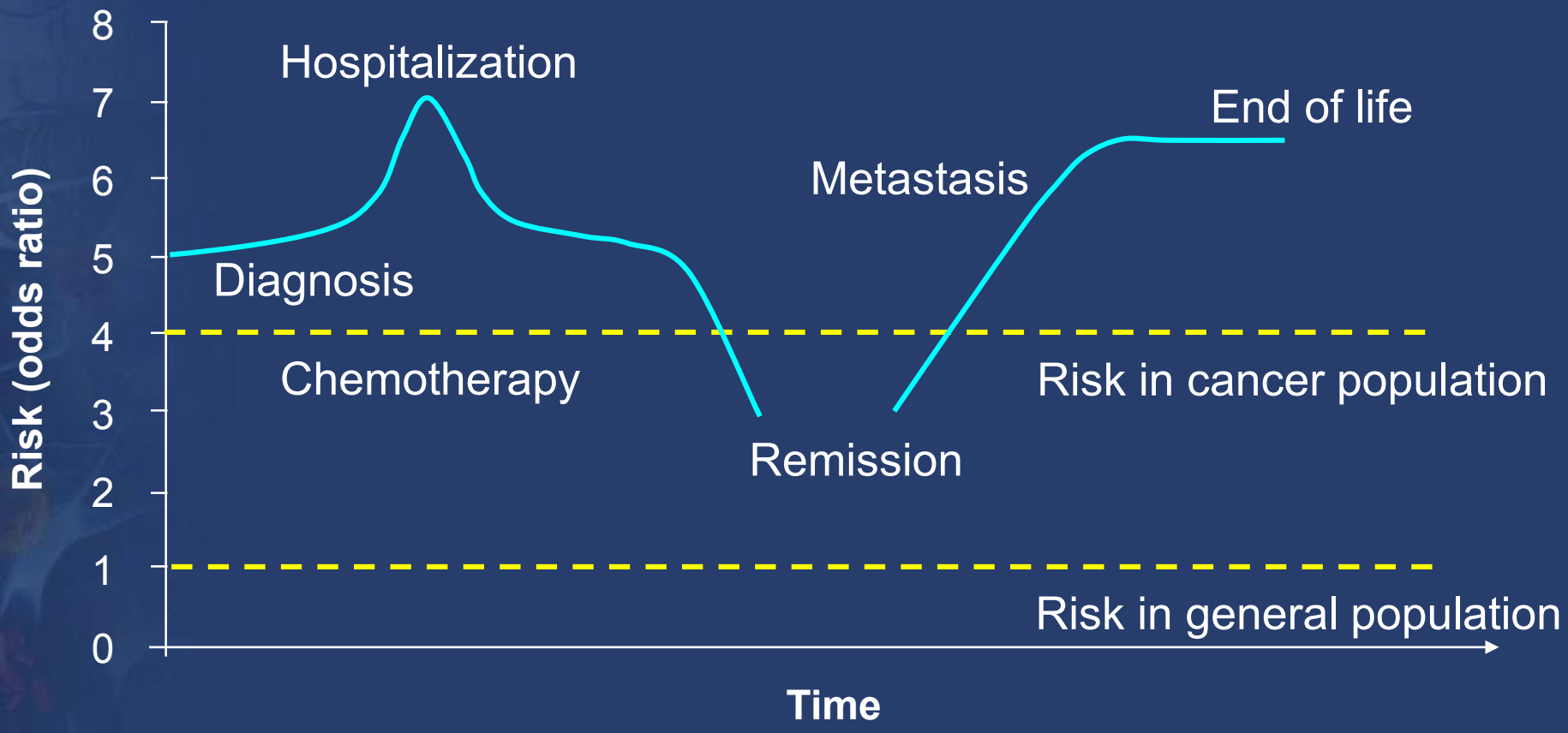
1. Lyman GH, et al. J Clin Oncol. 2009;27:4821-46.
2. Khorana AA, et al. J Thromb Haemost. 2007;5:632-4.
3. Lyman GH, et al. J Clin Oncol. 2007;25:5490-505.
4. Gao S, et al. Expert Rev Anticancer Ther. 2004;4:303-20.

# Effect of Malignancy on Risk of Venous Thromboembolism (VTE)




Blom et. al. *JAMA* 2005;293:715

# Risk of VTE persists also after hospital discharge




Rao MV, et al. Who's at risk for thrombosis? In: Francis CW, Khorana AA, editors. Cancer-associated thrombosis: new findings in translational science, prevention, and treatment. New York: Informa Healthcare; 2007. p. 169-92.

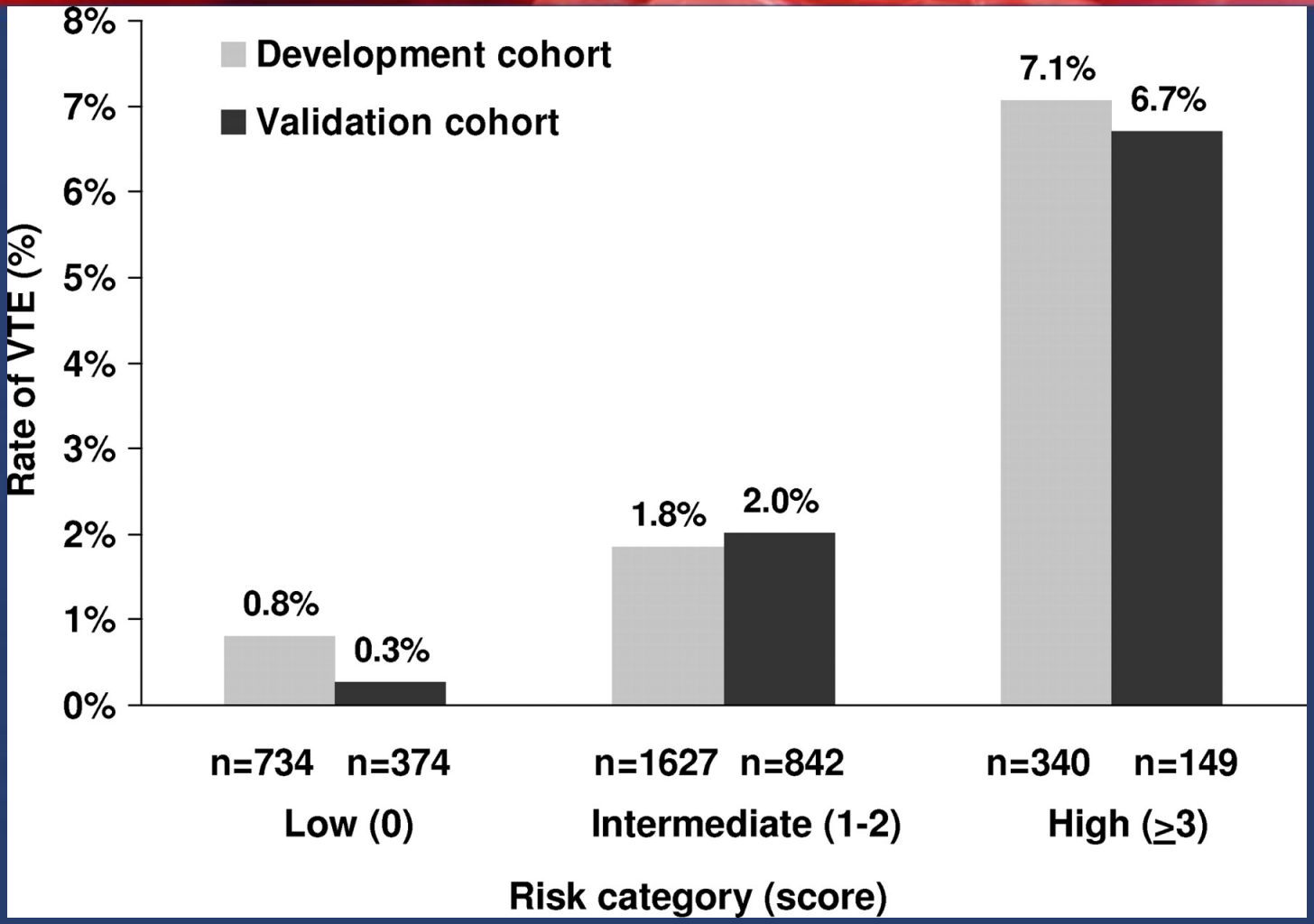
# AIMS OF PRIMARY THROMBOPROPHYLAXIS

- REDUCE VTE RATE WITHOUT INCREASING CLINICALLY MEANINGFUL BLEEDING
- IMPROVING SURVIVAL

# AMBULATORY CANCER PATIENTS RECEIVING CHEMOTHERAPY

## WHO'S AT RISK FOR THROMBOSIS

# RATE OF VTE: CLINICAL SCORE




Khorana, A. A. et al. Blood 2007

# IS THE KHORANA SCORE USEFUL FOR ROUTINE ACTIVITY?

# ISSUES WITH KHORANA SCORE (1)

- 83% OF PATIENTS KHORANA RISK SCORE ≲ 2
  53% KHORANA RISK SCORE 0-1

- VTE IN THE FIRST SIX MONTHS, 23.4% HIGH RISK KHORANA SCORE. KHORANA RISK SCORE ≲ 2 76.6%.

MULDER HEMATOLOGICA 2019

# ISSUES WITH KHORANA SCORE (2)

Low performance in lung cancer

Dynamic risk: we need a dynamic biomarker

Adjuvant therapy?

Chemotherapy regimen is not included

Hormonotherapy

Targeted therapy?

# ISSUES WITH KHORANA SCORE (3)

- SOME OF MAJOR KILLERS EXCLUDED

- PROSTATE CANCER
- MELANOMA
- BRAIN TUMOURS

# TWO PHASES IN CLINICAL TRIALS

## FIRST PHASE

- Efficacy and safety of LMWH in unselected patients with cancer (ie, without risk stratification)

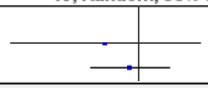
## SECOND PHASE

- DOACs in high-risk patients
- Risk stratification: Khotana score

# COCHRANE METANA-ANALYSIS
# DI NISIO 2016

**Figure 3. Forest plot of comparison: 1 Anticoagulants versus control: symptomatic VTE, outcome: 1.2 Symptomatic VTE: LMWH versus no thromboprophylaxis.**

| Study or Subgroup | LMWH Events | LMWH Total | No thromboprophylaxis Events | No thromboprophylaxis Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.2.1 Dalteparin** | | | | | | |
| Altinbas 2004 | 0 | 42 | 1 | 42 | 1.1% | 0.33 [0.01, 7.96] |
| Kakkar 2004 | 4 | 190 | 5 | 184 | 6.7% | 0.77 [0.21, 2.84] |

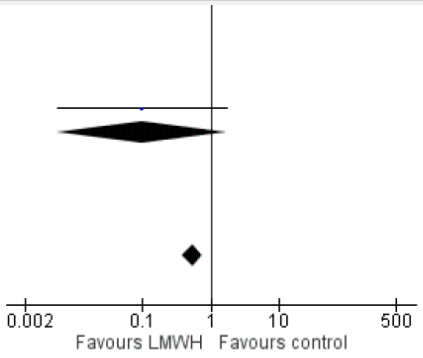



| | | | | | | |
|---|---|---|---|---|---|---|
| **Symptomatic DVT** Follow-up: median 10 months | RR 0.49 (0.35 to 0.67) | **High-risk population**[3] 29 per 1000 | 14 per 1000 | 15 per 1000 fewer events (10 to 19 fewer) | 5310 (8) | ⊕⊕⊕⊕ **high**[7] | LMWH decreases the incidence of symptomatic DVT across different cancer types |
| **1-year mortality** Follow-up: median 12 months | RR 0.93 (0.80 to 1.09) | **High-risk population**[3] 587 per 1000 | 546 per 1000 (470 to 640) | 41 per 1000 fewer deaths (117 fewer to 53 more) | 2304 (8) | ⊕⊕◯◯ **low**[8] | LMWH may decrease the incidence of death across different cancer types |
| **Clinically relevant bleeding** Follow-up: median 12 months | RR 3.40 (1.20 to 9.63) | **High-risk population**[3] 17 per 1000 | 57 per 1000 (20 to 162) | 40 per 1000 more clinically relevant bleeds (3 to 145 more) | 3105 (4) | ⊕⊕⊕◯ **moderate**[9] | LMWH probably increases the incidence of clinically relevant bleeding across different cancer types |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (P = 0.02)

| | | | | | | |
|---|---|---|---|---|---|---|
| **1.2.5 Bemiparin** | | | | | | |
| Lecumberri 2013 | 0 | 20 | 4 | 18 | 1.4% | 0.10 [0.01, 1.75] |
| **Subtotal (95% CI)** | | **20** | | **18** | **1.4%** | **0.10 [0.01, 1.75]** |
| Total events | 0 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.58 (P = 0.11) | | | | | | |
| **Total (95% CI)** | | **1849** | | **1435** | **100.0%** | **0.54 [0.38, 0.75]** |
| Total events | 52 | | 86 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 8 (P = 0.88); I² = 0%
Test for overall effect: Z = 3.61 (P = 0.0003)
Test for subgroup differences: Chi² = 2.21, df = 4 (P = 0.70), I² = 0%



# PROTECHT: RESULTS

**Thromboembolic events by treatment group and cancer site**

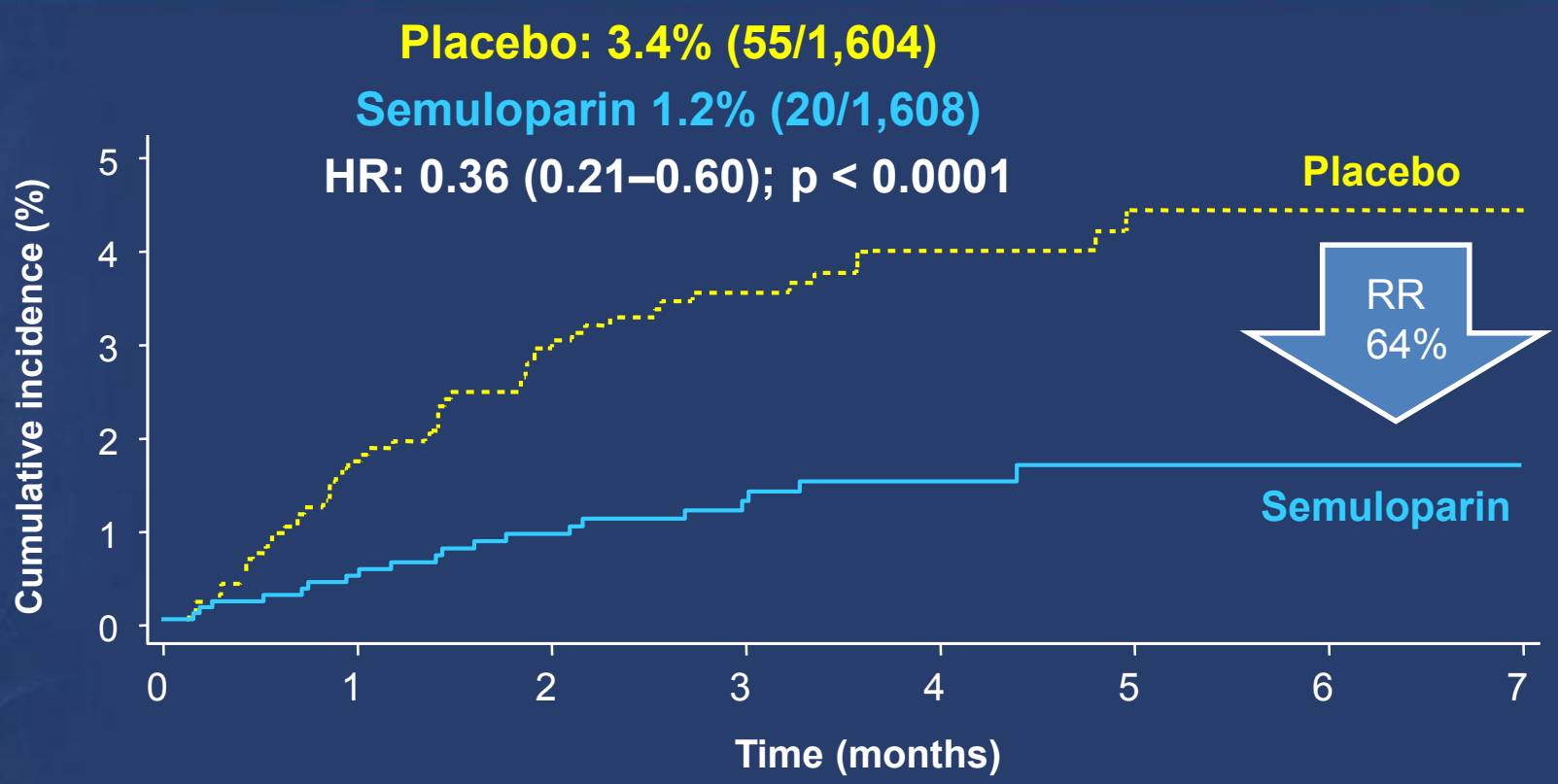
| | Nadroparin (n = 769) | Placebo (n = 381) |
|---|---|---|
| Overall thromboembolic events, N (%) | 15 (2.0)* | 15 (3.9) |
| deep-vein thrombosis | 8 (1.0) | 8 (2.1) |
| pulmonary embolism | 3 (0.4) | 3 (0.8) |
| visceral venous thrombosis | 1 (0.1) | 1 (0.3) |
| stroke and peripheral thrombosis | 3 (0.4) | 3 (0.8) |
| Thromboembolic event by cancer site, n/N (%) | | |
| lung | 7/199 (3.5) | 7/80 (8.8) |
| gastrointestinal | 4/272 (1.5) | 4/148 (2.7) |
| pancreas | 3/36 (8.3) | 1/17 (5.9) |
| other | 1/262 (0.4) | 3/136 (2.2) |

*p = 0.02 one-sided

- 5 (0.7%) patients in the nadroparin group and 0 (0%) in the control group had a major bleeding event (p = 0.18)

Agnelli G, et al. Lancet Oncol. 2009;10:943-9.

# SAVE-ONCO: primary efficacy end-point
# Composite of symptomatic DVT and any PE




**Number at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 1,604 | 1,375 | 1,212 | 985 | 689 | 403 | 201 | 92 |
| Semuloparin | 1,608 | 1,410 | 1,227 | 986 | 681 | 384 | 197 | 77 |

Agnelli G, et al. NEJM 2012

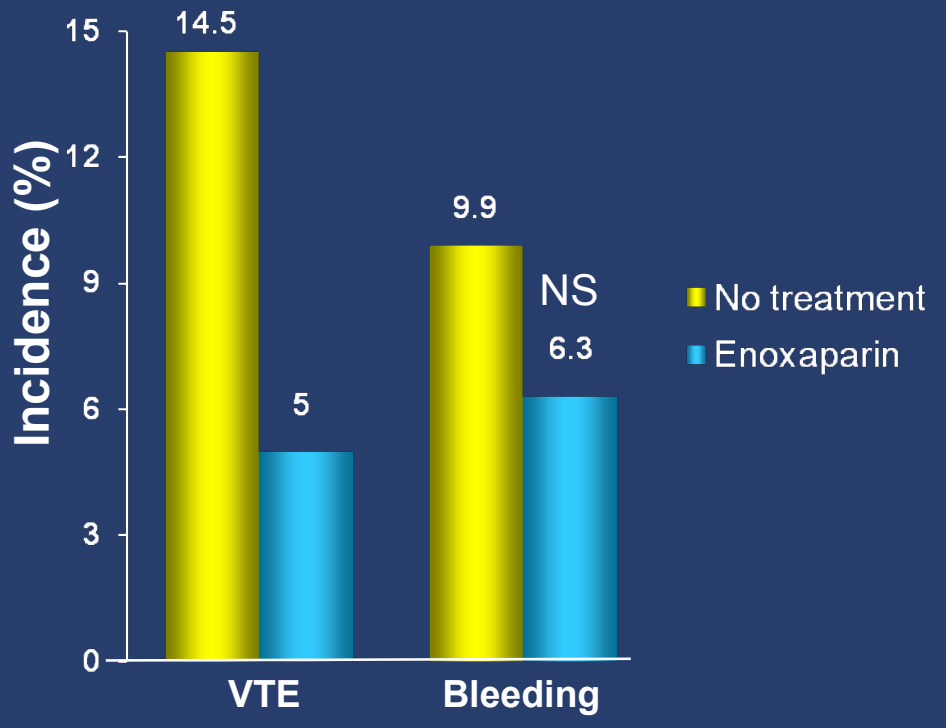
# PROSPECT-CONKO 004

**Study design**

- RCT, 312 patients
- Pancreatic cancer
- GFFC vs Gem chemo
- Enoxaparin 1 mg/kg/day* vs none

**Results**

- 12 week incidence of VTE: 14.5% (control) vs 5% (enoxaparin)
- RR: 65% reduction
- No difference in PFS, OS

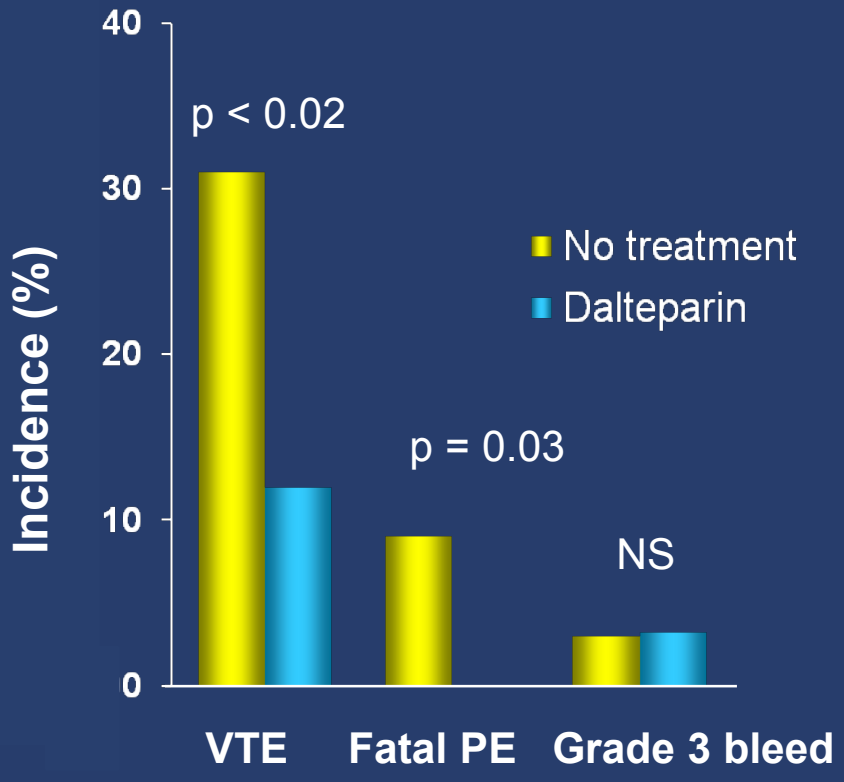



*1 mg/kg once daily s.c. for the first 12 weeks, thereafter 40 mg once daily.
GFFC = gemcitabine, cisplatin, 5-fluorouracil, folinic acid.

Riess HB, et al. J Thromb Haemost. 2009;7(Suppl 2):[abstract LB-MO-003].

# UK – FRAGEM Study

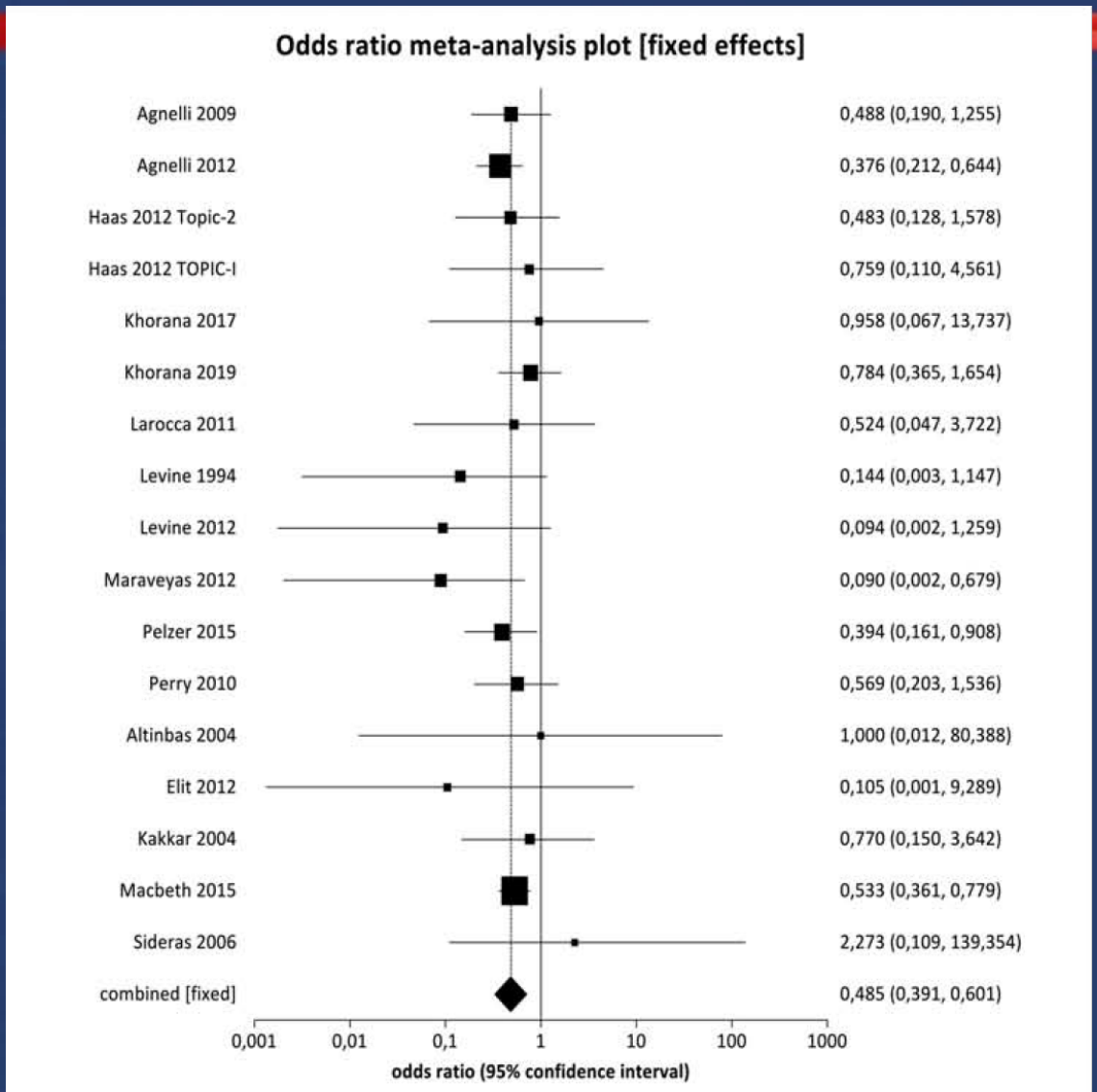
- 123 patients receiving chemotherapy for APC
- Randomized to gemcitabine or gemcitabine + dalteparin
- Dalteparin 200 IU/kg once daily x 4 weeks, then 150 IU/kg × 8 weeks
- Primary outcome: all TE (arterial, venous, incidental) at 3 months




APC = metastatic pancreatic cancer.

Maraveyas A, et al. Eur J Cancer. 2012.

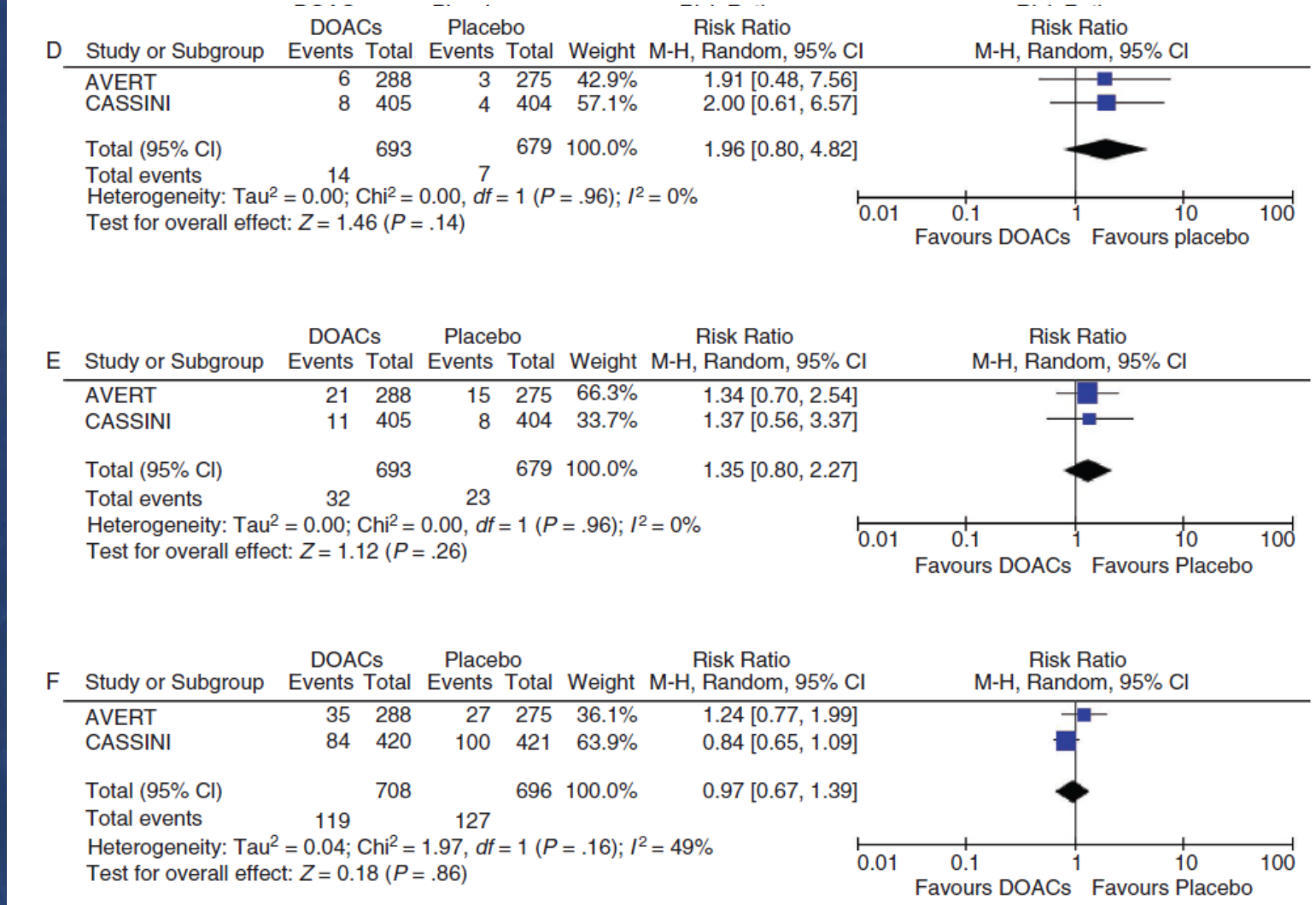
# NEW META-ANALYSIS ON VTE IN AMBULATORY CANCER PATIENTS




Becattini Hematologica 2019

# DOAC FOR PRIMARY THROMBOPROPHYLAXIS IN AMBULATORY CANCER PATIENTS: GUIDANCE FROM THE SCC OF THE ISTH

## Wang et al. JTH 2019



# POOLED ANALYSES IN A BASKET WITH ORANGES AND APPLES

| | CASSINI° | AVERT* |
|---|---|---|
| ANTICOAGULANT | RIVAROXABAN | APIXABAN |
| KHORANA SCORE | ≥ 2 | ➢ 2 |
| PLANNED DURATION | 6 MONTHS | 6 MONTHS |
| PRIMARY ENDPOINTS | DVT/PE, VTE DEATH | DVT/PE, VTE DEATH |

* Carrier NEJM 2019, ° Khorana NEJM 2019

# POOLED ANALYSES IN A BASKET WITH ORANGES AND APPLES

| | CASSINI | AVERT |
|---|---|---|
| SCREENING LOWER EXTREMITY ULTRASOUND | YES BASELINE 8, 16, 24 WEEKS | NO |
| MYELOMA | EXCLUDED | YES |
| BRAIN TUMOURS | EXCLUDED | YES |
| MAYOR BLEEDING | 2% Rivaroxaban<br>1% Placebo | 3.5% APIXABAN<br>1.8% PLACEBO |
| MAIN PATIENTS | STOMACH AND PANCREAS | LYMPHOMA AND GYNECO CANCERS |
| SIX MOTHS MORTALITY | 22% | 11% |

**BOTH TRIALS WERE NOT POWERED FOR SAFETY**

* Carrier NEJM 2019, ° Khorana NEJM 2019

# Direct Oral Anticoagulants for Thromboprophylaxis in Ambulatory Patients with Cancer

Giancarlo Agnelli, M.D.

**Table 1. Cumulative Analysis of the AVERT and CASSINI Trials.***

| Outcome | CASSINI Trial | | AVERT Trial | | Cumulative Values | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Rivaroxaban | Placebo | Apixaban | Placebo | DOACs | Placebo | Relative Risk (95% CI) | Absolute Difference | No. Needed to Treat or Harm† |
| | *number/total number (percent)* | | | | | | | *percentage points* | |
| Primary efficacy outcome | | | | | | | | | |
| ITT analysis | 25/420 (6.0) | 37/421 (8.8) | 12/288 (4.2) | 28/275 (10.2) | 37/708 (5.2) | 65/696 (9.3) | 0.56 (0.38–0.83) | –4.1 | 24 |
| Analysis during treatment period | 11/420 (2.6) | 27/421 (6.4) | 3/288 (1.0) | 20/275 (7.3) | 14/708 (2.0) | 47/696 (6.8) | 0.29 (0.16–0.53) | –4.8 | 21 |
| Symptomatic VTE: ITT analysis | 15/420 (3.6) | 19/421 (4.5) | 9/288 (3.1) | 22/275 (8.0) | 24/708 (3.4) | 41/696 (5.9) | 0.58 (0.35–0.94) | –2.5 | 40 |
| Major bleeding | 8/405 (2.0) | 4/404 (1.0) | 10/288 (3.5) | 5/275 (1.8) | 18/693 (2.6) | 9/679 (1.3) | 1.96 (0.88–4.33) | 1.3 | 77 |
| Death from any cause | 84/420 (20.0) | 100/421 (23.8) | 35/288 (12.2) | 27/275 (9.8) | 119/708 (16.8) | 127/696 (18.2) | 0.92 (0.73–1.16) | –1.4 | 71 |

# DRUG-DRUG INTERACTIONS SHORCOMINGS FOR DOACs

- NO SPECIFIC DATA AVAILABLE ON DRUG–DRUG INTERACTIONS BETWEEN DOACS AND CANCER THERAPIES

- DOACS ARE SUBSTRATES OF CYP3A4, P-GP OR BCRP, TARGETED AGENTS ARE ALSO SUBSTRATES FOR CYP3A4, P-GP

Carrier Blood Jan 2019

# CONCLUSIONS

- FOR THE VAST MAJORITY OF AMBULATORY PATIENTS PRIMARY PROPHYLAXIS IS NOT INDICATED
- STUDIES ON SPECIFIC TUMOURS NEEDED
- MORE DATA ON DOACS IN GI CANCERS/AND INTERACTION WITH NEW DRUGS ARE AWAITED