







Apixaban for the prevention of Venous thromboEmbolism in high-Risk ambulatory cancer patients receiving chemoTherapy: **AVERT** Trial.

Marc Carrier and Phil Wells

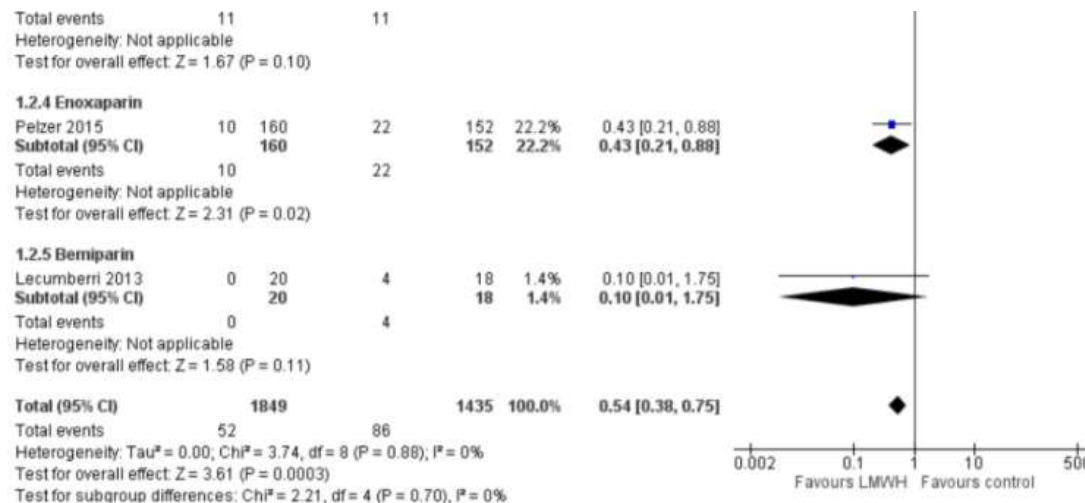
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|------------------------------|--|
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Thromboprophylaxis in ambulatory cancer patients

| Study or Subgroup | LMWH | | No thromboprophylaxis | | Weight | Risk Ratio | Risk Ratio |
|-------------------|--------|-------|-----------------------|-------|--------|--------------------|---|
| | Events | Total | Events | Total | | IV, Random, 95% CI | 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] |  |
| Maraveyas 2012 | 4 | 59 | 11 | 60 | 9.6% | 0.37 [0.12, 1.10] |  |
| Perry 2010 | 11 | 99 | 13 | 87 | 20.1% | 0.74 [0.35, 1.57] |  |
| Sideras 2006 | 4 | 68 | 5 | 70 | 7.0% | 0.82 [0.23, 2.94] |  |
| Subtotal (95% CI) | | 458 | | 443 | 44.5% | 0.64 [0.39, 1.06] |  |

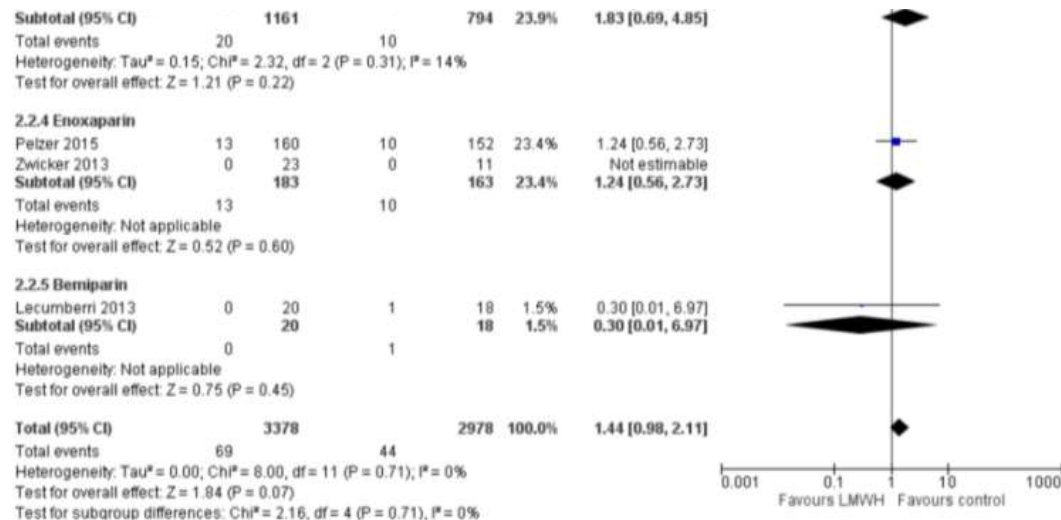
Risk Ratio (VTE):
0.54 (95 %CI: 0.38 to 0.75)



Thromboprophylaxis in ambulatory cancer patients

| Study or Subgroup | Favours LMWH Events | Total | No thromboprophylaxis Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|--------------------------|------------------------|-------------|---------------------------------|-------------|--------------|----------------------------------|----------------------------------|
| 2.2.1 Dalteparin | | | | | | | |
| Kakkar 2004 | 1 | 190 | 0 | 184 | 1.4% | 2.91 [0.12, 70.87] | |
| Khorana 2015 | 1 | 50 | 1 | 48 | 2.0% | 0.96 [0.06, 14.92] | |
| Macbeth 2016 | 12 | 1101 | 8 | 1101 | 18.6% | 1.50 [0.62, 3.66] | |
| Maraveyas 2012 | 2 | 59 | 2 | 62 | 4.0% | 1.05 [0.15, 7.22] | |
| Perry 2010 | 5 | 99 | 1 | 87 | 3.3% | 4.39 [0.52, 36.89] | |
| Sideras 2006 | 2 | 68 | 5 | 70 | 5.7% | 0.41 [0.08, 2.05] | |
| Subtotal (95% CI) | | 1567 | | 1552 | 35.0% | 1.29 [0.67, 2.47] | |

**Risk Ratio (Major bleeding):
1.44 (95 %CI: 0.98 to 2.11)**



Clinical practice guidelines

- Ambulatory cancer patients receiving chemotherapy

Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients.

Patients with cancer should be periodically assessed for VTE risk.

Oncology professionals should educate patients about the signs and symptoms of VTE.

VTE risk score for cancer patients

Table 2. Predictive model for chemotherapy-associated VTE¹⁶

| Patient characteristics | Risk score |
|---|------------|
| Site of cancer | |
| Very high risk: stomach, pancreas | 2 |
| High risk: lung, lymphoma, gynecologic, bladder, testicular | 1 |
| Prechemotherapy platelet count $\geq 350\,000/\text{mm}^3$ or more | 1 |
| Prechemotherapy hemoglobin level $< 10\text{ g/dL}$ and/or planned use of erythropoiesis-stimulating agents | 1 |
| Prechemotherapy leukocyte count $> 11\,000/\text{mm}^3$ | 1 |
| Body mass index $\geq 35\text{ kg/m}^2$ or more | 1 |

High-risk score, ≥ 3 ; intermediate-risk score, 1-2; low-risk score, 0.

Validation of Khorana risk score

Table 3. Rates of VTE in select studies validating a risk score for chemotherapy-associated VTE

| Study | Type/follow-up | N | Low-risk | Intermediate-risk | High-risk |
|-----------------------------------|---|------|-----------------|-----------------------------------|-----------|
| Ay et al, 2010 ²⁷ | Prospective/643 d | 819 | 1.5% | 9.6% (score = 2) 3.8% (score = 1) | 17.7% |
| Khorana et al, 2010 ²⁸ | Prospective/3 mo | 30 | 1 | | 27% |
| Moore et al, 2011 ¹ | Retrospective, cisplatin-based chemotherapy only | 932 | 13% | 17.1% | 28.2% |
| Mandala et al, 2011 ³ | Retrospective, phase 1 patients only/2 mo | 1415 | 1.5% | 4.8% | 12.9% |
| George et al, 2011 ²⁸ | Subgroup analysis of SAVE-ONCO, ³⁴ /3.5 mo (placebo arm) | 1604 | 1.3% | 3.5% | 5.4% |
| Verso et al, 2012 ²⁹ | Subgroup analysis of PROTECT (placebo arm) | 381 | 3% (scores 0-2) | | 11.1% |

Khorana AA et al. Hematology Am Soc Hematol Educ Program. 2012;2012:626-30.

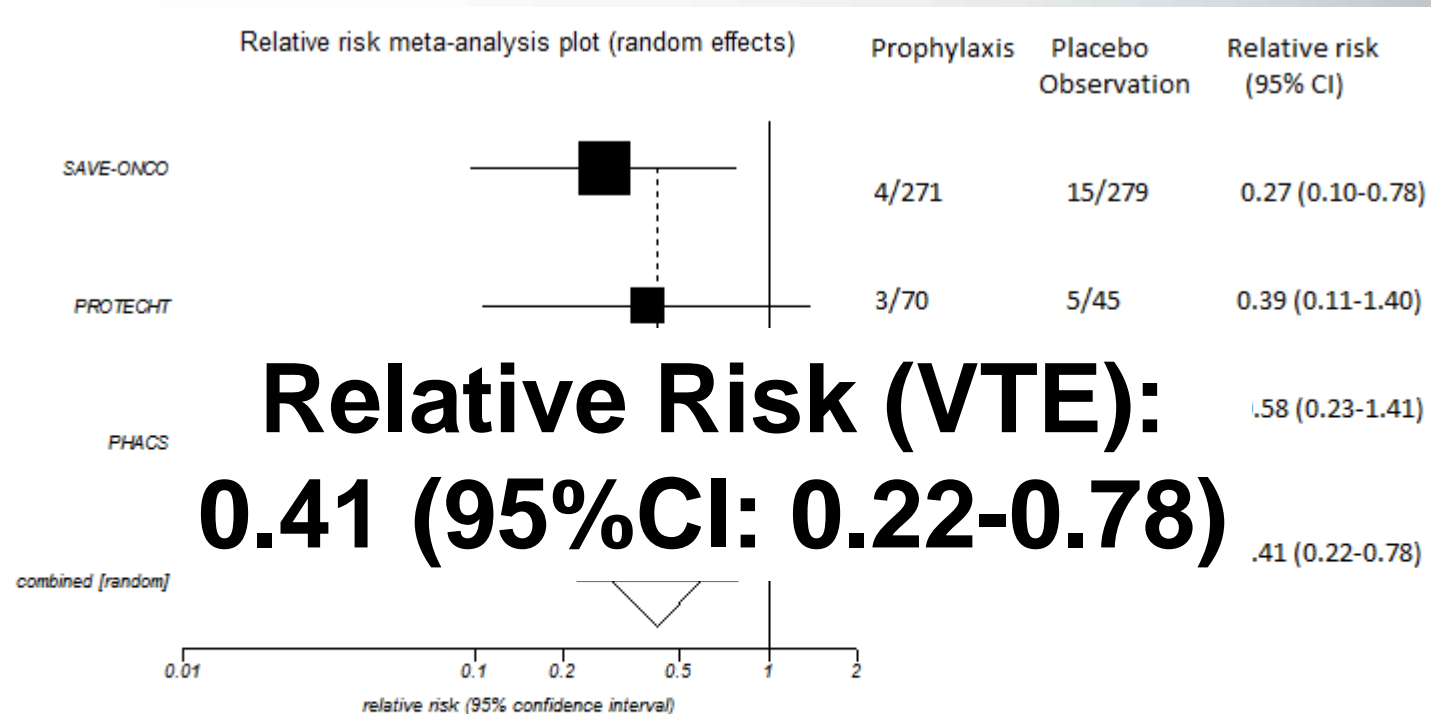
Vienna risk score

Table 2. Two different risk models for identification of cancer patients at high risk of VTE

| Khorana VTE risk assessment score ⁵ | | | Points |
|---|----------------|--|--------|
| Site of cancer | Very high risk | Stomach, pancreas | 2 |
| | High risk | Lung, lymphoma, gynecologic, bladder, testicular | 1 |
| Platelet count | | $\geq 350 \times 10^9/L$ | 1 |
| Hemoglobin and/or use of erythropoiesis-stimulating agents | | $< 10 \text{ g/dL}$ | 1 |
| Leukocyte count | | $> 11 \times 10^9/L$ | 1 |
| Body mass index | | $\geq 35 \text{ kg/m}^2$ | 1 |
| Vienna VTE risk assessment score, ¹⁹ addition of | | | |
| D-dimer | | $\geq 1.44 \mu\text{g/mL}$ | 1 |
| sP-selectin | | $\geq 53.1 \text{ mg/mL}$ | 1 |

In the CATS, brain tumors (high-grade glioma) were allocated to the very high risk sites of cancer.

Efficacy of LMWH in high risk patients



Apixaban for VTE prevention in cancer patients

- Phase II trial with apixaban for the prevention of thromboembolism in patients with metastatic cancer
- VTE rate: (0% in each treatment group)

Table 2 Study outcomes

| Outcome | Apixaban 5 mg (<i>n</i> = 32) | | Apixaban 10 mg (<i>n</i> = 29) | | Apixaban 20 mg (<i>n</i> = 32) | | Placebo (<i>n</i> = 29) | |
|-------------------------|-----------------------------------|--------|------------------------------------|--------|------------------------------------|--------|--------------------------|--------|
| | <i>n</i> (%) | 95% CI | <i>n</i> (%) | 95% CI | <i>n</i> (%) | 95% CI | <i>n</i> (%) | 95% CI |
| Major bleeding | 0 | 0.0–11 | 0 | 0.0–12 | 2 (6.3) | 0.8–21 | 1 (3.4) | 0.1–18 |
| CRNM bleeding | 1 (3.1) | 0.1–16 | 1 (3.4) | 0.1–18 | 2 (6.3) | 0.8–21 | 0 | 0.0–12 |
| Major and CRNM bleeding | 1 (3.1) | 0.1–16 | 1 (3.4) | 0.1–18 | 4 (12.5) | 3.5–29 | 1 (3.4) | 0.1–18 |
| DVT ± PE | 0 | 0.0–11 | 0 | 0.0–12 | 0 | 0.0–11 | 3 (10.3) | 2.2–27 |
| Grade ≥ 3 AEs* | 2 (6.3) | 0.8–21 | 0 | 0.0–12 | 1 (3.1)† | 0.1–16 | 0 | 0.0–12 |
| All | 3 (9.4) | 2.0–25 | 1 (3.4) | 0.1–18 | 4 (12.5) | 3.5–29 | 4 (13.8) | 3.9–32 |

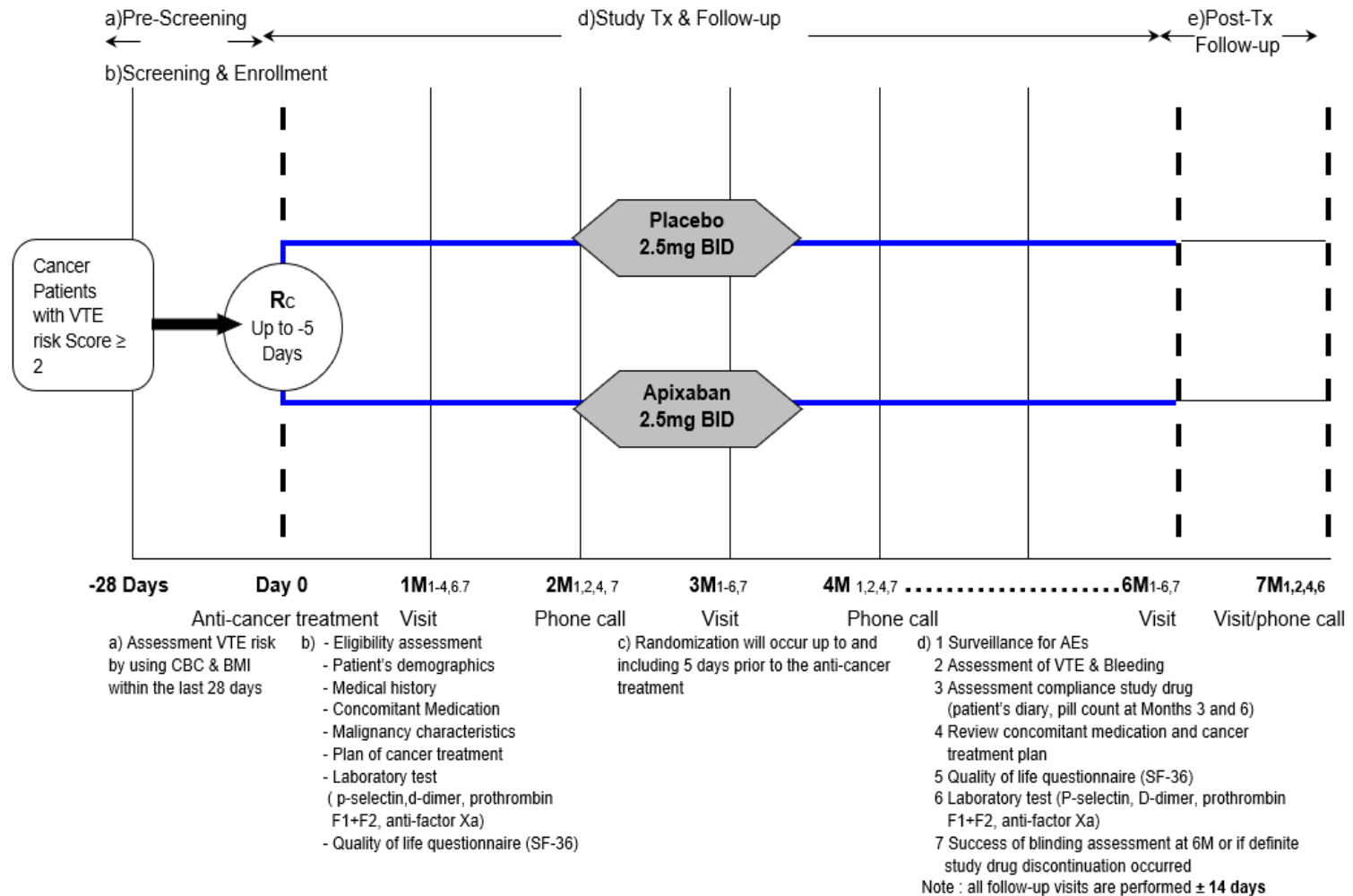
AE, adverse event; CI, confidence interval; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism.

*Considered to be related to study drug. †Adjudicated as a major bleed.

AVERT trial

- Apixaban 2.5 mg PO BID vs. placebo
- Khorana risk score ≥ 2
- FU: 6 months
- Primary outcome: Symptomatic VTE
- Sample size: 574 patients
- Funding: CIHR, BMS
- Clinical trial number: NCT02048865

Study flow



Update

- Last patients randomized
 - April 2018
- Expected Analysis
 - October 2018



Thank you

