2ND GESCAT SYMPOSIUM

CAT - How to Improve Results and Patient Experience

# Duration of anticoagulation on prophylaxis and treatment in Cancer Associated Thrombosis

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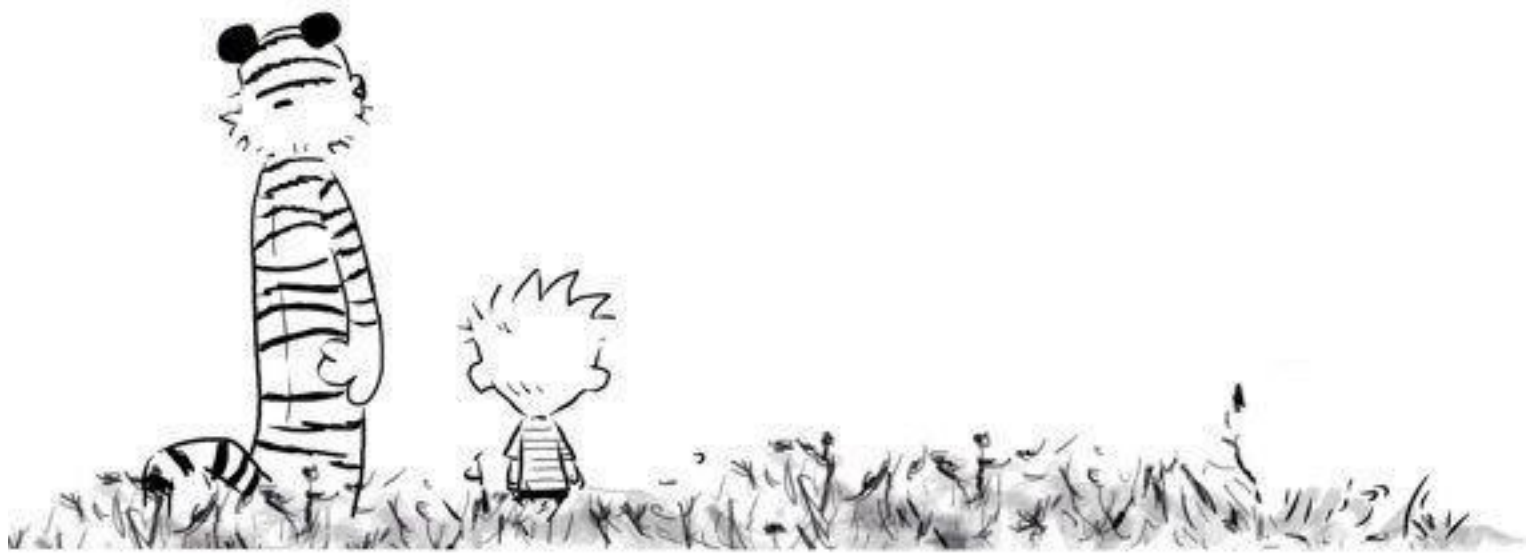
SÃO JOÃO

# Conflict of interests

- None

except I am a **Calvin & Hobbes** fan…

LET'S GO EXPLORING



# Prophylaxis of Cancer Associated Thrombosis (CAT)

## Surgical patient

- **All** patients with malignant disease undergoing major **surgical intervention** should be offered pharmacologic **thromboprophylaxis** with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications;
  - ✓ Prophylaxis should be commenced **preoperatively**;
  - ✓ In lower-risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a **case-by-case** basis;
  - ✓ Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for **at least 7 to 10 days**;
  - ✓ Extended prophylaxis with LMWH for **up to 4 weeks** post-operatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer, who have high-risk features, such as restricted mobility, obesity, history of venous thromboembolism (VTE), or with additional risk factors.

Key NS, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. JCO, 2019.

# Prophylaxis of CAT
## Hospitalized medical patient

- Hospitalized patients who have active malignancy should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications during the **admission period**;

- Routine pharmacologic thromboprophylaxis **should not be offered** to patients admitted for the sole purpose of minor procedures or chemotherapy infusion;

Key NS, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. JCO, 2019.

# Prophylaxis of CAT
## Ambulatory patients

- Thromboprophylaxis with LMWH or direct oral anticoagulants (DOACs) should be offered to high-risk ambulatory patiens with cancer, according to specific Risk Assessment Models (RAMs) like Khorana, Onkotev or COMPASS-CAT, unless there are significant risk factors for bleeding and drug interactions;

  ✓Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and **duration of prophylaxis** in this setting.

Key NS, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. JCO, 2019.

# Treatment of CAT

- Anticoagulation for the **initial 5 to 10 days** may involve LMWH, UFH or rivaroxaban;

- For long-term anticoagulation LMWH, edoxaban or rivaroxaban for **at least 6 months** are preferred because of improved efficacy over vitamin K antagonists (VKAs);
  - ✓ There is an increase in major bleeding risk with DOACs, particularly observed in gastrointestinal and potentially genitourinary malignancies;
  - ✓ Patients with advanced age, obese, frail, with renal function impairment should be considered to LMWH;
  - ✓ Caution with DOACs is also warranted in patients with high risk for bleeding;
  - ✓ Drug-drug interaction should be checked prior to using a DOAC;

- Anticoagulation with LMWH or DOACs **beyond the initial 6 months should be offered to select patients** with active cancer, such as those with metastatic disease or those receiving chemotherapy;
  - ✓ Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile.

Key NS, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. JCO, 2019.

Thank you for your attention!

The end…


I'M A MAN OF FEW WORDS.
MAYBE IF YOU READ MORE, YOU'D HAVE A LARGER VOCABULARY.

# Real-world data on anticoagulant therapy utilization

- In the Humedica database, a massive health information technology database from United States, 8222 adult patients with history of active cancer and thrombosis, were identified between July 2007 and March 2014;
- 28% of these patients were not treated with any anticoagulant therapy, 26% received parenteral therapy only and the remainder received either an oral anticoagulant alone (14%) or parenteral plus oral therapy (32%);
- The mean duration of parenteral therapy was only **1.3 months** whereas oral anticoagulant therapy was given for **2.8 months**.

Masseria C, et al. Venous thromboembolism recurrence and bleeding risk among cancer patients using a large commercial database. Abstract presented at American Heart Association Scientific Sessions. 7-11 November 2015.

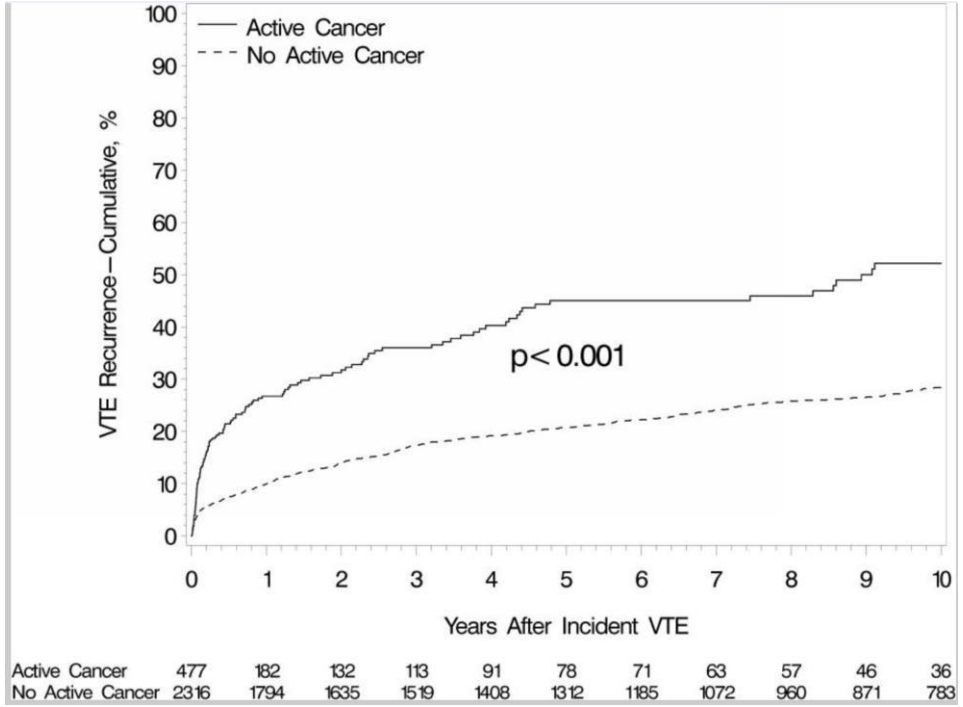
# HealthCare Integrated Research Database

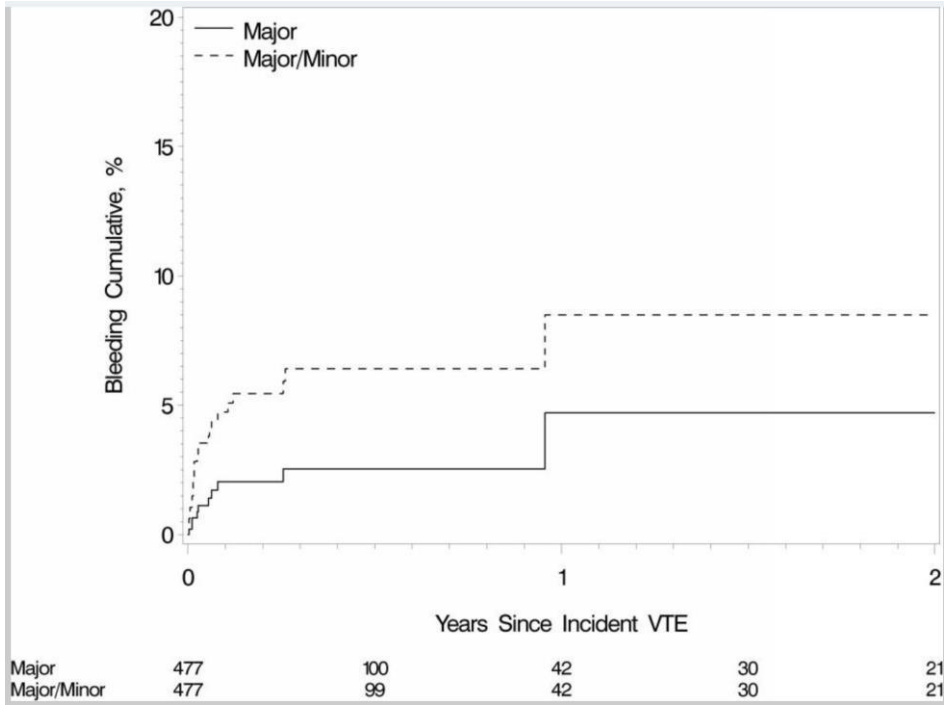
- Between June 2007 and September 2011, 328 cancer patients with new VTE and a minimal of 1 year of follow-up were identified;
- Their mean duration of treatment was **297 days** (standard deviation 6-271)
  - ✓89% were treated with warfarin.
- Patients rated as having a high or intermediate risk of bleeding were less likely to discontinue than those with a low bleeding risk;
  - This finding remained even after adjustment for the risk of VTE recurrence;
  - Further exploration of the data to understand this unexpected observation was limited by the nature of the dataset.

Kaatz S, et al. Association between anticoagulant treatment duration and risk of venous thromboembolism recurrence and bleeding in clinical practice. Thromb Res. 2014.

# Rochester Epidemiology Project database

- In the Rochester Epidemiology Project database, the adjusted cumulative risks of recurrence vs major bleeding are 16.6% vs 2.0% at 6 months and **19.6% vs 4.0% at 1 year**;




- Based on these estimates, the case fatality of bleeding must be at least five to eightfold higher than that of recurrent VTE in order to justify stopping anticoagulation (**patient / cancer / treatment conditions should be taken in consideration**).

Chee CE, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood, 2014.

# Bleeding in the real-world setting

- In the Humedica database, active cancer patients with thrombosis had an incidence rate of 31.2 per 100 person-years for major bleeding during follow-up;
- **Clinical factors** associated with increased risk of **major bleeding** included:

✓ age > 65 years;
✓ heart disease;
✓ heart failure;
✓ renal disease;
✓ hepatic disease;
✓ peripheral arterial disease;
✓ diabetes;
✓ hypertension;
✓ hemorrhagic stroke;
✓ prior major bleeding;
✓ prior fracture/trauma;
✓ emergency room visits;
✓ hospitalization.

Masseria C, et al. Venous thromboembolism recurrence and bleeding risk among cancer patients using a large commercial database. Abstract presented at American Heart Association Scientific Sessions. 7-11 November 2015.

# RIETE database and major bleeding

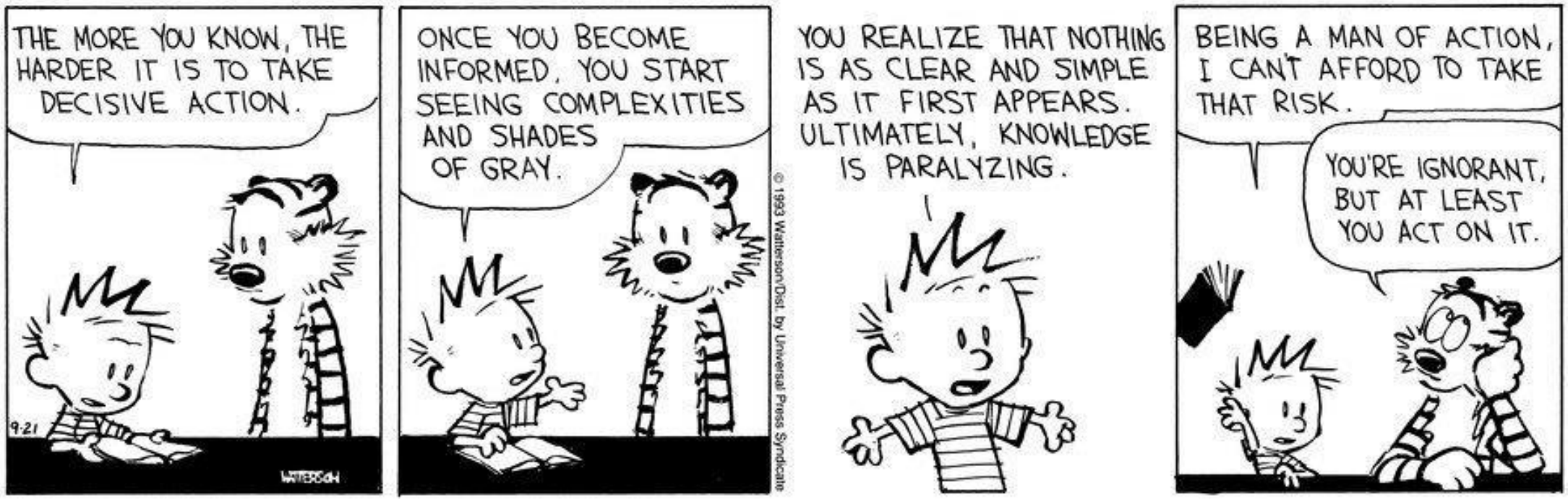
- The Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry also provides real-world estimates of the incidence of outcome events after a diagnosis of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE);
- Since 2001, this ongoing, international registry has been collecting prospective data from consecutive patients;
- In a report that included data up to May 2007 of 3805 cancer patients, 156 **(4.1%) had major bleeding** during the first 3 months of treatment, but there was no information on the incidence beyond 3 months;
- On multivariate analysis, recent major bleeding, creatinine clearance<30 mL/min, immobility for >4 days, metastatic disease and tumor type had odds ratios ranging from 1.6 to 2.4 for major bleeding.

Trujillo-Santos J, et al; RIETE Registry. Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost, 2008.

# Rochester Epidemiology Project database

- In the Mayo Clinic Rochester Epidemiology Project database, the cumulative risk of **major bleeding was 4.0% at 1 year**, adjusted for death, for patients with cancer-associated VTE treated with warfarin;
- Most of the bleeding events occurred early during the **first 3 months** of treatment;
- Thereafter, the incidence of major bleeding stabilizes at approximately 0.2% per month.

Chee CE, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. Blood, 2014.


THE MORE YOU KNOW, THE HARDER IT IS TO TAKE DECISIVE ACTION.
9-21
WATTERSON
ONCE YOU BECOME INFORMED, YOU START SEEING COMPLEXITIES AND SHADES OF GRAY.
© 1993 Watterson/Dist. by Universal Press Syndicate
YOU REALIZE THAT NOTHING IS AS CLEAR AND SIMPLE AS IT FIRST APPEARS. ULTIMATELY, KNOWLEDGE IS PARALYZING.
BEING A MAN OF ACTION, I CAN'T AFFORD TO TAKE THAT RISK.
YOU'RE IGNORANT, BUT AT LEAST YOU ACT ON IT.

# Daltecan study

- The primary aim of the DALTECAN study was to determine the safety of dalteparin between 6 and 12 months in cancer-associated VTE;
- 334 patients with active cancer and newly diagnosed VTE were enrolled in a prospective, multicenter study and received subcutaneous dalteparin for 12 months;
- The rates of bleeding and recurrent VTE were evaluated at months 1–6 and 7–12.
- Major bleeding occurred in 3.6% in the first month, 1.1% during months 2–6 and 0.7% during months 7–12.
- Recurrent VTE occurred in 5.7% for month 1, 3.4% during months 2–6 and 4.1% during months 7–12;
- Conclusions:
  - ✓ Major bleeding was less frequent during dalteparin therapy beyond 6 months.
  - ✓ **The risk of developing major bleeding complications or VTE recurrence was greatest in the first month of therapy and lower over the subsequent 11 months.**

Francis CW, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. JTH, 2015.

# TiCAT study

- The primary aim of the TiCAT study was to determine the safety of long-term tinzaparin use in patients with CAT, beyond 6 months;
- A prospective, open, single arm, multicentre study in patients with CAT receiving treatment with tinzaparin was performed;
- The rate of clinically relevant bleeding events and VTE recurrence were evaluated;
- 247 patients were recruited, with a crude incidence of major bleeding of 4.9%;
- The rate of clinically relevant bleeding during months 1–6 was 0.9% and during months 7–12 was 0.6% per patient and month;
- The incidence of VTE recurrence at months 1–6 was 4.5% and at months 7–12 was 1.1%.
- Conclusion: **treatment with tinzaparin beyond 6 months is safe in patients with CAT**.

Jara-Palomares L, et al. Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study. TR, 2017.

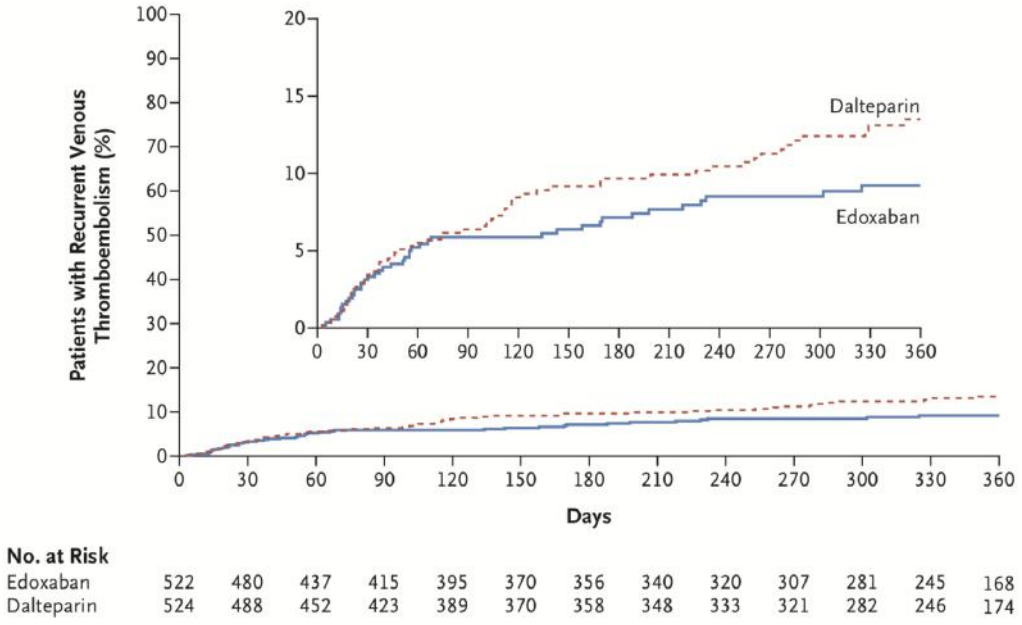
# Hokusay VTE Cancer trial

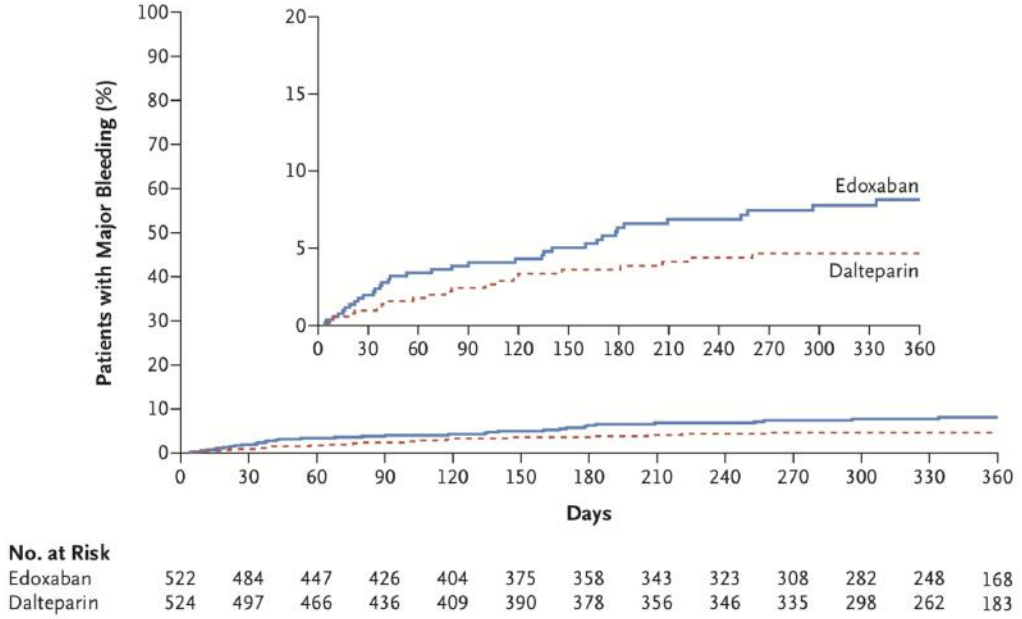
- 1046 patients with cancer who had acute symptomatic or incidental VTE were randomized to receive edoxaban or subcutaneous dalteparin;
- Treatment was given for at least 6 months and up to 12 months;
- The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration;
- Recurrent venous thromboembolism occurred in 7.9% in the edoxaban group and in 11.3% in the dalteparin group;
- Major bleeding occurred in 6.9% in the edoxaban group and in 4.0% in the dalteparin group.

Raskob GE, et al. Edoxaban for the Treatment of Cancer- Associated Venous Thromboembolism. NEJM, 2018.

# Hokusay VTE Cancer trial

- The median duration of the assigned treatment was 211 days (76 to 357) in the edoxaban group and 184 days (85 to 341) in the dalteparin group;




- In the Hokusay VTE Cancer trial the risk of developing major bleeding complications was greatest in the first 2 months of therapy although was still present in the subsequent 10 months.

Raskob GE, et al. Edoxaban for the Treatment of Cancer- Associated Venous Thromboembolism. NEJM, 2018.

# D-dimer (DD) and high-sensitivity C-reactive protein (hs-CRP) levels to predict venous thromboembolism recurrence after discontinuation of anticoagulation for cancer-associated thrombosis

- Prospective, multicenter study to evaluate CAT with ≥3 months of anticoagulation that was subsequently discontinued;
- Blood samples were taken when patients stopped the anticoagulation and 21 days later to determine the DD and hs-CRP levels;
- All patients were followed up for 6 months to detect VTE recurrence.
- Results:
  - ✓ In this study, 6-month VTE recurrence was 8.8%, which decreased to 1.6% or 1.5% if DD was ≤ 600 ng/mL or hs-CRP was ≤ 4.5 mg/L at 21 days, respectively;
  - ✓ These results highlight the importance of determining the appropriate duration of treatment for CAT.

Jara-Palomares L, et al. D-dimer and high-sensitivity C-reactive protein levels to predict venous thromboembolism recurrence after discontinuation of anticoagulation for cancer-associated thrombosis. BJC, 2018.


THIS WILL BE MY STRONGEST FORT EVER!
© 1994 Watterson/Dist. by Universal Press Syndicate
WITH THESE MASSIVE WALLS, I'LL BE SAFE FROM ANY ATTACK!
HELLLP!!

# Conclusions (with a good dose of common sense…)

- Regarding thromboprophylaxis in cancer patients, the duration of anticoagulation is well establish in the surgical setting, less so for the hospitalized medical patients and even less for the ambulatory patients;
  - ✓ More robust and prospective data are needed;
  - ✓ RAMs could be useful in helping determine when to stop anticoagulation;

- The duration of anticoagulation for the treatment CAT as a minimal period of duration (3 months), and an optimal period of duration according to the strength of the data (6 months);
  - ✓ After this anticoagulation can be stopped if there is no evidence of active cancer, no ongoing anti-cancer treatment or the bleeding risk is high;

- The patient must be, *has to be*, part of the decision process.


HI, HOBBES! WHATCHA DOIN'?
NOTHING.
NOTHING AT ALL?
NOPE.
I'LL HELP.
PLEASE DO.
6-15

Thank you all for your attention!

And especially to Bill Watterson 😉😂