



# ICT 2023

28th International  
Congress on Thrombosis

# Assessment of Bleeding Risk

## Update in cancer-associated thrombosis

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## Declaration of Conflict of Interest

- I have no potential conflict of interest to report



## Overview

- **Venous Thromboembolism in Oncology**
- **Bleeding Risk Factors in CAT patients**
- **Bleeding Risk Assessment - Risk Scores**
- **Anticoagulant Agent - VKA vs LMWH vs DOAC**
- **Contraindications for Anticoagulation**





# Venous Thromboembolism in Oncology

## Increased incidence of VTE

- Improvement of diagnostic methods and means;
- New treatments increase the risk of VTE;
- Increased patient survival;
- Valorization of VTE in cancer patients:
  - Suspension and delay of cancer treatment;
  - Requires long-term treatment (increased risk of VTE recurrences);
  - High costs for the patient and society.



Scientific investment in the study of the **pathophysiology of coagulopathy** in oncology!



# Venous Thromboembolism in Oncology

## Thrombosis associated cancer currently constitutes:

- Most frequent complication in cancer patients
- 2nd cause of death in the cancer population (1st cause is metastasis)
- 1st cause of death during chemotherapy treatment

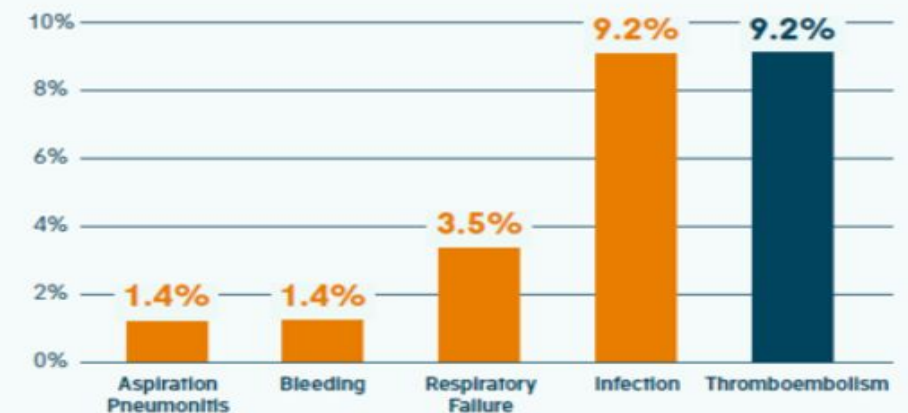
### Oncological Disease

- 4-20% cancer patients have VTE
- VTE in 50% of cancer patients autopsied

### Venous Thomboembolism

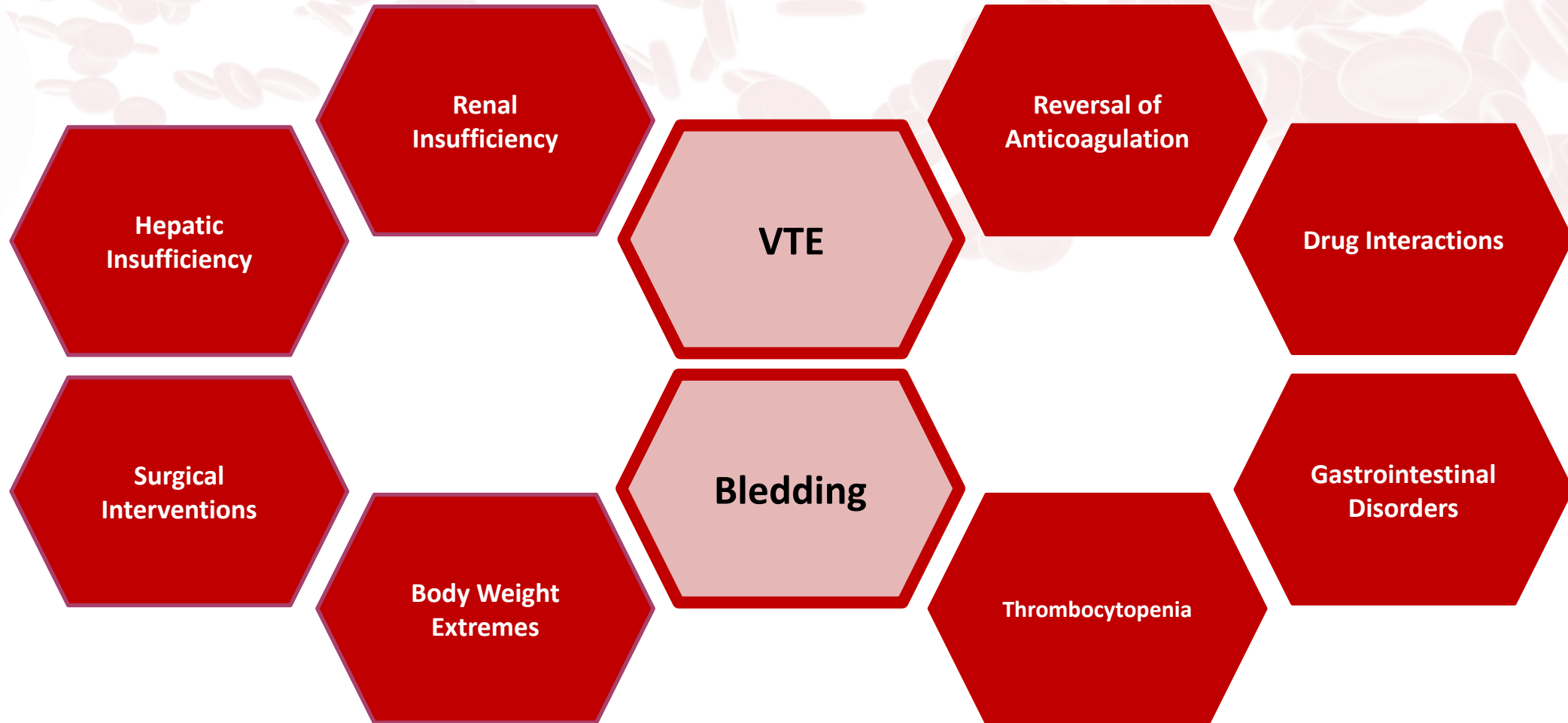
- 20% patients with VTE have active cancer
- 4-12% of patients with idiopathic VTE have underlying cancer

### Main causes of death for cancer patients (excluding disease progression)





# Venous Thromboembolism in Oncology





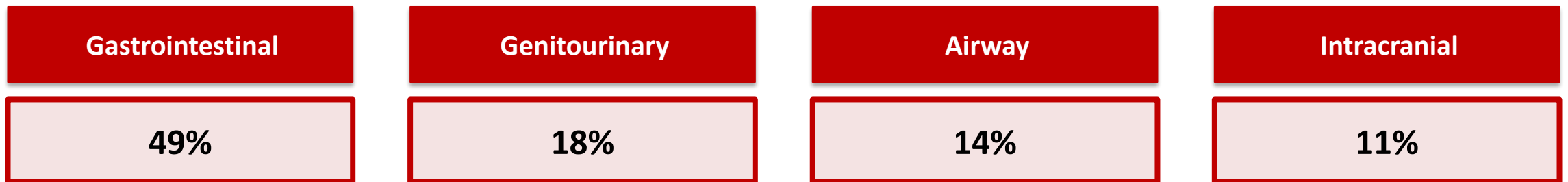
# Bleeding Risk in Oncology

- Bleeding is **the most feared complication** related to anticoagulant treatment of VTE.
  - Occurrence at a rate of 7.22 per 100 patient years (depending on pharmacological class)
- In more severe situations (PTE with hemodynamic instability | extensive iliofemoral DVT)
  - **9.9% major hemorrhage** and 1.7% intracranial or life-threatening hemorrhage
- Particularly **high risk of bleeding** in the **1<sup>st</sup> month of treatment**
  - Risk of VTE recurrence if treatment is discontinued due to bleeding complications
- **Individualized assessment and application of bleeding risk scores:**
  - Reduction in the overall risk of bleeding (identification of risk factors)
  - Class of anticoagulant, adjusted dose and appropriate period



# Bleeding Risk in Oncology

- Clinical practice guidelines recommend using **LMWH or DOAC for a minimum 3-6 months**
  - Preferred option for the treatment of CAT with personalized approach
- Long-term use of anticoagulation is associated with **non-negligible bleeding risk** - The most serious adverse effect
  - Bleeding complications have been reported 2-3 times more in cancer patients
- Bleeding mainly occurs at the **site of primary tumor or metastasis**





## Bleeding Risk Factors

- Advanced age (> 75 years)
- Type of primary oncological disease
- Metastatic disease (intracranial lesions)
- Obesity (BMI  $\geq$  40)
- Kidney and Liver Disease (stage  $\geq$  2)
- Thrombocytopenia
- VTE history
- Recent major bleeding





## Cancer Type and Stage

- **The incidence of bleeding varies according to tumor location:**
  - Statistically significant differences in the first 6 months of hypocoagulation (OR 3.3 - 95% CI)
  - Metastatic disease associated with an increased risk to bleeding compared to local disease (OR 1,6 - 95% CI)

| Colorectal cancer                  | Prostate cancer                    | Lung cancer                        | Breast cancer                       |
|------------------------------------|------------------------------------|------------------------------------|-------------------------------------|
| 12 events<br>per 100 patients-year | 13 events<br>per 100 patients-year | 11 events<br>per 100 patients-year | 4.1 events<br>per 100 patients-year |

- **Tumors of the Central Nervous System under anticoagulation:**
  - Therapeutic doses of LMWH increases the risk of ICH compared with no anticoagulation (OR 3.66 - 95% CI)



## Cancer Type and Stage

- **Gastrointestinal tumor and other non-neoplastic lesions**
  - Mucositis, esophagitis, peptic or duodenal ulcer
  - Major concern with anticoagulation - DOAC exerts a local anticoagulant effect after absorption
  - LMWH is a safer option in patients with high risk of GI bleeding
  
- **Mucositis may favor GI bleeding**
  - Bleeding complications have been reported 2-3 times more in cancer patients
  - 20-40% patients receiving conventional chemotherapy
  - 80% patients in conditioning for hematopoietic stem cell transplantation
  - 100% patients receiving head and neck radiation therapy





## Anemia

**Anemias was associated with a twofold higher rate of major and fatal bleeding in CAT patients**

**Anemia is a common condition in cancer patients occurring in > 40% of cases**

**The incidence of chemotherapy-induced anemia may reach up to 90%**

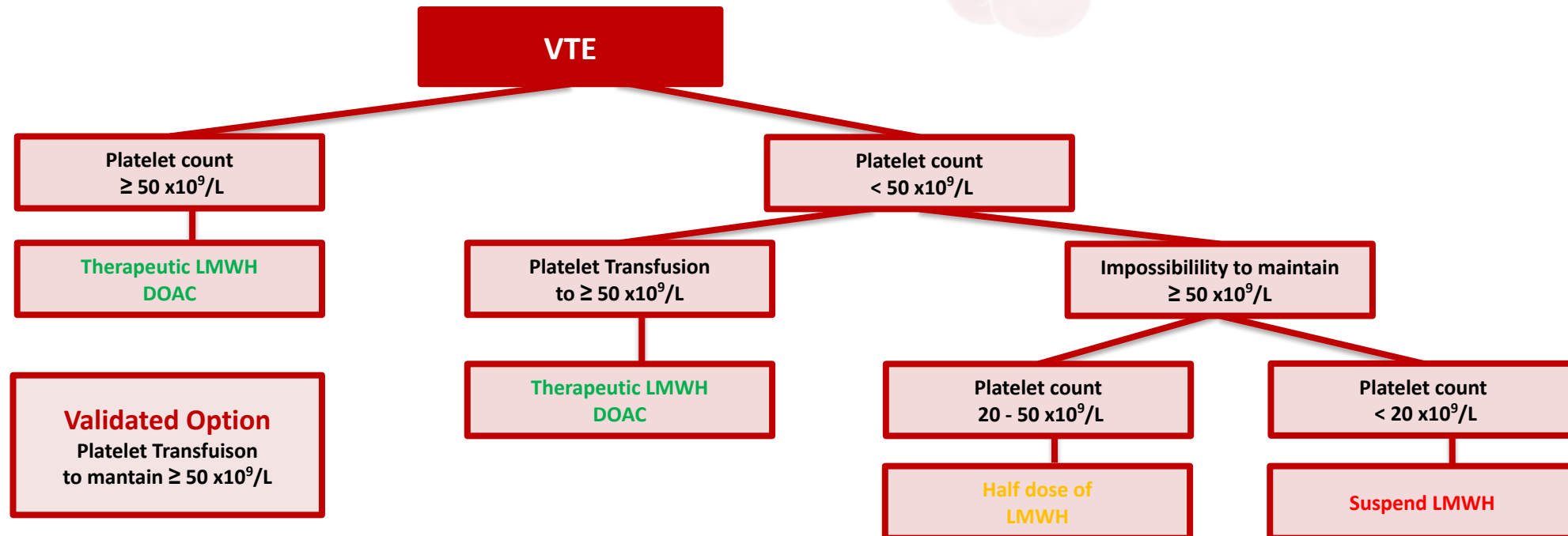
**Particularly common in lung (32%) and gynecological (42%) cancers**



# Thrombocytopenia

Severe thrombocytopenia is associated with a high prevalence of bleeding:

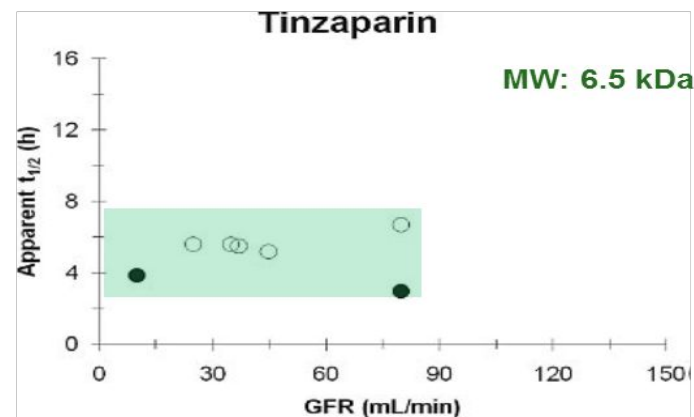
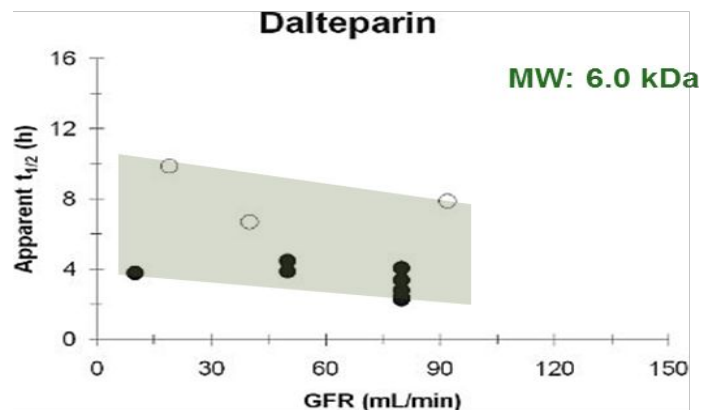
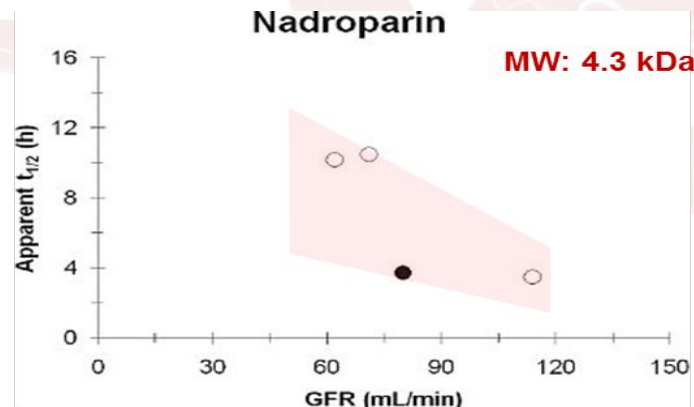
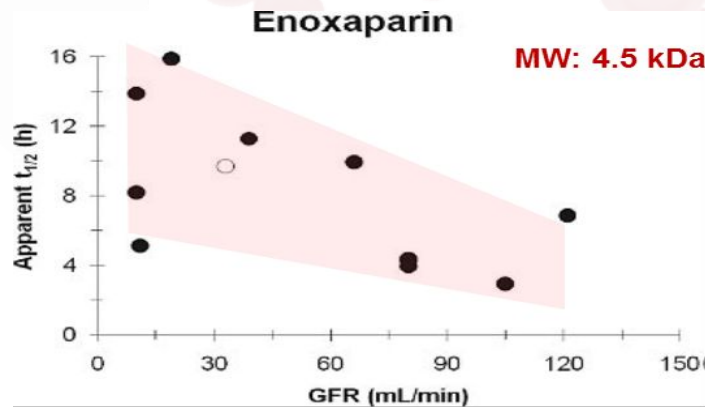
- LMWH should be preferred over oral anticoagulation in CAT patients having thrombocytopenia
- Lack of data on the safety of DOAC





# Chronic Kidney Disease

- Renal Failure is present in **50-60% of patients** diagnosed with cancer.



**LMWH are not interchangeable**



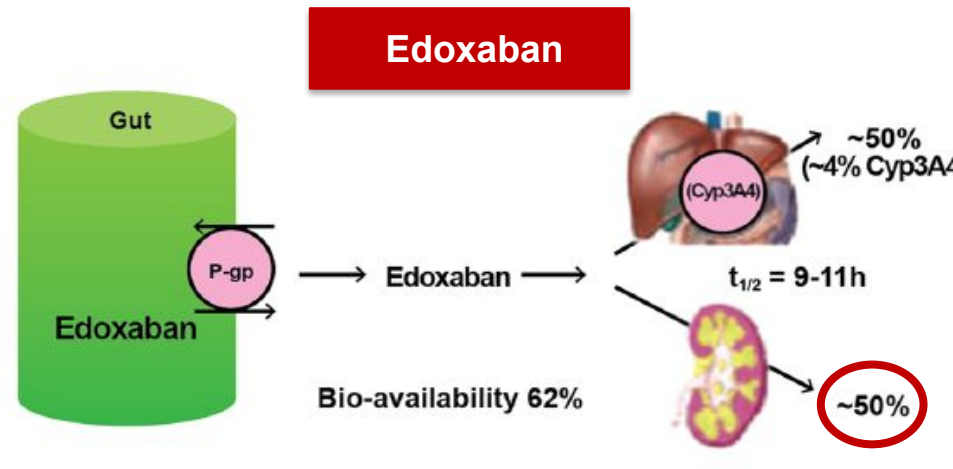
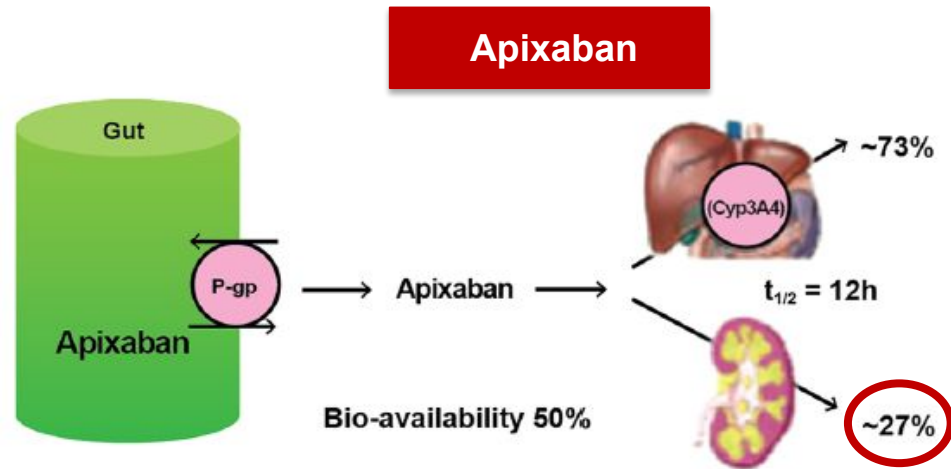
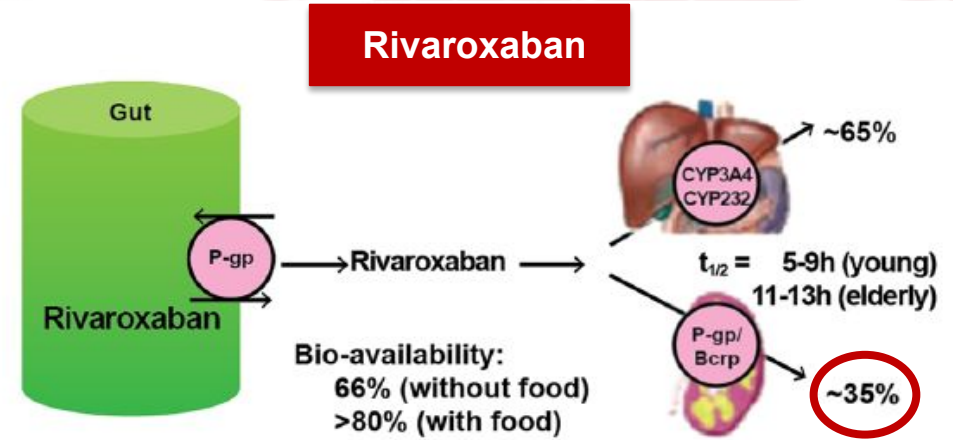
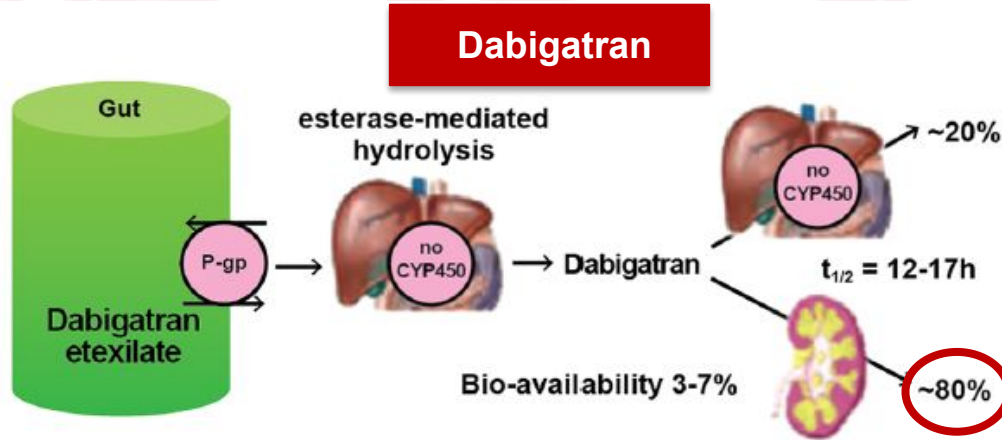
**Distinct elimination profile:  
Variable with renal function**



**Dalteparin and Tinzaparin are less  
dependent on the renal pathway  
Less variation in elimination half-life  
for different GFRs**

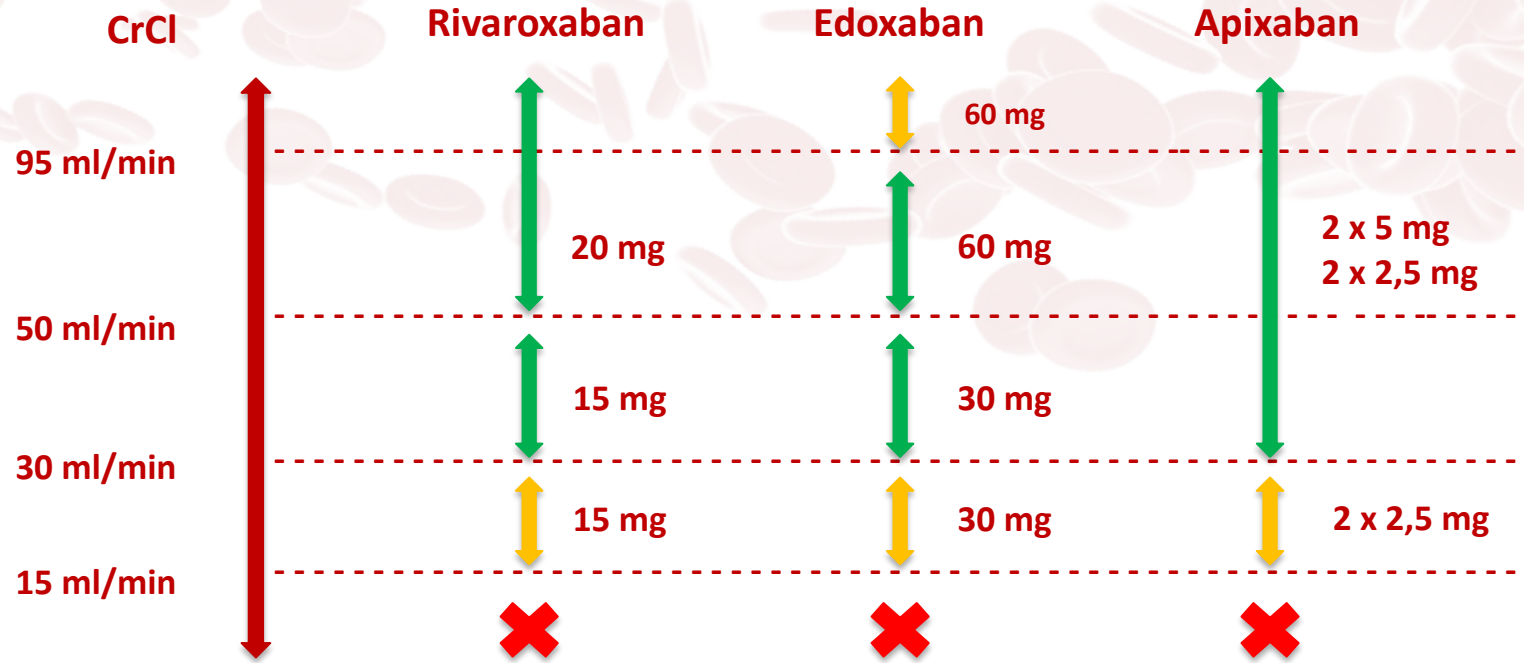


# Chronic Kidney Disease





# Chronic Kidney Disease



- The prescription of **DOACs in full dose is not recommended** in cases with Severe IR (FG<30)
- Lack of evidence in severe IR (exclusion in studies of patients with GF < 30, apixaban < 25)
- **LMWH is the recommended option** (Tinzaparin less dependent on renal elimination)



# Drug-drug Interactions

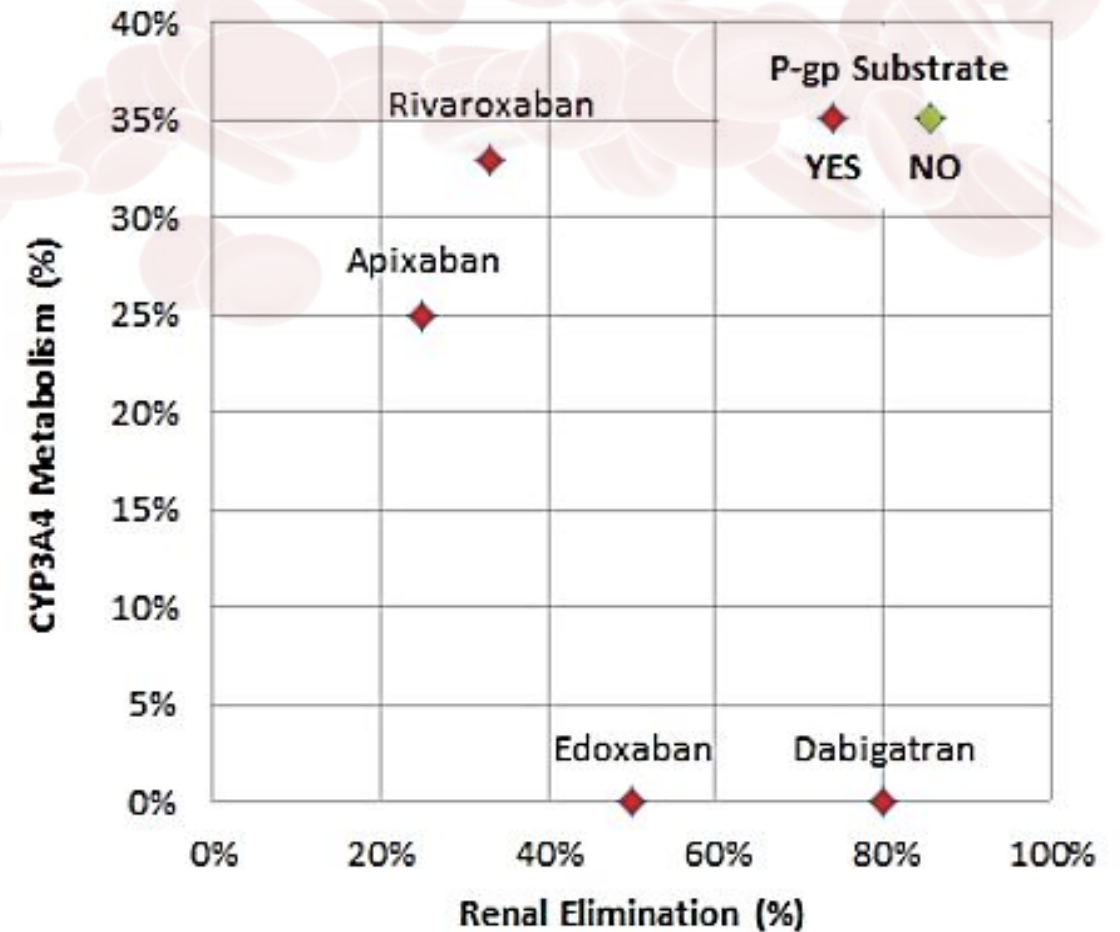
## Transport | Metabolism | Elimination Direct Oral Anticoagulant Properties

|             | P-gp substrate | CYP3A4 substrate (% of drug metabolized via CYP3A4) | % renal elimination |
|-------------|----------------|---|---------------------|
| Dabigatran  | Yes            | No  | ≈ 80                |
| Rivaroxaban | Yes            | Yes (≈ 33) <sup>a</sup>                             | ≈ 33                |
| Apixaban    | Yes            | Yes (≈ 25) <sup>b</sup>                             | ≈ 25                |
| Edoxaban    | Yes            | No  | ≈ 50                |

**CYP3A4:** Cytochrome 3A4 | **P-gp:** permeable glycoprotein

**a:** Total 66% of hepatic metabolism equally distributed between CYP3A4 and CYP2J2

**b:** Total 25% hepatic metabolism, mainly by CYP3A4, with minor contribution from CYP1A2, 2J2, 2C8, 2C9, and 2C19





# Drug-drug Interactions

Alfentanil  
Amiodaron  
Bipridil  
carvedilol  
clarithromycin  
Conivaptan  
Cyclosporin

## P-glycoprotein inhibitors

Diltiazem  
Dronedron  
Duloxetine

Indinavir  
Itraconazole  
Ketoconazole  
Palitinib  
Lovastatin  
Mefloquine  
Mifepristone  
Nelfinavir  
Nicardipine  
Posaconazole

**Increased DOAC Levels - ↑ Bleeding**

## Glycoprotein 3A4 inhibitors

Clarithromycin  
Saquinavir  
Sacubitril  
Cyclosporin  
Tamoxifen  
Indinavir  
Telaprevir  
Itraconazole  
Testosterone  
Ketoconazole  
Icagrelor  
Mifepristone  
Verapamil  
Nelfinavir  
Posaconazole  
Ritonavir  
Saquinavir  
Tamoxifen  
Telaprevir

## P-glycoprotein inducers

Barbiturates  
Carbamazepine  
Dexamethasone  
Phenytoin  
Rifampicin  
Saint John's herb

**DOAC Levels Reduction - ↓ Effectiveness**

## Gp-P and CYP3A4 inducers

Barbiturates  
Carbamazepine  
Dexamethasone  
Phenytoin  
Rifampicin  
Saint John's herb



# Bleeding Risk Assessment | Atrial Fibrillation

| HAS-BLED Score |   |        |
|----------------|---|--------|
| HAS-BLED       | Description   | Points |
| H              | Uncontrolled hypertension with systolic $\geq 160$ mmHg                                     | 1      |
| A              | Renal Function Change (creatinine $\geq 200$ $\mu\text{mol/l}$ ) and Liver (3x upper limit) | 1 ou 2 |
| S              | History of Cerebral Vascular Accident   | 1      |
| B              | History of bleeding, anemia or bleeding diathesis   | 1      |
| L              | Unstable INR (<60% time within therapeutic range)   | 1      |
| E              | Age $\geq 65$ years   | 1      |
| D              | Medication that alters hemostasis (AAS or Clopidogrel) and Alcoholism                       | 1 ou 2 |
| Maxumim Score  |   | 9      |



# Bleeding Risk Assessment | Venous Thromboembolism

| RIETE Score                         |             |
|-------------------------------------|-------------|
| Variable                            | Punctuation |
| Age > 75 years                      | 1           |
| Recent major bleeding               | 1.5         |
| Immobilization $\geq$ 4 days        | 1           |
| Metastatic Cancer                   | 2           |
| Anemia                              | 1           |
| Platelets < 100,000/mm <sup>3</sup> | 1           |
| Prolonged prothrombin time          | 1           |
| Clearance Creatinine < 30 ml/min    | 1           |
| DistalDVT                           | 1           |
| Low Risk                            | < 1.5       |
| Medium Risk                         | 1.5 - 4     |
| High Risk                           | > 4         |



# Bleeding Risk Assessment | Risk Scores

**HAS-BLED**

**mORBI**

**Koijer**

**ATRIA**

**HEMORR<sub>2</sub>HAGES**

**Einstein Model**

**ACCP-VTE Risk**

**VTE-BLEED**

**Hokusai Model**

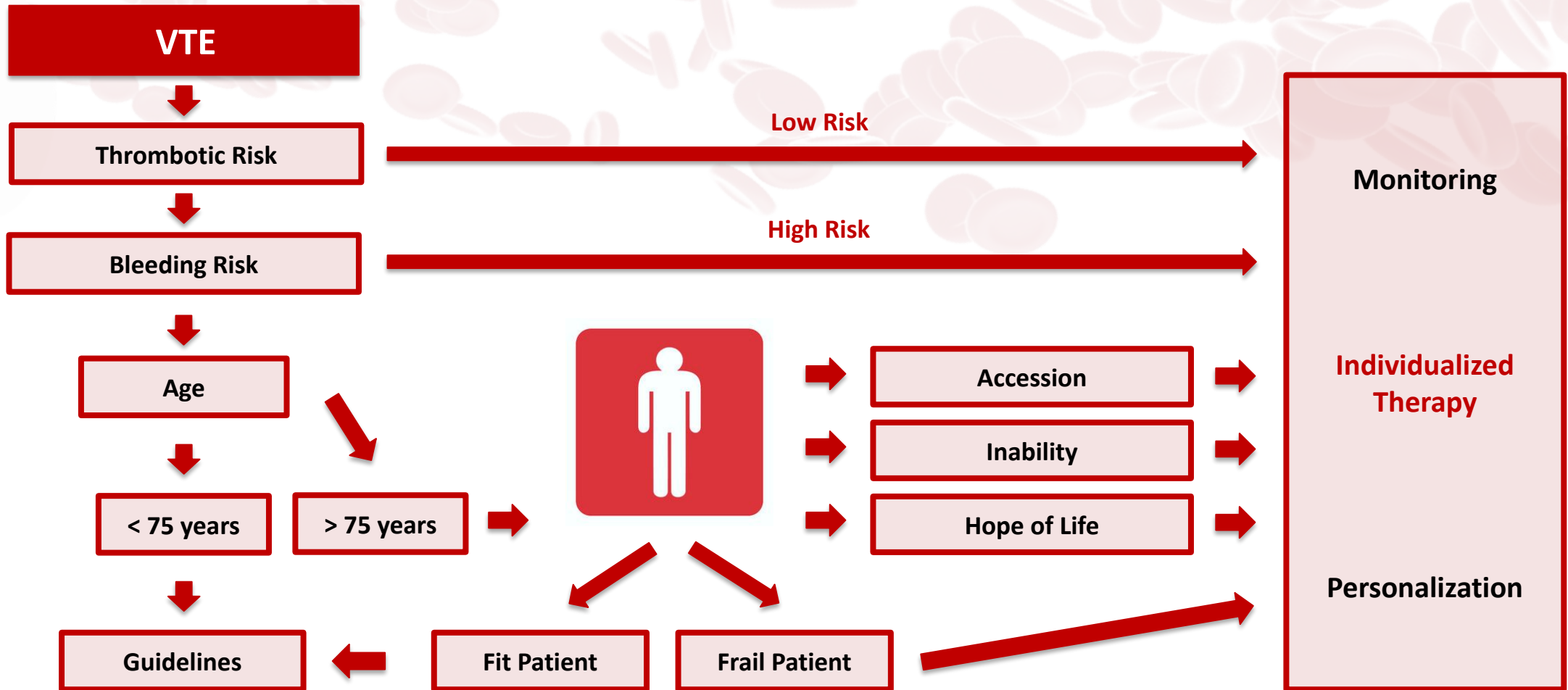


# Bleeding Risk Assessment | Risk Scores

|             | CAT-BLEED   | PREDICT-AI  |
|-------------|---|---|
| Variables   | <ul style="list-style-type: none"><li>▪ Locally advanced or metastatic cancer</li><li>▪ Genitourinary Cancer</li><li>▪ Creatinine Clearance</li><li>▪ Antineoplastic treatment with digestive toxicity (previous month)</li><li>▪ Age &gt; 75 years</li><li>▪ GI cancer and treatment with edoxaban</li></ul> | <ul style="list-style-type: none"><li>▪ Hemoglobin Levels</li><li>▪ Presence of Metastases</li><li>▪ Age</li><li>▪ Platelet Count</li><li>▪ Leukocyte count</li><li>▪ Creatinine Levels</li></ul> |
| Validation  | No  | Yes (externally in TESEO cohort)  |
| Publication | PMID:34544170   | Pending   |

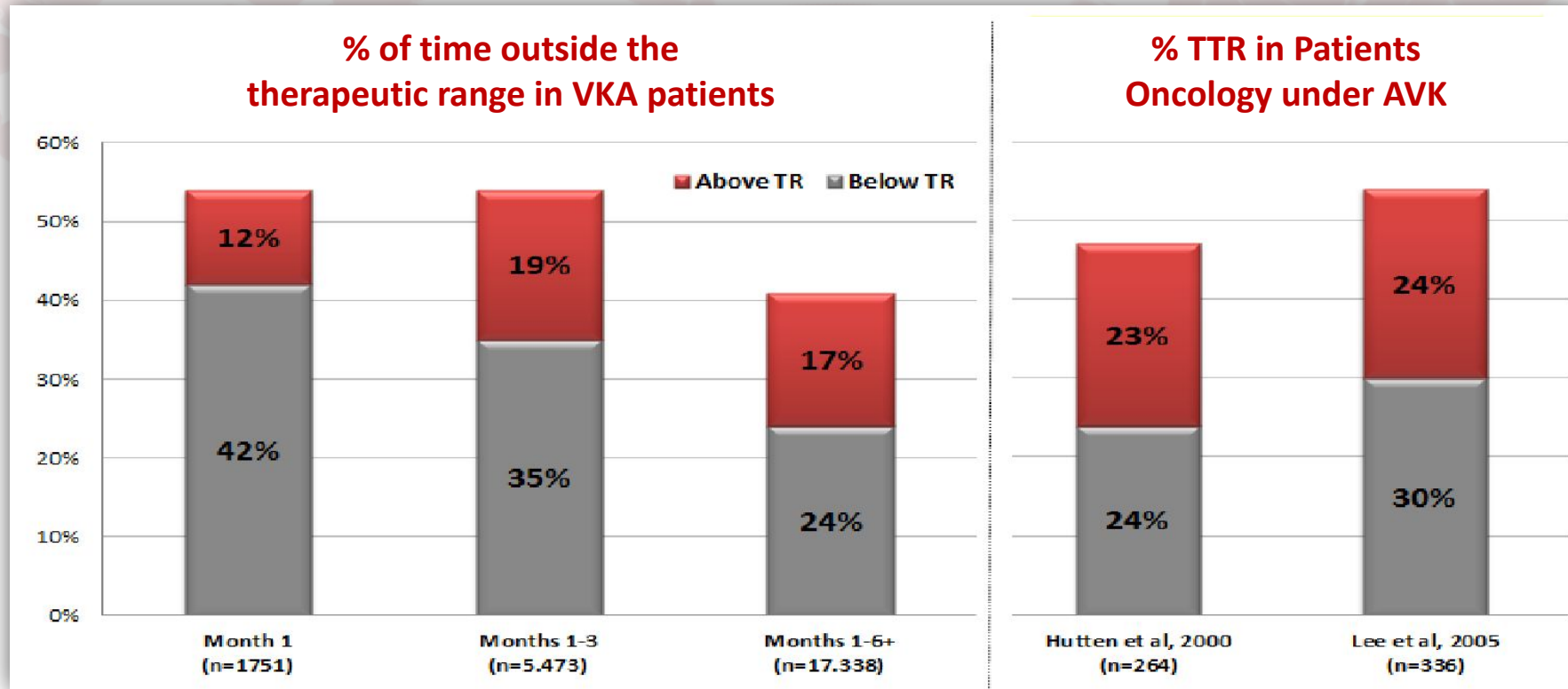


# Venous Thromboembolism in Oncology





## Anticoagulant Agent | LMWH vs VKA



When prescribing anticoagulation with a **Vitamin K Antagonist**,  
Time in Therapeutic Range (TTR) is around 50%



# Anticoagulant Agent | LMWH vs VKA

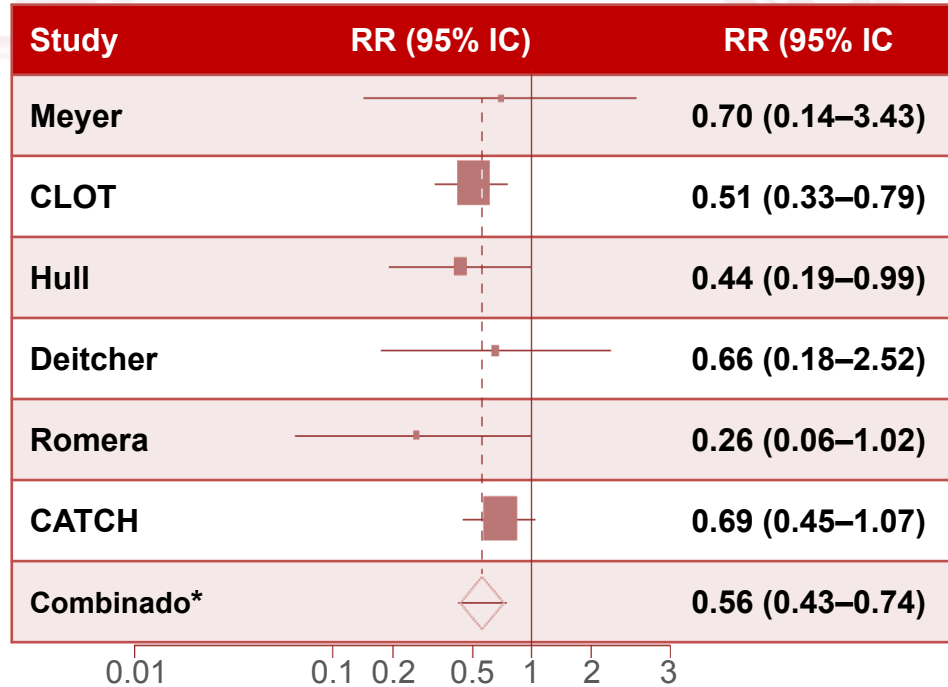
| sTUDY                                 | Drugs                         | Patients | VTE Recurrence (%)            | Risk Reduction | Major Bleeding                 |    |
|---------------------------------------|-------------------------------|----------|-------------------------------|----------------|--------------------------------|----|
|                                       |                               |          |                               |                | %                              | P  |
| <b>CLOT</b><br>Lee et al, 2003        | Dalteparin<br>vs<br>Warfarin  | 676      | Dalteparin 8<br>Warfarin 15,8 | 52%            | Dalteparin 6<br>Warfarin 4     | NS |
| <b>LITE</b><br>Hull et al, 2006       | Tinzaparin<br>vs<br>Warfarin  | 200      | Tinzaparin 7<br>Warfarin 16   | 56%            | Tinzaparin 7<br>Warfarin 7     | NS |
| <b>CATCH</b><br>Lee et al, 2014       | Tinzaparin<br>vs<br>Warfarin  | 900      | Tinzaparin 6,9<br>Warfarin 10 | 35%            | Tinzaparin 2,9<br>Warfarin 2,7 | NS |
| <b>CANTHANOX</b><br>Meyer et al, 2002 | Enoxaparin<br>vs<br>WVarfarin | 146      | Enoxaparin 10<br>Warfarin 21  | 30%            | Enoxaparin 7<br>Warfarin 16    | NR |
| <b>ONCENOX</b><br>Deicher et al, 2006 | Enoxaparin<br>vs<br>Warfarin  | 101      | Enoxaparin 5<br>Warfarin 10   | 31%            | Enoxaparin 8,8<br>Warfarin 2,9 | NS |

NS not significant | NR not reported

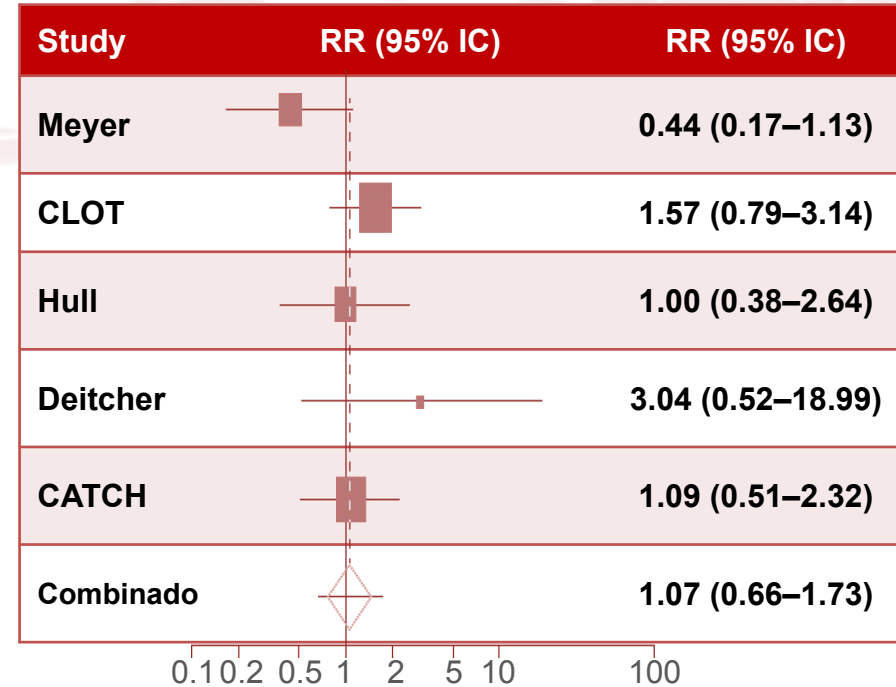


# Anticoagulant Agent | LMWH vs VKA

## Recurrent VTE



## Major Bleeding



**LMWH is associated with a significantly decreased risk of recurrent VTE**  
**no significant increase in major bleeding episodes vs VKA**

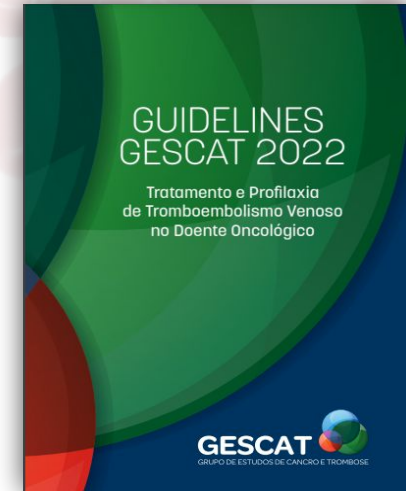
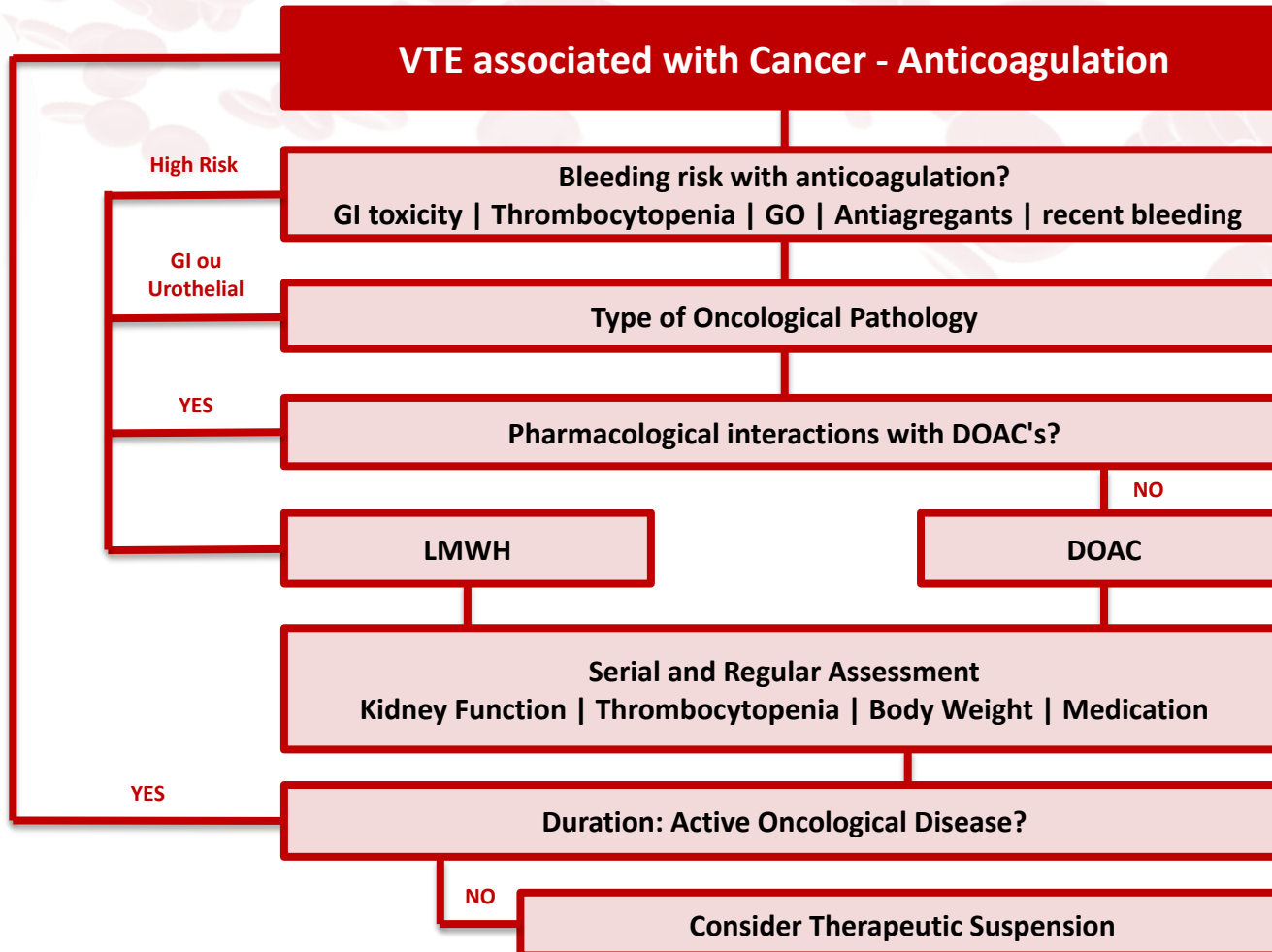


# VTE in Oncology | Anticoagulant Agent

|                                      | LMWH  | DOAC  |
|--------------------------------------|---|---|
| High thrombotic and hemorrhagic risk | 1st line of treatment due to its proven efficacy and safety profile   | If no <b>gastrointestinal/urothelial tumour</b> , low bleeding risk and no drug interactions                          |
| Renal insufficiency                  | Preferred in patients with <b>CrCl 30-50 ml/min</b><br>Tinzaparin without bioaccumulation up to <b>CrCl 20 ml/min</b> | HOKUSAI-VTE-Cancer excludes patients <b>ClCr &lt; 30 ml/min</b> and reduced edoxaban dose between <b>30-50 ml/min</b> |
| Hepatic insufficiency                | No restrictions on the use of LMWH  | Limited use due to lack of evidence   |
| Body weight                          | Consider LMWH if Weight < 40 kg or > 120 kg<br><b>Monitoring with Anti-Xa Activity</b>                                | <b>Limited use</b> in underweight patients  |
| Disease Stage                        | Higher proportion of patients with metastatic cancer, symptomatic CT and worse <b>Performance Status</b>              | Patients with earlier disease stages<br><b>Performance Status mostly &lt; 2</b>                                       |
| Gastrointestinal Disorders           | Preferable if compromised gastro-intestinal absorption  | High bleeding risk in gastrointestinal pathology or if medication with toxicity                                       |
| Polypharmacy                         | <b>No drug interactions</b>   | P-glycoprotein substrates<br>apixaban also from cytochrome P450 (CYP3A4)  |



# VTE in Oncology | Anticoagulant Agent



- Other factors to consider:**
- Patient Preference
  - Body weight
  - tumor burden
  - VTE type
  - Comorbidities



# Bleeding Risk

## Contraindications for Anticoagulation

### Absolute

Active major bleeding (>2 EC in 24 h)  
irreversible or potentially fatal

Severe malignant hypertension  
not controlled

Severe coagulopathy  
not compensated

Hemorrhagic diathesis  
cereditary or acquired

Thrombocytopenia  
< 20,000/mm<sup>3</sup>

Surgeries or invasive procedures  
(epidural anesthesia or lumbar puncture)

### Relative

Intracranial or spinal injury with  
high risk of bleeding

Peptic ulcer or GI ulceration  
with high risk of bleeding

Active bleeding with  
vital commitment

CNS hemorrhage in the  
last 4 weeks

Major surgery or severe bleeding  
in the last 2 weeks

Thrombocytopenia  
< 50,000/mm<sup>3</sup>

### Filter in the Inferior Vena Cava:

- If contraindications for anticoagulation
- VTE recurrence under adequate anticoagulation

### Exceptional Condition

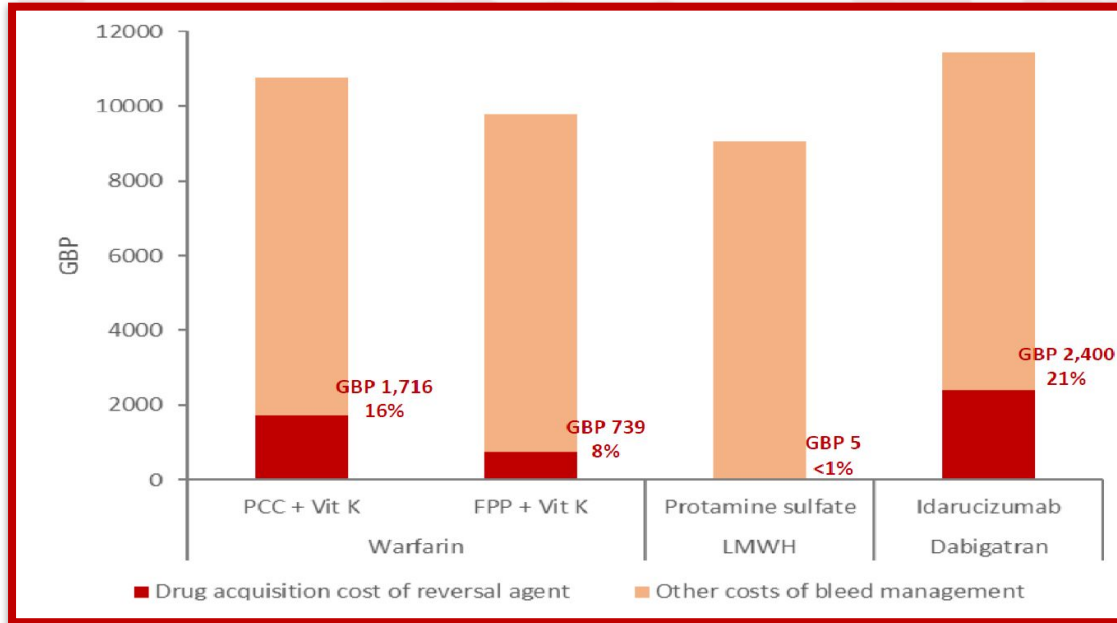
Potential complications:  
Migration and perforation



# Bleeding | Health Cost Assessment

The cost of major bleeding events associated with anticoagulant treatment - an estimation of costs

*The ISPOR Europe, 2019*



| Reversal Agent     | Cost (dolar) |
|--------------------|--------------|
| Vitamin K          | 0.38         |
| Protamine Sulfate  | 4.96         |
| FFP S/D (Octaplas) | 615 - 738    |
| PCC (Octaplex)     | 980 - 1225   |
| PCC (Beriplex)     | 892 - 1275   |

The costs associated with controlling **life-threatening bleeding** can represent about **21% of the expenses** inherent to hospitalization for this reason.



## Take-Home Messages

- Cancer patients have a **multiplicity of factors** that increase the **bleeding risk**
  - Associated with the **oncologic disease** and with ongoing treatments (chemo, radio and immuno)
- The assessment of bleeding risk should be performed with risk scores (some with external validation)
  - Optimize the prognosis and minimizing the **number of bleeding episodes**
- **Thrombotic and hemorrhagic risk** must be balanced during the treatment period:
  - Selection of anticoagulant drug, appropriate dose and period of treatment

A serial assessment of **risk factors in cancer patients** allows adequate therapy with effective improvement in mortality and **quality of life**



# ICT 2023

28th International  
Congress on Thrombosis

# Thank You For Your Attention

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