MAYO CLINIC | School of Continuous Professional Development

# CANCER RELATED VENOUS THROMBOEMBOLISM

## PROPHYLAXIS AND TREATMENT

# LEARNING OBJECTIVES

- Discuss **indications** for **anticoagulation prophylaxis** in cancer patients
- Discuss role of **direct oral anticoagulants** and **low molecular weight heparin** in treatment of cancer associated venous thromboembolism
- Challenging scenarios – management of bleeding and thrombocytopenic patients

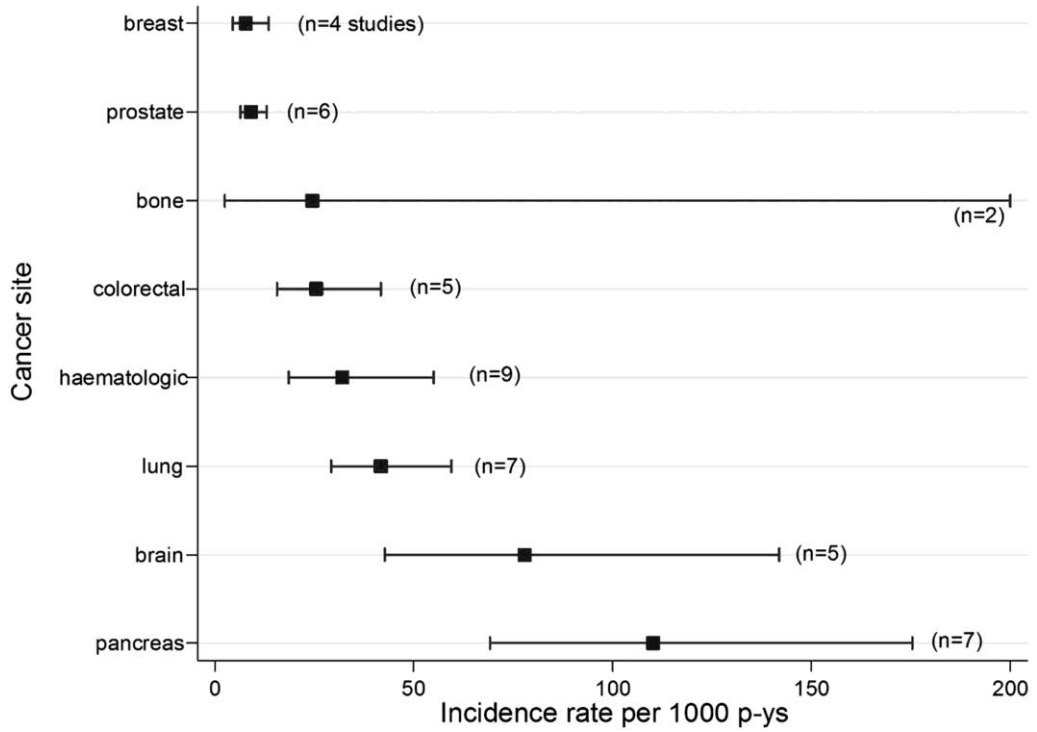
# CANCER AND THROMBOSIS

- 20% of venous thromboembolism cases are associated with cancer
- 20% of cancer patients develop venous thrombosis
- 4-7 x higher risk of Venous Thromboembolism (VTE)
- 3 x higher risk of recurrent VTE
- 2 x higher risk of bleeding with Anticoagulation
- 10 x higher risk of death compared to patients without cancer

Blood Adv. 2021;5 (4):927-974
*Cancer Res; 76(13); 3671–5*
Cancer. 2007 Nov 15;110(10):2339-46

# RISK FACTORS

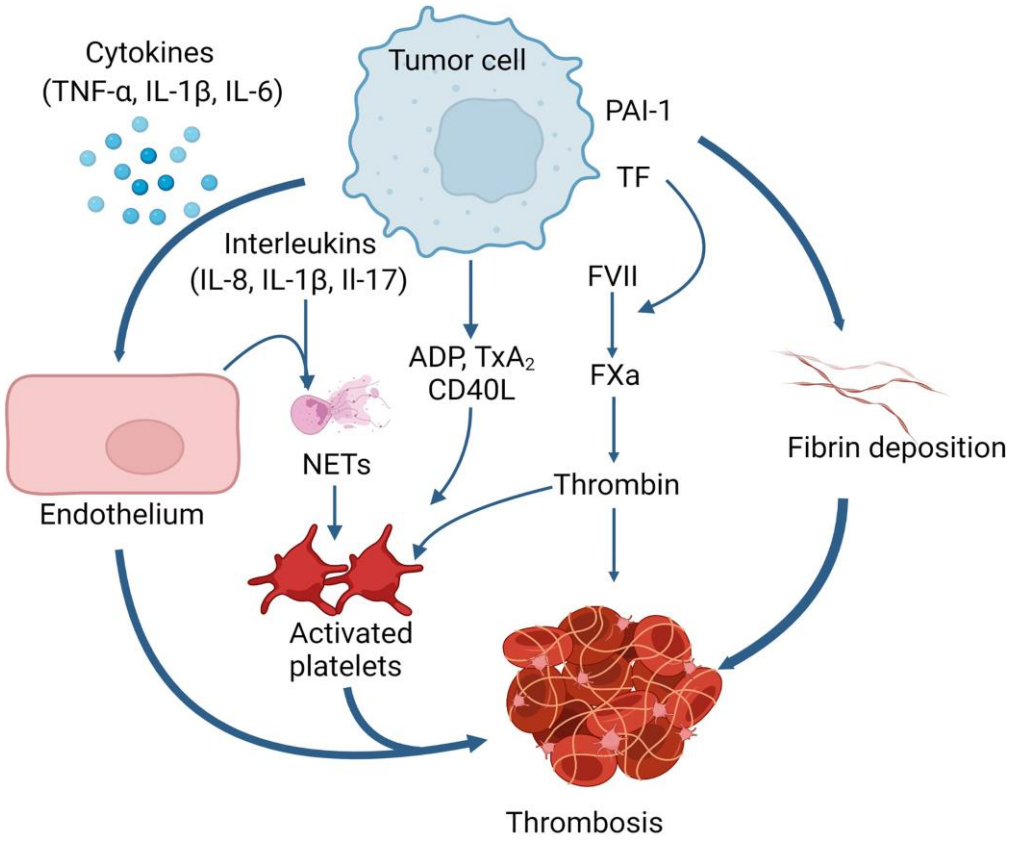
- Cancer type
- Cancer genetics (i.e. Jak2 V617F)
- Cancer stage and grade
- Type of treatment
- Underlying comorbidities (i.e prior history ofVTE, thrombophilia carrier)




Jasmijn F. Timp et al. Blood 2013;122:1712-1723

# MECHANISM OF THROMBOSIS IN CANCER

- **Extracellular vesicles** may contain **Tissue Factor**
- **Neutrophil extracellular traps**
- **Inflammatory cytokines** - TNFα, IL -1β, IL6, VEGF
- **Extracellular microRNAs**




**Pathogenesis of Cancer-Associated Thrombosis**

Image from Girardi et al. ATVB. Volume: 43, Issue: 6, Pages: 824-831, DOI: (10.1161/ATVBAHA.123.318779)

# THROMBOSIS PROPHYLAXIS IN HOSPITALIZED PATIENTS

- For **hospitalized medical** patients with cancer:

  thromboprophylaxis recommended during hospitalization

  LWWH over UFH

  no need in transplant admissions or with short procedures

Blood Adv. 2021;5 (4):927-974
Journal of Clinical Oncology 2020 38:5, 496-520

# THROMBOSIS PROPHYLAXIS IN HOSPITALIZED PATIENTS

- For **patients with cancer undergoing surgery**:
  low bleeding risk – pharmacologic prophylaxis
  high bleeding risk – mechanical prophylaxis
  high thrombosis risk but without high bleeding risk – both mechanical and pharmacologic prophylaxis
- Extended prophylaxis **up to 4 weeks** with major abdominal/pelvic cancer surgery

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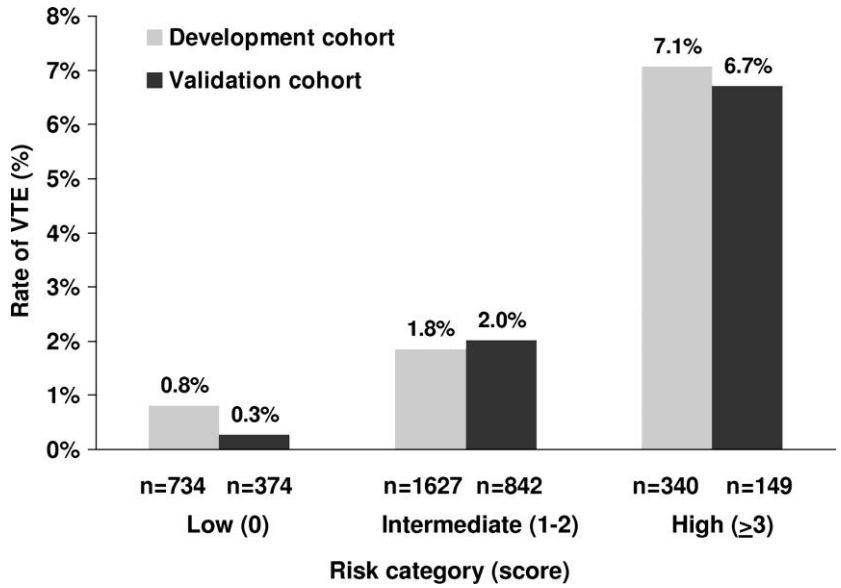
# AMBULATORY PATIENTS
## KHORANA RISK SCORE

| Patient Characteristics | Risk score |
|---|---|
| **Site of cancer** | |
| -Very high risk (stomach, pancreas) | 2 |
| -High risk (lung, lymphoma, gyn, GU) | 1 |
| Prechemotherapy plt count ≥ 350 $x10^9/L$ | 1 |
| Prechemotherapy Hgb < 10 g/dL or use of Red Cell growth factors | 1 |
| Prechemo WBC count >11 $x10^9/L$ | 1 |
| BMI ≥ 35 kg/m2 | 1 |




0 = low risk
1-2= intermediate risk
>2 = high risk

Khorana et al. Blood. 2008 May 15;111(10):4902-7

# OTHER PREDICTION MODELS

- **PROTECHT** score = Khorana + chemotherapeutic agents (cisplatin, carboplatin and gemcitabine)
- Vienna Cancer and Thrombosis Study (**CATS**) score = Khorana + D-dimer and soluble P-selectin
- **CONKO** score = Khorana – BMI + PS

# MORE PREDICTION MODELS

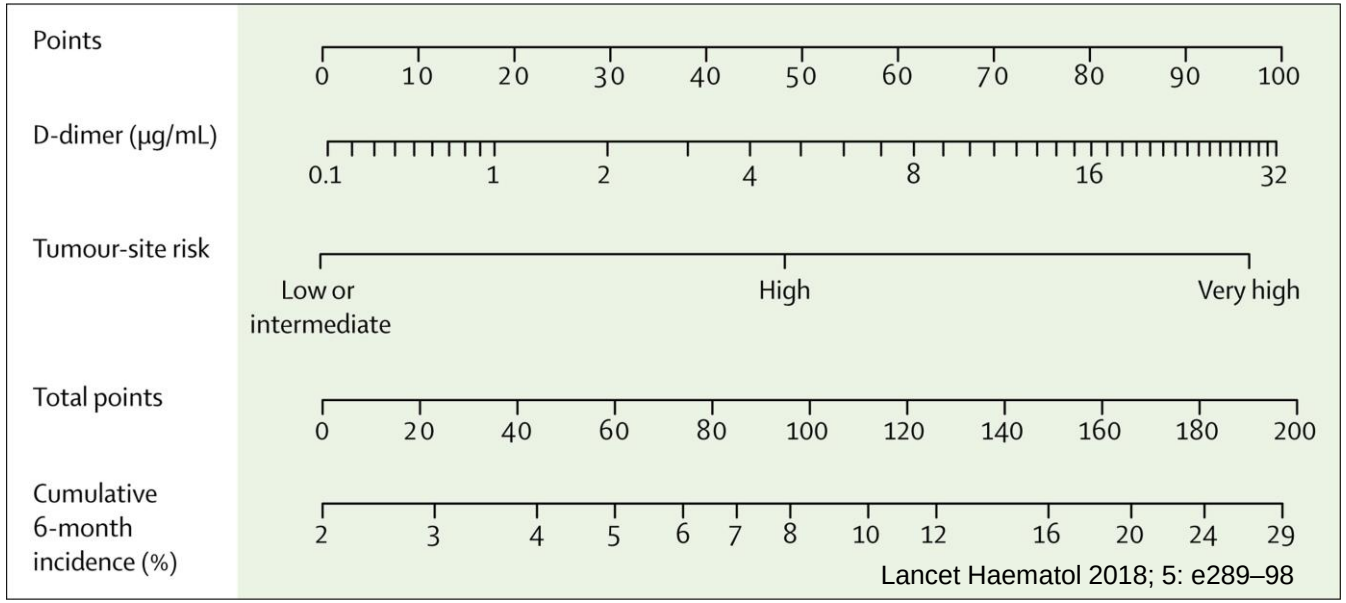
- **COMPASS-CAT**

| VTE predictors | score |
|---|---|
| Cancer-related risk factors | |
| Endocrine therapy or Anthracycline | **6** |
| Time since dg <6 mo | **4** |
| CVC | **3** |
| Advanced stage | **2** |
| Predisposing risk factors | |
| CV risk factors (at least 2 of: Hx of PAD, ischemic stroke, CAD, Htn, hyperlipidemia, DM, obesity) | **5** |
| Recent hospitalization for acute illness | **5** |
| Personal VTE history | **1** |
| Biomarkers | |
| Plt count > 350 $10^9$/L | **2** |

Low/Intermediate risk: 0–6 (1.7% had VTE); high risk: > 7 (13.3%)

The Oncologist 2017;22:1222–1231

- New **VIENNA** model




Lancet Haematol 2018; 5: e289–98

- **ONKOTEV** = Khorana score > 2 + metastatic disease + vascular or lymphatic compression + previous VTE event.

# PREVENTION OF VTE IN AMBULATORY CANCER PATIENTS - LMWH

| Study (LMWH in pts with advanced cancers) | VTE in LMWH vs no prophy | Major bleed in LMWH vs no prophy |
|---|---|---|
| Kakkar et al 2004 | 2.4% vs 3.3% | 0.5% vs 0 |
| Agnelli et al 2009 | 2% vs 3.9 % | 0.7% vs 0 |
| Khorana et al 2015 | 12% vs 21% | 2% vs 2% |
| Sideras et al 2005 | 6% vs 7% | 3% vs 7% |
| Doormaal et al 2011 | 6.5% vs. 5.8% | 4.1% vs 3.5% |

# PREVENTION OF VTE IN AMBULATORY CANCER PATIENTS - DOACS

**Avert** trial 2.5 mg bid Apixaban vs placebo

VTE rates Apixaban 4.2% vs 10.2% placebo

Major bleeding rates Apixaban 3.5% vs 1.8% placebo

**Cassini** trial 10 mg daily Rivaroxaban vs placebo

VTE rates Rivaroxaban 6% vs 8.8% placebo

Major bleeding rates Rivaroxaban 2% vs 1% placebo

N Engl J Med. Volume 380(8):711-719 February 21, 2019
N Engl J Med 2019; 380:720-728

# THROMBOPROPHYLAXIS IN AMBULATORY CANCER PATIENTS

- No thromboprophylaxis in low risk patients

- In high risk patients
  ASH suggests
  ISTH suggests
  ASCO may be offered
  NCCN consider

Blood Adv. 2021;5 (4):927-974
Oncologist. 2021 Jan;26(1):e24-e40

# LMWH BETTER THAN WARFARIN

CLOT trial
- Recurrent VTE: 15.7 % warfarin vs 7.9 % dalteparin
- Major Bleeding: 6%  warfarin vs 4% dalteparin

CATCH trial
- Recurrent VTE: 10% warfarin vs 6.9% tinzaparin
- Major Bleeding: 2.7% warfarin vs 2.4% tinzaparin

Lee A, et al. N Engl J Med, 2003; 349: 146-53.
Lee et al. JAMA. 2015 Aug 18;314(7):677-86

# DIRECT ORAL ANTICOAGULANTS VS LMWH

## Edoxaban

Recurrent VTE: 7.9% vs 11.3%
Major bleeding: 6.9% vs 4.0 %

## Rivaroxaban

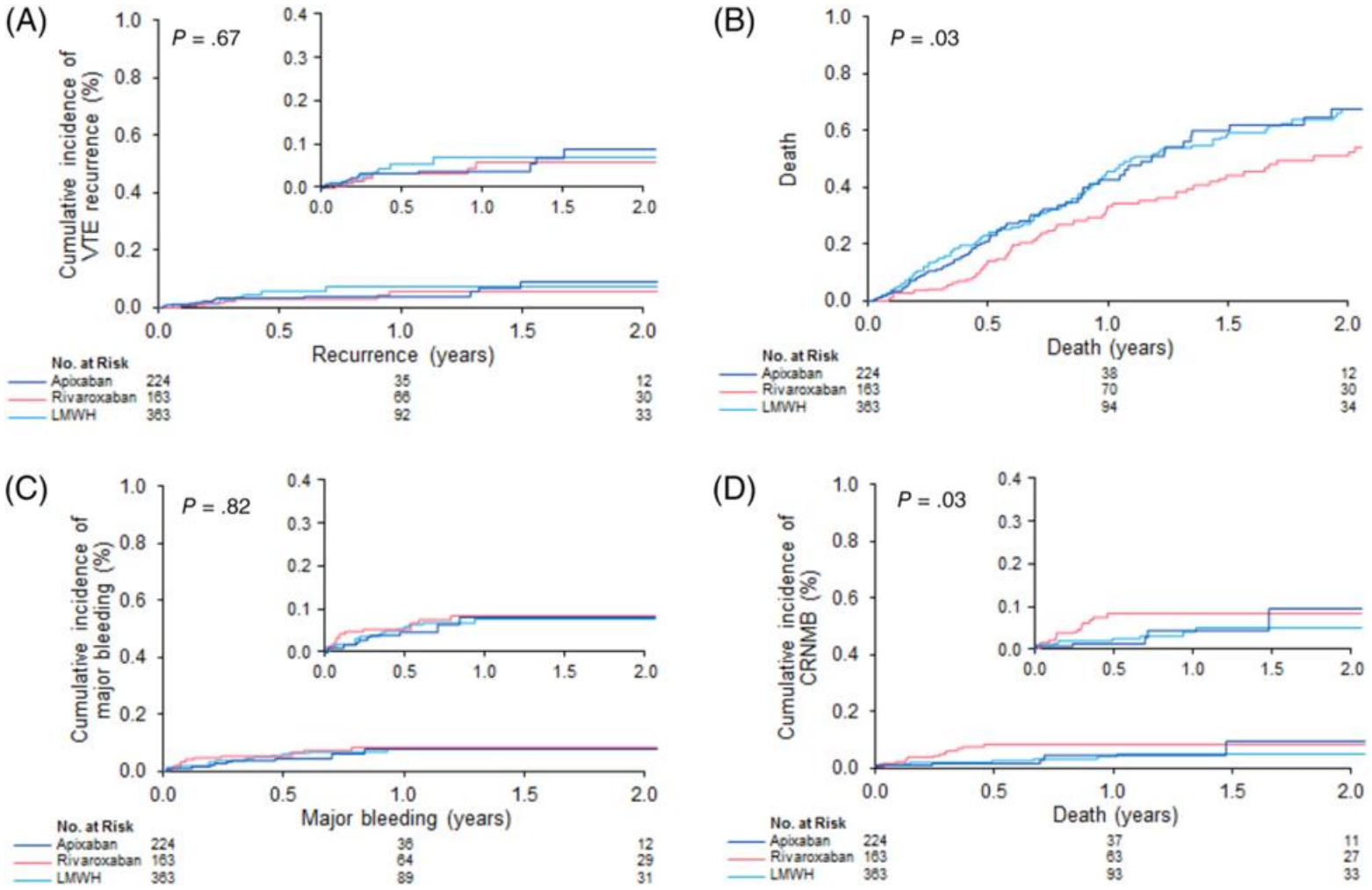
Recurrent VTE: 4% vs 11%
Major bleeding: 6% vs 4%

## Apixaban

Recurrent VTE: 5.6% vs 7.9 %
0.7% vs 6.3%
Major bleeding: 3.8% vs 4.0%
0 vs 1.4%

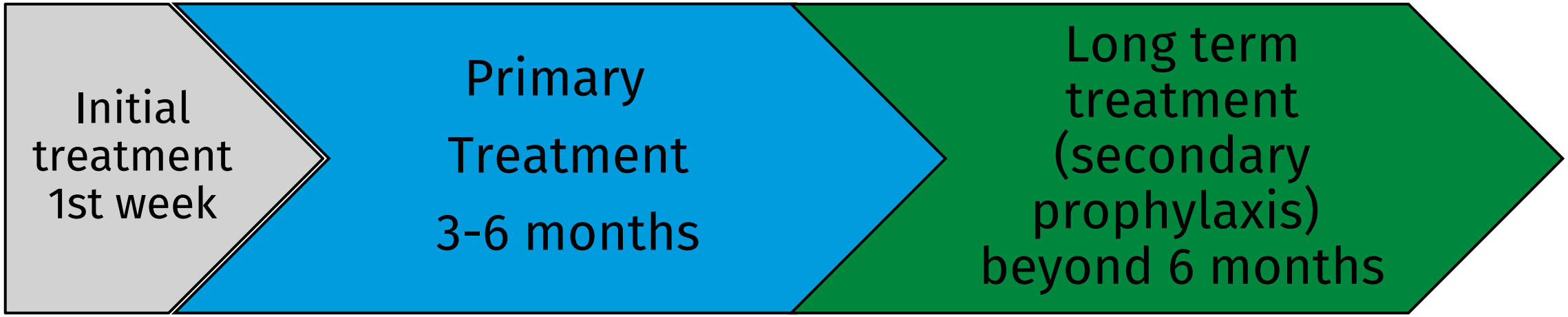
GE Raskob et al. N Engl J Med 2018;378:615-624
J Thromb Haemost. 2020;18:411-421
J Thromb Haemost.2020 Apr;18(4):905-91
Agnelli et al. N Engl J Med 2020; 382:1599-1607

# COMPARISON OF DOACS AND LMWH



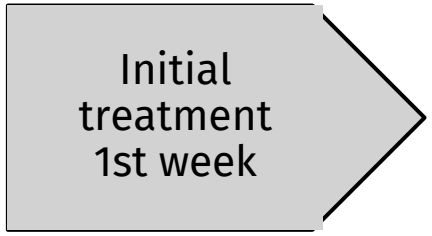

AJH, Volume:94(11):1185-1192

# TREATMENT OF CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM



# INITIAL TREATMENT

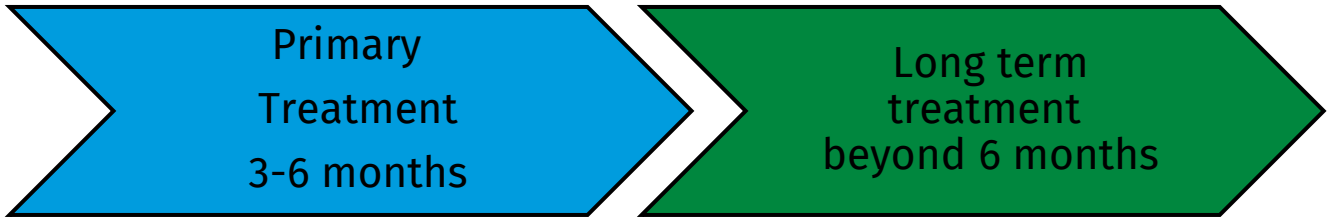
- Direct oral anticoagulant: Apixaban, Rivaroxaban or LMWH
- LMWH favored over unfractionated heparin (except in severe renal failure)
- Caution with DOACs in patients with gastrointestinal cancers and GU cancers with bleeding risk




Blood Adv. 2021;5 (4):927-974

# SHORT AND LONG  TERM TREATMENT

- Direct oral anticoagulant such as Apixaban, Edoxaban or Rivaroxaban preferred over LMWH
- Continue treatment beyond 6 months in patients with active cancer
- Unclear if DOAC dose can be reduced with long term treatment

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# CANCER VTE SCENARIOS

- In patients with cancer should you treat with anticoagulation:
  - Incidental PE **YES**
  - Subsegmental PE **YES** (case by case ASCO 2019 guidelines)
  - Visceral/splanchnic vein thrombosis **YES** though observation is also an option

  Can you keep CVC in patients with cancer and CVC-related clot **YES**
- For patients with cancer and recurrent VTE despite receiving therapeutic LMWH consider increasing the LMWH dose to a supratherapeutic level
- IVC filter is not recommended for prevention in recurrent VTE (may be offered per ASCO 2019 guideline)

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# ANTICOAGULATION IN THROMBOCYTOPENIC PATIENT

- Cut off 50 k/uL for therapeutic anticoagulation
- Consider intermediate or prophylactic anticoagulation with plt count 20-50 k/uL
- Consider timing of acute clot (< 3 months vs >3 months), type of tumor and treatment

Hanny Al-Samkari et al. Blood Adv, 2019, Figure 1.

# ANTICOAGULATION IN BRAIN CANCER

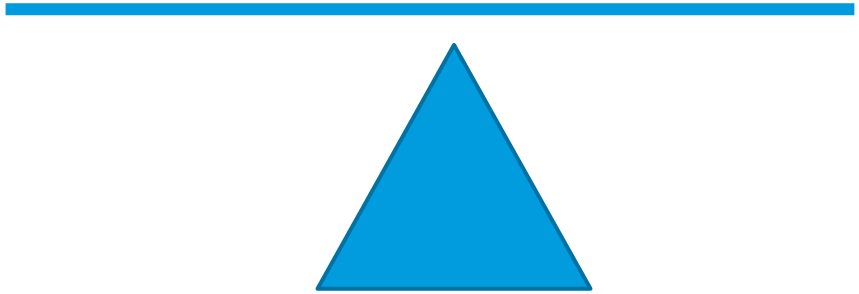
- Is not contraindicated but caution advised
- Does not significantly increase risk of ICH in patients with brain mets
- Significantly increased ICH risk in primary brain cancer
- DOACS do not increase bleeding risk over LMWH (?may decrease)
- IVC filters not very effective

# BLEEDING IN CANCER PATIENTS REQUIRING ANTICOAGULATION

## TO ANTICOAGULATE OR NOT TO ANTICOAGULATE?

| Absolute contraindications to AC |
| --- |
| Active major, serious, or potentially life-threatening bleeding |
| Severe, uncontrolled malignant hypertension |
| Severe, uncompensated coagulopathy , Severe platelet dysfunction or inherited bleeding disorder |
| Persistent, severe thrombocytopenia (< 20,000/uL) |
| High-risk invasive procedure in a critical site |
| DOAC only -oncurrent use of potent P-glycoprotein or CYP3A4 inhibitors or inducers |

Location: PE >> distal DVT or CVC- associated DVT
Timing: < 3 months vs >3 months
Type of tumor and stage
Mutational status of tumor
Treatment



# IN SUMMARY

- Cancer patients are at high risk of thrombotic as well as bleeding complications
- Consider prophylactic anticoagulation in patients with cancer and high risk of thrombosis
- DOACs or LMWH are recommended for initial treatment of thrombosis in cancer patients with DOACs preferred for short as well as long term therapy
- Long term anticoagulation is recommended as long as patient is at high thrombotic risk
- Anticoagulation can be continued with thrombocytopenia, especially if plt count >50k, use clinical judgment

# THANK YOU