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FOR Health Professionals

# The CAT's out of the bag: Management of cancer associated thrombosis in the era of DOACs

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# Presenter disclosure

- **Marc Carrier:**

- **Relationships with commercial interests:**
  - **Grants/Research Support: BMS, Leo Pharma, Pfizer**
  - **Speakers Bureau/Honoraria: NA**
  - **Consulting Fees: Sanofi, Bayer, BMS, Pfizer, Leo Pharma, Valeo**
  - **Other: NA**

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# Learning objectives

- Review the epidemiology and clinical relevance of venous thromboembolic complications in cancer patients
- Summarize the evidence on the efficacy and safety of different anticoagulant regimens (LMWH or DOAC) for the management of cancer-associated thrombosis (CAT)
- Discuss how to tailor anticoagulation based on specific patient characteristics (e.g. Tumor types, intra-cranial metastatic disease or primary brain tumor, drug-to-drug interactions)

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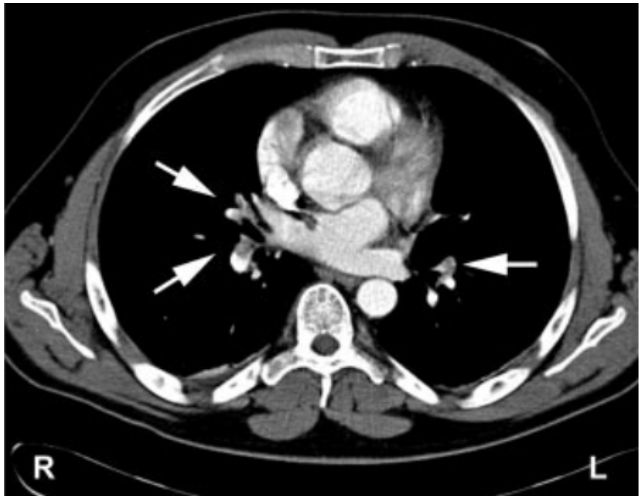
# Mr. MT

**77 years old with hormone-naïve metastatic (bone and brain) prostate cancer recently started on ADT and docetaxel**

- Presented to the ER with progressive SOB and pleuritic chest pain.
- HR: 100 beats/min; BP: 105/60;RR: 22; T: 36.7C and 95% of on room air
- PMdHx: HTN, DM2
- Hb: 115 g/L; plt: 350 X 10^9/L; CrCl: 65 cc/min
- CTPA reporting a **bilateral segmental PEs**




Schaefer WM et al. Der Nuklearmediziner 99-56.35:27;

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# Incidence

**Annual incidence of VTE in the general population is 117 per 100,000**

- Cancer alone was associated with a 4.1-fold risk of thrombosis
- Chemotherapy increased the risk 6.5-fold

**Combining these estimates yields an approximate annual incidence of venous thromboembolism (VTE) of 1 per 200 in a population of cancer patients**

Heit JA et al. *Arch Intern Med*. 2000; 160: 809–815.

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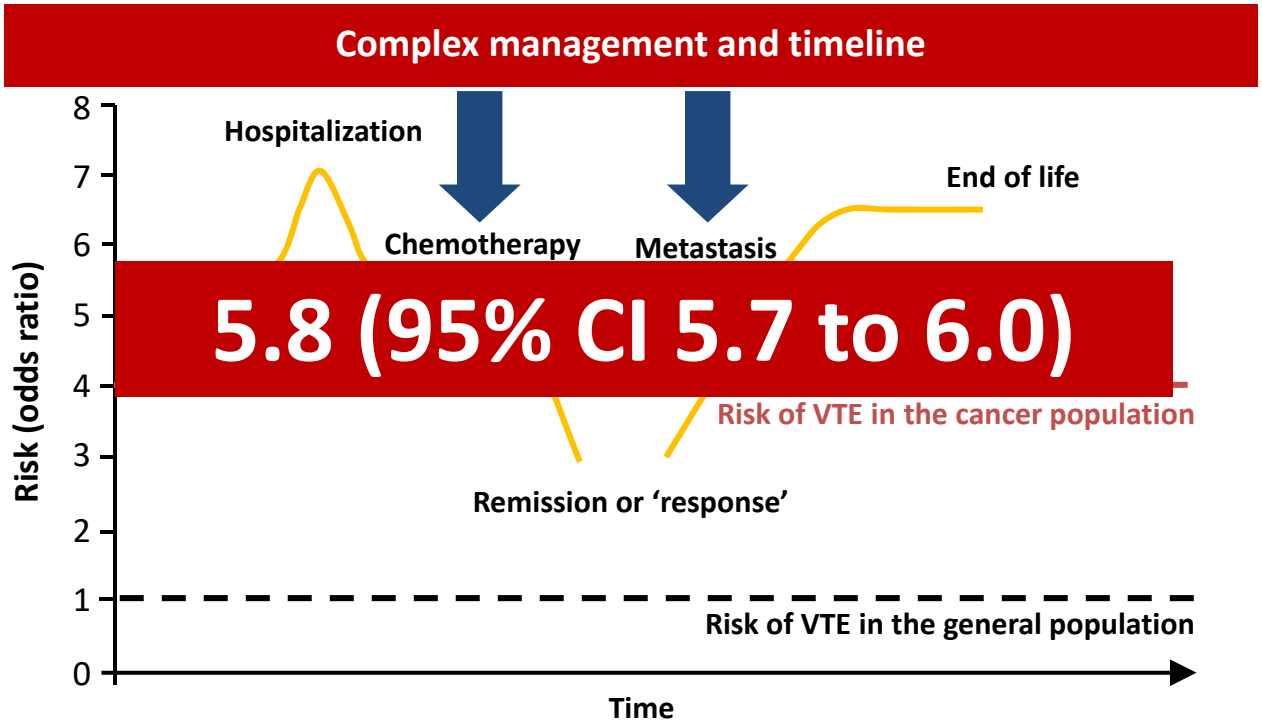
# Cancer and VTE




Lyman GH, *Cancer* 2010;7:1334–1349

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# Incidence rate of CAT by cancer type

Incidence rate (95% CI) of first VTE per 100 person-years by cancer type

| Age | Total ≥18 |
|---|---|
| Bladder | **2.7** (2.4–3.0) |
| Breast | **3.2** (2.9–3.4) |
| Colon | **6.7** (6.3–7.2) |
| Lung | **10.1** (9.5–10.8) |
| Prostate | **4.4** (4.0–4.7) |
| Uterus | **7.0** (5.9–8.3) |
| Haematological | **4.5** (4.1–4.8) |
| Brain | **12.1** (10.3–14.0) |
| Ovary | **11.9** (10.6–13.2) |
| Pancreas | **14.6** (12.9–16.5) |
| Stomach | **10.8** (9.5–12.3) |

Cohen AT et al, *Thromb Haemost* 2017;117:57–65

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# Patient demographics

Patients with active cancer and a first VTE (N=6592)

| | DVT (n=3055) | PE (n=3537) | Total (N=6592) |
|---|---|---|---|
| **Common cancer types, n (%)** | | | |
| **Prostate (males)** | 278 (19.1) | 287 (16.1) | **565 (17.5)** |
| **Breast (females)** | 225 (14.0) | 281 (16.0) | **506 (15.1)** |
| **Lung** | 315 (10.3) | 603 (17.0) | 918 (13.9) |
| **Colon** | 384 (12.6) | 443 (12.5) | 827 (12.5) |
| **Haematological** | 360 (11.8) | 309 (8.7) | 669 (10.1) |
| **Ovarian (females)** | 136 (8.5) | 182 (10.3) | 318 (9.5) |
| **Bladder** | 186 (6.1) | 133 (3.8) | 319 (4.8) |
| **Uterus (females)** | 83 (5.2) | 58 (3.3) | 141 (4.2) |
| **Pancreas** | 129 (4.2) | 131 (3.7) | **260 (3.9)** |
| **Stomach** | 104 (3.4) | 133 (3.8) | **237 (3.6)** |
| **Brain** | 79 (2.6) | 87 (2.5) | 166 (2.5) |

Cohen AT et al, *Thromb Haemost* 2017;117:57–65

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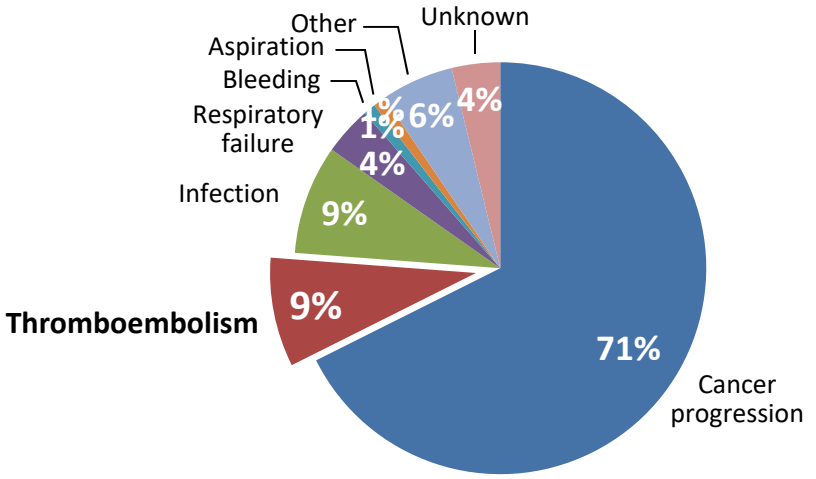
# VTE as a cause of death

- Thromboembolism is the **second leading** cause of death in patients with cancer
- Annual death rate for VTE: 448 per 100,000 cancer outpatients
  - **47-fold increase** over the general population

**Cancer outpatient mortality**




1. Khorana AA et al, *J Thromb Haemost* 2007;5:632–634; 2. Khorana AA et al, *Thromb Res* 2010;125:490–493

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# Factors for clinicians to consider in selecting appropriate anticoagulant for patients with CAT

- Efficacy
- Safety
- Tumour type
- Presence of CNS metastases
- Concomitant conditions
- Drug-drug interactions (DDIs)
- Patient perspective

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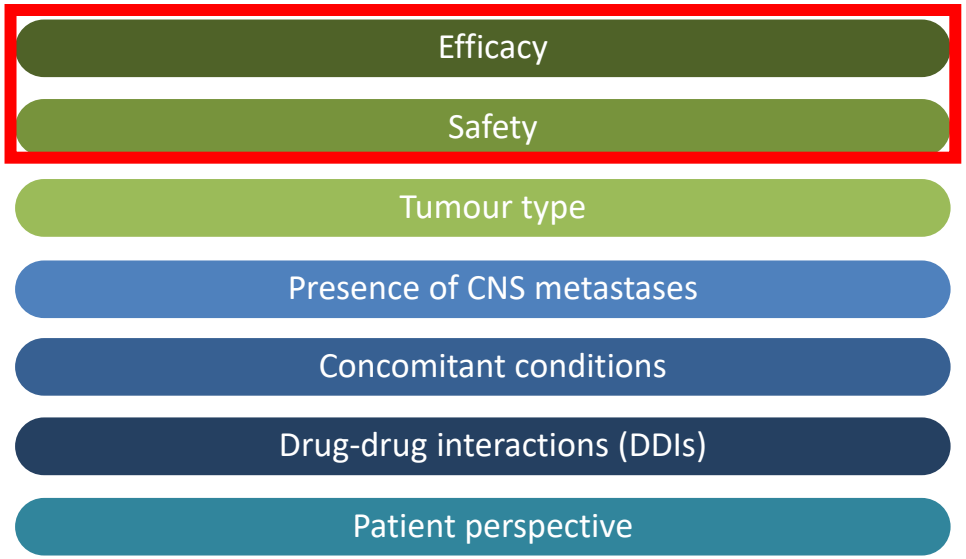
# Factors for clinicians to consider in selecting appropriate anticoagulant for patients with CAT



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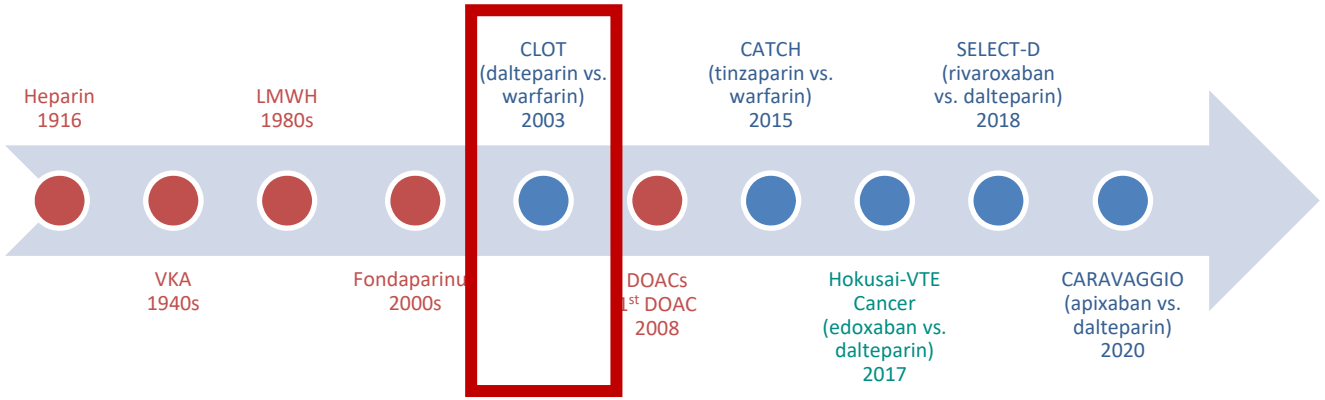
# Evolution of anticoagulant therapy: Treatments and trials



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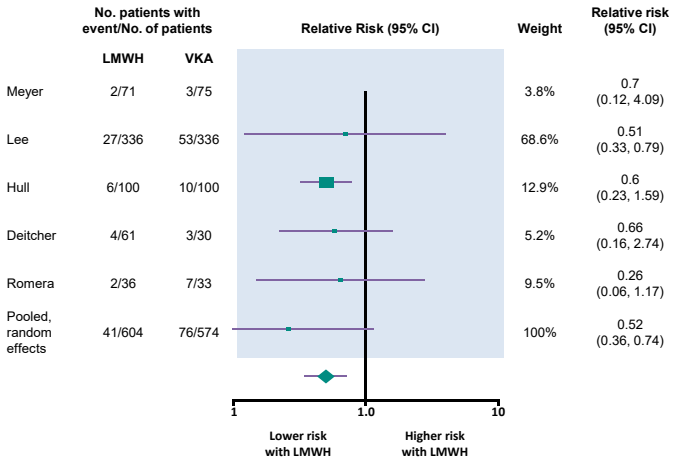
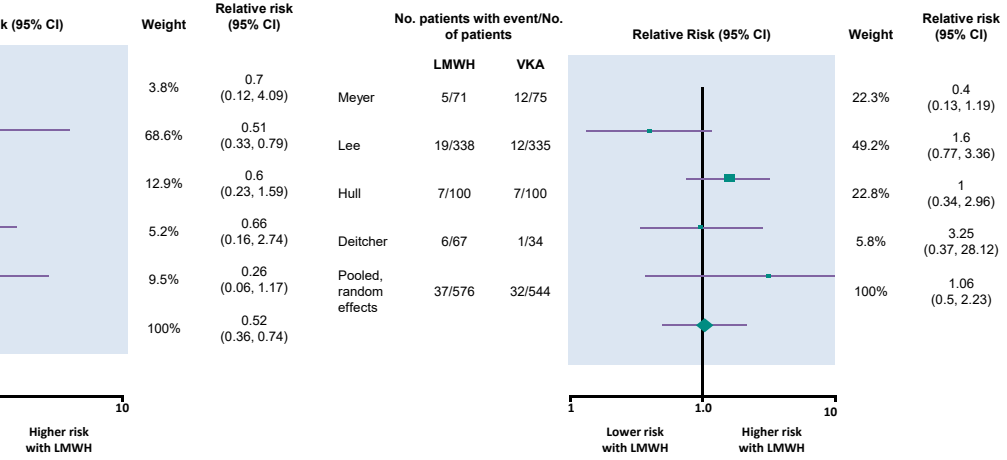
# LMWH vs. VKA: Meta-analysis

## Recurrent VTE




## Major Bleeding




**Significantly lower risk of VTE recurrence with LMWH vs. VKA, with similar risk of major bleeding**

Carrier M et al. *Thromb Res*. 2014;134:1214-9.

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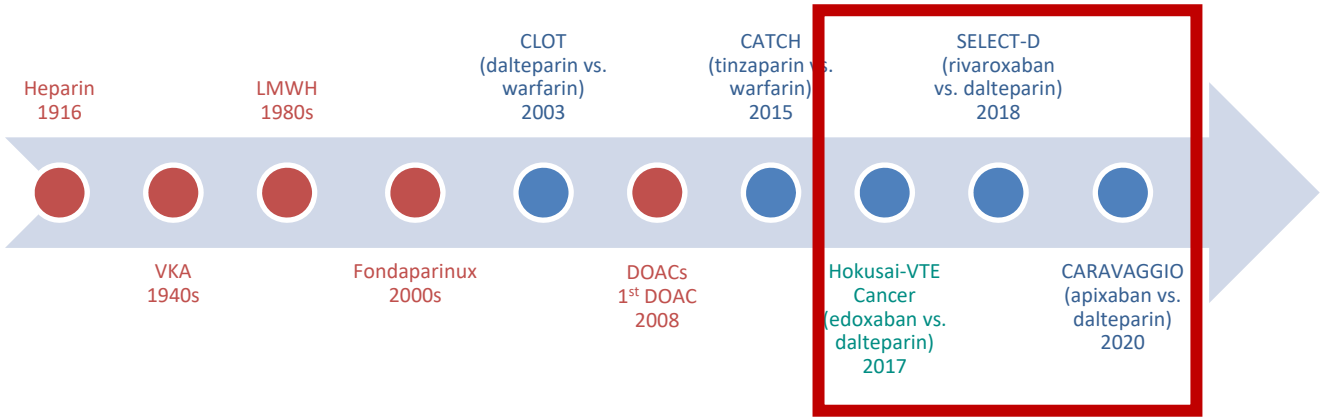
# Evolution of anticoagulant therapy: Treatments and trials



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# DOAC vs. LMWH for acute CAT

| | HOKUSAI-VTE Cancer | SELECT-D | CARAVAGGIO |
|---|---|---|---|
| **Trial design:** | Non-inferiority Phase 3 | Pilot | Non-inferiority Phase 3 |
| **Sample size** | 1046 | 406 | 1155 |
| **DOAC:** | LMWH X 5 days then edoxaban 60 mg PO daily | Rivaroxaban 15 mg BID X 21 days then 20 mg daily | Apixaban 10 mg BID X 7 days then 5 mg BID |
| **LMWH:** | Dalteparin 200 U/kg daily X 1 month the 150 U/Kg daily | Dalteparin 200 U/kg daily X 1 month the 150 U/Kg daily | Dalteparin 200 U/kg daily X 1 month the 150 U/Kg daily |
| **Dose reduction of DOAC:** | < 60 kg; CrCl: 30-50 cc/min; drug-to-drug interactions | NA | NA |
| **Primary outcome:** | Recurrent VTE or major bleeding | Recurrent VTE | Recurrent VTE |
| **Duration of treatment** | 12 months | 6 months | 6 months |

Raskob GE et al. N Engl J Med. 2018 Feb 15;378(7):615-624 Young AM, et al. J Clin Oncol 2018 Jul 10;36(20):2017-2023; Agnelli et al. N Engl J Med 2020; 382:1599-1607

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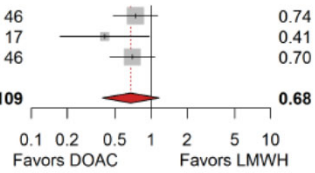
# Main outcomes at 6 months from Hokusai-VTE Cancer, SELECT-D and Caravaggio

## Recurrent VTE

| Study | DOAC agent | DOAC Patients | DOAC Event | LMWH Patients | LMWH Event | RR | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|
| Hokusai VTE Cancer | edoxaban | 522 | 34 | 524 | 46 | 0.74 | [0.48; 1.14] | 45.4% |
| SELECT-D | rivaroxaban | 203 | 7 | 203 | 17 | 0.41 | [0.17; 0.97] | 11.2% |
| Caravaggio | apixaban | 576 | 32 | 579 | 46 | 0.70 | [0.45; 1.08] | 43.4% |
| **Random effects model** | | **1301** | **73** | **1306** | **109** | **0.68** | **[0.39; 1.17]** | **100.0%** |

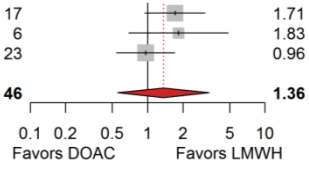
Heterogeneity: $I^2$ = 0%, $\tau^2$ < 0.0001, $p$ = 0.48




## Major bleeding

| Study | DOAC agent | DOAC Patients | DOAC Event | LMWH Patients | LMWH Event | RR | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|---|
| Hokusai VTE Cancer | edoxaban | 522 | 29 | 524 | 17 | 1.71 | [0.95; 3.08] | 40.3% |
| SELECT-D | rivaroxaban | 203 | 11 | 203 | 6 | 1.83 | [0.69; 4.86] | 18.0% |
| Caravaggio | apixaban | 576 | 22 | 579 | 23 | 0.96 | [0.54; 1.71] | 41.7% |
| **Random effects model** | | **1301** | **62** | **1306** | **46** | **1.36** | **[0.55; 3.35]** | **100.0%** |

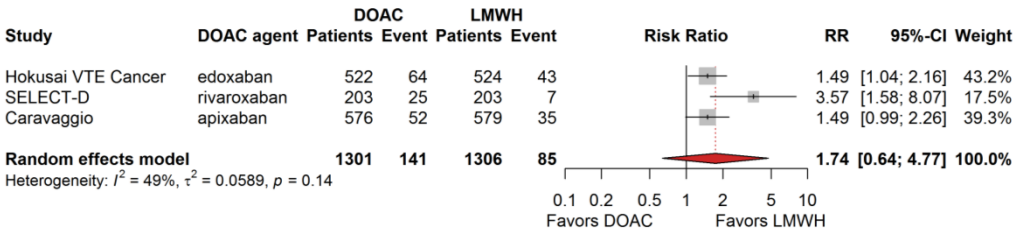
Heterogeneity: $I^2$ = 15%, $\tau^2$ = 0.0379, $p$ = 0.31




Mulder et al., Blood 2020 : doi/10.1182/blood.2020005819

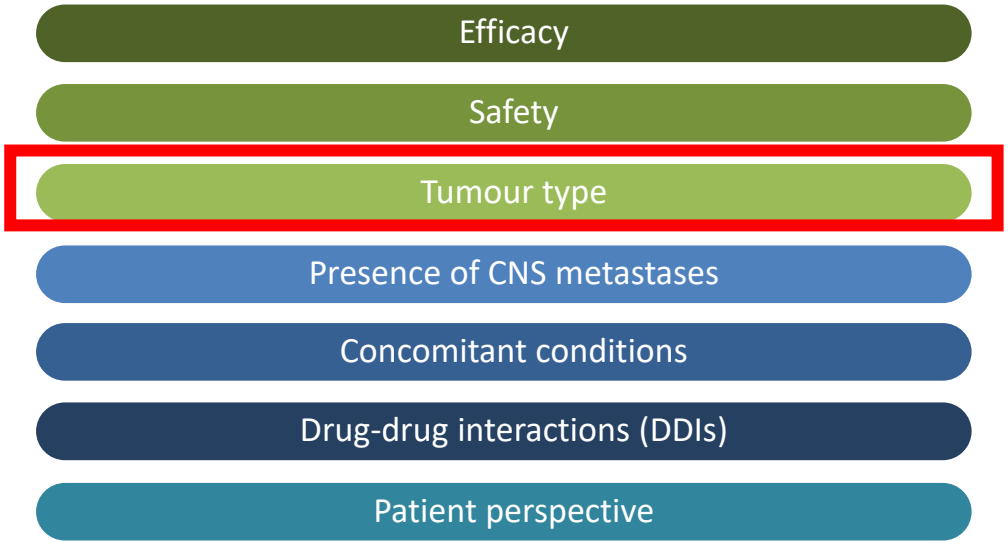
# Secondary outcome at 6 months from Hokusai-VTE Cancer, SELECT-D and Caravaggio

## CRNMB




Mulder et al., Blood 2020 : doi/10.1182/blood.2020005819

# Factors for clinicians to consider in selecting appropriate anticoagulant for patients with CAT



# Hokusai-VTE Cancer: Types of outcomes contributing to major bleeding

| | Edoxaban (n=522) | Dalteparin (n=524) |
|---|---|---|
| **Major bleeding** | **36 (6.9%)** | **21 (4.0%)** |
| **Fatal** | 0 | 2 (0.4%) |
| **ICH** | 2 (0.4%) | 4 (0.8%) |
| **Upper GI** | **17 (3.8%)** | **3 (0.6%)** |
| **Lower GI** | 3 (0.6%) | 3 (0.6%) |
| **GU** | 5 (1.0%) | 0 |
| **Other** | 6 (1.1%) | 7 (1.3%) |

Excess major bleeding with edoxaban mainly due to upper GI

Raskob GE et al. *N Engl J Med.* 2018;378:615-24.

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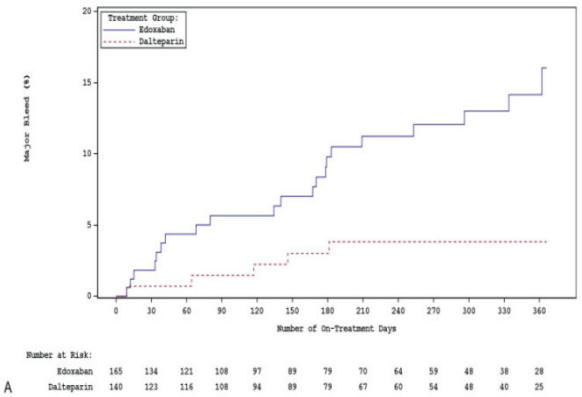
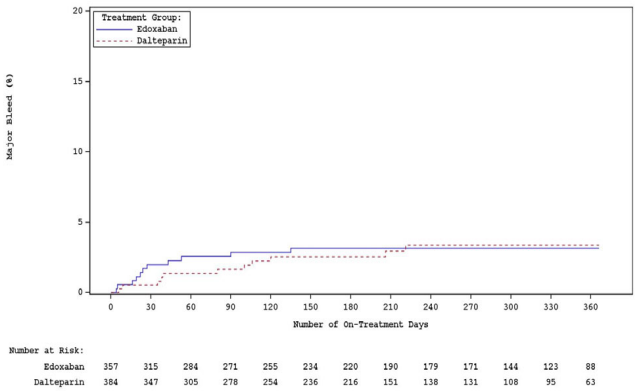
# Hokusai-VTE Cancer: Types of cancers contributing to major bleeding

## Major bleeding events (edoxaban vs. LMWH) according to tumor types

### GI cancers




### Non-GI cancers




Kraaijpoel et al. Thromb Haemost 2018;118:1439–1449.

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# SELECT-D: Types of outcomes contributing to major bleeding

| | Rivaroxaban (n=203) | Dalteparin (n=203) |
|---|---|---|
| **Major bleeding** | **11** | **6** |
| **Esophageal** | 3 | 1 |
| **Stomach** | 2 | 3 |
| **Lower GI** | 1 | 0 |
| **GI, site unknown** | 2 | 0 |
| **GU** | 1 | 0 |
| **Other** | 2 | 2 |

Excess major bleeding with rivaroxaban mainly due to GI bleeds

Young AM et al. *J Clin Oncol.* 2018;36:2017-23.

# CARAVAGGIO: Types of outcomes contributing to major bleeding

| | Apixaban (n=576) | Dalteparin (n=579) |
|---|---|---|
| **Bleeding Site** | **Major bleeding** | **Major bleeding** |
| **Total, n (%)** | 22 (3.8) | 23 (4.0) |
| Fatal | 0 | 2 |
| Abdominal | 1 | 0 |
| Intracranial | 0 | 2 |
| Intraspinal | 0 | 1 |
| Pericardial | 1 | 0 |
| Intra-articular | 0 | 1 |
| Retroperitoneal | 0 | 1 |
| Cutaneous | 1 | 1 |
| GU | 4 | 1 |
| Lung | 1 | 1 |
| Muscle | 0 | 2 |
| Upper airways | 1 | 2 |
| **GI** | 11 | 10 |
| Upper | 5 | 6 |
| Lower | 6 | 4 |
| Undetermined site | 2 | 2 |

Agnelli G et al. *N Engl J Med 2020; 382:1599-1607*

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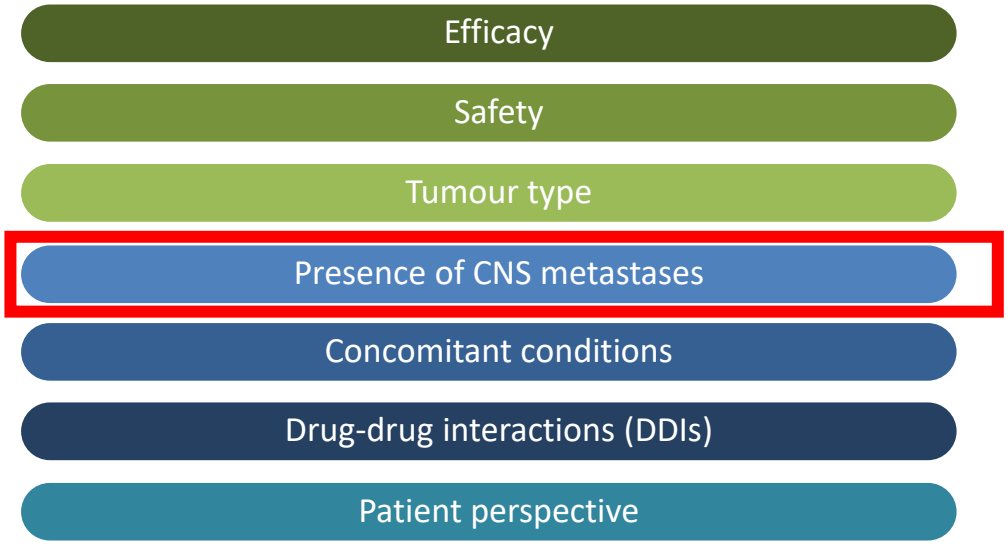
# Factors for clinicians to consider in selecting appropriate anticoagulant for patients with CAT



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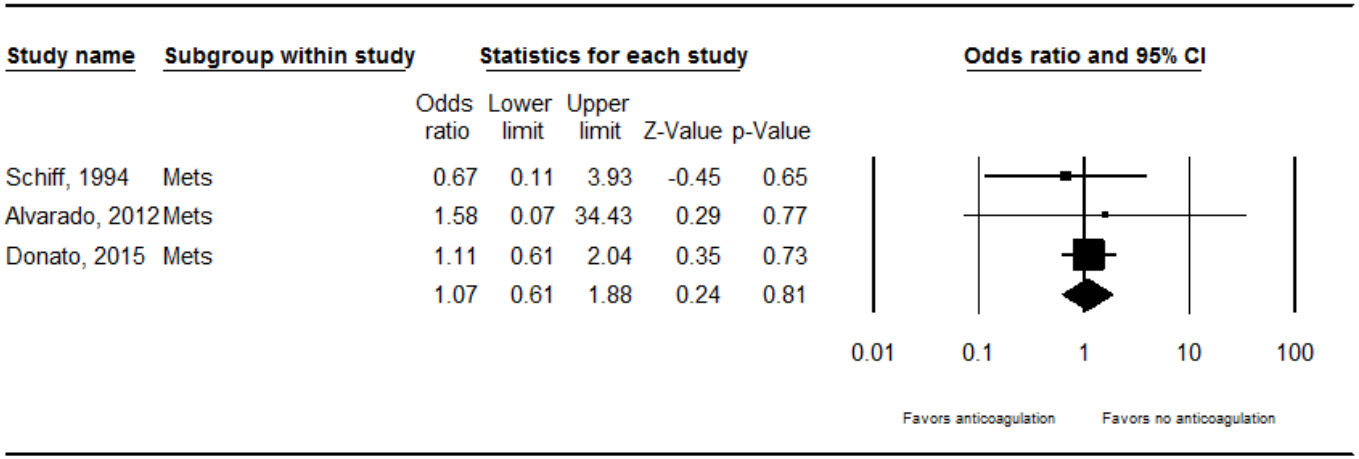
# Risk of intracranial hemorrhage with LMWH or warfarin and intracranial metastatic disease

Intracranial disease




**OR: 1.07 (95% CI 0.61-1.88, P=0.81, $I^2$=0%)**

Zwicker J, et al. *J Thromb Haemostas.* 2016;14(9):1736-1740.

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# Risk of ICH with DOACs for patient with brain tumors and intracranial metastasis

- A cohort study evaluating the safety of DOACs in patients with cancer-associated thrombosis and intracranial metastatic disease or primary brain tumours .
- 67 patients with primary brain tumours
  - DOACs (n=20); LMWH (n=47)
  - **No patients with primary brain tumour receiving DOAC had ICH**
- 105 patients with intracranial metastatic disease
  - DOACs (n=21); LMWH (n=84)
  - **DOACs did not increase the risk of ICH relative to LMWH in patients with intracranial brain metastasis**

Carney BJ et al. J Thromb Haemost 2019 Jan;17(1):72-76.

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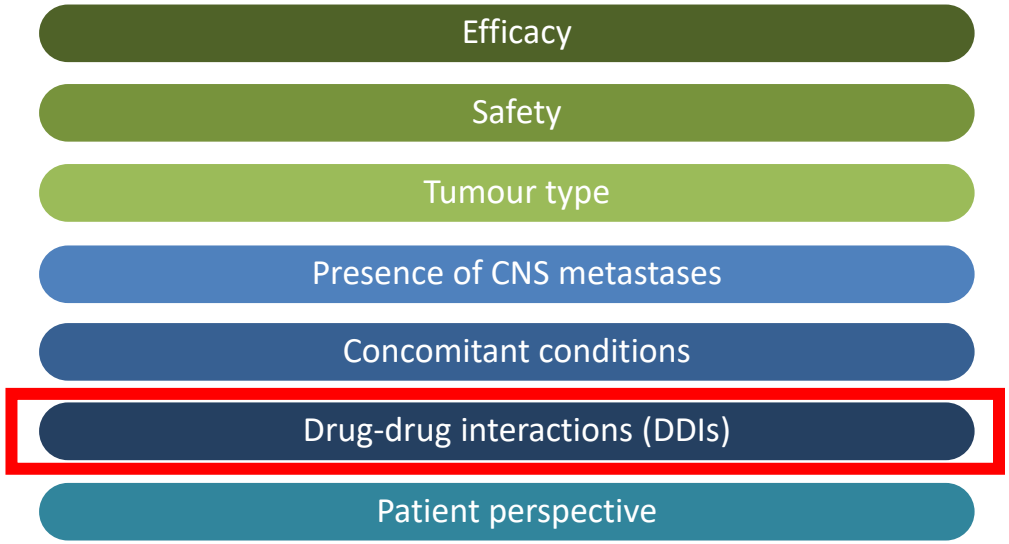
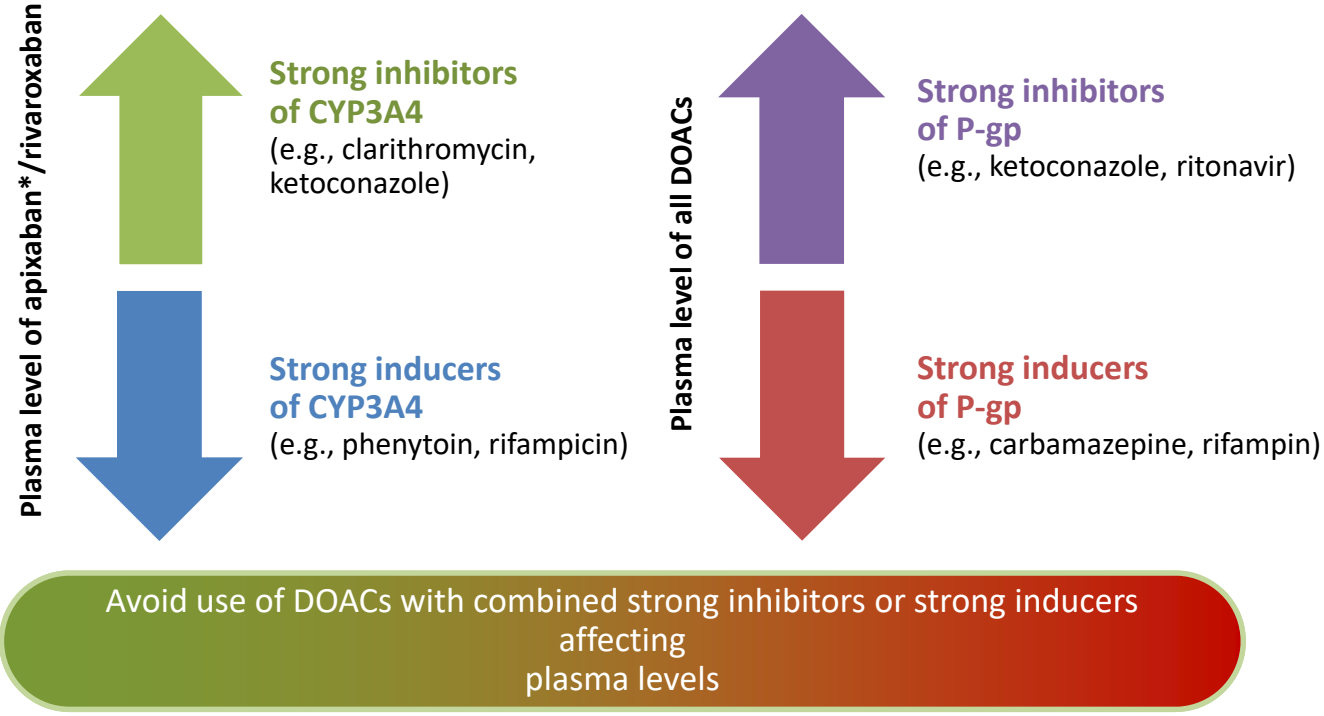
# Factors for clinicians to consider in selecting appropriate anticoagulant for patients with CAT



# Clinical relevance of DDIs with DOACs




Avoid use of DOACs with combined strong inhibitors or strong inducers affecting plasma levels

# Drug-drug interactions

Risk of hospitalization with hemorrhage among patients taking clarithromycin or azithromycin and DOACs

Table 2. Thirty-Day Rate of Hemorrhage With Clarithromycin vs Azithromycin Among Patients Taking DOACs

| Characteristic | No. of events | Cumulative incidence, % | HR (95% CI) | |
|---|---|---|---|---|
| | | | Unadjusted | Adjusted |
| Major hemorrhage | | | | |
| Clarithromycin | 51/6592 | 0.77 | 1.81 (1.27-2.57) | 1.71 (1.20-2.45)[a] |
| Azithromycin | 79/18 351 | 0.43 | | |
| Any hemorrhage or receipt of pRBC transfusion | | | | |
| Clarithromycin | 109/6592 | 1.65 | 1.53 (1.21-1.93) | 1.53 (1.21-1.94)[a] |
| Azithromycin | 199/18 351 | 1.08 | | |

Drug-drug interactions were associated with a small but statistically significantly greater 30-day risk of hospital admission with major hemorrhage.

Hill K et al. JAMA Intern Med 2020 Aug 1;180(8):1052-1060

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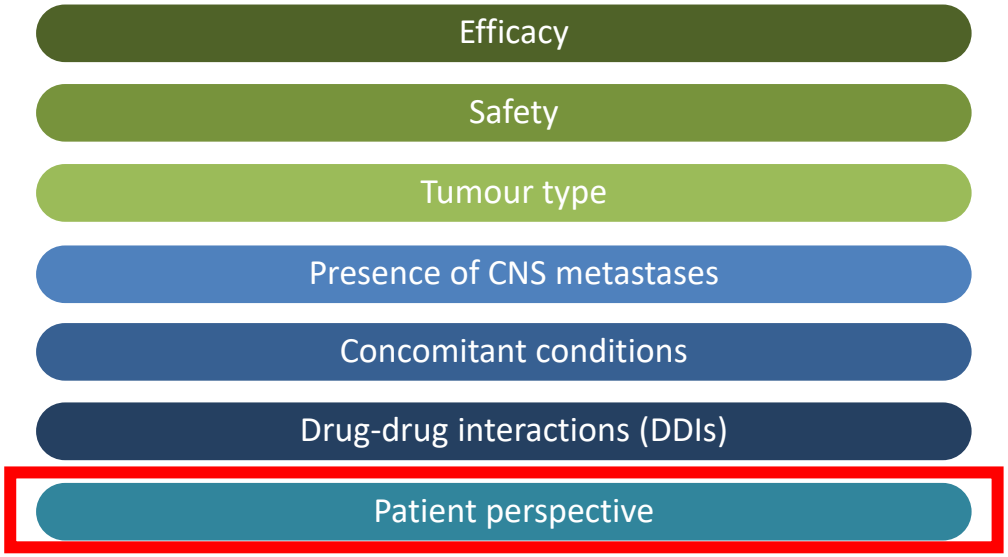
# Factors for clinicians to consider in selecting appropriate anticoagulant for patients with CAT



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# Patient's perspective

**Most important attributes for anticoagulation choices**

1. Does not interfere with cancer treatment
2. Efficacy and safety
3. Route of administration

Noble SI et al. *Haematologica.* 2015; 100:1486–1492.

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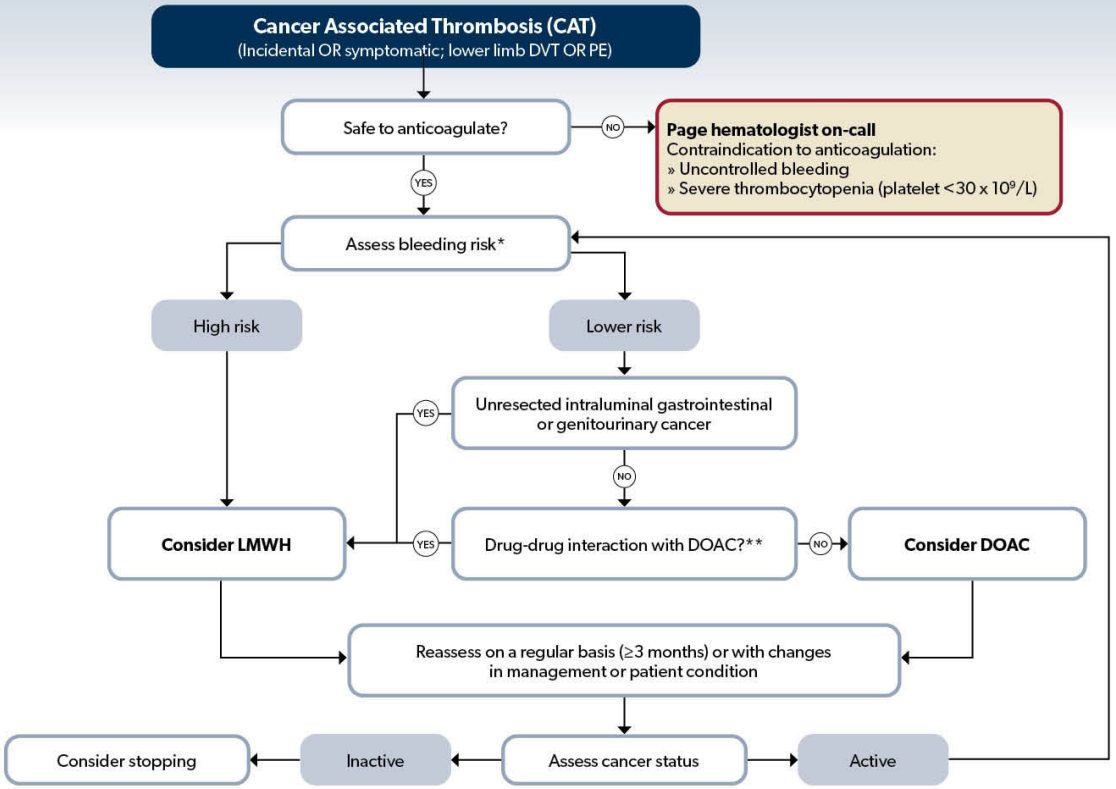
# Most Recent Recommendations: *ASH 2021 Guidelines for management of VTE: Prevention and treatment in patients with cancer*

- **Recommendation 20**
  - For patients with cancer and VTE, the ASH guideline panel *suggests* DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯)
- **Recommendation 23**
  - For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

Lyman G et al. *Blood Adv* (2021) 5 (4): 927–974.
Available at: https://doi.org/10.1182/bloodadvances.2020003442

# Cancer Associated Thrombosis (CAT)




***Risk factors for bleeding (any of):**

1. Acute recent and/or life-threatening bleeding
2. High risk of GI bleeding [e.g., previous variceal bleed, angiodysplasia, treatment-associated toxicity]
3. High risk intracranial lesion [e.g., glioma]
4. Functional hepatic impairment [Child-Pugh class C]
5. Thrombocytopenia [<50 x $10^9$/L]
6. Use of antiplatelet agents

**Other factors to consider:**

» Patient preferences, after discussion of risks and benefits
» Drug coverage and cost
» Body weight (consider LMWH in patients with weight >150 kg and agent with weight-adjustable dosing in patients with weight <50 kg)
» Burden of cancer (e.g., recurrence or progression) and burden of VTE (consider LMWH for patients with severe symptoms, e.g., iliofemoral DVT, submassive PE, any thrombolysed patient)
» Significant GI surgery or absorption disorders (consider LMWH for patients with impaired GI absorption)

** Pharmacist led pharmacokinetic review
**DVT** = deep vein thrombosis
**PE** = pulmonary embolism
**LMWH** = low molecular weight heparin
**DOAC** = direct oral anticoagulant

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# Key takeaway

- DOACs, including apixaban, edoxaban, and rivaroxaban, provide an effective option to LMWH for some/most patients with CAT and are preferred for most patients

- Use of some DOACs in patients with GI cancers and history of GI bleeding is associated with higher rates of bleeding

- Patient characteristics, including bleeding risk, cancer origin, comorbidities, and potential DDIs, need to be considered when choosing a specific DOAC

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# *Thank you*

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