Use of Pharmacologic VTE Prophylaxis Post-Discharge From Acute Care Hospitalization

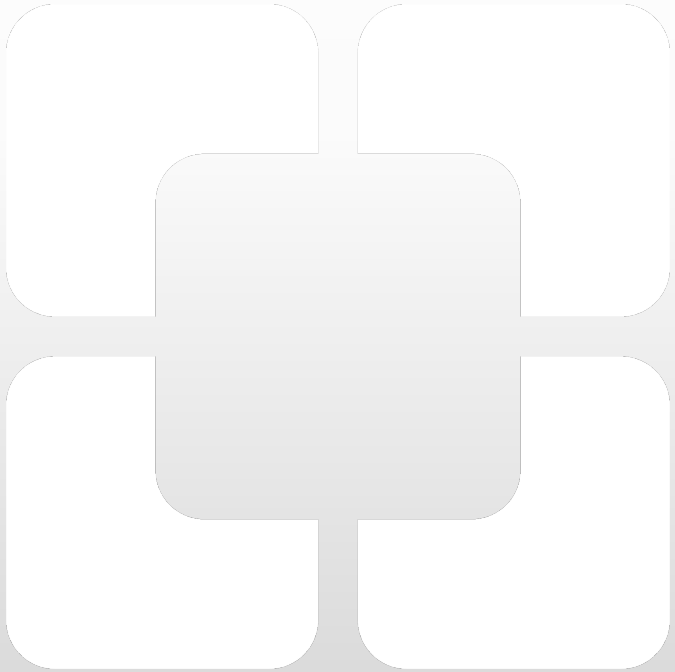
Alok A. Khorana, MD, FACP, FASCO

@aakonc

Sondra and Stephen Hardis Chair in Oncology Research

Professor of Medicine, Cleveland Clinic Lerner College of Medicine

Taussig Cancer Institute and Case Comprehensive Cancer Center



Case Western Reserve University | Case Comprehensive Cancer Center

CLOT Consortium Linking Oncology with Thrombosis

Cleveland Clinic

My Disclosures

Company	Role
Janssen	Co-chair, SC, CASSINI
Bayer	Co-Chair, SC, CASSINI
BMS	Consulting, research grant to institution
Sanofi	Consulting
SeaGen	Consulting
Leo Pharma	Consulting; Member, SC, CATCH
Anthos	Consulting
Parexel	Consulting
Medscape	CME faculty

VTE in hospitalized patients is common

Half of VTE events occur due to hospital admission for surgery (24%) or medical illness (22%)

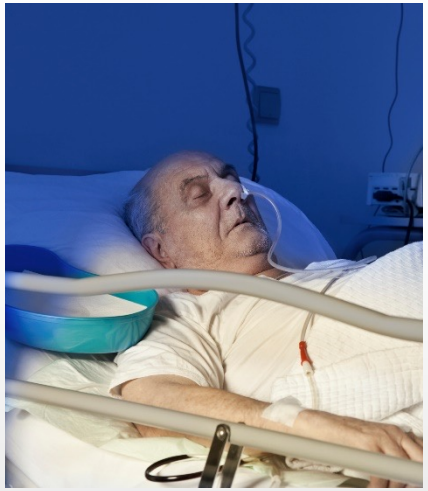
Risk factors for VTE in hospital include cancer, older age, prior VTE, central lines, immobility

40% of hospitalized patients have 3 or more risk factors for VTE

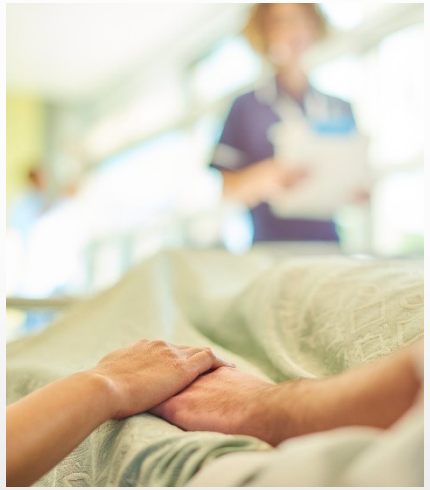
Increase in thrombosis risk in medical inpatients persists **45 to 60 days** after discharge

Hospitalized Patient Population Is Diverse

Acutely Ill Medical Patient
Patients hospitalized for medical illness



Critically Ill Patient
Patients suffering from immediately life-threatening illness requiring admission to intensive care unit



Cancer Patients
Active cancer patients hospitalized for acute medical illness; patients with history of cancer (in remission)

COVID-19 Patients
Some may be at high risk post-discharge

Who is at risk for VTE in hospital?

- Risk Assessment Models (RAMs) can identify inpatients at high risk
- ***Examples:*** Padua, IMPROVE-VTE Scores

These RAMs are not extensively validated for guiding decisions about prophylaxis

Padua RAM: Factors
Previous VTE
Thrombophilia
Active cancer
Age > 70 years
Reduced mobility
Recent trauma/surgery
Heart or respiratory failure
Acute MI or stroke
Hormonal treatment
Obesity (BMI > 30)
Infection/rheumatologic

IMPROVE-VTE RAM: Factors
Previous VTE
Thrombophilia
Active cancer
Age > 60 years
Immobilization of ≥ 7 days
Lower limb paralysis
ICU/CCU stay

Spyropoulos Chest 2011
Leizorovicz Circulation 2004

What is the rationale for extending VTE prophylaxis beyond hospital discharge?

- Most hospital-related VTE events occur **out of hospital,** in the first month after discharge
- VTE risk in medical patients is elevated for 45-60 days post-discharge
- Duration of inpatient prophylaxis is shortening as the average hospital length of stay decreases

Huang Am J Med 2014
Cohen NEJM 2016
Cohen NEJM 2014
Goldhaber NEJM 2011

Recommendation

In acutely ill hospitalized medical patients, the panel recommends **inpatient over inpatient plus extended duration outpatient VTE prophylaxis** *(strong recommendation, moderate certainty).*

Extended prophylaxis (30-40 days) compared with **in-hospital prophylaxis** (any agent):

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)
		Risk difference with extended prophylaxis
Mortality	**1.00** (0.89 to 1.12)	**0 fewer deaths per 1,000** (5 fewer to 5 fewer)
PE	**0.63** (0.39 to 1.03)	**1 fewer PE per 1,000** (3 fewer to 0 fewer)
Symptomatic proximal DVT	**0.54** (0.32 to 0.91)	**3 fewer DVT per 1,000** (4 fewer to 1 fewer)
Major bleeding	**2.09** (1.33 to 3.27)	**4 more bleeds per 1,000** (1 more to 8 more)

Quality of Evidence (GRADE): Lo Moderat Stron

Recommendation

In acutely ill hospitalized medical patients, the panel recommends **inpatient VTE prophylaxis with LMWH only**, rather than inpatient and extended duration outpatient VTE prophylaxis with DOACs *(strong recommendation, moderate certainty)*

Extended DOAC prophylaxis (30-40 days) compared with **shorter LMWH prophylaxis**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with shorter duration non-DOAC inpatient prophylaxis	*Risk difference with extended prophylaxis with DOAC*
Mortality	**1.01** (0.89 to 1.14)	49 per 1,000	**0 fewer deaths per 1,000** (5 fewer to 7 more)
PE	**0.67** (0.41 to 1.09)	4 per 1,000	**1 fewer PE per 1,000** (2 fewer to 0 fewer)
Symptomatic proximal DVT	**0.62** (0.36 to 1.05)	6 per 1,000	**2 fewer DVT per 1,000** (4 fewer to 0 fewer)
Major bleeding	**1.99** (1.08 to 3.65)	4 per 1,000	**4 more bleeds per 1,000** (0 more to 10 more)

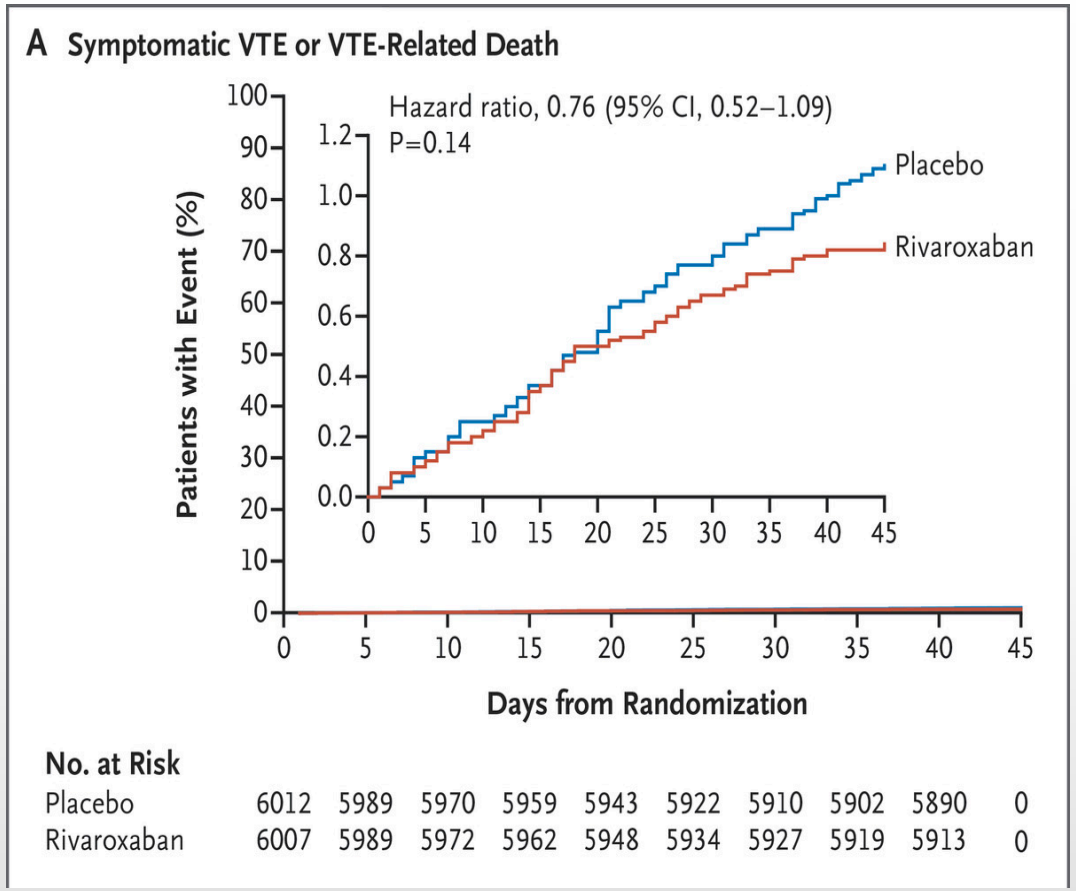
Quality of Evidence (GRADE): Lo Moderat Stron

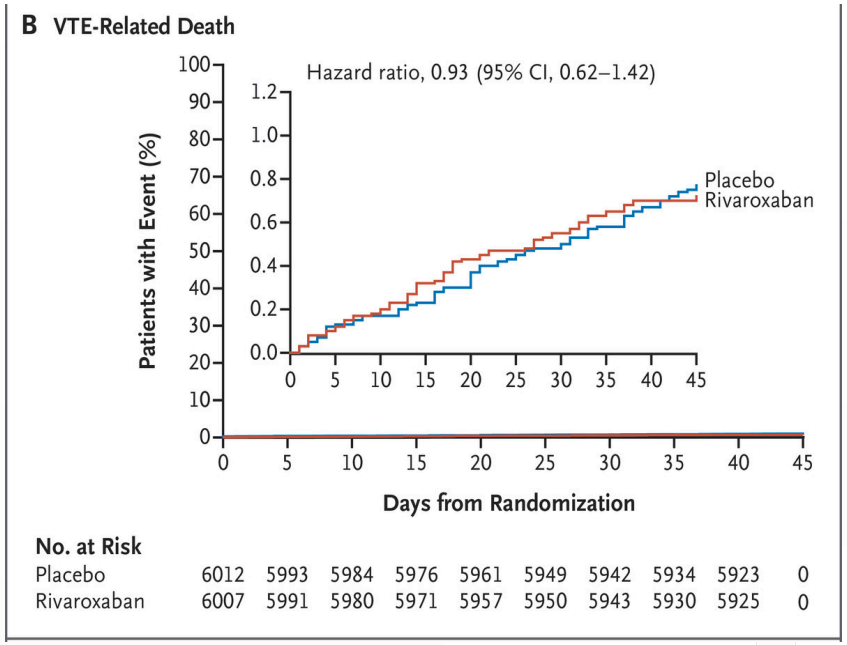
In summary, why is routine post-discharge extended prophylaxis currently not recommended?

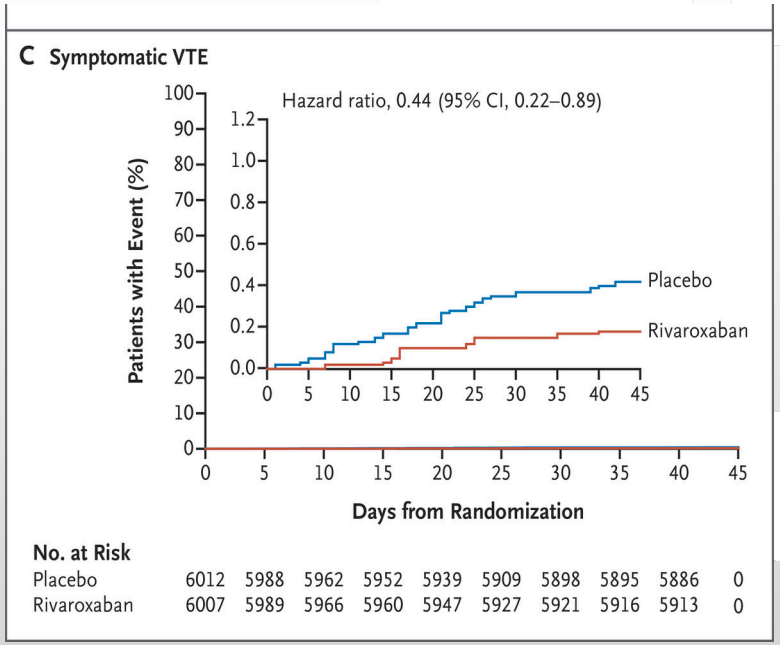
- Extended prophylaxis ***may*** reduce PE and DVT, but absolute impact on VTE reduction is very small
  (1 to 3 fewer VTE per 1,000 patients treated), and is similar to number of bleeding events caused

- Extended prophylaxis does not impact mortality

- Possible that the three included RCTs (APEX, MAGELLAN, ADOPT) did not select patients at sufficiently high risk for VTE
  - However, the recent **MARINER trial** *(Spyropoulos NEJM 2018)* also did not show significant reduction
    in VTE despite use of a **modified IMPROVE VTE risk score** to select high-risk medical inpatients for
    extended prophylaxis with rivaroxaban

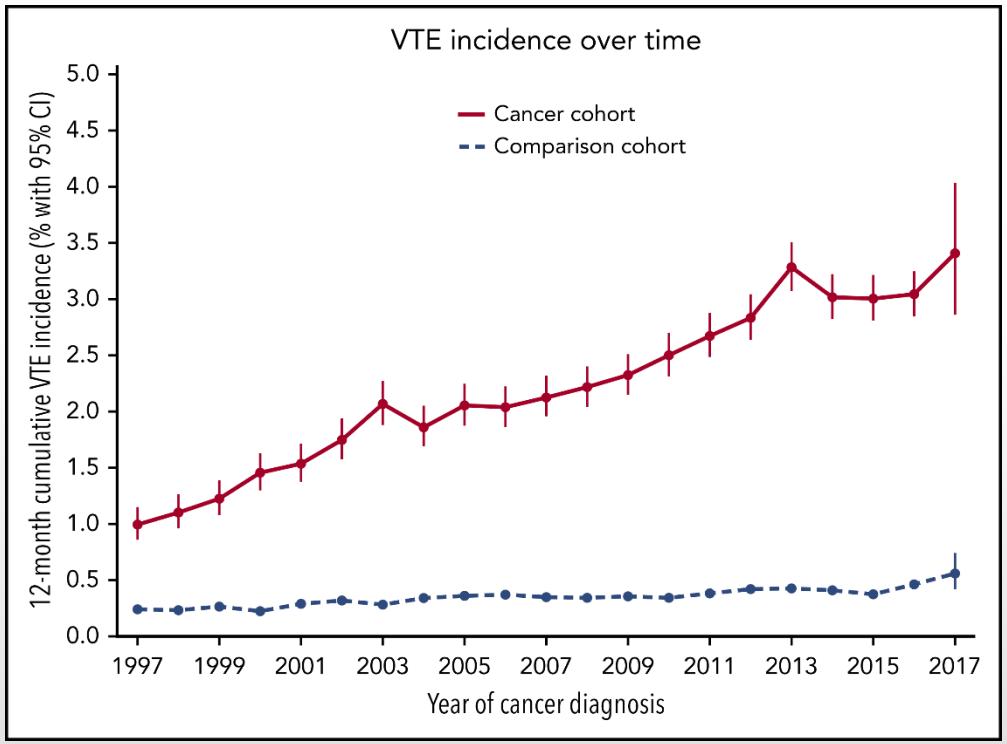


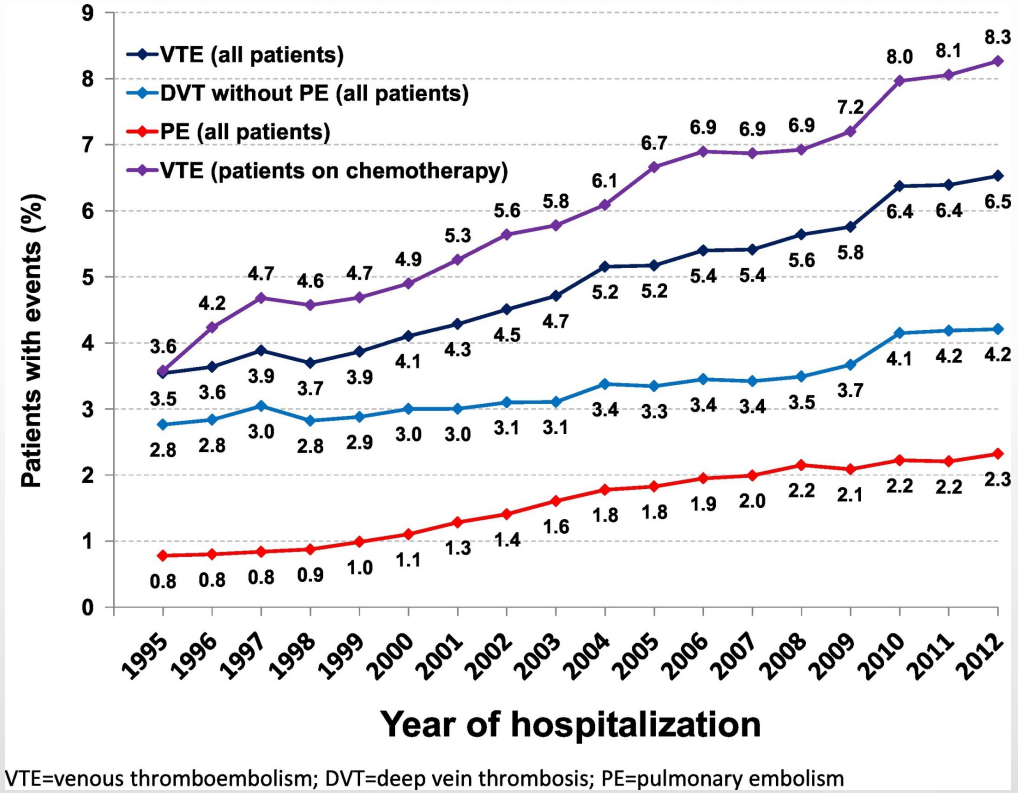




Special Populations: Cancer and COVID-19

Alarming Rise in Cancer-Associated VTE

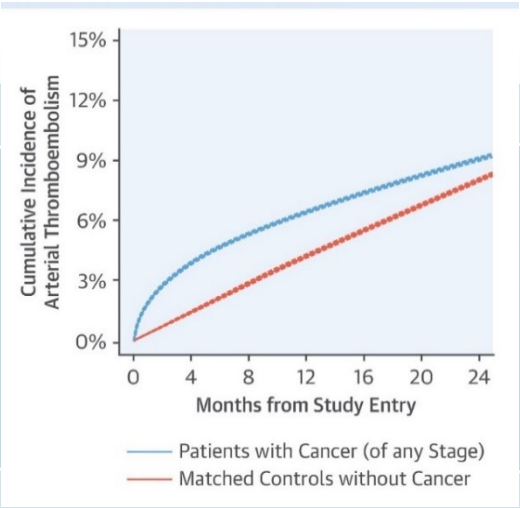


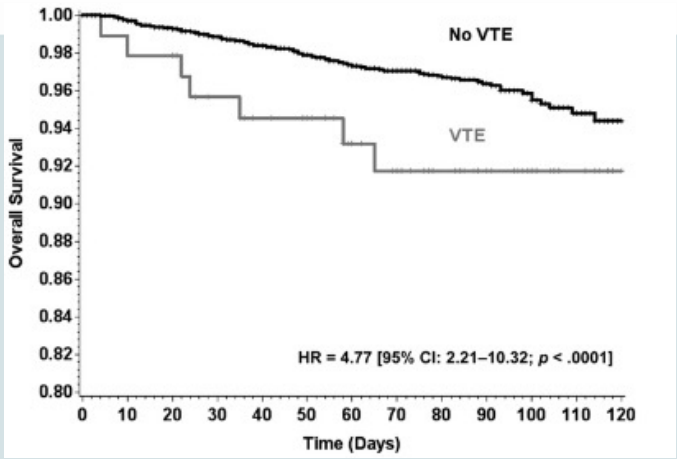


VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism

Mulder et al, *Blood* 2021; Lyman et al *Throm Res*, 2018

Cancer-associated Thrombosis Is Highly Consequential For People With Cancer





Highly Prevalent

VTE and ATE

Rates of arterial events 4.7% at 6 months

Mortality

VTE + arterial events accounted for 9% of deaths

VTE associated with early mortality during chemotherapy

(adj HR=4.8, p <0.0001)

Morbidity

3-fold increase in all-cause hospitalizations (mean 1.38 v 0.55/patient)

3-fold increase in days in hospital (10.19 v 3.37)

Delayed treatment

Navi et al. *J Am Coll Cardiol* 2017; Khorana et al. *J Thromb Haemost* 2007; Kuderer et al, *Oncologist* 2016;Khorana et al, *Clin Econ Outcomes Res* 2013

The road to prevention is complicated

If “1 in 5” cancer patients will get CAT, this implies **4 of 5 cancer patients will never get CAT**

Post-surgical

FAME, CANBESURE, Enoxacan-1,2

Medical inpatient

MEDENOX, PREVENT, ARTEMIS

Outpatient

PROTECHT, SAVE-ONCO, CONKO-04, FRAGEM, ***CASSINI, AVERT***

Preventing CAT

Implementation science

Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score

A systematic review and meta-analysis of six randomized trials

4,626 ambulatory cancer patients starting chemotherapy

with a Khorana score of 2 or higher (Intermediate-to-high risk of VTE)

Randomized to thromborpophylaxis or control

DOACs

OR

LMWH

VS

OR

Standard care

Khorana score 2 or higher (intermediate-to-high risk of VTE)

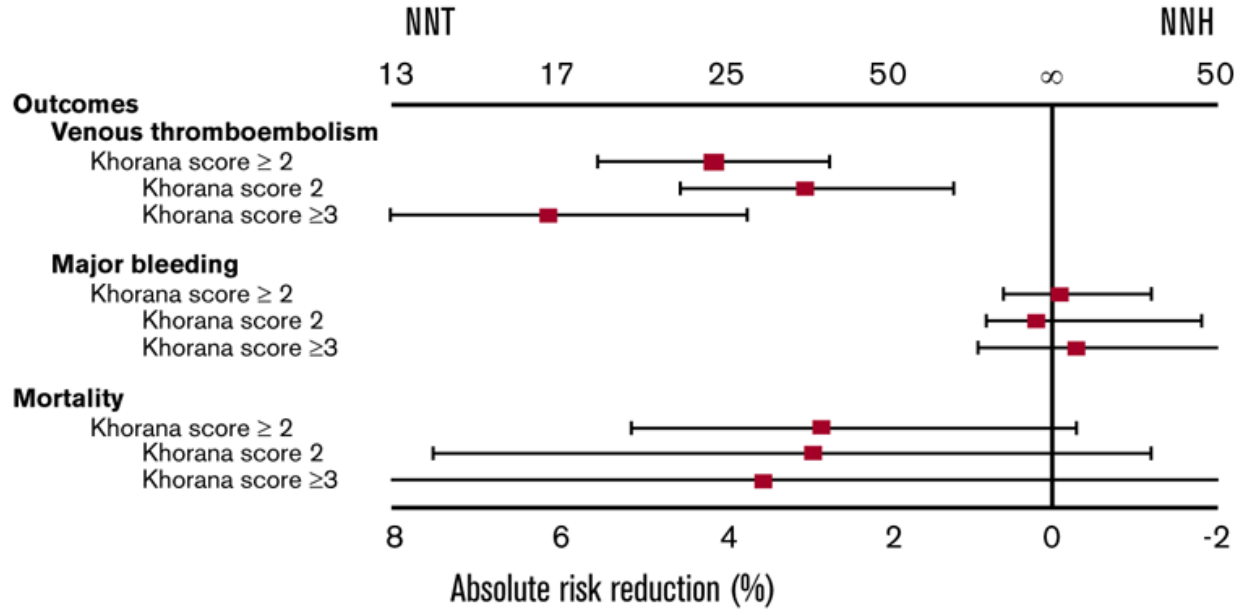
	RR
VTE	0.51 (95% CI 0.34 - 0.67)
MB	1.06 (95% CI 0.69 - 1.67)
Death	0.90 (95% CI 0.82 - 1.01)

n=2,837 → Khorana score 2 (intermediate risk of VTE)

	RR
VTE	0.58 (95% CI 0.36 - 0.83)
MB	0.88 (95% CI 0.45 - 2.30)
Death	0.90 (95% CI 0.74 - 1.04)

n=1,781 → Khorana score 3 or higher (high risk of VTE)

	RR
VTE	0.45 (95% CI 0.28 - 0.67)
MB	1.11 (95% CI 0.64 - 1.92)
Death	0.91 (95% CI 0.68 - 1.24)



Bosch et al, *Blood Adv*, 2020

Updated Guidelines for Primary Prevention

ASCO

Recommendation 2.1. Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer (Type: evidence based; Evidence quality: intermediate to high; Strength of recommendation: strong).

Recommendation 2.2. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) provided there are no significant risk factors for bleeding and no 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 (Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH;

ITAC CME

International Initiative on Thrombosis and Cancer

5 Primary prophylaxis with direct oral anticoagulant (rivaroxaban or apixaban) is recommended in patients who are ambulatory who are receiving systemic anticancer therapy at intermediate-to-high risk of VTE, identified by cancer type (ie, pancreatic) or by a validated risk assessment model (ie, a Khorana score ≥2), and not actively bleeding or not at a high risk of bleeding (grade 1B).

ISTH

1. We suggest the use of DOACs as primary thromboprophylaxis in ambulatory cancer patients starting chemotherapy with Khorana score ≥2 in patients with no drug-drug interactions and not at high risk for bleeding (such as patients with gastroesophageal cancers). Currently, apixaban and rivaroxaban are the only DOACs with evidence from randomized clinical trials. A final treatment decision should be made after considering the risk of both VTE and bleeding, as well as patients' preference and values.

NCCN

Intermediate or high risk for VTE (Khorana score ≥2)
- **Consider oral anticoagulant prophylaxis for up to 6 months or longer, if risk persists[b,h] (See VTE-B for dosing)**
  - **Apixaban**
  - **Rivaroxaban**

Low risk for VTE (Khorana score <2)
- **No routine VTE prophylaxis**

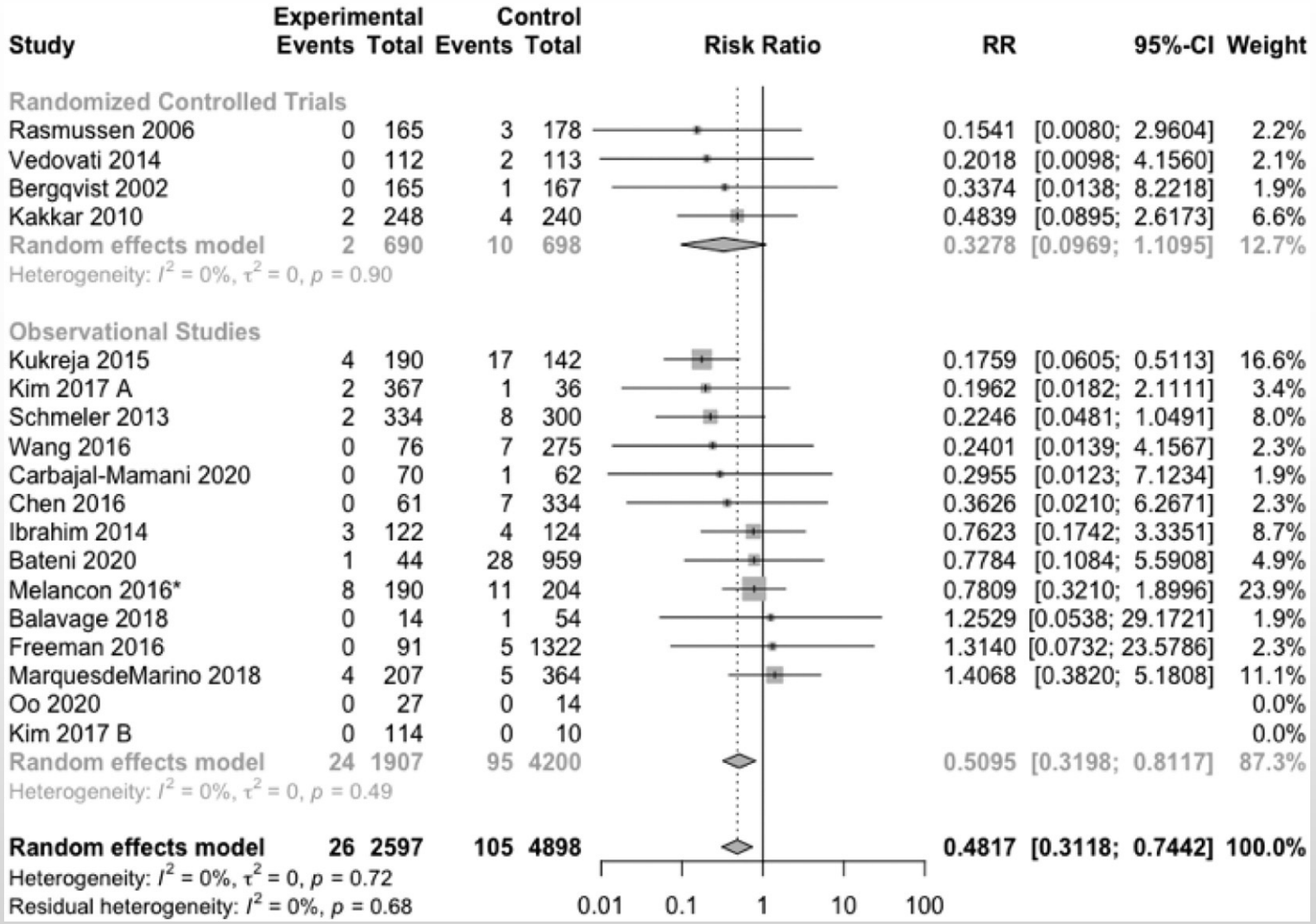
American Society of Hematology

Recommendations 14 and 15

For ambulatory patients with cancer receiving systemic therapy, the ASH guideline panel *recommends* no thromboprophylaxis over oral thromboprophylaxis with VKAs (strong recommendation, very low certainty in the evidence of benefits ⊕◯◯◯ but high certainty about the harms ⊕⊕⊕⊕). For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Remarks: Classification of patients as being at low, intermediate, or high risk for VTE should be based on a validated risk assessment tool (ie, Khorana score) complemented by clinical judgment and experience. The panel noted that, even for patients at high risk for thrombosis, thromboprophylaxis should be used with caution for those at high risk for bleeding. The direct factor Xa inhibitors apixaban and rivaroxaban are the only DOACs that were evaluated for the primary prophylaxis for ambulatory patients with cancer receiving chemotherapy.

Extended Thromboprophylaxis After Surgery



Knoll et al, *Throm Res* 2021

Extended Prophylaxis Post-Surgery

Extended duration thromboprophylaxis was associated

- with significant reduction in clinical VTE (1.0% vs 2.1%; risk ratio (RR) 0.48, 95%CI: 0.31 to 0.74; $I^2 = 0$)

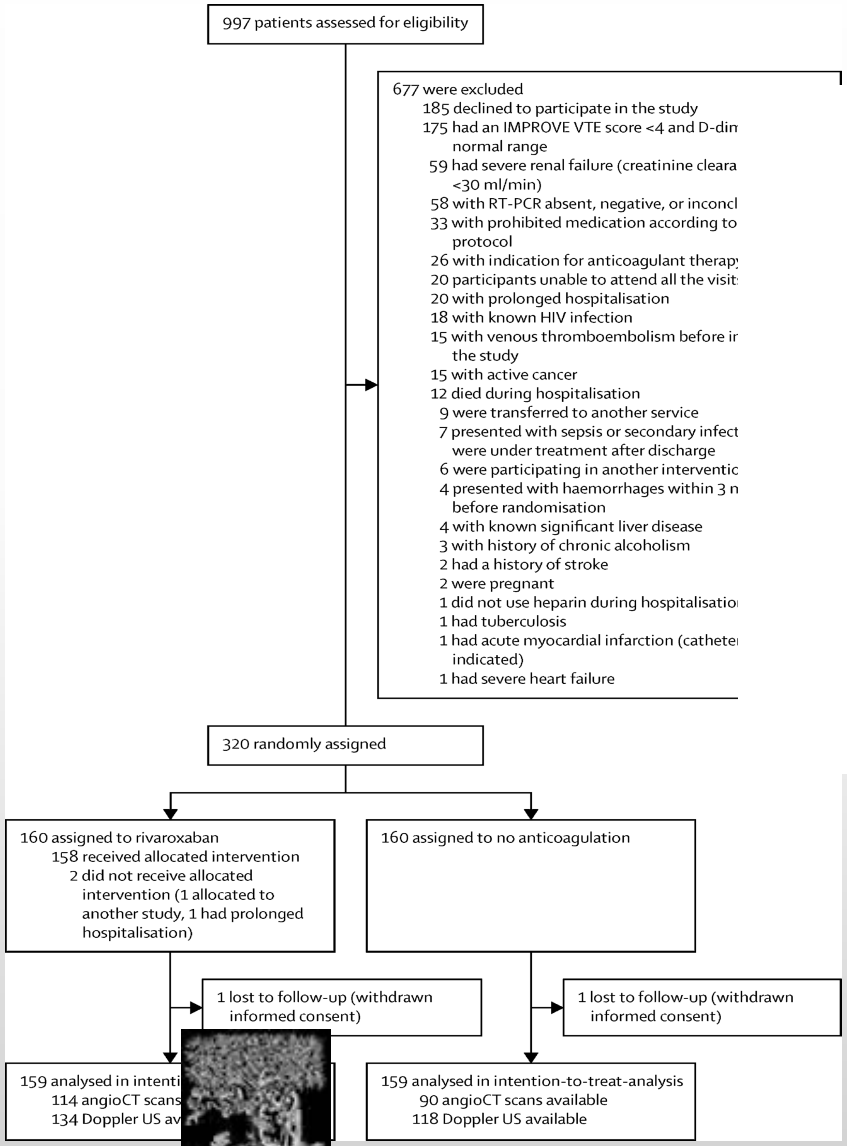
- without a significant increase in clinically-relevant bleeding (4.0% vs. 4.9%; RR 1.0, 95%CI: 0.66 to 1.5, $I^2 = 0$).

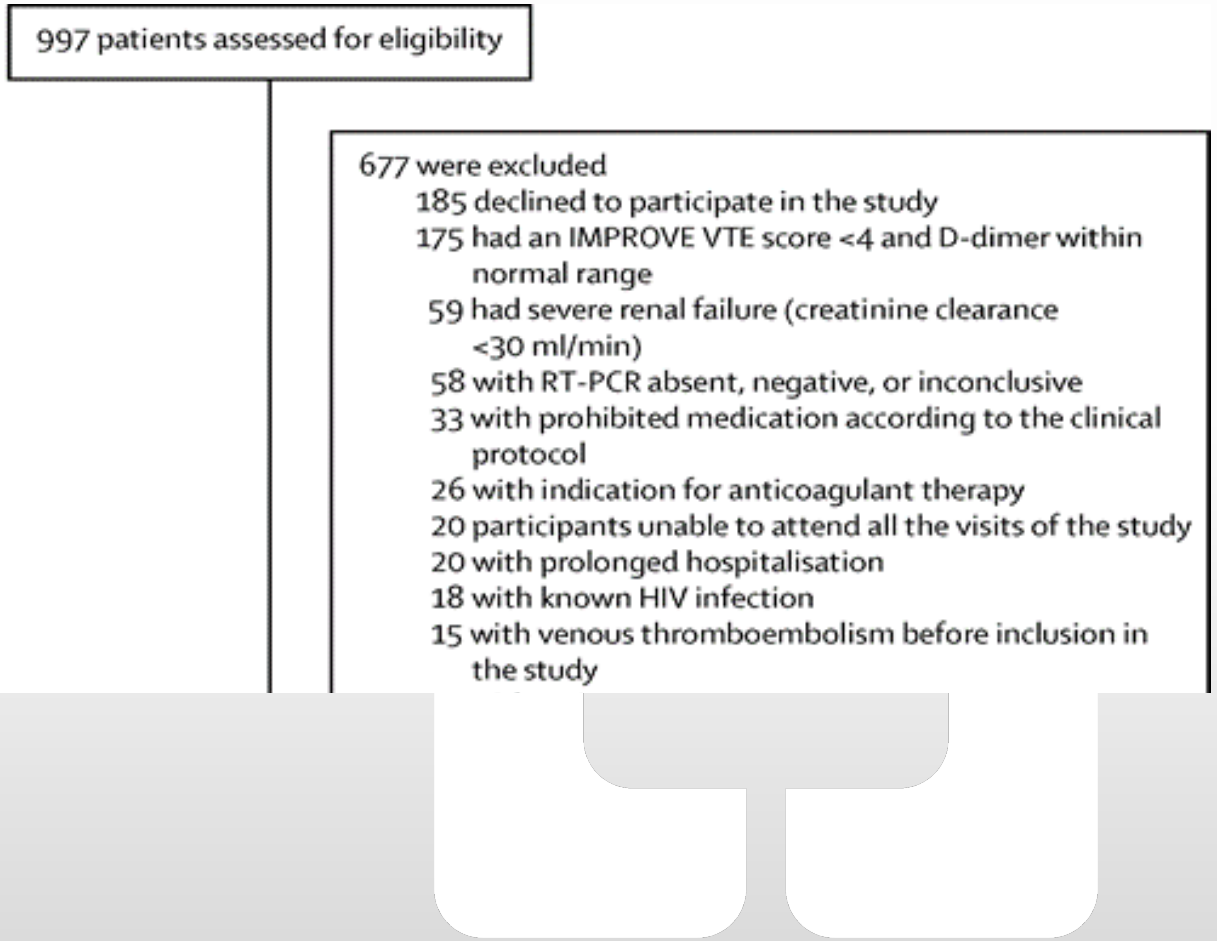
Knoll et al, *Throm Res* 2021

Why Post-COVID-19 Thromboprophylaxis?

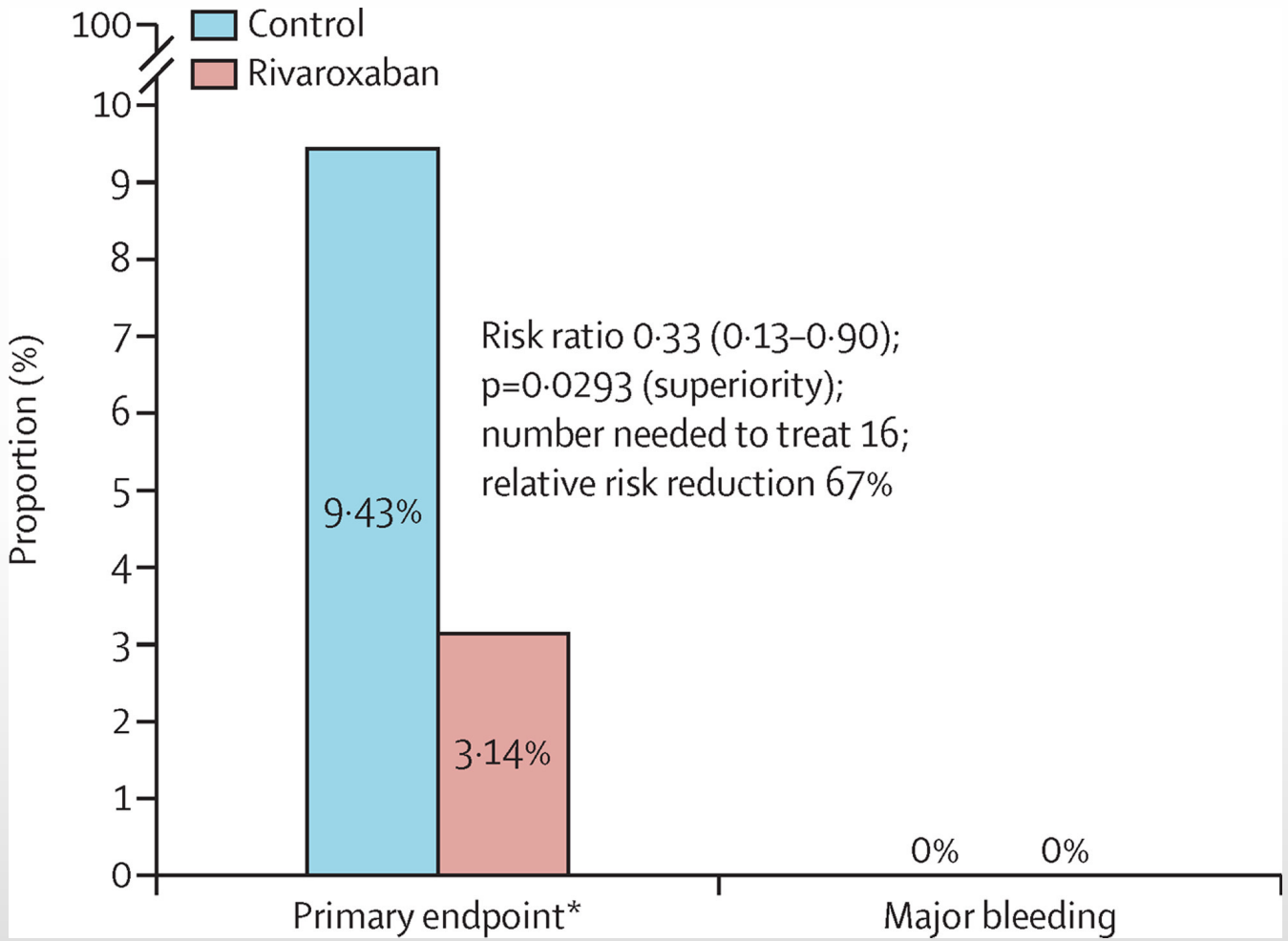
- Thrombotic events complicate COVID-19 at higher rates than previously observed
- No consensus on the use of extended thromboprophylaxis beyond the hospital stay.
- Multiple studies show post-discharge incidence of symptomatic VTE ranging from <1% to 2·5%
- MICHELLE randomized COVID-19 pts with high IMPROVE scores at hospital discharge to either prophylactic rivaroxaban (10 mg/day) or no anticoagulation for 35 days

MICHELLE trial





The Lancet 2022 39950-59DOI: (10.1016/S0140-6736(21)02392-8)



The Lancet 2022 39950-59DOI: (10.1016/S0140-6736(21)02392-8)

Conclusions

Post-discharge VTE is a public health problem

- But population is heterogeneous
- Risk stratification does not identify clearly high-risk populations that may benefit
- Conceptually, post-discharge prophyalxis is needed, but we are not there yet

Exceptions for cancer and COVID-19

- Rates are higher in these populations
- CASSINI and AVERT have demonstrated benefits with low-dose DOACs in primary prevention in high-risk cancer patients (not necessarily post-discharge)
- MICHELLE has demonstrated benefit with rivaroxaban but applicable to small subgroup and confirmatory trials are awaited