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

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# My Disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen</td>
<td>Co-chair, SC, CASSINI</td>
</tr>
<tr>
<td>Bayer</td>
<td>Co-Chair, SC, CASSINI</td>
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<tr>
<td>BMS</td>
<td>Consulting, research grant to institution</td>
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<tr>
<td>Sanofi</td>
<td>Consulting</td>
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<tr>
<td>SeaGen</td>
<td>Consulting</td>
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<td>Leo Pharma</td>
<td>Consulting; Member, SC, CATCH</td>
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<tr>
<td>Anthos</td>
<td>Consulting</td>
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<tr>
<td>Parexel</td>
<td>Consulting</td>
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<tr>
<td>Medscape</td>
<td>CME faculty</td>
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</tbody>
</table>
VTE in hospitalized patients is common

<table>
<thead>
<tr>
<th>Half of VTE events occur due to hospital admission for surgery (24%) or medical illness (22%)</th>
<th>Risk factors for VTE in hospital include cancer, older age, prior VTE, central lines, immobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% of hospitalized patients have 3 or more risk factors for VTE</td>
<td>Increase in thrombosis risk in medical inpatients persists 45 to 60 days after discharge</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Padua RAM: Factors</th>
<th>IMPROVE-VTE RAM: Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>Previous VTE</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Active cancer</td>
<td>Active cancer</td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>Age &gt; 60 years</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>Immobilization of ≥ 7 days</td>
</tr>
<tr>
<td>Recent trauma/surgery</td>
<td>Lower limb paralysis</td>
</tr>
<tr>
<td>Heart or respiratory failure</td>
<td>ICU/CCU stay</td>
</tr>
<tr>
<td>Acute MI or stroke</td>
<td></td>
</tr>
<tr>
<td>Hormonal treatment</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td></td>
</tr>
<tr>
<td>Infection/rheumatologic</td>
<td></td>
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</tbody>
</table>

These RAMs are not extensively validated for guiding decisions about prophylaxis.
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
## Outcomes

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

## 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):
### 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:**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effect: RR (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Risk with shorter duration non-DOAC inpatient prophylaxis</th>
<th>Risk difference with extended prophylaxis with DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.01 (0.89 to 1.14)</td>
<td>49 per 1,000</td>
<td>0 fewer deaths per 1,000 (5 fewer to 7 more)</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>0.67 (0.41 to 1.09)</td>
<td>4 per 1,000</td>
<td>1 fewer PE per 1,000 (2 fewer to 0 fewer)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic proximal DVT</td>
<td>0.62 (0.36 to 1.05)</td>
<td>6 per 1,000</td>
<td>2 fewer DVT per 1,000 (4 fewer to 0 fewer)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.99 (1.08 to 3.65)</td>
<td>4 per 1,000</td>
<td>4 more bleeds per 1,000 (0 more to 10 more)</td>
<td></td>
</tr>
</tbody>
</table>
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.
Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome and Its Components.

A Symptomatic VTE or VTE-Related Death

Hazard ratio, 0.76 (95% CI, 0.52–1.09)
P = 0.14

No. at Risk
Placebo 6012 5989 5970 5959 5943 5922 5910 5902 5890 0
Rivaroxaban 6007 5989 5972 5962 5948 5934 5927 5919 5913 0

B VTE-Related Death

Hazard ratio, 0.93 (95% CI, 0.62–1.42)

No. at Risk
Placebo 6012 5993 5984 5976 5961 5949 5942 5934 5923 0
Rivaroxaban 6007 5991 5980 5971 5957 5950 5943 5930 5925 0

C Symptomatic VTE

Hazard ratio, 0.44 (95% CI, 0.22–0.89)

No. at Risk
Placebo 6012 5988 5962 5952 5939 5909 5898 5895 5886 0
Rivaroxaban 6007 5989 5966 5960 5947 5927 5921 5916 5913 0
Special Populations:
Cancer and COVID-19
Alarming Rise in Cancer-Associated VTE

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

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.
Preventing CAT

Post-surgical
FAME, CANBESURE, Enoxacan-1,2

Medical inpatient
MEDENOX, PREVENT, ARTEMIS

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

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)

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 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)

n=1,781

Randomized to thromboprophylaxis or control

- DOACs vs PLACEBO
- LMWH vs Standard care

Outcomes

- Venous thromboembolism
  - Khorana score ≥ 2
  - Khorana score 2
  - Khorana score ≥ 3

- Major bleeding
  - Khorana score ≥ 2
  - Khorana score 2
  - Khorana score ≥ 3

- Mortality
  - Khorana score ≥ 2
  - Khorana score 2
  - Khorana score ≥ 3

NNT

| 13 | 17 | 25 | 50 | ∞ | 50 |

Absolute risk reduction (%)

8 6 4 2 0 -2

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Bosch et al, Blood Adv, 2020
Updated Guidelines for Primary Prevention

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).

Intermediate or high risk for VTE (Khorana score ≥2)
- Consider oral anticoagulant prophylaxis for up to 6 months or longer, if risk persists \(^{b,d} \) (See VTE-B for dosing)
  - Apixaban
  - Rivaroxaban
- Low risk for VTE (Khorana score <2)
- No routine VTE prophylaxis

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 gastrectophageal 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.

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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Risk Ratio</th>
<th>RR [95%-CI]</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rasmussen 2006</td>
<td>0</td>
<td>165</td>
<td>3</td>
<td>0.1541</td>
<td>[0.0080; 2.9604]</td>
</tr>
<tr>
<td>Vedovati 2014</td>
<td>0</td>
<td>112</td>
<td>2</td>
<td>0.2018</td>
<td>[0.0098; 4.1560]</td>
</tr>
<tr>
<td>Bergqvist 2002</td>
<td>0</td>
<td>165</td>
<td>1</td>
<td>0.3374</td>
<td>[0.0138; 8.2218]</td>
</tr>
<tr>
<td>Kakkar 2010</td>
<td>2</td>
<td>248</td>
<td>4</td>
<td>0.4839</td>
<td>[0.0895; 2.6173]</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td>2</td>
<td>690</td>
<td>10</td>
<td>0.3278</td>
<td>[0.0969; 1.1095]</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$, $\tau^2 = 0$, $p = 0.90$</td>
<td></td>
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</tr>
</tbody>
</table>

| **Observational Studies** |                           |                      |            |             |         |
| Kukreja 2015            | 4                         | 190                  | 17         | 0.1759      | [0.0605; 0.5113] | 16.6%  |
| Kim 2017 A              | 2                         | 367                  | 1           | 0.1962      | [0.0182; 2.1111] | 3.4%   |
| Schmeler 2013           | 2                         | 334                  | 8           | 0.2246      | [0.0481; 1.0491] | 8.0%   |
| Wang 2016               | 0                         | 76                   | 7           | 0.2401      | [0.0139; 4.1567] | 2.3%   |
| Carbajal-Mamani 2020    | 0                         | 70                   | 1           | 0.2955      | [0.0123; 7.1234] | 1.9%   |
| Chen 2016               | 0                         | 61                   | 7           | 0.3626      | [0.0210; 6.2671] | 2.3%   |
| Ibrahim 2014            | 3                         | 122                  | 4           | 0.7623      | [0.1742; 3.3351] | 8.7%   |
| Bateni 2020             | 1                         | 44                   | 28          | 0.7784      | [0.1084; 5.5908] | 4.9%   |
| Melancon 2016*          | 8                         | 190                  | 11          | 0.7809      | [0.3210; 1.8996] | 23.9%  |
| Balavaghi 2018          | 0                         | 14                   | 1           | 1.2529      | [0.0538; 29.1721] | 1.9%   |
| Freeman 2016            | 0                         | 91                   | 15          | 1.3140      | [0.0732; 23.5786] | 2.3%   |
| MarquesdeMarino 2018    | 4                         | 207                  | 5           | 1.4068      | [0.3820; 5.1808] | 11.1%  |
| Oo 2020                 | 0                         | 27                   | 0           | 0.0000      | 0.0000   | 0.0%   |
| Kim 2017 B              | 0                         | 114                  | 0           | 0.0000      | 0.0000   | 0.0%   |
| **Random effects model** | 24                        | 1907                 | 95          | 0.5095      | [0.3198; 0.8117] | 87.3%  |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.49$ |

Extended Thromboprophylaxis After Surgery

Knoll et al, *Throm Res* 2021

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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; I² = 0)

• without a significant increase in clinically-relevant bleeding (4.0% vs. 4.9%; RR 1.0, 95%CI: 0.66 to 1.5, I² = 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

997 patients assessed for eligibility

677 were excluded
185 declined to participate in the study
175 had an IMPROVE VTE score <4 and D-dimer within normal range
59 had severe renal failure (creatinine clearance <30 ml/min)
58 with RT-PCR absent, negative, or inconclusive
33 with prohibited medication according to protocol
26 with indication for anticoagulant therapy
20 participants unable to attend all the visits
20 with prolonged hospitalisation
18 with unknown HIV infection
15 with acute thromboembolism before inclusion in the study
15 with active cancer
12 died during hospitalisation
9 were transferred to another service
7 presented with sepsis or secondary septic shock
6 were under treatment after discharge
4 presented with haemorrhages within 3 n
4 with known significant liver disease
3 had a history of chronic alcoholism
2 had a history of stroke
2 were pregnant
1 did not use heparin during hospitalisation
1 had tuberculosis
1 had acute myocardial infarction (catheter indicated)
1 had severe heart failure

290 randomly assigned
160 assigned to rivaroxaban
58 received allocated intervention
2 did not receive allocated intervention (1 allocated to another study, 1 had prolonged hospitalisation)

160 assigned to no anticoagulation

1 lost to follow-up (withdrawn informed consent)

359 analysed in intention-to-treat analysis
114 angiography scans available
114 Doppler US available

359 analysed in intention-to-treat analysis
150 angiography scans available
118 Doppler US available
Risk ratio 0.33 (0.13–0.90);
p = 0.0293 (superiority);
number needed to treat 16;
relative risk reduction 67%
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 prophylaxis 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