Prevention and treatment of VTE in patients with cancer

An Educational Slide Set

American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism

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Clinical Guidelines

American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism: Prevention and Treatment in Patients with Cancer


Background: Venous thromboembolism (VTE) is a common complication among patients with cancer. Patients with VTE are at a markedly increased risk for morbidity and mortality.

Objectives: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support physicians, nurses, and other health care professionals in their decisions about the prevention and treatment of VTE in patients with cancer.

Method: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The guideline development process was supported by the American Society of Hematology, Clinical Practice Guidelines Development, and Evaluation (CPEGDE) approach used to assess evidence and make recommendations.

Results: Recommendations address mechanical and pharmacological prophylaxis in hospitalized medical patients with cancer; those undergoing a surgical procedure; and ambulatory patients receiving cancer chemotheraphy. The recommendations also address the use of anticoagulation for the initial short-term, and long-term treatment of VTE in patients with cancer.

Conclusions: Strong recommendations include not using thromboprophylaxis in ambulatory patients receiving cancer chemotherapy at a low risk of VTE and using low molecular weight heparin (LMWH) to treat initial and recurrent VTE in patients with cancer. Conditional recommendations include using thromboprophylaxis in hospitalized medical patients with cancer, LMWH or fondaparinux for surgical patients with cancer, LMWH or direct oral anticoagulants (DOAC) in inpatient patients with cancer receiving chemotherapy at a high risk of VTE and LMWH or DOAC for initial treatment at VTE in patients with cancer.
ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prevention of VTE in Medical Hospitalized Patients
3. Treatment of Acute VTE (DVT and PE)
4. Optimal Management of Anticoagulation Therapy
5. **Prevention and Treatment of VTE in Patients with Cancer**
6. Heparin-Induced Thrombocytopenia (HIT)
7. Thrombophilia
8. Pediatric VTE
9. VTE in the Context of Pregnancy
10. Diagnosis of VTE
11. VTE in Latin America
12. Anticoagulation in Patients with COVID-19
How were these ASH guidelines developed?

**PANEL FORMATION**
Each guideline panel was formed following these key criteria:
- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of COI

**CLINICAL QUESTIONS**
10 to 20 clinically-relevant questions generated in PICO format (population, intervention, comparison, outcome)

Example: PICO question “Should pre-operative thromboprophylaxis vs. post-operative thromboprophylaxis be used in patients with cancer undergoing a surgical procedure?”

**EVIDENCE SYNTHESIS**
Evidence summary generated for each PICO question via systematic review of health effects plus:
- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

**MAKING RECOMMENDATIONS**
Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.
How patients and clinicians should use these recommendations

<table>
<thead>
<tr>
<th></th>
<th>STRONG Recommendation (“The panel recommends...”)</th>
<th>CONDITIONAL Recommendation (“The panel suggests...”)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For patients</strong></td>
<td>Most individuals would want the intervention.</td>
<td>A majority would want the intervention, but many would not.</td>
</tr>
<tr>
<td><strong>For clinicians</strong></td>
<td>Most individuals should receive the intervention.</td>
<td>Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making.</td>
</tr>
</tbody>
</table>
Objectives

By the end of this session, you should be able to

1. Describe recommendations for primary prophylaxis in patients with cancer undergoing surgery
2. Describe recommendations for primary prophylaxis in ambulatory patients with cancer receiving systemic therapy
3. Select appropriate anticoagulant therapy for VTE in patients with cancer
4. Describe recommendations for treatment of incidental PE in patients with cancer
What is this chapter about?

Patients with cancer are at greater risk for VTE than the general population resulting in considerable morbidity, mortality and costs.

Treatment decisions should be individualized taking into account consequences of VTE and/or bleeding events.

This chapter provides evidence-based recommendations on prevention and treatment of VTE in patients with cancer.
Case 1: Primary prophylaxis in patients with cancer undergoing surgery

67 year old female with newly diagnosed stage IIIa colorectal cancer (T1N2aM0)

Past Medical History: Hypertension, dyslipidemia

Medications: Amlodipine, rosuvastatin

Admitted to hospital:
Planned laparoscopic hemicolecotomy
No symptoms of VTE or bleeding
Weight 80 kg
You judge that your patient is at moderate to high risk of perioperative VTE and low risk of surgical bleeding.

What strategy do you recommend for thromboprophylaxis?

A. Mechanical thromboprophylaxis only
B. Dalteparin 5,000 units SC daily post-operatively
C. Dalteparin 5,000 units SC daily starting 12 hours pre-operatively
D. Unfractionated heparin 5,000 units SC BID post-operatively
**Recommendation**

In **patients with cancer undergoing a surgical procedure**, the ASH guideline panel suggests using either LMWH or fondaparinux for thromboprophylaxis rather than UFH (**conditional recommendation based on low certainty in the evidence about effects**).

### LMWH versus UFH for thromboprophylaxis

<table>
<thead>
<tr>
<th>Outcomes (Quality of Evidence)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with UFH</td>
<td>Risk difference with LMWH</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 0.82 (0.63 to 1.07)</td>
<td>109 out of 2155 (5.1%)</td>
</tr>
<tr>
<td>PE</td>
<td>RR 0.52 (0.20 to 1.34)</td>
<td>19 out of 3138 (0.6%)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>RR 0.67 (0.27 to 1.69)</td>
<td>11 out of 1144 (1.0%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 1.01 (0.69 to 1.48)</td>
<td>Not reported (5.6%)</td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>RR 1.01 (0.69 to 1.48)</td>
<td>32 out of 627 (5.1%)</td>
</tr>
</tbody>
</table>

**Quality of Evidence (GRADE):** Low Moderate High
Recommendation

In **patients with cancer undergoing a surgical procedure**, the ASH guideline panel suggests using either LMWH or fondaparinux for thromboprophylaxis rather than UFH (*conditional recommendation based on low certainty in the evidence about effects*).

**Fondaparinux** versus **LMWH** for thromboprophylaxis

<table>
<thead>
<tr>
<th>Outcomes (Quality of Evidence)</th>
<th>Relative effect (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with LMWH</td>
<td>Risk difference with Fondaparinux</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 0.40 (0.14 to 1.12)</td>
<td>72 per 1,000</td>
</tr>
<tr>
<td>PE</td>
<td>RR 0.40 (0.14 to 1.12)</td>
<td>72 per 1,000</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>RR 0.40 (0.14 to 1.12)</td>
<td>72 per 1,000</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 1.34 (0.81 to 2.22)</td>
<td>22 per 1,000</td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low ★ Moderate ★★ High ★★★
Remarks

• UFH is generally preferred over LMWH for patients with cancer with severe renal impairment (defined as a creatinine clearance < 30 mL/min)

• If planning for extended thromboprophylaxis (continuing pharmacological thromboprophylaxis at home), the guideline panel suggests the use of LMWH
**Recommendation**

In **patients with cancer undergoing a surgical procedure**, the ASH guideline panel suggests using post-operative thromboprophylaxis over pre-operative thromboprophylaxis (*conditional recommendation based on low certainty in the evidence about effects*).

### Outcomes (Quality of Evidence) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | Risk with immediate post-op prophylaxis | Risk difference with pre-operative prophylaxis
--- | --- | --- | --- | ---
Mortality | RR 0.74 (0.50 to 1.09) | 27 per 1,000 | 7 fewer deaths per 1,000 (13 fewer to 2 more)
PE | RR 0.20 (0.01 to 4.16) | 1 per 1,000 | 1 fewer PE per 1,000 (1 fewer to 3 more)
Symptomatic DVT | RR 0.86 (0.62 to 1.19) | 51 per 1,000 | 7 fewer DVTs per 1,000 (19 fewer to 10 more)
Major bleeding | RR 1.55 (1.14 to 2.12) | 29 per 1,000 | 16 more bleeds per 1,000 (4 more to 32 more)
Case 1, continued

- You prescribe dalteparin 5,000 IU subcut daily post-operatively
- Your patient’s post-operative course is uneventful and discharge is planned on post-operative day 3

What duration of pharmacological thromboprophylaxis do you recommend?

A. Discontinue pharmacological thromboprophylaxis at discharge
B. Discontinue pharmacological thromboprophylaxis once your patient is ambulatory
C. Continue pharmacological thromboprophylaxis at home for 7 days
D. Continue pharmacological thromboprophylaxis at home for 4 weeks
In **patients with cancer who had undergone a major abdominal/pelvic surgical procedure**, the ASH guideline panel suggests continuing pharmacological thromboprophylaxis post discharge rather than discontinuing at the time of hospital discharge (conditional recommendation based on very low certainty in the evidence about effects).

### Quality of Evidence (GRADE): Low        Moderate        Strong

<table>
<thead>
<tr>
<th>Outcomes (Quality of Evidence)</th>
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<th>Anticipated absolute effects (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Risk with limited prophylaxis</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 1.14 (0.73 to 1.78)</td>
<td>Not stated</td>
</tr>
<tr>
<td>PE</td>
<td>RR 0.18 (0.02 to 1.46)</td>
<td>17 per 1,000</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>RR 0.67 (0.11 to 4.06)</td>
<td>29 per 1,000</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 0.83 (0.29 to 2.35)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
Remarks

• We only identified evidence to assess the benefits and harms of extended thromboprophylaxis in patients undergoing major abdominal/pelvic surgery.

• This recommendation should not be extended to other surgical procedures.

• Patients should be provided comprehensive anticoagulation education including self-injection technique during hospitalization to facilitate continuation of thromboprophylaxis after discharge.
Case 1, Continued:

• Four weeks later, your patient is seen in the Oncology clinic
• Adjuvant chemotherapy (oxaliplatin, leucovorin, fluorouracil) is planned

Physical examination:
Weight 80 kg, BMI 25 kg/m²
Well healed surgical incisions
No evidence of DVT or PE

Laboratory Investigations (pre-chemotherapy)
Hemoglobin 115 g/L
Leukocyte count 13 x 10⁹/L
Platelet count 405 x 10⁹/L
Creatinine 55 µmol/L
You judge that your patient is at moderate to high risk of VTE and low risk of bleeding.

What strategy do you recommend for **thromboprophylaxis**?

A. No thromboprophylaxis  
B. Mechanical thromboprophylaxis only  
C. **Apixaban 2.5 mg twice daily**  
D. Dalteparin 5,000 IU SC daily
# Khorana risk score

<table>
<thead>
<tr>
<th><strong>Site of primary tumor</strong></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gyne, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>All others</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Platelet count</strong></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt; 350 \times 10^9$/L</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Hemoglobin</strong></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 100$ g/L or use of ESAs</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>WBC</strong></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt; 11 \times 10^9$/L</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>BMI</strong></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&gt; 35$ kg/m$^2$</td>
<td>1</td>
</tr>
</tbody>
</table>

# Khorana risk score

<table>
<thead>
<tr>
<th>Site of primary tumor</th>
<th>Score</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gyne, bladder, testicular)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>All others</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

| **Platelet count** > $350 \times 10^9$/L | 1     | 405 $\times 10^9$/L |
| **Hemoglobin** < 100 g/L or use of ESAs | 1     | 115 g/L             |
| **WBC** > $11 \times 10^9$/L             | 1     | 13 $\times 10^9$/L  |
| **BMI** > 35 kg/m²                       | 1     | 25 kg/m²            |

Khorana risk score

What is this patient’s risk of VTE?

- Low (≤1) risk category: 5.5%
- High (≥2) risk category: 8.9%

Recommendations

In ambulatory patients with cancer at low risk of thrombosis receiving systemic therapy, the ASH guideline panel suggests no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation based on moderate certainty in the evidence about effects).

In ambulatory patients with cancer at intermediate risk of thrombosis receiving systemic therapy, the ASH guideline panel suggests either thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation based on moderate certainty in the evidence about effects).

In ambulatory patients with cancer at high risk of thrombosis receiving systemic therapy, the ASH guideline panel suggests thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation based on moderate certainty in the evidence about effects).
## Recommendation

In **ambulatory patients with cancer at high risk of thrombosis** receiving systemic therapy, the ASH guideline panel suggests **thromboprophylaxis with a DOAC (apixaban or rivaroxaban)** over no thromboprophylaxis (conditional recommendation based on moderate certainty in the evidence about effects).

<table>
<thead>
<tr>
<th>Outcomes (Quality of Evidence)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk with no thromboprophylaxis</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 0.94 (0.64 to 1.38)</td>
<td>185 per 1,000</td>
</tr>
<tr>
<td>PE</td>
<td>RR 0.24 (0.12 to 0.47)</td>
<td>60 per 1,000</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>RR 0.61 (0.31 to 1.21)</td>
<td>95 per 1,000</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 1.65 (0.72 to 3.80)</td>
<td>14 per 1,000</td>
</tr>
</tbody>
</table>

Quality of Evidence (GRADE): Low - Moderate - High
Other considerations

- Classification of patients as low, moderate or high-risk for VTE should be based on a validated score (i.e. Khorana score) complemented by **clinical judgment and experience**.

- In patients at high risk for thrombosis, thromboprophylaxis should be used with caution in those with a high risk of bleeding.
Case 2: Treatment of cancer associated VTE

A 44 year old female presents to the ED with a 3-day history of right leg swelling and pain.

A doppler ultrasound of the right leg reveals an **occlusive DVT in the right superficial femoral, popliteal and trifurcation veins**.

**Past Medical History:** Locally advanced breast cancer, grade 3 invasive ductal carcinoma, ER/PR negative, HER2 negative, grade 3 invasive ductal carcinoma.

**Medications:** Neo-adjuvant dose dense AC/T (doxorubicin, cyclophosphamide, paclitaxel).

**Laboratory investigations in the ED:**
- Hemoglobin 109 g/L
- Leukocyte count 11 x 10⁹/L
- Platelet count 334 x 10⁹/L
- Creatinine 60 µmol/L
Case 2

What initial treatment do you recommend?

A. IVC filter insertion
B. Tinzaparin 175 IU/kg once daily
C. Edoxaban 60mg once daily
D. Unfractionated heparin infusion
Definitions

The ASH guideline panel divided the treatment course of VTE in cancer patients into three phases:

1. **Initial treatment** (within the first week of diagnosis)

2. **Short-term treatment** (3 to 6 months from diagnosis)

3. **Long-term treatment** (> 6 months from diagnosis)
Recommendation

In **patients with cancer and VTE**, the ASH guideline panel suggests either DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE in patients with cancer (*conditional recommendation based on very low certainty in the evidence about effects)*.

If a DOAC is not used, we recommend LMWH over UFH for initial treatment of VTE in patients with cancer (*strong recommendation based on moderate certainty in the evidence about effects)*.

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes (Quality of Evidence)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with LMWH</td>
<td>Risk difference with DOAC</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 3.00 (0.12 to 73.21)</td>
<td>0 fewer deaths per 1,000 (0 fewer to 0 fewer)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>RR 0.20 (0.01 to 4.04)</td>
<td>11 fewer recurrent events per 1,000 (14 fewer to 43 more)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 0.33 (0.01 to 8.13)</td>
<td>2 fewer bleeds per 1,000 (3 fewer to 21 more)</td>
</tr>
</tbody>
</table>

* Based on results of the SELECT-D and ADAM-VTE trials only
Remarks

• Only two DOACs (apixaban and rivaroxaban) have been approved for the initial treatment period.

• DOACs should be used carefully in patients with gastrointestinal cancers because of a higher risk of GI bleeding.

• UFH might be preferred over LMWH for the patient with cancer with severe renal impairment (defined as creatinine clearance < 30 mL/min).

• The use of fondaparinux might be considered in patients with cancer and VTE and a prior history of heparin induced thrombocytopenia.
Case 2, continued

Four weeks later, your patient undergoes an uncomplicated right modified radical mastectomy.

She is seen in your outpatient clinic one week post-operatively.

Her right leg swelling and pain has improved and she has no bleeding.

What is your recommendation?

A. Continue tinzaparin 175 IU/kg once daily
B. Switch to VKA (warfarin) with target INR 2.5
C. **Switch to rivaroxaban 20mg once daily**
D. Discontinue anticoagulation
Recommendation

For the **short-term treatment of VTE (first 3-6 months)** in patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban or rivaroxaban) over LMWH (**conditional recommendation based on low certainty in the evidence about effects**).

DOAC is also suggested over VKA (**conditional recommendation based on very low certainty in the evidence about effects**).

If a DOAC is not used, the ASH guideline panel suggests LMWH over VKA (**conditional recommendation based on moderate certainty in the evidence about effects**).
For the short-term treatment of VTE (first 3-6 months) in patients with active cancer, the ASH guideline panel suggests DOAC (apixaban, edoxaban or rivaroxaban) over LMWH (conditional recommendation based on low certainty in the evidence about effects).

**Outcomes**

<table>
<thead>
<tr>
<th>Outcomes* (Quality of Evidence)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)*</th>
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</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>RR 0.99 (0.83 to 1.18)</td>
<td>Risk with LMWH: 245 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk difference with DOAC: 2 fewer deaths per 1,000 (42 fewer to 44 more)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>RR 0.62 (0.43 to 0.90)</td>
<td>Risk with LMWH: 83 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk difference with DOAC: 32 fewer recurrent events per 1,000 (47 fewer to 8 fewer)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 1.31 (0.83 to 2.06)</td>
<td>Risk with LMWH: 34 per 1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk difference with DOAC: 10 more bleeds per 1,000 (6 fewer to 36 more)</td>
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* Follow-up: 12 months
Case 2, continued

Three months later, your patient has a surveillance CT scan showing metastatic deposits in the liver and bone.

An MRI brain is negative for intracranial metastases.

Palliative chemotherapy is planned.

**Laboratory investigations:**

- Hemoglobin 99 g/L
- Leukocyte count 13 x 10⁹/L
- Platelet count 89 x 10⁹/L
- Creatinine 84 µmol/L
Case 2, continued

What duration of anticoagulation do you recommend?

A. Discontinue anticoagulation now
B. Discontinue anticoagulation after 3 months
C. Discontinue anticoagulation after 6 months
D. Continue anticoagulation indefinitely
In patients with active cancer and VTE, the ASH guideline panel suggests long-term anticoagulation for secondary prophylaxis (longer than 6 months) rather than short term treatment alone (3-6 months) (conditional recommendation based on low certainty in the evidence about effects).

<table>
<thead>
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<th>Outcomes* (Quality of Evidence)</th>
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<tr>
<td></td>
<td></td>
<td>Risk with short term treatment (3-6 mos)</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 1.38 (0.85 to 2.23)</td>
<td>24 per 1,000</td>
</tr>
<tr>
<td>PE</td>
<td>RR 0.66 (0.29 to 1.51)</td>
<td>50 per 1,000</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>RR 0.54 (0.23 to 1.27)</td>
<td>138 per 1,000</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>RR 1.25 (0.68 to 2.30)</td>
<td>15 per 1,000</td>
</tr>
</tbody>
</table>

* Mean follow-up: 31 months

Quality of Evidence (GRADE): Low
Recommendation

In patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel suggests continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation based on very low certainty in the evidence about effects).

<table>
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<tbody>
<tr>
<td></td>
<td>RR 0.70 (0.45 to 1.09)</td>
<td>Risk with definite duration (&lt; 12 mos) 15 per 1,000 Risk difference with indefinite duration of therapy 5 fewer deaths per 1,000 (8 fewer to 1 more)</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 0.23 (0.12 to 0.44)</td>
<td>27 per 1,000 21 fewer recurrent PE per 1,000 (24 fewer to 15 fewer)</td>
</tr>
<tr>
<td>PE</td>
<td>RR 0.20 (0.11 to 0.38)</td>
<td>95 per 1,000 76 fewer recurrent events per 1,000 (85 fewer to 59 fewer)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>RR 2.21 (1.32 to 3.44)</td>
<td>7 per 1,000 9 more bleeds per 1,000 (3 more to 18 more)</td>
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</tbody>
</table>
Remarks

• Long-term anticoagulation can be discontinued when patients are no longer at high risk of recurrent VTE or if patients are entering the last weeks of life.

• The decision to anticoagulate for a prolonged period will be dependent on the type and stage of cancer (e.g., metastatic cancer or not), long-term prognosis, and periodic re-evaluation of risk of thrombosis and bleeding, comorbidities, costs and patient preferences and values.

• The choice of anticoagulant must also be based on the specific clinical setting to minimize risk, after careful consideration of bleeding risk, drug-drug interactions, patient’s preference, and the availability of treatment options including cost considerations.
Anticoagulation at the end of life

- Observational data support stopping anticoagulants and antithrombotic drugs as death approaches.

- Observational data have shown:
  - A high risk of clinically relevant bleeding (7-10%) in the last weeks of life
  - That bleeding is strongly associated with use of anticoagulants (HR 1.48, 95% CI 1.02-2.15) and antiplatelet drugs (HR 1.67, 95% CI 1.15-2.44)
Case 2, Summary

- **Initial treatment** (within first week of diagnosis)
  - Recommendation 20: DOAC or LMWH

- **Short-term treatment** (3 to 6 mos. from diagnosis)
  - Recommendation 23: DOAC over LMWH

- **Long-term treatment** (> 6 mos. from diagnosis)

- **End of life**
  - Discontinue anticoagulant therapy
Case 3: Treatment of incidental PE

53 year old male with metastatic renal cell carcinoma (to bones, liver)

Past Medical History: Hypothyroidism, depression

Medications: Levothyroxine, escitalopram, cabozantinib (TKI drug)

Seen in outpatient clinic:
Routine staging CT shows bilateral segmental/subsegmental pulmonary emboli
Bilateral leg doppler ultrasound negative for DVT
He is asymptomatic with normal vital signs

Laboratory investigations:
Hemoglobin 129 g/L
Leukocyte count 12 x 10^9/L
Platelet count 330 x 10^9/L
Creatinine 94 μmol/L
What is your treatment recommendation?

A. Clinical observation only
B. IVC filter insertion
C. Start apixaban 10mg BID x 1 week, followed by apixaban 5mg BID
D. Start warfarin (target INR 2.5)
In patients with cancer and incidental (unsuspected) PE, the ASH guideline panel suggests short-term anticoagulation treatment rather than observation (conditional recommendation based on very low certainty in the evidence about effects).

**Recommendation**

<table>
<thead>
<tr>
<th>Outcomes (Quality of Evidence)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>RR 0.81 (0.67 to 0.98)</td>
<td>Risk with observation: 369 per 1,000 Risk difference with treatment: 70 fewer deaths per 1,000 (122 fewer to 7 fewer)</td>
</tr>
<tr>
<td>Symptomatic PE*</td>
<td>RR 0.36 (0.18 to 0.72)</td>
<td>Risk with observation: 60 per 1,000 Risk difference with treatment: 39 fewer recurrent PE per 1,000 (49 fewer to 17 fewer)</td>
</tr>
<tr>
<td>Symptomatic recurrent DVT*</td>
<td>RR 0.19 (0.08 to 0.48)</td>
<td>Risk with observation: 48 per 1,000 Risk difference with treatment: 39 fewer recurrent events per 1,000 (44 fewer to 25 fewer)</td>
</tr>
<tr>
<td>Major bleeding*</td>
<td>RR 3.00 (1.21 to 7.47)</td>
<td>Risk with observation: 22 per 1,000 Risk difference with treatment: 44 more bleeds per 1,000 (5 more to 414 more)</td>
</tr>
</tbody>
</table>

* Follow-up: 3 months

**Quality of Evidence (GRADE):**
- Low
- Moderate
- Strong
Remarks

• Clinicians should use clinical judgment when considering anticoagulation for incidental PE, sub-segmental PE or splanchnic vein thrombosis.

• Factors that should be considered include diagnostic certainty, chronicity (age of thrombus), extent of thrombosis, associated symptoms and bleeding risks.

• If therapeutic anticoagulation is warranted, the ASH guideline panel recommends use of the same anticoagulants recommended for treatment of cancer-associated thrombosis.
Other guideline recommendations that were not covered in this session

- Primary prophylaxis in hospitalized medical patients with cancer
- Primary prophylaxis for patients with cancer and a central venous catheter
- Treatment versus observation for patients with cancer and SSPE or visceral/splanchnic vein thrombosis
- Treatment of patients with cancer and recurrent VTE despite anticoagulation
Some future priorities for research

- Optimal choice, dosing and duration of parenteral anticoagulation to prevent VTE in hospitalized patients with cancer
- Cost effectiveness of primary prophylaxis for ambulatory patients with cancer
- Primary prophylaxis for patients with cancer and a central venous catheter (treatment duration, agent of choice)
- Comparative safety, efficacy and cost effectiveness of oral agents versus parenteral therapy for VTE in patients with cancer
- Treatment versus observation for patients with cancer and incidental/subsegmental PE or splanchnic vein thrombosis
In Summary: Back to our Objectives

1. Describe recommendations for primary prophylaxis in patients with cancer undergoing surgery
   – Prophylaxis with LMWH or fondaparinux recommended over UFH
   – Extended thromboprophylaxis (4 weeks) for major abdominal/pelvic surgery

2. Describe recommendations for primary prophylaxis in ambulatory patients with cancer receiving systemic therapy
   – Pharmacological prophylaxis (DOACs) for patients at moderate to high risk of VTE

3. Select appropriate anticoagulant therapy for VTE in patients with cancer
   – Initial treatment (within 1 week): LMWH or DOACs
   – Short-term treatment (3-6 months): DOACs over LMWH
   – Long-term treatment (> 6 months): Indefinite anticoagulation

4. Describe recommendations for treatment of incidental PE in patients with cancer
   – Anticoagulation rather than observation
Acknowledgements

• ASH Guideline Panel team members
• Knowledge Synthesis team members
• McMaster University GRADE Centre
• Author of this ASH VTE Slide Set: Siraj Mithoowani MD, MHPE (McMaster University)

See more about the ASH VTE guidelines at www.hematology.org/vte