



Prophylaxis for Hospitalized and Non-Hospitalized Medical Patients

An Educational Slide Set

American Society of Hematology 2018 Guidelines
for Management of Venous Thromboembolism

Slide set authors:

Eric Tseng MD MScCH, University of Toronto
Mary Cushman MD MSc, University of Vermont



American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and non-hospitalized medical patients

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CLINICAL GUIDELINES

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

Holger J. Schünemann,^{1,2a} Mary Cushman,^{3,4a} Allison E. Burnett,⁵ Susan R. Kahn,⁶ Jan Beyer-Westendorf,^{7a} Frederick A. Spencer,¹ Suely M. Rezende,⁸ Neil A. Zakai,⁹ Kenneth A. Bauer,¹⁰ Francesco Dentali,¹¹ Jill Lansing,¹² Sara Balduzzi,¹³ Andrea Darzi,¹⁴ Gian Paolo Morgano,¹⁵ Ignacio Neumann,¹⁶ Robby Nieuwlaat,¹⁷ Juan J. Yepes-Nuñez,¹⁸ Yuan Zhang,¹⁹ and Wojtek Wiercioch²⁰

¹Department of Medicine and ²Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada; ³Department of Medicine and ⁴Department of Pathology and Laboratory Medicine, University of Vermont Larner College of Medicine and University of Vermont Medical Center, Burlington, VT; ⁵Preventive Antithrombotic Services, University of New Mexico Health Sciences Center, Albuquerque, NM; ⁶Department of Medicine, McGill University and Lady Davis Institute, Montreal, QC, Canada; ⁷Thrombosis Research Unit, Division of Hematology, Department of Medicine I, University Hospital "Carl Gustav Carus", Dresden, Germany; ⁸King's Thrombosis Service, Department of Hematology, King's College London, United Kingdom; ⁹Department of Internal Medicine, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; ¹⁰Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; ¹¹Department of Medicine and Surgery, Inedra University, Varese, Italy; ¹²Totale University of New York, Albany, NY; ¹³Cochrane Italy, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy; and ¹⁴Department of Internal Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Background: Venous thromboembolism (VTE) is the third most common vascular disease. Medical inpatients, long-term care residents, persons with minor injuries, and long-distance travelers are at increased risk.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) intend to support patients, clinicians, and others in decisions about preventing VTE in these groups.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline-development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and adult patients. The Grading of Recommendations Assessment, Development and Evaluation approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 19 recommendations for acutely ill and critically ill medical inpatients, people in long-term care facilities, outpatients with minor injuries, and long-distance travelers.

Conclusions: Strong recommendations included provision of pharmacological VTE prophylaxis in acutely or critically ill inpatients at acceptable bleeding risk, use of mechanical prophylaxis when bleeding risk is unacceptable, against the use of direct oral anticoagulants during hospitalization, and against extending pharmacological prophylaxis after hospital discharge. Conditional recommendations included not to use VTE prophylaxis routinely in long-term care patients or outpatients with minor VTE risk factors. The panel conditionally recommended use of graduated compression stockings or low-molecular-weight heparin in long-distance travelers only if they are at high risk for VTE.

Summary of recommendations

Background

Venous thromboembolism (VTE) is the third most common cardiovascular diagnosis, with an incidence rate of ~1 in 1000 annually in middle age and increasing to nearly 1% annually in nonagenarians.¹ About 50% of all VTE events occur as a result of a current or recent hospital admission for surgery or acute medical illness.^{2,3} Hospital-acquired VTE is preventable, with interventions including anticoagulants and mechanical measures, including compression stockings and intermittent pneumatic compression.

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This JLS and M.C. are joint first authors.

Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH Web page hematology.org/vte.

The full-text version of this article contains a data supplement.

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ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
- 2. Prophylaxis in Hospitalized and Non-Hospitalized Medical 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

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 LMWH versus UFH be used for VTE prophylaxis in critically ill patients?”

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.

How patients and clinicians should use these recommendations

	STRONG Recommendation ("The panel recommends...")	CONDITIONAL Recommendation ("The panel suggests...")
For patients	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making .

VTE in medical inpatients 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

Patient groups addressed in this chapter



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



Chronically Ill Medical Patient

Those with medical
conditions who may be
cared for in long-term
care facilities



Long-distance Traveler

Those traveling by air
for ≥ 4 hours



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

The following outcomes were rated by the panel as critical to decision-making:

- High value was placed on avoiding these outcomes
- Asymptomatic VTE were not considered critical outcomes

Mortality

Pulmonary Embolism (PE)

Moderate to Severe Deep Vein Thrombosis (DVT)

Major Bleeding



Case: Medical Inpatient Admission

82 year old male

Past Medical History: Emphysema, type 2 diabetes, obesity (body mass index [BMI] of 42 kg/m²), provoked DVT 15 years ago (after appendectomy)

Medications: Tiotropium, metformin, amlodipine, ramipril

Admitted to: Internal Medicine Ward with pneumonia

Treated with: antibiotics, supplemental oxygen

He is not ambulating on the ward due to dyspnea and generalized weakness.



Which ONE of the following options would you suggest for thromboprophylaxis during this medical inpatient's hospital admission?

- A. Subcutaneous low molecular weight heparin (LMWH)
- B. Direct oral anticoagulant (Betrixaban, Rivaroxaban, or Apixaban)
- C. Graduated compression stockings
- D. No prophylaxis because patient is low thrombosis risk

Our patient's risk factors for VTE

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

Recommendation

- In **acutely ill medical patients**, the panel suggests using **UFH, LMWH, or fondaparinux** rather than no parenteral anticoagulant (*conditional recommendation, low certainty*)
- The panel suggests using LMWH (*low certainty*) or fondaparinux (*very low certainty*) rather than UFH (*conditional recommendation*)

Parenteral anticoagulant compared with **no parenteral anticoagulant**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no parenteral anticoagulant	Risk difference with parenteral anticoagulant
● Mortality	0.97 (0.91 to 1.04)	69 per 1,000	2 fewer deaths per 1,000 (6 fewer to 3 more)
● PE	0.59 (0.45 to 0.78)	10 per 1,000	4 fewer PE per 1,000 (6 fewer to 2 fewer)
● Symptomatic proximal DVT	0.28 (0.06 to 1.37)	4 per 1,000	3 fewer DVT per 1,000 (4 fewer to 1 more)
● Major bleeding	1.48 (0.81 to 2.71)	7 per 1,000	3 more bleeds per 1,000 (1 fewer to 12 more)

Recommendation

In **acutely or critically ill medical patients**, the panel suggests using pharmacological VTE prophylaxis over mechanical prophylaxis (*conditional recommendation, very low certainty*)

Pharmacologic prophylaxis compared with **mechanical prophylaxis**
(*graduated compression stockings or pneumatic compression devices*):

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with pharmacologic prophylaxis	Risk difference with mechanical prophylaxis
● Mortality	0.95 (0.42 to 1.13)	18 per 1,000	1 fewer death per 1,000 (11 fewer to 21 more)
● PE	1.54 (0.48 to 4.93)	1 per 1,000	1 more PE per 1,000 (1 fewer to 4 more)
● Symptomatic proximal DVT	2.20 (0.22 to 22.09)	2 per 1,000	2 more DVT per 1,000 (1 fewer to 38 more)
● Major bleeding	0.87 (0.25 to 3.08)	28 per 1,000	4 fewer bleeds per 1,000 (21 fewer to 58 more)

Recommendation

In acutely ill hospitalized **medical patients**, the panel recommends using LMWH over DOACs for VTE prophylaxis (*strong recommendation, moderate certainty*)

Any DOAC compared with **prophylactic LMWH**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with prophylactic LMWH	Risk difference with any DOAC
● Mortality	0.64 (0.21 to 1.98)	1 per 1,000	0 fewer deaths per 1,000 (1 fewer to 1 more)
● PE	1.01 (0.29 to 3.53)	1 per 1,000	0 fewer PE per 1,000 (1 fewer to 3 more)
● Symptomatic proximal DVT	1.03 (0.34 to 3.08)	2 per 1,000	0 fewer DVT per 1,000 (1 fewer to 4 more)
● Major bleeding	1.70 (1.02 to 2.82)	2 per 1,000	2 more bleeds per 1,000 (0 fewer to 4 more)*

*these estimates apply to low baseline bleeding risk

You start VTE prophylaxis with **prophylactic LMWH** for this internal medicine admission

Two days into the hospital admission, your patient is admitted to the **critical care unit** with respiratory failure and septic shock

- He is intubated and started on vasopressors
- His labs:

Labs on Transfer to ICU

Hemoglobin	12.0 g/dL
Platelets	103 x 10 ⁹ /L
Leukocytes	15.6 x 10 ⁹ /L
Creatinine	1.47 mg/dL (eGFR 49 mL/min/1.73 m ²)



Your patient has been transferred to the intensive care unit (ICU), and has mild thrombocytopenia and acute kidney injury.

Which ONE of the following options would you recommend for thromboprophylaxis now?

- A. Subcutaneous LMWH
- B. Subcutaneous Unfractionated Heparin (UFH)
- C. Graduated Compression Stockings
- D. Graduated Compression Stockings combined with LMWH

Recommendation

In **critically ill medical patients**, the panel suggests using LMWH over UFH (conditional recommendation, moderate certainty)

LMWH compared with UFH in critically ill patients:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with UFH	Risk difference with LMWH
● Mortality	0.90 (0.75 to 1.08)	243 per 1,000	24 fewer deaths per 1,000 (61 fewer to 19 more)
● PE	0.80 (0.44 to 1.46)	11 per 1,000	2 fewer PE per 1,000 (6 fewer to 5 more)
● Symptomatic proximal DVT	0.87 (0.60 to 1.25)	25 per 1,000	3 fewer DVT per 1,000 (10 fewer to 6 more)
● Major bleeding	0.98 (0.76 to 1.27)	53 per 1,000	1 fewer bleeds per 1,000 (13 fewer to 14 more)
● Heparin-induced thrombocytopenia	0.42 (0.15 to 1.18)	6 per 1,000	4 fewer episodes per 1,000 (5 fewer to 1 more)

Critically ill patients may require other prophylaxis options due to hepatic or renal dysfunction.



Recommendation

In **acutely and critically ill medical patients**, the panel suggests pharmacological VTE prophylaxis alone over mechanical combined with pharmacological VTE prophylaxis (*conditional recommendation, very low certainty*)

Mechanical combined with pharmacologic compared with **pharmacologic alone**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with pharmacologic prophylaxis alone	Risk difference with combined prophylaxis
● Mortality	0.50 (0.05 to 5.30)	8 per 1,000	4 fewer deaths per 1,000 (8 fewer to 34 more)
● PE	0.35 (0.05 to 2.22)	1 per 1,000	1 fewer PE per 1,000 (1 fewer to 1 more)
● Symptomatic proximal DVT	0.13 (0.04 to 0.40)	2 per 1,000	2 fewer DVT per 1,000 (2 fewer to 1 fewer)
● Major bleeding	2.83 (0.30 to 26.70)	28 per 1,000	51 more bleeds per 1,000 (20 fewer to 720 more)

Case: Back to our patient

- You decide to continue **prophylactic LMWH without mechanical prophylaxis** after your patient's transfer to the ICU
- Three days into his ICU admission, he develops **upper GI bleeding**
- Gastroscopy reveals a small gastric ulcer with a visible bleeding vessel; this vessel is clipped

Hemoglobin	7.5 g/dL
Platelets	88 x 10 ⁹ /L
Leukocytes	13.0 x 10 ⁹ /L
Creatinine	1.47 mg/dL (eGFR 49 mL/min/1.73 m ²)



Your patient has had recent upper GI bleeding. You decide to withhold pharmacologic prophylaxis to ensure hemostasis.

Which of the following options for thromboprophylaxis would you suggest at this time?

- A. Graduated Compression Stockings
- B. Pneumatic Compression Devices
- C. Calf exercises
- D. No mechanical prophylaxis is needed

Recommendation

In **acutely and critically ill medical patients** who are not receiving pharmacological VTE prophylaxis, the panel suggests either pneumatic compression devices or graduated compression stockings for VTE prophylaxis (*conditional recommendation, very low certainty*)

Pneumatic compression devices compared with **graduated compression stockings**:

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with graduated compression stockings	Risk difference with pneumatic compression
● Mortality	3.43 (0.15 to 79.74)	0 per 1,000	0 fewer deaths per 1,000 (0 fewer to 0 fewer)
● PE	0.38 (0.02 to 8.86)	43 per 1,000	27 fewer PE per 1,000 (43 fewer to 342 more)
● Symptomatic proximal DVT	0.16 (0.01 to 2.98)	130 per 1,000	110 fewer DVT per 1,000 (129 fewer to 258 more)

Case continued: Discharge from hospital

- Your patient recovers from his upper GI bleed and septic shock, and is transferred back to the internal medicine ward.
- Within a few days he is started back on LMWH for pharmacologic VTE prophylaxis.
- He has been in hospital for a total of 9 days and is being discharged back to his home, as his pneumonia has resolved.



You are discharging your patient after an acute medical illness. He has received prophylaxis with LMWH in hospital for 9 days. He is ambulatory and back on his usual medications.

What would you recommend on discharge for VTE prophylaxis?

- A. Stop LMWH on the day of discharge
- B. Extend LMWH for 3 weeks post-discharge
- C. Switch LMWH on discharge to a DOAC, and continue the DOAC for 3 weeks post-discharge
- D. Graduated compression stockings for 3 weeks post-discharge



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



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)
		<i>Risk difference with extended prophylaxis</i>
● 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)

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)	
		<i>Risk with shorter duration non-DOAC inpatient prophylaxis</i>	<i>Risk difference with extended prophylaxis with DOAC</i>
● 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)

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

Case Conclusion and a Visitor

- On discharge you stop LMWH, and he does not receive extended VTE prophylaxis out of hospital. He recovers and does not develop VTE.
- Two months later, the patient's 50 year old niece decides to visit him from England (7 hour flight to Baltimore).
- She is has a history of unprovoked DVT 4 years ago, and her BMI is 38 kg/m². She is currently not on anticoagulant or antiplatelet therapy.

This patient's niece has a history of unprovoked VTE, and her BMI is 38. She is boarding a long-distance flight (> 4 hours).

What would you suggest for VTE prophylaxis during her flight?

- A. LMWH
- B. Graduated compression stockings
- C. Aspirin
- D. No prophylaxis is needed

Air Travel and VTE

- **Long-distance travelers:** 4-hour flight or longer
- Air travel associated with 2.8-fold increase in risk of VTE; risk increases with flight duration
- Several risk factors increase risk of VTE multiplicatively with risk of prolonged air travel
 - Pregnancy, cancer, plaster casts, hormonal therapy, oral contraception

Recommendation

- In people at **increased VTE risk** the panel suggests using **graduated compression stockings or prophylactic LMWH** for long-distance travel (*conditional recommendation, very low certainty*)
- If compression stockings or LMWH are not used, aspirin should be used instead of no prophylaxis (*conditional recommendation, very low certainty*)

Who is at increased risk?

- Recent surgery
- Prior VTE
- Postpartum women
- Active malignancy
- 2+ risk factors including combinations of the above with **hormonal replacement therapy, obesity, or pregnancy**

- LMWH, stockings, and ASA have small, uncertain benefit
- There is no evidence regarding use of DOACs for prophylaxis during air travel

Stockings, LMWH, and aspirin have small, very uncertain effects on VTE prevention – and the estimated absolute benefits are very small

Intervention	Relative Effects (RR, 95% CI) on VTE Prevention (compared with no intervention)	Absolute Risk Difference with each intervention (compared with no prophylaxis)
Graduated Compression Stockings	● 0.10 (0.04 to 0.25)	<ul style="list-style-type: none"> • 3 fewer PE per 1,000,000 (3 fewer to 3 fewer) • 1.8 fewer asymptomatic DVT per 10,000 (1.9 fewer to 1.5 fewer)
LMWH	● 0.10 (0.10 to 2.11)	<ul style="list-style-type: none"> • 3 fewer PE per 1,000,000 (3 fewer to 4 more) • 17.8 fewer asymptomatic DVT per 10,000 (1.9 fewer to 2.2 more)
Aspirin	● 0.75 (0.13 to 4.32)	<ul style="list-style-type: none"> • 1 fewer PE per 1,000,000 (3 fewer to 12 more) • 0.5 fewer asymptomatic DVT per 10,000 (1.7 fewer to 6.5 more)



Applying these guidelines to our patient: why are these recommendations “conditional?”

50 year old female

What is her approximate

Baseline annual risk \approx 1 in 100

Daily VTE risk \approx 1 in 1000

VTE risk per flight \approx 1 in 1000

What is the benefit of

RR 0.10 (95% CI 0.01-2)

Approximate VTE risk per flight with LMWH = 3% x 0.10 = 0.3% (high uncertainty, 95% CI 0.03% to 6.3%)

There is very low certainty and small absolute effect size in these estimates

Physicians must take patient-centered factors into account



However, patients without VTE risk factors do not merit prophylaxis for air travel

Recommendation

In long-distance travelers **without risk factors for VTE**, the panel suggests not using graduated compression stockings, LMWH, or aspirin for VTE prophylaxis (*conditional recommendation, very low certainty*)



Case: Conclusion

- Given her history of previous VTE and obesity, you feel that she merits VTE prophylaxis either with graduated compression stockings or LMWH during her flight.
- She receives prophylactic LMWH on the morning of her 7-hour flight, and does not develop VTE.

Other guideline recommendations that were not covered in this presentation

For these topics, conditional recommendations were made based on weak or very weak quality of evidence

- Medical outpatients with **minor provoking risk factors** for VTE (immobility, minor injury, illness, infection)

- **Chronically ill** medical patients or **nursing home** patients



Some of the 29 identified future priorities for research

- Optimal prophylaxis dosing for obese, underweight, renal patients
- Utility of mechanical prophylaxis in medical outpatients at high risk
- Bleeding and thrombosis risk estimation in medical and critically ill patients
- More study of post discharge measures to prevent VTE
- Comparison of different forms of mechanical prophylaxis to each other
- Comparison of combined approaches (mechanical plus pharmacologic) versus pharmacologic prophylaxis alone
- Utility of prophylaxis in high-risk chronically ill/nursing home patients
- Effectiveness and safety of DOACs for prophylaxis during air travel

In Summary: Back to our Objectives

1. Describe VTE prophylaxis recommendations for patients hospitalized with a **medical illness** or **critical illness**
 - Risk assessment models, LMWH compared with DOACs
2. Describe VTE prophylaxis recommendations for patients **discharged from hospital** after an acute medical illness
 - Extended versus in-hospital prophylaxis, LMWH compared with DOACs
3. Identify when **long-distance travelers** may benefit from receiving VTE prophylaxis
 - Graduated compression stockings or LMWH for those with strong VTE risk factors



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