



ASH CLINICAL PRACTICE GUIDELINES
VENOUS THROMBOEMBOLISM (VTE)



Optimal Management of Anticoagulation Therapy

An Educational Slide Set

American Society of Hematology 2018 Guidelines
for Management of Venous Thromboembolism

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Clinical Guidelines

American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy

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CLINICAL GUIDELINES

American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy

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Background Clinicians confront numerous practical issues in optimizing the use of anticoagulants to treat venous thromboembolism (VTE).

Objective These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians and other health care professionals in their decisions about the use of anticoagulants in the management of VTE. These guidelines assume the choice of anticoagulant has already been made.

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 patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations, which were subject to public comment.

Results The panel agreed on 25 recommendations and 2 good practice statements to optimize management of patients receiving anticoagulants.

Conclusions Strong recommendations included using patient self-management of international normalized ratio (INR) with home point-of-care INR monitoring for vitamin K antagonist therapy and against using periprocedural low-molecular-weight heparin (LMWH)-bridging therapy. Conditional recommendations included basing treatment dosing of LMWH on actual body weight, not using anti-factor Xa monitoring to guide LMWH dosing, using specialized anticoagulation management services, and resuming anticoagulation after episodes of life-threatening bleeding.

Summary of recommendations

Anticoagulant therapy is complex and associated with both substantial benefits (reduced risk for thrombus extension and fatal pulmonary embolism [PE] in the setting of acute illness and recurrent venous thromboembolism [VTE] thereafter) and risks (life-threatening bleeding complications).¹ Recognizing and mitigating risk for harm from anticoagulants requires an evidence-based approach to anticoagulant management and patient education. These guidelines focus on the optimal management of anticoagulant drugs for the prevention and treatment of VTE following the choice of an anticoagulant. Key management strategies for optimal use of anticoagulants include initial anticoagulant dose selection (recommendation 1), drug-interaction management (recommendation 2), point-of-care international

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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

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
“In patients with VKA-related life-threatening bleeding during treatment for VTE, should 4-factor PCC vs. FFP be used?”

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 . |

Objectives

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

1. Describe recommendations for monitoring anticoagulant therapy
2. Describe recommendations for managing anticoagulant-associated bleeding
3. Identify drug-drug interactions relevant to the use of direct oral anticoagulants (DOACs)



What is this chapter about?

Anticoagulants carry benefits (reducing thrombus extension, fatal PE) and risks (life-threatening bleeding)

Recognizing and mitigating risk for harm from anticoagulants requires evidence-based approach to management

This chapter focuses on the **optimal management of anticoagulants** for preventing and treating VTE
(after choice of anticoagulant has already been made).

Case 1: New Deep Vein Thrombosis

52 year old female

Past Medical History: Asthma, Diabetes, Obesity (weight 160 kg)

Medications: Tiotropium, Salbutamol, Metformin

Seen in the Emergency Department with:

Swollen right calf x 4 days, no clear provoking risk factors.

Elevated D-Dimer.

Diagnosis: Proximal right leg deep vein thrombosis (superficial femoral and popliteal veins) on compression ultrasound



You decide to treat this patient with low molecular weight heparin (LMWH), bridging to a Vitamin K antagonist (VKA).

Considering her high body mass (160 kg), how would you select her initial dose of LMWH?

- A. Dose should be capped at the highest available syringe size
- B. Dose should be based on actual body weight
- C. Dose should be based on calculated “ideal body weight” (based on age, gender, and height)
- D. Dose should be adjusted by peak anti-factor Xa levels



Recommendation

In **obese patients receiving LMWH for acute VTE**, the panel suggests initial LMWH dose according to **actual body weight** rather than a fixed maximum daily dose (capped dose) (*conditional recommendation, very low certainty*)

Dosing of LMWH based on **actual body weight** compared with **capped doses**:

| Outcomes (Quality of Evidence) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|-----------------------------------|-----------------------------|---------------------------------------|--|
| | | Risk with capped LMWH doses | Risk difference using actual body weight |
| ● Mortality | Not estimable | 0 out of 47 (0.0%) | Not estimable |
| ● PE | RR 0.76 (0.11 to 5.45) | 1 out of 47 (2.1%) | 5 fewer PE per 1,000 (19 fewer to 95 more) |
| ● Symp. Prox DVT | RR 0.76 (0.11 to 5.45) | 1 out of 47 (2.1%) | 5 fewer DVT per 1,000 (19 fewer to 95 more) |
| ● Major bleeding | Not estimable | 0 out of 47 (0.0%) | Not estimable |

Low quality evidence, so benefit/harm unclear. Panel also considered:

- Desire to avoid underdosing large patients
- Poor correlation between anti-Xa levels and bleeding

Recommendation

In **obese patients receiving LMWH for treatment of VTE**, the panel suggests against using anti-factor Xa concentration monitoring to guide LMWH dose adjustment (*conditional recommendation, very low certainty*)

Dosing LMWH based on **monitoring anti-Xa concentration** compared with **no monitoring**:

| Outcomes (Quality of Evidence) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|-----------------------------------|-----------------------------|---------------------------------------|--|
| | | Risk with no anti-Xa monitoring | Risk difference with anti-Xa monitoring |
| ● Mortality | Not reported | Not reported | Not reported |
| ● PE | RR 3.06 (0.19 to 48.27) | 1 out of 193 (0.5%) | 11 more PE per 1,000 (4 fewer to 245 more) |
| ● Symp. Prox DVT | RR 1.53 (0.14 to 16.61) | 2 out of 193 (1.0%) | 5 more DVT per 1,000 (9 fewer to 162 more) |
| ● Major bleeding | RR 3.91 (0.67 to 22.95) | 2 out of 193 (1.0%) | 30 more bleed per 1,000 (3 fewer to 227 more) |

Low quality evidence, so benefit/harm was unclear.

Panel also considered:

- Concerns about anti-Xa test standardization and reproducibility
- Weak correlation between bleeding and anti-Xa levels

Case 1, Continued:

- You start LMWH based on actual body weight, and also start overlapping VKA. After 8 days, her INR is therapeutic and LMWH is stopped.
- You see her in follow-up in 3 months, and the decision is made to continue with VKA for secondary VTE prevention.
- 5 months later, she requires an **elective colonoscopy** as part of her routine age-appropriate cancer screening.

Your patient had an unprovoked DVT 8 months ago, and now requires a colonoscopy.

What would you recommend for management of her VKA anticoagulation around the time of her elective procedure?

- A. Postpone procedure by 4 months to lower VTE risk
- B. Interrupt VKA before procedure, and give periprocedural “bridging” anticoagulation with LMWH
- C. Interrupt VKA before procedure, and give periprocedural “bridging” anticoagulation with unfractionated heparin
- D. Interrupt VKA before procedure, and do not provide any “bridging” anticoagulation

Recommendation

In patients at **low to moderate risk of recurrent VTE** who require interruption of VKA for invasive procedures, the panel **recommends against periprocedural bridging** with LMWH or UFH in favour of VKA interruption alone (*strong recommendation, moderate certainty*)

Periprocedural bridging compared with **interruption of VKA** therapy alone:

| Outcomes (Quality of Evidence) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|-----------------------------------|------------------------------|---------------------------------------|---|
| | | Risk with VKA interruption alone | Risk difference with periprocedural bridging |
| ● Mortality | Not estimable | 0 out of 1,236 (0.0%) | 0 fewer deaths per 1,000 (0 fewer to 0 fewer) |
| ● PE | Not reported | Not reported | Not reported |
| ● Symp. Prox DVT | RR 0.34 (0.02 to 6.58) | 3 out of 1,236 (0.2%) | 2 fewer DVT per 1,000 (2 fewer to 13 more) |
| ● Major bleeding | RR 31.73 (4.14 to 243.19) | 1 out of 1,236 (0.1%) | 25 more bleed per 1,000 (3 more to 196 more) |

*Despite low quality evidence, **strong recommendation against bridging because:***

- Bridging LMWH consistently associated with increase in bleeding
- Possible reduction in risk of recurrent VTE is very small in this population

VTE Recurrence Risk Stratification

| High Risk | Moderate Risk | Low Risk |
|--|---|---|
| <ul style="list-style-type: none">• VTE within past 3 months• Deficiency of protein C, protein S, or antithrombin• Antiphospholipid antibody syndrome• Multiple thrombophilic abnormalities | <ul style="list-style-type: none">• VTE within past 3-12 months• Heterozygous factor V Leiden• Prothrombin 20210 mutation• Recurrent VTE• Active cancer | <ul style="list-style-type: none">• VTE > 12 months previously• No other risk factors |

Aside: What if this patient was on a DOAC and required a scheduled invasive procedure?

Recommendation

In patients interrupting DOAC therapy for **scheduled invasive procedures**, the panel suggests **against** performing laboratory testing for DOAC anticoagulant effect prior to procedures (*conditional recommendation, very low certainty*)

Remarks:

- Net health benefit/harm of DOAC laboratory testing before procedures is uncertain
- *May consider* testing when DOAC effect may be prolonged (renal failure, interacting drugs), time of last dose unclear, high procedural bleeding risk

Back to Case 1:

- You interrupt VKA 6 days prior to colonoscopy, without providing bridging anticoagulation. The colonoscopy proceeds uneventfully, and she is started back on VKA post-operatively.
- 3 years later she falls and strikes her head on the ground. She is taken to the Emergency Room.
- A computed tomography (CT) scan demonstrates a **large subarachnoid hemorrhage** with mass effect. Her Glasgow Coma Scale is 9, her neurologic status is deteriorating, and she requires urgent neurosurgery. **INR is 2.4.**

Your patient who is on VKA for management of VTE has a large traumatic intracerebral hemorrhage. INR is 2.4.

What would you suggest for reversal of her VKA anticoagulant therapy?

- A. IV Vitamin K alone
- B. Prothrombin Complex Concentrate (PCC) alone
- C. Fresh Frozen Plasma (FFP) alone
- D. IV Vitamin K and PCC**
- E. IV Vitamin K and FFP

Recommendation

In patients with **life-threatening bleeding** during VKA treatment for VTE who have an elevated INR, the panel suggests using 4-factor PCC rather than FFP, in addition to cessation of VKA and intravenous vitamin K (*conditional recommendation, very low certainty*)

PCC compared with **FFP**, in addition to intravenous vitamin K cessation of VKA:

| Outcomes (Quality of Evidence) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|-----------------------------------|-----------------------------|---------------------------------------|--|
| | | Risk with FFP | Risk difference with PCC |
| ● Mortality | RR 0.92 (0.37 to 2.28) | 18 of 145 (12.4%) | 10 fewer deaths per 1,000 (78 fewer to 159 more) |
| ● PE | RR 7.71 (0.44 to 136.11) | 0 of 23 (0.0%) | 15 more PE per 1,000 (0 fewer to 0 fewer) |
| ● Symp. Prox DVT | RR 2.57 (0.11 to 60.24) | 0 of 23 (0.0%) | 4 more DVT per 1,000 (2 fewer to 13 more) |
| ● Major bleeding | RR 1.34 (0.78 to 2.29) | 12 of 132 (9.1%) | 31 more bleed per 1,000 (20 fewer to 117 more) |

Given low certainty of effects, other driving factors for PCC recommendation:

- PCC: less volume overload, faster reduction of INR compared with FFP
- PCC easier to administer

Case 1: Summary

Dosing of LMWH in obese individuals should be based on actual body weight. Peak anti-factor Xa concentrations are not helpful

In individuals on VKA who are at low to moderate risk of VTE recurrence, bridging anticoagulation for invasive procedures increases bleeding without reducing VTE, and is not recommended

Individuals taking VKA who have life-threatening bleeding should receive PCC (not FFP) in addition to intravenous vitamin K



Case 2: Managing DOAC-associated bleeding

70 year old male on **rivaroxaban 20 mg daily** for VTE prevention after recurrent unprovoked pulmonary emboli.

Past History: Hypertension, Epilepsy (in remission, off anti-seizure medications x 5 years)

Seen in the Emergency Department with:

Frequent melena x 48 hours. Last dose of rivaroxaban was 4 hours ago.

Hemoglobin has dropped from 12.0 g/dL (2 months ago) to 6.0 g/dL today. Blood pressure is 95/60, heart rate is 115 beats per minute

Diagnosis: Upper GI bleeding exacerbated by rivaroxaban

Your patient is presenting with acute, life-threatening upper GI bleeding while on an oral direct Xa inhibitor.

What management would you suggest for his DOAC-associated bleeding?

- A. Cessation of Xa inhibitor only
- B. 4-factor Prothrombin Complex Concentrate
- C. Coagulation factor Xa (recombinant) – andexanet
- D. Fresh Frozen Plasma
- E. Idarucizumab

Two relevant recommendations:

For patients with **life-threatening bleeding** during oral direct Xa inhibitor treatment for VTE:

- The panel suggests using either 4-factor PCC as an addition to cessation of the DOAC, or cessation of the DOAC alone (*conditional recommendation, very low certainty*)
- The panel suggests using coagulation factor Xa (recombinant) in addition to cessation of the DOAC, rather than no coagulation factor Xa (recombinant) (*conditional recommendation, very low certainty*)

These recommendations do NOT apply to non-life-threatening bleeding.

Managing bleeding on Xa inhibitors

- Two main approaches
 - 4-factor PCC
 - Recombinant coagulation factor Xa (andexanet)
- However, the evidence for benefit and harm for either approach is very limited, so the panel *does not offer a recommendation for one approach over the other*

Limitations of Current Studies

- **4-factor PCC and coagulation factor Xa have not been directly compared**
- Studies of both approaches have lacked a suitable comparator group



These recommendations concerning reversal of direct Xa inhibitors do not apply to non-life-threatening bleeding

In non-life-threatening bleeding, cost likely would outweigh potential benefit

Small but quantifiable increased risk of thromboembolism associated with PCC administration

Thromboembolic risks of recombinant coagulation factor Xa are uncertain



What if your patient had been taking dabigatran instead, and presented with life-threatening upper GI bleeding?

What management would you suggest for emergent dabigatran-associated major hemorrhage?

- A. Cessation of dabigatran only
- B. 4-factor Prothrombin Complex Concentrate
- C. Coagulation factor Xa (recombinant) – andexanet
- D. Fresh Frozen Plasma
- E. Idarucizumab



Recommendation

In patients with **life-threatening bleeding** during dabigatran treatment for VTE, the panel suggests using **idarucizumab in addition to cessation of dabigatran** rather than no idarucizumab (*conditional recommendation, very low certainty*)

Remarks:

- Compared with non-idarucizumab control group, patients receiving idarucizumab may have had less worsening or recurrence of bleeding (RR 0.12 [95% CI, 0.03 to 0.43])
- In one cohort study, 6.3% of patients who received idarucizumab for uncontrolled bleeding developed arterial or venous thrombosis within 90 days



Is there a role for measuring DOAC anticoagulant effect when managing DOAC-related bleeding?

| Drug | Suggested Test | Interpretation |
|---------------------------------|--------------------------------------|--|
| Dabigatran | Thrombin Time | Normal TT excludes clinically relevant levels |
| Rivaroxaban, Edoxaban, Apixaban | Drug-specific Anti-Xa activity level | Normal anti-Xa activity likely excludes clinically relevant levels |

Benefits and risks of measuring DOAC levels in bleeding patients are uncertain

Do not delay treatment of DOAC-associated bleeding while waiting for DOAC test results

It is advisable not to rely on any single strategy in isolation to assess DOAC effect during bleeding management but instead to use a comprehensive approach.

Recommendation

In patients receiving DOAC therapy for the treatment of VTE, the panel suggests against measuring DOAC anticoagulant effect during management of **bleeding** (*conditional recommendation, very low certainty*)

Remarks:

- Low quality of evidence evaluating impact of measuring DOAC levels in bleeding patients
- Benefits and harms of measuring DOAC anticoagulant effects are uncertain
- ***Best not to delay intervention for bleeding*** while waiting for DOAC test result

Back to Case 2:

- Your patient receives 4-Factor PCC, and his rivaroxaban is temporarily suspended. He is started on an intravenous proton pump inhibitor.
- Gastroscopy reveals a 2 x 2 cm ulcer with a visible vessel that is clipped, and the patient's bleeding stops.
- He is discharged home on no antithrombotic therapy, to be reassessed at a later date.



This patient has been receiving anticoagulant therapy with a direct factor Xa inhibitor for recurrent VTE. He has had a recent upper GI bleed.

How long after his bleeding event would you wait before resuming anticoagulant therapy?

- A. Within 1 week
- B. Between 2 weeks to 3 months
- C. Between 3 to 6 months
- D. Do not resume anticoagulant therapy

Recommendation

In patients receiving anticoagulation therapy for VTE who survive an episode of **major bleeding**, the panel suggests resumption of oral anticoagulation therapy within 90 days rather than discontinuation (*conditional recommendation, very low certainty*)

Resumption versus **discontinuation** of anticoagulant therapy for VTE after major bleeding:

| Outcomes (Quality of Evidence) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|-----------------------------------|----------------------------------|---------------------------------------|---|
| | | Risk without resumption | Risk difference with resumption |
| ● Mortality | RR 0.59 (0.45 to 0.77) | 845 of 2,455 (34.4%) | 141 fewer death per 1,000 (79 fewer to 189 fewer) |
| ● PE | RR 0.26 (0.08 to 0.82) | 12 of 425 (2.8%) | 21 fewer PE per 1,000 (from 5 fewer to 26 fewer) |
| ● Symp. Prox DVT | RR 0.66 (0.25 to 1.75) | 11 of 464 (2.4%) | 8 fewer DVT per 1,000 (18 fewer to 18 more) |
| ● Major bleeding | RR 1.54 (1.18 to 2.02) | 230 of 3,304 (7.0%) | 38 more bleeds per 1,000 (13 more to 71 more) |

Increase in risk of recurrent bleeding offset by improvement in all-cause mortality

Applies to patients requiring long-term or indefinite anticoagulation

Back to Case 2:

- 3 weeks after the bleeding event, your patient has had no further bleeding and his hemoglobin concentration is stable.
- You start him back on rivaroxaban 20 mg daily. There is no further bleeding.
- 6 months later your patient has a seizure, which is felt by a neurologist to be due to his underlying epilepsy. The neurologist would like to start the antiseizure medication **carbamazepine**.



Which of the following antiseizure medications, when taken concomitantly with DOACs, may reduce DOAC plasma concentrations?

- A. Phenytoin
- B. Phenobarbital
- C. Carbamazepine
- D. All of the above

Recommendation

For patients requiring administration **of inhibitors or inducers of P-glycoprotein or strong inhibitors or inducers of CYP enzymes**, the panel suggests using an alternative anticoagulant (such as VKA or LMWH) rather than a DOAC for the treatment of VTE (*conditional recommendation, very low certainty*)

Remarks:

- DOAC absorption is mediated by **P-glycoproteins (P-gp)**
- **CYP3A4 enzymes** are involved in the metabolism of Xa inhibitors (not dabigatran)

| | P-gp | CYP3A4 |
|------------|--|---|
| Inhibitors |  DOAC effect |  DOAC effect |
| Inducers |  DOAC effect |  DOAC effect |

Drugs known to affect P-gp and/or CYP3A4

| | P-gp | CYP3A4 |
|--|--|---|
| Inhibitors  DOAC effect | Verapamil Dronedarone Itraconazole Ketoconazole Voriconazole Clarithromycin | Atazanavir Darunavir Itraconazole Ketoconazole Nefazodone Clarithromycin |
| Inducers  DOAC effect | Rifampin Carbamazepine Phenytoin Barbiturates St. John's wort | Rifampin Carbamazepine Phenytoin Barbiturates St. John's wort |

Carbamazepine is a CYP3A4 and P-gp inducer, which would result in decreased serum concentrations of rivaroxaban. You decide to transition your patient from rivaroxaban to VKA.

What directions would you give your patient to transition from Rivaroxaban to VKA?

- A. Use LMWH bridging therapy
- B. Use intravenous heparin bridging therapy
- C. Use subcutaneous heparin bridging therapy
- D. Overlap DOAC and VKA until INR is therapeutic

Recommendation

In patients transitioning from **DOAC to VKA**, the panel suggests overlapping DOAC and VKA therapy until the INR is within the therapeutic range over using LMWH or UFH “bridging therapy” (*conditional recommendation, very low certainty*)

Remarks:

- Effect of using LMWH bridging therapy during transitions is very uncertain
- Use of LMWH is certain to increase burden and cost
- Be aware of varying potential of DOACs to influence (increase) INR test – if overlap strategy used, INR should be measured just before next DOAC dose



Case 2: Summary

Do not delay the treatment of DOAC-associated major hemorrhage while waiting for DOAC laboratory test results

In individuals with VTE who require indefinite anticoagulation, consider resuming anticoagulation within 90 days of a major bleeding event

Avoid DOACs in individuals who require concomitant treatment with strong inhibitors or inducers of P-glycoprotein or CYP3A4

Other guideline recommendations that were not covered in this session

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

- VKA management: point-of-care INR testing, INR recall interval
- Anti-factor Xa monitoring for LMWH in renal dysfunction
- Strategies for medication adherence and patient education
- Monitoring of renal function while on DOAC therapy

Future Priorities for Research

- Outcomes when DOACs used with P-gp/CYP3A4 inhibitors or inducers
- Outcomes when DOAC tests used for bleeding management
- Role for measuring DOAC anticoagulant effect before procedures
- Identifying when PCC should be used for reversal of Xa inhibitors
- Effectiveness of PCC versus coagulation factor Xa (recombinant) for reversal of bleeding on direct Xa inhibitors
- Timing of anticoagulant resumption after major bleeding

In Summary: Back to our Objectives

1. Describe recommendations for monitoring anticoagulant therapy
 - Monitoring of DOAC anticoagulant effect is not necessary
2. Describe recommendations for managing anticoagulant-associated bleeding
 - PCC and intravenous Vitamin K for VKA reversal
 - Consider PCC or coagulation factor Xa for reversal of Xa inhibitors
 - Idarucizumab for dabigatran reversal
3. Identify drug-drug interactions relevant to the use of direct oral anticoagulants (DOACs)
 - Certain antiseizure, antifungal, antibiotic, HIV medications



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See more about the **ASH VTE guidelines** at <http://www.hematology.org/VTEguidelines>