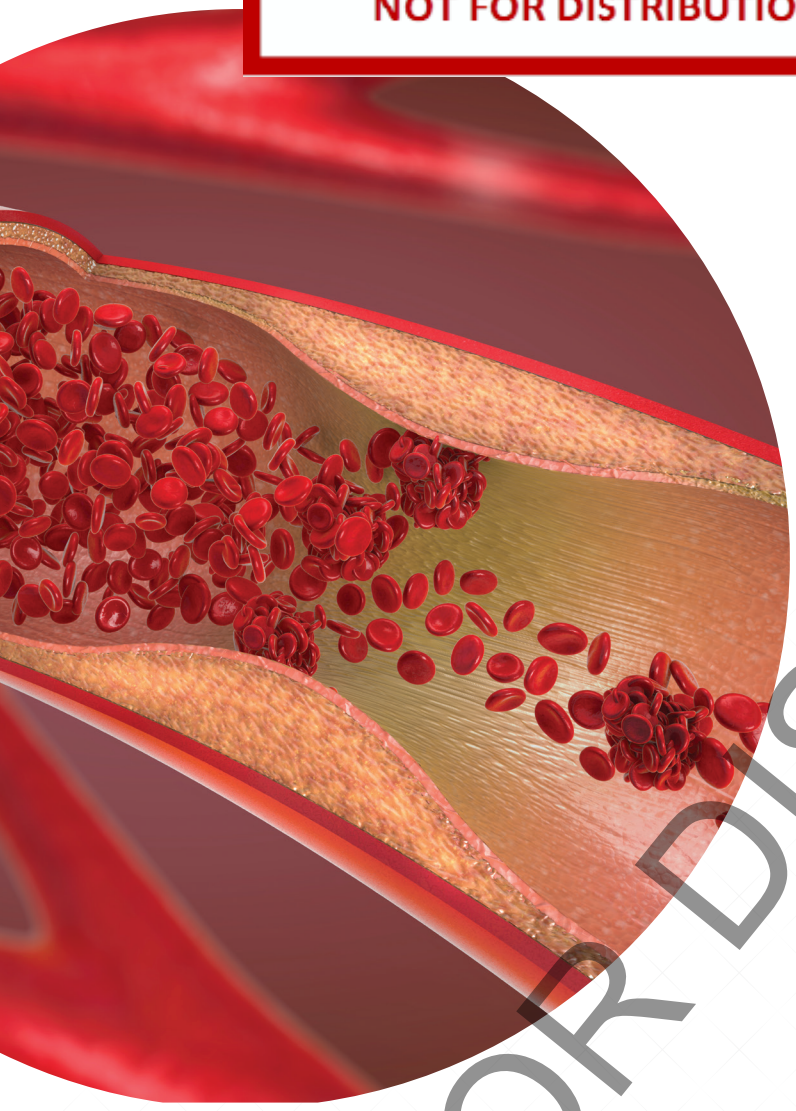
ASH CLINICAL PRACTICE GUIDELINES
VENOUS THROMBOEMBOLISM (VTE)

NOT FOR DISTRIBUTION

POCKET GUIDE



Management of Anticoagulation Therapy

A POCKET GUIDE FOR THE CLINICIAN

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The recommendations in this guide are based on the American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Optimal Management of Anticoagulation Therapy

Context

Treatment of venous thromboembolism (VTE) using anticoagulant therapy is complex and associated with both substantial benefits and risks. The information in this pocket guide is intended to support patients, clinicians, and other health care professionals in making evidence-based decisions about the management of commonly prescribed anticoagulant drugs for the prevention and treatment of VTE. This guide assumes the selection of the specific anticoagulant medication has already been made.

Anticoagulation Dosing and Management

Anticoagulation therapy is the main treatment for VTE and must be applied with knowledge and skill in order to achieve the optimal balance between reduction in recurrent VTE and the risk of potentially life-threatening bleeding. Several anticoagulant options are available including vitamin K-antagonists (VKAs) such as warfarin, and direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. Each anticoagulant medication has unique dosing and monitoring requirements that can be affected by patient-specific factors such as weight, renal function, and the presence of interacting medications. Reversal of the anticoagulant effect and management of bleeding is also specific to each anticoagulant therapy.

INITIAL DOSE SELECTION FOR LOW MOLECULAR WEIGHT HEPARIN

In patients receiving weight-based low molecular weight heparin (LMWH) therapy for initial treatment of acute VTE, including those with obesity (body mass index >30), the ASH guideline panel **suggests** using actual body weight for LMWH dose selection rather than dose selection based on a fixed maximum daily dose (i.e., capped dose) C.

MONITORING LOW MOLECULAR WEIGHT HEPARIN THERAPY

For patients with renal dysfunction (creatinine clearance of <30 mL/min) receiving LMWH therapy for treatment of VTE, the ASH guideline panel **suggests *against*** using anti–factor Xa concentration monitoring to guide LMWH dose adjustment C. Instead of monitoring anti–factor Xa concentrations, providers should consider using doses adjusted for renal function as recommended in product labeling (e.g., enoxaparin) or switching to an alternative anticoagulant with lower renal clearance, such as unfractionated heparin (UFH) or a different LMWH.

For patients with obesity receiving LMWH therapy for treatment of VTE, the ASH guideline panel **suggests *against*** using anti–factor Xa concentration monitoring to guide LMWH dose adjustment C. Providers should consider dosing LMWH based on actual body weight and not monitoring anti–factor Xa concentrations, similar to the approach used in patients without obesity.

POINT-OF-CARE INR TESTING

For patients receiving maintenance VKA therapy for treatment of VTE, the ASH guideline panel **recommends** using patient self-management (PSM), where patients perform point-of-care international normalized ratio (INR) testing at home and self-adjust their VKA doses ✓.[1] For patients where PSM is not an option, the ASH guideline panel suggests patient self-testing (PST), where patients perform point-of-care INR testing at home and receive VKA dosing instructions from their anticoagulation provider, over the usual practice of INR testing performed in the clinic C.

1 For those patients with demonstrated ability to perform PSM and who can afford this option.

TRANSITIONS BETWEEN ANTICOAGULANTS

For patients transitioning from DOAC to VKA, the ASH guideline panel **suggests** overlapping DOAC and VKA therapy until the INR is within the therapeutic range instead of using LMWH- or UFH-bridging therapy C.[1] To minimize DOAC interference with the INR, measure the INR just before the next DOAC dose if overlapping DOAC therapy is used. However, providers will need to be aware of the drug half-life when interpreting INR results and the varying potential among DOACs to influence INR results (Table 1).

[1] Note that this option may not be possible if the baseline INR is already in the therapeutic range before starting VKA therapy.

Table 1 – DOAC Half-Life

Medication	Half-life in healthy subjects[1]	Potential to prolong the PT[2]
Apixaban	12 hours	+
Dabigatran	12 to 17 hours	++
Edoxaban	10 to 14 hours	+++
Rivaroxaban	5 to 9 hours	+++

[1] According to product package labelling

[2] Prothrombin time (PT) prolongation can vary considerably depending on the degree of drug exposure and the type and sensitivity of the reagent

SPECIALIZED ANTICOAGULATION MANAGEMENT SERVICES (AMS)

For patients receiving anticoagulation therapy for treatment of VTE, the ASH guideline panel **suggests** using specialized AMS care (where available) rather than care provided by the patient's regular health care provider C. Patients enrolled in an AMS have a reduced risk of developing pulmonary embolism (PE) and a higher time in therapeutic range (for patients receiving VKA therapy) than patients receiving care from their regular health care providers.

Anticoagulation Interruption, Reversal, and Resumption

INVASIVE PROCEDURE MANAGEMENT

For patients at low to moderate risk of recurrent VTE (Table 2) who require interruption of VKA therapy for invasive procedures, the ASH guideline panel **recommends *against*** periprocedural bridging with LMWH or UHF in favor of interruption of VKA alone ✓. LMWH bridging consistently increases the risk for bleeding without providing additional protection against recurrent VTE in this patient population.

Table 2 – Recurrent VTE Risk Stratification

High Risk	Moderate Risk	Low Risk
VTE within past 3 months	VTE within past 3-12 months	No VTE within the last 12 months and no other VTE risk factors
Confirmed deficiency of protein C, protein S, or antithrombin	Heterozygous factor V Leiden	
Antiphospholipid antibody syndrome	Heterozygous prothrombin 20210 mutation	
Multiple thrombophilic abnormalities (e.g., compound heterozygous for prothrombin 20210 mutation and factor V Leiden or homozygous factor V Leiden)	History of recurrent VTE	
	Active cancer	

For patients interrupting DOAC therapy for scheduled invasive procedures, the ASH guideline panel **suggests *against*** performing laboratory testing for DOAC anticoagulant effect prior to procedures for most patients as the sole method to determine absence of anticoagulant effect C. However, confirming the absence of DOAC affect may be advisable in scenarios where anticoagulant effect may be prolonged (e.g., patients with renal dysfunction and/or on interacting drugs), when DOAC interruption cannot be reliably confirmed by the patient/caregiver (e.g., urgent or emergent invasive procedures), or for patients undergoing a procedure that entails a very high risk of bleeding.

EXCESSIVE ANTICOAGULATION AND BLEEDING MANAGEMENT

The ASH guideline panel **suggests** that aggressive reversal of anticoagulation therapy should be reserved for life-threatening bleeding (Table 3) due to high costs and potential for thromboembolic complications C.

Table 3 – Anticoagulation Reversal

Anticoagulant	Bleeding Severity	INR	Response
VKA	No clinically relevant bleeding	>4.5 but <10	Temporary cessation of VKA without the addition of vitamin K C
	Life-threatening	Elevated >1.3	Stop VKA and administer 4-factor prothrombin complex concentrates (PCCs)1 **and up to 10 mg of** IV vitamin K C
Oral direct Xa inhibitor2	Life-threatening		Stop oral direct Xa inhibitor alone C **or** Stop oral direct Xa inhibitor and administer 4 factor prothrombin complex concentrates (PCCs) C **vs.** Stop oral direct Xa inhibitor and administer coagulation factor Xa (recombinant), inactivated-zhzo (if available) C
Dabigatran	Life-threatening		Stop dabigatran **and** administer idarucizumab C
Low-molecular weight heparin (LMWH)	Life-threatening		Stop LMWH **and** administer protamine C
Unfractionated Heparin (UFH)	Life-threatening		Stop UFH **and** administer protamine C

[1] PCCs are suggested for use instead of fresh-frozen plasma (FFP) in the case of life-threatening bleeding associated with VKA anticoagulation due to ease of administration, less risk for volume overload, and other advantages (e.g., viral inactivation).

[2] When deciding between coagulation factor Xa (recombinant), inactivated-zhzo and 4-factor PCC, there was insufficient information available for the ASH guideline panel to recommend one treatment over the other. Coagulation factor Xa (recombinant), inactivated-zhzo administration in addition to stopping oral direct Xa inhibitors is preferred to stopping oral direct Xa inhibitors alone; whereas the panel suggests no preference for stopping oral direct Xa inhibitors and administering 4-factor PCC over stopping oral direct Xa inhibitors alone.

ANTICOAGULATION RESUMPTION FOLLOWING BLEEDING

For patients receiving anticoagulation therapy for VTE who survive an episode of major bleeding, the ASH guideline panel **suggests** resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy C. This recommendation specifically applies to patients who require long-term or indefinite anticoagulation (i.e., are at moderate to high risk for recurrent VTE, are not at high risk for recurrent bleeding, and are willing to continue anticoagulation therapy).

Strength of Recommendations and Quality of Evidence

The methodology for determining the strength of each recommendation and the quality of the evidence supporting the recommendations was adapted from GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926. More details on this specific adaptation of the GRADE process can be found in American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Optimal Management of Anticoagulation Therapy.[1]

Strength of Recommendation	
✓	**Strong recommendations** - Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
C	**Conditional recommendations** - Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

How to Use This Pocket Guide

ASH pocket guides are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. The information included in this guide is not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the unique clinical presentation of an individual patient, ideally though a shared process that considers the patient's values and preferences with respect to all options and their possible outcomes. Decisions may be constrained by realities of a specific clinical setting, including but not limited to institutional policies, time limitations, or unavailability of treatments. ASH pocket guides may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, these pocket guides may become obsolete. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

The complete 2018 ASH Clinical Practice Guidelines for Management of VTE: Anticoagulation Therapy[1] include additional remarks and contextual information that may affect clinical decisionmaking. To learn more about these guidelines, visit ***hematology.org/vteguidelines***.

Conflict of interest information for Drs. Witt, Clark, Skov, and Crowther may be found at ***hematology.org/pocketguidescoi***.

[1] Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257-3291.

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