QUICK REFERENCE

Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic Drug-Associated Bleeding Complications in Adults

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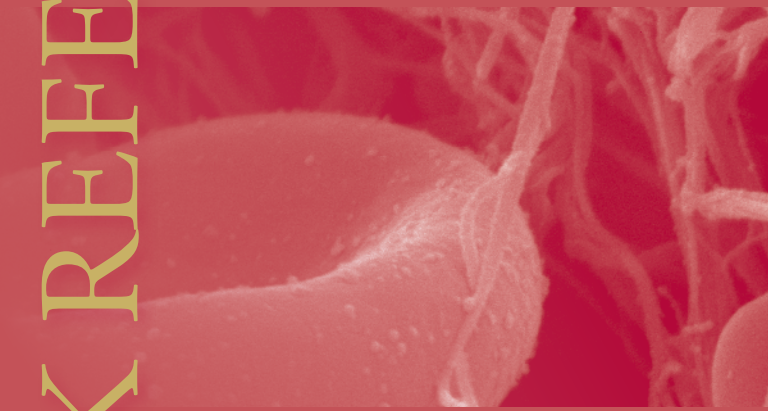

Presented by the American Society of Hematology, adapted in part from the American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (9th Edition).

*This pocket guide is a revision of the 2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults

Look for this pocket guide as a downloadable app by searching for "ASH Guides" in the iTunes store or Android market.

AMERICAN SOCIETY OF HEMATOLOGY®

III. ANTIPLATELET AGENT REVERSAL

Aspirin, Aspirin/Dipyridamole (Aggrenox®), Clopidogrel (Plavix®), Prasugrel (Effient®), Ticagrelor (Brilinta®)

General Considerations

1. Plasma half-lives
   a. Clopidogrel, dipyridamole, prasugrel, ticagrelor: 7-10 hours
   b. Low-dose aspirin (150 mg daily): 2-4.5 hours
   c. Overdose aspirin (>4000 mg): 15-30 hours
2. Reversibility of antiplatelet effect
   a. Aspirin, clopidogrel,and prasugrel inhibit platelet function for lifetime of the platelets. Inhibition takes 7-10 days to resolve as new platelets are generated.
   b. Ticagrelor is a reversible inhibitor, so platelet function normalizes after drug clearance. Hold a minimum of 5 days to reverse effect. Unclear if platelet transfusion will be effective in reversing effect if given within 5-7 days of last dose.
3. Circulating drug or active metabolites can inhibit transfused platelets.
4. Must consider indication for use in decision to reverse
   a. Risk of coronary stent occlusion (which can be fatal) within 3 months of bare metal stent implantation; period of risk is likely longer for drug-eluting stents.
   b. Consult cardiologist or current guideline recommendations if uncertain.

Reversal of Antiplatelet Agents

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding)
• Discontinue agent 5-10 days prior to procedure	• Consider platelet transfusion prior to high risk bleeding procedures	• **HASHTI** • Consider platelet transfusion

This document summarizes selected recommendations from the: American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (9th Edition).

This guide is intended to provide the practitioner with clear principles and strategies for quality patient care and does not establish a fixed set of rules that preempt physician judgment.

For further information, please see the complete guidelines on the Chest Website at *http://journal.publications.chestnet.org/issue.aspx?journalid=99&issueid=23443* or refer to the Practice Guidelines section of the ASH website at *www.hematology.org/practiceguidelines*. You may also contact the ASH Department of Quality Improvement Programs at 202-776-0544.

Images courtesy of Kenneth Mann, PhD, and Matthew Whelihan, MS.

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Abbreviations: PCC, prothrombin complex concentrates, rFVIIa, recombinant factor VIIa

* Commonly available tests to assess for presence of dabigatran are the aPTT and for rivaroxaban the PT. These tests may be prolonged when dabigatran and rivaroxaban are used at recommended doses but they do not reliably measure the anticoagulant activity. Therapeutic levels of apixaban may not elevate the PT. To measure anticoagulant activity, the ecarin clotting time (ECT) or dilute thrombin time for dabigatran and chromogenic anti-Factor Xa assays using validated calibrators and controls may be used for rivaroxaban and apixaban.

** Dabigatran, rivaroxaban and apixaban are excreted in the urine, therefore maintain adequate diuresis. Rivaroxaban and apixaban are highly protein bound so dialysis is not effective.

C. Converting Between Anticoagulants[1]

Current anticoagulant	Anticoagulant to be converted to	Procedure
Warfarin (INR 2-3)	Dabigatran or Apixaban	Discontinue warfarin and start dabigatran or apixaban when INR <2.0
Warfarin (INR 2-3)	Rivaroxaban	Discontinue warfarin and start rivaroxaban when INR <3.0
LMWH or Heparin	Dabigatran	Start dabigatran 0-2 hours before administration of last LMWH/Heparin dose, or at same time as discontinuation of infusional heparin.
LMWH or Heparin	Rivaroxaban or Apixaban	Discontinue LMWH or heparin and initiate rivaroxaban or apixaban 0-2 hours prior to next scheduled LMWH/Heparin dose.
Dabigatran	LMWH or Heparin	CrCl ≥ 30 ml/min: start 12 hours after last dose of dabigatran CrCl < 30 ml/min: start 24 hours after last dose of dabigatran
Rivaroxaban	Warfarin (INR 2-3)	-US: Initiate warfarin and a parental anticoagulant 24 hours after discontinuation of rivaroxaban -Canada: Continue rivaroxaban concomitantly with warfarin until INR ≥2.0 and then discontinue rivaroxaban[2]
Rivaroxaban or Apixaban	LMWH or Heparin	Initiate LMWH/Heparin 24 hours after discontinuation of Rivaroxaban or Apixaban.
Apixaban	Warfarin	Discontinue Apixaban and start warfarin 24 hours later[3]. If continuous anticoagulation desired, initiate alternative anticoagulant while starting warfarin. Canada: Continue apixaban concomitantly with warfarin until INR ≥2.0 and then discontinue apixaban[1]

Abbreviations: CrCl, creatinine clearance; INR, international normalized ratio; LMWH, low molecular weight heparin

Conversion to and from rivaroxaban based on 20 mg daily dose for non-valvular atrial fibrillation.

[1] Pradaxa® product monograph 2010, Xarelto® product monograph 2011, Eliquis® product monograph 2012

[2] Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. To minimize this phenomenon, measure INR at rivaroxaban trough. If continuous anticoagulation desired, stop rivaroxaban and initiate alternative anticoagulant while starting warfarin. Xarelto® product monograph 2011

[3] Apixaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining appropriate dose of warfarin. To minimize this phenomenon, measure INR at apixaban trough.

2. Reversal of Low-Molecular-Weight Heparins [Dalteparin (Fragmin®), Enoxaparin (Lovenox®), Tinzaparin (Innohep®)] and Fondaparinux[1] (Arixtra®)

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding)

• Hold day of procedure
• Once-daily regimens
  ◦ ½ dose day prior
• Twice-daily regimens
  ◦ Hold evening dose day prior
	• Wait 12-24 hours if possible
	• Consider protamine sulfate if delay not possible for high bleeding risk procedure
		• **HASHTI**
		• Protamine sulfate
		• Consider rVIIa

[1]Fondaparinux has no specific antidote

3. Protamine Dose for Reversal of Heparin and LMWH

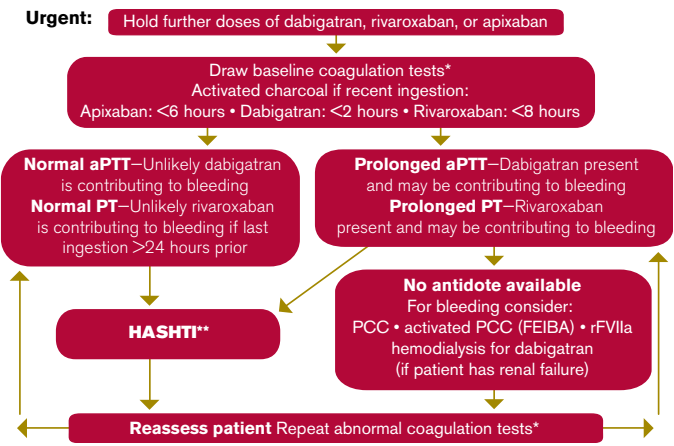
Agent*	Half-Life	Protamine Sulfate Dosing for Reversal
All		**Maximum dose is 50 mg**
Heparin	1-2 hours	• 1 mg per 90-100 units heparin given in previous 2-3 hours ◦ e.g., 25-35 mg if 1000-1250 units/hour heparin infusion
Enoxaparin	4.5 hours	• 1 mg per 1 mg Enoxaparin in previous 8 hours
Dalteparin	2.2 hours	• 1 mg per 100 units Dalteparin in previous 8 hours
Tinzaparin	3.9 hours	• 1 mg per 100 units Tinzaparin in previous 8 hours

*Half-life is longer with subcutaneous administration for all agents so may require monitoring with PTT (heparin) or anti-Xa level (LMWH) every 3 hours with repeat protamine (0.5 mg per indicated amount of LMWH or heparin) if bleeding continues.

4. Reversal of Dabigatran, Rivaroxaban or Apixaban

Non-urgent: Hold further doses (refer to table for recommended duration). Consider longer times for major surgery, placement of spinal or epidural catheter or port.

Dabigatran	Rivaroxaban	Apixaban
CrCl > 50 ml/min: Hold 1-2 days CrCl < 50 ml/min: Hold 3-5 days or longer. Half Life: 12-14 hours Drug presence may be assessed by thrombin time.	Hold at least 24 hours Half Life: 5-9 hours (with normal renal function). Drug presence may be assessed by anti-Xa assay.	Hold 24 to 48 hours Half Life: 8-15 hours. Drug presence may be assessed by anti-Xa assay.



I. ANTICOAGULANT DOSING

A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

General Considerations

1. Round weight-based dose to nearest prefilled syringe size for LMWH.
2. No dose cap for obesity except dalteparin in cancer patients.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or <60 kg.
4. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets declining.
   - If heparin exposure in previous 3 months, CBC on day 3 rather than day 7.
5. Use LMWH with caution if at all, and monitor anti-Xa levels if creatinine clearance (CrCl) <30 ml/min.

Subcutaneous Dosing

Enoxaparin:	1 mg/kg every 12 hours or 1.5 mg/kg daily - For cancer patients and those at high bleeding or thrombosis risk, favor twice-daily dosing
Dalteparin:	200 IU/kg daily or 100 IU/kg every 12 hours
Tinzaparin:	175 IU/kg daily
Fondaparinux:	<50 kg: 5 mg daily. 50-100 kg: 7.5 mg daily. >100 kg: 10 mg daily
Unfractionated heparin:	333 IU/kg x 1, then 250 IU/kg every 12 hours

B. Initial Warfarin Dosing for Venous Thromboembolism or Atrial Fibrillation in Ambulatory Outpatients, Target INR 2.0-3.0

General Considerations

1. Obtain baseline PT/INR and investigate if abnormal.
2. Determine use of potential warfarin interacting medications.
3. Document target INR and prescribed warfarin tablet strength.
4. Provide patient education on safety, monitoring, drug and food interactions.
5. For acute thrombosis, overlap with heparin/LMWH/fondaparinux for 5+ days until INR therapeutic.
6. Recommend first INR check on day 3-4.
7. Clinical judgment should supersede this nomogram.

Day	INR	DAILY DOSE
1-3	Not required	5 mg*
3 or 4	1.0-1.3	7.5 mg
	1.4-1.5	5 mg
	1.6-1.8	5/2.5 mg alternating
	>1.9	2.5 mg
	≥2.0	Hold x 1 day, then 2.5 mg†
7 & 10	≤ 1.5	Increase by 15% of ADD
	1.6-1.9	Increase by 10% of ADD
	2.0-3.0	**No Change**
	3.1-3.5	Decrease by 10% of ADD
	3.6-4.0	Decrease by 15% of ADD
	> 4.1	Hold 1 day, decrease by 15% (or more)†
	≥ 6.0	Consider Vitamin K†

Abbreviations: ADD = average daily dose

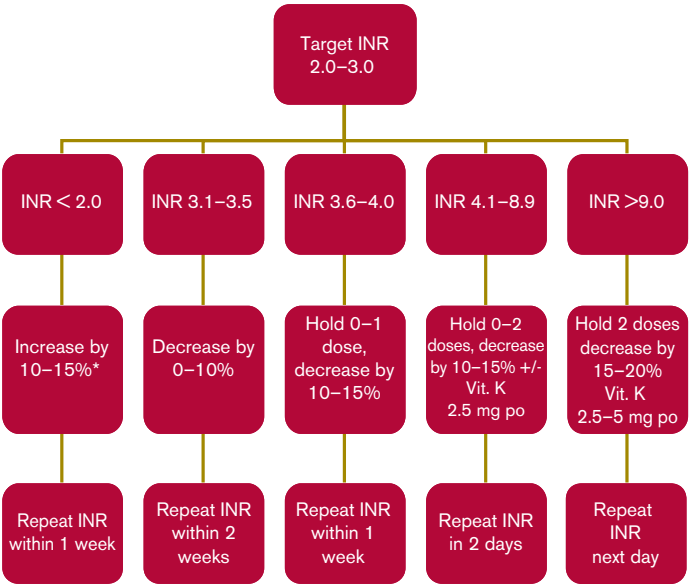
* 2.5 mg for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity; 5-7.5 mg for young healthy patients

† Check INR more frequently

C. Chronic Warfarin Dose Adjustment in Non-Bleeding Patients

This nomogram is suggested for **non-bleeding patients** with target INR 2.0-3.0 who are out of range and who are not at high risk of bleeding.

1. If INR >3.0 confirm no bleeding.
2. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.
3. Clinical judgment should supersede this nomogram.



*Consider 15% increase if INR ≤1.5 without explanation

D. Dabigatran Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

Dose:

CrCl >30 ml/min*: 150 mg orally, twice daily
Avoid use in patients with CrCl <30 and taking P-glycoprotein inhibitors (e.g., dronedarone, ketoconazole)
Avoid use in patients taking P-glycoprotein inducers (e.g., rifampin)

Dose adjustments:

CrCl 15-30 ml/min*: 75 mg orally, twice daily
CrCl 30-50 and taking P-glycoprotein inhibitors: 75 mg orally, twice daily

No recommendation for CrCl <15 ml/min or on dialysis. Outside US—patients with CrCl >30 ml/min and age >75 years or propensity for GI bleeding: 110 mg twice daily.

E. Rivaroxaban Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation and to Treat Venous Thromboembolism

- Avoid use in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, ritonavir).
- Avoid use in patients taking strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort); this may lead to reduced rivaroxaban plasma concentrations.

1. Atrial fibrillation
   - CrCl >50 ml/min: 20 mg once daily with evening meal*
   - CrCl 15-50 ml/min: 15 mg once daily with evening meal*
   - CrCl <15 ml/min: Avoid use

*US labeling: Outside US—give with a meal at same time each day; may be given with breakfast.

2. Venous Thromboembolism
   - 15 mg every 12 hours for 21 days followed by 20 mg once daily, taken with food
   - Not recommended if CrCl <30 ml/min

F. Apixaban Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

Dose: 5 mg twice daily
- CrCl <15 ml/min: Avoid use
- Avoid use in patients taking strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort).

Dose adjustments:
Dose 2.5 mg twice daily if:
1. Two or more of the following are present:
   - Age ≥80 years
   - Body weight ≤60 kg
   - Serum creatinine ≥1.5 mg/dL (133 µmol/L)

   OR
2. Use of strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g.,ketoconazole, itraconazole, ritonavir, clarithromycin)

Do not administer apixaban in patients with both #1 and #2.

II. ANTICOAGULANT REVERSAL

A. General Principles of Management of Anticoagulant-Associated Bleeding

HASHTI
1. **H**old further doses of anticoagulant
2. Consider **A**ntidote
3. **S**upportive treatment
   a. Volume resuscitation (intravenous fluids)
   b. Hemodynamic support (inotropes, monitoring)
4. Local or surgical **H**emostatic measures
   a. Anti-fibrinolytic agents can be considered (aminocaproic acid, tranexamic acid)
5. **T**ransfusion
   a. Red blood cells for severe or symptomatic anemia
   b. Platelets if thrombocytopenia (<50 x 10^9/L) or patient on long-acting antiplatelet agents
6. **I**nvestigate for bleeding source

Definitions Used for Reversal Situations

Non-urgent:	Reversal is elective (procedures >5 days away)
Urgent (without bleeding):	Reversal needed within hours
Urgent (with bleeding):	Immediate reversal

B. Agents to Stop Bleeding

Agent	Dose	Comments
Vitamin K	1-10 mg IV/PO	• Infusion reactions rare; administer over 20-30 min • Takes 6 (IV) to 24 (PO) hours to reverse warfarin • Large doses can cause warfarin resistance on resumption • Subcutaneous or intramuscular administration not recommended
Protamine sulfate	12.5-50 mg IV	• Full reversal of unfractionated heparin • 60-80% reversal of LMWH • No reversal of fondaparinux
Platelets	1 apheresis unit 5-8 whole blood units	• Used in patients receiving antiplatelet therapy • Raise platelet count by 30 x 10^9/L • Goal platelet count 50-100 x 10^9/L (indication dependent)
Frozen plasma (FFP)	10-30 mL/kg (1 unit = ~250 ml)	• Replaces all coagulation factors, but cannot fully correct ◦ Hemostasis usually requires coagulation factor levels ~30% ◦ Factor IX may only reach 20% • Short half-life, may need repeat dosing after 6 hours • Large volume, can take hours to thaw and infuse
Prothrombin complex concentrates (PCC)	25-50 units/kg IV (lower doses studied)	• Rapid, complete INR correction in warfarin-treated patients • Small volume infusion over 10-30 minutes • Risk of thrombosis 1.4%; contraindicated with history of HIT • Short half-life, may need repeat dose after 6 hours • Consider concurrent FFP if 3-factor PCC used
Recombinant factor VIIa (rFVIIa)	15-90 micrograms/kg (lower doses studied)	• Rapid infusion of small volume • Rapid complete INR correction in warfarin patients, but may not correct bleeding because only restores FVIIa • Risk of thrombosis 5-10% • Short half-life, may need repeat dose after 2 hours
Aminocaproic acid	4-5 g IV/po over 1 hr, then 1 g/hr x 8 hrs (maximum dose 30 g/24 hrs)	• May increase risk of thrombosis • May accumulate in patients with renal impairment, reduce loading dose or infusion rate • Caution or avoid use in hematuria due to upper urinary tract origin
Tranexamic acid	1300 mg po q8h	• Labeled indication for menorrhagia • Use for other indications currently off label

1. Reversal of Warfarin (Coumadin®, Jantoven®)

Non-Urgent	Urgent (Not bleeding)	Urgent (Bleeding)
• Stop 5 days prior to procedure • Check INR 1-2 days prior ◦ If INR >1.5 administer vitamin K 1-2 mg PO	• If procedure can be delayed 6-24 hours, vitamin K 5-10 mg PO/IV; otherwise: ◦ FFP or PCC prior to procedure. Repeat in 6-12 hours if INR >1.5 and ◦ Vitamin K 5-10 mg PO/IV if sustained reversal is desired	• **HASHTI** • Vitamin K 5-10 mg IV; repeat in 12 hours as needed • PCC or FFP; repeat every 6 hours as needed