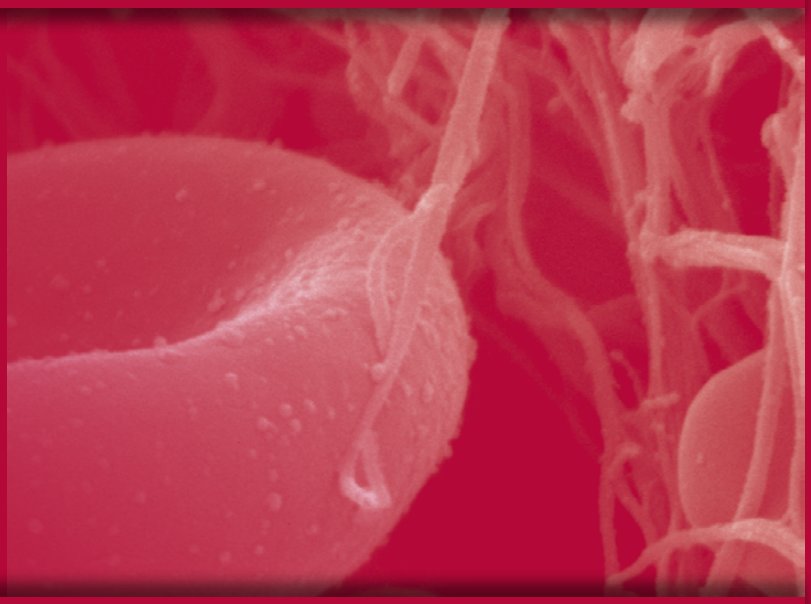
QUICK REFERENCE

2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults



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AMERICAN SOCIETY OF HEMATOLOGY®

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.
2. No dose cap for obesity except dalteparin in cancer patients.
3. Consider monitoring anti-Xa heparin levels for weight >120 kg or <60 kg.
4. Repeat CBC day 7 to assess for heparin-induced thrombocytopenia.
   a. If heparin exposed in prior 6 months, CBC on day 3.
5. LMWH not recommended if creatinine clearance (CrCl) <30 ml/min.

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
In cancer patients for long-term treatment: 200 IU/kg daily for 4 weeks (cap at 18,000 IU), then:
a. ≤56kg: 7,500 IU daily
b. 57-68 kg: 10,000 IU daily
c. 69-82 kg: 12,500 IU daily
d. 83-98 kg: 15,000 IU daily
e. >98 kg: 18,000 IU daily

Tinzaparin: 175 IU/kg daily

Fondaparinux: Daily dose: <50 kg: 5 mg. 50-100 kg: 7.5 mg. >100 kg: 10 mg.

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.

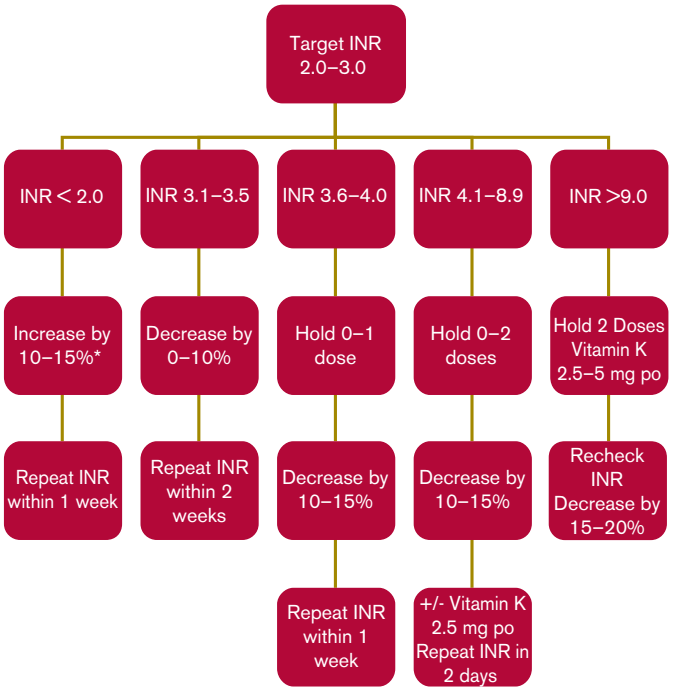
Day	INR	DAILY DOSE
1-3	–	5mg*
3 or 4	1.0-1.3	7.5mg
	1.4-1.5	5mg
	1.6-1.8	5/2.5 mg alternating
	>1.9	2.5mg
	≥2.0	Hold x 1 day, then 2.5mg†
7 & 10	≤ 1.5	Increase by 15% of ADD
	1.6-1.9	Increase by 10% of ADD
	2.0-3.0	**No Change**
	3.1-3.5	Decrease by 10% of ADD
	3.6-4.0	Decrease by 15% of ADD
	> 4.1	Hold 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. Refer to nomogram.



*Consider 15% increase if INR ≤1.5 without explanation

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

CrCl >30 ml/min: 150 mg orally, twice daily
Outside US: 110 mg twice daily for age >75 or propensity for GI bleeding

CrCl 15-30 ml/min: 75 mg orally, twice daily*

* U.S. labeling; no recommendation for CrCl <15 ml/min or on dialysis

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: volume resuscitation, inotropes as needed
4. Local or surgical **H**emostatic measures: topical agents (aminocaproic acid, tranexamic acid)
5. **T**ransfusion (red cells, platelets, FFP as indicated)
6. **I**nvestigate for bleeding source

Definitions Used for Reversal Situations

Non-urgent: Reversal is elective (procedures >7 days away)
Urgent (without bleeding): Reversal needed within hours
Urgent (with bleeding): Emergency reversal

B. Anticoagulant Reversal Agents

Agent	Dose	Comments
Vitamin K	1-10 mg IV/PO, not SQ or IM	• 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
Protamine sulfate	12.5-50 mg IV	• Full reversal of unfractionated heparin • 60%-80% reversal of LMWH • No reversal of fondaparinux

Agent	Dose	Comments
Platelets	1 apheresis unit 5-8 whole blood units	• 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 = ~250ml)	• Replaces all coagulation factors, but cannot fully correct ◦ Hemostasis usually requires factor levels ~30% ◦ Factor IX may only reach 20% • May need repeat dose after 6 hours • Large volume, takes hours to thaw and infuse
Prothrombin complex concentrates (PCC)	25-50 units/kg IV (lower doses studied)	• Rapid INR correction in warfarin patients • Small volume infusion over 10-30 minutes • Risk of thrombosis 1.4% • Contraindicated with history of HIT • May need repeat dose after 6 hours • Consider adding FFP if 3-factor PCC used
Recombinant factor VIIa (rFVIIa)	15-90 units/kg (lower doses studied)	• Rapid infusion of small volume • Rapid INR correction of warfarin, but may not correct bleeding because only restores FVIIa • Risk of thrombosis 5-10% • May need repeat dose after 2 hours

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 high and ◦ Vitamin K 5-10 mg PO/IV if sustained reversal is desired	• HASHTI • Vitamin K 5-10 mg IV; repeat every 12 hours as needed • PCC or FFP; repeat every 6 hours as needed

2. Reversal of Low-Molecular-Weight Heparins (Enoxaparin/ Lovenox®, Dalteparin/Fragmin®, 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

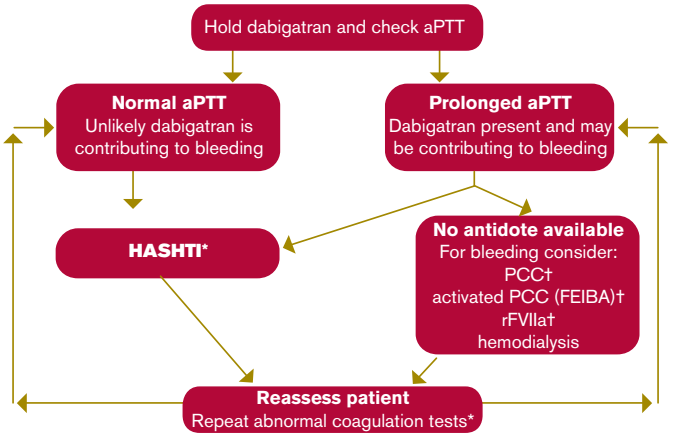
Agent*	Half-Life	Protamine Sulfate Dosing for Reversal
All Heparin	1-2 hours	**Maximum dose is 50 mg** • 1 mg per 90-100 units heparin given in previous 2-3 hours • e.g., 25-35 mg if 1000-1250 units/hour heparin infusion
Enoxaparin	4.5 hours	• 1 mg per 1 mg Enoxaparin in previous 8 hours
Dalteparin	2.2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

Non-urgent: Hold further doses of dabigatran
CrCl > 50 ml/min: Hold 1-2 days
CrCl < 50 ml/min: Hold 3-5 days
Consider longer times for major surgery, placement of spinal or epidural catheter or port

Urgent:



Abbreviations: PCC = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa
* Dabigatran primarily excreted in the urine, therefore maintain adequate diuresis
† Experimental evidence supports these agents but no clinical trial data available; PCC may not lower PTT

C. Converting Anticoagulants to and from Dabigatran[1]

Current Anticoagulant	Anticoagulant to be Converted to	Procedure
Warfarin (INR 2-3)	Dabigatran	Discontinue warfarin and start dabigatran when INR <2.0
Dabigatran	Warfarin (INR 2-3)	• CrCl >50 ml/min: start warfarin 3 days before stopping dabigatran • CrCl 31-50 ml/min: start warfarin 2 days before stopping dabigatran • CrCl 15-30 ml/min: start warfarin 1 day before stopping dabigatran • CrCl <15 ml/min: no recommendation
LMWH, heparin	Dabigatran	Start dabigatran 0-2 hours before administration of last heparin/LMWH dose, or at same time as discontinuation of infusional heparin
Dabigatran	LMWH, 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

Abbreviations: CrCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin
[1] Pradaxa ® product monograph, 2010

III. Antiplatelet Agent Reversal

Aspirin, Dipyridamole/Persantine®/Aggrenox®, Clopidogrel/Plavix®, Ticlopidine/Ticlid®, Prasugrel/Effient®, Ticagrelor/Brilinta®

General Considerations

1. Half-lives
   a. Clopidogrel, ticlopidine, 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 anti-platelet effect
   a. Aspirin, clopidogrel, ticlopidine, and prasugrel inhibit platelet function for lifetime of platelet. 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.
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 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** • Platelet transfusion

About this Clinical Quick Reference Guide

This document summarizes selected recommendations from the: American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th 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.

Complete guidelines are available at:

Chest website:
http://chestjournal.chestpubs.org/content/133/6_suppl/110S.abstract

ASH website: *www.hematology.org/practiceguidelines*

For further information, contact the ASH Department of Government Relations, Practice, and Scientific Affairs at 202-776-0544.

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

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