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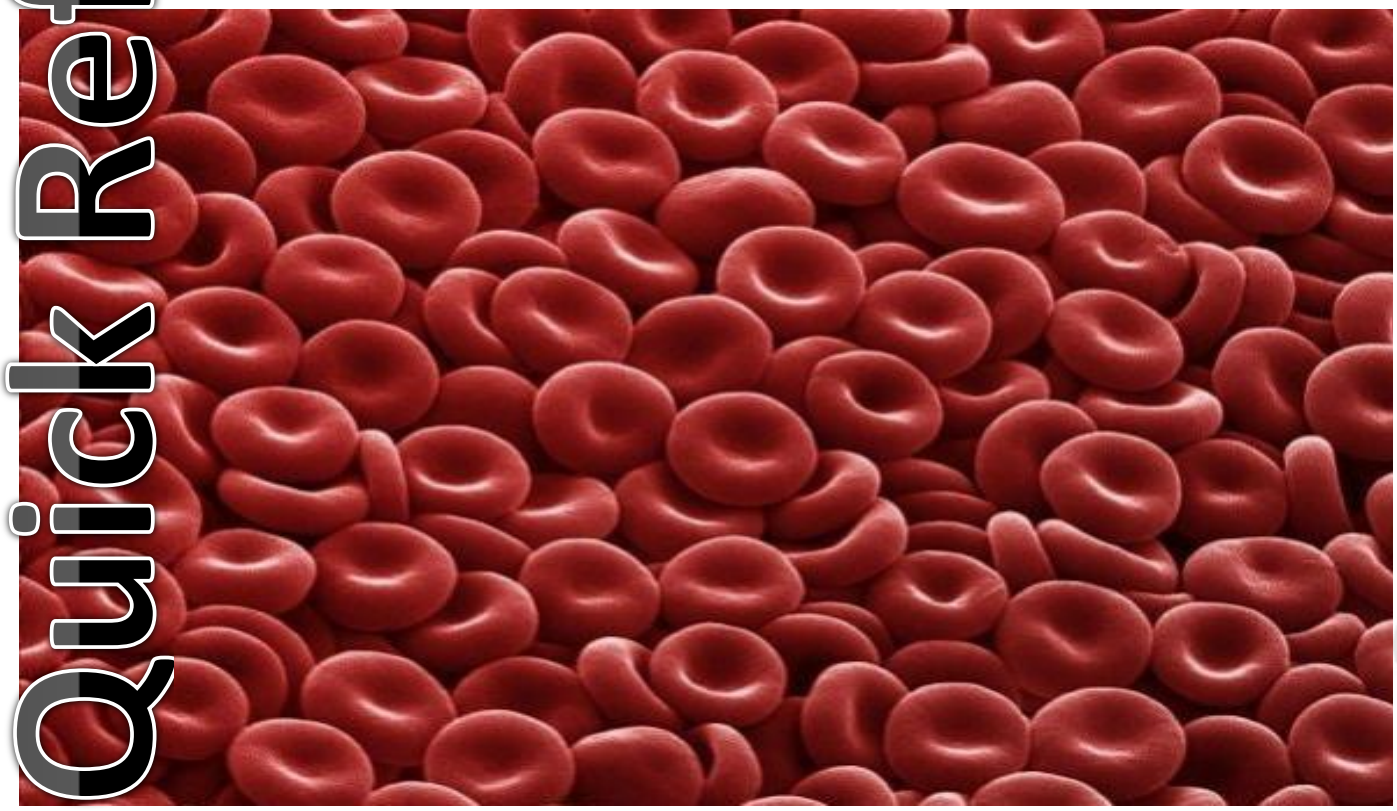
Quick Reference

EMMC Guide on Management of Anticoagulant and Anti-Platelet Agent Associated Bleeding Complications in Adults

February, 2013



EMHS MEMBER

Quick Index To Reversal Recommendations

Anti-Platelet Medications

Anticoagulant Medications

General Principles of Management of Anticoagulant-Associated Bleeding

HASHTI

Hold further doses of anticoagulant (or anti-platelet agent)

Consider ***A***ntidote (e.g. Vitamin K, protamine)

*S*upportive treatment:

- volume resuscitation, inotropes as needed
- optimize oxygenation

Hemostatic measures:

- Local or topical agents (fibrin glue, sealants, hemostatic agents, topical aminocaproic acid or tranexamic acid)
- Systemic *h*emostatic measures (intravenous tranexamic acid)
- Surgical intervention
- Interventional radiology, e.g. embolization

Transfusion

- Red cells, platelets, FFP, cryo as indicated
- Factor concentrates: Factor VIIa, Prothrombin Complex Concentrate (PCC), FEIBA

Investigate for bleeding source

Anticoagulant Reversal Agents/Procoagulants/Anti-Fibrinolytics

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 • Use smaller doses if mechanical heart valve (1 -2 mg)
Protamine sulfate	12.5-50 mg IV	• Full reversal of unfractionated heparin • 60-80% reversal of LMWH • No reversal of fondaparinux • May require repeat dose after a few hours
Platelets	1 apheresis unit	• Raise platelet count by 30 x 10^9/L • Goal platelet count 35-100 x 10^9/L (indication dependent)

Frozen Plasma (FP)	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%
		• Usually in combination with PCC
		• Risk of acute lung injury and circulatory overload
		• Large volume, takes hours to thaw and infuse, must be type specific
		• May need repeat dose after 6 hours

Prothrombin complex concentrates (PCC) Profilnine®	30-50 units/kg IV	• Preferred for rapid INR correction in warfarin patients • May be useful in reversal of rivaroxiban (Xarelto) • Not proven useful in reversal of dabigatran (Pradaxa) • Small volume infusion over 10-30 minutes • Risk of thrombosis low • Contraindicated in active HIT with thrombosis • Consider adding Frozen Plasma FP (1-2 units), if INR greater than 4.9 • May need repeat dose after 6 hours
Recombinant factor VIIa (rFVIIa) NovoSeven ®	15-30 units/kg	• Infusion of small volume over 10-20 minutes • Rapid INR correction of warfarin, but may not correct bleeding because only restores FVIIa • Unknown value in correcting bleeding with DTI's, anti- Xa inhibitors, clopidogrel and related drugs • Risk of thrombosis 5-10% with higher doses • Studies fail to show mortality benefit • If patient still bleeding, consider dose increase to 30-60 units/kg, if dose repeated. • May need repeat dose after 2 hours
Amicar	4-5 grams over one hour	• Loading dose 4-5 grams over one hour. Followed by one gram/hour maximum 30 grams/day.
Tranexamic Acid	10-30 mg/kg	• Loading dose usually 10-30 mg/kg, followed by maintenance dose of 1-2 mg/kg per hour.
DDAVP	0.3-0.4 mcg/kg	• Infuse over 30 minutes in 100 ml saline

Definitions Used for Reversal Situations

Non-urgent:	Reversal is elective (procedures > 12-24 hours)
Urgent (without bleeding):	Reversal needed within hours (6-12 hours)
Urgent (with bleeding):	Emergency Reversal

Reversal of Warfarin (Coumadin®): see Warfarin reversal Power Plan

Laboratory testing: Prothrombin Time (PT/INR)

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding or surgery within 6 hours)
• Stop 5 days prior to procedure • Check INR 1-2 days prior • If INR greater than 1.5 administer Vitamin K 1-2 mg PO • For supra-therapeutic INR, consider Vitamin K 5-10 mg PO	• If procedure can be delayed 6-24 hours, vitamin K 5-10 mg IV; <u>Otherwise:</u> • PCC prior to procedure. In addition, consider 1-2 units of FP for INR greater than 4.9. Repeat every 6-12 hours until 2 successive results are at desired target • Vitamin K, 5-10 mg IV if sustained reversal is desired	• HASHTI • Vitamin K, 5-10 mg IV; repeat every 12 hours as needed • PCC or PCC plus Frozen Plasma (FP); repeat every 4-6 hours as needed

Reversal of Low-Molecular-Weight Heparins (enoxaparin/Lovenox®, Dalteparin/Fragmin®, Tinzaparin/Innohep® and Fondaparinux[+] (Arixtra®)

Laboratory testing: When appropriate, anti-Xa assay

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding or surgery within 6 hours)

• 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 procedures – will reverse 60% of activity (1mg for every 1 mg enoxaparin)
		• HASHTI
		• Protamine sulfate (1mg for every 1 mg of enoxaparin)
		• No proven role for rVIIa or PCC.
		• No role for Frozen Plasma (FP)

[+]Fondaparinux has no specific antidote. Consider 30 µg/kg, Factor VIIa for life-threatening bleeding (no proven benefit).		

Protamine Dose for Reversal of Heparin and LMWH

Agent	Half-Life*	Protamine Sulfate Dosing Reversal

Standard Heparin	1-2 hours	MAXIMUM dose is 50 mg
		• 1 mg per 100 units heparin given in previous 2-3 hours
		  ○ e.g. – 20-30 mg if 1000 units/hour heparin infusion
		  ○ Check thrombin time in 2 hours and consider more protamine if still prolonged

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 for LMWH or heparin) if bleeding continues.		

Reversal of Bivalirudin (Angiomax®)

Laboratory testing: PTT for monitoring; Ecarin Clot Time and Activated Clot Time may be used

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding or surgery within 6 hours)
• Short half-life ($t_{1/2}$ =25 minutes) • Cleared by the kidneys (20%) and by proteolytic cleavage	• If procedure can be delayed, delay until PTT, Ecarin Clot Time (ECT) or Activated Clot Time (ACT) returns to normal	• HASHTI • No antidote • Drug is can be removed by hemodialysis but generally not indicated due to short half-life • Consider Factor VIIa (no proven benefit) only for life-threatening intracranial hemorrhage

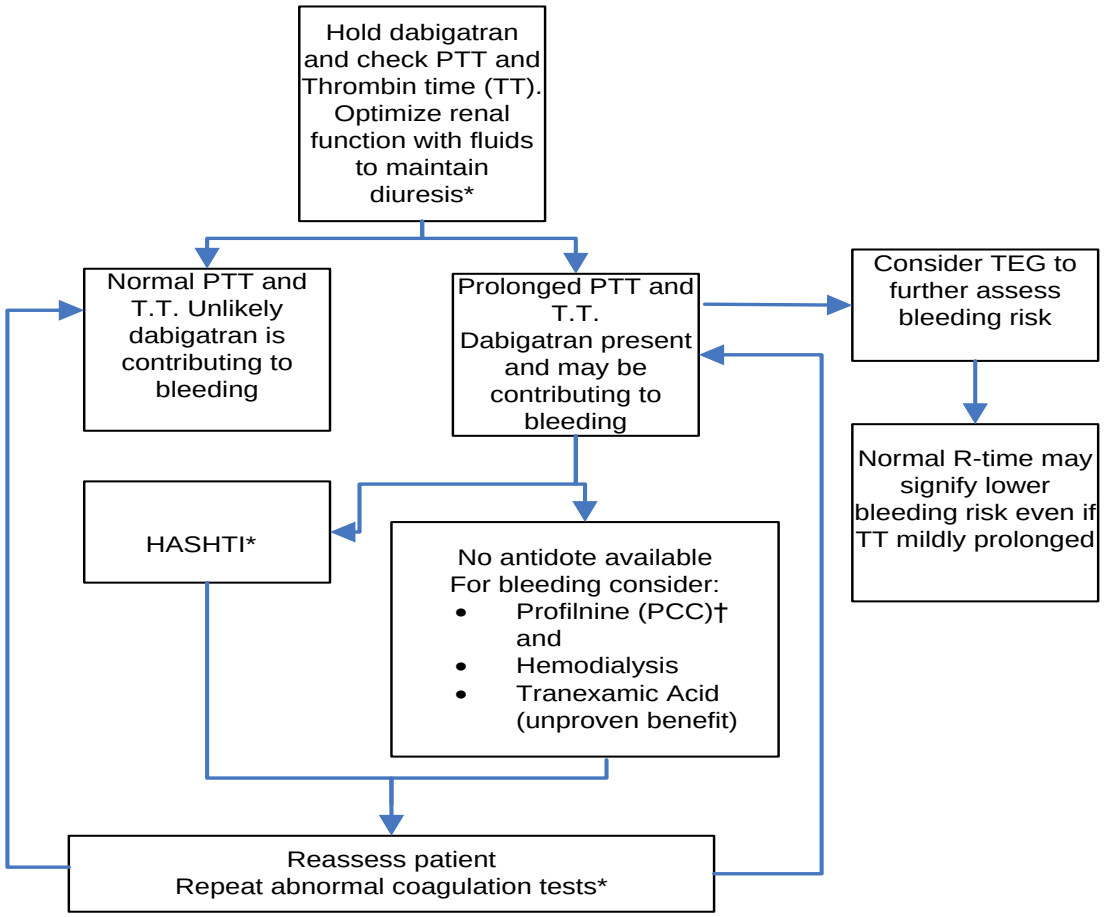
Reversal of Dabigatran (Pradaxa)

Laboratory testing: Ecarin clotting time can be used to adjust therapy; thrombin time is too sensitive but a normal result rules out Dabigatran; PTT will be prolonged but does not predict bleeding; PT/INR may be increased

Non-Urgent: Hold further doses of dabigatran

- CrCL greater than 50 ml/min: Hold 1-2 days
- CrCl less than 50ml/min: Hold 3-5 days
- Consider longer times for major surgery, placement of spinal or epidural catheter or port

Urgent or Emergent: (Serious bleeding or immediate need for major surgery):



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

Reversal of Apixaban (Eliquis)

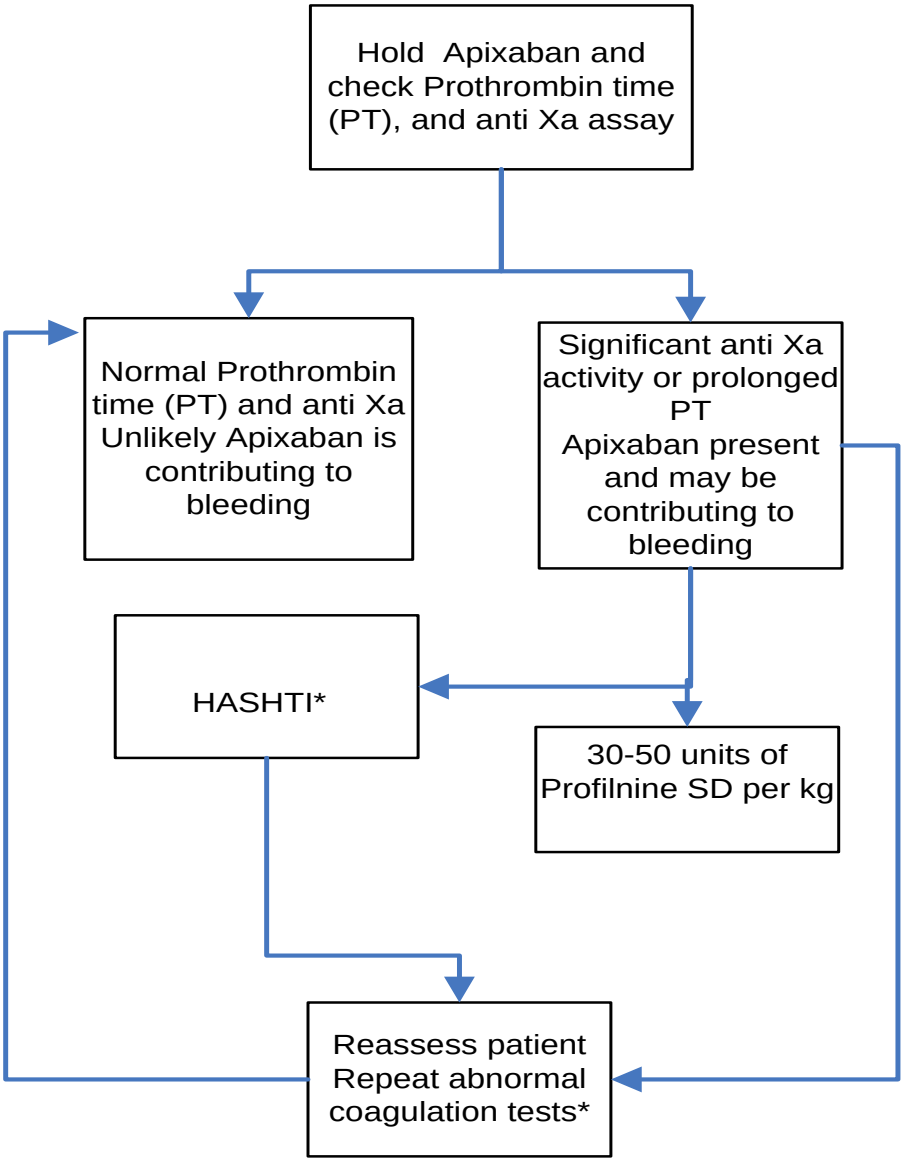
Laboratory testing: PT/INR prolonged; PTT prolonged at higher concentrations; Changes in PT/PTT small at therapeutic doses and variable; Anti-Xa accurate if proper standard is used

Non-Urgent: Hold further doses of Apixaban

- For at least 24 hours before surgery or procedures for a low risk of bleeding or 48 hours for elective surgery or procedures with a moderate or high risk of clinically significant bleeding
- For mild to moderate bleeding consider prothrombin complex concentrate, 30-50 micrograms/kg

Urgent or Emergent: (Serious bleeding or immediate need for major surgery):

- There is no established way to reverse the anticoagulant effect of apixaban which can be expected to persist for at least 24 hours (2 half-lives) in patients with normal renal function.
- A specific antidote is not available
- Apixaban is not dialyzable
- If bleeding occurs within a few hours of the last dose, activated oral charcoal may reduce absorption
- Prothrombin Complex Concentrate may be considered but has not been evaluated in clinical trials


Hold Apixaban and check Prothrombin time (PT), and anti Xa assay
Normal Prothrombin time (PT) and anti Xa Unlikely Apixaban is contributing to bleeding
Significant anti Xa activity or prolonged PT Apixaban present and may be contributing to bleeding
HASHTI*
30-50 units of Profilnine SD per kg
Reassess patient Repeat abnormal coagulation tests*

Antiplatelet Agent Reversal

COX-1 Inhibitors
Aspirin, Dipyridamole/Persantine®/Aggrenox®

P2Y12 Inhibitors
Clopidogrel/Plavix®, Ticlopidine/Ticlid®, Prasugrel/Effient®, Ticagrelor/Brilinta®

GPIIbIIIa Inhibitors
Eptifibatide/Integrilin®, Tirofiban/Aggrastat®

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 (greater than 4,000 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. Half-life is 7-9 hours for drug and its active metabolite.
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
        i. Period of risk is likely longer for drug-eluting stents, perhaps up to one year.
    b. Consult cardiologist if uncertain.
    c. Risk of reversal in some cases may be worse than risk of bleeding.

Reversal – Aspirin or Aggrenox

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding or surgery within 6 hours)
Discontinue 2 days prior to procedure Do NOT discontinue in patients treated for coronary or cerebrovascular disease	• Laboratory testing to evaluate platelet function, e.g. PFA 100 to evaluate for aspirin effect if neurosurgery or eye surgery anticipated	• HASHTI • Laboratory testing to evaluate platelet function • Consider platelet transfusion (1 unit) for critical neurosurgery/eye surgery ONLY; usually not necessary • DDAVP, µg/kg as alternative to platelets • Consider hematology or transfusion medicine consult

Reversal – P2 Y12 Inhibitors (Clopidogrel and Prasugrel)

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding or surgery within 6 hours)
Discontinue agent 5-10 days prior to procedure	• Laboratory testing to evaluate platelet function, e.g.; Plavix inhibition test for Plavix, Prasugrel, Ticagrelor • Consider platelet transfusion (1 unit) if inhibition test result is < 195 PRU prior to high risk bleeding procedures • Recommend hematology or transfusion medicine consult	• HASHTI • Laboratory testing to evaluate platelet function • Platelet transfusion (1 unit) if inhibition test result is < 195 PRU; 2 units if critical neurosurgery/eye surgery or if dual agent therapy • Consider fibrinogen concentrate, 30 mg/kg if fibrinogen is < 200 mg/dl • Recommend hematology or transfusion medicine consult

Reversal – GP IIb/IIIa Inhibitors (Integrilin and Aggrastat)

Non-Urgent	Urgent (Not Bleeding)	Urgent (Bleeding or surgery within 6 hours)
Discontinue agent; will be cleared in 2-4 hours	• Wait 2-4 hours for elimination of drug • If platelet count < 20,000/µl, consider transfusion of 1 unit of platelets (Integrilin rarely associated with thrombocytopenia	• HASHTI • Platelet transfusion (1 unit) if intervention is truly emergent or serious bleeding

APPENDIX

Anticoagulant Conversion Chart		
Current Anticoagulants	Anticoagulant to be Converted to	Procedure
Warfarin (INR 2-3)	Dabigatran	Discontinue warfarin and start dabigatran when INR is less than 2.
Dabigatran	Warfarin (INR 2-3)	• CrCl greater than 50 ml/min: start warfarin 3 day 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 less than 15 ml/min: no recommendation
LMWH, fondaparinux, heparin	Dabigatran	• Start dabigatran when the next dose of LMWH, fondaparinux or heparin would have been due. • Start dabigatran at same time as discontinuation of heparin infusion.
Dabigatran	LMWH, fondaparinux, heparin	• CrCL greater than 30 ml/min: start 12 hours after last dose of dabigatran • CrCL less than 30 ml/min: start 24 hours after last dose of dabigatran *(not fondaparinux)*
Warfarin	Rivaroxaban	• Discontinue warfarin • Start rivaroxaban when the INR is less than 3 to avaoid periods of inadequate anticoagulation.
Rivaroxaban	Warfarin	• Stop rivaroxaban and start warfarin with a full anticoagulant bridging dose of LMWH or fondaparinux. • Continue both warfarin and anticoagulant bridge for a minimum of 5 days and until the INR is within the desired therapeutic range.
LMWH, fondaparinux, heparin	Rivaroxaban	• Start rivaroxaban when the next dose of LMWH, fondaparinux or heparin would have been due. • Start rivaroxaban at same time as discontinued of heparin infusion.
Rivaroxaban	LMWH, fondaparinux, heparin	• Start LMWH, fondaparinux or heparin when the next dose of rivaroxaban would have been due.

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

[1] Pradaxa ® product monograph, 2010

This document summarizes selected recommendations from the: American College of Chest Physicians Evidenced-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition), practice guidelines from ASH and recommendations from other references.

*This guide is intended to provide the practitioner with the clear principles and strategies for quality patient care and does **not** establish a fixed set of rules or a standard of care that preempt physician judgment. Many of the recommendations are based on low level evidence and expert opinion.*

References:

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