Perioperative Management of Patients who are Receiving New Anticoagulants

James D. Douketis MD, FRCPC, FACP, FCCP

Department of Medicine,

St. Joseph's Healthcare Hamilton and McMaster University, Hamilton, Canada

Potential conflict of interests

12e congrès annuel de la SSVQ

Les URGENCES vasculaires : une approche interdisciplinaire

23, 24 et 25 novembre 2012

Dr James Douketis, Speaker

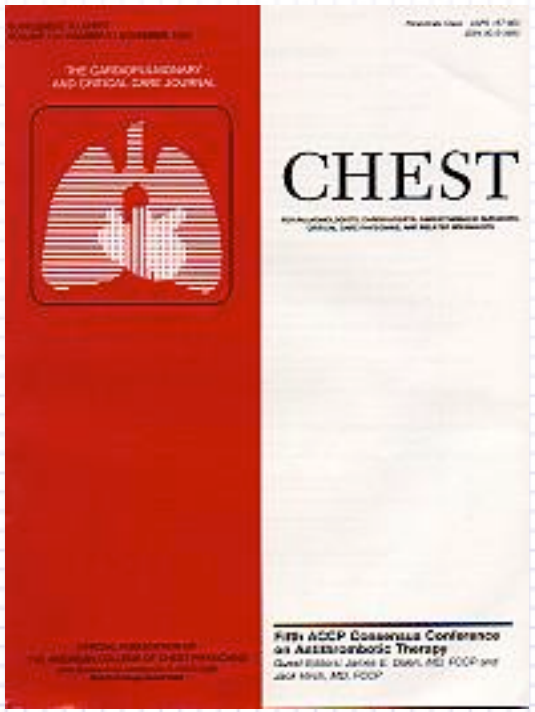
Consultant, advisor : Boehringer-Ingelheim 2010-2012
Consultant, advisor : Bristol-Meyer Squib 2010-2011
Consultant, advisor : Bayer 2011-2012

Presentation Objectives

- **To have an approach to the perioperative management of patients receiving warfarin and require elective surgery.**
- **To have an approach to the perioperative management of patients who are receiving a NOAC and require elective surgery.**
- **To be able to interpret *coagulation tests* in patients receiving a NOAC.**

Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (9th Edition)

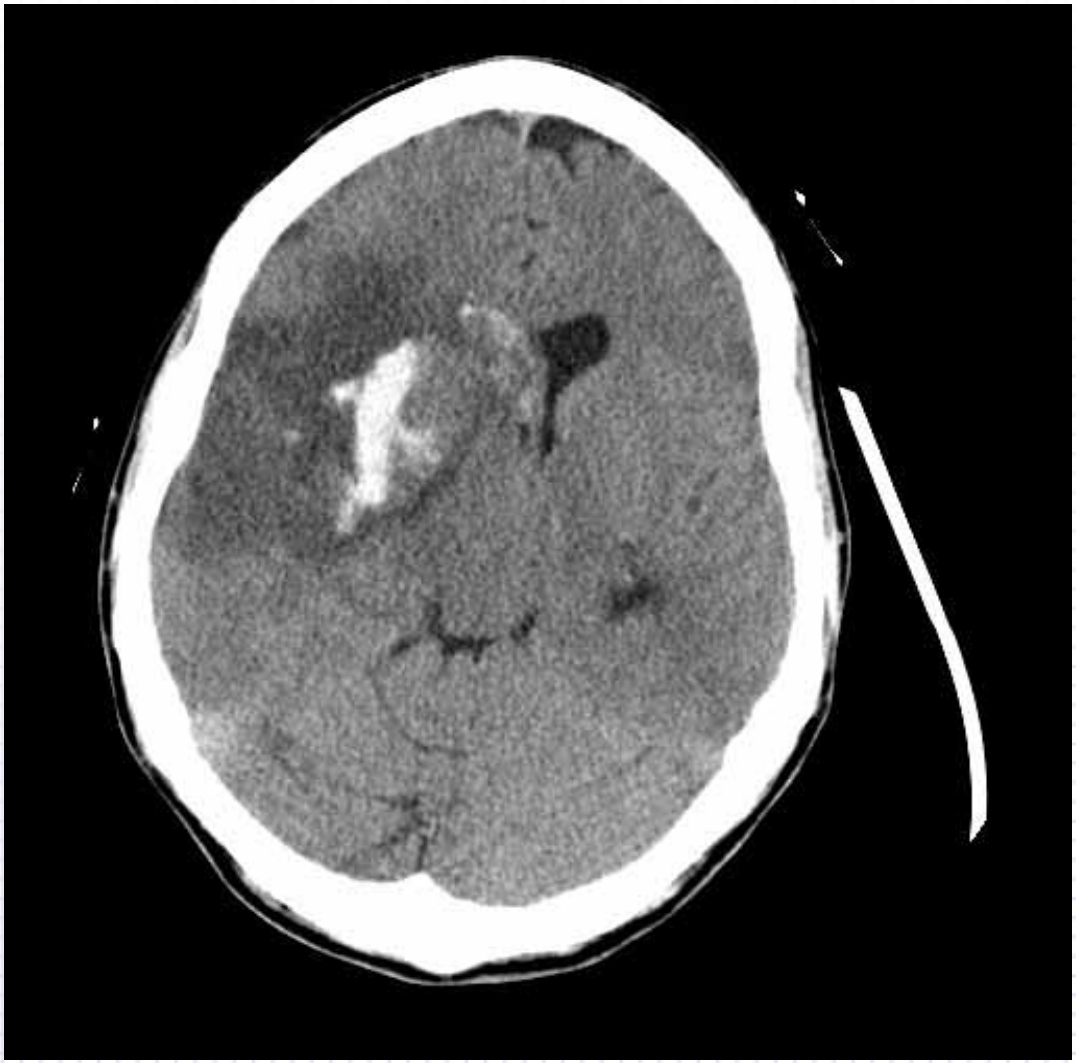
Perioperative Management of Antithrombotic Therapy



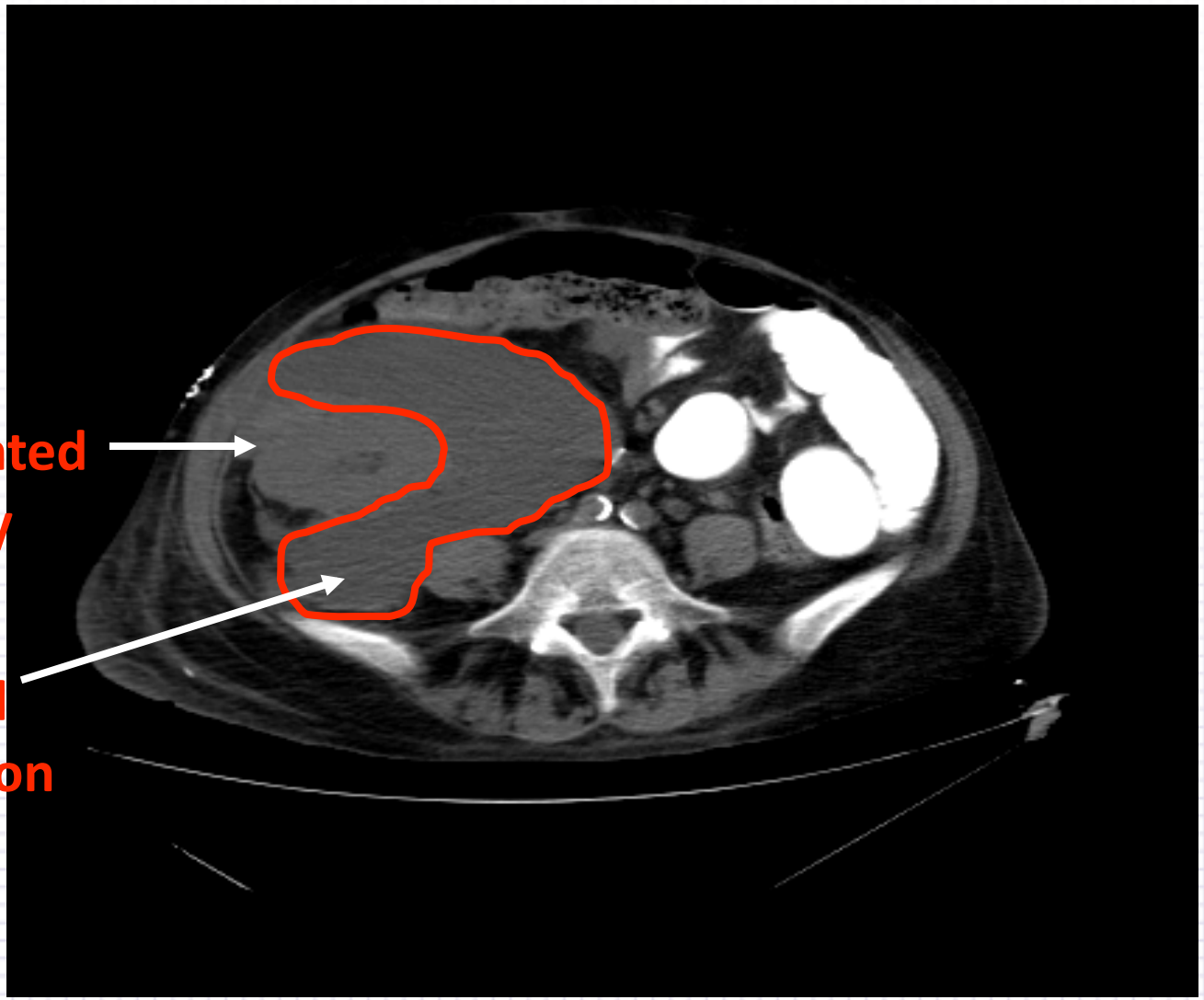
Chest 2012;141(Suppl):e326S-e350S

http://www.chestjournal.org

Hemorrhagic Transformation of Embolic Stroke



Perinephric (transplant) Hematoma



Perioperative Anticoagulation: Key Questions

Is interruption of antithrombotic (anticoagulant or antiplatelet) therapy in the perioperative period needed?

In patients who are undergoing minor surgical or invasive procedure (e.g., dental, skin or cataract), interruption of antithrombotic therapy may not be required.

Perioperative Anticoagulation: Key Questions

***If antithrombotic therapy is interrupted before surgery, is 'bridging' needed*? Need for bridging driven by TE risk:**

- **In *high-risk patients*, the need to prevent TE will dominate management irrespective of bleeding risk; the potential consequences of TE may justify bridging.**
- **In *moderate-risk patients*, a single perioperative strategy is not dominant and management will depend on individual patient risk assessment.**
- **In *low-risk patients*, the need to prevent TE will be less dominant and bridging may be avoided.**
- **In *all patients*, judicious use of postoperative bridging is needed to minimizing bleeding that would have the undesired effect of delaying resumption of antithrombotic therapy after surgery.**

Perioperative Anticoagulation: Key Questions

What are bridging anticogulation regimens?

- *A 'high-dose' (therapeutic-dose) regimen: also used for acute VTE/ACS (e.g., enoxaparin, 1 mg/kg BID)*
- *A 'low-dose' (prophylactic-dose) regimen: also used to prevent postop VTE (e.g., enoxaparin 30 mg BID or 40 mg QD)*
- *An 'intermediate-dose' regimen: recently studied, intermediate in intensity between a high- and low-dose regimen (e.g., enoxaparin 40 mg BID)*
- *ACCP guideline recommendations refer to therapeutic-dose regimen because (a) most widely studied, (b) widely used, and (c) considered most important because of potential to confer the greatest benefit and harm*

Risk Stratification for Thromboembolism (TE)

- Suggested scheme based on indirect evidence from non-perioperative studies involving patients not receiving adequate treatment (i.e., placebo in AF trials, ASA only in MHV trials)

- A limitation of this risk stratification scheme is that individual patient factors may trump this classification:
  - e.g., high-risk patients may also be those with AF and prior stroke + 1 additional risk factor ($CHADS_2$ = 3) even though such patients are classified as moderate-risk
  - e.g., patients with remote (>1 year ago) but severe VTE may be perceived as high-risk even though they would be classified as low-risk

Suggested Risk Stratification: *Mechanical Heart Valves*

High Risk

- any mitral valve prosthesis
- older (caged-ball or tilting disc) aortic valve prosthesis
- recent (< 6 months) stroke or TIA

Moderate Risk

- bileaflet aortic valve and at least one of:
- atrial fibrillation, prior stroke or TIA, hypertension, diabetes, congestive heart failure, age >75 yrs

Low Risk

- bileaflet aortic valve without atrial fibrillation and no other stroke risk factors

Suggested Risk Stratification: *Atrial Fibrillation*

High Risk

- **$CHADS_2$ score = 5-6**
- **recent (within 3 months) stroke or TIA**
- **rheumatic valvular heart disease**

Moderate Risk

- **$CHADS_2$ score = 3-4**

Low Risk

- **$CHADS_2$ score = 0-2 *and* no prior stroke or TIA**

Suggested Risk Stratification: *Venous Thromboembolism*

High Risk

- recent VTE (<3 months ago)
- severe thrombophilia (e.g., antiphospholipid antibodies)

Moderate Risk

- VTE within the past 3-12 months
- non-severe thrombophilia (e.g., heterozygous factor V mutation)
- recurrent VTE
- active cancer (treated within 6 months or palliative)

Low Risk

- prior VTE >12 months ago and no other risk factors

Risk Stratification for Bleeding

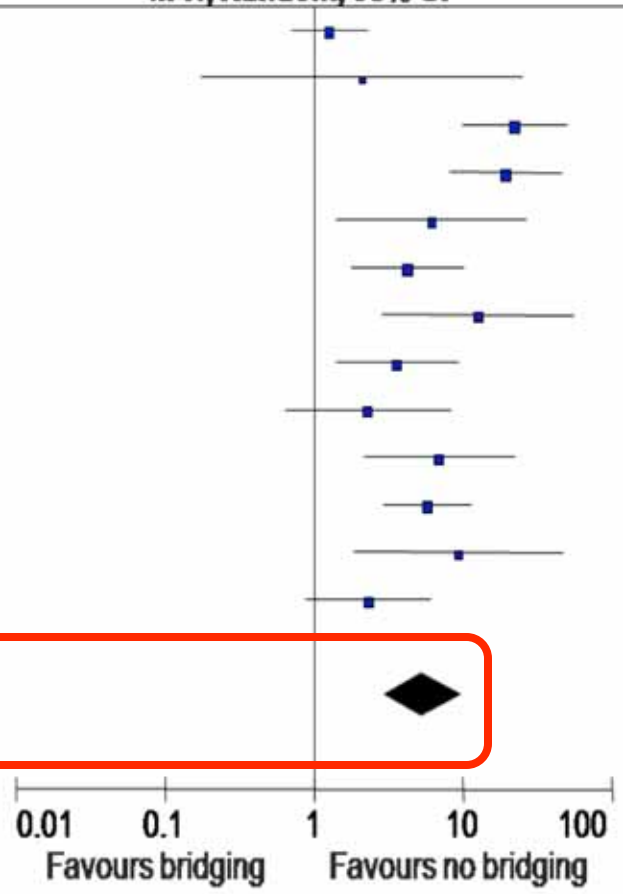
High bleeding-risk surgeries/procedures include:

- **Urologic surgery/procedures: TURP, bladder resection or tumor ablation, nephrectomy or kidney biopsy**
- **Pacemaker or ICD implantation**
- **Colonic polyp resection, especially >1-2 cm sessile polyps; ERCP and sphincterotomy**
- **Vascular organ surgery: thyroid, liver, spleen**
- **Bowel resection**
- **Major surgery involving considerable tissue injury: cancer surgery, joint arthroplasty, reconstructive plastic surgery**
- **Cardiac, intracranial or spinal surgery**

Evidence: Perioperative risk for bleeding with bridging (meta-analysis)

Study or Subgroup	Bridging Events	Bridging Total	No bridging Events	No bridging Total	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	36	342	18	213	1.27 [0.70, 2.31]
Dotan et al., 2002	2	20	1	20	2.11 [0.18, 25.35]
Ercan et al., 2010	11	44	21	1421	22.22 [9.92, 49.81]
Garcia et al., 2008	14	108	9	1185	19.46 [8.21, 46.14]
Ghanbari et al., 2010	6	29	3	74	6.17 [1.43, 26.68]
Jaffer et al., 2010	24	229	7	263	4.28 [1.81, 10.14]
Marquie et al., 2006	21	114	2	114	12.65 [2.89, 55.34]
McBane et al., 2010	34	514	5	261	3.63 [1.40, 9.39]
Robinson et al., 2009	20	113	3	35	2.29 [0.64, 8.24]
Tischenko et al., 2009	9	38	5	117	6.95 [2.16, 22.33]
Tompkins et al., 2010	23	155	15	513	5.78 [2.94, 11.40]
Varkarakis et al., 2005	2	25	7	762	9.38 [1.85, 47.64]
Wysokinski et al., 2008	15	204	6	182	2.33 [0.88, 6.13]
Total (95% CI)		**1935**		**5160**	**5.40 [3.00, 9.74]**
Total events	217		102		

Heterogeneity: $I^2 = 77\%$

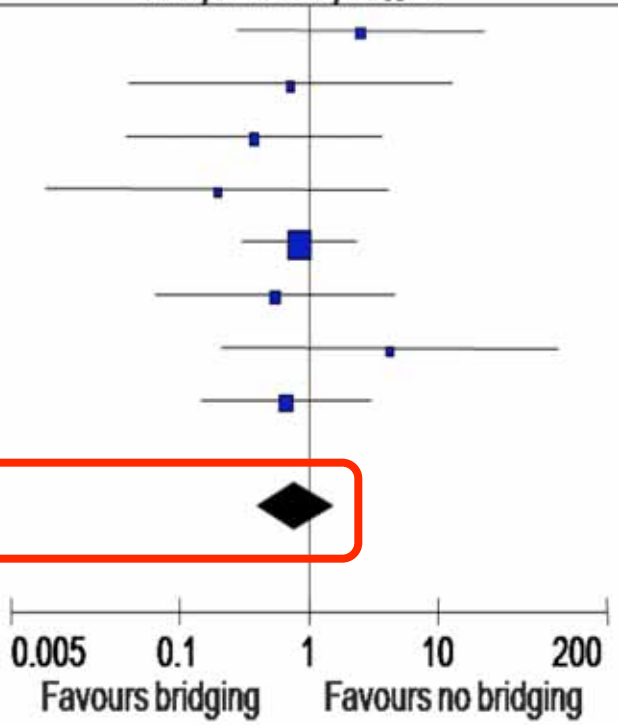


Bridging associated with an increase in *overall* bleeding

Yudin J, et al. *Blood* 2011 (abstract)

Evidence: Perioperative risk for TE with bridging (meta-analysis)

Study or Subgroup	Bridging Events	Bridging Total	No bridging Events	No bridging Total	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	4	342	1	213	2.51 [0.28, 22.60]
Garcia et al., 2008	0	108	7	1185	0.72 [0.04, 12.76]
Jaffer et al., 2010	1	229	3	263	0.38 [0.04, 3.68]
Marquie et al., 2006	0	114	2	114	0.20 [0.01, 4.14]
McBane et al., 2010	10	514	6	261	0.84 [0.30, 2.35]
Tompkins et al., 2010	1	155	6	513	0.55 [0.07, 4.59]
Varkarakis et al., 2005	0	25	3	762	4.25 [0.21, 84.56]
Wysokinski et al., 2008	3	204	4	182	0.66 [0.15, 3.01]
Total (95% CI)		**1691**		**3493**	**0.80 [0.42, 1.54]**
Total events	19		32		
Heterogeneity: $I^2 = 0\%$					



No significant risk reduction for TE with heparin bridging

….BUT, major potential for confounding

Yudin J, et al. *Blood* 2011 (abstract)

Case Vignette No. 1

A 68 year old female on chronic warfarin for recurrent deep vein thrombosis (most recent was 1 year ago) will undergo 2 dental extractions that will include local anesthetic injections…

Patient has concerns about dental bleeding…

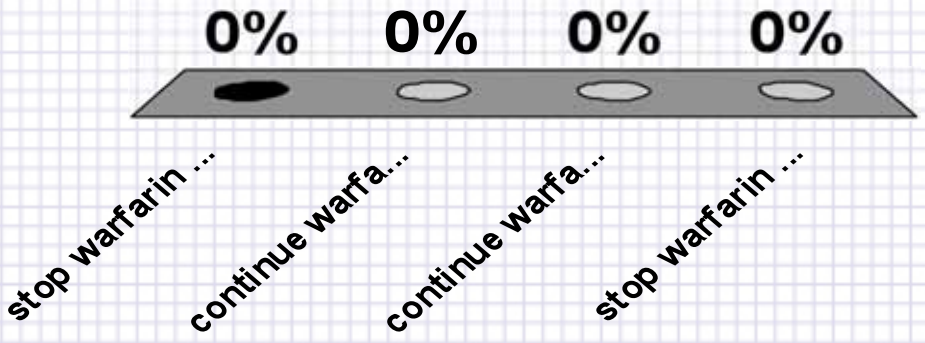
Case Vignette No. 1: Management Options

1) stop warfarin at day -5 before procedure, give therapeutic-dose bridging with LMWH (e.g., enoxaparin, 1 mg/kg BID)

3) continue warfarin without dose reduction and give prohemostatic mouthwash (e.g., tranexamic acid) before and after procedure

5) continue warfarin without dose reduction

7) stop warfarin 2 days before procedure and resume after procedure



Evidence: Patients Requiring Minor Procedures

- ***Recommendation***: **In patients who require minor dental surgery and are receiving a VKA, we suggest *<u>either</u>* continuing VKA with a oral prohemostatic mouthwash *or* stopping VKAs 2-3 days before the procedure *<u>instead of</u>* alternative strategies (Grade 2C).**
- ***Recommendation***: **In patients who require minor skin procedures and are receiving a VKA, we suggest continuing VKAs around the procedure and optimizing local hemostasis *<u>instead of</u>* other strategies (Grade 2C).**
- ***Recommendation***: **In patients who require cataract surgery and are receiving a VKA, we suggest continuing VKAs around the surgery *<u>instead of</u>* other strategies (Grade 2C).**

Case Vignette No. 2

78-year old female with a mechanical aortic valve and AF is receiving warfarin (target INR: 2.5-3.5)

CHADS score = 2

- age >75 yrs
- hypertension

scheduled for elective hip replacement…

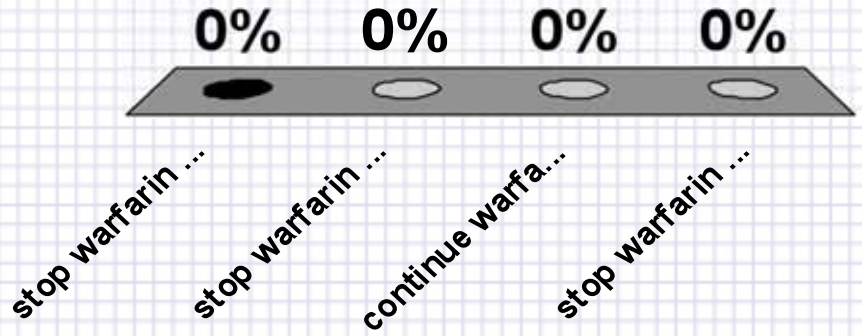
What to do pre-operatively?

1) stop warfarin 5 days pre-op, administer therapeutic-dose bridging with LMWH (e.g., enoxaparin, 1 mg/kg BID) pre- and post-op

2) stop warfarin 5 days pre-op, administer low-dose LMWH pre- and post-op (e.g., dalteparin, 5000 IU QD)

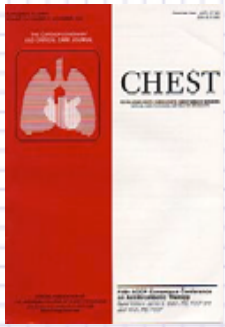
3) continue warfarin but reduce dose 50% starting 5 days pre-op

4) stop warfarin 5 days pre-op and resume after procedure

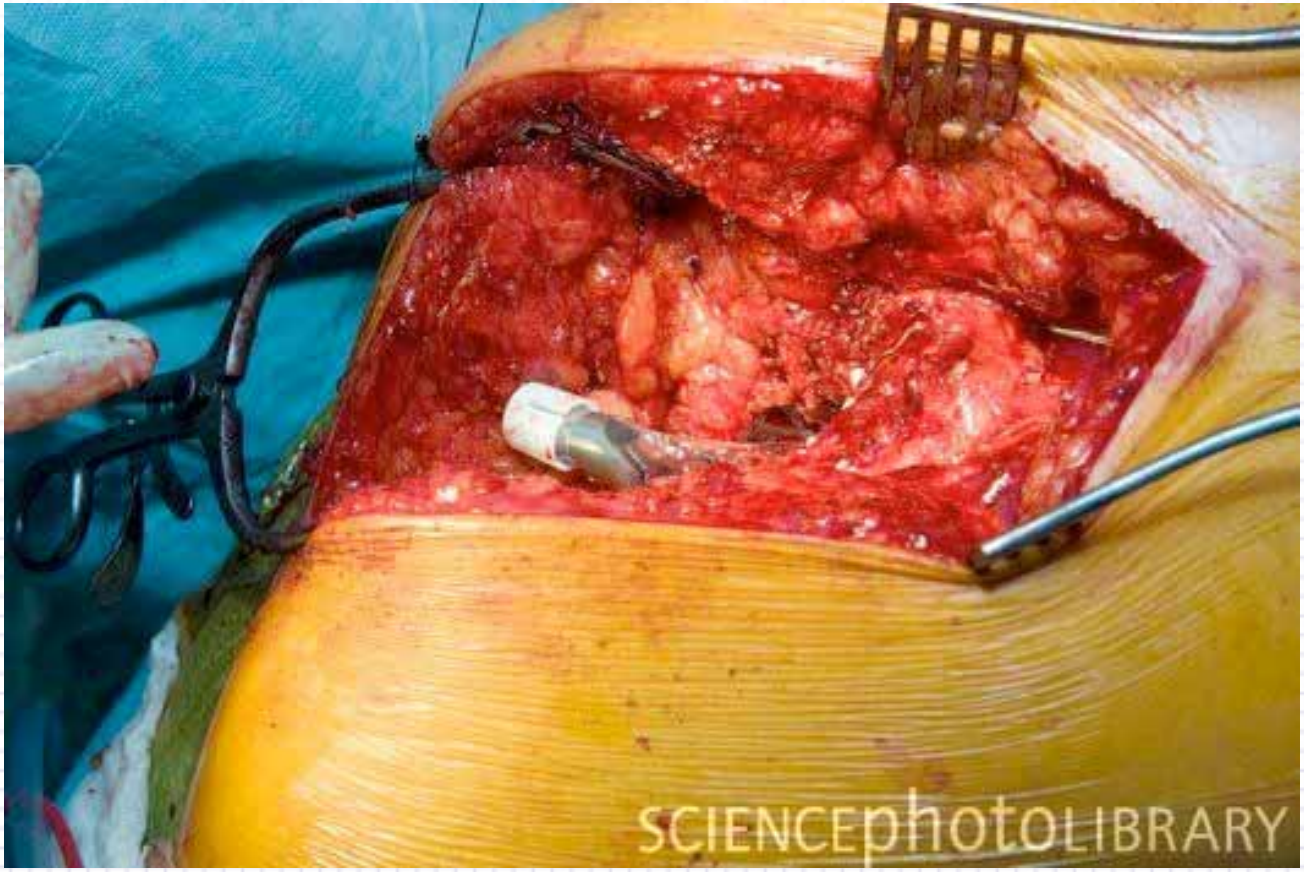


Evidence: Patients at High TE Risk having Major Surgery

- ***Recommendation***: **In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs ~5 days before surgery *instead of* stopping VKA closer to surgery (Grade 1C).**
- ***Recommendation***: **In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs ~12-24 hrs after surgery (evening or next morning) and when there is adequate hemostasis *instead of* later resumption of VKAs (Grade 2C).**
- ***Recommendation***: **In patients with a mechanical heart valve, atrial fibrillation or VTE at high risk for TE, we suggest bridging anticoagulation *instead of* no bridging (Grade 2C).**



Concerns about post-op bleeding with bridging…



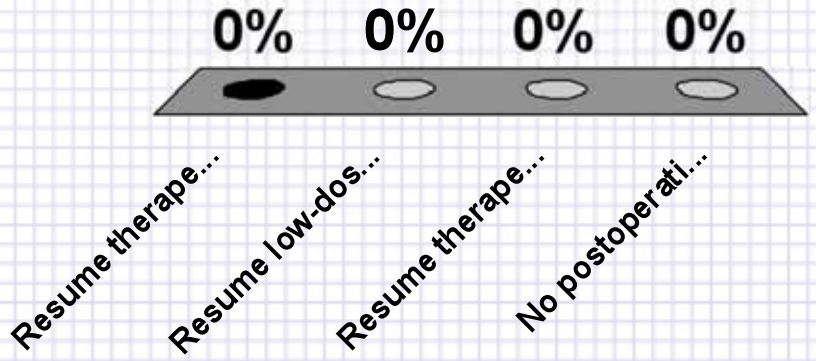
What to do post-operatively?

1) Resume therapeutic-dose bridging (enoxaparin, 1 mg/kg) within 24 hrs after surgery

2) Resume low-dose enoxaparin, 40 mg once-daily

3) Resume therapeutic-dose bridging (enoxaparin, 1 mg/kg) 48-72 hrs after surgery

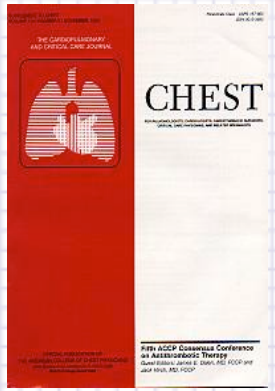
4) No postoperative bridging; only resume warfarin 5 after procedure



Perioperative Administration of Bridging

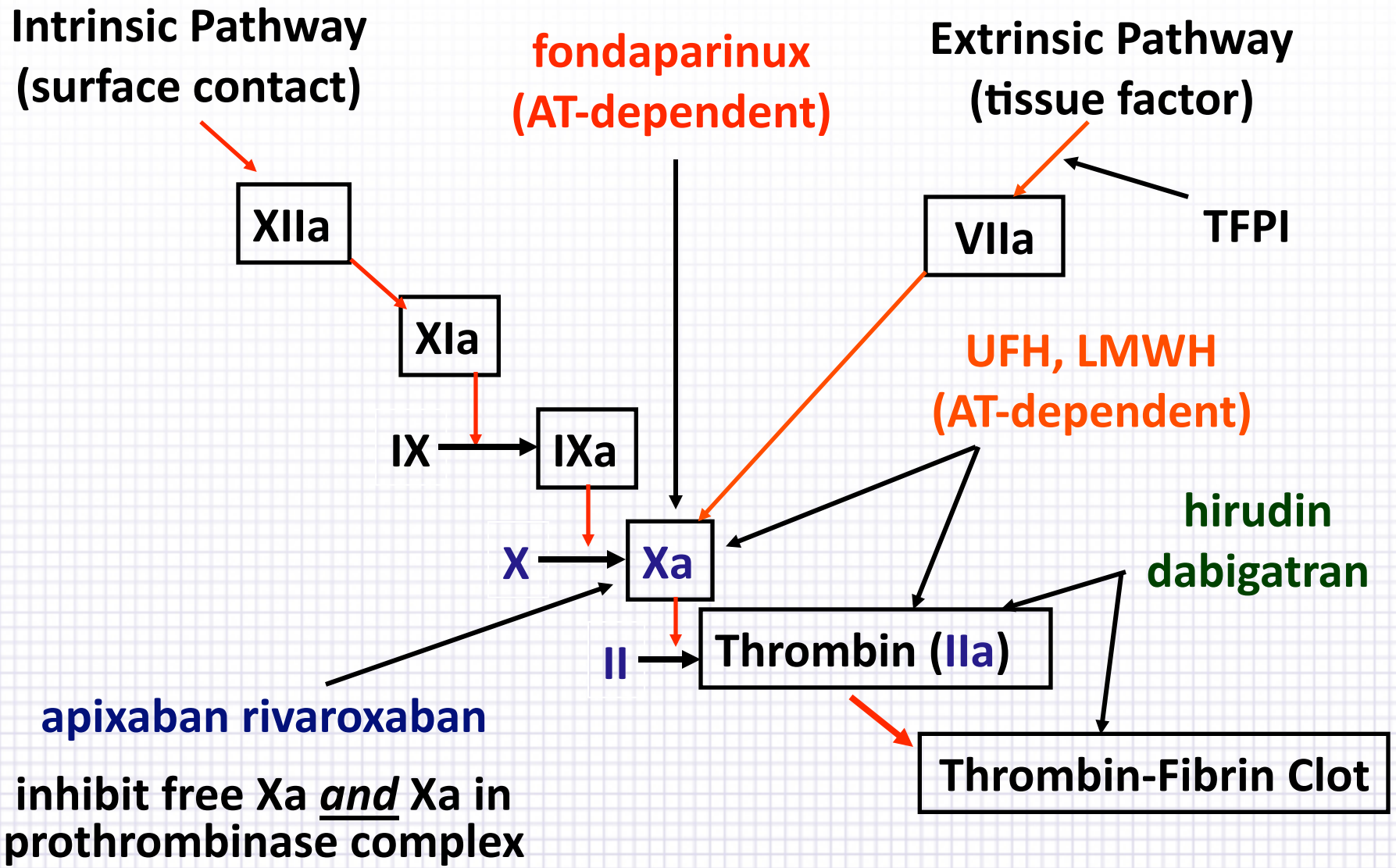
- ***Recommendation***: **In patients who are receiving bridging with therapeutic-dose LMWH, we suggest administering the *last pre-operative dose* of LMWH approximately *24 hrs before surgery* instead of 12 hrs before surgery (Grade 2C).**

- ***Recommendation***: **In patients who are receiving bridging with therapeutic-dose LMWH and are having high bleeding-risk surgery, we suggest *resuming* therapeutic-dose LMWH *48-72 hrs after surgery* instead of resuming within 24 hrs after surgery (Grade 2C).**



Presentation Objectives

- To have an approach to the perioperative management of patients receiving warfarin and require elective surgery.
- To have an approach to the perioperative management of patients who are receiving a NOAC and require elective surgery.
- To be able to interpret ***coagulation tests*** in patients receiving a NOAC.


Intrinsic Pathway
(surface contact)
fondaparinux
(AT-dependent)
Extrinsic Pathway
(tissue factor)
XIIa
VIIa
TFPI
XIa
UFH, LMWH
(AT-dependent)
IX
IXa
hirudin
dabigatran
X
Xa
II
Thrombin (IIa)
apixaban rivaroxaban
Thrombin-Fibrin Clot
inhibit free Xa *and* Xa in
prothrombinase complex

NOACs: *Drugs, indications, and doses*

- **Dabigatran**
  - DVT prophylaxis….150 mg or 220 mg OD
  - AF……..150 mg BID (110 mg BID, 75 mg BID)
  - VTE……..150 mg BID
- **Rivaroxaban**
  - DVT prophylaxis….10 mg OD
  - AF and VTE……20 mg OD
- **Apixaban**
  - DVT prophylaxis….2.5 mg BID
  - AF……5 mg BID

Case Vignette No. 1

78-year old female with AF, on dabigatran 150 mg BID, is scheduled for elective hip replacement…to receive spinal/epidural anesthesia

CHADS score = 4 (prior TIA, age >75 yrs, hypertension)

wt = 65 kg, creatinine = 120 μmol/L

CrCl = 35 mL/min (moderate renal insufficiency)

What to do pre-operatively with dabigatran?

1. Stop dabigatran ***1 day*** before surgery (skip 2 doses)
2. Stop dabigatran ***4 days*** before surgery (skip 8 doses)
3. Stop dabigatran ***5 days*** before surgery and bridge (enoxaparin 1 mg/kg BID) starting 3 days pre-op
4. Stop dabigatran ***5 days*** before surgery and give low-dose bridging (enox. 40 mg OD) starting 3 days pre-op

Pharmacologic Properties of Anticoagulants: Old vs. New

Property	"Old" Anticoagulants				New Anticoagulants		
	warfarin	UFH	LMWH	fonda-parinux	dabiga-tran	riva-roxaban	apixaban
Mode of action	VKA	indirect IIa + Xa inhibitor	indirect Xa (IIa) inhibitor	indirect Xa inhibitor	direct IIa inhibitor	direct Xa inhibitor	Direct Xa inhibitor
Bioavail	100%	100%	100%	100%	6-7%	80%	80%
Peak action	4-5 days	<0.5 h IV 0.5 h SC	2-4 hrs	2-4 hrs	1-3 hrs	1-3 hrs	1-3 hrs
Half-life	36-42 hrs	1-1.5 hrs	3-4 hrs	17-21 hrs	14-17 hrs	9-15 hrs	9-14 hrs
Route of clearance	multiple	reticulo-endoth.	>80% renal	100% renal	80% renal	35% renal	25% renal

Douketis JD. *Curr Pharm Des* 2010;16:3436

Pre-operative Management of Dabigatran

Renal function (CrCl)	Estimated half-life (hrs)	Stop dabigatran	before surgery
		higher-risk for bleeding	*low-risk for bleeding*
≥50 mL/min (mild dysfunction or normal)	14-17	2-3 days	1 day
30 to <50 mL/min (moderate dysfunction)	18-24	4 days	2-3 days
<30 mL/min (severe dysfunction)	>24	>5 days	2-5 days

Van Rijn J, et al. *Thromb Haemost* 2010;103:1116

Anticoagulant Interruption in RE-LY: Patients

- 4,591 (25% of all) patients studied with *first* treatment interruption for surgery/procedure (8% urgent)
- Surgery/procedure types
  - 22% diagnostic (e.g., colonoscopy)
  - 10% pacemaker/ICD insertion
  - 10% dental
  - 9% cataract
  - 6% joint replacement
  - 43% other surgery

Healey JS, et al. *Circulation* 2012;126:343

Perioperative Dabigatran Management in RE-LY

- Pre-operative
  - last dose dabigatran 49 h (range: 35-85) pre-op
  - last dose warfarin 114 h (range: 87-114) pre-op
- Post-operative
  - anticoagulation resumed at discretion of treating physician, when hemostasis secured

Healey JS, et al. *Circulation* 2012;126:343

Anticoagulant Interruption in RE-LY: Outcomes

- ***Any*** surgery/procedure: No significant difference in major bleeding
  - dabigatran, 110 mg…… 3.8%
  - dabigatran, 150 mg…… 5.1%
  - warfarin…… 4.6%
- ***Urgent*** surgery/procedure: No significant difference in major bleed
  - dabigatran, 110 mg…… 17.8%
  - dabigatran, 150 mg…… 17.7%
  - warfarin…… 21.6%
- Incidence of stroke or TE low and not significantly different between treatment arms

Healey JS, et al. *Circulation* 2012;126:343

What to do post-operatively? (bleeding as expected)

1. Resume dabigatran (150 mg BID) evening after surgery
2. Resume dabigatran 1st post-op day (24 h after surgery)
3. Resume dabigatran on 3rd post-op day
4. Start low-dose LMWH (enox. 30 mg BID) within 24 hrs post-op and resume dabigatran on 3rd post-op day

Post-operative Management of Dabigatran

Surgery Type	Suggested Approach	Alternative
Major (or high bleed risk) surgery	resume 150 mg BID 48-72 hrs post-op	substitute 75 or 150 mg dose *daily* for 2-3 days
Minor (or low bleed risk) surgery	resume 150 mg BID 24 hrs post-op	resume 24-48 hrs post-op

Douketis JD. *Curr Pharm Des* 2010;16:3436

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Case Vignette No. 2

A *63*-year old woman with AF and mitral valve disease, on dabigatran 150 mg BID, falls and fractures her hip.

Presents to ER on Friday at 1PM and requires urgent hip repair…her last dabigatran dose was 4 hrs ago.

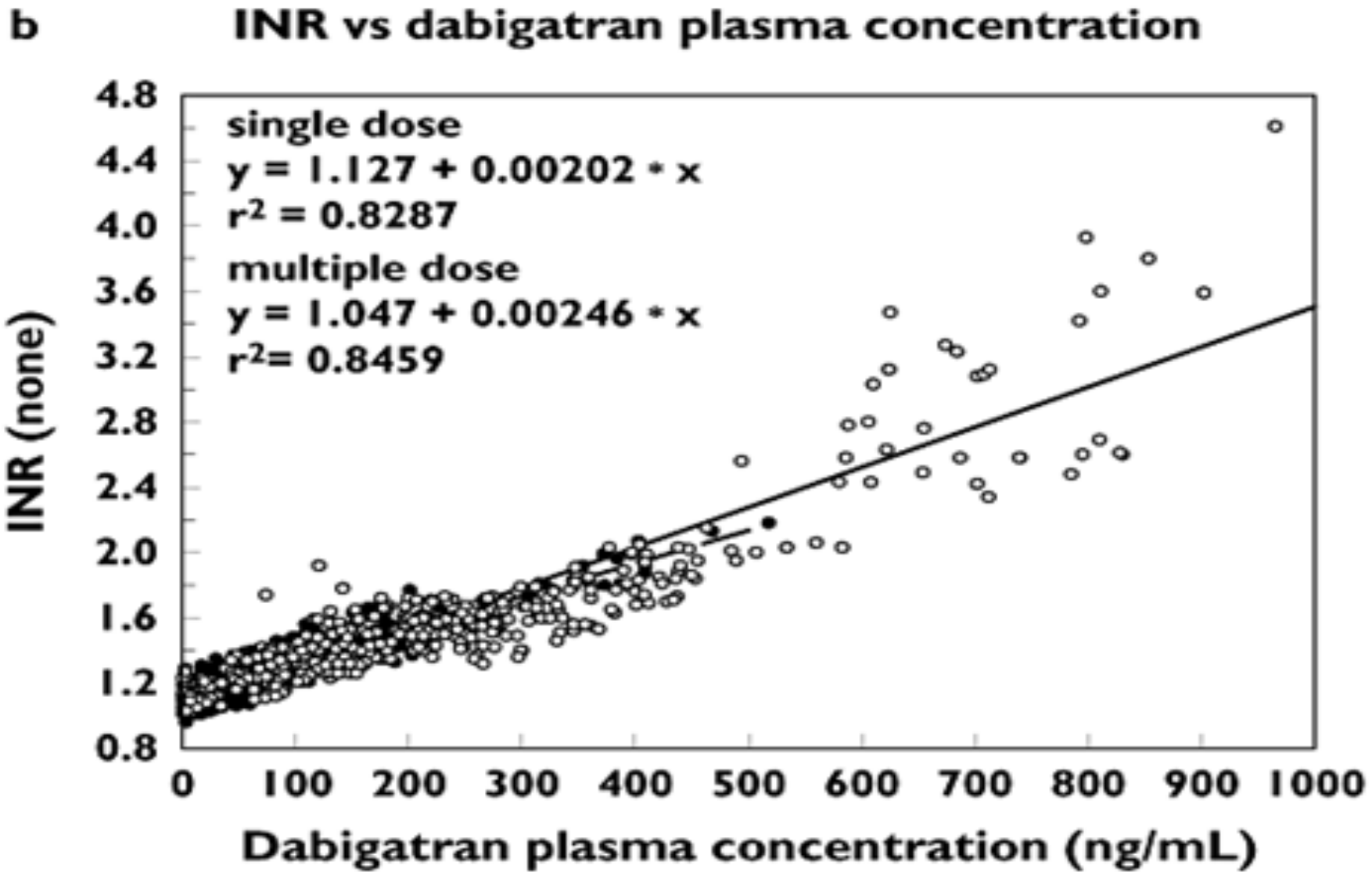
weight = 65 kg

serum creatinine = 100 μmol/L (CrCL = 52 mL/min)

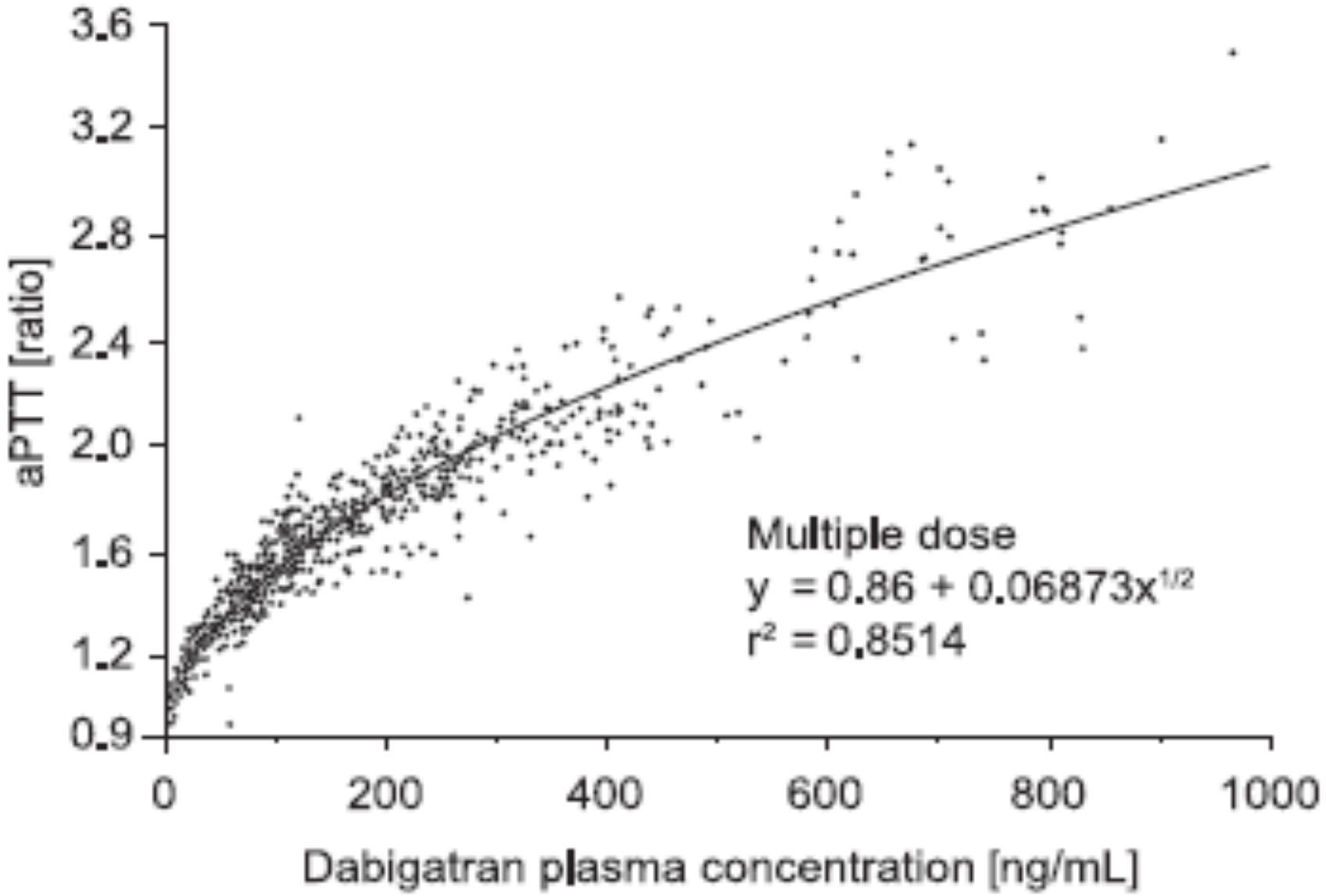
What to do pre-operatively?

1. Give 30 IU/kg PCC and take to OR that evening
2. Give 4 units FFP and take to OR that evening
3. Wait 24 hrs after last dabigatran dose and take to OR
4. Wait 24 hrs after last dabigatran dose and take to OR only if pre-op aPTT (or TT) normal
5. Wait 2 days (skip 4 dabigatran doses) and take to OR

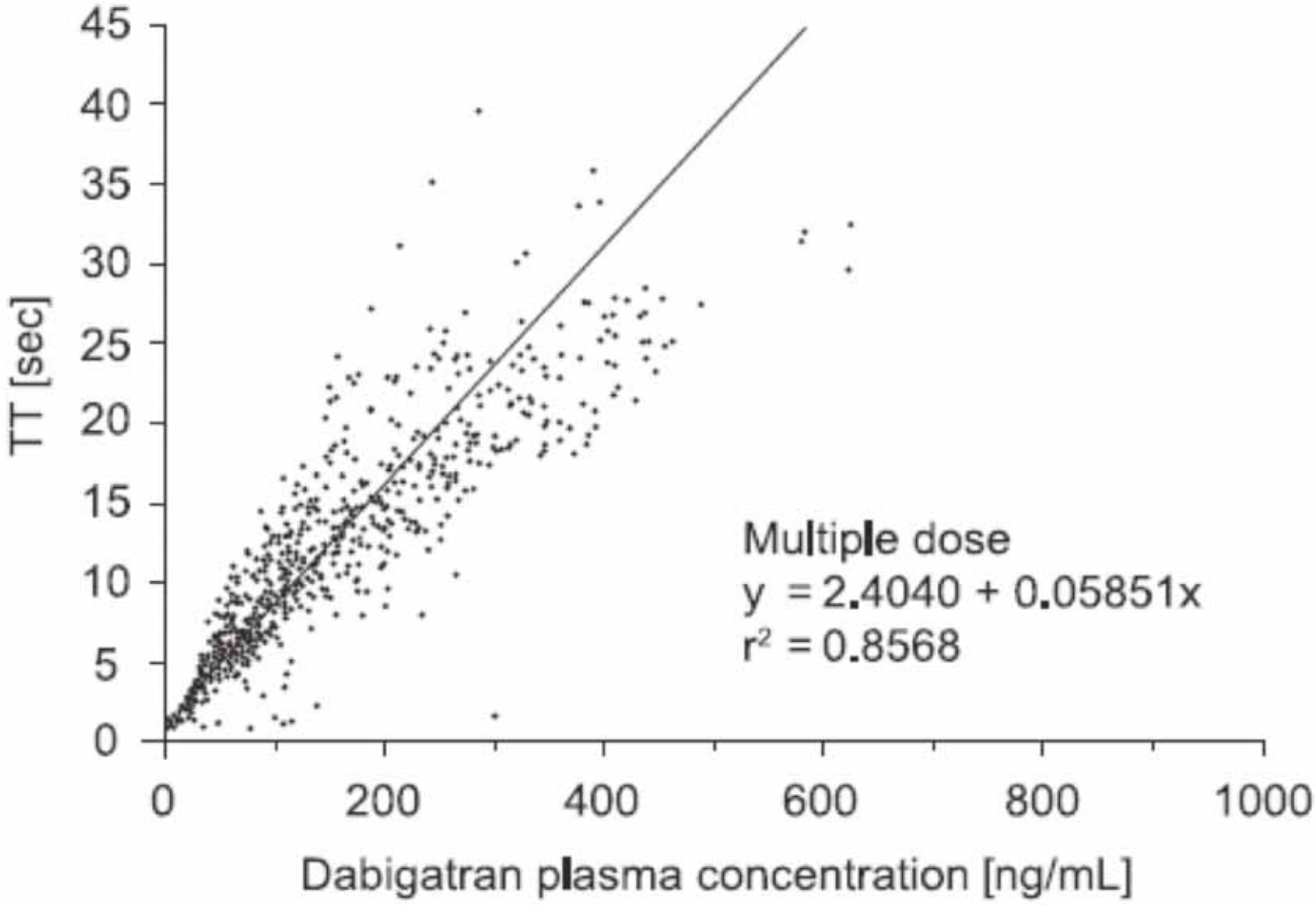
Effect of Dabigatran on INR



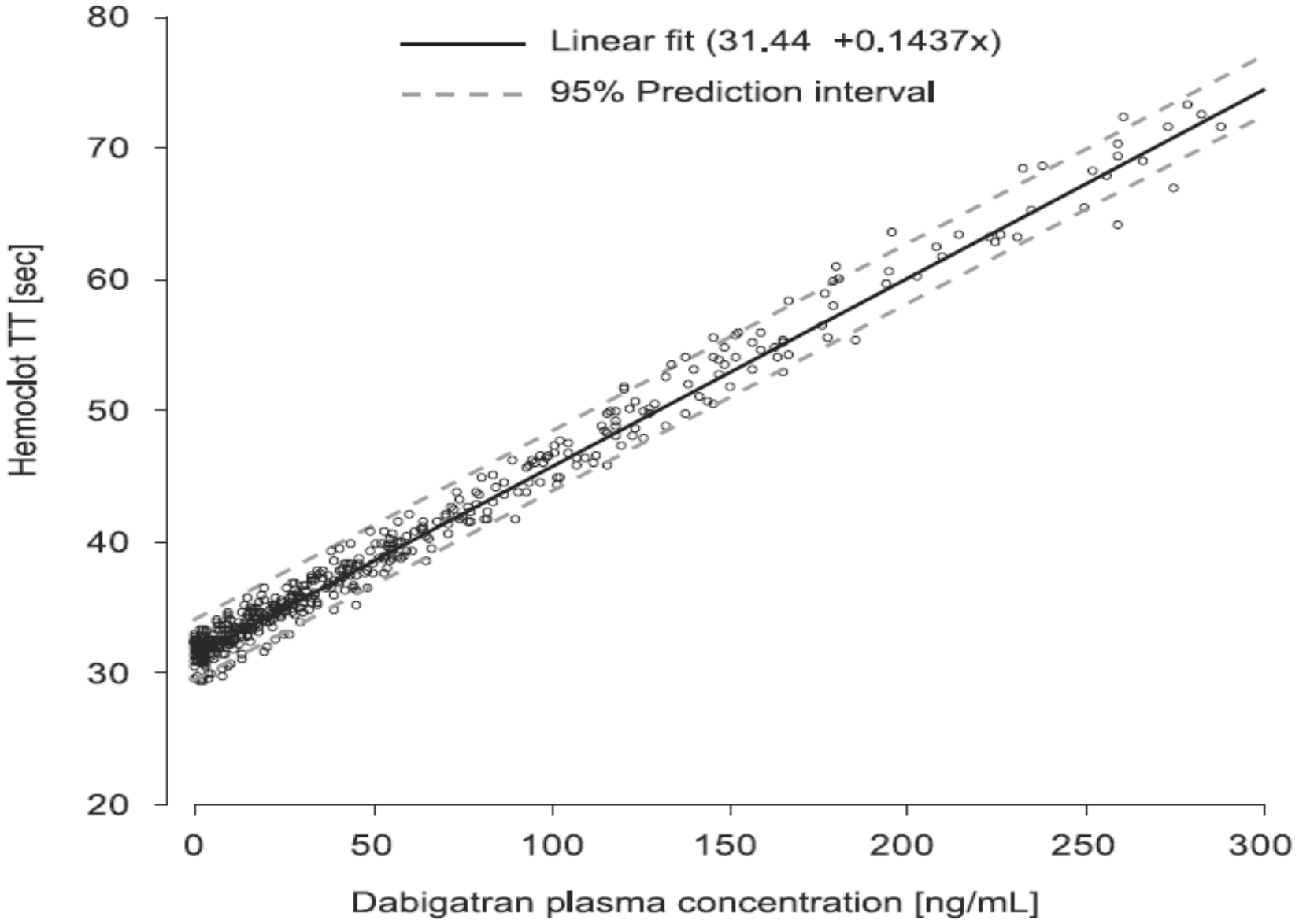
Effect of Dabigatran on aPTT



Effect of Dabigatran on Thrombin Time



Effect of Dabigatran on Dilute Thrombin Time (Hemoclot)



Lab Monitoring of Dabigatran around Surgery

- **Step 1: partial thromboplastin time (PTT)**
  - **qualitative test (for screening)**
  - **if ↑PTT (and no other cause), likely some dabigatran effect**
  - **if normal PTT, no clinically significant dabigatran effect**
  - ***For reassurance of no residual anticoagulant effect…***
- **Step 2: thrombin time (TT) *or* Hemoclot test**
  - **quantitative test…*BUT* standard TT is too sensitive**
  - **if normal TT (<30 sec) or if normal Hemoclot test, no detectable dabigatran anticoagulant effect**

Lab Monitoring of Rivaroxaban/Apixaban around Surgery

- **Step 1: prothrombin time (PT)**
  - qualitative test (for screening)
  - if ↑PT (and no other cause), likely some rivaroxaban effect… *BUT* assay-dependent
  - if normal PT, no clinically significant rivaroxaban effect
  - *for more reassurance that no residual anticoagulant effect…*
- **Step 2: anti-factor Xa assay**
  - LMWH-calibrated anti-factor Xa assay
  - labs can develop rivaroxaban/apixaban – calibrated assays

Presentation Objectives and Take-home Messages

- Perioperative management of patients receiving ***warfarin***:

  Consider: TE and bleeding risk assessments to determine if VKA interruption needed and whether heparin bridging needed

  –minimize post-op bleeding: bleed = delay anticoagulation = ↑TE risk

- Perioperative management of patients receiving a ***NOAC***:

  Consider: 1) drug half-lives (9-17 hrs); 2) effect of renal function; 3) rapid peak effect (1-3 hrs); 4) surgery/procedure type

- Interpretation of ***coagulation tests*** in patients receiving a NOAC:

  Consider: 1) aPTT and TT for dabigatran; 2) PT and anti-Xa for rivaroxaban/apixaban