Reversal of Antiplatelets and Direct Oral Anticoagulants

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TRANSFUSION MEDICINE 101
CAMP WITH THE BANK

Disclosures

I have received speaker fees or advisory board fees from the following entities:

- Fresenius Kabi, Pfizer Pharmaceuticals, Inari Medical

By the end of today's session, you should be able to:

1. Describe pharmacokinetic principles of DOACs

2. Discuss the perioperative management of patients on DOACs who are undergoing invasive procedures

3. Describe the hemostatic management and reversal strategies for patients who are bleeding while on DOACs

4. Describe reversal strategies for patients on antiplatelet agents

Distinction between PERIOPERATIVE and BLEEDING management

<u>Managing DOACs around:</u>

elective procedures should not require the use of reversal strategies *(just hold the drug for long enough)*

urgent or emergent procedures often involves the use of reversal strategies *(do you have enough time?)*

bleeding involves the use of reversal and hemostatic strategies

You are evaluating a 74 yo male who is on **dabigatran 110 mg BID** for atrial fibrillation ($CHADS_2$ 4). He is going for **elective total knee arthroplasty**. His weight is 78 kg, and creatinine is 160 umol/L.

How long should you hold his anticoagulant therapy before surgery?

a. 10 doses
b. 8 doses
c. 6 doses
d. 4 doses
e. 2 doses

ELECTIVE procedure

NON-BLEEDING patient

DOAC half life is relatively short **but** highly reliant on renal function, concomitant drugs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Time to peak	1-3 hrs	2-4 hrs	1-2 hrs	1-2 hrs
Half-life	14-17 hrs	7-11 hrs	8-14 hrs	10-14 hrs
Renal clearance	80%	33%	25%	50%
Interactions	PGP	PGP + 3A4	PGP + 3A4	PGP (only 4% CYP3A4)

Interruption recommendations* from Thrombosis Canada are based on expected half-life of DOACs

Drug	Renal Function (half-life)	High Bleeding Risk (<10% residual activity accepted)	Moderate Bleeding Risk (12-25% residual activity accepted)
Dabigatran	CrCL > 50 (7-17 hr) CrCL 30-49 (17-20 hr)	Skip 4 doses (2 days) Skip 8 doses (4 days)	Skip 2 doses (1 day) Skip 4 doses (2 days)
Rivaroxaban	CrCL > 30 (7-11 hr)	Skip 2 doses (2 days)	Skip 1 dose (1 day)
Apixaban	CrCL> 30 (8-12 hr)	Skip 4 doses (2 days)	Skip 2 doses (1 day)
Edoxaban	CrCL > 30 (10-14 hr)	Skip 2 doses (2 days)	Skip 1 dose (1 day)

*In addition to no anticoagulant on day of procedure

TC Clinical Guides 2018

What is the procedural bleeding risk?

High Bleeding Risk *(2-day risk of major bleed ≥ 2%)*	**Low Bleeding Risk** *(2-day risk of major bleed < 2%)*	**Minimal Bleeding Risk**
Cancer surgery Orthopedic surgery Urologic surgery/TURP Cardiac surgery Spinal surgery Gastrointestinal surgery Kidney biopsy Colonic polyp resection Neuraxial anesthesia	Arthroscopy Lymph node biopsy Coronary angiogram Colonoscopy +/- biopsy Laparoscopic chole. Hernia repair Bronchoscopy +/- biopsy	Minor derm. procedures Cataract procedure Minor dental procedures Pacemaker or ICD*

Spyropoulos JTH 2017

American Society for Regional Anesthesia (ASRA) Guidelines for Neuraxial Block differ from Thrombosis Canada

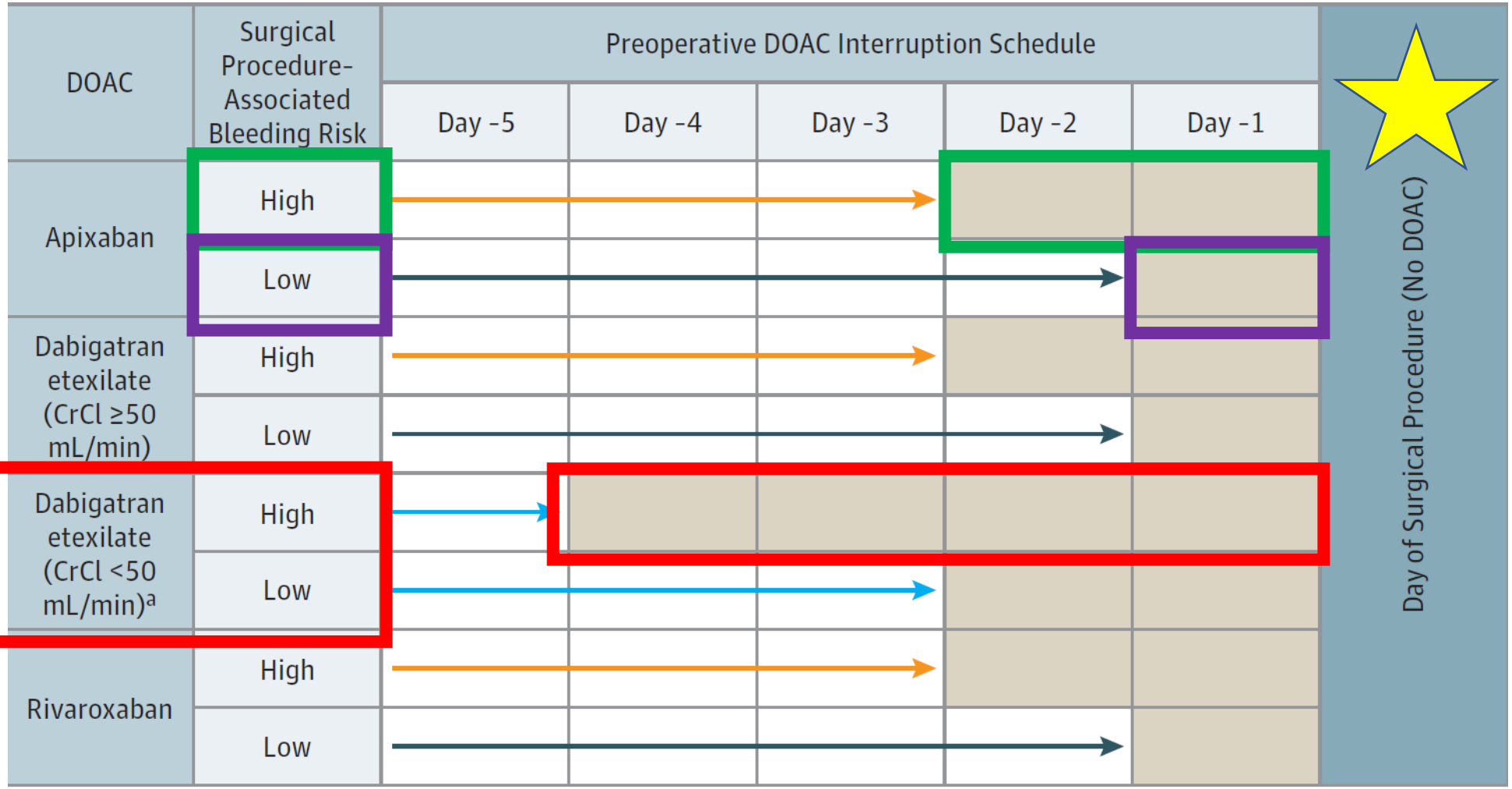
- **Stop Warfarin 5 days prior**, with normal INR

- **Stop Dabigatran 120 hours prior**; *consider graded approach*
  - CrCl > 80 – 72 hours prior (3 days)
  - CrCl 50-79 – 96 hours prior (4 days)
  - CrCl 30-49 – 120 hours prior (5 days)
  - CrCL < 30 – do not perform neuraxial block
  - **if earlier, consider measuring thrombin clotting time or residual Dabigatran level

- **Stop Rivaroxaban, Apixaban, or Edoxaban 72 hours prior**
  - **if earlier, consider measuring anti-Xa level

Horlocker ASRA 2018

The PAUSE study used a standard interruption strategy before surgery: 2 days for high risk, 1 day for low risk (double if dabigatran with CrCl < 50)



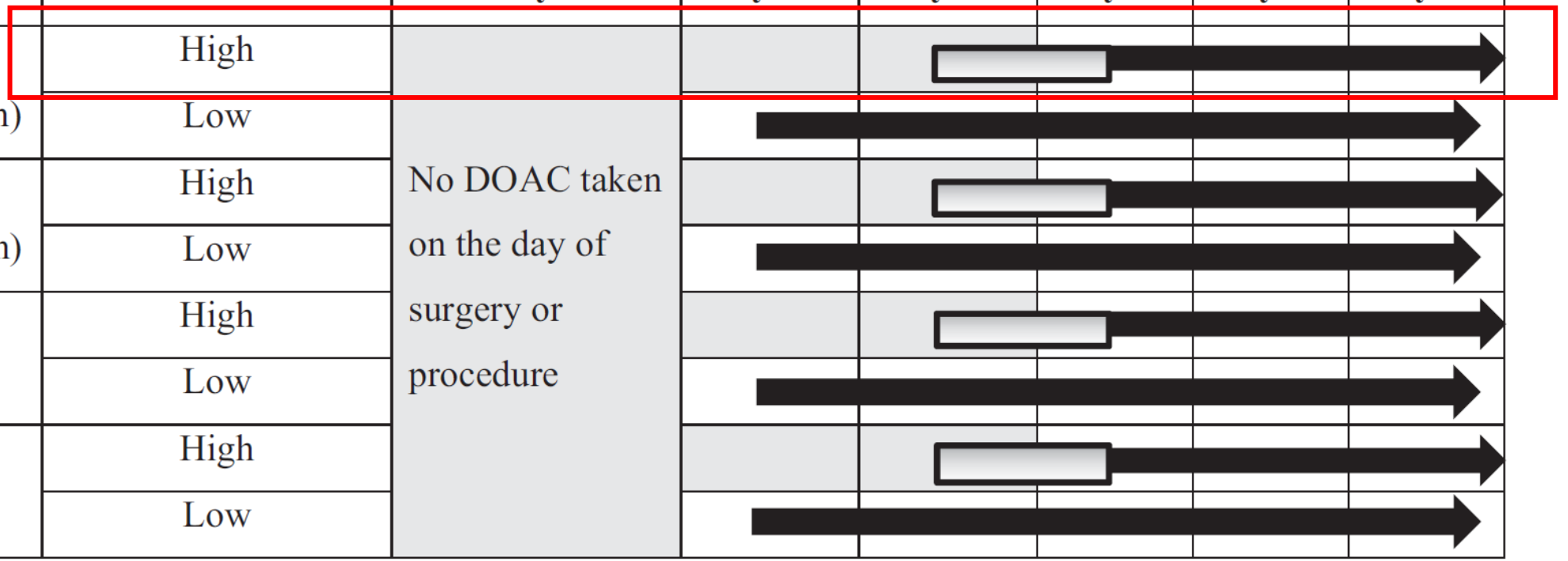
SURGERY DATE

Dabi CrCL < 50

Douketis JAMA Intern Med 2019

The PAUSE study also used a standardized resumption algorithm

DOAC type	Surgery/procedure bleed risk	Day 0	Post-procedure resumption timing of DOAC				
			Day +1†	Day +2‡	Day +3	Day +4	Day +5
Dabigatran (CrCl ≥50 mL/min)	High	No DOAC taken on the day of surgery or procedure					
	Low						
Dabigatran (CrCl <50 mL/min)	High						
	Low						
Rivaroxaban	High						
	Low						
Apixaban	High						
	Low						



Douketis Thromb Haemost 2017

With this protocol, 98.9% of high-risk patients had little to no serum DOAC effect

Apixaban n = 1257
Dabigatran n = 668
Rivaroxaban n = 1082

Mean $CHADS_2$ 2
Mean CrCl 77-85 ml/min
20-47% lower dose DOAC
12-15% concomitant ASA
33% high bleeding risk*

Prospective cohort
30 day follow-up

85% had pre-operative DOAC levels

98.9% (823/832) of high-risk patients had minimal to no residual DOAC effect (<50 ng/ml)

85-93% of high-risk patients had DOAC level < 30 ng/ml

*22% of high-risk group had neuraxial anesthesia (total 7.3%)

Douketis JAMA Intern Med 2019

You are evaluating a 74 yo male who is on **dabigatran 110 mg BID** for atrial fibrillation ($CHADS_2$ 4). He is going for **elective total knee arthroplasty**. His weight is 78 kg, and creatinine is 160 umol/L.

How long should you hold his anticoagulant therapy before surgery?

a. 10 doses
b. 8 doses
c. 6 doses
d. 4 doses
e. 2 doses

CrCl is 40 ml/min
He needs a neuraxial block
ASRA = 120 hours (5 days)
PAUSE, TC = 96 hours (4 days)

IN SUMMARY: For ELECTIVE PROCEDURES, you need to know expected DOAC elimination and bleeding risk of procedure.

You are evaluating a 74 yo male who is on **rivaroxaban 20 mg daily** for AF. He has fallen and sustained ICH, and he requires **emergent decompressive craniotomy**.

CrCL is 55 ml/min. His last dose of Rivaroxaban was **14 hours ago**. INR is 1.0 (normal), aPTT is 22 s (normal), and thrombin clotting time is 15 s (normal).

What is the next most appropriate step?

EMERGENT procedure

BLEEDING patient

a. Proceed to neurosurgery immediately
b. Only proceed to neurosurgery if Rivaroxaban level is confirmed < 30 ng/ml
c. Prothrombin Complex Concentrate 2000 units
d. Andexanet Alfa 400 mg IV bolus
e. Idarucizumab 5 mg IV bolus

Standard coagulation tests are of limited or unknown utility in managing emergent procedures

Lab test	Dabigatran	Rivaroxaban, Apixaban, Edoxaban
PT, INR	• Variable effect (usually < 2.0 at peak serum concentrations)	• Riva and Edox can increase PT/INR • Apix has minimal effect
aPTT	• Non-linear increase	• Riva, Edox, Apix can increase aPTT (not always)
Thrombin Time	• Increases TT • If normal, there is no effect	• No effect
Anti-Xa level	• No effect	• Can be used to measure • Drug-specific calibration
Dilute TT, ECT	• Can be used to measure • Drug-specific calibration	• No effect

Adapted from Thrombosis Canada

What is a clinically relevant DOAC (anti-Xa) level?

- Unclear
- Consensus: **< 30 ng/ml = absence of anticoagulant effect**

  30-50 = minimal residual amount

  > 50 ng/ml = likely presence of anticoagulant effect

TABLE 1] Expected Steady-State Peak and Trough Concentrations of Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in Patients With Atrial Fibrillation

Drug	Dose	Peak (ng/mL)	Trough (ng/mL)	References
Dabigatran	150 mg bid	64-443	31-225	120,121
Rivaroxaban	20 mg daily	189-419	6-87	51
Apixaban	5 mg bid	91-321	41-230	94
Edoxaban	60 mg daily	120-250	10-40	12

Sholzberg JAMA 2018; Samuelson Chest 2017

What is a clinically significant DOAC (anti-Xa) level? *(based on very low quality evidence)*

< 30 ng/ml – for high risk surgery

> 50 ng/ml + major bleeding – consider reversal strategies or antidote

< 100 ng/ml – IV thrombolysis is likely safe

> 200 ng/ml – concentration associated with a consistent peri-procedural bleeding risk

What is Prothrombin Complex Concentrate (PCC)?

- 4-factor = II, IX, X, VII
  - **Octaplex, Beriplex**

- **Reversal agent** for VKA (replacing K-dependent factors)
- Acts quickly for warfarin reversal (correction of INR within 10-15 minutes), but short half-life in this population (6 hours, due to VII)
- Thromboembolism risk in warfarin reversal is **1.4%**

Mangram J Crit Care 2016
Dentali Thromb Haemost 2011

PCC appears to be effective hemostatic therapy in bleeding patients. However 1) no randomization with placebo, 2) prothrombotic signal, 3) almost no data from periprocedural setting

Majeed et al. Blood 2017

- Prosp. cohort of 84 patients on rivaroxaban or apixaban who received median 2000 units PCC for major bleeding (70% ICH, 16% GIB)

→Hemostasis "effective" in 69% of patients; 2 strokes

Piran et al. systematic review of PCC in major bleeding, RPTH 2019:

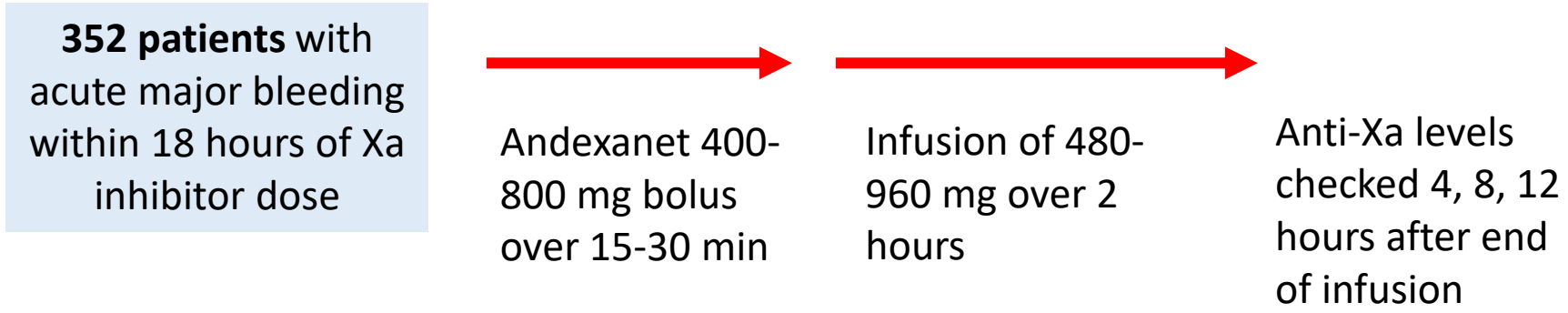
- Pooled proportion of 69% had "effective" management of major bleeding; thromboembolism rate 4%

Majeed Blood 2017
Piran 2019 RPTH

How does PCC affect coagulation in patients taking DOACs?

- Acts as a **hemostatic agent** by providing coagulation factors and increasing thrombin generation
- Is NOT a **reversal agent / antidote**
- It affects coagulation parameters (increased ETP, reduced PT) but does NOT impact on apixaban “levels”

Xa inhibitors: Andexanet alfa might be effective, but product not available and evidence poor



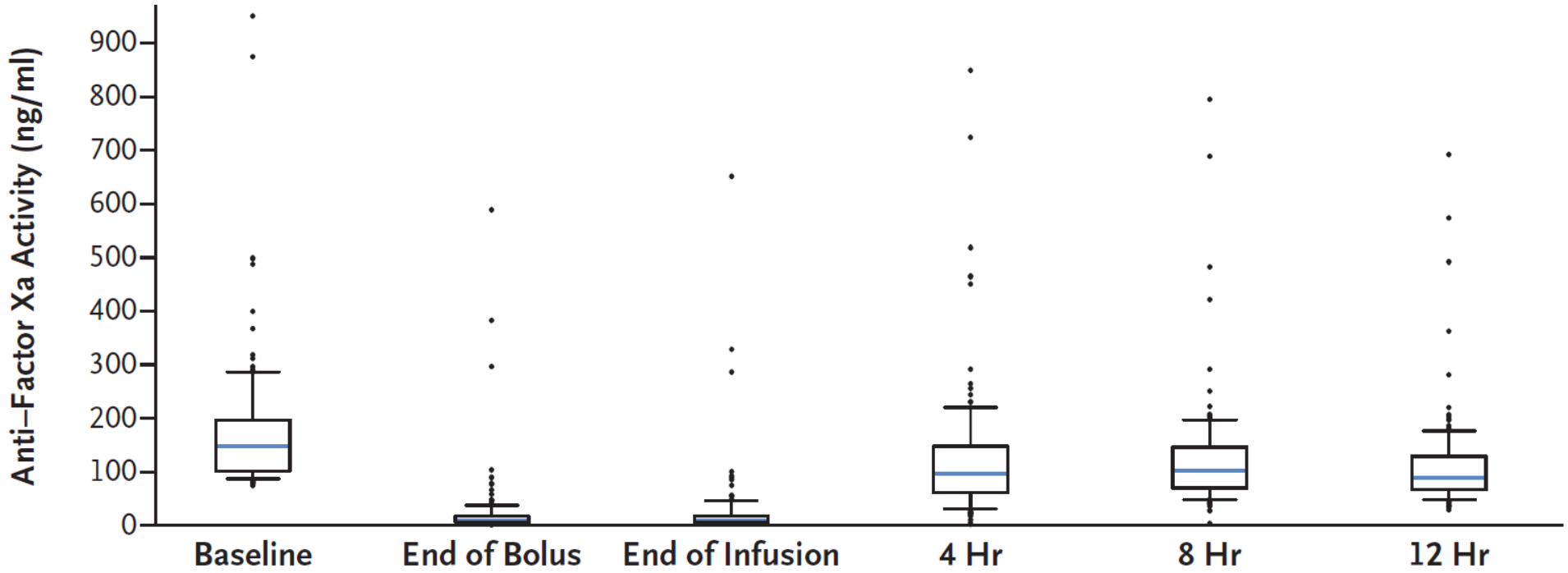
- 75-90% reduction in anti-Xa levels of Apix, Riva, LMWH after bolus
- 204/289 (71%) good or excellent hemostatic efficacy at 12 hours
- However, 10% thrombosis rate within 30 days, no control group

Hemostasis was NOT correlated with anti-Xa level

Connolly NEJM 2019

Andexanet reduces anti-Xa level effectively Approved by Health Canada but not accessible

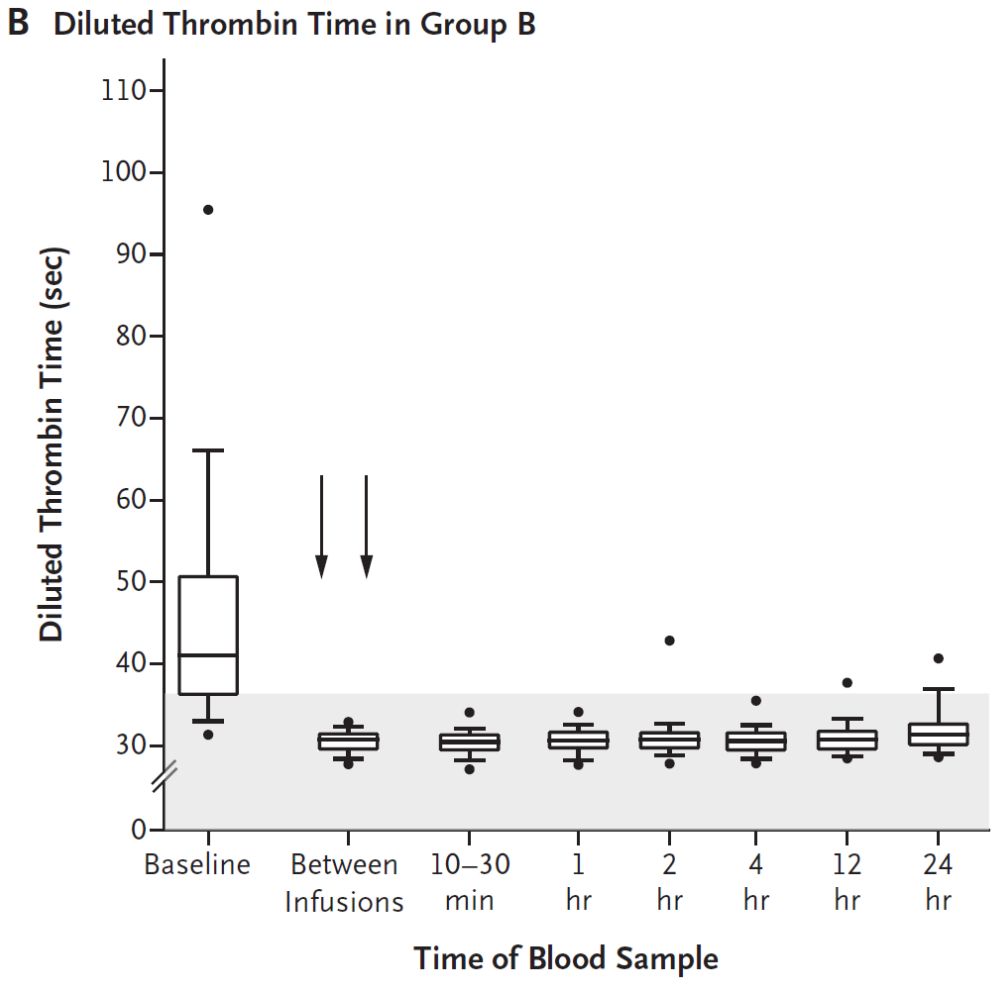
A Patients Who Received Apixaban



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	149.7	11.1	11.5	97.2	104.6	91.2
Percent Change		–92	–92	–32	–34	–38
(95% CI)		(–93 to –91)	(–93 to –91)	(–38 to –29)	(–36 to –27)	(–41 to –34)

Connolly NEJM 2019

Dabigatran: Idarucizumab is an effective reversal agent for urgent procedures



Idarucizumab 5 mg given to 202 patients undergoing procedures

Median time to procedure was 1.6 hours

Hemostasis “normal” in 93%, mildly abnormal in 5%, moderately abnormal in 2%

At 90 days, thrombosis rate was 7.4%

Pollack NEJM 2018

Other considerations

- Timing of last dose
- Renal function (expected half-life)
- Concomitant medications (CYP3A4 or P-glycoprotein inhibitors, antiplatelet agents)
- Think about adjuncts (TXA)

You are evaluating a 74 yo male who is on **rivaroxaban 20 mg daily** for AF. He has fallen and sustained ICH, and he requires **emergent decompressive craniotomy**.

CrCL is 55 ml/min. His last dose of Rivaroxaban was **14 hours ago**. INR is 1.0 (normal), aPTT is 22 s (normal), and thrombin clotting time is 15 s (normal).

These coagulation tests are not helpful!

What is the next most appropriate step?

a. Proceed to neurosurgery immediately
b. Only proceed to neurosurgery if Rivaroxaban level is confirmed < 30 ng/ml
c. Prothrombin Complex Concentrate 2000 units
d. Andexanet Alfa 400 mg IV bolus
e. Idarucizumab 5 mg IV bolus

SUMMARY: Anticoagulant Reversal for Bleeding or Urgent Invasive Procedures

Drug	Reversal Agent
LMWH	**Protamine** (max 50 mg) For Enoxaparin: < 8 hr, 1 mg per 1 mg Enox; > 8 hr, 0.5 mg per 1 mg Enox For Tinzaparin, Dalteparin: < 8 hr, 1 mg per 100 anti-Xa units; > 8 hr, 0.5 mg per 100 anti-Xa units
IV Heparin	**Protamine** 1 mg per 100 units UFH (add up total heparin dose over 2 hours). Max 50 mg
Warfarin	**Vitamin K** 5-10 mg IV. **Prothrombin Complex Concentrate** 1000-3000 units
Dabigatran	**Idarucizumab** 5 g (two consecutive 2.5 g doses) Or FEIBA 50 IU/kg
Rivaroxaban, Apixaban, Edoxaban	**PCC** (typical dose is 2000 units x 1)

So, how to handle specific situations?

(Credit: Dr. Carolyne Elbaz)

Bruising, hemorrhoidal bleeding, subconjunctival hemorrhage, minor epistaxis?

- Continue DOAC; rule out concomitant interfering meds (NSAIDs, antiplatelet agents)

Major non-life threatening bleed (ex. stable GI bleed, severe menorrhagia or epistaxis, significant hematuria)

- Hold DOAC, interventional management, supportive care, +/- TXA
- Reversal strategy based on stability and expected kinetics of drug

So, how to handle specific situations?

(Credit: Dr. Carolyne Elbaz)

Life-threatening bleeding (unstable GI bleed, ICH, retroperitoneal hemorrhage, major trauma, etc.)

- Hold DOAC, interventional or surgical measures, supportive care
- Anticoagulant reversal strategies (PCC, Idarucizumab) based on expected kinetics of drug – **you do NOT need to wait for lab results**

Common antiplatelet agents vary in half-life and time to offset

Gelbennegger and Jilma 2022

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Target	COX-1	P2Y12	P2Y12	P2Y12
Blockade	Irreversible	Irreversible	Irreversible	Reversible
T1/2 parent drug	20 min	6 hr	< 5 min	6-12 hr
Onset of action	Within 1 hr	Within 2 hr	30 min-4 hr	30 min-4 hr
Offset of action	3-4 days	5-7 days	7-10 days	3-5 days
Reversal strategy	Plt transf. DDAVP	Plt transf. DDAVP	Plt transf. DDAVP	Bentracimab

The PATCH study seemed to suggest harm from platelet transfusions in patients on antiplatelets with ICH who were NOT undergoing surgery

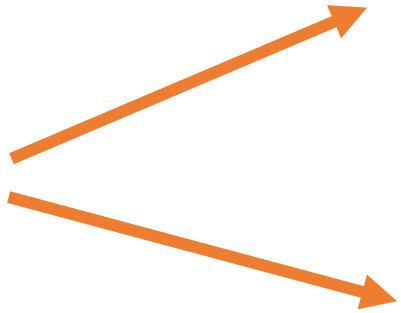
190 patients with ICH occurring while on antiplatelet at least 7 days prior (enrolled within 6 hr)

73% COX i (ASA) only
19% COX-i + dipyridamole
4% ADP-i (clopidogrel) only
3% COX-i + ADP-i

Mean platelet count 229
NO surgery planned

65% supratentorial deep, 33% supratentorial lobar, 2% infratentorial
29% age 80+

PLT transfusion
ASA: 1 dose
ADP-i: 2 doses



Standard care

Primary outcome (odds of a shift towards death or dependence at 3 months):
HIGHER in platelet transfusion group (adjusted PR 2.05)

Survival at 3 months:
LOWER in platelet transfusion group (68%) than standard care group (77%) – OR 0.62

Modified Rankin Score 3-6 at 3 months:
SIMILAR between two groups

Baharoglu et al. Lancet 2016

Desmopressin (DDAVP) might help with antiplatelet associated hemorrhage

- RATIONALE: Increases plasma Von Willebrand Factor, Factor VIII, and increases formation of procoagulant platelets and platelet adhesion

- Side effects: hypotension, hyponatremia, facial flushing, theoretical thrombotic risk

- Dose is 0.3-0.4 mcg/kg IV (for 70 kg = about 20 mcg)

Limited evidence suggests that DDAVP may be helpful in antiplatelet-associated hemorrhage

2017 meta-analysis of 10 RCTs of patients on antiplatelet (6) or platelet dysfunction from CP bypass (4) and n = 596 patients

Key conclusions: DDAVP groups had

- Less red cell transfusions
- Less blood loss intra-operatively
- Lower risk of re-operation due to bleeding

Desborough JTH 2017

Society of Critical Care Medicine 2018 recommendations reflect these uncertainties

Neurocrit Care (2016): 6-46

All based on low-quality evidence

- Suggest AGAINST platelet transfusion for antiplt-associated ICH if patient will NOT undergo surgery
- Suggest platelet transfusion for patients with ASA- or ADP inhibitor-associated ICH who will undergo neurosurgery
- Suggest AGAINST platelet transfusion in NSAID- or GPIIb/IIIa inhibitor-related ICH, even in context of neurosurgery

Society of Critical Care Medicine 2018 recommendations reflect these uncertainties

Neurocrit Care (2016): 6-46

All based on low-quality evidence

- In candidates for platelet transfusion, suggest an initial dose of one single-donor apheresis unit of platelets

- Consider a single dose of DDAVP (0.4 mcg/kg IV) in patients with ICH associated with ASA or ADP inhibitors (can be given in addition to platelet transfusion if undergoing neurosurgery)

In Summary: What I do for antiplatelet-associated major hemorrhage

Intracranial hemorrhage, no neurosurgery planned

- No platelet transfusion
- Consider DDAVP and TXA

Intracranial hemorrhage, neurosurgery planned

- Platelet transfusion (ASA – 1 dose, Ticagrelor/Clopidogrel – 2 dose)
- Consider DDAVP and TXA

Major GI hemorrhage

- No platelet transfusion
- No DDAVP or TXA (NB. HALT-IT study)

HALT-IT 2020 Lancet

Back to our objectives

1. Describe pharmacokinetic principles of DOACs
   - Short half-life, highly reliant on renal clearance
2. Discuss the perioperative management of patients on DOACs who are undergoing invasive procedures
   - Pharmacokinetics and procedural bleeding risk
3. Describe the hemostatic management and reversal strategies for patients who are bleeding while on DOACs
   - Role of PCC, Idarucizumab
4. Describe reversal strategies for patients on antiplatelet agents
   - Not everyone needs a platelet transfusion

Thank you.

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