



## Disclosure

- **Relevant Financial Conflicts of Interest**
  - **CE Presenter, Taylor Cairns:**
    - No relevant conflicts of interest exist
  - **CE mentor(s), Sarah Laliberte:**
    - No relevant conflicts of interest exist
- **Off-Label Uses of Medications**
  - This presentation will not include off-label uses of medications

### OPERATION STOP THE BLEED: Perioperative Antithrombotic Management Updates

Taylor Cairns  
PGY1 Pharmacy Resident  
University of Utah Health  
Taylor.Cairns@hsc.utah.edu  
March 30<sup>th</sup>, 2023



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## Learning Objectives – Pharmacists

*At the conclusion of this activity, participants should be able to successfully...*

1. Identify factors that affect the decision making process in managing antithrombotic therapy in the perioperative period
2. Analyze the risks of thrombosis and bleeding for a patient
3. Evaluate when to interrupt antithrombotic therapy and when to bridge with parenteral anticoagulation
4. Design a perioperative plan for patients on antithrombotic therapy
5. Describe updates to the CHEST 2022 Guidelines for perioperative management of antithrombotic therapy



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## Learning Objectives – Technicians

*At the conclusion of this activity, participants should be able to successfully...*



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## Patient Case

JM is a 68 y/o male scheduled for a knee replacement with orthopedic surgery on April 24<sup>th</sup>, 2023.

Past Medical History:

- Atrial fibrillation (CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 3)
- Hypertension
- Diabetes

He is currently taking **apixaban (Eliquis) 5 mg twice daily** and the team asks the pharmacist how to manage this medication with his upcoming surgery.



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## Guideline Update

- The American College of Chest Physicians (CHEST) released updated guidelines in August, 2022 titled “Perioperative Management of Antithrombotic Therapy”
- Updated from the 2012 Guidelines



Douketis JD, et al. *Chest*. 2022

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## Perioperative Antithrombotic Management

- **Antithrombotic therapy:** anticoagulation or antiplatelet agents
- **Perioperative period:** 1 week before until 4 weeks after a surgery/procedure
- How do we manage antithrombotic agents in patients requiring an elective operation?



Douketis JD, et al. *Chest*. 2022

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## Oral Antithrombotic Agents

### Anticoagulants

#### Vitamin K antagonist (VKA)

- Warfarin (Coumadin)

#### Direct oral anticoagulant (DOAC)

- Apixaban (Eliquis)
- Rivaroxaban (Xarelto)
- Dabigatran (Pradaxa)
- Edoxaban (Savaysa)

### Antiplatelet agents

#### COX inhibitor

- Aspirin

#### P2Y<sub>12</sub> Inhibitors

- Ticagrelor (Brilinta)
- Clopidogrel (Plavix)
- Prasugrel (Effient)



Douketis JD, et al. *Chest*. 2022

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## Parenteral Antithrombotic Agents

### Anticoagulants

#### Indirect thrombin inhibitors

- Unfractionated heparin (UFH)
- Low-molecular weight heparin (LMWH)
  - Enoxaparin (Lovenox)
  - Dalteparin (Fragmin)
- Fondaparinux (Arixtra)

### Anticoagulants (cont.)

#### Direct thrombin inhibitors

- Bivalirudin
- Argatroban

### Antiplatelet agents

#### P2Y12 inhibitor

- Cangrelor



## Warfarin



## Questions to Guide Decision Making

Do we need to interrupt warfarin therapy?

How long should we hold warfarin for the operation?

Will the patient require bridging?



## Questions to Guide Decision Making

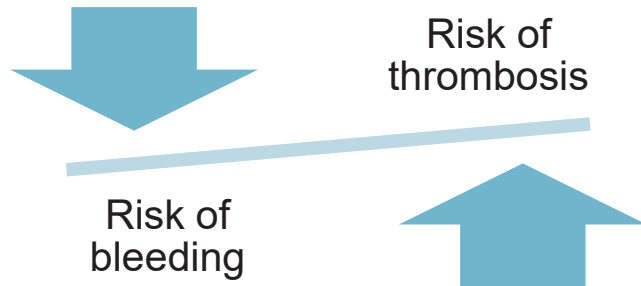
Do we need to interrupt warfarin therapy?

How long should we hold warfarin for the operation?

Will the patient require bridging?



## Risk vs. Benefit of Interrupting Therapy



Douketis JD, et al. *Chest*. 2022

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## BRUISE CONTROL Trial - 2013

Compared **continued warfarin** vs. **warfarin interruption plus heparin bridge** for pacemaker or cardioverter-defibrillator (ICD) implantation

- Patients:  $\geq 5\%$  risk of thromboembolism
- Design: 1:1 randomized trial, open-label
- Enrollment: 681 patients from Canada and Brazil



Birnie DH, et al. *N Engl J Med*. 2013

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## BRUISE CONTROL Trial – 2013

Primary Outcome	Heparin Bridge (N= 338)	Continued Warfarin (N= 343)	P Value
<b>Clinically significant hematoma</b>	54 (16.0%)	12 (3.5%)	< 0.001
- Prolonging hospitalization	16 (4.7%)	4 (1.2%)	0.006
- Requiring interruption of anticoagulation	48 (14.2%)	11 (3.2%)	< 0.001
- Requiring evacuation	9 (2.7%)	2 (0.6%)	0.03



Birnie DH, et al. *N Engl J Med*. 2013

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## Guideline recommendations

- In patients receiving warfarin undergoing a **pacemaker or ICD implantation**, it is recommended to **continue** warfarin (*strong recommendation*) \* update
- In patients receiving warfarin who undergo a ... **minor dental, dermatologic, ophthalmologic procedures** ... the authors suggest **continuing** warfarin (*conditional recommendation*)



Douketis JD, et al. *Chest*. 2022

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## Minimal Procedural Bleed Risk

**Definition:** 30 day major bleed risk ~ 0%

**Examples:**

- Minor dental procedures
- Minor dermatologic procedures
- Ophthalmologic surgery
- Pacemaker or cardioverter-defibrillator device implantation

Antithrombotic therapy can be safely **continued without interruption**



## Low-to-Moderate Procedural Bleed Risk

**Definition:** 30 day major bleed risk ~ 0-2%

**Examples:**

- Abdominal hysterectomy
- Abdominal hernia repair
- Arthroscopy
- Bronchoscopy biopsy
- Cutaneous/lymph node biopsies
- Endoscopy/colonoscopy\*
- Coronary angiography
- Foot/hand surgery
- Hemorrhoidal surgery
- Laparoscopic cholecystectomy

Antithrombotic therapy **should be interrupted** prior to the operation

*\*It is reasonable to treat all endoscopies/colonoscopies as high-risk procedures since it is often unknown if polypectomy will be required*



## High Procedural Bleed Risk

**Definition:** 30 day major bleed risk  $\geq$  2%

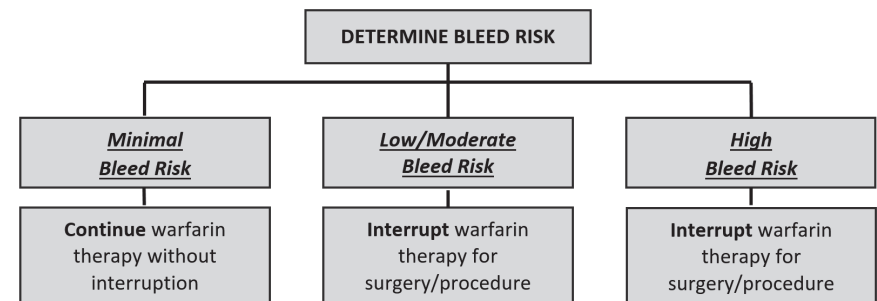
**Examples:**

- Major orthopedic surgery
- Any major operation (> 45 minutes)
- Bladder/prostate surgery
- Cardiothoracic surgery
- GI surgery
- Neurosurgery
- Retinal surgery
- Vascular surgery
- Solid tumor resection
- Reconstructive plastic surgery
- Highly vascularized organs (kidneys, liver, spleen)
- Neuraxial anesthesia
- Epidural injections

Antithrombotic therapy **should be interrupted** prior to the operation



## VKA Decision Pathway



## Questions to Guide Decision Making

Do we need to interrupt warfarin therapy?

**How long should we hold warfarin for the operation?**

Will the patient require bridging?



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## How long to hold warfarin before an operation?

- Warfarin should be stopped  $\geq$  **5 days** prior to elective operation
- Half life: 20 – 60 hours
  - Factor II: 60 hours
  - Factor VII: 4 to 6 hours
  - Factor IX: 24 hours
  - Factor X: 48 to 72 hours
- Verify INR goal with surgeon and check INR 1-2 days prior to operation
- Routine use of vitamin K is not recommended



Douketis JD, et al. *Chest*. 2022; Coumadin [package insert]. 2005.

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## When to resume warfarin after an operation?

- Resume warfarin within 24 hours after an operation
- Takes 4 – 8 days to see the full effect of warfarin
- Guidelines recommend resuming warfarin at the patient's usual dose
  - May consider doubling the dose for 1-2 days to achieve a therapeutic INR quicker



Douketis JD, et al. *Chest*. 2022

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## Questions to Guide Decision Making

Do we need to interrupt warfarin therapy?

How long should we hold warfarin for the operation?

**Will the patient require bridging?**



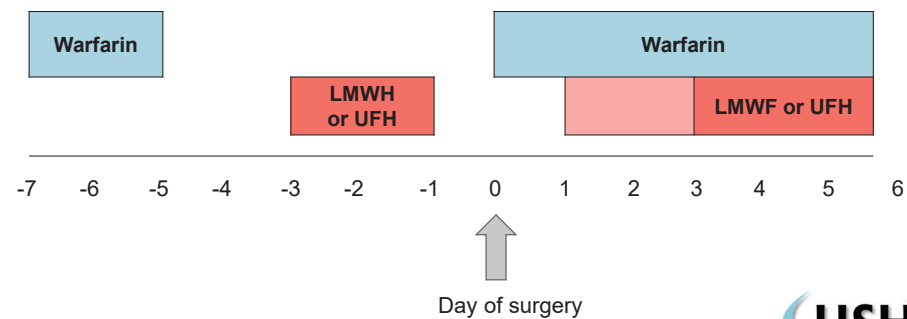
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## What is bridging?

- The use of short-acting parenteral anticoagulants (LMWH or UFH) when warfarin therapy is interrupted and INR is subtherapeutic
- First dose ~ 3 days prior to surgery
- Resume  $\geq$  24 hours post-op if low to moderate bleed risk
- Resume  $\geq$  48 – 72 hours post-op if high bleed risk
- Continue until INR therapeutic



## Warfarin Interruption and Bridge



## LMWH Bridge

- More commonly used than UFH
- Enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily
- Dalteparin 100 IU/kg twice daily or 200 IU/kg daily
- No aPTT or anti-Xa monitoring needed
- Half-life: ~3-5 hours
- Hold ~ 24 hours prior to operation



## UFH Bridge

- Less commonly used than LMWH
  - Used inpatient, chronic kidney disease, LVAD protocol etc.
- IV bolus followed by IV continuous infusion
- Titrate to one of the following:
  - aPTT 1.5-2x normal
  - Anti-factor Xa level 0.35-0.70 IU/mL
- Half-life: 1-2 hours
- Hold  $\geq$  4 hours prior to operation



## Example Bridge Plan

	Date	Enoxaparin (AM)	Enoxaparin (PM)	Warfarin (PM)	Comments
-6	3/11	--	--	5 mg	Last warfarin dose
-5	3/12	--	--	--	
-4	3/13	--	--	--	
-3	3/14	80 mg	80 mg	--	
-2	3/15	80 mg	80 mg	--	
-1	3/16	80 mg	--	--	Check INR
0	3/17	--	--	5 mg	Check with provider if OK to restart as instructed below.
1	3/18	--	--	5 mg	
2	3/19	--	80 mg	5 mg	
3	3/20	80 mg	80 mg	5 mg	
4	3/21	80 mg	80 mg	5 mg	
5	3/22	80 mg	80 mg	5 mg	Recheck INR



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## BRIDGE Trial - 2015

Compared warfarin interruption **without a bridge** vs. **with a dalteparin bridge** in patients with atrial fibrillation requiring an elective procedure

- Design: randomized, double-blind, placebo-controlled trial
- Patients: CHA<sub>2</sub>DS<sub>2</sub>-VASc < 7
- Enrollment: 1,884 patients



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Douketis JD, et al. *N Engl J Med.* 2015.

## BRIDGE Trial - 2015

Outcomes	No bridging (N= 918)	Bridging (N= 895)	P Value
Arterial thromboembolism	4 (0.4%)	3 (0.3%)	0.01 for noninferiority 0.73 for superiority
Major bleeding	12 (1.3%)	29 (3.2%)	0.005 for superiority



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Douketis JD, et al. *N Engl J Med.* 2015.

## PERIOP<sub>2</sub> Trial - 2021

Compared warfarin interruption **with placebo bridge** vs. **dalteparin bridge** in patients with atrial fibrillation or mechanical heart valve requiring an operation

- Design: randomized, double-blind, placebo-controlled trial
- Patients: 79% atrial fibrillation only, 21% prosthetic valve (44% mitral, 56% aortic)
- Enrollment: 1,471 patients



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Kovacs MJ, et al. *BMJ.* 2021.



## PERIOP<sub>2</sub> Trial - 2021

Outcomes	Atrial fibrillation			Mechanical Valve		
	No bridging (N= 496)	Bridging (N= 670)	P Value	No bridging (N= 154)	Bridging (N= 150)	P Value
<b>Primary</b>						
Major thromboembolism	8 (1.6%)	7 (1.0%)	0.39	0 (0%)	1 (0.7%)	0.49
<b>Secondary</b>						
Major bleeding	10 (2.0%)	10 (1.5%)	0.49	3 (2.0%)	1 (0.7%)	0.62
Clinically relevant non-major bleeding	20 (4.0%)	42 (6.3%)	0.09	5 (3.3%)	8 (5.3%)	0.37



Kovacs MJ, et al. *BMJ*. 2021.

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## Determine if bridging is required

- Bridging increases the risk of bleeding
- Does not reduce the risk of thromboembolic events in most patients
- NOT recommended in most patients who require warfarin interruption unless they are at HIGH risk for thromboembolism
  - Strong recommendation against bridging in most patients with atrial fibrillation <sup>\*update</sup>



Douketis JD, et al. *Chest*. 2022

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## High Risk Thromboembolism

### Mechanical heart valve

- Mitral valve with major risk factors for stroke (eg, history of multiple strokes, perioperative stroke, or valve thrombosis) <sup>\*update</sup>
- Caged ball or tilting-disc valve in mitral or aortic position
- Recent stroke or TIA < 3 months prior <sup>\*update</sup>
- Consider if history of embolism with short-term interruption of antithrombotic therapy



Douketis JD, et al. *Chest*. 2022

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## High Risk Thromboembolism

### Atrial Fibrillation

- CHA<sub>2</sub>DS<sub>2</sub>VASc score ≥ 7 or CHADS<sub>2</sub> score of 5 or 6
- Recent stroke or TIA < 3 months prior
- Rheumatic valvular heart disease
- Consider if history of embolism with short-term interruption of antithrombotic therapy



Douketis JD, et al. *Chest*. 2022

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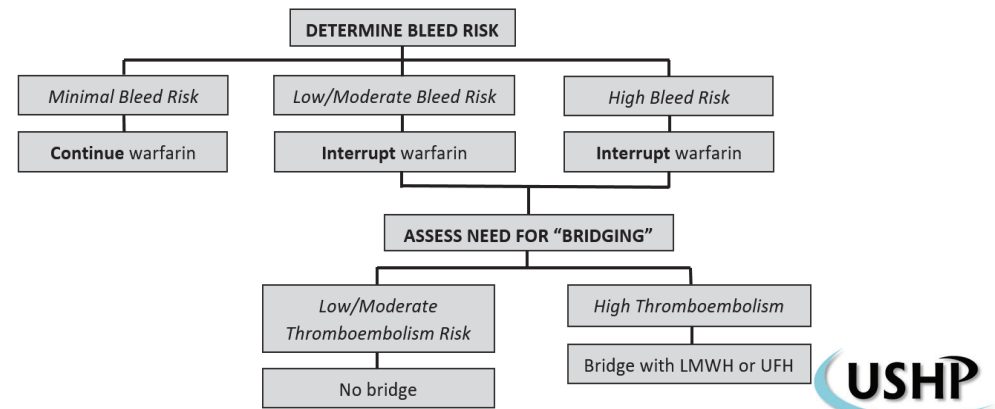
## High Risk Thromboembolism

### Venous Thromboembolism (VTE)

- Recent VTE < 3 months and especially 1 month
- Severe thrombophilia (eg, protein C/S or antithrombin deficiency, antiphospholipid syndrome, homozygous factor V Leiden)
- Active cancer associated with high VTE risk (eg, pancreatic, brain, gastric, and esophageal cancer) <sup>\*update</sup>
- Consider if history of embolism with short-term interruption of antithrombotic therapy



## VKA Decision Pathway - Review



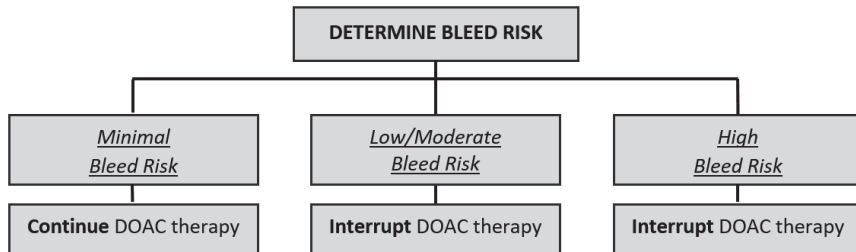
## Direct Oral Anticoagulants (DOACs)

## Direct Oral Anticoagulants (DOACs)

- Half-life: 9 – 14 hours
  - Dabigatran: up to 28 hours with renal impairment
- Do NOT need to bridge with LMWH or UFH
- Do NOT need to routinely check anti-Xa levels



## DOAC Decision Pathway



## DOAC Perioperative Interruption

DOAC	Surgery/ Procedure Bleeding Risk	Periprocedural Day									
		-5	-4	-3	-2	-1	0	1	2	3	4
Apixaban Rivaroxaban Edoxaban Dabigatran CrCl ≥ 50 ml/min	Low to moderate	✓	✓	✓	✓	X	X	✓	✓	✓	✓
Apixaban Rivaroxaban Edoxaban Dabigatran CrCl ≥ 50 ml/min	High	✓	✓	✓	X	X	X	X	?	?	✓



## Renal Impairment with Dabigatran

DOAC	Surgery/ Procedure Bleeding Risk	Periprocedural Day									
		-5	-4	-3	-2	-1	0	1	2	3	4
Dabigatran CrCl < 50 ml/min	Low to moderate	✓	✓	✓	X	X	X	✓	✓	✓	✓
Dabigatran CrCl < 50 ml/min	High	✓	X	X	X	X	X	X	?	?	✓



## Antiplatelet Therapy

\* Recommendations are conditional and may vary on a case-by-case basis



## Minor Procedures

- Continue antiplatelet therapy (aspirin or P2Y12 inhibitor)
- If receiving dual antiplatelet therapy (DAPT) can **continue aspirin** and **hold the P2Y12 inhibitor**



## Non-Cardiac Surgery or CABG

- Continue ASA (if interruption required, stop  $\leq$  7 days <sup>\*update</sup>)
- P2Y12 inhibitors
  - Ticagrelor (Brilinta): hold 3-5 days prior
  - Clopidogrel (Plavix): hold 6 days prior <sup>\*update</sup>
  - Prasugrel (Effient): hold 7 days prior <sup>\*update</sup>
- May resume within 24 hours post-op
- Routine platelet function testing is NOT recommended



## Coronary Stents and DAPT

- Delay elective procedure when able
- Stent placed in last 6 – 12 weeks: continue both or hold one agent
- Stent placed in last 3 – 12 months: hold P2Y12 inhibitor
- Bridging is not recommended in most patients

\*\*Timing of stent placement, type of stent, location of the stent and the number and length of stents should be considered



## Summary

- Majority of the CHEST Guideline recommendations are conditional recommendations
  - Only two strong recommendations in the guidelines (based on the results of the BRIDGE, PERIOP2, and BRUISE trials)
- Individualize the plan for each patient based on risk of bleeding and/or thrombosis
  - Bleed risk of the procedure
  - Thrombosis risk for the patient
  - Indication for antithrombotic therapy
  - Patient history of bleeding and/or thrombosis



## How to Locate Surgeries/Procedures in EPIC

The screenshot shows the EPIC Chart Review interface. The top navigation bar includes tabs for Summary, Chart Review, Notes, Orders, Results, Medications, Verify, and Admission. Under the Chart Review tab, there are sub-tabs for Encounters, Notes, Labs/Path/Micro, Surgery, Imaging, CV, and Procedures. The Surgery and Procedures tabs are highlighted with red boxes. Below the navigation bar, there are filters for Default, Me, PHARMACY - CLINICAL, and University Hospital. A table below shows a recent visit on 02/09/2023 for a Surgery performed by Orthopaedics - Gililland, J, with the description LEFT CONVERSION...



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## Back to the Patient Case

JM is 68 y/o male scheduled for a **knee replacement** with orthopedic surgery on April 24<sup>th</sup>, 2023.

Past Medical History:

- Atrial fibrillation (CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 3)
- Hypertension
- Diabetes

He is currently taking **apixaban (Eliquis) 5 mg twice daily** and the team asks the pharmacist how to manage this medication with his upcoming surgery.



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## References

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