Perioperative Management of Oral Anticoagulation

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Faculty Disclosures

There are no actual or potential conflicts of interest associated with this presentation.

- Victoria Lambert
- Janki Shah

Learning Objectives

- Review recommendations for when to interrupt oral anticoagulation therapy
- Review guidelines for determining thromboembolic risk
- Review recommendations for bridging therapy implementation as clinically indicated
- Review cases for appropriate method to manage oral anticoagulation interruption based on risk stratification
- Apply case-specific monitoring parameters for anticoagulation bridge therapy

What's the hype about interrupting anticoagulation therapy?

- Anticoagulation serves an important role in reducing the risk of thromboembolism or stroke
- A number of patients are at risk of developing arterial or venous thromboembolism if anticoagulation therapy needs to be withheld
- Patients will eventually need to undergo some type of procedure
- Perioperative management is a common clinical dilemma

What do we do?

Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.
Dubois V et al. Thromb J. 2017;15:14.

When to interrupt anticoagulation and implement "bridging"?

- Ask yourself 4 questions…
  - Does anticoagulation need to be withheld?
  - What is the patient's risk for clotting?
  - What is the patient's risk for bleeding?
  - What oral anticoagulant is the patient taking?

What is bridging therapy?

- "In the absence of a universally accepted definition, we define bridging anticoagulation as the administration of a short-acting anticoagulant, for an ~10-12 day period during interruption of VKA therapy when the INR is not within a therapeutic range".

Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.

Ask the Audience

- Warfarin therapy must be interrupted for all surgical procedures?

a. True
b. False
c. Not sure

Does anticoagulation need to be withheld?

- Continue anticoagulation:
  - Dental procedures (2C)
  - Cataract Removal (2C)
  - Endoscopy (diagnostic)
  - Joint injections*
    - Knees, wrist, hip
  - Minor dermatologic procedures (2C)
    - Consider procedures that do not pose increased bleeding risk while on anticoagulation

*** CAUTION: spinal/epidural procedures + anticoagulants INCREASE risk of hematoma = possible paralysis**

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.
Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.
Grant PJ et al. Anesthesiol Clin. 2009;27(4):761-77.

Discontinue oral anticoagulation therapy:

- Orthopedic surgeries
  - TKR, THR
- Biopsy
  - Breast, Lung
- Neurosurgery
- Hernia Surgery
- Colonoscopy
  - Family history of cancer/polyps

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.
Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.

Ask the Audience

- To assess the risk of clotting, we need to review?

a. The patient's anticoagulation indication
b. The type of procedure
c. Co-morbidities
d. All of the above

What is the patients' risk of clotting?

- Considerations
  - Underlying indication for anticoagulation therapy
  - Patient's risk factors for thromboembolism
    - Morbid obesity, hypercoagulable state, immobility
  - Duration of anticoagulation cessation
    - MHV – TE risk 0.046%/day
    - A fib – TE risk 0.013%/day

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.
Grant PJ et al. Anesthesiol Clin. 2009;27(4):761-77.

- Limited studies have been done to guide warfarin interruption for atrial fibrillation
  - Atrial fibrillation: BRIDGE Trial provides some insight into risk stratification
    - NOT applicable to VTE and mechanical valve patients
- Further studies are warranted for warfarin interruption in other disease states
- To date, there are no validated risk stratification schemes to reliably separate VKA-treated patients into risk strata for thromboembolism and bleeding.
- Advance planning and coordination is required to optimally manage perioperative anticoagulation

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.
Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.
Jaffer AK et al. Am J Med. 2010;123(2):141-50
McBane RD et al. Arterioscler Thromb Vasc Biol. 2010;30(3):442-8.

Thrombosis Risk

- Chest guidelines vs. ASH guidelines
- Evidence based practice guidelines which incorporate data from existing literature.
  - Atrial fibrillation
  - Mechanical Heart Valves
  - VTE

} Most common indications for long term anticoagulation

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.
Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.
Witt DM et al. Blood Adv. 2018;2(22):3257-3291.

Strength of the Recommendations Grading System

CHEST Guidelines		
Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength Supporting Evidence
Strong - 1A High quality evidence	Benefit>risk/burden or vice versa	RCT, exceptionally strong evidence from observational studies
Strong - 1B Moderate quality evidence	Benefit>risk/burden or vice versa	RCT with limitations, strong evidence from observational studies
Strong - 1C Low or very low quality evidence	Benefit>risk/burden or vice versa	Evidence for at least one critical outcome with serious flaws or indirect evidence
Weak - 2A High quality evidence	Benefit closely balanced with risks + burdens	RCT, exceptionally strong evidence from observational studies
Weak - 2B Moderate quality evidence	Benefit closely balanced with risks + burdens	RCT with limitations, strong evidence from observational studies
Weak - 2C Low or very low quality evidence	Uncertainty in estimates of benefits, risks, and burden; benefits, risk + burden may be closely balanced	Evidence for at least one critical outcome with serious flaws or indirect evidence

ASH Guidelines	
Type of Recommendation	Strength of Recommendation
Strong Recommendation	Most individuals should follow the recommended course of action.
Conditional Recommendation	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient ' s values and preferences

Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.
Witt DM et al. Blood Adv. 2018;2(22):3257-3291.

Risk Stratification for Perioperative TE

Risk	Mechanical Heart Valve	Venous Thromboembolism	Atrial Fibrillation
High	• Mitral Mechanical Valve • Any mechanical valve with history Stroke/ TIA • Aortic mechanical valve with the following risk factors: AF, prior stroke/ TIA, HTN, DM, CHF, age >75, EF <35%	• VTE within 3 months Severe thrombophilia (protein C, S or antithrombin deficiency, APAS, or multiple thrombophilias) • Active cancer treated within 6 months • Recurrent VTE occurring with previous interruption of anticoagulant therapy	• $CHADS_2$ score: ≥ 5 • CHA_2DS_2-VASc score ≥ 7 • Stroke or TIA within 3 months • Rheumatic valvular heart disease • Hx of ischemic stroke or systemic embolism occurring with previous interruption of anticoagulant therapy
Low	• Bileaflet aortic valve prosthesis without AF and no other risk factors for stroke	• Single VTE event greater than 12 months ago and no other risk factors • Non-severe thrombophilia (heterozygous Factor V Leiden mutation)	• $CHADS_2$ score: 0-4 • CHA_2DS_2-VASc Score: 0-6 • No prior stroke or TIA

Witt DM et al. Blood Adv. 2018;2(22):3257-3291.
Woller SC. Anticoagulation update: DOACs, VTE Guideliens, Bridging, and iCentra. 2016.

What is $CHADS_2$ Scoring?

- Clinical prediction rule for estimating the risk of stroke in patients with nonrheumatic atrial fibrillation.
- Used to determine the degree of anticoagulation needed.

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S

Ask the Audience

- Which is the correct description of $CHADS_2$ scoring?
  - a. CHF, hypertension, age >65, DM, prior history of stroke
  - b. Cardiomyopathy, hypertension, age >75, DM, prior history of stroke
  - c. CHF, hypertension, age > 75, DM, prior history of stroke
  - d. CHF, hyperlipidemia, age >75, DM, prior history of stroke

$CHADS_2$ Score

$CHADS_2$ Risk Criteria	Score
CHF	1
Hypertension	1
Age ≥ 75	1
DM	1
Stroke/Tia	2

Total Score	Risk Level	Stroke Rate
0-2	Low	1.9-4
3-4	Intermediate	5.9-8.5
5-6	High	12.5-18.2

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S
Gage BF et al. JAMA. 2001;285(22):2864-70.

What about CHA_2DS_2VASc?

- Refinement of $CHADS_2$
  - Additional common stroke risk factors
    - Female gender, vascular disease, age range 65-74
- Max score is 9
  - More patients classified as high risk?
  - Score ≥2 may benefit from anticoagulation therapy
  - More patients require bridging for warfarin interruption?

CHA_2DS_2-VASc Score

CHA2DS2 VASc Risk Criteria	Score
CHF	1
Hypertension	1
Age ≥ 75	2
DM	1
Stroke/Tia	2
Vascular Disease*	1
Agr 65-74	1
Female sex	1

Total Score	Risk Level	Stroke Rate
0-4	Low	1.3-4
5-6	Intermediate	6.7-9.8
7-9	High	9.6-15.2

- Prior myocardial infarction, peripheral artery disease, aortic plaque

January CT et al. Circulation. 2014;130(23):2071-104.

Pre Procedure Planning

- Low/Intermediate TE Risk
  - Hold warfarin 5 days prior to procedure (Grade 1C)
  - No Bridging (Grade 2C)
  - Check INR 1 day prior to procedure
  - If INR > 1.5, consider administering a low dose of po Vitamin K ie) 1 mg
- High TE Risk
  - Bridging anticoagulation suggested instead of no bridging (Grade 2C)
  - Refers to therapeutic dose bridging regimen - most widely studied and used in clinical practice

Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.
Witt DM et al. Blood Adv. 2018;2(22):3257-3291.

Pre Procedure Plan

- For the bridging patient
  - Aim to minimize ATE or VTE
  - No established single "heparin" bridging regimen
  - Variability exists in
    - The type of anticoagulant
    - Intensity of anticoagulation
    - Timing of perioperative administration

Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.

Types of Bridging Strategies

- High dose (therapeutic dose)
  - similar to that used in acute TE
- Low dose (prophylactic dose)
  - doses used typically to prevent postop VTE or prophylaxis in hospitalized patients
- Intermediate dose
  - Based on patient specific considerations
    - Eg. Bleeding risk of patient

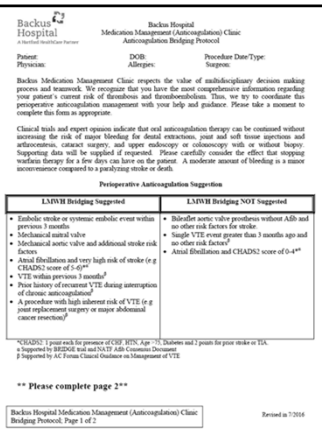
Douketis JD et al. UpToDate; 2019.

Implementing bridging

- What does the provider need to know before implementation of LMWH?
  - Allergies
  - Weight
  - Creatinine Clearance
  - Platelet count
  - INR

William W Backus Hospital Anticoagulation Clinic

- Bridging protocol
  - High Risk
    - hold warfarin 5 days prior to procedure
    - initiate enoxaparin 1.5mg/kg sc daily when INR is below the patients defined therapeutic range
    - Day prior to procedure, administer 0.75mg/kg



Backus Hospital
Medication Management (Anticoagulation) Clinic
Anticoagulation Bridging Protocol

Patient: DOB: Procedure Date/Type:
Physician: Allergies: Surgeon:

Backus Medication Management Clinic respects the value of multidisciplinary decision making process and teamwork. We recognize that you have the most comprehensive information regarding your patient's current risk of thrombosis and thromboembolism. Thus, we try to coordinate this perioperative anticoagulation management with your help and guidance. Please take a moment to complete this form as appropriate.

Clinical trials and expert opinion indicate that oral anticoagulation therapy can be continued without increasing the risk of major bleeding for dental extractions, joint and soft tissue injections and arthrocentesis, cataract surgery, and upper endoscopy or colonoscopy with or without biopsy. Supporting data will be supplied if requested. Please carefully consider the effect that stopping warfarin therapy for a few days can have on the patient. A moderate amount of bleeding is a minor inconvenience compared to a paralyzing stroke or death.

Perioperative Anticoagulation Suggestion

LMWH Bridging Suggested	LMWH Bridging NOT Suggested
• Embolic stroke or systemic embolic event within previous 3 months • Mechanical mitral valve • Mechanical aortic valve and additional stroke risk factors • Atrial fibrillation and very high risk of stroke (e.g CHADS2 score of 5-6)[a] • VTE within previous 3 months[b] • Prior history of recurrent VTE during interruption of chronic anticoagulation[b] • A procedure with high inherent risk of VTE (e.g joint replacement surgery or major abdominal cancer resection)[b]	• Bileaflet aortic valve prosthesis without Afib and no other risk factors for stroke • Single VTE event greater than 3 months ago and no other risk factors[b] • Atrial fibrillation and CHADS2 score of 0-4[a][b]

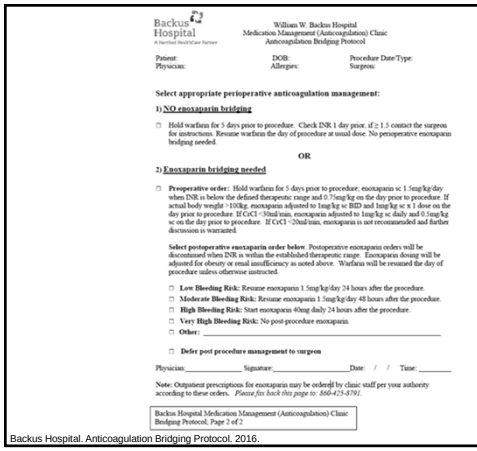
*CHADS2: 1 point each for presence of CHF, HTN, Age >75, Diabetes and 2 points for prior stroke or TIA.
a Supported by BRIDGE trial and NATF Afib Consensus Document
b Supported by AC Forum Clinical Guidance on Management of VTE

**** Please complete page 2****

Backus Hospital Medication Management (Anticoagulation) Clinic Bridging Protocol; Page 1 of 2

Revised in 7/2016

Backus Hospital. Anticoagulation Bridging Protocol. 2016.



Backus Hospital
William W. Backus Hospital
Medication Management (Anticoagulation) Clinic
Anticoagulation Bridging Protocol

Patient: DOB: Procedure Date/Type:
Physician: Allergies: Surgeon:

Select appropriate perioperative anticoagulation management:

1) NO enoxaparin bridging

☐ Hold warfarin for 5 days prior to procedure. Check INR 1 day prior, if ≥ 1.5 contact the surgeon for instructions. Resume warfarin the day of procedure at usual dose. No perioperative enoxaparin bridging needed.

OR

2) Enoxaparin bridging needed

☐ **Preoperative order:** Hold warfarin for 5 days prior to procedure; enoxaparin sc 1.5mg/kg/day when INR is below the defined therapeutic range and 0.75mg/kg on the day prior to procedure. If actual body weight >165kg, enoxaparin adjusted to 1mg/kg sc BID and 1mg/kg sc x 1 dose on the day prior to procedure. If CrCl <30ml/min, enoxaparin adjusted to 1mg/kg sc daily and 0.5mg/kg sc on the day prior to procedure. If CrCl <20ml/min, enoxaparin is not recommended and further discussion is warranted.

Select postoperative enoxaparin order below. Postoperative enoxaparin orders will be discontinued when INR is within the established therapeutic range. Enoxaparin dosing will be adjusted for obesity or renal insufficiency as noted above. Warfarin will be resumed the day of procedure unless otherwise instructed.

☐ **Low Bleeding Risk:** Resume enoxaparin 1.5mg/kg/day 24 hours after the procedure.
☐ **Moderate Bleeding Risk:** Resume enoxaparin 1.5mg/kg/day 48 hours after the procedure.
☐ **High Bleeding Risk:** Start enoxaparin 40mg daily 24 hours after the procedure.
☐ **Very High Bleeding Risk:** No post-procedure enoxaparin.
☐ **Other:** _____

☐ **Defer post procedure management to surgeon**

Physician:_____ Signature:_____Date: / / Time: _____

Note: Outpatient prescriptions for enoxaparin may be ordered by clinic staff per your authority according to these orders. *Please fax back this page to: 860-425-8791.*

Backus Hospital Medication Management (Anticoagulation) Clinic Bridging Protocol; Page 2 of 2

Backus Hospital. Anticoagulation Bridging Protocol. 2016.

Post Procedure

- Anticipate bleeding risk (preop) and hemostasis (postop)
- Factors affecting the risk for surgery related bleeding:
  - How close to surgery is the anticoagulant administered?
  - What is the dose of anticoagulant?
  - What type of surgery and its bleeding risk?

Procedures associated with **HIGH** bleeding risk

- Major surgery – expected duration> 1 hr
- Bowel resection or any major abdominal procedure
- Kidney biopsy
- Radical Prostatectomy
- Neurosurgical
- Heart valve replacement
- Joint replacement

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.

Bleeding and Bridging Continued (specific to warfarin)

- PROSPECT Trial, Dunn et al.
  - Prospective, multicenter, cohort study.
  - 260 patients, 24 sites
  - Afib and DVT patients received bridging with full dose enoxaparin

…"bleeding risk varied markedly by the extensiveness of procedure: incidence of major bleeding - invasive procedures 0.7%, minor surgery 0%, major surgery 20%."

Dunn AS et al. J Thromb Haemost 2007; 5:2211-8.

Bleeding and Bridging continued

- Risk of TE with Short-term Interruption of Warfarin Therapy, (Garcia, et al.)
  - Prospective, observational cohort study
  - Total of 1293 interruptions, 101 sites
  - Most common indications: afib, VTE, MHV
  - Patients were bridged with heparin or LMWH

…"of 108 interruptions bridged, 13% had a bleeding event: 3.7% major; 9.3% significant, non major"

Garcia DA et al. Arch Intern Med. 2008;168(1):63-9.

The BRIDGE Study

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

https://www.youtube.com/watch?v=pl2kxVxLTzg

Thrombosis.TV. ISTH 2015 - Thomas Ortel, Chief, Division of Hematology, Professor of Medicine and Hematology and Medical Director, Clinical Coagulation Laboratory, Duke University Medical Center - The management of patients with atrial fibrillation on warfarin who need treatment interruption for surgery/procedure is a common clinical problem. Bridging with low-molecular-weight heparin has been used to minimize the time that patients are not anticoagulated to mitigate the risk for arterial thromboembolism. This study seeks to determine the efficacy and safety of bridging anticoagulation.

Douketis JD et al. N Engl J Med. 2015;373(9):823-33.

The BRIDGE Study Details

- Randomized double blind placebo controlled
- Elective or scheduled procedures
- US & Canada, 108 sites
- Patients with atrial fibrillation, mean $CHADS_2$ = 2.3
  - ~38% had a $CHADS_2$ score >/= 3
- Warfarin held x 5 days prior to procedure
- Randomized to LMWH (Dalteparin) vs placebo injection
  - Total of 1884 patients randomized: 950 placebo injection, 934 Dalteparin
  - Injection started 3 days before procedure until 24 hours prior to procedure
- Post procedure
  - Bridged with placebo or LMWH with warfarin
  - Patients followed for 30 days post procedure

Douketis JD et al. N Engl J Med. 2015;373(9):823-33.

BRIDGE Study Results

- Placebo vs. LMWH
  - Risk of stroke – holding warfarin alone non-inferior to bridging
- Incidence of arterial thromboembolism
  - [illegible] to bridging group, [illegible] the placebo group
  - P = 0.01 for noninferiority
- Incidence of major bleeding
  - Bridge arm 3.2%, non bridge 1.3%. P = 0.005 for superiority
- Limitations
  - No prosthetic valve or VTE patients
  - ¾ of group male….think CHA_2DS_2VASc
  - Less patients in the non bridge group had h/o stroke

Net clinical benefit in favor of no bridging

Douketis JD et al. N Engl J Med. 2015;373(9):823-33.

Bruise Control

- Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation
  - Multicenter, single blind, RCT
  - Randomly assign patients with annual TE risk >/= 5% to continue warfarin or bridge with heparin
  - Primary outcome – clinically significant device pocket hematoma

Birnie DH et al. N Engl J Med. 2013;368(22):2084-93.

Bruise Control Results

- 681 pts randomized
  - 343 continue warfarin vs 338 bridge with IV heparin or full dose LMWH
- Primary outcome
  - 3.5% in the continue warfarin arm developed pocket hematoma vs 16% in the bridging arm
    - P < 0.001
  - Continue warfarin arm reported increased satisfaction with AC therapy

Authors do not apply results to patients on DOACs

Birnie DH et al. N Engl J Med. 2013;368(22):2084-93.

Case #1 – GH

- GH is a 66 year old male on indefinite warfarin therapy for a h/o multiple DVT's including when warfarin therapy had been interrupted. INR range of 2-3. PMH includes HTN, hyperlipidemia, diverticulitis. GH is scheduled for colon resection.
  1) What is GH's TE risk level when warfarin is withheld?
  2) What perioperative plan should be implemented?

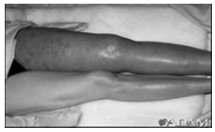
Risk Stratification for Perioperative TE

Risk	Mechanical Heart Valve	Venous Thromboembolism	Atrial Fibrillation
High	• Mitral Mechanical Valve • Any mechanical valve with history Stroke/ TIA • Aortic mechanical valve with the following risk factors: AF, prior stroke/ TIA, HTN, DM, CHF, age >75, EF <35%	• VTE within 3 months Severe thrombophilia (protein C, S or antithrombin deficiency, APAS, or multiple thrombophilias) • Active cancer treated within 6 months • Recurrent VTE occurring with previous interruption of anticoagulant therapy	• $CHADS_2$ score: ≥ 5 • CHA_2DS_2-VASc score ≥ 7 • Stroke or TIA within 3 months • Rheumatic valvular heart disease • Hx of ischemic stroke or systemic embolism occurring with previous interruption of anticoagulant therapy
Low	• Bileaflet aortic valve prosthesis without AF and no other risk factors for stroke	• Single VTE event greater than 12 months ago and no other risk factors • Non-severe thrombophilia (heterozygous Factor V Leiden mutation)	• $CHADS_2$ score: 0-4 • CHA_2DS_2-VASc Score: 0-6 • No prior stroke or TIA

Witt DM et al. Blood Adv. 2018;2(22):3257-3291.
Woller SC. Anticoagulation update: DOACs, VTE Guidelines, Bridging, and iCentra. 2016.

GH's risk?

- Thromboembolic
  - High
    - h/o recurrent DVTs while warfarin therapy was interrupted



Post Procedure

- For Warfarin
  - Resume warfarin approximately 12-24 hours after surgery (evening of or next morning) and when adequate hemostasis achieved (Grade 2C)
- LMWH
  - As per risk selection for bleeding

Douketis JD et al. Chest. 2012;141(2 Suppl):e326S-e350S.

Post Procedure

- Low/intermediate risk patient (William W Backus Hospital protocol)
  - Resume warfarin the evening of the procedure at usual dosing
  - Follow-up INR check ~ 1 week after resumption of warfarin

Backus Hospital. Anticoagulation Bridging Protocol. 2016.

Post Procedure

- High Risk

Minor Surgery/Low Bleeding Risk	Resume enoxaparin 1.5mg/kg/day 24 hrs post procedure
Moderate Bleeding Risk	Resume enoxaparin 1.5mg/kg/day 48 hours after procedure
High Bleeding Risk	Enoxaparin 40mg daily starting 24 hours after procedure
Very High Bleeding Risk	No post- procedure enoxaparin

Resume warfarin day of procedure

Continue enoxaparin post procedure until INR is therapeutic

Backus Hospital. Anticoagulation Bridging Protocol. 2016.

Ask the Audience

- Routine monitoring of AntiXa levels is necessary for LMWH bridging patients?

  a. True
  b. False

Monitoring continued

- Anti Xa monitoring may be considered if…
  - Severe renal insufficiency
    - CrCl < 30ml/min or SCr > 2 g/dL
  - Extremes of body weight

Chest guidelines suggest against the routine use of Anti Xa levels to monitor the anticoagulant effect of LMWH during bridging (Grade 2 C)

Douketis JD et al. Chest. 2008;133(6 Suppl):299S-339S.

GH – High risk for TE / High bleeding risk surgery

- Pre procedure
  - Hold warfarin 5 days prior to procedure
  - Initiate enoxaparin 1.5mg/kg sc daily when INR is below patients established INR range
  - Day before procedure initiate 0.75mg/kg sc x1
- Post Procedure
  - Restart warfarin night of procedure at usual dosing
  - Enoxaparin 40mg sc daily 24 hours after procedure
  - Continue enoxaparin bridge until INR therapeutic

or at discretion of treating MD; hemostasis should be assured

GH's Bridge Plan

Date	Warfarin dose	INR	Enoxaparin dose	Plt count
Day 5 pre procedure	0			Ordered w/ preop labs
Day 4 pre procedure	0	2		
Day 3 pre procedure	0	1.8	1.5mg/kg sc daily	
Day 2 pre procedure	0		1.5mg/kg sc daily	
Day 1 pre procedure	0	Goal < 1.5	0.75mg/kg sc x1	
Day 0 – Surgery Day	5mg		**HOLD**	
Day 1 post procedure	5mg		40mg sc daily	
Day 2 post procedure	5mg		40mg sc daily	
Day 3 post procedure	5mg	1.4	40mg sc daily	ORDER
Day 4 post procedure	5mg	1.7	40mg sc daily	
Day 5 post procedure	5mg	2.1	40mg sc daily	

DOACs for Bridging?

- Fast onset and offset
- No need for injection as the currently available NOACs for Afib and VTE are oral

The use of DOACs has not been adequately studied as a bridging agent and are not currently recommended at this time for bridging

Safety and Efficacy unknown for this purpose

Case #2 MJ – Risk Selection

- MJ is an 80 year old male on warfarin indefinitely for atrial fibrillation with an INR range of 2-3. PMH includes hypertension and overactive bladder.
- MJ is scheduled for colonoscopy and gastroenterologist wants warfarin held.

- What is his risk for clot?
- What plan should be implemented?

Ask the Audience

- What is MJ's TE risk?
  a. low
  b. high

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Witt DM et al. Blood Adv. 2018;2(22):3257-3291.
Woller SC. Anticoagulation update: DOACs, VTE Guidelines, Bridging, and iCentra. 2016.

Summary of Perioperative Management for Warfarin Interrupted Patients

- Low/Intermediate TE risk patient
  - Hold warfarin 5 days prior to procedure
  - Resume warfarin night of procedure or when hemostasis assured
- High TE risk patient
  - Hold warfarin 5 days prior to procedure
  - Start LMWH when INR below defined range
  - Resume warfarin night of procedure or when hemostasis assured
  - Resume LMWH 24 hours after procedure or when hemostasis assured
  - Discontinue LMWH when INR in therapeutic range

LMWH

- Enoxaparin
  - Anti Xa and antithrombin effects
  - $T_{1/2}$: 7 hours
  - Weight based dosing (ABW)
  - Thrombocytopenia risk < 3%
  - Risk major hemorrhage 4% or less
  - Dosing: 1.5mg/kg sc daily or 1mg/kg sc bid
- Dalteparin
  - Anti Xa and antithrombin effects
  - $T_{1/2}$: 3-5 hours
  - Weight based dosing (ABW)
  - Thrombocytopenia risk < 1%
  - Risk major hemorrhage 0-4.6%
  - Dosing: 200 IU/kg sc q24 hr. Max 18,000 IU
    - Dosage based on TBW up to 190kg

Fragmin (dalterparin) [package insert]. Pfizer; 2010.
Lovenox (enoxaparin) [package insert]. Sanofi-Aventis; 2018.

Other Injectables

Fondaparinux
- Inhibitor of factor Xa
- $T_{1/2}$: 17-21 hours
- Fixed dosing
- Thrombocytopenia risk ~ 0.5% up to 3%
- Risk of major hemorrhage < 3%; up to 5% in pts < 50kg
- Body weight
  - < 50kg : 5mg
  - 50-100kg : 7.5mg
  - >100kg : 10mg
    - SC once daily dosing

Arixtra (fondaparinux) [package insert]. GlaxoSmithKline; 2010.

Other considerations

- Who will perform injections?
- Does patient have RX coverage?
- Is patient homebound following surgery?
- Does patient understand instructions?
  - Provide written instructions

Down the pipeline

- PERIOP-2
  - Double blind randomized controlled trial of Post-Operative LMWH Bridging Therapy vs Placebo Bridging Patients Who Are at High Risk for Arterial TE

U.S. National library of Medicine. https://clinicaltrials.gov/ct2/show/NCT00432796.

Moving on to DOACs

Leaving Warfarin-ville

Perioperative Management of Direct Oral Anticoagulants (DOACs)

- Anti Xa Inhibitors
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
  - Edoxaban (Savaysa®)
  - Betrixaban (Bevyxxa®)
- Direct Thrombin Inhibitor
  - Dabigatran (Pradaxa®)

Bevyxxa (betrixaban) [package insert]. Portola Pharmaceuticals; 2017.
Eliqiuis (apixaban) [package insert]. Bristol-Myers Squibb; 2016.
Pradaxa (dabigatran) [package insert]. Boehringer Ingelheim; 2011.
Savaysa (edoxaban) [package insert]. Daiichi Sankyo; 2015.
Xarelto (rivaroxaban) [package insert]. Janssen; 2016.

DOAC Indications

Drug	Nonvalvular Atrial Fibrillation	DVT and/or PE Treatment	Extended VTE Prophylaxis	VTE Prophylaxis	Stable CAD or PVD
Dabigatran	+	+*	+	+ (THA)	
Apixaban	+	+	+	+ (THA/TKA)	
Rivaroxaban	+	+	+	+ (THA/TKA)	+
Edoxaban	+	+*			
Betrixaban				+ (in hospitalized patients	

Bevyxxa (betrixaban) [package insert]. Portola Pharmaceuticals; 2017.
Eliqiuis (apixaban) [package insert]. Bristol-Myers Squibb; 2016.
Pradaxa (dabigatran) [package insert]. Boehringer Ingelheim; 2011.
Savaysa (edoxaban) [package insert]. Daiichi Sankyo; 2015.
Xarelto (rivaroxaban) [package insert]. Janssen; 2016.

DOAC Interruption Considerations

- Does the DOAC need to be withheld?
- What is the patient's risk for clotting?
- What is the patient's risk for bleeding?
- What is the renal function?
- DOAC half life?

Pharmacokinetics

Medication	Urinary Excretion	Half Life
Rivaroxaban	80%	5-9 hours
Apixaban	~27% parent drug	8-15 hours
Edoxaban	~50%	10-14 hours
Betrixaban	11%	19-27 hours
Dabigatran	80%	12-17 hours

Bevyxxa (betrixaban) [package insert]. Portola Pharmaceuticals; 2017.
Eliqiuis (apixaban) [package insert]. Bristol-Myers Squibb; 2016.
Pradaxa (dabigatran) [package insert]. Boehringer Ingelheim; 2011.
Savaysa (edoxaban) [package insert]. Daiichi Sankyo; 2015.
Xarelto (rivaroxaban) [package insert]. Janssen; 2016.

DOAC Package Insert Interruption Recommendations

- Dabigatran
  - CrCl >/= 50ml/min 1-2 days
  - CrCl < 50ml/min 3-5 days
- Apixaban
  - Low bleeding risk 24 hours prior
  - Moderate to high bleeding risk 48 hours prior
- Rivaroxaban
  - At least 24 hours prior
  - Consider > 24 hours if increased bleeding risk vs urgency of procedure
- Edoxaban
  - At least 24 hours prior

Bevyxxa (betrixaban) [package insert]. Portola Pharmaceuticals; 2017.
Eliquis (apixaban) [package insert]. Bristol-Myers Squibb; 2016.
Pradaxa (dabigatran) [package insert]. Boehringer Ingelheim; 2011.
Savaysa (edoxaban) [package insert]. Daiichi Sankyo; 2015.
Xarelto (rivaroxaban) [package insert]. Janssen; 2016.

2017 ACC Consensus Decision Pathway for Perioperative Management of Patients with Nonvalvular Atrial Fibrillation

TABLE 2 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (46,60-67).

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

Doherty JU et al. J Am Coll Cardiol. 2017;69(7):871-898.

American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication

Table 4. Summary of Recommended Perioperative Anticoagulation Management Strategies

Category	High bleeding risk procedure	Low bleeding risk procedure
High thromboembolic risk		
Warfarin	Give last dose 6 d before operation, bridge with LMWH or UFH, resume 24 h postoperatively.	Give last dose 6 d before operation, bridge with LMWH or UFH, resume 24 h postoperatively.
DOAC	Give last dose 3 d before operation,* resume 2 to 3 d postoperatively.	Give last dose 2 d before operation,* resume 24 h postoperatively.
Intermediate thromboembolic risk		
Warfarin	Give last dose 6 d before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively.	Give last dose 6 d before operation, determine need for bridging by clinician judgment and current evidence, resume 24 h postoperatively.
DOAC	Give last dose 3 days before operation,* resume 2 to 3 d postoperatively.	Give last dose 2 d before operation,* resume 24 h postoperatively.
Low thromboembolic risk		
Warfarin	Give last dose 6 d before operation, bridging not recommended, resume 24 h postoperatively.	Give last dose 6 d before operation, bridging not recommended, resume 24 h postoperatively.
DOAC	Give last dose 3 d before operation,* resume 2 to 3 d postoperatively.	Give last dose 2 d before operation,* resume 24 h postoperatively.

*In patients with CrCl < 50 mL/min on dabigatran, the last dose should be given 3 d before the procedure for low bleeding risk surgery, and 4 to 5 d before the procedure for high bleeding risk operation.
DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

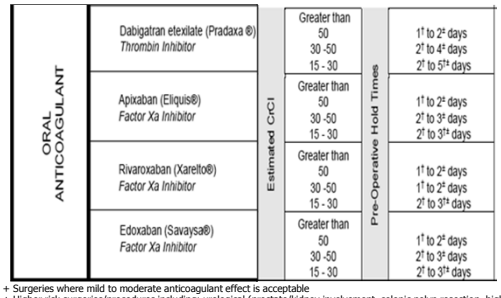
Hornor MA et al. J Am Coll Surg. 2018;227(5):521-536.e1.

PAUSE Study

- PAUSE: Perioperative Anticoagulant Use for Surgery Evaluation
- Included patients
  - AF taking DOAC requiring interruption for an elective procedure
- Excluded patients
  - Severe renal dysfunction
- Methods
  - Standardized protocol based on DOAC PK parameters, procedure associated bleeding risk, and CrCl
    - Low bleeding risk procedure: Hold DOAC 1 day prior to and after
    - High bleeding risk procedure: hold DOAC 2 days prior to an after
- Outcomes
  - Major bleeding <2%
  - ATE <1%

Douketis JD et al. Thromb Haemost. 2017;117(12):2415-2424.

Hartford HealthCare Perioperative DOAC management reference



+ Surgeries where mild to moderate anticoagulant effect is acceptable
‡ Higher risk surgeries/procedures including: urological (prostate/kidney involvement, colonic polyp resection, highly vascular organs eg. Liver, spleen, joint replacement, cancer surgery, cardiac or neurosurgical, neuroaxial anesthesia : No or minimal anticoagulant effect is acceptable.

Hartford Healthcare. Perioperative cessation of Anticoagulant Medications. 2019.

Case #3 - CC

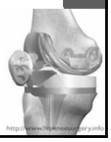
- CC is a 79 year old male on apixaban 5mg bid indefinitely for the diagnosis of atrial fibrillation. PMH inclusive of hypertension and GERD. CC is scheduled for Left Total Knee Replacement.
- Relevant information: 5'10", 86.4kg, Scr 1.5
  - How should CC's apixaban therapy be managed for surgery?

Ask the Audience

- CC's TE risk can be classified as
  a. low
  b. high

CC's Apixaban Interruption

a. Crcl is 48.8ml/min, hold apixaban 2-3 days prior to surgery
b. Crcl is 41.2ml/min, hold apixaban 5 days prior to surgery
c. CrCl is 41.2ml/min, interruption is not needed
d. Crcl is 48.8ml/min, hold apixaban 7 days prior to surgery



DOAC Resumption

- In general:
  - High bleeding risk - 24 to 72 hours
  - Low bleeding risk - 6-8 hours
- Bleeding risk considerations
- Hemostasis
- Mechanical VTE prophylaxis in hospitalized patients if anticoagulation resumption is delayed
- Prolonged cessation of anticoagulation post operatively, can consider VTE prophylaxis.

Dubois V et al. Thromb J. 2017;15:14.

Summary

- Determine if anticoagulation needs to be withheld for procedure
- Determine risk for thromboembolism or stroke
- Determine bleeding risk
  - Pre and post procedure
  - Hemostasis achieved
- Implement monitoring parameters
- Patient education and teaching is important throughout entire perioperative period

THANK YOU

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