Anticoagulant Cases

12

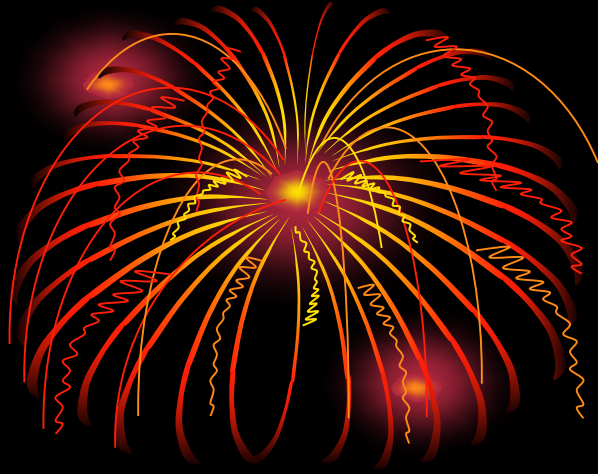
11

9

8

7

4



Intrinsic + Common = aPTT

Extrinsic + Common = PT

10

5

Common Pathway

2

1

Xa Inhibitors

rivaroxaban (Xarelto)
apixaban (Eliquis)
edoxaban (Savaysa)

What is true regarding the INR of patients receiving a Xa inhibitor?

1. Xa inhibitors do NOT prolong the INR
2. At high doses but not at low doses, Xa inhibitors prolong the INR
3. Xa inhibitors prolong the INR in a time-dependent fashion

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A 95 y/o F is receiving rivaroxaban for afib

- SCr = 0.91mg/dL, CrCl ~40mL/min

	Day 1	Day 3	Day 4	Day 5	Day 7
INR	2.7	1.8	3.7	2.6	2.1
Rivaroxaban Dose	15mg	held	15mg	15mg	15mg
Time between rivaroxaban And INR	unknown	32hrs	7hrs	13.3hrs	19hrs

What is the significance of these INR fluctuations?

1. None
2. Bleeding rate are higher with elevated INRs
3. Thrombosis rates are lower with elevated INRs

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37 y/o F switched from warfarin to rivaroxaban

- Rivaroxaban 15mg BID initiated for new DVT
- Pt had received 6 doses of warfarin
- Rivaroxaban was started the evening of Day 1 (after INR was drawn)

	Day 1	Day 2	Day 2 (following am dose)	Day 3
INR	1.9	3.6	6.0	2.0
Time between rivaroxaban and INR		8.5hrs	4.75hrs	~24hrs

What is the significance of Anti-Xa levels in patients receiving rivaroxaban?

1. None
2. Anti-Xa levels can be used to estimate drug exposure
3. Anti-Xa levels have been associated with risk of bleeding and risk of thrombosis

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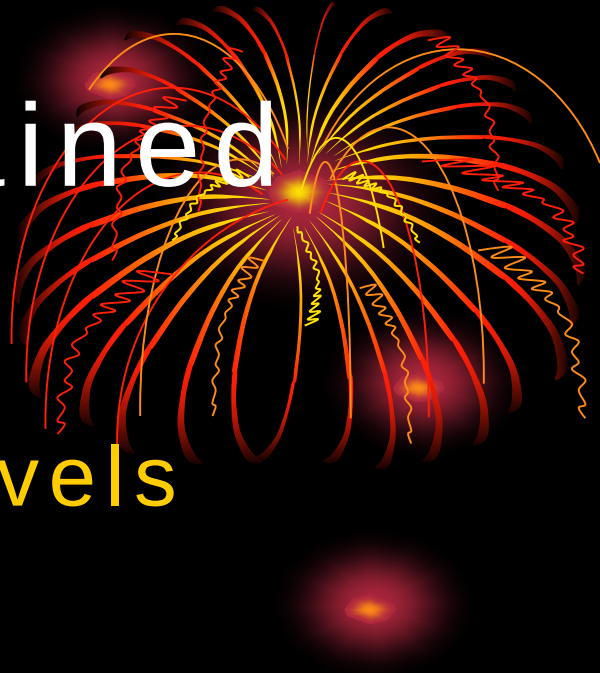
What is the significance of Anti-Xa levels in patients receiving rivaroxaban?

- Rivaroxaban anti-Xa trough concentrations:
  - 20mg daily
    - Median = 32ng/mL
    - 5-95th percentile = 6-239ng/mL

- Pernod G, Albaladejo P, Godier A, et al. Arch Cardiovasc Dis 2013

What Can Be Obtained at BUMCP?



- Two types of anti-Xa levels available
- “heparin” anti-Xa levels
- “LMWH” anti-Xa levels
- We DO NOT have reagents calibrated for rivaroxaban or apixaban

In Summary

- Timing of administration matters (aPTT, INR, and anti-Xa levels)
  - Don’t draw INRs – clinical significance unknown
- Anti-Xa levels specifically calibrated to rivaroxaban or apixaban are current NOT available
- Available anti-Xa levels do not provide useful information regarding degree of anticoagulation

Reversal of Xa Inhibitors

- No FDA approved agent (yet!)
- 3-Factor PCC is our formulary treatment of choice
  - We do NOT carry 4-Factor PCC
- Dose is 25-50units/kg (max dose 5,000units)
- ~$1.0/unit

What is 3-Factor PCC called in Cerner (i.e. how does it appear on the MAR)?

1. Prothrombin complex concentrate
2. PCC 3-factor
3. Factor 9 complex
4. KCentra

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2. PCC 3-factor
3. Factor 9 complex (Profilnine)
4. KCentra

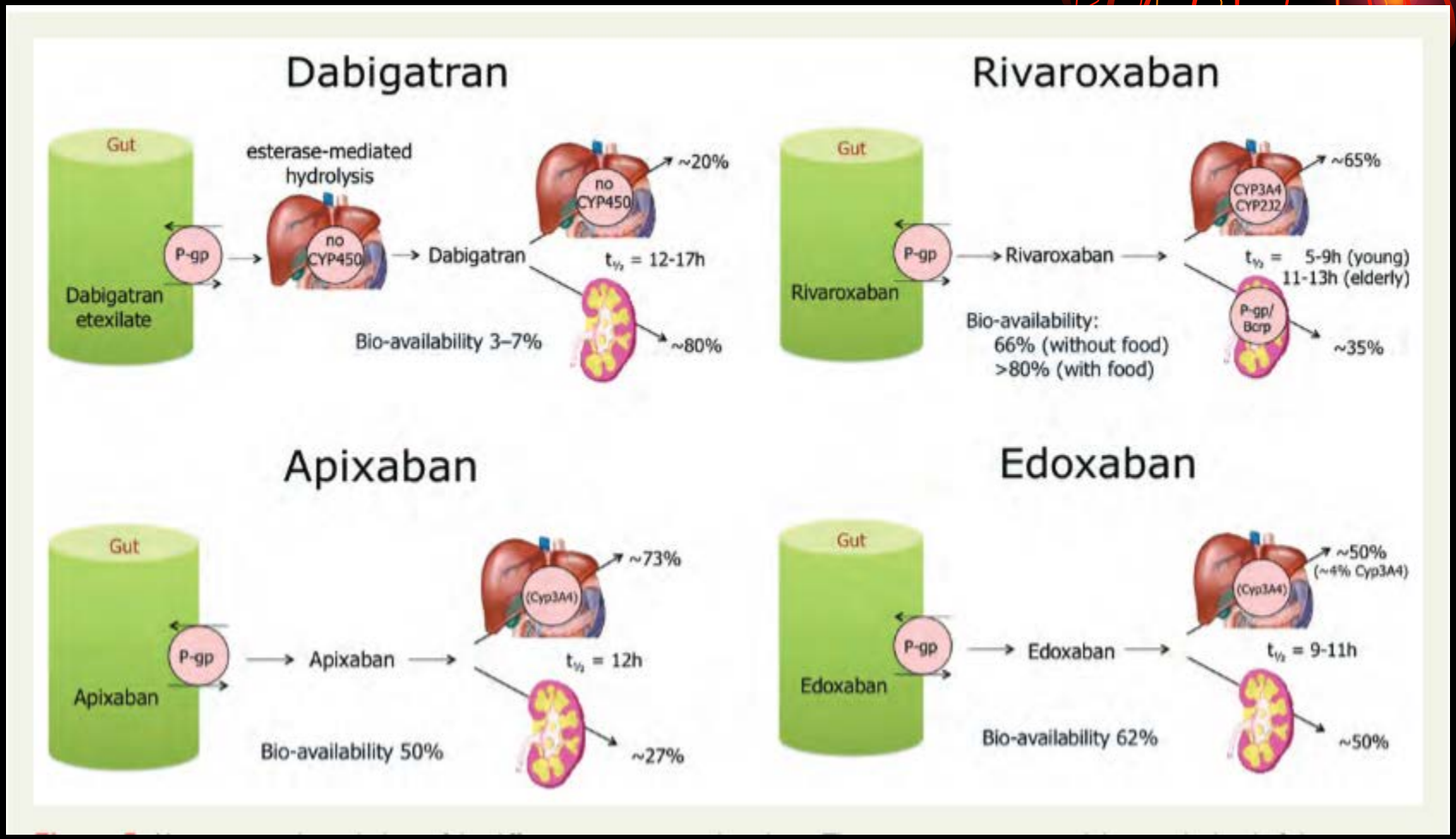
(Relative) Contraindications for Xa Inhibitors?

- A 69 y/o male with history of epilepsy is found to have new onset afib
  - Takes phenobarbital and phenytoin
- S/P ablation
- Apixaban is initiated

Phenobarbital and phenytoin would be expected to do what to the apixaban concentration?

1. Decrease apixaban concentration, possibly leading to excessive stroke
2. Increase apixaban concentration, possibly leading to excessive bleeding
3. Increase apixaban absorption, possibly leading to excessive stroke
4. No effect

Drug Interactions



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Warfarin

What is NOT an important consideration when selecting an initial warfarin dose?

1. Age
2. Weight
3. Gender
4. Hepatic function
5. Renal function

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Initial Dose Selection

- Warfarin sensitivity risk factors include:
  - Age
  - Hepatic function
  - Drug interactions
  - Gender
  - Dietary factors (vitamin K intake)
  - Recent cardiothoracic surgery

Signficant drug interactions with warfarin include:

1. Cefepime, Primaxin, Zosyn
2. Augmentin, cefazolin, ceftriaxone
3. Bactrim, fluconazole, metronidazole
4. Voriconazole, nafcillin, penicillin

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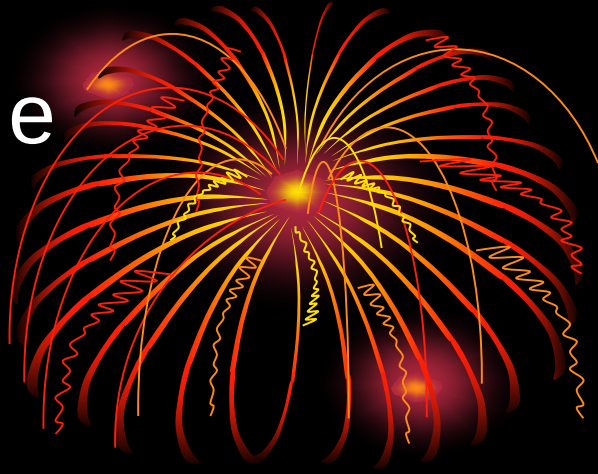
4. Voriconazole, nafcillin, penicillin

These would be expected to increase or decrease the INR?

Which of the following are INDUCERS of warfarin metabolism?



1. Nafcillin
2. Rifampin
3. Phenobarbital
4. 2 and 3
5. All of the above

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Warfarin “Loading Dose”

The CHEST Guidelines (2012) endorse a warfarin loading dose of:

1. 10mg x1 dose
2. 10mg x2 doses
3. 15mg x1 dose
4. 10mg x3 doses

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4. 10mg x3 doses

CHEST/ACCP Guidelines (2012)

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on INR measurements rather than starting with the estimated maintenance dose (Grade 2C)

74 y/o F with new onset afib

- No hepatic labs available
- Baseline INR 1.0

	Day 1	Day 2	Day 3
INR	1.0	1.1	2.0
Warfarin Dose	10mg	10mg	

82 y/o F presents with dizziness

- PMH: HTN, chronic back pain
- Found to have afib w/ RVR
- Baseline INR 1.2, Alb 3.1

- Initial warfarin dose?

82 y/o female started on warfarin for afib

- Received 10mg warfarin x1
- Pharmacist intervention:
  - Dose ↓ 5mg on day 2
- Dronedarone started Day 2

	Day 1	Day 2	Day 3
INR	-	1.2	3.3, >16
Warfarin Dose	10mg	5mg	-

Summary

- 2.5 – 7.5mg reasonable starting dose, depending on risk factors for warfarin sensitivity
  - Age, hepatic function, drug interactions, gender, etc.
- Carefully select patients for 10mg loading dose, if desired

Rapidly Rising INRs

- 74 y/o F with new onset afib
  - No hepatic labs available
  - Baseline INR 1.0
- What dose do you want on day 3?

	Day 1	Day 2	Day 3
INR	1.0	1.1	2.0
Warfarin Dose	10mg	10mg	

Which patient population was most poorly managed, based on a retrospective review at BUMCP?

1. Patients with major bleeding
2. Patients with nonmajor bleeding
3. Patients requiring reversal for a procedure
4. Patients with an elevated INR but no bleeding

Retrospective Review of Warfarin Reversal at BUMCP

- 360 encounters (BUMCP and Baywood)
- Of those receiving vitamin K with an elevated INR (no bleeding, no procedure):
  - Only 20% had a therapeutic INR 48hrs later
  - Most INRs were subtherapeutic (53%)

Which patient population was most poorly managed, based on a retrospective review at BUMCP?

1. Patients with major bleeding
2. Patients with nonmajor bleeding
3. Patients requiring reversal for a procedure
4. Patients with an elevated INR but no bleeding

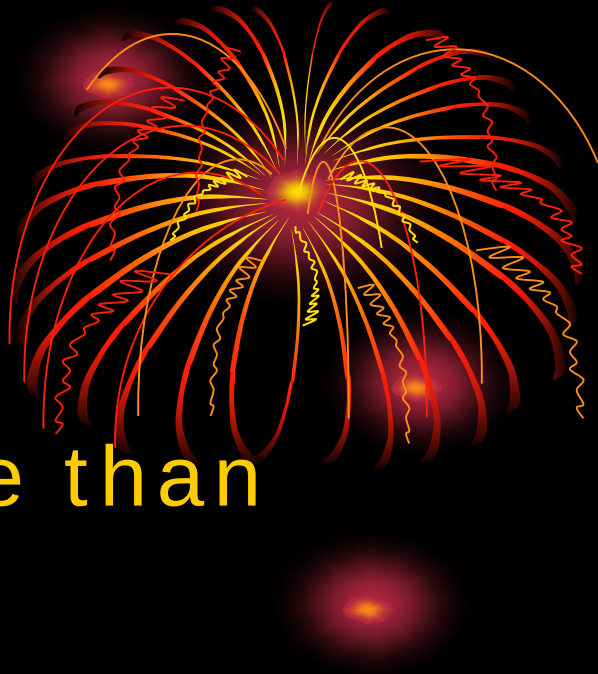
Vitamin K dose for Reversal in a patient with elevated INR but no bleeding is:

1. 1mg PO
2. 2.5mg PO
3. 5mg PO
4. 1mg IV
5. 1 and 2
6. All of the above

Vitamin K dose for Reversal in a patient with elevated INR but no bleeding is:

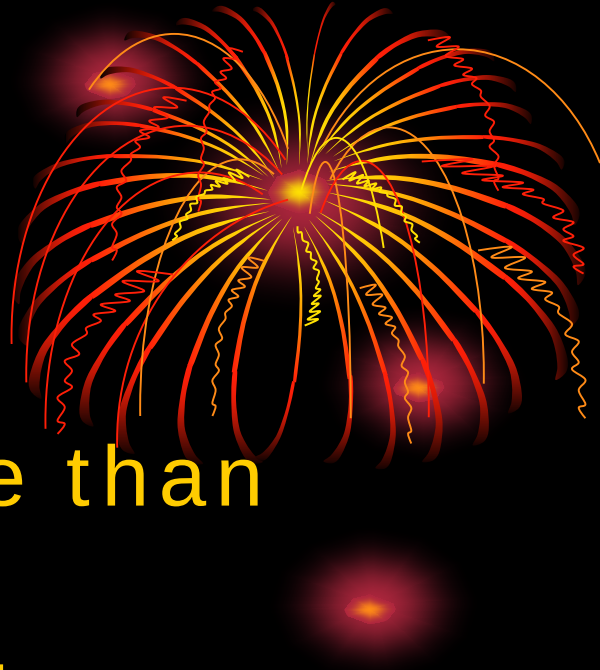
1. 1mg PO
2. 2.5mg PO
3. 5mg PO
4. 1mg IV
5. 1 and 2
6. All of the above

Warfarin Reversal



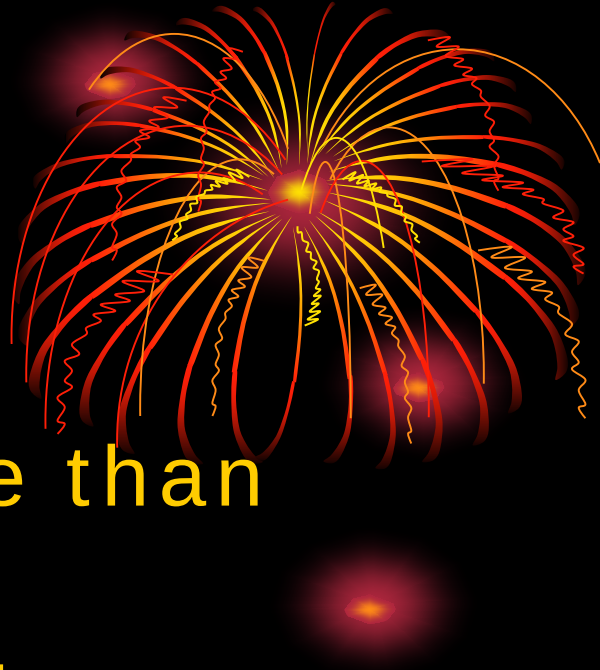
- When do you need more than vitamin K alone?

Warfarin Reversal



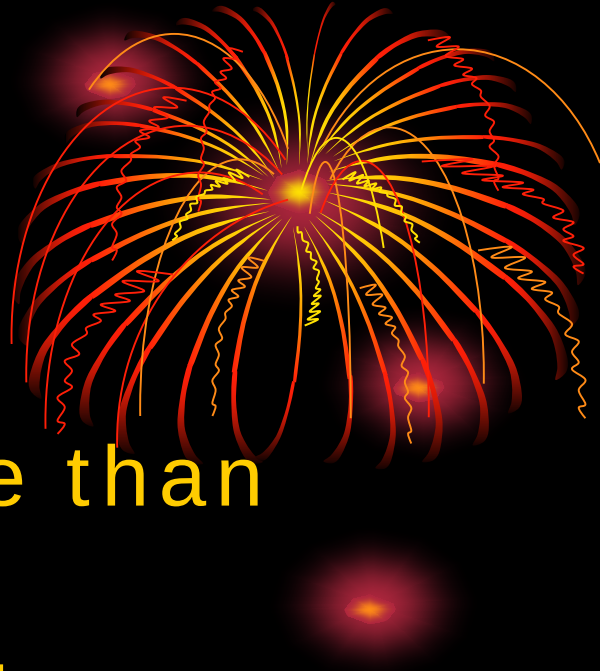
- When do you need more than vitamin K alone?
  - Timing and urgency are key considerations

Warfarin Reversal



- When do you need more than vitamin K alone?
  - Timing and urgency are key considerations
- What are additional options?

Warfarin Reversal



- When do you need more than vitamin K alone?
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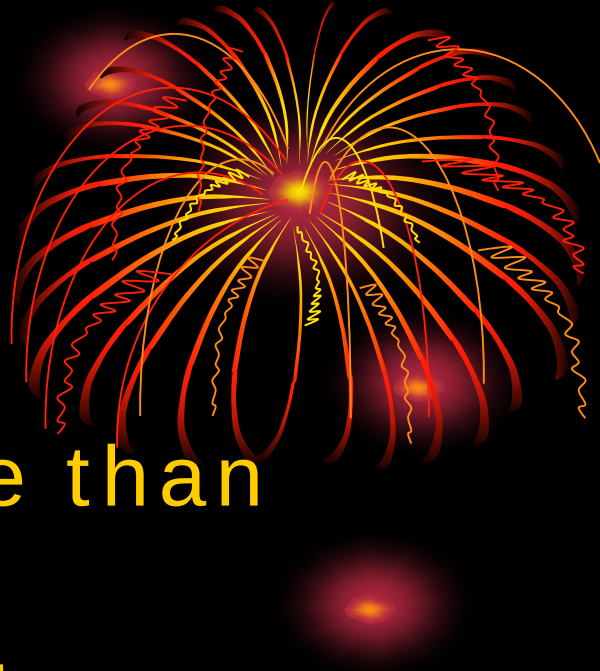
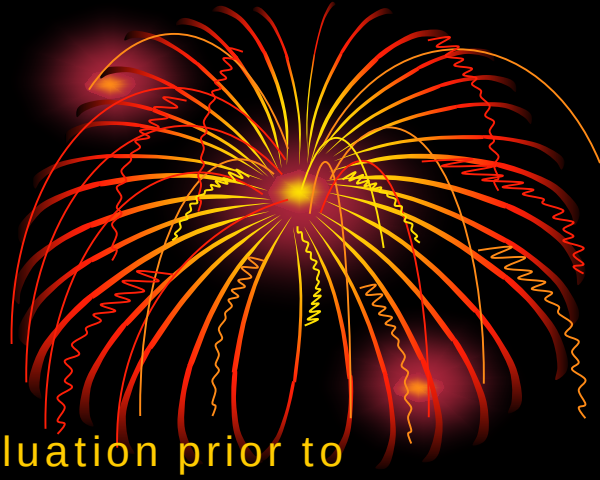
- What are additional options?
- Are they used alone or in combination with vitamin K?

Warfarin Reversal



- When do you need more than vitamin K alone?
  - Timing and urgency are key considerations
- What are additional options?
- Are they used alone or in combination with vitamin K?
- Always consider long term plan

Bridging



- A 58-year-old man is seen for preoperative evaluation prior to umbilical hernia repair scheduled in 1 week. He has been in good health except for increasing pain at the site of his umbilical hernia. He has experienced no incarceration of his hernia. He exercises regularly without symptoms. He has no history of stroke or transient ischemic attack. Medical history is notable for aortic valve replacement with bileaflet mechanical prosthesis performed 3 years ago for a bicuspid aortic valve and decreasing exercise capacity. Medications are warfarin and low-dose aspirin.
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Bridging

- Laboratory studies show a normal serum creatinine level.
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- An electrocardiogram performed 2 months ago showed normal sinus rhythm with normal intervals. An echocardiogram from 2 months ago showed normal left ventricular function and normal function of the mechanical aortic valve prosthesis.
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- In addition to continuing aspirin and stopping warfarin 5 days before surgery, which of the following is the most appropriate management for preoperative anticoagulation bridging?
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- A. Intravenous unfractionated heparin
- B. Prophylactic dose subcutaneous enoxaparin
- C. Therapeutic dose subcutaneous enoxaparin
- D. No bridging anticoagulation

How I treat anticoagulated patients undergoing an elective procedure or surgery
Alex C. Spyropoulos1 and James D. Douketis2
BLOOD, 11 OCTOBER 2012 VOLUME 120, NUMBER 15

Table 1. Suggested risk stratification for perioperative thromboembolism[7]

Risk category	MHV	Atrial fibrillation	VTE
High (> 10%/y risk of ATE or > 10%/mo risk of VTE)	Any mechanical mitral valve	$CHADS_2$ score of 5 or 6	Recent (< 3 mo) VTE
	Caged-ball or tilting disc valve in mitral/aortic position	Recent (< 3 mo) stroke or TIA	Severe thrombophilia
			Deficiency of protein C, protein S or antithrombin
	Recent (< 6 mo) stroke or TIA	Rheumatic valvular heart disease	Antiphospholipid antibodies
			Multiple thrombophilias
Intermediate (4%-10%/y risk of ATE or 4%-10%/mo risk of VTE)	Bileaflet AVR with major risk factors for stroke	$CHADS_2$ score of 3 or 4	VTE within past 3-12 mo
			Recurrent VTE
			Nonsevere thrombophilia
			Active cancer
Low (< 4%/y risk of ATE or < 2%/mo risk of VTE)	Bileaflet AVR without major risk factors for stroke	$CHADS_2$ score of 0-2 (and no prior stroke or TIA)	VTE > 12 mo ago

TIA indicates transient ischemic attack; AVR, aortic valve replacement; ATE, arterial thromboembolism; VTE, venous thromboembolism; and MHV, mechanical heart valve.

What is the risk of thrombosis?

Table 2. Procedural bleeding risks[7,26,27,65]

High (2-day risk of major bleed 2%-4%)
Heart valve replacement
Coronary artery bypass
Abdominal aortic aneurysm repair
Neurosurgical/urologic/head and neck/abdominal/breast cancer surgery
Bilateral knee replacement
Laminectomy
Transurethral prostate resection
Kidney biopsy
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
PEG placement
Endoscopically guided fine-needle aspiration
Multiple tooth extractions
Vascular and general surgery
Any major operation (procedure duration > 45 minutes)
Low (2-day risk of major bleed 0%-2%)
Cholecystectomy
Abdominal hysterectomy
Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endonosonography without fine-needle aspiration
Pacemaker and cardiac defribillator insertion and electrophysiologic testing
Simple dental extractions
Carpal tunnel repair
Knee/hip replacement and shoulder/foot/hand surgery and arthroscopy
Dilatation and curettage
Skin cancer excision
Abdominal hernia repair
Hemorrhoidal surgery
Axillary node dissection
Hydrocele repair
Cataract and noncataract eye surgery
Noncoronary angiography
Bronchoscopy ± biopsy
Central venous catheter removal
Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies

This table is based on definitions derived from surgical/subspecialty societies in anticoagulant bridging or anticoagulant bridging management studies.

What is the risk of bleeding?

To bridge or not to bridge....

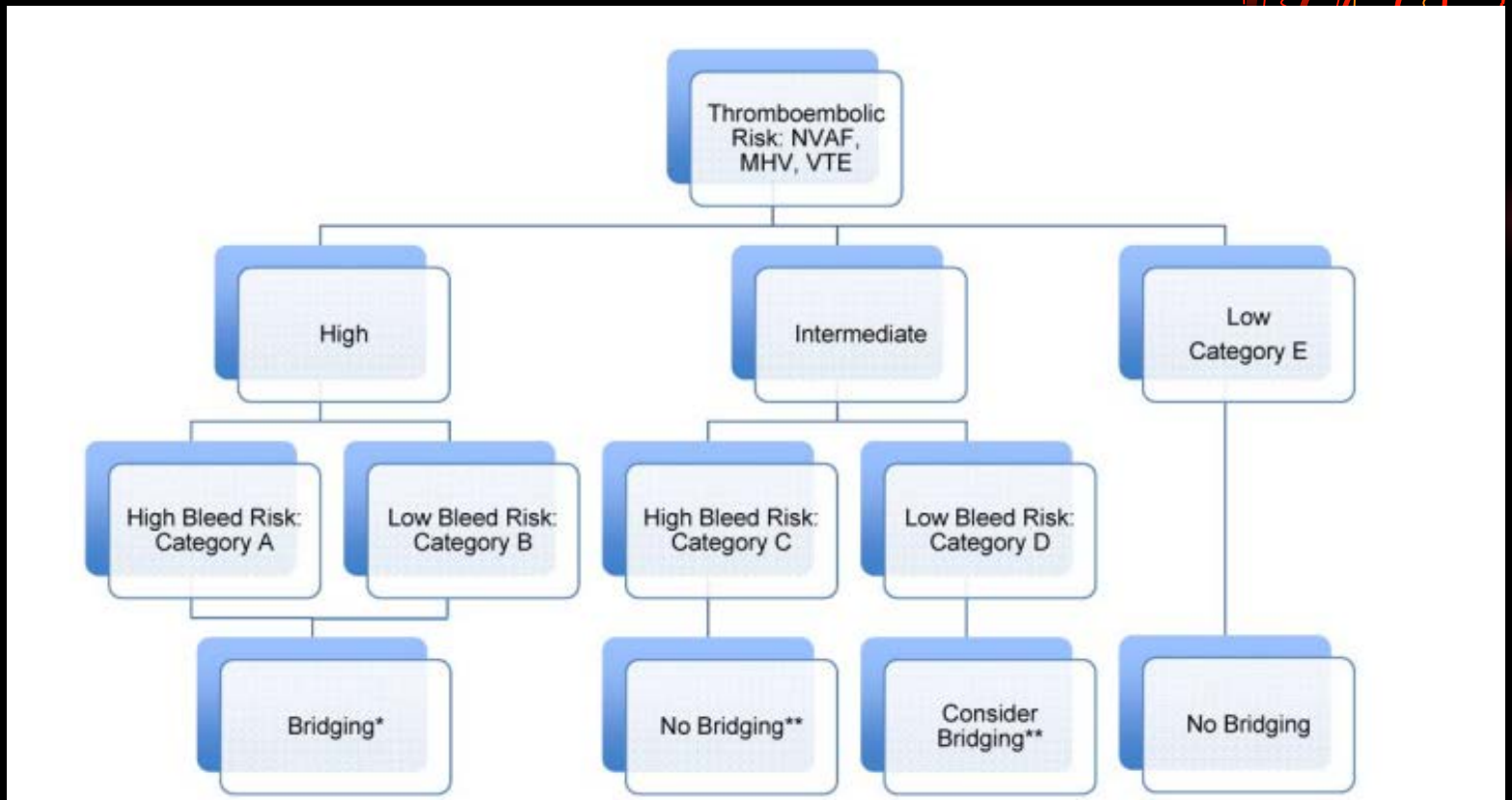


Figure 1. Suggested periprocedural heparin bridging strategies for patients on chronic VKA based on patient thromboembolic and procedural bleed risk. Data from the 9th edition ACCP Guidelines: all grade 2C, except intermediate TE risk.[7] *For high-bleed risk procedures: wait a full 48-72 hours before reinitiating postprocedural heparin (LMWH) bridging (especially treatment dose); stepwise increase in postprocedural heparin (LMWH) dose from prophylactic dose first 24-48 hours to intermediate/treatment dose; no postprocedural heparin (LMWH) bridging in very high bleed risk procedures (ie, major neurosurgical or cardiovascular surgeries) but use of mechanical prophylaxis. **Based on individual patient- and procedural-related risk factors for thrombosis and bleeding.

Table 3. Periprocedural anticoagulation and bridging protocol

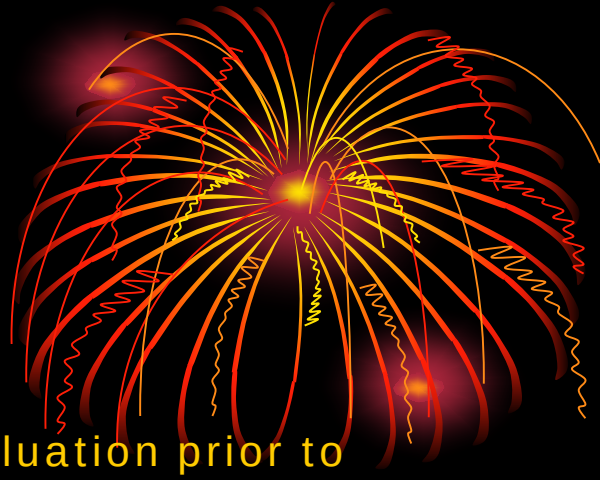
Day	Intervention
Preprocedural intervention	
−7 to −10	Assess for perioperative bridging anticoagulation; classify patients as undergoing high-bleeding risk or low-bleeding risk procedure; check baseline labs (Hgb, platelet count, creatinine, INR)
−7	Stop aspirin (or other antiplatelet drugs)
−5 or −6	Stop warfarin
−3	Start LMWH at therapeutic or intermediate dose*
−1	Last preprocedural dose of LMWH administered no less than 24 h before start of surgery at half the total daily dose; assess INR before the procedure; proceed with surgery if INR < 1.5; if INR > 1.5 and < 1.8, consider low-dose oral vitamin K reversal (1-2.5 mg)
Day of procedural intervention	
0 or +1	Resume maintenance dose of warfarin on evening of or morning after procedure†
Postprocedural intervention	
+1	Low-bleeding risk: restart LMWH at previous dose; resume warfarin therapy High-bleeding risk: no LMWH administration; resume warfarin therapy
+2 or +3	Low-bleeding risk: LMWH administration continued High-bleeding risk: restart LMWH at previous dose
+4	Low-bleeding risk: INR testing (discontinue LMWH if INR > 1.9) High-bleeding risk: INR testing (discontinue LMWH if INR > 1.9)
+7 to +10	Low-bleeding risk: INR testing High bleeding risk: INR testing

*LMWH regimens include enoxaparin 1.5 mg/kg once daily or 1.0 mg/kg twice daily subcutaneously; dalteparin 200 IU/kg once daily or 100 IU/kg twice daily subcutaneously; and tinzaparin 175 IU/kg once daily subcutaneously. Intermediate-dose LMWH (ie, nadroparin 2850-5700 U twice daily subcutaneously; enoxaparin 40 mg twice daily subcutaneously) has been less studied in this setting

†Loading doses (ie, 2 times the daily maintenance dose) of warfarin have also been used.

How to do it... the nitty gritty...

Bridging



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